Understanding the mode of action of lynamicin D

Bisindolyl alkaloids represent a large family of natural products that exhibit potent and diverse biological activities such as anti-inflammatory, antimicrobial, antiviral and antitumor. Some of these secondary metabolites are currently evaluated in clinical trials for the treatment of various cancer types such as staurosporine, a potent inhibitor of protein kinase C and rebecamycin, a topoisomerase I inhibitor. The bisindole pyrroles, lynamicins were isolated from the marine actinomycete, NPS12745 and were found to exhibit a broad-spectrum antimicrobial activity with MIC values in the low micromolar range. In this study WE have developed the first total synthesis of lynamicin D and have performed several experiments to shed light into the molecular mechanisms that govern its biological activity.

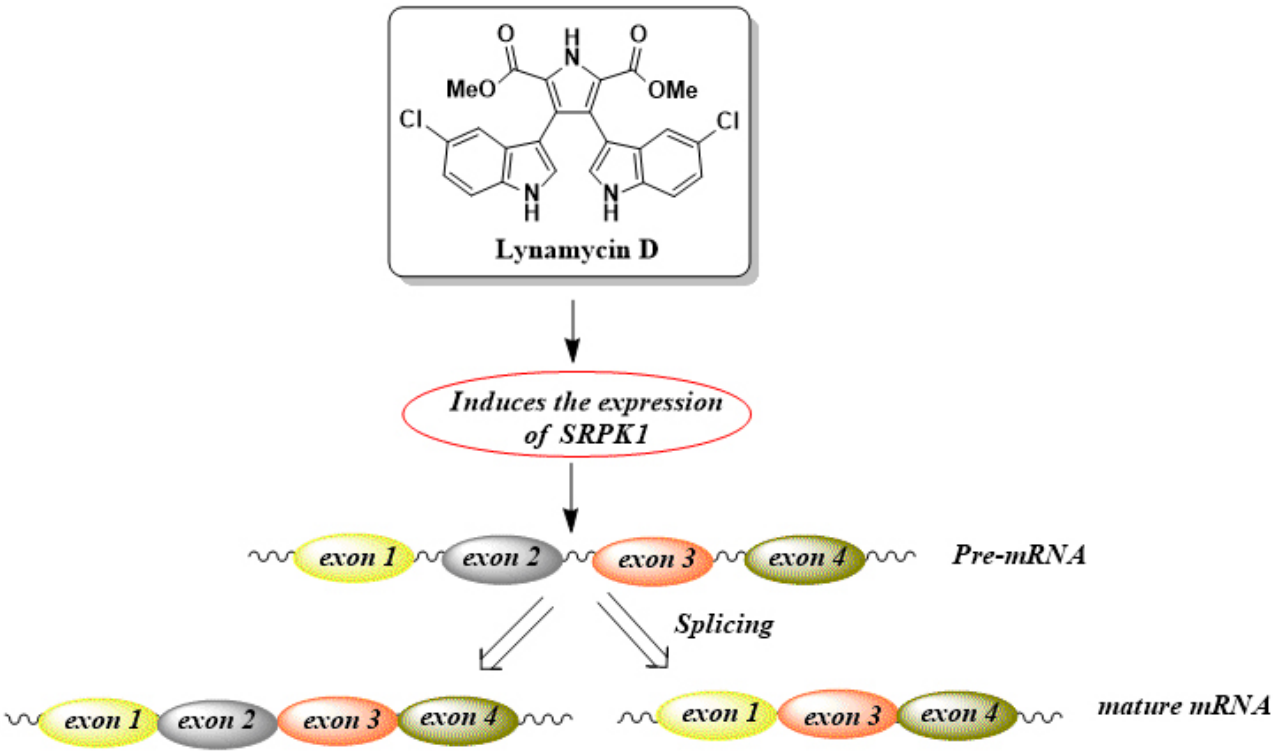

Fig. 1. Lynamicin D an affects splicing by inducing the expression of SR Protein Kinase 1.

The synthesis of lynamicin D involved a Suzuki coupling as the key step for the assembly of bisindole pyrrole skeleton. The spectral and analytical data (^{1}H, ^{13}C NMR, MS) of synthetic lynamicin were identical to those of the natural lynamicin D. Susequently, the viability of various tumor cell lines by MTT assays in the presence of lynamicin D was assessed. It was found that the viability of HeLa (human cervix adenocarcinoma), A549 (human lung carcinoma), and T98G (human brain glioblastoma multiforme) was not significantly affected after treatment with different

concentrations of lynamicin D for 48 h. Inspired by the biological activities the indolocarbazole topoisomerase I inhibitor NB-506, we have tested whether lynamicin D could affect pre-mRNA splicing. It was found that it affects splicing of the insulin, SRp20 and SMN2 minigenes similarly to SRPK1 kinase, the key kinase involved in both constitutive and alternative splicing. We have also shown that lynamicin D does not affect the activity and subcellular localization of SRPK1, but it induces the expression the levels of SRPK1 in cells.

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Publication

Lynamicin D an antimicrobial natural product affects splicing by inducing the expression of SR protein kinase 1.
Sigala I, Ganidis G, Thysiadis S, Zografos AL, Giannakouros T, Sarli V, Nikolakaki E
Bioorg Med Chem. 2017 Mar 1