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Student : B303098002 林祐辰藥三 A

Topic:

The synthesis of Diclofenac and the following structure modification

Introduction

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Publication Year(s) Examples: 1995, 1995-1999, 1995-, -1995

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27. **Synthesis, activity and formulations of pharmaceutical compounds for treatment of oxidative stress and/or endothelial dysfunction**

By Del Soldato, Piero

From PCT Int. Appl. (2000), WO 2000061537 A2 20001019. Language: English, Database: CAPLUS

Compds. A-B-C-N(O)s and A-C1[N(O)s]-B1 or their salts [s is an integer 1 or 2, preferably s = 2; A is the radical of a drug and is such as to meet the pharmacol. tests reported in the description; C and C1 are two bivalent radicals; the precursors of the radicals B and B1 are such as to meet the pharmacol. test reported in the description] were prepd. for use as pharmaceuticals. Thus, (S,S)-N-acetyl-S-(6-methoxy- α -methyl-2-naphthalenylacetyl)cysteine 4-nitroxybutyl ester was prepd. (NCX 2101) from naproxene and N-acetylcysteine in the first of 28 synthetic examples given. Pharmacol. test exa...

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28. **Nitrosothiol esters of diclofenac: synthesis and pharmacological characterization as gastrointestinal-sparing prodrugs**

By Bandarage, Upul K.; Chen, Liqing; Fang, Xinqin; Garvey, David S.; Glavin, Alicia; Janero, David R.; Letts, L. Gordon; Mercer, Gregory J.; Saha, Joy K.; Schroeder, Joseph D.; et al

From Journal of Medicinal Chemistry (2000), 43(21), 4005-4016. Language: English, Database: CAPLUS

Despite its widespread use, **diclofenac** has gastrointestinal liabilities common to nonsteroidal antiinflammatory drugs (NSAIDs) that might be reduced by concomitant administration of a gastrointestinal cytoprotectant such as nitric oxide (NO). A series of novel **diclofenac** esters contg. a nitrosothiol (-S-NO) moiety as a NO donor functionality has been synthesized and evaluated in vivo for bioavailability, pharmacol. activity, and gastric irritation. All S-NO-**diclofenac** derivs. acted as orally bioavailable prodrugs, producing significant levels of **diclofenac** in plasma within 15 min after oral ...

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29. **Synthesis and anti-phlogistic potency of some new non-proteinogenic amino acid conjugates of "Diclofenac"**

By Abo-Ghalla, Mohamed Hassan; Shalaby, A. M.; El-Eraqi, W. I.; Awad, H. M.

From Amino Acids (1999), 16(3-4), 425-440. Language: English, Database: CAPLUS

In search for more potent, particularly less ulcerogenic gastritis that hopefully replace the universal NSAID "**Diclofenac**", (2-[(2,6-di-chlorophenyl)amino]-phenylacetic acid, C.A.S. 15307-86-5), twelve new non-proteinogenic amino acid conjugates of the drug, namely that of sarcosine, β -alanine, D-leucine and D-phenylalanine, were synthesized and biol. screened for their anti-inflammatory, analgesic and ulcerogenic activity in rats. "**Diclofenac**" amino acid esters (IIa-d), were synthesized via the corresponding HOSu or HOBt active esters. Alk. hydrolysis (NaOH) followed by acidification (KHSO₄...

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28. Nitrosothiol esters of **diclofenac**: **synthesis** and pharmacological characterization as gastrointestinal-sparing prodrugs

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Nitrosothiol Esters of Diclofenac: Synthesis and Pharmacological Characterization as Gastrointestinal-Sparing Prodrugs^{†,‡}

Upul K. Bandarage,* Liqing Chen, Xinqin Fang, David S. Garvey, Alicia Glavin, David R. Janero, L. Gordon Letts, Gregory J. Mercer, Joy K. Saha, Joseph D. Schroeder, Matthew J. Shumway, and S. William Tam
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Section: Benzene, Its Derivatives, and Condensed Benzenoid Compounds

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Upul K. Bandarage,* Liqing Chen, Xinqin Fang, David S. Garvey, Alicia Glavin, David R. Janero, L. Gordon Letts, Gregory J. Mercer, Joy K. Saha, Joseph D. Schroeder, Matthew J. Shumway, and S. William Tam

