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ScienceDirect
Bioorganic & Medicinal Chemistry 16 (2008) 405–412
Bioorganic & Medicinal Chemistry

Facile preparation of new 4-phenylamino-3-quinolinecarbonitrile Src kinase inhibitors via 7-fluoro intermediates: Identification of potent 7-amino analogs

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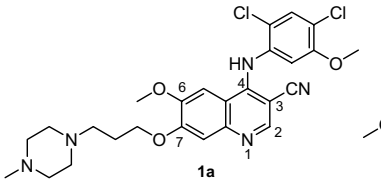
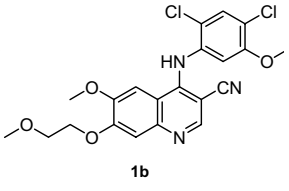
Received 9 August 2007; revised 11 September 2007; accepted 13 September 2007
Available online 18 September 2007

Abstract—A more efficient preparation of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-7-fluoro-6-methoxy-3-quinolinecarbonitrile (**2**), the penultimate intermediate in the synthesis of bosutinib (**1a**), was developed. New 7-alkoxy-4-phenylamino-3-quinolinecarbonitrile Src inhibitors were prepared from **5** and **9**, the 6-ethoxy and 6-hydrogen analogs of **2**. In addition, the fluoro group of **2** was readily displaced by primary and secondary amines to give 7-amino analogs. Two of these 7-amino analogs, **15** and **18**, were potent Src inhibitors with in vivo activity.

1. Introduction

The non-receptor tyrosine kinase Src plays a fundamental role in several signal transduction pathways.[1–3] Tumors often contain high levels of this kinase and recent studies suggest that Src is a major player in tumor progression and metastatic growth.[4–6] Src phosphorylates focal adhesion kinase (FAK),[7] resulting in an increase in cell motility, and β-catenin, resulting in a disruption of E-cadherin associated cell–cell contacts.[8,9] These events contribute to a breakdown in tissue structure that facilitates the dispersion of cancer cells. As a result of these findings, several small molecule Src inhibitors are being pursued for the treatment of cancer, including pyrido[2,3-*d*]pyrimidines,[10] pyrrolo[2,3-*d*]pyrimidines,[11] purines,[12] quinazolines,[13] thiazoles,[14] and benzotriazines.[15]





Bosutinib, SKI-606, (**1a**), a Src kinase inhibitor with a 3-quinolinecarbonitrile core is currently in Phase II clinical trials for the treatment of solid tumors.[16,17] The original preparation of **1a** started with methyl vanillate and was executed in eight steps.[18,19] Several analogs of **1a**, with diverse 7-alkoxy groups are also potent Src kinase inhibitors including the 7-(2-methoxyethoxy) derivative **1b**.[20] This analog was initially prepared by a nine-step route. Subsequently it was found that 7-alkoxy-4-phenylamino-3-quinolinecarbonitriles could be obtained by displacement of the 7-fluoro group of **2** with alcohols.[21] For example, treatment of **2** with 3-(4-methylpiperazin-1-yl)propanol in dimethylformamide in the presence of sodium hydride provided **1a**. This key 7-fluoro intermediate not only shortened the route to previously prepared Src inhibitors, but also facilitated the preparation of new analogs. We report here an improved synthesis of **2**, along with further exploration of reactions of both **2** and some additional 7-fluoro-3-quinolinecarbonitrile derivatives that allow for the preparation of novel Src kinase inhibitors.

2. Chemistry

The initial route to **2** involved a thermal cyclization that was not optimal for large scale synthesis.[21] As shown in Scheme 1, a new route was developed, wherein reaction

Keywords: Src; 3-Quinolinecarbonitrile; SKI-606; kinase.
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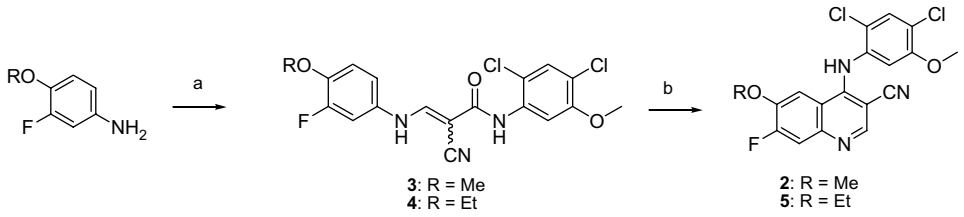
doi:10.1016/j.bmc.2007.09.028



Scheme 1. Reagents: (a) 2-cyano-*N*-(2,4-dichloro-5-methoxyphenyl)acetamide, triethylothofomate, *iso*-propanol; (b) phosphours oxychloride, acetonitrile.

