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Carborane Analogues of Fenoprofen Exhibit Improved Antitumor Activity

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Fenoprofen is a widely used nonsteroidal anti-inflammatory drug (NSAID) against rheumatoid arthritis, degenerative joint disease, ankylosing spondylitis and gout. Like other NSAIDs, fenoprofen inhibits the synthesis of prostaglandins by blocking both cyclooxygenase (COX) isoforms, COX-1 the "house-keeping" enzyme and COX-2 the induced isoform from pathological stimuli. Unselective inhibition of both COX isoforms results in many side effects, but off-target effects have also been reported. The steric modifications of the drugs could afford the desired COX-2 selectivity. Furthermore, NSAIDs have shown promising cytotoxic properties. The structural modification of fenoprofen using bulky dicarba-*closo*-dodecaborane(12) (carborane) clusters and the biological evaluation of the carborane analogues for COX inhibition and antitumor potential showed that the carborane analogues exhibit stronger antitumor potential compared to their respective aryl-based compounds.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most important therapeutics for treatment of pain, fever and inflammation.[1,2] Their mode of action was reported in the 1970s, by Vane and coworkers as preventing the synthesis of prostaglandins by blocking cyclooxygenase (COX).[3]

Cyclooxygenase (COX) is a protein dimer located in the cell on the luminal side of the endoplasmic reticulum and nuclear envelope. It exists in two isoforms, COX-1 and COX-2. COX-1 is known as the 'house-keeping' enzyme responsible for the moderation of homeostatic processes such as cytoprotection of gastric mucosa, renal blood flow regulation and platelet aggregation. COX-2 on the other hand is induced by several stimuli, such as hormones, growth factors, mitogens, oncogenes and disorders of water-electrolyte homeostasis, which are related with pathological disorders such as inflammation and tumor growth.[1,4,5]

Studies of the COX isoforms have shown that COX-1 and COX-2 share a similar structure with high sequence conservation;[2,6] thus, many of the NSAIDs show a non-selective mode of action. The non-selective inhibition of COX results in many undesired side effects, mainly related with gastrointestinal ulcer and renal toxicity.[7] However, off-target effects have also been described, which are apparently completely independent of COX inhibition and prostanoid signaling.[8] Further studies on the COX isoforms revealed that besides many similarities, the cavity of the active site of COX-2 is approximately 25% larger than that of COX-1 due to an accessible side pocket and a larger channel.[6] Therefore, one key to COX-2 selectivity and thus, reduction of the COX-1 related side effects is the steric modification of the drug molecule.[5,9]

The research interest in NSAIDs advanced further, when their cytotoxic properties were revealed.[10] It was reported that NSAIDs display anticancer effects through inhibition of COX-2, because this isoform is overexpressed in human premalignant and malignant tissues. Additionally, NSAIDs promote apoptosis through mechanisms that are independent of COX inhibition.[11]

Fenoprofen (Scheme 1) is an NSAID, available upon prescription in the US (Nalfon®) and UK (Fenopron®), that is used for treating rheumatoid arthritis, degenerative joint disease, ankylosing spondylitis and gout. It is a propionic acid derivative which is also used as painkiller during acute pain after injuries or inflammation after surgery.[12,13] Like other NSAIDs, fenoprofen non-selectively binds to both COX isoforms and thus inhibits the synthesis of prostaglandins. Compared to aspirin, fenoprofen shows milder side effects which are mainly related to abdominal discomfort, dyspepsia, nausea, constipation and skin rash. In case of an overdose or long exposure, it causes vomiting, hepatotoxicity and gastric ulcers.[12,13] *In vitro* studies showed that fenoprofen has low cytostatic potential when

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tested on different cancer cell lines and human fibroblasts, due to its low lipophilicity which interferes with the cell uptake.[14]

Aiming for improvement of COX-2 selectivity, metabolic stability, anticancer potential and prolongation of the plasma half-life of the drugs, one promising way is the incorporation of carboranes as phenyl mimetics for structural modification of a conventional drug.[5,15,16–22]

Dicarba-*closo*-dodecaborane(12) (*closo*-$C_2B_{10}H_{12}$, carboranes) are icosahedral borane derivatives with ten BH and two CH vertices. Depending on the CH positions within the cluster, three different isomers are reported, namely *ortho*- (1,2-), *meta*- (1,7-) and *para*-carborane (1,12-$C_2B_{10}H_{12}$) (Figure 1, **2**–**4**).[23]

Carboranes are known for their remarkable properties such as their hydrophobicity, low toxicity, and their chemical, thermal and metabolic stability. Due to a slightly larger van-der-Waals diameter compared to a phenyl ring (carborane: 5.25 Å, phenyl ring: 4.72 Å), carboranes became a novel prominent tool for structural modification of established drugs that contain at least one phenyl ring.[22]

Following this strategy, our group has reported the structural modification of numerous commercial NSAIDs using carboranes as phenyl mimetics.[5,16–22] One of the first carborane modified NSAID to be published was asborin, the carborane analogue of aspirin,[21] and more recently we reported the structural modification of mefenamic acid using the three carborane isomers (Scheme 1). The carborane-containing analogues of mefenamic acid exhibited higher anti-cancer potential against both HCT116 (human colorectal carcinoma) and SW480 (human colorectal adenocarcinoma) cell lines compared to commercial mefenamic acid while the *nido* derivative was the most potent for COX inhibition. However, no isoform selectivity was observed.[16] Similar observations were made for other carborane analogues of NSAIDs indicating the existence of potential off-targets inside the cells and thus making them interesting as improved antitumor agents.[16,18,19,24]

Herein we present the structural modification of fenoprofen as a commercial drug by incorporation of carborane clusters, their characterization and biological evaluation *in vitro* for COX-isoform selectivity and cytotoxicity.

