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Process Development of the Synthetic Route to Sulamserod Hydrochloride

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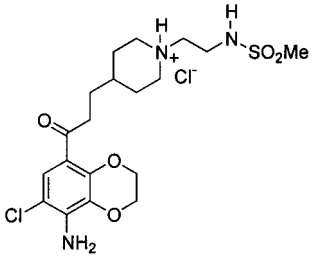
Abstract:

Sulamserod hydrochloride is a potent 5-HT_4 receptor antagonist and was a clinical candidate for the treatment of gastrointestinal disorders. Process development of the fairly long synthetic route (12 linear, 14 overall steps) was undertaken. Process improvements were highlighted by aromatic chlorination choices in making dichlorobenzodioxan 2 and acetylaminochloroketone 7, a transfer hydrogenation reducing a nitro group and simultaneous aromatic dechlorination without ketone reduction to give aminoketone 5, and use of the potential mutagenic iodosulfonamide 14 to make quaternary salt 11. The chemistry was scaled-up into pilot plant reactor vessels to produce multikilogram amounts of Sulamserod hydrochloride suitable for drug development.

Introduction

Sulamserod hydrochloride is a potent selective 5-HT_4 receptor antagonist. The pK_i for Sulamserod hydrochloride



Sulamserod hydrochloride

has been determined to be 9.9−10.7 in human, guinea pig, and rat tissues using in vitro radioligand binding assays.[1] It has been proposed that an antagonist for the 5-HT_4 receptor would be useful for the treatment of gastrointestinal disorders.[2,3] A program was launched with Sulamserod hydrochloride as the lead clinical candidate. The production of multikilogram lots of Sulamserod hydrochloride was required for the development needs from toxicology, formulation, the clinic, and pharmacology. To meet production requirements, process development of a synthesis resulting in a scalable synthetic route to Sulamserod hydrochloride was needed.

The synthetic route to Sulamserod hydrochloride is outlined in Schemes 1 and 2. The route was used by medicinal chemistry but had several shortcomings as a route for supplying bulk quantities of drug substance.[1] The route was very long (12 linear steps, 14 overall) and required many chromatographic purifications, and the chemistry at several steps needed major modifications. Despite these problems, this synthetic route was chosen and used in process development to supply drug substance. The reasons for this decision were lack of a significantly better alternative synthetic route, high potency of the drug (therefore, low projected demand for material), and belief that the existing route could be turned into a suitable process with adequate development time. We report the process development of the synthetic route to Sulamserod hydrochloride in this paper.

Results and Discussion

The dichlorination of benzodioxan **1** was investigated using the initial procedure of chlorine gas as the chlorination source.[1,4] The procedure was optimized to yield 72−76% of pure dichlorobenzodioxan **2** by using CH_2Cl_2 as the reaction solvent and a MeOH drown to force out product. The procedure worked well and could have been used in a pilot plant or plant environment, but there were several problems associated with using chlorine gas. Chlorine gas is a regulated toxic gas and in our pilot plant facilities required specialized detection equipment which would have necessitated additional cost and time. The amount of chlorine gas that we could have at any one time was also strictly limited. A procedure generating chlorine in situ by adding hydrogen peroxide to aqueous HCl did work but was plagued by producing colored dichlorobenzodioxan **2**.

The procedure used for dichlorination of **1** was based on *N*-chlorosuccinimide (NCS) as the chlorinating source. The process was optimized using HOAc as the reaction solvent and a water drown yielding 75% of pure dichlorobenzodioxan **2**. The reaction was run between 70 and 100 °C which consumed the NCS quickly, so that the reaction exotherm was easily controlled by the addition rate of the NCS. The water drown was optimized to a fairly narrow range because if there was too little water, succinimide crystallized out, and if there was too much water, other impurities were forced

