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Design, synthesis and preliminary antiproliferative activity studies of new diheteroaryl thioether derivatives

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ABSTRACT

A series of structurally new diheteroaryl thioether analogs was designed, prepared and screened toward MGC-803, MKN-45, EC-109 and H1650. Most of the target compounds displayed moderate to potent antiproliferative activities. Among them, compound **5** showed the best antiproliferative activity against the tested cell lines with the half maximal inhibitory concentration (IC_{50}) values below 10 μM. In addition, flow cytometry analysis showed that compound **5** increased Bax expression, down-regulated expression of Bcl-2, cleaved caspases-3/9, finally inducing apoptosis of MKN-45 cells as well as arrested the cell cycle at G2/M phase. This study suggests that the diheteroaryl thioethers are a class of emerging chemotypes for developing antitumor agents or biological probes, and compound **5** could serve as a good starting point to design new apoptosis inducers.

Introduction

(Hetero)diaryl thioether chemotypes have attracted particular attention of medicinal community due to their profound and diverse biological activities such as antibacterial,[1] anticancer,[2,3] antituberculosis,[4,5] and anti-HIV activity.[6,7] As shown in Fig. 1, heteroarylthioquinoline **A** showed highly potent inhibition against Mycobacterium tuberculosis (Mtb) with an MIC value of 3.2 μM, while no cytotoxicity was observed against mouse fibroblast cells.[8] Compound **B** with substituted mercapto benzothiazole at 7′-position of purine ring, displayed strong *in vivo* efficacy in N87 cancer xenograft model by targeting heat shock protein 90 (Hsp90).[9] And compound **C**, structurally featuring the thioether tethered diheteroaryl scaffold, was recently reported by our group to be a potent LSD1 inhibitor and showed selectivity to LSD1 over MAO-A/B.[10] Compound **D**, as an effective tubulin polymerization inhibitor, significantly inhibited MCF-7 cell growth at nanomolar range.[11]

Following our previous work on the synthesis of new *N*-heterocycles with anticancer potentials,[10,12–14] we herein report the synthesis of a series of new diheteroaryl thioether derivatives, their antiproliferative activity and preliminary mechanisms of inducing cancer cell death.

The general synthetic route was illustrated in Scheme 1. The intermediate derivatives **2a–f** were synthesized by condensation of commercially available 4,6-dichloro-2-(propylthio)pyrimidin-5-amine **1** with primary amine in the presence of DIPEA in DMF. The obtained intermediates **2a–f** then reacted with ethyl glyoxalate in the mixed AcOH/EtOH under heating to afford intermediates **3a–f**,[15] which then reacted with various mercaptoheteroaryl analogs in the presence of TEA in EtOH to produce the target compounds **4–19**.

All of the target compounds were screened for their antiproliferative activities against four cancer cell lines including MKN-45 and MGC803 (human gastric cancer lines), EC-109 (human esophageal cancer line), and H1650 (human lung cancer line), by using the MTT assay, and 5-fluorouracil (5-FU) was employed as the reference drug.[16] The antiproliferative results were summarized in Tables 1 and 2. To fully investigate the SARs (structure-activity relationship studies) of the diarylthioether derivatives, modifications were focused on two parts, while keeping the pteridin-7(8*H*)-one scaffold intact: (a) Incorporation of various *N*-heteroarene fragments (R^2); (b) Variation of substituents attached to the nitrogen atom of the pteridin-7(8*H*)-one core (R^1).

As shown in Table 1, the effect of R^2 group on the antiproliferative activity was initially investigated. In general, most of the target compounds showed moderate to good growth inhibition against the tested cancer cell lines. Particularly, compound **5** with

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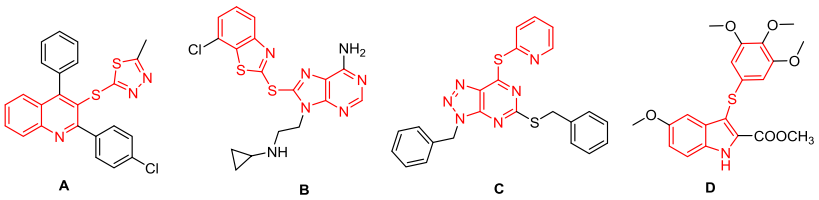
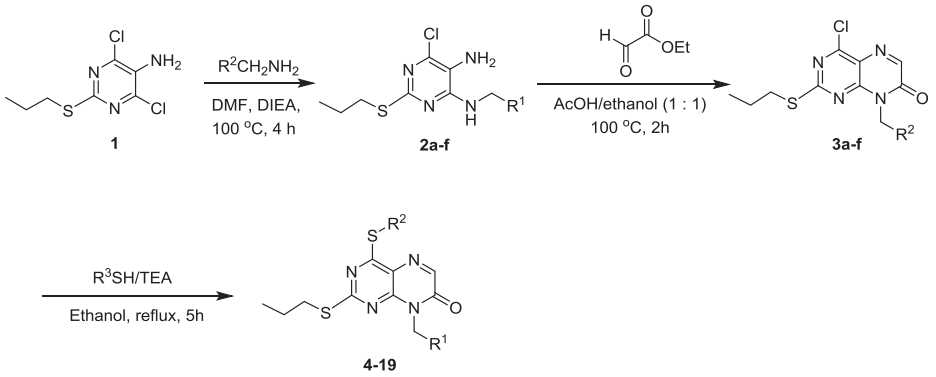
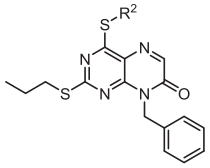


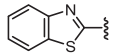
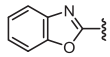
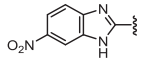
Fig. 1. Biologically active diheteroaryl thioether derivatives.



Scheme 1. Synthesis of diheteroaryl thioether derivatives.

Table 1
Antiproliferative evaluation of compounds **4**–**14**.



Compound	R^2	IC_{50} (μM)[a]			
		MGC-803	MKN-45	EC-109	H1650
4		7.77 ± 1.42	5.30 ± 0.72	33.22 ± 4.06	15.12 ± 2.32
5		5.10 ± 1.49	2.97 ± 0.96	7.07 ± 2.18	9.07 ± 1.12
6		24.73 ± 0.56	>64	>64	35.12 ± 2.68
7		4.79 ± 1.13	9.06 ± 1.08	>64	>64
8		5.55 ± 1.44	18.99 ± 1.20	15.09 ± 3.55	42.12 ± 3.61
9		13.12 ± 1.62	30.03 ± 3.24	31.98 ± 2.52	59.22 ± 6.69
10		7.96 ± 1.34	12.73 ± 1.15	22.29 ± 1.96	12.27 ± 1.88
11		>64	38.71 ± 1.88	>64	>64
12		11.94 ± 1.17	14.57 ± 0.88	49.37 ± 1.81	31.63 ± 2.05
13		10.97 ± 2.22	11.37 ± 1.37	35.79 ± 2.91	26.72 ± 3.12
14		8.02 ± 1.36	10.40 ± 1.29	45.22 ± 3.52	18.22 ± 0.98
5-FU	–	7.52 ± 0.98	8.89 ± 1.65	6.21 ± 0.75	14.25 ± 2.73

[a] Inhibitory activity was assayed by exposure for 48 h to substance and expressed as concentration required to inhibit tumor cell proliferation by 50% (IC_{50}). The IC_{50} values were calculated using IBM SPSS Statistics (Version 22). Data are presented as the means ± SDs of three independent experiments.