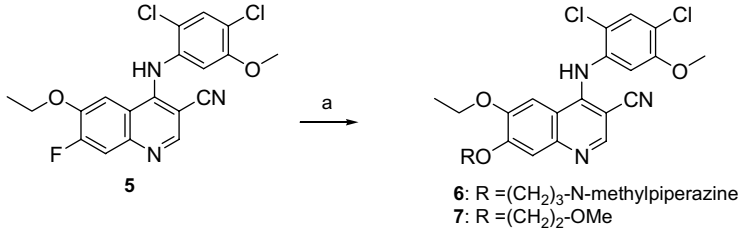
of 3-fluoro-p-anisidine, 2-cyano-*N*-(2,4-dichloro-5-methoxyphenyl)acetamide, and triethylorthoformate provided the 2-cyano-2-propenamide intermediate **3** as a mixture of *cis* and *trans* isomers.[22] Treatment of **3** with phosphorus oxychloride in acetonitrile resulted in direct formation of **2**. This route avoided the high temperature step of the original route and was also shorter and convergent. A variation of this chemistry was also used to prepare the 7-iodo and 7-bromo analogs of **2**.[23] Scheme 2 shows the versatility of this synthetic sequence. Reaction of 4-ethoxy-3-fluoroaniline under similar conditions led to the 6-ethoxy derivative **5**, via intermediate **4**. Analogous to the earlier reaction with **2**, treatment of **5** with 3-(4-methylpiperazin-1-yl)propanol provided **6**, the 6-ethoxy analog of **1a**. Additional alcohols could be used in this reaction, with 2-methoxyethanol providing **7**, the 6-ethoxy analog of **1b**.

The further versatility of these 7-fluoro intermediates is shown in Scheme 3. Formation of the amidine of 2-amino-4-fluorobenzoic acid with dimethylformamide diethyl acetal followed by reaction with the anion of acetonitrile resulted in **8**. Chlorination of **8** with phosphorus oxychloride followed by addition of 2,4-dichloro-5-methoxyaniline gave **9**. Treatment of **9** with 3-(4-methylpiperazin-1-yl)propanol provided **10**, while treatment of **9** with 2-methoxyethanol provided **11**, the 6-desmethoxy analogs of **1a** and **1b**, respectively. Alternatively, the reaction sequence could be varied such that the initial step is displacement of the 7-fluoro group of **8**, with subsequent conversion of the 4-one substituent to chloro and finally, displacement of the 4-chloro group with an aniline. This route is exemplified by the reaction of **8** with 2-methoxyethanol to give **12**. In order for this transformation to go to completion, it was necessary to use a large excess of sodium hydride and the alcohol as the solvent. Reaction of **12** with thionyl chloride and a catalytic amount of *N*,*N*-dimethylformamide provided **13**, with subsequent treatment with 2,4-dichloroaniline resulting in **14**, the 5-desmethoxy aniline derivative of **11**.

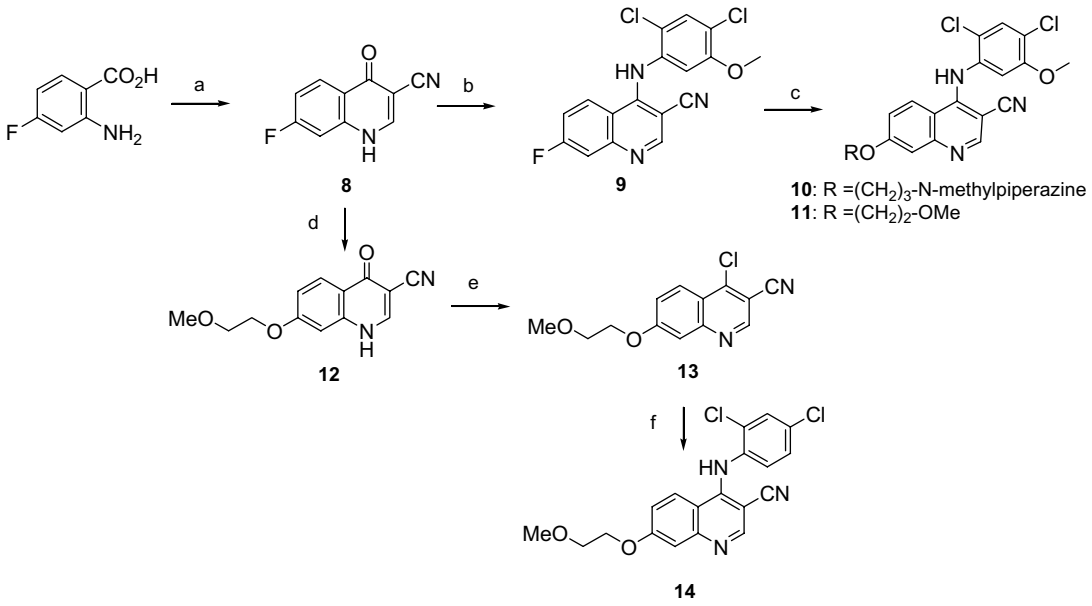
While there are several reports of 7-alkoxy-3-quinolinecarbonitrile Src inhibitors, 7-amino analogs have not been previously disclosed in the literature. We were pleased to find that the 7-fluoro group of **2** could be readily displaced with amines.[24,25] As shown in Scheme 4, reaction of **2** with 1-(3-aminopropyl)-4-methylpiperazine in 1-methyl-2-pyrrolidinone at elevated temperature provided **15**, the 7-amino analog of **1a**. The 7-amino analog of **1b**, namely **16**, was obtained by reaction of **2** with 2-methoxyethylamine, using the amine as the solvent, and heating in a sealed tube. The solubilizing amine group was further varied to include morpholine (**17**) and dimethylamine (**18**). The 7-fluoro group of **2** was also readily displaced by secondary amines, as demonstrated by the reaction of **2** with *N*,*N*,*N*′-trimethyl-1,3-propanediamine to provide **19**.

