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Development of Large-Scale Routes to Potent GPR119 Receptor Agonists

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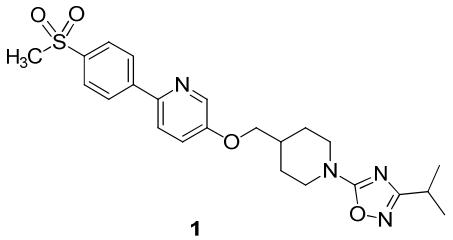
API Chemistry Department, Analytical Science & Development Department, Particle Sciences and Engineering Department, GlaxoSmithKline, 709 Swedeland Road King of Prussia, Pennsylvania 19406, United States

ABSTRACT: Practical and scalable syntheses were developed that were used to prepare multi-kilogram batches of GSK1292263A (**1**) and GSK2041706A (**15**), two potent G protein-coupled receptor 119 (GPR119) agonists. Both syntheses employed relatively cheap and readily available starting materials and both took advantage of an S_NAr synthetic strategy.

INTRODUCTION

GSK1292263A (**1**), a G protein-coupled receptor 119 (GPR119) agonist, has been explored as a treatment for type 2 diabetes (Figure 1).[1] Numerous articles describing GPR119 agonists have been disclosed, and a number of these compounds have been progressed into clinical trials.[2-3] This particular compound was on a rapid timeline for development when the project entered our process chemistry department; this required quick identification of a synthetic route which offered the versatility of being robust and safe for both immediate lab-scale synthesis to produce gram quantities of drug substance and for subsequent rapid scale-up to pilot-plant kilogram quantities.



1

Figure 1. Structure of GSK1292263A (**1**)

Original Process. The initial route of synthesis, employed for the early deliveries of **1**, was convergent and consisted of six steps (see Scheme 1).[4] The overall 43% yield of this route, from 6-bromopyridin-3-ol (**2**), was very good. However, the active pharmaceutical ingredient (API) **1** contained relatively high levels of various hydroperoxide impurities. These hydroperoxide impurities arose partly because the oxidation procedure used to synthesize the methyl aryl sulfone portion of **1** was the last step of the molecule's synthesis, namely the conversion of aryl sulfide **9** with Oxone™ to sulfone **1.** Several API-related hydroperoxide impurities were also found to form during the final stage of the synthesis where a re-crystallization procedure was used to control the polymorphic form of the API.[5] These hydroperoxide impurities showed up, for example, when **1** was re-crystallized in methyl ethyl ketone. Three major API-related hydroperoxide impurities; namely **10**, **11**, and **12**; were identified in some of the clinical batches made from the initial route (see Figure 2). The presence of these hydroperoxide impurities did not at first appear to be a problem. Unfortunately, when two of the three hydroperoxides identified, namely **11** and **12**, were shown to be mutagenic via Ames testing, the presence of these hydroperoxides became a critically important issue in regards to this route of synthesizing API **1**.[6,7]

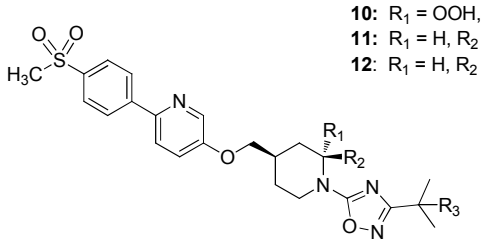
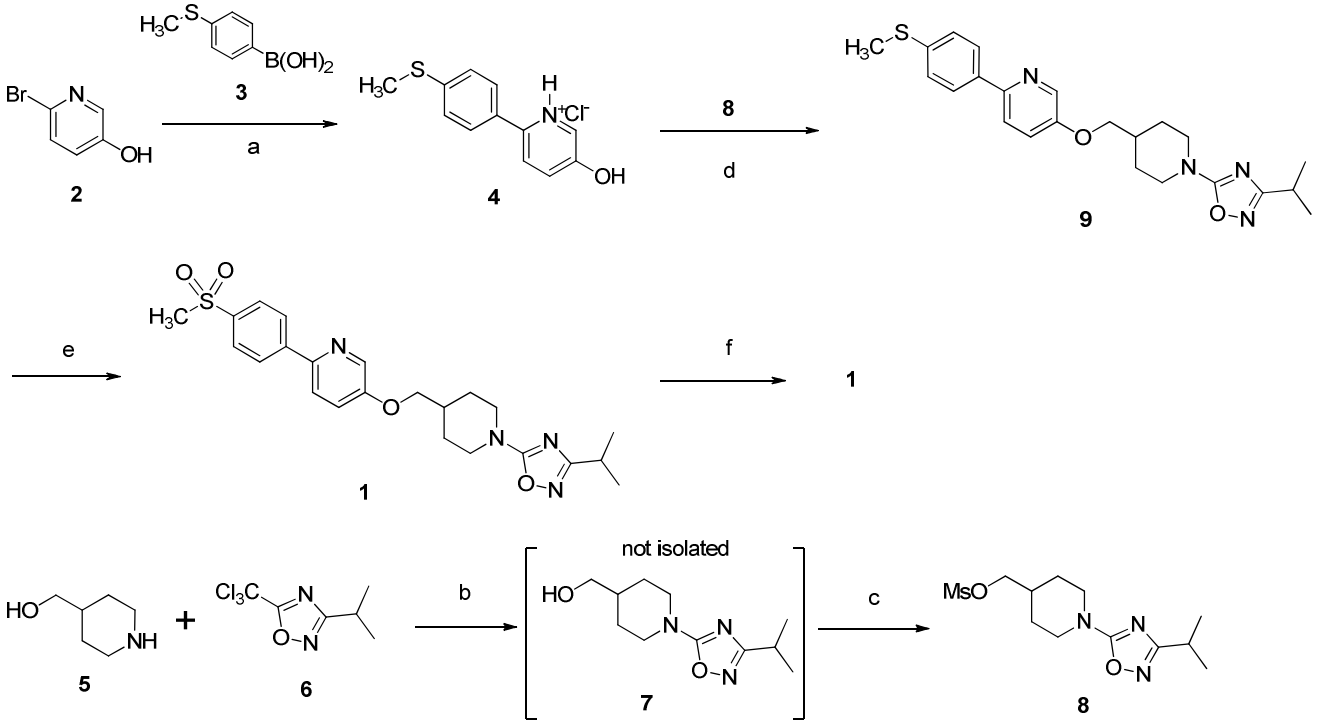


