Chapter 5
Furan Tagged Triazole Ligated Pyridine Scaffolds: New Entries to the Drug Chemical Space

5.1. Introduction

Even though a large number of molecules are reported to add to the drug molecular library, most of them fail to get in to the lead chemical space due to the lack of many properties. Introduction of novel, practical and efficient methods for the generation of more complex drug candidates involves the formation of new chemical bonds selectively and systematically. And more research should be done to improve the quality of drug molecular library as well as the screening collection. This is possible only through improvement of the quality of the building blocks (scaffolds) that are used to synthesize them\(^1\). Development of drug chemical space essentially needs the exploration of pharmacophores in various forms.

As aforementioned, privileged scaffolds are vital for the drug discovery process. In the previous chapters, we have concentrated our attention to develop the privileged scaffold coumarin in different ways. And we have developed a triazole ligated template containing pyridine and coumarin for the development of hybrid molecule\(^2\). As an extension of this work we thought of replacing coumarin by another pharmacophore and study its effect on the photophysical as well as biological properties. Among various pharmacophores, we selected furan because of its structural similarity to coumarin. Like coumarins, furan also contains a lactone ring system as a promising structural feature. Furan is a well-known structural unit capable to impart the
desired properties in functional materials\textsuperscript{3}. These are versatile building blocks for the development of various cyclic and acyclic compounds displaying diverse biological activities. Compounds bearing furanoid rings (Fig. 5.1) have been reported to have a broad spectrum of biological roles suggesting that the $\alpha,\beta$-unsaturated lactone is a promising pharmacophore for drug design\textsuperscript{4}. Furan moiety is reported to be a part of many drugs available in the market. For instance, Ranitidine (Zantac®, GSK) is a well-established furan derived antibiotic discovered in 1976 and commercialized by the early 1980’s\textsuperscript{5}. It act as H2-receptor antagonist and lowers stomach acid levels and therefore used to treat stomach ulcers. Another example of furan containing drug is nitrofurantoin which is an antibiotic used in the treatment of urinary tract infections\textsuperscript{6}. In addition to this, there are reports in the literature about the use of furan moiety in various biological activities such as antifungal, antiviral, antitumor, antibacterial, anti-inflammatory and antiglycemic activities etc\textsuperscript{7}.

Prompted by the above consideration, we thought of improving the drug-like molecular library by developing novel scaffolds with more effective drug-likeness character. For which, furan moiety is well suitable as an efficient pharmacophore and can be incorporated to the peptidic template with the pyridine functionality to form a linear peptidomimetic. For this class of compounds, we designed and synthesized a series of 3-substituted furan azides using alternative Mannich type reaction and used for clicking with pyridine alkynes to form a triazole derivative. The large dipole moment of the triazole moiety enables it to act as a hydrogen bond acceptor, which helps in improving the solubility\textsuperscript{8}. Therefore, combination of the novel properties of pyridine and furan pharmacophores ligated through triazole moiety offers a novel compound with improved activity.
5.2. Results and discussions

The study started with the synthesis of pyridine alkynes 4.1a and 4.1b as discussed in the previous chapter. For the azido part, we have used 2-acetyl-5-methyl furan. The bromoamido ketone derivatives of furan was synthesized using an alternative Mannich type four-component reaction of bromopropionitrile with different aromatic aldehydes and 2-acetyl-5-methyl furan in the presence of an acid chloride using BF₃·Et₂O as catalyst. The bromoamido ketones (5.1) were then converted to the azides (5.2) by treating with sodium azide under basic condition in DMF at room temperature to afford the products in good to excellent yield.

Using the CuAAC click chemistry, the azide and alkyne fragments were then assembled as shown in table 5.2. In a representative reaction, an equimolar mixture of 4.1a and 5.2a were
mixed with 0.2 equiv of CuSO₄ and 0.4 equiv of sodium ascorbate in a mixed solvent system containing tert-butanol, water, and DMSO (4:2:1) at room temperature (table 5.2). After 12 h, the reaction mixture was diluted with cold water to afford the triazole ligated pyridine-furan click product 5.3a (92% yield) in solid form.

5.2.1. Photophysical studies of the newly synthesized azides

Following the synthesis, we next moved on to the photophysical characterization of the synthesized products. The fluorescence study of alkynes 4.1a and 4.1b were the same as obtained in the previous chapter. In the case of azides (5.2 a-f), all of them absorbs in the range of 312-348 nm and the emission maxima were observed in the ranges 466-477. The Stokes shift values were obtained in the range from 121-161 nm. The maximum Stokes shift value (161 nm) is observed for compound 5.2a (Fig. 5.2) with absorption maximum at 316 nm and emission maximum at 477 nm.

