ADC Case Study

Custom Synthesis of ADC Linker-payload SET

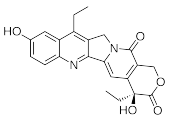
Creative Biolabs
Antibody-drug Conjugate

Introduction

The warhead of an antibody-drug conjugate (ADC) is comprised of a cytotoxic payload drug and a molecular linker that covalently bridges the antibody and the payload. With an extensive library of payload drugs and linkers, plus years of experience in synthetic and conjugation chemistry, Creative Biolabs is dedicated to helping our clients design and prepare highly customized linker and drug-linker complexes for the creation of ADCs using our featured "DrugLnk" services. From conventional payload-linkers bearing auristatin or maytansinoid derivatives to more innovated warheads such as topoisomerase inhibitors, we have created many unique compounds tailored to clients' special projects.

Presented here is a case study for the synthesis of two customized payload-linker complexes via the "DrugLnk" organic synthesis service. SN38 is the payload of choice and two cleavable linkers are used to formulate the SN38-linker complexes. For the protection of custom IP, the reaction conditions, catalysts, as well as solvents are omitted from the synthesis routes.

SN38: a novel payload for ADC development



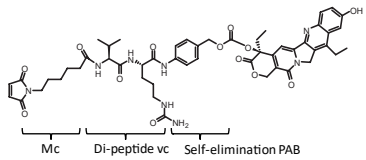
SN38 is an antineoplastic drug. It is the active metabolite of irinotecan (an analog of camptothecin - a topoisomerase I inhibitor) but is 1000 times more active than irinotecan. So far, two ADCs bearing SN38 as payload, both developed by Immunomedics, have entered clinical trial stage.

CBL has extensive experience with SN38-related payload-linker synthesis. The successful cases include the synthesis of Mc-vc-PAB-SN38, a relatively simple synthesis involving 3 steps, and that of CL2A-SN38 (proprietary for Immunomedics), a much more complex construct that requires 10-step synthesis.

SN38 ADCs in clinical trials

SN38 (irinotecan prodrug)						
Sacituzumab govitecan (also known as IMMU-132)	IgG1	TROP2	CL2A-SN38	Immunomedics (licensed to Seattle Genetics)	TNBC (phase III)	NCT02574455
Labetuzumab govitecan (also known as IMMU-130)	IgG1	CEACAM5	CL2A-SN38	Immunomedics	Metastatic CRC (phase II)	NCT01915472

Case 1: Mc-vc-PAB-SN38

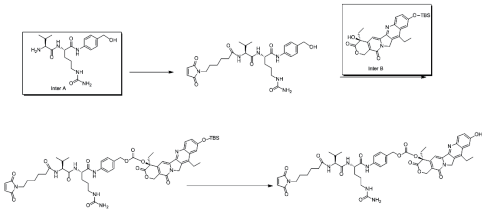


Compound specifics:

1. Chemical formula: C51H58N8O13
2. MW: 991.05
3. Elemental analysis: C-61.82; H-5.86; N-11.31; O-21.01

Synthesis route design:

Based on the structure of Mc-vc-PAB-SN38, a 3-step synthesis route was designed.



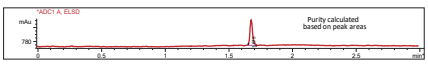
Synthesis of Mc-vc-PAB-SN38:

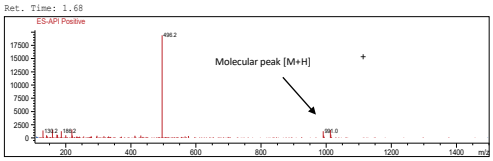
1. Reactions for each step were carried out in optimized conditions with suitable solvents and catalysts, if necessary.
2. The yields of each step were recorded and reported, and the products from each step were characterized by LC-MS to ensure the correct MW.
3. The final product: Mc-vc-PAB-SN38 was characterized by both LC-MS and 1HNMR to assess purity and validate structure.
4. Synthesis lead time was 3 weeks.

