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Design, synthesis and pharmacological evaluation of omeprazole-like agents with anti-inflammatory activity

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ABSTRACT

A new series of novel benzimidazole derivatives containing substituted pyrid-2-yl moiety and polyhydroxy sugar conjugated to the *N*-benzimidazole moiety has been synthesized and evaluated as orally bioavailable anti-inflammatory agents with anti-ulcerogenic activity. The anti-inflammatory and anti-ulcerogenic activities of these compounds were compared to diclofenac and omeprazole, respectively. In carrageenan-induced paw oedema assay, 2-methyl-*N*-((3,4-dimethoxypyridin-2-yl)methyl)-1*H*-benzimidazol-5-amine (**12d**) and 1-(1,2,3,5-tetrahydroxy-α-D-mannofuranose)-5-(((3,4-dimethoxypyridin-2yl)methyl)amino)-2-methyl-1*H*-benzimidazole (**15d**) displayed dose-dependent anti-inflammatory activities by decreasing the inflammation by 62% and 72%, respectively which is comparable to that of diclofenac (73%). In contrast to diclofenac, the anti-inflammatory activity of these compounds was not only free from any side effects on the gastric mucosa but also showed significant anti-ulcerogenic activity in rat pyloric ligation and ethanol-induced gastric ulcer models similar to that of omeprazole. Together, these findings suggest that **12d** and **15d** are potent anti-inflammatory agents with concurrent anti-ulcerogenic activity and support its clinical promise as a component of therapeutic strategies for inflammation, for which the gastric side effects are always a major limitation.

1. Introduction

Gastrointestinal toxicity is the most common adverse effect of the currently available non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, indomethacin, and naproxen. Such adverse effects are manifested by dyspepsia, ulcers, or bleeding.[1] The gastrointestinal damage from NSAIDs is generally attributed to two factors; first, the local irritation by carboxylic acid group present in many NSAIDs (topical effect); second, the decreased tissue prostaglandin production, which undermines the physiological role of cytoprotective prostaglandins in maintaining gastrointestinal integrity and homeostasis.[2] The pharmacology of NSAIDs is linked to the inhibition of prostaglandin biosynthesis from arachidonic acid by inhibiting cyclooxygenases.[3] Therefore, patients treated with NSAIDs for long periods of time, may suffer from noticeable gastrointestinal toxicity. Consequently, synthetic approaches based on chemical mimicking NSAIDs have been taken with the aim of improving its safety profile. The concurrent use of NSAIDs with gastric proton pump enzyme (H^+/K^+-ATPase) inhibitors represents a major approach to minimize such adverse effects.[4,5] Many pharmaceutical companies have spent considerable efforts in the identification of irreversible and reversible inhibitors of the H^+/K^+-ATPase. Substances belonging to the class of irreversible inhibitors are called proton pump inhibitors (PPIs)[6–8] such as omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole. PPIs are widely used as acid inhibitory agents for the treatment of disorders related to gastric acid secretion.[9,10]

Many of PPIs are benzimidazole derivatives[11,12] which consist of two fragments of benzimidazole and pyridine. These PPIs act as prodrugs owing to protonation of the pyridine ring under the gastrointestinal acid environment, resulting in a chemical rearrangement which forms sulfenic acid then sulfonamide by dehydration. The active enzyme inhibitor is either the sulfenic acid or the sulfonamide which reacts with cysteine residues of the H^+/K^+-ATP enzyme (Fig. 1).[13–15] Omeprazole, a benzimidazole proton pump inhibitor, has anti-inflammatory and antioxidant properties besides its ability to stimulate gastric mucus secretion.[16] Benzimidazole and its derivatives represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities including anti-inflammatory and analgesic.[17] The unique

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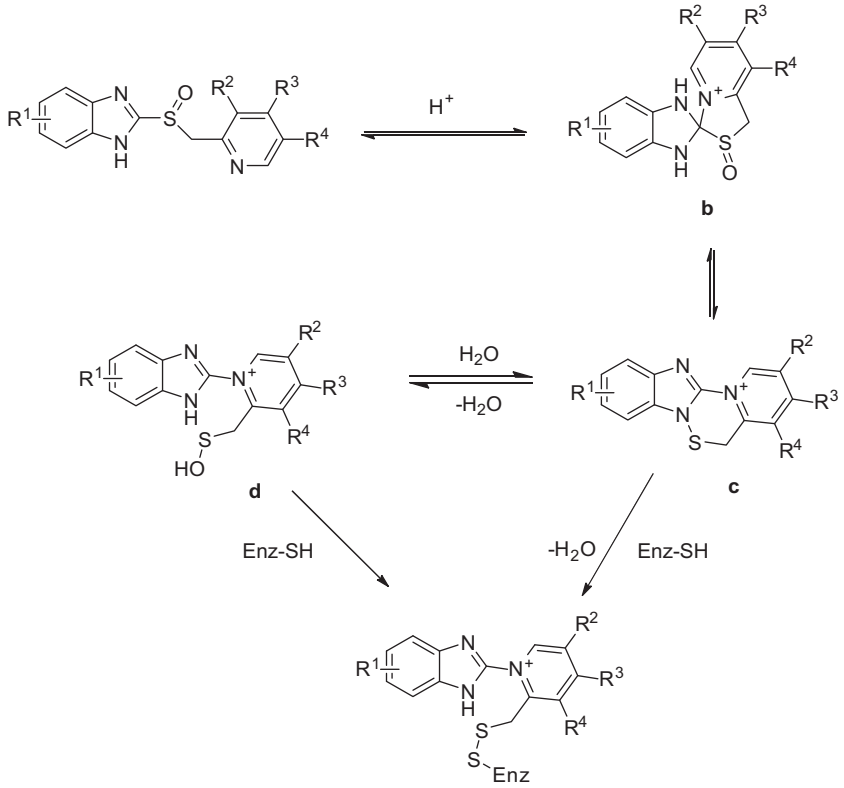


