(R)-PZQ Project

Aim: To replace existing racemic PZQ supply to Third World with the single enantiomer equivalent

Benefits/Motivations:

1) It is no longer regarded as acceptable in Western medicine to develop racemic drugs, and as a point of principle the same should apply elsewhere
2) Activity in racemic PZQ is stated to lie entirely in the (R)- enantiomer
3) The (S)- isomer is not known to be actively harmful, but does:
    a. Present an extra burden upon the liver
    b. Confer a significant bitter taste to the racemate, which is reduced in the single (R)- isomer. This could aid in achieving patient compliance
4) The above factors could enable a beneficial adjustment of dosage size/regimen to improve effectiveness, reduce side-effects

Challenges:

1) Cost of goods – present efforts upon schistosomiasis treatment are largely charitably funded. There is a responsibility to use the money to best effect, and present WHO strategy is to run a 5-year program in a country and then withdraw, handing responsibility over to the national authorities. Clearly they will seek best value …….
2) Process – existing methods are based upon chromatographic resolution of PZQ. Potential alternatives include chiral auxiliary methods, classical resolution of an intermediate amine-based synthesis, biocatalytic or chemoselective reduction of intermediate enamine. Work in progress…..
3) Formulation – current racemate is tabletted and has long history (since 1970's). Properties of single enantiomer relatively unknown (forms a hemihydrate from aq MeOH). Unknown stability, polymorphism, compressibility etc. NB Cannot form salts, hence limited ability to change properties
4) Toxicology, DMPK etc. Some published info on single enantiomer drug, but needs collection and critical review. Are studies of the standard required in 2010+ ? Do they reflect current or potential dose levels ?
5) Schistosomiasis not a single disease – about a dozen related parasites exist, with geographical boundaries. Target organs may vary with specific parasite.
6) Side-effects of treatment include nausea, diarrhoea, headaches etc. Uncertain how much is due to the drug alone, as quick kill of parasite burden in blood/organs has its own effects. Treatment of certain forms of disease (eg brain) is recommended as in-patient only. (? Diagnosis method ?)

Opportunities:

1) There is an existing vetinary use of rac-PZQ. Could be a market for (R)-PZQ – easier dosing of reduced bitterness formulation ?
2) Current world experts in rac-PZQ production are in South Korea. They could be approached re either their own research in field, or to gauge interest in taking on anything new. What is their evaluation of benefit or single enantiomer ?
3) Stated price is 7c per 600 mg tablet.

Resources:

1) Matt Todd leads a lab in Sydney, and has funding of $400k AU for synthetic studies.
2) Matt is prime contact for Schisto research on The Synaptic Web
3) WHO is supportive of single enantiomer switch. Not sure if they actively fund any part of the program however.
4) Bill Gates foundation supports WHO program with $40M US.

Possible Priorities:

1) To undertake comprehensive review of existing clinical, pre-clinical, DMPK, tox etc data on racemic and single enantiomer forms
    a. Evaluate satisfactory areas of coverage
    b. Identify areas of weakness or nill cover
    c. Consider dosing levels (a) trialled (b) practiced
2) Conceptualise a set of trials to fill out the picture/address any issues in the above
    a. Estimate approximate quantity of single enantiomer needed for trials
    b. Consider “ethics committee” for approval to run trials – who would do this ?
3) Formulation:
    a. Review all available knowledge of physical properties rac- vs (R)-
    b. Does data suggest simple substitution is possible ?
    c. Define appropriate number and scale of trials to progressively address drug delivery at appropriate levels, rates
    d. Use the above to predict required quantities of API, in staged fashion, for:
        i. Crystallisation & Polymorphism screening
        ii. Pre-formulation studies on lead candidate(s)
        iii. Formulation development
        iv. Supply of Ph I clinical trials stock
        v. Supply of Ph IIa and IIb clinical trial stock
        vi. Phase III clinical trials – how many centres, patients ?
4) API Supply
    a. It is assumed that the most effective/reliable way to get single enantiomer stock in the short term (1-2 years) will be to resolve racemic API. This can be done by SMB chiral chromatography, operating under GMP conditions, using GMP racemic API.
    b. Establish as far as possible the exact conditions employed already, and what limitations encountered.
    c. Identify possible locations for (a) conventional chromatography (b) SMB. Do these have any concept or realisation of, cGMP ? Generate proposal and attempt to “sell” to facility owner.