

Ritonavir and Fluticasone Interaction and Resulting Cushing's Syndrome

Poster Team: Allison Dembeck, Joseph Dvorak and Stacy Menzer

Jmol Design Team: James Lokken, Boris Rempel and Tristin Sabin

School of Pharmacy, Concordia University Wisconsin, 12800 Lake Shore Dr., Mequon, WI, 53097

Educators: Daniel S. Sem, Ph.D., Christopher W. Cunningham, Ph.D.

Mentors: Matthew Carleton, PharmD, St. Luke's, Milwaukee, WI; Valerie Huibregtse, PharmD, CVS,

Fox Point, WI; and Lisa Boerner, PharmD, Lakeview Pharmacy, Racine, WI

ABSTRACT

In the world of medications, many drugs interact with each other. One such interaction involves the anti human immunodeficiency virus (HIV) drug ritonavir and the inhaled steroid fluticasone. These two medications may result in an increased level of glucocorticoids in the blood leading to a syndrome known as Cushing's Syndrome. This interaction is brought on when ritonavir binds to CYP3A4 in the liver, an enzyme which metabolizes many drugs including fluticasone, and inhibits it. Fluticasone levels increase and more of the drug binds to its receptor. This causes more of the glucocorticoid receptors (GR) to modify the transcription of the DNA which leads to serious complications such as Cushing's Syndrome.

INTRODUCTION

Figure 1
Cushing's Syndrome in a man showing symptoms of excess weight especially in the abdominal and chest area, a lump on his upper back and stretch marks or striae. All are signs of an increased level of glucocorticoids.



<http://www.mayoclinic.com/health/medical/IM00313>

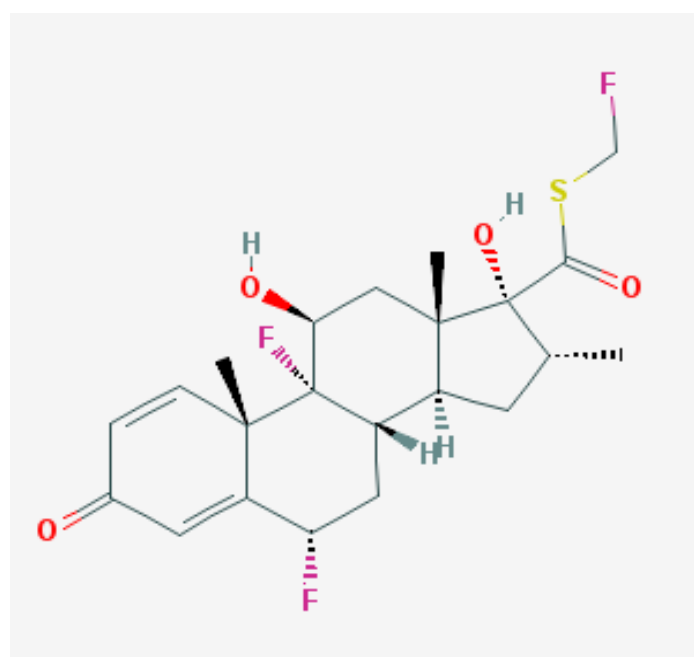


Figure 2
2D structure of Fluticasone
http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=5311101&loc=ec_rcs

A patient walks into a clinic. He has been having unusual symptoms for the past two weeks after starting fluticasone. The patient, SR, explains he thought the symptoms were normal side effects of his antiretroviral medication, ritonavir, until he started seeing bruises, stripes on his abdomen, and his face getting rounder. His weight is taken and he has gained twenty pounds in the last 2 weeks. After further exam a mass of fat is found at SR's lower cervical and upper thoracic vertebrae. Labs are scheduled for the next day checking early morning plasma cortisol levels and a thirty minute synthetic adrenocorticotropic hormone (ACTH) stimulation test. The results come back with a plasma cortisol level below 3 mcg/dL, which indicates adrenal insufficiency. The level of ACTH before the stimulation test was found to be lower than normal, which indicates a secondary or tertiary adrenal insufficiency (Fois, 2008). With these lab values and the physical signs of the patient, SR is diagnosed with Cushing's Syndrome. Cushing's Syndrome is a possible drug induced disease state brought upon by an interaction between the antiretroviral human immunodeficiency virus (HIV) drug ritonavir and the glucocorticoid fluticasone. The features and interactions of the molecules are explained below.

