Synthesis and Src Kinase Inhibitory Activity of a Series of 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-furyl-3-quinolinecarbonitriles

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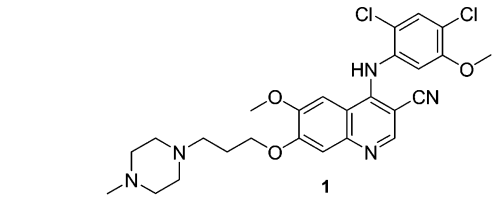
Compound **1** (SKI-606, bosutinib), a 7-alkoxy-4-[(2,4-dichloro-5-methoxyphenyl)amino]-3-quinolinecarbonitrile, is a potent inhibitor of Src kinase activity. We previously reported that analogs of **1** with thiophene groups at C-7 retained the Src activity of the parent compound. The corresponding C-7 furan analogs were prepared and it was found that the 3,5-substituted furan analog had increased activity compared to that of the 2,5-substituted furan isomer. Addition of a methoxy group at C-6 decreased the Src inhibitory activity of the C-7 2,5-substituted furan analog but increased the activity of the C-7 3,5-substituted furan isomer. This compound, **10**, was a more potent Src inhibitor than **1** in both enzymatic and cell-based assays. The kinase selectivity profile of **10** was similar to that of **1**, with **10** also inhibiting the activity of Abl and Lck. When tested in a solid tumor xenograft model, **10** had comparable oral activity to that of **1**.

Introduction

The tyrosine kinase Src is a member of a family of related kinases known as the SFKs (Src family kinases) that function as key regulators of signal transduction pathways. Src is the prototype member of this family and was first exemplified by its oncogenic viral variant v-Src. It was shown over 25 years ago that c-Src, the cellular counterpart of v-Src, encodes a tyrosine specific kinase, which unlike v-Src is tightly regulated. Src has been the focus of extensive studies,[1,2] and recently, there has been an upsurge in interest in pursuing Src as an oncology target.[3,4] Some of the renewed attention in Src is a result of studies showing its important role in tumor progression and metastatic growth.[5] Phosphorylation of focal adhesion kinase by Src results in increased cell motility, while Src-mediated phosphorylation of β-catenin weakens E-cadherin-associated cell−cell contacts.[6] This loosening of the tissue's structure allows for the movement and spreading of cancer cells. In addition, vascular endothelial growth factor induced vascular permeability is dependent on Src kinase activity.[7,8] There are several reports that indicate small molecule Src inhibitors prevent tumor cell extravasation.[7,9−15] Another reason for the renewed interest in Src is the discovery that several Src inhibitors not only inhibit Abl kinase more potently than Gleevec (imatinib), an Abl inhibitor that is the first line of treatment for chronic myelogenous leukemia (CML), but also block the activity of several Gleevec-resistant Abl mutations.[16−19] The Src/Abl dual inhibitor BMS-354825 (dasatinib) was recently approved by the FDA for the treatment of CML.[20−23]

Compound **1** (SKI-606, bosutinib), a 7-alkoxy-3-quinolinecarbonitrile, is a dual inhibitor of Src and Abl kinases that is currently in clinical trials for the treatment of both solid tumors and CML.[24−27] It was previously disclosed that related 3-quinolinecarbonitriles, having a 3,5- or 2,5-disubstituted thiophene at C-7, analogs **2a** and **2b**, retained much of the activity of **1** when tested in both a Src enzyme assay and a cell proliferation assay employing Src-transformed rat fibroblasts.[28] While the C-7 phenyl analog **2c** had comparable activity to **2a** and **2b** in the Src enzyme assay, it had reduced activity in the Src cell assay.[29] The activity of the C-7 thiophene analogs led us to pursue other heteroaryl groups at this position, including the C-7 furan analogs presented here.



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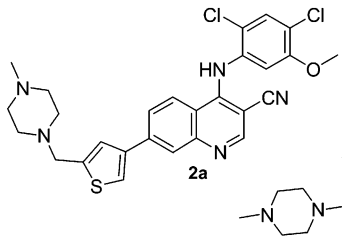
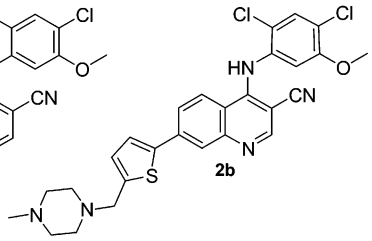
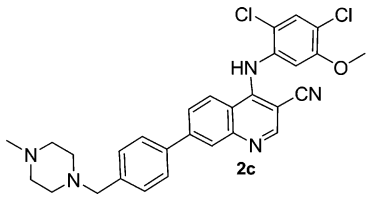


2a



2b



2c

Chemistry

As depicted in Scheme 1, tetrakis(triphenylphosphine)-palladium(0)-catalyzed Suzuki coupling of the C-7 bromo intermediate **3**[28] with 2-formyl-4-furanboronic acid provided the intermediate aldehyde **4**. Reductive amination of **4** with 1-methylpiperazine and sodium triacetoxyborohydride resulted in **5**. In a similar fashion, dichlorobis(triphenylphosphine)palladium-(II)-catalyzed Stille coupling of **3** with tributyl[5-(1,3-dioxolan-2-yl)-2-furanyl]stannane,[30] followed by acid hydrolysis, provided aldehyde **6**. Subsequent reductive amination of **6** with 1-methylpiperazine resulted in **7**. By following the reaction sequence used to convert **3** to **5**, the C-7 triflate intermediate **8**[29] was reacted with 2-formyl-4-furanboronic acid to provide aldehyde

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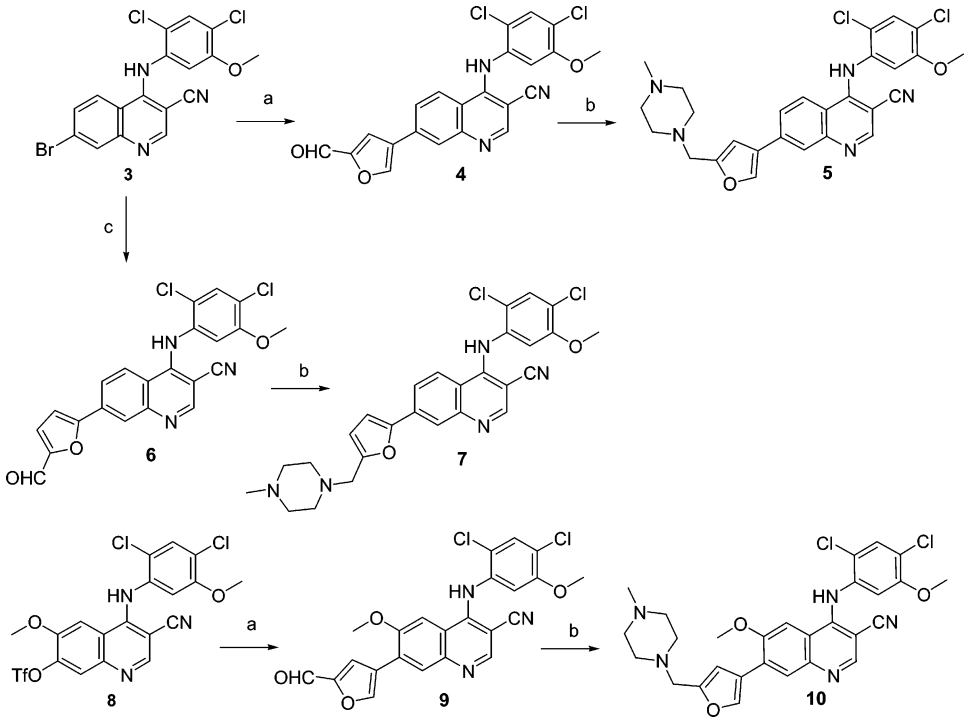
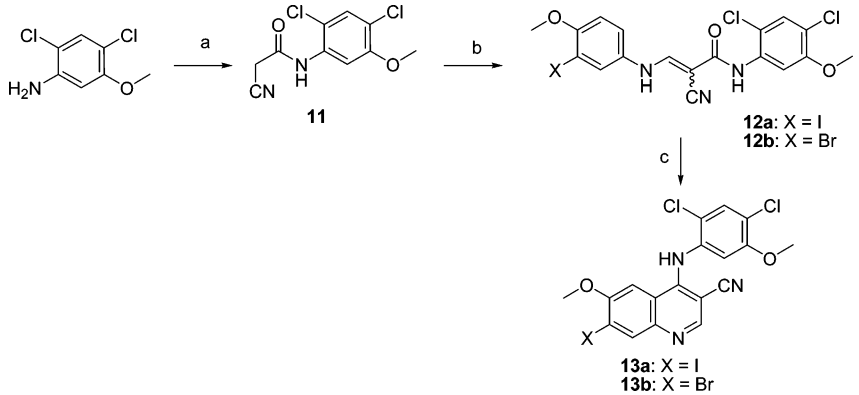
Scheme 1[a]



[a] Reagents: (a) 2-formyl-4-furanboronic acid, $(Ph_3P)_4Pd$, DME, satd aq $NaHCO_3$; (b) 1-methylpiperazine, $Na(OAc)_3BH$, CH_2Cl_2, HOAc, NMP (for **5**) or DMF (for **7** and **10**); (c) (1) tributyl[5-(1,3-dioxolan-2-yl)-2-furanyl]stannane, $(Ph_3P)_2PdCl_2$, dioxane; (2) 2 N HCl, THF.