Figure 2. Structure of the three mutagenic hydroperoxide impurities found in the API.

Scheme 1. Initial Route to GSK1292263A (**1**)[a]



[a]Reagents and conditions: a) 5% $Pd(OAc)_2$, 15% PPh_3, K_2CO_3, IPA/water, isolated as the HCl salt in 60-72% yield; b) acetonitrile, 75-85% yield; c) MsCl, Et_3N, DCM; d) K_2CO_3, DMSO, 75-80% yield; e) Oxone™, EtOH-water, H_2SO_4, 95% yield; f) methyl ethyl ketone re-crystallization to correct form (polymorph), 85-90% yield.

RESULTS AND DISCUSSION

At first, methods to remove the hydroperoxides from API **1** synthesized via the initial route were studied in order to find a way to obtain **1** with acceptable hydroperoxide levels. The sum of hydroperoxides 11 and 12 in the API had to be controlled to <5 ppm. These experiments revealed that the hydroperoxides related to **1** react rapidly at room temperature with triphenylphosphine (TPP) to afford triphenyl-phosphine oxide (TPPO) and presumably the corresponding alcohols.[8] For example, treating a THF solution of **1** containing hydroperoxides at a total level of 96 ppm with commercially available styrene-divinylbenzene polymer resin, containing ~3 mmol of covalently bound TPP per gram of resin,[9] for just an hour at room temperature eliminated approximately 98% of the hydroperoxides. Nevertheless, identifying either a modified route of synthesizing **1** without forming any hydroperoxides or a reliable re-crystallization procedure to remove potential hydro-peroxides to safe levels was felt to be a more ideal long term strategy going forward.

Modified Route. The second route of synthesizing **1** reduced the levels of these hydroperoxide impurities by moving the sulfide-to-sulfone transformation one step earlier in the synthetic sequence (see Scheme 2); this strategy provided an additional opportunity to purge the unwanted hydroperoxides via an additional crystallization. Unfortunately, the hydroperoxide issue did not completely disappear as hydroperoxide impurities were still found to form in the final re-crystallization procedure used to control the polymorphic form of the API; especially when the solvent utilized was methyl ethyl ketone (MEK). An extensive solvent screen was undertaken to find an alternative re-crystallization solvent to MEK. A seeded re-crystallization of the API **1** from anhydrous 2-MeTHF afforded the desired polymorph with minimal hydroperoxide formation in comparison to the previous solvent. The presence of the stabilizer butylated hydroxytoluene (BHT) in the anhydrous 2-MeTHF solvent was hypothesized as playing a role in minimizing the hydroperoxide formation. However, this modified route still included the use of potentially genotoxic methanesulfonate **8** which needed to be controlled at low levels in the drug substance. Primarily for this reason, an alternative synthesis was desired.

The second GPR119 agonist molecule. At about this time, our department began working on the GSK2041706A (**15**) API molecule (see Figure 3). This

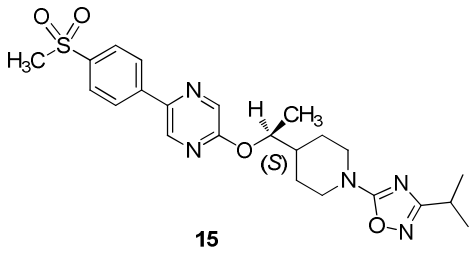
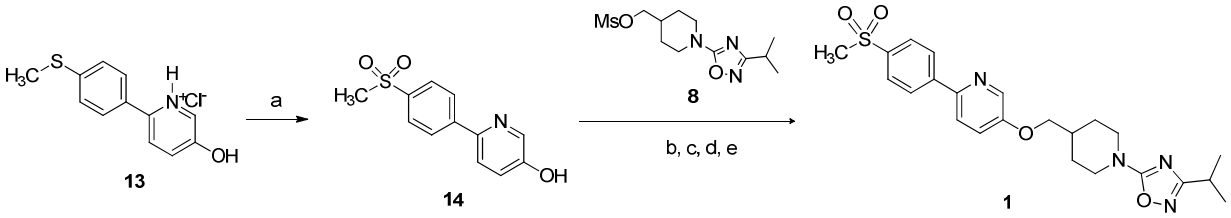


Figure 3. Structure of GSK2041706A (**15**)

Scheme 2. Second Route to GSK1292263A (**1**)[a]



