NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

The Organic Chemistry of Drug Design in a Case of Schizophrenia

by

Brahmadeo Dewprashad, Department of Science, Borough of Manhattan Community College, The City University of New York
Vishnu Tiwari, Psychiatry and Behavioral Sciences, The University of Miami Miller School of Medicine

Freddie was diagnosed with schizophrenia in his final year of high school, but with the support of nurturing parents and his caring psychiatrist, he was able to graduate with high honors. While living with his parents he proceeded to a hometown community college and completed two years with similar academic success, although he found the organic chemistry courses challenging.

Key to his maintenance of a nearly normal lifestyle was the fact that he was prescribed an antipsychotic agent (100 mg chlorpromazine, twice daily) and that his parents ensured that he took the medication at the appropriate times. As such, Freddie and his parents felt that he was ready to proceed to a senior college of his choice and live away from home.

In senior college, Freddie found it difficult to regularly take his prescribed medication. Slowly, his performance began to decline. He grew fearful of his classmates and began to hear indistinct voices talking to him at night. Freddie required admission to a psychiatric hospital and was stabilized. He presented the next month back to his outpatient psychiatrist.

"How are you doing, Freddie?" asked Dr. Ruiz with concern. "I believe it's been over two months since I last saw you."

"I've been okay, but I kept hearing voices and there was a misunderstanding between me and my classmates. They took me to the ER, and I was asked to see you afterwards," replied Freddie.

"Have you been able to take your medication regularly?" asked Dr. Ruiz.

"I swear I've been taking my medication," stated Freddie adamantly.

"Do you mean every day, or were you missing a day or two?" probed Dr. Ruiz.

"College is so stressful. With all the stress, I might have forgotten to take my medications for a few days. I promise I'll do better next time. When I was home, my parents used to administer the medication. When I came to college, I wanted to be independent, so I asked them to stop phoning me to remind me to take my medications. Also, I'm embarrassed to take my medication in front of my roommate, and he's always in the room. I wish he'd go out sometimes," explained Freddie in exasperation.

"I'd like to change your medication to one which you have to take only once per day. That should make it easier for you to adhere to. In addition, this medication should cause less drowsiness than your current medication. Also, you will be less likely to experience dry mouth or constipation. However, a few, but not insignificant, number of patients can develop sustained muscle contractions. It's important to monitor for any such symptoms and let me know if you experience them so that we can address them. I'm sending a prescription to your pharmacy for the medication, which is fluphenazine 5 mg," stated Dr. Ruiz.

"Thanks. The drowsiness from my current medication prevented me from studying as much as planned to. I'll take my new medication daily," promised Freddie.

"Great. It should be helpful to you if you take the medication at a specific time every day and make a note of it," suggested Dr. Ruiz.

Freddie returned to campus with a renewed sense of optimism. He took his daily dose of fluphenazine for a few days and kept a record of it. However, as midterm exams were coming up, he started studying in the library till late and came to his room very tired; his medication usage became irregular. In time, he started hearing voices telling him that he would fail his exams. He got alarmed and went to see his psychiatrist again.

"How have you been sleeping?" asked Dr. Ruiz.

"I was doing well for a while and then I started hearing voices again," explained Freddie.

"Have you been taking the fluphenazine regularly?" asked Dr. Ruiz.

"I thought I was, but I noticed I have quite a bit left over. I must have forgotten when I got busy," explained Freddie.

"When you were taking the fluphenazine, did you notice less drowsiness?" asked Dr. Ruiz

"Yes. You were correct in that it causes less drowsiness," stated Freddie.

"There are medications that are longer acting and would not have to be taken daily. I feel that these might work better for you. How do you feel about taking those?" asked Dr Ruiz.

"Sure, that would be great," agreed Freddie.

"The medication that I am considering for you has to be injected but would only have to be taken every two to three weeks," explained Dr. Ruiz.

"No, no, no! I hate injections. I'm terrified of needles. When I went to the ER, they gave me an injection. It was so painful. Now when I think about injections, I get terrified. I promise I'll take my medications regularly," pleaded Freddie.

"I want you think about it. I know how hard you are trying and how stressful college can be. I want to help you navigate college successfully so that you can go on to study medicine, become a psychiatrist, and help others as you had planned," pleaded Dr. Ruiz.

"I'll think about it, but no injections for now. I don't even know if the new medication given by injection will work as well as the one that I'm taking," countered Freddie.