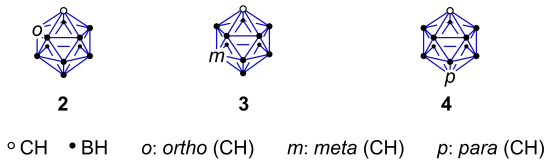
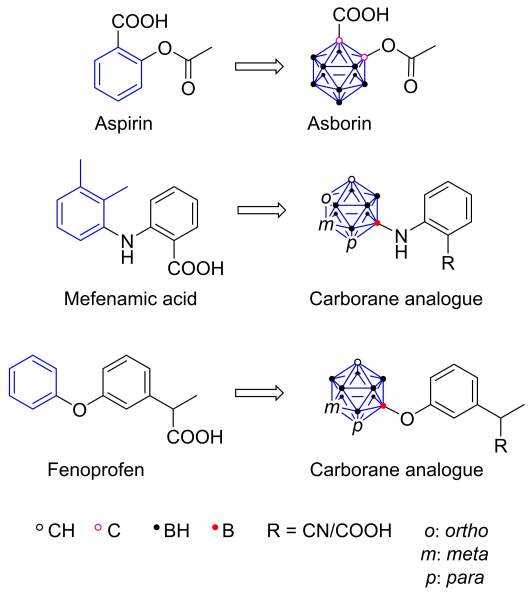


Figure 1. Structural isomers of dicarba-*closo*-dodecaborane(12).

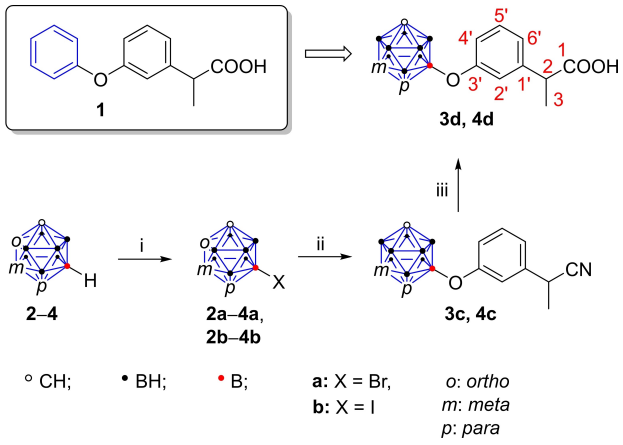


Scheme 1. Carboranes as phenyl mimetics: aspirin[21], mefenamic acid,[16] and fenoprofen and their respective carborane analogues (this work).

Results and Discussion

Molecular design and synthesis

Fenoprofen (**1**) is a propionic acid derivative and consists of two phenyl rings linked *via* an oxygen bridge. To improve COX-2 selectivity and metabolic stability, one of the phenyl rings was substituted with a carborane cluster following a three-step synthesis: (i) halogenation of the clusters (**2a**–**4a** and **2b**–**4b**) adopting previously reported conditions,[16,25] followed by (ii) Pd-catalyzed B–O coupling of the halo-carborane with racemic 2-(3-hydroxyphenyl)propionitrile (**5**) to the corresponding racemic nitriles **3c** and **4c** and finally (iii) the hydrolysis under acidic media affording the racemic carboxylic acids **3d** and **4d** (Scheme 2).



Scheme 2. Fenoprofen (**1**) and its carborane analogues containing the *meta* and *para* isomer (nitriles **3c** and **4c**, carboxylic acids **3d** and **4d**). Synthetic approach: i) halogenation of the clusters; for iodination: 0.5 equiv. of I_2, mixture of HNO_3/H_2SO_4 (1:1 (v/v)) in glacial acetic acid, 60–80 °C for 1–4.5 h, 81–97%; for bromination: 0.5–1 equiv. Br_2, mixture of HNO_3/H_2SO_4 (1:1 (v/v)) in glacial acetic acid, 60–80 °C for 1 h, or $AlCl_3$ in carbon disulfide, refluxing for 21 h, 70–83%;[16,25] ii) B–O coupling of the halo-carborane with 2-(3-hydroxyphenyl) propionitrile (**5**) under SPhos-Pd-G3–SPhos–K_3PO_4 or SPhos-Pd-G4–SPhos–KO*t*-Bu as catalyst in 1,4-dioxane, 50–80 °C, 25 min–2 h, 65–79%; iii) hydrolysis of the nitrile derivatives with aqueous H_2SO_4 (40 vol%) for 20 h–3 d, 70–91%.

The bromination of the *ortho* isomer **2** and the iodination of the three carborane isomers **2**–**4** leading to **2a** as well as **2b**–**4b** were reported in detail previously by us.[16] Adopting the published procedure, the bromination of the *meta* isomer (1,7-dicarba-*closo*-dodecaborane) was successfully established, and compound **3a** (9-bromo-1,7-dicarba-*closo*-dodecaborane) was obtained in 74% yield. The bromination of the *para* isomer (1,12-dicarba-*closo*-dodecaborane) was unsuccessful using this procedure, but following the synthesis reported by Sieckhaus and co-workers,[25] compound **4a** (2-bromo-1,12-dicarba-*closo*-dodecaborane) was obtained in good yield (70%).

The metal-catalyzed cross-coupling reactions of carboranes have been recently reviewed by Dziedzic and Spokoyny.[26] However, the B–O coupling of halo-carboranes was reported to be a very challenging task. Kabytaev and co-workers concluded that the coupling reaction of iodo-carboranes **2b**–**4b** with phenols under Pd(dba)$_2$–BINAP–NaH conditions (dba = dibenzylideneacetone, BINAP = 2,2′-bis(diphenylphosphino-1,1′-binaphthyl) was only successful for the *para* isomer **4b**, but unsuccessful for the *ortho* and *meta* isomer. The low reactivity and deboronation of iodo-carboranes **2b** and **3b** to the respective *nido* species under Lewis-basic conditions were the main drawbacks.[27] Furthermore, Dziedzic *et al.* reported the importance of electron-rich biaryl phosphine ligands (XPhos, Sphos and DavePhos, Figure 2) for a successful B–O coupling reaction of 9-bromo-*meta*-carborane (**3a**).[28]

Based on the previously reported results, we studied the B–O coupling reaction of 2-(3-hydroxyphenyl)propionitrile with the brominated (**2a**–**4a**) and iodinated (**2b**–**4b**) carboranes. The reactions were performed under nitrogen in 1,4-dioxane using different Pd precatalysts, namely Pd(dba)$_2$/BINAP, SPhos-Pd-G3 and SPhos-Pd-G4 (Figure 2), and bases (for optimization of catalyst and reaction conditions see Table S1, Supporting Information).

