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Tributyltin(IV) Butyrate: A Novel Epigenetic Modifier with ER Stress- and Apoptosis-Inducing Properties in Colon Cancer Cells

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Abstract

Organotin(IV) compounds are a class of non-platinum metallo-conjugates exhibiting antitumor activity. The effects of different organotin types has been related to several mechanisms, including their ability to modify acetylation protein status and to promote apoptosis. Here, we focus on triorganotin(IV) complexes of butyric acid, a well-known HDAC inhibitor with antitumor properties. The conjugated compounds were synthesized and characterised by FTIR spectroscopy, multi-nuclear (^{1}H, ^{13}C and ^{119}Sn) NMR, and mass spectrometry (ESI-MS). In the triorganotin(IV) complexes, an anionic monodentate butyrate ligand was observed, which coordinated the tin atom on a tetra-coordinated, monomeric environment similar to ester. FTIR and NMR findings confirm this structure both in solid state and solution. The antitumor efficacy of the triorganotin(IV) butyrates was tested in colon cancer cells and, among them, tributyltin(IV) butyrate (BT2) was selected as the most efficacious. BT2 induced G2/M cell cycle arrest, ER stress, and apoptotic cell death. These effects were obtained using low concentrations of BT2 up to 1 µM, whereas butyric acid alone was completely inefficacious, and the parent compound TBT was poorly effective at the same treatment conditions. To assess whether butyrate in the coordinated form maintains its epigenetic effects, histone acetylation was evaluated and a dramatic decrease in acetyl-H3 and -H4 histones was found. In contrast, butyrate alone stimulated histone acetylation at a higher concentration (5 mM). BT2 was also capable of preventing histone acetylation induced by SAHA, another potent HDAC inhibitor, thus suggesting that it may activate HDACs. These results support a potential use of BT2, a novel epigenetic modulator, in colon cancer treatment.

Keywords: ER stress; HDAC inhibitors; apoptosis; colon cancer; histone acetylation; triorganotin(IV) butyrates.

PubMed Disclaimer

Figures

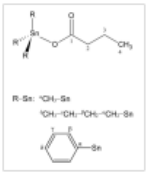

Figure 1 Proposed structure for R 3...

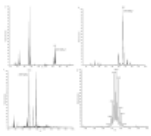

Figure 2 Positive full scan spectra of...

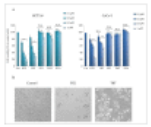

Figure 3 Tributyltin(IV) butyrate (BT2) induces cytotoxic...

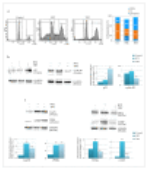

Figure 4 Tributyltin(IV) butyrate (BT2) induces cell...

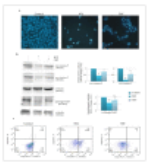

Figure 5 Tributyltin(IV) butyrate (BT2) activates caspase-dependent...

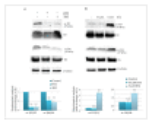

Figure 6 Tributyltin(IV) butyrate (BT2) remarkably reduces...

All figures (7)

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