A QSAR Study of Artemisinin Analogs

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What is Artemisinin?

- Treatment for drug resistant *P. falciparum*
- Rapid clearance of cerebral malaria
- Some analogs are neurotoxic
Mode of Action

- Two modes are theorized
  - The active conformation is simply the energetically minimized conformation
  - Artemisinin complexes with hemin via the peroxy moiety to generate bioactive radicals

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Backbone Structures
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Miscellaneous Structures

- Only 2 acyclic structures present
Handling the Compounds

- The dataset contained several enantiomers:
- The dataset also contained charged species
Previous Study

- CoMFA & Hologram QSAR\(^a\) (seems similar to atom pair fragment descriptors)
- \(r^2\) & \(q^2\) was used to assess quality of models
- Model *goodness of fit* was characterized by the ration of standard error to activity range (s/AR)
- Part of the study also included racemates.
Endpoint Details

- All the analogs are assumed to act via similar mechanisms.

- All were tested using the same assay - in vitro against chloroquine resistant & mefloquine sensitive *P. falciparum* W-2 clone.

- Due to interday variations of IC$_{50}$ for artemisinin, relative activity (RA) was taken as the property under study.
Relative Activity

- RA is calculated using:

\[ RA = \frac{IC_{50} \text{ of artemisinin}}{IC_{50} \text{ of analog}} \times \frac{MW \text{ of artemisinin}}{MW \text{ of analog}} \]

- \( \log \) RA is used in the study
Plan of Action

- Structures were drawn in with Corina
- Optimization with PM3 was skipped
- Ignore enantiomeric pairs and cap charged species with hydrogens
- MPOLR, MRFRAC & GEOWIND could not be used
Plan of Action

- Initially carry out a study with topological indices
- Atom pair fragments may be something to look into
- Would hydrophobicity be useful in this situation?