

## Pancreas

- Glandular organ in the abdomen
- Makes pancreatic juices (contain digestive enzymes)
- Produces hormones (e.g. insulin)

NIH National Cancer Institute. Pancreas. *NCI Dictionary of Cancer Terms*, <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/pancreas>

## Pancreatic Cancer

- 7<sup>th</sup> most deadly cancer, 5% survival rate
- Affects 496,000 people globally, causing 466,000 deaths in 2020
- Projected to surpass breast cancer as 3<sup>rd</sup> leading cause of cancer death by 2025

*CA. Cancer J. Clin.* **2021**, 71, 209–249.  
*Ann. Surg. Oncol.* **2014**, 21, 747–751.

## Treatments

- Surgical resection → only chance for cure
  - Subsequent chemotherapy improves long-term outcomes
- Almost 85% of patients are not eligible for surgical resection
  - Few who are eligible risk a 66–92 % chance of recurrence within 2 years of the surgery
- Chemotherapy remains main form of treatment for patients with advanced pancreatic cancer

## Why?

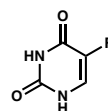
- Lack of early diagnostic tools → late diagnosis
  - Symptoms early on are vague or not present

*Lancet.* **2020**, 395, 2008–2020.

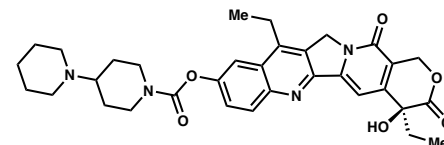
*Ann. Surg. Oncol.* **2014**, 21, 747–751.

## Most Common Pancreatic Cancer Chemotherapies

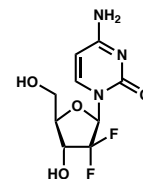
- FOLFIRINOX
  - 5-fluorouracil, folinic acid, irinotecan, and oxaliplatin
- gemcitabine
- nanoparticle albumin-bound paclitaxel (nab-paclitaxel)



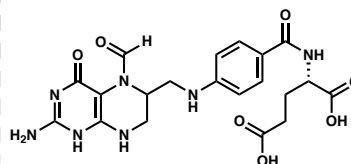
5-fluorouracil



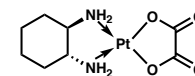
irinotecan



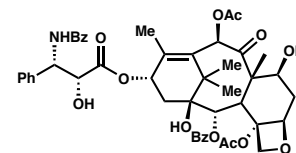
gemcitabine



folinic acid

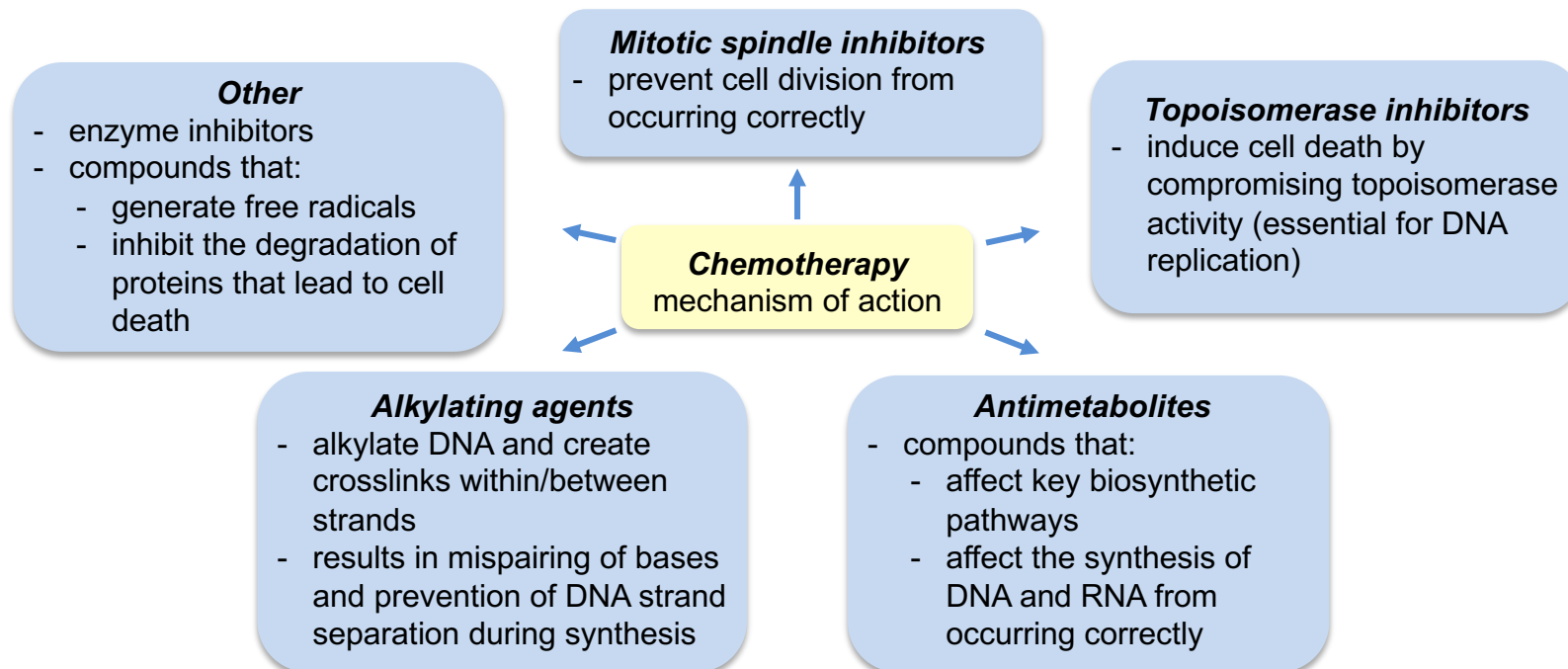


oxaliplatin



paclitaxel (taxol)

*Lancet.* **2020**, 395, 2008–2020



*Int. J. Mol. Sci.* **2020**, *21*, 3233–3257.

