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Exploration of the Activity, Delivery and Activation of Androgen Receptor Potential Indane Scaffold Antagonists for Prostate Cancer Treatment

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Exploration of the Activity, Delivery and Activation of Androgen Receptor Potential Indane Scaffold Antagonists for Prostate Cancer Treatment

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Abstract

Androgen receptor (AR)-targeted therapy remains the gold standard strategy for the treatment of advanced prostate cancer. Several compounds of Indane derivatives have been reported to exhibit significant AR antagonist capabilities, starting at a concentration as low as 0.1 μM [2][3][4]. However, an anti-prostate cancer lead molecule derived from an Indane-related scaffold remains elusive. The project will investigate the interaction of novel bioactive indane scaffolds as androgen receptor antagonists through *in silico* and *in vitro* screening to complete the hit-to-lead, while also investigating potential drug delivery and drug activation/sensitisation mechanisms using a combination of colloid nanomaterials and cold atmospheric plasma to target AR-independent, recurrent prostate cancer.

Aims and Objectives

- **This project aims to identify, design and develop potential anti-prostate cancer Indane-related scaffold hits and lead molecules.**
- **To perform *in vitro* cytotoxicity and anti-proliferative assays of the compounds (based on *in-silico* screening) against selected androgen receptor-dependent prostate cancer cell lines.**
- **To investigate potential drug delivery using gold and silver nanoparticles for prostate cancer treatment.**
- **To investigate potential drug delivery and drug activation/sensitisation mechanisms using a combination of colloid nanomaterials and cold atmospheric plasma to target AR-independent, recurrent prostate cancer.**

Introduction

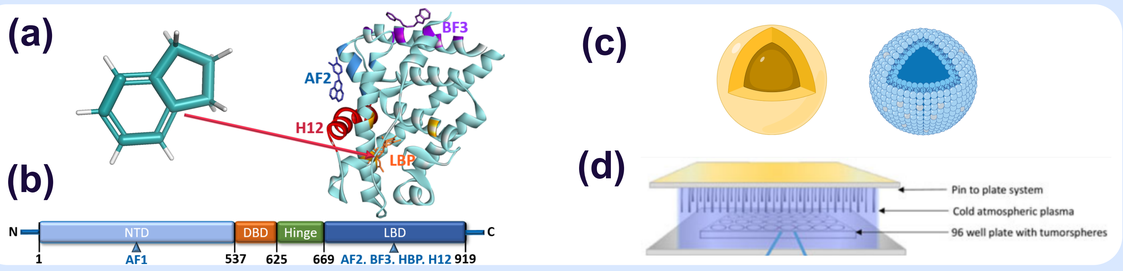
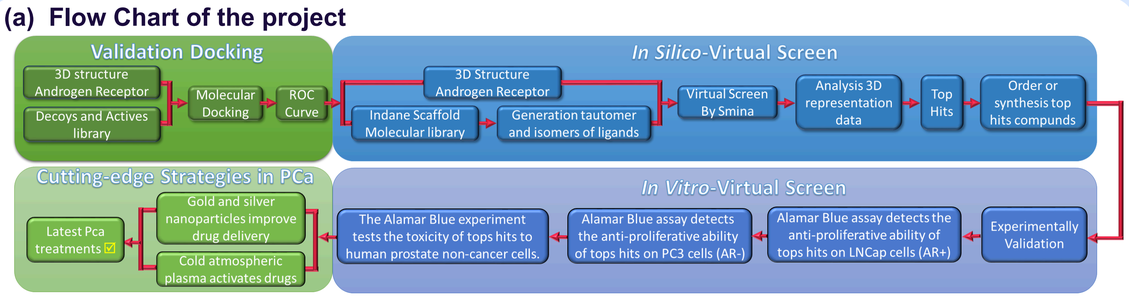


