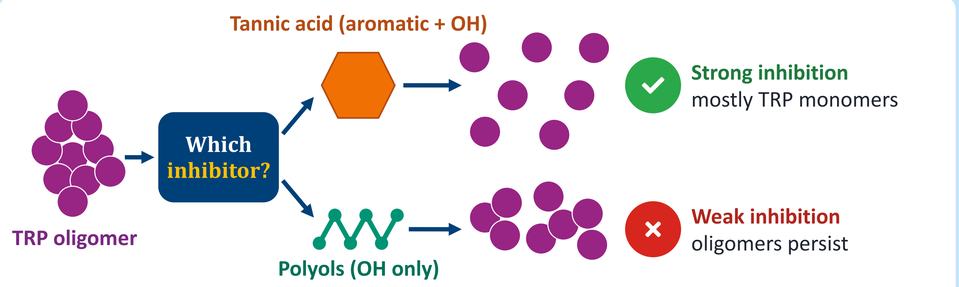
Mechanistic Role of Different Functional Groups in Inhibiting Tryptophan Self-Assembly

Comparison between Aromatic and Nonaromatic Hydroxyl Moiety-Rich Chemical Compounds

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KEY FINDING

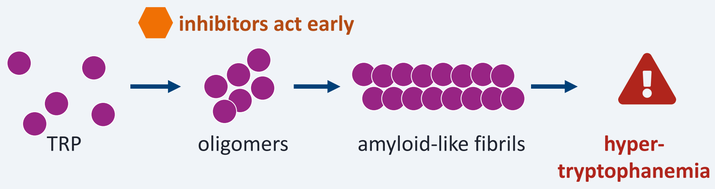
Aromatic rings, not hydroxyl groups, make tannic acid a strong inhibitor of tryptophan aggregation.

MD + free-energy study: tannic acid vs sorbitol and mannitol

Evidence at a glance

- **~50% vs ~6%** — TRP monomers with one TA vs neat TRP
- **~1.36 ns vs ~39 ps** — TA-TRP π − π vs H-bond lifetime
- **≈ −4.5 kcal/mol** — PMF minimum for TA; no prominent well for polyols

Why It Matters

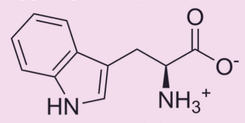


- Excess TRP self-assembles into amyloid-like fibrils, linked to **hypertryptophanemia**; no effective therapy yet.
- Tannic acid (TA) potently inhibits TRP fibrillation but carries both aromatic rings and OH groups; polyols (OH only) also inhibit amyloid aggregation.

Question: which group does the work, the aromatic ring (π − π stacking) or the hydroxyl groups (H-bonding)?

Molecules Compared

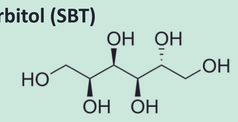
L-Tryptophan (TRP)



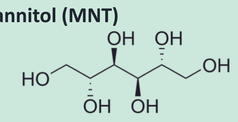
aromatic indole ring

Polyols

Sorbitol (SBT)



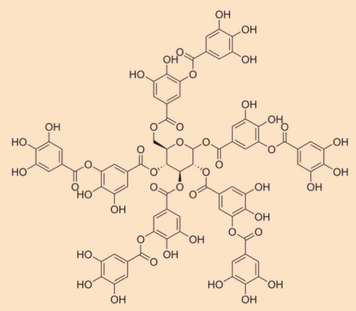
Mannitol (MNT)



0 rings · **6** OH · 182 g/mol each

Tannic acid (TA)

polyphenol (aromatic rings + OH)



10 aromatic (galloyl) rings
25 hydroxyl groups
1701 g/mol

Approach

1. **Model** — HF/6-31G* → GAFF + RESP charges · TIP3P water · GROMACS 2022.5
2. **Systems** — 24 TRP + 1 TA, or 1–10 SBT / MNT (incl. mass-matched S10, M10)
3. **Sample** — 500 ns MD × 3 replicas; last 250 ns analyzed
4. **Analyze** — Oligomers · π − π and H-bond lifetimes · residence time · PMF (umbrella sampling, WHAM)