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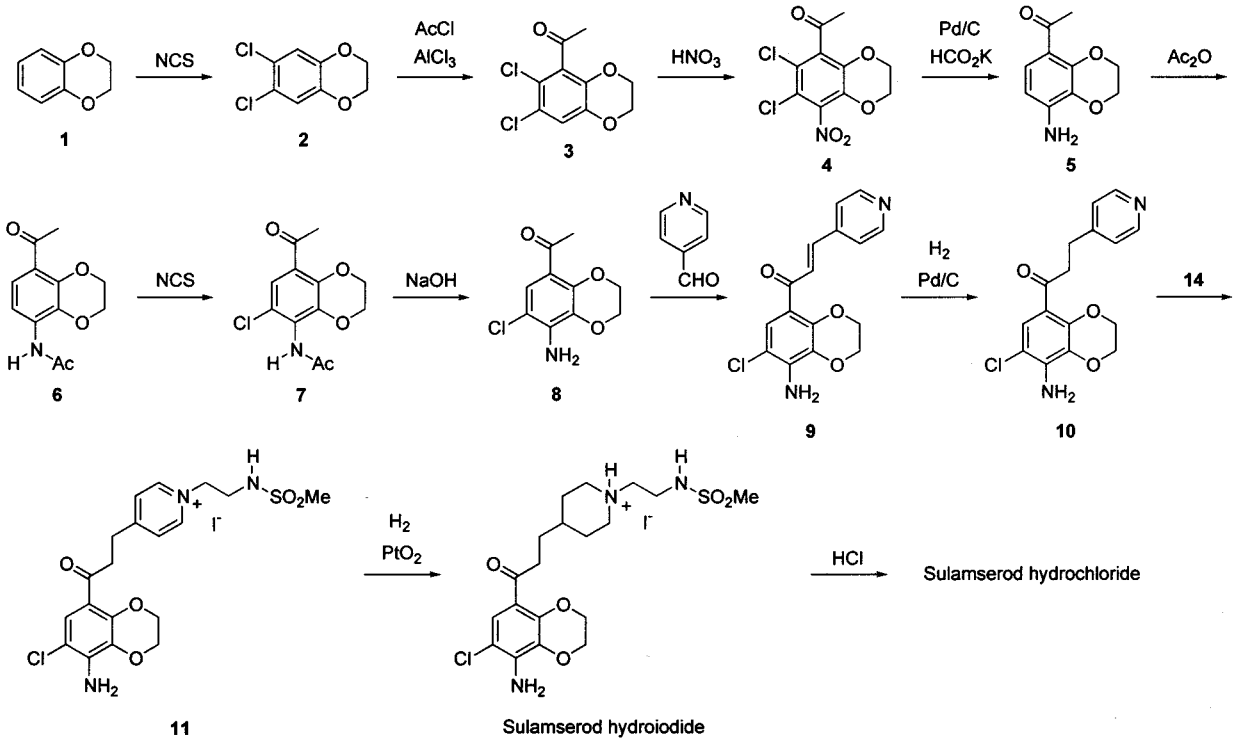
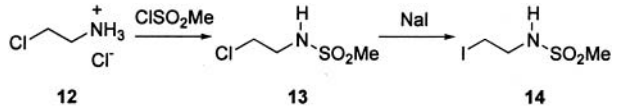
Scheme 1. **Synthetic route to Sulamserod hydrochloride**



Scheme 2. **Synthetic route to iodosulfonamide 14**

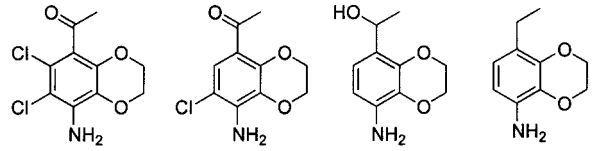


out. The NCS was added as a slurry in HOAc, avoiding difficult direct solids addition to the reaction vessel.

The process optimization of the conversion of dichlorobenzodioxan **2** to methyl ketone **3** focused on the order of the addition of reagents and the number of equivalents necessary for complete conversion in a reasonable time frame. It was convenient to charge the solid components first to the reaction vessel (dichlorobenzodioxan **2**, aluminum chloride) before sealing the porthole on the reaction vessel and then charging the liquid components (CH_2Cl_2, acetyl chloride). This avoided any difficult solids addition. The crystallization procedure used MeOH as the crystallization solvent and included a seeding during cool-down which ensured large, easily filtered crystals.

The safety analysis and process optimization of the nitration of methyl ketone **3** to nitroketone **4** took an enormous effort and has been reported previously.[5]

The reduction of nitroketone **4** was done in medicinal chemistry by reduction of the nitro functionality first by hydrogenation using Pd/C catalyst under neutral conditions with hydrogen gas followed by dechlorination either as a separate step or in the same pot by base addition. The streamlining of the process by carrying out both the nitro reduction and the dechlorination in the same reaction vessel was very attractive but was plagued by several shortcomings. The dechlorination was susceptible to stalling before completion, and desired aminoketone **5** was contaminated by various amounts of under-reduced and over-reduced impurities **15**−**18**. The process was most significantly improved



by eliminating hydrogen gas and switching to a transfer hydrogenation.[6] The source of the hydrogen was chosen as potassium formate because it produced KOH needed in the neutralization of HCl produced from the dechlorination, and unlike ammonium formate does not produce a sublimate which tends to clog condenser units. By switching to the transfer hydrogenation, the hydrogenation could be run to completion, eliminating the under-reduced by-products, and remarkably not causing over-reduction of the ketone functionality. Typically, the transfer hydrogenation in the pilot plant did stall out near completion but was easily finished off by addition of a small charge of additional catalyst. THF was added during the work-up to help fully solubilize aminoketone **5** and force out inorganic salts before filtration.

