

RATIONAL DRUG-DESIGN

The foundations

- the biological activity of a substance depends on the geometrical and electronic properties of its molecules
 - ♣ it is possible to find relationships between molecular properties and biological activity
- when a biologically active substance acts, it binds to a receptor.
 - ♣ the interactions between the molecule and the receptor are intermolecular interactions that can be studied computationally

drug design

- makes use of all the identified correlations between the physico-chemical and molecular characteristics of a substance and its biological activity
- utilises computational techniques to predict the possible activities of not-yet synthesised compounds

two major approaches

- study of possible derivatives of known drugs, to identify compounds that can be expected to have more effective action
- “de novo” design – building molecular structures having:
 - ♣ the desired pharmacological patterns
 - ♣ sites for possible interactions with the receptor.

main issues

apt for computational chemistry studies

- clarification of important aspects of the mechanisms of the action of existing drugs
- structure-activity relationships for existing drugs
- suggestion of modifications of existing structures and prediction of their expected activity
- targeting important biochemicals (e.g., enzymes) pertaining to the life-cycle of plasmodium and attempting to design structures that can block their activity
- study of active compounds isolated from natural products and proposition of derivatives.

theoretical chemistry and physical chemistry studies

- involve perspectives that are more rarely taken into consideration within research from other areas or point of views
- can complement the research done within other areas without risks of duplication, and collaborate with it
- can contribute to a more complete comprehension of the chemistry involved in malaria, from the parasite biochemistry to its effects on the human organism

in particular, computational chemistry

- implies comparatively lower costs, what makes it affordable for many institutions

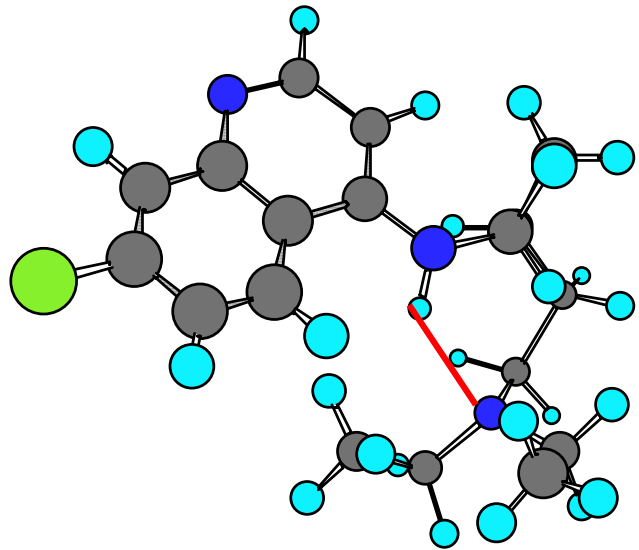
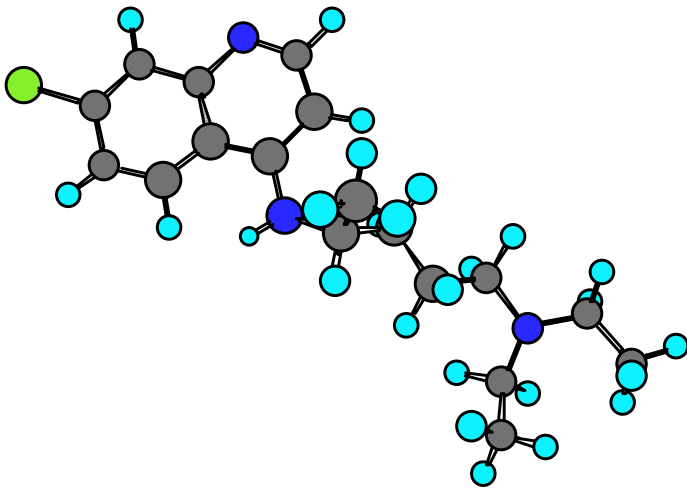
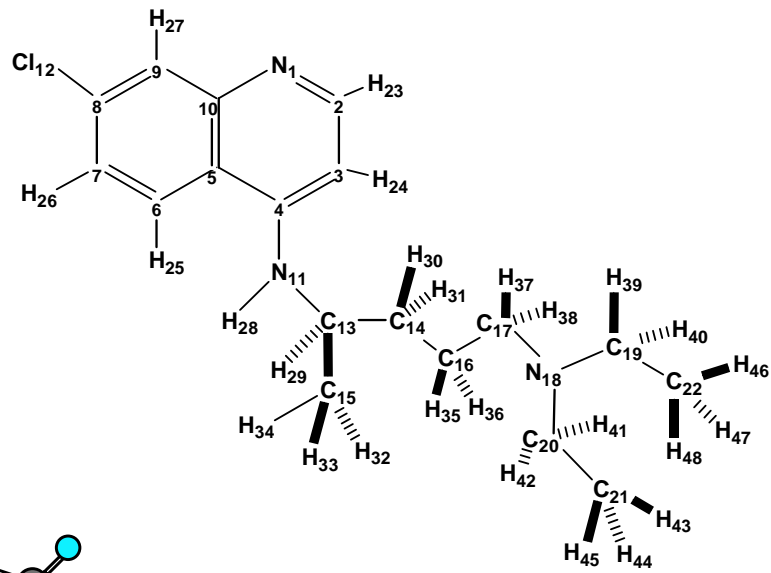
PEDAGOGICAL INITIATIVES

