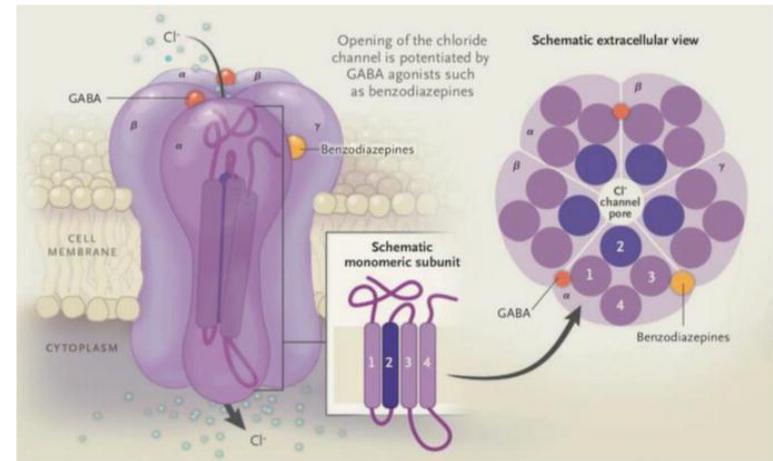


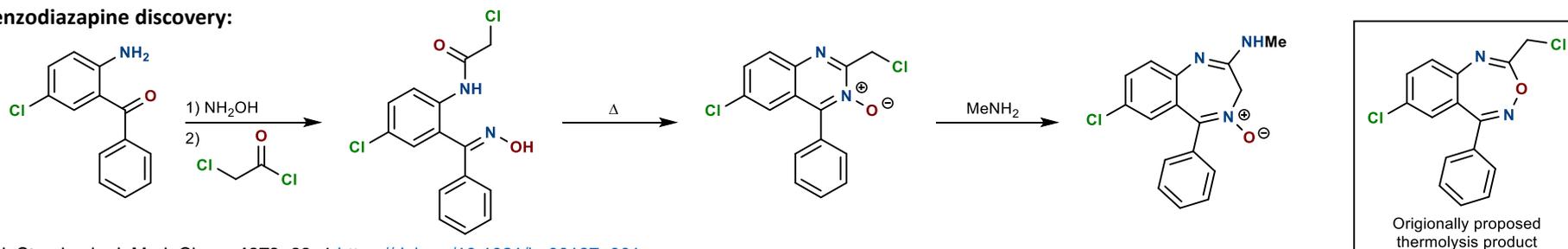
- Benzodiazepines are a structural class of compounds that are generally used as hypnotics, anxiolytics, anticonvulsants, amnestics and muscle relaxants
- Chlordiazepoxide was initially discovered in 1957 while looking for new tranquilizers, and 3 years later it was being sold under the trademark Librium
- Diazepam was quickly found to be 3-10 times as potent as Chlordiazepoxide and by 1963 was sold under the trade mark Valium
- Between 1968 and 1982 Valium was the highest selling drug in the US, selling more than 2 billion tablets in 1978 alone.
- In 2017 Alprazolam was the 21st most prescribed medication in the US with more than 25 million prescriptions

- Benzodiazepines are positive allosteric modulators of the GABA_A receptor, a ligand-gated ion channel that is permeable to chloride ions when activated.
- When bound these compounds alter the receptor into a confirmation that has a much higher affinity for GABA, increasing the frequency of the opening of the channel.
- This causes an inhibitory effect on neurotransmission by diminishing the chance for a successful action, leading to sedative and anxiolytic effects
- Benzodiazepines bind at the interface of the α - and γ -subunits, but not all α -subunits bind benzodiazepines. α 1-, α 2-, α 3-, and α 5-subunits bind strongly to benzodiazepines while α 4- and α 6- do not.
- Substitution on at different positions on the benzodiazepine core leads to different binding affinities for different subunits and leads to different pharmacological effects.
 - For example strong binders of the α 1- and α 5-subunits leads to stronger sedation properties while α 2- and α 3-subunit binders have greater anxiolytic effects



