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Sequential one-pot synthesis of bis(indolyl)glyoxylamides: Evaluation of antibacterial and anticancer activities

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ABSTRACT

A series of bis(indolyl)glyoxylamides **10a–n** has been designed and synthesized. In situ generated indole-3-glyoxalylchloride from the reaction of readily available indole **9** with oxalyl chloride was treated with tryptamine to produce bis(indolyl)glyoxylamides **10a–n** in 82–93% yields. All the synthesized bis(indolyl) glyoxylamides were well characterized and tested for their antibacterial activity against Gram-positive and Gram-negative bacterial strains. Compounds **10d**, **10g** and **10i** were found to display potent antibacterial activity against Gram-negative strain. Further, the cytotoxicity of bis(indolyl)glyoxylamides **10a–n** were evaluated against a panel of human cancer cell lines. Of the screened analogues, compound **10f** (IC_{50} = 22.34 μM; HeLa, 24.05 μM; PC-3, 21.13 μM; MDA-MB-231 and 29.94 μM; BxPC-3) was identified as the most potent analogue of the series. Exposure of PC-3 cells to either **10a** or **10f** resulted in increased levels of cleaved PARP1, indicating that bis(indolyl)glyoxylamides induce apoptosis in PC-3 cells. Most importantly, compounds **10d**, **10g** and **10i** were completely ineffective in mammalian cells, suggesting that they target bacterial-specific targets and thus will not display any toxicity in host cells.

Indole is a core substructure in a wide range of biologically active natural products isolated from marine organisms.[1] Particularly, diverse indole alkaloids represent an emerging class of natural products due to their biological potential as antimicrobial, anti-HIV, antipsychotic, antidepressant, antioxidant, anti-inflammatory and antitumour.[2] Among the indole alkaloids, bisindoles are a class of compounds which have received increasing attention due their diverse and profound biological activities including antimicrobial, anticancer, anti-HIV antileishmanial and anti-inflammatory.[3] Due to unique structural features and associated activities, bisindole alkaloids continue to serve as potential targets for synthetic and biomedical purposes. Literature review on bisindole scaffold reveals its wide presence in many antibacterial and anticancer lead molecules.[4] Bartik and co-workers isolated three new bisindole alkaloids namely topsentin (**1a**), bromotopsentin (**1b**) and deoxytopsentin (**1c**) from the Mediterranean sponge *Topsentia genitrix*, near Banyuls in France.[5] Topsentin (**1a**) exhibited anticancer activity (IC_{50} ~4–40 μM) towards cultured human and murine tumor cells whereas bromotopsentin (**1b**, IC_{50} = 12 μg/mL) and deoxytopsentin (**1c**, IC_{50} = 6.3 μg/mL) were found to be cytotoxic against human broncopulmonary (NSCLC-N6) cancer cells. Deoxytopsentin **1c** also showed potent antibacterial activity against various bacteria (MIC = 3.12–12.5 μg/mL).[4] Among the four bisindole alkaloids isolated by Kobayashi and co-workers from Okinawan tunicate *Rhopalaea* sp.,[6] Rhopaladin B (**2a**) exhibited inhibitory activity against cyclin dependent kinase 4 (IC_{50} = 12.5 μg/mL) and c-erbB-2 kinase (IC_{50} = 7.4 μg/mL). Rhopaladin C (**2b**) with C_6-bromo moiety was found to display activity against *Sarcina lutea* and *Corynebacterium xerosis* bacterial strains (MIC = ~16 μg/mL).[7] Hamacanthin A (**3**) containing a six-membered pyrazinone spacer unit was isolated from a deep-water marine sponge *Hamacantha* sp. and found to possess significant antimicrobial activity against *Candida albicans*, *Cryptococcus neoformans*, and *Bacillus subtilis*.[8] With a similar pyrazinone linker, in 1995 Capon and co-workers reported the isolation of dragmacidin D (**4**) from marine sponge *Spongosorites* sp. and evaluated their biological activities. Compound **4** was more active towards bacteria including *Escherichia coli* (MIC = 15.6 μg/mL); *Bacillus subtilis* (MIC = 3.1 μg/mL); *Pseudomonas aeruginosa* (MIC = 62.5 μg/mL). Also, it was more cytotoxic against P388 murine (IC_{50} = 1.4 μg/mL) and A-549 (IC_{50} = 4.5 μg/mL) human lung cancer cells (Fig. 1).[9]

