

### Examples how Natural Products can be Decorated with (Self-Immolative) Linkers

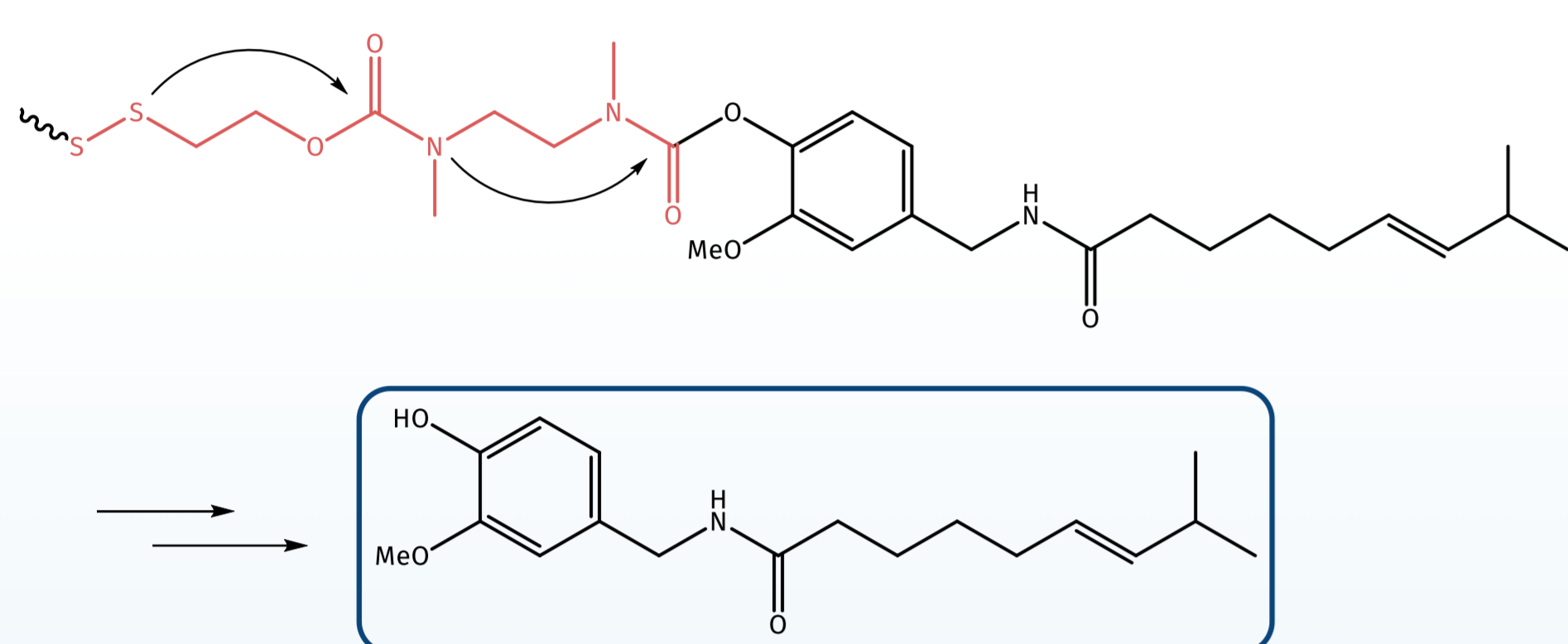
#### Capsaicin:

A natural alkaloid found in chilly peppers, paprika.

Responsible for the burning sensation in peppers

- an analgesic in topical ointments
- pain relieve in muscles and joints
- Reduction of peripheral neuropathy

