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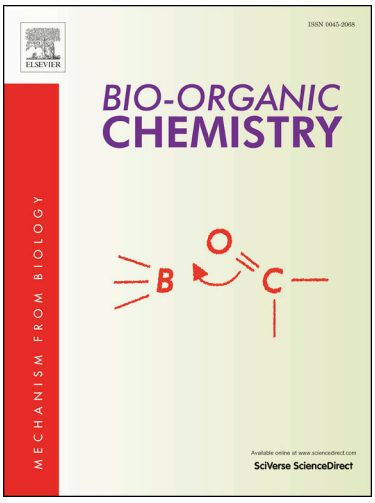


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# Antiproliferative activity of cycloalkanecarboxamide derivatives possessing sulfonate or sulfamate moiety

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## Abstract

A series of cycloalkanecarboxamide-containing sulfonate and sulfamate derivatives were prepared, and their antiproliferative activity was tested against NCI-60 cancer cell lines panel. Compound **1f** possessing cyclohexyl and *p*-(*tert*-butyl)benzenesulfonate moieties was the most active among all the target compounds. It exerted broad-spectrum anticancer activity against all the nine cancer types involved in the NCI-60 panel. Additionally, compound **1g** containing cyclohexyl and *p*-fluorobenzenesulfonate moieties was the most potent against HT29 colon cancer cell line ($IC_{50}$ = 4.73 μM) with selectivity index more than 4.23 towards HT29 than normal fibroblasts. It exerts its antiproliferative activity against HT29 through the induction of

apoptosis (increasing caspase 3/7 activity) but not necrosis. Structure-activity relationship studies are presented in detail.

*Keywords: Anticancer; Antiproliferative; Apoptosis; Sulfamate; Sulfonate.*

## 1. Introduction

Cancer usually originates from cells that transform and lose control of cell growth and division into unrestrained aggressive behavior with the ability to invade surrounding tissues. This transformation is linked to changes and mutations in the genetic material caused by different intrinsic or extrinsic mutagens [1]. Cancer is classified as the second cause of death after heart disease internationally. The World Health Organization (WHO) reported that cancer caused 9.6 million deaths in 2018. One in each six death cases worldwide occur due to cancer [2]. Consequently, it is one of the most serious diseases that required urgent development of more efficient and selective anticancer agents.

Several sulfonate and sulfamate derivatives have been reported as antiproliferative agents [3-12]. Examples of them are illustrated in Figure 1. We have previously reported a series of cycloalkanecarboxamide-possessing sulfonate and sulfamate derivatives as inhibitors of steroid sulfatase or nucleotide pyrophosphatase enzymes (Figure 1) [13, 14]. In this article, we report the cell-based antiproliferative activity of the target compounds **1a-z** against NCI-60 tumor cell lines of 9 types of cancer [15]. The most active compounds were tested for potency against cancer and normal cell lines to investigate their selectivity indexes.

