



Predicting binding modes of flavonoids to DNA using AutoDock Vina

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DNA-Ligand Binding: Numerous pharmaceutical compounds rely on the ability of small molecules to bind to DNA. There are three ways in which small molecules can bind to DNA: groove binding, intercalation and mixed binding.

Groove Binding

The helical nature of DNA generates two grooves, the major groove and minor groove. Small molecules can bind to the minor groove by wrapping themselves around the minor groove.

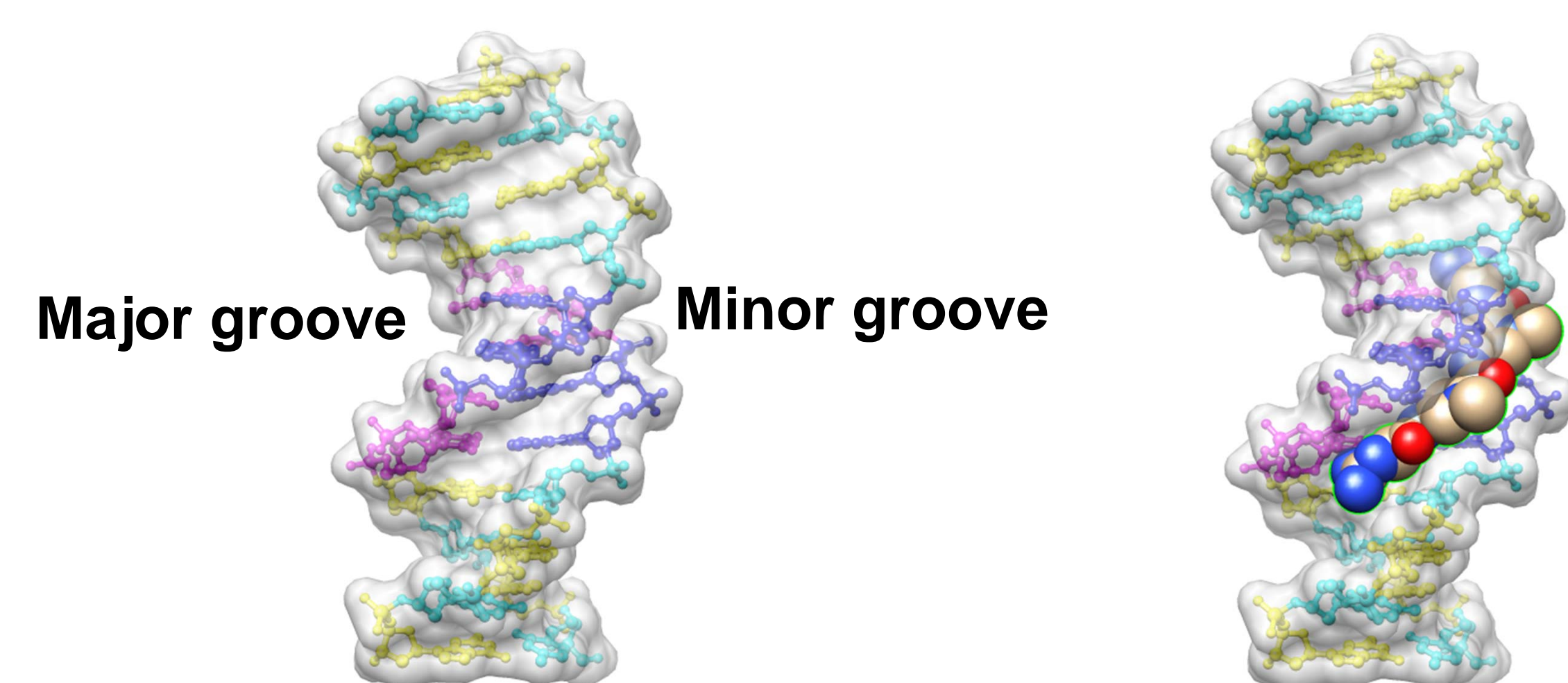


Figure 1: The helical nature of DNA leads to the formation of two grooves, the major groove and the minor groove (left). A small molecule can wrap themselves around the helix and bind to the minor groove of DNA (right).

