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Click chemistry inspired one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles and their Src kinase inhibitory activity

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ABSTRACT

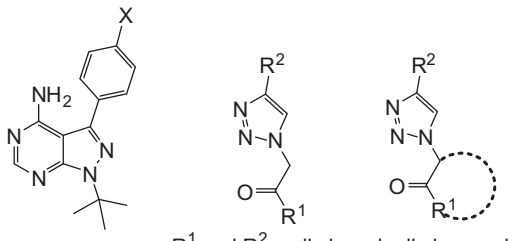
Two classes of 1,4-disubstituted 1,2,3-triazoles were synthesized using one-pot reaction of α-tosyloxy ketones/α-halo ketones, sodium azide, and terminal alkynes in the presence of aq PEG (1:1, v/v) using the click chemistry approach and evaluated for Src kinase inhibitory activity. Structure–activity relationship analysis demonstrated that insertion of C_6H_5– and 4-$CH_3C_6H_4$– at position 4 for both classes and less bulkier aromatic group at position 1 in class 1 contribute critically to the modest Src inhibition activity (IC_{50} = 32–43 μM) of 1,4-disubstituted 1,2,3-triazoles.

Protein tyrosine kinases (PTKs) catalyze the phosphorylation of phenolic group of tyrosine residue in many substrate proteins by the transfer of γ-phosphate moiety of ATP. PTKs play a crucial role in the signal transduction pathways. The non-receptor tyrosine kinases of the Src family, Src, Yes, Lck, Fyn, Lyn, Fgr, Hck, Blk, and Yrk, share a great deal of structural homology and are present in the cytoplasm.[1] Src tyrosine kinase plays a prominent role in regulating cell growth and differentiation. Src has been implicated in development of variety of cancers. Src mutations and/or overexpression has been correlated with tumor growth, metastasis, and angiogenesis.[2]

Various structural motifs have been reported to target Src kinase[3] such as quinolinecarbonitriles,[4] ATP-phosphopeptide conjugates,[5] pyrazolopyrimidines,[6] purines,[7] imidazo[1,5-*a*]pyrazines,[8] benzotriazines,[9] pyrimidoquinolines,[10] pyridopyrimidinones,[11] and quinazolines.[12] Imatinib, a well known marketed PTK inhibitor, is used to treat a number of malignancies like chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GISTs). Dasatinib is another marketed kinase inhibitor that inhibits Src family tyrosine kinases and BCR/ABL and is approved to use after Imatinib treatment. A 3-quinolinecarbonitrile-based Src kinase inhibitor, Bosutinib, is undergoing rigorous trials for cancer treatment.[13]

X-ray studies of phenylpyrazolopyrimidine inhibitors in Hck kinase-PP1 and Lck kinase-PP2[14] complexes have revealed a deep hydrophobic binding pocket near the ATP binding site of Src family kinases for the aryl moiety of the pyrazolopyrimidine template. We have previously shown that the hydrophobic interaction of the phenyl group with hydrophobic pocket is essential for the binding of 3-phenylpyrazolopyrimidines (Fig. 1) to the ATP binding site.[15] The pyrazolopyrimidine core resembles the purine core of ATP itself and bind in the nucleotide binding site in the position normally occupied by the adenine base. Any substituent attached to N^1 of pyrazole occupies a mostly hydrophobic cavity in PP1. Most of this hydrophobic cavity remains unfilled. This cavity, in part, formed from side chains of helix αC and helix αD.

Herein, we describe synthesis and evaluation of 1,4-disubstituted 1,2,3-triazoles (Fig. 1) as a novel template for Src kinase inhibition. The 1,2,3-triazoles are important heterocycles that are



PP1 X = Me
PP2 X = Cl

R^1 and R^2 = alkyl, cycloalkyl, or aryl

Figure 1. Chemical structures of 3-phenylpyrazolopyrimidines and 1,4-disubstituted 1,2,3-triazoles.