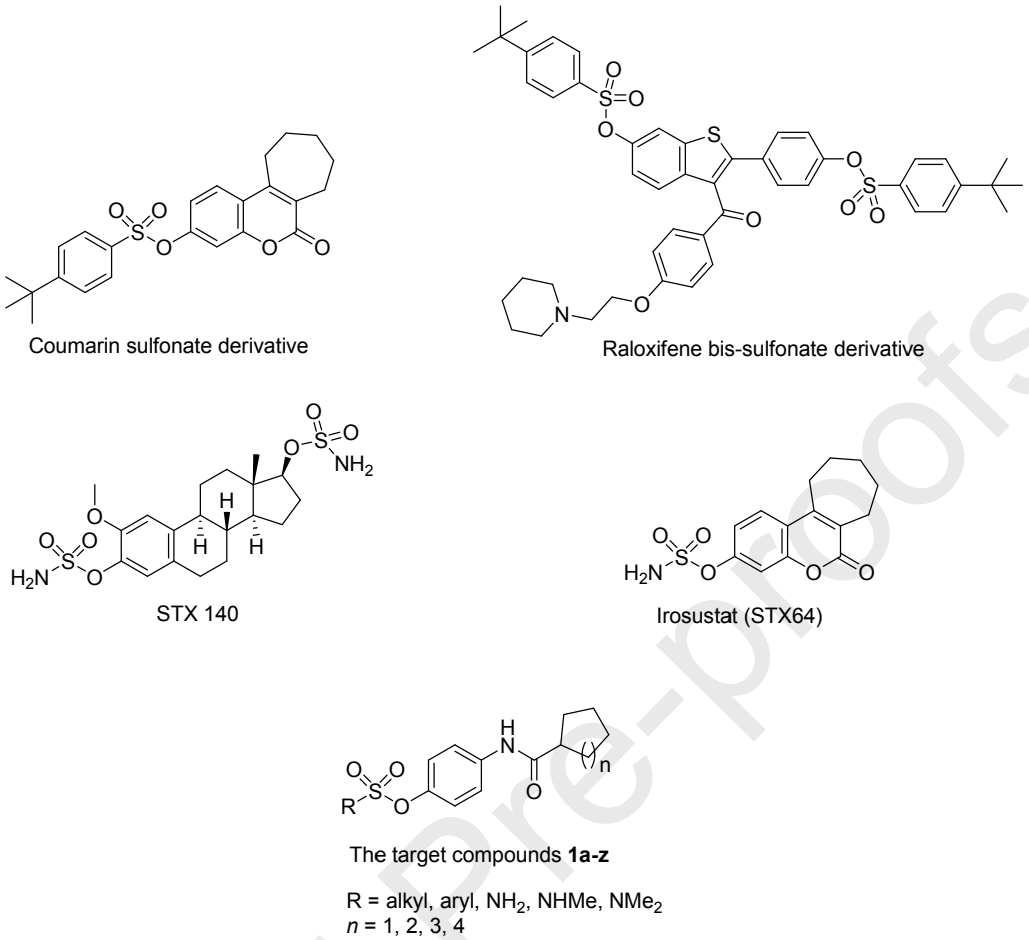


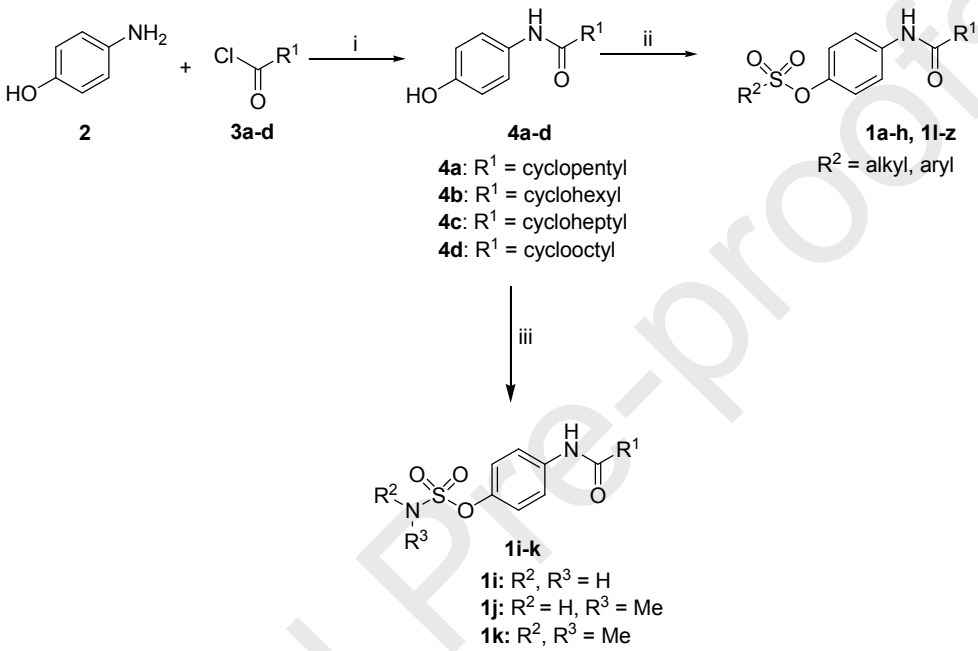

**Figure 1.** Structures of reported antiproliferative sulfonate or sulfamate derivatives and the target compounds **1a-z**.

## 2. Results and discussion

### *2.1. Chemical synthesis*

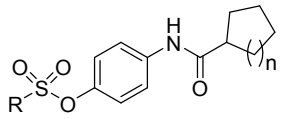
The final compounds **1a-z** were prepared via the 2-step synthetic pathway shown in Scheme 1. The reaction of 4-aminophenol (**2**) with the appropriate cycloalkanecarbonyl chloride **3a-d** produced the relevant phenolic intermediates **4a-d**. In order to avoid diacylation and retain the OH group free, the acid chloride was diluted in acetone and added slowly to a mixture of 4-aminophenol and potassium carbonate in acetone while swirling. Sulfonate derivatives **1a-h** and **1l-z** were synthesized through the reaction of the phenolic compounds **4a-d** with appropriate

sulfonyl chloride reagents in the presence of triethylamine. Furthermore, sulfamate derivatives **1i-k** were obtained through the interaction of **4b** with the appropriate (substituted) sulfamoyl chloride using NaH. All the final compounds were purified by flash column chromatography and were characterized by spectral analysis. Table 1 illustrates the target compounds' structures.




**Scheme 1.** (i) anhydrous $K_2CO_3$, acetone, 0 ºC, rt, 4 h, 65-80%; (ii) appropriate sulfonyl chloride derivative, $Et_3N$, anhydrous THF, 0 ºC, rt, 2 h, 43-91%; (iii) (substituted) sulfamoyl chloride, NaH, anhydrous, DMF, 0 ºC, rt, overnight, 83-90%.

**Table 1.** Structures of the target compound **1a-z**.



| Compound No. | *n* | R |
|---|---|---|
| **1a** | 2 | Me |
| **1b** | 2 | Et |
| **1c** | 2 | *n*-Pr |
| **1d** | 2 | Ph |
| **1e** | 2 | 4-Me($C_6H_4$) |
| **1f** | 2 | 4-*tert*-butyl($C_6H_4$) |
| **1g** | 2 | 4-F($C_6H_4$) |
| **1h** | 2 | 4-$CF_3$($C_6H_4$) |
| **1i** | 2 | $NH_2$ |
| **1j** | 2 | NHMe |
| **1k** | 2 | $NMe_2$ |
| **1l** | 1 | Ph |
| **1m** | 1 | 4-Me($C_6H_4$) |
| **1n** | 1 | 4-*tert*-butyl($C_6H_4$) |
| **1o** | 1 | 4-F($C_6H_4$) |
| **1p** | 1 | 4-$CF_3$($C_6H_4$) |
| **1q** | 3 | Ph |
| **1r** | 3 | 4-Me($C_6H_4$) |
| **1s** | 3 | 4-*tert*-butyl($C_6H_4$) |
| **1t** | 3 | 4-F($C_6H_4$) |
| **1u** | 3 | 4-$CF_3$($C_6H_4$) |
| **1v** | 4 | Ph |
| **1w** | 4 | 4-Me($C_6H_4$) |
| **1x** | 4 | 4-*tert*-butyl($C_6H_4$) |

| | | |
|---|---|---|
| **1y** | 4 | 4-F($C_6H_4$) |
| **1z** | 4 | 4-$CF_3$($C_6H_4$) |

*2.2. Structure-activity relationship*

In the beginning, we synthesized the cyclohexyl analogues **1a-k** and tested the compounds selected by the National Cancer Institute (NCI, Bethesda, Maryland, USA) against the NCI-60 cancer cell line panel of nine different cancer types [15]. The mean inhibition percentages of each tested compound against the whole panel are shown in Figure 2. It is obvious that the aryl sulfonate derivatives **1d-h** are more active than the alkyl sulfonates **1b,c** and the sulfamate derivatives **1i-k**. As the aryl derivatives are more hydrophobic than alkyl or (substituted)amino, it could be hypothesized that the aryl sulfonates could be more able to cross the cell membrane and produce stronger antiproliferative effects due to higher cellular exposure to the compound. Furthermore, the aryl rings might form stronger hydrophobic interaction with the receptor site(s) such as nucleotide pyrophosphatases (NPP1 and NPP3) [14]. Any or both of these two explanations could rationalize the stronger activity of aryl sulfonates than alkyl sulfonates or sulfamate analogues.

