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A Large Scale Process for the Preparation of Thymitaq

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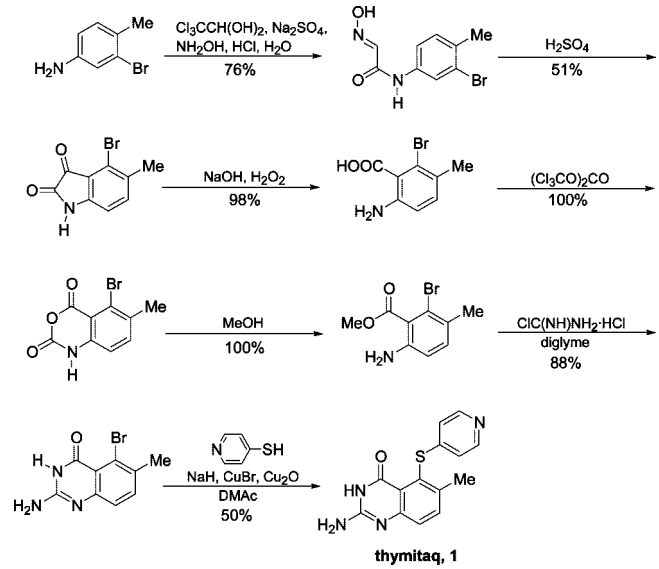
Abstract:

The large scale manufacturing of the anticancer agent 2-amino-6-methyl-5-(pyridin-4-ylsulfanyl)-3*H*-quinazolin-4-one dihydrochloride (thymitaq) from 6-bromo-5-methylanthranilic acid is described. The chemical route consists of two chemical steps: formation of a bromoquinazolinone and a copper-mediated Ullman-like coupling between 4-mercaptopyridine and the bromoquinazolinone. During process development, sodium hydride was replaced with sodium hydroxide and a method for removal of copper, based on 2,4,6-trimercapto-*s*-triazine, was developed. A number of purification operations were performed to ensure a product of pharmaceutical quality.

Introduction

2-Amino-6-methyl-5-(pyridin-4-ylsulfanyl)-3*H*-quinazolin-4-one dihydrochloride (**1**) known as thymitaq is intended for treatment of inoperable primary liver cancer (hepatocellular carcinoma or HCC). It is a noncompetitive, high affinity antifolate thymidylate synthetase inhibitor.[1] This enzyme catalyses the reaction of deoxyuridine monophosphate to deoxythymidylate by a reductive methylation using 5,10-methylenetetrahydrofolate as cofactor. This transformation is the exclusive source of deoxythymidylate for DNA synthesis. Lack of thymidylate would lead to cell death due to the absence of thymine, unless an exogenous supply of thymidine is in place. It is believed that thymitaq displays less of the side effects usually connected with drugs working by the same mechanism.[2,3] Initially thymitaq was synthesised following a medicinal chemistry route[1] (Scheme 1). Although this route did not include chromatographic purification and the yields in most of the steps were good, such synthesis is not appropriate for large-scale manufacturing. Recently Chen and Wan described a modified small-scale route to thymitaq.[4] In the present article we describe the large-scale manufacture of thymitaq of a quality that meets the specifications required for pharmaceuticals. A number of different impurities appeared during the synthesis, and much work was performed to eliminate these impurities. The key element to success was removal of trace amounts of copper using 2,4,6-trimercapto-*s*-triazine trisodium salt (TMT-15) as a metal scavenger.