NitroMed, Inc., 12 Oak Park Drive, Bedford, Massachusetts 01730

Received April 19, 2000

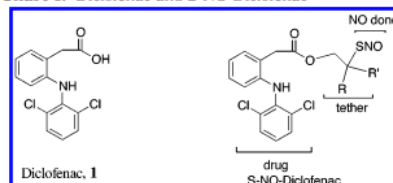
Despite its widespread use, diclofenac has gastrointestinal liabilities common to nonsteroidal antiinflammatory drugs (NSAIDs) that might be reduced by concomitant administration of a gastrointestinal cytoprotectant such as nitric oxide (NO). A series of novel diclofenac esters containing a nitrosothiol (-S-NO) moiety as a NO donor functionality has been synthesized and evaluated in vivo for bioavailability, pharmacological activity, and gastric irritation. All S-NO-diclofenac derivatives acted as orally bioavailable prodrugs, producing significant levels of diclofenac in plasma within 15 min after oral administration to mice. At equimolar oral doses, S-NO-diclofenac derivatives (**20a**–**21b**) displayed rat antiinflammatory and analgesic activities comparable to those of diclofenac in the carrageenan-induced paw edema test and the mouse phenylbenzoquinone-induced writhing test, respectively. All tested S-NO-diclofenac derivatives (**20a**–**21b**) were gastric-sparing in that they elicited markedly fewer stomach lesions as compared to the stomach lesions caused by a high equimolar dose of diclofenac in the rat. Nitrosothiol esters of diclofenac comprise a novel class of NO-donating compounds having therapeutic potential as nonsteroidal antiinflammatory agents with an enhanced gastric safety profile.

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) are widely used for the treatment of pain, fever, and inflammation, particularly arthritis.^{1–3} Among the most popular NSAIDs, diclofenac (**1**) (Chart 1) has been approved in 120 countries since its introduction 25 years ago⁴ and is ranked 30th among the top 200 drugs with respect to new prescriptions and refills in the United States alone.⁵

The pharmacological activity of NSAIDs is related to the suppression of prostaglandin H₂ (PGH₂) biosynthesis from arachidonic acid by inhibiting the activity of the enzyme cyclooxygenases (COXs).⁶ Recently, it was discovered that COX exists in two isoforms, COX-1 and

Chart 1. Diclofenac and S-NO-Diclofenac



70 000 hospitalizations and 7000 deaths annually in the United States.¹³ GI damage from NSAIDs is generally attributed to two factors: local GI irritation by the carboxylic acid moiety common to most NSAIDs ("topical

2. Read it and elevate the important concept and my opinion of this journal.

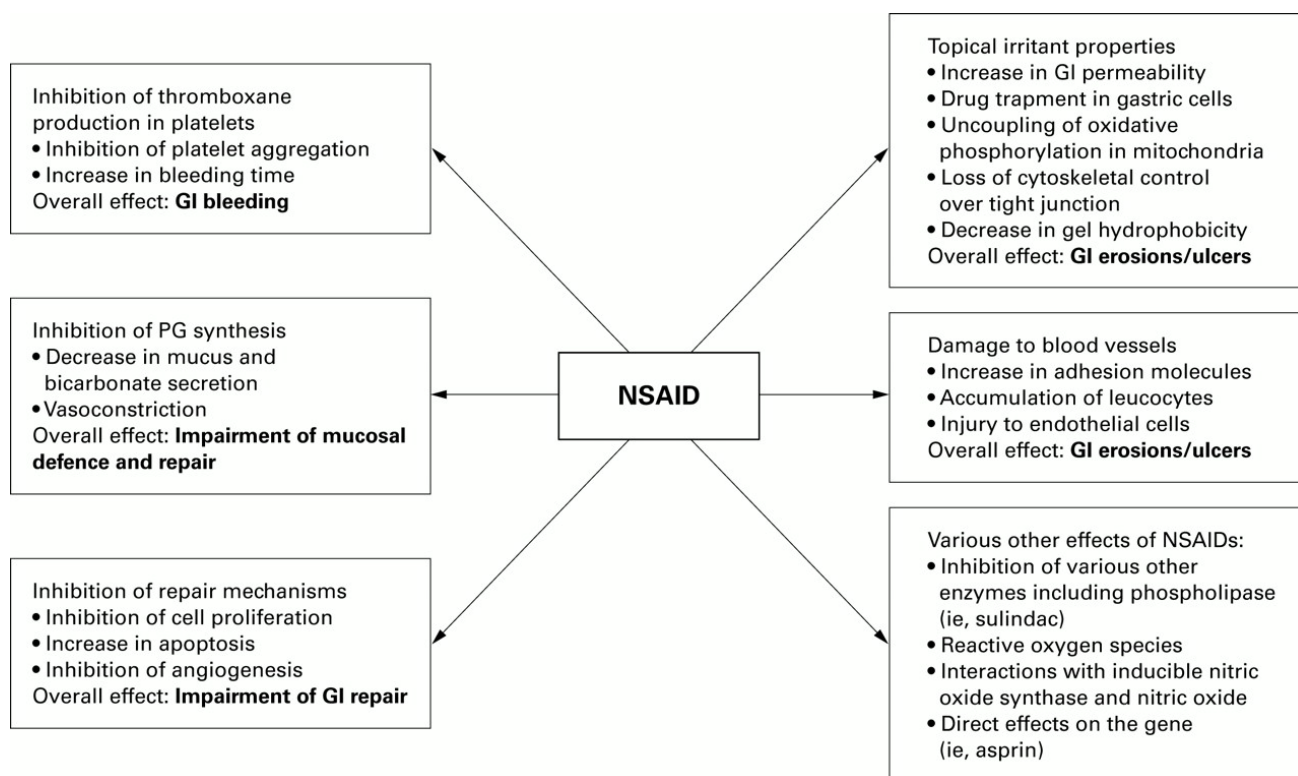
(1) Introduction of Diclofenac and the mechanism of GI tract irritation cause by NSAIDs.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain, fever, and inflammation, particularly arthritis. Among the most popular NSAIDs, diclofenac has been approved in 120 countries since its introduction 25 years ago and is ranked 30th among the top 200 drugs with respect to new prescriptions and refills in the United States alone.

