

Enhancing bioactive-peptide by conformationally controlled mimetics

LITERATURE SEMINAR #3

Y.KAMIMURA

1. Introduction

2. Major secondary structures and its mimetics

- α -helix
- Example of α -helix mimetic PPI inhibitor
- β -sheet
- Example of β -sheet mimetic PPI inhibitor
- Turns
- Example of β -turn mimetics

3. Summary

4. Appendix

1. Introduction

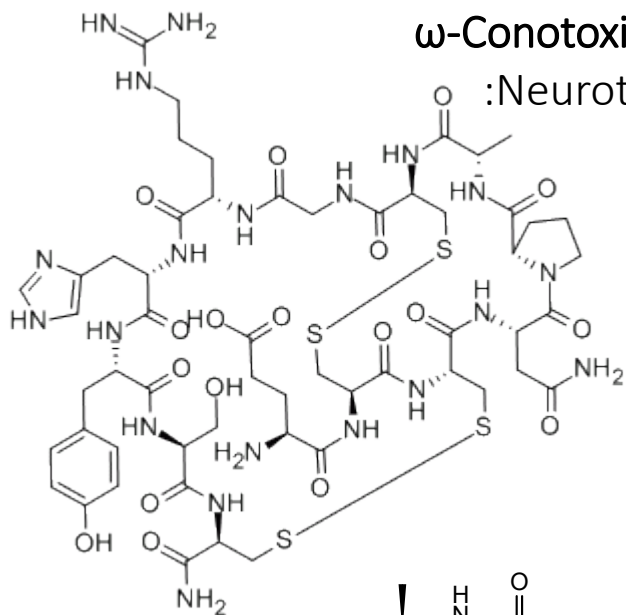
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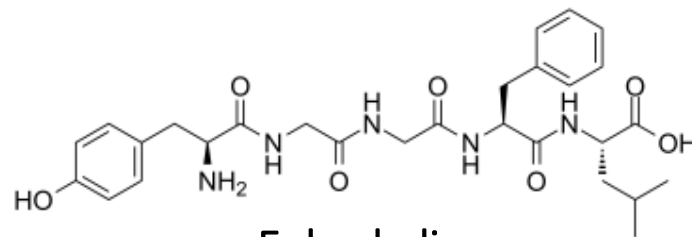
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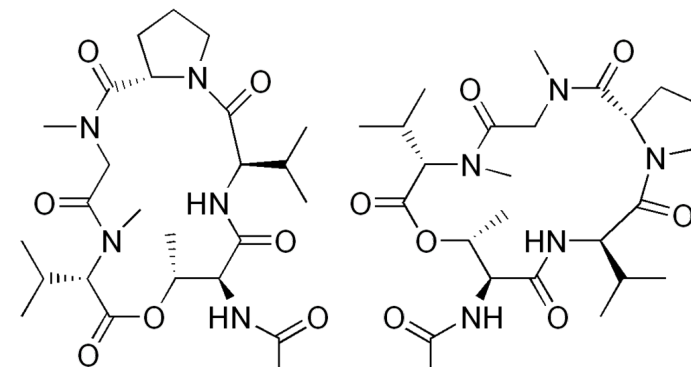
Bioactive Peptides



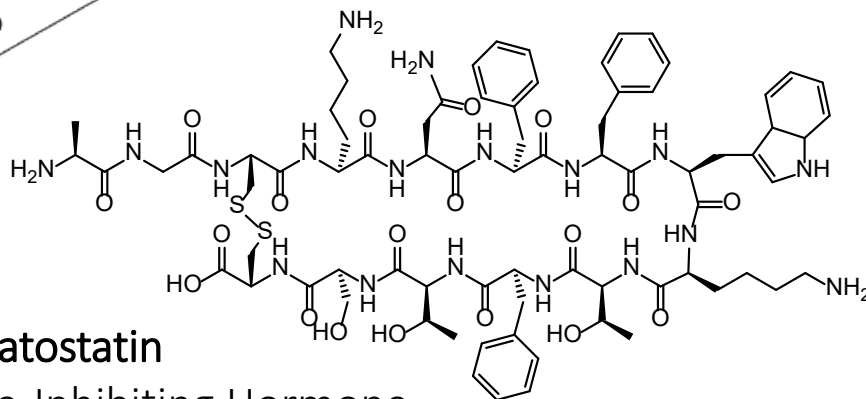
ω-Conotoxin MVIIA
:Neurotoxin



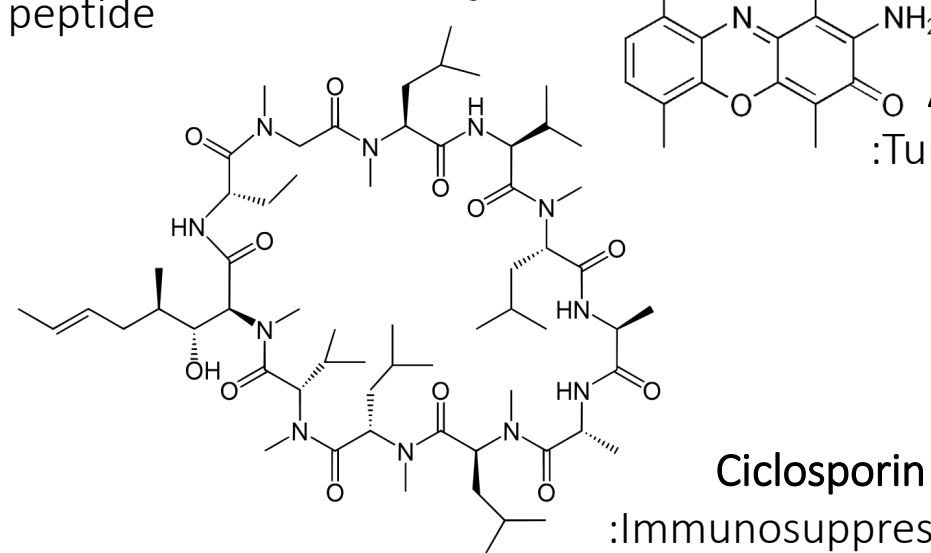
Enkephalin
:Endogenous opioid peptide



Actinomycin D
:Tumorsuppressants



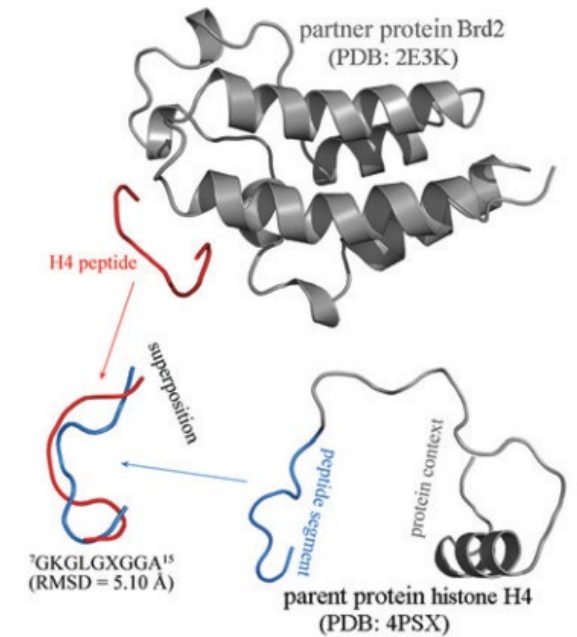
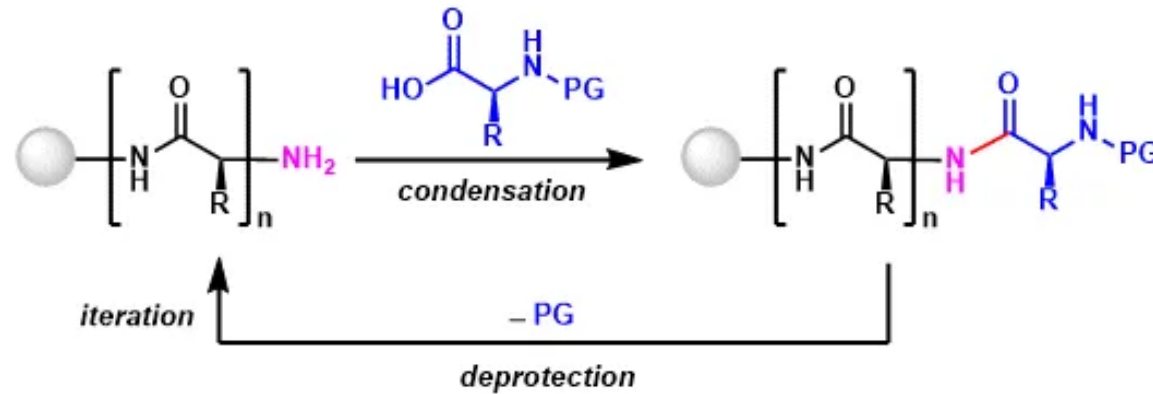
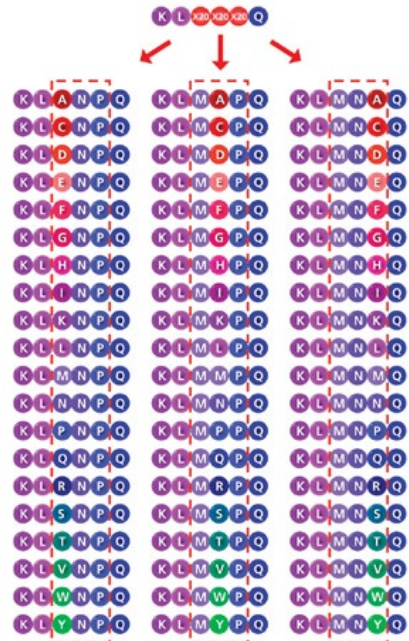
Somatostatin
:Growth Hormone-Inhibiting Hormone



Ciclosporin
:Immunosuppressants

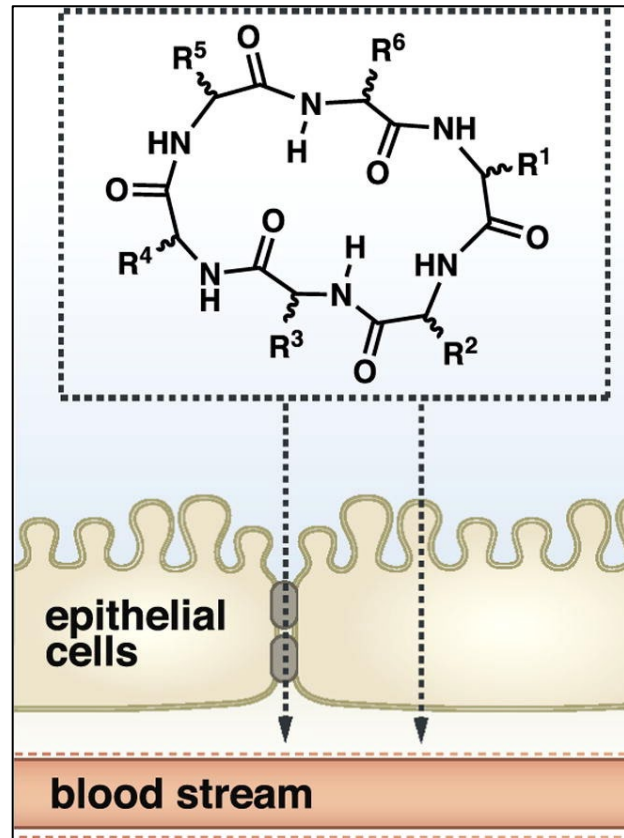
Peptides show strong, wide spectrum of bioactivity.

Advantages of peptide as bioactive substance

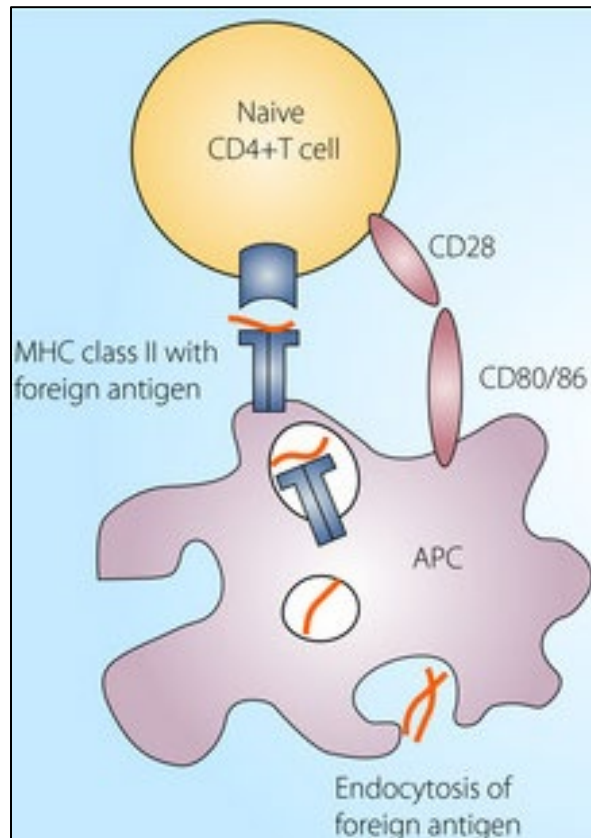


- ✓ Limitless diversity
- ✓ The ease of synthesis and analysis
- ✓ Inherent biological relevance

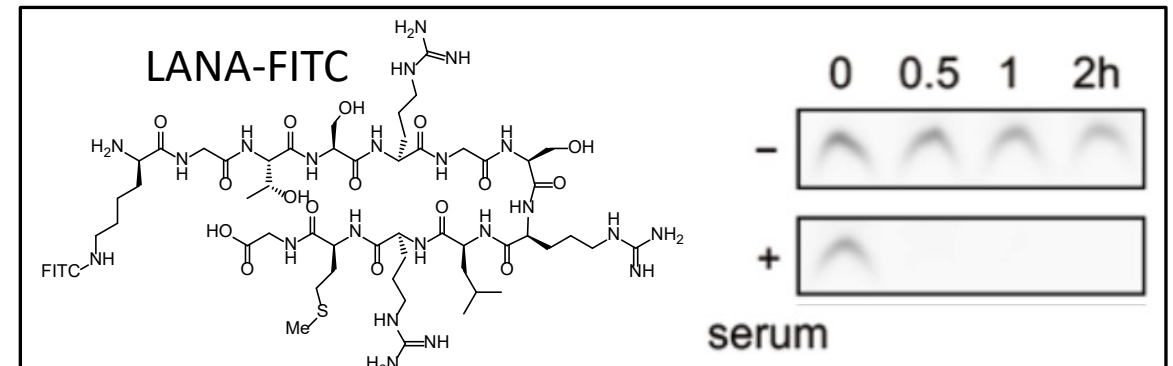
Disadvantages of peptide as bioactive substance



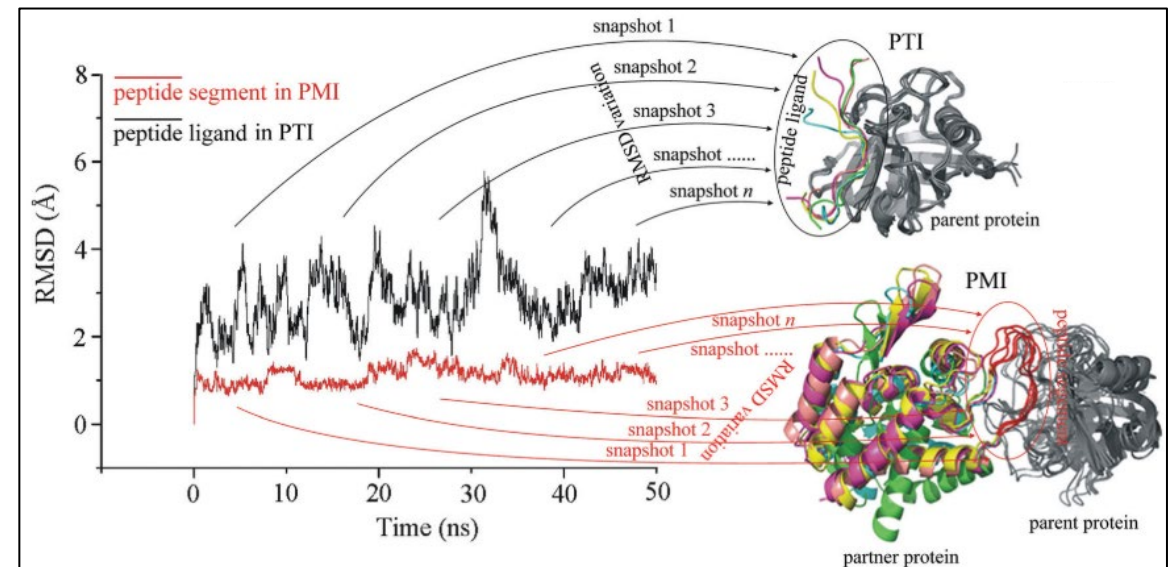
X Low bioavailability



X Immunogenicity

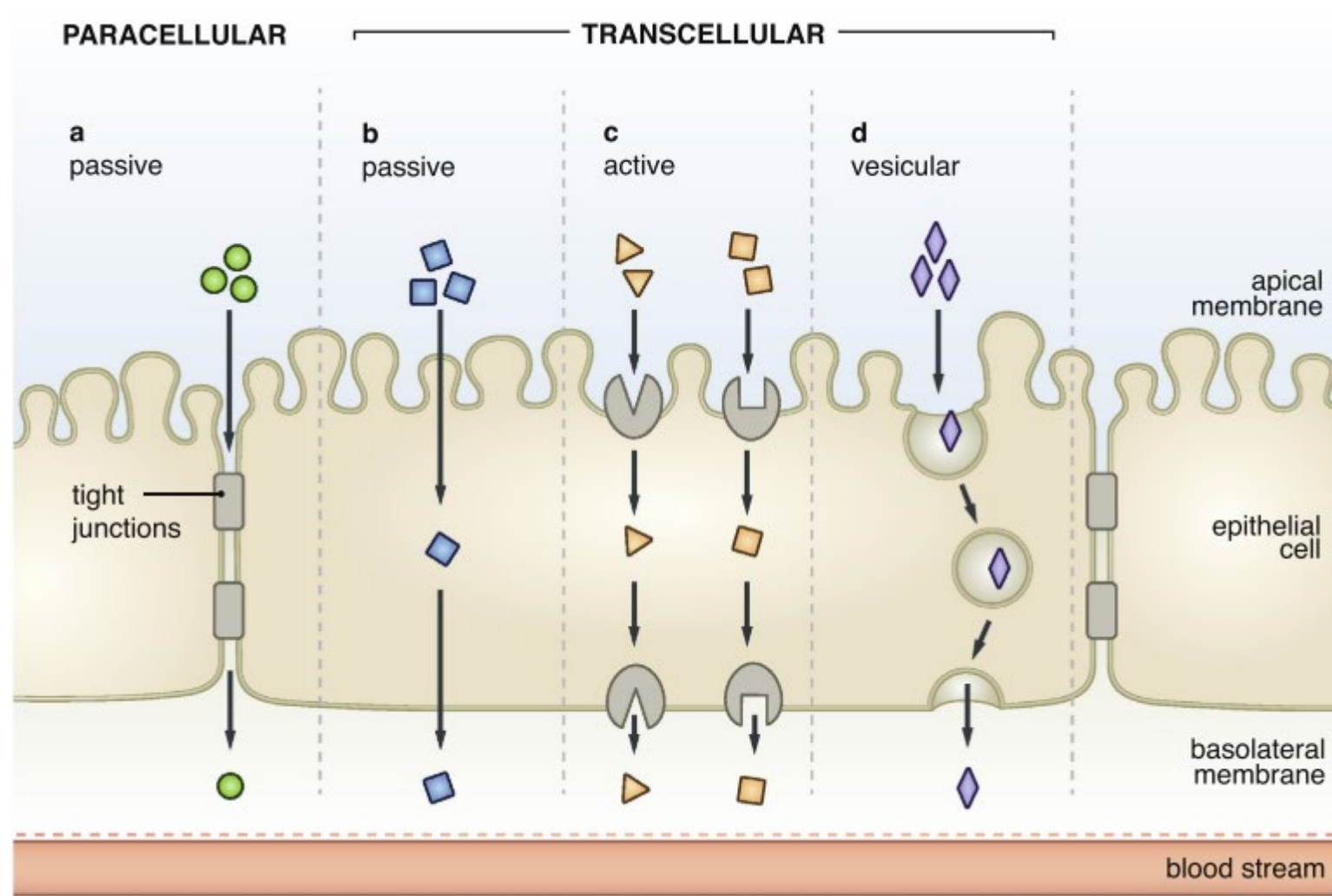


X Low stability in cell/vivo



X High flexibility

Pathway of the intestinal uptake of peptides



Peptidomimetics

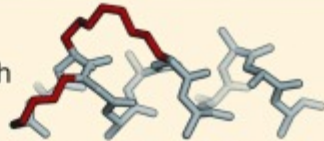
Peptides

natural peptide sequences derived from proteins and (non) ribosomal peptides



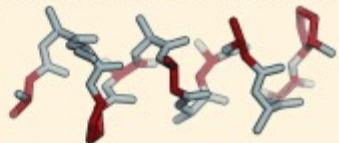
Class A - modified peptides

peptides mainly formed by α -amino acids with minor side chain or backbone alterations



Class B - modified peptides / foldamers

peptides with various backbone and side chain alterations also including foldamers



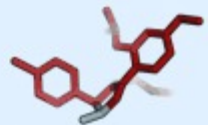
Class C - structural mimetics

small molecule-like scaffolds that project substituents in analogy to peptide side chains



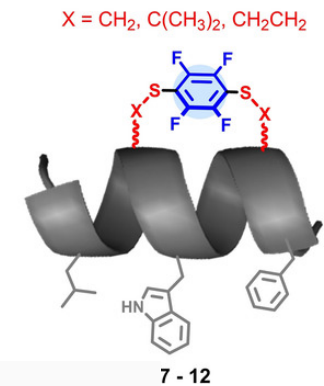
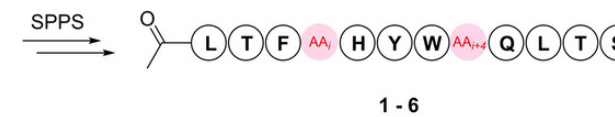
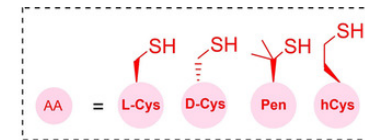
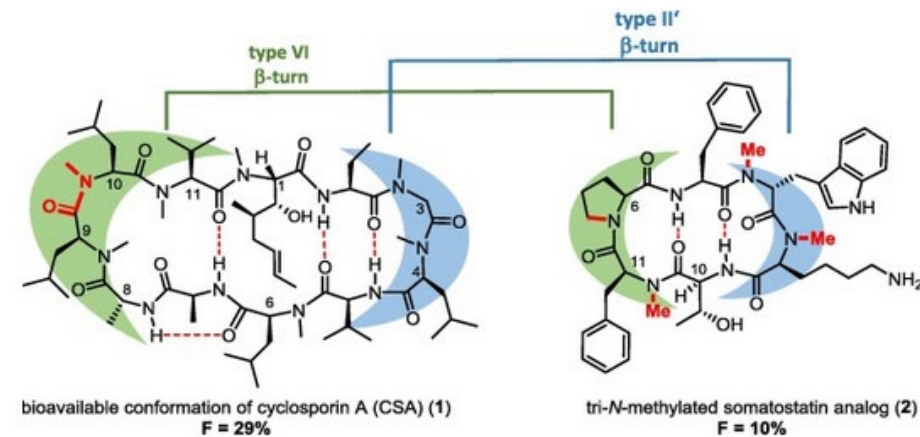
Class D - mechanistic mimetics

molecules that mimic the mode of action of a peptide without a direct link to its side chains



peptidic character

small molecules



Peptidomimetics

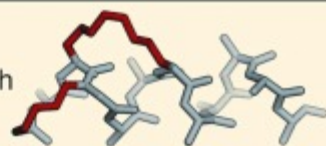
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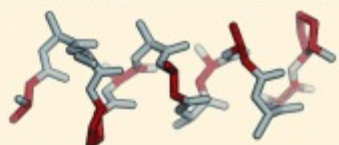
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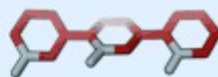
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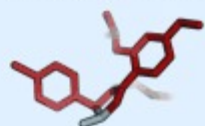
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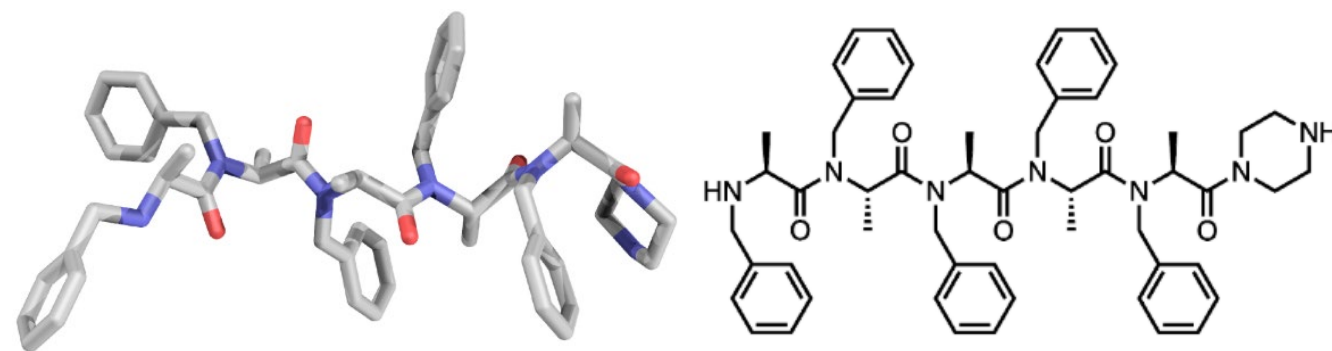
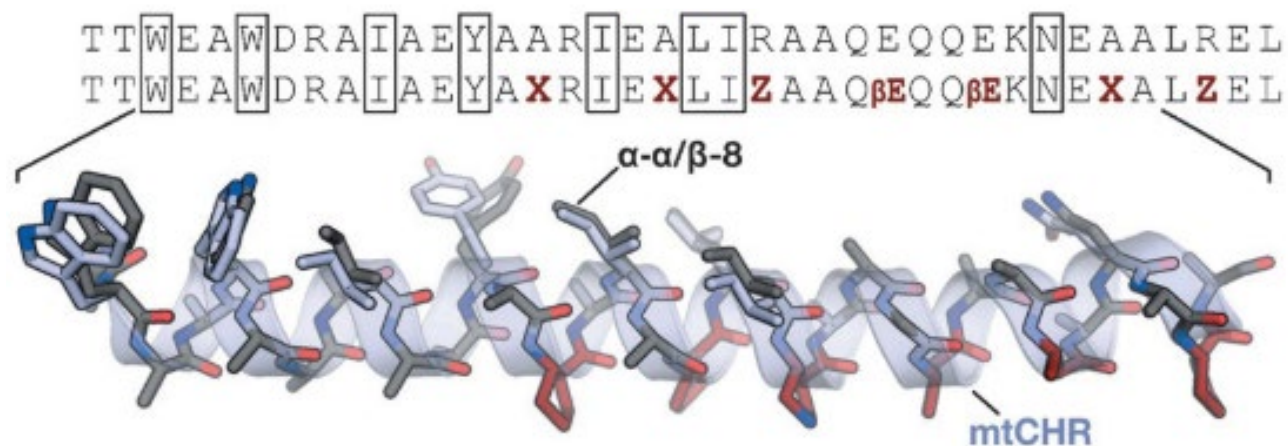


