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Synthesis and Preliminary Screening of the Biological Activity of Sulindac Sulfoximine Derivatives

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Abstract: Sulindac is a well-known anti-inflammatory agent, sometimes employed as an adjuvant in antitumor therapy. Due to the recent interest in sulfoximine for its potential chemotherapeutics, we decided to transform sulindac and its methyl ester into the corresponding sulfoximines to test their antitumor activity. These compounds were fully characterized. Eventually, sulindac, sulindac methyl ester and the two novel corresponding sulfoximines were tested against malignant cells of U-87 glioblastoma, MCF-7 human breast cancer, HepG2 human liver hepatocellular carcinoma, CaCo-2 human colon cancer, and HeLa human cervical cancer. Interesting preliminary results were observed that encourage new investigations in this research theme.

Keywords: sulfoximines; sulindac; sulfoxides; antiproliferative activity

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1. Introduction

Anti-inflammatory agents have been studied as adjuvants in cancer therapy during the past four decades [1,2]. This therapeutic strategy is well recognized, and its side effects are controlled. Sulindac was one of the anti-inflammatory agents employed for this purpose [3,4]. Sulindac is an aryl methyl sulfoxide prodrug. It is inactive in vitro but is activated upon metabolic reduction to sulindac sulfide in vivo. Thus, the sulfide is the corresponding drug and it is active both in vitro and in vivo [3,4].

Sulindac is a bioprecursor prodrug and therefore differs from its active metabolite from a physicochemical and biological point of view [5]. Sulindac sulfide blocks prostaglandin synthesis [6]. Moreover, sulindac and its metabolites (i.e., sulindac sulfide 3a and sulindac sulfone 3b, Figure 1) have been reported to shown interesting effects in the prevention of colon carcinogenesis, as shown in human trials, including their potential properties as antiapoptotic agents [7,8]. As a further example, the amide of Sulindac sulfide, which actually has reduced COX inhibitory activity compared to sulindac, showed interesting antitumor activity against human colon cancer. Therefore, many other amide derivatives of sulindac were synthesized and their activity was tested against cancer cell lines (prostate, colon, and breast) and against lymphoblastic leukemia cell lines with satisfactory antitumor activity and a clear reduction in side effects [9,10].

Combining two chemotherapeutic agents into a single drug is a common strategy to enhance their activity. A representative example is shown with the combination of platinum complexes, known anticancer agents, with anti-inflammatory drugs [11–13]. It was reported that these complexes enter tumor cells more efficiently. Later, the two species are released and act. It was reported that this strategy resulted in fewer side effects, with increased therapeutic efficiency.

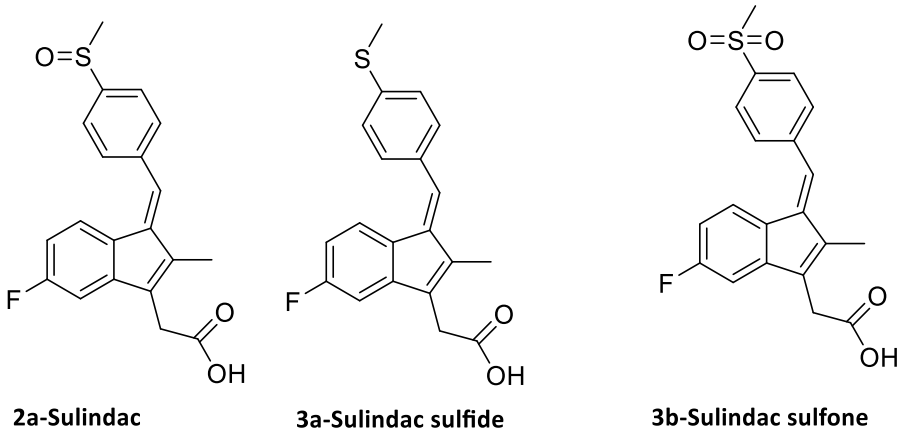


Figure 1. Structures of sulindac, sulindac sulfide and sulindac sulfone.