![Normalized absorption and emission spectra of the azide 5.2a](image)

**Figure 5.2.** The normalized absorption and emission spectra of the azide 5.2a (Stokes shift value 161 nm) in DMSO at neutral pH.
Table 5.1. Synthesis of furan based azides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bromo derivative</th>
<th>Azide</th>
<th>Yield (%)</th>
<th>Absₘₓ / Emₘₓ (nm)</th>
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<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Bromo derivative 1" /></td>
<td><img src="image2" alt="Azide 1" /></td>
<td>92%</td>
<td>316/477</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Bromo derivative 2" /></td>
<td><img src="image4" alt="Azide 2" /></td>
<td>71%</td>
<td>348/475</td>
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<tr>
<td>3</td>
<td><img src="image5" alt="Bromo derivative 3" /></td>
<td><img src="image6" alt="Azide 3" /></td>
<td>83%</td>
<td>312/471</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Bromo derivative 4" /></td>
<td><img src="image8" alt="Azide 4" /></td>
<td>88%</td>
<td>318/473</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Bromo derivative 5" /></td>
<td><img src="image10" alt="Azide 5" /></td>
<td>85%</td>
<td>348/472</td>
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<tr>
<td>6</td>
<td><img src="image11" alt="Bromo derivative 6" /></td>
<td><img src="image12" alt="Azide 6" /></td>
<td>79%</td>
<td>345/466</td>
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Table 5.2: CuAAC reaction for the synthesis of click products

<table>
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<tr>
<th>Entry</th>
<th>Compound</th>
<th>Yield (%)</th>
<th>$\text{Abs}_{\text{max}}$ nm</th>
<th>$\text{Em}_{\text{max}}$ nm</th>
<th>Stokes shift nm</th>
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<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Compound 5.3a" /></td>
<td>91%</td>
<td>306</td>
<td>479</td>
<td>173</td>
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<tr>
<td>2</td>
<td><img src="image" alt="Compound 5.3b" /></td>
<td>88%</td>
<td>300</td>
<td>468</td>
<td>168</td>
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<tr>
<td>3</td>
<td><img src="image" alt="Compound 5.3c" /></td>
<td>72%</td>
<td>351</td>
<td>477</td>
<td>126</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Compound 5.3d" /></td>
<td>86%</td>
<td>349</td>
<td>474</td>
<td>125</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Compound 5.3e" /></td>
<td>78%</td>
<td>306</td>
<td>468</td>
<td>162</td>
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<tr>
<td>6</td>
<td><img src="image" alt="Compound 5.3f" /></td>
<td>83%</td>
<td>328</td>
<td>468</td>
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Table 5.2 continues...

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<th>Entry</th>
<th>Compound</th>
<th>Yield(%)</th>
<th>$\text{Abs}_{\text{max}}$ nm</th>
<th>$\text{Em}_{\text{max}}$ nm</th>
<th>Stokes shift nm</th>
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<tbody>
<tr>
<td>7</td>
<td>5.3g</td>
<td>96%</td>
<td>304</td>
<td>481</td>
<td>177</td>
</tr>
<tr>
<td>8</td>
<td>5.3h</td>
<td>86%</td>
<td>300</td>
<td>471</td>
<td>171</td>
</tr>
<tr>
<td>9</td>
<td>5.3i</td>
<td>71%</td>
<td>304</td>
<td>478</td>
<td>174</td>
</tr>
<tr>
<td>10</td>
<td>5.3j</td>
<td>89%</td>
<td>347</td>
<td>473</td>
<td>126</td>
</tr>
<tr>
<td>11</td>
<td>5.3k</td>
<td>81%</td>
<td>302</td>
<td>465</td>
<td>163</td>
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<tr>
<td>12</td>
<td>5.3l</td>
<td>85%</td>
<td>310</td>
<td>462</td>
<td>152</td>
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</table>
5.2.2. Photophysical studies of the pyridine-triazole-furan conjugates

