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Process Development of 5-Fluoro-3-[3-[4-(5-methoxy-4-pyrimidinyl)-1-piperazinyl]propyl]-1*H*-indole Dihydrochloride

Neal G. Anderson,*[,†,▽] Thomas D. Ary,[†] James L. Berg,[†] Peter J. Bernot,[†] Yeung Y. Chan,[†] Chien-Kuang Chen,[†] Merrill L. Davies,[†] John D. DiMarco,[‡] Ronald D. Dennis,[†] Rajan P. Deshpande,[†] Hoang D. Do,[†,§] Roberto Droghini,[||] William A. Early,[†] Jack Z. Gougoutas,[‡] John A. Grosso,*[,†] John C. Harris,[†] Oscar W. Haas,[†] Paul A. Jass,[†] Daniel H. Kim,[†] Gus A. Kodersha,[†] Atul S. Kotnis,[†] Jean LaJeunesse,[||] David A. Lust,[†] Gary D. Madding,[†] Sandeep P. Modi,[†] Jerome L. Moniot,[†] Andrew Nguyen,[†] Venkatapuram Palaniswamy,[†] Douglas W. Phillipson,[†] James H. Simpson,[†] Dominique Thoraval,[||] David A. Thurston,[†] Kai Tse,[†] Robert E. Polomski,[†] Donald L. Wedding,[†] and William J. Winter[†]

Department of Chemical Process Development, Pharmaceutical Research Institute, Bristol-Myers Squibb Co., P.O. Box 191, New Brunswick, New Jersey 08903-0191, Department of Solid State Chemistry, Pharmaceutical Research Institute, Bristol-Myers Squibb Co., P.O. Box 4000, Princeton, New Jersey 08543-4000, and Chemical Process Research, Bristol-Myers Squibb Co., 100 Boulevard de l'Industrie, Candiac, Quebec, J5R 1J1 Canada

Abstract:

5-Fluoro-3-[3-[4-(5-methoxy-4-pyrimidinyl)-1-piperazinyl]-propyl]-1*H*-indole dihydrochloride (1) facilitates 5-HT neurotransmission and was an antidepressant drug candidate. The development of a safe, rugged process for the large-scale, chromatography-free preparation of this compound is described. The main areas of optimization included a Fischer indole synthesis, preparation and chlorination of a monohydroxypyrimidine, and coupling of the resultant fragments to prepare the drug substance.

Introduction

5-Fluoro-3-[3-[4-(5-methoxy-4-pyrimidinyl)-1-piperazinyl]-propyl]-1*H*-indole dihydrochloride (**1**) interacts strongly with seratonergic 5-HT_{1D} and 5-HT_{1A} receptors and is a potent transport inhibitor of 5-HT.[1] On the basis of the combined influence of these receptor interactions, it was hoped that **1** would be a robust and rapid-onset agent for the treatment of clinical depression. This paper describes the development of chemical processes for the preparation of the title compound for use in toxicology, formulation development, and phase-I and phase-II clinical trials. As chemical process development is an iterative activity with aims to optimize the safety, quality, and productivity of chemical processes, this document follows that stepwise thread in describing development of the process. The retrosynthetic analysis is shown in Figure 1.

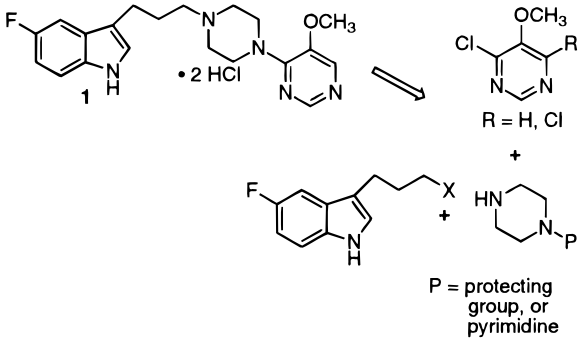

Figure 1. **Structure of 1 and retrosynthetic analysis.**

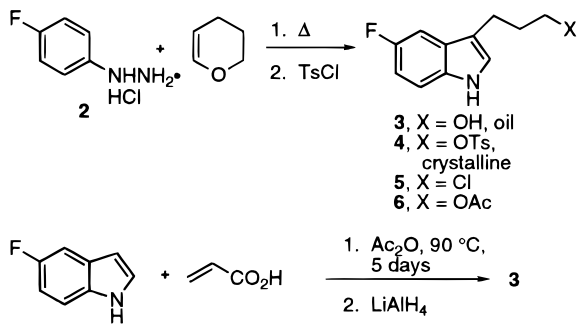

Figure 2. **Preparation of tosylate 4 from 2 or 5-fluoroindole.**

Results and Discussion

Preparation of Tosylate 4. Three different processes for **1** were developed during the course of this project. An intermediate common to all routes was the 5-fluoroindolyl tosylate **4** (Figure 2). This crystalline compound was selected for development over other noncrystalline intermediates, e.g., the alcohol, chloride, bromide, and mesylate. An early assembly of **4** involved the addition of acrylic acid to 5-fluoroindole;[2] however, the 5-day reaction time made this approach unattractive for scale-up operations. Since (4-fluorophenyl)hydrazine hydrochloride (**2**) was more readily available than 5-fluoroindole, we turned our efforts to the preparation of **4** via the Fischer indole synthesis.[3]

[†] Department of Chemical Process Development.

[‡] Department of Solid State Chemistry.

[§] Current address: Proctor & Gamble Pharmaceuticals, Cincinnati, OH 45241.

[||] Chemical Process Research.

[▽] Current address: Neal G. Anderson, Process Development Consultant, 129 Upper Creek Rd., Stockton, NJ 08559.

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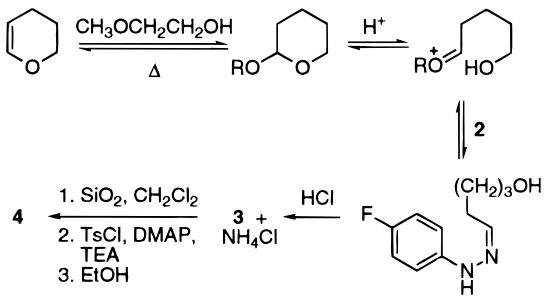

Figure 3. **Original preparation of 4 on scale.**

An exhaustive literature search revealed only patent references to the preparation of 5-halohomotryptophols,[4,5] and relatively few 5-haloindoles are referenced by Robinson.[3] In the first pilot-plant campaign the Fischer indolization was conducted with dihydropyran (DHP), in an adaptation of the procedure of Grandberg.[6] Probably DHP is opened with solvent and reacts with **2**. After indolization was complete, dichloromethane was added and methoxyethanol was removed by extraction into water. The rich organic phase was slurried with silica gel, absorbing some impurities, and the filtrate was subjected to tosylation. Intermediate **4** was crystallized by dissolution in warm ethanol (Figure 3).

On a 10-kg scale, yields of **4** from the first campaign were 42−50%, and subsequent laboratory indolizations−tosylations gave erratic yields. Issues targeted for further development were eliminating the use of 2-methoxyethanol (the biological exposure limit is a time weighted average (TWA) of 5 ppm over 8 h), dichloromethane, and silica gel. We reexamined the preparation of **4**.

The major impurity formed during the indolization was isolated by preparative chromatography and identified as the triol **7**. A trace of the pyrazole(s) **10** was also present. The tritosylate **8** was similarly identified from the mother liquor of **4**. Three other compounds were prepared as potential impurities, but none of these compounds were detected by HPLC analysis in the indolization streams (Figure 4).

The grade of silica gel was identified as responsible for variable laboratory yields by the original process. Flash chromatography grade silica gel reduced the level of the triol impurity **7** from 4.5 area % to 1.5 area %, while bulk silica gel from another supplier was ineffective. When streams of **3** containing **7** were carried on to the tosylation, yields of isolated **4** suffered, apparently because the tritosylate **8** inhibited the crystallization of **4**. On the basis of moisture content (loss on drying at 150 °C/4 h) the flash chromatography grade silica gel was less active (Table 1). Since impurity **7** is neutral, pore radius is perhaps the key criterion for absorption of **7**, with the larger pore size of the flash chromatography grade silica gel allowing the triol **7** to

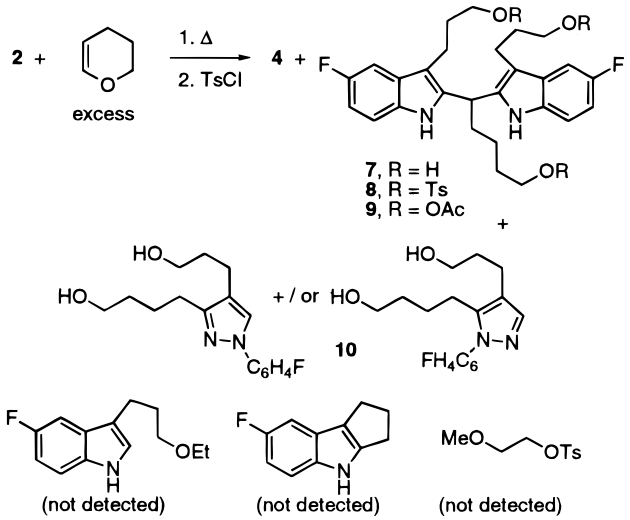

Figure 4. **Impurities in the preparation of 4.**

Table 1. **Comparison of silica gel characteristics**

assay	flash-chromatography silica	silica purchased for scale-up
mesh size	230−400	70−230
pH of aqueous suspension	6.5	3.0
moisture content, %	6.2	3
surface area, m^2/g	460	600
mean particle size, μm	50	150
scanning electron microscopy	planar surfaces	heterogeneous, regularly sized
average pore radius, Å	34	12

penetrate and be absorbed from the reaction mixture. Although the cause of enhanced absorptivity in the one grade of silica gel was not unequivocally identified, the use of a particular grade of silica gel should be evaluated on a case-by-case basis.