Nowadays, considerable interest is attached to the molecular class of sulfoximines [14,15], compounds that are isosteres with sulphones. Sulfoximines are small hydrophilic molecules with a sulfur atom in a stable configuration also connected to a nitrogen atom that is nucleophilic and basic. The basicity of nitrogen allows metal ion coordination and the formation of salts with strong acids. Moreover, sulfoximine moiety is metabolized by an oxidative process to its corresponding sulfoxide and sulfone by the cytochrome P450 family [16]. The proposed mechanism of reaction consists of an initial oxidation of the imine nitrogen with the release of nitrous derivatives to yield the sulfoxide. When the secondary or tertiary amines are replaced with sulfoximines in various bioactive compounds, interesting pharmacological, physicochemical and drug metabolism properties emerge, because sulfoximine derivatives, although similar in pharmacological potency and lipophilicity, exhibit more possibilities of hydrogen bonding [17].

Sulfoximines were synthesized for the first time more than seventy years ago, but they were seldom employed on a large scale until new and effective synthetic methods were discovered [15–19]. For example, a simple protocol of wide applicability for the synthesis of sulfoximines is based upon the reaction of the corresponding sulfoxides with $PhI(OAc)_2$ as the oxidant and solutions of ammonium carbamate as the N source.

The resulting availability of sulfoximines has encouraged new investigations into the applications of these compounds as bioactive compounds. A recent review highlighted the opportunity connected to sulfoximines in the period 2013–2020, analyzing the enzymes that could be inhibited [14,15]. Compounds containing the sulfoximine group showed interesting activities as anti-asthmatics, spasmolytics, benzodiazepine receptor partial agonists, and COX-2 enzyme inhibitors. A very promising field of application is the investigation of their antitumor activity, targeting the inhibition of cyclin-dependent kinases (CDKs). The study of CDK inhibitors with sulfoximines has led to the identification of a compound (whose acronym is BAY 1000394) endowed with remarkable antiproliferative activity, good solubility, and specificity, and which has also been studied in the clinical phase on patients with solid tumors at an advanced stage [8].

In the past work of some of us, we reported the synthesis of chiral sulfoxides by enantioselective oxidation of sulfides with *tert*-butyl hydroperoxide (TBHP) in the presence of a 1:2 complex between $Ti(i\text{-}PrO)_4$ and (*S*,*S*)- or (*R*,*R*)-hydrobenzoin. This oxidation protocol has proved to be very useful for the synthesis of different types of chiral sulfoxides obtainable in good yields with high enantiomeric purity. In this context, we reported the synthesis of chiral sulindac esters obtained by enantioselective oxidation of the corresponding sulfides. The products were obtained with moderate yield and with a high enantiomeric purity. Then, the esters were hydrolyzed to yield chiral sulindac (2a) [20]. Taking into account all these aspects, and our experience of the synthesis of racemic and enantiopure sulfoxides [15,19,20], and in particular of sulindac alkyl esters [20] and of sulfoximine [19], we decided to synthesize the sulfoximines of sulindac derivatives and to test the bioactivity

of these compounds, in which the anti-inflammatory sulindac is combined with the new possibilities connected with the sulfoximine moiety.

2. Materials and Methods

2.1. Synthesis

All reagents were purchased at the highest commercial quality from Sigma–Aldrich and used without further purification. Preparative column chromatography was carried out using Macherey–Nagel silica gel (60, particle size 0.063–0.2 mm). Macherey–Nagel aluminum sheets with silica gel 60 F254 were used for TLC analyses. New compounds were characterized by ^{1}H-NMR, ^{13}C-NMR and HR–MS analysis. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on an Agilent 500 spectrometer at 500 and at 125 MHz, respectively. High-resolution mass spectra were recorded with an Agilent HPLC QTOF spectrometer via direct infusion of the samples. Sulindac 2a is commercially available, whereas sulindac methyl ester 1a was prepared according to the literature [20].

