

# Baclofen: Interaction with GABA<sub>B</sub> Receptor Leading to CNS Depression

Poster Team: Elizabeth Kelling, Nicole Kurszewski, Melissa Sachse, Madeline Schober, Robert Wolf

Jmol Team: Andrew Ackerman, David Antoine, Jonathan Foust, Jillian Godlewski, Andrew Saether

Faculty Advisors: Daniel Sem, Ph. D. and Ernest Stremski, MD, MBA

Institution: Concordia University Wisconsin School of Pharmacy, Mequon, WI 53097



## Abstract

Trauma, such as spinal shock, is a major cause of muscle spasticity leading to rigid muscles and intense pain. GABA<sub>B</sub> receptor agonists, such as baclofen, are a common treatment for spasticity because they are effective in reducing muscle tone and, thus, muscle spasticity. The treatment for long term pain management following such traumas often includes opioid analgesic medications as well. Providers prescribing both GABA<sub>B</sub> agonists with opioid analgesic should be cautious as concomitant use of these drugs can cause increased central nervous system (CNS) side effects such as respiratory depression, loss of consciousness, and hypotension.<sup>1</sup>

## Introduction

A 55 year old male was admitted to the ED after being ejected from his vehicle. He suffered from multiple scapular and thoracic spine fractures resulting in spinal shock. The patient experienced severe muscle spasticity and pain associated with his trauma. As a result, the patient was started on the maximum dose of 80 mg per day of baclofen by mouth for spasticity, as well as fentanyl and oxycodone to manage his pain. The pharmacist closely monitored the patient for signs and symptoms of CNS depression and adjusted doses of therapies accordingly.

### Baclofen<sup>2</sup>

- GABA analogue
- First line treatment for muscle spasticity
- Acts as a selective agonist targeting GABA<sub>B</sub> receptors
- Concomitant use of baclofen with opioid analgesics can enhance the effects of CNS side effects leading to respiratory depression or sedation
- Binds six amino acids in the active site of the GABA<sub>B</sub> receptor via van der Waals and hydrogen bonds

