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A novel chromone-based as a potential inhibitor of ULK1 that modulates autophagy and induces apoptosis in colon cancer

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Abstract
Aim: Chromones are promising for anticancer drug development. Methods & results: 12 chromone-based compounds were synthesized and tested against cancer cell lines. Compound 8 showed the highest cytotoxicity (LC50 3.2 μM) against colorectal cancer cells, surpassing 5-fluorouracil (LC50 4.2 μM). It suppressed colony formation, induced cell cycle arrest and triggered apoptotic cell death, confirmed by staining and apoptosis markers. Cell death was accompanied by enhanced reactive oxygen species formation and modulation of the autophagic machinery (autophagy marker light chain 3B (LC3B); adenosine monophosphate-activated protein kinase (AMPK); protein kinase B (PKB); UNC-51-like kinase (ULK)-1; and ULK2). Molecular docking and dynamic simulations revealed that compound 8 directly binds to ULK1. Conclusion: Compound 8 is a promising lead for autophagy-modulating anti-colon cancer drugs. © 2024 Informa UK Limited, trading as Taylor & Francis Group.

Author Keywords
apoptosis; autophagy; chromone; colon cancer; ULK1 inhibitor

Index Keywords
2 (3,4 dimethoxyphenyl) 3 (4 fluorophenyl) 7 methoxy 4h chromen 4 one, 2 (3,4 dimethoxyphenyl) 3 [4 (hydroxymethyl)phenyl] 7 methoxy 4h chromen 4 one, 2 (4 hydroxy 3 methoxyphenyl) 7 methoxy 4h chromen 4 one, 3 (3,4 dimethoxyphenyl) 1 (2 hydroxy 4 methoxyphenyl)prop 2 en 1 one, 3 bromo 2 (3,4 dimethoxyphenyl) 7 methoxy 4h chromen 4 one, 3 [4 (chloromethyl)phenyl] 2 (3,4 dimethoxyphenyl) 7 methoxy 4h chromen 4 one, 4 [2 (3,4 dimethoxyphenyl) 7 methoxy 4 oxo 4h chromen 3 yl]benzaldehyde, antineoplastic agent, chromone derivative, cytotoxic agent, fluorouracil, hydroxymethylglutaryl coenzyme A reductase kinase, phosphotransferase, protein kinase B, reactive oxygen metabolite, transferase, UNC 51 like kinase 1, UNC 51 like kinase 2, unclassified drug, antineoplastic agent, chromone derivative, protein kinase inhibitor, reactive oxygen metabolite, serine threonine protein kinase

ULK1, signal peptide, ULK1 protein, human; apoptosis, Article, autophagy (cellular), cell cycle arrest, colon cancer, colony formation, colorectal cancer cell line, controlled study, drug cytotoxicity, drug determination, drug effect, drug structure, drug synthesis, human, human cell, LC50, molecular docking, molecular dynamics, cell proliferation, chemical structure, chemistry, colon tumor, drug screening, drug therapy, metabolism, molecular docking, pathology, structure activity relation, synthesis, tumor cell line; Antineoplastic Agents, Apoptosis, Autophagy, Autophagy-Related Protein-1 Homolog, Cell Line, Tumor, Cell Proliferation, Chromones, Colonic Neoplasms, Drug Screening Assays, Antitumor, Humans, Intracellular Signaling Peptides and Proteins, Molecular Docking Simulation, Molecular Structure, Protein Kinase Inhibitors, Reactive Oxygen Species, Structure-Activity Relationship

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