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Process Improvements for the Preparation of Kilo Quantities of a Series of Isoindoline Compounds

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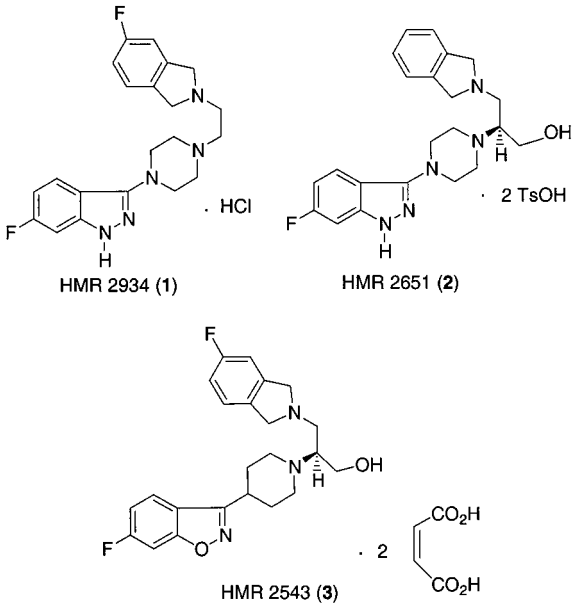
Abstract:

A series of isoindoline analogues with either an indazole (HMR 2934, HMR 2651) or benzisoxazole (HMR 2543) appendage were prepared for the proposed treatment of psychiatric disorders such as obsessive compulsive disorder and attention deficit disorder. The isoindoline compounds were prepared by reduction of the corresponding phthalimides with $LiAlH_4$. One compound was not chiral, and the other two required an enantioselective synthesis. The key step for these optically active analogues involved the coupling by an S_N2 process of either a piperazynyl intermediate or a piperdinyl intermediate with methyl 3-benzyloxy-2-trifluoromethansulfonatopropionate. The products for these two analogues had >98% ee. Process improvements led to the multi-kilogram syntheses of each of these compounds.



Introduction

Drugs for the treatment of psychiatric disorders such as obsessive compulsive disorder and attention deficit disorder are continuing targets of the pharmaceutical industry. Indazoles **1** and **2** and benzisoxazole **3** bearing an isoindoline appendage[1] were advanced as potential drug candidates, and kilogram supplies of active pharmaceutical ingredient (API) were required to support their development. Herein, we describe process improvements in the syntheses of isoindolines **1**−**3** leading to the preparation of kilo quantities of each of these compounds.

HMR 2934

Compound **1** (HMR 2934) has the simplest structure of the isoindolines that were prepared; however, some key elements in the synthesis and handling of isoindolines as well as the synthesis of the core indazole heterocycle were established with this compound.[2] The synthesis of **1** required two pieces as shown in Scheme 1. Piperazine **4** was prepared in a straightforward manner by alkylation of piperazine with bromoacetonitrile. A small amount of the dialkylation product was also observed which was removed in the next step. The key to the isolation of piperazine **4** was treating the reaction mixture with gaseous carbon dioxide to precipitate the excess piperazine as the carboxylate salt. In total, over 10 kg of **4** was prepared for the synthesis of HMR 2934. The other component required for the synthesis of **1** was prepared from chlorofluorobenzoic acid **5** as shown. Thus, acid **5** was converted into the corresponding tosyl hydrazone by reaction with thionyl chloride followed by treatment with tosylhydrazine. Conversion to the intermediate chloroimidate **7** was accomplished using thionyl chloride. Coupling of piperazine **4** and chloroimidate **7** was performed by addition of solid chloroimidate **7** to a solution of piperazine **4**. The order and mode of addition was critical to obtain a high yield of intermediate **8**, as exposure of chloroimidates to catalytic organic bases will promote conversion to tetrazene derivatives such as **9**.[3,4] In addition, a tertiary amine such as Et_3N

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(1) For a recent review of isoxazole chemistry, see: Bonnett, R.; North, S. A. The Chemistry of Isoindoles. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1981; Vol 29, p 341.

(2) For a description of earlier work done on the indazole synthesis, see: (a) Hendrix, J. A.; Shimshock, S. J.; Shutske, G. M.; Tomer, J. D., IV; Kapples, K. J.; Palermo, M. G.; Corbett, T. J.; Vargas, H. M.; Kafka, S.; Brooks, K. M.; Laws-Ricker, L.; Lee, D. K. H.; de Lannoy, I.; Bordeleau, M.; Rizkalla, G.; Owolabi, J.; Kamboj, R. K. *ChemBioChem* **2002**, *3*, 999. (b) Leroy, V.; Lee, G. E.; Lin, J.; Herman, S. H.; Lee, T. B. *Org. Process Res. Dev.* **2001**, *5*, 179. (c) Strupczewski, J. T.; Bordeau, K. J. U.S. Patent 4,954,503, 1990.

(3) Tetrazene **9** becomes the major product if the mode of addition is reversed. The amount of tetrazene **9** formed was not typically quantified, as it readily precipitates during sample preparation for analyses.

(4) Catalytic Et_3N has been described to promote tetrazene formation; see: Shawali, A. S.; Fahmi, A.-G. A. *J. Heterocycl. Chem.* **1977**, *14*, 1089.

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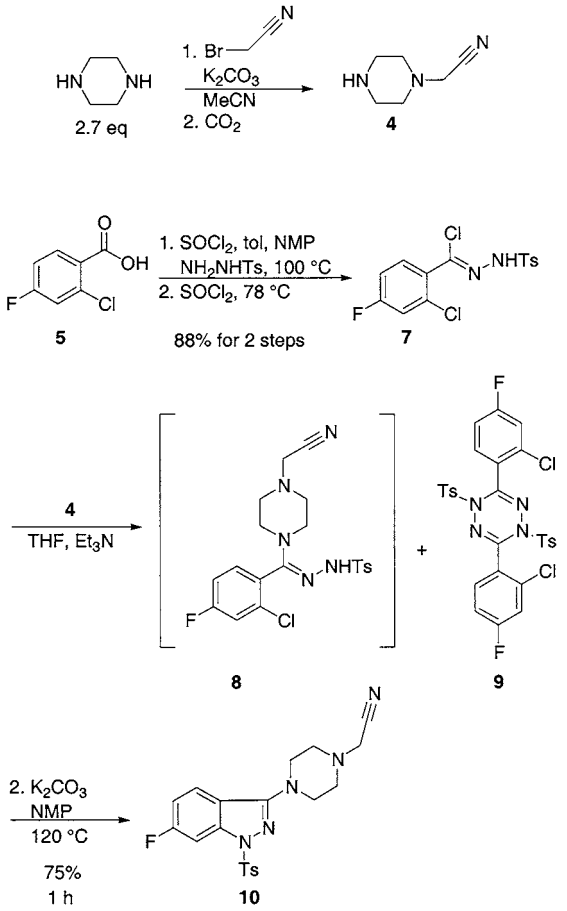
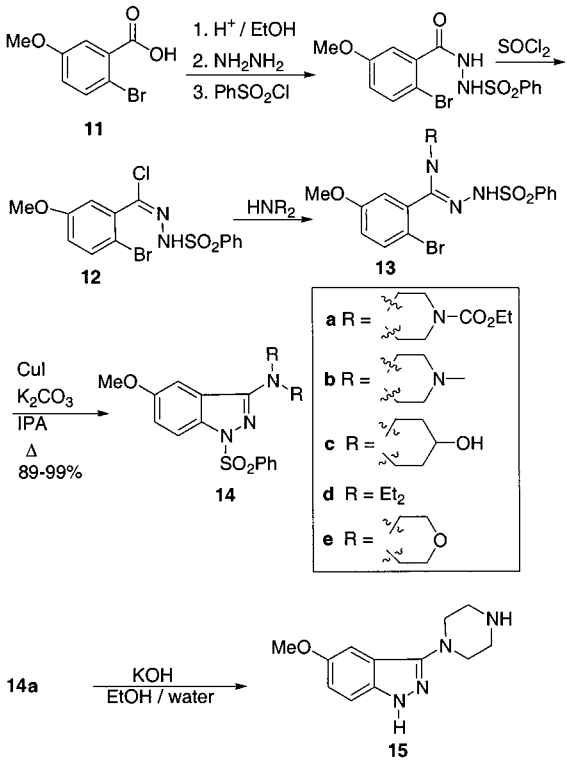
Scheme 1



or DABCO has been employed to scavenge the HCl during the reaction; however, to maximize yields and the ease of the preparation of piperazine **4**, a second equivalent of **4** was used in this case. Intermediate **8** was not isolated but was subjected directly to the cyclization conditions to provide indazole **10**. The use of powdered instead of granular K_2CO_3 was essential in order to obtain good rates for indazole formation.

Other Aspects of Indazole Formation. During the course of this drug development program, we also prepared 6-methoxy-substituted indazole derivatives. Thus, bromoacid **11** was converted to chloroimidate **12** as shown in Scheme 2. The chloroimidate was treated with a variety of amines to generate the intermediate **13**. Interestingly, when one tries to thermally cyclize (up to 160 °C) intermediate **13**, a much more electron-rich derivative compared to **8**, in the presence of powdered K_2CO_3, less than 2% of indazole formation was observed. However, the use of catalytic CuI (2.6 mol %) promotes cyclization so that excellent yields are obtained for the series of indazoles **14a**−**e**. In addition, refluxing *i*-PrOH can be used as the solvent under these conditions. This process was used to prepare 100-g quantities of the unprotected piperarzinyl derivative **15** after removal of the ethyl carbamate and benzenesulfonate groups from **14a**. In the campaign for the preparation of HMR 2934, the use of catalytic CuI lowered the required reaction temperature to 70−80 °C from 120 °C for the cyclization of **8** to indazole **10**, but this added little advantage and was not used.

Scheme 2



The completion of the HMR 2934 (**1**) campaign required conversion of the nitrile functionality of **10** into the isoindoline moiety (Scheme 3). This transformation was accomplished by first reduction of nitrile **10** to the corresponding primary amine using hydrogen and Raney-Ni as the catalyst. The presence of ammonia is essential, as the catalyst does not turnover under the conditions employed without ammonia present, presumably because of catalyst complexation to the product amine. In addition, this process was much easier operationally than the $LiAlH_4$ method previously used in the discovery route, where isolation of the primary amine from the aluminum salts was problematic.[2] The amine was not isolated but rather was converted directly to phthalimide **16** by reaction with fluorophthalic anhydride. Conversion to the phthalimide was very exothermic and required careful temperature control to ensure generation of the intermediate amide acid. The reaction was subsequently heated to 50 °C to promote dehydration to the desired phthalimide **16**.

