Description of a Novel Fameshifting Site in the 5'UTR of SARS-CoV-2 as a Potential Drug Target

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Abstract

SARS-CoV-2 is an enveloped positive-sense single-stranded RNA coronavirus that causes COVID-19 whose present outbreak has cost a high number of casualties throughout the world. The aim of this work was to scan the SARS-CoV-2 genome in search for new therapeutic targets. We found a sequence in the 5'UTR (NC 045512:74-130), consisting of a typical heptamer next to a structured region that may cause frameshifting. The potential biological value of this region is shown by its similarity with other coronaviruses related with SARS-CoV and its sequence conservation within isolates from SARS-CoV-2. We have predicted the secondary structure of the region by means of different bioinformatic tools. We have chosen a probable secondary structure to proceed with a 3D reconstruction of the structured segment. We carried out virtual docking on the 3D structure to look for a binding site and then for drug ligands from a database of lead compounds. Several molecules that would probably administered as oral drugs show promising binding affinity within the structured region and so it would be possible interfere the potential regulatory role of our sequence of interest.

Full Text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed. However, the manuscript can be downloaded and accessed as a PDF.

Figures

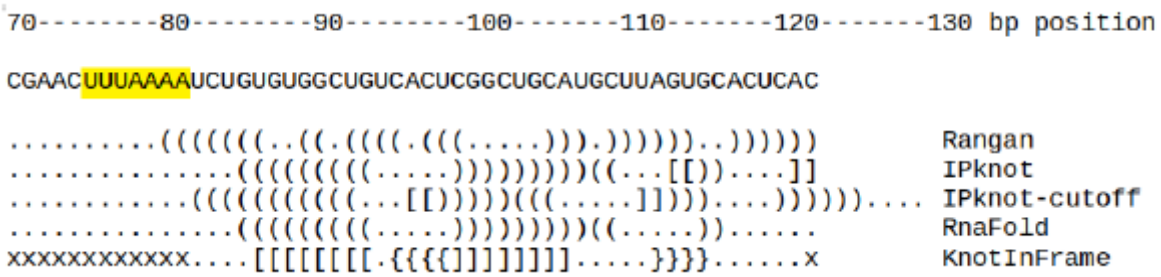

Figure 1

Segment of 5'UTR NC_045512 sequence and different predicted secondary structures. The slippery heptamer is highlighted in yellow.

