Design and Synthesis of Novel Azo–Estradiol Conjugates: Effects of Para-Substituents on Radical Scavenging Activity

Rovira-Denton, Ricardo (School: Colegio San Ignacio de Loyola)

Oxidative stress is a harmful bodily process which is linked to diseases like cancer and heart disease. Azo dyes have demonstrated bioactivity, specifically antioxidant and antibacterial properties. Estradiol binds to the estrogen receptor in hormone-dependent breast cancer cells and has been shown to inhibit TNBC. However, azo dyes and estradiol conjugates haven't been evaluated to determine potential dual-action properties. This study synthesized a novel molecular class of aniline-derived azo–estradiol conjugates (4-H, 4-Cl, 4-Br) and tested their antioxidant activity. Synthesis proceeded through diazotization, followed by electrophilic aromatic substitution with estradiol to form the azo linkage. Isolated yields for all conjugates exceeded 40%. Purification included liquid-liquid extraction and column chromatography. To characterize the compounds, melting point range, FT-IR spectroscopy, and NMR spectroscopy were analyzed. Radical scavenging activity was evaluated through the ABTS assay, and log-transformed linear regression was used to analyze dose-response behavior. The most effective antioxidant was the 4-chloroaniline-derived azo–estradiol (IC50=273.25 μg/mL), followed by the 4-bromoaniline-derived azo–estradiol (IC50=360.40 μg/mL), and lastly by the aniline-derived azo–estradiol (IC50=426.60 μg/mL). Dose-response trends were significant (R^2>0.90, $p<0.05$). Results showed that halogen substitution improves antioxidant activity through substituent electronic effects that stabilize radical intermediates within the conjugated azo–aromatic system. These compounds have promising biomedical potential due to cost-effective synthesis, antioxidant activity, and lipophilic structures, which is expected to improve drug delivery and hormone-related targeting in breast cancer.

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