Claims:

1. A covalent conjugate of an alpha amino acid ester and an inhibitor of the activity of the target intracellular enzyme p38 MAP kinase, wherein:

the ester group of the conjugate is hydrolysable by one or more intracellular carboxylesterase enzymes to the corresponding acid;

the nitrogen of the amino group of the amino acid ester is substituted but not directly linked to a carbonyl moiety, or is left unsubstituted; and

the alpha amino acid ester is conjugated to the inhibitor at a position remote from the binding interface between the inhibitor and the p38 MAP kinase enzyme, wherein the position of conjugation is remote when the conjugate has a potency in a cellular activity assay at least as high as that of the unconjugated inhibitor in the same assay, which cellular activity assay is a TNFα inhibition assay carried out in human whole blood.

2. A covalent conjugate of an alpha amino acid ester and an inhibitor of the activity of the target intracellular enzyme p38 MAP kinase, wherein:

the ester group of the conjugate is hydrolysable by one or more intracellular carboxylesterase enzymes to the corresponding acid;

the nitrogen of the amino group of the amino acid ester is substituted but not directly linked to a carbonyl moiety, or is left unsubstituted and

the alpha amino acid ester is conjugated to the inhibitor such that the binding mode of the conjugated inhibitor and the said corresponding acid to the p38 MAP kinase enzyme is the same as that of the unconjugated inhibitor, wherein the binding mode is the same when the conjugate has a potency in a cellular activity assay at least as high as that of the unconjugated inhibitor in the same assay, which cellular activity assay is a TNFα inhibition assay carried out in human whole blood.

3. A conjugate as claimed in claim 1 or claim 2 wherein the covalently conjugated alpha amino acid ester is not the C-terminal element of a dipeptide motif of the conjugated inhibitor.

4. A conjugate as claimed in any one of the preceding claims wherein the inhibitor is one which binds non-covalently to the p38 MAP kinase enzyme.

5. A conjugate as claimed in any one of the preceding claims wherein the alpha amino acid ester is covalently conjugated to the inhibitor through a linker radical.

6. A conjugate as claimed in any one of the preceding claims wherein the alpha amino acid ester is conjugated to the inhibitor via the amino group of the amino acid ester.

7. A conjugate as claimed in any one of claims 1 to 5 wherein the alpha amino acid ester is conjugated to the inhibitor via the alpha carbon of the amino acid ester.

8. A conjugate as claimed in any one of the preceding claims wherein the ester is hydrolysable by cells containing one or more of the intracellular carboxylesterase enzymes hCE-1, hCE-2 and hCE-3 to the corresponding alpha amino acid.

9. A conjugate as claimed in any one of claims 1 to 6 wherein the ester is hydrolysable by cells containing the intracellular carboxylesterase enzyme hCE-1 to the corresponding alpha amino acid and not by cells containing hCE-2 or hCE-3.

10. A conjugate as claimed in claim 9 wherein the nitrogen of the amino group of the amino acid ester is substituted but not directly linked to a carbonyl moiety.

11. A pharmaceutical composition comprising a conjugate as claimed in any of claims 1 to 10 and a pharmaceutically acceptable carrier.

12. A pharmaceutical composition as claimed in claim 11 which is adapted for topical administration and wherein in the conjugate (a) when the alpha amino acid ester is linked to the inhibitor via its amino group, the carbon adjacent to the alpha carbon of the alpha amino acid ester is monosubstituted, or (b) when the alpha amino acid ester is linked to the inhibitor via a carbon atom of the amino acid, the adjacent carbon atom to that carbon atom of the amino acid is unsubstituted.

13. A method of preparing a covalent conjugate for increasing or prolonging the intracellular potency and/or residence time of an inhibitor of the activity of the target intracellular enzyme p38 MAP kinase comprising structural modification of the inhibitor by covalent attachment thereto of an alpha amino acid ester at a position remote from the binding interface between the inhibitor and the p38 MAP kinase enzyme, the ester group of the conjugate being hydrolysable by one or more intracellular carboxylesterase enzymes to the corresponding acid;

wherein

the nitrogen of the amino group of the amino acid ester is substituted but not directly linked to a carbonyl moiety, or is left unsubstituted; and

the position of conjugation is remote when the conjugate has a potency in a cellular activity assay at least as high as that of the unconjugated inhibitor in the same assay, which cellular activity assay is a TNFα inhibition assay carried out in human whole blood.