The most problematic step of the synthesis involved reduction of the phthalimide functionality to the desired isoindoline **1**, owing to the relatively facile oxidation of the isoindoline to the corresponding isoindole **17**.[1,5] Indeed, the reduction of the phthalimide moiety was initially accomplished using Red-Al at 85 °C (the reaction proceeds much slower at lower temperatures) to provide isoindole **17** as the major product and not the isoindoline. This mixture was treated with $NaB(OAc)_3H$ to reduce **17** to **1**. This process although tedious provided a reasonable yield of the desired isoindoline **1**. We decided to explore other conditions for the direct transformation of the phthalimide to the isoindoline

(5) For leading references for the oxidation of isoindolines to isoindoles, see: Kreher, R. P.; Herd, K. J. *Chem. Ber.*, **1988**, *121*, 1827. Kreher, R.; Kohl, N.; Use, G. *Angew. Chem.; GE* **1982**, *94*, 634−635.

Scheme 3

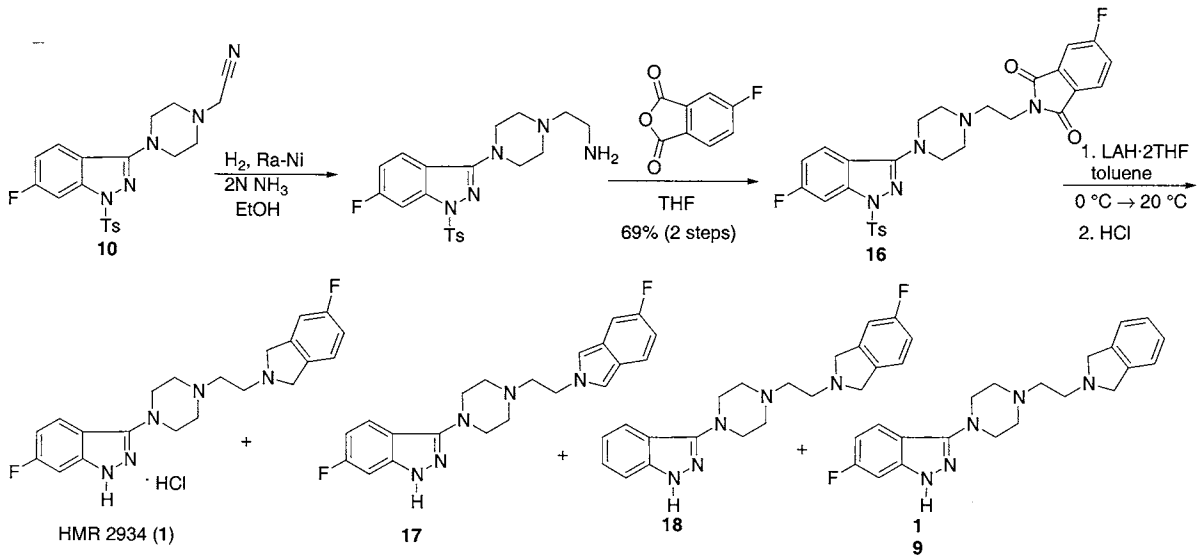


Table 1. **Reduction of Phthalimide 16 to Isoindoline 1**

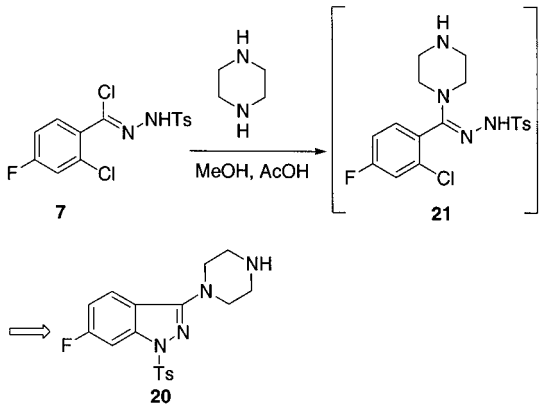
entry	scale (g)	reducing agent	temp (°C)	isoindoline **1**: isoindole **17**	des-fluoro products **18** (%), **19** (%)
1	103	Red-Al	85	<10:>90	3.3, 6.1
2	10	Red-Al	85	<10:>90	0.67, 3.3
3	4	Red-Al	85	<10:>90	0.08, 1.3
4	36	$LiAlH_4$/THF	70	70:30	0.08, 1.2
5	650	$LiAlH_4$/THF	70	70:30	0.3, 1.3
6	2	$LiAlH_4$·2THF/tol	45	60:40	0.55, 0.88
7	4	$LiAlH_4$·2THF/tol	25	93:7	0.38, 0.70
8	1	$LiAlH_4$·2THF/tol	0−5	>93:<7	0.18, 0.68

(see Table 1). Quite nicely, the use of $LiAlH_4$·2THF complex in toluene provided high conversion to the desired isoindoline **1** with minimal formation of isoindole **17**, even at 0 °C.[6] However, control of the reaction temperature was essential to minimize isoindole **17** and des-fluoro products **18** and **19**. Even though small amounts of isoindole **17** could be removed in subsequent steps, the des-fluoro products were inseparable from the final product. An additional aspect of using the $LiAlH_4$·2THF complex in toluene was the relative ease of the workup with water to provide easy removal of the aluminum salts by filtration. After the $LiAlH_4$ reduction, the free base of the isoindoline was converted to the dihydrochloride salt for purification by digesting the solid in methanol. Finally, the dichloride salt was converted to the monohydrochloride salt as the final drug substance. A total of 3.7 kg of HMR 2934 (**1**) was prepared using this chemistry.

HMR 2651

After the preparation of HMR 2934, the back-up compound HMR 2651 (**2**) was advanced as the leading candidate. This compound possesses the indazole heterocycle as well as the isoindoline moiety. A synthetic advantage for HMR 2651 was that the isoindoline does not have the fluoro substituent, so it is less prone to oxidation compared to HMR 2934. A disadvantage is that HMR 2651 has a chiral center in the molecule, and the optical purity of the drug substance and intermediates need to be monitored to ensure the desired optical purity in the final product.

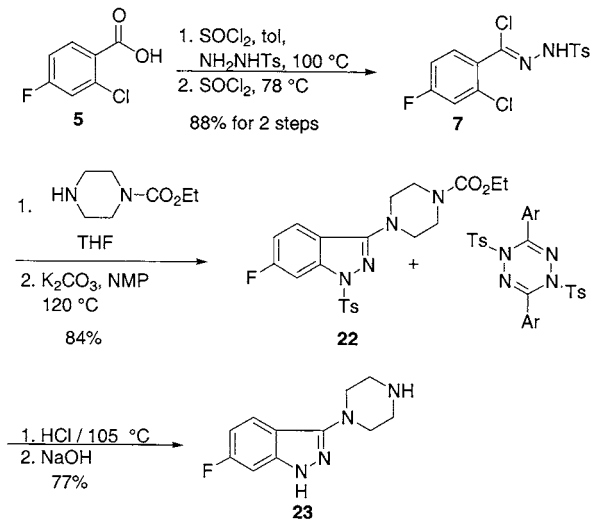
Scheme 4



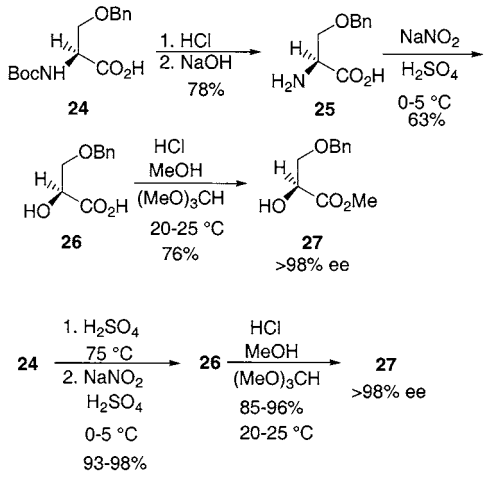
The synthesis of **2** required an unfunctionalized piperazine **20**. Previous studies used a monoprotected piperazine derivative for the construction of the desired piperazine intermediate. Subsequent deprotection of the piperazine was thus required. The use of simple piperazine in this process would avoid the deprotection step and would also retain the tosyl group on the indazole nitrogen; the unprotected indazole causes some complications at a later stage in the synthesis (vide infra). Attempts to prepare the unsubstituted piperazinyl derivative directly were explored by treating chloroimidate **7** with excess piperazine (Scheme 4). After much experimentation, we found that the best conditions for the generation of intermediate **21** involved the use of a 10-fold excess of piperazine with MeOH containing a small amount of AcOH as solvent, principally because of problems associated with the solubility of piperazine. However, when the cyclization was performed with or without Cu-catalysis, a substantial amount of byproducts were formed and the overall yield of indazole **20** was about 20−30% for the two steps.

(6) The use of the soluble LAH•2THF species in scale-up is our preferred reducing agent. It is easy to handle, and issues with slurries are avoided. In addition, the workup to remove the aluminum salts is easily accomplished.

Scheme 5



Scheme 6



Because the reaction with simple piperazine seemed untenable, we decided to prepare piperazinyl indazole **22** using ethylcarbamylpiperazine (Scheme 5). Once again, the order of addition is critical to minimize the formation of the tetrazene. Instead of using a tertiary amine such as Et_3N or DABCO to scavenge the HCl during the reaction, a second equivalent of inexpensive ethylcarbamylpiperazine was used to increase the yield of the process. The tosyl and carbamate groups were removed in the next stage by treatment with HCl at 105 °C to provide indazole **23**.

The chiral portion of the molecule was prepared from an L-serine derivative (Scheme 6). Boc-protected compound **24** was used as the starting material, because it is available in kilogram quantities. Initially, the boc-group was removed with HCl, and amino acid **25** was isolated to ensure removal of residual chloride which generated impurities in the diazotization step. Subsequently, we found that removal of the boc-group of **24** with H_2SO_4 eliminated the need for isolation and this solution could be directly treated with sodium nitrite for the diazotization chemistry to give hydroxy acid **26**. Subsequently, hydroxy acid **26** was converted to methyl ester **27** using standard conditions. No loss of optical purity was observed in this sequence as >98% ee of methyl ester **27** was obtained. However, care had to be taken in the concentration of methyl ester **27** to ensure no epimerization of the center occurred.

