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(54) PEGYLATED INTERFERON ALFA-CCR5 ANTAGONIST COMBINATION HIV THERAPY

PEGYLIERTES INTERFERON ALPHA IN KOMBINATION MIT EINEM CCR5 ANTAGONISTEN FÜR
EINE HIV THERAPIE

PHARMACOTHERAPIE ANTI-VIH UTILISANT UNE COMBINAISON D'UN
PEG-INTERFERON-ALPHA ET D'UN ANTAGONISTE CCR5

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(56) References cited:
WO-A-97/42969 **WO-A-98/25617**
WO-A-98/48840 **WO-A-99/17773**

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EP 1 175 224 B1

Description

BACKGROUND OF THE INVENTION

[0001] The present invention relates to the use of a pegylated interferon-alfa and a CCR5 antagonist for the preparation of a medicament for the treatment of HIV-1 infections as well as HIV-1 and HCV co-infections in patients. The treatment involves administering a therapeutically effective amount of pegylated interferon-alfa in association with a therapeutically effective amount of a CCR5 antagonist sufficient to lower HIV-1-RNA.

[0002] The global health crisis caused by Human Immunodeficiency Virus-1 ("HIV-1"), the causative agent of Acquired Immunodeficiency Syndrome (AIDS), is unquestioned, and while recent advances in drug therapies have been successful in slowing the progression of AIDS, there is still a need to find a safer, more efficient, less expensive way to control the virus.

[0003] It has been reported that the CCR5 gene plays a role in resistance to HIV infection. HIV infection begins by attachment of the virus to a target cell membrane through interaction with the cellular receptor CD4 and a secondary chemokine co-receptor molecule, and proceeds by replication and dissemination of infected cells through the blood and other tissue. There are various chemokine receptors, but for macrophage-tropic HIV, believed to be the key pathogenic strain that replicates *in vivo* in the early stages of infection, the principal chemokine receptor required for the entry of HIV into the cell is CCR5. Therefore, interfering with the interaction between the viral receptor CCR5 and HIV can block HIV entry into the cell. The present invention relates to the use of small molecules which are CCR5 antagonists in association with pegylated interferon-alfa to treat patients having HIV-1 infections.

[0004] A-M. Vandamme et al., *Antiviral Chemistry & Chemotherapy*, 9:187-203 (1998) disclose current clinical treatments of HIV-1 infections in man including at least triple drug combinations or so-called Highly Active Antiretroviral Therapy ("HAART"); HAART involves various combinations of nucleoside reverse transcriptase inhibitors ("NRTI"), non-nucleoside reverse transcriptase inhibitors ("NNRTI") and HIV protease inhibitors ("PI"). In compliant drug-naïve patients, HAART is effective in reducing mortality and progression of HIV-1 to AIDS. However, these multidrug therapies do not eliminate HIV-1 and long-term treatment usually results in multidrug resistance.

[0005] Further, WO 98/25617 discloses substituted piperazines as modulators of chemokine receptor activity, stating the invention is concerned with compounds which inhibit the entry of HIV into target cells.

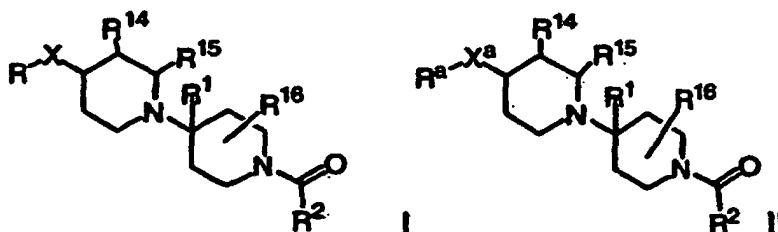
[0006] WO 99/17773 discloses substituted 3-(4-piperidiny)indoles as modulators, agonists or antagonists of the CCR5 receptor and stating that receptor modulators may be useful in the treatment of HIV infection.

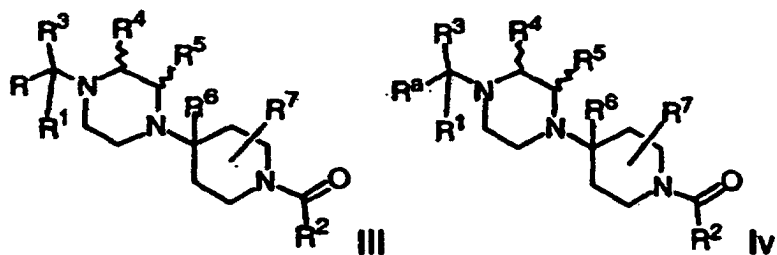
[0007] WO 98/48840 discloses PEG₁₂₀₀₀-IFN alpha and its use in treating viral infection.

[0008] Development of new drug therapies to provide better HIV-1 treatment remains a priority.

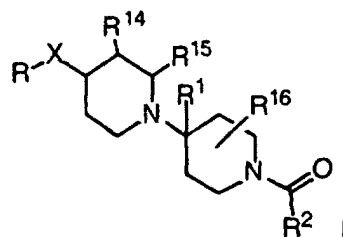
SUMMARY OF THE INVENTION

[0009] The present invention provides the use of a pegylated interferon-alfa and a CCR5 antagonist for the preparation of a medicament for the treatment of HIV-1 infections in patients wherein the CCR5 antagonist is represented by the structural formula I or II or III or IV

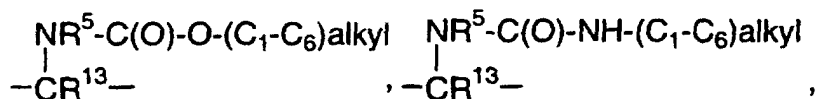
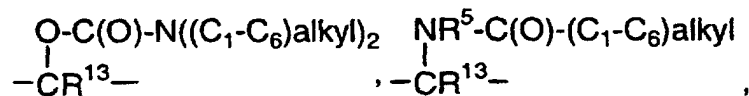
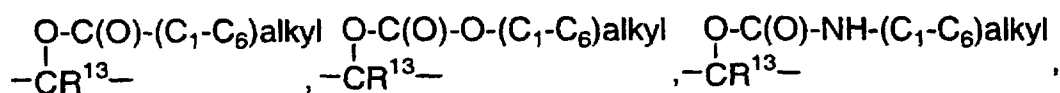
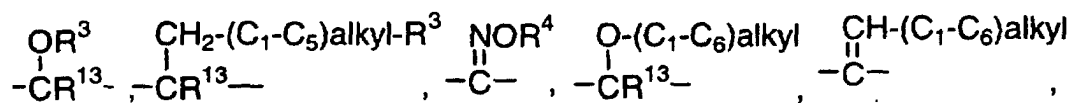


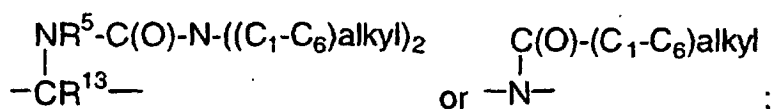


or a pharmaceutically acceptable salt of I or II or III or IV,
wherein in the CCR5 antagonist compounds represented by structural formula I:



X is $-\text{C}(\text{R}^{13})_2-$, $-\text{C}(\text{R}^{13})(\text{R}^{19})-$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{NH}-$, $-\text{N}((\text{C}_1-\text{C}_6)\text{alkyl})-$,



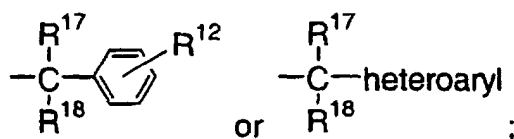


R is R⁶-phenyl, R⁶-pyridyl, R⁶-thiophenyl or R⁶-naphthyl;

R¹ is hydrogen, C₁-C₆ alkyl or C₂-C₆ alkenyl;

R² is R⁷, R⁸, R⁹-phenyl; R⁷, R⁸, R⁹-substituted 6-membered heteroaryl; R⁷, R⁸, R⁹-substituted 6-membered heteroaryl N-oxide;

R¹⁰, R¹¹-substituted 5-membered heteroaryl; naphthyl; fluorenyl; diphenylmethyl

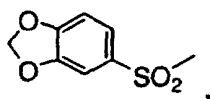


R³ is R⁶-phenyl, R⁶-heteroaryl or R⁶-naphthyl;

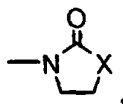
R⁴ is hydrogen, C₁-C₆ alkyl, fluoro-C₁-C₆ alkyl, cyclopropylmethyl, -CH₂CH₂OH, -CH₂CH₂-O-(C₁-C₆)alkyl, -CH₂C(O)-O-(C₁-C₆)alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH(C₁-C₆)alkyl or -CH₂C(O)-N((C₁-C₆)alkyl)₂;

R⁵ and R¹¹ are independently selected from the group consisting of hydrogen and (C₁-C₆)-alkyl;

R⁶ is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-phenyl, R¹⁴-benzyl, CH₃C(=NOCH₃)-, CH₃C(=NOCH₂CH₃)-,



-NH₂, -NHCOCF₃, -NHCONH(C₁-C₆ alkyl), -NHCO(C₁-C₆ alkyl), -NHSO₂(C₁-C₆ alkyl), 5-membered heteroaryl and



wherein X is -O-, -NH- or -N(CH₃)-;

R⁷ and R⁸ are Independently selected from the group consisting of (C₁-C₆)alkyl, halogen, -NR²⁰R²¹, -OH, -CF₃, -OCH₃, -O-acyl, and -OCF₃;

R⁹ is R⁷, hydrogen, phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR²⁰, pyridyl, pyridyl N-oxide, pyrimidinyl, pyrazinyl, -N(R²⁰)CONR²¹R²², -NHCONH(chloro-(C₁-C₆)alkyl), -NHCONH((C₃-C₁₀)-cycloalkyl(C₁-C₆)alkyl), -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyl)₂, -NHSO₂(C₁-C₆)alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyl, C₃-C₁₀ cycloalkyl, -SR²³, -SOR²³, -SO₂R²³, -SO₂NH(C₁-C₆ alkyl), -OSO₂(C₁-C₆)alkyl, -OSO₂CF₃, hydroxy(C₁-C₆)alkyl, -CONR²⁰R²¹, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyl, -CO₂R²⁰, -Si(CH₃)₃ or -B(OC(CH₃)₂)₂;

R¹⁰ is (C₁-C₆)alkyl, -NH₂ or R¹²-phenyl;

R¹² is 1 to 3 substituents independently selected from the group consisting of hydrogen, (C₁-C₆) alkyl, -CF₃, -CO₂R²⁰, -CN, (C₁-C₆)alkoxy and halogen;

R¹³, R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen and (C₁-C₆)alkyl;

R¹⁷ and R¹⁸ are independently selected from the group consisting of hydrogen and C₁-C₆ alkyl, or R¹⁷ and R¹⁸ together are a C₂-C₅ alkylene group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;

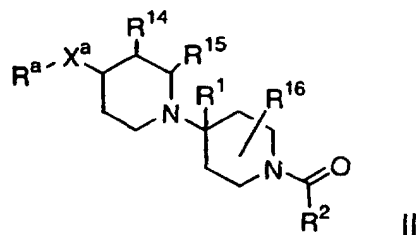
R¹⁹ is R⁶-phenyl, R⁶-heteroaryl, R⁶-naphthyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀)cycloalkyl(C₁-C₆)alkyl or (C₁-C₆)alkoxy

(C₁-C₆)alkyl;

R²⁰, R²¹ and R²² are independently selected from the group consisting of H and C₁-C₆ alkyl; and

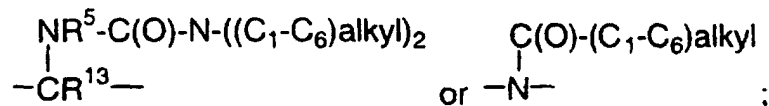
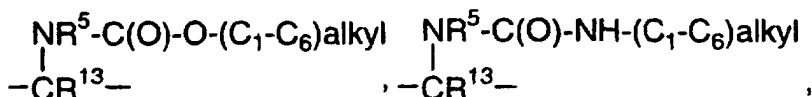
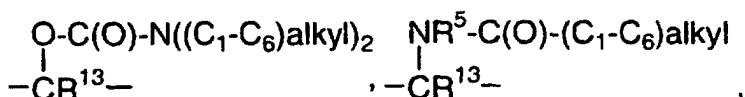
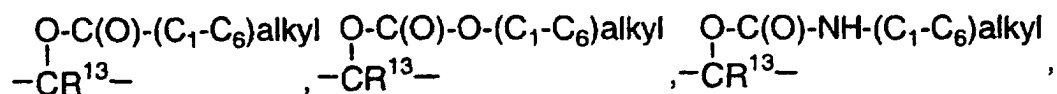
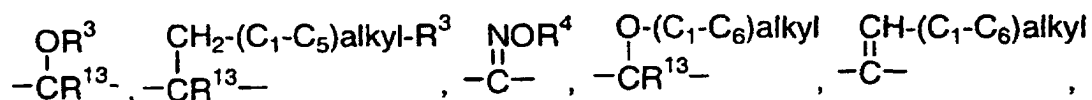
R²³ is C₁-C₆ alkyl or phenyl;

and wherein in the CCR5 antagonist compounds represented by the structural formula II:



or a pharmaceutically acceptable salt thereof, wherein

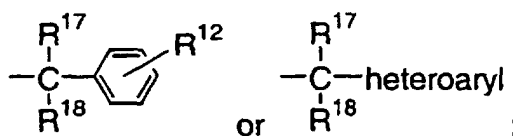
(1) X^a is -C(R¹³)₂-, -C(R¹³)(R¹⁹)-, -C(O)-, -O-, -NH-, -N((C₁-C₆)alkyl)-,



R^a is R^{6a}-phenyl, R^{6a}-pyridyl, R^{6a}-thiophenyl or R⁶-naphthyl;

R¹ is hydrogen, C₁-C₆ alkyl or C₂-C₆ alkenyl;

R² is R⁷, R⁸, R⁹-phenyl; R⁷, R⁸, R⁹-substituted 6-membered heteroaryl; R⁷, R⁸, R⁹-substituted 6-membered heteroaryl N-oxide; R¹⁰, R¹¹-substituted 5-membered heteroaryl; naphthyl; fluorenyl; diphenylmethyl

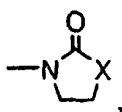


R³ is R¹⁰-phenyl, pyridyl, pyrimidyl, pyrazinyl or thiazolyl;

R⁴ is hydrogen, C₁-C₆ alkyl, fluoro-C₁-C₆ alkyl, cyclopropylmethyl, -CH₂CH₂OH, -CH₂CH₂-O-(C₁-C₆)alkyl, -CH₂C(O)-O-(C₁-C₆)alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH(C₁-C₆)alkyl or -CH₂C(O)-N((C₁-C₆)alkyl)₂;

R⁵ and R¹¹ are independently selected from the group consisting of hydrogen and (C₁-C₆)-alkyl;

R^{6a} is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, -CF₃, CF₃O-, -CN, -CF₃SO₂-, R¹²-phenyl, -NHCOCF₃, 5-membered heteroaryl and



wherein X is -O-, -NH- or -N(CH₃)-

R⁶ is independently selected from the group consisting of R^{6a} and CH₃SO₂-;

R⁷ and R⁸ are independently selected from the group consisting of (C₁-C₆)alkyl, halogen, -NR²⁰R²¹, -OH, -CF₃, -OCH₃, -O-acyl, and -OCF₃;

R⁹ is R⁷, hydrogen, phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR²⁰, pyridyl, pyridyl N-oxide, pyrimidinyl, pyrazinyl, -N(R²⁰)CONR²¹R²², -NHCONH(chloro-(C₁-C₆)alkyl), -NHCONH((C₃-C₁₀)-cycloalkyl(C₁-C₆)alkyl), -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyl)₂, -NHSO₂(C₁-C₆)alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyl, C₃-C₁₀ cycloalkyl, -SR²³, -SOR²³, -SO₂R²³, -SO₂NH(C₁-C₆)alkyl, -OSO₂(C₁-C₆)alkyl, -OSO₂CF₃, hydroxy (C₁-C₆)alkyl, -CON R²⁰R²¹, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyl, -CO₂R²⁰, -Si(CH₃)₃ or -B(OC(CH₃)₂)₂;

R¹⁰ is (C₁-C₆)alkyl, -NH₂ or R¹²-phenyl;

R¹² is 1 to 3 substituents independently selected from the group consisting of hydrogen, (C₁-C₆) alkyl, -CF₃, -CO₂R²⁰, -CN, (C₁-C₆)alkoxy and halogen;

R¹³, R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen and (C₁-C₆)alkyl;

R¹⁷ and R¹⁸ are independently selected from the group consisting of hydrogen and C₁-C₆ alkyl, or R¹⁷ and R¹⁸ together are a C₂-C₅ alkylene group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;

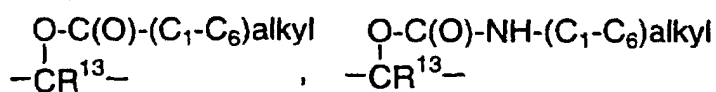
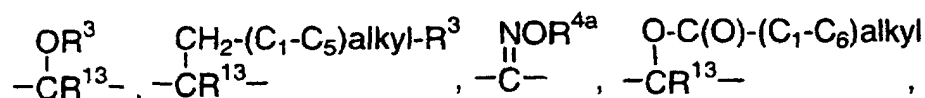
R¹⁹ is R⁶-phenyl, R⁶-heteroaryl, R⁶-naphthyl, C₃ C₁₀ cycloalkyl, (C₃-C₁₀)cycloalkyl(C₁-C₆)alkyl or (C₁-C₆)alkoxy(C₁-C₆)alkyl;

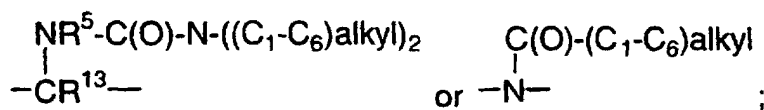
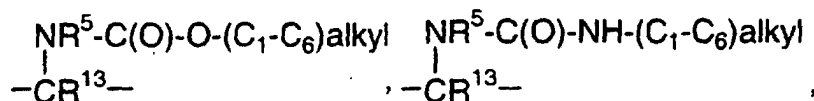
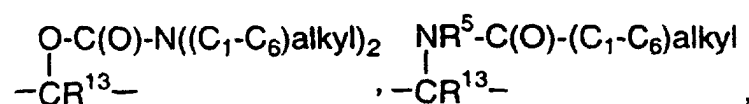
R²⁰, R²¹ and R²² are independently selected from the group consisting of H and C₁-C₆ alkyl; and

R²³ is C₁-C₆ alkyl or phenyl; or

(2):

X^a is -C(R¹³)(R¹⁹)-, -C(O)-, -O-, -NH-, -N((C₁-C₆)alkyl)-,





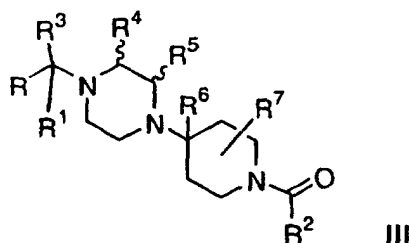
R^a is R^{6b}-phenyl, R^{6b}-pyridyl or R^{6b}-thiophenyl;

R^{4a} is fluoro-C₁-C₆ alkyl, cyclopropylmethyl, -CH₂CH₂OH, -CH₂CH₂-O-(C₁-C₆)alkyl, -CH₂C(O)-O-(C₁-C₆)alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH-(C₁-C₆)alkyl or -CH₂C(O)-N((C₁-C₆)alkyl)₂;

R^{6b} is CH₃SO₂⁻; and

R¹, R², R³, R⁵, R¹⁴, R¹⁵, R¹⁶ and R¹⁹ are as defined in II(1);

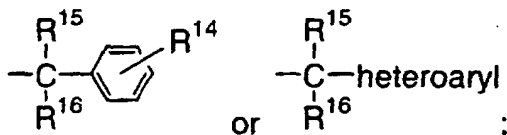
and wherein in the CCR5 antagonist compounds represented by the structural formula III:



R is R⁸-phenyl, R⁸-pyridyl, R⁸-thiophenyl or R⁸-naphthyl;

R¹ is hydrogen or C₁-C₆ alkyl;

R² is R⁹, R¹⁰, R¹¹-phenyl; R⁹, R¹⁰, R¹¹-substituted 6-membered heteroaryl; R⁹, R¹⁰, R¹¹-substituted 6-membered heteroaryl N-oxide; R¹², R¹³-substituted 5-membered heteroaryl; naphthyl; fluorenyl; diphenylmethyl



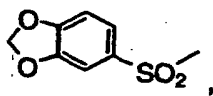
R³ is hydrogen, C₁-C₆ alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkyl(C₁-C₆)alkyl, R⁸-phenyl, R⁸-phenyl(C₁-C₆)alkyl, R⁸-naphthyl, R⁸-naphthyl(C₁-C₆)alkyl, R⁸-heteroaryl or R⁸-heteroaryl(C₁-C₆)alkyl;

R⁴, R⁵, R⁷ and R¹³ are independently selected from the group consisting of hydrogen and (C₁-C₆)alkyl;

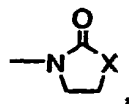
R⁶ is hydrogen, C₁-C₆ alkyl or C₂-C₆ alkenyl;

R⁸ is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, C₁-C₆ alkyl,

C₁-C₆ alkoxy, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-phenyl, R¹⁴-benzyl, CH₃C(=NOCH₃), CH₃C(=NOCH₂CH₃),



-NH₂, -NHCOCF₃, -NHCONH(C₁-C₆ alkyl), -NHCO(C₁-C₆ alkyl), -NHSO₂(C₁-C₆ alkyl), 5-membered heteroaryl and



wherein X is -O-, -NH- or -N(CH₃)-;

R⁹ and R¹⁰ are independently selected from the group consisting of (C₁-C₆)alkyl, halogen, -NR¹⁷R¹⁸, -OH, -CF₃, -OCH₃, -O-acyl, -OCF₃ and -Si(CH₃)₃;

R¹¹ is R⁹, hydrogen, phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR¹⁷, pyridyl, pyridyl N-oxide, pyrimidinyl, pyrazinyl, -N(R¹⁷)CONR¹⁸R¹⁹, -NHCONH(chloro-(C₁-C₆)alkyl), -NHCONH (C₃-C₁₀) cycloalkyl(C₁-C₆)alkyl, -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyl)₂, -NHSO₂(C₁-C₆)alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyl, C₃-C₁₀ cycloalkyl, -SR²⁰, -SOR²⁰, -SO₂R²⁰, -SO₂NH(C₁-C₆ alkyl), -OSO₂(C₁-C₆)alkyl, -OSO₂CF₃, hydroxy(C₁-C₆)alkyl, -CON R¹⁷R¹⁸, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyl, -CO₂R¹⁷, -Si(CH₃)₃ or -B(OC(CH₃)₂)₂;

R¹² is (C₁-C₆)alkyl, -NH₂ or R¹⁴-phenyl;

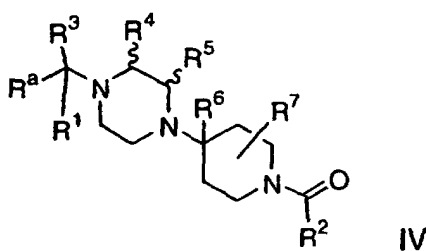
R¹⁴ is 1 to 3 substituents independently selected from the group consisting of hydrogen, (C₁-C₆) alkyl, -CF₃, -CO₂R¹⁷, -CN, (C₁-C₆)alkoxy and halogen;

R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen and C₁-C₆ alkyl, or R¹⁵ and R¹⁶ together are a C₂-C₅ alkylene group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;

R¹⁷, R¹⁸ and R¹⁹ are independently selected from the group consisting of H and C₁-C₆ alkyl; and

R²⁰ is C₁-C₆ alkyl or phenyl;

and wherein in the CCR5 antagonist compounds represented by the structural formula IV:

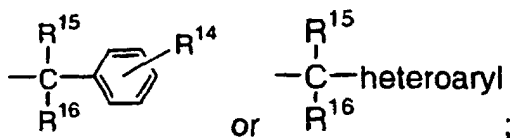


or a pharmaceutically acceptable salt thereof, wherein

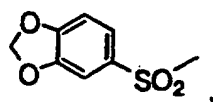
(1) R^a is R^{8a}-phenyl, R^{8b}-pyridyl, R^{8b}-thiophenyl or R⁸-naphthyl;

R¹ is hydrogen or C₁-C₆ alkyl;

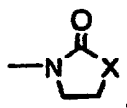
R² is R⁹, R¹⁰, R¹¹-phenyl; R⁹, R¹⁰, R¹¹-substituted 6-membered heteroaryl; R⁹, R¹⁰, R¹¹-substituted 6-membered heteroaryl N-oxide; R¹², R¹³-substituted 5-membered heteroaryl; naphthyl; fluorenyl; diphenylmethyl,



R^3 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $(\text{C}_1\text{-C}_6)\text{alkoxy}(\text{C}_1\text{-C}_6)\text{alkyl}$, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl $(\text{C}_1\text{-C}_6)\text{alkyl}$, R^8 -phenyl, R^8 -phenyl $(\text{C}_1\text{-C}_6)\text{alkyl}$, R^8 -naphthyl, R^8 -naphthyl $(\text{C}_1\text{-C}_6)\text{alkyl}$, R^8 -heteroaryl or R^8 -heteroaryl $(\text{C}_1\text{-C}_6)\text{alkyl}$;
 R^4 , R^5 , R^7 and R^{13} are independently selected from the group consisting of hydrogen and $(\text{C}_1\text{-C}_6)\text{-alkyl}$;
 R^6 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_2\text{-C}_6$ alkenyl;
 R^8 is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $-\text{CF}_3$, $\text{CF}_3\text{O-}$, $\text{CH}_3\text{C(O)-}$, $-\text{CN}$, $\text{CH}_3\text{SO}_2\text{-}$, $\text{CF}_3\text{SO}_2\text{-}$, R^{14} -phenyl, R^{14} -benzyl, $\text{CH}_3\text{C(=NOCH}_3\text{)}$, $\text{CH}_3\text{C(=NOCH}_2\text{CH}_3\text{)}$,

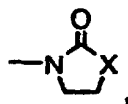


$-\text{NH}_2$, $-\text{NHCOCF}_3$, $-\text{NHCONH}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{NHCO}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{NHSO}_2(\text{C}_1\text{-C}_6 \text{ alkyl})$, 5-membered heteroaryl and



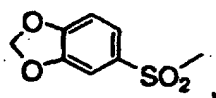
wherein X is $-\text{O-}$, $-\text{NH-}$ or $-\text{N(CH}_3\text{)-}$;

R^{8a} is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, $-\text{CF}_3$, $\text{CF}_3\text{O-}$, $-\text{CN}$, $\text{CF}_3\text{SO}_2\text{-}$, R^{14} -phenyl, $-\text{NHCOCF}_3$, 5-membered heteroaryl and

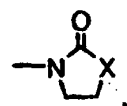


wherein X is as defined above;

R^{8b} is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, $-\text{CF}_3$, $\text{CF}_3\text{O-}$, $\text{CH}_3\text{C(O)-}$, $-\text{CN}$, $\text{CF}_3\text{SO}_2\text{-}$, R^{14} -benzyl, $\text{CH}_3\text{C(=NOCH}_3\text{)}$, $\text{CH}_3\text{C(=NOCH}_2\text{CH}_3\text{)}$,



$-\text{NHCOCF}_3$, 5-membered heteroaryl and



wherein X is as defined above;

R^9 and R^{10} are independently selected from the group consisting of $(\text{C}_1\text{-C}_6)\text{alkyl}$, halogen, $-\text{NR}^{17}\text{R}^{18}$, $-\text{OH}$, $-\text{CF}_3$, $-\text{OCH}_3$, $-\text{O-acyl}$, $-\text{OCF}_3$ and $-\text{Si(CH}_3\text{)}_3$;

R^{11} is R^9 , hydrogen, phenyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CHO}$, $-\text{CH=NOR}^{17}$, pyridyl, pyridyl N-oxide, -pyrimidinyl, pyrazinyl, $-\text{N(R}^{17}\text{)CONR}^{18}\text{R}^{19}$, $-\text{NHCONH(chloro-(C}_1\text{-C}_6\text{)alkyl)}$, $-\text{NHCONH(C}_3\text{-C}_{10}\text{) cycloalkyl(C}_1\text{-C}_6\text{)}$

alkyl), -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyl)₂, -NHSO₂(C₁-C₆)alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyl, C₃-C₁₀ cycloalkyl, -SR²⁰, -SOR²⁰, -SO₂R²⁰, -SO₂NH(C₁-C₆)alkyl, -OSO₂(C₁-C₆)alkyl, -OSO₂CF₃, hydroxy(C₁-C₆)alkyl, -CON R¹⁷R¹⁸ -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyl, -CO₂R¹⁷, -Si(CH₃)₃ or -B(OC(CH₃)₂)₂;

R¹² is (C₁-C₆)alkyl, -NH₂ or R¹⁴-phenyl;

R¹⁴ is 1 to 3 substituents independently selected from the group consisting of hydrogen, (C₁-C₆) alkyl, -CF₃, -CO₂R¹⁷, -CN, (C₁-C₆)alkoxy and halogen;

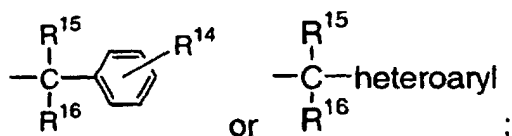
R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen and C₁-C₆ alkyl, or R¹⁵ and R¹⁶ together are a C₂-C₅ alkylene group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;

R¹⁷, R¹⁸ and R¹⁹ are independently selected from the group consisting of H and C₁-C₆ alkyl; and

R²⁰ is C₁-C₆ alkyl or phenyl; or

(2) R^a is R⁸-phenyl, R⁸-pyridyl or R⁸-thiophenyl;

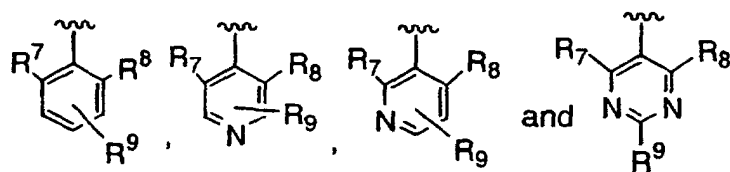
R² is fluorenyl, diphenylmethyl



and R¹, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹ and R²⁰ are as defined in IV(1).

[0010] Preferred are compounds of formula I wherein R is R⁶-phenyl, especially wherein R⁶ is a single substituent, and especially wherein the R⁶ substituent is in the 4-position. Also preferred are compounds of formula I wherein R¹³, R¹⁴, R¹⁵ and R¹⁶ are each hydrogen or methyl, especially hydrogen. Also preferred are compounds of formula I wherein X is -CHOR³, -C(R¹³)(R¹⁹)- or -C(=NOR⁴)-; a preferred definition for R³ is pyridyl, especially 2-pyridyl, a preferred definition for R⁴ is (C₁-C₆)alkyl, especially methyl, ethyl or isopropyl, a preferred definition for R¹³ is hydrogen, and a preferred definition for R¹⁹ is R⁶-phenyl. For compounds of formula I, R¹ is preferably (C₁-C₆)alkyl, especially methyl.

[0011] In compounds of formula I, R² is preferably R⁷, R⁸, R⁹-phenyl, R⁷, R⁸, R⁹-pyridyl or an N-oxide thereof, or R⁷, R⁸, R⁹-pyrimidyl. When R² is pyridyl, it is preferably 3- or 4-pyridyl, and when pyrimidyl, it is preferably 5-pyrimidyl. The R⁷ and R⁸ substituents are preferably attached to carbon ring members adjacent to the carbon joining the ring to the rest of the molecule and the R⁹ substituent can be attached to any of the remaining unsubstituted carbon ring members, for example as shown in the following structures:



[0012] Preferred R⁷ and R⁸ substituents are: (C₁-C₆)alkyl, especially methyl; halogen, especially chloro; and -NH₂. A preferred R⁹ substituent is hydrogen.

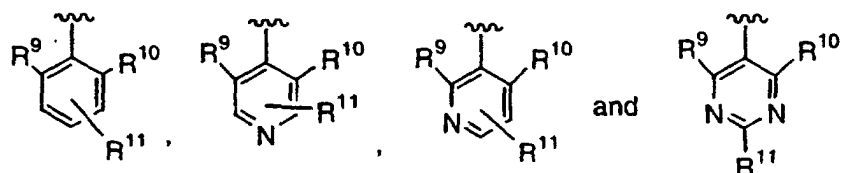
[0013] Preferred are compounds of formula II(1) wherein R^a is R^{6a}-phenyl, especially wherein R^{6a} is a single substituent, and especially wherein the R^{6a} substituent is in the 4-position. Also preferred are compounds of formula II(1) wherein X^a is -CHOR³, -C(R¹³)(R¹⁹)- or -C(=NOR^{4a})-; a preferred definition for R³ is pyridyl, especially 2-pyridyl, a preferred definition for R⁴ is (C₁-C₆)alkyl, especially methyl, ethyl or isopropyl, a preferred definition for R¹³ is hydrogen, and a preferred definition for R¹⁹ is R⁶-phenyl. For compounds of formula II(1), R¹ is preferably (C₁-C₆)alkyl, especially methyl. Also for compounds of formula II(1), R¹⁴, R¹⁵ and R¹⁶ are preferably hydrogen.

[0014] Preferred are compounds of formula II(2) wherein R^a is R^{6b}-phenyl, especially wherein R^{6b} is a single substituent, and especially wherein the R^{6b} substituent is in the 4-position. Also preferred are compounds of formula II(2) wherein X^a is -CHOR³, -C(R¹³)(R¹⁹)- or -C(=NOR^{4a})-; a preferred definition for R³ is pyridyl, especially 2-pyridyl, preferred definitions for R^{4a} are cyclopropylmethyl and trifluoroethyl, a preferred definition for R¹³ is hydrogen, and a preferred definition for R¹⁹ is R⁶-phenyl. For compounds of formula II(2), R¹ is preferably (C₁-C₆)alkyl, especially methyl. Also for compounds of formula II(2), R¹⁴, R¹⁵ and R¹⁶ are preferably hydrogen.

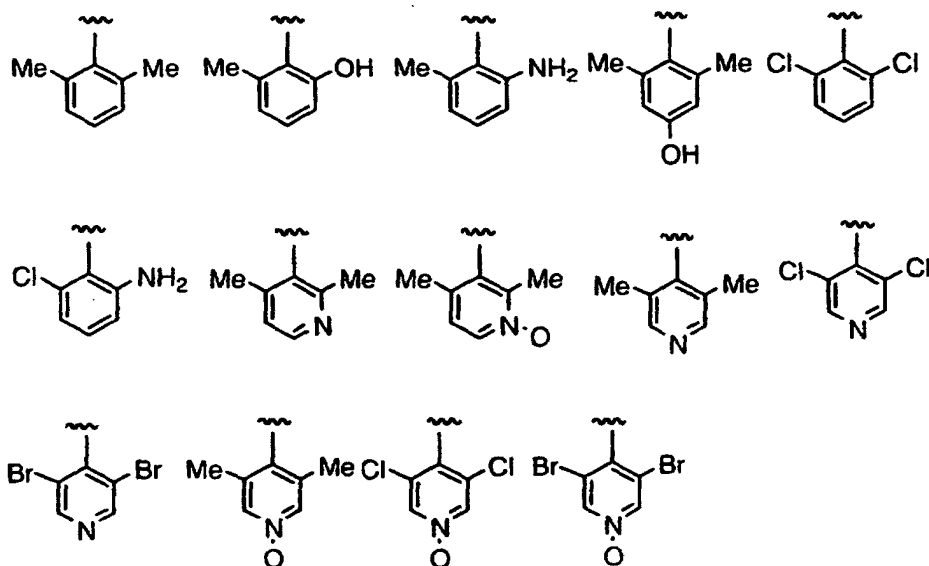
[0015] In compounds of formula II(1) and (2), R² is preferably R⁷, R⁸, R⁹-phenyl; R⁷, R⁸, R⁹-pyridyl or an N-oxide thereof; or R⁷, R⁸, R⁹-pyrimidyl. When R² is pyridyl, it is preferably 3- or 4-pyridyl, and when pyrimidyl, it is preferably 5-pyrimidyl. The R⁷ and R⁸ substituents are preferably attached to carbon ring members adjacent to the carbon joining the ring to the rest of the molecule and the R⁹ substituent can be attached to any of the remaining unsubstituted carbon ring members as shown above for compounds of formula I. Preferred R⁷ and R⁸ substituents for compounds of formula I are: (C₁-C₆)alkyl, especially methyl; halogen, especially chloro; and -NH₂; a preferred R⁹ substituent is hydrogen.