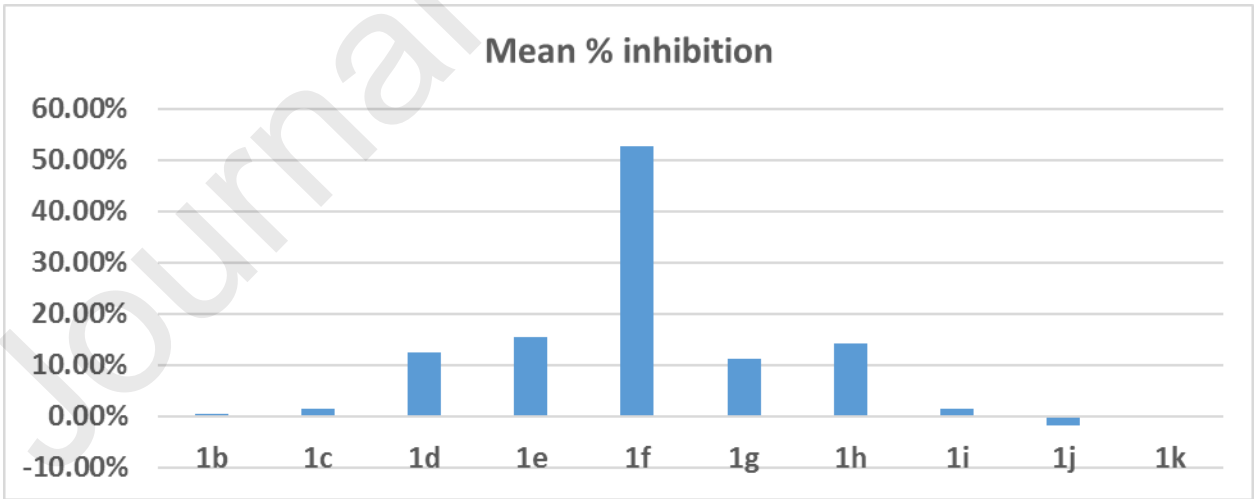



**Figure 2.** Mean % inhibition values of compounds **1b-k** over the NCI-60 cell line panel at a single-dose concentration of 10 μM. They were calculated by dividing the summation of % inhibition values over the number of tested cell lines.

The inhibitory effects of compounds **1d-h** against each single cell line of the NCI-60 panel are illustrated in Figure 3. Compounds **1d**, **1e**, and **1g** demonstrated the highest activity against HT29 colon cancer cell line. Among them, compound **1e** possessing *p*-toluenesulfonate moiety was the most active (% inhibition = 87.0%). Compound **1f** containing *p*-(*tert*-butyl)benzenesulfonate exerted broad-spectrum anticancer activity against all the nine subpanels. Its highest inhibitory effect was against T-47D breast cancer cell line and RPMI-8226 leukemia cell line (% inhibition values are 99.1% and 86.38%, respectively). The *tert*-butyl group is bulkier and more hydrophobic than the other substituents in the other arylsulfonate derivatives, so it might enhance the activity by its hydrophobicity and/or steric effect(s). Compound **1h** possessing *p*-(trifluoromethyl)benzenesulfonate moiety exerted selectivity towards the CNS cancer subpanel compared to its results against the cell lines of the other eight cancer types.

