

# Linkerology®

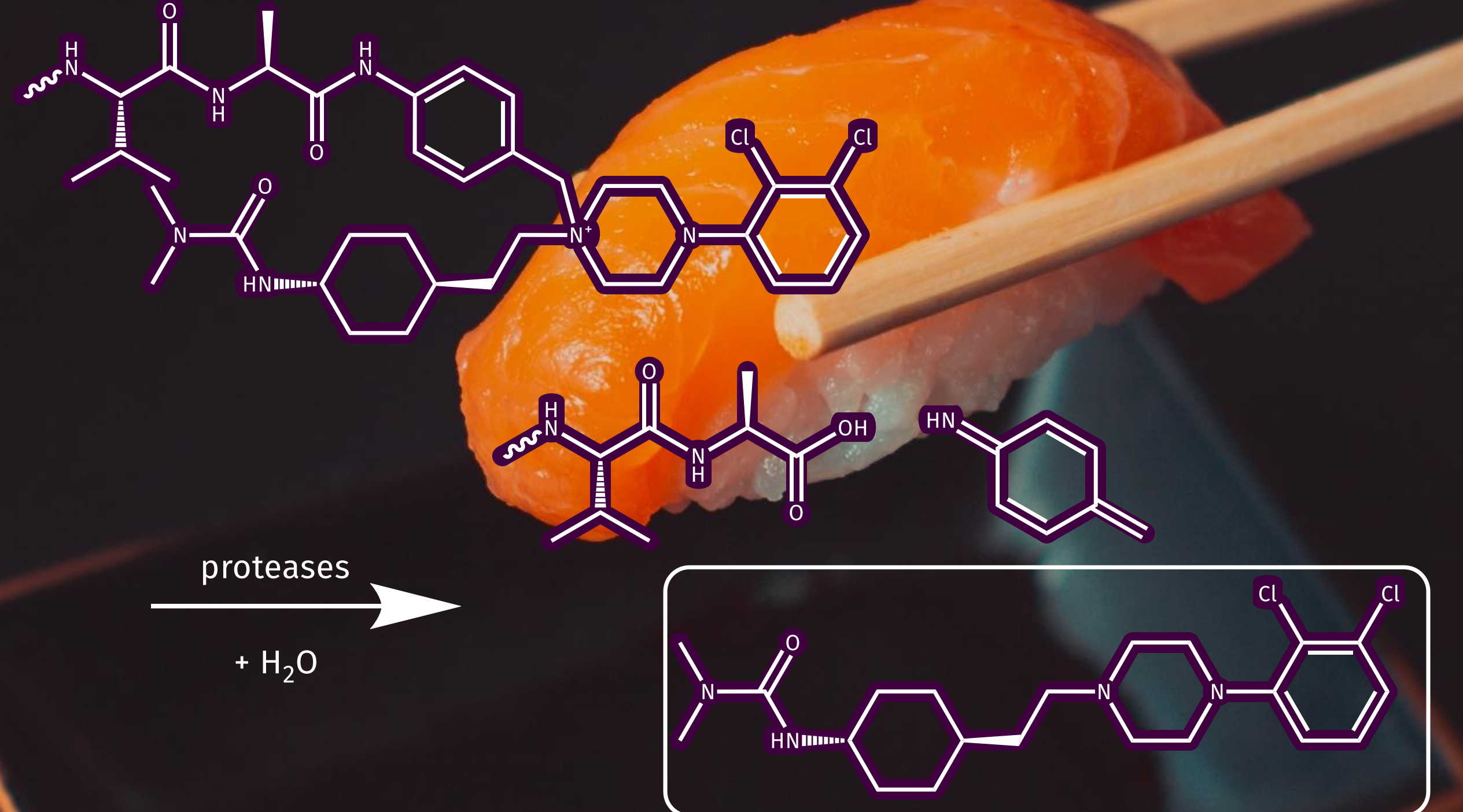
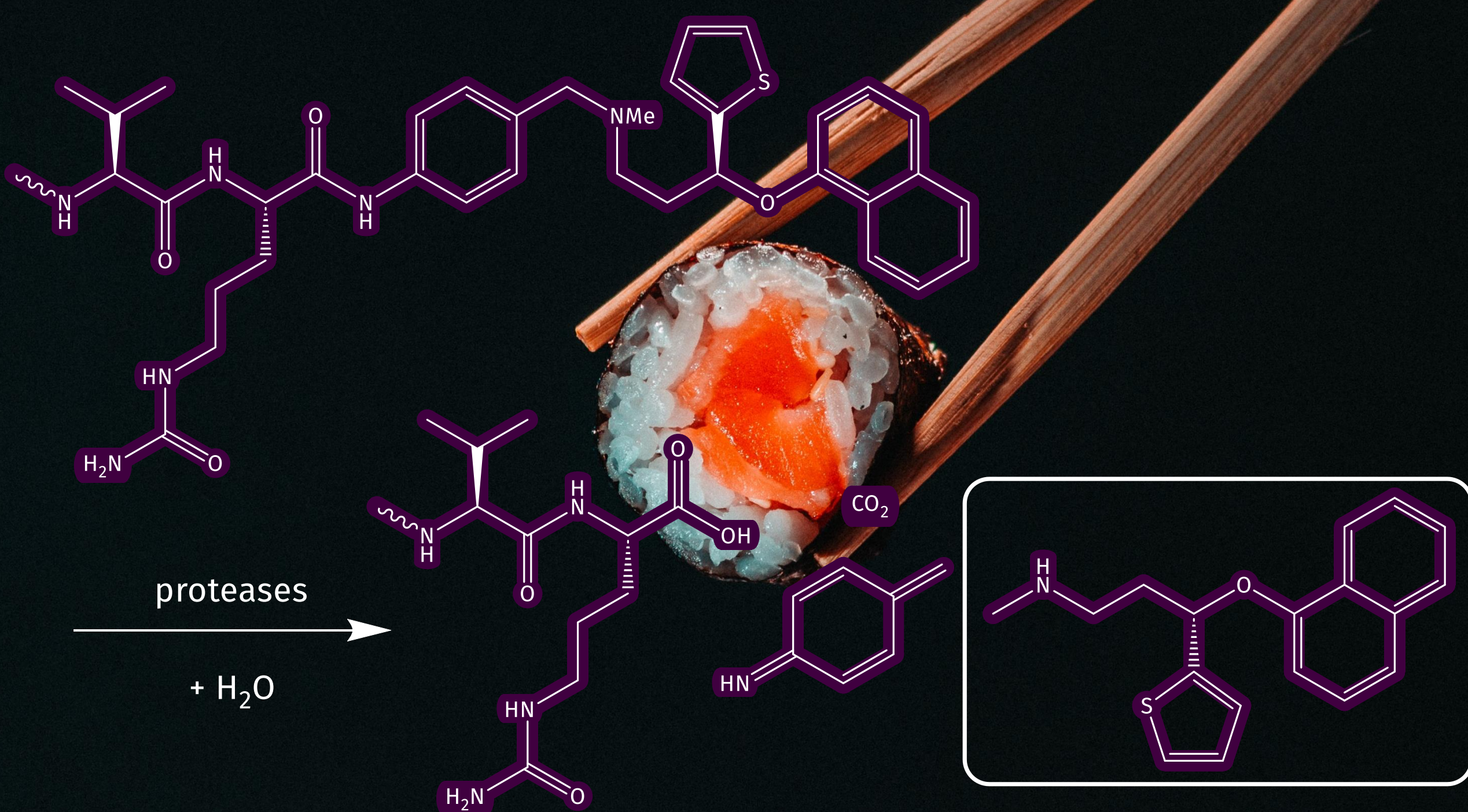
2023 # 07 – Conjugation of Small Molecule Drugs



