

# An Efficient Fischer Indole Synthesis of Avitriptan, a Potent 5-HT<sub>1D</sub> Receptor Agonist

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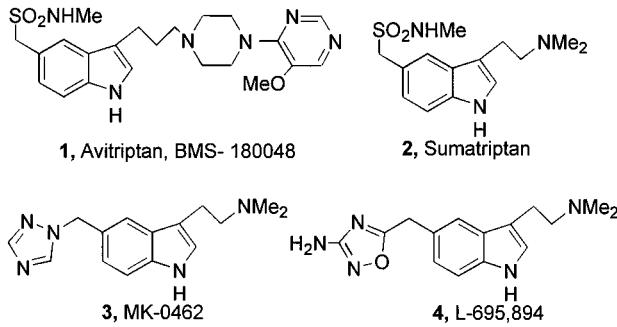
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An efficient synthesis of the antimigraine drug candidate avitriptan (**1**, BMS 180048) is reported. The key step is a two-phase Fischer indolization reaction between hydrazine **6** and 5-chlorovaleraldehyde, **20**, to give the chloropropylindole **35**, which is susceptible to acid-catalyzed degradation under the reaction conditions required for its formation. Sequential coupling of **35** with piperazine, **26**, and 4-chloro-5-methoxypyrimidine, **24**, gives the title compound in 40–45% overall yield. Significant improvements in the syntheses of the known starting materials, hydrazine **6**, 5-chlorovaleraldehyde, **20**, and 4-chloro-5-methoxypyrimidine, **24**, were also achieved.

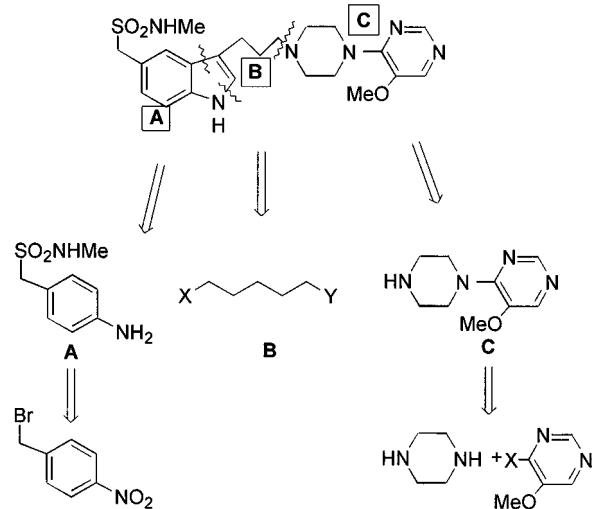
## Introduction

Among the many biologically active indoles, serotonin (5-hydroxytryptamine, 5-HT) is known to exhibit antimigraine activity, and numerous serotonin-like compounds are currently under investigation as 5-HT<sub>1D</sub> receptor agonists for the treatment of migraine headache. Sumatriptan, **2**, is the first of these to be commercialized,<sup>1</sup> and several others, including MK 0462, **3**,<sup>2</sup> L-695,894, **4**,<sup>3</sup> and avitriptan (**1**, BMS 180048), are under development. Avitriptan has been shown to exhibit similar 5-HT<sub>1D</sub> agonist activity to sumatriptan in cerebral arteries in a number of animal models,<sup>4</sup> but did not elicit a response in 5-HT<sub>2</sub> receptors in either porcine coronary artery or rat thoracic aorta,<sup>5</sup> indicating that it may be a more selective vasoconstrictor than sumatriptan. These results make it an attractive candidate for development as an antimigraine drug.



A retrosynthetic analysis of **1** (Scheme 1) shows that it consists of three basic subunits; an appropriately

Scheme 1



substituted aniline **A**, a five-carbon chain **B** to complete construction of the indole ring and form the three-carbon linkage to **C**, the piperazinylpyrimidine. There are a number of different options for putting these subunits together, some of which are demonstrated in the known literature syntheses of this compound.

The indole portion of avitriptan has been prepared by a zinc chloride-catalyzed Fischer indolization of hydrazine **6** with dihydropyran, **7**, to give the hydroxypropylindole **8** (Scheme 2);<sup>6</sup> by a more convergent route in which the **B** and **C** subunits were combined to form diethyl acetal **10** and then reacted with **6** in a Fischer indolization to give **1** directly (Scheme 3);<sup>7</sup> and by a palladium-catalyzed heteroannulation reaction of iodoaniline **12** with silyl-

\* Abstract published in *Advance ACS Abstracts*, December 1, 1997.  
(1) Hopkins, S. J. *Drugs Today* **1992**, *28*, 155.

(2) MK-0462 *Drugs Future* **1995**, *20*(7), 676–679.

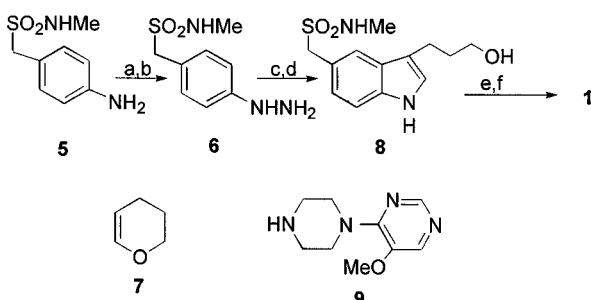
(3) Chen, C.-Y.; Senanayake, C. H.; Bill, T. J.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. R. *J. Org. Chem.* **1994**, *59*, 3738.

(4) (a) Saxena, P. R.; De Vries, P.; Wang, W.; Heilegers, J. P. C.; VanDenBrink, A. M.; Bax, W. A.; Yocca, F. D. *Naunyn-Schmiedebergs Arch. Pharmacol.* **1997**, *355*, 295. (b) Wiener, H. L.; Thloyd, G. P.; Yocca, F. D. *FASB J. Abstr.* **1995**, *9*, A347.

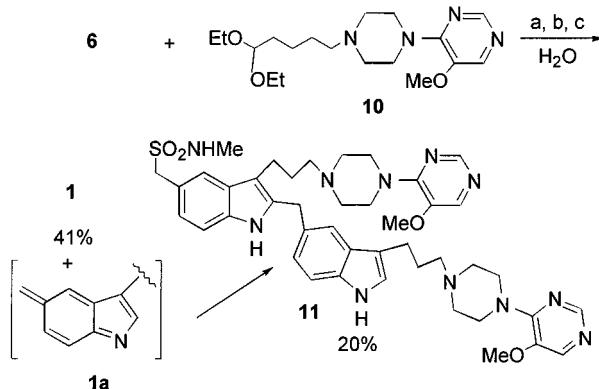
(5) Sarbin, N. S.; Gylys, J. A.; Iben, L. G.; Mahle, C. D.; Izzarelli, E. M.; Parker, E. M.; Noonan, J. W.; Williams, A. D.; Smith, D. W.; Hamel, E.; Yocca, F. D. *FASB J. Abstr.* **1995**, *9*, A347.

(6) Smith, D. W.; Yocca, F. D.; Yevich, J. P.; Mattson, R. J.; Williams, A.; Ruediger, E. H. U.S. Patent 5,300,506, 1994.

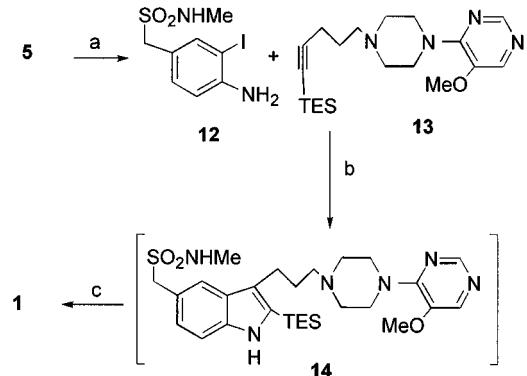
(7) Remuzon, P.; Dussy, C.; Jacquet, J. P.; Soumeillant, M.; Bouzard, D. *Tetrahedron Lett.* **1995**, *6227*.

Scheme 2<sup>a</sup>

<sup>a</sup> Key: (a) NaNO<sub>2</sub>, HCl; (b) SnCl<sub>2</sub>; (c) 7, EtOH; (d) ZnCl<sub>2</sub>, DME; (e) MsCl, TEA; (f) 9, KI, DIPEA.

Scheme 3<sup>a</sup>

<sup>a</sup> Key: (a) pH 1, rt, 10 min; (b) pH 4.8, 80 °C, 15 min; (c) pH 1, 80 °C, 60 min, then 12 N HCl.

Scheme 4<sup>a</sup>

<sup>a</sup> Key: (a) NaHCO<sub>3</sub>, I<sub>2</sub>; (b) Pd(OAc)<sub>2</sub>, PPh<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, NaCl, ACN, H<sub>2</sub>O; (c) aqueous HCl.

alkyne 13 (Scheme 4).<sup>8</sup> The latter route has been used to prepare bulk drug on a multikilogram scale. The two Fischer indolization routes have only been done on a small scale, and the yield of the indolization step in each case was rather low (26% yield of 8 from 5 and 41% yield of 1 from 6, respectively). The yield in the palladium-catalyzed heteroannulation is considerably better, with a 65–70% overall yield of 1 from 5.

Nonetheless, a Fischer indolization route was seen as potentially more economical, mainly because the five-carbon aldehyde equivalent required should be considerably less expensive than the analogous alkyne required

for the palladium route. The major difficulty with the Fischer indolization is that the indole is subject to degradation under the acid-catalyzed conditions required for its formation. Remuzon<sup>7</sup> (Scheme 3) has proposed the formation of the reactive imine intermediate **1a**, formed by the acid-catalyzed extrusion of methyl sulfonamide from **1**, which in turn attacks the 2-position of the indole ring to form the 2,5-bis indole **11**. We herein describe our efforts at overcoming this difficulty in developing an economical and scaleable Fischer indole synthesis of avitriptan.

## Results and Discussion

**Synthesis of Arylhydrazone Precursor 6.** Aniline **5** was initially prepared by a literature method<sup>9</sup> and then later modified to incorporate an improved synthesis of the aromatic nitro precursor.<sup>10</sup> Hydrazine **6** was prepared by treatment of **5** with NaNO<sub>2</sub> in aqueous HCl followed by reduction of the resulting diazonium salt with SnCl<sub>2</sub>.<sup>11</sup> This procedure used 5 equiv of SnCl<sub>2</sub> relative to **5** and provided **6** as the hydrochloride salt in 65% yield. In our hands, this procedure gave a solid that filtered very slowly and was contaminated with up to 10% of inorganic salts. The diazonium salt formation did not go to completion, with up to 20% of unreacted **5** in some cases. This problem was found to be due to the tendency of **5**, which is insoluble in the H<sub>2</sub>O/HCl reaction mixture, to remain as unreactive aggregates in the reaction mixture even with vigorous agitation. This problem was alleviated by sonicating the reaction mixture during the diazonium salt formation, but this was not possible on a large scale. An alternative solution was found to be an in situ conversion of **5** to its hydrochloride salt. Heating a slurry of **5** in H<sub>2</sub>O/HCl until a solution was formed, followed by cooling to –5 °C, gave a slurry of the HCl salt, which was then completely dissolved on treatment with 1.05 equiv of NaNO<sub>2</sub>, indicating complete conversion to the diazonium salt.

