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A Practical and Efficient Method for the Synthesis of Sorafenib and Regorafenib

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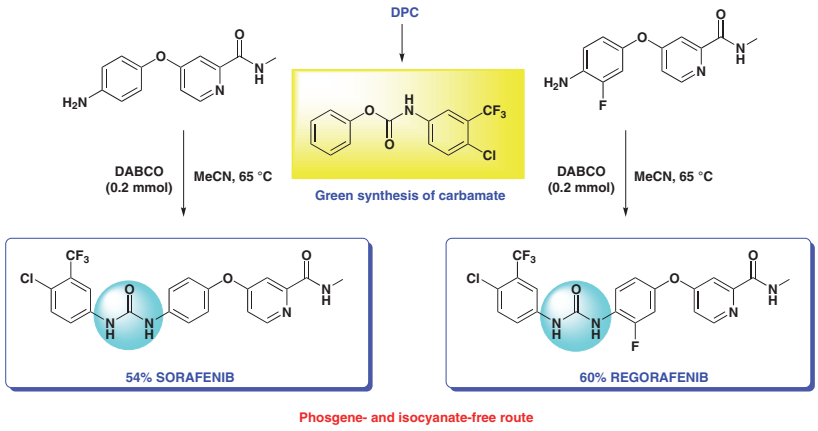

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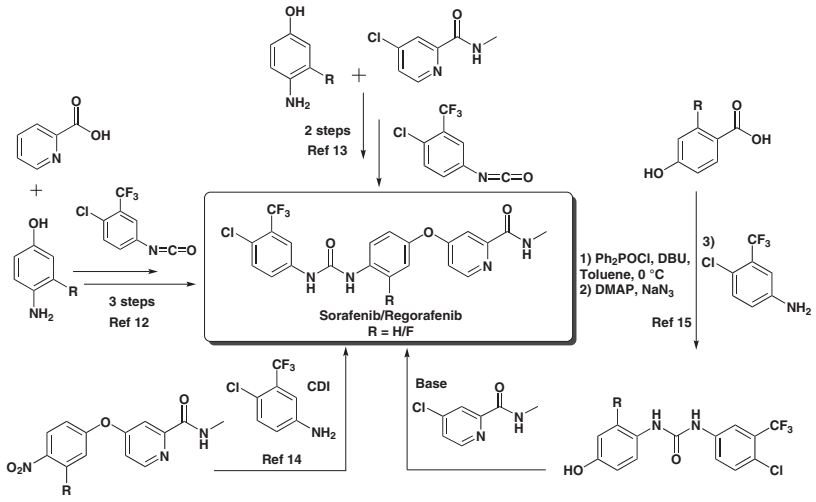
Abstract Efficient, practical syntheses of sorafenib and regorafenib have been achieved in a manner that is free from the problems associated with previously reported methods. The process involved preparation of 4-(4-aminophenoxy)-*N*-methylpicolinamide (sorafenib intermediate) and 4-(4-amino-3-fluorophenoxy)-*N*-methylpicolinamide (regorafenib intermediate) using only a single base and did not require the use of an inert atmosphere. The reaction of intermediates with phenyl 4-chloro-3-(trifluoromethyl)phenyl carbamate, prepared using water-assisted synthesis of carbamates, was used to install the main urea functionality in these molecules.

Key words sorafenib, regorafenib, diphenyl carbonate, unsymmetrical urea, carbamate

Kinase-regulated biochemical pathways play crucial roles in the formation, progression, and maintenance of cancer, and therefore are targets for the development of novel, efficient, and targeted anticancer therapies.[1] VEGFR, EGFR, RAF, and aurora kinases are abundantly expressed in various cancers, and their almost perfect interactions with pharmacophores containing diaryl urea makes these kinase receptors ideal targets for developing anticancer drug molecules. The urea oxygen atom is a superior acceptor and the urea NH moiety is a favoured hydrogen-bond donor, making urea an attractive drug candidate.[2] Sorafenib, the first diaryl urea-based oral multikinase inhibitor approved for the treatment of cancer in humans, appeared to be a landmark discovery in the development of anticancer drugs.[3] Since then, several medicinal chemistry initiatives have improved the pharmacological and pharmacokinetic properties of sorafenib and also explored its activity against other types of cancers. As stated earlier, the urea moiety has appeared as a core scaffold in many kinase inhibitors that have now been approved as anti-cancer drugs.[3]

Sorafenib was discovered as an emerging drug aimed at the Ras-Raf-MEK-ERK oncogenic pathway,[4] from evaluation of a large library of compounds against Raf1 (or c-Raf) kinase. This study resulted in the identification of 3-thienyl urea, which was chosen for further development;[5] however, no substantial improvement in therapeutic efficacy was achieved. Then, Bayer and Onyx Pharmaceuticals synthesized another new library of bis-aryl ureas using a parallel synthesis approach in order to quickly extend the earlier SAR studies.[6] The essential role of the urea moiety in the Raf1 kinase inhibition was established and Sorafenib, with a c-Raf IC50 of 6 nM, was discovered through modification of the heterocyclic moiety and distal pyridine ring of the molecule. This drug has been demonstrated to be effective in both preclinical and clinical investigations against many types of human cancer.[7]

