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Arylpropionic acid-derived NSAIDs: New insights on derivatization, anticancer activity and potential mechanism of action

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ABSTRACT

NSAIDs displayed chemopreventive and anticancer effects against several types of cancers. Moreover, combination of NSAIDs with anticancer agents resulted in enhanced anticancer activity. These findings have attracted much attention of researchers working in this field. The 2-arylpropionic acid-derived NSAIDs represent one of the most widely used anti-inflammatory agents. Additionally, they displayed antiproliferative activities against different types of cancer cells. Large volume of research was performed to identify molecular targets responsible for this activity. However, the exact mechanism underlying the anticancer activity of profens is still unclear. In this review article, the anticancer potential, structure activity relationship and synthesis of selected profen derivatives were summarized. This review is focused also on non-COX targets which can mediate the anticancer activity of this derivatives. The data in this review highlighted profens as promising lead compounds in future research to develop potent and safe anticancer agents.

Abbreviations: A549, human non-small lung cancer cell line; 2-AF, 2-aminofluorene; AKR1C3 enzyme, Aldo-keto Reductase 1C3; Akt, protein kinase B; ANGPTL4, angiopoietin-like protein 4; anti-MDR, anti-multi-drug resistance; 2APAs, 2-arylpropionic acids; B16 − F10, murine melanoma cells; Bel-7402, hepatocellular carcinoma; Bel-7402/5-FU, 5-FU resistant hepatocellular carcinoma; C logP, calculated logP; C6, glioma cell line; colo 205, human colon cancer; CDK1/2, cyclin-dependent kinase 1/2; CEM, human T-lymphocyte leukemia; COX-1/2, cyclooxygenases-1/2; ct-DNA, calf thymus DNA; DU-145, human prostate cancer cells; EGCG, epigallocatechin-3-gallate; EGFR, epidermal growth factor receptor; EPB, epirubicin; 5-FU, 5-fluorouracil; GBM, glioblastoma multiforme; Glut-1, glucose transporter-1; GM07492A, normal human lung fibroblasts; GSK-3b, glycogen synthase kinase-3b; H23, non-small-cell lung cancer cell line; H358, non-small-cell lung cancer cell line; H 460, non-small-cell lung cancer cell line; HaCaT, non-tumor human keratinocytes cell line; HCT 116 HCT-11, HCT15, human colon cancer cell lines; HeLa, human cervical carcinoma; Hep2, larynx cell line; HepG2, human liver cancer cell line; HGF, human gingival fibroblast; HIF-1, hypoxia-inducible factors; Hsp70, heat shock protein; HT29, human colon cancer cells; Ibu, ibuprofen; IC_{50}, half maximal inhibitory concentration; K-562, human erythroleukemic cell line; L1210, murine leukemia; LDH-A, lactate dehydrogenase-A; LNCaP, prostate cancer cell line; L-O2, human liver cells; 5-LOX, 5-lipoxygenase; MCF-7, breast cancer cell; MDA-MB-231, metastatic mammary adenocarcinoma cell line; MIA PaCa-2, human, Caucasian, pancreas, carcinoma; MKN-45, human gastric cancer cell line; MMP-9, matrix metalloproteinase-9; MMPs, matrix metalloproteinases; MO59J, human glioblastoma cell line; M-phase, mitotic phase; MTS, 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxy-phenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium; MTT, 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NAT, *N*-acetyltransferase; NF-κB, nuclear factor-κB; NHA, normal human astrocytes; NPs, nanoparticles; Npx, naproxen; NSAIDs, non-steroidal anti-inflammatory drugs; NSCLC, non-small-cell lung cancer; p38 MAPK, P38 mitogen-activated protein kinases; $P75^{NTR}$, the neurotrophin receptor p75; PC3, human prostate cancer cells; PEG, polyethylene glycol; Fmoc, 9-fluorenylmethoxycarbony; 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; PGE2, prostaglandin E2; PGIA, phospho-glycerol-ibuprofen-amide; PI, phospho-ibuprofen; PI3-K, phosphatidylinositol 3-kinase; PIA, phospho-ibuprofen amide; PKs, protein kinases; PLGA, poly (lactic-*co*-glycolic acid); PTX, paclitaxel; RGD, arginylglycylaspartic acid; S-phase, synthesis phase; STAT-3, signal transducer and activator of transcription 3; SW 620, human colon cancer; SW480, human colon carcinoma; T24/83, human bladder cell line; TNF, tumor necrosis factor; Trx, thioredoxin; U118-MG, human glioma cell line; U251, human glioblastoma; U373, human anaplastic astrocytoma; U87-MG, human glioma cell line; UM-UC-14, University of Michigan-Urothelial Carcinoma-14; UM-UC-5, human bladder cancer cell; VEGF, vascular endothelial growth factor; WI 38, normal lung cell

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1. Introduction

1.1. History

Profens are 2-arylpropionic acid (2APA)-derived nonsteroidal anti-inflammatory drugs (NSAIDs). They represent a subclass of NSAIDs which share 2-arylpropionic acid scaffold. Profens include large number of drugs such as ibuprofen, ketoprofen, naproxen, fenoprofen, flurbiprofen, carprofen, suprofen, benoxaprofen, pranoprofen and tiaprofenic acid, Fig. 1. Ibuprofen was discovered in 1960s in Boots Group during the research to find a new NSAID with better safety profile than aspirin [1]. Four years later, naproxen was introduced to the market. Moreover, ketoprofen was synthesized and by Rhône-Poulenc chemists. Ketoprofen with the short half-life and wide therapeutic window was released to the market in 1973 [2]. Fenoprofen was also introduced to the market in 1973. Flurbiprofen, carprofen, suprofen, benoxaprofen and tiaprofenic acid were introduced in 1980s, while the pranoprofen eye drops was approved in 1999 by china food and drug administration (CFDA).

1.2. Chemistry

Chemically, all profens bear the characteristic 2-aryl-propionic acid moiety. Except for tiaprofenic acid, other profens possess a substituted/fused phenyl ring directly attached to the α-carbon of propionic acid, Fig. 1. The 2APA are optically active compounds due to the presence of chiral carbon (α-carbon of propionic acid). Accordingly, two enantiomers, namely S- and R-enantiomers exist, Fig. 2. The biological activity and metabolic pathways of the 2APAs are stereospecific [3]. The S-enantiomer is the biologically active/more active isomer as an anti-inflammatory agent. Although the R-enantiomer is considered to be less active or inactive as anti-inflammatory agent, most of the drugs in this class are usually marketed as racemic mixtures. It was also reported that the inactive or less active R-enantiomer undergoes inversion to the active or more active S- enantiomer *in vivo* by isomerase enzyme [4]. This inversion of configuration of the R-enantiomer resulted in clinical benefits. The R-enantiomer of some 2APAs displayed anticancer activity; hence 2APAs are used as racemic mixture for their anti-inflammatory or for their chemopreventive effect.

1.3. Diverse pharmacological activities

Profens represent an important subclass of NSAIDs that have been used clinically as analgesic, antipyretic and anti-inflammatory agents [5,6]. Moreover, they have displayed diverse biological activities which are not basically related to inflammation or COX inhibition. Ibuprofen has demonstrated antibacterial activity against gram negative bacteria [7]. Carprofen and ibuprofen displayed specific antitubercular activity [8]. Moreover, ibuprofen has displayed antifungal activity against candida species [9]. On the other hand, conjugation of 2APAs with compounds with antioxidant or anticholinergic activities resulted in conjugates combining the activities of the two compounds [10].

1.4. COX and cancer

Since 1983, where the antiproliferative effect of sulindac was first observed in reducing colon adenomas [11], huge efforts have been exerted in evaluation of anticancer potential of NSAIDs. The role that COX enzymes play in cancer was investigated in many reports. The overexpression of COX-2 in various types of tumors provided an evidence for this opinion [12–14]. COX-2 inhibitors may also act synergistically or additively with anticancer agents to prevent or treat cancer [15]. Based on these reports, the mechanism of action of anticancer activity of NSAIDs can be mediated through one of the following:

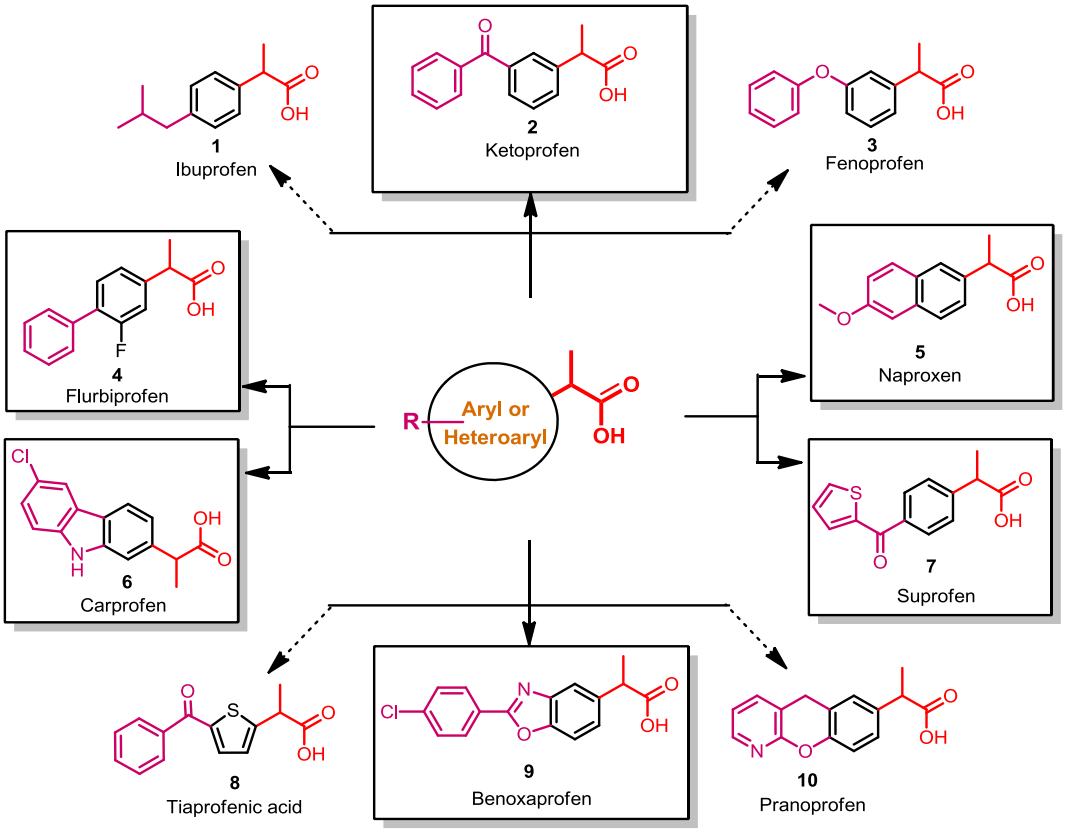


Fig. 1. Chemical structure of 2-Arylpropionic acid-derived NSAIDs (profens).

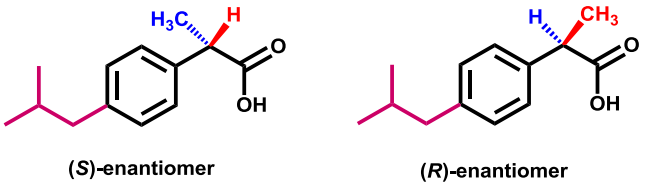


Fig. 2. *S*- and *R*-enantiomers of ibuprofen.

1.4.1. COX-dependent anticancer activity

One of the strong evidences which supported the role of COX enzymes in cancers is the over overexpression of COX-2 in different types of solid tumors [12–15]. The peroxidase part of COX enzymes may play an important role in cancer [16]. In addition, initiation of tumors in the epithelial cells of mammary glands was associated with overexpression of COX-2 [17]. The overexpression of COX-2 was also associated with development of resistance to the stimulated apoptosis in the intestinal epithelial cells [18]. Moreover, overexpression of COX-2 promotes metastasis and angiogenesis [19,20], inhibits apoptosis [21] and activates pro-carcinogen [22], Fig. 3.

Accordingly, COX inhibitors may mediate their anticancer activity through inhibition of metastasis [23], angiogenesis [24], and NF-kB [25]. In addition, NSAIDs induced apoptosis and inhibited tumor growth *in vivo* [26]. The induction of apoptosis was mediated by blocking Akt activation [27] or downregulation of Bcl-X(L) [28], Fig. 3. These findings drived a large volume of research in this area in the last three decades [29–31].

Recently, COX-1 overexpression in certain types of cancers was also reported [29]. The genetic disruption of both COX-1 and COX-2 were reported to decrease carcinogenesis [29]. Moreover, several evidences supporting the role of COX-1 in cancer were reported. The anticancer activity of selective COX-1 inhibitors provided a strong evidence for the important role of COX-1 in cancers [29–31].

1.4.2. COX-independent anticancer activity

On the other hand, many reports have attributed the anticancer activity of NSAIDs to their effects on targets other than COXs. The following are some of the evidences which support COX-independent mechanism of action. (1) Both selective and nonselective COX-2 inhibitors displayed anticancer activity [32,33]. (2) Some of NSAIDs have displayed anticancer activity although they lack COX inhibitory activity [34]. (3) Several of NSAIDs have displayed antiproliferative activity against COX-2 positive/negative cancer cells [35]. (4) Some of NSAIDs have similar COX inhibitory activity although they have different anticancer activity against the same cell lines [36]. (5) Additionally,

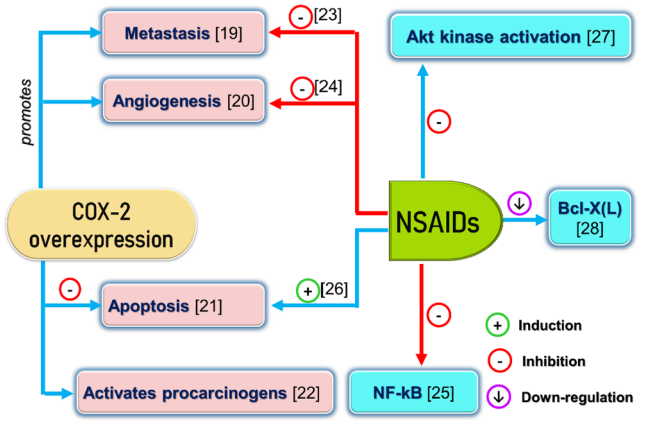


Fig. 3. Effects of COX-2 overexpression and NSAIDs on different targets/processes involved in cancers.

NSAIDs inhibit the growth of cancer cells at concentration higher than that required for COX inhibition [37]. All these findings encouraged researchers to investigated other potential targets which can mediated the anticancer activity of NSAIDs [38].

Generally, a great volume of research was carried out to investigate the role of NSAIDs in prevention and treatment of cancers [39,40]. But the research in this field encountered many problems which still need answers. Of these, (1) the absence of clear mechanism of action; (2) the presence of several studies which reported NSAIDs as risk-enhancing agents in cancer [41,42]; (3) most of the research in this filed has focused on aspirin-based and selective COX-2 inhibitor NSAIDs. Accordingly, it was of interest to review the literature for other NSAIDs. Profens were selected as one of the most widely used non-aspirin NSAIDs. In this review article, the anticancer potential, SAR, potential COX-independent mechanism of action and synthetic routs of selected profen derivatives were summarized.

2. Anticancer activities of profens and their derivatives

2.1. Ibuprofen

2.1.1. Ibuprofen and anticancer activity

Janssen et al. have investigated the antiproliferative effect of both S- and R-enantiomers of ibuprofen on HCT-116 colon cancer cell line [43]. The results revealed the ability of the two enantiomers inhibit proliferation of HCT-116 cells. These findings may support COX independent mechanism of ibuprofen [43,44]. By considering the IC_{50} values of the two enantiomers against HT-116 cells, no significant difference can be observed, Fig. 4. In addition, the apoptosis and cell cycle arrest induced by the two enantiomers in cancer cells were mediated by other targets such as p53, neutrophin receptor ($p75^{NTR}$) or Bax signaling pathways [38,43].

Palayoor et al. [45] have examined the effect of ibuprofen and other NSAIDs on the hypoxia-inducible factors (HIF) in PC3 and DU-145 cells. The study revealed the ability of ibuprofen to reduce the level of HIF-1α and HIF-2α. The reduction of HIFs was COX-2-independent and associated with downregulation of vascular endothelial growth factor (VEGF) and glucose transporter-1 (Glut-1).

Leidgens et al. [46] have examined the antiproliferative effect of ibuprofen against three human glioma cell lines including HTZ-349, A172, and U87MG. The results revealed strong inhibition of cellular growth and migration by ibuprofen. The two drugs decreased STAT-3 phosphorylation and induced c-myc expression and less lactate dehydrogenase-A (LDH-A) alteration at high doses. The study indicated that ibuprofen may exert its antiproliferative activity through COX- and lactate-independent mechanisms.

Khwaja et al. [38] have also provided an evidence that anticancer activity of NSAIDs is not mediated purely by inhibition of COX-2. Moreover, other targets such as the tumor and metastasis suppressor (neurotrophin receptor, $P75^{NTR}$) was suggested as potential target.

The ability of ibuprofen to induce $p75^{NTR}$ protein was evaluated where the results revealed comparable effect with that of R-flurbiprofen and indomethacin. The induction of $p75^{NTR}$ seems to be receptor specific. Moreover, the induction of $p75^{NTR}$ was dependent also on the type of cancers. It was observed that cell lines from urogenital system and

Fig. 4. Anticancer effect of the S- and R-ibuprofen against HT-116 cells.

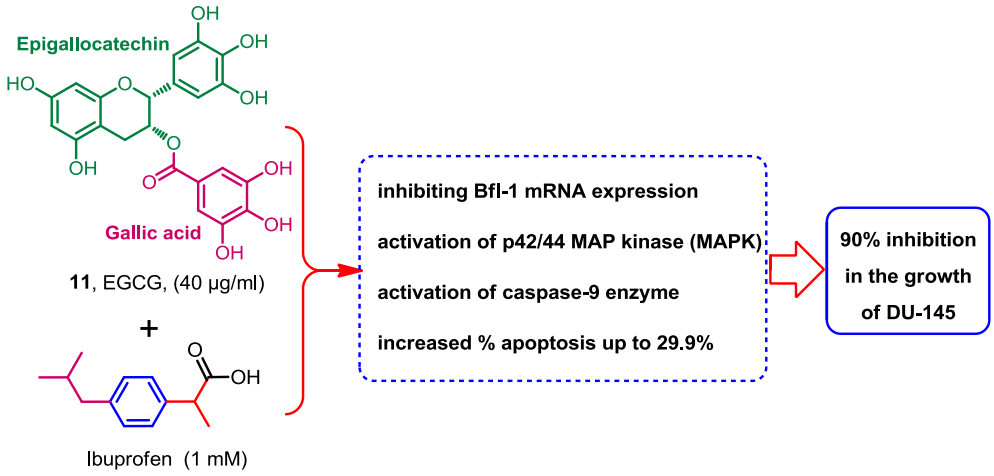


Fig. 5. The effect of EGCG-ibuprofen combination of DU-145 cells.

colon are more affected than breast or lung cancers. This study suggested that anticancer activity of ibuprofen is mediated by induction of $p75^{NTR}$ protein [38].

Targeting the enzymes involved in biotransformation and metabolism of hormones represents also a new strategy in treatment of hormonal dependent cancers such as prostate cancer, breast cancer and endometrial cancer. The peripheral 17β-hydroxysteroid dehydrogenase AKR1C3 is one of these enzymes which catalyzes the reduction of androstenedione and estrone to the more potent testosterone and estrone, respectively [47]. Accordingly, AKR1C3 enzyme represents a promising target for development of new anticancer agents that can target hormonal dependent cancers.

NSAIDs have been distinguished as potent inhibitors of AKR1C3. Gobec et al. have investigated the inhibitory activity of several NSAIDs on activity of AKR1C3 [48]. Ibuprofen displayed potent inhibitory activity of AKR1C3 enzyme with IC_{50} value of 33 μM. These results revealed that various members of profen family including ibuprofen are suitable inhibitors of the oxidative reaction catalyzed by AKR1C3. They can be considered as excellent initiatives for the design of new inhibitors of AKR1C3.

In addition, the cancer specific growth protein (tNOX) was identified also as a new target for NSAIDs including ibuprofen and naproxen [49]. tNOX is a surface protein responsible for the increase in cell size after cell division. It was considered as alternative target to COX-2 that can mediate anticancer activity of NSAIDs. Ibuprofen and naproxen specifically inhibited tNOX in HeLa and BT-20 cancer cell lines. A clear correlation could be observed between IC_{50} values for inhibition of both cellular growth and tNOX in HeLa cells.

In prostate epithelial cells, $P75^{NTR}$ was reported to play an important role as a tumor suppressor [50]. Treatment of PC3 and DU-145 prostate cancer cells by ibuprofen resulted in a decrease in their survival which was mediated by induction of $P75^{NTR}$ [51]. The increased level of $P75^{NTR}$ protein was mediated by an increase in stability of the $P75^{NTR}$ mRNA rather than upregulation of transcription. The increased stability of $P75^{NTR}$ mRNA was mediated by p38 MAPK pathway [51].

The emerging role of 15-hydroxyprostaglandin dehydrogenase (15-PGDH) as a tumor suppressor was also in focus. Chi et al. [52] have studied the effect of several NSAIDs on activity of 15-PGDH in colon (HT29) cancer cells. Among these, ibuprofen displayed more than twofold increase in 15-PGDH activity after 24 h treatment at 50 μM. Accordingly, the anticancer activity of ibuprofen could be dependent on the induction of 15-PGDH expression.

Bonelli et al. [53] have investigated the antiproliferative activity of ibuprofen on MKN-45 cells. They have reported that the anticancer activity of ibuprofen was mediated by its effect on cell cycle and induction of apoptosis which are independent on COX inhibition. The changes in gene expression caused by ibuprofen were studied using microarray. The results of microarray analysis suggested that ibuprofen affect cell cycle through affecting the expression of p53 and p53-induced genes. In addition, significant expression of the genes associated with apoptosis was observed 72 h after treatment with ibuprofen. Cell cycle analysis revealed an early block at G1 phase. An increase in reactive oxygen species was also observed intracellularly [53].

