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Identification of 3-amido-4-anilinoquinolines as potent and selective inhibitors of CSF-1R kinase

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ABSTRACT

3-Amido-4-anilinoquinolines are potent and highly selective inhibitors of CSF-1R. Their synthesis and SAR is reported, along with initial efforts to optimize the physical properties and PK through modifications at the quinoline 6- and 7-positions.

Solid tumors comprise a number of cell types in addition to malignant cells, including macrophages. These tumor-associated macrophages (TAMs) are believed to play a number of roles to promote tumor progression and metastasis.[1] Upon recruitment to the tumor environment, macrophages release pro-angiogenic factors such as VEGF, proteases important for invasion, and other growth factors involved in the growth and motility of tumor cells such as EGF. Monocyte/macrophage development and proliferation depends upon the signaling pathway of the receptor tyrosine kinase CSF-1R and its ligand CSF-1 (also known as macrophage colony stimulatory factor, M-CSF). Inhibition of this pathway could therefore be expected to reduce TAM levels, leading to multiple effects on tumor types in which macrophages have a significant presence.

Despite extensive efforts within the oncology field to develop kinase inhibitors, uncertainty remains over the relative merits of selective compounds versus less selective or "multi-targeted" inhibitors.[2] Targeted molecules offer the clearest indication that in vivo effects result from the intended in vitro activity. Also, toxicity derived from additional activity against other kinases is likely to be reduced.[3] However, inhibition of a single kinase may not be sufficient to achieve a clinical benefit, either through the built-in redundancy of signaling pathways, or the ability of tumors to acquire resistance.[4] Inhibitors with activity against multiple kinases may in fact be more effective, and several multi-targeted kinase inhibitors are now commercially available. An alternative approach to multi-targeted agents is the combination of selective ones. A highly selective CSF-1R inhibitor would test the hypothesis of whether reduced levels of tumor-associated macrophages could impact tumor progression. Used alone or in combination with other agents, such an inhibitor might offer a safe and effective therapeutic option.

Screening of a subset of the AstraZeneca collection, containing compounds known or expected to inhibit kinases, identified several series with good activity against CSF-1R. Most of the hits were derived from earlier AZ kinase projects, and many of these possessed poor general kinase selectivity, or belonged to a series in which selectivity against a key enzyme such as KDR appeared difficult to achieve. The bisamide series offered a relatively selective profile; work to optimize that series was reported recently.[5]

The most promising of the hit series, in terms of both CSF-1R potency and kinase selectivity, were the 3-amido-4-anilino-6,7-dimethoxyquinolines. One of the screening hits is shown in Figure 1 (**1**: IC_{50} = 19 nM).

Another attractive feature of the amidoquinolines was the potential to optimize the physical properties and PK profile. From

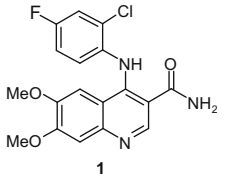

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Figure 1. Amidoquinoline screening hit **1**.

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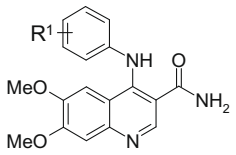
our modeling studies, the binding of the amidoquinolines to CSF-1R is believed to occur through the quinoline and amide nitrogens. The 6- and 7-positions point towards the kinase solvent channel, and are therefore available for the introduction of solubilizing groups. Such a strategy has been widely pursued within AZ and elsewhere, on well-known kinase inhibitor scaffolds such as the quinazolines[6] and cyanoquinolines.[7]

