Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Derivatives with Anti-Cancer Activity

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Abstract
Nonsteroidal anti-inflammatory drugs (NSAIDs) are a diverse class of drugs commonly used for the treatment of inflammatory conditions, have been found to be highly effective in preventing and treating many types of cancers. However, toxicity from cyclooxygenase (COX) inhibition and the suppression of physiologically important prostaglandins limits their use for cancer chemoprevention and prompted researchers to manipulate their structures to attain NSAIDs derivatives with an enhanced anti-cancer activity with gastrointestinal sparing property. Reports discussed in this review will be those of NSAIDs derivatives and some miscellaneous agents that display anti-cancer activity against variety of cancer cell lines.

Keywords: NSAIDs; Cancer; Chemoprevention; NSAIDs derivatives

1. Introduction

1.1. Non steroidal antiinflammatory drugs (NSAIDs)

Non steroidal antiinflammatory drugs NSAIDs are among the most frequently prescribed drugs in modern medicine. They are very effective in the alleviation of pain, fever and inflammation [1]. Millions of patients worldwide have found pain relief in their use since the discovery of the soothing properties of willow bark more than 3,500 years ago [2]. NSAIDs exert their antiinflammatory effect through inhibition of cyclooxygenase an enzyme that catalyzes the transformation of arachidonic acid...
to prostaglandins and thromboxanes [3]. The global burden of cancer continues to increase largely because of the aging and growth of the world population alongside an increasing adoption of cancer-causing behaviors, particularly smoking, in economically developing countries. Based on the GLOBOCAN 2008 estimates, about 12.7 million cancer cases and 7.6 million cancer deaths are estimated to have occurred in 2008; of these, 56% of the cases and 64% of the deaths occurred in the economically developing world [4]. The first report of a protective role for aspirin against cancer development appeared in 1988, documenting a negative association with colorectal cancer. Subsequently a very large number of studies have been carried out demonstrating similar effects in the colon and/or rectum. Beneficial effects have also been described for other organs [5]. In terms of their antineoplastic activity, in vitro studies have shown that the mechanism is mainly due to the induction of apoptosis and prevention of cell proliferation [6]. Other mechanistic studies suggest that a COX-independent or off-target effect, possibly involving phosphodiesterase-5 (PDE-5) inhibition and cyclic guanosine monophosphate (cGMP) elevation to induce apoptosis may contribute to their antineoplastic properties [7].

Chemical structures of most common NSAIDs.
1.2. NSAIDs derivatives

Designing of NSAIDs prodrugs was not only successful in reducing some of side effects of NSIADs, but also it has been proved to contribute to the enhancement other properties such as improvement of physicochemical properties, optimizing route of administration and enhancement of pharmaceutical profile[8].

Literature review also provided that coupling of NSAIDS to amines was evidenced to be effective in reducing -specially- the GIT side effects of those drugs by masking the acidic moiety in the parent drug molecule. These derivatives also exhibited other effects such as antioxidant and anticancer activity[9].

2. (S)-Naproxen Derivatives

Naproxen and naproxen prodrugs with different amino acids esters have been synthesized and evaluated for their antiproliferative activity by Aboul-fadl et al. against HT29 colon cancer cell line. Naproxen displayed weak tumor cell growth inhibitory activity, causing only 60% inhibition at the top dose of 2000 µM. Nearly all derivatives (1) inhibited tumor cell growth with IC$_{50}$ values ranging from 14.6 - 120 µM [10].

\[ \text{Ester prodrugs of Naproxen (1)} \]

\[
\begin{array}{c}
\text{R= Aromatic or aliphatic chain, } \\
\text{R'}= -\text{CH}_3 \text{ or } -\text{CH}_2\text{CH}_3, n=0 \text{ or } 1, \\
\text{Prodrug of glycine ethyl ester (3) was the most potent derivatives and it has shown selective as well as dose-dependent activity against HT29, SW480 and HCT11 with IC$_{50}$ values ranging from 11.9-17.6 µM and the normal human colonocyte cell line, NCM460 was found to be less sensitive with IC$_{50}$ of 70.7 µM.} \\
\text{Glycine ethyl ester prodrug of Naproxen (3)}
\end{array}
\]

