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Discovery and preliminary structure–activity relationship studies of novel benzotriazine based compounds as Src inhibitors

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Abstract—We report the discovery and preliminary SAR studies of a series of structurally novel benzotriazine core based small molecules as inhibitors of Src kinase. To the best of our knowledge, benzotriazine template based compounds have not been reported as kinase inhibitors. The 3-(2-(1-pyrrolidinyl)ethoxy)phenyl analogue (**43**) was identified as one of the most potent inhibitors of Src kinase.

Src is the prototype member of the Src-family of tyrosine kinases, which comprises eleven highly homologous proteins including Src, Yes, Fyn, Lyn, Hck, Blk, Brk, Fgr, Frk, Srm, and Yrk.[1] Src is dysregulated in several types of cancer and involved in metastases and tumor progression, particularly those of breast, metastatic colorectal,[2] ovarian,[3] and pancreatic cancers.[4–6] Src plays a role in myocardial infarction, osteoporosis, stroke, and neurodegeneration.[7] Under basal conditions, Src is tightly regulated by keeping it in an inactive conformation. However, different physiological stimuli lead to up-regulation of Src resulting in adhesion and cytoskeletal changes, altered gene expression, and increased cell proliferation. Due to the involvement of Src in several diseases, inhibitors of Src have potential utility in myocardial infarction,[8] aggressive forms of cancer, osteoporosis, and stroke.[9,10] Several Src inhibitors have been reported recently.[11–17]

As part of our drug discovery efforts, we have identified and developed novel benzotriazine based compounds as a new class of Src inhibitors. To the best of our knowledge, benzotriazine template based compounds have not been reported as kinase inhibitors. Our screening efforts using recombinant human Src resulted in the identification of novel core template **1** (Table 1).[18] Compound **1** displayed low micromolar activity against Src ($IC_{50} = 3.6\ \mu M$). Computational studies suggested that compound **1** was binding at the ATP-pocket and the ring nitrogen at the 2-position is involved as a hydrogen bond acceptor, while the 3-amino group is involved as a hydrogen bond donor at the hinge region. Compound **1** binds in the ATP pocket of Src in a manner similar to that seen with compound **42** depicted in Figure 1. Both compounds orient the 7-phenyl ring orthogonal to the benzotriazine core,[19] positioning this ring deep within the hydrophobic pocket. The pocket has enough space to accommodate small substituents on the phenyl moiety. The 3-amino group is oriented toward the solvent accessible hydrophobic channel. This latter portion of the binding pocket displays a greater tolerance towards various groups in the benzotriazine series as we will demonstrate. Based on this binding mode, we have designed, synthesized, and tested several analogues of 7-phenyl-3-amino-1,2,4-benzotriazine by substituting

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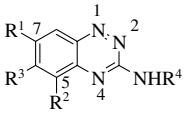
Table 1. Inhibition of Src kinase activity by the 3-aminobenzo-[1,2,4]triazine analogs with R^1 through R^4 modifications



Compound	R^1	R^2	R^3	R^4	IC_{50} (μM)
1	2,6-Cl_2 Ph	Me	H	H	3.6
6	Ph	H	H	H	>50
7	3-OH Ph	H	H	H	12
8	3,4-Methylenedioxy Ph	H	H	H	12
9	2-Naphthyl	H	H	H	5.2
10	2,6-Me_2 Ph	H	H	H	2.2
11	2-Cl Ph	Me	H	H	>50
12	2,6-Me_2 Ph	Me	H	H	7.4
13	2-Cl-5-OH Ph	Me	H	H	1.5
14	2,6-Me_2 Ph	H	H	Ph	1.5
15	2,6-Me_2 Ph	Me	H	Ph	0.41
16	2,6-Me_2 Ph	Me	Me	Ph	0.13
17	2,4,6-Me_3 Ph	Me	H	Ph	>50

