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Communications to the Editor

Kilogram-Scale Synthesis of the CXCR4 Antagonist GSK812397

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Abstract:

An improved, scalable synthesis of the CXCR4 antagonist GSK812397 is described. This new route was recently scaled up in 50 L fixed equipment to afford 1.2 kg of drug substance in five steps with an overall yield of 20% and >99% chemical and enantiomeric purity.

Introduction

CXC chemokine receptor 4 (CXCR4) is a 7-transmembrane protein which functions in part as a host co-receptor for a number of HIV-1 strains.[1] It is believed that targeting CXCR4 would be beneficial in suppressing the replication of several cytopathic late-stage viruses; therefore, CXCR4 antagonists are among the most promising new classes of experimental anti-HIV drugs.[2,3] GSK812397 is a potent antagonist of CXCR4,[4] and thus a candidate for the treatment of HIV infection.[5] In order to evaluate the clinical potential of GSK812397, kilogram quantities of the drug candidate were required. The original synthetic route to GSK812397 is shown in Scheme 1. While this route was used for the synthesis of up to several grams of drug substance, it suffered from a number of safety and throughput issues which made it unsuitable for the synthesis of larger quantities. Benzylidine **2**, while obtainable in high yield from tetrahydroquinoline **1**, required purification by high-vacuum distillation.[6] Next, cleavage of the olefin to generate ketone **3** was cleanly conducted on small scale by ozonolysis/crystallization from diethyl ether. Due to the inherent instability of the intermediate ozonide and the well-documented propensity of diethyl ether to form explosive peroxides,[7] we felt that scaling up this reaction would be unsafe. The synthesis of aldehyde **9** was quite laborious and low-yielding, required two high-temperature fluoride displacement processes (the second of which was found to badly etch glassware), and utilized a MnO_2/chloroform oxidation which posed significant waste disposal concerns. The overall route required 12 steps with a yield of 5−7%, and several highly colored intermediates necessitated purification by silica gel chromatography.

Results and Discussion

We saw several opportunities to reduce the overall step count, make the synthesis more convergent and scalable, and introduce safer and more environmentally benign reagents and intermediates. The two key fragments we envisioned were imidazopyridine aldehyde **9** and *N*-methyl quinolineamine **12**, Scheme 2.

We felt that **9** could be accessed without the multiple changes in oxidation state by conducting the nucleophilic aromatic substitution with *N*-methylpiperazine directly on fluoroaldehyde intermediate **8**. This indeed turned out to be the case, and we were able to achieve an 80% yield of **9** directly from **8** by running the reaction at 80 °C using *N*-methylpiperazine as the solvent. We then turned our attention to the use of the 5-bromo analogue **13** (Scheme 3). Since the starting material 2-amino-6-bromopyridine (**14**) is commercially available, use of this intermediate would allow us to avoid the high-pressure amination and fluorinated intermediates. While the bromoimidazopyridine **13** could be formed in good yield, substitution of the less reactive bromide with *N*-methylpiperazine required elevated temperatures and suffered from extensive decomposition. By preforming the lithium salt of *N*-methylpiperazine with *n*-butyl lithium, however, we were able to obtain excellent conversion to **9**. Presumably, the first equivalent of piperazine serves the dual role of protecting the aldehyde as the lithio hemiaminal **15** while simultaneously activating the imidazopyridine ring for nucleophilic attack *via* chelation with the imidazole nitrogen. After acidic workup and rebasification/extraction, the desired product was crystallized as the oxalate salt, providing up to 70% isolated yields for this stage.[8]

Concurrently with the efforts described above, we were pursuing a scalable alternative to (8*S*)-*N*-methyl-5,6,7,8-tetrahydro-8-quinolinamine (**12**). We were aware of a number of