objectives

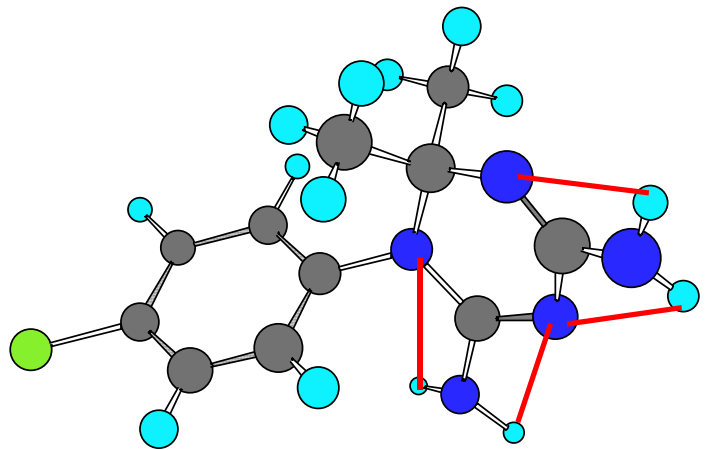
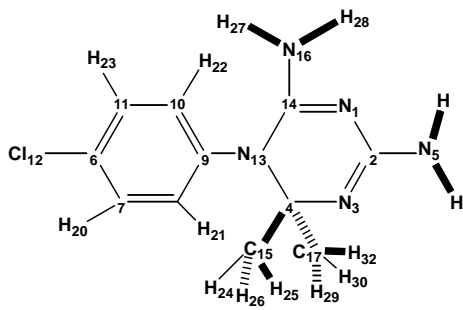
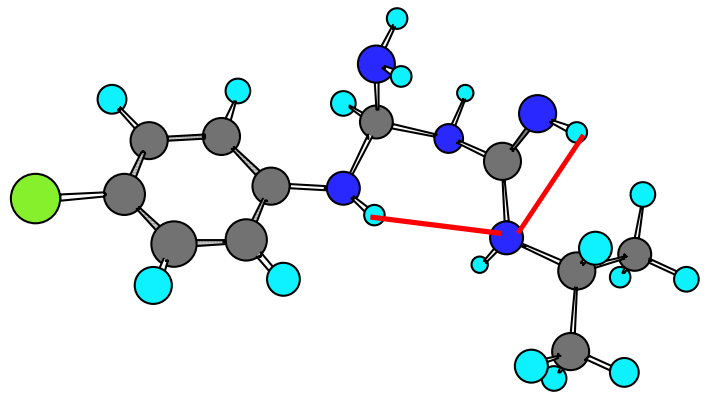
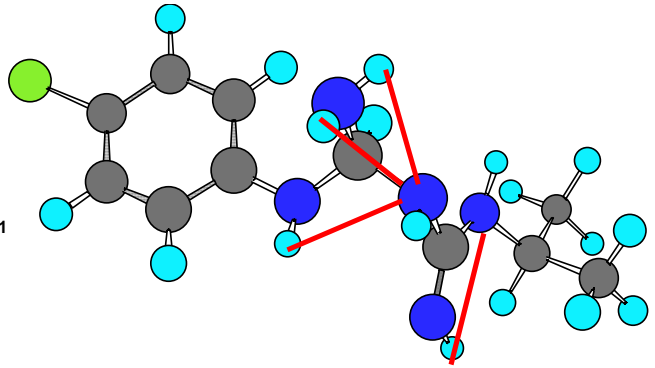
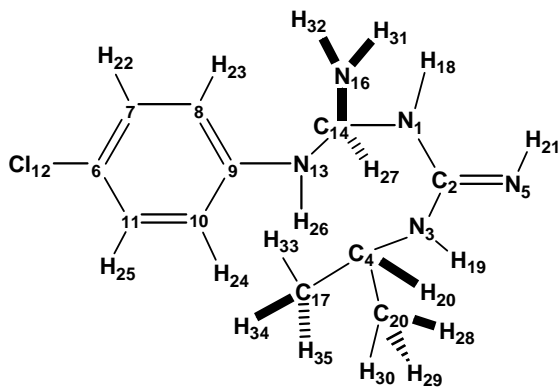
- attract chemistry students' attention
 - ♣ so that they come to consider malaria-related research as a field of interest for chemists
- increase the total number and background-diversity of specialists involved in active research