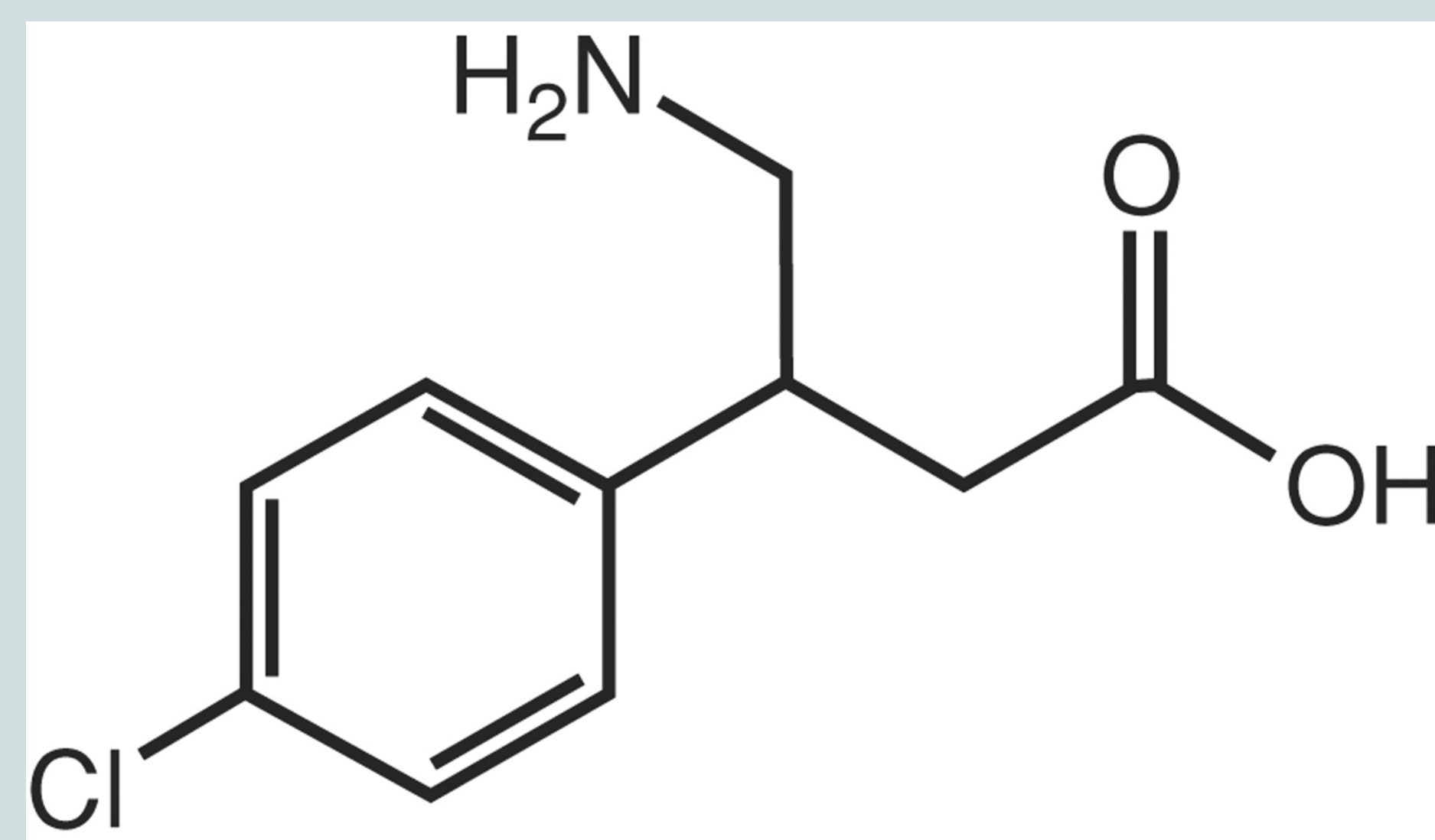


Figure 1. Baclofen Structure  
Obtained from: [alcalcal.oxfordjournals.org](http://alcalcal.oxfordjournals.org)

### GABA<sub>B</sub> Receptor<sup>2</sup>

- Inhibitory receptor that stops neurotransmitter release
- Metabotropic transmembrane G-coupled protein receptor, made up of 2 subunits, GBR1 and GBR2
- When bound with GABA, potassium channels open leading to an efflux of potassium, which causes hyperpolarization of the cell
- Stimulation of inhibitory neurons decreases action potentials and causes sedation.

