Green Chemistry

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/d0gc03316b

Beyond organic solvents: synthesis of a 5-HT$_4$ receptor agonist in water†

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Received 1st October 2020,
Accepted 3rd November 2020

DOI: 10.1039/d0gc03316b

rsc.li/greenchem

Reducing or eliminating organic solvent use in pharmaceutical manufacturing is perhaps the most effective way to reduce the environmental, health, and safety impacts of drug substance manufacturing. With this in mind, we have developed a process to manufacture an investigational 5-HT$_4$ receptor agonist that is conducted almost entirely in water, including multiple controlled isolations. Key transformations carried out in aqueous media include a benzimidazole cyclization, amide bond formation, reductive amination, and a selective oxidation of an aliphatic alcohol. Compared to the first-generation manufacturing process using organic solvents, the aqueous process described here uses 77% less material inputs, 94% less organic solvent, and, surprisingly, 48% less water, while improving overall yield from 35% to 56%.

Imagining a future without organic solvents

Since the first mass-produced drugs were introduced more than 130 years ago, organic solvents have played a key role in pharmaceutical manufacturing. Large quantities of solvent are used at every stage of a typical drug manufacturing process to solubilize organic reaction components, separate and purify chemical mixtures, and isolate products. By one estimate, organic solvents make up 56% by mass of the material inputs used to manufacture active pharmaceutical ingredients (API).[1] Despite a long history of solvent use, the pharmaceutical industry has only recently begun to reckon with the full costs of its dependence on organic solvents, costs that include a substantial environmental burden and serious risks to the health and safety of workers. A full accounting of these costs has prompted some in the pharmaceutical industry to begin working toward a future where life-changing medicines are manufactured without the use of organic solvents.

A variety of new technologies and approaches will be needed to achieve this goal, but one of the most promising existing strategies for removing organic solvents from drug manufacturing processes involves using water as an alternative reaction medium. Water is non-toxic and non-flammable, making it inherently safer than many organic solvents. Moreover, a qualitative analysis suggests that water has significantly lower life cycle impacts than organic solvents.[2] A growing body of research has demonstrated that a wide variety of organic reactions can be successfully adapted to aqueous media using micelle-forming surfactants or "on-water" methodology.[3] Researchers at Novartis have expanded on this work, demonstrating that aqueous micellar media can serve as the reaction medium for a variety of transformations during pharmaceutical manufacturing on multi-kg scales, often providing superior outcomes over conventional solvents.[4] A key innovation enabling scale-up of reactions in aqueous micellar media involves using small amounts of an organic co-solvent.[5]

Although there has been progress in adapting organic chemistry to aqueous reaction conditions, replacing organic solvents with water during workup, purification, and isolation of reaction products has received comparatively little attention. On average, reactions make up just 25% of the unit operations used in API manufacturing, while the remaining 75% of unit operations consist of extractions, crystallizations, filtrations, and other operations related to product purification and isolation.[1] It is unsurprising then that an informal survey of Takeda's API manufacturing processes indicates that the majority of organic solvent used during manufacturing is devoted to purification and product isolation. Therefore, in order to realize the full environmental and safety benefits of conducting chemistry in water, there is an urgent need to develop isolations from aqueous media that further reduce our reliance on organic solvents while providing the physical properties and high product purities required for pharmaceutical use. With this in mind, we set out to re-develop one of Takeda's API manufacturing processes with the goal of running the entire process, including isolations, in water.