"I'm glad that you'll consider it. Now that you are in college and interested in medicine, I suggest that you spend some time reading and learning about the medications and how they work. You are currently taking fluphenazine 5 mg daily. What I'm now proposing is fluphenazine decanoate, which would have to be taken once every two to three weeks. It's basically the same medication you're taking and will work as well. However, it's been modified to be longer acting," explained Dr. Ruiz.

"I'd still like to think about it," countered Freddie.

"Okay, do some reading on how these drugs work and we'll meet in two weeks to decide on the new longer-action medication that has to be given by injection. I'll leave some literature on these medications with the receptionist. Please take it before leaving and read it. I recall that when we were discussing some of the challenges you were facing, you mentioned that you are now taking a course in pharmacology. I encourage you to obtain additional information from your pharmacist and do some additional reading on your medications. In the meantime, I'd like to help you to remember to take your current medication daily. Would it be all right if my office sends you a text to remind you to take your medication over the next two weeks?" offered Dr. Ruiz.

"Sounds okay to me, but I really don't need the text reminders," countered Freddie.

"Let's give it a try, just for two weeks," pleaded Dr. Ruiz.

"Well okay, two weeks," Freddie stipulated.

Pre-Case Questions

Read the following webpage from MedLinePlus to learn about schizophrenia: <https://medlineplus.gov/schizophrenia.html>. Then answer the following questions that cover chemical concepts needed to undertake the case study

1. Identify and label all the functional groups in the following molecule.

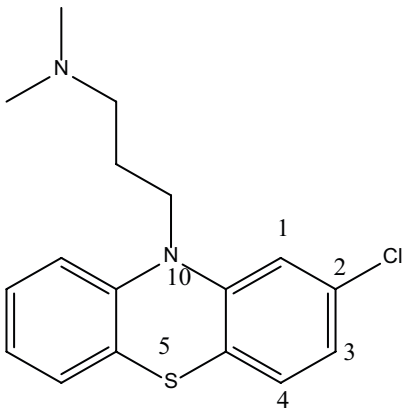

Figure 1. Chlorpromazine.

2. Using suitable examples, explain the difference between electron withdrawing (EWG) and electron donating groups (EDG).

3. For chlorpromazine, identify which part(s) of the molecular structure are rigid and flat and which part(s) are flexible and can have several conformations.

4. Draw chlorpromazine with the flexible part in a different conformer than that shown above (Figure 1).

5. Provide the IUPAC name for the compound shown below (Figure 2) and explain how you arrived at the name.

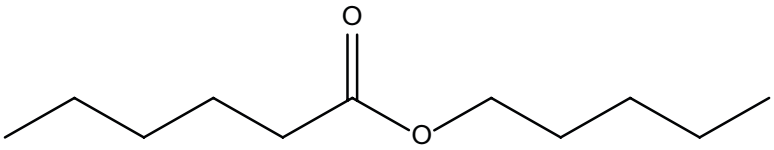

Figure 2. Unknown compund.

6. Using structures, outline a reaction scheme (including reaction conditions) for the single-step synthesis of the compound in Question 5 utilizing the Fisher esterification reaction.

7. Rank the reactants and organic product in order of their relative oil (fat) solubility. Explain the rationale for your ranking.

8. Using structures, outline a reaction scheme for the hydrolysis for the compound in Question 5.

9. Many organic drug molecules are weak acids or weak bases and can be ionized in the body. The degree of such ionization depends on the pK_a of the molecule and the pH of its environment and can be determined by the Henderson-Hasselbalch equation, shown below:

$$pH = pK_a + \log [\text{acid form}]/[\text{base form}]$$

The major constituent of blood and interstitial fluid is water. These fluids have a pH around 7.35–7.45. A pH value of 7.4 can be used in the calculations.

Acetaminophen (Figure 3) is a weak base, and its conjugate acid has pK_a of 9.5.

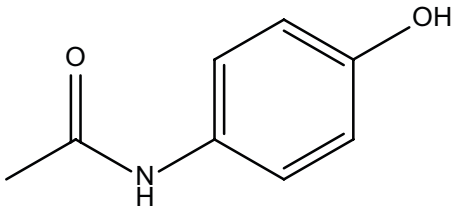

Figure 3. Acetaminophen.

a. Write a reaction scheme for the reaction of acetaminophen with water to form its conjugate acid.

b. Calculate the % of the conjugate acid of acetaminophen that would form in interstitial fluid.

c. Which form predominates in the interstitial fluid?