Scheme 2[a]



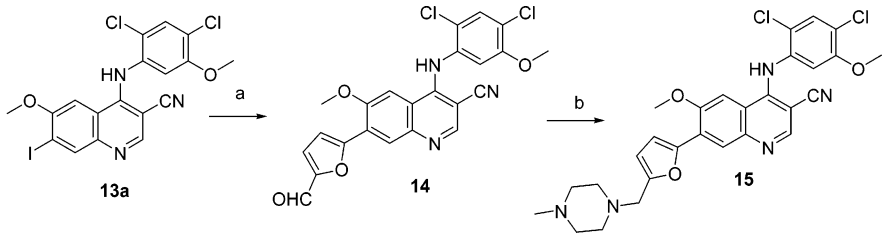
[a] Reagents: (a) cyanoacetic acid, 1,3-diisopropylcarbodiimide, THF; (b) 3-bromo or 3-iodo-4-methoxyaniline, triethylorthoformate, *i*-PrOH; (c) phosphorus oxychloride, acetonitrile.

9, which was converted to **10** via reductive amination with 1-methylpiperazine.

While triflate **8** readily coupled with boronic acids and stannane derivatives, its preparation from methyl vanillate was rather cumbersome, requiring nine steps. To facilitate the preparation of 6-methoxy analogs, an improved route to **8** was essential. Another option was to identify a facile route to an alternative intermediate, and it was decided to target the C-7 aryl iodine. It was envisioned that this analog could be synthesized by adapting methodology initially utilized for the large-scale preparation of 4-phenylamino-3-quinolinecarbonitriles.[31] As shown in Scheme 2, reaction of 2,4-dichloro-5-methoxyaniline with cyanoacetic acid and 1,3-diisopropylcarbodiimide gave the acetamide derivative **11**. Treatment of **11** with 3-iodo-4-methoxyaniline and triethylorthoformate in *iso*-propanol provided **12a**, which upon subsequent phosphorus oxychloride-mediated ring closure in acetonitrile resulted in formation of the desired 7-iodo-3-quinolinecarbonitrile **13a**. The versatility of this reaction sequence is highlighted by the ready preparation of 7-bromo-3-quinolinecarbonitrile **13b** from 3-bromo-4-methoxyaniline.

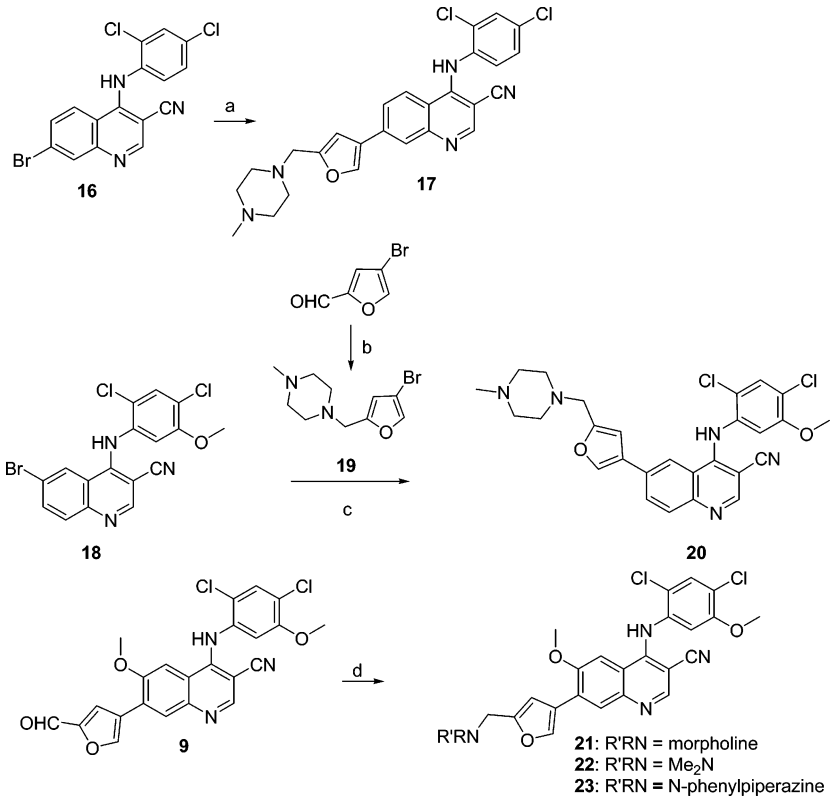
As shown in Scheme 3, we were pleased to observe that **13a** rapidly coupled with tributyl[5-(1,3-dioxolan-2-yl)-2-furanyl]-stannane, with subsequent acid treatment providing aldehyde **14**. Reductive amination of **14** with 1-methylpiperazine resulted in **15**. The analog of **5** lacking the methoxy group at C-5 of the aniline, namely **17**, was prepared by reaction of **16**[28] with 2-formyl-4-furanboronic acid, followed by reductive amination (Scheme 4). The isomer of **5** where the furan substituent is at C-6, namely **20**, was prepared from the C-6 bromo derivative **18**[28] by a slightly different route. Intermediate **19** was obtained by reductive amination of 4-bromo-2-furaldehyde with 1-methylpiperazine. In situ formation of the trimethylstannane derivative of **19** by reaction with hexamethylditin in the presence of tetrakis(triphenylphosphine)palladium(0) and subsequent coupling with **18** provided **20**. Analogs of **10** were readily obtained by varying the amine used in the reductive amination reaction

Scheme 3[a]



[a] Reagents: (a) (1) tributyl[5-(1,3-dioxolan-2-yl)-2-furanyl]stannane, $(Ph_3P)_2PdCl_2$, dioxane; (2) 2 N HCl, THF; (b) 1-methylpiperazine, $Na(OAc)_3BH$, CH_2Cl_2, NMP, HOAc.

Scheme 4[a]



[a] Reagents: (a) (1) 2-formyl-4-furanboronic acid, $(Ph_3P)_4Pd$, DME, satd aq $NaHCO_3$; (2) 1-methylpiperazine, $Na(OAc)_3BH$, CH_2Cl_2, NMP, HOAc; (b) 1-methylpiperazine, $Na(OAc)_3BH$, CH_2Cl_2, HOAc; (c) $(Me_3Sn)_2$, $(Ph_3P)_4Pd$, dioxane; (d) morpholine or 2 M dimethylamine in THF or 1-phenylpiperazine, $Na(OAc)_3BH$, CH_2Cl_2, DMF, HOAc.

of **9** (Scheme 4). This route was used to prepare **21**−**23**, the morpholine, dimethylamine, and *N*-phenylpiperazine analogs.

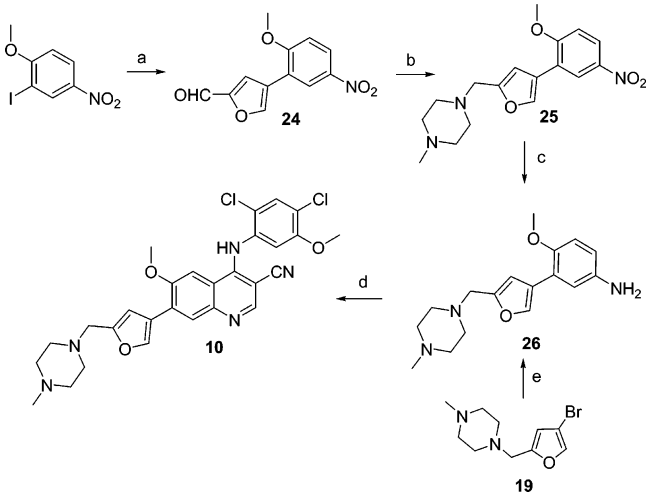
An alternative route to **10** based on the chemistry used to prepare **13a** and **13b** was investigated. To this end, as shown in Scheme 5, palladium-catalyzed coupling of 2-iodo-4-nitroanisole with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-furancarboxaldehyde provided **24**. Reductive amination of **24** with 1-methylpiperazine led to **25**, with subsequent catalytic hydrogenation of the nitro group giving aniline **26**. Intermediate **26** was also prepared by in situ conversion of **19** to the corresponding boronic acid, followed by coupling to 3-iodo-4-methoxyaniline. Reaction of **26** and **11** with triethylorthoformate in *iso*-propanol and subsequent ring closure with phosphorus oxychloride in butyronitrile provided **10**.

