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Synthetic Chemistry Case Study: Preparation of Heterocyclic Synthons for Dibenzo[e,h]azulenes

Objective:

• Design of novel tetracyclic compounds as potential anti-inflammatory drugs (inhibitors of TNF-a production)

Challenge:

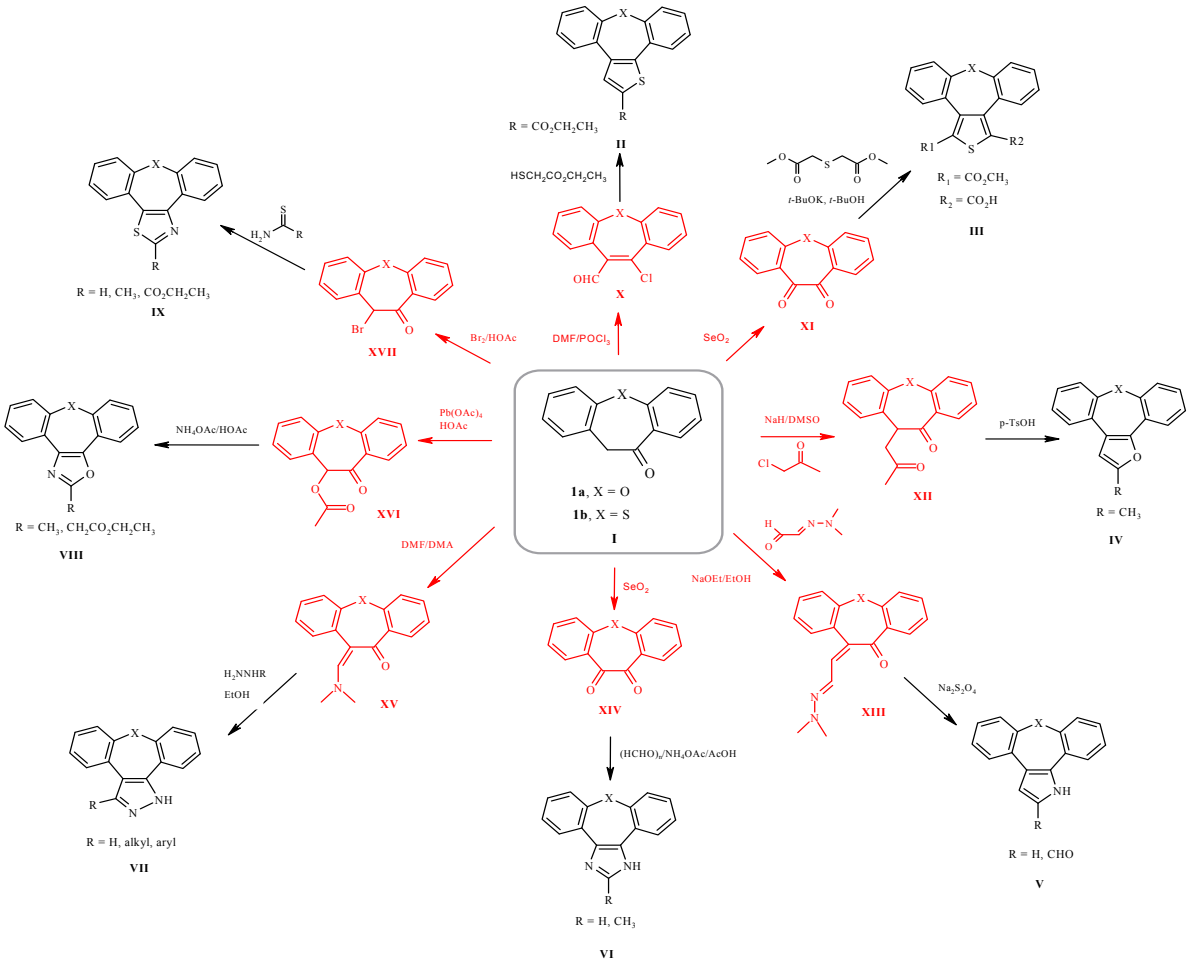
• Use of dibenzo[b,f]oxepin- and thiepin-10(11H)-one (I) as common precursors for the synthesis of an array of five membered heterocycles (II – IX)

Summary:

• 1st award for the most perspective and inventive work presented at poster; XXI. European Colloquium on Heterocyclic Chemistry, 12-15 September 2004., Sopron, Hungary; 8 patent applications; 7 publications

• Designed and optimized synthetic routes to dibenzo[b,f]oxepin- and -thiepin-10(11H)-ones (I), key intermediate

Preparation of heterocyclic synthons for dibenzo[e,h]azulenes:



