Anti-cancer Compounds from Arizona State University

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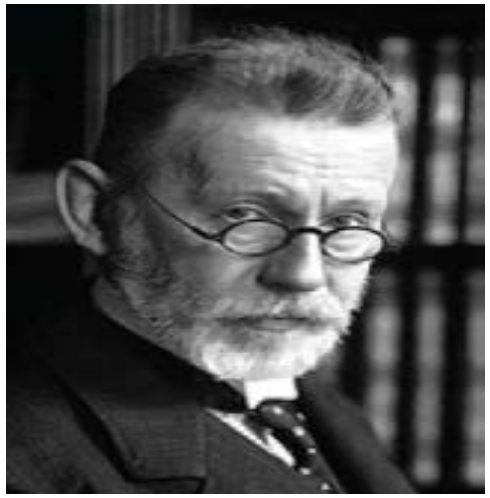
Prof. George Robert Pettit



ADC as a Modern Version of Ehrlich's Magic Bullet

Prof. Pettit from Arizona State University (ASU) is one of the key players that helped advance antibody drug conjugate (ADC) technology

Paul Ehrlich, George Koehler and Cesar Milstein, and Bob Pettit (clockwise from top left)

Nature Biotechnology 30 (7), 631- 637 (2012)

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Prof. George Robert Pettit

- A world renowned medicinal chemist with more than 800 publications
- Spent more than half century working on the discovery and development of anti-cancer compounds
- Discovered several hundred anti-cancer compounds from various natural sources
- Discovered and studied 19 separate drug classes
- An impressive portfolio of issued patents and patent applications
- Coined the term “statins” for these anti-cancer compounds long before that term was used for cholesterol lowering drugs
- Discovered dolastatin 10, one of the most cytotoxic compounds ever
- Synthesized numerous derivatives of dolastatin 10 with desirable medicinal properties
- Synthesized auristatin E, one of the most promising anti-cancer compounds

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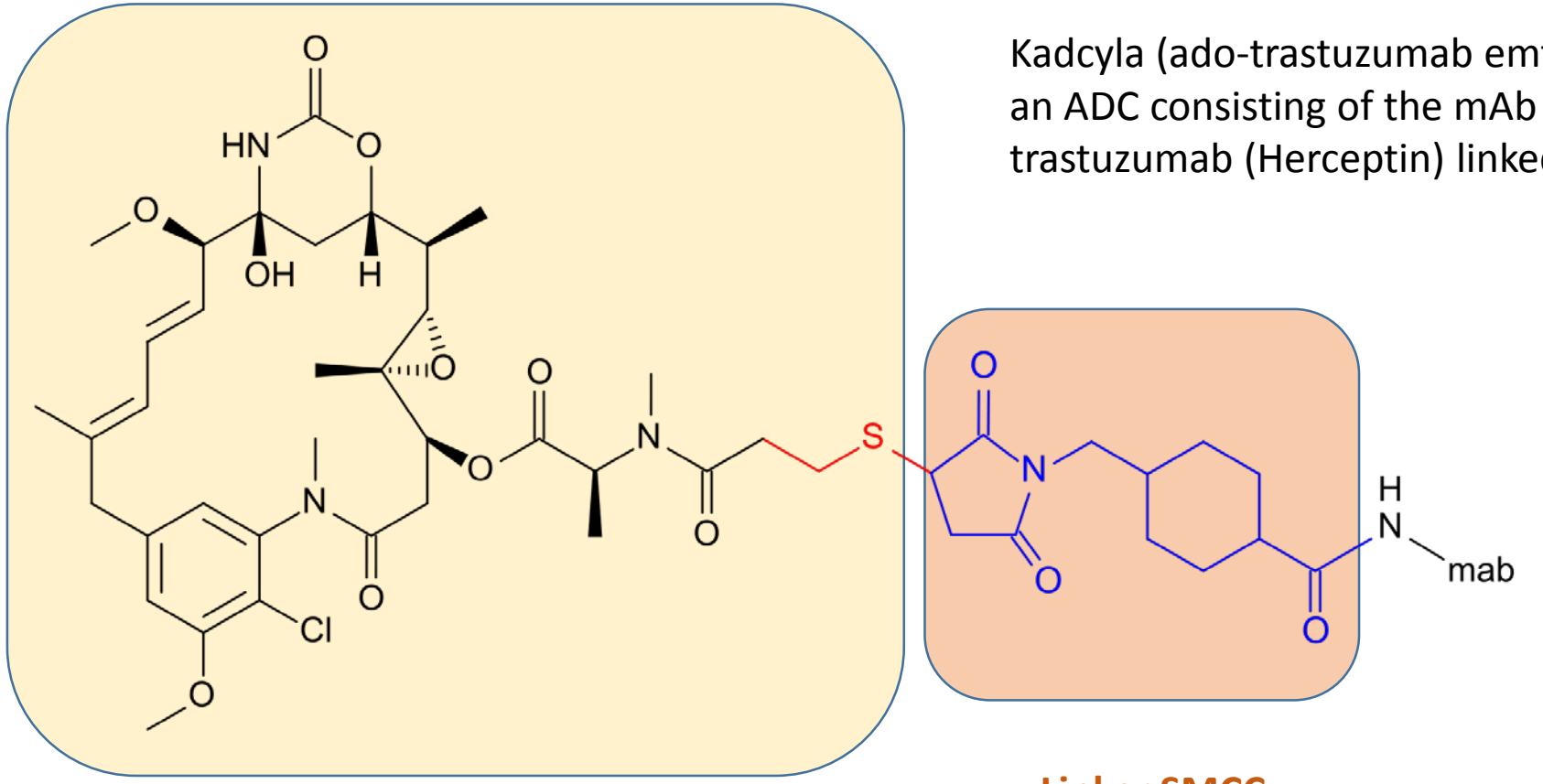
Typical Antibody-Drug Conjugate (ADC)