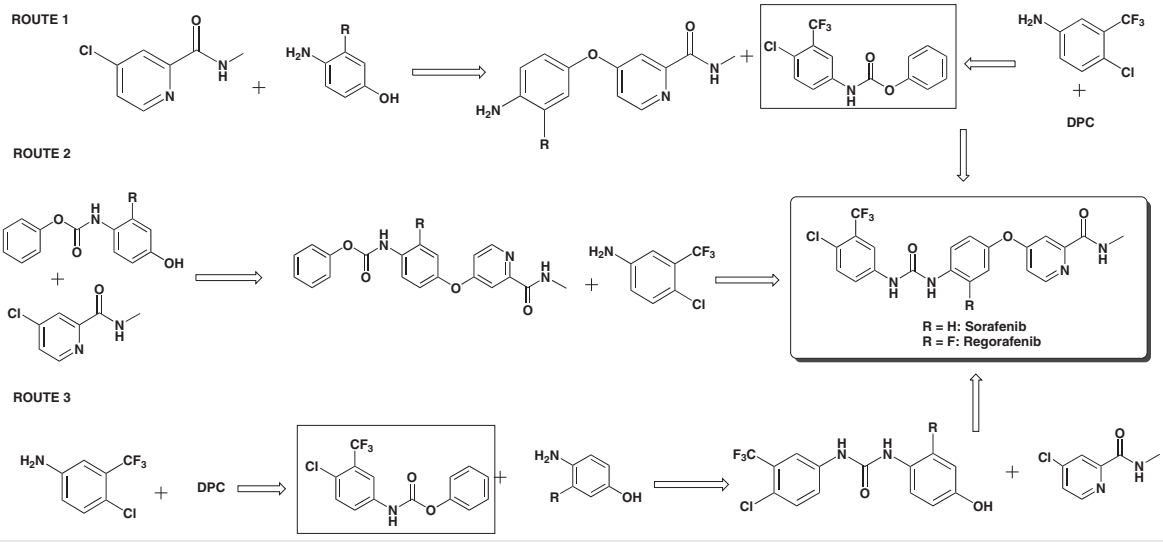
Regorafenib,[8] a fluorinated analogue of sorafenib, exhibited a pharmacodynamic profile similar to that of sorafenib, but with improved clinical performance mainly due to the presence of the fluorine atom on the middle ring of the molecule. Regorafenib was first approved for the treatment of metastatic colorectal cancer in 2012,[9] and later used for advanced hepatocarcinoma in 2017.[10] This was followed by an exploration of sorafenib to improve and expand its activity.



Scheme 1 Summary of reported synthetic approaches to sorafenib and regorafenib

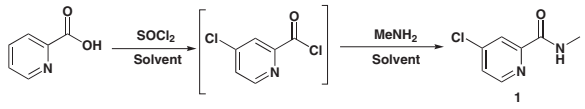
The FDA took over a decade to approve sorafenib for advanced RCC treatment from its selection as a lead molecule in 1994. Regorafenib's Phase I dose escalation trial was conducted when sorafenib was approved, and it took nearly seven years for the FDA to approve it for the treatment of metastatic colorectal cancer.[11] A review of the literature revealed that the preparation of sorafenib involved reaction of 4-aminophenol with 4-chloro-*N*-methyl picolinamide to form 4-(4-aminophenoxy)-*N*-methylpicolinamide intermediate, which then reacted with an isocynate to give the product (Scheme 1);[12–15] the analogous use of 4-amino-3-fluorophenol gave regorafenib. These methods have drawbacks such as: (a) use of toxic haloformates and isocyanates, which are typically prepared using phosgene gas; (b) complex reaction operations; (c) generation of impurities during the synthesis, and (d) inert reaction rendering the processes hazardous, costly, and unsafe. Therefore, there is a need to develop a facile, safe, and practical synthesis of sorafenib and regorafenib with an objective of curtailing the cost of manufacturing of these molecules. Herein, we report a practical and an efficient synthesis of sorafenib and regorafenib.[16,17]

Three possible routes to sorafenib were envisaged, as depicted in Scheme 2. Route 1 involved the synthesis of diaryl ether from 4-chloro-*N*-methylpicolinamide and *p*-aminophenol, followed by reaction with the intermediate (4-chloro-3-(trifluoromethyl)phenyl)carbamate. Route 2 involved the synthesis of diaryl ether from reaction of phenyl



