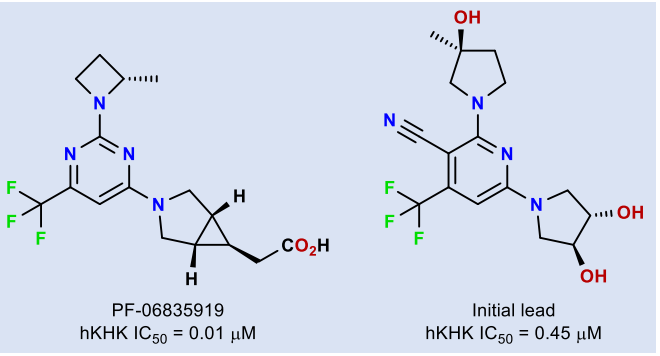
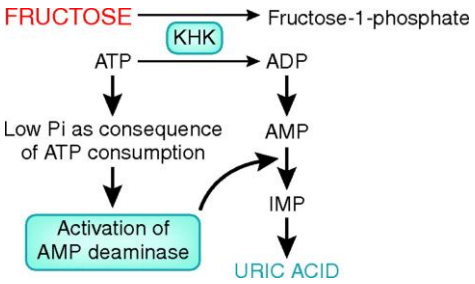
DRUG of the week