Options

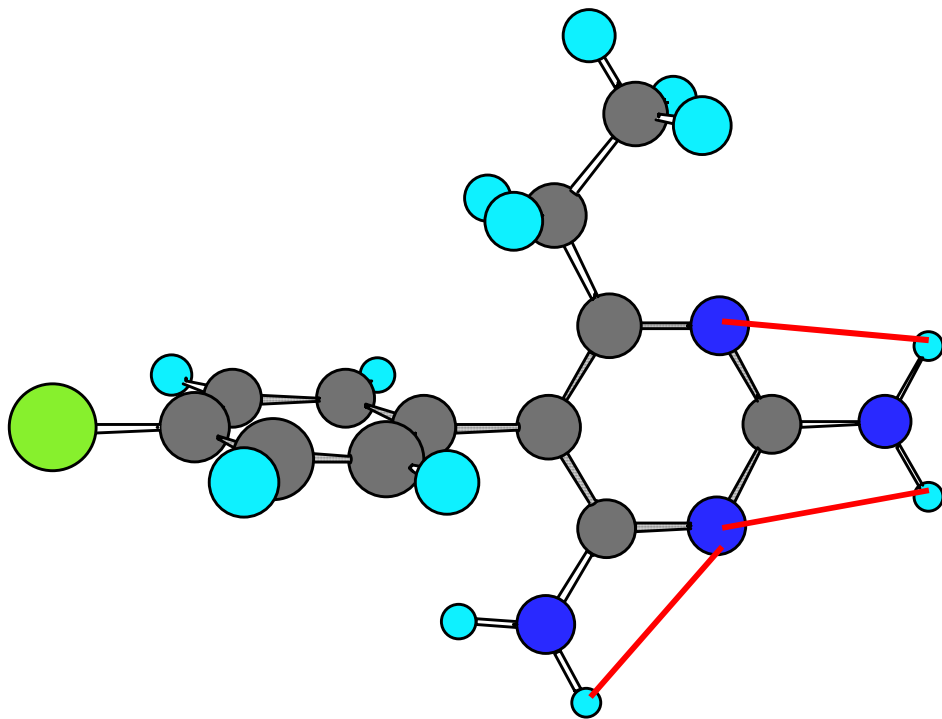
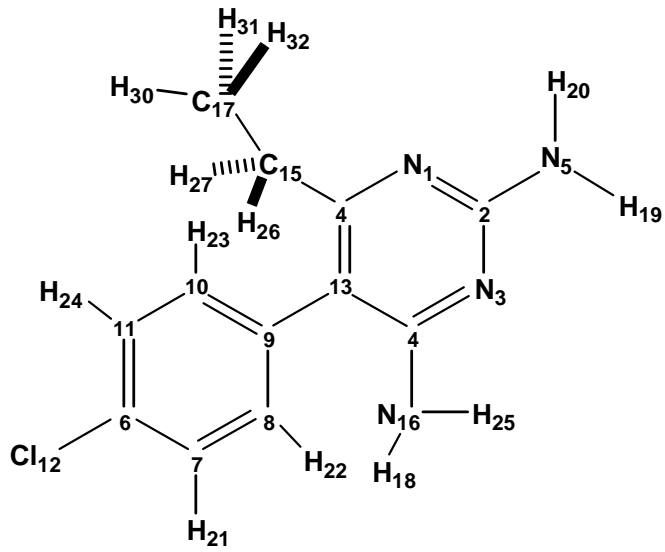
- familiarizing students with basic information
 - ♣ incorporate information about malaria into the training of chemistry students, with major focus on the chemical aspects.
- making available material:
 - ♣ designed for chemistry students
 - ♣ adequately informative
 - ♣ accessible to undergraduate students
- maximising integration between teaching and research, so that students perceive malaria-related research as
 - ♣ relevant and interesting
 - ♣ feasible in their own context
 - ♣ integral component of research in their department
- utilising examples from malaria-related studies within the practical components of theoretical chemistry courses



