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A new pathway *via* intermediate 4-amino-3-fluorophenol for the synthesis of regorafenib

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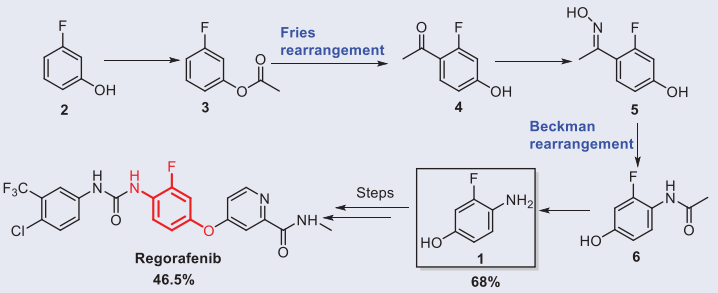
ABSTRACT

A practical synthetic route to regorafenib, in which the target compound was obtained *via* a 10-step synthesis starting from 2-picolinic acid, 4-chloro-3-(trifluoromethyl)aniline, and 3-fluorophenol, is reported. Crucial to the strategy is the preparation of 4-amino-3-fluorophenol *via* Fries and Beckman rearrangements using an economical and practical protocol. The main advantages of the route include inexpensive starting materials and an acceptable overall yield. A scale-up experiment was carried out to provide regorafenib with 99.96% purity in 46.5% total yield.

GRAPHICAL ABSTRACT



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KEYWORDS
Regorafenib; Fries rearrangement; Beckman rearrangement; Optimization

Introduction

Regorafenib (**1,** Figure 1), a broad-spectrum kinase inhibitor developed by Bayer, was approved by U.S. FDA for the treatment of metastatic colorectal cancer in 2012.[1] It inhibits tumor angiogenesis and proliferation by inhibiting various enzymes (VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, FGFR, c-KIT, etc.) that promote tumor tissue growth.[2]

From a structural perspective, regorafenib features three substituted aromatic rings functionalized with a urea group and an ether group. Retrosynthetically, this structure is most straightforwardly dissociated to the commercially accessible building blocks **2**, **3**,

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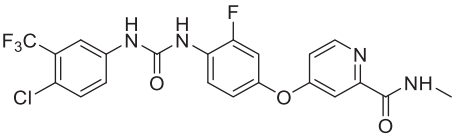
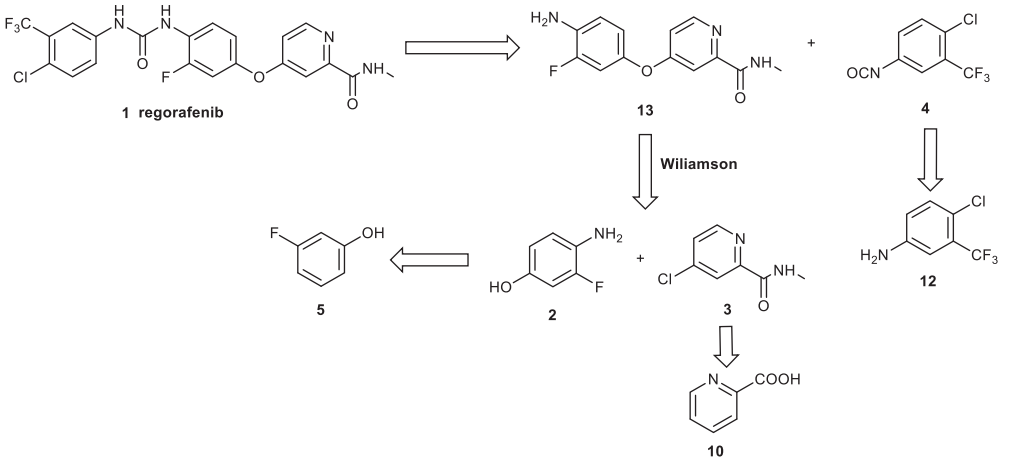