[a]Reagents and conditions: a) 1.2 eq Oxone™, EtOH/water; b) K_2CO_3, DMSO; c) DCM/aq. 5% NaCl solution extraction; d) 2-MeTHF crystallization; e) seeded 2-MeTHF re-crystallization to correct form (polymorph).

molecule represented a second GPR119 agonist candidate with the company. The convergent synthesis of **15**, which our department initially received for scale-up, efficiently employed an asymmetric hydrogenation to synthesize the stereogenic center of (*R*)-1-(pyridin-4-yl)ethanol (**18**) from the corresponding achiral 1-(pyridin-4-yl)ethanone (**16**) (see Scheme 3).[4] The strategy employed in this asymmetric transformation using RuCl(*p*-cymene)[(*R*,*R*)-Ts-DPEN][10] (**24**) had been reported earlier (Figure 4).[11] This initial synthesis of API **15**, however, suffered from a couple of challenges that made further scale-up difficult. These challenges included a low yielding Mitsunobu reaction between **19** and **20** and the generation of a potentially dangerous aryl diazonium salt intermediate during the conversion of pyrazinamine **23** to pyrazinol **20**.

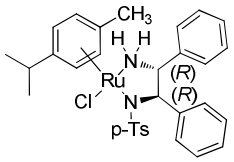


Figure 4. Structure of chiral catalyst **24**

Attempts to synthesize pyrazinol **20** directly from coupling boronic acid **21** and 5-bromopyrazin-2-ol (**25**) were surprisingly disappointing (see Figure 5); even after extensive screening of a variety of reaction conditions, Suzuki-Miyaura conditions to afford this transformation in high yield could not be found. The chemical nature of **25** in regards to oxidative addition must be fairly different from 6-bromo-3-pyridinol (**2**) since the latter was successfully used in an analogous Suzuki-Miyaura reaction in the synthesis of **1**.

Improving the yield of the low-yielding Mitsunobu reaction was challenging primarily because of a concomi tant olefin side-product formation; this olefin was theo rized to be **26** although its precise chemical structure was not conclusively identified (see Figure 5). Under a variety of different Mitsunobu reaction conditions examined, olefin **26** was consistently generated at approximately 16% conversion from the non-isolated alcohol **19**. Olefin **26** was generated in similar quantities even when S_N2 conditions were employed using mesylate **27** in lieu of the

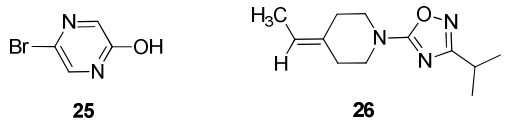


Figure 5. Structure of 5-bromopyrazin-2-ol (**25**) and the unwanted Mistunobu reaction side-product (**26**)

Mitsunobu reaction (see Figure 6). The yield of the Mitsunobu reaction was also low due to the inherent difficulties of isolating **15** away from the triphenylphosphine oxide produced in the reaction.

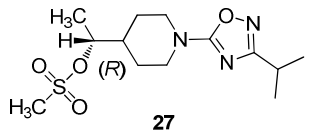
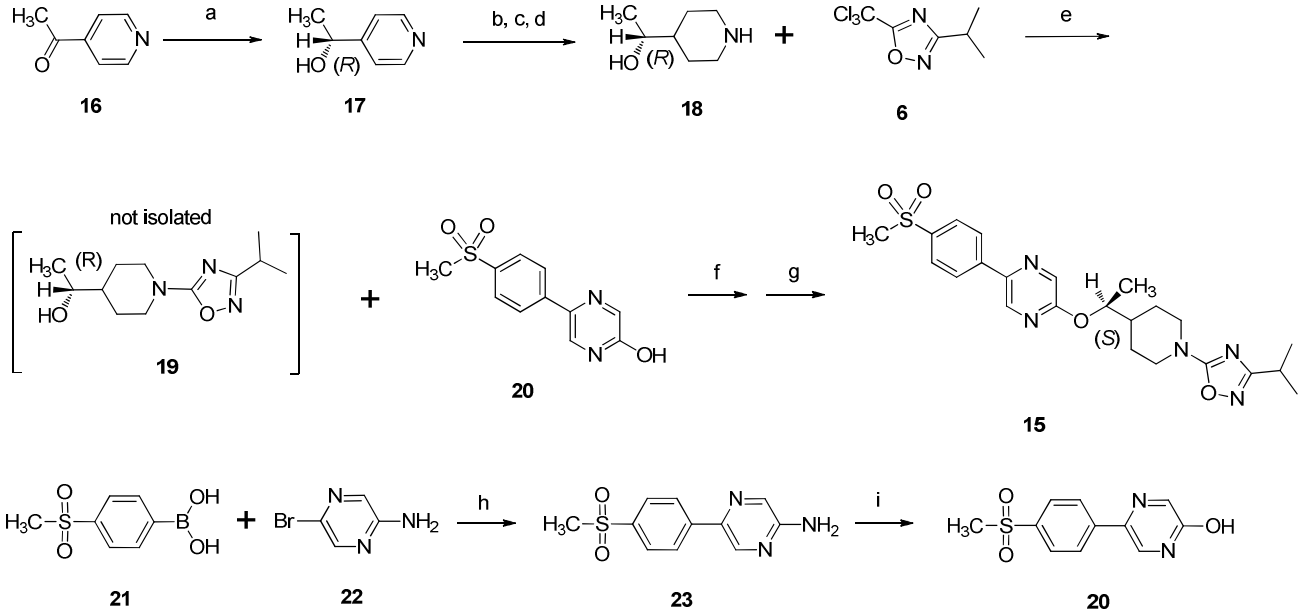


