TARGETING CHEMOTHERAPY RESISTANCE IN HYPOXIC TUMOURS: RATIONAL DESIGN AND DEVELOPMENT OF NOVEL CARBONIC ANHYDRASE IX INHIBITORS FOR ANTICANCER THERAPY

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SUMMARY

Hypoxic solid tumours frequently develop acidic microenvironments that contribute to therapy resistance, tumour progression, and poor clinical outcome. Carbonic anhydrase IX (CA IX) is strongly induced under hypoxic conditions and supports tumour pH regulation by promoting extracellular acidification while helping cancer cells maintain intracellular pH homeostasis. Because of its tumour-associated expression and extracellular catalytic domain, CA IX represents an attractive target for the development of selective anticancer agents.

This thesis aimed to prioritise newly designed CA IX inhibitor candidates using an integrated rational drug design workflow. The work combined ChEMBL data curation, reproducible KNIME-based QSAR modelling, applicability domain analysis, molecular docking into selected CA IX structures, QikProp-based physicochemical and ADMET profiling, and preliminary synthesis of selected compounds. Regression and classification QSAR models were developed and validated using both random and Murcko scaffold-based splitting strategies. Scaffold-based validation was used as a more stringent estimate of model generalisation toward less familiar chemical scaffolds.

The computational workflow identified Series 3 as the most balanced group from a ligand-based perspective, while some Series 2 compounds were retained as exploratory high-potency candidates. Docking into 5FL4 and 6QN2 showed that ligand-based and structure-based rankings did not fully overlap, supporting the use of docking as a complementary prioritisation tool. Compound **3k** emerged as the most balanced candidate overall, combining QSAR support, favourable docking in 6QN2, and acceptable predicted drug-like properties. Compound **2f** was retained as a strong exploratory candidate, while **4d15** was interpreted as a docking-driven outlier. Four selected sulfonamide-containing triazole derivatives were synthesised as preliminary experimental candidates, although enzymatic inhibition data were not available within the timeframe of this thesis.

Overall, this work established a reproducible computational prioritisation framework and provided an initial set of candidates for future CA IX inhibition assays, selectivity evaluation, and further optimisation.