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

Tilal Elsaman*, Musab M. Ali

Department of Pharmaceutical Chemistry, College of Pharmacy, Omdurman Islamic University, P.O. Box 2547, Khartoum 11452, Sudan
*Author to whom correspondence should be addressed; E-Mail: Tilochem@yahoo.com;
Tel.: +249121127273; fax: +249 14676220

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

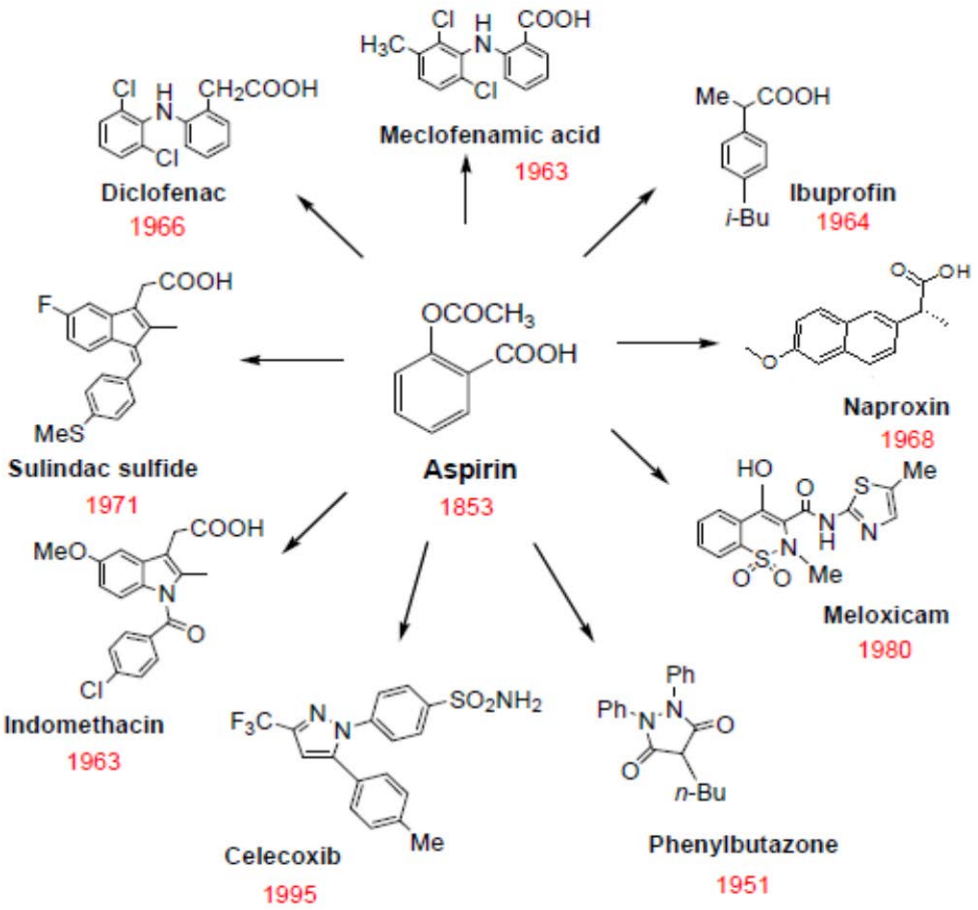
{**Citation:** Tilal Elsaman, Musab M. Ali. Nonsteroidal anti-inflammatory drugs (NSAIDs) derivatives with anti-cancer activity. American Journal of Research Communication, 2016, 4(4):} www.usa-journals.com, ISSN: 2325-4076.

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.

