

Drug Repurposing For The Inhibition Of 17 β -HSD1 in Endometriosis: A Pharmacophore-Guided Virtual Screening Study

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INTRODUCTION

Endometriosis is an Estrogen-Dependent Disease (EDD) that affects **1 in 10** women of reproductive age worldwide, yet remains difficult to diagnose and treat. Current therapies are largely focused on pain management and hormonal suppression, with the latter being proven to affect systemic estrogen. This study focuses on local estrogen biosynthesis and targets 17 β -HSD1, a key intracrine enzyme that converts weak estrone (E1) to the biologically potent estradiol (E2).

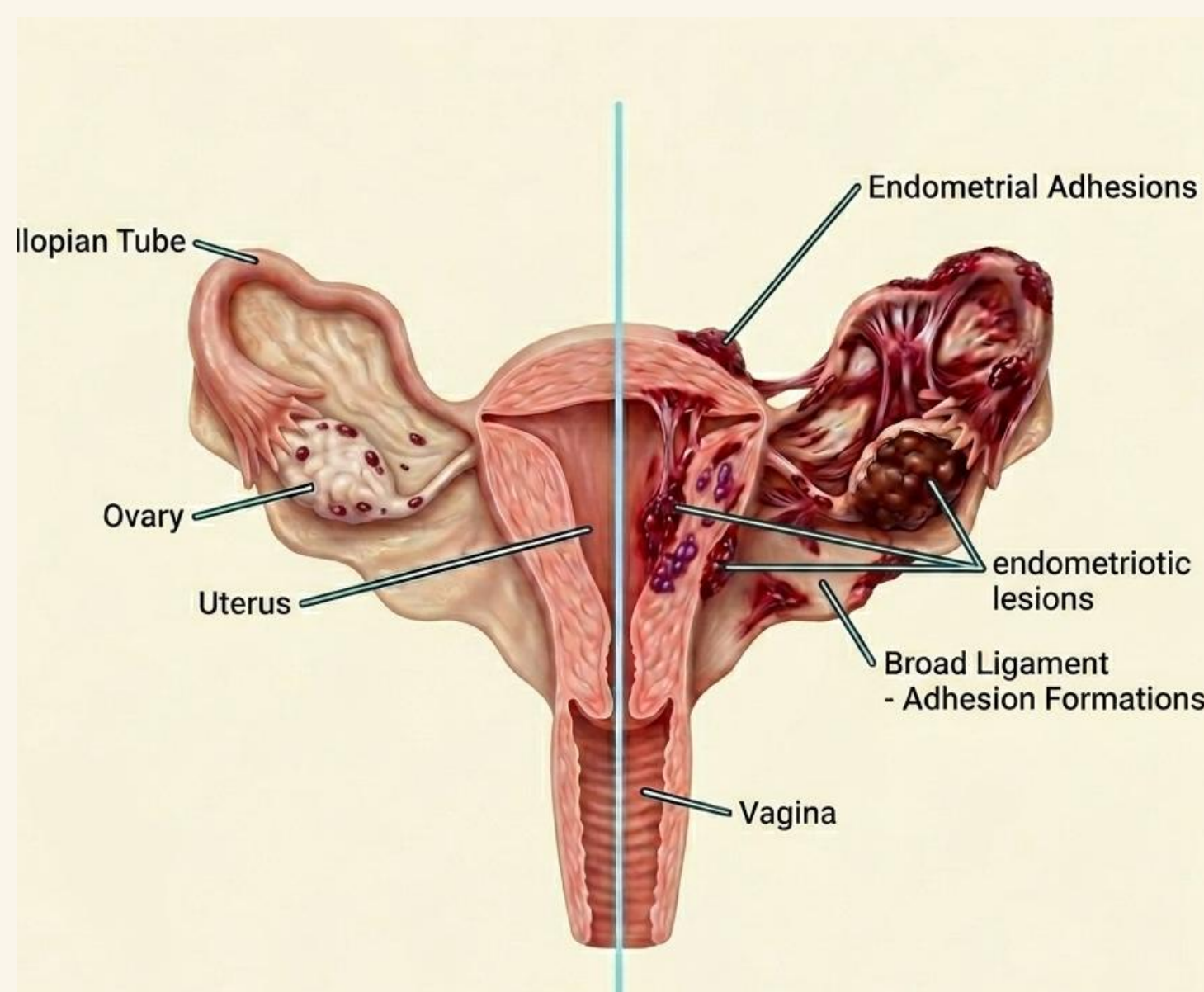


Figure 1: Healthy vs endometriotic female reproductive system

OBJECTIVE

To employ computational techniques in discovering repositionable inhibitors of 17 β -HSD1 from the DrugBank library, in order to reduce local estradiol production and mitigate the progression of endometriosis.