Scheme 1. **Medicinal chemistry route to thymitaq**



Results and Discussion

A number of reagents can be used to form quinazolinones from substituted anthranilic acids. It was found that 1-amidino-1,2,4-triazole hydrochloride[5] was convenient for our purpose. By heating a mixture of anthranilic acid **2**[6] (1 equiv), 1-amidino-1,2,4-triazole hydrochloride (2.8. equiv) and triethylamine (1 equiv) in *N*,*N*-dimethylformamide at 65−70 °C quinazolinone **3** was formed in good yield (Scheme 2). The progress of the reaction was monitored by HPLC, and after 12 h the reaction was complete. Addition of methyl *tert*-butyl ether precipitated the product, which was isolated via centrifugation. The filter cake contained substantial amounts of hydrogen chloride, which must be removed prior to the next step. By slurrying the moist filter cake with aqueous ammonium hydroxide and again performing the isolation via centrifugation, an intermediate free from hydrogen chloride was obtained. The substance was dried under reduced pressure at 60 °C for over 3 days. Despite the long drying time, still 1−3% of water remained in the substance.

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(6) This material was purchased from a custom manufacturer.

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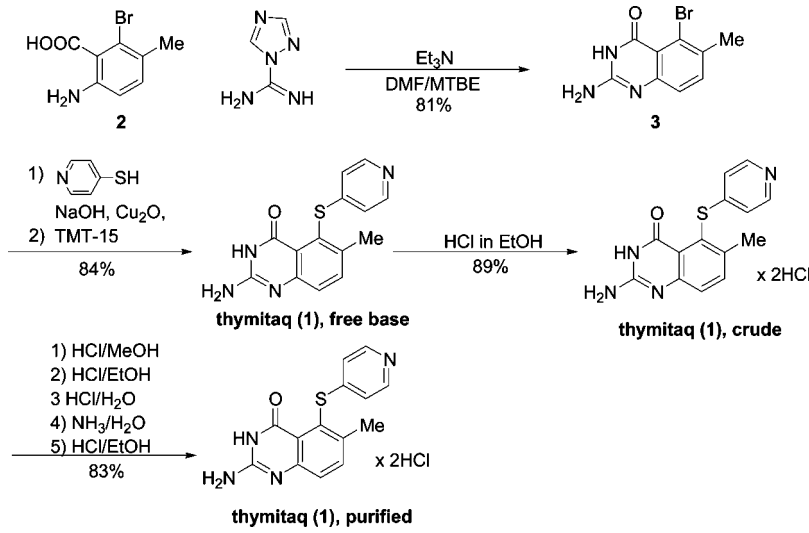
Scheme 2. **Large-scale route to thymitaq**



In practice it was not possible to obtain a totally dry substance. This fact affected the choice of base in the next step. Use of 2.8 equiv of 1-amidino-1,2,4-triazole hydrochloride was necessary to form the reactive disubstituted intermediate, which was suspected to be slightly unstable under the present reaction conditions (Figure 1). Different guanylating reagents were tested during the development, but most of them failed. Cyanamide (30−60 equiv) gave **3** in 60−70% yield. In addition to the moderate yield and large excess of reagent, cyanamide polymerised under the reaction conditions. Chloroformamidine hydrochloride gave good conversion on a small scale, but on a larger laboratory scale the reagent was destroyed. Guanylpyrazole gave various results and low purity. Guanylbenzotriazole gave good conversion, but up to 10% of unknown impurities were detected. *O*-Methyl isourea did not work at all. In light of these findings the use of 1-amidino-1,2,4-triazole hydrochloride seems to be superior.

The loading of *N*,*N*-dimethylformamide was kept as low as possible (4 L/kg anthranilic acid **2**) to facilitate the precipitation with methyl-*tert*-butyl ether. The yield was 81%, and the purity 97.5% or higher. The amount of related substances was 2−2.5%. To complete the core of the molecule, quinazolinone **3** was coupled with 4-mercaptopyridine in an Ullman-like reaction mediated by base and copper(I) oxide in *N*,*N*-dimethylacetamide to give **1** as the free base (Scheme 2).[7] A mixture of **3** (1 equiv), 4-mercaptopyridine (1.6 equiv), sodium hydroxide (1.5 equiv), and copper(I) oxide (0.56 equiv) in *N*,*N*-dimethylacetamide was heated at 80−90 °C for 4 h, and the progress of the reaction was monitored by HPLC. After the reaction was completed, water and hydrochloric acid were added and the pH was adjusted to below 1.5. The low pH was necessary to completely dissolve all of **1**. The substance contained substantial amounts of *N*,*N*-dimethylacetamide, which was removed by slurrying the mixture in aqueous ammonium hydroxide, isolating the solid, and washing with water followed by dissolution in water and hydrochloric acid. Repeated addition of aqueous ammonium hydroxide gave a precipitate, which was isolated via centrifugation followed by drying under reduced pressure.