Naproxen was found to be inactive to inhibit colon tumor cell growth, but weakly inhibited the growth of normal colonocytes with an IC$_{50}$ of 490.8 µM. These results demonstrate that the amide modification of naproxen can increase tumor potency as well as selectivity for tumor cells by a COX-1 and COX-2 independent mechanism since these derivatives did not inhibit COX enzyme.
Jolly Deb and his colleague synthesized a novel derivative of (S)-Naproxen Sodium which proved to be effective in-vitro against Human Breast Cancer. Introducing a terminal Amide functionality in the parent naproxen molecule was the approach to this novel derivative (4).

![Chemical structure of (4)](image)

The synthesized derivative was tested in-vitro against MCF-7 (poorly invasive) and MDA-MB-231 (highly invasive) human cancer cell. Results show that the derivative was effective against both types of cells with IC$_{50}$ of approximately 3 μM and 6 μM, respectively. Early induction of apoptosis with subsequent activation of intrinsic caspase-cascade without an evidence of delaying cell cycle was the proved mechanism of the observed effects [11].

3. Sulindac Derivatives

Series of sulindac sulfide (SS) derivatives (5a &b) with carboxylate modifications was screened for tumor cell growth and COX inhibitory activity. A sulindac sulfide amide (SSA) with a N,N-dimethylethyl amine substitution (5b) was found to lack COX-1 and COX-2 inhibitory activity, yet potently inhibit the growth of human colon tumor cell lines, HT-29, SW480, and HCT116 with IC$_{50}$ values of 2 to 5 μmol/L compared with 73 to 85 μmol/L for SS. The mechanism of growth inhibition involved the suppression of DNA synthesis and apoptosis induction. Moreover, SSA has potential safety and efficacy advantages for colon cancer chemoprevention as well as utility for treating malignant disease if combined with chemotherapy [12].

![Chemical structures of 5a and 5b](image)

Sulindac sulphide derivatives

4. Ibuprofen Derivatives

Novel conjugates of the ibuprofen with nontoxic oligo (3-hydroxybutyrate) (OHBs), (6), were prepared and revealed significant antiproliferative activity against HT-29 and HCT 116 colon cancer...
cells. These conjugates are less toxic as was shown in oral acute toxicity test in rats compared to the parent drugs. Although the mechanism of antiproliferative activity of the prepared conjugates has to be established, it might be partially related to more effective cellular uptake of the conjugate than the free drug [13].

Ibuprofen oligo 3-hydroxybutyrate (6)

These results presented lead to the conclusion that the conjugation of ibuprofen with oligomers of OHBs can be a novel kind of modification to increase anticancer potential of the drug.

5. Diclofenac Derivatives

A series of novel Thiolated and non Thiolated polyaspartamide polymer conjugates of Diclofenac (7a &b) were synthesized by Zorc et al. and tested in-vitro for possible antiproliferative effects against six Human cell lines five of which were derived from five cancer types (HeLa, MCF-7, SW 620, MiaPaCa-2, Hep-2) and one from diploid fibroblasts (WI 38).

The synthesized compounds exhibited strong growth inhibitory effects against all cell lines with the IC50 concentrations ranging between 26 and 67µgml−1[14].

The mechanism of antitumor activity of these novel derivatives is poorly understood but efficacy of these derivatives could be attributed to advantages of polymer - drug conjugates over other drug delivery systems.

