ACS Green Chemistry Institute
Pharmaceutical Roundtable

Peter J. Dunn Award Nomination Form

Closing Date for Submissions: Friday, January 31, 2020

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Name of Nominee and Contact Info: Dan Bailey, Takeda Pharmaceuticals, 35 Landsdowne St. Cambridge, MA 02139, dan.bailey@takeda.com, (617) 551-2986

Green Chemistry Technology Title: Beyond organic solvents: Synthesis of a 5-HT_4 receptor agonist in water

Submission date: 1/31/2020

Focus area selection: This nomination simultaneously comprises all three focus area, as greener reaction conditions were developed for an entire six step synthesis (all reactions and isolations from water), while two steps required the invention of new chemistry in water not previously reported in the literature, and the overall synthetic commercial route was shortened by two steps due to these advances.

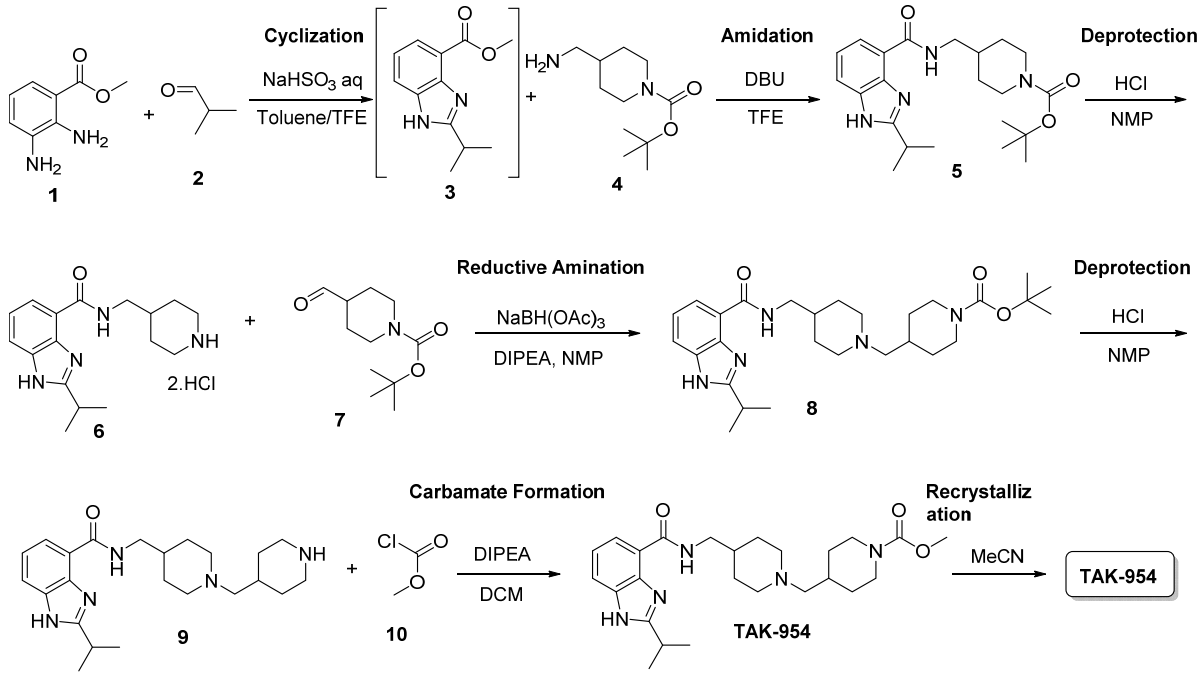
Abstract: Given the environmental challenges and consequences of using organic solvents, we set out to demonstrate the feasibility of implementing reactions that make use of aqueous media in Takeda's portfolio using the TAK-954 process as a test case. We redeveloped the six-step TAK-954 manufacturing sequence to be run almost entirely in water, replacing five separate organic solvents used in the enabling route, while implementing five direct isolations from aqueous media. Key transformations carried out in aqueous media include a benzimidazole cyclization, amidation, reductive amination, and a selective oxidation of an aliphatic alcohol. Importantly, the reductive amination and aliphatic alcohol oxidation had not been previously described in the literature using this new surfactant technology, thus new methodologies were invented specifically for this application (although expected to be broadly applicable to related transformations). This work culminated in a four step (longest linear) approach to an investigational 5-HT_4 receptor agonist which has been demonstrated at full commercial scale. In addition to shortening the synthetic route by two steps and removing the vast majority of organic solvents from the process, the overall PMI was dramatically reduced from 350 to only 111. By shifting the reaction and isolation media from organic solvents to water, the portion of the PMI attributable to solvents was reduced from 223 to 19. Perhaps more surprisingly, the portion of the PMI attributable to water was also reduced from 106 to 76.