Kadcyla (ado-trastuzumab emtansine): an ADC consisting of the mAb trastuzumab (Herceptin) linked to DM1



Maytansine DM1

Linker SMCC

Genentech
A Member of the Roche Group

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ASU's IP Portfolio of Anti-cancer Compounds

- A large portfolio of issued patents and pending applications
- Compounds described in this presentation have long patent life (at least 10 years)
- Highly potent as inhibitors of cancer cell growth
- Suitable as payloads for ADCs
- Some are suitable for anti-cancer applications as free (unconjugated) drugs
- Derived from natural sources or synthetic derivatives of natural compounds
- Synthetic schemes have been worked out for a majority of these compounds
- Most compounds have chemical groups that are readily amenable for conjugation chemistries
- Some compounds are available in prodrug forms to improve safety and widen therapeutic window of ADCs
- Several compounds with novel mechanism of action
- Compounds are available for licensing as well as for further development under sponsored research

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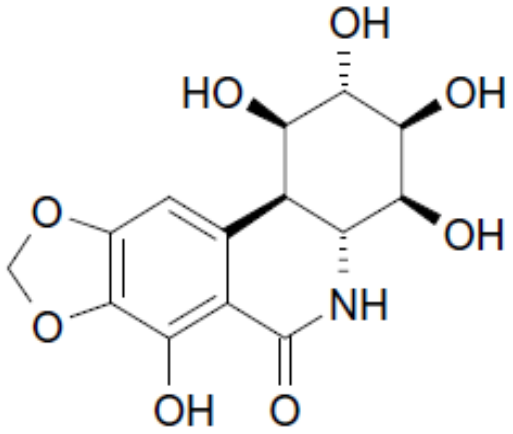
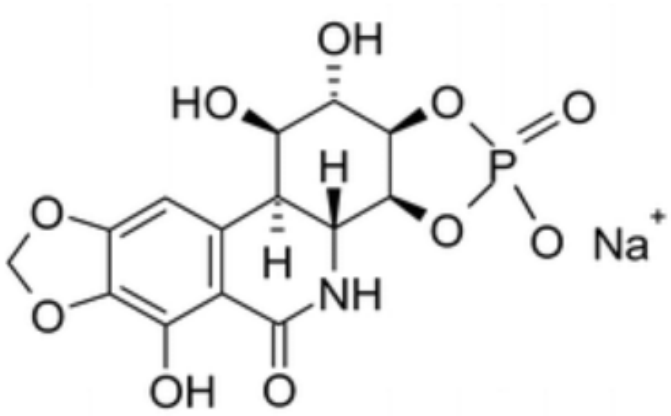
Pancratistatin and its Cyclophosphate Derivative