The best results for the synthesis of racemic nitrile **4c** (79% yield) from the brominated carborane **4a** were obtained with SPhos-Pd-G3–SPhos–K_3PO_4 as catalytic system in 1,4-dioxane (2 h, 80 °C). For the racemic nitrile **3c** (65% yield) the best results were found when also the brominated carborane **3a** was reacted using SPhos-Pd-G4–SPhos–KO*t*-Bu as catalytic system in 1,4-dioxane (25 min, 50 °C). Unfortunately, the B–O coupling reaction of the *ortho* isomer **2a** or **2b** to give the coupled nitrile **2c** failed, even after a reaction time of six days at 100 °C using SPhos-Pd-G3–SPhos–K_3PO_4 as catalytic system in 1,4-dioxane. The formation of the *nido* derivative and the low reactivity of the halogenated substrates **2a** and **2b** were the main drawbacks.

The final step in the synthetic protocol was the acidic hydrolysis of the racemic nitriles **3c** and **4c** in refluxing aqueous H_2SO_4 (40 vol%) to obtain the racemic carboxylic acids **3d** and **4d** in good to excellent yields (70–91%). Both nitriles (**3c**, **4c**) and carboxylic acids (**3d**, **4d**) were fully characterized by spectral analysis, tested for stability and solubility, and their purity was confirmed by HPLC (see the Supporting Information for details).

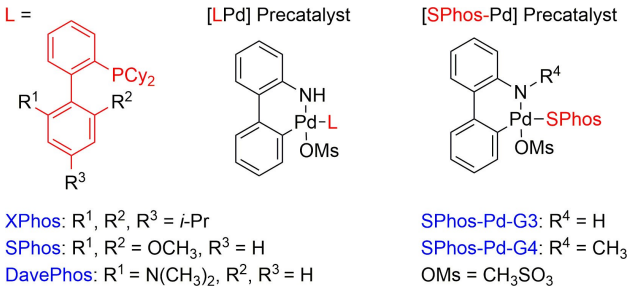


Figure 2. Palladium precatalyst and ligands commonly used for B–O coupling.

Biological evaluation: potential for COX inhibition and cytotoxicity

COX inhibition studies

Racemic compounds **3c**, **3d**, **4c**, and **4d** were tested *in vitro* for their inhibitory potential toward ovine COX-1 and human recombinant COX-2 using the *COX Fluorescent Inhibitor Screening Assay Kit* (Cayman Chemical Company) and the selective COX-2 inhibitor celecoxib as well as the COX-1 inhibitor SC-560 as controls (Table 1). An initial screening of the compounds at a concentration of 100 μM revealed that propionic acid derivatives (**3d** and **4d**) as well as the *para*-carborane propionitrile derivative (**4c**) inhibited neither COX-1 nor COX-2. The propionitrile *meta*-carborane (**3c**) was found to inhibit 55% of COX-2 activity suggesting an IC_{50} value in this range while 32% inhibition of COX-1 activity indicated a slightly higher IC_{50} value. However, the rather low inhibition potential did not warrant further more detailed determination of IC_{50} values for this subset of compounds. Of note, while celecoxib and SC-560 showed reasonable inhibitory potential, fenoprofen (**1**), used as a reference compound in this assay, did not show COX inhibitory effects at all (Table 1). This is in contrast to the IC_{50} value of fenoprofen that was determined by Warner and coworkers for a COX-1, WBA-COX-2 (Human Whole Blood Assay)

Table 1. Results of the COX inhibition assay and determination of lipophilicity (log $D_{7.4}$).

	% Inhibition at 100 μM (mean ± SD)		$logD_{7.4,HPLC}$
	COX-1	COX-2	
1	5.5 ± 1.2	n.i.	
3c	32.3 ± 1.1	54.5 ± 1.1	3.90
3d	n.i.[a]	n.i.	1.41
4c	n.i.	n.i.	4.20
4d	5.1 ± 1.2	n.i.	2.20
	IC_{50} [μM]		
	COX-1	COX-2	
Celecoxib[b]	> 100	0.091 ± 0.017	–
SC-560[c]	0.028 ± 0.014	n.d.	–

[a] n.i. = no inhibition (% inhibition below 5%). [b] Celecoxib served as reference for COX-2 inhibition: pIC_{50} ($pIC_{50} = -log_{10}(IC_{50}[M])$) was found to be 7.58 ± 0. (mean ± SD, n = 3; IC_{50} = 91 ± 17 nM). [c] SC-560 served as reference for COX-1 inhibition: pIC_{50} was found to be 7.58 ± 0.19 (mean ± SD, n = 3; IC_{50} = 28 ± 14 nM).

and WHMA-COX-2 assay (William Harvey Human Modified Whole Blood Assay). They reported that fenoprofen inhibits 50% of each assay at 3.4 μM (for COX-1), 41 μM for WBA-COX-2 and 5.9 μM concentration for WHMA-COX-2 assay.[29]

Determination of hydrophobicity (logD) by HPLC

The lipophilicity was determined as $\log D_{7.4,HPLC}$ value by an HPLC method originally described by Donovan and Pescatore[30] (Table S5). As expected the nitriles **3c** and **4c** have a considerably higher lipophilicity of 3.90 and 4.20, respectively, compared to the corresponding carboxylic acid derivatives **3d** (1.41) and **4d** (2.20).

Studies of the cytotoxic potential

For the assessment of the cytotoxic potential of the carboranyl analogues of fenoprofen, five human cancer cell lines were used: A375 melanoma, A549 lung carcinoma, MCF7 breast cancer, and HT29 and HCT116 colon carcinoma. Cell viability was determined after 72 h using MTT and CV assays and viability curves are presented (Supporting Information, Figure S44). The resulting IC_{50} values are given in Table 2. Except in the case of **3c** on HCT116 and MCF7 where the results obtained with MTT and CV assay were well synchronized, in all treatments IC_{50} values obtained from CV assays were significantly higher. Light microscopy studies of treated cell cultures revealed that the results obtained by CV assays were equivalent to a visible decrease in cell viability. According to IC_{50} values, the most potent compound is **3c** in COX-2 overexpressing MCF7 and COX-2 negative HCT116 cells, followed by **4c**, with almost two times lower potential in comparison to **3c**. Furthermore, IC_{50} values of the same compounds obtained on peritoneal exudate cells isolated from healthy mice were higher than 200 μM, indicating that these experimental drugs are selectively cytotoxic toward malignant cells (Supporting Information, Figure S44). Cell viability assessment revealed that all experimental compounds except **3d** are much more active than fenoprofen (**1**). In concordance with our data, treatment of colorectal adenocarcinoma cell lines HT29, DLD-1 and SW480 with fenoprofen for six days resulted in IC_{50} values over 240 μM,[31] and an IC_{50} value of 200 μM was reported for A549 cells.[32] Flow cytometric assessment of **3c** and **4c** on the most sensitive cell line (MCF7) revealed impressive antiproliferative effects of **3c** and **4c** determined by carboxyfluorescein succinimidyl ester (CFSE) staining after 72 h, with 83.9% and 79.5% of undivided cells, respectively (Figure 3A). Concordantly, analysis of the cell cycle distribution confirmed cell accumulation in the hypodiploid compartment, together with a decreased number of cells in the S and G_2/M phase, suggesting that enhanced apoptosis together with loss of dividing potential is the basic mechanism behind the viability decrease induced by **3c** and **4c** (Figure 3B). Accordingly, a significant presence of apoptotic cells in the early and late phase in response to the treatments was observed (Figure 3C). Apoptosis was not accompanied by caspase activation, while autophagy was strongly and sustainably inhibited by both treatments (Figure 3D, Supporting Information, Figure S45). Suppressed autophagy can be tightly connected with apoptotic cell death induction, since this process often mediates removal of damaged cell organelle, thus preventing the apoptotic cell death.[33] Production of reactive oxygen species (ROS) was only slightly enhanced after 72 h, excluding their involvement in intracellular damage induction and underlining the possible role of **3c** and **4c** in signaling modulation behind cell division arrest (Supporting Information, Figure S46).