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Peptidomimetics

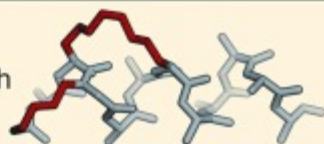
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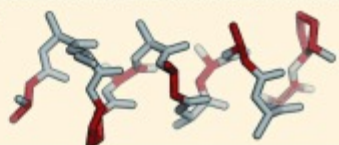
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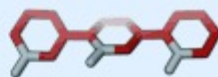
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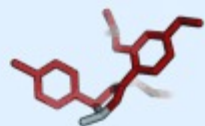
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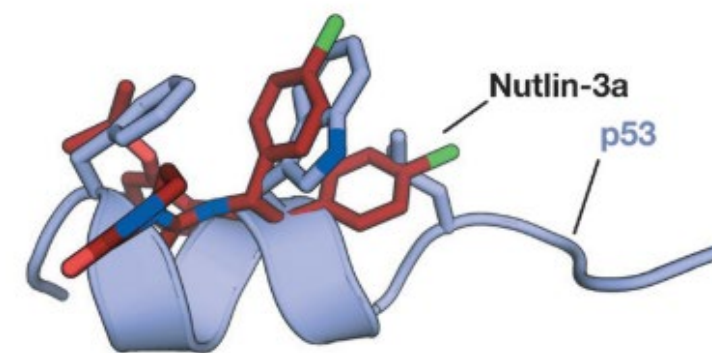
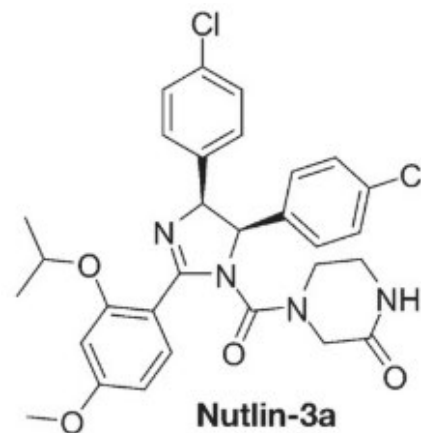
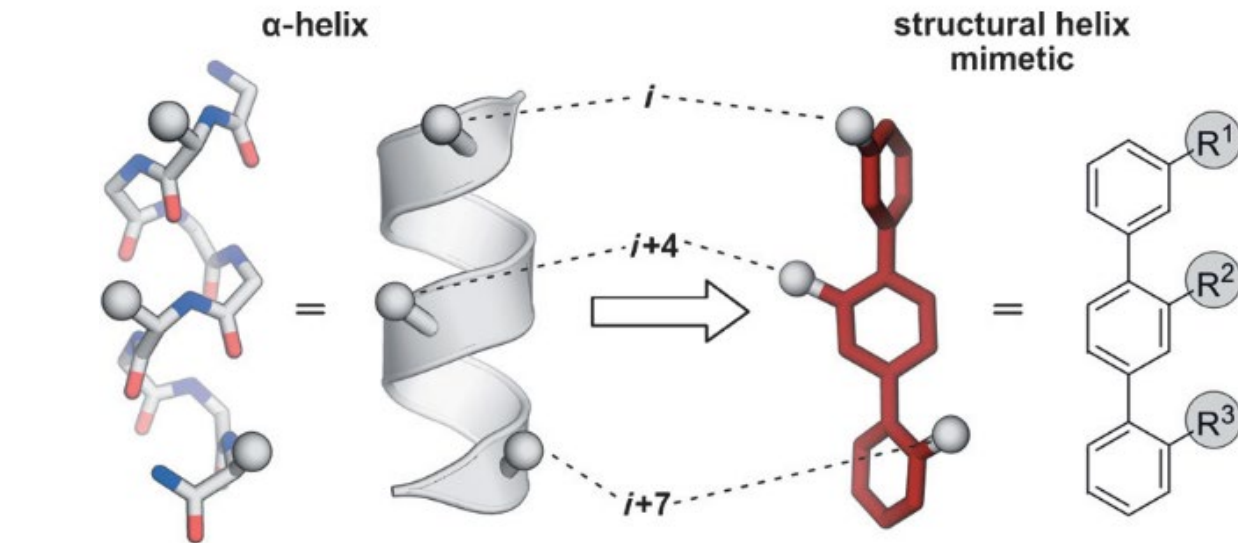


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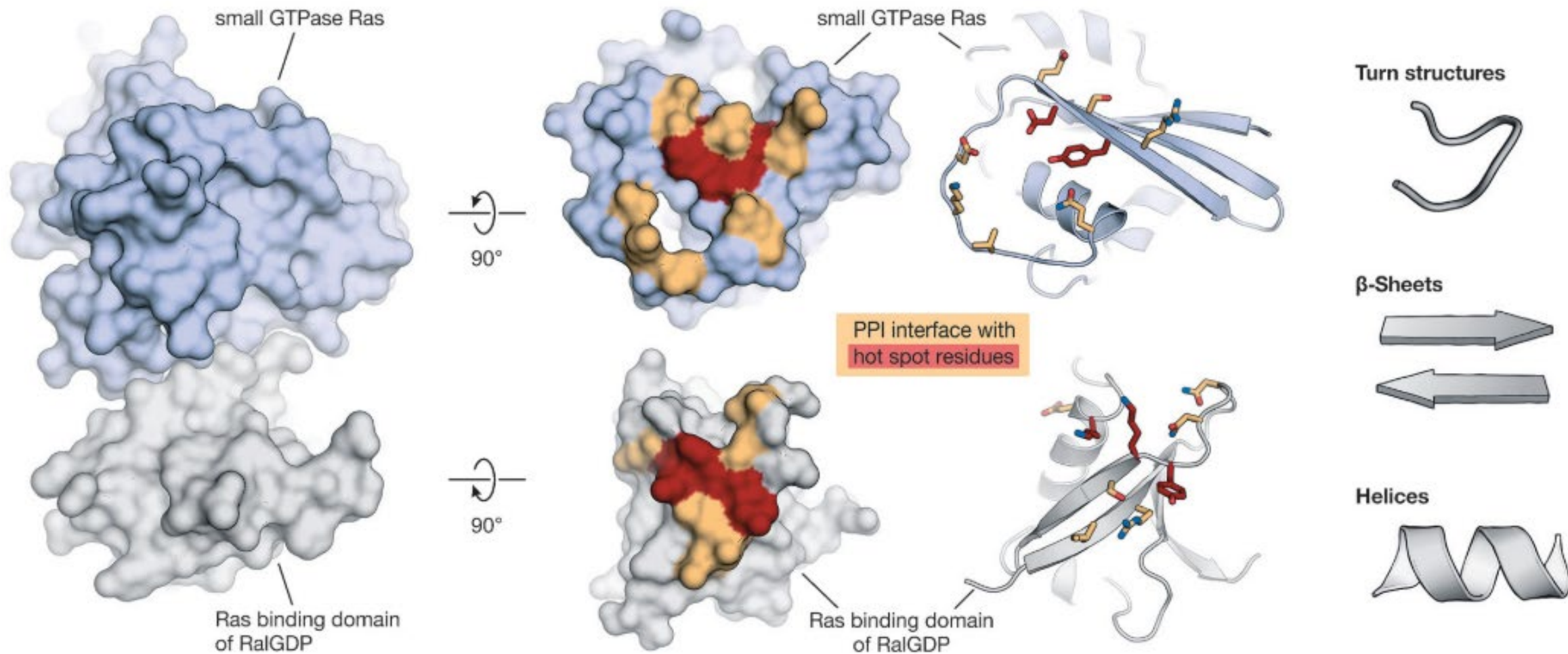
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small molecules



Mimicking Peptide-Protein Interactions



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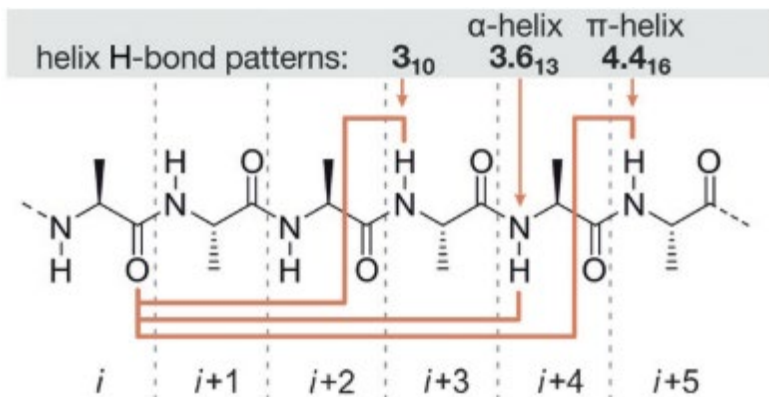
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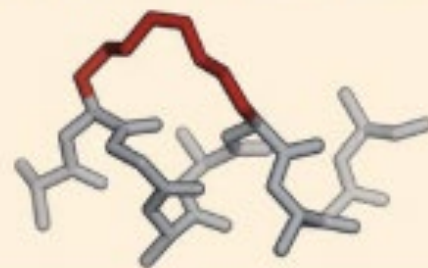
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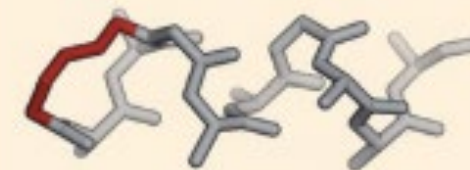
α -helix and its mimetics



Side chain to side chain cross-link



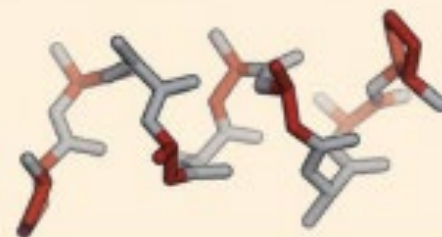
N-Terminal cap

 α -Helix

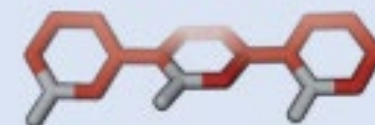
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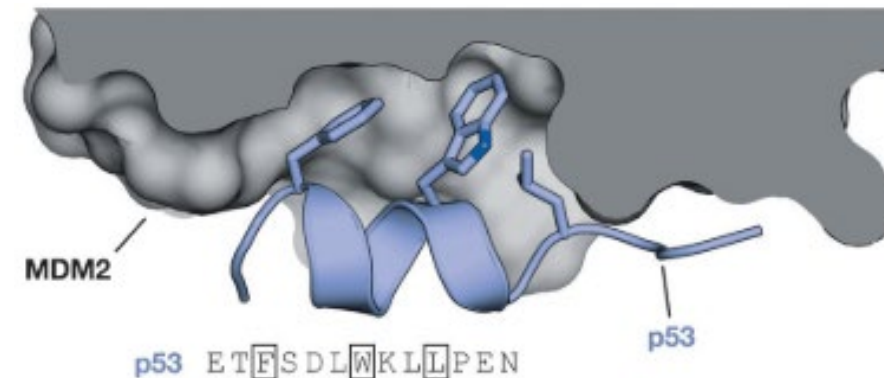
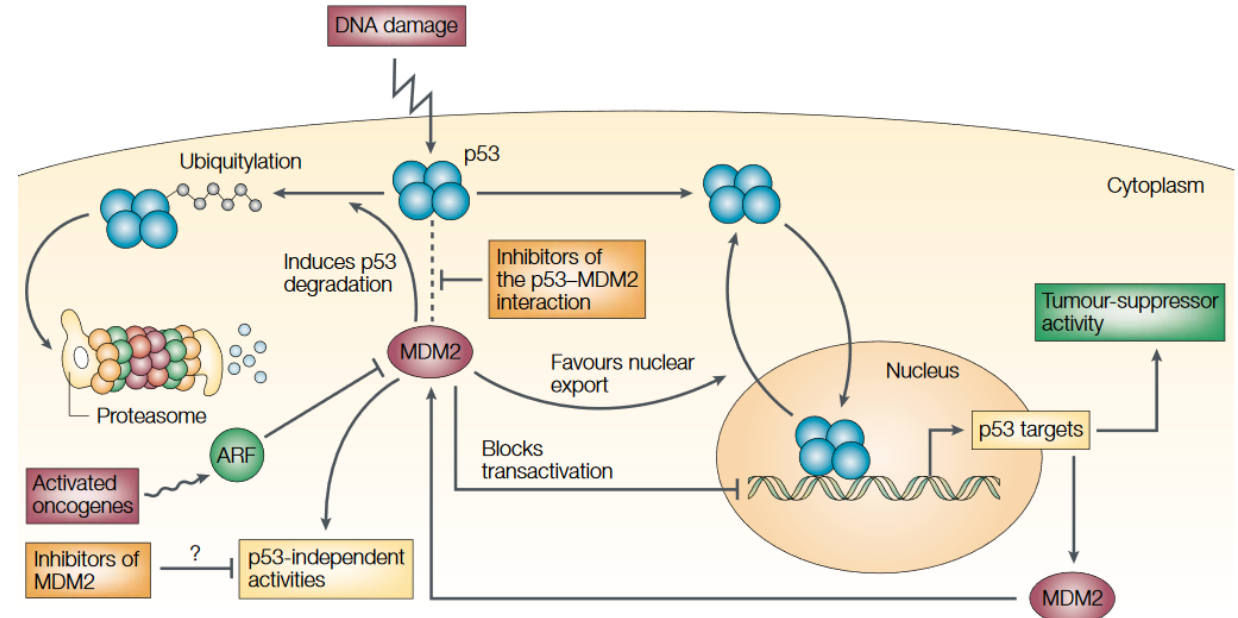
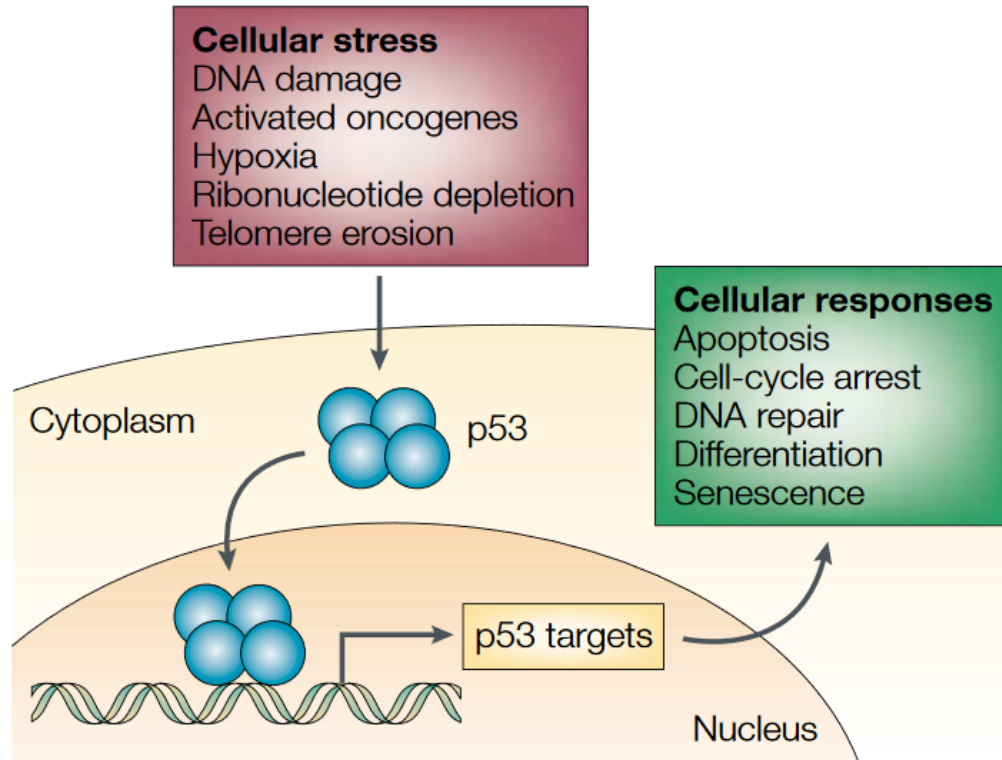
Foldamers



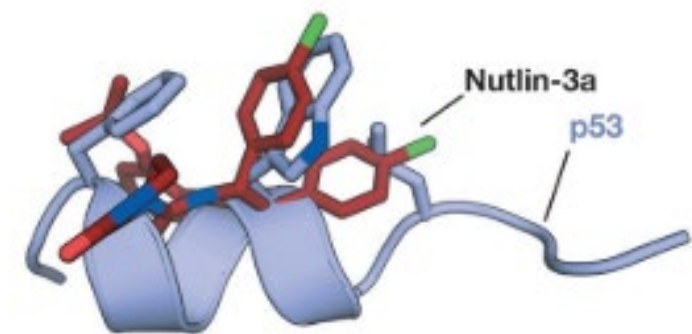
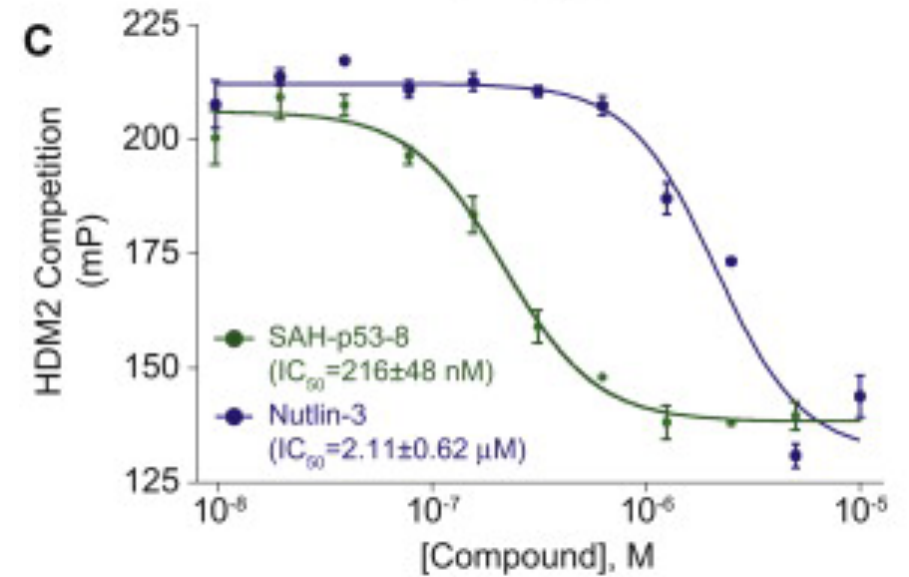
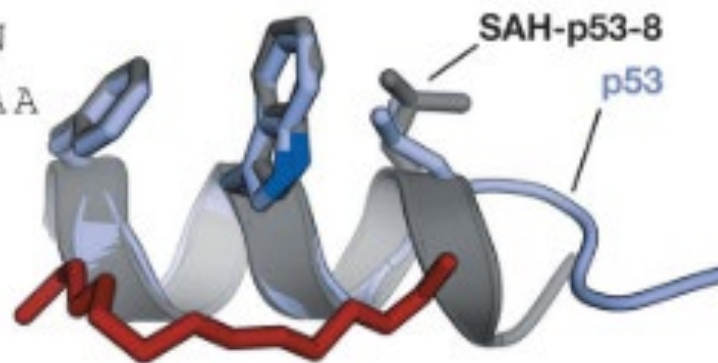
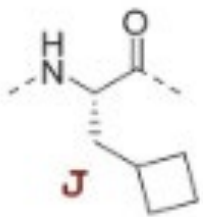
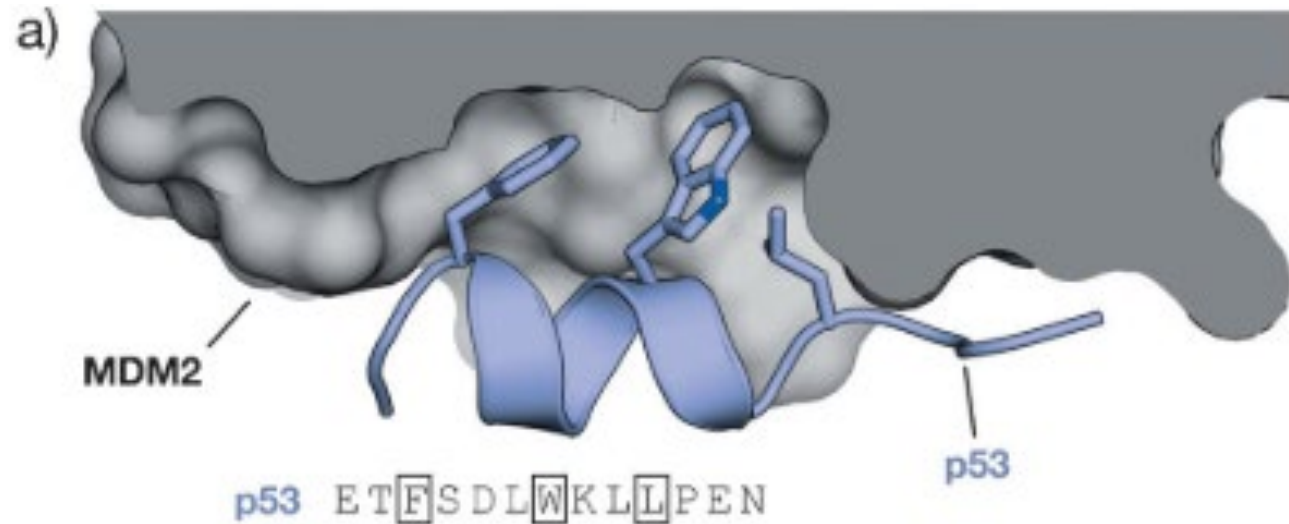
Structural mimetics



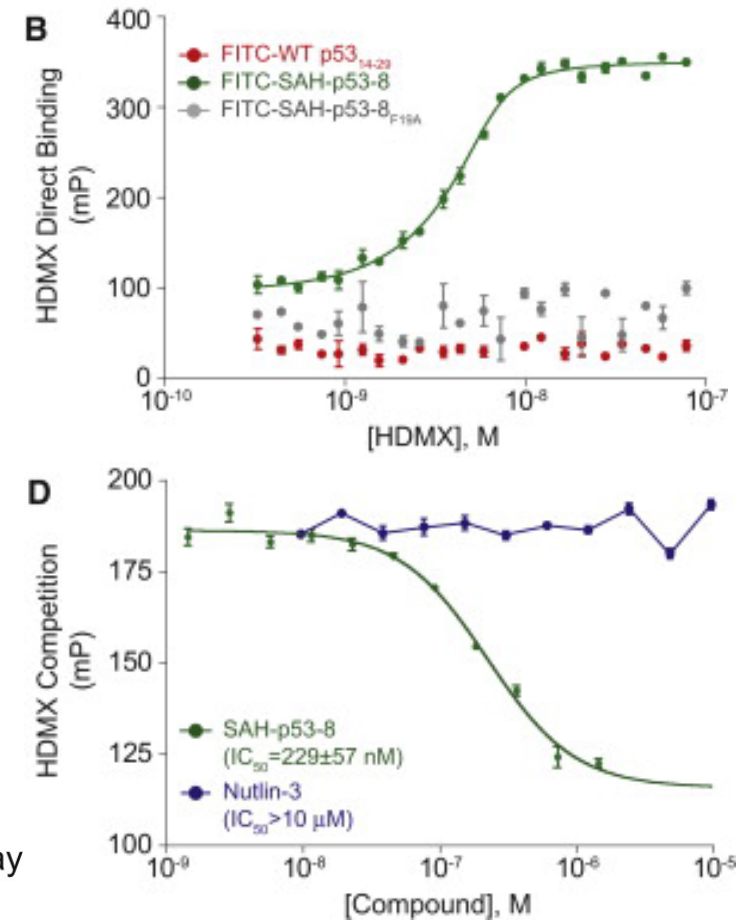
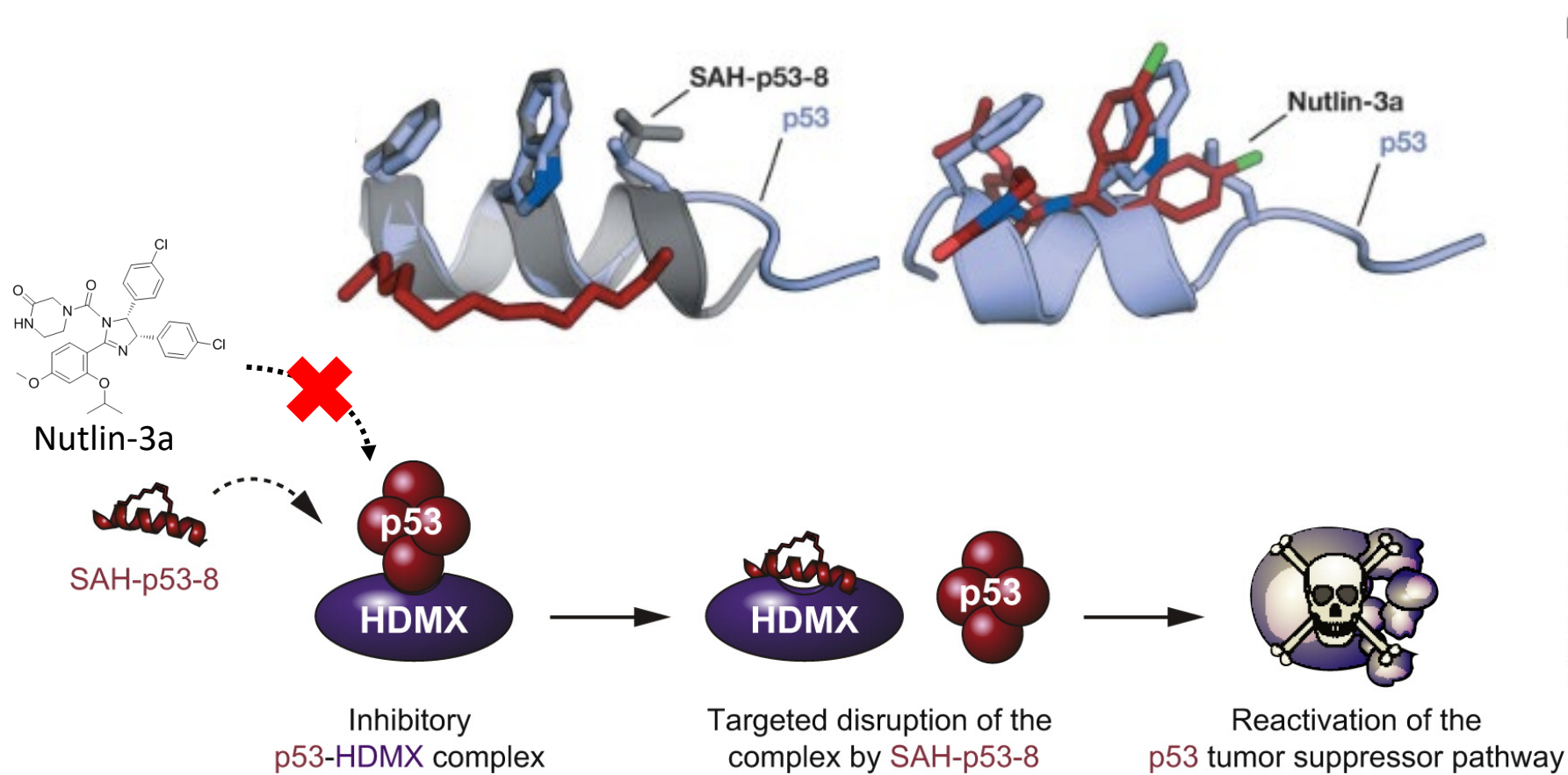
α -helix in p53-MDM2 interaction



Example: Sidechain Crosslinking



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| SAH-p53-8 can also bind to HDMX.

| HDM2 inhibition by Nutlin-3a can be compromised by overexpression of HDMX which do not bind to Nutlin-3a.