Ritonavir

- Protease Inhibitor
- Inhibits processing of polypeptides which prevents viral replication including HIV
- Inhibits P450 CYP3A4 by irreversibly binding to the enzyme
- Decreases metabolism of CYP3A4 substrates

Fluticasone

- Glucocorticoid
- Binds to glucocorticoid receptor (GR)
- GR activation causes the complex to bind to DNA and modulate transcription
- Indicated for allergic rhinitis due to inhibition of histamine release

Ritonavir decreases metabolism of fluticasone which is a CYP3A4 substrate. There is more fluticasone in the body which binds to GR and increases DNA modulation. These modulations can lead to Cushing's Syndrome.

MOLECULAR STORY

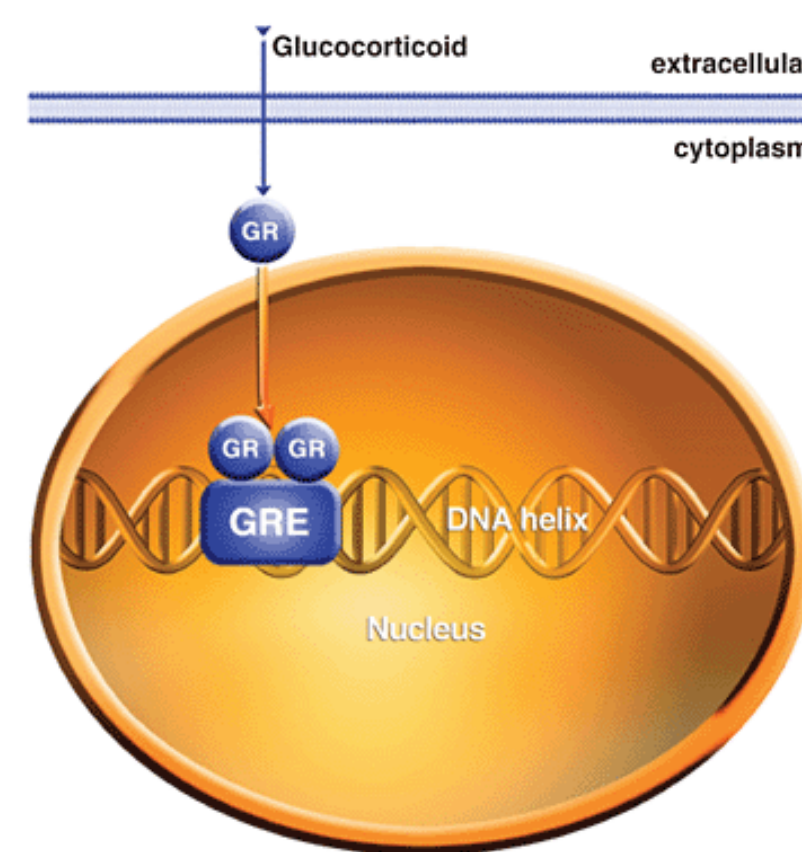


Figure 3
Due to fluticasone's lipophilic nature, it can easily pass through the cell's plasma membrane and activate the GR. Upon binding, the protein complex dissociates from the chaperone molecules and the GR translocates into the nucleus. In the nucleus, the GR binds as a homodimer to regulatory elements in promoter regions of GR-responsive genes, causing transactivation or transrepression of protein synthesis (Schacke et al., 2002).
<http://pubs.niaaa.nih.gov/publications/arh313/196-214.htm>

Figure 4
Fluticasone is shown at the binding site of GR with all of the interactions holding the steroid in the active site. The glucocorticoid receptor lipophilic pocket accommodates the furoate ester very efficiently (Biggadike, et al., 2008). The 3-keto group of fluticasone furoate hydrogen bonds with Gln570 and Arg611. The Asn564 on the receptor hydrogen bonds to the 11β-hydroxyl and the 17β-fluoromethylthio-fluorine of the fluticasone molecule. Additionally, there are strong van der Waals interactions within the 17α pocket. The important residues that have strong interactions in the pocket include Gln642, Tyr735 and Thr739, as well as Met560, Leu563, Met639, Met643, Met646, Cys736 and Ile747 (not shown).