Ibuprofen has displayed *in vitro* antiproliferative activity at high concentrations. Enhancing the anticancer activity of ibuprofen could reduce the dose required to achieve the desired response. Several studies were performed to evaluate the release and biological effect of ibuprofen from nanoparticles. Bonelli et al. [54] have reported poly (lactic-*co*-glycolic acid) (PLGA) nanoparticles (NPs) with better antiproliferative activity against human gastric adenocarcinoma (MKN-45) cells at very low concentrations. Treatment of MKN-45 cells by ibuprofen-loaded PLGA NPs resulted in antiproliferative activity even at concentration 100 times less than ibuprofen. To investigate the potential mechanism of action, real-time PCR was used to analyze Angiopoietin-like protein 4 (ANGPTL4, known also as peroxisome proliferator-activated receptor gamma (PPARγ)) in MKN-45 cells. The cells treated with ibuprofen-loaded PLGA NPs showed higher level of Angiopoietin-like protein 4 mRNA (ANGPTL4 mRNA) than those treated with ibuprofen. The overexpression of ANGPTL4 was reported to inhibit the proliferation of cancer cells [55].

Tewari et al. have also investigated the effect of ibuprofen and aspirin on proliferation of HeLa cells. Ibuprofen decreased viability of HeLa cells to 80% and 70% at a concentration of 100 μM and 500 μM, respectively. The cell death caused by ibuprofen was significantly lesser than that caused by aspirin [56].

NSAIDs displayed antiproliferative activity in different phenotypes which suggested that they have targeted a general pathway existing in different cancers. Encouraged by this conclusion, Norvaisas et al. [57] have examined the ability of several NSAIDs to inhibit protein kinases (PKs) including ABL1, B-RAF, C-RAF, EGFR, FLT1, FLT3, FMS, FYN, KDR, KIT, RET, and SRC. Of these NSAIDs, ibuprofen displayed mild inhibition of several kinases.

2.1.2. *Ibuprofen combinations*

Several combinations of ibuprofen and anticancer agents were evaluated for their growth inhibitory activity against different types of cancer cells. The combinations of ibuprofen and epigallocatechin-3-gallate (EGCG) **11** (Fig. 5) was evaluated for their effect on the growth of DU-145 prostate cancer cells [58]. Treatment of DU-145 cells with ibuprofen and EGCG resulted in 25% and 20% inhibition of cellular growth, respectively. On the other hand, Ibuprofen-EGCG combination displayed 90% inhibition in growth of DU-145 cells. In addition,

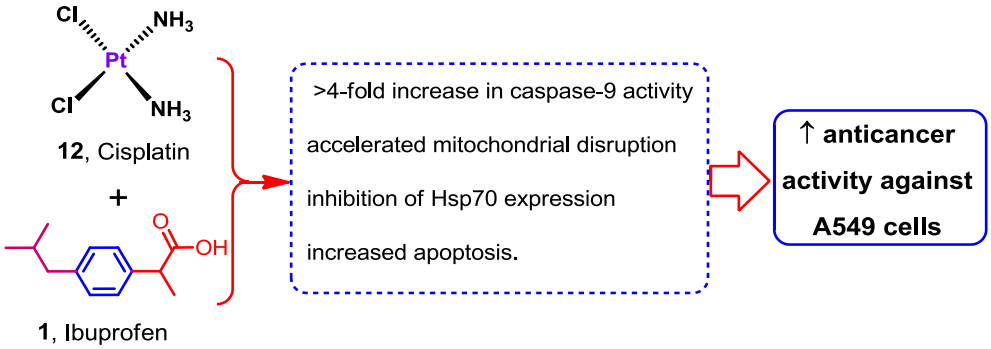


Fig. 6. The effects of cisplatin-ibuprofen combination on A549 cells.

ibuprofen (1 mM)-EGCG (40 μg/ml) combination increased apoptosis to 29.9% compared to 5.4% for EGCG (40 μg/ml) and 11.6% for ibuprofen (1 mM). The induced apoptosis after treatment with ibuprofen- EGCG combination was mediated by inhibition of the anti-apoptotic protein Bfl-1 mRNA expression, increasing the phosphorylation (activation) of p42/44 MAP kinase (MAPK) and activation of caspase-9 enzyme [58].

The stress-inducible heat shock protein Hsp70 (a member of human Hsp70 family) is usually overexpressed in different types cancers and plays an important role in cell survival. Endo et al. [59] have reported the ability of ibuprofen to inhibit Hsp70 expression through transcriptional inactivation resulting in enhancing the anticancer effect of cisplatin *in vitro*. Ibuprofen accelerated mitochondrial disruption caused by cisplatin and increased apoptosis. The mechanism of these effects was mediated by the inhibition of Hsp70 expression, Fig. 6. The enhanced anticancer activity of cisplatin-ibuprofen combination could provide several advantages such as reducing the doses of cisplatin and decreasing toxicity/drug resistance [59].

2.1.3. Ibuprofen derivatives

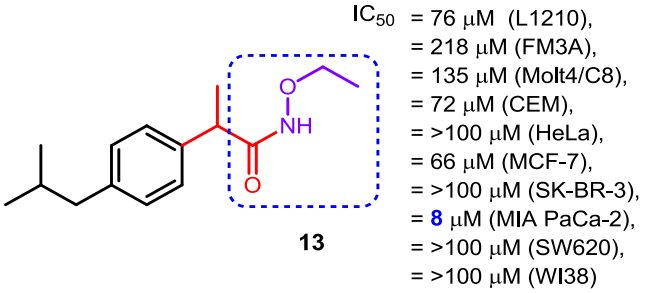
2.1.3.1. Ibuprofen hydroxamic acid/carbazide derivatives. Pavelic et al. [60] have investigated the anticancer activity of hydroxamic acid derivative **13** against several human cancer cell lines and normal human fibroblasts (WI38). The results of MTT assay revealed weak to potent cytotoxic activity for compound **13** with certain selectivity for cancer over normal cells. Compound **13** showed the highest activity against MIA PaCa-2 cells with IC_{50} value of 8 μM, Fig. 7.

Pavelic et al. [60] have also investigated the possible mechanism of action of compound **13**. Cell cycle analysis of MIA PaCa-2 cells treated with compounds **13** showed significant decrease in G0/G1 population with accumulation of cells in S phase. The anticancer activity of compound **13** was mediated through induction of p53-independent S phase cell cycle arrest and activation caspase 3-dependent apoptosis.

The results of western blot analysis of compound **13** revealed inhibition of the pro-survival Akt signaling pathway after 48 with complete depletion of the pAkt. The observed inhibition in cellular viability was attributed partially to the Akt-mediated pro-survival signaling [60].

Perkovic et al. [61] have reported several semicarbazide and carbamoylcarbazide derivative of ibuprofen **14a-k**, Fig. 8. These compounds were evaluated for their anticancer activities against a panel of 6 cancerous cell lines including murine leukemia (L1210), human T-lymphocyte (CEM), human cervical carcinoma (HeLa), human colon carcinoma (HCT 116), human breast carcinoma (MCF-7) and human lung carcinoma (H460). The new compounds were also evaluated for their antiproliferative activity against a non-tumor human keratinocytes cell line (HaCaT). Compound **14g** (Fig. 8) was the most active against the six cancerous cell lines with IC_{50} values in the range of 6–23 μM, where the MCF-7 cells were the most sensitive (IC_{50} = 6 μM).

Compound **14g** (Fig. 8) with the bulky lipophilic (diphenylmethyl) group showed the high calculated logP (*C*logP) and displayed 46% inhibition of soybean lipoxygenase (LOX). Compound **14g** was also investigated for antiviral activity against a broad panel of DNA and RNA viruses but the results revealed no activity [61].



IC_{50} = 76 μM (L1210),
= 218 μM (FM3A),
= 135 μM (Molt4/C8),
= 72 μM (CEM),
= >100 μM (HeLa),
= 66 μM (MCF-7),
= >100 μM (SK-BR-3),
= **8** μM (MIA PaCa-2),
= >100 μM (SW620),
= >100 μM (WI38)

Fig. 7. Anticancer activity of compound **13** expressed in IC_{50} (μM).

2.1.3.2. Ibuprofen-NO releasing agents. Yeh et al. [62] have evaluated anticancer activity of NO-Ibuprofen **15** against HT-29 and HCT-15 colon cancer cell lines. The results revealed IC_{50} values of 48 and 57 μM against HT-29 and HCT-15, respectively, Fig. 9.

The anticancer activity of compound **15** was increased by 21- and 18-fold greater than the parent ibuprofen against HT-29 and HCT-15 cell lines, respectively. The ability of compound **15** to inhibit growth in the COX-producing (HT-29) and nonproducing (HCT-15) provided an evidence that the mechanism of action is COX-independent [62].

The ibuprofen-thioesters **16a,b** (Fig. 9) were evaluated for their anticancer activity against HepG2, MCF-7, HTC-116 and Caco-2 cancer cell lines using MTT assay [63]. The results revealed weak anticancer activity for compound **16a** (IC_{50} = 80.41–94.83 μM), while compound **16b** was nearly inactive against HepG2, MCF-7 and Caco-2 cancer cells at 100 μM.

Williams et al. [64] have evaluated anticancer potential of NO-ibuprofen (NCX 2210) **17** against HT-29 colon cancer cell line. Enhanced anticancer activity of compound **17** (IC_{50} = 42 μM) over ibuprofen (IC_{50} > 1000 μM) was observed, Fig. 10. Compound **17** induced apoptosis in HT-29 cells and blocked the transition of cells from G0-G1 to S phase.

2.1.3.3. Phospho-ibuprofen (PI) derivatives. Bartels et al. [65] have developed phospho-glycerol-ibuprofen-amide (PGIA) **18** which displayed potent anticancer activity against glioblastoma multiforme (GBM), Fig. 11. MTT assay was used to evaluate the anticancer activity of PGIA **18** (Fig. 11) against human GBM cells. The results revealed up to five-fold increase in anticancer activity compared with the parent ibuprofen. PGIA **18** displayed potent antiproliferative effect against U87-MG GBM cells with 87% inhibition in the growth, while the LN-229 was more sensitive to PGIA where growth inhibition reached 91%. *In vivo*, PGIA **18** was two-fold more potent than ibuprofen in reducing the growth of U118-MG and U87-MG xenografts. Compound **18** displayed also selectivity for GBM over normal human astrocytes (NHA). The pharmacokinetics of PGIA **18** were improved on

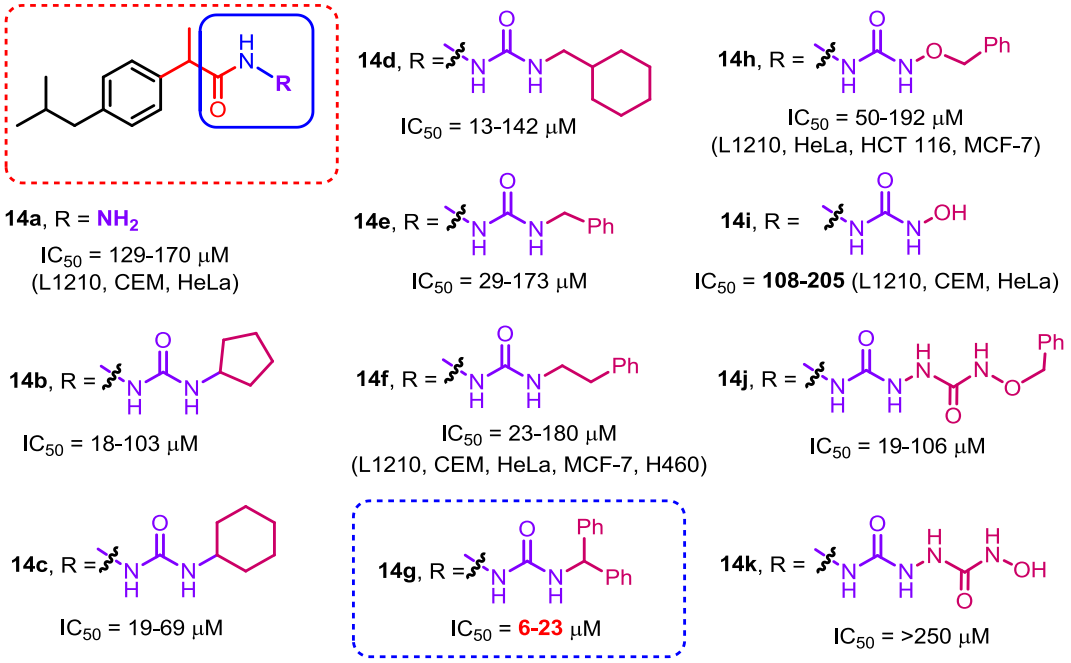


Fig. 8. Compounds **14a-k** and their anticancer activities (IC_{50} values) against L1210, CEM, HeLa, HCT116, MCF-7 and H460 cells.

formulation in polymeric nanoparticles which improved its delivery to the brain.

Compound **18** induced G1/S cell cycle arrest. Investigation of the potential mechanism of action revealed the ability to decrease cyclin D1 which overexpressed in GBM cancer cells [65].

In attempt to decrease toxicity of NSAIDs and increase their efficacy, Xie et al. [66] have synthesized phospho-ibuprofen (MDC-917) **19**, Fig. 12. Compound **19** displayed potent anticancer activity with IC_{50} values of 67.4, 59.1 and 81.6 μM against HT-29, SW480 and HCT-11 cell lines, respectively. Compound **19** was 16–23 times more potent than ibuprofen (IC_{50} = 1057–1516 μM) against the three cancer cell lines, Fig. 12.

Metabolic studies of MDC-917 **19** revealed similar metabolites with that produced from the parent ibuprofen, but at much lower level [66]. These findings provided an explanation for the enhanced safety of PI compared to ibuprofen as previously reported by Huang et al. [67].

Phospho-ibuprofen (PI, MDC-917) **19** (Fig. 12) was reported as anti-arthritis agents capable of treating inflammation and relieving pain. The mechanism of anti-inflammatory activity was mediated by inhibition of PGE2 synthesis with reduced toxicity in GIT [67]. Moreover, MDC-917 **19** displayed anticancer activity against colon cancer mediated by the induction of apoptosis [66].

Sun et al. [68] have evaluated the anticancer activity of phospho-ibuprofen (MDC-917) **19** (Fig. 12) against MCF-7 (estrogen receptor positive) and MDA-MB-231 (estrogen receptor negative) breast cancer cell lines. The results showed that compound **19** at 400 mg/kg/day inhibit the growth of MDA-MB231 xenografts by 266%, while the growth of MCF-7 xenografts was inhibited 51% by PI 300 mg/kg/day and 181% by Lipo-PI 300 mg/kg/day.

The anticancer effect of compound **19** was dependent to large extent on the induction of oxidative stress. Moreover, suppression of the thioredoxin (Trx) system plays a critical role in the mechanism of action of this compound [68].

Mattheolabakis et al. [69] have formulated compound **19** (Fig. 12) into pegylated liposomes (consisting of soy-PC and PEG2000-PE) to overcome the problem of the solubility. The new liposomes were less than 150 nm diameter and showed long stability. The anticancer activity of the new liposomes was evaluated both *in vivo* and *in vitro*. The liposomal formulation of P-I displayed improved anticancer activity in the xenograft tumor model in nude mice compared to the parent P-I **19**.

The effectiveness of compound **19** (Fig. 12) in long-term use to prevent colon cancer was investigated by Ouyang et al. [70]. A great decrease in GIT side effects on modification of Ibuprofen into Phospho-Ibuprofen, with retention of the anti-inflammatory and anticancer effects. The study attributed these effects to the inhibition of COX-2 and PGE2 production, inhibition of NF-κB activation, and suppression of β-catenin signaling pathway.

Other studies suggested also that phospho-ibuprofen **19** (Fig. 12) exerted its anticancer activity through the induction of oxidative stress (in tumor only), apoptosis and reduction of inflammatory cytokines [71].

Although compound **19** (Fig. 12) have displayed potent anticancer activity, but it has limited stability due to the rapid hydrolysis of the ester group. To overcome this problem, Cheng et al. [72] have

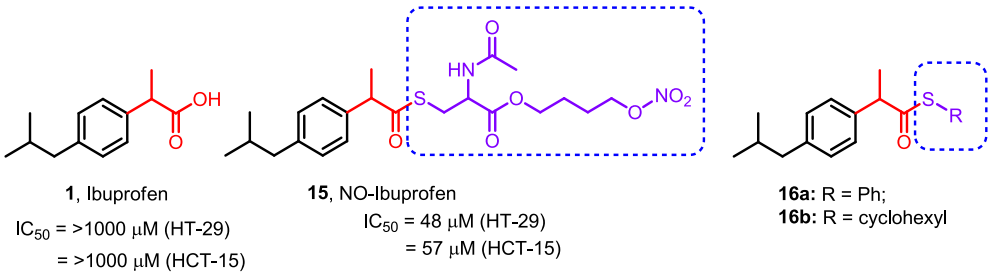


Fig. 9. Chemical structure of ibuprofen **1**, NO-ibuprofen **15** and compound **16a,b**.

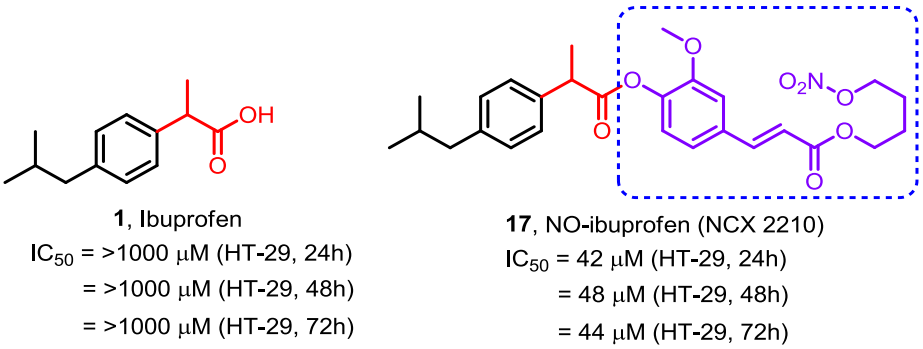


Fig. 10. Anticancer activity of ibuprofen **1** and NO-ibuprofen **17** against HT-29 cancer cells.

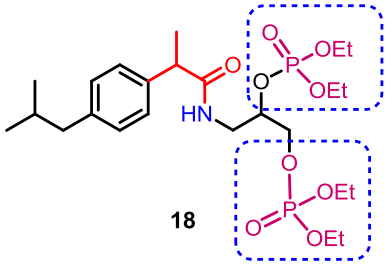


Fig. 11. Phosphor-glycerol ibuprofen amide (PGIA) **18**.

synthesized the amide (PIA) **20** as a metabolically stable analog of the phospho-ibuprofen **19**, Fig. 13. Moreover, the synthesized PIA **20** was formulated in nanocarriers. The liposomal PIA formulation was metabolically stable to hydrolysis by carboxylesterases.

Evaluation of anticancer activity of the new PIA liposomal formulation revealed a tenfold increase in potency compared to ibuprofen in suppressing the growth of human A549, H23 and H358 non-small-cell lung cancer (NSCLC) cell lines. PIA induced two to fivefold increase in apoptosis. These effects were mediated by alteration of cytokinetics and induction of oxidative stress [72].

Wittine et al. [73] have reported the 3-hydroxypropanamide **21** and phosphoramidate **22** bearing ibuprofen moieties, Fig. 14. The new compounds were evaluated for their anticancer activity against a panel of eight cancer cell lines, and the results were expressed in IC_{50} (μM), Fig. 14. In addition, selectivity and toxicity of the new compounds were investigated using normal human diploid fibroblast (WI 38). The phosphoramidate **22** displayed more potent antiproliferative activity than 3-hydroxypropanamide **21**, specially against HeLa (cervical), MIA PaCa-2 (pancreatic), SW 620 (colonA7), MCF-7 (breast) and H460 (lung) carcinoma. Evaluation of the antiproliferative activity against WI 38 revealed IC_{50} value of 21 μM.

Kłobucki et al. [74] have reported a novel series of phosphatidylcholines containing ibuprofen **23–26**, Fig. 15. The new compounds were evaluated for their anticancer activity against human promyelocytic leukemia (HL-60), Caco-2, and normal porcine epithelial intestinal (IPEC-J2) cells using WST-1 cell proliferation assay. The results revealed IC_{50} values in the range of 64.51–77.42 μM against HL-60 cells, compared to 106.32 μM for ibuprofen. Toxicity studies revealed that compounds **23** and **24** are less toxic to normal IPEC-J2 cells than compounds **25** and **26**.

2.1.3.4. Ibuprofen-metal complexes. Lopes et al. [75] have reported ruthenium complexes with NSAIDs. Of these, the *cis*-[Ru(ibu)(dppm)2]PF6 **27** (Fig. 16) was synthesized and evaluated for cytotoxic activity against a panel of human cancer (HepG2, MCF-7 and MO59J) cell lines and a human normal (GM07492A, normal lung fibroblasts) cell line.

The results suggested the existence of electrostatic interactions between ruthenium complexes and calf thymus DNA (ct-DNA). The complex **27** displayed moderate to high cytotoxic activity with IC_{50} values in the range of 5–9 μM, which was higher than cisplatin (IC_{50} = 6.3–34 μM) [75].

Ribeiro et al. [76] have reported Ruthenium-ibuprofen $[Ru_2(ibp)_4Cl]$ complex **28**, Fig. 17. The antiproliferative of this complex was investigated against Hep2 (human larynx), T24/83 (human bladder) and C6 (rat glioma). The results revealed no significant effect on Hep2 and T24/83 proliferation, while proliferation of C6 cancer cells was significantly inhibited. The antiproliferative activity of $[Ru_2(ibp)_4Cl]$ complex **28** may be mediated by dual mechanisms (anti-angiogenic and anti-matrix metalloprotease). These results could be clinically critical for pharmacological intervention in certain gliomas [76].

