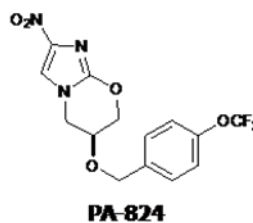
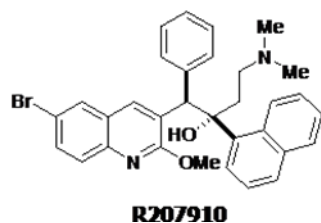


New Therapeutics For Some Very Old Diseases

Our research program is focused on the identification of new chemical entities directed at both *Mycobacterium Tuberculosis* and *Plasmodium Falciparum* (Malaria). Compounds will be designed and synthesized at Princeton with the goal of identifying molecules with appropriate activity and pharmaceutical properties as well as being economically viable for use throughout the world. This economic issue constrains the set of structures and the complexity of the chemistry to a level that we believe is achievable in an academic laboratory.

TB RESEARCH OVERVIEW

- Multiple Drug Resistant Tuberculosis (MDR-TB) is a Global Problem – exacerbated by susceptibility of HIV patients with 2 Million Deaths per year.
- Research Goal is to Design & Synthesize “Chiral” Molecules with Improved Efficacy and Simplified Treatment Paradigms Based on the ATP Synthase Inhibitor TMC207 (R207910) and the Nitroimidazole Class of Cell Wall Synthesis Inhibitors [PA-824]. (cf. C.M. Sasseti & E.J. Rubin; *Nature Medicine* 13, 279, 2007).
- Economically Viable & Scalable Syntheses of both series is critical



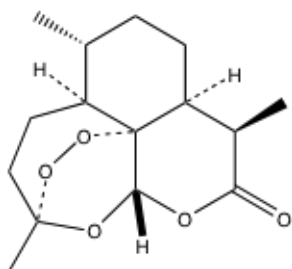
Reducing Neurotoxicity in Anti-Malarial Chemotherapy

Modern Drug Discovery and Development have been able to capitalize on scientific advances in our understanding of both the molecular and biological sciences. The combination of improved analytical techniques with improved understanding of the blood brain barrier now enables the Pharmaceutical Industry to design molecules which can selectively cross into the brain, or be rigorously excluded. While this approach has become a cornerstone of efforts toward new therapies for neurodegenerative diseases [Alzheimer's, Parkinson's], it has rarely been applied to economically less viable targets like malaria.

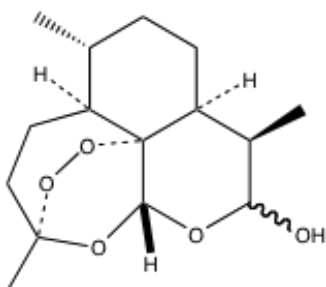
Chemical modification of existing anti-malarial drugs to optimize physicochemical properties leveraging recent advances in our understanding of transport will identify molecules far less likely to reach the brain. The result will be reduced potential for neurotoxicity.

Artemisinin (**1**) is a natural product found in the leafy portions of Qinghaosu (*Artemisia annua* – annual wormwood). It has been used in Chinese herbal medicine since 168 B.C.. Artemisinin and its analogues, especially when used in combination therapy (ACT), have become an essential part of treatment for chloroquine resistant malaria. A major concern identified by scientists at Walter Reed¹ is neurotoxicity.

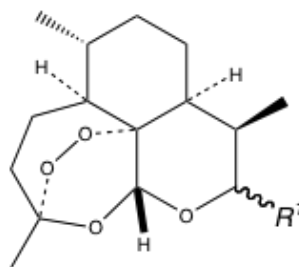
We are modifying readily available dihydro-Artemisinin (**2**) to provide a series of molecules which will be unable to cross the blood-brain barrier. Molecules will be identified by optimizing polar surface area without decreasing the high antimalarial activity and useful pharmacokinetics of Artemisinin.



Artemisinin **1**



dihydro-Artemisinin **2**



Artemisinin derivatives

- R¹ = S-Alkyl
- R¹ = SAryl
- R¹ = S-Heterocycle
- R¹ = Aryl
- R¹ = Alkyl
- R¹ = NR'R''
- R¹ = O-Alkyl
- R¹ = O-Aryl
- R¹ = O-Heterocycle
- R¹ = O-Sugar

Four logical characteristics should define an ideal “next generation” therapy with reduced neurotoxicity :

- 1) low penetration into the central nervous system
- 2) will not form the dihydro-artemisinin metabolite
- 3) economically viable for the third world
- 4) active against emerging Artemisinin resistant strains

References

- 1) D.L. Wesche, M. A. DeCoster, F.C. Tortella & T.G. Brewer; *Antimicrobial Agents & Chemotherapy*, 1994, 38, 1813-1819
- 2) World Health Organization “Facts on ACTs” (Artemisinin-based Combination Therapies); January 2006 Update; WHO website: http://www.rbm.who.int/cmc_upload/0/000/015/364/RBMInfosheet_9.htm