3. Biology

A cell-based assay was used to evaluate these compounds as Src inhibitors. This assay uses a rat fibroblast line that expresses a v-Src fusion with the catalytic domain of human c-Src.[18] Inhibition of the anchorage independent proliferation of these cells is a direct result of the inhibition of Src activity. Analogs **1a** and **1b** had IC_{50}s in this assay of 100 and 190 nM, respectively.[19,20] As shown in Table 1, the 6-ethoxy analogs of **1a** and **1b**, **6**, and **7**, had comparable IC_{50} values of 85 and 180 nM. A more pronounced effect was observed with the 6-desmethoxy analogs **10** and **11** with these analogs being 7- to 8-fold less active than **1a** and **1b**. Removal of the 5-methoxy group from the aniline of **11** resulted in another large decrease in activity with **14** having an IC_{50} value of greater than 10 μM. The 7-amino analog of **1a**, namely **15**, had reduced activity, as did **16**, the



Scheme 2. Reagents: (a) ROH, sodium hydride, *N*,*N*-dimethylformamide.

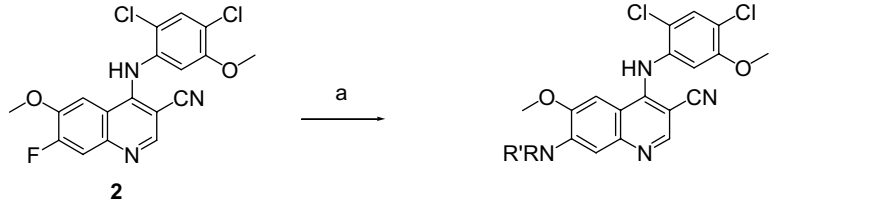


Scheme 3. Reagents: (a) 1—Dimethylformamide diethyl acetal; 2—*n*-butyl lithium, acetonitrile; (b) 1—thionyl chloride, cat. *N*,*N*-dimethylformamide, 2—2,4-dichloro-5-methoxyaniline, pyridine HCl, 2-ethoxyethanol; (c) ROH, sodium hydride, *N*,*N*-dimethylformamide; (d) sodium hydride, 2-methoxyethanol; (e) thionyl chloride, cat *N*,*N*-dimethylformamide; (f) 2,4-dichloro-5-methoxyaniline, pyridine HCl, 2-ethoxyethanol.

7-amino analog of **1b**. Two additional amino analogs, **17** and **18**, had comparable activity to **15**. However, methylation of the 7-amino group of **18** led to decreased activity, with **19** having an IC_{50} value of only 2.7 μM.

Selected analogs were tested in an ELISA format Src kinase assay,[18] wherein **1a** and **1b** were previously reported to have IC_{50} values of 1.2 and 2.9 nM, respectively.[19,20] There was a good correlation of the rank order of activity seen in this isolated Src enzyme assay with that observed in the Src cell assay.[26] The 6-ethoxy analog of **1a**, **6**, had an IC_{50} value of 1.2 nM, and **15**, the 7-amino analog of **1a**, was also potent having an IC_{50} value of 1.8 nM. While **18** had an IC_{50} value of 2.3 nM, **19**, its methylated derivative, had reduced activity (IC_{50} = 31 nM).

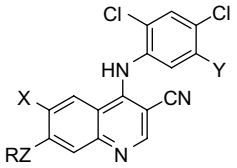
The 7-amino analogs **15** and **18** had acceptable properties as measured in standard pharmaceutical profiling assays. Compound **15** had a solubility of 32 μg/mL at pH 7.4 and a permeability of 10.7×10^{-6} cm/s, as measured in a PAMPA assay. Compound **18** had increased solubility (>100 μg/mL at pH 7.4) compared to **15**, and a slightly decreased permeability of 7.3×10^{-6} cm/s. Both compounds gave less than 34% inhibition of CYPS 3A4, 2D6, and 2C9 when tested at 3 μM, and had good stability in mouse plasma with more than 70% of the parent remaining after 300 min. Administration of a single 50 mg/kg po dose of **15** (vehicle of 0.5% methylcellulose and 0.4% polysorbate 80) to nude mice provided plasma levels of 790, 520, and 100 ng/mL after 4, 8, and 24 h, respectively. A similar study with **18** provided plasma levels of 610, 410, and 80 ng/mL. In an earlier study, **1a** had plasma levels of 1060 and 47 ng/mL at time points of 4 and 24 h.[17] Since the exposure levels of **15** and **18** met the criteria for evaluation in vivo, both compounds were tested in an efficacy study. The HT29 human colon tumor line was chosen due to the reproducible activity of **1a** in this xenograft model.[17] In the first study the tumors were staged to approximately 250 mg in size prior to dosing. Both **15** and **1a** were administered as a single oral dose of 150 mg/kg for 14 days. At the end of dosing, **15** provided a T/C of 63%, while **1a** provided a T/C of 40%. In the second



15: R =$(CH_2)_3$-N-methylpiperazine, R' = H
16: R =$(CH_2)_2$-OMe, R' = H
17: R =$(CH_2)_3$-morpholine, R' = H
18: R =$(CH_2)_3$-NMe_2, R' = H
19: R =$(CH_2)_3$-NMe_2, R' = Me

Scheme 4. Reagents: (a) RR′NH, 1-methyl-2-pyrrolidinone or sealed tube.

