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Facile Preparation of 3-(1-Piperazinyl)-1H-indazoles

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Abstract:

Pre-clinical evaluation of a potential antipsychotic agent required a convenient synthesis of 3-(1-piperazinyl)-1H-indazole derivatives. Improvements of the original preparation provided a five-step sequence to an unsubstituted piperazine intermediate, with a 67% overall yield. All intermediates were isolated by filtration.

Introduction

3-Aminoindazole derivatives (**1**, Figure 1) have been identified as potent dopamine receptor antagonists, useful for antipsychotic treatment,[1] as well as non-steroidal anti-inflammatory compounds with analgesic properties.[1,2] For the preclinical evaluation of 3-piperazinylindazole derivative **2** (Figure 2), we needed an efficient preparation of unsubstituted piperazine **3**. The preparation of *N*,*N*-disubstituted 3-aminoindazoles usually involves the substitution of 2- or 3-nitro-[3,4] or 3-haloindazole[5] derivatives with the appropriate secondary amine. Another approach is a late stage-indazole formation.[1,6] This paper describes improvements in the chemistry for the preparation of of *N*,*N*-disubstituted 3-aminoindazoles.[6]

Original Route. The original medicinal chemistry synthesis involved seven steps starting from commercially available ester **4** (Scheme 1).[6] Ester **4** was treated with hydrazine hydrate to provide hydrazide **5** in 87% yield. Sulfonylation of **5** with phenylsulfonyl chloride in pyridine gave 90% yield of sulfonamide **6**. Formation of the corresponding imidoyl chloride **7** was achieved in 72% yield using thionyl chloride. Imidoyl chloride **7** was treated with 2 equiv of 1-methylpiperazine to afford imidate **8** in 73% yield. Cyclization of **8** with potassium carbonate in DMF using a copper catalyst gave indazole **9** in 71% yield. Deprotection of **9** was achieved by first converting the methyl group of the piperazine to a cyano group with cyanogen bromide to afford a 75% yield of **10**. The use of a chloroformate was unsuccessful in cleaving the piperazinyl methyl group. Treatment of **10** with LAH gave indazole **3** in 73% yield by removing both the cyano and sulfonyl groups. The overall yield for the preparation of **3** was 18.4%.[6]

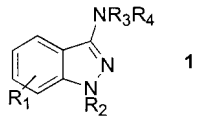


Figure 1.

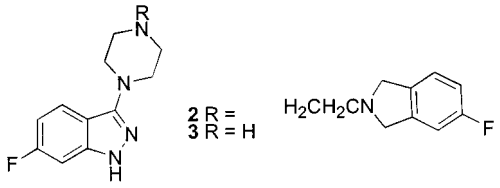
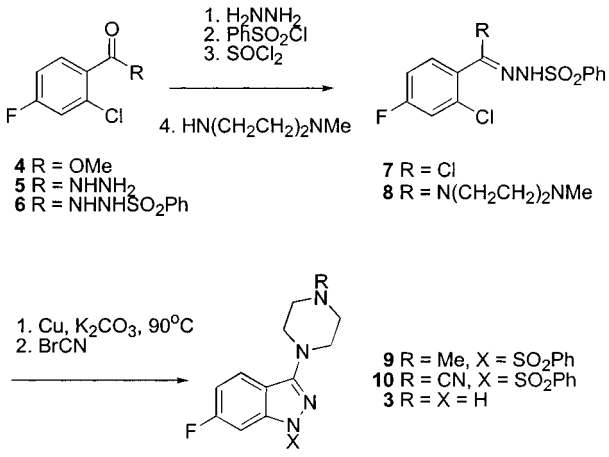


Figure 2.

Scheme 1



Results and Discussion

We wanted to improve the original synthesis, reduce the number of steps and intermediates, and eliminate the need for chromatographic purifications. The first obvious improvement was the use of tosylhydrazine, thus eliminating the sulfonylation reaction. Commercially available acid **11** was converted to acid chloride **12** with thionyl chloride in toluene (Scheme 2). The excess thionyl chloride was co-distilled with toluene, and tosylhydrazine was added portionwise at 75 °C. This reaction does not need an extra base, as the hydrochloric acid generated is not soluble in toluene at that temperature; it is trapped using a scrubber. The desired hydrazide **13** was isolated in 96% yield by filtration after cooling the reaction mixture. The formation of the imidoyl chloride **14** was achieved with thionyl chloride at 75 °C.