In attempt to potentiate the anticancer activity of kiteplatin, Curci et al. [77] have synthesized a Pt(IV) prodrug of kiteplatin with two molecules of ibuprofen. The produced conjugate **29** (Fig. 18) showed remarkable cytotoxic activity. It displayed IC_{50} values of 0.45 and 0.26 μM against HCT15 and HCT116 cancer cell lines, respectively. These activities were higher than kiteplatin and cisplatin (IC_{50} = 7–17 μM). The potentiated activity of ibuprofen-kiteplatin complex **29** could be attributed to accumulation of the complex in cancer cells and increased lipophilicity.

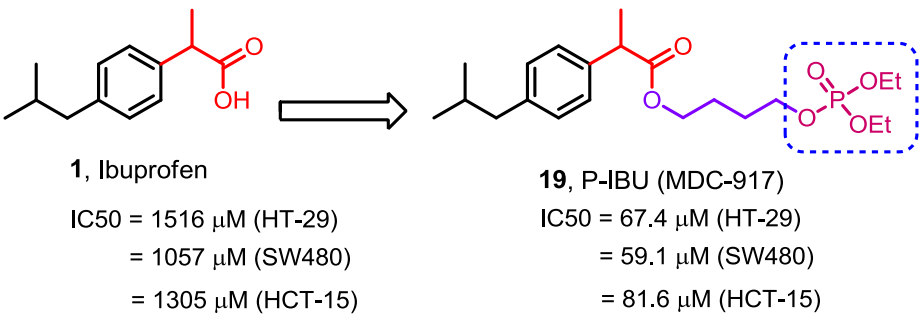
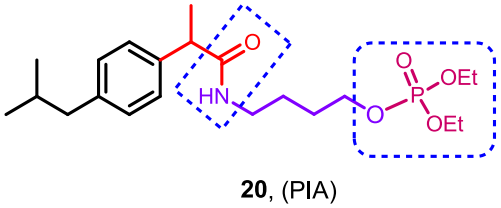


Fig. 12. Ibuprofen **1** and MDC-917 **19** with their anticancer activities (IC_{50} values) against HT-29, SW480 and HCT-15 cell lines.



20, (PIA)

Fig. 13. Phospho-ibuprofen amide (PIA) **20**.

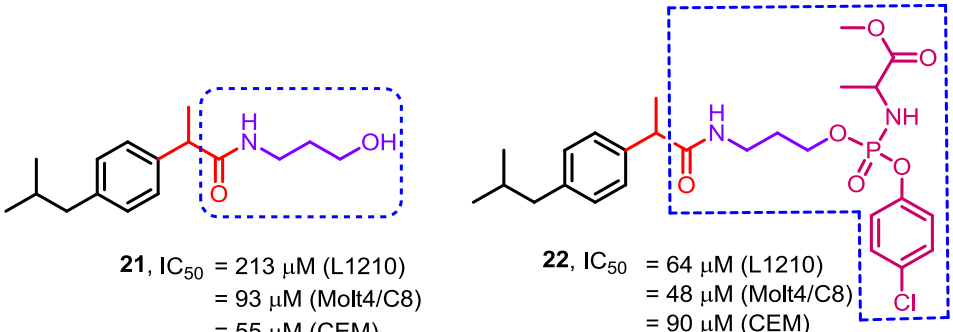
2.1.3.5. Ibuprofen hybrids. Garrido et al. [78] have designed and synthesised the pregnadiene-ibuprofen hybrid **30**, Fig. 19. The new compound was evaluated for antiproliferative activity against U373 cell line, in comparison to the parent drugs (NSAIDs and the steroidal alcohol). Compound **30** displayed a significant decrease in number of U373 cells at 10 μM.

Based on a previous report [79], inhibition of 5α-reductase enzyme by Michael type addition was suggested as a possible mechanism of action for antiproliferative activity of the hybrid **30** due to the presence of α,β-unsaturated carbonyl groups.

In addition, Banekovich et al. [80] have reported a series of riboflavin-dexibuprofen conjugates **31a-e** covalently attached through via alkylene spacer were synthesized, Fig. 20. The new conjugates were evaluated for their anticancer activity against MCF-7 and HT-29 cancer cell lines. The conjugates **31a-e** displayed anticancer activity comparable to that of 5-fluorouracil (5-FU) with IC_{50} values in the range of 8–15 μM. Among these conjugates, compound **31c** was the most active against HT-29 and MCF-7 cells. On the other hand, the parent dexibuprofen displayed very weak or no inhibitory activity against the tested cell lines. Enzymatic studies on human platelets indicated significant inhibition of COX-1 [80].

Compounds **31a-e** were evaluated for their COX-1 and 12-LOX inhibitory activities [80]. Compounds **31a-e** decreased COX-1 activity by 15–43% compared to 90% for dexibuprofen. Compound **31e** was the most active as COX-1 inhibitor (43%). On the other hand, none of these compounds displayed significant inhibition of 12-LOX (inhibition < 11%), while dexibuprofen displayed 29% inhibition of 12-LOX.

Zhang et al. [81] have reported ibuprofen-podophyllotoxin conjugate **32** as potential anti-multi-drug resistance (anti-MDR) agents, Fig. 21. Compound **32** synthesized from reaction of podophyllotoxin with ibuprofen. The new compounds were evaluated for their



21, IC_{50} = 213 μM (L1210)
= 93 μM (Molt4/C8)
= 55 μM (CEM)
= >100 μM (HeLa)
= >100 μM (MIA PaCa-2)
= >100 μM (SW 620)
= >100 μM (MCF-7)
= >100 μM (H 460)

22, IC_{50} = 64 μM (L1210)
= 48 μM (Molt4/C8)
= 90 μM (CEM)
= 15 μM (HeLa)
= **13** μM (MIA PaCa-2)
= 21 μM (SW 620)
= 14 μM (MCF-7)
= 19 μM (H 460)
= 21 (WI 38)

Fig. 14. 3-Hydroxypropanamide **21** and phosphoramidate **22** derivatives.

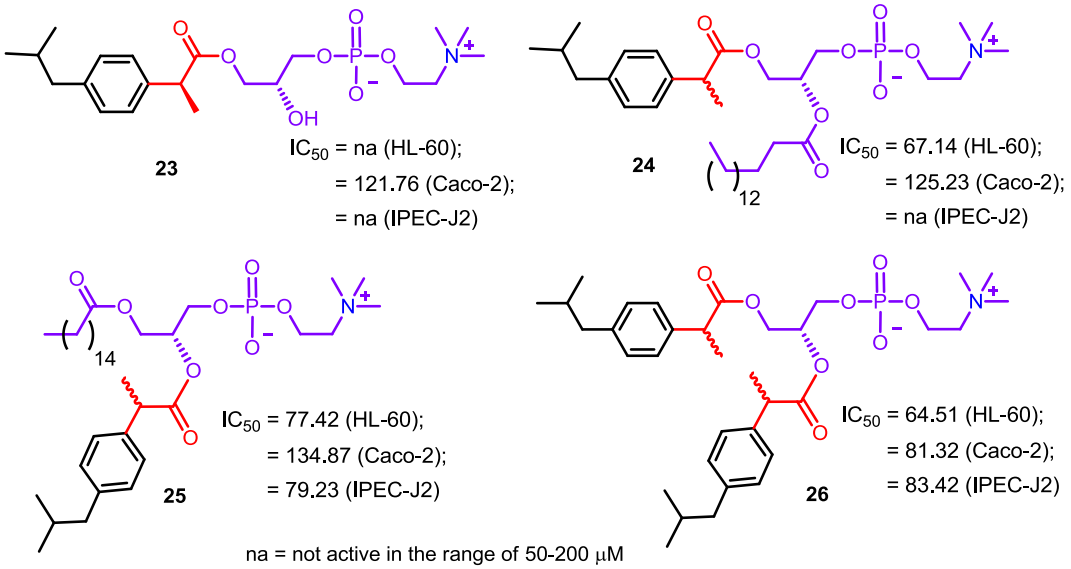


Fig. 15. Chemical structures of ibuprofen-phosphatidylcholines **23–26**.

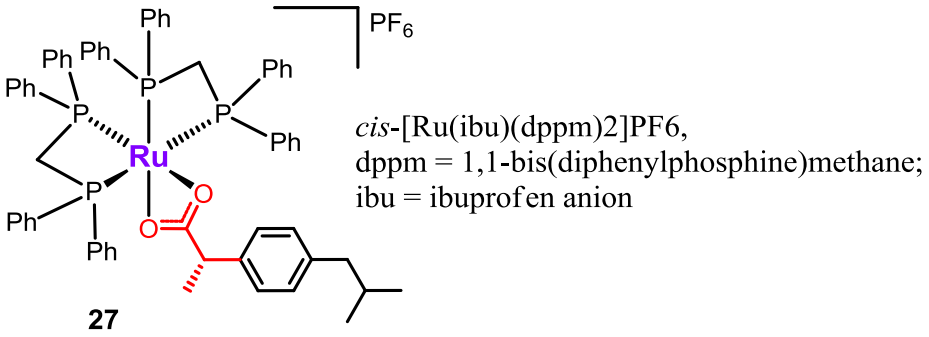


Fig. 16. Chemical structure of *cis*-[Ru(ibu)(dppm)2]PF6 complex **27**.

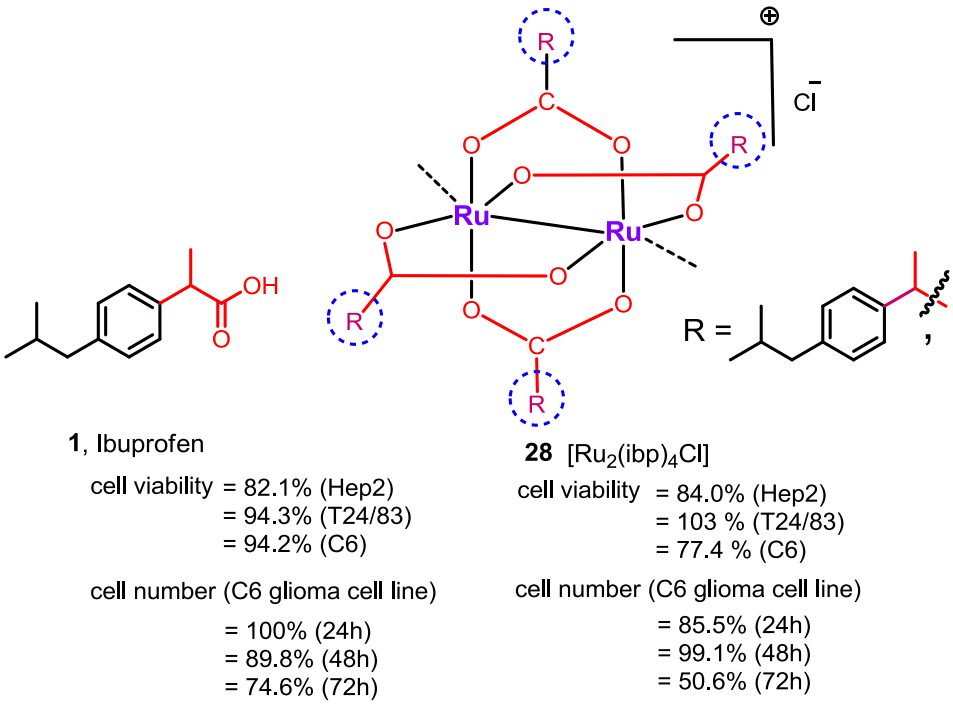


Fig. 17. Ibuprofen **1** and [Ru2(ibp)4Cl] **28** and their effect on cell viability/cell number of various cell lines.

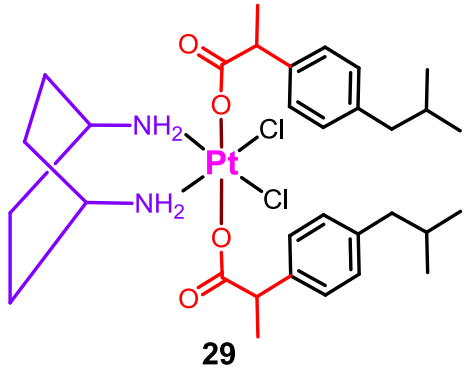


Fig. 18. Chemical structure of ibuprofen-kiteplatin complex **29**.

antiproliferative activity against Bel-7402 hepatocellular carcinoma and the Bel-7402/5-FU resistant cancer cell, in addition to normal L-O2 cells. The results revealed the ability of compound **32** to inhibit growth of Bel-7402 and Bel-7402/5-FU with IC_{50} values of 18.88 and 10.28 μM, respectively. Compound **32** displayed high antiproliferative activity against the resistance cell line with resistance factor (RF) of 0.54.

Mechanistic study of compounds **32** revealed the ability to trigger cell cycle arrest at the S and G2 phases, induce apoptosis, inhibit tubulin polymerization in Bel-7402/5-FU cells. Western blot analysis of Bel-7402/5-FU cells treated with compound **32** revealed a slight decrease in CDK1, CDK2 and Cyclin A levels [81].

Rayam et al. [82] have reported several new hybrids by incorporating ibuprofen, 1,3,4-oxadiazole, and 1,2,3-triazole moieties **33a-l** (Fig. 22). These hybrids **33a-l** were designed bearing both electron donating and withdrawing substituents on the phenyl ring. Their anticancer activities were investigated using MTT assay. The results revealed that compound **33e** was the most active in inhibiting the growth of HeLa and MCF-7 cancer cell lines with IC_{50} values of 27.5 and 31.03 μg/mL, respectively.

2.1.3.6. Ibuprofen-bearing polymers. Zawidlak-Wegrzynska et al. [83] have reported the conjugates **34a,b** by incorporating ibuprofen with nontoxic-oligo(3-hydroxybutyrate) (OHB). The MTT assay was used to evaluate the anticancer activity of the conjugate **34a** (IB4) and **34b** (IB6) against HT-29 and HCT 116 cancer cells. The results revealed a significant increase in antiproliferative activity of the new conjugates compared to ibuprofen, Fig. 23. The conjugate **34a** displayed antiproliferative activity higher than that of conjugate **34b**. The

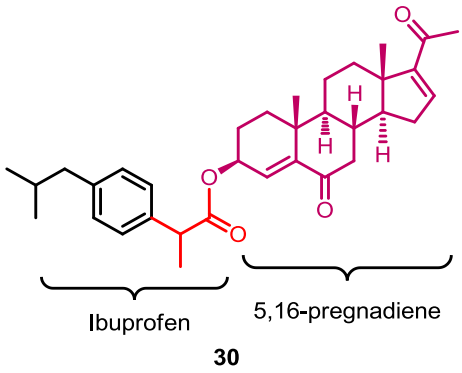


Fig. 19. Chemical structure of pregnadiene-ibuprofen hybrid **30**.

enhanced activity of these conjugates could be due to the improved intracellular uptake compared to ibuprofen. Moreover, they showed lesser toxicity than ibuprofen where no mortality was observed in WIST rats 14 days after the treatment.

Pedro-Hernández et al. [84] have reported four conjugates of ibuprofen and resorcinarene-polyamidoamine PAMAM-dendrimers **35a,b** and **36a,b**. These four can be classified chemically in to two generations, the first generation **35a,b** (Fig. 24) which bears eight ibuprofen moieties, while the second generation **36a,b** (Fig. 25) has sixteen moieties of ibuprofen. The dendrimers **36a,b** release free ibuprofen at 76% and 80%, respectively, which was higher than was released from **35a,b** (65 and 68%).

The new dendrimers **35a,b** and **36a,b** were evaluated for their anticancer activity against a panel of five cancer cell lines and the normal human gingival fibroblast (HGF), Fig. 25. They displayed higher cytotoxic activity than cisplatin and ibuprofen towards human glioblastoma (U251) and human mammary adenocarcinoma (MCF-7, MDA) cell lines. Dendrimer **36b** displayed the highest anticancer activity against U251, K-562, MCF-7, and MDA cell lines with IC_{50} values in the range of 3–3.5 μM [84].

Zhang et al. [85] have reported inulin-ibuprofen polymer **37** (Fig. 26) that was used in the preparation of RGD targeted epirubicin (EPB) loaded nanoparticles. The prepared nanoparticles showed easy intracellular uptake into cancer cells and release EPB in pH dependent manner. Better *in vitro* anticancer activity was observed with RGD conjugated EPB loaded nanoparticles over the non-conjugated nanoparticles. Moreover, the conjugated nanoparticles displayed higher anticancer activity *in vivo* than both free EPB and non-conjugated nanoparticles.

Zhao et al. [86] have developed a PEG2K-Fmoc-Ibuprofen (PEG2K-FIbu) **38** as a nanomicellar carrier, Fig. 27. The developed carrier **38** was loaded with paclitaxel (PTX). The PTX-loaded PEG2K-FIbu micelles displayed slower release of PTX than other taxol formulations. The anticancer activity of the PTX-loaded PEG2K-FIbu micelles was evaluated in comparison to taxol. The results revealed comparable anticancer activity *in vitro*, while PTX-loaded PEG2K-FIbu micelles displayed more pronounced therapeutic efficacy than taxol was observed *in vivo*.

Hasegawa et al. [87] have prepared amphiphilic polymeric ibuprofen prodrug micelles (PEG-PIBU) **39**, Fig. 28. The copolymer **39** was prepared from the reaction of different molar concentrations of acrylamide derivative of ibuprofen with PEG pyrrole carbodithioate. The release of ibuprofen from this copolymer was pH and time dependent.

The antiproliferative activity of the copolymer 39 was evaluated against HeLa and murine melanoma (B16–F10) cells [87]. The results revealed comparable antiproliferative effect to ibuprofen in HeLa cells. On the other hand, the copolymer **39** showed no effect in B16–F10 cells, while ibuprofen reduced cellular viability to 85% (at 0.5 Mm) [87].

In conclusion, the anticancer activity of ibuprofen and its derivatives could be mediated by several non-COX targets. The targets were summarized in Fig. 29.

2.2. Ketoprofen

2.2.1. Ketoprofen and anticancer activity

Cheng et al. [88] have studied the antiproliferative effect of ketoprofen **2** against colo 205 and the tumor *N*-Acetyltransferase (NAT)

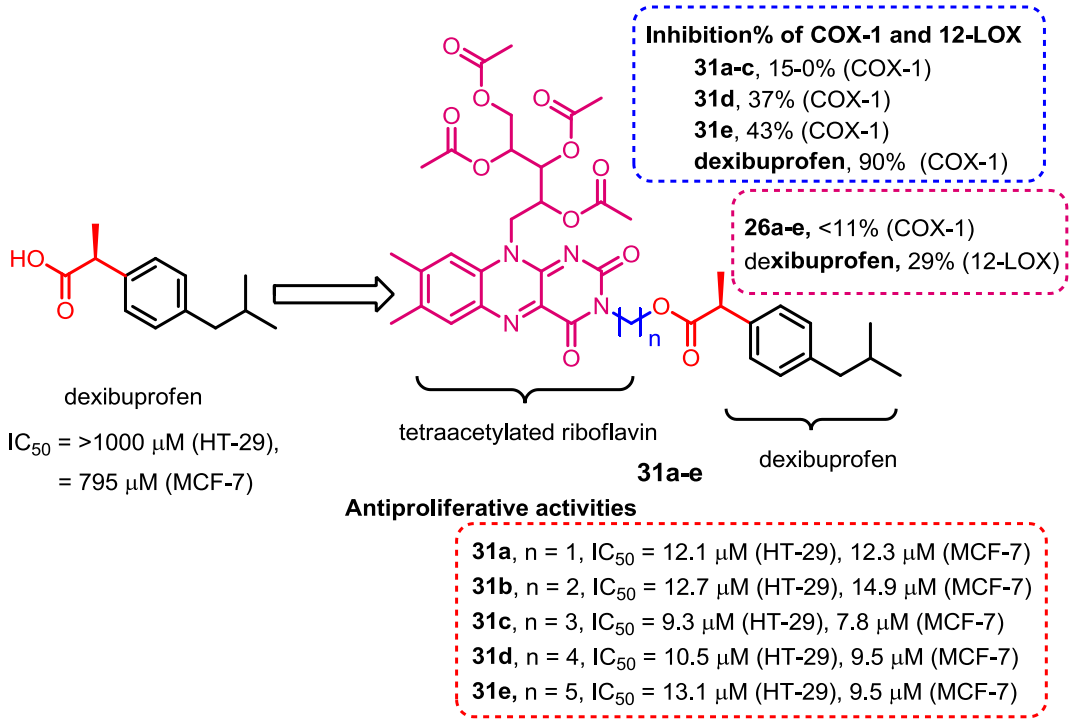


Fig. 20. Riboflavin-dexibuprofen conjugates **31a-e** and their activity against HT-29 and MCF-7, COX-1 and 12-LOX inhibitory activity.

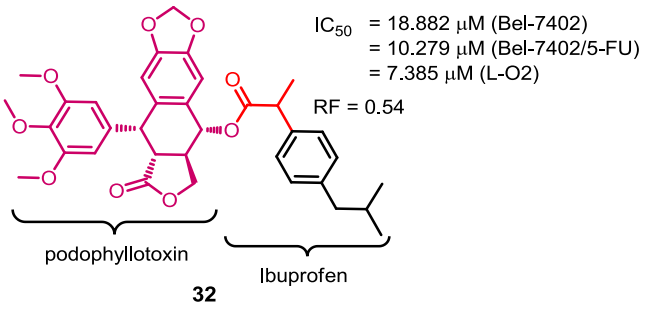


Fig. 21. Ibuprofen-podophyllotoxin conjugate **32** with its antiproliferative activity (IC_{50}) against Bel-7402, Bel-7402/5-FU and L-O2 cells.

Activity. The results revealed inhibition of NAT by ketoprofen in dose and time-dependent manner. The decrease in NAT activity was mediated by the effect of ketoprofen on NAT mRNA where the level of NAT mRNA decreased with increasing the concentration of ketoprofen. Moreover, ketoprofen decreased the formation of 2-aminofluorene (AF)-DNA adduct in colon cancer cell.