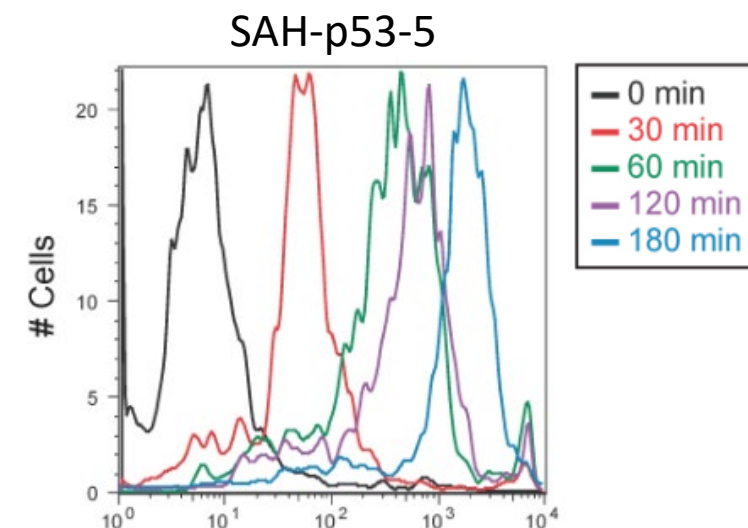
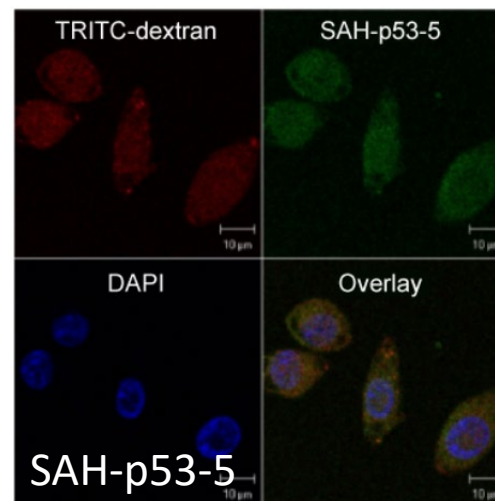
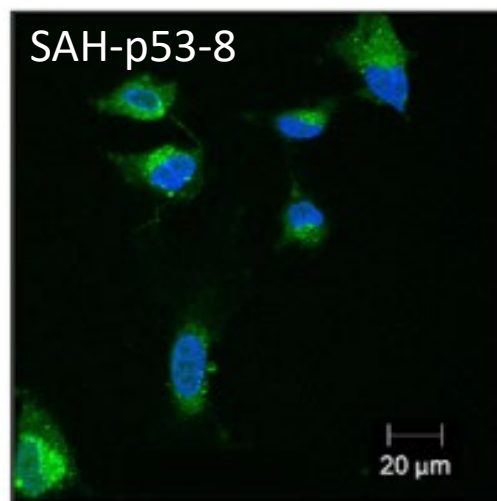
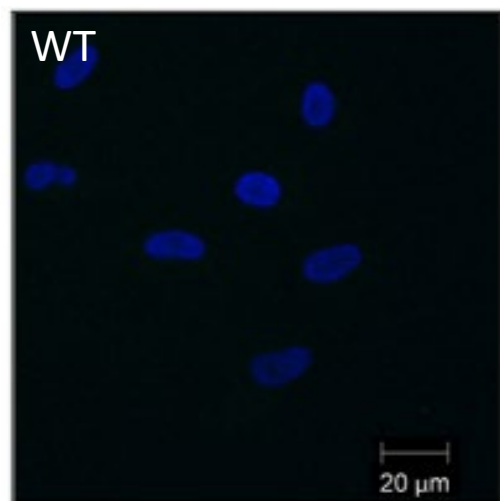
Example: Sidechain Crosslinking

Compound	Sequence * = R_8 * = S_5	Charge at pH 7.4	α helicity	K_d (nM)	Cell permeable	Cell death
WT	Ac-LSQETFSDLWKLLPEN-NH ₂	-2	11%	410±19	no	-
SAH-p53-1	Ac-LSQETFSD*WKLLPE*-NH ₂	-2	25%	100±8	no	-
SAH-p53-2	Ac-LSQE*FSDLWK*LPEN-NH ₂	-2	10%	400±50	no	-
SAH-p53-3	Ac-LSQ*TFSDLW*LLPEN-NH ₂	-2	12%	1200±89	no	-
SAH-p53-4	Ac-LSQETF*DLWKLL*EN-NH ₂	-2	59%	0.92±0.11	no	-
SAH-p53-5	Ac-LSQETF*NLWKLL*QN-NH ₂	0	20%	0.80±0.05	yes	-
SAH-p53-6	Ac-LSQQTF*NLWRLL*QN-NH ₂	+1	14%	56±11	yes	-
SAH-p53-7	Ac-QSQQTF*NLWKLL*QN-NH ₂	+1	36%	50±10	yes	-
SAH-p53-8	Ac-QSQQTF*NLWRLL*QN-NH ₂	+1	85%	55±11	yes	+
SAH-p53-8 _{F19A}	Ac-QSQQTA*NLWRLL*QN-NH ₂	+1	39%	>4000	yes	-
UAH-p53-8	Ac-QSQQTF*NLWRKK*QN-NH ₂	+1	36%	100±10	yes	-

Membrane permeable

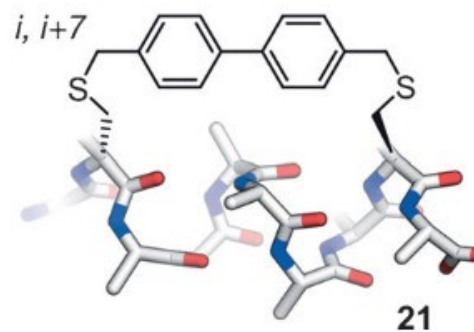
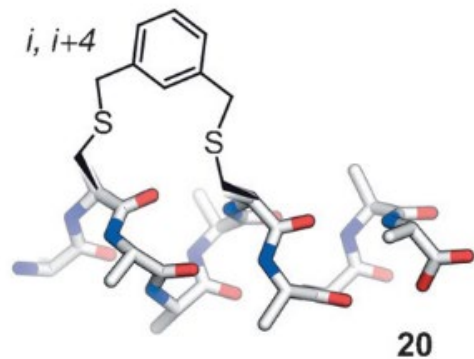
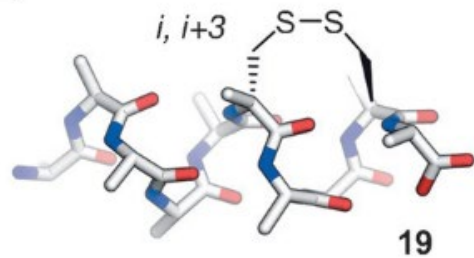
Stabilized

Low flexibility and high affinity

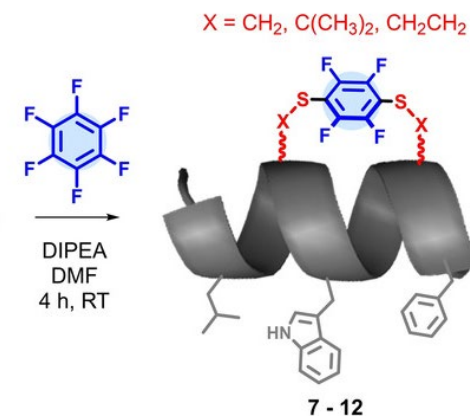
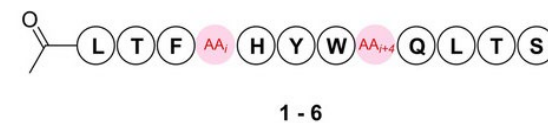
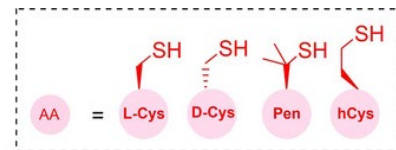
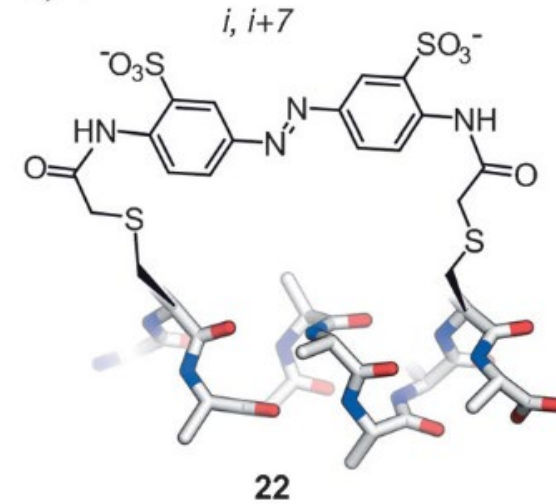


Sidechain crosslinking

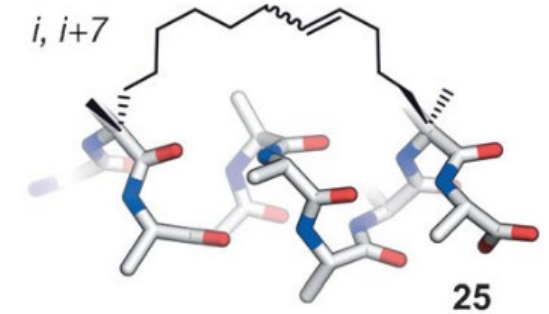
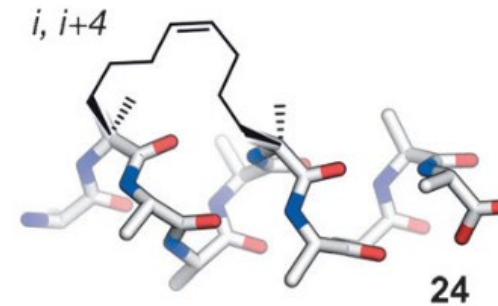
Thiol based cross-links



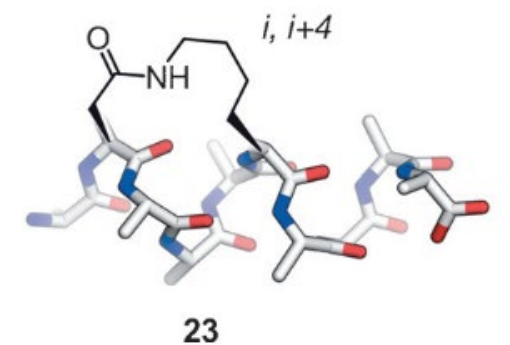
b) photo-switchable cross-link



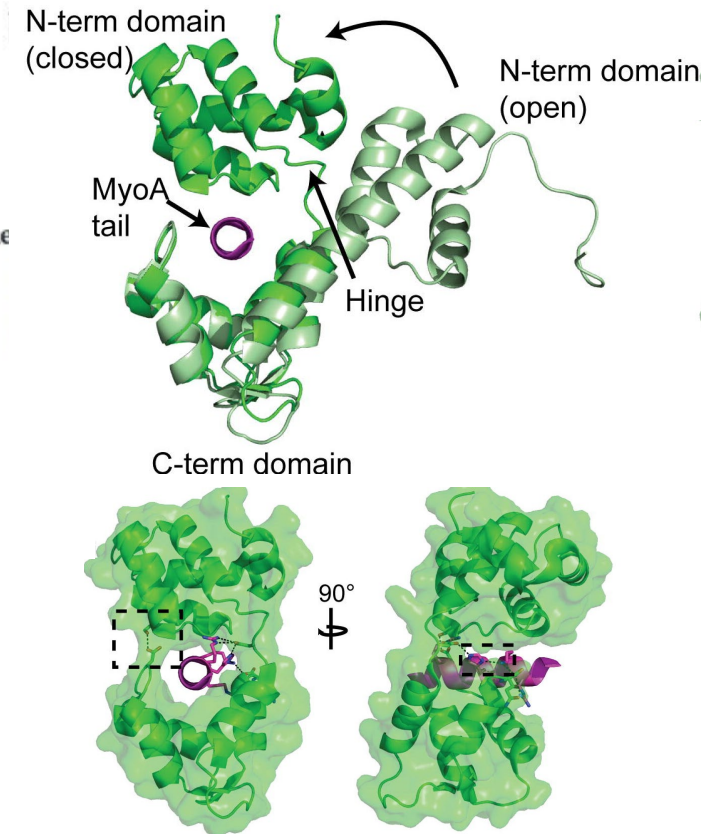
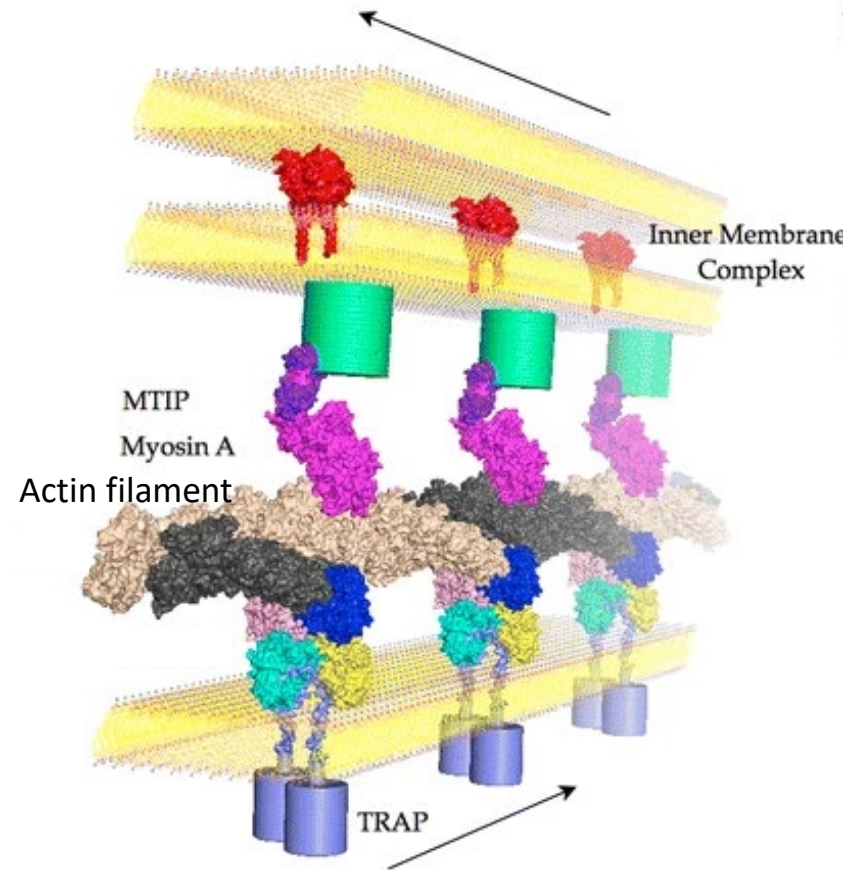
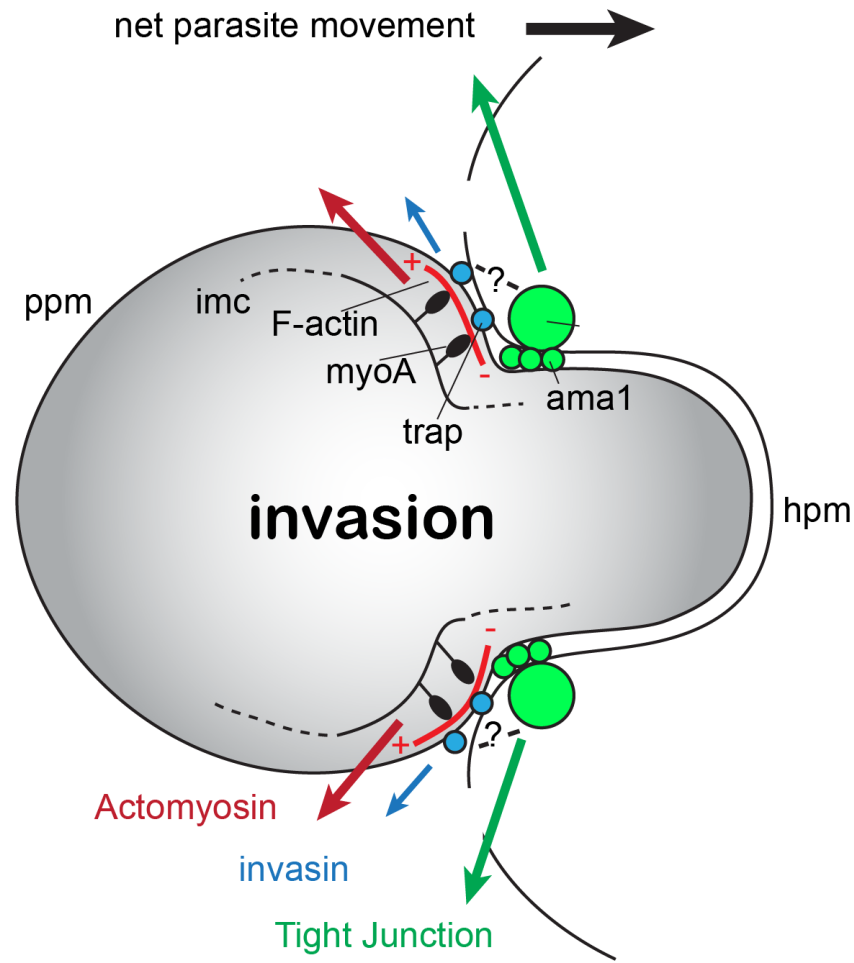
Ring-closing metathesis based cross-link



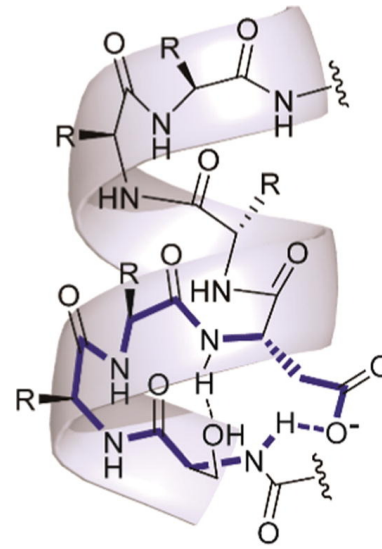
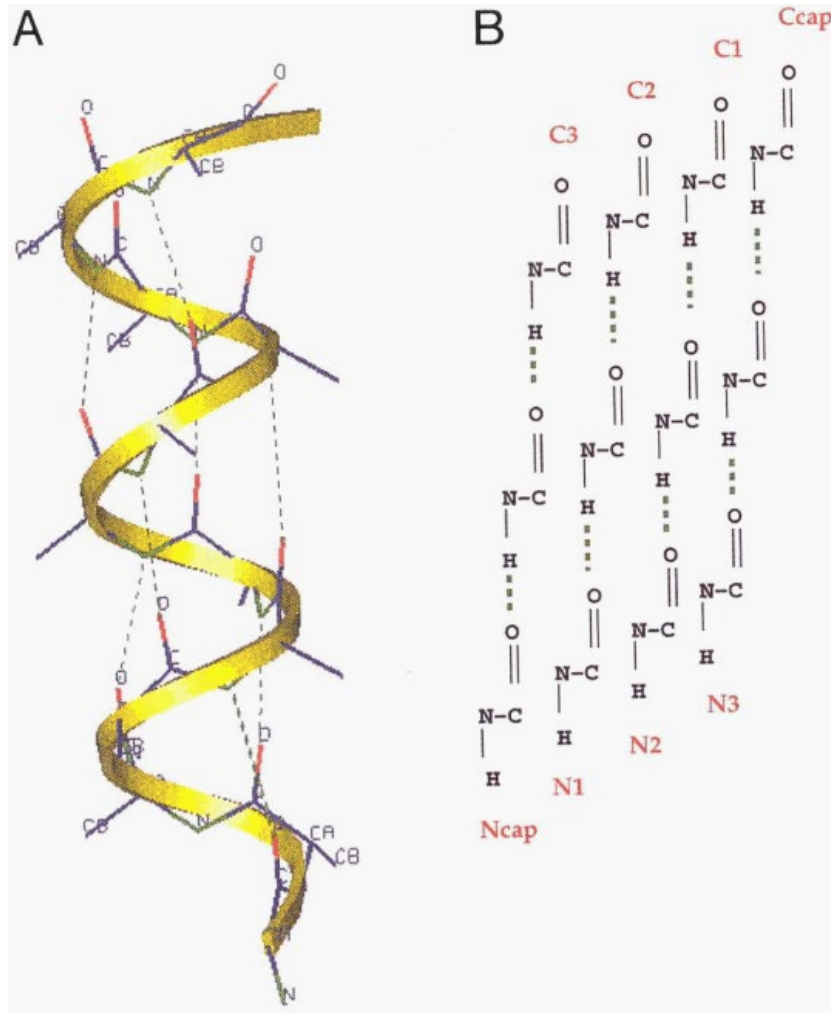
Lactam cross-links



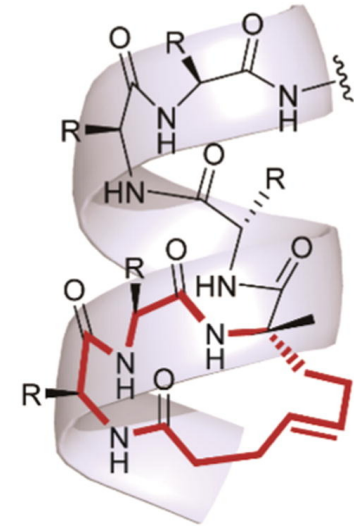
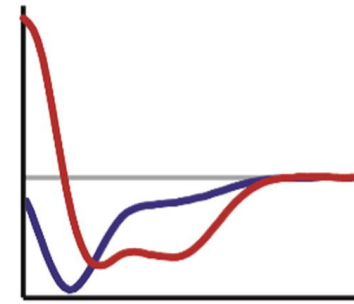
α -helix in Invasion of malaria parasite to host cell



N-terminal capping



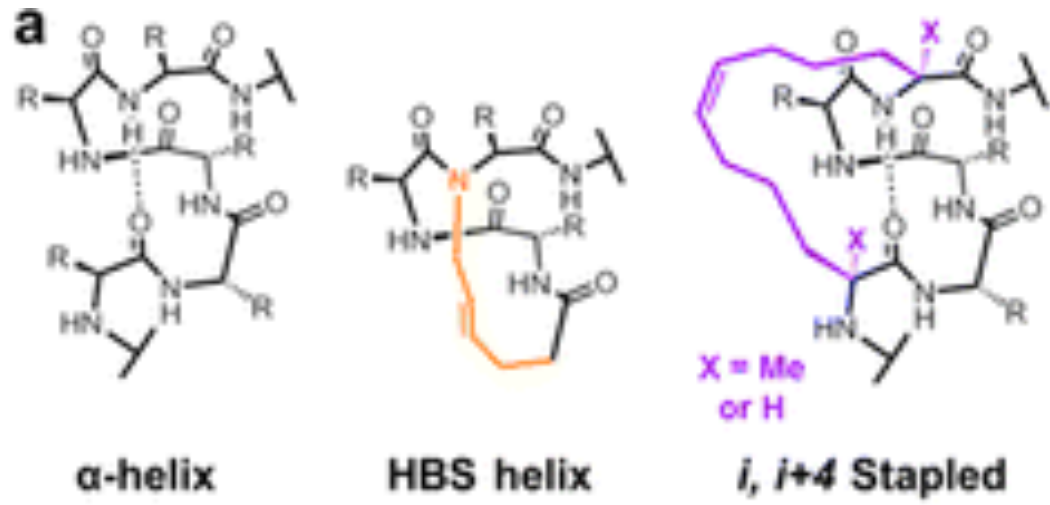
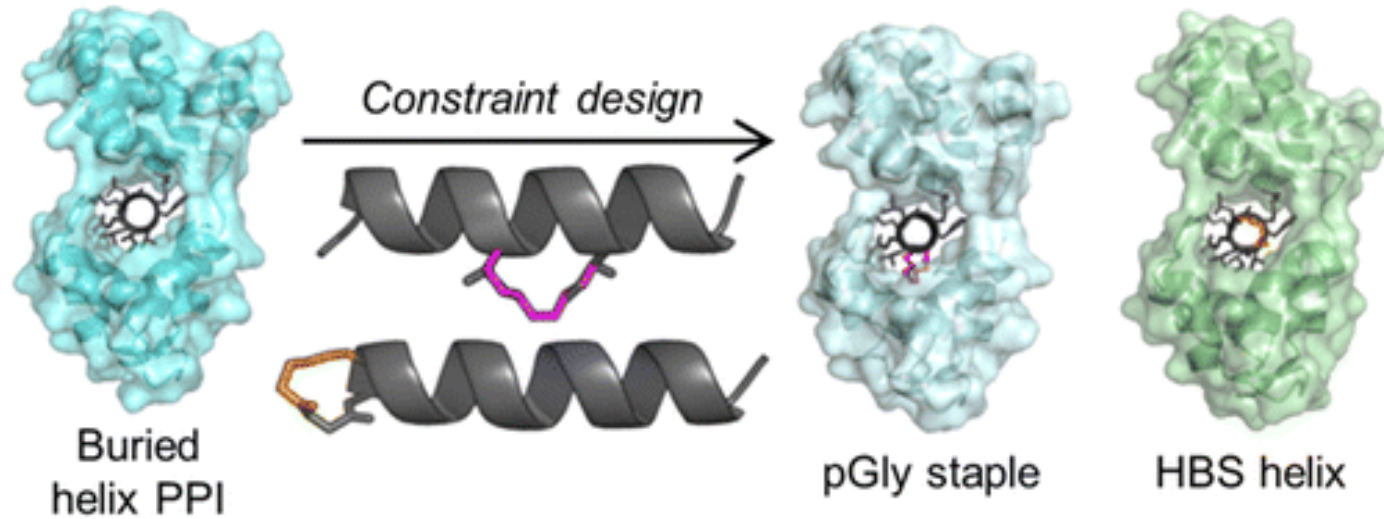
N-capping box



stapled N-capping box

- Hydrogen-bond acceptor amino acids such as Asn, Asp are enriched at N-terminal of α -helix.
- Nucleation of helix by such interaction induce the formation of α -helix.

