Developing a Therapeutic Analog for Thalidomide

Thalidomide was widely used after World War II as a sedative and later as a treatment for morning sickness. Unfortunately, after its widespread use, it was discovered that thalidomide causes very serious side effects—in particular, birth defects such as phocomelia (limb malformation). The drug was banned in 1962, and these events resulted in important changes to the way the FDA approves drugs. Now, despite the inherent dangers, thalidomide is used for treatment of nausea related to chemotherapy, where benefit of treatment outweighs the inherent dangers.

It is understood that thalidomide exists as two **enantiomers**; one is a teratogen that causes birth defects, while the other has therapeutic properties. Rapid **racemization** occurs at neutral pH, so both enantiomers are formed at roughly an equal mixture in the blood, which means that, even if only the therapeutic isomer is used, both will form once introduced in the body. The racemization is illustrated below in **Figure 1**.

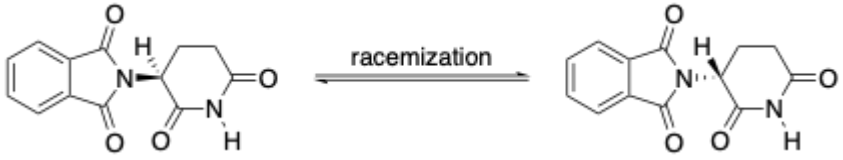

Figure 1: The rapid racemization of thalidomide.

Furthermore, both enantiomers are subject to **acid hydrolysis** once in the stomach at lower pH, which could produce products that are teratogens. The structure of thalidomide and two thalidomide hydrolysis products are shown below in **Figure 2**. For these reasons, it is important to prevent both the racemization and the subsequent hydrolysis of thalidomide.

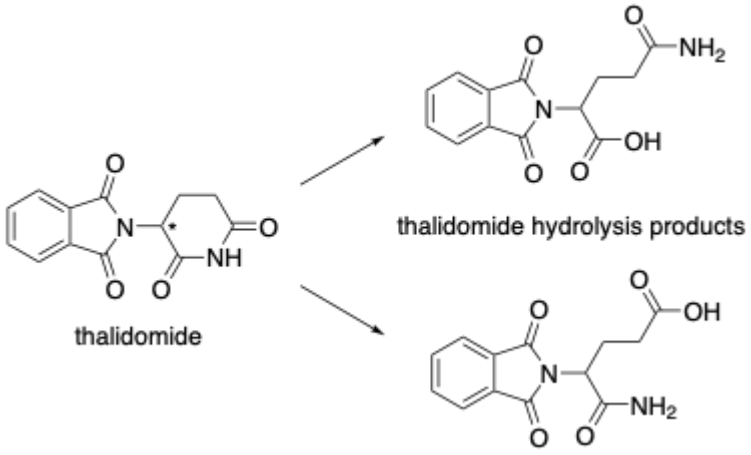

Figure 2: Thalidomide and two thalidomide hydrolysis products. The stereocenter is shown (*).

You are an OB-GYN at the Mayo Clinic. A colleague, who is an oncologist at the University of Minnesota, has approached you about a potential collaboration on a human clinical trial. This

trial will propose and test the efficacy of thalidomide **analogs** for the treatment of nausea in cancer patients. (See note on the third page for an explanation of an analog.)

As an organic expert in the chemical pathways that lead to birth defects, you are writing an email to your collaborator. Your goal will be to propose a structural difference that will make the thalidomide analog unreactive toward both racemization and hydrolysis. You must provide descriptions of the structure and reactivity of thalidomide toward racemization and hydrolysis as well as descriptions of the structural differences in the proposed analog that will make it unreactive to both of these processes. The oncologist is not an expert in organic chemistry. Therefore, carefully consider which organic chemistry terms to use and when to define or explain them. Use clear and concise language, striking a balance between organic jargon and oversimplified explanations.

