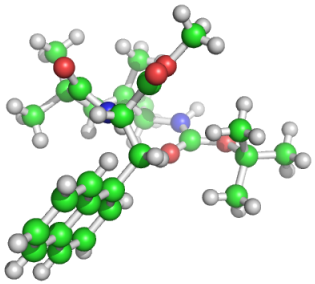
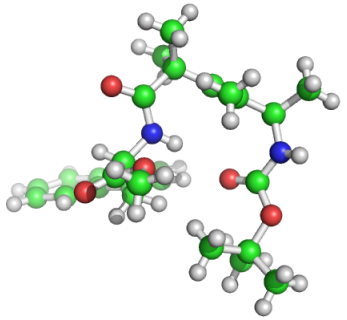


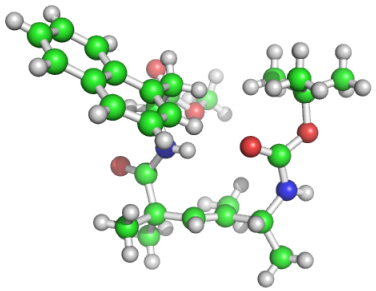


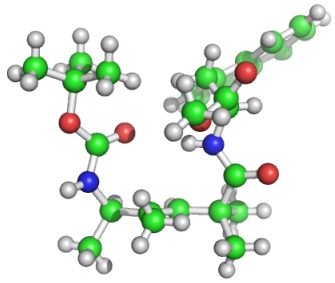
Boc-Ala-Aib-OH: A New E-Alkene Dipeptide Isostere β-Turn Mimic & its Application to a Cdc25 Inhibitor

Gary C. Davis, PhD.

Research Topic Seminar

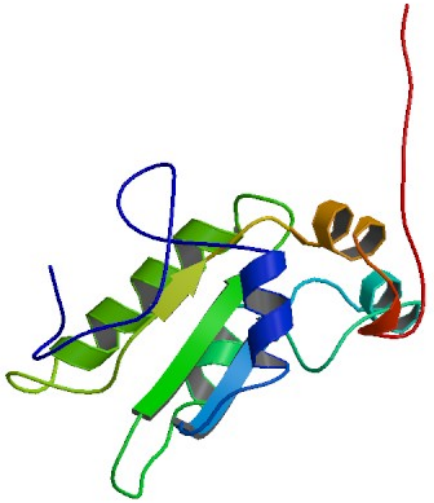
January 9, 2010





Outline

- Cdc25
- BASF cdc25 peptide inhibitor
- Review of β-turns
- Synthesis
- Other applications of turn mimic
- Future goals
- Summary

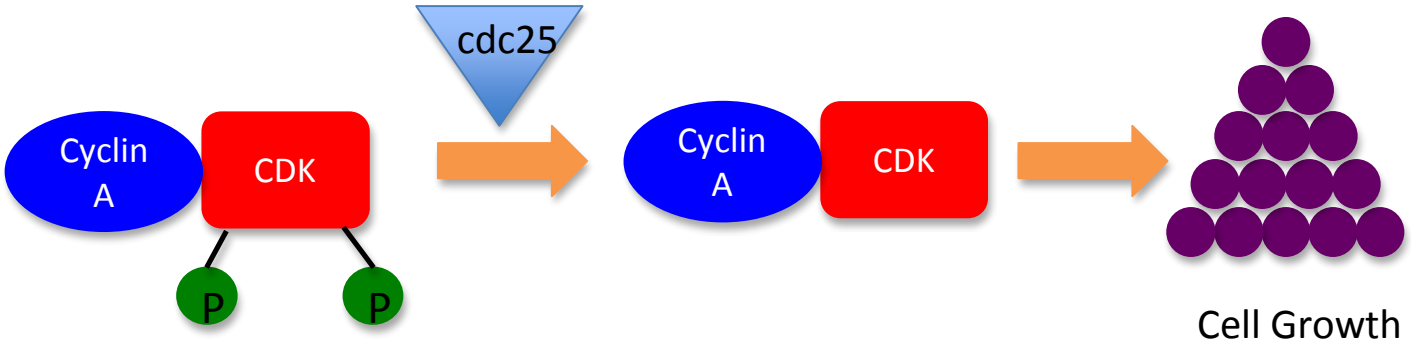


Cdc25A

image from: http://upload.wikimedia.org/wikipedia/en/8/80/PBB_Protein_CDC25A_image.jpg