Example: N-terminal capping

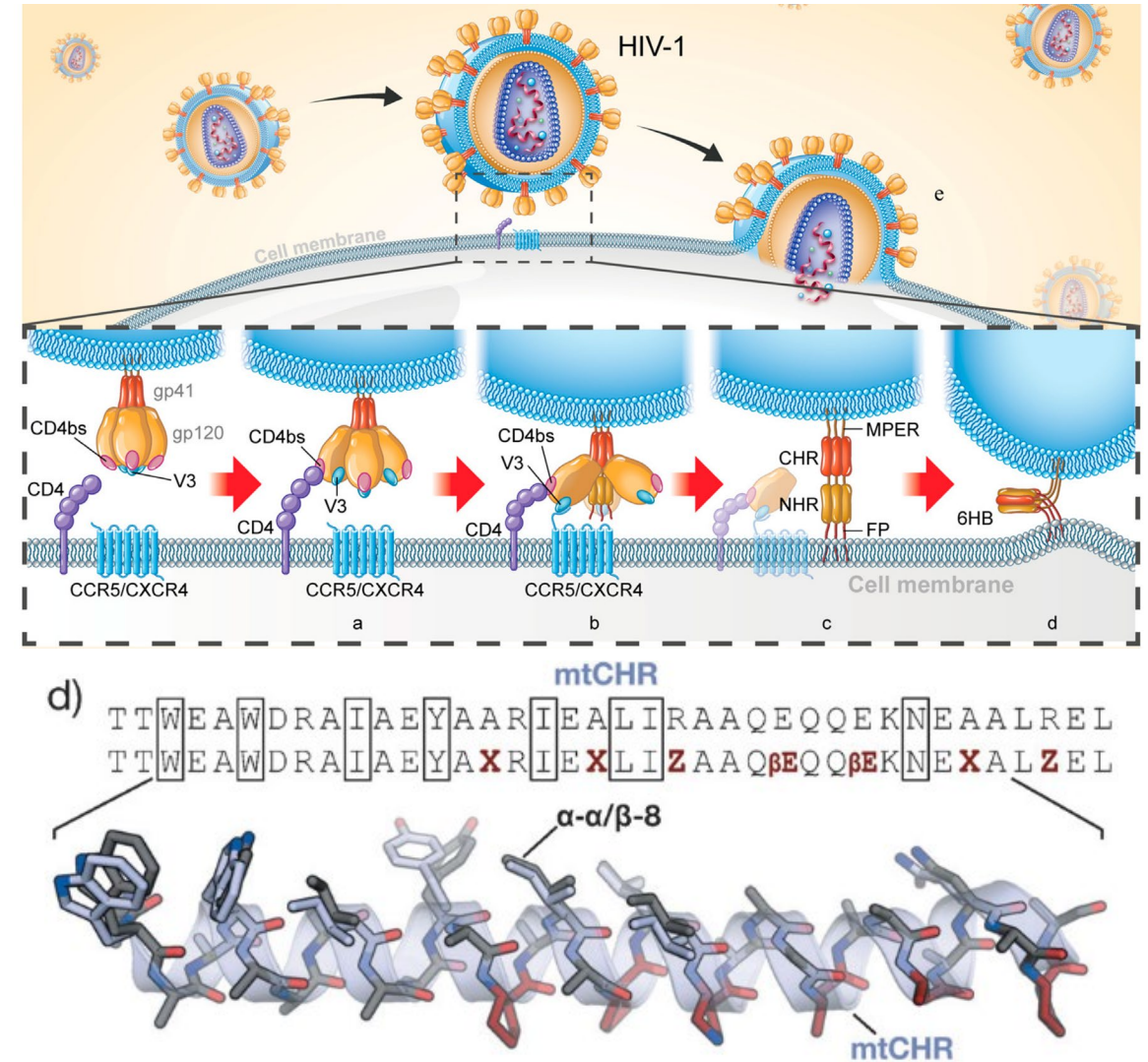
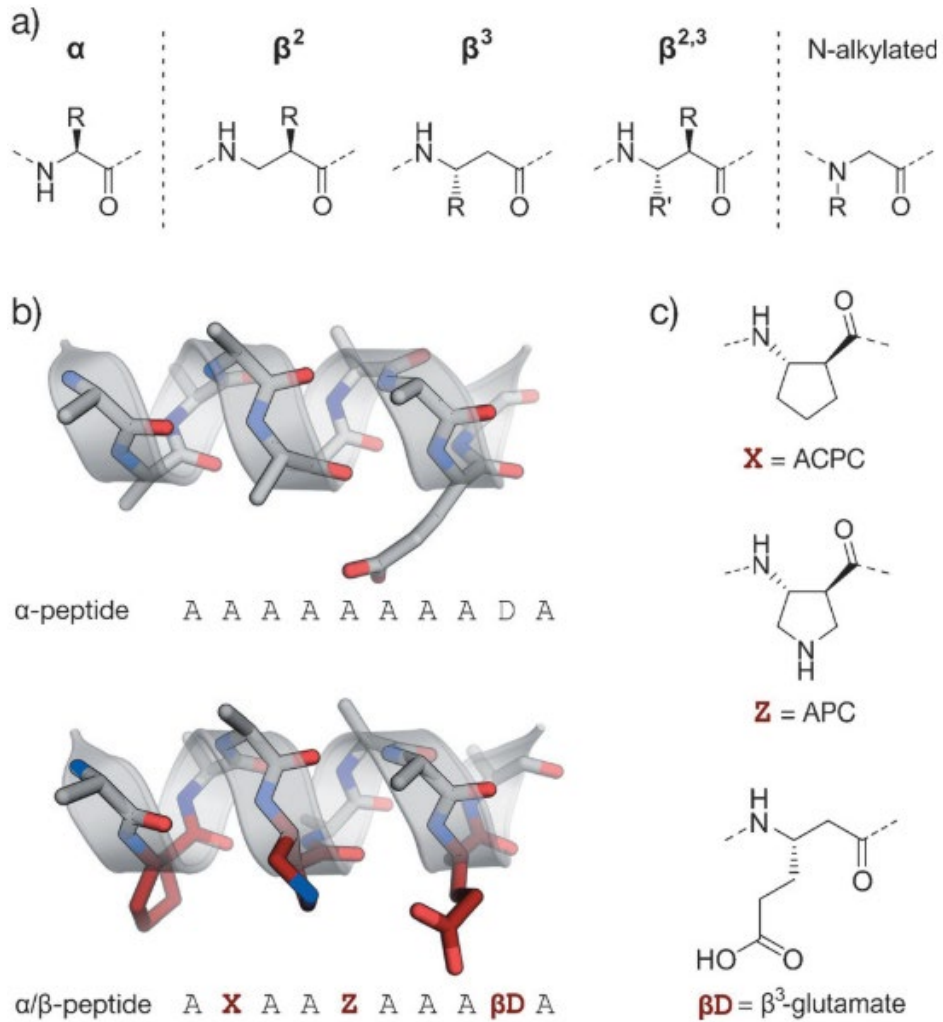


c

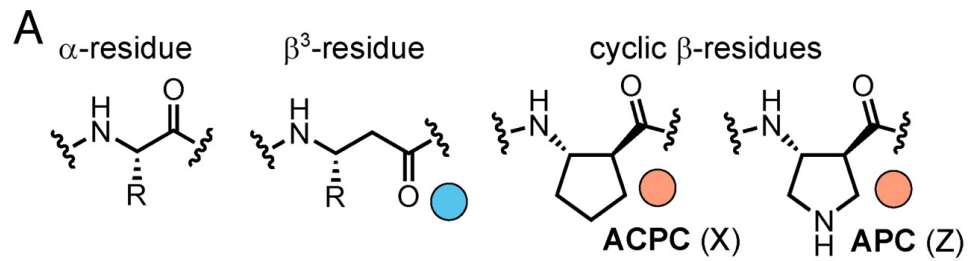
		800	805	810	815
WT myoA		K N I P S L L R V Q A H I R K K M V A Q			
HBS	R806A	X N I † S L L R V Q A H I R K K M V			
	R806A	X N I † S L L A V Q A H I R K K M V			
pAla	801,805	K N * P S L * R V Q A H I R K K M V			
	807,811	K N I P S L L R * Q A H * R K K M V			
X=Me	811,815	K N I P S L L R V Q A H * R K K * V			
	R806A	K N I P S L L A V Q A H * R K K * V			
	$i, i+7$	K N I P S ω L R V Q A H * R K K M V			
	X=Me				
pGly	801,805	K N γ P S L γ R V Q A H I R K K M V			
	807,811	K N I P S L L R γ Q A H γ R K K M V			
X=H	811,815	K N I P S L L R V Q A H γ R K K γ V			
	R806A	K N I P S L L A V Q A H γ R K K γ V			

	ΔT_m ($^{\circ}\text{C}$)	FRET IC_{50} (μM)
WT myoA	19.3 \pm 0.9	4.4 \pm 0.7
HBS myoA	16.1 \pm 0.8	2.4 \pm 0.3
HBS myoA R806A	13.0 \pm 0.7	>100
pAla[801,805]	14.2 \pm 1.4	8.0 \pm 2.2
pGly[801,805]	25.9 \pm 0.2	1.6 \pm 0.4
pAla[807,811]	15.9 \pm 1.1	10.0 \pm 2.6
pGly[807,811]	19.3 \pm 0.4	4.9 \pm 1.6
pAla[811,815]	16.2 \pm 0.9	4.3 \pm 0.8
pGly[811,815]	16.3 \pm 0.8	10.6 \pm 2.7
pAla R806A	12.5 \pm 1.0	>100
pGly R806A	10.3 \pm 0.8	>100
$i, i+7$ staple	9.8 \pm 0.4	9.8 \pm 4.1

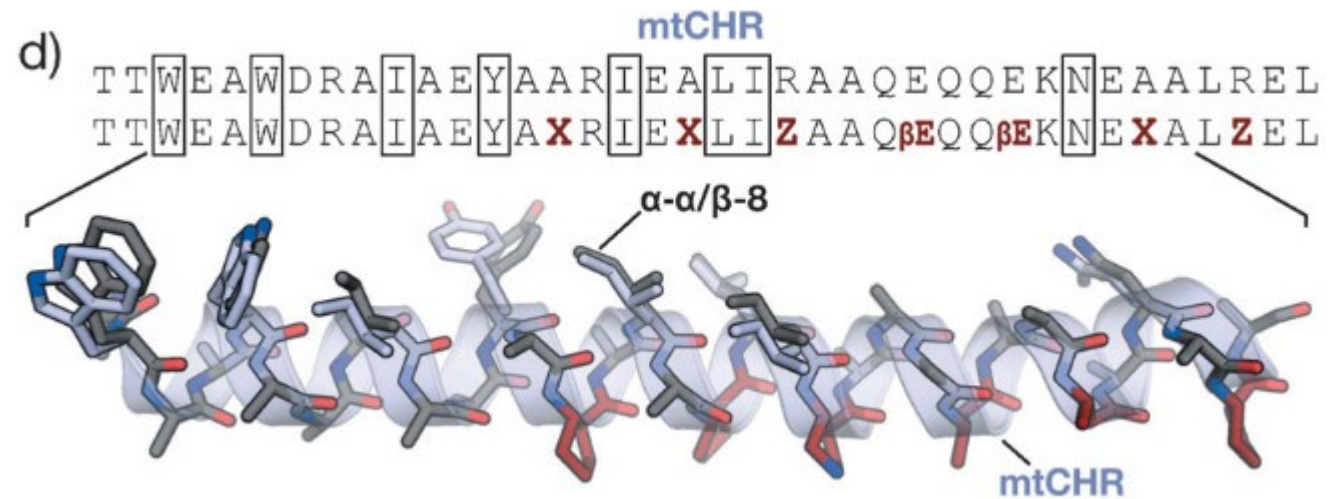
Foldamers (α/β -peptides)



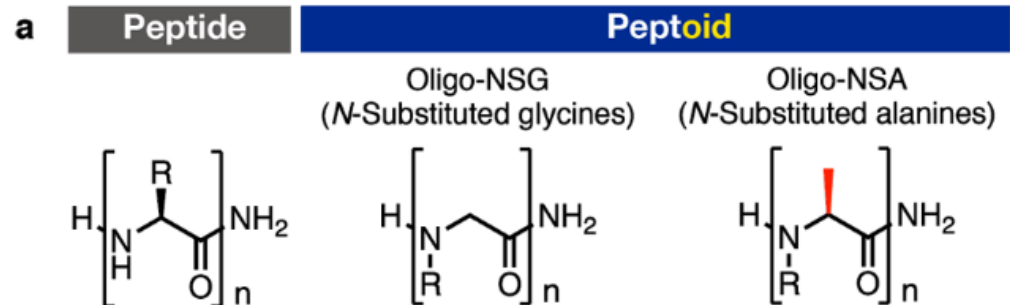
Example: Foldamers (α/β -peptides)



Oligomer	gp41-5 binding affinity by FP*	NHR + CHR stability by CD [†]	Stability to Proteinase K [‡]	Cell-cell fusion inhibition [§]	Inhibition of HIV-1 infectivity, IC ₅₀ , nM [¶]			
	K _i , nM	T _{m,app} , °C	t _{1/2} , min	IC ₅₀ , nM	X4 strains		R5 strains	
					NL4-3	HC4	CC 1/85	DJ258
3	< 0.2	77	0.7	9 ± 3	5 ± 0.6	27 ± 4	140 ± 20	58 ± 6
4	3,800	-1	14	390 ± 40	700 ± 60	590 ± 100	1300 ± 100	960 ± 200
5	< 0.2	67		7 ± 2	10 ± 2	55 ± 8	270 ± 20	280 ± 90
6	15							
7	0.4							
8	0.3	65						
9	83							
10	9	55	200	5 ± 2	28 ± 3	59 ± 10	180 ± 30	110 ± 40
11	> 10,000							
T-20 (Enfuvirtide, as control)					700 ± 100	250 ± 20	1400 ± 400	330 ± 60



Foldamers (Peptoids)



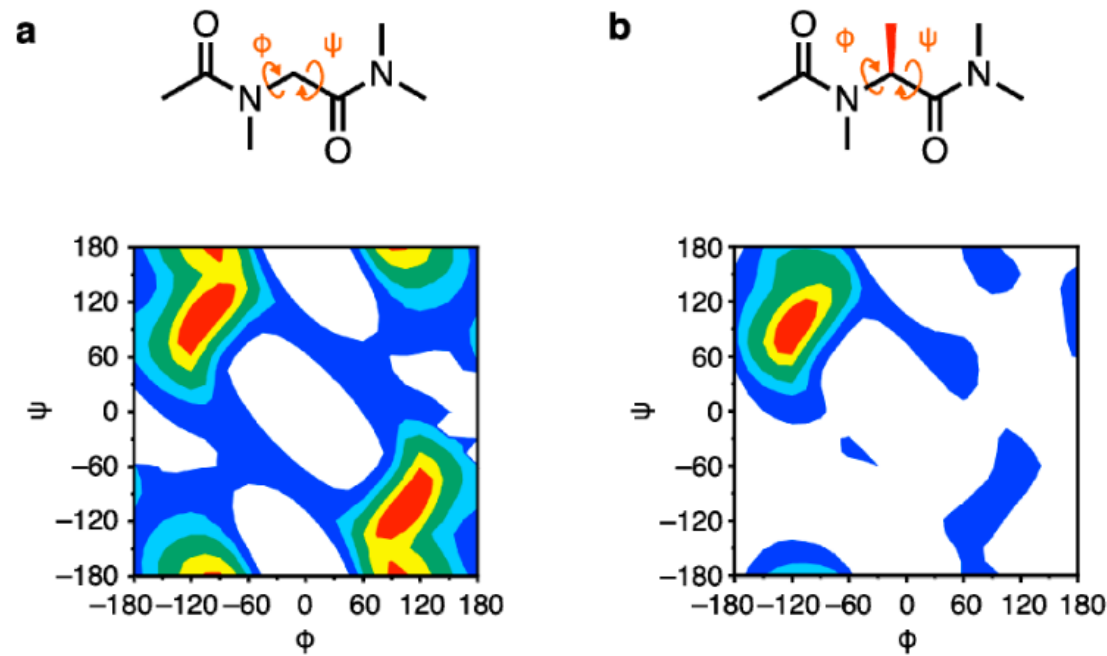
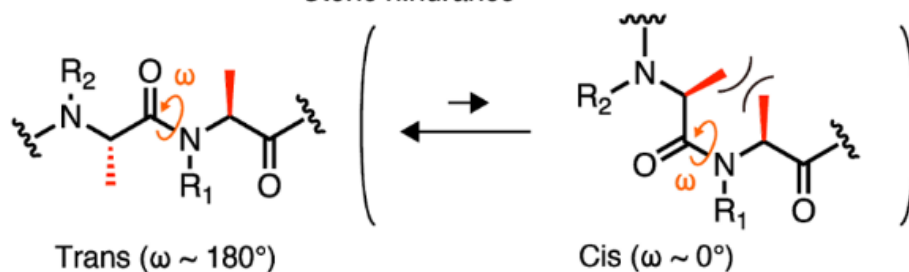
b Restriction of rotation about ϕ and ψ angles

Pseudo-1,3-allylic strains

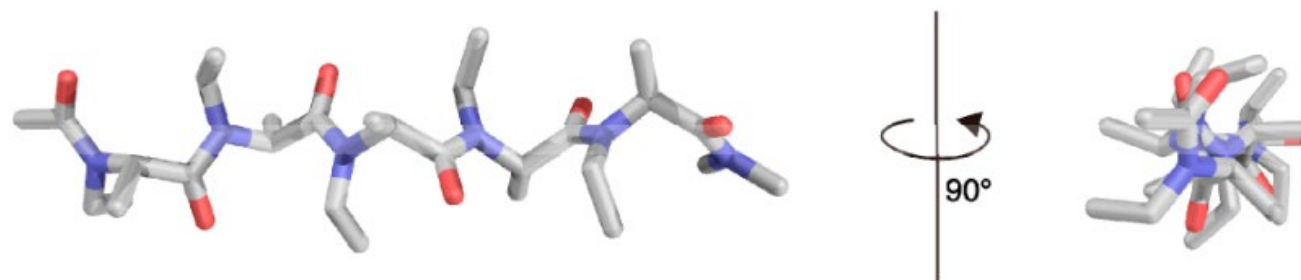


c Restriction of rotation about ω angle

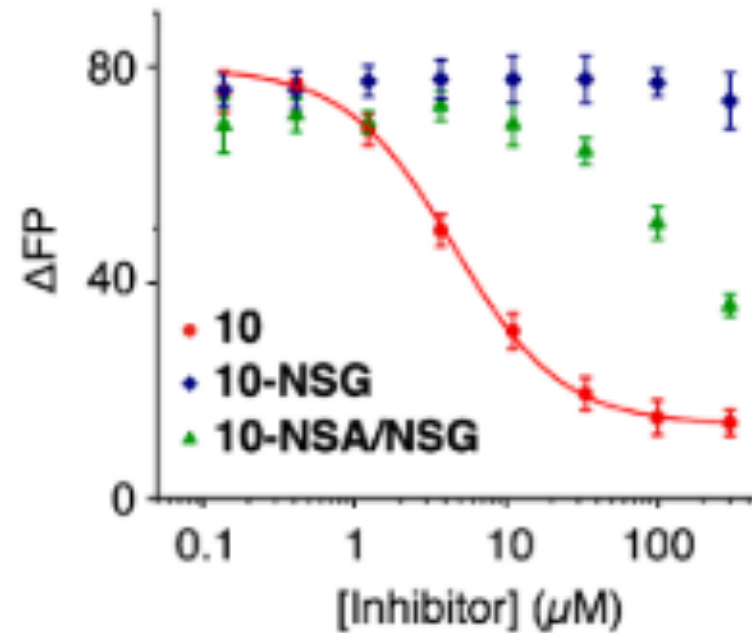
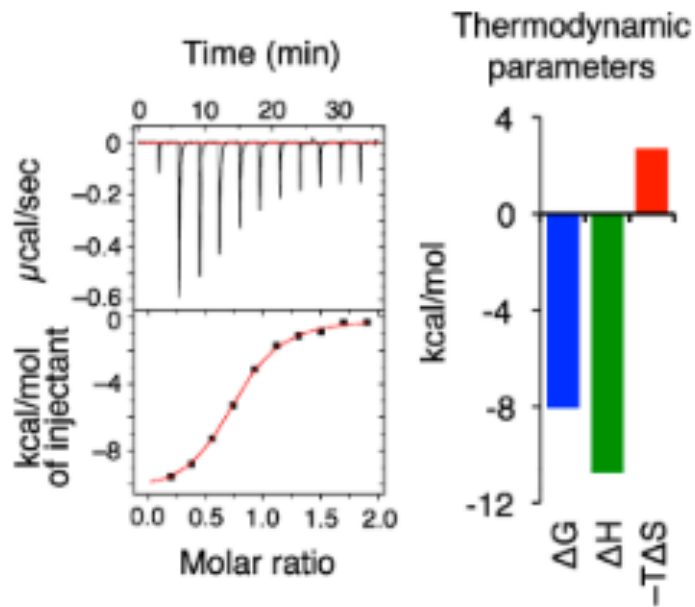
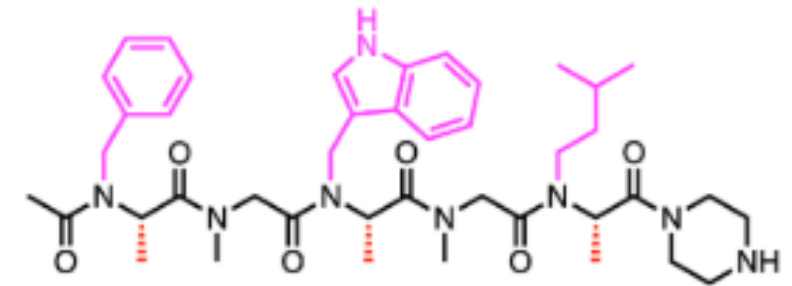
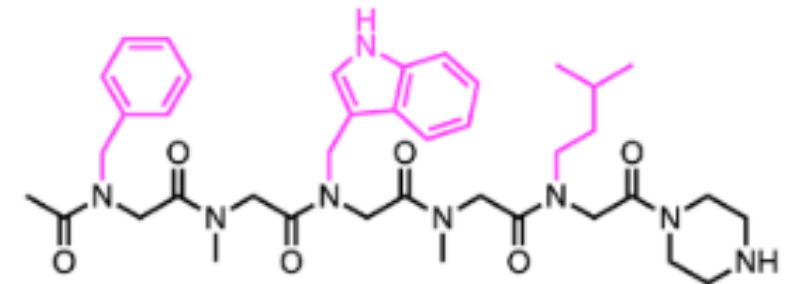
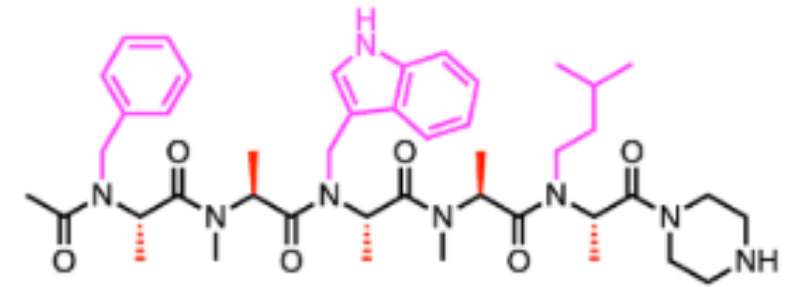
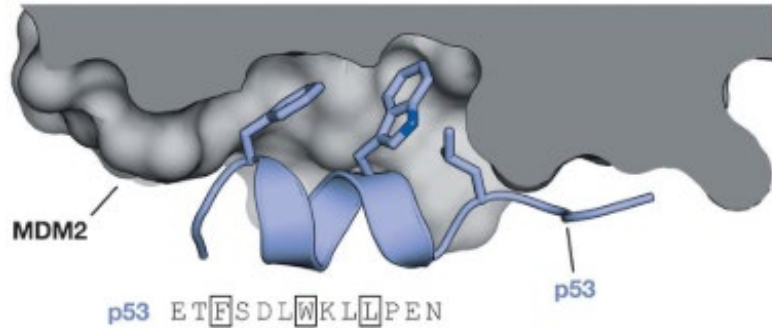
Steric hindrance



A model structure of oligo-NSA with $\chi = -100^\circ$



Example: Foldamer (Peptoid)



1. Introduction

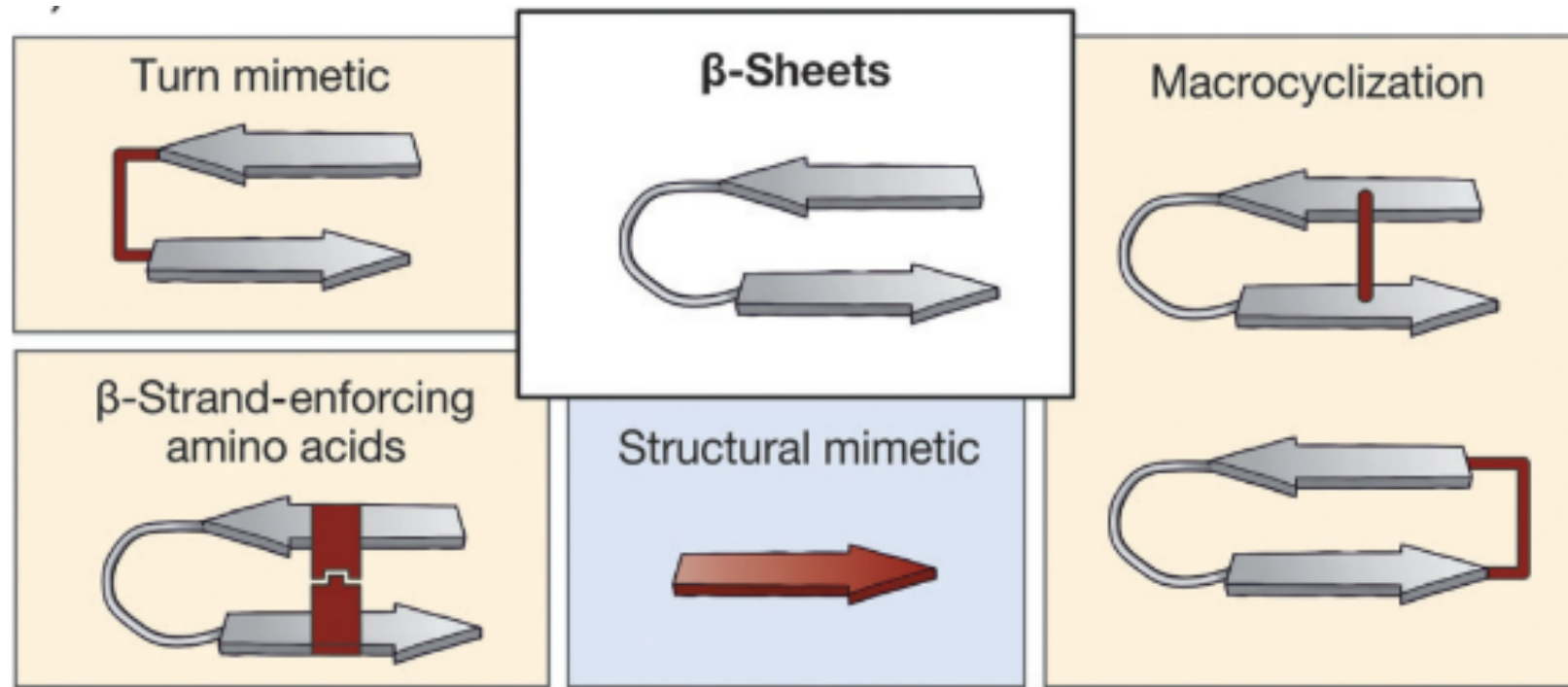
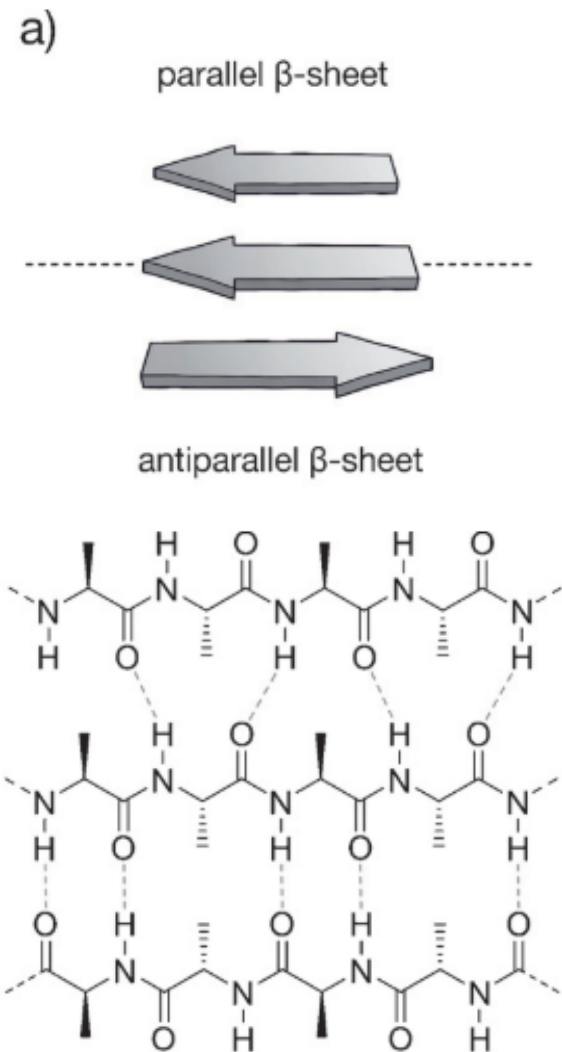
2. Major secondary structures and its mimetics

- α -helix
- Example of α -helix mimetic PPI inhibitor
- β -sheet
- Example of β -sheet mimetic PPI inhibitor
- Turns
- Example of β -turn mimetics

3. Summary

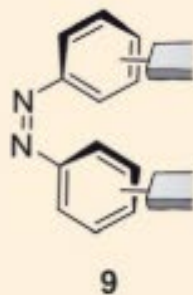
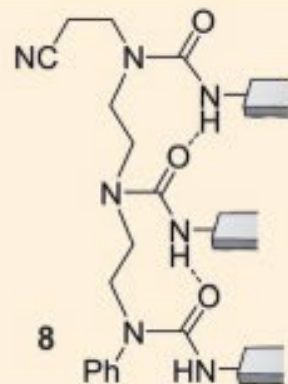
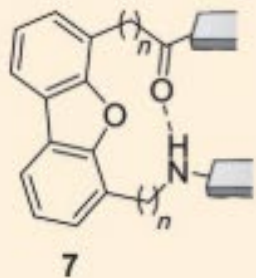
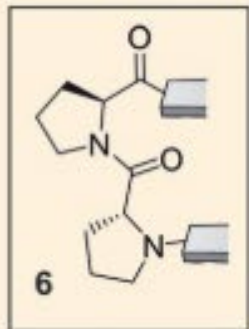
4. Appendix

β -sheet

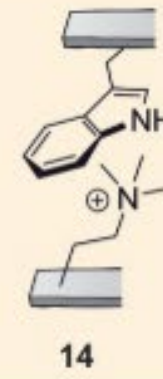
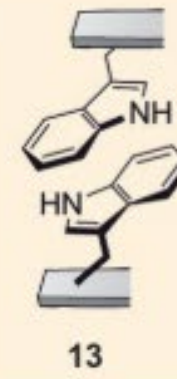
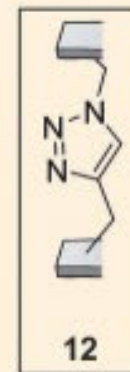
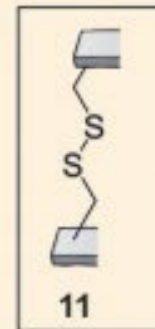
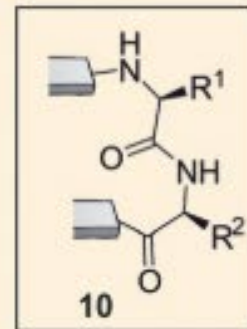