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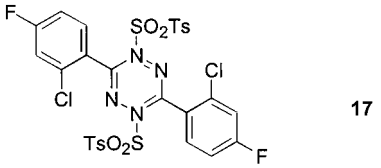

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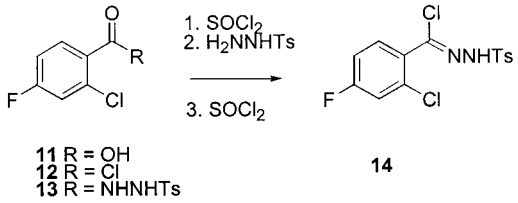
Figure 3.

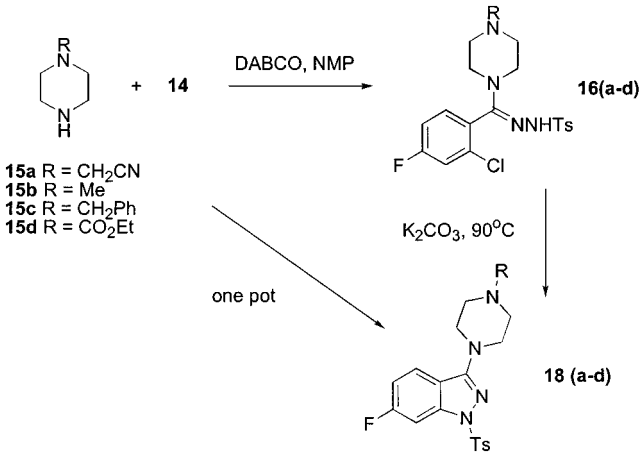
Scheme 2



11 R = OH
12 R = Cl
13 R = NHNHTs

14

Scheme 3



After cooling, heptane was added to precipitate **14**. Imidoyl chloride **14** was isolated by filtration in 96% yield.

We then turned our attention to indazole formation. The first step is the formation of imidate **16** from imidoyl chloride **14** and a suitable piperazine **15** (Scheme 3). Although stable as a solid, imidoyl chloride **14** forms tetrazine **17** (Figure 3) when in solution.[7] The rate of tetrazine **17** formation depends on the solvent and temperature and is promoted by bases (piperazine **15** as well as imidate **16**). For example, when imidoyl chloride **14** is added to *N*-methyl-2-pyrrolidinone (NMP) at room temperature, tetrazine **17** rapidly forms and precipitates as a white solid. On a larger scale, the yield of the tetrazine by-product can amount to about 20%. However, when the solution of the imidate is made and kept cold, much less tetrazine is formed, and no precipitation occurs. Another potential problem for this reaction is the need to use an excess of piperazine (2.0 equiv, Table 1, entry 1) to neutralize the acid formed. This can be a problem with expensive or noncommercially available piperazines. We therefore investigated the possibility of using less piperazine **15** along with an additional base in this reaction. The results are shown in Table 1 for 1-cyanomethylpiperazine **15a** (R = CH_2CN) in NMP to afford imidate **16a**.

The use of a tertiary amine (*n*-Bu_3N) did not provide a good conversion of starting material to product, and the imidate **16a** was isolated in 74% yield (entry 2). This result is consistent with the fact that the piperazine is the most basic amine of the system, and only 50% of it can be converted to **16a** in the absence of a stronger base. The use of a more basic amine (DABCO) solved this problem, and imidate **16a** was isolated in good yield (entry 3). The amount of the piperazine used can be decreased further to 1.1 equiv without any loss of yield (entry 4). The amount of DABCO used can also be decreased to 0.7 equiv (entry 5) with no adverse effect on the yield. Further reduction gave a lower yield of imidate **16a** (entry 6).

