Silstatins 1-8 and Structural Modifications: Antineoplastic Agents

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Technology description

The promise of marine derived microorganisms as productive sources of new anticancer and antiproliferative drugs continues to expand. Previously, Dr. Pettit and his team isolated and determined the structures of two very potent cancer cell growth inhibitors, cyclodepsipeptides from Bacillus silvestris, carried by a South Pacific crab. Subsequently, they completed the total synthesis of bacillistatin 2. Structurally, the bacillistatins are similar to valinomycin, a well-known antibiotic and cytotoxic cyclodepsipeptide that acts as a carrier-type potassium ionophore. With the recent advent in the antibody-drug conjugate (ADC) technology, there is a renewed interest in natural products as a source of potent payload for ADCs.

Dr. Pettit and his team at Arizona State University have expanded upon their earlier discovery of the remarkable anticancer bacillistatins from Bacillus silvestris and conducted SAR and other structural modifications such as availability of a free hydroxyl group for ADC and other prodrug linkage. This has resulted in seven structural modifications designated Silstatins 1-8 where the exceptional cancer cell growth inhibition of some of them ranges from GI50 10-3-10-4 μg/mL. Silstatin 7 was converted to a glucuronic conjugate that has a potential application as a pro-drug.

These potent cancer cell growth inhibitors have a long patent life and are highly amenable to conjugation to further increase their utility and selectivity as well as reduce potential side effects.

Application area

Cancer cell growth inhibitors
Suitable as payloads for ADCs
Glucuronide derivative of Silstatin 7 (prodrug: releases Silstatin 7 in vivo)
Potential application as a free drug

Advantages

Highly potent inhibitors of cancer cell growth
Suitable as payloads for ADCs
Hydroxyl group for convenient conjugation to antibodies through a linker
Glucuronide derivative of Silstatin 7 as a pro-drug

Potential application as a free drug
Intrinsic tumor targeting property
Mechanism of action - Likely to act as K+ ionophore
Total synthesis achieved

Institution

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