6. Ketoprofen and Fenoprofen Derivatives

A series of fenoprofen and ketoprofen amide derivatives were synthesized by Marjanovic et al. and were tested on proliferation of different human tumor cell lines and normal human fibroblasts in vitro.
[15]. Fenoprofen and ketoprofen showed modest antiproliferative activity, whereas the growth inhibitory activity of the tested amides clearly demonstrates that the substituents linked by an amide bond are essential for the significantly stronger cytostatic activity, probably because of a greater lipophilicity and/or better cell uptake. Additionally, it was shown that the most active derivatives were 8a and 8b which are cyclohexyl-bearing compounds induced cell cycle arrest at the G1 phase, as well as apoptosis, which are major mechanisms of NSAIDs antitumor activity.

\[
8a \quad \text{and} \quad 8b
\]

\textbf{Fenoprofen and Ketoprofen Amide derivatives}

Compounds 8a and 8b inhibited more strongly the growth of tumor cells than the growth of normal fibroblasts. Marjanovic et al. suggested that their investigations should form the basis for further research and synthetic optimization of novel NSAID amides as potential prodrugs for antitumor therapy or chemopreventive application with less-toxic side effects [15].

Zorc et al. also synthesized a novel Fenoprofen derivative (9) that was tested in-vitro for anti-tumor activity.

\[
\text{Fenoprofen Polymer conjugate (9)}
\]

The method used for synthesis and Biological evaluation was the same as the approach used for Diclofenac derivative with the IC\(_{50}\) concentrations of \(\geq 160\mu\text{gml}^{-1}\) suggesting inferior activity than the Diclofenac derivative[14].

\section*{7. Celecoxib Derivatives}

Although Celecoxib is a known selective COX-2 inhibitor, some evidence shows that tumor inhibiting activity of Celecoxib is COX-independent, suggesting that it act through Induction of apoptosis and arresting of cell cycle [16].
A series of novel structures (10) referred as ‘second generation Celecoxib derivatives’ lacking COX-2 inhibitory activity were synthesized and evaluated for their anticancer activity against human oral cancer lines by Steven M. D’Ambrosio and his colleagues who made a structural modification in

![Second generation celecoxib derivatives (10a-p)](image)

Compounds (10a-p) were designed by introducing polar substituent at the terminal phenyl moiety of Celecoxib, this modification greatly enhances their apoptosis and cell cycle delay. Activation of caspases 9, 3 and 8 with the accompanying disruption of mitochondrial membrane is the suggested mechanism of the apoptotic effects of these derivatives[17].

A novel nitro-oxy derivative of celecoxib (11) was also synthesized by Claudia bocca et al and they proved that the derivative which modified to have two NO releasing moieties was similarly effective as parent Celecoxib molecule when tested in-vitro against COX-2-positive (HT-29) and -negative (SW-480) colon cancer cells.

![Nitro-oxy Derivative of Celecoxib (11)](image)

Mechanism behinds this effects is attributed to induction of apoptosis with a suggestion of presence of COX-2-dependent actions [18].

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8. NO-NSAIDs

Novel nitric oxide (NO)-donating NSAIDs (12a-f), consisting of a traditional NSAIDs, acetyl salicylic acid 12a, salicylic acid 12b, indomethacin 12c, ibuprofen 12d, flurbiprofen 12d and sulindac 12e to which a NO releasing moiety is attached through covalent modification of carboxylate moiety [19].

NO-NSAIDs (12a-f), the Traditional NSAID is shown in red colour. The spacer molecule links the traditional NSAID to –NO₂, which can release NO

All NO-NSAIDs have greater potency in inhibiting HT-29 and HCT-15 colon cancer cell growth compared to their NSAID counterparts: the IC₅₀s of the NO-NSAIDs were enhanced between 7- and 689-fold in HT-29 cells and 1.7 to 1083-fold in HCT-15 cells over those of the corresponding NSAIDs. Their growth inhibitory effect is due to a profound cell kinetic effect consisting of reduced cell proliferation and enhanced cell death. Since HT-29 cells express cyclooxygenases, but HCT-15 does not and this effect appears independent of COX in the colon cancer cells. Thus, the structural modification of these traditional NSAIDs leading to NO-NSAIDs enhances their potency in inhibiting colon cancer cell growth. This study suggests that the enhanced potency imparted on NSAIDs by this chemical structural modification represents a pharmacological property that may be a general one for this class of compounds [19].

