Design and Synthesis of New Dihydroorotate Dehydrogenase Inhibitors as Potent Antimalarials

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1. Malaria
   - Malaria infects between 300-500 million people annually and causes up to 2 million deaths. The following map indicates the distribution of malaria according to the World Health Organisation (WHO).

2. A Target for New Drugs
   - De novo pyrimidine biosynthesis is an attractive and potentially selective target for the development of new therapeutics against P. falciparum. Unlike human cells, which can both synthesize and salvage pyrimidine bases, P. falciparum lacks any pathway for the salvage of preformed pyrimidine bases or nucleosides and relies completely on a de novo biosynthesis pathway.

3. Structure of DHODH
   - The X-ray crystal structure of human (Hs) DHODH is an α-β barrel with orotate and FMN stacked in the active site, elaborated by 2 helices thought to form the channel for CoQ. The inhibitor A77-1726 is bound within this putative ‘ubiquinone channel’ and makes H-bonding contacts to R136 and Y356 respectively.

4. SPROUT: Drug Design Software
   - SPROUT is divided into five modules, allowing the user to develop small molecular inhibitors de novo or alternatively dock existing inhibitors or fragments of these and design improvements that may result in increased binding affinities.

5. Targeting the Ubiquinone Site
   - Previous work in the group has used SPROUT to design simple inhibitors that target the ubiquinone channel. They make H-bonds to histidine-185 and arginine-265 residues and satisfy the hydrophobic central portion of the ubiquinone channel. One such active compound is:

6. A New Inhibitor
   - In keeping with the design criteria a range of analogues were designed and synthesised. Compound MD 2/108 was found to be active in PΔHODH:

7. Developing our Lead Compound
   - The following analogues were synthesised and tested:

8. Next Generation of Inhibitors
   - SPROUT was used for lead optimisation, starting with MD 2/155 as the lead and modifying the biphenyl ‘tail’.

9. What makes a Good Inhibitor?
   - We have established that a BIPHENYL TAIL is required for an active inhibitor.

10. Synthesis of Inhibitors
    - All of the inhibitors were synthesised according to a CARBOXYLIC ACID ROUTE or an AMINE ROUTE.

11. Conclusions and Future Work
    - We have successfully applied SPROUT to design potent inhibitors of both human and Plasmodium falciparum dihydroorotate dehydrogenase.

12. References

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