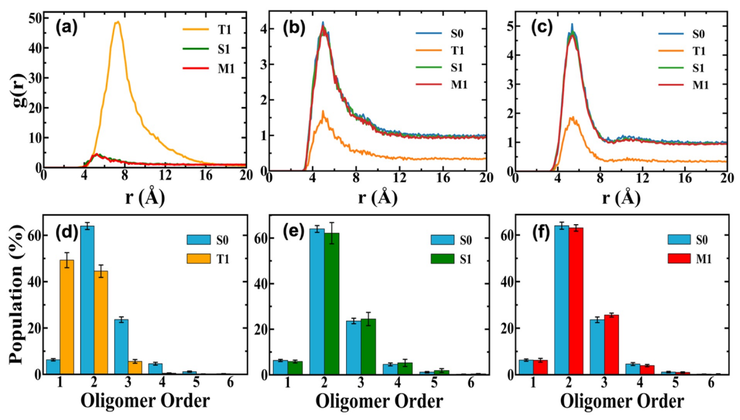
Reliability: 3 independent MD run · SEM error bars (block averaging) · convergence checked

Results

S0 neat TRP · **T1** + 1 TA · **S1 / M1** + 1 SBT / MNT · **S10 / M10** + 10 SBT / MNT

1 Oligomer break-up

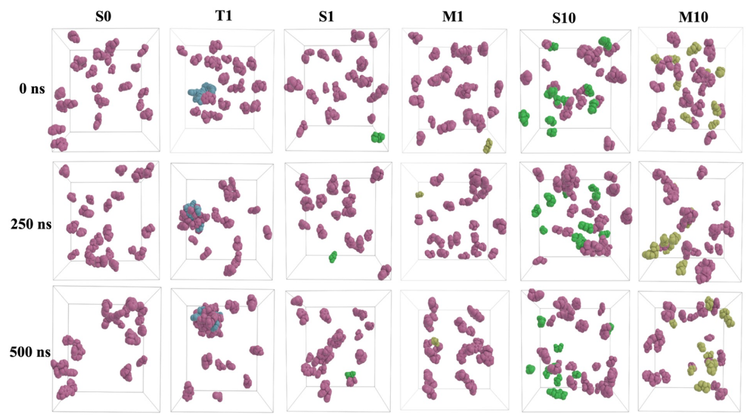
One TA disperses TRP oligomers; equimolar polyol does not.



(a) TA−TRP association far exceeds polyol−TRP; *(b, c)* TRP−TRP and indole-ring RDFs drop sharply only with TA; polyols overlap neat TRP; *(d–f)* monomers rise from ~6% to ~50% only with TA.

2 Simulation snapshots

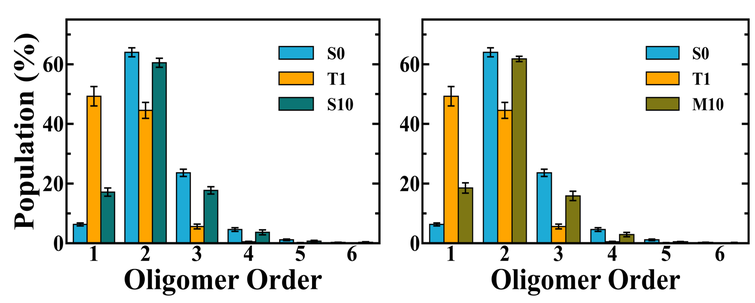
TRP binds to TA instead of forming extended oligomers.



*Snapshots at 0, 250 and 500 ns (water hidden): TRP **mauve**, TA **cyan**, SBT **green**, MNT **yellow**.*

3 Not a size effect

Ten mass-matched polyols still fall short of one TA.



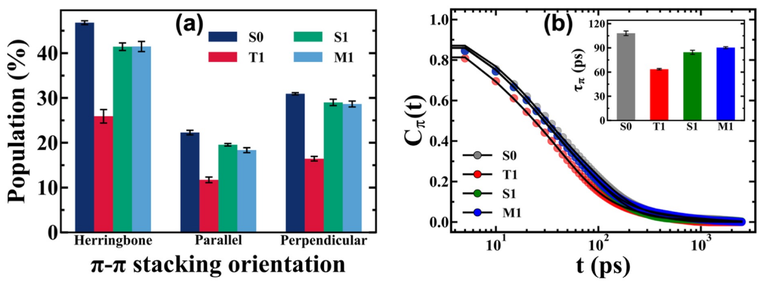
1 TA (T1)
1701 g/mol · 25 OH · 10 rings
→ **~50% monomers**

10 SBT or MNT
~1820 g/mol · 60 OH · 0 rings
→ **only ~17–19% monomers**

TRP oligomer populations with 10 SBT (S10) or 10 MNT (M10), at 10× the inhibitor concentration of T1.

