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Photoisomerization-Dependent Glycan Binding of Engineered Lectin-like Peptides: Toward Light-Controlled Bioactivity of Lectins.

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Aim

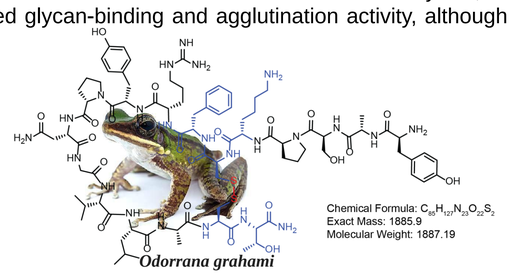
To uncover the molecular and conformational principles that govern glycan recognition by lectin-like peptides, with Odorranalectin serving as a model scaffold, and to determine how backbone preorganization, rigidity, and macrocycle topology shape biological activity. These structure-activity relationships were further exploited to guide the rational design of photoresponsive diarylethene-containing macrocycles, aiming to achieve reversible, light-controlled modulation of peptide conformation and glycan-binding function.

Odorranalectin

Odorranalectin [1] represents a compact lectin-like peptide scaffold for studying structure-dependent glycan recognition. Our systematic re-evaluation showed that, although several previously reported glycan interactions could not be reproduced, native Odorranalectin retained binding to selected glycans and displayed additional interactions with serum proteins. Structural studies further indicated a preference for a rigid β-turn-like conformation rather than a classical lectin fold, suggesting that conformational preorganization is an important determinant of its molecular recognition properties. This concept was further supported by a series of Odorranalectin-derived macrocycles, in which increased structural rigidity was associated with enhanced glycan-binding and agglutination activity, although excessive activity also introduced safety-related effects.

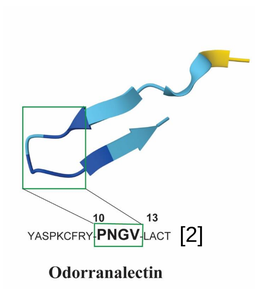
The main literature data are given below:

- Odorranalectin is a 17-residue disulfide-constrained peptide (YASPKCFRYPNGVLACT) from *Odorrana grahami*.
- NMR shows a β-turn structure stabilized by a S6-S16 bond.
- It is plasma-stable, low toxicity / low cytotoxicity.
- Binding specificity was tested by hemgglutination-inhibition and SPR assays.
- Only L-fucose inhibited agglutination [1].



Chemical Formula: $C_{85}H_{127}N_{23}O_{22}S_2$
Exact Mass: 1885.9
Molecular Weight: 1887.19

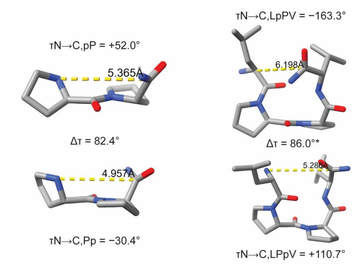
Derivatives of Odorranalectin



№	Sequence	Modification	K_D, ASF
1	**YASPKCFRYPNGVLACT**	native	356μM
2	YASPKC**f**RYPNGVLACT	f	973μM
3	TCALVGNPYRFCKPSAY	revers	n/a
4	YASPKCFRY**pP**GVLACT	pP	417μM
5	YASPKCFRY**Pp**GVLACT	Pp	840μM
6	YASPKCFRYPNG**pP**ACT	pP	3.14mM
7	YASPKCFRYPNG**Pp**ACT	Pp	3.75mM
8	YASPKCFRY**LpPV**GVLACT	LpPV	1.37mM
9	YASPKCFRY**LPpV**GVLACT	LpPV	126μM
10	YASPKCFRYPNG**LpPV**ACT	LPpV	594μM
11	YASPKCFRYPNG**LPpV**ACT	LPpV	3.75mM
12	YASPKCFRY**LpPV**LACT	LPpV	1.97mM
13	YASPKCFRY**LPpV**LACT	LPpV	611μM
14	YASPKCFR**LpPV**GVLACT	LPpV	1.40mM
15	YASPKCFR**LPpV**GVLACT	LPpV	539μM

