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Nimesulide analogues: From anti-inflammatory to antitumor agents

Mafalda Catarro[a], João L. Serrano[a], Susana S. Ramos[b], Samuel Silvestre[a,c], Paulo Almeida[a,*]

[a] CICS-UBI – Health Sciences Research Center, University of Beira Interior, Av. Infante D. Henrique, 6200-506 Covilhã, Portugal
[b] FibEnTech – UBI, Materiais Fibrosos e Tecnologias Ambientais, University of Beira Interior, Rua Marquês d'Ávila e Bolama, 6200-001 Covilhã, Portugal
[c] CNC – Center for Neuroscience and Cell Biology, University of Coimbra, Rua Larga, 3004-517 Coimbra, Portugal

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ABSTRACT

Nimesulide is a nonsteroidal anti-inflammatory drug possessing analgesic and antipyretic properties. This drug is considered a selective cyclooxygenase-2 (COX-2) inhibitor and, more recently, has been associated to antitumor activity. Thus, numerous works have been developed to modify the nimesulide skeleton aiming to develop new and more potent and selective COX-2 inhibitors as well as potential anticancer agents. This review intends to provide an overview on analogues of nimesulide, including the general synthetic approaches used for their preparation and structural diversification and their main anti-inflammatory and/or antitumor properties.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently used group of pharmaceuticals in the treatment of acute and chronic inflammation. Their main therapeutic target is cyclooxygenase (COX) enzymes, which mediate the bioconversion of arachidonic acid to prostanoids involved, namely, in inflammatory reactions [1,2]. The central anti-inflammatory mechanism of action of NSAIDs is the blockage of prostanoids synthesis through inhibition of COXs [1–6].

COXs exist under three known isoforms. Of these, cyclooxygenase-1 (COX-1) is a constitutive isoform responsible for the physiological production of prostanoids, whereas COX-2 is induced and stimulated by a large variety of cytokines, growth factors, oncogenes, lipopolysaccharides and tumor promoters, being its expression associated to pathological conditions. Cyclooxygenase-3 (COX-3) is the more recent discover isoform and has been considered a COX-1 variant. Despite the lack of knowledge on its functions, this isoform is associated with pain and fever processes. [3–8].

COX-1 and COX-2 share 60% of homology, nevertheless the existence of three fundamental differences in the amino acids on the active sites that distinguish these isoforms. These differences lie on the substitution of isoleucine by valine at positions 523 and 434 of COX-1 and histidine-513 by arginine, resulting in an increased size (about 20%), shape and hydrophilicity of COX-2 active site [9,10], which have been considered an important requisite for the development of selective COX-2 inhibitors [1–4].

Inflammation has been identified as one of the key targets on cancer prevention and treatment strategies. In this context, a COX-2 overexpression can be detected in several solid cancers [5,7,11–15]. This expression is mainly associated with an increased production of prostaglandin-E_2 (PGE2), an immunoregulatory molecule that is involved in different stages of carcinogenesis. In fact, PGE2 can modulate cell proliferation, inhibit apoptosis by several mechanisms and promote carcinogenesis, tumor invasiveness and metastization, contributing to cancer progression [4,7,8,12,16,17]. Thus, it is expectable that NSAIDs as well as other drugs inhibiting COX-2 can potentially present anticancer activity and may offer an important role in cancer prevention and treatment [18–21]. As a representative example, nimesulide is a NSAID with selective COX-2 inhibition and has been considered a molecule with potential interest in cancer prevention and treatment [22–32]. Because of this knowledge, the design and development of nimesulide structural analogues envisioning their use as anticancer agents have been performed over the years. In this review, the development of nimesulide analogues, including the main synthetic approaches, as well as their main anti-inflammatory and/or potential anticancer activities is presented.

Abbreviations: Ac, acetyl; Ar, aryl (other than heteroaryl, phenyl and derivatives); Bu, butyl; Bn, benzyl; COX, cyclooxygenase; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; COX-3, cyclooxygenase-3; Cy, cyclohexyl; DMAP, 4-dimethylaminopyridine; DMF, dimethylformamide; ED_{50}, half-medium effective dose; EDCI, 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride; Et, ethyl; FDA, Food and Drug Administration; HetAr, heteroaryl; Hex, hexyl; IC_{50}, half-medium inhibitory concentration; IPr, isopropyl; LPS, lipopolysaccharide; LTEDaro, long-term estrogen-deprived MCF-7aro; Me, methyl; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltatrazolium bromide; NSAIDs, nonsteroidal anti-inflammatory drugs; PGE2, prostaglandin-E_2; PGG2, prostaglandin-G_2; PGH2, prostaglandin-H_2; Pr, propyl; Ph, phenyl; Py, pyridine; SRB, sulforhodamine B; THF, tetrahydrofuran; TMPD, *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine; USA, United States of America

[*] Corresponding author.
E-mail address: paulo.almeida@ubi.pt (P. Almeida).

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2. Nimesulide

Nimesulide, chemically known as *N*-(4-nitro-2-phenoxyphenyl)methanesulphonanilide, is a NSAID with analgesic and antipyretic properties and belongs to the class of selective COX-2 inhibitors. This drug is usually administered orally in a dosage of 100 mg twice daily for a very wide range of disorders, namely, arthritic conditions, musculoskeletal complaints, headaches, cancer pain and vascular diseases. The most common side effects of this drug include gastrointestinal complaints, and the major concern on its use has been the potential liver toxicity [5,33–41].

In order to enhance the bioavailability of nimesulide, Rapposelli *et al* developed a water-soluble nimesulide prodrug which inhibited the oedema formation in a dose-dependent manner with a statistical significance at doses of 2.5 and 5.0 mg/kg, whereas nimesulide modestly decreased the oedema formation at the highest dose of 5.0 mg/kg [42].

George Moore and collaborators in Riker Laboratories – USA, discovered Nimesulide in 1971. This drug, designated by R-805 in clinical trials, was developed before the discovery of prostaglandins role in inflammation and pain processes. In 1980, the Helsinn Healthcare acquired the worldwide licensing rights for nimesulide and in 1985 its production started. This drug is presently available in more than 50 countries worldwide, although has never been filed for Food and Drug Administration (FDA) in the USA neither has been approved in the United Kingdom, Australia, Canada and New Zealand and therefore has never been marketed in these countries [33,34,36,43,44]. In the same year, it was first introduced in Italy and Portugal [34,43]. However, after the discovery of its potential hepatotoxic effects and due to safety concerns, nimesulide has been withdrawn from the market in many countries such as Finland and Spain in 2002 and in Ireland in 2007 [33,44,45].

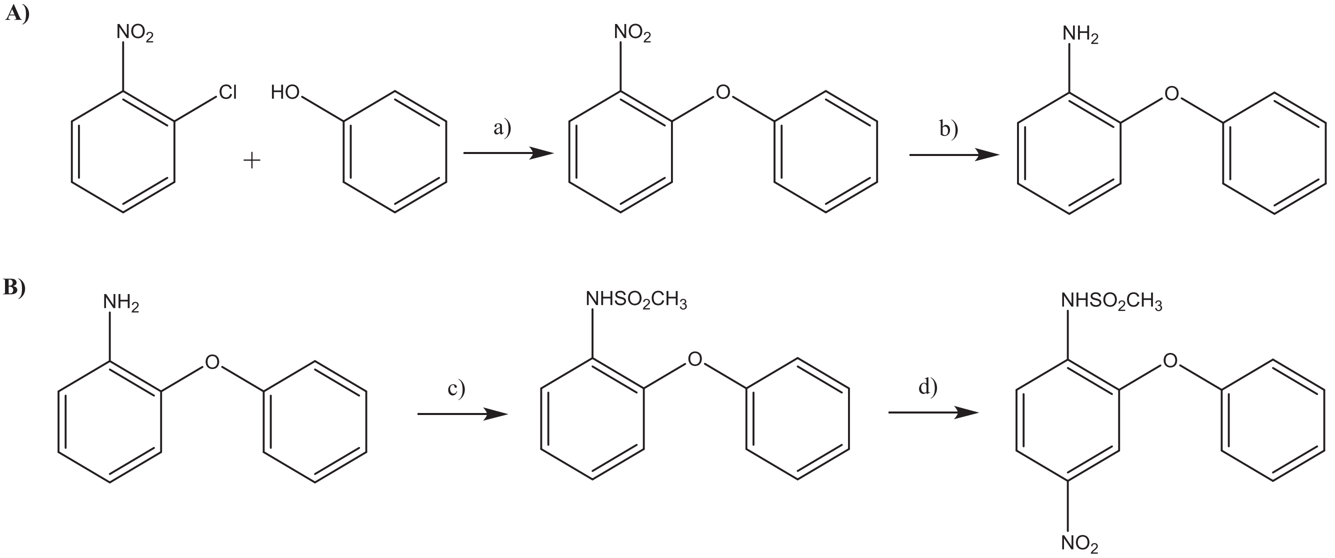
Nimesulide synthesis comprises at least four steps: arylether formation, nitration, reduction and mesylation, not necessarily in this order. In the original patent, the presented synthesis starts from 2-phenoxyaniline (Scheme 1A) mesylation, followed by nitration to afford nimesulide (Scheme 1B) [46]. In the succeeding years, several synthesis and production techniques of nimesulide were described also starting from *ortho*-choronitrobenzene [33,47].

In 2000, a Portuguese patent claimed a new synthesis trough the formation of the nimesulide aryl ether from 4-nitro-2-chloromethanesulfonamide using a silver salt as catalyst under ultrasound irradiation and therefore changing the order of reacting events in relation to the typical synthesis already described [48]. In 2005, a practical large-scale synthesis of nimesulide was described also starting from 2-chloronitrobenzene, which reacts with triphenylphosphate yielding 2-phenoxynitrobenzene, followed by the traditional reduction, mesylation and selective nitration affording the drug with a remarkable 55% overall yield [47]. More recently, a new synthetic approach of nimesulide was developed starting from 2-amino-5-nitrophenol and based on the copper-mediated arylation of phenols [49].

Accumulating evidence has been demonstrating that nimesulide can be considered a relevant candidate in cancer prevention and treatment. In fact, nimesulide has shown multiple anticancer effects including the reduction of cell proliferation [22–26,28,29] and the apoptosis induction [27,28,30–32] in different types of cancer cells. Furthermore, it was also reported that this drug has chemopreventive effects against the development of intestinal polyps in Min mice [50].