In contrast to the previous case with coumarin moiety presented in chapter 4, were we have obtained a difference in absorption/emission properties depending upon the alkyne part; here in the case of furans, such specific distinctions were not observed. All the click products prepared by using the two different alkynes showed similar fluorescence behavior. All absorbed in the range of 300-350 nm corresponding to an emission maxima ranges from 470-481 nm with a Stokes shift maximum of 177 nm. But still, for similar patterns, slight substituent dependent photophysical properties were observed. For example, the compound 5.3a showed an emission maximum of 479 nm. The methoxy substituted version of this compound i.e.; 5.3g showed a red shift of 2 nm (481 nm). This pattern was seen in all the remaining combinations. As in the previous case, the highest emission maximum (481 nm) among the selected compounds was obtained for methoxy substituted version of 5.3a and was selected for further analysis. We took the peptidomimetic 5.3g as a representative one for studying the fluorescence behavior. 5.3g is a combination of alkyne 4.1b and azide 5.2a. In summary, in the case of furan also the general trend of exhibiting longer emission wavelength by alkynes, azides and the click peptidomimetics with strong electron donating substituents such as -OCH₃ as structural component existed.
5.3. Biological property evaluation

5.3.1. Primary evaluation of drug-likeness

The drug property descriptors of all the click products were calculated and are tabulated in table 5.3. Here, compared to the pyridine-triazole-coumarin conjugates, the logP values are below 5 except for two molecules and are drug-like according to Lipinski’s rule. The azides have logP values in the range from -4.10 to -2.57 with a molecular weight ranging from 357-415. All the click products have molecular weight from 738-826. As mentioned in the previous chapter, this library of molecules can also be categorized as beyond rule of 5 (bRo5) molecules since these have molecular weight exceeding 500 (MW> 500) and one or more properties deviating from eRo5. Hence these are also candidates which can address difficult to drug target classes.
Table 5.3. The Drug-likeness parameters of pyridine-triazole-furan Peptidomimetics

<table>
<thead>
<tr>
<th>Sl No.</th>
<th>Compound code</th>
<th>milogP</th>
<th>tPSA</th>
<th>MW</th>
<th>nON</th>
<th>nOHNH</th>
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<td>4.92</td>
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<td>738.83</td>
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<td>3</td>
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<tr>
<td>2</td>
<td>5.3b</td>
<td>4.01</td>
<td>221.30</td>
<td>796.87</td>
<td>15</td>
<td>3</td>
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<tr>
<td>3</td>
<td>5.3c</td>
<td>4.42</td>
<td>212.06</td>
<td>766.84</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>5.3d</td>
<td>5.54</td>
<td>185.76</td>
<td>743.25</td>
<td>12</td>
<td>3</td>
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<td>5.3e</td>
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<td>231.58</td>
<td>753.80</td>
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<td>3</td>
</tr>
<tr>
<td>6</td>
<td>5.3f</td>
<td>4.37</td>
<td>212.06</td>
<td>766.84</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>5.3g</td>
<td>4.51</td>
<td>204.23</td>
<td>768.86</td>
<td>14</td>
<td>3</td>
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<tr>
<td>8</td>
<td>5.3h</td>
<td>3.60</td>
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<td>3</td>
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<tr>
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<td>5.3i</td>
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<td>15</td>
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<td>3</td>
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<tr>
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<td>5.3l</td>
<td>3.96</td>
<td>221.30</td>
<td>796.87</td>
<td>15</td>
<td>3</td>
</tr>
</tbody>
</table>

5.3.2. The in vitro anti cancer evaluation of pyridine-triazole-furan conjugate

The anticancer property was studied against MCF-7 cell lines using 5.3g as a representative from the library.

5.3.2. (A): In vitro cytotoxicity of synthesized 5.3g

Cell viability was determined by MTT assay. MCF-7 cells were seeded in 96-well plates at a concentration of 1.0x10^4 cells/wells and incubated overnight at 37°C in a 5% CO₂ humidified environment. Then the cells were treated with different concentrations of the sample 5.3g like 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100 µM/mL (dissolved with RPMI medium 1640), respectively. Controls were cultivated under the same conditions without addition of 5.3g. The treated cells were incubated for 48 h for cytotoxicity analysis. The cells were then subjected for MTT assay. The stock concentration (5 mg/mL) of MTT was prepared and 100 µL of MTT was added in each wells and
incubated for 4 h. Purple colored formazan crystals were observed and these crystals were dissolved with 100 µL of dimethyl sulphoxide (DMSO), and read at 620 nm in a multi well ELISA plate reader (Thermo, Multiskan).

The concentration at which fifty percentage of cell death occurs was observed at 30 μM/mL concentration.

5.3.2. (B): Morphological observation

MCF-7 cells were grown (1×10^5 cells/cover slip) and incubated with 5.3g at their IC_{50} concentration and then they were fixed in methanol:acetic acid (3:1, v/v). The cover slips were gently mounted on glass slides for the morphometric analysis. Morphological changes of MCF-7 cells were analyzed under the Nikon (Japan) bright field inverted light microscopy at 40× magnification.

