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4-Anilino-7-pyridyl-3-quinolinecarbonitriles as Src kinase inhibitors

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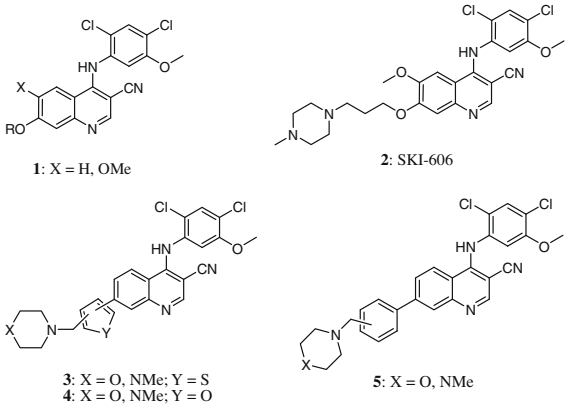
ABSTRACT

A series of 4-anilino-7-pyridyl-3-quinolinecarbonitriles was prepared as Src kinase inhibitors. A systematic SAR study of substitutions on both the pyridine ring and the 3-quinolinecarbonitrile core established the requirements for optimal activity. The lead compound, **17**, showed potent activity in both the Src enzyme assay and cell assays, and demonstrated in vivo anti-tumor activity in a xenograft model.

Protein kinases are important targets in cancer therapeutics due to the important roles they play in signal transduction pathways that regulate cell proliferation and survival in response to external stimuli.[1] Depending on their protein substrate specificity, kinases are categorized as serine/threonine kinases or tyrosine kinases. Src kinase is a member of the Src family of non-receptor protein tyrosine kinases. It plays an essential role in signal transduction pathways controlling proliferation, migration and angiogenesis.[2] Extensive research has demonstrated that small molecule Src inhibitors may be useful for the treatment of a variety of disease states, including cancer and osteoporosis.[3] A 2-amino-1,3-thiazole-5-carboxamide multi-kinase (including Src kinase) inhibitor dasatinib (SPRYCEL®) was approved for treatment of Philadelphia chromosome-positive leukemias.[4] Other structural classes of Src kinase inhibitors including pyrrolo[2,3-*d*]pyrimidines,[5a] pyrido[2,3-*d*]pyrimidines,[5b] oxindoles,[5c] purines,[5d] and quinazolines[5e] have been reported in the literature.

We previously reported that 7-alkoxy-4-anilino-3-quinolinecarbonitriles **1** are potent inhibitors of Src kinase activity.[6] Among these, analog **2** (SKI-606) is currently in clinical trials. We then prepared analogs of **1** with a substituted thiophene **3**,[7] a substituted furan **4**,[8] or a substituted phenyl group **5**[9] at C-7 as Src inhibitors. In our continuing search for an optimal Src kinase inhibitor, we further extended our SAR studies and prepared analogs with a pyridine ring at C-7.



A general synthetic approach to 4-anilino-7-pyridyl-3-quinolinecarbonitriles **11**–**14** and **17**–**21**, in which the quinoline core is linked to the C-2 position on the pyridine ring, via an intermediate **8**, is shown in Scheme 1. Compound **8** was prepared by bromination of bromo-methylpyridines **6**, followed by SN2 replacement of the benzylic bromide with amines. From compound **8**, bromo-lithium exchange followed by quenching with tributyltin chloride provided tributylpyridylstannanes **9**, which then underwent Stille coupling with 7-bromo-3-quinolinecarbonitrile **10a**[7] or 7-iodo-3-quinolinecarbonitrile **10b**[7] to furnish the desired products **11**–**14** and **17**–**21** (Tables 1 and 2). This approach is generally applicable to synthesis of the final compounds described in this Letter. However, it is not efficient in the generation of a large number of analogues with different amino groups since the amine was introduced at an early stage.