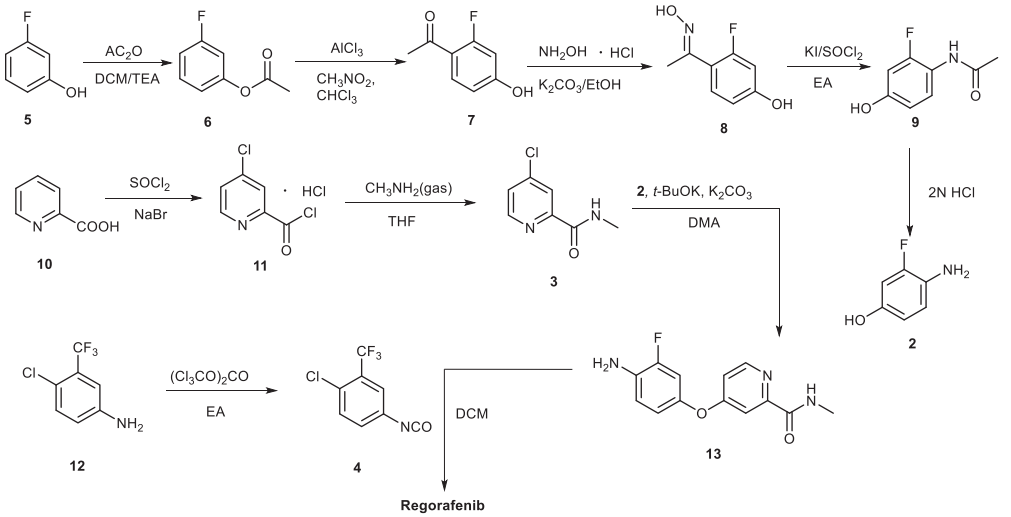
Figure 1. Chemical structure of regorafenib (**1**).



Scheme 1. Retrosynthetic Analysis of Regorafenib.

and **4** (Scheme 1), which had previously been established according to the synthesis of sorafenib.[3] In the initial work, picolinamide **13** was obtained *via* Williamson ether synthesis with aminophenol **2** and picolinamide **3** as the raw materials and then was coupled with isocyanate **4** to afford regorafenib **1**.[4] An improved synthetic method for the Williamson reaction, where aminophenol **2** was converted to a more nucleophilic imine by reaction with 4-methyl-2-pentanone, followed by a Williamson esterification, was reported.[5]

As intermediate **2** is a key fragment in the synthesis of regorafenib, several synthetic methods have been reported for its preparation. Schlegel and Johnson disclosed a method where 3-fluorophenol as a starting material provided **2** with a total yield of 19% *via* nitration and reduction reactions.[6,7] The main drawbacks of this approach were that the isomer 3-fluoro-6-nitrophenol, dinitro compounds, quinones, oxides, and other byproducts were readily produced, which greatly reduced the yield. Furthermore, the reduction process required expensive palladium on carbon as a catalyst, thereby increasing the cost. Hodgson et al. developed another method to obtain **2** from 3-fluoroaniline in five steps with a total yield of 20%.[8] The process involving amino protection, nitration, deprotection, diazotization, hydrolysis, palladium-on-carbon reduction, and steam distillation was complex and cumbersome, leading to a low yield. In 2016, Ye et al. reported two synthetic routes that avoided the safety and regioselectivity issues associated with nitration reactions.[9,10] In the first route, the 2,4-difluoronitrobenzene substrate was subjected to etherification, $AlCl_3$-mediated demethylation, and reduction based on a composite catalyst (nickel nitrate/palladium chloride/tetrabutyl titanate), affording **2**. The second route was a long synthetic procedure in which the starting material 4-nitrophenol underwent reduction, sulfonation, fluorine substitution, and



Scheme 2. Alternative Synthetic Route to Regorafenib.

desulfonation to provide the product with a total yield of 60%. Klausener et al. prepared **2** using *o*-fluoronitrobenzene as the starting material.[11] Because of the use of porous extractors, this method was not applicable to industrial production. Sun et al.[12] optimized the reaction conditions based on Klausener's work and prepared **2** in 56% yield. However, this process needed expensive platinum catalysts and produced a considerable amount of *o*-fluoroaniline. Muddasani et al. disclosed a patent for the optimization of the synthetic process for regrofeinib; this patent described a method for obtaining **2** by refluxing *o*-fluoronitrobenzene in the presence of aluminum and oxalic acid dihydrate, but the subsequent treatment process was very complicated.[4]