The diazonium salt solution was then added to a slurry of SnCl<sub>2</sub>·2H<sub>2</sub>O in concentrated HCl at –20 °C. Since **6** begins to precipitate shortly after the addition is started, a solution is never obtained, presumably leading to inclusion of SnCl<sub>2</sub> in the product. By lowering the amount of SnCl<sub>2</sub> from 5 to 3 equiv and substituting anhydrous SnCl<sub>2</sub>, which dissolves more readily in concentrated HCl than the dihydrate, the HCl salt of **6** was routinely obtained in 85–90% yield with less than 1% inorganic tin.

In the course of this work a rather surprising 15–20% lower yield of **6** was obtained when a vendor sample of the HCl salt of **5** was evaluated. These reactions were characterized by visible gas evolution toward the end of the NaNO<sub>2</sub> addition and during the addition of the diazonium salt solution to SnCl<sub>2</sub>, presumably N<sub>2</sub> evolution from decomposition of the diazonium salt. These results were difficult to explain in light of the high chemical purity of this material. In reviewing the history of **5**, however, it was determined that all samples of **5** prepared in-house were made by catalytic hydrogenation of the corresponding nitro compound, while the vendor sample was believed to be made by a dissolving metal

(9) Macor, J. E.; Blank, D. H.; Post, R. J.; Ryan, K. *Tetrahedron Lett.* **1993**, 33, 8011.

(10) Reid, J. G.; Reddy, J. P. *Org. Process Res. Dev.* **1997**, submitted.

(11) Dowle, M. D.; Coates, I. H. U.S. Patent 4,816,470, 1989.

**Table 1. Aldehydes or Equivalent Used in Indolization Reactions**

Aldehyde	Prepared from	% Yield
	commercially available	-
	DHP	63
	1,5-pentanediol or tetrahydropyran (THP)	48 59
	" "	59
	DHP	40
	18 + 9	32
	THP	75

reduction. A trace metal analysis<sup>12</sup> of the vendor and in-house sample of **5** revealed 50 ppm of iron in the vendor sample and none in the in-house sample, clearly implicating it in the diazonium salt decomposition. This conclusion was confirmed when an in-house sample of **5** was spiked with 250 ppm iron and less than 10% yield of **6** was obtained. The mechanism of this iron-catalyzed decomposition is unclear. It is possibly similar to the Sandmeyer or Gatterman reactions, in which copper salts or copper metal in acid convert diazonium salts to aryl halides or diaryl compounds, respectively, with evolution of N<sub>2</sub>. In any event, in the present case it is critical that **5** be free of trace contamination with iron.

**Preparation of Aldehydes or Equivalent.** In the course of developing the indolization, several different aldehydes or aldehyde equivalents (Table 1) were used. For the overall synthesis to be economical, it was necessary that this portion of the molecule be prepared from an inexpensive and readily available starting material. 2-Hydroxytetrahydropyran, **15**, was prepared by the HCl-catalyzed hydration of dihydropyran (DHP).<sup>13</sup> 5-Bromopentanaldehyde, **16**, was initially prepared by Swern oxidation of the corresponding alcohol obtained from the HBr bromination of 1,5-pentanediol to give 5-bromopentanol<sup>14</sup> and then later by TEMPO-catalyzed NaOCl oxidation.<sup>15</sup> The TEMPO oxidation not only gave a higher yield but also eliminated environmental concerns with the obnoxious dimethyl sulfide odor from the Swern

(12) Trace metal analyses were done by an ICP method, Analytical Research and Development, Bristol-Myers Squibb Co., Syracuse, NY.

(13) Woods, G. F. *Organic Syntheses*; Wiley: New York, 1955, Collect. Vol. III, pp 470–471.

(14) Kelkar, S. V.; Joshi, G. S.; Reddy, G. B.; Kulkarni, G. H. *Synth. Commun.* **1989**, *19*, 1369.

(15) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, F. J. *J. Org. Chem.* **1987**, *52*, 2559.

oxidation. This procedure was hampered somewhat by overbromination in the first step to give 5–10% of 1,5-dibromopentane, so 5-bromopentanol was subsequently prepared by a modification of the method of Kulkarni and Patil<sup>16</sup> by treatment of THP with BBr<sub>3</sub>. Bromoaldehyde **16** proved to be somewhat unstable, so it was generally converted without isolation to dimethyl acetal **17** in quantitative yield by treatment with HC(OCH<sub>3</sub>)<sub>3</sub>, MeOH, and HCl gas.

The neopentyl acetal **18** was also prepared, but by a different route<sup>17</sup> from DHP and neopentyl glycol, followed by bromination with PBr<sub>3</sub>. This material was used to prepare **19** by coupling with piperazinylpyrimidine **9** for use in a convergent route similar to Scheme 3. Surprisingly, **19** was fairly resistant to hydrolysis in aqueous acid, with 90% conversion to the corresponding aldehyde achieved only under extremely dilute concentrations.

Finally, 5-chloropentanaldehyde, **20**, was prepared by the TEMPO-catalyzed oxidation of 5-chloropentanol, which was in turn prepared from THP by a modification of a previously published procedure of Cason.<sup>18</sup> Treatment of tetrahydropyran (THP) with acetyl chloride and catalytic ZnCl<sub>2</sub> gave 5-chloropentyl acetate, which was further converted to 5-chloropentanol by basic hydrolysis. Fortunately, chloroaldehyde **20** proved to be considerably more stable than its bromo counterpart, **16**, eliminating the need to make the acetal. The synthesis of **20** has been done on a fairly large scale (1 kg for the first step, 200 g for the TEMPO-catalyzed oxidation) in 75% overall yield from THP. Both **16** and **20** were also prepared by the Rosenmund reduction of the respective acid chlorides,<sup>19</sup> but in our hands the reductions did not go to completion. Also, these acid chlorides, while commercially available, were relatively expensive.

**Synthesis of Piperazinylpyrimidine 9.** At the start of this work, it was not known whether completion of the synthesis from a suitably derivatized propylindole such as **8** (Scheme 2) would be better accomplished by coupling with the preformed piperazinylpyrimidine **9** or by a stepwise coupling with piperazine, **26**, followed by coupling with chloromethoxypyrimidine, **24**. Since it is more convergent, the former was thought to offer certain advantages over the stepwise method. Thus, an efficient synthesis of **9** was undertaken (Scheme 5). Anderson and co-workers<sup>20</sup> give a detailed description of the synthesis of 4-chloro-5-methoxypyrimidine, **24**, by condensation of methyl methoxyacetate, **21**, with ethyl formate, followed by treatment with formamidine, **22**, to give 4-hydroxy-5-methoxypyrimidine, **23**. Chlorination of **23** with POCl<sub>3</sub> in the presence of DIPEA in toluene gave **24** in 82–88% yield. While a few other chlorinating agents and reaction conditions were attempted, none were found to be superior to these. However, **24** has been reported to be an

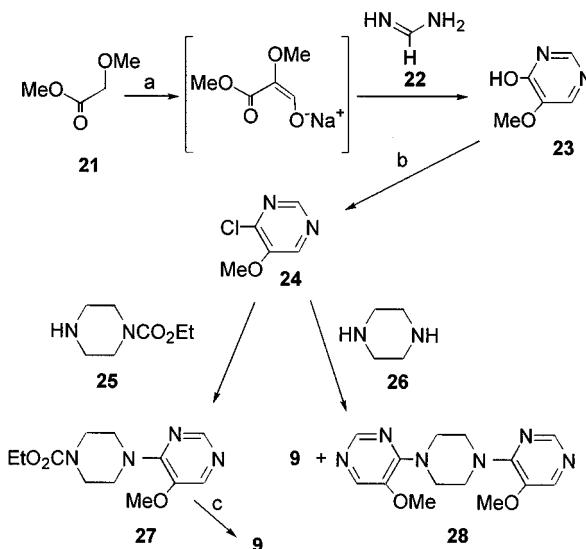
(16) Kulkarni, S. U.; Patil, V. D. *Heterocycles* **1982**, *18*, 163.

(17) Bartels, G. U.S. Patent 4,847,391, 1989.

(18) Cason, J.; Wallcave, L.; Whiteside, C. N. *J. Org. Chem.* **1949**, *14*, 37.

(19) The reduction of 4-chlorobutyryl chloride by hydrogenation in the presence of 10% Pd/C and 2,6-lutidine and subsequent conversion of the resulting aldehyde to the dimethyl acetal is described in ref 3.

(20) Anderson, N. G.; Ary, T. D.; Berg, J. L.; Bernot, P. J.; Chan, Y. Y.; Chen C.-K.; Davies, M. L.; DiMarco, J. D.; Dennis, R. D.; Deshpande, R. P.; Do, H. D.; Droghini, R.; Early, W. A.; Gougoutas, J. Z.; Gross, J. A.; Harris, J. C.; Haas, O. W.; Jass, P. A.; Kim, D. H.; Kodresha, G. A.; Kotnis, A. S.; LaJeunesse, J.; Lust, D. A.; Madding, G. A.; Modi, S. P.; Moniot, J. L.; Nguyen, A.; Palaniwamy, V.; Phillipson, D. W.; Simpson, J. H.; Thoraval, D.; Thurston, D. A.; Tse, K.; Polomski, R. E.; Wedding, D. L.; Winter, W. L. *Org. Process Res. Dev.* **1997**, *1*, 300.

Scheme 5<sup>a</sup>

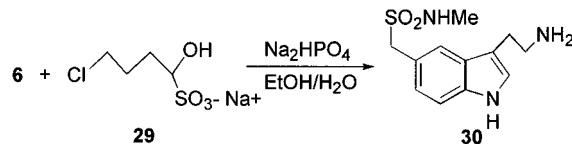
<sup>a</sup> Key: (a)  $\text{HCO}_2\text{Et}$ ,  $\text{NaOMe}$ ,  $\text{MeOH}$ ; (b)  $\text{POCl}_3$ , DIPEA; (c)  $\text{NaOH}$ .

unstable solid that yellowed on standing.<sup>21</sup> As a result, **24** was generally stored at 0 °C as a solution in toluene. Under these conditions it appeared to be stable indefinitely. We felt that there may be advantages to isolating the solid, so an effort to do this was undertaken. Up to this point, isolation of the solid was done by concentrating the toluene solution to dryness and subliming the residue. This gave a white crystalline material, which turned yellow within a few hours to a few days when stored at room temperature. Storage under these conditions for 30 days led to a 10–15% loss in potency (determined by HPLC). Since sublimation is generally not practical on a large scale, an alternate method for the isolation of the crystalline material was needed.