![Figure 5.4](image_url)

**Figure 5.4.** MTT assay results confirming the in vitro cytotoxicity effect of 5.3g against the MCF-7 cells. The detected IC_{50} concentration was 30 μM/mL.
5.3.2. (C): DAPI (4, 6-diamidino-2-phenylindole, dihydrochloride) staining

MCF-7 cells were treated with 5.3g at its IC50 concentration (30 µM/mL) for 48 h, and then fixed with methanol: acetic acid (3:1, v/v) prior to washing with PBS. The washed cells were then stained with 1 mg/mL DAPI (4,6-diamidino-2-phenylindole, dihydrochloride) for 20 min in the dark atmosphere. Stained images were recorded with fluorescent microscope with appropriate excitation filter. The bright filed and fluorescence microscopic images are shown in fig. 5.5. As shown in this the strong bluish fluorescence and cellular uptake observed in the imaging studies with 5.3g reveals that these molecules have high potency against breast cancer cell lines (MCF-7).

Figure 5.5. Bright field and fluorescence microscopy image of IC50 concentration of 5.3g treated on MCF-7 cells. The DAPI nuclear staining of control cells (d) and 5.3g treated cells (e & f) exhibited condensed form of nuclear materials in apoptotic cells which are indicated by arrows.
5.4. Structure elucidation by spectroscopy

5.4.1: Structure elucidation of 3-azido-N-(1-(4-methoxyphenyl)-3-(5-methylfuran-2-yl)-3-oxopropyl)propanamide 5.2a

For the general discussion, the compound 5.2a is taken as the representative for the azido derivative of furan \( \beta \)-amido ketones. The molecule is numbered as shown in Figure 5.6. The FT-IR spectrum of the compound 5.2a (Fig. 5.7) gives major absorptions at 3433, 2928, 2101, 1653, 1608, 1509, 1457, 1287, 1248, and 1176 cm\(^{-1}\). The \(-\text{NH}\) stretching vibration band of the acetamido group occurs at 3433 cm\(^{-1}\). The formation of azide is confirmed by the band at 2101 cm\(^{-1}\) which is the characteristic peak of the azide linked to the carbon at position 1. The peak at 1653 cm\(^{-1}\) corresponds to the amide I band, i.e., the band due to the C=O stretching vibration of (C2) and the amide II band which arises from the interaction between the N-H bending and the C-N stretching of the C-N-H group is obtained at 1608 cm\(^{-1}\).
The initial information obtained about the azide is further confirmed by the $^1$H NMR spectrum (Fig. 5.8). The singlet obtained at $\delta = 8.30$ is due to the amide bond (NH). The aromatic proton at position 15 of the furan ring appears as a doublet at 7.96-7.94. Another doublet at 6.0-5.96 corresponds to the neighboring proton at position 16. Other downfield resonances; a quartet at $\delta$ 7.65-7.60, a triplet at $\delta$ 7.53-7.49 corresponds to the remaining aromatic protons. The CH proton at position 5 is obtained as a triplet between $\delta$ 5.20-5.17. The CH$_2$ protons at position 12 were obtained as a doublet of doublet at $\delta$ 3.66-3.55 and 3.25-3.18 with approximately equal coupling constants. The singlet obtained at $\delta$ 2.55 is due to the three protons of the methyl group at position 18.
In the $^{13}$C NMR spectrum, the ketone carbonyl carbon C13 and the amide carbonyl C3 are observed at $\delta$ 202 and 172 respectively (Fig. 5.9). The peak appeared at $\delta$ 160 is due to the carbon C9. The furanyl carbons at C14 appeared at $\delta$ 155 and at C17 are obtained at $\delta$ 64. The signals at $\delta$ 140, 135, 131, 130, 128, 122 and 116 are due to the remaining aromatic carbons. The peak at $\delta$ 70.21 is due to the carbon at position 12. The methyl carbons at C19 and at C18 is appeared at $\delta$ 56 and at $\delta$ 15. The remaining three up field resonances i.e., at $\delta$ 51, 46, and 33 are attributed to C5, C1, and C2 respectively.
Figure 5.9. $^{13}$CNMR spectrum of the compound 5.2a

5.4.2: Structure elucidation of 3-((4-(2-amino-3, 5-dicyano-6-(phenylthio) pyridin-4-yl) phenoxy) methyl)-1H-1, 2, 3-triazol-1-yl)-N-(1-(4-methoxyphenyl)-3-(5-methylfuran-2-yl)-3-oxopropyl) propanamide 5.3g