Conclusion

The racemic carborane analogues of fenoprofen bearing a nitrile (**3c** and **4c**) or a carboxylic acid group (**3d** and **4d**) were prepared in a three-step synthesis. The coupling reaction was most efficient when brominated carboranes (**3a** and **4a**) were used as educt and SPhos-Pd-G4–SPhos–KO*t*-Bu (for **3c**) or SPhos-Pd-G3–SPhos–K_3PO_4 (for **4c**) as catalytic system in 1,4-dioxane for the B–O coupling. Due to deboronation and low reactivity of the *ortho* isomers (**2a** and **2b**), the coupling reactions were unsuccessful. All products were fully characterized and tested for their potential as COX inhibitors and antitumor agents. The screening with ovine COX-1 and human recombinant COX-2 assays showed that only racemic compound **3c** was a rather unselective inhibitor. On the other hand, the carborane analogues of fenoprofen were found to be superior to the original drug in terms of tumor cell cytotoxicity. Their antitumor action is realized through inhibition of proliferation and caspase-independent apoptosis. Moreover, they were

Table 2. IC_{50} values [μM] of carboranyl analogues of fenoprofen obtained from MTT and CV viability assays (at least three independent experiments).

	1	3c	3d	4c	4d	1	3c	3d	4c	4d
	MTT[a]					CV[b]				
A549	>200	143.7±0.8	>200	80.8±2.8	125.6±7.8	>200	121.2±3.8	>200	178.1±2.4	148.7±8.5
A375	>200	48.7±1.2	>200	66±2.1	148.8±1.8	>200	72.8±2.9	>200	112.7±2.1	162±4.3
HT29	>200	41.9±3.5	>200	71.1±1.8	160.4±2.8	>200	>200	>200	>200	>200
HCT116	>200	47.7±2.9	>200	69.9±1.2	144.7±1.5	>200	48.7±1.8	>200	91.9±4.0	164.8±7.4
MFC-7	>200	38±1.7	>200	47.9±0.8	139.3±1.3	>200	40.7±0.8	>200	71.3±2.1	159.7±3.7

[a] 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide. [b] Crystal violet.