Results and Discussion

As shown in Table 1, the 3,5-disubstituted furan analog **5** was about 3-fold more potent than the 2,5-isomer **7** in both the Src enzyme and cell assays. This is in contrast to what was seen with the corresponding thiophene derivatives **2a** and **2b**, which were equipotent. The 6-methoxy analog of **5**, namely **10**, had an IC_{50} of 0.78 nM in the Src enzyme assay and an IC_{50} of 15 nM in the Src cell assay, making **10** a more potent Src inhibitor than **1**. This increase in activity correlated with what was seen in a series of C-7 alkenyl and alkynyl 3-quinolinecarbonitriles, where the C-6 methoxy analogs were consistently more potent than the C-6 unsubstituted analogs.[32,33] However, these results contrasted with what was observed with the C-7 phenyl analogs where the *N*-ethylpiperazine analog of **2c** was a more potent Src inhibitor than its C-6 methoxy derivative.[29] Interestingly, **15**, the C-6 methoxy analog of **7**, had reduced activity compared to that of **7**. Therefore, there is a large disparity in the activity of **10** and its 2,5-isomer **15**, with **15** having an IC_{50} in the Src enzyme assay of 13 nM and an IC_{50} in the Src cell assay of 550 nM.

We previously reported several examples where removal of the methoxy group at C-5 of the aniline headpiece lead to decreased Src activity.[33−35] This analog of **5**, namely **17**, was less potent than **5** in both the Src enzyme and cell assays. We also previously showed that several C-6-substituted 3-quinolinecarbonitriles were less potent than their corresponding C-7-substituted isomers, with these substituents including alkoxy,[36]

Scheme 5[a]



[a] Reagents: (a) 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-furancarboxaldehyde, $(Ph_3P)_4Pd$, DME, satd aq $NaHCO_3$; (b) 1-methylpiperazine, $Na(OAc)_3BH$, CH_2Cl_2, NMP, HOAc; (c) 10% Pd on C, H_2, MeOH; (d) (1) **11**, triethylorthoformate, *i*-PrOH; (2) phosphorus oxychloride, butyronitrile; (e) (1) tri-*iso*-propyl borate, *n*-butyl lithium, hexane, THF; (2) [1,1′bis-(diphenylphosphino)ferrocene]-dichloropalladium(II) complex with dichloromethane, 3-iodo-4-methoxyaniline, DME, aq Na_2CO_3.

thiophene,[28] along with ethenyl and ethynyl groups.[32,33] As expected based on these earlier findings, the isomer of **5** where the furan group is at C-6, namely **20**, had reduced activity compared to **5**.

The activity in the Src enzyme and cell assays of analogs of **10**, wherein the 1-methylpiperazine group was replaced with other amines, is shown in Table 1. While the morpholine analog **21** was slightly less potent than **10**, the dimethylamine analog, **22**, retained the activity of **10**. Reduced activity was observed with the 1-phenylpiperazine analog, **23**, in both the enzyme and cell assays (IC_{50} = 3.6 and 34 nM, respectively). When tested against a panel of kinases, **10** had IC_{50} values of greater than 1 μM for the inhibition of CDK4, AKT, KDR, and PDK-1 and an IC_{50} of 230 nM for the inhibition of EGFR. Potent activity was seen against Abl kinase, with **10** having an IC_{50} of 0.40 nM in an enzymatic Abl assay. This dual inhibition of Src and Abl kinases was also observed with **1** and other related C-7 alkoxy 3-quinolinecarbonitriles.[25,35] For the C-7 alkoxy analogs, the magnitude of the Abl inhibition correlated with that of Src. However, **5**, **22**, and **23** had comparable Abl activities, with IC_{50} values in the range of 0.43 to 0.68 nM, while the Src IC_{50} values for these three analogs were 2.7, 0.75, and 3.6 nM, respectively. In a cell proliferation assay with Lck-transformed rat fibroblasts, **10** had an IC_{50} of 20 nM, demonstrating a lack of selectivity for Src over another SFK.

In pharmaceutical profiling assays, **10** had a permeability of 2×10^{-6} cm/s in a PAMPA assay, with low solubility at neutral pH. However, as expected due to the presence of the *N*-methyl piperazine group, decreasing the pH to 4.5 increased the solubility to 63 μg/mL. After a 30 min incubation with rat liver microsomes, 72% of the compound remained unchanged. Prior to testing in a xenograft assay, a stability study with nude mouse liver microsomes was performed and **10** was found to have an estimated half-life of 32 min. Nude mice were given a single oral dose of 50 mg/kg of **10** in a vehicle consisting of 0.5% methylcellulose and 0.4% polysorbate 80. The plasma concentrations of **10** at 4, 8, and 24 h were determined to be 1140, 1030, and 103 ng/mL, respectively, exposure levels that should support once a day dosing. When administered orally in several solid tumor xenograft models, **1** was previously shown to have the most robust activity against HT29 tumors, therefore, this colon line was chosen for an in vivo study with **10**.[26] The tumors were staged to approximately 250 mg in size prior to a single daily oral administration of 25, 50, and 150 mg/kg of **10** for 21 days. As shown in Figure 1, a dose response was observed in this model. The 150 mg/kg dose of **10** provided a T/C of 38% at day 21, with no toxicity seen in any of the animals.

Conclusion

Continuing optimization of the 4-[2,4-dichloro-5-methoxyphenyl)]amino-3-quinolinecarbonitrile series of Src inhibitors resulted in the identification of **10**, a C-7 3,5-disubstituted furan derivative. This analog was more potent than its 2,5-disubstituted furan isomer **15** in inhibiting Src activity in vitro. In the course of this work, a concise synthetic route to a key intermediate was developed that allowed for the facile preparation of **10**. The new Src kinase inhibitor reported here demonstrated in vivo activity in a colon tumor xenograft model, and further studies with **10** (SKI-758) are underway.

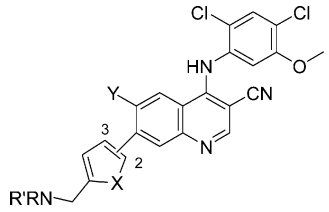
Experimental Section

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) and high-resolution 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.

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-(5-formyl-3-furyl)-3-quinolinecarbonitrile (4). A mixture of **3**[28] (429 mg, 1.60 mmol), 2-formyl-4-furanboronic acid (280 mg, 2.01 mmol), and tetrakis(triphenylphosphine)palladium(0) (20 mg) in 20 mL of ethylene glycol dimethyl ether and 14 mL of saturated aqueous sodium bicarbonate was heated at reflux for 2 h and then cooled to room temperature. The reaction mixture was partitioned between dichloromethane and water. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated in vacuo. Diethyl ether was added to the residue, and the solid was collected by filtration to provide 348 mg (78% yield) of **4** as a light yellow solid, mp 246−248 °C; ^{1}H NMR (DMSO-d_6/TFA) δ 3.90 (s, 3H), 7.61 (s, 1H), 7.89 (s, 1H), 8.19 (s, 1H), 8.25 (s, 1H), 8.34 (d, J = 10 Hz, 1H), 8.84 (d, J = 10 Hz, 1H), 8.98 (s, 1H), 9.23 (s, 1H), 9.76 (s, 1H); MS 438.0 $(M + H)^+$. Anal. ($C_{22}H_{13}Cl_2N_3O_3 \cdot 1.75H_2O$) C, H, N.

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-{5-[(4-methylpiperazin-1-yl)methyl]-3-furyl}-3-quinolinecarbonitrile (5). A mixture of **4** (150 mg, 0.34 mmol) and 1-methylpiperazine (0.19 mL, 1.71 mmol) in 4 mL of dichloromethane and 1 mL of 1-methyl-2-pyrrolidinone was cooled to 0 °C. Sodium triacetoxyborohydride (370 mg, 1.75 mmol) was added followed by 0.08 mL of acetic acid. The resulting mixture was stirred at 0 °C for 10 min then at room temperature for 3 h. The mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic phase was dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with a gradient of 10% methanol in ethyl acetate to 1% ammonium hydroxide in 30% methanol in ethyl acetate. Trituration with diethyl ether provided 109 mg (61% yield) of **5** as a white solid, mp 210−212 °C; ^{1}H NMR (DMSO-d_6) δ 2.15 (s, 3H), 2.25−2.39 (br s, 4H), 2.39−2.49 (br s, 4H), 3.54 (s, 2H), 3.86 (s, 3H), 6.98 (s, 1H), 7.30 (s, 1H), 7.71 (s, 1H), 7.91 (d, J = 8 Hz, 1H), 8.03 (s, 1H), 8.40 (s, 1H), 8.44−8.56 (m, 2H), 10.13 (s, 1H); MS