Recent studies in this context have also been focused on the development of novel poly(ethyleneglycol)-*block*-poly(ε-caprolactone) nanoparticles encapsulating nimesulide with anticancer effects. Specifically, it was demonstrated that these nimesulide-encapsulated nanoparticles had a significant antiproliferative activity against MCF-7 breast cancer cells in a dose-dependent manner, displaying a higher potential for nimesulide delivery to breast cancer treatment than the conventional treatment [51]. Moreover, nimesulide was conjugated to hyaluronic acid to develop a hyaluronic acid-nimesulide delivery system and the results demonstrated that this conjugate showed high selectivity against the HT-29 colon adenocarcinoma cell line as well as exhibited remarkable antitumor activity by apoptotic mechanisms in HT-29 xenografted mice [52].

Further researches on the combination of nimesulide with other chemotherapeutic drugs or radiotherapy were also performed. For example, in implanted hepatoma in mice, nimesulide combined with 5-fluorouracil had a synergistic effect on tumor growth inhibition, apoptosis induction and reduction of PGE-2 expression [53]. Similarly, the combination of nimesulide and cisplatin showed a synergistic action in cell growth inhibition and/or apoptosis induction in human lung adenocarcinoma cell line [54] as well as in different types of leukemia cells [55]. Nimesulide also potentiated the cytotoxicity of doxorubicin against human lung cancer (A549 and H460) and colon adenocarcinoma (SW620) cell lines, with prominent apoptotic effect in A549 lung cancer cells [56]. Different studies involving the concomitant use of nimesulide and radiotherapy demonstrated that this drug was a strong radiosensitizer in A549 cells, leading to an increase in apoptosis



Scheme 1. Synthesis of intermediate 2-phenoxyaniline (A) and patented synthesis of nimesulide (B) [33,47] and references cited therein. Reagents and conditions: (a) KOH, Δ; (b) Zn, EtOH; (c) CH_3SO_2Cl, Et_3N, xylene; (d) HNO_3, $NaNO_2$, AcOH.

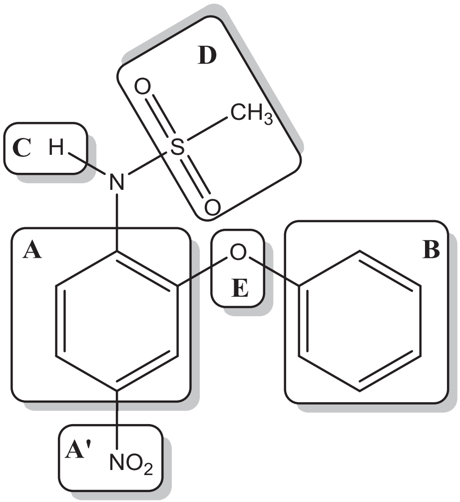


Fig. 1. Relevant modifications A-E of nimesulide skeletal (adapted from [59–64]).

[57,58].

3. Nimesulide analogues

Taking into account the hepatotoxicity associated to nimesulide usage and the interest in the increase of its selective anti-inflammatory and anticancer activities, the scientific community has been attracted to develop nimesulide analogues with higher potency, selectivity and improved pharmacological profile. In this sense, the modifications of one or more **A-E** positions of nimesulide structure (Fig. 1) were explored and the pharmacological effects of its analogues so obtained were studied.

Some well-established and representative nimesulide analogues with several useful modifications were developed usually aiming to develop improved anti-inflammatory agents (Fig. 2). **NS-398** presents a cyclohexyl group in **B** position instead of the phenoxy group [65]. The replacement of the electron withdrawing nitro group by methyl ketone and the introduction of 2,4-difluoro atoms in the phenoxy ether group leads to **FK-3311** [65]. **Flosulide**, also known as **CGP 28238**, is an analogue where the methyl ketone group of **FK-3311** was substituted by a conformationally restricted fused cyclopentanone [65]. **L-745337** is the thioether congener of **flosulide** [65]. **JCC76** has a 2,5-dimethylbenzyl group in **B** position, a ciclohexylcarboxamide group in **A'** position and the acidic sulphonamide hydrogen (**C** position) was replaced by a methyl group [66–69]. The replacement of ciclohexylcarboxamide group of **JCC76** by a 3,4-dimethoxyphenyl group originated the compound **NSC751382** [68,69]. **FJ29** [70,71] and **T-614** [72] present a pyridinesulfonamide and a chromonesulfonamide ring instead of the nitrophenylsulfonamide group, respectively. Moreover, **FJ29** is the only analogue with a trifluoromethyl group in **D** position [70,71].

3.1. *Synthesis*

Similarly to nimesulide, the synthesis of the majority of their analogues lies on the same methodologies involving once again arylether formation, nitration, reduction and mesylation steps. Thus, structural modifications of known analogues such as **flosulide** [73–77], **L-745337** [74,78],**FK-3311** [77,79], **NS-398** [63,80], **JCC76** [62,68], **NSC751382** [64,69] and **T-614** [81] have also been performed. Other synthetic approaches started from nimesulide by modifying the groups already present [42,63,82–89]. In this subsection are presented representative and more recent examples of nimesulide analogues synthesis.

A palladium-mediated approach was developed to introduce unsaturated moieties at the position 4 of nimesulide skeleton, providing novel analogues with structural diversity. In this strategy, the starting material *N*-(4-iodo-2-phenoxyphenyl)methanesulfonamide was synthesized after reduction of the nitro group of nimesulide followed by conversion of the arylamine group to the corresponding 4-iodo. Then, the 4-iodo analogue participated in C—C bond forming reactions under palladium catalysis, specifically in coupling reactions, resulting in the corresponding alkynyl, alkenyl and aryl substituted compounds (Scheme 2) [86].

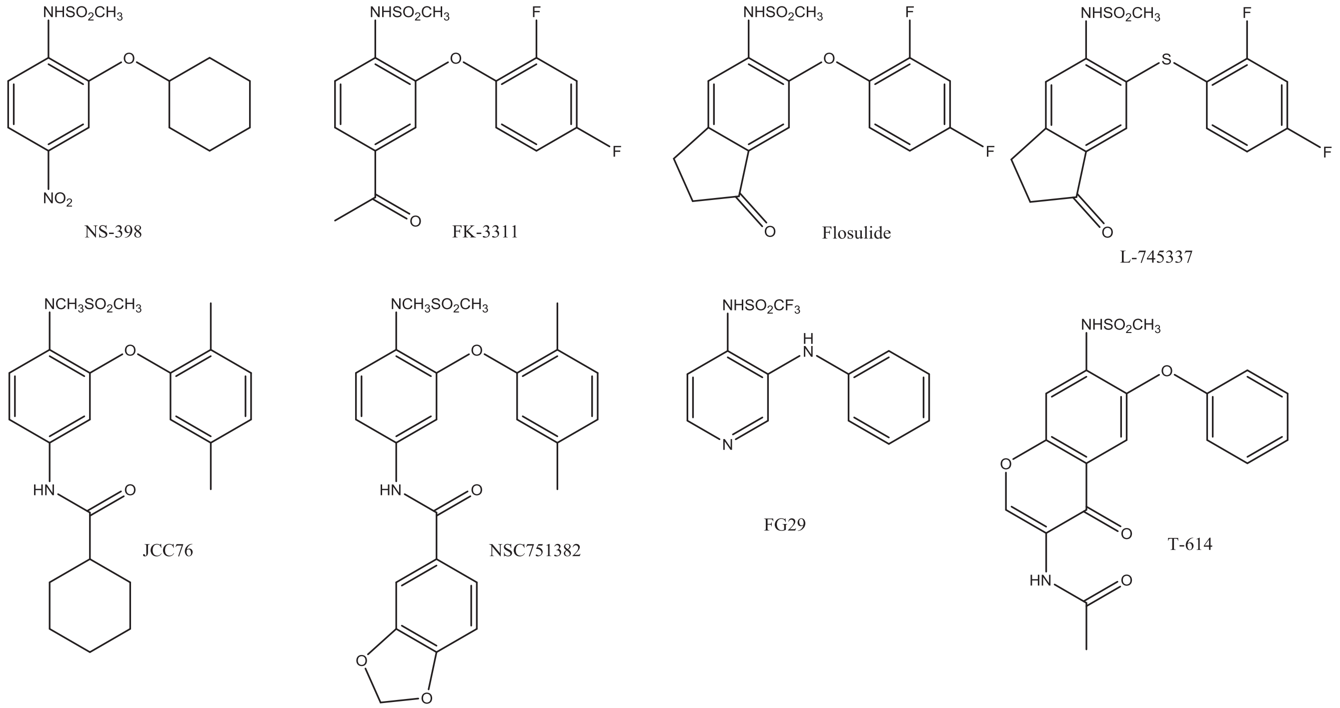
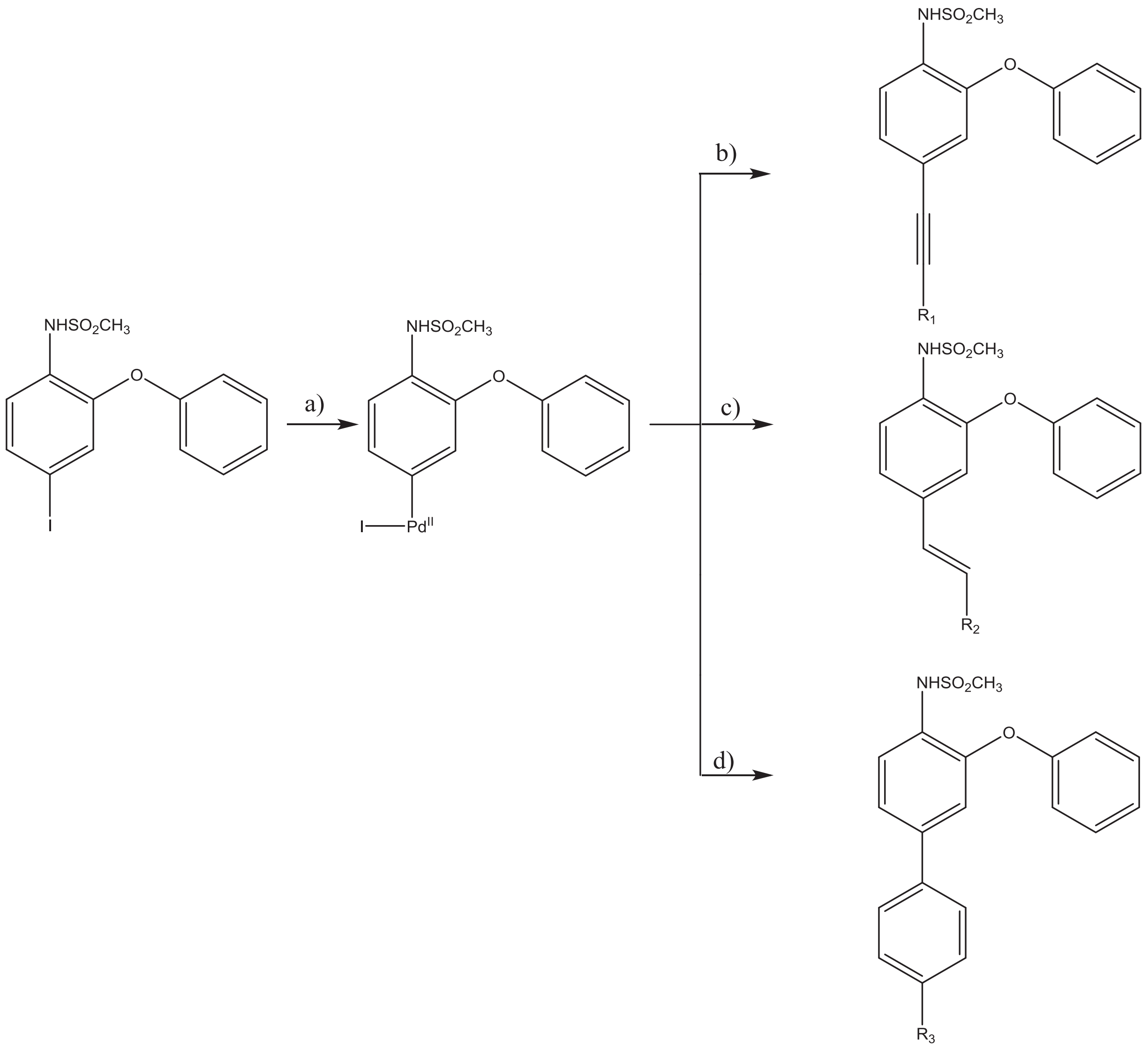


