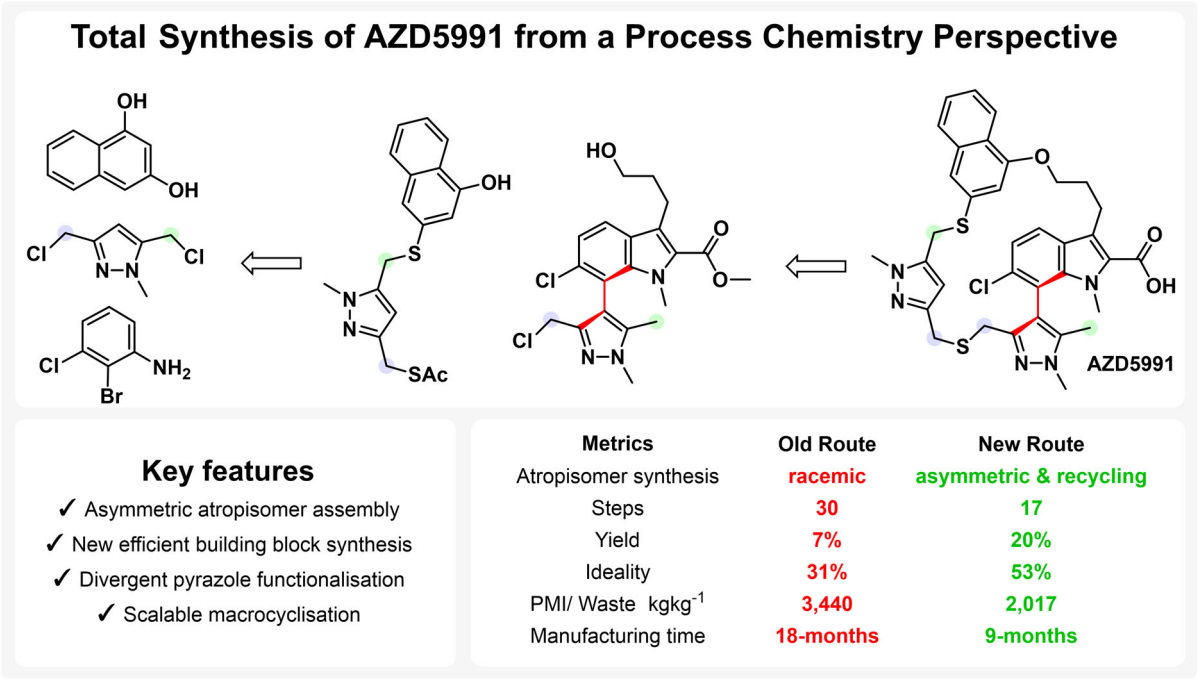

AZD5991 is arguably the most complex active pharmaceutical ingredient in AstraZeneca's "small molecule" development portfolio. The previous thirty step racemic synthesis was able to supply toxicity and pharmacokinetics studies however, was not deemed commercially viable from a financial and environmental standpoint.(1) The identification of a long term route was therefore critical to enable the robust manufacture of drug substance for clinical activities and launch. This symposium will showcase our unpublished approach to total synthesis from a process development perspective through the complete redesign of our synthetic strategy from the ground up. We will explore asymmetric approaches towards the atropisomer core, new routes towards each of the four heterocyclic building blocks, including a divergent pyrazole functionalisation, and the coupling of these in a scalable macrocyclisation process.

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1) Tron, A.E., Belmonte, M.A., Adam, A. et al. Discovery of Mcl-1-specific inhibitor AZD5991 and preclinical activity in multiple myeloma and acute myeloid leukemia. Nat Commun 9, 5341 (2018). https://doi.org/10.1038/s41467-018-07551-w