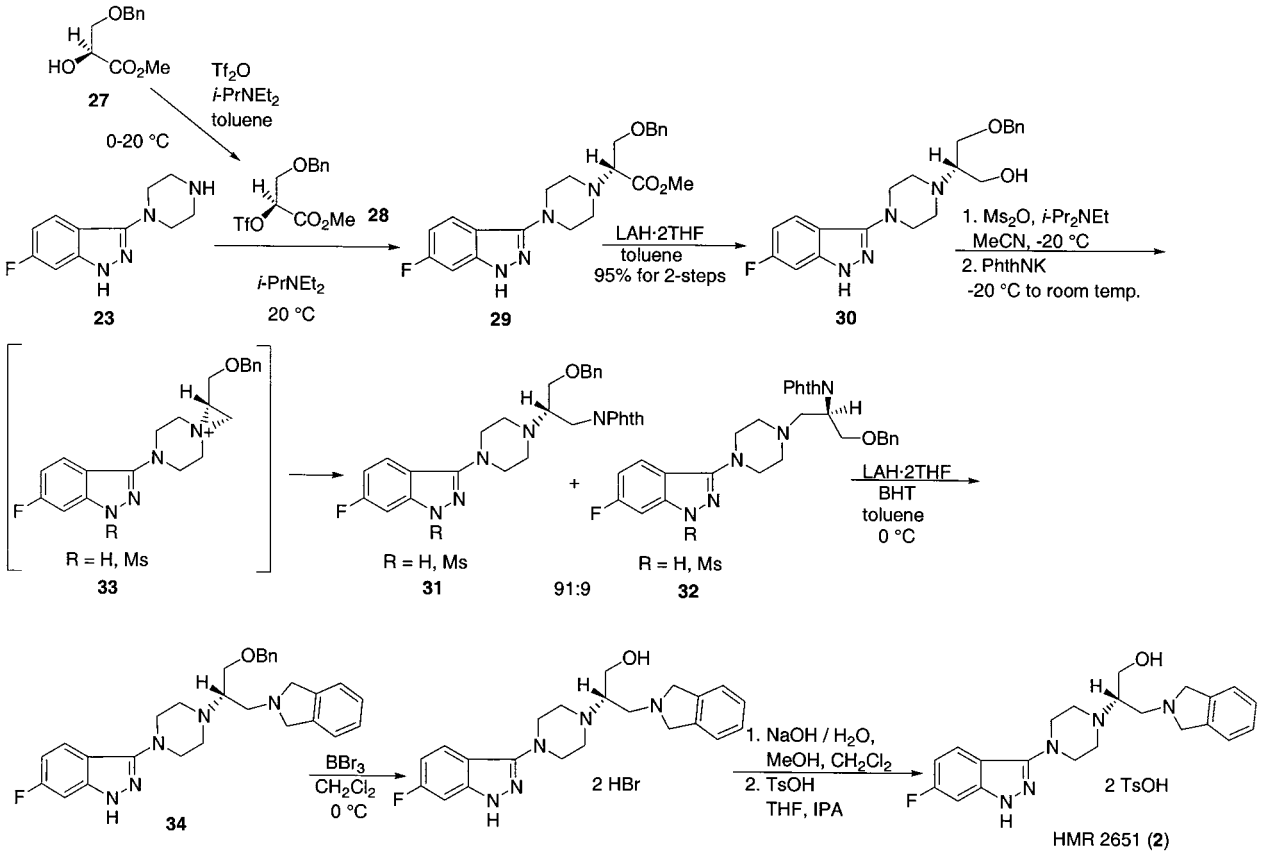
With the two pieces in hand, coupling via the triflate was readily accomplished (Scheme 7). Thus, treatment of a solution of alcohol **27** in toluene at 0 °C by slow addition of triflic anhydride to control the exothermic reaction provided a toluene solution of triflate **28**. This solution was directly added to a solution of piperazine **23** to provide the coupled product **29**. Complete inversion of the triflate center was observerd, as no signicant loss of optical purity was observed. Reduction of ester **29** with $LiAlH_4$·2THF gave primary alcohol **30**. These steps proceeded smoothly on a kilo scale. The next sequence of events required the conversion of primary alcohol **30** to the isoindoline moiety. In this case, we decided to use a Gabriel approach for the conversion of alcohol **30** to phthalimide **31** by transformation of the alcohol to an appropriate leaving group for displacement with potassium phthalimide. Initially, a Mitsunobu reaction was used for this reaction, but the production of the side products (triphenylphosphine oxide and dihydro-DEAD) in this reaction made it very unattractive for scale-up. We then focused on the preparation of the mesylate. Unfortunately, the use of mesyl chloride resulted in substantial formation of the chloro adduct that was less reactive to displacement with potassium phthalimide. We found that mesyl anhydride provided smooth transformation of the alcohol to the mesylate at low temperatures, and now addition of the potassium phthalimide provided **31**. A complication that was unknown during the scale-up of this process was the generation of regioisomer **32** in the reaction. Isomer **32** presumably is formed via aziridinium intermediate **33** by competitive addition of the phthalimide to either the primary or secondary site of the aziridinium moiety.[7] This impurity was not an issue, as it was removed in subsequent steps of the process. Another complication in the mesylate forming step that also hampered detection of regioisomer **32** is that the indazole nitrogen is mesylated to some extent (10−20%.) This phenomenon required the use of 1.5 equiv of mesyl anhydride to obtain complete conversion of alcohol **30** to the intermediate mesylate. However, the mesyl group on the indazole is removed upon reduction with $LiAlH_4$·2THF to isoindoline **34**. The reduction process developed for HMR 2934 (**1**) worked even more efficiently in this case, because unsubstituted isoindoline **34** was less prone to oxidation to the corresponding isoindole. Isoindoline **34** was not isolated but was treated directly with boron tribromide to remove the benzyl group to provide **2** as the dihydrobromide salt. Conversion of the dihydrobromide salt to the ditosylate salt was subsequently done to provide the desired salt form of the API. This process was used to prepare over 4 kg of HMR 2651 (**2**).

HMR 2543

Following the preparation of HMR 2651 (**2**), back-up compound HMR 2543 (**3**) was selected for further develop-

(7) The extent of aziridinium formation in this process will be discussed in a subsequent publication describing an alternative synthesis involving an aziridinium approach for the preparation of compounds **2** and **3**.

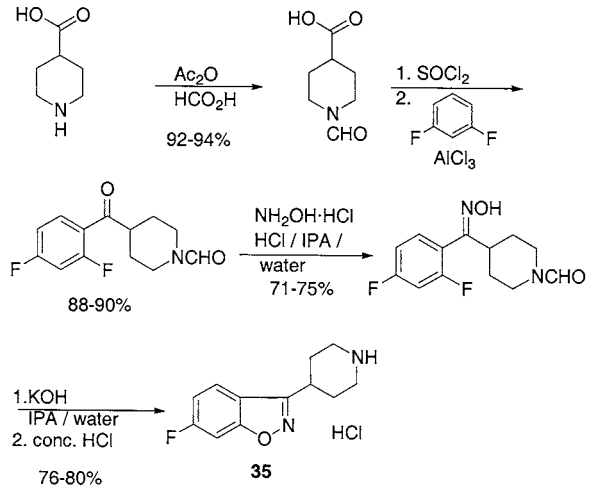
Scheme 7



ment. This compound is structurally similar to both predecessor compounds in that it has the fluoro-substituted isoindoline moiety (HMR 2934) and the chiral appendage (HMR 2651.) However, the indazole functionality with a piperazine appendage has been changed to a benzisoxazole group[8] with a piperidine moiety. The strategy was similar for the construction of HMR 2543 compared to HMR 2651, involving the coupling of piperidine **35** with triflate **28**. Piperidine **35** had been previously prepared in-house on a multikilogram scale (Scheme 8.)[9]

With both pieces in hand, coupling of piperidine **35** with triflate **28** occurred smoothly to provide ester **36** (Scheme 9). Ester **36** was reduced with $LiAlH_4$·2THF to give alcohol **37**. Now the phthalimide moiety could be incorporated into the molecule as before. However, in the case of HMR 2543 (**3**), the preparation of potassium fluorophthalimide **38** was required and readily achieved by treatment of fluorophthalic anhydride with formamide and subsequent formation of the potassium salt with KOH (Scheme 10). Similar to case of HMR 2651, during the mesylate formation and displacement reaction, a mixture of phthalimide regioisomers **39** and **40** was obtained, presumably via an aziridinium intermediate.[5]