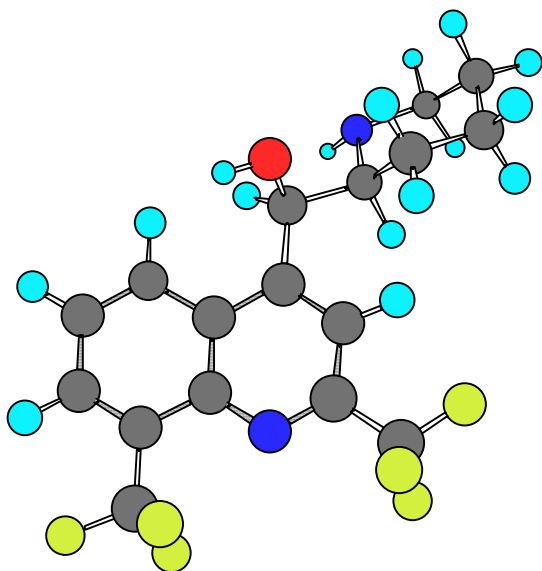
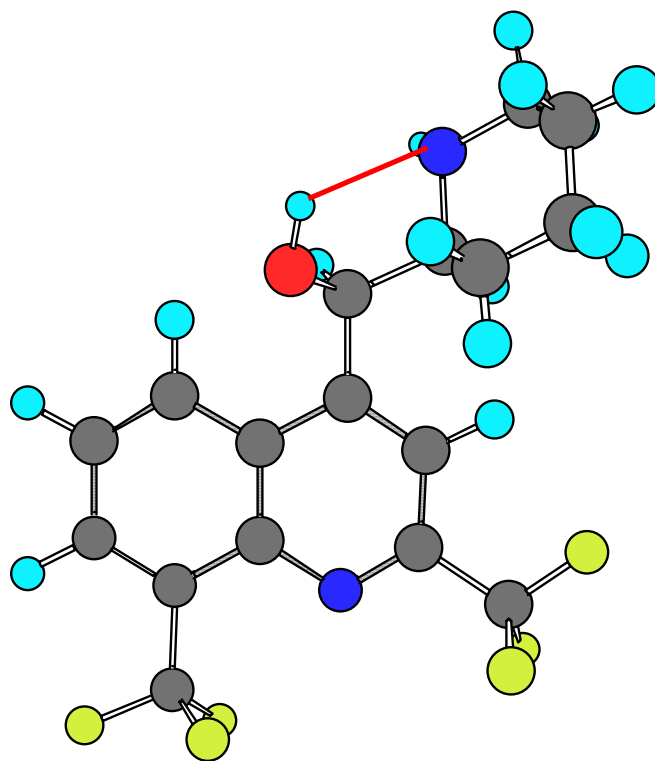
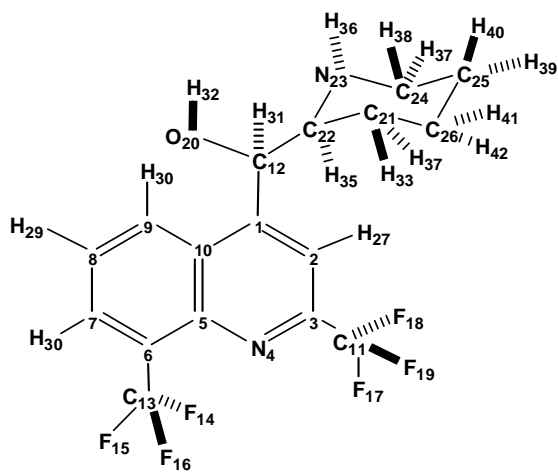
CHLOROQUINE