2.2. Biological Activity

2.2.1. Cell Cultures and Treatment

The human glioblastoma U-87, human breast carcinoma MCF-7, human liver hepatocellular carcinoma HepG2, human colon cancer CaCo-2, and human cervical cancer HeLa cell lines were maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 2 mM L-glutamine, 50 U/mL penicillin and 50 mg/mL streptomycin in a humid atmosphere of 95% air and 5% CO_2 at 37 °C. Prior to cell treatment, the medium was replaced with fresh medium containing test compounds in the range 1–150 μM.

2.2.2. Cell Viability Assay

The number of living cells was evaluated by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay according to protocols previously described [21]. Briefly, 100 μL of cell suspension was plated in 96-well plates at a density of ~5000 cells/well. After 1 day's incubation at 37 °C in a humid atmosphere with 5% CO_2, the culture medium was replaced with 100 μL of fresh medium or medium containing different concentrations of the test compounds. Untreated cells were used as positive control. After the incubation period of 72 h, 10 μL of a 0.5% (*w*/*v*) MTT/PBS solution was added to each well and the incubation was prolonged further for 2 h. After this period, medium was removed and replaced with 100 μL of DMSO. The absorbance registered at λ = 570 nm of the individual well was measured by a microplate reader (Wallac Victor3, 1420 Multilabel Counter, Perkin-Elmer). Cell viability test results were expressed as dose–effect plots of the mean of three different experiments at each tested dose or IC_{50} values obtained using nonlinear regression in CalcuSyn v.1.1.1 software (Biosoft, Cambridge, UK).

2.2.3. COX Inhibition Assay

Compounds under investigation were evaluated for their ability to inhibit ovine COX-1 or human COX-2 enzyme measuring the extent (%) of enzyme activity inhibition at 50 μM. The inhibition of the enzyme was evaluated by using a colorimetric COX inhibitor screening assay kit (Catalog No. 7601050, Cayman Chemicals, Ann Arbor, MI, USA) following the manufacturer's instructions. COX is a bifunctional enzyme exhibiting both cyclooxygenase and peroxidase activities. The cyclooxygenase component catalyzes the conversion of arachidonic acid into the hydroperoxide PGG_2, and then the peroxidase component catalyzes PGG_2 reduction into the corresponding alcohol PGH_2, the precursor of PGs, thromboxane, and prostacyclin. The colorimetric COX inhibitor screening assay colorimetrically measures the peroxidase activity of the cyclooxygenases monitoring the appearance of oxidized N,N,N′,N′-tetramethyl-*p*-phenylenediamine (TMPD) at ʎ = 590 nm. Stock solutions of test compounds were dissolved in DMSO.

2.2.4. Statistical Analysis

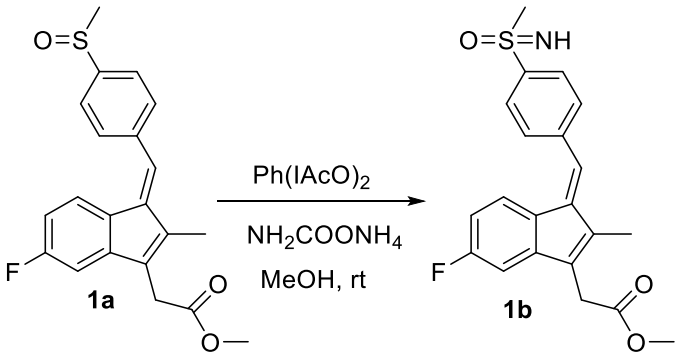
Results are expressed as mean ± SD from three independent experiments and analyzed using GraphPad Prism 5.0. For cell viability tests, the IC_{50} values were calculated with GraphPad Prism 5.0 using the nonlinear regression curve on dose–effect curves.

