

# Aliskiren as an Antihypertensive Drug

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## ABSTRACT

Aliskiren is a direct renin inhibitor in the Renin-Angiotensin-Aldosterone System (RAAS). It acts to decrease plasma renin activity by directly binding the renin molecule and inhibiting the conversion of angiotensinogen to angiotensin I, an early step in RAAS. This makes aliskiren an effective antihypertensive agent. It is very tolerable for patients, which serves to increase compliance and leads to better patient outcomes.

## INTRODUCTION

### Clinical Case Study

CK is a 48 year old woman with hypertension who was diagnosed two years ago. CK started treatment for her hypertension by taking hydrochlorothiazide 25 mg once a day and lisinopril 5 mg once a day. CK experienced an anaphylactic reaction to lisinopril and immediately discontinued therapy. She then began treatment with verapamil 180 mg once a day. After 18 months of therapy, CK started to experience swelling in her feet, ankles, and legs. Verapamil was discontinued and aliskiren, a direct renin inhibitor, 150 mg by mouth once daily was started.

### History<sup>1</sup>

- 1898, Renin-Angiotensin-Aldosterone System (RAAS) discovered
- 1970s, angiotensin converting enzyme (ACE) inhibitors introduced
- 1970s, angiotensin receptor blockers (ARB) introduced
- 2007, Aliskiren approved by FDA

### Development<sup>1</sup>

#### Problem:

- ACE inhibitors and ARBs do not fully block RAAS
- Renin is more than just an enzyme

#### Potential solutions:

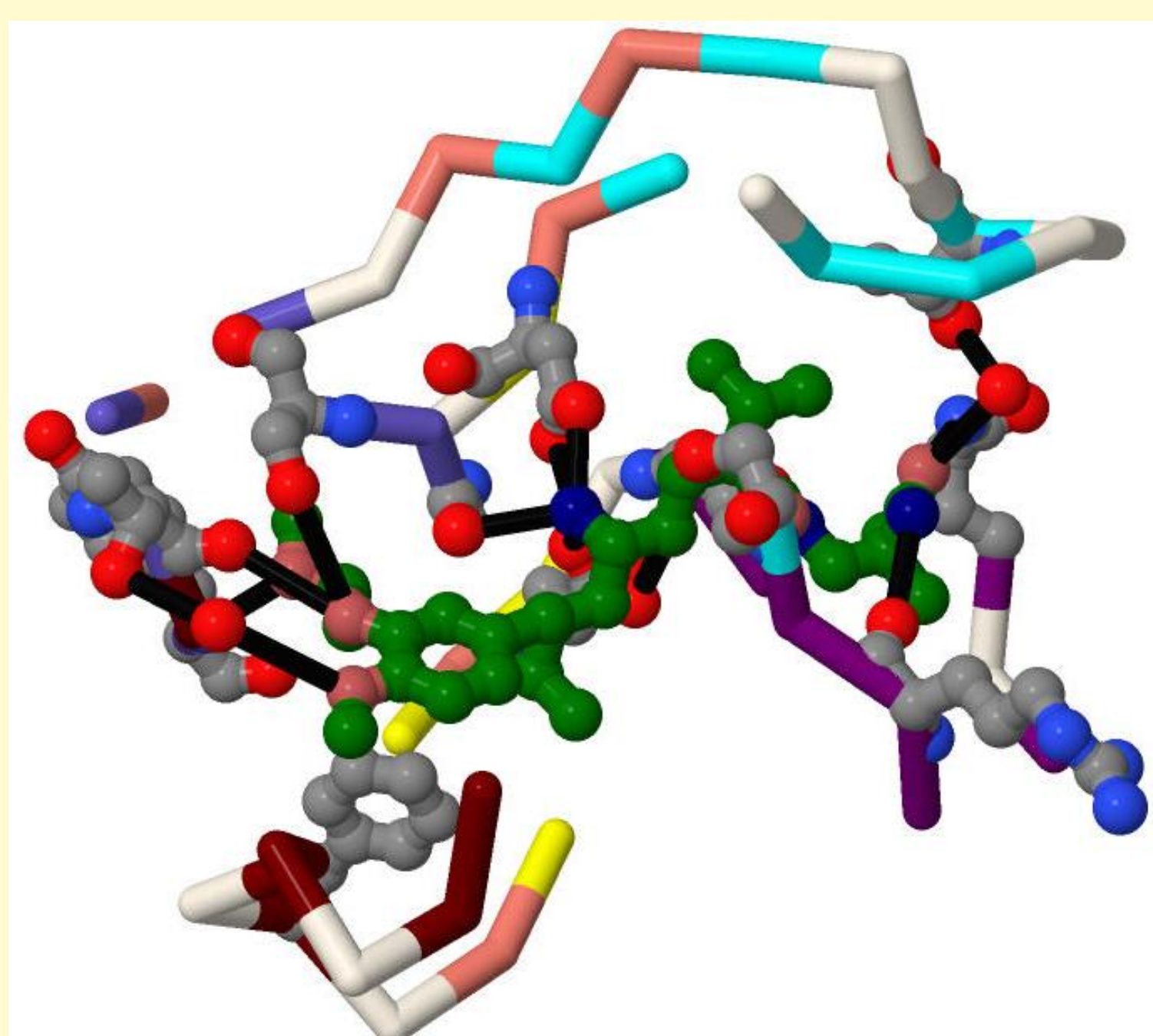
- Peptide analogues of angiotensinogen and dipeptide transition-state analogs
- Lacked stability, bioavailability, efficacy and cost-effectiveness