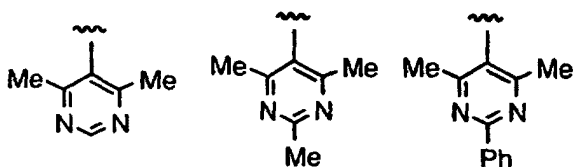
[0016] Preferred are compounds of formula III wherein R is R⁸-phenyl or R⁸-naphthyl, especially wherein R⁸ is a single substituent, and especially wherein the R⁸ substituent is in the 4-position. For R⁸-phenyl, preferred R⁸ substituents are -CF₃, -OCF₃, CH₃SO₂-, CH₃CO-, CH₃C(=NOCH₃)-, Br and I. For R⁸-naphthyl, R⁸ is preferably C₁-C₆ alkoxy. Also preferred are compounds of formula III wherein R³ is hydrogen, (C₁-C₆) alkyl, R⁸-phenyl. R⁸-benzyl or R⁸-pyridyl; more preferred definitions for R³ are methyl, ethyl, phenyl, benzyl and pyridyl. R¹ is preferably hydrogen. For compounds of formula III, R⁶ is preferably hydrogen or methyl, especially methyl. R⁴ is preferably methyl; R⁵ and R⁷ are each preferably hydrogen.

[0017] In compounds of formula III, R² is preferably R⁹, R¹⁰, R¹¹-phenyl, R⁹, R¹⁰, R¹¹-pyridyl or an N-oxide thereof, or R⁹, R¹⁰, R¹¹-pyrimidyl. When R² is pyridyl, it is preferably 3- or 4-pyridyl, and when pyrimidyl, it is preferably 5-pyrimidyl. The R⁹ and R¹⁰ substituents are preferably attached to carbon ring members adjacent to the carbon joining the ring to the rest of the molecule and the R¹¹ substituent can be attached to any of the remaining unsubstituted carbon ring members, for example as shown in the following structures:



[0018] Preferred R⁹ and R¹⁰ substituents are: (C₁-C₆)alkyl, especially methyl; halogen, especially chloro or bromo, -OH and -NH₂. When R² is phenyl, R¹¹ is preferably hydrogen or -OH; when R² is pyridyl, R¹¹ is preferably hydrogen; and when R² is pyrimidyl, R¹¹ is preferably hydrogen, methyl or phenyl. Examples of particularly preferred R² groups are as follows:



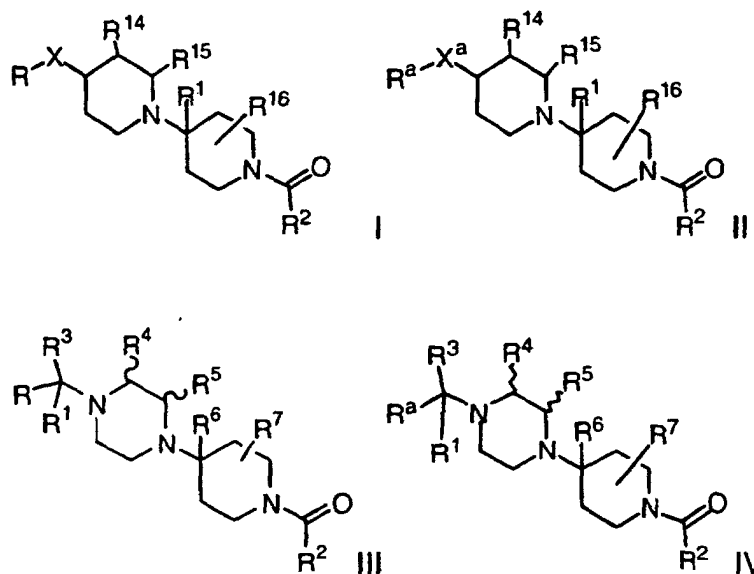


[0019] Preferred compounds of formula IV are those defined in (1).

[0020] More preferred are those of formula IV(1) wherein R^a is R^{8a} -phenyl or R^8 -naphthyl, wherein R^{8a} is $-CF_3$, CF_3O- or halogen and R^8 is C_1-C_6 alkoxy. The R^{8a} or R^8 substituent is preferably a single substituent; it is especially preferred that the R^{8a} or R^8 substituent is in the 4-position. Also preferred are compounds of formula IV(1) wherein R^3 is hydrogen, (C_1-C_6) alkyl, R^8 -phenyl, R^8 -benzyl or R^8 -pyridyl; more preferred definitions for R^3 are methyl, ethyl, phenyl, benzyl and pyridyl. R^1 is preferably hydrogen. For compounds of formula IV(1), R^6 is preferably hydrogen or methyl, especially methyl. R^4 is preferably methyl; R^5 and R^7 are each preferably hydrogen.

[0021] R^2 in formula IV(1) is preferably as defined for formula III, i.e., R^9 , R^{10} , R^{11} -phenyl, R^9 , R^{10} , R^{11} -pyridyl or an N-oxide thereof, or R^9 , R^{10} , R^{11} -pyrimidyl, wherein the R^9 , R^{10} , R^{11} -substitution is as defined above for preferred compounds of formula III.

[0022] The present invention also provides the use of a pegylated interferon- α , a CCR5 antagonist, ribavirin and HAART for the preparation of a medicament for the treatment of patients co-infected with HIV-1 and HCV. The treatment comprises administering a therapeutically effective amount of pegylated interferon- α in association with a therapeutically effective amount of ribavirin and a therapeutically effective amount of HAART and a therapeutically effective amount of a CCR5 antagonist represented by the structural formula I or II or III or IV:



or a pharmaceutical salt of a compound of the formula I or II or III or IV; sufficient to lower HIV-1-RNA and HCV-RNA plasma levels.

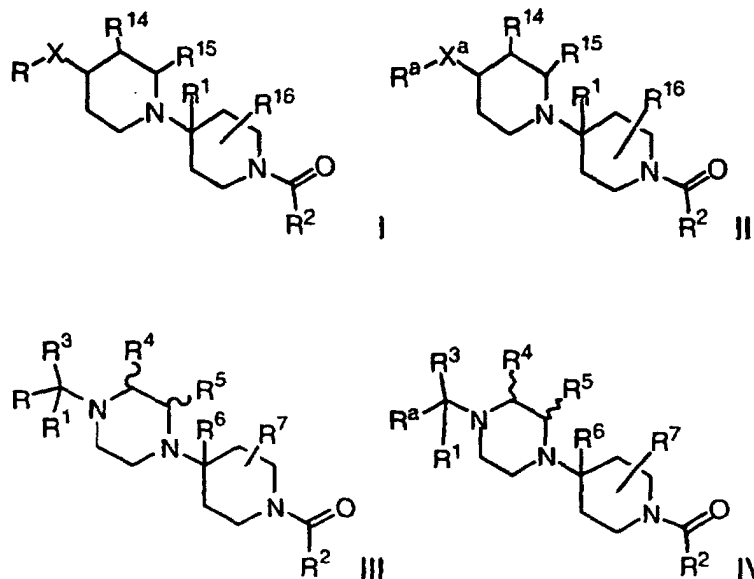
wherein X, R, and R^1 to R^{16} are as defined in formula 1; and

wherein X, R^a and R^1 to R^{16} are as defined in formula II(1) and II(2) and

wherein R, and R^1 to R^{17} are as defined in formula III; and

wherein R^a , and R^1 to R^{17} are as defined in formula IV.

[0023] The present invention also provides the use of pegylated interferon- α , HAART and a CCR5 antagonist for the preparation of a medicament for the treatment of pediatric patients infected with HIV-1. The treatment comprises administering a therapeutically effective amount of pegylated interferon- α in association with a therapeutically effective amount of HAART and a therapeutically effective amount of a CCR5 antagonist represented by the structural formula I or II or III or IV:



or a pharmaceutical salt of compounds or II or III or IV;

sufficient to lower HIV-1-RNA plasma levels.

wherein X, R, and R¹ to R¹⁶ are as defined in I; and

wherein X^a, R^a, and R¹ to R¹⁶ are as defined in II(1) and II(2);

wherein R, and R¹ to R¹⁷ are as defined in formula III; and

wherein R^a, and R¹ to R¹⁷ are as defined in formula IV.

DETAILED DESCRIPTION

[0024] As used herein, the following terms are used as defined below unless otherwise indicated.

[0025] Alkyl (including the alkyl portions of alkoxy, alkylamino and dialkylamino) represents straight and branched carbon chains and contains from one to six carbon atoms.

[0026] Alkenyl represents C₂-C₆ carbon chains having one or two unsaturated bonds, provided that two unsaturated bonds are not adjacent to each other.

[0027] Substituted phenyl means that the phenyl group can be substituted at any available position on the phenyl ring.

[0028] Acyl means a radical of a carboxylic acid having the formula alkyl-C(O)-, aryl-C(O)-, aralkyl-C(O)-, (C₃-C₇) cycloalkyl-C(O)-, (C₃-C₇)cycloalkyl(C₁-C₆)alkyl-C(O)-, and heteroaryl-C(O)-, wherein alkyl and heteroaryl are as defined herein; aryl is R¹²-phenyl or R¹²-naphthyl; and aralkyl is aryl-(C₁-C₆)alkyl, wherein aryl is as defined above.

[0029] Heteroaryl represents cyclic aromatic groups of 5 or 6 atoms or bicyclic groups of 11 to 12 atoms having one or two heteroatoms independently selected from O, S or N, said heteroatom(s) interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character. For 6-membered heteroaryl rings, carbon atoms can be substituted by R⁷, R⁸ or R⁹ groups. Nitrogen atoms can form an N-oxide. All regioisomers are contemplated, e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl. Typical 6-membered heteroaryl groups are pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and the N-oxides thereof. For 5-membered heteroaryl rings, carbon atoms can be substituted by R¹⁰ or R¹¹ groups. Typical 5-membered heteroaryl rings are furyl, thienyl, pyrrolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl and isoxazolyl. 5-Membered rings having one heteroatom can be joined through the 2- or 3- position; 5-membered rings having two heteroatoms are preferably joined through the 4-position. Bicyclic groups typically are benzo-fused ring systems derived from the heteroaryl groups named above, e.g. quinolyl, phthalazinyl, quinazolinyl, benzofuranyl, benzothienyl and indolyl.

[0030] Preferred points of substitution for 6-membered heteroaryl rings at R² are described above. When R² is a 5-membered heteroaryl group, the R¹⁰ and R¹¹ substituents are preferably attached to carbon ring members adjacent to the carbon joining the ring to the rest of the molecule, and R¹¹ is preferably alkyl; however, if a heteroatom is adjacent to the carbon joining the ring to the rest of the molecule (i.e., as in 2-pyrrolyl), R¹⁰ is preferably attached to a carbon ring member adjacent to the carbon joining the ring to the rest of the molecule.

[0031] Halogen represents fluoro, chloro, bromo and iodo.

[0032] Fluoro(C₁-C₆)alkyl represents a straight or branched alkyl chain substituted by 1 to 5 fluoro atoms, which can be attached to the same or different carbon atoms,

e.g., -CH₂F, -CHF₂, -CF₃, F₃CCH₂- and -CF₂CF₃.

[0033] The present method of treating patients having HIV-1 infections comprises administering a therapeutically effective amount of pegylated interferon-alfa and a therapeutically effective amount of a CCR5 antagonist compound represented by structural formula I or II or III or IV as a combination therapy or in association with a therapeutically effective amount of at least one of ribavirin, interleukin-2("IL-2"), interleukin-12("IL-12"), , and pentafuside alone or in combination with an anti-HIV-1 therapy, especially, HAART in accordance with good clinical practice to minimize HIV-1 RNA plasma levels. See for example A-M. Vandamme et al., in *Antiviral Chemistry & Chemotherapy*, 9:187-203 (1998) and "Drugs for HIV Infection" in *The Medical Letter* Vol. 39 (Issue 1015) December 5, 1997, pages 111-116. In a preferred aspect of the present invention, the combination of a pegylated interferon alpha and a CCR5 antagonist of formulas I to IV is administered to a patient infected with HIV-1, or co-infected with HIV-1 and HCV, in association with ribavirin and HAART. It is a special feature of the present invention that each of pegylated interferon alpha, the CCR5 antagonists of formulas I to IV and the components of HAART has a different mechanism of action in treating HIV-1.

[0034] It is another special feature of the present invention that the pegylated interferon alpha and the CCR5 antagonists of formulas I to IV do not cause cross-resistance with each other or with the components of HAART. The initiation of the administration of a therapeutically effective amount of the combination of a pegylated interferon alpha, ribavirin, and a CCR5 antagonist compound represented by structural formula I or II or III or IV and HAART may occur before, after or concurrently with administering a therapeutically effective amount of combination of a pegylated interferon-alfa and a CCR5 antagonist compound represented by structural formula I or II or III or IV in accordance with the present invention. In an embodiment of the present invention, the method of treating patients having HIV-1 infections comprises two treatment time periods. In the first treatment time period, a combination of a therapeutically effective amount of pegylated interferon-alfa and a CCR5 antagonist compound represented by structural formula I or II or III or IV is administered for a first treatment time period sufficient to lower HIV-1-RNA plasma levels, preferably by a power of 10, more preferably by at least two powers of ten, i.e., at least 10², lower than the initial HIV-1-RNA plasma level. In the second treatment time period, the method entails continuing the administration of a therapeutically effective amount of a combination of pegylated interferon-alfa in association a CCR5 antagonist compound represented by structural formula I or II or III or IV and a therapeutically effective amount of HAART in accordance with good clinical practice to minimize HIV-1-RNA plasma levels. A-M. Vandamme et al., *Antiviral Chemistry & Chemotherapy*, 9:187-203 (1998) disclose current clinical treatments of HIV-1 infections, including when to start multidrug therapy and which drugs to combine. The triple drug therapy may include two NRTIs and one PI, but there are many issues to be considered in the choice of the precise HAART for any patient. See for example, Tables 1 & 2 and Figure 2 in A-M. Vandamme et al., listed hereinabove.

[0035] The terms "CCR5 antagonist compound" and "CCR5 antagonists" as used herein mean any compound that interferes with the interaction between the viral receptor CCR5 and HIV-1 to block entry of HIV-1 into the cell. Assays, e.g., the CCR5 Membrane Binding Assay, the HIV-1 Entry and the HIV-1 Entry Replication Assays, inter alia, are presented herein after to identify a compound as a CCR5 antagonist and to determine its CCR5 antagonist activity.

[0036] The term "patients having HIV-1 infections" as used herein means any patient -including a pediatric patient- having HIV-1 infection and includes treatment-naïve patients and treatment-experienced patients having the HIV-1 infection as well as treatment-naïve patients and treatment-experienced patients co-infected with the HIV-1 and hepatitis C virus ("HCV").

[0037] The term "pediatric patient" as used herein means a patient below the age of 17, and normally includes those from birth to 16 years of age.

[0038] The term "treatment-naïve patients" as used herein means patients having HIV-1 or co-infected with the HIV-1 and HCV who have never been treated with any anti-retroviral drugs, e.g., NRTI, NNRTI, PI or any interferon, including but not limited to interferon-alfa, or pegylated interferon alfa.

[0039] The term "treatment-experienced" patients as used herein means those patients having HIV-1 or co-infected with the HIV-1 and HCV who have initiated some form of anti HIV therapy including, but not limited to HAART or some form of anti-HCV therapy, including but not limited to interferon-alfa, pegylated interferon alfa or ribavirin.

[0040] The term "patients having hepatitis C infections" as used herein means any patient-including a pediatric patient- having hepatitis C and includes treatment-naïve patients having hepatitis C infections and treatment-experienced patients having hepatitis C infections as well as those pediatric, treatment-naïve and treatment-experienced patients having chronic hepatitis C infections.

[0041] These patients having hepatitis C include those who are infected with multiple HCV genotypes including type 1 as well as those infected with, e.g., HCV genotypes 2, 3, 4, 5 and/or 6 and other possible HCV genotypes.

[0042] The term "treatment-naïve patients having hepatitis C infections" as used herein means patients with hepatitis C who have never been treated with ribavirin or any interferon, including but not limited to interferon-alfa, or pegylated interferon alfa.

[0043] The term "treatment-experienced patients having hepatitis C infections" as used herein means patients with hepatitis C who have been treated with ribavirin or any interferon, including but not limited to interferon-alfa, or pegylated interferon alfa, including relapsers and non-responder.

[0044] The term "relapsers" as used herein means treatment-experienced patients with hepatitis C who have relapsed after initial response to previous treatment with interferon alone, or in combination with ribavirin.

[0045] The term "non-responders" as used herein means treatment-experienced patients with hepatitis C who have not responded to prior treatment with any interferon alone, or in combination with ribavirin.

[0046] When the pegylated interferon-alfa administered is a pegylated interferon alfa-2b, the therapeutically effective amount of pegylated interferon alfa-2b administered during the treatment in accordance with the present invention, including in first and second treatment time periods, is in the range of about 0.1 to 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered per week, in single or divided doses, preferably once a week (QW) or twice a week (BIW), preferably in the range of about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week (QW) or in the range of about 0.05 to about 4.5 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week (BIW), or is in the range of about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered per week, preferably in the range of about 0.5 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week (QW) or in the range of about 0.25 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week, or is in the range of about 0.75 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered per week, most preferably is in the range of about 0.75 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered once a week or about 0.375 to about 0.75 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week.

[0047] When the pegylated interferon-alfa administered to pediatric patients is a pegylated interferon alfa-2b, the therapeutically effective amount of pegylated interferon alfa-2b administered during the treatment in accordance with the present invention, including in first and second treatment time periods is in the range of about 0.1 to 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered per week, in single or divided doses, preferably once a week (QW) or twice a week (BIW), more preferably about 0.1 to about 9.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week (QW), or about 0.05 to about 4.5 micrograms per kilogram of pegylated interferon alfa-2b administered per week, in single or divided doses, preferably once a week (QW) or twice a week (BIW), more preferably about 0.05 to about 4.5 micrograms per kilogram of pegylated interferon alfa-2b administered once a week, or preferably about 0.75 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered in single or divided doses, preferably once a week (QW) or twice a week (BIW), more preferably about 0.75 to about 3.0 micrograms per kilogram of pegylated interferon alfa-2b administered once a week or about 0.375 to about 1.5 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week, and most preferably about 2.25 to about 2.6 micrograms per kilogram of pegylated interferon alfa-2b administered once a week or about 1.1 to about 1.3 micrograms per kilogram of pegylated interferon alfa-2b administered twice a week (BIW).

[0048] When the pegylated interferon-alfa administered is a pegylated interferon alfa-2a, the therapeutically effective amount of pegylated interferon alfa-2a administered during the treatment in accordance with the present invention, including in first and second treatment time periods, is in the range of about 50 micrograms to about 500 micrograms per week, preferably about 150 micrograms to about 250 micrograms per week, or preferably about 180 micrograms to about 250 micrograms per week or preferably about 150 micrograms to about 180 micrograms per week or most preferably about 180 micrograms per week. or alternatively the effective amount is in the range of about 50 micrograms to about 500 micrograms once a week ("QW"), preferably about 150 micrograms to about 250 micrograms QW, or preferably about 180 micrograms to about 250 micrograms QW or preferably about 150 micrograms to about 180 micrograms QW or most preferably about 180 micrograms QW or alternatively the effective amount is in the range of about 25 micrograms to about 250 micrograms twice a week ("BIW"), preferably about 75 micrograms to about 125 micrograms BIW, preferably about 75 micrograms to about 125 micrograms BIW, or preferably about 75 micrograms to about 90 micrograms BIW, or most preferably about 90 micrograms BIW.

[0049] When the pegylated interferon-alfa administered to a pediatric patient is a pegylated interferon alfa-2a, the therapeutically effective amount of pegylated interferon alfa-2a administered during the treatment in accordance with the present invention, including in first treatment time period is in the range of about 50 micrograms to about 500 micrograms once a week ("QW"), preferably about 300 micrograms to about 375 micrograms QW or the therapeutically effective amount of pegylated interferon alfa-2a administered to a pediatric patient is in the range of about 50 micrograms to about 250 micrograms twice a week, preferably about 150 micrograms to about 190 micrograms once a week.

[0050] Ribavirin is administered to the patient in association with pegylated interferon-alfa, that is, before, after or concurrently with the administration of the pegylated interferon alfa. The pegylated interferon-alfa dose is preferably administered during the same period of time that the patient receives doses of ribavirin. The amount of ribavirin administered concurrently with the pegylated interferon-alfa is from about 400 to about 1600 mg per day, preferably about 600 to about 1200 mg/day or about 800 to about 1200 mg/day and most preferably about 1000 to about 1200 mg/kg a day. The pegylated interferon-alfa dose is also preferably administered to the pediatric patient during the same

period of time that such patient receives doses of ribavirin. The amount of ribavirin administered to the pediatric patient concurrently with the pegylated interferon-alfa is from about 8 to about 15 mg per kilogram per day, preferably about 8, 12 or 15 mg per kilogram per day, in divided doses.

[0051] Pegylated interferon-alfa formulations are not effective when administered orally, so the preferred method of administering the pegylated interferon-alfa is parenterally, preferably by subcutaneous, IV, or IM, injection. Ribavirin may be administered orally in capsule, tablet or liquid form in association with the parenteral administration of pegylated interferon-alfa. Of course, other types of administration of both medicaments, as they become available are contemplated, such as by nasal spray, transdermally, by suppository, by sustained release dosage form, and by pulmonary inhalation. Any form of administration will work so long as the proper dosages are delivered without destroying the active ingredient.

[0052] The term "nucleoside and nucleotide reverse transcriptase inhibitors" ("NRTI" s) as used herein means nucleosides and nucleotides and analogues thereof that inhibit the activity of HIV-1 reverse transcriptase, the enzyme which catalyzes the conversion of viral genomic HIV-1 RNA into proviral HIV-1 DNA.

[0053] Typical suitable NRTIs include zidovudine (AZT) available under the RETROVIR tradename from Glaxo-Wellcome Inc., Research Triangle, NC 27709; didanosine (ddI) available under the VIDEX tradename from Bristol-Myers Squibb Co., Princeton, NJ 08543; zalcitabine (ddC) available under the HIVID tradename from Roche Pharmaceuticals, Nutley, NJ 07110; stavudine (d4T) available under the ZERIT trademark from Bristol-Myers Squibb Co., Princeton, NJ 08543; lamivudine (3TC) available under the EPIVIR tradename from Glaxo-Wellcome Research Triangle, NC 27709; abacavir (1592U89) disclosed in WO96/30025 and available under the ZIAGEN tradename from Glaxo-Wellcome Research Triangle, NC 27709; adefovir dipivoxil [bis(POM)-PMEA] available under the PREVON tradename from Gilead Sciences, Foster City, CA 94404; lobucavir (BMS-180194), a nucleoside reverse transcriptase inhibitor disclosed in EP-0358154 and EP-0736533 and under development by Bristol-Myers Squibb, Princeton, NJ 08543; BCH-10652, a reverse transcriptase inhibitor (in the form of a racemic mixture of BCH-10618 and BCH-10619) under development by Biochem Pharma, Lava, Quebec H7V, 4A7, Canada; emtricitabine [(-)-FTC] licensed from Emory University under Emory Univ. U.S. Patent No. 5,814,639 and under development by Triangle Pharmaceuticals, Durham, NC 27707; beta-L-FD4(also called beta-L-D4C and named beta-L-2', 3'-dideoxy-5-fluorocytidine) licensed by Yale University to Vion Pharmaceuticals, New Haven CT 06511; and DAPD, the purine nucleoside, (-)-beta-D-2,6,-diaminopurine dioxolane disclosed in EP 0656778 and licensed by Emory University and the University of Georgia to Triangle Pharmaceuticals, Durham, NC 27707; and lodenosine (FddA), 9-(2,3-dideoxy-2-fluoro-b-D-threo-pentofuranosyl)adenine, a acid stable purine-based reverse transcriptase inhibitor discovered by the NIH and under development by U.S. Bioscience Inc., West Conshohocken, PA. 19428.

[0054] The term "non-nucleoside reverse transcriptase inhibitors" ("NNRTI"s) as used herein means non-nucleosides that inhibit the activity of HIV-1 reverse transcriptase.

[0055] Typical suitable non-nucleoside reverse transcriptase inhibitors include nevirapine (BI-RG-587) available under the VIRAMUNE tradename from Boehringer Ingelheim, the manufacturer for Roxane Laboratories, Columbus, OH 43216; delaviradine (BHAP, U-90152) available under the RESCRIPTOR tradename from Pharmacia & Upjohn Co., Bridgewater NJ 08807; efavirenz (DMP-266) a benzoxazin-2-one disclosed in WO94/03440 and available under the SUSTIVA tradename from DuPont Pharmaceutical Co., Wilmington, DE 19880-0723; DuPont 961 and DuPont 083 also under development by DuPont Pharmaceutical Co., Wilmington, DE 19880-0723; PNU-142721, a furopyridine-thiopyrimidine under development by Pharmacia and Upjohn, Bridgewater NJ 08807; capravirine(formerly AG-1549 or Shionogi # S-1153); 5-(3,5-dichlorophenyl)-thio-4-isopropyl-1-(4-pyridyl)methyl-1H-imidazol-2-ylmethyl carbonate disclosed in WO 96 /10019 and under clinical development by Agouron Pharmaceuticals, Inc., LaJolla CA 92037-1020; MKC-442 1-(ethoxymethyl)-5-(1-methylethyl)-6-(phenylmethyl)-(2,4(1H,3H)-pyrimidinedione discovered by Mitsubishi Chemical Co. and under development by Triangle Pharmaceuticals, Durham, NC 27707; and (+)-calanolide A (NSC-675451) and B coumarin derivatives disclosed in NIH U.S. Patent No. 5,489,697, licensed to Med Chem Research, which is co-developing (+) calanolide A with Vita-Invest as an orally administrable product.

[0056] The term "protease inhibitor" ("PI") as used herein means inhibitors of the HIV-1 protease, an enzyme required for the proteolytic cleavage of viral polyprotein precursors (e.g., viral GAG and GAG Pol polyproteins), into the individual functional proteins found in infectious HIV-1. HIV protease inhibitors include compounds having a peptidomimetic structure, high molecular weight (7600 daltons) and substantial peptide character, e.g. CRIXIVAN(available from Merck) as well as nonpeptide protease inhibitors e.g., VIRACEPT (available from Agouron).

[0057] Typical suitable protease inhibitors include saquinavir (Ro 31-8959) available in hard gel capsules under the INVIRASE tradename and as soft gel capsules under the FORTOUASE tradename from Roche Pharmaceuticals, Nutley, NJ 07110-1199; ritonavir (ABT-538) available under the NORVIR tradename from Abbott Laboratories, Abbott Park, IL 60064; indinavir (MK-639) available under the CRIXIVAN tradename from Merck & Co., Inc., West Point, PA 19486-0004; MK-994, under development by Merck & Co., inc., West Point, PA 19486-0004; nelfinavir (AG-1343) available under the VIRACEPT tradename from Agouron Pharmaceuticals, Inc., LaJolla, CA 92037-1020; Ag 1776 under development by Agouron Pharmaceuticals, Inc., LaJolla, CA 92037-1020; amprenavir (141W94), a non-peptide pro-

tease inhibitor, tradename AGENERASE, under development by Vertex Pharmaceuticals, Inc., Cambridge, MA 02139-4211 and available from Glaxo-Wellcome, Research Triangle, NC under an expanded access program; lasinavir (BMS-234475) available from Bristol-Myers Squibb, Princeton, NJ 08543 (originally discovered by Novartis, Basel, Switzerland (CGP-61755); DMP-450, a cyclic urea discovered by Dupont and under development by Triangle Pharmaceuticals; BMS-2322632, PD 178390 under development by Pake-Davis. Morris Plains, NJ 07050; an azapeptide under development by Bristol-Myers Squibb, Princeton, NJ 08543 as a 2nd-generation HIV-1 PI; and ABT-378 under development by Abbott, Abbott Park, IL 60064; and AG-1549 an orally active imidazole carbamate discovered by Shionogi (Shionogi #S-1153) and under development by Agouron Pharmaceuticals, Inc., LaJolla CA 92037-1020;

[0058] The term "anti-HIV-1 therapy" as used herein means any anti-HIV-1 drug found useful for treating HIV-1 infections in man alone, or as part of multidrug combination therapies, especially the triple and quadruple combination therapies called HAART.

[0059] Typical suitable anti-HIV-1 therapies include, but are not limited to multidrug combination therapies such as (i) at least three anti-HIV-1 drugs selected from two NRTIs, one PI, a second PI, and one NNRTI; and (ii) at least two anti-HIV-1 drugs selected from , NNRTIs and PIs ;see Talbes I, II and III, hereinafter.

[0060] Typical suitable HAART - multidrug combination therapies- include (a) triple combination therapies such as two NRTIs and one PI; or (b) two NRTIs and one NNRTI ; and (c) quadruple combination therapies such as two NRTIs , one PI and a second PI or one NNRTI. In treatment-naïve patients, it is preferred to start anti-HIV-1 treatment with the triple combination therapy; the use of two NRTIs and one PI is preferred unless there is intolerance to PIs. Drug compliance is essential. The CD4⁺

and HIV-1-RNA plasma levels should be monitored every 3-6 months. Should viral load plateau, a fourth drug,e.g., one PI or one NNRTI could be added. See the Table A hereinbelow.

Table A

ANTI-HIV-1 MULTI DRUG COMBINATION THERAPIES	
A. Triple Combination Therapies	
1.	Two NRTIs ¹ + one PI ²
2.	Two NRTIs ¹ + one NNRTI ³
B. Quadruple Combination Therapies ⁴	
	Two NRTIs + one PI + a second PI or one NNRTI
C. ALTERNATIVES: ⁵	
	Two NRTI ¹ One NRTI ⁵ + one PI ² Two PIs ^{6±} one NRTI ⁷ or NNRTI ³ One PI ² + one NRTI ⁷ + one NNRTI ³

FOOTNOTES TO TABLE A

1. One of the following: zidovudine + lamivudine; zidovudine + didanosine; stavudine + lamivudine; stavudine + didanosine; zidovudine + zalcitabine; See also Table I

2. indinavir, nelfinavir, ritonavir or saquinavir soft gel capsules.

Ritonavir is used less frequently because of troublesome adverse effects. The old formulation of saquinavir was used least often because of its poor bioavailability and limited effectiveness, but the new saquinavir formulation should be more effective. See also Table III.

3. Nevirapine or delavirdine. See also Table II

4. See A-M. Vandamme et al Antiviral Chemistry + Chemotherapy 9:187 at p 193-197 and Figures 1 + 2.

5. Alternative regimens are for patients unable to take a recommended regimen because of compliance problems or toxicity, and for those who fail or relapse on a recommended regimen. Double nucleoside combinations may lead to HIV- resistance and clinical failure in many patients.

6. Most data obtained with saquinavir and ritonavir (each 400 mg bid).See also Table III

7. Zidovudine, stavudine or didanosine. See also Table I

[0061] Other anti-HIV-1 drugs useful for administration in association with pegylated interferon alfa include hydroxyurea, ribavirin, IL-2 and IL-12, and Yisum Project No. 11607 . These above-listed anti-HIV-1 drugs may also be administered in association with pegylated interferon alfa in association with any anti-HIV-1 drug therapy, especially the triple and quadruple drug combinations called HAART.

[0062] Hydroxyurea (Droxia) is a ribonucleoside triphosphate reductase inhibitor, the enzyme involved in the activation of T-cells. Hydroxyurea discovered at the NCI is under development by Bristol-Myers Squibb. In preclinical studies,

it was shown to have a synergistic effect on the activity of didanosine and has been studied with stavudine.

[0063] Yisum Project No. 11607, a synthetic protein based on the HIV -1 Vif protein under preclinical development by Yisum Research Development Co., Jerusalem 91042, Israel.

[0064] IL-2 is disclosed in Ajinomoto EP-0142268, Takeda EP-0176299, and Chiron U. S. Patent Nos. RE 33653, 4530787, 4569790, 4604377, 4748234, 4752585, and 4949314 is available under the PROLEUKIN(aldesleukin) trade-name from Chiron Corp., Emeryville, CA 94608-2997 as a lyophilized powder for IV infusion or sc administration upon reconstitution and dilution with water; doses of about 1 to about 20 million IU/day, sc is preferred; a dose of about 15 million IU/day, sc is more preferred.

[0065] IL-12 is disclosed in WO96/25171 and is available from Roche Pharmaceuticals, Nutley, NJ 07110-1199 and American Home Products, Madison, NJ 07940; a dose of about 0.5 microgram/kg/day to about 10 microgram/kg/day, sc.

[0066] Pentafuside (DP-178, T-20) a 36-amino acid synthetic peptide, disclosed in U.S. Patent No. 5,464,933 licensed from Duke University to Trimeris which is developing pentafuside in collaboration with Duke University; pentafuside acts by inhibiting fusion of HIV-1 to target membranes. Pentafuside (3-100 mg /day) is given as a continuous sc infusion or injection together with efavirenz and 2 PI's to HIV-1 positive patients refractory to a triple combination therapy; use of 100 mg/day is preferred. A second generation fusion inhibitor T-1249 (39aa) is under development by Trimeris. Other inhibitors under development include CXCR4, AM03100, and INTERGRASE by Merck & Co.

[0067] Ribavirin, 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide, available from ICN Pharmaceuticals, Inc., Costa Mesa, California, is described in the Merck Index, compound No. 8199, Eleventh Edition. Its manufacture and formulation is described in U.S. Patent No. 4,211,771.

[0068] The pegylated inteferon alfa, PEG₁₂₀₀₀-IFN-alfa2b (available from Schering-Plough Research Institute, Kenilworth, NJ) increased the *in vitro* anti HIV-1 activity of ribavirin. The combination of PEG₁₂₀₀₀-IFN-alfa2b and ribavirin inhibited HIV replication *in vitro* using phytohemagglutinin ("PHA" - P) - activated peripheral blood mononuclear cells ("PBMCs") at doses corresponding to plasmatic concentrations observed in animals and man. Healthy PBMCs were separated from a buffy-coat of one HIV-seronegative blood donor by Ficoll-Hypaque density gradient centrifugation. PBMCs were activated by 1 µg/ml phytohemagglutinin (PHA-P) for two days in cell culture medium A: RPMI 1640 supplemented with 10% heat-inactivated (+56°C, 45 min.) fetal calf plasma (FCS), 2 mM L-glutamine and a tri-antibiotic mixture (penicillin, streptomycin, neomycin; PSN). After these two days, cells were washed and cultured at one million cell per milliliter in cell culture medium B: cell culture medium A supplemented with 20 IU/ml recombinant human interleukin-2. Cells were maintained at +37°C in a 5% CO₂-air humidified atmosphere. Experiments were repeated twice with cells of other blood donors. In total, three independent experiments were performed.

