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Synthesis and evaluation of antiproliferative activity of substituted N-(9-oxo-*9H*-xanthen-4-yl)benzenesulfonamides

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Abstract

Several novel *N*-(9-oxo-*9H*-xanthen-4-yl)benzenesulfonamides derivatives were prepared as potential antiproliferative agents. The *in vitro* antiproliferative activity of the synthesized compounds was investigated against a panel of tumor cell lines including breast cancer cell lines (MDA-MB-231, T-47D) and neuroblastoma cell line (SK-N-MC) using MTT colorimetric assay. Etoposide, a well-known anticancer drug, was used as a positive standard drug. Among synthesized compounds, 4-methoxy-*N*-(9-oxo-*9H*-xanthen-4-yl)benzenesulfonamide **(5i)** showed the highest antiproliferative activity against MDA-MB-231, T-47D, and SK-N-MC cells. Furthermore, pentafluoro derivatives **5a** and **6a** exhibited higher antiproliferative activity than doxorubicin against human leukemia cell line (CCRF-CEM) and breast adenocarcinoma (MDA-MB-468) cells. Structure-activity relationship studies revealed that xanthone benzenesulfonamide hybrid compounds can be used for development of new lead anticancer agents.

Keywords

Antiproliferative Activity; Benzenesulfonamides; Cancer; Xanthone

Cancer is known as one of the leading causes of mortality throughout the world, a disease characterized by uncontrolled cell growth, metastasis, and invasion. Inhibition of cancer cell proliferation is one of the most important principles in the treatment of cancer using anticancer compounds. The difficulty to diagnose the disease at the earlier stages, narrow

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Supplementary Material
Supplementary data associated with this article can be found, in the online version.

therapeutic indices of chemotherapeutic agents, and the development of multidrug resistance are some of the major obstacles, which has made cancer treatment challenging and caused high mortality rate worldwide.[1,2]

Among different classes of chemotherapeutic agents, compounds that act by DNA intercalation, such as the 9-anilinoacridine amsacrine and the xanthone derivative dimethylxanthenone-4-acetic acid (DMXAA) have attracted particular attention, due to their high therapeutic potential. The data for xanthone binding studies with DNA indicate that the planar tricycle moiety serves as an important feature for designing new DNA intercalators.[3–6]

In addition, sulfonamide derivatives have been found to possess potent anticancer activities through a variety of mechanisms such as cell cycle perturbation in the G1 phase, disruption of microtubule assembly, angiogenesis inhibition, and functional suppression of the transcriptional activator NF-Y.[7–9] Based on the diverse biological activities of the xanthones and aryl sulfonamides, we designed and synthesized a series of novel hybrid compounds containing both xanthone and sulfonamide entities in one molecule and evaluated them for their antiproliferative activity.

The general procedure for the synthesis of substituted *N*-(9-oxo-*9H*-xanthen-4-yl) benzenesulfonamide **5a–i** and **6a–g** is depicted in Scheme 1. 2-(2-Nitrophenoxy)benzoic acid (**1**) was prepared according to the previously reported method.[10,11] Compound **1** underwent cyclization in the presence of sulfuric acid (H_2SO_4) under reflux conditions to afford nitro-*9H*-xanthen-9-one **2**.[12] Subsequent reaction of **2** with stannous chloride dehydrates in concentrated hydrochloric acid afforded corresponding amino-*9H*-xanthen-9-one **3**. Finally, the reaction of **3** with the substituted benzenesulfonamide **4** in the presence of triethylamine in chloroform afforded *N*-(9-oxo-*9H*-xanthen-4-yl)benzenesulfonamides **5a–i** and **6a–g**. The chemical structures of final products were confirmed with ^{1}H NMR, 13C NMR, and mass spectroscopy.

The antiproliferative activities of compounds **5a–i** and **6a–g** were evaluated by MTT reduction assay against two different breast cancer cell lines (MDA-MB-231 and T-47D) and a neuroblastoma cell line (SK-N-MC) (Table 1). Compound **5i** containing a 4-methoxy group on the phenyl ring was the most potent compound in this series against these three cell lines. This compound exhibited higher antiproliferative activity against SK-N-MC (IC_{50} = 25.2 μM) and T-47D (IC_{50} = 19.7 μM) cell lines when compared with etoposide. Compound **5i** showed 1.7-fold higher antiproliferative activity against T-47D cell line when compared with control drug etoposide (IC_{50} = 32.7 μM).