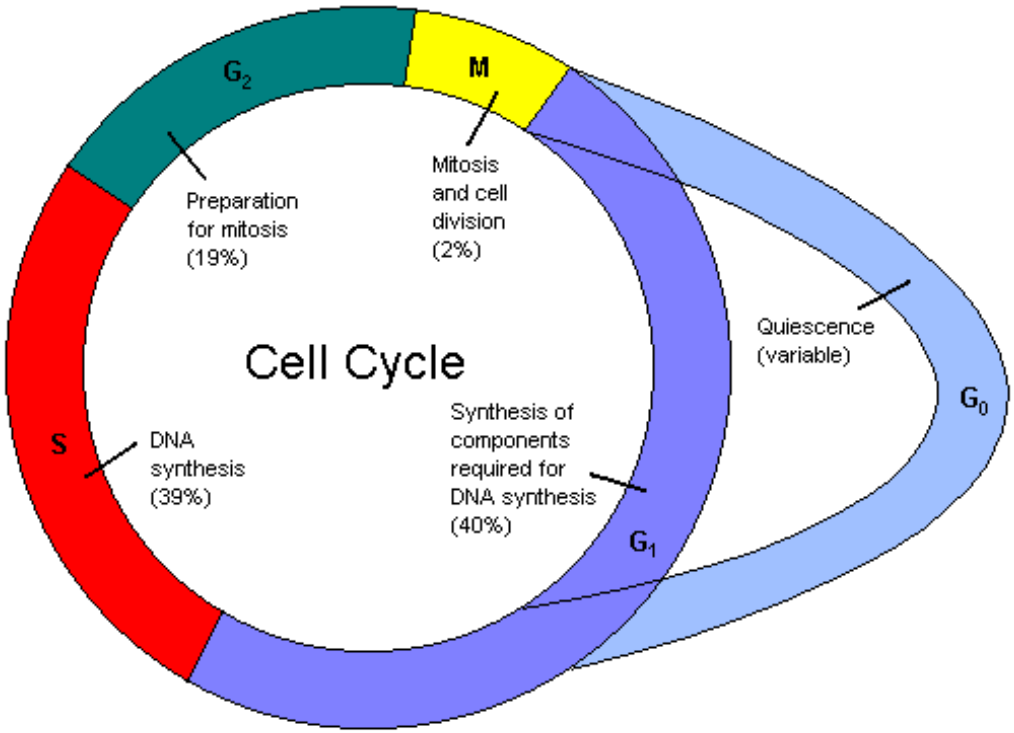
What Are Cdc25's?

- Cell-division cycle 25: family of dual-specificity phosphatases.
- Three homologues in humans (cdc25A, cdc25B, cdc25C).
- Regulation of cell-cycle progression by activating CDKs.



- Cdc25A and B are overexpressed in various cancers such as: breast, ovarian, prostate, lung, colorectal, oesophageal, thyroid, laryngeal, hepatocelular, gastric, pancreatic, endometrial, head and neck cancer, neuroblastoma, glioma, and non-Hodgkin lymphoma.

The Cell Cycle

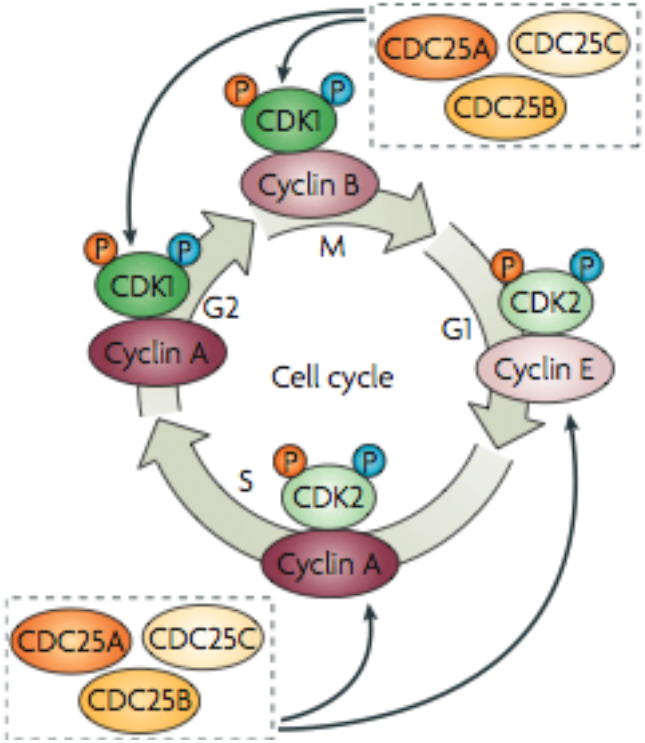


- Gap 1 (G_1)
- Synthesis (S)
- Gap 2 (G_2)
- Mitosis (M)

image from: http://www.ch.ic.ac.uk/local/projects/s_liu/Html/Graphics/CellCycle.gif

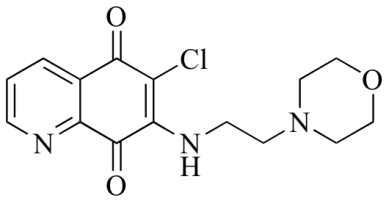
Cdc25 Target Cancer Therapy

- Inhibition of cdc25 is a possible therapy for inhibition of cancer cell growth
- Targeting strategies: active site or protein-protein interaction
- Inhibition results in reversible cell-cycle arrest.
- In some cases apoptosis is triggered.