#### Solution (Aliskiren):

- Direct renin inhibition by binding to it specifically
- Does not have shortfalls of previous drugs

### Structural Design<sup>2</sup>

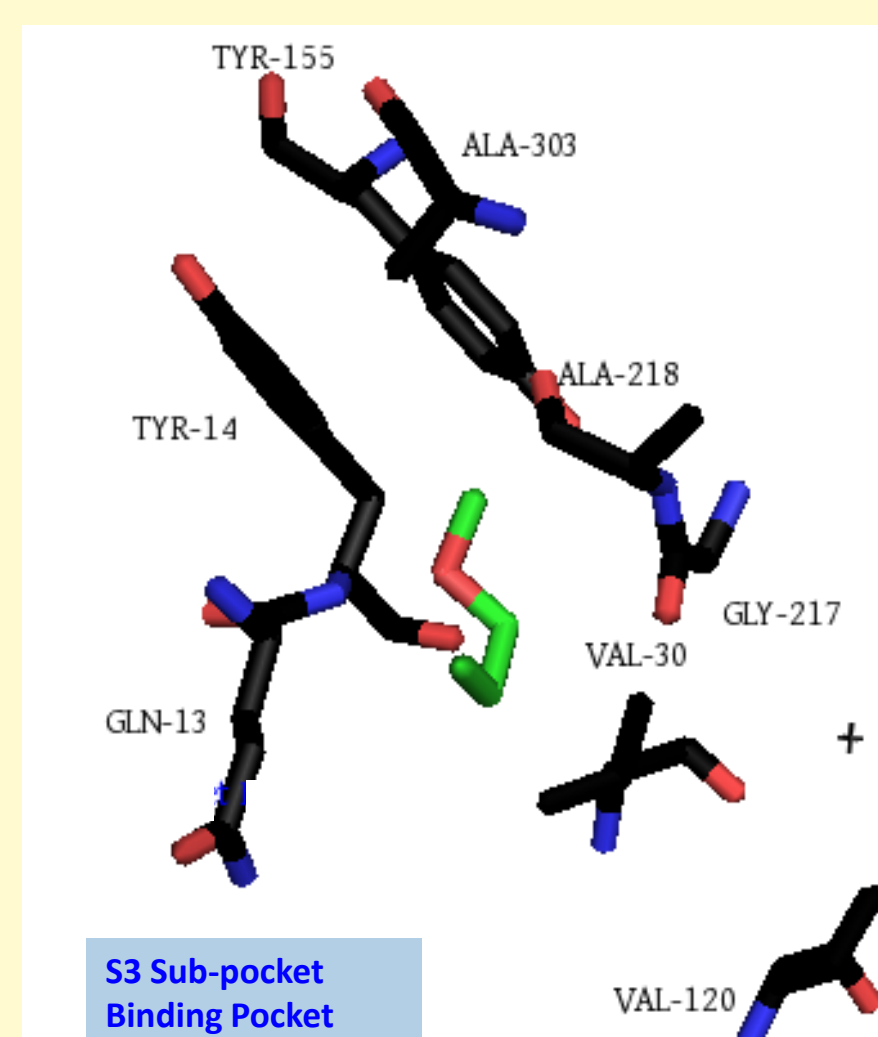
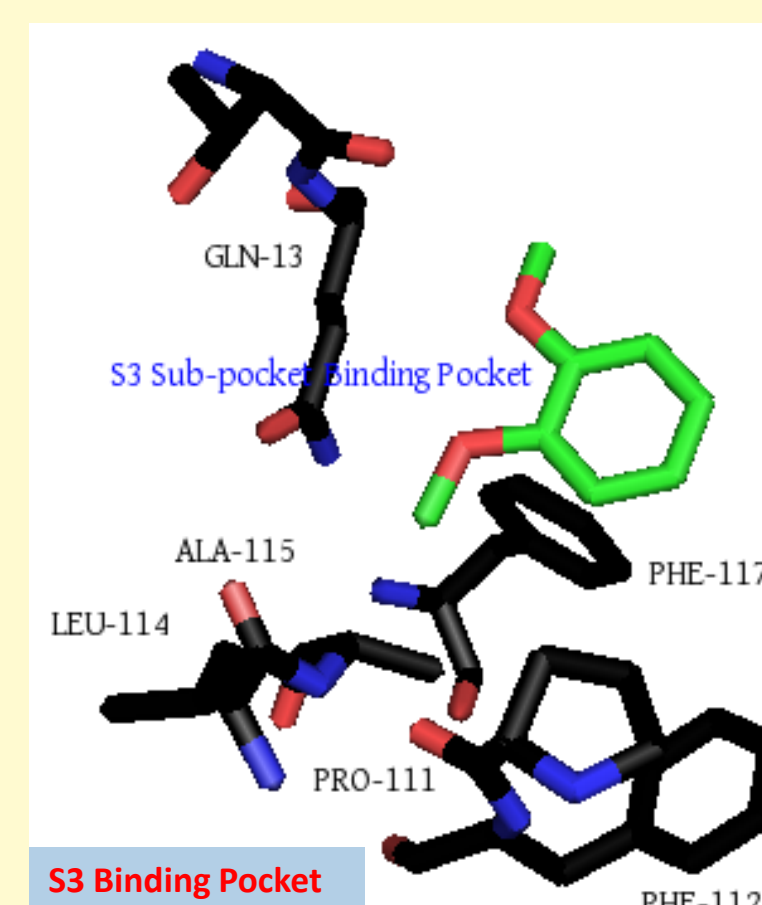
- X-ray crystallography identified specific binding sites on renin
- S1/S3 pocket chosen as drug target due to large size and hydrophobic properties
- Peptide was removed and lipophilic moieties added to previous attempts
- Aliskiren has high affinity to renin S1/S3 pocket and reduced side effects