In general, the compounds were more potent against SK-N-MC cell line when compared with other tested cell lines. Compounds **5i** and **6c** exhibited higher antiproliferative activity (IC_{50} = 24.9–25.2 μM) against SK-N-MC cell line in comparison with etoposide (IC_{50} = 33.4 μM). 3-Chloro-2-methylbenzene sulfonamide analog **6d** with IC_{50} value of 30.4 μM showed higher antiproliferative activity than etoposide against MDA-MB-231 cell line.

Structure-activity relationship studies revealed that the antiproliferative activity of synthesized compounds was partly influenced by the type of substituents positioned on the phenyl ring. Most of the compounds bearing chlorine substitution in the 6 position of xanthone ring showed generally more antiproliferative activity compared with the corresponding compounds without the chlorine moiety (**6a**, **6b**, **6c**, **6e** versus **5a**, **5b**, **5c**, **5d**, **5e**, **5g**, respectively).

Among the compounds without a substituted chlorine on the xanthone ring, compound **5i** with **a** 4-methoxy group on benzenesulfonamide ring was the most potent compound, suggesting that the presence of an electron donor group on benzenesulfonamide ring increases the antiproliferative activity in this series of compounds. Introducing a methyl group in the position 2 of the benzenesulfonamide ring in compound **5f** led to significant increased antiproliferative activity compared to compound **5b**. Similarly, compound **6d** with 2-methyl substitution showed enhanced antiproliferative activity compared to **6b** suggesting that methyl substitution in position 2 of the benzenesulfonamide ring could result to increased antiproliferative activity in both substituted xanthone series of compounds with or without chlorine group.

Alternatively, antiproliferative activity of substituted benzenesulfonamides derivatives were evaluated against human leukemia (CCRF-CEM), breast adenocarcinoma (MDA-MB-468), and colorectal carcinoma (HCT-116) cell lines at the concentration of 50 μM (Figure 1) to determine whether the compounds are consistently cytotoxic against other cancer cell lines and to compare their activity with doxorubicin (Dox). Compounds **5a**, **5c**, **6a**, and **6d** exhibited consistent antiproliferative activity against all three cell lines. Among all the compounds, compounds **5a** and **6a** exhibited the highest antiproliferative activity against all the cell lines. For example, compound **6a** inhibited the cell proliferation of HCT-116 (86%), CCRF-CEM (75%), and MDA-MB-468 (65%). Structure-activity relationship (SAR) revealed that the presence of five fluorine on the second ring improved the antiproliferative activity significantly (**5a** and **6a**) against these three cell lines. Compounds **5a** (79 and 79%) and **6a** (86 and 75%) showed higher antiproliferative activity than Dox (63 and 73%) against HCT-116 and CCRF-CEM cells, respectively. Furthermore, compound **6d** (86%) was more active than Dox against HCT-116 cells and was consistently active against CCRF-CEM and MDA-MB-468 cells. Compound **5i** that showed high antiproliferative activity against SK-N-MC and T-47D in the previous assay was consistently cytotoxic against HCT-116 (71%) and CCRF-CEM (77%) cells.

Compounds **5e**, **5g**, **5h**, **5f**, and **6g** demonstrated modest antiproliferative activities (40–74%) against all three cell lines. Furthermore, nine compounds **5b**, **5d**, **5h**, **6b**, **6c, 6e,** and **6f** exhibited significantly higher antiproliferative activity against HCT-116 and MDA-MB-468 cell lines that CCRF-CEM cells. For example, **6c**, **6e**, and **6f** inhibited HCT-116 by 68, 63, 68% and MDA-MB-468 cells by 66, 60, and 71%, respectively. The presence of either chlorine or bromine groups on both rings decreased the antiproliferative activity as shown in compounds **6b–c**, **6e**, **6f**.