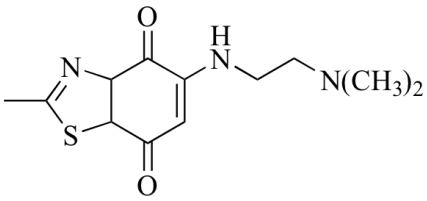


Boutros, R.; Lobjois, V.; Ducommun, B. *Nature Cancer Reviews* **2007**, 7, 495-507.

Known Cdc25 Inhibitors



NSC663284



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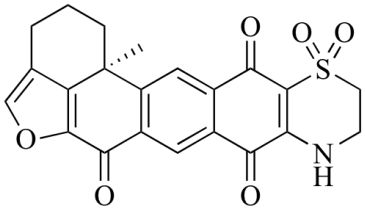
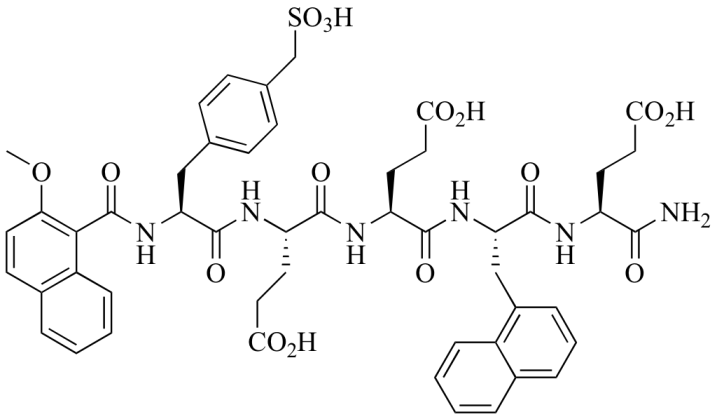


Adociaquinone B

- Usually not isoform selective.
- Para-quinoids most common.
- Mechanism of action: irreversible oxidation of the cysteine residue in catalytic domain to sulfonic acid.

Lazo, J. S. et al. *J. Med. Chem*. **2001**, 44, 4042-4049.
Brezak M. C. et al. *Mol. Caner Ther.* **2005**, 4, 1378-1387.
Cao, S. et al. *Bioorg. Med. Chem.* **2005**, 13, 999-1003.