Table 1. **Preparation of imidate 16a**

entry	piperazine **15a**, equiv	amine (equiv)	isolated yield of **16a**, %
1	2.0	–	87
2	1.5	*n*-Bu_3N (2)	74
3	1.5	DABCO (1)	83
4	1.1	DABCO (1)	83
5	1.1	DABCO (0.7)	87
6	1.1	DABCO (0.55)	78

Table 2. **Preparation of Indazoles 18**

compound	R group	indazole **18**	yield (%)
15a	CH_2CN	**a**	71
15b	CH_3	**b**	77
15c	CH_2Ph	**c**	71
15d	CO_2Et	**d**	84

Having achieved a good conversion of **14** to imidate **16**, we then looked at the indazole formation. We realized that the copper catalyst used for such a cyclization reaction is not necessary with the fluorine substituent on the aromatic ring. Any substrate lacking the electron-withdrawing group did require copper(0) or copper(I) as a catalyst. Thus, treating imidate **16a** with milled potassium carbonate in NMP at 95 °C afforded indazole **18a** in 96% yield (Scheme 3).

To further reduce the number of steps, we next investigated the possibility of converting **14** to **18** in one pot. We already had demonstrated that NMP was a suitable solvent for both imidate formation and cyclization. After the in situ formation of imidate **16a**, milled K_2CO_3 was added to the mixture, and the reaction was warmed to 95 °C. The one-pot reaction required the use of more K_2CO_3 than the two-step process, because of the presence of DABCO salts in the mixture. Nonetheless, indazole **18a** could be isolated in 71% yield by filtration, after precipitating the product by dilution of the mixture with methanol followed by water (Scheme 3). Dilution of the reaction mixture with water, without prior addition of methanol, resulted in occasional precipitation of indazole **18a** as a gum.

The generality of this one-pot indazole formation was evaluated by looking at other piperazines **15**, and the results are summarized in Table 2. There was no major variation in yield with the different dibasic piperazines, and the corresponding indazoles **18** were isolated in good yield. The use of piperazine carbamate **15d** gave indazole **18d** in slightly better yield (entry 4).

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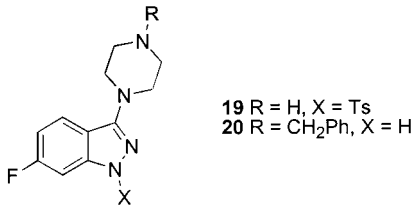
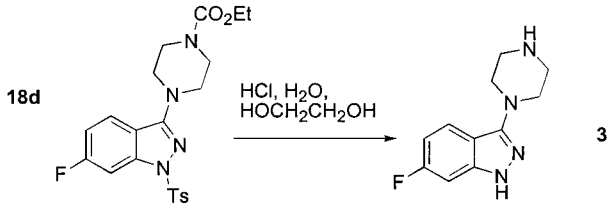


Figure 4.

Scheme 4



The preparation of unsubstituted indazole **3** required the removal of both the indazole *N*-tosyl group and the piperazine R group. We decided to use an R group that would allow simultaneous removal of both groups. Indazoles **18c** (R = CH_2Ph) and **18d** (R = CO_2Et) were potential compounds which would allow this transformation. Moreover, these protecting groups should be easier to remove than the methyl group of **18b** that required the use of cyanogen bromide.

The removal of the benzyl group of **18c** was achieved by hydrogenation over Pd/C in 96% yield to afford indazole **19** (Figure 4). Attempts to remove both benzyl and tosyl groups of **18c** with HBr failed to yield **3**, and only removal of the sulfonamide group was achieved to afford **20**. It was contaminated with some brominated indazole by-products. The use of HBr to fully deprotect indazole **18d** led to the formation of the desired indazole **3** along with some brominated indazole side products. Attempts to avoid bromination of the indazole ring by using concentrated hydrochloric acid were first unsuccessful because of the low solubility of **18d** in that medium. We solved the solubility problem by using ethylene glycol as a co-solvent. Under these reaction conditions, deprotected indazole **3** was isolated in 87% yield as a dihydrochloride salt monohydrate (Scheme 4).

Summary

The improved route provided a five-step reaction sequence to indazole **3** with a 67% overall yield. All of the intermediates and products were isolated by filtration, without the need for chromatographic purification.

Experimental Section

Proton NMR data were recorded on Varian 200 or 300 spectrometers. Commercially available materials were used as received. Reactions run at room temperature are in the 19−24 °C range. The HPLC conditions listed in the procedures refer to the following conditions: Nucleosil C-18 column, 5 μm, 4.6 × 250 mm; mobile phase $NH_4H_2PO_4$ (0.05N)/CH_3CN 55/45 v/v; flow rate 1.0 mL/min; UV detection 240 nm.