β -sheet mimetics

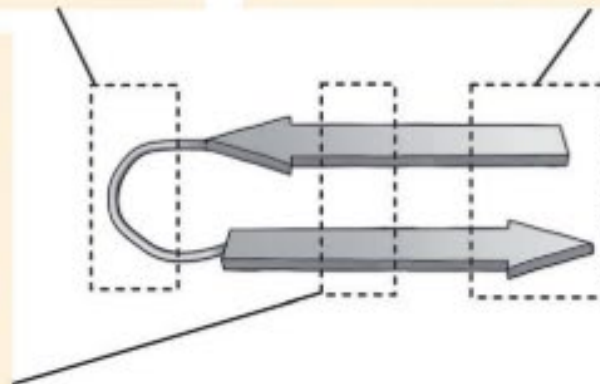
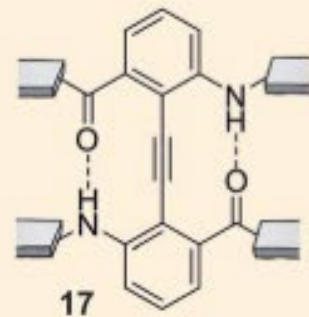
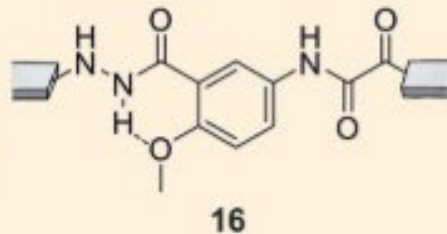
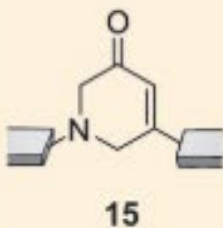
Turn mimetics



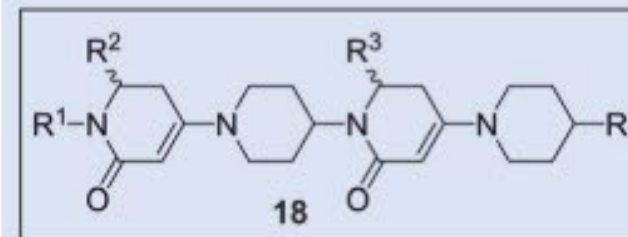
Macrocyclization



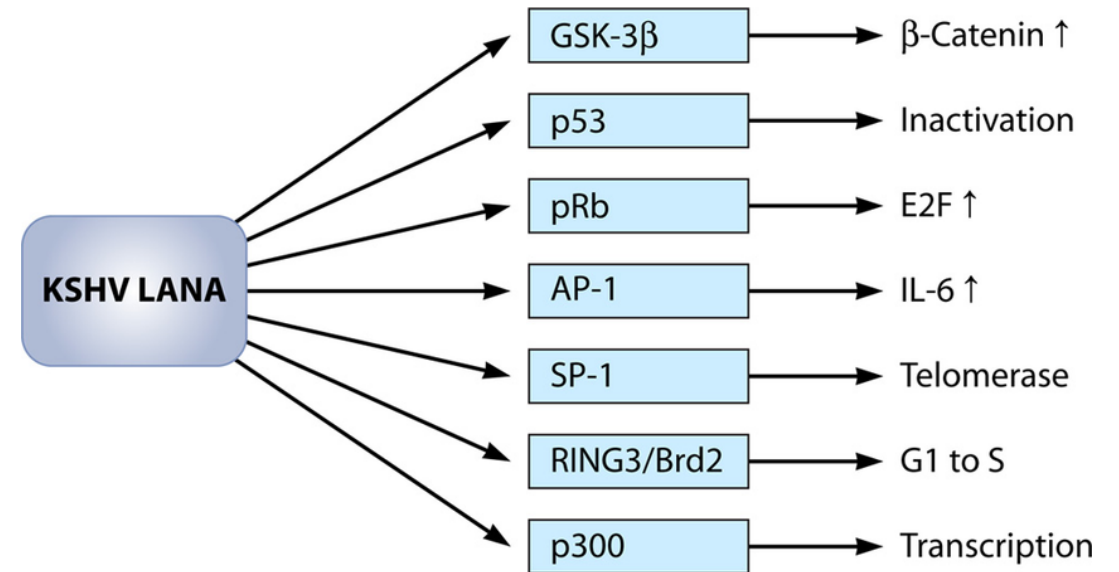
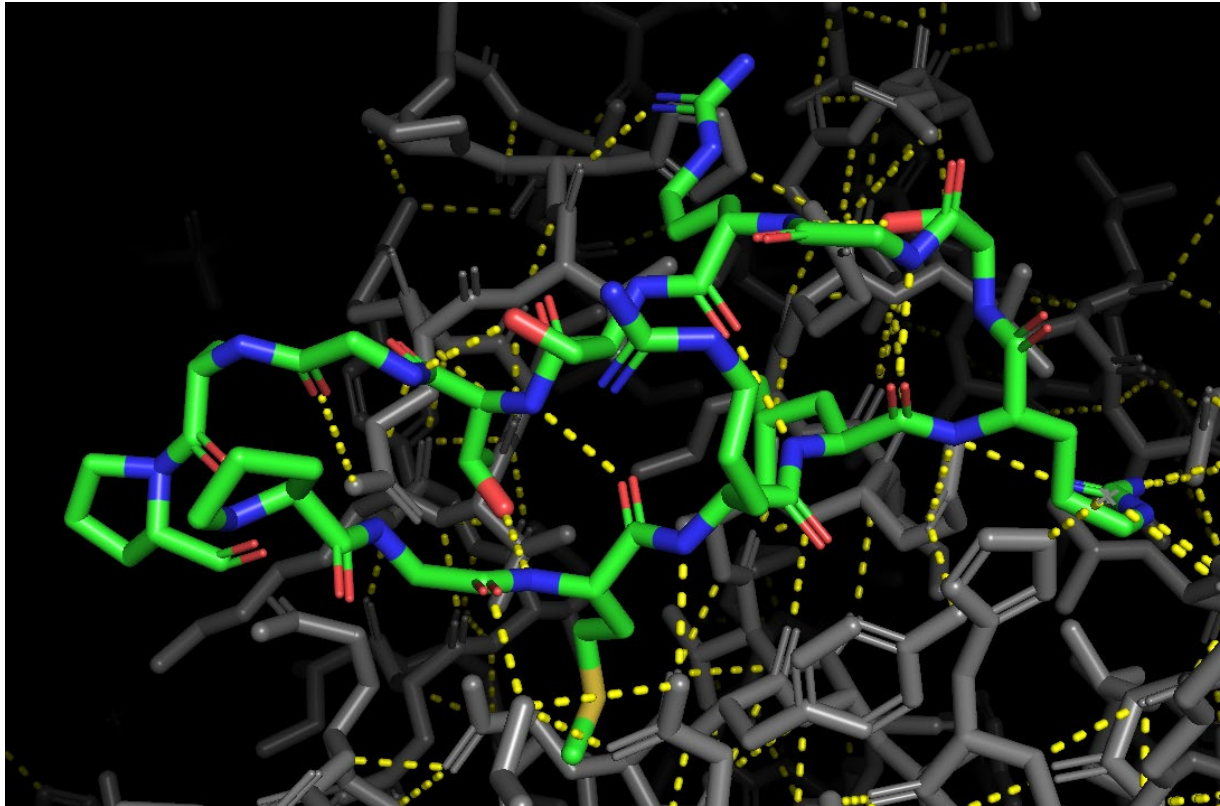
β -Strand-enforcing amino acids



Structural mimetic



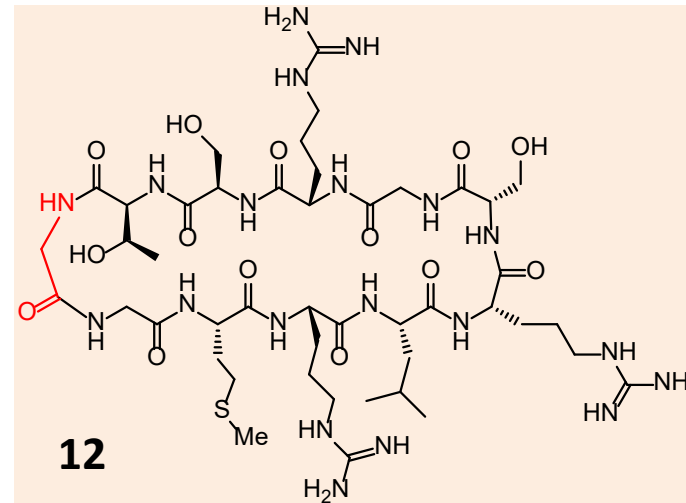
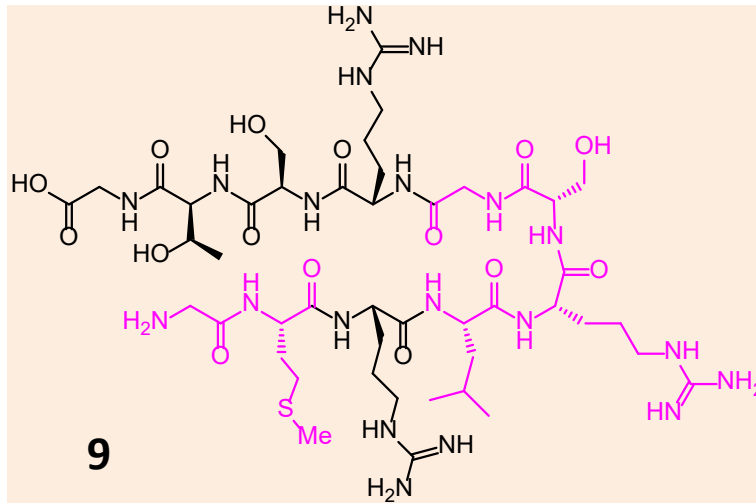
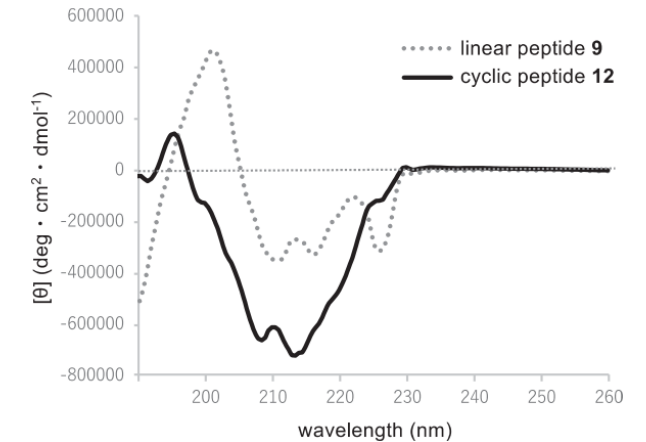
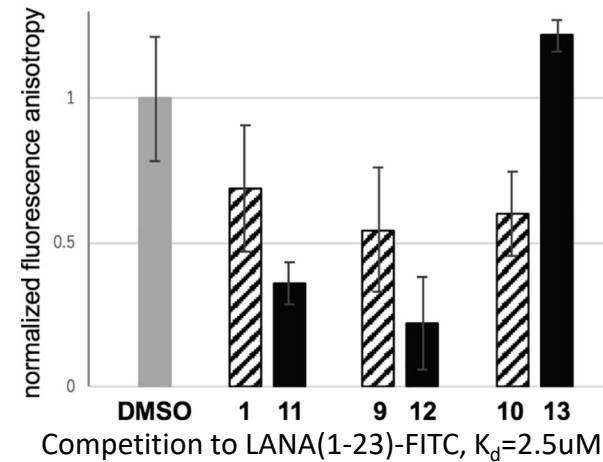
LANA peptide



- | LANA peptide is nucleosome binding site of latency-associated nuclear antigen-1 (LANA-1)
- | LANA-1 is a multifunctional protein involved in tumorigenesis by Kaposi's sarcoma-associated herpesvirus(KSHV).

Example: Macrocyclization

- N-terminal LANA 4–16 peptide **1**: acetyl-PGMRLRSGR**S**TGA-NH₂
2: acetyl-PGVRLRSGRSTGA-NH₂
3: acetyl-PGLRLRSGRSTGA-NH₂
4: acetyl-PG**I**RLRSGRSTGA-NH₂
5: acetyl-PG**F**RLRSGRSTGA-NH₂
6: acetyl-PGMRLRSGR**S**HGA-NH₂
7: acetyl-PGMRLRSGR**S**KGA-NH₂
8: acetyl-PGMRLRSGR**S**RGA-NH₂
 N-terminal LANA 5–15 peptide **9**: acetyl-GMRLRSGRSTG-NH₂
 N-terminal LANA 6–14 peptide **10**: acetyl-MRLRSGRST-NH₂
 N-terminal LANA 4–16 cyclic peptide **11**: *cyclo*[PGMRLRSGRSTGA]
 N-terminal LANA 5–15 cyclic peptide **12**: *cyclo*[GMRLRSGRSTG]
 N-terminal LANA 6–14 cyclic peptide **13**: *cyclo*[MRLRSGRST]



$$K_{d,(LANA(1-23)-FITC)}=200\text{nM}$$

$$IC_{50,(9)}=614\text{nM}$$

$$IC_{50,(12)}=204\text{nM}$$

Simple macrocyclization increased the affinity 3-fold.

1. Introduction

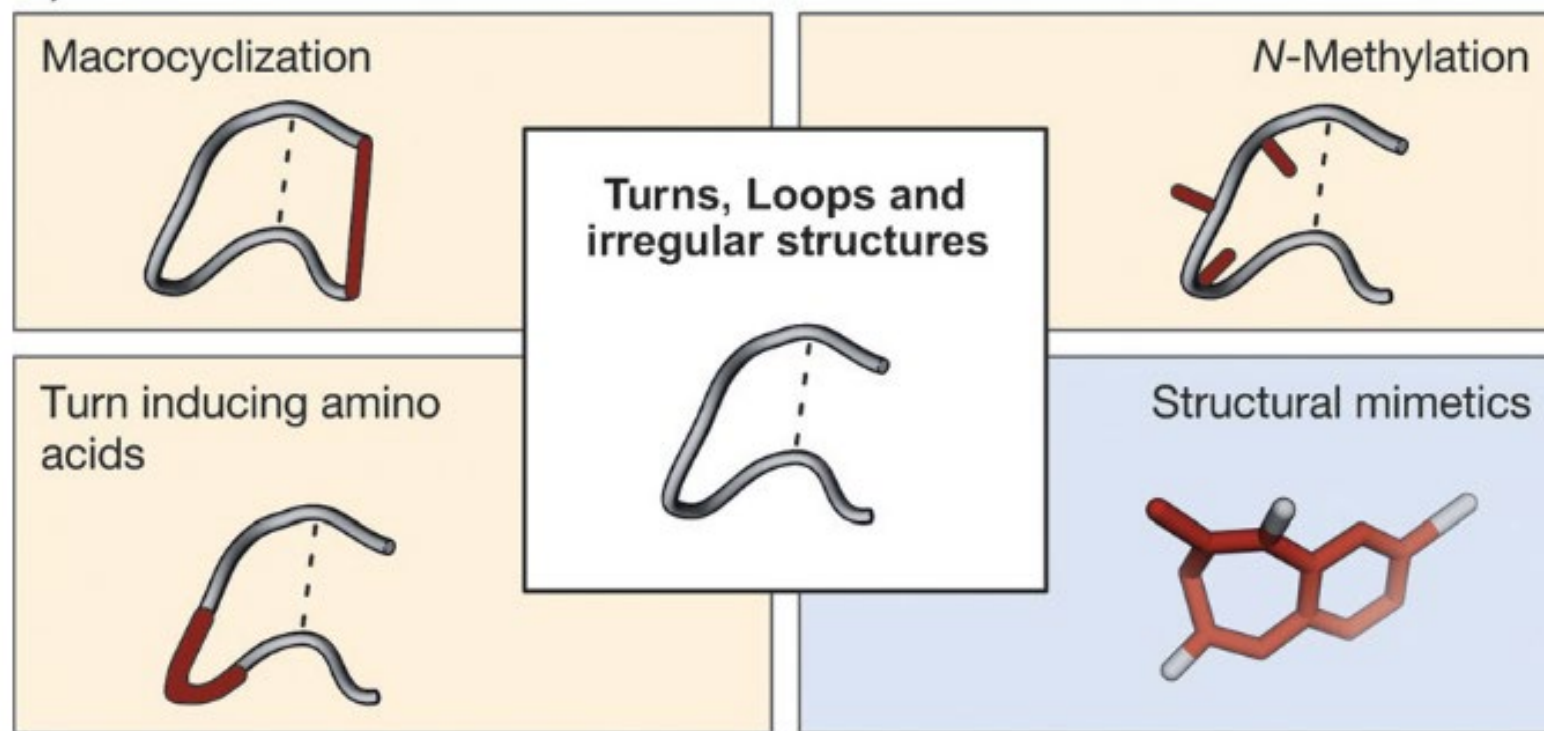
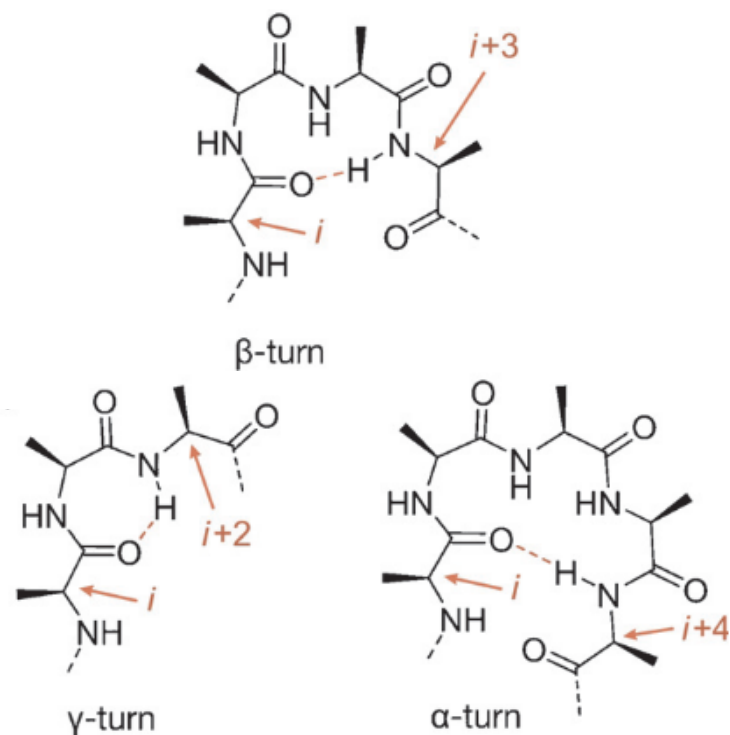
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- α -helix
- Example of α -helix mimetic PPI inhibitor
- β -sheet
- Example of β -sheet mimetic PPI inhibitor
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- Example of β -turn mimetics

3. Summary

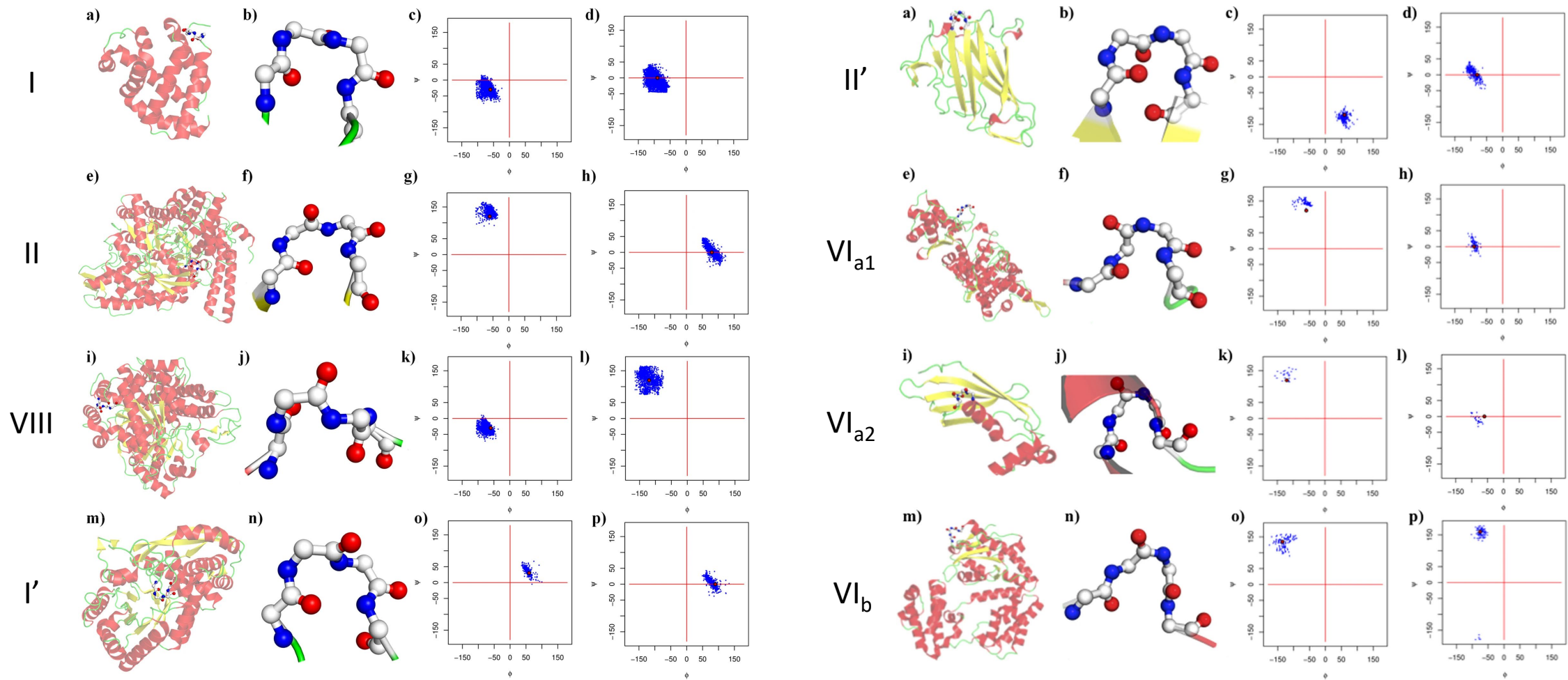
4. Appendix

Turn and its mimetics

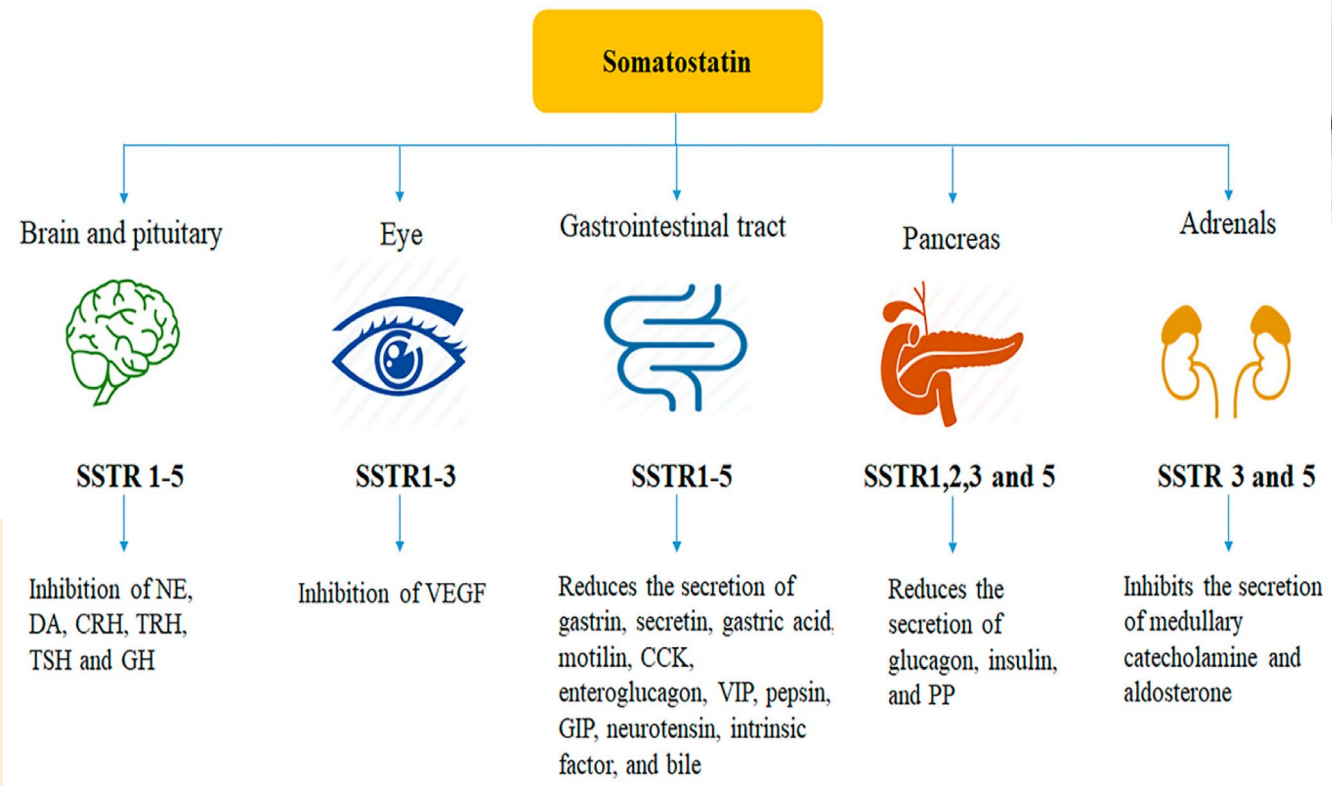
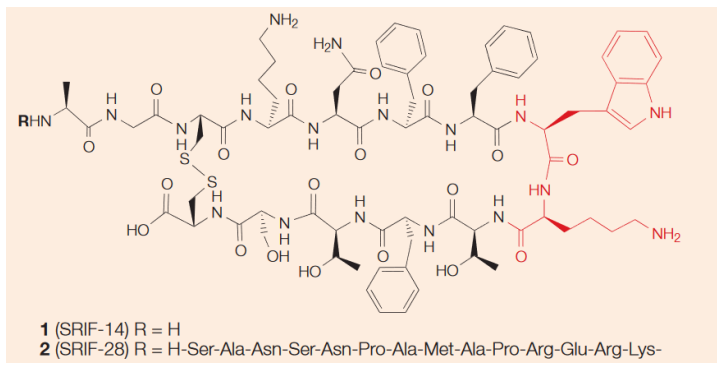
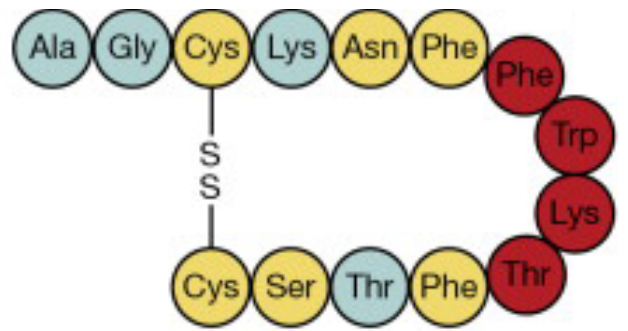


- Turns are often found as substructures of β -sheets.
- Turns often play crucial role in presenting hotspot residues.