Intercalation

The normal spacing between adjacent base pairs in DNA is 3.5 Angstroms. Small, planar molecules can insert themselves between two adjacent base pairs widening the gap between them to around 7 Angstroms. This enlarged space is called an intercalation gap. (Figure 2)

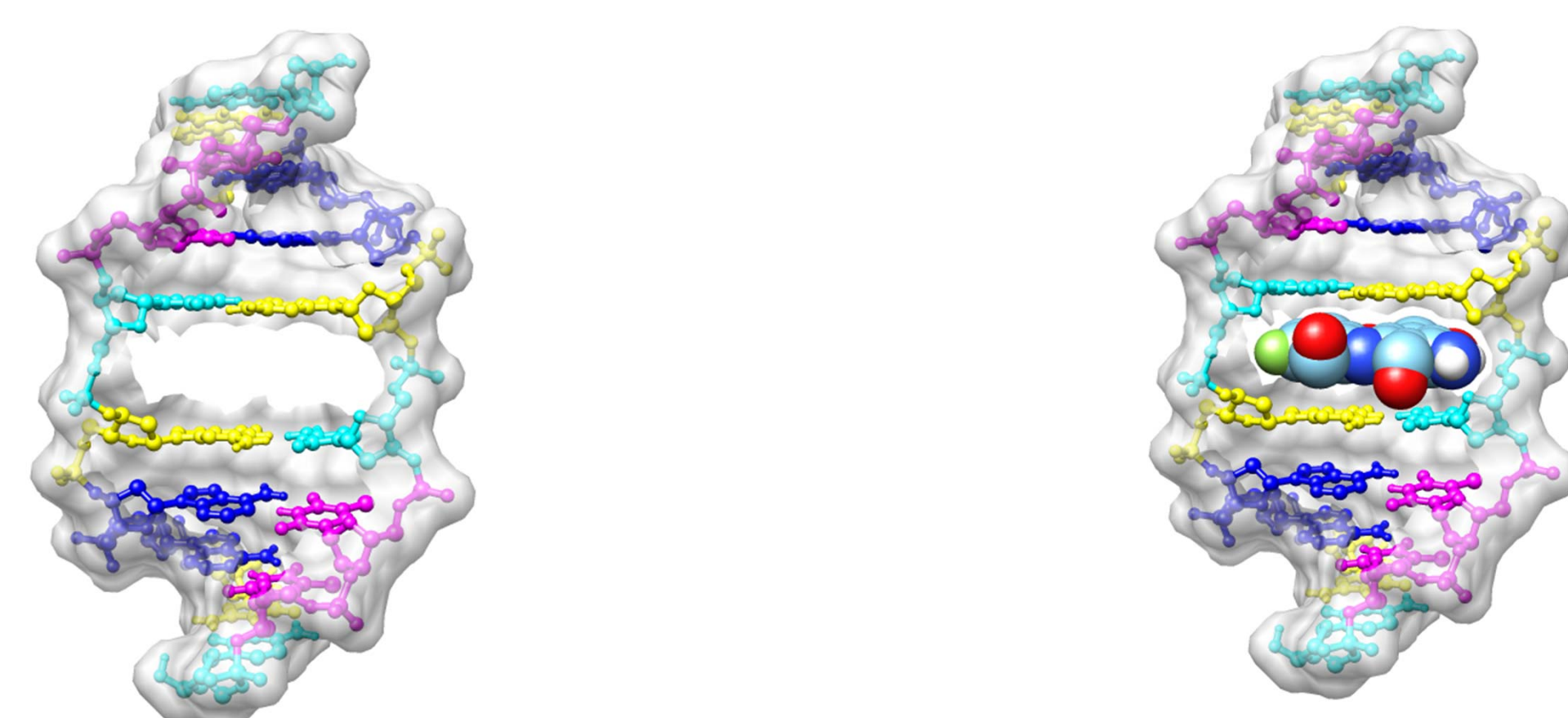


Figure 2: An intercalation gap can form if the distance between adjacent base pairs in the DNA helix increase (left). Planar molecules can slide between the DNA base pairs and intercalate between them (right).

Mixed Binding

Mixed binding can occur when a part of a ligand intercalates and the rest of it lies in the minor groove.

Molecular Docking: Molecular docking is the use of a computer program to try to predict how a ligand will interact with a receptor. Molecular docking has long been used to examine how ligands interact with proteins, however, less attention has been given to using docking software to examine ligand-DNA binding. In the last 10 years, however, efforts¹ have been made to analyze how well various docking software are able to predict the binding modes of small molecules to DNA.

