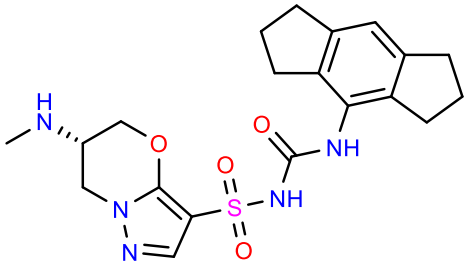
GDC-2394

- Went to phase I clinical trials to as a treatment for heart disease
- Researchers wanted to evaluate pharmacokinetic properties
- Failed due to safety concerns, 3% of patient population had serious side effects

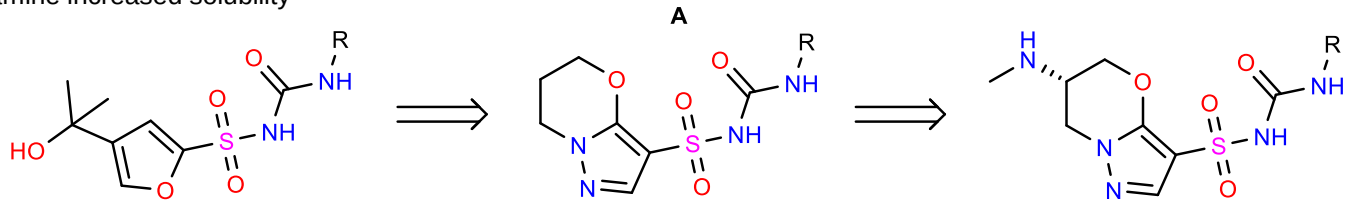


Genentech
A Member of the Roche Group

https://genentech-clinicaltrials.com/en/trials/cardiovascular-disorder/is-it-safe-for-people-to-take-a-new-medicine-gdc-2394-and-ho.html

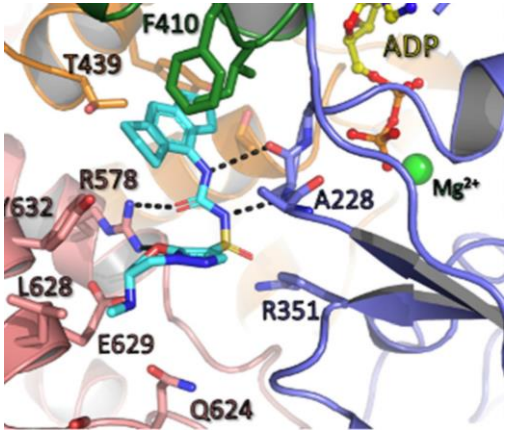
Scaffold optimization

- A 1998 patent by Pfizer disclosed MCC950/CRID3/CP-456773
- Failed phase II clinical trials due to high does required
- Remove furan due to possible toxicity when metabolized
- Switching to phenyl removed activity, and N containing heterocycles restored activity
- Compound A was insoluble in low pH regions, and precipitated in the kidneys of cynomolgus monkeys
- Addition of the amine increased solubility



Biology

- IL-1β, which is a proinflammatory cytokine, is released by a multi protein complex called an inflammasome
- NLRP3 is the inflammasome that GDC-2394 targets, and it monitors the integrity of the cytoplasm
- Binding to NLRP3 inhibits IL-1β release
- GDC-2394's arene moiety fits in a hydrophobic pocket, and both the urea and oxazine have key H-bonding interactions
- NLRP3 plays a key role in the release of pro inflammatory signals in Alzheimer's, cardiovascular disease, atherosclerosis, and more