## Molecular Story

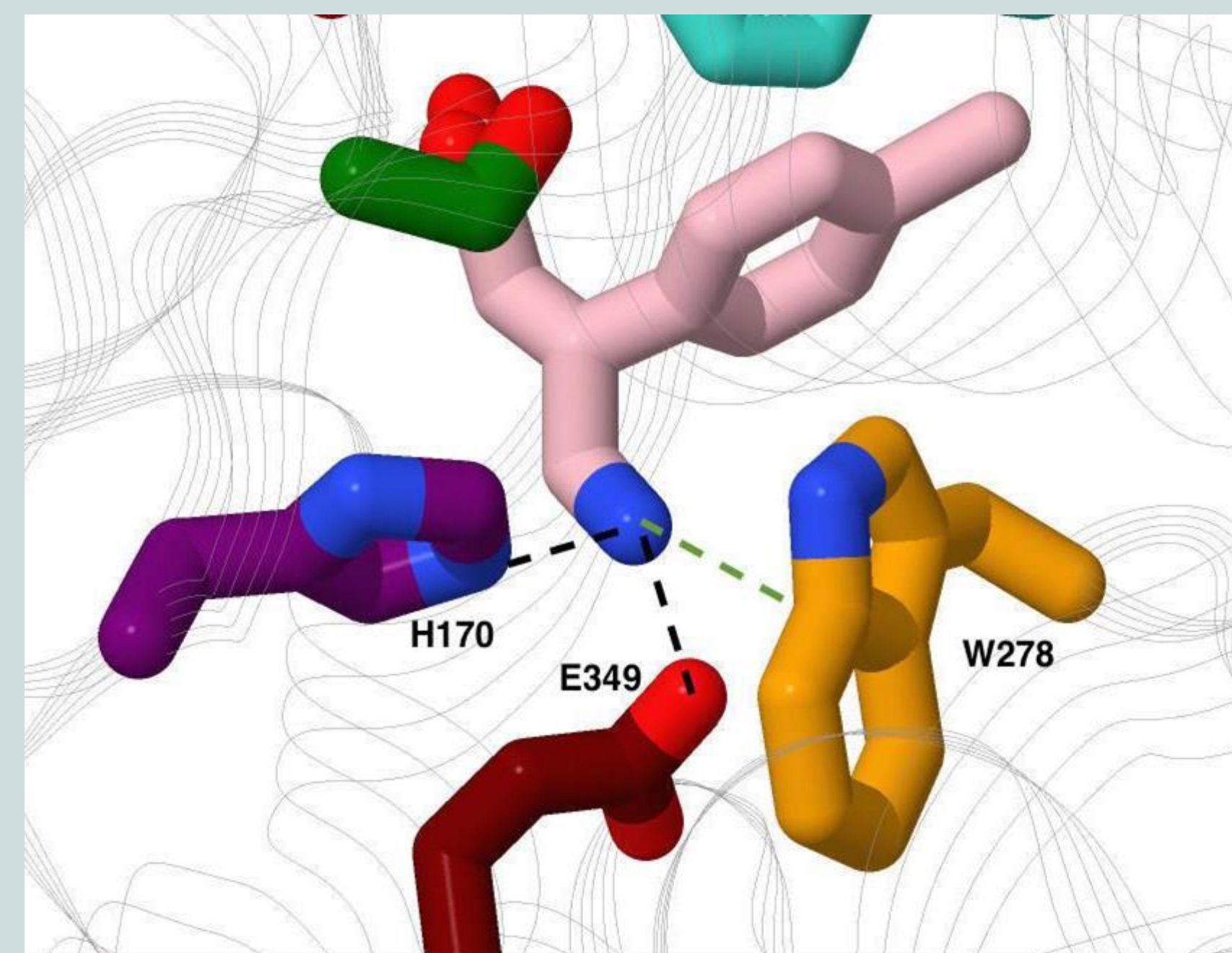


Figure 2. Hydrogen bonding interactions between Baclofen's amine group and Histidine-170 and Glutamate-349. Figure also displays the amine undergoing van der Waals interactions with Tryptophan-278. Rendered from 4MS4.pdb

### Amine<sup>2,3</sup>

In vivo, the amine group on baclofen has a positive charge that is essential for the hydrogen binding interactions with the GABA<sub>B</sub> receptor. This group interacts with the amino acids Histidine-170, Glutamate-349, and Tryptophan-278 via hydrogen bonds. Two of the protons on the amine interact with the double bonded nitrogen in the imidazole ring of Histidine-170 and the nucleophilic oxygen in Glutamate-349. The nitrogen in the amine interacts with the phenyl group of Tryptophan-278 via van der Waals hydrophobic interactions in the active site. (Figure 2)

### Carboxylic Acid<sup>2,3</sup>

In vivo, the carboxylic acid group on baclofen is deprotonated, resulting in a negative charge that allows it to interact with different amino acids compared to the amine group. The main amino acids that the carboxylic acid group interacts with are Serine-130, Serine-153, and Tyrosine-250. Both oxygen atoms, with two lone pairs on the carboxylic acid group, form multiple hydrogen bonds with Serine-153 and Serine-130. Tyrosine-250 only forms one hydrogen bond to the carboxylic acid group. (Figure 3)