Preparation of 2-Chloro-4-fluorobenzoic 2-[(4-Methylphenyl)sulfonyl]hydrazide (13). Thionyl chloride (1.05 equiv, 375 g, 229 mL) was added to a solution containing 2-chloro-4-fluorobenzoic acid (3.0 mol, 524 g, 1.0 equiv), toluene (2100 mL) and 1-methyl-2-pyrrolidinone (0.5 mL) at 75 °C with stirring over 1 h. The reaction mixture was heated for 2 h at 75 °C. A mixture of toluene and thionyl chloride (186 g) was distilled at head temperature (45−81 °C) and pot temperature (76−90 °C) over 1 h. The residue was diluted with toluene (194 mL) to afford a solution of 2-chloro-4-fluorobenzoyl chloride (**12**), which was 97.5% pure by HPLC (after reaction of an aliquot with excess diethylamine). The solution was diluted with toluene (6.0 L) and tosylhydrazine (0.98 equiv, 552.1 g) was added at room temperature. The mixture was heated to 75 °C for 2 h with stirring. The mixture was cooled to 8 °C and filtered after 1 h. The white solid was rinsed with cold toluene (3 × 465 mL) and suction-dried to afford **13** as a white solid (972 g, 96.4% yield). The product was 99.4% pure by HPLC: mp 146−147 °C; M^+ 343. ^{1}H NMR ($CDCl_3$) δ 2.4 (s, 3H), 7.0 (dt, J = 7,1 Hz, 1H), 7.1 (dd, J = 7,1 Hz, 1H), 7.3 (d, J = 7 Hz, 2H), 7.5 (b, 2H), 7.8 (d, J = 7 Hz, 2H), 8.3 (d, J = 4 Hz, 1H).

Preparation of 2-Chloro-4-fluorobenzoyl Chloride 4-(Methylphenylsulfonyl)hydrazone (14). Thionyl chloride (5 equiv, 1678 g, 1024 mL) was added to 50% of **13** (1.41 mol, 483 g, 0.50 equiv) at room temperature in one portion. The mixture was heated to 75 °C for 1.5 h and cooled to 60 °C, and another portion of **13** (1.41 mol, 483 g, 0.5 equiv) was added. The mixture was heated to 75 °C for 2 h and cooled to 7 °C, and heptane (6750 mL) was added to precipitate the product. The resulting slurry was cooled to 5 °C for 1 h and filtered, and the solid was rinsed with cold heptane (3 × 450 mL). The solid was suction dried under nitrogen for 3 h to afford **14** (985 g, 96.0% yield) as a white solid: mp 145−147 °C; M^+ 361. ^{1}H NMR ($CDCl_3$) δ 2.4 (s, 3H), 7.0 (dt, J = 7,1 Hz, 1H), 7.1 (dd, J = 7,1 Hz, 1H), 7.3 (m, 3H), 7.8 (d, J = 7 Hz, 2H), 8.3 (s, 1H). Anal. Calcd for $C_{14}H_{11}Cl_2FN_2O_2S$: C, 46.55; H, 3.07; N, 7.76. Found: C, 46.62; H, 2.91; N, 7.84.

Preparation of 1-Cyanomethylpiperazine (15a). To a solution of piperazine (46.0 g, 534 mmol) in isopropyl alcohol (260 mL) was slowly added chloroacetonitrile (20.2 g, 16.9 mL, 267 mmol) over 20 min. The mixture was stirred at room temperature for another hour and filtered. The piperazine cake was washed with ethyl acetate (50 mL), and the filtrate was concentrated in vacuo. The residue was dissolved in ether (100 mL) and cooled to 5 °C, and the resulting slurry was filtered. The filtrate was concentrated in vacuo to afford a yellow liquid (35.1 g). The residue was distilled under reduced pressure to afford **15a** as a colorless liquid (11.7 g, 35% yield, bp 57−58 °C, 30 mmHg). ^{1}H NMR ($CDCl_3$) δ 1.7 (s, 1H), 2.55 (m, 4H), 3.95 (m, 4H), 3.5 (s, 2H).