Figure 6. Structure of mesylate **27**

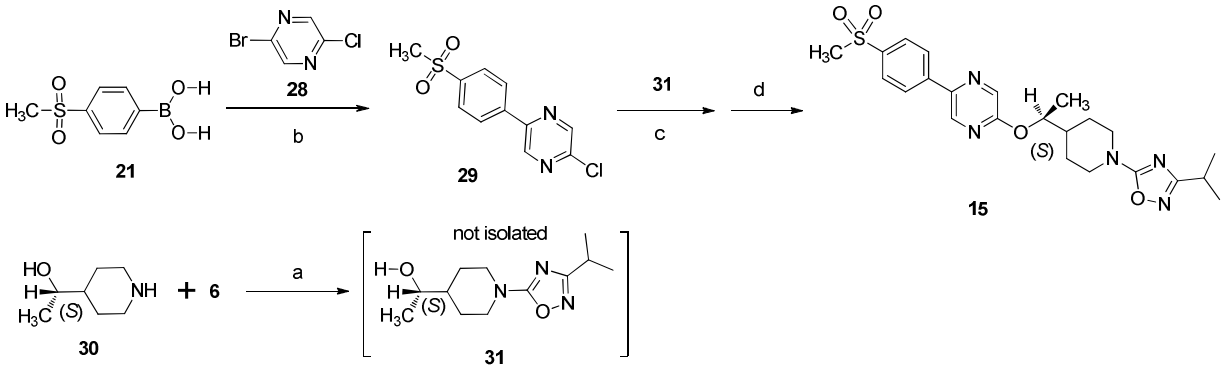
Alternative strategies for synthesizing **15** were quickly examined. The low yielding Mitsunobu reaction was successfully replaced with a nucleophilic aromatic substitution reaction (S_NAr) where alcohol **31**, the enantiomer of alcohol **19**, was reacted with aryl chloride **29** under basic conditions to afford **15** in very high yield (see Scheme 4). Chiral alcohol **31** was synthesized in the same manner as **19** with the exception that the ruthenium-based asymmetric reduction reaction with **16** was carried out using a catalyst containing the ligand of the opposite enantiomer of that in **24**, namely RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN]. Fortunately, the cost of this second catalyst was identical to its enantiomer. A Suzuki-Miyaura reaction was used to synthesize **29** from boronic acid **21** and 2-bromo-5-chloropyrazine **28** in very good yield. The modified synthesis of **15** using the S_NAr strategy affords the GPR119 target molecule in five convergent steps in approximately 33% overall yield. This represents an increase in the overall yield of about 10% in comparison to the initial scale-up route of synthesis. More importantly, the S_NAr strategy eliminated the need to employ potentially hazardous diazonium salt chemistry to synthesize intermediate hydroxy aromatic molecules such as **20**. All stages of the modified synthesis were successfully scaled-up to

Scheme 3. Initial Route to GSK2041706A (**15**)[a]



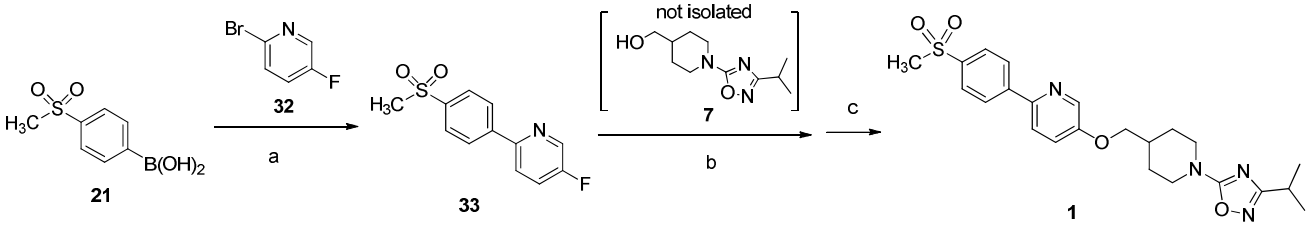
[a]Reagents and conditions: a) 0.3 mol% Chiral Catalyst **24,** formic acid, triethylamine, 80% yield (92% ee); b) 15 wt% $Pt(O)_2$, hydrogen (1 atm), acetic acid, methanol; c) aqueous sodium hydroxide/MTBE, d) MTBE recrystallization to increase enantiomeric purity to >95% ee (47% yield over two steps); e) 15 mol% DBU, methanol, 1-2 days, >90% yield; f) Ph_3P, DIAD, THF (crystallized from aqueous methanol), 50% yield (>95% ee); g) re-crystallization in aqueous acetonitrile to correct form; h) Na_2CO_3, $Pd(PPh_3)_4$, p-dioxane/MeOH, reflux, 98% yield; i) $NaNO_2$, H_2SO_4, water, 90% yield.

Scheme 4. Final Route to GSK2041706A (**15**)[b]



[b]Reagents and conditions: a) DBU, MeOH; b) 0.4-0.5 mol% $Pd(dppf)Cl_2 \cdot DCM$, aq. 2M Na_2CO_3 solution, DME, 70-90% yield; c) 2 eq NaOtBu, THF, Darco G-60 (activated carbon), 70-85% yield; d) seeded aqueous acetonitrile re-slurry to correct form (polymorph), 95-99% yield.

