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A small diversity library of α-methyl amide analogs of sulindac for probing anticancer structure-activity relationships

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) have a variety of potential indications that include management of pain and inflammation as well as chemoprevention and/or treatment of cancer. Furthermore, a specific form of ibuprofen, dexibuprofen or the *S*-(+) form, shows interesting neurological activities and has been proposed for the treatment of Alzheimer's disease. In a continuation of our work probing the anticancer activity of small sulindac libraries, we have prepared and screened a small diversity library of α-methyl substituted sulindac amides in the profen class. Several compounds of this series displayed promising activity compared with a lead sulindac analog.

The non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of minor pain and chronic inflammatory diseases such as rheumatoid arthritis. A number of these drugs possess antipyretic activity in addition to having analgesic and anti-inflammatory effects, and thus have use in the treatment of fever. These effects are attributed to the ability of the NSAIDs to inhibit the cyclooxygenases (COX), which convert arachidonic acid to prostaglandins (PGs).[1] Three distinct COX isozymes have been characterized; COX-1 is responsible for the regulation of prostaglandin biosynthesis in normal tissues and serves an important role in gastric cytoprotection and renal homeostasis, COX-2 is an inducible enzyme important for acute inflammatory responses and pyrexia in the body, while COX-3 currently has no established role in humans. Evidence is mounting that the NSAIDs may play a role in the treatment of patients with familial adenomatous polyposis and for the chemoprevention of colorectal cancer.[2,3] Experimental data as well as epidemiological and clinical studies suggest that the regular use of NSAIDs in a chemoprevention regimen can reduce the incidence of colorectal cancer by approximately 30–50%.[4,5] However, upper gastrointestinal, renal, or cardiovascular side effects resulting from COX inhibition limit the utility of NSAIDs for prevention regimens as they typically require high dosages and chronic administration.[6–10] It is now clear that NSAIDs demonstrate a variety of activities beyond COX inhibition and their effects on tumor cells may be a result of multifarious activities.[11] While NSAIDs are believed to exhibit their anticancer properties through inhibition of COX-2 that is overexpressed in various tumor cells, several COX-2 independent mechanisms have also been suggested for the chemopreventive and antineoplastic properties of NSAIDs. Other activities include activation of apoptosis, inhibition of angiogenesis, modulation of the adaptive immune system or direct inhibition of cancer cell growth by blocking signal transduction pathways responsible for cell proliferation.[12–17]

As a member of the NSAIDs, sulindac has been shown to dramatically induce regression of adenomas in familial adenomatous polyposis (FAP) patients, prevent recurrence of adenomas[18,19] and reduce the risk of colon cancer and prostate cancer.[20–22] As such, it has been studied extensively and is clinically used as a chemopreventive agent.[13] Sulindac is considered a prodrug that is reductively metabolized *in vivo* to the more active sulfide as well as oxidized to the more hydrophilic and less active sulfone (see Fig. 1). While sulindac contains a chiral sulfoxide group that reduces lipophilicity of the scaffold and improves solubility of the drug, the commercial compound is racemic, and the reversible cycling between the methyl sulfide and the methyl sulfoxide would scramble any chirality making the study of the effects of chirality at this center difficult in an *in vivo* setting. Oxidation to the sulfone is irreversible and the more hydrophilic product is considerably less active as a COX inhibitor.

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; COX, cyclooxygenase; PG, prostaglandin; FAP, familial adenomatous polyposis; SSA, sulindac sulfide amide; SAR, structure-activity relationship; qHTS, quantitative high-throughput screen; CPC, choroid plexus carcinoma; ALL, acute lymphoblastic leukemia

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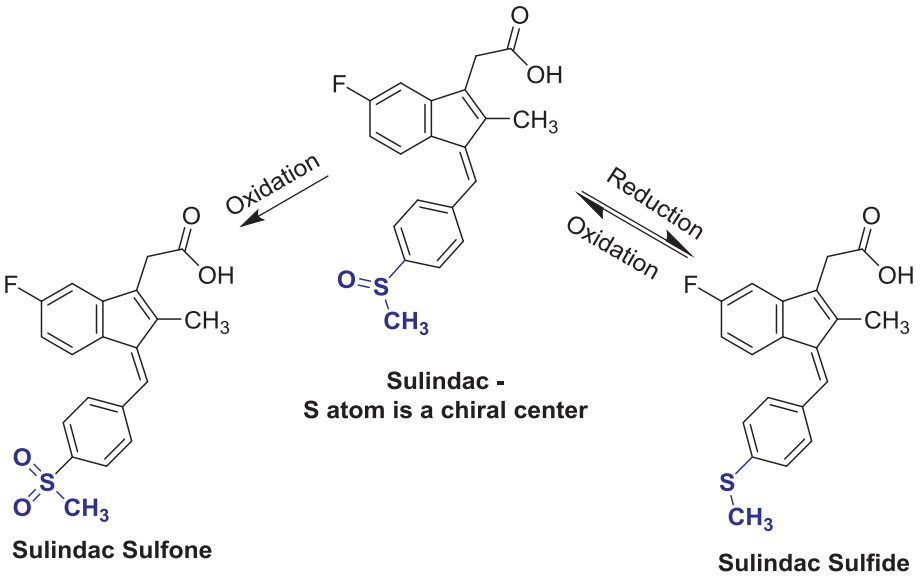

Fig. 1. *In vivo* metabolic cycling (oxidation/reduction) of the sulindac sulfoxide moiety.

