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Novel 1, 3, 4-Oxadiazole derivatives suppress HepG2 cells via p53 mediated intrinsic pathway of apoptosis

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A series of novel 1,3,4-Oxadiazole derivatives (OSD, OCOD, ONOD) were synthesised and characterized. Their structures were confirmed on the basis of IR, NMR and mass spectroscopy and molecular weights were found in the range 300-325g. In the present study the potential of these derivatives was investigated on human hepatocellular carcinoma cells, HepG2. Antiproliferative activity was determined by MTT and SRB assays. The derivatives showed dose dependent response and the IC50 were found in the range of 50-100 μM. Further treatment of HepG2 cells by fluorescent cell staining methods (confocal microscopy) and DNA fragmentation study (agarose gel electrophoresis) resulted in events marked by apoptosis such as nuclear condensation and DNA damage. The cells undergoing apoptosis upon treatment with OSD were quantified using flow cytometry and were significantly higher ($p < 0.05$) than standard drug cisplatin. The expression of genes involved in the intrinsic pathway of apoptosis was studied by PCR and western blotting. The results showed that the induction of apoptosis in HepG2 cells was associated with increased expression of the tumor suppressor gene, p53. The constitutive expression of anti-apoptotic protein Bcl-2 decreased after treatment, whereas the expression of proapoptotic protein Bax increased. Also the levels of Caspase-9 and Caspase-3 were up regulated in HepG2 cells after OSD treatment. Analysis of this data suggest that 1,3,4-oxadiazole derivatives induce apoptosis by intrinsic pathway mediated through p53. The finding confirms the potential of the 1,3,4-oxadiazole derivative compound, OSD, as an agent with chemotherapeutic and cytostatic activity in human hepatocellular carcinoma.

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