Following chlorination and workup under the Anderson conditions, a ca. 0.4 M solution of **24** in toluene was obtained. This solution was concentrated to 4 M, diluted with heptane at 50–60 °C, and treated with activated carbon, and on cooling, **24** crystallized as white needles in 75% yield. This material began to discolor after several days at room temperature and lost 3–5% potency after 10 months storage at room temperature. However, only slight discoloration and no loss in potency was observed over the same time period at 0 °C, making it suitable as an isolated intermediate.

Two approaches were investigated for the preparation of piperazinylpyrimidine **9** from **24**, one using the protected (ethoxycarbonyl)piperazine **25** and the other using unprotected piperazine **26**. The latter was preferred, since it eliminated the deprotection step, but it proved to be difficult to prevent formation of and effect subsequent removal of the bis-substituted piperazine **28**. When 6 equiv of **26** was used, ca. 3% of **28** relative to **9** was produced. Buffered basic water washes removed most of the excess piperazine, and **9** was crystallized in 70–75% yield from  $\text{BuOAc}/\text{heptane}$ . However, the crystallization was ineffective at reducing the amount of **28**, and the product also contained 2–5% residual piperazine. Efforts at more complete removal of piperazine with more or larger water washes simply led to significant losses

Scheme 6



of **9** to the washes. Pearlman and co-workers<sup>22</sup> solved the problem of removing a bis-substituted impurity for a similar piperazinylpyridine by selectively extracting the product into water at pH 5 and isolating by precipitation at pH 12, but this did not work in our case because **9** proved to be too soluble in water even at basic pH. Since both piperazine and **28** lead to problems in subsequent steps, a process using the protected piperazine **25** was developed instead. This eliminated both the formation of **28** and the need for extraordinary measures to remove the large excess of piperazine, since only a slight excess of **25** was used. Deprotection of the coupled product **27** was done by treatment with 50% NaOH in *n*-BuOH at 90 °C. Ultimately, this three-step procedure was run without isolation of the intermediates to give a 65% yield of **9** from hydroxypyrimidine **23**.

**Indolization.** The difficulty in carrying out traditional Fischer indolization reactions with the (*N*-methylsulfonamido)methyl substituent at the 4-position of aryl hydrazine **6** is well documented.<sup>23</sup> The only relatively high yield for a Fischer indolization using **6** as a substrate was described by Albinson and co-workers in a later sumatriptan patent.<sup>24</sup> In this case, the HCl salt of **6** and the bisulfite adduct of 4-chlorobutanal, **29**, were heated in EtOH/H<sub>2</sub>O in the presence of  $\text{Na}_2\text{HPO}_4$  to give (aminoethyl)indole **30** in 63.5% yield (Scheme 6). The  $\text{Na}_2\text{HPO}_4$  presumably buffers the reaction to keep the pH from getting too low, thereby inhibiting decomposition of the indole. Note, however, that the primary chloride is displaced *in situ* under the reaction conditions to give the (aminoethyl)indole rather than the (chloroethyl)indole, which would not be suitable in our case.

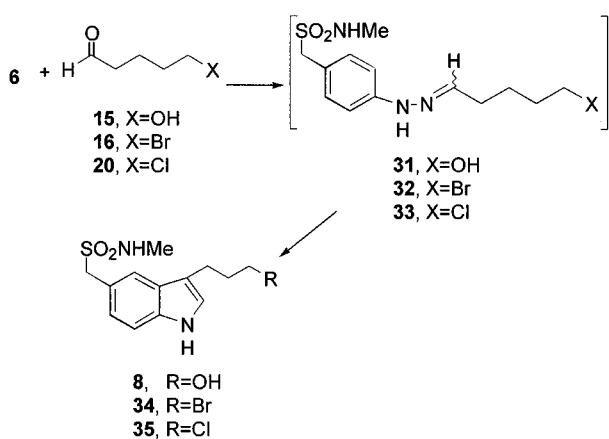
All of our early work confirmed these results. Simply stated, the Fischer indolization requires an acid catalyst, and these indoles are unstable to acid. To circumvent this difficult problem, a two-phase indolization was proposed. In principle, the organic-soluble indole would be extracted as it is formed into a less acidic organic phase from a strongly acidic aqueous phase necessary for the indolization to take place. This should reduce acid-induced degradation of the indole. The theory was first tested using hydrazine **6** and 2-hydroxytetrahydropyran, **15**, (Scheme 7), and improved indolization yields were immediately obtained. After considerable optimization, a reproducible yield of 50–55% of (hydroxypropyl)indole **8** was obtained after chromatography. Under the optimized reaction conditions, the intermediate hydrazone **31** was cleanly formed by treatment of **6** with **15** in EtOH/

(22) Pearlman, B. A.; Perrault, W. R.; Shephard, K. P.; LaPean, L. A.; Krook, M. A.; Dobrowolski, P. J.; Lyster, M. A.; McMillan, M. W.; Knoechel, D. J.; Evenson, G. N.; Watt, W. *Org. Process Res. Dev.* **1997**, *1*, 106.

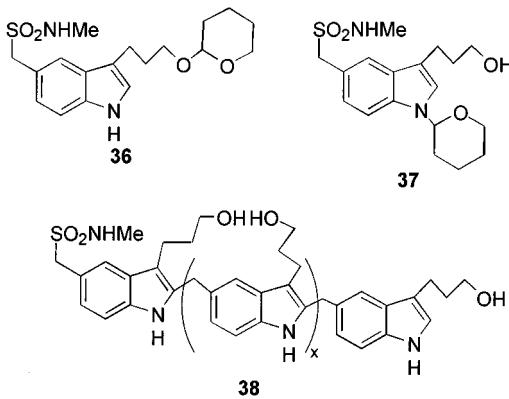
(23) The early patent literature on sumatriptan and its analogues describe several Fischer indolizations using **6** as the substrate. The yields are uniformly low, typically in the 20–30% range, most requiring chromatographic purification. For specific examples, see: Dowles, M. D.; Coates I. H. U.S. Patent 4,816,470, 1989. Oxford, A. W. U.S. Patent 5,037,845, 1991. Macor and coauthors (see ref 9) describe the Fischer indolization route to a conformationally restricted analogue of sumatriptan as entirely unsuccessful.

(24) Albinson, F. D.; MacKinnon, J. W. M.; Crookes, D. L. U.S. Patent 5,103,020, 1992.

Scheme 7



$\text{H}_2\text{O}$  at room temperature, isolated by extraction into 1,2-dichloroethane (DCE), and then heated at reflux after addition of 2 equiv of 6 M phosphoric acid ( $\text{pH} \sim 0.6$ ). The indolization was generally complete in 1–2 h, and the crude product was isolated by separation of the phases and concentration of the DCE phase to a residue. While these results represented a significant yield increase over the single-phase indolizations, continued optimization efforts provided no further yield improvement. Three impurities totaling 15–20% were isolated by chromatography of the crude product.



Structures **36** and **37** can be formed by the reaction of **8** with excess **15**, while **38** ( $x = 0$ ) results from electrophilic attack of a reactive azoquinone methide (analogous to **1a**, Scheme 3) at the 2-position of the indole ring in **8**, as previously discussed. Although **38** was the only impurity of this type isolated, it is also possible that linear polymers of **38** ( $x \geq 1$ ) form. This is suggested by the presence of varying amounts of tarry material that is insoluble in both the organic and aqueous phases. Interestingly, heating **8** at reflux under the two-phase reaction conditions produced a 14% yield of **38** after only 1 h, conclusively demonstrating that the dimerization reaction takes place in the two-phase system. An additional problem was that **8** was not crystalline, so the only means of purification was by chromatography.

These results prompted us to examine other aldehydes under the two-phase conditions. The first was 5-bromoaleraldehyde, **16**, which would provide an indole product not requiring hydroxyl activation prior to alkylation of a piperazinyl moiety in the subsequent step. Under the same conditions optimized for the (hydroxypropyl)indole, reaction of bromohydrazone **32** was considerably more sluggish, with 20% unreacted after 10 h

at reflux. Nonetheless, the HPLC profile of the reaction looked fairly clean, showing mainly a mixture of (bromopropyl)indole **34** and unreacted **32**. In a survey of higher boiling solvents, it was found that the indolization went to completion in *n*-butyl acetate (BuOAc) in 2 h, but the yield of **34** after chromatography was a modest 35%. A serendipitous discovery that removal of the 6 M phosphoric acid phase partway through the reaction and replacement with fresh acid led to an *increased reaction rate and improved the yield to 50%*. Further optimization of the protocol for the phosphoric acid phase exchanges resulted in reproducible in-solution yields of 55–59%, but isolation of the product as a crystalline solid was still only 40%.

At this point, large quantities of 5-chlorovaleraldehyde, **20**, became available through development of the TEMPO-catalyzed oxidation,<sup>15</sup> and its substitution for **16** resulted in a 10% increase in yield to 65–70% of (chloropropyl)indole **35**. The reasons for this increase are not entirely obvious, but a comparison of the HPLC profile for the indolization indicate that both the chlorohydrazone **33** and the indole **35** are more stable than their bromo counterparts.

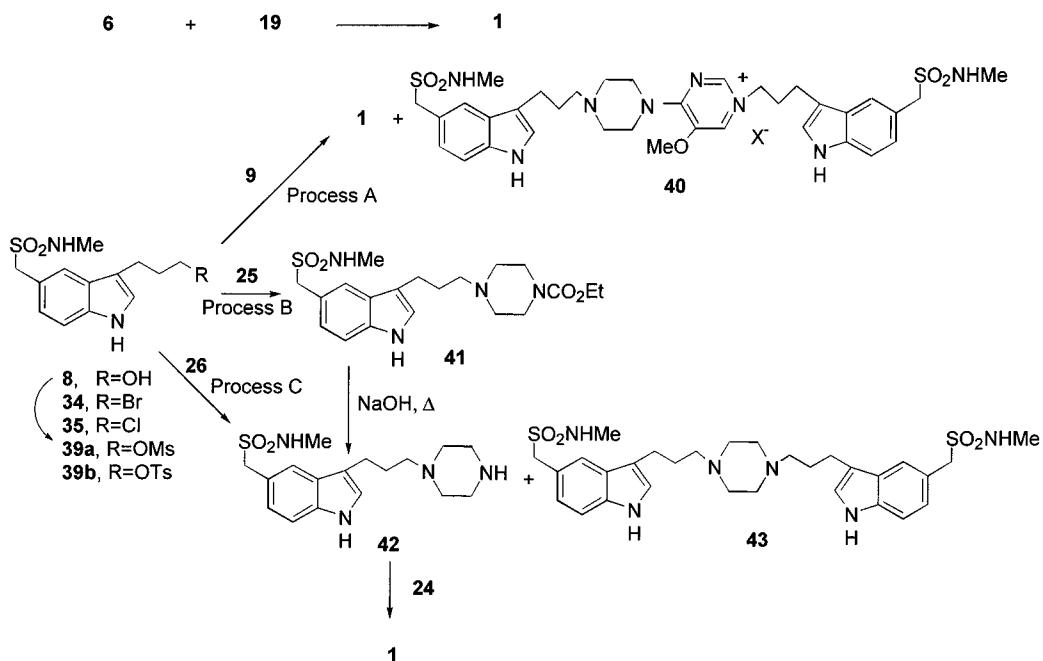
Several other advantages were realized in switching to chloro aldehyde **20**. First, it was much easier to make than **16**. Second, the aldehyde itself was stable, making it unnecessary to convert it to the dimethyl acetal. This also made it easier to make the hydrazone, since the acetal did not need to be reconverted to the aldehyde. Third, the in-solution yield of indole was ca. 10% higher; and finally, it was easier to crystallize so that the isolated yield of chloroindole **35** was actually ca. 20% higher than the yield of bromoindole **34**.