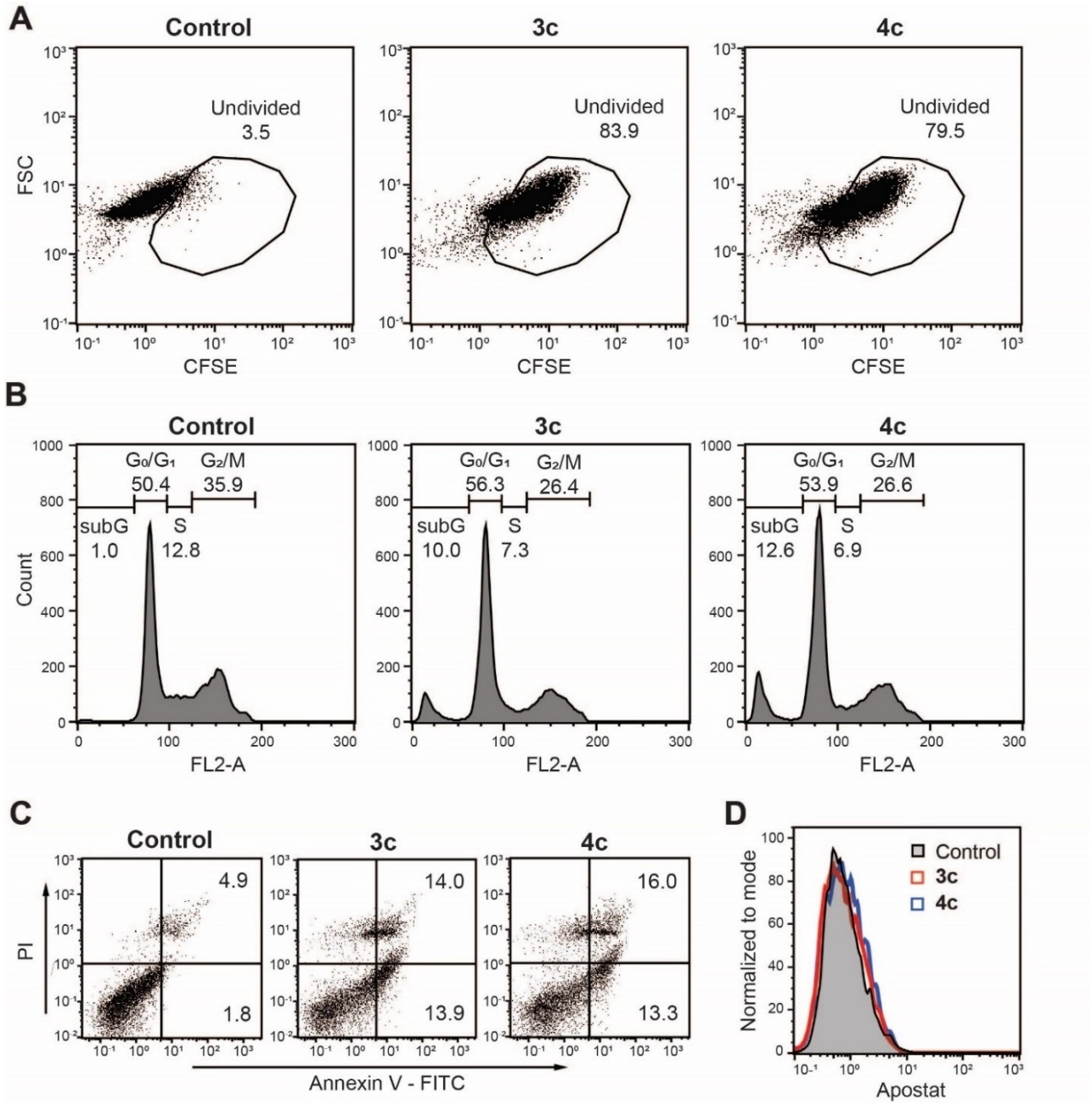


Figure 3. The carborane analogues of fenoprofen **3c** and **4c** inhibit MCF7 cell proliferation and induce caspase-independent apoptosis. MFC7 cells (1.5×10^5/well) were exposed to an IC_{50} dose of **3c** (40 μM) and **4c** (70 μM); after 72 h the cells were analyzed by flow cytometry: (A) cell proliferation, (B) cell-cycle distribution, (C) apoptosis and (D) caspase activation analysis. Representative dot plots (A, C) and histograms (B, D) are shown from at least three independent experiments.

also effective in non-COX-2-expressing cells, suggesting that there are potential off-targets in the cells.

Experimental Section

Syntheses

Materials and methods: All commercially available reagents were purchased from common suppliers and used without further purification. Reactions including carboranes were carried out under a nitrogen atmosphere using the Schlenk technique. For column chromatography, silica gel (60 Å) from Acros was used. The particle size was in the range of 0.035–0.070 mm. Reactions were monitored by thin-layer chromatography (TLC) using silica gel 60 F_{254}-coated

glass plates from Merck with a fluorescence indicator. Carborane containing compounds were stained with a 5% solution of palladium dichloride in methanol. 1,4-dioxane was dried over CaH and further distilled over sodium/benzophenone prior to use. NMR data were collected with an Avance DRX 400 spectrometer (^{1}H-NMR, 400.13; ^{13}C-NMR, 100.63 MHz; ^{11}B-NMR. 128.38 MHz) or an Ascend 400 spectrometer (^{1}H-NMR, 400.16 MHz; ^{13}C-NMR, 100.63 MHz; ^{11}B-NMR, 128.38 MHz) from Bruker. The ^{1}H- and ^{13}C-NMR spectra were referenced to tetramethylsilane (TMS) and the ^{11}B-NMR spectra to the Ξ scale.[34] Deuterated solvents were purchased from Eurisotop with a deuteration rate of 99.80%. The chemical shifts are reported in parts per million (ppm). High-resolution ESI mass spectrometry (HR-ESI-MS) was carried out on an Impact II from Bruker Daltonics. The simulation of the mass spectra was conducted with a web-based program from Scientific Instrument Services Inc. (Palmer, MA, USA).[35] The IR spectra were obtained with a Nicolette IS5 (ATR) from Thermo Fisher Scientific (Waltham, MA, USA). The signal intensity was classified as weak (w), medium (m), or strong (s). Analytical HPLC was performed with the following system: column Luna C18 (Phenomenex, 250×4.6 mm, 5 µm) with a guard column, Agilent 1200 HPLC: pump G1311A, auto sampler G1329A, column oven G1316A, degasser G1322A, UV detector G1315D, γ detector Gabi Star (Raytest), flow rate = 1 mL/min, (A) MeCN/ (B) H_2O + 0.1% TFA (trifluoroacetic acid), gradient $t_{0\,min}$ 45/55, $t_{3.0\,min}$ 45/55, $t_{28.0\,min}$ 95/5, $t_{34.0\,min}$ 95/5, $t_{35.0\,min}$ 45/55, $t_{40\,min}$ 45/55. The products were monitored at λ = 220 or 254 nm. Data for X-ray structures were collected on a Gemini diffractometer (Rigaku Oxford Diffraction) using Mo-K_α radiation (λ = 71.073 pm). Data reduction was performed with CrysAlis Pro[36] including the program SCALE3 ABSPACK[37] for empirical absorption correction. All structures were solved by dual-space methods with SHELXT-2018[38] and refined with SHELXL-2018.[39] With the exception one minor 9% disordered fraction in **4d**, all non-hydrogen atoms were refined with anisotopic displacement parameters. **3d** and **4d** are isotypic and highly disordered. Hydrogen atoms were calculated on idealized positions and carborane carbon atoms could not be localized. Further details and CCDC numbers are given in the Supporting Information. The melting points were determined in glass capillaries using a Gallenkamp apparatus and are uncorrected. The halogenated products (**2a**–**4a** and **2b**–**4b**) were prepared according to previously reported procedures.[16,25] Racemic 2-(3-hydroxyphenyl)propionitrile (**5**) was synthesized following the patent by Allegretti *et al.*[40] The catalysts SPhos-Pd-G3 and SPhos-Pd-G4 were purchased from Sigma Aldrich or synthesized following the reported protocol (details in Supporting Information).[41]