Results

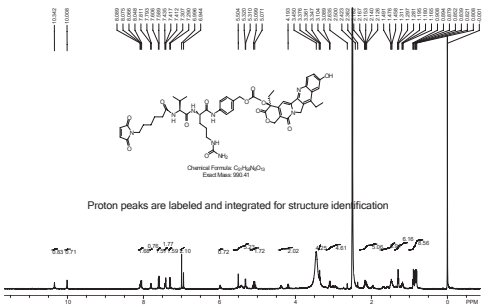
Mc-vc-PAB-SN38 was successfully synthesized in 3 weeks. Final product is characterized as:

1. Purity: > 95% by LC-MS

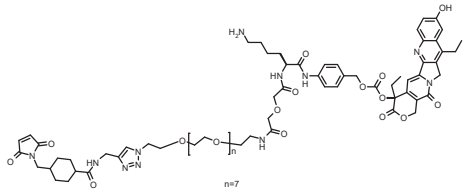




2. Structure confirmation: compound structure validated by 1HNMR



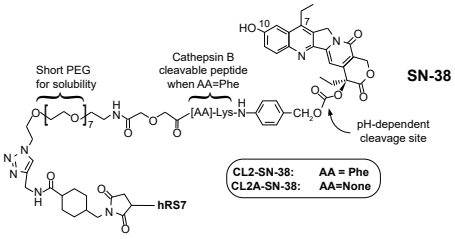
Case 2: CL2A-SN38



Compound specifics:

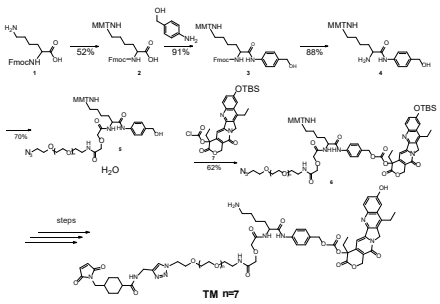
1. Chemical formula: C73H97N11O21
2. MW: 1479.7
3. Elemental analysis: C-59.88; H-6.63; O-22.97; N-10.52

CL2A-SN38 structure breakdown:



Synthesis route design:

Based on the structure of CL2A-SN38, a 10-step synthesis route was designed.

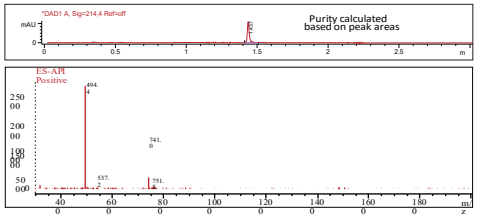


Synthesis of CL2A-SN38:

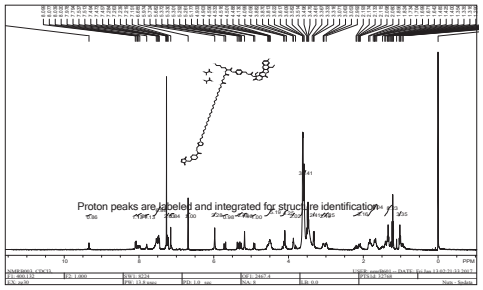
1. Reactions for each step were carried out in optimized conditions with suitable solvents and catalysts, if necessary.
2. The yields of each step were recorded and reported, and the products from each step were characterized by LC-MS to ensure the correct MW.
3. The final product: CL2A-SN38 was characterized by both LC-MS and 1HNMR to assess purity and validate structure.
4. Synthesis lead time was 10 weeks.

Results

CL2A-SN38 was successfully synthesized in 10 weeks. Final product is characterized as:



2. Structure confirmation: compound structure validated by 1HNMR



Conclusions

1. Using the "DrugLnk" custom synthesis service, Creative Biolabs successfully synthesized two SN38-linker complexes.
2. "DrugLnk" custom synthesis service is well-suited for simple synthesis tasks with only a few steps and complex organic synthesis with multiple steps (in this case, a 10-step synthesis was successfully demonstrated).
3. The compounds prepared by the "DrugLnk" custom synthesis service are correct in structure and show excellent purity.

References

1. Ramesh, M., Ahlawat, P., Srinivas, N.R. Biomed Chromatogr. 2010, 24: 104-123.
2. Cardillo, T.M., Govindan, S.V., Sharkey, R.M., *et al.* Bioconjug Chem. 2015, 26: 919-931.
3. Sharkey, R.M., Govindan, S.V., Cardillo, T.M., *et al.* Mol Cancer Ther. 2012,11: 224-234.
4. Jain, N., Smith, S.W., Ghone, S., *et al.* Pharm Res. 2015, 32: 3526-3540.

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