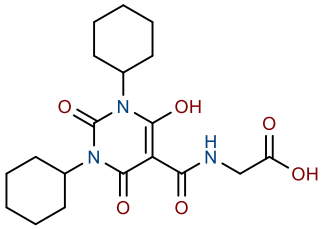
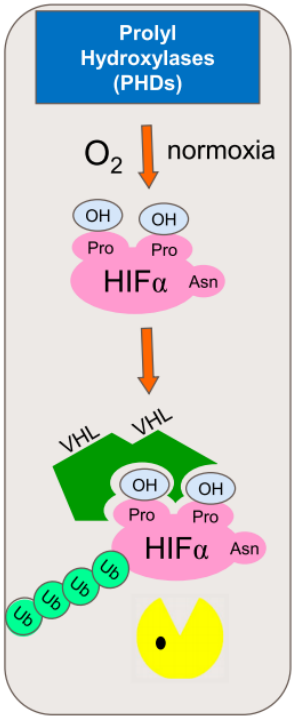
GSK1278863 (Daprodustat) GSK

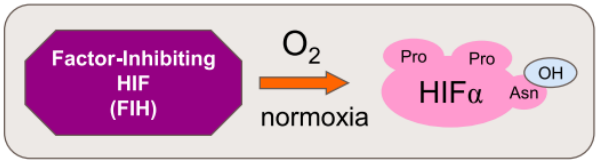


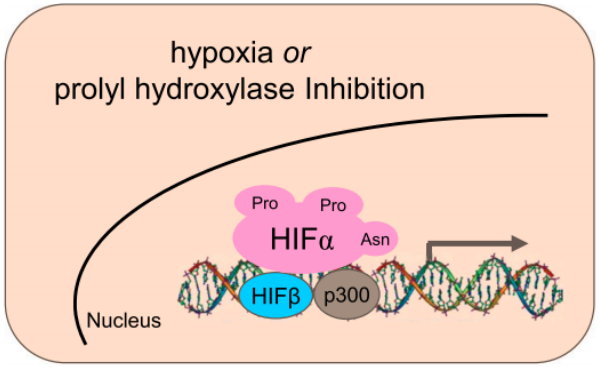
Daprodustat

- In anemic patients with chronic kidney disease one common course of action is high doses of recombinant human erythropoietin (EPO).
- An alternative solution to anemia is promoting increased EPO production by increasing cellular concentrations of hypoxia-inducible factors (HIFs).
- HIFs control physiological responses to hypoxia through transcription of HIF-responsive genes
- In normoxia HIFs are deactivated in two ways
    1. Prolyl hydroxylases hydroxylate conserved proline residues in HIFs and marks them for ubiquitination and degradation.
    2. Factor-Inhibiting HIF (FIH) hydroxylate an asparagine residue in HIF preventing association of p300 and subsequent transcription of HIF-responsive genes.
- Inhibition of PHDs can effectively increase cellular concentrations of HIFs

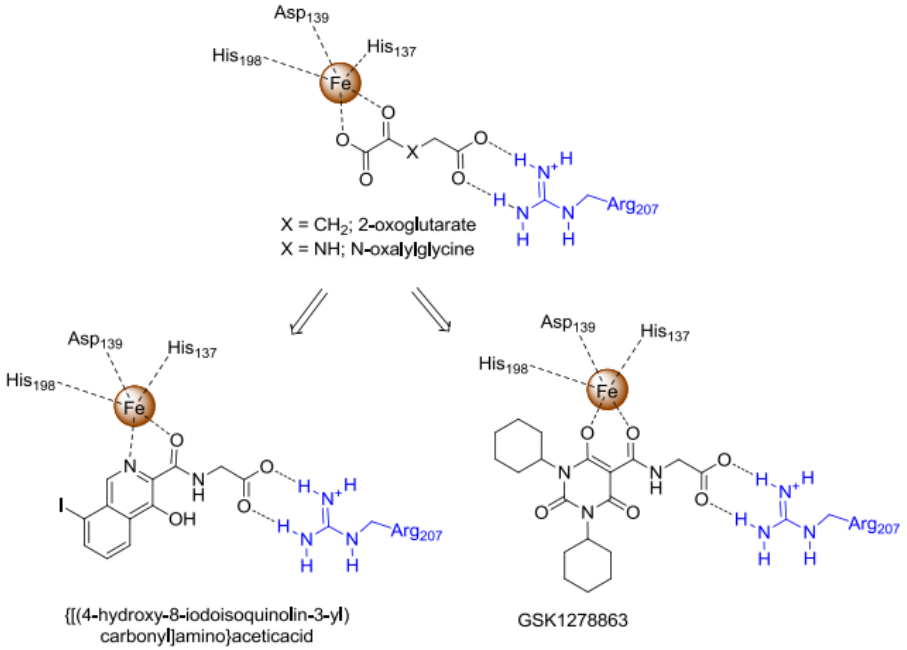
Mode of Action







Transcription of HIF-responsive genes e.g. *EPO* → Increased Erythropoiesis → Alleviation of Anemia