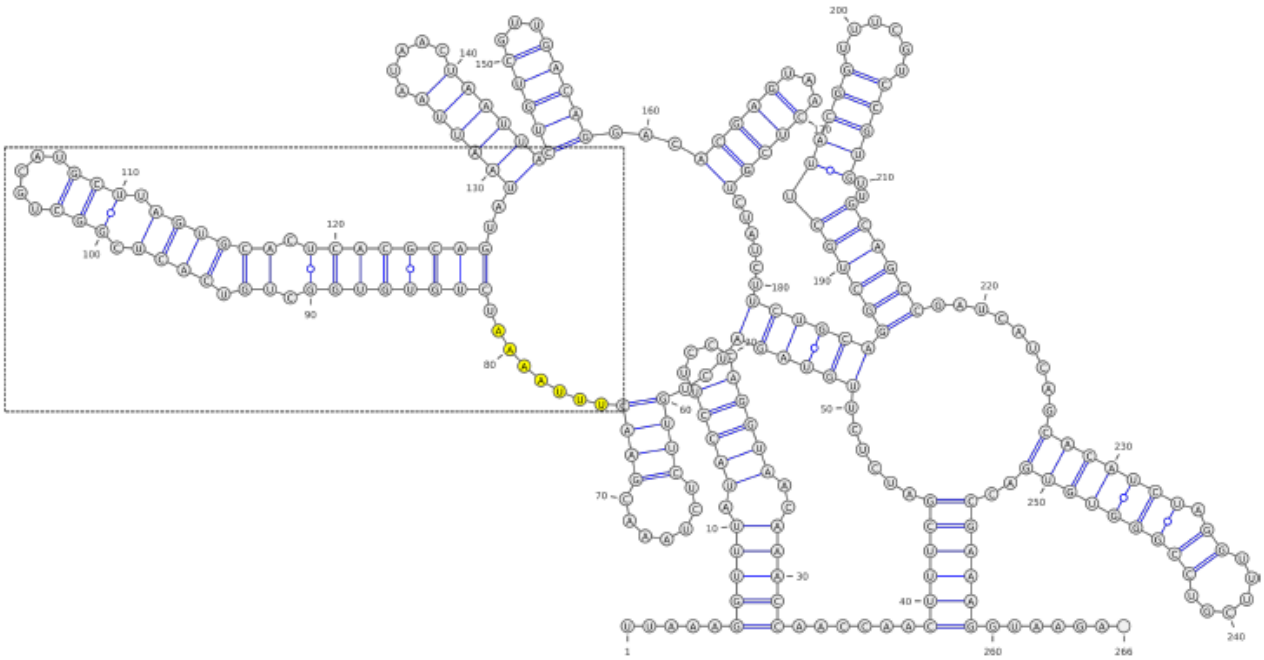

Figure 2

Secondary structure of 5'UTR region of NC_045512 as predicted by RNAfold. Region of interest framed on the top left. Slippery sequence in yellow.

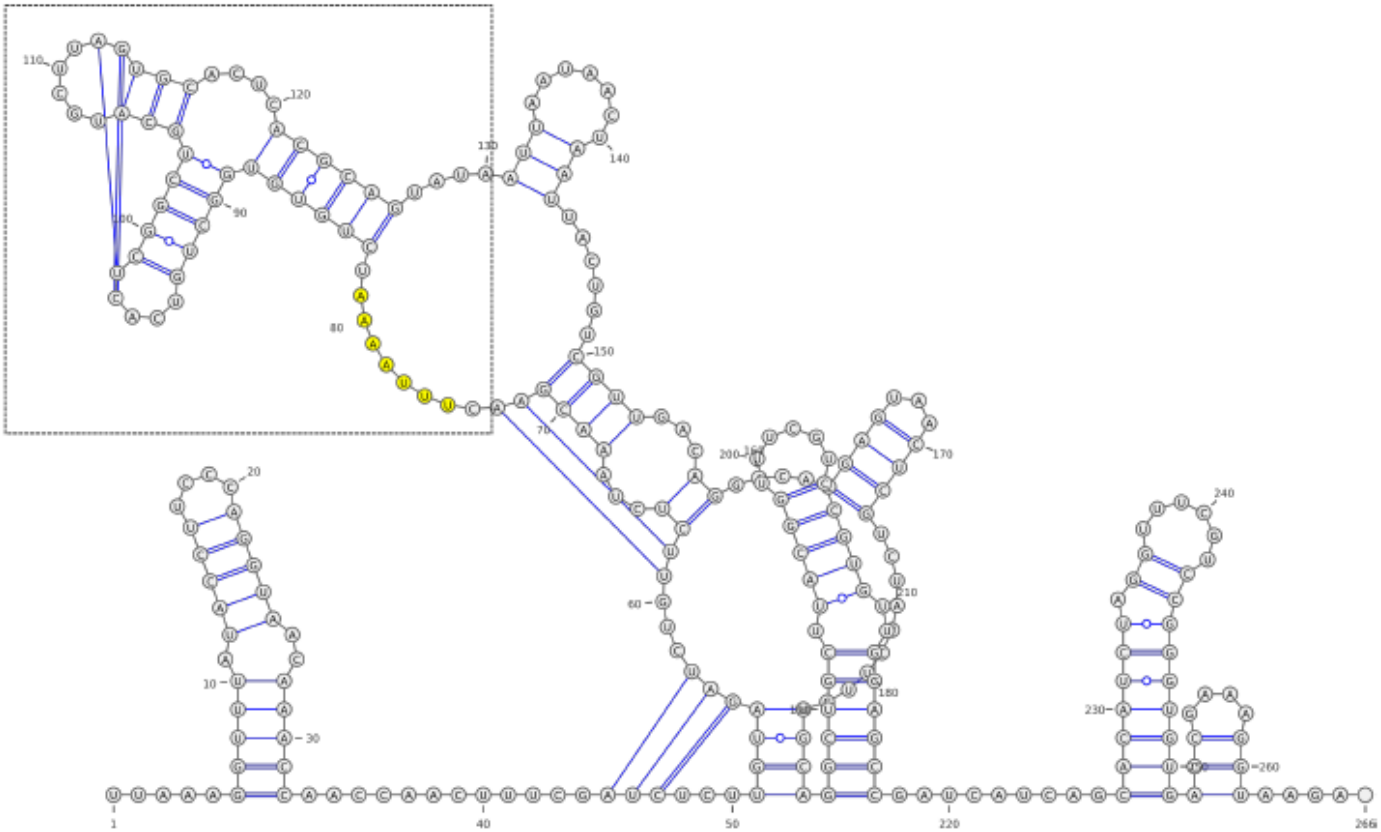

Figure 3

Secondary structure of 5'UTR region of NC_045512 as predicted by IPKnot.Region of interest framed on the top left. Slippery sequence in yellow.