Scheme 8

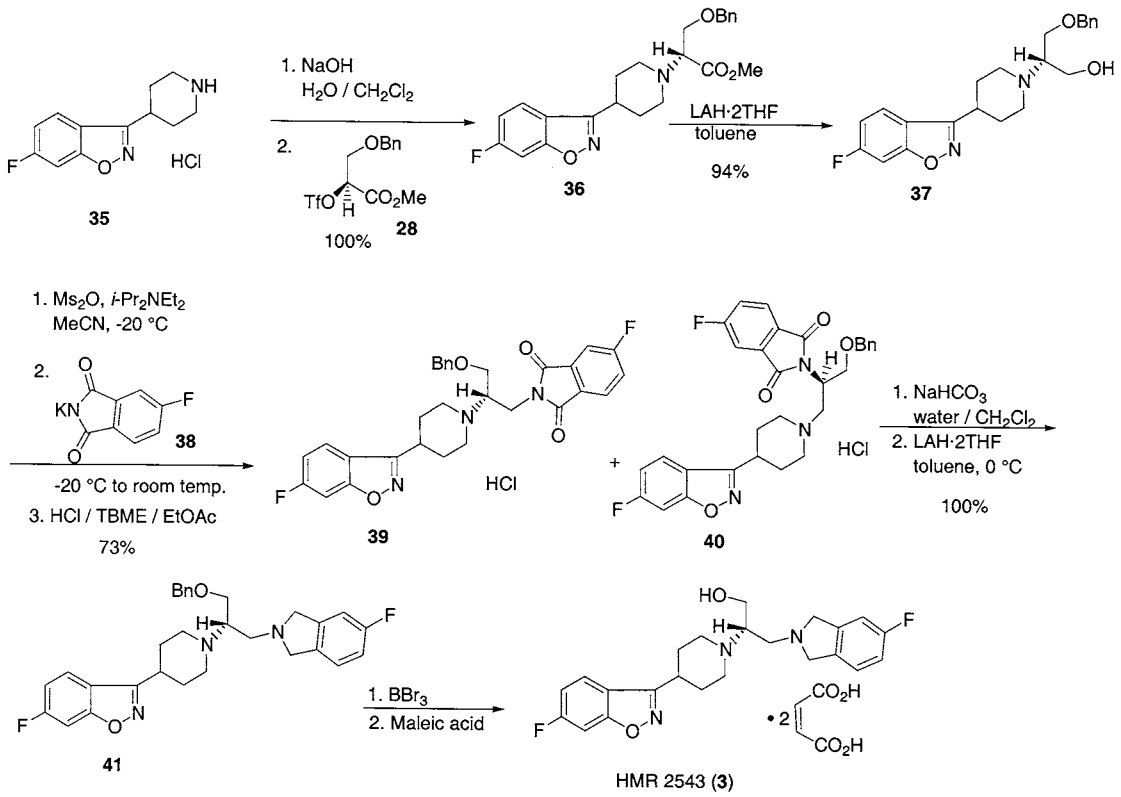


However, in this case, phthalimide **39** was isolated as the hydrochloride salt and the undesired isomer remained in the filtrate. Reduction of phthalimide **39** with $LiAlH_4$·2THF proceeded smoothly to provide isoindoline **41**. Note that, in the case of the benzisoxazole **39**, there is no complication of a mesylated nitrogen as was the case for the synthesis of HMR 2543. Compound **41** was not isolated but reacted with boron tribromide to remove the benzyl group to give **3** as the dihydrobromide salt. Subsequent transformation to the dimaleate salt provided the desired drug substance. This process was used to prepare 3.5 kg of HMR 2543 (**3**).

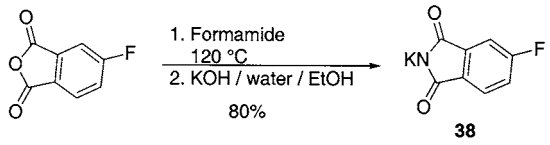
(8) For a recent review of isoxazole chemistry, see: Guartieri, F.; Gianella, M. 1,2-Benzisoxazoles. In *The Chemistry of Heterocycles*; Grunanger, P., Vita-Finzi, P., Eds.; Isoxazoles, Vol. 49 Part 2; John Wiley & Sons: New York, 1999; Chapter 1.

(9) Strupczewski, J. T.; Allen, R. C.; Gardner, B. A.; Schmid, B. L.; Stache, U.; Glamkowski, E. J.; Jones, M. C.; Ellis, D. B.; Huger, F. P.; Dunn, R. W. *J. Med. Chem.* **1985**, *28*, 761. Strupczewski, J. T.; Gardner, B. A.; Allen, R. C. U.S. Patent 4,355,037, 1982.

Scheme 9



Scheme 10



Summary

In summary, we have described the multikilogram synthesis of a series of isoindolines from the simple compound HMR 2934 to the more complex molecules HMR 2651 and HMR 2543. The improvements identified during these campaigns facilitated the rapid scale-up and ensured that the availability of drug substance remained off the critical path for drug development.

Experimental Section

General. NMR spectra were recorded on a Varian XL 300 and/or Varian GEMINI-300 spectrometers at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Reactions were conducted under a nitrogen atmosphere unless otherwise noted. Spectral and elemental analyses were performed by the Analytical and Structural Sciences Department, Cincinnati.

4-Cyanomethylpiperazine (4). Piperazine (2.0 kg, 23.2 mole) was dissolved in 10 L of acetonitrile at 50 °C. Chloroacetonitrile (642 g) was dissolved in 4 L of acetonitrile, and the solution was then added over 3.5 h to the reaction mixture in order to keep the formation of dicyanomethyl piperazine to a minimum. The reaction was monitored by GC as stated in the following. The reaction mixture was stirred for an additional 30 min, cooled to ambient temperature, and the solid was filtered off. The filtrate was placed in a reaction flask, stirred, and CO_2 (g) was bubbled into the mixture to form the carbonate salt of the unreacted piperazine (the temperature changed from 20 °C to 42 °C). The CO_2 (g) addition was stopped once the temperature started to drop. The carbonate salt was filtered off, and the filtrate evaporated to a residue at 45 °C/50 Torr to give 1.07 kg of *N*-cyanomethylpiperazine (99% yield) as an oil that was 87% pure (GC). GC method: Hewlett-Packard 5890 GC with a 3392A integrator; injector temperature = 250 °C; detector temperature = 270 °C; oven temperature = 100 °C for 2 min and then 100−250 °C at 20 °C/min. The capillary column used was an HP-1 methyl silicone gum (10 m × 0.53 mm × 2.65 μm film thickness).

{**[Chloro(2-chloro-4-fluorophenyl)methylene]hydrzide**}-**4-methylbenzenesulfonic Acid (7).** A mixture of 2.8 kg (16.0 mol) of 2-chloro-4-fluorobenzoic acid, toluene (34 L), and 1-methyl-2-pyrrolidinone [NMP] (200 mL) was stirred and heated under nitrogen at 78 °C. Thionyl chloride (1.3 L, 17.8 mol) was added to the reaction mixture over a 2-h period while the temperature was maintained at 78 °C. The mixture was stirred for 2 h at 85 °C and then cooled to 60 °C, and 3.8 kg (20.4 mol) of *p*-toluenesulfonylhydrazide was added portionwise over 10 min while a temperature of 60 °C was maintained. The mixture was heated at 100 °C for 3 h and cooled to 25 °C, and heptane (30 L) was added. The resulting solid was filtered off, washed with heptane (10 L), and air-dried. The solid was returned to the reaction vessel under nitrogen, and thionyl chloride (11 L) was added over 15 min at 25 °C. The mixture was slowly heated to and maintained at 78 °C for 3.5 h until gas evolution stopped. The mixture was cooled to 25 °C, heptane (40 L) was added,

and the resulting slurry was stirred at 10 °C for an additional 18 h. The solid was filtered and washed with heptane (10 L) to give 6.1 kg of crude **7**. The solid was recrystallized from ethyl acetate (5L), toluene (25 L), and heptane (40 L) at 80 °C. The resulting mixture was stirred for 18 h while cooling to 10 °C, and then the solid was collected by filtration, washed with heptane (20 L), and air-dried to give 5.70 kg of **7** (98%, 99.6% HPLC purity, t_R **7** = 5.2 min). HPLC Method A: Nucleosil C18 250 × 4 mm^2 (5 micron); wavelength = 240 nm; 1 mL/min; 55% ACN/45% H_2O with 0.05 N ammonium dihydrogen phosphate. ^1H NMR ($CDCl_3$) δ 8.32 (s, 1), 7.91−7.81 (m, 2), 7.44−6.94 (m, 4), 2.42 (s, 3), 1.62 (s, 1).

6-Fluoro-3-[1-(4-cyanomethylpiperazinyl)]-1-(4-methylphenyl)sulfonyl-1*H*-indazole (10). A mixture of *N*-cyanomethylpiperazine (2.9 kg, 23 mol, 80−90% pure) and THF (32 L) was stirred at 25 °C while **7** (3.5 kg, 9.7 mol) was added portionwise over 2 h as a solid while an internal temperature of 21−29 °C was maintained. After 30 min at 25 °C, the THF was removed at 35 °C (50 Torr.) The residue was dissolved in NMP (14 L), and 5.5 kg of *finely milled* K_2CO_3 was added. The stirred mixture was heated at 126 °C for 1 h, and the reaction progress was followed by HPLC [(Method A) t_R **10** = 13.0 min]. The mixture was cooled to 40 °C, and methanol (14 L) was added. Water (56 L) was slowly added over a 45-min period at 25 °C, and the resulting precipitate was slurried for an additional 18 h. The solid was collected by filtration, washed with 60 L of water, and then dried at 70 °C/50 Torr for 18 h to give 2.9 kg (73%, 98.9% HPLC purity) of **10**: ^1H NMR ($CDCl_3$) δ 7.96−6.95 (m, 7), 3.58 (s, 2), 3.48 (m, 4), 2.71 (m, 4), 2.37 (s, 3).

6-Fluoro-3-[4-[2-(5-fluoro-1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyl]-1-piperazinyl]-1-[(4-methylphenyl)sulfonyl]-1*H*-indazole (16). A mixture of **10** (1.32 kg, 3.2 mol), Raney Ni (Davidson lot no. 8149, 840 g "wet"), and 2 N NH_3 in ethanol (12 L) was placed under 200 psi of hydrogen and heated at 80 °C. After 4 h, the hydrogen uptake ceased. The mixture was cooled and filtered through a bed of Celite, which was washed with ethanol (8 L). The filtrate was concentrated at 35 °C/50 Torr. The residue was dissolved in CH_2Cl_2 (20 L) and dried over 1 kg of $MgSO_4$. The drying agent was filtered off, washed with CH_2Cl_2 (2 L), and the filtrate was concentrated at 30 °C/50 Torr. (*Hydrogenations were run on a 1.3-kg scale and were combined for the following step.*) The foamy residues from four hydrogenation runs (5.1 kg) were dissolved in THF (16 L) and cooled to 15 °C. To this mixture was added 4-fluorophthalic anhydride (2.23 kg, 1.1 eq, 14 mol) dissolved in THF (7.5 L) at a rate so that the reaction temperature did not exceed 20 °C. The mixture was heated at 70 °C for 18 h, and the reaction was monitored by HPLC Method B: Nucleosil C18 250 × 4 mm^2 (5 micron); wavelength = 240 nm; 1 mL/min; 70% ACN/30% H_2O with 0.05 N ammonium dihydrogen phosphate; t_R **10** = 5.3 min; t_R **16** = 8.9 min. THF was removed via distillation at 40 °C/50 Torr. Ethanol (14 L) was added and the remaining THF was removed until the distillation temperature remained at 78 °C. Another portion of ethanol (8 L) was added, and the mixture was heated at 78 °C for 18 h. The mixture was cooled to 5 °C, and the solid was collected by filtration and washed with ethanol (10 L). The solid was dried at 60 °C/50 Torr to give 5.4 kg (75%, 97.8% HPLC purity) of **16**: ^1H NMR (d_6-DMSO) δ 7.98−7.12 (m, 10), 3.71 (m, 2), 3.28 (m, 6), 2.58 (m, 4), 2.22 (s, 3).