Examples how Small Molecule Drugs can be Decorated with Self-Immolative Linkers

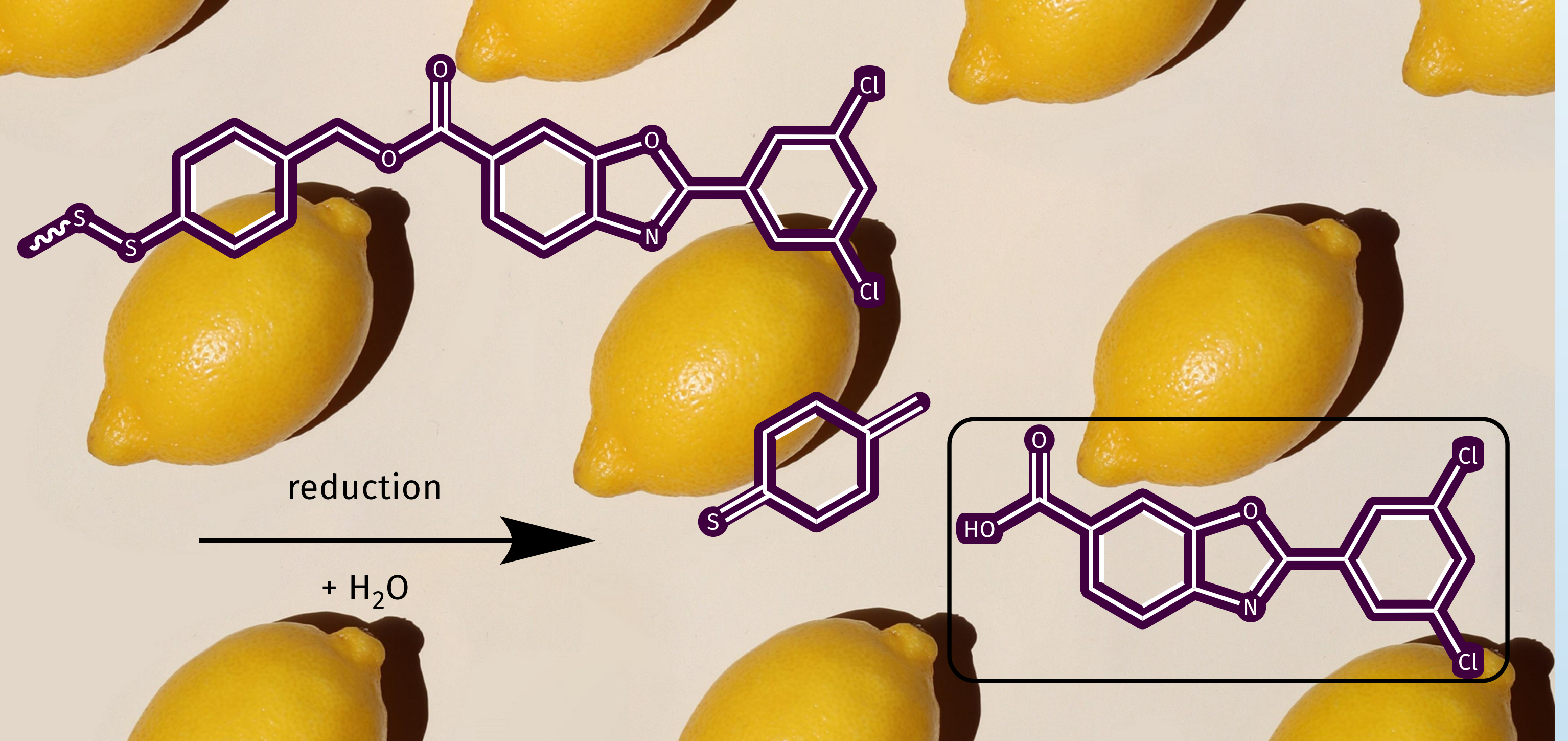
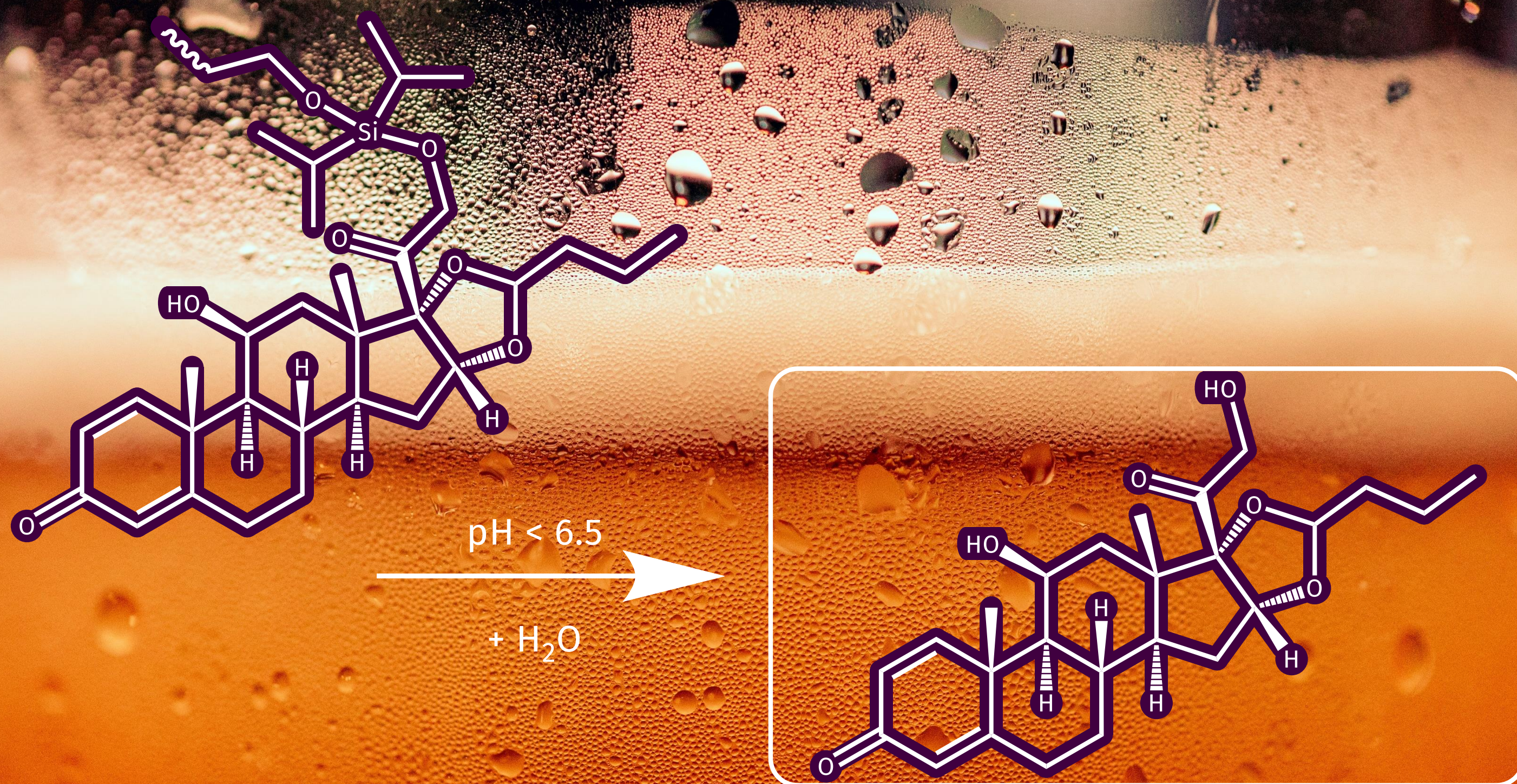
Functional group	Secondary amine
Brand names	Cymbalta, Drizalma Sprinkle, Irenka
Generic name	Duloxetine
Route of administration	Oral
Drug class	Serotonin-norepinephrine reuptake inhibitor
Sales in 2022	\$328 Million
Indications	Major depressive disorder, generalized anxiety disorder, neuropathic pain, chronic musculoskeletal pain, fibromyalgia
CAS #	116539-59-4