In conclusion, a series of 18 novel xanthone sulphonamide derivatives were synthesized and evaluated for their anticancer activity against a panel of cancer cell lines. Compound **5i** containing a 4-methoxy group was more antiproliferative than etoposide against SK-N-MC and T-47D cells. Furthermore, the assay results showed that pentafluoro derivatives **5a** and **6a** had higher antiproliferative activity against HCT-116 and CCRF-CEM cells than Dox. Structure-activity relationship studies provided insights for designing the next generation of xanthone benzenesulfonamide hybrid prototypes and development of new lead compounds as antiproliferative agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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16. ***General procedure for the synthesis of substituted N-(9-oxo-9H-xanthen-4-yl) benzenesulfonamide (5)***. Triethylamine (15 mmol) was added to a stirring solution of **3** (12 mmol) and appropriate benzenesulfonyl chloride (13 mmol) in chloroform (50 mL). The reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC using CH_2Cl_2 as a mobile phase. When compound **3** was consumed, the precipitate was filtered and purified by column chromatography (silica gel) using CH_2Cl_2 as the eluent.

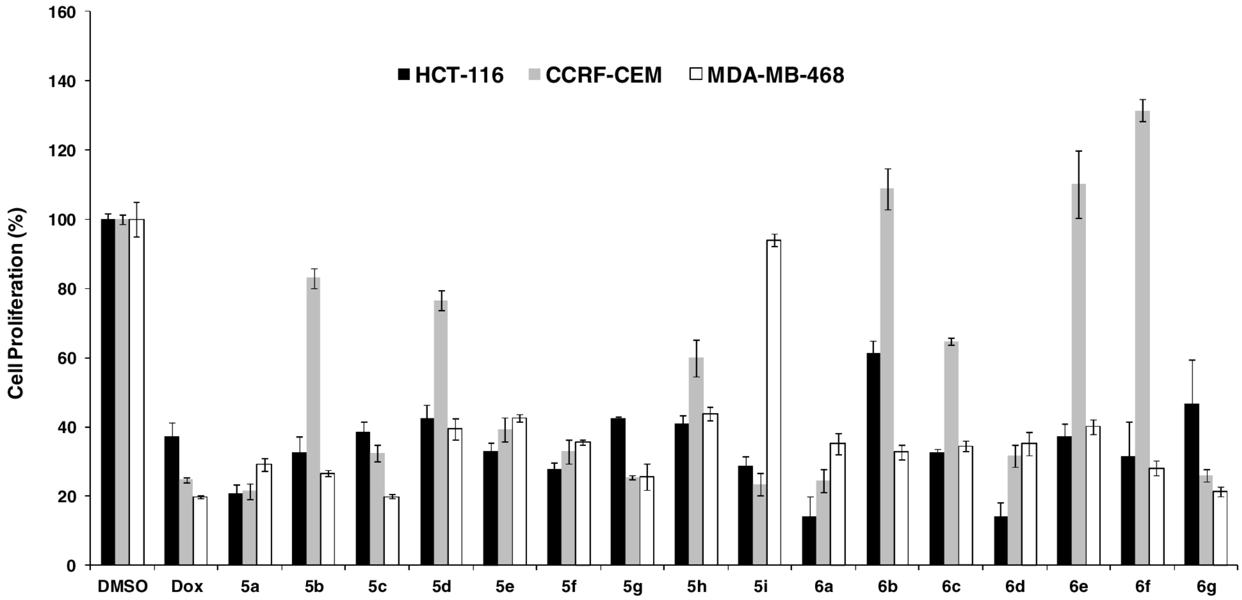
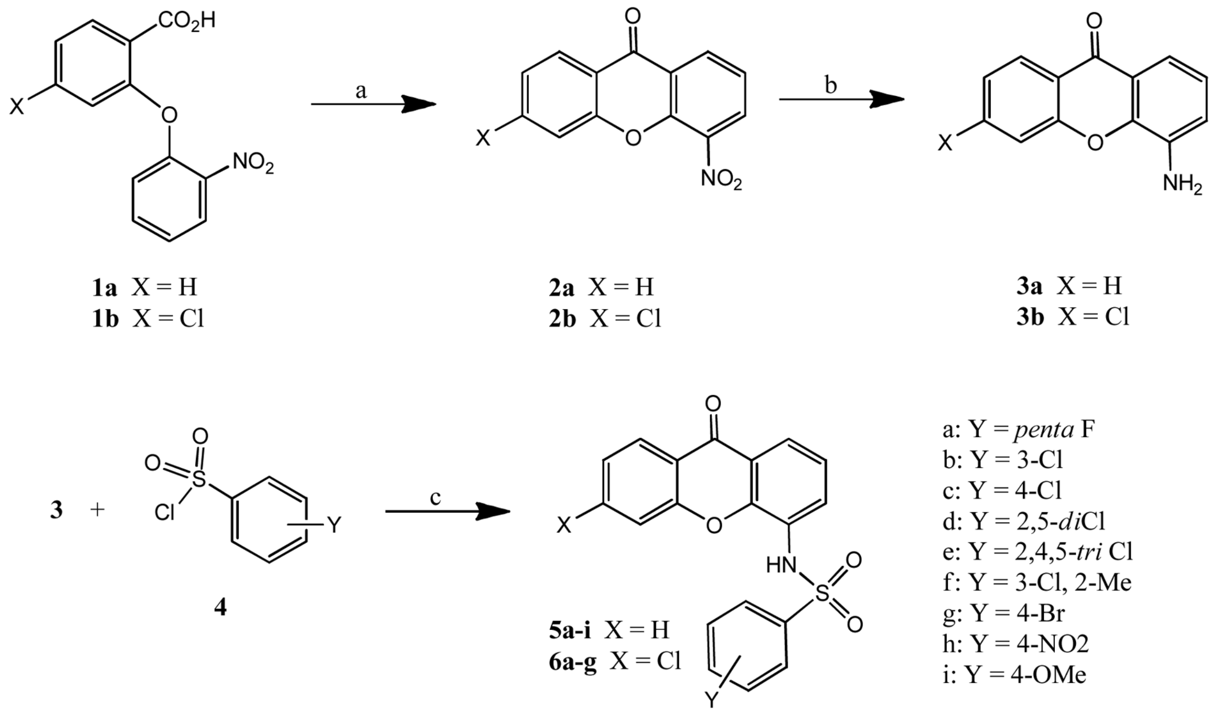