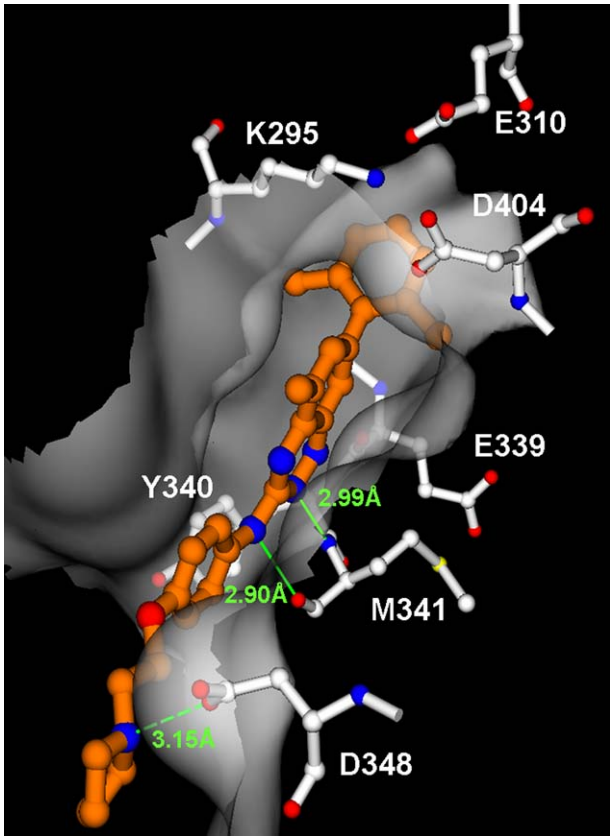
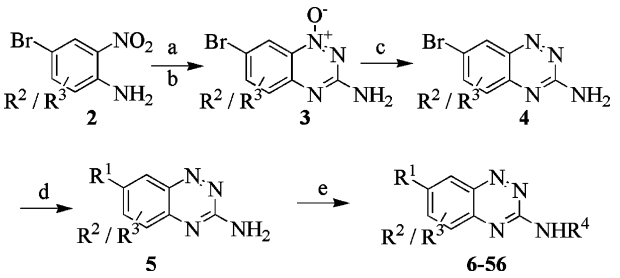


Figure 1. Compound **42** in the ATP binding pocket of Src kinase.

different groups both on the left side (5-, 6-, and 7-positions) and the right side (3-position) of this compound.

The benzotriazines studied were synthesized as shown in Scheme 1. Appropriately substituted 3-bromo-2-nitroanilines (**2**) were reacted with cyanamide under acidic conditions to give intermediate guanidines. These guanidines were cyclized with sodium hydroxide to give 1-oxobenzotriazines (**3**).[20,21] *N*-Oxides (**3**) were reduced using Raney nickel to give 3-amino-7-bromobenzotriazines (**4**) in good yield. Various aryl substituted benzotriazines (**5**) were prepared by treating 3-amino-7-bromobenzotriazines (**4**) with aryl boronic acids under Suzuki coupling conditions.[22] The final compounds (**6**–**56**) were prepared from **5** in good yield by Buchwald–Hartwig cross-coupling reactions using palladium and xantphos.[23]

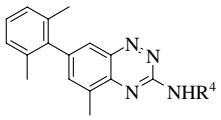


Scheme 1. Reagents and conditions: (a) NH_2CN, 37% aq HCl, 110 °C, 1.5 h; (b) 30% aq NaOH, 110 °C, 0.5 h, 65% over two steps; (c) 10% Raney Ni, H_2, EtOH, rt, 4 h, 80%; (d) $R^1B(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, DME/EtOH/H_2O (4:1:1), Δ, 3 h, 80%; (e) R^4Br, $Pd_2(dba)_3$, xantphos, Cs_2CO_3, dioxane, Δ, 12 h, 70%.