[0069] PBMCs were infected with 1,000 50% Tissue Culture Infectious Doses (TCID₅₀) of the reference HIV-1-LAI strain [F.Barre'-Sinoussi, Science, 1983, 220, 868-871]. This strain has been amplified using PHA-P-activated umbilical blood mononuclear cells (UBMC). Viral stock has been then titrated on PHA-P activated PBMC by end-point dilution. TCID₅₀ was then calculated using Karber's formula [Arch. Exp. Path. Pharmacol., 1931, 162, 126-133].

[0070] PEG₁₂₀₀₀-IFN-α2b and ribavirin, alone and in combination, and AZT used as a control, were administered 24 hours before HIV-1 infection and maintained all along the culture. Three doses of PEG₁₂₀₀₀-IFN-α2b and ribavirin were used.

[0071] 200,000 PHA-P-activated PBMCs were added to each well of 96-well microplates. Cells were 24 hour-pre-treated prior to infection with the reference HIV-1-LAI strain. Twice a week, cell supernatants were collected, and drugs and medium were renewed. At day 7, RT activity were determined in cell supernatants, and potential cytotoxic effects of drugs and drug combinations were evaluated by microscopic observation.

[0072] Viral replication was measured by determining reverse transcriptase ("RT") activity in cell supernatants using Retro-Sys® kit, according to manufacturer's recommendations (Innovagen, Lund, Sweden).

[0073] Effective doses were calculated using cumulative RT activities with Chou J. and TC. microcomputer software.

[0074] The combined effects were analyzed using either the combination index (CI) [Chou & Talalay, 1984] with J and TC Chou microcomputer software, or the fractionary inhibitory concentration (FIC) index [Antimicrob. Agents Chemother., 1987, 31, 1613-1617]. When the CI or FIC index is equal to 1, the combination is additive. When it is below 1.0, the combination is synergistic, and when it is above 1.0, the combination is judged as antagonistic.

[0075] PEG₁₂₀₀₀-IFN-alfa2b as well as the combination of PEG₁₂₀₀₀-IFN-alfa2b and ribavirin inhibited the HtV replication at doses corresponding to plasmatic concentrations measured in mice and HIV-1 infected patients [BE. Gilbert, et al. Antimicrob. Agents Chemother., 1988, 32, 117-121; E. Connor et al., Antimicrob. Agents Chemother., 1993, 37, 537-539].

[0076] These above-listed anti-HIV-1 drugs may also be administered in association with pegylated interferon alfa in association with any anti-HIV-1 drug therapy, especially the triple and quadruple drug combinations called HAART.

[0077] The term " interferon-alfa " as used herein means the family of highly homologous species-specific proteins that inhibit viral replication and cellular proliferation and modulate immune response. Typical suitable interferon-alfas include, but are not limited to, recombinant interferon alfa-2b such as Intron-A interferon available from Schering Corporation, Kenilworth, N.J., recombinant interferon alfa-2a such as Roferon interferon available from Hoffmann-La Ro-

che, Nutley, N.J., recombinant interferon alpha-2C such as Berofer alpha 2 interferon available from Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT., interferon alpha-n1, a purified blend of natural alfa interferons such as Sumiferon available from Sumitomo, Japan or as Wellferon interferon alpha-n1 (INS) available from the Glaxo-Wellcome Ltd., London, Great Britain, or a consensus alpha interferon such as those described in U.S. Patent Nos. 4,897,471 and 4,695,623 (especially Examples 7, 8 or 9 thereof) and the specific product available from Amgen, Inc., Newbury Park, CA, or interferon alfa-n3 a mixture of natural alfa interferons made by Interferon Sciences and available from the Purdue Frederick Co., Norwalk, CT., under the Alferon Tradename. The use of interferon alfa-2a or alpha 2b is preferred. Since interferon alpha 2b, among all interferons, has the broadest approval throughout the world for treating chronic hepatitis C infection, it is most preferred. The manufacture of interferon alpha 2b is described in U.S. Patent No. 4,530,901.

[0078] The term "pegylated interferon alfa" as used herein means polyethylene glycol modified conjugates of interferon alfa, preferably interferon alfa-2a and -2b. The preferred polyethylene-glycol-interferon alfa -2b conjugate is PEG₁₂₀₀₀-interferon alfa 2b. The phrases "12,000 molecular weight polyethylene glycol conjugated interferon alpha" and "PEG₁₂₀₀₀-IFN alfa" as used herein mean conjugates such as are prepared according to the methods of International Application No. WO 95/13090 and containing urethane linkages between the interferon alfa-2a or -2b amino groups and polyethylene glycol having an average molecular weight of 12000.

[0079] The preferred PEG₁₂₀₀₀-interferon alfa-2b is prepared by attaching a PEG polymer to the epsilon amino group of a lysine residue in the IFN alfa-2b molecule. A single PEG₁₂₀₀₀ molecule is conjugated to free amino groups on an IFN alfa-2b molecule via a urethane linkage. This conjugate is characterized by the molecular weight of PEG₁₂₀₀₀ attached. The PEG₁₂₀₀₀-IFN alfa-2b conjugate is formulated as a lyophilized powder for injection. The objective of conjugation of IFN alfa with PEG is to improve the delivery of the protein by significantly prolonging its plasma half-life, and thereby provide protracted activity of IFN alfa.

[0080] Other interferon alfa conjugates can be prepared by coupling an interferon alfa to a water-soluble polymer. A non-limiting list of such polymers include other polyalkylene oxide homopolymers such as polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof. As an alternative to polyalkylene oxide-based polymers, effectively non-antigenic materials such as dextran, polyvinylpyrrolidones, polyacrylamides, polyvinyl alcohols, carbohydrate-based polymers and the like can be used. Such interferon alfa-polymer conjugates are described in U.S. Patent No. 4,766,106, U.S. Patent No. 4,917,888, European Patent Application No. 0 236 987, European Patent Application Nos. 0 510 356, 0 593 868 and 0 809 996 (pegylated interferon alfa-2a) and International Publication No. WO 95/13090.

[0081] Pharmaceutical composition of pegylated interferon alfa-suitable for parenteral administration may be formulated with a suitable buffer, e.g., Tris-HCl, acetate or phosphate such as dibasic sodium phosphate/monobasic sodium phosphate buffer, and pharmaceutically acceptable excipients (e.g., sucrose), carriers (e.g. human plasma albumin), toxicity agents (e.g. NaCl), preservatives (e.g. thimerosal, cresol or benylalcohol), and surfactants (e.g. tween or polysorbates) in sterile water for injection. The pegylated interferon alfa-may be stored as lyophilized powders under a refrigeration at 2°-8°C. The reconstituted aqueous solutions are stable when stored between 2° and 8°C and used within 24 hours of reconstitution. See for example U.S. Patent Nos. 4,492,537; 5,762,923 and 5,766,582. The reconstituted aqueous solutions may also be stored in prefilled, multi-dose syringes such as those useful for delivery of drugs such as insulin. Typical suitable syringes include systems comprising a prefilled vial attached to a pen-type syringe such as the NOVOLET Novo Pen available from Novo Nordisk, as well as prefilled, pen-type syringes which allow easy self-injection by the user. Other syringe systems include a pen-type syringe comprising a glass cartridge containing a diluent and lyophilized pegylated interferon alfa powder in a separate compartment.

[0082] Certain CCR5 antagonist compounds represented by the structural formula I or II or III or IV may exist in different isomeric (e.g., enantiomers, diastereoisomers and atropisomers) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures.

[0083] Certain compounds of formulas I or II or III or IV will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

[0084] Certain basic compounds of formulas I or II or III or IV also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respec-

tive salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

[0085] All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds of formulas I or II for purposes of the invention.

[0086] Compounds of the formula I or II or III or IV are the invention of other inventive entities. Compounds of the formula I or II are disclosed, together with methods of making them, in commonly-owned U.S. Patent Application (Attorney's Docket # IN01031) and compounds of the formula or III or IV in commonly-owned U.S. Patent Application SN (Attorney's Docket # IN01032), each of which were filed on the same date as this application, both of which are hereby incorporated by reference

[0087] Compounds of formulas I or II or III or IV can be also made by the procedures known in the art, for example by the procedures described in the following reaction schemes, by the methods described in the examples below, and by using the methods described in WO96/26196, WO98/05292, WO98/10425 and WO98/06697.

[0088] For preparing pharmaceutical compositions from the compounds of formula I or II or III or IV, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

[0089] Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

[0090] Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

[0091] Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

[0092] The compounds of formula I or II or III or IV may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

[0093] Preferably the compounds of formula I or II or III or IV is administered orally.

[0094] Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

[0095] The quantity of active compound of formula I or II or III or IV in a unit dose of preparation may be varied or adjusted from about 10 mg to about 500 mg, preferably from about 25 mg to about 300 mg, more preferably from about 50 mg to about 250 mg, and most preferably from about 55 mg to about 200 mg, according to the particular application.

[0096] The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

[0097] The amount and frequency of administration of the compounds of formula I or II or III or IV and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration of the compounds of formula I or II or III or IV can range from about 100 mg/day to about 300 mg/day, preferably 150 mg/day to 250 mg/day, more preferably about 200 mg/day, in two to four divided doses.

[0098] A person suffering from chronic hepatitis C infection may exhibit one or more of the following signs or symptoms:

(a) elevated ALT,

(b) positive test for anti-HCV antibodies,

(c) presence of HCV as demonstrated by a positive test for the presence of HCV-RNA in the serum,

(d) clinical stigmata of chronic liver disease,

(e) hepatocellular damage.

[0099] In a preferred aspect of the present invention, a therapeutically effective amount of the combination therapy of pegylated interferon-alfa and a CCR5 antagonist compound represented by structural formula I or II or III or IV is administered in association with a therapeutically effective amount of ribavirin and anti-retroviral therapy, e.g., HAART, to the patient having HIV-1 infection and exhibiting one or more of the above signs or symptoms in the first and second treatment time periods in amounts sufficient to eliminate or at least alleviate one or more of the signs or symptoms, and to lower the HCV-RNA plasma levels by at least a power of ten, and preferably to eradicate detectable HCV-RNA at least by the end of the second treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period. The sum of the first and second treatment time periods is about 40-50 weeks, and preferably is 48 weeks. Administration of the ribavirin may be discontinued after the end of the second time period depending upon the judgment of the attending clinician.

[0100] The term "no detectable HCV-RNA" in the context of the present invention means that there are fewer than 100 copies of HCV-RNA per ml of plasma of the patient as measured by quantitative, multi-cycle reverse transcriptase PCR methodology. HCV-RNA is preferably measured in the present invention by research-based RT-PCR methodology well known to the skilled clinician. This methodology is referred to herein as HCV-RNA/qPCR. The lower limit of detection of HCV-RNA is 100 copies/mL. Serum HCV-RNA/qPCR testing and HCV genotype testing will be performed by a central laboratory. See also J. G. McHutchinson et al. (N. Engl. J. Med., 1998, 339:1485-1492), and G. L. Davis et al. (N. Engl. J. Med. 339:1493-1499).

[0101] In a preferred embodiment of the present invention, those patients co-infected with HIV-1 and HCV infections are treated with a combination therapy of pegylated interferon alfa and a CCR5 antagonist compound represented by structural formula I or II or III or IV in association with ribavirin and a HAART combination considered appropriate by the attending clinician and the patient; use of the interferon alfa-2b-ribavirin combination therapy sold by Schering Corp. under the REBETRON tradename is preferred. See also J. G. McHutchinson et al. (N. Engl. J. Med., 1998, 339:1485-1492), and G. L. Davis et al. (N. Engl. J. Med. 339:1493-1499). Ribavirin, 1- β -D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide, available from ICN Pharmaceuticals, Inc., Costa Mesa, California, is described in the Merck index, compound No. 8199, Eleventh Edition. Its manufacture and formulation is described in U.S. Patent No. 4,211,771.

[0102] For the pediatric patient co-infected with the HIV-1 and HCV infections, a suitable HAART includes a NRTI + a PI, e.g., Nelfinavir + a NNRTI, e.g., Efavirenz in combination with the dosages and dosage regimens for pegylated interferon alfa and ribavirin listed herein above. See also Tables I-IV herein below. A human growth hormone such as the polypeptide hormone, somatropin, of recombinant rDNA origin, available under the HUMATROPE tradename from Eli Lilly & Co., Indianapolis, IN 46285, may be administered to these pediatric patients in the dosage and administration schedule listed in the product information sheet in consultation with the attending clinician to reduce retardation of growth associated with pegylated interferon alfa treatment.

[0103] HAART is administered to the patient in association with pegylated interferon-alfa, that is, the pegylated interferon-alfa dose may be administered before, after or during the same period of time that the patient receives doses of HAART. A human growth hormone such as the polypeptide hormone, somatropin, of recombinant rDNA origin, available under the HUMATROPE tradename from Eli Lilly & Co., Indianapolis, IN 46285, may also be administered in association with HAART and pegylated interferon alfa to the pediatric patient having HIV-1 infection in the dosage and administration schedule listed in the product information sheet in consultation with the attending clinician.

[0104] In a preferred embodiment of the present invention, pegylated interferon alfa is administered to HIV-1 infected patients prior to initiation of a CCR5 antagonist compound represented by structural formula I or II or III or IV and of HAART, and preferably about two to about four weeks prior to initiation of HAART. In another preferred embodiment of the present invention, administration of pegylated interferon alfa is initiated concurrently, i.e., on the same day with the administration of a CCR5 antagonist compound represented by structural formula I or II or III or IV and HAART. In another preferred embodiment of the present invention the pegylated interferon-alfa is administered after the HIV-1 infected patient has initiated use of a CCR5 antagonist compound represented by structural formula I or II or III or IV and HAART.

[0105] The goal of the HIV-1 therapy of the present invention is to reduce the HIV-1-RNA viral load below the detectable limit. The "detectable limit of HIV-1-RNA" in the context of the present invention means that there are fewer than about 200 to fewer than about 50 copies of HIV-1-RNA per ml of plasma of the patient as measured by quantitative, multi-cycle reverse transcriptase PCR methodology. HIV-1-RNA is preferably measured in the present invention by the methodology of Amplicor -1 Monitor 1.5 (available from Roche Diagnostics) or of Nuclisens HIV-1 QT -1. This methodology is described by Schooley, RT, Antiviral Therapy (1997), 2 (Suppl. 4):59-70.

[0106] The doses and dosage regimen of the NRTIs, NNRTIs, PI, pentafuside, IL-2, IL-12, a CCR5 antagonist compound represented by structural formula I or II or III or IV and pegylated interferon alfa will be determined by attending

clinician in view of the approved doses and dosage regimen in the package insert or as set forth in the protocol taking into consideration the age, sex and condition of the patient and the severity of the HIV-1 and HCV infections. For the pediatric patient infected with the HIV-1, or co-infected with the HIV-1 and HCV infections a suitable HAART includes a NRTI+ a PI, e.g., Nelfinavir +a NNRTI, e.g., Efavirenz in combination with the dosages and dosage regimens for pegylated interferon alfa and ribavirin listed herein above. See also Tables I-IV hereinafter for dosages and dosage regimens.

[0107] The following clinical protocol may be used to administer the anti- HIV-1 therapy of the present invention. Many modifications of this clinical protocol will be obvious to the skilled clinician, and the following Study Design should not be interpreted as limiting the scope of the method of this invention which is only limited by the claims listed hereinafter. See for example J. G. Hutchinson et al. (N. Engl. J. Med., 1998, 339:1485-1492), and G. L. Davis et al. (N. Engl. J. Med. 339:1493-1499).

[0108] The study population should include male and female patients diagnosed with HIV-1 infection who are either treatment naive or treatment-experienced and should be included if they meet the following inclusion and exclusion criteria:

Subject Inclusion Criteria:

[0109]

- Subjects diagnosed with HIV-1 infection who are either treatment naive or treatment-experienced.
 - HIV-RNA by Amplicor test, Version 1.5 of greater than 500 copies/mL.
 - CD4⁺ count greater than 100 copies/ml, preferably greater than 200 cells/mL.
 - Subjects in good physical health with clinically acceptable safety laboratory test results and ECG.
 - The following laboratory parameters must be met:
 - ◆ Platelet count •100,00/mL
 - ◆ Hemoglobin •9 gm/dL (90 gm/L)
 - ◆ Absolute neutrophil count •1500/ μ L
 - ◆ Creatinine $\leq$ 1.5 times the upper limit of normal
 - ◆ SGOT/SGPT $\leq$ 5 x upper limit of normal
 - ◆ Bilirubin $\leq$ 2.5 x upper limit of normal
 - A negative urine pregnancy test (females only)
- Subjects must be willing and able to give written informed consent and be able to adhere to the schedule set forth in the protocol.

Subject Exclusion Criteria

[0110]

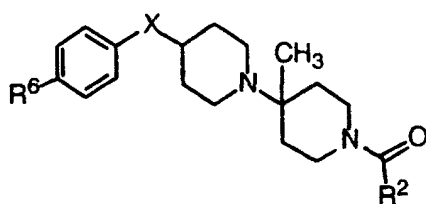
- Females who are breast-feeding or pregnant or who are not using adequate birth control.
- Subject with allergy to E. coli proteins
- Subjects with a significant past medical/psychiatric history, specifically depression or dementia.

[0111] In a preferred embodiment of the present invention, the subjects will be randomized to receive pegylated interferon alfa 2b, i.e., PEG₁₂₀₀₀-interferon alfa 2b at doses between 0.5 and 4.5 micrograms per kilogram e.g. at doses of 0.5, 1.0, 1.5, 3.0 or 4.5 micrograms per kilogram by subcutaneous injection once a week. The amount of ribavirin administered concurrently with the pegylated interferon-alfa is from about 400 to about 1600 mg per day, preferably about 600 to about 1200 mg/day or about 800 to about 1200 mg/day and most preferably about 1000 to about 1200 mg/kg a day.

[0112] The quantity of CCR5 antagonist compound of formula I or II or III or IV in a unit dose of formulation may be varied or adjusted from about 10 mg to about 500 mg, preferably from about 25 mg to about 300 mg, more preferably from about 50 mg to about 250 mg, and most preferably from about 55 mg to about 200 mg, according to the particular application.

[0113] HAART may also be initiated before or concurrently with the administration of the pegylated interferon alfa 2b, i.e., PEG₁₂₀₀₀-interferon alfa 2b, a CCR5 antagonist compound of formula I or II or III or IV and ribavirin.

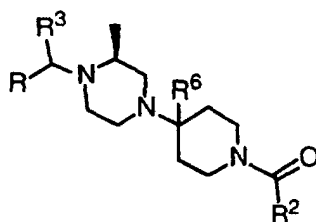
[0114] CCR5 antagonist compounds of the following structures are representative of formulas I and II useful in the present invention:



wherein R^6 , X and R^2 are as defined in the following table:

R^6	X	R^2
Br		
Br		
Br		
Br		
Br		
F_3C-		

[0115] CCR5 antagonist compounds of the following structures are representative of formulas III and IV useful in the present invention:



wherein R, R^3 , R^6 and R^2 are as defined in the following table:

R	R ³	R ⁶	R ²
		-CH ₃	
		-CH ₃	
	H	-CH ₃	
		H	
		-CH ₃	
		-CH ₃	

[0116] The actual dosages employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

Overall Design and Plan of the Study:

[0117] The primary efficacy objective will be lowering of the HIV-I-RNA plasma levels by a factor of 10 or greater. Plasma HIV-1-RNA/qPCR testing will be performed by a central laboratory. A positive HIV-1-RNA assay result will be required at Baseline; only patients positive for HIV-1-RNA will be eligible to participate.

Table I

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI) DOSAGE & DOSAGE REGIMEN	
NRTI (Tradename, Marketer)	Usual adult dosage
Zidovudine, AZT (Retrovir - Glaxo Wellcome)*	200 mg PO tid or 300 mg PO bid
Stavudine (Zerit - Bristol-Myers Squibb)*	40 mg PO bid ¹
Didanosine (Videx - Bristol-Myers Squibb)*	200 mg PO bid ²
Lamivudine (Epivir - Glaxo Wellcome)*	150 mg PO bid ³
Zalcitabine (Hivid - Roche)	0.75 mg PO tid
Zidovudine plus lamivudine (Combivir - Glaxo Wellcome)	1 tablet PO bid ⁴
Abacavir (Ziagen-Glaxo-Wellcome)	200 or 400 mg PO tid

Footnotes Table I

* Available in a liquid formulation.

¹ For patients less than 60 kg, 30 mg PO bid.

² With tablets; for patients < 60 kg, 125 mg PO bid; > 60 kg, 200 mg PO bid; With powder, dosage varies from 167 mg (< 60 kg) to 250 mg PO (< 60 kg) bid. Doses should be taken at least 30 minutes before meals or at least two hours afterward.

³ For patients less than 50 kg, 2 mg/kg PO bid.

⁴ Each tablet contains 300 mg of zidovudine and 150 mg of lamivudine.

EP 1 175 224 B1

Table I (continued)

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI) DOSAGE & DOSAGE REGIMEN	
NRTI (Tradename, Marketer)	Usual adult dosage
Adefovir dipivoxil (Prevon-Gilead Sciences)	125 or 200 mg PO qd ⁵
Lobucavir (BMS-180194-BMS)	200 mg PO bid ⁶ 200 mg PO, qid
BCH-10652 (Biochem Pharma)	400 mg PO, qid ⁷
Emitricitabine ((-)-FTC-Triangle Pharmaceuticals)	200 mg PO qd ⁸
Beta-L-FD4 (B-L-D4C-Vion Pharmaceutical)	0.2-25 mg/ky/day ⁹
DAPD (Triangle Pharmaceuticals)	— 10
Lodensine (FddA-U.S. Bioscience)	1.6-3.2 mg/Kg PO bid ¹¹

⁵ Available under an expanded access program - a NIH-sponsored Phase III Trial

⁶ Phase II.

⁷ Phase I/II; see PharmaProjects, sections J5A & J5Z.

⁸ Phase II/III; see PharmaProjects, sections J5A & J5Z.

⁹ Preclinical; active in duck HBV model; see PharmaProjects, sections J5A & J5Z.

¹⁰ Preclinical; active po and IV; DAPD is a prodrug of another dioxolene purine, DXG. See PharmaProjects, sections J5A & J5Z.

¹¹ Phase II, FddA has potential for once-a-day dosage.

TABLE II

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI) Dosage and Dosage Regimen	
NNRTI (Tradename, Marketer)	Usual adult dosage and Dosage Regimen
Nevirapine (Viramune - Roxane)	200 mg PO bid ¹
Delavirdine (Rescriptor - Pharmacia & Upjohn)	400 mg PO tid
Efavirenz (Sustiva, Dupont)	200 mg PO qid ²
PNU-142721 (Pharmacia + Upjohn)	— ³
AG-1549 (Agouvon Pharmaceuticals)	— ⁴
MKC-442 (Triangle Pharmaceuticals)	750 mg PO bid ⁵
(+)-Calanolide A (Med Chem Research)	800 mg PO ⁶

¹ For the first two weeks of treatment with nevirapine, to decrease the risk of rash, patients should take only one 200-mg tablet per day.

² Quadruple Therapy of efavirenz with indinavir + 2 NRTIs or Triple Therapy of efavirenz + AZT + lamivudine.

³ Preclinical Phase: see PharmaProjects, sections J5A & J5Z

⁴ Phase I/II evaluating dose and concomitant use with other anti-HIV-1 therapies; see Pharmaprojects, sections J5A & J5Z.

⁵ Triple Therapy of (a) MKC-442 with stavudine and either lamivudine or didanosine or (b) MKC-442 with nelfinavir (qv) and NRTIs.

⁶ Phase I; see Pharmaprojects, sections J5A & J5Z

TABLE III

Protease Inhibitor (PI) Dosage and Dosage Regimen	
PI (Tradename, Marketer)	Dosage + Dosage Regimen
Saquinavir (Invirase - hard gel capsule- Roche)	600 mg PO tid ¹
(Fortovase - soft gel capsule -Roche)	1100 mg PO tid ¹
Ritonavir (Norvir - Abbott)	600 mg PO bid ²
Indinavir (Crixivan - Merck)	800 mg PO qid ³
Nelfinavir (Viracept - Agouron)	750 mg PO tid ⁴

¹ With, or within two hours after, a full meal.

² With food. The liquid formulation has an unpleasant taste; the manufacturer suggests taking it with chocolate milk or a liquid nutritional supplement.

³ With water, one hour before or two hours after a meal. Patients taking indinavir should drink at least 48 ounces (1.5 liter) of water daily.

⁴ With food.

EP 1 175 224 B1

TABLE III (continued)

Protease Inhibitor (PI) Dosage and Dosage Regimen	
PI (Tradename, Marketer)	Dosage + Dosage Regimen
Agenerase (Amprenavir, 141 W94, Glaxo)	900 mg - 1200 mg PO bid ⁵
Lasinavir (BMS-234475, BMS)	— ⁶
DMP-450 (Triangle Pharmaceuticals)	— ⁷
BMS-2322623 (BMS)	— ⁸
ABT-378 (Abbott)	60 mg PO bid ⁹

⁵ Quadruple Combination Therapy of amprenavir with AZT + lamivudine + abacavir.

⁶ Phase I/II; see Pharmaprojects, sections J5A & J5Z.

⁷ Phase II; see Pharmaprojects, sections J5A & J5Z.

⁸ Preclinical Studies; Prodrug esters of BMS 2322623 enhance oral absorption; see Pharmaprojects, sections J5A & J5Z.

⁹ Phase I Studies show ABT-378 to be 10X more potent than ritonavir; see Pharmaprojects sections J5A & J5Z.

TABLE IV

Other Anti-HIV-1 Drugs	
Drug (Trade Name, Marketer)	Usual Adult Dosage and Dosage Regimen
Hydroxyurea (Droxia, BMS)	1000 mg PO qid ¹
Ribavirin (Rebetol, Schering-Plough)	600mg-1200mg/day, PO
IL-2 (Proleukin, Chiron Corp.)	1 - 20 milliam IU/day, sc
IL-12 (Roche)	0.5-10 micrograms/kg/day, sc
Yissum Project No. 11607 (Yissum)	— ²

¹ Triple Therapy of hydroxyurea with 400 mg ddl + 500 mg AZT; see PharmaProjects, section B3C1

² Preclinical; see Pharmaprojects, sections J5A & J5Z.

The following assays can be used to identify a compound as a CCR5 antagonist as well as to determine the CCR5 antagonistic activity of the compounds of formulas I to IV. These assays are disclosed in commonly-owned U.S. Patent Application (Attorney's Docket # IN01031) and commonly-owned U.S. Patent Application SN (Attorney's Docket # IN01032), filed on the same date as this application

CCR5 Membrane Binding Assay:

[0118] A high throughput screen utilizing a CCR5 membrane binding assay identifies inhibitors of RANTES binding. This assay utilizes membranes prepared from NIH 3T3 cells expressing the human CCR5 chemokine receptor which have the ability to bind to RANTES, a natural ligand for the receptor. Using a 96-well plate format, membrane preparations are incubated with ¹²⁵I-RANTES in the presence or absence of compound for one hour. Compounds are serially diluted over a wide range of 0.001 ug/ml to 1 ug/ml and tested in triplicates. Reaction cocktails are harvested through glass fiber filters, and washed thoroughly. Total counts for replicates are averaged and data reported as the concentration required to inhibit 50 percent of total ¹²⁵I-RANTES binding. Compounds with potent activity in the membrane binding assay are further characterized in secondary cell-based HIV-1 entry and replication assays.

HIV -1 Entry Assay:

[0119] Replication defective HIV-1 reporter virions are generated by cotransfection of a plasmid encoding the NL4-3 strain of HIV-1 (which has been modified by mutation of the envelope gene and introduction of a luciferase reporter plasmid) along with a plasmid encoding one of several HIV-1 envelope genes as described by Connor et al, *Virology*, 206 (1995), p. 935-944. Following transfection of the two plasmids by calcium phosphate precipitation, the viral supernatants are harvested on day 3 and a functional viral titer determined. These stocks are then used to infect U87 cells stably expressing CD4 and the chemokine receptor CCR5 which have been preincubated with or without test compound. Infections are carried out for 2 hours at 37°C, the cells washed and media replaced with fresh media containing compound. The cells are incubated for 3 days, lysed and luciferase activity determined. Results are reported as the concentration of compound required to inhibit 50% of the luciferase activity in the control cultures.

HIV-1 Replication Assay:

[0120] This assay uses primary peripheral blood mononuclear cells or the stable U87-CCR5 cell line to determine the effect of anti-CCR5 compounds to block infection of primary HIV-1 strains. The primary lymphocytes are purified from normal healthy donors and stimulated *in vitro* with PHA and IL-2 three days prior to infection. Using a 96-well plate format, cells are pretreated with drug for 1 hour at 37 °C and subsequently infected with an M-tropic HIV-1 isolates. Following infection, the cells are washed to remove residual inoculum and cultured in the presence of compound for 4 days. Culture supernatants are harvested and viral replication measured by determination of viral p24 antigen concentration.

Calcium Flux Assay:

[0121] Cells expressing the HIV coreceptor CCR5 are loaded with calcium sensitive dyes prior to addition of compound or the natural CCR5 ligand. Compounds with agonist properties will induce a calcium flux signal in the cell, while CCR5 antagonists are identified as compounds which do not induce signaling by themselves but are capable of blocking signaling by the natural ligand RANTES.

GTPγS Binding Assay:

[0122] A GTPγS binding assay measures receptor activation by CCR5 ligands. This assay measures the binding of ³⁵S labeled-GTP to receptor coupled G-proteins that occurs as a result of receptor activation by an appropriate ligand. In this assay, the CCR5 ligand, RANTES, is incubated with membranes from CCR5 expressing cells and binding to the receptor activation (or binding) is determined by assaying for bound ³⁵S label. The assay quantitatively determines if compounds exhibit agonist characteristics by inducing activation of the receptor or alternatively antagonist properties by measuring inhibition of RANTES binding in a competitive or non-competitive fashion.

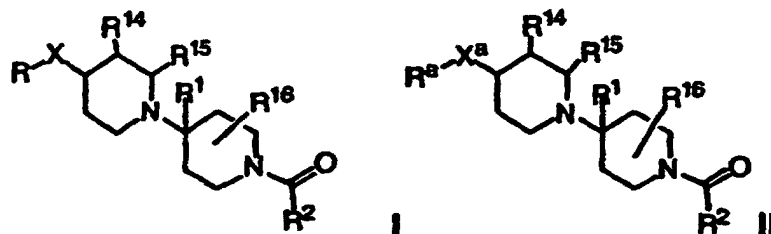
Chemotaxis Assay:

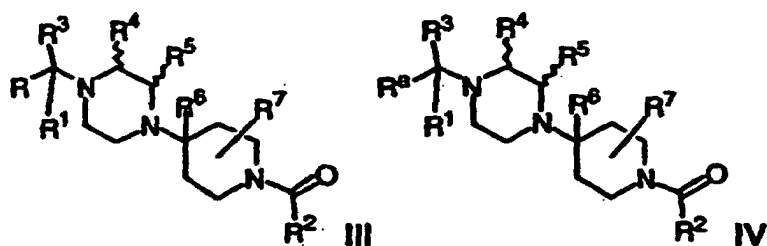
[0123] The chemotaxis assay is a functional assay which characterizes the agonist vs. antagonist properties of the test compounds. The assay measures the ability of a non-adherent murine cell line expressing human CCR5 (BaF-550) to migrate across a membrane in response to either test compounds or natural ligands (i.e., RANTES, MIP-1β). Cells migrate across the permeable membrane towards compounds with agonist activity. Compounds that are antagonists not only fail to induce chemotaxis, but are also capable of inhibiting cell migration in response to known CCR5 ligands.

[0124] In the assay to determine inhibition of RANTES binding, compounds of the formulas I-IV range in activity from a K_i of about 0.5 to about 1500 nM, with preferred compounds having a range of activity from about 0.5 to about 750 nM, more preferably about 0.5 to 300 nM, and most preferably about 0.5 to 50 nM.

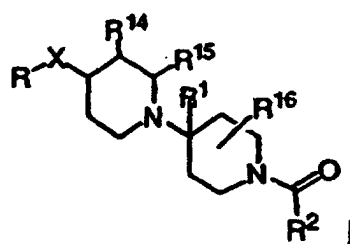
Claims

1. The use of a pegylated interferon-alfa and a CCR5 antagonist for the preparation of a medicament for the treatment of HIV-1 infections in patients wherein the CCR5 antagonist is represented by the structural formula I or II or III or IV:

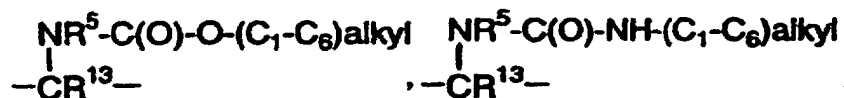
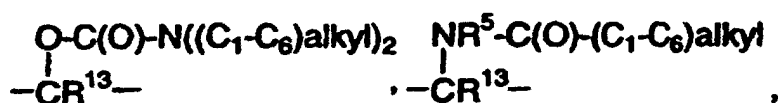
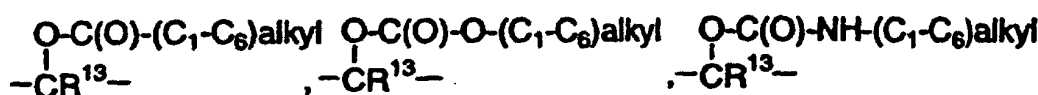
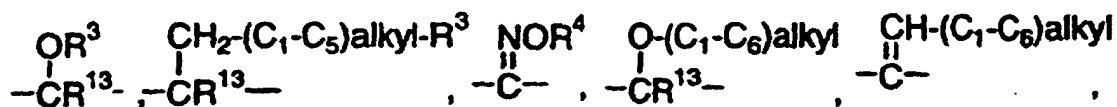


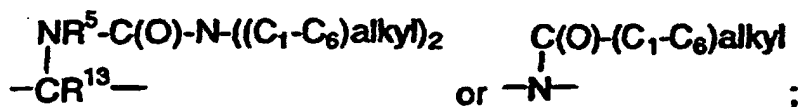


or a pharmaceutically acceptable salt of I or II or III or IV,
wherein in the CCR5 antagonist compounds represented by structural formula I:



X is $-\text{C}(\text{R}^{13})_2-$, $-\text{C}(\text{R}^{13})(\text{R}^{19})-$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{NH}-$, $-\text{N}((\text{C}_1-\text{C}_6)\text{alkyl})-$.