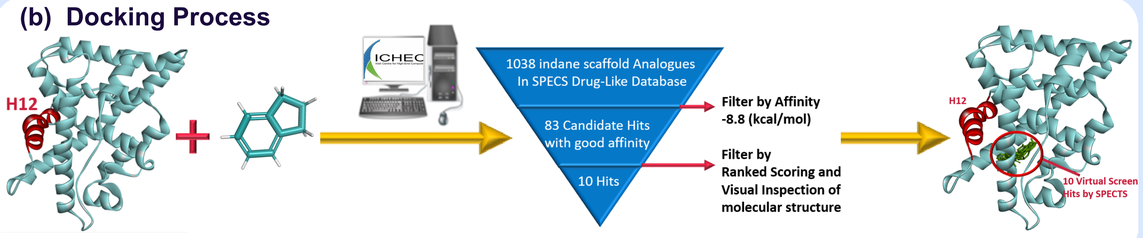
Figure 1: (a) Indane related scaffolds. (b) Androgen receptor and Schematic of AR LBD showing location of cyproterone acetate in LBP (Orange) (PDB ID: 2OZ7), AV6 in AF-2 (Bule) (PDB ID: 2YHD), 17W in BF-3 (Violet) (PDB ID: 4HLW), and helices 12 (Red) . (c) Drug delivery of gold and silver nanoparticles. (d) Pin-to-plates cold atmospheric plasma system.

Methodology

(a) Flow Chart of the project



(b) Docking Process



(c) Alamar Blue Assay Protocol

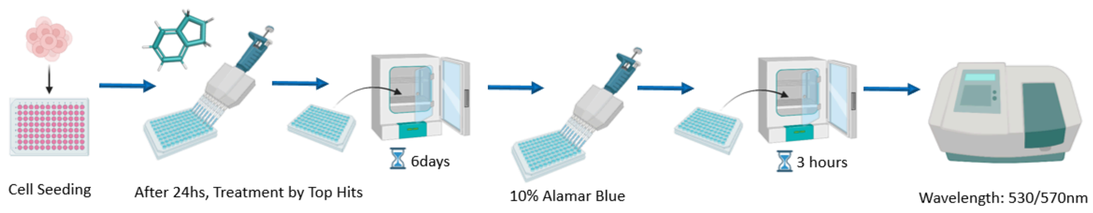


Figure 2: (a) Project flow chart. The first phase involves careful validation of the gridbox parameters, docking algorithm and scoring function using decoys and antagonists (antagonist database). The results of this validation were used to generate ROC curves and determine affinity thresholds. This threshold is then applied to filter the virtual screening results of the indane scaffold library. Phase II, KNIME workflow for generating tautomers and isomers of indan scaffold molecules. PyMOL and Autodock Tools simplify docking preparation, including grid setup, charge addition, and hydrogen incorporation. OpenBabel manages file format conversion of 2D/3D ligands and proteins and implements energy minimization using GAFF force fields. Finally, SMINA software was used to perform large-scale molecular docking on ICHEC. In the third stage, in vitro anti-proliferation experiments were conducted to verify the docking results. In the fourth stage, gold and silver nanoparticles are used to promote targeted drug delivery and explore the role of CAP on drug activation. (b)10 Virtual Screen potential hits from SPECS database. (c) Alamar Blue Assay Protocol.

Results

1. *In Silico*- 2D Docking Result of AR with SPECS Top Hits

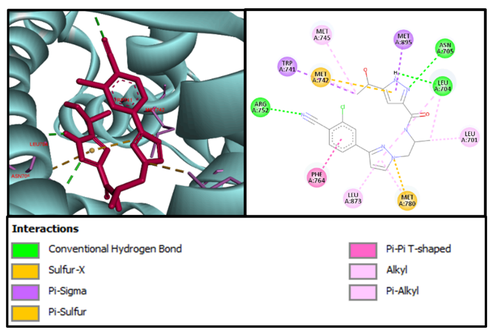


Figure 3: 3D (on left) and 2D (on right) images of Darolutamide docked with androgen receptor (PDB-ID: 2OZ7_wt) using SMINA to dock and BIOVIA Discovery Studio 2021 to generate the images.