Gobec et al. have also investigated the inhibitory activity of ketoprofen against AKR1C3 enzyme [48]. The results revealed 12% inhibition in AKR1C3 activity at 50 μM concentration. These results indicated that ketoprofen is less active as AKR1C3 than ibuprofen (IC_{50} = 33 μM).

2.2.2. Ketoprofen derivatives

Zovko et al. [89] have reported a new series of ketoprofen amides **40a-c**, Fig. 30. These compounds were evaluated for their anticancer activity against a panel of cancer cell lines using MTT assay [90].

The results revealed stronger anticancer activity for the amide derivatives **40a-c** than the parent ketoprofen [90]. Compound **40a** was the most active where it inhibited the growth in the five cancer cell lines (Hep-2, HeLa, MiaPaCa-2, SW620 and MCF-7) with IC_{50} values in the range of 13–20 μM. Compound **40a** inhibited the growth of normal fibroblast WI 38 cells with IC_{50} value of 34 μM, indicating selectivity toward cancer cells. The anticancer activity of compound **40a** was mediated by induction of apoptosis and arrest cell cycle at the G1 phase.

Pavelic et al. [60] have also investigated the anticancer activity of ketoprofen derivatives **41a-c**, Fig. 31. Compound **41b** displayed the highest activity against MIA PaCa-2 cell line (IC_{50} = 17.7 μM), while compound **41c** was the most active against MIA PaCa-2 cell line (IC_{50} = 2.2 μM).

Cell cycle analysis of MIA PaCa-2 cells treated with compounds **41c** (Fig. 31) showed significant decrease in G0/G1 population with accumulation of cells in S phase. A marked increase in G2/M population after treatment with compound **41c** was also observed. These findings suggested that the anticancer activity of compound **41c** is mediated by induction of p53-independent S phase arrest and activation caspase 3-dependent apoptosis [60].

Moreover, compounds **41a-c** were investigated for their antiviral activity. Compound **41c** was the only derivative which showed marginal antiviral activity but with low selectivity suggesting that this activity could be due to an underlying cellular toxicity [60].

Beziere et al. [91] have reported a series of ketoprofen-NO hybrids **42a-c**, Fig. 32. These compounds were evaluated for their COX inhibitory activities, NO release and antiproliferative activity against PC3 cancer cell line. The new hybrids inhibited the proliferation of PC3 cells and exhibited COX inhibitory activity comparable to ketoprofen. Accordingly, it was clear that antiproliferative activity of these compounds is not due to COX activity alone.

Although the new compounds **42a-c** displayed higher selectivity for

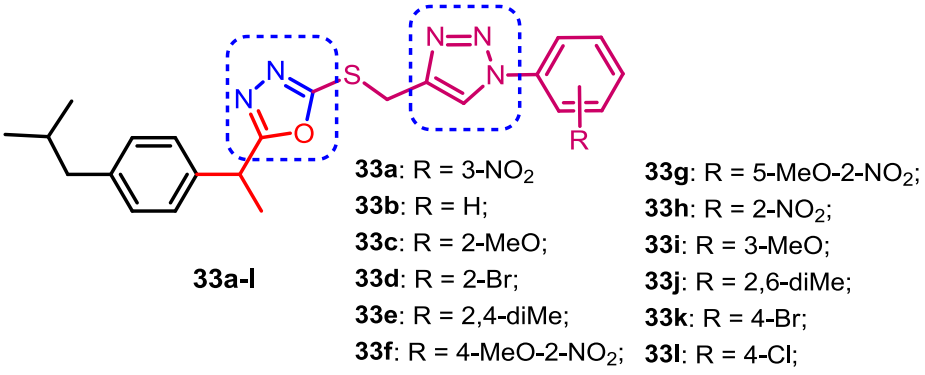


Fig. 22. Ibuprofen-oxadiazole-triazole derivatives **33a-l**.

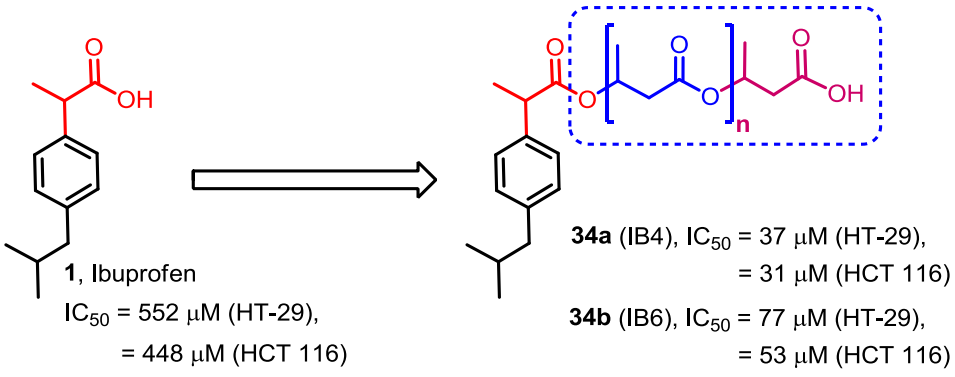


Fig. 23. Ibuprofen and Ibu–OHB **34a,b** conjugates, (n = average number of 3-hydroxybutyrate units).

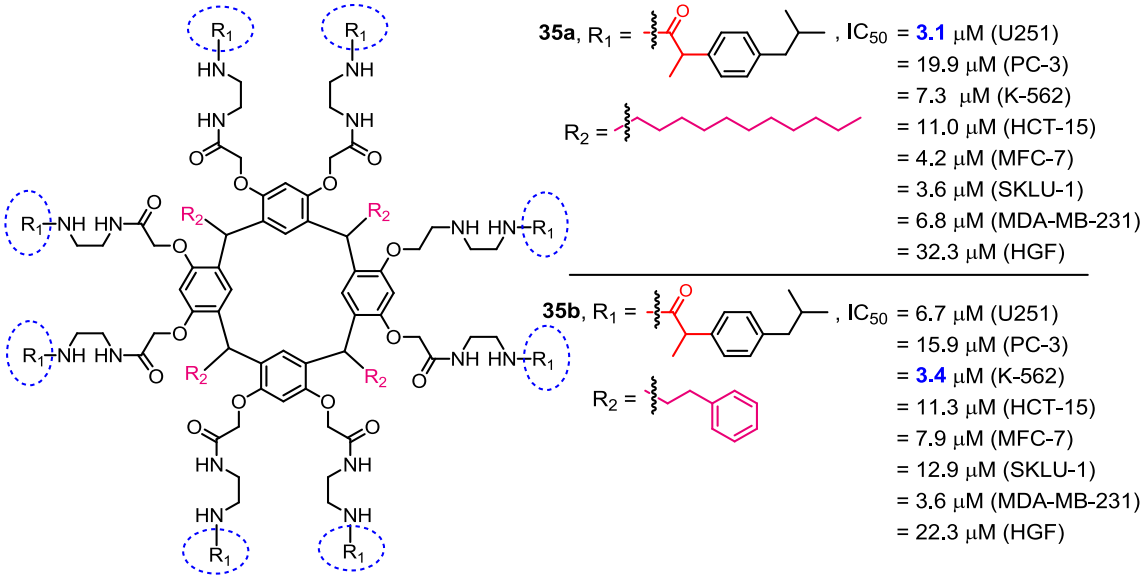


Fig. 24. Ibuprofen-resorcinarene-polyamidoamine PAMAM-dendrimers **35a,b** with their antiproliferative activities.

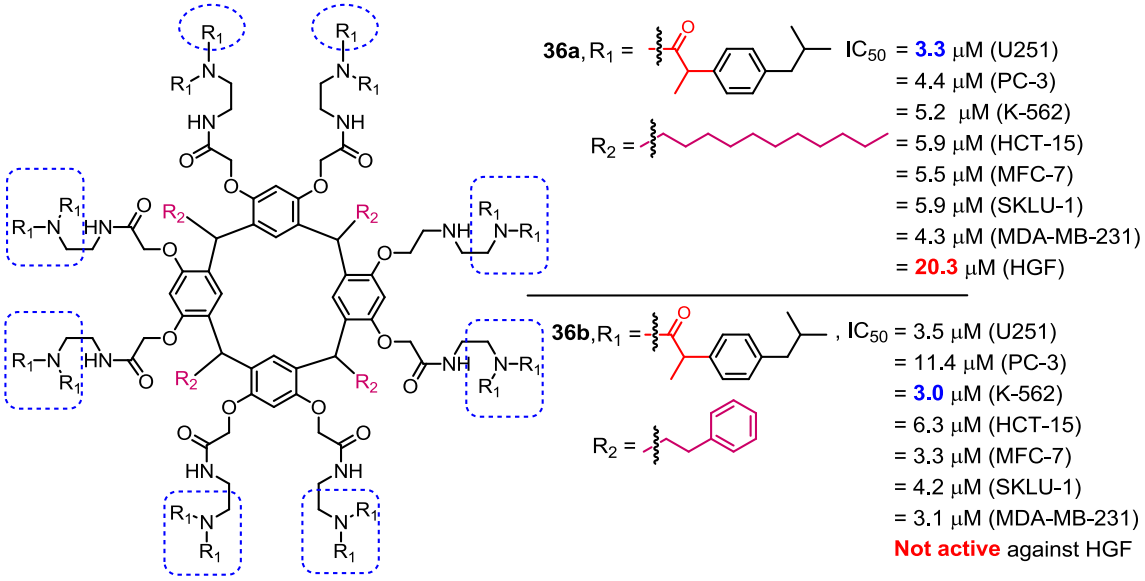
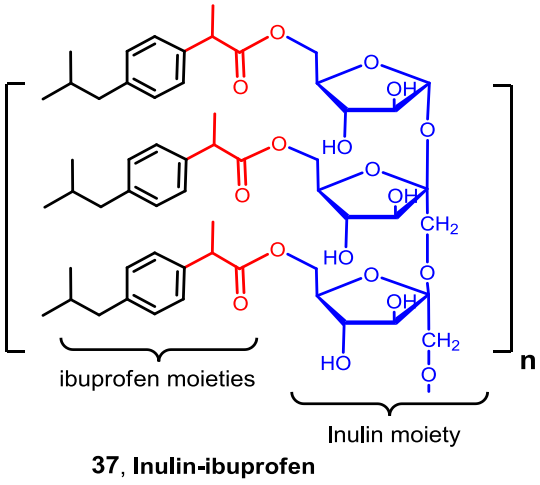


Fig. 25. Ibuprofen-resorcinarene-polyamidoamine PAMAM-dendrimers **36a,b** with their antiproliferative activities.



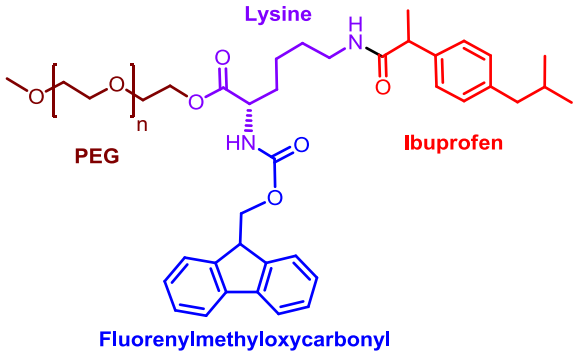
37, **Inulin-ibuprofen**

Fig. 26. Inulin-ibuprofen polymer **37**.

COX-2 compared to their parent ketoprofen, but these inhibitions of COX-2 were not sufficient for such antiproliferative effect. The new derivatives release NO which contributes to their anticancer activities [91].

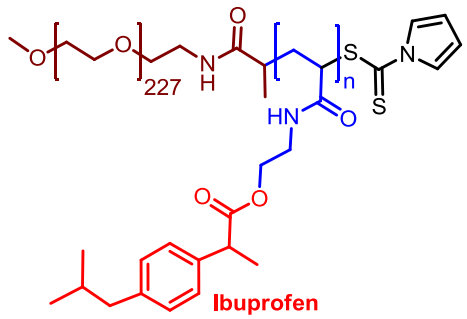
On the other hand, ketoprofen thioesters **43a,b** (Fig. 33) were evaluated for anticancer activity of against four (HepG2, MCF-7, HTC-116 and Caco-2) cancer cell lines [63]. The results revealed higher anticancer for compound **43b** (IC_{50} = 9.36–21.73 μM) than compound **43a** (IC_{50} = 48.11–72.19 μM). *In vitro*, compound **43b** displayed IC_{50} value of 0.66 μM against COX-2, while the IC_{50} value against COX-1 was above 50 μM indicating high selectivity for COX-2 (SI > 75.8). In addition, compound **43b** showed also weak inhibition of HER4 and cSrc kinases with inhibition% of 4 and 5%, respectively.

Wittine et al. [73] have also reported the 3-hydroxypropanamide **44** and phosphoramidate **45** bearing ketoprofen moieties, Fig. 34. The phosphoramidate **45** displayed more potent antiproliferative activity than compound **44** against all the tested cancer cell lines. Evaluation of antiproliferative activity of compound **45** against WI 38 revealed IC_{50} value of 30 μM indicating selective antiproliferative activity against



38

Fig. 27. PEG2K-Fmoc-Ibuprofen (PEG2K-FIbu) **38**.



39

Fig. 28. PEG-PIBU copolymer **39**.

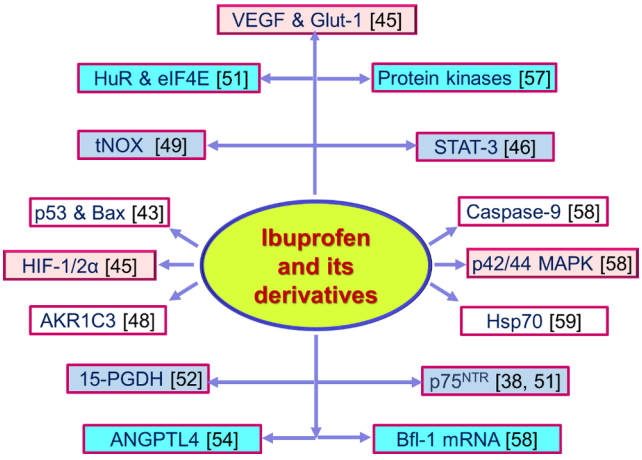


Fig. 29. Different non-COX targets which could mediate the anticancer potential of ibuprofen and its derivatives.

HeLa, MIA PaCa-2, SW 620, MCF-7 and H460 cancer cells.

Compound **46** (Fig. 35) was synthesized among a series of NSAIDs linked to pregnadiene reported by Garrido et al. [78]. Unlike the ibuprofen hybrid **30**, compound **46** did not display growth inhibitory activity against U373 cell line.

Perkovic et al. [61] have reported several semicarbazide and carbamoylcarbazide derivative of the reduced ketoprofen **47a-k**, Fig. 36. These compounds were evaluated for their anticancer activities against a panel of 6 cancer cell lines. Compound **47g** with the bulky lipophilic (diphenylmethyl) group was the most active against the six cell lines with IC_{50} values in the range of 4–19 μM, where H460 cells were the most sensitive (IC_{50} = 4 μM). Moreover, compound **47g** inhibited soybean lipoxygenase (LOX) with IC_{50} value of 51.5 μM.

2.3. Fenoprofen

2.3.1. Fenoprofen and anticancer activity

Hixson et al. [92] have investigated the antiproliferative activity of several NSAIDs against three colon (HT-29, DLD-1 and SW480) cancer cell lines. Among these, fenoprofen **3** exhibited growth inhibitory activity against the three cell lines with IC_{50} values in the range of 240–360 μM. These results revealed also a slightly higher activity for fenoprofen over ibuprofen (IC_{50} = 320–520 μM).

2.3.2. Fenoprofen derivatives

Zovko et al. [93] have reported a series of fenoprofen amides **48a-g**, Fig. 37. Evaluation of anticancer activity of these compounds against a panel of five cancer cell lines revealed the highest activity for compound **48d** (IC_{50} = 13–21 μM). Moreover, compound **48d** induced apoptosis and arrested cell cycle at the G1 phase [90].

In addition, Mathew et al. [94] have reported a series of 15 fenoprofen amides derivatives **49a-o** as potential anticancer agents, Fig. 38. Compounds **49f-h** displayed variable antiproliferative activities against HT29 cancer cell line with IC_{50} values in the range of 7.46–35.72 μM. Only three derivatives (**49j, 49k** and **49o**) of these amides displayed antiproliferative activity against PC3. Among the tested amides, compound **49k** was the most active (IC_{50} = 7.46 μM). Moreover, compounds **49k** and **49o** displayed antiproliferative activity against MDA-MB-231 cells with IC_{50} values of 30.8 and 13.22 μM, respectively. The amides derivatives **49a-o** were screened for their effect on Wnt/β-catenin pathway which has pays an important in proliferation and differentiation of cells [95], but the results revealed weak activity.

The *N*-ethoxy-2-(3-phenoxyphenyl)propanamide **50** was investigated for the potential antiproliferative activity by Pavelic et al. [60]. The results revealed the highest activity against CEM cells with IC_{50} value of 54 μM, Fig. 39. The antiviral activity of compound **50** was also investigated, but the results revealed no pronounced activity.

Perkovic et al. [61] have reported a series of eleven fenoprofen semicarbazide and carbamoylcarbazide derivatives. The new compounds **51a-k** (Fig. 40) were evaluated for their activity as anticancer agents against a panel of six cancer cell lines. Among these derivatives, compound **51g** with bulky lipophilic groups displayed the highest anticancer activity with IC_{50} values in the range of 3–15 μM. The H460 cells showed the highest sensitivity (IC_{50} = 3 μM). Compound **51g** was nearly two times more selective for HCT 116, MCF-7 and H460 cells over the non-tumor HaCaT cells.

The new compounds **51a-k** (Fig. 40) were evaluated for their inhibitory activity against soybean lipoxygenase (LOX) [61]. The results revealed no inhibitory activity for compounds **51b**, **51j** and **51k** against soybean LOX enzyme. The remaining compounds displayed inhibitory activity in the range of 3–81%. Among these, compound **51g** was the highest active inhibitory inhibitor of LOX enzyme (IC_{50} = 60 μM). Moreover, it displayed complete inhibition of lipid peroxidation.

Wittine et al. [73] have reported the 3-hydroxypropanamide **52** and phosphoramidates **53** bearing fenoprofen moieties, Fig. 41. The two compounds were evaluated for their anticancer activity against a panel of eight cancer cell lines. Compound **53** displayed higher anticancer activity (IC_{50} = 5–39 μM) than 3-hydroxypropanamide **52**, against the eight cancer cell lines where MIA PaCa-2, HeLa and SW 620 cells were the most sensitive to compound **53** (IC_{50} < 10 μM). Compound **53** inhibited the growth of normal human diploid fibroblast (WI 38) with IC_{50} value of 20 μM.

Polymer-drug conjugated have displayed improved drug solubility, higher stability and sustained release than the parent drugs [96]. Accordingly, new polymer-fenoprofen conjugate **54** [97,98] were prepared, Fig. 42. The antiproliferative activity of the conjugate **54** was evaluated against a panel of five cancerous cell lines (HeLa, MCF-7, SW 620, MiaPaCa-2, Hep-2) using MTT assay. Toxicity and selectivity of the new conjugate was also evaluated using normal fibroblast (WI 38) cells. The new conjugate **54** displayed antiproliferative activity against MCF-

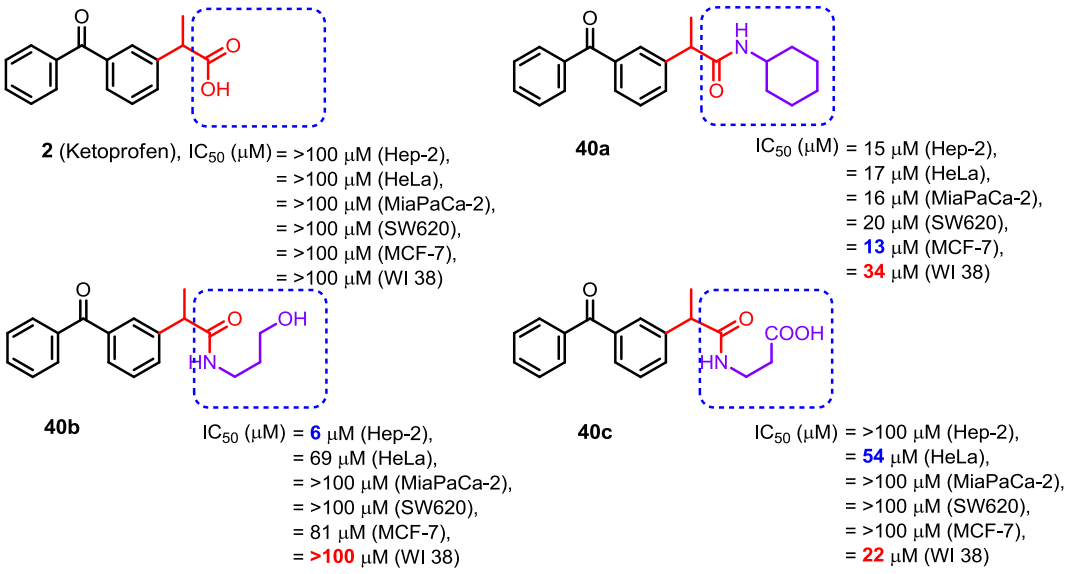


Fig. 30. Ketoprofen **2** and ketoprofen amide derivatives **40a-c** with their anticancer activities (IC_{50} values).