Your email should be approximately between 500-700 words (1-2 pages) in length. It should address the following points:

1. Provide thorough descriptions of the mechanisms of both racemization and acid hydrolysis, highlighting the critical structural features of thalidomide and their role in these mechanisms.
    a. When racemization occurs, what changes occur in the molecule?
    b. When hydrolysis occurs, what changes occur in the molecule?
2. Propose a thalidomide analog (one compound) that would not undergo racemization or hydrolysis. Explain what structural features are in place that would inhibit or prevent these processes.

You can and should include figures of schemes, structures, or mechanisms, if that supports your response. We suggest that you have the figure(s) in front of you—ready to color-code or mark-up in various ways—and that you use your visible thinking to guide your audience through your explanation. Any images that you include in your response, *including the figures in this prompt or those that you draw in ChemDraw or on paper*, must have the original source cited using either ACS or APA format. Given your audience, your written response should suffice so that the explanations can be understood without the figures. **You will be graded only on your written response.**

An analog is a compound that is very similar to but has small structural differences from the pharmaceutical target. For example, m-cresol (shown in Figure 3 below) is an analog of phenol.

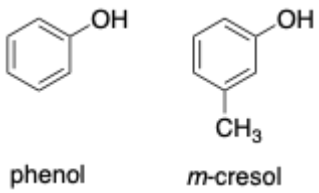

Figure 3: Phenol and m-cresol, an analog of phenol.

Thalidomide Peer Review Rubric

Peer Review Guidelines:

- Print and read over your peer's essay to quickly get an overview of the piece.
- Read the essay more slowly keeping the rubric in mind.
- Highlight the pieces of texts that let you directly address the rubric prompts in your online responses.
- In your online responses, focus on larger issues (higher order concerns) of content and argument rather than lower order concerns like grammar and spelling.
- Be very specific in your responses, referring to your peer's actual language, mentioning terms and concepts that are either present or missing, and following the directions in the rubric.
- Use respectful language whether you are suggesting improvements to or praising your peer.

1. How well does the author explain the process of racemization in thalidomide? Suggest some ways that the author could improve their mechanism description, including discussing what changes occur in the thalidomide molecule through the racemization mechanism.

2. How well does the author explain the process of hydrolysis in thalidomide? Suggest some ways that the author could improve their mechanism description, including discussing what changes occur in the thalidomide molecule through the hydrolysis mechanism.

3. Does the author propose a reasonable thalidomide analog that would not undergo racemization or hydrolysis? To what extent does the author explain the specific structural features that are present in the thalidomide analog that would stop racemization and/or hydrolysis from occurring?

4. In what ways did the author use and define organic chemistry terms that may be unfamiliar to a non-organic chemist? Comment on ways the author could enhance the clarity of their email by translating the definitions of the organic chemistry into their own words.

Revision Prompt

Revising writing means re-seeing it, and the process of reading and commenting on the writing of others as well as receiving feedback from your peers gives you a way of seeing your own writing differently. Meaningful revision means changes at the sentence and paragraph level, usually involving a minimum of three sentences. *You will not receive full credit for revision unless you make meaningful revisions to your writing.*

Things to keep in mind while doing your revision…

- Re-read the prompt
- Re-read the rubric and consider what a complete and effective response would include, noting what you do not fully address
- You may want to make a list of effective content you noticed in the writing of your peers
- You might read and summarize the feedback you received from your peers
- With these things in mind, re-read your draft and mark places where you can improve the content
- Revise and submit your response
- *After* completing this assignment, please follow the link to respond to a survey about the writing assignment:

Checklist from Thalidomide Peer Review Rubric:

1. The racemization mechanism of thalidomide should be explained. In your description, be sure to describe what changes are happening in the thalidomide molecule throughout the racemization mechanism.

2. The hydrolysis mechanism of thalidomide should be explained. In your description, be sure to describe what changes are happening in the thalidomide molecule throughout the hydrolysis mechanism.

3. Be sure that your proposed thalidomide analog would not undergo racemization or hydrolysis. In the explanation of your analog, you should explain structural features that prevent the analog from being racemization and/or hydrolyzed.

4. Be sure that any organic chemistry specific terms that are used in your email are defined and explained in a way a non-organic chemistry expert can understand.

5. Double check that you include citations for any outside sources using APA or ACS format. Images that you did not draw yourself must be cited.