Scheme 2 Proposed retrosynthetic schemes for sorafenib and regorafenib

Table 1 Optimization of Reaction Conditions for the Preparation of 4-Chloro-*N*-methylpicolinamide (**1**)



Entry	Reaction conditions		Yield (%)[a]
	Step 1	Step 2	
1	$SOCl_2$, DMF, 45 °C, 12 h	2M $MeNH_2$ in THF, 0–3 °C, 3 h, N_2	nd
2	$SOCl_2$, DMF, 60 °C, 16 h	2M $MeNH_2$ in THF, 0–3 °C, 4 h, N_2	nd
3	$SOCl_2$, THF, 75 °C, 16 h	2M $MeNH_2$ in THF, 0–3 °C, 4 h, N_2	nd
4	$SOCl_2$, toluene, DMF (0.1 mL), 75 °C, 16 h	2M $MeNH_2$ in THF, 0–3 °C, 4 h, N_2	nd
5	$SOCl_2$, chlorobenzene, NaBr (cat.), 85 °C, 19 h	40% aq. $MeNH_2$, 0–3 °C, 4 h	80
6	$SOCl_2$ (3.5 eq.), THF, DMF (0.1 mL), 70 °C, 16 h	40% aq. $MeNH_2$, 0–3 °C, 4 h	95

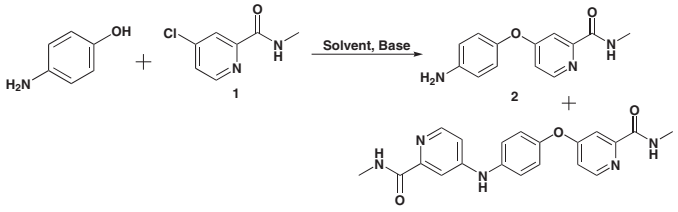
[a] Isolated yield; nd = desired product not detected.

(4-hydroxyphenyl) carbamate with 4-chloro-*N*-methylpicolinamide, followed by reaction of this carbamate intermediate with 4-chloro-3-trifluoromethyl aniline. Route 3 involved the synthesis of urea first, i.e., 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-hydroxyphenyl)urea, followed by diaryl ether formation from its reaction with 4-chloro-*N*-methylpicolinamide to yield sorafenib. Use of 4-amino-3-fluorophenol in place of *p*-aminophenol was expected to lead to regorafenib.

Route 1 was explored by reacting picolinic acid with $SOCl_2$ to produce 4-chloropicolinyl chloride, which, upon *in-situ* reaction with methylamine, produced 4-chloro-*N*-methylpicolinamide (**1**);[13] optimization of reaction conditions is summarised in Table 1. Use of DMF, THF, and toluene as solvents, $SOCl_2$ (2 equivalents) in the chlorination step, and 2 M solution of methylamine in THF did not lead to product formation (entries 1–4), but reaction in chlorobenzene with a catalytic amount of NaBr/DMF at 85 °C and use of 40% aq. methylamine gave 80% yield of 4-chloro-*N*-methylpicolinamide (**1**). Further improvement of the yield to 95% was observed when 3.5 equivalents of thionyl chloride were used in THF, along with a catalytic amount of DMF and 40% aq. methylamine.

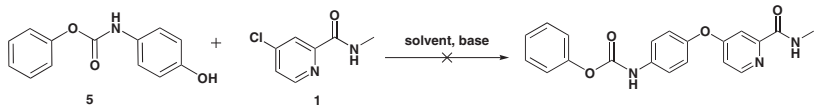
In the next step, 4-aminophenol was reacted with 4-chloro-*N*-methylpicolinamide (**1**) to yield 4-(4-aminophenoxy)-*N*-methylpicolinamide (**2**) under different reaction conditions (Table 2). The best yield obtained was very low (25%; entry 6) and, under all the reaction conditions detailed in Table 2, *N*-methyl-4-(4-((2-(methylcarbamoyl)pyridin-4-yl)amino)phenoxy)picolinamide[18] was formed as

Table 2 Synthesis of 4-(4-Aminophenoxy)-*N*-methylpicolinamide (**2**)

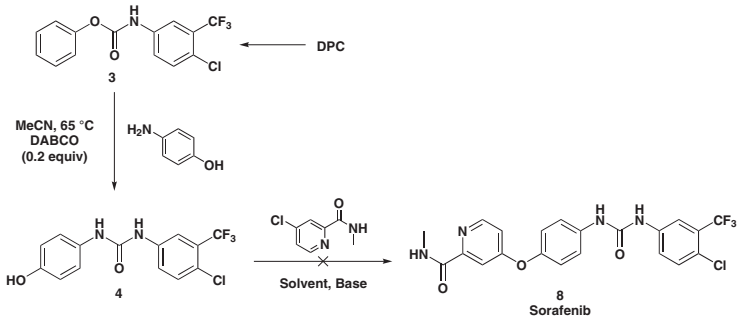


Entry	Reaction conditions	Yield (%)[a]
1	THF (dry), KOtBu, 70 °C, 24 h	no reaction
2	acetone, K_2CO_3, 70 °C, 20 h	no reaction
3	acetone, KOtBu, 70 °C, 24 h	no reaction
4	DMF (dry), KOtBu, 80 °C, 6 h	nd
5	DMF (dry), KOtBu, 80–110 °C, 6 h	nd
6	DMF (dry), KOtBu, K_2CO_3, 80 °C, 8 h	25[13]

[a] Isolated yield; no reaction = starting materials remained unreacted; nd = desired product not detected.