During the initial development sodium hydride was the base of choice. Sodium hydride in solvents like *N*,*N*-dimethylformamide and *N*,*N*-dimethylacetamide is a well-known safety hazard,[8] and therefore an alternative was required. As mentioned above quinazolinone **3** may contain substantial amounts of water, which makes the situation even more challenging. After some testing, sodium hydroxide was found to be a good alternative. Byproduct **5** (Figure 2) was observed to form to a higher extent when using sodium hydroxide instead of sodium hydride. This byproduct was, however, efficiently removed later in the process. Also sodium methoxide and sodium carbonate facilitated the reaction but gave slower reactions and larger amounts of byproduct.

Having a synthetic sequence including noncatalytic amounts of heavy metals in the penultimate step is not an ideal situation. The issue with removal of more than 0.5 equiv of copper can be divided into three phases: (a) removal of bulk quantities of copper, (b) removal of most residual copper, (c) removal of trace amounts of copper. Copper(I) oxide used in this Ullman-like coupling undergoes disproportionation to copper(0) and copper(II) when treated with hydrochloric acid. The consequence is that copper will appear in three different oxidation states with different solubility properties. Copper(0) and a major part of copper(I) salts can be separated from a solution *via* filtration, but some of the copper(0) will go into solution under acidic conditions. Copper(II) and to some extent copper(I) are soluble in acids, and copper(II) is also soluble in aqueous ammonia. Indeed substantial amounts of copper(0) and copper(I) were separated by filtration in the operation described above. Generally speaking, the levels of copper were reduced by a factor of 5−10. Also some copper(II) was removed by the ammonia treatment. Laboratory experiments revealed that repeated treatment with hydrochloric acid was not sufficient to remove trace amounts of copper. Thus, the removal of copper necessitates a multifaceted approach. Removal of trace amounts

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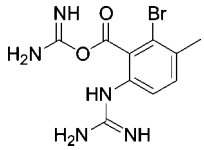
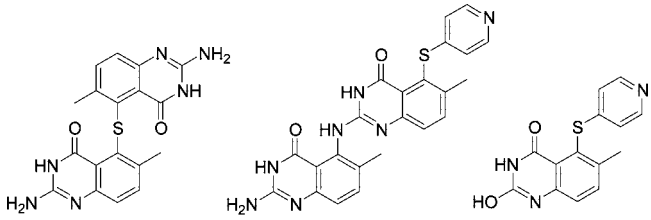