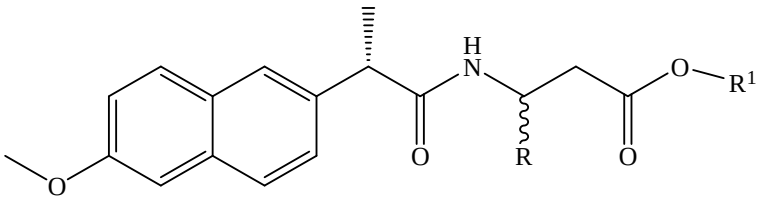
1.2. NSAIDs derivatives

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

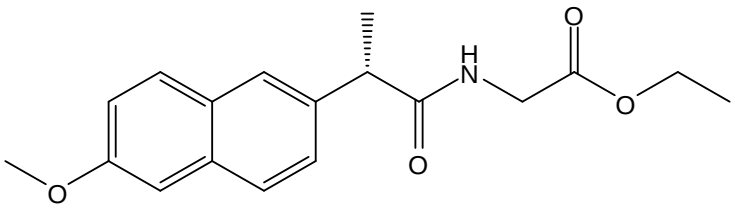
Naproxen and naproxen prodrugs with different amino acids esters have been synthesized and evaluated for their antiproliferative activity by Aboul-fadl et al. againist HT29 colon cancer cell line. Naproxen displayed weak tumor cell growth inhibitory activity, causing only 60% inhibition at the top dose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



Ester prodrugs of Naproxen (1)

R= Aromatic or aliphatic chain, $\mathbf{R^1}$= -CH_3 or –CH_2CH_3, **n**=0 or 1,

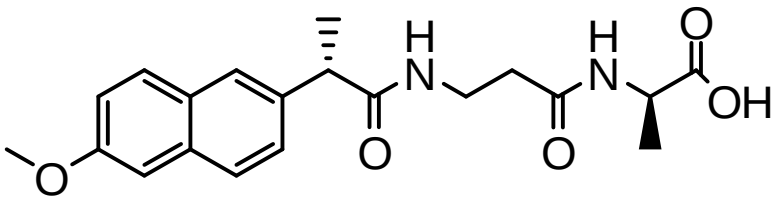
Prodrug of glycine ethyl ester **(3)** was the most potent derivatives and it has shown selective as well as dose-dpendent activity against HT29, SW480 and HCT11 with IC_{50} values ranging from 11.9-17.6 µM and the normal human colonocyte cell line, NCM460 was found to be less sensitive with IC_{50} of 70.7 µM**.**



Glycine ethyl ester prodrug of Naproxen (3)

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-virto* against Human Breast Cancer. Introducing a terminal Amide functionality in the parent naproxen molecule was the approach to this novel derivative **(4).**

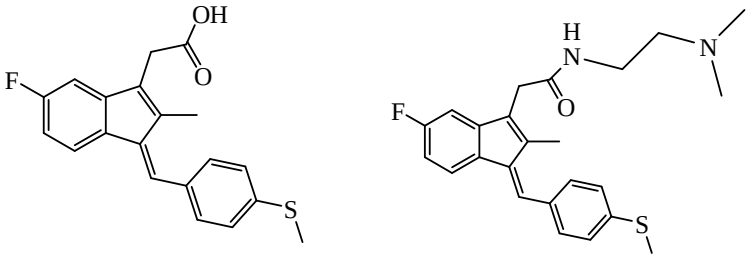


(4)

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].



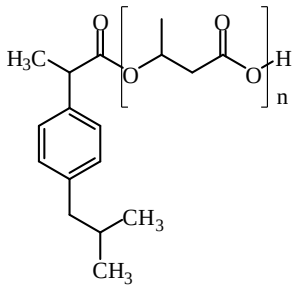
5a **5b**

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].