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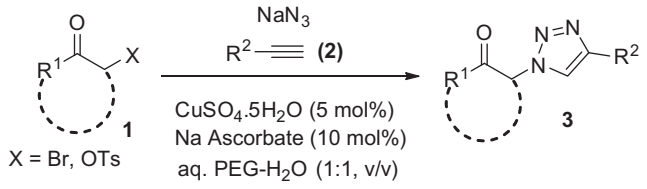
reported to possess several biological properties including anti-HIV,[16] antiallergic,[17] antifungal,[18] and antimicrobial,[19] activities. The 1,2,3-triazole based compounds have been previously reported to inhibit p38 MAP kinase and PfPK7 protein kinase.[20]

We hypothesized that substitution at N_1 and position 4 of 1,2,3-triazoles with hydrophobic residues may occupy and interact with the hydrophobic binding pocket of Src ATP binding site similar to that of 3-phenylpyrazolo-pyrimidines. The hydrophobic interactions of the hydrophobic groups with several amino acids in the hydrophobic pockets may contribute to the enhancement of potency. Furthermore, the attachment of hydrophobic group to 1,2,3-triazoles may generate novel geometric features that might contribute to binding of such compounds to Src kinase.

Preparation of 1,2,3-triazoles (**3a**–**z** and **4a**–**m**) has been widely explored using click chemistry approach due to its complete specificity, efficiency, simple reaction workup procedure, and quantitative reaction yield of the products.[21] Furthermore, multicomponent reactions have been contributing considerably for the drug discovery by putting forth multiple arrays of compounds with diverse substitution patterns expeditiously.[22] The synthetic strategy of these reactions can yield complex molecules with several new bonds and points of diversity in one pot thus alleviating the labor involved over a series of reaction workups.[23]

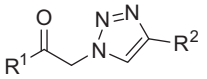
The facile and eco-friendly synthesis of these derivatives involves a one-pot reaction of α-tosyloxy ketones/α-halo ketones, sodium azide, and terminal alkynes in the presence of aq PEG 400 (1:1, v/v) at room temperature under 'Click' conditions[24] (Scheme 1). The convenient preparation of 1,2,3-triazoles involves initial nucleophilic substitution reaction of α-tosyloxy ketones/α-halo ketones with sodium azide to generate in situ α-azido ketones which is followed by Cu (I) catalyzed regioselective cycloaddition reaction with alkynes. The protocol is broadly applicable for the preparation of 1,2,3-triazoles as demonstrated by the use of various α-tosyloxy ketones/α-halo ketones (aliphatic, aromatic and cyclic) and alkynes (alkyl and aryl). Both the α-tosyloxy ketones and α-halo ketones reacted with almost the same efficiency. It was observed that the α-tosyloxy ketones required marginally shorter reaction time when compared to α-halo ketones. Moreover, α-tosyloxy ketones are ideal substitutes for the lachrymatory α-halo ketones. The mild reaction conditions and simple workup allowed us to rapidly prepare various substituted 1,2,3-triazoles in good yields (60–90%). After completion of the reaction, the contents were simply diluted with water, filtered, and dried to obtain 1,2,3-triazole which was finally recrystallized from ethyl acetate/hexane. The IR spectra of all the compounds exhibited a strong band at about 1685 cm^{-1}. In ^1H NMR a characteristic singlet was observed for triazolyl C_5–H at about δ 7.90 ppm. All the synthesized compounds were characterized by IR, ^1H NMR, and mass spectroscopy.

Two classes of compounds with R^1-CO(CH)-substitution at position 1 were synthesized using this procedure. The first class of compounds (**3a**–**z**) (Table 1) includes 1,2,3-triazoles where R^1 is a hydrophobic residue, such as phenyl, substituted phenyl, coumarinyl, 2-thienyl, or other nonaromatic substituents (i.e., CH_3, OCH_3, $N(C_2H_5)$). In class 2 compounds (**4a**–**m**) (Table 2), R^1 is a cyclopentanone-2-yl, cyclohexanone-2-yl, or cycloheptanone-2-yl. The substitution at position 4 (R^2) is phenyl, substituted phenyl, short alkyl, or a heteroaromatic (i.e., 2-pyridyl, 3-thienyl). The diversity of hydrophobic substitutions at R^1 and R^2 positions allowed the structure–activity relationship analysis of 1,4-disubstituted 1,2,3-triazoles.



Scheme 1. Synthesis of 1,4-disubstituted 1,2,3-triazoles.