Figure 1. **Disubstituted intermediate in the quinazolinone-forming step.**



5 **6** **7**

Figure 2. **Byproducts in thymitaq.**

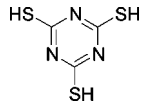


Figure 3. **TMT.**

of metals in drug substances originating from catalysts and reagents is a general challenge, since metal contents on the ppm level is often required. High metal content is a particular problem, when steps late in the synthetic sequence are catalysed by metals and where the drug substance is a good ligand for the metal. Indeed pyridine substructures are well-known to coordinate to metals like Pd and Cu; even copper(I) chain polymers with thiopyridines are known.[9] There are numerous approaches to removing precious and transition metals, mainly palladium.[10] Removal of copper from organic compounds has been performed with EDTA,[11] thioacetamid,[12] ammonia,[13] TFA/H_2SO_4,[14] oxalic acid,[15] and pyridine.[16] To remove the last amounts of copper, precipitation of copper sulfide via gaseous hydrogen sulfide treatment was used initially. Aside from having a disgusting smell, hydrogen sulfide is very poisonous, actually more poisonous than for instance hydrogen cyanide. To address the high copper content in thymitaq, 2,4,6-trimercapto-*s*-triazine (TMT) was examined as an alternative to hydrogen sulfide (Figure 3) since mercapto compounds in general show high affinity for heavy metals. TMT and the corresponding 15% sodium salt solution in water (TMT-15) have been used to remove heavy metals in a number of applications like waste-water,[17] flue gases,[18] soils,[19] and pharmaceuticals.[10] However, TMT does not bind to trivalent species like Al^{3+}, Fe^{3+}, or Cr^{3+}. Laboratory tests with TMT-15 were performed, and the results encouraged us to implement this reagent to eliminate trace amounts of copper in large-scale manufacturing.

The coupling product from above was mixed with water and TMT-15 followed by stirring for 1 h. The pH was adjusted with hydrochloric acid, and compressed air was bubbled into the mixture for 1 h. The aim of the addition of compressed air was to oxidise copper(I) chelated with the pyridine ring to copper(II). Six more portions of TMT-15 were added with 20-min intervals. Removal of copper was monitored by introducing hydrogen sulfide (g) to a small sample; the occurrence of a precipitate was observed. It was necessary to add TMT-15 in portions to obtain efficient removal of copper. An equilibrium is probably responsible for the phenomena. Mosely et al. were also forced to use repeated addition when removing copper with EDTA.[11] To keep **1** in solution a low pH was maintained by addition of hydrochloric acid. The optimum pH range for TMT-15 is between 6 and 10, but many metals can still be precipitated in strongly acidic media. In addition, complexes between TMT and metals are stable over a wide pH range. To facilitate filtration of the TMT−copper complex, activated charcoal and Celite were added. The mixture was stirred for 1 h and passed through a series of filters. Subsequent treatment with aqueous ammonium hydroxide and workup gave **1** in 84% yield. The purity of **1** was 85−87%, and the levels of copper were reduced to 15−25 ppm. Major impurities were **5** (2.5−3%) and **6** (4−5%) (Figure 2). Compound **6** was formed when **1** was alkylated at the primary amino group by **3**, and **7** (Figure 2), which may be formed by hydrolysis of **1**, was detected at levels below 0.1%. The water content was 5−6%.

Compound **1** was then converted to its dihydrochloride in 89% yield by treatment with hydrochloric acid in ethanol (Scheme 2). An excess of acid was required since some acid will be lost during reflux. In that case the less soluble monohydrochloride will precipitate. This operation increased the purity to 92−93%, and a reduction of the copper content was observed.

At this stage the crude product contained 2.5−3% of impurity **5**. In contrast to **1**, compound **5** is not soluble in hot acidic methanol. To remove this impurity, a hot filtration was performed which was quite a challenge. The insoluble **5** consisted of very small particles, which made filtration tremendously time consuming. The filter setup designed for this step was a 1 μm polypropylene bag filter as prefilter followed by a 0.5 μm polypropylene cartridge filter. The 1 μm bag filter was not able to retain the material to be removed; therefore the filtrate was passed on to the cartridge filter. A number of combinations of filters were examined, and a combination of 1