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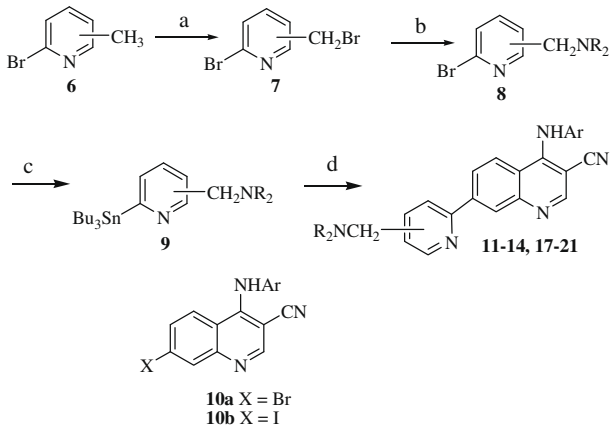
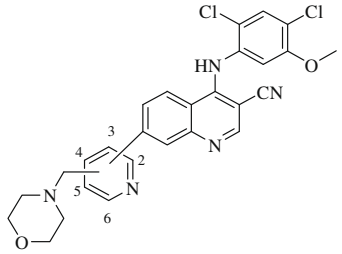


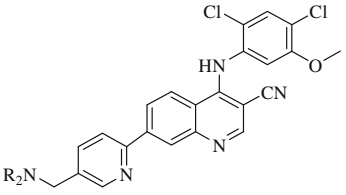
Scheme 1. Reagents: (a) 1 equiv NBS; (b) HNR_2; (c) *n*-BuLi, nBu_3SnCl; (d) **10a** or **10b**, $PdCl_2(PPh_3)_2$.

Table 1
Src inhibitory activity of compounds **11–16**



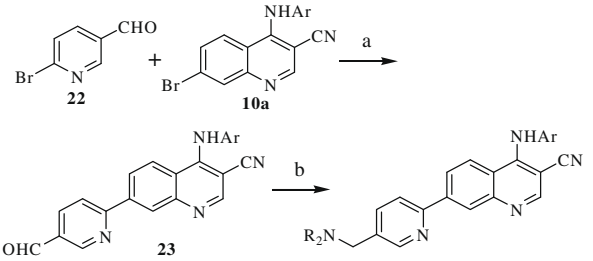
Compd	Pyridyl isomer	Src enzyme IC_{50} (nM)[6e]	Src cell IC_{50} (nM)[6a]
11	2,3	950	>10,000
12	2,4	26	310
13	2,5	2.9	170
14	2,6	24	860
15	3,5	36	2800
16	3.6	7.0	330

Table 2
Src inhibitory activity of compounds **13**, **17–21**

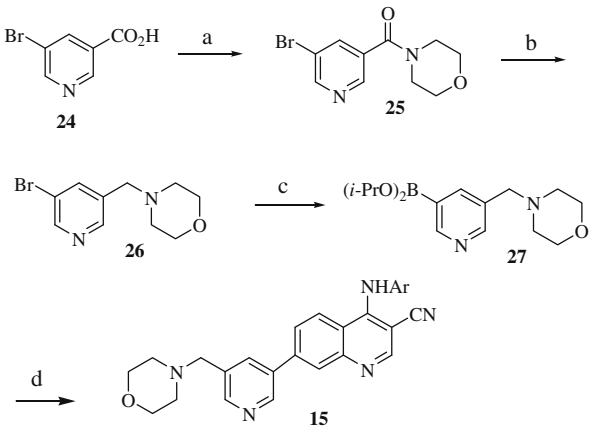


Compd	NR_2	Src enzyme IC_{50} (nM)[6e]	Src cell IC_{50} (nM)[6a]
13	4-Morpholinyl	2.9	170
17	4-Methyl-1-piperazinyl	4.0	61
18	4-Thiomorpholinyl	5.1	230
19	1-Oxido-4-thiomorpholinyl	1.9	96
20	1,1-Dioxido-4-thiomorpholinyl	1.8	130
21	Dimethylamino	3.9	130

A more efficient route to analogues of **13** (the most potent isomer in Table 1) with various amino groups is shown in Scheme 2. Starting from 6-bromonicotinaldehyde **22**, palladium-catalyzed selective cross-coupling[10] between **22** and **10a** gave the desired



Scheme 2. Reagents: (a) 1 equiv Me_6Sn_2, $Pd(PPh_3)_4$; (b) HNR_2, $NaCNBH_3$.