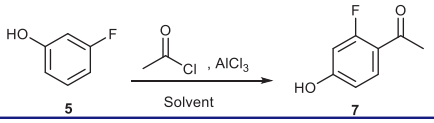
Herein, we discuss our attempts to develop a safe, scalable process for the synthesis of **2** and seek to define a more efficient and cost-effective route to regorafenib that is appropriate for more sustainable long-term supply of the drug.

Results and discussion

Initially, our study focused on the synthesis of intermediate **2**. The synthetic route to **2** from commercially available 3-fluorophenol **5** involved esterification with acetic anhydride to afford acetate **6**. Then, **6** was transformed *via* Fries rearrangement using aluminum chloride to yield ketone **7**.[13] The reaction between **7** and hydroxylamine hydrochloride in the presence of potassium carbonate furnished the intermediate oxime **8**. Compound **8** was transformed into acetamide **9** *via* Beckmann rearrangement catalyzed by potassium iodide and thionyl chloride.[14] Then, **9** was hydrolyzed to afford **2** (Scheme 2).

Having established a route to the synthesis of intermediate **2**, we turned our efforts toward the synthesis of regorafenib. The fragment of picolinamide **3** was prepared using picolinic acid **10** as a raw material in a procedure involving chlorination and amidation. Another fragment, compound **4**, was synthesized by treating aniline **12** with triphosgene. The Williamson etherification reaction of intermediate **2** with **3** in the presence of

Table 1. Friedel–Crafts acylation reaction.[a]



Entry	$AlCl_3$ (equiv)	Solvent	Temp (°C)	Yield (%)[b]
1	1.1	DCE	0	5
2	1.1	DCE	0→reflux	8
3	2.5	DCE	0→rt	D[c]
4	1.1	DCM	0→rt	D

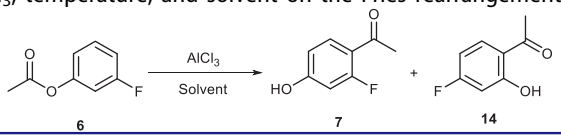
[a]Standard conditions: aluminum chloride (31.2 mmol), 3-fluorophenol (27.6 mmol), solvent (100 mL).
[b]Isolated yield after chromatography.
[c]Detected by the TLC analysis but not isolated.

potassium *tert*-butoxide afforded **13**, which was subsequently condensed with **4** to give regorafenib **1**.

Having established the above mentioned synthetic route, we also investigated possible ways to simplify the synthesis. One approach to shorten the synthesis was to make compound **7** *via* a direct Friedel–Crafts acylation of **5**. However, much lower yields were obtained under numerous conditions (Table 1, entries 1–4). An attempt to improve yield by increasing either the temperature or the amount of aluminum chloride used was unsuccessful (entries 2 and 3). The use of Friedel–Crafts acylation failed mainly due to the electron-withdrawing fluorine group and acetylation of the phenolic hydroxyl group as a side reaction.[15a] The failure of direct Friedel–Crafts acylation led us to use the Fries rearrangement to achieve acylation.