3. Results and Discussion

3.1. Synthesis of Sulindac Derivatives

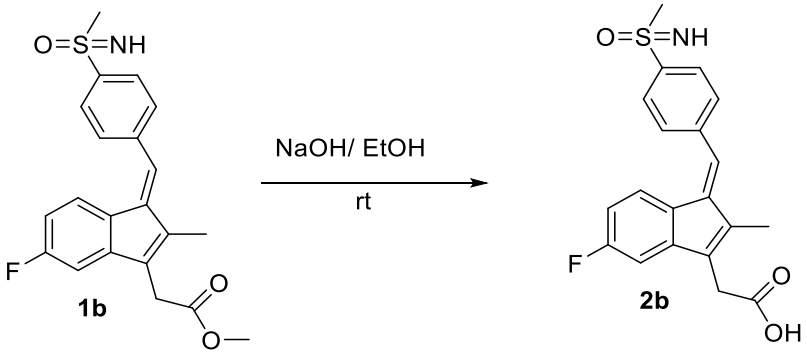
Sulindac methyl ester **1a** was prepared by reacting sulindac **2a** with methanol in $BF_3{\cdot}CH_3OH$ for 4h at 50 °C and subsequently purifying by chromatography.

Sulindac methyl ester sulfoximine **1b** was synthesized by applying a literature protocol [18,19] (Scheme 1). Sulindac methyl ester **1a** was reacted with (diacetoxyiodo)benzene [$Ph(IAcO)_2$] and ammonium carbamate [NH_2COONH_4] in MeOH for 30 min and later purified by chromatography (Scheme 1).



Scheme 1. Synthesis of sulindac methyl ester sulfoximine (**1b**).

An attempt to obtain sulindac sulfoximine **2b** directly from sulindac **2a**, by using the NH transfer shown in the previous Scheme, gave low yields and separation issues. On the other hand, we synthesized **2b** by the hydrolysis of sulindac methyl ester sulfoximine **1b** (Scheme 2).



Scheme 2. Synthesis of sulindac sulfoximine (**2b**).

Methyl (*Z*)-2-(5-fluoro-2-methyl-1-(4-(methylsulfinyl)benzylidene)-1*H*-inden-3-yl) acetate (1a). Compound 1a was synthesized according to the literature [20] by adding 300 mg (0.84 mmol) of sulindac **2a** and 1.29 mL (1.68 mmol) of $BF_3{\cdot}CH_3OH$ to a 50 mL flask in 8 mL of methanol. The mixture is reacted for 4 h at 50 °C. After this time, the solvent is evaporated under vacuum. The crude mixture is purified by silica gel column chromatography using diethyl ether as eluent, to yield a yellow solid product (295 mg, 95% yield).

^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.74–7.69 (m, 2H), 7.68–7.63 (m, 2H), 7.15 (broad s, 1H), 7.14 (dd, *J* = 8.4, *J* = 5.2 Hz, 1H), 6.87 (dd, *J* = 9.0, *J* = 2.4 Hz, 1H), 6.56 (ddd, *J* = 9.0, *J* = 8.4, *J* = 2.4 Hz, 1H), 3.71 (s, 3H), 3.57 (s, 2H), 2.81 (s, 3H), 2.20 (s, 3H).

^{13}C-NMR ($CDCl_3$, 125 MHz) δ 170.7, 163.3 (d, *J* = 246.2 Hz), 146.7 (d, *J* = 7.9 Hz), 145.5, 141.7, 139.7, 138.2, 131.7 (d, *J* = 2.7 Hz), 130.2, 129.5 (d, *J* = 2.7 Hz), 128.2, 123.8, 123.6 (d, *J* = 6.6 Hz), 110.8 (d, *J* = 22.4 Hz), 106,1 (d, *J* = 24.2 Hz), 52.2, 43.9, 31.6, 10.5.

Methyl-(*Z*)-2-(5-fluoro-2-methyl-1-(4-(methylsulfonimidoyl)benzylidene)-1*H*-inden-3-yl)acetate (1b). Compound **1b** was synthesized by adding 370 mg (1 mmol) of sulindac methyl ester **1a**, 970 mg (3 mmol) of (diacetoxiodo)benzene and 310 mg (4 mmol) of ammonium carbamate to a 50 mL flask in 5 mL of methanol. The mixture was reacted for 30 min at room temperature. After this time, the solvent was evaporated under vacuum. The crude mixture was purified by silica gel column chromatography using *n*-hexane/acetone 1:1 as eluent, to yield a yellow oil product (320 mg, 82 % yield). HRMS(ESI-TOF), *m*/*z*: calculated for $[C_{21}H_{20}FNO_3S + Na]^+$ 408.1046, found $[M + Na]^+$ 408.1047.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ 8.04–8.01 (m, 2H), 7.68–7.63 (m, 2H), 7.12–7.06 (m, 2H), 6.83 (dd, *J* = 8.8, *J* = 2.2 Hz, 1H), 6.52 (td, *J* = 8.9, *J* = 2.3 Hz, 1H), 3.67 (s, 3H), 3.58 (broad s, 1H) 3.53 (s, 2H), 3.24 (s, 3H), 2.16 (m, 3H).