In its final form, the procedure for the preparation of **35** from **6** is quite simple. The HCl salt of **6** is reacted with 1.15 equiv of **20** and 1.0 equiv of Et<sub>3</sub>N (BuOAc, 0–5 °C). After removal of the precipitated Et<sub>3</sub>N·HCl by filtration, the BuOAc solution of hydrazone **33** was added to a mixture of BuOAc and 3.6 equiv of 6 M phosphoric acid at 105 °C at a rate such that reflux of the reaction mixture was maintained. During the course of the reaction, the lower aqueous phase was twice removed and replaced with fresh phosphoric acid. When the reaction was complete, the phases were separated and the organic fraction was washed with water and aqueous NaHCO<sub>3</sub>. After concentrating to a small volume, **35** is crystallized by seeding and addition of 1:1 BuOAc/heptane. The isolated activity yield is usually 65–70% and the mother liquor loss is less than 5%.

The two-phase indolization is not devoid of side reactions. The chloro analogue of the 2,5-bis-indole **38** ( $x = 0$ ) has been isolated, so it is clear that acid-induced degradation similar to other Fischer indolizations is occurring. It is equally clear that these side reactions have been dramatically reduced, and in addition, most of the side products are removed in the aqueous phosphoric acid phase, facilitating isolation of the product from the organic phase.

**Final Assembly of Avitriptan.** **1.** Several approaches for the final assembly of avitriptan were investigated. Early in development, we were attracted to the convergent route of Remuzon (Scheme 3), in which the piperazinylpyrimidine is already incorporated into the five-carbon aldehyde equivalent and the indolization is the last step in the synthesis. Thus, hydrazine **6** was treated with neopentyl acetal **19** under the aqueous acidic conditions similar to those described, but the yield of **1**

Scheme 8



was less than 10%. These reactions were characterized by large amounts of tarry residues. The two-phase indolization was not attempted with this substrate, since the amine product would not be extracted into the organic phase under acidic conditions, and work on this approach was discontinued.

The next most convergent route involved coupling of the terminally functionalized propylindoles with piperazinylpyrimidine **9** (Scheme 8, process A). (Hydroxymethyl)indole **8** was converted to either the mesylate **39a** or tosylate **39b** by standard procedures, and each was coupled with **9** under a variety of conditions. While **1** was the major product, these reactions were characterized by long reaction times and the formation of two major impurities, hydrolysis back to **8** and overalkylation to give the quaternary ammonium salt **40**.<sup>25</sup> The best conditions were found to be treating indole **39b** with 1.1 equiv of **9** in refluxing acetone in the presence of excess DIPEA. The tosylate worked slightly better than the mesylate, with less formation of **40**. Addition of water increased the reaction rate but enhanced the amount of hydrolysis to **8**. Since none of the intermediates in this route were crystalline, the entire sequence was ultimately run from hydrazine **6** without any purification until the isolation of **1** as a hydrochloride salt. Fortunately, **1** forms a highly crystalline hydrated dihydrochloride, which greatly simplified isolations in all of this work.

The best overall yield of **1** from **6** in the telescoped process was 33%, and the isolated HCl salt generally contained 1–2% of **40**. Similar results were obtained with the (halopropyl)indoles **34** and **35** under the same reaction conditions, although the level of **40** was somewhat higher, 3–5%. The coupling with (chloropropyl)indole **35** was considerably more sluggish, however, and required the addition of 1–2 equiv of NaI to achieve >95% conversion. The overall yield of **1** from **6** via **35** was considerably higher (40–45%), however, mainly due to the higher yield in the indolization.

(25) The structure of impurity **40** was tentatively determined by LC/MS and then confirmed by independent synthesis (see the Experimental Section). Which nitrogen is quaternary has not been conclusively determined.

The problem of contamination with quaternary salt **40** proved to be very challenging. Despite numerous attempts at lowering the level of **40** by modification of reaction conditions, it was always produced at levels of at least 3–5% relative to **1** and did not purge in the isolation of the HCl salt. The only nonchromatographic means of successfully reducing the level of **40** was by adsorption on activated carbon during recrystallization of the HCl salt, which reduced the level from 3 to 5% to a still unacceptably high level of 1–1.5%. For mainly this reason, an alternate route to **1** was sought.

The sequential coupling of **35** with piperazine followed by reaction with chloromethoxypyrimidine, **24**, was yet another possible process (Scheme 8, process C). As in the synthesis of **9**, the options were to use a protected piperazine, such as **25**, thus preventing bis-alkylation, or to use a large excess of unprotected piperazine **24**, in hopes that overalkylation could be controlled or the overalkylated material easily removed. In fact, the amount of bis-alkylated impurity **43** relative to the desired monoalkylated piperazinylindole **42** turned out to be dependent exclusively on the amount of piperazine relative to **35**. At a 5:1 molar equiv ratio, 10% of **43** was produced; at 10:1, 5%; at 20:1, 2%; and these ratios were unaffected by how the reaction was run. Since excess piperazine also had to be removed prior to coupling with **24**, 10 equiv of piperazine provided a convenient compromise between the formation of too much **43** and dilution of the product with too much piperazine. Unfortunately, when a 95:5 mixture of **42**:**43** was coupled with **24** and the HCl salt of **1** was isolated in the usual manner, the product was still contaminated with 5% of **43**.

Alternatively, the process utilizing protected piperazine **25** (Scheme 8, process B) should completely avoid the formation of **43**. The three chemical steps of this process; namely, the coupling of **35** with **25**, deprotection of the resulting (ethoxycarbonyl)piperazinyl indole **41**, and the coupling with **24** were run without the isolation of the intermediates. This process was relatively efficient, and

**1** was isolated as its dihydrochloride dihydrate in 60% overall yield from **35**, essentially free of any significant impurities.

Although product quality was excellent, there were still a few drawbacks. To get complete conversion to **41** in the coupling of **35** and **25** in refluxing EtOH, 1.5 equiv of NaI was required. Besides being an added cost factor, it was found that **1** formed a partial iodide salt, which was difficult to purify, unless the NaI was removed. This necessitated addition of a water immiscible cosolvent, EtOAc, in the workup so that the NaI could be removed with a water wash. Then a solvent exchange back to EtOH was required for the deprotection/decarboxylation step. This step required a surprisingly large excess of 10 equiv of NaOH in refluxing EtOH to effect complete conversion to piperazinylindole **42**, and the excess NaOH also had to be removed in the workup. This was accomplished by neutralization with concentrated HCl and removal of the precipitated NaCl by filtration. The last step, coupling of **42** and **24**, was done by adding a toluene solution of **24** to the EtOH solution of **42** in the presence of NaHCO<sub>3</sub>, and **1** was isolated by adding water and concentrated HCl to precipitate the HCl salt. All of these extra operations had a large impact on the productivity of the process, so a reexamination of the two-step process utilizing the coupling of piperazine with chloro indole **35** was undertaken.

From a productivity perspective, this approach has a number of advantages. Besides the obvious one less step, the coupling of **35** with 10 equiv of piperazine **26** in *n*-BuOH/H<sub>2</sub>O at 100 °C gave complete conversion to a 95:5 mixture of 42:43 in 1 h *without* using NaI. This made the problem essentially that of finding an efficient and practical means of removing **43**.

Piperazinylindole **42** has some potentially useful physical properties. We have been unable to crystallize it, but it does form a crystalline oxalate salt. So apparently does **43**, as it did not purge by isolating the oxalate salt of **42**. It is quite soluble in water and polar organic solvents, but not nonpolar solvents. It can actually be extracted from water saturated with NaCl by water-immiscible polar solvents. Unfortunately, **43** appeared to possess most of these same properties. Ultimately, the difference in the partitioning coefficients in an aqueous-organic system of the three major components present at the end of this reaction (piperazine > **42** > **43**) was used to develop a way to separate them. Modifications to the ionic strength and pH of the aqueous phase were made to amplify otherwise minor differences.

Excess piperazine was selectively extracted from the reaction mixture in butanol with saturated NaCl at pH 9 with minimal loss of **42**, which was then selectively extracted into water at pH 8.5, leaving all but traces of **43** in the BuOH phase. The only problem with this procedure was that it required multiple extractions with large volumes of water to extract enough **42** to make the process useful. To solve this problem, a three-stage countercurrent extraction was developed in which the original BuOH reaction mixture was extracted with smaller portions of water at successively lower pH. This removed essentially all of **42** from the BuOH, since its partitioning into water is higher at lower pH. However, some of **43** is also extracted into water at the lower pH, so the combined aqueous solution is back-extracted sequentially through two separate portions of BuOH to give an aqueous solution containing 0.1% or less of **43** relative to **42**. There was usually a 5–10% loss of **42**

through the extraction process, so the activity yield from **35** was about 85%.

Up to this point, the coupling of **42** with **24** had been done in anhydrous organic solvents with toluene as a cosolvent, since **24** was prepared in toluene and stored as a solution in toluene (*vide supra*). We were therefore pleasantly surprised when it was discovered that this reaction actually worked better in water, with or without an organic cosolvent, making it quite simple to combine these two steps. Solid NaHCO<sub>3</sub> and 1.3 equiv of **24** were simply added to the aqueous solution of **42** from the previous step, and conversion to **1** was generally complete after heating at reflux (90 °C) for ca. 1 h. The reaction worked equally well using solid **24** or the toluene solution in a two-phase system. Concerns that **24** would hydrolyze to hydroxypyrimidine **23** under the aqueous reaction conditions proved to be groundless. The product was isolated by acidifying the reaction mixture at 50 °C with 6 N HCl, and the HCl salt of **1** crystallized on cooling. This procedure gave purer product than any other procedure used to this point in ca. 70% yield from **35**. The product could be purified further by recrystallization of the HCl salt from aqueous NaCl. After this purification, the yield from **35** was ca. 65%.