Table 1. Inhibition of Src Kinase Activity by 7-Furyl-3-quinolinecarbonitriles



	isomer	X	Y	NRR′	Src enzyme IC_{50} (nM)	Src cells IC_{50} (nM)
1					3.8[35]	100[24]
2a	3,5	S	H	*N*-Me-piperazine	3.8	69[28]
2b	2,5	S	H	*N*-Me-piperazine	2.3	64[28]
2c	1,4-phenyl		H	*N*-Me-piperazine	5.0	390[29]
5	3,5	O	H	*N*-Me-piperazine	2.7	46
7	2,5	O	H	*N*-Me-piperazine	7.5	120
10	3,5	O	OMe	*N*-Me-piperazine	0.78	15
15	2,5	O	OMe	*N*-Me-piperazine	13	550
17	des 5-OMe isomer of **5**				11	260
20	6-furyl isomer of **5**				84	2800
21	3,5	O	OMe	morpholine	1.5	31
22	3,5	O	OMe	NMe_2	0.75	21
23	3,5	O	OMe	*N*-Ph-piperazine	3.6	34

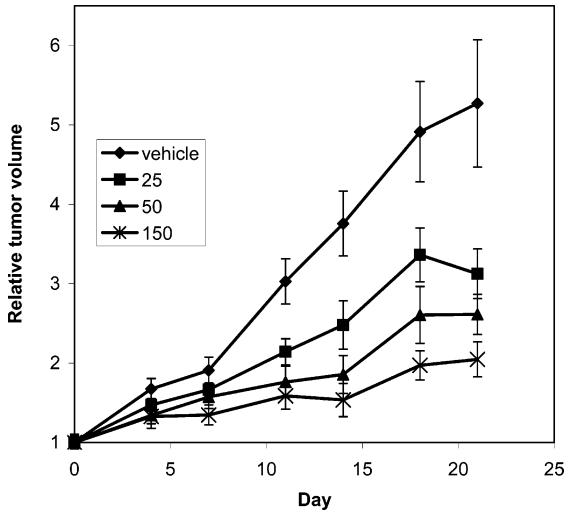


Figure 1. Antitumor activity of **10** vs an HT-29 xenograft. Tumors were staged to approximately 250 mg in volume prior to oral dosing at 25, 50, and 150 mg/kg once a day for 21 days, with 10 animals per group.

522.1, 524.1 $(M + H)^+$; HRMS calcd, 522.14581; found, 522.14558 $(M + H)^+$. Anal. ($C_{27}H_{25}Cl_2N_5O_2 \cdot 0.25H_2O$) C, H. N: calcd, 13.29; found, 12.81.

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-(5-formyl-2-furyl)-3-quinolinecarbonitrile (6). A mixture of **3**[28] (200 mg, 0.42 mmol), tributyl[5-(1,3-dioxolan-2-yl)-2-furanyl]stannane[30] (220 mg, 0.50 mmol), and a catalytic amount of dichlorobis(triphenylphosphine)palladium(II) in 5 mL of dioxane was heated at reflux for 4 h. The mixture was concentrated in vacuo and partitioned between ethyl acetate and saturated aqueous sodium chloride. The organic layer was washed with water, dried over sodium sulfate, and concentrated in vacuo to provide 130 mg (64% yield) of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-7-[5-(1,3-dioxolan-2-yl)-2-furyl]-3-quinolinecarbonitrile as a yellow solid.

A solution of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-7-[5-(1,3-dioxolan-2-yl)-2-furyl]-3-quinolinecarbonitrile (90 mg, 0.19 mmol) in 2 mL of tetrahydrofuran and 1 mL of 2 N hydrochloric acid was stirred at room temperature for 4 h. The mixture was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic layer was dried over sodium sulfate and filtered through silica gel. The filtrate was concentrated in vacuo to provide 40 mg (48% yield) of **6** as a yellow solid, mp > 250 °C; ^{1}H NMR (DMSO-d_6/TFA) δ 3.87 (s, 3H), 7.43 (s, 1H), 7.67 (d, $J = 4$ Hz, 1H), 7.76 (d, $J = 4$ Hz, 1H), 7.79 (s, 1H), 8.26 (d, $J = 9$ Hz, 1H), 8.34 (s, 1H), 8.72 (d, $J = 9$ Hz, 1H), 8.87 (s, 1H), 9.72 (s, 1H); MS 438.3 $(M + H^+)$. Anal. ($C_{22}H_{13}Cl_2N_3O_3$) C, H, N.

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-{5-[(4-methyl-1-piperazinyl)methyl]-2-furyl}-3-quinolinecarbonitrile (7). 1-Methylpiperazine (0.065 mL, 0.56 mmol) was added to a suspension of **6** (200 mg, 0.45 mmol) in 3 mL of dichloromethane and 1 mL of *N*,*N*-dimethylformamide. The reaction mixture was cooled to 0 °C and sodium triacetoxyborohydride (500 mg, 2.36 mmol) was added. After stirring at 0 °C for 1 h, a catalytic amount of acetic acid was added and the reaction mixture was allowed to warm to room temperature. The reaction was quenched by the addition of water and then partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with a gradient of 10% methanol in dichloromethane to 20% methanol in dichloromethane to provide 95 mg (40% yield) of **7** as a light yellow solid, mp 157−160 °C; ^{1}H NMR (DMSO-d_6/TFA) δ 2.82 (s, 3H), 3.24 (br s, 4H), 3.49 (br s, 4H), 3.88 (s, 3H), 4.07 (s, 2H), 6.75 (d, $J = 3$ Hz, 1H), 7.42 (d, $J = 3$ Hz, 1H), 7.47 (s, 1H), 7.83 (s, 1H), 8.13−8.26 (m, 2H), 8.69 (d, $J = 9$ Hz, 1H), 8.92 (s, 1H); MS 522.3 $(M + H)^+$. Anal. ($C_{27}H_{25}Cl_2N_5O_2 \cdot 0.9\ H_2O$) C, H, N.

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-(5-formyl-3-furyl)-6-methoxy-3-quinolinecarbonitrile (9). A mixture of **8**[29] (835 mg, 1.60 mmol), 2-formyl-4-furanboronic acid (446 mg, 3.21 mmol), and tetrakis(triphenylphosphine)palladium(0) (20 mg) in 40 mL of ethylene glycol dimethyl ether and 25 mL of saturated aqueous sodium bicarbonate was heated at reflux for 3 h and then cooled to room temperature. The reaction mixture was partitioned between dichloromethane and water. The aqueous layer was extracted with 10% methanol in ethyl acetate. The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated in vacuo. Diethyl ether was added to the residue, and the solid was collected by filtration to provide 723 mg (48% yield) of **9** as a light yellow solid, mp 238−241 °C; ^{1}H NMR (DMSO-d_6) δ 3.88 (s, 3H), 4.09 (s, 3H), 7.38 (s, 1H), 7.76 (s, 1H), 8.01 (s, 1H), 8.29 (br s, 2H), 8.48 (s, 1H), 8.77 (s, 1H), 9.71 (s, 1H), 9.87 (s, 1H); MS 468.0 $(M + H)^+$; HRMS calcd, 468.05124; found, 468.0511$(M + H)^+$.

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-{5-[(4-methylpiperazin-1-yl)methyl]-3-furyl}-3-quinolinecarbonitrile (10). A mixture of **9** (200 mg, 0.43 mmol) and 1-methylpip-

erazine (0.24 mL, 2.2 mmol) in 5 mL of dichloromethane and 1 mL of *N*,*N*-dimethylformamide was cooled to 0 °C. Sodium triacetoxyborohydride (470 mg, 2.22 mmol) was added in portions, followed by a few drops of acetic acid. The resulting mixture was stirred at 0 °C for 10 min then at room temperature for 5.5 h. The mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic phase was dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with a gradient of 10% methanol in ethyl acetate to 1% ammonium hydroxide in 20% methanol in ethyl acetate to provide 120 mg (51% yield) of **10** as a light yellow solid, mp 179−181 °C; ^{1}H NMR (DMSO-d_6) δ 2.15 (s, 3H), 2.23−2.36 (br s, 4H), 2.38−2.49 (br s, 4H), 3.54 (s, 2H), 3.87 (s, 3H), 4.06 (s, 3H), 7.01 (s, 1H), 7.33 (s, 1H), 7.74 (s, 1H), 7.94 (s, 1H), 8.10 (s, 1H), 8.28 (s, 1H), 8.43 (s, 1H), 9.82 (s, 1H); MS 552.1 $(M + H)^+$; HRMS calcd, 552.15638; found, 552.15599 $(M + H)^+$. Anal. ($C_{28}H_{27}Cl_2N_5O_3 \cdot 0.25H_2O$) C, H, N.