14. A method of preparing a covalent conjugate for increasing or prolonging the intracellular potency and/or residence time of an inhibitor of the activity of the target intracellular enzyme p38 MAP kinase comprising structural modification of the inhibitor by covalent attachment thereto of an alpha amino acid ester such that the binding mode of the conjugated inhibitor and the said corresponding acid to the p38 MAP kinase enzyme is the same as that of the unconjugated inhibitor, the ester group of the conjugate being hydrolysable by one or more intracellular carboxylesterase enzymes to the corresponding acid;

wherein

the nitrogen of the amino group of the amino acid ester is substituted but not directly linked to a carbonyl moiety, or is left unsubstituted; and

the binding mode is the same when the conjugate has a potency in a cellular activity assay at least as high as that of the unconjugated inhibitor in the same assay, which cellular activity assay is a TNFα inhibition assay carried out in human whole blood.

15. A method according to claim 13 or claim 14 wherein the covalently conjugated alpha amino acid ester is not the C-terminal element of a dipeptide motif of the conjugated inhibitor.

16. A method according to any one of claims 13 to 15 wherein the inhibitor is one which binds non-covalently to the p38 MAP kinase enzyme.

17. A method according to any one of claims 13 to 16 wherein the alpha amino acid ester is covalently conjugated to the inhibitor through a linker radical.

18. A method according to any one of claims 13 to 17 wherein the alpha amino acid ester is conjugated to the inhibitor via the amino group of the amino acid ester.

19. A method according to any one of claims 13 to 17 wherein the alpha amino acid ester is conjugated to the inhibitor via the alpha carbon of the amino acid ester.

20. A method as claimed in any one of the claims 13 to 19 wherein the ester is hydrolysable by cells containing one or more of the intracellular carboxylesterase enzymes hCE-1, hCE-2 and hCE-3 to the corresponding alpha amino acid.

21. A method as claimed in any of claims 13 to 18 wherein the ester is hydrolysable by cells containing the intracellular carboxylesterase enzyme hCE-1 to the corresponding alpha amino acid and not by cells containing hCE-2 or hCE-3.

22. A method as claimed in claim 21 wherein the nitrogen of the amino group of the amino acid ester is substituted but not directly linked to a carbonyl moiety.

23. An *in vitro* method of selectively increasing or prolonging the intracellular potency of a inhibitor of the activity of the target intracellular enzyme p38 MAP kinase in macrophages and/or monocytes relative to other cell types, comprising treating a mixed population of cells *in vitro* or *in vivo* with a conjugate of the inhibitor as claimed in claim 10.

24. A covalent conjugate of an alpha amino acid ester and an inhibitor of the activity of the target intracellular enzyme p38 MAP kinase for use in a method of treatment of the human or animal body by therapy, wherein:

the ester group of the conjugate is hydrolysable by one or more intracellular carboxylesterase enzymes to the corresponding acid;

the nitrogen of the amino group of the amino acid ester is substituted but not directly linked to a carbonyl moiety, or is left unsubstituted; and

the alpha amino acid ester is conjugated to the inhibitor at a position remote from the binding interface between the inhibitor and the p38 MAP kinase enzyme, wherein the position of conjugation is remote when the conjugate has a potency in a cellular activity assay at least as high as that of the unconjugated inhibitor in the same assay, which cellular activity assay is a TNFα inhibition assay carried out in human whole blood.

25. A covalent conjugate of an alpha amino acid ester and an inhibitor of the activity of the target intracellular enzyme p38 MAP kinase for use in a method of treatment of the human or animal body by therapy, wherein:

the ester group of the conjugate is hydrolysable by one or more intracellular carboxylesterase enzymes to the corresponding acid;

the nitrogen of the amino group of the amino acid ester is substituted but not directly linked to a carbonyl moiety, or is left unsubstituted; and

the alpha amino acid ester is conjugated to the inhibitor such that the binding mode of the conjugated inhibitor and the said corresponding acid to the p38 MAP kinase enzyme is the same as that of the unconjugated inhibitor, wherein the binding mode is the same when the conjugate has a potency in a cellular activity assay at least as high as that of the unconjugated inhibitor in the same assay, which cellular activity assay is a TNFα inhibition assay carried out in human whole blood.

26. A covalent conjugate for use according to claim 24 or claim 25 wherein the covalent conjugate is as defined in any one of claims 3 to 10.

27. Use of a conjugate as claimed in any one of claims 1 to 8 in the manufacture of a medicament for increasing or prolonging the intracellular potency and/or residence time of an inhibitor of the activity of a p38 MAP kinase enzyme.

28. Use of a conjugate as claimed in claim 9 or claim 10 in the manufacture of a medicament for selectively increasing or prolonging the intracellular potency and/or residence time of an inhibitor of the activity of a p38 MAP kinase enzyme in macrophages and/or monocytes relative to other cell types.