Classification of β -turns by Venkatachalam



Somatostatin



Acromegaly



Pituitary gigantism

Intrinsic macrocyclization

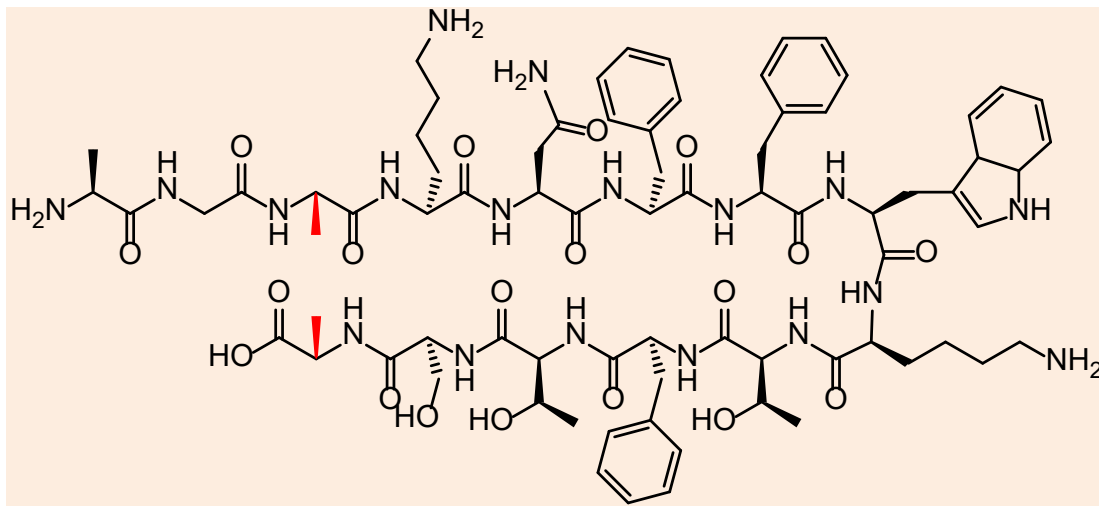
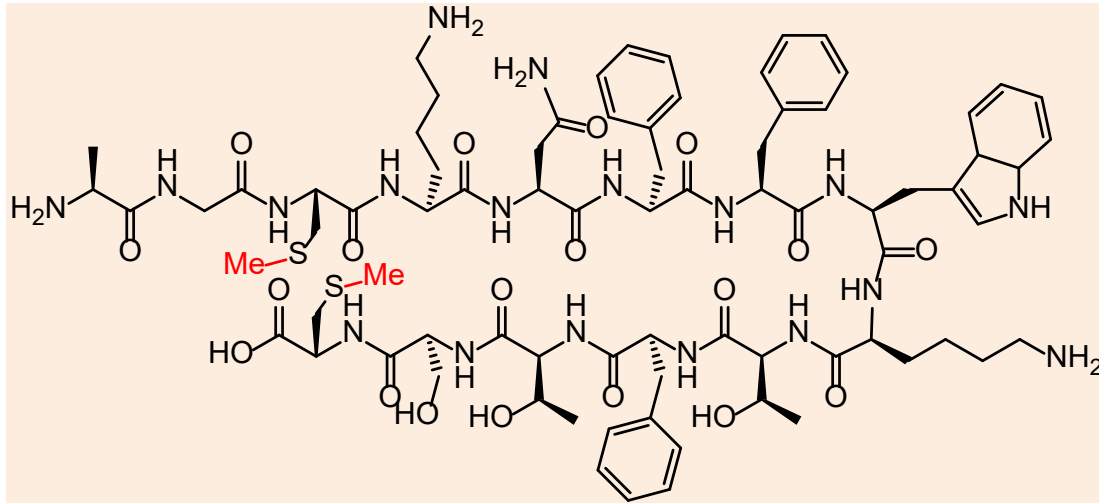
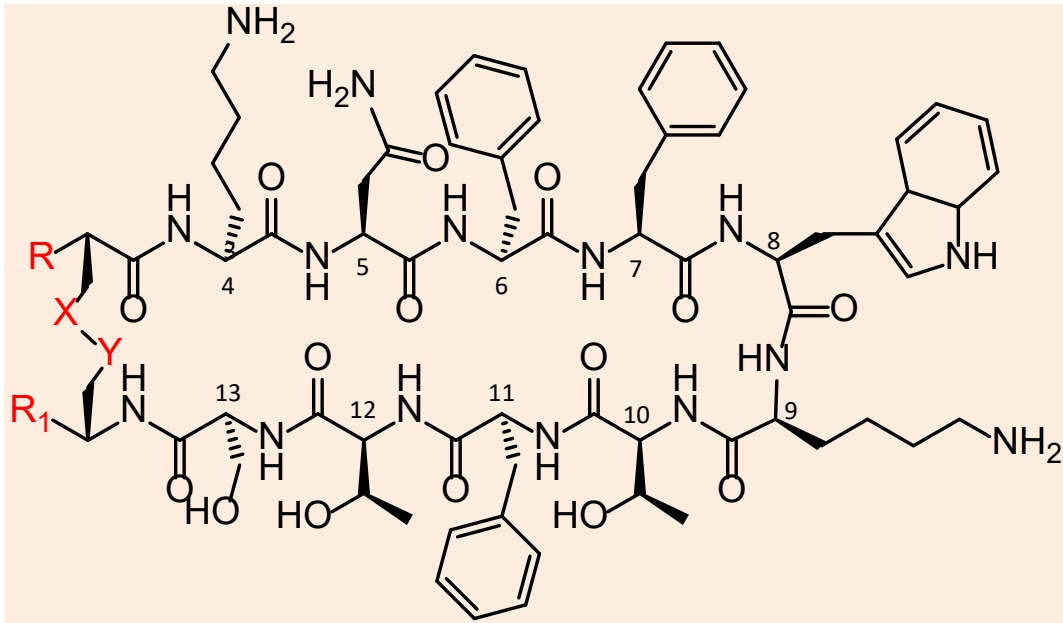


Table I. Specific Biological Activity of Somatostatin Analogs

No.	Compd	% specific activity of somatostatin (95% confidence limits)	
		<i>In vitro</i>	<i>In vivo</i> ^a
1	Somatostatin	100	100
2	[SMe-Cys ^{3,14}]- Somatostatin	4.0 (2.0–6.0)	0.6 (0.25–1.05)
3	[Ala ^{3,14}]- Somatostatin	0.6 (0.32–0.95)	2.0 (0.80–3.4)
4	[Des-Ala ¹ -Gly ² -H ₂]- Somatostatin	33 (20–50)	89 (72–110)
5	[Des-Ala ¹ -Gly ²]- Somatostatin	65 (42–98)	71 (57–88)
6	[NAc-Cys ³ -H ₂]- Somatostatin	30 (18–47)	99 (80–122)
7	[NAc-Cys ³]- Somatostatin	39 (25–60)	105 (86–130)

^aAll peptides were administered intravenously.

Stabilization of macrocycle



Ia, R = H-Ala-Gly-NH-; R¹ = CO₂H; X = Y = S (somatostatin)

b, R = H; R¹ = CO₂H; X = Y = S

c, R = H; R¹ = CO₂H; X = Y = CH₂

d, R = R¹ = H; X = Y = CH₂

Table II. Biological Activities: Inhibition of Gastric Secretion and Growth Hormone Release

Com- pound	Gastric secretion ^a		Growth hormone ^b
	ED ₈₀ , $\mu\text{g}/(\text{kg min}^{-1})$ (95% C.L.)	Rel. pot. (95% C.L.)	Rel. pot. (95% C.L.)
Somato- statin	0.06 (0.02, 0.10)	1.0	1.0
Ic	0.04 (0.03, 0.07)	1.35 (0.65, 2.54)	0.5 (0.08, 1.59)
Id	0.07 (0.02, 0.17)	0.89 (0.37, 1.91)	0.5 (0.31, 0.84)

D-Trp at $i+1$ position improved the activity

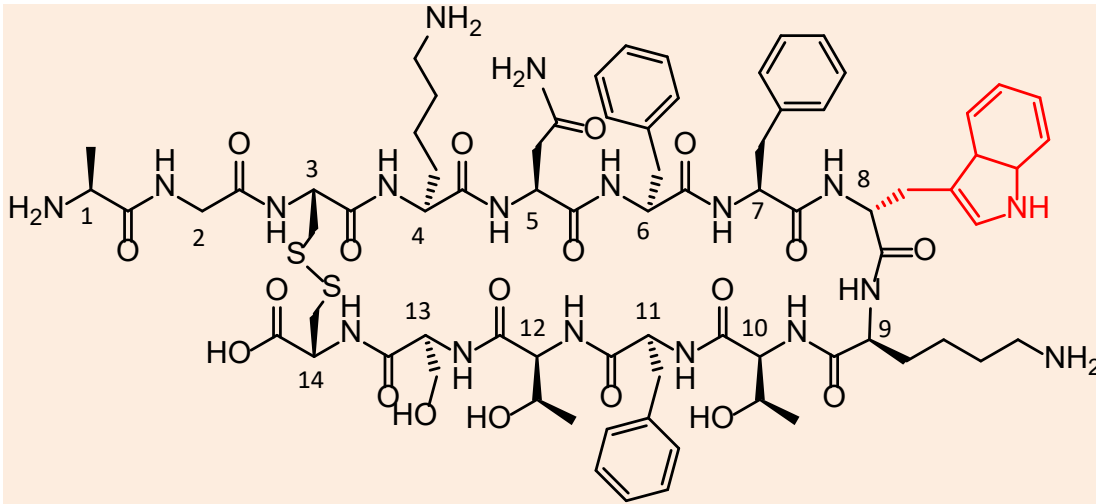


TABLE II. Relative Potencies of Somatostatin and D-Trp⁸-Somatostatin

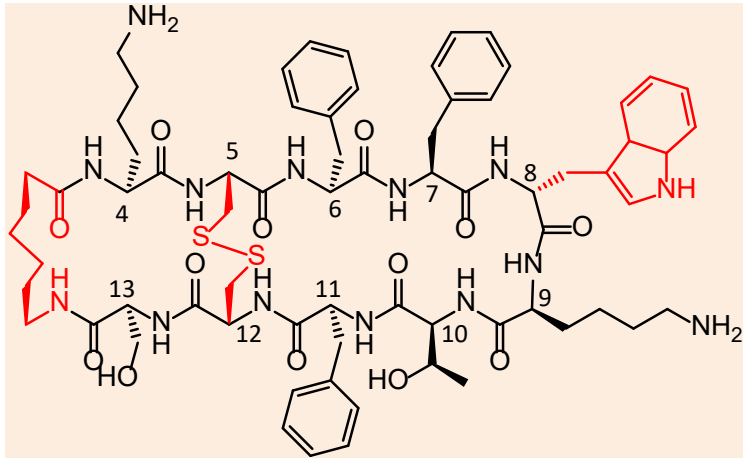
	<u>In vitro</u> GH	<u>In vivo</u> Glucagon	<u>In vivo</u> Insulin
Somatostatin	100	100	100
D-Trp ⁸ -somatostatin	848(518-1416) ^a	639(205-1665) ^a	821(368-2195) ^a

a) 95% confidence limits are shown in parenthesis.

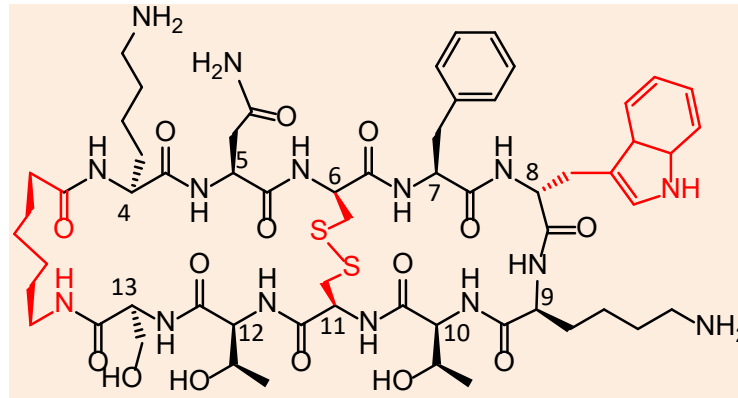
| D-amino acid at $i+1$ position is known to be strong inducer of β -turn structure.

| Introduction of D-Trp at position 8 improved the activity by 8-fold.

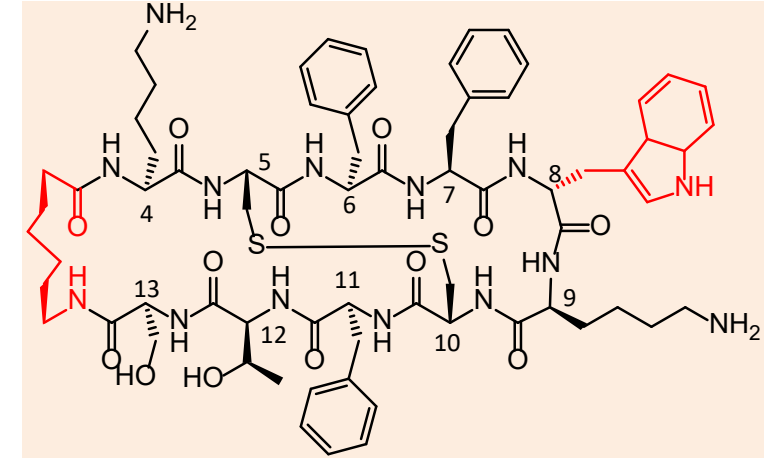
Search for active conformation



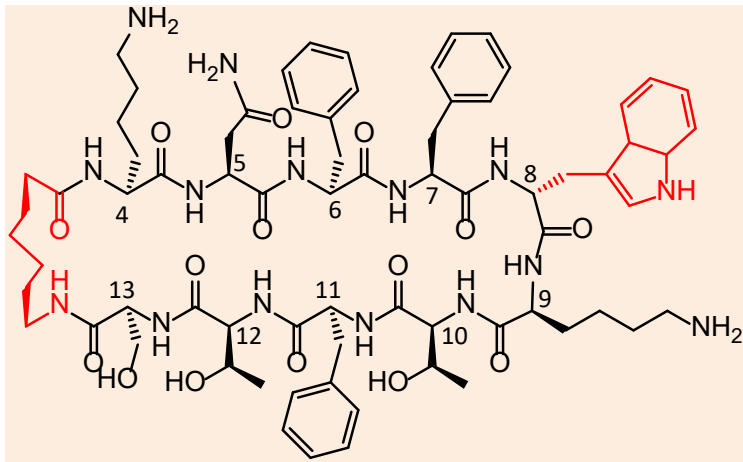
III, IIa (Cys \rightarrow Cys(Acm))



VI, V (Cys=Cys(Acm))



IV, IIb (Cys=Cys(Acm))



Cyclic analog

Table 2. Inhibition of release (relative potency of somatostatin = 1)*

Compd.	Glucagon	Insulin	Growth hormone		Gastric secretion
			<i>In vitro</i>	<i>In vivo</i>	
IIa	1.2 (0.2–8.5)	0.8 (0.3–2.1)	1.0 (0.8–1.1)	1.2 (0.02–16.7)	0.1
III	1.4 (0.3–12.4)	1.5 (0.9–2.7)	0.37 (0.29–0.48)	1.9 (0.35–8.33)	0.1
IIb	0.3 (0.03–1.0)	0.6 (0.3–1.2)	1.7 (1.0–2.9)	0.5 (0.2–1.3)	<0.01
IV	†	0.06 (0.03–0.11)	0.08 (0.03–0.18)	0.5 (0.2–1.1)	<0.01
V	0.2 (0.02–0.96)	0.14 (0.05–0.37)	0.32 (0.24–0.43)	0.13 (0.01–0.61)	<0.01
VI	1.3 (0.28–8.4)	1.1 (0.64–1.94)	0.88 (0.82–0.95)	0.9 (0.14–15.2)	0.1

* 95% confidence limits are given in parentheses.

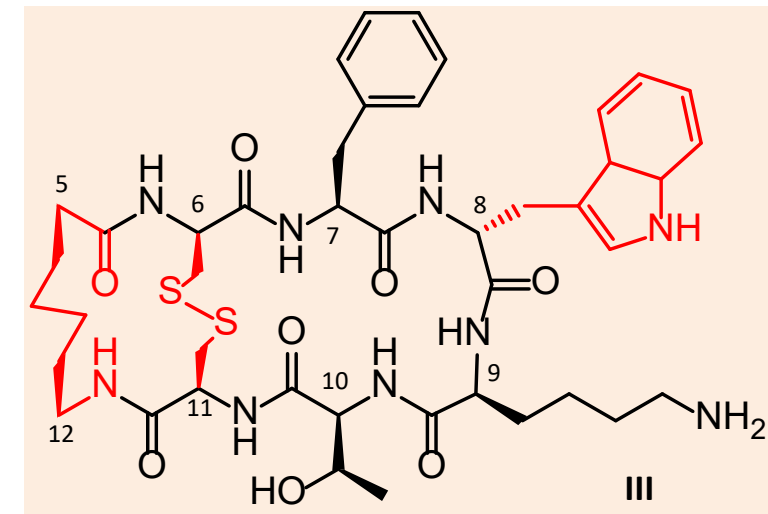
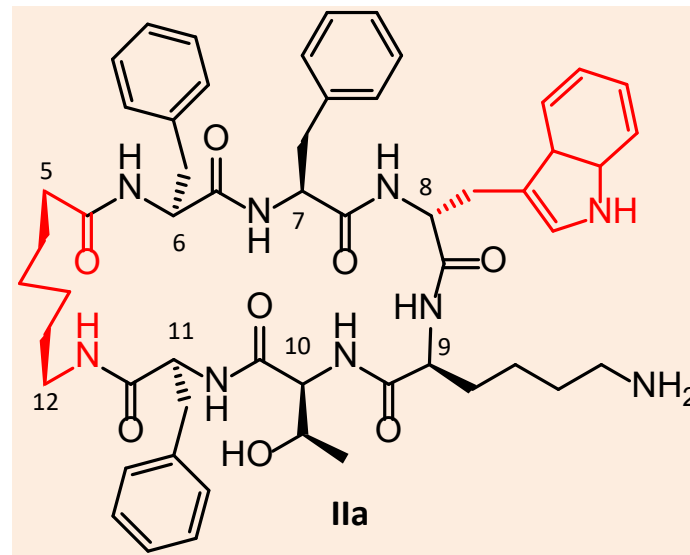
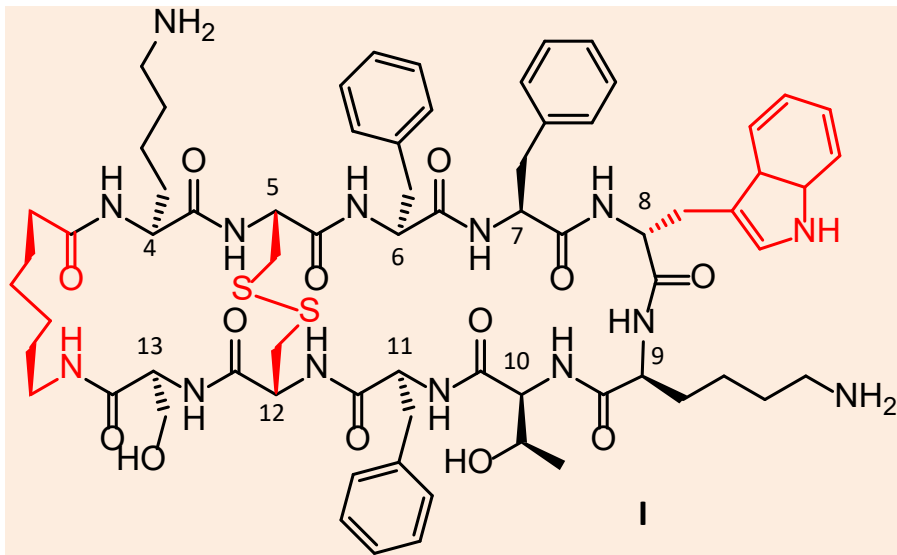
† No activity at doses up to 500 μ g; a compound of relative potency ≥ 0.02 would have been detected.

Extraction of the essential structure

Table 2 Inhibition of release (relative potency of somatostatin = 1)

Compound	Glucagon	Insulin	Growth hormone		Gastric secretion
			<i>In vitro</i>	<i>In vivo</i>	
I	1.4 (0.26–12.40)	1.53 (0.92–2.66)	0.37 (0.29–0.48)	1.88 (0.35–8.33)	0.10
IIa	0.86 (0.44–1.53)	0.88 (0.30–2.45)	0.93 (0.69–1.2)	0.65 (0.20–4.61)	0.03
IIb		0.020 (0.003–0.060)	0.03 (0.02–0.04)	0.14 (0.05–0.29)	0.03
IIc	0.041 (0.004–0.150)	0.10 (0.05–0.19)	0.14 (0.12–0.16)	—	<0.01
III	2.66 (1.32–6.10)	3.50 (2.31–6.38)	1.24 (0.81–1.88)	2.55 (0.99–11.1)	0.05

Shorter bi-cyclic peptide resulted in ca. 2.5-fold increase in the activity.



Macrocyclization by β -turn inducing amino acids

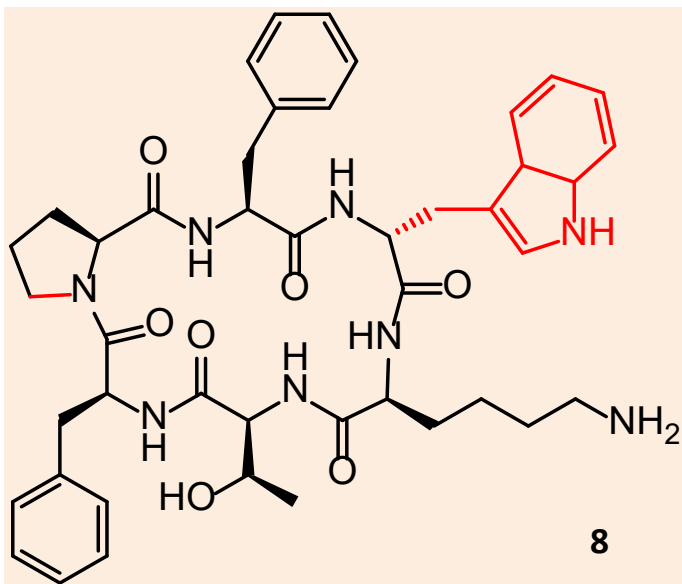
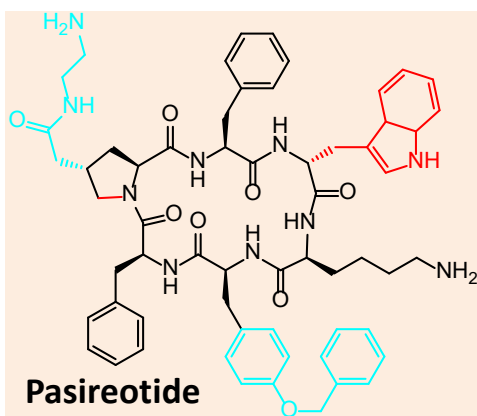


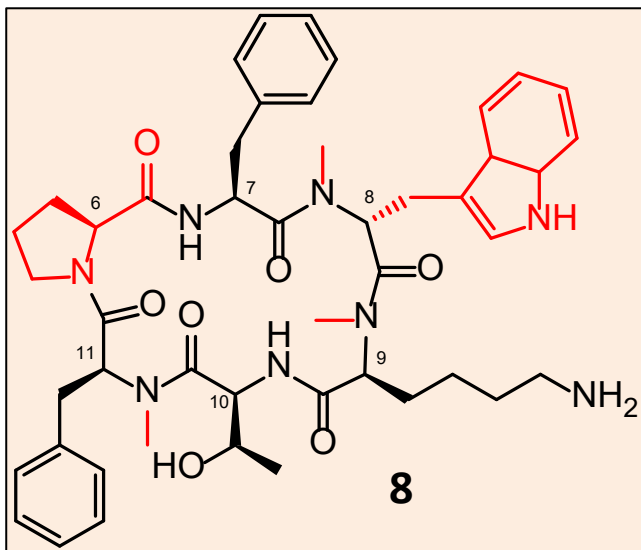
Table 2 Inhibition of growth hormone release by somatostatin analogues *in vivo*

Compound	Dose ($\mu\text{g per kg}$)	Route of administration	Growth hormone (ng ml^{-1})	Time (h)
None	—	s.c.	353 ± 130	5
I Cyclo(Aha-Cys-Phe-D-Trp-Lys-Thr-Cys)	125	s.c.	534 ± 300	5
I Cyclo(Aha-Cys-Phe-D-Trp-Lys-Thr-Cys)	250	s.c.	221 ± 123	5
I Cyclo(Aha-Cys-Phe-D-Trp-Lys-Thr-Cys)	500	s.c.	$31 \pm 11^*$	5
8 Cyclo(Pro-Phe-D-Trp-Lys-Thr-Phe)	250	s.c.	207 ± 49	5
8 Cyclo(Pro-Phe-D-Trp-Lys-Thr-Phe)	500	s.c.	470 ± 222	5
8 Cyclo(Pro-Phe-D-Trp-Lys-Thr-Phe)	750	s.c.	$9 \pm 1^*$	5
None	—	p.o.	$1,064 \pm 177$	3
8 Cyclo(Pro-Phe-D-Trp-Lys-Thr-Phe)	25,000	p.o.	$99 \pm 55^+$	3
None	—	p.o.	$1,124 \pm 341$	1
8 Cyclo(Pro-Phe-D-Trp-Lys-Thr-Phe)	25,000	p.o.	$9 \pm 4^\ddagger$	1
None	—	p.o.	$1,128 \pm 338$	1
I Cyclo(Aha-Cys-Phe-D-Trp-Lys-Thr-Cys)	25,000	p.o.	$140 \pm 48^\S$	1

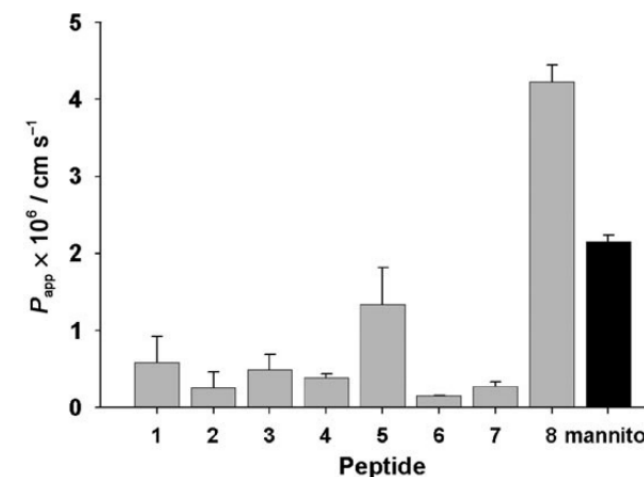
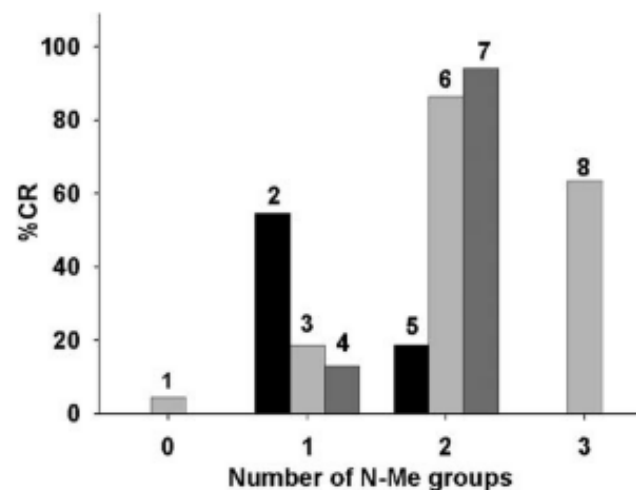
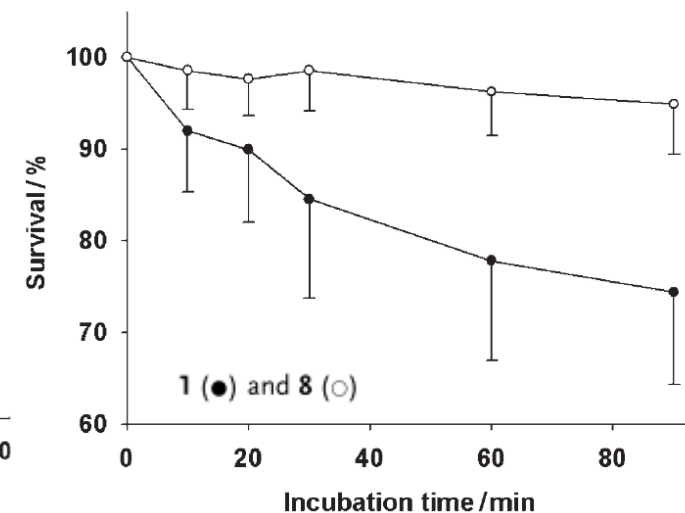
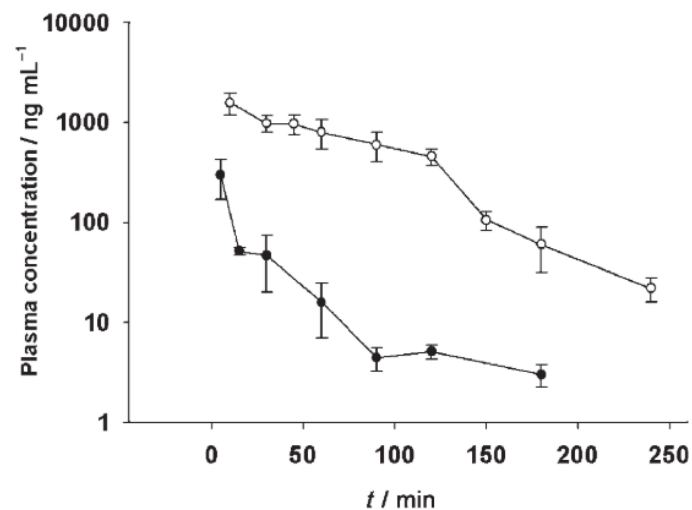


Incorporation of turn inducing sequence resulted in improved effect p.o.