Amidine 16a from 14 (No Added Base). To a solution of 1-cyanomethylpiperazine (**15a**) (346 mg, 2.77 mmol) in dry NMP (1 mL) was added dropwise a solution of imidoyl chloride **14** (500 mg, 1.38 mmol) in 3 mL of NMP over 5

min. The resulting yellow solution was stirred at room temperature for 40 min, powdered potassium carbonate (287 mg, 2.07 mmol) was added, and the mixture was stirred at 40 °C for 4 h. The reaction was cooled to room temperature and added slowly to 10 mL of stirred water. The resulting solid was filtered and dried at 40 °C (30 mmHg) overnight to afford imidate **16a** as an off-white solid (540 mg, 87% yield, 98% HPLC purity). ^{1}H NMR ($CDCl_3$) δ 2.4 (s, 3H), 2.5 (m, 4H), 3.2 (m, 4H), 3.5 (s, 2H), 6.2 (s, 1H), 7.05 (d, J = 7 Hz, 2H), 7.2 (m, 3H), 7.8 (d, J = 7 Hz, 2H).

Amidine 16a from 14 (Tertiary Amine Added). The procedure was the same as the above procedure, except that the imidoyl chloride **14** solution was added to a mixture of the piperazine and the tertiary amine (see Table 1) in NMP.

Preparation of 4-[6-Fluoro-1-[(4-methylphenyl)sulfonyl]-1H-indazol-3-yl]-1-cyanomethylpiperazine (18a) from 16a. A mixture of amidine **16a** (89.4 g, 0.199 mol corrected for purity) and milled potassium carbonate (55.3 g, 0.4 mol, 2 equiv) in NMP (270 mL) was heated to 90−95 °C under N_2 for 4 h and cooled to room temperature. The mixture was diluted with water (540 mL, 6:1 v/v NMP) over 15 min, and the resulting slurry was cooled to 10 °C and filtered after 1 h. The solid was washed with cold water (2 × 300 mL) and dried in a vacuum oven at 85 °C to afford indazole **18a** as a light tan solid (78.8 g, 95.8% yield): mp 170−171 °C; external standard HPLC 99.8% w/w purity. ^{1}H NMR ($CDCl_3$) δ 2.4 (s, 3H), 2.75 (m, 4H), 3.55 (m, 4H), 3.6 (s, 2H), 7.0 (dt, J = 7,1 Hz, 1H), 7.2 (d, J = 7 Hz, 2H), 7.6 (m, 1H), 7.75 (d, J = 7 Hz, 2H), 7.8 (dd, J = 7, 1 Hz, 1H).

Preparation of 4-[6-Fluoro-1-[(4-methylphenyl)sulfonyl]-1H-indazol-3-yl]-1-cyanomethylpiperazine (18a) from 14. To a stirred mixture of 1-cyanomethylpiperazine **15a** (22.9 g, 183 mmol, 1.1 equiv) and 1,4-diazabicyclo[2.2.2]-octane (0.7 equiv, 13.0 g, 0.116 mol) in dry NMP (60 mL) under N_2 was added dropwise a cooled (0 °C) solution of imidoyl chloride **14** (60.0 g, 0.166 mol, 1.0 equiv) in NMP (180 mL) (made by dissolving the solid in cold NMP and keeping the solution cold to avoid dimerization of the imidoyl chloride) over 60 min. The addition funnel was rinsed with NMP (60 mL), and the mixture was stirred for 1 h at room temperature. To the stirred mixture was added milled potassium carbonate (91.8 g, 4.0 equiv, 0.664 mol), the slurry was heated to 90−95 °C under N_2, and the reaction was followed by HPLC. After completion of the cyclization (4 h), the mixture was cooled in a water bath, and cold water (600 mL) was added slowly. After stirring for 15 min, the resulting slurry was filtered, and the solid was washed with cold water (2 × 120 mL). The solid was suspended in MeOH (350 mL), stirred at room temperature for 40 min, and filtered. The light-tan solid was dried in vacuo (40 °C, 30 mmHg) overnight to afford indazole **18a** (48.8 g, 70.9% yield, 99.8% HPLC purity).