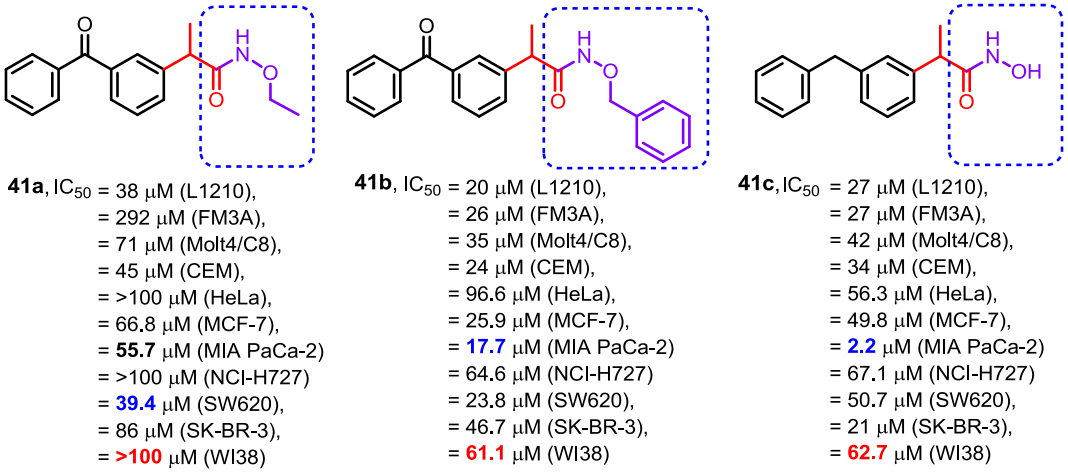


Fig. 31. Ketoprofen derivative **41a-c** and their anticancer activity (IC_{50} values).

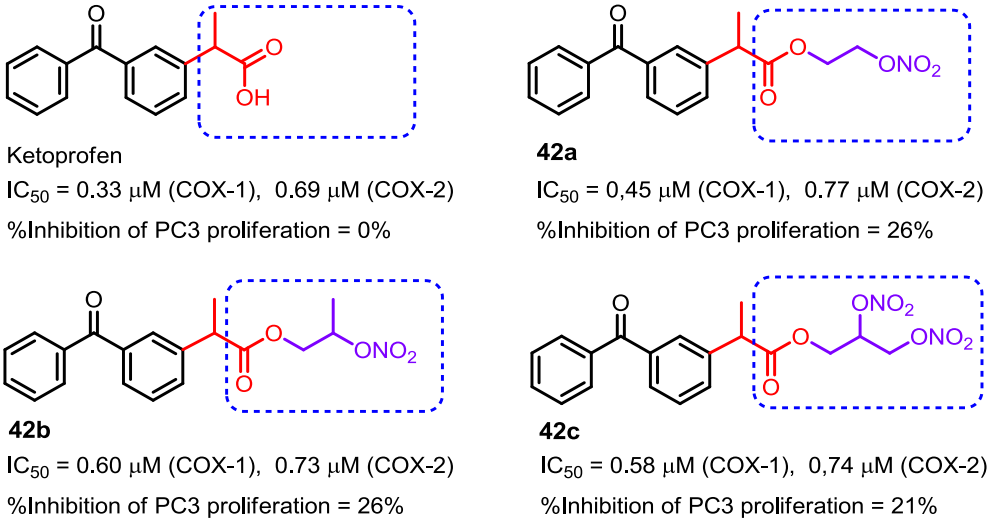
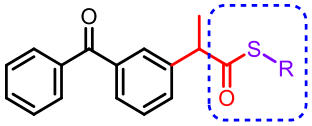


Fig. 32. Ketoprofen **1** and compounds **42a-c** with COX-1/2 inhibitory and antiproliferative activities.



43a: R = Ph;
43b: R = cyclohexyl

Fig. 33. Ketoprofen thioesters **43a,b**.

7 cells with IC_{50} value of 88 ± 57 μg/mL, while fenoprofen displayed IC_{50} ≥ 160 μg/mL.

2.4. Flurbiprofen

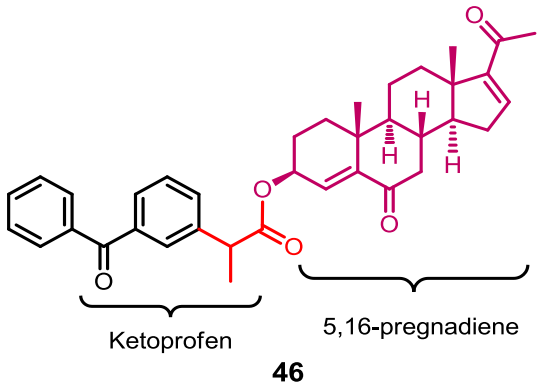
2.4.1. Flurbiprofen and anticancer activity

Flurbiprofen **4** was investigated among several NSAIDs for their effect on expression of 15-PGDH in human HT29 cancer cell line [52]. The results revealed the highest induction of 15-PGDH mRNA expression for flurbiprofen. In addition, flurbiprofen induced the expression of metalloproteinase-1 (TIMP-1) which acts as inhibitor of matrix metalloproteinase-9 (MMP-9) which is responsible for degradation of 15-PGDH. Flurbiprofen was able to down-regulate the expression of MMP-9 resulting in an increase in the level of 15-PGDH [52].

Like other profens, the S-isomer of flurbiprofen has COX inhibitory activity, while the R-isomer is inactive [99]. McCracken et al. have reported that anticancer activity of R-flurbiprofen is independent on COX inhibition or prostaglandin biosynthesis [100]. Moreover, the anticancer activity of flurbiprofen was reported against diverse types of cancers including human brain tumors [101], mouse intestinal polyposis [102] and mouse prostate cancer [103].

King et al. [101] have reported an increase in p53 protein level and enhanced level of COX-2 in Daoy cells after treatment with flurbiprofen. These findings suggested that suppression of tumor growth by flurbiprofen could be due to the interaction of COX-2 with p53. Moreover, Grösch et al. have also reported that the anticancer activity of R-flurbiprofen was mediated by induction of apoptosis which is dependent at least partly on the induction of the tumor suppressor p53 [104].

On the other hand, Quann et al. [105] have reported that induction of apoptosis in prostate (PC-3, DU-145, and LNCaP) cancer cell lines was mediated by $p75^{NTR}$ protein. Among the tested NSAIDs, both R-flurbiprofen and ibuprofen were the most active in inducing $p75^{NTR}$ protein.



46

Fig. 35. Ketoprofen-5,16-pregnadiene hybrid **46**.

2.4.2. Flurbiprofen derivatives

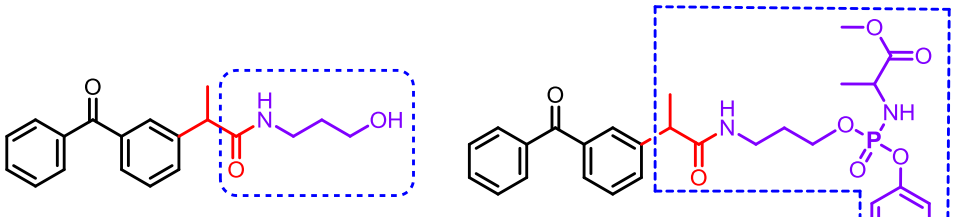
Later, Quann et al. [51] have reported that induction of $p75^{NTR}$ mRNA expression by R- flurbiprofen was mediated through p38 MAPK pathway.

Cıkla et al. [106] have synthesized the hydrazide **55** and 4-thiazolidinone ring **56** bearing flurbiprofen moieties, Fig. 43. The antiproliferative activity of the two compounds was evaluated in NCI (national cancer institute). Compound **56** exhibited the highest growth inhibitory activity (growth% = 20.80–43.50%). Among the tested cell lines, leukemia SR was the most sensitive to compound **56**.

The **MDC-813** (Fig. 44) was found to induced apoptosis and inhibited the growth of SW480 colon and MCF-7 breast cancer cells. The induction of apoptosis was mediated by oxidative stress [71].

Flurbiprofen-NO **58** (Fig. 45) bearing nitric oxide-releasing moiety was evaluated for the anticancer activity against HT-29 and HCT-15 colon cancer cell lines [62]. The results revealed potent anticancer activity with IC_{50} values of 98 and 285 μM against HT-29 and HCT-15, respectively. Compound **58** displayed up to ninefold increase in anticancer activity, compared to the parent flurbiprofen. The ability of flurbiprofen-NO to inhibit growth in the COX-producing HT-29 cells and HCT-15 cells which does not express COX enzymes provided an evidence that the mechanism of action of compound **58** is COX-independent.

El-Azab et al. [63] have reported two flurbiprofen derivatives **59a,b**, Fig. 46. The results of the MTT assay of these compounds revealed higher anticancer activity for compound **59b** (IC_{50} = 10.52–26.81 μM) than compound **59a** (IC_{50} = 63.61–78.11 μM) against HepG2, MCF-7, HTC-116 and Caco-2 cancer cell lines. Mechanistic of studies compound **59b**



44, IC_{50} = 273 μM (L1210)
= 97 μM (Molt4/C8)
= 71 μM (CEM)
= >100 μM (HeLa)
= >100 μM (MIA PaCa-2)
= >100 μM (SW 620)
= >100 μM (MCF-7)
= >100 μM (H 460)

45, IC_{50} = 44 μM (L1210)
= 40 μM (Molt4/C8)
= 40 μM (CEM)
= 19 μM (HeLa)
= **14** μM (MIA PaCa-2)
= 17 μM (SW 620)
= **14** μM (MCF-7)
= 18 μM (H 460)
= **30** μM (WI 38)

Fig. 34. Ketoprofen amide **44** and phosphoramidate **45** derivatives and their anticancer activities.

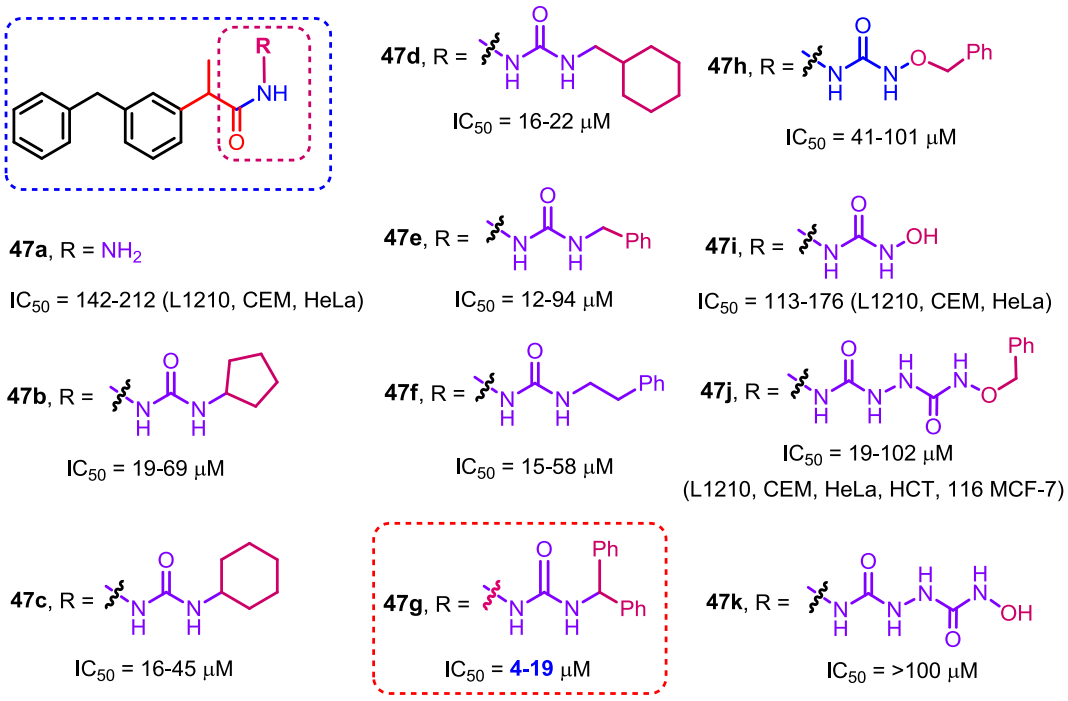


Fig. 36. Anticancer activities (IC_{50} values) of compounds **47a-k** against L1210, CEM, HeLa, HCT116, MCF-7 and H460 cancer cell lines.

revealed potent inhibitory activity for COX-2 (IC_{50} = 0.69 μM) than COX-1 (IC_{50} > 50 μM). Moreover, compound **59b** showed very weak inhibitory activity (3%) of HER4 and cSrc kinases (3%).

2.5. Naproxen

2.5.1. Naproxen and anticancer activity

Kim et al. [107] have investigated the anticancer activity of naproxen **5** and the potential non-COX targets involved in mechanism of action. Cell viability assay revealed the ability of naproxen to decrease viability and inhibit anchorage-independent growth in UM-UC-5 and UMUC-14 urinary bladder cancer cells. Kinase inhibition assay revealed the ability of naproxen to inhibit phosphoinositide 3-kinase (PI3-K) activity only through direct interaction. Naproxen decreased also phosphorylation of Akt. Moreover, naproxen induced G1 cell cycle arrest and apoptosis in UM-UC-5 and UMUC-14 cells. Different targets which mediate the anticancer activity of naproxen were presented in Fig. 47.

In addition, Gobec et al. [48] have investigated naproxen among several NSAIDs for their inhibitory activity against AKR1C3 enzyme. The results revealed the highest inhibitory activity for naproxen **5** with IC_{50} value of 0.48 μM.

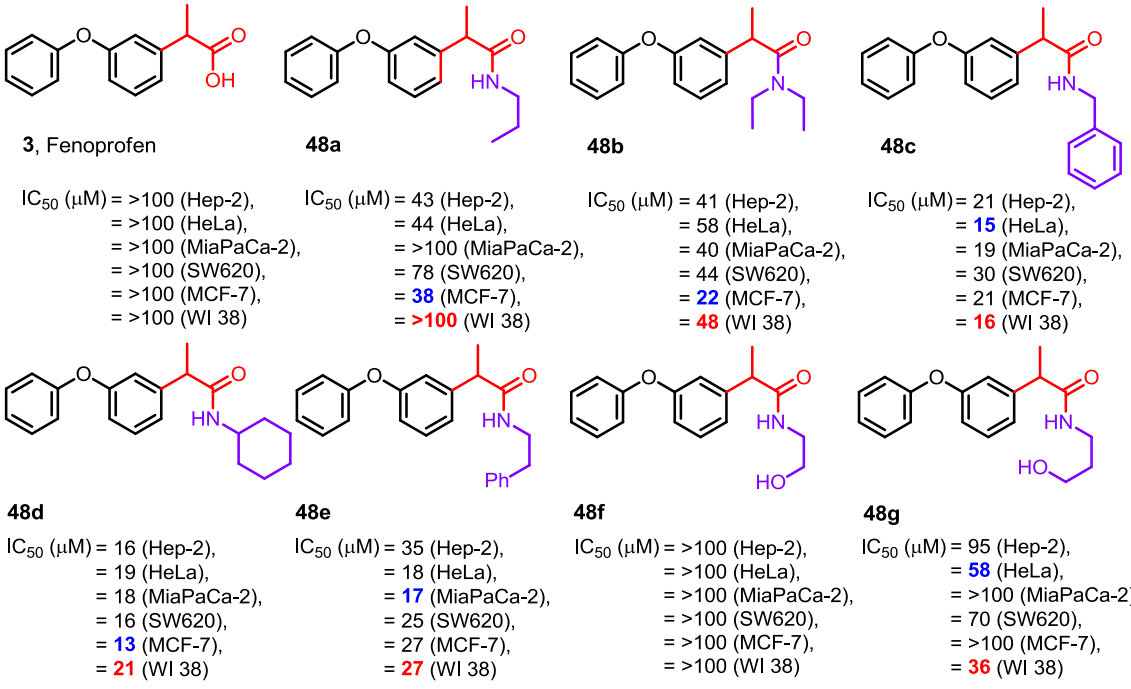


Fig. 37. Fenoprofenamides **48a-g** with their anticancer activities.

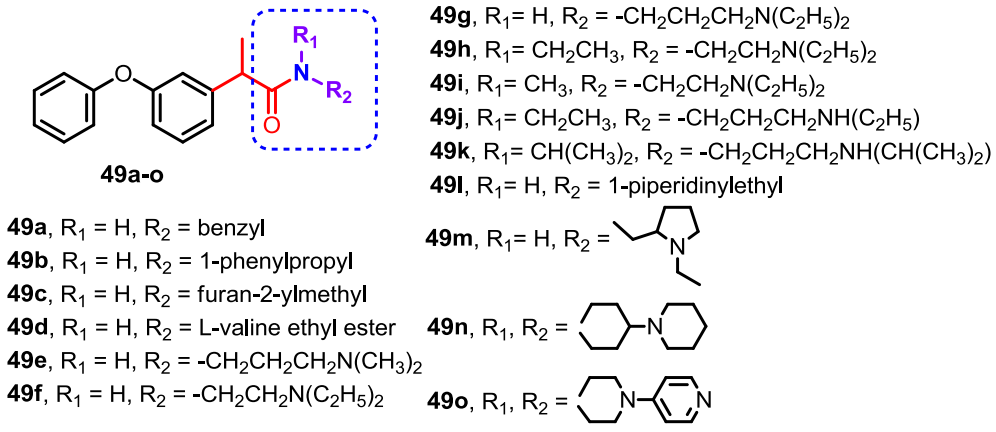


Fig. 38. Chemical structure of fenoprofen amides **49a-o**.

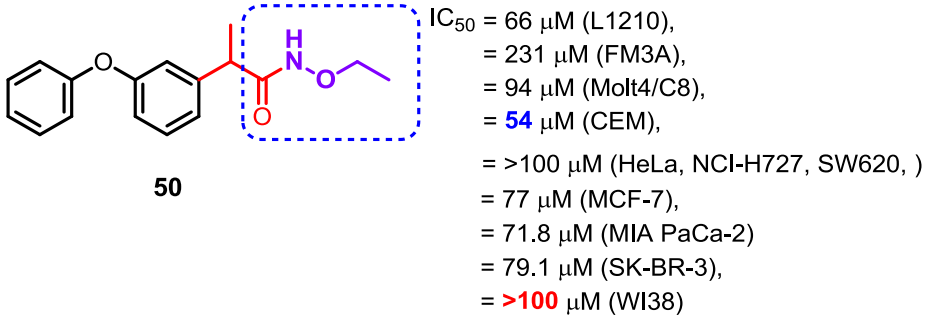


Fig. 39. . Antiproliferative activity of compound **50** against various cell lines.

Motawi et al. [108] have evaluated the anticancer activity of naproxen **5** against six cancer cell lines, using tryptophan blue and MTT assay. The results revealed potent anticancer activities against the tested cell lines with IC_{50} values in the range of 4.14–4.56 μM, Fig. 48. The anticancer activity of naproxen was associated in a parallel way with an increase in apoptotic changes, p53 level and caspase-3 expression. Naproxen **5** displayed also a powerfully inhibition of glycogen synthase kinase-3b (GSK-3b) with IC_{50} value of 1.5 μM.

2.5.2. Naproxen derivatives

Naproxen thioesters **60a,b** (Fig. 49) were synthesized and evaluated for their anticancer activity against four (HepG2, MCF-7, HTC-116 and

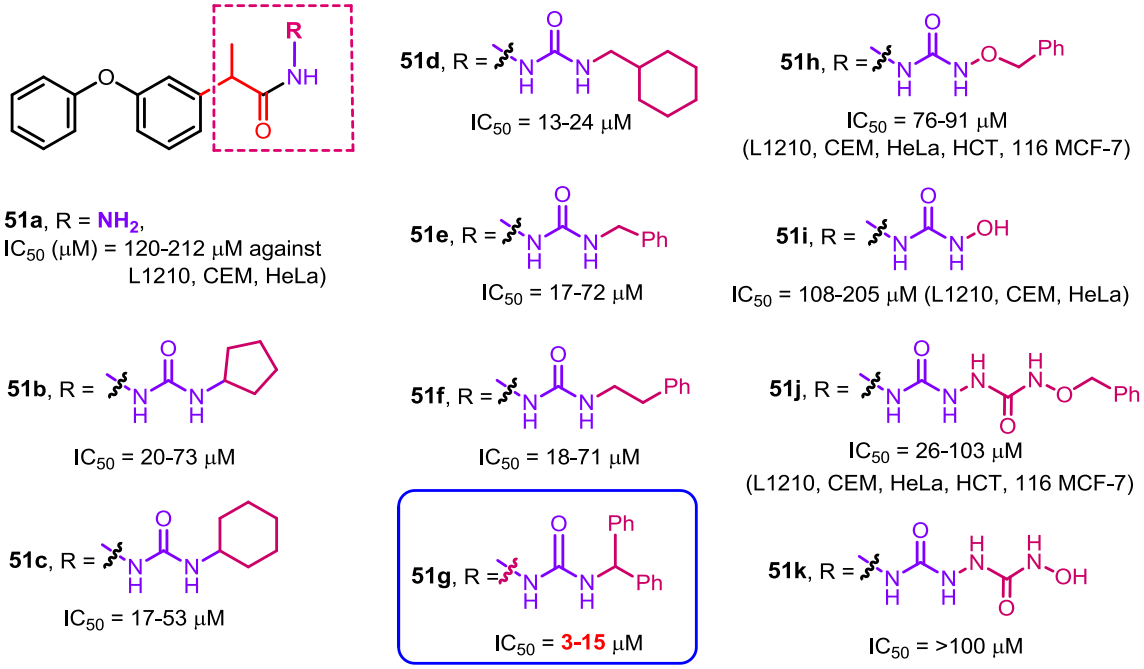


Fig. 40. Fenoprofen semicarbazide/carbamoylcarbazide derivatives **51a-k** with their anticancer activity against L1210, CEM, HeLa, HCT 116, MCF-7 and H460 cell lines.