In order to optimize the yield of **4** (and eliminate the need for SiO_2 treatment) we needed to minimize the formation of **7** and **10**, which were formed from a localized excess of DHP. Complete consumption of DHP by **2** prior to indolization would preclude formation of the triol. In absolute EtOH at room temperature, considerable DHP was consumed after 1 h (GC analysis), but the conversion produced a large amount of the triol. When **2** was only partly soluble in the solvent(s) chosen, e.g., in MeOH, aqueous MeOH, aqueous EtOH, propylene glycol, 2,2,2-trifluoroethanol, or 2,2,2-trichloroethanol, reactions led to levels of triol **7** as high as 17%. Dissolution of **2** was effected by adding Et_3N to a suspension in EtOH, but no appreciable formation of **3** was found after several hours at reflux. Reaction in pyridine[7] led to the formation of a new impurity. Reaction in acetic acid or $AcOH/Ac_2O$ produced not only the alcohol **3** but also the acetate **6** and what was later identified as the triacetate **9** of the triol **7**. These approaches were discarded in favor of an optimized preparation of **4**.

The optimal solvent combination for the indolization of DHP and **2** was water and propylene glycol, available in food-grade quality. DHP was added to a solution of **2** (1

(4) Use of (4-bromophenyl)hydrazine and DHP/methoxyethanol to make the 5-Br analog of **3**: Gylys, J. A.; Ruediger, E. H.; Smith, D. W.; Solomon, C.; Yevich, J. P. U.S. 5,382,595, 1995. Preparation of 5-chloro analog of **3** from 5-chloroindole: Smith, D. W.; Yocca, F. D.; Yevich, J. P.; Mattson, R. J. EP-464604 A2 921018. The preparation of other dihalo homotryptophols can be found in these references.

(5) After this work was completed the preparation of **3** in 97.4% yield from **2** and DHP in 2-methoxyethanol was published: WO 95/35293 (1995), assigned to VITA-INVEST, S.A. In our hands this preparation did not behave as described.

(6) Use of aqueous dioxane: Grandberg, I. I.; Moskvina, T. P. *Izv. Timiryazevsk. Skh. Akad.* **1973**, 167 (*Chem. Abstr.* **1973**, *79*, 91889s). Demerson, C. A.; Humber, L. G.; Philipp, A. *J. Med. Chem.* **1976**, *19*, 391.

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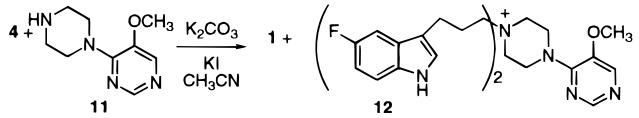

Figure 5. **Generation of 1 and a quaternary ammonium impurity through process A.**

equiv) in water and propylene glycol (5:2) at 95−100 °C with the theory that the Fischer indolization (or at least the initial imine formation) would be rapid and consume DHP before it could react with indole **3**. Extending the addition of DHP to at least 30 min ensured there would be little build-up of DHP. A relatively dilute concentration of 0.3 M was chosen to decrease the rate of formation of **7** (second-order in concentration of **3**). At reaction completion, streams were typically analyzed by HPLC at 96% of **3** and 1% of **7**. Propylene glycol was removed by extraction into water, and **3** was carried on to the tosylation as a MTBE extract, which was analyzed for at least 98 area % of **3** by HPLC.

Tosylation of **3** under conventional conditions (TsCl, catalytic DMAP, Et_3N, CH_2Cl_2) required about 2 h at −5 to +2 °C. At warmer conditions, the propyl chloride **5** (reaction of **3** with Ph_3P and CCl_4) was produced. In CH_2Cl_2 the yield was 64−67%. Tosylation in EtOAc (20−25 °C, 18−24 h) provided returns of about 75%. In each case the product **4** was crystallized from absolute EtOH, with a purity of at least 99%.

Process A. Early synthetic efforts aimed at supplying gram quantities of drug substance utilized the tosylate **4** and the pyrimidinylpiperazine **11** in refluxing acetonitrile in the presence of catalytic potassium iodide and potassium carbonate to afford a modest yield (60%) of the desired product. The main drawback to this approach was the formation of 2−20% of the quaternized byproduct **12** which could not be completely removed by recrystallization (Figure 5). While a variety of permutations of the reaction conditions were examined, i.e., elimination of potassium iodide, alternate bases, alternate solvents, and lower temperatures, no set of conditions was discovered which could completely suppress formation of the quaternized byproduct.

Processes B and C. As a means to circumvent the quaternization issue, two second-generation syntheses were developed which utilized a protected piperazine in the key bond-forming step (Figure 6). The common intermediate was the indole piperazine **13**.

Preparation of 13. The key synthetic transformation for the success of this approach was the alkylation of a protected piperazine with the tosylate **4** (Figure 7). Prior to the examination of protected piperazines, reaction of **4** with 10 equiv of piperazine was shown to give a 90:10 mixture of mono- and dialkylated material, and a suitable purification and isolation protocol could not be found. *N*-Benzylpiperazine was employed successfully in the alkylation, and minimal quaternization was observed; however, sluggish catalytic debenzylation precluded further development with this substrate. A ready alternative was alkylation of *N*-carbethoxypiperazine (1.5 equiv) in refluxing 2-propanol containing 1.5 equiv of diisopropylethylamine (DIPEA). Formation of ca. 5% of the corresponding isopropyl ether derived from **4** had little effect on the subsequent hydrolysis

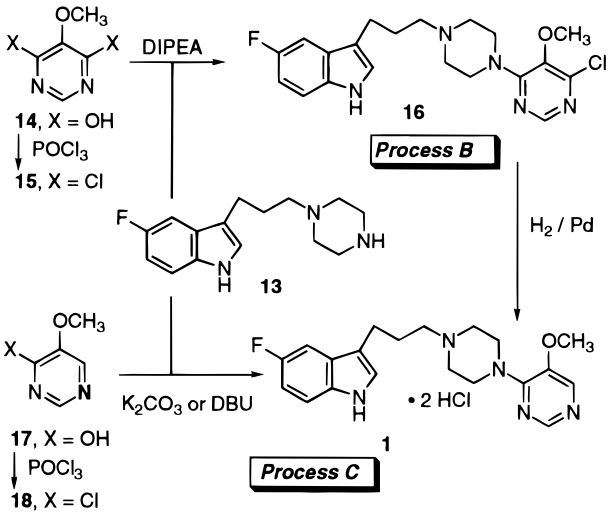

Figure 6. **Processes B and C.**

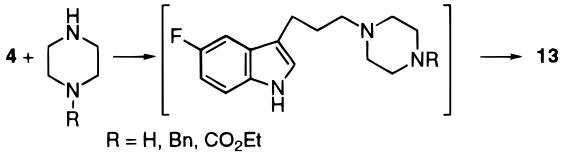

Figure 7. **Preparation of 13.**

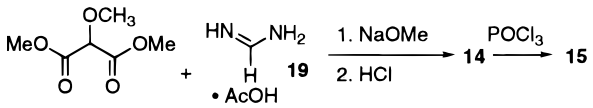

Figure 8. **Preparation of 14 and 15.**

and was effectively removed in the crystallization of **13**. The addition of a large excess (45 equiv) of sodium hydroxide and water, followed by heating at reflux for 4 h, cleanly deprotected the piperazine. The addition of more water induced phase separation with the product remaining in the upper phase. Distillative replacement of 2-propanol by water followed by cooling led to crystallization of **13**. On a 20-kg scale, this convenient one-pot procedure afforded an 85% yield of **13** at 99.5% purity.

A subsequent process tripled the throughput in preparing **13**. Coupling **4** with *N*-carbethoxypiperazine (1.75 equiv) in refluxing *n*-butyl acetate (bp 129−131 °C) without any additional base was complete in 0.5−1 h, and the byproduct tosic acid was washed out with dilute NaOH. After the *n*-BuOAc was removed under reduced pressure, EtOH was added and hydrolysis of the urethane was carried out with 50% NaOH. Water was added, and **13** was crystallized in a fashion similar to that described above.