Acetate **6** was synthesized on the kilogram scale *via* acetylation of **5** in 99.8% yield, thus setting the stage for the key Fries rearrangement. While the Fries rearrangement is normally promoted using a large excess of aluminum chloride, we managed to optimize the amount of aluminum chloride used to only 1.5 equiv (Table 2, entries 2–4).[15b] Efforts to improve the conversion rate and promote the consumption of **6** by elevating the temperature were unsuccessful (entries 5 and 8). An attempt to optimize the reaction by using more polar solvents proved successful, but further studies revealed an issue with residual nitrobenzene; however, nitromethane proved to be optimal in terms of yield and ease of use (entries 8–10). When **6** was mixed with aluminum chloride in nitromethane by one-time addition, intense heat was released, resulting in a sticky substance that immediately solidified. Moreover, the reaction did not proceed smoothly. These issues made workup inconvenient and decreased the yield. This problem was solved by adding acetate **6** in a dose-controlled manner (entries 11–12). Under these optimized conditions, the desired product was isolated in 82% yield (entry 11). It is speculated that nitromethane can dissolve $AlCl_3$. The $AlCl_3$–CH_3NO_2 complex, an addition product formed after dissolution, is more reactive than $AlCl_3$. However, considering the safety issues caused by the $AlCl_3$–CH_3NO_2 system in scale-up preparation, we tried to carry out the Fries rearrangement catalyzed by the $AlCl_3$–CH_3NO_2 system in chloroform (entry 13). Fortunately, this procedure was successful in reducing the amount of nitromethane used to 1.5 equiv while maintaining a satisfactory yield of 80%. Finally, compound **6** (1.0 equiv) was added in portions to a solution of aluminum chloride (1.5 equiv), nitromethane (1.5

Table 2. Effects of $AlCl_3$, temperature, and solvent on the Fries rearrangement.[a]



				Yield (%)[d]		
Entry	$AlCl_3$ (equiv)	Solvent	Temp (°C)	6	7	14
1	1.0	DCM	25	80	7	ND[e]
2	1.0	DCM	40	76	8	ND
3	1.5	DCM	40	73	25	ND
4	1.7	DCM	40	70	24	ND
5	1.7	$CHCl_3$	60	50	26	15
6	1.7	$CHCl_3$	40	70	25	ND
7	1.5	$CHCl_3$	40	69	23	ND
8	1.5	$PhNO_2$	90	10	30	50
9	1.5	$PhNO_2$	40	46	43	ND
10	1.5	CH_3NO_2	40	48	45	ND
11[b]	1.5	CH_3NO_2	40	10	82	ND
12[bc]	1.5	CH_3NO_2	40	12	85	ND
13[bc]	1.5	$CH_3NO_2/CHCl_3$[f]	40	12	80	ND

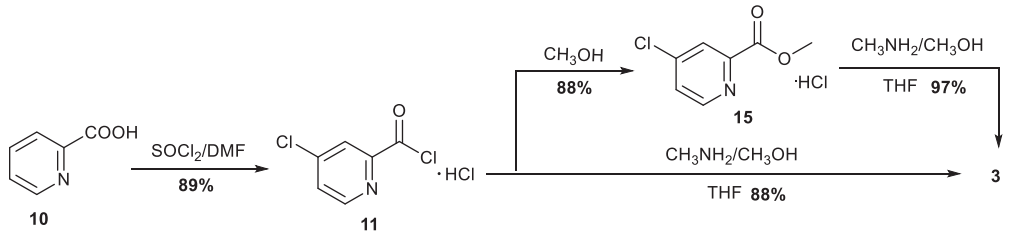
[a]Standard conditions: **6** (13 mmol), solvent (15 mL).
[b]**6** was added to a solution of $AlCl_3$, nitromethane, and solvent.
[c]The loading of **6** was 800 g.
[d]Isolated yield after chromatography except entry 12.
[e]Not detected by TLC analysis. [f]CH_3NO_2 (1.5 equiv, 420 mL) was added.

equiv), and $CHCl_3$ at room temperature, and the resulting solution was then stirred at 40 °C to obtain compound **7**. The crude product **7** was dissolved in alkaline solution, purified by washing with ethyl acetate and adjusted to pH 5. The product was isolated by filtration and recrystallized from water. This process was successfully reproduced on an 800 g scale (entry 13).

Subsequently, a method for the synthesis of compound **9** was developed and optimized. The Beckmann rearrangement reaction was then investigated using a literature procedure, where ammonium hydroxide was added dropwise to a mixture of 70% aqueous sulfuric acid and oxime **8** at 20 °C until pH 8.[16] However, only 50% yield of the desired product **9** was obtained. The low yield could be explained by the hydrolysis of oxime **8** back to ketone **7**, as indicated by TLC analysis. Therefore, it became logical for us to attempt the rearrangement reaction under nonaqueous conditions.