## MOLECULAR STORY

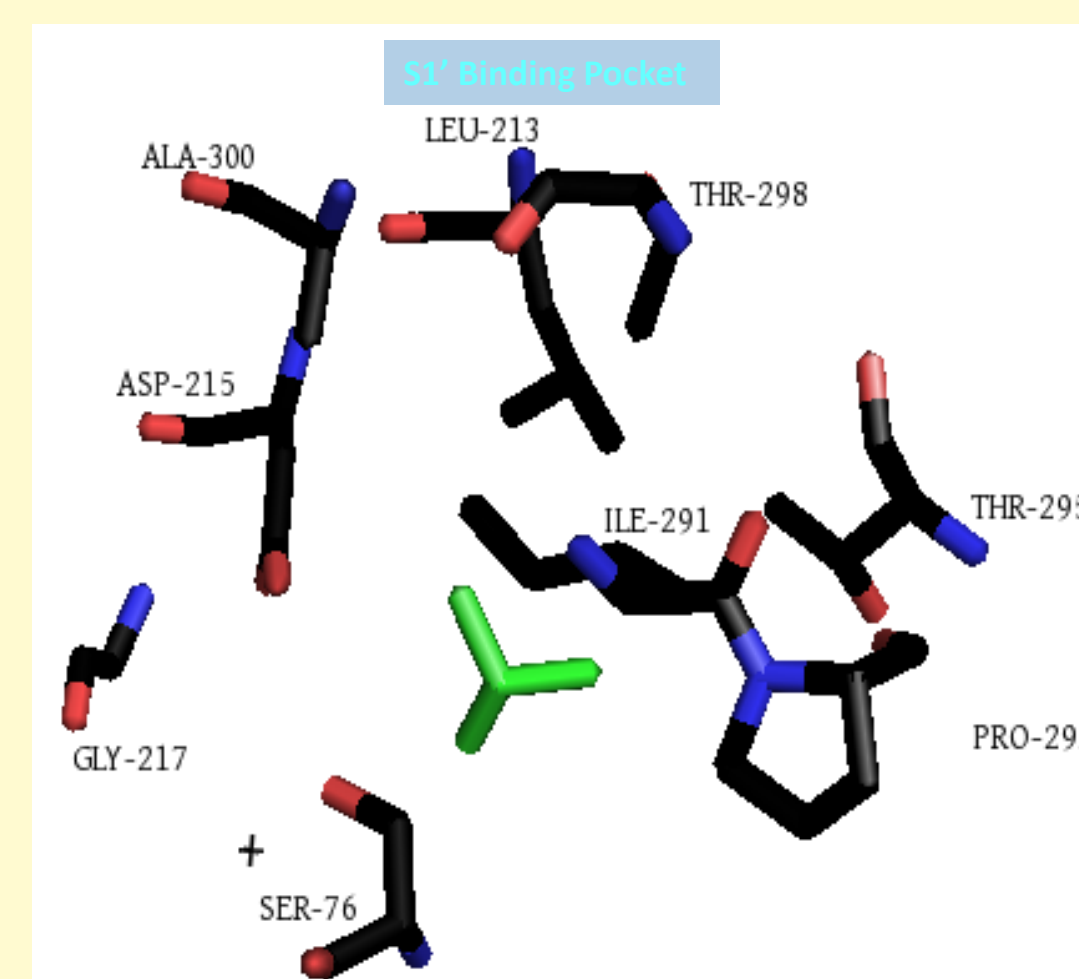
### S3 binding pocket<sup>3</sup> (Red) – at right

- Thr12, Gln13, Pro111, Phe112, Leu114, Ala115, and Phe117