^{13}C-NMR ($CDCl_3$, 125 MHz) δ 170.6, 163.4 (d, *J* = 247 Hz), 146.8 (d, *J* = 8.8 Hz), 142.2 (d, *J* = 2.5 Hz), 141.3, 138.1, 133.1, 132.2 (d, *J* = 2.3 Hz), 130.2, 128.0, 127.3, 123.6 (d, *J* = 9.0 Hz), 110.8 (d, *J* = 22.7 Hz), 106,2 (d, *J* = 24.0 Hz), 52.2, 45.8, 31.5, 10.5.

(*Z*)-2-(5-fluoro-2-methyl-1-(4-(methylsulfonimidoyl)benzylidene)-1*H*-inden-3-yl)acetic acid (2b). Sulindac methyl ester sulfoximine (0.1 g, 0.26 mmol) 1b was added to an aqueous solution 1 M of sodium hydroxide (0.5 mmol) and 5 mL of ethanol. The mixture was stirred for 30 min at room temperature. After this time, the ethanol was evaporated. The crude mixture was treated with a saturated ammonium chloride solution and extracted three times with ethyl acetate. The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated under vacuum. The crude reaction mixture was purified by column chromatography on silica gel (ethyl acetate/methanol 1:1), affording a yellow oil product (75 mg, 78 % yield). HRMS (ESI-TOF), *m*/*z*: calcd for $[C_{20}H_{18}FNO_3S + H]^+$ 372.1069, found $[M + H]^+$ 372.1056.

^{1}H-NMR (acetone-d^6, 500 MHz,) δ 8.10–8.08 (m, 2H), 7.78–7.76 (m, 2H), 7.39–7.36 (broad s, 1H), 7.23 (dd, *J* = 8.3, 5.2 Hz, 1H), 7.03 (dd, *J* = 9.2, 2.1 Hz, 1 H), 6.62 (td, *J* = 9.3, 2.2 Hz, 1H), 4.97(s, 1H), 3.65 (broad s, 2H), 3.14 (broad s, 3H), 2.13 (s, 3H).

^{13}C-NMR (DMSO-d^6, 125 MHz) δ 174.6, 163.0 (d, *J* = 244 Hz), 148.1–147.9 (broad), 143.8, 141.4, 140.9, 137.4, 130.1, 129.9–129.7 (broad), 129.0, 127.9, 126.6, 123.5 (d, *J* = 9.1 Hz), 110.7, (d, *J* = 22.4 Hz), 106,8 (d, *J* = 23.7 Hz), 46.24, 33.4, 10.6.

Graphical representations of the NMR and HRMS spectra of the new molecules **1b** and **2b** are available in the Supplementary Materials.

3.2. Cytotoxicity Studies

Cytotoxicity of compounds **1a, 1b**, **2a**, and **2b** was studied in vitro as ability to interfere with cell survival on a panel of different tumor cells lines by MTT conversion assay [21]. The IC_{50} values obtained from dose–response curves (shown in Figure 2) or the percentage cell viability values obtained at the maximum of tested dose (150 μM) were collected (Table 1). As evidenced by the curves in Figure 2 **1b**, **2a** and **2b** compounds showed comparable toxicity to the HepG-2 cell line in reference to **1a** (70 ± 2 μM); in particular; **1b** showed the highest toxicity value with an IC_{50} equal to 58 ± 4 μM (See Table 1). Moreover, **1b** induced comparable cytotoxicity to **1a** on U87 and CaCo-2 cells, and **2b** on HeLa cell lines. Compounds **2a** and **2b** showed no toxicity on U87, CaCo-2 or MCF7 cell lines at the tested concentration of 150 μM (Table 1).