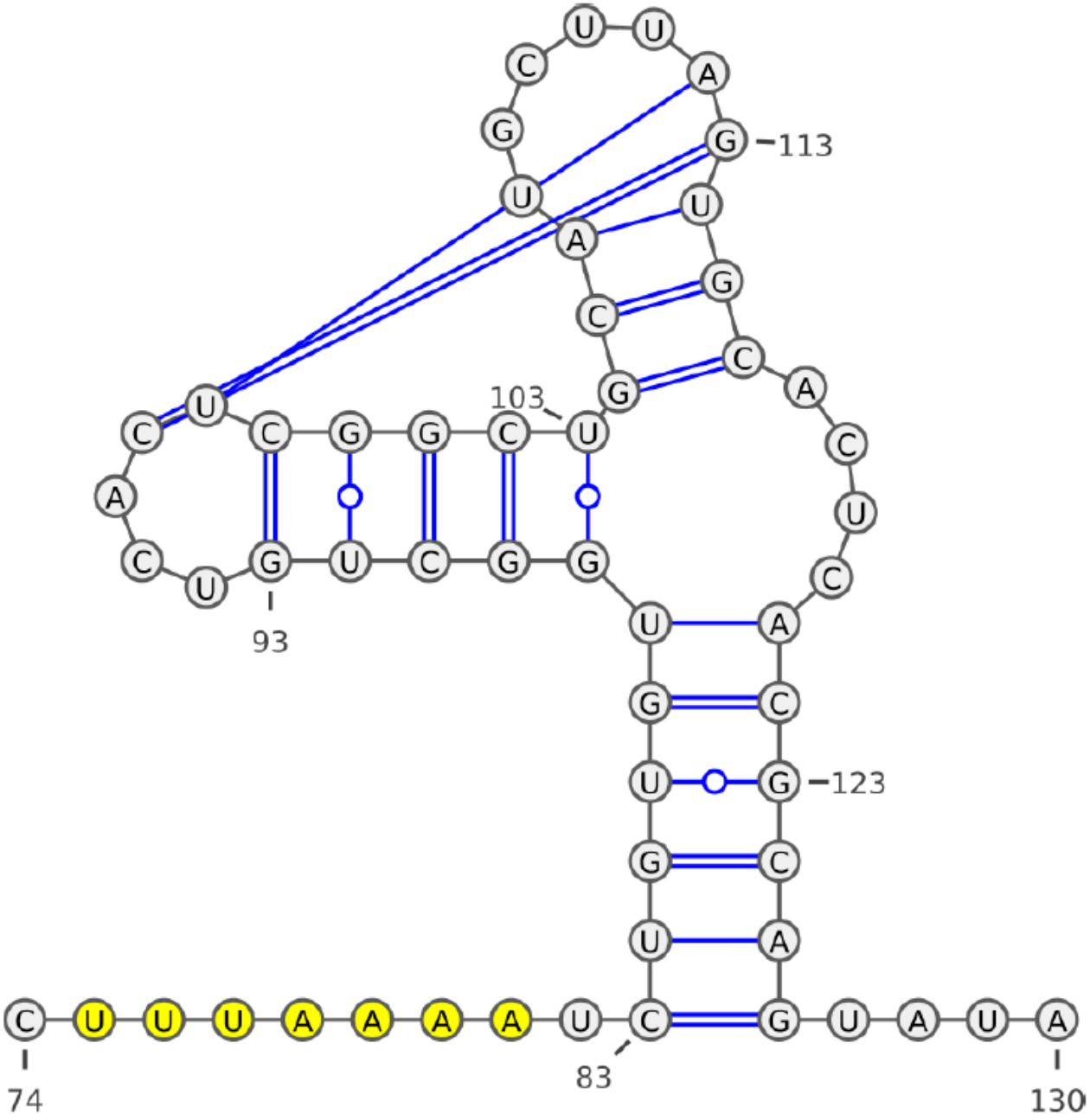

Figure 4

Detail of the secondary struture predicted by IPKnot from posi-tions 74:130 of NC_045512. Slippery sequence in yellow.