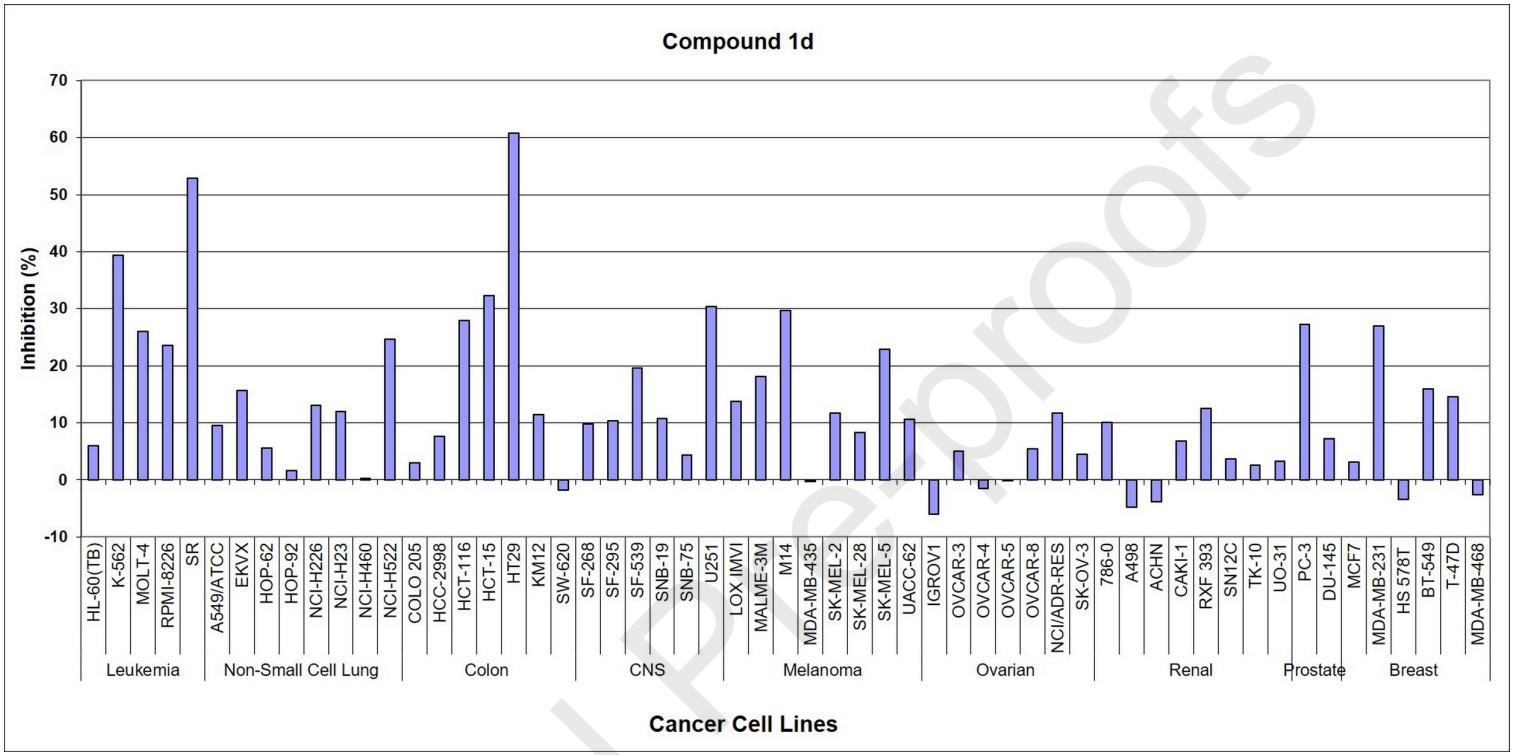



Figure 3a

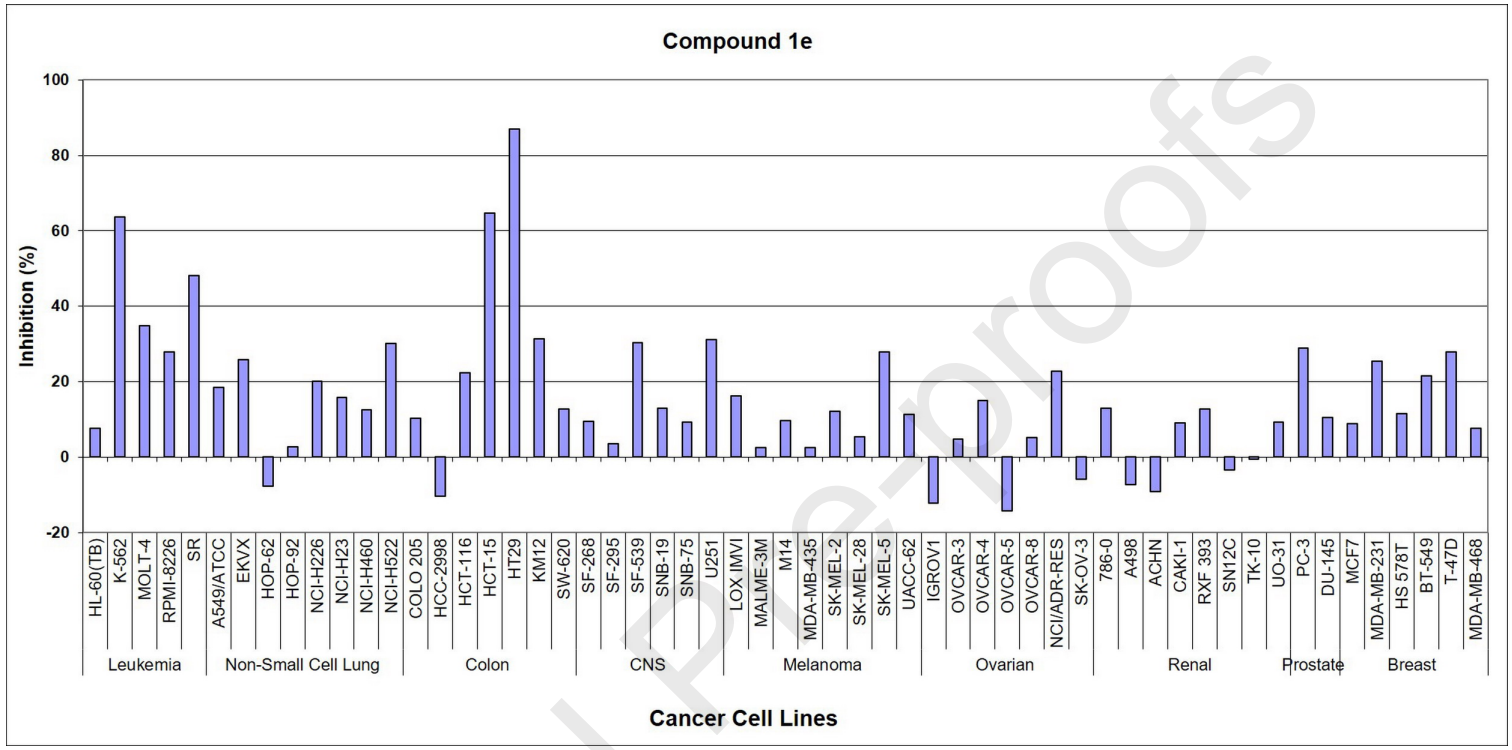



Figure 3b

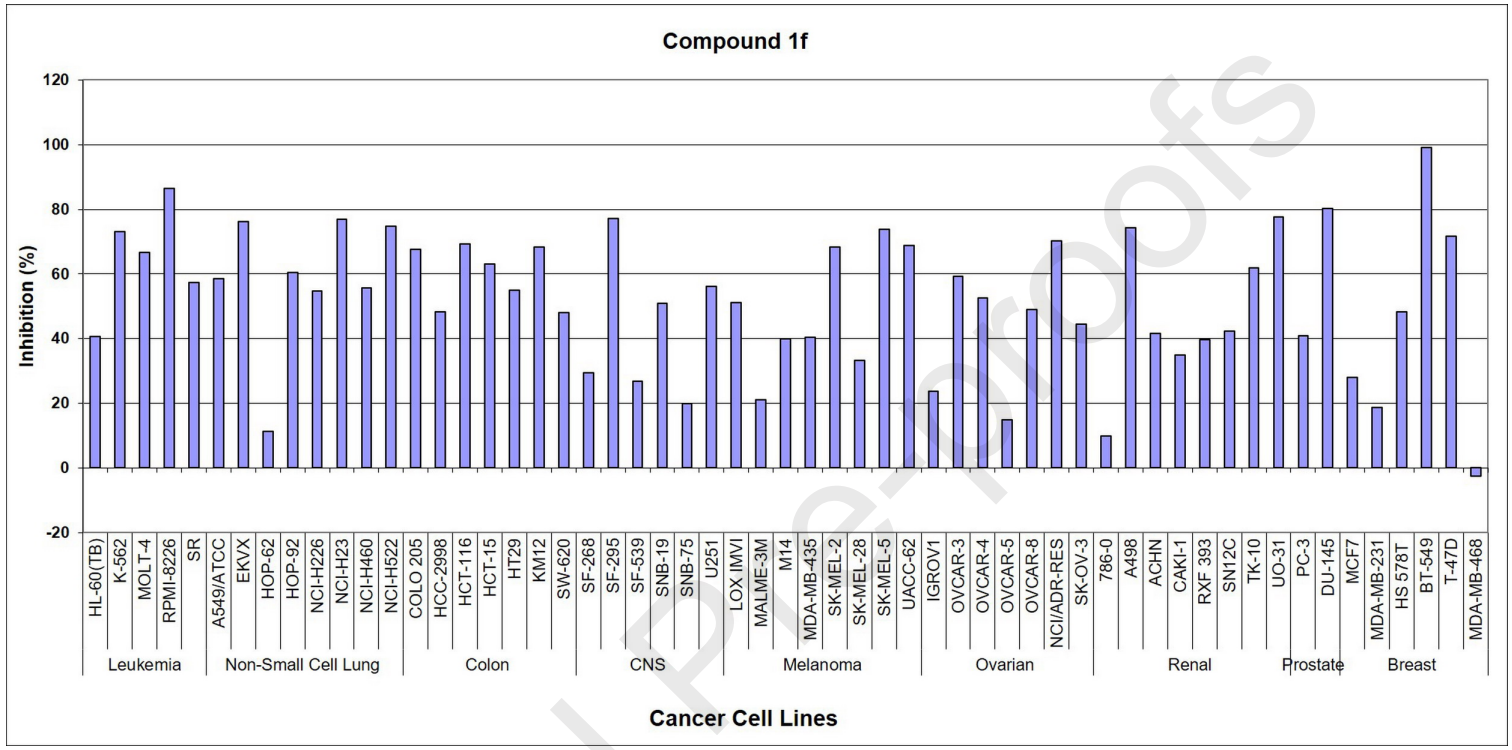



Figure 3c

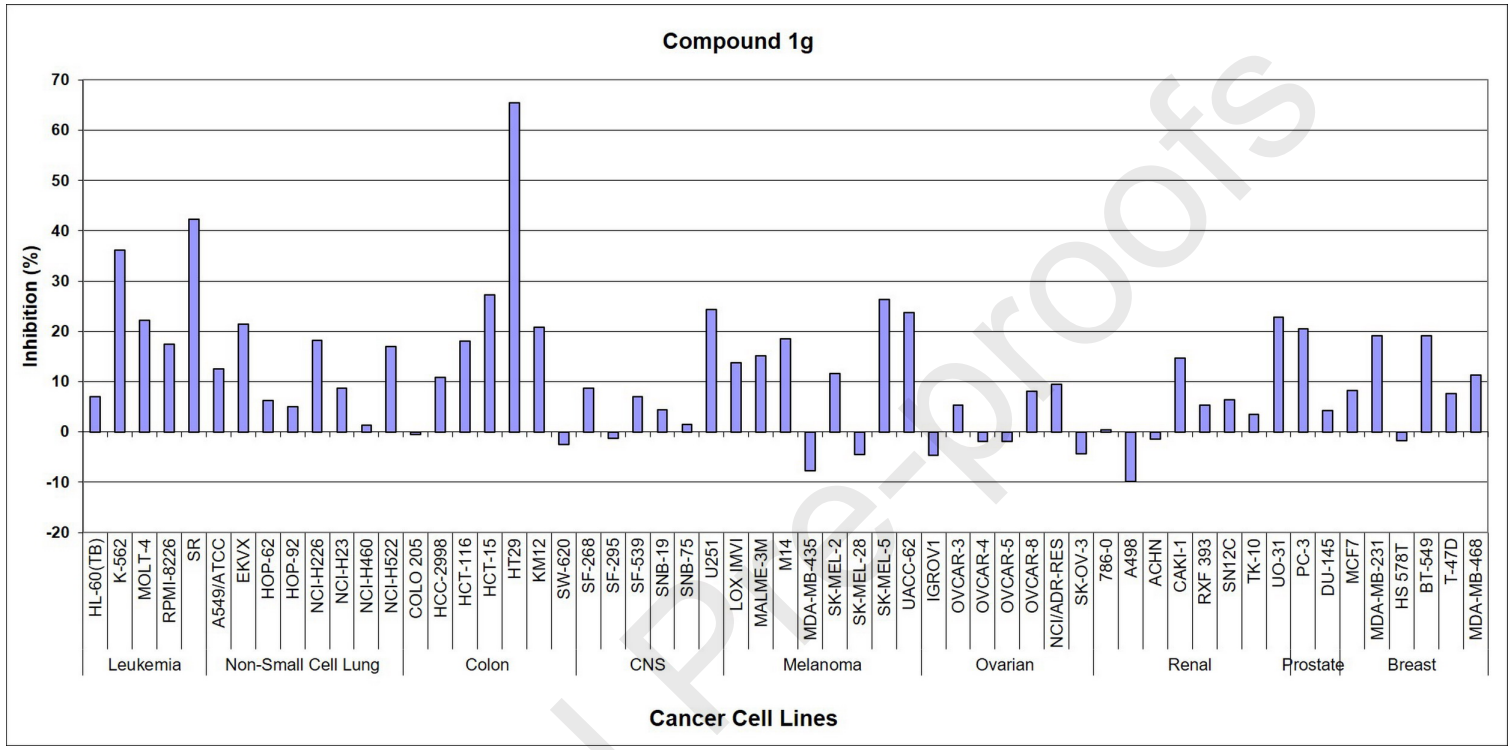



Figure 3d

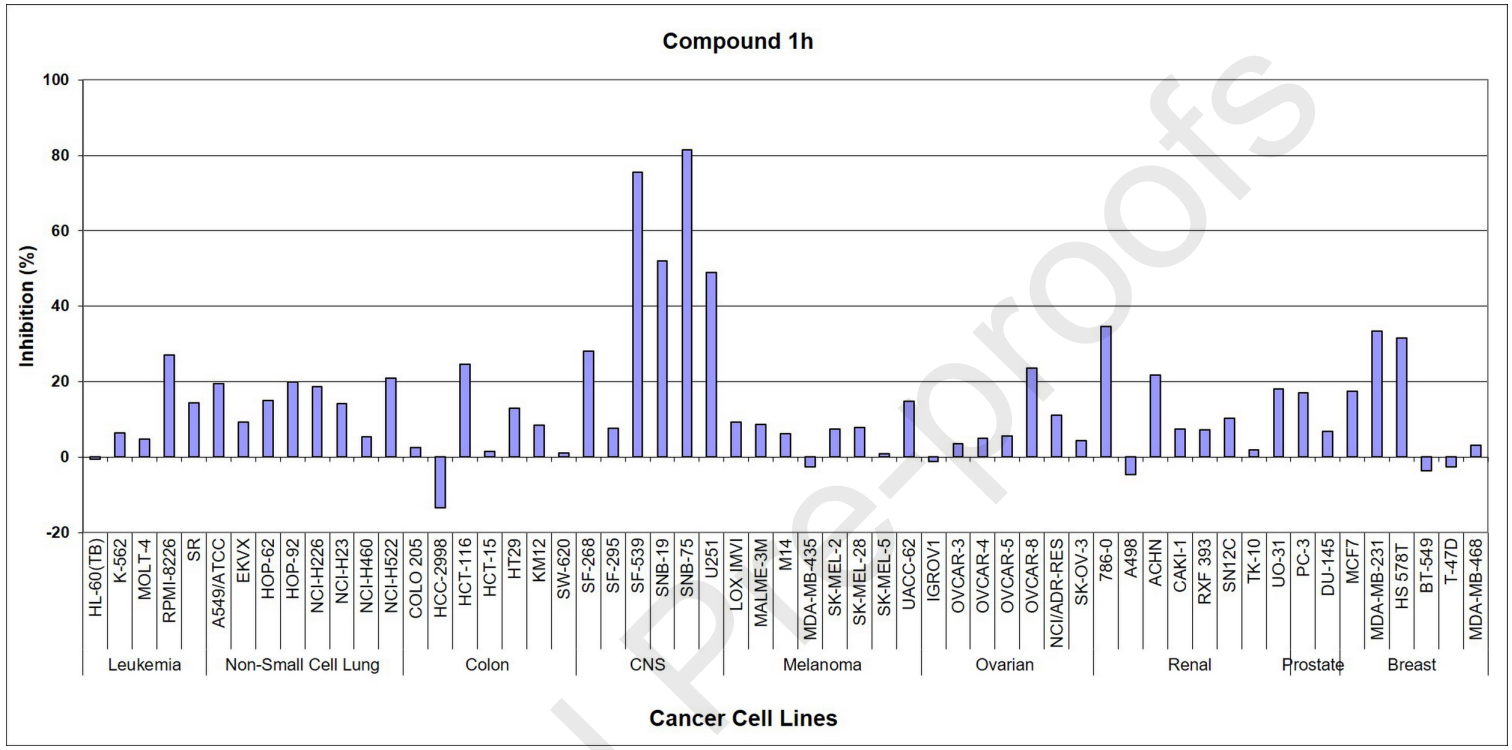



Figure 3e

**Figure 3.** % inhibition values of compounds **1d** (Fig. 3a), **1e** (Fig. 3b), **1f** (Fig. 3c), **1g** (Fig. 3d), and **1h** (Fig. 3e) against the NCI-60 cancer cell lines.

After that, we decided to focus on the aryl sulfonate derivatives only as they were more promising than the corresponding alkyl sulfonates and sulfamates. The cyclohexyl ring of compounds **1d-h** was replaced with smaller (cyclopentyl ring, compounds **1l-p**) or expanded (cycloheptyl derivatives **1q-u** and cyclooctyl **1v-z**) rings. These derivatives that were accepted by the NCI were tested over the NCI-60 panel also, and the effect of ring size on activity