AN IMPROVED ONE-POT SYNTHESIS OF 3,6-BIS(3'-INDOLYL)-1,4-DIMETHYLPIPERAZINE-2,5-DIONE

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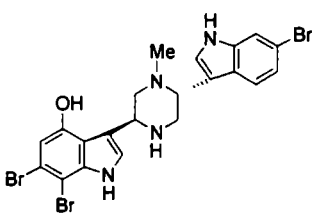
Abstract: An improved procedure for the large-scale preparation of 3,6-bis(3'-indolyl)-1,4-dimethylpiperazine-2,5-dione is presented.

For decades, new chemicals have been extracted from plants and small animals with the hopes of finding natural products with interesting biological properties. Attractive biological properties include anticancer, antibacterial and antiviral activity. Nicotine, morphine and mitomycin antibiotics are examples of natural products containing nitrogen, or alkaloids, with interesting biological properties. Once found to have beneficial properties, these new molecules, extracted in very small quantities, are often synthesized by organic chemists to conduct large-scale testing on mammals.
The dragmacidin series of bisindolyl piperazines represents a new class of marine natural products isolated from deep sea sponges and tunicates. The first member of this series, dragmacidin (**1**), was reported in 1988.[1] The discovery of dragmacidins A **2** and B **3** quickly followed.[2]



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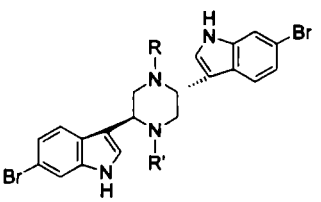


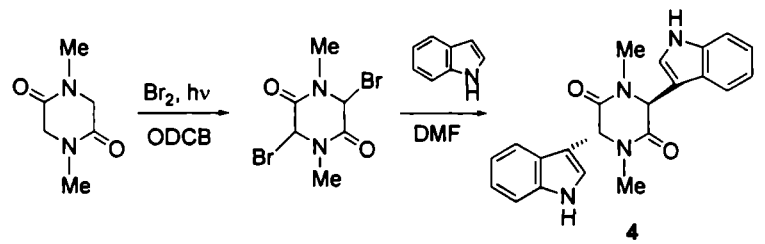
2 R = R' = Me
3 R = H, R' = Me

Recently, new attention has been given to these compounds as four new dragmacidin alkaloids, dragmacidins C-F, have been reported.[3] All exhibit anticancer properties, and some also exhibit antifungal and anti-inflammatory properties. All members of the series contain a central piperazine ring and two indole units.

No synthetic route to any bisindolyl piperazine had been reported until the corresponding author successfully accomplished the *first* synthesis of a dragmacidin alkaloid, dragmacidin B **3**, in 1994.[4] Later that year, the first synthesis of dragmacidin was reported.[5] It was not until 2000 before the synthesis of another member of this series was reported.[6] The discovery of new members and new properties has initiated a resurgence of interest in the dragmacidins. Today the dragmacidins represent and important series of new lead compounds in the search of anticancer chemotherapeutic agents.

Our attempts to prepare novel derivatives of the dragmacidin alkaloids have resulted in an improved, one-pot synthesis of 3,6-bis(3'-indolyl)-1,4-dimethylpiperazine-2,5-dione **4**, an important intermediate in the synthesis of Dragmacidin B. The previous one-pot procedure involved refluxing 1,4-dimethylpiperazine-2,5-dione, N-bromosuccinimide and AIBN in CCl_4 for 2.5 hours followed by the addition of indole in DMF. A two-step procedure has also been reported.[7]

In our improved one-pot procedure (Scheme 1), 1,4-dimethylpiperazine-2,5-dione is refluxed with Br_2 in o-dichlorobenzene (ODCB) for 10 minutes. Additionally, the reaction is subjected to a sunlamp during the reflux and for an additional 25 minutes while the system is cooling. We discovered that by decanting the solvent of the cooled solution and immediately adding indole in DMF a higher yield of the product was obtained. The solution was stirred overnight and then poured into MeOH. After crystallization from MeOH, yields as high as 65% were achieved for the preparation of 3,6-bis(3'-indolyl)-1,4-dimethylpiperazine-2,5-dione **4.**



Scheme 1. Improved synthesis of 3,6-bis(3'-indolyl)-1,4-dimethylpiperazine-2,5-dione **4.**

Acknowledgement

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