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Editorial

Surviving Your First Week in Medicinal Chemistry

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Like many, I entered my first medicinal chemistry role (∼2.5 years ago) from an organic chemistry background, with little knowledge of medicinal chemistry and drug discovery. This is the most common route to becoming a medicinal chemist—it's no secret that hiring managers prefer to hire entry-level medicinal chemists from synthetic organic chemistry backgrounds. I then experienced the "on-the-job" medicinal chemistry training which is commonplace within the industry. This approach has its advantages and disadvantages.[1] But this is not the focus of this writing. Instead, I aim to give actionable advice to help young organic chemists transition into medicinal chemistry.

WHAT DO DRUG MOLECULES LOOK LIKE AND HOW DO WE MAKE THEM?

As most new medicinal chemists come from an organic chemistry background, their role at first is synthesis-based, with little emphasis on drug design. These chemists will often be mentored by a colleague who is well-trained in medicinal chemistry and drug discovery. Understanding what typical drug molecules look like and how they are made would be advantageous in this scenario. Throughout this publication I will use the term "drug" to describe molecules that can affect a biological target—this can include approved pharmaceuticals as well as molecules in development. Students will have been exposed to many different types of chemical structures throughout their university classes. But usually, the structures covered are quite different from what is common within medicinal chemistry. A great resource for finding the structures of popular drug molecules is the "Top 200 Drugs Poster", which is compiled by the Njardarson group each year.[2] This gives an overview of what structures and functional groups are frequently found in drug molecules, such as amides and heterocycles, and groups that are not commonly seen, such as aldehydes and epoxides. There has been some great work done analyzing the most common functional groups in bioactive molecules and how these have evolved over time.[3] Another problem is that most reactions taught in university chemistry courses are not routinely used in the synthesis of these molecules. For example, many organic chemistry courses and textbooks focus heavily on enol/enolate-based reactions which are not commonly used in medicinal chemistry. A great exercise is to go back to the previously mentioned posters, think about the retrosynthesis of these molecules, and compare them to the syntheses which can be found online. It becomes clear that the most common types of reactions are amide couplings, SnAr reactions, and palladium-catalyzed cross couplings. Again, a lot of great work has been done analyzing which reactions are most commonly used and how that has evolved with time.[4]

WHAT INTERACTIONS CAN THESE MOLECULES MAKE?

Most drugs exert their biological effects through binding to proteins, usually by activating (agonism) or blocking (antagonism) the protein's natural function. Common protein−drug targets include G-coupled protein receptors (GCPRs), protein kinases, and ion channels.[5] Drugs bind to protein targets through favorable intermolecular forces between the drug molecule and the protein. The most common interactions are hydrophobic, hydrogen bond, pi−pi stacking, and salt bridge (ionic).[6] These are enthalpic binding forces, but there are also important entropic contributions, resulting from the conformational freedom of the molecule and changes in solvation upon binding.[7] Importantly, the structure of the molecule, i.e., the functional groups present and their spatial orientation, has a direct impact on what binding interactions can be made. Functional groups can form one or more different interactions. For example, a secondary amide group can act as a hydrogen bond acceptor through oxygen, a hydrogen bond donor through the N−H bond, or both. Alternatively, it may not be directly involved in any interactions at all and rather acts as a structural linker for other functional groups. As drug molecules contain different functional groups and structures, multiple interactions can be formed, which all contribute to the binding interaction. Through systematic changes to the molecule's structure, it is possible to determine what features are key for binding (known as the pharmacophore), as well as which ones increase or decrease binding to the protein of interest. This is called the structure−activity relationship (SAR) of a molecule and is a key part of the medicinal chemistry process.[8] Normally the goal is to increase the binding interaction to the protein of interest. But if the aim is to improve the selectivity of the molecule against other proteins, the goal is to decrease the binding interaction. While I have been talking about things qualitatively, binding interactions can be quantified using the dissociation binding constant (K_D). Information on the assays and methods used to determine these values can be found in

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biochemistry or medicinal chemistry textbooks.[9] It is important to note that just because a molecule binds to a protein (affinity), that does not mean it induces the changes needed to produce the desired effect (efficacy). Efficacy is commonly measured through IC_{50} when the molecule is acting as an inhibitor or EC_{50} when the molecule is having another effect.

