



## Synthesis of 3-phenylpyrazolopyrimidine-1,2,3-triazole conjugates and evaluation of their Src kinase inhibitory and anticancer activities

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### ARTICLE INFO

#### Article history:

Received 24 December 2010

Revised 10 January 2011

Accepted 12 January 2011

Available online 15 January 2011

#### Keywords:

Anticancer activity

Click reaction

Phenylpyrazolopyrimidine

Src kinase

1,2,3-Triazole

Tyrosine kinase

### ABSTRACT

A series of two classes of 3-phenylpyrazolopyrimidine-1,2,3-triazole conjugates were synthesized using click chemistry approach. All compounds were evaluated for inhibition of Src kinase and human ovarian adenocarcinoma (SK-Ov-3), breast carcinoma (MDA-MB-361), and colon adenocarcinoma (HT-29). Hexyl triazolyl-substituted 3-phenylpyrazolopyrimidine exhibited inhibition of Src kinase with an IC<sub>50</sub> value of 5.6 μM. 4-Methoxyphenyl triazolyl-substituted 3-phenylpyrazolopyrimidine inhibited the cell proliferation of HT-29 and SK-Ov-3 by 73% and 58%, respectively, at a concentration of 50 μM.

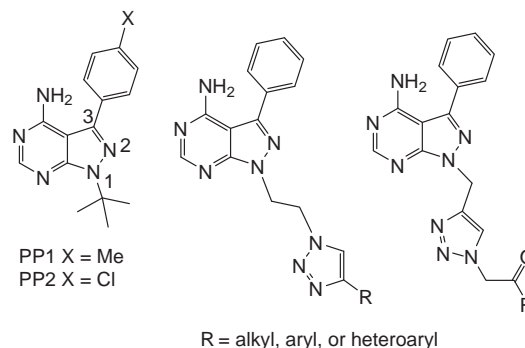
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Phosphorylation of many protein substrates occurs in the presence of protein tyrosine kinases (PTKs) that catalyze the transfer of γ-phosphate group from ATP to specific tyrosine residues. PTKs have critical roles in the signal transduction pathways. Src family kinases (SFKs) are a family of nine different PTKs, including c-Src, c-Yes, Fyn, Lck, Lyn, Hck, Frk, Blk, and c-Fgr of which Src is the prototype.<sup>1</sup> SFKs have important roles in the regulation of a wide variety of normal cellular signal transduction pathways, such as cell division, growth factor signaling, differentiation, survival, adhesion, migration, and invasion.<sup>2</sup> Src tyrosine kinase expression is frequently elevated in a number of epithelial tumors including colon, breast, prostate, lung, ovary, and pancreas compared with the adjacent normal tissues. Src kinase is a key modulator of cancer cell invasion and metastasis.<sup>3–6</sup>

In recent years development of Src kinase inhibitors for the treatment of cancer is a subject of major interest.<sup>7</sup> A number of inhibitors of protein kinases<sup>8</sup> such as quinazolines,<sup>9</sup> quinolinecarbonitriles,<sup>10</sup> pyrazolopyrimidines,<sup>11</sup> imidazo[1,5-*a*]pyrazines,<sup>12</sup> benzotriazines,<sup>13</sup> ATP-phosphopeptide conjugates,<sup>14</sup> pyrimidoquinolines,<sup>15</sup> and pyridopyrimidinones<sup>16</sup> have been investigated for the treatment of cancer, chronic inflammatory diseases, and other indications.<sup>17</sup> Imatinib is a 2-phenylaminopyrimidine non-selective PTK inhibitor of ABL, c-Kit, and PDGFR approved for the treatment of a number of malignancies like chronic myelogenous

leukemia (CML) and gastrointestinal stromal tumors (GISTs).<sup>18</sup> However, various imatinib-resistant mutations are generated spontaneously on Abl over long-term course of treatment.<sup>19</sup> Dasatinib (BMS-354825) is a pyrimidinylthiazole-based ATP-competitive dual SRC/ABL inhibitor<sup>20</sup> approved to use in patients with CML after imatinib treatment. Bosutinib (SKI-606), a 3-quinolinecarbonitrile-based Src kinase inhibitor, is known to suppress migration and invasion of human breast cancer cells.<sup>21</sup>