## Conclusion

An efficient and practical synthesis of the antimigraine drug candidate, avitriptan, was developed in an overall 40–45% yield from aniline **5**. The key step is a novel two-phase Fischer indolization reaction, despite both substrate and product being susceptible to acid-induced degradation.

## Experimental Section

**General Methods.** <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 360 and 90.6 MHz, respectively. Mass spectra were obtained using a Micromass triple quadrupole mass spectrometer equipped with electrospray and APCI interfaces. Melting points and boiling points are uncorrected. All solvents and reagents were used as purchased from vendors without further purification. Reactions were monitored by TLC, GC, or reversed-phase HPLC. Column chromatography was done using ICN 32–63 µm, 60 Å silica gel. 4-Amino-*N*-methylbenzenemethanesulfonamide, **5**,<sup>9</sup> 2-hydroxytetrahydropyran, **15**,<sup>13</sup> 5-bromopentanol,<sup>16</sup> 5-chlorovaleraldehyde, **20**,<sup>15</sup> 5-bromovaleraldehyde, neopentyl acetal, **18**,<sup>17</sup> and 4-hydroxy-5-methoxy-pyrimidine, **23**,<sup>21</sup> were prepared according to previously reported procedures.

**4-Hydrazino-*N*-methylbenzenemethanesulfonamide, Hydrochloride (6).** A stirred mixture of *N*-methyl-4-amino-*N*-methylbenzenemethanesulfonamide, **5** (80.1 g, 400 mmol), concentrated HCl (800 mL), and water (400 mL) under Ar was heated until a complete solution was obtained (~70 °C). The solution was cooled to –5 °C, and the HCl salt of **5** precipitated. To the resulting slurry was added a prechilled (0–5 °C) solution of NaNO<sub>2</sub> (29.0 g, 420 mmol) in water (400 mL) beneath the surface of the mixture at a rate such that an internal temperature of –5 to 0 °C was maintained. The resulting clear solution was added by cannula with positive Ar pressure to a stirred solution of SnCl<sub>2</sub> (227.5 g, 1200 mmol) in concentrated HCl (800 mL) at –20 °C at a rate such that an internal temperature of –10 to –20 °C was maintained. The resulting slurry was stirred at –20 °C for 1.5 h, and then the solid was collected by filtration on a coarse sintered glass filter. The solid was washed with cold (0–5 °C) EtOH (2 × 200 mL) and dried to constant weight in vacuo at 40 °C to give the HCl salt of **6** as a white solid (87.8 g, 87%): <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 2.40 (d, 3 H, *J* = 5.0 Hz), 4.08 (s, 2 H), 6.77 (m, 1 H), 6.84 (d, 2 H, *J* = 8.3 Hz), 7.11 (d, 2 H, *J* = 8.3 Hz), 8.28 (br s, 1 H),

10.23 (br s, 3 H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  29.7, 56.1, 115.0, 123.8, 132.1, 146.3; ES $^+$  MS  $m/z$  216 (16)  $\text{MH}^+$ .

**5-Bromoaleraldehyde Dimethyl Acetal (17).** A stirred solution of 5-bromopentanol (29 g, 174 mmol) in  $\text{CH}_2\text{Cl}_2$  (150 mL) was cooled to  $-5^\circ\text{C}$ , and a solution of KBr (2.0 g, 16.8 mmol) in water (10 mL) was added. TEMPO (5 mg, 32  $\mu\text{mol}$ ) was also added. To the resulting vigorously stirred mixture was added a cold ( $0$ – $5^\circ\text{C}$ ) 5.25% aqueous NaOCl solution (265 mL, 187 mmol) that had been adjusted to pH 9 with saturated aqueous NaHCO<sub>3</sub>. The NaOCl solution was added in a thin stream during 5–6 min, and the temperature was maintained at  $<10^\circ\text{C}$ . On completion of the addition, the reaction mixture was stirred for an additional 3 min, and confirmation that the reaction was complete was achieved by TLC. The phases were separated, and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 15$  mL). The  $\text{CH}_2\text{Cl}_2$  fractions were combined, and the resulting solution was washed with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (100 mL), diluted with water (50 mL), dried over MgSO<sub>4</sub>, and filtered. The bromoaldehyde **16** could be isolated at this point by concentrating in vacuo to a residue, but usually it was converted directly to the dimethyl acetal. HC(OCH<sub>3</sub>)<sub>3</sub> (22 mL, 201 mmol) and MeOH (15 mL) were added to the  $\text{CH}_2\text{Cl}_2$  solution containing **16**, and HCl gas was bubbled through the mixture for 5 s. After the solution was stirred for 30 min at  $20^\circ\text{C}$ , the reaction completion was verified by TLC. Triethylamine ( $\sim 1$  mL) was added to adjust the pH to 8, and the mixture was washed with water (200 mL), dried over MgSO<sub>4</sub>, and concentrated in vacuo to give crude **17** as a colorless oil (38 g). The crude product was vacuum distilled through a Vigreux column to yield purified **17** (28.4 g, 78% yield): bp  $57$ – $60^\circ\text{C}/1.5$  Torr;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.30 (m, 2 H), 1.41 (m, 2 H), 1.66 (m, 2 H), 3.11 (s, 6 H), 3.19 (t, 2 H,  $J = 6.8$  Hz), 4.15 (t, 1 H,  $J = 5.6$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  24.8, 33.2, 34.0, 35.0, 54.3, 105.8.

**Isolation of Crystalline 4-Chloro-5-methoxypyrimidine (24).** 4-Hydroxy-5-methoxypyrimidine **23** (60 g, 467 mmol) was converted to a toluene solution (945 mL) containing 58 g of **24** following the procedure of Anderson.<sup>21</sup> The solution was concentrated in vacuo to a volume of  $\sim 100$  mL, warmed to  $60^\circ\text{C}$ , and diluted with heptane (400 mL). The hot solution was treated with activated carbon (3 g) for 10 min, which was removed by filtration through a Celite pad. The pad was washed with hot ( $60^\circ\text{C}$ ) heptane (75 mL), and this wash was combined with the original filtrate. The product crystallized as white needles on cooling. The crystal slurry was stirred at  $0$ – $5^\circ\text{C}$  for 1 h, and then the solid was collected by filtration, washed with heptane (100 mL), and dried to constant weight in vacuo at room temperature to give **24** as a white crystals (51.0 g, 74% yield): mp  $62$ – $64^\circ\text{C}$  (lit.<sup>22</sup> mp  $63$ – $64^\circ\text{C}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.05 (s, 3 H), 8.35 (s, 1 H), 8.94 (s, 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  57.0, 140.0, 150.5 (two signals), 150.8; ES $^+$  MS  $m/z$  145 (100)  $\text{MH}^+$ .

**5-Methoxy-4-piperazinylpyrimidine (9).** To a stirred solution of **24** (229.3 g, 1.586 mol) in  $\text{CH}_2\text{Cl}_2$  (700 mL) under  $\text{N}_2$  at  $20^\circ\text{C}$  was added triethylamine (331.6 mL, 2.379 mol) dropwise while the temperature of the reaction mixture was maintained at  $20$ – $30^\circ\text{C}$ . To the resulting solution was added ethyl 1-piperazinecarboxylate (**25**) (278.8 mL, 1.903 mol) dropwise, maintaining the temperature at  $20$ – $30^\circ\text{C}$  during the addition. The solution was heated at reflux as  $\text{CH}_2\text{Cl}_2$  was removed by distillation until  $\sim 200$  mL was removed, at which point the reflux temperature was  $\sim 60^\circ\text{C}$ . Heating at reflux was continued for 8–10 h, and the reaction was complete (HPLC). The reaction mixture was cooled to  $25^\circ\text{C}$ , diluted with  $\text{CH}_2\text{Cl}_2$  (200 mL) and water (400 mL), and then adjusted to pH 7.0 with either concentrated HCl or 50% NaOH. The phases were separated, and the organic phase was washed with water (100 mL). The combined aqueous phase was back-extracted with  $\text{CH}_2\text{Cl}_2$  (100 mL). The combined organic phase containing the protected piperazinylpyrimidine **27** was carried on to the next step without isolation. The solution was heated and  $\sim 500$  mL of  $\text{CH}_2\text{Cl}_2$  removed by distillation, causing the reflux temperature to increase to  $60$ – $70^\circ\text{C}$ . This mixture was cooled to just below reflux, and  $n$ -BuOH (200 mL) was added. Heating and distillation were continued until the pot temperature reached  $105^\circ\text{C}$ , and then the mixture was cooled to 80

$^\circ\text{C}$  and more  $n$ -BuOH (900 mL) was added. After the mixture was cooled to  $35$ – $50^\circ\text{C}$ , 50% NaOH (830 mL) and water (200 mL) were added, the resulting mixture was heated at  $90^\circ\text{C}$  for 10 h, and the reaction was complete (HPLC). The reaction mixture was cooled to  $25^\circ\text{C}$ , water (1000 mL) was added, and stirring was continued until all of the solids dissolved. The phases were separated, and the organic phase was washed with water ( $4 \times 250$  mL). The combined aqueous washes were back-extracted with  $n$ -BuOH (150 mL), and the combined  $n$ -BuOH solution was concentrated in vacuo to a viscous oil. The oil was diluted with  $n$ -BuOAc (100 mL) and seeded with **9**. After the mixture was stirred for 15 min, heptane (100 mL) was added and stirring continued until a thin slurry formed. More heptane (1100 mL) was added slowly during 30 min, and the resulting slurry was stirred at  $20$ – $25^\circ\text{C}$  for 10 h, and then  $0$ – $5^\circ\text{C}$  for 3 h. The solid was collected by filtration, washed with heptane (200 mL), and dried to constant weight in vacuo to give **9** as a white solid (196.4 g, 63.8% yield): mp  $60$ – $64^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.96 (m, 4 H), 3.72 (m, 4 H), 3.85 (s, 3 H), 7.89 (s, 1 H), 8.33 (s, 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  45.7, 47.5, 55.5, 136.8, 142.3, 150.3, 154.1; ES $^+$  MS  $m/z$  195 (100)  $\text{MH}^+$ . Bis-substituted impurity **28**, produced in some batches, was isolated by flash chromatography on silica gel (2% MeOH in  $\text{CH}_2\text{Cl}_2$ ): mp  $211$ – $213^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.79 (s, 8 H), 3.82 (s, 6 H), 7.86 (s, 2 H), 8.29 (s, 2 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  47.0, 56.5, 137.6, 143.3, 151.2, 154.8; ES $^+$  MS  $m/z$  303 (30)  $\text{MH}^+$ .