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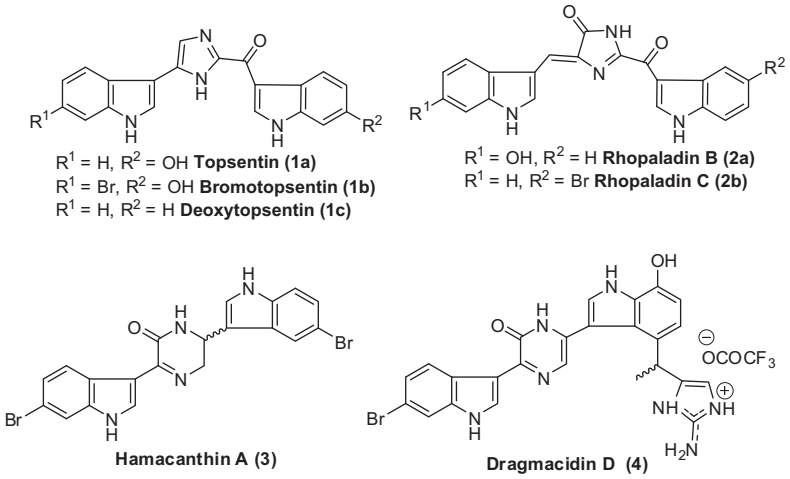
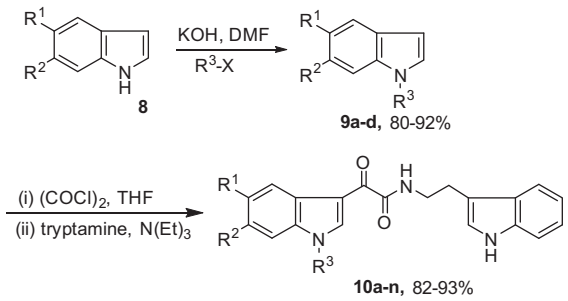


Figure 1. Representative examples of bisindole alkaloids as antibacterial and anticancer agents.

In recent past numerous bisindoles containing linear as well as cyclic linkers have been identified as antibacterial and anticancer agents (Fig. 2).[10] Kumar et al. prepared 3,2′-linked bis-indoles **5** which were found to be active against Gram-positive and Gram-negative bacteria.[11] In 2011, Singh group investigated a series of *N*-1, C-3 and C-5 trisubstituted bisindoles bearing glyoxylamide functionality **6** as potent antimicrobial agents.[12]

Recently, we have discovered 2-(3′-indolyl)-*N*-arylthiazole-4-carboxamides and carbazolyl glyoxamides **7** as anticancer and antibacterial agents.[13,14] Inspired from our previous results and profound antibacterial and anticancer properties of bisindoles, in this report we designed novel bis(indolyl)glyoxylamides by retaining the key structural features of bisindoles and glyoxylamides as depicted in Figure 2.

Bis(indolyl)glyoxylamides **10a–n** were prepared by following the synthetic route illustrated in Scheme 1. *N*-Alkyl indoles **9a–d** were prepared by following the reported reaction condition in 80–92%.[14] Initially, the reaction of indole **9** with oxalyl chloride generated indole-3-glyoxylylchloride. Further reaction of indole-3-glyoxylylchloride with tryptamine afforded bis(indolyl)-glyoxylamide **10** in 82–93% yields.



Scheme 1. Synthesis of bis(indolyl)glyoxylamides **10a–n**.

Preparation of compound **10** was further simplified by performing the reaction in a sequential one-pot fashion. From the reaction of indole **9** and oxalyl chloride in situ generated

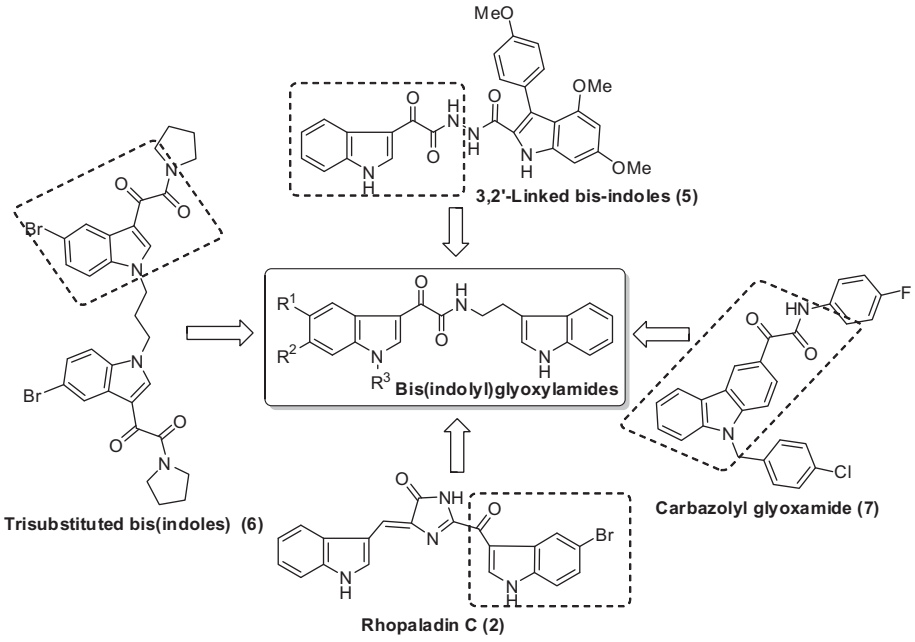


Figure 2. Rational design of bis(indolyl)glyoxylamides **10a–n**.