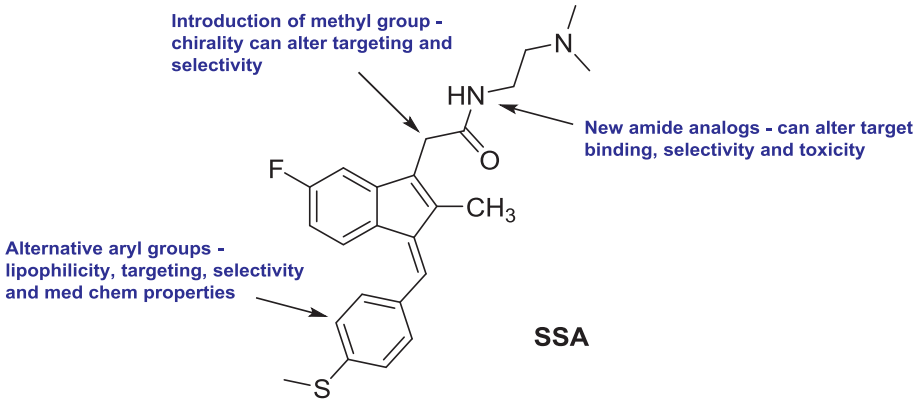

Fig. 2. Overview of our structural modifications relative to our lead agent **SSA** in order to study the SAR of this class.

The biological mechanism of the antineoplastic effect of the sulindac metabolites appears to involve the selective induction of apoptosis as demonstrated in human breast, lung, prostate and colon cancer cell lines.[23–26] Our earlier studies suggested that a relatively simple alteration to sulindac in the form of sulindac sulfide amide (**SSA**) (Fig. 2) can virtually abolish COX-related activity and toxicity while enhancing anticancer activity *in vitro* and maintaining similar *in vivo* xenograft activity[27] in a chemoprevention protocol. It is notable that the metabolic oxidation-reduction cycling demonstrated for sulindac (Fig. 1) has also been shown to happen for the sulindac analog **SSA** yielding both the sulfoxide and sulfone metabolites *in vivo*.[27]

Fig. 2 shows our lead agent **SSA** and modifications reported herein to develop a broader SAR for the sulindac amides exemplified by **SSA**.

There are several broad classes of NSAIDs including the salicylates (e.g., aspirin) and the acetates or 2-aryl acetic acids (e.g., indomethacin). Sulindac belongs to the NSAID acetic acid class and is considered an indene-3-acetic acid. Addition of an α-Me group as indicated in Fig. 2 would introduce a chiral center transforming the scaffold into the NSAID profen class or a 2-aryl propionic acid (e.g., ibuprofen – Advil® and naproxen – Aleve®). Most NSAID propionic acids, including ibuprofen, are sold as racemic mixtures. However, naproxen is available commercially as the *S*-isomer prepared by precipitation of an insoluble salt via the Pope-Peach method of chiral resolution. The impact of chirality at the α-Me position has been extensively studied for ibuprofen. Dexibuprofen, or (*S*)-(+)-ibuprofen, has been analyzed for toxicity and side effects, uptake, and neurological activity versus racemic ibuprofen. In fact, dexibuprofen has demonstrated varied and improved effects for Alzheimer's disease.[28] Hence, we were interested in how introduction of an α-Me group would impact activity of **SSA** analogs against three common cancer cell lines from colon, breast, and prostate cancers that are standard cell lines used for preliminary chemoprevention and anticancer screening. We initiated a diversity program involving preparation of a sulindac profen core (α-Me sulindac) as shown in Fig. 2 followed by diversification at both the amide position and the indene aryl group in order to study the structure-activity relationships in the profen amide series of sulindac. Herein, we present the preparation and preliminary screening of a series of novel sulindac amide derivatives containing a methyl group at the α-position with various alterations in the amide and aryl linkers. Our lead agent, **SSA** (Fig. 2) was used as a standard control compound for comparison, as it shows improved activity relative to the clinical NSAID sulindac against colon cancer cells *in vitro* as well as good activity *in vivo* in a murine chemoprevention model of colon cancer.[27]

Preparation of α-methyl sulindac amides **3–59** started with esterification of commercially available sulindac sulfide (to form **3–29**), (±)-sulindac (to prepare **30–56**), or a sulindac 3,4,5-trimethoxyphenyl analog (to afford **57–59**) in the presence of MeOH/thionyl chloride. The corresponding methyl esters were formed in 90–96% yields. The introduction of the key α-methyl group was carried out using LDA and CH_3I at −78 °C to furnish racemic or diastereomeric α-methyl sulindac