- US Patent 7,351,830- estimated expiration in 2025
- US Patent 6,949,647- estimated expiration in 2021
- Cyclophosphate derivative almost 1,000-fold more soluble and has higher bioavailability
- Potent anti-cancer activity against cancer cells *in vitro* as well as *in vivo* in xenograft mouse model
- Does not act by the inhibition of tubulin polymerization or inducing DNA cleavage
- Novel mechanism(s) of action: decreases mitochondrial membrane potential and induces apoptosis by activating caspase-3 and flipping of phosphatidyl serine to the outer leaflet of the plasma membrane; also activates the Fas receptor within membranous lipid rafts; causes increase in the production of reactive oxygen species (ROS); and causes accumulation of cells in G2/M phase
- Selectively induces apoptosis in cancer cells while sparing normal cells
- Potential for application as a free (unconjugated) drug
- Total synthesis achieved
- Anti-viral activity against Japanese encephalitis virus (JEV)- 80-85% inhibition
- Anti-parasite activity

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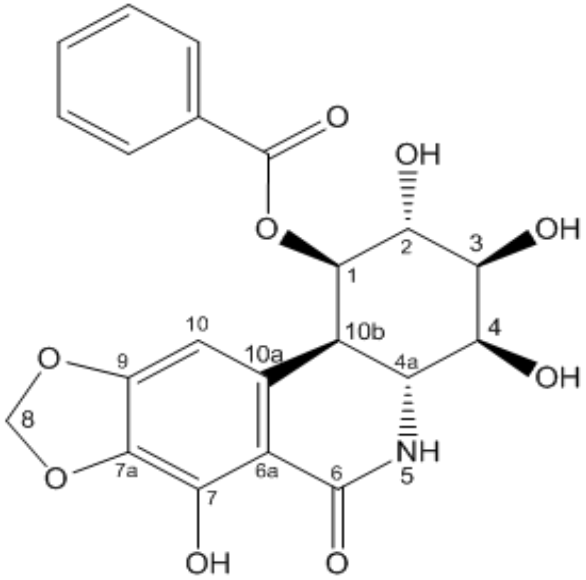
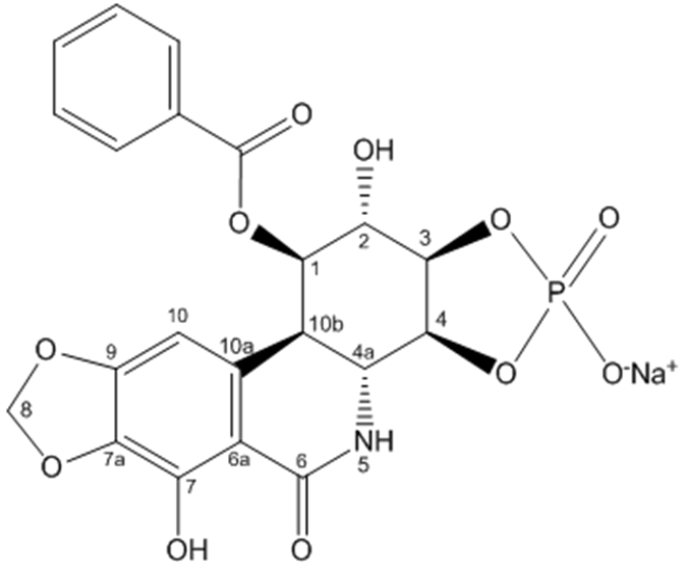
Phenpanstatin and its Cyclophosphate Derivative





- US Patent 7,541,346- estimated expiration 12/15/25
- US Patent 6,777,578- estimated expiration 4/27/21
- Total synthesis achieved
- Highly potent: anti-cancer activity in nM range
- Does not act by the inhibition of tubulin polymerization or inducing DNA cleavage
- Novel mechanism of action: thought to act through mitochondria