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/d0gc03316b

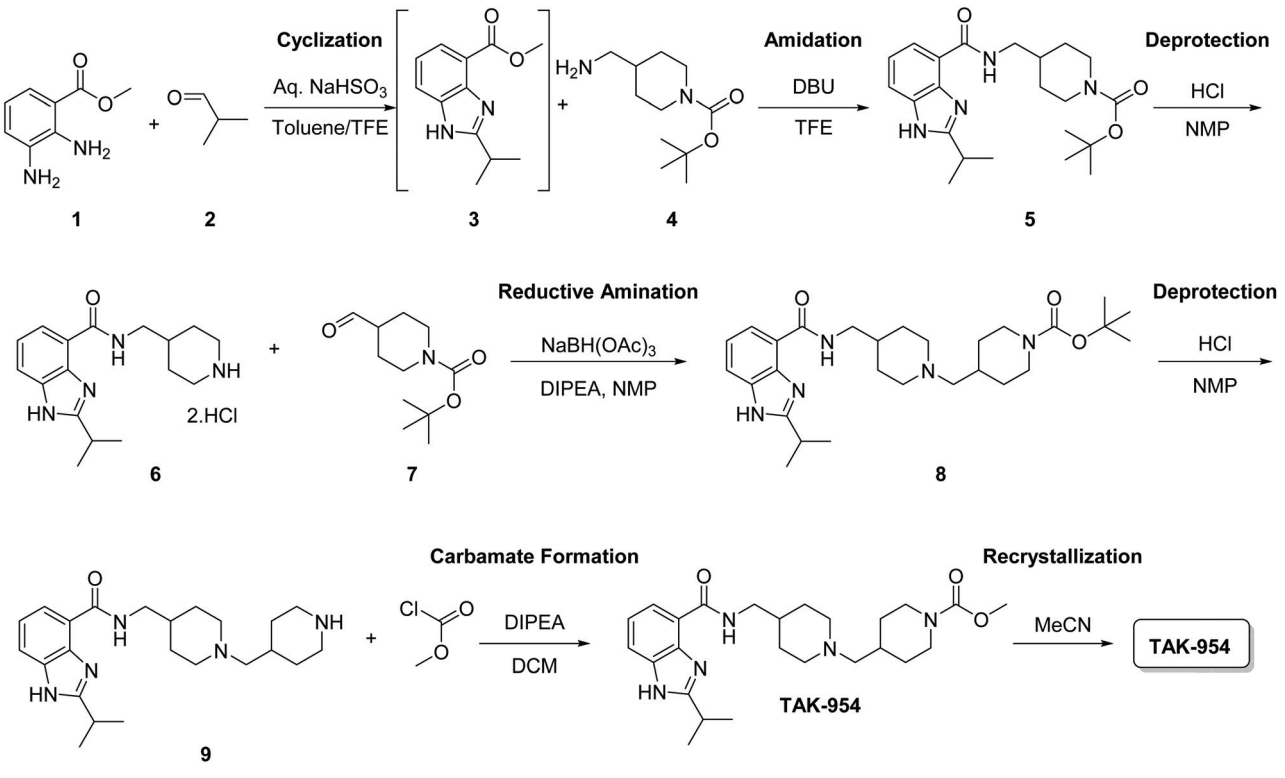
Results and discussion

TAK-954, the target API, is a 5-HT_4 receptor agonist currently under investigation by Takeda for the treatment of post-operative gastrointestinal dysfunction. The first-generation manufacturing route used to supply clinical material through Phase 2 is shown in Scheme 1. The synthetic sequence begins with condensation of the preformed bisulfite adduct of aldehyde **2** with diamine **1** to give benzimidazole **3**,[6] which is then directly coupled with amine **4** in the presence of DBU to form amide **5**. Boc-deprotection of **5** yields amine **6**, which is isolated as a bis-HCl salt. Piperidine **7** is then installed *via* reductive amination followed by a second Boc-deprotection to give amine **9**. Finally, methyl chloroformate is used to form the methyl carbamate moiety of **TAK-954**. A cooling recrystallization from acetonitrile controls the crystal form and purity of **TAK-954**.

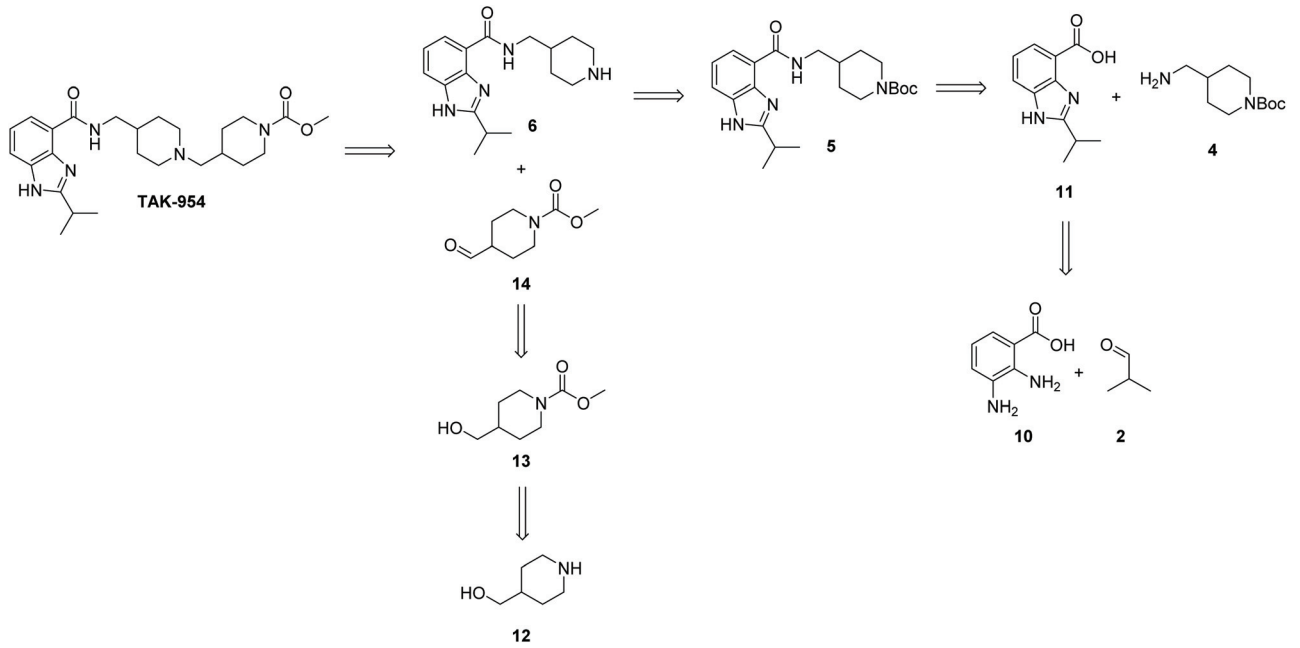
This manufacturing sequence was executed multiple times on production scale without issue, providing high-purity API for clinical studies. The overall yield is an acceptable 35%. On the other hand, the overall process mass intensity (PMI), at 350, is quite high given the modest complexity of the target molecule. An obvious synthetic inefficiency at the center of the sequence contributes to the poor PMI: two non-productive steps are devoted to converting t-butyl carbamate **8** to methyl carbamate **TAK-954**. This inefficient protection/deprotection strategy was originally implemented to avoid using the methyl carbamate analogue of **7**, which was assessed to make an unacceptable registrational starting material[15] due to poor material properties and difficulty of isolation. In addition to problems with process efficiency, five separate organic solvents are used in the manufacturing sequence, most of which are categorized as hazardous or problematic in the CHEM21 Solvent Guide.[7]

