CHEM MAJOR NEWS

In Conjunction with the American Chemical Society
Student Affiliates at the University of Pittsburgh

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Welcome Back!

Hello all,

Welcome back everyone! We hope you had a relaxing winter break and a fun holiday season. Moving into the spring semester things are a bit up in the air right now with the shelter in place being active until the 26th. We will host virtual meetings for that duration and will look to return to in-person meetings after. We have a great list of speakers lined up, including past graduate of DSAS and some fun social events planned. Keep your eyes open for emails regarding upcoming meetings, Saturday Science, and other events as we hope to return to the previous status after January. As a reminder, all of our meetings are on Friday at noon in 150 CHVRN.
Good luck in the spring semester and we hope to see you all soon!

Jack Levickas
ACS Newsletter Co-Editor

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An Itch for Knowledge: How Antihistamine Drugs Work

Written by Jacob Kuzy, B.S. Chemistry 2021

Antihistamines are a broad class of drugs, which treat conditions caused by the hormone histamine, that get by acting as an antagonist at histamine receptors. While common antihistamines such as Benadryl (diphenhydramine) are well known for their anti-allergy uses, the antihistamine family is chemically rich with diverse medical uses[1]. Dramamine, a close cousin of Benadryl is used to treat motion sickness, and Famotidine manages gastrointestinal conditions[2]. Also classified as a monoamine neurotransmitter, histamine has far-reaching effects all over the body which becomes apparent to anyone unfortunate to suffer a severe allergic reaction. Luckily, the physiological mechanisms of antihistamines are relatively well understood so let's take a deep dive into how antihistamines function!

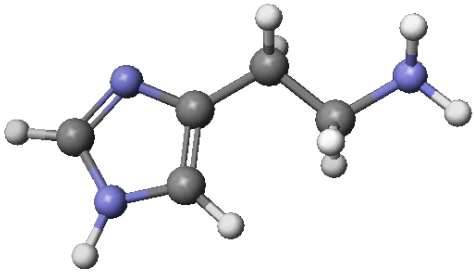


Figure 1: Histamine Structure, C5H9N3

History and Chemistry:

Histamine (Figure 1) was first isolated as β-iminazolylethylamine from mold ergot by British physiologists Sir Henry Dale and P.P. Laidlaw in 1910[3]. The name histamine was used later, meaning "tissue amine". Dale would later go on win the Nobel Prize in Physiology in 1936 for his study of acetylcholine in neurons.[2] The first histamine antagonist or antihistamine produced was called piperoxin in 1937; the compound was found to protect guinea pigs from the effects of histamine. In humans, the first successful antihistamine Antergan was used in 1942, but it was quickly replaced with Neoantergan which is still used in some circumstances today (called pyrilamine or mepyramine). Additionally, in 1938, French scientists Lévy-Brühl and Ungar demonstrated that histamine with synthesized from the amino acid histidine by pneumococcus bacteria and Balantidium coli.[4] When comparing the two molecules, it is easy to see how the enzyme histidine decarboxylase catalyzes the formation of histamine (Figure 2).

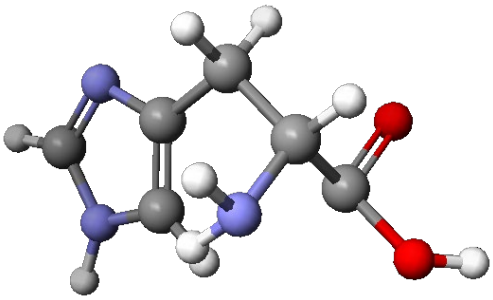


Figure 2: Histidine Structure, C6H9N3O2

Some notable chemical properties of histamine include its imidazole ring which is attached to an ethylamine. Under physiological conditions, the amine of the side-chain is protonated with a pKa of about 9.8.[5] This amino group proves useful in the formation of salt bridges which will be later discussed[6]. Like histidine, the imidazole ring of histamine is thought to be versatile in ligand binding due to its nearly neutral pKa of 6.

