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Synthesis of methanesulphonamido-benzimidazole derivatives as gastro-sparing antiinflammatory agents with antioxidant effect

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ABSTRACT

A series of 5-methanesulphonamido benzimidazole derivatives were designed by combining the structural features of clinically useful anti-inflammatory drugs (nimesulide and rofecoxib) and antiulcer drugs (lansoprazole, omeprazole, etc.) based on physicochemical and 3D similarity studies. The compounds were evaluated for their anti-inflammatory activity in carrageenan induced rat paw edema model taking rofecoxib and indomethacin as standard drugs. *In vitro* antioxidant activity of the compounds was assessed by potassium ferricyanide reducing power (PFRAP) assay. The compounds **9**, **10** and **11** showed anti-inflammatory activity comparable to the standard group and were also non-ulcerogenic at the test doses. Compounds **6**–**11** exhibited good antioxidant effect in the concentration range (1.0–50.0 μmol/ml. Preliminary theoretical ADME profiling of the compounds based on computation of selected physicochemical properties showed an excellent compliance with Lipinski's rule.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are accepted as a keystone in the treatment of inflammatory diseases and possess anti-inflammatory, antipyretic, and analgesic effects. These are the most widely used medications worldwide for their anti-inflammatory, antipyretic, and analgesic effects[1] and are prescribed as first choice in the treatment of various rheumatic disorders and other degenerative inflammatory joint diseases. These are also used for some distinct indications in paediatrics such as Kawasaki disease, Patent Ductus Arteriosus (PDA) closure, and Juvenile Idiopathic Arthritis (JIA).[2] The important mediators of inflammation[3,4] accounting for the characteristic vasodilation and erythema at the site of inflammation include the prostaglandins PGE_2[5], PGD_2[6] and PGI_2[7] which are produced *via* arachidonic acid metabolism.

NSAIDs cause inhibition of the enzyme cyclooxygenase resulting in disruption of the biosynthesis of prostaglandins (PGE_2, PGD_2 and PGI_2) and thromboxanes.[8] Although NSAIDs are generally well tolerated agents, but their chronic use has been associated with several undesirable side effects including gastrointestinal PUB (perforation, ulceration and bleeding), dyspepsia[9] and renal toxicity.[10] The strategic designing of the inhibitors of the inducible form of cyclooxygenase enzyme (selective COX-2 inhibitors)[11] has yielded several new generation anti-inflammatory drugs with improved gastric and renal tolerance. However, several of these agents had to face an early withdrawal from the market in many countries on cardiotoxicity (rofecoxib, valdecoxib, parecoxib) and hepatotoxicity (nimesulide and more recently, lumiracoxib) concerns.[12,13] The local generation of reactive oxygen species is known to play an important role in the gastric ulceration associated with conventional NSAIDs therapy[14] and could be possibly involved in cardiovascular complications of coxibs.[15] Radical scavenging antioxidant activities of some benzimidazole derivatives have been recently investigated.[16] Hence, anti-inflammatory molecules with reducing (antioxidant) potential should exhibit lower gastrointestinal toxicity.[17] In this context, the present work describes the design and synthesis of a novel class of benzimidazole derivatives, investigation of their anti-inflammatory activity, antioxidant and ulcerogenic potential. Benzimidazole nucleus is the parent nucleus present in clinically useful antiulcer agents (proton pump inhibitors PPIs) such as omeprazole, lansoprazole, rabeprazole and pantoprazole and several synthetic routes are reported in literature for preparation of benzimidazole derivatives.[18,19] Hence, the present work was envisaged to explore the benzimidazole nucleus for developing anti-inflammatory compounds with the underlying hypothesis that these should potentially retain gastric tolerability of this nucleus. Compound **4a** (Fig. 1), a butyl phenyl ether derivative had emerged as a representative lead compound from our recently reported series of 3-alkoxy-4-methanesulfonamido acetophenone based anti-inflammatory agents lacking gastrointestinal toxicity.[20]

A benzimidazole core was envisaged as a probable replacement for the phenyl alkyl ether moiety in **4a** (or nimesulide) with the

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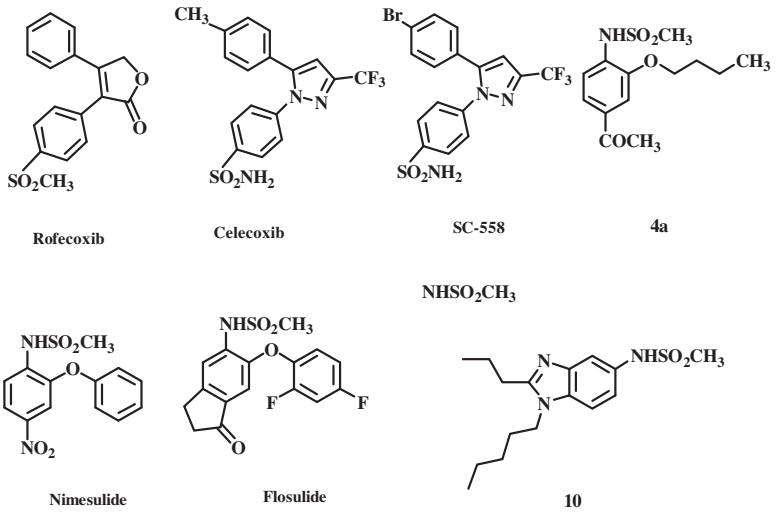