Scheme 3 Attempted synthesis of phenyl 4-((2-(methylcarbamoyl)pyridin-4-yl)oxy)phenyl carbamate



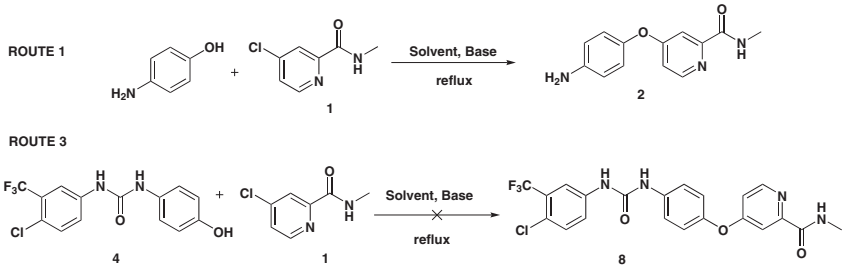
Scheme 4 Attempted synthesis of sorafenib (**8**) from 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-hydroxyphenyl)urea (**4**)

the major compound in ca. 10 to 40% yield. Due to low yield of the intermediate 4-(4-aminophenoxy)-*N*-methylpicolinamide (**2**) and formation of an impurity in the reaction, further *in situ* reaction with phenyl 4-chloro-3-(trifluoromethyl)phenyl carbamate to afford sorafenib was not performed and Route 1 was abandoned at this stage.

Route 2 was explored by synthesizing phenyl (4-hydroxyphenyl) carbamate (**5**) from the reaction of diphenyl carbonate (2.0 equiv) and amine (1.0 equiv) in aqueous organic medium in the presence of ammonium acetate under reflux reaction conditions, and this was followed by reaction with 4-chloro-*N*-methylpicolinamide (**1**) to synthesize the diaryl ether intermediate. This approach was to eliminate the formation of impurities arising from the aromatic nucleophilic substitution reactions of the free amino group present in 4-aminophenol molecule (Route 1). Different reaction conditions were explored such as use of a range of organic and inorganic bases (e.g., KOtBu, Cs_2CO_3, NaH and K_2CO_3) in different solvents (e.g., acetone, DMF, THF) in a temperature range of 60 °C to 130 °C for 2–24 h to synthesize phenyl 4-((2-(methylcarbamoyl)pyridin-4-yl)oxy)phenyl carbamate, but all failed to yield the desired product (Scheme 3), which was planned to react with 4-chloro-3-trifluoromethyl aniline to afford sorafenib.

Finally, Route 3 (Scheme 4) was explored and instead of phenyl (4-hydroxyphenyl) carbamate (**5**), the reaction between phenyl 4-chloro-3-(trifluoromethyl)phenyl carbamate (**3**) and *p*-aminophenol in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) base in acetonitrile at 65 °C for 30 min gave 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-

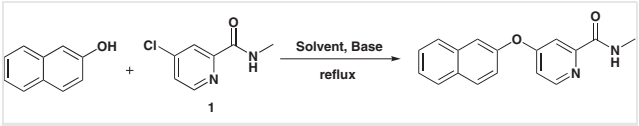
Table 3 Synthesis of 4-(4-Aminophenoxy)-*N*-methylpicolinamide (**2**) (Route 1) and Attempted Synthesis of Sorafenib (**8**) (Route 3)



Entry	Reaction conditions	Yield (%)[a]
Route 1	Cs_2CO_3, DMF, 110 °C, 2 h	98
Route 3	Cs_2CO_3, DMF, 110 °C, 2–6 h	no reaction

[a] Isolated yield.

hydroxyphenyl)urea (**4**), which was reacted further with 4-chloro-*N*-methylpicolinamide in the presence of KOtBu, and K_2CO_3, at different reaction temperatures, under Cu catalysed conditions, using TMEDA as ligand in the presence of DMF as a solvent, but to no avail and there was no sign of the desired product.