Tables 1–3 summarize the structure–activity relationships for the inhibition of Src for a series of analogues with modifications at R^1 through R^4. These compounds were evaluated using recombinant human Src, PTK2 (a tyrosine kinase substrate), and ATP. The initial SAR efforts were focused on the modifications of the 7-phenyl group. The removal of a methyl group on the benzotriazine resulted in a compound with comparable potency to **1** (data not shown). However, the removal of a chlorine atom (**11**) or two chlorine atoms (data not shown) and removal of the two chlorine atoms and the methyl group on the core (**6**) from **1** resulted in complete loss of potency (Table 1). The *ortho* substitutions on the phenyl ring orient this group perpendicular to the plane of the benzotriazine, facilitating the binding of the moiety deep within the hydrophobic pocket. Our observations in Src are consistent with the previous findings that showed 2,6-disubstitutions on analogous phenyl rings play a key role in enhancing the binding within the hydrophobic pocket of Src[24] and Lck.[25,26] The introduction of a 3-hydroxyl group (**7**) or 3,4-methylenedioxy group (**8**) on the 7-phenyl ring did not improve the potency when compared to **1**. 2,6-Dimethylphenyl substituted compounds without a methyl group at the 5-position (**10**) or with a 5-methyl group (**12**) resulted in compounds with comparable potency to **1**. The introduction of a third methyl group on the 7-phenyl group resulted in compound **17** with loss of potency. These findings are consistent with the homology model that shows tolerances in hydrophobic pocket are restricted to small, specifically positioned groups.

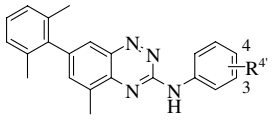
A phenyl substitution on the 3-amino group of **10** and **12** resulted in compounds **14** and **15** with improved potency. Compound **15** was approximately 10-fold more potent than **1**. Methyl groups both at the 5- and

Table 2. Inhibition of Src kinase activity by the 3-aminobenzo-[1,2,4]triazine analogs with R^4 modifications



Compound	R^4	IC_{50} (μM)
18	8-Quinolinyl	>50
19	4-*n*BuPh	>50
20	3-ClPh	0.13
21	4-N(Me)$_2$Ph	0.24
22	2-MeOPh	>50
23	4-MeOPh	0.14
24	4-EtOPh	0.11
25	3-Me Ph	0.18
26	2,3-Me$_2$Ph	>50
27	2,4-Me$_2$Ph	>50
28	2,5-Me$_2$Ph	>50
29	3,4-Me$_2$Ph	0.96
30	3-SO$_2$NH$_2$Ph	0.14
31	2-Pyridyl	>50
32	4-Pyridyl	0.04
33	COMe	>50
34	COPh	1.8

Table 3. Inhibition of Src kinase activity by the 3-aminobenzo-[1,2,4] triazine analogs with $R^{4'}$ modifications



Compound	$R^{4'}$	IC_{50} (μM)
35	4-(2-Diethyl amino) ethoxy	0.010
36	3-(2-Diethyl amino) ethoxy	0.010
37	4-(4-(2-Ethoxy) morpholino)	0.032
38	4-(1-(2-Ethoxy)-4-methylpiperazino)	0.021
39	4-(1-(2-Propoxy)-4-methylpiperazino)	0.036
40	3-(1-(2-Ethoxy)-4-methylpiperazino)	0.041
41	3-(1-(2-Propoxy)-4-methylpiperazino)	0.040
42	4-(2-(1-Pyrrolidinyl) ethoxy)	0.007
43	3-(2-(1-Pyrrolidinyl) ethoxy)	0.006
44	4-(2-Pyrrolidin-1-yl-ethyl)-sulfonamido	0.009
45	3-(2-Pyrrolidin-1-yl-ethyl)-sulfonamido	0.026
46	4-(*N*,*N*-Dimethylamino)ethylcarboxamido	0.008
47	*N*-(2-Pyrrolidin-1-yl-ethyl)-benzamido	0.018
48	3-(4-Methyl-piperazine-1-sulfonyl)	0.320
49	4-(4-Methyl-piperazine-1-sulfonyl)	0.137
50	3-(Piperazine-1-sulfonyl)	0.480
51	4-(Piperazine-1-sulfonyl)	0.128
52	Piperazin-1-yl-methanone	0.013
53	4-Methylpiperazin-1-yl-methanone	0.019
54	3-(*N*,*N*-Dimethylaminoethyl)sulfonamido	0.041
55	3-(*N*,*N*-Dimethylaminopropyl)sulfonamido	0.029
56	4-(*N*,*N*-Dimethylaminoethyl)sulfonamido	0.015