Process B. Preparation of Dihydroxypyrimidine 14. Condensation of formamidine with dimethyl methoxymalonate in the presence of sodium methoxide in methanol cleanly gave the salt of the dihydroxypyrimidine **14**.[8] Neutralization with concentrated hydrochloric acid followed by distillative exchange of the solvent for water afforded crystalline **14**. On a 10-kg scale this convenient one-pot process provided **14** with a yield of 73% at 99.7 area % by HPLC (Figure 8).

(8) Bretschneider, H.; Richter, W.; Kloetzer, W. *Monatsh. Chem.* **1965**, *96*, 1661.

Process B. Preparation of Dichloropyrimidine 15. Phosphorus oxychloride is the reagent most commonly used to chlorinate hydroxypyrimidines, and routinely chlorinations with $POCl_3$ are conducted at reflux (ca. 105 °C) without solvents and employ 10−20 equiv of reagent.[9] Acetonitrile,[10] benzene,[11] and dichloromethane[12] have been used as solvents. Phosphorus pentachloride,[13] DMF,[14] dimethylaniline,[15] diethylaniline,[16] lithium chloride,[17] and tetraethylammonium chloride[18] are often used in conjunction with $POCl_3$. The Vilsmeier reagent derived from DMF is also a common reagent.[19] When chlorinations are complete, excess reagent is removed by distillation or by quenching with large amounts of ice and water. Often purification is effected by column chromatography.

Phosphorus oxychloride was the preferred reagent for the chlorination of **14**. Chlorination of **14** with $SOCl_2$ was examined in various solvents (DMF, CH_2Cl_2, toluene, or acetonitrile) and proceeded to completion only in DMF. Thionyl chloride with the addition of catalytic DMF to various solvents also led to incomplete reactions. Chlorinations with oxalyl chloride or the Zollinger reagent (dimethylformamidinium chloride, made from $SOCl_2$ and DMF) also were unsuccessful. $POCl_3$ showed the most promise.

When **14**, Et_3N (1 equiv), and $POCl_3$ (2.2 equiv) were combined at 25 or 45 °C and heated to drive the reaction to completion, a substantial exotherm resulted. The temperature of the reaction mixture was easily regulated by adding $POCl_3$ (2.2 equiv in toluene) to a toluene suspension of **14** and Et_3N at 100−105 °C, and chlorinations were complete in about 1 h. Following an aqueous workup the dichloropyrimidine **15** could be isolated as a crystalline solid in 85% yield; however, the quality of the toluene extract was high enough that isolation of **15** was not necessary and served only to decrease the overall yield. To prepare for the coupling, the rich extract was concentrated under reduced pressure to about one-quarter of the volume, most of the toluene being removed. By HPLC quantitation, typical yields were about 95%.

Process B. Telescopic Coupling of 13 and 15. Acetonitrile was preferred for the coupling, as **16** crystallized from this solvent. To drive the alkylations to completion a number of bases were examined. With 1 N NaOH, couplings were complete in ca. 15 min, but these conditions were not expected to be rugged for scale-up, as **15** was found to be unstable in aqueous base at elevated temperatures. Reactions proceeded readily in the presence of Et_3N, but Et_3N·HCl contaminated the product **16**. Couplings in the presence of DIPEA (1.2 equiv) proceeded readily, and the byproduct

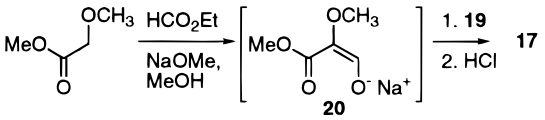

Figure 9. **Preparation of 17.**

DIPEA·HCl remained dissolved in the mother liquor. Cooling the completed coupling mixture to 40−50 °C led to crystallization of **16**. On a 20-kg scale the telescoped process afforded an 85% yield (calculated from **14**) of the penultimate **16**, with a purity of 100% vs standard.

Process B. Preparation of 1 by Hydrogenolysis of 16. Initial hydrogenolyses were complete in 48−72 h with palladium on carbon in the presence of KOH. Without the added base hydrogenolyses were stalled, as the product hydrochloride salt crystallized on the surface of the catalyst. The addition of magnesium hydroxide neutralized the HCl as it was generated, but filtration rates were slow on scale, due to the slimy magnesium salts. The use of calcium hydroxide as the base led to improved filtration rates. At 35 °C the slurries were filtered by pressure through a bed of diatomaceous earth. These conditions avoided premature crystallizations of both **1** and the corresponding free base.

Hydrogenolyses were complete in ca. 4 h at 55−65 °C/20 psi, when calcium hydroxide and SDA 3A EtOH (95:5:5 EtOH:MeOH:water) were used. When absolute EtOH was used, deprotection was extended to 8−12 h. In general, no more than 0.1 area % of the desfluoro byproduct was generated. The hydrogenolysis was successfully demonstrated on a 21-kg scale, affording an 86% yield of bulk drug substance with a purity of 99.8−100% vs standard.

Following implementation of process B on pilot-plant scale, two disadvantages were noted. Residual Pd was found in initial batches at levels ranging up to 130 ppm, and it was difficult to reduce further the levels of this contaminant. For example, filtration through diatomaceous earth or a 0.3-μm filter and subsequent crystallization reduced the Pd levels to about 48 ppm. Secondly, manufacturing sites were limited to those with facilities for hydrogenolysis. Therefore an alternative route was sought.

Development of Process C. The earlier preparations of **1** (processes A and B) were driven by the convenient literature preparation[8] of the dihydroxypyrimidine **14**. By utilizing the monohydroxypyrimidine **17**[20,21] we eliminated one step overall (Figure 6), increased flexibility in selecting manufacturing sites, and avoided the difficulties of extensive repurification of the bulk drug substance to reduce palladium levels.

Process C. Formation of Monohydroxypyrimidine 17. Deprotonation of methyl methoxyacetate in tetrahydrofuran at 5−10 °C with sodium methoxide in the presence of ethyl formate followed by warming to room temperature induced the crossed Claisen condensation, yielding the sodium salt of the β-keto ester, **20** (Figure 9). The addition of the methyl methoxyacetate to a slurry of sodium methoxide and ethyl formate in THF facilitated temperature control and maxi-

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(21) Preparation of **17** by desulfurization of 2-mercapto-4-hydroxy-5-methoxypyrimidine: Chesterfield, J. H.; McOmie, J. F. W.; Tute, J. S. *J. Chem. Soc.* **1960**, 4590.

mized the yield of **20**. Upon complete formation of **20**, formamidine and sodium methoxide were added and the mixture was heated to reflux for 20 h to complete the cyclization.

Isolation of the water-soluble hydroxypyrimidine without contamination by NaCl proved challenging. Continuous deionization or ion-exchange resin treatment (IRC-50) in either batch or column mode was effective in desalting **17**; however, purification greater than 85−90% was difficult, and recovered yields were too low to warrant development. Aqueous crystallization in the presence of organic cosolvents led to considerable levels of salt in the product. The optimal approach was to crystallize from water. Acidification of the methanolic reaction mixture with concentrated hydrochloric acid to pH 5.3 led to precipitation of the bulk of the salt byproducts. Filtration at 35−45 °C proved critical to remove the salt without concomitant precipitation of **17**. Distillative replacement of methanol with water, readjustment to pH 5.3 with sodium hydroxide, and cooling afforded the hydroxypyrimidine **17** as a tan crystalline solid. Crystallization from more acidic or more basic conditions sharply decreased the yield. On a 10-kg scale the process afforded a 57% yield of **17** having HPLC purity of 99.5%. Usually an additional 10−20% was lost to the crystallization mother liquor.

Process C. Chlorination of Monohydroxypyrimidine 17. When the conditions used for chlorination of **14** were used for chlorination of **17**, poor quality **18** resulted. A number of conditions and solvents were examined before toluene was selected for the chlorination of **17**. As chlorination in neat $POCl_3$ might have required distillation to remove excess reagent, this approach was rejected for safety considerations. Chlorination with $POCl_3$ and triethylamine in ethyl acetate was abandoned due to safety concerns,[22] and similar concerns precluded chlorination in *n*-butyl acetate. A method employing thionyl chloride and catalytic DMF in methylene chloride was abandoned, due to environmental considerations regarding the solvent. Chlorinations with $POCl_3$ in acetonitrile, MTBE, or methyl isobutyl ketone (MIBK) were abandoned, as these reactions were slower than chlorination in toluene or produced higher levels of impurities. Toluene and $POCl_3$ were chosen for developing the chlorination.

Initially the $POCl_3$ chlorination was developed with Et_3N in toluene, affording **18** as a 0.16 M solution in toluene in laboratory yields of 90−94%. The product was not isolated from the extract, as in the laboratory some material was lost due to entrainment during concentration. The extract was successfully telescoped in laboratory couplings to prepare **1** in a two-step corrected yield of 71−76% (based on **17**) with purities of 99−100%. However, direct application of the process on scale led to recovery of 23−34% of unreacted **17**.