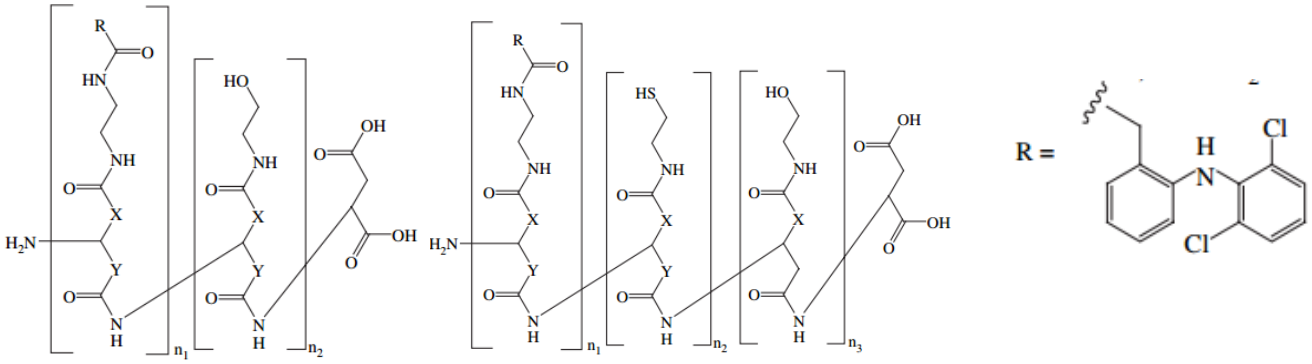


Ibuprofen oligo 3-hydroxybutyrate (6)

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).



7a **7b**

Diclofenac polymer conjugates

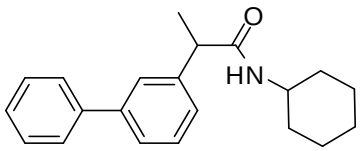
The synthesized compounds exhibited strong growth inhibitory effects against all cell lines with the IC_{50} concentrations ranging between 26 and 67µgml^{-1}[14].

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.

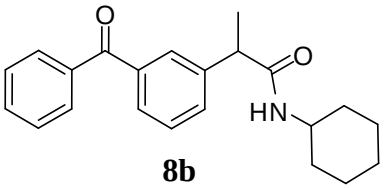
6. Ketoprofen and Fenoprofen Derivatives

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

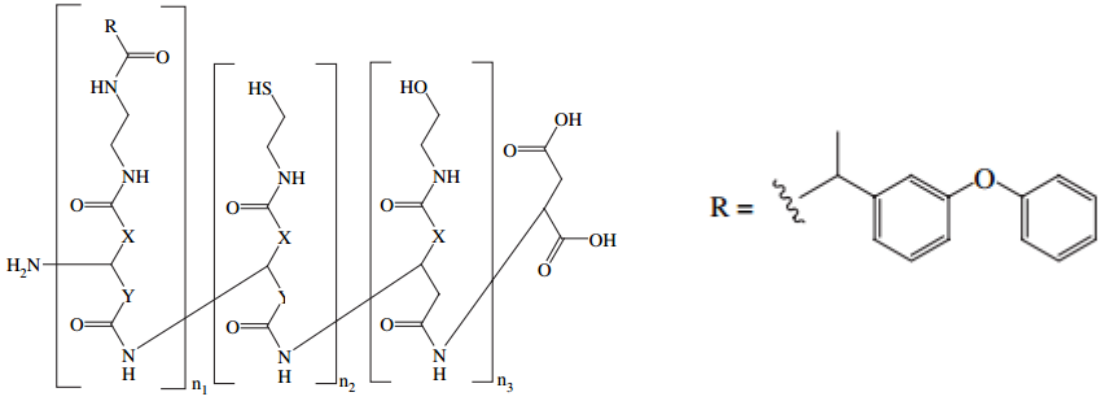


8b

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.