Scheme 5. Final Route to GSK1292263A (**1**)[c]



[c]Reagents and conditions a) 0.25 mol% Pd(*t*-$Bu_3P)_2$, triethylamine, EtOH/water, 85-95% yield; (b) KOtBu, DMPU/THF, 85-95% yield; (c) Darco G-60 (activated carbon), 2-MeTHF, seeded re-crystallization to correct form (polymorph) 75-85% yield.

synthesize about 5 kilograms of **15**. Hydroperoxide formation was not as much of an issue for **15** versus the GPR119 agonist **1**; the recrystallization of **15** in aqueous acetonitrile was employed to ensure that the correct form was synthesized.[12]

Final Route. Based upon the success of the new **15** synthesis, an analogous S_NAr approach to the synthesis of **1** was examined (see Scheme 5). The Suzuki reaction between boronic acid **21** and 2-bromo-5-fluoropyridine **32** afforded the coupled product **33** in very good yield. This Suzuki-Miyaura reaction was initially carried out using in situ prepared tetrakis-(triphenylphosphine)-palladium (0). Subsequent experimentation showed that the palladium loading could be reduced from 0.05 eq to 0.0025 eq. by switching to Pd(*tert*-Bu3P)2. The strategically important S_NAr reaction between **33** and alcohol **7** also proceeded smoothly and in very good yield. Initially carried out using sodium *tert*-butoxide in a mixed solvent system of DMSO/THF, the ultimate S_NAr reaction conditions employed potassium tert-butoxide as base in a mixed solvent system of DMPU/THF. All stages of the synthesis were later successfully scaled-up to synthesize about 71 kilograms of API **1** in multiple 20-25 kilogram batches.

CONCLUSIONS

The process development and synthesis for two GPR119 receptor agonists, namely GSK1292263A (**1**) and GSK2041706A (**15**), has been described. An S_NAr strategy was found to be applicable to the synthesis of both API targets; such a strategy enabled the employment of relatively cheap and commercially available starting materials. Highly cost-effective and robust processes for the large-scale manufacture of both molecules were subsequently developed.

EXPERIMENTAL SECTION

General Procedures. All materials were purchased from commercial suppliers and used without further purification. All non-aqueous reactions were performed in dry glassware or glass-line reactors under an atmosphere of dry nitrogen. Organic solutions were concentrated via rotary evaporation at about 30 mmHg at less than 55 °C except where noted.

NMR spectra were measured on a Bruker DRX400 operated at 400 and 100 MHz, for 1H and 13C, respectively, with data reported as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), integration and coupling constant (J, Hz). Elemental analysis, high resolution mass spectra, melt solvates, infrared spectra (IR), and thermogravimetric analyses (TGA) were obtained from GlaxoSmithKline Analytical Chemistry Department.

Preparation of 2-chloro-5-(4-(methylsulfonyl)phenyl)pyrazine (**29**).

Semi-solid 2-bromo-5-chloropyrazine (**28**) (4.06 kg, 21.0 mol), solid (4-(methanesulfonyl)phenyl)boronic acid (**21**) (4.96 kg, 24.8 mol), and solid $PdCl_2$(dppf) [1,1'-bis(diphenylphosphino)ferrocene palladium (II) chloride] as a complex with dichloromethane (0.0857 kg, 0.105 mol), and finally DME (20.3 L) were charged to a reaction vessel at room temperature. The resulting slurry was stirred at 25 °C and then treated with an aqueous 2.0 M sodium carbonate solution (28.4 L). The resulting biphasic reaction mixture was heated to 65-70 °C with stirring and stirred at 65-70 °C for 7 h. The reaction mixture was cooled to 25 °C and treated with water (40.6 L). The reaction mixture was stirred for 1 h and filtered. The reaction vessel was rinsed with water (2 X 20.3 L) and this rinse was added to the wet cake. The wet cake was charged to a clean vessel. The wet cake was treated an aqueous 1.0 N sodium hydroxide solution (81.2 L) with stirring at 25 °C. The resulting slurry was stirred at 25 °C for 2 h and then filtered. The wet cake was washed with an aqueous 10 wt% ammonium chloride solution (40.6 L) and with water (40.6 L). The wet cake was air dried for 2 h. The partially dried wet cake was then charged to a clean vessel. The wet cake was treated with dichloromethane (101.5 L) at 25 °C. The resulting slurry was stirred at 25 °C for 2 h and then filtered through a Celite impregnated filter pad (ErtelAlsop Micro-Media XL Series Filter Pad) to remove the unwanted boric acid salts. The pad of Celite was rinsed with dichloromethane (2 X 81.2 L) to retrieve any desired product **29** that may have stuck to the pad. The filtrates were combined and concentrated about 40.6 L. The resulting slurry was treated with MTBE (81.2 L) and concentrated to approximately 40.6 L. The slurry was treated with MTBE (81.2 L) and concentrated to about 40.6 L. The slurry was treated one final time with MTBE (81.2 L) and concentrated to approximately 60.9 L. The slurry was heated to approximately 50 °C and stir at 50 °C for 1 h. The slurry was cooled to 25 °C. The slurry was stirred at 25 °C for 1 h and then filtered. The wet cake was rinsed with MTBE (2 X 20.3 L). The wet cake was dried in a vacuum oven at 45 °C to afford 4.18 kg (15.6 mol; 74.2% yield) of **29** as a cream-colored solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.24 (d, J = 1.5 Hz, 1H), 8.93 (d, J = 1.2 Hz, 1H), 8.38 (d, J = 8.5 Hz, 2H), 8.09 (d, J = 8.5 Hz, 2H), 3.29 (s, 3H). ^{13}C NMR (100.6 MHz, DMSO-d_6) 149.0, 148.5, 144.6, 142.7, 142.4, 139.8, 128.2, 128.1, 43.9. HRMS calcd for $C_{11}H_{10}ClN_2O_2S$ (M + H)+ 269.0146, found, 269.0143.