DETAILED DESCRIPTION OF NOMINATED GREEN TECHNOLOGY:

(1) Problem. Organic solvents are estimated to make up 60% of all waste generated during API manufacturing, accounting for some 9 billion kg of waste per year industry-wide. Disposing of this waste is costly, but, perhaps more concerning, many widely-used solvents are hazardous to workers and the environment and are derived from non-renewable petroleum. As a result, organic solvents have come under increasing regulatory scrutiny in recent years. Amid growing concerns over the use of organic solvents in chemical manufacturing, water has emerged as a promising alternative reaction medium. A growing body of research has demonstrated that a wide variety of organic reactions can be successfully adapted to aqueous reaction media using micelle-forming surfactants, often providing superior outcomes over conventional solvents. While application of this technology

across the pharmaceutical industry has been extremely limited to this point, even more problematic is the challenge of isolating products directly from aqueous media via crystallization in order to obtain the very high product purities required for pharmaceutical use. To our knowledge, no examples of a complete total synthesis of a pharmaceutical from exclusively aqueous media, including isolations, has yet been reported prior to this work. **Scheme 1** outlines our original synthetic process used to deliver **TAK-954** for clinical studies up to Phase 2. This chemistry was already highly developed and running at full commercial scale in what was expected to be very close to the final commercial process. However, this synthetic process suffers from a number of disadvantages. Five different organic solvents are used in the process, the majority of which are categorized as problematic or hazardous according to the Chem21 solvent selection guide. Additionally, two non-productive steps were devoted to converting t-butyl carbamate **8** to methyl carbamate **TAK-954**. This inefficient protection/deprotection strategy was originally implemented to avoid using the corresponding methyl carbamate piperidine aldehyde (not shown), which was assessed to make an unacceptable registrational starting material due to poor material properties and difficulty of isolation. The overall synthetic yield for this route was an acceptable 35% with a relatively poor overall PMI of 350.