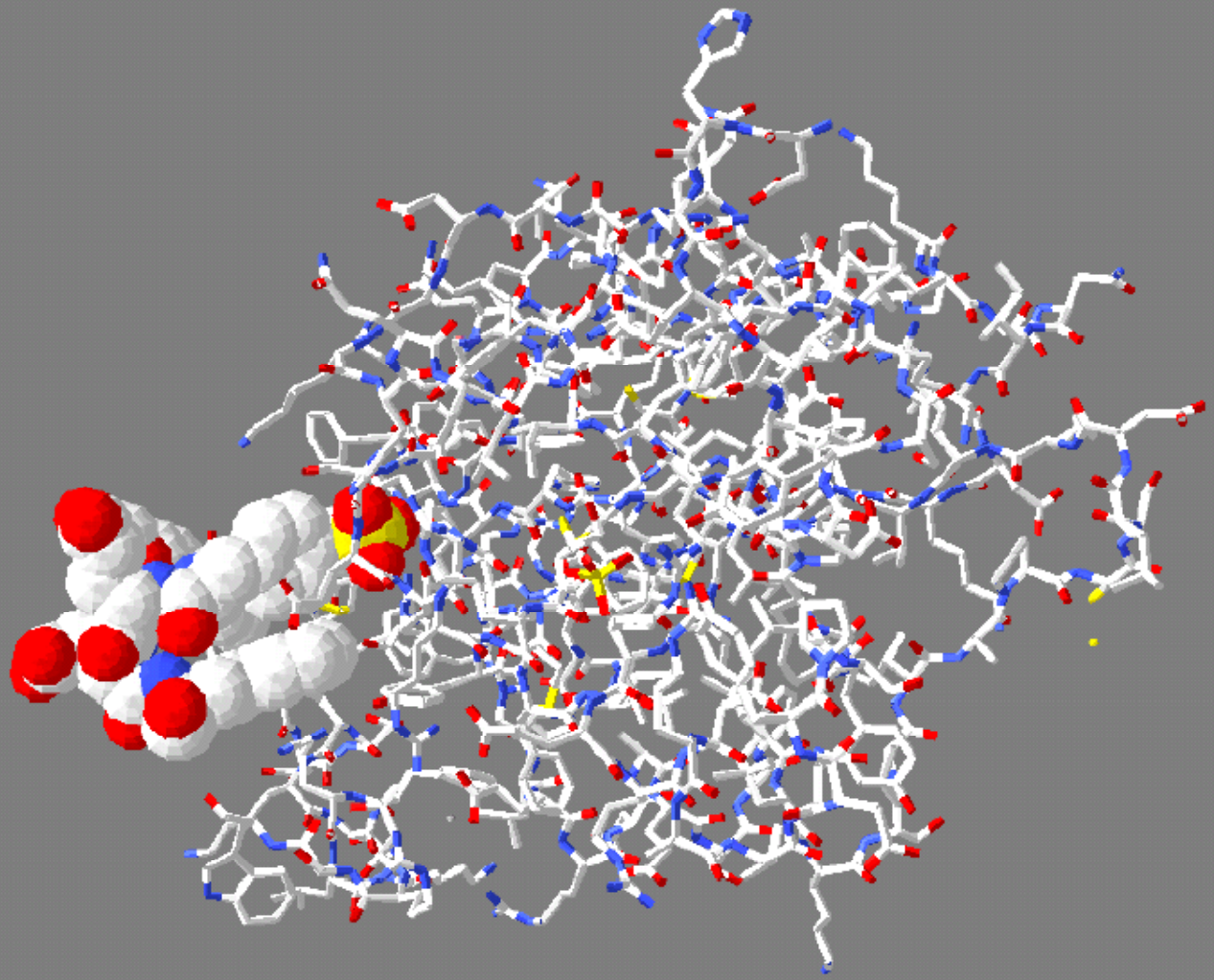
BASF Ligand



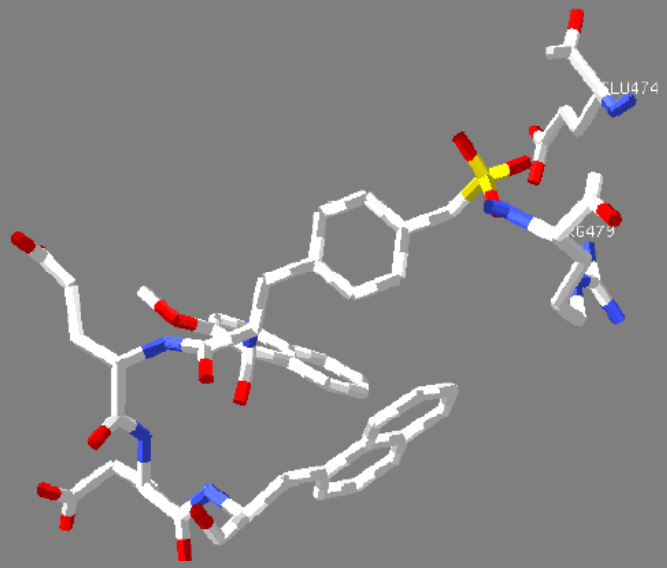
- Part of a patent describing discovery of cdc25 inhibitors.
- Lead compound co-crystallized with cdc25B.
- Contains a β-turn.
- No biological data for the analog shown.

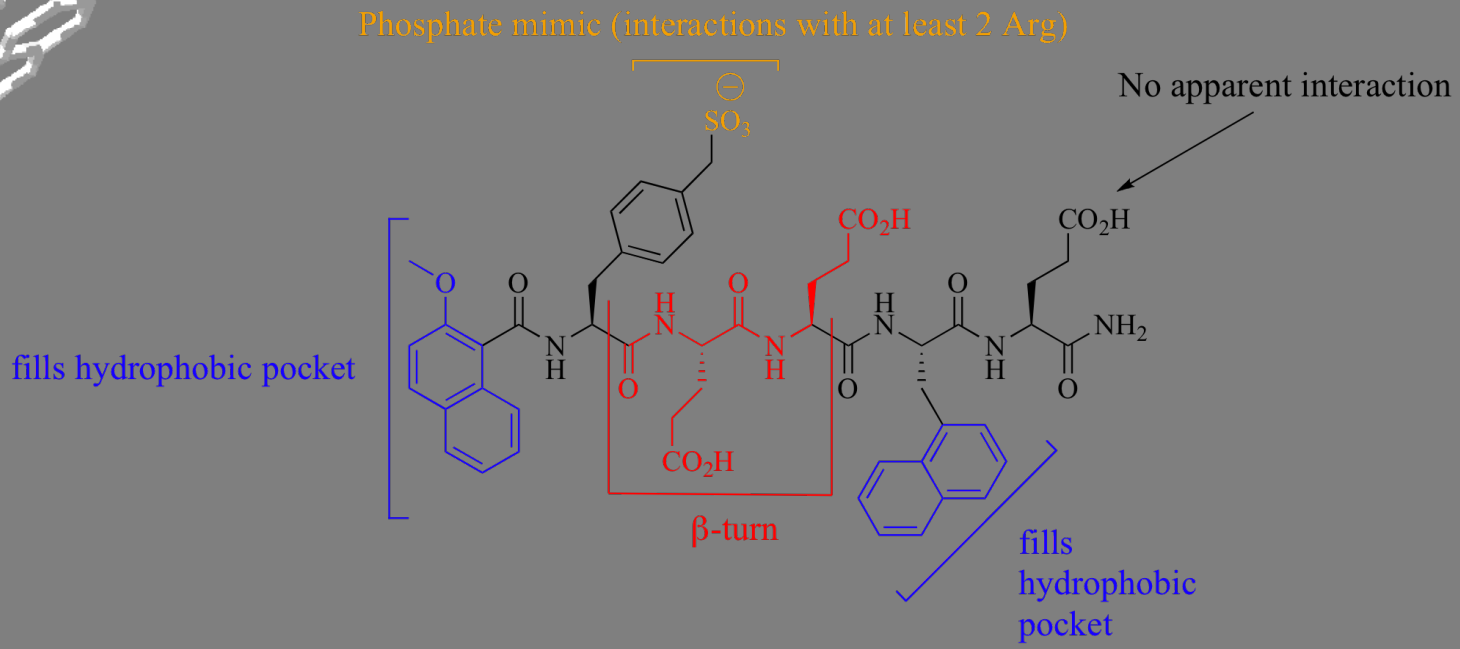
Taylor, Neil R.; Borhani, David; Epstein, David; Rudolph, Johannes; Ritter, Kurt; Fujimori, Taro; Robinson, Simon; Eckstein, Jens; Haupt, Andreas; Walker, Nigel; Dixon, Richard W.; Choquette, Deborah; Blanchard, Jill; Kluge, Arthur; Pal, Kollol; Bockovich, Nicholas; Come, Jon; Hediger, Mark. **Method of identifying inhibitors of Cdc25.** U.S. Pat. 2002/0183249 A1, Dec. 5, 2002