### Gap in knowledge

Only modest progress in pancreatic cancer treatments over last decade

Greater than 90% of patient deaths (for all cancer, not specific to pancreatic) are due to the resistance of cancer cells to the chemotherapy

### Potential Solution

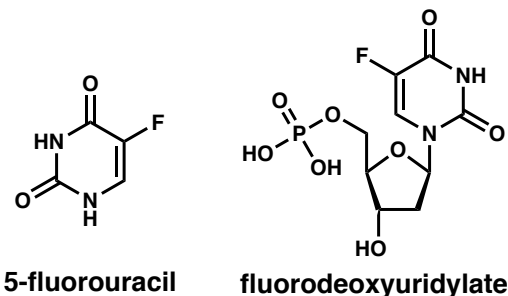
→ Develop new screening strategies for high-risk patients to detect pancreatic tumours at earlier stages

→ Identify new enzymes in cancer cells to target, and develop inhibitors for these targets that can be used as novel therapies and alternative treatment strategies

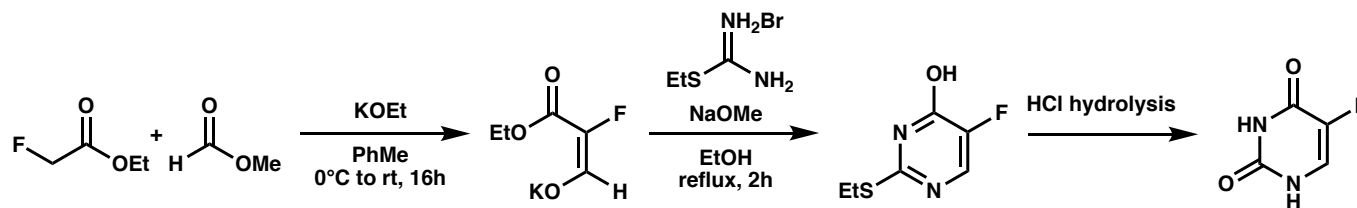
*Lancet.* **2020**, *395*, 2008–2020.  
*Int. J. Mol. Sci.* **2020**, *21*, 3233–3257.

**5-fluorouracil**

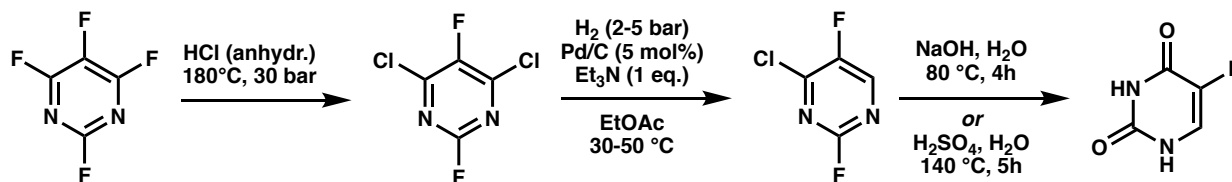
- Antimetabolite chemotherapy
- used to treat > 2 million patients
- 4200+ related publications and patent applications
- Metabolism of 5-fluorouracil generates fluorodeoxyuridylate which inhibits thymidylate synthase, causing cell death



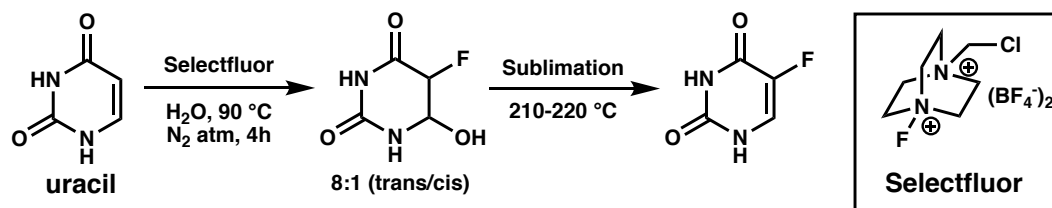
*Molecules.* **2020**, *25*, 3438.  
*Gen. Pharmac.* **1998**, *31*, 661–666.  
*J. Fluorine Chem.* **1989**, *45*, 417-430.

**First synthesis: Heidelberger (1957)**

*J. Am. Chem. Soc.* **1957**, *79*, 4559-4560.

**Industrial synthesis: Baasner and Klauke (1989)**

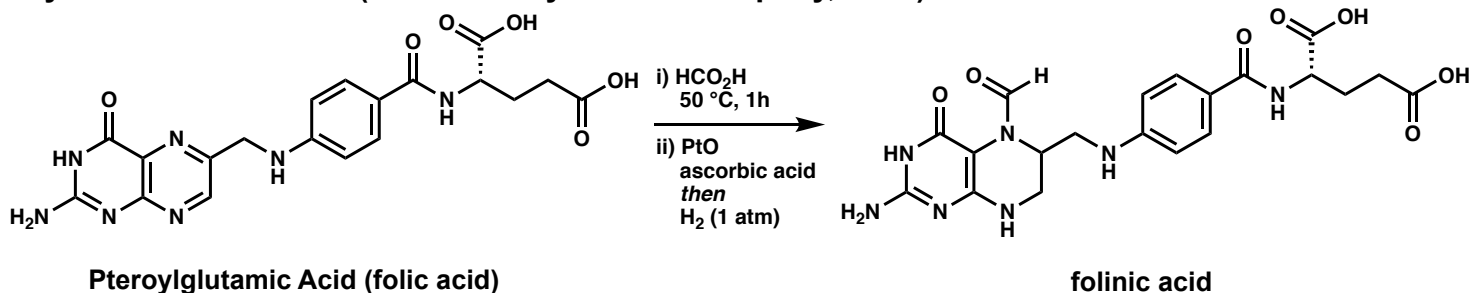
*Molecules.* **2020**, *25*, 3438  
*J. Fluorine Chem.* **1989**, *45*, 417-430.

