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Synthesis and biological evaluation of pyrazolylthiazole carboxylic acids as potent anti-inflammatory–antimicrobial agents

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ABSTRACT

Current Letter presents design, synthesis and biological evaluation of a novel series of pyrazolylthiazole carboxylates **1a**–**1p** and corresponding acid derivatives **2a**–**2p**. All 32 novel compounds were tested for their in vivo anti-inflammatory activity by carrageenan-induced rat paw edema method as well as for in vitro antimicrobial activity. All the tested compounds exhibited excellent AI activity profile. Three compounds **1p** (R = Cl, R^1 = Cl), **2c** (R = H, R^1 = F) and **2n** (R = Cl, R^1 = OCH_3) were identified as potent anti-inflammatory agents exhibiting edema inhibition of 93.06–89.59% which is comparable to the reference drug indomethacin (91.32%) after 3 h of carrageenan injection while most of the other compounds displayed inhibition ⩾80%. In addition, pyrazolylthiazole carboxylic acids (**2a**–**2p**) also showed good antimicrobial profile. Compound **2h** (R = OCH_3, R^1 = Cl) showed excellent antimicrobial activity (MIC 6.25 μg/mL) against both Gram positive bacteria comparable with the reference drug ciprofloxacin (MIC 6.25 μg/mL).

Inflammation is the immune response of tissues to external injury which can be categorized as acute or chronic. The former is the initial response of the body to harmful stimulus identified by the increased movement of macrophages and neutrophils in infected tissues while chronic inflammation is due to progressive movement of the mononucleated cells at the injury site leading to destruction of tissues by cell death.[1]

Anti-inflammatory drugs are known to inhibit one or more isoforms of cyclooxygenase (COX) enzyme that catalyzes the conversion of arachidonic acid (AA) into prostaglandins (PGs) and thromboxanes. COX enzyme is a rate-limiting enzyme that exists in two isoforms; constitutive (COX-1) and inducible (COX-2). COX-1 is believed to be a housekeeping enzyme constitutively present in platelets and all tissues. It produces PGs involved in important physiological functions, such as gastric mucosal cytoprotection, renal homeostasis, and platelet aggregation. COX-2 is an inducible, short lived enzyme present in brain, kidney and endothelial cells and facilitates the release of PGs in the inflammatory process.[2–4]

Conventional non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin and ibuprofen are nonselective inhibitors of both the isoforms of COX thereby leading to a number of renal and gastrointestinal (GI) side effects.[5] To overcome the gastrointestinal side effects, selective COX-2 inhibitors such as celecoxib,[6] rimonabant,[7] valdecoxib,[8] rofecoxib,[9] deracoxib[10] etc., which block the production of PGs in inflammatory cells,[11] have been developed since 1999. Success of these 'coxibs' led to an increased attention towards development of more candidates like the approved COX-2 selective inhibitors which are typical models of the diarylheterocycles template.[12]

Resistance of microbes to existing antimicrobial drugs is a cause of serious concern. Considering the obvious advantages of monotherapy against inflammation as well as microbial infection, research efforts are underway to develop dual anti-inflammatory–antimicrobial drugs with minimum GI side effects and high safety margin.[13]

Thiazole[14–17] and pyrazole nuclei[18–23] are ubiquitous motifs representing an interesting array of heterocyclic compounds exhibiting a wide range of biological activities such as antimicrobial, anti-inflammatory, antitubercular, anticonvulsant, antitumor etc. Motivated by these findings, and in continuation of our ongoing research program in the field of 4-functionalized pyrazole analogues[24–27] and other biologically active heterocyclic compounds[28–34] we present in this Letter, design, synthesis and evaluation of pyrazolylthiazole carboxylic acids (**2a**–**2p**) and their ester analogues (**1a**–**1p**) as dual anti-inflammatory–antimicrobial agents (Fig. 1). Thiazole ring possessing carboxylic group have been incorporated at N-1 position

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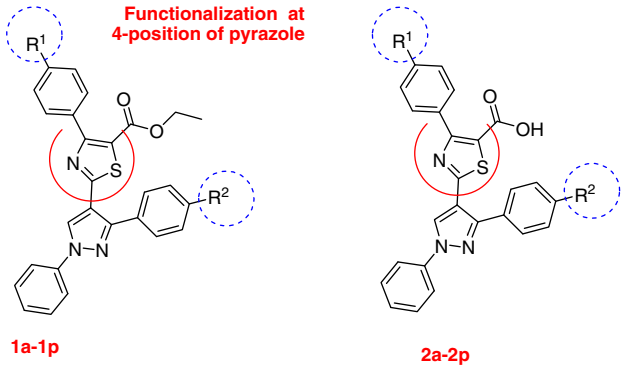