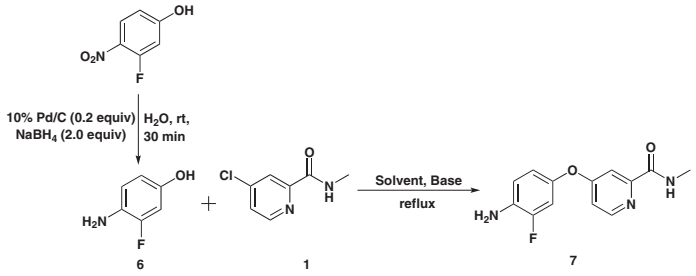


Scheme 5 A model reaction to understand diaryl ether formation

In all of the above reactions, diaryl ether synthesis was the bottleneck, and either no diaryl ether was formed or a low yield of ether was accompanied by the formation of a large amount of impurities.

Thereafter, it was decided to conduct a model reaction with 4-chloro-*N*-methylpicolinamide and 2-naphthol (Scheme 5) to prepare the diaryl ether. Different organic and inorganic bases (e.g., Cs_2CO_3, K_2CO_3, NaOH, Et_3N, DBU) in different solvents were examined, and caesium carbonate in DMF was found to give the desired product within 2 h refluxing at 110 °C with complete consumption of starting

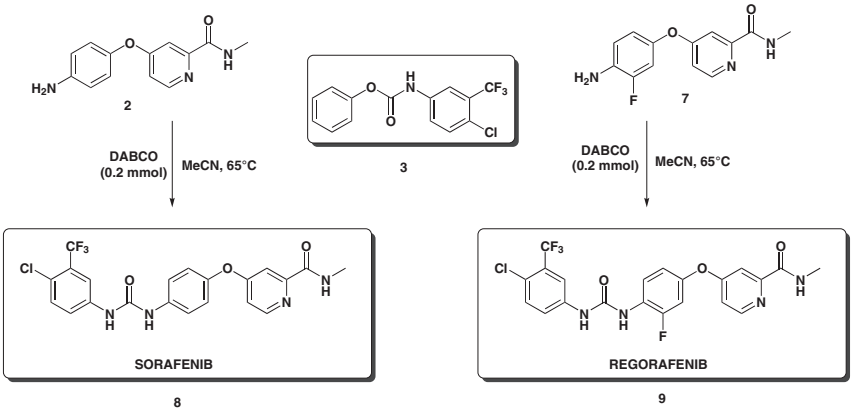
Table 4 Synthesis of 4-(4-Amino-3-fluorophenoxy)-*N*-methylpicolinamide (**7**)



Entry	Reaction conditions	Yield (%)[a]
1	Cs_2CO_3, DMF, 110 °C, 24 h	no reaction
2	Cs_2CO_3, DMF, 130 °C, 16 h	no reaction
3	KOtBu, DMSO, 120 °C, 6 h	80[18]

[a] Isolated yield.

Table 5 Synthesis of Sorafenib and Regorafenib



Entry	Reaction conditions	Yield (%)[a]
Sorafenib	DABCO, MeCN, 65 °C	54
Regorafenib	DABCO, MeCN, 65 °C	60

[a] Isolated yield.

material and an isolated yield of ca. 80%. The use of DBU or K_2CO_3 gave a trace amount of the desired product after 48 h of refluxing and no reaction was observed in NaOH or Et_3N.

Encouraged by the outcome of the model reaction, reactions of 4-aminophenol (Route 1) and 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-hydroxyphenyl)urea (**4**) (Route 2) with 4-chloro-*N*-methylpicolinamide (**1**) were carried out (Table 3). In the presence of Cs_2CO_3 as base and DMF as the solvent at 110 °C for 2 h, the diaryl ether intermediate **2** of sorafenib was isolated in 98% yield but the reaction of urea **4** with **1** gave no reaction.

Therefore, instead of urea, reaction of 4-amino-3-fluorophenol (**6**) with 4-chloro-*N*-methylpicolinamide (**1**) in the presence of KOtBu in DMF at 120 °C after 6 h gave the regorafenib intermediate 4-(4-amino-3-fluorophenoxy)-*N*-methylpicolinamide (**7**)[18] in an isolated yield of 80% (Table 4); however, to our surprise, no product **7** was formed when reaction was carried out in DMF containing caesium carbonate base.

Ultimately, phenyl 4-chloro-3-(trifluoromethyl)phenyl carbamate (**3**) and 4-(4-aminophenoxy)-*N*-methylpicolinamide (**2**) reacted in the presence of a catalytic amount of DABCO in acetonitrile at 60 °C for a duration of 1–2 h to afford sorafenib (**8**) in 54% isolated yield for the final step and overall yield of 45%. Likewise, reaction of phenyl 4-chloro-3-(trifluoromethyl)phenyl carbamate (**3**) with 4-(4-amino-3-fluorophenoxy)-*N*-methylpicolinamide (**7**) afforded regorafenib (**9**) in 60% isolated yield and an overall yield of 41% for the process (Table 5)

In conclusion, practical and efficient processes to access both sorafenib and regorafenib have been developed that avoid the use of hazardous and moisture-sensitive reagents such as phosgene, isocyanates, chroformates and carbonyldiimidazole. No inert environment was used during the process and in place of two bases, only one base was used. Overall yields for the synthesis of sorafenib and regorafenib were excellent considering the chemistry involved in the synthesis.

