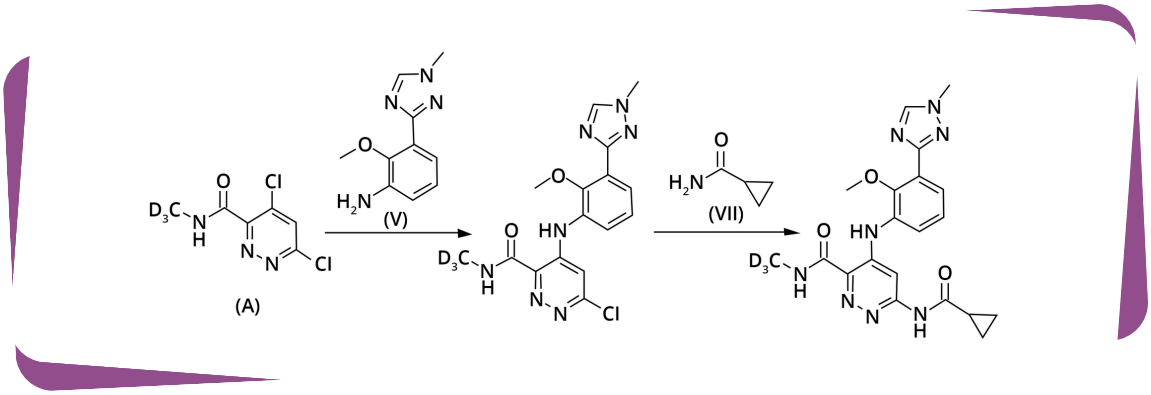
WHITE PAPER

Curia´s patented process for intermediates useful for Deucravacitinib

Deucravacitinib, (6-(cyclopropanecarboxamido)-4-[2-methoxy-3-(1-methyl-1 H- 1 ,2,4- triazol-3-yl)anilino]-N-(2 H3)methylpyridazine-3-carboxamide), is a tyrosine kinase 2 (TYK2) inhibitor used for the treatment of plaque psoriasis.

Several synthetic methods for preparing Deucravacitinib and intermediates thereof have been disclosed, wherein Deucravacitinib is generally obtained from the dichloro intermediate (A) by nucleophilic aromatic substitution with compound (V), followed by palladium catalyzed amidation with compound (VII) (e.g. WO2014/074661 , W02020/086616, WO2022/193499, Wrobleski et al., Journal of Medicinal Chemistry 2019, 62, 8973-8995).



However, the methods disclosed in the prior art for the preparation of the key dichloro intermediate (A) apparently are not efficient enough. WO2014074661 and Moslin et al., Journal of Medicinal Chemistry 2019, 62, 8953- 8972, disclose the preparation of this key compound from 4,6-dihydroxy-pyridazine-3- carboxylic acid, by chlorination with POCl to provide a di-chloro acid chloride intermediate, followed by reaction with methyl-d3-amine hydrochloride. This process yields the desired product with only a 33% yield. A similar strategy is disclosed in W02020086616 (37% yield) and WO2022193499 describes the synthesis of the dichloro intermediate (A) wherein the overall yield from the dichloro ester B1 is only 46%.

Though several processes for the preparation of Deucravacitinib and its key dichloro intermediate have been disclosed, they give rise to the desired product in low yield. Methods disclosed in the prior art for the purification of crude Deucravacitinib include:

(a) recrystallization from NMP and iPrOH (as disclosed in WO2018/183649 or WO20 18/183656), or

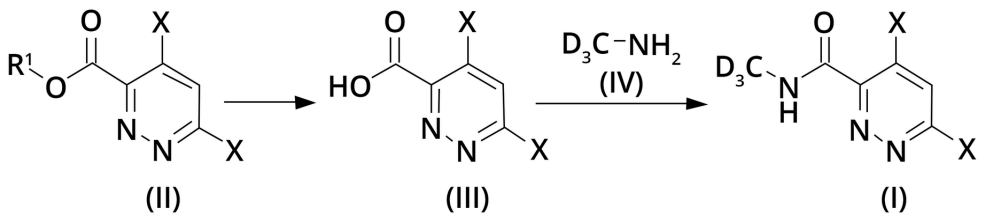
(b) purification by column chromatography (as disclosed in WO2014/074661 or WO2022/193499).

Purification method (a), i.e. using NMP and iPrOH as disclosed in WO2018/183649, yields a very stable crystalline form of Deucravacitinib. However, this method gives rise to Deucravacitinib with a high content of residual solvents. Accordingly, the product obtained by purification method (a) would be unsuitable for pharmaceutical applications without further purification.

The drawbacks of using purification method (b), i.e. column chromatography, are that this method is only suitable when the sample quantity is small and, further, it is a costly method and requires high solvent volumes. Thus, this method is not suitable for industrialization.

Curia´s patented process

Curia patented a new process for the preparation of Deucravacitinib and intermediates thereof. In particular, Curia´s scientists found that a compound of formula (I), or a salt or solvate thereof, which is a key intermediate in the manufacture of Deucravacitinib, can be very efficiently prepared by hydrolysis of an ester of formula (II).



Curia´s process solved the problem of providing a purification method that allows obtaining Deucravacitinib with levels of residual solvents that are acceptable according to the requirements of the US Pharmacopoeia or the ICH guideline of the European Medicines Agency, by a crystallization method, without further purification needed to obtain the compound having amounts of residual solvents acceptable for pharmaceutical products.

For further details, please check Curia Spain patent application WO2025/186427.

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