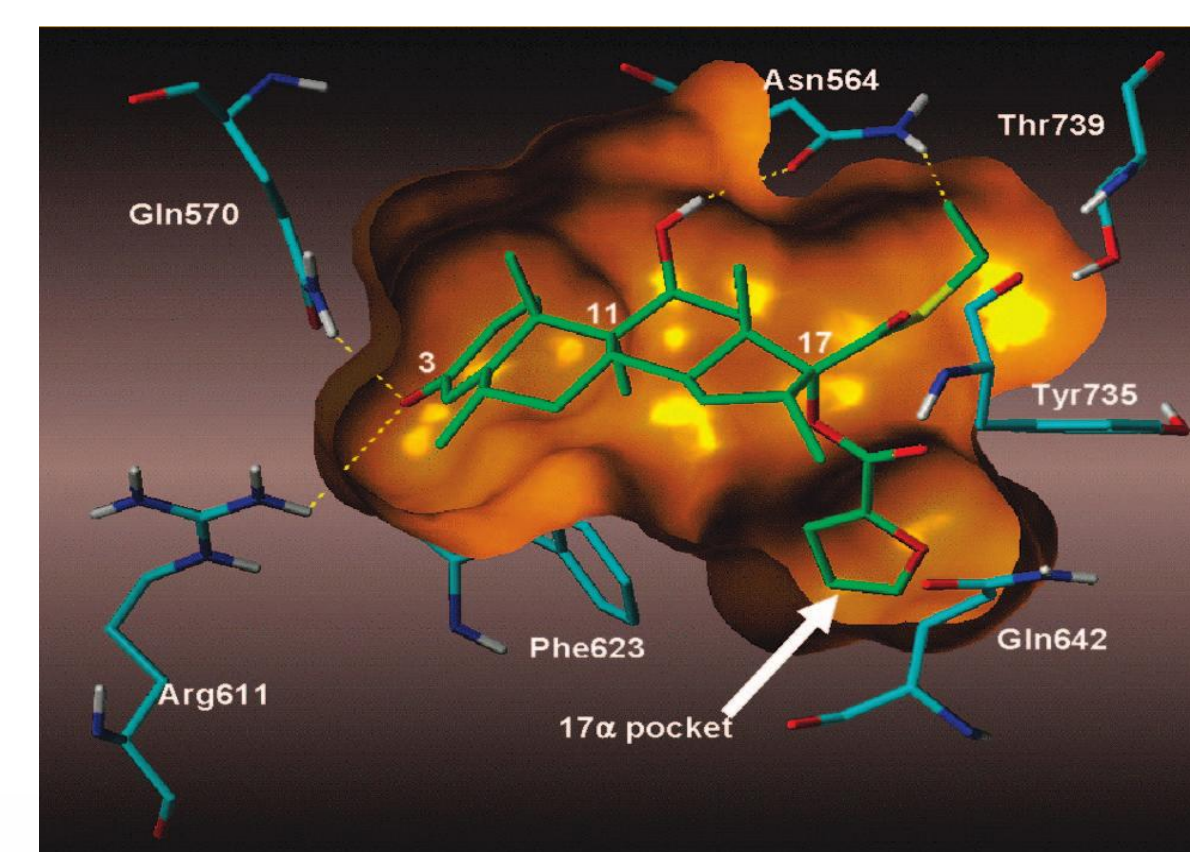