In thinking about how to adapt this sequence to aqueous conditions, we envisioned several changes to the synthetic route, which are summarized in the retrosynthetic analysis in Scheme 2. These changes were intended to both improve the route's overall efficiency and to ensure that the chemistry used in the route is amenable to aqueous conditions. The most significant change involved installing the second piperidine ring with the desired methyl carbamate already in place, providing direct access to **TAK-954** and removing two steps from the overall route. Because aldehyde **14** is not readily available, we planned to prepare it through carbamoylation and oxidation of hydroxymethylpiperidine **12**. We then hoped to derivatize aldehyde **14** in order to obtain a crystalline solid form suitable for use as a registrational starting material. The bond disconnections in the earlier steps would remain unchanged. However, preliminary experiments indicated that direct amidation of methyl ester **3** with amine **4** is not feasible in aqueous media due to competitive ester hydrolysis. Instead, we decided to pursue a more conventional amide coupling of carboxylic acid **11** and amine **4** mediated by an activating agent. The corresponding diamine starting material was therefore changed from methyl ester **1** to carboxylic acid **10**.

Initially, the first step, benzimidazole cyclization, was run as a slurry-to-slurry process due to the poor solubility of



Scheme 1 First-generation **TAK-954** manufacturing sequence.



Scheme 2 Retrosynthetic analysis of **TAK-954** showing proposed second-generation process in water.

diamine starting material **10** and benzimidazole product **11** in water at neutral pH. However, these conditions led to the formation of two regioisomeric impurities at levels as high as 20 HPLC area %. The two impurities were identified as **15a** and **15b** (Fig. 1), resulting from bis addition of aldehyde **2** to diamine **10** followed by cyclization and a 1,3-hydride shift. Two factors were found to contribute to the formation of **15a** and **15b**: (1) free aldehyde **2** reacts with diamine **10** to exclusively give the two bis addition impurities, and (2) the presence of an excess of the bisulfite adduct of **2** favors formation of the bis addition impurities. In order to suppress the formation of **15a** and **15b**, we addressed each of these factors separately. First, we optimized the amount of sodium bisulfite used to preform the bisulfite adduct of **2** to ensure that diamine **10** was not exposed to any residual free aldehyde. Since the bisulfite adduct exists in equilibrium with the free aldehyde in aqueous solution, an excess of sodium bisulfite (3 equiv.) was required to push this equilibrium completely toward the bisulfite adduct. Next, we looked at controlling the relative amounts of bisulfite adduct and diamine available to react during the reaction. Under the initial reaction conditions, the bisulfite adduct of **2** is fully dissolved while diamine **10** is poorly soluble, meaning a large excess of bisulfite adduct is available to react with diamine **10** in the solution phase throughout the reaction, precisely the situation we need to avoid in order to suppress the formation of the bis-addition impurities. Attempts to improve the solubility of diamine **10** through the addition of a surfactant (2 wt% TPGS-750-M) failed to impact the formation of the bis-addition impurities. However, the acid functionality of **10** and the aqueous reaction medium provided an opportunity to use pH to control solubility. Addition of sodium hydroxide (2 equiv.) to the reaction mixture led to full dissolution of acid **10**. Finally, we implemented a slow addition of a solution of the bisulfite adduct of **2** to the solution of **10** in aqueous hydroxide in order to maintain an excess of diamine **10** throughout the reaction. These changes, summarized in Fig. 1, resulted in suppression of **15a** and **15b** to undetectable levels. Next, we implemented a direct isolation of benzimidazole **11**, again using pH to control solubility. Slow addition of aqueous HCl to the product mixture over two hours at room temperature led to crystallization of **11**, which was then isolated *via* filtration in 79% yield. The step PMI is 24.5, and no organic solvents or surfactants are used during the reaction or isolation.