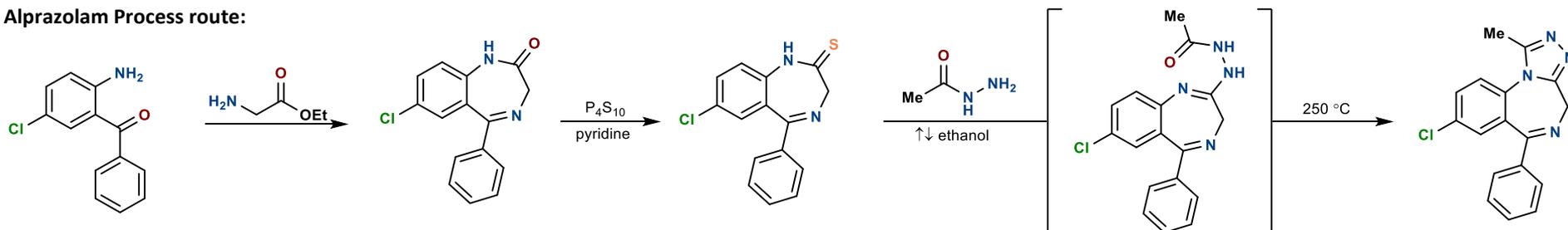
- Alprazolam (Xanax) is a short-acting benzodiazepine and is most commonly used for the treatment of anxiety disorders, panic disorders, and chemotherapy-induced nausea.
- Common side effects include sleepiness, depression, headaches and anterograde amnesia
- Long-term use can cause adaptive changes in the GABA_A receptor potentially leading to tolerance and physical dependence; slow dose reduction is recommended.
- In the US benzodiazepines are the most frequently used pharmaceutical for recreation due to their widespread use and account for 35% of all drug-related visits to the emergency room.
 - This is most often due to the synergistic effects they display when taken in combination with other drugs, such as alcohol and barbiturates potentially leading to fatal respiratory depression

Benzodiazapine discovery:



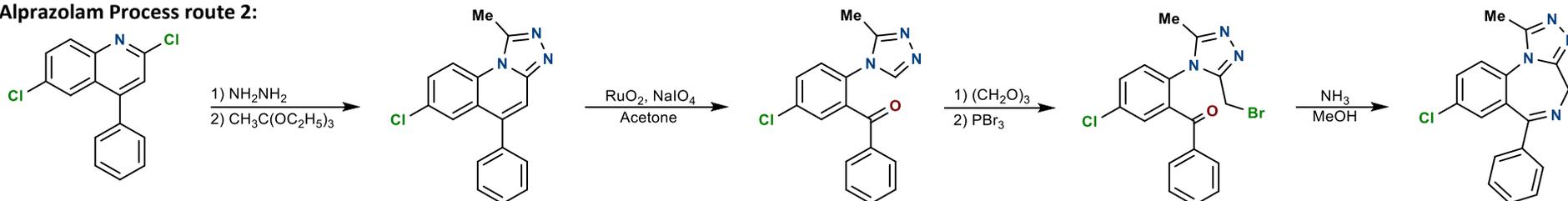
L.H. Sternbach, *J. Med. Chem.* **1979**, 22, 1 <https://doi.org/10.1021/jm00187a001>

Alprazolam Process route:



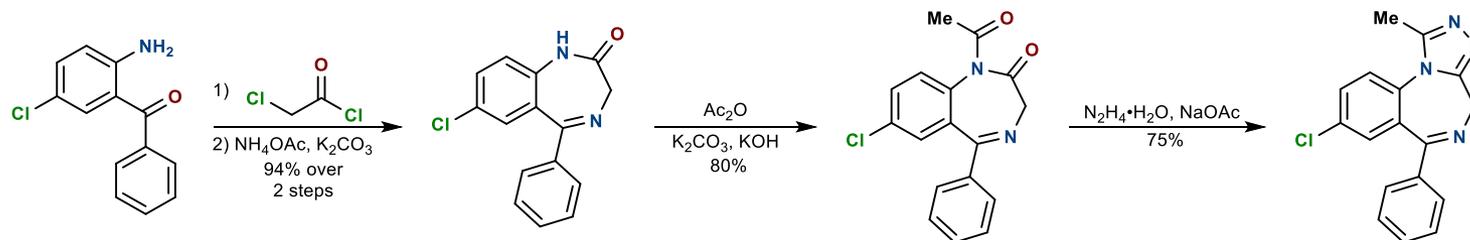
H.B. Jackson, U.S. Pat. 3.987.052, **1976** <https://patentimages.storage.googleapis.com/f8/ad/68/d76c81073aaf70/US3987052.pdf>

Alprazolam Process route 2:



J. Hester, U.S. Pat. 3.709.898, **1972** <https://patentimages.storage.googleapis.com/17/b8/0c/230bddcd68991/US3709898.pdf>

Asakere 2016:



N. Asakere *Med. Chem. Res.* **2016** 25, 1538 <https://doi.org/10.1007/s00044-016-1585-z>