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Synthesis and anticancer evaluation of spermatinamine analogues

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ABSTRACT

Spermatinamine was isolated from an Australian marine sponge, *Pseudoceratina* sp. as an inhibitor of isoprenylcysteine carboxyl methyltransferase (Icmt), an attractive and novel anticancer target. Herein, we report the synthesis of spermatinamine analogues and their cytotoxic evaluation against three human cancer cell lines, that is, cervix adenocarcinoma (HeLa), breast adenocarcinoma (MCF-7), and prostate carcinoma (DU145). Analogues **12**, **14** and **15** were found to be the most potent against one or more cell lines with the IC_{50} values in the range of 5–10 μM. The obtained results suggested that longer polyamine linker along with aromatic oxime substitution provided the most potent analogue compounds against cancer cell lines.

Bromotyrosine secondary metabolites are marine invertebrates derived natural products and have been described for their variety of biological activities including: anticancer, antimicrobial, antifouling, antiviral, ATPase regulator, calcium channel modulator, etc.[1] More than 300 bromotyrosine-derived alkaloids are currently known and divided into six categories according to their chemical structures: simple bromotyrosine derivatives (suberedamines A),[2] oximes (spermatinamine),[3] bastadins ((*E*,*E*)-*Bastadin* 19),[4] spirocyclohexadienylisoxazolines (11-hydroxyaerothionin),[5] and other more complex structural classes. The anticancer activity of bromotyrosine-derived natural products has also been investigated and a significant number of compounds have been found to elicit anticancer activity, both in vitro and in vivo.[6–8]

Spermatinamine (**1**), a polyamine alkaloid, containing a bromotyrosyl-spermine-bromotyrosyl sequence was isolated from an Australian marine sponge, *Pseudoceratina* sp. as an inhibitor of isoprenylcysteine carboxyl methyltransferase (Icmt).[3] Icmt is an attractive and novel anticancer target and the various studies have provided strong evidence that tumorigenesis can be markedly impaired in cells by blocking Icmt activity.[9] Polyamines have been described earlier for their variety of cellular functions and cancer associations.[10–12] Polyamines analogues are being developed as anticancer drugs to target polyamines metabolic enzymes.[10,12–16] The ability of different types of polyamines to recognise different receptor systems provided the rationale for developing polyamines as drugs selective for different biological targets.[17] Polyamines could be considered as a skeleton key in the drug-receptor recognition process because it can assume different conformations in order to enable interaction between the drug and the receptor.[18] Recently, Hillgren et al.[19] reported the isolation and characterisation of four novel bromotyrosine polyamine alkaloids, pseudoceramines A–D (**2**–**5**) from marine sponge, *Pseudoceratina* sp. as inhibitors of the type III secretion (T3S) system of Gram-negative bacterium *Yersinia pseudotuberculosis* (see Fig. 1).

As minor structural variations can have considerable effect on the biological activity of these natural compounds, we synthesized a number of spermatinamine analogues by modifying the polyamine linker between the two-bromotyrosine rings and the substitution on oxime group. The compounds were then evaluated against three human cancer cell lines, that is, cervix adenocarcinoma (HeLa), breast adenocarcinoma (MCF-7), and prostate carcinoma (DU145) by using MTT assay. To the best of our knowledge no such study on the anticancer activities of spermatinamine analogues has been performed to date, which is necessary for an eventual lead optimisation within this class of modified natural products.

Spermatinamine was synthesized by following the recently reported synthetic route[19] with an overall yield of ~55% (over 4 steps). In our synthetic strategy, 3,5-dibromo-5-methoxybenzaldehyde was used as starting material to prepare *dibromo-O-methyltyrosine* which was then converted to azalactone (**6**) by reacting it