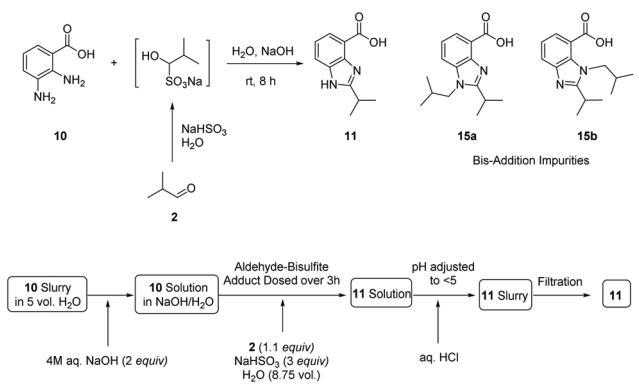
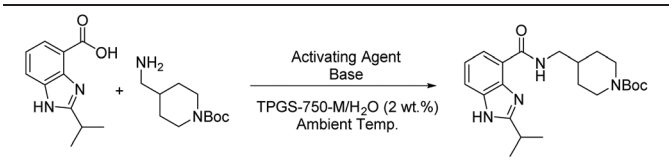


Fig. 1 Benzimidazole cyclization in water (top). Process flow diagram showing optimized conditions (bottom).

The next step, coupling of acid **11** and amine **4** to form amide **5**, requires an activating agent. Published examples of amide bond formation in aqueous media feature a variety of

different activating agents.[8] Without a clear sense of which activating agent was best suited to the formation of amide **5**, we screened several different classes of activating agents, including those that form acid chlorides, mixed anhydrides, activated esters, and other activated species (Table 1). Ultimately, conditions employing TCFH and NMI (Table 1, entry 9) proved to be most effective, giving nearly complete conversion to amide **5** with faster reaction kinetics than the next most effective activating agent, DMTMM, while also offering superior atom economy and lower cost. TCFH/NMI conditions were developed by chemists at Bristol-Meyers Squibb, who originally identified acetonitrile as the optimal solvent for this transformation.[9] However, we found that formation of amide **5** using the published TCFH/NMI conditions proceeds cleanly and rapidly in water, provided that TCFH is added to the reaction mixture last. We believe this is the first example of a TCFH/NMI mediated amide bond formation under aqueous conditions. Both TCFH itself and the activated acyl imidazolium intermediate would appear to be prone to hydrolysis in an aqueous environment, but in the presence of amine **4** the desired reaction pathway is evidently favored over hydrolysis. The reaction is extremely fast at ambient temperature, typically reaching >95% conversion within ten minutes of TCFH addition. The starting materials, acid **11** and amine **4**, are fully soluble in the reaction mixture after addition of NMI. The amide product, however, is poorly soluble under the reaction conditions and precipitates as it forms. Because the reaction kinetics are so fast, this reactive precipitation process was rapid and uncontrolled and initially resulted in product gumming and oiling, making isolation *via* filtration impossible. Rather than introducing an immiscible organic solvent to extract the oiled-out product, we focused our efforts on developing a controlled reactive crystallization to allow for direct isolation of the product. TCFH was initially added in a single portion, but in order to reduce the degree of product supersaturation over the course of the reaction we instead implemented addition of TCFH in three equal portions, waiting 15 minutes between each addition. Next, we introduced a small amount of THF co-solvent (15 vol%) to the reaction mixture in order to modestly improve the product solubility, again with the goal of reducing the degree of product supersaturation. Finally, experiments with and without surfactant (2 wt% TPGS-750 M) revealed that the presence of surfactant had no impact on the reaction profile, but inhibited the reactive crystallization, exacerbating product gumming. Surfactant was therefore removed from the reaction mixture. With these changes, amide **5** was isolated in 91% yield as a crystalline solid by direct filtration once the reaction was complete. As an added benefit to conducting the isolation in aqueous media, water-soluble reaction by-products, including tetramethyl urea and NMI salts, along with any residual starting materials, **11** and **4**, are rejected during filtration. The step PMI is 9.2. No surfactants and a minimal amount of organic solvent are used during the reaction and isolation.