Preparation of 4-[6-Fluoro-1-[(4-methylphenyl)sulfonyl]-1H-indazol-3-yl]-1-methylpiperazine (18b). To a stirred mixture of 1-methylpiperazine (22.8 g; 1.1 equiv, 0.182 mol) and 1,4-diazabicyclo[2.2.2]octane (0.7 equiv, 13.0 g, 0.116 mol) in NMP (180 mL) under N_2, was added dropwise a cooled to 0 °C solution of imidoyl chloride **14** (60.0 g, 0.166 mol, 1.0 equiv) in NMP (180 mL) (made by dissolving the solid in cold NMP and keeping the solution cold to avoid dimerization of the imidoyl chloride) over 50 min. The addition funnel was rinsed with NMP (60 mL), and the mixture was stirred 1 h at room temperature. To the stirred mixture was added milled potassium carbonate (91.8 g, 4.0 equiv, 0.664 mol), the slurry was heated to 90−95 °C under N_2, and the reaction was followed by HPLC. After completion of the cyclization (4 h), the mixture was cooled in a water bath, and cold water (600 mL) was added slowly. After stirring for 15 min the slurry was filtered. The solid was suspended in MeOH (350 mL), stirred at room temperature for 30 min, and filtered. The light-tan solid was dried in vacuo (40 °C, 30 mmHg) overnight to afford indazole **18b** (52.8 g, 76.8% yield, 99% HPLC purity): mp 146−148 °C. ^{1}H NMR ($CDCl_3$) δ 2.3 (s, 3H), 2.4 (s, 3H), 2.6 (m, 4H), 3.5 (m, 4H), 7.0 (dt, J = 9, 2 Hz, 1H), 7.2 (d, J = 8 Hz, 2H), 7.6 (dd, J = 9,5 Hz, 1H), 7.75 (d, J = 8 Hz, 2H), 7.9 (dd, J = 9,2 Hz, 1H).

Preparation of 4-[6-Fluoro-1-[(4-methylphenyl)sulfonyl]-1H-indazol-3-yl]-1-phenylmethylpiperazine (18c). To a stirred mixture of 1-benzylpiperazine (2.68 g, 15.2 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.7 equiv, 1.09 g, 9.7 mmol) in dry NMP (5 mL) under N_2 was added dropwise a cold solution of imidoyl chloride **14** (5.00 g, 13.8 mmol) in NMP (15 mL) (made by dissolving the solid in cold NMP and keeping the solution cold to avoid dimerization of the imidoyl chloride) over 12 min. The addition funnel was rinsed with NMP (5 mL), and the dark green/brown mixture was stirred for 2 h at room temperature. To the stirred mixture was added milled potassium carbonate (7.66 g, 4.0 equiv, 55.4 mmol), and the slurry was heated to 90−95 °C under N_2 for 4 h. The mixture was cooled in a water bath, and cold water (50 mL) was added slowly. After stirring for 10 min the slurry was filtered. The solid was suspended in MeOH (30 mL), stirred at room temperature for 30 min, and filtered. The light-tan solid was dried in vacuo (40 °C, 30 mmHg) overnight to afford indazole **18c** (4.55 g, 70.9% yield): mp 165−167 °C. ^{1}H NMR ($CDCl_3$) δ 2.4 (s, 3H), 2.6 (m, 4H), 3.5 (m, 4H), 3.6 (s, 2H), 6.9 (dt, J = 7,1,Hz, 1H), 7.2 (d, J = 7 Hz, 2H), 7.3 (m, 5H), 7.5 (m, 1H), 7.75 (d, J = 7 Hz, 2H), 7.8 (dd, J = 7,1 Hz, 1H).

Preparation of 4-[1-[(4-Methylphenyl)sulfonyl]-6-fluoro-1H-indazol-3-yl]-1-piperazinecarboxylic Acid Ethyl Ester (18d). To a mixture of 1-carboethoxypiperazine (470 g, 2.97 mol, 1.1 equiv), and 1,4-diazabicyclo[2.2.2]octane (227 g, 2.02 mol, 0.75 equiv) in NMP (1950 mL) cooled to 0−2 °C was added slowly a cooled (0 °C) solution of **14** (1.35 mol, 0.5 equiv, 488 g) in cold NMP (1460 mL) over 75 min. Another cooled solution of **14** (1.35 mol, 0.5 equiv, 488 g) in cold NMP (1460 mL) was prepared and added slowly to the cooled mixture. During the addition the mixture became acidic; therefore, another portion of DABCO (15.2 g, 0.05 equiv) was added. After the addition, the mixture was allowed to warm to room temperature overnight. Milled potassium carbonate (3.0 equiv, 1120 g) was added, and the mixture was heated to 100−105 °C until the cyclization was complete (2.5 h). The mixture was allowed to cool to room