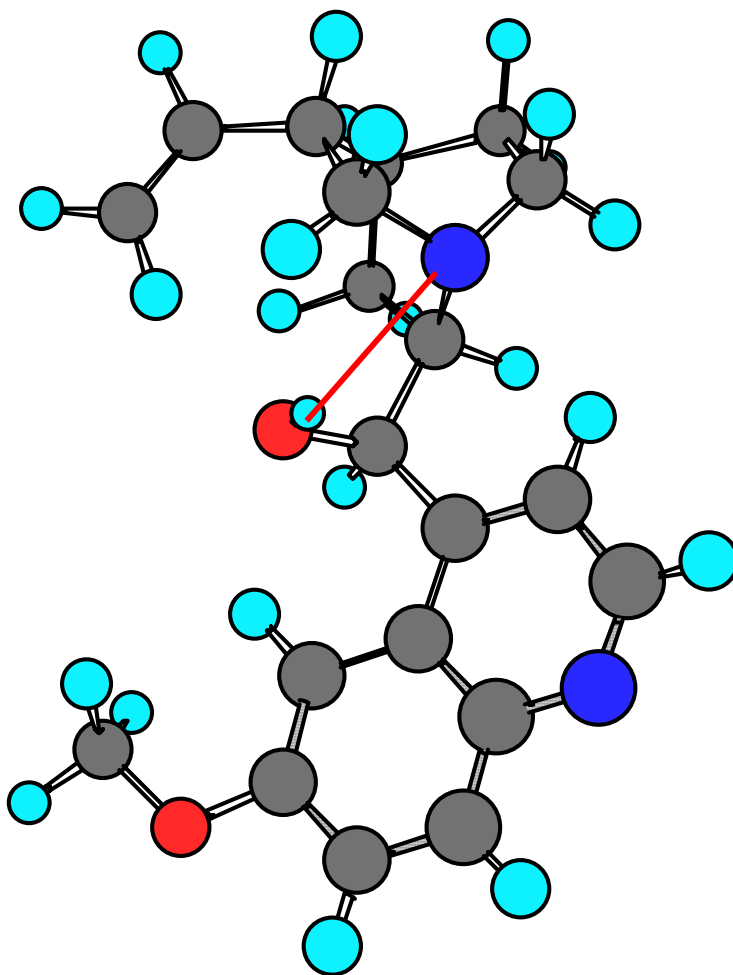
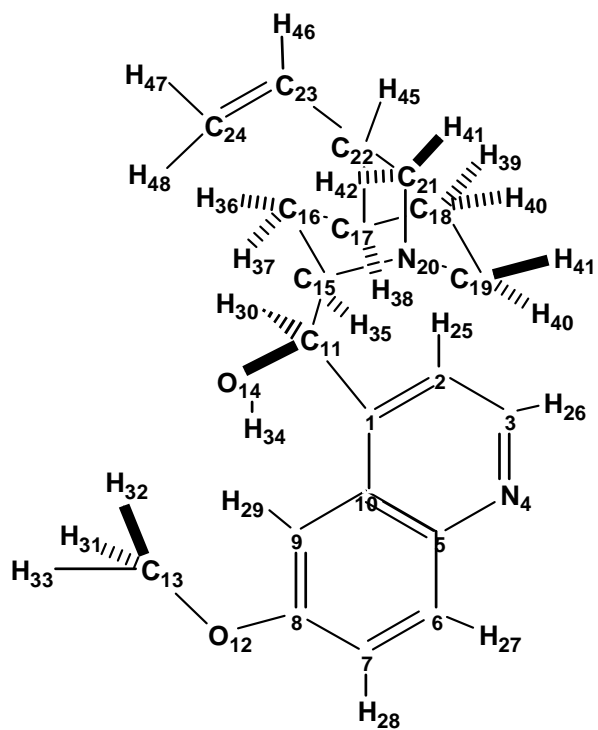
chloroguanide
cycloguanil