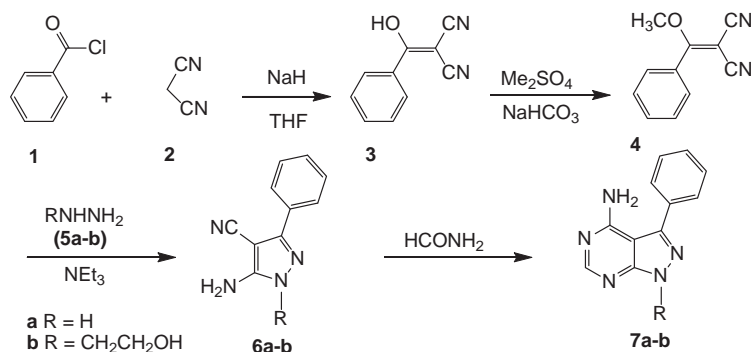
Crystallographic studies of an ATP mimic, AMP-PNP, bound to c-Src (PDB 2SRC)<sup>22</sup> and complexes of 3-phenylpyrazolopyrimidine



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

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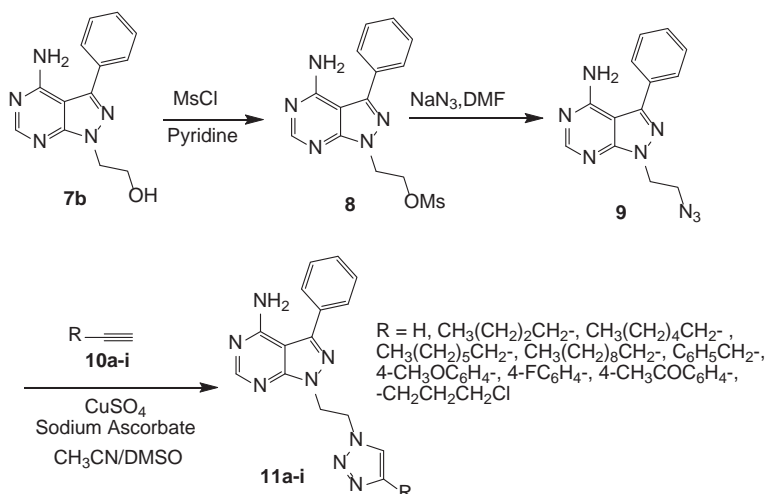
Scheme 1. Synthesis of N<sup>1</sup>-substituted PhPP scaffolds.

derivatives (PP1 and PP2) (Fig. 1) as ATP-binding site inhibitors with Hck (PDB 1QCF)<sup>23</sup> and Lck (PDB 1QPE)<sup>24</sup> have revealed that the pyrazolopyrimidine core of PP1 and PP2 mimic the adenine base of ATP in binding to the nucleotide binding site. We have previously shown that 3-phenyl group contributes significantly to Src kinase inhibitory activity through a hydrophobic interaction with a large hydrophobic pocket in the ATP-binding site.<sup>25a</sup> Another cavity is formed from side chains of helix  $\alpha$ C and helix  $\alpha$ D. This cavity is normally occupied by carbohydrate moiety followed by triphosphate group of ATP and remains mostly unfilled by *tert*-butyl of 3-phenylpyrazolopyrimidines (PP1 and PP2).