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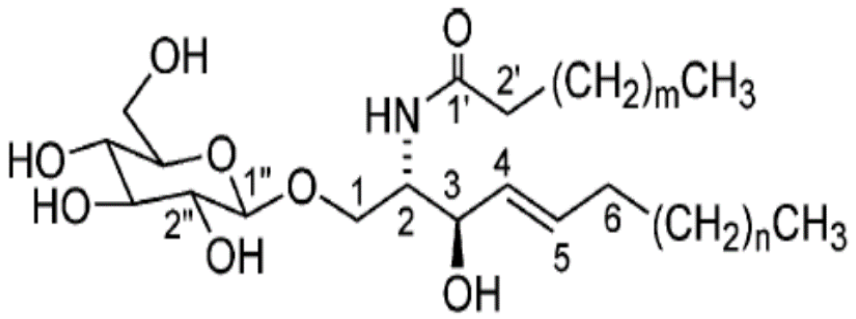
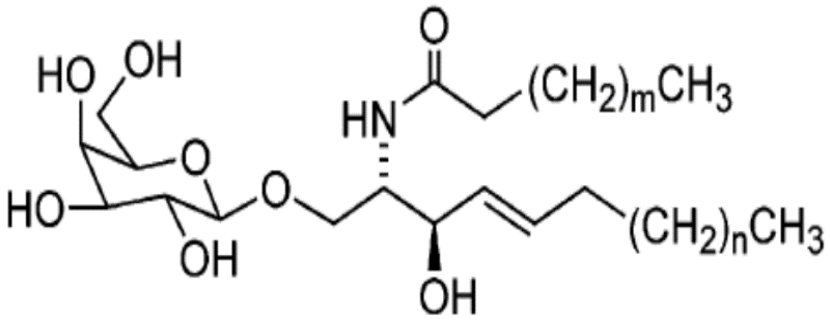
Turbostatin 1-4



1, m = 13, n = 9
2, m = 15, n = 9



3, m = 13, n = 9
4, m = 15, n = 9

- US Patent 8,053,416- estimated expiration 2/12/28
- Cerebrosides (glycosphingolipid) in nature
- Potent inhibitors of the growth of cancer cells
- Could possibly have other therapeutic activities associated with cerebrosides: immunosuppressive, immunostimulatory, Alzheimer's disease, COX2 inhibition, antiviral, antibacterial, antifungal, etc
- Mechanism of action: not known
- Synthetic route available

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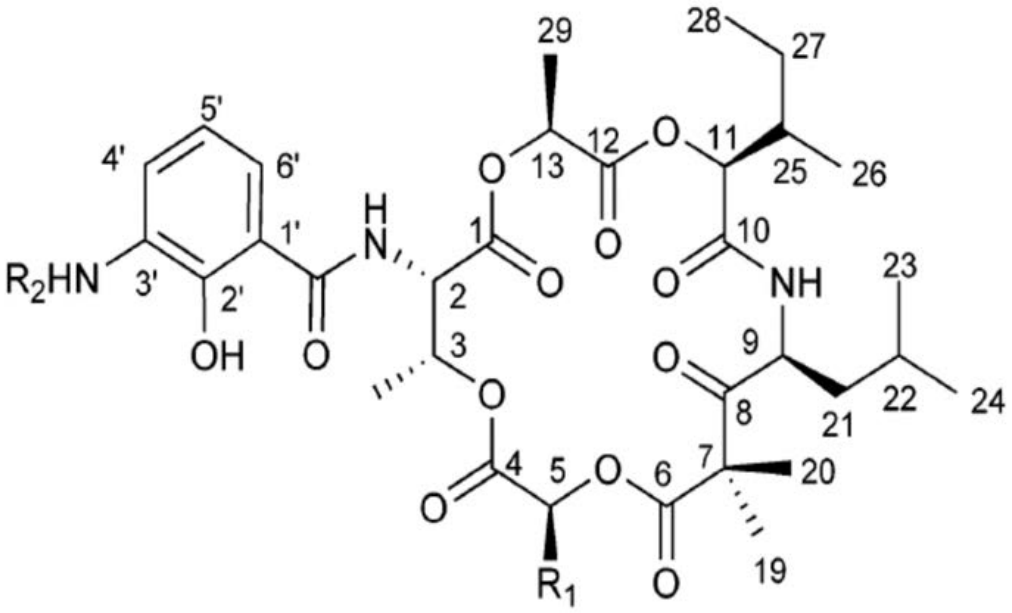
Kitastatin (cyclodepsipeptide)



Respirantin: $R_1 = CH_2CH(CH_3)_2$, $R_2 = CHO$
Kitastatin: $R_1 = CH_2CH(CH_3)_2$, $R_2 = H$