Scheme 3. Reagents: (a) CDI, morpholine; (b) $BH_3{\cdot}Me_2S$; (c) *n*-BuLi, $(i\text{-PrO})_3B$; (d) $Pd(PPh_3)_4$, **10a**.

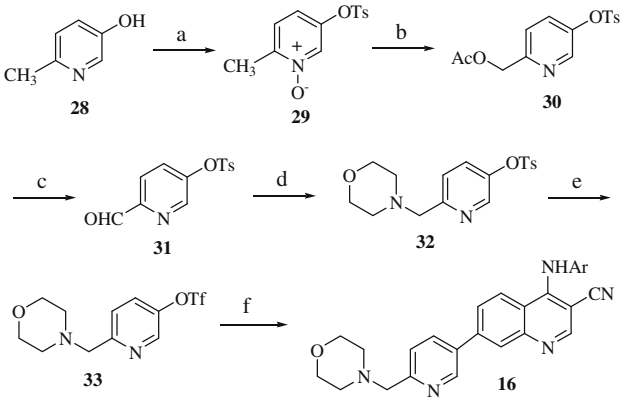
product **23** selectively, due to the different reactivity of the two aryl bromides **22** and **10a**. Reductive amination of aldehyde **23** gave the final products. This approach has the advantage that the amino groups are introduced at the last step of the synthesis, allowing for the parallel synthesis of analogues with different amino groups.

The synthesis of 3,5-pyridyl isomer **15** (Scheme 3) started from 5-bromonicotinic acid **24**. Amidation followed by reduction gave morpholinomethyl pyridine **26**. Bromo-lithium exchange followed by boronic acid formation and Suzuki coupling led to compound **15** (Table 1).

The synthesis of 3,6-isomer **16** is shown in Scheme 4. Starting from 5-hydroxy-2-methylpyridine **28**, tosylation and *N*-oxide formation, followed by treatment with acetic anhydride gave compound **30**. Deacetylation of the latter and oxidation afforded the desired aldehyde **31**. Reductive amination, removal of the tosyl group followed by triflation gave **33**, which was coupled with **10a**. The desired compound **16** was isolated from the reaction mixture.

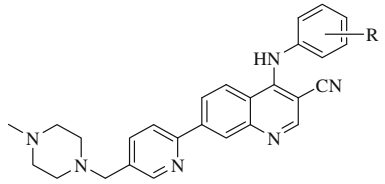
Compounds **34** and **35** (Table 3) were prepared in the same manner as compound **17**, starting from 7-bromo-4-(3,4,5-trimethoxyanilino)-3-quinolinecarbonitrile[11a] and 7-bromo-4-(2,4-dichloroanilino)-3-quinolinecarbonitrile,[11b] respectively.

Compounds **11–21**, **34**, and **35** were evaluated in a Src kinase assay[12] and a Src cellular assay.[6a] The cell based assay for Src inhibition is a 3 day proliferation assay measuring the anchorage independent growth of rat fibroblasts expressing activated human Src. Antiproliferative activity in this assay correlates with the inhibition of Src dependent phosphorylation of cellular substrates. Table 1 shows Src inhibitory activity of compounds **11–16**, with the quinolinecarbonitrile core attached at the C-2 or C-3 position on the pyridyl ring, and a (4-morpholinyl)methyl group attached at the C-3, C-4, C-5, or C-6 position on the pyridyl ring. Compound **13**, bearing a quinolinecarbonitrile core at the C-2 position and the



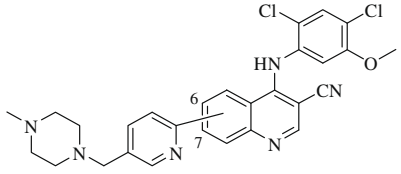
Scheme 4. Reagents: (a) TsCl, then *m*CPBA; (b) Ac_2O; (c) CH_3OH, then MnO_2; (d) morpholine, $NaCNBH_3$; (e) NaOH, then Tf_2O; (f) **10a**, Me_6Sn_2, $PdCl_2(PPh_3)_2$.

