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ORIGINAL ARTICLE

Synthesis and pharmacological evaluation of 5-methyl-2-phenylthiazole-4-substituted heteroazoles as a potential anti-inflammatory and analgesic agents

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KEYWORDS

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Thiazole;
Ulcerogenic potential

Abstract A series of novel 5-methyl-2-phenylthiazole-4-substituted-heteroazole derivatives (**6–15**) have been synthesized. The structures of these compounds were established by IR, ^{1}HNMR, Mass spectral data and elemental analyses. Compounds were evaluated for their anti-inflammatory and analgesic activities as well as gastric ulcerogenic effects. Derivatives **9**, **10**, **14** and **15** exhibited moderate to good anti-inflammatory and analgesic activities in carrageenan-induced rat paw edema and acetic acid-induced writhing in mice respectively, with low ulcerogenicity compared with the standard drug diclofenac sodium.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of pain and inflammation. Most currently used NSAIDs have limitations for therapeutic uses, since they cause gastrointestinal and renal side effects which are inseparable from their pharmacological activities. These compounds act via inhibition of the enzyme cyclooxygenase, thus preventing prostaglandin synthesis. In the early 1990s, it was discovered that the enzyme exists as two isomers, one constitutive (COX-1) and the other inducible (COX-2) (Hla and Neilson, 1992). COX-1 is an enzyme that is constitutively expressed and provides cytoprotection in the gastrointestinal (GI) tract; whereas inducible COX-2 mediates inflammation (Almansa et al., 2003). The traditional NSAIDs cause inhibition of both enzymes. In fact, most of them show greater selectivity for COX-1 than COX-2 (Jackson and Hawkey, 1999). Consequently long term therapy with nonselective NSAIDs may cause gastrointestinal complications ranging from stomach irritation to life-threatening GI ulceration and bleeding (Allison et al., 1992). Therefore, selective COX-2 inhibitors with better safety profile have been marketed as a new generation of NSAIDs (Tally et al., 2000). But careful prospective examination of coxibs has revealed unexpected cardiovascular adverse effects (Dogne and Pratico, 2005).

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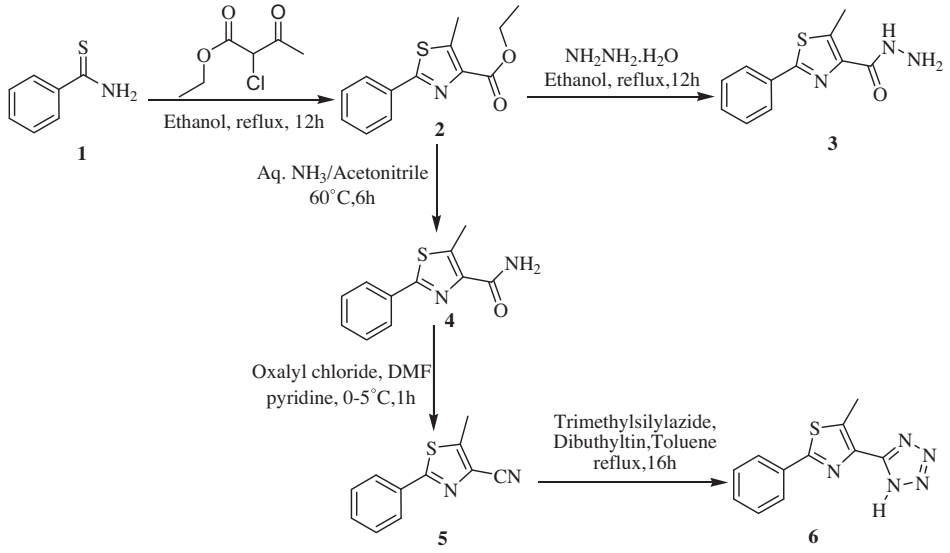
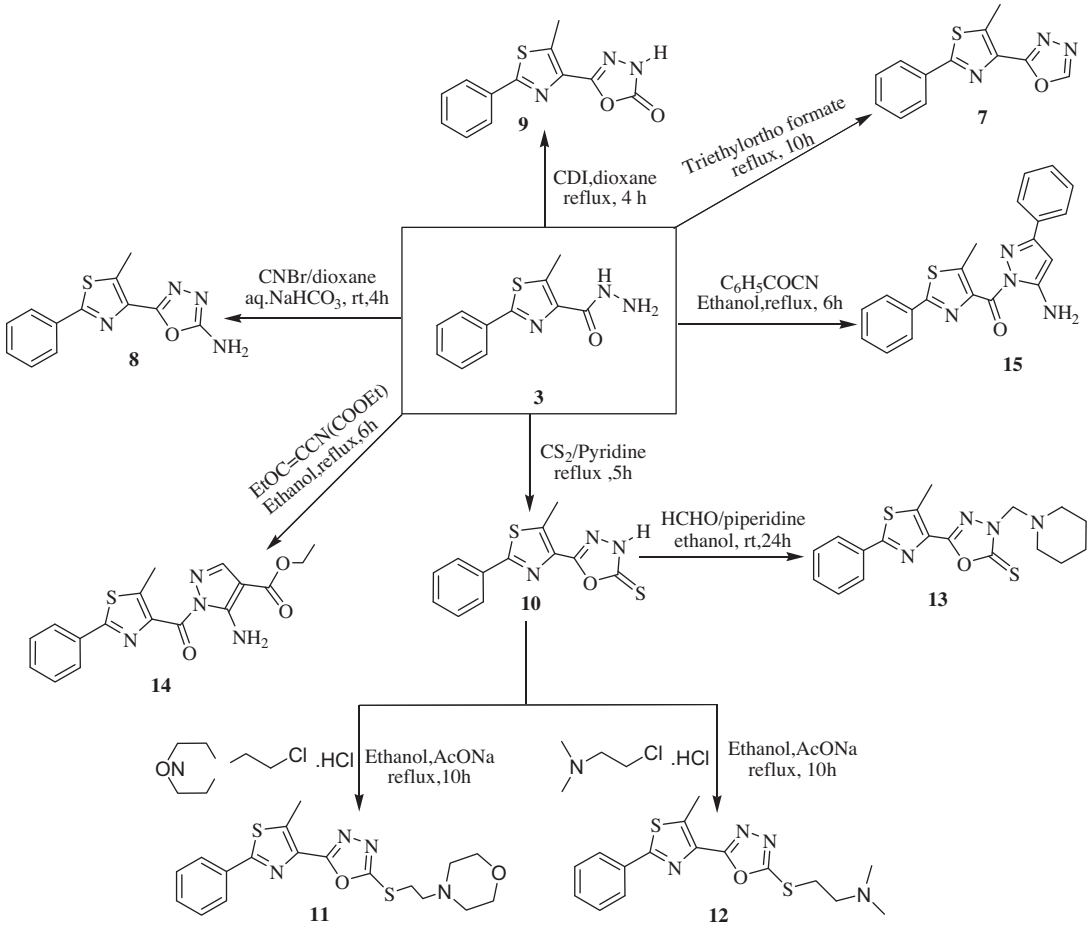


Scheme 1 Synthesis of intermediate **3** and target compound **6.**



Scheme 2 Synthesis of target compounds **7**–**15.**

Most of the clinical NSAIDs possess acidic carboxyl (COOH) group, which further cause GI irritation by direct contact of –COOH group in GIT at doses very close to anti-inflammatory ones. These serious side effects limit the use of NSAIDs as a safer drug for the treatment of inflammation. Several studies have described the derivatization of the carboxylate function of representative NSAID with less acidic azoles: thiazole (Giri et al., 2009), oxadiazole (Akhter et al., 2009),