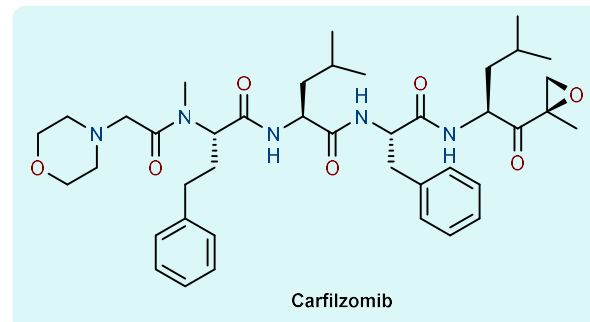
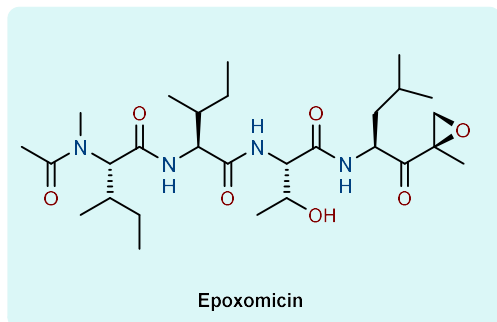
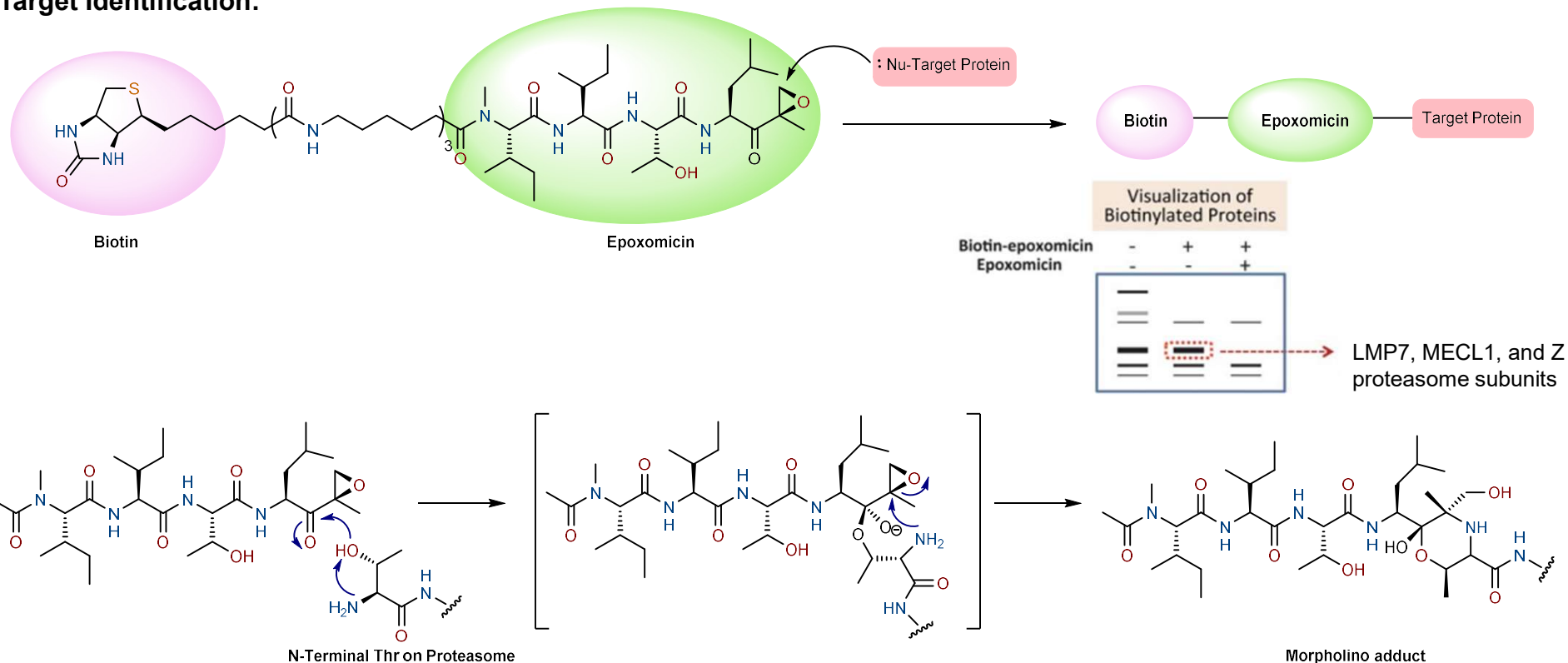


- Discovered by BMS from an *Actinomycetes* strain
- Displayed promising activity against murine B16 melanoma tumors



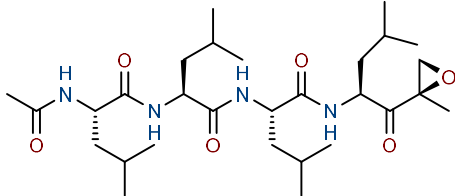
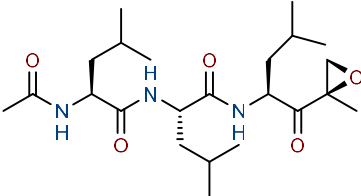
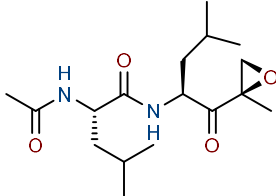
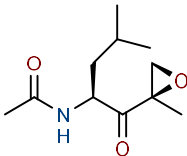
- Covalently binds 20S proteasome
- Use to treat relapsed or refractory multiple myeloma
- Approved in July 2012 “thus concluding the long journey from natural product pariah to FDA-approved cancer drug”