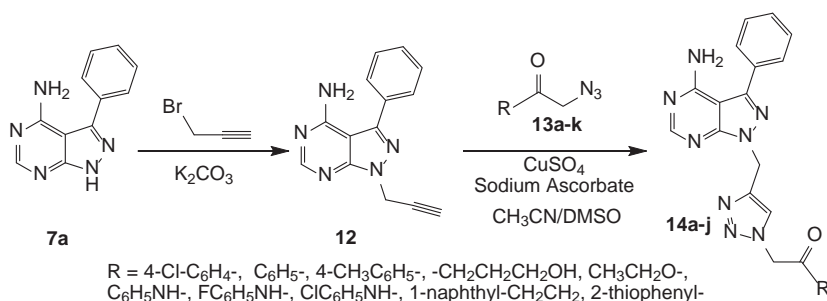
In continuation of our efforts to design or identify new Src kinase inhibitors,<sup>14,25</sup> we investigated whether that variation of N<sub>1</sub> substitution in 3-phenylpyrazolopyrimidines with different

1,2,3-triazoles containing hydrophobic residues can occupy and/or interact with amino acids of this cavity and contribute to the enhancement of Src kinase inhibitory potency. Herein, we describe synthesis and evaluation of Src kinase inhibitory activity of two classes of 3-phenylpyrazolopyrimidine (PhPP)-1,2,3-triazole conjugates (Fig. 1), in which the pyrazolo ring of PhPP is attached through an ethylene or a methylene linker to positions 1 and 4 of the triazole, respectively. All the compounds were synthesized under click reaction conditions.

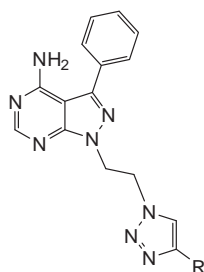
Synthesis of PhPP scaffolds (7a–b) was achieved according to the previously reported procedure with slight modification as shown in Scheme 1.<sup>25,26</sup> 2-Benzoylmalononitrile (3) was synthesized from the reaction of benzoyl chloride (1) with malononitrile (2) in the presence of sodium hydride in THF. Methylation of 3 with



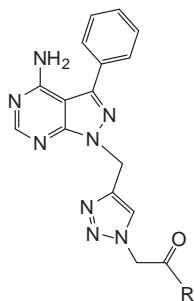
Scheme 2. Synthesis of PhPP-1,2,3-triazole conjugates 11a–i.



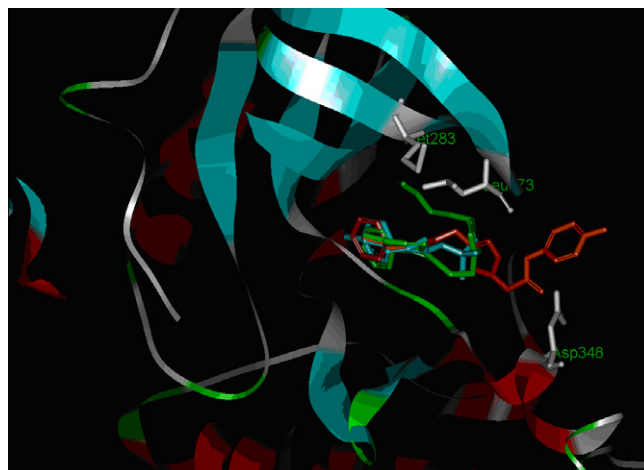
Scheme 3. Synthesis of PhPP-1,2,3-triazole conjugates 14a–j.