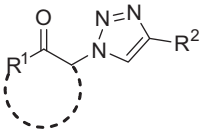
Table 1
The Src kinase inhibitory activities of 1,2,3-triazoles **3a**–**z** (class 1)



Compd	R^1	R^2	IC_{50}[a] (μM)
3a	C_6H_5	C_6H_5	>100.0
3b	C_6H_5	4-$CH_3C_6H_4$	41.6
3c	C_6H_5	4-F-3-$CH_3C_6H_3$	81.0
3d	C_6H_5	2-Pyridyl	NA[b]
3e	Styryl	C_6H_5	>100.0
3f	C_6H_5	*n*-Butyl	NA
3g	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	49.8
3h	4-$CH_3C_6H_4$	4-F-3-$CH_3C_6H_3$	82.3
3i	4-$OCH_3C_6H_4$	C_6H_5	>100.0
3j	4-$OCH_3C_6H_4$	3-$CH_3C_6H_4$	72.8
3k	4-ClC_6H_4	C_6H_5	139.0
3l	4-ClC_6H_4	4-$CH_3C_6H_4$	108.7
3m	4-ClC_6H_4	4-FC_6H_4	NA
3n	4-ClC_6H_4	4-$OCH_3C_6H_4$	NA
3o	4-ClC_6H_4	3-Thienyl	>150.0
3p	4-BrC_6H_4	4-$CH_3C_6H_4$	NA
3q	4-BrC_6H_4	4-FC_6H_4	NA
3r	4-BrC_6H_4	*n*-Butyl	NA
3s	4-BrC_6H_4	1-Cl-butan-4-yl	>100.0
3t	Coumarin-3-yl	C_6H_5	89.5
3u	Coumarin-3-yl	4-$CH_3C_6H_4$	>150.0
3v	2-Thienyl	C_6H_5	32.5
3w	CH_3	C_6H_5	>150.0
3x	CH_3	4-$CH_3C_6H_4$	>150.0
3y	OCH_3	C_6H_5	>100
3z	$N(C_2H_5)$	C_6H_5	>150.0
Staurosporine	—	—	0.3
PP2	—	—	2.8

[a] The concentration of the compound that inhibited enzyme activity by 50%.
[b] Less than 10% enzyme inhibitory activity was observed up to the concentration of 75 μM.

Table 2
The Src kinase inhibitory activity of compounds **4a**–**m** (class 2)



Compd	R^1	R^2	IC_{50}[a] (μM)
4a	Cyclopentan-1-on-2-yl	C_6H_5	105.5
4b	Cyclopentan-1-on-2-yl	4-$CH_3C_6H_4$	62.1
4c	Cyclopentan-1-on-2-yl	3-Thienyl	NA[b]
4d	Cyclopentan-1-on-2-yl	4-$OCH_3C_6H_4$	NA
4e	Cyclopentan-1-on-2-yl	4-FC_6H_4	NA
4f	Cyclopentan-1-on-3-yl	C_6H_5	NA
4g	Cyclohexan-1-on-2-yl	C_6H_5	43.2
4h	Cyclohexan-1-on-2-yl	4-$CH_3C_6H_4$	33.9
4i	Cyclohexan-1-on-2-yl	3-Thienyl	NA
4j	Cyclohexan-1-on-2-yl	4-FC_6H_4	NA
4k	Cyclohexan-1-on-2-yl	4-$OCH_3C_6H_4$	NA
4l	Cyclohexan-1-on-3-yl	C_6H_5	NA
4m	Cycloheptan-1-on-2-yl	4-$CH_3C_6H_4$	66.1

[a] The concentration of the compound that inhibited enzyme activity by 50%.
[b] Less than 10% enzyme inhibitory activity was observed up to the concentration of 75 μM.

An array of 39 diversely substituted 1,2,3-triazoles (20 novel compounds) was evaluated against Src kinase. The results of Src kinase inhibitory activity of compounds in classes 1 and 2 are shown in Tables 1 and 2, respectively.

In general, the compounds in class 1 with R^1 as nonaromatic alkyl groups (Me, *N*-ethyl, OMe, **3w**–**z**) exhibited weak Src kinase inhibition with IC_{50} values more than 100 μM or minimal inhibitory activity at highest concentration tested (375 μM). Furthermore, compounds with large aromatic groups such as styryl (**3e**), 3-coumarinyl (e.g., **3t**, **3u**) or aromatic groups with a bulky substitution (4-ClC_6H_4, 4-BrC_6H_4) in **3k**–**q** showed weak Src inhibitory potency. Attempts to improve the activity by introducing an aliphatic substituent at R^2 (**3r**, **3s**) also resulted in poor inhibition, suggesting that the size of aromatic moiety at R^1 position is critical, and a bulky moiety at this position must be avoided. In contrast, the introduction of less bulkier unsubstituted phenyl and thienyl groups at position 1 in compounds **3b** (IC_{50} = 41.6 μM) and **3v** (IC_{50} = 32.5 μM) in class 1 significantly improved the Src inhibitory activities.