For the structural elucidation of the click products, compound 5.4g is taken as a representative and is numbered as shown in figure 5.10. In the $^1$HNMR spectrum, the amide (-NH) proton at position 25
is observed as a doublet at $\delta = 8.60-8.58$. The aromatic peaks extend from 7.98-7.12. The peaks from 7.84 to 7.17 correspond to the 15 aromatic protons. Singlet obtained at $\delta = 7.66$ correspond to the triazole proton. The five aromatic protons cause the peaks from 7.60-7.51 as a multiplet. The peak at $\delta 5.73$ correspond to the two amino protons at position 1. The two groups of methoxy protons at positions C40 and C41 appeared as a singlet at $\delta 3.82$. The two protons at position 27 are at different environments and they appeared as a doublet of doublet between 3.76-3.72 and at 3.61-3.50 with approximately equal coupling constants. The two protons at position 22 were obtained at 4.90. The three protons of the methyl group appeared as a singlet at $\delta 2.59$.

![Figure 5.11. $^1$HNMR spectrum of the compound 5.3g](image)

Figure 5.11. $^1$HNMR spectrum of the compound 5.3g
In the $^{13}$C NMR spectrum (Fig. 5.12) the ketone carbonyl carbon at C$_{28}$, and the amide carbonyl at C$_{25}$, are observed at their characteristic regions, at δ 195 and 187 respectively. The amino carbonyl peak (C1) is observed at δ 172.73. The carbons at position C3 and C17 caused the values at δ 168, 166 respectively. The aromatic carbons gave the peaks at δ 159, 158, 158, 148, 148, 134, 130, 129, 129, 127, 126, 115, and 115. The nitrile carbon peaks (C$_{12}$ & C$_{13}$) appears at δ 113 and 112 respectively. The methyl carbon at C24 appears at δ 31. The peak at δ 93 and 86 is due to C4 & C2 respectively. The remaining up field signals at δ 78, 78, 55, 46 and 45 are credited to the carbons C$_{20}$, C$_{27}$, C$_{40}$, C$_{26}$, and C$_{23}$ respectively.

**Figure 5.12.** $^{13}$CNMR spectrum of the compound 5.3g
5.5. Conclusion

We have successfully replaced the relatively toxic coumarin pharmacophore with a furan moiety. The scaffolds thus obtained showed good photophysical as well as biological activities. In contrast to coumarin peptidomimetics, here, all the molecules showed similar emission values with slightly higher value with the methoxy substituted version of pyridine alkynes. However, the Stokes shift values as well as highest emission maxima are less than that of coumarin-triazole-pyridine conjugate. The representative molecule (5.3g) showed potent anti cancer activity against MCF-7 cells with an IC50 value of 30 µM/mL. Which shows that the furan tagged molecules are more efficient in anti cancer activity than the coumarin decorated one. Due to the polyfunctional nature of the final molecules, furan scaffolds seems to be good precursors for various lead molecules.

5.6. Experimental

5.6.1. Typical experimental procedure for the synthesis of 3-azido-N-(1-(4-methoxyphenyl)-3-(5-methylfuran-2-yl)-3-oxopropyl)propanamide 5.2a: A mixture of 4-methoxybenzaldehyde (134 mg, 1 mmol), 2-acetyl-5-methyl furan (356 mg, 1mmol), and 3-bromopropionitrile (133 mg, 1 mmol) in acetonitrile (8 ml) were stirred in the presence of catalytic amount of BF₃·Et₂O at room temperature for 4 h. After completion of the reaction as indicated by TLC, the reaction mixture was poured into ice cold water and extracted with CH₂Cl₂ (15 ml). Evaporation of the solvent followed by
purification on silica gel (100–200 mesh), ethyl acetate/hexane (3:1) afforded 3-bromo-N-(1-(4-methoxyphenyl)-3-(5-methylfuran-2-yl)-3-oxopropyl) propanamide **5.1a**. The resulted bromide (394 mg, 1 mmol), K$_2$CO$_3$ (414 mg, 3 mmol), NaN$_3$ (65 mg, 1 mmol) were dissolved in dimethylacetamide and stirred for 6–8 h. After completion, the reaction mixture was poured into ice cold water and the precipitate was filtered, dried under vacuum to afford the azide **5.2a**