When DIPEA was substituted for triethylamine, improved process ruggedness was expected and demonstrated. When

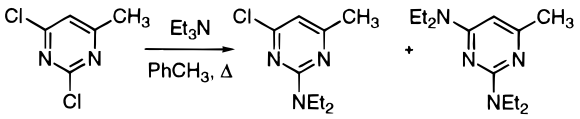

Figure 10. **Reaction of chloropyrimidines with Et_3N.**

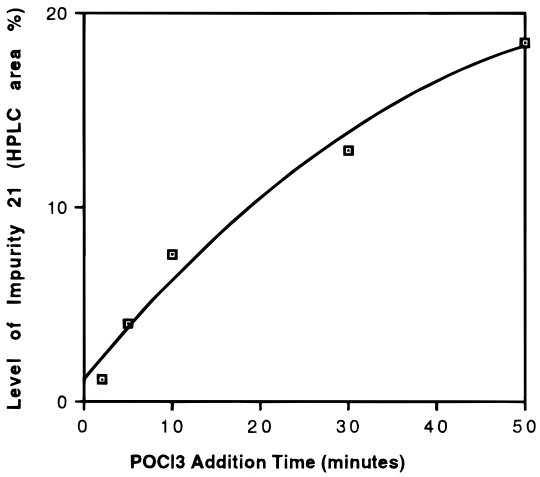

Figure 11. **Formation of impurity 21 with extended addition.**

Et_3N was used as the base during the chlorination, a viscous oil separated out, which entrapped **17** and hindered conversion to **18**. In-process sampling of reaction supernatants gave erroneous indications that chlorinations were complete. With diisopropylethylamine, the chlorination mixture became two liquid phases that were readily dispersed in each other, and chlorinations proceeded readily. The DIPEA process has been demonstrated on a 35-kg scale, producing **18** in 85−87% yields as a 0.4 M toluene solution without concentration or isolation.

The tendency toward improved reactions with increased bulkiness of the amine has literature precedent. Trialkylamines have been shown to react with chloropyrimidines (Figure 10), and such byproducts are minimized when bulkier tertiary amines are used.[23,24] Reaction of phosphorylating reagents with tertiary amines is also decreased with bulkier amines, diisopropylethylamine being preferred.[25] Whether due to increased reaction fluidity or decreased levels of byproducts, the bulkiness of diisopropylethylamine aids the chlorination of **17** to **18**.

Process C. Dimer Formation in the Preparation of Monochloropyrimidine 18. During initial lab development with DIPEA, process ruggedness was not demonstrated when the $POCl_3$ addition was extended to times expected for routine scale-up. When $POCl_3$ was added over about 5 min to a hot suspension of **17** and diisopropylethylamine in toluene, in-process HPLC assay revealed ca. 95 area % for **18**, with one major impurity at ca. 4 area %. When addition times were extended to 30 min, the levels of the major impurity rose and the **18** yield dropped (Figure 11). As the reaction concentration increased, the yields decreased, and the levels of this impurity rose. The structure of this impurity

(22) By hazard analyses, both $POCl_3$/TEA/EtOAc and $POCl_3$/TEA/toluene mixtures containing 30% of $POCl_3$ showed exothermic decomposition, with the onset of decomposition of the EtOAc mixture occurring 35 °C below the toluene mixture. The thermal runaway hazard of thionyl chloride and EtOAc in the presence of metallic zinc has been noted: *Chem. Eng. News* **1992**, June 1, 2. Wang, S. S. Y.; Kiang, S.; Merkl, W. *Process Saf. Prog.* **1994**, *13*, 153. We decided to avoid the risk of using $POCl_3$, another chlorinating agent, in the presence of EtOAc.

(23) Boyle, P. H.; Gillespie, P. *J. Chem. Res., Synop.* **1989**, 282.

(24) Preferred chlorination in the presence of tri-*n*-propylamine was proposed: Gershon, H.; Grefig, A. T.; Clarke, D. D. *J. Heterocycl. Chem.* **1987**, *24*, 205, 1243.

(25) Grabowski, E. J. J.; Hughes, D. L. U.S. 4,894,450, 1990. On the reactivity and use of diisopropylethylamine, see also: Braithwaite, M. J.; Ketteman, C. L. *Chem. Br.* **1993**, 1042.

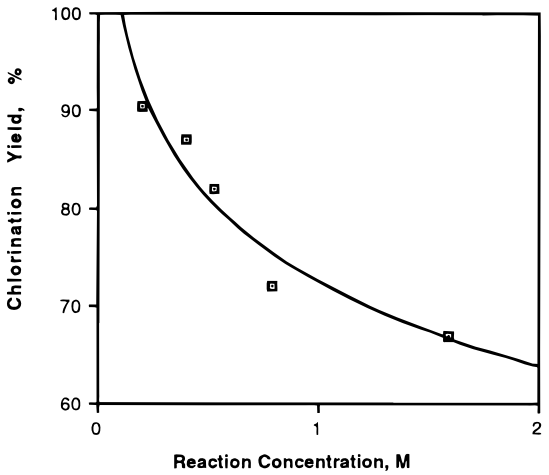

Figure 12. **Effect of reaction concentration for chlorination of 17.**

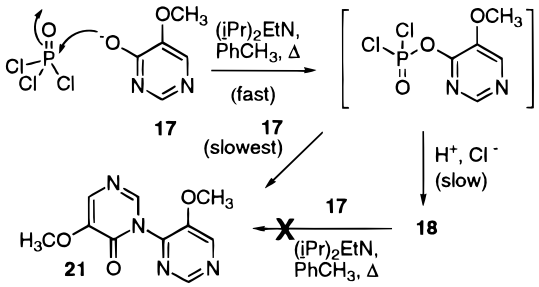

Figure 13. **Proposed mechanism of chlorination and dimerization.**

was investigated, to minimize its formation and improve process ruggedness.

HPLC/MS investigations showed two impurities in the chlorination reaction, each with M + 1 = 235. The major impurity in the chlorination was isolated by preparative chromatography and was quickly shown by NMR to be nonsymmetrical. Its structure was solved unequivocally by single-crystal X-ray analysis[26] as the dimer **21** (Figure 13). Conceivably the other impurity with M + 1 = 235 is the regioisomer in which the N1 pyrimidone nitrogen is arylated by the pyrimidine. When **17** was treated with $POCl_3$ and DIPEA in the presence of **18**, increased levels of **21** did not result, indicating that **21** did not form from **18**.

We were able to find no other literature examples of the ring system of **21**. The sometimes-erratic yields reported in the literature for chlorination of 4-hydroxypyrimidines are possibly related to formation of N-arylated byproducts similar to **21**.

Chlorination of 17. Addition Order. When **17** was treated with $POCl_3$ (1.1 equiv) and DIPEA (1.1 equiv) at room temperature and heated gradually to 60−70 °C, formation of **21** was reduced to ca. 2−4%. Even under these conditions most of the impurity was formed before the $POCl_3$ addition was half completed, i.e., when the concentration of **17** was relatively high.

To demonstrate process ruggedness in the event of mischarged reagents on scale, DIPEA and $POCl_3$ (0.8 equiv each) were charged to a laboratory chlorination, resulting in incomplete consumption of **17** and formation of 8.4 area % of the impurity **21**. After cooling to ca. 25 °C and recharging with 0.3 equiv each of DIPEA and $POCl_3$, the reaction was completed upon heating at 60−70 °C for 1 h. HPLC analysis of the toluene solution of **18** after workup indicated yields of 82−88% with at least 98.4 area % by HPLC. Most of **21** was removed by the aqueous washes. Thus the process was demonstrated to be rugged with respect to undercharging the reagents.

In the optimized chlorination process all components were combined at room temperature, and the reaction mixture was heated gradually to 60−70 °C and held at that temperature until the reaction was complete (ca. 1 h). In the laboratory and the pilot plant, no difficulties were found in controlling the reaction exotherm. It is likely that the current addition protocol minimizes the formation of **21** by allowing the phosphorylation of the starting material before the reaction temperature is high enough to encourage reaction of **18** with a reactive intermediate.[27]

Chlorination of 17. Reaction Concentration. As was the case for chlorinations with $POCl_3$ and Et_3N, chlorination in the presence of diisopropylethylamine also showed a decreased yield with increased concentration. Dimerization and perhaps other intermolecular reactions are implicated. Although a slightly increased yield was demonstrated for chlorination at 0.2 M, the increased solvent and processing costs were anticipated to offset the small yield gain, and chlorination at 0.4 M was developed.