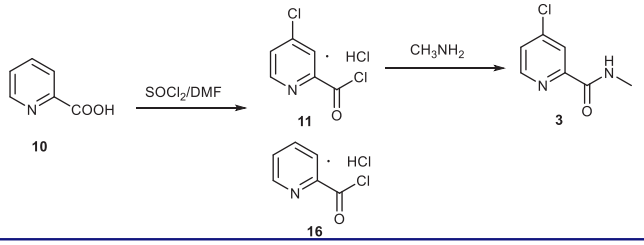
Encouraged by the report by Chen et al. that thionyl chloride and potassium iodide could be conducive to the Beckmann rearrangement, we added thionyl chloride (0.1 equiv) and potassium iodide (0.01 equiv) to the reaction mixture.[17] The reaction worked well in ethyl acetate, which, compared with other solvents, is a preferred class 3 solvent. Crude **9** was obtained from ethyl acetate and was directly used in the next step. Hydrolysis carried out in 2 N aqueous hydrochloric acid at 80 °C afforded **2** in satisfactory yield. High-purity **2** (98.7% (relative area) using HPLC analysis) was obtained *via* decolorization using a small amount of sodium dithionite and activated carbon that had been preprocessed by dilute nitric acid and crystallized from water.

The synthesis of compound **3** in 76% overall yield through a sequence of chlorination, esterification, and amidation reactions using 2-picolinic acid as the starting material was reported in the literature (Scheme 3).[18] However, byproduct **16** may be



Scheme 3. Reported Synthetic Routes to Intermediate **3**.

Table 3. Preparation of intermediate 3 in "One Pot".[a]



				Yield (%)	
Entry	$SOCl_2$ (equiv)	Temp (°C)	Methylamine (equiv)	11	3
1[b]	2.5	80→110	–	52	–
2[b]	3	110	–	55	–
3	6	80	–	73	–
4	10	80	–	96	–
5[bc]	3	80	40% methylamine (10)	–	60
6[c]	6	80→0	40% methylamine (10)	–	70
7[c]	6	80→-10	40% methylamine (10)	–	79
8[c]	6	80→0	methylamine (gas, 10)	–	95
9[c]	6	80→-10	methylamine (gas, 10)	–	96
10[cd]	6	80→0	methylamine (gas, 10)	–	93

[a]Standard conditions: **10** (60 mmol), 3 drops of DMF.
[b]Toluene as solvent (50 mL).
[c]Sodium bromide (0.4 equiv) was added to the reaction system.
[d]The loading of **10** was 210 g.

formed due to incomplete chlorination (Table 3, entries 1–3). Interestingly, formation of this byproduct can be minimized by using a large excess of thionyl chloride (10 equiv). The reaction was optimized by reducing the thionyl chloride amount to 6 equiv along with the addition of sodium bromide (0.4 equiv), as reported in the literature (entries 5–10).[19] In fact, with 6 equiv of thionyl chloride, it can function as the reaction solvent, providing a faster reaction rate and a cleaner reaction profile. After the reaction was complete, the excess thionyl chloride was distilled off under reduced pressure, and the residue was directly used in the next step.

To avoid the ester intermediate, we investigated direct amidation with methylamine. We found that a certain amount of acyl chloride was hydrolyzed when 40% aqueous methylamine was used. As anticipated, this problem was avoided by using methylamine gas generated by adding 40% aqueous methylamine (10 equiv) to solid sodium hydroxide (equipment setup is shown in Figure S13). Compound **3** was isolated in 93–96% yield. This process was successfully reproduced on a 210 g scale (entry 10).

Table 4. Effects of the amounts of 2, potassium *tert*-butoxide and potassium carbonate on the formation of **13**.[a]

Entry	**2** (equiv)	*t*-BuOK (equiv)	K_2CO_3 (equiv)	Time (hour)	Yield (%)[b]
1	1.0	1.2	–	20	80
2	1.2	2.0	–	18	55
3	1.0	1.2	0.5	3	87
4	1.0	1.2	1.0	4	85
5	1.0	1.2	0.1	18	84
6	1.0	2.0	0.5	4	72
7	1.0	1.5	0.5	4	80
8	1.1	1.2	0.5	3	92

[a]Standard conditions: **3** (39 mmol), DMA (50 mL), 85 °C, argon.
[b]Isolated yield after column chromatography.