5.6.2. **Typical experimental procedure for the synthesis of 3-(4-((2-amino-3,5-dicyano-6-(phenylthio)pyridin-4-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(1-(4-methoxyphenyl)-3-(5-methylfuran-2-yl)-3-oxopropyl)propanamide 5.3a:** An equimolar amount 2-amino-6-(phenylthio)-4-(4-(prop-2-yn-1-yloxy)phenyl) pyridine-3,5-dicarbonitrile **4.1a** (47.75 mg, 0.12 mmol) and the furan azide **5.2a** (52.5 mg, 0.12 mol) were dissolved in minimum amount of DMSO. To this, a solvent mixture contains 2 ml of t-BuOH, 1 ml of water, CuSO$_4$.5H$_2$O (200 mg) and sodium ascorbate (150 mg) was added and the mixture was stirred at room temperature for 12 h. and then poured in to cold water. The precipitated click product was filtered, washed with water and dried under vacuum to afford **5.3a** in pure form (180 mg, 92%).$^1$H-NMR(500 MHz, DMSO-$d_6$): 8.60-8.56 (1H, q), 7.98-7.97 (2H, d), 7.74 (1H, s), 7.66-7.60 (4H, m), 7.59-7.51(5H, m), 7.44-7.42 (1H, d, J= 8 Hz), 7.36-7.28 (2H, m), 7.24 (1H, s), 7.21-7.19 (1H, d, J= 12 Hz), 7.14-7.12 (1H, d, J= 8 Hz), 5.732 (1H, s), 4.90 (1H, s), 3.82 (2H, s), 5.19 (1H, s), 3.76-3.72 (1H, J= 5 Hz, J= 14 Hz, dd), 3.61-3.50 (1H, J = 6 Hz, J = 16 Hz , dd), 2.59-2.54 (1H, m); FT-IR (KBr)
ν\text{max}: 3434, 3230, 2922, 2213, 1723, 1673, 1625, 1607, 1546, 1508, 1455, 1263, 1181, 1022, 752 cm$^{-1}$

5.6.3. Spectral data of compounds

3-bromo-N-(1-(4-methoxyphenyl)-3-(5-methylfuran-2-yl)-3-oxopropyl)propanamide \textit{5.1a}: $^1$H NMR (500 MHz, DMSO-$d_6$): 2.54-2.50 (4H, d), 7.719 (1H, s), 3.53 (2H, s), 4.65 (1H, s), 4.90 (1H, s), 5.106 (1H, s), 5.44 (1H, s), 5.54 (1H, s), 7.17-7.16 (1H, d), 7.54-7.50 (1H, t), 7.60-7.58 (1H, t); FT-IR (KBr) ν\text{max} 3446, 1636, 1594, 1513, 1344, 1108 cm$^{-1}$

4-(1-(3-bromopropanamido)-3-(5-methylfuran-2-yl)-3-oxopropyl)-2-methoxyphenyl acetate \textit{5.1b} $^1$H NMR (500 MHz, DMSO-$d_6$): 2.44-2.40 (6H, s), 6.26 (2H, s), 6.408-6.38 (3H, d), 6.99 (1H, s), 7.11 (1H, s), 7.30-7.26 (2H, d), 7.44 (3H, s), 7.74-7.2 (d, 3H), 8.08 (s, 3H), 8.13 (s, 1H), 8.20-8.18 (5H, d), 8.31 (2H, s), 8.43 (1H, s),

4-(1-(3-bromopropanamido)-3-(5-methylfuran-2-yl)-3-oxopropyl)phenyl acetate \textit{5.1c} FT-IR (KBr) ν\text{max}: 3423, 2923, 2853, 1719, 1647, 1607, 1560, 1519, 1489, 1455, 1346, 1226, 1176, 1110, 1028, 856, 759 cm$^{-1}$

3-azido-N-(1-(4-methoxyphenyl)-3-(5-methylfuran-2-yl)-3-oxopropyl)propanamide \textit{5.2b} $^1$H NMR (500 MHz, DMSO-$d_6$): δ 1.315 (2H, s), 2.506 (2H, d), 3.51 (1H, s), 5.51 (2H, s), 5.91 (1H, s), 7.5-7.40 (1H, d), 7.29-7.25 (4H, d), 5.26 (3H, s), 7.59 (4H, s) 7.72 (3H, s), 7.84 (2H, s), 8.32 (2H, s); FT-IR (KBr) ν\text{max}: 3444,
2936, 2102, 1764, 1604, 1509, 1464, 1419, 1369, 1268, 1198 cm$^{-1}$

ESIMS: m/z. 438.0924 (M+Na), Exact mass: 414.1539.

