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Green Chemistry Technology Title: Greener Manufacturing of Belzutifan (MK-6482) Featuring a Photo-Flow Bromination

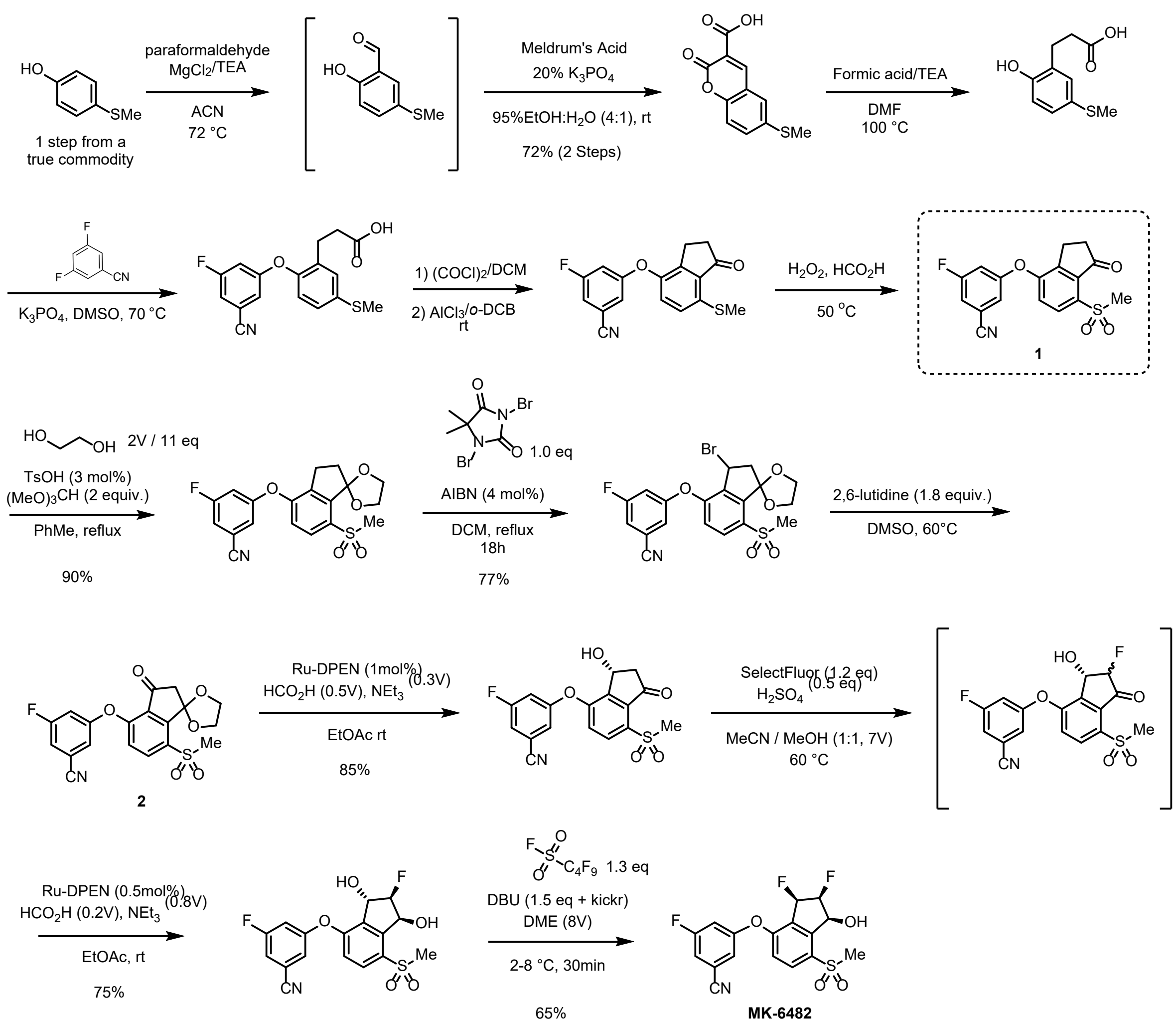
Submission date: December 18, 2020

Focus area selection: This nomination comprises elements of all three areas of focus for this award. First, the synthetic route to manufacture belzutifan (MK-6482) was significantly improved notably with respect to the early steps of the synthesis, providing a more direct route from commodity chemicals to API. Second, significant improvements were made to reaction conditions, especially in the oxidation sequence, which greatly improved the sustainability of the process. Finally, these improved conditions were only made possible via the introduction of an enabling technology, photo-flow, which proved critical to rendering this route viable and reaching our sustainability goals.