**Notable synthesis: Lal (1995)**

*J. Org. Chem.* **1995**, *60*, 7340-7342.

**Folic acid**

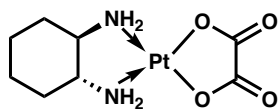
- Often administered in addition to 5-fluorouracil
- Inhibitor to many folate dependent enzymes
- Derivative of folic acid, a necessary vitamin to mammals

**Synthesis: Roth et al. (American Cyanamid Company, 1952)**

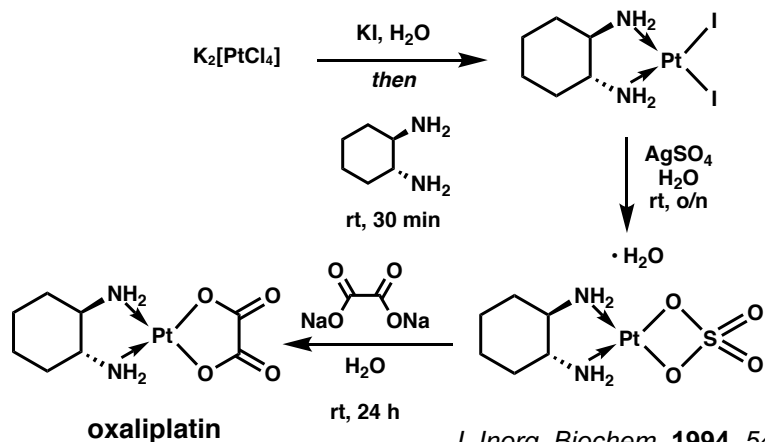
*Trends in Biochem. Sci.* **1993**, 18, 102-106.  
*J. Am. Chem. Soc.* **1952**, 74, 3247–3252.

**Oxaliplatin**

- Used to treat a variety of cancers
- Causes inter- and intra-strand crosslinks in DNA, thereby inhibiting DNA synthesis

**oxaliplatin**

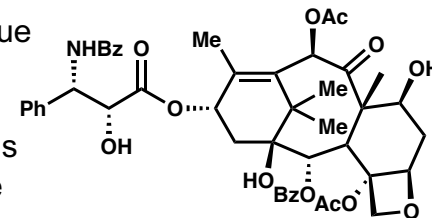
*Cancer Chemother. Pharmacol.* **2005**, 55, 301–305.

**Synthesis: Khokhar (1994)**

*J. Inorg. Biochem.* **1994**, 54, 39-47.

**Nab-paclitaxel (nanoparticle albumin-bound taxol):**

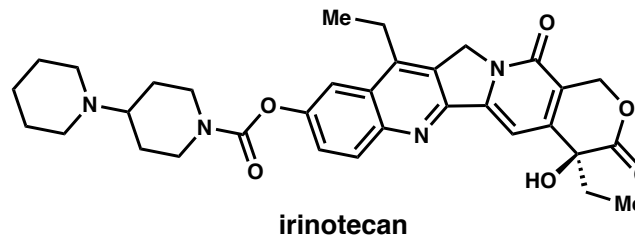
- Prevents division by promoting microtubule assembly
- Bound to human serum albumin using high-pressure homogenization of taxol in the presence of albumin
- Taxol is hydrophobic – requires use of Cremophor EL (CrEL) to deliver drug
  - CrEL can cause acute hypersensitivity reactions and neurological toxicity
- Nab-paclitaxel developed to improve the solubility of taxol (doesn't require use of CrEL)
- Tumor cells actively take up albumin via active transport due to increased nutrient need
  - increases concentration of nab-paclitaxel in tumor cells
  - improves the toxicity of the drug
- Nab-paclitaxel can be administered in 30 mins vs 3 h for CrEL-bound taxol



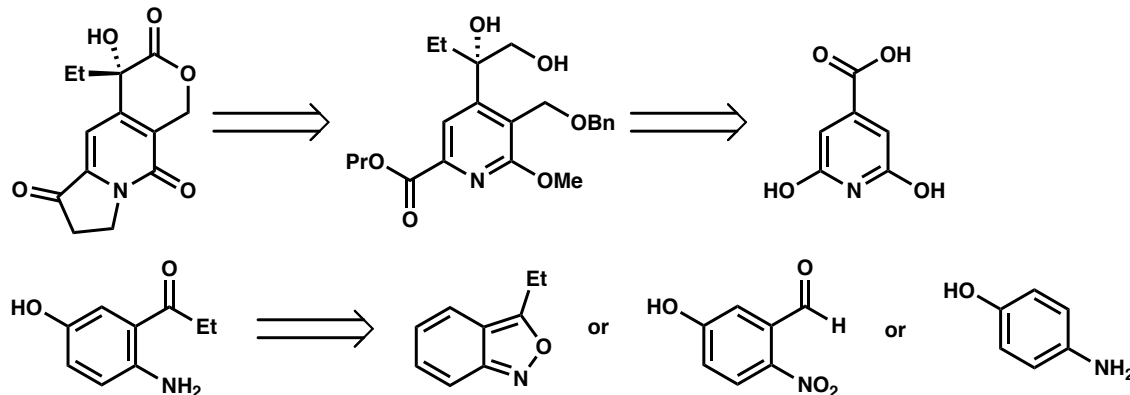
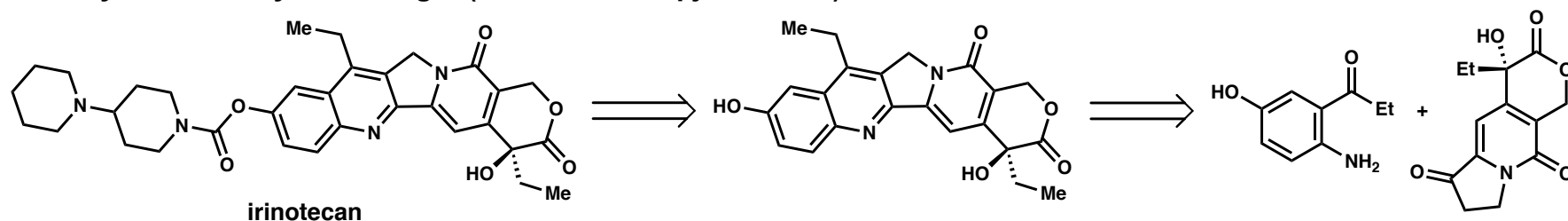
*Expert Opin. Pharmacother.* **2010**, 11, 1413-1432.  
*Future Oncol.* **2005**, 1, 755-762.

