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In silico prediction of the antagonistic activity of natural compounds on neuropeptide S receptor 1 in endometriosis

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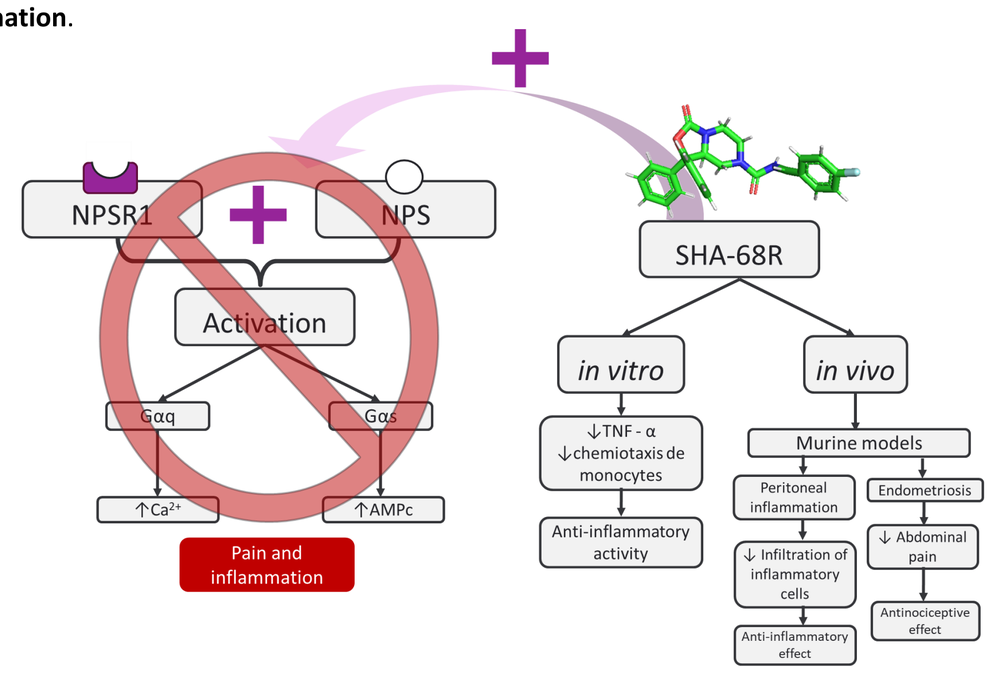
INTRODUCTION & AIM

Endometriosis affects approximately 10-15% of women of reproductive age, manifesting as dysmenorrhea, abnormal bleeding, infertility, and chronic inflammation.

The Neuropeptide S Receptor 1 (**NPSR1**) is a genetically validated therapeutic target. Its inhibition prevents the binding of neuropeptide S, **disrupting intracellular pathways linked to pain and inflammation**.



Aim:
To identify and evaluate natural compounds containing the CNC(=O)N pharmacophore - based on the selective antagonist SHA-68R—as potential NPSR1 antagonists for endometriosis treatment.

METHOD

Fragment-Based Screening
CNC(=O)N motif used to search natural product databases → 54 candidate molecules selected.

2D-QSAR Modeling
Molecular descriptors analyzed to predict antagonist activity (pKB).

Pharmacokinetics & Drug-Likeness
Evaluated using SwissADME and Deep-pkCSM.

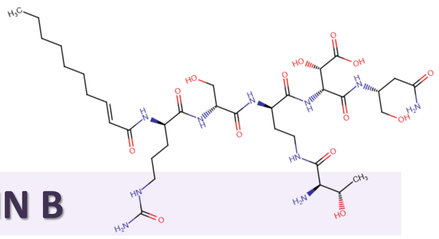
Molecular Docking
- NPSR1 structure retrieved from GPCRdb (PDB: npsr1_human).
- Binding affinity (ΔG°) predicted using AutoDock VINA 1.1.2.

Interaction Analysis
Top candidates visualized using Discovery Studio 2D.

RESULTS & DISCUSSION

QSAR Analysis

- 54 natural compounds containing the CNC(=O)N fragment were screened.
- Multiple candidates showed promising predicted pKB values using 2D-QSAR modeling.



Top Candidate - **ROTIHIBIN B**

Binding affinity

ΔG°: -8.7 kcal/mol

Key interactions:

Multiple hydrogen bonds with NPSR1 active site

Physicochemical profile:

- Exceeds Lipinski's Rule of Five
- High polarity and molecular weight

Pharmacokinetic profile *(in silico):*

- Poor oral absorption predicted by SwissADME
- No blood–brain barrier penetration
- Low toxicity risk
- Moderate metabolic stability

Compared to SHA-68R:

- Comparable binding affinity
- Less favorable oral bioavailability

Insight:
Rotihibin B's structural features and interaction profile suggest it as a viable lead compound for further optimization.

CONCLUSION

Rotihibin B emerges as a promising natural NPSR1 antagonist, with strong binding affinity and acceptable pharmacokinetics. Despite violating some drug-likeness rules, its bioactivity and interaction profile support its potential as a lead scaffold for novel endometriosis therapies.

FUTURE WORK / REFERENCES

Structural optimization to improve drug-likeness
- *In vitro*/*in vivo* validation of NPSR1 antagonism
- Design of analogs with enhanced selectivity and bioavailability
- Integration into drug discovery pipelines for gynecological inflammatory diseases

References