RESEARCH ENVISAGED

NSAIDs are one of the most widely used class of drugs worldwide. These agents are used for the treatment of patients with rheumatoid arthritis and various other diseases associated with inflammation, fever and pain.\(^1\) However, the major limitation of NSAID therapy is the higher incidence of GI damage including gastric ulceration, perforation and their associated complications, and these affect a large number of patients taking these drugs on long term basis.

The pharmacological activity of NSAIDs is related to their ability to inhibit the production of PGs from arachidonic acid by inhibiting the activity of the enzyme COX. Various conventional NSAIDs in clinical use have been shown to inhibit COX, leading to a marked reduction in PG synthesis. Now, it is well known that COX exists in two isoforms namely COX-I and COX-II.\(^2,11\) COX-I is constitutive and provides cytoprotection in the GI tract, whereas COX-II is inducible which mediates inflammation. The mucosal integrity in normal GI tract is primarily maintained by PGs that are derived from COX-I and therefore inhibition of COX-I rather than COX-II by NSAIDs is responsible for their ulcerogenic GI side effects.\(^12,13\) These observations stimulated an intense and competitive race to design and develop selective COX-II inhibitors as safer NSAIDs devoid of their GI side effects and number of such derivatives such as celecoxib, rofecoxib etc., collectively named as coxibs, have been introduced in the market for clinical use. However, long term use of these selective COX-II inhibitors revealed some potential limitations including ulcer exacerbation in high risk patients, delayed gastrointestinal ulcer healing, kidney toxicity, as well as cardiovascular side effects.\(^14-16\) These observations indicate that safety of these agents is questionable on their long term use and recently, some of the coxibs have been withdrawn from the market. Therefore, the initial enthusiasm of developing selective COX-II inhibitors has faded away and need for designing and developing safer NSAIDs devoid of their ulcerogenic side effects still remains.

Review of literature in preceding section reveals that involvement of various ROS is responsible for the formation of gastric ulcers associated with long term NSAIDs use.\(^101-103,132\) Based on these observations, it has been suggested that concomitant use of an antioxidant and NSAID may decrease the risk of
gastrointestinal toxicity and make the therapy safer.\textsuperscript{212,213} However, there is an added advantage in giving such agents in the form of a single chemical entity. Such hybrid molecules consisting of two different therapeutic agents having complementary pharmacological activities are named as mutual prodrugs, which are designed with improved physicochemical properties and at the same time release the parent molecules at the site of action.\textsuperscript{215} On these lines, a number of NSAID-antioxidant mutual prodrugs devoid of their ulcerogenic side effects have been reported (vide supra).\textsuperscript{217-219,225} In the University Institute of Pharmaceutical Sciences, also, a number of NSAID-antioxidant prodrugs have been synthesized and these agents have been found to exhibit retention of antiinflammatory activity of the parent drug molecules, with significantly reduced ulcerogenic side effects.\textsuperscript{223,224}

These observations indicated that there is merit to carry out studies in this area of drug research for the design and development of NSAID-antioxidant mutual prodrugs as safer therapeutic agents. For this purpose, well known and widely used NSAID diclofenac (33) has been selected. This agent has reasonable safety except gastrointestinal side effect similar to other conventionally used NSAIDs. These observations prompted to design and develop diclofenac-antioxidant mutual prodrugs with the objective of optimizing the therapeutic utility of this potential NSAID. For this purpose, a number of antioxidant phytophenols including guaiacol (129), eugenol (130), thymol (131), vanillin (132), sesamol (133), umbelliferone (134) and phytoalcohol menthol (135) have been selected as promoieties for conjugation with diclofenac. These naturally occurring compounds have been traditionally in use as food additives and therefore have...
well documented safety profile. Structures of these agents are shown in Figure 18.

Based on these facts, it was decided to conjugate diclofenac with these phytophenols through different spacer. The structures (136,137) of the model compounds are given in the Figure 19.

It was also decided to evaluate these derivatives for their physicochemical and pharmacological activities.