Case Study: Route Selection and Scale-up

Questions

Part A) Analysis of the Discovery Route

1. What are the advantages of the Medicinal Chemistry route for a discovery team?

2. A key problematic step is the intra molecular cyclisation to give SB-218093.
    a. On scale-up this step gave poor to moderate yields of product – assuming the worst case yield at this stage of 30% SB-218093, how much bromofluorotoluene would be needed to make 3,000kg of SB-214857?
    b. Assuming a cost for bromofluorotoluene of £500/kg (estimated) what would the cost of the starting material to prepare 3,000 kg of SB-214857 using the medicinal chemistry route?

3. Another undesirable feature of this step is the erratic quality of the SB-218096 produced.
    a. The ee (enantiomeric excess) could vary between 100 and 91% - does this matter?
    b. What is the possible quality impact on the drug substance?

4. 3Å molecular sieves were added to try to suppress the racemisation process. The charge was 5 kg/ 1 kg of input material.
    a. What weight of 3Å sieves would be needed to make 3,000 kg SB-214857 (assume a yield of 30% for SB-218096)?
    b. What would you do with these after the reaction?
    c. How much waste would be generated if 200 tonnes SB-214857 was manufactured and at what cost for disposal (assuming landfill tax at £80 per tonne)?

5. Looking at the efficiency of making the 4,4'-bipiperidine synthon, how much 4,4'-bypyridine would be needed for 3,000 kg of SB-214857?

Part B) Analysis of the Manufacturing Route

1. What attributes of the manufacturing route are more attractive for use on scale?

2. Given a 24% yield overall yield of SB-214857:
    a. How much 2-nitrobenzylalcohol is needed to make 3,000 kg SB-214857?
    b. What would this cost at £70/kg (estimated) for 2-nitrobenzyl alcohol = using the manufacturing route?

3. How much 4,4'-bipiperidine is required to make 3,000 kg SB-214857 via the manufacturing route?

4. The lipase resolution works with many 1,4-benzodiazepines and can be successfully positioned later in the synthesis e.g. on racemic methyl esters of SB-270051 or esters of SB-214857 – what are the benefits and disadvantages of an early vs late stage resolution?

Part C) Stereochemistry

1. Apart from l-aspartic acid and bioresolution, suggest some alternative bio/chemo routes to set the S-stereochemistry at C-2 of the 1,4 –benzodiazipine ring (the R enantiomer is inactive).
    a. What would be the advantages and disadvantages of the different approaches?

2. A number of other biocatalytic routes to make chiral intermediates used in the manufacturing route exist – what would be the benefits and drawbacks of using a chiral metal catalyst to reduce SB 235348 compared to a whole cell bioreduction?

Part D) Process Development - *Consider the manufacturing route*

1. Your plant has the capacity to convert 300 kg of starting material per week through to SB-214857 – Comment on the throughput of both routes.

2. Are there any reagents/transformations that would give rise to safety concerns/need special handling on scale?

3. What potential safety and quality issues do you envisage as a consequence of the reagent choices (transfer hydrogenation with Pd/cyclohexene vs hydrogenation with Raney nickel) to reduce the aromatic nitro group?

4. What are the benefits of recycling the R enantiomer? What quality issues could this give rise to?

5. What other potential impurities would you look for in the API?

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