- US Patent 8,415,294, estimated expiration 5/11/29
- US Patent 8,663,154, estimated expiration 6/5/28
- Strong anti-cancer activities
- Also have anti-fungal and anti-bacterial activities
- Related to respirantin, which belongs to the antimycin family of antibiotics
- Total synthesis achieved
- Mechanism of action- not known

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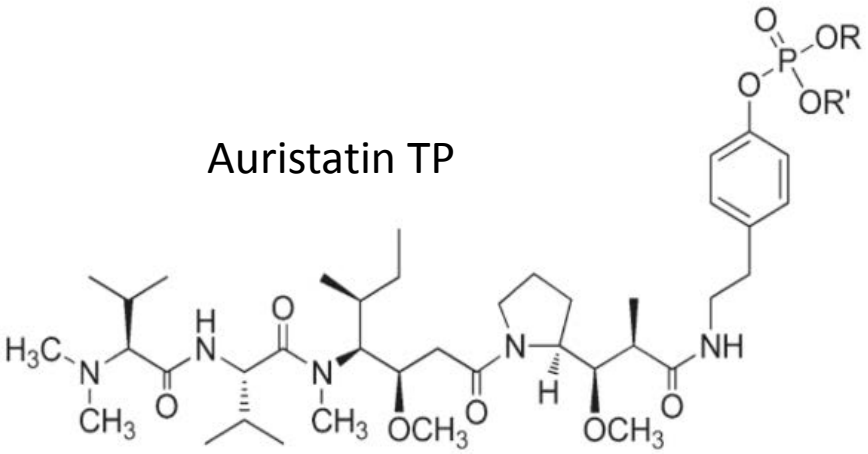
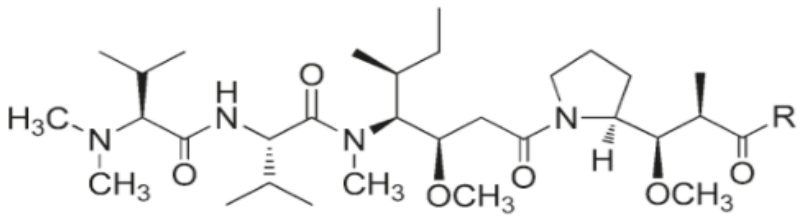
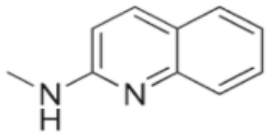
Auristatin tyramine phosphate (TP) and auristatin aminoquinoline (AQ)

Auristatin TP

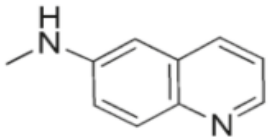




4, auristatin 2-AQ, R =



5, auristatin 6-AQ, R =



- Long patent life expected
  - US Patent 9,044,518, estimated expiration 3/29/32
  - Patent applications pending in US, EPO, JP, AU and CA
- Auristatin TP compounds are tyramine phosphate modifications of dolastatin 10 in the form of water-soluble salts with higher bioavailability. The salts are dephosphorylated by serum phosphatases to yield the active drug, which is then transported intracellularly
- Auristatin TP compounds exhibit superior cancer cell growth inhibitory properties against a panel of murine and human cancer cell lines. The *in vitro* data is quite comparable to those of dolastatin 10 and auristatin PE.
- Ease of conjugation through a phosphate group (TP) or terminal methyl group (AQ)
- Total synthesis achieved
- Mechanism of action- presumably inhibition of tubulin polymerization and anti-angiogenic activity

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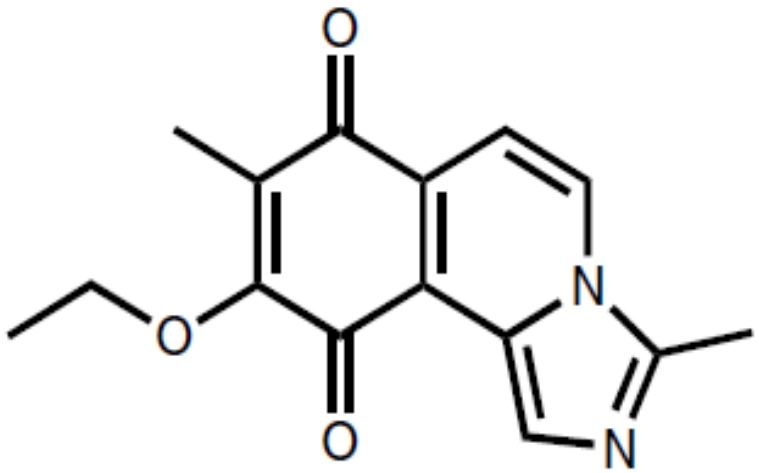
Cribrostatin-6