4-(1-(3-azidopropanamido)-3-(5-methylfuran-2-yl)-3-oxopropyl)phenyl acetate 5.2c: $^1$H NMR (500 MHz, DMSO-$d_6$): 7.60 (1H, s), 7.55 (1H, s), 7.53 (1H, s), 7.51 (1H, s), 7.18-7.16 (1H, d, J= 8 Hz), 4.91 (1H, s), 3.61 (1H, s), 3.17 (1H, s), 2.55 (1H, s); FT-IR (KBr) $\nu_{max}$: 3444, 2102, 1752, 1656, 1508, 1438, 1369, 1199 cm$^{-1}$

3-azido-N-(1-(4-chlorophenyl)-3-(5-methylfuran-2-yl)-3-oxopropyl)propanamide 5.2d: $^1$H NMR (500 MHz, DMSO-$d_6$): 7.71 (s,1H), 7.59 (s,1H), 7.50 (d,2H), 7.23-7.18 ( t, 2H), 7.13-7.11 (d,1H), 4.89 (s,2H), 4.30 (s,1H), 3.81 (s,3H), 2.55-2.50 (d,2H), 1.11 (s, 3H); $^{13}$CNMR(100MHz, DMSO-$d_6$): 166.1, 159.6, 158.7, 158.1, 134.7, 130.1, 129.6, 129.4, 127.1, 126.4, 115.4, 114.8, 93.4, 86.7, 78.5, 55.5; FT-IR (KBr) $\nu_{max}$: 3434, 2921.63, 2101, 1636, 1448, 1205, 1024 cm$^{-1}$

4-(1-(3-(4-(2-amino-3,5-dicyano-6-(phenylthio)pyridin-4-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)propanamido)-3-(5-methylfuran-2-yl)-3-oxopropyl)-2-methoxyphenyl acetate 5.3b: $^1$H NMR (500 MHz, DMSO-$d_6$): 7.70-7.50(1H, t), 7.45 (1H, s), 7.44 (2H, s), 7.39-7.35 (3H, d), 7.34 (2H, s), 7.26-7.2 (5H, m), 7.12 (3H, s), 6.96 (1H, s), 6.07 (1H, s), 5.52 (3H, s), 5.45-5.41 (3H, d), 5.38 (2H, s), 5.34-5.10 (2H, m), 4.94-4.73 (3H, t), 4.63-4.60 (2H, d), 3.81-3.6 (2H, m), 2.50 (2H, s), 1.22-1.16 (6H, s); FT-IR (KBr) $\nu_{max}$: 3468, 3351, 3293, 3222, 2923, 2853, 2212, 1725, 1697, 1608, 1578, 1547, 1508, 11474, 1455, 1263, 1233, 11848, 1023, 755 cm$^{-1}$
4-((1-(3-(4-((4-(2-amino-3,5-dicyano-6-(phenylthio)pyridin-4-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)propanamido)-3-(5-methylfuran-2-yl)-3-oxopropyl)phenyl acetate 5.3c: $^1$H NMR (500 MHz, DMSO-$d_6$): 3.81 (3H, s), 3.70 (1H, s), 2.50 (2H, s), 7.52 (2H, s), 7.48-7.41 (2H, m), 7.27-7.25 (1H, d), 7.03-7.01 (2H, d), 6.87-6.86 (3H, d), 8.60 (1H, s), 7.93-7.92 (1H, d), 7.74-7.71 (3H, t); FT-IR (KBr) $\nu_{\text{max}}$: 3458, 3346, 3254, 2923, 2215, 1724, 1625, 1607, 1546, 1509, 1455, 1253, 1142, 1019, 755 cm$^{-1}$; ESI-MS: m/z. 787.1661 (M+Na), Exact mass: 764.8662.

3-((4-((4-(2-amino-3,5-dicyano-6-(phenylthio)pyridin-4-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-(5-methylfuran-2-yl)-1-(3-nitrophenyl)-3-oxopropyl)propanamide 5.3e: $^1$H NMR (500 MHz, DMSO-$d_6$): 7.83-7.81(1H, d), 7.52-7.49 (1H, t), 7.40-7.37 (4H, t), 7.67-7.65 (2H, d), 5.48-5.44 (1H, m), 3.69-3.65 (1H, dd, J= 8 Hz, J= 16 Hz), 3.37-3.33 (1H, dd, J= 8 Hz, J= 16 Hz), 1.96 (2H, s), 1.50 (3H, s), 1.20-1.18 (2H, dd, J= 8 Hz); FT-IR (KBr) $\nu_{\text{max}}$: 3447, 2923, 2853, 2104, 1719, 1653, 1608, 1560, 1513, 1490, 1456, 1375, 1221, 1172, 1108, 1019, 757 cm$^{-1}$.