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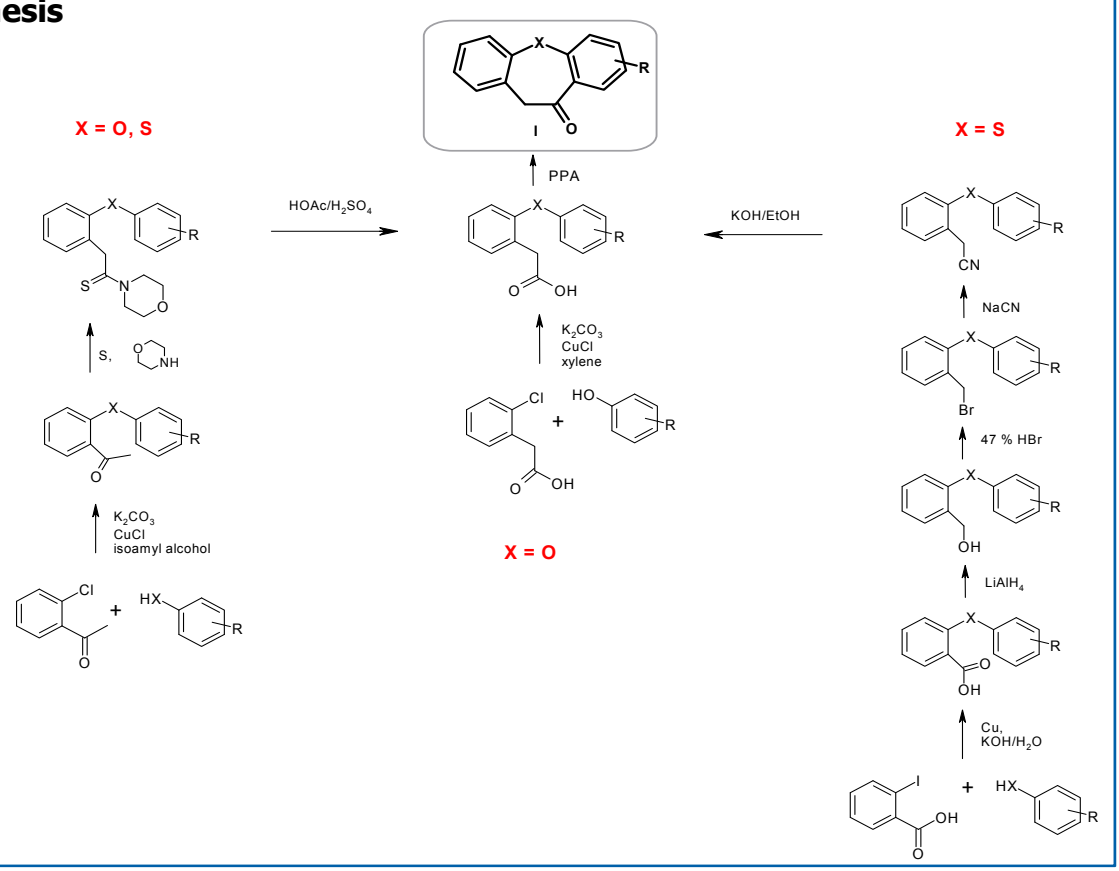
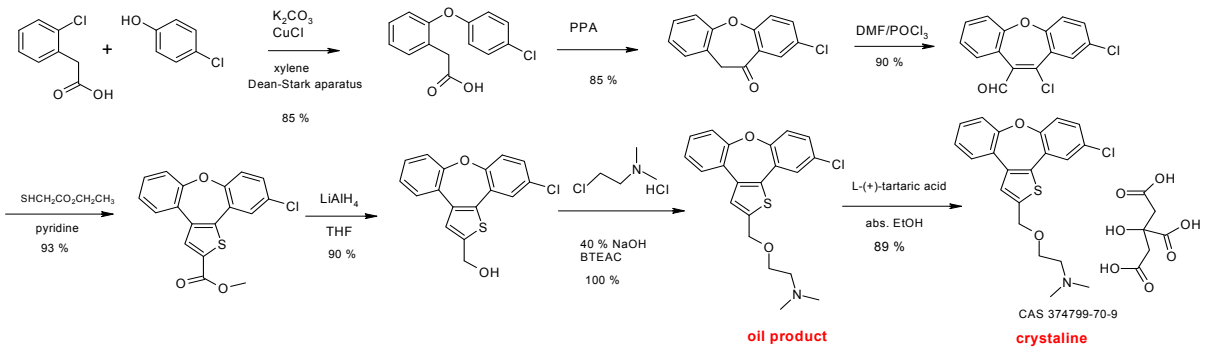
Gram scale synthesis



Summary:

- From 1-thia-dibenzo[e,h]azulene class (II) 1 Pre-clinical andidate compound obtained
  - optimised and provided scale-up synthesis (HR 2003000914 A2)
  - 7 synthetic steps, up to 100 g of final product, 48% overall yield
  - no column chromatography, crystalline material as final product (salt form)
  - identification and isolation of metabolites



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WO 2001087890 ; US 20030153750; HR 2003000914 A2, WO 2003084962, WO 2003097649, WO 2003099823, WO 2003099822, WO 2003084964, WO 2003099827

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