2-Cyano-*N*-(2,4-dichloro-5-methoxyphenyl)acetamide (11). A solution of 2,4-dichloro-5-methoxyaniline (5.00 g, 26 mmol) and cyanoacetic acid (2.28 g, 26.8 mmol) in 50 mL of tetrahydrofuran was heated to reflux and 1,3-diisopropylcarbodiimide (4.2 mL, 26.8 mmol) was added dropwise. After 30 min, the mixture was cooled to ∼15 °C in an ice bath. The solid was collected by filtration and washed with tetrahydrofuran. The filtrate was slowly poured into water and stirred for 30 min. The white solid was collected by filtration, washing with water, and then it was dissolved in 500 mL of ethyl acetate. The solution was dried over sodium sulfate and concentrated in vacuo to give 5.90 g (88% yield) of **11** as a white solid, mp 180−181 °C; ^{1}H NMR (DMSO-d_6) δ 3.84 (s, 3H), 4.02 (s, 2H), 7.58 (s, 1H), 7.66 (s, 1H), 10.00 (s, 1H); MS 257.0 $(M - H)^-$. Anal. ($C_{10}H_8Cl_2N_2O_2$) C, H, N.

(2*E*/*Z*)-2-Cyano-*N*-(2,4-dichloro-5-methoxyphenyl)-3-[(3-iodo-4-methoxyphenyl)amino]-2-propenamide (12a). To a suspension of **11** (5.00 g, 19.30 mol) in 400 mL of *iso*-propanol was added 3-iodo-4-methoxyaniline (5.80 g, 23.16 mmol). This mixture was heated to reflux to give a clear yellow solution. Triethylorthoformate (8.60 mL, 52.11 mmol) was added dropwise, and the reaction mixture was heated at reflux overnight. An additional 10 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 collected by filtration, washing with *iso*-propanol, and dried overnight at ∼40 °C under reduced pressure. Suspension in hot ethyl acetate, followed by addition of cold hexanes, gave 8.50 g (85% yield) of **12a** as a yellow solid, mp 289−290 °C; MS 516.8 $(M + H)^+$. Anal. ($C_{18}H_{14}Cl_2IN_3O_3 \cdot 0.5H_2O$) C, H, N.

(2*E*/*Z*)-3-[[3-Bromo-4-methoxyphenyl]amino]-2-cyano-*N*-(2,4-dichloro-5-methoxyphenyl)-2-propenamide (12b). To a suspension of **11** (900 mg, 3.46 mmol) in 100 mL of *iso*-propanol was added 3-bromo-4-methoxyaniline (700 mg, 3.46 mmol). The mixture was heated to reflux and triethylorthoformate (3.3 mL, 19.8 mmol) was added dropwise. Heating at reflux was continued for 6 h. The mixture was filtered while still warm, and the white solid was collected and washed with *iso*-propanol to give 376 mg (23% yield) of **12b**, mp > 250 °C; MS 467.7 $(M - H)^-$. Anal. ($C_{18}H_{14}BrCl_2N_3O_3$) C, H, N.

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-iodo-6-methoxy-3-quinolinecarbonitrile (13a). To a suspension of **12a** (720 mg, 1.39 mmol) in 40 mL of acetonitrile was added 0.2 mL of methanol. The mixture was heated to reflux, and phosphorus oxychloride (1.24 mL, 13.9 mmol) was added dropwise. This solution was heated at reflux overnight. After 24 h, the mixture was cooled in an ice bath, and the solid was collected by filtration, washing with cold acetonitrile (40 mL) and then suspended in tetrahydrofuran (100 mL). To both the acetonitrile filtrate and the tetrahydrofuran suspension was added concentrated ammonium hydroxide, and the mixtures were 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 200 mg (29% yield) of **13a**, as a yellow solid, mp 253−254 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.86 (s, 3H), 4.00 (s, 3H), 7.33 (s, 1H), 7.74 (s, 1H), 7.86 (s, 1H), 8.39 (s, 1H), 8.43 (s, 1H), 9.61 (s, 1H); MS 500.0 $(M + H)^+$. Anal. ($C_{18}H_{12}Cl_2IN_3O_2 \cdot H_2O$) C, H, N.

7-Bromo-4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-3-quinolinecarbonitrile (13b). A suspension of **12b** (4.00 g, 8.50 mmol) in 200 mL of acetonitrile was heated to reflux, and phosphorus oxychloride (5.0 mL) was added dropwise. The reaction mixture was heated at reflux overnight, cooled to room temperature, and concentrated in vacuo. The residue was cooled to 0 °C, and saturated aqueous sodium bicarbonate was added. The mixture was stirred for 1 h and then extracted with a large volume of ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and filtered. The filtrate was reduced in volume until solids appeared. The solids were collected by filtration, washing with diethyl ether and hexanes, to provide 1.73 g (45% yield) of **13b** as a light tan solid, mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.87 (s, 3H), 4.04 (s, 3H), 7.41 (s, 1H), 7.78 (s, 1H), 7.99 (s, 1H), 8.22 (s, 1H), 8.48 (s, 1H), 9.93 (s, 1H); MS 449.9 $(M - H)^-$. Anal. ($C_{18}H_{12}BrCl_2N_3O_2$) C, H, N.

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-(5-formyl-2-furyl)-3-quinolinecarbonitrile (14). A mixture of **13a** (1.20 g, 2.40 mmol), tributyl[5-(1,3-dioxolan-2-yl)-2-furanyl]stannane[30] (1.50 g, 3.49 mmol), and a catalytic amount of dichlorobis(triphenylphosphine)palladium(II) in 50 mL of dioxane was heated at reflux for 4 h. The mixture was partitioned between ethyl acetate and brine. The organic layer was dried over magnesium sulfate, filered, and concentrated in vacuo. Purification by column chromatography, eluting with a gradient of 100% hexane to 100% ethyl acetate, provided 988 mg (80% yield) of 4-[(2,4-dichloro-5-methoxyphenyl}-amino]-7-[5-(1,3-dioxolan-2-yl)-2-furyl]-6-methoxy-3-quinolinecarbonitrile as a yellow solid.

A solution of 4-[(2,4-dichloro-5-methoxyphenyl}amino]-7-[5-(1,3-dioxolan-2-yl)-2-furyl]-6-methoxy-3-quinolinecarbonitrile (937 mg, 1.83 mmol) in 30 mL of tetrahydrofuran and 15 mL of 2 N hydrochloric acid was stirred at room temperature overnight. The mixture was slowly added to 80 mL of saturated sodium bicarbonate and stirred for 40 min. The solids were collected by filtration, washing with water, followed by ethyl acetate, to provide 649 mg (76% yield) of **14** as a yellow solid, mp > 250 °C; ^{1}H NMR (DMSO-d_6) δ 3.87 (s, 3H), 4.11 (s, 3H), 7.39 (s, 1H), 7.44 (d, J = 4 Hz, 1H), 7.71 (d, J = 4 Hz, 1H), 7.76 (s, 1H), 8.05 (s, 1H), 8.33 (s, 1H), 8.49 (s, 1H), 9.72 (s, 1H), 9.92 (s, 1H); MS 468. $(M + H)^+$. HRMS calcd, 468.05124; found, 468.05104.

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-{5-[(4-methyl-1-piperazinyl)methyl]-2-furyl}-3-quinolinecarbonitrile (15). 1-Methylpiperazine (0.24 mL, 2.16 mmol) was added to a suspension of **14** (200 mg, 0.42 mmol) in 5 mL of dichloromethane and 1 mL of 1-methyl-2-pyrrolidinone. The reaction mixture was cooled to 0 °C, and sodium triacetoxyborohydride (470 mg, 2.22 mmol) was added, followed by a few drops of acetic acid. The reaction mixture was stirred at room temperature overnight and then partitioned between saturated sodium bicarbonate and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with a gradient of 100% dichloromethane to 20% methanol in dichloromethane, to provide 164 mg (69% yield) of **15** as a yellow solid, mp 225−227 °C; ^{1}H NMR (DMSO-d_6/TFA) δ 2.82 (s, 3H), 3.19 (br s, 4H), 3.49 (br s, 4H), 3.89 (s, 3H), 4.04 (s, 2H), 4.14 (s, 3H), 6.74 (d, J = 3 Hz, 1H), 7.35 (d, J = 3 Hz, 1H), 7.53 (s, 1H), 7.88 (s, 1H), 8.18 (s, 1H), 8.33 (s, 1H), 8.96 (s, 1H); MS 552.2 $(M + H)^+$. Anal. ($C_{28}H_{27}Cl_2N_5O_3 \cdot 0.5H_2O$) C, H, N.

4-[(2,4-Dichlorophenyl)amino]-7-{5-[(4-methylpiperazin-1-yl)methyl]-3-furyl}-3-quinolinecarbonitrile (17). A mixture of **16**[28] (310 mg, 0.78 mmol), 2-formyl-4-furanboronic acid (220 mg, 1.58 mmol), and tetrakis(triphenylphosphine)palladium(0) (20 mg) in 15 mL of ethylene glycol dimethyl ether and 10 mL of saturated aqueous sodium bicarbonate was heated at reflux for 1 h and then cooled to room temperature. The reaction mixture was partitioned

between 10% methanol in ethyl acetate and water. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. Diethyl ether was added to the residue and the solid was collected by filtration to provide 130 mg (41% yield) of the intermediate aldehyde derivative as a yellow-orange solid.

