

DRUG DISCOVERY AT THE WALTER & ELIZA HALL INSTITUTE & LA TROBE UNIVERSITY - COLLABORATIVE PROJECTS

Medicinal Chemistry PhD projects 2010;

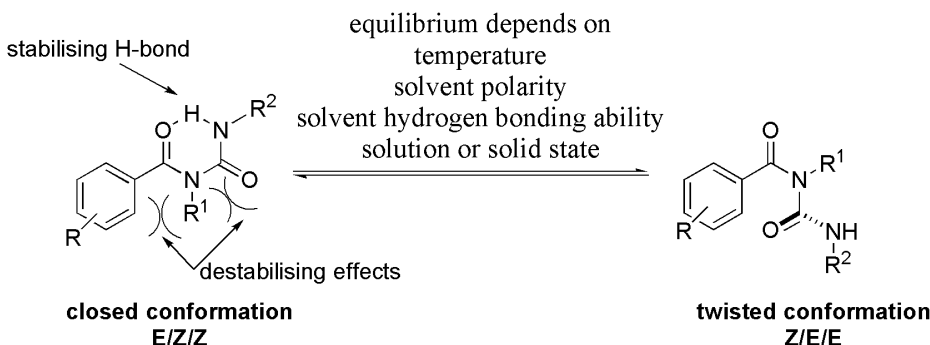
Prospective Honours Students Please Note: certain projects below are highly suited also to exciting Honours projects. Supervisors for projects below will comprise Andrew Hughes (La Trobe) and Jonathan Baell (WEHI) and additionally either Guillaume Lessene, Brad Sleebs, Georgina Holloway, Jean-Jacques Youte, Chinh Bui. Research may take place at either La Trobe or WEHI laboratories or a combination of the two.

The medicinal chemistry group has many exciting Honours and PhD projects. Those listed below represent just a sample of potential projects that could be undertaken.

1. Acylureas: Delineation of their conformational behavior and application as mimics of the alpha helix

Initial Contact Point: Guillaume Lessene/Jonathan Baell

The benzoylurea scaffold has been developed in our laboratory as a possible alpha-helix mimetic. Extensive study on the core and its stereoelectronic properties led us to unveil the interesting properties of this moiety. In particular, the unusual electronic separation between the two amide groups that forms the benzoylurea.



Part of our ongoing interest in this field is to widen the investigation to include other benzoylureas and other types of acylureas, so that we can fully understand all the factors that cause one conformation to be preferred over the other.

This project involves synthesis of the model compounds, use of spectroscopic tools such as IR, NMR, variable temperature NMR and *ab-initio* calculations.

The project has potential outcomes in the following fields:

- Understanding better the role of hydrogen bonding in more complex systems such as proteins.
- Control of the conformation of the acylurea scaffold with the possibility of the two conformations (twisted/closed) available in different environments leading to the concept of "conformational prodrug".
- The first full elucidation of factors that direct acylurea conformation.

We have recently published a foundation study in the Journal of Organic Chemistry¹

1. Lessene G, Smith BJ, Gable RW, Baell JB. Characterization of the two fundamental conformations of benzoylureas and elucidation of the factors that facilitate their conformational interchange. *J. Org. Chem.* 2009, **74** (17), pp 6511-6525.

2. Discovery of Novel Treatments for Neglected Diseases

Initial Contact Point: Jonathan Baell

We have an ongoing interest the treatment of neglected diseases ^{1,2} and have a diverse array of projects in the arena of neglected disease research, for example:

(i) Modified Eflornithine with improved pharmacokinetics. Sleeping sickness (Human African Trypanosomiasis) is a debilitating illness caused by kinetoplastic protozoan parasites such as *Trypanosoma brucei*, transmitted by the bite of the Tsetse fly. Available treatments are few, old and stage-specific. For stage 2 disease, only 2 treatments exist: melarsoprol- an arsenic derivative that is painful and toxic, and eflornithine. The latter is particularly difficult to administer, requiring trained health staff and constant hospitalization (requiring 56 infusions of 2 hours over 14 days). Surprisingly, this compound has attracted little attention in the way of chemical modification to improve its pharmacokinetic properties. The aim of this project is to design and synthesize new eflornithine-like compounds with potent antiparasitic activity and improved pharmacokinetic properties.

(ii) Novel Benznidazole Drugs. Caused by the kinetoplastic protozoan parasite *Trypanosoma cruzi*, Chagas disease is primarily transmitted by large, blood-sucking reduviid insects widely known as "the kissing bugs" in endemic countries. Benznidazole is used to treat acute and early indeterminate disease, but requires a long treatment period (30-60 days), dose-dependent toxicity, high rate of patient non-compliance and no paediatric strengths. There are some key features of the benznidazole molecule that have never been investigated synthetically, but which could reduce toxic side effects. The aim of this project is to design and synthesize more tolerable benznidazole-based therapeutics.

(iii) New tropane-based treatments for Chagas disease. We have discovered some potent and novel compounds that potently kill *T. cruzi* at levels of low ng/ml. These compounds are limited by the presence of labile linkages, but there are certain synthetic modifications that may render these more stable. The aim of this project will be to design novel and more potent isosteres of these tropane-based trypanocides.

1. Holloway GA, BAELL JB, Fairlamb AH, Novello PM, Parisot JP, Richardson J, Watson KG & Street IP. Discovery of 2-iminobenzimidazoles as a new class of Trypanothione Reductase inhibitor by high throughput screening. *Bioorg. Med. Chem. Lett.* **17**, 1422-1427 (2007).

2. Holloway, GA, Charman, WN, Fairlamb, AH, Brun, R, Kaiser, M, Kostewicz, E, Novello, PM, Parisot, JP, Richardson, J, Street, IP, Watson, KG, Baell, JB. Trypanothione reductase high-throughput screening campaign identifies novel classes of inhibitors with anti-parasitic activity. *Antimicrob. Agents Chemother.* **53**, 2824-2833 (2009).

3. Identification of new PAINS (Pan Assay Interference Compounds)

Initial Contact Point: Jonathan Baell/Georgina Holloway

Over the last six years, the WEHI Biotechnology centre has undertaken well over 35 high throughput screening (HTS) campaigns. Many of these are based on Alphascreen® Technology. We have recently analysed our historical data set and identified compounds that interfere in these assays and that so incur significant resource costs.¹ However, there have been many other HTS campaigns undertaken that use different assay technologies and we have not analysed these to identify new

classes of problematic compounds. To do so could be of general interest to the burgeoning academic HTS worldwide community that is currently reporting such compounds in the literature as viable starting points for drug development whereas in reality they are unlikely to be so. The aim of this project is to identify these hitherto unreported problematic compounds.

1. Baell JB, Holloway GA. New substructure filters for removal of pan assay interference compounds [PAINS] from screening libraries and for their exclusion in bioassays. *J. Med. Chem.* (submitted).