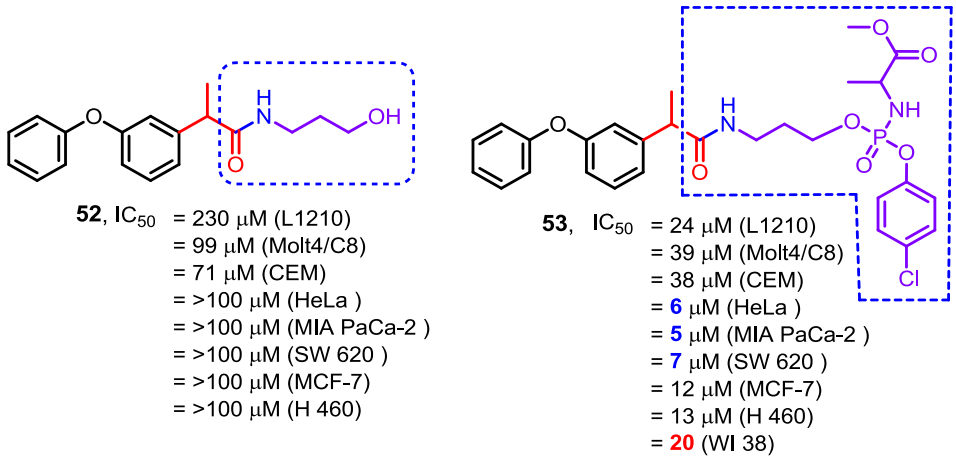


Fig. 41. Fenoprofen amide **52** and phosphoramidate **53** with their anticancer activities (IC_{50}).

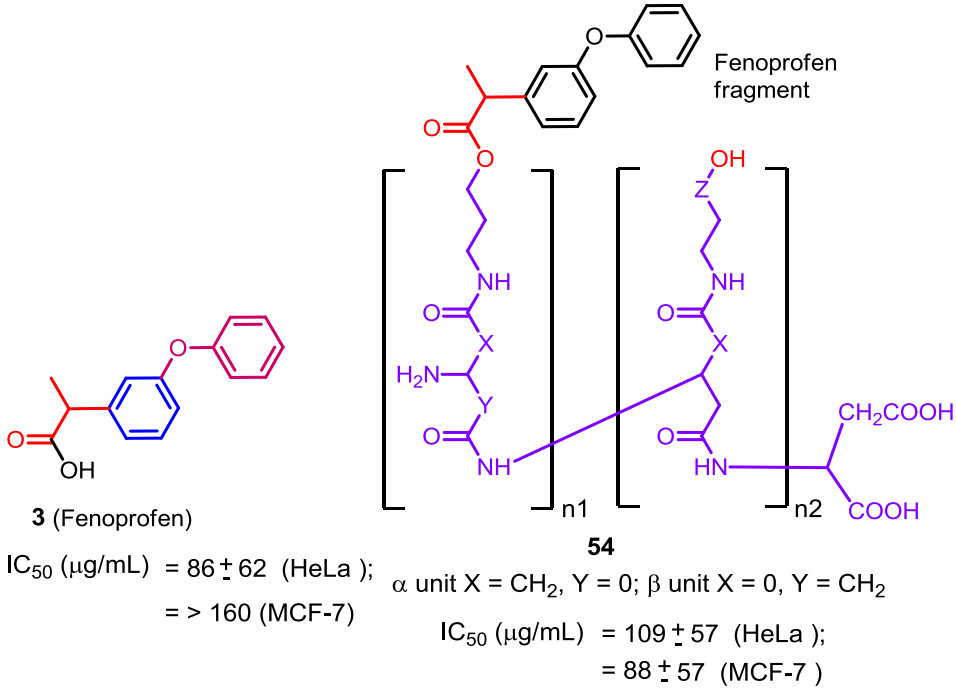


Fig. 42. Fenoprofen **3** and polymer-fenoprofen conjugate **54** with their anticancer activities.

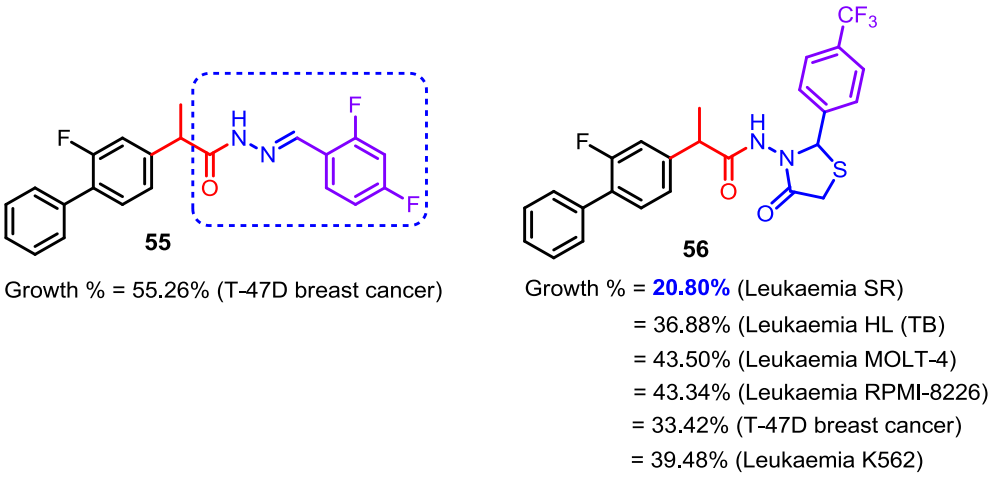
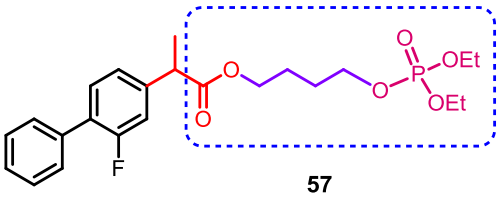


Fig. 43. Flurbiprofen derivatives **55** and **56** with their growth inhibitory activity against breast cancer/leukemia cells.



57
(MDC-813)

Fig. 44. Phospho-flurbiprofen (**MDC-813**) **57**.

Caco-2) cancer cell lines using MTT assay [63]. Compound **60b** displayed higher anticancer activity than the phenyl analog **60a**.

Deb et al. [109] have reported a new series of naproxen derivatives **61a-d**, Fig. 50. The new compounds were evaluated for their anticancer activities against MCF-7 and MDA-MB-231 cancer cells. Of these derivatives, compound **61d** displayed higher anticancer activity than naproxen sodium. The anticancer activity of compound **61d** was mediated by induction of apoptosis, induction of caspase-3/9, and inhibition of COX.

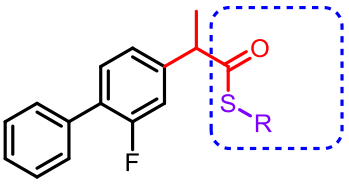
Aboul-Fadl et al. [110] have reported a new series of naproxen amide derivatives **62a-m**, Fig. 51. The new compounds were evaluated for their anticancer activities against HT-29 cancer cell line. Except for compound **62c,d**, all the remaining compounds displayed higher anticancer activities than naproxen sodium with IC_{50} values in the range of 11.4–209 μM. Among these, compound **62a** was the most potent. The anticancer activity of compound **62a** was COX-independent and was mediated by induction of apoptosis evidenced by the activation of caspase-3/7 enzymes in HT116 cells.

The triazole derivatives **63a-m** (Fig. 52) were prepared from naproxen and evaluated for their anticancer activity against three prostate cancer (PC-3, DU-143 and LNCaP) cell lines using 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxy-phenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium (MTS) assay [111]. The results revealed weak anticancer activity for compounds **63a-m**. Among these, compound **63g** was the most active against DU-145 and PC-3 cells with IC_{50} values of 87.2 and 115.1, respectively.

Tolan et al. [112] have evaluated the antitumor activity of a series of Pt (IV) complexes with naproxen, Fig. 53. These complexes **64a-g** were synthesized based on cisplatin, carboplatin and oxaliplatin scaffold.

The metal complexes **64a-g** (Fig. 53) displayed remarkable anti-inflammatory activity. Moreover, they exhibited up to thirteen-fold increase in cytotoxic activity compared to cisplatin [112]. The new complexes **64a-g** showed IC_{50} values in the range of 3.92–19.12 μM, as compared with naproxen (IC_{50} > 100 μM) [112].

Ribeiro et al. [76] have reported diruthenium-naproxen ($[Ru_2(npx)_4(H_2O)2]PF_6$) complex **65** (Fig. 54) and investigated its effect on proliferation of Hep2 (human larynx), T24/83 (human bladder) and C6 (rat glioma). The results revealed no significant effect on Hep2 and T24/83 proliferation, while growth of C6 cancer cells was significantly



59a: R = Ph;
59b: R = cyclohexyl

Fig. 46. Flurbiprofen thioesters **59a,b**.

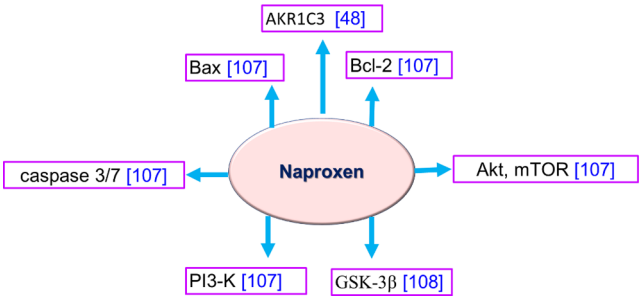
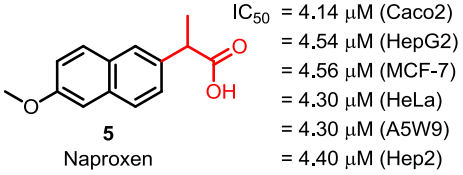


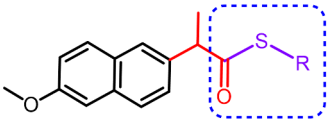
Fig. 47. The potential targets for anticancer activity of naproxen **5**.



5
Naproxen

IC_{50} = 4.14 μM (Caco2)
= 4.54 μM (HepG2)
= 4.56 μM (MCF-7)
= 4.30 μM (HeLa)
= 4.30 μM (A5W9)
= 4.40 μM (Hep2)

Fig. 48. Naproxen **5** and its antiproliferative activities.



60a: R = Ph;
60b: R = cyclohexyl

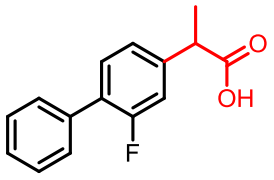
60a: IC_{50} = **36.75** μM (HepG2);
= 42.61 μM (MCF-7);
= 51.17 μM (HCT-116);
= 63.78 μM (Caco-2)

60b: IC_{50} = **19.74** μM (HepG2);
= 28.90 μM (MCF-7);
= 39.52 μM (HCT-116);
= 35.60 μM (Caco-2)

Fig. 49. Naproxen thioesters **60a,b** and their antiproliferative activities.

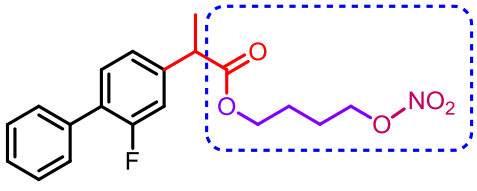
inhibited by the $[Ru_2(npx)_4(H_2O)2]PF_6$ **65**.

Tabares et al. [113] have reported two new Ru(II) organometallics complexes, based on Ru(II)-η6-*p*-cymene framework with naproxen-pyridineamide **66**, and naproxen **67**, Fig. 55. The two complexes were evaluated for their growth inhibitory activity against NCI-H460 and A549 lung cancer cells using MTT assay. The results revealed that compound **67** is inactive (IC_{50} > 200 μmol/L), while compound **66**



4, Flurbiprofen

Flurbiprofen, IC_{50} = 782 μM (HT-29)
= 450 μM (HCT-15)



58, Flurbiprofen-NO

Flurbiprofen, IC_{50} = 98 μM (HT-29), ratio = 9
= 285 μM (HCT-15), ratio = 1.7

Fig. 45. Flurbiprofen **4** and flurbiprofen-NO **58** with their growth inhibitory activity against HT-29 and HCT-15 cells.

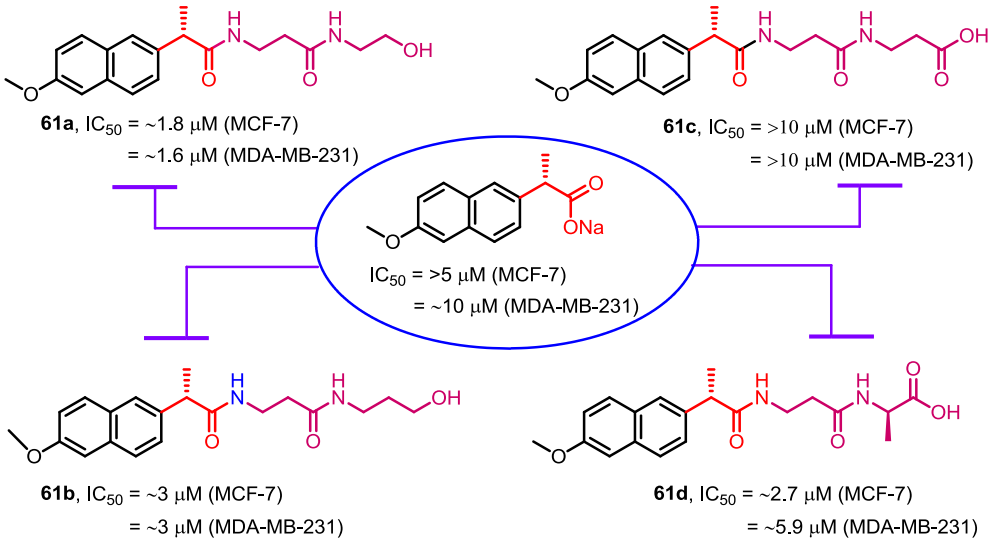
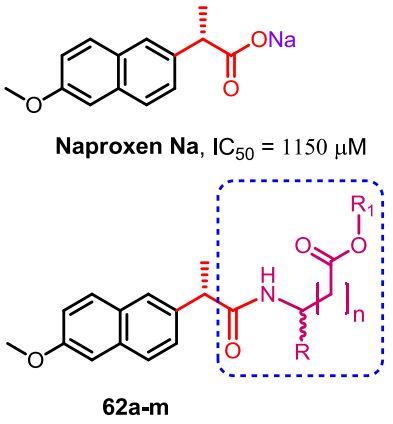
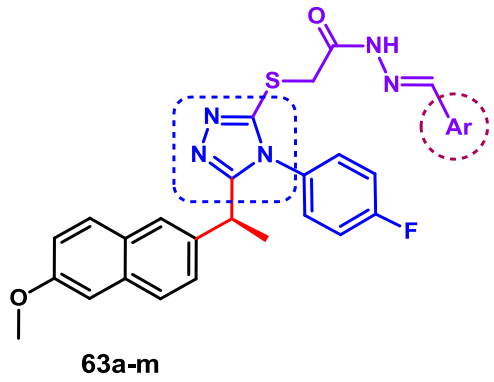


Fig. 50. Naproxen **5** with its amide derivative **61a-d** with their anticancer activities (IC_{50} values).



62a, n = 0, R = H, R1 = Et, IC_{50} = **14.6** μM;
62b, n = 1, R = H, R1 = Et, IC_{50} = 123 μM;
62c, n = 0, R = CH_3, R1 = Me, IC_{50} = **>250** μM;
62d, n = 0, R = CH_3, R1 = Me, IC_{50} = **>250** μM;
62e, n = 0, R = CH_3, R1 = Et, IC_{50} = 175 μM;
62f, n = 0, R = C_2H_5, R1 = Me, IC_{50} = 209 μM;
62g, n = 0, R = -$CH(CH_3)_2$, R1 = Et, IC_{50} = 29.4 μM;
62h, n = 0, R = -$CH(CH_3)_2$, R1 = Me, IC_{50} = 102 μM;
62i, n = 0, R = -$CH_2CH(CH_3)_2$, R1 = Me, IC_{50} = 34.5 μM;
62j, n = 0, R = -$CH_2CH(CH_3)_2$, R1 = Me, IC_{50} = 74.1 μM;
62k, n = 0, R = -CH_2COOCH_3, R1 = Me, IC_{50} = 120 μM;
62l, n = 0, R = -CH_2CH_2-SCH_3, R1 = Et, IC_{50} = 49.3 μM;
62m, n = 0, R = -CH_2-Ph, R1 = Et, IC_{50} = 33.6 μM

Fig. 51. Naproxen Sodium and naproxen amides **62a-m** with their growth inhibitory activities against HT-29 cancer cells.



63a: Ar = 2-chloro-6-fluorophenyl
63b: Ar = 2,4-dichlorophenyl
63c: Ar = 2,6-dichlorophenyl
63d: Ar = 3,4-dichloro
63e: Ar = 2-fluorophenyl
63f: Ar = 2-chlorophenyl
63g: Ar = 4-chlorophenyl
63h: Ar = 3-bromophenyl
63i: Ar = 4-bromophenyl
63j: Ar = 4-nitrophenyl
63k: Ar = 4-methylphenyl
63l: Ar = 4-methoxyphenyl
63m: Ar = 3,5-bis trifluoromethylphenyl

Fig. 52. Naproxen-hydrazide-hydrazone **63a-m**.

inhibited cell proliferation with GI_{50} values of 161 and 145.3 μmol/L against NCI-H460 and A549 cells, respectively.

Tabrizi et al. [114] have reported a new Ru-based complex **68** containing ibuprofen and naproxen moieties, Fig. 56. The cytotoxic activity of this complex was evaluated against three cancer cell lines including MCF-7 and MDA-MB-231, and HT-29 using MTT assay. The MCF-7 and MDA-MB-231 were the most sensitive. The results revealed IC_{50} values of 0.91 and 1.32 μM against MCF-7 and MDA-MB-231 cells, respectively. Moreover, complex **68** displayed IC_{50} values of 4.71 and 108.20 μM against MCF-10A and HEK293 normal cells, respectively. Mechanistic study of complex **68** revealed a strong COX-2 inhibitory activity and an increase ROS (reactive oxygen species) production in MCF-7 cells.

Skiba et al. [115] reported four $Re(CO)_3$-based complexes containing four different NSAID (aspirin, indomethacin, ibuprofen and naproxen) ligands, Fig. 57. The complexes which contain ibuprofen **69** and naproxen **70** ligands displayed very weak inhibitory activity against HeLa human cancer cells with IC_{50} values of 371 and 306 μM,

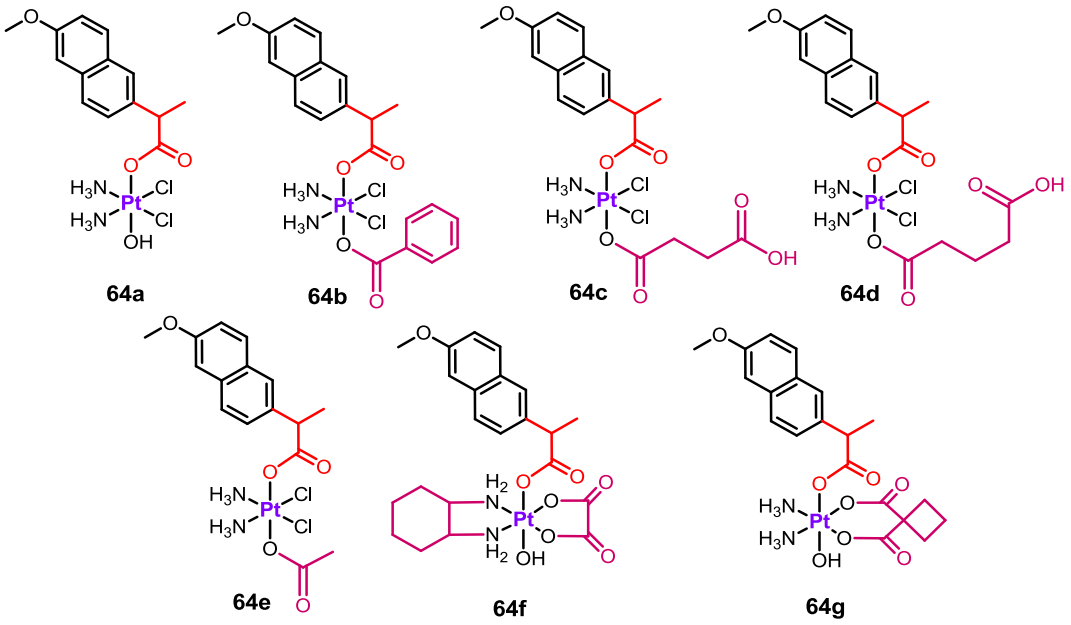


Fig. 53. Naproxen-platinum (IV) complexes **64a-g**.

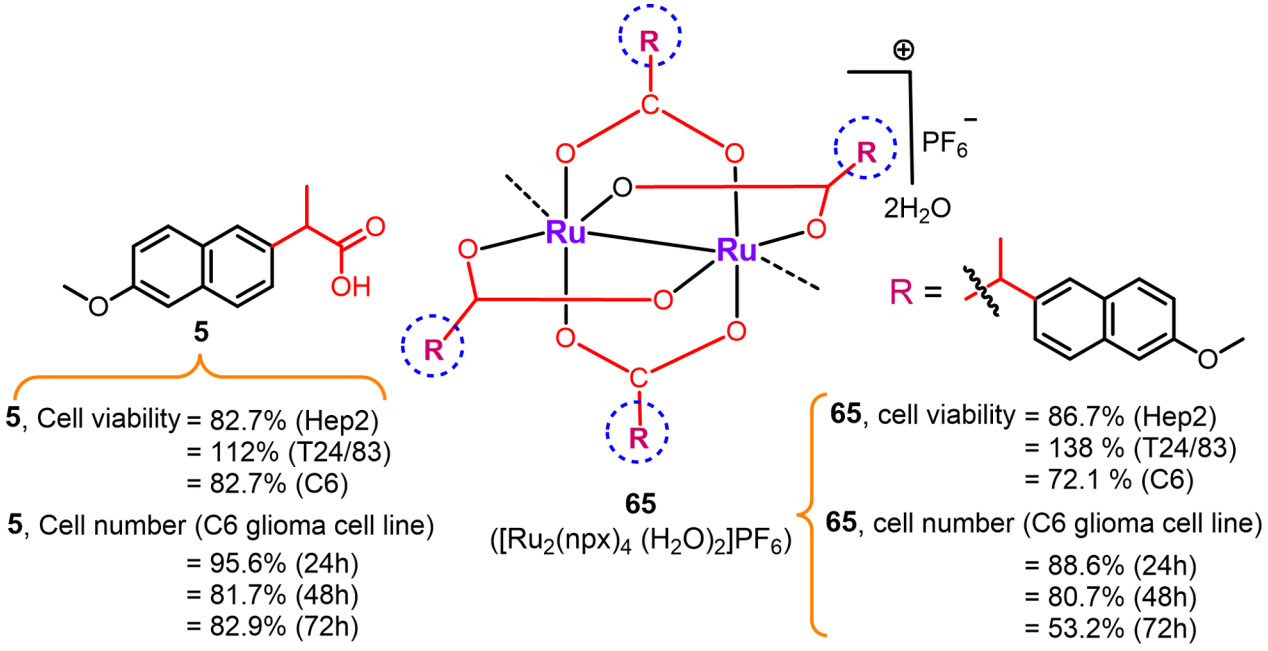


Fig. 54. Naproxen (npx) **5** and $[Ru_2(npx)_4\ (H_2O)2]PF_6$ **65** and their antiproliferative activities.