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μm polypropylene bag filter and a 0.45 μm filter made of microfibreglass with polypropylene support worked. The major drawback was that the filtration was very time-consuming and consumed many cartridges. To be able to design a better filtration procedure, characterisation of the particles of compound **5** was necessary. A combination of microscopy and sedimentation studies revealed the following: the size of the particles was relatively homogeneous uniform, spherical, and ~2 μm in diameter. Both single particles and aggregated particles were present, and sedimentation will occur if the mixture is left without stirring. To finally solve the problem a new filter (PROGRAF 51) was chosen in combination with sedimentation. This procedure worked satisfactorily when tested at a laboratory scale, and the filtration became much easier. These findings are, however, not yet implemented at a larger scale. In general most of the different filtrations were difficult to perform, and prefiltration with the aid of serial filters was necessary. The filtrate from above was concentrated at reduced pressure and cooled overnight which caused precipitation of the product which was isolated via centrifugation and then recharged in ethanol and hydrochloric acid. After a brief reflux the mixture was cooled to 0 °C and left overnight. Centrifugation and drying gave a solid in 86% yield. The solid was dissolved in water and hydrochloric acid after which activated charcoal and Celite were added followed by filtering and treatment of the filtrate with ammonium hydroxide to precipitate the product. After a second centrifugation, drying and sieving a fine powder was obtained. This powder was refluxed in ethanol and hydrochloric acid followed by cooling which gave a precipitate isolated via centrifugation. Drying under reduced pressure and sieving gave pure **1** dihydrochloride as a white solid. The yield was 99% in this step and 83% from the crude dihydrochloride. Analysis of the final product showed it to be >99.5% pure. The levels of **5**, **6**, and **7** were 0.05−0.10%, 0.06−0.13%, and 0.02%, respectively. The only solvent found was ethanol (0.05−0.07%), and the amount of TMT was 70 ppm. Because of the chelating character of **1** an analysis of selected metals was performed using AAS. Indeed a number of metals were found. The copper content was 2−6 ppm, and 13−15 ppm iron was found. Nickel, chromium, and zinc were also found, all at the 1−2 ppm level or lower. To our surprise we detected lead in the substance. The level was 5−9 ppm where 10 ppm was the allowed amount. An investigation revealed that copper(I) oxide contained small amounts of lead, although lead was not in the specification from the supplier. A survey of different suppliers uncovered lead contents ranging from 10 to nearly 3000 ppm. There was a correlation between the lead content in Cu_2O and the lead content in **1** in laboratory experiments. If the lead content in Cu_2O is high it will remain high in **1** despite treatment with TMT-15. On the other hand using Cu_2O with a lead content below the specification will give a product with low lead content. TMT works well for positive divalent metal ions such as Cu(II) and Pb(II),[20] but it is uncertain if complexes are formed with Pb(IV) species. The results indicate that the level of lead does not follow the level of copper. However, reduction of the lead content occurs in the purification steps.

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Conclusions

A method for large scale manufacturing of thymitaq was developed. The method consisted of two chemical steps and several purification operations. Despite the tedious purification, the method gave a good yield and a high quality product. Thymitaq acts as a chelating agent, and to avoid ligation with metals all reactions were carried out in glass-lined reactors and solutions were stored in polyethylene containers. All contact with metal in, e.g., hoses, connections, etc., was avoided. A synthesis including noncatalytic amounts of metal in the penultimate step is not an ideal choice. However, we have demonstrated that it is possible to remove trace amounts of copper using TMT-15 as a metal scavenger. It was also demonstrated that the hazardous sodium hydride could be replaced with sodium hydroxide. Moreover, it was important to use a copper(I) oxide free of lead contaminants.

Experimental Section

General. HPLC analyses on Quinazolinone **3** were performed using a C18 Selectapore 90M, 250 mm × 4.6 mm, 5 μ, 90 Å from Vydac. Gradient elution conditions were employed; ramping from 87/13 ammonium acetate (0.1 M) in water/acetonitrile to 55/45 during 14 min followed by a 4 min hold. The flow rate was 2.25 mL/min, and UV detection at 245 nm. Thymitaq **1** was analysed using a Primeshere C18-HC, 150 mm × 4.6 mm, 5 μ, 110 Å from Phenomenex. Gradient elution employed ramping from 78/22 phosphate buffert/methanol (buffert: 3.20 g of Na_2HPO_4 and 3.06 g of KH_2PO_4 in 900 mL of water and 100 mL of methanol) to 100% methanol during 15 min followed by a 5 min hold. The flow rate was 1.0 mL/min, and the UV detection at 254 nm. NMR spectra were recorded at 300.14 MHz (proton) and 75.47 MHz (carbon), respectively. Solvents and reagents were obtained from commercial sources and were used as such without further purification. All reactors used are standard multipurpose equipment. All reactions on the pilot-plant scale are for safety reasons routinely carried out under an atmosphere of nitrogen.