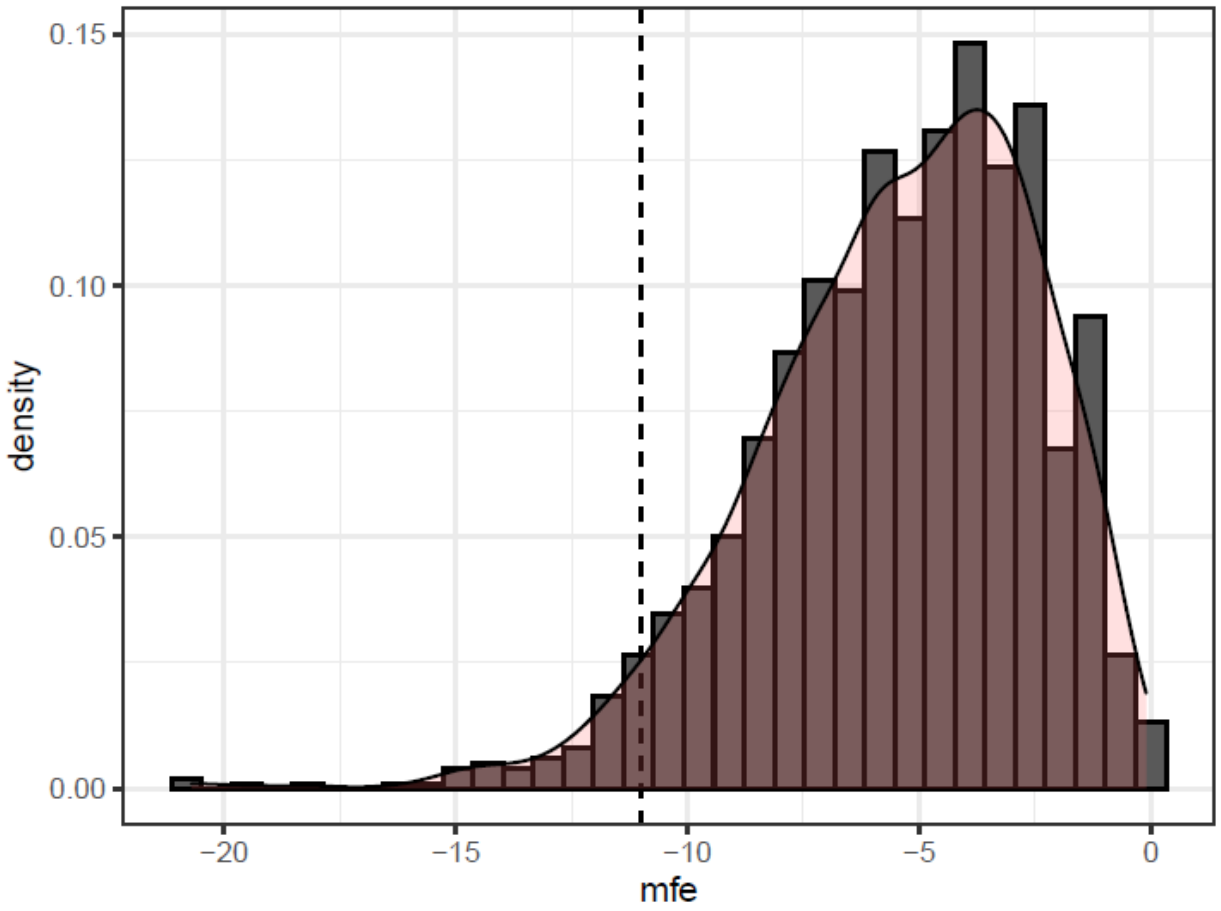

Figure 5

The histogram and density curve of the minimum free energy values of random sequences from NC_45512.2 of the same length as the sequence of interest. The vertical line at -11 Kcal/mol shows the computed MFE for the sequence of interest.