**1-[4-(5-Methoxy-4-pyrimidinyl)-1-piperazinyl]pentan-5-ol, Neopentyl Acetal, HCl salt (19).** To a stirred mixture of **9** (12.0 g, 62 mmol) and **18** (23.3 g, 93 mmol) in water (15 mL) at  $20^\circ\text{C}$  was added 19.1 M NaOH (4.9 mL, 93 mmol) dropwise. The resulting mixture was heated at  $40^\circ\text{C}$  for 18 h and then extracted with BuOAc (150 mL). The BuOAc solution was washed with water ( $5 \times 30$  mL) and concentrated in vacuo to an oil (26 g). The oil was dissolved in BuOAc (100 mL), and concentrated HCl (5.2 mL, 62 mmol) was added. The resulting mixture was concentrated in vacuo to azeotropically remove the water, and the remaining crystal slurry was cooled to  $15^\circ\text{C}$ . The solid was collected by filtration, washed with BuOAc (50 mL) and heptane (50 mL), and dried to constant weight in vacuo to give **19** as an off-white solid (15.0 g, 60% yield). An analytical sample of **19** was prepared by recrystallization from IPA:  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  0.51 (s, 3 H), 0.91 (s, 3 H), 1.20 (m, 2 H), 1.38 (m, 2 H), 1.56 (m, 2 H), 2.87 (m, 4 H), 3.21 (m, 4 H), 3.34 (m, 6 H), 3.71 (s, 3 H), 4.27 (s, 1 H), 7.99 (s, 1 H), 8.18 (s, 1 H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  21.5, 22.3, 23.6, 30.6, 34.5, 43.9, 51.2, 56.2, 57.2, 76.9, 101.7, 138.2, 143.5, 150.4, 154.0; ES $^+$  MS  $m/z$  365 (100)  $\text{MH}^+$ .

**N-Methyl-3-(3'-hydroxypropyl)-1*H*-indolyl-5-methanesulfonamide (8).** To a stirred solution of the HCl salt of **6** (5.04 g, 20.0 mmol) in EtOH (50 mL)/water (40 mL) under Ar at  $20^\circ\text{C}$  was added a solution of **15** (2.45 g, 24.0 mmol) in EtOH (10 mL). The pH was adjusted to 3.5 with 50% NaOH, and the mixture was heated at  $60^\circ\text{C}$  for 3 h, at which point conversion to hydrazone **31** was complete (HPLC). The reaction mixture was cooled to  $20^\circ\text{C}$ , adjusted to pH 10 with 50% NaOH, and concentrated in vacuo to remove most of the EtOH. The residual two-phase mixture was extracted with EtOAc ( $3 \times 50$  mL). The combined EtOAc solution was washed with saturated NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to give **31** as a viscous orange oil as a  $\sim 3$ :1 mixture of isomers, which was carried on directly to the next step.  $^1\text{H}$  NMR of major isomer (DMSO- $d_6$ ):  $\delta$  1.47 (m, 4 H), 2.20 (m, 2 H), 2.50 (d, 3 H,  $J = 5.3$  Hz), 3.40 (m, 2 H), 4.13 (s, 2 H), 4.43 (m, 1 H), 6.80 (m, 3 H), 7.10 (m, 3 H), 9.72 (s, 1 H). The oil was dissolved in 1,2-dichloroethane (300 mL), and 6 M phosphoric acid was added (12 mL, 72 mmol). The resulting two-phase mixture was stirred vigorously and heated at reflux for 1.5 h, at which point the reaction was complete (HPLC). The reaction mixture was cooled, and the phases were separated. The aqueous phosphoric acid phase was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 50$  mL). The combined organic phase was washed with saturated NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to give the crude product (4.49 g). This material was purified by flash chromatography on silica gel ( $\text{CH}_2\text{Cl}_2$ , MeOH, NH<sub>4</sub>OH, 95:5:0.5) to give **8** as a viscous yellow oil (2.80 g, 50%

yield):  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  1.82 (m, 2 H), 2.56 (d, 3 H,  $J$  = 5.0 Hz), 2.73 (t, 2 H,  $J$  = 7.7 Hz), 3.49 (m, 2 H), 4.36 (s, 2 H), 4.47 (t, 1 H,  $J$  = 5.2 Hz), 6.78 (q, 1 H,  $J$  = 5.0 Hz), 7.09 (dd, 2 H,  $J$  = 8.6, 1.8 Hz) 7.33 (d, 1 H,  $J$  = 8.6 Hz), 7.53 (s, 1 H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  22.0, 29.8, 34.1, 57.5, 61.4, 112.0, 115.5, 120.4, 121.7, 123.6, 124.5, 128.1, 136.9; ES $^+$  MS  $m/z$  283 (21)  $\text{MH}^+$ , 565 (52) 2M +  $\text{H}^+$ . Three impurities giving another 20% yield were also isolated from the chromatography. **36**:  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  1.30–1.95 (m, 8 H), 2.55 (d, 3 H,  $J$  = 5.0 Hz), 2.72 (m, 2 H), 3.35 (m, 2 H), 3.70 (m, 2 H), 4.35 (s, 2 H), 4.53 (s, 1 H), 6.80 (m, 1 H), 7.07 (d, 1 H,  $J$  = 8.6 Hz), 7.15 (s, 1 H), 7.27 (d, 1 H,  $J$  = 8.6 Hz), 7.38 (s, 1 H), 7.52 (s, 1 H). **37**: mp 118–120 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  1.34–1.90 (m, 8 H), 2.32 (d, 3 H,  $J$  = 5.0 Hz), 2.47 (t, 2 H,  $J$  = 7.2 Hz), 3.25 (m, 2 H), 3.49 (m, 1 H), 3.72 (m, 1 H), 4.13 (s, 2 H), 4.23 (br s, 1 H), 5.33 (d, 1 H,  $J$  = 9.5 Hz), 6.54 (m, 1 H), 6.92 (d, 1 H,  $J$  = 8.6 Hz), 7.07 (s, 1 H), 7.27 (d, 1 H,  $J$  = 8.6 Hz), 7.29 (s, 1 H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  21.9, 23.7, 25.7, 29.8, 31.1, 33.8, 57.2, 61.3, 68.0, 83.3, 111.1, 116.2, 121.6, 122.0, 123.5, 125.0, 128.9, 136.6; ES $^+$  MS  $m/z$  367 (100)  $\text{MH}^+$ . **38**:  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  2.03 (m, 4 H), 2.78 (d, 3 H,  $J$  = 5.0 Hz), 2.92 (m, 2 H), 2.98 (m, 2 H), 3.72 (t, 4 H,  $J$  = 6.3 Hz), 4.36 (s, 2 H), 4.57 (s, 2 H), 4.69 (br s, 2 H), 6.99 (q, 1 H,  $J$  = 5.0 Hz), 7.19 (d, 1 H,  $J$  = 8.1 Hz), 7.24 (d, 1 H,  $J$  = 8.6 Hz), 7.30 (d, 1 H,  $J$  = 1.8 Hz), 7.46 (d, 1 H,  $J$  = 8.1 Hz), 7.47 (d, 1 H,  $J$  = 8.1 Hz), 7.67 (s, 1 H), 7.70 (s, 1 H), 10.86 (s, 1 H), 10.93 (s, 1 H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  21.1, 22.1, 29.8, 32.8, 34.1, 34.9, 41.1, 61.4, 61.5, 111.2, 112.0, 115.1, 118.7, 120.2, 121.2, 122.6, 123.2, 123.7, 128.2, 129.1, 130.1, 135.9, 136.1, 137.0; ES $^+$  MS  $m/z$  470 (70)  $\text{MH}^+$ .

**N-Methyl-3-(3'-bromopropyl)-1*H*-indolyl-5-methane-sulfonamide (34).** To a stirred hazy solution of the HCl salt of **6** (10.07 g, 40.0 mmol) in EtOH (100 mL)/water (50 mL) under Ar at 20 °C was added **17** (10.13 g, 48.0 mmol) dropwise during 1–2 min. The resulting mixture was stirred for 1 h as the pH dropped from 2.2 to 1.1. The pH was adjusted to 4.0 with 50% NaOH, and after 15 min conversion to bromohydrazone **32** was complete (HPLC). The reaction mixture was clarified by filtration through a Celite pad, which was washed with EtOH (25 mL). The filtrate was concentrated in vacuo to remove EtOH, and the aqueous residue was extracted with BuOAc (3 × 100 mL). The combined BuOAc phase was washed with saturated NaCl, dried over MgSO<sub>4</sub>, and filtered through a Celite pad, which was washed with BuOAc (25 mL). Crude **32** could be isolated as a ~3:1 mixture of isomers by concentrating to a residue but was generally carried on to the indolization step without isolation.  $^1\text{H}$  NMR of the major isomer (DMSO- $d_6$ ):  $\delta$  1.60 (m, 2 H), 1.85 (m, 2 H), 2.25 (m, 2 H), 2.50 (d, 3 H,  $J$  = 4.0 Hz), 3.54 (m, 2 H), 4.13 (s, 2 H), 6.83 (m, 3 H), 7.10 (m, 3 H), 9.77 (br s, 1 H). The filtrate was added to 6 M H<sub>3</sub>PO<sub>4</sub> (24 mL, 144 mmol) in a jacketed reactor equipped with a bottom drain. The resulting two-phase mixture was stirred vigorously and heated at reflux (jacket temperature of 110 °C) for 30 min. Stirring was stopped, the lower aqueous H<sub>3</sub>PO<sub>4</sub> phase was drained off, and fresh 6 M H<sub>3</sub>PO<sub>4</sub> (24 mL, 144 mmol) was added. Heating and stirring were resumed for an additional 30 min. Stirring was stopped, and the H<sub>3</sub>PO<sub>4</sub> phase exchange was done once more. Heating and stirring were continued an additional 30 min, at which point no **32** remained (HPLC). The reaction mixture was cooled to 20 °C, and the phases were separated. The BuOAc phase was washed with saturated NaHCO<sub>3</sub> and saturated NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to give **34** as a pale orange crystalline solid (9.35 g). This material assayed at 87% purity by HPLC vs a standard for an overall activity yield of 59%. An analytical sample was prepared by recrystallization from BuOAc: mp 108–109 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  2.39 (m, 2 H), 2.77 (d, 3 H,  $J$  = 5.0 Hz), 3.05 (t, 2 H,  $J$  = 7.2 Hz), 3.79 (t, 2 H,  $J$  = 6.6 Hz), 4.57 (s, 2 H), 6.99 (q, 1 H,  $J$  = 5.0 Hz), 7.31 (dd, 1 H,  $J$  = 8.5, 1.6 Hz), 7.40 (d, 1 H,  $J$  = 1.6 Hz), 7.55 (d, 1 H,  $J$  = 8.5 Hz), 7.75 (s, 1 H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  24.0, 29.8, 33.8, 35.8, 57.4, 112.1, 113.8, 120.7, 121.6, 124.0, 124.7, 127.9, 136.9; ES $^-$  MS  $m/z$  343 (100) M – H<sup>+</sup>.