**Linker-conjugated Capsaicin** undergoes self-immolative fragmentation upon reduction

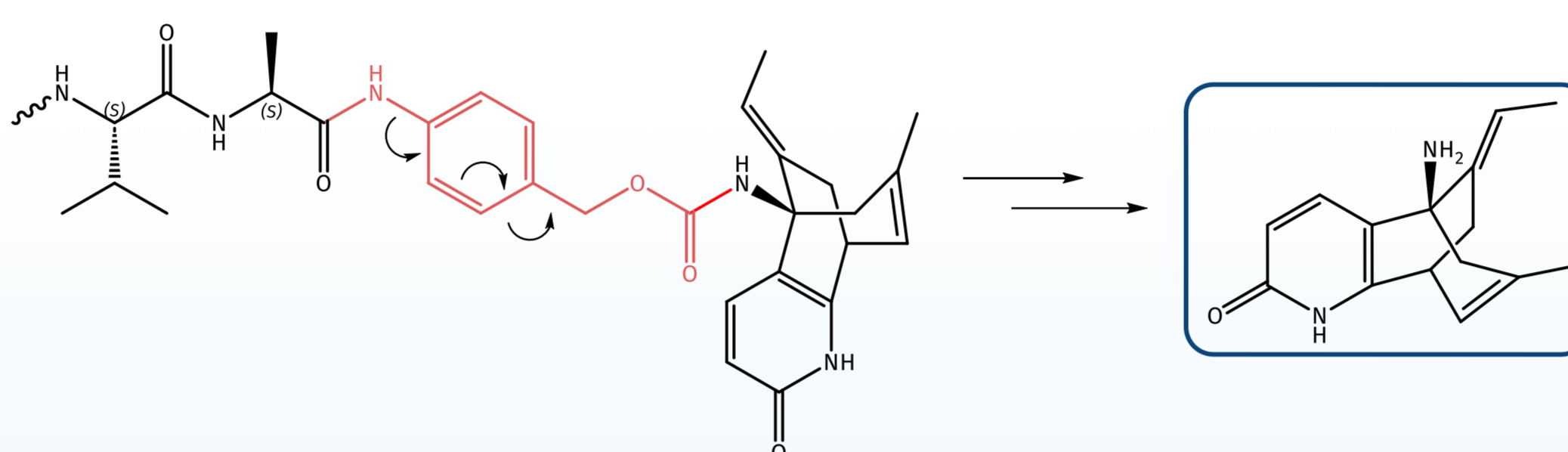


#### Huperzine A:

A natural alkaloid found in clubmoss family.

- acetylcholine esterase inhibitor
- NMDA agonist
- treatment of neurodegenerative (Alzheimer's)
- supplement to improve memory and cognitive functions