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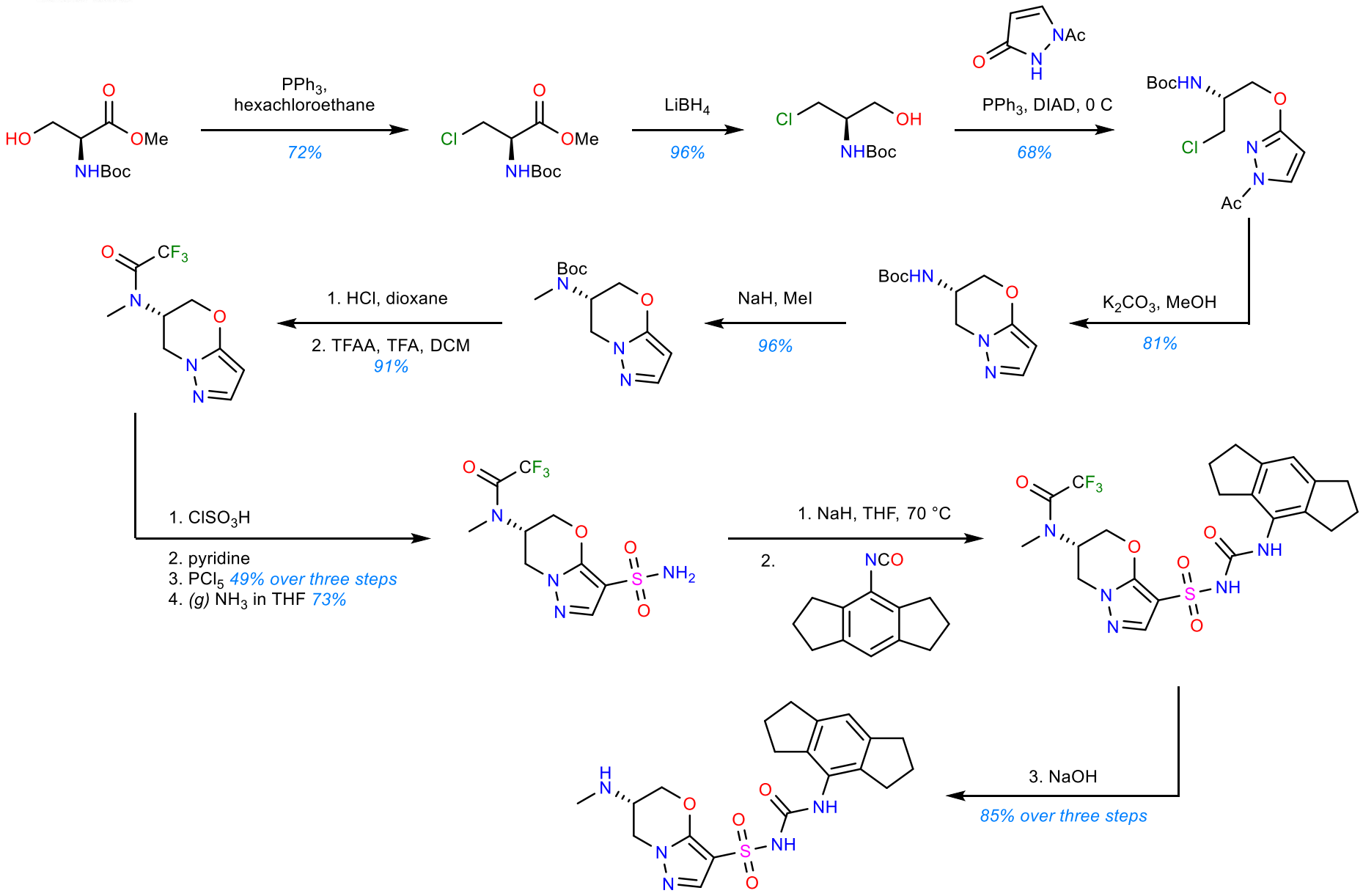
GDC-2394


HO
OMe
NHBoc
PPh3, hexachloroethane
72%
Cl
OMe
NHBoc
LiBH4
96%
Cl
OH
NHBoc
NAc
O
N
H
PPh3, DIAD, 0 C
68%
BocHN
O
Cl
N
N
Ac
K2CO3, MeOH
81%
BocHN
O
N
N
NaH, MeI
96%
Boc
N
O
N
N
1. HCl, dioxane
2. TFAA, TFA, DCM
91%
O
CF3
N
O
N
N
1. ClSO3H
2. pyridine
3. PCl5 49% over three steps
4. (g) NH3 in THF 73%
O
CF3
N
O
O
S
NH2
O
N
N
1. NaH, THF, 70 °C
2.
NCO
O
CF3
N
O
O
S
NH
NH
O
N
N
3. NaOH
85% over three steps
H
N
O
O
S
NH
NH
O
N
N