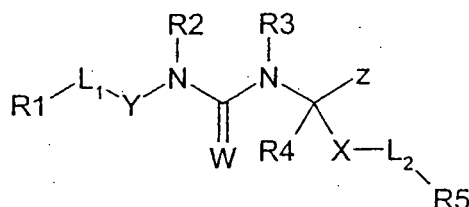


ABSTRACT

162162

UREA DERIVATIVES AS INTEGRIN $\alpha 4$ ANTAGONISTS

5 Novel antagonists of $\alpha 4\beta 1$ integrin and/or $\alpha 4\beta 7$ integrin of the general Formula I:

**Formula I**

10 or a pharmaceutically acceptable salt thereof,
wherein:

15 R1 is C₃₋₁₀alkyl, C₃₋₁₀alkenyl, C₃₋₁₀alkynyl, cycloalkyl, cycloalkyl-C₁₋₁₀alkyl, cycloalkyl-C₂₋₁₀alkenyl, cycloalkyl-C₂₋₁₀alkynyl, heterocyclyl, heterocyclyl-C₁₋₁₀alkyl, heterocyclyl-C₂₋₁₀alkenyl, heterocyclyl-C₂₋₁₀alkynyl, aryl, aryl-C₁₋₁₀alkyl, aryl-C₂₋₁₀alkenyl, aryl-C₂₋₁₀alkynyl, heteroaryl, heteroaryl-C₁₋₁₀alkyl, heteroaryl-C₂₋₁₀alkenyl, or heteroaryl-C₂₋₁₀alkynyl; wherein said alkyl, alkenyl, and alkynyl groups or moieties are unsubstituted
20 or substituted with one to four substituents, which may be the same or different and are independently selected from Ra; and wherein said cycloalkyl, heterocyclyl, aryl and heteroaryl groups or moieties are unsubstituted or substituted with one to four substituents, which may be the same or different and are independently selected from Rb;

25 R2 is hydrogen, C₁₋₆alkyl, C₀₋₂alkylcycloalkyl, C₀₋₂alkylaryl or C₀₋₂alkylheteroaryl wherein said aryl and heteroaryl groups or moieties are unsubstituted or substituted with one to four substituents, which may be the same or different and are independently selected from Ra;

30 R3 and R4 are independently hydrogen or C₁₋₄alkyl;

R2 and R3, together with the atoms to which they are attached, may form a 4-8 membered ring;



G00002

R5 is C₁₋₆alkyl, cycloalkyl, cycloalkyl-C₁₋₄alkyl, heterocyclyl, heterocyclyl-C₁₋₄alkyl, aryl, aryl-C₁₋₄alkyl, heteroaryl, or heteroaryl-C₁₋₄alkyl; wherein said alkyl groups or moieties are unsubstituted or substituted with one to four substituents, which may be the same or different and are independently selected from Ra; and wherein said cycloalkyl, heterocyclyl, aryl and heteroaryl groups or moieties are unsubstituted or substituted with one to four substituents, which may be the same or different and are independently selected from Rb;

L1 is -S-, -S(O)-, -S(O)₂-, -C(O)-, -C(O)O-, -C(S)-, -N(Rc)-, -CH₂-, -CH₂N(Rc)-, -CON(Rc)-, -CSN(Rc)-, -N(Rc)CO-, -N(Rc)CS-, -S(O)₂N(Rc)- or -N(Rc)S(O)₂-;

L2 is a covalent bond, -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -N(Rc)-, -CON(Rc)-, -OC(O)N(Rc)-, -CSN(Rc)-, -N(Rc)CO-, -N(Rc)C(O)O-, -N(Rc)CS-, -S(O)₂N(Rc)-, -N(Rc)S(O)₂-, -N(Rc)CON(Rc)-, or -N(Rc)CSN(Rc)-, wherein if two Rc substituents are present, these may be the same or different;

W is O, S, NH, N(Rc), or NCN;

X is -(CH₂)_naryl-, or -(CH₂)_nheteroaryl-; wherein said aryl and heteroaryl moieties are unsubstituted or substituted with one to four substituents, which may be the same or different and are independently selected from Rb;

Y is monocyclic aryl, or monocyclic heteroaryl containing one or two heteroatoms selected from N, O and S, wherein said aryl and heteroaryl moieties are unsubstituted or substituted with one to four substituents, which may be the same or different and are independently selected from Rb;

Z is -C(O)ORd, -P(O)₂ORd, -S(O)₂ORd, -S(O)₂N(Rd)(Rd), -C(O)NH₂, -C(O)N(Re)S(O)₂Rd, -S(O)₂N(Re)C(O)Rd, -5-tetrazolyl, or -C(O)Rd; wherein if two Rd groups are present these may be the same or different;

Ra is -OH, -ORe, -NO₂, halogen, -S(O)Re, -S(O)₂Re, -SRe, -S(O)₂ORe, -S(O)NreRe, -S(O)₂NreRe, -NreRe, -O(CReRe)_mNreRe, -C(O)Re, -CO₂Re, -CO₂(CReRe)_mCONreRe, -OC(O)Re, -CN, -C(O)NreRe, -NreC(O)Re, -OC(O)NreRe, -NreC(O)ORe, -NreC(O)NreRe, -CRe(N-ORe), -CFH₂, -CF₂H, Ra, or -CF₃; wherein if two or more Re groups are present these may be the same or different;

Rb is a group selected from -OH, -ORe, -NO₂, halogen, -S(O)Re, -S(O)₂Re, -SRe, -S(O)₂ORe, -S(O)NReRe, -S(O)₂NReRe, -NReRe, -O(CReRe)_mNReRe, -C(O)Re, -CO₂Re, -CO₂(CReRe)_mCONReRe, -OC(O)Re, -CN, -C(O)NReRe, -NReC(O)Re, -OC(O)NReRe, -NReC(O)ORe, -NReC(O)NReRe, -CRe(N-ORe), -CFH₂, -CF₂H, Ra, -CF₃, C₁₋₆alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, cycloalkyl, cycloalkyl-C₁₋₄alkyl, heterocyclyl, heterocyclyl-C₁₋₄alkyl, aryl, aryl-C₁₋₄alkyl, heteroaryl or heteroaryl-C₁₋₄alkyl; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl groups or moieties are unsubstituted or substituted with one to four substituents which may be the same or different and are independently selected from Ra;

10

Rc is hydrogen, C₁₋₁₀ alkyl or cycloalkyl; wherein said alkyl or cycloalkyl groups or moieties are unsubstituted or substituted with one to four substituents which may be the same or different and are selected from Ra;

15

Rd is hydrogen, C₁₋₆alkyl, cycloalkyl, cycloalkyl-C₁₋₄alkyl, heterocyclyl, heterocyclyl-C₁₋₄alkyl, aryl, aryl-C₁₋₄alkyl, heteroaryl, or heteroaryl-C₁₋₄alkyl; wherein said alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl groups or moieties are unsubstituted or substituted with one to four substituents which may be the same or different and are independently selected from Ra;

20

Re is hydrogen, or C₁₋₄alkyl.

n is an integer from 0 to 2;

25

m is an integer from 1 to 6