P = L-Pro; p = D-Pro; f-D-Phe

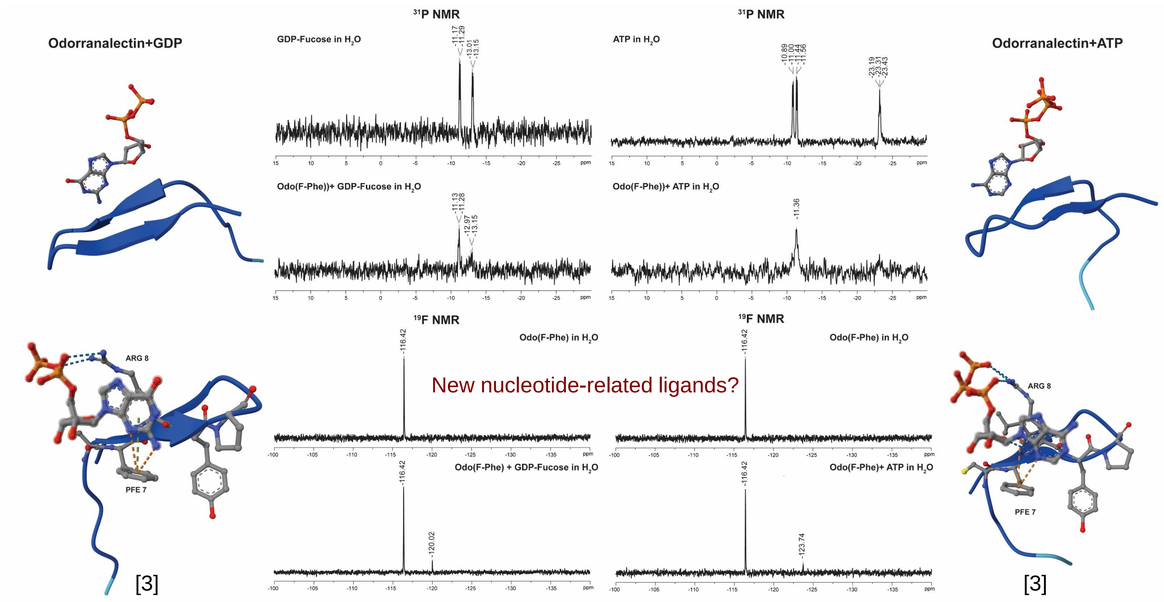
Model based on pseudo-dihedral angle



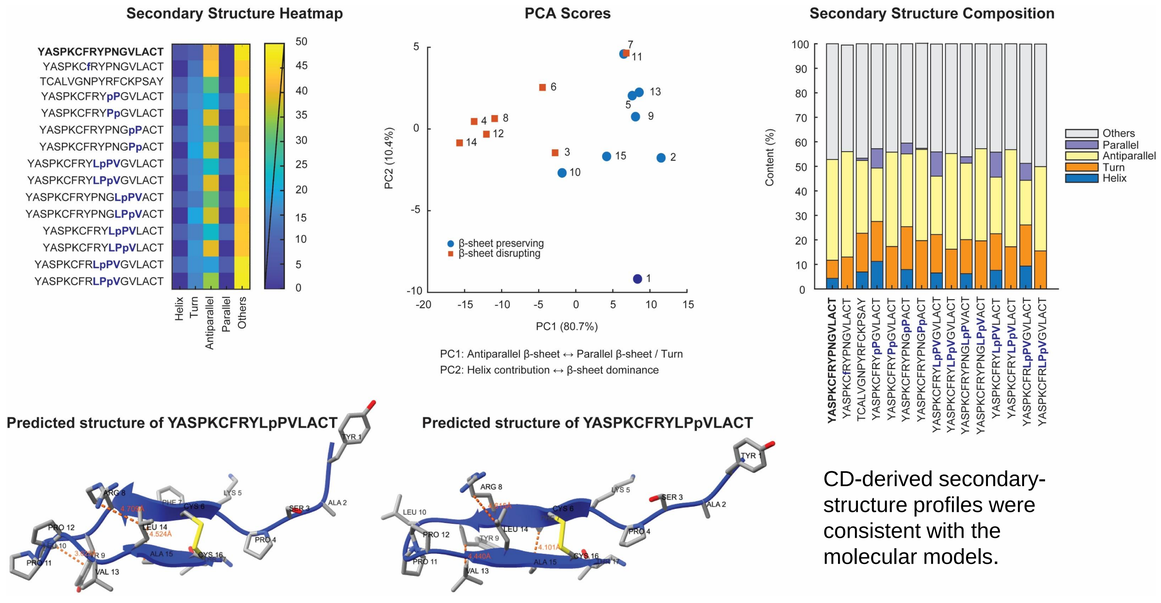
*For τN→C, the shortest angular difference was used because dihedral angles are periodic.

We established a conformational model library of Odorranalectin analogues incorporating pP/Pp and LpPV/LPpV motifs to determine how peptide preorganization influences biological activity. We then used