Figure 1. Mechanism of acid transformation of 2-[(2-pyridylmethyl)sulfinyl]benzimidazole derivatives. First, the gastric acidity causes protonation of the pyridine ring into intermediate, **b**. Then, a chemical rearrangement forms sulfenic acid **c**, which forms sulfonamide **d** by dehydration. The active enzyme inhibitor is either the sulfenic acid **c** or the sulfonamide **d** which reacts with cysteine of the H^+/K^+-ATP enzyme.[13–15]

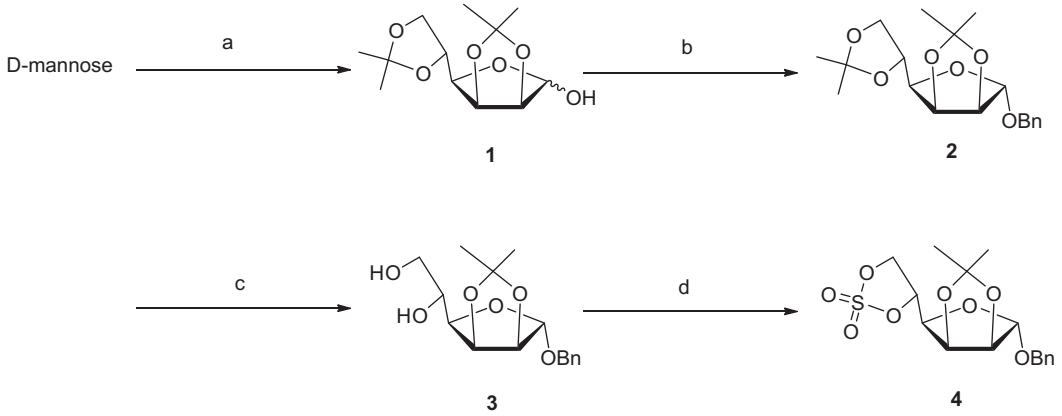
structural features and pharmaceutical activities of benzimidazoles have encouraged us to synthesize novel orally bioavailable 2-methyl-N-substituted benzimidazole sugar conjugates and study its anti-inflammatory and anti-ulcerogenic activities.

2. Results and discussion

2.1. Chemistry

2,3:5,6-Di-*O*-isopropylidene-D-mannofuranose (**1**) was prepared by the reaction of D-mannose with acetone in the presence of catalytic amount of concentrated sulfuric acid.[18–20] Benzylation of 2,3:5,6-di-*O*-isopropylidene-D-mannose (**1**) using benzyl bromide and sodium hydride afforded a mixture of anomers **2α**:**2β** (6.8:1), which was separated by column chromatography. Only the α-isomer was isolated by crystallization using ethyl acetate/hexane, the β-anomer was not considered.[21,22]

Selective acid catalyzed hydrolysis of **2** gave diol **3**.[21] Cyclic sulfate **4** was obtained by the treatment of compound **3** with thionyl chloride, $RuCl_3{\cdot}3H_2O$ and $NaIO_4$ in anhyd CCl_4. All products were purified by column chromatography and the structure of the synthesized compounds was determined by ^1H, ^{13}C NMR (Scheme 1). Cyclic sulfate **4** is at least as reactive as epoxides and its reactivity is the result of its ring strain which may be due to angle strain and the partial double bond character between the ring oxygen and sulfur atom. In addition, the use of cyclic sulfate in the synthesis



Scheme 1. Preparation of cyclic sulfate. Reagents and conditions: (a) acetone, H_2SO_4, Na_2CO_3, rt, 75%; (b) NaH, THF, benzyl bromide, rt, 86%; (c) 80% acetic acid, reflux, 89%; (d) thionyl chloride, CCl_4, $RuCl_3{\cdot}3H_2O$, $NaIO_4$, rt, 91%.