Table 1. Src inhibitory activity



	X	Y	Z	R	Src IC_{50} nM[18]
1a	OMe	OMe	O	$(CH_2)_3$N-Me-piperazine	100[19]
1b	OMe	OMe	O	$(CH_2)_2OMe$	190[20]
6	OEt	OMe	O	$(CH_2)_3$N-Me-piperazine	85
7	OEt	OMe	O	$(CH_2)_2OMe$	180
10	H	OMe	O	$(CH_2)_3$N-Me-piperazine	710
11	H	OMe	O	$(CH_2)_2OMe$	1,600
14	H	H	O	$(CH_2)_2OMe$	>10,000
15	OMe	OMe	NH	$(CH_2)_3$N-Me-piperazine	360
16	OMe	OMe	NH	$(CH_2)_2OMe$	1,500
17	OMe	OMe	NH	$(CH_2)_3$N-morpholine	390
18	OMe	OMe	NH	$(CH_2)_3NMe_2$	300
19	OMe	OMe	NMe	$(CH_2)_3NMe_2$	2,700

xenograft study, the tumors were staged to 235 mg and administration of **18** and **1a** as a single oral dose of 150 mg/kg for 14 days resulted in a T/C of 75% for **18** and a T/C of 51% for **1a**. The reduced activity of both **15** and **18** in this model may be a reflection of the reduced Src activity of these compounds compared to **1a**.

We are continuing to prepare new 7-amino-4-anilino-3-quinolinecarbonitriles via the various 7-fluoro intermediates. In addition, we have found that the 7-fluoro group of **2** is readily displaced by sulfur nucleophiles including ethanethiol and benzyl mercaptan and more highly functionalized 7-thiol analogs are in progress.[23]

4. Conclusions

A new route to **2**, the key 7-fluoro-3-quinolinecarbonitrile used in the preparation of the clinical compound **1a**, was reported. The synthesis and use of additional 7-fluoro-3-quinolinecarbonitrile intermediates to prepare new C-6 substituted analogs was disclosed along with the finding that 7-amino-3-quinolinecarbonitriles could be obtained by reaction of **2** with primary or secondary amines. Two of these 7-amino derivatives, **15** and **18**, had in vivo efficacy, albeit lower than that of **1a**.

5. Experimental

5.1. General methods

Melting points were determined in open capillary tubes on a Meltemp melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded using a DRX-400 spectrometer. Chemical shifts (δ) are in parts per million referenced to Me_4Si. Electrospray (ES) mass spectra were recorded in positive mode on a Micromass Platform spectrometer. Electron impact (EI) mass spectra were obtained on a Finnigan MAT-90 spectrometer. Solvents and reagents obtained from commercial sources were used without purification, unless noted. The reported yields are for purified material and are not optimized. Reactions were carried out under an inert atmosphere, either nitrogen or argon. Flash chromatography was performed with Baker 40 μM silica gel.

5.1.1. 2-Cyano-*N*-(2,4-dichloro-5-methoxyphenyl)-3-[(3-fluoro-4-methoxyphenyl)amino]-2-propenamide (3). To a suspension of 2-cyano-*N*-(2,4-dichloro-5-methoxyphenyl)acetamide[23] (1.00 g, 3.86 mmol) in 200 mL of *iso*-propanol was added 3-fluoro-*p*-anisidine (0.60 g, 4.25 mmol). This mixture was heated to reflux to give a clear yellow solution. To this solution, triethylorthoformate (1.72 mL, 10.34 mmol) was added dropwise and the reaction mixture was heated at reflux overnight. An additional 2 mL of triethylorthoformate was added and the mixture was heated at reflux overnight. An additional 2 mL of triethylorthoformate was added and the mixture was heated at reflux overnight. The mixture was allowed to cool to room temperature and the white solid was collected by filtration, washed with *iso*-propanol, and dried overnight at ~40 °C under reduced pressure. Purification by suspension in hot ethyl acetate followed by addition of cold hexanes gave 1.08 g (68%) of **3** as a white solid, mp 275–276 °C; MS 408.1 $(M-H)^-$. Analysis for $C_{18}H_{14}Cl_2FN_3O_3$: calcd C, 52.70; H, 3.44; N, 10.24. Found: C, 52.44; H, 3.26; N, 10.14.

5.1.2. 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-fluoro-6-methoxy-3-quinolinecarbonitrile (2). To a suspension of **3** (360 mg, 0.88 mmol) in 40 mL of acetonitrile was added 100 μL of methanol. The reaction mixture was heated to reflux and phosphorous oxychloride (0.65 mL, 7.0 mmol) was added dropwise via syringe. After 2 h the mixture became a clear orange solution. This solution was heated at reflux overnight. After 24 h, the reaction mixture was cooled in an ice-bath and the solid was collected by filtration, washing with

cold acetonitrile and then suspended in tetrahydrofuran. The acetonitrile filtrate and the tetrahydrofuran suspension were combined, concentrated ammonium hydroxide was added and the mixture stirred for 1 h. Water was added and stirring was continued for 2 h. The resulting solids were combined, washed with hot water, and dried under reduced pressure at ~40 °C, overnight, to provide 189 mg (55%) of **2** as orange crystals, mp 219–221 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.87 (s, 3H), 4.02 (s, 3H), 7.36 (s, 1H), 7.65–7.80 (m, 2H), 8.08 (d, J = 9 Hz, 1H), 8.48 (s, 1H), 9.85 (s, 1H); MS 392.0 $(M-H)^+$. Analysis for $C_{18}H_{12}Cl_2FN_3O_2 \cdot 0.5\ H_2O$: calcd C, 53.88; H, 3.27; N, 10.48. Found: C, 54.09; H, 3.20; N, 10.24.