4-((1-(3-((4-(2-amino-3,5-dicyano-6-(phenylthio)pyridin-4-yl)-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)propanamido)-3-(5-methylfuran-2-yl)-3-oxopropyl)-2-methoxyphenyl acetate 5.3h: FT-IR (KBr) $\nu_{\text{max}}$: 3469, 3352, 3293, 3223, 2922, 2852, 2212.92, 1725, 1629, 1609, 1549, 1508, 1455, 1376, 1264, 1234, 1120, 1022, 825 cm$^{-1}$; ESI-MS: m/z. 848.2509 (M+Na), Exact mass: 825.8756.
4-(1-(3-(4-((4-(2-amino-3,5-dicyano-6-(phenylthio)pyridin-4-yl)-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)propanamido)-3-(5-methylfuran-2-yl)-3-oxopropyl)phenyl acetate 5.3i: $^1$H NMR (500 MHz, DMSO-$d_6$): 7.83-7.82 (d, 1H), 7.50-7.47 (t, 1H), 7.38-7.35 (t, 1H), 7.28-7.26 (d, 1H), 7.16-7.08 (m, 2H), 6.87-6.86 (d, 1H), 5.76-5.73 (m, 1H), 3.71-3.67 (dd, 1H), 3.42-3.37 (1H, dd, J= 8 Hz, J= 16 Hz), 1.49 (s, 3H), 1.19 (s, 1H); FT-IR (KBr) $\nu_{\text{max}}$: 3459, 3346, 3254, 3221, 3075, 2960, 2923, 2852, 2215, 2127, 1725, 1625, 1546, 1509, 1455, 1425, 1371, 1322, 1258, 1219, 1142, 1020, 755 cm$^{-1}$

3-(4-((4-(2-amino-3,5-dicyano-6-(phenylthio)pyridin-4-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-(5-methylfuran-2-yl)-1-(3-nitrophenyl)-3-oxopropyl)propanamide 5.3k: FT-IR (KBr) $\nu_{\text{max}}$: 3425, 3352, 3227, 3218, 2923.56, 2212, 1724, 1627, 1607, 15791, 1548, 1509 1455, 1291, 1250, 1181, 1119, 1024, 755 cm$^{-1}$; ESIMS: m/z. 801.2373 (M+Na), Exact mass: 778.8159.

2-(1-(3-(4-((4-(2-amino-3,5-dicyano-6-(phenylthio)pyridin-4-yl)-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)propanamido)-3-(5-methylfuran-2-yl)-3-oxopropyl)phenyl acetate 5.3l: FT-IR (KBr) $\nu_{\text{max}}$: 3458, 3346, 3254, 3221, 3076, 2960, 2923, 2852, 2215, 2127, 1725, 1625, 1607, 1546, 1509, 1455, 1424, 1371, 1305, 1253, 1142, 1021, 755 cm$^{-1}$
References


Supplementary material

Copies of $^1$H NMR, $^{13}$C NMR, FT-IR and Mass spectra of selected compounds.
FT-IR spectrum of the compound 5.1a

$^{1}$HNMR spectrum of the compound 5.1a
FT-IR spectrum of the compound 5.1b

\[
\text{\textsuperscript{1}HNMR spectrum of the compound 5.1b}
\]
FT-IR spectrum of the compound 5.1c

FT-IR spectrum of the compound 5.2b
$^1$HNMR spectrum of the compound 5.2b

Mass spectrum of the compound 5.2b
FT-IR spectrum of the compound 5.2c

\[ \text{FT-IR spectrum of the compound 5.2c} \]

\[ \text{HNMR spectrum of the compound 5.2c} \]

\[ \text{HNMR spectrum of the compound 5.2c} \]
FT-IR spectrum of the compound 5.2d

\[ \text{FT-IR spectrum of the compound 5.2d} \]

\[ \text{HNMR spectrum of the compound 5.2d} \]
$^{13}$CNMR spectrum of the compound 5.2d

FT-IR spectrum of the compound 5.3a
$^1$HNMR spectrum of the compound 5.3a

FT-IR spectrum of the compound 5.3b
$^1$HNMR spectrum of the compound 5.3b

FT-IR spectrum of the compound 5.3c
\(^1\)HNMR spectrum of the compound 5.3c

Mass spectrum of the compound 5.3c
FT-IR spectrum of the compound 5.3e

¹HNMR spectrum of the compound 5.3e
FT-IR spectrum of the compound 5.3h

Mass spectrum of the compound 5.3h
FT-IR spectrum of the compound 5.3i

\[ \text{HNMR spectrum of the compound 5.3i} \]
FT-IR spectrum of the compound 5.3k

Mass spectrum of the compound 5.3k
FT-IR spectrum of the compound 5.3l