the resulting structure–activity relationships as a predictive framework for diarylethene-containing derivatives, enabling prediction of activity from their light-dependent conformational state, backbone geometry, and degree of structural preorganization.

Nucleotide-related ligand interactions

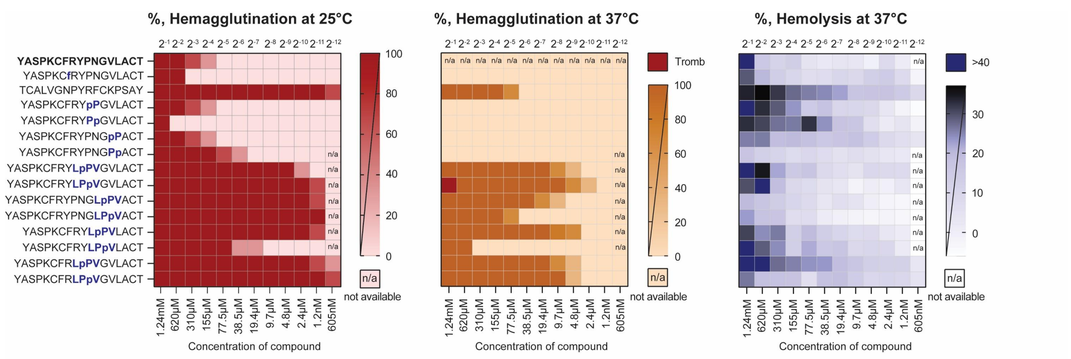


Secondary structure



CD-derived secondary-structure profiles were consistent with the molecular models.

