International Conference & Exihibition on
Analytical and Bioanalytical Techniques 2010
ANANBIOANAL - 2010
Pharmaceutical R & D Summit
doi:10.4172/2155-9872.1000020

Inhibitors of Caspases as New Therapeutic Agents

N.Mallikarjuna Rao

Department of Biochemistry,G S L Medical College, Rajahmundry, India

Caspases are diverse group of enzymes involved in apoptosis and inflammation. Activation of caspases contributes to large number of pathological conditions a) Apoptic disorders such as myocardial infarction, lung diseases, liver diseases and neuronal diseases b) Inflammatory disorders such as rheumatoid arthritis, osteoarthritis, gout and psoriasis. Inhibition of caspase activity is therapeutically effective in these disorders. Active site structure based approach, Structure activity relationship (SAR) based approach, peptidomimetics, high trough put screens (HTS) and fragment based approach teethering are currently used to discover caspase inhibitors. Caspases are cysteine proteases containing cysteine at active site and cleaves-D(Asp)-X-bonds. Active site cysteine and nearby histidine forms catalytic diad. Binding of negatively charged aspartic acid moiety of the substrate is favoured by positively charged arginine and glutamine. Catalysis of peptide bond cleavage by caspase involves formation of tetrahedral transition state thio hemi katal initiated by active site cysteine acting as nucleophile. Near by histidine residue aids product release. Inhibition by reversible inhibitors involves formation of thio hemi katal similar to tetrahedral transition state analog of substrate. A reversible caspase inhibitor pralancasan (VX-740) is discovered by active site directed approach. Clinical trials show that pralancasan is an effective anti inflammatory drug. Irreversible caspase inhibitors forms thio ether adduct resulting in inactivation of enzyme. An irreversible peptidomimetic inhibitor emricasan (1DN-6556) is designed from di peptide backbone which is effective in apoptic driven disorders. Isatins, a group of small molecule inhibitors are identified by high through put screens. Isatins contains a carbonyl group which is critical for inhibitory activity. Caspases are inactivated due to interaction of carbonyl group of isatins with active site Cysteine.