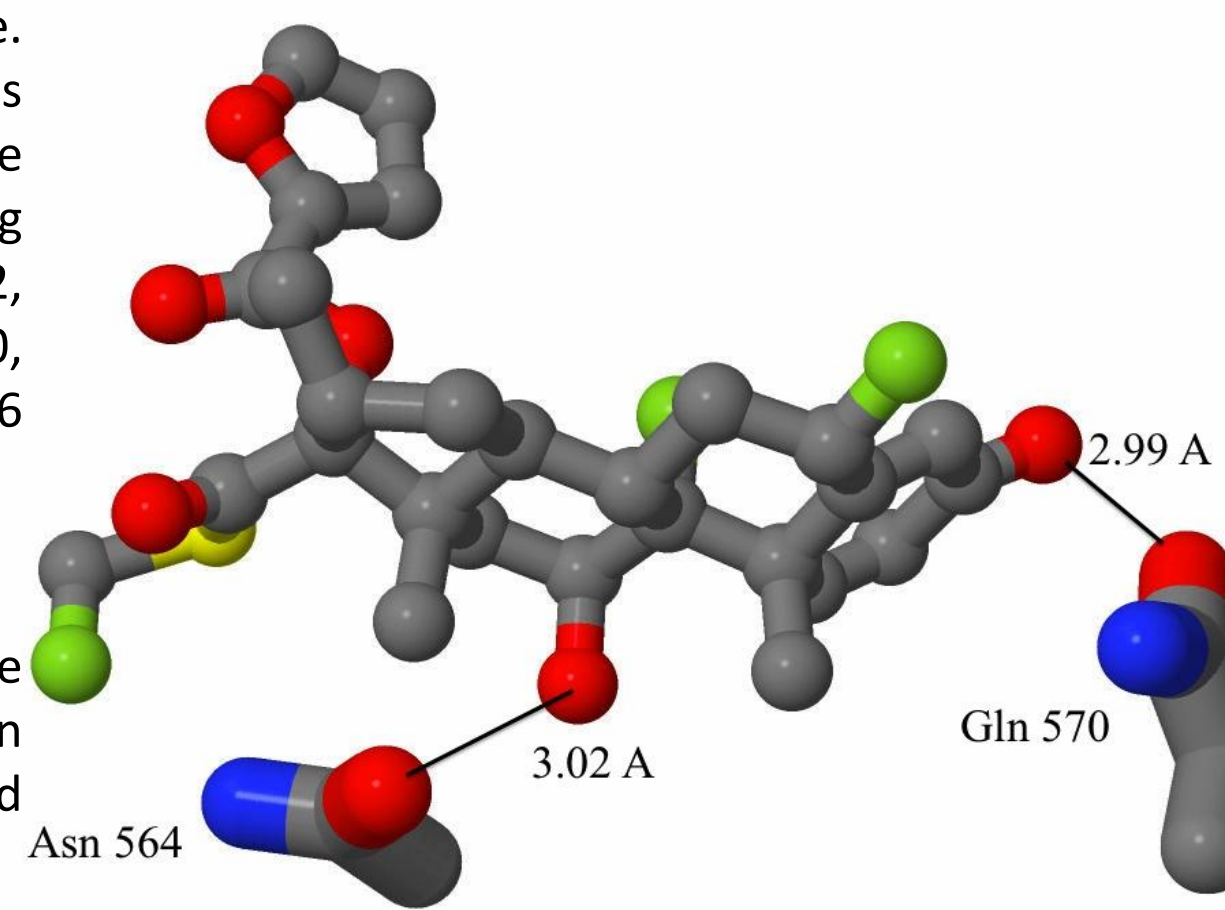