***rac*-2-[*O*-(1,7-Dicarba-*closo*-dodecaboran-9-yl)-phenyl]propionitrile (3c)**: An oven-dried 50 mL Schlenk flask was charged with **3a** (1 mmol, 223 mg), KO*t*-Bu (1.1 mmol, 121 mg), SPhos-Pd-G4 (5 mol%, 39.6 mg) and SPhos (5 mol%, 20.5 mg) and evacuated three times. The mixture was suspended in 10 mL dry 1,4-dioxane and **5** (2 mmol, 294.3 mg) was added *via* syringe. The resulting mixture was heated with stirring for 25 min at 50 °C. The reaction progress was monitored by TLC (*n*-hexane/ethyl acetate, 4:1 (v/v)). After cooling to room temperature, the crude mixture was diluted with 15 mL DCM and filtered through a celite pad. The solvent was evaporated and the crude oily mass was further purified *via* column chromatography (*n*-hexane/ethyl acetate, 4:1 (v/v)) yielding **3c** as light yellow paste (188.8 mg, 65.2%, 0.633 mmol). TLC (*n*-hexane/ethyl acetate, 4:1): R_f = 0.48; ^{1}H-NMR ($(CD_3)_2CO$): δ 7.35 (m, 1H, CH_{aryl}), 7.09 (dd, $^3J_{HH}$ = 7.4, 1.4 Hz, 2H, CH_{aryl}), 7.00 (dt, $^3J_{HH}$ = 8.1, 1.4 Hz, 1H, CH_{aryl}), 4.17 (q, $^3J_{HH}$ = 7.2 Hz, 1H, C*H*), 3.55 (s, 2H, C$H_{cluster}$), 3.06–1.61 (br, 9H, B*H*), 1.61 (d, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3) ppm; ^{11}B{^{1}H}-NMR ($(CD_3)_2CO$): δ 8.4 (s, 1B, *B*O), −8.3 (s, 2B, *B*H), −12.2 (s, 1B, *B*H), −14.8 (s, 2B, *B*H), −16.5 (s, 2B, *B*H), −19.8 (s, 1B, *B*H), −25.4 (s, 1B, *B*H) ppm; ^{11}B-NMR ($(CD_3)_2CO$): δ 8.4 (s, 1B, *B*O), −8.4 (d, J_{BH} = 161.6 Hz, 2B, *B*H), −12.3 (d, J_{BH} = 148.7 Hz, 1B, *B*H), −14.2 to −17.2 (br, 4B, *B*H), −19.9 (d, J_{BH} = 181.2 Hz, 1B, *B*H), −25.4 (d, J_{BH} = 182.3 Hz, 1B, *B*H) ppm; ^{13}C{^{1}H}-NMR ($(CD_3)_2CO$): δ 159.2 (*C*, C-3′), 139.5 (*C*, C-1′), 130.1 (*C*H, C-5′), 121.5 (*C*N, C-1), 120.4 (*C*H, C-6′), 119.5 (*C*H, C-4′), 118.7 (*C*H, C-2′), 50.7 (*C*H, C$H_{cluster}$), 30.4 (*C*H, C-2), 20.7 (*C*H_3, C-3) ppm; IR (ATR, cm^{-1}): 3059 (m-w, νCH, νCH_3), 2922 (s, ν$CH_{cluster}$), 2598 (s, νBH), 1587–1439 (m-w, νCC), 1273 (m, COB), 731 (m, νBB); HR-ESI-MS (positive mode, MeCN), *m/z* $[M+Na]^+$: calculated for $C_{11}H_{19}B_{10}NNaO$: 312.2367, found 312.2360; the observed isotopic pattern agreed with the calculated one. HPLC: t_R = 20.95 min; purity: 96.7% relative area (220 nm).

***rac*-2-[*O*-(1,7-Dicarba-*closo*-dodecaboran-9-yl)-phenyl]propionic acid (3d)**: A 50 mL round-bottom flask was charged with **3c** (114.9 mg, 0.39 mmol) and 19.5 mL of aqueous H_2SO_4 (40 vol%). The resulting oily suspension was heated with stirring for 20 h at 120 °C. The reaction was monitored by TLC (*n*-hexane/ ethyl acetate, 7:3 (v/v)). At the end of the reaction, a gray suspension was formed. After cooling to room temperature the mixture was poured onto ice-cold water for precipitation. The resulting suspension was transferred to a separatory funnel, and the crude product was extracted with diethyl ether (3×50 mL). The organic phases were collected and dried over Na_2SO_4. After filtration and evaporation, the crude product was obtained as a gray powder. Further purification of the crude product *via* column chromatography (*n*-hexane/ethyl acetate, 7:3 (v/v)) yielded **3d** as white powder (109.9 mg, 0.356 mmol, 91.4%); mp: 159–160 °C; TLC (*n*-hexane/ethyl acetate, 7:3 (v/v)): R_f = 0.29; ^{1}H-NMR ($(CD_3)_2CO$): δ 10.67 (s, 1H, COO*H*), 7.23 (t, $^3J_{HH}$ = 7.8 Hz, 1H, CH_{aryl}), 7.02 (d, $^3J_{HH}$ = 2.2 Hz, 1H, CH_{aryl}), 6.98 (d, $^3J_{HH}$ = 7.6 Hz, 1H, CH_{aryl}), 6.89 (dd, $^3J_{HH}$ = 8.2, 2.5 Hz, 1H, CH_{aryl}), 3.72 (q, $^3J_{HH}$ = 7.1 Hz, 1H, C*H*), 3.51 (s, 2H, C$H_{cluster}$), 3.04–1.83 (br, 9H, B*H*), 1.42 (d, $^3J_{HH}$ = 7.1 Hz, 3H, CH_3) ppm; ^{11}B{^{1}H}-NMR ($(CD_3)_2CO$): δ 8.5 (s, 1B, *B*O), −8.4 (s, 2B, *B*H), −12.3 (s, 1B, *B*H), −14.9 (s, 2B, *B*H), −16.6 (s, 2B, *B*H), −19.9 (s, 1B, *B*H), −25.5 (s, 1B, *B*H) ppm; ^{11}B-NMR ($(CD_3)_2CO$): δ 8.5 (s, 1B, *B*O), −8.4 (d, J_{BH} = 160.9 Hz, 2B, *B*H), −12.3 (d, J_{BH} = 148.2 Hz, 1B, *B*H), −14.2 to −17.3 (br, 4B, *B*H), −19.9 (d, J_{BH} = 183.3 Hz, 1B, *B*H), −25.5 (d, J_{BH} = 181.3 Hz, 1B, *B*H) ppm; ^{13}C{^{1}H}-NMR ($(CD_3)_2CO$): δ 174.5 (*C*OOH, C-1), 158.8 (*C*, C-3′), 142.8 (*C*, C-1′), 129.3 (*C*H, C-5′), 121.3 (*C*H, C-6′), 119.3 (*C*H, C-2′), 118.5 (*C*H, C-4′), 50.6 (*C*H, C$H_{cluster}$), 44.7 (*C*H, C-2), 18.2 (*C*H_3, C-3) ppm; IR (ATR, cm^{-1}): 3300–2500 (s, νb, νOH), 3052 (m-w, νCH, νCH_3), 2922 (s, ν$CH_{cluster}$), 2598 (s, νBH), 1702 (s, νCO), 1598–1445 (m-w, νCC), 1264 (m, COB), 741 (m, νBB); HR-ESI-MS (negative mode, MeCN), *m/z* $[M-H]^-$: calculated for $C_{11}H_{19}B_{10}O_3$: 307.2452, found 307.2340; the observed isotopic pattern agreed with the calculated one. HPLC: t_R = 16.80 min; purity: 98.8% relative area (254 nm). The structure was confirmed by X-ray structure analysis (see Supporting Information).