A mixture of this aldehyde (106 mg, 0.26 mmol) and 1-methylpiperazine (0.15 mL, 1.35 mmol) in 4 mL of dichloromethane and 1 mL of 1-methyl-2-pyrrolidinone was cooled to 0 °C. Sodium triacetoxyborohydride (300 mg, 1.42 mmol) was added, followed by a few drops of acetic acid. The resulting mixture was stirred at 0 °C for 10 min and then at room temperature for 2 h. The mixture was partitioned between ethyl acetate and water. The organic phase was dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with a gradient of 10% methanol in ethyl acetate to 1% ammonium hydroxide in 25% methanol in ethyl acetate. Trituration with diethyl ether provided 48 mg (38% yield) of **17** as a light yellow solid, mp 183−186 °C; ^{1}H NMR (DMSO-d_6/TFA) δ 2.84 (s, 3H), 3.06−3.62 (br s, 8H), 4.13 (s, 2H), 7.19 (s, 1H), 7.61 (dd, J = 8, 2 Hz, 1H), 7.68 (d, J = 8 Hz, 1H), 7.90 (d, J = 2 Hz, 1H), 8.12 (s, 1H), 8.16 (d, J = 9 Hz, 1H), 8.64 (s, 1H), 8.69 (d, J = 9 Hz, 1H), 9.01 (s, 1H); MS 492.0 (M + H)$^+$. Anal. ($C_{26}H_{23}Cl_2N_5O\cdot1.20H_2O$) C, H, N.

1-[(4-Bromo-2-furyl)methyl]-4-methylpiperazine (19). To a solution of 4-bromo-2-furaldehyde (500 mg, 2.86 mmol) in 20 mL of dichloromethane was added 1-methylpiperazine (1.58 mL, 14.3 mmol). The solution was cooled to 0 °C, and sodium triacetoxyborohydride (3.03 g, 14.3 mmol) was added in portions, followed by 0.07 mL of acetic acid. The reaction mixture was stirred at room temperature overnight. Saturated aqueous sodium bicarbonate was added, and the mixture was stirred for 2 h. The reaction mixture was extracted with dichloromethane, and the organic phase was washed with brine and dried over sodium sulfate. Filtration and concentration in vacuo, followed by flash column chromatography, eluting with a gradient of methanol in dichloromethane (0% to 20%), with a second flash column chromatography, eluting with a gradient of methanol in ethyl acetate (0% to 15%) to 1% concentrated ammonium hydroxide in 20% methanol in ethyl acetate, provided 426 mg of **19** (58% yield) as a yellow oil; ^{1}H NMR (DMSO-d_6) δ 2.13 (s, 3H), 2.29 (br s, 4H), 2.54 (br s, 4H), 3.46 (s, 2H), 6.48 (s, 1H), 7.82 (s, 1H); MS 259.0 (M +H)$^+$.

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-{5-[(4-methyl-1-piperazinyl)methyl]-3-furyl}-3-quinolinecarbonitrile (20). A mixture of **19** (135 mg, 0.52 mmol), hexamethylditin (170 mg, 0.52 mmol), and tetrakis(triphenylphosphine)palladium(0) (42 mg) in 6 mL of 1,4-dioxane was heated at 103 °C for 3 h. To the reaction mixture was added **18**[28] (200 mg, 0.47 mmol) and tetrakis-(triphenylphosphine)palladium (0) (16 mg). The temperature was increased to 110 °C, and the reaction mixture was kept at this temperature for 20 h. After cooling to room temperature, the reaction mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic phase was dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with a gradient of dichloromethane to 10% methanol in dichloromethane. The resultant oil was purified by preparative thin layer chromatography, developing with 10% methanol in dichloromethane. Trituration with hexane and ethyl acetate provided 24 mg of **20** (10% yield) as a yellow solid, mp 192−195 °C; ^{1}H NMR (DMSO-d_6/TFA) δ 2.89 (s, 3H), 3.21−3.72 (br s, 8H), 3.91 (s, 3H), 4.43 (s, 2H), 7.32 (s, 1H), 7.62 (s, 1H), 7.92 (s, 1H), 8.09 (d, J = 8 Hz, 1H), 8.43 (d, J = 8 Hz, 1H), 8.58 (s, 1H), 8.99 (s, 1H), 9.22 (s, 1H); MS 522.1 (M + H)$^+$. Anal. ($C_{27}H_{25}Cl_2N_5O_2\cdot1.30H_2O$) C, H, N.

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[5-(morpholin-4-ylmethyl)-3-furyl]-3-quinolinecarbonitrile (21). Compound **21** was prepared from **9** according to the route used to prepare **10**: mp 164−166 °C; ^{1}H NMR ((DMSO-d_6) δ 2.39−2.46 (br s, 4H), 3.50−3.60 (complex m, 6H), 3.87 (s, 3H), 4.06 (s, 3H), 7.05 (s, 1H), 7.36 (s, 1H), 7.75 (s, 1H), 7.94 (s, 1H), 8.12 (s, 1H), 8.30 (s, 1H), 8.44 (s, 1H), 9.81 (s, 1H); MS 539.1 (M + H)$^+$. Anal. ($C_{27}H_{24}Cl_2N_4O_4\cdot0.50H_2O$) C, H, N.

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-{5-[(dimethylamino)methyl]-3-furyl}-3-quinolinecarbonitrile (22). Compound **22** was prepared from **9** according to the route used to prepare **10**: mp 133−138 °C; ^{1}H NMR (DMSO-d_6) δ 2.20 (s, 6H), 3.49 (s, 2H), 3.87 (s, 3H), 4.07 (s, 3H), 7.03 (s, 1H), 7.38 (s, 1H), 7.76 (s, 1H), 7.95 (s, 1H), 8.13 (s, 1H), 8.30 (s, 1H), 8.45 (s, 1H), 9.82 (s, 1H); MS 497.1 (M + H)$^+$; HRMS calcd, 497.11418; found, 497.11291 (M + H)$^+$. Anal. ($C_{25}H_{22}Cl_2N_4O_3\cdot1.50H_2O$) C, H. N: calcd, 10.68; found, 10.11.

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-{5-[(4-phenylpiperazin-1-yl)methyl]-3-furyl}-3-quinolinecarbonitrile (23). Compound **23** was prepared from **9** according to the route used to prepare **10**: mp 201−203 °C; ^{1}H NMR (DMSO-d_6) δ 2.52−2.62 (br s, 4H), 3.09−3.19 (br s, 4H), 3.34 (s, 2H), 3.87 (s, 3H), 4.07 (s, 3H), 6.77 (t, J = 7 Hz, 1H), 6.92 (d, J = 8 Hz, 2H), 7.09 (s, 1H), 7.20 (t, J = 8 Hz, 2H), 7.38 (s, 1H), 7.76 (s, 1H), 7.95 (s, 1H), 8.14 (s, 1H), 8.32 (s, 1H), 8.45 (s, 1H), 9.83 (s, 1H); MS 614.1 (M + H)$^+$; HRMS calcd, 614.17203; found, 614.17153 (M + H)$^+$. Anal. ($C_{33}H_{29}Cl_2N_5O_3\cdot0.50H_2O$) C, N. H: calcd, 4.85; found, 4.37.

4-(2-Methoxy-5-nitrophenyl)-2-furaldehyde (24). To a mixture of 2-iodo-4-nitroanisole (565 mg, 2.02 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-furancarboxaldehyde (670 mg, 3.03 mmol) in 20 mL of ethylene glycol dimethyl ether and 12 mL of aqueous saturated sodium bicarbonate was added 80 mg of tetrakis(triphenylphosphine)palladium(0). The mixture was heated to reflux overnight then allowed to cool to room temperature. An attempt to partition the reaction mixture between 10% methanol in ethyl acetate and water led to a large amount of insoluble material. These solids were collected by filtration and washed with water and ethyl acetate to provide 259 mg (52% yield) of **24** as a light brown solid; ^{1}H NMR (DMSO-d_6) δ 4.07 (s, 3H), 7.37 (d, J = 9 Hz, 1H), 8.20−8.29 (m, 2H), 8.55 (d, J = 3 Hz, 1H), 8.69 (s, 1H), 9.68 (s, 1H); MS 247.1 (M − H)$^-$.