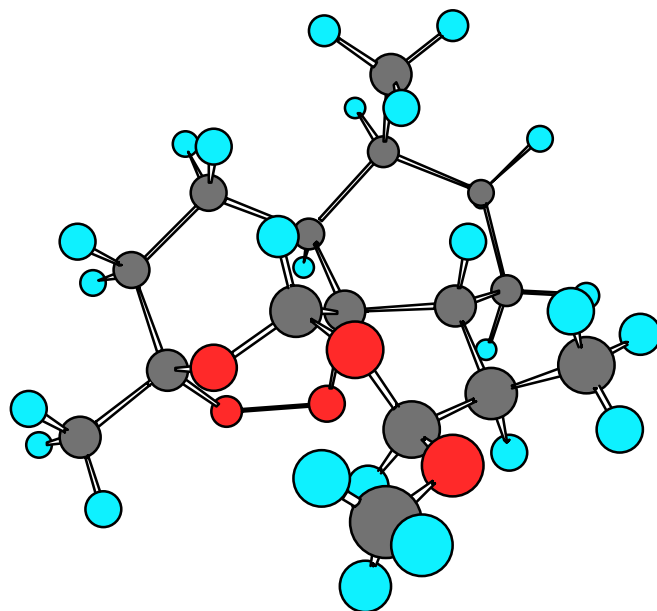
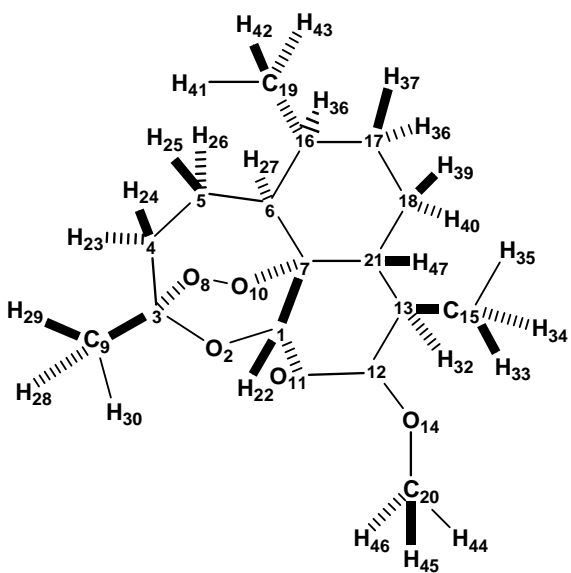
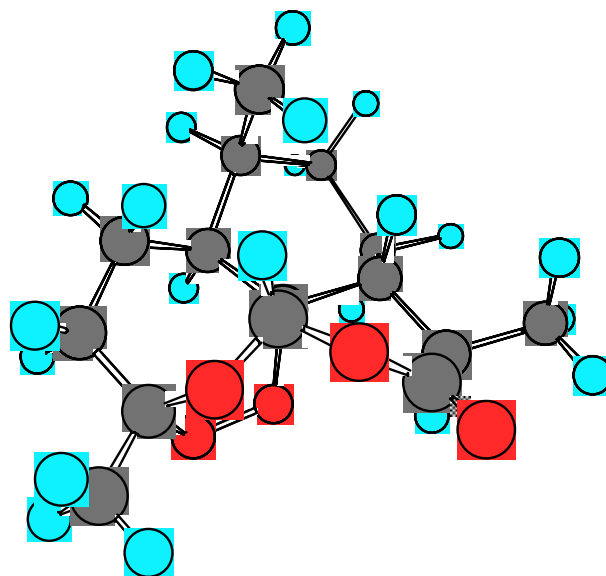
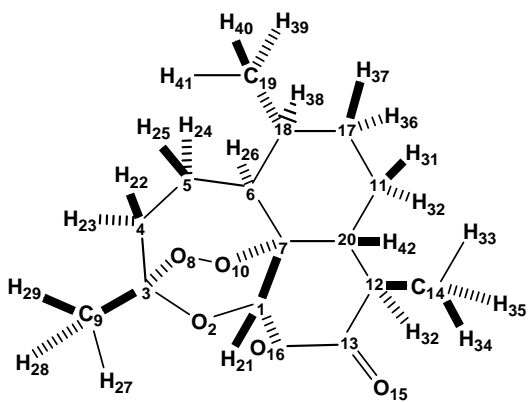
pyrimethamine