**Irinotecan**

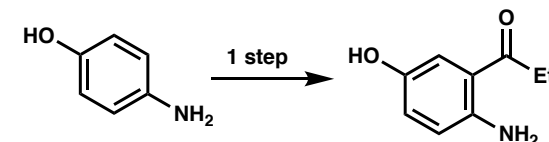
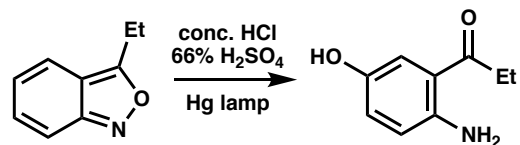
- Synthetic analog to naturally occurring alkaloid camptothecin
- Inhibits DNA topoisomerase I
- Carbamate hydrolyzed by carboxylesterase into highly active metabolite, SN-38



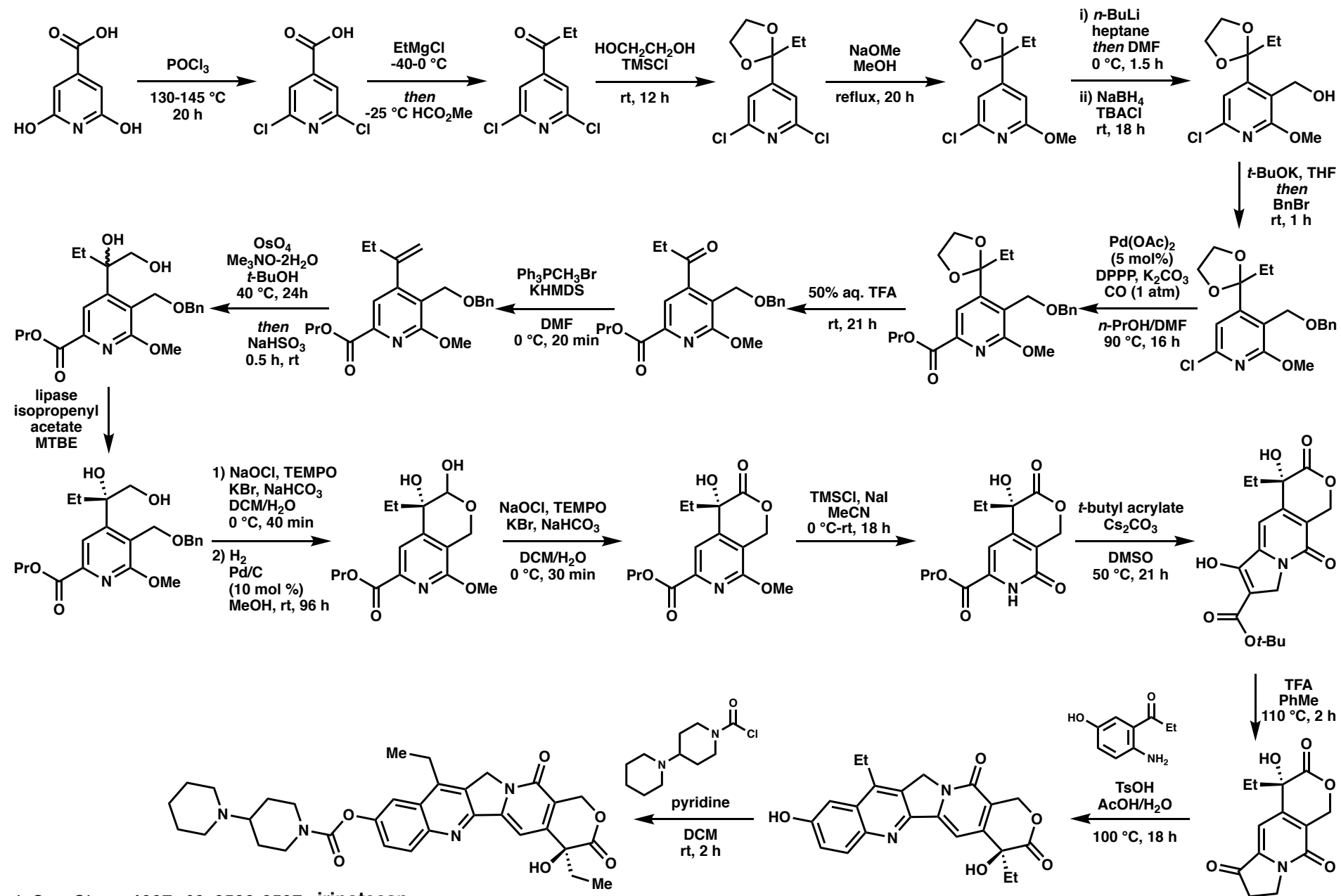
*Pharmacogenomics*, **2004**, 5, 835-843.  
*Biomed. Chromatogr.* **2010**, 24, 104-123.