Chlorination of 17. Chlorination Workup. Upon quenching with water, some of the **18** was lost to the aqueous phase (about pH 0.1). Hydrolysis of the product at this pH was anticipated in the event of extended processing upon scale-up. Basifying a quenched mixture to about pH 7 with aqueous NaOH produced unwieldy emulsions. Quenching with 1.6 equiv of dilute aqueous NaOH produced two phases that separated readily, and less of the product was lost to the aqueous phase (about pH 0.7−0.9). A saturated sodium bicarbonate wash was then employed to ensure removal of any residual acid from the rich organic phase. The concentration of dissolved water in the toluene extract of **18** was only 0.05 vol %, and additional water in the coupling was shown to decrease the yield of **1**. Neither washing the toluene extract with brine nor cooling lowered the dissolved-water content. Hence significantly detrimental amounts of water could enter the alkylation step only by entrainment during transfer, and clean phase splits were important.

Monochloropyrimidine 18. Stability. Although isolated **18** has shown decomposition with storage,[21] 0.4 M solutions of **18** in toluene were stable in glass or stainless steel containers for as long as 1 year at ca. 5 °C. The toluene solution is incompatible with polyethylene-lined or carbon-steel drums.

Formation of 1 via Process C. In initial process C investigations, **13** was dissolved in EtOAc and treated with a toluene solution of **18**, in the presence of K_2CO_3.[28] After

(26) Coordinates from the X-ray determinations have been deposited in the Cambridge Crystallographic Database and can be obtained upon request to the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(27) A phosphorylated intermediate was identified by ^{31}P NMR in the chlorination of triacetyl guanosine (ref 18). We were not able to detect any phosphorylated intermediate leading to **18** by ^{31}P NMR.

(28) For a similar heterogeneous coupling with K_2CO_3, cf.: Simms, J. C. U.S. Patent 4,351,939, 1982.

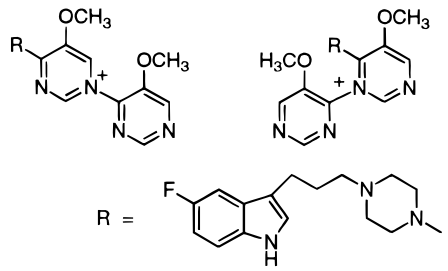

Figure 14. **Quaternary amine impurities from process C.**

coupling was completed, the inorganic byproducts were washed out, the rich toluene extract was diluted with water and ethanol, and the product was crystallized after acidification with concentrated HCl. The overall two-step isolated yield of **1** in this toluene/ethyl acetate method was 71−76%.

Two preparations of **1** were carried out on a 20-kg scale using K_2CO_3. Scrutiny of these batches revealed levels of two late-eluting impurities totalling 0.08 and 0.05 area %, respectively, for the two batches. These impurities, which coeluted with toluene, had not been observed during in-process monitoring nor in lab batches. By HPLC/MS studies these impurities were determined to be equivalent to the products from reaction of **1** with **18**, and the quaternary salts depicted in Figure 14 were proposed. The heterogeneous alkylation may have rendered some of **13** unavailable for reaction with **18**, resulting in reaction of **1** with **18**. With the concern that further scale-up would produce increased levels of these impurities, homogeneous alkylation conditions were sought.

Process C. Minimizing Impurity Formation. A series of amine bases was investigated, including DBU (pK_b 13.2[29]), triethylamine, pyridine, tri-*n*-propylamine, tri-*n*-butylamine, diisopropylethylamine (pK_b 10.4[29]), and 4-methylmorpholine. Bases other than DBU required the addition of ethanol for homogeneous reactions, and alkylations were relatively slow, generating considerable impurities. The addition of ethanol resulted in lower yields due to losses during the aqueous workup. In the presence of 1.1 equiv of DBU, **13** dissolved in toluene at about 60 °C without a cosolvent. Perhaps the strongly basic DBU and **13** (for indole nitrogen, p*K* 16.3 expected[30]) formed an ion pair at 60 °C, facilitating dissolution; since tributylamine did not lead to dissolution of **13** under these conditions, more than lipophilicity is involved. Adding the toluene solution of **18** to a toluene solution of 1.05 equiv of **13** and DBU at 60−70 °C resulted in ca. 80% conversion after the addition was complete. The batch temperature was increased to 100−115 °C to complete conversion in 2−3 h. No detectable quaternary impurities and low or undetectable levels of other impurities were formed. Homogeneity was achieved with DBU initially, and a well-dispersed oil formed after about 30 min of reaction.

Process C. Development of a Rugged Crystallization for 1. A thermally controlled crystallization was developed for good process control. When the coupling was complete, ethyl acetate (for organic solubility) and water were added to the alkylation mixture, and without any pH adjustment the byproduct DBU·HCl was readily removed by extraction into the aqueous phase. Optimal amounts of 8 mL of water and 35 mL of 190 proof SDA 3A alcohol for every 1 g of **13** were charged to the organic extract, and a solution was obtained at 70 °C. The solution was acidified to pH 1.0−1.5 with 37% HCl. The rich extract remained homogeneous during the pH adjustment, as desired to ensure reproducible pH adjustments. Crystallization occurred when the batch was cooled to ca. 60 °C. Under these conditions it was possible to reheat the crystal slurry for complete dissolution at ca. 75 °C, near the reflux temperature. After crystallization, the batch was cooled to ca. 20 °C and then further cooled to ca. 0 °C for optimal yield and quality. The DBU process afforded a 75% yield of **1**, at 100% purity.

Isolation of 1. Under all crystallization conditions studied, the product crystallized as very small whiskerlike needles. The crystal size and shape were unchanged by aging, temperature control, solvent effects, seeding, or agitation. Attempts to grow material for single-crystal X-ray analysis were unsuccessful. Throughout the investigations only one polymorph was identified.

Some slow-filtering batches were observed. High-sheer agitation broke up crystal aggregates, decreasing the rate of filtration. For speed of filtering, evenness of cake loading, and efficiency of washing, a centrifuge was preferred over a horizontal filter, and cake heights of 1 in. were optimal. Excess HCl in the wet cakes was found to corrode 316 stainless steel, but corrosion was not seen with a pH range from 3.1 to 3.6 (pH measurement of a suspension of wet cake in deionized water). To ensure that dryers were not corroded by excess HCl in the wet cakes, washing with aqueous EtOH was continued until a suspension of **1** in water was no more acidic than pH 3.1. Vacuum drying at 50−80 mbar and a jacket temperature of 34 to 37 °C afforded **1** with the desired levels of HCl and water (see below), with minimal risk of overdrying. Under these conditions ethanol is rapidly removed, but loss of water is relatively slow.

Crystal Characteristics of 1. Piperazine **1** is a dihydrochloride salt, with 7.0−7.4 wt % of water (theory for dihydrate is 7.53% water). The dihydrochloride is the preferred form: attempts to form the monohydrochloride salt by crystallizing the free base in the presence of 1 equiv of HCl led to the isolation of the dihydrochloride, in about 50% yield. The empirically derived hydration range was established by equilibrating six representative batches at 43% relative humidity. Product **1** can be overdried even with careful control of the HCl content, but the material readily absorbs moisture to the equilibrium hydration level upon standing. The hydrated structure of **1** was characterized by solid state FT-IR and ^{13}C NMR spectroscopy as containing loosely associated water, and it was not possible to determine the site(s) at which the water was bound. Fluorine did not take part in water binding.

Conclusions. Two iterations of the development cycle were conducted, yielding substantial improvements in product quality, process safety, and productivity. A seven-step convergent synthesis was realized, affording a 48% yield over the longest linear sequence and a 28% yield overall. All key intermediates were crystalline, and no special processing

(29) Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *pKa Prediction for Organic Acids and Bases*; Chapman and Hall: New York, 1981; pp 22−25.

(30) The p*K* of 5-fluoroindole is 16.3: Searjeant, E. P.; Dempsey, B. *Ionization Constants of Organic Acids in Aqueous Solution*; Pergamon: New York, 1979; p 400.

equipment was needed, ensuring maximum manufacturing-site flexibility. Bulk drug substance was reproducibly prepared in high quality with consistent physical and chemical characteristics.

Experimental Section

General Procedures. All melting points are uncorrected. NMR spectra were run at 300 or 400 MHz (^{1}H) and 75 or 100 MHz (^{13}C). All reactions were conducted under nitrogen.