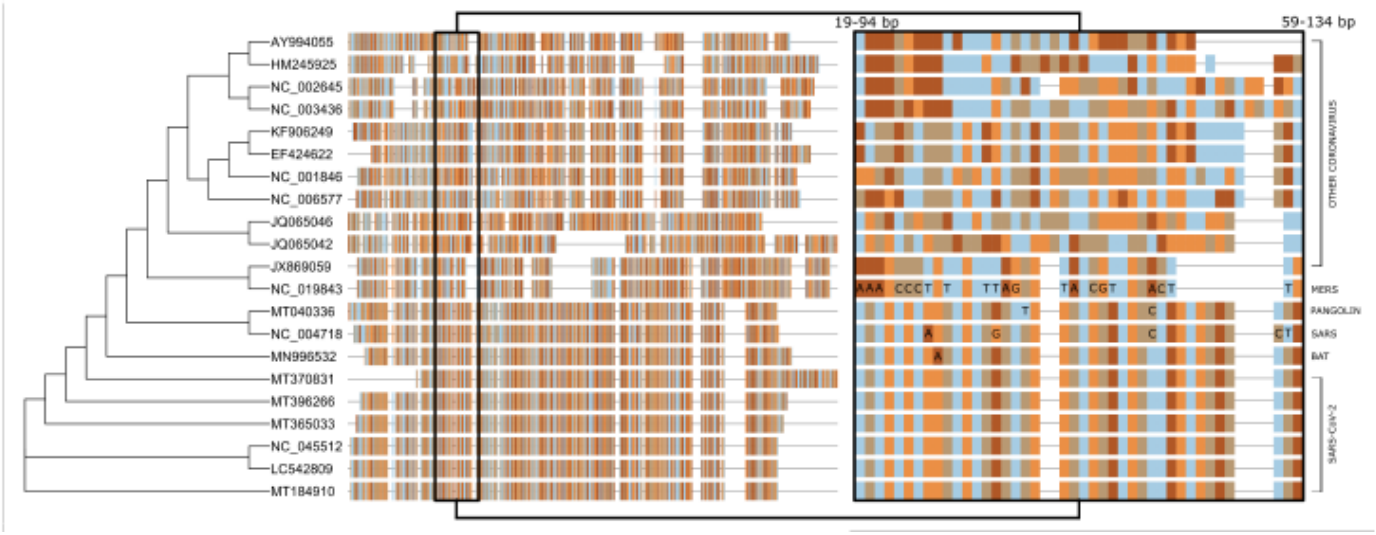

Figure 6

A cladogram and multiple sequence alignment. The middle part shows the alignment of the region in 21 coronaviruses. On the left, are shown the groups of sequences in terms of similarity. A zoomed in view on the region of the sequence of interest is shown on the right.

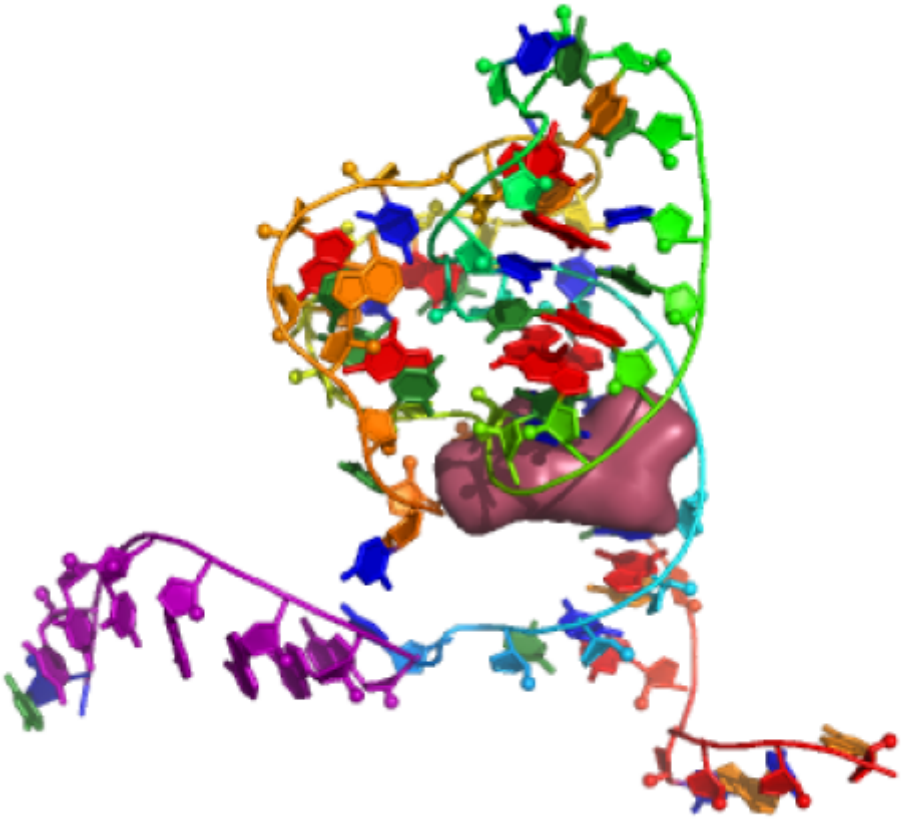

Figure 7

Graphical representation of the nucleotide backbone of the se-quence of interest. The sequence of interest is shown from the 5' end (left) to the 3' end (right). The rounded purple volume in the middle shows the active site as predicted by the AutoDock suite tools. The slippery sequence is on the left bottom, in purple colour, the rest of nucleotide pieces are coded accorging to chemical composition.