**Retrosynthetic analysis: Henegar (Pharmacia & Upjohn, 1997)**

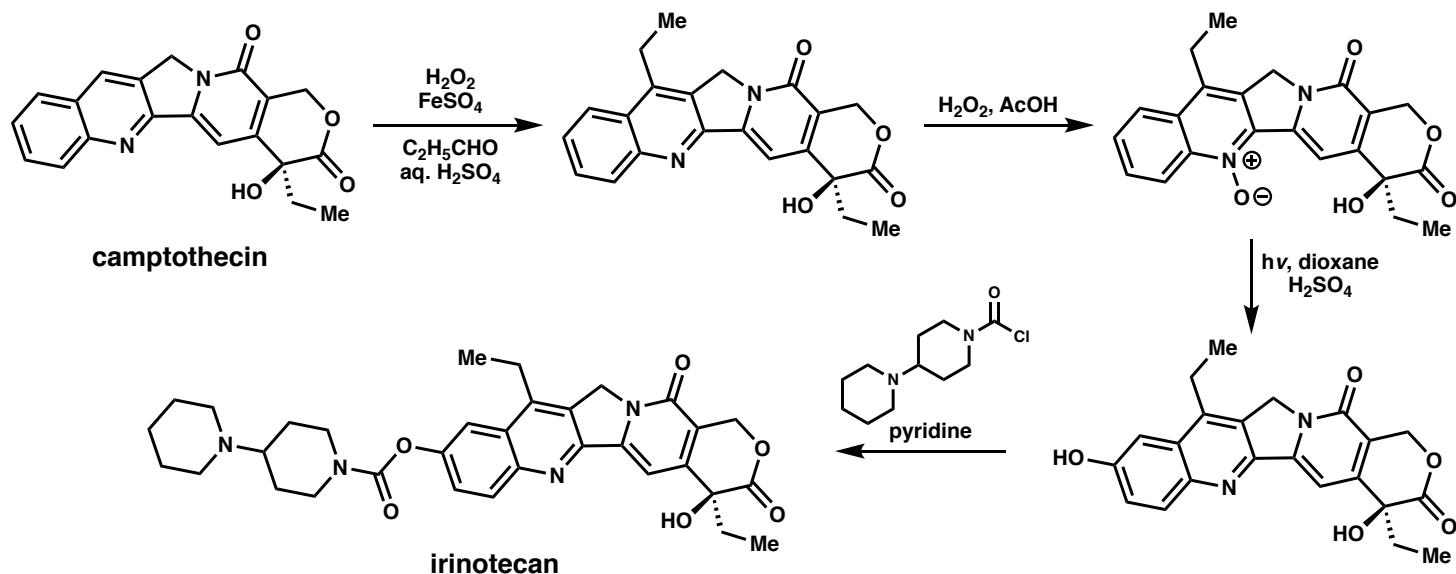
*J. Org. Chem.* **1997**, 62, 6588-6597.

**Synthesis**

*J. Org. Chem.* **1997**, 62, 6588-6597.  
*Helv. Chim. Acta.* **1971**, 54, 2111-2113.



## Semi-synthesis: Sawada (1991)

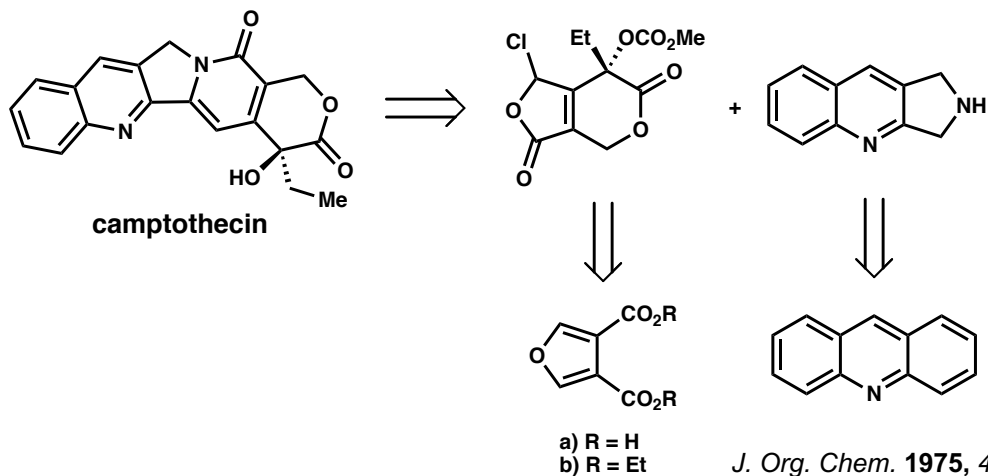


Chem. Pharma. Bull. 1991, 39, 1446-1454.