- Methyl group interacting with Leu114 and Ala115
- Phenyl group interacting with Pro111, Phe112, and Phe117



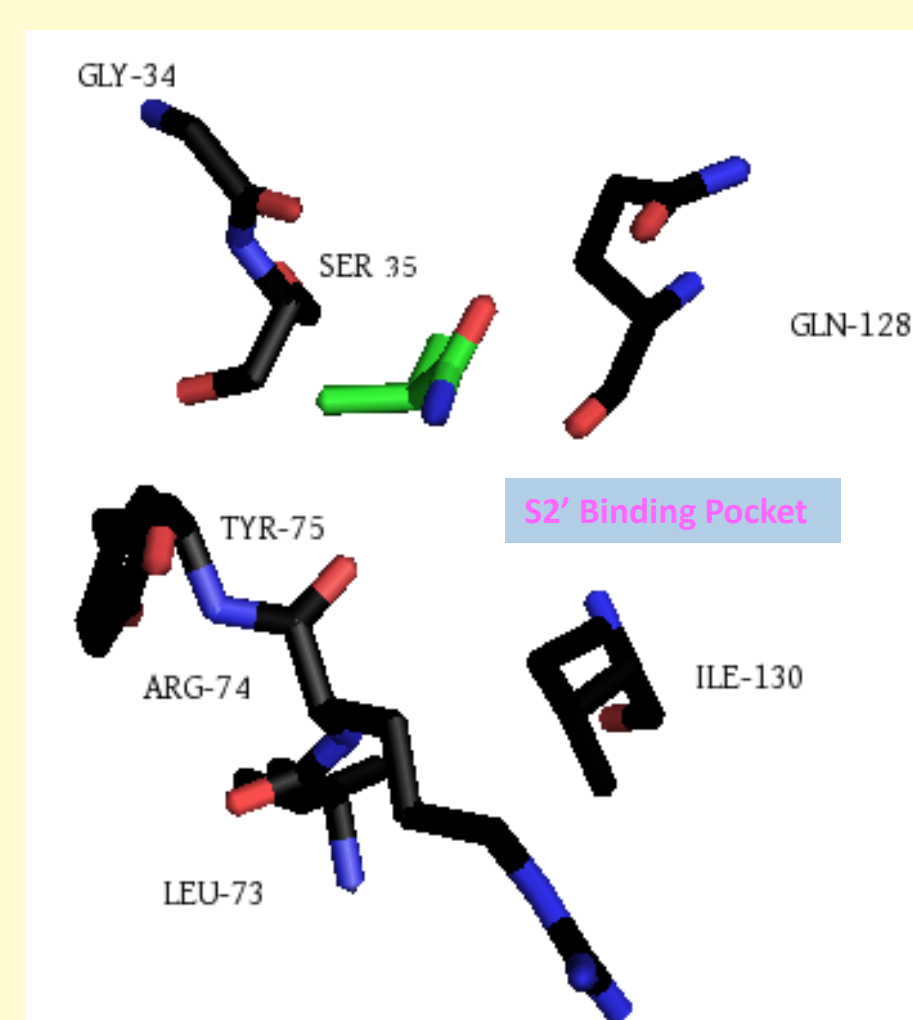
### S3<sup>SP</sup> binding pocket<sup>3</sup> (Blue) – at left