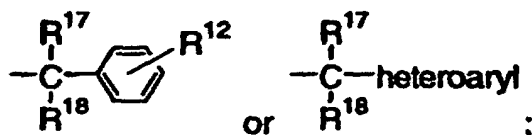




R is R⁶-phenyl, R⁶-pyridyl, R⁶-thiophenyl or R⁶-naphthyl;

R¹ is hydrogen, C₁-C₆ alkyl or C₂-C₆ alkenyl;

R² is R⁷, R⁸, R⁹-phenyl; R⁷, R⁸, R⁹-substituted 6-membered heteroaryl; R⁷, R⁸, R⁹-substituted 6-membered heteroaryl N-oxide; R¹⁰, R¹¹-substituted 5-membered heteroaryl; naphthyl; fluorenyl; diphenylmethyl

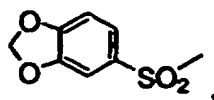


R³ is R⁶-phenyl, R⁸-heteroaryl or R⁶-naphthyl;

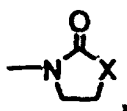
R⁴ is hydrogen, C₁-C₆ alkyl, fluoro-C₁-C₆ alkyl, cyclopropylmethyl, -CH₂CH₂OH, -CH₂CH₂-O-(C₁-C₆)alkyl, -CH₂C(O)-O-(C₁-C₆)alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH(C₁-C₆)alkyl or -CH₂C(O)-N((C₁-C₆)alkyl)₂;

R5 and R¹¹ are independently selected from the group consisting of hydrogen and (C₁-C₆)-alkyl;

R⁶ is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-phenyl, R¹⁴-benzyl, CH₃C(=NOCH₃)-, CH₃C(=NOCH₂CH₃)-,



-NH₂, -NHCOCF₃, -NHCONH(C₁-C₆ alkyl), -NHCO(C₁-C₆ alkyl), -NHSO₂(C₁-C₆ alkyl), 5-membered heteroaryl and



wherein X is -O-, -NH- or -N(CH₃)-;

R⁷ and R⁸ are independently selected from the group consisting of (C₁-C₆)alkyl, halogen, -NR²⁰R²¹, -OH, -CF₃, -OCH₃, -O-acyl, and -OCF₃;

R⁹ is R⁷, hydrogen, phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR²⁰, pyridyl, pyridyl N-oxide, pyrimidinyl, pyrazinyl, -N(R²⁰)CONR²¹R²², -NHCONH(chloro-(C₁-C₆)alkyl), -NHCONH((C₃-C₁₀)-cycloalkyl(C₁-C₆)alkyl), -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyl)₂, -NHSO₂(C₁-C₆)alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyl, C₃-C₁₀ cycloalkyl, -SR²³, -SOR²³, -SO₂R²³, -SO₂NH(C₁-C₆ alkyl), -OSO₂(C₁-C₆)alkyl, -OSO₂CF₃, hydroxy (C₁-C₆)alkyl, -CONR²⁰R²¹, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyl, -CO₂R²⁰, -Si(CH₃)₃ or -B(OC(CH₃)₂)₂;

R¹⁰ is (C₁-C₆)alkyl, -NH₂ or R¹²-phenyl;

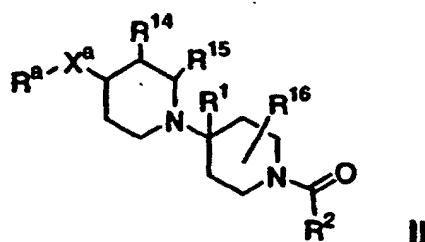
R¹² is 1 to 3 substituents independently selected from the group consisting of hydrogen, (C₁-C₆) alkyl, -CF₃, -CO₂R₂₀, -CN, (C₁-C₆)alkoxy and halogen;

R¹³, R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen and (C₁-C₆)alkyl;

R¹⁷ and R¹⁸ are independently selected from the group consisting of hydrogen and C₁-C₆ alkyl, or R¹⁷ and R¹⁸ together are a C₂-C₅ alkylene group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;

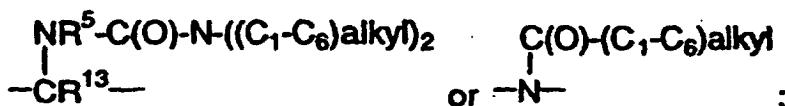
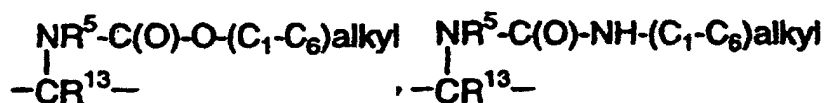
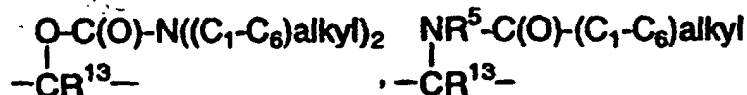
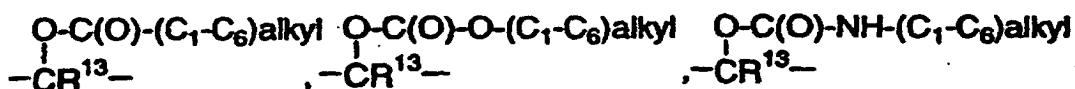
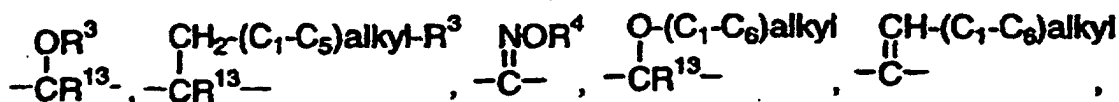
R¹⁹ is R⁶-phenyl, R⁶-heteroaryl, R⁶-naphthyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀)cycloalkyl(C₁-C₆)alkyl or (C₁-C₆)alkoxy(C₁-C₆)alkyl;

R²⁰, R²¹ and R²² are independently selected from the group consisting of H and C₁-C₆ alkyl; and
 R²³ is C₁-C₆ alkyl or phenyl;
 and wherein in the CCR5 antagonist compounds represented by the structural formula II:

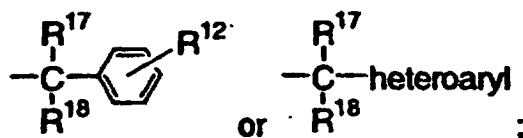


or a pharmaceutically acceptable salt thereof, wherein

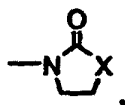
(1) X^a is -C(R¹³)₂-, -C(R¹³)(R¹⁹)-, -C(O)-, -O-, -NH-, -N((C₁-C₆)alkyl)-,



R^a is R^{6a}-phenyl, R^{6a}-pyridyl, R^{6a}-thiophenyl or R⁶-naphthyl;
 R¹ is hydrogen, C₁-C₆ alkyl or C₂-C₆ alkenyl;
 R² is R⁷, R⁸, R⁹-phenyl; R⁷, R⁸, R⁹-substituted 6-membered heteroaryl; R⁷, R⁸, R⁹-substituted 6-membered heteroaryl N-oxide; R¹⁰, R¹¹-substituted 5-membered heteroaryl; naphthyl; fluorenyl; diphenylmethyl



R³ is R¹⁰-phenyl, pyridyl, pyrimidyl, pyrazinyl or thiazolyl;
 R⁴ is hydrogen, C₁-C₆ alkyl, fluoro-C₁-C₆ alkyl, cyclopropylmethyl, -CH₂CH₂OH, -CH₂CH₂-O-(C₁-C₆)
 alkyl, -CH₂C(O)-O-(C₁-C₆)alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH(C₁-C₆)alkyl or -CH₂C(O)-N((C₁-C₆)alkyl)₂;
 R⁵ and R¹¹ are independently selected from the group consisting of hydrogen and (C₁-C₆)-alkyl;
 R^{6a} is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, -CF₃,
 CF₃O-, -CN, -CF₃SO₂-, R¹²-phenyl,
 -NHCOCF₃, 5-membered heteroaryl and



wherein X is -O-, -NH- or -N(CH₃)-;

R⁶ is independently selected from the group consisting of R^{6a} and CH₃SO₂-;
 R⁷ and R⁸ are independently selected from the group consisting of (C₁-C₆)alkyl, halogen, -NR²⁰R²¹,
 -OH, -CF₃, -OCH₃, -O-acyl, and -OCF₃;

R⁹ is R⁷, hydrogen, phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR²⁰, pyridyl, pyridyl N-oxide, py-
 rimidinyl, pyrazinyl, -N(R²⁰)CONR²¹R²², -NHCONH(chloro-(C₁-C₆)alkyl), -NHCONH((C₃-C₁₀)-cycloalkyl
 (C₁-C₆)alkyl), -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyl)₂, -NHSO₂(C₁-C₆)alkyl, -N(SO₂CF₃)₂,
 -NHCO₂(C₁-C₆)alkyl, C₃-C₁₀ cycloalkyl, -SR²³, -SOR²³, -SO₂R²³, -SO₂NH(C₁-C₆ alkyl), -OSO₂(C₁-C₆)alkyl,
 -OSO₂CF₃, hydroxy(C₁-C₆)alkyl, -CON R²⁰R²¹, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyl, -CO₂R²⁰, -Si
 (CH₃)₃ or -B(OC(CH₃)₂)₂;

R¹⁰ is (C₁-C₆)alkyl, -NH₂ or R¹²-phenyl;

R¹² is 1 to 3 substituents independently selected from the group consisting of hydrogen, (C₁-C₆) alkyl,
 -CF₃, -CO₂R²⁰, -CN, (C₁-C₆)alkoxy and halogen;

R¹³, R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen and (C₁₀C₆)
 alkyl;

R¹⁷ and R¹⁸ are independently selected from the group consisting of hydrogen and C₁-C₆ alkyl, or R¹⁷
 and R¹⁸ together are a C₂-C₅ alkylene group and with the carbon to which they are attached form a spiro ring
 of 3 to 6 carbon atoms;

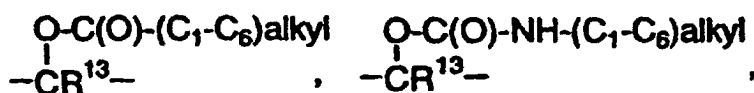
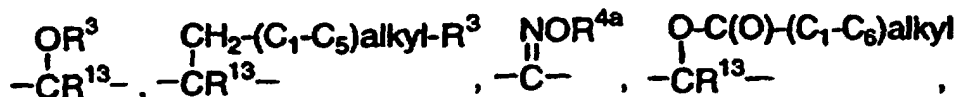
R¹⁹ is R⁵-phenyl, R⁶-heteroaryl, R⁶-naphthyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀)cycloalkyl(C₁-C₆)alkyl or
 (C₁-C₆)alkoxy(C₁-C₆)alkyl;

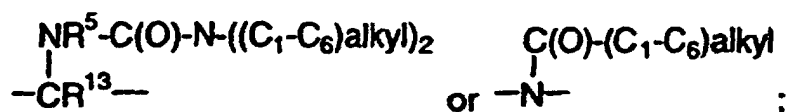
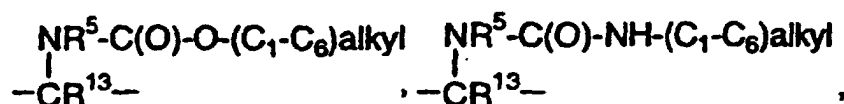
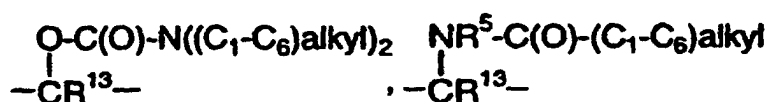
R²⁰, R²¹ and R²² are independently selected from the group consisting of H and C₁-C₆ alkyl; and

R²³ is C₁-C₆ alkyl or phenyl; or

(2):

X^a is -C(R¹³)(R¹⁹)-, -C(O)-, -O-, -NH-, -N((C₁-C₆)alkyl)-,





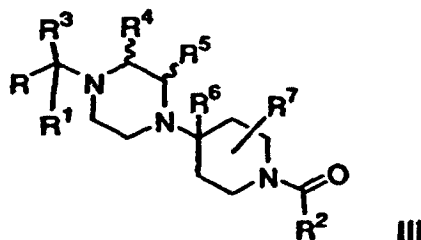
R^a is R^{6b}-phenyl, R^{6b}-pyridyl or R^{6b}-thiophenyl;

R^{4a} is fluoro-C₁-C₆ alkyl, cyclopropylmethyl, -CH₂CH₂OH, -CH₂CH₂-O-(C₁-C₆)alkyl, -CH₂C(O)-O-(C₁-C₆)alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH-(C₁-C₆)alkyl or -CH₂C(O)-N((C₁-C₆)alkyl)₂;

R^{6b} is CH₃SO₂-; and

R¹, R², R³, R⁵, R¹⁴, R¹⁵, R¹⁶ and R¹⁹ are as defined in II(1);

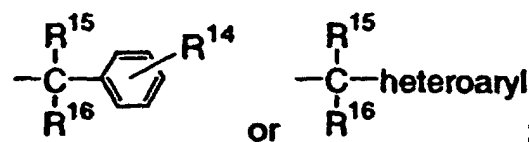
and wherein in the CCR5 antagonist compounds represented by the structural formula III:



R is R⁸-phenyl, R⁸-pyridyl, R⁸-thiophenyl or R⁸-naphthyl;

R¹ is hydrogen or C₁-C₆ alkyl;

R² is R⁹, R¹⁰, R¹¹-phenyl; R⁹, R¹⁰, R¹¹-substituted 6-membered heteroaryl; R⁹, R¹⁰, R¹¹-substituted 6-membered heteroaryl N-oxide; R¹², R¹³-substituted 5-membered heteroaryl; naphthyl; fluorenyl; diphenylmethyl

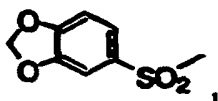


R³ is hydrogen, C₁-C₆ alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkyl(C₁-C₆)alkyl, R⁸-phenyl, R⁸-phenyl(C₁-C₆)alkyl, R⁸-naphthyl, R⁸-naphthyl(C₁-C₆)alkyl, R⁸-heteroaryl or R⁸-heteroaryl(C₁-C₆)alkyl;

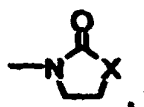
R⁴, R⁵, R⁷ and R¹³ are independently selected from the group consisting of hydrogen and (C₁-C₆)-alkyl;

R⁶ is hydrogen, C₁-C₆ alkyl-or C₂-C₆ alkenyl;

R⁸ is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, C₁-C₆-alkyl, C₁-C₆ alkoxy, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-phenyl, R¹⁴-benzyl, CH₃C(=NOCH₃), CH₃C(=NOCH₂CH₃),



-NH₂, -NHCOCF₃, -NHCONH(C₁-C₆ alkyl), -NHCO(C₁-C₆ alkyl), -NHSO₂(C₁-C₆-alkyl), 5-membered heteroaryl and



wherein X is -O-, -NH- or -N(CH₃)-;

R⁹ and R¹⁰ are independently selected from the group consisting of (C₁-C₆)alkyl, halogen, -NR¹⁷R¹⁸, -OH, -CF₃, -OCH₃, -O-acyl, -OCF₃ and -Si(CH₃)₃;

R¹¹ is R⁹, hydrogen, phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, CH=NOR¹⁷, pyridyl, pyridyl N-oxide, pyrimidinyl, pyrazinyl, -N(R¹⁷)CONR¹⁸R¹⁹, -NHCONH(chloro-(C₁-C₆)alkyl), -NHCONH (C₃-C₁₀) cycloalkyl (C₁-C₆)alkyl, -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyl)₂, -NHSO₂(C₁-C₆)alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyl, C₃-C₁₀ cycloalkyl, -SR²⁰, -SOR²⁰, -SO₂R²⁰, -SO₂NH(C₁-C₆ alkyl), -OSO₂(C₁-C₆)alkyl, -OSO₂CF₃, hydroxy(C₁-C₆)alkyl, -CON R¹⁷R¹⁸, -CON(CH₂CH₂-O-CH₃)₂, -OCONH (C₁-C₆)alkyl, -CO₂R¹⁷, -Si(CH₃)₃ or -B(OC(CH₃)₂)₂;

R¹² is (C₁-C₆)alkyl, -NH₂ or R¹⁴-phenyl;

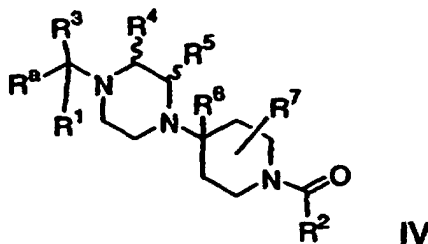
R¹⁴ is 1 to 3 substituents independently selected from the group consisting of hydrogen, (C₁-C₆) alkyl, -CF₃, -CO₂R¹⁷, -CN, (C₁-C₆)alkoxy and halogen;

R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen and C₁-C₆ alkyl, or R¹⁵ and R¹⁶ together are a C₂-C₅ alkylene group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;

R¹⁷, R¹⁸ and R¹⁹ are independently selected from the group consisting of H and C₁-C₆ alkyl; and

R²⁰ is C₁-C₆ alkyl or phenyl;

and wherein in the CCR5 antagonist compounds represented by the structural formula IV:



or a pharmaceutically acceptable salt thereof, wherein

(1) R^a is R^{8a}-phenyl, R^{8b}-pyridyl, R^{8b}-thiophenyl or R⁸-naphthyl;

R¹ is hydrogen or C₁-C₆ alkyl;

R² is R⁹, R¹⁰, R¹¹-phenyl; R⁹, R¹⁰, R¹¹-substituted 6-membered heteroaryl; R⁹, R¹⁰, R¹¹-substituted 6-membered heteroaryl N-oxide; R¹², R¹³-substituted 5-membered heteroaryl; naphthyl; fluorenyl; diphenyl-methyl,

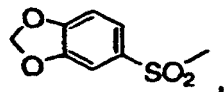
R³ is hydrogen, C₁-C₆ alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkyl(C₁-C₆)alkyl, R⁸-phenyl, R⁸-phenyl(C₁-C₆)alkyl, R⁸-naphthyl, R⁸-naphthyl(C₁-C₆)alkyl, R⁸-heteroaryl or R⁸-heteroaryl

(C₁-C₆)alkyl;

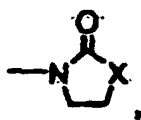
R⁴, R⁵, R⁷ and R¹³ are independently selected from the group consisting of hydrogen and (C₁-C₆)-alkyl;

R⁶ is hydrogen, C₁-C₆ alkyl or C₂-C₆ alkenyl;

R⁸ is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-phenyl, R¹⁴-benzyl, CH₃C(=NOCH₃), CH₃C(=NOCH₂CH₃),

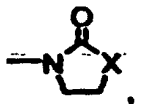


-NH₂, -NHCOCF₃, -NHCONH(C₁-C₆ alkyl), -NHCO(C₁-C₆ alkyl), -NHSO₂(C₁-C₆ alkyl), 5-membered heteroaryl and



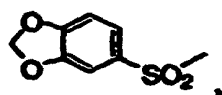
wherein X is -O-, -NH- or -N(CH₃)₂;

R^{8a} is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, -CF₃, CF₃O-, -CN, CF₃SO₂-, R¹⁴-phenyl, -NHCOCF₃, 5-membered heteroaryl and

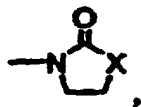


wherein X is as defined above;

R^{8b} is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, -CF₃, CF₃O-, CH₃C(O)-, -CN, CF₃SO₂-, R¹⁴-benzyl, CH₃C(=NOCN₃), CH₃C(=NOCH₂CH₃),



-NHCOCF₃, 5-membered heteroaryl and



wherein X is as defined above;

R⁹ and R¹⁰ are independently selected from the group consisting of (C₁-C₆)alkyl, halogen, -NR¹⁷R¹⁸, -OH, -CF₃, -OCH₃, -O-acyl, -OCF₃ and -Si(CH₃)₃;

R¹¹ is R⁹, hydrogen, phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR¹⁷, pyridyl, pyridyl N-oxide, pyrimidinyl, pyrazinyl, -N(R¹⁷)CONR¹⁸R¹⁹, -NHCONH(Chloro-(C₁-C₆)alkyl), -NHCONH(C₃-C₁₀) cycloalkyl (C₁-C₆)alkyl, -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyl)₂, -NHSO₂(C₁-C₆)alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyl, C₃-C₁₀ cycloalkyl, -SR²⁰, -SOR²⁰, -SO₂R²⁰, -SO₂NH(C₁-C₆ alkyl), -OSO₂(C₁-C₆)alkyl, -OSO₂CF₃, hydroxy(C₁-C₆)alkyl, -CON R¹⁷R¹⁸, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyl, -CO₂R¹⁷, -Si(CH₃)₃ or -B(OC(CH₃)₂)₂;

R¹² is (C₁-C₆)alkyl, -NH₂ or R¹⁴-phenyl;

R¹⁴ is 1 to 3 substituents independently selected from the group consisting of hydrogen, (C₁-C₆) alkyl,

-CF₃, -CO₂R₁₇, -CN, (C₁-C₆)alkoxy and halogen;

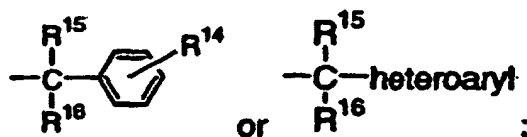
R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen and C₁-C₆ alkyl, or R¹⁵ and R¹⁶ together are a C₂-C₅ alkylene group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;

R¹⁷, R¹⁸ and R¹⁹ are independently selected from the group consisting of H and C₁-C₆ alkyl; and

R²⁰ is C₁-C₆ alkyl or phenyl; or

(2) R^a is R⁸-phenyl, R⁸-pyridyl or R⁸-thiophenyl;

R² is fluorenyl, diphenylmethyl,



and R¹, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹ and R²⁰ are as defined in IV(1).

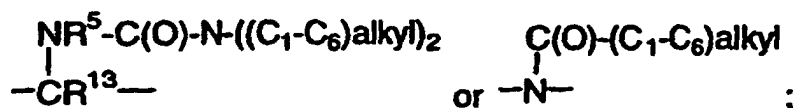
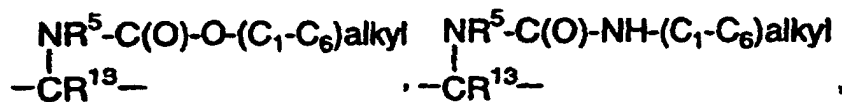
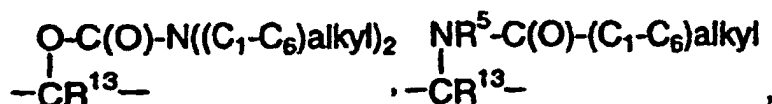
2. The use of claim 1, wherein the patients are treatment-naïve or treatment-experienced patients.
3. The use of any preceding claim, wherein the patients are treatment-naïve or treatment-experienced pediatric patients.
4. The use of any preceding claim, wherein the pegylated interferon-alfa to be administered is pegylated interferon alfa-2a or pegylated interferon alfa-2b.
5. The use of any preceding claim, wherein the treatment comprises a therapeutically effective amount of pegylated interferon-alfa in association with a therapeutically effective amount of a CCR5 antagonist sufficient to lower HIV-1-RNA levels in such patients.
6. The use of any preceding claim, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b wherein amount of pegylated interferon alfa-2b to be administered is in the range of about 0.1 to about 9.0 micrograms per kilogram per week, preferably in the range of about 0.5 to about 3.0 microgram per kilogram per week, and more preferably is in the range of about 0.75 to about 1.5 micrograms per kilogram per week.
7. The use of any preceding claim, wherein the pegylated interferon-alfa to be administered is a pegylated interferon alfa-2a and the amount of pegylated interferon alfa-2a to be administered is in the range of about 50 to about 500 micrograms per week, preferably in the range of about 150 to about 250 micrograms per week, or preferably in the range of about 180 to about 250 micrograms per week, and more preferably is in the range of about 150 to about 180 micrograms once per week.
8. The use of any preceding claim, wherein the treatment further comprises a therapeutically effective amount of at least one of ribavirin, IL-2, IL-12, pentafuside atone or in combination with a therapeutically effective amount of an anti-HIV-1 drug therapy.
9. The use of any preceding claim wherein the patients are co-infected with HIV-1 and HCV and wherein the treatment further comprises a therapeutically effective amount of ribavirin and a therapeutically effective amount of an anti-HIV-1 drug therapy.
10. The use of claim 8 or 9 wherein the anti-HIV-1 drug therapy is HAART.
11. The use of a pegylated interferon-alfa, a CCR5 antagonist ribavirin and HAART for the preparation of a medicament for the treatment of HIV-1 and HCV co-infections in patients wherein the CCR5 antagonist is represented by the structural formula I or II or III or IV:



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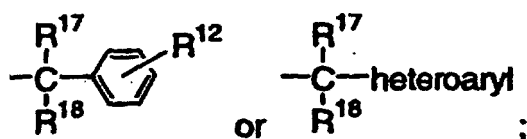
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R is R⁶-phenyl, R⁶-pyridyl, R⁶-thiophenyl or R⁶-naphthyl;

R¹ is hydrogen, C₁-C₆ alkyl or C₂-C₆ alkenyl;

R² is R⁷, R⁸, R⁹-phenyl; R⁷, R⁸, R⁹-substituted 6-membered heteroaryl; R⁷, R⁸, R⁹-substituted 6-membered heteroaryl N-oxide; R¹⁰, R¹¹-substituted 5-membered heteroaryl; naphthyl; fluorenyl; diphenylmethyl

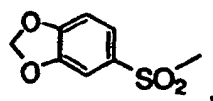


R³ is R⁶-phenyl, R⁶-heteroaryl or R⁶-naphthyl;

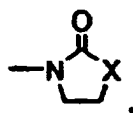
R⁴ is hydrogen, C₁-C₆ alkyl, fluoro-C₁-C₆ alkyl, cyclopropylmethyl, -CH₂CH₂OH, -CH₂CH₂-O-(C₁-C₆)alkyl, -CH₂C(O)-O-(C₁-C₆)alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH(C₁-C₆)alkyl or -CH₂C(O)N((C₁-C₆)alkyl)₂;

R⁵ and R¹¹ are independently selected from the group consisting of hydrogen and (C₁-C₆)alkyl;

R⁶ is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂, R¹⁴-phenyl, R¹⁴-benzyl, CH₃C(=NOCH₃)-, CH₃C(=NOCH₂CH₃)-,



-NH₂, -NHCOCF₃, -NHCONH(C₁-C₆ alkyl), -NHCO(C₁-C₆ alkyl), -NHSO₂(C₁-C₆ alkyl), 5-membered heteroaryl and



wherein X is -O-, -NH- or -N(CH₃)-;

R⁷ and R⁸ are independently selected from the group consisting of (C₁-C₆)alkyl, halogen, -NR²⁰R²¹, -OH, -CF₃, -OCH₃, -O-acyl, and -OCF₃;

R⁹ is R⁷, hydrogen, phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR²⁰, pyridyl, pyridyl N-oxide, pyrimidinyl, pyrazinyl, -N(R²⁰)CONR²¹R²², -NHCONH(chloro-(C₁-C₆)alkyl), -NHCONH((C₃-C₁₀)-cycloalkyl(C₁-C₆)alkyl), -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyl)₂, -NHSO₂(C₁-C₆)alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyl, C₃-C₁₀ cycloalkyl, -SR²³, -SOR²³, -SO₂R²³, -SO₂NH(C₁-C₆)alkyl, -OSO₂(C₁-C₆)alkyl, -OSO₂CF₃, hydroxy (C₁-C₆)alkyl, -CONR²⁰R²¹, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyl, -CO₂R²⁰, -Si(CH₃)₃ or -B(OC(CH₃)₂)₂;

R¹⁰ is (C₁-C₆)alkyl, -NH₂ or R¹²-phenyl;

R¹² is 1 to 3 substituents independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, -CF₃, -CO₂R²⁰, -CN, (C₁-C₆)alkoxy and halogen;

R¹³, R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen and (C₁-C₆)alkyl;

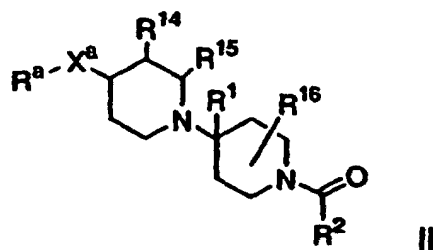
R¹⁷ and R¹⁸ are independently selected from the group consisting of hydrogen and C₁-C₆alkyl, or R¹⁷ and R¹⁸ together are a C₂-C₅ alkylene group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;

R¹⁹ is R⁶-phenyl, R⁶-heteroaryl, R⁶-naphthyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀)cycloalkyl(C₁-C₆)alkyl or (C₁-C₆)alkoxy(C₁-C₆)alkyl,

R²⁰, R²¹ and R²² are independently selected from the group consisting of H and C₁-C₆alkyl; and

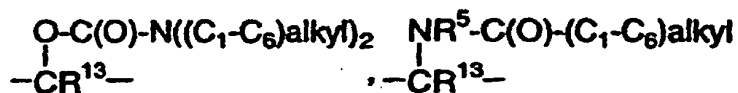
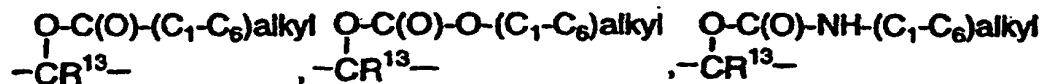
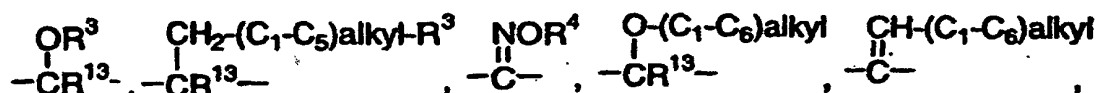
R²³ is C₁-C₆alkyl or phenyl;

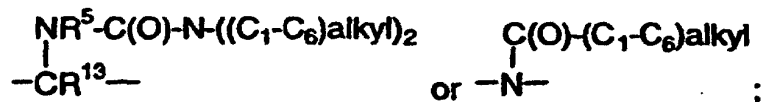
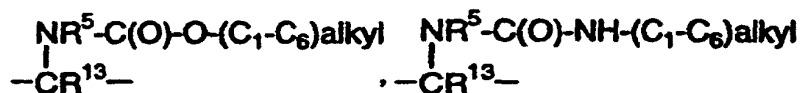
and wherein in the CCR5 antagonist compounds represented by the structural formula II:



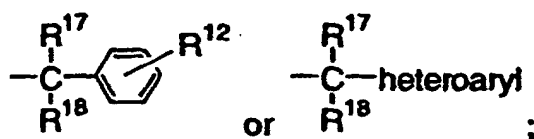
or a pharmaceutically acceptable salt thereof, wherein

(1) X^a is -C(R¹³)₂-, -C(R¹³)(R¹⁹)-, -C(O)-, -O-, -NH-, -N((C₁-C₆)alkyl)-,

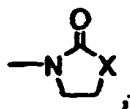




R^a is R^{6a}-phenyl, R^{6a}-pyridyl, R^{6a}-thiophenyl or R⁶-naphthyl;
 R¹ is hydrogen, C₁-C₆ alkyl or C₂-C₆ alkenyl;
 R² is R⁷, R⁸, R⁹-phenyl; R⁷, R⁸, R⁹-substituted 6-membered heteroaryl; R⁷, R⁸, R⁹-substituted 6-membered heteroaryl N-oxide; R¹⁰, R¹¹ -substituted 5-membered heteroaryl; naphthyl; fluorenyl; diphenylmethyl



R³ is R¹⁰-phenyl, pyridyl, pyrimidyl, pyrazinyl or thiazolyl;
 R⁴ is hydrogen, C₁-C₆ alkyl, fluoro-C₁-C₆ alkyl, cyclopropylmethyl, -CH₂CH₂OH, -CH₂CH₂-O-(C₁-C₆)alkyl, -CH₂C(O)-O-(C₁-C₆)alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH(C₁-C₆)alkyl or -CH₂C(O)-N((C₁-C₆)alkyl)₂;
 R⁵ and R¹¹ are independently selected from the group consisting of hydrogen and (C₁-C₆)-alkyl;
 R^{6a} is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, -CF₃, CF₃O-, -CN, -CF₃SO₂-, R¹²-phenyl, -NHCOCF₃, 5-membered heteroaryl and

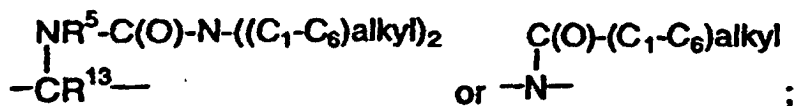
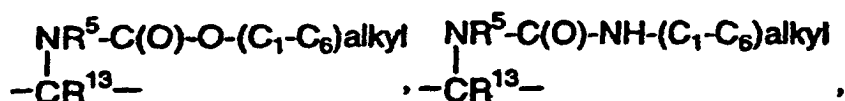
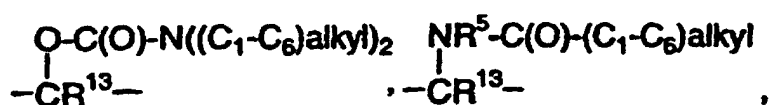
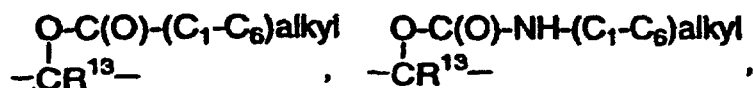
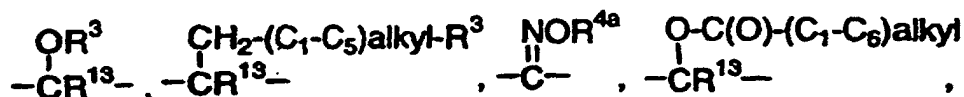


wherein X is -O-, -NH- or -N(CH₃)- ;

R⁶ is independently selected from the group consisting of R^{6a} and CH₃SO₂-;
 R⁷ and R⁸ are independently selected from the group consisting of (C₁-C₆)alkyl, halogen, -NR²⁰R²¹, -OH, -CF₃, -OCH₃, -O-acyl, and -OCF₃;
 R⁹ is R⁷, hydrogen, phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR²⁰, pyridyl, pyridyl N-oxide, pyrimidinyl, pyrazinyl, -N(R²⁰)CONR²¹R²², -NHCONH(chloro-(C₁-C₆)alkyl), -NHCONH((C₃-C₁₀)-cycloalkyl (C₁-C₆)alkyl), -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyl)₂, -NHSO₂(C₁-C₆)alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyl, C₃-C₁₀ cycloalkyl, -SR²³, -SOR²³, -SO₂R²³, -SO₂NH(C₁-C₆ alkyl), -OSO₂(C₁-C₆)alkyl, -OSO₂CF₃, hydroxy(C₁-C₆)alkyl, -CON R²⁰R²¹, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyl, -CO₂R²⁰, -Si(CH₃)₃ or -B(OC(CH₃)₂)₂;
 R¹⁰ is (C₁-C₆)alkyl, -NH₂ or R¹²-phenyl;
 R¹² is 1 to 3 substituents independently selected from the group consisting of hydrogen, (C₁-C₆) alkyl, -CF₃, -CO₂R²⁰, -CN, (C₁-C₆)alkoxy and halogen;
 R¹³, R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen and (C₁-C₆)alkyl;
 R¹⁷ and R¹⁸ are independently selected from the group consisting of hydrogen and C₁-C₆ alkyl, or R¹⁷ and R¹⁸ together are a C₂-C₅ alkylene group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;
 R¹⁹ is R⁶-phenyl, R⁶-heteroaryl, R⁶-naphthyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀)cycloalkyl(C₁-C₆)alkyl or (C₁-C₆)alkoxy(C₁-C₆)alkyl;
 R²⁰, R²¹ and R²² are independently selected from the group consisting of H and C₁-C₆ alkyl; and
 R²³ is C₁-C₆ alkyl or phenyl; or

(2):

