Scale-up synthesis, stability and physicochemical evaluation of 2,2-difluoro-β-alanine

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Background of the project

β-Alanine is an integral part of natural products

- naturally occurring β-amino acid
- a component of carnosine and anserine
- a part of pantothenic acid (vitamin B_5)
- small molecule neurotransmitter

β-alanine
- involved in creating bioactive peptides and protein secondary structure mimics
- regarded as a novel molecular tool for designing gamma-turns

(non)-backbone modifications
out of 20 amino acids pool
possible sites for altering

A

carnosine (R = H)
anserine (R = Me)

- intramuscular pH buffer
- scavengeer of ROS
- antiglycating agent
- increase the Hayflick limit
- Cu-chelating agent
- neuroprotective effect

B

Coenzyme A

- fatty acid synthesis
- energy production
- antioxidant function

- increases stability, lipophilicity
- alters pKa, solubility, conformation
- isoster for the carbonyl group
- venerable motif in drug design

VENERABLE STRATEGY IN MODERN BIOMEDICAL & AGROCHEMICAL INVESTIGATIONS

convenient sites for modification

intriguing reactivity/activity aspects

HALMARKS OF THIS WORK

- optimized & validated 500+ grams access
- NH_2 and CO_2H orthogonal protection
- precursor for $CF_2CH_2NH_2$ group
- CO_2H based heterocyclizations with access to a wide range of $HetCF_2CH_2NH_2$ buiding blocks

well-develloped C1 electrophilic unit for building heterocycles

HetAr
- backbone-carrier
- modifier of MedChem relevant properties

actively investigated ethylamine fragment isosteric to bioamines

relatively well developed and used in clinical trials

azolyl derivatives - *elusive chemotype* of difluoroethylamines

Ion channel modulator
GILEAD SCIENCES INC
Pat. CA2774715, *2018*

Tyrosine kinase inhibitors
ROCHE HOLDING AG
Pat. KR2014/15162, *2014*

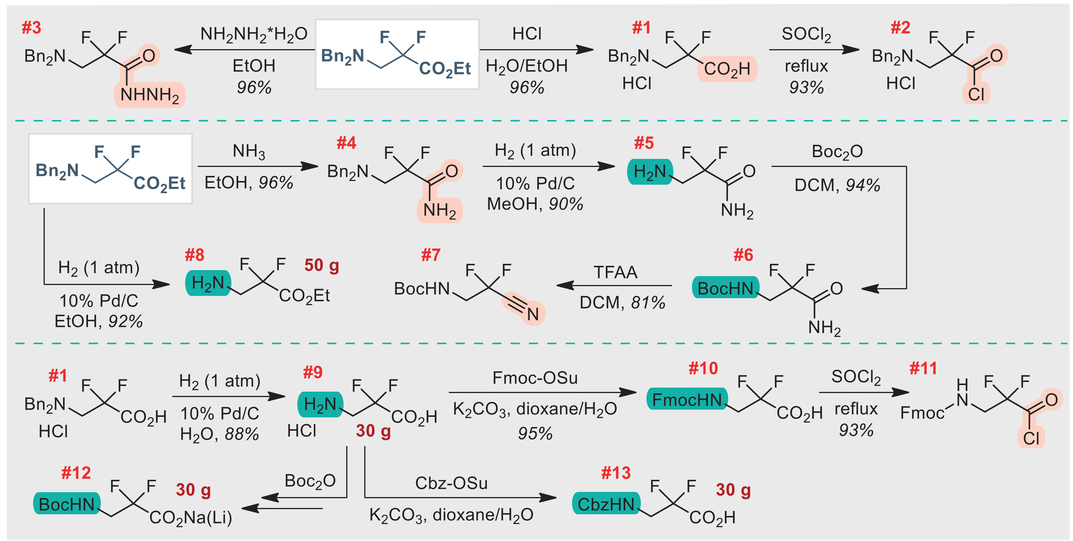
Ferroportin inhibitor
PFIZER INC
Pat. EP3894416, *2022*

6 steps
< 20% yield

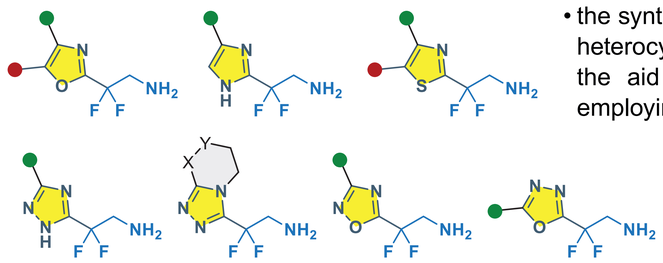
histamine analog

SYNOPSIS OF OUR INVESTIGATIONS CONCERNING A PURPOSE-ORIENTED SYNTHESIS OF 2,2-DIFLUORO-β-ALANINES

- the synthesis of the principal intermediate – ethyl 3-(dibenzylamino)-2,2-difluoropropanoate – is based on a literature method (*Tetrahedron Lett.* **2003**, *44*, *2375-2377*), which was validated and scaled up to over 500 g of the ester
- all derivatives of 2,2-difluoroalanine were prepared from the starting ester on >10 grams scale
- alanine-derived building blocks are crystalline well-storable compounds; derivatives **#1** and **#2** are new



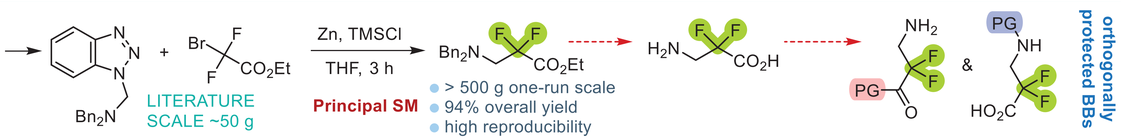
STEP 2. A short outline of constructed MedChem relevant $HetCF_2CH_2NH_2$



- the synthesis of a wide range of 5-membered heterocycles has been accomplished with the aid of optimized classical approaches employing dinucleophilic species

Ar, Alk, OH, NH_2, NHAc
X = CH_2, NH; **Y** = CH_2, NH

STEP 1. Elaboration and optimization of protocols toward β-alanines



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