Introduction

Malaria:
Malaria has plagued humans for millennia, skillfully adapting itself for life as a parasite. Between 300 and 500 million people are infected each year with one of the four species of protozoon that cause malaria: Plasmodium falciparum, P. ovale, P. vivax, P. malariae. Despite the advances in modern medicine, malaria still kills 1 to 2 million people each year, most of whom are children. Moreover, malaria parasites have formed significant resistance to antimalarials in the past several decades (1).

The Screening Program at the Broad:
The Broad Institute operates a high throughput screening program designed to discover novel compounds that are active against *P. falciparum*, the species of malaria responsible for 75% of all malaria cases. Over 80,000 compounds have been screened in the program’s in vitro assay system. Of the compounds screened, nearly 200 were found to inhibit parasite growth and possess the necessary chemical scaffolds for drug design.

Active Compounds:
In collaboration with Genzyme, active compounds, or “hits,” were screened at their Waldham site. Compounds must both be active against *P. falciparum* and have low cytotoxicity in human cell lines for drug development to continue. One compound that meets both of these requirements is a triazole-based molecule that had not previously been known to possess antimalarial attributes. To demonstrate the efficacy of the triazole-based compounds, seven similar commercially available compounds were screened. The results showed that these compounds require a 3-(imidazolyl)triazole motif for activity against *P. falciparum*.

The “Hit”

Results

Retro synaptic Analysis

Using the principle of retrosynthetic analysis, we worked backwards from the desired product and determined a possible synthetic pathway as well as a commercially available starting material.

The Synthetic Pathway: Step 3

Optimization of Reaction Conditions

Although the first two reactions in the chemical pathway produced the product at high yield, the reaction from substance 3 to 4 and 5 required optimization of the process.

Synthesis of 4

Four different reaction conditions were tried to optimize the production of 4. Refluxing reactions were performed in DMSO, MeOH and DMF. The reaction that proved best was done in THF at room temperature. The graphs show two of the reactions, each analyzed with chromatography techniques. Each peak on the graphs shows the presence of a unique compound.

Synthesis of 5

Four different reaction conditions were tried to optimize the production of 5. Compound 3 was reacted in DMF with DIEA (an organic base) and in DMSO with KOH. It was also reacted without base in THF and refluxed in MeOH. The refluxing reaction proved most effective.

The Synthetic Pathway: Steps 4 and 5

Analogue Synthesis

Variable Groups for 8A-C

| A | R = Ph, R' = Me, Yield: 97% |
| B | R = Crs (Hantzsch), MeOH, Yield: Unknown |
| C | R = (3a)-3-Chloro-Propanoic Acid, MeOH, Yield: Unknown |

The project is designed to develop a synthetic pathway by which this molecule may be produced. Once established, this pathway will facilitate biological testing of this molecule and its analogs.

Conclusions

This project has successfully produced a viable pathway for production of the original “hit.” Moreover, the synthetic pathway provides three points of diversity for the synthesis of analogs.

Future Research

- Once the analogs have been purified, the compounds will be put through in vitro assays in which their efficacy against *P. falciparum* will be measured.
- In parallel, Genzyme will conduct testing to assess the pharmacokinetic properties of the molecules.
- The structure activity relationships (SAR) of these molecules can then be analyzed.
- The synthesis of different analogs based on this data can begin.
- If efficacy warrants, then the molecules will continue toward drug development.

Literature Cited


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