Synthesis and Characterization of Some Heteroaromatic Derivatives of 3-But-2-enoyl-chromen-2-one and Their Potential as Anti-inflammatory Agents

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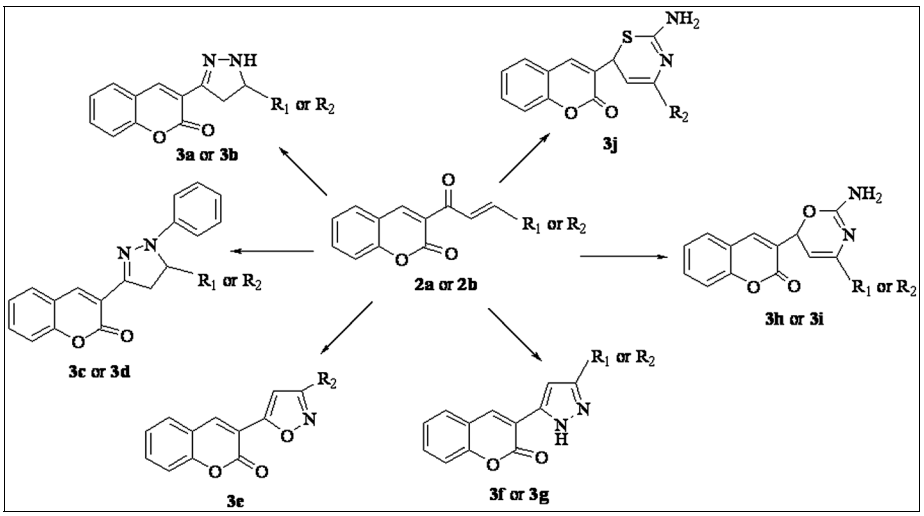

A novel series of chromen-2-ones containing pyrazole, isoxazole, oxazine, and thiazine substitutions have been synthesized by reacting 3-[3-(4-chloro-phenyl)-acryloyl]-chromen-2-one and 3-[3-(3-methoxy-phenyl)-acryloyl]-chromen-2-one with various cyclizing agents such as hydrazine, phenylhydrazine, urea, and thiourea. The structures of all the synthesized compounds were confirmed by the use of IR, ^{1}H-NMR, mass spectroscopy, and elemental analysis data. All the newly synthesized compounds were evaluated for their anti-inflammatory activity at a dose of 100 mg/kg body weight in carrageenan-induced rat paw edema model. The entire series of the compounds exhibited moderate to good anti-inflammatory activity, with the percentage inhibition of edema formation ranging from 39.99 to 63.15 against the reference drug ibuprofen (100 mg/kg) that showed 78.96% inhibition at the third hour. Compounds **3a**, **3c**, and **3d** showed good inhibitory activity, whereas compounds **3b**, **3e**, **3f**, and **3j** showed moderate inhibitory activity at the third hour.

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INTRODUCTION

Inflammation is a complex phenomenon involving humoral and cellular reactions through a number of inflammatory mediators [1]. The classical nonsteroidal anti-inflammatory drugs (NSAIDs) are important therapeutic agents widely used in the treatment of pain and inflammation [2,3]. The existence of the enzyme cyclooxygenase (COX) in its two distinct isoforms, and thus nonselective action of classical NSAIDs, results in certain mechanism-based side effects including dyspepsia, gastrointestinal ulcerations, bleeding, and nephrotoxicity [4,5]. Therefore, development of novel compounds having anti-inflammatory and analgesic activities with an improved safety profile is still a necessity. Thus, the discovery of novel anti-inflammatory agents has been attracting a lot of interest [6,7]. Chromen-2-ones (Coumarins) have been reported to possess anti-inflammatory, anticancer, antimicrobial activities, and antioxidant properties [8–14]. Coumarin and its hydroxy-derivative can reduce tissue edema and inflammation by inhibiting prostaglandin biosynthesis, which involves fatty acid hydroperoxy intermediates. Natural products such as esculetin, fraxetin, daphnetin, and other related coumarin derivatives are recognized as inhibitors not only of the lipoxygenase and cycloxygenase enzymic systems, but also of the neutrophil-dependent superoxide anion generation [15]. Pyrazole derivatives such as phenylbutazone, oxyphenbutazone, and celecoxib exhibit anti-inflammatory, antipyretic, and analgesic properties [16]. 3,4-Diarylisoxazole scaffold is one of the frequently found pharmacophore in a wide variety of NSAIDs (such as Valdecoxib), protein kinase