## Camptothecin

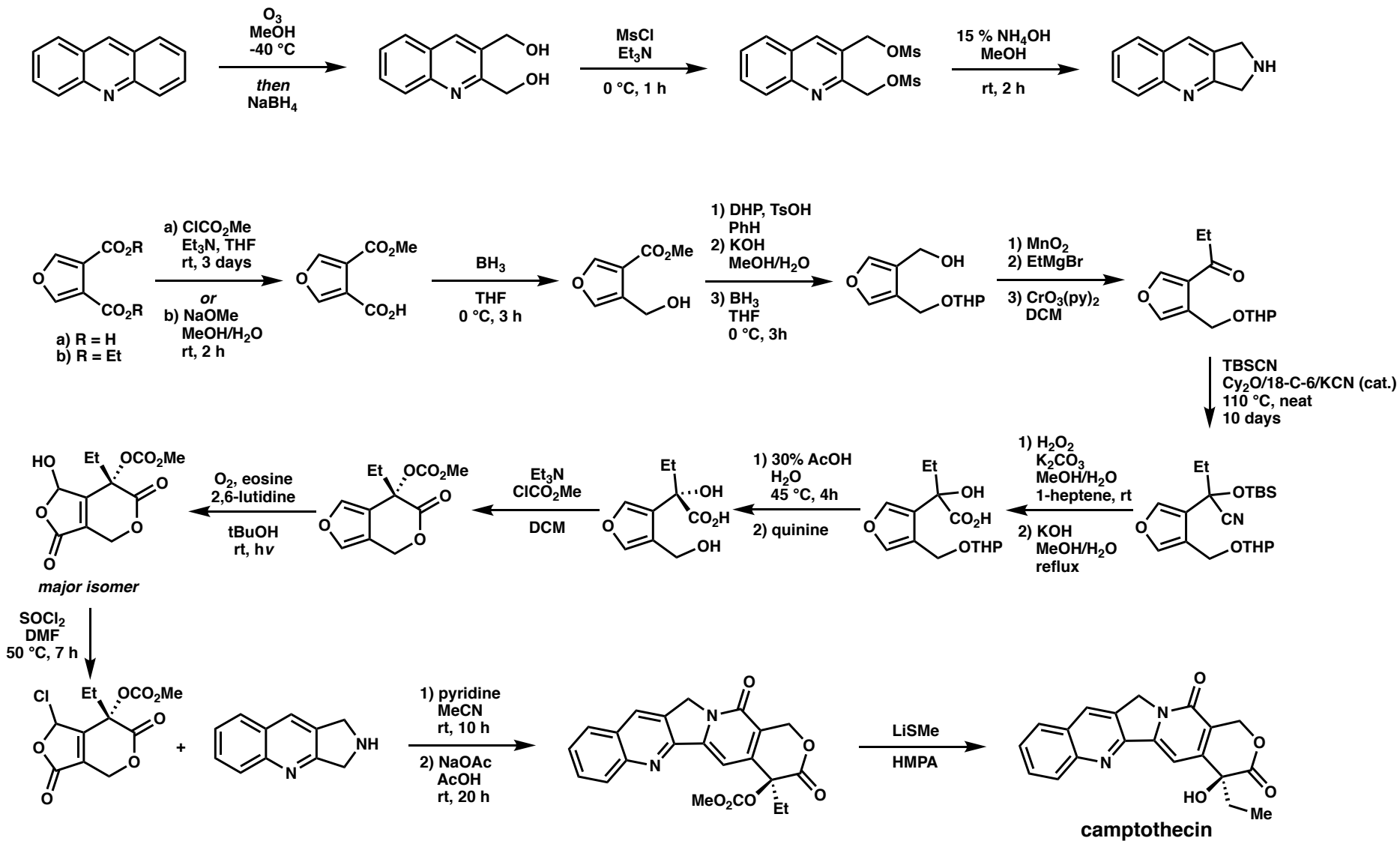
- Isolated in 1958 from *Camptotheca acuminata* (a tree native to China and Tibet)
- Used in traditional Chinese medicine
- First total synthesis of naturally occurring *S* enantiomer by E. J. Corey in 1975
- Less water-soluble than irinotecan