2-Amino-5-bromo-6-methyl-3-*H*-quinazolin-4-one (3). A glass-lined reactor was charged with DMF (201 kg) and 6-bromo-5-methylanthranilic acid **2** (53.5 kg, 232 mol) under stirring. After 30 min of stirring, triethylamine (23.5 kg, 231 mol) and 1-amidino-1,2,4-triazole hydrochloride (96.0 kg, 651 mol) were added and the stirring was continued for 10 min. The mixture was then heated to 65−70 °C, and the progress of the reaction was monitored with HPLC. After 12 h the reaction was completed and the mixture was allowed to cool to ~40 °C. Methyl-*tert*-butyl ether (394 kg) was added under stirring. After stirring for 1 h the mixture was cooled to 4 °C and the precipitate was isolated via centrifugation. The filter cake was washed with methyl-*tert*-butyl ether (40 kg). The filter cake was recharged to the reactor together with water (533 kg). The mixture was stirred for 10 min after which aqueous ammonium hydroxide (40.5 kg, 27% w/w) was added. After 40 min of stirring the pH was checked to be above 8.5, and again the product was isolated via centrifugation. The filter cake was washed with water (60 kg). Drying under vacuum (8 mbar) at 60−70 °C for 88 h gave the title compound (48.0 kg, 81%) as a beige solid.

IR 3104 broad, 1660, 1595, 1462 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.96 (s, broad, 1H), 7.48 (t, J = 8.4 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.38 (s, broad, 2H), 2.34 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 160.7, 151.7, 151.4, 135.7, 132.1, 123.4, 121.9, 115.0, 23.2.