cribrostatin 6

- US Patent 7,317,020- estimated expiration 2/22/24
- Anti-cancer, anti-fungal and anti-bacterial activities
- Induces reactive oxygen species (ROS) and apoptotic cell death; does not induce cell cycle arrest
- A notable ability to induce cell death even in quiescent (non-dividing) cells as well as in cells that are resistant to standard anti-cancer agents
- Potential for use in combination therapy
- Although a quinone, its primary mechanism of action does not seem to involve the inhibition of topoisomerase or direct DNA damage
- Synthetic route available

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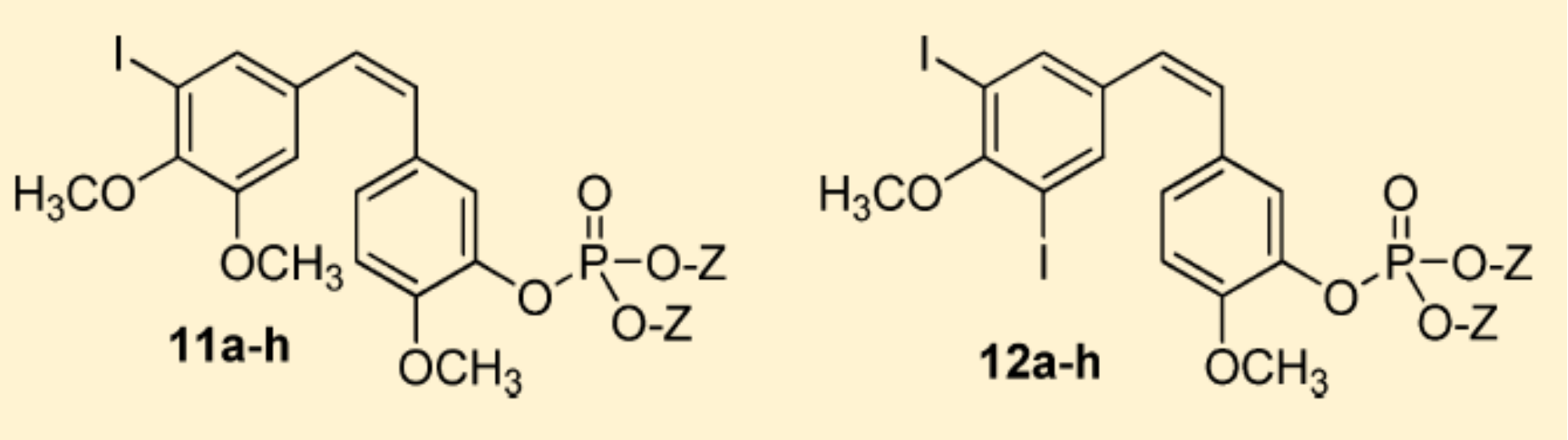
Halocombstatins



Iodocombstatin phosphate (11a–h) and diiodocombstatin phosphate prodrugs (12a–h)-derivatives of combretastatin A-4 phosphate. Z = 8 different substitutent groups

- Halogenated derivatives of combretastatins
- US Patent 7,223,747- estimated expiration 2/22/25, covers iodo-combstatins (mono and di as well as their phosphate forms)
- Potent inhibition of cancer cell growth
- Mechanism of action: inhibition of tubulin polymerization
- Potential application for thyroid cancer treatment as these compounds are likely to accumulate in the thyroid carcinoma tissue
- Synthetic route available