Abstract: Belzutifan (MK-6482) is an important new hypoxia-inducible factor-2α (HIF-2α) inhibitor for the treatment of patients with cancer and other non-oncology diseases. This important new medicine was acquired through the purchase of Peloton Therapeutics by our company in mid-2019. A robust and green manufacturing process for its synthesis needed to be developed in extremely short order to be able to deliver this important medicine to patients. Over the past 18 months, the team has developed a new process aimed at increasing efficiency and greatly improving its sustainability. Notably, the PMI of the process has been significantly improved (73% reduction), and the yield was improved nearly 5-fold. A notable technological advance was the development and execution of a visible light mediated bromination performed in flow. This application constitutes the first example of a photo-flow reaction run on manufacturing scale at our company and represents the linchpin of the synthesis. As far as has been disclosed in the literature, this may also constitute the 1st example of a photo-flow reaction on manufacturing scale in the industry.

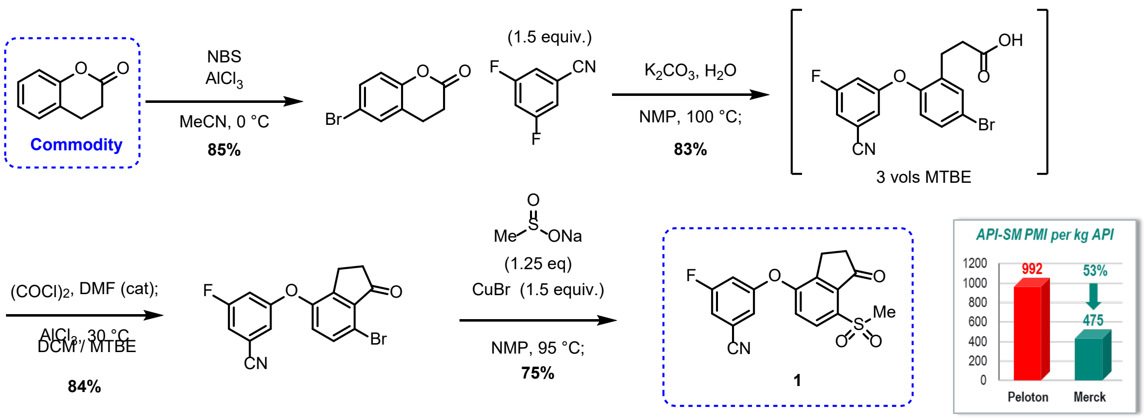
DETAILED DESCRIPTION OF NOMINATED GREEN TECHNOLOGY

(1) Problem. In mid-2019, Merck & Co., Inc., Kenilworth, NJ, USA announced the acquisition of Peloton Therapeutics, a clinical-stage biopharmaceutical company. MK-6482, now known as belzutifan, was the most advanced asset from this deal. Correspondingly, its development was accelerated to enable our company to bring this important medicine to patients. The inherited chemical route for MK-6482 is presented in Scheme 1. Given the stage of development at the time, the efficiency and long-term sustainability of the process failed to meet our standards for a manufacturing route. Of particular concern were: 1) the long linear synthesis of key intermediate **1**, which was subject to several restrictions in manufacturing due to inadequate production of the starting material; 2) a highly inefficient, variable and hazardous oxidation sequence to manufacture ketal **2**; 3) an unacceptable PMI for the overall process. As always, addressing these concerns was critical order to ensure robust and sustainable supply of belzutifan, and a team was formed in order to address the specific following goals: 1) Design a more direct synthesis of ketone **1** that utilizes a readily available commodity starting material and avoids stench issues; 2) Develop a green, safe and robust oxidation sequence to synthesize ketal **2**. 3) Reduce the overall PMI, and increase the overall yield of the process ahead of validation and launch.