Case Questions

1. Freddie learned that the medication, chlorpromazine, that he was previously taking, has the structure shown below (Figure 4) and belongs to a class of anti-psychotic agents known as phenothiazines, the name of their basic ring structure. He learned that these medications are believed to act by modulation of dopamine neurotransmission in the mesolimbic and mesocortical pathways of the brain. He also learned that an electron withdrawing group (EWG) at the 2 position is needed for activity and that increasing electronegativity of this group results in increasing potency. Freddie noticed that the dose he was given for fluphenazine (Figure 5) was much less than that he was taking for chlorpromazine, an indication that the former was more potent than the latter. As he compared the two structures, he felt he understood why. What differences in the two structures would likely lead him to such a conclusion? (6 points)

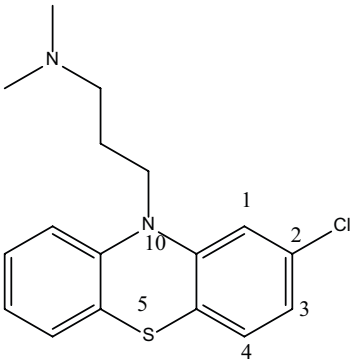

Figure 4. Chlorpromazine.

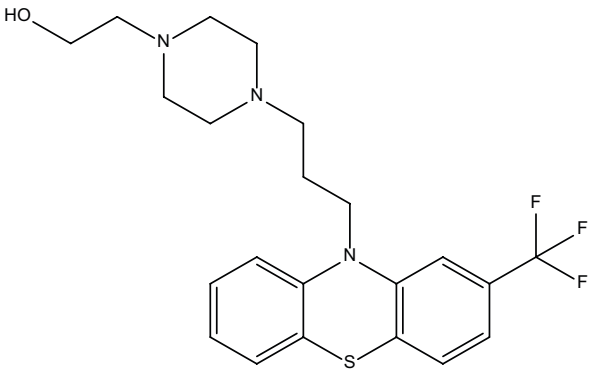

Figure 5. Fluphenazine.

2. Freddie also learned that in this class of drugs, the nitrogen at position 10 is usually substituted with a three-carbon chain connected to a N, which may have other substituents. If the chain length is shortened, the compounds would not be active. He tried to understand why this is so and surmised that for there to be activity, there must be some interaction between the EWG at position 2 and some part of the chain arising from the N at position 10. He tried to understand why there was such an interaction and did so by looking at the structure of chlorpromazine and addressing the following questions. Answer the questions to determine the rationale for his supposition. (16 points total, 2 for each part)
   a. What would be the charge or partial charge on the EWG at position 2?

   b. Is there any portion of the chain that has a charge or partial charge (in the unchanged molecule) that would likely be attracted to the charge/partial charge on the EWG? Rationalize your answer.

   c. The conjugate acid of tertiary amines have a pK_a of around 11. Write a reaction scheme (using structures) for any reaction you think would occur with chlorpromazine in interstitial fluid. Explain how you arrived at this reaction.

   d. Calculate the % of the chlorpromazine that is converted to its conjugate acid in interstitial fluid. The pH of interstitial fluid is 7.35–7.45 as indicated in pre-case Question 9. However, the pK_a for the chlorpromazine is

not available and can be best estimated to the unit place. As such, use a pH of 7 for interstitial fluid and a pK_a of 11 for chlorpromazine in this calculation.

e. Which form predominates in the interstitial fluid?

f. Draw the form of chlorpromazine (in interstitial fluid) where there would be intramolecular attraction between the EWG and the side chain.

g. Use the structure in the previous question and show the part of the side chain that likely interacts with the EWG.

h. Use the structure in the previous question and show the molecule in a conformation that would facilitate such interaction.

3. Freddie looked at the structure of fluphenazine and noticed that the structure seemed very different from chlorpromazine and wondered whether they both could have the same mechanism of action. To answer that, he tried drawing the form that fluphenazine exits in the body and a possible conformer that would lend itself to interaction between the EWG and the side chain. Try drawing such a conformer to see if that is possible. (6 points)