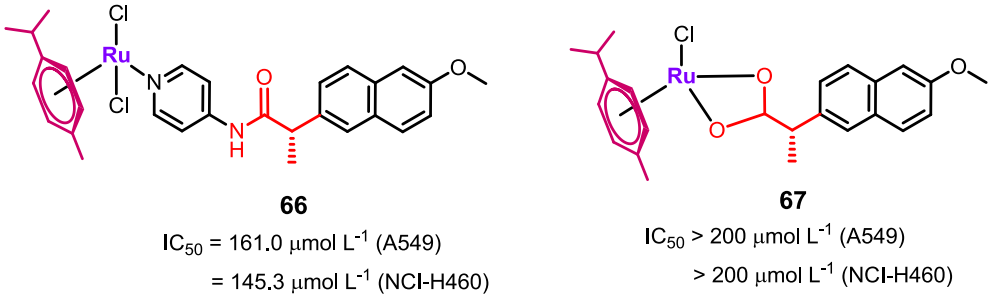


Fig. 55. Ru(II)-*p*-cymene complex with naproxen-pyridineamide **66**, and naproxen **67**.

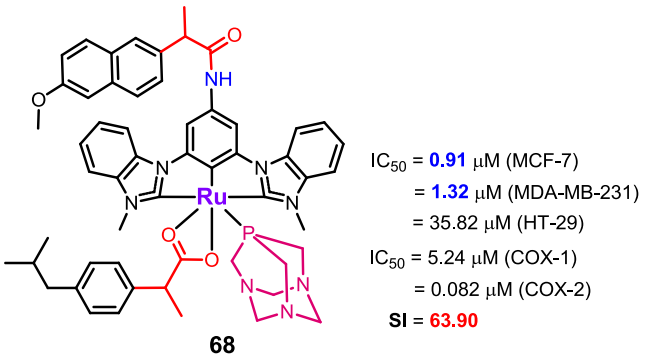


Fig. 56. [Ru(CCC-Nap)(Ibu)(PTA)] complex **68** with cytotoxicity and COX inhibitory activities.

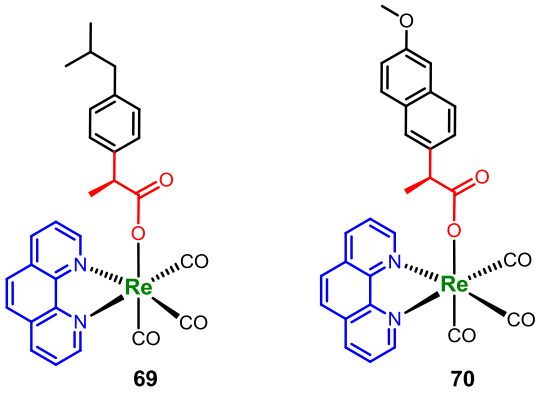


Fig. 57. *fac*-[Re(CO)$_3$(phen)(ibuprofen] **69** and *fac*-[Re(CO)$_3$(phen)(naproxen] **70** complexes, phen = 1,10-phenanthroline.

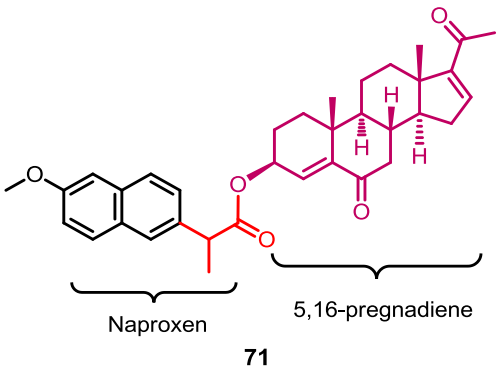


Fig. 58. Naproxen-pregnadiene hybrid **71**.

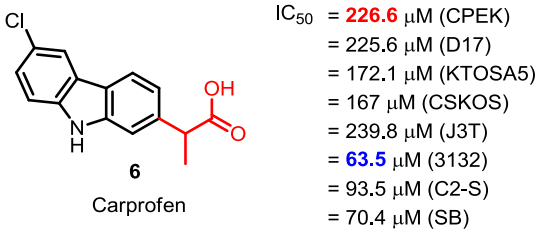


Fig. 59. Carprofen **6** and its activity against seven cancer and one normal (CPEK) cell lines.

respectively.

Garrido et al. [78] have reported the naproxen-pregnadiene hybrid **71**, Fig. 58. This hybrid **71** was evaluated for anticancer activity against U373 cell line. The results revealed moderate antiproliferative activity against U373 cells with IC$_{50}$ value of 17.74 μM, compared to 3.02 μM for the parent steroidal alcohol.

2.6. Carprofen

2.6.1. Carprofen and anticancer activity

Using the 2-phenyl propionic acid pharmacophore, Khwaja et al. [116] have screened a database of 30 million compounds where carprofen **6** displayed high probability to induce P75^{NTR} level. Carprofen induced P75^{NTR} expression in prostate PC-3, DU-145, and bladder T24 cell lines, but no induction in P75^{NTR} was observed in MCF-7 cells. Carprofen displayed potent P75^{NTR}-dependent apoptosis in prostate cancer cells mediated by phosphorylation and activation of p38 MAPK pathway.

Pang et al. [117] have studied the effect of carprofen **6** on survival of a panel of canine cancer and one normal cell lines, Fig. 59. Among the tested cell lines, lymphoma 3132 cell line was the most sensitive to carprofen (IC$_{50}$ = 63.4 μM). The antiproliferative activity of carprofen was mediated by induction of apoptosis which may be caspase-independent. Moreover, carprofen increased the pro-survival Bcl2 protein without affecting the level of pro-apoptotic Bax protein.

2.6.2. Carprofen derivatives

Beziere et al. [91] have reported carprofen-NO releasing hybrids **72a**,**b**, Fig. 60. The two hybrids were evaluated for their COX inhibitory and antiproliferative activities against PC3 cells. The results revealed more potent antiproliferative activity for the hybrids **72a,b** (IC$_{50}$ = 48 μM), compared to weak antiproliferative activity for the parent carprofen. The results suggested that NO release contributes to the antiproliferative activity rather than COX inhibition alone.

2.7. Suprofen

2.7.1. Suprofen and anticancer activity

Suprofen **7** is a nonselective COX inhibitor which has higher selectivity for COX-1 [91], Fig. 61. Beziere et al. have investigated the antiproliferative activity of suprofen against PC3 cell line. The results of this study revealed no antiproliferative activity [91].

2.7.2. Suprofen derivatives

Beziere et al. [91] have also reported a series of suprofen-NO hybrids **73a-c** with antiproliferative activity against PC3 cancer cells, Fig. 61. The new compounds displayed COX inhibitory activity with IC$_{50}$ values in the range of 0.48–0.58 μM against COX-1 and in the range of 2.70–5.80 μM against COX-2, which was comparable to the parent suprofen. Compounds **73a-c** displayed also antiproliferative activity against PC3 cells with inhibition % in the range of 7–33%. The significant increase in antiproliferative activity of these hybrids seems to be due to effect of NO-release rather than COX inhibition.

2.8. Tiaprofenic acid, benoxaprofen and pranoprofen

Unlike other profens, tiaprofenic acid **8**, Benoxaprofen **9** and pranoprofen **10** (Fig. 1) were not deeply investigated for their anticancer potential. Accordingly, no or only very little data are available about their anticancer activity [57].

3. Synthesis of selected profens derivatives

In this section, the chemical synthesis of selected profens (ibuprofen, ketoprofen and fenoprofen) and their derivatives will be discussed.

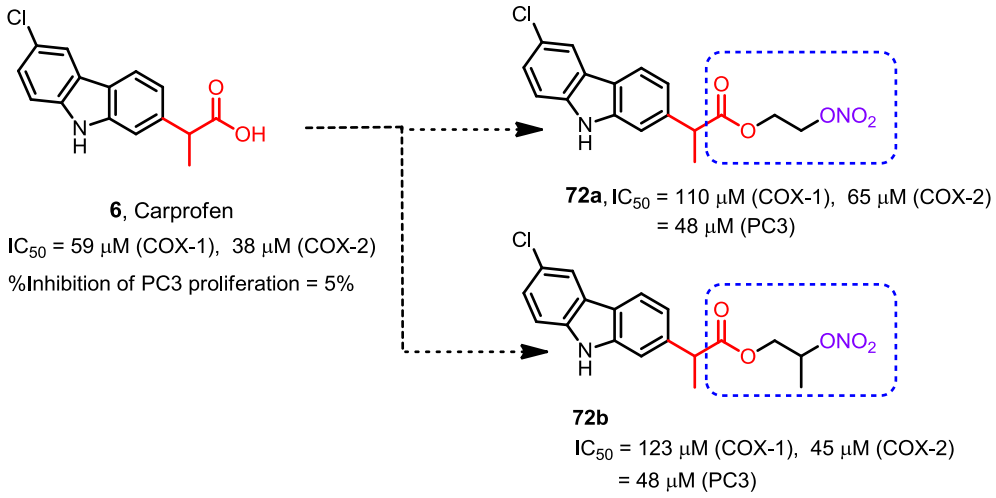


Fig. 60. Carprofen **6** and Carprofen-NO releasing derivatives **72a**,**b** with their COX inhibitory activity and antiproliferative activity against PC3 cells.

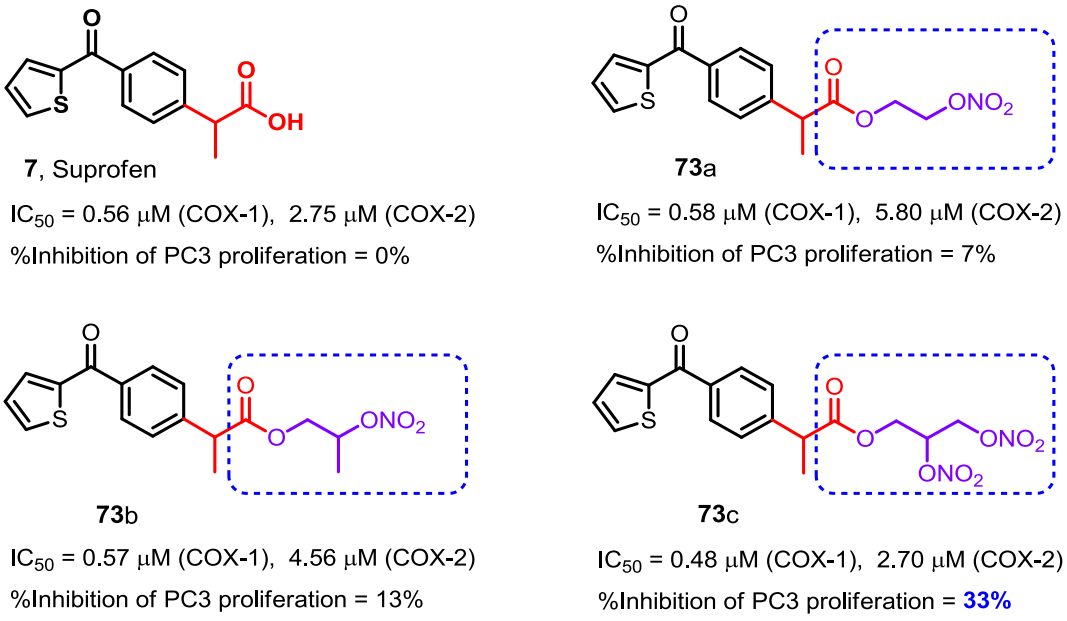
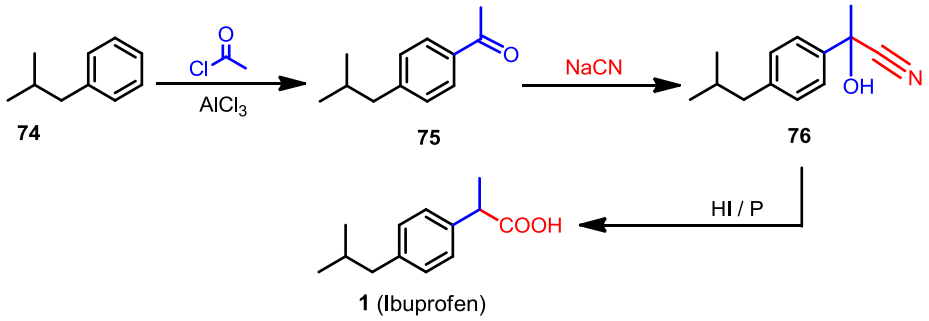


Fig. 61. Suprofen **7** and suprofen-NO releasing derivatives **73a-c** with their COX inhibitory activity and the antiproliferative activity against PC3 cells.



Scheme 1. Synthesis of ibuprofen **1**.

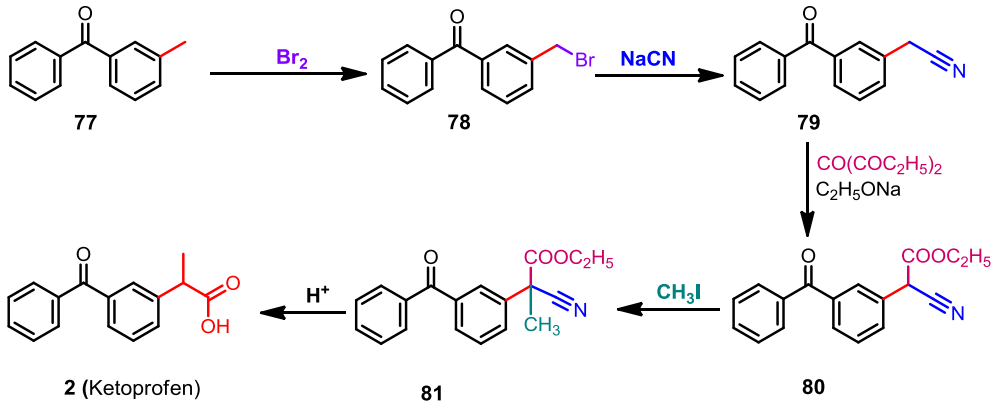
3.1. Synthesis of profens

3.1.1. Synthesis of ibuprofen 1

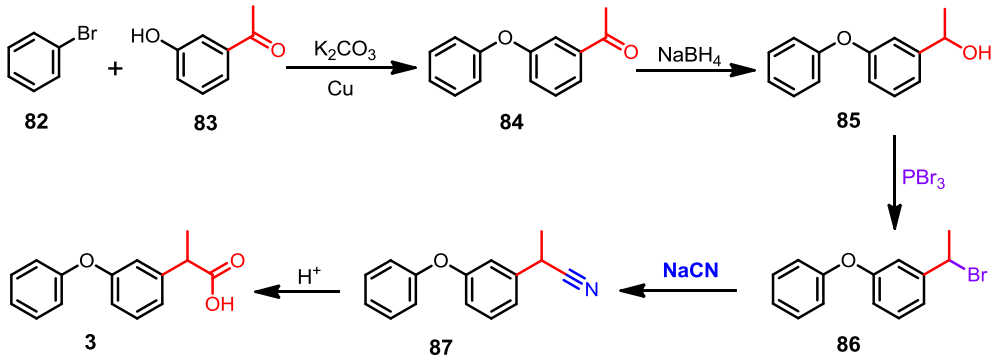
Synthesis of ibuprofen **1** from isobutylbenzene **74** was outlined in Scheme 1. Acetylation of isobutylbenzene **74** with acetyl chloride give compound **75** which on reaction with sodium cyanide gave the nitrile **76**. Ibuprofen was obtained from acid hydrolysis of compound **76** [118–120].

3.1.2. Synthesis of ketoprofen 2

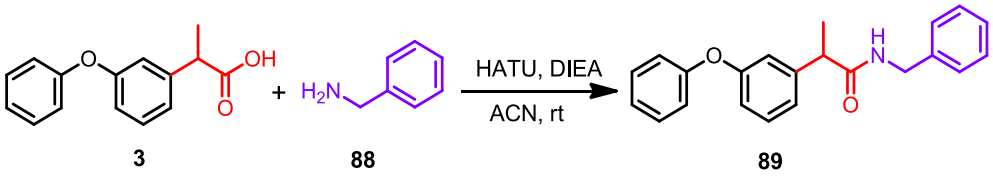
Ketoprofen **2** was synthesized by bromination from the benzophenone **77**, to gave 3-bromo-methylbenzophenone **78**, Scheme 2. The reaction of compound **78** with sodium cyanide produced 3-cyano-methylbenzophenone **79**. The later was reacted with carbonic acid



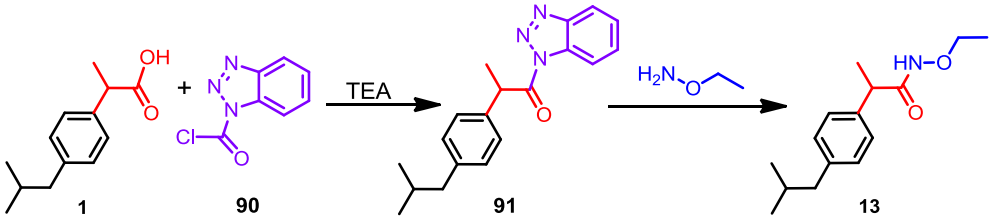
Scheme 2. Synthesis of ketoprofen **2**.



Scheme 3. Synthesis of fenoprofen **3**.



Scheme 4. Synthesis of fenoprofen amide **89**.



Scheme 5. Synthesis of ibuprofen hydroxamic acid **13**.

diethyl ester in the presence of sodium ethoxide. The obtained cyanoacetic ester derivative **80** was alkylated with methyl iodide to give compound **81** which afforded ketoprofen after acidic hydrolysis [120–122].

3.1.3. Synthesis of fenoprofen 3

The reaction of bromobenzene **82** with hydroxyacetophenone **83** in the presence of the acid removing potassium carbonate yielded the 1-(3-phenoxyphenyl)ethenone **84**, Scheme 3. Reduction of the carbonyl group in compound **84** with sodium borohydride followed by reaction of the produced alcohol **85** with phosphorous tribromide afforded the 1-(1-bromoethyl)-3-phenoxybenzene **86**. Treatment of compound **86** with sodium cyanide followed by acid hydrolysis afforded fenoprofen **3** [120,123,124].

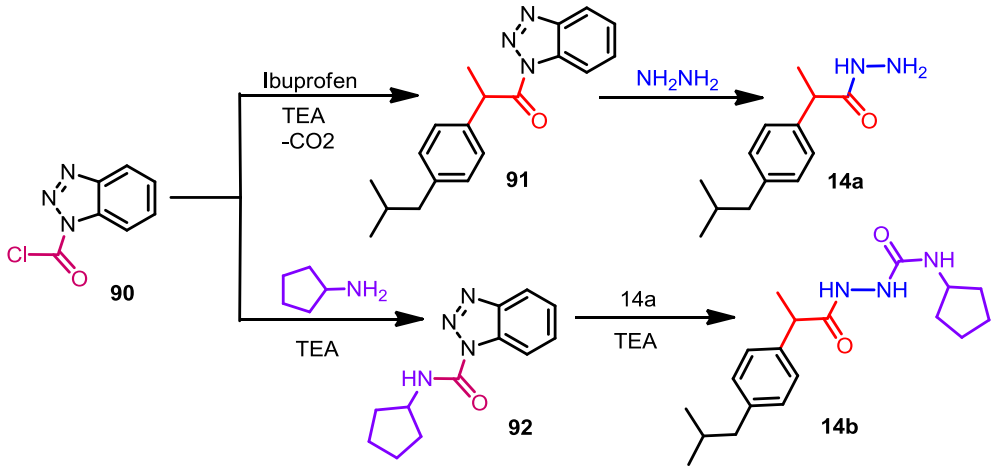
3.2. Derivatization of profens

3.2.1. Synthesis of fenoprofen amide 89

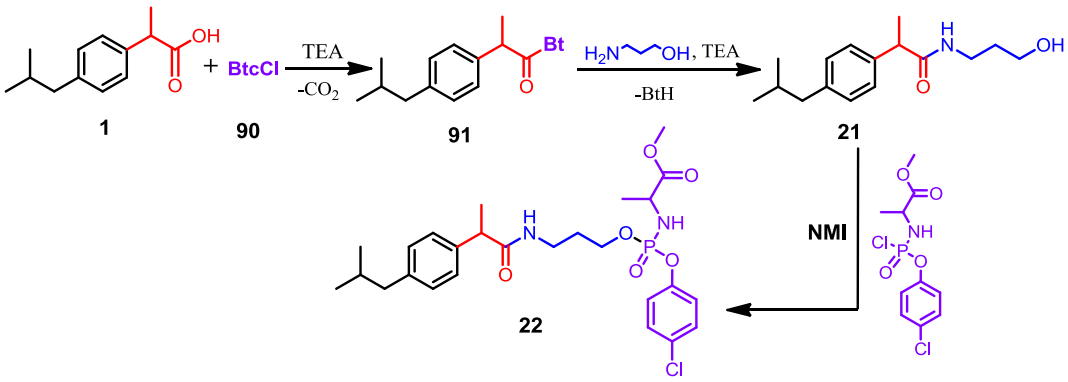
Mathew et al. [94] have synthesized *N*-benzyl fenoprofen amide **89** from the reaction of benzylamine **88** with fenoprofen, Scheme 4. The amide coupling reagent HATU (hexafluoro-phosphate azabenzotriazole tetramethyl uronium) was used as the catalyst in this reaction.