Flavonoids: Flavonoids are a class of naturally occurring antioxidants. Two subclasses of flavonoids, flavones and isoflavones (Figure 3) are known to bind to DNA. We set out to determine whether or not, the commonly used docking program AutoDock Vina could correctly predict the binding mode of 12 different flavonoids, all of which are known intercalators.

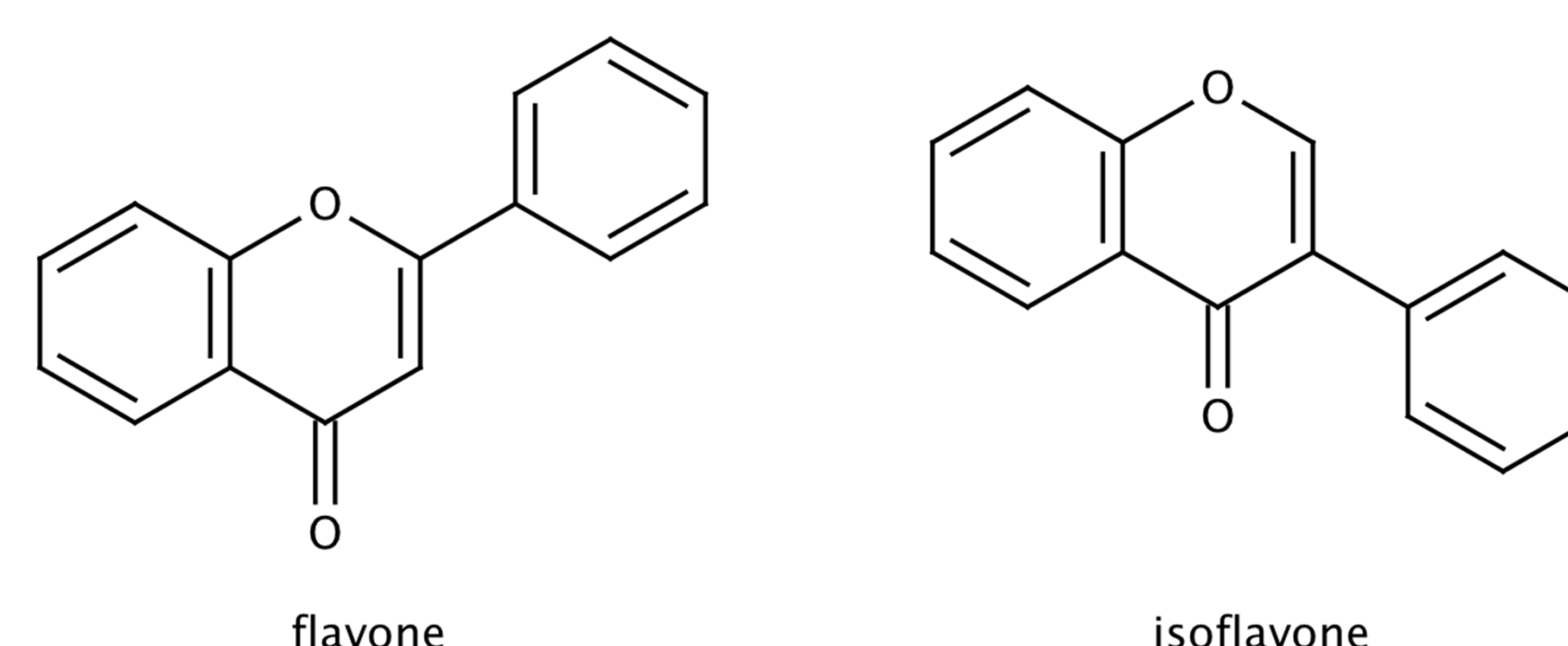


Figure 3: Structure of flavone and isoflavone

Each of the twelve flavonoids differs in the number and position of -OH groups present.

Methods: A strand of DNA featuring an intercalated ligand (ellipticine) was taken from the Protein Data Bank (PDB Code 1Z3F). The ellipticine molecule was removed and hydrogen atoms were added using Chimera. Flavonoid structures were generated by altering a quercetin molecule optimized at the M062X/6-31+G* level of theory, using the Gaussian 09 software program. Molecular docking was carried out using AutoDock Vina² with the interface present in Chimera³ using an exhaustiveness of 8 and requesting 10 binding modes. All structures were visualized in Chimera. For each flavonoid we classified each of the 10 structures as either intercalation, groove binding, or mixed, and made note of which mode was predicted to be the lowest energy.

