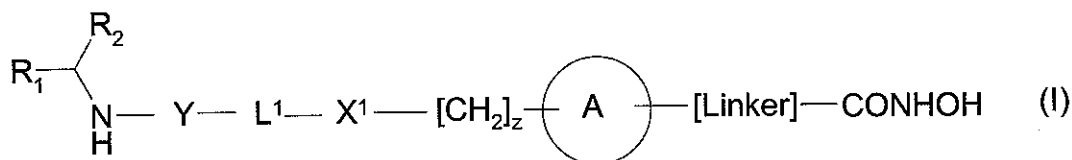


Enzyme Inhibitors

Abstract

Compounds of formula (I) are inhibitors of histone deacetylase activity, and are useful in the treatment of, for example, cancers::



wherein R_1 is a carboxylic acid group ($-COOH$), or an ester group which is hydrolysable by one or more intracellular carboxyesterase enzymes to a carboxylic acid group; R_2 is the side chain of a natural or non-natural alpha amino acid; Y is a bond, $-C(=O)-$, $-S(=O)_2-$, $-C(=O)O-$, $-C(=O)NR_3-$, $-C(=S)-NR_3-$, $-C(=NH)NR_3$ or $-S(=O)_2NR_3-$ wherein R_3 is hydrogen or optionally substituted C_1 - C_6 alkyl; L^1 is a divalent radical of formula $-(Alk^1)_m(Q)_n(Alk^2)_p-$ wherein m , n and p are independently 0 or 1, Q is (i) an optionally substituted divalent mono- or bicyclic carbocyclic or heterocyclic radical having 5 - 13 ring members, or (ii), in the case where both m and p are 0, a divalent radical of formula $-X^2-Q^1-$ or $-Q^1-X^2-$ wherein X^2 is $-O-$, $S-$ or NR^A- wherein R^A is hydrogen or optionally substituted C_1 - C_3 alkyl, and Q^1 is an optionally substituted divalent mono- or bicyclic carbocyclic or heterocyclic radical having 5 - 13 ring members, Alk^1 and Alk^2 independently represent optionally substituted divalent C_3 - C_7 cycloalkyl radicals, or optionally substituted straight or branched, C_1 - C_6 alkylene, C_2 - C_6 alkenylene, or C_2 - C_6 alkynylene radicals which may optionally contain or terminate in an ether ($-O-$), thioether ($-S-$) or amino ($-NR^A-$) link wherein R^A is hydrogen or optionally substituted C_1 - C_3 alkyl; X^1 represents a bond; $-C(=O)$; or $-S(=O)_2-$; $-NR_4C(=O)-$, $-C(=O)NR_4-$, $-NR_4C(=O)NR_5-$, $-NR_4S(=O)_2-$, or $-S(=O)_2NR_4-$ wherein R_4 and R_5 are independently hydrogen or optionally substituted C_1 - C_6 alkyl; z is 0 or 1; A represents an optionally substituted mono-, bi- or tri-cyclic carbocyclic or heterocyclic ring system wherein the radicals $R_1R_2NH-Y-L^1-X^1-[CH_2]_z-$ and $HONHCO-[LINKER]-$ are attached different ring atoms; and $-[Linker]-$ represents a divalent linker radical linking a ring atom in A with the hydroxamic acid group $CONHOH$, the length of the linker radical, from the terminal atom linked to the ring atom of A to the terminal atom linked to the hydroxamic acid group, is equivalent to that of an unbranched saturated hydrocarbon chain of from 3-10 carbon atoms.

(No Suitable Figure)