Modification of an with μ-opioid receptor affinity to reduce lipophilicity
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The di-iodinated peptide DMT-D-Ala-Phe-Phe (DAPP) was found to have high affinity and selectivity for μ-opioid receptors of cancer cells. Radioliodination of this peptide could aid in imaging of tumors; however, the molecule’s high lipophilicity would not allow easy travel in vivo. In order to reduce lipophilicity but keep the μ-receptor affinity, two alternative peptides were produced using solid phase synthesis: DMT-D-Ala-Phe-Orn and DMT-Nva-Phe-Orn. Their structure and purity were evaluated using LCMS and amino acid analysis. To further reduce the lipophilicity, two methods for mono-iodination were investigated on Boc protected dimethyltyrosine (Boc-DMT). In the first, commonly accepted iodination method, N-iodosuccinamide (NIS) was used as the iodinating reagent. Two equivalents of NIS were reacted with Boc-DMT in phosphate buffer solution (pH 7.4). A mixture of mono- and di-iodinated products was produced, and the percent di-iodinated product increased with reaction time. The second iodination method used bis(pyridine)iodonium tetrafluoroborate (IPy₂BF₄) as the iodinating agent with tetrafluoroboric acid (HBF₄) catalyst. Optimization of this method was done by varying the reaction time, solvent, and equivalents of IPy₂BF₄. The optimal conditions (those producing the most mono-iodinated products and least by-products) were found to be using 2 equivalents of IPy₂BF₄ for 5 minutes in methanol. The scale of the reaction did not affect the reaction speed or product distribution. After work up with water and ethyl acetate, the mono-iodinated Boc-DMT will be purified through column chromatography. The 2 new peptides should be synthesized again with the iodinated Boc-DMT. Lipophilicity of these new molecules should be tested. Mono-radio-iodination can be done using the same method, and biological evaluations of the molecules will be conducted.