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White Paper

Use of Payload Core Compounds to Accelerate ADC Clinical Development Timelines

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With their ability to target specific cells and minimize off-target toxicity, antibody drug conjugates (ADCs) are being leveraged to treat serious diseases including cancer. To date, eleven ADCs have been approved and hundreds are in development. These complex biologics consist of a targeting antibody, a cytotoxic payload, and a linker. The linker attaches the payload to the antibody and is designed to be stable in circulation and often releases the payload once the ADC is inside the targeted cells.

While more than forty natural product classes have been used as payloads, most of the ADCs that have entered the clinic incorporate derivatives of two natural products: dolastatin 10 and maytansine (Figure 1). Dolastatin 10 is a tubulin inhibitor isolated from the Indian Ocean sea hare *(Dolabella auricularia)* and is included in five commercially available ADCs. Maytansine, derived from an east African shrub *(Maytenus ovatus)* is also a tubulin inhibitor and is used in one commercial ADC.

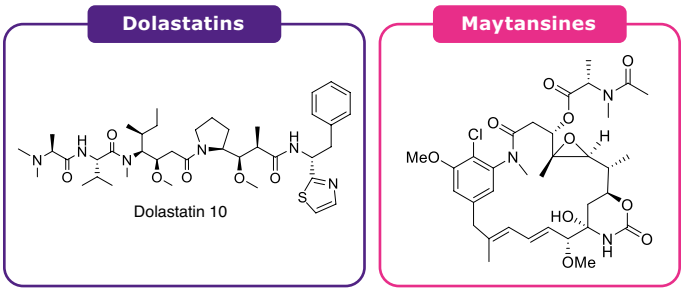


Figure 1.
Chemical structures of dolastatin 10 and maytansines.

Access to Payloads

For developers of ADCs, gaining access to the desired payload can be challenging as their synthesis is more complex compared to most other small molecules, requiring a multi-step, labor-intensive process. For research purposes, some commonly used payloads can be purchased off-the-shelf from a number of different suppliers. Clinical development, however, requires a secure GMP supply; in this case, there is a potential to license the compound. This can require a fair amount of time for negotiation and costs and typically includes milestones and royalty payments. A further challenge is that the specific structure might not be available, as licensing ultimately depends on the willingness of the originator.

Novel compounds are typically synthesized from scratch either in-house or in conjunction with a contract development and manufacturing organization (CDMO). The synthetic route must be established, along with a reliable and robust process for production and testing methods to identify possible impurities. The impurity profile then needs to be managed throughout development and manufacturing.

Figure 2 shows the lengthy and complex synthetic approach to making a dolastatin 10 derivative. The stereogeneic centers in each of these compounds must be managed from a purity profile; the total number of resulting compounds that must be managed can exceed 500. Two to four years and more than €5 million may be required to establish the synthetic process to produce the clinical supply. Whether synthesizing directly or licensing, the ADC developer must also manage and navigate the extensive patent landscape to ensure freedom to operate. Further complicating the use of a 15–20 step complex synthesis will be ongoing supply chain challenges, as well as the need for quality assurance and regulatory compliance.

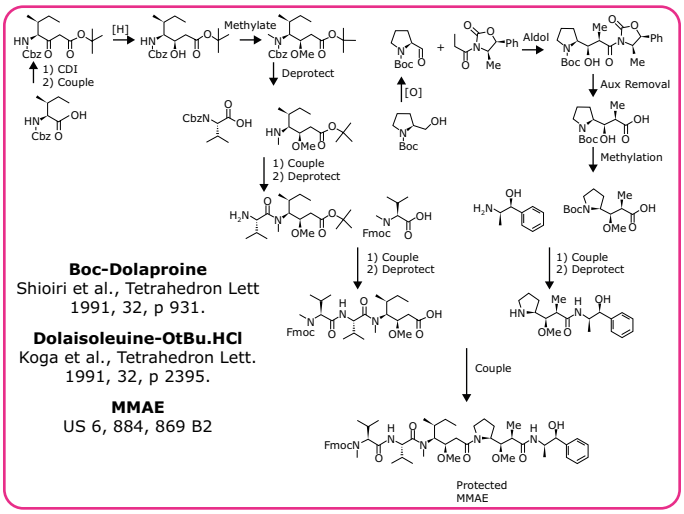


Figure 2.

The traditional synthetic approach to making a Dolastatin 10 derivative requires 16 steps.

A More Efficient Approach to Payload Synthesis

Use of a GMP-quality payload intermediate as a starting point for payload synthesis enables a more efficient process for research and process development chemists and chemistry, and manufacturing controls (CMC) teams. These intermediate compounds are the core of the active ingredients of Dolastatin 10 and maytansine natural products. By using these cores as the starting point, what may have required a 15–20 step chemical synthesis will become three to four steps.

