CHEMISTRY 4000

Problem Set #1: Rofecoxib (aka Vioxx®)

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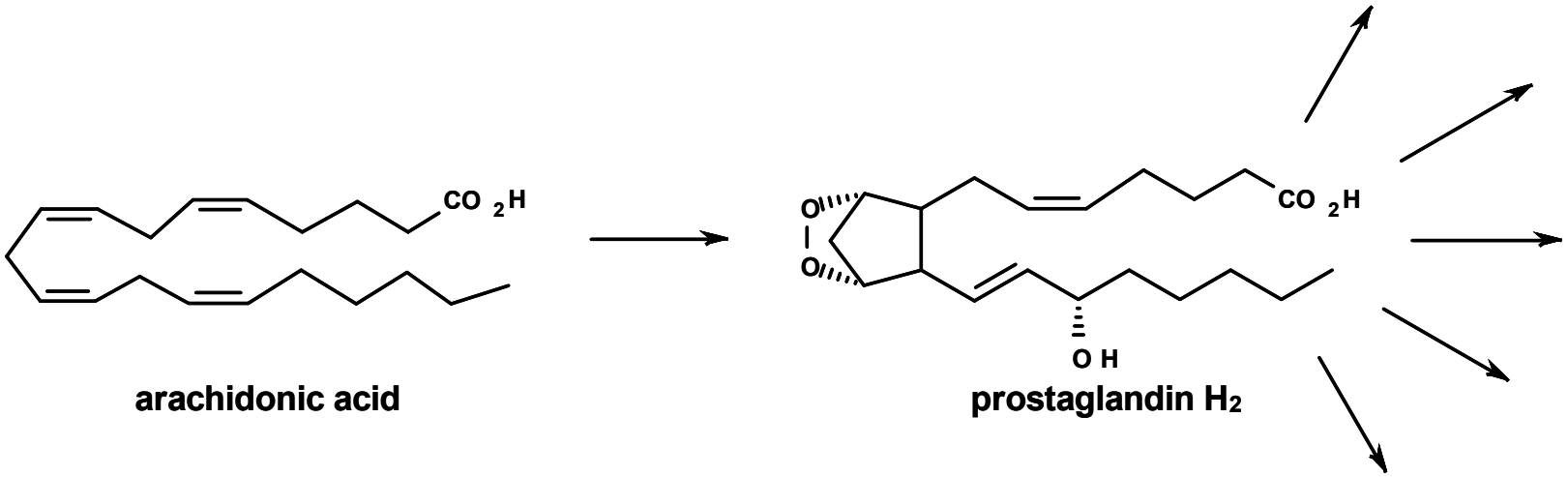
Dr. Susan Findlay

Rofecoxib (aka Vioxx®)

- Rofecoxib was approved by the Vioxx® was launched by Merck in 1999; however it was withdrawn from the market in 2004 after prolonged use was associated with an increased risk of heart attack and stroke.
- Rofecoxib was a non-steroidal anti-inflammatory drug (NSAID). Other NSAIDS include aspirin, ibuprofen and naproxen (Aleve®).
- Rofecoxib was used to alleviate symptoms of rheumatoid arthritis, osteoarthritis and other inflammatory disorders. Because it targeted a different enzyme than the other NSAIDs listed above, it was hoped that it would cause fewer gastrointestinal side effects while having comparable (or better) anti-inflammatory activity.
  - Aspirin, etc. target COX-1 whereas rofecoxib, etc. target COX-2. (COX is short for cyclooxygenase.)
  - The COX-2 pathway was discovered in 1991 and, because it is upregulated during inflammation, it was anticipated that this would be a more specific target than COX-1 (which produces homeostatic prostaglandins and is therefore always active).

Rofecoxib (aka Vioxx®)

- Both COX-1 and COX-2 function by converting arachidonic acid into prostaglandin H_2, which other enzymes further convert into other prostaglandins:

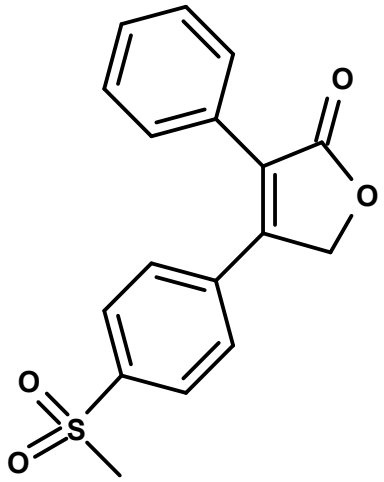


arachidonic acid **prostaglandin H_2**

- Inhibition of this pathway has been shown to be effective against inflammation.

Rofecoxib (aka Vioxx®)

- The structure of rofecoxib is:



- Merck patented several syntheses of rofecoxib. Time-permitting, we will look at two of these syntheses – one used at the laboratory scale and one used at the process scale.