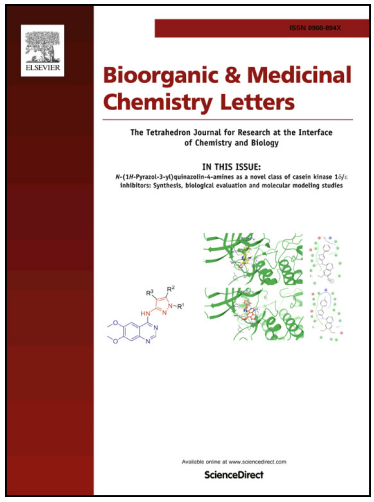
Accepted Manuscript



Diverse amide analogs of sulindac for cancer treatment and prevention

Bini Mathew, Judith V. Hobrath, Michele C. Connelly, R. Kiplin Guy, Robert C. Reynolds

PII: S0960-894X(17)30918-6
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.09.022
Reference: BMCL 25286

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 2 August 2017
Revised Date: 4 September 2017
Accepted Date: 11 September 2017

Please cite this article as: Mathew, B., Hobrath, J.V., Connelly, M.C., Kiplin Guy, R., Reynolds, R.C., Diverse amide analogs of sulindac for cancer treatment and prevention, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.09.022

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

Diverse amide analogs of sulindac for cancer treatment and prevention

Bini Mathew[a], Judith V. Hobrath[b], Michele C. Connelly[c], R. Kiplin Guy[d], Robert C. Reynolds[e*]
[a]*Drug Discovery Division, Southern Research Institute, 2000 Ninth Avenue South, Birmingham, AL 35205, USA*
[b]*Drug Discovery Unit, College of Life Sciences, University of Dundee, Dundee DD1 5EH, United Kingdom*
[c]*Department of Chemical Biology & Therapeutics, St Jude Children's Research Hospital, 262 Danny Thomas Place, Mailstop 1000, Memphis, TN 38105-3678 USA*
[d]*The University of Kentucky College of Pharmacy, 214H BioPharm Complex, Lexington, KY 40536-0596, USA*
[e]*Division of Hematology and Oncology, The University of Alabama at Birmingham, Birmingham, Alabama 35294, USA*

Abstract: Sulindac is a non-steroidal anti-inflammatory drug (NSAID) that has shown significant anticancer activity. Sulindac sulfide amide (**1**) possessing greatly reduced COX-related inhibition relative to sulindac displayed *in vivo* antitumor activity that was comparable to sulindac in a human colon tumor xenograft model. Inspired by these observations, a panel of diverse sulindac amide derivatives have been synthesized and their activity probed against three cancer cell lines (prostate, colon and breast). A neutral analog, compound **79** was identified with comparable potency relative to lead **1** and activity against a panel of lymphoblastic leukemia cell lines. Several new series also show good activity relative to the parent (**1**), including five analogs that also possess nanomolar inhibitory potencies against acute lymphoblastic leukemia cells. Several new analogs identified may serve as anticancer lead candidates for further development.

Key words: NSAIDs; sulindac; amides; cancer

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a chemically diverse family of drugs commonly used clinically to treat a variety of inflammatory conditions including pain associated with arthritis. A number of these drugs possess antipyretic activity in addition to having analgesic and anti-inflammatory action, and thus have utility in the treatment of pain and fever. These are widely known to be cyclooxygenase (COX) inhibitors. The COX enzymes participate in the metabolism of prostaglandins. For example, COX-1 enzymes produce prostaglandins that are important for the stomach lining and kidney function. COX-2 enzymes are crucial to anti-inflammatory reactions in the body.[1] Many currently marketed NSAIDs have both COX-1 and COX-2 inhibitory effects. Although the class is highly used both clinically and over the counter, chronic COX inhibition is

*Corresponding author. Tel.: +1-(205) 934-8276; Fax: +1-(205) 934-2543. E-mail: rcr12lkt@uab.edu

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; COX, cyclooxygenase; SSA, sulindac sulfide amide; SAR, structure-activity relationship; AA, amino acid; ALL, acute lymphoblastic leukemia; CPC, choroid plexus carcinoma; TPSA, topological polar surface area; LipE, lipophilic efficiency.

Download English Version:

https://daneshyari.com/en/article/7780669

Download Persian Version:

https://daneshyari.com/article/7780669

Daneshyari.com