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(1) Zhang, Y. J.; Moore, J. P. *J. Virol.* **1999**, 3443.
(2) Seibert, C.; Sakmar, T. P. *Curr. Pharm. Des.* **2004**, 2041.
(3) For a related recent example described in this journal, please see: Crawford, J. B.; Chen, G.; Gauthier, D.; Wilson, T.; Carpenter, B.; Baird, I. R.; McEachern, E.; Kaller, A.; Harwig, C.; Atsma, B.; Skerlj, R.; Bridger, G. J. *Org. Process Res. Dev.* **2008**, *12*, 823.
(4) Gudmundsson, K.; Boggs, S. D. PCT Int. Appl. WO 2006026703, 2006; *CAN* **2006**, *144*, 274.
(5) Over 33 million people were living with HIV as of 2007 according to UNAIDS, www.unaids.org.
(6) Kelly, T. R.; Lebedev, R. L. *J. Org. Chem.* **2002**, *67*, 2197.
(7) Urben, P. G. *Bretherick's Handbook of Reactive Chemical Hazards*, 5th ed.; Butterworth-Heinemann: Oxford, 1995; Vol. 1.

(8) The high pH needed to extract **9** from water leads to competitive disproportionation to the corresponding alcohol and carboxylic acid *via* the Cannizarro reaction. We have more recently found that phosphate buffer considerably reduces the rate of disproportionation and aids in extracting the product into an organic phase.

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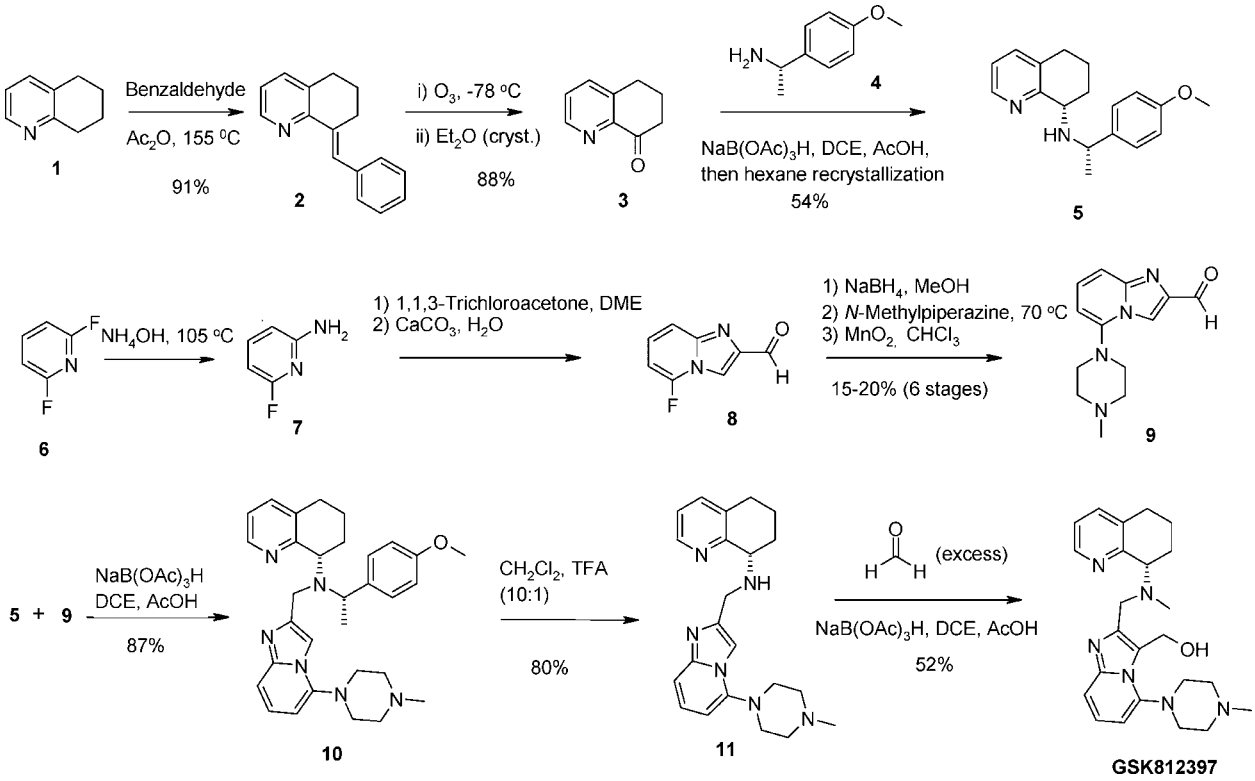
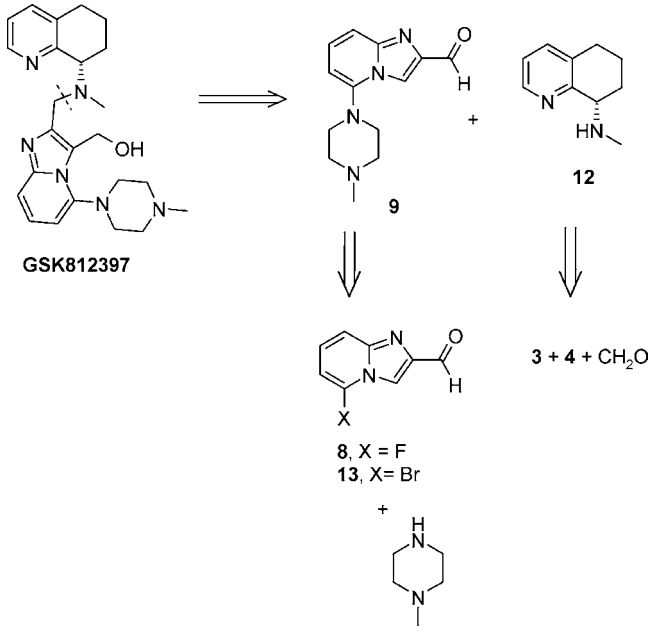
Scheme 1