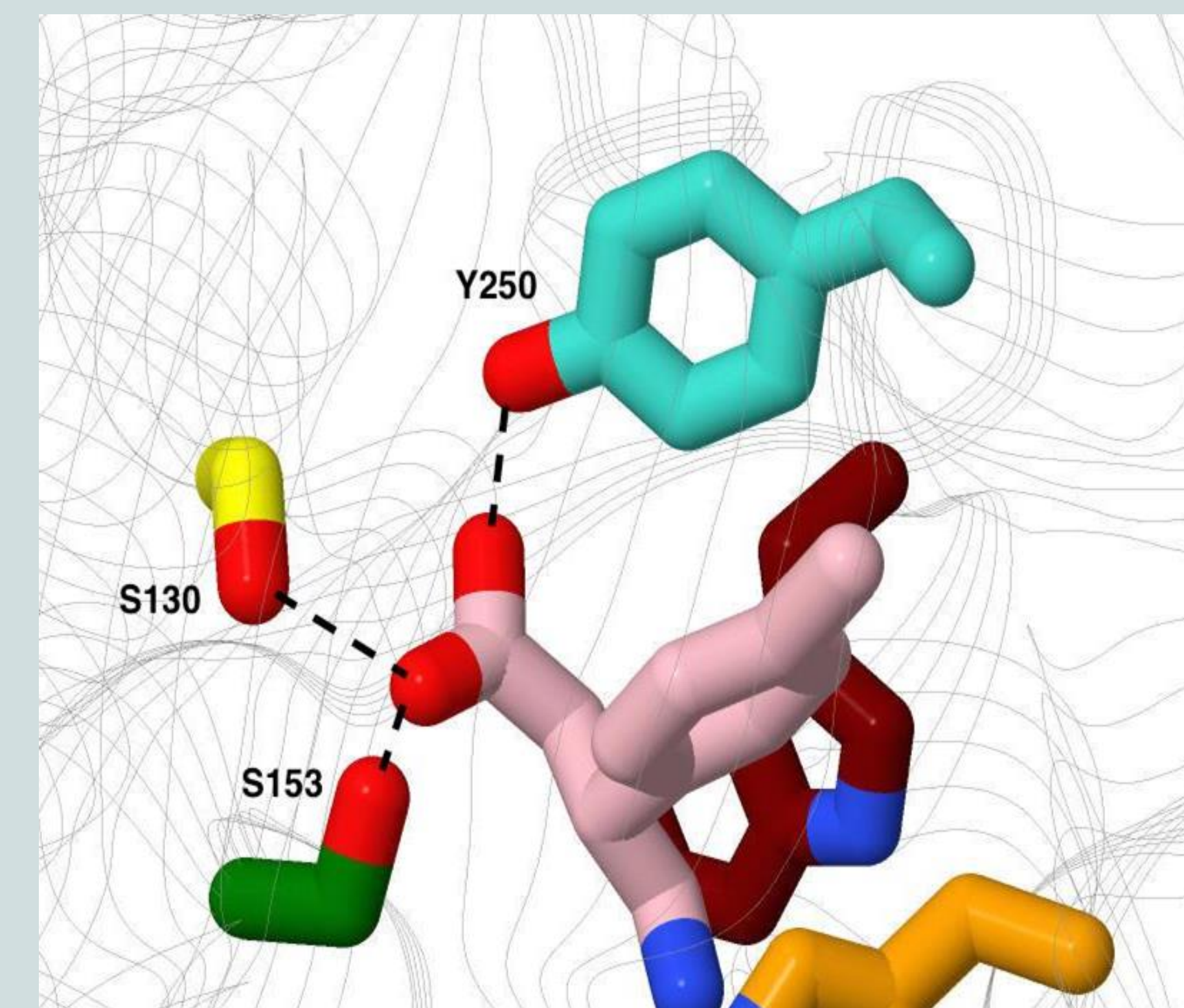


Figure 3. Hydrogen bonding between the carboxylic acid of Baclofen and the amino acid serine-130, Serine-153 and Tyrosine-250. Rendered from 4MS4.pdb

### Beta-Chlorophenyl<sup>2,3</sup>

The beta-chlorophenyl group in baclofen partakes in the van der Waals hydrophobic interactions with Tyrosine-250 and Tryptophan-278. This ring interacts with these two amino acids to create molecular ring stacking. The indole ring of Tryptophan-278 flips around to accommodate the beta-chlorophenyl ring substituent of baclofen, allowing the formation of the aromatic ring stacking interactions. (Figure 4)