4. Freddie wondered how it was possible for fluphenazine to be converted to a form which has such a much longer duration of action but would act as its original form. He learned that the duration of action of phenothiazines can be prolonged by use of long chain fatty esters of the medication. The esters are dissolved in sesame oil and injected intramuscularly from where it gradually seeps into the muscle and then into the systemic circulatory system (where it is hydrolyzed by plasma esterase) and taken to cells including those of the brain. He wondered how fluphenazine decanoate could be synthesized and whether there would be changes in other parts of the molecule (during the synthesis) that would affect its function. Answer his question by writing a reaction scheme (using structures) to show how the decanoate can be made from fluphenazine and any additional reagents needed. Which reagent will you use in excess and why? Bear in mind that relative costs are an important consideration when deciding which of the reactants to use in excess. Compounds that require multistep synthesis are generally more expensive than compounds found in nature in significant amounts. (10 points)

5. Freddie wondered if fluphenazine decanoate could indeed be hydrolyzed in his body and whether a different drug (than fluphenazine) would be formed. Answer his question by writing a reaction scheme (using structures) to show the hydrolysis of the decanoate and the products formed. Identify the products. (10 points)

6. Freddie learned that there was another long-acting form of fluphenazine in the form of the enanthate. Freddie wondered whether the enanthate would be acting longer than the decanoate. Address his question by answering the following questions. (16 points total, 4 points for each part)
   a. Compare the structure of fluphenazine enanthate (Figure 6) with that of the decanoate.

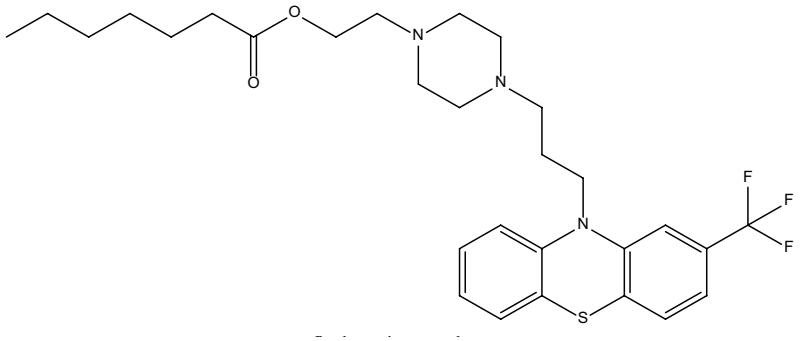

Figure 6. Fluphenazine enanthate.

   b. Compare the oil solubility of both. Will their oil solubility be similar or very different? If so, which would be more oil soluble and why?

   c. Which will likely stay longer in the sesame oil depot at the site of injection? Explain the reason for your answer.

   d. Which will likely have a longer duration of action? Explain the reason for your answer.

7. Freddie found that the fluphenazine caused him less drowsiness than the chlorpromazine that he had been previously taking. He was curious as to the reason for this and looked critically at the structures of several phenothiazine anti-psychotic medications. He found that perphenazine also causes less sleepiness than chlorpromazine. What differences in the structures could have contributed to fluphenazine causing less sleepiness? (3 points)

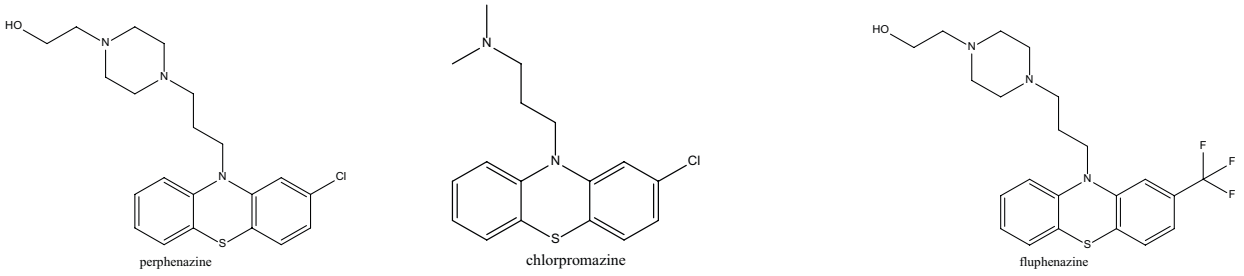

Figure 7. Comparison of perphenazine, chlorpromazine, and fluphenazine.

Post-Case Questions

1. If you were tasked with designing a new antipsychotic agent that would be a more longer acting than fluphenazine decanoate, propose a structure of a compound that you think should be synthesized and tested. Explain the reasoning underlying your design. (4 points)

2. Do you think that Freddie, in his follow-up visit, would be more amenable to be administered fluphenazine decanoate by injection because of his investigation and subsequent understanding of the mode of action of the medication? Explain the rationale for your answer. (3 points)