Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 569–572

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Syntheses and Biological Activities of Bis(3-indolyl)thiazoles, Analogues of Marine Bis(indole)alkaloid Nortopsentins[1]

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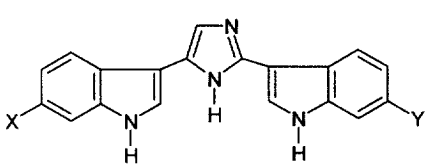
Received 17 October 1998; accepted 7 January 1999

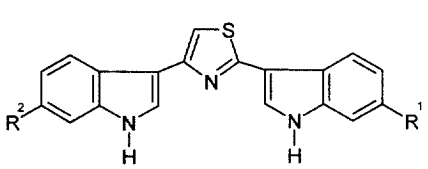
Abstract: The thiazole analogues of the marine bis(indole)alkaloid nortopsentins, 2,4-bis(3-indolyl)thiazoles, were synthesized using Hantzsch reaction between indole-3-thioamides and 3-(α-bromoacetyl)indoles as the key step, and these analogues showed potent cytotoxic activities against a variety of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

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.



1 X=H, Y=Br (nortopsentin A)
2 X=Br, Y=H (nortopsentin B)
3 X=Y=Br (nortopsentin C)
4 X=Y=H (nortopsentin D)



5 R^1=R^2=H
6 R^1=H, R^2=Br
7 R^1=Br, R^2=H
8 R^1=R^2=Br

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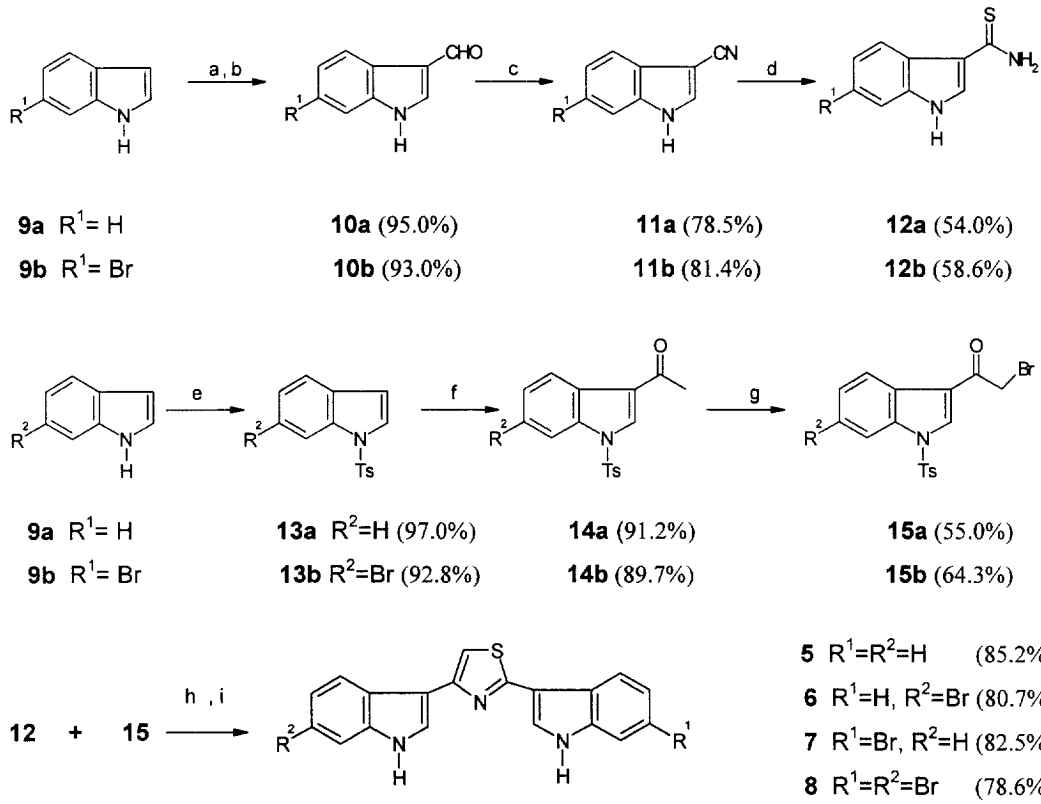
PII: S0960-894X(99)00037-2

Synthetic Chemistry:

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



Conditions and Reagents: a. $POCl_3$, DMF, -10°C-rt.; b. aq.NaOH, reflux; c. $(NH_4)_2HPO_4$, $CH_3CH_2CH_2NO_2$, HOAc, reflux; d. thioacetamide, HCl/DMF, reflux; e. TsCl, aq NaOH, Bu_4NHSO_4, toluene, rt.; f. Ac_2O, $AlCl_3$, CH_2Cl_2, 0°C-rt.; g. $CuBr_2$, $CHCl_3$-EtOAc(1:1), reflux; h. ab.EtOH, reflux; i. NaOH, MeOH, reflux.

Scheme 1

Indole and 6-bromoindole[5-7] 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 conditions[10-11] Attempting to prepare the indole-3-thioamide by treating the corresponding indole-3-carboxamide with Lawesson's reagent[12-14] was failed, only indole-3-carbonitrile **11** was isolated.

The NH groups of indole **9** was protected with *p*-toluenesulfonyl chloride under phase transfer condition[15-16] to give *N*-toluenesulfonylindole **13** in high yield. Friedel-Crafts acylation of *N*-toluenesulphonylindole gave 3-acetylindoles **14** in excellent yields.[17] Bromination **14** with copper(II) bromide in refluxing $CHCl_3$/EtOAc[18-19] afforded the α-bromoketone **15** in moderate yield.

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**.

Table 1. Cancer cell growth inhibitory activity of compounds **5-8** *in vitro* (GI_{50} values in μM).

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

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 μM 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 μM to 31.5μM, 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*.

Acknowledgement:

We are grateful to Dr. E. Sausville and his collegues in NCI, NIH for carrying out the biological assays.

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