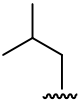
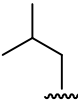
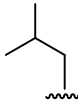
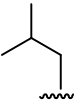

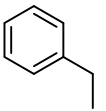
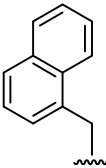
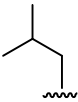

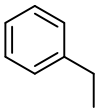
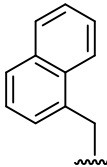
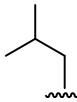
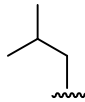
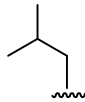
Target Identification:



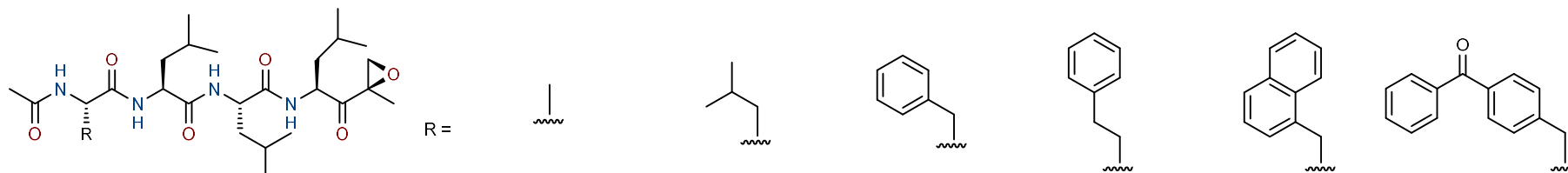
Crews, C. *Nat. Prod. Rep.* **2013**, 30, 600. <https://doi.org/10.1039/C3NP20126K>. Crews, C. *Proc. Natl. Acad. Sci.* **1999**, 96, 10403. <https://doi.org/10.1073/pnas.96.18.10403>.

Optimization:

Kinetic constants for inhibition of: $k_{obs}/[I]$ ($M^{-1}s^{-1}$)				
Chymotrypsin-like activity	14000 (50-150 nM)	780 (1-2.5 μ M)	3.1 (100-160 μ M)	-
Trypsin-like activity	-	5.1 (100-150 μ M)	-	-
Post-glutamyl peptide hydrolyzing act.	9.2 (100-160 μ M)	120 (8-12 μ M)	-	-

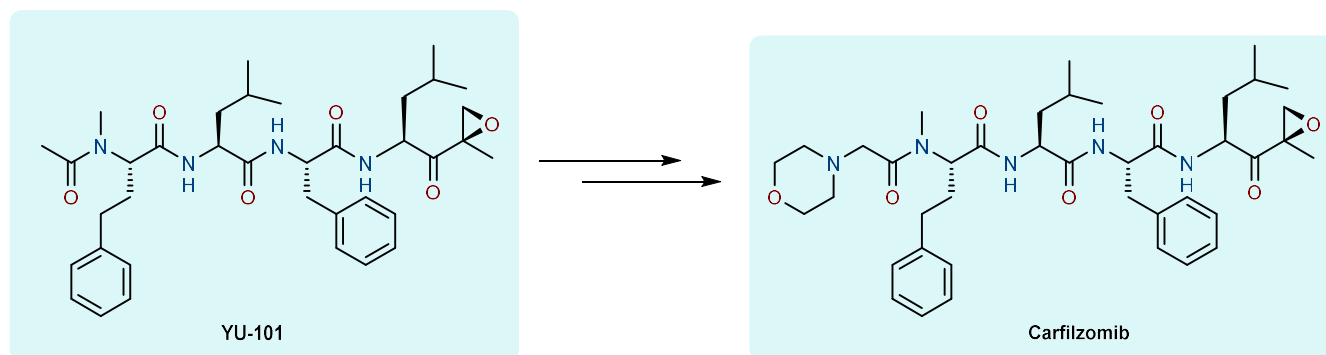
Kinetic constants for inhibition of: $k_{obs}/[I]$ ($M^{-1}s^{-1}$)	R ₁ =						
							
	R ₂ =						
							
Chymotrypsin-like activity	14000 (50-150 nM)	16000 (80-120 nM)	54000 (40-60 nM)	29000 (60-120 nM)	1300 (500-1000 nM)	8500 (200-400 nM)	31000 (40-100 nM)
Trypsin-like activity	-	4.1 (100-150 μ M)	-	-	2.0 (120-150 μ M)	-	-
Post-glutamyl peptide hydrolyzing act.	9.2 (100-160 μ M)	20 (60-80 μ M)	-	-	130 (10-16 μ M)	-	-

Optimization:



Kinetic constants for inhibition of:
 $k_{obs}/[I]$ ($M^{-1}s^{-1}$)

Chymotrypsin-like activity	5300 (400-800 nM)	14000 (50-100 nM)	37000 (40-80 nM)	63000 (40-80 nM)	29000 (60-120 nM)	23000 (90-150 nM)
Trypsin-like activity	3.8 (100-150 μ M)	-	5.5 (100-150 μ M)	5.4 (120-150 μ M)	-	-
Post-glutamyl peptide hydrolyzing act.	220 (8-12 μ M)	9.2 (100-160 μ M)	78 (20-40 μ M)	50 (30-50 μ M)	-	-



Prof. Craig Crews (Yale)



For process route, see:

Siddiqi, POTW: https://8cf9eb7e-b5ec-48cd-9fdd-580cfdeede43.filesusr.com/ugd/ad93af_f5c8ff6434c145a695b4fe46a1c75e99.pdf

Bock, POTW: https://8cf9eb7e-b5ec-48cd-9fdd-580cfdeede43.filesusr.com/ugd/06e0dc_ea257c986eae4b92939596eda35916fb.pdf