With an acceptable route to key intermediates **2** and **3** in hand, the two remaining procedures were the Williamson ether synthesis and coupling reaction. Several issues with the etherification-condensation step needed to be addressed to develop a route suitable for further scale-up.

Picolinamide **13** was obtained in the presence of potassium *tert*-butoxide in 80% yield, but according to the literature procedure, the Williamson reaction took 20 h to go to completion a (Table 4, entry 1).[4b] To shorten the reaction time, our study focused on increasing the molar ratio of potassium *tert*-butoxide (entry 2); however, the yield was dramatically reduced, presumably due to the formation of varying amounts of the bis-addition product when significantly more than 1 equiv of potassium *tert*-butoxide was present.

Inspired by the synthesis of sorafenib, we added anhydrous potassium carbonate (0.5 equiv) was to the Williamson etherification reaction mixture, which clearly shortened the reaction time and maintained the yield (entry 3).[3d] Interestingly, the conversion of **13** remained essentially unchanged when the molar ratio of potassium carbonate was raised to 1 equiv (entry 4). It is not clearly understood how potassium carbonate affected the rate, but our studies indicated that a dramatically shorter reaction time was not witnessed when less than 0.5 equiv of this base was employed (entry 5). However, a slight excess of **2** (1.1 equiv) could effectively promote the reaction in 92% yield (entry 8). Finally, this process was successfully reproduced on a 165 g scale, as shown in the experimental section.

Compound **12** could be condensed with **13** in the presence of *N,N*'-carbonyldiimidazole (CDI) to afford the desired product.[3d] The drawback of this method was that the self-condensation byproduct readily formed.

Consequently, isocyanato **4** was prepared *via* the reaction of **12** and bis(trichloromethyl)carbonate by utilizing toluene as the solvent in 72% yield in accordance with the literature.[3c] Strangely, some product was lost during vacuum distillation due to possible formation of the product-toluene binary azeotrope. The optimized conditions consisted of ethyl acetate serving as the solvent and refluxing for 1 h. The target product was obtained by distillation at 120 °C (0.1 MPa) under reduced pressure in 95% yield.

After the high-quality key intermediates **13** and **4** were obtained, the title compound regorafenib (**1**) was readily prepared through a nucleophilic addition reaction between the two fragments using dichloromethane as the solvent, and product **1** was isolated as a white solid by filtration.

In summary, a concise and efficient synthesis of key intermediate **2** was developed. Intermediate **2** was synthesized in 68% overall yield through a 5-step sequence involving esterification, Fries rearrangement, condensation, Beckmann rearrangement, and hydrolysis. Compared with traditional synthetic methods, this method avoided isomer formation, steam distillation, and catalytic hydrogenation, making it suitable for industrial applications. Moreover, the synthetic methods for intermediate **3** and **4** reported in the literature were also optimized.

Meanwhile, we provide an alternative method for the production of regorafenib, and this method is acceptable in both product quality and yield. The method proceeds in ten convergent steps to afford the product with a total yield of 46.5% and HPLC purity of 99.96%. All of the intermediates and the final target were isolated cleanly in high yield.

Experimental section

General

All of the starting materials, reagents, and solvents are commercially available and used without further purification. Melting points were determined with an X-4 apparatus and were uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Ascend 400 and 600 (Billerica, MA, USA) using tetramethylsilane (TMS) as an internal standard. Electrospray ionization mass spectrometry (ESI-MS) analyses were recorded on an Agilent 1100 Series MSD Trap SL (Santa Clara, CA, USA). The reactions were monitored using thin-layer chromatography (TLC; HG/T2354-92, GF254), and compounds separated using TLC were visualized with UV light. The purity of regorafenib was determined by HPLC using a Shimadzu LC-20A series instrument. The HPLC analysis data were reported in relative area % and were not adjusted to weight %.