Figure 5
The distances in Angstroms that were calculated by the Jmol software between fluticasone and the amino acid Asn564 and Gln570 are shown in Figure 4.



The binding and mechanism of action of fluticasone is described in figures 3-5. As fluticasone levels increase in the blood, there is more modulation of DNA by the GR. This rise in fluticasone levels results from simultaneously treating the patient with ritonavir, which inhibits fluticasone metabolism by irreversibly binding to CYP3A4. Ritonavir's interaction is explained in figures 6-7.

Figure 6
One of the closest bonds between ritonavir and CYP3A4 involves the iron atom in the center of CYP3A4's heme and the nitrogen atom of the thiazole group of ritonavir. The thiazole nitrogen binds both the ferric and ferrous form of the iron at a distance of about 0.23 nanometers (Sevrioukova, 2010).

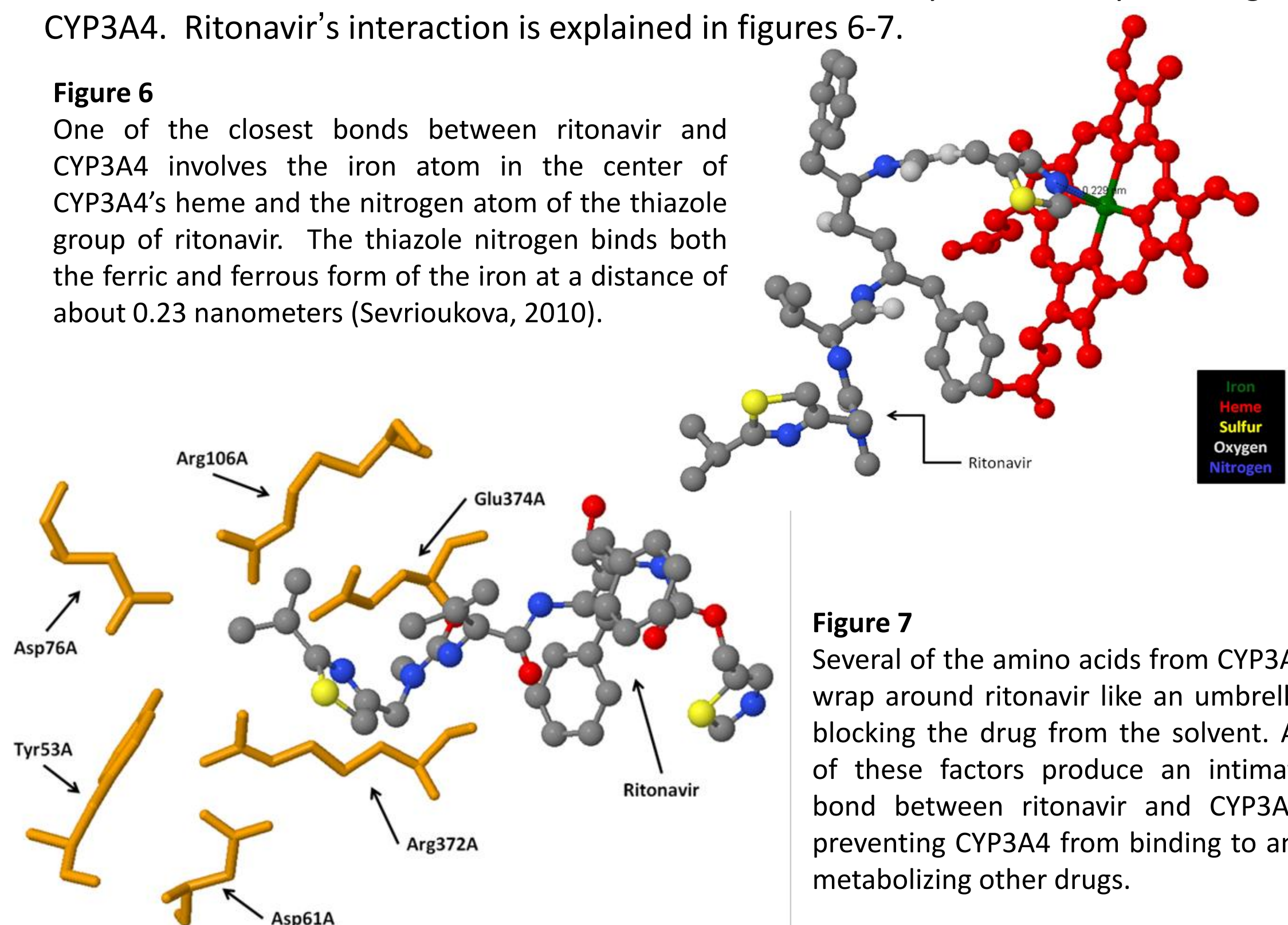


Figure 7
Several of the amino acids from CYP3A4 wrap around ritonavir like an umbrella, blocking the drug from the solvent. All of these factors produce an intimate bond between ritonavir and CYP3A4, preventing CYP3A4 from binding to and metabolizing other drugs.

WHAT'S THE NEXT STEP?

Prevention of Cushing's Syndrome can be done both through therapeutic and pharmacologic alterations. In a clinical setting, the increased levels of fluticasone are most often prevented by decreasing the dosage or frequency of fluticasone that the patient administers. However, medicinal chemists have also approached the issue of CYP3A4 inhibition, by creating Protease Inhibitors (PI) with different structures that do not bind with as high an affinity to CYP3A4 that Ritonavir exhibits.