- Gln13, Tyr14, Val30, Val120, Tyr155, Gly217, Ala218, and Ala303
- Amine of Tyr14 is proton donor; hydrogen bonds with the ether in the chain
- Remaining amino acids have hydrophobic interactions with the rest of the chain



### S1' binding pocket<sup>3</sup> (Cyan) – at right

- Ser76, Leu213, Asp215, Ile291, Pro292, Thr295, Thr298, Ala300, and Gly217
- Pocket is hydrophobic
- All of the amino acids have hydrophobic interactions with aliskiren in this pocket

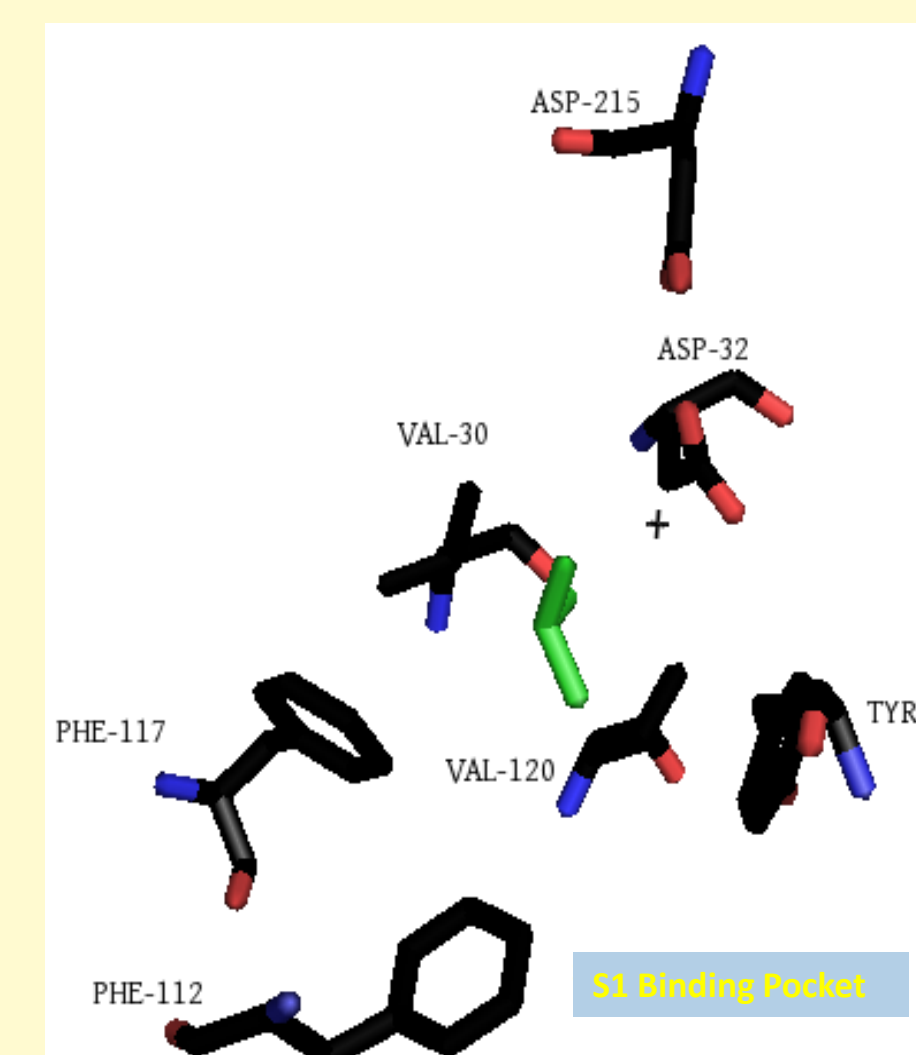


### S2' binding pocket<sup>3</sup> (Magenta) – at left

- Gly34, Ser35, Leu73, Arg74, Tyr75, Gln128, and Ile130
- Gln128 oxygen side chain hydrogen bonds with a water molecule in the S2' pocket
- Arg74 oxygen accepts a hydrogen bond from hydrogen attached to nitrogen in the amide of aliskiren
- Remaining amino acids in the pocket have hydrophobic interactions with aliskiren

### S1 binding pocket<sup>3</sup> (Yellow) – at right

- Val30, Asp32, Tyr75, Phe112, Phe117, Val120, and Asp215
  - Occupied by the isopropyl group closer to the phenyl ring
  - Pocket is hydrophobic
  - All of the amino acids have hydrophobic interactions with aliskiren in this pocket
- Other Interacting portions
- Amino acids that interact include Asp32, Gly34, Ser76, Asp215, and Gly217



## ADDRESSING THE CLINICAL PROBLEM OF BIOAVAILABILITY

The direct renin inhibitors are an exciting new class of medications; however a major barrier to their success has historically been low oral bioavailability. Aliskiren has emerged as an effective inhibitor of the RAAS system, and an effective antihypertensive agent. Unfortunately the bioavailability of aliskiren is quite low, around 2.5%. Due to the low bioavailability of the aliskiren molecule, the majority of the administered medication travels through the gastrointestinal (GI) tract unabsorbed which has been found to lead to diarrhea and other adverse GI effects.<sup>2</sup>