6-Fluoro-3-[4-[2-(5-fluoro-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-piperazinyl]-monohydochloride-1*H*-indazole [HMR 2934 Monohydrochloride (1)]. To a slurry of 95% $LiAlH_4$ (1.1 kg, 26.9 mol, 4 eq) in toluene (22.5 L) cooled to 5−15 °C was slowly added THF (4.36 L, 53.7 mol, 2 equiv to $LiAlH_4$) to form a 1 M $LiAlH_4$·2THF complex in toluene solution. This mixture was warmed to 35 °C for 30 min and then stirred at 20 °C for 18 h. (1 M $LiAlH_4$·2THF solutions in toluene are commercially available.)

The $LiAlH_4$ solution was cooled to 0 °C, and **16** (3.8 kg, 6.7 mol) was added in 500 g portions over a 1.5-h period while the mixture maintained an internal temperature of <8 °C. The temperature of the reaction mixture was raised to 20 °C, and the reaction progress was monitored by HPLC Method B: t_R compound **16** = 8.9 min; t_R isoindoline **1** = 3.0 min; t_R isoindole **18** = 4.5 min. After 4.5 h, the mixture was cooled to 0 °C and slowly hydrolyzed with water (2.4 L). (*Caution: water addition must stay below 15−20 °C or oxidation will proceed; THF (16L) was added during this process due to the thick nature of the aluminum salts and insolubility of the free base in toluene.*) The mixture was filtered through a Nutsche filter and washed with 3 × 8 L of THF. The filtrate was washed with saturated sodium bicarbonate (10 L) and brine (10 L). The organic solution was dried over 1.5 kg of $MgSO_4$. The drying agent was filtered off and washed with THF (8 L), and the solvent was removed at 20 °C/50 Torr to give 2.4 kg of HMR 2934 as the free base as a 93:7 mixture of isoindoline **1** and isoindole **18** based upon HPLC analysis.

The free base was dissolved in 16 L of methanol containing 0.1 M 2,6-di-*tert*-butyl-4-methylphenol (BHT), and to this was added, in one portion, 1 N HCl in diethyl ether (12.5 L, 2 equiv), followed by 12 L of diethyl ether. The mixture was stirred at 15 °C for 18 h, and the solid was collected by filtration and washed with *tert*-butyl methyl ether (TBME) (10 L) to give 2.45 kg of HMR 2934 (**1**) as the dihydrochloride salt. This solid and a 1.98-kg sample prepared in a similar fashion were combined and digested in 40 L of methanol at 60 °C for 30 min, cooled to 15 °C, filtered, and dried at 85 °C/30 Torr to give 3.51 kg (57%, 95.4% HPLC purity) of HMR 2934 as the dihydrochloride [HPLC Method C: Waters Symmetry C18 (5 micron); wavelength = 240 nm; 1 mL/min; 20% ACN/80% water (0.05 N sodium phosphate); 20 min linear gradient to 40: 60. t_R of **1** = 12.1 min].

A. Further Purifications. Two batches were combined (4.9 kg) and digested 3 times in 55 L of methanol at 60 °C for 30 min (following the same procedure previously mentioned for filtration.) A total of 3.96 kg (80% for these purifications. 98.6% HPLC purity, Method C) of HMR 2934 (**1**) as the dihydrochloride salt was obtained. (*Overall reduction and purification yield was 47%.*)

Precooled ethyl acetate (30 L)/THF (30 L) and 1 N KOH (40 L) were combined at 10 °C, and to this stirred mixture was added HMR 2934 dihydrochloride (3.9 kg, 8.5 mol). The mixture was stirred for 30 min at 10 °C. The phases were separated, and the aqueous phase was extracted with 2 L of a 1:1 ethyl acetate/THF. The combined organic extracts were washed twice with saturated sodium bicarbonate (40 L each) and dried over Na_2SO_4 (5 kg). The drying agent was filtered off and washed with ethyl acetate (10 L) followed by diethyl ether (8 L), and the solvent was removed at <20 °C/50 Torr to give 3.19 kg of the free base of HMR 2934 (**1**). The free base was dissolved in THF (50 L), and to this was added 1 M HCl in Et_2O (7.49 L, 0.90 equiv) over a 20-min period at 19 °C. The mixture was stirred for 30 min and filtered through a Nutsche filter (6 h for filtration). The solid was washed with THF (2 L), followed by two slurries with 32 and 24 L of diethyl ether. The solid was dried at 85 °C/30 Torr for 5 h and then slowly cooled to 25 °C under 30 Torr for 15 h to give 3.20 kg (89%, 98.5% HPLC purity, Method C) of HMR 2934 (**1**) as the monohydrochloride salt: Karl Fischer (0.5% H_2O); Cl^- titration (theory 8.44%; found 8.40%). ^{1}H NMR (d_6-DMSO) δ 12.18 (s, 1), 7.81 (m, 1), 7.38−6.76 (m, 5), 4.24 (m, 4), 4.01 (m, 6), 3.28 (m, 2), 3.02 (m, 4). Anal. Calcd for $C_{21}H_{24}ClF_2N_5$: C 60.06; H, 5.76; N, 16.67. Found: C; 59.77; H, 5.98; N, 16.83.

Methoxy Indazoles. α-Chloro-2-bromo-5-methoxybenzaldehyde-2-phenylsulfonylhydrazone (12). Step 1: A mixture of 2.99 kg (12.9 mol) of 2-bromo-5-methoxybenzoic acid, 192 mL (3.6 mol) of H_2SO_4 and 6.0 L of EtOH was charged to a 22-L three-necked flask fitted with a stirrer, condenser, and heating mantle. The stirred mixture was heated at reflux for 20 h. Heating was discontinued, and 600 g (4.34 mol) of potassium carbonate was carefully added (foaming) portionwise. Solvent was removed at 40 °C/50 Torr. The residue obtained was extracted with 2 × 6 L of CH_2Cl_2. Organic extracts were combined, dried ($MgSO_4$), and filtered to remove drying agent which was washed with CH_2Cl_2. The filtrate was concentrated at 25 °C/50 Torr to give 3.17 kg of ethyl 2-bromo-5-methoxybenzoate: ^{1}H NMR ($CDCl_3$) δ 7.50 (d, 1, J = 9 Hz), 7.29 (d, 1, J = 3.1 Hz), 6.87 (dd, 1, J = 3 Hz, 9 Hz), 4.40 (q, 2H, J = 7 Hz), 3.81 (s, 3), 1.41 (t, 3, J = 7 Hz).

Step 2: A solution of 2.45 L (50.5 mol) of hydrazine monohydrate and 6.0 L of absolute EtOH was charged to a 22-L three-necked flask fitted with a stirrer, condenser, thermometer, and dropping funnel. The stirred solution was heated to 78 °C, and then 3.17 kg (12.2 mol) of ethyl 2-bromo-5-methoxybenzoate was added over 1.5 h. The stirred mixture was heated at reflux for 7 h and then stirred while cooling to room temperature overnight. Product which crystallized was filtered off, washed with absolute EtOH, and then air-dried at ambient temperature to give 2.33 kg (78%) of 2-bromo-5-methoxybenzoylhydrazide: mp 172−173 °C; ^{1}H NMR (DMSO-d_6) δ 9.50 (bs, 1H, exchangeable with D_2O), 7.51 (d, 1, J = 9 Hz), 6.90−6.97 (m, 2), 4.44 (d, 2, J = 4 Hz, exchangeable with D_2O), 3.76 (s, 3).

Step 3: A mixture of 58.0 g (0.24 mol) of 2-bromo-5-methoxybenzoylhydrazide and 350 mL of pyridine was charged to a 1-L three-necked flask fitted with a magnetic stirrer, thermometer, cooling bath, and continuous nitrogen purge. The stirred solution was cooled to and maintained at −10 °C while 31.3 mL (0.25 mol) of benzenesulfonyl chloride was added via syringe over 25 min. Stirring was continued at −10 °C for 30 min, and then the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 2 h. The reaction mixture was poured into a mixture of 580 mL of ethyl acetate and 1.6 L of water. After the mixture was stirred for 5 min, the organic phase was separated and washed with a solution of 580 mL H_2O/120 mL saturated NaCl. The organic phase was separated and evaporated to a viscous residue at 70 °C/50 Torr, and then the residue was diluted with 500 mL of H_2O. The viscous residue solidified readily. Solid was filtered off, washed with 3 × 100 mL of H_2O, and then air-dried to give 90 g of crude product (odor of pyridine). Crude product was dissolved in 540 mL of boiling 2-propanol. The sample was gravity filtered to remove trace insolubles, and then the filtrate stood at ambient temperature for 8 h. The solid which crystallized was filtered off, washed with 2 × 100 mL of 2-propanol, and then dried at 45 °C/50 Torr for 16 h to give 78.4 g (86%) of 2-bromo-5-methoxybenzoic acid 2-phenylsulfonyl hydrazide: mp 149−150 °C; ^{1}H NMR (DMSO-d_6) δ 10.56 (bs, 1H, D_2O exchangeable), 10.24 (bs, 1H, D_2O exchangeable), 7.96−7.81 (m, 2), 7.72−7.48 (m, 4), 6.98 (dd, 1, J = 4, 8 Hz), 6.74 (d, 1, J = 4 Hz), 3.78 (s, 3). Elemental analysis calculated for $C_{14}H_{13}BrN_2O_4S$: C, 43.65; H, 3.40; N, 7.27. Found: C, 43.75, 43.67; H, 3.44, 3.34; N, 7.25, 7.26.

Step 4: A mixture of 500 g (1.30 mol) of 2-bromo-5-methoxybenzoic acid 2-phenylsulfonylhydrazide and 1.25 L of thionyl chloride was charged to a 5-L three-necked flask fitted with a stirrer, heating mantle, and condenser. The stirred mixture was heated at gentle reflux, and the off gases were passed into 5 L of H_2O. Off-gassing ended about 2 h after reaching reflux. A total of 625 mL of $SOCl_2$ was distilled from the reaction mixture at atmospheric pressure. The residue was vigorously stirred while 2.5 L of hexane were slowly added. After the mixture was stirred for 30 min, the white solid which precipitated was filtered off, washed with hexane, and then air-dried at ambient temperature to give 495 g (94%) of **12**: mp 105−107 °C; ^{1}H NMR ($CDCl_3$) δ 8.32 (s, 1), 8.02−7.97 (m, 2), 7.67−7.51 (m, 3), 7.42 (d, 1, J = 8 Hz), 6.88−6.80 (m, 2), 3.78 (s, 3).