X^a is -C(R¹³)(R¹⁹)-, -C(O)-, -O-, -NH-, -N((C₁-C₆)alkyl)-,



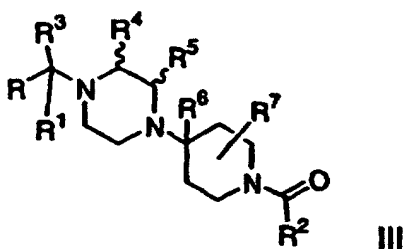
R^a is R^{6b}-phenyl, R^{6b}-pyridyl or R^{6b}-thiophenyl;

R^{4a} is fluoro-C₁-C₆ alkyl, cyclopropylmethyl, -CH₂CH₂OH, -CH₂CH₂-O-(C₁-C₆)alkyl, -CH₂C(O)-O-(C₁-C₆)alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH-(C₁-C₆)alkyl or -CH₂C(O)-N((C₁-C₆)alkyl)₂;

R^{6b} is CH₃SO₂-; and

R¹, R², R³, R⁵, R¹⁴, R¹⁵, R¹⁶ and R¹⁹ are as defined in II(1);

and wherein in the CCR5 antagonist compounds represented by the structural formula III:

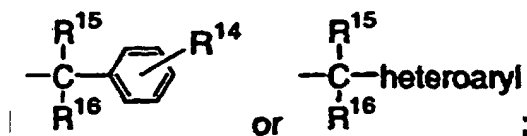


R is R⁸-phenyl, R⁸-pyridyl, R⁸-thiophenyl or R⁸-naphthyl;

R¹ is hydrogen or C₁-C₆ alkyl;

R² is R⁹, R¹⁰, R¹¹-phenyl; R⁹, R¹⁰, R¹¹-substituted 6-membered heteroaryl; R⁹, R¹⁰, R¹¹-substituted 6-membered heteroaryl N-oxide; R¹², R¹³-substituted 5-membered heteroaryl; naphthyl; fluorenyl; diphe-

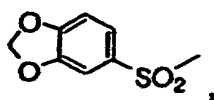
nylmethyl



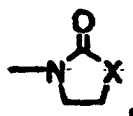
R³ is hydrogen, C₁-C₆ alkyl, (C₁-C₆)alkoxyC₁-C₆alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkyl(C₁-C₆)alkyl, R⁸-phenyl, R⁸-phenyl(C₁-C₆)alkyl, R⁸-naphthyl, R⁸-naphthyl(C₁-C₆)alkyl, R⁸-heteroaryl or R⁸-heteroaryl(C₁-C₆)alkyl;

R⁴, R⁵, R⁷ and R¹³ are independently selected from the group consisting of hydrogen and (C₁-C₆)-alkyl; R⁶ is hydrogen, C₁-C₆ alkyl or C₂-C₆ alkenyl;

R⁸ is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-phenyl, R¹⁴-benzyl, CH₃C(=NOCH₃), CH₃C(=NOCH₂CH₃),



-NH₂, -NHCOCF₃, -NHCONH(C₁-C₆ alkyl), -NHCO(C₁-C₆ alkyl), -NHSO₂(C₁-C₆ alkyl), 5-membered heteroaryl and



wherein X is -O-, -NH- or -N(CH₃)-;

R⁹ and R¹⁰ are independently selected from the group consisting of (C₁-C₆)alkyl, halogen, -NR¹⁷R¹⁸, -OH, -CF₃, -OCH₃, -O-acyl, -OCF₃ and -Si(CH₃)₃;

R¹¹ is R⁹, hydrogen, phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR¹⁷, pyridyl, pyridyl N-oxide, pyrimidinyl, pyrazinyl, -N(R¹⁷)CONR¹⁸R¹⁹, -NHCONH(chloro-(C₁-C₆)alkyl), -NHCONH (C₃-C₁₀) cycloalkyl (C₁-C₆)alkyl, -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyl)₂, -NHSO₂(C₁-C₆)alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyl, C₃-C₁₀ cycloalkyl, -SR²⁰, -SOR²⁰, -SO₂R²⁰, -SO₂NH(C₁-C₆ alkyl), -OSO₂(C₁-C₆)alkyl, -OSO₂CF₃, hydroxy(C₁-C₆)alkyl, -CON R¹⁷R¹⁸, -CON(CH₂CH₂-O-CH₃)₂, -OCONH (C₁-C₆)alkyl, -CO₂R¹⁷, -Si(CH₃)₃ or -B(OC(CH₃)₂)₂;

R¹² is (C₁-C₆)alkyl, -NH₂ or R¹⁴-phenyl;

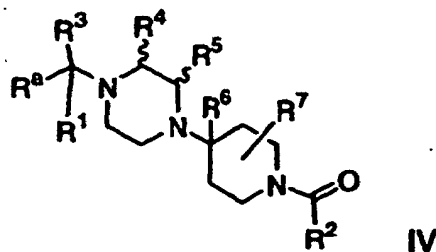
R¹⁴ is 1 to 3 substituents Independently selected from the group consisting of hydrogen (C₁-C₆) alkyl, -CF₃, -CO₂R¹⁷, -CN, (C₁-C₆)alkoxy and halogen;

R¹⁵ and R¹⁶ are Independently selected from the group consisting of hydrogen and C₁-C₆ alkyl, or R¹⁵ and R¹⁶ together are a C₂-C₅ alkylene group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;

R¹⁷, R¹⁸ and R¹⁹ are independently selected from the group consisting of H and C₁-C₆ alkyl; and

R²⁰ is C₁-C₆ alkyl or phenyl;

and wherein in the CCR5 antagonist compounds represented by the structural formula IV:

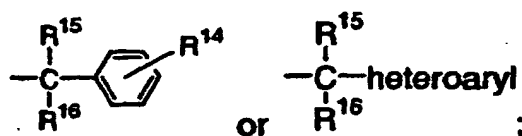


or a pharmaceutically acceptable salt thereof, wherein

(1) R^a is R^{8a}-phenyl, R^{8a}-pyridyl, R^{8b}-thiophenyl or R⁸-naphthyl;

R¹ is hydrogen or C₁-C₆ alkyl;

R² is R⁹, R¹⁰, R¹¹-phenyl; R⁹, R¹⁰, R¹¹-substituted 6-membered heteroaryl; R⁹, R¹⁰, R¹¹-substituted 6-membered heteroaryl N-oxide; R¹², R¹³-substituted 5-membered heteroaryl; naphtha; fluorenyl; diphenyl-methyl,

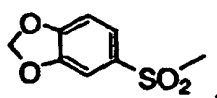


R³ is hydrogen, C₁-C₆ alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkyl(C₁-C₆)alkyl, R⁸-phenyl, R⁸-phenyl(C₁-C₆)alkyl, R⁸-naphthyl, R⁸-naphthyl(C₁-C₆)alkyl, R⁸-heteroaryl or R⁸-heteroaryl (C₁-C₆)alkyl;

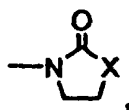
R⁴, R⁵, R⁷ and R¹³ are independently selected from the group consisting of hydrogen and (C₁-C₆)-alkyl;

R⁶ is hydrogen, C₁-C₆ alkyl or C₂-C₆ alkenyl;

R⁸ is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-phenyl, R¹⁴-benzyl, CH₃C(=NOCH₃), CH₃C(=NOCH₂CH₃),

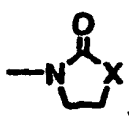


-NH₂, -NHCOCF₃, -NHCONH(C₁-C₆ alkyl), -NHCO(C₁-C₆ alkyl), -NHSO₂(C₁-C₆ alkyl), 5-membered heteroaryl and



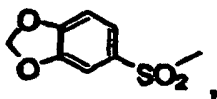
wherein X is -O-, -NH- or -N(CH₃)-;

R^{8a} is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, -CF₃, CF₃O-, -CN, CF₃SO₂-, R¹⁴-phenyl, -NHCOCF₃, 5-membered heteroaryl and

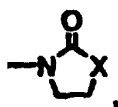


wherein X is as defined above;

R^{8b} is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, -CF₃, CF₃O-, CH₃C(O)-, -CN, CF₃SO₂-, R¹⁴-benzyl, CH₃C(=NOCH₃), CH₃C(=NOCH₂CH₃),



-NHCOCF₃, 5-membered heteroaryl and



wherein X is as defined above:

R⁹ and R¹⁰ are independently selected from the group consisting of (C₁-C₆)alkyl, halogen, -NR¹⁷R¹⁸, -OH, -CF₃, -OCH₃, -O-acyl, -OCF₃ and -Si(CH₃)₃;

R¹¹ is R⁹, hydrogen, phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR¹⁷, pyridyl, pyridyl N-oxide, pyrimidinyl, pyrazinyl, -N(R¹⁷)CONR¹⁸R¹⁹, -NHCONH(chloro-(C₁-C₆)alkyl), -NHCONH (C₃-C₁₀) cycloalkyl (C₁-C₆)alkyl, -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyl)₂, -NHSO₂(C₁-C₆)alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyl, C₃-C₁₀ cycloalkyl, -SR²⁰, -SOR²⁰, -SO₂R²⁰, -SO₂NH(C₁-C₆ alkyl), -OSO₂(C₁-C₆)alkyl, -OSO₂CF₃, hydroxy(C₁-C₆)alkyl, -CON R¹⁷R¹⁸, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyl, -CO₂R¹⁷, -Si(CH₃)₃ or -B(OC(CH₃)₂)₂;

R¹² is (C₁-C₆)alkyl, -NH₂ or R¹⁴-phenyl;

R¹⁴ is 1 to 3 substituents independently selected from the group consisting of hydrogen, (C₁-C₆) alkyl, -CF₃, -CO₂R¹⁷, -CN, (C₁-C₆)alkoxy and halogen;

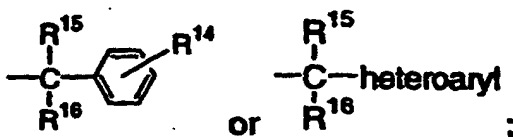
R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen and C₁-C₆ alkyl, or R¹⁵ and R¹⁶ together are a C₂-C₅ alkylene group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;

R¹⁷, R¹⁸ and R¹⁹ are independently selected from the group consisting of H and C₁-C₈ alkyl; and

R²⁰ is C₁-C₆ alkyl or phenyl; or

(2) R^a is R⁸-phenyl, R⁸-pyridyl or R⁸-thiophenyl;

R² is fluorenyl, diphenylmethyl,



and R¹, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹ and R²⁰ are as defined in IV(1).

12. The use of claim 11, wherein the patients are treatment- experienced patients or treatment-naïve patients.

13. The use of claim 11, wherein the patients are treatment- experienced patients or treatment-naïve pediatric patient.

14. The use of claim 11, wherein the pegylated interferon-alfa to be administered is pegylated interferon alfa-2a or pegylated interferon alfa-2b.

15. The use of claim 14, wherein the pegylated interferon-alfa to be administered is a pegylated interferon alfa-2b and wherein the amount of pegylated interferon alfa-2b to be administered is in the range of about 0.1 to about 9.0 micrograms per kilogram per week, preferably in the range of about 0.5 to about 3.0 micrograms per kilogram per week, and more preferably is in the range of about 0.75 to about 1.5 micrograms per kilogram per week.

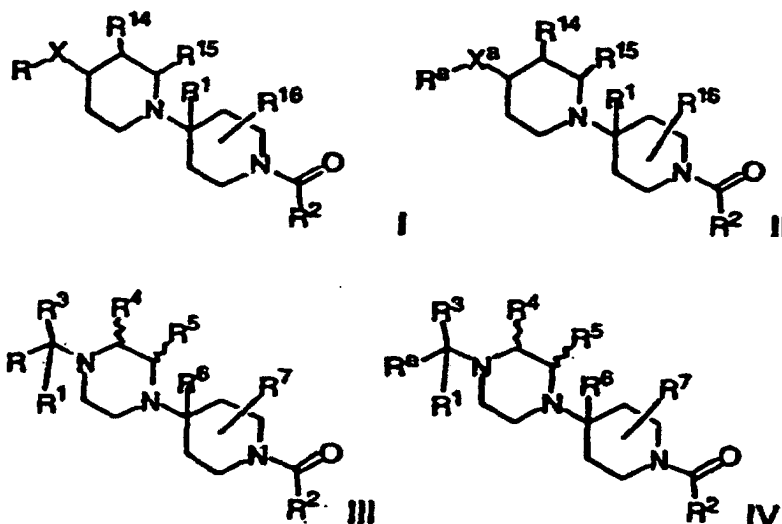
16. The use of claim 14, wherein the pegylated interferon-alfa to be administered is a pegylated interferon alfa-2a and the amount of pegylated interferon alfa-2a to be administered is in the range of about 50 to about 500 micrograms per week, preferably in the range of about 150 to about 250 micrograms per week, and more preferably in the range of about 180 to about 250 micrograms per week, or preferably is in the range of about 150 to about 180 micrograms per week,.

17. The use of claim 11, wherein the patient is a pediatric patient and the amount of nbavirin is in a range of about 8 to about 15 mg per kilogram per day, in divided doses.

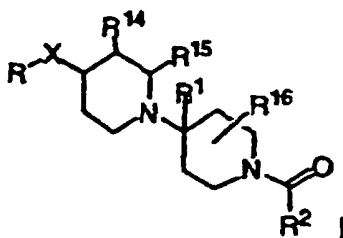
18. The use of claim 11, wherein the amount of ribavirin is from about 400 to about 1600 mg per day, preferably about 600 to about 1200 mg/day or about 800 to about 1200 mg/day and most preferably about 1000 to about 1200 mg/kg a day.

Patentansprüche

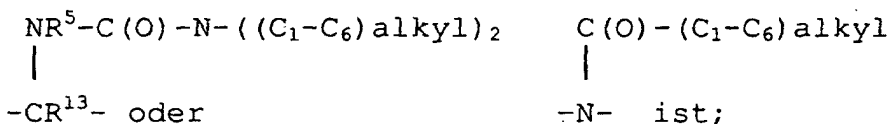
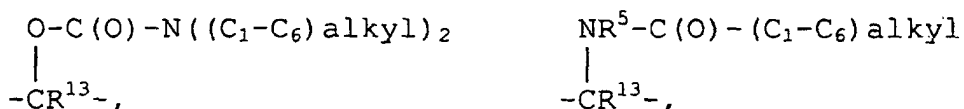
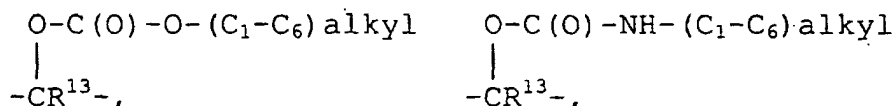
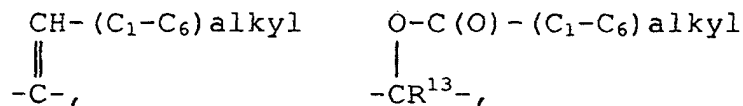
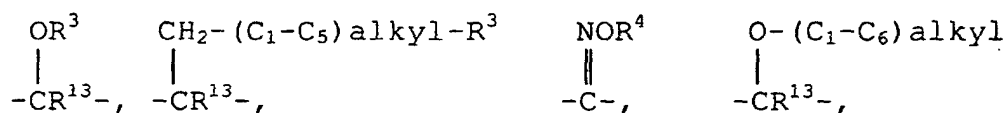
1. Verwendung von einem pegylierten Interferon- α und einem CCR5-Antagonisten zur Herstellung eines Medikaments zur Behandlung von HIV-1-Infektionen bei Patienten, wobei der CCR5-Antagonist durch die Strukturformel I oder II oder III oder IV wiedergegeben wird:



oder einem pharmazeutisch annehmbaren Salz von I oder II oder III oder IV, wobei in den CCR5-Antagonistverbindungen, die durch Strukturformel I wiedergegeben werden,



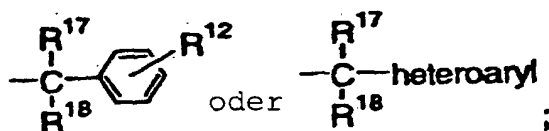
X -C(R¹³)₂-, -C(R¹³)(R¹⁹)-, -C(O)-, -O-, -NH-, N((C₁- bis C₆)-alkyl)-,



R⁶-Phenyl, R⁶-Pyridyl, R⁶-Thiophenyl oder R⁶-Naphthyl ist;

R¹ Wasserstoff, C₁- bis C₆-Alkyl oder C₂- bis C₆-Alkenyl ist,

R² R⁷, R⁸, R⁹-Phenyl; R⁷, R⁸, R⁹-substituiertes 6-gliedriges Heteroaryl; R⁷, R⁸, R⁹-substituiertes 6-gliedriges Heteroaryl-N-oxid; R¹⁰, R¹¹-substituiertes 5-gliedriges Heteroaryl; Naphthyl; Fluorenyl; Diphenylmethyl;



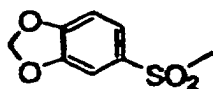
ist;

R³ R⁶-Phenyl, R⁶-Heteroaryl oder R⁶-Naphthyl ist;

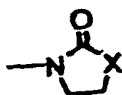
R⁴ Wasserstoff, C₁- bis C₆-Alkyl, Fluor-C₁- bis C₆-alkyl, Cyclopropylmethyl, -CH₂CH₂OH, -CH₂CH₂-O-(C₁- bis C₆)-Alkyl, -CH₂C(O)-O-(C₁- bis C₆)-Alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH(C₁- bis C₆)-Alkyl oder -CH₂C(O)-N((C₁- bis C₆)-Alkyl)₂ ist;

R⁵ und R¹¹ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und (C₁- bis C₆)-Alkyl;

R⁶ 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Halogen, C₁- bis C₆-Alkyl, C₁- bis C₆-Alkoxy, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-Phenyl, R¹⁴-Benzyl, CH₃C(=NOCH₃)-, CH₃C(=NOCH₂CH₃)-,



-NH₂, -NHCOCF₃, -NHCONH(C₁- bis C₆-Alkyl), -NHCO(C₁- bis C₆-Alkyl), -NHSO₂(C₁- bis C₆-Alkyl), 5-gliedrigem Heteroaryl und



wobei X -O-, -NH- oder -N(CH₃)- ist;

R⁷ und R⁸ unabhängig ausgewählt sind aus der Gruppe bestehend aus (C₁- bis C₆)-Alkyl, Halogen, -NR²⁰R²¹, -OH, -CF₃, -OCH₃, -O-Acyl und -OCF₃;

R⁹ R⁷, Wasserstoff, Phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR²⁰, Pyridyl, Pyridyl-N-oxid, Pyrimidinyl, Pyrazinyl, -N(R²⁰)CONR²¹R²², -NHCONH(Chlor-(C₁- bis C₆)alkyl, -NHCONH((C₃- bis C₁₀)-Cycloalkyl(C₁- bis C₆)alkyl), -NHCO(C₁- bis C₆)Alkyl, -NHCOCF₃, -NHSO₂N((C₁- bis C₆)Alkyl)₂, -NHSO₂(C₁- bis C₆-Alkyl), -N(SO₂CF₃)₂, -NHCO₂(C₁- bis C₆-Alkyl, C₃- bis C₁₀-Cycloalkyl, -SR²³, -SOR²³, -SO₂R²³, -SO₂NH(C₁- bis C₆-Alkyl), -OSO₂(C₁- bis C₆-Alkyl, -OSO₂CF₃, Hydroxy(C₁- bis C₆-alkyl, -CONR²⁰R²¹, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁- bis C₆-Alkyl, -CO₂R²⁰, -Si(CH₃)₃ oder -B(OC(CH₃)₂)₂ ist;

R¹⁰ (C₁- bis C₆)-Alkyl, -NH₂ oder R¹²-Phenyl ist;

R¹² 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, (C₁- bis C₆)-Alkyl, -CF₃, -CO₂R²⁰, -CN, (C₁- bis C₆)-Alkoxy und Halogen;

R¹³, R¹⁴, R¹⁵ und R¹⁶ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und (C₁- bis C₆)-Alkyl;

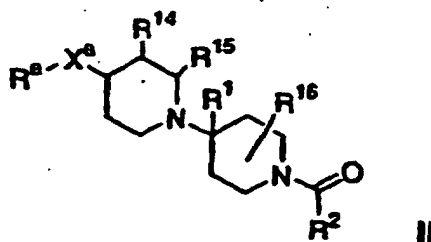
R¹⁷ und R¹⁸ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und C₁- bis C₆-Alkyl, oder R¹⁷ und R¹⁸ zusammen eine C₂- bis C₅-Alkylengruppe sind und mit dem Kohlenstoff, an den sie gebunden sind, einen Spiroring mit 3 bis 6 Kohlenstoffatomen bilden;

R¹⁹ R⁶-Phenyl, R⁶-Heteroaryl, R⁶-Naphthyl, C₃- bis C₁₀-Cycloalkyl, (C₃- bis C₁₀)-Cycloalkyl(C₁- bis C₆)-alkyl oder (C₁- bis C₆)-Alkoxy(C₁- bis C₆)-alkyl ist;

R²⁰, R²¹ und R²² unabhängig ausgewählt sind aus der Gruppe bestehend aus H und C₁- bis C₆-Alkyl; und

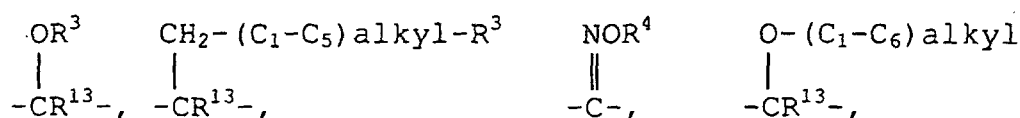
R²³ C₁- bis C₆-Alkyl oder Phenyl ist;

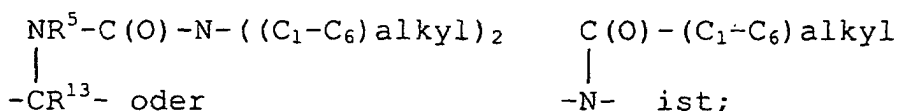
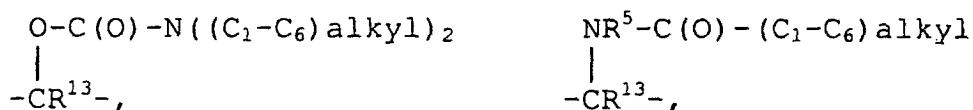
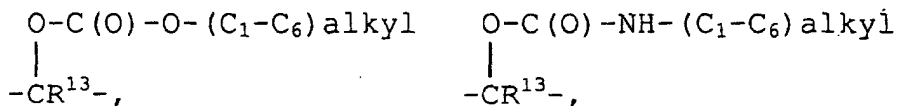
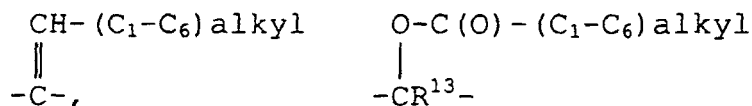
und wobei in den CCR5-Antagonistverbindungen, die durch die Strukturformel II wiedergegeben werden,



oder einem pharmazeutisch annehmbaren Salz davon,

(1) X^a -C(R¹³)₂-, -C(R¹³)(R¹⁹)-, -C(O)-, -O-, -NH-, -N((C₁ bis C₆)-alkyl)-,

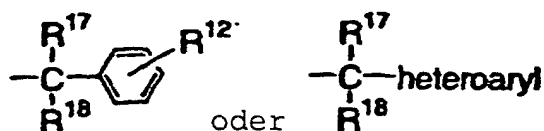




R^a R^{6a}-Phenyl, R^{6a}-Pyridyl, R^{6a}-Thiophenyl oder R⁶-Naphthyl ist;

R¹ Wasserstoff, C₁- bis C₆-Alkyl oder C₂- bis C₆-Alkenyl ist;

R² R⁷, R⁸, R⁹-Phenyl; R⁷,R⁸,R⁹-substituiertes 6-gliedriges Heteroaryl; R⁷,R⁸,R⁹-substituiertes 6-gliedriges Heteroaryl-N-oxid; R¹⁰,R¹¹-substituiertes 5-gliedriges Heteroaryl; Naphthyl; Fluorenyl; Diphenylmethyl;



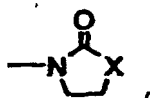
ist;

R³ R¹⁰-Phenyl, Pyridyl, Pyrimidyl, Pyrazinyl oder Thiazolyl ist;

R⁴ Wasserstoff, C₁- bis C₆-Alkyl, Fluor-C₁- bis C₆-alkyl, Cyclopropylmethyl, -CH₂CH₂OH, -CH₂CH₂-O-(C₁- bis C₆)-Alkyl, -CH₂C(O)-O-(C₁- bis C₆)-Alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH(C₁ bis C₆)-Alkyl oder -CH₂C(O)-N((C₁- bis C₆)-Alkyl)₂ ist;

R⁵ und R¹¹ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und (C₁- bis C₆)-Alkyl;

R^{6a} 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Halogen, -CF₃, CF₃O-, -CN, CF₃SO₂-, R¹²-Phenyl, -NHCOCF₃, 5-gliedrigem Heteroaryl und



wobei X -O-, -NH- oder -N(CH₃)- ist;

R⁶ unabhängig ausgewählt ist aus der Gruppe bestehend aus R^{6a} und CH₃SO₂-;

R⁷ und R⁸ unabhängig ausgewählt sind aus der Gruppe bestehend aus (C₁- bis C₆)-Alkyl, Halogen, -NR²⁰R²¹, -OH, -CF₃, -OCH₃, -O-Acyl und -OCF₃;

R⁹ R⁷, Wasserstoff, Phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR²⁰, Pyridyl, Pyridyl-N-oxid, Pyrimidinyl, Pyrazinyl, -N(R²⁰)CONR²¹R²², -NHCONH(Chlor-(C₁- bis C₆)-alkyl, -NHCONH((C₃- bis C₁₀)-Cycloalkyl(C₁- bis C₆)-alkyl), -NHCO(C₁- bis C₆)-Alkyl, -NHCOCF₃, -NHSO₂N((C₁- bis C₆)-Alkyl)₂, -NHSO₂(C₁- bis C₆)-Alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁- bis C₆)-Alkyl, C₃- bis C₁₀-Cycloalkyl, -SR²³, -SOR²³, -SO₂R²³, -SO₂NH(C₁- bis C₆-Alkyl), -OSO₂(C₁- bis C₆)-Alkyl, -OSO₂CF₃, Hydroxy(C₁- bis C₆)-alkyl, -CONR²⁰R²¹, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁- bis C₆)-Alkyl, -CO₂R²⁰, -Si(CH₃)₃ oder -B(OC(CH₃)₂)₂ ist;

R¹⁰ (C₁- bis C₆)-Alkyl, -NH₂ oder R¹²-Phenyl ist;

R¹² 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, (C₁- bis C₆)-Alkyl, -CF₃, -CO₂R²⁰, -CN, (C₁- bis C₆)-Alkoxy und Halogen;

R¹³, R¹⁴, R¹⁵ und R¹⁶ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und (C₁- bis C₆)-Alkyl;

R¹⁷ und R¹⁸ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und C₁- bis C₆-Alkyl, oder R¹⁷ und

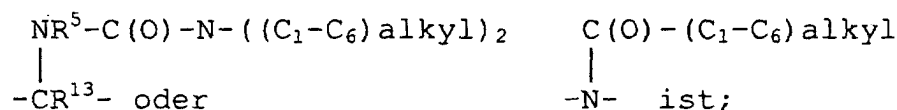
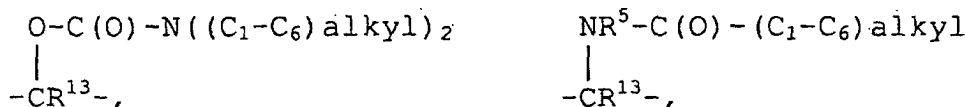
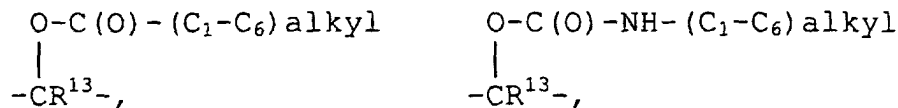
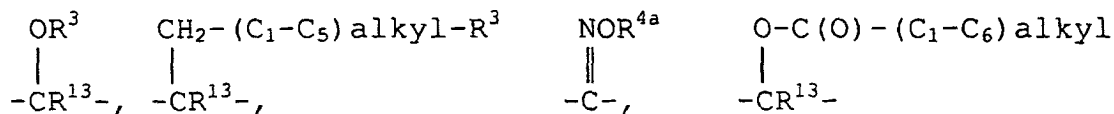
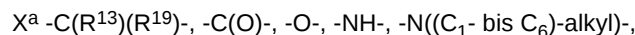
R¹⁸ zusammen eine C₂- bis C₅-Alkylengruppe sind und mit dem Kohlenstoff, an den sie gebunden sind, einen Spiroring mit 3 bis 6 Kohlenstoffatomen bilden;

R¹⁹ R⁶-Phenyl, R⁶-Heteroaryl, R⁶-Naphthyl, C₃- bis C₁₀-Cycloalkyl, (C₃- bis C₁₀)-Cycloalkyl(C₁- bis C₆)-alkyl oder (C₁- bis C₆)-Alkoxy(C₁- bis C₆)-alkyl ist;

R²⁰, R²¹ und R²² unabhängig ausgewählt sind aus der Gruppe bestehend aus H und C₁- bis C₆-Alkyl; und

R²³ C₁- bis C₆-Alkyl oder Phenyl ist; oder

(2) :



EP 1 175 224 B1

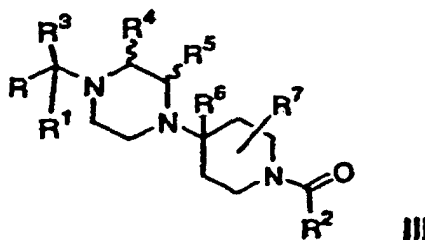
R^a R^{6b}-Phenyl, R^{6b}-Pyridyl oder R^{6b}-Thiophenyl ist;

R^{4a} Fluor-C₁- bis C₆-alkyl, Cyclopropylmethyl, -CH₂CH₂OH, -CH₂CH₂-O-(C₁- bis C₆)alkyl, -CH₂C(O)-O-(C₁- bis C₆)alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH-(C₁- bis C₆)-alkyl) oder -CH₂C(O)-N((C₁- bis C₆)alkyl)₂ ist;

R^{6b} CH₃SO₂- ist und

R¹ R², R³, R⁵, R¹⁴, R¹⁵, R¹⁶ und R¹⁹ wie in II(1) definiert sind;

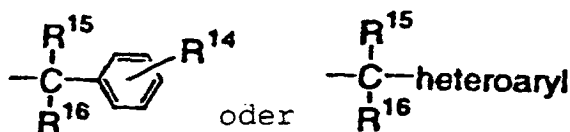
und wobei in den CCR5-Antagonistverbindungen, die durch die Strukturformel III wiedergegeben werden,



R⁸ R⁸-Phenyl, R⁸-Pyridyl, R⁸-Thiophenyl oder R⁸-Naphthyl ist;

R¹ Wasserstoff oder C₁- bis C₆-Alkyl ist;

R² R⁹, R¹⁰, R¹²-Phenyl; R⁹, R¹⁰, R¹¹-substituiertes 6-gliedriges Heteroaryl; R⁹, R¹⁰, R¹¹-substituiertes 6-gliedriges Heteroaryl-N-oxid; R¹², R¹³-substituiertes 5-gliedriges Heteroaryl; Naphthyl; Fluorenyl; Diphenylmethyl;



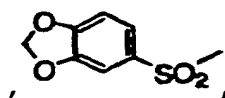
ist;

R³ Wasserstoff, C₁- bis C₆-Alkyl, (C₁- bis C₆)-Alkoxy-(C₁ bis C₆)alkyl, C₃- bis C₁₀-Cycloalkyl, C₃- bis C₁₀-Cycloalkyl(C₁- bis C₆)alkyl, R⁸-Phenyl, R⁸-Phenyl(C₁- bis C₆)alkyl, R⁸-Naphthyl, R⁸-Naphthyl(C₁- bis C₆)alkyl, R⁸-Heteroaryl oder R⁸-Heteroaryl(C₁- bis C₆)alkyl ist;

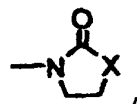
R⁴, R⁵, R⁷ und R¹³ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und (C₁- bis C₆)-Alkyl;

R⁶ Wasserstoff, C₁- bis C₆-Alkyl oder C₂- bis C₆-Alkenyl ist;

R⁸ 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Halogen, C₁- bis C₆-Alkyl, C₁- bis C₆-Alkoxy, -CF₃, CF₃O-, CH₃C(O)-; -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-Phenyl, R¹⁴-Benzyl, CH₃C(=NOCH₃), CH₃C(=NOCH₂CH₃),



-NH₂, -NHCOCF₃, -NHCONH(C₁- bis C₆-Alkyl), -NHCO(C₁- bis C₆-Alkyl), -NHSO₂(C₁- bis C₆-Alkyl), 5-gliedrigem Heteroaryl und



wobei X -O-, -NH- oder -N(CH₃)- ist;

R⁹ und R¹⁰ unabhängig ausgewählt sind aus der Gruppe bestehend aus (C₁- bis C₆)-Alkyl, Halogen, -NR¹⁷R¹⁸, -OH, -CF₃, -OCH₃, -O-Acyl, -OCF₃ und -Si(CH₃)₃;

R¹¹ R⁹, Wasserstoff, Phenyl, -NO₂, -CN, -CH₂F, -CHF₂ CHO, -CH=NOR¹⁷, Pyridyl, Pyridyl-N-oxid, Pyrimidinyl, Pyrazinyl, -N(R¹⁷)CONR¹⁸R¹⁹, -NHCONH(Chlor-(C₁- bis C₆)-alkyl), -NHCONH((C₃- bis C₁₀)-Cycloalkyl(C₁- bis C₆)-alkyl), -NHCO(C₁- bis C₆)-alkyl, -NHCOCF₃, -NHSO₂N((C₁- bis C₆)-alkyl)₂, -NHSO₂(C₁- bis C₆)-Alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁- bis C₆)-Alkyl, C₃- bis C₁₀-Cycloalkyl, -SR²⁰, -SOR²⁰, -SO₂R²⁰, -SO₂NH(C₁- bis C₆)-Alkyl, -OSO₂(C₁- bis C₆)-Alkyl, -OSO₂CF₃, Hydroxy(C₁- bis C₆)-alkyl, -CONR¹⁷R¹⁸, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-bis C₆)-Alkyl, -CO₂R¹⁷, -Si(CH₃)₃ oder -B(OC(CH₃)₂) ist;

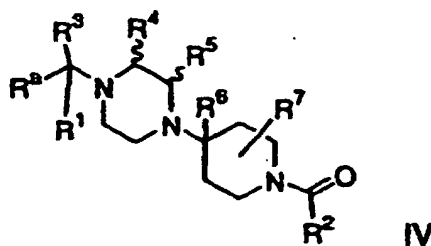
R¹² (C₁- bis C₆)-Alkyl, -NH₂ oder R¹⁴-Phenyl ist;

R¹⁴ 1 bis 3 Substituenten ist, die unabhängig; ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, (C₁- bis C₆)-Alkyl, -CF₃, -CO₂R¹⁷, -CN, (C₁- bis C₆)-Alkoxy und Halogen;

R¹⁵ und R¹⁶ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und C₁- bis C₆-Alkyl, oder R¹⁵ und R¹⁶ zusammen eine C₂- bis C₅-Alkylengruppe, sind und mit dem Kohlenstoff, an den sie gebunden sind, einen Spiroring mit 3 bis 6 Kohlenstoffatomen bilden;