**Table 1**The Src kinase inhibitory activities of compounds **11a–i** (class 1)

Compds	R	IC <sub>50</sub> <sup>a</sup> (μM)	Log P <sup>c</sup> (calcd)
<b>9</b>	—	6.2	—
<b>11a</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> —	>75	2.83
<b>11b</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> CH <sub>2</sub> —	5.6	3.89
<b>11c</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> CH <sub>2</sub> —	>75	4.41
<b>11d</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>8</sub> CH <sub>2</sub> —	>75	5.47
<b>11e</b>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> —	NA <sup>b</sup>	2.81
<b>11f</b>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> —	17.4	3.06
<b>11g</b>	4-FC <sub>6</sub> H <sub>4</sub> —	29.6	3.25
<b>11h</b>	4-CH <sub>3</sub> COC <sub>6</sub> H <sub>4</sub> —	>75	2.60
<b>11i</b>	—CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Cl	NA	2.01
Staurosporine	—	0.3	—
PP2	—	2.8	3.57

<sup>a</sup> The concentration that inhibited enzyme activity by 50%.<sup>b</sup> Less than 10% enzyme inhibitory activity was observed up to the concentration of 250 μM.<sup>c</sup> Calculated partition coefficient using ChemBioDraw Ultra 12.0.**Table 2**The Src kinase inhibitory activities of compounds **14a–j** (class 2)

Compds	R	IC <sub>50</sub> <sup>a</sup> (μM)	Log P <sup>c</sup> (calcd)
<b>14a</b>	4-Cl-C <sub>6</sub> H <sub>4</sub> —	>75	2.89
<b>14b</b>	C <sub>6</sub> H <sub>5</sub> —	>75	2.11
<b>14c</b>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub> —	>75	2.60
<b>14d</b>		>75	1.88
<b>14e</b>		23.1	1.82
<b>14f</b>		16.4	2.22
<b>14g</b>		>75	2.79
<b>14h</b>		NA <sup>b</sup>	3.83
<b>14i</b>	—CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	9.1	0.32
<b>14j</b>	CH <sub>3</sub> CH <sub>2</sub> O—	12.7	1.35
Staurosporine	—	0.3	—
PP2	—	2.8	—

<sup>a</sup> The concentration that inhibited enzyme activity by 50%.<sup>b</sup> Less than 10% enzyme inhibitory activity was observed up to the concentration of 250 μM.<sup>c</sup> Calculated partition coefficient using ChemBioDraw Ultra 12.0.**Figure 2.** Comparison of structural complexes of Src kinase with different PhPP derivatives. **11b** (green), PP1 (blue), and **14f** (red) based on molecular modeling. The compounds and side chains of amino acids are rendered in stick styles. Compounds are in the lowest energy conformers predicted. The figure is drawn using the Accelrys visualization system.

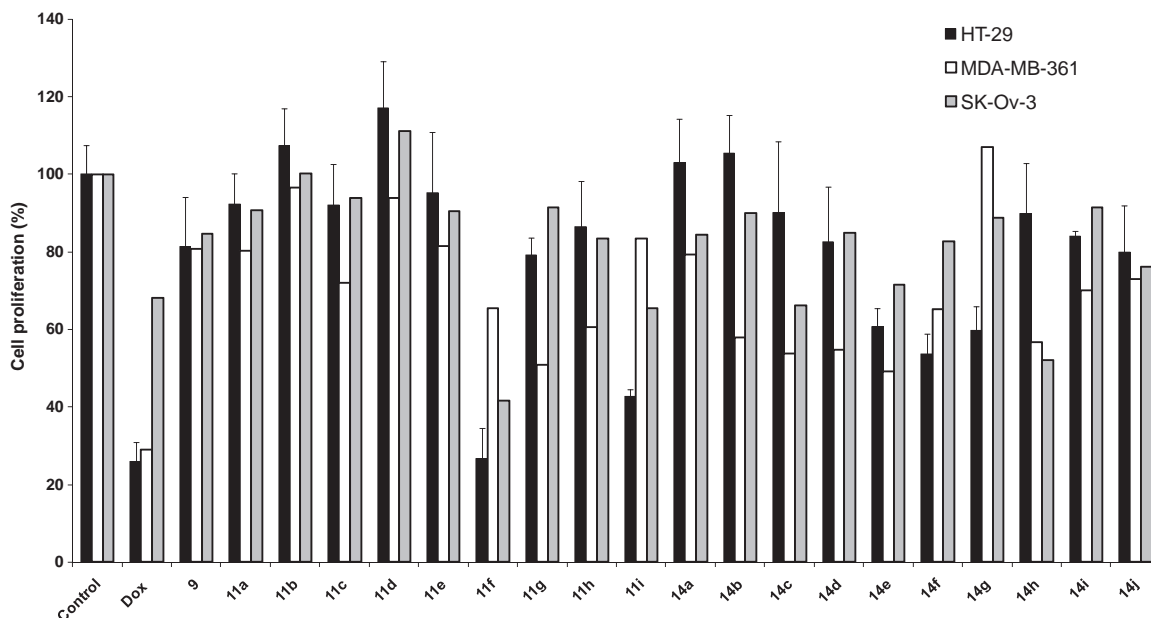
dimethyl sulfate in the presence of sodium bicarbonate in dioxane afforded 2-(methoxyphenylmethylene)malononitrile (**4**), which was cyclized by treatment with hydrazine hydrochloride or 2-hydroxyethyl hydrazine in the presence of triethylamine to afford 5-amino-3-phenyl-1*H*-pyrazole-4-carbonitrile (**6a**) or 5-amino-1-(2-hydroxyethyl)-3-phenyl-1*H*-pyrazole-4-carbonitrile (**6b**), respectively. Reaction of (**6a–b**) with formamide at 180 °C for 24 h afforded the corresponding PhPP scaffolds **7a** and **7b** in 72% and 76% yields, respectively.