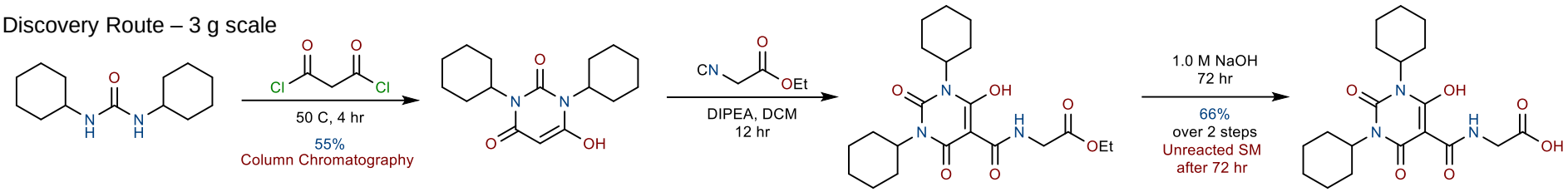


Daprodustat mimics the N-oxalylgycine substrate of PHDs and competitively binds the active site.
Chelation to the iron center and H-bonding to an active site argenine is critical for the binding of N-oxalylglycine and also Daprodustat.

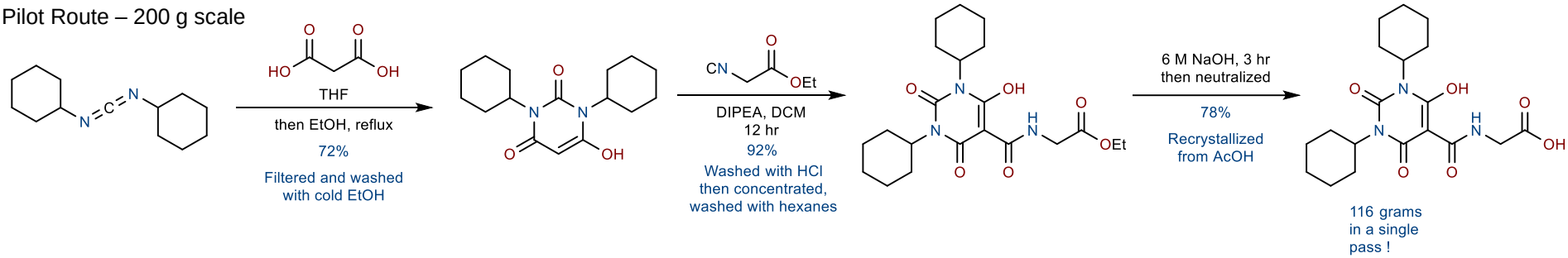
GSK1278863 (Daprodustat) GSK

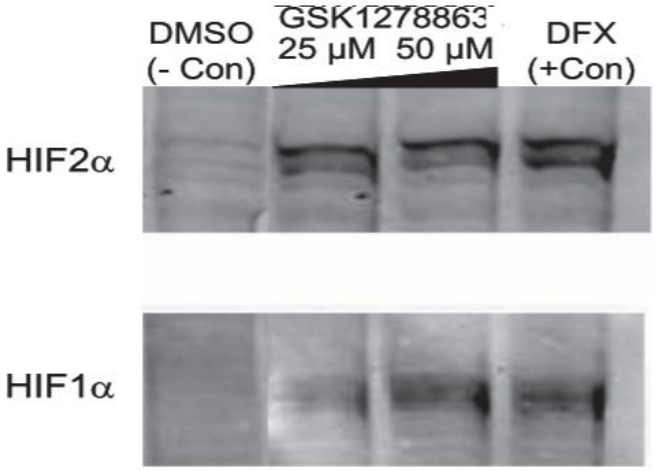
Synthesis

Discovery Route – 3 g scale

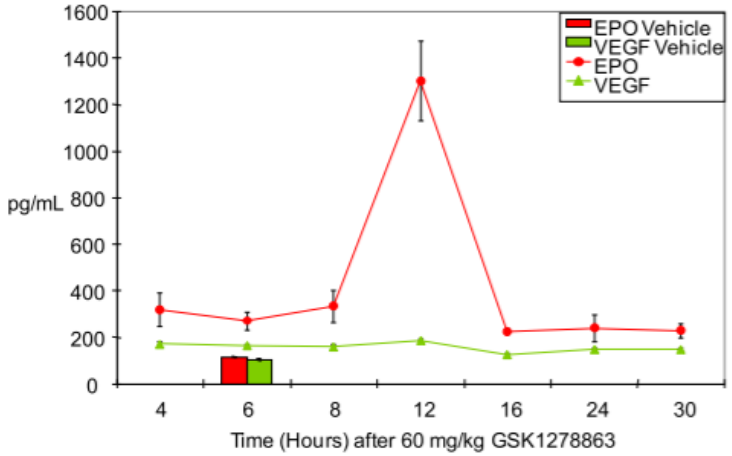


Pilot Route – 200 g scale





Western blot analysis of vehicle treated cells, Daprodustat treated cells, and DFX treated control cells show accumulation of HIF1a and HIF2a after 6 hours.



EPO concentrations in plasma of Daprodustat and vehicle treated mice.

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