R¹⁷, R¹⁸ und R¹⁹ unabhängig ausgewählt sind aus der Gruppe bestehend aus H und C₁- bis C₆-Alkyl; und R²⁰ C₁- bis C₆-Alkyl oder Phenyl ist;

und wobei in den CCR5-Antagonistverbindungen, die durch die Strukturformel IV

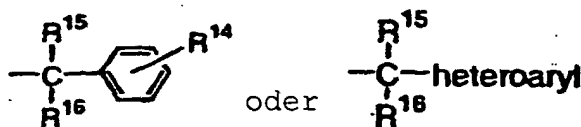


wiedergegeben werden, oder einem pharmazeutisch annehmbaren Salz davon,

(1) R^a R^{8a}-Phenyl, R^{8b}-Pyridyl, R^{8b}-Thiophenyl oder R⁸-Naphthyl ist;

R¹ Wasserstoff oder C₁- bis C₆-Alkyl ist;

R² R⁹, R¹⁰, R¹¹-Phenyl; R⁹, R¹⁰, R¹¹-substituiertes 6-gliedriges Heteroaryl; R⁹, R¹⁰, R¹¹-substituiertes 6-gliedriges Heteroaryl-N-oxid; R¹², R¹³-substituiertes 5-gliedriges Heteroaryl; Naphthyl; Fluorenyl; Diphehylmethyl;



ist;

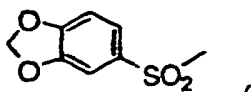
R³ Wasserstoff, C₁- bis C₆-Alkyl, (C₁- bis C₆)-Alkoxy(C₁- bis C₆)-alkyl; C₃- bis C₁₀-Cycloalkyl, C₃- bis C₁₀-Cycloalkyl(C₁- bis C₆)-alkyl, R⁸-Phenyl, R⁸-Phenyl(C₁- bis C₆)-alkyl, R⁸-Naphthyl, R⁸-Naphthyl(C₁- bis C₆)-alkyl; R⁸-Heteroaryl oder R⁸-Heteroaryl(C₁- bis C₆)-alkyl ist;

R⁴, R⁵, R⁷ und R¹³ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und (C₁-bis C₆)-Alkyl;

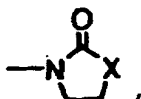
R⁶ Wasserstoff, C₁- bis C₆-Alkyl oder C₂- bis C₆-Alkenyl ist;

R⁸ 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff,

Halogen, C₁- bis C₆-Alkyl, C₁- bis C₆-Alkoxy, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-Phenyl, R¹⁴-Benzyl, CH₃C(=NOCH₃), CH₃C(=NOCH₂CH₃),

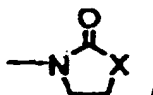


-NH₂, -NHCOCF₃, -NHCONH(C₁ bis C₆-Alkyl), -NHCO(C₁- bis C₆-Alkyl), -NHSO₂(C₁- bis C₆-Alkyl), 5-gliedrigem Heteroaryl und



wobei X -O-, -NH-, oder -N(CH₃)- ist;

R^{8a} 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Halogen, -CF₃, CF₃O-, -CN, CF₃SO₂-, R¹⁴-Phenyl, -NHCOCF₃, 5-gliedrigem Heteroaryl und

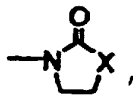


wobei X wie zuvor definiert ist;

R^{8b} 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Halogen, -CF₃, CF₃O-, CH₃C(O)-, -CN, CF₃SO₂-, R¹⁴-Benzyl, CH₃C(=NOCH₃), CH₃C(=NOCH₂CH₃),



-NHCOCF₃, 5-gliedrigem Heteroaryl und



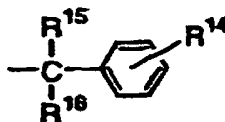
wobei X wie zuvor definiert ist;

R⁹ und R¹⁰ unabhängig ausgewählt sind aus der Gruppe bestehend aus (C₁- bis C₆)-Alkyl, Halogen, -NR¹⁷R¹⁸, -OH, -CF₃, -OCH₃, -O-Acyl, -OCF₃ und -Si(CH₃)₃;

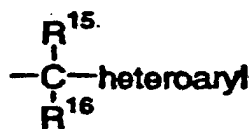
R¹¹ R⁹, Wasserstoff, Phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR¹⁷, Pyridyl, Pyridyl-N-oxid, Pyrimidinyl, Pyrazinyl, -N (R¹⁷) CONR¹⁸R¹⁹, -NHCONH (Chlor (C₁- bis C₆)alkyl), -NHCONH ((C₃- bis C₁₀) Cycloalkyl (C₁- bis C₆) alkyl) , -NHCO(C₁- bis C₆) Alkyl, -NHCOCF₃, -NHSO₂N ((C₁- bis C₆) Alkyl)₂, -NHSO₂(C₁- bis C₆) -Alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁- bis C₆)-Alkyl, C₃- bis C₁₀-Cycloalkyl, -SR²⁰, -SOR²⁰, -SO₂R²⁰, -SO₂NH(C₁- bis C₆-Alkyl), -OSO₂(C₁- bis C₆)-Alkyl, -OSO₂CF₃, Hydroxy(C₁- bis C₆)-alkyl, -CONR¹⁷R¹⁸, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁- bis C₆)-Alkyl, -CO₂R¹⁷, -Si(CH₃)₃ oder -B(OC(CH₃)₂)₂ ist;

R¹² (C₁- bis C₆)-Alkyl, -NH₂ oder R¹⁴-Phenyl ist;

R¹⁴ 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, (C₁- bis C₆)-Alkyl, -CF₃, -CO₂R¹⁷, -CN, (C₁- bis C₆)-Alkoxy und Halogen;
 R¹⁵ und R¹⁶ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und C₁- bis C₆-Alkyl, oder R¹⁵ und R¹⁶ zusammen eine C₂- bis C₅-Alkylengruppe sind und mit dem Kohlenstoff, an den sie gebunden sind, einen Spiroring mit 3 bis 6 Kohlenstoffatomen bilden;
 R¹⁷, R¹⁸ und R¹⁹ unabhängig ausgewählt sind aus der Gruppe bestehend aus H und C₁- bis C₆-Alkyl; und
 R²⁰ C₁- bis C₆-Alkyl oder Phenyl ist; oder
 (2) R^a R⁸-Phenyl, R⁸-Pyridyl oder R⁸-Thiophenyl ist; R² Fluorenyl, Diphenylmethyl;



oder



ist;

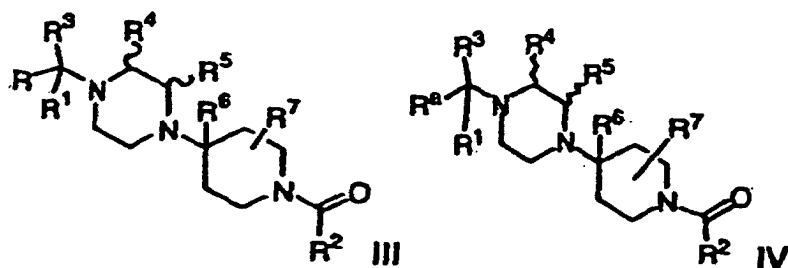
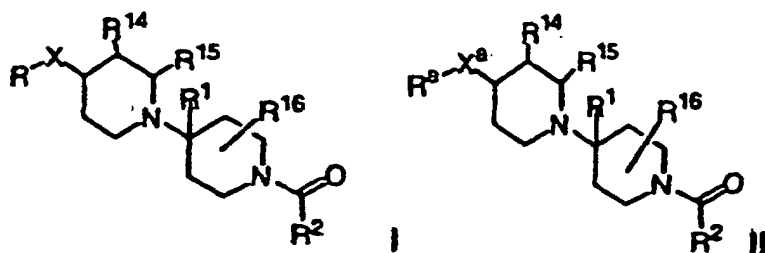
und R¹, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹ und R²⁰ wie in IV(1) definiert sind.

2. Verwendung nach Anspruch 1, bei der die Patienten Erstbehandlungspatienten oder behandlungserfahrene Patienten sind.
3. Verwendung nach einem der vorhergehenden Anspruch, bei der die Patienten pädiatrische Erstbehandlungspatienten oder behandlungserfahrene Patienten sind.
4. Verwendung nach einem der vorhergehenden Ansprüche, bei der das zu verabreichende pegylierte Interferon- α pegyliertes Interferon- α -2a oder pegyliertes Interferon- α -2b ist.
5. Verwendung nach einem der vorhergehenden Ansprüche, bei der die Behandlung eine therapeutisch wirksame Menge pegyliertes Interferon- α zusammen mit einer therapeutisch wirksamen Menge eines CCR5-Antagonisten umfasst, die ausreichen, um HIV-1-RNA-Gehalte bei solchen Patienten herabzusetzen.
6. Verwendung nach einem der vorhergehenden Ansprüche, bei der das verabreichte pegylierte Interferon- α ein pegyliertes Interferon- α -2b ist und wobei die Menge an zu verabreichendem pegyliertem Interferon- α -2b im Bereich von etwa 0,1 bis etwa 9,0 Mikrogramm pro Kilogramm pro Woche, vorzugsweise im Bereich von etwa 0,5 bis etwa 3,0 Mikrogramm pro Kilogramm pro Woche und besonders bevorzugt im Bereich von etwa 0,75 bis etwa 1,5 Mikrogramm pro Kilogramm pro Woche liegt.
7. Verwendung nach einem der vorhergehenden Ansprüche, bei der das zu verabreichende pegylierte Interferon- α ein pegyliertes Interferon- α -2a ist und wobei die Menge an zu verabreichendem pegyliertem Interferon- α -2a im Bereich von etwa 50 bis etwa 500 Mikrogramm pro Woche, vorzugsweise im Bereich von etwa 150 bis etwa 250 Mikrogramm pro Woche, oder bevorzugt im Bereich von etwa 180 bis etwa 250 Mikrogramm pro Woche und besonders bevorzugt im Bereich von etwa 150 bis etwa 180 Mikrogramm einmal wöchentlich liegt.
8. Verwendung nach einem der vorhergehenden Ansprüche, bei der die Behandlung ferner eine therapeutisch wirksame Menge von mindestens einem von Ribavirin, IL-2, IL-12, Pentafusid allein oder in Kombination mit einer therapeutisch wirksamen Menge einer Anti-HIV-1-Arzneimitteltherapie umfasst.
9. Verwendung nach einem der vorhergehenden Ansprüche, bei der die Patienten mit HIV-1 und HCV coinfiziert sind

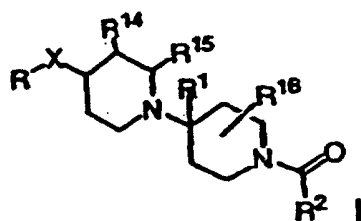
und wobei die Behandlung ferner eine therapeutisch wirksame Menge Ribavirin und eine therapeutisch wirksame Menge einer Anti-HIV-1-Arzneimitteltherapie umfasst.

10. Verwendung nach Anspruch 8 oder 9, bei der die Anti-HIV-Arzneimitteltherapie HAART ist.

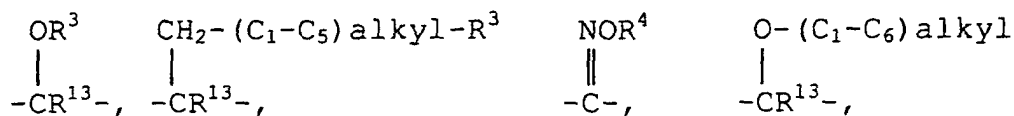
11. Verwendung von einem pegylierten Interferon- α , einem CCR5-Antagonisten, Ribavirin und HAART zur Herstellung eines Medikaments zur Behandlung von HIV-1- und HCV-Coinfektionen bei Patienten, wobei der CCR5-Antagonist durch die Strukturformel I oder II oder III oder IV wiedergegeben wird:

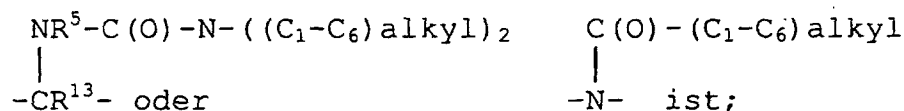
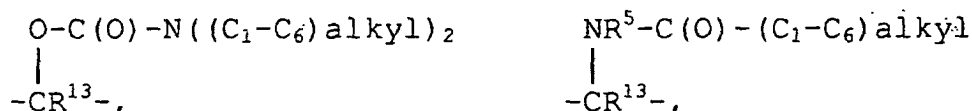
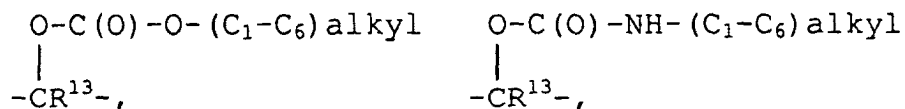
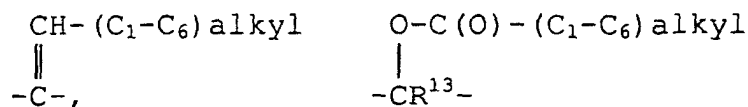


oder einem pharmazeutisch annehmbaren Salz von I oder II oder III oder IV, in einer Menge; die ausreicht, um die HIV-1-RNA- und HCV-RNA-Gehalte herabzusetzen, wobei in den CCR5-Antagonistverbindungen, die durch Strukturformel I wiedergegeben werden,



X -C(R¹³)₂-, -C(R¹³)(R¹⁹)-, -C(O)-, -O-, -NH-, N((C₁- bis C₆)-alkyl)-,

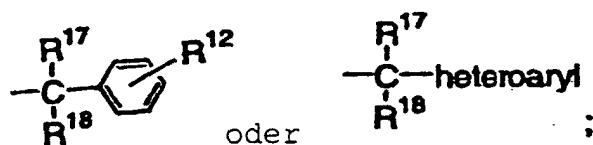




R⁶-Phenyl, R⁶-Pyridyl, R⁶-Thiophenyl oder R⁶-Naphthyl ist;

R¹ Wasserstoff, C₁- bis C₆-Alkyl oder C₂- bis C₆-Alkenyl;

R² R⁷, R⁸, R⁹- Phenyl; R⁷, R⁸, R⁹-substituiertes 6-gliedriges Heteroaryl; R⁷, R⁸, R⁹-substituiertes 6-gliedriges Heteroaryl-N-oxid; R¹⁰, R¹¹-substituiertes 5-gliedriges Heteroaryl; Naphthyl; Fluorenyl; Diphenylmethyl;



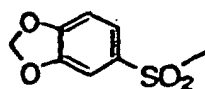
ist;

R³ R⁶-Phenyl, R⁶-Heteroaryl oder R⁶-Naphthyl ist;

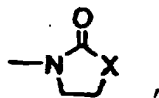
R⁴ Wasserstoff, C₁- bis C₆-Alkyl, Fluor-C₁- bis C₆-Alkyl, Cyclopropylmethyl, -CH₂CH₂OH, -CH₂CH₂-O-(C₁- bis C₆)-Alkyl, -CH₂C(O)-O-(C₁- bis C₆)-Alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH(C₁ bis C₆)-Alkyl oder -CH₂C(O)-N((C₁- bis C₆)-Alkyl)₂ ist;

R⁵ und R¹¹ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und (C₁- bis C₆)-Alkyl;

R⁶ 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Halogen, C₁- bis C₆-Alkyl, C₁- bis C₆-Alkoxy, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-Phenyl, R¹⁴-Benzyl, CH₃C(=NOCH₃)-, CH₃C(=NOCH₂CH₃)-,



-NH₂, -NHCOCF₃, -NHCONH(C₁- bis C₆-Alkyl), -NHCO(C₁- bis C₆-Alkyl), -NHSO₂(C₁- bis C₆-Alkyl), 5-gliedrigem Heteroaryl und



wobei X -O-, -NH- oder -N(CH₃)- ist;

R⁷ und R⁸ unabhängig ausgewählt sind aus der Gruppe bestehend aus (C₁- bis C₆)-Alkyl, Halogen, -NR²⁰R²¹, -OH, -CF₃, -OCH₃, -O-Acyl und -OCF₃;

R⁹ R⁷, Wasserstoff, Phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR²⁰, Pyridyl, Pyridyl-N-oxid, Pyrimidinyl, Pyrazinyl, -N(R²⁰)CONR²¹R²², -NHCONH(Chlor-(C₁- bis C₆)alkyl, -NHCONH((C₃- bis C₁₀)-Cycloalkyl(C₁- bis C₆)alkyl), -NHCO(C₁- bis C₆)Alkyl, -NHCOCF₃, -NHSO₂N((C₁- bis C₆)Alkyl)₂, -NHSO₂(C₁- bis C₆)-Alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁- bis C₆)-Alkyl, C₃- bis C₁₀-Cycloalkyl, -SR²³, -SOR²³, -SO₂R²³, -SO₂NH(C₁- bis C₆-Alkyl), -OSO₂(C₁- bis C₆)-Alkyl, -OSO₂CF₃, Hydroxy(C₁- bis C₆)-alkyl, -CONR²⁰R²¹, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁- bis C₆)-Alkyl, -CO₂R²⁰, -Si(CH₃)₃ oder -B(OC(CH₃)₂)₂ ist;

R¹⁰ (C₁- bis C₆)-Alkyl, -NH₂ oder R¹²-Phenyl ist;

R¹² 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, (C₁- bis C₆)-Alkyl, -CF₃, -CO₂R²⁰, -CN, (C₁- bis C₆)-Alkoxy und Halogen;

R¹³, R¹⁴, R¹⁵ und R¹⁶ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und (C₁- bis C₆)-Alkyl;

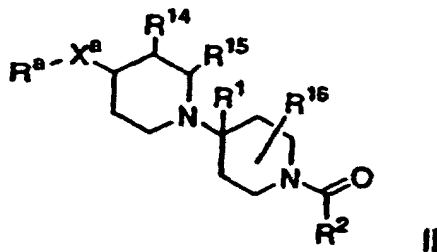
R¹⁷ und R¹⁸ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und C₁- bis C₆-Alkyl, oder R¹⁷ und R¹⁸ zusammen eine C₂- bis C₅-Alkylengruppe sind und mit dem Kohlenstoff, an den sie gebunden sind, einen Spiroring mit 3 bis 6 Kohlenstoffatomen bilden;

R¹⁹ R⁶-Phenyl, R⁶-Heteroaryl, R⁶-Naphthyl, C₃- bis C₁₀-Cycloalkyl, (C₃- bis C₁₀)-Cycloalkyl(C₁- bis C₆)-alkyl oder (C₁- bis C₆)-Alkoxy(C₁- bis C₆)-alkyl ist;

R²⁰, R²¹ und R²² unabhängig ausgewählt sind aus der Gruppe bestehend aus H und C₁- bis C₆-Alkyl; und

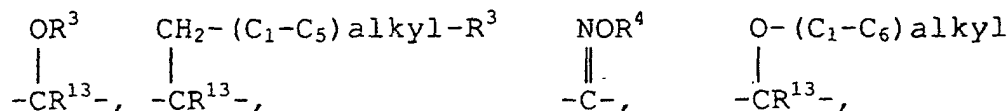
R²³ C₁- bis C₆-Alkyl oder Phenyl ist;

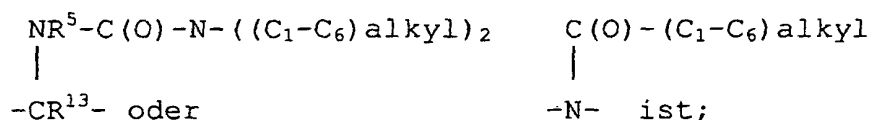
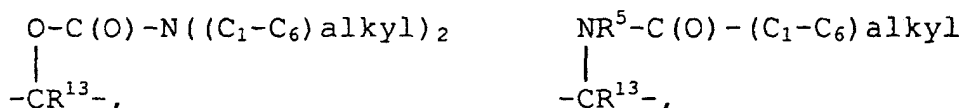
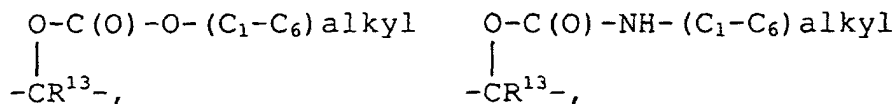
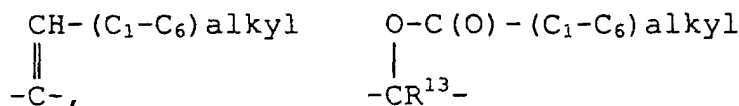
und wobei in den CCR5-Antagonistverbindungen, die durch die Strukturformel II wiedergegeben werden,



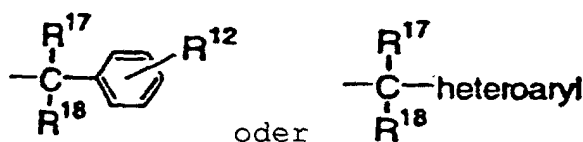
oder einem pharmazeutisch annehmbaren Salz davon,

(1) X^a -C(R¹³)₂-, -C(R¹³)(R¹⁹)-, -C(O)-, -O-, -NH-, N((C₁ bis C₆)-alkyl)-,

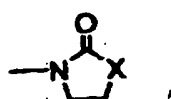




R^a R^{6a}-Phenyl, R^{6a}-Pyridyl, R^{6a}-Thiophenyl oder R^{6a}-Naphthyl ist;
R¹ Wasserstoff, C₁- bis C₆-Alkyl oder C₂- bis C₆-Alkenyl ist;
R² R⁷, R⁸, R⁹-Phenyl; R⁷, R⁸, R⁹-substituiertes 6-gliedriges Heteroaryl; R⁷, R⁸, R⁹-substituiertes 6-gliedriges
Heteroaryl-N-oxid; R¹⁰, R¹¹-substituiertes 5-gliedriges Heteroaryl; Naphthyl; Fluorenyl; Diphenylmethyl;



ist;
R³ R¹⁰-Phenyl, Pyridyl, Pyrimidyl, Pyrazinyl oder Thiazolyl ist;
R⁴ Wasserstoff, C₁- bis C₆-Alkyl, Fluor-C₁- bis C₆-alkyl, Cyclopropylmethyl, -CH₂CH₂OH, -CH₂CH₂-O-(C₁- bis
C₆)-Alkyl, -CH₂C(O)-O-(C₁- bis C₆)-Alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH(C₁ bis C₆)-Alkyl oder -CH₂C(O)-N((C₁-
bis C₆)Alkyl)₂ ist;
R⁵ und R¹¹ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und (C₁- bis C₆)-Alkyl;
R^{6a} 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff,
Halogen, -CF₃, CF₃O-, -CN, CF₃SO₂-, R¹²-Phenyl, -NHCOCF₃, 5-gliedriges Heteroaryl und



wobei X -O-, -NH- oder -N(CH₃)- ist;

R⁶ unabhängig ausgewählt ist aus der Gruppe bestehend aus R^{6a} und CH₃SO₂-;

R⁷ und R⁸ unabhängig ausgewählt sind aus der Gruppe bestehend aus (C₁- bis C₆)-Alkyl, Halogen, -NR²⁰R²¹, -OH, -CF₃, -OCH₃, -O-Acyl und -OCF₃;

R⁹ R⁷, Wasserstoff, Phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR²⁰, Pyridyl, Pyridyl-N-oxid, Pyrimidinyl, Pyrazinyl, -N(R²⁰)CONR²¹R²², -NHCONH(Chlor-(C₁- bis C₆)-alkyl, -NHCONH((C₃- bis C₁₀)-Cycloalkyl(C₁- bis C₆)-alkyl), -NHCO(C₁- bis C₆)-Alkyl, -NHCOCF₃, -NHSO₂N((C₁- bis C₆)-Alkyl)₂, -NHSO₂(C₁- bis C₆)-Alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁- bis C₆)-Alkyl, C₃- bis C₁₀-Cycloalkyl, -SR²³, -SOR²³, -SO₂R²³, -SO₂NH(C₁- bis C₆-Alkyl), -OSO₂(C₁- bis C₆)-Alkyl, -OSO₂CF₃, Hydroxy(C₁- bis C₆)-alkyl, -CONR²⁰R²¹, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁- bis C₆)-Alkyl, -CO₂R²⁰, -Si(CH₃)₃ oder -B(OC(CH₃)₂)₂ ist;

R¹⁰ (C₁- bis C₆)-Alkyl, -NH₂ oder R¹²-Phenyl ist;

R¹² 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, (C₁- bis C₆)-Alkyl, -CF₃, -CO₂R²⁰, -CN, (C₁- bis C₆)-Alkoxy und Halogen;

R¹³, R¹⁴, R¹⁵ und R¹⁶ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und (C₁- bis C₆)-Alkyl;

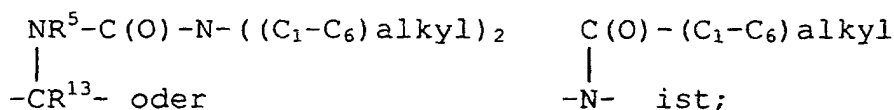
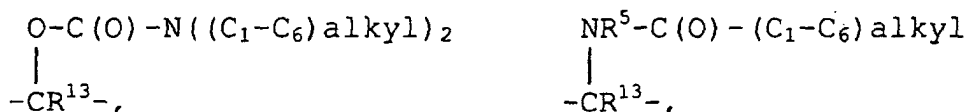
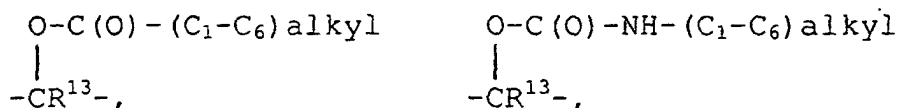
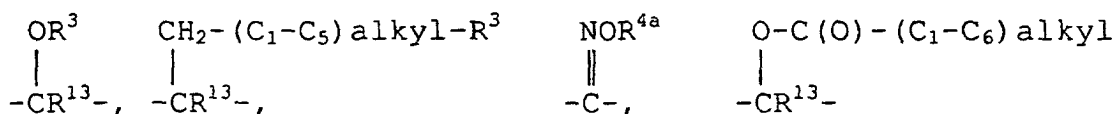
R¹⁷ und R¹⁸ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und C₁- bis C₆-Alkyl, oder R¹⁷ und R¹⁸ zusammen eine C₂- bis C₅-Alkylengruppe sind und mit dem Kohlenstoff, an den sie gebunden sind, einen Spiroring mit 3 bis 6 Kohlenstoffatomen bilden;

R¹⁹ R⁶-Phenyl, R⁶-Heteroaryl, R⁶-Naphthyl, C₃- bis C₁₀-Cycloalkyl, (C₃- bis C₁₀)-Cycloalkyl(C₁- bis C₆)-alkyl oder (C₁- bis C₆)-Alkoxy(C₁- bis C₆)-alkyl ist;

R²⁰, R²¹ und R²² unabhängig ausgewählt sind aus der Gruppe bestehend aus H und C₁- bis C₆-Alkyl; und R²³ C₁- bis C₆-Alkyl oder Phenyl ist; oder

(2):

X^a-C(R¹³)(R¹⁹)-, -C(O)-, -O-, -NH-, N(C₁- bis C₆)-alkyl)-,



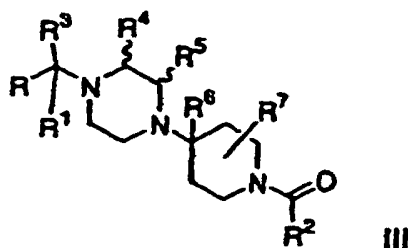
R^a R^{6b}-Phenyl, R^{6b}-Pyridyl oder R^{6b}-Thiophenyl ist;

R^{4a} Fluor-C₁- bis C₆-alkyl, Cyclopropylmethyl, -CH₂CH₂OH, -CH₂CH₂-O-(C₁-bis C₆)alkyl; -CH₂C(O)-O-(C₁- bis C₆)alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH-(C₁- bis C₆)alkyl, -CH₂C(O)-NH-((C₁- bis C₆)-alkyl)₂ ist;

R^{6b} CH₃SO₂- ist und

R¹, R², R³, R⁵, R¹⁴, R¹⁵, R¹⁶ und R¹⁹ wie in II(1) definiert sind;

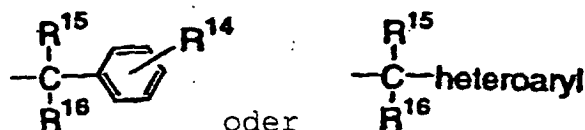
und wobei in den CCR5-Antagonistverbindungen, die durch die Strukturformel III wiedergegeben werden,



R⁸ R⁸-Phenyl, R⁸-Pyridyl, R⁸-Thiophenyl oder R⁸-Naphthyl ist;

R¹ Wasserstoff oder C₁- bis C₆-Alkyl ist;

R² R⁹, R¹⁰, R¹¹-Phenyl; R⁹, R¹⁰, R¹¹-substituiertes 6-gliedriges Heteroaryl; R⁹, R¹⁰, R¹¹-substituiertes 6-gliedriges Heteroaryl-N-oxid; R¹², R¹³-substituiertes 5-gliedriges Heteroaryl; Naphthyl; Fluorenyl; Diphenylmethyl;



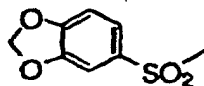
ist;

R³ Wasserstoff, C₁- bis C₆-Alkyl, (C₁- bis C₆)-Alkoxy-(C₁ bis C₆)alkyl, C₃- bis C₁₀-Cycloalkyl, C₃- bis C₁₀-Cycloalkyl(C₁- bis C₆)alkyl, R⁸-Phenyl, R⁸-Phenyl(C₁- bis C₆)alkyl, R⁸-Naphthyl, R⁸-Naphthyl(C₁- bis C₆)alkyl, R⁸-Heteroaryl oder R⁸-Heteroaryl(C₁- bis C₆)alkyl ist;

R⁴, R⁵, R⁷ und R¹³ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und (C₁- bis C₆)-Alkyl;

R⁶ Wasserstoff, C₁- bis C₆-Alkyl oder C₂- bis C₆-Alkenyl ist;

R⁸ 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Halogen, C₁- bis C₆-Alkyl, C₁- bis C₆-Alkoxy, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-Phenyl, R¹⁴-Benzyl, CH₃C(=NOCH₃), CH₃C(=NOCH₂CH₃),



-NH₂, -NHCOCF₃, -NHCONH(C₁- bis C₆-Alkyl), -NHCO(C₁- bis C₆-Alkyl), -NHSO₂(C₁- bis C₆-Alkyl), 5-gliedrigem Heteroaryl und



sind, wobei X -O-, -NH- oder -N(CH₃)- ist;

R⁹ und R¹⁰ unabhängig ausgewählt sind aus der Gruppe bestehend aus (C₁- bis C₆)-Alkyl, Halogen, -NR¹⁷R¹⁸, -OH, -CF₃, -OCH₃, -O-Acyl, -OCF₃ und -Si(CH₃)₃;

R¹¹R⁹, Wasserstoff, Phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR¹⁷, Pyridyl, Pyridyl-N-oxid, Pyrimidinyl, Pyrazinyl, -N(R¹⁷)CONR¹⁸R¹⁹, -NHCONH(Chlor-(C₁-bis C₆)alkyl), -NHCONH((C₃- bis C₁₀)-Cycloalkyl(C₁- bis C₆)alkyl), -NHCO(C₁-bis C₆)alkyl, -NHCOCF₃, -NHSO₂N((C₁- bis C₆)alkyl)₂, -NHSO₂(C₁- bis C₆)-Alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁- bis C₆)-Alkyl, C₃- bis C₁₀-Cycloalkyl, -SR²⁰, -SOR²⁰, -SO₂R²⁰, -SO₂NH(C₁- bis C₆-Alkyl), -OSO₂(C₁- bis C₆)-Alkyl, -OSO₂CF₃, Hydroxy(C₁-bis C₆)-alkyl, -CONR¹⁷R¹⁸, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁- bis C₆)-Alkyl, -CO₂R¹⁷, -Si(CH₃)₃ oder -B(OC(CH₃)₂)₂ ist;

R¹² (C₁- bis C₆)-Alkyl, -NH₂ oder R¹⁴-Phenyl ist;

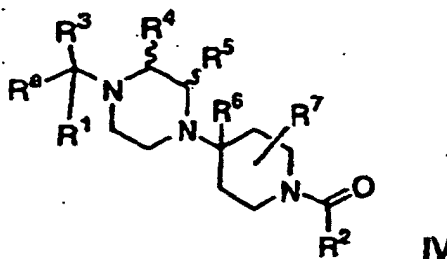
R¹⁴ 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, (C₁- bis C₆)-Alkyl, -CF₃, -CO₂R¹⁷, -CN, (C₁- bis C₆)-Alkoxy und Halogen;

R¹⁵ und R¹⁶ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und C₁- bis C₆-Alkyl, oder R¹⁵ und R¹⁶ zusammen eine C₂- bis C₅-Alkylengruppe sind und mit dem Kohlenstoff, an den sie gebunden sind, einen Spiring mit 3 bis 6 Kohlenstoffatomen bilden;

R¹⁷, R¹⁸ und R¹⁹ unabhängig ausgewählt sind aus der Gruppe bestehend aus H und C₁- bis C₆-Alkyl; und

R²⁰ C₁- bis C₆-Alkyl oder Phenyl ist;

und wobei in den CCR5-Antagonistverbindungen, die durch die Strukturformel IV

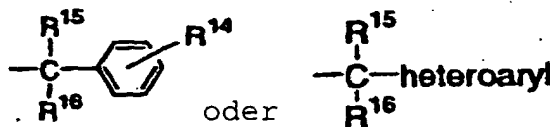


wiedergegeben werden, oder einem pharmazeutisch annehmbaren Salz davon,

(1) R^a R^{8a}-Phenyl, R^{8b}-Pyridyl, R^{8b}-Thiophenyl oder R⁸-Naphthyl ist;

R¹ Wasserstoff oder C₁- bis C₆-Alkyl ist;

R² R⁹, R¹⁰, R¹¹-phenyl; R⁹, R¹⁰, R¹¹-substituiertes 6-gliedriges Heteroaryl; R⁹, R¹⁰, R¹¹-substituiertes 6-gliedriges Heteroaryl-N-oxid; R¹², R¹³-substituiertes 5-gliedriges Heteroaryl; Naphthyl; Fluorenyl; Diphenylmethyl;



ist;

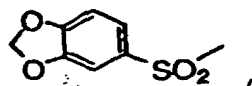
R³ Wasserstoff, C₁- bis C₆-Alkyl, (C₁- bis C₆)Alkoxy(C₁-bis C₆)alkyl; C₃- bis C₁₀-Cycloalkyl, C₃- bis C₁₀-Cycloalkyl (C₁- bis C₆)alkyl, R⁸-Phenyl, R⁸-Phenyl(C₁- bis C₆) alkyl, R⁸-Naphthyl, R⁸-Naphthyl(C₁- bis C₆)-alkyl; R⁸-Heteroaryl oder R⁸-Heteroaryl(C₁- bis C₆)alkyl ist;

EP 1 175 224 B1

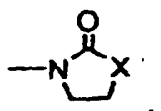
R⁴, R⁵, R⁷ und R¹³ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und (C₁-bis C₆)-Alkyl;

R⁶ Wasserstoff, C₁- bis C₆-Alkyl oder C₂- bis C₆-Alkenyl ist;

R⁸ 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Halogen, C₁- bis C₆-Alkyl, C₁- bis C₆-Alkoxy, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-Phenyl, R¹⁴-Benzyl, CH₃C(=NOCH₃), CH₃C(=NOCH₂CH₃),

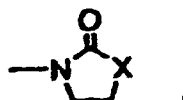


-NH₂, -NHCOCF₃, -NHCONH(C₁-bis C₆-Alkyl), -NHCO(C₁- bis C₆-Alkyl), -NHSO₂(C₁- bis C₆-Alkyl), 5-gliedrigem Heteroaryl und



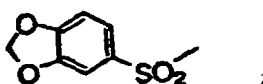
wobei X -O-, -NH- oder -N(CH₃)- ist;

R^{8a} 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Halogen, -CF₃, CF₃O-, -CN, CF₃SO₂-, R¹⁴-Phenyl, -NHCOCF₃, 5-gliedrigem Heteroaryl und

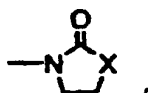


wobei X wie zuvor definiert ist;

R^{8b} 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Halogen, -CF₃, CF₃O-, CH₃C(O)-, -CN, CF₃SO₂-, R¹⁴-Benzyl, CH₃C(=NOCH₃), CH₃C(=NOCH₂CH₃),



-NHCOCF₃, 5-gliedrigem Heteroaryl und

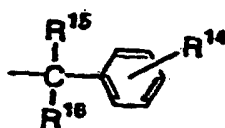


wobei X wie zuvor definiert ist;

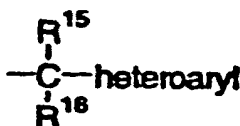
R⁹ und R¹⁰ unabhängig ausgewählt sind aus der Gruppe bestehend aus (C₁- bis C₆)-Alkyl, Halogen, -NR¹⁷R¹⁸, -OH, -CF₃, -OCH₃, -O-Acyl, -OCF₃ und -Si(CH₃)₃;

R¹¹ R⁹, Wasserstoff, Phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR¹⁷, Pyridyl, Pyridyl-N-oxid, Pyrimidinyl, Pyrazinyl, -N(R¹⁷)CONR¹⁸R¹⁹, -NHCONH(Chlor(C₁- bis C₆)alkyl), -NHCONH((C₃- bis C₁₀)Cycloalkyl(C₁- bis C₆)alkyl), -NHCO(C₁- bis C₆)Alkyl, -NHCOCF₃, -NHSO₂N((C₁- bis C₆)Alkyl)₂, -NHSO₂(C₁- bis C₆)-Alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁- bis C₆)-Alkyl, C₃- bis C₁₀-Cycloalkyl, -SR²⁰, -SOR²⁰, -SO₂R²⁰, -SO₂NH(C₁- bis C₆-Alkyl), -OSO₂(C₁- bis C₆)-Alkyl, -OSO₂CF₃, Hydroxy(C₁- bis C₆)-alkyl, -CONR¹⁷R¹⁸, -CON(CH₂CH₂-

O-CH₃)₂, -OCONH(C₁- bis C₆)-Alkyl, -CO₂R¹⁷, -Si(CH₃)₃ oder -B(OC(CH₃)₂)₂ ist;
R¹² (C₁- bis C₆)-Alkyl, -NH₂ oder R¹⁴-Phenyl ist;
R¹⁴ 1 bis 3 Substituenten ist, die unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff,
(C₁-bis C₆)-Alkyl, -CF₃, -CO₂R¹⁷, -CN, (C₁- bis C₆)-Alkoxy und Halogen;
R¹⁵ und R¹⁶ unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff und C₁- bis C₆-Alkyl,
oder R¹⁵ und
R¹⁶ zusammen eine C₂- bis C₅-Alkylengruppe sind und mit dem Kohlenstoff, an den sie gebunden sind, einen
Spiroring mit 3 bis 6 Kohlenstoffatomen bilden;
R¹⁷, R¹⁸ und R¹⁹ unabhängig ausgewählt sind aus der Gruppe bestehend aus H und C₁- bis C₆-Alkyl; und
R²⁰ C₁- bis C₆-Alkyl oder Phenyl ist; oder
(2) R^a R⁸-Phenyl, R⁸-Pyridyl oder R⁸-Thiophenyl ist;
R² Fluorenyl, Diphenylmethyl,



oder



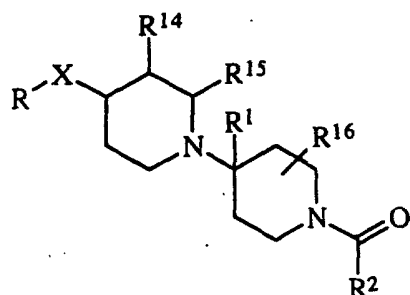
ist;
und R¹, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹ und R²⁰ wie in IV(1) definiert
sind.