temperature overnight, and ice water (1.1 L, 1:1 vs K_2CO_3) was added. The mixture was stirred at room temperature for 15 min and then transferred to 20 L of ice water in an extraction bowl. The flask was rinsed with more cold water (3.9 L). The slurry in water (total 24.9 L, 5:1 v/v vs NMP) was stirred for another 15 min at 5−10 °C and filtered. The solid was washed with cold water (3 × 3.3 L) and suction-dried to afford indazole **18d** as a light-tan solid (1010 g, 83.9% yield): mp 129 °C; M^+ 482. ^{1}H NMR ($CDCl_3$) δ 1.3 (t, J = 7 Hz, 3H), 2.4 (s, 3H), 3.4 (m, 4H), 3.6 (m, 4H), 4.2 (q, J = 7 Hz, 2H), 7.0 (dt, J = 7,1 Hz, 1H), 7.2 (d, J = 7 Hz, 2H), 7.55 (m, 1H), 7.75 (d, J = 7 Hz, 2H), 7.85 (dd, J = 7,1 Hz, 1H). A small portion was recrystallized from MeOH to afford an analytically pure sample. Anal. Calcd for $C_{21}H_{23}ClFN_4O_4S$: C, 52.23; H, 5.01; N, 11.60. Found: C, 51.95; H, 4.86; N, 11.53.

Preparation of 6-Fluoro-1-[(4-methylphenyl)sulfonyl]-3-(1-piperazenyl)-1H-indazole (19). A mixture of indazole **18c** hydrochloride salt (500 mg, 1.0 mmol) and 10% Pd/C in methanol (20 mL) was hydrogenated at 50 psi for 18 h. The catalyst was removed by filtration over a bed of Celite, and the filtrate was concentrated in vacuo to afford indazole **19** as a hydrochloride salt (400 mg, 96.6% yield, 96.5 HPLC purity): M^+ 374. ^{1}H NMR (DMSO) δ 2.3 (s, 3H), 3.1 (m, 4H), 3.6 (m, 4H), 7.25 (dt, J = 7, 1 Hz, 1H), 7.4 (d, J = 7 Hz, 2H), 7.7 (d, J = 7 Hz, 2H), 7.8 (dd, J = 7, 1 Hz, 1H), 8.0 (m, 1H), 9.2 (b, 2H).

Preparation of 6-Fluoro-3-(1-piperazinyl)-1H-indazole Dihydrochloride Monohydrate (3). To a mixture of 37% w/w HCl (4.77 L), water (2.05 L), and ethylene glycol (340 mL) was added **18d** (1364 g, 3.3 mol). The mixture was heated to 93 °C for 74 h. The reaction mixture was filtered still warm to remove any tetrazine present in the starting material. The mixture was concentrated to a quarter of the original volume, and 1-propanol (5:1 vol) was added. Azeotropic distillation eliminated 1.9 L of water/1-propanol mixture. More 1-propanol (1.4 L) was added, and the mixture was cooled to 5 °C and filtered after 1 h. The solid was rinsed with cold 1-propanol (4 × 500 mL), and suction-dried to afford tan **3** (833 g, 2.84 mol, 87% yield, 99.6% HPLC purity): M^+ 221, mp 239−246 °C. ^{1}H NMR (DMSO) δ, 3.2 (m, 4H), 3.6 (m, 4H), 6.85 (t, J = 7 Hz, 1H), 7.2 (d, J = 7 Hz, 2H), 7.85 (dd, J = 7, 4 Hz, 1H). A small sample was recrystallized (MeOH) to afford an analytically pure sample. Anal. Calcd for $C_{11}H_{17}Cl_2FN_4O$: C, 42.46; H, 5.51; N, 18.00. Found: C, 42.66; H, 5.28; N, 17.98.

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