Fig. 2. Representative nimesulide analogues.



Scheme 2. Synthesis of starting material *N*-(4-iodo-2-phenoxyphenyl)methanesulfonamide [86]. Reagents and conditions: (a) Pd^0; (b) R_1CCH, Sonogashira conditions; (c) R_2CHCH_2, Heck conditions; (d) *p*-$R_3PhB(OH)_2$, Suzuki conditions. R_1 = CO_2CH_3, $CO_2CH_2CH_3$, CO_2nBu, Ph, CN; R_2 = F, OCH_3; CH_2OH; R_3 = $C(CH_3)_2OH$, $CH_2(CH_2)_4CH_3$, $C(CH_3)_3$.

In order to find synergistic effects the combination of structural features of nimesulide and other groups such as 1,2,3-triazole [90,91], glycolamide esters [92], succimides [93], *N*-substituted cyclic imides [94], 1,3-benzodioxolyl-*N*-acylarylhydrazones [95] and thioureas [96] were described. Moreover, the synthetic approach starting from 2-amino-5-nitrophenol is one of the most explored strategies used to modify different moieties of nimesulide [49,59–61,97–99].

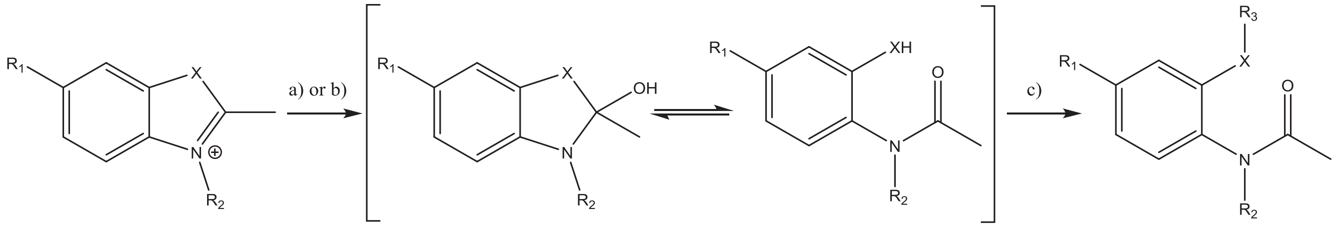
The hydrolysis of benzoazolium salts is a different strategy to prepare nimesulide analogues. Specifically, this approach started from the base-catalyzed hydrolysis of *N*-alkyl-2-methylbenzoazolium salts and resulted in the opening of the heterocyclic ring. The intermediates *N*-alkyl-(2-hydrochalcogen)acetanilides, resulting from the cleavage of the 2-hydroxyazole moiety of the initial intermediate, were *in situ* alkylated to afford the corresponding (2-alkylchalcogen)-*N*-alkylacetanilides (Scheme 3) [100–102].

Another interesting synthesis to obtain pyridinic nimesulide analogues started from the *N*-oxidation of 3-bromopyridine, followed by nitration of position 4 which affords 3-bromo-4-nitropyridine-*N*-oxide. This *N*-oxide was condensed with substituted phenols, thiophenols, or anilines, followed by the reduction of the nitro group to the corresponding aminopyridine, which was further condensed with alkane- or trifluoromethanesulfonyl chloride to afford the corresponding sulfonamides (Scheme 4) [70,71,84,85,103].

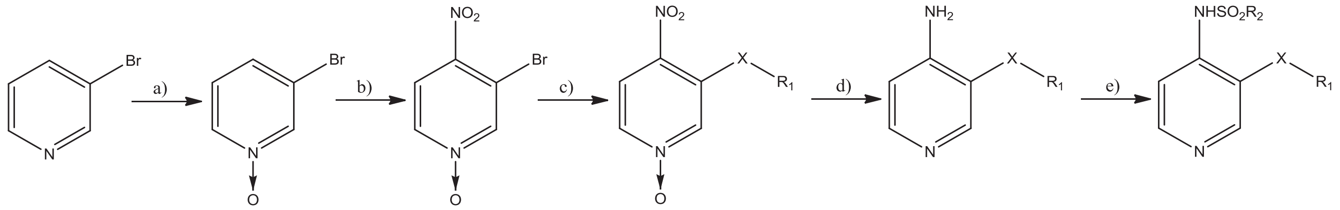
Interesting pyridine acyl sulfonamide analogues were prepared by means of the coupling of pyridine-1,6-dicarboylic acid in the presence of 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride (EDCI) and 4-dimethylaminopyridine (DMAP), forming substituted benzenesulfonamides (Scheme 5) [104].

The synthesis of quinolinic derivatives is relatively more diversified. As a representative example, Pal *et al* developed a series of 1-alkylnyl substituted 1,2-dihydroquinolines started with a Vilsmeier-Haack cyclization of *N*-phenylacetamide and hydrolysis of a chloro intermediate, resulting in the quinoline nimesulide analogue. This quinoline reacted with propargyl bromide which by a palladium-catalysed reaction afforded several alkynyl analogues (Scheme 6) [88].

Additionally, Bose *et al* established a route toward similar quinoline and pyrrol-5-one fused heterocycle systems [105]. Moreover, the synthesis of 2,3-diaryl-4(3*H*)-quinazolinones was described starting from the reaction of aryl acid chlorides with anthranilic acid. The 2-aryl-3,1-benzoxazin-4(3*H*)-ones so obtained were heated in the presence of aryl amines to afford the corresponding substituted diamides. The subsequent cyclization of these diamides resulted in the final anti-



Scheme 3. Synthesis of acetanilides [100–102]. Reagents and conditions: (a) R_2X, CH_3CN, reflux; (b) R_2X, (105–120 °C); (c) 1. NEt_3, 96% EtOH, reflux; 2. EtOH, NaOH, R_3X, reflux. R_1 = H, NO_2, $NHCOCH_3$; R_2 and/or R_3 = Me, Et, Pr, Hex, Bn, MeBn, MeCy, 2,4-diMeBn; X = O, S, Se.



Scheme 4. Synthesis of pyridinic analogues [70,71,84,85,103]. Reagents and conditions: (a) H_2O_2, AcOH, reflux; (b) HNO_3, H_2SO_4, reflux; (c) R_1X, reflux; (d) Fe, $AcOH/H_2O$, reflux; (e) R_2SO_2Cl, K_2CO_3, CH_3CN, 0–3 °C. R_1 = C_5H_9, Cy, C_7H_{13}, Ph, Ph derivatives; R_2 = Me, CF_3, $CF_3(CH_2)_2$; X = O, S, NH, NCH_3, SO, SO_2.

inflammatory quinazolinones (Scheme 7) [106].

3.2. Biological activity

3.2.1. Anti-inflammatory activity

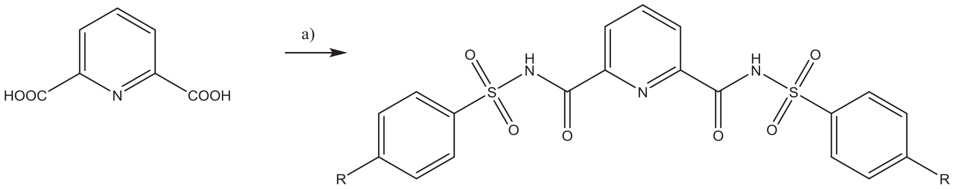
As previously mentioned, nimesulide, as well as its known analogues, can be useful in a range of inflammatory disorders, mainly acting through COX-2 inhibition [5,33–41], presenting IC_{50} values of 10.48 µM and 0.18 µM for COX-1 and COX-2, respectively [33]. In this context, several approaches have been used to develop nimesulide analogues looking for new and more potent and selective inhibitors of this enzyme and are herein revised.

NS-398 (Fig. 2) is a selective COX-2 inhibitor that acts in a time-dependent manner. This compound selectively inhibited prostanoid production on inflamed tissues and has a higher specificity for prostanoid synthesis inhibition than nimesulide. Furthermore, its anti-inflammatory, analgesic and antipyretic properties were almost equipotent to the observed with indomethacin, although the gastrointestinal and renal adverse damage are weaker [107–109]. In another study, it had been found that the introduction of a methyl at the *N* atom of the **NS-398** sulfonamide group resulted in a loss of COX-2 inhibitory activity [80]. Therefore, the acidic sufonamidic hydrogen is determinant for the inhibition of this enzyme.

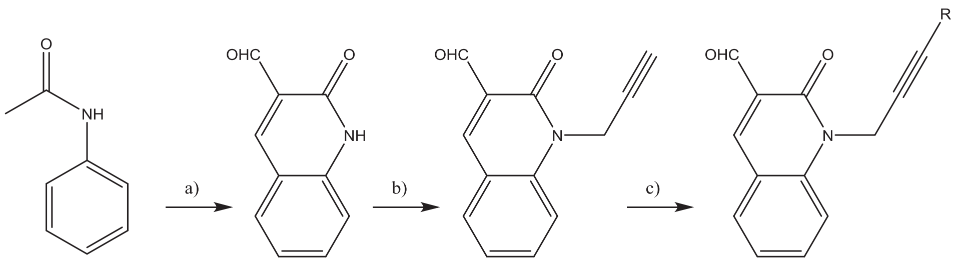
FK-3311 (Fig. 2), as well as the analogues with cyano and amide groups instead of the acetyl (**A'** position), have an anti-inflammatory activity relatively similar to the observed with the presence of a nitro group in the same position. In fact, **FK-3311** and its cyano analogue were selected as candidates for further development [77]. Continuing the previous work, Nakamura *et al* modified the atom between the two cyclic systems (**E** position) of **FK-3311** and it was concluded that the sulfur and oxygen analogues lead to a higher activity than the observed with a nitrogen atom. The **A'** position was also modified and it was demonstrated that the oxime, 1-hydroxyethyl and 1-aminoethyl analogues showed moderate to excellent anti-inflammatory activity [79].