Table 1 Activating agent screen for amide coupling of intermediates **11** and **4**[a]



11 **4** **5**

Entry	Activating agent	Base	Conversion to **5**[b] (%)
1[c]	Thionyl chloride	K_2CO_3	59
2	Isobutyl chloroformate	NMM	30
3	Cyanuric chloride	NMM	19
4	EDCI/HOBt	NMM	34
5	TNTU	DIPEA	16
6	EEDQ	None	22
7	COMU	2,6-Lutidine	47
8	DMTMM	NMM	97
9	TCFH	NMI	>98

EDCI: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide; HOBt: 1-Hydroxybenzotriazole; TNTU: *O*-(5-Norbornene-2,3-dicarboximido)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate; EEDQ: *N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline; COMU: (1-Cyano-2-ethoxy-2-oxoethylidenaminooxy) dimethylamino-morpholino-carbenium hexafluorophosphate; DMTMM: 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride; TCFH: Chloro-*N*,*N*,*N*′,*N*′-tetramethylformamidinium hexafluorophosphate; NMM: 4-methylmorpholine; NMI: 1-Methylimidazole. [a] Reaction conditions: 1.2 mmol **11**, 1.2 mmol **4**, 2.5 mL TPGS-750-M (2 wt% in H_2O). [b] HPLC area %. [c] The acid chloride of **11** was pre-formed in neat thionyl chloride before addition to an aqueous solution of **4** and K_2CO_3.

Next, the Boc protecting group was removed from piperidine **5**.[10] Use of 3 equiv. of aqueous HCl led to complete deprotection of **5** within 1 hour at 50 °C. 4 Volume % of acetonitrile co-solvent was included to avoid product oiling during isolation. Both starting material **5** and product **6** are fully soluble under the acidic reaction conditions. Once the deprotection is complete, addition of aqueous sodium hydroxide leads to crystallization of piperidine **6**, which is directly isolated *via* filtration in 88% yield. The step PMI is 24.0, and no surfactant and a minimal amount of organic solvent is used.

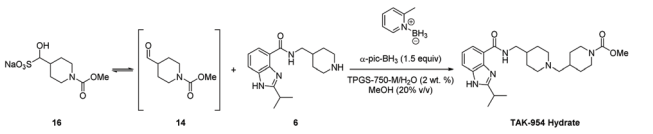
With the first three steps of the synthesis complete, we turned our attention to preparing aldehyde **14**, which is required for formation of **TAK-954** *via* reductive amination with piperidine **6**. Because methyl carbamate **13** and aldehyde **14** are both water-soluble oils, we envisioned a telescoped reaction sequence where hydroxymethylpiperidine **12** is carbamoylated at the piperidine nitrogen followed by oxidation of the primary alcohol to an aldehyde, all without intermediate isolation. Finally, we hoped that conversion of aldehyde **14** to its corresponding bisulfite adduct would allow for isolation of the product as a crystalline solid, which could serve as a stable, well-defined registrational starting material. Carbamoylation of **12** proceeded smoothly and rapidly in water using potassium carbonate as base and methyl chloroformate as the carbamoylating reagent at ambient temperature. Surfactant and organic co-solvent were tolerated but were not required due to the high aqueous solubility of the reaction components and products. The next step, oxidation of primary, aliphatic alcohol **13** to aldehyde **14** proved more challenging. TEMPO/bleach

conditions led to a product mixture consisting of the desired aldehyde, overoxidized carboxylic acid, and unreacted alcohol in a roughly 1 : 1 : 1 ratio. Notably, we obtained similarly poor selectivity when using anhydrous dichloromethane as solvent for this transformation, suggesting that the poor selectivity is related to the substrate and oxidation conditions rather than to the aqueous reaction medium. Given the poor selectivity of the TEMPO/bleach conditions, we screened a variety of other oxidation conditions, including several metal-catalyzed aerobic oxidation conditions, which, unfortunately, showed little to no reactivity.‡ Ultimately, the conditions that gave the best conversion and selectivity involved catalytic TEMPOL with diacetoxyiodobenzene as terminal oxidant, which cleanly converted alcohol **13** to aldehyde **14** with no overoxidation, even after prolonged reaction times. Because diacetoxyiodobenzene is poorly water soluble, 2 wt% TPGS-750 M and THF co-solvent were needed for the oxidation to proceed. Once the oxidation was complete, addition of sodium metabisulfite to the reaction mixture led to formation of bisulfite adduct **16**. However, due to its high solubility in water, an organic antisolvent was required to crystallize and isolate bisulfite adduct **16**. Ethanol was selected for this purpose both for its suitability as an antisolvent and for its environmental and safety profile. Addition of ethanol led to crystallization of bisulfite adduct **16**, which was isolated *via* filtration. Because they share similar solubility profiles, several reaction by-products, presumably including acetate salts, residual sodium bisulfite, and residual potassium carbonate, tend to precipitate along with the bisulfite adduct product. As a result, the bisulfite adduct is isolated in 70–80% assay potency. The impurities making up the remaining 20–30% of the assay value, however, are well tolerated in the next step. The three-step telescoped sequence delivers the bisulfite adduct in 38% assay corrected yield with a PMI of 27.1.