Table 1: Affinity of Top Hits

Top Hits Name	Affinity (kcal/mol)
Compound 1	-10.2
Compound 2	-9.4
Compound 3	-9.3
Compound 4	-10.1
Compound 5	-9.5
Compound 6	-10.1
Compound 7	-9.6
Compound 8	-9.3

2. *In Vitro*- Antiproliferative Result with SPECS Top Hits

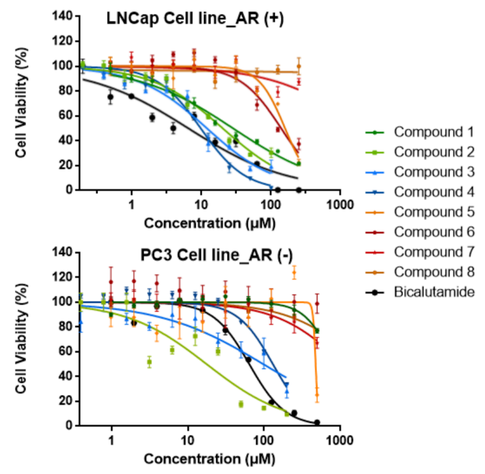


Table 2: IC_{50} Value of SPECS Top Hits

Top Hits Name	LNCaP (AR+) IC_{50} (μM)	PC3 (AR-) IC_{50} (μM)
Compound 1	28.52	>100
Compound 2	20.28	>100
Compound 3	12	>100
Compound 4	9.755	>100
Compound 5	>100	>100
Compound 6	>100	>100
Compound 7	>100	>100
Compound 8	>100	>100
Bicalutamide	6.497	64.31

[a] PC-3, and LNCaP, human prostate cancer cell line.
[b] IC_{50} values were the mean ± standard deviation.

Figure 4: Antiproliferative activity of top specs hits.

3. Cytotoxicity test of AgNPs and AuNPs

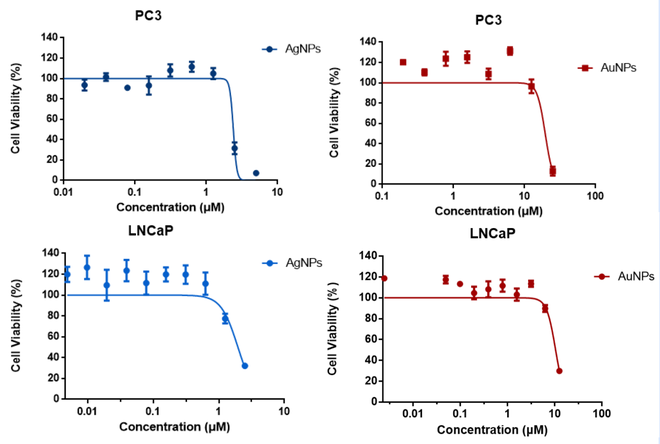


Figure 5: Antiproliferative activity of AgNPs and AuNPs.

4. Cytotoxicity test of CAP.

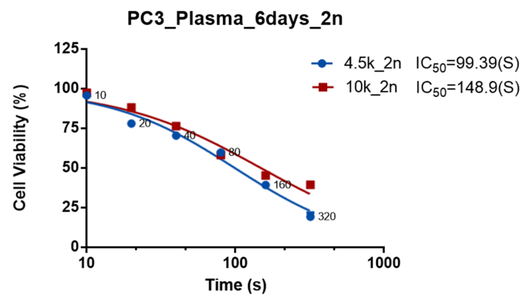


Figure 6: Antiproliferative activity of Pin-to-plates system cold atmospheric plasma from 10s to 320s for PC3 prostate cancer cell line.

Conclusion and Future Work

- **The project currently validates through *in vitro* screening eight potentially bioactive indane scaffolds to be androgen receptor antagonists based on *in silico* screening results. Four of them have lower IC_{50} values.**
- **Future work includes testing the activity of the four virtually screened AR antagonists and benchmarking studies with large-scale molecular dynamics (Amber/Gromacs/NAMD are all available on Kay) or QM/MM simulations.**
- **Based on the *in vitro* results, SAR studies and molecular structure optimization were performed on this new scaffold as a potential anti-prostate cancer drug.**
- **For drug delivery of gold and silver nanoparticles, the next step is to realize the role of drug carriers to improve targeted delivery.**
- **CAP has the potential to be combined with indane drugs as a programmable therapy by enhancing drug uptake, increased cancer cell sensitisation, and facilitating drug activation.**

Acknowledgement

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