Early PR&D at SpiroChem:

CEP-439, from the MedChem route to the first scale-up

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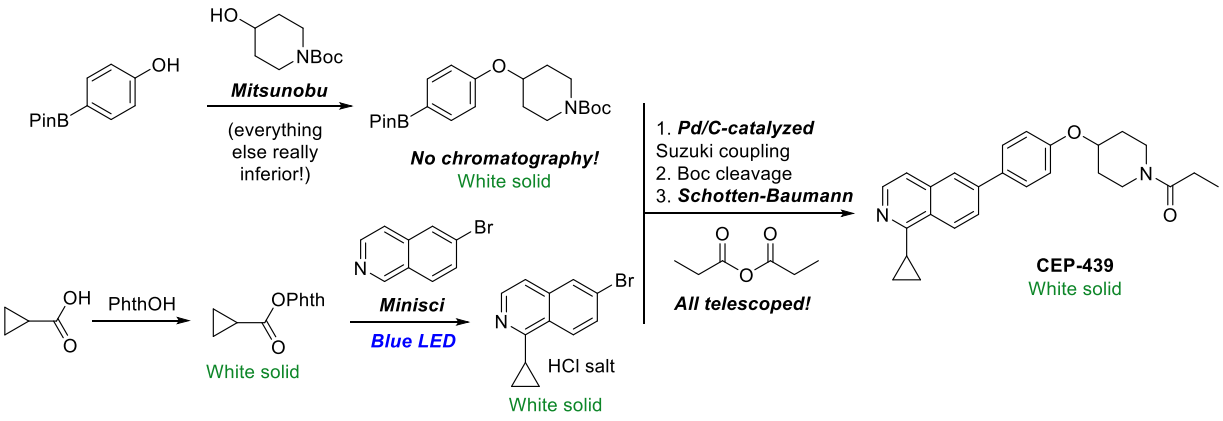
Fatty acid synthase (FASN) is a multi-enzyme complex involved in the biosynthesis of palmitate from acetyl- and malonyl-CoA in the presence of NADPH. Fatty acids are normally preferentially acquired from the diet, and thus FASN is expressed at low levels in normal tissues; in contrast, a heightened need for fatty acids leads to overexpression and activity of FASN for de novo lipogenesis in pathological states, including cancer,[1] inflammatory diseases,[2] viral infections[3] and metabolic diseases,[4] making FASN an attractive therapeutic target.[5]

Cephalon's **CEP-439** and analogues are 1,4-substituted piperidine derivatives, with demonstrated activity as fatty synthase inhibitor.[6] As part of a validation program, SpiroChem was contracted to prepare 20-25 g of **CEP-439** as tool compound for tox studies. However short, the discovery route is rather ill-described in the original patent with 6 steps LLS plus one offline step, including two-Pd-catalyzed steps, scale-unfriendly reagents, expensive starting materials, and low overall yield. Furthermore, FTO was considered advantageous. We thus engaged in a route scouting exercise, to validate a synthetic route mitigating COGs, increasing throughput, and with potential for scale. After validation of a new synthetic route starting from readily available raw materials on scale, we developed the synthetic and isolation steps to enable throughput.

In this poster, we will show our workflow and how we successfully took advantage of cutting-edge technologies, including photoflow and our Peschl photoreactor, as well as HTE to enable and accelerate both the route scouting and development phases, and delivered a short, scalable chromatography-free 4-step synthetic route and released the target 25 g in 3 months.



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