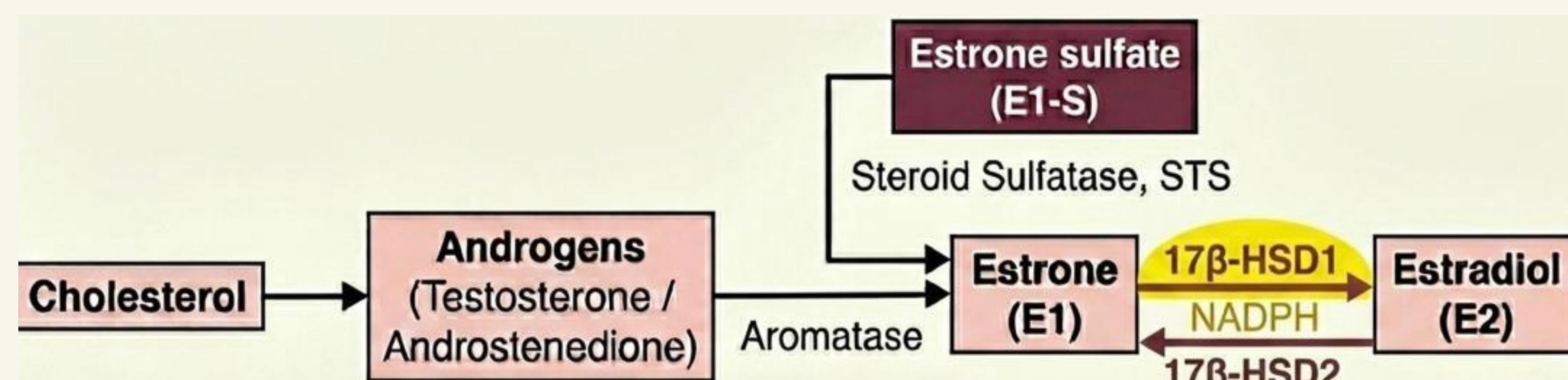


Figure 2 : Intracrine Estrogen Biosynthesis in Endometriosis: The Central Role of 17 β -HSD1