Preparation of (S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethanol (**31**).

Solid (*S*)-1-(piperidin-4-yl)ethanol (**30**) (6.99 kg, 54.1 mol), 3-isopropyl-5-(trichloromethyl)-1,2,4-oxadiazole (**6**) (14.96 kg, 65.2 mol), and MeOH (7.69 L) were charged to a reaction vessel at room temperature. The resulting solution was stirred at 25 °C. The reaction mixture was then treated with DBU (1.24 kg, 8.1 mol) and MeOH (7.69 L). The reaction mixture was stirred at 25 °C for 72 h. The reaction mixture was cooled to 20 °C and then slowly treated with aqueous 2.0 N sodium hydroxide solution

(15.4 L) at a rate such that the process temperature remained below 30 °C. The reaction mixture was then stirred at 25 °C for 2 h during which time all of the remaining starting material **6** decomposed to various non-chromophoric ring-opened molecules. The reaction mixture was diluted with MTBE (69.9 L). The resulting two-phase solution was vigorously stirred before the layers were allowed to settle and separate. The lower aqueous layer was drained and saved. The organic layer was drained and saved. The vessel was charged with the aqueous layer. The aqueous layer was extracted with additional MTBE (2 X 35.0 L). The organic layers were combined and charged into a vessel. The organic layer was washed with with an aqueous 10% w/w sodium dihydrogenphosphate solution (2 X 30.8 L) followed with an aqueous 10% w/w sodium carbonate solution (2 X 30.8 L). The organic layer containing product **31** was concentrated in vacuo to a minimum stir volume. The concentrated solution was treated with THF (139.8 L) and concentrated again in vacuo to about 24.5 L. The product **31** as a solution in THF was used in the following step without further purification.

Preparation of GSK2041706A (**15**) as a mixture of polymorphic forms

Solid **29** (3.00 kg, 11.16 mol) (1 wt, 1 eq), **31** [2.81 kg, 11.74 mol; a solution in THF (about 12 L)], and then THF (4.5 L) were charge to a reactor. The resulting reaction mixture was cooled to 0 °C and then slowly treated with sodium tert-butoxide (2.14 kg, 22.27 mol) as a solution in THF (15 L) at a rate such that the process temperature remained below 10 °C. After the addition of the base was complete, the process temperature was increased to about 25 °C. The reaction mixture was stirred at about 25 °C for 2 h. The reaction mixture was treated with acetic acid (0.670 kg, 11.2 mol) and then with water (9 L). The resulting biphasic reaction mixture was stirred at about 25 °C for 1 h and then treated with aqueous 20% NaCl solution (3 L) and stirred for about 15 min. The layers were separated and the organic layer was treated with aqueous 20% w/w sodium bisulfite solution (12 L). The process temperature was increased to 60 °C and the contents of the reactor were stirred for 1 h at 60 °C. The process temperature was deceased to 25 °C. The layers were separated and the organic layer was treated with Darco G-60 powder. The process temperature was increased to 60 °C and the contents of the reactor were stirred for 1 h. The hot solution was filtered through a Celite impregnated filter pad (ErtelAlsop Micro-Media XL Series Filter Pad) into multiple 20-L containers. The contents of the container were filtered through a clarifying filter cartridge into a second clean reactor. The organic layer was concentrated in vacuo to about 9 L. The contents of the reactor were diluted with isopropanol (18 L). The reaction mixture was concentrated in vacuo to about 15 L. The reactor was charged with water (18 L). The process temperature was increased to 70 °C over 45 min. The contents of the reactor were stirred at 70 °C for about 1 h and then slowly cooled to 25 °C over 3 h and the resulting slurry was left to stir at 25 °C overnight. The contents of the reactor were filtered. The wet cake was washed with with an aqueous methanol solution (12 L) (3:2 ratio of MeOH/water). The wet cake was dried in a vacuum oven at 60 °C to afford 3.84 kg (8.13 mol; 72.8% yield) of **15** as an off-white colored solid.

Conversion of GSK2041706A (**15**) as a mixture of polymorphic forms to a single form

Solid **15** (1.90 kg, 4.02 mol) was charged to a vessel and then treated with an aqueous 33.2 %v/v acetonitrile solution (47.5 L) at room temperature with stirring. The resulting slurry was treated with crystalline seed material and then stirred at room temperature overnight. The slurry was filtered and the wet cake was washed with an aqueous 33.2 %v/v acetonitrile solution (9.5 L). The crystals were dried in a vacuum oven at 60 °C to afford 1.82 kg (3.85 mol; 95.8% yield) of **15** as an off-white colored solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (bs, 1H), 8.40 (bs, 1 H), 8.28 (d, *J* = 8.5 Hz, 2H), 8.02 (d, *J* = 8.5 Hz, 2H), 5.17-5.09 (m, 1H), 4.09-3.95 (m, 2H), 3.27 (s, 3H), 3.16-2.99 (m, 2H), 2.80 (q, *J* = 6.9 Hz, 1H), 1.98-1.85 (m, 2H), 1.83-1.70 (m, 1H), 1.47-1.33 (m, 2H), 1.31 (d, *J* = 6.3 Hz, 3H), 1.17 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100.6 MHz, DMSO-d_6) 175.3, 170.9, 159.8, 142.6, 141.2, 141.0, 139.1, 135.7, 128.1, 126.9, 75.7, 46.0, 45.9, 44.0, 40.2, 27.1, 27.0, 26.7, 20.7, 16.9. HRMS calcd for $C_{23}H_{30}N_5O_4S$ $(M + H)^+$ 472.2013, found, 472.2009.