Scheme 2



literature reports describing the synthesis of the requisite ketone **3**.[6,9] However, we found it more prudent to purchase ketone **3** which is available from a number of suppliers.[10] Reductive amination with (1*S*)-1-[4-(methyloxy)phenyl]ethylamine (**4**) installed the desired stereogenic center with approximately 9:1 diastereoselectivity. The product was isolated as a crystalline solid in 97:3 diastereomeric ratio (63% yield). We found that this reaction could be conducted in the absence of acetic acid and with the crystallization solvent replaced with heptane.[11] An alternative approach to **5** comprising imine isolation and subsequent treatment with $NaBH_4$ in ethanol at 0 °C or below led to comparable yields but inferior diastereoselectivity (5:1 dr). Lastly, *N*-methylation, removal of the chiral auxiliary, and treatment of the free base with oxalic acid in 2-propanol afforded **12** as the oxalate salt[12] in 65−75% isolated yield.

To complete the synthesis, the key coupling of **9** and **12** and subsequent API formation was achieved *via* reductive amination in the presence of triethylamine followed by heating the corresponding tertiary amine intermediate **16** with aqueous formaldehyde. GSK812397 was isolated as the crystalline free base and its absolute stereochemistry confirmed by single crystal X-ray (Figure 1), which also revealed an intramolecular hydrogen bond between the pyridine nitrogen and the hydroxyl proton.

Conclusion

Our team was able to reduce the overall step count from 12 to 5 steps by purchasing ketone **3** and streamlining the syntheses of **9** and **12**. In so doing, we increased the yield to 20% overall (with >99% purity and 99.4% ee) and were able to scale up the chemistry described in Scheme 3 in 50-L fixed equipment to produce 1.2 kg of GSK812397 for use in 28-day tox and phase I clinical studies.