Synthesis of 1-(2-fluoro-4-hydroxyphenyl)ethanone (7)

To a solution of aluminum chloride (1.04 kg, 7.8 mol) and nitromethane (420 mL) in CHCl3 (3 L), acetate 6 (800 g, 5.2 mol) was added in portions at room temperature, and then the mixture was heated to 40 °C. After 15 h, the reaction was complete, as monitored using TLC. The reaction was cooled to room temperature and slowly poured into 1 N hydrochloric acid (8 L) containing crushed ice (1 kg). After stirring adequately, the organic layer was separated. The aqueous layer was extracted two additional times (2 L × 2). The combined organic layers were washed with water until the pH was 4–5 and were concentrated in vacuo to provide black oil. The black oil was dissolved in ethyl acetate (3.6 L) and extracted with 15% NaOH (2 L × 4). The aqueous layer was collected and adjusted to pH 5 using 6 N hydrochloric acid. The pink precipitate was filtered to provide 682 g of crude product. The crude product was dissolved in hot water (6.5 L), decolorized with active carbon (20 g), then filtered and recrystallized to give ketone **7** as a pale yellow tabular crystal (640 g, 80%). Mp 120–122 °C, (Lit.[19] Mp 120–121 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.85 (t, $J = 8.4$ Hz, 1H), 6.85 (s, 1H), 6.73 (dd, $J = 2.0$ Hz, 2.4 Hz, 1H), 6.64 (dd, $J = 2.0$ Hz, 2.4 Hz, 1H), 2.63 (d, $J = 5.2$ Hz, 3H).

Synthesis of N*-(2-fluoro-4-hydroxyphenyl)acetamide (9)*

To a solution of fluorophenol 5 (610 g, 3.6 mol) in dried ethyl acetate (3 L), potassium iodide (6 g, 0.04 mol) and thionyl chloride (9 mL, 1 mmol) was added dropwise at room temperature. The mixture was heated to 65 °C. After 3 h, the reaction was complete, as monitored using TLC. The mixture was cooled to room temperature and concentrated *in vacuo* to give **9** as a pale brown solid, Mp 121–122 °C, (Lit.[20] Mp 124 °C). Spectral properties for intermediate **9**, ESI MS(m/z): 170.1 $[M+H]^+$, 339.1 $[2M+Na]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.71 (s, 1H), 9.39 (s, 1H), 7.39 (t, $J = 8.8$ Hz, 1H), 6.59 (dd, $J = 2.4$ Hz, 2.8 Hz, 1H), 6.54 (dd, $J = 2.4$ Hz; 2.8 Hz, 1H), 2.00 (s, 3H).

Synthesis of 4-(4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)-3-fluorophenoxy)-N-methylpicolinamide (regorafenib, 1)

To a solution of intermediate **13** (288 g, 1.1 mol) and dichloromethane (960 mL), isocyanate **4** (292 g, 1.3 mol) in dichloromethane (500 mL) was added dropwise at 0 °C under argon. The mixture was stirred at room temperature, and a brown solid precipitated after 20 min. The mixture was stirred for 16 h and then filtered. The precipitate was suspended in diethyl ether (2 L) and stirred for 2 h. Then, the mixture was filtered and dried under vacuum for 4 h at 35 °C to provide **1** (478 g, 90%) as a white solid with 99.96% HPLC purity. Mp: 206–207 °C, ESI MS (m/z): 483.3 $[M+H]^+$, 505.3 $[M+Na]^+$. HRMS (ESI): *m/z* calcd for $C_{21}H_{15}ClF_4N_4O_3$ $[M+Na]^+$ 505.0661, found 505.0667. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.40 (s, 1H), 9.78 (s, 1H), 9.11 (s, 1H), 8.58 (d, $J = 5.96$ Hz, 1H), 8.12–8.21 (m, 2 H), 7.64-7.69 (m, 2H), 7.60 (d, $J = 8.8$ Hz, 1H), 7.34 (dd, $J = 2.8$ Hz, 2.4 Hz, 1H), 7.30 (dd, $J = 2.4$ Hz, 2.4 Hz, 1H), 7.08 (d, $J = 1.52$ Hz, 1H), 2.81 (d, $J = 4.68$ Hz, 3H).

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