Results: For each of the 12 flavonoids, the lowest energy binding mode was predicted to be intercalation, although most flavonoids showed a variety of possible binding modes when looking over all 10 structure (Figure 4). Examples of what these binding modes look like for the flavonoids is shown in Figure 5.

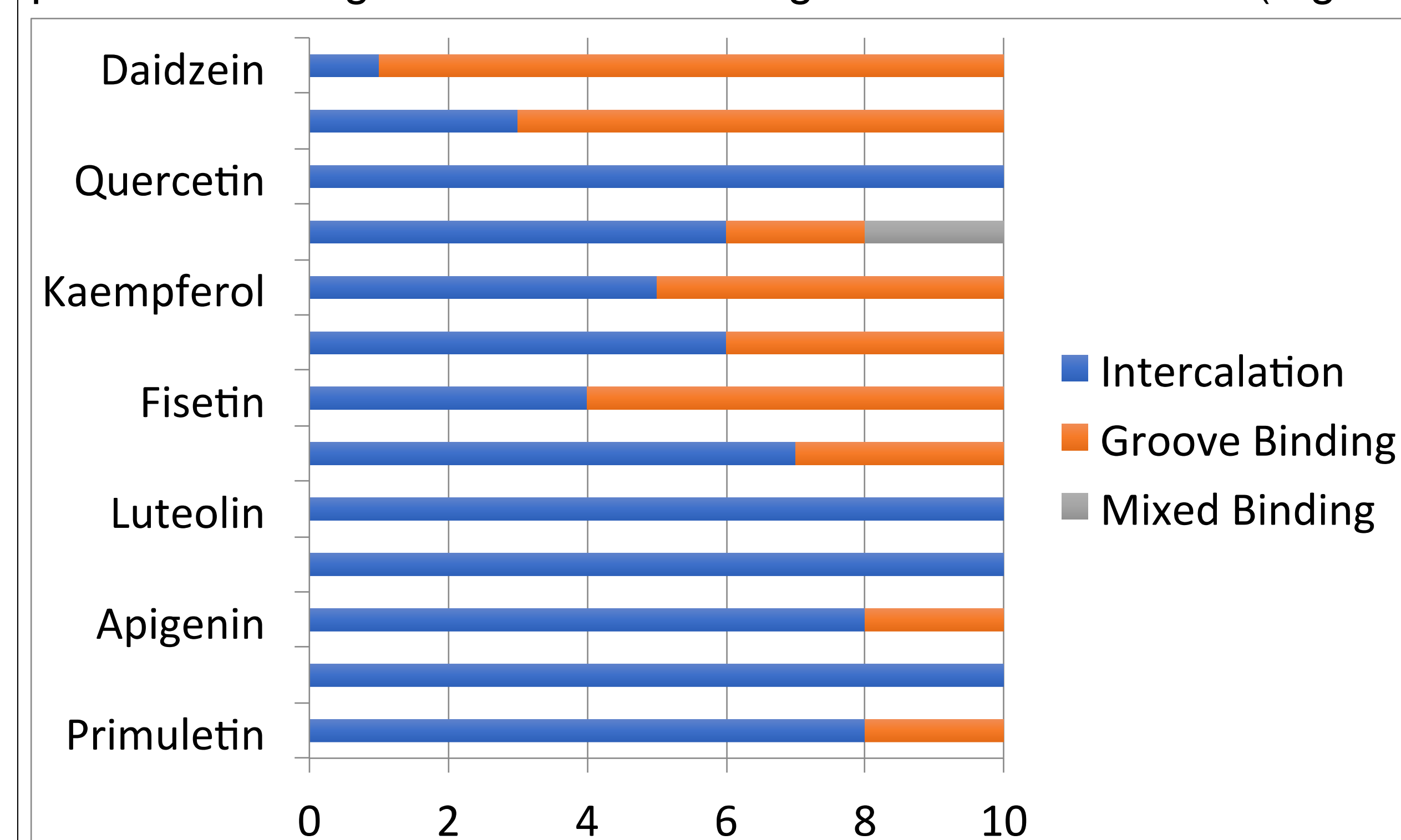


Figure 4: Distribution of predicted binding modes among the 10 generated structures