The direct chlorination of aminoketone **5** would have been an expedient route to aminochloroketone **8**, but under all conditions attempted, it produced unacceptably impure product. The acetylation of aminoketone **5** was essential for clean introduction of the chloro group. The initial procedure

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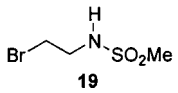
of two separate steps for the conversion of aminoketone **5** to acetylaminochloroketone **7** was replaced with a process that in one pot did the same conversion. The one-pot process used HOAc as the solvent and acetic anhydride for acetylation followed by NCS as the chlorinating agent.

The conversion of acetylaminochloroketone **7** to enone **9** was best done in one pot but as two separate steps. The all-at-once approach did not work nearly as well. The inefficiency of having to put on the acetyl group on the amino functionality for clean chlorine introduction was of little overall consequence, because it was put on and taken off in the same reaction vessel as that for other steps, causing little additional labor costs.

The optimization of the hydrogenation of enone **9** to pyridine **10** was straightforward. The best solvent for the hydrogenation was found to be THF. THF provided good solubility compared to other typical hydrogenation solvents, thus, keeping the reaction volume at a reasonable level.

The medicinal chemistry effort used bromosulfonamide **19** for the conversion of pyridine **10** to quaternary salt **11**, because it was accessible in one step from 2-bromoethylamine. Upon process optimization, it was found that iodosulfonamide **14** was superior to bromosulfonamide **19**, because the reaction time between pyridine **10** and iodosulfonamide **14** was shorter and produced purer quaternary salt **11**. The additional step required to make iodosulfonamide **14** compared to bromosulfonamide **19** was not in the long



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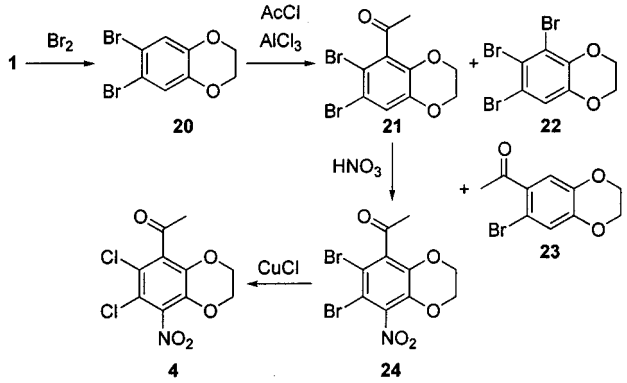
linear route to make Sulamserod hydrochloride, and therefore, was not a serious cost concern. Early in the process development effort, iodosulfonamide **14** was recognized as a potential mutagen; thus, an Ames assay was conducted. Iodosulfonamide **14** did prove mutagenic in the Ames salmonella gene mutation assay. A decision was made to outsource production of iodosulfonamide **14** to a group better able to handle containment issues during manufacturing of this material in reactor vessels. To expedite the outsourcing of iodosulfonamide **14**, the process development work was done in-house, and only the manufacturing was outsourced.

The process optimization of the conversion of quaternary salt **11** to Sulamserod hydroiodide focused on solvent and catalyst choice. The catalyst initially used was PtO_2 and could not be replaced with anything less expensive despite significant experimentation. The complete solubility of quaternary salt **11** was determined not to be a critical factor for the hydrogenation to proceed. The solvent for hydrogenation was optimized to maximize the solubility of Sulamserod hydroiodide produced; thus, upon completion the reaction solution could be filtered to remove only the catalyst. One interesting finding was the hydrogenation could be done in DMF, but the catalyst was very difficult to filter off. An extractive work-up procedure converted Sulamserod hydroiodide to Sulamserod free base. Sulamserod free base was converted to Sulamserod hydrochloride in ethanol with HCl, consistently producing the only known anhydrous polymorph.

Scheme 3. **Attempted aromatic chlorine introduction**



The manufactured Sulamserod hydrochloride was closely examined at a quantification limit of 1 ppm for the presence of the potential mutagen iodosulfonamide **14** and none was found.