Table 1
CSF-1R enzyme and cell activity for **1**–**28**



Compound	R^1	IC_{50}[17] (μM)	Cell (μM)
1	—	0.200	5.6
2	2-F	0.009	0.45
3	2-Cl	0.022	0.7
4	2-Br	0.036	1.8
5	2-Me	0.052	1.8
6	3-F	0.033	1.2
7	3-Cl	0.018	0.42
8	3-Me	0.038	0.62
9	4-F	0.030	0.97
10	4-Cl	0.031	0.53
11	4-OMe	0.046	1.1
12	4-NMe_2	0.100	1.5
13	2,3-F	0.026	0.49
14	2-F, 3-Cl	0.013	0.12
15	2,3-Me	0.031	0.27
16	2-Me, 3-Cl	0.029	0.25
17	2,3-Cl	0.006	0.09
18	2,4-F	0.025	0.40
19	2-F, 4-Me	0.010	0.25
20	2-F, 4-Cl	0.018	0.59
21	2,4-Cl	0.052	4.0
22	3,4-F	0.028	1.4
23	3-Cl, 4-F	0.016	0.33
24	3,4-Cl	0.009	0.23
25	2,5-F	0.015	0.43
26	2-F, 5-Me	0.013	0.21
27	3,5-F	0.100	1.2
28	3,5-Cl	0.022	0.36

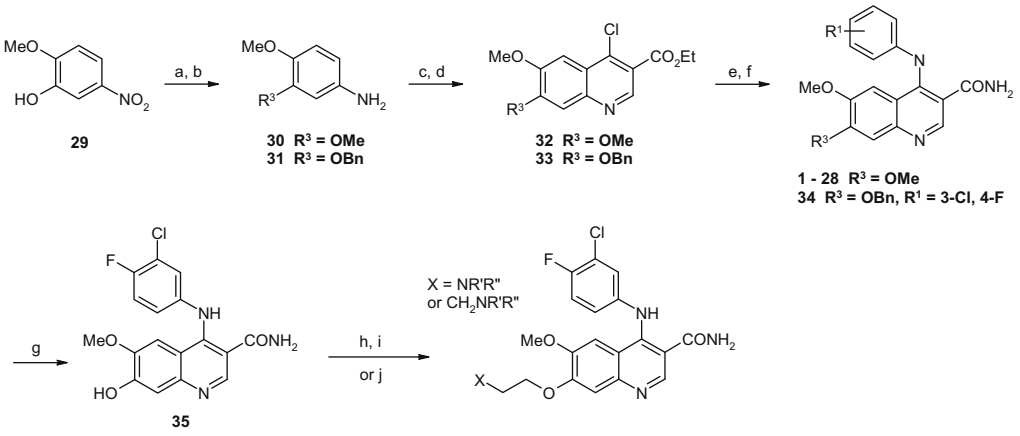
3-Amido-4-anilinoquinolines have been reported by another group as inhibitors of CSF-1R, with modifications to the aniline substituent and a 7-aryl group giving good cell potency and oral PK.[8] Other structural classes of CSF-1R inhibitor have also been reported.[9–15]

The AZ collection contained a set of analogs in the dimethoxy scaffold, and some initial aniline SAR was generated quite rapidly (Table 1). A range of substituents are tolerated in the enzyme, but only the most potent of these gave good activity in our cell proliferation assay.[16] 2,3-Disubstituted anilines (**13–17**) typically gave the most potent compounds, but other substitution patterns including 3,4-Cl (**24**) and 2-F, 5-Me (**26**) also gave good cell potency.

Compounds **1**–**28** were prepared from 3,4-dimethoxyaniline **30** via the route shown in Scheme 1. Preparation of the chloroester **32** has been reported via a thermal cyclization of a diethyl malonate intermediate and subsequent chlorination step,[18] but we found that heating the malonate intermediate with $POCl_3$ in toluene gave the chloroester in one pot. Hydrolysis of the ester, chlorination and then treatment with aqueous ammonia gave the chloroamide. Most aniline additions were performed in ethanol, with the product HCl salt readily isolated by filtration.

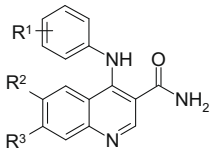
Solubility, plasma protein binding, and rat PK data were collected for several of the dimethoxyquinolines (Table 2). The most potent example (**17**, 2,3-Cl) had very poor physical properties, high clearance and no oral exposure. The 4-F (**9**) and 2,4-F (**18**) examples were less potent in the cell assay, but had lower plasma protein binding, good bioavailability and low to moderate in vivo clearance.