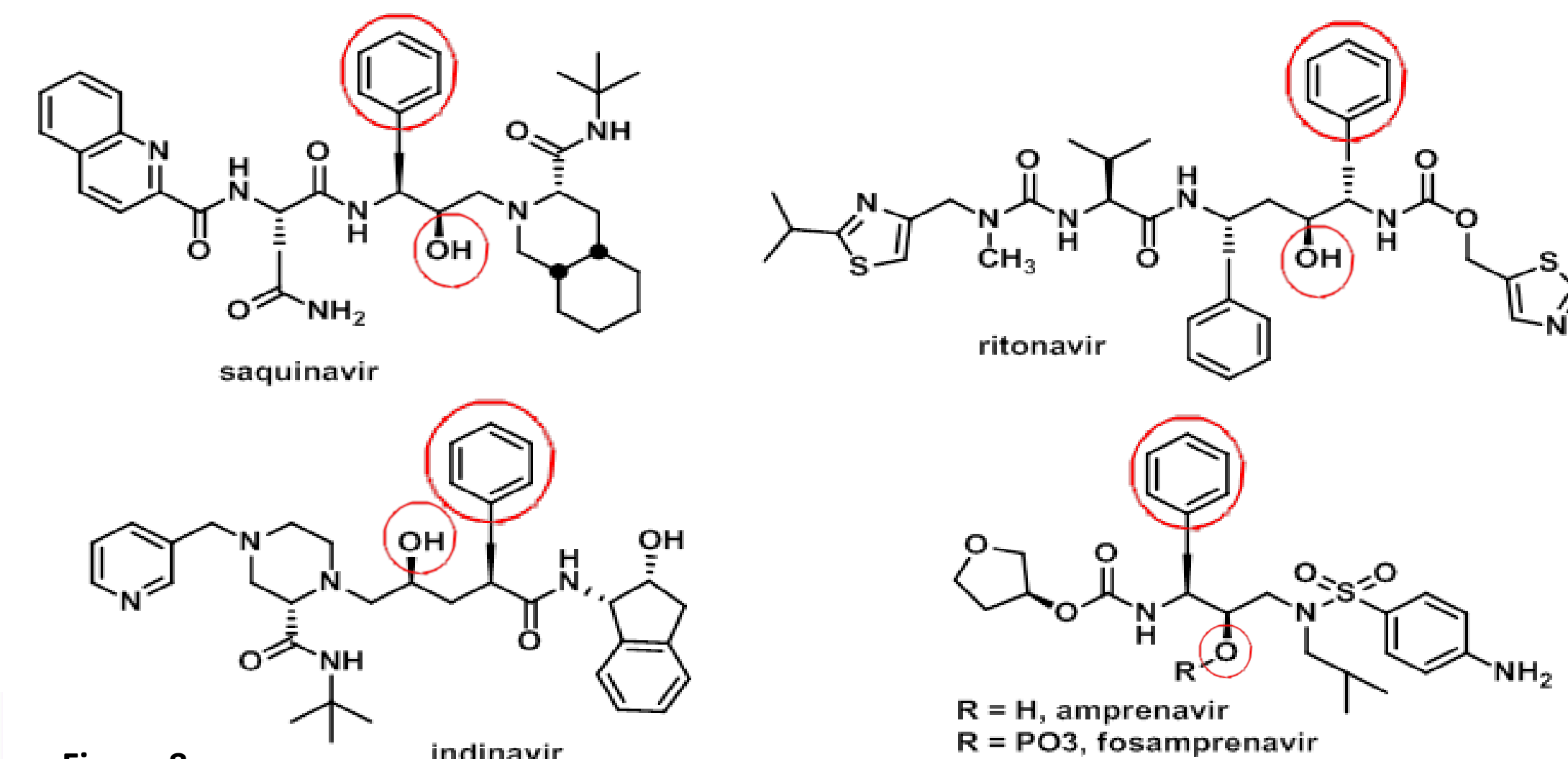


Figure 8
Structures of various Protease Inhibitors, with Phe and hydroxyl side-groups encircled in red (Cunningham, 2012)

While maintaining the Phenylalanine (Phe) side group, but changing the backbone of the PI molecule to make it look less like a peptide, the drug will display less affinity for the CYP3A4 enzyme. The Phe must be maintained in order for the drug's mechanism of action to proceed; that being, to bind to the virus' protease and inhibit its function. However, by altering the position of the hydroxide, or by modifying the side-groups of the backbone, such as in saquinavir, indinavir, amprenavir, or fosamprenavir, the metabolism of the molecule will also be modified. These modifications to the PI structure may help limit the inhibition of CYP3A4 and related enzymes, and may be an alternative method to preventing the associated increase in fluticasone and other drugs normally metabolized by these enzymes.

SUMMARY

Cushing's Syndrome results from chronic exposure to elevated levels of circulating free glucocorticoids. Cushing's Syndrome may be endogenous; however, the most common cause of Cushing's Syndrome is use of supraphysiological amounts of exogenous glucocorticoids (Newell-Price et al., 2006). This is the case with fluticasone mediated, iatrogenic Cushing's Syndrome. It can be caused from ritonavir binding irreversibly with CYP3A4 so fluticasone is not metabolized by that enzyme. Fluticasone then has a much longer half life and can cause Cushing's Syndrome from an excess of the drug circulating in the blood.

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