WHAT DOES "DRUG-LIKE" MEAN?

While the chemical structure of a molecule impacts how it interacts with its target protein, it also affects how the molecule is processed by the body. This is because molecular structure impacts the physicochemical properties of the molecule. These physical and chemical properties have a clear impact on the absorption, distribution, metabolism, elimination, and toxicology (ADMET) of the compound. These subsequently impact the drug metabolism and pharmacokinetics (DMPK) of the molecule. "Drug-like" to describe properties or molecules is a common term within medicinal chemistry but is poorly defined. This term is normally used to describe molecules that obey Lipinski's rule of 5 (which is 4 rules, based on multiples of 5).[10] These give guidelines for the physicochemical properties needed for an orally administered drug. The properties described in this rule—LogP, molecular weight, and numbers of hydrogen bond donors and acceptors—are among the most important to medicinal chemists. The vast majority of the approved orally administered drugs follow these guidelines. Compounds with physicochemical properties outside these guidelines have a higher chance of facing problems in DMPK. For example, it is well known that compounds that have a high LogP are more likely to cause problems with toxicology or metabolism. Other properties of "drug-like molecules" include having no reactive or toxic groups.[11] However, there are exceptions. For example, covalent inhibitors have reactive groups, as the goal is to bind to a nucleophilic amino acid within the protein.

HOW IS A DRUG DEVELOPED? A SIMPLIFIED OVERVIEW

When starting a new role, it's nice to see how you fit into the project and which stage the project is in. All drug discovery projects need a chemical starting point or "hit", which is a molecule that displays a desired activity toward a drug target.[12] Depending on the project and the screening methods used, this can mean anything from a molecule that binds to a protein target to a molecule that shows activity in an enzymatic or cellular assay. Traditionally these compounds were identified through screening large libraries of molecules, known as high-throughput screening (HTS). More recent methods include DNA-encoded libraries, fragment-based drug discovery, and virtual screening. This is known as hit identification. Once hit molecules have been identified, follow-up assays are carried out to confirm they are true hits and not false positives resulting from problems with the compound or assay. Ideally, this would result in more than one chemically distinct group of molecules, called a series. The hit-to-lead phase involves the expansion of these hits to determine which series is most promising and could be further optimized. In this phase, analogues of the hit molecules are synthesized to establish the key pharmacophore and SAR of the series. This can involve rational changes to assess the SAR, as well as more explorative analogues. The goal of these activities is to establish how and where these molecules can be modified to improve potency and physicochemical properties. It is becoming increasingly common to pay further attention to DMPK profiles in this stage, to reduce the risk of problems in this area further down the development timeline.[13] Lead optimization involves the synthesis of more specific analogues to address key issues within the series. These will be different for each program and depend on the molecules that have been progressed through the hit-to-lead phase. This can include trying to synthesize molecules which are more potent and selective as well as analogues which improve any pharmacokinetic issues, such as low metabolic stability or low bioavailability. Other considerations in this phase can include making sure the molecule is patentable and can be made on a sufficient scale for further testing. During all these phases, a huge amount of work concerning biology and pharmacology will be carried out, but that is not within the scope of this paper. It is clear that the majority of the medicinal chemistry effort is within hit-to-lead and lead optimization phases, so this is where you are likely to find yourself when starting a new role.

CONCLUSION

Medicinal chemistry is a huge subject which has significant crossover with areas of pharmacology and biology. To become a great medicinal chemist, you need to have excellent medicinal chemistry knowledge, as well as a good understanding of these overlapping areas. This can seem daunting at first, which is why I have tried to give immediately actionable advice. But while you can get the knowledge and best practices, the experience is hard to replicate. This likely explains why the on-the-job training model has been, and still is, so common within this industry. However, working on becoming more familiar with medicinal chemistry concepts is a great place to start. All of the topics discussed here can be found in more detail in the referenced articles and textbooks as well as many others to gain a more in-depth understanding of these areas.

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Notes

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