5.1.3. 2-Cyano-*N*-(2,4-dichloro-5-methoxyphenyl)-3-[(4-ethoxy-3-fluorophenyl)amino]-2-propenamide (4). To a suspension of 2-cyano-*N*-(2,4-dichloro-5-methoxyphenyl)acetamide[25] (5.9 g, 22.7 mmol) in 400 mL of *iso*-propanol was added 4-ethoxy-3-fluoroaniline (3.7 g, 23.8 mmol). This mixture was heated to reflux to give a clear solution. To this solution, triethylorthoformate (11.6 mL, 69.6 mmol) was added dropwise and the reaction mixture was heated at reflux for 18 h. Additional triethylorthoformate (11.6 mL, 69.6 mmol) was added dropwise and the reaction mixture was heated at reflux for 42 h. The mixture was allowed to cool to room temperature and the solid was collected by filtration, washed with ethyl acetate, and then dried in vacuo at 40 °C to give 6.4 g (67%) of **4** as a gray solid, mp 245–247 °C; MS 424.1 $(M-H)^+$. Analysis for $C_{19}H_{16}Cl_2FN_3O_3$: calcd C, 53.79; H, 3.80; N, 9.90. Found: C, 53.39; H, 3.97; N, 9.69.

5.1.4. 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-fluoro-3-quinolinecarbonitrile (5). A suspension of **4** (6.28 g, 14.8 mmol) in 54 mL of acetonitrile and 2.0 mL of methanol was heated to reflux and phosphorous oxychloride (8.3 mL, 88.8 mmol) was added dropwise. The mixture was heated at reflux for 17 h. The resultant solution was concentrated in vacuo and acetonitrile was added to the residue. The solid was collected by filtration, washing with acetonitrile. The solid was suspended in tetrahydrofuran and neutralized with concentrated ammonium hydroxide. After stirring for 30 min, water was added and the mixture was stirred for 1 h. The solid was collected by filtration, washing with water, followed by 1:1 diethyl ether and hexane. The light yellow solid was dried in vacuo to provide 2.2 g (37%) of **5**, mp 185–187 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.95 (t, J = 7 Hz, 3H), 3.87 (s, 3H), 4.29 (q, J = 7 Hz, 2H), 7.39 (s, 1H), 7.66–7.81 (m, 2H), 8.09 (d, J = 9 Hz, 1H), 8.49 (s, 1H), 9.80 (s, 1H); MS 406.1 $(M-H)^+$. Analysis for $C_{19}H_{14}Cl_2FN_3O_2 \cdot 0.4\ H_2O$: calcd C, 55.20; H, 3.61; N, 10.16. Found: C, 55.25; H, 3.53; N, 10.15.

5.1.5. 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile (6). A mixture of **5** (200 mg, 0.49 mmol), 3-(4-methylpiperazin-1-yl)propanol (155 mg, 0.98 mmol) and sodium hydride (196 mg of a 60% dispersion in mineral oil, 4.6 mmol) in 5 mL of dimethylformamide was heated at 125 °C for 3 h. The reaction mixture was then poured into saturated aqueous sodium bicarbonate and stirred for 1 h. The aqueous solution was extracted with 10% methanol in dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by preparative thin layer chromatography, eluting with 15% methanol in dichloromethane. Trituration with hexane provided 116 mg (44%) of **6** as a light brown solid, mp 137–138 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.42 (t, J = 7 Hz, 3H), 1.96 (m, 2H), 2.16 (s, 3H), 2.24–2.49 (complex m, 10H), 3.85 (s, 3H), 4.20 (m, 4H), 7.32 (s, 2H), 7.74 (s, 1H), 7.82 (s, 1H), 8.40 (s, 1H), 9.57 (s, 1H); MS 542.0 $(M-H)^-$. Analysis for $C_{27}H_{31}Cl_2N_5O_3 \cdot 0.6\ H_2O$: calcd C, 58.40; H, 5.84; N, 12.61. Found: C, 58.31; H, 5.71; N, 12.43.

5.1.6. 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-(2-methoxyethoxy)-3-quinolinecarbonitrile (7). A mixture of **5** (138 mg, 0.34 mmol), 2-methoxyethanol (4 mL) and sodium hydride (54 mg of a 60% dispersion in mineral oil, 1.36 mmol) was heated at reflux overnight. Additional sodium hydride (135 mg of a 60% dispersion in mineral oil, 3.38 mmol) was added and the reaction mixture was heated at reflux overnight. Additional sodium hydride (54 mg of a 60% dispersion in mineral oil, 1.36 mmol) was added and the reaction mixture was heated at reflux overnight. The reaction mixture was cooled to room temperature and partitioned between ice water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by preparative thin layer chromatography, eluting with 5% methanol in dichloromethane to give a deep yellow solid, which was washed with diethyl ether containing dichloromethane, to provide 105 mg (67%) of **7** as a light tan solid, mp 215–217 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.43 (t, J = 7 Hz, 3H), 3.35 (s, 3H), 3.76 (m, 2H), 3.86 (s, 3H), 4.22 (q, J = 7 Hz, 2H), 4.30 (m, 2H), 7.33 (s, 1H), 7.36 (s, 1H), 7.74 (s, 1H), 7.82 (s, 1H), 8.41 (s, 1H), 9.59 (s, 1H); MS 462.1 $(M-H)^+$. Analysis for $C_{22}H_{31}Cl_2N_3O_4 \cdot 0.3\ H_2O$: calcd C, 56.49; H, 4.66; N, 8.99. Found: C, 56.59; H, 4.64; N, 8.95.