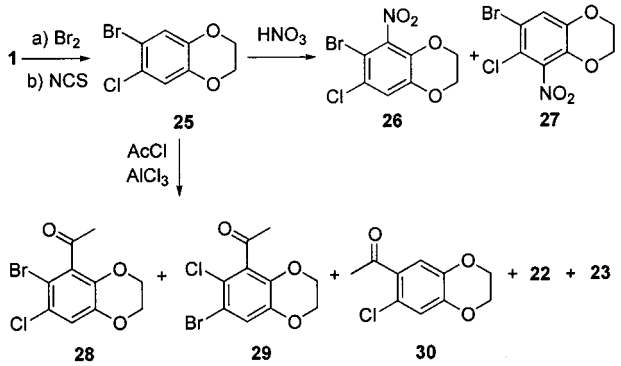
During process development several general strategies were used. The isolation of many intermediates, which is labor intensive, was deemed worthwhile. The loss of a single campaign would have meant a serious delay in the program. Therefore, the close analysis of many intermediates provided quick feedback on how the synthesis was progressing and left the opportunity for additional purifications before a serious contaminant threatened a batch. Solids addition to a reaction was avoided throughout process development. The difficulty and safety issues associated with solids addition was of too great a concern. A general strategy of running a reaction followed by addition of an antisolvent and temperature control to crystallize out intermediates was used repeatedly throughout the synthesis. This strategy simplified work-ups and made isolation by filtration convenient. The annual demand for Sulamserod hydrochloride was not expected to be more than 5 metric tons per year due to low clinical dose (1−2.5 mg, q.d.). The low demand made a relatively long synthetic route to Sulamserod hydrochloride viable as the long-term route with expected improvements coming from additional process development in manufacturing.

Attempted Alternative Aromatic Chlorine Introduction

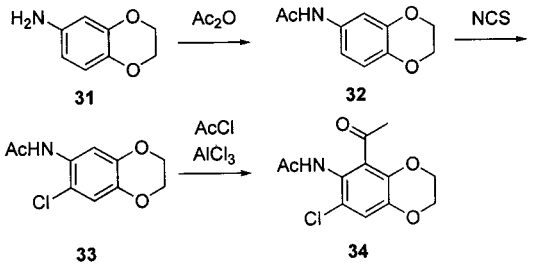
The development of a shorter route to Sulamserod hydrochloride was desired. One strategy that was particularly attractive was an alternate selective introduction of the aromatic chlorine of Sulamserod. Three different routes for the selective introduction of the aromatic chlorine of Sulamserod were tried, see Schemes 3−5.

With the introduction of bromine into the 6- and 7-positions of benzodioxan **1**, it was planned to displace one bromine with a chlorine atom selectively at the correct position for Sulamserod, and reduce the other bromine, see Scheme 3. The bromination of benzodioxan **1** proceeded well, but the acetylation of dibromobenzodioxan **20** produced desired **21** along with major "halogen dance" by-products **22** and **23**. The nitration of **21** was fine. Unfortunately, the attempted selective displacement of one bromine atom from dibromide **24** only yielded dichloride **4**.

Scheme 4. **Second attempted aromatic chlorine introduction**



Scheme 5. **Third attempted aromatic chlorine introduction**



Trying to circumvent the problem of selective displacement of one bromine from dibromide **24**, a route incorporating a chlorine and bromine initially was attempted, see Scheme 4. The bromination and chlorination of benzodioxan **1** yielded bromochlorobenzodioxan **25**. Unfortunately, the nitration of bromochlorobenzodioxan **25** was unselective, yielding both nitro compounds **26** and **27**. The acetylation of bromochlorobenzodioxan **25** gave an unacceptable mixture of **22**, **23**, **28**−**30**.

A third approach to selective introduction of the aromatic chlorine of Sulamserod planned to use the amino functionality of aniline **31** to direct introduction of the other groups onto the aromatic ring and eventually reduce off the amino functionality, see Scheme 5. From commercially available aniline **31** acetylation and chlorination yielded desired **33**. However, the introduction of the methyl ketone functionality proved troublesome, requiring large excess acetyl chloride and aluminum chloride. Methyl ketone **34** produced was also unacceptably impure.

Summary

The synthetic route to Sulamserod hydrochloride underwent process development to yield a route which produced multikilogram amounts of drug and was capable of transitioning to a manufacturing environment. The chief process improvements included eliminating all chromatographic purifications, developing reactor friendly processes, and improving the chemistry at all steps to give a reliable and scalable process.

