

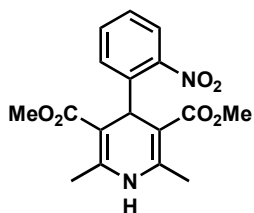
(S)- amlodipine

**Fast Facts:**

- Approved for medical use in 1992
- Calcium channel blocker used to treat hypertension, coronary artery disease, and angina (mainly)
- Currently on the WHO list of essential medicines
- In 2016, fifth most prescribed medication in the US (75 million prescriptions)
- Commonly used in combination with other medications to expand upon mechanisms of action, alleviate side effects
- S isomer is more active than R, sold as either racemate or enantiopure

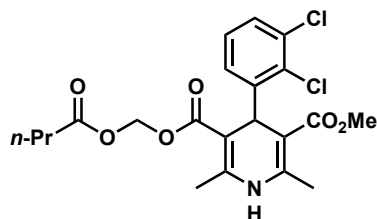
**Economics (US):**

- Drug costs < \$25 a month/person in the US
- CVD results in a \$ 555 billion price tag (2017)
- Expected to be > \$ 1 trillion by 2035
- Half of Americans expected to have a cardiovascular disease in their lifetime
- "Existing evidence of economic burden does not appear aligned with policy priorities in terms of research volume, pathologies studied and methodological quality"

**related pharmaceuticals**

nifedipine

1<sup>st</sup> generation  
calcium channel blocker



clevidipine

- approved in 2008
- half-life roughly 1 minute
- administered by IV only

**Veterinary Use**

- Front line for CVD for cats
- Less effective for dogs
- Sometimes used for kidney disease in cats
- Used often due to low side effects

**Mechanism of Action:**

Blocks voltage dependant L-type calcium channels

- Selective for smooth muscle cells

Less calcium in muscle means decreased contractility

Leads to decreased blood pressure and peripheral vascular pressure

- Leads to relief of Angina, also blocks spasms of coronary arteries
- Cardiac output remains stable

The mechanism of action is the same in cats and dogs

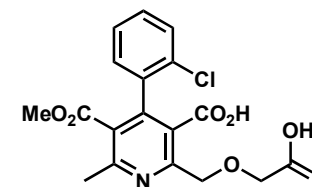
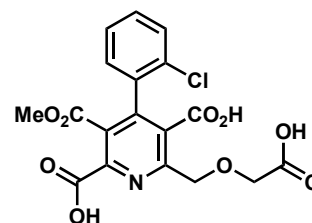
**Pharmacokinetics/Pharmacodynamics:**