The final step of the manufacturing sequence involves the reductive amination of piperidine **6** with bisulfite adduct **16** to produce **TAK-954**. In thinking about how to approach this transformation, we foresaw two challenges. First, reductive amination requires the loss of an equivalent of water during imine formation, presenting a potential thermodynamic barrier to reaction progress in an aqueous environment.§ And second, we needed to devise a protocol that would allow for use of the bisulfite adduct in the reductive amination, presumably by regenerating the parent aldehyde.¶ In order to investigate the direct use of bisulfite adduct **16** in the reductive amination, we initially chose to separate the regeneration of parent aldehyde **14** from the reductive amination itself (Table 2, entry 1). Exposure of bisulfite adduct **16** to aqueous sodium hydroxide led to full conversion to the parent aldehyde, which was then used as a solution without further manipulation in the subsequent reductive amination. Micellar media (2 wt% TPGS-750 M in water) and an organic cosolvent (20 vol% methanol) were used in the reductive amination both to provide a lipophilic environment within the micelles where imine formation would be favorable and to overcome the poor aqueous solubility of piperidine **6** and **TAK-954** at neutral to basic pH. α-Picoline-borane was selected as reducing agent for its aqueous stability. Under these conditions, piperidine **6** and a solution of aldehyde **14** in aqueous hydroxide reacted cleanly to form **TAK-954**. No reduction of aldehyde **14** was observed. Next, we attempted to combine regeneration of the parent aldehyde with the reductive amination (Table 2, entry 2). Adding exogenous base (sodium acetate) to the reaction mixture allowed for the direct use of bisulfite adduct **16**, giving a reaction profile that was comparable to experiments where the parent aldehyde was regenerated separately. However, while optimizing the amount of exogenous base, we found that the base could be omitted entirely without affecting the progress or purity of the reductive amination (Table 2, entry 3). This result suggests that in an aqueous environment, the bisulfite adduct exists in equilibrium with the parent aldehyde, allowing the reductive amination to proceed without the need to fully regenerate the parent aldehyde before the start of the reaction. This discovery made for an operationally simple reaction protocol where the bisulfite adduct is used directly as an aldehyde surrogate: after all reaction components are combined, the mixture is warmed to 50 °C and reaches full conversion to **TAK-954** within 8 hours.

The pH-dependent solubility of **TAK-954** in water provided an opportunity to design a controlled crystallization directly from the reductive amination product mixture. However, upon addition of sodium hydroxide, **TAK-954** oiled out of solution. Although the product oil droplets eventually crystallized, a

Table 2 Optimization of aldehyde regeneration protocol[a]



Entry	Method of aldehyde regeneration	Base	Conversion to **TAK-954**[b] (%)
1	Full regeneration prior to addition of other reaction components	NaOH (3 equiv.)	>99%
2	*In situ* regeneration in the presence of other reaction components	NaOAc (2 equiv.)	>99%
3	*In situ* regeneration in the presence of other reaction components	None	>99%

[a] Reaction conditions: 0.17 mmol **6**, 0.25 mmol bisulfite adduct of **14**, 0.25 mmol α-picoline-borane, base as noted, 0.5 mL TPGS-750-M (2 wt% in H_2O), 0.1 mL MeOH, 60 °C, 8 h. [b] HPLC area %.

‡ See ESI† for details of alternative oxidation conditions that were screened.

