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Commentary

The role of aromatic stacking in drug-drug interactions

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Having studied and worked in the fields of pharmacology and structural biology my first reaction to reading an article or attending a lecture about a class of chemical compounds or biomolecules regardless of whether they are nucleotides, proteins or lipids is to look up their structure or sequence, as the chemical structure of molecules is what defines their character, that is their mechanism of action. Most cancer therapeutic agents such as Taxol (paclitaxel) which is widely used to target solid tumors are rich in aromatic structures. These patients are often depressed and are on psychotropic medications, which also contain two or more aromatics. It is unknown whether these two groups of compounds directly interact.

A quick look at my trusted Goodman and Gillman textbook "The Pharmacological Basis of Therapeutics" and my "Physician Desk Reference" confirmed that most antidepressants and cancer drugs are aromatics. I looked up the structure of Taxol and it contained 3 aromatic rings, which made me suspect that the aromatic rings in the antidepressants and in Taxol interacted forming what's known as aromatic stacking or π– π interaction [1,2], which are non-covalent interactions (NCX) between aromatic compounds. If compounds stack then they are no longer available to interact with their targets, that is the Taxol does not go to the tumor and the antidepressants to the receptors that control mood.

To test my theory, I purchased Taxol and 5 of the most commonly used antidepressants Haloperidol, Diazepam, Clonazepam, Sertraline and Fluoxetine. They all contain two aromatic rings. I then prepared five solutions, each a mixture of Taxol and one of the antidepressants. Then assayed each mixture solution using Electrospray Ionization Mass Spectrometry (ESI-MS) a technique which ionizes molecules generating a spectrum in which each peak is a Molecular ion (MH^+), that is the molecular weight of the molecule (M) + a proton (H^+) for each compound in a sample. In all five samples three peaks were detected one for [taxol+ H^+] another for the [antidepressant in this particular solution + H^+] and a third for [Taxol + antidepressant + H^+], demonstrating that indeed NCX were formed between Taxol and each of the antidepressants.

To confirm the composition of the NCXs, I performed MS/MS also known as tandem MS on each NCX peak. MS/MS is a technique used to break down selected ions into their fragment components, and indeed in each case the fragmentation of the NCX molecular ion resulted in two peaks one for taxol and the other for the antidepressant forming the complex with Taxol [3-5].

However, this did not explain why the abundance of the complexes varied depending on which antidepressant was in the solution. So next, I modeled the chemical structure of all molecules with Spartan 10. The modeling measured the distance between the rings in each molecule. The data suggested that differences in the stability of the NCXs are likely due to the role the distance between the aromatic rings in both the paclitaxel and each antidepressant medications played.

Since π–π stacking resulting in formation of NCXs could involve one or two of the rings in Taxol and one or two of the antidepressant drugs aromatic rings. If the interaction was between the two rings on both the taxol and the antidepressant, then the complex NCX was more abundant and more stable and the distance between aromatic rings in each compound might explain the

results, i.e., the closer the value of the aromatic rings' distance in each antidepressant to the rings in Taxol, the higher the affinity of the compounds to interact, and the more stable the NCX will be.

Indeed, Haloperidol was the least interactive in terms of NCX formation, had a linear structure and a distance of 15.555 Å between its rings, Furthermore, the distance between its two aromatic groups is 1.8 times larger compared to Taxol 8.652 Å, thus making the π–π stacking less efficient, as it probably involved only one ring on each molecule.

Diazepam was the second least interactive, in terms of complex formation, and its structure was the most compact and the distance between its two aromatic rings was 6.401 Å, approximately 75% of the distance of the aromatic groups in taxol, also suggesting that only one ring was involved. While Clonazepam and Sertraline distances were 7.164 Å and 7.235 Å respectively and formed more NCX with Taxol.

However, fluoxetine formed the most stable and abundant NCX with taxol. The distance between its aromatic rings 8.905 Å is the closest to Taxol's rings distance 8.652 Å, suggesting that probably both rings on each molecule interacted with the rings on the other, thus explaining why fluoxetine and Taxol formed abundant and more stable NCXs, than the other antidepressants that most likely had only one ring involved in the interactions (Figure 1).

The data points to the importance of the distance between two aromatic rings in each molecule for the formation of stable π–stacking between two compounds as well as the abundance and stability of the NCXs formed.

Much more work needs to be done using animal models to determine how such interactions can cause serious therapeutic interferences.

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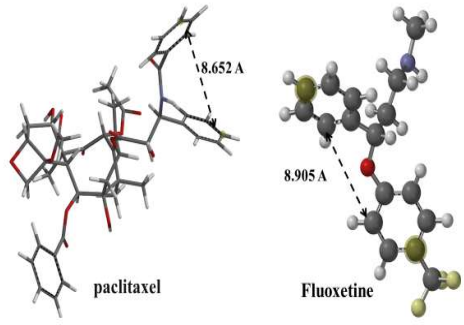

Figure 1: Structure of Paclitaxel and Fluoxetine.