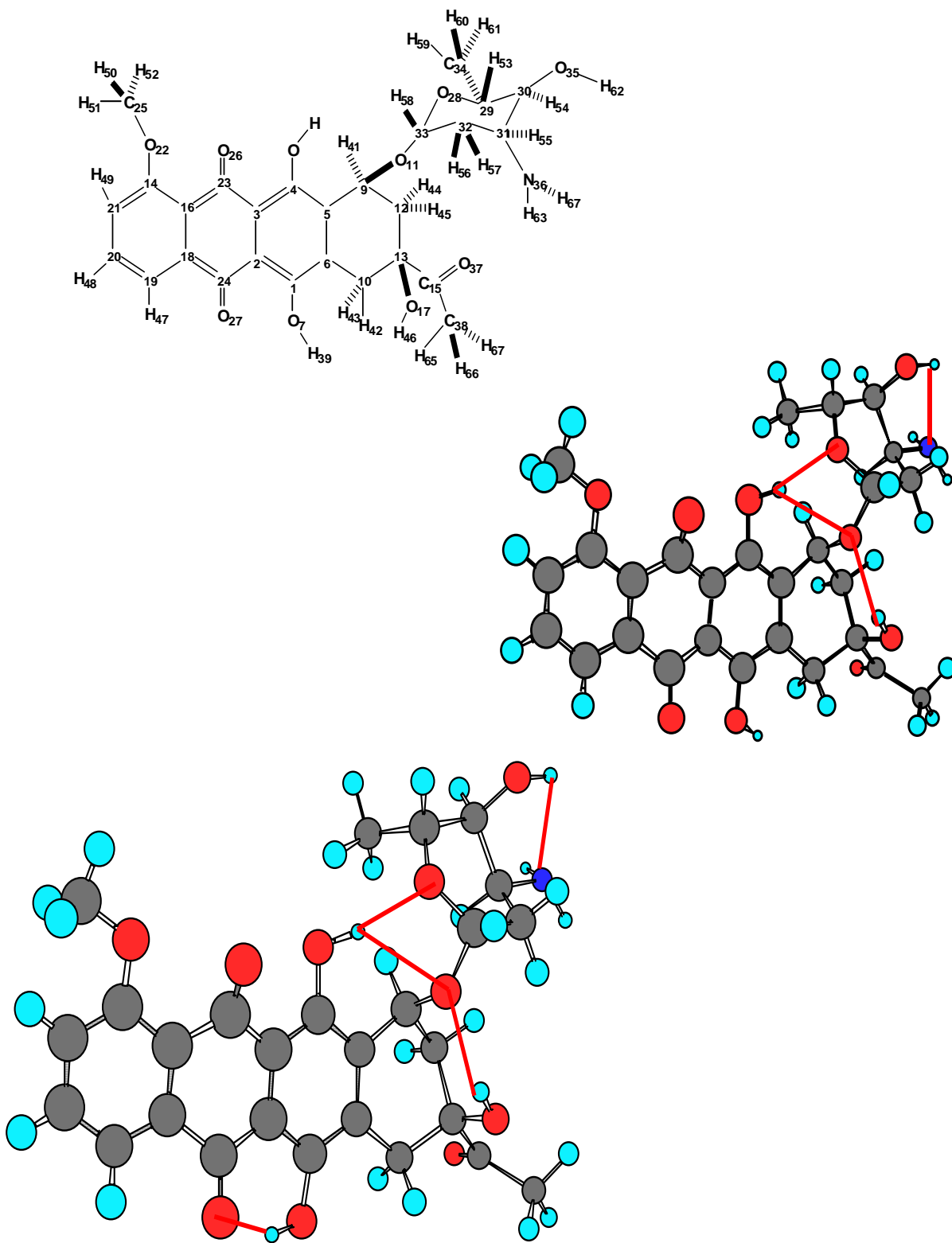
mefloquine



quinine



artemisin
artemether



daunorubicin

STARTING COMPUTATIONAL RESEARCH

experiment

- proposing the computational study of a biologically active molecule from indigenous flora and from traditional medicine as postgraduate project

features highlighted

- feasibility (at simple levels) within existing (or easily attainable) facilities
 - ♣ variety of features that can be highlighted by simplest computational approaches (e.g., semi-empirical)
- possibility of attracting students' interest
- possibility of achieving good familiarisation with the main aspects of the study of molecules and their properties / activities

- possibility of developing simpler studies into higher level ones if more powerful computational facilities become available
- relevance of interactions with centres/experts with long established expertise

CONCLUSIONS

The enhancement of computational chemistry studies on malaria-related molecules in African universities:

- is a realistic option
- can
 - ♣ integrate with ongoing research activities
 - ♣ advance knowledge from indigenous medicine
 - ♣ value and develop molecules from indigenous natural products
 - ♣ expand chemists' involvement in malaria research
 - ♣ provide new insight into a variety of aspects.