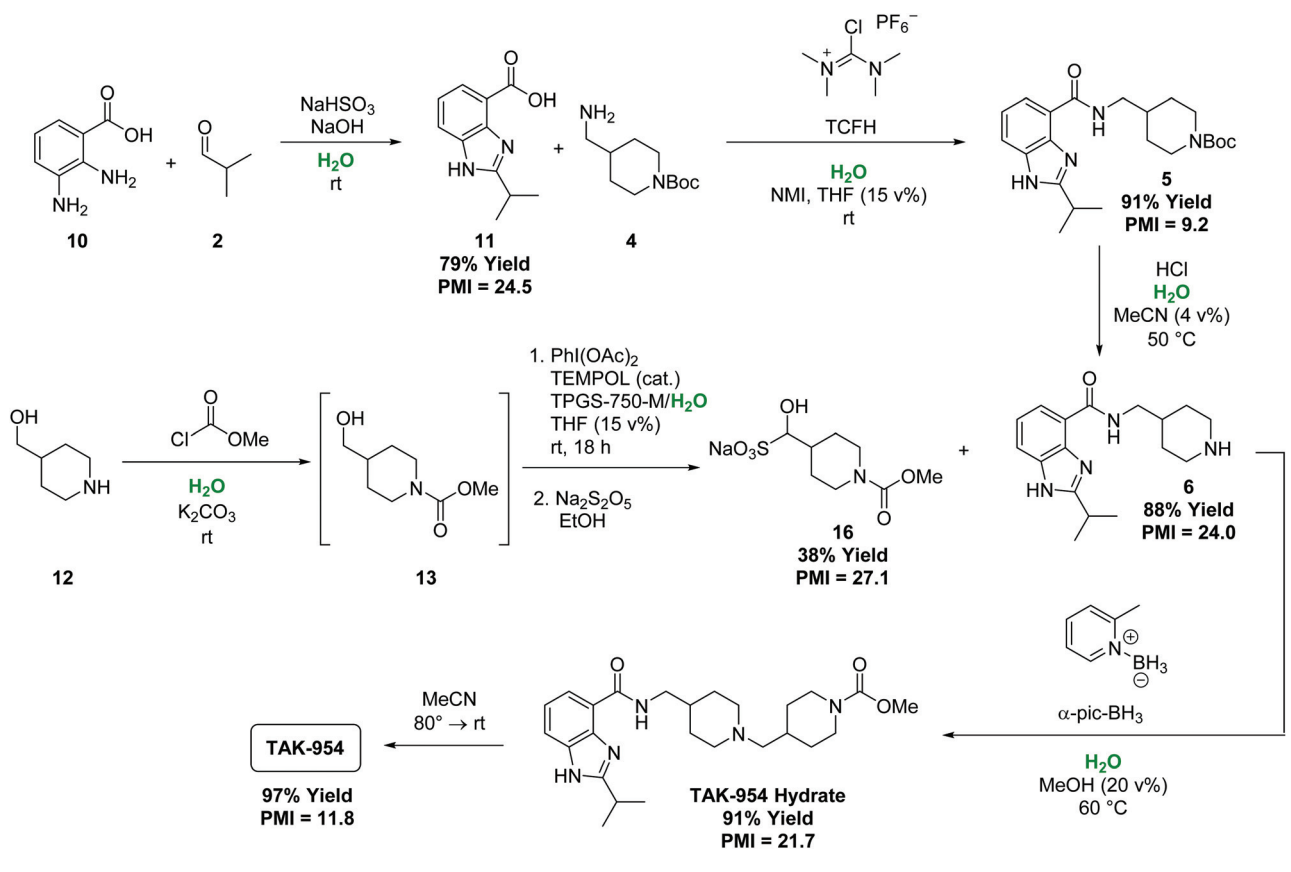
§ Literature examples of reductive aminations in aqueous media were limited but encouraging. Alinezhad and coworkers reported several high-yielding reductive aminations in aqueous micellar media using sodium borohydride as reducing agent and CTAB as surfactant,[11] while Kikugawa and coworkers reported "on water" reductive aminations of poorly soluble substrates using α-picoline-borane as reducing agent.[12]

¶ Researchers at Amgen have developed reductive amination conditions in methanol that allow for the direct use of bisulfite adducts by introducing exogenous base to regenerate the parent aldehyde *in situ*.[13]

crystallization that proceeds through an oil phase risks entraining impurities and does not allow for control of the physical properties of the crystalline solid. Initial attempts to mitigate product oiling by seeding the product mixture and slowing the rate of hydroxide addition failed. Instead, we implemented a reverse addition crystallization where the product mixture is slowly added to a **TAK-954** seed bed in aqueous hydroxide, leading to direct crystallization of **TAK-954** as a hydrate and avoiding product oiling. Reductive amination followed by direct isolation provides the **TAK-954** hydrate in 91% yield with a step PMI of 21.7. However, the pharmaceutically desired crystal form of **TAK-954** is an anhydrate. Earlier form screening and competitive slurry experiments indicated that it is not possible to isolate the anhydrate form from aqueous media. Therefore, a non-aqueous recrystallization was required to convert the **TAK-954** hydrate to the desired anhydrate form. The acetonitrile cooling crystallization developed for the first-generation route was used for this purpose, delivering the anhydrate in 97% yield. This recrystallization represents the only operation carried out in non-aqueous media in the entire manufacturing sequence and was unavoidable given crystal form requirements.