Ethyl 1-{[(Phenylsulfonyl)hydrazono](2-bromo-5-methoxyphenyl)methyl}-4-piperazinecarboxylate (13a). To a solution of 158 g (1.0 mol) of ethyl 1-piperazinecarboxylate in 600 mL of THF cooled below 5 °C was added 200 g (0.50 mol) of chloride **12** dropwise over 2 h while the reaction temperature was maintained below 5 °C. The solution was allowed to warm to room temperature. After 6 h, 600 mL of water and 100 mL of a 10% aqueous $KHSO_4$ solution were added. (NOTE: $KHSO_4$ is necessary to dissolve the excess piperazinecarbamate.) EtOAc (1 L) was added and the organic phase was washed with brine. The combined aqueous phases were extracted with 400 mL of

EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated. The crude oil was dissolved in 500 mL of hot EtOAc, and 500 mL of heptane was added. After the mixture was allowed to stand for 3 d, complete crystallization had occurred. The solid was collected and air-dried for 3 days to give 246 g (94%) of **13a**: mp 102−106 °C; ^{1}H NMR δ 9.78 (br s, 1), 7.93−7.56 (m, 5), 7.49 (d, 1, J = 9 Hz), 6.92 (dd, 1, J = 3, 9 Hz), 6.40 (d, 1, J = 3 Hz), 4.05 (q, 2, J = 7 Hz), 3.65 (s, 3), 3.47 (m, 4), 3.09 (m, 4), 1.18 (t, 3, J = 7 Hz).

3-(4-Ethylcarbamyl-1-piperazinyl)-5-methoxy-1-phenylsulfonyl-1*H*-indazole (14a). A mixture of 100 g (0.19 mol) of **13a**, 32 g (0.23 mol) of powdered K_2CO_3, and 1.0 g (0.005 mol) of CuI in 0.5 L of 2-propanol was heated to reflux for 5.5 h. An aliquot was removed and concentrated. ^{1}H NMR showed complete conversion. The mixture was cooled to ∼60 °C, and 1 L of water was added. After 30 min, the mixture was cooled with an ice bath. The solid was collected, washed with water, and allowed to air-dry for 3 days to give 84 g (99%) of **14a**: mp 140−141 °C; ^{1}H NMR δ 8.00−7.20 (m, 8), 4.08 (q, 2, J = 7 Hz), 3.81 (s, 3), 3.50 (m, 4), 3.38 (m, 4), 1.21 (t, 3, J = 7 Hz). Anal. Calcd. for $C_{21}H_{24}N_4O_5S$: C, 56.74; H, 5.44; N, 12.60. Found: C, 57.10; H, 5.23; N, 12.54.

5-Methoxy-3-(1-piperazinyl)-1*H*-indazole (15). To a solution of 200 g (3.0 mol) of KOH in 600 mL of EtOH and 600 mL of water was added 120 g (0.27 mol) of **14a**. The mixture was heated to reflux. After 18 h, the solution was cooled to room temperature. The pH was adjusted to <2 by the addition of 6 N HCl (∼800 mL). This solution was extracted with EtOAc (3 × 0.5 L), discarding the organic phase. The pH of the aqueous phase was adjusted to >9 by the addition of a 10% NaOH solution. This solution was extracted with $CHCl_3$ (3 × 0.5 L.) The combined organic phases were dried ($MgSO_4$) and concentrated. Toluene (500 mL) was added to the residue to induce crystallization. The solid was collected and dried in a vacuum oven at 60 °C for 8 h to give 31.8 g (51%) of **15**: mp 173−175 °C; ^{1}H NMR δ 11.81, (s, 1), 7.24 (d, 1, J = 9 Hz), 7.02 (d, 1, J = 2 Hz), 6.93 (dd, 1, J = 2, 9 Hz), 3.79 (s, 3), 3.19 (m, 4), 2.86 (m, 4). Anal. Calcd. for $C_{12}H_{16}N_4O$: C, 62.05; H, 6.94; N, 24.12. Found: C, 61.89; H, 6.97; N, 24.15.

6-Fluoro-3-[1-(4-ethoxycarbonyl)piperazinyl]-1-(4-methylphenyl)sulfonyl-1*H*-indazole (22). A solution of ethyl 1-piperazinecarboxylate (6.0 kg, 41.4 mol) in THF (60 L) was stirred at 20 °C, and **7** (6.0 kg, 16.6 mol) was added in small portions over a period of 2.5 h. After 0.5 h at 20 °C, the reaction mixture was stripped to a residue at 40 °C/50 Torr. This residue was dissolved in NMP (30 L), and finely ground potassium carbonate (9.0 kg) was added. The mixture was heated to 125 °C (a small exotherm occurred between 110 and 120 °C) and held at this temperature for 1 h. The reaction was monitored by HPLC Method D: Waters Symmetry C18, 3.9 × 150 mm^2; wavelength = 214 nm; flow 1 mL/min; solvent A, 25% ACN/75% buffer; solvent B, 45% ACN/55% buffer; buffer, 0.05 M NaH_2PO_4, pH = 3.0; gradient 100% A to 100% B over 30 min (HPLC t_R of **7** = 5.0 min, t_R of **22** = 8.8 min). The reaction mixture was cooled to 65 °C, and 30 L of EtOH was added. The solution was divided into two equal portions, and 60 L of H_2O was added to each half with good agitation. The product crystallized and was collected by filtration. The combined solids were washed with 60 L of H_2O and air-dried to give 6.06 kg (84%, 95% HPLC purity) of **22**: ^{1}H NMR (d_6-DMSO) δ 8.20−7.41 (m, 7), 4.24 (q, 2, J = 7 Hz), 3.68 (m, 4), 3.58 (m, 4), 2.43 (s, 3), 1.38 (t, 3, J = 7 Hz). Anal. Calcd For $C_{21}H_{23}FN_4O_4S$: C, 56.49; H, 5.19; N, 12.55. Found: C, 56.24; H, 5.34; N, 12.30.

6-Fluoro-3-(1-piperazinyl)-1*H*-indazole (23). A mixture of **22** (6.0 kg, 13.3 mol) in H_2O (10 L) and ethylene glycol (12.5 L) was stirred while HCl was added (37%, 32.5 L). The mixture was heated to 105 °C and maintained at this temperature for 20 h. The reaction was monitored by HPLC Method D: t_R **22** = 8.8 min, t_R **23** = 2.0 min. The reaction mixture was cooled to 40 °C and gravity filtered to remove insoluble material. The filtrate was concentrated at 60 °C/50 Torr, and the residue was chased with three portions of *i*-PrOH (6 L) to remove residual water. The residue was slurried in *i*-PrOH (12 L) and cooled at 5 °C overnight. The solid was filtered off, washed twice with 6 L portions of 5 °C *i*-PrOH, and air-dried to give 4.1 kg of **23** as the hydrochloride salt.

The hydrochloride salt was dissolved in 40 L of H_2O, and $KHCO_3$ (3.0 kg, 30.0 mol) was added in small portions (final pH = 8.0). The precipitated solid was collected by filtration, washed 3 times with H_2O (6 L), and air-dried to give 2.42 kg of **23** as the monohydrate. After the solid was dried in a vacuum oven at 80 °C/50 Torr for 20 h, 2.25 kg (77%, 97.5% HPLC purity, Method D) of **23** as the monohydrate was produced: ^{1}H NMR (d_6-DMSO) δ 12.01 (s, 1), 7.78 (m, 1), 7.08 (m, 1), 6.80 (m, 1), 3.21 (m, 4), 2.84 (m, 4).

(*S*)-3-Benzyloxy-2-hydroxypropanoic Acid (26). A mixture of boc-*O*-benzyl-L-serine **24** (2.00 kg, 6.77 mol) in 2 N H_2SO_4 (8 L) was stirred and heated at 75 °C for 1 h. TLC: EtOAc, R_f boc-*O*-benzyl-L-serine **24** = 0.7, R_f deprotected amino acid **25** = 0.0. The resulting solution was cooled to 0 °C, and a solution of $NaNO_2$ (835 g, 12.1 mol) in H_2O (8 L) was added over 2 h while the temperature was maintained between 0 and 5 °C. After complete addition, the reaction mixture was stirred at this temperature for 10 h followed by stirring at ambient temperature for 2 h. The reaction mixture was adjusted to pH = 4 with 1.25 L of 50% NaOH. EtOAc (12 L) was added, and the layers were vigorously stirred while the aqueous layer was adjusted to a pH of 2 with 0.2 L of H_2SO_4. [There is an unidentified white solid that forms between the organic and aqueous layer before the pH adjustment with H_2SO_4. This solid dissipates when the pH reaches 2 and the organic layer visually becomes dark orange.] The aqueous layer was extracted further with EtOAc (2 × 12 L). The combined extracts were dried over Na_2SO_4. The drying agent was filtered off and washed with EtOAc (4 L), and the filtrate was concentrated at 40 °C/50 Torr to give 1.26 kg (93%) of **26**: ^{1}H NMR ($CDCl_3$) δ 7.38−7.28 (m, 5), 4.59 (m, 2), 4.38 (m, 1), 3.78 (m, 2).

Methyl (*S*)-3-Benzyloxy-2-hydroxypropionate (27). A mixture of **26** (3.94 kg, 20.1 mol), MeOH (27 L), and freshly prepared methanolic HCl (1 M, 8.2 L) was stirred at ambient temperature for 1.5 h. Trimethyl orthoformate (4.39 L) was added, and the mixture was stirred at ambient temperature for 18 h. The solution was concentrated at 20 °C/30 Torr, and the resulting oil was dissolved in 50 L of methyl *tert*-butyl ether (MTBE). Decolorizing charcoal (500 g) and $MgSO_4$ (500 g) were added to the stirred solution and then filtered through filter aid (the high dilution was used to remove the small amounts of benzyloxy-L-serine present). The solution was then concentrated at 20 °C/30 Torr to give 3.59 kg (85%, 98.4% ee chiral HPLC purity, Method E) of **27**. The ee was determined by HPLC Method E: Chiralcel OD, 4:1 heptane/ethanol with 0.5% $HNEt_2$, isocratic, 1 mL/min, wavelength = 254. t_R of methyl (*S*)-3-benzyloxy-2-hydroxypropionate (**27**) = 8.7 min; t_R of enantiomer = 9.8 min. ^1H NMR ($CDCl_3$) δ 7.39−7.26 (m, 5), 4.58 (m, 2), 4.35 (m, 1), 3.79 (s, 3), 3.77 (s, 2), 3.20 (br s, 1).

