Development of DDAH1 inhibitors to regulate angiogenesis in cancer

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Introduction

- Nitric oxide (NO) is an important cellular signaling molecule involved in many biological and pathological pathways.

- High NO levels are associated with poor prognostic outcomes in breast, prostate and colorectal cancers[1-3].

- Endothelial NO promotes angiogenesis (growth of new blood vessels) via inhibiting apoptosis and enhancing cell proliferation, encouraging tumor growth.

- Inhibition of dimethylarginine dimethylaminohydrolase 1 (DDAH1) is an effective strategy to reduce NO synthesis, angiogenesis and tumor cell proliferation in cancer cells[4].

Aims

- To synthesise novel DDAH1 inhibitors with increased potency for applications in cardiovascular disease and cancer.

Methods

- Novel drug molecules were designed based on known inhibitors of DDAH1 and their corresponding inhibitory concentration (IC_{50}) values[4] as a measure of inhibitory potential.

- AutoDock Vina[5] computational software was used to predict ligand-enzyme interactions and affinity of novel drug molecules. Models were visualized using UCSF Chimera[6] depicted in Figure 3.

- Binding mode predictions of proposed chemical structures were compared to L-257, an effective inhibitor of DDAH1.

Chemical Structure Scheme

L-257   **MAD #1-6**
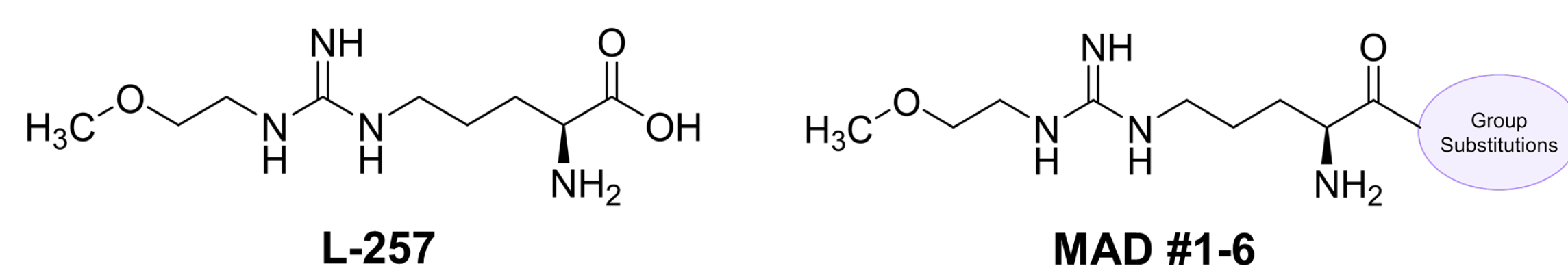
Figure 1 – Left: Chemical structure of the DDAH-1 inhibitor L-257. Right: Chemical structure of the proposed novel molecules MAD #1-6 differing by functional group substitutions at the carbonyl carbon atom of each molecule.

