Structure–activity relationship studies of 4-methylcoumarin derivatives as anticancer agents


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Abstract

© 2015 Informa Healthcare USA, Inc. All rights reserved: reproduction in whole or part not permitted. Context: Cancer is a leading cause of death worldwide and novel chemotherapeutic agents with better efficacy and safety profiles are much needed. Coumarins are natural polyphenolic compounds with important pharmacological activities, which are present in many dietary plants and herbal remedies. Objectives: The objective of this study is to investigate natural and synthetic coumarin derivatives with considerable anticancer capacity against three human cancer cell lines. Materials and methods: We synthesized 27 coumarin derivatives (mostly having 4-methyl moiety) and examined their cytotoxic effect on three human cancer cell lines, K562 (chronic myelogenous leukemia), LS180 (colon adenocarcinoma), and MCF-7 (breast adenocarcinoma) by MTT reduction assay. Screened compounds included 7-hydroxy-4-methylcoumarins (7-HMCs), 7-acetoxy-4-methylcoumarins (7-AMCs), and different dihydroxy-4-methylcoumarin (DHMC) and diacetoxy-4-methylcoumarin (DAMC) derivatives. Some compounds with methoxy, amine, and bromine substitutions were also examined. Results: 7,8-DHMCs bearing alkyl groups at C3 position were the most effective subgroup, and of which, the most potent is compound 11, with an n-decyl chain at C3, which had IC50 values of 42.4, 25.2, and 25.1 μM against K562, LS180, and MCF-7 cells, respectively. The second most active subgroup was 7,8-DAMCs containing ethoxycarbonylmethyl and ethoxycarbonylethyl moieties at C3 position. Compound 27 (6-bromo-4-bromomethyl-7-hydroxycoumarin), the only derivative containing bromine also showed reasonable cytotoxic activities (IC50 range: 32.7-45.8 μM). Discussion and conclusion: This structure–activity relationship (SAR) study of 4-methylcoumarins shows that further investigation of these derivatives may lead to the discovery of novel anticancer agents.