Functional group	Tertiary amine
Brand names	Vraylar, Reagila
Generic name	Cariprazine
Route of administration	Oral
Drug class	Atypical antipsychotic
Sales in 2022	\$ 2.038 Billion
Indications	Schizophrenia, bipolar mania, bipolar depression, major depressive disorder
CAS #	839712-12-8



Functional group	Alcohol
Brand names	Pulmicort, Rhinocort, Entocort
Generic name	Budesonide
Route of administration	Oral, nasal, tracheal, rectal, inhalation
Drug class	Corticosteroid
Sales in 2022	\$645 Million
Indications	Asthma and chronic obstructive pulmonary disease
CAS #	51333-22-3

Functional group	Carboxylic acid
Brand names	Vyndaqel, Vyndamax
Generic name	Tafamidis
Route of administration	Oral
Drug class	Pharmacological chaperone
Sales in 2022	\$2.447 Billion
Indications	Transthyretin amyloidosis, familial amyloid cardiomyopathy, familial amyloid polyneuropathy, transthyretin amyloidosis
CAS #	594839-88-0



## Linkerology® - Conceptual Overview

Carrier	Surface Treatment & Conjugation Chemistry	Cleavage	Fragmentation	Functionality of Natural Product
Metal surface	Affinity of sulfur to gold and silver	<b>Enzymatic hydrolysis:</b> • Val-Ala • Val-Cit • Phe-Lys • Gly-Phe-Leu-Gly • Ala-Leu-Ala-Leu • Cyclobutyl-Ala • Cyclobutyl-Cit • Glucuronic acid	<p><i>p</i>-Aminobenzyl <i>p</i>-Hydroxybenzyl</p> <p>CO<sub>2</sub></p> <p>Oxathiolone</p> <p>X = NH, S</p> <p>Dimethylimidazolidinone</p>	Primary & secondary amines Tertiary amines Alcohols Phenols Carboxylic acids
Metal oxide	Chelat formation			
Silicates	Affinity of silicon and oxygen	<b>Reduction</b> 	H <sub>2</sub> N— R <sub>1</sub> N— R <sub>2</sub> HO— HO—	
<b>Carbon:</b> • Nanotubes • Fullerenes	Nitrenen addition via photoactivation of perfluoroarylazides			
<b>Plastic polymers:</b> • Teflon • Polyethylene • Polystyrene • Latex	Ammonia or acrylic acid plasma followed by amide bond formation			
<b>Biopolymers:</b> • Peptides • Proteins • Antibodies • Single Chain • Nanobodies • Camelids • Oligonucleotides • Aptamers	Thioether formation with maleimide Disulfide bond formation Acylation of Amines His-Tag acylation Click conjugation (CuCAAC, SPAAC, IEDDA) Enzyme supported conjugation: HaloTag® CLIP-Tag™ SNAP-Tag® Sequence dependent conjugation (Sortase)			