Pharmacology and Physiology:

Histamine is present throughout the entire body as a chemical messenger with especially high concentrations in the lungs, skin, and gastrointestinal tract.[7] Normally, histamine is synthesized and stored in white blood cells called basophils and mast cells to be released into tissues. When an allergic reaction occurs, histamine is sent out to bind to receptors called G protein coupled receptors (GPCRs) all over the body. A principal function

of histamine is to increase the permeability of blood vessels so that fluid moves out into the surrounding tissues, causing swelling.[1] This classic function of histamine is associated with H1 receptors. H2 receptors are present in parietal cells in the stomach which bind histamine produced by enterochromaffin-like (ECL) cells. Histamine stimulates parietal cells to increase hydrochloric acid secretion in the stomach. In the brain, histamine has another role as an excitatory neurotransmitter, mediating the wakefulness state.[9] An area of the hypothalamus called the tuberomammillary (TM) nucleus produces histamine, often called the wakefulness center of the brain. Additional functions of histamine are inflammation, smooth muscle contraction, and decreasing blood pressure[5,7].

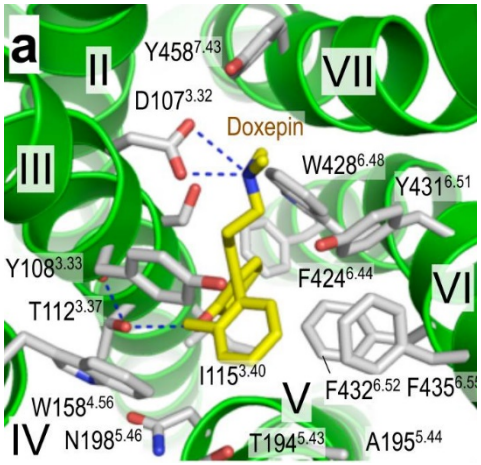


Figure 3: Binding of doxepin (yellow) to H1 receptor[10]

At their core, antihistamines are histamine antagonists, meaning they bind to histamine receptors which prevent actual histamine from binding.[1] There are four classes of histamine receptors H1, H2, H3, and H4, but H1 and H2 are the target of current antihistamine drugs. Antihistamine drugs can thus be categorized as targeting H1 or H2 receptors. H1 receptor-targeting drugs such as Diphenhydramine (Benadryl), Chlorpheniramine, and Cyclizine have FDA approved treatments including allergic rhinitis, sinusitis, angioedema, atopic dermatitis.

H1 receptor drugs can be further divided into first-generation and second-generation drugs. First-generation drugs such as pyrilamine (Neoantergan) and doxepin are effective at binding H1 receptors, but they easily cross the blood-brain barrier into the central nervous system.[10] This is due to the highly non-polar nature of drugs like doxepin which is seen in Figure 3 with three aromatic rings. Recent studies visualizing the ligand-binding in H1 receptors have found amino acid tryptophan (W428) as critical in the stabilization for both histamine and antihistamines like doxepin.[6,10] Also seen in Figure 3 is the salt bridge formed by the amine group of doxepin and the aspartic acid (D107) of the H1 receptor.[6] Because of the penetration of the blood-brain barrier in first generation H1 drugs, sedative effects are observed due to histamine's role in wakefulness from the TM nucleus.[9] Second-generation H1 drugs like cetirizine and olopatadine possess a new carboxylic moiety which significantly increases polarity and decreases access to the brain, hence the lack of sedative effect in these drugs. While first-gen drugs have a duration of pharmacological action of 4-6 hours, second-gen drugs have a duration of 12-24 hours.

H2 receptor drugs like cimetidine, famotidine, and nizatidine treat gastrointestinal conditions caused by excessive stomach acid (produced by parietal cells).[1] In the brain, H2 receptors have also been identified, but their function is still unknown.[2] Ongoing research continues the search for clinical benefit in H3 and H4 receptor antagonists. Despite their differing functions, all four histamine receptors are highly conserved with an evolutionary history older than mammals.[8] Contrary to prior thoughts, Ravhe et al. recently demonstrated an early vertebrate origin for all four histamine receptors, meaning you could probably use Benadryl on your pet Komodo dragon. There is also promising research into the H3 receptor's role in treatment of narcolepsy.[11] As the exact mechanisms of histamine receptors are explored, there is hope of better managing this peculiar messenger molecule histamine.

The University of Pittsburgh Department of Chemistry

is proud to announce

The Siska, McKeever, & Wass

Summer Undergraduate Research Fellowships

- These Undergraduate Research Fellowships will be awarded this Summer 2022.

