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Pyrazole as a Promising Scaffold for the Synthesis of Dual Acting Anti-inflammatory-Antimicrobial Agents

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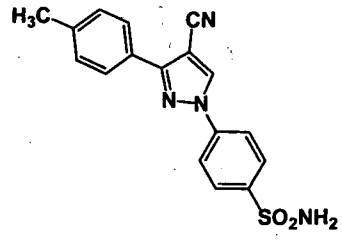

Non-steroidal anti-inflammatory drugs (NSAIDs) have been recognized as important therapeutic agents for the treatment of rheumatoid arthritis and its variants. However, large doses of NSAIDs or long term use usually results in gastrointestinal mucosal damage, intolerance and renal toxicity. Despite the efforts that had been made to improve the pharmacological profile of NSAIDs, ulcerogenicity remains the most limiting problem in their clinical use. A major breakthrough in anti-inflammatory research occurred when it was discovered that COX exists in three isoforms COX-1, COX-2 and COX-3 which are regulated differently. The discovery of the inducible isoform COX-2 spurred the search for novel anti-inflammatory agents devoid of the undesirable effects associated with classical nonselective NSAIDs. Consequently, a new generation of COX-2 selective inhibitors has been clinically used with the hope that they would exhibit a reduced risk in gastrointestinal events. Among this class of compounds, celecoxib; 4 [5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide was shown to be a potent and a gastrointestinal safe anti-inflammatory and analgesic agent. Celecoxib is considered a typical model of pyrazole containing diaryl heterocyclic template that is known to inhibit COX-2 selectively.

Most of inflammatory conditions associated with infection or vice versa, co-administration of multiple drugs for treatment of inflammatory conditions associated with microbial infection is a major risk especially in the case of patients with impaired liver or kidney functions. A mono therapy of a drug with dual anti-inflammatory antimicrobial activity would be preferred from the pharmacoeconomic and patient compliance point of view. This premise was one of the goals of our research program aimed at the discovery of new pyrazoles that would possess dual anti-inflammatory-antimicrobial activities. The synthesized novel pyrazole compounds showed pronounced dual activities. They represent a promising class of safer pyrazole containing compounds with interesting pharmacological profile.