Oral bioavailability of 60%

Half-life is around 40h, steady state achieved after 7-8 days

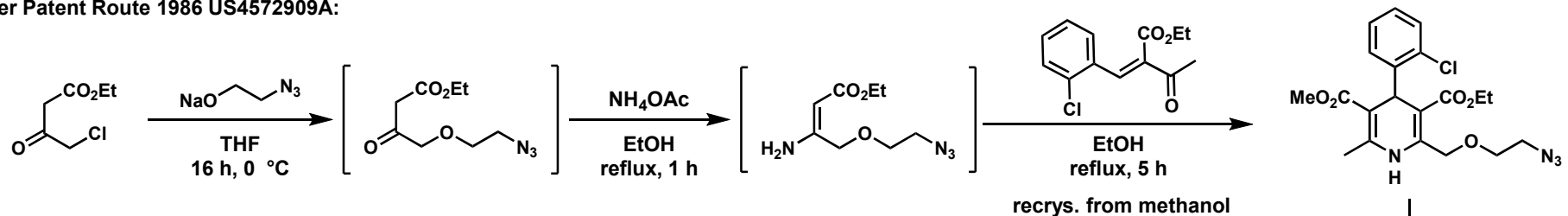
CYP3A4 major metabolic pathway

No dihydropyridine intermediates found in urine

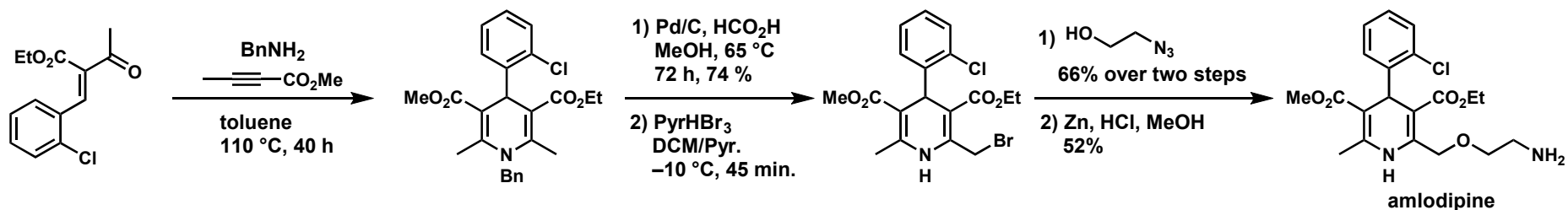


major metabolites

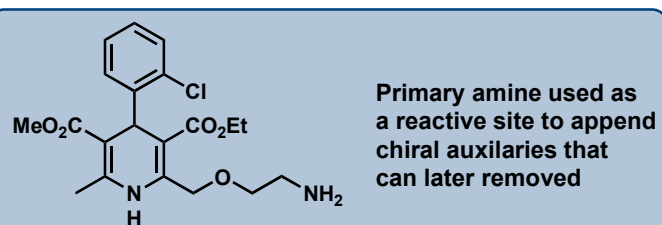
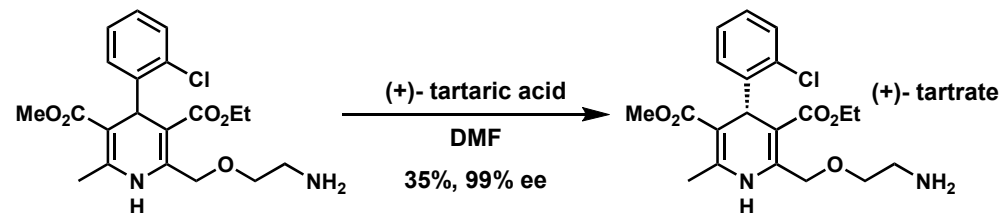
Pfizer Patent Route 1986 US4572909A:



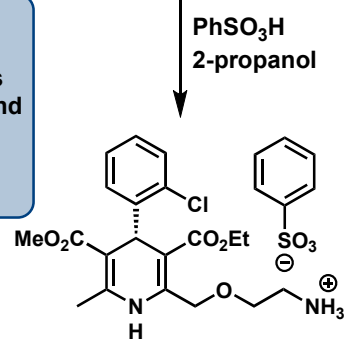
Aza-Diels-Alder route:



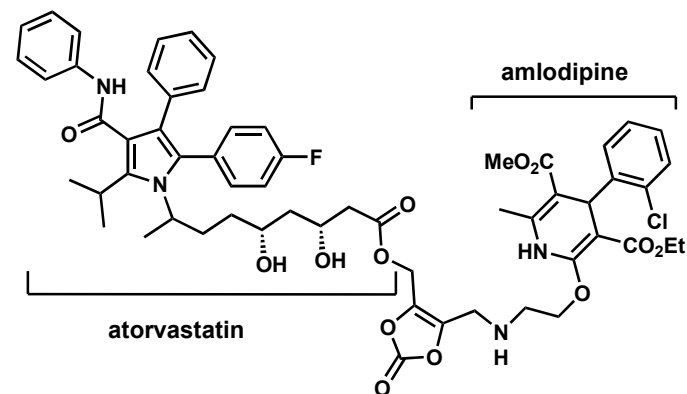
Methods for separation of the more potent (S)-enantiomer



selective cocrystal formation with the (s)- enantiomer



Mutual drug strategy:



mutual prodrug, covalently linked linker is cleaved in vivo

synergistic effect to treat atherosclerosis, hypertension

US Patent: US6737430B2

Bull. Korean Chem. Soc. 2002, 23, 143

OPRD, 2010, 14, 640