1-{[4-(2-Methoxy-5-nitrophenyl)-2-furyl]methyl}-4-methylpiperazine (25). A mixture of **24** (230 mg, 0.93 mmol) and 1-methylpiperazine (0.90 mL, 8.1 mmol) in 20 mL of dichloromethane and 2 mL of 1-methylpyrrolidinone was cooled to 0 °C. Sodium triacetoxyborohydride (1.21 g, 5.7 mmol) was added in portions, followed by a few drops of acetic acid. The resulting mixture was stirred at 0 °C for 10 min then at room temperature for 1.5 h. The mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic phase was dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with a gradient of 20% methanol in ethyl acetate to 1% ammonium hydroxide in 20% methanol in ethyl acetate. Trituration with diethyl ether and hexane provided 57 mg (18% yield) of **25** as a light yellow solid; ^{1}H NMR (DMSO-d_6) δ 2.14 (s, 3H), 2.25−2.36 (br s, 4H), 2.38−2.46 (br s, 4H), 3.52 (s, 2H), 4.04 (s, 3H), 6.96 (s, 1H), 7.31 (d, J = 8 Hz, 1H), 8.14−8.20 (m, 2H), 8.38 (d, J = 3 Hz, 1H); MS 332.1 (M + H)$^+$. Anal. ($C_{17}H_{21}N_3O_4$) C, H, N.

(4-Methoxy-3-{5-[(4-methylpiperazin-1-yl)methyl]-3-furyl}-phenyl)amine (26). To a solution of **25** (396 mg, 1.19 mmol) in 20 mL of methanol was added 10% palladium on carbon (40 mg). The resulting mixture was treated with hydrogen in a Parr shaker until hydrogen uptake ceased. The reaction mixture was filtered through Celite and the filtrate concentrated in vacuo to give 358 mg (100% yield) of **26** as a brown oil; ^{1}H NMR (DMSO-d_6) δ 2.14 (s, 3H), 2.29 (br s, 4H), 2.40 (br s, 4H), 3.49 (s, 2H), 3.72 (s, 3H), 4.61 (s, 2H), 6.47 (d, J = 8 Hz, 1H), 6.58 (s, 1H), 6.78 (d, J = 9 Hz, 1H), 6.80 (s, 1H), 7.91 (s, 1H); MS 302.1 (M + H)$^+$.

Alternative Preparation of 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-{5-[(4-methylpiperazin-1-yl)methyl]-3-furyl}-3-quinolinecarbonitrile (10). To a suspension of **11** (261 mg, 1.01 mmol) in 5 mL of *iso*-propanol was added triethylorthoformate (0.504 mL, 3.03 mmol). The mixture was heated to reflux and **26** (320 mg, 1.06 mmol) in 9 mL of *iso*-propanol was added dropwise. This mixture was heated at reflux for 25 h. The mixture

was allowed to cool to room temperature, and the solid was collected by filtration, washing with *iso*-propanol, to provide 465 mg (81% yield) of (2*E*/*Z*)-2-cyano-*N*-(2,4-dichloro-5-methoxyphenyl)-3-[(4-methoxy-3-{5-[(4-methyl-1-piperazinyl)methyl]-3-furanyl}-phenyl)amino]-2-propenamide as a gray solid.

A suspension of (2*E*/*Z*)-2-cyano-*N*-(2,4-dichloro-5-methoxyphenyl)-3-[(4-methoxy-3-{5-[(4-methyl-1-piperazinyl)methyl]-3-furanyl}-phenyl)amino]-2-propenamide (196 mg, 0.34 mmol) in 3.3 mL of butyronitrile was heated to 105 °C, and phosphorus oxychloride (0.192 mL, 2.1 mmol) was added dropwise. The resultant mixture was heated at 120 °C for 24 h. After cooling, the reaction mixture was concentrated in vacuo, and the residue was treated with saturated aqueous sodium carbonate, followed by extraction into dichloromethane. The organic phase was dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with a gradient of dichloromethane to 20% methanol in dichloromethane. Trituration with diethyl ether gave 46 mg (24% yield) of **10** as a yellow solid.

Alternative Preparation of (4-Methoxy-3-{5-[(4-methylpiperazin-1-yl)methyl]-3-furyl}phenyl)amine (26). To a solution of **19** (1.43 g, 5.52 mmol) and tri-*iso*-propyl borate (1.76 g, 9.38 mmol) in 20 mL of tetrahydrofuran at −78 °C was added 1.6 M *n*-butyl lithium in hexane (5.38 mL, 8.61 mmol) over 10 min. After stirring at −78 °C for 10 min, the temperature of the reaction mixture was allowed to rise to room temperature. Water (1.0 mL) was added, and the solvents were removed in vacuo. The residue was dissolved in 20 mL of ethylene glycol dimethyl ether and 3-iodo-4-methoxyaniline (1.06 mg, 4.25 mmol), and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1; 87 mg, 0.11 mol) were added. A solution of 2.25 g of sodium carbonate in 6.5 mL of water was added, and the resulting mixture was heated at reflux for 3 h. The mixture was cooled to room temperature and partitioned between ethyl acetate and water. The aqueous layer was further extracted with ethyl acetate, and the organic layers were combined, washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with a gradient of 5% methanol in dichloromethane to 10% to provide 900 mg (70% yield) of **26** as a dark red oil.

Assay Protocols

The Src enzyme,[35] Src cell,[36] Abl enzyme,[35] and Lck cell[37] assays were performed as previously reported. The protocol used for the HT29 xenograft study was also reported previously.[26]

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Supporting Information Available: Elemental analysis data for compounds **4**−**7**, **10**−**13b**, **15**, **17**, **20**−**23**, and **25** and standard deviations for Src inhibition data are shown in Table 1 (2 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Martin, G. S. The road to Src. *Oncogene* **2004**, *23*, 7910−7917.
(2) Parsons, S. J.; Parsons, J. T. Src family kinases, key regulators of signal transduction. *Oncogene* **2004**, *23*, 7906−7909.
(3) Summy, J. M.; Gallick, G. E. Treatment for advanced tumors: SRC reclaims center stage. *Clin. Cancer Res.* **2006**, *12*, 1398−1401.
(4) Chen, T.; George, J. A.; Taylor, C. C. Src tyrosine kinase as a chemotherapeutic target: is there a clinical case? *Anti-Cancer Drugs* **2006**, *17*, 123−131.
(5) Summy, J. M.; Gallick, G. E. Src family kinases in tumor progression and metastasis. *Cancer Metastasis Rev.* **2003**, *22*, 337−358.
(6) Avizienyte, E.; Wyke, A. W.; Jones, R. J.; McLean, G. W.; Westhoff, M. A.; Brunton, V. G.; Frame, M. C. Src-induced de-regulation of E-cadherin in colon cancer cells requires integrin signalling. *Nat. Cell Biol.* **2002**, *4*, 632−638.
(7) Weis, S.; Cui, J.; Barnes, L.; Cheresh, D. Endothelial barrier disruption by VEGF-mediated Src activity potentiates tumor cell extravasation and metastasis. *J. Cell Biol.* **2004**, *167*, 223−229.
(8) Criscuoli, M. L.; Nguyen, M.; Eliceiri, B. P. Tumor metastasis but not tumor growth is dependent on Src-mediated vascular permeability. *Blood* **2005**, *105*, 1508−1514.
(9) Yezhelyev, M. V.; Koehl, G.; Guba, M.; Brabletz, T.; Jauch, K. W.; Ryan, A.; Barge, A.; Green, T.; Fennell, M.; Bruns, C. J. Inhibition of SRC tyrosine kinase as treatment for human pancreatic cancer growing orthotopically in nude mice. *Clin. Cancer Res.* **2004**, *10*, 8028−8036.
(10) Trevino, J. G.; Summy, J. M.; Lesslie, D. P.; Parikh, N. U.; Hong, D. S.; Lee, F. Y.; Donato, N. J.; Abbruzzese, J. L.; Baker, C. H.; Gallick, G. E. Inhibition of SRC expression and activity inhibits tumor progression and metastasis of human pancreatic adenocarcinoma cells in an orthotopic nude mouse model. *Am. J. Pathol.* **2006**, *168*, 962−972.
(11) Nam, J. S.; Ino, Y.; Sakamoto, M.; Hirohashi, S. Src family kinase inhibitor PP2 restores the E-cadherin/catenin cell adhesion system in human cancer cells and reduces cancer metastasis. *Clin. Cancer Res.* **2002**, *8*, 2430−2436.
(12) Summy, J. M.; Trevino, J. G.; Lesslie, D. P.; Baker, C. H.; Shakespeare, W. C.; Wang, Y.; Sundaramoorthi, R.; Metcalf, C. A., III; Keats, J. A.; Sawyer, T. K.; Gallick, G. E. AP23846, a novel and highly potent Src family kinase inhibitor, reduces vascular endothelial growth factor and interleukin-8 expression in human solid tumor cell lines and abrogates downstream angiogenic processes. *Mol. Cancer Ther.* **2005**, *4*, 1900−1911.
(13) Hiscox, S.; Morgan, L.; Green, T. P.; Barrow, D.; Gee, J.; Nicholson, R. I. Elevated Src activity promotes cellular invasion and motility in tamoxifen resistant breast cancer cells. *Breast Cancer Res. Treat.* **2006**, *97*, 263−274.
(14) Zheng, R.; Yano, S.; Matsumori, Y.; Nakataki, E.; Muguruma, H.; Yoshizumi, M.; Sone, S. Src tyrosine kinase inhibitor, M475271, suppresses subcutaneous growth and production of lung metastasis via inhibition of proliferation, invasion, and vascularization of human lung adenocarcinoma cells. *Clin. Exp. Metastasis* **2005**, *22*, 195−204.
(15) Rucci, N.; Recchia, I.; Angelucci, A.; Alamanou, M.; Del Fattore, A.; Fortunati, D.; Susa, M.; Fabbro, D.; Bologna, M.; Teti, A. Inhibition of protein kinase c-Src reduces the incidence of breast cancer metastases and increases survival in mice: Implications for therapy. *J. Pharm. Exp. Ther.* **2006**, *318*, 161−172.
(16) Boschelli, D. H. Dual inhibitors of Src and Abl tyrosine kinases. *Drug Des. Rev.—Online* **2004**, *1*, 203−214.
(17) Cortes, J.; Kantarjian, H. New targeted approaches in chronic myeloid leukemia. *J. Clin. Oncol.* **2005**, *23*, 6316−6324.
(18) Manley, P. W.; Cowan-Jacob, S. W.; Mestan, J. Advances in the structural biology, design and clinical development of Bcr-Abl kinase inhibitors for the treatment of chronic myeloid leukaemia. *Biochim. Biophys. Acta* **2005**, *1754*, 3−13.
(19) Martinelli, G.; Soverini, S.; Rosti, G.; Baccarani, M. Dual tyrosine kinase inhibitors in chronic myeloid leukemia. *Leukemia* **2005**, *19*, 1872−1879.
(20) Shah, N. P.; Tran, C.; Lee, F. Y.; Chen, P.; Norris, D.; Sawyers, C. L. Overriding Imatinib resistance with a novel ABL kinase inhibitor. *Science* **2004**, *305*, 399−402.
(21) Lombardo, L. J.; Lee, F. Y.; Chen, P.; Norris, D.; Barrish, J. C.; Behnia, K.; Castaneda, S.; Cornelius, L. A. M.; Das, J.; Doweyko, A. M.; Fairchild, C.; Hunt, J. T.; Inigo, I.; Johnston, K.; Kamath, A.; Kan, D.; Klei, H.; Marathe, P.; Pang, S.; Peterson, R.; Pitt, S.; Schieven, G. L.; Schmidt, R. J.; Tokarski, J.; Wen, M.-L.; Wityak, J.; Borzilleri, R. M. Discovery of *N*-(2-chloro-6-methyl-phenyl)-2-(6-(4-(2-hydroxyethyl)-piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide (BMS-354825), a dual Src/Abl kinase inhibitor with potent antitumor activity in preclinical assays. *J. Med. Chem.* **2004**, *47*, 6658−6661.
(22) Talpaz, M.; Shah, N. P.; Kantarjian, H.; Donato, N.; Nicoll, J.; Paquette, R.; Cortes, J.; O'Brien, S.; Nicaise, C.; Bleickardt, E.; Blackwood-Chirchir, M. A.; Iyer, V.; Chen, T. T.; Huang, F.; Decillis, A. P.; Sawyers, C. L. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N. Engl. J. Med.* **2006**, *354*, 2531−2541.
(23) U.S. Food and Drug Administration. FDA gives rapid approval for a new treatment for a rare type of leukemia. http://www.fda.gov/bbs/topics/NEWS/2006/NEW01400.html (accessed 2006).