2-Amino-6-methyl-5-(pyridin-4-ylsulfanyl)-3*H*-quinazolin-4-one (1, Free Base). A glass-lined reactor was charged with grounded sodium hydroxide (8.56 kg, 214 mol) and dimethylacetamide (169 kg). The mixture was stirred for 15 min after which 4-mercaptopyridine (25.5 kg, 229 mol) was added. The mixture was stirred for 1 h at a temperature below 27 °C, and then **3** (36.0 kg, 142 mol) and copper(I) oxide (11.5 kg, 80.4 mol) were added. The mixture was heated to 80−90 °C, and the progress of the reaction was monitored with HPLC. After 4 h the reaction was completed and the mixture was cooled to below 30 °C over a 1 h period. A mixture of hydrochloric acid (76 kg, 36% w/w) and water (858 kg) was added which gave a pH just below 1. After stirring for 15 min, the mixture was left unstirred overnight. The reaction mixture was passed through a series of filters: a 10 μm bag filter, a 1 μm bag filter, and finally a 0.45 μm cartridge filter. The filters were washed with water (142 kg), and the combined liquids were stored in a polyethylene container. The content of the container was transferred to a glass-lined reactor, and aqueous ammonium hydroxide (67 kg, 27% w/w) was added. After stirring for 30 min the pH was recorded to be 9.5. The precipitated product was isolated via centrifugation and washed with water. The wet filter cake was recharged in the reactor together with water (558 kg). Hydrochloric acid (76 kg, 36% w/w) was added, and the substance went into solution. Aqueous ammonium hydroxide (67 kg, 27% w/w) was added. After stirring for 35 min the precipitate was collected via centrifugation. The filter cake was washed with water (141 kg) and then recharged in the reactor with water (558 kg). 2,4,6-Trimercapto-*s*-triazine water solution 15% w/w (TMT-15, 14 kg) was added, and the mixture was stirred for 1 h. Hydrochloric acid (61 kg, 36% w/w) was added, and the pH was lowered to below 1. Compressed air was bubbled into the stirred reaction mixture for 1 h. TMT-15 (7.5 kg) was added, and at 20-min intervales, additional 7.5 kg portions were added (6 more additions, total 52.5 kg). The pH was kept low by addition of hydrochloric acid (total 2.1 kg, 36% w/w). After verification of removal of copper, Carboraffin P (activated charcoal, 4.5 kg), water (15 kg), and Celite 521 (1.5 kg) were added. The mixture was stirred for 1 h, and then the reaction mixture was passed through a series of filters: a 25 μm bag filter, a 1 μm bag filter, and finally a 0.45 μm cartridge filter. The filters were washed with water (94 kg), and the combined liquids were stored in a polyethylene container. The solution was charged into a glass-lined reactor, and aqueous ammonium hydroxide was added (53 kg, 27% w/w). The precipitated product was isolated via centrifugation, and then the filter cake was washed with water (180 kg) and absolute ethanol (44 kg). Drying under vacuum (9 mbar) at 60−70 °C for 48 h gave the title compound (34.0 kg, 84%) as an off-white solid. Mp 300−301 °C (lit. 301−302[1]); IR 3070 broad, 1664, 1579, 1466 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.23 (d, J = 5.7 Hz, 2H), 7.59 (d, J = 8.5 Hz, 1H), 7.29 (d, J = 8.5 Hz, 1H), 6.83 (dd, J_1 = 4.6 Hz, J_2 = 1.6 Hz, 2H), 6.42 (s, broad, 2H), 2.32 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 160.8, 152.0, 151.8, 150.3, 149.1, 137.5, 136.2, 126.7, 126.1, 119.6, 118.3, 20.7.

2-Amino-6-methyl-5-(pyridin-4-ylsulfanyl)-3*H*-quinazolin-4-one Dihydrochloride, Crude (1, Dihydrochloride). In a glass-lined reactor were added absolute ethanol (165 kg), water (8.5 kg), and **1** (free base, 43 kg, 152 mol) under stirring. Hydrochloric acid (33 kg, 326 mol, 36% w/w) was added, and the mixture was stirred for 10 min. The mixture was then heated to reflux and then immediately cooled to below 10 °C during 2.5 h. The precipitated product was isolated via centrifugation and washed with absolute ethanol (24 kg). Drying under vacuum (8 mbar) at 60−70 °C for 12 h gave the dihydrochloride (48 kg, 89%) as an off-white solid.

2-Amino-6-methyl-5-(pyridin-4-ylsulfanyl)-3*H*-quinazolin-4-one Dihydrochloride, Purified. In a glass-lined reactor were added methanol (668 kg) and crude **1**, dihydrochloride (48.4 kg, 136 mol) under stirring. After 10 min hydrochloric acid (8.2 kg) was added, and the mixture was heated to reflux and maintained at this temperature for 30 min. The hot solution was filtered through a 1 μm bag filter and then through a 0.45 μm cartridge filter. The filters were washed with methanol (20 kg), and the combined liquids were concentrated by removing methanol (760 L) by distillation at reduced temperature. The resulting slurry was cooled to 0 °C and kept at this temperature overnight. The product was isolated via centrifugation and washed with absolute ethanol (33 kg). The filter cake was recharged together with absolute ethanol (182 kg), water (8.2 kg), and hydrochloric acid (3.1 kg, 36% w/w). The mixture was stirred for 10 min, then heated to reflux, immediately cooled to 0 °C, and left at this temperature overnight. The product was collected via centrifugation and washed with absolute ethanol (28 kg). Drying under vacuum (8 mbar) at 65 °C for 12 h gave a solid (42 kg, 86%).