Preparation of (1-(3-isopropyl-1,2,4-oxadiazol-5-yl)-piperidin-4-yl)methanol (**7**)

Liquid **6** (73.0 kg, 318.10 mol), piperidin-4-ylmethanol (**5**) (73.0 kg, 633.85 mol) and acetonitrile (54.8 L) were charged to a vessel at ambient temperature. The resulting slurry was then heated to 60 °C; during the heating process the reaction mixture became a homogeneous solution. The reaction mixture was stirred at 60 °C for 16 h. The reaction mixture was cooled to 20 °C, treated with aqueous 1 M hydrochloric acid solution (350.4 L) and then stirred at that temperature for 30 min. The vessel was charged with toluene (292 L) and the resulting biphasic solution was stirred for 30 min. The layers were allowed to settle and separate. The bottom aqueous layer was separated and saved. The organic layer was saved. The aqueous layer was placed into a vessel and extracted with toluene (2 X 146 L). The organic layers were combined and concentrated in vacuo to afford **7** as a brown-colored solvent-free solution (219 L). The crude product **7** was used in the following step without further purification.

Preparation of 5-fluoro-2-(4-(methylsulfonyl)-phenyl)pyridine (**33**)

Solid (4-(methanesulfonyl)phenyl)boronic acid (**21**) (34.4 kg, 171.98 mol), bis(tri-t-butyl phosphine)palladium (0) (0.2025 kg, 0.396 mol), ethanol (139.5 L), solid 2-bromo-5-fluoropyridine (**32**) (27.9 kg, 158.53 mol), and water (139.5 L) were charged into a reactor. The reaction was heated with stirring to 25 °C. Triethylamine (24.1 kg, 238.17 mol) was then charged to the reactor at such a rate

that the reaction temperature remained between 25 °C and 35 °C. After the addition of triethylamine was complete, the reaction mixture was heated to about 55 °C and stirred at that temperature until complete by HPLC (reaction was deemed complete when <1.5% **32** was seen). The reaction was cooled to about 20 °C, treated with water (279 L), and the mixture was stirred for 2 h. The resulting solids were filtered and the wet cake was washed with water (2 X 69.8 L). The wet cake **33** was charged into a vessel and dissolved in THF (399.0 L). Solid L-cysteine (8.09 kg) (a palladium scavenger) was dissolved in water (198.1 L) and added to the **33** solution. The resulting mixture was stirred at about 60 °C for 1 h. The reaction mixture was filtered and transferred to a clean vessel. The layers were allowed to settle and separate. The aqueous bottom layer was separated and transferred to a vessel and back-extracted with DCM (139.5 L). The biphasic solution was stirred for 15 min; the stirring was halted and the layers were allowed to separate. The DCM-based organic layer, after filtration, was combined with the first THF-base organic layer with stirring. After the stirring was halted and the layers separated, the aqueous layer was discarded. The DCM/THF based organic layer containing **33** was then distilled down to about 279 L. Ethanol (390.6 L) was added and the solution was concentrated to about 279 L. The temperature of the ethanol solution was adjusted to about 55 °C and then slowly cooled to about 0 °C at a rate of 0.5 °C/min. The resulting slurry was then stirred for at least 2 hours at 0 °C. The slurry was then filtered. The wet cake was washed with cold EtOH (2 X 139.5 L). The wet cake was dried under vacuum at about 50 °C to afford 35.8 kg (142.5 mol; 89.9% yield) of **33** as a white colored solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.73 (d, *J* = 2.8 Hz, 1H), 8.31 (bd, *J* = 8.8 Hz, 2H), 8.20 (dd, *J* = 8.8, 4.3 Hz, 1H), 8.04 (bd, *J* = 8.5 Hz, 2H), 7.91 (td, *J* = 8.8, 3.0 Hz, 1H), 3.27 (s, 3H). ^{13}C (100.6 MHz, DMSO-d_6) 158.3, 151.3, 142.7, 141.3, 138.4, 128.0, 127.8, 125.0, 124.8, 123.3, 123.2, 44.0. HRMS calcd for $C_{12}H_{11}FNO_2S$ $(M + H)^+$ 252.0489, found, 252.0485.

Preparation of intermediate grade GSK1292263A (**1**)