Hemagglutination, hemolysis, toxicity



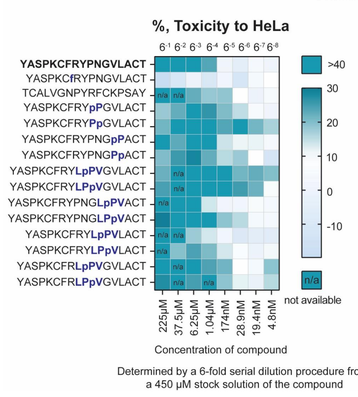


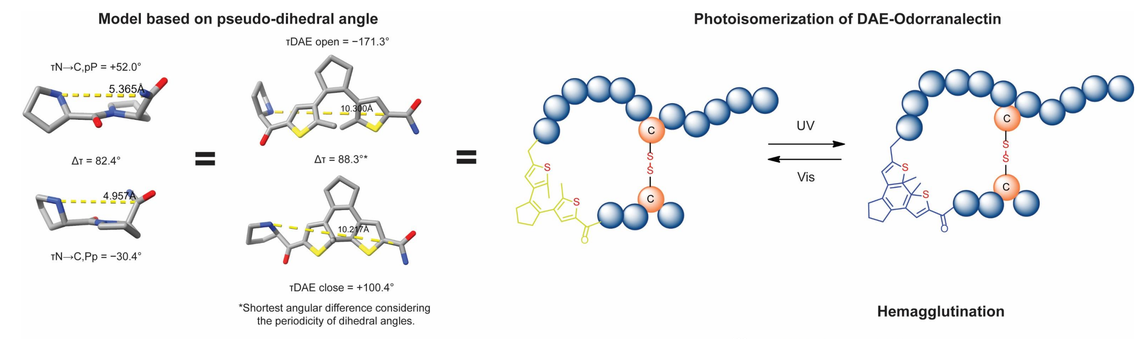
Table Inhibition of hemagglutination by monosaccharides, ATP, Inosytol

№	Sequence	Modification	L-Fuc, mM	D-Fuc, mM	L-Gal, mM	D-Gal, mM	ATP, mM	Inosytol, mM
1	**YASPKCFRYPNGVLACT**	native	+ n/a +/- n/a	+ n/a +/- n/a	+ n/a n/a n/a	n/a n/a n/a n/a	+ +/- +/- n/a	+/- n/a +/- n/a
6	YASPKCFRYPNG**Pp**ACT	pP	+ + + +	+ + + +	n/a n/a n/a n/a	n/a n/a n/a n/a	+ + + +	n/a n/a n/a n/a
7	YASPKCFRYPNG**PP**ACT	Pp	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
12	YASPKCFRY**LpPV**LACT	LPpV	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
13	YASPKCFRY**LPpV**LACT	LpPV	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
14	YASPKCFR**LpPV**GVLACT	LPpV	- - - -	- - - -	- - - -	- - - -	+ + + -	+ - - -
15	YASPKCFR**LPpV**GVLACT	LpPV	- - - -	- - - -	- - - -	- - - -	+ + - -	- - - -

+ Hemagglutination inhibition
- None hemagglutination inhibition
+/- Partial Inhibition of Hemagglutination
n/a not available

The library-derived analogues did not discriminate between the tested sugar enantiomers.

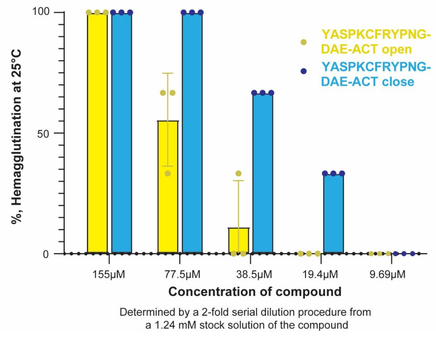
DAE-Odorranalectin



Conclusion and Outlook

The conformational model successfully reproduced the activity trends observed for the diarylethene-containing derivatives, supporting its use as a predictive framework for photoresponsive peptide design. Sugar-inhibition studies will be performed to further validate the glycan-recognition mechanism, while future work will extend this approach to larger lectin systems, including UEA-I (*Ulex europaeus agglutinin I*). Importantly, the concept will not be limited to diarylethene photoswitches, but will be expanded toward alternative photoresponsive scaffolds to enable broader and more versatile light-controlled modulation of lectin–glycan interactions.

Hemagglutination



References:

1. Li, J.X., et al., *Odorranalectin Is a Small Peptide Lectin with Potential for Drug Delivery and Targeting.* Plos One, 2008. **3**(6).
2. The UniProt Consortium , UniProt: the Universal Protein Knowledgebase in 2025, *Nucleic Acids Research*, Volume 53, Issue D1, 6 January 2025, Pages D609–D617.
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