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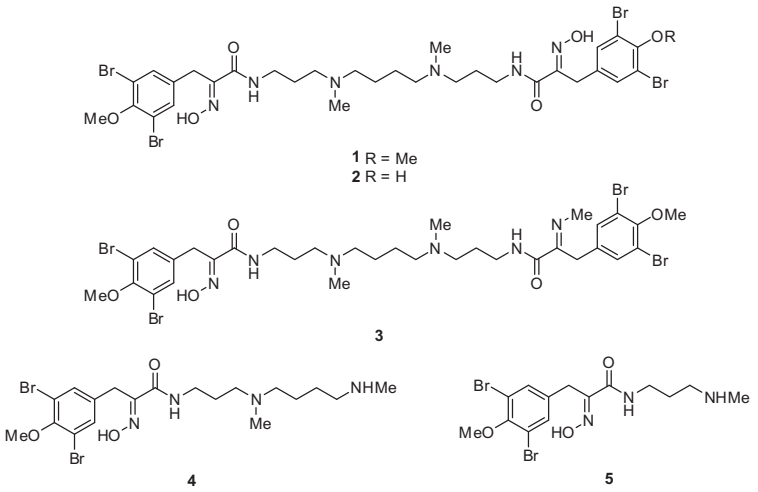
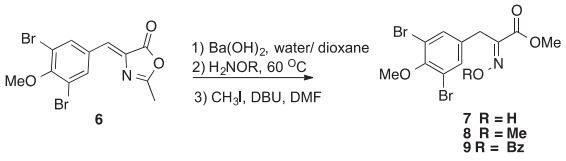


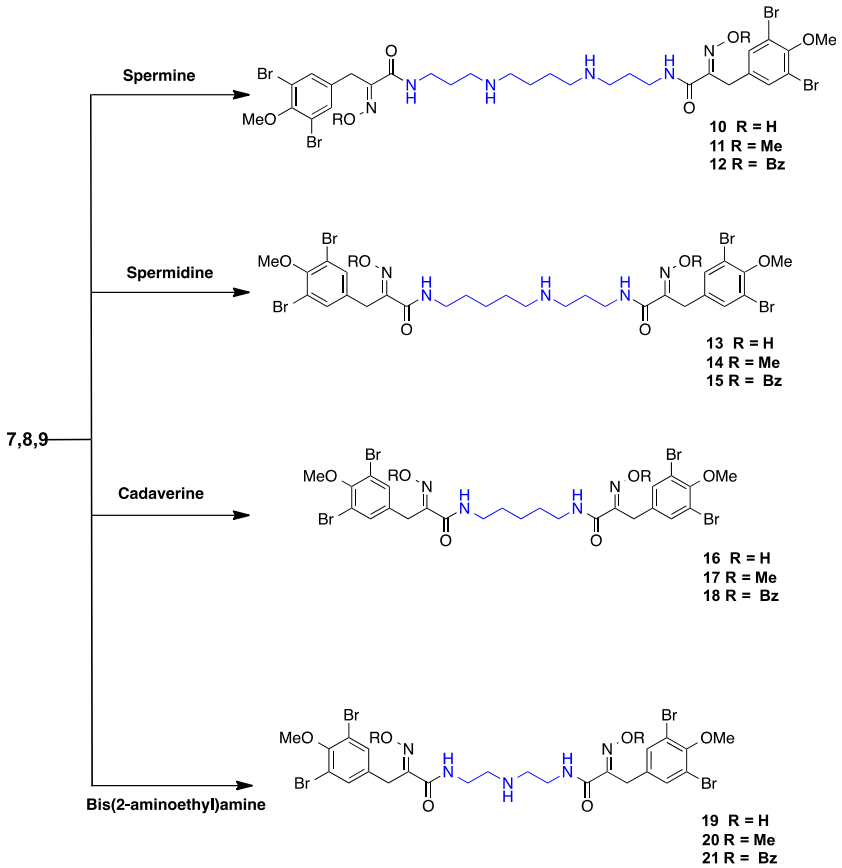
Figure 1. Structures of spermatinamine (**1**) and pseudoceramines A–D (**2**–**5**).



Scheme 1. Synthesis of substituted oxime methyl esters (2–4).

with *N-acetylglycine*.[20] The synthesized azalactone (**1**) was then hydrolysed by using barium hydroxide followed by addition of different types of hydroxylamine hydrochloride (R = H, Me, Bz) which yielded three types of substituted hydroxamic acid. The hydroxamic acid analogues were converted to methyl esters (**7**–**9**) by reacting it with methyl iodide in presence of DBU as a catalyst as shown in Scheme 1.[21] It is noteworthy that most of reaction products were reasonably pure and column chromatography purification was needed only in the final step. The oxime geometry was determined as (E) based on NMR and as reported earlier.[22,23]

Methyl esters (**7**–**9**) were then coupled with various types of polyamines[20,24] as shown in Scheme 2. This efficient synthesis afforded the products (**10**–**21**) with approx. 50–55% yield. The polyamines chosen for the coupling were biogenic polyamines,



Scheme 2. Synthesis of spermatinamine analogues (**10**–**21**).