Neuroprotection by Caspase inhibitors for the Development of Anti-Apoptotic Drug

The caspase family of cysteine proteases has two different classes of caspases involved in apoptosis, the initiator caspases and the executioner caspases. Caspase 3 and 7, among effector caspase, has been implicated in neuronal apoptosis during normal brain development and in delayed neuronal cell death after brain injury. The latter observations have suggested that this is a potential therapeutic target which has led to the development of selective and potent caspase-3/7 inhibitors. Several reversible and irreversible peptide-based compounds have been shown to reduce apoptosis. But the potential problems of peptide-based caspase inhibitors are their poor metabolic stability, limited cell penetration and unfavorable physico-chemical profile, which have resulted in a search for small molecular inhibitors of caspase-3/7. A series of isatin sulfonamide analogs were prepared and their potencies for inhibiting caspase were evaluated. These compounds have nanomolar potency for inhibiting the executioner caspases, and have a low potency for inhibiting initiator caspases. Alternatively a series of quinolines derivatives were synthesized and evaluated biologically. These series compounds also showed nanomolar potency with moderate selectivity against caspase-3/7.

Reference