was investigated. The mean % inhibition values of the target compounds with different ring sizes are depicted in Figure 4. The effect of cycloalkane ring size on activity was found to be parabolic. Increasing the ring size from cyclopentyl to cyclohexyl increased the activity, but further ring expansion to cycloheptyl or cyclooctyl was detrimental to the activity.

It was also noticeable that the *tert*-butylbenzenesulfonate analogues **1s** and **1x** were more active than the corresponding analogues possessing the same cycloalkyl ring size and different terminal aryl moieties. This finding is similar to the results of compound **1f** upon comparison with the other cyclohexyl analogues.

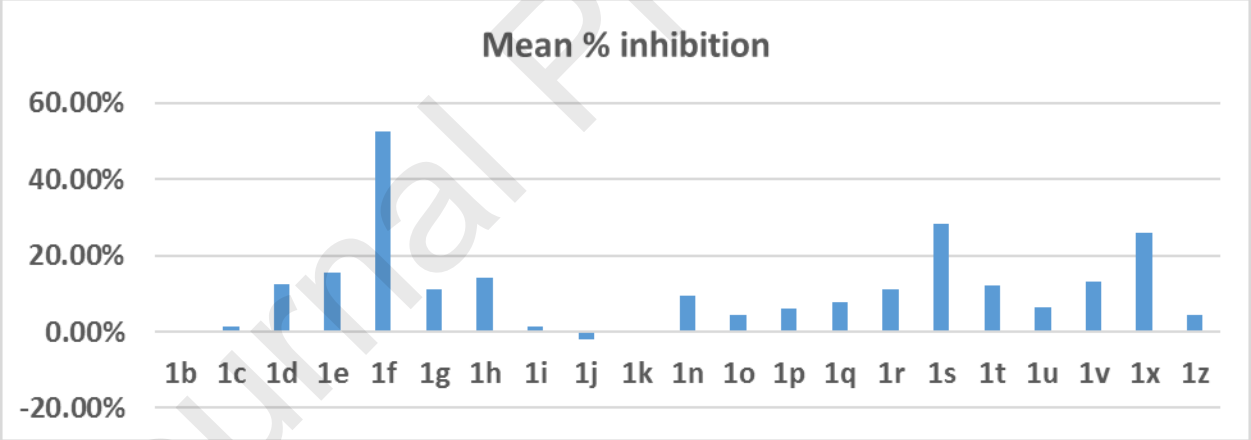



**Figure 4.** Comparison of mean % inhibition values of all the tested compounds. Data of compounds **1b-k** are taken from Figure 2.

The most active compounds **1d-h** were further tested in 5-dose testing mode by MTT assay against A-549 lung cancer, HT29 colorectal cancer, and MCF7 breast cancer cells in order to investigate their potency. We have followed the protocol reported in the literature [5]. They

were also tested against fibroblasts to study the selectivity indexes of these compounds against cancer cells compared to normal cells. The results are summarized in Table 2. Among the five tested compounds, compound **1f** was the most potent against MCF7 breast cancer cell line. Its selectivity towards cancer cells than fibroblasts is higher than that of doxorubicin. In addition, compound **1g** possessing *p*-fluorobenzenesulfonate was the most potent against HT29 colon cancer cell line. It was more selective against it than fibroblasts and even than the other two tested cancer cell lines. Its selectivity index is more than 2.6 times the selectivity index of doxorubicin.