## Retrosynthetic analysis: Corey (1975)



J. Org. Chem. 1975, 40, 2140-2141.

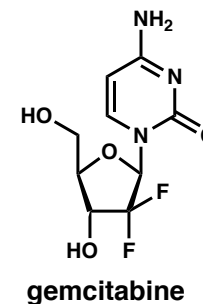
## Synthesis



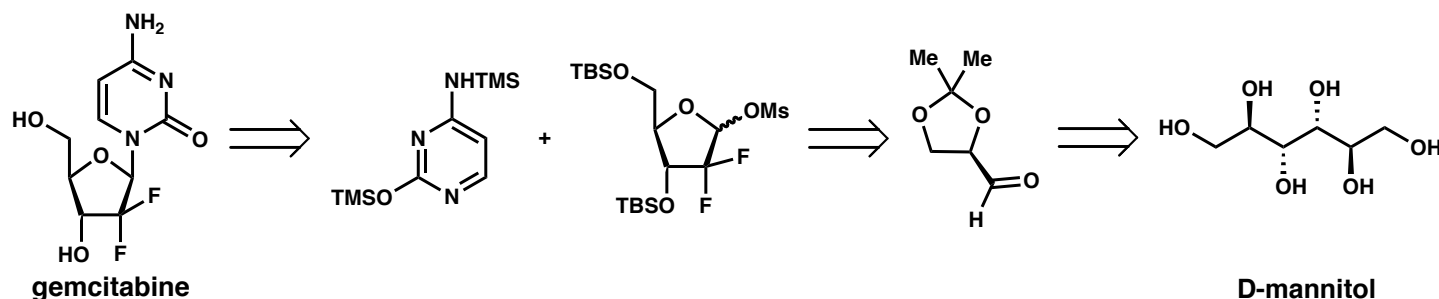


**Gemcitabine**

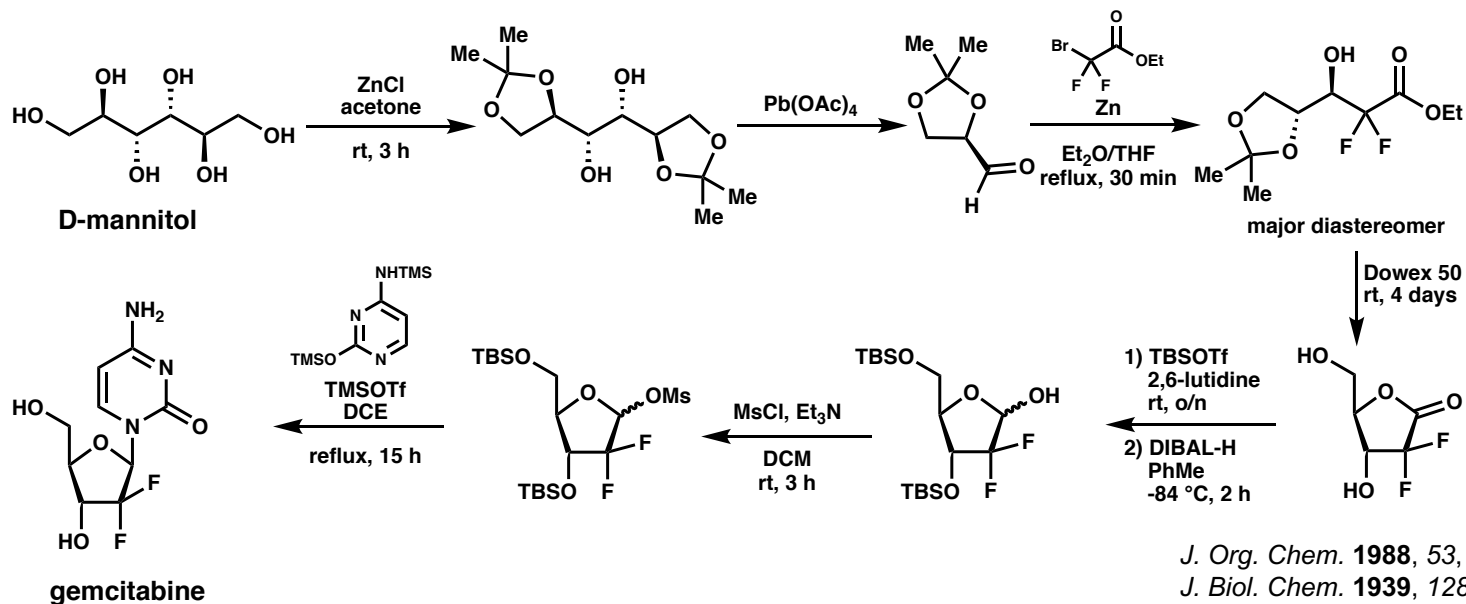
- Prodrug
  - Active form → di- and triphosphate
- Inhibits DNA synthesis thereby causing cell death
- Lilly Research Laboratories branded drug as HCl salt (Gemzar)
- With patent, \$1 billion/year drug
- Used to treat a variety of cancers including pancreatic, ovarian and breast cancer
- Patent has expired and has led to the development of alternative approaches



*Carbohydrate Research.* **2015**, 406, 71-75.  
*J. Org. Chem.* **1988**, 53, 2406-2409.

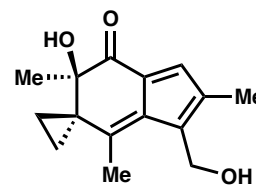
**Retrosynthetic analysis: Hertel (Lilly Research Laboratories, 1988)**

## Synthesis



## Irofulven

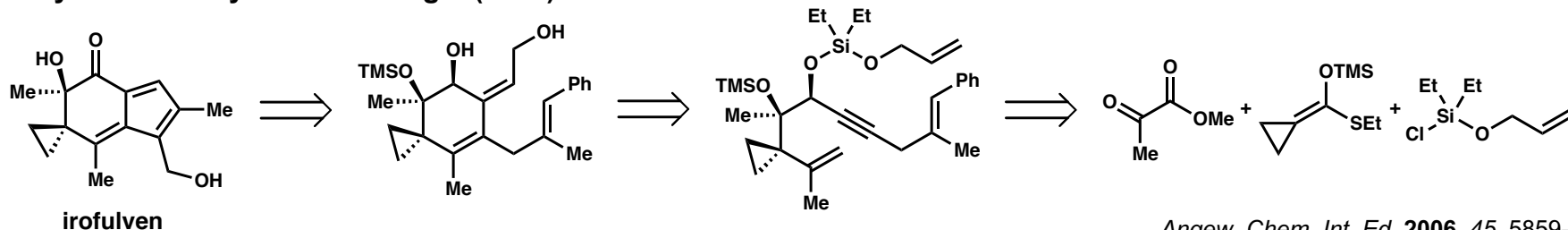
- Novel, experimental chemotherapy
- Undergoing phase I and II clinical trials to treat a variety of cancers
- Alkylating agent
- Inhibits DNA synthesis via cyclopropyl ring opening