All reagents and starting materials were supplied by commercial sources and were used as such without purification unless otherwise noted. All reactions were performed in round-bottom flasks under reflux conditions and also in screw-capped vials. The progress of reactions were monitored by thin-layer chromatography (TLC). TLC plates were visualized under UV light and also in an iodine chamber. The ^1H and ^{13}C NMR spectra were obtained in DMSO-d_6 as a solvent using 500, 600 and 125, 151 MHz spectrometer, respectively, with internal reference standard of $SiMe_4$. High-resolution mass spectra (HRMS) were obtained in electron spray ionization (ESI) mode and LC-MS/LTQ was obtained in APCI mode. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (*J*) are reported in Hz. The abbreviations used to characterize the signals are: s = singlet, d = doublet, dd = double of doublet, t = triplet, m = multiplet.

4-Chloro-*N*-methylpicolinamide (1)[18]

A solution of picolinic acid (5 g, 41.0 mmol) in anhydrous THF (8 mL) containing DMF (6.0 mmol) was heated to 50 °C, and to this mixture was added, dropwise, thionyl chloride ($SOCl_2$) (10.0 mL, 140.0 mmol), and the temperature of the reaction mixture was raised to 70 °C and kept at this temperature for 16 h. After cooling to room temperature, the reaction mixture was diluted and washed with toluene (twice) and dried under reduced pressure to obtain a dark-purple liquid. To this crude material (4.24 g) was added, portionwise, an aqueous solution containing 40% (w/w) methylamine (20 mL, 0.6 mol) and the above mixture was stirred at 0–10 °C for 4 h. Upon completion of the reaction, the reaction mixture was taken up in water and extracted with EtOAc (three times). The organic phase was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give a dark-brown oil. Further purification of the crude material using column chromatography (dichloromethane/acetone) afforded 4-chloro-*N*-methylpicolinamide (**1**).

Yield: 95% (3.8 g); brown oil.

^1H NMR (DMSO-d_6, 400 MHz): δ = 8.87 (d, *J* = 3.9 Hz, 1 H), 8.62 (d, *J* = 5.3 Hz, 1 H), 8.08–7.96 (m, 1 H), 7.75 (dd, *J* = 5.3, 2.2 Hz, 1 H), 2.82 (s, 3 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 163.10, 151.77, 149.99, 144.45, 126.24, 121.76, 26.05.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_7H_7ClN_2NaO$: 192.0236; found: 192.2047; calcd for $C_7H_7ClN_2O$: 170.5960; found [M + 1] 171.0217.

4-(4-Aminophenoxy)-*N*-methylpicolinamide (2)[13]

To a stirred solution of 4-aminophenol (3.0 mmol) in *N*,*N*-dimethyl formamide at room temperature was added caesium carbonate (3.0 mmol) and the reaction mixture was further stirred for 10 min. 4-Chloro-*N*-methylpicolinamide (**1**) (3.0 mmol) was then added and the mixture was heated at 110 °C for 2 h. Upon completion of the reaction, the mixture was cooled to room temperature, quenched with water (10 mL), and extracted with ethyl acetate (4 × 20 mL). The combined organic layer was washed with water (2 × 15 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to afford a red-brown oil, which was recrystallized from diethyl ether to give 4-(4-aminophenoxy)-*N*-methylpicolinamide (**2**).

Yield: 98% (715 mg); red-brown solid; mp 135–136 °C.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.70 (d, *J* = 4.7 Hz, 1 H), 8.41 (d, *J* = 5.6 Hz, 1 H), 7.29 (d, *J* = 2.7 Hz, 1 H), 7.03 (dd, *J* = 5.5, 2.3 Hz, 1 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 6.61 (t, *J* = 5.9 Hz, 2 H), 5.14 (s, 2 H), 2.73 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 167.31, 164.43, 152.80, 150.67, 147.40, 143.35, 122.10, 115.40, 114.20, 108.86, 26.51.

LCMS-LTQ (ESI): *m*/*z* calcd for $C_{13}H_{13}N_3O_2$: 243.2707; found: 243.9620.

Phenyl 4-Chloro-3-(trifluoromethyl)phenyl Carbamate (3)[14,15]

A suspension of diphenyl carbonate (5.0 mmol) and ammonium acetate (5.0 mmol) in a mixture of THF/H_2O (10:90) was stirred at room temperature, and to this suspension was added 4-chloro-3-(trifluoromethyl)aniline (2.5 mmol), portionwise. The resulting reaction mixture was heated at reflux at 80 °C and, upon completion of the reaction as monitored by thin-layer chromatography, the product was extracted with EtOAc. The combined EtOAc fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product, which was purified by column chromatography (hexane/EtOAc, 5–15%) to afford phenyl 4-chloro-3-(trifluoromethyl)phenyl carbamate (**3**).