**N-Methyl-3-(3'-chloropropyl)-1*H*-indolyl-5-methane-sulfonamide (35).** To a stirred slurry of the HCl salt of **6** (50.34 g, 200 mmol) in BuOAc (500 mL) under Ar at 0–5 °C

was added **20** (27.73 g, 230 mmol), followed by triethylamine (28 mL, 200 mmol). The resulting mixture was stirred for 1.5 h at 0–5 °C, at which point conversion to chlorohydrazone **33** was complete (HPLC). The reaction mixture was filtered through a Celite pad to remove the precipitated triethylamine hydrochloride, and the pad was washed with BuOAc (80 mL). Crude **33** could be isolated as a ~3:1 mixture of isomers by concentrating the filtrate but generally was carried on directly to the indolization reaction:  $^1\text{H}$  NMR of the major isomer (DMSO- $d_6$ )  $\delta$  1.60 (m, 2 H), 1.75 (m, 2 H), 2.27 (m, 2 H), 2.51 (d, 3 H,  $J$  = 5.0 Hz), 3.66 (t, 2 H,  $J$  = 6.4 Hz), 4.13 (s, 2 H), 6.82 (m, 3 H), 7.03 (m, 3 H), 9.76 (s, 1 H). The filtrate was cooled to 0–5 °C and added dropwise to a vigorously stirred mixture of BuOAc (300 mL) and 6 M H<sub>3</sub>PO<sub>4</sub> (120 mL, 720 mmol) at 105–108 °C in a jacketed reactor equipped with a bottom drain. The addition was done as fast as possible while still maintaining a reflux of the reaction mixture. Stirring was stopped 15 min after completion of the addition, the lower aqueous H<sub>3</sub>PO<sub>4</sub> phase was drained off, and fresh 6 M H<sub>3</sub>PO<sub>4</sub> (120 mL, 720 mmol) was added. Heating and stirring were resumed for 30 min, and then the aqueous H<sub>3</sub>PO<sub>4</sub> phase exchange was done once more. After an additional 45 min–1.5 h the reaction was complete by HPLC. The phases were separated, and the BuOAc phase was washed with cold (0–5 °C) water (2 × 200 mL), followed by saturated NaHCO<sub>3</sub> (2 × 200 mL), and then concentrated in vacuo to a volume of ~100 mL. This solution was seeded with ~10 mg of crystalline **35** and BuOAc:hexane (1:1, 60 mL) added slowly until a thick crystal slurry was obtained. Crystallization was completed by further slow addition of hexane (60 mL). The crystal slurry was stirred for 1 h at 20 °C, and then the solid was collected by filtration, washed with BuOAc:hexane (1:4, 50 mL), and dried to constant weight in vacuo at 20 °C to give **35** as a tan crystalline solid (44.11 g, 73%). This material assayed at 87% purity by HPLC vs standard for an isolated activity yield of 64%. An analytical sample was prepared by recrystallization from EtOAc: mp 102–104 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  2.12 (m, 2 H), 2.57 (d, 3 H,  $J$  = 5.0 Hz), 2.84 (t, 2 H,  $J$  = 7.2 Hz), 3.71 (t, 2 H,  $J$  = 6.6 Hz), 4.37 (s, 2 H), 6.81 (q, 1 H,  $J$  = 5.0 Hz), 7.12 (dd, 1 H,  $J$  = 8.5, 1.6 Hz), 7.21 (d, 1 H,  $J$  = 1.6 Hz), 7.36 (d, 1 H,  $J$  = 8.5 Hz), 7.56 (s, 1 H), 10.90 (s, 1 H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  22.8, 29.8, 33.6, 46.0, 57.4, 112.1, 113.9, 120.7, 121.6, 124.0, 124.7, 127.9, 136.9; ES $^-$  MS  $m/z$  299 (100) M – H<sup>+</sup>.

**4-(5-Methoxy-4-pyrimidinyl)-1-[3-[5-[(methylamino)sulfonyl]methyl]-1*H*indol-3-ylpropyl]piperazine (1) from 8.** To a stirred solution of **8** (4.17 g, 14.8 mmol) in pyridine (45 mL) under Ar at 0–5 °C were added DMAP (0.18 g, 1.5 mmol) and *p*-toluenesulfonic anhydride (5.96 g, 17.7 mmol). The reaction mixture was stirred at 0–5 °C for 1 h, at which point HPLC showed the reaction was complete. The reaction mixture was concentrated in vacuo, and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The organic solution was washed with 1 N HCl (2 × 30 mL) and water (3 × 30 mL). The combined aqueous washes were back-extracted with CH<sub>2</sub>Cl<sub>2</sub> (30 mL), and the combined organic solution was dried over MgSO<sub>4</sub> and concentrated in vacuo to give tosylindole **39b** as a viscous yellow oil (6.05 g):  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  2.02 (m, 2 H), 2.43 (s, 3 H), 2.68 (s, 3 H), 2.79 (t, 2 H,  $J$  = 7.1 Hz), 4.05 (t, 2 H,  $J$  = 6.2 Hz), 4.33 (s, 2 H), 6.95 (s, 1 H), 7.17 (d, 1 H,  $J$  = 8.0 Hz), 7.35 (m, 3 H), 7.57 (s, 1 H), 7.78 (d, 2 H,  $J$  = 8.2 Hz), 8.18 (br s, 1 H). This material was used directly in the next step by dissolving in acetone (42 mL) and *N,N*-diisopropylethylamine (3.1 mL, 17.7 mmol) and adding **9** (5.74 g, 29.5 mmol). The reaction mixture was heated at reflux for 2.5 h, at which point conversion to **1** was complete (HPLC). EtOAc (50 mL) and water (25 mL) were added, and the phases were separated. The aqueous phase was extracted with EtOAc (30 mL). The organic phases were combined and washed with saturated NaHCO<sub>3</sub> and saturated NaCl, dried over MgSO<sub>4</sub>, and concentrated in vacuo to give the crude product as a foam (5.81 g). This material was purified by flash chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>, MeOH, NH<sub>4</sub>OH, 95:5:0.5) to give **1** as an off-white foam (3.59 g, 53% yield). An analytical sample was prepared by crystallization from anhydrous EtOH: mp 173–174 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  1.75 (m, 2 H), 2.29 (t, 2 H,  $J$  = 7.2 Hz),

2.37 (m, 4 H), 2.46 (d, 3 H,  $J = 5.0$  Hz), 2.63 (t, 2 H,  $J = 7.4$  Hz), 3.61 (m, 4 H), 3.75 (s, 3 H), 4.27 (s, 2 H), 6.70 (q, 1 H,  $J = 5.0$  Hz), 7.00 (d, 1 H,  $J = 8.6$  Hz), 7.07 (d, 1 H,  $J = 1.8$  Hz), 7.24 (d, 1 H,  $J = 8.6$  Hz), 7.44 (s, 1 H), 7.94 (s, 1 H), 8.16 (s, 1 H), 10.73 (s, 1 H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  23.3, 27.9, 29.8, 47.1, 53.7, 57.0, 57.5, 58.5, 112.0, 115.4, 120.5, 121.7, 123.7, 124.5, 128.1, 136.8, 138.6, 143.3, 151.0, 154.6; ES<sup>+</sup> MS  $m/z$  459 (27) MH<sup>+</sup>.

**4-(5-Methoxy-4-pyrimidinyl)-1-[3-[5-[(methylamino)sulfonyl]methyl]-1*H*-indol-3-yl]propylpiperazine (**1**) by coupling of **35** and **9**. Process A.** A stirred mixture of **35** (9.03 g, 30.0 mmol), **9** (7.0 g, 36.0 mmol), NaI (8.99 g, 60.0 mmol), and *N,N*-diisopropylethylamine (6.3 mL, 36.0 mmol) in acetone (30 mL) under Ar was heated at reflux for 18 h. HPLC at this point showed 4% unreacted **35** relative to **1**. The reaction mixture was cooled to 20 °C and diluted with acetone (30 mL) and water (30 mL), and the pH was adjusted to 4.0 with 6 N HCl. The clear brown solution was seeded and cooled to 0 °C, and the product began to crystallize. The final pH was adjusted to 2.0, and the crystal slurry was stirred at 0–5 °C for 2 h. The solid was collected by filtration, washed with acetone (2 × 25 mL), and dried to constant weight in vacuo at 20 °C to give the HCl salt of **1** as a tan solid (15.10 g). This material assayed at 63.4% purity<sup>26</sup> by HPLC vs a standard for a 70% activity yield of **1** from **35**. Recrystallization from aqueous NaCl upgraded the purity to 72.9%. The only detectable impurity was the overalkylated quaternary salt **40**, at 1.4% relative to **1**:  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  2.01 (m, 2 H), 2.39 (s, 3 H), 2.63 (t, 2 H,  $J = 7.2$  Hz), 2.98 (m, 4 H), 3.44 (m, 2 H), 3.61 (m, 2 H), 3.77 (s, 3 H), 4.20 (s, 2 H), 4.76 (m, 2 H), 6.69 (br s, 1 H), 6.95 (d, 1 H,  $J = 8.1$  Hz), 7.09 (d, 1 H,  $J = 2.2$  Hz), 7.19 (d, 1 H,  $J = 8.1$  Hz), 7.41 (s, 1 H), 8.07 (s, 1 H), 8.51 (s, 1 H), 10.86 (s, 1 H), 11.72 (br s, 1 H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  22.7, 24.5, 29.9, 44.6, 51.2, 56.2, 57.4, 58.3, 112.1, 113.7, 120.7, 121.6, 124.1, 124.7, 127.5, 127.8, 136.9, 142.5, 145.8, 155.2.

**Quaternary Salt Impurity **40**.** A stirred mixture of **35** (3.00 g, 10.0 mmol), **9** (1.11 g, 5.71 mmol), NaI (2.85 g, 19.0 mmol), and *N,N*-diisopropylethylamine (1.99 mL, 11.40 mmol) in acetone (7.5 mL) under Ar was heated at reflux for 22 h. HPLC showed a ~1:1 mixture of **40** to **1**. The reaction mixture was concentrated in vacuo to a residue, which was chromatographed on a flash column of silica gel (CH<sub>2</sub>Cl<sub>2</sub>, MeOH, NH<sub>4</sub>-OH; 85:15:0.5) to give **40** as a foam (0.88 g) contaminated with about 15% of **1**:  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  2.13 (m, 2 H), 2.36 (m, 2 H), 2.61 (s, 3 H), 2.62 (s, 3 H), 2.84 (m, 4 H), 3.28–3.71 (m, 8 H), 3.95 (s, 3 H), 4.41 (m, 6 H), 5.03 (br s, 2 H), 6.84 (m, 2 H), 7.16 (m, 2 H), 7.30 (s, 2 H), 7.40 (m, 2 H), 7.59 (s, 1 H), 7.61 (s, 1 H), 8.40 (s, 1 H), 8.86 (s, 1 H), 9.89 (br s, 1 H), 10.94 (s, 1 H), 10.99 (s, 1 H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  21.6, 21.7, 24.1, 29.0, 29.8, 50.6, 53.6, 54.9, 55.5, 56.5, 56.6, 57.3, 57.8, 111.1, 111.2, 112.6, 112.7, 119.7, 119.8, 120.6, 120.8, 123.1, 123.2, 123.8, 123.9, 126.8, 126.9, 127.5, 135.9, 136.0, 140.9, 145.8, 153.1; ES<sup>+</sup> MS  $m/z$  723 (8) MH<sup>+</sup>.