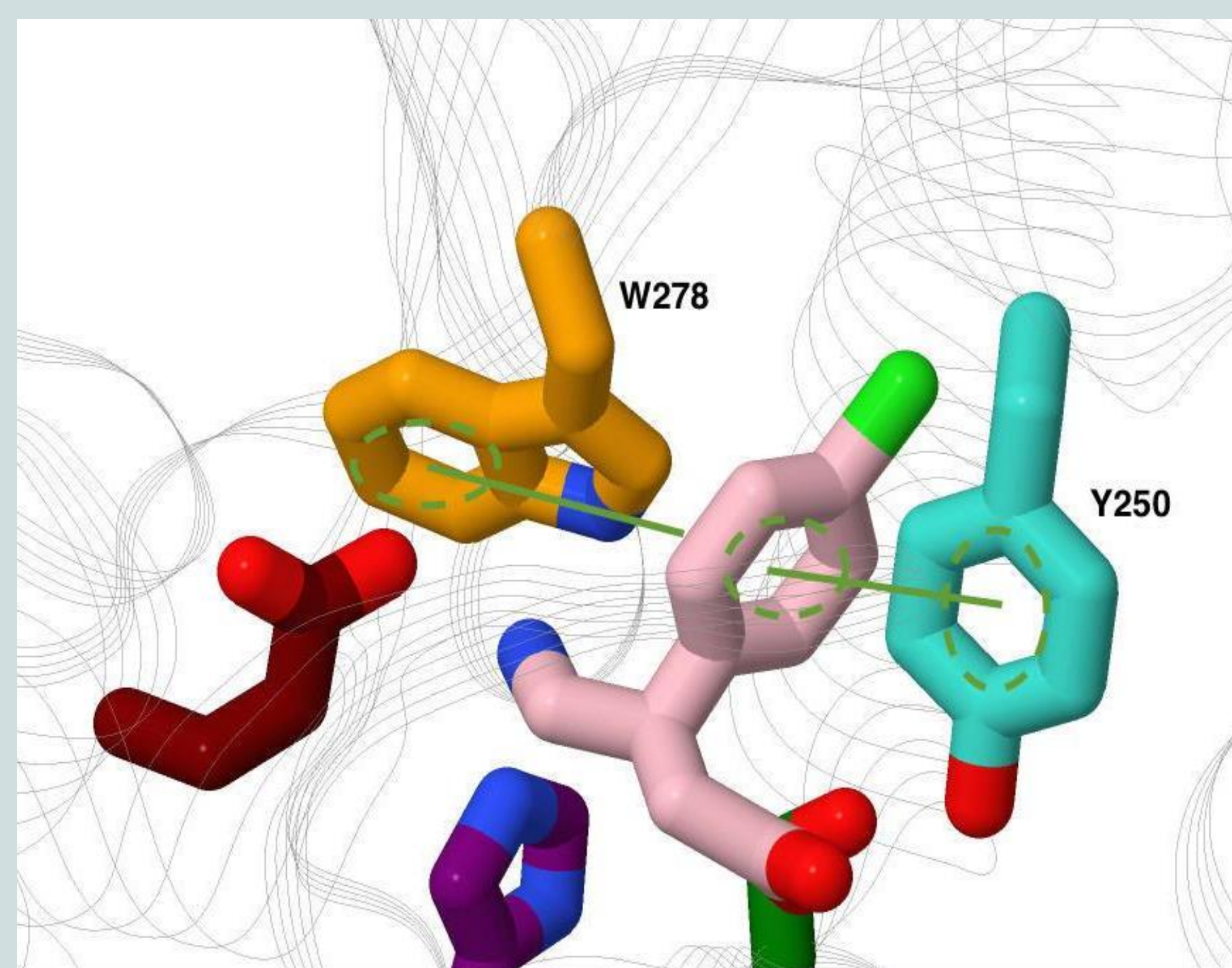


Figure 4. Pi stacking interaction between the Beta-Chlorophenyl group of baclofen and Tyrosine-250 and Tryptophan-278. Rendered from 4MS4.pdb

## Future Research

A current challenge with baclofen administration is the drug's ability to cause CNS depression. Baclofen acts on GABA<sub>B</sub> receptors both in the brain and spinal cord. This undesirable activation of GABA<sub>B</sub> receptors in the brain can cause clinically significant sedative effects.<sup>1</sup> Currently, baclofen is being administered intrathecally to produce a localized effect in the spinal cord. One possibility for further improvement in the mechanism of action of baclofen is to give it higher affinity for the GABA<sub>B</sub> receptors in the spinal cord. The enhancement of receptor specificity could lead to the possibility of other, more accommodating dosage forms. Having baclofen preferentially bind in the spinal cord over the brain would decrease the CNS depressant effects that are most concerning regarding patient safety.

