15th International Conference on the Chemistry of Se &Te
Universidade Federal de Santa Catarina, Florianópolis – Brazil
Nov 28 - Dec 02, 2022 – Hotel Jurerê Beach Village – www.iccst15.com.br

Designing Se-mall Molecules as Potential Cancer Therapeutics

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Our studies and literature evidence have shown that the position of the selenium (Se) atom as well as other structural features of a small molecule dictate the overall potency of a compound. This is particularly true in terms of their application as cancer therapeutics as several newly designed Se molecules have shown promising therapeutic efficacy in preclinical cancer models. Over the past few years, our laboratory has been involved in designing and synthesizing novel Se-containing drug-like compounds. Notable examples include the incorporation of Se into naturally occurring isothiocyanates to create potent isoselenocyanates and into temozolomide (TMZ) to obtain Se-TMZ which effectively reduced tumor growth in various cancer models. More recently, through extensive SAR studies based on compounds designed by incorporating Se in NSAID structures, we identified a novel Se-aspirin hybrid selenazolidine analog AS-10. Traditionally, the synthesis of selenazolidines requires the use of isoselenocyanate or selenourea intermediates and/or several catalysts. However, AS-10 and its analogs followed an easy and highly efficient method to obtain bioactive selenazolidines. In the first step, an unexpected cyclization takes place between 2-bromoethylamine hydrobromide and KSeCN to render selenazolidine intermediate which reacts with one molecule of acid chloride to form the monosubstituted selenazolidine intermediate through a S_NAc mechanism. Finally, depending on the nature of the acid chloride used the disubstituted selenazolidine is formed with another molecule of acid chloride. Our studies suggest that the most critical condition is the position of the acyl group, which ought to be in a benzylic position to selectively obtain disubstituted selenazolidines, while the aliphatic acyl chlorides lead preferably to monosubstituted selenazolidines or a mixture of the two. Hence, depending on the nature of the acid chloride and the reaction temperature, the ratio of the obtained products can be modulated. Interestingly, the selenazolidine-derived from aspirin (AS-10) possessed striking antitumor activity. It was >300 times more potent than aspirin and showed efficacy in both in vitro and in vivo cancer models, both as a single agent and in combination with chemotherapy. Overall, our studies clearly demonstrate that the appropriate incorporation of Se into small drug-like molecules can significantly enhance anticancer activity, and thus designing novel Se compounds could be a valid avenue to create future cancer drugs.