Flosulide (Fig. 2) is considered a selective COX-2 inhibitor with an IC_{50} value of 14.7 nM [110]. Further studies aiming to develop **flosulide** analogues starting from safrole were performed and the results evidenced that two derivatives with a *N*-methylsulfonamide moiety (Fig. 3A) and the corresponding retrosulfonamide group (Fig. 3B) were more active than nimesulide, having an inhibition of 46% and 43.1% at a dose of 100 µmol/Kg, respectively, in a carrageenan-induced pleurisy assay [76].

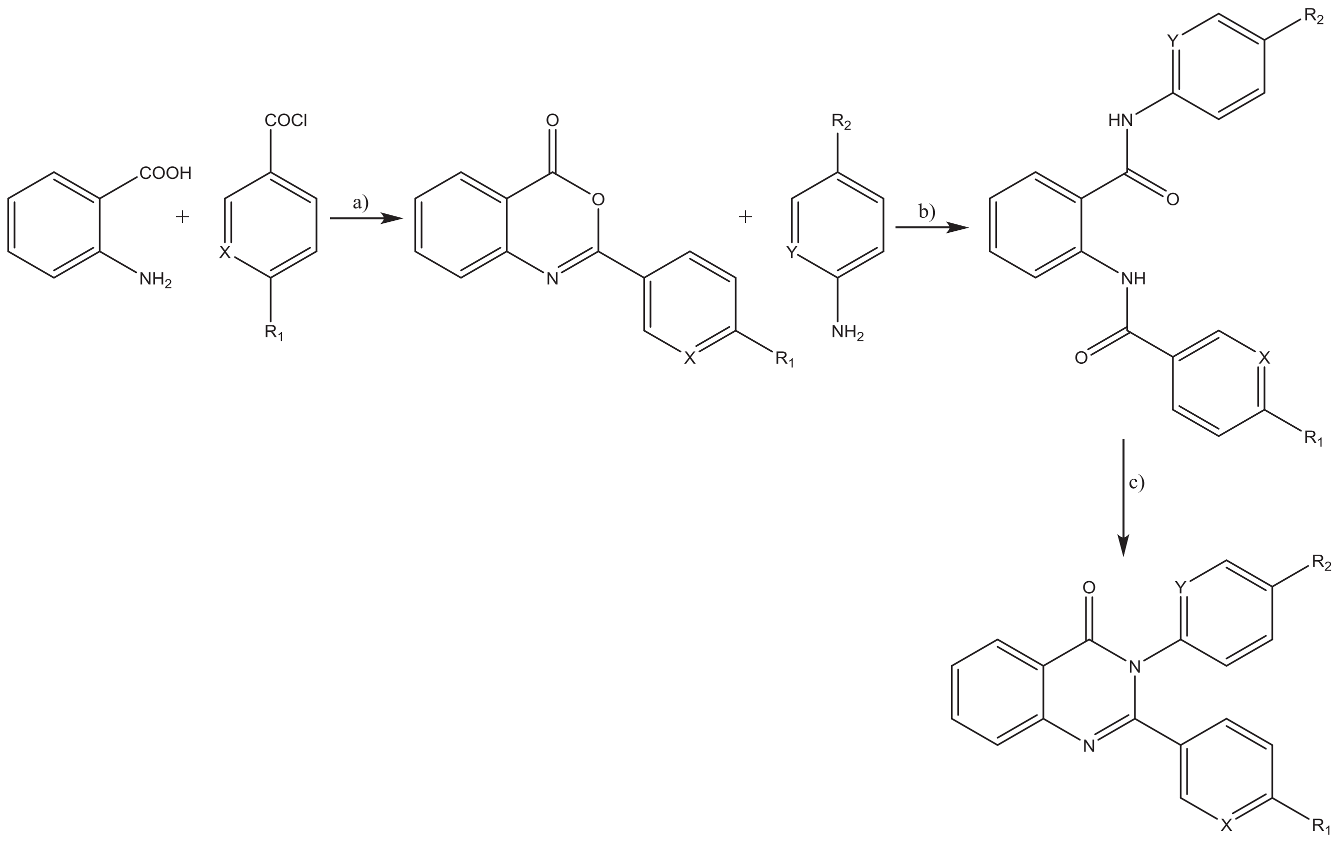
Another study with 5-methanesulfonamido-1-indanones similar to **flosulide** had shown that the 2,4-halogenphenyl related compounds had potent in vitro COX-2 inhibitory activity and *in vivo* anti-inflammatory effects, with prominence for 2,4-difluorophenyl analogue. Alkyl groups larger than methyl were not tolerated at either position of the phenyl ring (**B** position). Furthermore, it was verified that the presence of oxygen and sulfur atoms in **E** position was associated with higher potency and selectivity. This study revealed the compound **L-745337** (Fig. 2) as a potent and selective COX-2 inhibitor (IC_{50} value of 0.023 µM) with *in vivo* potency and no marked induction of stomach lesions [74,111]. In another research work, a series of 2-mercaptopyridine and thiazole derivatives were developed to improve the **L-745337** anti-inflammatory activity. Of these, it was demonstrated that 6-(4-ethyl-2-thiazolylthio)-5-methanosulfamido-3*H*-isobenzofuran-1-one



Scheme 5. Synthesis of pyridine acyl sulfonamide analogues [104]. Reagents and conditions: (a) $RPhSO_2NH_2$, EDCI/DMAP, CH_2Cl_2, Δ. R = H, F, Cl, Br, Me.



Scheme 6. Synthesis of quinolinic analogues [88]. Reagents and conditions: (a) 1. $POCl_3$, DMF, reflux; 2. $AcOH/H_2O$, reflux; (b) C_3H_3Br, K_2CO_3, DMF; (c) RI, Pd $(OAc)_2$, CuI, Et_3N, THF. R = Ph derivatives (such as *o*-CH_3Ph, *p*-OCH_3Ph, *p*-ClPh, *o*-ClPh, *p*-NO_2Ph, *m*-NO_2Ph).



Scheme 7. Synthesis of 2,3-diaryl-4(3*H*)-quinazolinones [106]. Reagents and conditions: (a) Fe (powder), NaCl, CH_3OH, Δ; (b) CH_3SO_2Cl, Py; (c) $(Ac)_2O$, Py. R_1 and/or R_2 = H, Me, OCH_3, F, Cl, NO_2, $NHCOCH_3$, $NHSO_2CH_3$; X and/or Y = C, N.

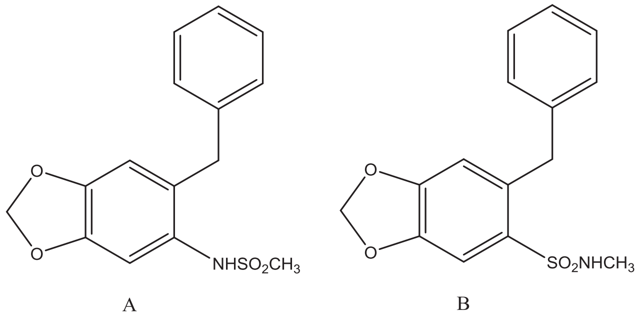


Fig. 3. Flosulide analogues with *N*-methylsulfonamide group (A) and retro-sulfonamide group (B) [76].

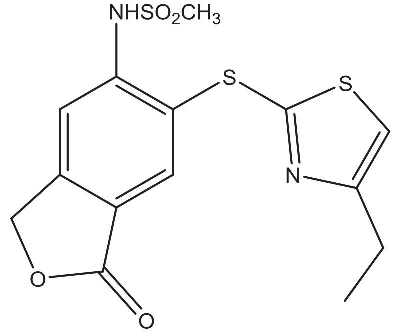


Fig. 4. 6-(4-Ethyl-2-thiazolylthio)-5-methanosulfamido-3*H*-isobenzofuran-1-one [78].

(Fig. 4) has a very potent anti-inflammatory activity with a high *in vivo* efficacy in pain and fever rat models [78].

T-614 (Fig. 2) selectively inhibits the COX-2 activity in a concentration-dependent manner, being determined an IC_{50} value of 7.7 µg/mL and observed that only the prostaglandin production in inflamed tissues was reduced [72]. Based on these results, Inaba *et al* developed **T-614** analogues and their anti-inflammatory activity was evaluated in acute and chronic inflammation models. The results

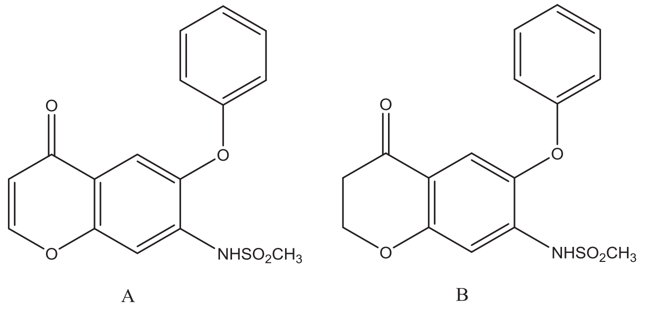


Fig. 5. Chromone (A) and 2,3-dihydro (B) analogues of T-614 [81].

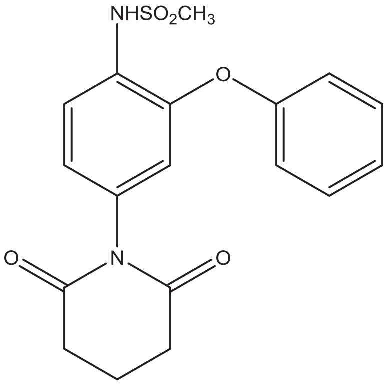


Fig. 6. 2,6-Dioxopiperidin-1-yl nimesulide analogue [94].

evidenced that the chromone system (Fig. 5A) was associated with a higher potency than its 2,3-dihydro analogue (Fig. 5B). However, the chromone analogue of **T-614** had a 2 to 3-fold weaker potency than nimesulide and **flosulide**. Subsequently, several modifications were performed to develop new derivatives with a large variety of substituents on the pyrone ring as well as on the phenyl. Of these, the introduction of alkyl groups in the pyrone ring was explored and it was observed that the 2-methyl analogue showed an acceptable potency. In addition, the presence of halogens in the phenyl ring increased their potency in relation to methyl and methoxy analogues [81].