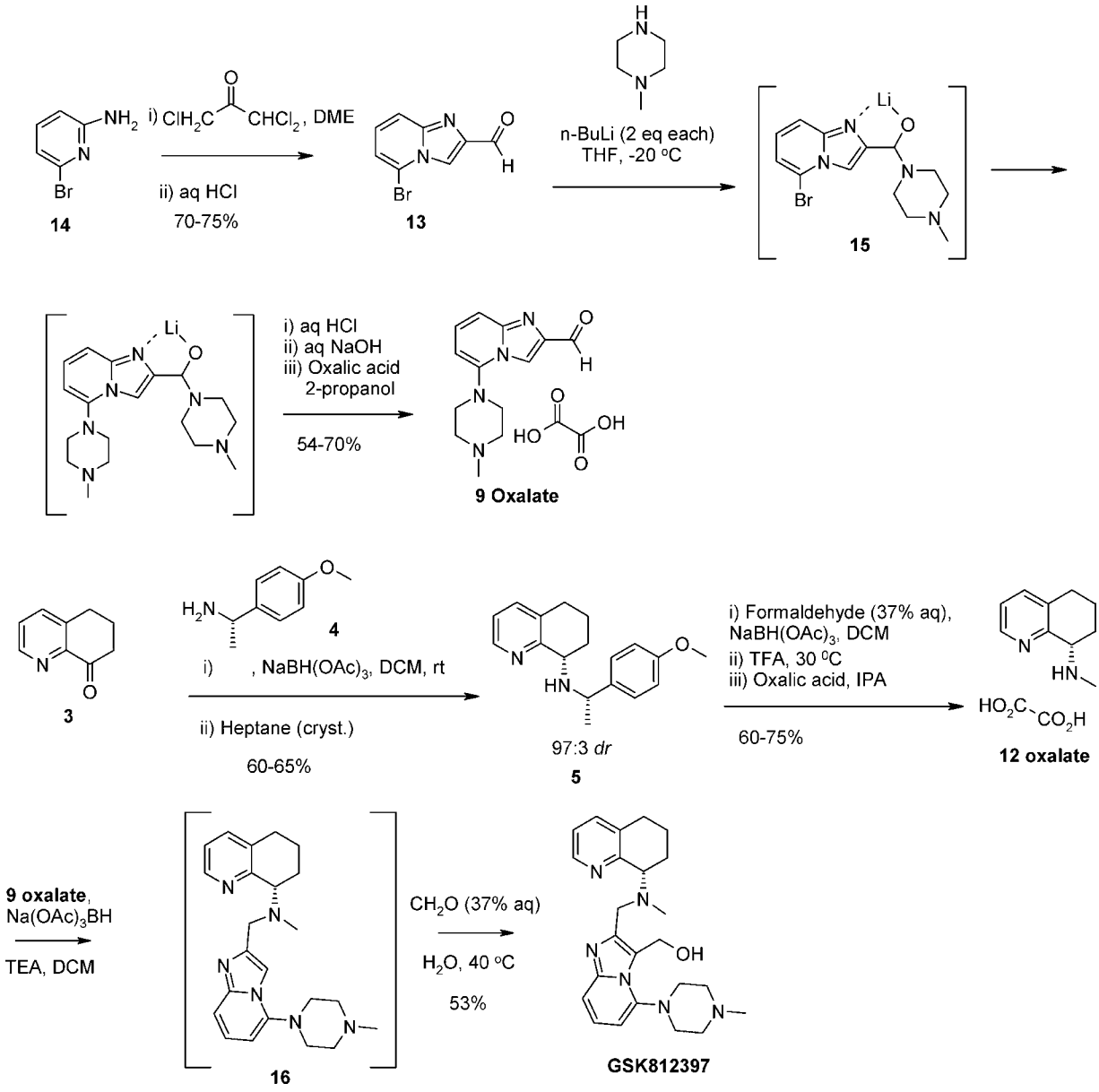
(9) (a) McEachern, E. J.; Yang, W.; Chen, G.; Skerlj, R. T.; Bridger, G. J. *Synth. Commun.* **2003**, *33* (20), 3497. (b) Koltunov, K. Yu.; Repinskaya, I. B *Russ. J. Org. Chem.* **2002**, *38* (3), 437. (c) Weber, H.; Von der Lippe, G. *Chem. Ber.* **1985**, *118* (10), 4086. (d) Jossang-Yanagida, A.; Gansser, C. *J. Heterocycl. Chem.* **1978**, *15* (2), 249. (e) Beschke, H. *Aldrichim. Acta* **1978**, *11*, 13. (f) Chu, F.; Flatt, L. S.; Anslyn, E. V. *J. Am. Chem. Soc.* **1994**, *116* (10), 4194.

(10) Kilogram quantities of ketone **3** were purchased from Astatech, Inc., Bristol, PA, U.S.A.

(11) Hexane is generally not preferred due to its longer static charge relaxation time, see: Lewis, R. J. *Hazardous Chemicals Desk Reference*, 6th ed.; Wiley-Interscience: New York, 2008.

(12) The free base of **12** was found to be unstable upon storage.