Compounds **7b** and **7a** were used for the synthesis of azido- and alkyne-substituted building blocks **9** and **12**, respectively, needed for click reactions. Synthesis of compound **9** was carried out by mesylation of **7b** followed by nucleophilic substitution with sodium azide in DMF (Scheme 2). Compound **12** was prepared by the reaction of **7a** with propargyl bromide in the presence of potassium carbonate in acetone at room temperature (Scheme 3). Only the N<sub>1</sub>-endocyclic amino group of PhPP derivatives was reacted with propargyl bromide. Unprotected N<sub>4</sub>-exocyclic amine was not reactive under these reaction conditions as shown previously.<sup>27</sup>

Two classes of PhPP-1,2,3-triazole conjugates (**11a–i** and **14a–j**) were prepared by the click chemistry approach using regioselective addition of **9** with different alkynes (**10a–i**) (Scheme 2) and **12** with different azides (**13a–k**) (Scheme 3) catalyzed by in situ generated copper(I) salt at room temperature. The reactions proceeded in high yields (76–88%) and in a regioselective manner. All the compounds were purified using column chromatography and characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, and HRMS spectroscopy. The IR spectra of the compounds (**14a–j**) exhibited a strong band at about 1685 cm<sup>−1</sup> confirming the presence of a carbonyl group. In <sup>1</sup>H NMR spectra of **11a–i** and **14a–j** a characteristic singlet was observed for triazolyl C<sub>5</sub>-H at about δ 7.90 ppm.

An array of 20 diversely substituted PhPP-1,2,3-triazole conjugates were evaluated against Src kinase. The results of Src kinase inhibitory activity of compounds in classes 1 (**11a–i**) and 2 (**14a–j**) are shown in Tables 1 and 2, respectively.

All compounds in class 1 showed less inhibitory activities when compared with that of PP2. A number of compounds **11b**, **11f**, and **11g** showed modest inhibitory activity (IC<sub>50</sub> = 5.6–29.6 μM) (Table 1). These data suggest that the presence of 1,2,3-triazole-substituted with bulky groups and attached through an ethylene to PhPP scaffold is less tolerated, possibly because the cavity cannot accommodate large groups. Furthermore, the substitutions may



**Figure 3.** Inhibition of HT-29, MDA-MB-361, and SK-Ov-3 cell proliferation by compounds **11a–i** and **14a–j** (50  $\mu$ M) after 72 h incubation. The results are shown as the percentage of the control DMSO that has no compound (set at 100%). All the experiments were performed in triplicate.

not be oriented appropriately in the cavity or may have unfavorable interactions.