**Challenge:** How to increase the bioavailability of the molecule without altering the molecule's ability to interact with the binding pockets of the renin molecule? In aliskiren, almost all of the accessible functional groups are important for drug binding within the binding pocket, making it less advantageous to consider altering these sites.

**Traditional approach:** Substitute more lipophilic functional groups or bioisosteres, at various places in the molecule that may increase lipophilicity while maintaining biological activity.

**Suggestion:** Replace methyl groups with fluorine or chlorine groups within the molecule to decrease polarity while hopefully maintaining biologic functionality throughout the molecule.

**Prediction:** Aliskiren molecule sits so tightly within the binding pocket of the renin protein it is difficult to predict the variability in efficacy such changes may present and whether or not making the molecule more bioavailable would be beneficial to decrease GI adverse effects

Although the aliskiren molecule represents a significant advancement in the management of hypertension, there remains much room for improvement in the bioavailability of these molecules, which poses a challenge to drug developers and medicinal chemists alike.

## SUMMARY

Aliskiren is a very effective antihypertensive agent that achieves high plasma concentrations, has a long half-life and preferential partitioning in the kidney. It also has a longer duration of action when compared to other antihypertensive agents because of a decreased rate of drug metabolism leading to longer acting antihypertensive effects. Aliskiren has many similar side effects to other antihypertensive drugs and is also active in the CYP 450 system. It is rarely used at this time due to cost, lesser familiarity and limited recommendations available.

CK has been on aliskiren for two months now and blood pressure readings have continuously been around 124/80 mmHg, well within her goal of <140/90 mmHg.

## REFERENCES

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