PF-06835919

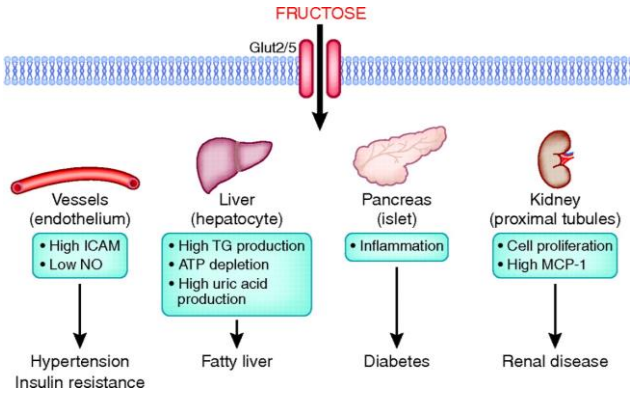
The SARLAH Group

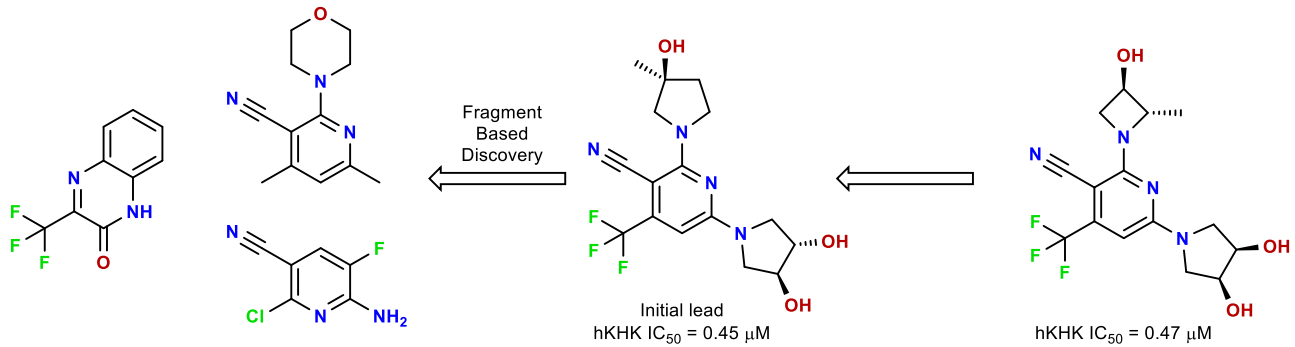


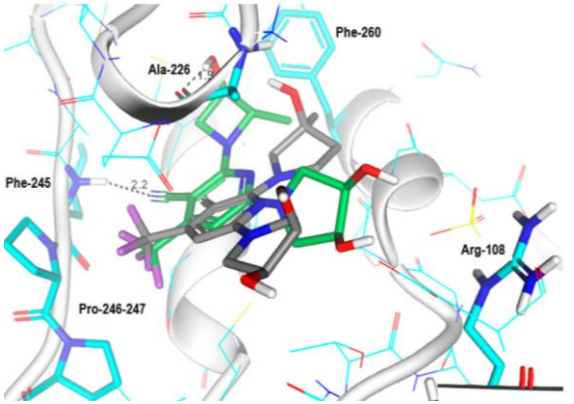
- PF-06835919 is a first in class pyrimidine based reversible inhibitor of Ketohexokinase (KHK), the enzyme that initiates the metabolic cascade of fructose by phosphorylating the 1-hydroxyl position.
- Its bioactivity proceeds through a mixed non-competitive pathway, by inhibiting the binding of ATP.
- Fragment screening efforts provided the initial 3-cyanopyridine lead and extensive SAR studies led to PF-06835919.
- PF-06835919 is currently in phase 2 clinical trials for the treatment of non-alcoholic fatty liver disease (NAFLD).



- Fructose intake has been associated with hypertension, non-alcoholic fatty liver disease (NAFLD), insulin resistance, and diabetes, renal disease and cardiovascular disease.
- The phosphorylation of fructose by KHK is less regulated than glucose phosphorylation and leads to ATP depletion, resulting in transient inhibition of protein synthesis.
- The resulting ADP can then be broken down to uric acid, increasing its concentration in the blood stream and leading to hypertension.
- Inhibition of KHK is considered a promising treatment of metabolic diseases supported by studies in KHK-null mice, demonstrating protection from fructose induced hyper-lipidemia, insulin resistance, obesity, and NAFLD.







K. Futatsugi *J. Med. Chem.* **2020**, *in press.* https://doi.org/10.1021/acs.jmedchem.0c00944, R. J. Johnson, *JASN*, **2010**,*12*, 2036 https://doi.org/10.1681/ASN.2010050506

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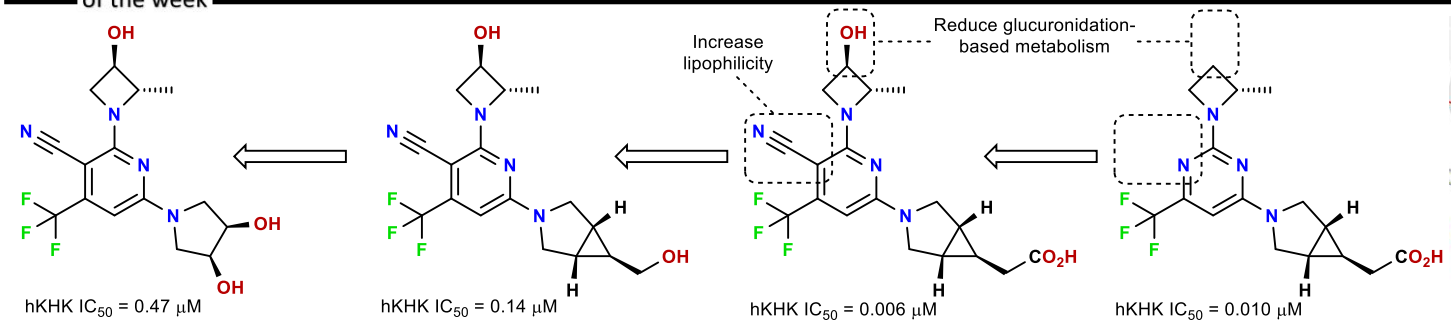
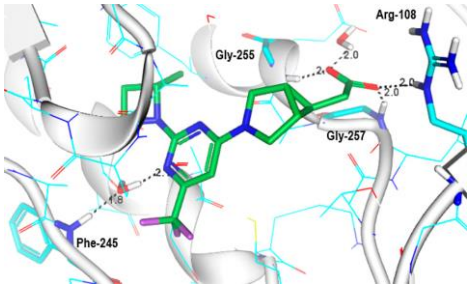
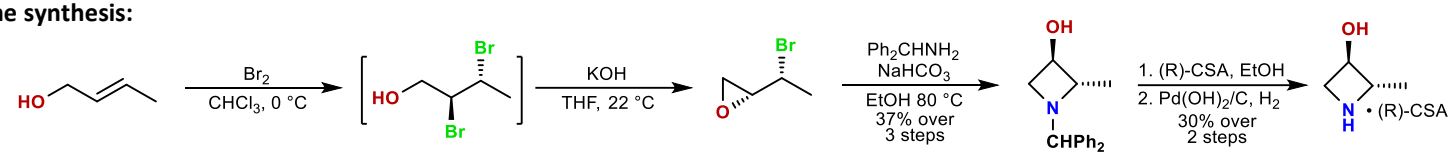
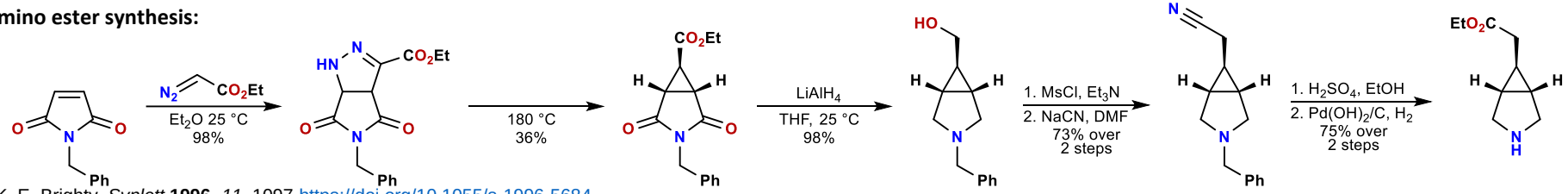