Compounds in class 2 exhibited more diverse inhibitory activities (Table 2). Compounds **14e**, **14f**, **14i**, and **14j** demonstrated modest Src inhibitory activities with  $IC_{50}$  values between 9.1 and 23.1  $\mu$ M. 1,2,3-Triazole-substituted with naphthyl (**14h**), tolyl (**14c**), and 4-chlorophenyl (**14a** and **14g**) showed significantly weak inhibitory potency, suggesting incorporation of bulky groups are less tolerated in the cavity. The presence of 1,2,3-triazole between PhPP scaffold and the substitution through a carbonyl group provides less flexibility for the substituted moieties at  $N_1$  position to be accommodated into cavity.

Molecular modeling and minimization was used to explore how the structures would fit within the ATP-binding site of the enzyme (Fig. 2). The modeling studies indicated that phenyl groups in **11b** and **14f** occupy the hydrophobic binding pocket similar to tolyl group of PP1 with slightly different orientations (Fig. 2). In case of **11b**, the flexible hexyl group is oriented towards the hydrophobic pocket possibly because of favorable hydrophobic interactions. On the other hand, the fluorophenyl group in **14f** is positioned towards the large cavity where the triphosphate group of ATP usually binds similar to that of *t*-butyl group of PP1, possibly because the amide moiety in **14f** does not allow flexibility seen in **11b**.

The effect of the inhibitors at the concentration of 50  $\mu$ M on the cell proliferation of cancer cells that overexpress c-Src was also evaluated against human ovarian adenocarcinoma cells (SK-Ov-3), breast carcinoma (MDA-MB-361), and colon adenocarcinoma (HT-29) cell lines (Fig. 3). All three cell lines express highly activated Src.<sup>28,29</sup> Compounds **11f** and **11i** inhibited the cell proliferation of colon cancer cells (HT-29) by 73% and 57%, respectively, (Fig. 3) whereas compounds **11f** and **14h** inhibited the growth of ovarian cancer cells (SK-Ov-3) by approximately 58% and 48%, respectively (Fig. 3). Compounds **11g** and **14e** were able to inhibit the cell proliferation of breast cancer cells (MDA-MB-361) by 49% and 51%, respectively (Fig. 3).

There were some correlation between Src kinase inhibitory potency of the compounds and the growth inhibition of cancer cells since compounds **11f**, **11g**, **14e**, and **14f** were modest Src kinase inhibitors. The data suggest that modest Src inhibition may lead to anticancer activities of these compounds, but this correlation

is not always perfect possibly because of the diversity in solubility (see calculated Log *P* values in Tables 1 and 2) and cellular uptake of these compounds in these cell lines as **11b** a modest Src kinase inhibitor was not a potent inhibitor of cell proliferation.

In summary, compounds **11b** and **14i** exhibited modest inhibitory potency ( $IC_{50}$  = 5.6–9.1  $\mu$ M) against Src kinase. Structure–activity relationship studies suggested that the incorporation of bulky groups at  $N_1$  position of PhPP is less tolerated. 4-Methoxyphenyl triazolyl-substituted 3-phenylpyrazolo-pyrimidine (**11f**) inhibited the cell proliferation of HT-29 by 73% at a concentration of 50  $\mu$ M. The data provide insights for further optimization of these compounds as Src kinase inhibitors and/or anticancer agents.

## Acknowledgments

We acknowledge Department of Science and Technology, New Delhi Project # SR-FTP-CS-34-2007, the American Cancer Society Grant # RSG-07-290-01-CDD, and National Science Foundation, Grant Number CHE 0748555 for the financial support.

## Supplementary data

Supplementary data (experimental procedures and characterization of compounds) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.01.047.

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