A series of nimesulide-based cyclic imides was evaluated in a carrageenan-induced rat model of inflammation. Of these, the 2,6-dioxopiperidin-1-yl analogue (Fig. 6) was the most potent anti-inflammatory agent, showing, at a dose of 100 mg/kg, an oedema inhibition of 20%, 25%, 45% and 40% after 1, 2, 3 and 4 h, respectively [94].

Chen *et al* developed several phenoxyphenyl pyrrolidine compounds as dual inhibitors of COX-2 and leukotriene A4 hydrolyase. The results demonstrated that the introduction of small electron withdrawing groups such as nitro and trifluoromethyl in the *ortho*-position of the phenyl ring (Fig. 7) increased the selectivity for COX-2 inhibition in comparison with COX-1. Furthermore, these two analogues inhibited PGE2 in a human whole blood assay, with IC_{50} values of 8.4 µM and 5.0 µM, respectively [112].

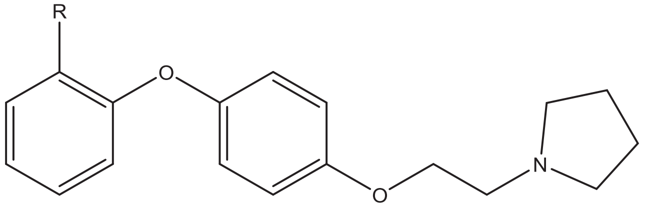


Fig. 7. 2,6-Dioxopiperidin-1-yl analogue based on nimesulide cyclic imides [112]. R = NO_2, CF_3.

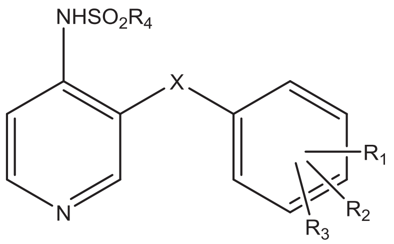


Fig. 8. Pyridinic analogues of nimesulide [10,70,71,103]. R_1, R_2 and/or R_3 = H, Me, Et, OCH_3, F, Cl, Br, I, OH, CN; R_4 = Me, CF_3, $(CH_2)_2CF_3$; X = O, S, NH, NCH_3, SO, SO_2.

In the development of nimesulide pyridinic analogues, it was observed that compound **FJ29** (Fig. 2) is more potent than nimesulide as COX-2 inhibitor but is less selective (IC_{50} values of 0.09 µM and 0.70 µM, and IC_{50}(COX-1)/IC_{50}(COX-2) ratio of 2.03 and 5.37, respectively) [70]. To explore the structure-activity relationship of **FJ29**, the COX-2 inhibitory activity of a series of pyridinic analogues (Fig. 8/Scheme 4) was evaluated [10,70,71,103].

The results showed that the substitution of the nimesulide nitrobenzene (**A** position) by a pyridine led to an important loss of COX-2 inhibitory activity. The replacement of the bridge oxygen (**E** position) by a sulfur atom enhanced the COX-2 activity, although the structure with a nitrogen atom is the best analogue, with an IC_{50} value of 0.09 µM. The methylation of this bridge nitrogen led to a drastically decrease on COX-2 inhibition and sulfinyl and sulfone groups in this **E** position led to inactive analogues. When comparing the inhibitory activity of methanesulfonamides with trifluoromethanesulfonamides, the results demonstrated that the trifluoromethyl group (**D** position) enhanced the COX-2 inhibition and selectivity. Additionally, the replacement of the trifluoromethanesulfonamide moiety by 3,3,3-trifluoropropanesulfonamide decreased drastically this COX inhibition. The effects of different substituents in the phenyl ring were also studied,nevertheless, the modification of the nature of **E** position also changed their activity. As an example, the introduction of halogens in analogues with ether linkage revealed that substituents in positions 3 and 4 decreased COX-2 inhibition whereas in analogues with a nitrogen bridge the COX-2 inhibitory activity increased, with prominence for the 3-bromine analogue, which displayed strong COX-2 inhibitory properties and selectivity. Moreover, in analogues with the nitrogen atom, the introduction of fluorine decreased the COX-2 selectivity although the iodine decreased the COX-2 inhibition but increase the selectivity. The methyl and ethyl substituted analogues showed weaker COX-2 inhibition, as well as electron withdrawing and hydrophilic substituents like cyano and hydroxyl groups that drastically decreased the COX-2 inhibitory activity. The replacement of the benzene ring by other rings was also investigated. Of these, the cyclohexane analogues had strong

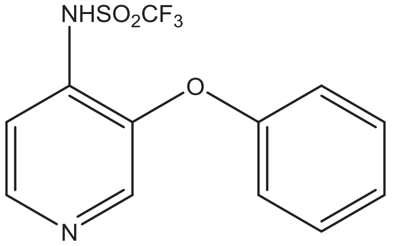


Fig. 9. *N*-(3-phenoxy-4-pyridinyl)triofloromethane-sulfonamide [85].

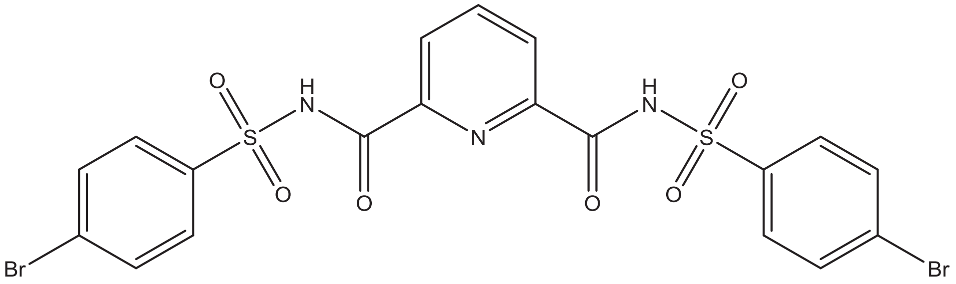


Fig. 10. N^2-N^6-bis[(4-*Bromophenyl*)*sulfonyl*]pyridine-2,6-dicarboxamide [104].

COX-2 inhibition whereas the increase of the size of the cycloalkane decreased the activity [10,70,71,103]. Moreover, Julémont *et al* described new *N*-(3-phenoxy-4-pyridinyl)trifluoromethanesulfonamides (Fig. 9/Scheme 4) presenting a strong COX-2 inhibitory activity, with an IC_{50} value of 0.4 μM, being more potent but less selective for COX-2 than nimesulide. Indeed, this compound was evaluated in a rat paw edema study and an interesting dose-dependent anti-inflammatory activity was observed [85].

Considering the reported anti-inflammatory and anticancer properties of pyridine acyl sulfonamide analogues, Lu *et al* developed compounds combining the pyridine ring and sulfonamide moieties. Interestingly, the majority of pyridinic compounds showed remarkable and selective COX-2 inhibition. Besides, N^2-N^6-bis[(4-bromophenyl) sulfonyl] pyridine-2,6-dicarboxamide (Fig. 10/Scheme 5) was the most potent COX-2 inhibitor with an IC_{50} value of 0.8 μM and was found to be promising to inhibit PGE2 [104].

In another study, Yadav *et al* developed 2,3-diaryl-4(3*H*)-quinazolinones (Scheme 7) and their anti-inflammatory, as well as COX-2 inhibitory activities, were evaluated. Of these, the 4-nitroquinazolinone derivative was the best compound, showing a COX-2 inhibition of 27.72% at 22 μM [106].

Table 1 summarizes the most relevant compounds associated with anti-inflammatory activity. Although some compounds seem to have significant anti-inflammatory activity, at the moment none has entered in clinical trials. However, several *in vivo* experiments were effected [70,74,78,111]. Nevertheless, these anti-inflammatory studies were designed and/or performed by academic researchers [10,70,71,76,80,85,103,104,106,110,112], pharmaceutical industries [72,74,77–79,81,107–109,111] or both [94].

3.2.2. Anticancer activity

As previously mentioned, COX-2 expression and activity have been associated with tumor progression, invasiveness and angiogenesis. Since nimesulide and its analogues inhibit this enzyme, it was expectable that these compounds had potential benefit in both cancer prevention and treatment. Consequently, the nimesulide skeleton has been considered as a basis to develop new anticancer drugs with better selectivity and pharmacological profile. However, other COX-2-independent mechanisms must be considered in the antitumoral effects of this class of structures. In fact, recent studies have found other relevant targets in cancer treatment for these compounds, namely aromatase [61,63,80,97,113–117], tubulin, heat shock protein 27 [64,69] and phosphodiesterase type 4 [83,88,90,91].

Several studies revealed that compound **NS-398** (Fig. 2) showed an important antiproliferative effect in different types of cancer cell lines [118–120]. Indeed, this nimesulide analogue reduced the cell viability of a large variety of cancer cells which overexpress COX-2 namely human gastric cancer (MKN45) [121], human colon cancer (Caco-2) [121], esophageal adenocarcinoma cell lines (FLO and SEG-1) [122] and hepatocellular carcinoma (Hep3B and HKCT-4) [123]. **NS-398** was also able to induce apoptosis in hepatoma [124], colorectal carcinoma [125,126], prostate cancer [127,128] and myeloma cell lines [129].

In order to evaluate the combination of **NS-398** with chemotherapeutics agents, Zhang et al. evidenced that dexamethasone and thalidomide increased the **NS-983** induced cell growth inhibition and apoptosis in a myeloma cell line [129], whereas Peng *et al* showed a cytotoxicity enhancement on human hypopharyngeal carcinoma cells treated with **NS-398** and etoposide or cisplatin [130].

Further cell proliferation studies with **NS-398** and **flosulide** (Fig. 2) evidenced that both compounds significantly reduced the proliferation of OSC-2 esophageal cancer cell line at 100 nM and 1 nM concentrations, respectively. In addition, it was observed that **flosulide** led to a massive induction of apoptosis and a suppression of mitotic activity in this cell line [131].

JCC76 (Fig. 2) is considered one of the nimesulide analogues with the most potent anticancer activity not only due to the low IC_{50} determined in *in vitro* studies but also because this effect was confirmed in *in vivo* experiments [67]. Actually, this compound led to a selective inhibition of the proliferation of breast cancer cell lines (SK-BR-3, BT-474, MCF-7, MDA-MD-453, MDA-MD-231 and LTEDaro) as well as inducted the apoptosis in three of these cell lines (SK-BR-3, BT-474 and LTEDaro), claiming to be a potential drug candidate against breast cancer [66,67].