**Table 2.** Potency and selectivity indexes of compounds **1d-h** against three cancer cell lines compared to doxorubicin. [a]

| Compound No. | $IC_{50}$ (µM) | | | | Selectivity Index (HT29) | Selectivity Index (A549) | Selectivity Index (MCF7) |
|---|---|---|---|---|---|---|---|
| | HT29 | A549 | MCF7 | Fibroblasts | | | |
| **1d** | **8.11** | **>20** | **>20** | **>20** | **>2.47** | **-** | **-** |
| **1e** | **5.45** | **>20** | **>20** | **9.21** | **1.69** | **-** | **-** |
| **1f** | **9.71** | **9.32** | **7.25** | **16.42** | **1.69** | **1.76** | **2.26** |
| **1g** | **4.73** | **>20** | **>20** | **>20** | **>4.22** | **-** | **-** |
| **1h** | **13.64** | **15.91** | **>20** | **14.83** | **1.09** | **0.93** | **-** |
| **Doxorubicin** | **1.20** | **1.32** | **0.94** | **1.94** | **1.62** | **1.47** | **1.72** |

[a] The selectivity indexes were calculated by dividing the $IC_{50}$ value against fibroblasts by the $IC_{50}$ value against the cancer cell line (n=6).

Furthermore, compound **1g** was further tested for the induction of apoptosis and necrosis over HT29 colon cancer cells. It was tested at 5 µM and 10 µM concentrations in caspase-3/7 and lactate dehydrogenase (LDH) release assays in order to investigate its ability to induce

apoptosis and necrosis, respectively. In caspase-3/7 apoptosis assay, compound **1g** increased caspases activity by 68% and 123% at 5 µM and 10 µM concentrations, respectively, compared to untreated cells (Figure 5). On the other hand, the compound was unable to cause LDH release at both of the tested concentrations. So it can be concluded that compound **1g** could exert its antiproliferative activity against HT29 cells through induction of apoptosis but not necrosis.

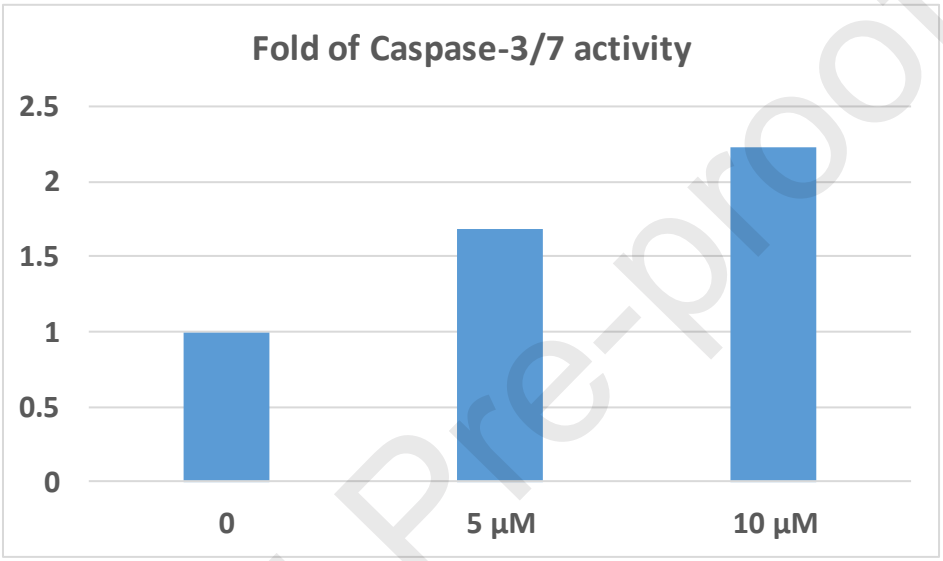



**Figure 5.** Caspase-3/7 activity after treatment of HT29 cells with compound **1g** (5 µM or 10 µM).

It is noteworthy that compounds **1f-h** exerted potential inhibitory activity against NPPs [14] but showed weak inhibitory effect against steroid sulfatase (STS) [13]. Compound **1f** showed selectivity towards NPP3 ($IC_{50}$ = 0.807 µM) than NPP1 and NPP2. Compound **1g** is a dual inhibitor of NPP1 and NPP3 ($IC_{50}$ values are 0.564 µM and 0.254 µM, respectively). In addition, compound **1h** is more selective against NPP1 ($IC_{50}$ = 0.387 µM) than NPP2 and NPP3 [14]. These inhibitory effects against NPPs could be, at least partially, a potential molecular mechanism of anticancer activity of compounds **1f-h**.

## 3. Conclusion

In conclusion, structure-activity relationship studies of this series of compounds showed that cyclohexanecarboxamide and aryl sulfonate moieties are optimal for anticancer activity. Compound **1f** showed a broad-spectrum activity over the NCI-60 panel, and this could be affected, at least in part, by its inhibition of NPP3 enzyme. Moreover, compound **1g** demonstrated high potency and selectivity towards HT29 colon cancer cell line than normal fibroblasts. Its antiproliferative activity could be induced by its ability to enhance caspase-3/7 activity and inhibition of NPP1/3 enzymes. Its selectivity index was more than 2.6 times higher than that of doxorubicin. So this work could be a step towards the development of safer anticancer agents.

## 4. Experimental

### 4.1. *Synthesis of compounds **4a-d** [13, 14]*

4-Aminophenol (100 mg, 0.916 mmol) was dissolved in acetone (15 mL), and anhydrous $K_2CO_3$ (152 mg, 1.1 mmol) was added to the solution. The mixture was stirred at ambient temperature for 15 min, and then cooled to 0 °C. Relevant cycloalkanecarbonyl chloride (0.833 mmol) was dissolved in acetone (10 mL), and the solution added dropwise to the reaction mixture at 0 °C with continuous stirring. The reaction temperature was then raised to room temperature, and stirring was continued for 4 h. The mixture was filtered, and the filtered solid was washed with acetone (2 x 10 mL). The combined filtrate and wash were completely evaporated. The remained residue was dissolved in ethyl acetate (10 mL) and extracted with dilute aqueous hydrochloric acid. The organic layer was then washed with saturated saline solution (2 x 10 mL), and dried using anhydrous $Na_2SO_4$. The organic solvent was evaporated under reduced pressure to get the title compounds. They were used in the next steps as such without further purification.