9. Phospho-NSAIDs

Phospho-NSAIDs (13a-c) are intriguing compounds that consist of an NSAID molecule that is connected to dialkylphosphate via a linker, this group of compounds has been extensively tested,

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especially phospho-aspirin 13a as anticancer agents. With regard to anticancer activity, phospho-sulindc 13b, phospho-ibuprofen 13c and phospho-flurbiprofen 13d and phospho-deoxysulindac 13e have been shown to inhibit tumor growth by suppressing cell proliferation and enhancing apoptosis. Compounds 13b and 13c were shown to be effective in vivo with no detectable animal toxicity [20].

Phospho-NSAIDs are proposed to act through a COX-independent mechanism [20] and/or induction of reactive oxygen and nitrogen species (RONS) [21]. In vivo, it was found that carboxylesterases 1 and 2 can hydrolyze phospho-NSAIDs. Recently, it has been determined that the intact phospho-NSAID molecule is required for its anticancer activity, and that inhibition of carboxylesterases enhances the efficacy of phospho-NSAIDs both in vitro and in vivo [22]. Huang et al. have concluded that, phospho-NSAIDs may have anticancer and cancer chemopreventive activity as potential and important alternative pharmacological actions for classical NSAIDs [23].

10. Phosphoramidate-NSAIDs Derivatives

A study involved synthetic optimisation of novel NSAID derivatives as prodrugs for anticancer therapy or chemopreventive applications with less toxic side effects, has proved that phosphoramidate derivatives of fenoprofen, ketoprofen, ibuprofen, indomethacine and diclofenac (fig 14) possess
significantly higher antiproliferative activities than the corresponding NSAID 3-hydroxypropylamides probably due to a better cell uptake [24].

\[ R = \text{NSAID} \]

\[ \text{NSAIDs Phosphoramidate Derivatives (14)} \]

Phosphoramidate strategy has also been applied to NSAIDs to synthesize novel NSAID derivatives as potential prodrugs for anticancer therapy or chemopreventive applications with less toxic side effects. Phosphoramidate derivatives have been synthesized as possible mutual prodrugs for FU, meloxicam 15a and ibuprofen 15b to selectively deliver the drugs into the cancer cells [25].

11. NSAIDs Nano-Prodrugs
Monomeric and dimeric nanoprodrugs of ibuprofen, indomethacin and naproxen 16-18a and 16-18b, respectively) have been prepared and evaluated for their effect on the proliferation of U87-MG glioma cells. The two nanoprodrugs 17a,b inhibited the cell growth more potently than the nanoprodrugs 16a,b, whereas the nanoprodrugs 18a,b did not show any significant effect. Remarkably, 17a,b did not show any effect at an equimolar concentration. Approximately, 4.4% of the nanoprodrugs 17a,b was found in the cell, whereas no 18a,b could be detected suggesting that the superior effect of the nanoprodrugs can be attributed to the efficient cellular uptake of the nanoprodrugs [26].

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Nanoprodrugs of some NSAIDs (16,17,18 a-b).

In extension of the previous work hydrophobic monomeric 19 and dimeric nanoprodrugs 20 of the NSAID flufenamic acid were prepared as potential anticancer agents. The nanoprodrugs were in the size range of 120 to 140 nm and physicochemically stable upon long-term storage as aqueous suspension, which is attributed to the strong hydrophobic interaction between prodrug molecules. Despite the highly hydrophobic nature and water insolubility, nanoprodrugs could readily be activated into the parent drug by porcine liver esterase, presenting a potential new strategy for novel NSAID prodrug design. The nanoprodrug inhibited the growth of U87-MG glioma cells with IC$_{50}$ of 20 $\mu$M, whereas flufenamic acid showed IC$_{50}$ of 100 $\mu$M, suggesting that more efficient drug delivery was achieved with nanoprodrugs [27].
References


16. Kddld


