A QSAR Study of Artemisinin Analogs

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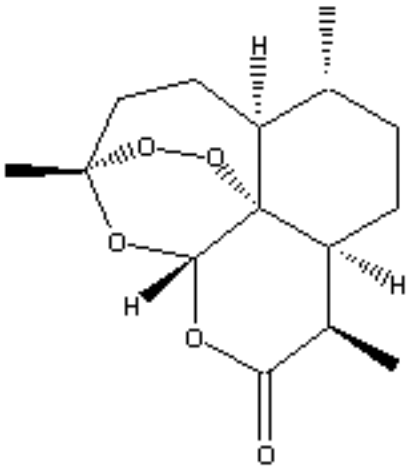
What is Artemisinin?



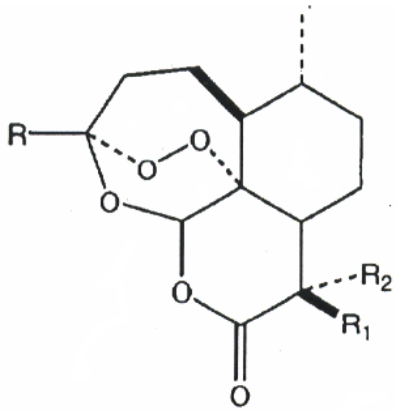
- Treatment for drug resistant *P. falciparum*
- Rapid clearance of cerebral malaria
- Some analogs are neurotoxic

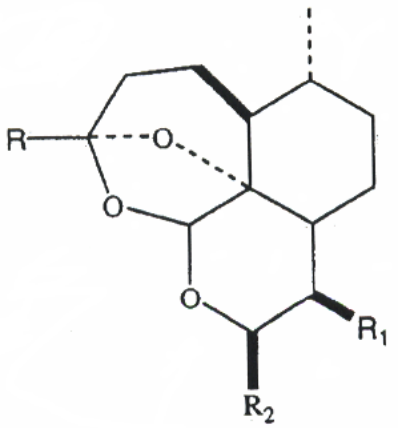
Mode of Action

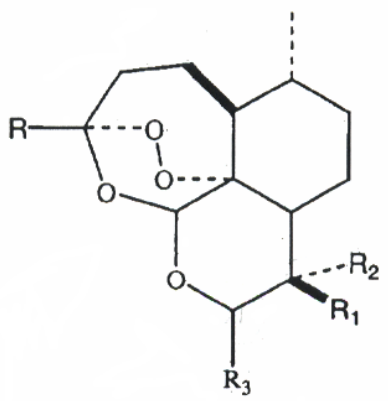
- Two modes are theorized
  - The active conformation is simply the energetically minimized conformation
  - Artemisinin complexes with hemin via the peroxy moiety to generate bio active radicals[a]

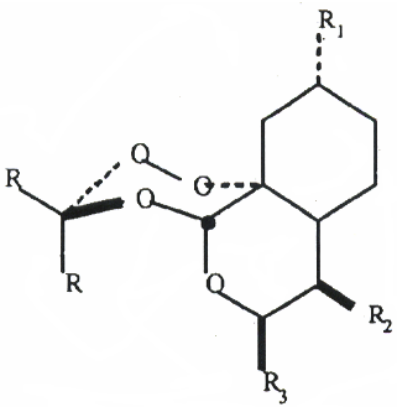
[a] S.R. Meshnick, *Trans. R. Soc. Trop. Med. Hyg.* **1994**, *88*, 31-32

