THEORETICAL AND EXPERIMENTAL STUDIES TOWARDS THE SYNTHESIS OF POTENTIAL ESTROGEN MIMICS

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Abstract: Naturally occurring compounds such as flavanoids and isoflavones, which are found in green tea, soybeans, and fish, have been shown to be beneficial in breast cancer treatment through binding to estrogen receptors. Other natural products such as 11-deoxyfistualrin-3 are cytotoxic against estrogen dependant MCF-7 breast cancer tissue. The investigation of the spiroisoxazoline, 11-deoxyfistularin-3, and the synthesis of closely related spiroisoxazoline analogues, can determine if this compound is an estrogen mimic, and which functional groups may be responsible for the biological response. The purpose of this project was to model 11-deoxyfistualrin-3 with known breast cancer pharmaceutical compounds to determine if there is any overlap of the functional groups in the estrogen receptor active site. If any overlap were present between the two compounds, then analogues of the natural product would be synthesized for \textit{in vitro} estrogen receptor binding studies. FlexS and FlexX molecular modeling programs were used to study the natural product, potential synthetic analogues, and the pharmaceutical compound. The synthesis of the 4,5-dihydroisoxazole precursor to an analogue of 11-deoxyfistularin-3 was accomplished by using 1,3-dipolar cycloaddition with a functionalized alkene. The cycloaddition of Methyl 2-(bromomethyl)acrylate with (4-Methoxyphenyl)hydroximoyl chloride using triethylamine in chloroform afforded only the 5,5 disubstituted 4,5-dihydroisoxazole regioisomer. The synthesis of the spiroisoxazoline, 8-Methoxy-3-phenyl-1-oxa-2-aza-spiro[4.5]deca-2,7-dien-6-one, was accomplished through the cyclization and alkylation of the decarboxylated isoxazoline precursor, 5-(2-Ethoxycarbonyl-3-oxo-butyl)-3-phenyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester.

Keywords: 11-Deoxyfistularin-3, MCF-7 breast cancer, and Spiroisoxazoline.

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