Potassium t-butoxide (28.1 kg, 250.42 mol) and THF (148.4 L) were added to a vessel. The resulting slurry was cooled to 0-5 °C. The vessel was then charged with a solution of crude **7** (29.58 kg, 131.33 mol) dissolved in DMPU (59.2 L) at a rate such that the temperature remained below 15 °C. The reaction mixture was stirred for 30 minutes at 0-5 °C. The vessel was treated with a solution of **33** (30.0 kg, 119.39 mol) in THF (121.5 L) and DMPU (29.6 L) at a rate such that the reaction temperature was kept below 15 °C. Once the addition was complete, the reaction was held for about 30 min at 0-5 °C and then warmed to 18-22 °C for approx-imately one hour. The reaction was quenched with an aqueous sodium sulphite solution [60.0 kg (476.03 mol) of solid sodium sulphite dissolved in 360 L of water]. The resulting biphasic solution was heated with stirring to about 45 °C and then allowed to settle and separate at 45 °C. The layers were separated. The organic layer was treated with water (150 L) and then subjected to atmospheric distillation to remove the THF solvent. Once the distillation was complete, the solution temperature was adjusted with stirring to 70 °C. The solution temperature was then slowly decreased with stirring from 70 °C to 50 °C at a rate of 0.1 °C per minute and then from 50 °C to 0-5 °C at a rate of 0.25 °C per minute. The resulting slurry was filtered; the wet cake was dried in a vacuum oven at 65 °C to afford 50.4 kg (110.4 mol; 92.5% yield) of **1** as a white colored solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (d, J = 3.0 Hz, 1H), 8.28 (d, J = 8.8 Hz, 2H), 8.06 (d, J = 8.8 Hz, 1H), 7.99 (bd, J = 8.5 Hz, 2H), 7.54 (dd, J = 8.8, 3.0 Hz, 1H), 4.03 (d, J=6.3 Hz, 2H), 4.03-3.97 (m, 2H), 3.25 (s, 3H), 3.20-3.09 (m, 2H), 2.81 (q, J = 6.7 Hz, 1H), 2.13-2.00 (m, 1H), 1.88 (bd, J = 12.8 H, 2H), 1.42-1.29 (m, 2H), 1.18 (d, J = 7.0 Hz, 6H). ^{13}C NMR (100.6 MHz, DMSO-d_6) 175.3, 170.9, 155.5, 147.0, 143.5, 140.5, 138.6, 127.9, 127.0, 122.4, 122.3, 72.5, 45.7, 44.1, 35.0, 28.0, 26.7, 20.8. HRMS calcd for $C_{23}H_{29}N_4O_4S$ $(M + H)^+$ 457.1904, found, 457.1900. Anal. Calcd for $C_{23}H_{28}N_4O_4S$: C, 60.51; H, 6.18; N, 12.27. Found: C, 60.64; H, 6.16; N, 12.24.

Preparation of API grade GSK1292263A (**1**)

In a nitrogen purged vessel, a stirring suspension of **1** (30.0 kg, 65.71 mol) in 2-methyl tetrahydrofuran (630 L) initially at ambient temperature was heated to 70-80 °C. The resulting homogeneous solution was transferred through an appropriate in-line filter containing activated carbon (Darco G-60, 5.01 kg) sandwiched between two layers of filtering agent (Celite 545, 2 X 20.1 kg into a second nitrogen purged and pre-heated reactor vessel. The filterpad was rinsed with additional methyl tetrahydrofuran (60 L) and the filtered solution was concentrated in vacuo to about 510 L. The concentrate was reheated to 70-80 °C. Once complete dissolution was established, the batch temperature was reduced to 55 °C over approximately 30 minutes and seeded with GSK1292263A (0.15 kg) suspended in a minimal amount of filtered 2-methyl tetrahydrofuran (0.18 L) (0.006 vol.). The mixture was then cooled to 35 °C at a rate of 0.1 °C/min and then cooled to 0 °C at a rate of 0.25 °C/min. The resulting slurry was then stirred at about 0 °C for 1 h. The product was filtered. The wet cake was rinsed with pre-chilled 2-methyl tetrahydrofuran (2 X 60 L). The material was dried at 60-65 °C under vacuum to afford 22.51 kg (49.30 mol; 75.0% yield) of **1** as a white colored solid.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Full characterization data for all new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E mail: richard.t.matsuoka@gsk.com.

†API Chemistry Department
‡Analytical Sciences & Development Department

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(9) This resin is often used for Wittig chemistry and then simply removed by filtration. See for example Bernard ,M.; Ford, W. T. *J. Org. Chem*., **1983**, *48*, 326.
(10) RuCl(*p*-cymene)[(*R*,*R*)-Ts-DPEN] is an abbreviation for RuCl[(*R*,*R*)-N-(*p*-toluenesulfonyl)-1,2-diphenyl-ethylene-diamine](p-cymeme).
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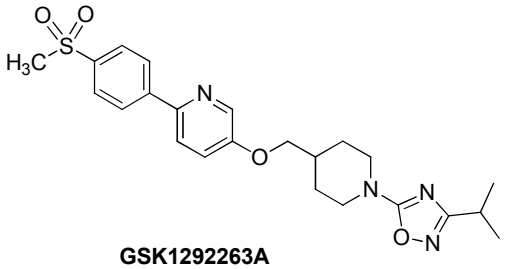
(12) A comprehensive crystal-form screening study of GSK2041706A (**15**) indicated that only two anhydrous polymorphic forms can be produced with melting points of 145.0 °C (Form 1) and 129.3 °C (Form 2). Interestingly, Form 2 was found to be more stable than Form 1 at temperatures below 60 °C as the two forms are enantiotropically related. Hence, Form 2 became the desired form for the API.

Table of Contents Graphic



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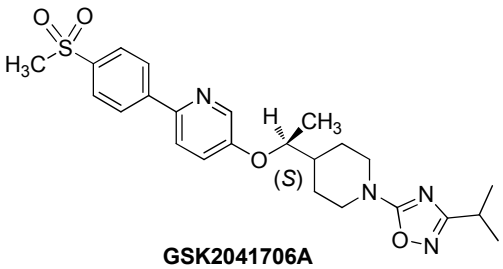

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