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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and in vitro evaluation of triphenylphosphonium derivatives of acetylsalicylic and salicylic acids: structure-dependent interactions with cancer cells, bacteria, and mitochondria

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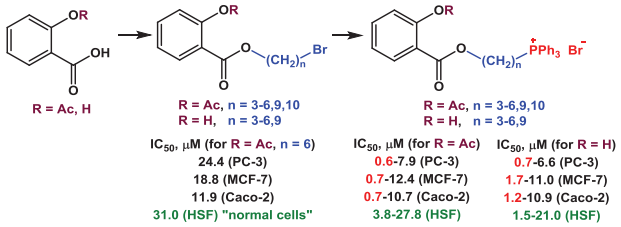
Abstract

Salicylic acid (SA) remains one of the most fruitful natural compounds to generate drug molecules with versatile activities. In this study, effective synthesis of SA and acetylsalicylic acid (ASA) derivatives with a carrier triphenylphoshonium (TPP) group was proposed. A series of SA and ASA conjugates linked with the TPP group via alkyl chain linker (C_3-C_{10}) was synthesized. The conjugates showed enhanced TPP-mediated cytotoxicity towards MCF-7, Caco-2, PC-3 cells in proportion to the linker length. **7e, 8e** (C_9), and **7f** (C_{10}) were the most active against the cancer cells with $IC_{50} = 0.6–1.9$ μM while were less toxic for HSF. Similarly, antibacterial (bactericidal) activity of the compounds against *S. aureus* increased with the linker elongation. The lowest MIC for SA and ASA derivatives were 4 and 1 μM, respectively. The TPP conjugates induced early linker length-dependent mitochondria depolarization and concurrent superoxide radical production in the cancer cells. The most lipophilic conjugates were found to specifically interact with ROS probe 2′,7′-dichlorofluorescin diacetate, forming mixed aggregates with the probe and inhibiting its fluorescence upon oxidation. These interactions were exploited to probe the compounds inside living cells. The results identify **7e** and **7f** as promising mitochondria-modulating and anticancer agents with increased cellular availability.

Graphical Abstract



Keywords Phosphonium salts · Salicylic acid · Acetylsalicylic acid · Anticancer activity · Anticancer activity · Mitochondrial potential

Introduction

Polyhydroxybenzoates are widespread secondary metabolites in plants with vital functions [1, 2]. Among them,

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