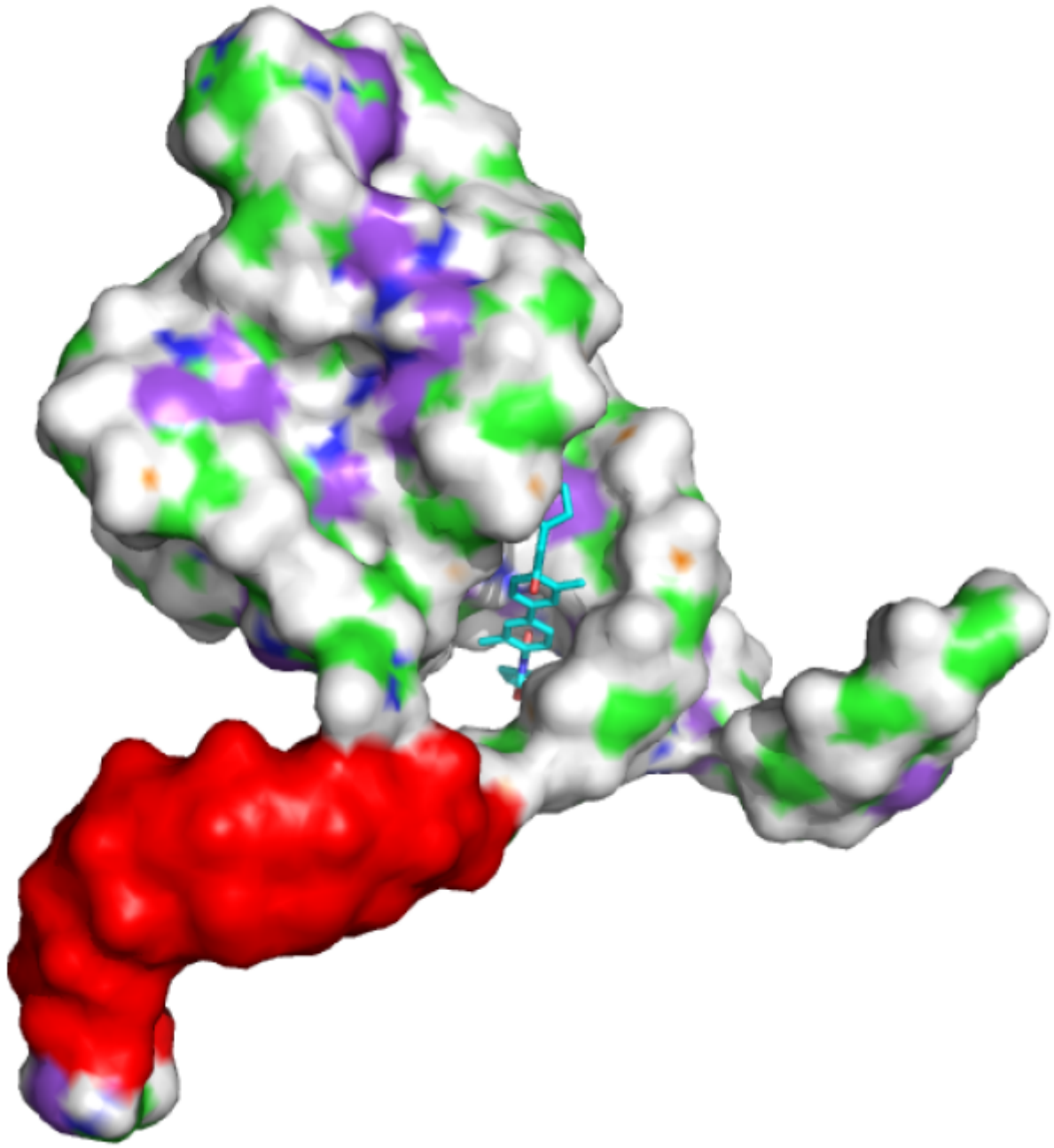

Figure 8

Side view of the sequence of interest in a surface representation. The red area on the left shows the slippery sequence. The active ligand site holds one of the best matches:NSC308835/pubChem328761 (see Table 3) in its docked position.