Aiming to optimize the antiproliferative effect and obtain additional structure-activity relationship data, Zhong *et al* synthesized a biotinylated analogue of compound **JCC76** (Fig. 11A) and evaluated its antiproliferative effect against the breast cancer cell line SK-BR-3. With this experimental study, an IC_{50} value of 2.21 μM was determined for this biotinylated analogue, occurring to a cell growth inhibition comparable to the observed with **JCC76** [62].

In a subsequent study, the cyclohexylamide group of **JCC76** was modified and the antiproliferative activity of the synthesized compounds was evaluated in the SK-BR-3 cell line. In fact, comparing benzylamide and benzamide moieties, it was verified that the benzamide group led to a higher antiproliferative activity. Additionally, this study revealed that single substituents in *meta* position or the introduction of chlorine in the *para* position of benzamide group decreased the activity. However, a bulky halogen such as bromine and iodine originated a higher activity than the observed with **JCC76**. Moreover, electron-donating groups like methoxy increased the antiproliferative activity whereas electron-withdrawing groups like nitro, cyano and trifluoromethyl as well as *para*-methyl and *para*-ethyl groups did not. In fact, following these studies, compound **NSC751382** (Fig. 2) was developed and it was observed that it inhibited the SK-BR-3 breast cancer cell growth near 10-fold more than **JCC76** (IC_{50} value of 0.20 μM and 1.38 μM, respectively). Then, the potential anticancer mechanism of action of **NSC751382** was evaluated and the results demonstrated that this compound induced cell apoptosis and inhibited cell mitosis at a similar concentration to inhibit cell growth. This suggested that **NSC751382** was able to induce cell apoptosis without significantly affecting cell proliferation. Then, this compound was evaluated in a screening against human tumor cell lines, inhibiting the growth of the sixty cancer cell lines in a dose-dependent manner, with determined IC_{50} values between 100 nM and 500 nM. Furthermore,

Table 1
Relevant nimesulide analogues associated with anti-inflammatory activity.

Compound	Activity	Assay	Results	Reference
NS-398 (Fig. 2)	Anti-inflammatory activity	Inhibition of adjuvant-induced arthritis in rats Inhibition of carrageenan-induced paw edema in rats	ED_{50} value of 1.14 mg/Kg ED_{50} value of 4.69 mg/Kg	[107]
FK-3311 (Fig. 2)		Inhibition of adjuvant-induced arthritis in rats (uninjected paw)	ED_{50} value of 3.2 mg/kg	[77]
FK-3311 (where CH_3CO- is replaced by -CN)			ED_{50} value of 0.31 mg/Kg	
FK-3311 (CH_3CO- and ether group are substituted by -CH(OH)CH_3 and thioether group)			Inhibition of 90% (dose of 10 mg/Kg)	[79]
Flosulide (Fig. 2)	COX-2 inhibition	Measurement of prostanoids production after stimulation by arachidonic acid (autoradiography assay and visualization with phosphoimaging system, intact rat mesangial cells)	IC_{50} value of 14.7 nM	[110]
Fig. 3A	Anti-inflammatory activity	Inhibition of carrageenan-induced pleurisy in rats	Inhibition of 46% (dose of 100 µmol/Kg; 0.1 mL/20 g)	[76]
Fig. 3B			Inhibition of 43.1% (dose of 100 µmol/Kg; 0.1 mL/20 g)	
L-745337 (Fig. 2)	COX-2 inhibition	Measurement of PGE2 production after stimulation by arachidonic acid (Whole cell COX-2 assay, osteossarcoma 143 cells)	IC_{50} value of 0.023 µM	[74]
Fig. 4		Measurement of PGE2 production after stimulation by arachidonic acid (PGE2 enzyme immunoassay kit, Chinese hamster ovary cells)	IC_{50} value of 0.013 µM	[78]
T-614 (Fig. 2)		Measurement of PGE2 production after stimulation by arachidonic acid (EIA PGE2 kit, competitive imuno assay)	IC_{50} value of 7.7 µg/mL	[72]
Fig. 7, R = NO_2	PGE2 inhibition COX-2 inhibition	Measurement of PGE2 by ELISA kit (Human whole blood assay) Absorption of oxidized TMPD during the reduction of PGG2 to PGH2 (chromogenic assay, 610 nm)	IC_{50} value of 8.4 µM IC_{50} value of 7.7 µM	[112]
Fig. 7, R = CF_3	PGE2 inhibition COX-2 inhibition	Measurement of PGE2 by ELISA kit (Human whole blood assay) Absorption of oxidized TMPD during the reduction of PGG2 to PGH2 (chromogenic assay, 610 nm)	IC_{50} value of 5.0 µM IC_{50} value of 41.4 µM	
FJ29 (Fig. 2)		Measurement of PGE2 production after stimulation by LPS (Human whole blood assay)	IC_{50} value of 0.09 µM	[70]
Fig. 9			IC50 value of 0.4 µM	[85]
Fig. 10		Measurement of PGE2 production after stimulation by arachidonic acid (EIA PGE2 kit, competitive imuno assay)	IC_{50} value of 0.8 µM	[104]
Scheme 7, R1 = NO_2, R_2 = CH_3, Y and X = C		Colorimetric COX ovine inhibitor assay kit	Inhibition of 27.72% (concentration of 22 µM)	[106]

ED_{50}: half-medium effective dose; LPS: lipopolysaccharide; PGG2: prostaglandin-G_2; PGH2: prostaglandin-H_2; TMPD: *N*,*N*,*N'*,*N''*-tetramethyl-*p*-phenylenediamine.

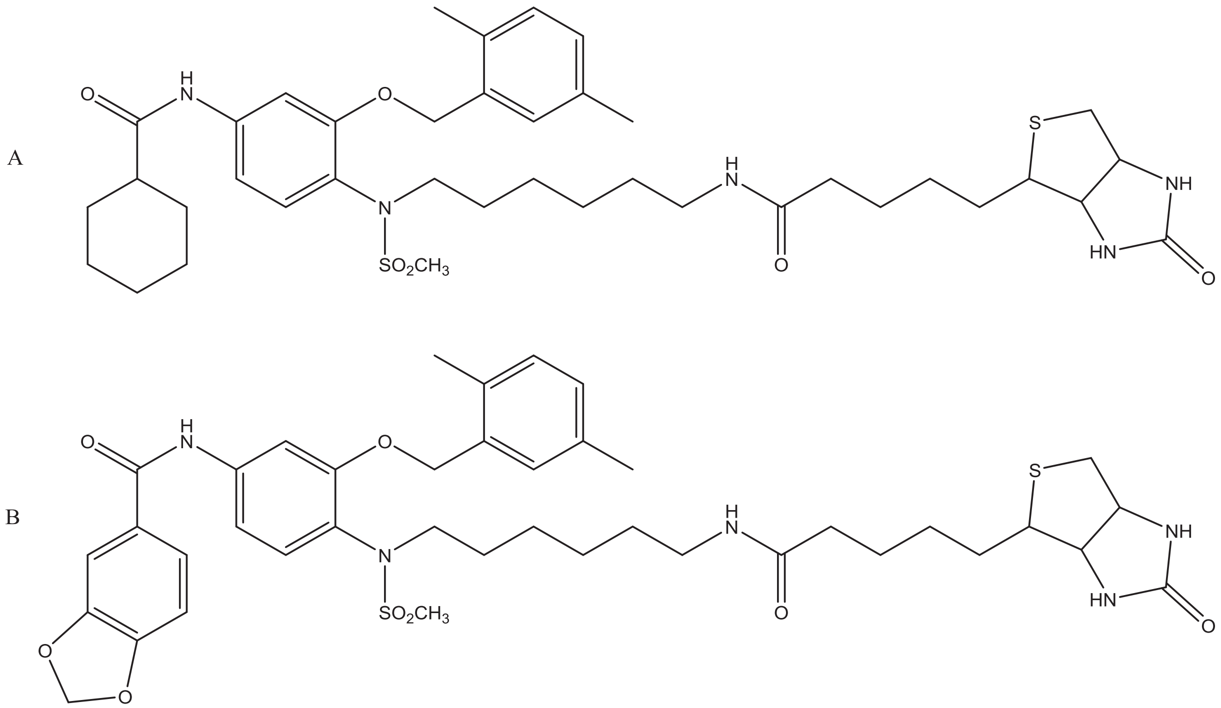


Fig. 11. Biotinylated JCC76 (A) and NSC751382 (B) analogues [62,69].

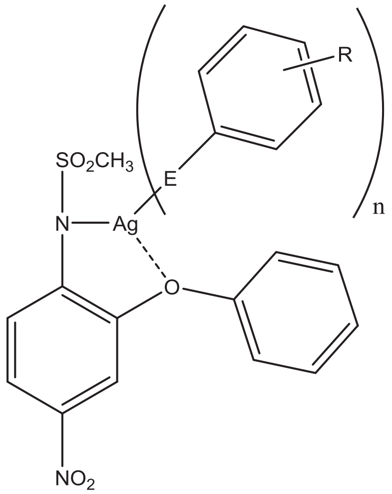


Fig. 12. Nimesulide silver metallodrugs [132]. R = Ph, Ph derivatives (such as o-CH_3Ph, p-CH_3Ph); E = P, As, Sb; n = 1, 2, 3.

NSC751382 was studied *in vivo* and the treatment significantly decreased the size of the tumors [68].

Continuing the previous work, Zhong et al. developed **NSC751382** analogues using combinatorial chemistry strategies. The antiproliferative effect of the synthesized compounds was also evaluated against SK-BR-3 breast cancer. In this study, it was observed that the non-sulfamidic ring (**B** position) was critical for the antiproliferative effect [64]. In fact, the most potent compounds were those with electron donating groups on 2- and 5-positions on the benzyl ring, such as 2,5-dicholo, 2,5-dimethoxy and 2,5-dimethyl. In the sulfamidic ring, 4-methoxybenzamide and 4-iodobenzamide analogues showed a higher potency of inhibition. Furthermore, the presence of a *N*-methyl group and a methylsulfonylamide favored this antiproliferative effect [64].

In other cytotoxicity study, Yi *et al* developed a biotinylated analogue of **NSC751382** (Fig. 11B). This compound also demonstrated antiproliferative activity against SK-BR-3 breast cancer cells, with an IC_{50} value of 2 μM [69].