To address the low aqueous solubility of the dimethoxyquinoline compounds, basic groups were introduced at the 6- and 7-positions. A set of 3-Cl, 4-F anilino compounds with amine side chains were prepared as shown in Scheme 1. 2-Methoxy-5-nitrophenol **29** was protected as the benzyl ether, and reduced with Raney Ni. From aniline **31**, similar chemistry previously described for the dimethoxy scaffold generated the 3-amido-4-anilinoquinoline **34**, with a benzyl protecting group at the 7-position. Treatment with thioanisole and TFA removed the benzyl group to give the hydroxyquinoline **35**. A Mitsunobu reaction with chloroethanol installed a suitable leaving group, which could be displaced with various amines. Alternatively, final compounds could be prepared by direct alkylation of the hydroxyquinoline with chloroalkylamines. Similar chemistry was used to install side chains at



Scheme 1. Preparation of examples **1**–**28** and **36**–**42**. Reagents and conditions: (a) BnBr, K_2CO_3, DMF, rt; (b) Raney Ni, H_2, EtOH; (c) diethylethoxymethylene malonate, CH_3CN, rt (R^3 = Me) or diethylethoxymethylene malonate, sealed tube, 120 °C (R^3 = Bn); (d) $POCl_3$, Tol, 100 °C; (e) i—NaOH, MeOH, rt; ii—$SOCl_2$, Tol, reflux, 2 h then acetone, NH_4OH, 0 °C; (f) aniline, cat. AcOH, EtOH, 80 °C or DMF, 100 °C (R^3 = Me) or 3-Cl, 4-F-aniline, cat. AcOH, DMF, sealed tube, 120 °C (R^3 = Bn); (g) thioanisole, TFA, reflux 3 h; (h) $ClCH_2CH_2OH$, DIAD, PPh_3, THF, 0–45 °C; (i) amine, cat. NaI, K_2CO_3, DMF, sealed tube, 100 °C; (j) chloroalkylamine, K_2CO_3, DMF, sealed tube, 100 °C.

Table 2
Enzyme and cellular potency, physical property data and rat PK upon iv (3 mpk) and po (10 mpk) dosing



Compound	R^1	R^2	R^3	IC_{50}[17] (μM)	Cell (μM)	Sol[19] (μM)	PPB (% free)	F (%)	Cl (ml/min/kg)	V_{ss} (L/kg)	$T_{1/2}$ (h)
9	4-F	MeO	MeO	0.030	0.97	12	6.0	96	7	0.3	0.9
14	2-F, 3-Cl	MeO	MeO	0.013	0.12	18	2.7				
17	2,3-Cl	MeO	MeO	0.006	0.09	<1	<0.7	—	115	4.1	0.5
18	2,4-F	MeO	MeO	0.025	0.40	54	5.6	100	23	0.9	0.6
19	2-F, 4-Me	MeO	MeO	0.010	0.25	7	1.2				
23	3-Cl, 4-F	MeO	MeO	0.016	0.33	6	3.3	24	59	1.8	0.6
25	2,5-F	MeO	MeO	0.015	0.43	14	5.4				
26	2-F, 5-Me	MeO	MeO	0.013	0.21	7	3.6				
36	3-Cl, 4-F	MeO	$Me_2N(CH_2)_2O$	0.012	0.56	>1000	16		210	40	2.1
37	3-Cl, 4-F	MeO	$(CH_2)_2CHNH(CH_2)_2O$	0.017	0.25	380	5.3		230	30	1.7
38	3-Cl, 4-F	MeO	$MeO(CH_2)_2NMe(CH_2)_2O$	0.018	0.30	>1000	6.5				
39	3-Cl, 4-F	MeO	$HO(CH_2)_2NMe(CH_2)_2O$	0.010	1.3	>1000	8.1				
40	3-Cl, 4-F	MeO	1-Pyrrolidinyl-$(CH_2)_2O$	0.017	0.34	970	18		270	52	2.4
41	3-Cl, 4-F	MeO	4-Me-Piperazinyl-$(CH_2)_3O$	0.007	0.40	270	17				
42	3-Cl, 4-F	MeO	4-OH-Piperidinyl-$(CH_2)_2O$	0.080	3.8	>1000	5.5				
43	3-Cl, 4-F	1-Pyrrolidinyl-$(CH_2)_2O$	MeO	0.013	0.48	257	27				
44	3-Cl, 4-F	4-Me-Piperazinyl-$(CH_2)_3O$	MeO	0.010	0.71	911	30				
45	2,3-Cl	$Me_2N(CH_2)_2NH$	MeO	<0.001	0.11	340	10				
46	2,3-Cl	1-Piperidinyl-$(CH_2)_2NH$	MeO	0.007	0.08	200	5.5		78	8.5	1.6
47	2,3-Cl	MeO	$Me_2N(CH_2)_2NH$	0.003	0.74	300	2.1		90	19	2.4
48	2,3-Cl	MeO	1-Piperidinyl-$(CH_2)_2NH$	0.015	0.48	110	0.6				
49	2,3-Cl	$Me_2N(CH_2)_2NH$	EtO	0.003	0.03	280	4.2				
50	2,3-Cl	1-Piperidinyl-$(CH_2)_2NH$	EtO	0.006	0.03	160			110	12	1.6
51	2,4-F	$Me_2N(CH_2)_2NH$	MeO	0.007	0.85	>1000	44				
52	2,4-F	1-Piperidinyl-$(CH_2)_2NH$	MeO	0.022	0.48	>1000	20				
53	2,4-F	1-Morpholinyl-$(CH_2)_2NH$	MeO	0.007	0.99	160	7.8				
54	2,4-F	MeO	$Me_2N(CH_2)_2NH$	0.023	3.0	>1000	44		220	36	1.9