5-Fluoro-3-[3-[(*p*-tolylsulfonyl)oxy]propyl]-1*H*-indole (4). To a solution of **2** (24.9 g, 153 mmol) in 1,2-propylene glycol (300 mL) and water (120 mL) at 95−100 °C was added dihydropyran (13.7 mL, 150 mmol) over 20−60 min. After 30−60 min the reaction was complete by HPLC, and the solution was cooled to about 50 °C and mixed with aqueous NaCl (25%, 160 mL). (HPLC conditions: YMC basic C18 column, 25 cm, 5 μm, held at 31 °C and eluted at 1.5 mL/min with 60:40 0.05 M NaH_2PO_4/CH_3CN, 220 nm.) The mixture was extracted with EtOAc (3 × 300 mL), and the combined organic extracts were washed with water (50 mL), aqueous $NaHSO_3$ (5%, 50 mL), aqueous $NaHCO_3$ (saturated, 50 mL), and water (50 mL). The extract was concentrated atmospherically to about 100 mL. If the moisture level was greater than 0.5% by Karl Fischer titration, additional EtOAc was added, concentration was continued, and the volume was adjusted with EtOAc to about 100 mL. The extract was held at 0−5 °C, and pyridine (29.7 g, 375 mmol) was added, followed by a solution of *p*-toluenesulfonyl chloride (57.2 g, 300 mmol) in EtOAc (100 mL). The developing suspension was stirred at 10−15 °C until no more than 3 area % of **3** was present by HPLC (15−20 h). (HPLC conditions: Waters μPorasil column, 30 cm, 10 μm, held at 31 °C and eluted with 0.5 vol % *i*-PrOH in CH_2Cl_2, 250 nm.) Then water (50 mL) was added and the biphasic mixture was stirred for at least 1 h to destroy excess TsCl. The organic phase was stirred with aqueous H_2SO_4 (20%, 50 mL) for 1 h and then extracted with aqueous $NaHCO_3$ (saturated, 50 mL). The organic extract was concentrated atmospherically to about 100 mL, and heptanes (50 mL) were added over 30 min. The mixture was cooled to 31−32 °C, seeded, and aged at 23−25 °C for 1 h with stirring. The suspension was further aged at 0−5 °C (1 h), and the product was collected by filtration and washed with EtOAc/heptanes (1:3, 2 × 50 mL, chilled to 0−5 °C). Drying at 40 °C/20 mmHg returned 71−75% of **4**, 97−99% pure by HPLC relative to standard.

For analytical purposes a sample of **4** was recrystallized from absolute EtOH (5 volumes) to return material with mp 103−103.5 °C. ^{1}H NMR ($CDCl_3$): δ 8.08 (br s, 1H), 7.76 (d, 2H, J = 8.2 Hz), 7.29 (d, 2H, J = 8.2 Hz), 7.23 (dd, 1H, J = 9.0, 4.5 Hz), 7.08 (dd, 1H, J = 9.7, 2.5 Hz), 6.92−6.86 (m, 2H), 4.06 (t, 2H, J = 5.9 Hz), 2.72 (t, 2H, J = 7.3 Hz), 2.42 (s, 3H), 1.98 (pseudo p, 2H). ^{13}C NMR ($CDCl_3$): δ 20.7, 21.5, 28.8, 69.9, 103.3 (d, J_{CF} = 23.5 Hz), 110.1 (d, J_{CF} = 26.3 Hz), 111.7 (d, J_{CF} = 9.5 Hz), 114.3 (d, J_{CF} = 4.8 Hz), 123.5, 127.4 (d, J_{CF} = 9.6 Hz), 127.7, 127.8, 132.7, 132.9, 144.7, 157.5 (d, J_{CF} = 234.2 Hz). IR (KBr): 3392, 1356, 1172 cm^{-1}. Anal. Calcd for $C_{18}H_{18}NO_3SF$: C, 62.23; H, 5.22; N, 4.03; S, 9.23; F, 5.47. Found: C, 62.18; H, 5.23; N, 3.96; S, 9.14; F, 5.44.

5-Fluoro-3-[3-(1-piperazinyl)propyl]-1*H*-indole (13). A solution of **4** (87.8 g, 0.25 mol), DIPEA (49.1 g, 0.38 mol), and ethyl 1-piperazinecarboxylate (60.1 g, 0.38 mol) in 2-propanol (415 mL, [H_2O] 0.021% by Karl Fischer (KF) titration) was held at reflux (85−87 °C) for 3 h, when HPLC analysis showed complete consumption of starting material. (HPLC conditions: Nova-Pak phenyl column, 15 cm × 3.9 mm, held at 30 °C and eluted at 1.0 mL/min with 40:60 CH_3CN/0.025 N NaOAc, 279 nm.) After cooling of the reaction mixture to 25 °C, 95% ethanol (450 mL) and 50% aqueous NaOH (610 mL) were added. After 4 h at reflux (80−82 °C), hydrolysis was complete by HPLC analysis and the mixture was cooled to 50 °C. Water (650 mL) was added to the resultant suspension, and the two layers were separated. The alcohols of the organic layer were exchanged for water (350 mL) by distillation at atmospheric pressure. The distillation was deemed complete when the pot temperature reached 100−102 °C and the distillate had a density of 0.99 g/mL. The aqueous solution was cooled to 0−5 °C over 30 min, held at 0−5 °C for 1 h, and then suction filtered on a Buchner funnel. The cake was washed with cold water (150 mL) and then dried in a vacuum oven (70 mmHg) at not more than 50 °C for ca. 18 h to give 55.5 g (84.1%) of **13**, mp 139.6 °C [endotherm by differential scanning calorimetry (DSC)], 0.25% KF, with 99.2 area % by HPLC assay. ^{1}H NMR (DMSO-d_6): δ 10.92 (s, 1H), 7.29 (dd, 1H), 7.19 (s, 1H), 6.90 (ddd, 1H), 2.51−2.71 (m, 6H), 2.04−2.26 (m, 6H), 2.04 (b, 1H), 1.71−1.82 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 22.0, 26.6, 45.4, 54.1, 58.0, 102.6 (d, J_{CF} = 22.6 Hz), 108.5 (d, J_{CF} = 26.4 Hz), 111.8 (d, J_{CF} = 9.0 Hz), 114.5 (d, J_{CF} = 4.5 Hz), 124.0, 127.2 (d, J_{CF} = 9.8 Hz), 132.6, 156.3 (d, J_{CF} = 230.9 Hz). IR (KBr): 2860, 1470, 1443, 1171, 1121 cm^{-1}. Anal. Calcd for $C_{15}H_{20}NOF$: C, 68.94; H, 7.71; N, 16.08. Found, C, 69.17; H, 7.66; N, 16.11.

5-Fluoro-3-[3-(1-piperazinyl)propyl]-1*H*-indole (13): High-Throughput Process. A solution of **4** (50.0 g, 144 mmol) and ethyl 1-piperazinecarboxylate (39.9 g, 251.9 mmol) in *n*-BuOAc (100 g) was held at reflux (129−131 °C) until coupling was complete by HPLC (0.5−1 h) and then cooled to about 95 °C. Aqueous NaOH (200 g, 3.5 wt %) was added, and the mixture was cooled to 20−30 °C. Additional aqueous NaOH (3.5 wt %) was added as necessary to adjust the mixture to pH ≥11, and the rich organic phase was concentrated (13 mbar, final pot temperature 70−80 °C) to an oil, ca. 1.5 wt % *n*-BuOAc by GC assay. EtOH (190 proof, 55 g) was added to the concentrate, followed by aqueous NaOH (50 wt %, 115.2 g, 1.44 mol), and the reaction mixture was held at reflux (85−90 °C) until hydrolysis was complete by HPLC assay (≤4 h). The mixture was diluted with water (160 g) and cooled to 20−30 °C, and the lower, aqueous phase was removed. The organic phase was polish-filtered through paper, and acetonitrile (10 g) was added to solubilize an unidentified impurity. The reddish-orange solution was seeded, and water (300 g) was added over 0.5 h at 15−25 °C. The product slurry was stirred for at least 0.5 h and filtered. The wet cake was washed with water (one cake volume, 140−150 mL) and dried under reduced pressure at 40−50 °C with an air bleed. The return was 33.3 g of **13**, 99.5% HPLC purity relative to standard, 89.4% yield corrected for purity.

4,6-Dihydroxy-5-methoxypyrimidine (14). A 1-L three-necked flask equipped with a mechanical stirrer, Claisen adapter, thermometer, reflux condenser, gas inlet adapter, and stopper was dried at 100 °C while being purged with nitrogen and was then cooled to 25 °C. The flask was charged with anhydrous methanol (310 mL) and cooled to 0−5 °C. Solid sodium methoxide (54.2 g, 1.0 mol) was added over 10 min while the temperature was maintained below 15 °C. The resulting solution was cooled to 0 °C, and dimethyl methoxymalonate (50.0 g, 42.6 mL, 0.30 mol) was added in one portion followed by the addition of formamidine acetate (31.7 g, 0.31 mol) while the temperature was maintained below 10 °C. The resulting light yellow suspension was stirred at 0−5 °C for 30 min, then heated to reflux at 60−65 °C, and held at reflux for 1 h. The light pink suspension was cooled to 0−5 °C and then quenched with concentrated HCl (82 mL) over 20 min while the temperature was maintained below 10 °C (final pH 1.1). The white suspension was stirred at 0−5 °C for 30 min and then suction filtered. The filter cake was suspended in distilled water (250 mL) and the suspension refluxed (95−100 °C) until a clear solution resulted. The solution was cooled to room temperature over 3 h and then to 0−5 °C. The suspension was stirred at 0−5 °C for 1 h, and the product was collected by filtration and washed with cold methanol (50 mL). Drying at 45−50 °C at 10 mmHg gave 26.9 g (61.3%) of **14**, mp 286.0 °C (DSC endotherm). ^{1}H NMR (DMSO-d_6): δ 3.63 (s, 3H), 7.81 (s, 1H), 11.8 (br, 2H). ^{13}C NMR (DMSO-d_6): δ 58.8, 126.2, 144.1, 160.0. IR (KBr): 3182, 1707, 1655, 1467, 1236 cm^{-1}. Anal. Calcd for $C_5H_6N_2O_3$: C, 42.21; H, 4.25; N, 19.68. Found: C, 42.29; H, 4.17; N, 19.92.