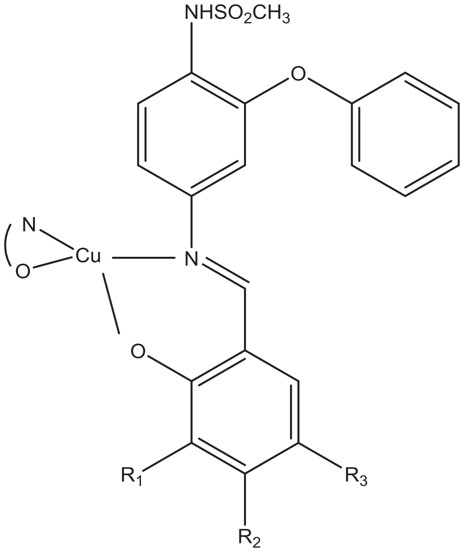


Fig. 13. Copper conjugates of nimesulide [89]. R_1, R_2 and/or R_3 = H, OH, OCH_3, *t*-Bu.

Structural modifications of the nimesulide skeleton also led to the development of novel nimesulide silver metallodrugs (Fig. 12) and their cytotoxicity was evaluated in two breast cancer cell lines (MCF-7 and MDA-MB-231). Interestingly, a higher antiproliferative effect of these compounds in both breast cancer cells when compared to cisplatin was observed [132].

In another different study, copper conjugates of nimesulide Schiff bases (Fig. 13) were prepared and their cytotoxic activity against pancreatic cancer cell lines (BxPC-3 and MiaPaCa) was evaluated. In fact, this study evidenced that these copper complexes led to agrowth inhibition of both cell lines higher than the observed for nimesulide, with IC_{50} values around 4–26 μM and 7–14 μM for BxPC-3 and MiaPaCa cell lines, respectively [89].

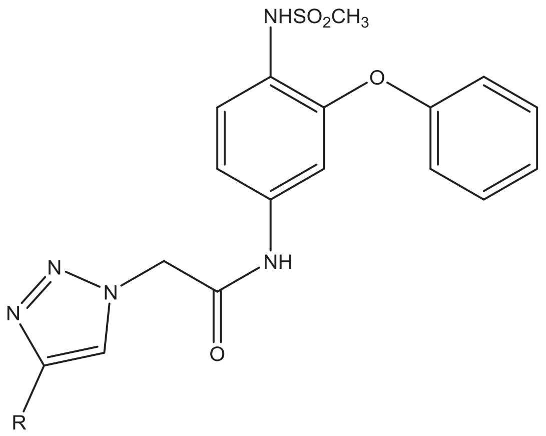


Fig. 14. 1,2,3-Triazole analogues [90,91]. (A) R = Ph; (B) R = *p*-CH_3Ph; (C) R = *p*-Cl(OCH_2Ph); (D) R = *p*-Cl(*m*-CH_3)[OCH_2Ph]; (E) R = *p*-NO_2(OCH_2Ph).

In order to optimize the potential antitumoral effects of nimesulide, several analogues of this drug were developed and their antiproliferative activity was evaluated against the long-term estrogen-deprived MCF-7aro (LTEDaro) breast cancer cell line. The results suggested that picolinyl and nitrogen-containing aromatic groups instead of the nitro substituent (**A′** position) decreased the activity. In addition, 2,5-dichlorobenzyl and 2,5-dimethylbenzyl groups were the most favorable in **B** position [59].

Again, based on the nimesulide skeleton, Su *et al* also synthesized new analogues and evaluated their cytotoxicity in SK-BR-3 breast cancer cells. It was observed that the presence of amine and acetamide substituents instead of the nitro group (**A′** position) decreased the antiproliferative activity whereas *N*-benzoyl or *N*-cyclohexanecarbonyl led to a significant inhibition of cell proliferation. Thus, this study evidenced the importance of a hydrophobic moiety at the **A′** position. Besides, bulky groups such as methylcyclohexyl, hexyl, 4-isopropylbenzyl, 2,5-dimethylbenzyl and methylnaphthalenyl in the non-sulfonamidic ring (**B** position) were important for the inhibition of cell growth. Actually, compounds with 2,5-dimethyl and 4-isopropylbenzyl were the most effective compounds in this study, with determined IC_{50} values of 6.5 μM and 20.1 μM, respectively. The effect of these compounds in other breast cancer cell lines (MCF-7, MDA-MB-31, BT-474) was studied and it was demonstrated that both are more potent than nimesulide in all cell lines, significantly suppressing the growth of BT-474 cancer cell line, with IC_{50} values of 13.5 μM and 44.7 μM, respectively. Moreover, small groups in **C** position such as a hydrogen or a methyl favored the antiproliferative activity. On the other hand, the introduction of carboxamide groups in **D** position decreased the cytotoxicity [60].

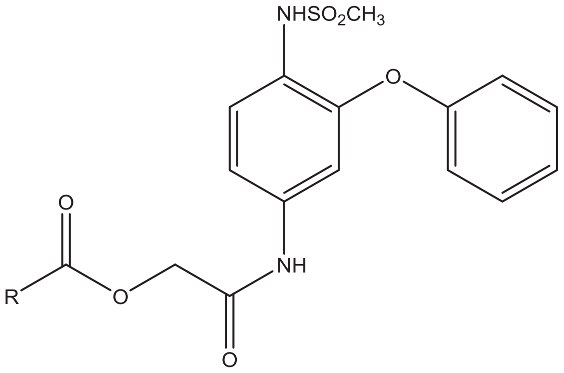


Fig. 15. Glycolamide ester nimesulide derivatives [92]. R = Me, Et, Ph, Ph derivatives (such as *o*-CH_3Ph, *p*-CH_3Ph, CHCHPh, *p*-NO_2Ph, *o*-$OCOCH_3$Ph), Ar.

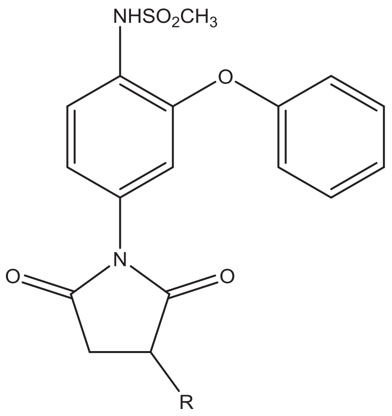


Fig. 16. Succinimide nimesulide analogues [93]. R = Ph, Ph derivatives (such as *p*-CH_3Ph, *p*-OCH_3Ph, *p*-ClPh, NHPh, $NHCOCH_2$OPh), Ar.

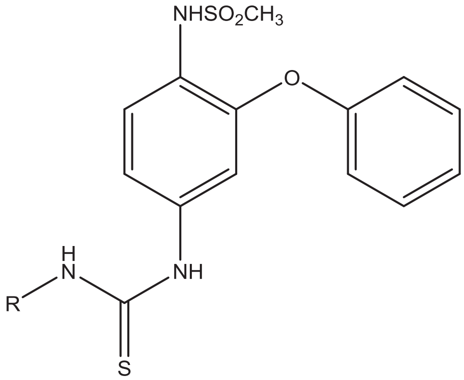


Fig. 17. Thiourea nimesulide analogues [96]. R = Me, Et, Pr, CH_2CHCH_2, Cy, Ph derivatives (such as CH_2CH_2Ph, *p*-Cl(CH_2CH_2Ph), *p*-NO_2Ph).

More recent reports described new nimesulide analogues in which several groups such as 1,2,3-triazole, glycolamide esters, succinimide and thioureas were introduced instead of its nitro substituent (**A′** position) as well as their cytotoxicity evaluation in different cancer cell lines. As example, triazole analogues with phenyl and *para*-methylphenyl substituted groups (Fig. 14A and B) showed a promising cytotoxic effect against HCT-15 human colon cancer cells with IC_{50} values of 21.0 μg/mL and 22.4 μg/mL, respectively, being more potent than doxorubicin [90]. In a subsequent study, the same research group designed new 1,2,3-triazole-nimesulide compounds and their cancer growth inhibitory properties were tested against several types of cancer cell lines. Among all the compounds tested, three revealed significant growth inhibition of lung (A549), liver (HepG2), cervical (HeLa) and prostate (DU145) cancer cell lines, with IC_{50} values between 6 μM and 10 μM (Fig. 14C–E) [91].

Glycolamide ester derivatives (Fig. 15) were prepared and evaluated against the HCT-15 cancer cell line and most of them had relevant antiproliferative effects at 25 μM. The compounds with *para* or *ortho* substituted benzyl groups attached to the ester carbonyl moiety were more potent (IC_{50} values around 18.92–24.40 μM) than nimesulide (IC_{50} value > 150 μM) [92].

The cytotoxicity of succinimide analogues of nimesulide (Fig. 16) was tested against the HCT-15 colon cancer cell line and it was determined IC_{50} values in the range of 20–25 μg/mL for some of these compounds [93].

On the other hand, similar thiourea analogues were not significantly cytotoxic to A549 human lung cancer cells, inhibiting only around 10% to 20% of cell growth at 10 μM (Fig. 17) [96].

In an effort to explore the potential anticancer interest of *ortho*-

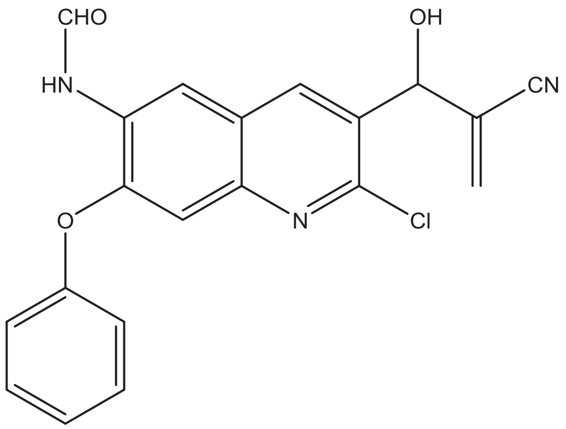


Fig. 18. *N*-(2-chloro-3-(2-cyano-1-hydroxyallyl)-7-phenoxyquinolin-6-yl)formamide [133].

alkylchalcogen-*N*-alkylacetanilides (Scheme 3) relatively similar to nimesulide, their antiproliferative effect was evaluated in human breast (MCF-7) and prostate (LNCaP) cancer cell lines as well as in normal human dermal fibroblasts (NHDF). The results revealed that these acetanilides showed low to moderate antiproliferative activity with prominence to the LNCaP cancer cell line. The most potent compounds were *O*- and/or *N*-benzyl and -hexyl acetanilides, being the most potent the disubstituted acetanilide with 2-methylbenzyl groups [101]. Continuing these studies, the antiproliferative effect of other *ortho*-(alkylthio)-*N*-alkylacetanilides was evaluated in the same type of cells. In general, these acetoacetanilides had a relevant selectivity for cancer cells and an important antiproliferative effect in both cancer cell lines, in special against MCF-7 breast cancer cells. Within this class of compounds, acetoacetanilides with methylcyclohexyl and/or 2,4-dimethylbenzyl groups linked to nitrogen amide group and/or sulfur atom had an interesting cytotoxicity in breast cancer cells. Moreover, the presence of methylcyclohexyl or 2,4-dimethylbenzyl groups increased the antiproliferative activity in both cancer cell lines, being these important substituents to the anticancer activity of these compounds [102].

