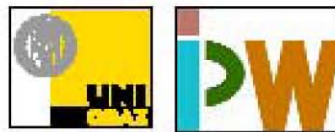


Derivatisation of Artemisinin to Dihydroartemisinin and further to Artesunate



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Criteria

- Higher yield
- More effective agent
- Cheaper agent
- Less toxic agent






Dihydroartemisinin

- 6.6g artemisinin suspended in 40ml methanol
- Ratio of artemisinin to NaBH_4 1:2.5
- Mixture of 30% acetic acid and ethyl acetate (1:1) is reached to stop the reaction (pH=5-6)
- Extraction with ethyl acetate several times
- Recrystallisation with ethyl acetate/ hexane (1:3)
- Yield about 95%




Artesunate

- 10g dihydroartemisinin suspended in 35ml ethyl acetate
- Ratio of dihydroartemisinin to triethylamin 1:1.1
- Ratio of dihydroartemisinin to succinic anhydride 1:2
- Breakdown with water and neutralisation with 2N H_2SO_4
- Extraction with ethyl acetate
- Recrystallisation with hexane/ ethyl acetate
- Yield about 95%



Conclusion-Dihydroartemisinin

- Protocol, which produces a high yield of dihydroartemisinin, while the amount of methanol and the amount of sodium borohydride needed for the reduction could be reduced
- The extracting agent ethyl acetate can be reused
- Unsolved problem: reusability of methanol



Conclusion-Artesunate

- Protocol for the esterification of dihydroartemisinin to artesunate with succinic anhydride and triethylamine
- Ethyl acetate
 - Less toxic than the solvents mentioned in literature
 - Reusable
- No catalyst needed (such as DMAP)



The End

Thank you for your attention!

Acknowledgement:

- MMV
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- Armin Presser



Scale up

| | unit | quant | recycling possible |
|---------------------------|------|-------|--------------------|
| Artemisinin | kg | 1.0 | no |
| Methanol (reaction) | l | 6.0 | no |
| Methanol (neutralisation) | l | 1.8 | yes |
| Sodium borohydride | kg | 0.3 | no |
| 30% Acetic Acid | l | 1.8 | no |
| Ethyl acetate | l | 7.5 | yes |
| Sodium sulphate | kg | 3.0 | no |

| | unit | quant | recycling possible |
|---------------------------|------|-------|--------------------|
| Dihydroartemisinin | kg | 1.0 | no |
| Ethyl acetate | l | 3.5 | yes |
| Triethylamin | l | 0.5 | no |
| Succinic anhydride | kg | 0.7 | no |
| Water | l | 5.0 | no |
| Sodium sulphate | kg | 3.0 | no |