Methyl 3-Benzyloxy-2*S*-{4-[6-fluoro-1-(4-methylphenyl)sulfonyl-1*H*-indazol-3-yl]piperazin-1-yl)-propionate (29). Triflate **28** formation: To a solution of **27** (2.39 kg, 11.4 mol) in toluene (19 L) cooled to 0 °C was added *N*,*N*-diisopropylethylamine (DIPEA) (1.98 L, 11.4 mol). The mixture was stirred while triflic anhydride (3.20 kg, 11.4 mol) was added over a 1.5-h period and the temperature was maintained at <5 °C. The reaction was warmed to 20 °C. After 1 h, the reaction was complete by TLC (silica gel; ethyl acetate/heptane 50:50; R_f **28** = 0.65; R_f **27** = 0.45; R_f **29** = 0.15). Coupling: To a mixture of **23** (2.50 kg, 11.4 mol) and DIPEA (1.98 L, 11.4 mol) in toluene (30 L) was added the previously mentioned triflate solution over a period of 10 min. The reaction was stirred at 20 °C overnight at which time the reaction was complete by HPLC Method D: t_R **23** = 1.3 min; t_R **29** = 20.8 min. The insoluble material was removed by filtration through filter aid and washed with toluene (6 L). The filtrate was concentrated at 20 °C/30 Torr to a final volume of about 16 L and carried on the next step.

3-Benzyloxy-2*S*-[4-(6-fluoro-1*H*-indazol-3-yl)piperazin-1-yl]-propan-1-ol (30). A 1 M solution of $LiAlH_4$·2THF complex in toluene (19.9 kg. 22.7 mol) was cooled to 0 °C, and the solution of **29** in toluene from the previously mentioned was added over 2 h while the reaction temperature was maintained between 0 and 5 °C. The mixture was warmed to 20 °C. After 1 h, the reaction was complete by HPLC Method D: t_R **29** = 20.8 min; t_R **30** = 9.4 min. The reaction mixture was cooled to 0 °C, and H_2O (1.65 L) was slowly added, followed by THF (16 L), and finally an additional 1.65 L of H_2O. After the mixture was stirred overnight at ambient temperature, 4 kg of Na_2SO_4 was added. After 1 h, the aluminum salts were removed by filtration through filter aid, and the filter cake was washed with THF (10 L). The filtrate was concentrated to a residue at 30 °C/50 Torr to give 4.03 kg of alcohol **30** as an amber oil.

2-(3-Benzyloxy-2*S*-{4-[6-fluoro-1*H*-indazol-3-yl]piperazin}-1-yl)propyl-isoindole-1,3-dione (31). Alcohol **30** (4.84 kg, 12.6 mol) was dissolved in acetonitrile (36 L) and cooled to −20 °C, and DIPEA (4.60 L, 26.4 mol) was added. A solution of methanesulfonic anhydride (4.40 kg, 20.1 mol) in acetonitrile (10 L) was added over 3 h while the temperature was maintained between −18 and −20 °C. The formation of the mesylate was complete by TLC: silica gel; EtOAc; R_f **30** = 0.25, R_f mesylate intermediate = 0.75. Potassium phthalimide (6.97 kg, 37.6 mol) was added in one portion at −20 °C, and the reaction mixture was slowly warmed to 20 °C over 1.5 h and then stirred overnight at ambient temperature. The reaction was monitored by HPLC Method D: t_R **30** = 9.4 min, t_R **31** = 25.2 min. The insoluble material was filtered off, and the filter cake was washed with 12 L of acetonitrile. The filtrate was stripped to a residue at 30 °C/30 Torr. The residue was dissolved in toluene (12 L) and this solution was filtered to remove some precipitated material. The toluene solution was used in the next step.

(3-Benzyloxy-(2*S*-{4-[6-fluoro-1H-indazol-3-yl]piperazin}-1-yl)-propyl)-isoindole (34). A 1 M solution of $LiAlH_4$·2THF complex in toluene (44.1 kg. 50.4 mol) was cooled to 0 °C and the solution of **31** in toluene from above was added over 1.5 h while the reaction temperature was maintained between 0 and 5 °C. The mixture was warmed to 20 °C and stirred at this temperature for 2 h. The reaction was monitored by HPLC Method D: t_R **31** = 25.4 min; t_R **34** = 24.1 min. The reaction was cooled to 0 °C, and H_2O (3.63 L) was slowly added, followed by THF (12 L), and finally an additional 3.63 L of H_2O. The reaction mixture was stirred overnight at ambient temperature, and then 10 kg of Na_2SO_4 was added. After 1 h, the aluminum salts were removed by filtration through filter aid, and the filter cake was washed with THF (28 L). The combined filtrates were stripped to a residue at 25 °C/30 Torr to give 4.45 kg (74%) of **34**.

(3-Hydroxy-(2*S*-{4-[6-fluoro-1H-indazol-3-yl]piperazin}-1-yl)-propyl)-isoindole Di-4-methylbenzenesulfonate [HMR 2651 (2)]. To a solution of **34** (4.05 kg, 8.34 mol) in CH_2Cl_2 (45 L) cooled to 0 °C was added a solution of boron tribromide (4.00 kg, 16.0 mol) in CH_2Cl_2 (16 L) over 1 h while the temperature was kept below 10 °C. (Caution: SCBA equipment and full body protective clothing should be used when working with this solution. One should take every effort to avoid contact and inhalation.) The solution was warmed to 15 °C and stirred at this temperature for 3 h. The reaction was monitored by HPLC Method D: t_R **34** = 24.1 min; t_R HMR 2651 (**2**) = 3.0 min. The reaction mixture was cooled to 5 °C, and MeOH (15 L) was added in a slow stream over 1 h while the temperature was kept below 10 °C. The reaction mixture was concentrated at 25 °C/30 Torr to a final volume of about 8 L and slowly added to 92 L of THF. The product was filtered off using a Nutsche filter, washed with THF (12 L), and dried on the filter under nitrogen to give 4.46 kg (96%) of HMR 2651 (**2**) as the dihydrobromide salt.

A mixture of CH_2Cl_2 (46 L), MeOH (8 L), and H_2O (32 L) was stirred, and HMR 2651 × 2HBr (4.49 kg, 8.06 mol) was added in small portions over a period of 30 min. The mixture was stirred, and 10% NaOH (6.5 L) was added over a period of 1 h to bring the pH to 10.0. The organic layer was separated, the aqueous layer extracted once with CH_2-

Cl_2 (10 L), the combined organic extracts dried over 5 kg of Na_2SO_4, and the solvent removed at 25 °C/50 Torr to give 2.66 kg (6.73 mol) of free base. The free base was dissolved in THF (5 L) and added to a solution of *p*-toluenesulfonic acid monohydrate (2.56 kg, 13.46 mol) in *i*-PrOH (13 L) at 55 °C. The solution was diluted with THF (16 L), seeded, cooled to a final temperature of 5 °C, and kept at this temperature for 1 h. The solid was collected by filtration, washed with THF (16 L), and dried in a vacuum oven at ambient temperature to give 2.09 kg (35%) of HMR 2651 (**2**) ditosylate.

HMR 2651 ditosylate (4.288 kg) and 2,6-di-*tert*-butyl-4-methylphenol (87 g) were dissolved in MeOH (104 L) at 65 °C (it was necessary to add 200 mL of H_2O to obtain a complete solution). The MeOH was removed by atmospheric distillation gradually replacing by the addition of *i*-PrOH (86 L) until a final volume of about 100 L was obtained. The solution was seeded with 256 g of HMR 2651 ditosylate and cooled over a 5 h-period to a final temperature of −20 °C and held at this temperature for 18 h. The solid was collected by filtration under nitrogen using a Nutchse filter, washed with *i*-PrOH (5 × 15 L) and dried in a vacuum oven at 25 °C/50 Torr for 18 h. The material was placed through a #10 sieve then dried an additional 8 h at 60 °C/50 Torr to give 3.73 kg (82%, 98.9% HPLC purity, Method D) of HMR 2651 (**2**) ditosylate. Overall, a 28% yield of **2** ditosylate was obtained from **34**: ^{1}H NMR (d6-DMSO) δ 12.22 (s, 2), 10.69 (br s, 1), 9.84 (br s, 1), 7.83 (m, 1), 7.46−6.80 (m, 14), 5.05−3.15 (m, 17), 2.28 (s, 6) Karl Fischer = 0.24%. Anal. Calcd. for $C_{22}H_{26}FN_5O$ x 2 $C_7H_8O_3S$ with 0.24% H_2O: C, 58.30; H, 5.57; N, 9.45. Found: C, 58.06; H, 5.57; N, 9.45.

Methyl 2-(3-Benzyloxy-2*S*-[4-fluorobenzo[*d*]isoxazol-3-yl]piperidin-1-yl)-propionate (36). Triflate **28** formation: A solution of **27** (3.75 kg, 17.8 mol) in toluene (35 L) was cooled to 0 °C, and DIPEA (2.28 kg, 17.7 mol) was added. Triflic anhydride (5.0 kg, 17.8 mol) was added over 1.5 h while the reaction temperature was maintained at <5 °C. The reaction was warmed to 15 °C. After 2 h, the reaction was complete by TLC (silica gel; ethyl acetate/heptane 50:50; t_R **28** = 0.65; t_R **27** = 0.45. A second portion of DIEA was added (2.28 kg, 17.7 mol). Coupling: Compound **35** as the hydrochloride salt was treated with 5 L of NaOH and 50 L of CH_2Cl_2. The organic layers were separated, dried over 1.0 kg of $MgSO_4$, filtered (wash with 10 L CH_2Cl_2), and concentrated to give 3.24 kg (14.7 mol) of **35** as the free base. The free base was dissolved in toluene (24 L), and this solution was cooled to 5 °C. The triflate solution from the previously mentioned was added over a period of 10 min. The reaction mixture was stirred at 17 °C overnight. The reaction was monitored by HPLC Method F: Waters Symmetry C18, 3.9 × 150 mm^2; wavelength = 240 nm; flow 1 mL/min; solvent A = ACN; solvent B = 0.1% TFA in water, 10:90 A/B 0−5 min, 5−25 min linear gradient to 50:50 and hold for 5 min, 30−35 min linear gradient to 100:0 and hold for 5 min (t_R **35** = 14.4 min; t_R **36** = 26.1 min). The insoluble material was removed by filtration through filter aid and washed with toluene (10 L). The filtrate was concentrated at 20 °C/30 Torr to give 6.6 kg (>100%) of **36**.