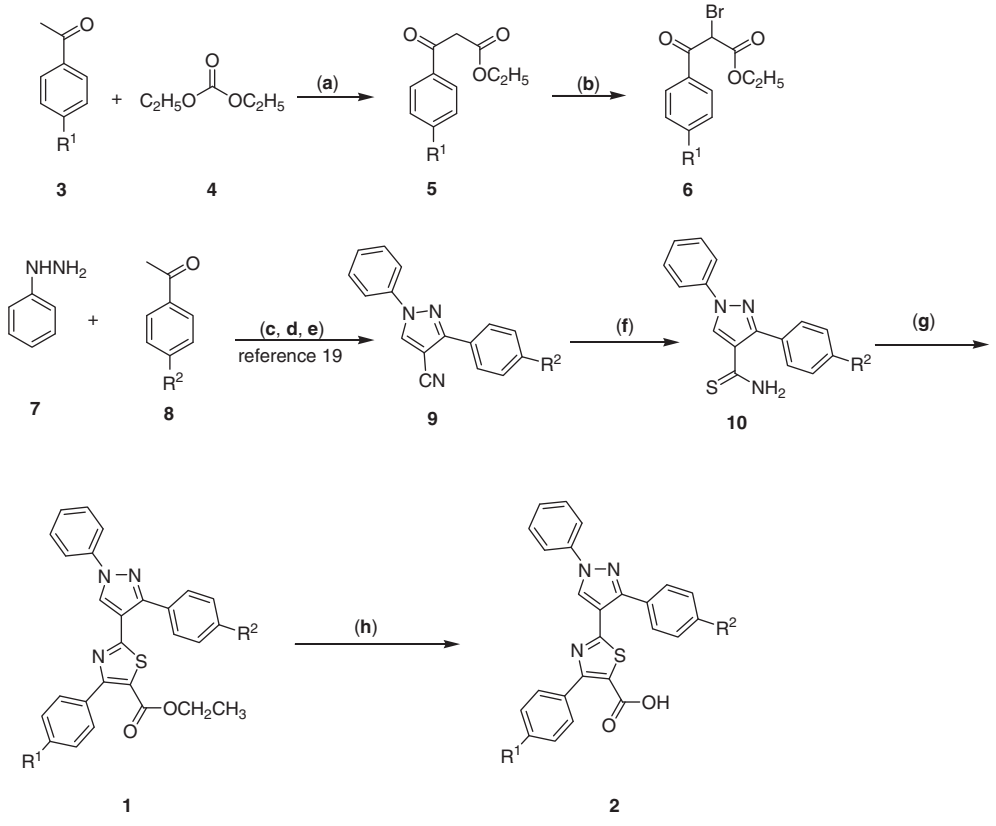
Figure 1. Pyrazolylthiazole carboxylates **1a–1p** and corresponding carboxylic acids **2a–2p**.

of pyrazole ring[35] in the past but here in this Letter, to the best of our knowledge, we have introduced the thiazolecarboxylic acid functionality at 4-position of pyrazole ring (**1a–1p** and **2a–2p**) for the first time (Fig. 1).

The synthetic strategy adopted for the synthesis of the target compounds is depicted in Scheme 1. The basic requirements for the synthesis of pyrazolylthiazole carboxylic acids (**2**) were the formation of ethyl 2-bromo-3-aryl-3-oxopropanoates (**6**) and 4-carbothioamidepyrazoles (**10**), which were prepared by multistep synthesis.

Ethyl 3-aryl-3-oxopropanoates **5** were prepared by the base catalyzed carbethoxylation of the appropriately substituted acetophenones **3** with diethyl carbonate **4**. Bromination of **5** was achieved by grinding ethyl 3-aryl-3-oxopropanoates **5** with NBS[36] without solvent leading to the exclusive formation of monobrominated pure products **6** in excellent yield. 4-Carbothioamidepyrazoles **10** were synthesized starting from appropriate acetophenones using a multistep strategy involving hydrazone synthesis, Vilsmeier–Haack reaction followed by oxidative amination and subsequent thiolysis of 4-cyanopyrazoles **9** by using H_2S gas under basic conditions in the presence of triethylamine as reported recently by our group.[25] The target compounds pyrazolylthiazole carboxylates **1a–1p** were synthesized by the condensation of appropriate 4-carbothioamidepyrazoles **10** with substituted ethyl 2-bromo-3-aryl-3-oxopropanoates (**6**) in the presence of catalytic amount of glacial acetic acid in refluxing ethanol for 5–6 h. Pyrazolylthiazole carboxylates **1a–1p** were converted into corresponding pyrazolylthiazole carboxylic acids **2a–2p** following basic hydrolysis of the ester group using sodium hydroxide (NaOH) solution under reflux for 3–4 h in good yield.

The newly synthesized target compounds (**1a–1p** and **2a–2p**) were characterized by rigorous analysis of their IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. IR spectra of pyrazolylthiazole



Comp No. / 1, 2	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p
R^1	H	OCH_3	F	Cl	H	OCH_3	F	Cl	H	OCH_3	F	Cl	H	OCH_3	F	Cl
R^2	H	H	H	H	OCH_3	OCH_3	OCH_3	OCH_3	F	F	F	F	Cl	Cl	Cl	Cl

Scheme 1. Reagents and conditions: (a) NaH, benzene, diethyl carbonate reflux; (b) NBS, grinding; (c) ethanol–water, reflux; (d) $POCl_3$/DMF, 50–60 °C, 6 h; (e) I_2/NH_3, THF stir overnight; (f) H_2S, NEt_3, pyridine, 10–12 h; (g) ethyl 2-bromo-3-aryl-3-oxopropanoate **6**, ethanol, 1–2 drops of glacial acetic acid, reflux; (h) NaOH/H_2O/C_2H_5OH, reflux.

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