***rac*-2-[*O*-(1,12-Dicarba-*closo*-dodecaboran-2-yl)-phenyl]propionitrile (4c)**: Compound **4c** was synthesized following the procedure for **3c** but with a different Pd-catalyst–ligand–base system. Reagents: **4a** (1 mmol, 223 mg), K_3PO_4 (4.2 mmol, 889 mg), SPhos-Pd–G3 (5 mol%, 39.8 mg) and SPhos (5 mol%, 20.5 mg). The mixture was suspended in 3 mL dry 1,4-dioxane and **5** (2 mmol, 294.3 mg) was added *via* syringe. The resulting mixture was heated with stirring for 2 h at 80 °C. The workup and purification via column chromatography (*n*-hexane/ethyl acetate, 4:1 (v/v)) yielded **4c** (229 mg, 79%, 0.791 mmol) as a yellow oil; TLC (*n*-hexane/ethyl acetate, 4:1 (v/v)): R_f = 0.66; ^{1}H-NMR ($(CD_3)_2CO$): δ 7.40 (m, 1H, CH_{aryl}), 7.17 (m, 2H, CH_{aryl}), 7.08 (m, 1H, CH_{aryl}), 4.20 (q, $^3J_{HH}$ = 7.2 Hz, 1H, C*H*), 3.88 (s, 1H, C$H_{cluster}$), 3.39 (s, 1H, C$H_{cluster}$), 3.01–1.29 (br, 9H, B*H*), 1.62 (d, $^3J_{HH}$ = 7.3 Hz, 3H, CH_3) ppm; ^{11}B{^{1}H}-NMR ($(CD_3)_2CO$): δ 2.2 (s, 1B, *B*O), −14.8 (s, 2B, *B*H), −16.5 (s, 4B, *B*H), −17.8 (s, 2B, *B*H), −23.5 (s, 1B, *B*H) ppm; ^{11}B-NMR ($(CD_3)_2CO$): δ 2.2 (s, 1B, *B*O), −14.1 to −18.5 (br, 8B, *B*H), −23.5 (d, J_{BH} = 166.4 Hz, 1B, *B*H) ppm; ^{13}C{^{1}H}-NMR ($(CD_3)_2CO$): δ 158.1 (*C*, C-3′), 139.8 (*C*, C-1′), 130.3 (*C*H, C-5′), 121.4 (*C*N, C-1), 121.4 (*C*H, C-6′), 119.6 (*C*H, C-4′), 118.8 (*C*H, C-2′),

65.5 (*C*H, $CH_{cluster}$), 60.7 (*C*H, $CH_{cluster}$), 30.4 (*C*H, C-2), 20.7 (CH_3, C-3) ppm; IR (ATR, cm^{-1}): 3053 (m-w, νCH, νCH_3), 2920 (s, $\nu CH_{cluster}$), 2604 (s, νBH), 1588–1440 (m-w, νCC), 1276 (s, COB), 733 (m, νBB); HR-ESI-MS (positive mode, MeCN), *m/z* $[2\,M+Na]^+$: calculated for $(C_{11}H_{19}B_{10}NO)_2Na$: 601.4844, found 601.4860; the observed isotopic pattern agreed with the calculated one. HPLC: $t_R = 23.91$ min; purity: 97.9% relative area (220 nm).

***rac*-2-[*O*-(1,12-Dicarba-*closo*-dodecaboran-2-yl)-phenyl]propionic acid (4d)**: Compound **4d** was synthesized following the procedure for **3d**. **4c** (203 mg, 0.68 mmol) was suspended in 35 mL aqueous H_2SO_4 (40 vol%). The mixture was stirred at 120 °C for 3 days. The workup and purification of the crude product *via* column chromatography (*n*-hexane/ethyl acetate, 7:3 (v/v)) yielded **4d** as a white solid (150.4 mg, 0.488 mmol, 70%); mp: 90–91 °C; TLC (*n*-hexane/ethyl acetate, 7:3 (v/v)): $R_f = 0.45$; ^{1}H-NMR ($(CD_3)_2CO$): δ 10.66 (s, 1H, COO*H*), 7.29 (t, $^3J_{HH} = 7.9$ Hz, 1H, CH_{aryl}), 7.08 (dd, $^3J_{HH} =$ 12.0, 5.1 Hz, 2H, CH_{aryl}), 6.98 (dd, $^3J_{HH} = 8.1$, 2.3 Hz, 1H, CH_{aryl}), 3.83 (s, 1H, C$H_{cluster}$), 3.76 (q, $^3J_{HH} = 7.1$ Hz, 1H, C*H*), 3.35 (s, 1H, C$H_{cluster}$), 3.08–1.25 (br, 9H, B*H*), 1.44 (d, $^3J_{HH} = 7.1$ Hz, 3H, CH_3) ppm; ^{11}B{^{1}H}-NMR ($(CD_3)_2CO$): δ 2.3 (s, 1B, *B*O), −14.7 (s, 2B, *B*H), −16.5 (s, 4B, *B*H), −17.9 (s, 2B, *B*H), −23.6 (s, 1B, *B*H) ppm; ^{11}B-NMR ($(CD_3)_2CO$): δ 2.3 (s, 1B, *B*O), −14.1 to −18.5 (br, 8B, *B*H), −23.6 (d, $J_{BH} = 166.5$ Hz, 1B, *B*H) ppm; ^{13}C{^{1}H}-NMR ($(CD_3)_2CO$): δ 174.4 (*C*OOH, C-1), 157.8 (*C*, C-3′), 143.1 (*C*, C-1′), 129.6 (*C*H, C-5′), 122.2 (*C*H, C-6′), 119.3 (*C*H, C-2′), 118.6 (*C*H, C-4′), 66.1 (*C*H, $CH_{cluster}$), 62.0 (*C*H, $CH_{cluster}$), 44.7 (*C*H, C-2), 18.1 (CH_3, C-3) ppm; IR (ATR, cm^{-1}): 3300–2500 (s, vb, νOH), 3051 (m-w, νCH, νCH_3), 2987 (s, $\nu CH_{cluster}$), 2600 (s, νBH), 1700 (s, νCO), 1585–1447 (m-w, νCC), 1260 (m, COB), 718 (m, νBB); HR-ESI-MS (negative mode, MeCN), *m/z* $[M-H]^-$: calculated for $C_{11}H_{19}B_{10}O_3$: 307.2452, found 307.2340; the observed isotopic pattern agreed with the calculated one. HPLC: $t_R = 20.30$ min; purity: 98.9% relative area (254 nm). The structure was confirmed by X-ray structure analysis (see Supporting Information).