**4-(5-Methoxy-4-pyrimidinyl)-1-[3-[5-[(methylamino)sulfonyl]methyl]-1*H*-indol-3-yl]propylpiperazine (**1**) From **35** by Three-Step Process B.** A stirred mixture of **35** (15.0 g, 50.0 mmol), NaI (11.25 g, 75.0 mmol), Na<sub>2</sub>CO<sub>3</sub> (6.36 g, 60.0 mmol), and ethyl 1-piperazinecarboxylate, **25** (8.06 mL, 55.0 mmol), in EtOH (75 mL) under Ar was heated at reflux for 8–10 h, at which point the reaction was complete by HPLC. The reaction mixture was cooled to 20 °C, and EtOAc (190 mL) and water (50 mL) were added. After all the solids dissolved, the phases were separated, and the organic phase was washed with water (2 × 100 mL). The combined aqueous phase was back-extracted with EtOAc (75 mL), and the upper phase was combined with the original organic phase and washed with saturated NaCl. The organic phase was assayed by HPLC vs standard, which showed it to contain 19.0 g (90% yield) of the protected piperazinylindole **41**. The standard was prepared

by making the oxalate salt of chromatographically purified **41**:  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  1.16 (t, 3 H,  $J = 7.0$  Hz), 1.96 (m, 2 H), 2.51 (d, 3 H,  $J = 4.0$  Hz), 2.70 (t, 2 H,  $J = 7.4$  Hz), 2.90 (m, 6 H), 3.53 (m, 4 H), 4.03 (q, 2 H,  $J = 7.0$  Hz), 4.31 (s, 2 H), 6.77 (m, 1 H), 7.06 (dd, 1 H,  $J = 8.6, 1.4$  Hz), 7.15 (d, 1 H,  $J = 1.4$  Hz), 7.30 (d, 1 H,  $J = 8.6$  Hz), 7.48 (s, 1 H), 10.89 (s, 1 H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  15.3, 22.8, 25.6, 29.8, 42.1, 51.9, 57.0, 57.4, 62.0, 112.1, 114.2, 120.6, 121.6, 123.9, 124.7, 127.9, 136.9, 155.2, 164.7; ES<sup>+</sup> MS  $m/z$  423 (100) MH<sup>+</sup>. The organic solution containing **41** was concentrated in vacuo to a volume of ~50 mL, and EtOH (200 mL) was added. This solution was concentrated in vacuo to a volume of ~140 mL to complete the solvent exchange from EtOAc to EtOH. NaOH (12.5 M, 36 mL, 450 mmol) was added and the resulting mixture heated at reflux for 5–10 h, at which point the reaction was complete by HPLC. The reaction mixture was cooled to 10–15 °C, diluted with EtOH (100 mL), and then neutralized to pH 8 with dropwise addition of concentrated HCl (34 mL, 408 mmol), maintaining the temperature at 20–30 °C. The mixture was further cooled to 10 °C, and the precipitated NaCl was removed by filtration. The filter cake was washed with EtOH (40 mL), and the filtrate was assayed by HPLC vs standard, which showed it to contain 14.8 g (95% yield) of the piperazinylindole **42**. The standard was prepared by making the oxalate salt of chromatographically purified **42**:  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  1.78 (m, 2 H), 2.37 (t, 2 H,  $J = 7.0$  Hz), 2.52 (m, 7 H), 2.68 (t, 2 H,  $J = 7.2$  Hz), 3.03 (m, 4 H), 4.33 (s, 2 H), 6.80 (m, 1 H), 7.05 (d, 1 H,  $J = 8.6$  Hz), 7.12 (d, 1 H,  $J = 1.8$  Hz), 7.30 (d, 1 H,  $J = 8.6$  Hz), 7.48 (s, 1 H), 10.86 (s, 1 H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  23.1, 27.7, 29.8, 43.8, 50.4, 57.4, 58.0, 112.0, 115.2, 120.4, 121.6, 123.8, 124.6, 128.1, 136.8, 165.7; ES<sup>+</sup> MS  $m/z$  351 (100) MH<sup>+</sup>. A solution of **24** (9.6 g, 66.4 mmol) in toluene (50 mL) and NaHCO<sub>3</sub> (7.43 g, 88.4 mmol) were added to the solution of **42** in EtOH, and the resulting mixture was heated at reflux. The reaction mixture was concentrated by distilling off solvent as the reaction proceeded until ~200 mL of distillate was collected. Heating at reflux was continued for 2–4 h until the reaction was complete by HPLC. The reaction mixture was cooled to 20 °C and diluted with EtOH (60 mL) and water (50 mL). The pH was adjusted to 4.0 with 6 N HCl, and the HCl salt of **1** began to crystallize. After stirring for 30 min, adjustment to a final pH of 2.0 was made. The crystal slurry was cooled to 0 °C and stirred for 2 h. The solid was collected by filtration, washed with EtOH (50 mL), and dried to constant weight in vacuo at 20 °C to give the HCl salt of **1** as a tan solid (27.6 g). This material assayed at 62.5% purity by HPLC vs standard for a 75% activity yield of **1** from **35**. Recrystallization from aqueous NaCl upgraded the purity to 78.0%. This material was identical with that produced by process A except that it did not contain impurity **40**.

**4-(5-Methoxy-4-pyrimidinyl)-1-[3-[5-[(methylamino)sulfonyl]methyl]-1*H*-indol-3-yl]propylpiperazine (**1**). From **35** by Two-Step Process C.** A stirred mixture of **35** (15.0 g, 50 mmol), piperazine (43.1 g, 500 mmol), *n*-BuOH (50 mL), and water (5 mL) was heated at 100 °C for 1 h, at which point HPLC showed that **35** had been consumed to give a 95:5 mixture of **42** to **43**. The reaction mixture was cooled to 20 °C, and saturated NaCl (80 mL) and water (25 mL) were added. The two-phase mixture was stirred vigorously, and the pH was adjusted to 9.0 with concentrated HCl (~9 mL). The phases were separated, and the organic phase was extracted with saturated NaCl (2 × 100 mL), each adjusted to pH 9.0 with concentrated HCl prior to the phase separation. Each of the three aqueous NaCl washes were extracted with the same portion of fresh *n*-BuOH (50 mL) and discarded. The original organic phase was sequentially extracted with four portions of water (50 mL at pH 8, 50 mL at pH 7, 50 mL at pH 6, 30 mL at pH 4). The pH was adjusted each time with concentrated HCl. The aqueous extracts were combined and back-extracted sequentially through two portions of *n*-BuOH of 50 mL each. The first portion of *n*-BuOH was the same one used to back-extract the saturated NaCl washes, and the second portion was fresh *n*-BuOH. These two portions of BuOH were then sequentially back-extracted with two fresh portions of water (30 mL at pH 6, 15 mL at pH 4). All aqueous phases were combined (~340 mL total volume), and the solution was

(26) Purity assays for **1** are as free base. The theoretical purity as base is 80.8% for the dihydrochloride dihydrate salt. Except for cases in which **40** was present, lower purities of the recrystallized HCl salt were due to NaCl or water in excess of 2 mol, rather than any organic impurity.

assayed by HPLC vs standard, which showed it to contain 14.8 g (85% yield) of **42**. This solution was carried on directly to the next step. NaHCO<sub>3</sub> (10.62 g, 126 mmol) and **24** (9.74 g, 67.4 mmol) were added, and the resulting mixture was heated at reflux for 2 h, at which point the reaction was complete by HPLC. The reaction mixture was cooled to 60 °C, NaCl (17 g) was added, and stirring was continued until all of the NaCl dissolved. The pH was adjusted to 3.0 with 6 N HCl (~20 mL), and on cooling the HCl salt of **1** began to crystallize at 35–40 °C. The crystal slurry was cooled to 0–5 °C and adjusted to a final pH of 2.0. After being stirred for 2 h at 0–5 °C, the solid was collected by filtration, washed with EtOH (2 × 25 mL), and dried to constant weight in vacuo at 20 °C to give the HCl salt of **1** as a tan solid (23.48 g). This material assayed at 66.6% purity by HPLC vs standard for a 68% activity yield of **1** from **35**. Recrystallization from aqueous NaCl upgraded the purity to 75%. This material was identical in all respects to that obtained from process B.

**Bis-alkylated Piperazine **43**.** A stirred mixture of **35** (5.0 g, 16.6 mmol), piperazine (2.1 g, 24.9 mmol), and *n*-BuOH (33 mL) was heated at 100 °C for 16 h, at which point HPLC showed a 1:1 mixture of piperazinylindole **42** to **43**. The reaction mixture was cooled and concentrated in vacuo to a residue, which was purified by flash chromatography on silica gel (EtOAc, MeOH; 1:1) to give **43** as a tan solid (1.75 g): <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.70 (m, 4 H), 2.29–2.95 (br s, 8 H), 2.31 (d, 6 H, *J* = 5.0 Hz), 2.48 (t, 4 H, *J* = 7.2 Hz), 3.22 (m, 4 H),

4.12 (s, 4 H), 6.65 (q, 2 H, *J* = 5.0 Hz), 6.86 (d, 2 H, *J* = 8.3 Hz), 6.94 (s, 2 H), 7.10 (d, 2 H, *J* = 8.3 Hz), 7.30 (s, 2 H), 10.77 (s, 2 H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 19.4, 23.1, 29.9, 56.9, 57.5, 112.0, 120.5, 121.7, 123.8, 124.6, 126.3, 128.0, 136.9; ES<sup>+</sup> MS *m/z* 615 (30) MH<sup>+</sup>.

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**Supporting Information Available:** <sup>1</sup>H NMR spectra for compounds **1**, **6**, **8**, **9**, **17**, **19**, **20**, **24**, **28**, and **31–43** and <sup>13</sup>C NMR spectra for **1**, **6**, **8**, **9**, **17**, **19**, **24**, **28**, **34**, **35**, **37**, **38**, and **40–43** (43 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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