6-positions of the benzotriazine ring help to improve the potency (**16**). The role of the methyl group on the core is not readily apparent since it does not seem to be involved in any obvious binding interactions. Potentially the 5-methyl group more effectively enhances filling hydrophobic space, or facilitates more optimal hinge binding interactions by eliminating alternative binding modes, or tilts the terminal phenyl ring for proper entrance into the hydrophobic pocket thus enhancing potency.

The SAR studies on the left side of the molecule resulted in the identification of the 2,6-dimethylphenyl group at the 7-position and a methyl group at the 5-or 6-position on the benzotriazine ring as preferred for the potency. While keeping the above groups constant, we explored several different groups on the 3-amino moiety (R^4 in Table 2). While a phenyl group on the 3-amino group (**15**) is beneficial, a quinolinyl group on the 3-amino (**18**) results in loss of potency. The 2-methoxyphenyl (**22**) substitution results in a loss of potency. The 4-methoxyphenyl substituted compound (**23**) and 4-ethoxy substituted compound (**24**) result in compounds with potency comparable to **15**, both 10-fold better than **1**. Modeling studies suggested that the groups at the 2-position in the above compounds might create steric clashes that are also reflected in data from compounds **22** and **26**–**28**. While the substitution of a 2-pyridyl group (**31**) results in a complete loss of potency, 4-pyridyl group substitution results in a compound (**32**) with 10-fold improvement in potency over **15**. The substitution of an acyl group (**33**) results in severe loss of potency, while a benzoyl group (**34**) on the 3-amino moiety results only in a 4-fold loss in potency. In the pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones series,[27] a large number of aliphatic and aromatic amino groups on the right side are tolerated and show low nM potency. However, in the benzotriazine series, we have discovered that the aromatic group proximal to the 3-amino position is essential for activity. Additionally either 3- or 4-substitution on the 3-amino *N*-phenyl group is preferred for potency thus showing the benzotriazine series displays unique characteristics that differ significantly from the other structurally related series in its tolerance toward 3-amino substituents.

Modeling studies indicated that the substitution of large groups either at the 3- or 4-position of the phenyl ring would be tolerated since these groups are extended into a solvent accessible area. We introduced several water-soluble groups at both the 4- and 3-positions to improve the aqueous solubility of these compounds. Further modeling suggested that a positively charged ionizable group in the solvent accessible area might potentially interact favorably with Asp-348 and improve the potency. Several compounds were prepared to address both the solubility and the interaction of such analogues with the aspartic acid. The introduction of the 2-(diethylamino)ethoxyphenyl group at the 4-position (**35**) resulted in a compound with improved potency (IC_{50} = 0.01 μM). When the 2-(diethylamino)ethoxyphenyl group was moved to the 3-position as in compound **36**, the potency did not change. Both of these compounds (**35** and **36**) were 40-fold more potent than **15** suggesting the importance of the Asp-348 interaction. We observed a similar trend with the 1-(2-ethoxy)-4-methylpiperazino group at the 3-position (**40**) and at the 4-position (**38**) on the

Table 4. In vitro evaluation of **42** in different kinases

Kinase	IC_{50} μM	Kinase	IC_{50} μM
Src	0.006	VEGFr2	0.555
Yes	0.001	Raf1-MEK1	0.069
Lck	0.013	Abl	0.020
Lyn	0.021	Abl (T315I)	5.99
Fyn	0.023	EphB4	0.064
Blk	1.32	Raf1	0.068
EGFr	0.965	PDGFrβ	0.006
FGFr1	0.96	CSK	0.659
Tie2	0.678	p70S6K	2.71

3-aminophenyl ring. Similarly, the 2-(1-pyrrolidinyl)ethoxy group at the 3-position (**43**) and at the 4-position (**42**) results in compounds with 60-fold improvement in potency compared to the corresponding phenyl analogue (**15**). Conformationally, restricted analogues (**48**–**51**) showed weaker potency over the more flexible analogues (**44**, **45**, and **54**–**56**). Earlier studies in the pyridopyrimidinone series have shown that the water-soluble group on the core does not play a significant role in improving the potency.[27] However, we have shown in this benzotriazine series that a water-soluble group plays a significant role in improving the potency of the molecules.