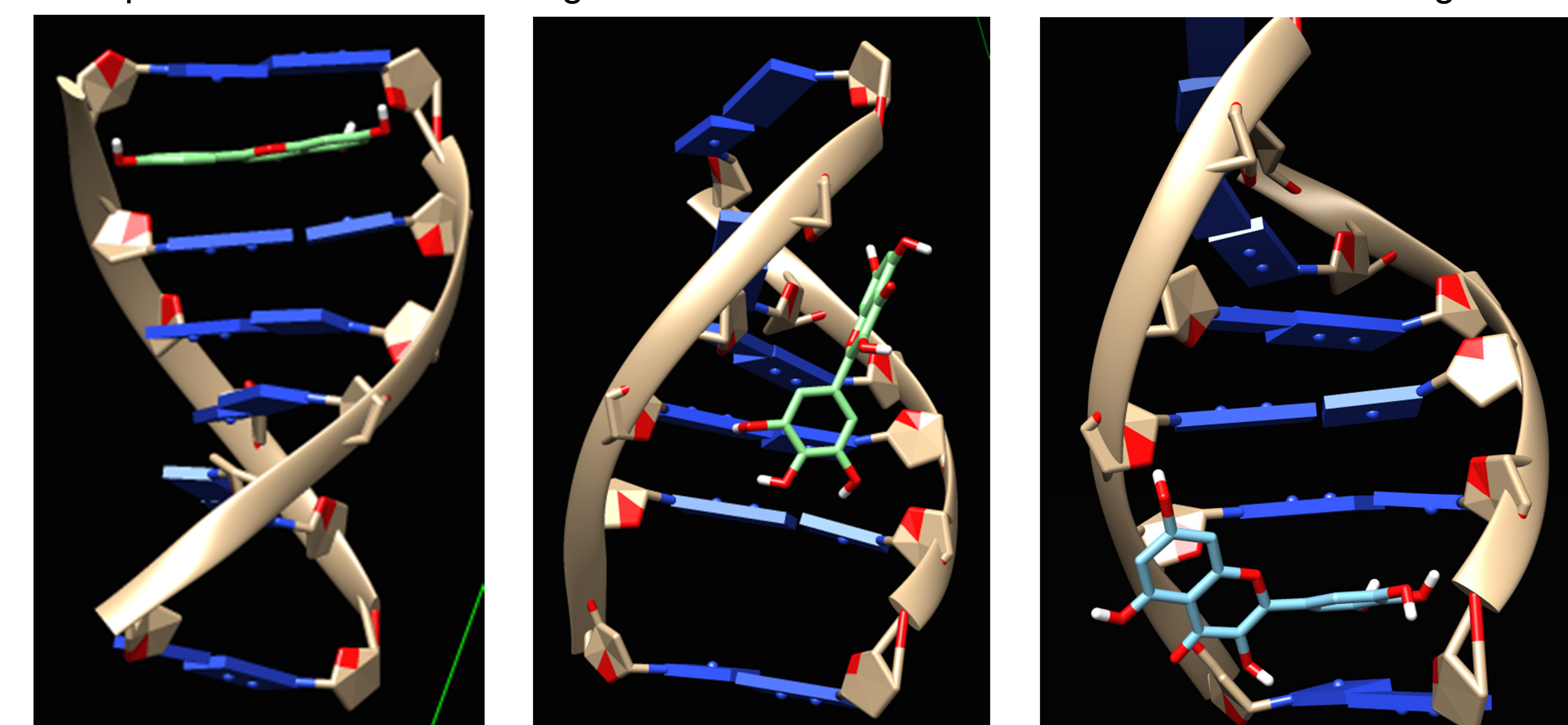


Figure 5: Examples of a flavonoid bound to DNA via intercalation (left), groove binding (center), and mixed binding (right).

Conclusions: AutoDock Vina was able to successfully predict the correct binding modes for the 12 flavonoids tested. This indicates that AutoDock Vina may be useful in predicting binding modes for flavonoids for which the binding mode is unknown or for potential drug candidates based on the flavone or isoflavone scaffold.

References:

- (1) Ricci, C. G.; Netz, P. A. *J. Chem. Inf. Model.* **2009**, *49*, 1925 – 1935.
- (2) Trott, O.; Olson, A. J.; *J. Comput. Chem.* **2010**, *31*, 455 – 461.
- (3) Pettersen, E. F.; Goddard, T. D.; Huang, C. C.; Couch, G. S.; Greenblatt, D. M.; Meng, E. C.; Ferrin, T. E. *J. Comput. Chem.* **2004**, *13*, 1605 – 1612.