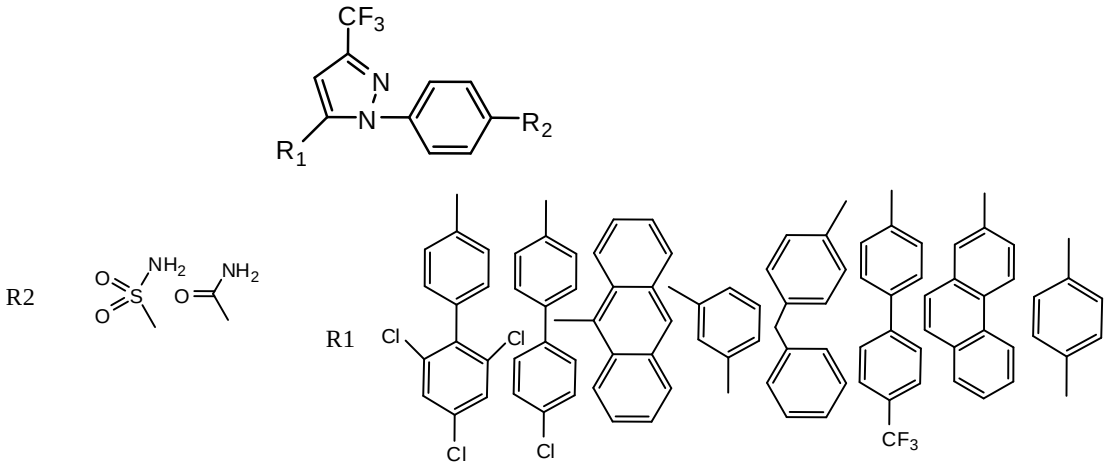
Fenoprofen Polymer conjugate (9)

The method used for synthesis and Biological evaluation was the same as the approach used for Diclofenac derivative with the IC_{50} concentrations of $\geq 160 \mu g ml^{-1}$ suggesting inferior activity than the Diclofenac derivative[14].

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

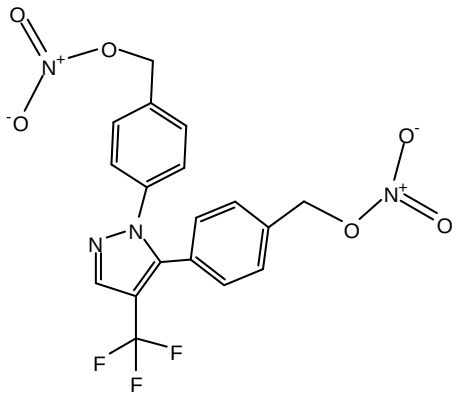


Second generation celecoxib derivatives (10a-p)

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.

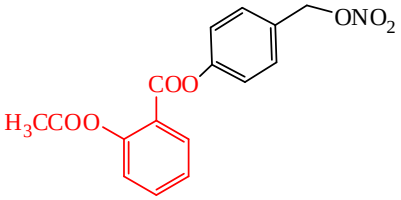


Nitro-oxy Derivative of Celecoxib (11)

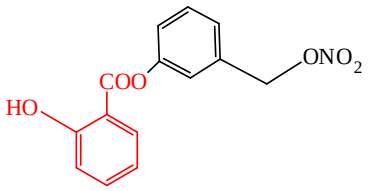
Mechanism behinds this effects is attributed to induction of apoptosis with a suggestion of presence of COX-2-dependent actions [18].

8. NO-NSAIDs

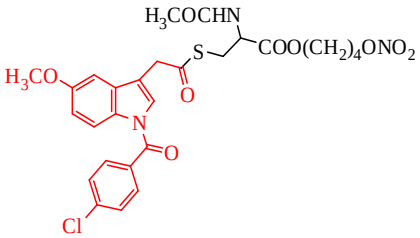
Novel nitric oxide (NO)-donating NSAIDs **(12a-f)**, consisting of a traditional NSAIDs, acetyl salicylic acid **12a**, salicylic acid **12b**, indomethacin **12c**, ibuprofen **12d**, flurbiprofen **12d** and sulindac **12e** to which a NO releasing moiety is attached through covalent modification of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



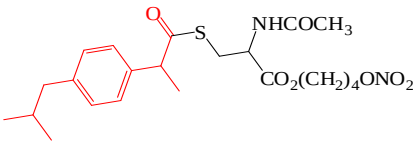
12 a



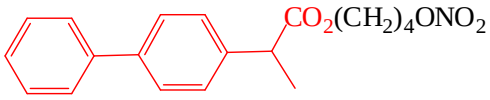
12 b



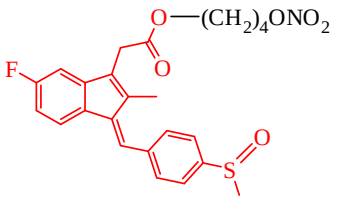
12 c



12 d



12 e



12 f

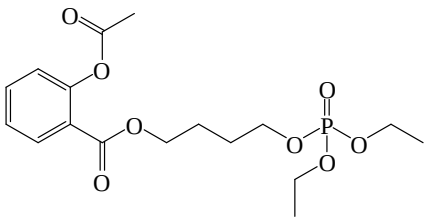
NO-NSAIDs (12a-f), the Traditional NSAID is shown in red colour. The spacer molecule links the traditional NSAID to –NO_2, which can release NO