The presence of an electron-donating methyl group in R^1 and R^2 phenyl ring in **3g** (IC_{50} = 49.8 μM) did not result in improved inhibition when compared with **3b**. The introduction of phenyl (**3a**), 4-F-3-$CH_3C_6H_3$ (**3c**), 2-pyridyl (**3d**), and *n*-butyl (**3f**) as R^2 group drastically decreased the Src inhibitory activity versus **3b**. Introduction of electronegative fluorine also did not improve the activity (**3h**, **3m**, and **3q**). These data indicate that the nature of R^2 group contributes significantly to the overall activity.

In order to explore the effect of nonaromatic cyclic functional groups at R^1 position in Src inhibitory activity, a series of analogs **4a**–**m** having different cyclic ketones and bearing nonaromatic groups at R^1 position were prepared and evaluated (Table 2). Compounds **4g** and **4h** with N_1 2-cyclohexanone and C4 phenyl/tolyl groups exhibited modest Src kinase inhibition with IC_{50} values of 43.2 and 33.9 μM, respectively. Introduction of 4-fluorophenyl, 4-methoxyphenyl and 3-thienyl substituents at C4 position of 1,2,3-triazole also led to the compounds (**4c**, **4d**, **4e**, **4i**, **4j**, and **4k**) with poor activity. Other compounds in class 2 showed diminished activity versus **4g** and **4h**, confirming the importance of R^2 groups in overall activity. Compound **4h** (IC_{50} = 33.9 μM), a modest Src kinase inhibitor, was selected for inhibitory selectivity assays against Lck, a member of Src family kinase, EGFR, a receptor tyrosine kinase, and Csk, a tyrosine kinase that phosphorylates Src. IC_{50} values in all cases were >100 μM (see, Fig. S1, Supplementary data). These data suggested that compound **4h** was selective against Src when compared with the selected kinases.

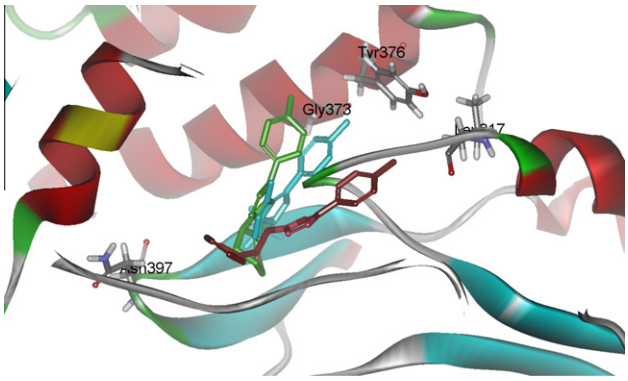


Figure 2. Comparison of structural complexes of Src kinase with different 1,2,3-triazoles (**3b**, red; **4h**, green) and PP1 (blue) based on molecular modeling. The compounds are rendered in stick styles. They are the lowest energy conformers predicted for the compounds.

Molecular modeling was utilized to examine how the structures would fit within the ATP binding site of the enzyme (Fig. 2). The modeling studies indicated that tolyl groups in **3b** and **4h** occupy the hydrophobic binding pocket similar to tolyl group of PP1 with slightly different orientations (Fig. 2). The substitution at N1 position of triazole occupied mostly the hydrophobic cavity of Src ATP binding site similar to that of *t*-butyl group of PP1. The compounds demonstrated only modest inhibitory potency possibly because of mostly hydrophobic interactions. The 4-amino group of PP1 and PP2 is hydrogen bonded to the side chain of Thr338 as well as the carbonyl of Glu339 that contributes significantly to their potency as Src kinase inhibitors.

In summary, compounds **3b**, **3g**, **3v**, **4g**, and **4h** exhibited modest Src kinase inhibitory activity among the synthesized 1,2,3-triazoles with IC_{50} values in the range of 32–43 μM. Comparison of moderately active compounds indicate that the insertion of C_6H_5– and 4-$CH_3C_6H_4$– at R^2 position in both groups with appropriate less bulkier group at R^1 position in class 1 is well tolerated for the modest Src inhibition activity of 1,2,3-triazoles. The structure–activity relationship data provide insights for further optimization of this scaffold and/or use in fragment-based discovery of Src kinase inhibitors.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.10.121.

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