Fig. 1. Chemical structures of gastro-sparing anti-inflammatory agents.

underlying hypothesis that the designed series of compounds would have a combined anti-inflammatory effect and GI tolerability. The present series of methanesulphonamido-substituted benzimidazole derivatives was designed based on physicochemical similarity (descriptor-based; tanimoto association coefficient) and 3D similarity studies (based on assessment of field similarity and shape similarity) with respect to **4a** and clinically useful gastro-sparing anti-inflammatory agents including diaryl substituted heterocycles/carbocycles (like celecoxib and rofecoxib) and methanesulfonyl substituted aryl ethers/thioethers represented by nimesulide and flosulide (Fig. 1). The computational studies were carried out using Dell XPS L502X, (Core i7; 6 GB RAM) running on Windows 10®. Three dimensional similarity studies were carried out with Forge V10™ (10.4.2 Revision 248766; evaluation version) (Cresset BioMolecular Discovery Ltd.). The standard drugs (reference molecules) in a defined 3D conformation generated using Chem3D 15.1 and energy minimized with MM2 force field to minimum RMS gradient of 0.100 were imported to Forge V10™ in .sdf (MDL file) format. Default settings were employed and standard scoring function was used based on 50% field similarity and 50% shape similarity to derive overall similarity. Design strategy showing the benzimidazole group borrowed from the PPIs replacing the central aryloxy/substituted groups in nimesulide/rofecoxib (retaining the methanesulphonamido function) is depicted in Fig. 2.

Chemical structures of the prepared compounds are shown in Table 1 and the various descriptors for physicochemical similarity studies are shown as Table S1 (supplementary data).

The results for the similarity studies of the designed compounds with respect to **4a** and the standard drugs are shown in Tables 2 and 3.

Excellent physicochemical and 3D similarity values were obtained for compounds **2** to **11** with respect to **4a**, as well as the standard drugs. The tanimoto coefficient for the proposed compounds **2** to **11** ranged from 0.756 to 0.991 (Table 2) and 3D similarity ranged from 0.671 to 0.858 (Table 3) indicating that inclusion of benzimidazole parent nucleus afforded very good structural similarity to the standard drugs which should possibly translate to their pharmacological profiles also. Fig. 3 shows near perfect alignment of compound **10** with nimesulide.

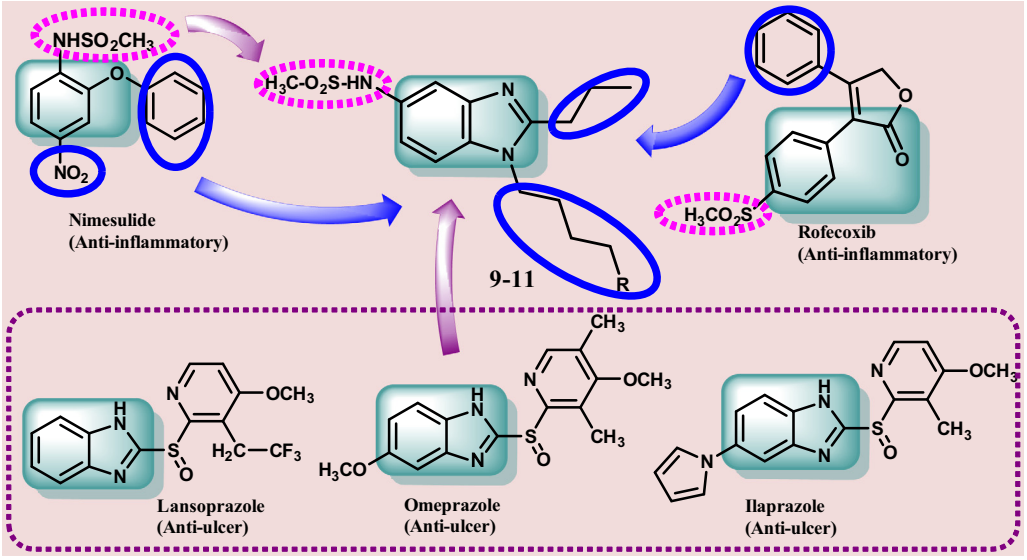

Fig. 2. Design strategy for compounds **9**–**11**: Benzimidazole nucleus from antiulcer drugs lansoprazole, omeprazole and ilaprazole coupled with methanesulphonamido function similar to anti-inflammatory agents nimesulide and rofecoxib.