The reason why NSAIDs cause GI irritation is:

- Local GI irritation by carboxylic acid moiety of the NSAIDs compounds.
- Inhibition COX-1 and decrease the producing of prostaglandin which responsible for the mucous (as a protection component) release from the GI tract, especially the stomach.

< this figure shows that how NSAIDs damage the GI tract. >



(2) Why NSAIDs need structure modification?

Since most of the NSAIDs show greater selectivity for COX-1 than COX-2, the GI irritation and injuries caused by chronic NSAIDs intake turned out to be a side effect that can't be neglected. And most of the structure modification is based on the idea of reducing GI irritation.

(3) The idea, organized note, and experimental result of this research

Topic:

Nitrosothiol Esters of Diclofenac: Synthesis and Pharmacological Characterization as

Gastrointestinal-Sparing Prodrugs

This journal indicated four methods to improve the NSAIDs safety:

a. **Mask –COOH group and turned it into prodrugs**

The prodrugs will hydrolyzed in vivo and release the parent NSAID drugs. However, this modification only reduces the local irritation, while the major problems of GI injuries caused by deficiency of PG which lead to the lack of mucous production haven't been solved.

b. **Change the target into highly COX-2 inhibitors**

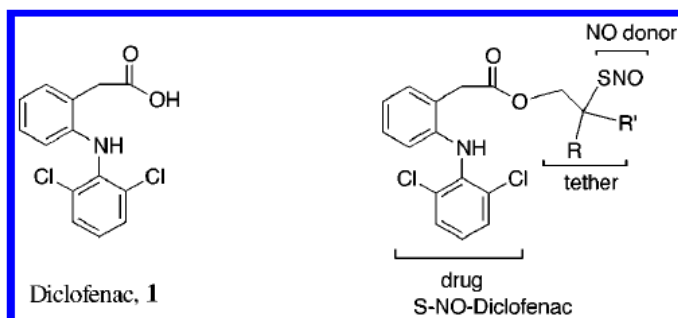
These modified drugs reduce the COX-1 blockade and the deficiency of prostaglandin and show a gastro-protective effect. These new developed drugs include celecoxib and rofecoxib. However the toxicity of these drugs still presence, such as –COOH group irritation, COX-1 blockade and COX-2 over blockade.

c. **Add NO to the parent NSAIDs**

When a nitro-oxybutyl group was added to diclofenac, it will release NO group which have a cyto-protective effect, help maintaining the blood flow of the GI tract and show an ulcer-healing effect at the experimental rats. But it occurs to have tolerance.

d. **Introduce to a nitrosothiol(–S–NO) moiety (most effectiveness) .**

Chart 1. Diclofenac and S-NO-Diclofenac



In this modification, the tertiary S-nitrosothiol structure is more stable than primary or secondary S-nitrosothiol compound.

e. In the GI lesions repair test, the diclofenac derivatives contain a (–S–NO) group have a stronger than derivatives with a –SH groups. Namely the repair effect of these 3 product is: Diclofenac < Diclofenac-SH < Diclofenac-S-NO.

3. The feeling of using SCI finder as a research tool.

In my opinion, I think SCI finder is a great research tool especially at the field of Medical Chemistry. Once you think about a new compound structure you can put it directly on SCI finder and the related information about this compound will be shown immediately. From all the data which was shown we can learn more about this compound, if it had already been synthesized. Such problems as, how to synthesis it? What are the pharmacological and toxicological properties of this compound? When I want to synthesis this compound and do further modification, where to buy the original ingredient of it? The SCI finder truly applied a great platform for us to search a great deal of useful information about the medicine modification. Besides, another advantage of SCI finder is that it is easy to get started. Even a beginner can find

useful information in a very short time. Maybe it is partly because the mode of SCI finder is similar to that of Pubmed which is wide spread and useful tool in searching the journal range from medicine, Pharmacognosy, Pharmacology, Toxicology, pharmaceuticals, and even dental-related knowledge.

Through this report I had changed my opinion toward Medical Chemistry, the obligatory subject of student who major in pharmacy. During the research and paper reading, I know more about the Chemical synthesis mechanism and start to think about why the functional group should be added right here? What is the outcome when this group was added to the different part of this compound? And how the structure relative activity influences this compound especially in the pharmacological aspects? This problem based learning certainly helps me understand more about this subject. Even though Medical Chemistry is not my favorite subject, I will learn to enjoy studying it and maybe the knowledge of this subject will bring me some surprising "presents" in the future.