Scheme 1. Original manufacturing process of MK-6482

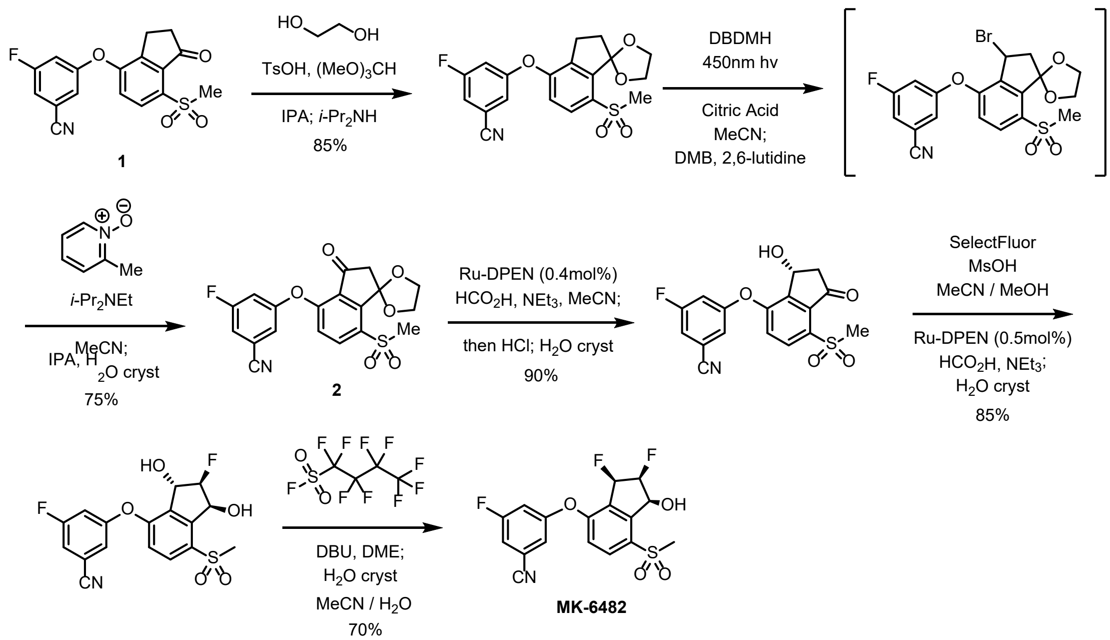
(2) Chemistry. The team quickly devised an alternative synthesis of key indanone intermediate **1**, which is the regulatory starting material for the synthesis. Our company's sustainability goals require us to consider all steps of a process through to commodity chemicals and look for opportunities to streamline and reduce waste in these processes (Scheme 2). In this case, in order to avoid handling an intermediate with a significant stench, a direct sulfonylation was developed from an appropriate halogenated indanone building block. The key indanone was readily accessed starting from the commodity chemical dihydrocoumarin which can be brominated, reacted in an S_NAr reaction to install the phenol side chain, followed by cyclization of the resulting acid via Friedel-Crafts reaction. Altogether, introduction of this improved route reduces the number of steps to ketone **1** by half and increases the yield by 50%. Coupled with process improvement, the PMI of this sequence is reduced by over 50% as well.



Scheme 2. Improved Manufacturing Process of Key Intermediate **1**

The team - and specifically the nominees for this award - turned their attention to resolving the key linchpin for this synthesis, the installation of a hydroxyl group on the indanone. The existing route relied on a batch radical brominating reaction that required dichloromethane (DCM) as reaction solvent in order to achieve high conversion. This undesirable set of conditions was made even more precarious given the challenges of using radical initiators in global supply chains and the corresponding difficult control of over-brominated impurities in this (or any) radical process. To make matters worse, this challenging step was followed by a Kornblum oxidation in dimethyl sulfoxide (DMSO), which itself presented several process safety concerns. Overall, this sequence exhibited poor reproducibility and PMI, in addition to presenting less than green reaction conditions.

The team aspired to develop a process that would run in a greener solvent, limiting the number of solvent changes across the oxidation sequence and enabling a robust control of impurities, a more streamlined process, and removal of aqueous workups. As shown in Scheme 3, It was quickly identified that the most reliable method to achieve the bromination entailed using a visible light initiated radical halogenation reaction, representing our company's maiden effort in incorporating photo-flow to a manufacturing process. This novel approach enabled elimination of DCM as solvent and provided complete control of reaction kinetics resulting in successful impurity control. Furthermore, the team devised an adapted Kornblum protocol that enabled the reaction stream to be used directly without workup or solvent switch. The oxidized indanone **2** can be isolated directly from the reaction mixture. It is noteworthy that considerable engineering and experimentation were invested in perfecting reactor and process design to achieve significant gains in terms of green chemistry, namely elimination of DCM and two aqueous workups. The use of continuous processing using a photo-flow reactor was critical to achieving our sustainability goals. In addition to key breakthroughs on the oxidation sequence, the team was able to leverage the same solvent for 5/6 steps in the final sequence enabling solvent recycling at the vendor. Overall, all aqueous workups were removed, and the PMI for this sequence was reduced by 73%.



Scheme 3. Improved Manufacturing Process for MK-6482

(3) Potential and Realized Benefits. This example constitutes the first application of a photo-flow reactor for commercial manufacturing scale for our company. The development of enabling technologies which lead to the most robust, efficient and green reaction conditions is a key area of focus for our process research and development group. The photo-flow capabilities established during this project form the basis of a new capability that can be used in any visible light mediated reaction going forward, including novel photoredox catalysis which is an emerging class of reactions in organic synthesis. Overall, the new process described above has several realized benefits in terms of sustainability. First, the synthesis of ketone **1**, the key intermediate used as a regulatory starting material was significantly improved, leading to an improvement in yield of 50% and reduction of overall PMI by 53%. Second, the GMP portion of the synthesis was greatly streamlined. Application of the photo-flow bromination led the way to a reaction sequence that enables recycling of MeCN, used in 5/6 steps. Process design and optimization reduced precious metal utilization by 50% and eliminated all aqueous workups culminating in a **-** 73% reduction in PMI. The overall yield of the process is now almost five-fold higher than the original route (19% vs. 4%). We expect to launch MK-6482 in the second half of 2021; the realization of these sustainability gains will have a significant impact in reducing the waste associated with this product and meeting our company's corporate sustainability goals.