12. Verwendung nach Anspruch 11, bei der die Patienten behandlungserfahrene Patienten oder Erstbehandlungspatienten sind.
13. Verwendung nach Anspruch 11, bei der die Patienten pädiatrische behandlungserfahrene Patienten oder Erstbehandlungspatienten sind.
14. Verwendung nach Anspruch 11, bei der das zu verabreichende pegylierte Interferon- α pegyliertes Interferon- α -2a oder pegyliertes Interferon- α -2b ist.
15. Verwendung nach Anspruch 14, bei der das zu verabreichende pegylierte Interferon- α ein pegyliertes Interferon- α -2b ist und wobei die Menge an zu verabreichendem pegyliertem Interferon- α -2b im Bereich von etwa 0,1 bis etwa 9,0 Mikrogramm pro Kilogramm pro Woche, vorzugsweise im Bereich von etwa 0,5 bis etwa 3,0 Mikrogramm pro Kilogramm pro Woche und besonders bevorzugt im Bereich von etwa 0,75 bis etwa 1,5 Mikrogramm pro Kilogramm pro Woche liegt.
16. Verwendung nach Anspruch 14, bei der das zu verabreichende pegylierte Interferon- α ein pegyliertes Interferon- α -2a ist und wobei die Menge an zu verabreichendem pegyliertem Interferon- α -2a im Bereich von etwa 50 bis etwa 500 Mikrogramm pro Woche, vorzugsweise im Bereich von etwa 150 bis etwa 250 Mikrogramm pro Woche und besonders bevorzugt im Bereich von etwa 180 bis etwa 250 Mikrogramm pro Woche, oder vorzugsweise im Bereich von etwa 150 bis etwa 180 Mikrogramm pro Woche liegt.
17. Verwendung nach Anspruch 11, bei der der Patient ein pädiatrischer Patient ist und die Menge an Ribavirin im Bereich von etwa 8 bis etwa 15 mg pro Kilogramm pro Tag in aufgeteilten Dosen liegt.

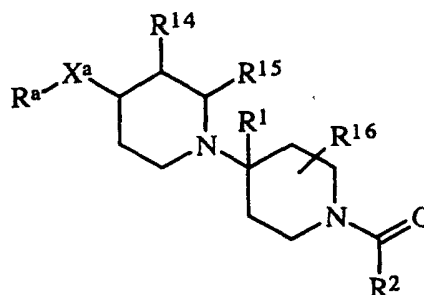
18. Verwendung nach Anspruch 11, bei der die Menge an Ribavirin etwa 400 bis etwa 1600 mg pro Tag, vorzugsweise etwa 600 bis etwa 1200 mg/Tag oder etwa 800 bis etwa 1200 mg/Tag und am meisten bevorzugt etwa 1000 bis etwa 1200 mg/kg pro Tag beträgt.

Revendications

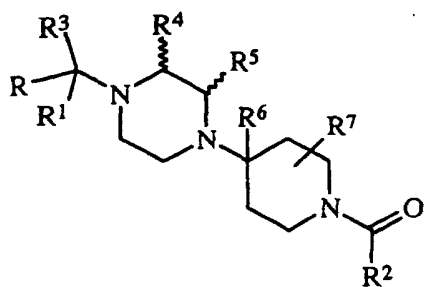
1. Utilisation d'un interféron- α pégylé et d'un antagoniste CCR5 pour la préparation d'un médicament destiné au traitement des infections par VIH-1 chez des patients, dans laquelle l'antagoniste CCR5 est un composé représenté par la formule développée I, II, III ou IV :



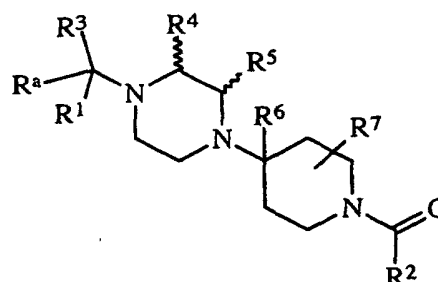
I



II

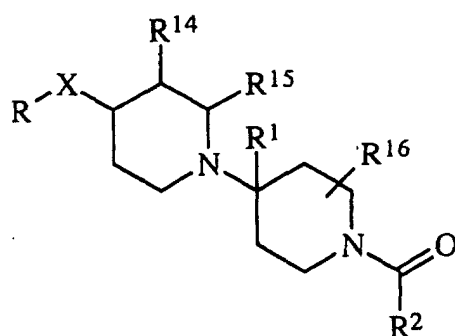


III



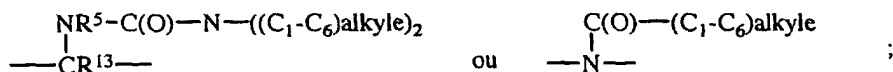
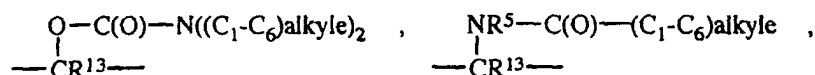
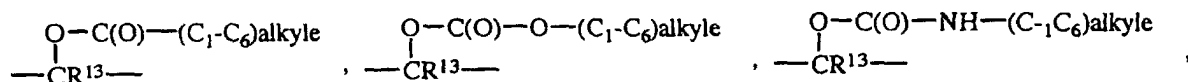
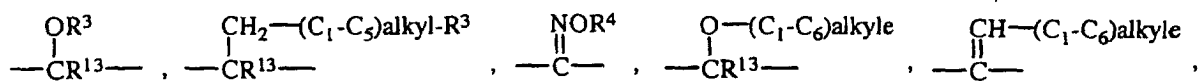
IV

ou un sel pharmaceutiquement acceptable d'un tel composé,
et dans laquelle, pour les composés antagonistes CCR5 représentés par la formule développée I :

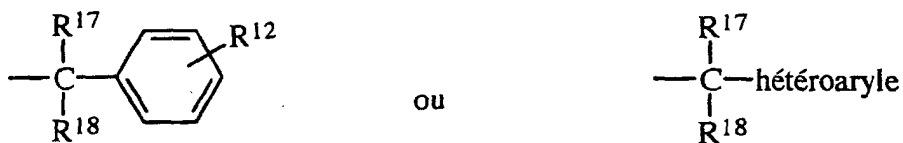


I

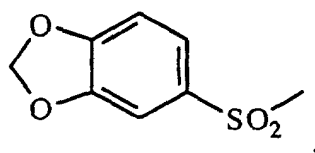
X représente un groupe $-(R^{13})_2-$, $-(R^{13})(R^{19})-$, $-C(O)-$, $-O-$, $-NH-$, $-N((C_1-C_6)\text{alkyle})-$,



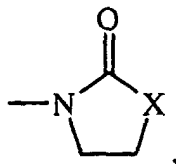
R représente un groupe R⁶-phényle, R⁶-pyridyle, R⁶-thiophényle ou R⁶-naphtyle,
 R¹ représente un atome d'hydrogène, un groupe alkyle en C₁ à C₆ ou un groupe alcényle en C₂ à C₆,
 R² représente un groupe R⁷, R⁸, R⁹-phényle, un groupe hétéroaryle à 6 chaînons, substitué par R⁷, R⁸, R⁹, un
 groupe hétéroaryle N-oxyde, à 6 chaînons, substitué par R⁷, R⁸, R⁹, un groupe hétéroaryle à 5 chaînons, substitué
 par R¹⁰, R¹¹, un groupe naphtyle, un groupe fluorényle, un groupe diphenylméthyle, ou un groupe



R³ représente un groupe R⁶-phényle, R⁶-hétéroaryle ou R⁶-naphtyle,
 R⁴ représente un atome d'hydrogène, un groupe alkyle en C₁ à C₆, un groupe fluoroalkyle en C₁ à C₆, un groupe
 cyclopropylméthyle, ou un groupe -CH₂CH₂OH, -CH₂CH₂-O-(C₁-C₆)alkyle, -CH₂C(O)-O-(C₁-C₆)alkyle, -CH₂C(O)
 NH₂, -CH₂C(O)-NH(C₁-C₆)alkyle ou CH₂C(O)-N((C₁-C₆)alkyle)₂,
 R⁵ et R¹¹ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆,
 R⁶ représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les
 groupes alkyle en C₁ à C₆, alcoxy en C₁ à C₆, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-phényle,
 R¹⁴-benzyle, CH₃C(=NOCH₃)-, CH₃C(=NOCH₂CH₃)-,



$-\text{NH}_2$, $-\text{NHCOCF}_3$, $-\text{NHCONH}(\text{C}_1\text{-C}_6 \text{ alkyle})$, $-\text{NHCO}(\text{C}_1\text{-C}_6 \text{ alkyle})$, $-\text{NHSO}_2(\text{C}_1\text{-C}_6 \text{ alkyle})$, hétéroaryle à 5 chaînons et



où X représente $-\text{O}-$, $-\text{NH}-$ ou $-\text{N}(\text{CH}_3)-$,

R^7 et R^8 représentent chacun indépendamment un atome d'halogène ou un groupe alkyle en C_1 à C_6 , $-\text{NR}^{20}\text{R}^{21}$, $-\text{OH}$, $-\text{CF}_3$, $-\text{OCH}_3$, $-\text{O-acyl}$ ou $-\text{OCF}_3$,

R^9 représente R^7 , un atome d'hydrogène ou un groupe phényle, $-\text{NO}_2$, $-\text{CN}$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CHO}$, $-\text{CH}=\text{NOR}^{20}$, pyridyle, pyridyl-N-oxyde, pyrimidinyle, pyrazinyle, $-\text{N}(\text{R}^{20})-\text{CONR}^{21}\text{R}^{22}$, $-\text{NHCONH}(\text{chloro}-(\text{C}_1\text{-C}_6) \text{ alkyle})$, $-\text{NHCONH}((\text{C}_3\text{-C}_{10})\text{-cycloalkyl}(\text{C}_1\text{-C}_6) \text{ alkyle})$, $-\text{NHCO}(\text{C}_1\text{-C}_6) \text{ alkyl}$, $-\text{NHCOCF}_3$, $-\text{NHSO}_2\text{N}((\text{C}_1\text{-C}_6) \text{ alkyl})_2$, $-\text{NHSO}_2(\text{C}_1\text{-C}_6) \text{ alkyle}$, $-\text{N}(\text{SO}_2\text{CF}_3)_2$, $-\text{NHCO}_2(\text{C}_1\text{-C}_6) \text{ alkyle}$, $(\text{C}_3\text{-C}_{10})\text{cycloalkyle}$, $-\text{SR}^{23}$, $-\text{SOR}^{23}$, $-\text{SO}_2\text{R}^{23}$, $-\text{SO}_2\text{NH}(\text{C}_1\text{-C}_6) \text{ alkyle}$, $-\text{OSO}_2(\text{C}_1\text{-C}_6) \text{ alkyle}$, $-\text{OSO}_2\text{CF}_3$, hydroxy($\text{C}_1\text{-C}_6$) alkyle, $-\text{CONR}^{20}\text{R}^{21}$, $-\text{CON}(\text{CH}_2\text{CH}_2\text{-O-CH}_3)_2$, $-\text{OCONH}(\text{C}_1\text{-C}_6) \text{ alkyle}$, $-\text{CO}_2\text{R}^{20}$, $-\text{Si}(\text{CH}_3)_3$ ou $-\text{B}(\text{OC}(\text{CH}_3)_2)_2$,

R^{10} représente un groupe alkyle en C_1 à C_6 , $-\text{NH}_2$ ou R^{12} -phényle,

R^{12} représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes alkyle en C_1 à C_6 , $-\text{CF}_3$, $-\text{CO}_2\text{R}^{20}$, $-\text{CN}$, et alcoxy en C_1 à C_6 ,

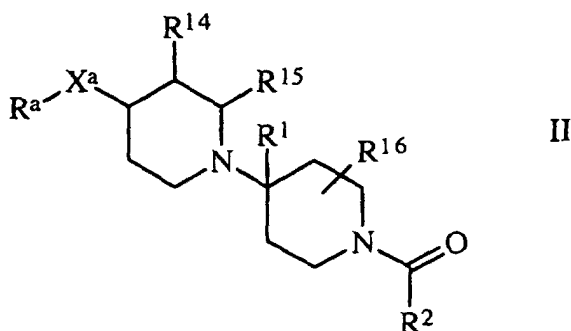
R^{13} , R^{14} , R^{15} et R^{16} représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C_1 à C_6 ,

R^{17} et R^{18} représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C_1 à C_6 , ou bien R^{17} et R^{18} représentent ensemble un groupe alkylène en C_2 à C_5 et forment avec l'atome de carbone auquel ils sont liés un noyau spiro ayant 3 à 6 atomes de carbone,

R^{19} représente un groupe R^6 -phényle, R^6 -hétéroaryle, R^6 -naphtyle, $(\text{C}_3\text{-C}_{10})\text{cycloalkyle}$, $(\text{C}_3\text{-C}_{10})\text{cycloalkyl}(\text{C}_1\text{-C}_6) \text{ alkyle}$ ou $(\text{C}_1\text{-C}_6)\text{alcoxy}(\text{C}_1\text{-C}_6) \text{ alkyle}$,

R^{20} , R^{21} et R^{22} représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C_1 à C_6 , et R^{23} représente un groupe alkyle en C_1 à C_6 ou un groupe phényle,

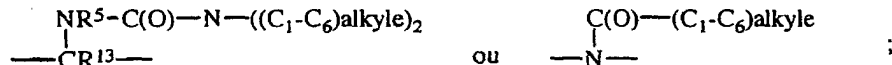
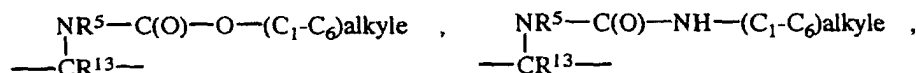
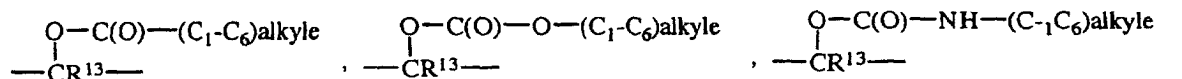
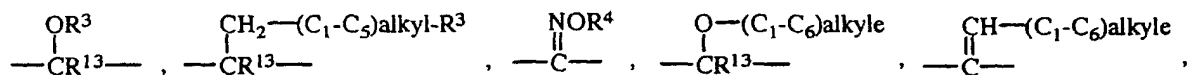
pour les composés antagonistes CCR5 représentés par la formule développée II :



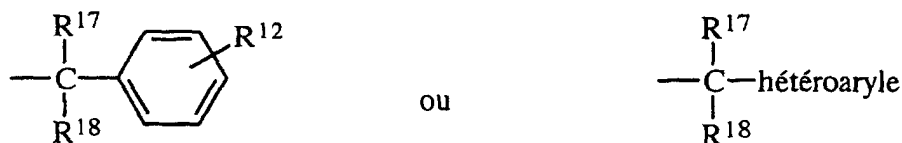
et leurs sels pharmaceutiquement acceptables,

(1) X^a représente un groupe

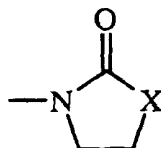
$-\text{C}(\text{R}^{13})_2-$, $-\text{C}(\text{R}^{13})(\text{R}^{19})-$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{NH}-$, $-\text{N}((\text{C}_1\text{-C}_6) \text{ alkyle})-$,



R^a représente un groupe R^{6a}-phényle, R^{6a}-pyridyle, R^{6a}-thiophényle ou R⁶-naphtyle,
 R¹ représente un atome d'hydrogène, un groupe alkyle en C₁ à C₆ ou un groupe alcényle en C₂ à C₆,
 R² représente un groupe R⁷, R⁸, R⁹-phényle, un groupe hétéroaryle à 6 chaînons, substitué par R⁷, R⁸, R⁹,
 un groupe hétéroaryle N-oxyde à 6 chaînons, substitué par R⁷, R⁸, R⁹, un groupe hétéroaryle à 5 chaînons,
 substitué par R¹⁰, R¹¹, un groupe naphtyle, un groupe fluorényle, un groupe diphénylméthyle, ou un groupe



R³ représente un groupe R¹⁰-phényle, pyridyle, pyrimidyle, pyrazinyle ou thiazolyne,
 R⁴ représente un atome d'hydrogène, un groupe alkyle en C₁ à C₆, un groupe fluoroalkyle en C₁ à C₆, un
 groupe cyclopropylméthyle, ou un groupe -CH₂CH₂OH, -CH₂CH₂-O-(C₁-C₆)alkyle, -CH₂C(O)-O-(C₁-C₆)alk-
 yle, -CH₂C(O)NH₂, -CH₂C(O)-NH(C₁-C₆)alkyle ou CH₂C(O)-N((C₁-C₆)alkyle)₂,
 R⁵ et R¹¹ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆,
 R^{6a} représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et
 les groupes -CF₃, CF₃O-, -CN, CF₃SO₂-, R¹²-phényle, -NHCOCF₃, hétéroaryle à 5 chaînons et



où X représente -O-, -NH- ou -N(CH₃)-,

R⁶ représente R^{6a} ou CH₃SO₂-,

R⁷ et R⁸ représentent chacun indépendamment un atome d'halogène ou un groupe alkyle en C₁ à C₆, -NR²⁰R²¹, -OH-, -CF₃, -OCH₃, -O-acyl ou -OCF₃, R⁹ représente R⁷, un atome d'hydrogène, ou un groupe phényle, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR²⁰, pyridyle, pyridyl-N-oxyde, pyrimidinyle, pyrazinyle, -N(R²⁰)-CONR²¹R²², -NHCONH(chloro-(C₁-C₆)alkyle), -NHCONH((C₃-C₁₀)-cycloalkyl(C₁-C₆)alkyle), -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyl)₂, -NHSO₂(C₁-C₆)alkyle, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyle, (C₃-C₁₀)cycloalkyle, -SR²³, -SOR²³, -SO₂R²³, -SO₂NH(C₁-C₆)alkyle, -OSO₂(C₁-C₆)alkyle, -OSO₂CF₃, hydroxy(C₁-C₆)alkyle, -CONR²⁰R²¹, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyle, -CO₂R²⁰, -Si(CH₃)₃ ou -B(OC(CH₃)₂)₂,

R¹⁰ représente un groupe alkyle en C₁ à C₆, -NH₂ ou R¹²-phényle,

R¹² représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes alkyle en C₁ à C₆, -CF₃, -CO₂R²⁰, -CN et alcoxy en C₁ à C₆,

R¹³, R¹⁴, R¹⁵ et R¹⁶ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆,

R¹⁷ et R¹⁸ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, ou bien R¹⁷ et R¹⁸ représentent ensemble un groupe alkylène en C₂ à C₅ et forment avec l'atome de carbone auquel ils sont liés un noyau spiro ayant 3 à 6 atomes de carbone,

R¹⁹ représente un groupe R⁶-phényle, R⁶-hétéroaryle, R⁶-naphtyle, (C₃-C₁₀)cycloalkyle, (C₃-C₁₀)cycloalkyl(C₁-C₆)alkyle ou (C₁-C₆)alcoxy(C₁-C₆)alkyle,

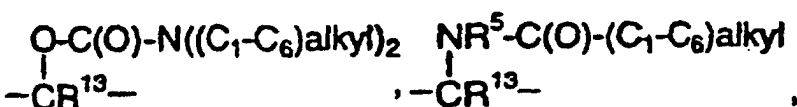
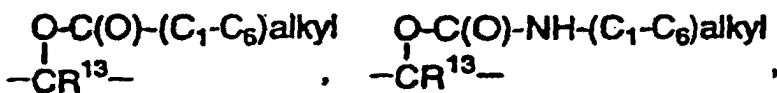
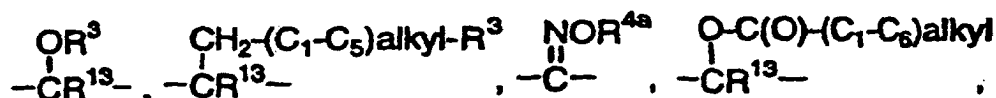
R²⁰, R²¹ et R²² représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, et R²³ représente un groupe alkyle en C₁ à C₆ ou un groupe phényle,

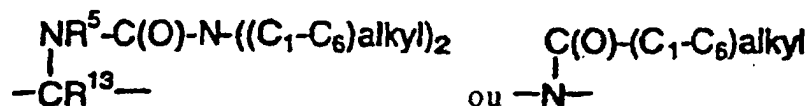
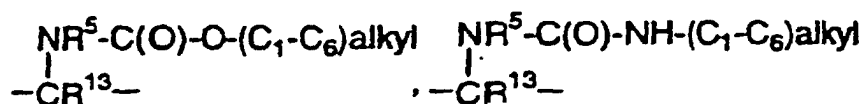
ou bien

(2)

X^a représente un groupe

-C(R¹³)(R¹⁹)-, -C(O)-, -O-, -NH-, -N((C₁-C₆)alkyl)-,



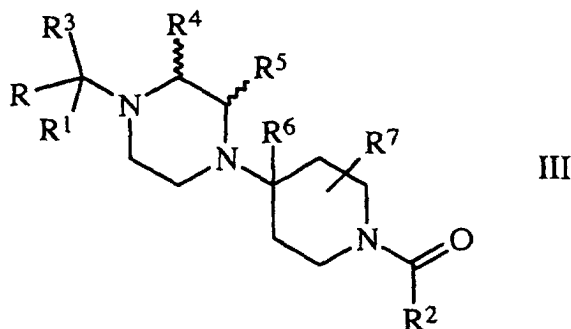


R^a représente un groupe R^{6b}-phényle, un groupe R^{6b}-pyridyle ou R^{6b}-thiophényle,
 R^{4a} représente un groupe fluoroalkyle en C₁ à C₆, un groupe cyclopropylméthyle, ou un groupe -CH₂CH₂OH,
 -CH₂CH₂-O-(C₁-C₆)alkyl, -CH₂C(O)-O-(C₁-C₆)alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH-(C₁-C₆)alkyl ou -CH₂C(O)-
 -N((C₁-C₆)alkyl)₂;

R^{6b} représente un groupe CH₃SO₂-, et

R¹, R², R³, R⁵, R¹⁴, R¹⁵, R¹⁶ et R¹⁹ ont les significations indiquées pour II (1),

pour les composés antagonistes CCR5 représentés par la formule développée III :



R représente un groupe R⁸-phényle, R⁸-pyridyle, R⁸-thiophényle ou R⁸-naphtyle,

R¹ représente un atome d'hydrogène ou un groupe alkyle en C₁ à C₆,

R² représente un groupe R⁹, R¹⁰, R¹¹-phényle, un groupe hétéroaryle à 6 chaînons, substitué par R⁹, R¹⁰, R¹¹, un groupe hétéroaryle N-oxyde à 6 chaînons, substitué par R⁹, R¹⁰, R¹¹, un groupe hétéroaryle à 5 chaînons, substitué par R¹², R¹³, un groupe naphtyle, un groupe fluorényle, un groupe diphenylméthyle, ou un groupe

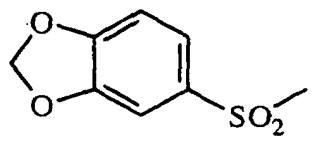


R³ représente un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, (C₁-C₆)alkoxy(C₁-C₆)alkyle, (C₃-C₁₀) cycloalkyle, (C₃-C₁₀)cycloalkyl(C₁-C₆)alkyle, R⁸-phényle, R⁸-phényl(C₁-C₆)alkyle, R⁸-naphtyle, R⁸-naphtyl (C₁-C₆)alkyle, R⁸-hétéroaryle ou R⁸-hétéroaryl(C₁-C₆)alkyle ;

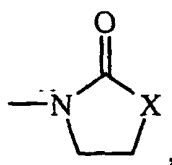
R⁴, R⁵, R⁷ et R¹³ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆,

R⁶ représente un atome d'hydrogène, un groupe alkyle en C₁ à C₆ ou un groupe alcényle en C₂ à C₆,

R⁸ représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes alkyle en C₁ à C₆, alcoxy en C₁ à C₆, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-phényle, R¹⁴-benzyle, CH₃C(=NOCH₃)-, CH₃C(=NOCH₂CH₃)-,



-NH₂, -NHCOCF₃, -NHCONH(C₁-C₆ alkyle), -NHCO(C₁-C₆ alkyle), -NHSO₂(C₁-C₆ alkyle), hétéroaryle à 5 chaînons et



où X représente -O-, -NH- ou -N(CH₃)-,

R⁹ et R¹⁰ représentent chacun indépendamment un atome d'halogène ou un groupe alkyle en C₁ à C₆, -NR¹⁷R¹⁸, -OH, -CF₃, -OCH₃, -O-acyle, -OCF₃ ou -Si(CH₃)₃,

R¹¹ représente R⁹, un atome d'hydrogène, ou un groupe phényle, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR¹⁷, pyridyle, pyridyl-N-oxyde, pyrimidyle, pyrazinyle, -N(R¹⁷)CONR¹⁸R¹⁹, -NHCONH(chloro-(C₁-C₆)alkyle), -NHCONH(C₃-C₁₀)cycloalkyl(C₁-C₆)alkyle, -NHCO(C₁-C₆)alkyle, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyle)₂, -NHSO₂(C₁-C₆)alkyle, -N(SO₂CF₃)₂, -N-HCO₂(C₁-C₆)alkyle, (C₃-C₁₀)cycloalkyle, -SR²⁰, -SOR²⁰, -SO₂R²⁰, -SO₂NH(C₁-C₆ alkyle), -OSO₂(C₁-C₆)alkyle, -OSO₂CF₃, hydroxy(C₁-C₆)alkyle, -CONR¹⁷R¹⁸, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyle, -CO₂R¹⁷, -Si(CH₃)₃ ou -B(OC(CH₃)₂)₂ ;

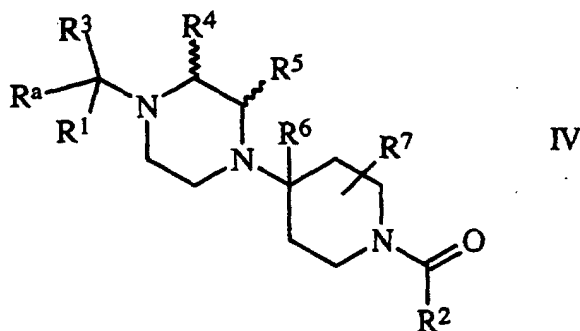
R¹² représente un groupe alkyle en C₁ à C₆, -NH₂ ou R¹⁴-phényle,

R¹⁴ représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes alkyle en C₁ à C₆, -CF₃, -CO₂R¹⁷, -CN et alcoxy en C₁ à C₆,

R¹⁵ et R¹⁶ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, ou bien R¹⁵ et R¹⁶ représentent ensemble un groupe alkylène en C₂ à C₅ et forment avec l'atome de carbone auquel ils sont liés un noyau spiro ayant 3 à 6 atomes de carbone,

R¹⁷, R¹⁸ et R¹⁹ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, et R²⁰ représente un groupe alkyle en C₁ à C₆ ou un groupe phényle,

et, pour les composés antagonistes CCR5 représentés par la formule développée IV :



et leurs sels pharmaceutiquement acceptables,

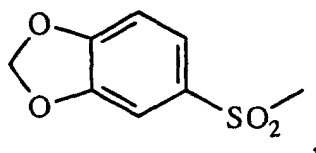
(1)R^a représente un groupe R^{8a}-phényle, R^{8b}-pyridyle, R^{8b}-thiophényle ou R⁸-naphtyle, R¹ représente un atome d'hydrogène ou un groupe alkyle en C₁ à C₆,

R² représente un groupe R⁹, R¹⁰, R¹¹-phényle, un groupe hétéroaryle à 6 chaînons, substitué par R⁹, R¹⁰, R¹¹, un groupe hétéroaryle N-oxyde à 6 chaînons, substitué par R⁹, R¹⁰, R¹¹, un groupe hétéroaryle à 5 chaînons, substitué par R¹², R¹³, un groupe naphthyle, un groupe fluorényle, un groupe diphénylméthyle, ou un groupe

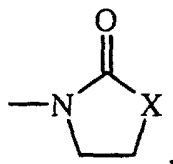


R³ représente un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, (C₁-C₆)alcoxy(C₁-C₆)alkyle, (C₃-C₁₀) cycloalkyle, (C₃-C₁₀)cycloalkyl(C₁-C₆)alkyle, R⁸-phényle, R⁸-phényl(C₁-C₆)alkyle, R⁸-naphtyle, R⁸-naphtyl (C₁-C₆)alkyle, R⁸-hétéroaryle ou R⁸-hétéroaryl(C₁-C₆)alkyle ;

R⁴, R⁵, R⁷ et R¹³ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, R⁶ représente un atome d'hydrogène, un groupe alkyle en C₁ à C₆ ou un groupe alcényle en C₂ à C₆, R⁸ représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes alkyle en C₁ à C₆, alcoxy en C₁ à C₆, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-phényle, R¹⁴-benzyle, CH₃C(=NOCH₃)-, CH₃C(=NOCH₂CH₃)-,

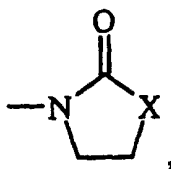


-NH₂, -NHCOCF₃, -NHCONH(C₁-C₆ alkyle), -NHCO(C₁-C₆ alkyle), -NHSO₂(C₁-C₆ alkyle), hétéroaryle à 5 chaînons et



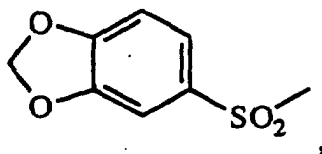
où X représente -O-, -NH- ou -N(CH₃)-,

R^{8a} représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes -CF₃, CF₃O-, -CN, CF₃SO₂-, R¹⁴-phényle, -NHCOCF₃, hétéroaryle à 5 chaînons et

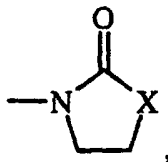


où X a les significations indiquées précédemment,

R^{8b} représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes -CF₃, CF₃O-, CH₃C(O)-, -CN, CF₃SO₂-, R¹⁴-benzyle, CH₃C(=NOCH₃), CH₃C(=NOCH₂CH₃),



-NHCOCF₃, hétéroaryle à 5 chaînons et



où X a les significations indiquées précédemment,

R⁹ et R¹⁰ représentent chacun indépendamment un atome d'halogène ou un groupe alkyle en C₁ à C₆, -NR¹⁷R¹⁸, -OH, -CF₃, -OCH₃, -O-acyle, -OCF₃ ou -Si(CH₃)₃,

R¹¹ représente R⁹, un atome d'hydrogène ou un groupe phényle, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR¹⁷, pyridyle, pyridyl-N-oxyde, pyrimidinyle, pyrazinyle, -N(R¹⁷)CONR¹⁸R¹⁹, -NHCONH (chloro-(C₁-C₆)alkyle), -NHCONH(C₃-C₁₀)cycloalkyl(C₁-C₆)alkyle, -NHCO(C₁-C₆)alkyle, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyle)₂, -NHSO₂(C₁-C₆)alkyle, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyle, (C₃-C₁₀)cycloalkyle, -SR²⁰, -SOR²⁰, -SO₂R²⁰, -SO₂NH(C₁-C₆ alkyle), -OSO₂(C₁-C₆)alkyle, -OSO₂CF₃, hydroxy(C₁-C₆)alkyle, -CONR¹⁷R¹⁸, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyle, -CO₂R¹⁷, -Si(CH₃)₃ ou -B(OC(CH₃)₂)₂ ;

R¹² représente un groupe alkyle en C₁ à C₆, -NH₂ ou R¹⁴-phényle,

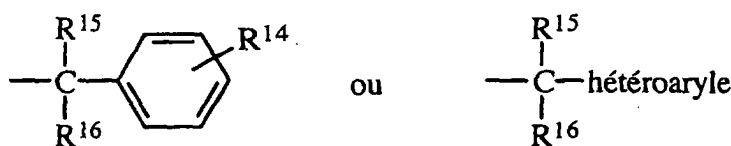
R¹⁴ représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes alkyle en C₁ à C₆, -CF₃, -CO₂R¹⁷, -CN et alcoxy en C₁ à C₆,

R¹⁵ et R¹⁶ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, où bien R¹⁵ et R¹⁶ représentent ensemble un groupe alkylène en C₂ à C₅ et forment avec l'atome de carbone auquel ils sont liés un noyau spiro ayant 3 à 6 atomes de carbone,

R¹⁷, R¹⁸ et R¹⁹ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, et R²⁰ représente un groupe alkyle en C₁ à C₆ ou un groupe phényle,

ou bien

(2) R^a représente un groupe R⁸-phényle, R⁸-pyridyle ou R⁸-thiophényle, R² représente un groupe fluorényle, diphénylméthyle,

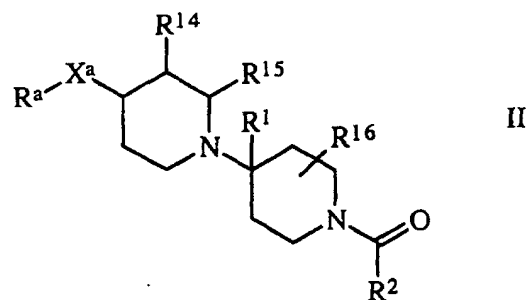
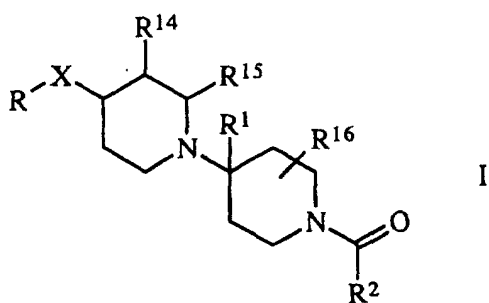


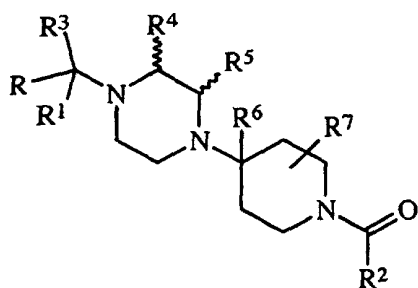
et R¹, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹ et R²⁰ ont les significations indiquées pour IV (1).