DOLCore™ and MAYCore™ are the core components that are structurally conserved across the various dolastatin 10 and maytansine payloads, respectively, that have been brought into the clinic (Figure 3). The DOLCore™ structure includes two handles for coupling to the ADC; one handle is typically reacted with standard peptide coupling conditions while the Boc protection can be removed with acid and then reacted with standard peptide coupling conditions.

Any version of dolastatin 10 that has ever entered the clinic can be produced from this core compound. In addition, these core compounds offer good control and understanding of the diastereoselectivity of all the reactions that are run and thus the impurity byproducts.

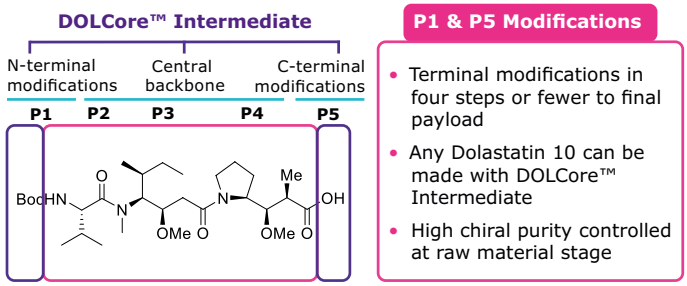


Figure 3.

Modifications of the DOLCore™ compound can made to address specific payload needs.

An assessment of all the stereogenic centers that can be an up or down and anything that has a reasonable chance of forming has been conducted and confirms the diastereomeric purity of the compounds. Potential impurities generated by theoretically labile stereocenters were independently synthesized; the chromatogram shown in Figure 4 shows a final product testing method for a typical lot of payload made using a DOLCore™ intermediate. Retention time markers of the commonly observed byproducts or impurities are quite low and are shown in blue with their problematic groups circled in red. The typical observed purity is >99.5 A% with D-Val-DOL and des-Me-DOL impurities present, indicating a high-quality product with very high diastereoselectivity. With use of a core compound as a starting material, the stereogenic centers only need to be managed during the final few steps which reduces risk and increases simplicity.

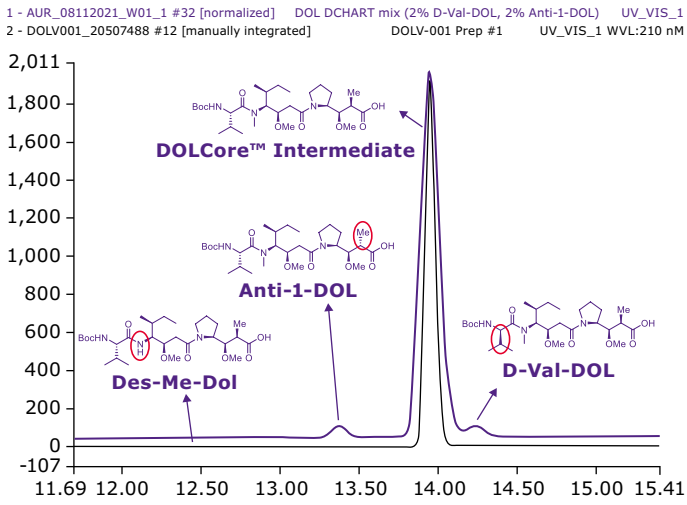


Figure 4.

DOLCore™ compound impurities are well controlled.

Figure 5 compares the synthesis of monomethyl auristatin E (MMAE) either starting from scratch or starting from the DOLCore™ compound. The conventional approach requires sixteen steps and creates a high number of labile centers that must be managed. By starting the process with DOLCore™ Intermediate, the synthesis route is reduced to just three chemical steps.