4,6-Dichloro-5-methoxypyrimidine (15). A suspension of **14** (49.8 g, 350.4 mmol) and Et_3N (35.5 g, 350.4 mmol) in toluene (600 mL) was heated to 100−105 °C, and $POCl_3$ (118.2 g, 770.9 mmol) in toluene (72 mL) was added over 30 min. The mixture was refluxed (110 °C) for 1 h, cooled to below 10 °C, and quenched with water (300 mL, chilled to 0−5 °C). The organic phase was washed with aqueous $NaHCO_3$ (saturated, 300 mL, 0−5 °C) and aqueous NaCl (saturated, 300 mL, 0−5 °C) and concentrated by rotary evaporation to remove most of the solvent. Heptane (400 mL) was added, and the slurry was cooled and held at 0−5 °C for 1 h. Filtration returned **15** (43.85 g, 69.9%, 98.6 area % by HPLC). A portion (38.6 g) was recrystallized from toluene/heptane (5:95) to afford 25.3 g (65.5% recovery) of crystalline **15**, 98.9 area % by HPLC, mp 56.8 °C (DSC endotherm). IR (KBr): 3447, 1516, 1370, 810 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.55 (s, 1H), 4.00 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 155.2, 152.2, 147.7, 61.1. Anal. Calcd for $C_5H_4Cl_2N_2O$: C, 33.55; H, 2.25; N, 15.65. Found: C, 33.67; H, 2.34; N, 15.60.

3-[3-[4-(6-Chloro-5-methoxy-4-pyrimidyl)-1-piperazinyl]propyl]-5-fluoro-1*H*-indole (16). A solution of **15** (20.66 g, 115.4 mmol), **13** (30.13 g, 115.4 mmol), and DIPEA (24.13 mL, 17.90 g, 138.5 mmol) in acetonitrile (375 mL, KF 0.3%) was held at reflux (82 °C) for ca. 1 h, and the reaction was judged complete by HPLC assay. (HPLC conditions: Phenomenex Bondex 10 C18 column, 3.9 × 300 mm, 10 μm, eluted at 1.0 mL/min with 40:60 CH_3CN/0.05 M phosphate buffer, pH 5, 220 nm.) The mixture was cooled to 40−50 °C over 30 min and held at 40−50 °C for another 30 min for good crystal growth. The suspension was cooled to 0−5 °C over 1 h and held at 0−5 °C for 1 h. The product was isolated by filtration and washed with cold (0−10 °C) acetonitrile (2 × 80 mL). Drying at 40−45 °C/50 mmHg for 10 h afforded 44.32 g (95.1%) of **16**, mp 165.8 °C (DSC endotherm). MS: (M + H) 404. IR (KBr): 3194, 2938, 1564, 1528, 986 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.93 (p, 2H, J = 6.9 Hz), 2.48 (t, 2H, J = 6.9 Hz), 2.80 (t, 2H, J = 6.9 Hz), 3.50 (s, 3H), 3.80 (b, 4H), 3.90 (b, 4H), 7.02 (t, 1H, J = 9.0 Hz), 7.33−7.47 (m, 3H), 8.29 (s, 1H), 11.00 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 158.1, 156.5, 153.5 (d, J = 231.9 Hz), 152.0, 136.2, 132.9, 127.4 (d, J = 9.7 Hz), 124.4, 114.6 (d, J = 9.9 Hz), 112.2 (d, J = 9.6 Hz), 108.7 (d, J = 26.1 Hz), 102.9 (d, J = 22.8 Hz), 59.4, 57.4, 52.8, 45.9, 26.9, 22.2. Anal. Calcd for $C_{20}H_{23}ClFN_5O$: C, 59.48; H, 5.74; N, 17.34; Cl, 8.78; F, 4.70. Found: C, 59.84; H, 5.80; N, 17.05; Cl, 8.78; F, 4.57.

4-Hydroxy-5-methoxypyrimidine (17). A 12-L four-necked flask was charged with NaOMe (600.0 g, 10.55 mol) and THF (2.80 L, KF 0.02%), and the suspension was chilled to 5−10 °C. Ethyl formate (543.8 g, 6.83 mol) was added, the temperature of the light-brown slurry being maintained at 5−10 °C. Methyl methoxyacetate (562.3 g, 5.35 mol) was added, the temperature being maintained at 5−10 °C. The ensuing purple solution was allowed to warm to 20−25 °C and stirred at that temperature. When the condensation was complete by GC assay, a solution of formamidine acetate (562.1 g, 5.35 mol) in MeOH (4.8 L) was added over 10−15 min, the temperature of the reaction mixture being maintained at 20−27 °C. [GC conditions: Restek Rtx-1 column (100% dimethyl polysiloxane), 30 m × 0.32 mm i.d. × 1 μm film thickness, split injector at 150 °C, FID at 300 °C, column oven held at 70 °C/5 min, ramped at 15 °C/min to 150 °C, held for 3 min at 150 °C, ramped at 30 °C/min to 250 °C, held at 250 °C/5 min.] NaOMe in MeOH (25 wt %, 1171.8 g, 5.42 mol) was added over 10−15 min, the temperature of the reaction mixture being maintained at 24−28 °C. The tan mixture was held at reflux (63−65 °C) until the level of residual formamidine decreased by no more than 1%/h by HPLC assay (19−20 h). (HPLC conditions: Jones Apex phenyl RP column, 4.6 × 150 mm, 5 μm, eluted at 1.0 mL/min with 33:67 CH_3CN/0.01 N KH_2PO_4 at pH 4.6, 206 nm.) The reaction mixture was cooled to 50 °C, water (730 mL) was added, and the mixture was transferred to a 22-L flask. The dark-brown reaction mixture was acidified from pH 11.8−12.4 to pH 5.3 with concentrated HCl (ca. 1.08 L, 13.1 mol), the temperature being maintained at 36−48 °C. The mixture was filtered through a pad of diatomaceous earth (560 g), and the filter cake was washed with MeOH (2 × 600 mL). The combined filtrates were concentrated at 50−60 °C/27−28 in.Hg to 20% of volume (2.8 L), and water (1.69 L) was added. Concentration was continued as described above to 2.4 L, and aqueous NaOH (50%, ca. 123 mL, 1.54 mol) was added to adjust from pH 4 to pH 5.3. The solution was stirred at 23−25 °C over ca. 17 h. The resulting crystalline suspension was cooled and stirred at 0−5 °C for 2−3 h. The product was collected by filtration, washed with EtOH (SD 3A, 190 proof, 2 × 600

mL, chilled to 0−5 °C), and dried at 50 °C/27−28 in.Hg to constant weight. The return was 399.5 g (59%) of tan solid, mp 203−213 °C (lit.[20] mp 210−211 °C, lit.[31] mp 218−220 °C), 97.5% purity vs standard by HPLC assay. A sample was recrystallized from boiling water to provide a reference standard, mp 208−211 °C. ^{1}H NMR (DMSO-d_6): δ 3.74 (s, 3H), 7.45 (s, 1H), 7.84 (s, 1H), 12.56 (b, 1H). ^{13}C NMR (DMSO-d_6): δ 55.8, 130.0, 141.8, 147.1, 156.9. IR (KBr): 2920, 1660, 1270, 1005, 900 cm^{-1}. Anal. Calcd for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.55; H, 4.76; N, 21.87.

4-Chloro-5-methoxypyrimidine (18). With vigorous agitation $POCl_3$ (3.60 mL, 38.6 mmol) was added over about 20 min to a suspension of **17** (4.52 g, 35.0 mmol corrected for purity) and DIPEA (6.73 mL, 38.6 mmol) in toluene (67 mL) at room temperature. The temperature was allowed to rise to 36−39 °C, and the reaction mixture was heated to 60−70 °C. [N.B.: The reaction mixture becomes two fluid phases which are readily dispersed with stirring. Each phase contains a significant amount of starting material and product.) The reaction mixture was held at 60−70 °C until the HPLC area ratio of **18** to **17** was ≥99:1, about 1.5 h. (HPLC conditions: YMC-Pak phenyl column, 250 mm × 4.6 mm i.d., 5 μm, eluted at 1.0 mL/min with 40:60 CH_3-CN/0.01 M ammonium phosphate, 210 nm.) The reaction mixture was cooled to 5−8 °C and quenched with aqueous sodium hydroxide (35 mL, 1.55 N), the temperature being maintained below 15 °C. The phases were separated, and the organic phase was extracted with aqueous $NaHCO_3$ (8 wt %, 12 mL), while the temperature of the mixture was maintained below 15 °C. The rich extract was polish-filtered through diatomaceous earth to remove any solids and used without any further purification for the preparation of **1**. By HPLC quantitation[32] the yield was 4.15−4.45 g (82−88%, 99.8 area % normalized for toluene: 66 mL, 0.42 M, ca. 60 mg of **18**/mL of solution).

