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Enantioselectivity in Modified Quinine Derivatives

Daniel Guilak
dguilak@pugetsound.edu

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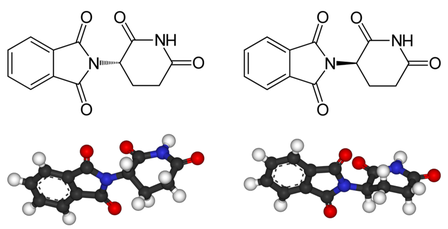
Daniel B. Guilak, Prof. William Dasher
University of Puget Sound Chemistry Department, Tacoma, Washington

Enantiomers and Their Importance

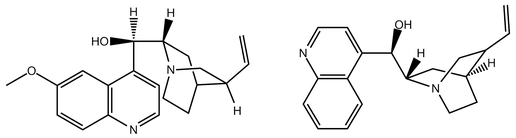
- An enantiomer is a non-superimposable mirror image of a compound – hence there are two which are usually denoted as "left" (*S*) and "right" (*R*).
- Enantioselection is extremely important in pharmaceuticals because biological systems have a very strong tendency to use only one of the two enantiomers of a compound (i.e., the human body is enantioselective).
  - In many cases, such as that of Ibuprofen (a chiral drug), one enantiomer will have a desired medicinal effect (pain relief) and the other will have a negligible medicinal effect.
  - However, in cases such as that of Thalidomide, a sleep-aid drug that was popular in the 1950s, one enantiomer of the compound performed its intended function (inducing drowsiness), but the other enantiomer of the compound purportedly caused birth defects (untested)[1].
- Enantioselection is an important and vital area of pharmaceutical research.



(*S*)-thalidomide (toxic) and (*R*)-thalidomide

Introduction to Quinine Research

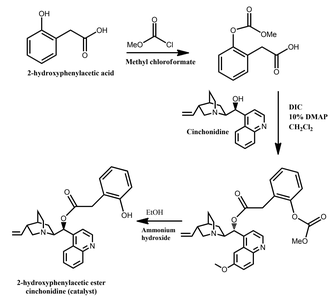
- Quinine is a compound found in the *cinchona* genus of tropical shrubs and trees which was used as the primary antimalarial drug from the 1600s until 1940[2].
- While it has since been superceded by different antimalarial drugs, quinine and its derivatives hold significance in pharmaceutical research due to their innate enantioselective properties when used as a chiral catalyst.
- My research has primarily been concerned with modifying the structure of cinchonidine to make it more effective at enantioselection.



Quinine (left) and cinchonidine (right), two quinolines (Courtesy of Wikimedia Commons).

Tethering

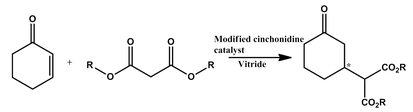
- We modify the structure of cinchonidine through the esterification of the hydroxyl group.
- Many different permutations have been attempted by myself and previous workers in Prof. Dasher's laboratory, but the two compounds that I focused on deriving were 2-hydroxyphenylacetic acid (shown) and 3-hydroxyphenylacetic acid.
- A methyl chloroformate protecting group is first added to the acid to prevent polymerization, and then the resultant compound is esterified to cinchonidine.



Scheme for synthesis of modified quinine alkaloid (quinine is shown).

Michael Reaction

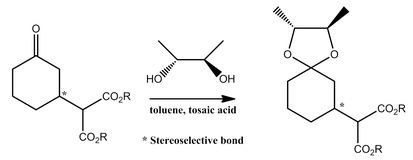
- The modified cinchonidine catalyst was then used in an asymmetric (stereoselective) Micheal reaction of a diester malonate to 2-cyclopentenone or cyclohexenone with the aid of reducing agent Vitride.



Scheme for Michael reaction of cyclohexenone and a diester malonate with the modified cinchonidine chiral catalyst.

Analysis by Chiral GC

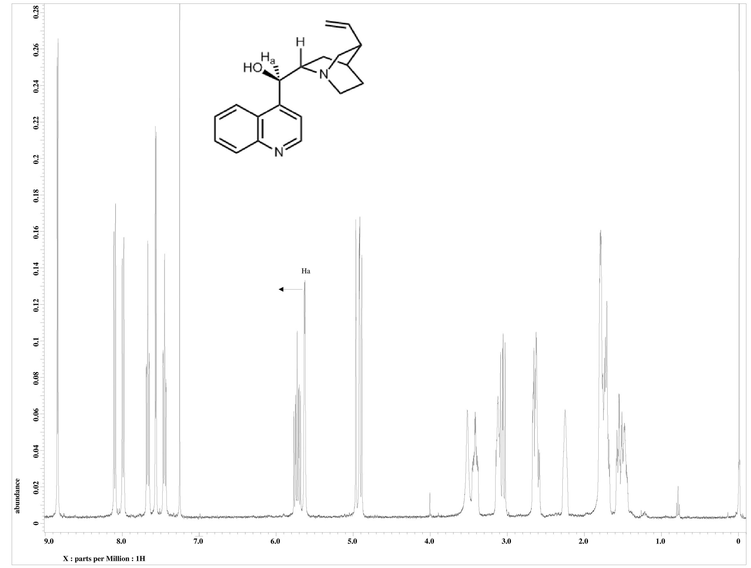
- In order to be able to determine the effectiveness in enantioselectivity by the chiral catalyst, the resultant product of the Michael reaction is reacted with a diol to form a ketal that is better picked up on a Chiral GC.



Scheme for converting Michael reaction product into a ketal.

Results and Discussion

- Each student who has worked on this problem has focused on a different variable in the pursuit of finding a solution with the best enantioselectivity. For example, it was previously determined that THF performed better than dichloromethane as a solvent in a Michael reaction with quinine as a chiral catalyst[3].
- My efforts of optimizing the reaction have been concerned with derivatizing the chiral catalyst (cinchonidine) in order to make it more effective – in this case, esterifying it.
- It is possible to determine when this reaction has effectively taken place when the HNMR of the catalyst shows that the carbinolic hydrogen doublet has shifted downfield by 0.5-0.6 ppm.



NMR of cinchonidine standard showing expected shift of carbinolic hydrogen after esterification.

References

1 Sirven, J. I. New Uses for Older Drugs: The Tales of Aspirin, Thalidomide, and Gabapentin. Mayo Clin. Proc. **2010**, 85, 508-511.

2 Ball, P. History of science: Quinine steps back in time. Nature **2008**, 451, 1065-1066.

3 Hanson, K. L. Analysis of Quinine as an Asymmetric Catalyst with the Michael Reaction and Synthesis of a Novel Class of Derivatized Quinines. B.S. dissertation, University of Puget Sound, Tacoma, WA, 2005.

Email: dguilak@pugetsound.edu