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Syntheses and Biological Activities of Bis(3-indolyl)thiazoles, Analogues of Marine Bis(indole)alkaloid Nortopsentins¹

Xiao-Hui Gu, Xiao-Zhuo Wan, Biao Jiang*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P.R.China Received 17 October 1998; accepted 7 January 1999

Abstract: The thiazole analogues of the marine bis(indole)alkaloid nortopsentins, 2,4-bis(3-indolyl)thiazoles, were synthesized using Hantzsch reaction between indole-3-thioamides and 3-(α -bromoacetyl)indoles as the key step, and these analogues showed potent cytotoxic activities against a variety of human cancer cell lines *in vitro*. © 1999 Elsevier Science Ltd. All rights reserved.

Introduction:

A number of bis(indole)alkaloids have been isolated from the marine environment over the past decade, which exhibit various biological activities including antibacterial, antiviral and cytotoxic activities. Nortopsentins A-C **1-3**, having a characteristic 2,4-bis(3-indolyl)imidazole skeleton, were isolated from the deep-water marine sponge *spongsorites ruetzleri*.² Nortopsentins A-C **1-3** and its analogue **4** exhibited *in vitro* cytotoxicity against P388 cells and antifungal activity against *candida albicans*.²⁻⁴ Due to the interesting biological activities and unique chemical structures of marine indolealkaloids and its low availability, marine indolealkaloids as lead compounds for discovery of new drugs have became an attractive field in medicinal chemistry. In our effort to search for novel antitumor compounds, syntheses and exploring the structure-activity relationships for marine bis(indole)alkaloids, we are interested in the thiazole analogues of nortopsentins. In this communication we wish to disclose an efficient syntheses and evaluation of cytotoxic activities of 2,4-bis(3-indolyl)thiazoles **5-8**, analogues of nortopsentins.



Synthetic Chemistry:

The synthetic route to the 2,4-bis(3-indolyl)thiazole was shown in Scheme 1.



Conditions and Reagents: a. POCl₃, DMF, -10^{0} C-rt.; b. aq.NaOH, reflux; c. (NH₄)₂HPO₄, CH₃CH₂CH₂NO₂, HOAc, reflux; d. thioacetamide, HCl/DMF, reflux; e. TsCl, aq NaOH, Bu₄NHSO₄, toluene, rt.; f. Ac₂O, AlCl₃, CH₂Cl₂, 0^{0} C-rt.; g. CuBr₂, CHCl₃-EtOAc(1:1), reflux; h. ab.EtOH, reflux; i. NaOH, MeOH, reflux.

Scheme 1

Indole and 6-bromoindole⁵⁻⁷ were converted to indole-3-carboxaldehyde 10 in high yields by Vilsmeier-Haack reaction with phosphorus oxychloride and dimethylformamide.⁸ The aldehyde 10 was then converted to the correponding nitrile 11 in one step after treatment with diammonium hydrogen phosphate, 1-nitropropane and acetic acid.⁹ The key thioamide 12 was obtained from the indole-3-carbonitrile 11 by Taylor's method using thioacetamide as a source of hydrogen sulfide under acidic conditions¹⁰⁻¹¹ Attempting to prepare the indole-3-thioamide by treating the corresponding indole-3-carboxamide with Lawesson's reagent¹²⁻¹⁴ was failed, only indole-3-carbonitrile 11 was isolated.

With thioamide 12 and α -bromoketone 15 in hand, the next stage was set to elaborate the thiazole ring using Hantzsch reaction.²⁰ Thus a mixture of the corresponding thioamide 12 and α -bromoketone 15 was refluxed in absolute ethanol for 0.5-1h, the bis(3-indolyl)thiazole product deposited from the reaction solution. After filtration, the products was obtained in excellent yields. Deprotection of the toluenesulfonyl group afforded the 2,4-bis(3-indolyl)thiazoles 5-8.²¹

Biological Activity:

2,4-bis(3-indolyl)thiazoles 5-8 were evaluated in the NCI's *in vitro* disease-oriented antitumor screening using sulforhodamine B (SRB) assay, $^{22-24}$ and the results are presented in Table 1.

Cell lines	5	6	7	8
K-562	3.27	18.8	5.61	4.69
MOLT-4	5.31	19.9	31.2	5.80
SR	1.77	6.36	12.2	3.40
NCI-H23	>100	14.5	25.8	14.1
HCT-15	>100	15.2	17.8	8.50
SF-295	33.6	14.6	9.23	4.81
MCF-7	>100	16.7	27.2	6.46
MDA-N	83.0	19.2	31.5	2.94

Table 1. Cancer cell growth inhibitory activity of compounds 5-8 in vitro (GI₅₀ values in µM).

As shown in **Table 1**, the compounds **5-8** exhibited cytotoxic activities against a variety of human cancer cell lines. Compound **5** afforded selectively GI_{50} of 1.77 μ M in the SR assay. In the NCI-H23, HCT-15 and MCF-7 assay, the GI_{50} of compound **5** exceeded 100. To test that possibility that substituted in the indole ring might result in a potency increase, the brominated compound **6**,**7**, **8** showed significant increase actives in NCI-H23, HCT-15, SF-295, MCF-7 and MDA-N assay, afforded GI_{50} of 2.94 μ M to 31.5 μ M, but approximate two to six fold less potent than the unsubstituted counterpart **5** in K-562, MOLT-4 and SR assay. Among the four compounds, dibrominated compound **8** had the broadest cytotoxic effect.

In conclusion, we have developed a highly efficient synthesis of bis(3-indolyl)thiazole, which are analogues of marine bis(indole)alkaloid of nortopsentins. The analogues exhibited important cytotoxic activities against a variety of human cancer cell lines *in vitro*.

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