Experimental Section

General Procedures. All materials were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen unless noted otherwise. All reactors were glass-lined steel vessels. ^{1}H NMR spectroscopy was performed at 300 MHz and ^{13}C NMR at 75 MHz. Reactions were monitored for completion by removing a small sample from the reaction mixture and analyzing the sample by TLC and HPLC.

6,7-Dichloro-2,3-dihydro-1,4-benzodioxin (2). In a 30-gal reactor was created a slurry of *N*-chlorosuccinimide (53.25 kg, 399 mol) in acetic acid (63.6 kg). Into a 50-gal reactor, the *N*-chlorosuccinimide slurry was added over 2 h to 2,3-dihydro-1,4-benzodioxin (**1**) (24.95 kg, 183 mol), keeping the temperature between 70 and 100 °C. A rinse of the slurry reactor and lines into the reaction with acetic acid (2 × 10 kg) was done. After complete addition, the reaction was aged 30 min at 90−100 °C. To the reaction mixture was added water (15.7 kg). The mixture was cooled to 20 °C and aged overnight. The resulting crystals were filtered off, washed with methanol (17.8 kg) and water (13 kg), and dried at 60−65 °C to give **2** (28.11 kg, 75%) as a white solid: mp 151.2−151.6 °C; ^{1}H NMR ($CDCl_3$) δ 4.24 (s, 4), 6.96 (s, 2); ^{13}C NMR ($CDCl_3$) δ 64.24 (CH_2), 118.50 (CH), 123.97 (C), 142.78 (C). Anal. Calcd for $C_8H_6Cl_2O_2$: C, 46.86; H, 2.95. Found: C, 46.82; H, 2.91.

5-Acetyl-6,7-dichloro-2,3-dihydro-1,4-benzodioxin (3). Into a 100-gal reactor was charged aluminum chloride (29.2 kg, 219 mol), **2** (27.86 kg, 135.9 mol), and dichloromethane (207 kg) followed by acetyl chloride (16.2 kg, 206 mol). The mixture was stirred at 18−24 °C for 18 h. The reaction mixture was added to cooled water (187 kg) in a 100-gal reactor, keeping the temperature between 1 and 25 °C. The resulting mixture was stirred at 20−25 °C for 1 h and then allowed to settle, and the two layers were separated. The organic phase was washed with 2 N HCl (99 kg), aqueous sodium bicarbonate (50 kg), and water (99 kg). In a 50-gal reactor, the organic phase was concentrated by distillation, removing most of the dichloromethane. The concentrate was dissolved in methanol (131 kg), and a portion of the solvent was distilled out (108 kg). The solution was cooled to 45 °C and seeded with authentic product (100 mg) which immediately initiated crystallization. The crystallization mixture was further cooled to 20−25 °C and aged overnight. Water (67 kg) was added to the crystallized solution, and the mixture was further cooled to 10−15 °C for 1 h. The mixture was filtered, and the cake was washed with methanol/water (10 kg/15 kg) and dried in a forced air oven at 40−50 °C to give **3** (32.86 kg, 98%) as a white solid: mp 89.5−90.1 °C; ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3), 4.27 (s, 4), 7.00 (s, 1); ^{13}C NMR ($CDCl_3$) δ 31.59 (CH_3), 64.16 (CH_2), 64.48 (CH_2), 118.75 (CH), 119.18 (C), 124.95 (C), 131.46 (C), 139.25 (C), 142.86 (C), 199.46 (C). Anal. Calcd for $C_{10}H_8Cl_2O_3$: C, 48.61; H, 3.26. Found: C, 48.52; H, 3.26.

5-Acetyl-6,7-dichloro-8-nitro-2,3-dihydro-1,4-benzodioxin (4). See ref 5.

5-Acetyl-8-amino-2,3-dihydro-1,4-benzodioxin (5). Into a 100-gal reactor was charged potassium formate (77.7 kg, 924 mol) and water (81 kg), creating a solution. To the solution was added methanol (51 kg). Into a 200-gal reactor was charged 10% palladium on carbon (11.6 kg, 50% water