Biological evaluation

Evaluation for COX Inhibition: The COX inhibition activity against ovine COX-1 and human COX-2 was determined using the fluorescence-based COX assay *COX Fluorescent Inhibitor Screening Assay Kit* (Cayman Chemical Company, Ann Arbor, MI, USA) according to the manufacturer's instructions as previously reported by us.[16]

Determination of Lipophilicity: The $\log D_{7.4,\ HPLC}$ values (Table S5) were determined as previously reported by us[42] utilizing an HPLC method originally described by Donovan and Pescatore.[30] The following HPLC system was used: Agilent 1100 HPLC (binary pump G1312A, autosampler G1313A, column oven G1316A, degasser G1322A, UV detector G1314A, γ detector Gabi Star (Paytest); column ODP-50 4B (Shodex Asahipak 50×4.6 mm); eluent: MeOH/phosphate buffer (10 mM, pH = 7.4), gradient $t_{0\ min}$ 30/70 – $t_{25\ min}$ 95/5 – $t_{27\ min}$ 95/5 – $t_{28\ min}$ 30/70 – $t_{40\ min}$ 30/70, flow rate = 0.6 mL/min. Hydrocortisone ($t_R = 9.61$ min, $\log D_{7.4} = 1.46$) and triphenylene ($t_R = 28.44$ min, $\log D_{7.4} = 5.49$) served as references. Toluene served as control and $\log D_{7.4}$ was found to be 2.72 (literature $\log D_{7.4} = 2.72$[30]).

Evaluation of cytotoxicity

Materials and methods: RPMI 1640, fetal bovine serum (FBS) and 100×penicillin/streptomycin mixture were purchased from Capricorn Scientific (Germany). Crystal violet (CV), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), propidium iodide (PI), trypsin, and cell culture-grade dimethyl sulfoxide (DMSO) were obtained from Sigma Aldrich (St. Louis, MO, USA), annexin V-FITC from BD Pharmingen (San Diego, CA, USA), ApoStat from R&D Systems (Minneapolis, MN, USA), acridine orange (AO) from Labo-Moderna (Paris, France), carboxyfluorescein succinimidyl ester (CFSE) and dihydrohodamine 123 (DHR) from Invitrogen (Carlsbad, CA, USA).

Human lung carcinoma (A549), human melanoma (A375), human colorectal adenocarcinoma (HT29), human colorectal carcinoma (HCT116) and human breast adenocarcinoma cells (MCF7) were cultured in HEPES-buffered RPMI-1640 supplemented with 10% FBS, 100 U/mL penicillin and 100 μg/mL streptomycin (culture medium). Peritoneal macrophages were collected from BALB/c mice by peritoneal lavage with ice-cold PBS and cultivated in RPMI-1640 medium supplemented with 5% FBS and antibiotics. The handling of animals and protocol for obtaining cells was in agreement with the rules of the European Union and approved by the Institutional Animal Care and Use Committee and IBISS (no. 02-09/16). All cell cultures were maintained at 37 °C in a humidified atmosphere with 5% CO_2.

Stock solutions (200 mM) of fenoprofen and the racemic carborane analogues **3c**, **3d**, **4c** and **4d** were prepared in DMSO and stored at −20 °C for a month; working solutions were prepared in culture medium just before the treatment.

Cell growth assays: A549 (4×10^3/well), A375 (5×10^3/well), HT29 (15×10^3/well), HCT116 (5×10^3/well) and MCF7 (8×10^3/well) cells were seeded in 96-well plates, left to attach overnight and treated for 72 h with 0–200 μM dose range of fenoprofen and the racemic carborane analogues **3c**, **3d**, **4c** and **4d**. Cell viability was estimated by the MTT and CV tests, as described elsewhere.[43] Peritoneal exudate cells (18×10^3/well) were exposed to **3c** and **4c** under the same experimental conditions. The formula published in Mijatovic *et al.* was used for the calculation of IC_{50} value.[44]

Flow cytometry analysis: For flow cytometry analysis, MCF7 cells were seeded in 6-well plates at 1.5×10^4/well density and treated with IC_{50} doses of **3c** (40 μM) and **4c** (70 μM) for the indicated period of time. Cells were stained with AnnexinV-FITC/PI for early and late apoptosis detection, ApoStat for detection of activated caspases, CFSE for estimation of cell proliferation rate, acridine orange (AO) for detection of treatment-induced autophagosomes, and DHR for detection of intracellular accumulation of reactive oxygen and nitrogen species (ROS/RNS), following previously published protocols.[45] For analysis of cell distribution within cell-cycle phases, tumor cells were collected at the end of the treatment, fixed in ice-cold 70% ethanol at 4 °C overnight, washed twice in PBS and incubated with PI (20 μg/mL) and RNase A (0.1 mg/mL) for 40 min at 37 °C in the dark. Flow cytometry analysis was performed with CyFlow® Space Partec flow cytometer (Sysmex) and data were analyzed with the FlowJo software (Tree Star).

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Carborane · cancer · COX inhibitors · drug design · fenoprofen

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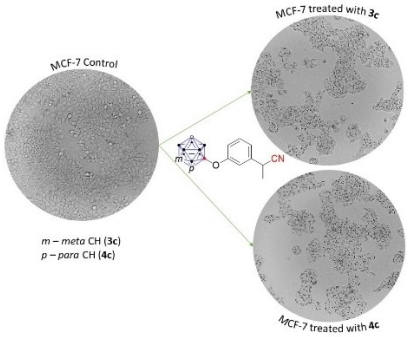
RESEARCH ARTICLE

The carborane analogues of fenoprofen bearing a nitrile (**3 c** and **4 c**) or carboxylic acid group (**3 d** and **4 d**) show superior antitumor activity compared to fenoprofen. Their antitumor action is realized through inhibition of proliferation and caspase-independent apoptosis. Furthermore, they were equally efficient in COX-2 non-expressing cells, indicating the existence of potential off-targets inside the cells.



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