3.2.2. Synthesis of ibuprofen-hydroxamic acid derivative 13

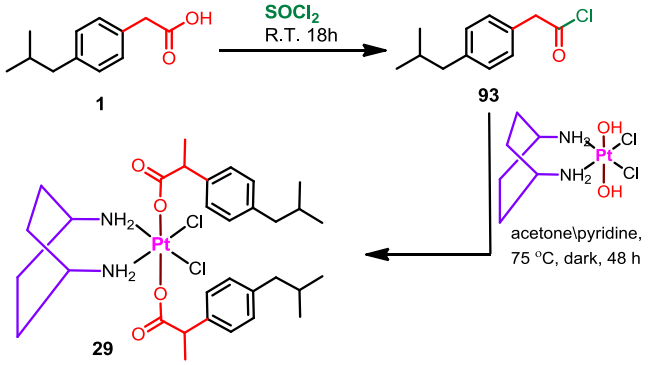
Rajic et al. [125] have synthesized several O-methyl/ethyl NSAID hydroxamic acid derivative. Of these, compound **13** was prepared in two steps, Scheme 5. Ibuprofen benzotriazolide **91** was prepared from the reaction of 1-benzotriazole carboxylic acid chloride (BtcCl) **90** with ibuprofen **1**. The reaction of compound **91** with *O*-ethylhydroxylamine in toluene in the presence of triethylamine (TEA) and sodium dithionite



Scheme 6. Synthesis of ibuprofen hydrazide **14a,b**.



Scheme 7. Synthesis of ibuprofen 3-hydroxypropanamide **21** and phosphoramidate **22**.



Scheme 8. Synthesis of ibuprofen-kiteplatin complex **29**.

to afford compound **13**.

Similarly, compounds **41a** and **50** can be prepared using the same reaction condition with replacement of ibuprofen with ketoprofen and fenoprofen, respectively.

3.2.3. Synthesis of ibuprofen hydrazides *14a,b*

Synthesis of compounds **14a,b** was reported by Perkovic et al. [61]. The 1-benzotriazole carboxylic acid chloride (BtcCl) **90** was reacted with ibuprofen flowed by treatment of the produced benzotriazolide **91** with hydrazine hydrate to afford compound **14a**, Scheme 6. Treatment of BtcCl **90** with cyclopentanamine gave compound **92** which was reacted with compound **14a** to afford the semicarbazide derivative **14b**.

3.2.4. Synthesis of 3-hydroxypropanamide *21* and phosphoramidate *22*

Wittine et al. [73] have synthesized 3-hydroxypropanamide **21** from the reaction of ibuprofen benzotriazolide **91** with hydroxypropyl amine, Scheme 7. Moreover, the phosphoramidate **22** was obtained on treatment of compound **21** with *p*-chlorophenyl(methoxyalaninyl)-phosphochloridate in THF.

3.2.5. Synthesis of ibuprofen-kiteplatin complex *29*

Curci et al. [77] have synthesized a new Pt(IV) prodrug **29** of kiteplatin bearing two molecules of ibuprofen, Scheme 8. Ibuprofen was converted to the acid chloride **93** using thionyl chloride. The produced acid chloride was reacted with dihydroxy platinum(IV) precursor *cis,-trans,cis*-[PtCl2(OH)2(*cis*-1,4-DACH)] to afford the final compound **29**.

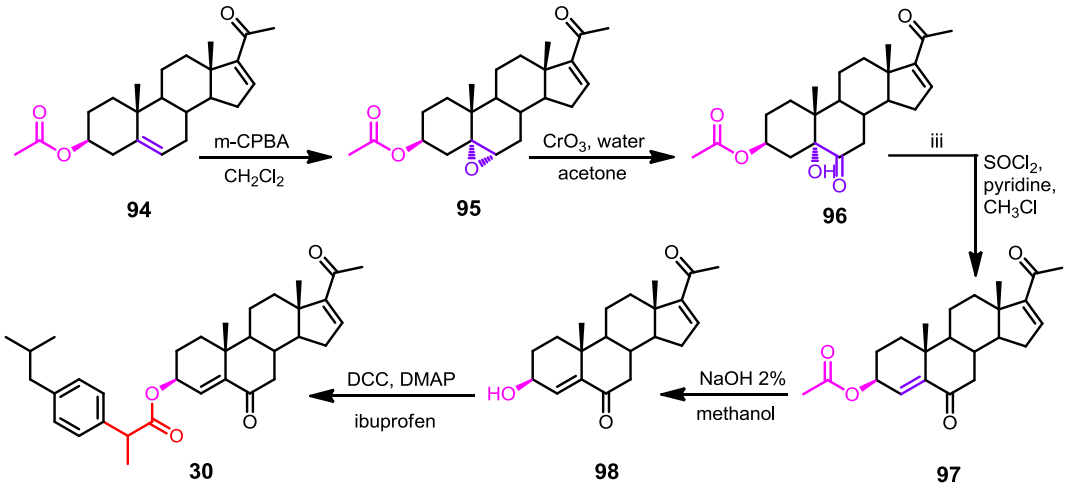
3.2.6. Synthesis of pregnadiene-ibuprofen hybrid *30*

Garrido et al. [78] have synthesised pregnadiene-ibuprofen hybrid **30** from 5,16-dehydropregnenolone acetate **94**, Scheme 9. The double bond at C5 in compound **94** underwent epoxidation by *m*-chloroperoxybenzoic acid (*m*-CPBA). The epoxide **95** was then treated with CrO_3 to give compound **96** which on treatment with thionyl chloride and pyridine produced compound **97**. Hydrolysis of the acetyl ester group in compound **97** with sodium hydroxide liberated the free alcohol **98** which was esterified with ibuprofen to give the target compound **30**.

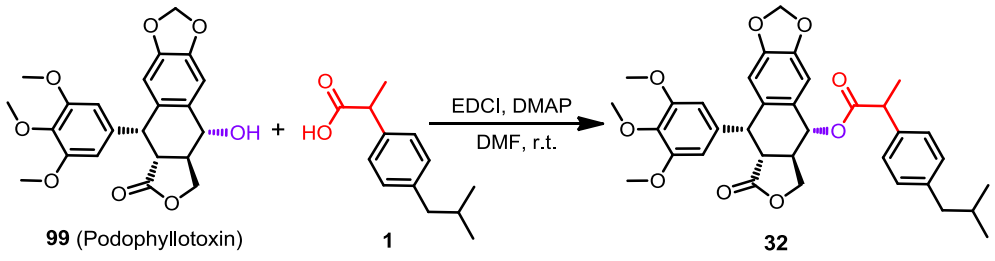
Similarly, compounds **46** (ketoprofen derivatives) and **71** (naproxen derivatives) were obtained using the same reaction condition (Scheme 9), with replacement of ibuprofen with the ketoprofen and naproxen, respectively [78].

3.2.7. Synthesis of Ibuprofen-podophyllotoxin conjugate *32*

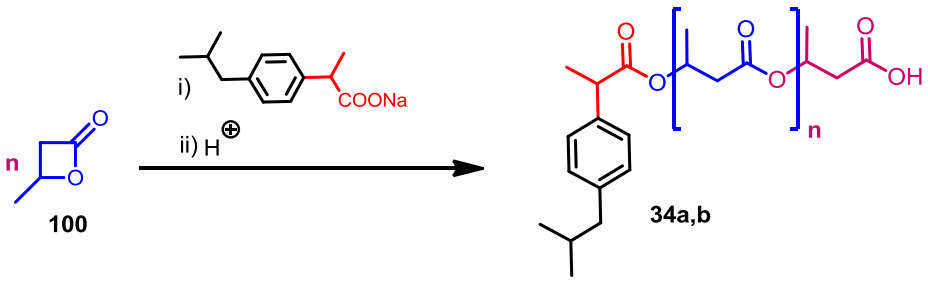
Zhang et al. [81] have prepared ibuprofen-podophyllotoxin conjugate **32** from the reaction of podophyllotoxin **99** with ibuprofen, Scheme 10. The esterification proceeded in DMF in the presence of 1-(3-



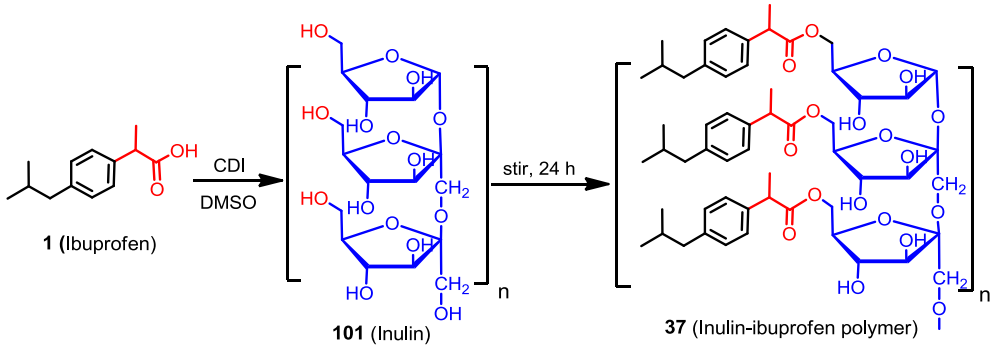
Scheme 9. Synthesis of pregnadiene-ibuprofen hybrid **30**.



Scheme 10. Synthesis of ibuprofen-podophyllotoxin conjugate **32**.



Scheme 11. Synthesis of ibuprofen-oligo(3-hydroxybutyrate) (OHB) derivatives **34a**,**b**.



Scheme 12. Synthesis of Inulin-ibuprofen polymer **37**.

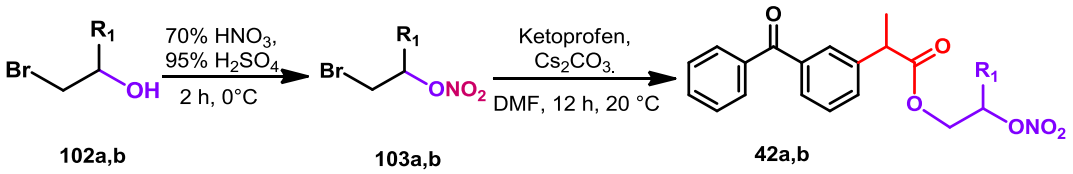
dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 4-dimethy-aminopyridine (DMAP) as coupling reagents.

3.2.8. Synthesis of ibuprofen-oligo(3-hydroxybutyrate) derivatives **34a,b**

Zawidlak-Wegrzynska et al. [83] have synthesized ibuprofen-oligo (3-hydroxybutyrate) (OHB) derivatives **34a**,**b**, Scheme 11. The polymerization occur through S_N2 reaction where the carboxylate anion of ibuprofen salt act as a nucleophile and attack the carbonyl carbon of (*R*,*S*)-β-butyrolactone **100**.

3.2.9. Synthesis of Inulin-ibuprofen polymer **37**

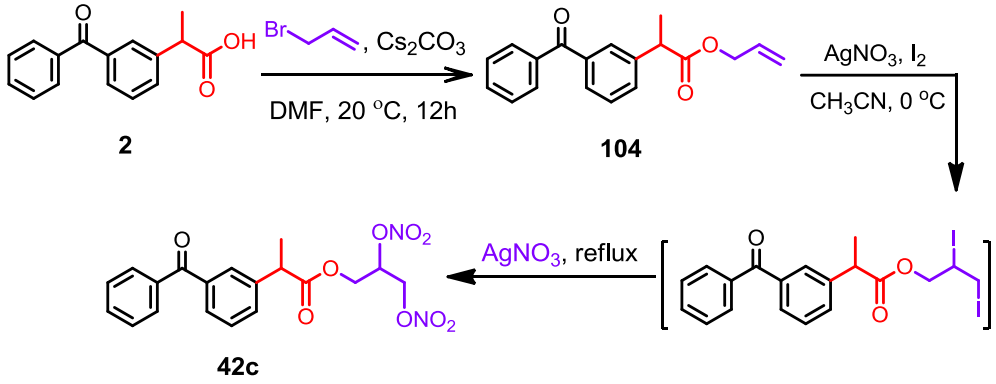
Synthesis of inulin-ibuprofen polymer **37** was reported by Zhang



102a,b **103a,b** **42a,b**

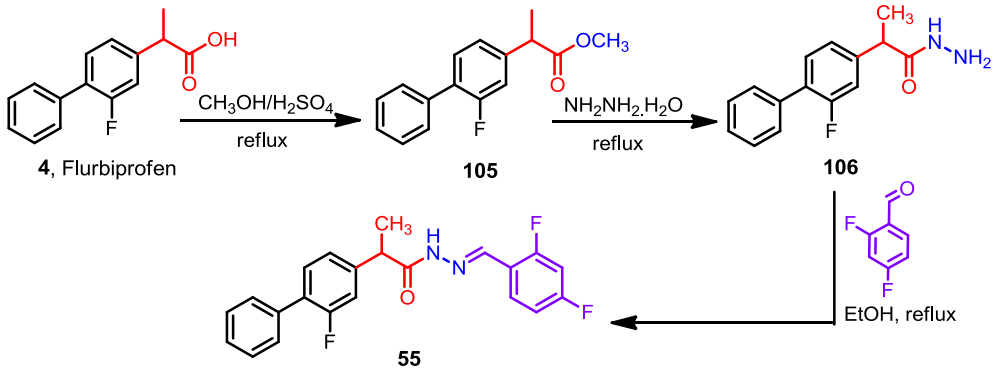
42a, 103a, 104a, R_1 = H,
42b, 103b, 104b, R_1 = CH_3

Scheme 13. Synthesis of ketoprofen-NO hybrids **42a,b**.



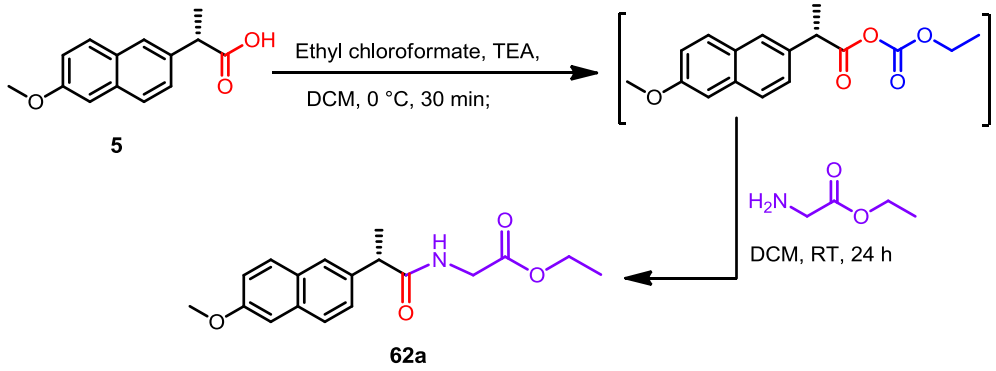
2 **104** **42c**

Scheme 14. Synthesis of ketoprofen-NO hybrid **42c**.



4, Flurbiprofen **105** **106** **55**

Scheme 15. Synthesis of compound **55**.



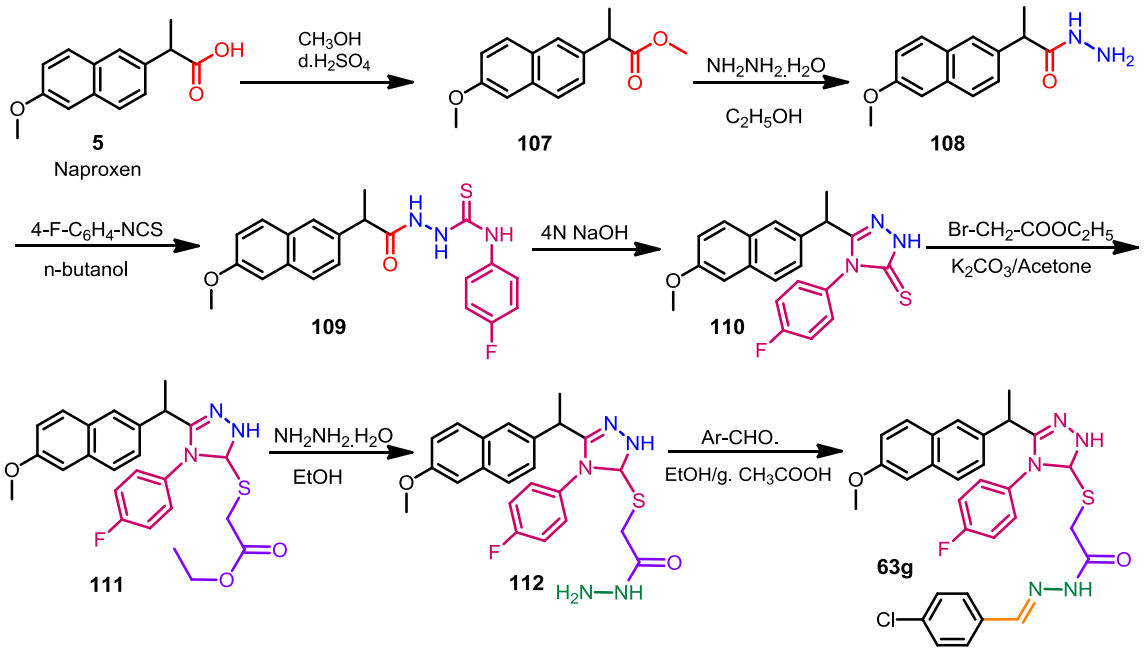
5 **62a**

Scheme 16. Synthesis of naproxen ethyl glycinate derivative **62a**.

et al. [85]. Briefly, a mixture of ibuprofen and the coupling agent *N,N′*-carbonyldiimidazole (CDI) was stirred in DMSO followed by addition of dextran **101** and stirred for 24 h at 80 °C to afford the target compound **37**, Scheme 12.

*3.2.10. Synthesis of compounds **42a,b***

Beziere et al. [91] have synthesized ketoprofen-NO hybrids **42a,b**. These hybrids were obtained by nitration of the alcohols **102a,b** followed by reaction of the obtained nitrate derivative **103a,b** with ketoprofen in DMF, Scheme 13. These reaction conditions was used also in



Scheme 17. Synthesis of naproxen ethyl glycinate derivative **63g**.

the preparation of compounds **72a**,**b** and **73a**,**b**, where ketoprofen was replaced by carprofen and suprofen, respectively.

*3.2.11. Synthesis of compound **42c***

Beziere et al. [91] have also prepared ketoprofen-NO hybrids **42c** from the reaction of ketoprofen with allyl bromide in DMF. The obtained allyl 2-(3-benzoylphenyl)propanoate **104** was reacted with silver nitrate to afford compound **42c**. Compound **73c** was synthesized from suprofen using the same reaction conditions, Scheme 14.

*3.2.12. Synthesis of compound **55***

Çıkla et al. [106] have synthesized compound **55** bearing flurbiprofen moiety, Scheme 15. Compound **105** was prepared by esterification of flurbiprofen with methanol. Treatment of the obtained ester **105** with hydrazine hydrate afforded the hydrazide **106**. Condensation of the amino group in compound **106** with 2,4-difluorobenzaldehyde gave the Schiff base **55**.

*3.2.13. Synthesis of naproxen ethyl glycinate derivative **62a***

Aboul-Fadl et al. [110] have synthesized the naproxen amide **62a**, Scheme 16. The solution naproxen **5** in dichloromethane (DCM) was treated with triethylamine (TEA) followed by dropwise addition of ethyl chloroformate. A solution of ethyl glycinate in DCM was added to reaction mixture to give compound **62a**.

*3.2.14. Synthesis of naproxen-1,2,4-triazol hybrid **63g***

Synthesis of compound **63g** was outlines in Scheme 17. The hydrazide derivative **108** was obtained on treatment of naproxen methyl ester **107** with hydrazine hydrate [111]. The reaction of compound **108** with 4-fluorophenyl isothiocyanate afforded compound **109** which underwent cyclization into triazole derivative **110**. Treatment of compound **110** with ethyl bromoacetate gave compound **111** which was converted to the hydrazide **112** by hydrazine hydrate. Condensation of the hydrazide **112** with the 4-chlorobenzaldehyde afforded the target compounds **63g**.

4. Conclusions

Like other NSAIDs, profen derivatives were intensively investigated for their anticancer potential and mechanism of action. Based on the data in this review, several conclusions can be made: (1) profen derivatives exhibited chemopreventive and therapeutic effects against different types of cancer cell lines; (2) both S- and R-enantiomers (which lack COX inhibitory activity) of profens have displayed anticancer activity; (3) profens derivatives exhibited IC_{50} values in millimolar to submicromolar range against different types cancer cells; (4) combination of profens and anticancer agents act synergistically or additively in prevention/treatment of cancers; (5) synergistic anticancer effects were also observed on hybridization of profen derivatives with anticancer agents such as pregnadiene, riboflavin and podophyllotoxin; (6) the metal complexes of profen derivatives with ruthenium, platinum and rhenium displayed remarkable cytotoxic activity; (7) incorporation of nitric oxide-bearing groups into arylpropionic acid scaffold increased their antiproliferative activity compared to their parent profens; (8) incorporation of phosphate-bearing moieties into arylpropionic acid scaffold enhanced their safety and anticancer potency compared to their parent drugs; (9) the potential non-COX targets which can mediate anticancer potential of profens derivatives were summarized in this review. In the light of these data, profen derivatives can provide chemopreventive and therapeutic effects against different types of cancers. The data in this review highlighted profens as promising lead compounds in future research to develop potent and safe anticancer agents.

Declaration of Competing Interest

Authors declared that there is no actual or potential conflict of interest and have approved the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.103224.

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