METHOD

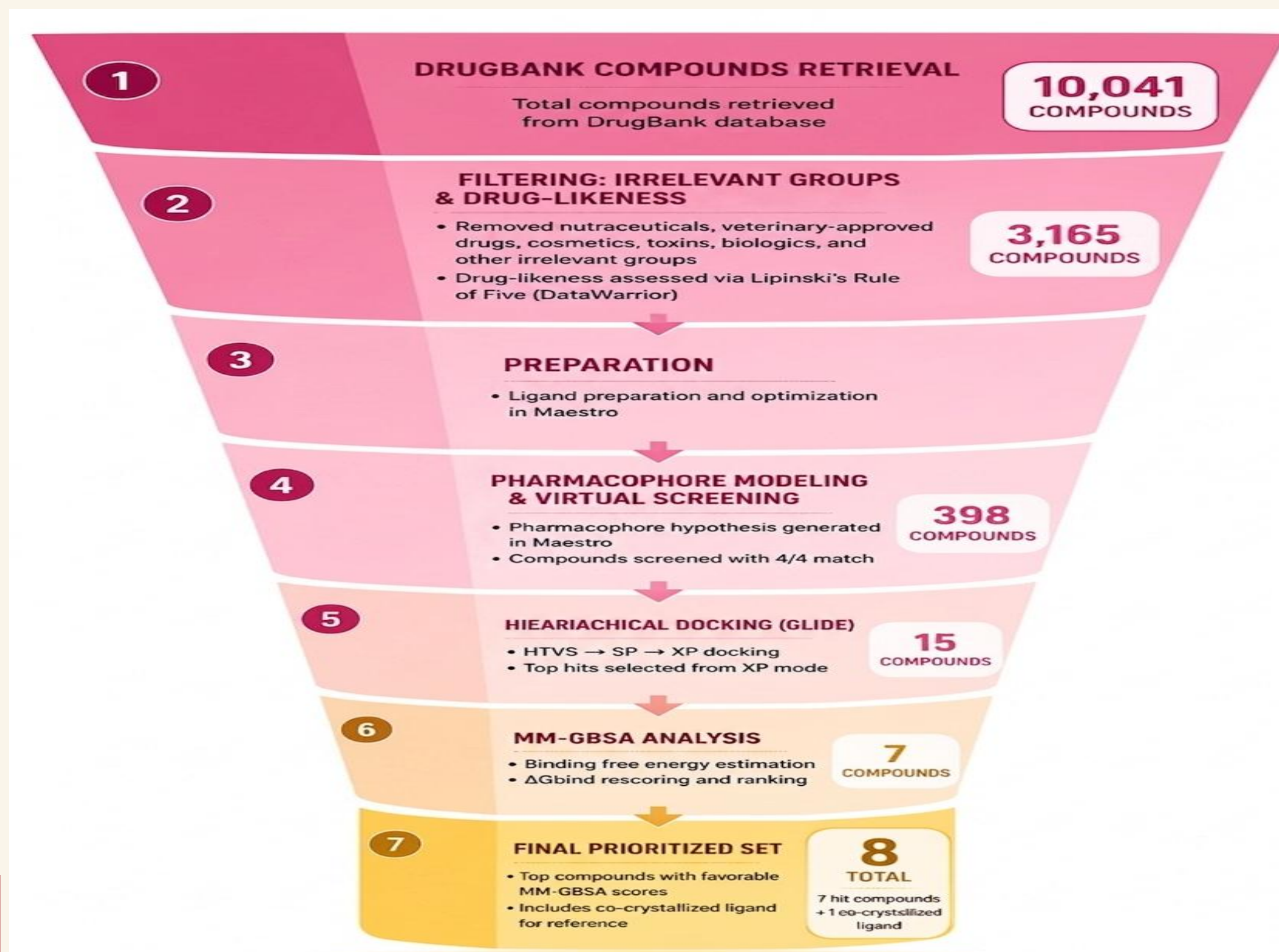


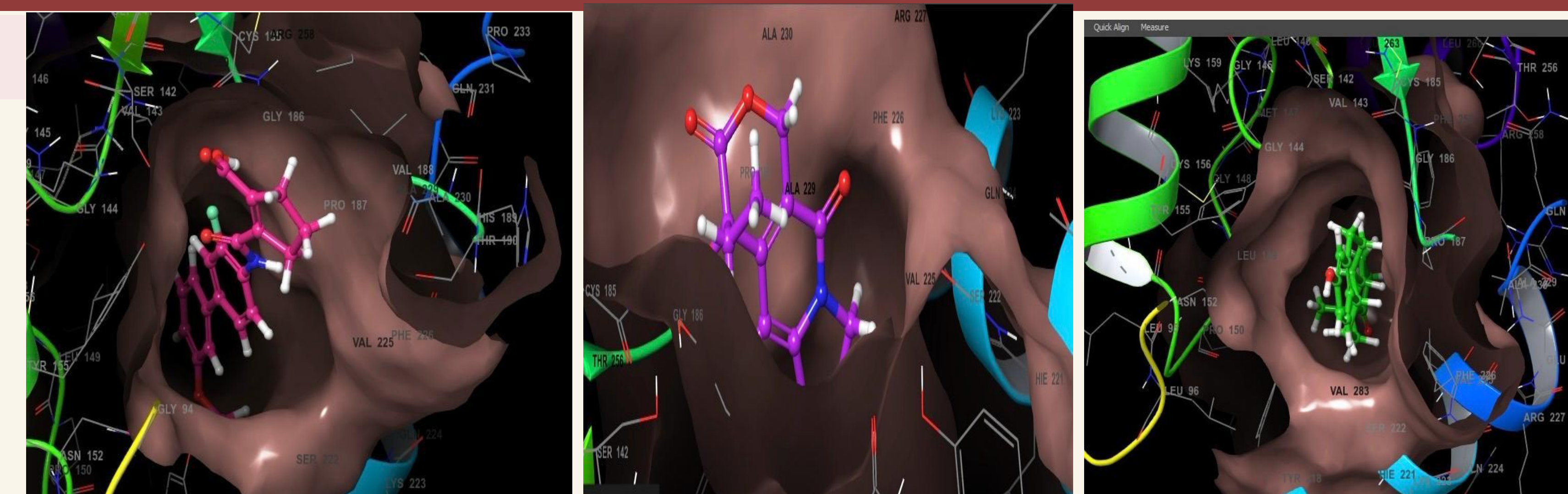
Figure 3 : Virtual Screening Workflow

Target: Human 17 β -HSD1

PDB ID: 6MNE

Resolution: 1.86 Å
Co-crystallized ligand: Estrone and NADPH

Ligand Library: DrugBank



Figures 4,5,6 :Comparative ligand interaction profiles of Vidofludimus, Rubitecan, and the co-crystallized ligand within the 17 β -HSD1 active site. All three ligands occupy the canonical binding cavity defined by catalytic (SER142, LYS159, TYR155), hydrophobic (VAL225, PHE259, PRO187, LEU149, MET279, VAL143), and recognition (HIE221, GLY282) residues.

CONCLUSION

Structure-based virtual screening identified seven lead compounds with stronger docking and MM-GBSA binding energies than estrone, the co-crystallized ligand of the enzyme. Most top hits were camptothecin derivatives, while Vidofludimus is a DHODH inhibitor that may be worth further exploration in relation to pyrimidine metabolism and Warburg-like metabolic reprogramming in endometriosis. By identifying promising repurposable drug candidates against 17 β -HSD1, this research advances **Sustainable Development Goal 3**, promoting better reproductive health and well-being for women living with endometriosis.

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RESULTS

COMPOUND	DRUG CLASS	DOCKING SCORE (kcal/mol)	MMGBSA (kcal/mol)
Exatecan	Anti-Cancer	-9.114	-55.24
Rubitecan	Anti-Cancer	-7.621	-62.15
Vidofludimus	MS, anti-rheumatism	-8.209	-53.32
7-Ethyl-10-Hydroxycamptothecin	Anti-Cancer	-8.203	-55.15
Estrone Sulfate	Hormone replacement	-8.114	-58.50
9-Aminocamptothecin	Anti-Cancer	-7.810	-57.20
Topotecan	Anti-Cancer	-7.372	-58.60
Estrone	Co-crystallized ligand	-6.888	-47.77