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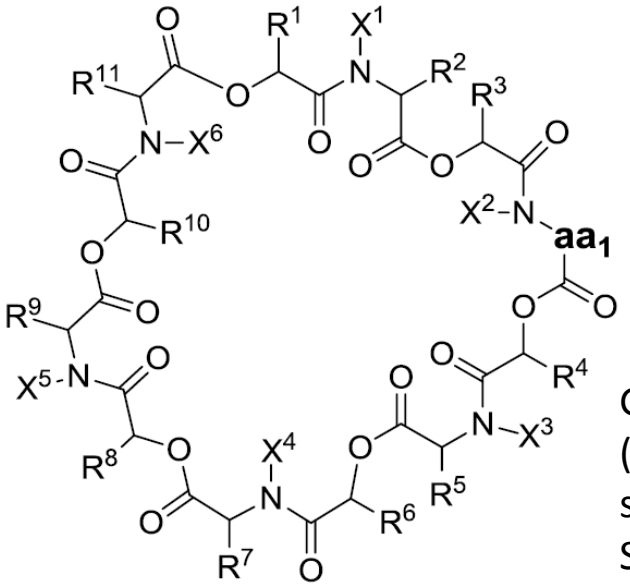
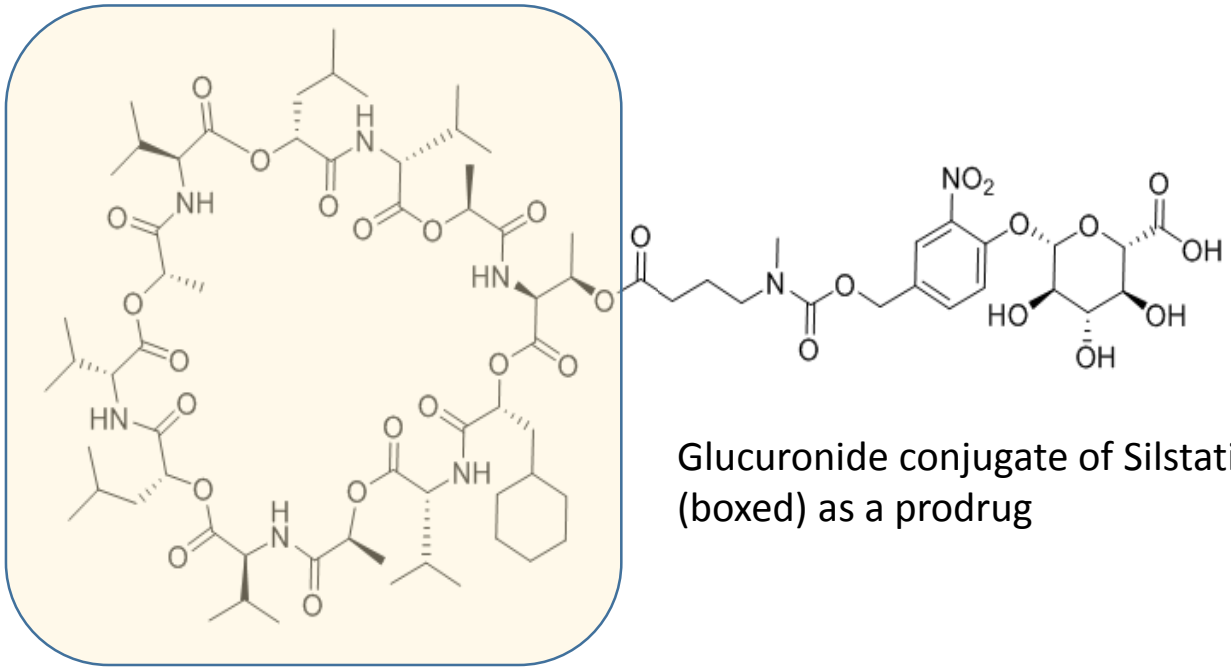
Silstatins



Generic structure of Silstatins (Combination of R and X substituents yields 8 distinct Silstatins)



Glucuronide conjugate of Silstatin 7 (boxed) as a prodrug

- Silstatins (-1 through -8): derivatives of Bacillistatins
- Highly potent inhibitors of cancer cell growth
  - GI_{50}: 10^{-3} to 10^{-4} µg/ml
- Suitable as payloads for ADCs
- Hydroxyl group for convenient conjugation to antibodies through a linker
- Glucuronide derivative of Silstatin 7
  - Prodrug
  - Releases Silstatin 7 *in vivo*
  - Reduced toxicity compared to Silstatin 7
  - Potential application as a free drug
  - Intrinsic tumor targeting property
- Long patent life expected
  - Patent application filed recently
- Mechanism of action- not known
  - Likely to act as K^+ ionophore
- Total synthesis achieved

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Contact for Licensing or Collaborative Opportunity

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