Salt Selection for L-224715 and L-2218

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Pharmaceutical R&D

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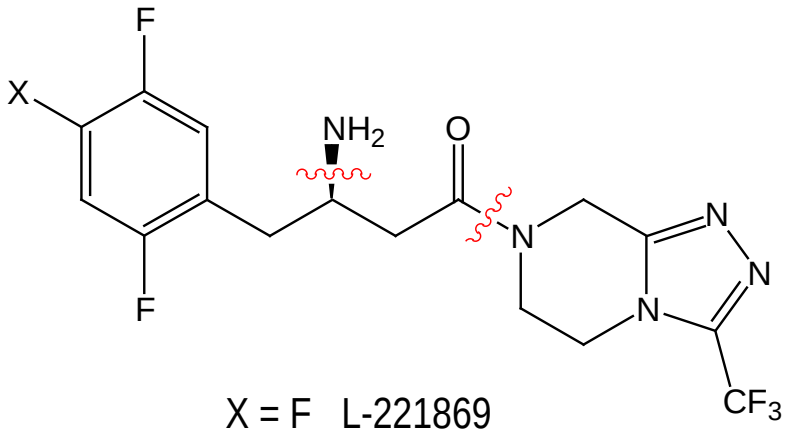
Formulation Design

L-221869, L-224715: Yun Liu, Tom Gandek

Pharmaceutically Acceptable Salts

- Soluble in water, wettable by water or organics
  - Improve or maintain bioavailability
  - Enable use of wet granulation to improve processibility
- Non-disproportionating in water (large pKa difference)
  - Maintains chemical form in water
- Low toxicity of counterion
  - e.g. oxalate
- Low/no pharmacological activity of counterion
  - e.g. amino acids
- Non-hygroscopic
- Acceptable morphology, compactibility

Evaluation of Free Bases



X = F L-221869
X = H L-224715

L-221869 free base

- crystalline
- pKa = 8.0
- solubility 2.2 mg/mL in

L-224715 free base

- crystalline
- pKa ca. 8
- solubility 5.9 mg/mL in

Both compounds:

- Bioavailability >50% in all species
- Hydrolysis of amide, de-amination observed
- Most stable in solution between pH 2-4

Formulation Plan for Phase I

Keep formulations as **simple** as possible while still maintaining **stability**:

1. **Dry-filled capsules** — Drug or salt filled directly into a capsule
   - Need good morphology/flow, density, stability with capsule
   - Evaluation at Quintiles (Mar 2002)
2. **Drug/excipient mixture filled in a capsule** — Binary mixture of drug and a suitable excipi with good flow properties
   - Need stability with capsule and excipient
   - Evaluation at Quintiles (Mar 2002) with mannitol
3. **Liquid-filled hard or soft capsule** — Drug suspension or solution filled in a caps
   - Need solubility and stability in liquid vehicle; stability with capsule

Test capsule formulations versus solution/suspension in dogs
Parallel development of tablet formulation for Phase II

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