wet), **4** (30.85 kg, 105.6 mol), water (31 kg), and methanol (226 kg). The mixture in the 200-gal reactor was brought to gentle reflux, and the contents of the 100-gal reactor were added over 2 h. Care was taken to avoid any ingress of air, and generated CO_2 was allowed to rapidly escape. After 25 h at reflux an additional charge of 10% palladium on carbon (0.5 kg) slurried in methanol (7.9 kg) was added to the reaction. After 43 h at reflux, solvent (183 kg) was distilled out of the reaction mixture. The mixture was cooled to 30−35 °C, and tetrahydrofuran (165 kg) was added. The solution (30−35 °C) was filtered through a bed of Celite (5 kg) packed into a filter. The cake was washed with 40−45 °C tetrahydrofuran (2 × 54 kg). In a 100-gal reactor, the filtrate was concentrated under vacuum until the volume of solution had been reduced to approximately 90 L, and crystallization of product had begun. To the mixture was added water (79 kg). The solution was cooled to 20−25 °C and aged for 1 h. The crystals were collected by filtration, washed with water (2 × 21 kg), and dried using a flow of N_2. Into a 100-gal reactor was charged the crude product and toluene (181 kg). The mixture was brought to reflux and concentrated by distillation (100 kg distillate). The solution was cooled to 5−10 °C and aged overnight. The crystals were filtered off and washed with hexanes (2 × 22 kg) to give **5** (18.24 kg, 89%) as an off white solid: mp 142.7−143.7 °C; ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3), 4.30−4.38 (m, 4), 6.30 (d, 1, J = 8.6), 7.36 (d, 1, J = 8.6); ^{13}C NMR ($CDCl_3$) δ 31.36 (CH_3), 63.73 (CH_2), 64.43 (CH_2), 106.75 (CH), 118.05 (C), 123.97 (CH), 130.06 (C), 141.05 (C), 144.83 (C), 196.66 (C). Anal. Calcd for $C_{10}H_{11}NO_3$: C,62.17; H, 5.74; N, 7.25. Found: C, 62.38; H, 5.71; N, 7.40.

5-Acetyl-8-acetylamino-7-chloro-2,3-dihydro-1,4-benzodioxin (7). Into a 50-gal reactor was charged **5** (17.9 kg, 92.6 mol) and acetic acid (140 kg) followed by acetic anhydride (10.6 kg, 104 mol). After 18 h, to the reaction mixture was added to *N*-chlorosuccinimide (15.1 kg, 113 mol) slurried in acetic acid (46 kg). The mixture was warmed to 50 °C. After 4 h, the solution was concentrated by vacuum distillation to a volume of 55 L. To the solution was added methanol (19.2 kg). The mixture was brought to reflux and then cooled to 35 °C which initiated crystallization. To the crystallization mixture was added water (301 kg). The mixture was aged at 20 °C for overnight. The crystals were filtered off, washed with water (2 × 71 kg), and dried in a N_2/vacuum oven at 50 °C to give **7** (22.06 kg, 88%) as a white solid, analytic sample crystallized from toluene: mp 185.3−186.8 °C; ^{1}H NMR ($CDCl_3$) δ 2.18 (s (br), 3), 2.57 (s, 3), 4.32−4.39 (m, 4), 7.03 (s (br), 1), 7.38 (s, 1); ^{13}C NMR δ 23.0 (CH_3, br), 31.61 (CH_3), 63.89 (CH_2), 64.08 (CH_2), 121.69 (CH), 123.49 (C), 126.58 (C), 126.84 (C), 140.54 (C), 142.93 (C), 168.6 (C, br), 196.77 (C). Anal. Calcd for $C_{12}H_{12}NClO_4$: C, 53.44; H, 4.48; N, 5.19. Found: C, 53.15; H, 4.41; N, 5.28.

8-Acetyl-7-chloro-5-(3-pyridin-4-yl-1-oxoprop-2,3-en-1-yl)-2,3-dihydro-1,4-benzodioxin (9). Into a 200-gal reactor was charged **7** (21.5 kg, 79.7 mol), methanol (170 kg), water (57 kg), and 45% potassium hydroxide (37.6 kg, 302 mol). The solution was refluxed for 4.5 h. The mixture was cooled to 20 °C, and 4-pyridinecarboxaldehyde (9.57 kg, 89.3 mol) and methanol (12 kg) were added. After 18 h, to the solution was added water (172 kg). The mixture was cooled for 3 h at 5−10 °C. The crystals were filtered off, washed with water (91 and 59 kg), and dried in a N_2/vacuum oven at 50 °C to give **9** (20.27 kg, 80%) as a bright orange solid: mp 207.5−208.4 °C; ^{1}H NMR (DMSO-d_6) δ 4.34−4.43 (m, 4), 5.90 (s (br), 2), 7.35 (s, 1), 7.51 (d, 1, J = 15.8), 7.68 (d (br), 2, J = 4.5), 7.86 (d, 1, J = 15.8), 8.64 (d (br), 2, J = 4.5); ^{13}C NMR (DMSO-d_6) δ 66.34 (CH_2), 67.04 (CH_2), 112.03 (C), 118.52 (C), 124.82 (CH), 125.70 (CH), 132.57 (C), 133.60 (CH), 140.56 (CH), 142.18 (C), 144.91 (C), 145.77 (C), 153.00 (CH), 188.53 (C). Anal. Calcd for $C_{16}H_{13}N_2ClO_3 \cdot$ 0.15 mol H_2O: C, 60.16; H, 4.20; N, 8.77. Found: C, 60.10; H, 4.11; N, 8.75.