5.1.7. 7-Fluoro-4-hydroxy-3-quinolinecarbonitrile (8). A suspension of 2-amino-4-fluorobenzoic acid (10.2 g, 65.8 mmol) and dimethylformamide diethyl acetal (58 mL) was heated at reflux for 6 h. The solution was cooled to room temperature and concentrated in vacuo. The dark oil was passed through a pad of magnesol eluting with methylene chloride to provide 17.2 g of ethyl 2-{[(1*E*)-(dimethylamino)methylidene]amino}-4-fluorobenzoate as a red oil, MS 239.1 $(M-H)^+$.

To a solution of 2.5 M *n*-butyl lithium in tetrahydrofuran (53.6 mL, 134 mmol) in 54 mL of tetrahydrofuran at −78 °C was added dropwise a solution of acetonitrile (7.1 mL, 136 mmol) in 100 mL of tetrahydrofuran. After stirring at −78 °C for 10 min, a solution of ethyl 2-{[(1*E*)-(dimethylamino)methylidene]amino}-4-fluorobenzoate (14.5 g, 60.9 mmol) in 100 mL of tetrahydrofuran was added over a period

of 1.5 h. Stirring was continued at −78 °C for 2 h, then the temperature was slowly allowed to warm to −10 °C. The mixture was then cooled to −78 °C and acetic acid (18.3 g, 305 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 3 days. The precipitate was collected by filtration washing with tetrahydrofuran, water, diethyl ether, ethyl acetate and then additional diethyl ether to give 7.95 g (69%) of **8** as an off-white solid, mp >250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31–7.39 (complex m, 2H), 8.19 (m, 1H), 8.73 (s, 1H); MS 187.0 $(M-H)^-$. Analysis for $C_{10}H_5FN_2O{\cdot}0.20\ H_2O$: calcd C, 62.63; H, 2.84; N, 14.61. Found: C, 62.55; H, 2.71; N, 14.29.

5.1.8. 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-fluoro-3-quinolinecarbonitrile (9). A mixture of **8** (2.02 g, 10.7 mmol) and a few drops of dimethylformamide in 16 mL of thionyl chloride was heated at reflux for 1.5 h. The reaction mixture was concentrated in vacuo. Toluene (20 mL) was added and the mixture was again concentrated in vacuo to provide 2.18 g of 4-chloro-7-fluoro-3-quinolinecarbonitrile as a yellow solid, MS 207.0 $(M-H)^+$. A mixture of 4-chloro-7-fluoro-3-quinolinecarbonitrile (2.10 g, 10.2 mmol), 2,4-dichloro-5-methoxyaniline (2.15 g, 11.2 mmol), and pyridine hydrochloride (1.18 g, 10.2 mmol) in 50 mL of 2-ethoxyethanol was heated at 115 °C for 3 h. After cooling, the mixture was concentrated in vacuo. The residue was suspended in saturated aqueous sodium bicarbonate and stirred for 4 h. The precipitate was filtered and washed with water and diethyl ether to provide 1.78 g (48%) of **9** as a tan solid, mp 199–201 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.83 (s, 3H), 7.12 (s, 1H), 7.44 (m, 1H), 7.49 (d, J = 10 Hz, 1H), 7.60 (s, 1H), 8.37 (s, 1H), 8.53 (s, 1H); MS 360.0 $(M-H)^-$. Analysis for $C_{17}H_{10}Cl_2FN_3\ O{\cdot}0.4\ H_2O$: calcd C, 55.28; H, 2.95; N, 11.38. Found: C, 55.45; H, 2.98; N, 11.13.

5.1.9. 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-[3-(4-methyl)piperazin-1-yl]propoxy]-3-quinolinecarbonitrile (10). To a solution of 3-(4-methylpiperazin-1-yl)propanol (174 mg, 1.1 mmol) in 7 mL of dimethylformamide at room temperature was added sodium hydride (220 mg of a 60% dispersion in mineral oil, 5.5 mmol) in portions. After the addition was complete, the mixture was heated at 100 °C for 10 min, then **9** (200 mg, 0.55 mmol) was added, and the resulting mixture was heated at 125 °C for 23 h. After cooling, the reaction mixture was concentrated in vacuo and the residue was treated with saturated aqueous sodium bicarbonate for 1 h. The precipitate was filtered, washed with water and air-dried, then purified by preparative thin layer chromatography, eluting with 15% methanol in dichloromethane. Trituration with a mixture of diethyl ether and hexane (1:1) provided 71 mg (26%) of **10** as a light tan solid, mp 154–156 °C. ^{1}H NMR (400 MHz, TFA/DMSO-d_6) δ 2.25 (m, 2H), 2.92 (s, 3H), 3.25–3.90 (complex m, 10H), 3.88 (s, 3H), 4.32 (m, 4H), 7.43 (s, 1H), 7.52–7.63 (complex m, 2H), 7.87 (s, 1H), 8.69 (s, 1H), 9.14 (s, 1H); MS 497.9 $(M-H)^-$. Analysis for $C_{25}H_{27}Cl_2N_5O_2{\cdot}0.8\ H_2O$: calcd C, 58.32; H, 5.60; N, 13.60. Found: C, 58.32; H, 5.30; N, 13.28.