The solid (42 kg) was charged in a glass-lined reactor together with water (523 kg) and stirred. Hydrochloric acid (12.6 kg, 36%, w/w) was added, and the mixture was stirred for 15 min. A slurry consisting of water (16.5 kg) and Carboraffin (activated charcoal) (3.8 kg) was added, and the suspension was stirred for 50 min. Celite 521 (3.8 kg) was added, and stirring was continued for 10 min. The reaction mixture was passed through a series of filters: a 10 μm bag filter, a 1 μm bag filter, and finally a 0.5 μm cartridge filter. The filters were washed with water (43 kg), and the combined liquids were charged in a glass-lined reactor. Aqueous ammonium hydroxide (44 kg, 27% w/w) was added under stirring. After 35 min the precipitate was isolated via centrifugation and washed with water (53 kg). Drying under vacuum (8 mbar) at 65 °C for 12 h gave a solid which was passed through a sieve to give a fine powder (32 kg, 97%). The powder (32 kg) was added to a glass-lined reactor together with absolute ethanol (127 kg) and water (4.6 kg) under stirring. After 10 min hydrochloric acid (31.5 kg, 36% w/w) was added, and the mixture was stirred for another 10 min. The mixture was heated to reflux and kept at this temperature for 35 min. The mixture was cooled to 0 °C and kept at this temperature overnight. The product was isolated via centrifugation and washed with absolute ethanol (42 kg). Drying under vacuum (8 mbar) at 65 °C for 24 h gave a solid which was

passed through a sieve to give **1** as a fine white powder (40 kg, 99%). IR 3042 broad, 1698, 1621, 1475 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.52 (d, $J = 6.5$ Hz, 2H), 8.44 (s, 2H), 7.93 (d, $J = 8.5$ Hz, 1H), 7.70 (d, $J = 8.5$ Hz, 1H), 7.53 (d, $J = 6.8$ Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 167.2, 163.0, 156.0, 146.5, 145.7, 145.5, 143.1, 130.2, 126.7, 126.1, 122.2, 25.8.

Physical Data for Impurities. 5: IR 3156 broad, 1685, 1622, 1466 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.64 (s, broad, 1H), 7.39 (d, $J = 8.5$ Hz, 1H), 7.15 (d, $J = 8.4$ Hz, 1H), 3.45 (s, broad, 2 H), 1.84 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 159.4, 150.8, 142.7, 138.7, 136.8, 135.4, 117.9, 116.0, 21.1; HRMS calcd for $C_{23}H_{20}N_7O_2S$ (M + H) 458.1411, found 458.1400.

6: IR 3170 broad, 1619, 1592, 1466 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.37 (d, $J = 6.0$ Hz, 2H), 7.67 (d, $J = 8.5$ Hz, 1H), 7.57 (d, $J = 8.5$ Hz, 1H), 7.36 (s, broad, 1H), 7.33 (d, $J = 8.6$ Hz, 2H), 7.14 (m, 3 H), 2.37 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 163.2, 161.3, 158.3, 151.8, 147.7, 144.7, 140.1, 137.9, 137.3, 130.1, 125.4, 121.2, 119.9, 115.9, 110.1, 21.4, 19.2; HRMS calcd for $C_{14}H_{12}N_3O_2S$ (M + H) 403.0948, found 403.0954.

7: IR 3046 broad, 1691, 1622, 1602 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.4 (s, 1H), 11.24 (s, 1H), 8.47 (d, $J = 7.0$ Hz, 2H), 7.78 (d, $J = 8.6$ Hz, 1 H), 7.48 (d, $J = 7.0$ Hz, 2 H), 7.40 (d, $J = 8.6$ Hz, 1 H), 2.37 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 162.3, 161.2, 149.7, 142.2, 140.5, 138.6, 137.2, 124.9, 121.3, 119.1, 115.1, 20.4; HRMS calcd for $C_{14}H_{12}N_3O_2S$ (M + H) 286.0659, found 286.0651.-

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