8-Acetyl-7-chloro-5-(3-pyridin-4-yl-1-oxoprop-1-yl)-2,3-dihydro-1,4-benzodioxin (10). Into a 200-gal reactor was charged **9** (19.7 kg, 62.2 mol), 10% palladium on carbon (2.5 kg, 50% water wet), and tetrahydrofuran (331 kg). The mixture was stirred under a hydrogen atmosphere for 3 h. The reaction mixture was filtered through a bed of Celite (3 kg), and the cake was washed with tetrahydrofuran (2 × 39 kg). In a 100-gal reactor the filtrate was concentrated by vacuum distillation to a volume of 20 L. To the concentrate was added 2-propanol (155 kg). The solution was concentrated by distillation (78 kg removed). The solution was cooled to 20 °C, aged overnight, and cooled to 5−10 °C for 2 h. The crystals were filtered off, washed with 2-propanol (30 kg) and dried in a N_2/vacuum oven at 50 °C to give **10** (16.01 kg, 81%) as a white solid: mp 152.1−153.5 °C; ^{1}H NMR (DMSO-d_6) δ 2.88 (t, 2, J = 7.4), 3.20 (t, 2, J = 7.4), 4.31−4.36 (m, 4), 5.76 (s (br), 2), 7.26 (d (br), 2, J = 4.5), 7.28 (s, 1), 8.44 (d (br), 2, J = 4.5); ^{13}C NMR (DMSO-d_6) δ 29.05 (CH_2), 42.94 (CH_2), 63.46 (CH_2), 64.16 (CH_2), 109.14 (C), 114.88 (C), 122.12 (CH), 123.87 (CH), 129.76 (C), 139.02 (C), 143.11 (C), 149.31 (CH), 150.61 (C), 194.88 (C). Anal. Calcd for $C_{16}H_{15}N_2ClO_3$: C, 60.29; H, 4.74; N, 8.79. Found: C, 60.22; H, 4.71; N, 8.76.

4-[3-(8-Amino-7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)-3-oxopropyl]-1-(1-methanesulfonylaminoeth-2-yl)-pyridinium Iodide (11). Into a 50-gal reactor was charged **10** (4.0 kg, 12.5 mol), **14** (5.3 kg, 21.3 mol), and acetonitrile (19 kg). The mixture was refluxed for 6 h. To the solution was added 2-propanol (48 kg). The solution was cooled to 25 °C, aged overnight, and cooled to 5−10 °C for 2 h. The crystals were filtered off, washed with 2-propanol (8 kg), and dried in a N_2/vacuum oven at 50 °C to give **11** (6.03 kg, 85%) as a white solid: mp 122.0−124.9 °C; ^{1}H NMR (DMSO-d_6) δ 2.91 (s, 3), 3.18 (t, 2, J = 6.9), 3.39 (t, 2, J = 6.9), 3.53−3.57 (m, 2), 4.33−4.37 (m, 4), 4.62 (t, 2, J = 5.3), 5.80 (s (br), 2), 7.29 (s, 1), 7.35 (t, 1, J = 6.0), 8.09 (d, 2, J = 6.6), 8.86 (d, 2, J = 6.6); ^{13}C NMR (DMSO-d_6) δ 25.48 (CH_3), 29.70 (CH_2), 41.86 (CH_2), 42.63 (CH_2), 59.89 (CH_2), 63.57 (CH_2), 64.34 (CH_2), 109.24 (C), 114.51 (C), 122.27 (CH), 127.48 (CH), 129.81 (C), 139.32 (C), 143.37 (C), 144.29 (CH), 162.84 (C), 194.07 (C). Anal. Calcd for $C_{19}H_{23}N_3ClIO_5S$: C, 40.19; H, 4.08; N, 7.40. Found: C, 40.24; H, 4.06; N, 7.47.