2. Utilisation selon la revendication 1, dans laquelle les patients sont des patients n'ayant pas subi de traitement ou des patients ayant fait l'expérience d'un traitement.
3. Utilisation selon la revendication 1 ou 2, dans laquelle les patients sont des patients de pédiatrie n'ayant pas subi de traitement ou ayant fait l'expérience d'un traitement.
4. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle l'interféron- α pégylé à administrer est l'interféron α -2a pégylé ou l'interféron α -2b pégylé.
5. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle le traitement comprend une quan-

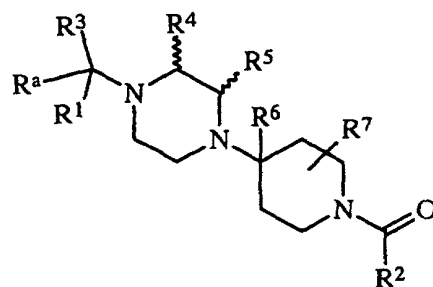
tité thérapeutiquement efficace d'interféron- α pégylé en association avec une quantité thérapeutiquement efficace d'un antagoniste CCR5, suffisante pour abaisser le niveau de ARN-VIH-1 chez de tels patients.

6. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle l'interféron- α pégylé administré est un interféron α -2b pégylé et la dose d'interféron α -2b pégylé à administrer est comprise dans l'intervalle allant d'environ 0,1 à environ 9,0 μg par kg et par semaine, de préférence dans l'intervalle allant d'environ 0,5 à environ 3,0 μg par kg et par semaine, et encore mieux dans l'intervalle allant d'environ 0,75 à environ 1,5 μg par kg et par semaine.
7. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle l'interféron- α pégylé à administrer est un interféron α -2a pégylé et la dose d'interféron α -2a pégylé à administrer est comprise dans l'intervalle allant d'environ 50 à environ 500 μg par semaine, de préférence dans l'intervalle allant d'environ 150 à environ 250 μg par semaine, ou de préférence dans l'intervalle allant d'environ 180 à environ 250 μg par semaine, et encore mieux dans l'intervalle allant d'environ 150 à environ 180 μg une fois par semaine.
8. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle le traitement comprend en outre une quantité thérapeutiquement efficace d'au moins un produit pris parmi la ribavirine, l'interleukine IL-2, l'interleukine IL-12, et le pentafuside, seule ou en combinaison avec une quantité thérapeutiquement efficace d'un médicament de thérapie anti-VIH-1.
9. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle les patients sont des patients ayant des infections simultanées par VIH-1 et VHC, et dans laquelle le traitement comprend en outre une quantité thérapeutiquement efficace de ribavirine et une quantité thérapeutiquement efficace d'un médicament de thérapie anti-VIH-1.
10. Utilisation selon la revendication 8 ou 9, dans laquelle la thérapie médicamenteuse anti-VIH-1 est une thérapie antirétrovirale hautement active (HAART).
11. Utilisation d'un interféron- α pégylé, d'un antagoniste CCR5, de ribavirine et de HAART pour la préparation d'un médicament destiné au traitement d'infections simultanées par VIH-1 et par VHC chez des patients, dans une quantité permettant d'abaisser les niveaux de ARN-VIH-1 et de ARN-VHC, utilisation dans laquelle l'antagoniste CCR5 est un composé représenté par l'une quelconque des formules développées I à IV suivantes :



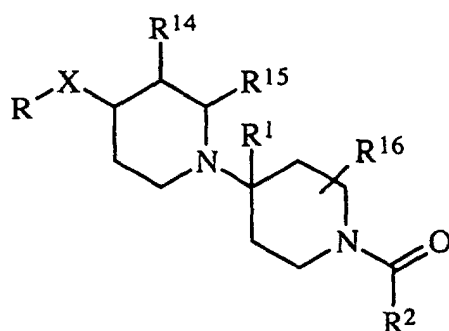


III



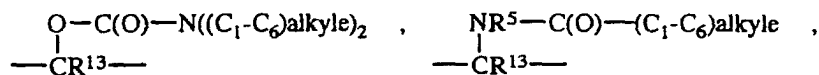
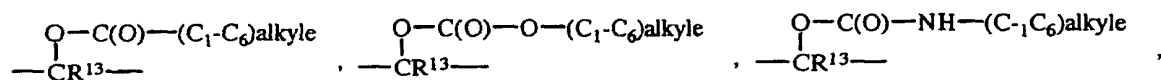
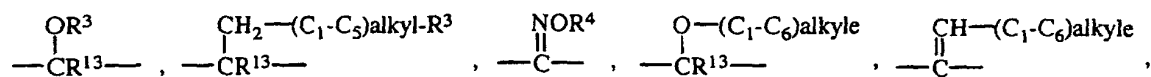
IV

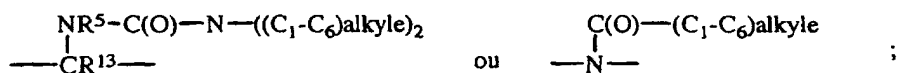
ou un sel pharmaceutiquement acceptable d'un tel composé,
et dans laquelle, pour les composés antagonistes CCR5 représentés par la formule développée 1 :



I

X représente un groupe $-C(R^{13})_2-$, $-C(R^{13})(R^{19})-$, $-C(O)-$, $-O-$, $-NH-$, $-N((C_1-C_6)\text{alkyle})-$,

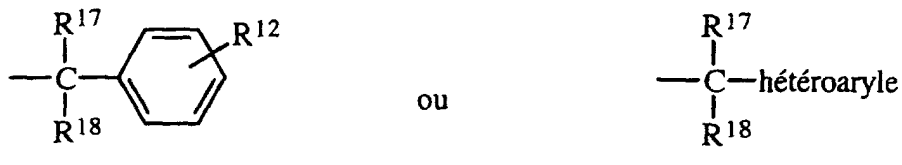




R représente un groupe R⁶-phényle, R⁶-pyridyle, R⁶-thiophényle ou R⁶-naphtyle,

R¹ représente un atome d'hydrogène, un groupe alkyle en C₁ à C₆ ou un groupe alcényle en C₂ à C₆,

R² représente un groupe R⁷, R⁸, R⁹-phényle, un groupe hétéroaryle à 6 chaînons, substitué par R⁷, R⁸, R⁹, un groupe hétéroaryle N-oxyde, à 6 chaînons, substitué par R⁷, R⁸, R⁹, un groupe hétéroaryle à 5 chaînons, substitué par R¹⁰, R¹¹, un groupe naphtyle, un groupe fluorényle, un groupe diphenylméthyle, ou un groupe

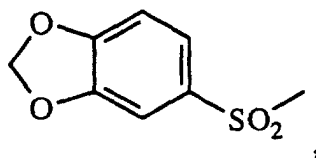


R³ représente un groupe R⁶-phényle, R⁶-hétéroaryle ou R⁶-naphtyle,

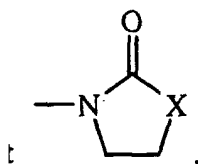
R⁴ représente un atome d'hydrogène, un groupe alkyle en C₁ à C₆, un groupe fluoroalkyle en C₁ à C₆, un groupe cyclopropylméthyle, ou un groupe -CH₂CH₂OH, -CH₂CH₂-O-(C₁-C₆)alkyle, -CH₂C(O)-O-(C₁-C₆)alkyle, -CH₂C(O)NH₂, -CH₂C(O)-NH(C₁-C₆)alkyle ou CH₂C(O)-N((C₁-C₆)alkyle)₂,

R⁵ et R¹¹ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆,

R⁶ représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes alkyle en C₁ à C₆, alcoxy en C₁ à C₆, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-phényle, R¹⁴-benzyle, CH₃C(=NOCH₃)-, CH₃C(=NOCH₂CH₃)-,



-NH₂, -NHCOCF₃, -NHCONH(C₁-C₆ alkyle), -NHCO(C₁-C₆ alkyle), -NHSO₂(C₁-C₆ alkyle), hétéroaryle à 5 chaînons et



où X représente -O-, -NH- ou -N(CH₃)-,

R⁷ et R⁸ représentent chacun indépendamment un atome d'halogène ou un groupe alkyle en C₁ à C₆, -NR²⁰R²¹, -OH, -CF₃, -OCH₃, -O-acyl ou -OCF₃,

R⁹ représente R⁷, un atome d'hydrogène ou un groupe phényle, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR²⁰, pyridyle, pyridyl-N-oxyde, pyrimidinyle, pyrazinyle, -N(R²⁰)-CONR²¹R²², -NHCONH(chloro-(C₁-C₆)alkyle), -NHCONH((C₃-C₁₀)-cycloalkyl(C₁-C₆)alkyle), -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyl)₂, -NHSO₂(C₁-C₆)alkyle, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyle, (C₃-C₁₀)cycloalkyle, -SR²³, -SOR²³, -SO₂R²³, -SO₂NH(C₁-C₆)alkyle, -OSO₂(C₁-C₆)alkyle, -OSO₂CF₃, hydroxy(C₁-C₆)alkyle, -CONR²⁰R²¹, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyle, -CO₂R²⁰, -Si(CH₃)₃ ou -B(OC(CH₃)₂)₂,

R¹⁰ représente un groupe alkyle en C₁ à C₆, -NH₂ ou R¹²-phényle,

R¹² représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les

groupes alkyle en C₁ à C₆, -CF₃, -CO₂R₂₀, -CN, et alcoxy en C₁ à C₆,

R¹³, R¹⁴, R¹⁵ et R¹⁶ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆,

R¹⁷ et R¹⁸ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, ou bien

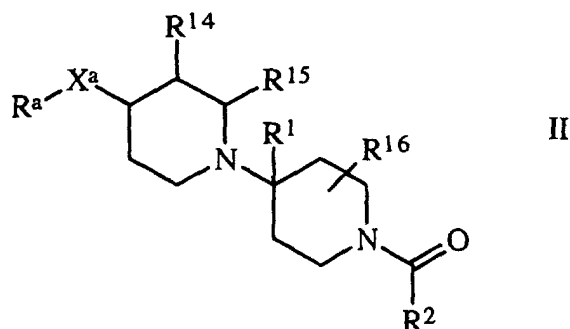
R¹⁷ et R¹⁸ représentent ensemble un groupe alkylène en C₂ à C₅ et forment avec l'atome de carbone auquel ils sont liés un noyau spiro ayant 3 à 6 atomes de carbone,

R¹⁹ représente un groupe R⁶-phényle, R⁶-hétéroaryle, R⁶-naphtyle, (C₃-C₁₀)cycloalkyle, (C₃-C₁₀)cycloalkyl (C₁-C₆)alkyle ou (C₁-C₆)alkoxy(C₁-C₆)alkyle,

R²⁰, R²¹ et R²² représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, et

R²³ représente un groupe alkyle en C₁ à C₆ ou un groupe phényle,

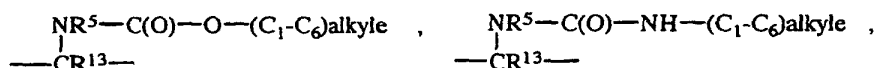
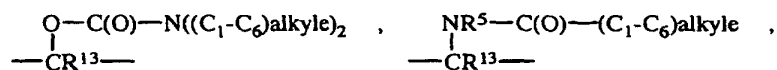
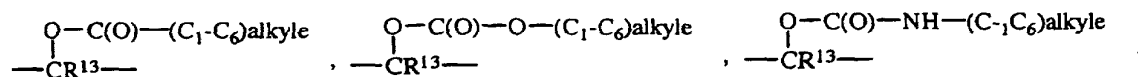
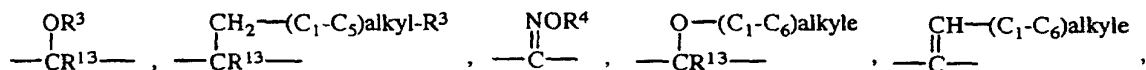
pour les composés antagonistes CCR5 représentés par la formule développée II :

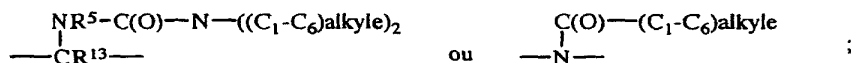


et leurs sels pharmaceutiquement acceptables,

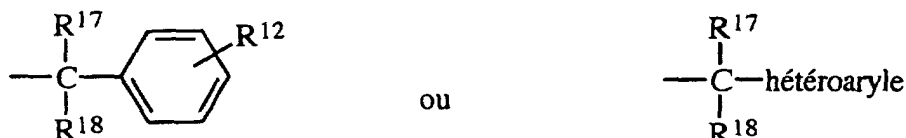
(1)X^a représente un groupe

-C(R¹³)₂-, -C(R¹³)(R¹⁹)-, -C(O)-, -O-, -NH-, -N((C₁-C₆)alkyle)-,

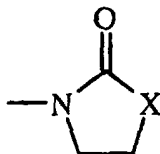




R^a représente un groupe R^{6a}-phényle, R^{6a}-pyridyle, R^{6a}-thiophényle ou R⁶-naphtyle,
 R¹ représente un atome d'hydrogène, un groupe alkyle en C₁ à C₆ ou un groupe alcényle en C₂ à C₆,
 R² représente un groupe R⁷, R⁸, R⁹-phényle, un groupe hétéroaryle à 6 chaînons, substitué par R⁷, R⁸, R⁹,
 un groupe hétéroaryle N-oxyde à 6 chaînons, substitué par R⁷, R⁸, R⁹, un groupe hétéroaryle à 5 chaînons,
 substitué par R¹⁰, R¹¹, un groupe naphtyle, un groupe fluorényle, un groupe diphenylméthyle, ou un groupe



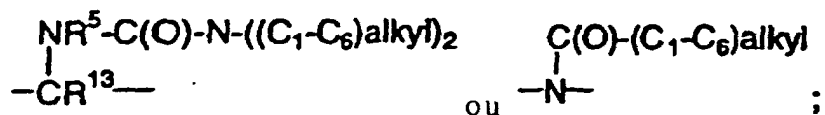
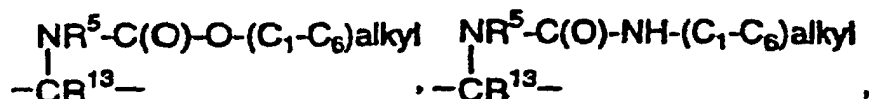
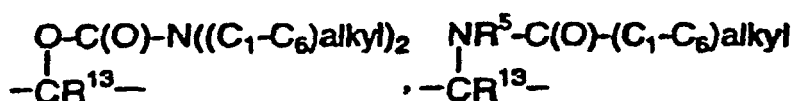
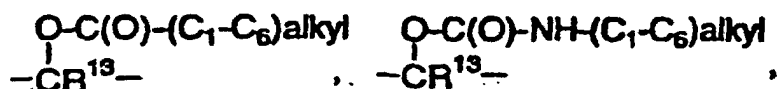
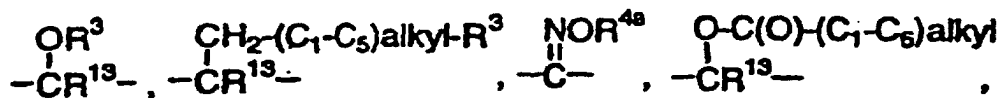
R³ représente un groupe R¹⁰-phényle, pyridyle, pyrimidyle, pyrazinyle ou thiazolyle,
 R⁴ représente un atome d'hydrogène, un groupe alkyle en C₁ à C₆, un groupe fluoroalkyle en C₁ à C₆, un
 groupe cyclopropylméthyle, ou un groupe -CH₂CH₂OH, -CH₂CH₂-O-(C₁-C₆)alkyle, -CH₂C(O)-O-(C₁-C₆)alk-
 yle, -CH₂C(O)NH₂, -CH₂C(O)-NH(C₁-C₆)alkyle ou CH₂C(O)-N((C₁-C₆)alkyle)₂,
 R⁵ et R¹¹ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆,
 R^{6a} représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et
 les groupes -CF₃, CF₃O-, -CN, CF₃SO₂-, R¹²-phényle, -NHCOCF₃, hétéroaryle à 5 chaînons et



où X représente -O-, -NH- ou -N(CH₃)-,
 R⁶ représente R^{6a} ou CH₃SO₂-,
 R⁷ et R⁸ représentent chacun indépendamment un atome d'halogène ou un groupe alkyle en C₁ à C₆,
 -NR²⁰R²¹, -OH-, -CF₃, -OCH₃, -O-acyl ou -OCF₃,
 R⁹ représente R⁷, un atome d'hydrogène, ou un 'groupe phényle, -NO₂, -CN, -CH₂F, -CHF₂, -CHO,
 -CH=NOR²⁰, pyridyle, pyridyl-N-oxyde, pyrimidinyle, pyrazinyle, -N(R²⁰)-CONR²¹R²², -NHCONH
 (chloro-(C₁-C₆)alkyle), -NHCONH((C₃-C₁₀)-cycloalkyl(C₃-C₆)alkyle), -NHCO(C₁-C₆)alkyl, -NHCOCF₃,
 -NHSO₂N((C₁-C₆)alkyl)₂, -NHSO₂(C₁-C₆)alkyle, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyle, (C₃-C₁₀)cycloalkyle,
 -SR²³, -SOR²³, -SO₂R²³, -SO₂NH(C₁-C₆ alkyle), -OSO₂(C₁-C₆)alkyle, -OSO₂CF₃, hydroxy(C₁-C₆)alkyle,
 -CONR²⁰R²¹, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyle, -CO₂R²⁰, -Si(CH₃)₃ ou -B(OC(CH₃)₂)₂,
 R¹⁰ représente un groupe alkyle en C₁ à C₆, -NH₂ ou R¹²-phényle,
 R¹² représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et
 les groupes alkyle en C₁ à C₆, -CF₃, -CO₂R²⁰, -CN et alcoxy en C₁ à C₆.
 R¹³, R¹⁴, R¹⁵ et R¹⁶ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁
 à C₆,
 R¹⁷ et R¹⁸ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, ou
 bien R¹⁷ et R¹⁸ représentent ensemble un groupe alkylène en C₂ à C₅ et forment avec l'atome de carbone
 auquel ils sont liés un noyau spiro ayant 3 à 6 atomes de carbone,
 R¹⁹ représente un groupe R⁶-phényle, R⁶-hétéroaryle, R⁶-naphtyle, (C₃-C₁₀)cycloalkyle, (C₃-C₁₀)cycloalkyl
 (C₁-C₆)alkyle ou (C₁-C₆)alcoxy(C₁-C₆)alkyle,
 R²⁰, R²¹ et R²² représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à
 C₆, et R²³ représente un groupe alkyle en C₁ à C₆ ou un groupe phényle,
 ou bien
 (2) :

X^a représente un groupe

-C(R¹³)(R¹⁹), -C(O)-, -O-, -NH-, -N((C₁-C₆)alkyl)-,



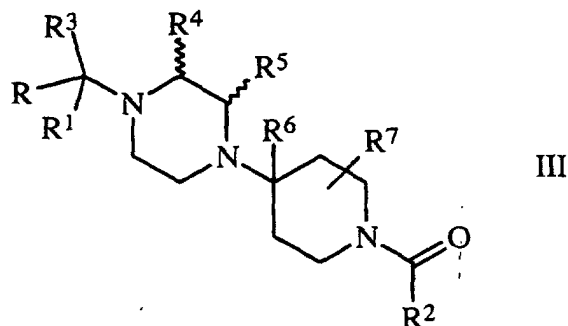
R^a représente un groupe R^{6b}-phényle, un groupe R^{6b}-pyridyle ou R^{6b}-thiophényle,

R^{4a} représente un groupe fluoroalkyle en C₁ à C₆, un groupe cyclopropylméthyle, ou un groupe -CH₂CH₂OH, -CH₂CH₂-O-(C₁-C₆)alkyl, -CH₂C(O)-O-(C₁-C₆)alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH-(C₁-C₆)alkyl ou -CH₂C(O)-N((C₁-C₆)alkyl)₂;

R^{6b} représente un groupe CH₃SO₂-, et

R¹, R², R³, R⁵, R¹⁴, R¹⁵, R¹⁶ et R¹⁹ ont les significations indiquées pour II (1),

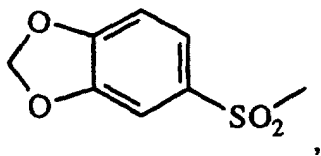
pour les composés antagonistes CCR5 représentés par la formule développée III :



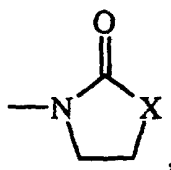
R représente un groupe R⁸-phényle, R⁸-pyridyle, R⁸-thiophényle ou R⁸-naphtyle,
 R¹ représente un atome d'hydrogène ou un groupe alkyle en C₁ à C₆,
 R² représente un groupe R⁹, R¹⁰, R¹¹-phényle, un groupe hétéroaryle à 6 chaînons, substitué par R⁹,
 R¹⁰, R¹¹, un groupe hétéroaryle N-oxyde à 6 chaînons, substitué par R⁹, R¹⁰, R¹¹, un groupe hétéroaryle
 à 5 chaînons, substitué par R¹², R¹³, un groupe naphtyle, un groupe fluorényle, un groupe diphénylmé-
 thyle, ou un groupe



R³ représente un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, (C₁-C₆)alcoxy(C₁-C₆)alkyle,
 (C₃-C₁₀)cycloalkyle, (C₃-C₁₀)cycloalkyl(C₁-C₆)alkyle, R⁸-phényle, R⁸-phényl(C₁-C₆)alkyle, R⁸-naphtyle,
 R⁸-naphtyl(C₁-C₆)alkyle, R⁸-hétéroaryle ou R⁸-hétéroaryl(C₁-C₆)alkyle ;
 R⁴, R⁵, R⁷ et R¹³ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en
 C₁ à C₆,
 R⁶ représente un atome d'hydrogène, un groupe alkyle en C₁ à C₆ ou un groupe alcényle en C₂ à C₆,
 R⁸ représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène,
 et les groupes alkyle en C₁ à C₆, alcoxy en C₁ à C₆, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-,
 R¹⁴-phényle, R¹⁴-benzyle, CH₃C(=NOCH₃)-, CH₃C(=NOCH₂CH₃)-,



-NH₂, -NHCOCF₃, -NHCONH(C₁-C₆ alkyle), -NHCO(C₁-C₆ alkyle), -NHSO₂(C₁-C₆ alkyle), hétéroaryle à
 5 chaînons et



où X représente -O-, -NH- ou -N(CH₃)-,

R⁹ et R¹⁰ représentent chacun indépendamment un atome d'halogène ou un groupe alkyle en C₁ à C₆, -NR¹⁷R¹⁸, -OH, -CF₃, -OCH₃, -O-acyle, -OCF₃ ou -Si(CH₃)₃,

R¹¹ représente R⁹, un atome d'hydrogène, ou un groupe phényle, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR¹⁷, pyridyle, pyridyl-N-oxyde, pyrimidinyle, pyrazinyle, -N(R¹⁷)CONR¹⁸R¹⁹, -NHCONH (chloro-(C₁-C₆)alkyle), -NHCONH (C₃-C₁₀)cycloalkyl(C₁-C₆)alkyle, -NHCO(C₁-C₆)alkyle, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyle)₂, -NHSO₂(C₁-C₆)alkyle, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyle, (C₃-C₁₀)cycloalkyle, -SR²⁰, -SOR²⁰, -SO₂R²⁰, -SO₂NH(C₁-C₆)alkyle, -OSO₂(C₁-C₆)alkyle, -OSO₂CF₃, hydroxy(C₁-C₆)alkyle, -CONR¹⁷R¹⁸, -CON(CH₂CH₂-O-CH₃)₂, OCONH(C₁-C₆)alkyle, -CO₂R¹⁷, -Si(CH₃)₃ ou -B(OC(CH₃)₂)₂ ;

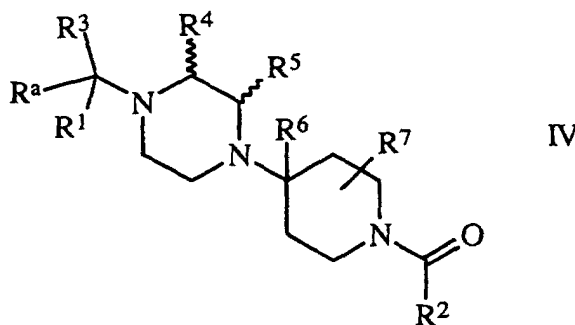
R¹² représente un groupe alkyle en C₁ à C₆, -NH₂ ou R¹⁴-phényle,

R¹⁴ représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes alkyle en C₁ à C₆, -CF₃, -CO₂R¹⁷, -CN et alcoxy en C₁ à C₆,

R¹⁵ et R¹⁶ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, ou bien R¹⁵ et R¹⁶ représentent ensemble un groupe alkylène en C₂ à C₅ et forment avec l'atome de carbone auquel ils sont liés un noyau spiro ayant 3 à 6 atomes de carbone,

R¹⁷, R¹⁸ et R¹⁹ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, et R²⁰ représente un groupe alkyle en C₁ à C₆ ou un groupe phényle,

et, pour les composés antagonistes CCR5 représentés par la formule développée IV :



et leurs sels pharmaceutiquement acceptables,

(1)R^a représente un groupe R^{8a}-phényle, R^{8b}-pyridyle, R^{8b}-thiophényle ou R⁸-naphtyle,

R¹ représente un atome d'hydrogène ou un groupe alkyle en C₁ à C₆,

R² représente un groupe R⁹, R¹⁰, R¹¹-phényle, un groupe hétéroaryle à 6 chaînons, substitué par R⁹, R¹⁰, R¹¹, un groupe hétéroaryle N-oxyde à 6 chaînons, substitué par R⁹, R¹⁰, R¹¹, un groupe hétéroaryle à 5 chaînons, substitué par R¹², R¹³, un groupe naphtyle, un groupe fluorényle, un groupe diphenylméthyle, ou un groupe

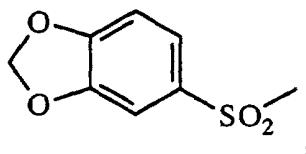


R³ représente un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, (C₁-C₆)alcoxy(C₁-C₆)alkyle, (C₃-C₁₀)cycloalkyle, (C₃-C₁₀)cycloalkyl(C₁-C₆)alkyle, R⁸-phényle, R⁸-phényl(C₁-C₆)alkyle, R⁸-naphtyle, R⁸-naphtyl(C₁-C₆)alkyle, R⁸-hétéroaryle ou R⁸-hétéroaryl(C₁-C₆)alkyle ;

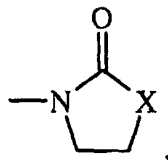
R⁴, R⁵, R⁷ et R¹³ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, R⁶ représente un atome d'hydrogène, un groupe alkyle en C₁ à C₆ ou un groupe alcényle en C₂ à C₆,

R⁸ représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes alkyle en C₁ à C₆, alcoxy en C₁ à C₆, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-

phényle, R¹⁴-benzyle, CH₃C(=NOCH₃)-, CH₃C(=NOCH₂CH₃)-,

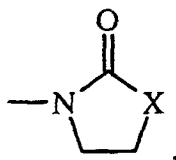


-NH₂, -NHCOCF₃, -NHCONH(C₁-C₆ alkyle), -NHCO(C₁-C₆ alkyle), -NHSO₂(C₁-C₆ alkyle), hétéroaryle à 5 chaînons et



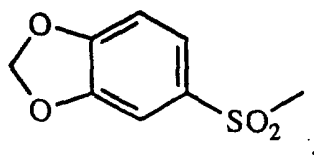
où X représente -O-, -NH- ou -N(CH₃)-,

R^{8a} représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes -CF₃, CF₃O-, -CN, CF₃SO₂-, R¹⁴-phényle, -NHCOCF₃, hétéroaryle à 5 chaînons et

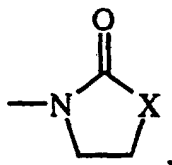


où X a les significations indiquées précédemment,

R^{8b} représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes -CF₃, CF₃O-, CH₃C(O)-, -CN, CF₃SO₂-, R¹⁴-benzyle, CH₃C(=NOCH₃), CH₃C(=NOCH₂CH₃),



-NHCOCF₃, hétéroaryle à 5 chaînons et



où X a les significations indiquées précédemment,

R⁹ et R¹⁰ représentent chacun indépendamment un atome d'halogène ou un groupe alkyle en C₁ à C₆,

-NR¹⁷R¹⁸, -OH, -CF₃, -OCH₃, -O-acyle, -OCF₃ ou -Si(CH₃)₃,

R¹¹ représente R⁹, un atome d'hydrogène ou un groupe phényle, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR¹⁷, pyridyle, pyridyl-N-oxyde, pyrimidinyle, pyrazinyle, -N(R¹⁷)CONR¹⁸R¹⁹, -NHCONH (chloro-(C₁-C₆)alkyle), -NHCONH(C₃-C₁₀):cycloalkyl(C₁-C₆)alkyle, -NHCO(C₁-C₆)alkyle, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyle)₂, -NHSO₂(C₁-C₆)alkyle, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyle, (C₃-C₁₀)cycloalkyle,

-SR²⁰, -SOR²⁰, -SO₂R²⁰, -SO₂NH(C₁-C₆ alkyle), -OSO₂(C₁-C₆)alkyle, -OSO₂CF₃, hydroxy(C₁-C₆)alkyle, -CONR¹⁷R¹⁸, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyle, -CO₂R¹⁷, -Si(CH₃)₃ ou -B(OC(CH₃)₂)₂;

R¹² représente un groupe alkyle en C₁ à C₆, -NH₂ ou R¹⁴-phényle,

R¹⁴ représente 1 à 3 substituants choisis indépendamment parmi les atomes d'hydrogène et d'halogène, et les groupes alkyle en C₁ à C₆, -CF₃, -CO₂R¹⁷, -CN et alcoxy en C₁ à C₆,

R¹⁵ et R¹⁶ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, ou bien R¹⁵ et R¹⁶ représentent ensemble un groupe alkylène en C₂ à C₅ et forment avec l'atome de carbone auquel ils sont liés un noyau spiro ayant 3 à 6 atomes de carbone,

R¹⁷, R¹⁸ et R¹⁹ représentent chacun indépendamment un atome d'hydrogène ou un groupe alkyle en C₁ à C₆, et R²⁰ représente un groupe alkyle en C₁ à C₆ ou un groupe phényle,

ou bien

(2)R^a représente un groupe R⁸-phényle, R⁸-pyridyle ou R⁸-thiophényle, R² représente un groupe fluorényle, diphénylméthyle,



et R¹, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹ et R²⁰ ont les significations indiquées pour IV (1).

12. Utilisation selon la revendication 11, dans laquelle les patients sont des patients ayant fait l'expérience d'un traitement ou des patients n'ayant pas subi de traitement.
13. Utilisation selon la revendication 11, dans laquelle les patients sont des patients de pédiatrie ayant fait l'expérience d'un traitement ou n'ayant pas subi de traitement.
14. Utilisation selon la revendication 11, dans laquelle l'interféron- α pégylé à administrer est l'interféron α -2a pégylé ou l'interféron α -2b pégylé.
15. Utilisation selon la revendication 14, dans laquelle l'interféron- α pégylé à administrer est un interféron α -2b pégylé et la dose d'interféron α -2b pégylé à administrer est comprise dans l'intervalle allant d'environ 0,1 à environ 9,0 μg par kg et par semaine, de préférence dans l'intervalle allant d'environ 0,5 à environ 3,0 μg par kg et par semaine, et encore mieux dans l'intervalle allant d'environ 0,75 à environ 1,5 μg par kg et par semaine.
16. Utilisation selon la revendication 14, dans laquelle l'interféron- α pégylé à administrer est un interféron α -2a pégylé et la dose d'interféron α -2a pégylé à administrer est comprise dans l'intervalle allant d'environ 50 à environ 500 μg par semaine, de préférence dans l'intervalle allant d'environ 150 à 250 μg par semaine et encore mieux dans l'intervalle allant d'environ 180 à environ 250 μg par semaine, ou de préférence dans l'intervalle allant d'environ 150 à environ 180 μg par semaine.
17. Utilisation selon la revendication 11, dans laquelle le patient est un patient de pédiatrie et la quantité de ribavirine administrée est comprise dans l'intervalle allant d'environ 8 à environ 15 mg par kg et par jour, l'administration ayant lieu en doses divisées.
18. Utilisation selon la revendication 11, dans laquelle la dose de ribavirine est d'environ 400 à environ 1600 mg/jour, de préférence d'environ 600 à environ 1200 mg/jour ou d'environ 800 à environ 1200 mg/jour, et en particulier d'environ 1000 à environ 1200 mg/kg et par jour.