Yield: 85% (671 mg); white solid; mp 160–165 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.69 (s, 1 H), 8.02 (s, 1 H), 7.73 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.65 (d, *J* = 8.7 Hz, 1 H), 7.40 (t, *J* = 7.8 Hz, 2 H), 7.23 (dd, *J* = 17.4, 7.6 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 152.26, 150.75, 138.85, 132.83, 130.30–129.70, 129.07, 126.27, 124.27, 123.73, 122.43, 119.30.

HRMS (ESI): *m*/*z* [M – 1] calcd for $C_{14}H_9ClF_3NO_2$: 314.0368; found: 314.0200.

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-hydroxyphenyl)urea (4)[15]

Phenyl 4-chloro-3-(trifluoromethyl)phenyl carbamate (1.2 mmol) and DABCO (0.2 mmol) were dissolved in acetonitrile (3 mL) at room temperature, and to this solution 4-aminophenol (1.0 mmol) was added, dropwise. The resulting reaction mixture was heated at reflux at 65 °C for 1 h. The obtained solid was filtered and the resultant residue was washed several times with hexane to obtain 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-hydroxyphenyl)urea (**4**).

Yield: 92% (304 mg); light-brown solid; mp 208–210 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.09 (s, 1 H), 8.98 (s, 1 H), 8.44 (s, 1 H), 8.06 (s, 1 H), 7.55 (d, *J* = 10.2 Hz, 2 H), 7.19 (d, *J* = 8.1 Hz, 2 H), 6.66 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 153.50, 153.16, 140.21, 132.42, 131.01, 123.30, 122.40, 121.55, 117.03, 115.73.

HRMS (ESI): *m*/*z* [M +1] calcd for $C_{14}H_{10}ClF_3N_2O_2$: 330.0469; found: 331.0466.

Phenyl (4-Hydroxyphenyl) Carbamate (5)

By following the process for the synthesis of **3**, 4-aminophenol was used to afford phenyl (4-hydroxyphenyl) carbamate (**5**).

Yield: 80% (459 mg); light-pink solid; mp 161–162 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.87 (s, 1 H), 9.19 (s, 1 H), 7.37 (t, *J* = 7.8 Hz, 3 H), 7.25 (d, *J* = 8.1 Hz, 2 H), 7.21 (d, *J* = 7.4 Hz, 2 H), 7.15 (d, *J* = 7.9 Hz, 3 H), 6.68 (d, *J* = 8.7 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 153.77, 152.37, 151.21, 130.56, 129.89, 125.76, 122.49, 120.87, 115.81.

HRMS (ESI): *m*/*z* [M + 1] calcd for $C_{13}H_{11}NO_3$: 229.0724; found: 230.0819.

4-Amino-3-fluorophenol (6)[14]

To a dry round-bottom flask were added 10% Pd/C (1.5 mmol), 3-fluoro-4-nitrophenol (1.02 g, 6.5 mmol), water (5 mL), and sodium borohydride (13.0 mmol). The mixture was stirred at 25 °C for 30 min, then filtered through a filter paper and the solvent was evaporated under reduced pressure to afford the desired product.

Yield: 98% (810 mg); greyish-brown solid; mp 170–172 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.76 (s, 1 H), 6.56 (dd, *J* = 10.4, 8.7 Hz, 1 H), 6.40 (dd, *J* = 13.1, 2.5 Hz, 1 H), 6.31 (dd, *J* = 8.6, 2.8 Hz, 1 H), 4.38 (s, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 152.40, 150.52, 149.00, 128.44, 117.67, 111.56, 103.38.

4-(4-Amino-3-fluorophenoxy)-*N*-methylpicolinamide (7)[18]

A solution of 4-amino-3-fluorophenol (**6**) (1.0 mmol) in *N*,*N*-dimethyl sulfoxide at room temperature was treated with potassium *tert*-butoxide (1.0 mmol) and stirred for 10 min at room temperature. 4-Chloro-*N*-methylpicolinamide (**1**) (1.0 mmol) was added and the mixture was then heated at 120 °C for 6 h. The mixture was cooled to room temperature, quenched with water (10 mL), and extracted with EtOAc (4 × 5 mL). The combined organics were washed with water (2 × 10 mL), dried over anhydrous $MgSO_4$, and evaporated to afford a red-brown oil. The oil was taken up in diethyl ether (10 mL), washed with brine (5 × 10 mL), and the ether layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford a dark-brown solid, which was recrystallized from diethyl ether to give 4-(4-amino-3-fluorophenoxy)-*N*-methylpicolinamide (**7**).

