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Full Research Paper

Structure-activity Study of Fluoro-substituted (-)-epigallocatechin-3-gallate Analogs as Proteasome Inhibitors

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Abstract: The cancer-preventive and anti-cancer effects of green tea are widely supported by findings from epidemiological, cell culture, animal and clinical studies. The most abundant catechin in green tea is (-)-epigallocatechin-3-gallate or (-)-EGCG that has been found to exhibit the most potent anticancer activity. We have reported that (-)-EGCG is the most effective proteasome inhibitor compared to all other natural green tea catechins tested (J Biol Chem. 2001;276:13322-30). However, (-)-EGCG is unstable in vivo. In order to discover more stable and more potent polyphenol proteasome inhibitors, we synthesized several novel (-)-EGCG analogs that contain one or two fluorine substituents on their D ring (F-EGCGs). We found that all the F-EGCGs are potent to inhibit the chymotrypsin-like activity of a purified 20S proteasome, and one of them (#165) is even more potent than natural (-)-EGCG. We also reported that a prodrug form of (-)-EGCG, called Pro-EGCG (1), in which all reactive hydroxyl groups were protected by acetates, increases the bioavailability, stability, proteasome-inhibitory and anticancer activities of (-)-EGCG in human breast cancer cells and tumors (Cancer Res. 2007;67:4303-10). In the current study, we synthesized an acetate-protected form of the F-EGCG analogs. We found that, compared to Pro-EGCG (1), the acetate-protected form of F-EGCG #165 exhibited greater potency to inhibit cellular proteasomal chymotrypsin-like activity, suppress cell proliferation and induce apoptosis in human leukemia Jurkat T cells. These data demonstrate that the

peracetate-protected F-EGCG analogs have a great potential to be developed into novel anti-cancer and cancer-preventive agents.