X-Ray of Bound BASF Ligand

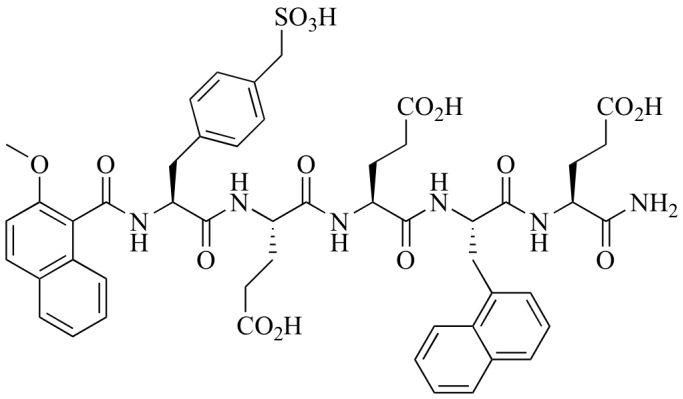


Characteristics of BASF Ligand

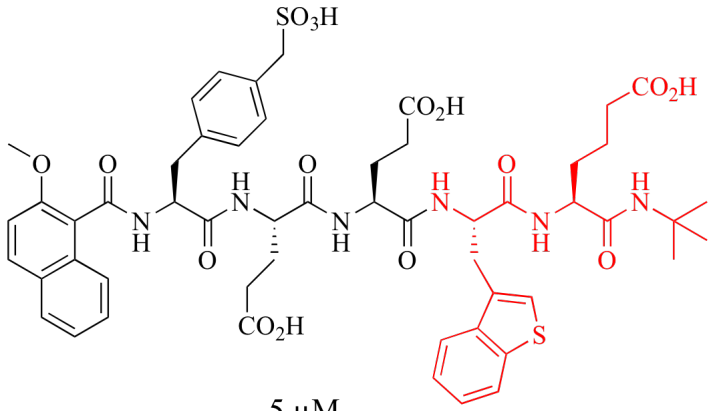




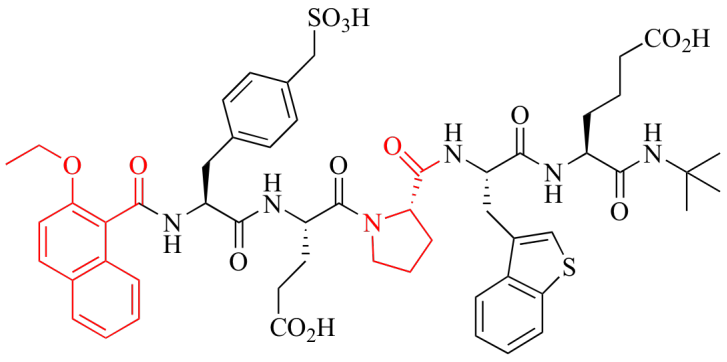
Derived SAR



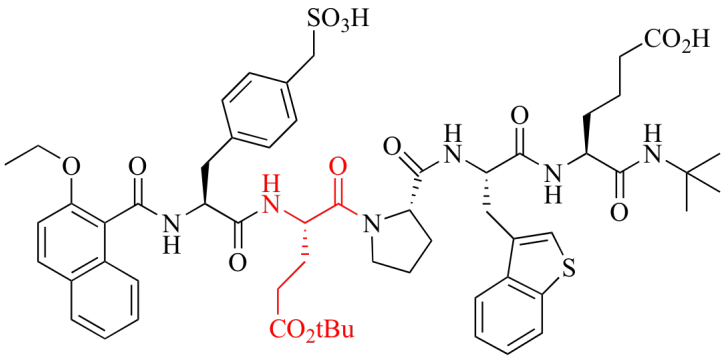
No Data



5 µM

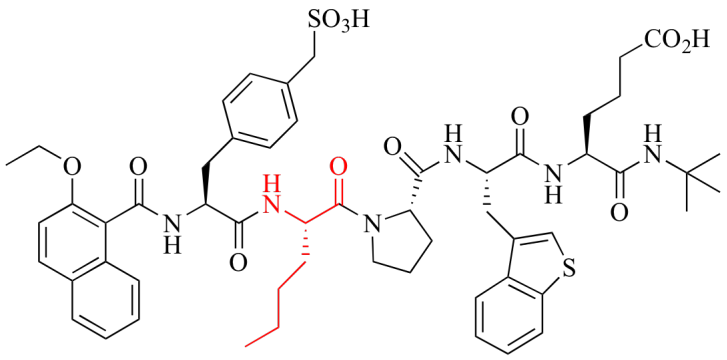


2.2 µM

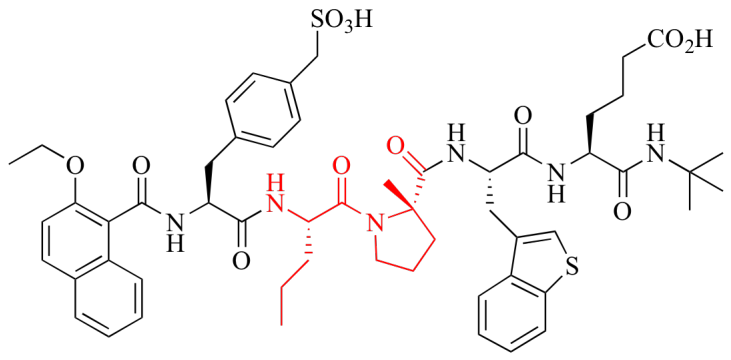


1.1 µM

Derived SAR Continued



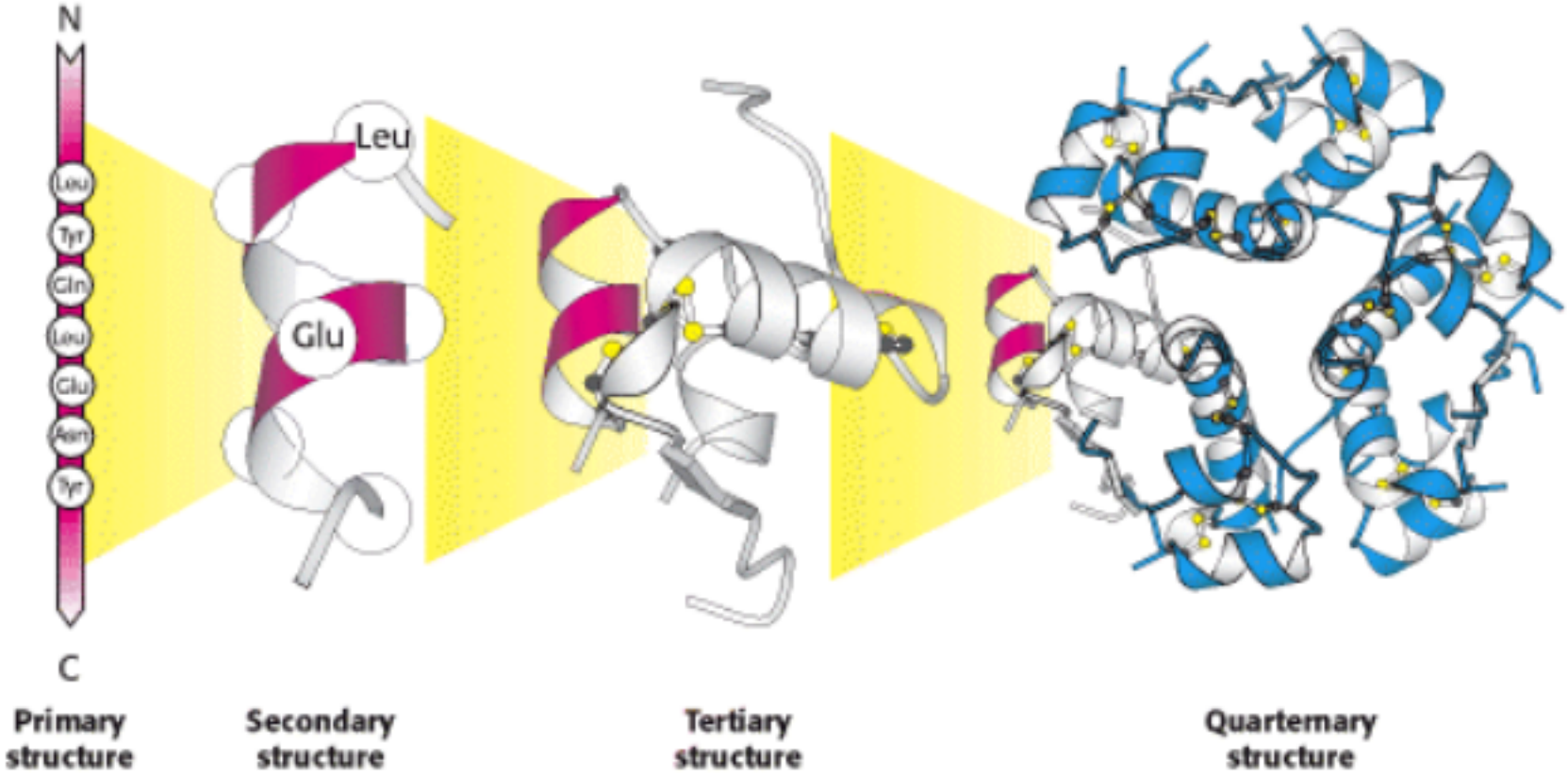
2.5 μM



1.5 μM

Turn conformation and the presence of sulfonic acid are most important for binding.

A Brief Biochem. Review

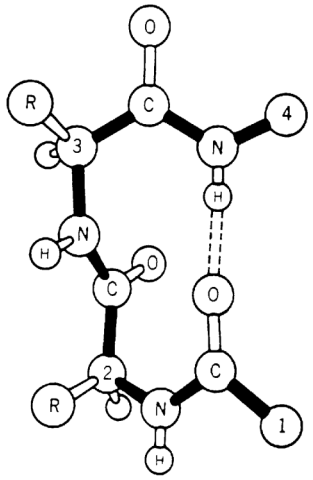


β-turns too!