2-hydroxy-azetidine synthesis:



Amino ester synthesis:



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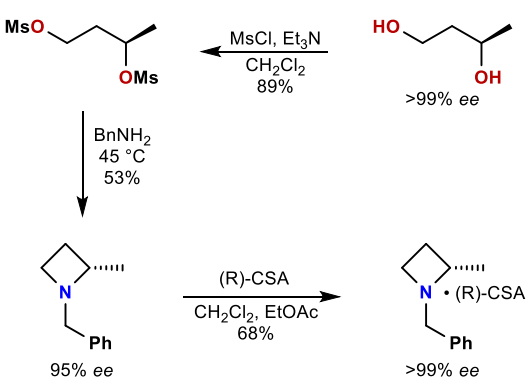
Azetidine synthesis:



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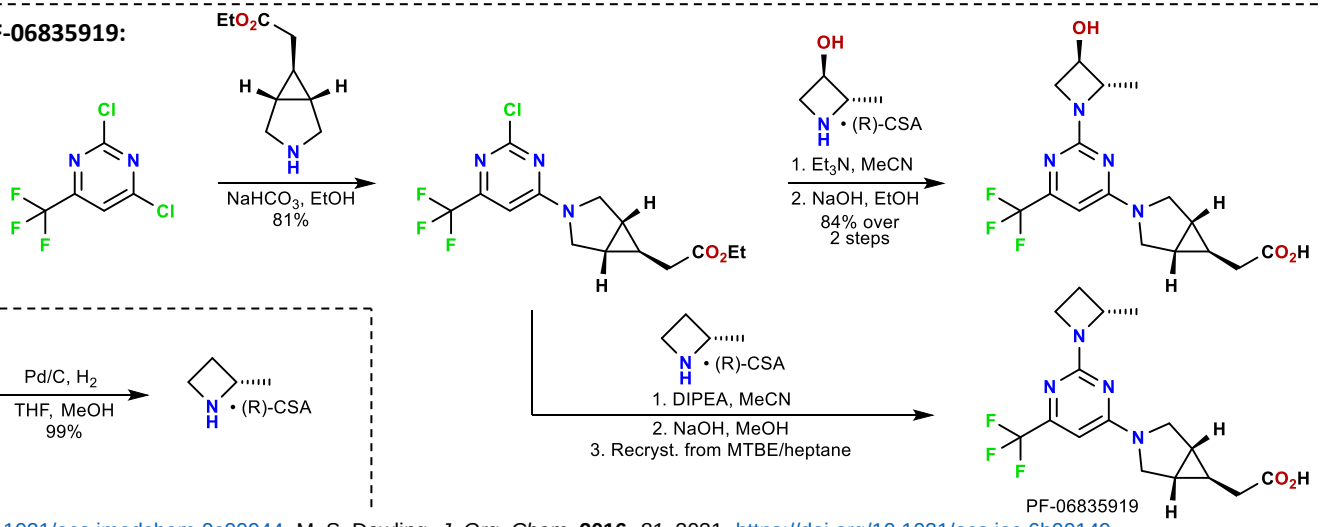

K. Futatsugi *J. Med. Chem.* **2020**, *in press.* https://doi.org/10.1021/acs.jmedchem.0c00944, M. S. Dowling, *J. Org. Chem.* **2016**, *81*, 3031. https://doi.org/10.1021/acs.joc.6b00149