(24) Boschelli, D. H.; Ye, F.; Wang, Y. D.; Dutia, M.; Johnson, S. L.; Wu, B.; Miller, K.; Powell, D. W.; Yaczko, D.; Young, M.; Tischler, M.; Arndt, K.; Discafani, C.; Etienne, C.; Gibbons, J.; Grod, J.; Lucas, J.; Weber, J. M.; Boschelli, F. Optimization of 4-phenylamino-3-quinolinecarbonitriles as potent inhibitors of Src kinase activity. *J. Med. Chem.* **2001**, *44*, 3965−3977.

(25) Golas, J. M.; Arndt, K.; Etienne, C.; Lucas, J.; Nardin, D.; Gibbons, J.; Frost, P.; Ye, F.; Boschelli, D. H.; Boschelli, F. SKI-606, a 4-anilino-3-quinolinecarbonitrile dual inhibitor of Src and Abl kinases, is a potent antiproliferative agent against chronic myelogenous leukemia cells in culture and causes regression of K562 xenografts in nude mice. *Cancer Res.* **2003**, *63*, 375−381.

(26) Golas, J. M.; Lucas, J.; Etienne, C.; Golas, J.; Discafani, C.; Sridharan, L.; Boghaert, E.; Arndt, K.; Ye, F.; Boschelli, D. H.; Li, F.; Titsch, C.; Huselton, C.; Chaudhary, I.; Boschelli, F. SKI-606, a Src/Abl inhibitor with in vivo activity in colon tumor xenograft models. *Cancer Res.* **2005**, *65*, 5358−5364.

(27) Coluccia, A. M. L.; Benati, D.; Dekhil, H.; De Filippo, A.; Lan, C.; Gambacorti-Passerini, C. SKI-606 decreases growth and motility of colorectal cancer cells by preventing pp60(c-Src)-dependent tyrosine phosphorylation of β-catenin and its nuclear signaling. *Cancer Res.* **2006**, *66*, 2279−2286.

(28) Boschelli, D. H.; Wang, D. Y.; Ye, F.; Yamashita, A.; Zhang, N.; Powell, D.; Weber, J.; Boschelli, F. Inhibition of Src kinase activity by 4-anilino-7-thienyl-3-quinolinecarbonitriles. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2011−2014.

(29) Berger, D.; Dutia, M.; Powell, D.; Wissner, A.; DeMorin, F.; Raifeld, Y.; Weber, J.; Boschelli, F. Substituted 4-anilino-7-phenyl-3-quinolinecarbonitriles as Src kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2989−2992.

(30) Yamamoto, M.; Izukawa, H.; Saiki, M.; Yamada, K. Oxidative substitution reactions of organotin compounds with lead tetraacetate. *J. Chem. Soc., Chem. Commun.* **1988**, *8*, 560−561.

(31) Sutherland, K. W.; Feigelson, G. B.; Boschelli, D. H.; Blum, D. M.; Strong, H. L. Process for the preparation of 4-amino-3-quinolinecarbonitriles and 7-aminothieno[3,2-*b*]pyridine-6-carbonitriles, US 2005043537, 2005.

(32) Barrios Sosa, A. C.; Boschelli, D. H.; Wu, B.; Wang, Y.; Golas, J. M. Further studies on ethenyl and ethynyl-4-phenylamino-3-quinolinecarbonitriles: Identification of a subnanomolar Src kinase inhibitor. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1743−1747.

(33) Barrios Sosa, A. C.; Boschelli, D. H.; Ye, F.; Golas, J. M.; Boschelli, F. Synthesis and inhibition of Src kinase activity by 7-ethenyl and 7-ethynyl-4-anilino-3-quinolinecarbonitriles. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2155−2158.

(34) Boschelli, D. H.; Ye, F.; Wu, B.; Wang, Y. D.; Barrios Sosa, A. C.; Yaczko, D.; Powell, D.; Golas, J. M.; Lucas, J.; Boschelli, F. Investigation of the effect of varying the 4-anilino and 7-alkoxy groups of 3-quinolinecarbonitriles on the inhibition of Src kinase activity. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3797−3800.

(35) Boschelli, D. H.; Wang, Y. D.; Johnson, S.; Wu, B.; Ye, F.; Barrios Sosa, A. C.; Golas, J. M.; Boschelli, F. 7-Alkoxy-4-phenylamino-3-quinolinecarbonitriles as dual inhibitors of Src and Abl kinases. *J. Med. Chem.* **2004**, *47*, 1599−1601.

(36) Boschelli, D. H.; Wang, Y. D.; Ye, F.; Wu, B.; Zhang, N.; Dutia, M.; Powell, D. W.; Wissner, A.; Arndt, K.; Weber, J. M.; Boschelli, F. Synthesis and Src kinase inhibitory activity of a series of 4-phenylamino-3-quinolinecarbonitriles. *J. Med. Chem.* **2001**, *44*, 822−833.

(37) Boschelli, D. H.; Wu, B.; Barrios Sosa, A. C.; Durutlic, H.; Chen, J. J.; Wang, Y.; Golas, J. M.; Lucas, J.; Boschelli, F. Synthesis and Src kinase inhibitory activity of 2-phenyl and 2-thienyl-7-phenylaminothieno[3,2-*b*]pyridine-6-carbonitriles. *J. Med. Chem.* **2005**, *48*, 3891−3902.

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