5.1.10. 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-(2-methoxyethoxy)-3-quinolinecarbonitrile (11). Following the procedure used to prepare **10**, a mixture of **9** (300 mg, 0.83 mmol), 2-methoxyethanol (187 mg 2.46 mmol), and sodium hydride (259 mg of a 60% dispersion in mineral oil, 27.5 mmol) in 6 mL of dimethylformamide was heated at 125 °C for 18 h to provide 194 mg (56%) of **11** as a tan solid, mp 182–183 °C. ^{1}H NMR (400 MHz, TFA/DMSO-d_6) δ 3.35 (s, 3H), 3.78 (m, 2H), 3.89 (s, 3H), 4.38 (m, 2H), 7.42 (s, 1H), 7.60 (s, 1H), 7.62 (d, J = 10 Hz, 1H), 7.88 (s, 1H), 8.71 (s, 1H), 9.21 (s, 1H); MS 416.1 $(M-H)^-$. Analysis for $C_{20}H_{17}Cl_2N_3O_3$: calcd C, 57.43; H, 4.10; N, 10.05. Found: C, 57.36; H, 4.09; N, 9.89.

5.1.11. 7-(2-Methoxyethoxy)-4-oxo-1,4-dihydro-3-quinolinecarbonitrile (12). A mixture of sodium hydride (500 mg of a 60% dispersion in mineral oil, 12.5 mmol) and **8** (1.30 g, 6.9 mmol) in 2-methoxyethanol (30 mL) was heated at reflux overnight. Additional sodium hydride (250 mg of a 60% dispersion in mineral oil, 6.25 mmol) was added and the reaction mixture was heated at reflux overnight. Additional sodium hydride (250 mg of a 60% dispersion in mineral oil, 6.25 mmol) was added and the reaction mixture was heated at reflux for 8 h. The reaction mixture was cooled to room temperature and partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The basic layer was acidified with aqueous hydrochloric acid and the resultant solid was collected by filtration to provide 1.05 g (62%) of **12** as a white solid, mp >250 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.32 (s, 3H), 3.70 (m, 2H), 4.21 (m, 2H), 7.02 (s, 1H), 7.08 (d, J = 9 Hz, 1H), 8.03 (d, J = 9 Hz, 1H), 8.61 (s, 1H), 12.60 (br s, 1H); MS 243.1 $(M-H)^-$ Analysis for $C_{13}H_{12}N_2O_3{\cdot}0.25\ H_2O$: calcd C, 62.77; H, 5.07; N, 11.26. Found: C, 62.53; H, 4.68; N, 11.22.

5.1.12. 4-Chloro-7-(2-methoxyethoxy)-3-quinolinecarbonitrile (13). A thick suspension of **12** (800 mg, 3.28 mmol) in 10 mL of thionyl chloride and a catalytic amount of dimethylformamide was heated at reflux for 1 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. Toluene was added and the solids were collected by filtration to provide 748 mg (87%) of **13** as an off-white solid, mp 143–145 °C. ^{1}H NMR (400 MHz, TFA/DMSO-d_6) δ 3.34 (s, 3H), 3.72 (m, 2H), 4.22 (m, 2H), 7.09 (m, 2H), 8.05 (d, J = 9.5 Hz, 1H), 8.65 (s, 1H), MS 263.2 $(M-H)^+$.

5.1.13. 4-[(2,4-Dichlorophenyl)amino]-7-(2-methoxyethoxy)-3-quinolinecarbonitrile (14). A mixture of **13** (262 mg, 1.0 mmol), 2,4-dichloroaniline (195 mg, 1.2 mmol), and pyridine hydrochloride (140 mg, 1.2 mmol) in 10 mL of 2-ethoxyethanol was heated at reflux for 30 min. The reaction mixture was cooled to room temperature, partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was washed with a 1:1 mixture of saturated aqueous sodium bicarbonate and 5 N sodium hydroxide. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by column chromatography, eluting with a gradient of 1:1 ethyl acetate:

hexane to all ethyl acetate provided 103 mg (26%) of **14**, mp 144–145 °C. ^{1}H NMR (400 MHz, TFA/DMSO-d_6) δ 3.35 (s, 3H), 3.77 (m, 2H), 4.38 (m, 2H), 7.40 (s, 1H), 7.60–7.65 (m, 2H), 7.73 (d, J = 9 Hz, 1H), 7.92 (s, 1H), 8.67 (d, J = 9Hz, 1H), 9.16 (s, 1H); MS 388.0 $(M-H)^-$. Analysis for $C_{19}H_{15}Cl_2N_3O_2$: calcd C, 58.78; H, 3.89; N, 10.82. Found: C, 58.86; H, 3.90; N, 10.76.

5.1.14. 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-{[3-(4-methylpiperazin-1-yl)propyl]amino}-3-quinolinecarbonitrile (15). A mixture of **2** (200 mg, 0.51mmol) and 1-(3-aminopropyl)-4-methylpiperazine (512 mg, 3.25 mmol) in 1.0 mL of 1-methyl-2-pyrrolidinone was heated at 105 °C for 29 h. The reaction mixture was cooled to room temperature and treated with saturated aqueous sodium bicarbonate for 1 h. The precipitate was filtered, washed with water, and air-dried, then purified by flash chromatography, eluting with a gradient of 5% methanol in dichloromethane to 25% methanol in dichloromethane. Trituration with ethyl ether containing several drops of dichloromethane provided 158 mg (59%) of **15** as an off-white solid, mp 215–217 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.80 (m, 2H), 2.20 (m, 2H), 2.92–2.49 (complex m, 10H), 3.28 (s, 3H), 3.84 (s, 3H), 3.99 (s, 3H), 6.68 (s, 1H), 6.76 (s, 1H), 7.22 (s, 1H), 7.64 (s, 1H), 7.70 (s, 1H), 8.30 (s, 1H), 9.29 (s, 1H); MS 529.2 $(M-H)^+$. Analysis for $C_{26}H_{30}Cl_2N_6O_2$: calcd C, 58.98; H, 5.71; N, 15.87. Found: C, 59.09; H, 5.77; N, 15.70.