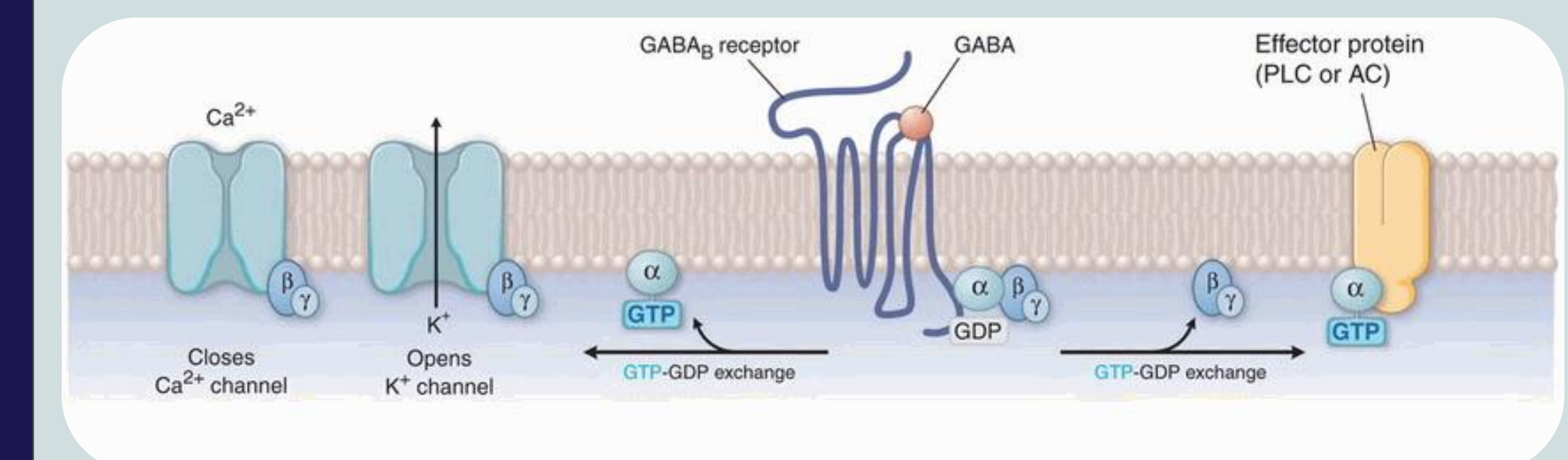


Fig. 5 Downstream signaling of the GABA<sub>B</sub> receptor  
Obtained from: Golan Figure 12.5<sup>4</sup>

## Summary

Baclofen is a medication used to treat muscle spasticity, which works by acting as an agonist to the GABA<sub>B</sub> receptor. The GABA<sub>B</sub> receptor is a metabotropic G-coupled protein receptor that functions to hyperpolarize the cell and decrease action potentials, causing relaxation of the muscle cells. Baclofen binds the GABA<sub>B</sub> receptor via hydrogen bonds and van der Waals interactions. The various components of the chemical structure of baclofen binds to six different amino acids on the GABA<sub>B</sub> receptor.

Since GABA<sub>B</sub> receptors are found in both the spinal cord and brain, patients taking baclofen should be cautious when taking other medications that cause sedation. Opioid analgesic medication can lead to increased CNS effects, such as respiratory depression, sedation, and hypotension and should be used with caution in conjunction. In our case, the patient was closely monitored for any signs or symptoms of CNS depression.

## References

1. Hudgeson, P.; Weightman, D. Baclofen in the Treatment of Spasticity. *British Medical Journal*. 1971;4: 15-17.
2. Geng Y, Bush M, et al. Structural mechanism of ligand activation in human GABA(B) receptor. *Nature*. 2013 Dec 12;504(7479):254-9. doi: 10.1038/nature12725.
3. Wieronska JM, Stachowicz K, Nowak G, Pilc A. The loss of Glutamate – GABA Harmony in Anxiety Disorders. In: Kalinin V, ed. *Anxiety Disorders*. Kraków, Poland; 2011. <http://www.intechopen.com/books/anxiety-disorders/the-loss-of-glutamate-gaba-harmony-in-anxiety-disorders>.
4. Golan DE, Tashjian AH, Armstrong EJ, Armstrong AW, eds. *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy*. 3<sup>rd</sup> ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.