**Linker-conjugated Huperzine A** undergoes self-immolative fragmentation in the presence of cathepsin B.

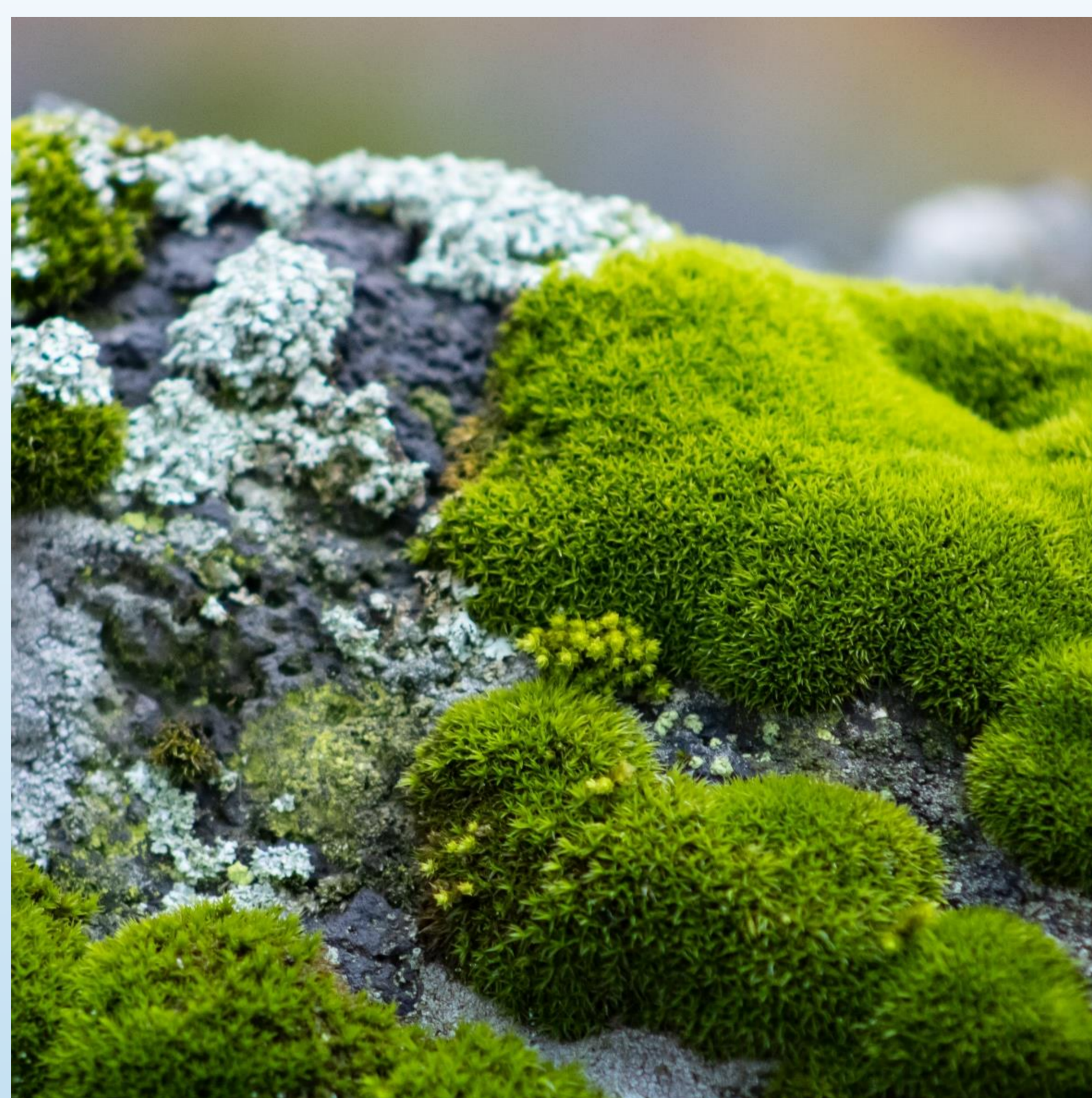
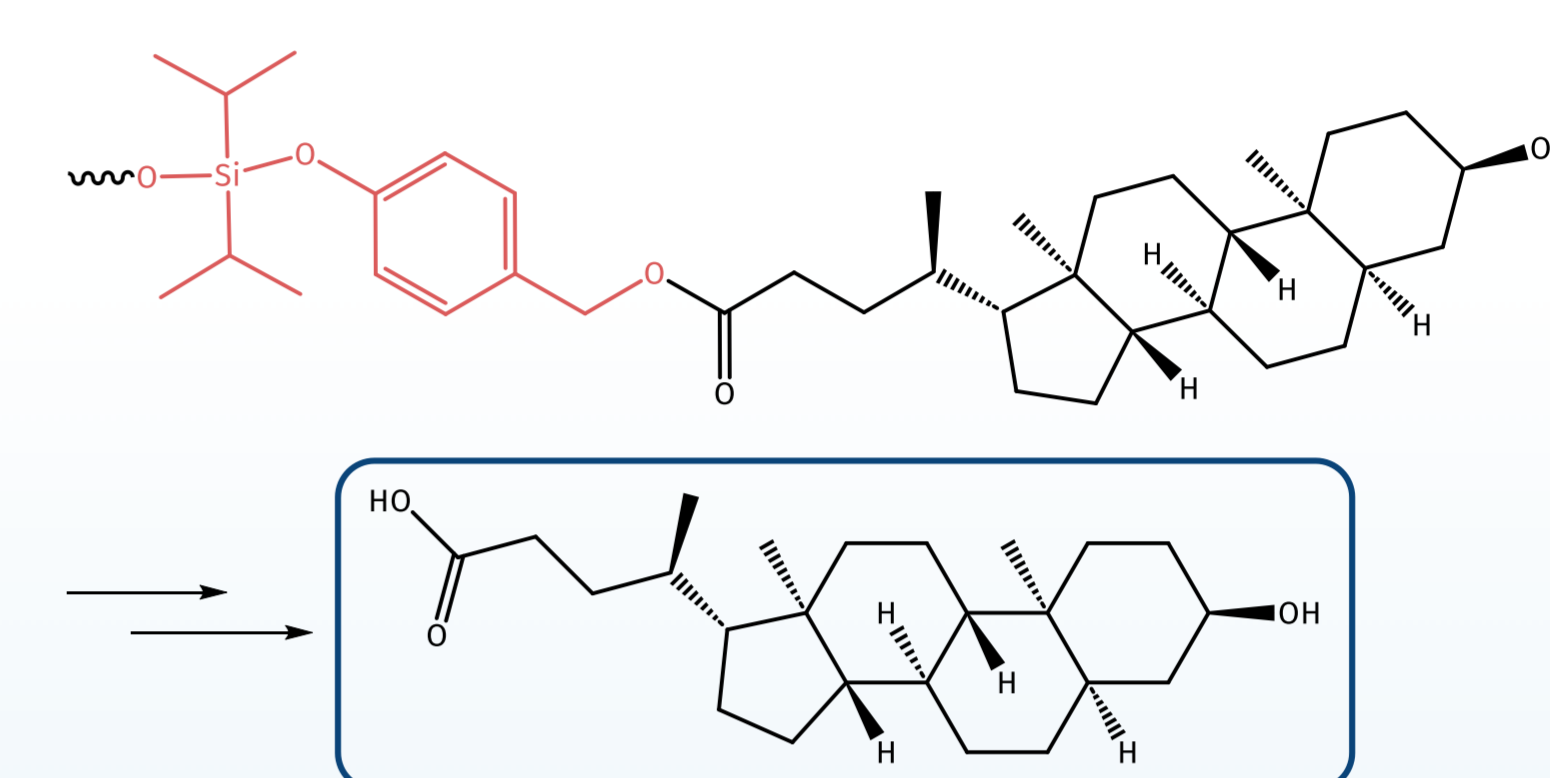