Sulamserod hydrochloride. In a 100-gal reactor **11** (6.0 kg, 10.6 mol), platinum oxide (792 g), water (30 kg), and methanol (48 kg) were stirred at 45−50 °C under a hydrogen atmosphere for 18 h. The warm reaction mixture was filtered through a filter coated with Celite (0.6 kg), and the cake was washed with 55−65 °C methanol/water (2 × 24/12 kg). The filtrate was concentrated in a 100-gal reactor by vacuum distillation to a volume of 60 L. The concentrate was cooled to 10 °C. To the concentrate was added 50% NaOH (1.0 kg), water (3 kg), and tetrahydrofuran (21 kg). The mixture was extracted three times with ethyl acetate (60 kg, 41 kg, 41 kg). The organic extracts were combined, washed with aqueous NaCl (50 kg), dried over sodium sulfate (20 kg), filtered, and concentrated in a 50-gal reactor by distillation to a volume of 13 L. To the concentrate was added ethanol (43 kg). The solution was warmed to 70 °C. To the solution was added concentrated hydrochloric acid (1.175 kg). The solution was cooled to 20 °C, aged overnight, and further cooled to 5 °C for 2 h. The crystals were filtered off, washed with ethanol (14 kg), and dried in a N_2/vacuum oven at 50 °C to give Sulamserod hydrochloride (4.5 kg, 88%) as a white solid: mp 198.9−199.9 °C; ^{1}H NMR (DMSO-d_6) δ 1.48−1.70 (m, 5), 1.80−1.84 (m, 2), 2.83−2.95 (m, 4), 2.98 (s, 3), 3.13−3.25 (m, 3), 3.40−3.52 (m, 3), 4.33−4.37 (m, 4), 5.72 (s (br), 2), 7.25 (s, 1), 7.52 (t, 1, J = 5.8), 10.59 (s (br), 1); ^{13}C NMR (DMSO-d_6) δ 28.61 (CH_2), 30.10 (CH_2), 32.55 (CH), 37.04 (CH_2), 38.95 (CH_3), 52.04 (CH_2), 55.55 (CH_2), 63.57 (CH_2), 64.21 (CH_2), 109.16 (C), 115.31 (C), 122.18 (CH), 129.89 (C), 138. 89 (C), 142.99 (C), 196.47 (C). Anal. Calcd for $C_{19}H_{29}N_3Cl_2O_5S$: C, 47.30; H, 6.06; N, 8.71. Found: C, 47.20; H, 6.01; N, 8.73.

***N*-(2-iodoethyl)methanesulfonamide (14).** Into a 22-L flask was placed 2-chloroethylamine hydrochloride (1.0 kg, 8.6 mol) and methylene chloride (8 L). To the solution was added *N*-methylmorpholine (1.82 kg, 18.0 mol), while maintaining the temperature between 0 and 15 °C. Methanesulfonyl chloride (1.1 kg, 10.2 mol) was added to the reaction mixture, maintaining the temperature between −25 and 20 °C. After 1.5 h, the mixture was washed with water (0.5 L), 2 N HCl (0.5 L), and water (0.5 L). The organic layer was dried over sodium sulfate, filtered, and concentrated to yield crude *N*-(2-chloroethyl)methanesulfonamide (1.24 kg, 92%) which was used without further purification. Into a 22-L flask was placed *N*-(2-chloroethyl)methanesulfonamide (1.20 kg, 7.6 mol), methyl ethyl ketone (8.0 L), and sodium iodide (2.0 kg, 13.3 mol). The mixture was refluxed for 2 h. The solution was cooled to 50−55 °C, filtered, and concentrated. The residue was dissolved in ethyl acetate (4.0 L)/hexane (1.0 L) and washed with water (0.6 L), sodium thiosulfate (0.1 kg)/water (0.5 L), and brine (0.5 L). The organic layer was dried over sodium sulfate, filtered, and concentrated to a solid. The residue was slurried in hexane, filtered, and dried to give **14** (1.61 kg, 85%) as a white solid: mp 70.9−72.2 °C; ^{1}H NMR ($CDCl_3$) δ 3.03 (s, 3), 3.31 (t, 2, J = 6.5), 3.50 (dt, 2, J = 6.5, 6.5), 5.03 (s (br), 1); ^{13}C NMR ($CDCl_3$) δ 4.59 (CH_2), 41.25 (CH_3), 45.30 (CH_2); ms m/z (M^+) 249. Anal. Calcd for $C_3H_8NIO_2S$: C, 14.47; H, 3.24; N, 5.62. Found: C, 14.51; H, 3.26; N, 5.57. **Caution:** This material was mutagenic in the Ames salmonella gene mutation assay in several tester strains. LD_{50} (oral-rat): 354 mg/kg.

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