3.3. COX Inhibition Studies

Sulindac sulfide, the active metabolite of the indene prodrug sulindac, shows a slow, tight-binding inhibition of both COX-1 and COX-2 (COX-1 IC_{50} = 115 nM and COX-2 IC_{50} = 140 nM) [22,23], and it is well known that sulindac sulfone and sulindac sulfoxide constitute, respectively, the inactive metabolite and the inactive prodrug of the correspond-

ing sulindac sulfide. Since the novel compounds are sulindac derivatives, we decided to test their ability to inhibit cyclooxygenases.

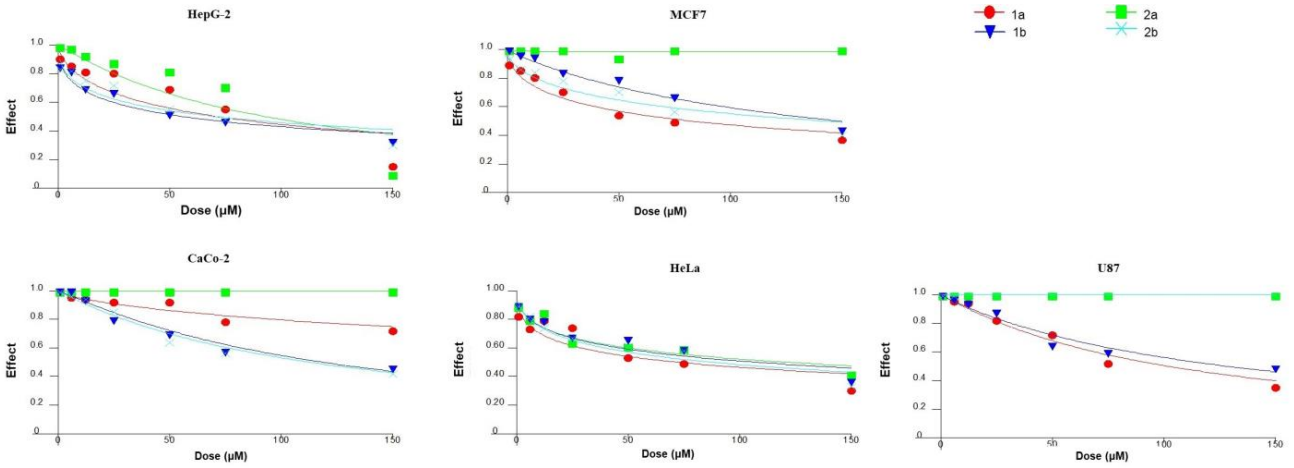


Figure 2. Dose (μM)–effect plots of the mean of three different cell viability experiments, conducted in various human cancer cell lines incubated for 72 h with compounds.

Table 1. IC_{50} values for cell viability of HepG-2, MCF7, U87, Caco-2 and HeLa cell lines after treatments with **1b**, **2b**, sulindac (**2a**) and sulindac methyl ester (**1a**).

	IC_{50} (μM) or % Cell Viability				
Compound	**HepG-2**	**MCF7**	**U87**	**CaCo-2**	**HeLa**
1b	58 ± 4	145 ± 9	130 ± 10	120 ± 9	105 ± 6
2a	93 ± 4	[1] 107 ± 8%	[1] 114 ± 7%	[1] 115 ± 7%	120 ± 5
2b	71 ± 3	145 ± 6	[1] 99 ± 5%	[1] 72 ± 6%	83 ± 6
1a	70 ± 2	80 ± 6	102 ± 8	100 ± 5	75 ± 2

[1] % Cell viability tested at 150 μM.

Only sulindac-OMe (**1a**) (Figure 3) has a very slight inhibitory activity (15% at 50 μM) against the COX-2 isoform. All other sulfoximine derivatives were found to be inactive (around 1% at 50 μM) in inhibiting both cyclooxygenase isoforms, but this does not hinder the activity of sulindac sulfide, since sulfoximines are "in vivo" metabolized by CytP450, and thus may also be considered prodrugs of sulindac sulfide itself.