#### Lithocholic acid:

Natural compounds in the class of secondary bile acids produced by gut bacteria.

- anti-cancer research
- selective killing of neuroblastoma cells in the presence of healthy cells.
- a remedy to gallstone disease

**Linker-conjugated Lithocholic acid** undergoes self-immolative fragmentation under acidic conditions.



### Linkerology® - Conceptual Overview

Carrier	Surface Treatment & Conjugation Chemistry	Cleavage	Fragmentation	Cargo Functionality
<b>Biopolymers:</b> <ul style="list-style-type: none"> <li>• Peptides</li> <li>• Proteins</li> <li>• Antibodies</li> <li>• Single Chain</li> <li>• Nanobodies</li> <li>• Camelids</li> <li>• Oligonucleotides</li> <li>• Aptamers</li> </ul>	Thioether formation with maleimide Disulfide bond formation Acylation of amines His-Tag acylation Click conjugation (CuCAAC, SPAAC, IEDDA) Enzyme supported conjugation: <ul style="list-style-type: none"> <li>• HaloTag®</li> <li>• CLIP-Tag™</li> <li>• SNAP-Tag®</li> </ul> Sequence dependent conjugation (Sortase)	<b>Enzymatic hydrolysis:</b> <ul style="list-style-type: none"> <li>• Val-Ala</li> <li>• Val-Cit</li> <li>• Phe-Lys</li> <li>• Gly-Phe-Leu-Gly</li> <li>• Ala-Leu-Ala-Leu</li> <li>• Cyclobutyl-Ala</li> <li>• Cyclobutyl-Cit</li> <li>• Glucuronic acid</li> </ul>	p-Aminobenzyl p-Hydroxybenzyl p-Mercaptobenzyl Oxathiolone Dimethylimidazolidinone	Primary & secondary amines $\text{H}_2\text{N}$ Tertiary amines $\text{R}_1\text{-N-R}_2$ Alcohols Phenols $\text{HO}$ Carboxylic acids $\text{HO-C(=O)}$
<b>Carbon:</b> <ul style="list-style-type: none"> <li>• Nanotubes</li> <li>• Fullerenes</li> </ul>	Nitrenen addition via photoactivation of perfluoroarylazides	Reduction 	$\text{CO}_2$ 	
<b>Metals:</b> <ul style="list-style-type: none"> <li>• Gold</li> <li>• Silver</li> </ul>	Affinity of sulfur to gold and silver	Acidic hydrolysis 		
Metal oxide	Chelat formation			
<b>Plastic polymers:</b> <ul style="list-style-type: none"> <li>• Teflon</li> <li>• Polyethylene</li> <li>• Polystyrene</li> <li>• Latex</li> </ul>	Ammonia or acrylic acid plasma followed by amide bond formation			
Silicates	Affinity of silicon and oxygen			