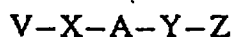


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ABSTRACT

VITAMIN B₁₂ MEDIATED ORAL DELIVERY SYSTEMS FOR GCSF AND EPO

The invention describes complexes between VB₁₂ analogues and either GCSF or EPO that retain both significant affinity for intrinsic factor (IF) in the VB₁₂ portion of the complex and significant bioactivity of the GCSF or EPO portion of the complex. The invention also concerns a process for the synthesis of these complexes. This is achieved at least in part, by using a spacer compound, which is linked covalantly between the VB₁₂ portion and the GCSF or EPO. The complexes preferably have the formula



wherein

V is vitamin B₁₂ or a vitamin B₁₂ analogue, or derivative, bonded to X either through a carboxylate group pendant to the corrin nucleus of VB₁₂ or through the central cobalt atom or to a functional group introduced onto the VB₁₂ molecule, X is selected from: -NHNH-,

-NH-, -O-, -S-, -SS- or -CH₂-, and A is an optionally substituted, saturated or unsaturated, branched or linear, C₁₋₅₀ alkylene, cycloalkylene or aromatic group, optionally with one or more carbons within the linear chain being replaced with N, O or S, and wherein the optional substituents are selected from carbonyl, carboxy, hydroxy, amino and other groups, and Y is the covalent linkage between A and Z where Y is selected from -NHCO-

-CONH-, -CONHNHCO-, -N=N-, -N=CH-, -NHCH₂-, -NHN=CH-, -NHNHCH₂-, -SS-, -SCH₂-, -CH₂S-, -NHCRNH-, -COO-, -OCO-, and R is O, S or NH₂, and Z is GCSF or EPO. The invention also describes reagents that can be used as probes for the detection of buried thiol groups of a protein or peptide, said reagent comprising a complex of either vitamin B₁₂ (or an analogue thereof) or more generally of any instrumentally or visually detectable label, covalently linked to a diradical spacer, said spacer having a terminal reactive group capable of forming a disulphide bond with a free thiol in said protein or peptides.

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