Yield: 80% (209 mg); red brown solid; mp 138–140 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.73 (d, *J* = 4.7 Hz, 1 H), 8.43 (d, *J* = 5.6 Hz, 1 H), 7.32 (d, *J* = 2.2 Hz, 1 H), 7.05 (dd, *J* = 5.4, 2.5 Hz, 1 H), 6.98 (dd, *J* = 11.7, 2.4 Hz, 1 H), 6.82 (t, *J* = 9.3 Hz, 2 H), 6.75 (dd, *J* = 8.6, 2.2 Hz, 1 H), 5.20 (s, 3 H), 2.75 (d, *J* = 4.8 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.92, 164.35, 152.87, 151.59, 150.78, 149.68, 142.67, 135.26, 117.86, 116.95, 114.21, 109.73–108.93, 108.93–108.50, 26.52.

HRMS (ESI): *m*/*z* [M+1] calcd for $C_{13}H_{12}FN_3O_2$: 261.2607; found: 262.0988.

4-(3-(3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido)phenoxy)-*N*-methylpicolinamide (Sorafenib) (8)[14,20]

Phenyl 4-chloro-3-(trifluoromethyl)phenyl carbamate (**3**) (3.25 mmol) and DABCO (0.5 mmol) were dissolved in acetonitrile (6 mL) at room temperature and 4-(4-aminophenoxy)-*N*-methylpicolinamide (**2**) (2.7 mmol) was added dropwise. The resulting reaction mixture was heated at reflux at 65 °C for 1 h. The obtained solid was filtered and the resultant residue was washed several times with hexane to obtain 4-(3-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)phenoxy)-*N*-methylpicolinamide (Sorafenib) (**8**).

Yield: 54% (610 mg); light-brown solid; mp 210–211 °C (lit. 210–211 °C).

IR (KBr): 3300–2900 (3N–H), 1705 (C=O), 1643 (C=O) cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.21 (s, 1 H), 8.99 (s, 1 H), 8.74 (d, *J* = 4.8 Hz, 1 H), 8.47 (d, *J* = 5.6 Hz, 1 H), 8.09 (s, 1 H), 7.61 (dd, *J* = 10.5, 8.8 Hz, 2 H), 7.58–7.53 (m, 3 H), 7.34 (d, *J* = 2.5 Hz, 1 H), 7.14 (d, *J* = 8.8 Hz, 2 H), 7.11 (dd, *J* = 5.6, 2.3 Hz, 1 H), 2.75 (d, *J* = 4.7 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.48, 164.31, 152.97, 150.88, 148.35, 139.85, 137.58, 132.51, 123.62, 122.87, 121.98, 121.03, 117.34, 114.53, 109.18, 26.52.

^{19}F NMR (500 MHz, DMSO-d_6): δ = –61.40 (CF_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{16}ClF_3NaN_4O_3$: 486.8250; found: 487.0758, 465.0940 [M + 1].

4-(3-(3-(4-Chloro-3-(trifluoromethyl)phenyl)ureido)-3-fluorophenoxy)-*N*-methylpicolinamide (Regorafenib) (9)[18]

To a stirred solution of phenyl 4-chloro-3-(trifluoromethyl)phenyl carbamate (**3**) (0.96 mmol) and DABCO (0.2 mmol) in acetonitrile (3 mL), at room temperature, was added 4-(4-amino-3-flurophenoxy)-*N*-methylpicolinamide (**7**) (0.8 mmol), dropwise. The mixture was heated at reflux at 65 °C and the progress of the reaction was monitored by TLC. Upon completion of the reaction, the crude material was filtered through filter paper and the residue was washed several times with hexane to give 4-(3-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)-3-fluorophenoxy)-*N*-methylpicolinamide (Regorafenib) (**9**).

Yield: 60% (278 mg); light-orange crystals; mp 204–205 °C (lit.[18] 206–207 °C).

IR (KBr): 3300–2921 (3N–H), 1700 (C=O), 1649 (C=O) cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 9.50 (s, 1 H), 8.77 (d, *J* = 4.7 Hz, 1 H), 8.72 (s, 1 H), 8.49 (d, *J* = 5.5 Hz, 1 H), 8.14 – 8.08 (m, 2 H), 7.59 (s, 2 H), 7.37 (d, *J* = 2.4 Hz, 1 H), 7.31 (dd, *J* = 11.5, 2.3 Hz, 1 H), 7.15 (dd, *J* = 5.6, 2.6 Hz, 1 H), 7.04 (d, *J* = 8.8 Hz, 1 H), 2.75 (d, *J* = 4.8 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.02, 164.54, 153.29, 152.69, 152.49 – 151.97, 151.04, 139.67, 132.66, 123.47, 123.08, 117.72, 117.33, 114.68, 113.71, 112.11, 110.78, 109.40, 29.55.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd. for $C_{21}H_{16}ClF_4N_4NaO_3$: 505.0661; found: 505.0664, 483.0845 [M + 1].

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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