Scheme 3



Experimental Section

HPLC purity was determined on a Hewlett-Packard series 1100 system using Agilent Eclipse XDB C18 columns (150 mm × 4.6 mm, 3.5 μm), and a mixture of water and acetonitrile as mobile phase (an 8-min linear gradient from 0 to 95% acetonitrile with constant 0.05% v/v TFA at a flow rate of 1.0 mL/min and UV detector at 220 nm). Chiral HPLC was obtained on an Agilent 1100 HPLC system with a ChiralPak AD column (240 mm × 4.6 mm, 5 μm) and 98:2:0.1 mixture of heptane/ethanol/diethylamine as mobile phase (gradient at a flow rate of 1.0 mL/min and UV detector at 218 nm).

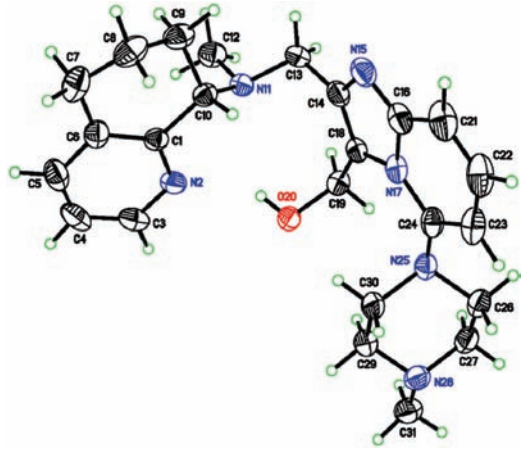


Figure 1. **X-ray crystal structure of GSK812397.**

5-Bromoimidazo[1,2-*a*]pyridine-2-carbaldehyde (13). 2-Amino-6-bromopyridine (3.0 kg, 17.3 mol) and dimethoxyethane (12 L) were combined and stirred at 25 °C under nitrogen. 1,1,3-Trichloroacetone (5.6 kg, 30.3 mol) was added to the solution in a single portion, and the reaction was warmed to 65 °C (jacket temperature) and maintained for ~2−4 h until judged complete by HPLC. The reaction was cooled to 10 °C, held for ~1 h and filtered. The solids were rinsed with dimethoxyethane (6 L). The solids were placed back in the reactor and treated with dimethoxyethane (12 L) and 2 N HCl

(12 L) and warmed to ~75 °C for 16−20 h or until judged complete by HPLC. The reaction was cooled to ~10 °C, and the pH was adjusted to ~8 with 3 N NaOH. The resulting solids were filtered and washed with water (10 L). The solids were dried at 50 °C for 16 h to yield **13** as an off-white solid (2.81 kg, 72% yield) ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1 H) 8.66 (s, 1 H) 7.72 (s, 1 H) 7.42 (s, 1 H) 7.35 (s, 1 H). HPLC t_R = 4.09 min.

5-(4-Methyl-1-piperazinyl)imidazo[1,2-*a*]pyridine-2-carbaldehyde, Oxalic Acid Salt (9 Oxalate). *N*-Methylpiperazine (3.1 kg, 31 mol) and tetrahydrofuran (10 L) were combined and stirred under nitrogen while cooling to −20 °C. *n*-Butyl lithium (2.5 M in hexanes, 10.4 L, 26.0 mol) was added to the reaction at a rate to maintain the temperature <−20 °C. The contents were stirred for 15−30 min after the end of the addition. A slurry of **13** (2.79 kg, 12.4 mol) in tetrahydrofuran (10 L) was added at a rate to maintain the reaction temperature <0 °C. The slurry was washed with additional tetrahydrofuran (6 L). The reaction was stirred for 30 min and warmed to ~−10 °C. After completion as determined by HPLC, the reaction was quenched by the addition of 6 N HCl to achieve pH 4.0 while maintaining the temperature <15 °C. The reaction was diluted with heptane (14 L), and the layers were separated. The lower (aqueous) layer was drained from the reactor, and the upper (organic layer) was washed with 1 N HCl (2 × 1.5 L). The combined aqueous layers were stirred at 20 °C and adjusted to pH 9 with 4 N NaOH. The aqueous layer was extracted with 10% iPrOH/CH_2Cl_2 (3 × 28 L), and the combined organic layers were washed with saturated $NaHCO_3$ solution (14 L) and evaporated at <25 °C to ~8.5 L. Isopropanol (28 L) was added, and the solution was concentrated under reduced pressure to ~8.5 L. Isopropanol (17 L) was added, and the reaction was treated with a solution of oxalic acid (1.0 kg, 11.1 mol) in isopropanol (7 L) at a rate to maintain good stirring and the temperature between ~25−40 °C. The reaction was stirred for 30 min, and the solids were collected and washed with isopropanol (8.5 L). The solids were dried at 50 °C to yield **9 oxalate** as a white solid (2.25 kg, 54% yield) ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1 H) 8.47 (s, 1 H) 7.41 (m, 2 H) 6.65 (m, 1 H) 3.34 (s, 8 H) 2.78 (s, 3 H); HPLC t_R = 2.69 min.