the quinoline 6-position (**43**, **44**), starting from 2-methoxy-4-nitrophenol.

All examples of this type (**36**–**44**) had excellent enzyme activity. Most retained the cell potency of the dimethoxy compound **23**, but those with additional hydrogen bond donors (**39, 42**) were less active in the cell (Table 2). These compounds were all found to have high aqueous solubility, and reduced plasma protein binding. Rat PK data was obtained for several examples (**36**, **37**, **40**), but the compounds suffered from extremely high in vivo clearance and minimal oral exposure.

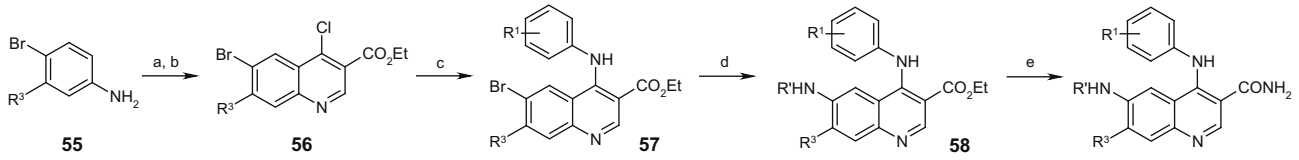
Compounds with basic side chains linked through a nitrogen atom were prepared next, with either 2,3-Cl (**45–50**) or 2,4-F aniline (**51–54**). The synthetic route (Scheme 2) was similar to that for the dialkoxy quinolines, but started from the appropriate bromoalkoxy aniline **55**. After preparation of the 4-chloroquinoline ester **56** and aniline addition, the amines were introduced under Buchwald–Hartwig coupling conditions.[20] Conversion of the various esters **58** to the amides was reliably achieved through treatment with formamide and methoxide.[21] 7-Aminoquinoline compounds were prepared in a similar fashion from 3-bromo-4-methoxyaniline.[22]

Like the alkoxyamines, however, these compounds had high in vivo clearance in rats (Table 2). Compounds with an amine at the 6-position typically retained the potency of dialkoxy examples with the corresponding aniline group, but switching the amine to the 7-position gave compounds with reduced cell potency (**47**, **48**, **54**). We speculated that demethylation of the 6- or 7-methoxy groups might be one of the mechanisms of clearance, and prepared some 7-EtO examples (**49**, **50**). There was no obvious impact on metabolism (**50** vs **46**), but cell potency was enhanced relative to 7-MeO.