All NO-NSAIDs have greater potency in inhibiting HT-29 and HCT-15 colon cancer cell growth compared to their NSAID counterparts: the IC_{50}s 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].

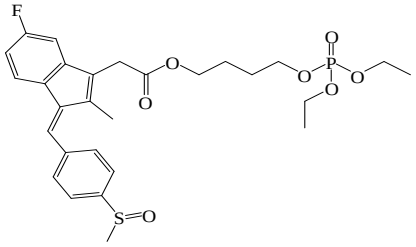
9. Phospho-NSAIDs

Phospho-NSAIDs **(13a-e)** 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,

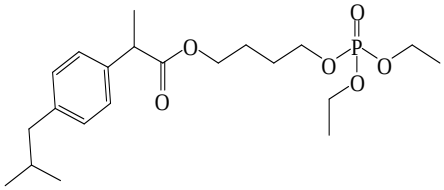
especially phospho-aspirin **13a** as anticancer agents. With regard to anticancer activity, phospho-sulindc **13b**, phospho-ibuprofen **13c** and phospho-flurbiprofen **13d** and phospho-deoxysulindac **13e** have been shown to inhibit tumor growth by suppressing cell proliferation and enhancing apoptosis.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



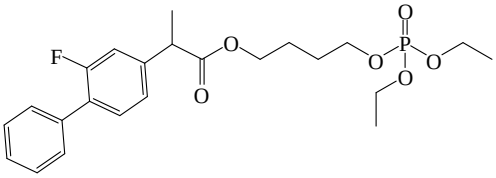
13a



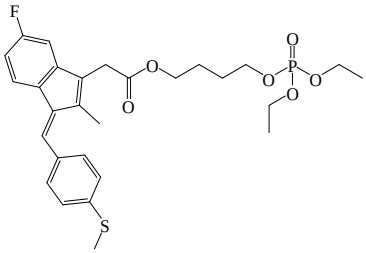
13b



13c



13d



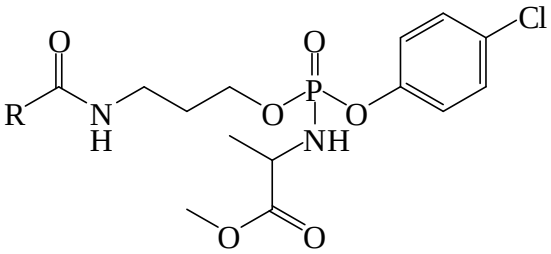
13e

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

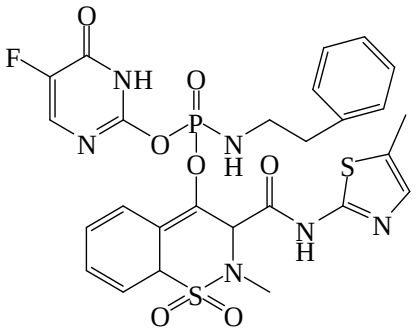
significantly higher antiproliferative activities than the corresponding NSAID 3-hydroxypropylamides probably due to a better cell uptake [24].



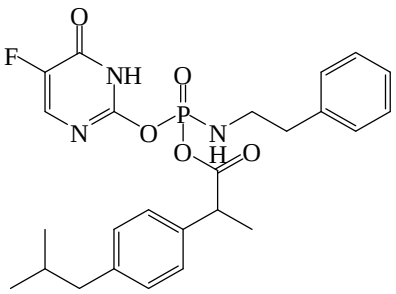
R=NSAIDS

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].



