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

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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.

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 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{10,11}

Compound 1 underwent cyclization in the presence of sulfuric acid (H\textsubscript{2}SO\textsubscript{4}) under reflux conditions to afford nitro-9H-xanthen-9-one 2.\textsuperscript{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 \textsuperscript{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 (IC₅₀ = 25.2 μM) and T-47D (IC₅₀ = 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 (IC₅₀ = 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 (IC₅₀ = 24.9-25.2 μM) against SK-N-MC cell line in comparison with etoposide (IC₅₀ = 33.4 μM). 3-Chloro-2-methylbenzene sulfonamide analog 6d with IC₅₀ 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.

Table 1-Antiproliferative activity (IC₅₀, 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).

<table>
<thead>
<tr>
<th>Compounds</th>
<th>X</th>
<th>Y</th>
<th>SK-N-MC IC₅₀ (μM)</th>
<th>MDA-MB-231 IC₅₀ (μM)</th>
<th>T-47D IC₅₀ (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>H</td>
<td>Penta</td>
<td>58.7±30.8</td>
<td>85±15.9</td>
<td>53.9±4.7</td>
</tr>
<tr>
<td>5b</td>
<td>H</td>
<td>3-Cl</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>58.6±1.8</td>
</tr>
<tr>
<td>5c</td>
<td>H</td>
<td>4-Cl</td>
<td>&gt;100</td>
<td>83.3±26.9</td>
<td>33.8±9.3</td>
</tr>
<tr>
<td>5d</td>
<td>H</td>
<td>2,5-di-Cl</td>
<td>95.8±28</td>
<td>&gt;100</td>
<td>53.3±4.5</td>
</tr>
<tr>
<td>5e</td>
<td>H</td>
<td>2,4,5-tri-Cl</td>
<td>78.5±6.4</td>
<td>60.4±17.2</td>
<td>36.3±9.2</td>
</tr>
<tr>
<td>5f</td>
<td>H</td>
<td>3-Cl,2-CH₃</td>
<td>38.3±4.7</td>
<td>67.5±8.3</td>
<td>56.5±28.7</td>
</tr>
<tr>
<td>5g</td>
<td>H</td>
<td>4-Br</td>
<td>47.9±20.7</td>
<td>85.4±24.7</td>
<td>63.4±9.8</td>
</tr>
<tr>
<td>5h</td>
<td>H</td>
<td>4-NO₂</td>
<td>90.9±16.4</td>
<td>96.3±49.2</td>
<td>52.7±22.4</td>
</tr>
<tr>
<td>5i</td>
<td>H</td>
<td>4-OCH₃</td>
<td>25.2±26.5</td>
<td>54.4±21</td>
<td>19.7±0.18</td>
</tr>
<tr>
<td>6a</td>
<td>Cl</td>
<td>Penta</td>
<td>40.8±8.2</td>
<td>40.2±4.6</td>
<td>39±18</td>
</tr>
<tr>
<td>6b</td>
<td>Cl</td>
<td>3-Cl</td>
<td>40.5±28.3</td>
<td>59.5±37</td>
<td>83±513</td>
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<tr>
<td>6c</td>
<td>Cl</td>
<td>2,4,5-tri-Cl</td>
<td>24.9±16.1</td>
<td>66.7±9.7</td>
<td>67.9±6.7</td>
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<tr>
<td>6d</td>
<td>Cl</td>
<td>3-Cl,2-CH₃</td>
<td>41.3±23.5</td>
<td>30.4±5.9</td>
<td>49.3±26.7</td>
</tr>
<tr>
<td>6e</td>
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<td>4-Br</td>
<td>37.1±12.7</td>
<td>45.3±3.8</td>
<td>46.9±17</td>
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<tr>
<td>6f</td>
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<td>&gt;100</td>
<td>63.1±20.7</td>
<td>76.1±16</td>
</tr>
<tr>
<td>6g</td>
<td>Cl</td>
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<td>&gt;100</td>
<td>62.3±0.2</td>
<td>45±11.3</td>
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<tr>
<td>Etoposide</td>
<td>-</td>
<td>-</td>
<td>33.4±11.7</td>
<td>36.6±5.9</td>
<td>32.7±5.5</td>
</tr>
</tbody>
</table>
sponsoring the core facility. Resources, NIH, and Grant Number 8 P20 GM103430-12 for RSG-07-290-01-CDD. We thank National Center for Research the financial support from the American Cancer Society Grant # of Tehran University of Medical Sciences. We also acknowledge higher antiproliferative activity than Dox (63 and 73%) against Compounds concentration of 50 µM (Figure 1) to determine whether the Compounds lines and to compare their activity with doxorubicin (Dox). 468), and colorectal carcinoma (HCT-116) cell lines at the leukemia (CCRF-CEM), breast adenocarcinoma (MDA-MB- benzenesulfonamides derivatives were evaluated against human cell lines 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.

Acknowledgments

This work was supported by grants from the Research Council of Tehran University of Medical Sciences. We also acknowledge the financial support from the American Cancer Society Grant # RSG-07-290-01-CDD. We thank National Center for Research Resources, NIH, and Grant Number 8 P20 GM103430-12 for sponsoring the core facility.

References and notes


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).
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 CH₂Cl₂ as a mobile phase. When compound 3 was consumed, the precipitate was filtered and purified by column chromatography (silica gel) using CH₂Cl₂ as the eluent.

**Supplementary Material**

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