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PII: S0960-894X(14)01378-X
DOI: http://dx.doi.org/10.1016/j.bmcl.2014.12.070
Reference: BMCL 22315

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 15 October 2014
Revised Date: 17 December 2014
Accepted Date: 19 December 2014

Please cite this article as: Verma, V.A., Pillow, T.H., DePalatis, L., Li, G., Phillips, G.L., Polson, A.G., Raab, H.E., Spencer, S., Zheng, B., The Cryptophycins as Potent Payloads for Antibody Drug Conjugates, *Bioorganic & Medicinal Chemistry Letters* (2015), doi: http://dx.doi.org/10.1016/j.bmcl.2014.12.070

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The cryptophycins are a potent class of cytotoxic agents that were evaluated as antibody drug conjugate (ADC) payloads. Free cryptophycin analog **1** displayed cell activity an order of magnitude more potent than approved ADC payloads MMAE and DM1. This potency increase was also reflected in the activity of the cryptophycin ADCs, attached via a either cleavable or non-cleavable linker.

Antibody drug conjugates (ADCs) are currently an emerging class of treatment for targeted therapies against cancer.[1-4] ADCs consist of an antibody conjugated to a potent cytotoxic agent that targets a specific antigen overexpressed on a tumor cell. The antibody directs the ADC to the preferred site of action and, following internalization, the cytotoxin is released, causing cell death. The recent approvals of ADCETRIS® (brentuximab vedotin)[5] and KADCYLA® (ado-trastuzumab emtansine)[6,7] have heralded in this new class of therapeutics with the potential to transform cancer treatments. As an indication of this promise, over 30 ADCs are currently in various clinical trials.[1,8]

However, the vast majority of clinical (and approved) ADCs utilize two payloads, auristatin and maytansine derivatives.[9] While the use of these cytotoxic agents has proven successful, the next generation of ADCs has the opportunity to make use of additional payloads with the potential to address current shortcomings such as selectivity, resistance, potency and undesirable physiochemical properties, amongst others.

The cryptophycins (Figure 1) were isolated from cyanobacteria of the genus *Nostoc* in the early 1990s and displayed potent activity against cancer cell lines.[10] Subsequently, they were found to bind to microtubules at the *vinca* binding site.[11-13] Significant efforts were put forth to advance this class of compounds clinically but results from clinical trials indicated unacceptable levels of toxicity at doses required for a therapeutic effect.[14,15] Although the cryptophycins were unable to advance as stand-alone agents, they possess characteristics that make them suitable as ADC payloads: a high level of potency, relative hydrophilicity (Figure 1), and lack of PgP susceptibility,[16] a common resistance mechanism for ADCs.[17-19] Additionally, while cryptophycin itself lacks a suitable chemical handle for attachment to an antibody, analogs have been described[20-22] that retain potency and incorporate a functional[23] handle in the form of a nucleophilic amine (Figure 1).

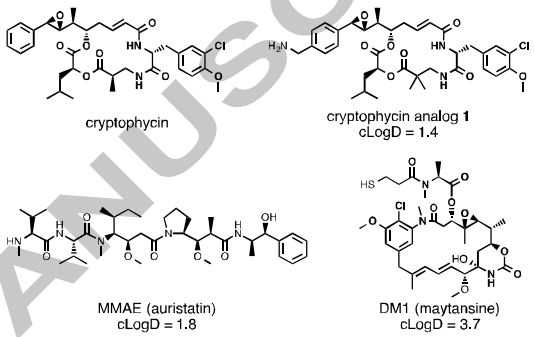

Figure 1. Cryptophycin, cryptophycin analog **1**, MMAE and DM1. cLogD calculated at pH 7.4.

The first step in evaluating the potential for a cryptophycin to function as an effective ADC payload was to confirm its single agent potency. As such, cryptophycin analog **1**[20] was assayed against a panel of cell lines comprising a variety of cancer cell types (Table 1.). The potent picomolar activity of compound **1** against this panel was consistent with potencies reported in the literature for the cryptophycin class[21] and indicated its potential to be effective as an ADC agent. Moreover, comparison to the approved ADC payload classes of the auristatins and the maytansines indicated potency increases of one to two orders of magnitude for cryptophycin **1** (Table 1).

Cell line	IC_{50} (nM)		
	1	MMAE	DM1SMe
MDA-MB-231 (breast)**)**	0.044	1.7	0.22
KPL-4 (breast)	0.014	0.23	0.060
MES-SA (uterine)	0.034	1.3	0.18
HCT-116 (colon)	0.024	0.49	0.079
DLD-1 (colon)	0.059	3.7	0.18
A2058 (skin)	0.015	0.44	0.063
BJAB (B-cell)	0.030	0.55	0.11