2-(3-Benzyloxy-2*S*-[4 fluorobenzo[*d*]isoxazol-3-yl]piperidin-1-yl)-propan-1-ol (37). A 1 M solution of $LiAlH_4$·2THF complex in toluene (40 L) was cooled to −2 °C, and a solution of **36** (6.6 kg) in toluene (8 L) was added over 2.5 h while the reaction temperature was kept between 0 and 5 °C. The mixture was warmed to 15 °C. After 2 h, the reaction was complete as shown by HPLC Method F: t_R **36** = 26.1 min; t_R **37** = 25.1 min. The reaction was cooled to 0 °C, and H_2O (2.8 L) was slowly added, followed by THF (20 L), and finally additional H_2O (2.8 L). The reaction mixture was stirred overnight at ambient temperature, and then 5 kg of Na_2SO_4 was added. After 1 h, the aluminum salts were removed by filtration through filter aid, and the filter cake washed with THF (20 L). The filtrate was concentrated to a residue at 30 °C/50 Torr to give 6.4 kg (93.5%) of **37** as an amber oil.

Potassium 4-Fluorophthalimide (38). Step 1: 4-Fluorophthalic anhydride (1.25 kg, 7.53 mol) and 3.75 L of formamide was charged to a 12-L flask. The stirred mixture was heated to and held at 120 °C for 150 min while the reaction was monitored by GC/MS [column HP-5 (30 m × 0.25 mm × 0.25 μm film); injector temperature 250 °C; temperature program was 50 °C for 1 min and then was heated to 300 °C at the rate of 20 °C/min; t_R 4-fluorophthalic anhydride = 6.7 min; t_R 4-fluorophthalimide = 8.1 min]. Upon completion, the reaction mixture was cooled to 115 °C and poured into 30 L of water. The resulting slurry was stirred for 1.5 h, and the solids were collected by filtration and washed with 3 × 1.5 L of water. The product was air-dried to give 1.01 kg (81%) of 4-fluorophthalimide: mp 178−179 °C. Anal. Calcd: C, 58.19; H, 2.44; N, 8.48. Found: C, 58.14; H, 2.59; N, 8.51.

Step 2: 4-Fluorophthalimide (967 g, 5.86 mol) and ethanol (15 L) were charged to a 22 L flask. The mixture was heated to 60 °C to achieve complete solution. A solution of 377 g of KOH (377 g, 7.92 mol) in water (406 mL) was added over 25 min. The resulting slurry was cooled and held at <10 °C for 1 h. Solids were collected by filtration and washed with 2 × 1 L of ethanol and then were dried at 40 °C/50 Torr to give 1.16 kg (98%) of **38**: Anal. Calcd: C, 47.28; H, 1.49; N, 6.89. Found: C, 47.16; H, 1.51; N, 6.84.

2-{3-Benzyloxy-2-(*S*)-[4-(6-fluorobenzo[*d*]isoxazol-3-yl)piperidin-1-yl]propyl}-5-fluoro-isoindole-1,3-dione Hydrochloride (39). To a solution of **37** (4.6 kg, 11.9 mol) in acetonitrile (36 L) cooled to 0 °C was added DIPEA (2.91 kg, 22.5 mol). Methanesulfonic anhydride (3.13 kg, 14.3 mol) dissolved in acetonitrile (5 L) was added over 70 min while the temperature was maintained between 0 and 3 °C. The formation of the mesylate was complete by TLC: silica gel; EtOAc; R_f **37** = 0.25; R_f of mesylate intermediate = 0.75. Potassium fluorophthalimide (2.0 kg, 9.8 mol) was added in one portion at 0 °C, and the reaction mixture was slowly warmed to 20 °C over 18 h. The reaction was complete as shown by HPLC Method F: t_R mesylate intermediate = 25.1 min; t_R **39** = 29.4 min. The reaction was concentrated to a residue at 30 °C/30 Torr and then partitioned between EtOAc

(50 L) and water (25 L). The EtOAc layer was washed with 10 L of brine, dried over $MgSO_4$ (2.0 kg), filtered, and concentrated to give 7.2 kg of **39** as the free base. This residue was dissolved in EtOAc (18 L), and 600 g of HCl in 6 kg of TBME was added. After 30 min, the resulting solid was collected by filtration and dried at 30 °C/50 Torr to give 4.05 kg (73%) of **39** as the hydrochloride salt.

2-{3-Benzyloxy-2-(*S*)-[4-(6-fluorobenzo[*d*]isoxazol-3-yl)piperidin-1-yl]propyl}-5-fluoro-isoindole (41). Phthalimide **39** as the hydrochloride salt (6.0 kg) was treated with CH_2Cl_2 (80 L) and saturated sodium bicarbonate (37 L). The organic phase was dried ($MgSO_4$) and concentrated to a residue. Compound **39** as the free base was dissolved into toluene (15 L). A 1.0 M solution of $LiAlH_4$·2THF complex in toluene (48 L) was cooled to −5 °C, and the toluene solution of **39** was added over 100 min while the reaction temperature was maintained between −5 and 5 °C. The mixture was warmed to 20 °C. After 1 h, the reaction was complete as shown by HPLC Method F: t_R **39** = 29.4 min; t_R **41** = 27.6 min. The reaction was cooled to −5 °C, and H_2O (3.6 L) was slowly added, followed by THF (24 L), and finally additional H_2O (3.6 L). After the mixture was stirred overnight at ambient temperature, Na_2SO_4 (6 kg) was added. After 1 h, the aluminum salts were removed by filtration through filter aid, and the filter cake was washed with THF (26 L). The combined filtrates were concentrated to a residue at 25 °C/30 Torr to give 5.6 kg (100%) of **41**.

3-(2,3-Dihydro-5-fluoro-1*H*-isoindol-2-yl)-2-(*S*)-[4-(6-fluoro-benzo[*d*]isoxazol-3-yl)piperidin-1yl]-propan-1-ol Dimaleate [HMR 2543 (3)]. A solution of **41** (5.6 kg, 11.1 mol) in CH_2Cl_2 (50 L) was cooled to −2 °C. To the mixture was added a solution of boron tribromide (7.6 kg, 30.4 mol) in CH_2Cl_2 (20 L) over 75 min while the temperature was kept below 5 °C. (Caution: SCBA equipment and full body protective clothing should be used when working with this solution. One should take every effort to avoid contact and inhalation.) The reaction was monitored by HPLC Method F: t_R **41** = 27.6 min; t_R **3** = 20.7 min. The reaction mixture was cooled to 5 °C, and MeOH (45 L) was added in a slow stream over a period of 3.5 h while the temperature was kept below 10 °C. The reaction mixture was concentrated at 25 °C/30 Torr. The resulting residue was stirred in THF (24 L) while 70 L TBME was added. The solid was collected by filtration using a Nutsche filter, washed with TBME (20 L), and dried on the filter under nitrogen to give 5.8 kg of HMR 2543 (**3**) as the dihydrobromide salt.

The salt was partitioned between CH_2Cl_2 (60 L) and saturated sodium bicarbonate in H_2O (40 L). The mixture was stirred, and 50% NaOH (300 mL) was added over a period of 1 h to bring the pH to 10.0. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 L). The combined organic extracts were dried over $MgSO_4$ (2 kg). The solvent was removed at 25 °C/50 Torr to give 4.3 kg of **3** as the free base. HMR 2543 (**3**) as the free base was dissolved in MeOH (80 L) and added to a solution of *p*-toluenesulfonic acid monohydrate (3.95 kg) in *i*-PrOH (13 L) at 55 °C. The methanol was removed by distillation, and 60 L of IPA was back added during the process to maintain a constant volume (the pot temperature remained at 74 °C). The solution was cooled to 0 °C and held at this temperature for 18 h. The resulting solids were collected by filtration, washed with IPA (10 L), and dried in a vacuum oven at ambient temperature to give 5.5 kg of HMR 2543 (**3**) as the ditosylate salt. The material was combined with a 3.7-kg batch and recrystallized using the previously mentioned procedure to give 5.8 kg (46%) of HMR 2543 (**3**) as the ditosylate salt.

HMR 2543 (**3**) ditosylate (5.8 kg) was treated with CH_2Cl_2 (60 L) and 1 M NaOH (40 L). The organic phase was dried (Na_2SO_4) and concentrated to give 2.98 kg of **3** as the free base. This free base was dissolved in 100 L of IPA. To this solution was added maleic acid (2.51 kg, 26.1 mol) and 150 g of BHT. The mixture was heated to 80 °C for 3 h and then slowly cooled to 22 °C over 4 h. The resulting solids were collected by filtration and washed with IPA (40 L) followed by THF (50 L) and TBME (50 L). ^{1}H NMR and HPLC analysis (Method F) showed the presence of *p*-TsOH, so the entire procedure was repeated. The final product was dried at 25 °C/30 Torr for 18 h, 40 °C/30 Torr for 18 h, 60 °C/30 Torr for 18 h, and finally 80 °C/30 Torr for 18 h to give 3.37 kg (67%) of HMR 2543 (**3**) as the dimaleate salt: ^{1}H NMR (d_6-DMSO) δ 8.03 (m, 1), 7.86 (m, 1), 7.60−7.07 (m, 4), 6.18 (s, 4), 4.24 (m, 4), 3.77−3.02 (m, 11), 2.08 (m, 4). Anal. Calcd for $C_{23}H_{25}F_2N_3O_2$·2 $C_4H_4O_4$: C, 57.67; H, 5.15; N, 6.51. Found: C, 57.67; H, 5.05; N, 6.38.

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Supporting Information Available

^{1}H NMR spectra of most compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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