(8*S*)-*N*-{(1*S*)-1-[4-(Methyloxy)phenyl]ethyl}-5,6,7,8-tetrahydro-8-quinolinamine (5). A slurry of sodium triacetoxyborohydride (4.54 kg, 21.4 mol) in dichloromethane (22 L) was treated with 6,7-dihydro-8(5*H*)-quinolinone (1.8 kg, 12.3 mol), followed by (1*S*)-1-[4-(methyloxy)phenyl]ethanamine (1.8 kg, 11.9 mol). The reaction was stirred vigorously at 22 °C for 24 h. The reaction was quenched with 1 N NaOH (27 L) to achieve pH 8 in the aqueous layer. The phases were separated, and the organic phase was treated with 1 N NaOH (3.5 L) to achieve pH 11 in the aqueous layer. The phases were separated. The dichloromethane solution was then concentrated to ~6 L and treated with heptane (18 L). The volume was concentrated to 9 L. Precipitation occurred upon cooling to 22 °C. The suspension was further cooled to 0 °C and filtered. The solids were dried at ambient temperature under vacuum with a slight nitrogen bleed to give **5** as a light brown solid (2.18 kg, 63%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (m, 1 H) 7.44 (m, 1 H) 7.29 (m, 2 H) 7.15 (m, 1 H) 6.83 (m, 2 H) 4.00 (m, 1 H) 3.70 (s, 3 H) 3.59−3.64 (m, 1 H) 2.66 (m, 1 H) 2.64 (s, 1 H) 2.53 (s, 1 H) 1.76 (s, 1 H) 1.64 (s, 1 H) 1.50 (s, 1 H) 1.39 (s, 1 H) 1.24 (m, 3 H). 97:3 dr by achiral HPLC. Achiral HPLC t_R's for each diastereomer: major = 3.40 min, minor = 3.52 min.

(8*S*)-*N*-Methyl-5,6,7,8-tetrahydro-8-quinolinamine, Oxalic Acid Salt (12 Oxalate). A slurry of sodium triacetoxyborohydride (2.44 kg, 11.5 mol) and **5** (2.17 kg, 7.7 mol) in dichloromethane (21.8 L) was cooled to 5 °C. Formaldehyde solution (37 wt % in water, 744 mL, 10 mol) was added slowly to maintain the temperature <25 °C. The solution was stirred for 30 min at 22 °C. The reaction was then quenched slowly with trifluoroacetic acid (7.3 L, 95 mol). Upon completion of the addition, the reaction was warmed up to 30 °C and stirred for 16 h. Water (11 L) was added, and the two phases were separated. The aqueous phase was washed with dichloromethane (14 L), and the combined organic phases were washed with water (2 × 5.5 L). The organic phase was discarded. The pH of the aqueous phase was raised to 8.5−9 by the addition of 6 N NaOH and the aqueous layer extracted with dichloromethane (3 × 13 L). The dichloromethane was exchanged for isopropanol by vacuum distillation to achieve a final volume of ~7 5 L. This solution was then treated with a solution of oxalic acid (588 g, 6.5 mol) in isopropanol (2.2 L) to induce precipitation. After stirring for 2 h, the suspension was filtered at 22 °C, and the solids were dried under vacuum at 22 °C to afford **12 oxalate** as a white solid (1.07 kg, 55% yield) ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.25 (br s, 1 H) 8.52 (s, 1 H) 7.69 (s, 1 H) 7.39 (s, 1 H) 4.39 (s, 1 H) 2.82 (s, 2 H) 2.65 (s, 3 H) 2.50 (s, 1 H) 2.32 (s, 1 H) 1.99 (s, 1 H) 1.80 (s, 1 H). Achiral HPLC t_R = 1.87 min.