The binding of **42** at the ATP pocket of Src kinase and the key amino acid interactions with **42** are shown in Figure 1. The 2,6-dimethyl phenyl group is positioned deep inside the hydrophobic pocket. The ring nitrogen at the 2-position is involved as a hydrogen bond acceptor with the NH of Met-341, while the 3-amino group is involved as a hydrogen bond donor with the carbonyl of Met-341 at the hinge region of the ATP binding pocket. The pyrrolidine nitrogen interacts with Asp-348. We have examined compound **42** for kinase selectivity (Table 4). Compound **42** is equipotent against other Src family members (Yes, Lck, Lyn, Fyn, and Blk), PDGFrβ and EphB4 receptor tyrosine kinases but has greatly reduced activity against VEGFr2, EGFr, and FGFr1. This benzotriazine series has significantly different selectivity than the structurally similar Src focused pyridopyrimidinone series,[27] which has pronounced activity against FGFr1 and reduced activity versus PDGFrβ.

In summary, we have developed a novel benzotriazine series as potent Src inhibitors. We have identified the key structural requirements for improving the activity in this series, whose SAR is distinct from that of other structurally analogous Src-inhibitors. Future studies will focus on further lead optimization of this series, pharmacokinetic properties, and in vivo pharmacology.

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18. The IC_{50} values for compounds were determined using a luminescence-based kinase assay with recombinant Src obtained from Invitrogen. In white, flat-bottomed, 96-well plates (Nunc) parallel assays were run at room temperature at a final volume of 50 μL. Each well contained 40 μL of buffer consisting of 40 mM Tris buffer, pH 7.4, containing 50 mM $MgCl_2$, 800 μM EGTA, 350 μM Triton X-100, 2 mM β-mercaptoethanol, 250 μM peptide substrate (PTK2; Promega), and an appropriate amount of Src (75–25 ng/well) such that the assay was linear over 60 min. The final concentrations of TargeGen compounds for IC_{50} value determinations ranged from 1000 to 0.01 μM by adding the appropriate amount of compound in 2.5 μL DMSO; the DMSO present in each assay was constant at 5%. The reaction was initiated by the addition of 10 μL ATP to a final assay concentration of 3 μM. After the reaction had proceeded for 60 min, 50 μL of Kinase-Glo reagent (Promega) was added to terminate the reaction. This solution was then allowed to proceed for an additional 10 min to maximize the luminescence reaction. Values were then measured using an Ultra 384 instrument (Tecan) set for luminosity measurements. Two control

reactions were also run: one reaction containing no compound and the second containing neither inhibitor nor peptide substrate. IC_{50} values were derived from experimental data using the non-linear curve fitting capabilities of Prism (Version 4; GraphPad Software).

19. While several crystal structures of the unphosphorylated form of Src are available (PDB codes 2SRC, 1FMK, 1Y57, 2PTK), it is known that kinases in the Src family undergo conformational change upon phosphorylation casting doubt on the relevance of these crystal forms to drug discovery. We felt that the crystal structure of the inactive form of Src is not useful for modeling studies. So the fully activated catalytic domain of human Src kinase was built based on available crystal structures of activated Lck. The catalytic domains of Src and Lck exhibit 67% sequence identity over 273 residues without gaps in the alignment; significantly, higher homology is exhibited in the ATP binding site. The model was built using the interactive programs InsightII and Homology from Accelrys. Models with and without ligands were subjected to energetic refinement including solvent using the Accelrys program Discover.
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