Biological evaluation of Indanetrione analogues in Inflammation.

Abstract:
Adenosine monophosphate activated protein kinase (AMPK) plays a key role in energy homeostasis. The serendipitous discovery of a novel pleiotropic anti-oxidant molecule, namely 2-(3, 4-dihydro-2h-pyrrolium-1-yl)-3oxoindan-1-olate, (DHPO) with anti-inflammatory, radio-protective, anti-diabetic and anti-allergic activities prompted us to explore related synthetic analogues for potential utility in treating the complex pathology of inflammation encompassing multiple-signaling pathways. Best molecules HMPH, HPID and HPID-1 phosphorylated AMPK in skeletal muscle, suggesting an AMPK-mediated mechanism. HMPH and HPID-1 induced glucose uptake in an insulin-mimetic pathway in adipocytes and metformin-mimetic pathways in skeletal muscle respectively. HPID-1 demonstrated the maximum potency in activating AMPK in skeletal muscles. HMPH, HMBH, HPID and HPID-1 were found to be anti-inflammatory with immunomodulatory mechanism of action. HMPH, HMBH, HPID and HPID-1 possess non-COX mediated multi-target and complex anti-inflammatory/immunomodulatory activity, probably mediated via TLR/NF-κB signaling cascade. HMPH and HPID were superior to other test compounds/diclofenac in attenuating symptoms of colitis and arthritis. All tested compounds showed a multimodal action, probably by acting upon the pleiotropic nodal control centre for energy homeostasis and metabolic provisioning towards tissue repair. Our results endorse multi-target drugs, an emerging trend in drug-discovery.