DDAH / NO Pathway
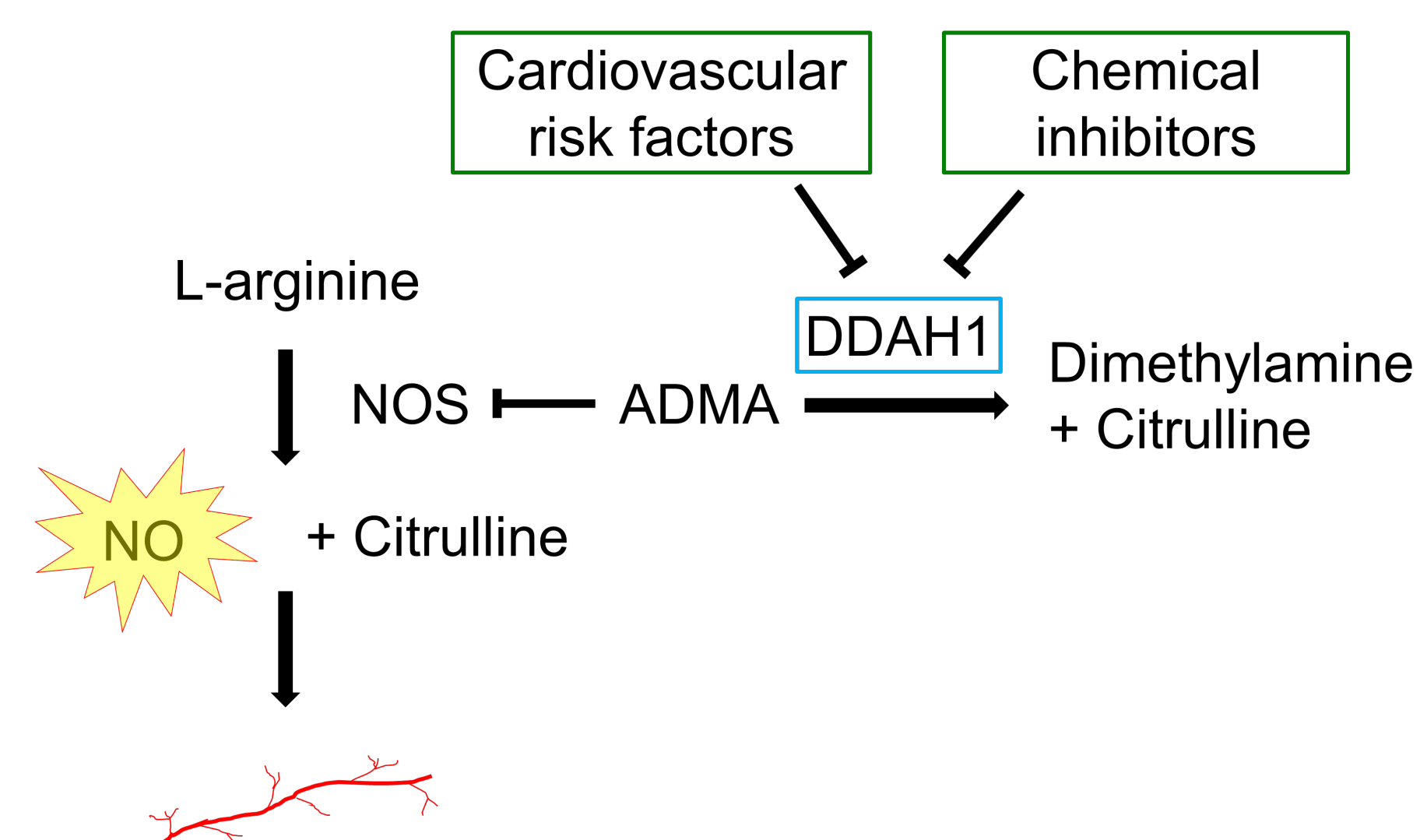
Figure 2 – Cardiovascular risk factors (e.g. diabetes mellitus, hypertension) or chemical inhibitors impair DDAH1 and NO synthesis. Accumulation of asymmetric dimethylarginine (ADMA) inhibits nitric oxide synthases (NOS), reducing NO levels and angiogenesis hence blood vessel growth in targeted cancer.