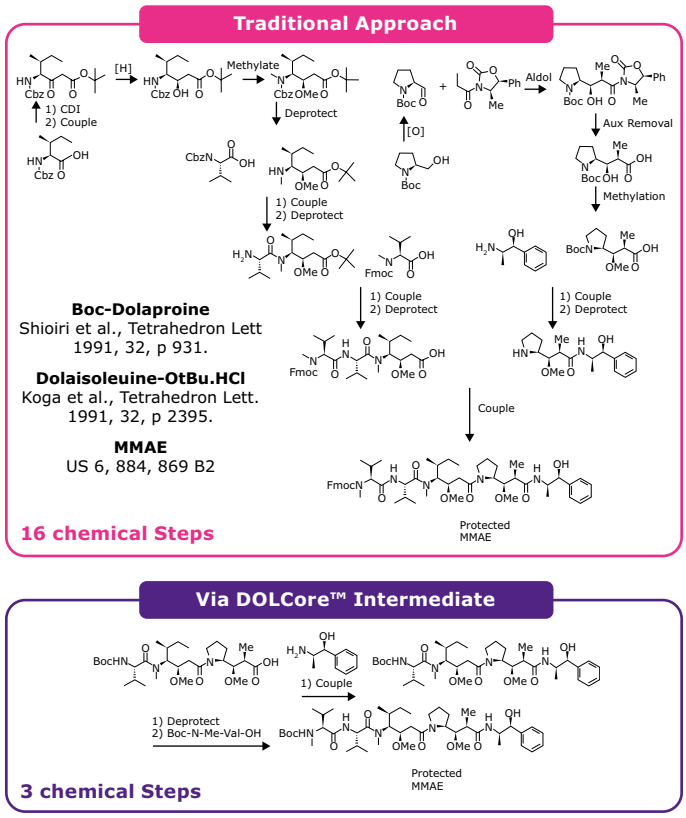


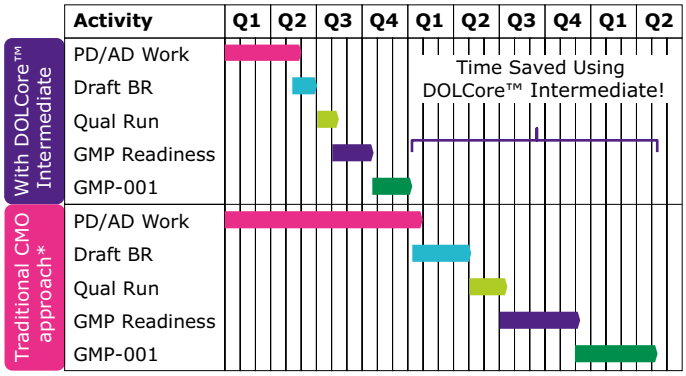
Figure 5.

Comparison on the conventional synthetic route of MMAE versus a process that begins with the DOLCore™ compound.

Time and Cost Savings

For researchers exploring a range of compounds, starting the synthetic route with a core compound accelerates the synthesis process, enabling many more compounds to be made and evaluated. From a CMC perspective, a shorter synthetic route increases speed to clinic because just a few steps must be performed and managed. Figure 6 summarizes the time savings with use of the off-the-shelf DOLCore™ compound as a starting point compared to a traditional CDMO approach to synthesizing a dolastatin 10 derivative.

With the traditional approach, development time may be more than one year given the length of the synthesis and the impurities to be managed. Following that initial synthesis, the typical sequence of events will be drafting the batch record, a non-GMP trial run, and GMP manufacturing, all of which can add up to two years.



*Assumes a 15-step process

Figure 6.

Using DOLCore™ versus a 15-step custom synthesis.

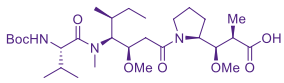
There are also significant cost savings across different phases of development with the use of DOLCore™ compared to traditional synthesis routes, as summarized in Figure 7. Costs include raw materials, development costs, and risk-associated costs. Accelerating the development timeline with the use of DOLCore™ allows for additional revenue to be generated within the patent exclusivity period.

	Route of Synthesis	Phase I	Phase I through Phase II	Phase I through Phase III
Time	Using DOLCore™ Intermediate	14 months	27 months	40 months
	Traditional Approach	41 months	78 months	116 months
Costs*	Using DOLCore™ Intermediate	$3M	$6M	$9.9M
	Traditional Approach	$6M	$12.7M	$20.7M

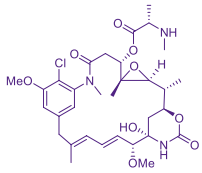
*Includes risk associated costs, raw materials and development costs

Figure 7.

Comparison of time and cost savings using a traditional synthetic route versus use of DOLCore™ Intermediate as a starting point.



DOLCore™ Intermediate



MAYCore™ Intermediate

Versatility	Speed	Reduced risk	Free Samples	Regulatory Support	Royalty – free	Exclusivity	
DOLCore™ Intermediate and MAYCore™ Intermediate can be modified to meet your specific linker-payload needs	DOLCore™ Intermediate reduces the number of synthesis steps from 15–20 **to 4 or fewer**	Supply chain risk reduction – Ready stock available	Free samples available now	Phase appropriate regulatory documents available	Royalty and milestone-free license	Earn **one extra year** of market exclusivity on the commercial drug	**Average increase in sales revenue of $175M USD***

*Based on time savings of developing a phase 1 candidate vs. a traditional approach and average 2020 sales revenue of commercial ADCs

Figure 8.

Summary of the benefits of DOLCore™ and MAYCore™ compounds for payload synthesis.

Figure 8 summarizes the benefits and value of starting with these core compounds for the synthesis of ADC payloads. These cores can significantly reduce the number of synthetic steps, accelerating workflows, reducing risks, and minimizing costs. Research chemists can make a larger number of compounds in a shorter period, while process and CMC teams can advance ADC candidates into the clinic with greater speed.

Both of these versatile core compounds are available without royalties or licensing fees and are backed with expert development and regulatory support.

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