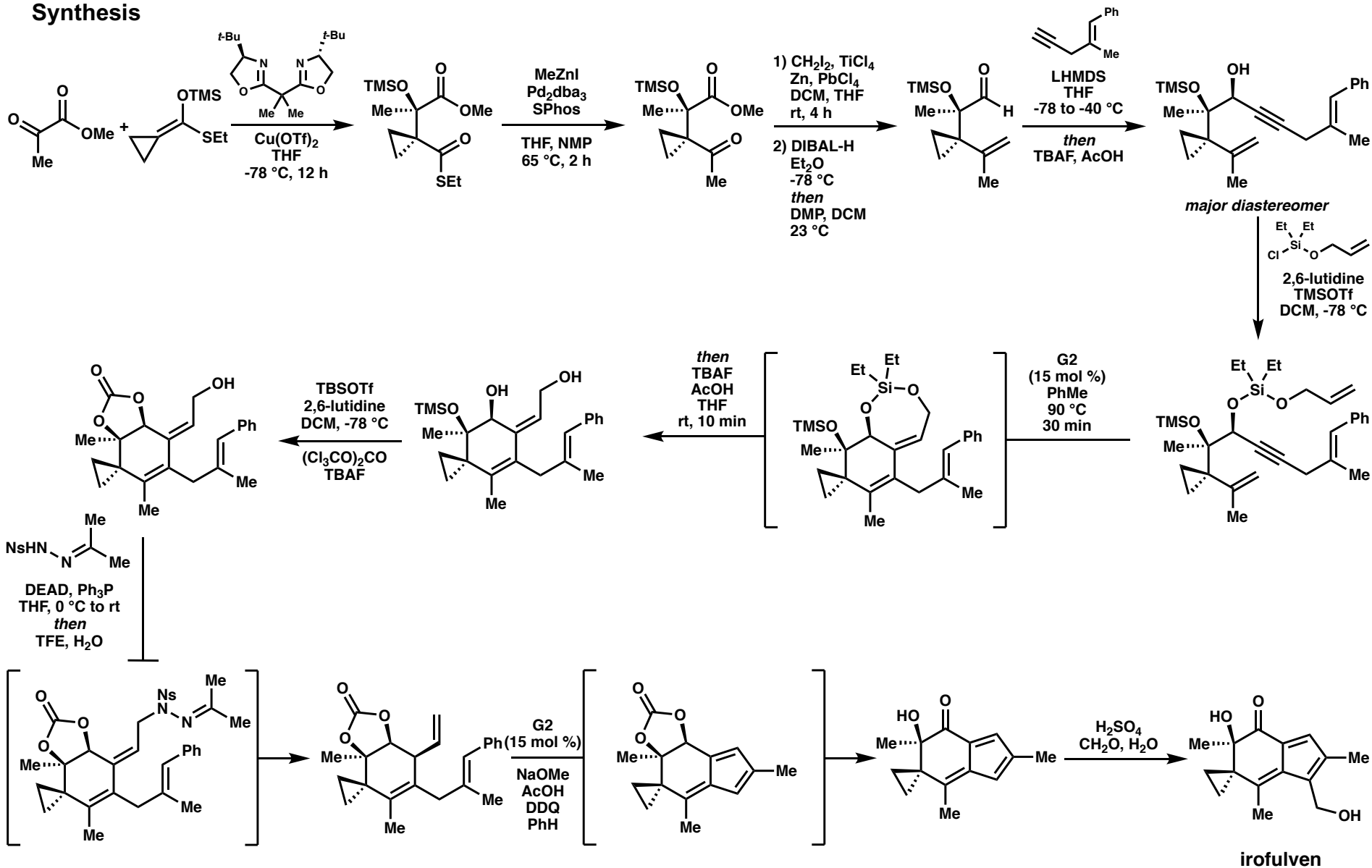
irofulven

*Angew. Chem. Int. Ed.* **2006**, 45, 5859-5863.*Cancer Chemother Pharmacol.* **2001**, 48, 467-472.

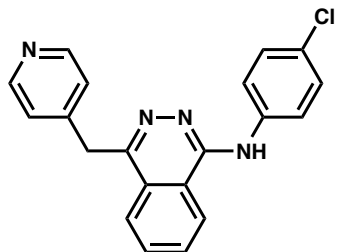
## Retrosynthetic analysis: Movassaghi (2006)



## Synthesis



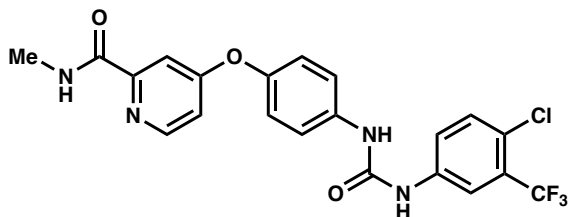
## Novel Therapies



**Vatalanib**

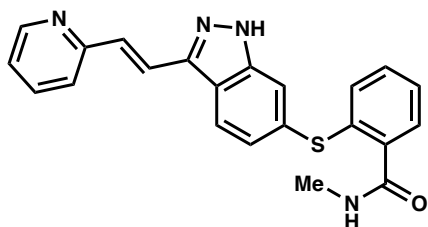
Used in phase II trial with gemcitabine

Used in phase I trial with gemcitabine



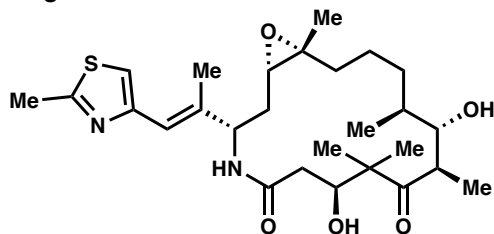
**Sorafenib**

Used in phase II trial with and without gemcitabine



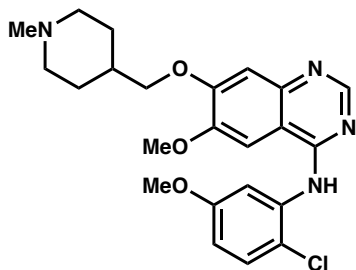
**Axitinib**

Used in phase II trial and 2 x as potent as taxol



**Ixabepilone**

Used in phase I/II trial with gemcitabine



**AZM475271**

*Expert Rev. Anticancer Ther.* **2008**, 8, 993-1002.

## Summary

- Most common pancreatic cancer chemotherapies are FOLFIRINOX (5-fluorouracil, folinic acid, irinotecan, and oxaliplatin), gemcitabine, and nab-paclitaxel
- Novel chemotherapies include irofulven and others

## Future directions

- Develop new screening strategies for high-risk patients to detect pancreatic tumours at earlier stages
- Further exploration of novel compounds as new chemotherapies

## Useful reviews

- Pancreatic cancer:  
*Lancet.* **2020**, 395, 2008–2020.
- Treatments:  
*Int. J. Mol. Sci.* **2019**, 20, 4543.
- 5-fluorouracil:  
*Molecules* **2020**, 25, 3438.
- Camptothecin and derivatives:  
*Tetrahedron* **2003**, 59, 8649-8687.
- Novel treatments:  
*Expert Rev. Anticancer Ther.* **2008**, 8, 993-1002.