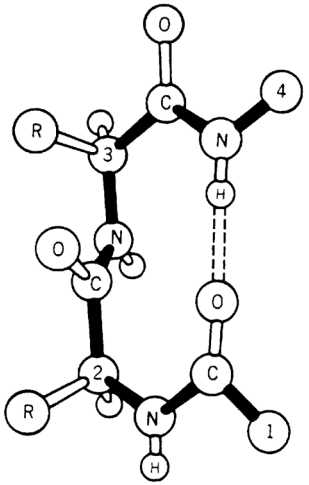
image from: Berg, J.; Tymoczko, J.; Stryer, L. *Biochemistry*, 5th ed.; W. H. Freeman and Co.; Chapter 3.

Types of β-Turns

Turn Type	Dihedral angles (°)			
	ϕ_{i+1}	ψ_{i+1}	ϕ_{i+2}	ψ_{i+2}
I	-60	-30	-90	0
I'	60	30	90	0
II	-60	120	80	0
II'	60	-120	-80	0
IV	-61	10	-53	17
VIa1	-60	120	-90	0
VIa2	-120	120	-60	0
VIb	-135	135	-75	160
VIII	-60	-30	-120	120



Type I

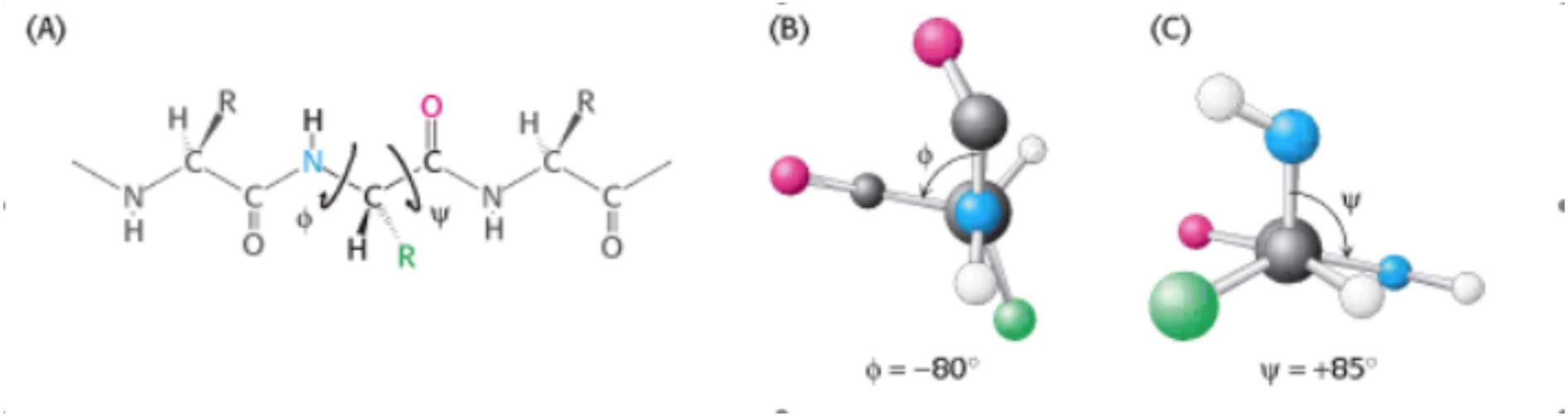


Type II

- Defined by 4 residues, hydrogen bonds between residues 2 and 4.
- Dehedral angles differentiate the turns.
- Types I, I', II, II' most common in protein structures.