Table 3
Src inhibitory activity of compounds **17**, **34**, and **35**



Compd	R	Src enzyme IC_{50} (nM)[6e]	Src cell IC_{50} (nM)[6a]
17	2,4-Dichloro-5-methoxy	4.0	61
34	3,4,5-Trimethoxy	18	360
35	2,4-Dichloro	12	460

Table 4
Src inhibitory activity of compounds **17**, **36**, and SKI-606



Compd	Isomer	Src enzyme IC_{50} (nM)[6e]	Src cell IC_{50} (nM)[6a]
17	7	4.0	61
36	6	130	2900
SKI-606		3.8	100

(4-morpholinyl)methyl group attached at the C-5 position on the pyridyl ring, was the most potent analogue in both the Src kinase assay and the Src cellular assay. Analogues with other substitution patterns proved to be less potent in both assays.

With the 3-quinolinecarbonitrile core attached at the C-2 position on the pyridyl ring, we then studied the effects of various amino groups at C-5 of the pyridine ring on Src inhibitory activity. As shown in Table 2, all the analogues (**17**–**21**) showed good potency in the Src kinase assay, with IC_{50} values ranging from 1.9 nM to 5.1 nM. In the Src cellular assay, compound **17**, with a 4-methyl-1-piperazinylmethyl group at the 5-position on the pyridyl ring, showed the highest potency.

The SAR of the anilino head-piece at the 4-position on the quinolinecarbonitrile core (Table 3) mimicked what we reported earlier on the 7-alkoxy-4-anilino-3-quinolinecarbonitrile series.[6a,b] Compared with a 2,4-dichloro-5-methoxyanilino group (**17**), both 3,4,5-trimethoxyanilino (**34**) and 2,4-dichloroanilino (**35**) groups gave lower potency in both the Src kinase assay and the Src cellular assay.

We further moved the 5-(4-methyl-1-piperazinylmethyl)-2-pyridyl group from the 7-position on the 3-quinolinecarbonitrile core (compound **17**) to the 6-position (compound **36**, prepared from 6-bromo-4-(2,4-dichloro-5-methoxyanilino)-3-quinolinecarbonitrile[7]). In agreement with what we reported earlier,[6b,7] the 6-analogue proved to be much less potent in both the Src kinase assay and the Src cellular assay (Table 4).

Compound **17**, the lead compound in the 4-anilino-7-pyridyl-3-quinolinecarbonitrile series, showed comparable activity with SKI-606 and the lead compound in the 7-furanyl-3-quinolinecarbonitrile series[8] in both the Src kinase assay and the Src cellular assay. It was further evaluated in an HT-29 colon tumor model,[6b] and showed oral efficacy comparable to that of SKI-606.

In summary, we prepared a series of 4-anilino-7-pyridyl-3-quinolinecarbonitriles as Src kinase inhibitors. A systematic SAR study illustrated requirements for optimal activity. The best potency was obtained when the quinolinecarbonitrile core was attached at the 2-position on the pyridyl ring, and a dialkylaminomethyl group was attached at the 5-position on the pyridyl ring. The SAR on the quinolinecarbonitrile core substitution resembled that observed in the 7-alkoxy-4-anilino-3-quinolinecarbonitrile series. The lead compound in the series, compound **17**, showed comparable activity with SKI-606 in both the Src kinase assay and the Src cellular assay, and demonstrated in vivo anti-tumor activity in a xenograft model.

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