### 4.2. *General method for synthesis of the target sulfonate derivatives **1a-h** and **1l-z** [13, 14]*

Compound **4a-d** (0.456 mmol) was dissolved in dry THF (10 mL) was cooled to 0 °C, and triethylamine (0.25 mL, 2.47 mmol) was added thereto. The appropriate sulfonyl chloride (0.90 mmol) was dissolved in dry THF (3 mL), and the solution was added dropwise to the reaction mixture at 0 °C. The reaction mixture was stirred at ambient temperature for 2 h. The mixture was quenched with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were washed with saturated saline (3 x 10 mL), and dried over anhydrous sodium sulfate. The organic solvent was evaporated under reduced pressure, and the crude residue was purified by normal phase column chromatography (silica gel, an appropriate ratio of hexane : ethyl acetate) to isolate pure product. The yield percentages and the spectral data are provided in the supplementary file.

### 4.3. *General method for synthesis of the target sulfamate derivatives **1i-k** [13]*

Compound **4b** (100 mg, 0.456 mmol) was dissolved in dry DMF (10 mL) and cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 18.2 mg, 0.456 mmol) was added to the reaction mixture under inert atmosphere. The appropriate sulfamoyl chloride (2.0 mmol) was dissolved in dry DMF (3 mL), and the resultant solution was added dropwise to the reaction mixture at 0 °C. The reaction mixture was stirred at ambient temperature overnight. The mixture was quenched with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic extract was washed with saline (3 x 10 mL), and dried over anhydrous sodium sulfate. Ethyl acetate was evaporated under reduced pressure, and the remained crude residue was purified by column chromatography (silica gel, an appropriate ratio of hexane: ethyl acetate) to isolate pure product. The yield percentages and the spectral data are provided in the supplementary file.

### 4.4. *NCI-60 screening protocol*

It was carried out as per the standard protocol of the NCI [15].

### 4.5. *MTT assay protocol [5]*

MTT assay was carried out to assess the effect of the synthesized compounds on cell viability and to determine the half-maximal inhibitory concentration ($IC_{50}$) of each compound as mentioned before with few modifications. A549, HT-29, MCF7, or fibroblast cells were seeded in 96-well tissue culture plates with a density of $4 \times 10^4$/well and incubated overnight. After that, the cells were treated with the newly synthesized compounds or doxorubicin as a positive control for 48 h. DMSO was used as a negative control. After treatment, the media was removed and the cells were incubated for 2 h at 37 $^oC$ with 200 µL media containing 0.5 mg/mL of MTT tetrazolium dye (Sigma-Aldrich). At last, the media were removed and 200 µL of DMSO was added to solubilize the formed violet crystals. Absorbance was measured at 570 nm using a microplate reader (Thermo Scientific, Massachusetts, USA).

### 4.6. *Caspase-3/7 apoptosis assay protocol*

Compound **1g** was dissolved in DMSO at 10 mM stock. Caspase-Glo 3/7 assay reagent was purchased from Promega (Madison, WI). HT29 cells were grown in RPMI-1640 medium supplemented with 10% FBS. 100 µg/mL penicillin and 100 µg/mL streptomycin were added to the culture medium. Cultures were maintained at 37 °C in a humidified atmosphere of 5% $CO_2$ and 95% air. 5 µM and 10 µM concentrations of compound **1g** were prepared. 250 nL of compound **1g** was delivered from the source plate to each well of a cell culture 384-well plate by Echo 550. 25 µL of culture medium containing 5000 of HT29 cells was added to the wells of the cell culture plate. The cells were incubated with the compound at 37 °C in presence of 5% $CO_2$ for 24 hours. 25 µL of Caspase-Glo 3/7 assay reagent was added to each well and incubated at 37 °C, 5% $CO_2$ for 1 hour. Luminescence of each sample well on the plate was measured by Envision 2104 Multilabel Reader (PerkinElmer, Santa Clara, CA).

### *4.7. LDH release assay*

Compound **1g** was dissolved in DMSO at 10 mM stock. Pierce LDH cytotoxicity assay kit was purchased from Thermo Scientific. HT29 cells were grown in RPMI-1640 medium

supplemented with 10% FBS. 100 µg/mL penicillin and 100 µg/mL streptomycin were added to the culture medium. Cultures were maintained at 37 °C in a humidified atmosphere of 5% $CO_2$ and 95% air. 20000 of HT29 cells in 90 µL of 1% FBS culture media in duplicates were seeded in the wells of a 96-well plate in an incubator at 37 °C, 5% $CO_2$ for overnight incubation. 5 µM and 10 µM concentrations of compound **1g** were added to the wells containing cells and incubated at 37 °C, 5% $CO_2$ for 3 hours. 10 µL of 10x lysis buffer was added to duplicate wells containing cells and incubated at 37 °C, 5% $CO_2$ for 45 minutes as a positive control. 50 µL of each sample medium was transferred to a 96-well flat-bottom plate in duplicate wells. 50 µL of the reaction mixture was transferred to each sample well and mixed by gentle shaking. The plate was incubated at room temperature for 30 minutes protected from light. The absorbance at 492 nm was measured immediately using an Envision 2104 Multilabel Reader (PerkinElmer, Santa Clara, CA).

The LDH release (%) was calculated using the formula below:

LDH release (%) = (Compound treated sample LDH activity-DMSO treated sample LDH activity) x 100/(Lysis buffer treated sample LDH activity- DMSO treated sample LDH activity)

**Acknowledgment**

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**Supplementary file**

The experimental procedures, charts of the NCI results, and representative spectral charts are available at

*Declaration of interest: None.*

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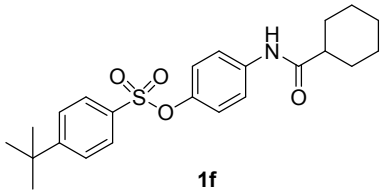
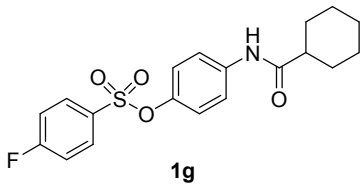


**1f**

Broad-spectrum antiproliferative activity



**1g**

High selectivity toward HT29 than fibroblasts

► Antiproliferative activity of a series of cycloalkanecarboxamides is reported.

► Compound **1f** is the most active with broad-spectrum antiproliferative activity.

► Compound **1g** is the most potent against HT29 colon cancer cell line ($IC_{50}$ = 4.73 μM).

► Compound **1g** is 4.23 times more selective toward HT29 than normal fibroblasts.

► Compound **1g** induces apoptosis in HT29 colon cancer cell line.

Declaration of interest: None.