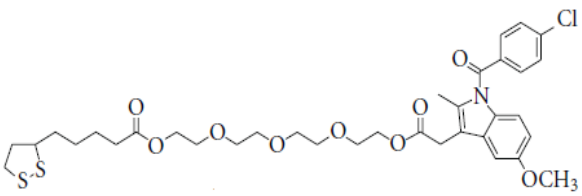
15a



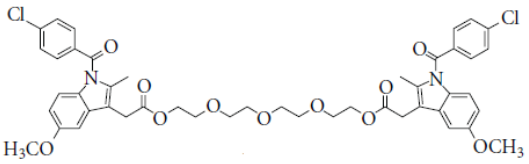
15b

11. NSAIDs Nano-Prodrugs

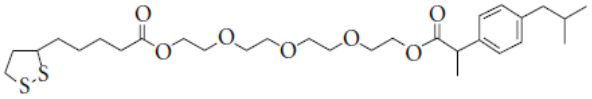
Monomeric and dimeric nanoprodrugs of ibuprofen, indomethacin and naproxen **16-18a** and **16-18b**, respectively**)** have been prepared and evaluated for their effect on the proliferation of U87-MG glioma cells. The two nanoprodrugs **17a,b** inhibited the cell growth more potently than the nanoprodrugs **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].



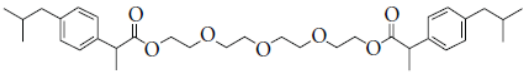
16a



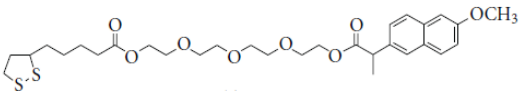
16b



17a



17b

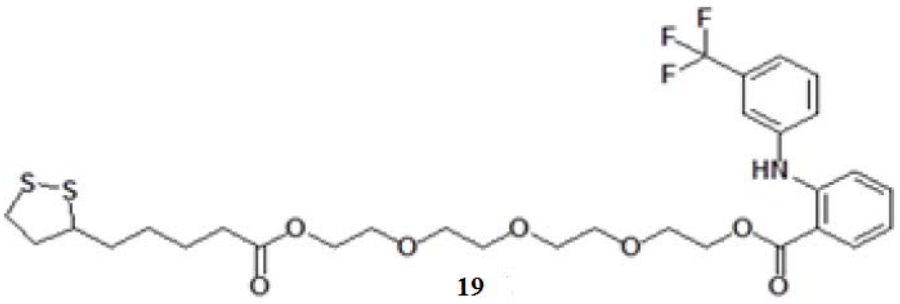


18a

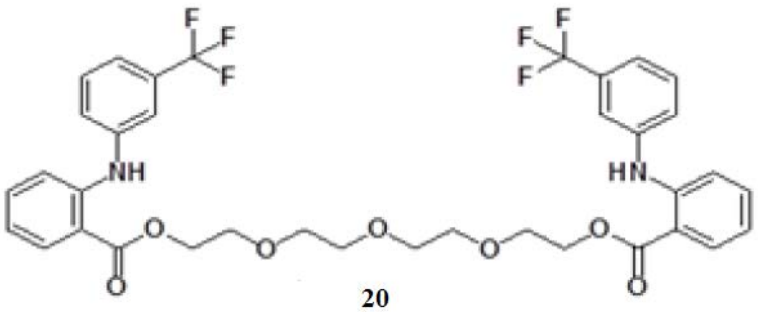
18b

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 μM, whereas flufenamic acid showed IC_{50} of 100 μM, suggesting that more efficient drug delivery was achieved with nanoprodrugs [27].