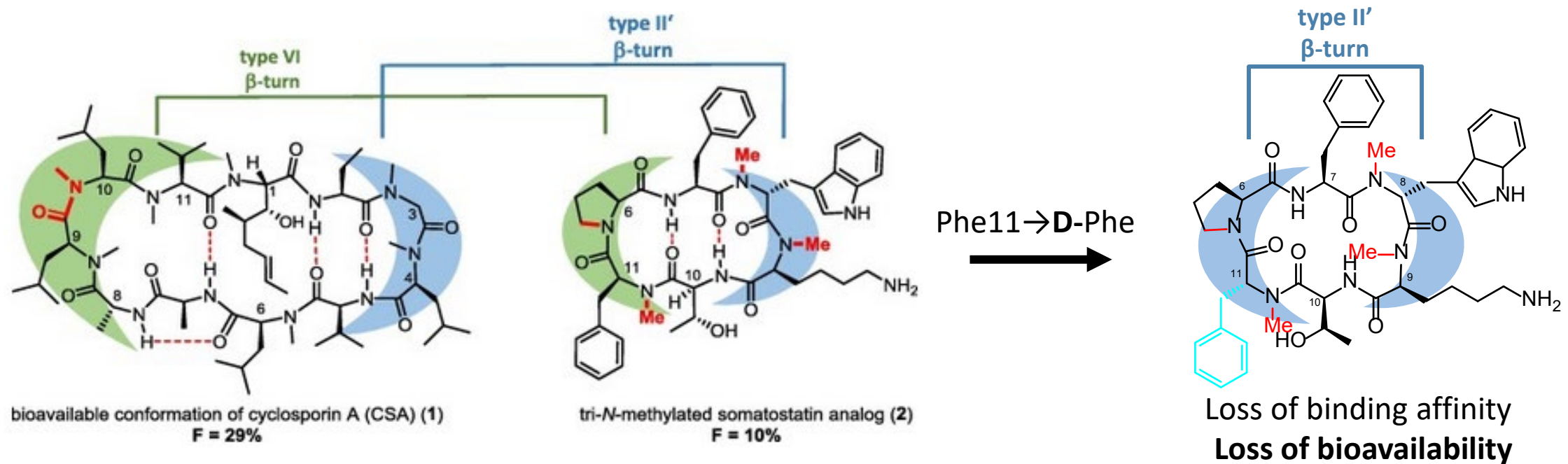
Further improvement by *N*-Methylation



Peptide	N-methylated amino acid	hsst 2 (pK_d)	hsst 5 (pK_d)
Octreotide	–	9.18	7.71
1	–	8.01	7.82
2	Lys ⁹	8.60	8.19
3	Phe ¹¹	7.93	8.28
4	D-Trp ⁸	7.61	7.87
5	Lys ⁹ , Phe ¹¹	7.96	7.39
6	D-Trp ⁸ , Lys ⁹	7.60	7.19
7	D-Trp ⁸ , Phe ¹¹	7.16	7.47
8	D-Trp ⁸ , Lys ⁹ , Phe ¹¹	7.21	7.22

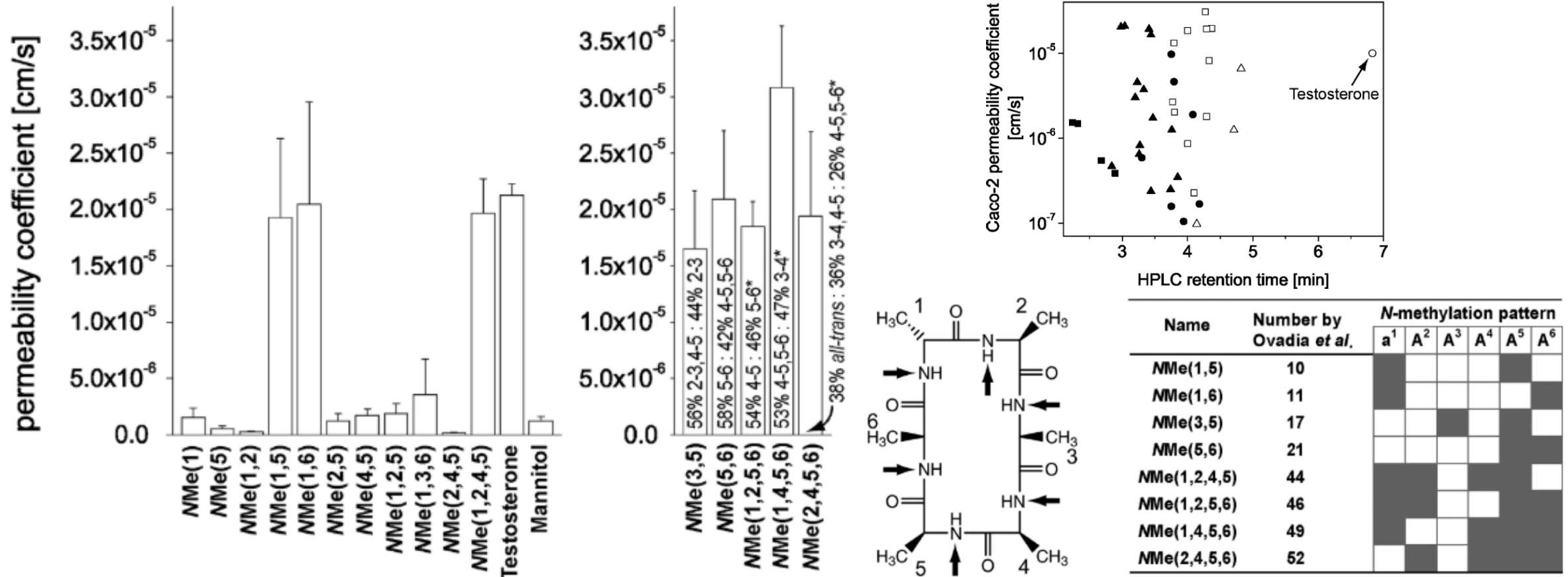


Relation between secondary structure and bioavailability



- | The **conformation** shown above seems to have effect on bioavailability.
- | The turn structure is the same as orally available peptide cyclosporin A.
- | Alteration of turn type resulted not only in the loss of binding affinity but also in the loss of bioavailability.

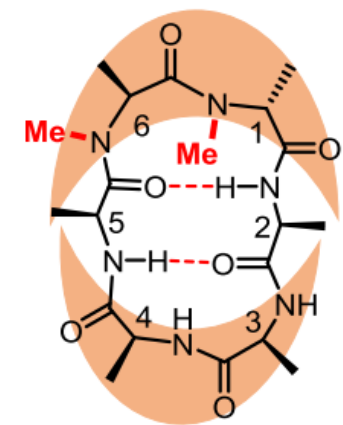
Relation between secondary structure and bioavailability



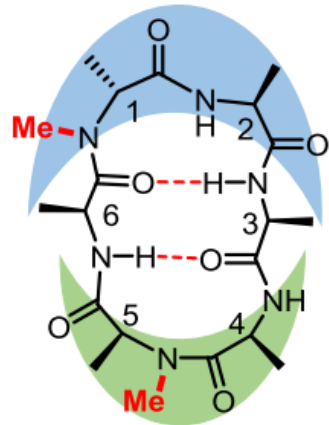
None of the parameters could not solely explain the tendency.

Methylation of N atom adjacent to D-Ala was common among the permeable peptides.

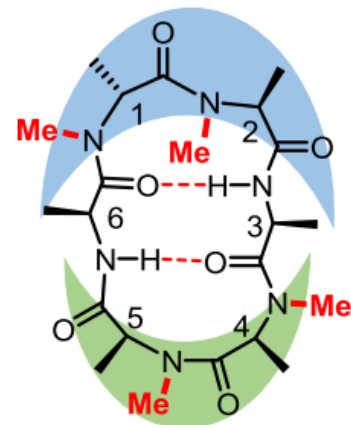
Relation between secondary structure and bioavailability



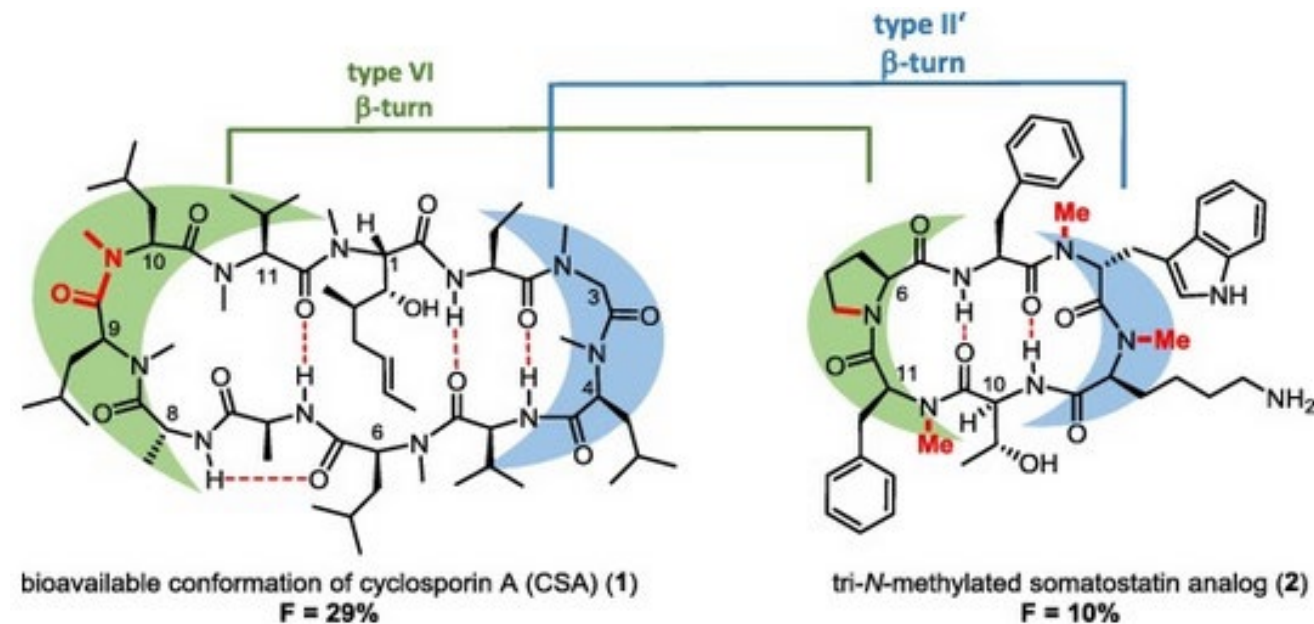
NMe-(1,6)-CHA (6)
*cyclo-(*aAAAA*A)*



NMe-(1,5)-CHA (7)
*cyclo-(*aAAA*AA)*



NMe-(1,2,4,5)-CHA (8)
*cyclo-(*a*AA*A*AA)*



2 of 3 bioavailable and conformationally uniform peptide showed β II'- β VI turn structure.

The structure is the same as cyclosporin A and the somatostatin analog.

Shielding of solvateable NH of lipophilic peptide improve permeability

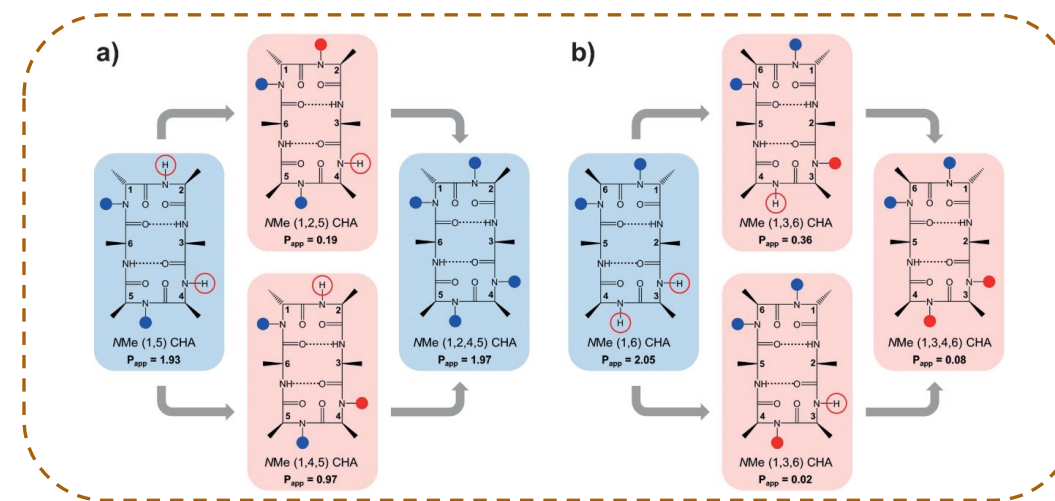
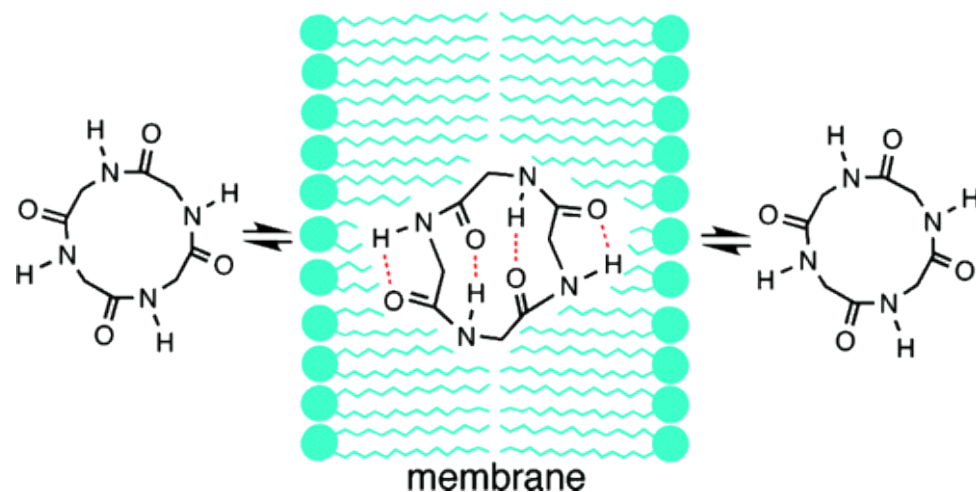
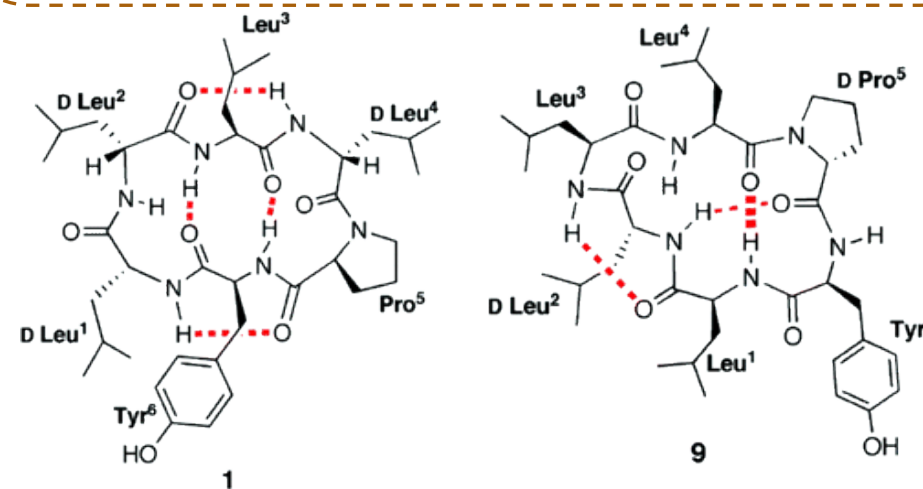


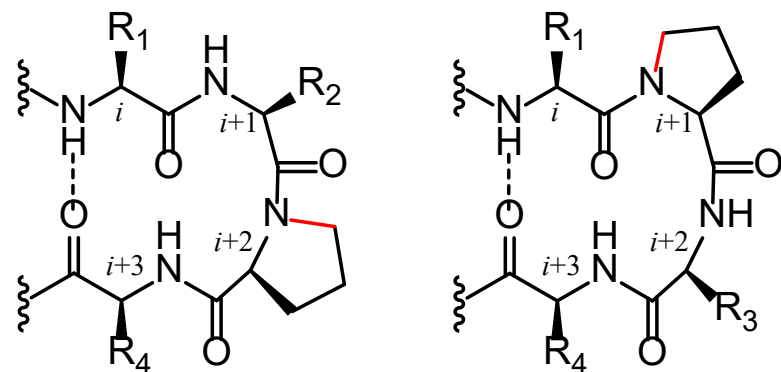
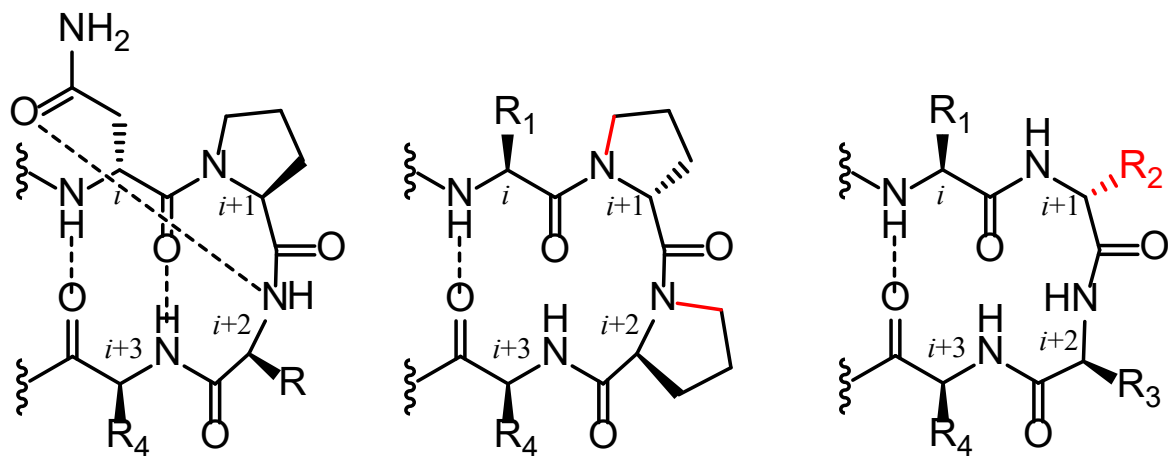
Table 1. The log P_E Values of Cyclic Peptide Diastereomers 1–9

compound	sequence	log P_E^a
1	cyclo[D-Leu-D-Leu-Leu-D-Leu-Pro-Tyr]	-6.2
2	cyclo[D-Leu-D-Leu-D-Leu-D-Leu-Pro-Tyr]	-7.0
3	cyclo[Leu-Leu-Leu-D-Leu-Pro-Tyr]	-7.1
4	cyclo[Leu-D-Leu-D-Leu-D-Leu-Pro-Tyr]	-7.2
5	cyclo[Leu-Leu-Leu-Leu-D-Pro-Tyr]	-7.3
6	cyclo[D-Leu-D-Leu-D-Leu-D-Leu-D-Pro-Tyr]	-7.3
7	cyclo[Leu-Leu-D-Leu-D-Leu-Pro-Tyr]	-7.3
8	cyclo[Leu-D-Leu-Leu-D-Leu-D-Pro-Tyr]	< -8.1 ^b
9	cyclo[Leu-D-Leu-Leu-Leu-D-Pro-Tyr]	< -8.1 ^b
1-lin cyclosporine A	Ac-D-Leu-D-Leu-Leu-D-Leu-Pro-Tyr-OAllyl	< -8.1 ^b -6.6

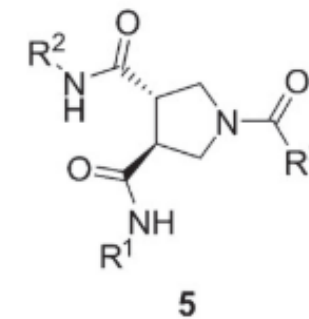
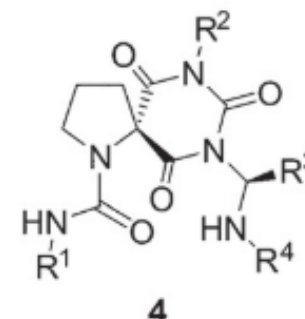
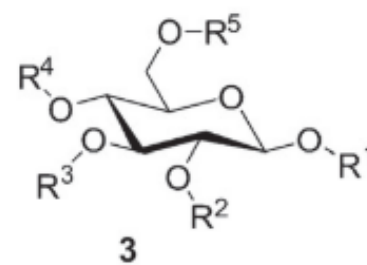
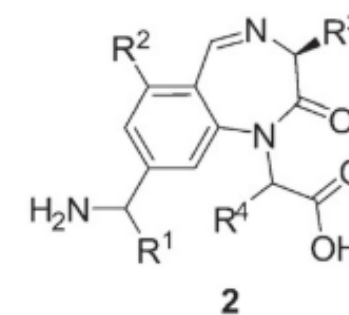
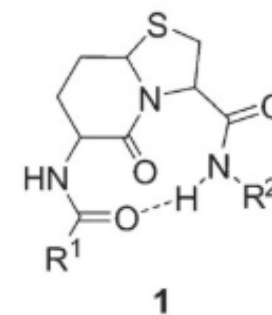
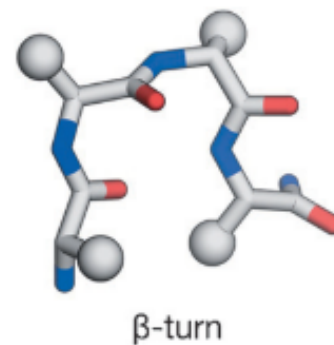


Blocking of NH does not generally improve bioavailability.

Turn inducing amino acids



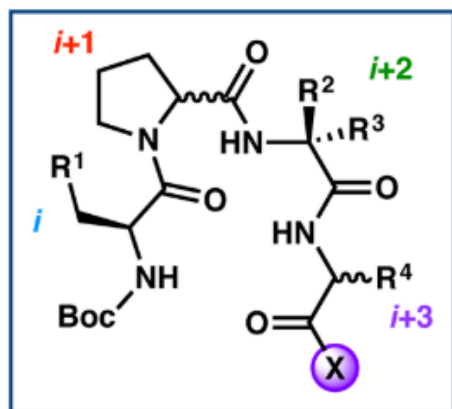
Proteinogenic



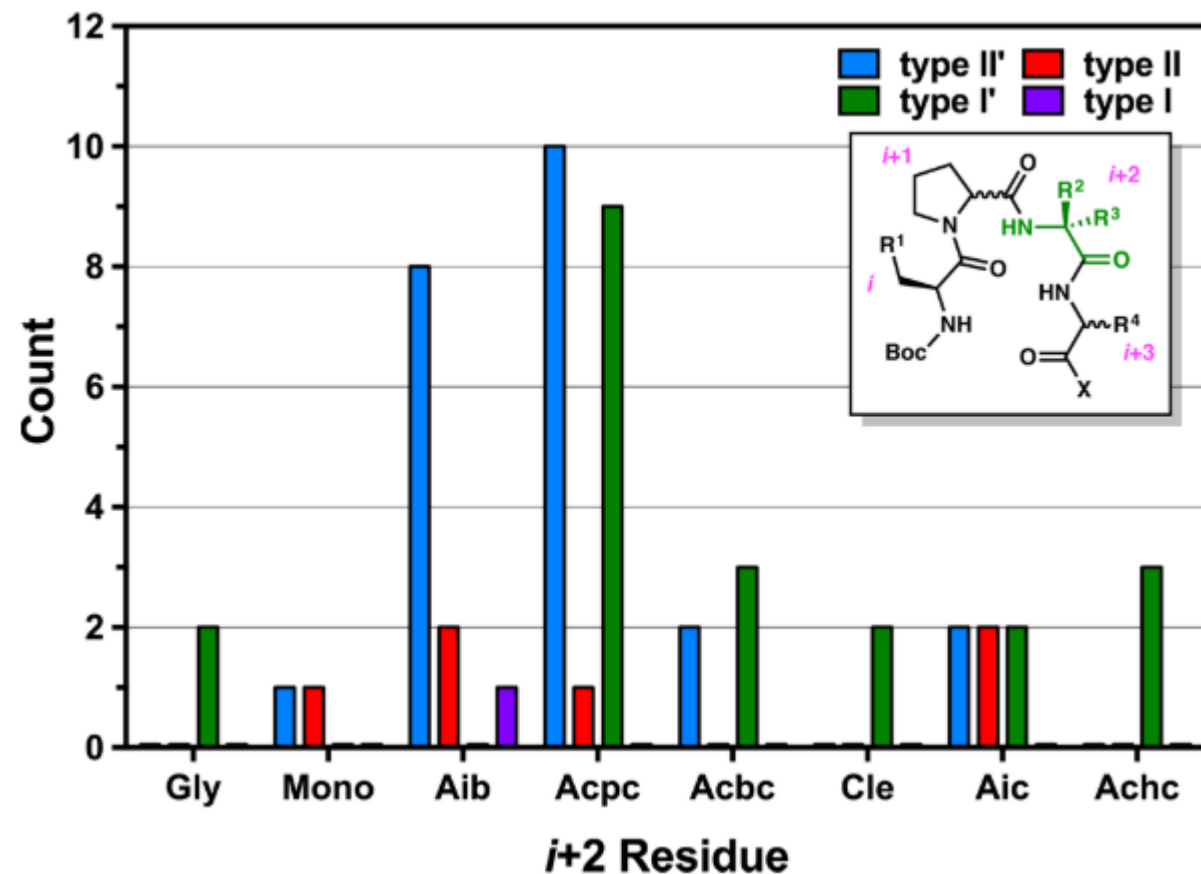
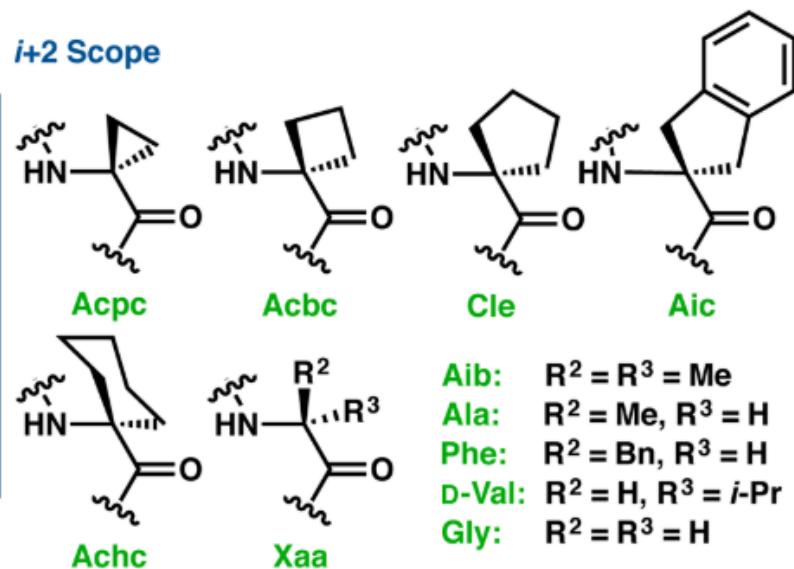
Non-Proteinogenic

Tendency of turn induced by Pro-Xaa sequence

β -Turn Scaffold

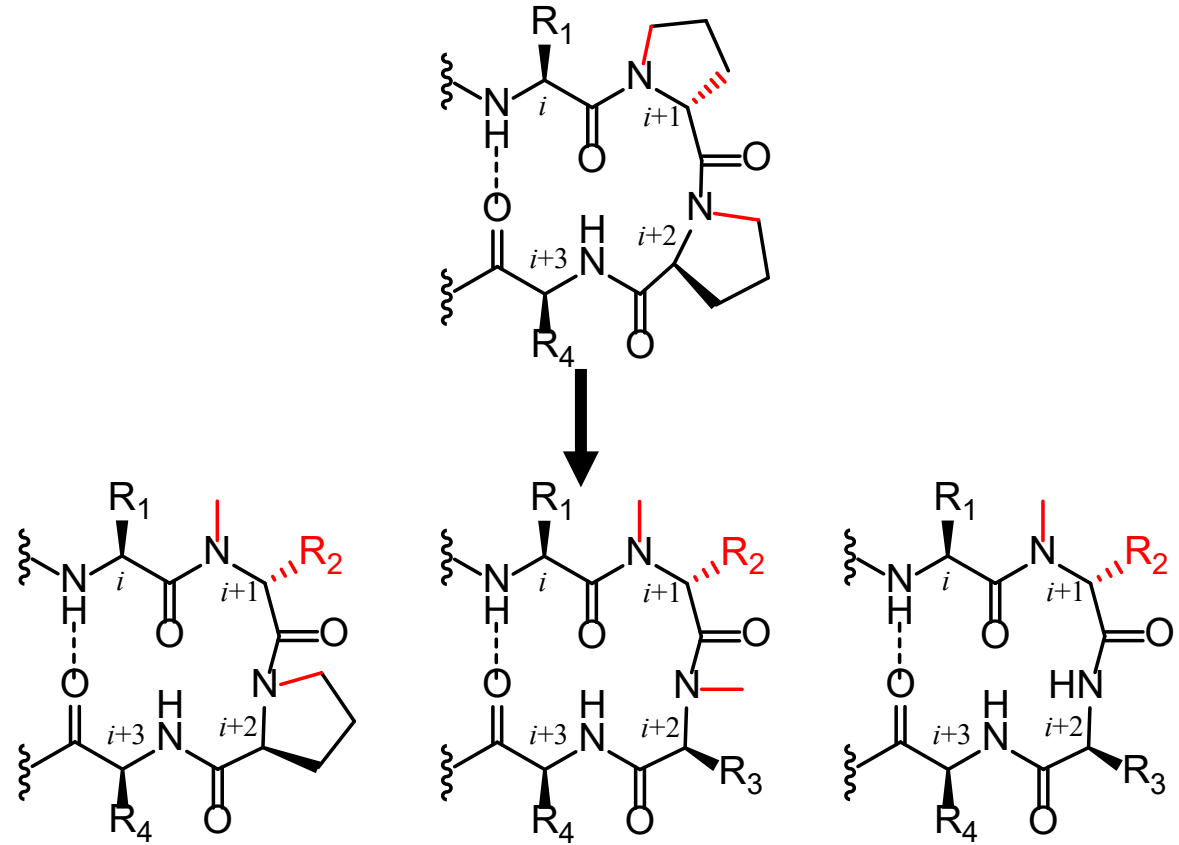
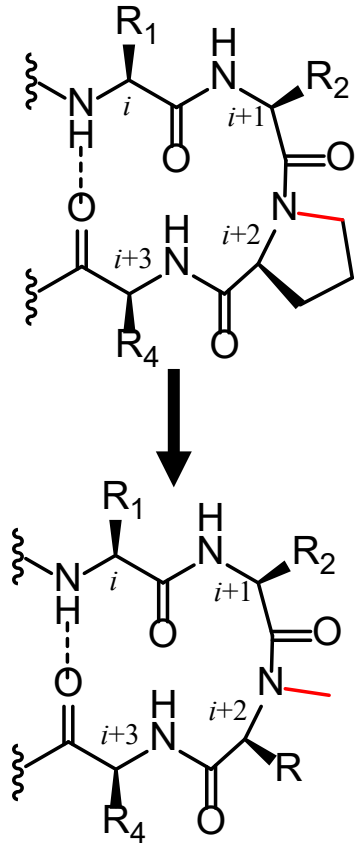


$i+2$ Scope



Induction of turn can be controlled, and indeed there are some major and strong turn inducer, the structure of turn induced will usually be highly dependent on the context.