As a result of its cell potency and oral PK profile, **18** was selected for assessment in our mouse pharmacodynamic (PD) model,[5] in which inhibition of pCSF-1R was measured 2 and 6 h after oral dosing. At 100 mpk,[23] the compound achieved 95% inhibition of pCSF-1R after 2 h, but this dropped off to 65% at 6 h.

Compound **18** was screened against a panel of 150 kinases at a concentration of 1 μM and displayed remarkable kinase selectivity. Apart from CSF-1R, significant activity was only observed against GSK3α and EphB4 (Table 3).[24]

In conclusion, 3-amido-4-anilinoquinolines are potent inhibitors of CSF-1R with excellent kinase selectivity. Compounds from the dimethoxy scaffold have at best moderate aqueous solubility. Some examples showed good bioavailability in rats, and we were able to demonstrate activity in a mouse PD model with compound **18**. Efforts to optimize the physical properties and PK profile through the introduction of basic side chains were unsuccessful. Other approaches to optimize the PK of this attractive scaffold are reported in the following paper.



55 56 57 58

Scheme 2. Preparation of examples **45**–**46** and **49**–**53**. Reagents and conditions: (a) diethylethoxymethylene malonate, CH_3CN, rt; (b) $POCl_3$, Tol, 100 °C; (c) aniline, cat. AcOH, EtOH, 80 °C or DMF, 100 °C; (d) amine, $Pd_2(dba)_3$, BINAP, Cs_2CO_3, Tol, 100 °C; (e) $HCONH_2$, DMF, NaOMe, 100 °C.

Table 3
Kinase selectivity of **18**

Kinase	% Inhibition
CSF-1R	97
GSK3α	87
EphB4	51
EphA5	28
MST1	22
MST2	20
Met	17
MKK4	17
JNK3	16
TBK1	15
140 kinases	<15

Acknowledgments

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16. A description of the cell assay is contained in Ref. 5.
17. Early compounds were screened in a HTRF enzyme assay, according to the following protocol: 5 μL compound is spotted into 384 well plate (Matrix flat bottom black). Twenty-five microliters substrate mix containing 120 nM poly EY-biotin (pET-BIOT, CisBio 61GT0BLB E:Y = 4:1) substrate and 60 μM ATP (Sigma A3377) in 1× buffer (0.067 M Hepes, 10 mM $MgCl_2$, 5 mM DTT, 0.005% Triton X-100) is added to each well. The reaction is initiated by addition of 20 μL CSF-1R enzyme mix in 1.25× buffer (1.58 μg CSF-1R enzyme prepared from His-tagged CSF-1R catalytic domain and expressed in Baculovirus; purified sequentially on Qiagen Ni-NTA Superflow, Mono Q HR 10/10, and Superdex 200 SEC and stored as aliquots in 20 mM Tris, pH 7.5, 150 mM NaCl, 1.5 mM DTT, 10% glycerol at −80 °C). The reaction is allowed to proceed at room temperature for 60 min and then terminated by addition of 25 μL Stop Solution (50 mM Hepes, 60 mM EDTA, 300 μg/mL, 26.7 nM PT LANCE Ab (Perkin-Elmer EU-W1024), and 180 nM Streptavidin-XL665 (CisBio 610SAXAB). The reaction is incubated at room temperature for 60 min before reading fluorescence at 665 nm on fluorescence plate reader (SpectraMax Molecular Devices, Sunnyvale, CA). IC_{50} determination of compound inhibition activity is monitored with 11 point, 3-fold dilution of compound as added to enzyme reaction. Compounds **24** and **45**–**54** were screened in the enzyme assay described in: Almeida, L.; Aquila, B.; Cook, D.; Cowen, S.; Dakin, L.; Ezhuthachan, J.; Ioannidis, S.; Lee, S.; Lyne, P.; Pontz, T.; Scott, D.; Su, M.; Zheng, X. WO 06067445 A2 20060629; *Chem. Abstr.*, *145*, 124467. The two assays gave comparable data when compounds were screened in both.
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23. Compound **18** was dosed as a suspension in 5% HPMC/TWEEN® 80.
24. KinaseProfiler Department, Millipore UK Limited, Gemini Crescent, Dundee Technology Park, Dundee DD2 1SW, UK.