19



20

References

1. Meek, L.I.; Mart, A. F.J.; Dee lar, V.; Vonkeman, E. H. Non-Steroidal Anti-Inflammatory Drugs: An Overview of Cardiovascular Risks, *Pharmaceuticals* 2010, *3*, 2146-2162.
2. Melnikova, I. Pain market. *Nat. Rev. Drug Discov.* 2010, *9*, 589-590.
3. Vane, J.R.; Botting, R.M. The mechanism of action of aspirin. *Thromb. Res*. 2003, *110*, 255-258.
4. Jemal, A.; Bray, F.; Melissa, M.; Ferlay, J.; Ward, E.; Forman, D. Global cancer statistics, *Cancer. J. Clin.* 2011, *61*, 69-90.
5. Wakabayashi, K. NSAIDs as Cancer Preventive Agents. *Asian Pacific Journal of Cancer Prevention* 2000, *1*, 97-113.
6. Chan, T.A. Nonsteroidal anti-inflammatory drugs, apoptosis, and colon-cancer chemoprevention. *Lancet. Oncol*. 2002, *3*, 166-174.
7. Piazza, G.A.; Keeton, A.B.; Tinsley, H.N.; Whitt, J.D.; Gary, B.D.; Mathew, B.; Singh, R.; Grizzle, W.E.; Reynolds, R.C. NSAIDs: Old Drugs Reveal New Anticancer Targets. *Pharmaceuticals* 2010, *3*, 1652-1667.
8. Amjad M. Qandil. Prodrugs of Nonsteroidal Anti-Inflammatory Drugs(NSAIDs), More Than Meets the Eye: A Critical Review.*International Journal of Pharmaceutical Science* 2012, 13, 17244-17274.
9. M.Himaja.;Poppy das.;Rout P.K.;sanjay Sharma.;Munirajasekhar D.;Karigar A.A.synthesis,docking and Antioxidant activity of some NSAIDs derivative of amine.
10. Tarek Aboul-Fadl.; Suliman S. Al-Hamad.; Kevin Lee.; Nan Li.; Bernard D. Gary.; Adam B. Keeton.; Gary A. Piazza,; Mohammed K. Abdel-Hamid. Novel non-cyclooxygenase inhibitory derivatives of naproxen for colorectal cancer chemoprevention. *Medicinal Chemistry Research*,2014,10
11. Jolly Deb.; Joydeb Majumder.; Sankar Bhattacharyya.; Siddhartha Sankar Jana. A novel naproxen derivative capable of displaying anti-cancer and anti-migratory properties against human breast cancer cells.*BioMedical Central*, Cancer 2014,14 ,1471-2407.
12. Gary A. Piazza.; Adam B. Keeton.; Heather N. Tinsley.; Bernard D. Gary.; Jason D. Whitt.; Bini Mathew.; Jose Thaiparambil.; Lori Coward.;Gregory Gorman.; Yonghe Li.; Brahma Sani.; Judith V. Hobrath.; Yulia Y. Maxuitenko.; Robert C. Reynolds. A Novel Sulindac Derivative That Does Not Inhibit Cyclooxygenases but Potently Inhibits Colon Tumor Cell Growth and Induces Apoptosis with Antitumor Activity. *CancerPreventionResearch*, 2009;2, 1940-6207.
13. Barbara Zawidlak.; Micha1 Kawalec.; Izabela Bosek.; Maria quczyk-Juzwa.; Gra_ zyna Adamus.; Aleksandra Rusin.; Piotr Filipczak.; Magdalena G1owala.; Katarzyna Wolan´ska.; Zdzis1aw

Krawczyk.; Piotr Kurcok. Synthesis and antiproliferative properties of ibuprofen–oligo(3-hydroxybutyrate) conjugates. *European Journal of Medicinal Chemistry*, 2010,45, 1833–1842.