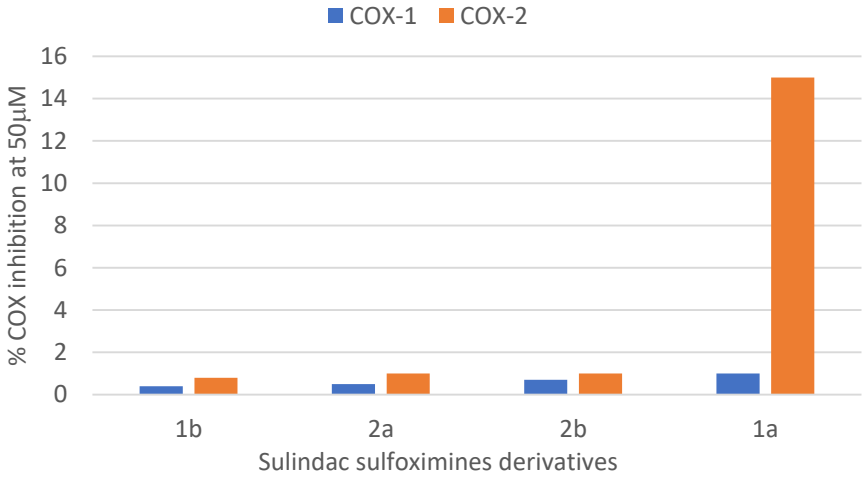


Figure 3. Percentage (%) of COX-1 inhibition of **1a**–**1b** and **2a**–**2b** at 50 μM final compound concentration. All compounds were tested at different concentrations (0.1–50 μM), but only the percentage of inhibition at the higher dose used is reported.

4. Conclusions

In summary, we reported the synthesis of two new sulindac derivatives: sulindac methyl ester sulfoximine and sulindac sulfoximine. The first one was obtained starting from sulindac methyl ester using $PhI(OAc)_2$ as the oxidant and solutions of ammonium carbamate as the N source. This simple and general methodology proved to be unsatisfactory when used directly on sulindac. Thus, sulindac sulfoximine was synthesized starting from the sulindac sulfoximine methyl ester. These new molecules were employed in preliminary studies on their biological activity. We observed a similarity of behavior with sulindac, both in terms of cytotoxicity on the panel of tumor cell lines investigated and in terms of inhibitory activity against COX. Among the other results, interesting values of cytotoxicity against the HepG-2 cell line in the case of the sulindac methyl ester sulfoximine. A hypothesis of activity can be connected to the possibility that these intermediates undergo activation by phase I or phase II metabolic enzymes to be transformed into an active metabolites. Further studies will be aimed at verifying whether the new sulfoximine derivatives are metabolically activated by the cytochrome P450 family, as occurs for sulindac itself, and could be configured precisely as bioprecursor molecules. Future studies will be devoted to the synthesis of chiral sulfoximines starting from the chiral methyl ester of sulindac and to the subsequent evaluation of their biological activity on a larger panel of cell lines of different origins.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/app132112002/s1. Figure S1 1H-NMR (500 MHz, CDCl3) spectrum of (**1b**); Figure S2 13C-NMR (125 MHz, CDCl3) spectrum of (**1b**); Figure S3 HRMS (ESI-TOF) spectrum of (**1b**); Figure S4 1H-NMR (500 MHz, Acetone-d6) spectrum of (**2b**); Figure S5 13C-NMR (125 MHz, DMSO-d6) spectrum of (**2b**); Figure S6 HRMS (ESI-TOF) spectrum of (**2b**).

Author Contributions: Synthesis of the molecules, C.C. and M.A.M.C.; biological tests, V.L., R.M.I., A.S., N.D. and M.G.P.; writing C.C., M.A.M.C., V.L., R.M.I., A.S., N.D. and M.G.P.; review and editing C.C. and M.A.M.C. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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