References

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Ligand-Enzyme Docking Results
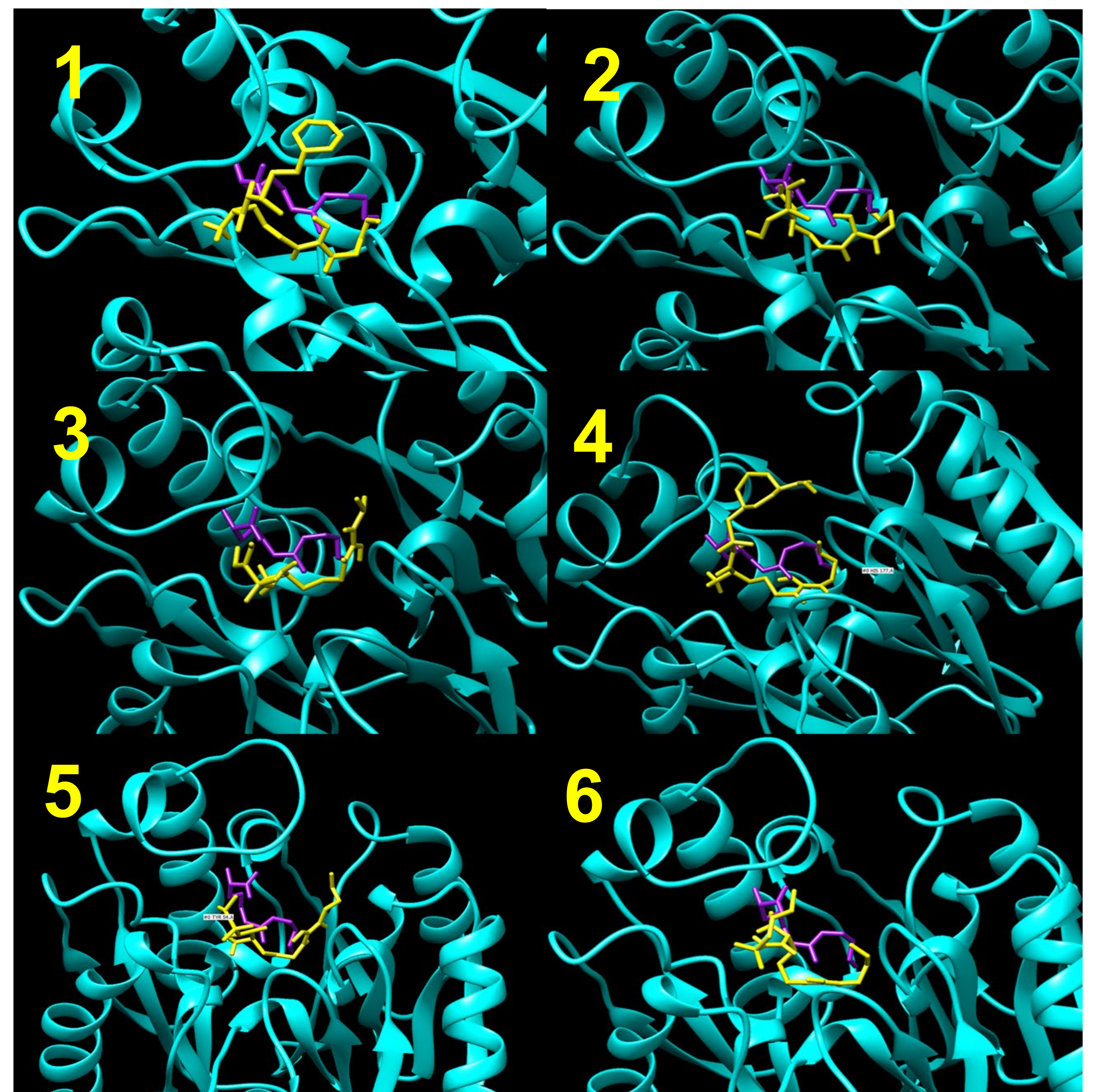
Figure 3 – Crystal structure of DDAH-1 (cyan) with L-257 (magenta) binding at the active site. Novel molecules MAD#1-6 (yellow) were "docked" to compare binding modes with L-257. Similar binding modes and chemical affinity of ligand-enzyme interactions depend on weak intermolecular forces such as hydrogen bonding, van der waals, dipole-dipole and dispersion forces, for example. Other factors include bond length, pH, molecular charge and size.

Discussion and Future Work

Docking results suggest these novel molecules show potential as inhibitors for DDAH1 enzyme. Similar binding modes compared to L-257 suggest comparable affinity. Binding modes were predicted from interactions of ligand functional groups and amino acid residues at physiological pH.

Additional interactions were observed in 1, 4 and 6 indicating a potential for increased binding affinity and superior potency.

Future work will focus on completing the synthesis of molecules MAD#1-6 followed by in vitro characterization of their inhibitory potential by measuring their effect on DDAH1 activity in semi-isolation and in cellular models.

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