- These Fellowships wil provide a Summer stipend of $3,500.00 to the recipient for work work carried out in the research lab of one of our faculty members.

- Please submit a letter of recommendation from a Faculty Mentor which includes your qualifications and details of the planned research project (1-2 pages) and a **one** page personal statement of your future goals to **Dr. George C. Bandik in Room 107 Chevron Science Center by February 15, 2022.** All nominations will be reviewed by our Undergraduate Curriculum Committee and the recipients will be recognized at our Undergraduate Spring Terms Awards Ceremony within the University of Pittsburgh, Department of Chemistry.

Deadline to receive all materials for these Fellowships is February 15, 2022.

American Chemical Society

Student Affiliates, University of Pittsburgh

Membership Application

This is a powerful professional organization for the benefit of individuals interested in chemistry and related fields. Our organization offers exciting extracurricular activities and many outstanding opportunities for our members, including:

1. **WEEKLY MEETINGS**-to plan activities, provide interesting speakers, discuss ideas, and keep students aware of what is happening in the scientific community.

2. **ANNUAL TRIPS**-Each year we sponsor (a) trip(s), to external chemistry environments, as well as for social enjoyment. Significantly reduced rates are available to active members. In the past few years we have traveled to New Orleans, Atlanta and New York.

3. **PROFESSIONAL NETWORKING**-Our organization has many opportunities to make contacts with professionals in both the scientific industry and academia. Student affiliates also have the opportunity to join the National ACS.

4. **SOCIAL ACTIVITIES**-We sponsor many activities throughout the year just for fun.

Our meetings are held every Friday at 12:00 noon in Room 150 Chevron Science Center. To join, complete the application form below and come to one of our meetings. Our first meeting will be <u>January 28, 2022</u> but you may join any time throughout the year.

Name: _____

School Address: _____

_____

Permanent Address: _____

_____

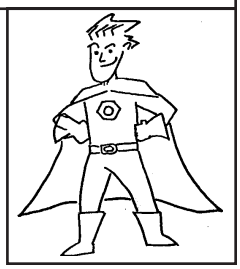
School Phone: _____ Home Phone: _____

Major: _____ Year in School **Fr.** **So.** **Jr.** **Sr.**

E-mail: _____

May we include your name, number and e-mail on the published phone list? **YES** **NO**

To submit this form by mail, send it to ACS-SA, Box 24, Chevron Science Center, University of Pittsburgh, Department of Chemistry, Pittsburgh, PA 15260. Be sure to include the $15.00 dues <u>(make checks payable to the University of Pittsburgh)</u>. It is possible to be active even if you can not attend the meetings. For more information, see our display case in the lobby of Chevron Science Center.



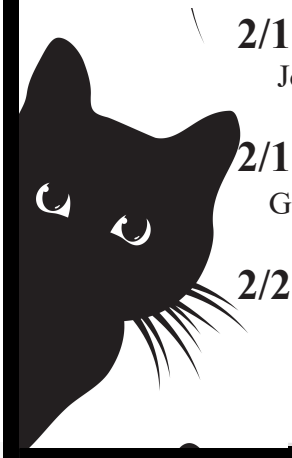
January & February 2022 ACS-SA Schedule

All Meetings are at Noon on Friday in 150 CHVRN

1/22 Officers/Seniors Affairs Meeting

1/28 Welcome Back Meeting

2/4 Undergraduate Experiences:
Join your peers to discuss outside the classroom opportunities



2/11 Saturday Science Preparation
Join us with Jake & Paul to get ready for this major outreach event

2/18 Registration with George
Get ready to register for Fall term 2231

2/25 Spring Birthday Celebration
(Saturday Science Eve)

Saturday Science Academy

Looking for something fun to do on February 26, 2022? Try Saturday Science!! It is an opportunity to help ambitious area high school students learn both general and organic chemistry in the lab. With your help, the students get to make crystal gardens, do a simple thin layer chromatography experiment, witness an acid base reaction with dry ice, measure the pH of some favorite soft drinks, and synthesize slime. Volunteers will play the role of a teacher: demonstrating the experiments, helping the students perform them, and finally, answering their questions. Saturday Science is a fun and rewarding volunteer experience in chemistry. So, are you still looking for something fun to do this year? Join us for the ACS-SA meeting on Friday February 11, 2022 at NOON in 150 CHVRN to plan for this great day.