Other study reported the anticancer potential of pyridine acyl sulfonamide analogues in three cancer cell lines: melanoma (B16-F10), human breast cancer (MCF-7) and liver cancer (HepG2). The results showed that these compounds had good antiproliferative activities with IC_{50} values between 1.2 μM and 20.2 μM, being the N^2-N^6-bis[(4-*bromophenyl*)*sulfonyl*]pyridine-2,6-dicarboxamide (Fig. 10/Scheme 5) the most potent compound of this series (IC_{50} values of 2.8 μM, 1.8 μM and 1.2 μM for B16-F10, MCF-7 and HepG2 cells, respectively) [104].

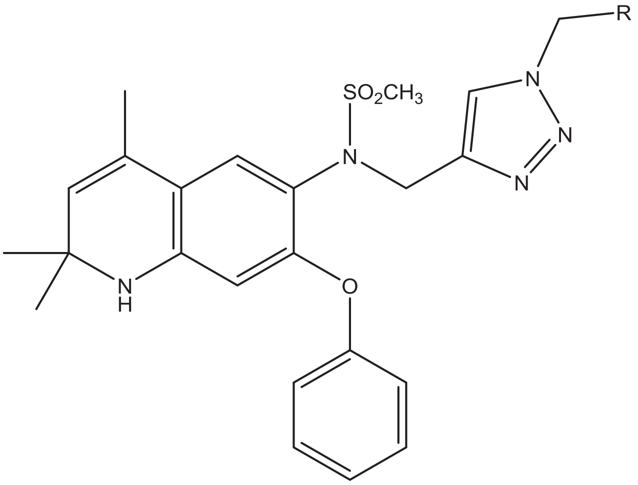


Fig. 19. 2,2,4-Trimethyl-1,2-dihydroquinolinyl substituted 1,2,3-triazole analogues [83]. R = CONHPh, *p*-CH_3(CONHPh), *m*-CH_3(CONHPh)), *p*-OCH_3(CONHPh), Ph derivatives, HetAr.

Several anticancer research works were also performed to explore the interest of quinolinic analogues of nimesulide. As example, Reddy *et al* evaluated the cytotoxic effect of quinolinic structures against the human prostate cancer cell line PC-3 and the results showed that all compounds were active against these cells, with prominence to *N*-(2-chloro-3-(2-cyano-1-hydroxyallyl)-7-phenoxyquinolin-6-yl)formamide (Fig. 18), with an IC_{50} value of 1.2 μg/mL [133].

In other study, Praveena *et al* synthesized 2,2,4-trimethyl-1,2-dihydroquinolinyl substituted 1,2,3-triazole analogues of nimesulide (Fig. 19) and evaluated their antiproliferative activity in four types of cancer cell lines: lung (A549), prostate (DU145), cervical (HeLa) and liver (HepG2). Interestingly, all these compounds were active against the A549 cell line, with prominence for three quinolinic analogues that showed effects comparable to the observed with doxorubicin (IC_{50} values between 8 μM and 9 μM). However, these compounds were less potent than doxorubicin against the other three cell lines [83].

Bose *et al* prepared and evaluated the cytotoxic activity of other quinolinic analogues against four types of human cancer cell lines: acute monocytic leukemia (THP-1), histiocytic lymphoma (U-937), promyelocytic leukemia (HL-60) and *T*-cell leukemia (Jurkat). The results showed that three of these compounds had potent cytotoxicity against the four cancer cell lines, with IC_{50} values around 2.59 μM and 9.02 μM [105].

Overall, several nimesulideanalogues present antiproliferative properties in different types of cell lines (Table 2). Although these compounds were not clinically tested, *in vivo* experiments were performed [67,68]. Moreover, these studies for the development of new anticancer drugs were effected by academic researchers [60–64,68,69,80,89,96,97,101,102,104,114–116,118,119,121,124–126,128–130,132,133], pharmaceutical industries [59,66,105,120] or both [67,83,88,91–93,113,117,122,131].

4. Conclusions

In conclusion, nimesulide is a NSAID that has shown anti-inflammatory and anticancer properties. In consequence, and in order to improve both biological activities and to establish a clearer structure–activity relationship, several studies were performed modifying the scaffold of this drug. As result of these efforts, a large number of chemical modifications of nimesulide skeleton were explored since the discovery of this drug and the pharmacological effects of the analogues so obtained were studied, providing a small library of analogues with a large structural diversity and pharmacologic interest. However, the link between COX-2 inhibition and anticancer activity of nimesulide and its analogues is still not clearly established since, in general, nimesulide and their analogues revealed both anticancer COX-2 dependent and independent mechanisms. Therefore, for the future, further studies can be expected to clarify this point as well as the continuous development of new nimesulide analogues with improved potency and more selective effects. In addition, the confirmation of the anticancer effects of the most interesting molecules should also be confirmed in additional *in vivo* studies.

Acknowledgements

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Table 2
Antiproliferative effects of nimesulide analogues in different types of cells.

Compound	Cell line	Assay	IC_{50}	Reference
JCC76 (Fig. 2)	SKBR-3	MTT assay, 72 h of compounds exposition	1.80 μM	[66,67]
	BT474		2.17 μM	
	MCF-7		22.10 μM	
	MDA-MD-453		3.93 μM	
	MDA-MD-231		19.58 μM	
	LTEDaro		2.75 μM	
	KBR-3	MTT assay, 48 h of compounds exposition	1.38 μM	[68]
Fig. 11A	SKBR-3		2.21 μM	[62]
Fig. 1, A = Ph, A’ = *p*-Br(NHCOPh), B = 2,5-diMeBn, C = CH_3, D = SO_2CH_3, E = O			0.22 μM	[68]
Fig. 1, A = Ph, A’ = di-2′,3′-OCH_3(NHCOPh), B = 2,5-diMeBn, C = CH_3, D = SO_2CH_3, E = O			0.19 μM	
Fig. 1, A = Ph, A’ = *p*-OCH_3(NHCOPh), B = 2,5-diMeBn, C = CH_3, D = SO_2CH_3, E = O			0.15 μM	[64,68]
Fig. 1, A = Ph, A’ = *p*-I(NHCOPh), B = 2,5-diMeBn, C = CH_3, D = SO_2CH_3, E = O			0.13 μM	[64,68]
NSC751382 (Fig. 2)			0.20 μM	[68]
Fig. 11B			2 μM	[69]
Fig. 1, A = Ph, A’ = *p*-I(NHCOPh), B = 2,5-OCH_3Bn, C = CH_3, D = SO_2CH_3, E = O			1.21 μM	[64]
Fig. 1, A = Ph, A’ = *p*-OCH_3(NHCOPh), B = 2,5-OCH_3Bn, C = CH_3, D = SO_2CH_3, E = O			2.56 μM	
Fig. 1, A = Ph, A’ = *p*-OCH_3(NHCOPh), B = 2,5-ClBn, C = CH_3, D = SO_2CH_3, E = O			0.49 μM	
Fig. 1, A = Ph, A’ = *p*-I(NHCOPh), B = 2,5-ClBn, C = CH_3, D = SO_2CH_3, E = O			0.66 μM	
Fig. 1, A = Ph, A’ = NHCOCy, B = 2,5-ClBn, C = CH_3, D = SO_2CH_3, E = O	LTEDaro	MTT assay, 72 h of compounds exposition	1.00 μM	[59]
Fig. 1, A = Ph, A’ = NHCOPh, B = 2,5-ClBn, C═H, D = SO_2CH_3, E = O			2.15 μM	
Fig. 1, A = Ph, A’ = NO_2, B = *p*- IPrBn, C = CH_3, D = SO_2CH_3, E = O	SKBR-3	MTT assay, 48 h of compounds exposition	20.1 μM	[60]
	BT-474		44.7 μM	
Fig. 1, A = Ph, A’ = NO_2, B = 2,5-diMeBn, C = CH_3, D = SO_2CH_3, E = O	SKBR-3		6.2 μM	
	BT-474		13.5 μM	
Fig. 1, A = Ph, A’ = NHCOPh, B = 2,5-diMeBn, C = CH_3, D = SO_2CH_3, E = O	SKBR-3		3.65 μM	
Fig. 12, R = Ph, E = P, n = 2	MCF-7	SRB assay, 24 h of compounds exposition	1.0 μM	[132]
	MDA-MB-231		2.3 μM	
Fig. 12, R = *o*-CH_3Ph, E = P, n = 1	MCF-7		2.7 μM	
	MDA-MB-231		3.3 μM	
Fig. 13, R1, *R3* = *t*-Bu, R_2 = H	BxPC-3	MTT assay, 96 h of compounds exposition	4.0 μM	[89]
	MiaPaCa-2		7.0 μM	
Fig. 14A	HCT-15	MTT assay, 48 h of compounds exposition	22.4 μg/mL	[90]
Fig. 14B			21.0 μg/mL	
Fig. 14C	A549		7.1 μM	[91]
	HepG2		7.5 μM	
	HeLa		7.8 μM	
	Du145		6.4 μM	
Fig. 14D	A549		6.7 μM	
	HepG2		9.8 μM	
	HeLa		7.9 μM	
	Du145		5.9 μM	
Fig. 14E	A549		6.6 μM	
	Du145		7.2 μM	
Fig. 15, R = *o*-$OCOCH_3$Ph	HCT-15		18.92 μM	[92]
Fig. 16, R = *p*-ClPh			20.64 μg/mL	[93]
Scheme 3, R1 = $NHCOCH_3$, R_2 and R_3 = MeCy, X = S	LNCaP		9.16 μM	[102]
	MCF-7		16.57 μM	
Scheme 3, R1 = $NHCOCH_3$, R_2 = MeCy, R_3 = 2,4-diMeBn, X = S	LNCaP		9.71 μM	
	MCF-7		20.83 μM	
Scheme 3, R1 = $NHCOCH_3$, R_2 = 2,4-diMeBn, R_3 = Hex, X = S	LNCaP		13.88 μM	
	MCF-7		21.56 μM	
Fig. 10	B16-F10		2.8 μM	[104]
	MCF-7		1.8 μM	
	HepG2		1.2 μM	
Fig. 18	PC-3		1.2 μg/mL	[133]
	THP-1		3.51 μM	[105]
	U-937		5.02 μM	
	HL-60		2.51 μM	
	Jurkat		5.18 μM	

MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltatrazolium bromide (MTT); Sulforhodamine B (SRB).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.102966.

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