Figure 1.
Inhibition of HCT-116, CCRF-CEM, and MDA-MB-468 cells by compounds **5a–i** and **6a–g** (50 μM) after 24 h incubation. The results are shown as the percentage of the control DMSO that has no compound (set at 100%). All the experiments were performed in triplicate (± SD).



Scheme 1.

Reagents and conditions: (a) H_2SO_4, reflux, 30 min; (b) $SnCl_2$, conc. HCl, 100 °C, 4 h then NaOH 10%, RT, 30 min; (c) Et_3N, $CHCl_3$, RT.

Table 1

Antiproliferative activity (IC_{50}, in μM) of compounds against different cancer cell lines, neuroblastoma cell line (SK-N-MC) and breast cancer cell line (MDA-MB-231, T-47D).

Compounds	X	Y	SK-N-MC IC_{50} (μM)	MDA-MB-231 IC_{50} (μM)	T-47D IC_{50} (μM)
5a	H	Penta F	58.7±30.8	85±15.9	53.9±4.7
5b	H	3-Cl	>100	>100	58.6±1.8
5c	H	4-Cl	>100	83.3±26.9	33.8±9.3
5d	H	2,5-di-Cl	95.8±28	>100	53.3±4.5
5e	H	2,4,5-tri Cl	78.5±6.4	60.4±17.2	36.3±9.2
5f	H	3-Cl,2-CH_3	38.3±4.7	67.5±8.3	56.5±28.7
5g	H	4-Br	47.9±20.7	85.4±24.7	63.4±9.8
5h	H	4-NO_2	90.9±16.4	96.3±49.2	52.7±22.4
5i	H	4-OCH_3	25.2±26.5	54.4±21	19.7±0.18
6a	Cl	Penta F	40.8±8.2	40.2±4.6	39±18
6b	Cl	3-Cl	40.5±28.3	59.5±37	83.±513
6c	Cl	2,4,5-tri-Cl	24.9±16.1	66.7±9.7	67.9±6.7
6d	Cl	3-Cl,2-CH_3	41.3±23.5	30.4±5.9	49.3±26.7
6e	Cl	4-Br	37.1±12.7	45.3±3.8	46.9±17
6f	Cl	4-NO_2	>100	63.1±20.7	76.1±1.6
6g	Cl	4-OCH_3	>100	62.3±0.2	45±11.3
Etoposide	-	-	33.4±11.7	36.6±5.9	32.7±5.5