5.1.15. 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[(2-methoxyethylamino]-3-quinolinecarbonitrile (16). A mixture of **2** (250 mg, 0.64 mmol) and 2-methoxyethylamine (1 mL) was heated at 105 °C in a sealed tube for 6 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with brine. The organic layer was dried over sodium sulfate, filtered, and concentrated. The residue was stirred with ethyl acetate then filtered to give 170 mg (45%) of **16** as a white solid, mp 165–166 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.30 (s, 3H), 3.42 (m, 2H), 3.59 (t, J = 6 Hz, 2H), 3.84 (s, 3H), 3.97 (s, 3H), 5.90 (s, 1H), 6.84 (s, 1H), 7.22 (s, 1H), 7.66 (s, 1H), 7.70 (s, 1H), 8.30 (s, 1H), 9.32 (s, 1H); MS 445.1 $(M-H)^-$. Analysis for $C_{21}H_{20}Cl_2N_4O_3$: calcd C, 56.39; H, 4.51; N, 12.53. Found: C, 56.11; H, 4.37; N, 12.17.

5.1.16. 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[(3-morpholin-4-ylpropyl)amino]-3-quinolinecarbonitrile (17). Via the procedure used to prepare **15**, **17** was obtained from **2** and 4-(3-aminopropyl)morpholine in 59% yield as an off-white solid, mp 220–221 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.80 (m, 2H), 3.35–2.48 (complex m, 6H), 3.24–3.35 (m, 2H), 3.36 (m, 4H), 3.84 (s, 3H), 3.98 (s, 3H), 7.33 (s, 1H), 6.60 (s, 1H), 6.79 (s, 1H), 7.21 (s, 1H), 7.65 (s, 1H), 7.70 (s, 1H), 8.30 (s, 1H), 9.28 (s, 1H); MS 516.1 $(M-H)^+$. Analysis for $C_{25}H_{27}Cl_2N_5O_3$: calcd C, 58.14; H, 5.27; N, 13.56. Found: C, 58.28; H, 5.40; N, 13.67.

5.1.17. 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-{[3-(dimethylamino)propyl]amino}-6-methoxy-3-quinolinecarbonitrile (18). Via the procedure used to prepare **16**, **18** was obtained from **2** and 3-dimethylamino-1-propylamine in 8% yield as a white solid, mp 165–167 °C, following flash column chromatography eluting with 30% methanol in dichloromethane. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.76 (m, 2H), 2.17 (s, 6H), 2.33 (t, J = 6 Hz, 2H), 2.90 (s, 3H), 3.26 (m, 2H), 3.84 (s, 3H), 3.97 (s, 3H), 6.37 (s, 1H), 6.77 (s, 1H), 7.21 (s, 1H), 7.63 (s, 1H), 7.70 (s, 1H), 8.30 (s, 1H), 9.27 (s, 1H); MS 474.1 $(M-H)^+$. Analysis for $C_{23}H_{25}Cl_2N_5O_2 \cdot 1.0$ H_2O: calcd C, 56.10; H, 5.53; N, 14.22. Found: C, 55.97; H, 5.68; N, 14.23. Via the procedure used to prepare **15** (use of 1-methyl-2-pyrrolidinone as solvent), **18** was obtained from **2** and 3-dimethylamino-1-propylamine in 44% yield as a white solid, mp 163–165 °C, following flash column chromatography eluting with a gradient of 5% methanol in dichloromethane to 1% aqueous ammonium hydroxide in 25% methanol in dichloromethane. Analysis for $C_{23}H_{25}Cl_2N_5O_2 \cdot 1.4$ H_2O: calcd C, 55.29; H, 5.61; N, 14.02. Found: C, 55.51; H, 5.54; N, 14.01.

5.1.18. 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-{[3-(dimethylamino)propyl]-(methyl)amino]-6-methoxy-3-quinolinecarbonitrile (19). Via the procedure used to prepare **16**, **19** was obtained from **2** and *N*,*N*,*N*′-trimethyl-1,3-propanediamine in 27% yield as a light yellow solid, mp 116–117 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.68 (m, 2H), 2.10 (s, 6H), 2.21 (t, J = 7 Hz, 2H), 2.90 (s, 3H), 3.85 (s, 3H), 3.99 (s, 3H), 7.10 (s, 1H), 7.27 (s, 1H), 7.72 (s, 1H), 8.33 (s, 1H), 9.51 (s, 1H); MS 486.2 $(M-H)^-$. Analysis for $C_{24}H_{27}Cl_2N_5O_2$: calcd C, 59.02; H, 5.57; N, 14.34. Found: C, 58.89; H, 5.67; N, 13.94.

Acknowledgments

The authors acknowledge the Wyeth Analytical Chemical Technology Department for the spectral data and pharmaceutical profiling results, Dr. Ana Carolina Barrios Sosa for the repreparation of **18**, the Wyeth Drug Safety and Metabolism Department for the nude mouse microsome stability and plasma level determinations, members of the Wyeth Oncology Department for the kinase profiling data and Carlo Etienne for assistance with the xenograft studies. We also thank Drs. Dennis Powell, Kim Arndt, Jay Gibbons, Phil Frost and Tarek Mansour for their support.

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