Title: **Synthesis and Cyclisation of a Peptide Inhibitor of the MDM2-p53 Interaction.**

Student: Andrea González Muñoz

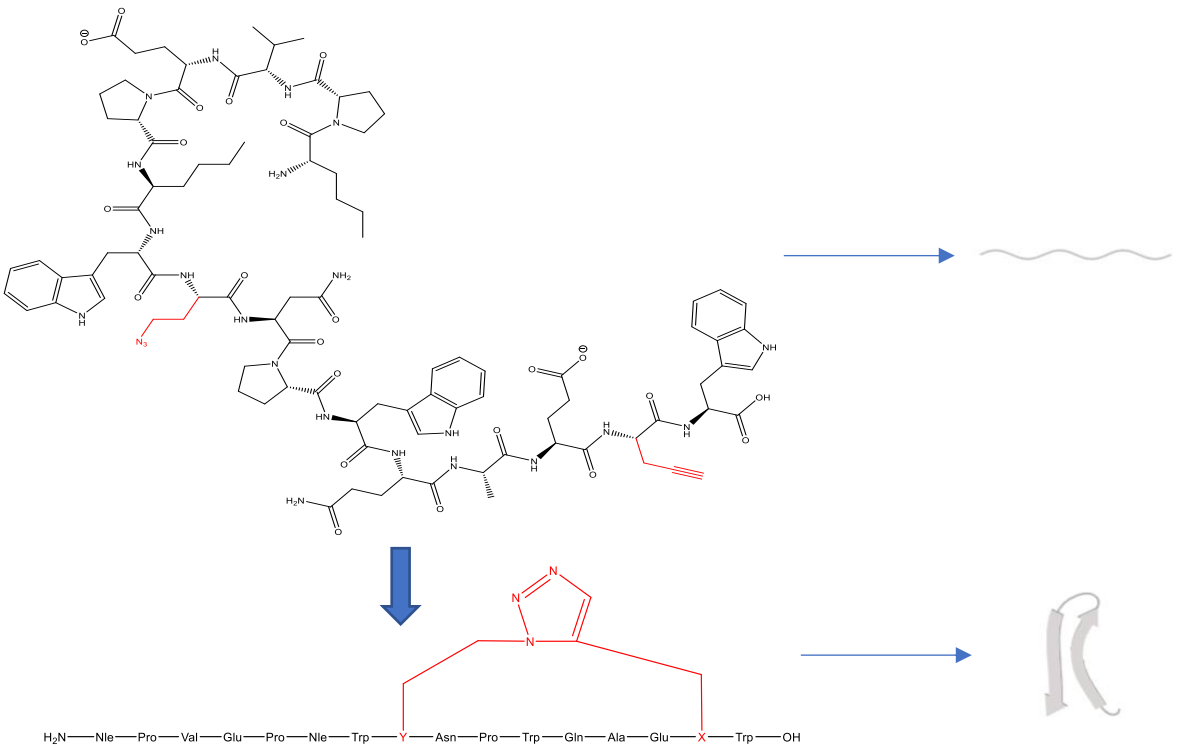
Date: February 2020

Supervisor/s: Dr. Andrew Jamieson
School of Chemistry, University of Glasgow.
Danielle Morgan
PhD Student

MDM2 (Murine Double Minute 2) is a negative regulator of the p53 tumor suppressor. MDM2 binds to the N-terminal transactivation domain of p53, forming a complex and targeting the protein for its degradation. Increased levels of MDM2 occur in many tumours, impeding the activity of p53. p53 is not able to carry out the apoptotic and cell cycle arrest functions in order to stop the growth of damaged cells. A peptide was identified from a Phage Display Library and assessed as a ligand capable to bind MDM2. In theory, this peptide could work as an inhibitor of the MDM2-p53 interaction. It is known that the bioactive conformation of the peptide is a turn. The main hypothesis of this project was to synthesise and cyclise the peptide, to adopt this conformation.

First step was to synthesise the peptide and then constrain it into a turn mimic using a staple. This process was accomplished by using a RuAAC, giving a 1,5-disubstituted 1,2,3-triazole bridge which works as a disulfide surrogate bridge mimic.

The completeness of the reaction was monitored using IR, observing the disappearance of the azide absorbance at 2100 cm^{-1}.



Scheme 1: *Synthesis and subsequent cyclisation of the peptide in order to constrain it into a turn conformation.*