A sample of **18** was prepared as a reference standard by removing the solvent under reduced pressure and sublimation (40 °C/ca. 50 mmHg): mp 62−62.5 °C (lit.[9] mp 60−62 °C, lit.[21] mp 63−64 °C). ^{1}H NMR ($CDCl_3$) and IR (KBr): consistent with described spectra.[9] ^{13}C NMR ($CDCl_3$): δ 56.6, 139.4, 150.1, 150.3 (two signals). Anal. Calcd for $C_5H_5N_2OCl$: C, 40.55; H, 3.67; N, 18.91; Cl, 23.94. Found: C, 40.83; H, 3.39; N, 18.94; Cl, 23.68.

5-Methoxy-3-(5-methoxypyrimidinyl)-4(3*H*)-pyrimidinone (21). A suspension of **17** (50.0 g, 0.397 mol) and DIPEA (76 mL, 0.436 mol) in toluene (750 mL) was heated to 100−105 °C, and a solution of $POCl_3$ (40.6 mL, 0.436 mol) in toluene (122 mL) was added over 1.5 h. After 2 h at 100−105 °C the reaction mixture was cooled to 0−5 °C and the reaction quenched with aqueous NaOH (1.5 N, 400 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 250 mL), and the latter extracts were combined and concentrated to a dark-red oil (ca. 15 g). The oil was dissolved at 50 °C in MeOH and EtOAc (30 and 8 mL). The dark red solution was slowly cooled to rt, held at rt for 1.5 h, and then chilled at 0−5 °C. The product was collected by filtration, washed with chilled MeOH (3 × 5 mL), and dried under ambient conditions to return 1.8 g, 97 area % by HPLC. This material was dissolved in MeOH/H_2O (20 and 1.5 mL) at 55 °C, slowly cooled to rt, and held at rt for 2 days. The product was collected by filtration, washed with chilled MeOH (3 × 3 mL), and dried under ambient conditions to return **21** (1.1 g, 2.3%), mp 173−174 °C, suitable for single-crystal X-ray analysis. ^{1}H NMR ($CDCl_3$): δ 3.92 (s, 3H), 4.02 (s, 3H), 7.46 (s, 1H), 7.91 (s, 1H), 8.64 (s, 1H), 8.88 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 56.8, 57.1, 128.2, 141.3, 143.1, 146.0, 147.5, 149.0, 151.2, 155.5. IR (KBr): 1670, 1600, 1305 cm^{-1}. Anal. Calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.36; H, 4.31; N, 23.88.

5-Fluoro-3-[3-[4-(5-methoxy-4-pyrimidinyl)-1-piperazinyl]propyl]-1*H*-indole Dihydrochloride (1): from Process B. To a 500-mL stirred pressure reactor were charged **16** (20.0 g, 48.7 mmol), $Ca(OH)_2$ (5.4 g, 73 mmol), and 5% Pd−C catalyst (50% water wet, 2.0 g). The reactor was purged with nitrogen, and EtOH (SDA 3A, 200 mL) was added. The mixture was heated to 60 °C, purged with hydrogen, and pressurized to 20 psig with hydrogen. The reaction mixture was vigorously agitated until the residual level of starting material was less than 0.3 area %, as determined by HPLC analysis. [HPLC conditions: Waters Nova-Pak phenyl column, 150 mm × 3.9 mm i.d., eluted at 1.0 mL/min with 35:65 CH_3CN/0.05 M phosphate buffer (pH 5.0), 220 nm.] After purging with nitrogen, diatomaceous earth (2.0 g) was added and the slurry was stirred for 30 min. The mixture was pressure-filtered through filter paper, and the filter cake was washed with EtOH (SDA 3A, 3 × 200 mL). The mother liquor was polish-filtered through paper a second time, and water (65 mL) was added. The mixture was warmed to 50 °C and acidified to pH 1.5 with concentrated HCl (ca. 8 mL). The resultant slurry was heated to 75 °C to provide a clear solution. The ethanolic cake washes from the initial filtration were heated to 50 °C and added to the product solution while the temperature was maintained at 75 °C. This solution was allowed to cool to 30 °C over 4 h, crystallization occurring at 65−70 °C. The slurry was cooled to 25 °C and stirred at that temperature for 12 h. The product was collected by filtration, washed with EtOH (SDA 3A, 200 mL, chilled to 0 °C), and dried under vacuum at ≤40 °C until the moisture content was 6−8% and the residual EtOH content (GC) was <1%. The return was 21.1 g (92%) of **1**, DSC decomposition endotherm maximum 225 °C. ^{1}H NMR (D_2O): δ 2.05−2.14 (m, 2H), 2.79 (t, 2H, J = 7.1 Hz), 2.96−3.21 (m, 4H), 3.34−3.72 (m, 4H), 3.88 (s, 3H), 4.98−5.28 (b, 2H), 6.96 (ddd, 1H, J = 2.3, 9.0, 9.3 Hz), 7.21 (s, 1H), 7.29 (dd, 1H, J = 2.3, 10.1 Hz), 7.38 (dd, 1H, J = 4.5, 9.0 Hz), 7.89 (s, 1H), 8.39 (s, 1H). ^{13}C NMR (D_2O): δ 21.6, 24.3, 44.5, 51.8, 57.0, 57.2, 103.4 (d, J_{CF} = 25.5 Hz), 110.5 (d, J_{CF} = 26.5 Hz), 113.1, 113.5, 125.0, 125.5, 127.2 (d, J_{CF} = 9.9 Hz), 133.3, 142.5, 144.7, 155.4, 157.8 (d, J_{CF} = 231.6 Hz). IR (KBr): 1738, 1600, 1440, 1360, 1192 cm^{-1}. Anal. Calcd for $C_{20}H_{24}N_5OF\cdot 2HCl\cdot 7.3\%\ H_2O$: C, 50.34; H, 6.31; N, 14.68; F, 3.98; Cl, 14.86. Found: C, 50.21; H, 6.24; N, 14.68; F, 3.98; Cl, 14.67.

(31) Br. 914,929, Jan 9, 1963, assigned to Hoffmann-LaRoche & Co.; cf.: *Chem. Abstr.* **1963**, *59*, 1659c.

(32) Original quantitations were calculated relative to a recently prepared sublimed sample of **18**. For greater convenience, quantitations were calculated against a standard of anisole.

5-Fluoro-3-[3-[4-(5-methoxy-4-pyrimidinyl)-1-piperazinyl]propyl]-1*H*-indole Dihydrochloride (1): from Process C. To a suspension of **13** (7.79 g, 29.6 mmol) in in toluene (39 mL) was added DBU (4.72 g, 31.0 mmol, 4.64 mL). The suspension was stirred vigorously and heated to 60−70 °C. When dissolution had occurred (ca. 15 min), a toluene solution of **18** (65.8 mL, 28.2 mmol) was added, the temperature of the reaction mixture being maintained at 60−70 °C. The reaction mixture was heated to 100−115 °C and held at 100−115 °C until the HPLC area ratio of **1** to **18** was ≥99 (2−3 h). As the coupling reaction progressed, two liquid phases formed, which were readily dispersed in each other with stirring. (HPLC conditions: Beckman ODS Ultrasphere column, 150 mm × 4.6 mm i.d., eluted at 1.5 mL/min with 62:27:11 0.1 M ammonium phosphate/CH_3-CN/MeOH, 220 nm.) The dispersion was cooled to 25−35 °C and mixed with EtOAc (39 mL) and water (39 mL). The upper, organic phase was washed with water (39 mL) and polish-filtered. To the filtrate were added EtOH (SDA 3A, 194 mL) and water (62 mL). The solution was heated to 70 ± 5 °C and adjusted to pH 1.0−1.5 (concd HCl, ca. 6 mL). Then EtOH (SDA 3A, 77 mL) was added, and the solution was held at 55−60 °C for 30 min to induce crystallization. The suspension was cooled to 0−5 °C over 4−5 h, and the product was collected by filtration and washed with aqueous EtOH (SDA 3A containing 8.5 wt % H_2O, 2 × 60 mL, 0−5 °C) until a 1 wt % suspension of wet cake in H_2O was measured at pH 3.1 or higher. The wet cake was dried at 35 °C/40−60 mmHg to afford 11.8 g of **1** (89.6%, corrected for 7.26 wt % water) containing ≤1.5 wt % EtOH by GC analysis. Samples of **1** prepared in this fashion were assayed at 99−100% purity relative to standard.

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Supporting Information Available

Solid-state conformational drawing of **21** (1 page). See any current masthead page for ordering and Internet access instructions.

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