images from: http://www.imtech.res.in/raghava/betaturns/turn.html

Anatomy of the Turn: Dihedral Angles



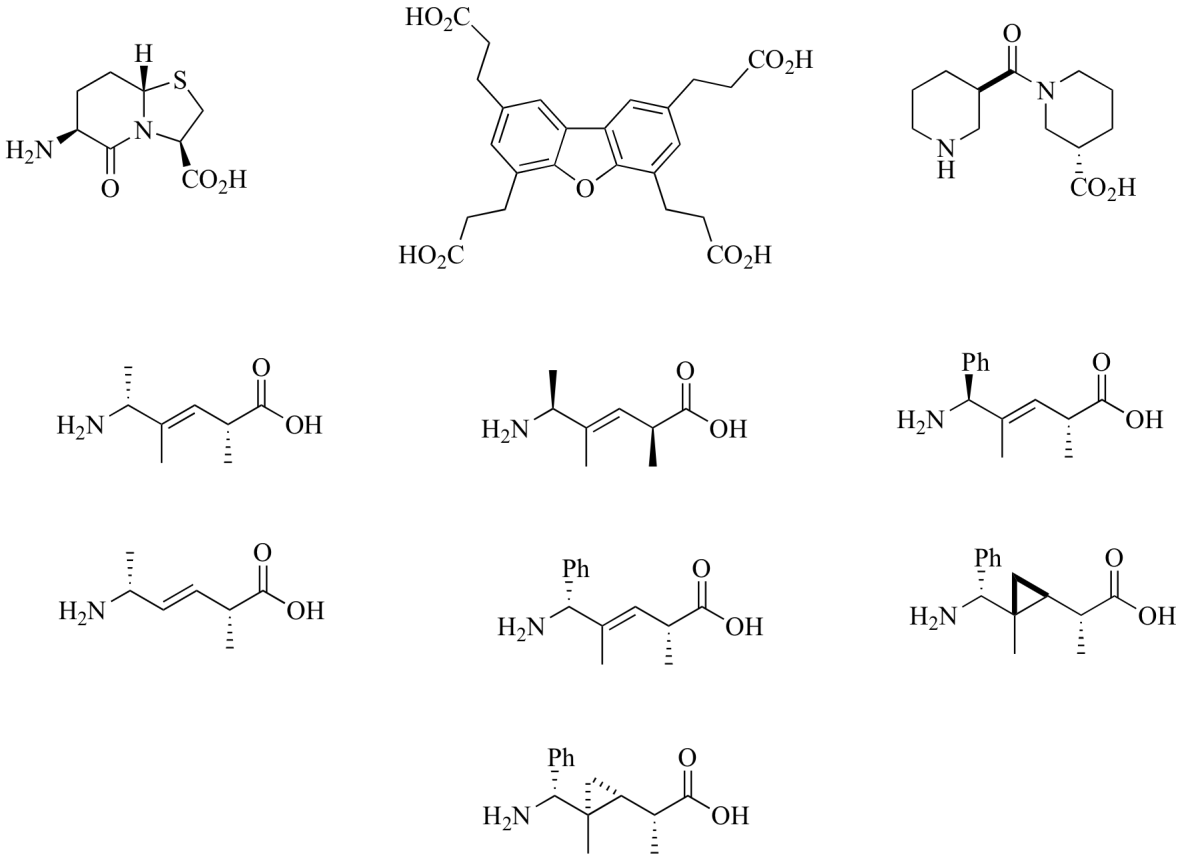
- Dihedral or torsion angles describe rotation about single bonds in peptide backbone.
- ϕ angle of rotation about bond between nitrogen and α-carbon.
- ψ angle of rotation about bond between α-carbon and carbonyl carbon.

image from: Berg, J.; Tymoczko, J.; Stryer, L. *Biochemistry*, 5th ed.; W. H. Freeman and Co.; Chapter 3.

Why are β-Turns Important?

- Protein-protein interactions usually achieved through specific conformations.
- β-turns are common recognition features.
- Peptidomimetics are used to incorporate these features into drug molecules.
- Mimicking these secondary structures should lead to more active inhibitors.

Known β-Turn Mimics



Wipf, P.; Xiao, J. *JOC*, **2005**, 7, 103-106.
Fuller, A.; Du, D.; Liu, F.; Davoren, J.; Bhabha, G.; Kroon, G.; Case, D.; Dyson, H.J.; Powers, E.; Wipf, P.; Gruebele, M.; Kelly, J. *PNAS* **2009**, 106, 11067-11072.

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