Proposal for Synthesizing Novel Drug to Treat the Neglected Disease Eumycetoma

Harmanjit Dhillon, Ram Tiwari, and Laura Murphy, Ph.D.
Division of Sciences and Mathematics, SIAS, University of Washington Tacoma
Tacoma, WA 98406

Introduction

Background:
Eumycetoma is a chronic inflammatory fungal infection primarily localized in the lower extremities (Fig. 1). The total cost for diagnostic imaging, surgical intervention, and medication is expensive and ~5x the monthly income of patients. Medical therapy for eumycetoma has proven to only have ~30% success rate. Thus, research in the discovery of a novel, cost-effective drug for eumycetoma is imperative to improve patient quality of life and access to treatment, as well as prevent an exponential increase in the disabled population.

Literature Review:
- Previous research suggests fosravuconazole and fenarimols with an isoxazole core inhibited activity of Lim2.
- Literature Review: life and access to treatment, as well as prevent an in the discovery of a novel, cost-effective drug for proven to only have ~30% success rate. Thus, research income of patients. Medical therapy for eumycetoma has total cost for diagnostic imaging, surgical intervention,

Objective
The project goal is to use literature review and rxn sequence (Fig. 5) to design 8 target compounds (Fig. 6,7) to screen for antifungal activity as potential antifungals for eumycetoma that are...
1. Long-term effective
2. Cost efficient
3. Address safety concerns associated with past treatments

Method
For Basic Target Compounds:
Six Step Reaction (Fig. 5)
1. Grignard
3-bromopyridine + boron trioxide + acetic acid + HCl + 20% aqueous ethanol
2. Thionyl chloride substitution
Phenyl pyridine + phenol + Thionyl chloride (2-3) phenylpyridine-1-carboxylic acid
3. BOC protection
Protected piperazine
4. Amine alkylation
BOC protected piperazine + 3-(Chloro(phenoxy)carbonyl)piperazine + tert-buty1 4-[phenyl(pyridin-3-yl)methyl]piperazine-1-carboxylate
5. BOC deprotection
Tert-buty1 4-[phenyl(pyridin-3-yl)methyl]piperazine-1-carboxylate + trifluoroacetic acid
6. Nucleophilic Acyl Substitution
1-Phenylpyridin-3-ylpiperazine + Ethyl chloroformate + Tert-buty1 4-[phenyl(pyridin-3-yl)methyl]piperazine-1-carboxylate

For Unique Developed Compound Based on Research:
1. Replace 3-bromopyridine from basic target compound with 3-Bromoisoazoloxine in Grignard reaction
2. Repeat steps 2-6 with same reagents

Materials/Budget

Chemicals/Supplies:
- Total cost for funding: $1200
- Vendors:
  - Sigma-Aldrich
  - Thermo Fisher Scientific
  - TCI

Purification, Data Analysis & Testing

Purification - Column chromatography, HPLC (UW-T)
Data Analysis - NMR (UW-S) & mass spec (UW-T)
In-Vitro Testing - Target compound with fungal cells to observe antifungal activity (collaboration with DNDI)

Progress & Future Outlook
- After the synthesis and purification of our target compounds, they will undergo in vitro testing through our DNDI collaborators.
- Future directions include:
  - Collaborator potentially doing in vivo testing with mice.
  - Modifying our target and trying another synthesis.
  - Observing short/long term effects, noting any potential side effects.
  - If target drugs are successful in testing then start clinical trials if target drugs are granted approval (DNDI).
  - If target drugs fail testing then use experimental data and mechanism of synthesis for more effective drugs in future.

References