14. M. Barbaric.; M. Kralj.; M. Marjanovic.; I. Husnjak.; K. Pavelic.; J. Filipovic´-Grcic´.; D. Zorc.; B. Zorc. Synthesis and in vitro antitumor effect of diclofenac and fenoprofen thiolated and nonthiolated polyaspartamide-drug conjugates. *European Journal of Medicinal Chemistry*, 2007, 42,20-29.
15. Marko Marjanovic.; Branka Zorc.; Lana Pejnovic.; Marijana Zovko.; Marijeta Kralj. Fenoprofen and Ketoprofen Amides as Potential Antitumor Agents. *Chem Biol Drug Des*, 2007, 69, 222–226.
16. Kddld
17. Haiming Ding.; Chunhua Han.; Jiuxiang Zhu.; Ching-Shih Chen.; Steven M. D'Ambrosio. Celecoxib derivatives induce apoptosis via the disruption of mitochondrial membrane potential and activation of caspase 9 .intrernational Journal Of Cancer, 2005, 113, 803– 810.
18. CLAUDIA BOCCA1.; FRANCESCA BOZZO.; ANDREA BASSIGNANA.;ANTONELLA MIGLIETTA. Antiproliferative Effect of a Novel Nitro-oxy Derivative of Celecoxib in Human Colon Cancer Cells: Role of COX-2 and Nitric Oxide. Anticancer Research, 2010,30,2659-2666.
19. Raymond K. Yeh.; Jie Chen.; Jennie L. Williams.; Mehdi Baluch.; Thomas R. Hundley.; Raphael E. Rosenbaum.; Srinivas Kalala.; Frank Traganos.; Francesca Benardini.; Piero del Soldato.; Khosrow Kashfi.; Basil Rigas. NO-donating nonsteroidal antiinflammatory drugs (NSAIDs) inhibit colon cancer cell growth more potently than traditional NSAIDs: a general pharmacological property?. *Biochemical Pharmacology.* 2004, 67 , 2197–2205.
20. Huang L., Mackenzie G., Ouyang N., Sun Y., Xie G., Johnson F., Komninou D., RigasN B., The novel phospho-non-steroidal anti-inflammatory drugs, OXT-328, MDC-22 and MDC-917, inhibit adjuvant-induced arthritis in rats, Br. J. Pharmacol.,162,1521 (2011).
21. Sun Y., Huang L., Mackenzie G. G., Rigas B., Oxidative stress mediates through apoptosis the anticancer effect of phospho-nonsteroidal anti-inflammatory drugs: Implications for the role of oxidative stress in the action of anticancer agents, J. Pharmacol. Exp.Ther., 338, 775 (2011).
22. Wong C. C., Cheng K. W., Xie G., Zhou D., Zhu C. H., Constantinides P P., Rigas B. Carboxylesterases 1 and 2 hydrolyze phospho-nonsteroidal anti-inflammatory drugs: Relevance to their pharmacological activity, J. Pharmacol. Exp. Ther., 340, 422 (2012).
23. Huang L., Zhu C., Sun Y., Xie G., Mackenzie G., Qiao G., Komninou D., Rigas B. Phospho-sulindac (OXT-922) inhibits the growth of human colon cancer cell lines: A redox/polyamine dependent effect, Carcinogenesis., 31, 1982 (2010).
24. Witteni K., Benci K., Rajic´ Z., Zorc B., Kralj M., Marjanovic´ M., Pavelic´ K., De Clercq E., Andrei G., Snoek R., Balzarini J., Mintas M. The novel phosphoramidate derivatives of NSAID

3-hydroxypropylamides: Synthesis, cytostatic and antiviral activity evaluations, Eur J. Med. Chem., 44, 143 (2009).

25. Dakhel Z. A., Mohammad M. H., Synthesis of 5-Fluorouracil Derivatives as Possible Mutual Prodrugs with Meloxicam and Ibuprofen for Targeting Cancer Tissues, Iraqi J. Pharm. Sci., 20, 9 (2011).
26. Lee B. S., Yuan X., Xu Q., Ko M.K., Nalla A.K., Frankiel I., Shear T., Black K.L., Yu J.S., Nanoprodrugs of NSAIDs Inhibit the Growth of U87-MG Glioma Cells, J. Nanomaterials., 1 (2010).
27. Lee B. S., Yoon C.W., Osipov A., Moghavem N, Nwachokor D., Amatya R., Na R,. Pantoja J. L., Pham M. D., Black K. L., Yu J. S., Nanoprodrugs of NSAIDs: Preparation and Characterization of Flufenamic Acid Nanoprodrugs, J. Drug Deliv., 1(2011).