Politechnika Śląska
Wydział Chemiczny
Katedra Chemii Organicznej, Bioorganicznej i Biotechnologii

mgr inż. Anna Byczek-Wyrostek

ROZPRAWA DOKTORSKA

Synteza i ocena aktywności biologicznej wybranych pochodnych kwasu dichloromukowego w warunkach *in vitro* wobec modelowych linii komórek nowotworowych

Synthesis and evaluation of biological activity of selected dichloromuco acid derivatives in vitro against model cancer cell lines

Promotor: prof. dr hab. inż. Krzysztof Walczak

Gliwice 2023

ABSTRACT OF PhD DISSERTATION

"Synthesis and evaluation of biological activity of selected mucochloric acid derivatives *in vitro* against model cancer cell lines"

Anna Byczek-Wyrostek, M.Sc., Eng.

Supervisor: Professor Krzysztof Walczak, PhD, DSc

The objective of the dissertation was to determine antiproliferative and anticancer properties of mucochloric acid derivatives containing various substitutes in the C4 and C5 positions of 2(5*H*)-furanone ring which allow modulation of the molecule's lipophilicity. The obtained data served as a basis for determining the mechanism of action of selected mucochloric acid derivatives.

The investigated compounds were prepared in reaction of 3,4-dichloro- or 3,4-dibromo-5-hydroxy-2(5*H*)-furanone with alcohols and aromatic amines. The obtained 5-alkoxy derivatives of 3,4-dichloromuco acid (**AB-09**, **AB-11**) display strong cytotoxic activity and better selectivity against cancer cells compared to the parent compound. The observed cytotoxic effect of the **AB-09** compound results from cell cycle arrest in the G2 phase. This derivative was also able to initiate caspase-independent apoptosis in A549 cells. Exposition of A549 cells to **AB-09** significantly decrease they clonogenic potential.

A separate group of derivatives consisted of silyl ethers of dihalogenomuco acid. Silyl derivatives exhibit a regulatory effect on proapoptotic activity. This effect is most noticeable in compounds **AB-22**, **AB-24** and **AB-25**. The first derivative, containing a *tert*-butyldimethylsilyl group, shows the best properties in inhibiting the proliferation of HCT 116 wt cells (IC_{50} = 1.4 μM), but it did not induce apoptosis. In contrast, the **AB-24** compound, containing a triisopropylsilyl (TIPS) group in its structure, induces cell death in the HCT 116 wt line in just 24 hours. This effect is ascribed to a better cell membrane penetration by silylated derivatives of 3,4-dibromomuco acid. The two most active compounds – **AB-24** and **AB-25** – have the highest LogP values (4.06 and 4.68 respectively). It can suggest that among all the investigated compounds these two can be the most effective in the penetration of cell membranes. Another explanation for the higher pro-apoptotic activity of **AB-24** is that the presence of a large TIPS group enhances the interaction between the molecule and its intracellular target.

It cannot be excluded that the obtained compounds can also act as prodrugs. It is known that depending on the steric hindrance on the silicon atom, the hydrolysis speed will differ significantly between the derivatives. It would confirm the hypothesis that the TIPS group in the **AB-24** compound increases its interaction with molecular targets. Initial research of the derivatives' activity shows that **AB-24** can act by targeting survivin what eventually leads to inducing caspase-dependant apoptosis.