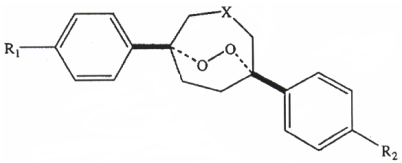
Backbone Structures

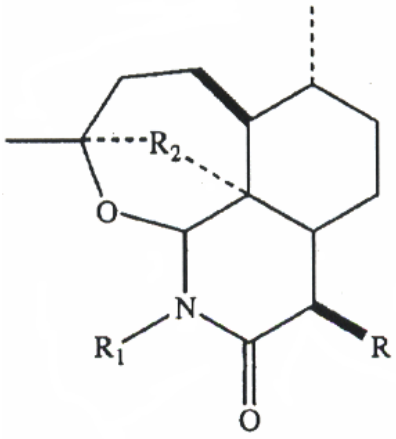




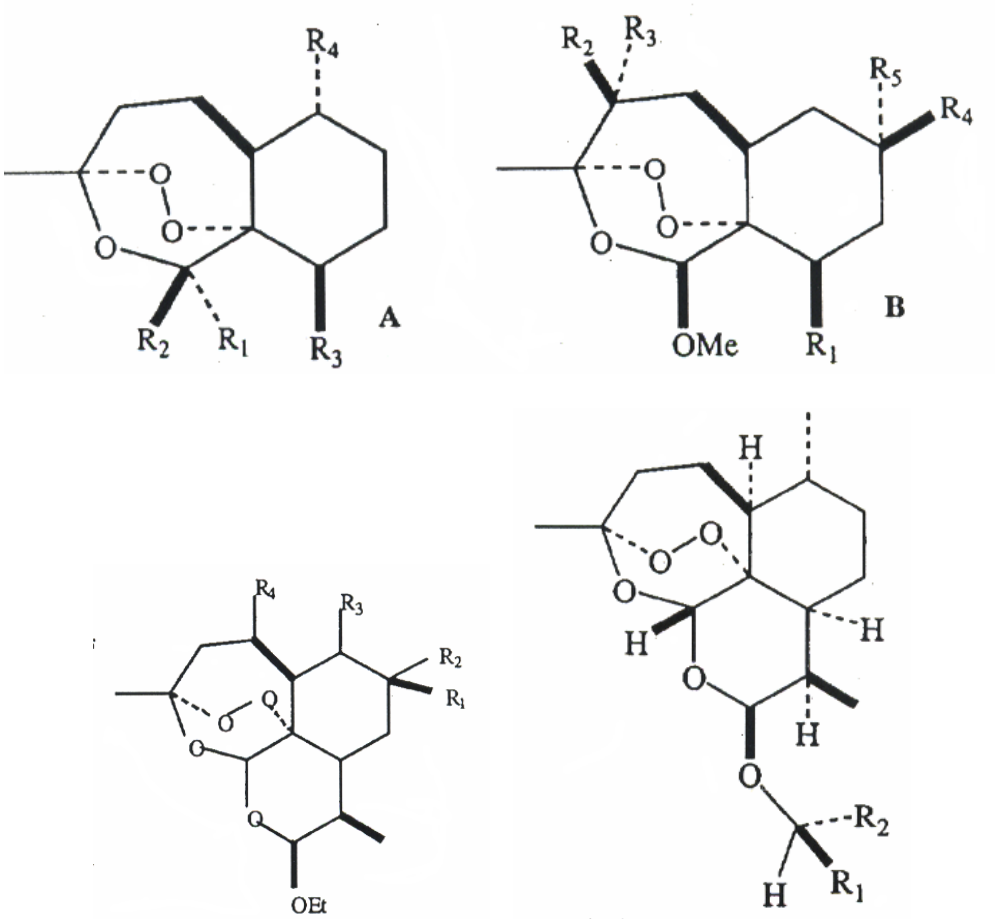




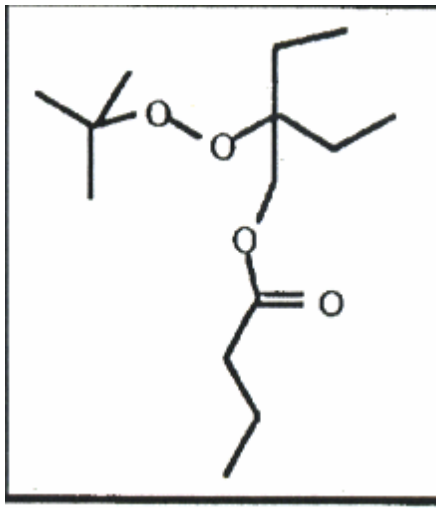




Backbone Structures



Miscellaneous Structures



- Only 2 acyclic stuctures 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

$$\mathrm{RA} = \frac{\mathrm{IC_{50}\ of\ artemisinin}}{\mathrm{IC_{50}\ of\ analog}} \times \frac{\mathrm{MW\ of\ artemisinin}}{\mathrm{MW\ of\ analog}}$$

- $\log$ 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?