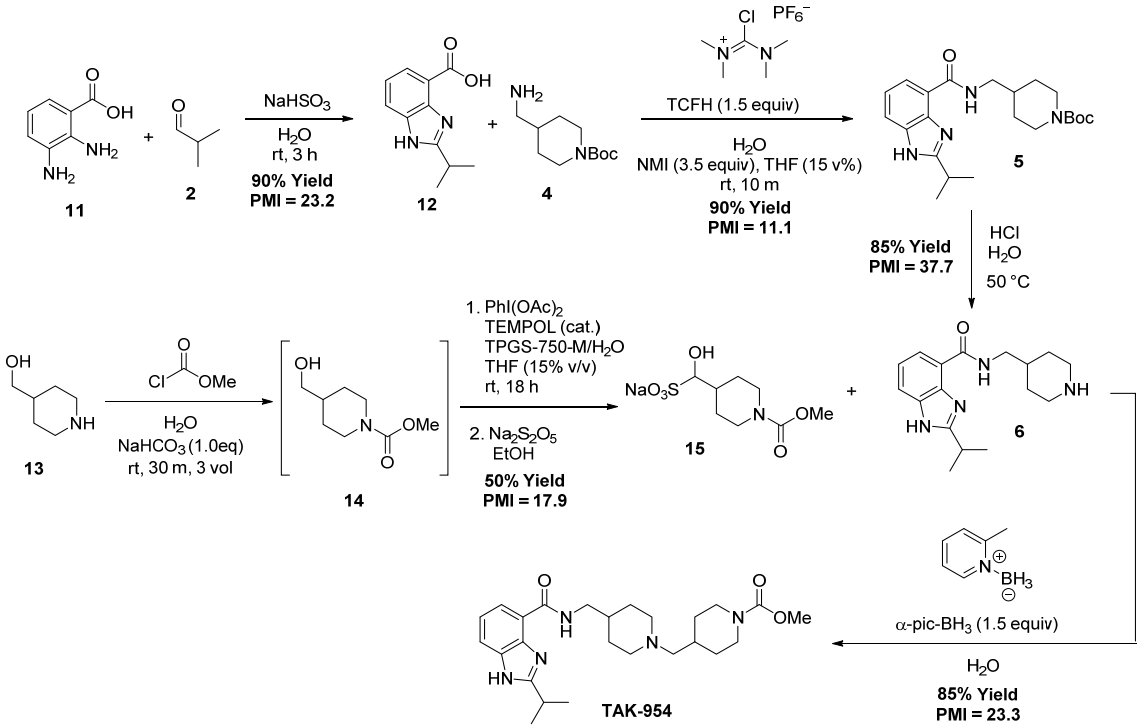
Scheme 1



(2) Chemistry. We originally conceived of this project as a test case to familiarize ourselves with existing aqueous surfactant chemistry, but it eventually blossomed into a highly successful second-generation manufacturing process suitable for commercial supplies where each chemistry step and subsequent isolation is preformed nearly exclusively under aqueous conditions, occasionally with the use of a modest amount of organic cosolvent to maintain a flowable slurry or emulsion. Scheme 2 details the final route to **TAK-954**. The benzimidazole condensation proceeds smoothly by adding the preformed bisulfite adduct of isobutyraldehyde **2** to a basic solution of diaminocarboxylic acid **11**. Upon neutralization with HCl, benzimidazole **12** is crystallized and isolated in 90% yield. A highly efficient amide coupling reaction makes use of a solution to slurry transformation to enable isolation from aqueous conditions. The two coupling partners, **12** and **4,** and the NMI base are suspended in water with a modest amount of THF cosolvent to ensure a controlled crystallization of amide **5** over the course of the reaction. The TCFH coupling reagent is added portion-wise and amide product **5** is simply filtered at the end of the reaction in 90% yield. We believe that this is the first time that TCFH has been shown to be an effective peptide coupling reagent in aqueous media, thus enhancing the arsenal of reagents available for use in aqueous chemistry. Subsequent Boc deprotection proceeds as a solution in aqueous HCl, and free amine **6** is crystallized by pH adjustment with NaOH in 85% yield. We envisioned that formation and use of bisulfite

adduct **15** would further streamline the synthetic route while providing a registrational starting material with suitable attributes (well-defined, crystalline solid). Thus, a one-pot two-step approach was developed to prepare bisulfite adduct **15** all under aqueous conditions. Carbamate formation proceeds smoothly in basic aqueous media modified by 2wt% TPGS-750-M surfactant. While oxidation of primary alcohol **14** to the aldehyde was initially very challenging, with other aqueous oxidation conditions failing to cleanly convert alcohol **14** to a single product, novel aqueous conditions making use of $PhI(OAc)_2$ with catalytic TEMPOL were highly effective for this transformation. After polish filtration to remove insoluble byproducts, $Na_2S_2O_5$ was added to form bisulfite adduct **15** which was crystallized by the addition of ethanol in 50% yield. The introduction of ethanol represents the largest usage of organic solvent in this entire synthesis but is required due to the very high solubility of the bisulfite adduct in water. However, ethanol is perhaps the greenest organic solvent available, and this proved to be a reasonable concession in order to have a crystalline and well-defined registrational starting material. While there are existing methodologies to convert activated alcohols to aldehydes in surfactant-enabled aqueous media, none have yet been reported to be efficient for un-activated aliphatic alcohols. We expect that this new methodology will be of keen interest to the synthetic organic community once its scope and limitations are evaluated (ongoing). With two coupling components in hand, we set out to develop a reductive-amination in surfactant-enabled aqueous media, which, by the time of our work, had not yet been described in the literature. We discovered that α-picoline-BH_3 was a suitable reductant to affect a reductive amination directly between free amine **6** and bisulfite adduct **15**, provided a small amount of MeOH cosolvent was used to maintain a stable emulsion throughout the reaction. Upon reaction completion, the resulting aqueous product mixture was added to a seed bed of **TAK-954** in aqueous sodium hydroxide solution resulting in crystalline **TAK-954** obtained as a hydrate in 85% yield. in >99.8 HPLC area percent purity. We expect that this new reductive amination methodology will be of high interest to the synthetic chemistry community, and especially the process chemistry community, given how frequently this transformation is used in pharmaceutical manufacturing processes. The pharmaceutically desired form is an anhydrate. While not exhaustively studied, competitive slurry experiments suggested that obtaining the anhydrous form of **TAK-954** from aqueous media was extremely unlikely. Therefore, a form conversion via recrystallization from acetonitrile was required. The final aqueous route to **TAK-954** proceeds in only 4 linear steps (6 total) in 59% overall yield, >99.8 HPLC area percent purity and with a PMI of 111, a very significant improvement from the previous approach.

Scheme 2



(3) Potential or realized benefits. While the yield, PMI and efficiency improvements are quite stark while moving from the initial route to the aqueous chemistry, the global demand for **TAK-954** is expected to be modest with an expected commercial batch size of only 100g. While the linear route has indeed been successfully run at this scale, and we anticipate no exceptional hurdles in scaling it up further, we believe the proof of concept to be a much more significant advance and benefit to society compared to the environmental consequences for this particular medicine. We believe that this work represents the very first complete application of aqueous surfactant chemistry to an entire manufacturing process of a complex pharmaceutical, especially encompassing multiple controlled crystallizations and isolations, all from aqueous media. In addition, we also developed two novel transformations to occur in surfactant-modified aqueous media that we expect to be highly useful to the organic chemistry community. We expect this work to inspire others in Pharma to follow suit and replace organic solvents with aqueous media in an increasing number of chemical transformations, or even entire sequences. This will certainly be the case at Takeda. Dan Bailey is being nominated for this award as he was the main driver of this project. His interest in surfactant chemistry prompted him to evaluate this chemistry for the TAK-954 project, which he executed with only the help of two university co-op students with minimal organic chemistry experience. At the time of submission, this work has been presented at the 2019 NESACS process chemistry symposium and we plan to present at the 2020 Spring ACS meeting, the 2020 GC&E conference, and the 2020 Pacifichem conference. We expect a manuscript to be submitted to Green Chemistry by the end of March 2020.