N-Methylation



N-Methylation can be seen as a surrogate of proline.

1. Introduction

2. Major secondary structures and its mimetics

- α -helix
- Example of α -helix mimetic PPI inhibitor
- β -sheet
- Example of β -sheet mimetic PPI inhibitor
- Turns
- Example of β -turn mimetics

3. Summary

4. Appendix

Summary

- | Stereopopulation controlled mimetics of peptide by the various artificial motifs improve the properties of peptides.
 - | Affinity, Bioavailability and membrane permeability, Metabolic stability, Immunogenicity
 - | For biological activity, rigidifying the structure at its active form is crucial.
 - | For bioavailability and membrane permeability,
 - | Conformational rigidity and scarcity of solvateable NH (N-methylation, intramolecular hydrogen bonding, steric shielding)
 - | Lipophilicity (lipophilic sidechains)
 - | Specific conformation (e.g. $\beta II'$ - βVI turn structure with cis peptide bond)
- have a positive effect in general.
- | The effect of each factor depends on the dominant transport pathway.
 - | For metabolic stability, unnatural structure is effective on the whole.

1. Introduction

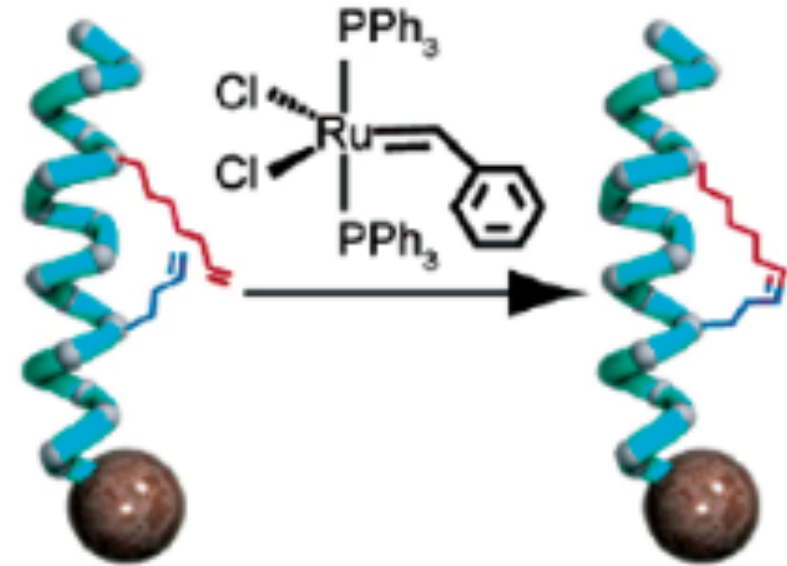
2. Major secondary structures and its mimetics

- α -helix
- Example of α -helix mimetic PPI inhibitor
- β -sheet
- Example of β -sheet mimetic PPI inhibitor
- Turns
- Example of β -turn mimetics

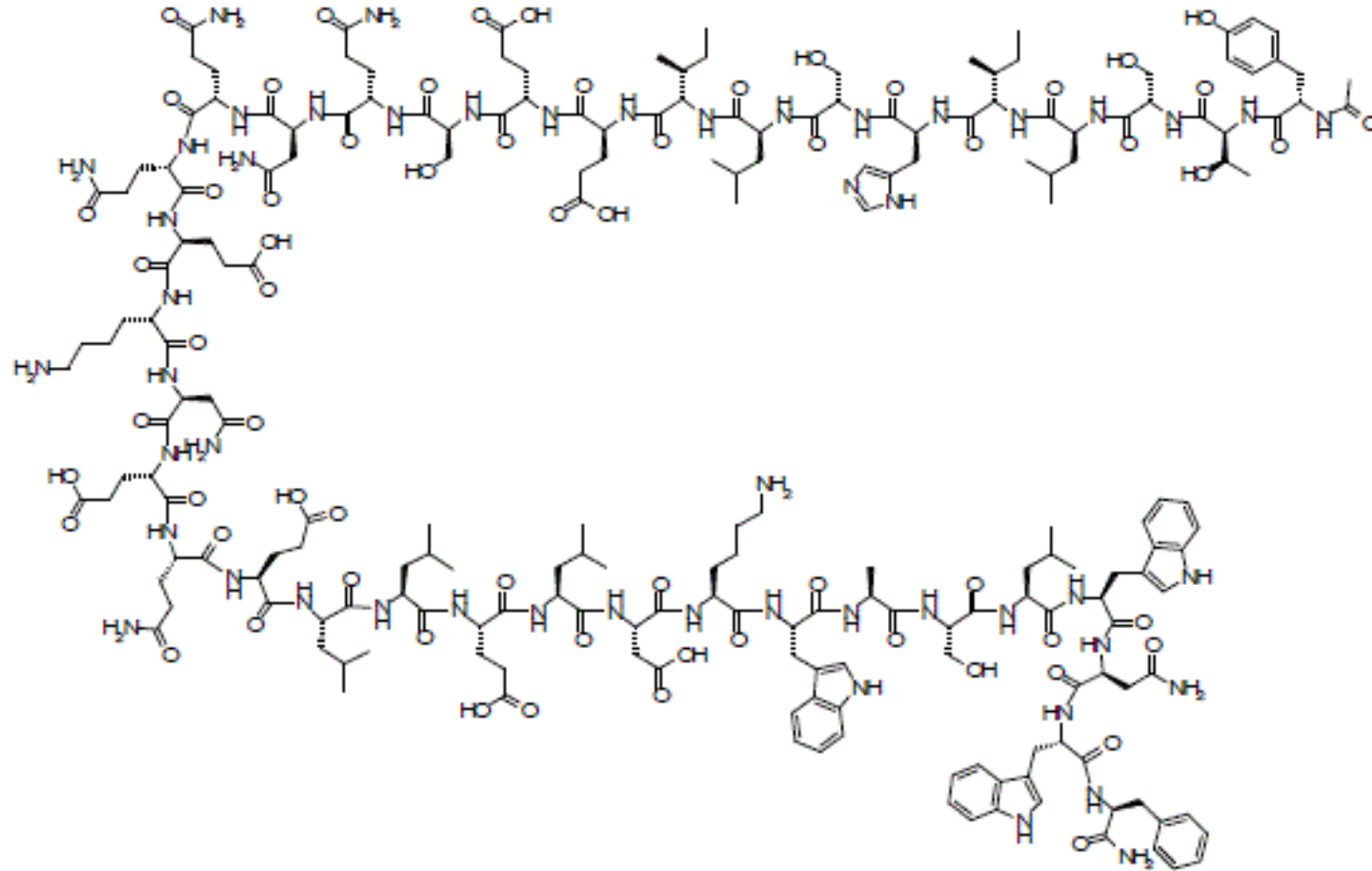
3. Summary

4. Appendix

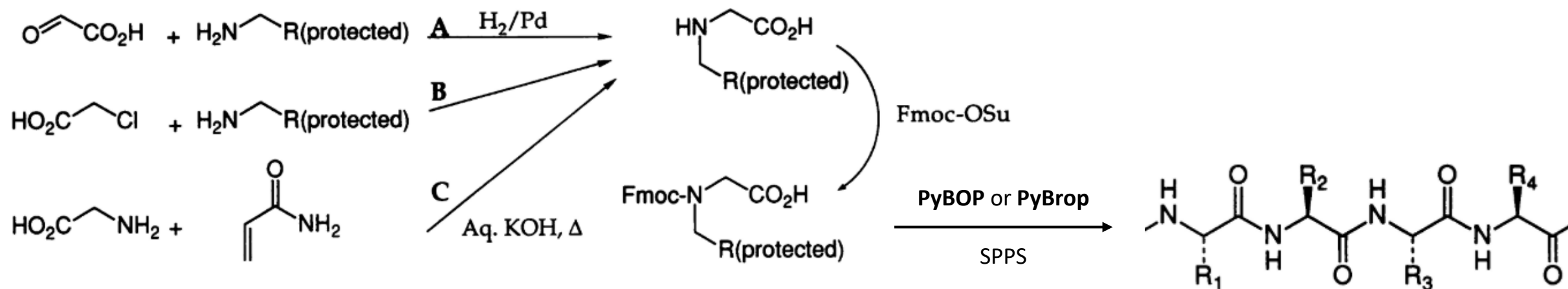
Synthesis of SAH-p53-x

A**D**

Structure of Enfuvirtide

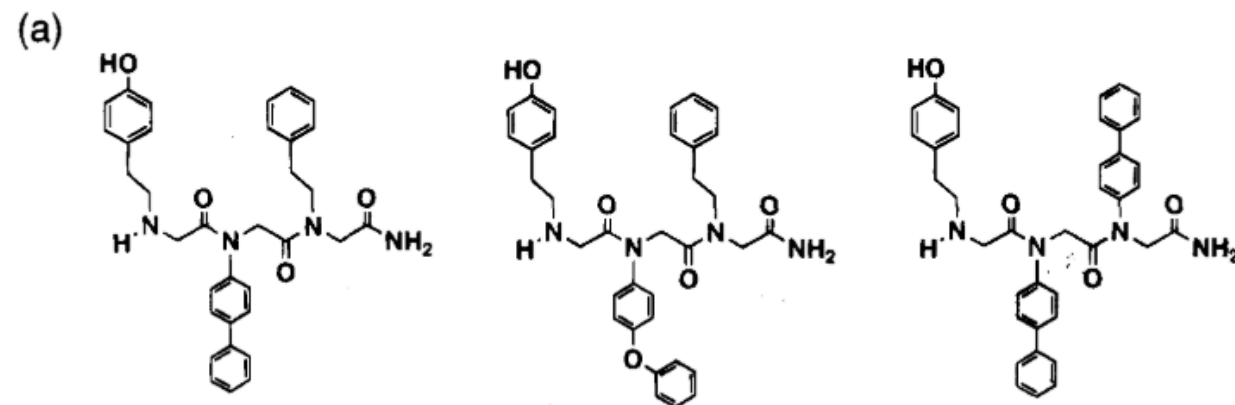


Synthesis Oligo N-substituted Glycine

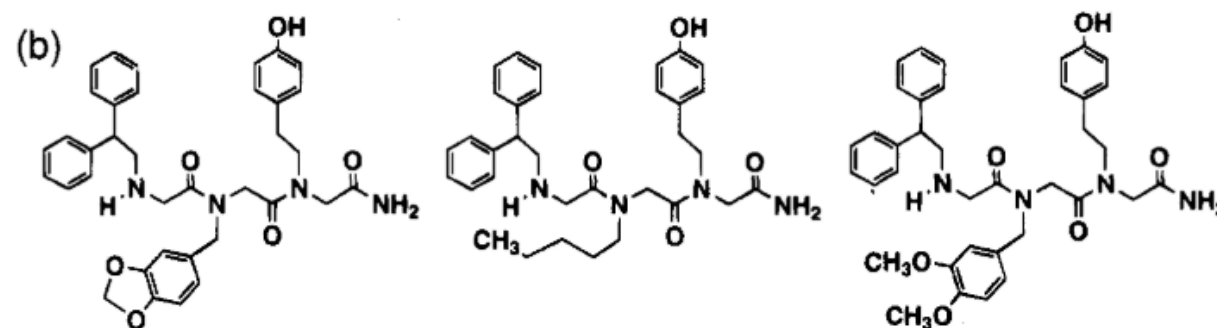


Only example of highly potent inhibitor made of oligo-NSG

N-Terminal Capping Groups			
Hydroxyl Set of Sidechains (O)			
Nhyb	Nhser	Nh Tyr	
Aromatic Set of Sidechains (A)			
Nbiph	Nhpe	Nnap	Ndpe
Diverse Set of Sidechains (D)			
Npen	Nmb		
Npop	Nmdb	Nmb	
Nmb	Nmb	Nmb	Nmb
Nmb	Nmb	Nmb	Nmb
Nmb	Nmb	Nmb	Nmb



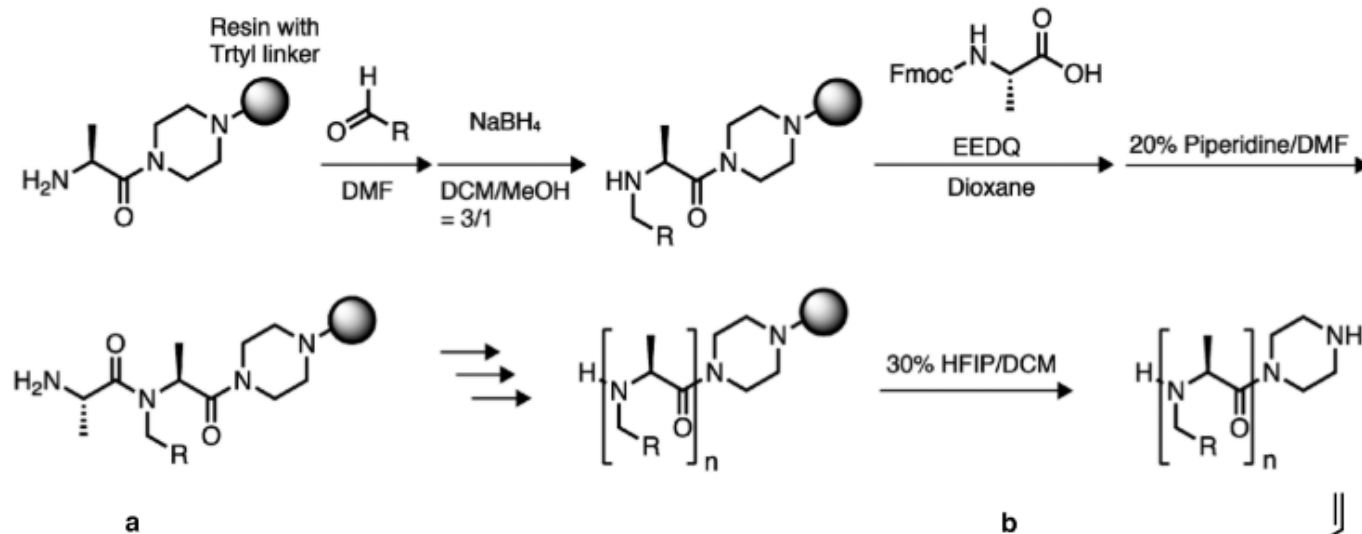
CHIR 2279 $K_i = 5$ nM CHIR 2283 $K_i = 140$ nM CHIR 2276 $K_i = 310$ nM
 α_1 -adrenergic receptor



CHIR 4531 $K_i = 6$ nM CHIR 4534 $K_i = 46$ nM CHIR 4537 $K_i = 31$ nM
 μ -opiate receptor

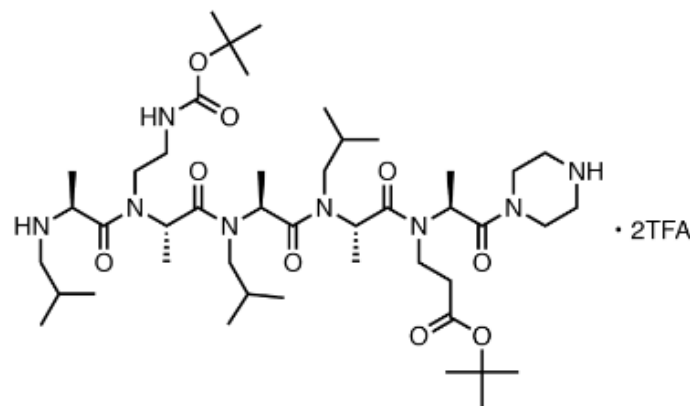
Synthesis of Oligo N-substituted Alanine

a Synthetic scheme

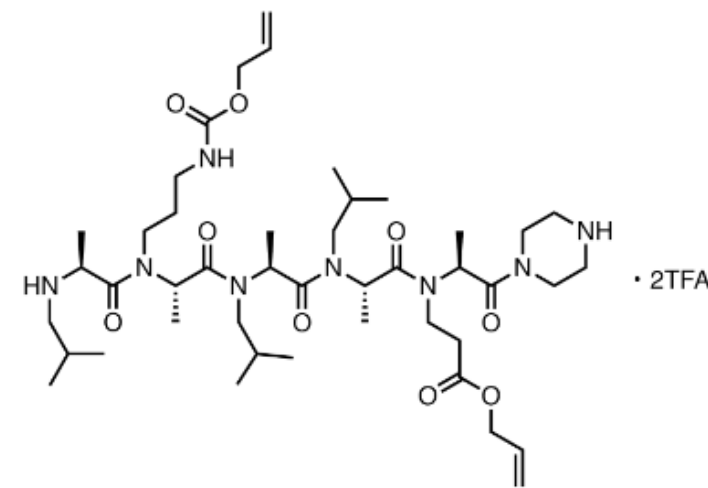


b

Compound	n	Yield (%)	
		HPLC	Isolated
1	1	82	80
2	2	85	71
3	3	72	54
4	4	83	55
5	5	50	47

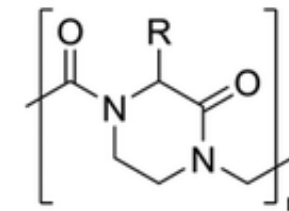
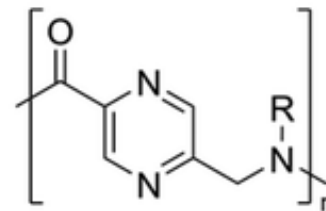
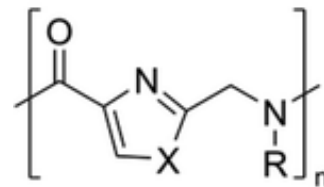
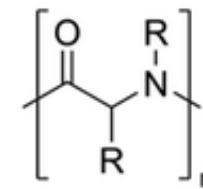
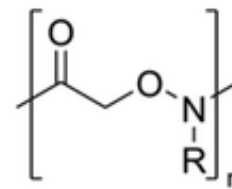
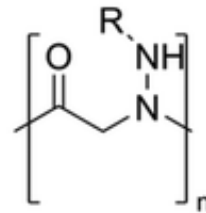
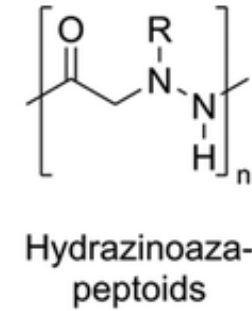
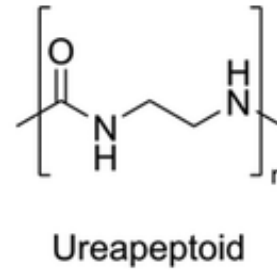
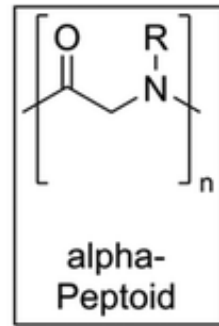


S6

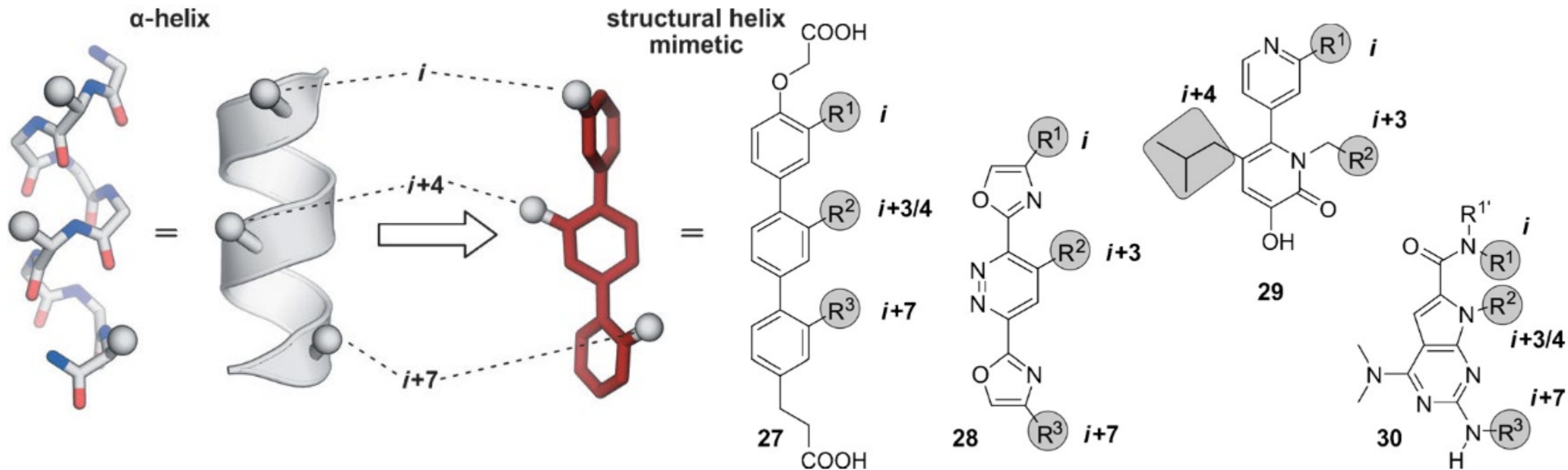


S7

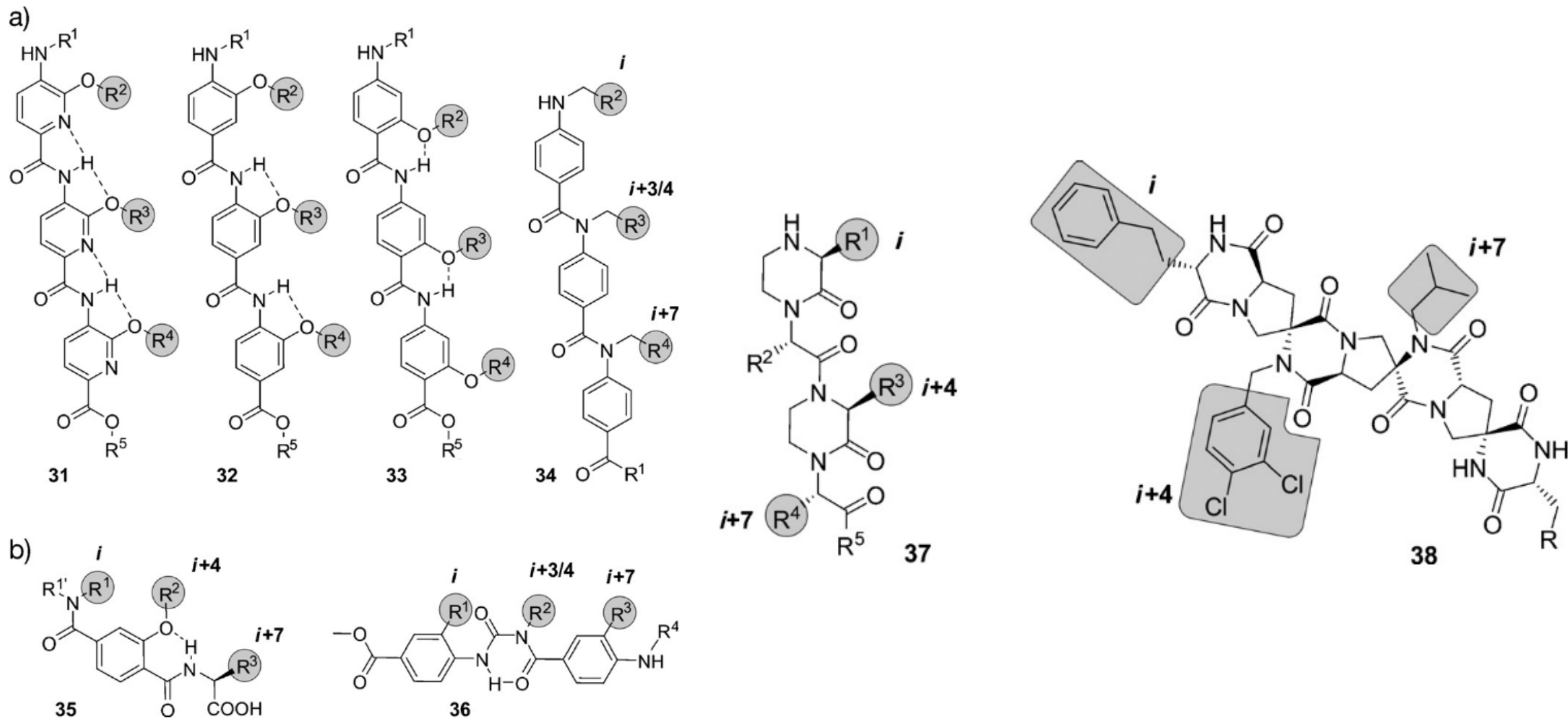
Other foldamers



C,D-type mimetics of α -helix



C,D-type mimetics of α -helix



Appendix: Population of β -turns

β -turn	(%)
I	38.21
II	11.81
VIII	9.84
I'	4.10
II'	2.51
VI _b	0.88
VI _{a1}	0.73
VI _{a2}	0.20
IV ^{ori}	31.72
Sum	100.00