For (8*S*)-*N*-methyl-5,6,7,8-tetrahydro-8-quinolinamine as free base: ^{1}H NMR ($CDCl_3$) δ 8.37 (d, 1H), 7.36 (d, 1H), 7.06 (dd, 1H), 3.65 (m, 1H), 2.76 (m, 2H), 2.53 (s, 3H), 2.11 (m, 1H), 1.97 (m, 1H), 1.75 (m, 2H); MS *m*/*z* 163 (M + 1).

[5-(4-Methyl-1-piperazinyl)-2-({methyl[(8*S*)-5,6,7,8-tetrahydro-8-quinolinyl]amino}methyl)imidazo[1,2-*a*]pyridin-3-yl]methanol (GSK812397). A slurry of sodium triacetoxyborohydride (1.86 kg, 8.78 mol) and **12 oxalate** (1.3 kg, 5.15 mol) in dichloromethane (13 L) was stirred at 20 °C. A solution of **9 oxalate** (2.07 kg, 6.18 mol) and triethylamine (1.25 kg, 12.4 mol) in dichloromethane (6.5 L) was added to the reaction at a rate to maintain the temperature <30 °C. The reaction was stirred at 20 °C for 16 h. The reaction was then quenched with 2 N NaOH to achieve pH 12 (~13 L). Methanol (6 L) was added to obtain a bilayer. The lower (organic) layer was separated and the aqueous layer washed with dichloromethane (4 × 5 L). The combined organic layers were evaporated to minimum stir volume (~6 L), and the solvent was exchanged for water to achieve a final volume of 6.5 L. This solution was maintained at 40 °C and treated with 37% aqueous formaldehyde (2.7 L, 35 mol). The solution was stirred at 40 °C for 24 h, and additional formaldehyde solution was added (1.35 L, 18 mol). The reaction was stirred for 72 h, cooled to 25 °C, and treated with saturated aqueous sodium bicarbonate (5.2 L) and dichloromethane (6.5 L). The layers were separated, and the aqueous layer was washed with additional dichloromethane (2 × 6.5 L). The combined organic layers were washed with saturated aqueous sodium bicarbonate (4 L), and the organic

layer was filtered through a bed of silica gel 60 (3.9 kg). The silica bed was washed with additional dichloromethane (3 × 6.5 L),and the combined organic solutions were concentrated to minimum stirring volume (~6.5 L). Ethyl acetate (13 L) was added and the solvent again evaporated to a final volume of 6.5 L. The solution was cooled slowly and crystallization occurred. The solids were filtered and rinsed with ethyl acetate (2.6 L). The solids were dried at 45 °C to give GSK812397 as a white solid (1.15 kg, 53%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 (s, 1 H) 7.23 (s, 1 H) 7.12 (s, 2 H) 6.53 (s, 1 H) 5.95 (s, 1 H) 5.09 (s, 2 H) 3.89 (s, 3 H) 3.30 (s, 4 H) 2.77 (s, 5 H) 2.64 (s, 1 H) 2.47 (s, 1 H) 2.27 (s, 5 H) 2.01 (s, 4 H) 1.89 (s, 2 H) 1.58 (s, 1 H). Purity by HPLC = 99.6% (t_R = 5.63 min), enantiopurity by Chiral HPLC = 99.8% (t_R = 6.49 min). $[\alpha]_D^{25}$ = +65.3 (c = 0.7 MeOH).

Acknowledgment

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Supporting Information Available

^{1}H NMR spectra for compounds **5**, **9 oxalate**, **12 oxalate**, **13**, and GSK812397. Chiral HPLC and X-ray crystallographic data for GSK812397.This material is available free of charge via the Internet at http://pubs.acs.org.

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