4 TRP–TRP stacking

TA weakens the π − π stacking that drives self-assembly.



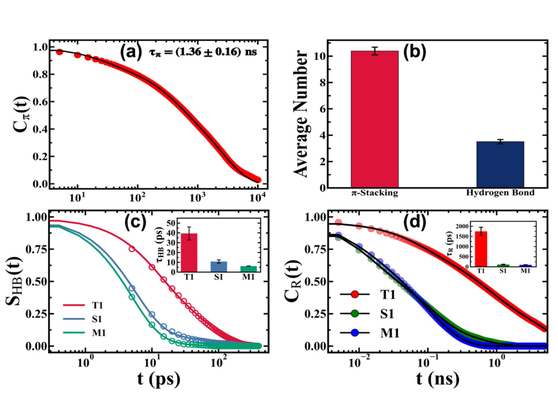
46.8% → 25.9%
herringbone TRP–TRP stacks

108 → 63.6 ps
TRP–TRP π − π lifetime

(a) Stacking geometries of TRP not bound to an inhibitor; *(b)* π − π decay, inset lifetimes. Polyols: marginal change.

5 π − π vs H-bonding

π − π stacking, not H-bonding, anchors TRP to TA.



~1.36 ns
TA–TRP π − π lifetime

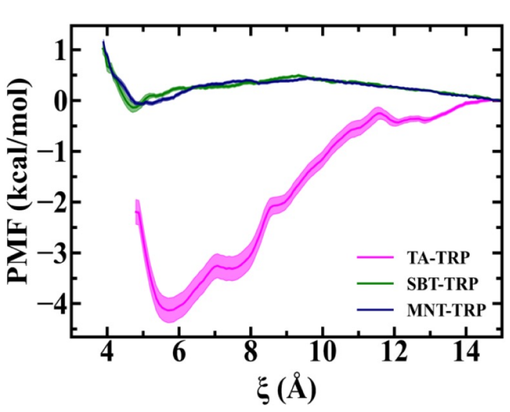
~39 ps
TA–TRP H-bond lifetime

~1.75 ns
TRP residence time near TA

(a) TA–TRP π − π decay; *(b)* ~3× more π − π contacts than H-bonds (TA−TRP); *(c, d)* H-bond and residence-time decays (polyols: ~0.1 ns).

6 Free energy (PMF)

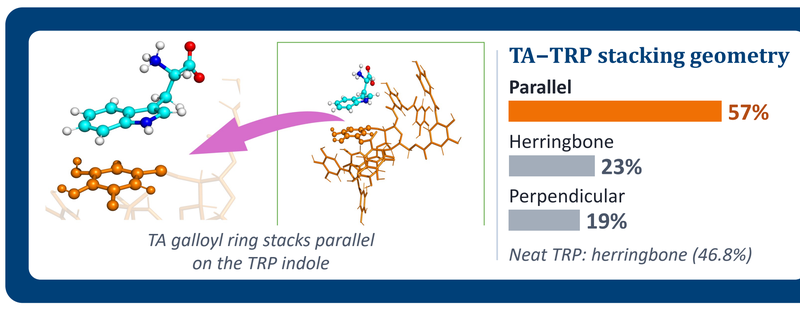
Only TA holds TRP in a free-energy well.



≈ −4.5 kcal/mol
TA–TRP PMF minimum (at ξ ≈ 5.8 Å)

SBT, MNT
no prominent minimum: weak, transient binding

PMF for pulling one TRP away from each inhibitor (umbrella sampling + WHAM; shading = bootstrap error).



TA galloyl ring stacks parallel on the TRP indole

Conclusions

- Aromaticity, not OH count or size, sets inhibition: 1 TA beats 10 polyols.
- Long-lived TA–TRP π–π stacking dominates; H-bonds only add stabilization.
- TA breaks native TRP–TRP stacking; only TA has a binding free-energy well.

Design principle

Aromatic scaffold + complementary polar groups → stronger TRP-aggregation inhibitors.

Next: use the PMF minimum and π–π lifetime as descriptors for functional-group-guided inhibitor screening.

References

[1] A. A. Mandal, S. Mitra, S. Chakrabarty, R. Biswas, *J. Phys. Chem. B* **2026**, 130, 8794–8804.
[2] T. Nandy, R. Biswas, *J. Photochem. Photobiol. A: Chem.* **2024**, 453, 115660.

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