Analysis of process improvements

The re-developed **TAK-954** manufacturing process is shown in Scheme 3. Water is commonly assumed to be an impractical solvent for organic chemistry due to the poor aqueous solubility of many organic compounds, but the first three steps of the **TAK-954** sequence challenge this assumption. Each of these steps is conducted entirely in water, and, aside from a small amount of organic co-solvent in steps 2 and 3, no surfactants or other solubilizing additives are used, yet all three reactions occur in the solution phase. Surfactant is used in subsequent steps in order to overcome the limited aqueous solubility of certain reaction components, and, in the case of the reductive amination, to overcome the thermodynamic limitations of imine formation in an aqueous environment. Throughout the manufacturing sequence, pH adjustments are used to manipulate the solubility of intermediates and the API in aqueous media, allowing reactions to occur in the solution phase while providing a means to purify and isolate products through direct crystallization without the need for organic solvent. As pharmaceutically relevant compounds often contain a high proportion of heteroatoms and one or more acidic or basic centers, manipulating pH to control the aqueous solubility of intermediates and APIs during drug manufacturing may be a generally applicable strategy. In the step 2 amide bond formation, however, we took a different approach to direct product isolation, implementing a reactive crystallization, a strategy that may be applicable in other instances where starting materials are water soluble while the product is not.



Scheme 3 Re-developed **TAK-954** manufacturing sequence in water.

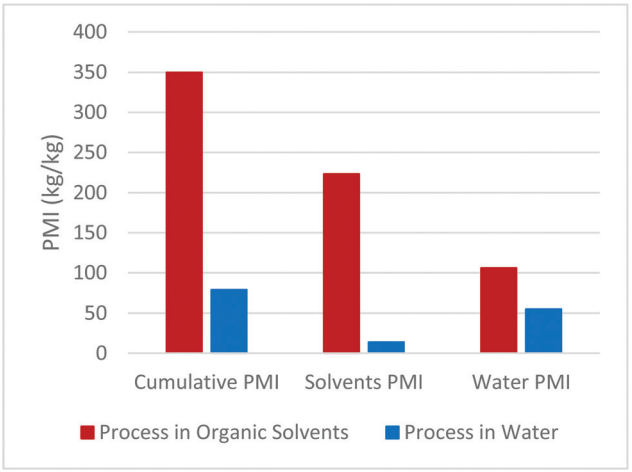


Fig. 2 Comparison of PMI between the first-generation **TAK-954** process in organic solvent and the re-developed, 4-step linear process in water.

The four-step linear sequence to **TAK-954** was successfully demonstrated on 100 g scale, sufficient to satisfy current clinical demand. However, we do not anticipate any barriers in further scaling this process if necessary. Notably, the process can be run using existing reactor trains and equipment found in typical manufacturing plants. In addition to the environmental, health, and safety benefits that come with replacing organic solvents with water, comparison of the aqueous four-step linear sequence to the organic-solvent-mediated first-generation route reveals dramatic improvements in process efficiency.‖ Overall yield was improved from 35% to 56%. Reductions in process mass intensity are illustrated in Fig. 2. Overall process mass intensity was reduced from 350 to 79, representing a 77% reduction in the amount of materials required to manufacture **TAK-954** API. By shifting the reaction and isolation media from organic solvents to water, the portion of the process mass intensity attributable to organic solvents was reduced from 223 to 14, representing a 94% reduction in solvent use. Perhaps more surprisingly, the portion of the process mass intensity attributable to water was reduced from 106 to 55, meaning that the manufacturing process in water uses 48% less water than the organic-solvent-based process. Like many conventional API manufacturing processes employing organic solvents as reaction media, the first-generation **TAK-954** process used large quantities of water during product workups and isolations. By improving the overall efficiency of the synthetic route and implementing direct isolations for each intermediate, we were able to significantly reduce water use, even as we shifted the bulk reaction and isolation medium from organic solvents to water. Due to differences between the two routes, the individual impurities present in the API produced using each route are slightly different, but both routes deliver the API with an acceptable overall purity of approximately 99.8 HPLC area %.

‖ Because the preparation of aldehyde 7 was not included in metrics calculations for the first-generation route, the preparation of the bisulfite adduct of aldehyde **14** was excluded from metrics calculations for the route in water to allow for a direct comparison of the two routes.

Conclusions

While a handful of examples of applications of aqueous reaction media to API synthesis have been published in recent years,[14] we believe this is the first reported example of an API manufacturing process conducted nearly exclusively in aqueous media, including multiple controlled crystallizations and isolations. We view this work as a proof of concept and expect that its benefits will extend beyond improving the sustainability of this particular drug. We hope to apply the techniques and approaches developed here to other API manufacturing processes at Takeda in order to continue to reduce our reliance on organic solvents.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We would like to thank Justin Quon for his advice in developing a crystallization of the crude API. Izumi Takagi contributed analytical support, and we are indebted to Ivan Dai for NMR analysis and interpretation.

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