CHAPTER III

Copper (II) Phthalocyanine Catalyzed One Pot MCR Synthesis of Alkyne Functionalized Mannich-Type Small Peptides

3.1 Introduction

β-amido or amino ketones are important class of small peptide-like molecules and these structural units are found in a wide range of medicinally relevant compounds. They are important building blocks for the synthesis of β-amino acids, β-lactams and β-amino alcohols and also they are the structural scaffolds found in natural nucleoside peptide antibiotics such as nikkomycins or neopolyoxins. In addition to this, amido ketones can be easily converted to the corresponding chiral amines by amide hydrolysis. The possibility for the formation of a stable adduct between electrophilic oxo group and nucleophilic residues (OH, SH) at the active site of enzymes along with the H bonding properties of amino group make β-amino/amido ketones as excellent substrates for the development of enzyme inhibitors. Chiral amino functionality is found in several pharmaceutically important compounds with varying chemotherapeutic properties (figure 3.1).

![Figure 3.1 Chiral amine based pharmaceutical drugs](image-url)
A widely accepted method for the synthesis of amino alcohols, amino ketones or chiral amines is the use of ketonic substrates and the asymmetric addition of hydrogen or hydride ion during the key stereo defining step. Scheme 3.1 represents a three step synthesis of amido compounds from ketonic substrates.

Scheme 3.1 Conventional three step synthesis of amino compounds from substrates

First step of this process is the oxime formation which is high yielding\(^5\) but the second step, radical rearrangement of the in situ formed O-acetylated oxime to an N-acetylenamide requires excess Fe in the presence of acetic anhydride at elevated temperature and provides poor to mediocre yields (30-69%).\(^6\) But alternative methods such as toluene reflux of the oxime with approximately equal molar quantities of acetic anhydride and Et\(_3\)P, and oxime conversion to N-acetylenamides using Rh/H\(_2\) and Ac\(_2\)O proved useful for the large scale production of enamides.\(^7\) For example, using this method, an advanced Zoloft-related enamide 3.11 (figure 3.2) was synthesised and enantioselectively hydrogenated at 75 kg scale.

Figure 3.2 Zoloft/Sertraline, chiral amine based pharmaceutical for depression

Despite the usefulness of this method for the synthesis of many of such compounds, the development of a more step economic protocol with high degree of chemo, regio and stereo control is still remains as an intellectual
challenge. The main reason for this is the difficulty in introducing nitrogen in a commodity chemical or in an advanced intermediate via robust methods. A recent addition in the search for the step economic synthesis of amido/amino ketones or alcohols is the development of a one pot multicomponent reaction (MCR) between a non-enolizable aldehyde, an enolizable ketone and acetonitrile in the presence of acetyl chloride (Scheme 3.2) leading to the stereoselective formation of $N$-substituted $\beta$-amino ketone derivatives that are easily convertible to the corresponding keto amines by amide hydrolysis.

Scheme 3.2 Lewis acid catalyzed stereoselective one step multicomponent synthesis of $\beta$-acetamido ketones useful as intermediates for chiral amines

The beauty of this method is the easiness in synthesising large number of highly functionalized amines or its derivatives that are otherwise difficult to access by conventional methods. Several improvements were reported over the years based on the attempts to improve the yield and stereo selectivity of the final product.

Consequently, a variety of new catalysts have been reported which includes cyanuric chloride, iodine, BiCl$_3$, metal bisulphates, CeCl$_3$·7H$_2$O, iron (III) chloride, SnCl$_2$·2H$_2$O, polyaniline-supported acid, silica sulphuric acid, zeolite H$\beta$, ZrOCl$_2$·8H$_2$O, ZnO nanoparticles, sulfamic acid, metal triflates, heteropoly acids, copper(II)tetrafluoroborate, ZnO, and SiCl$_4$-ZnCl$_2$. Many of these catalysts suffer serious drawback of poor stereoselectivity and are useful only for the synthesis of simple $\beta$-acetamido ketones. Very little attention has so far been given to the expansion of the substrate scope or the follow-up chemistry with $\beta$-amido ketones for developing highly functionalized structural scaffolds.

Although these catalysts are efficient for the synthesis of $\beta$-amido ketones, they are not applicable in some aspects, for example the difficulty in attain stereocontrol. Many processes require harsh reaction conditions such as
high temperature, long reaction time and inert atmosphere. Moreover, some of these protocols need column chromatography for the product purification. Hence, it is proposed to look into the possibility of developing a new catalytic protocol to afford high stereoselectivity, functional group tolerance, reusability of catalyst, substrate scope and product diversity.

In nature, the biological catalysts, more particularly porphyrins such as cytochromes, are responsible for catalyzing oxidation-reduction processes and electron transfer reactions on which all forms of life are dependent. These enzymes are tailored towards a specific substrate and work with high levels of stereo-, regio- and chemoselectivity. However, high price, stability and bulk availability issues limit their practical utility. Phtalocyanines (Pcs) have structural similarity with porphyrins and are very stable \( \pi \)-conjugated macrocyclic compounds that can form complexes with almost all metals and offer a high architectural flexibility in structure.\(^{32}\) Due to their greater stability than porphyrins, metal phthalocyanines (MPcs) (figure 3.3) attracted great attention for their applications as catalysts for homogenous and heterogeneous chemical reactions. The central metal ions in these chemical species can coordinate substrates at the axial positions, opening a route to design of new selective electrodes especially for applications in electro catalytic determination of compounds with biological importance.\(^{33}\)

![Figure 3.3 Metallophthalocyanine](image)

Metallophthalocyanines pay attention in synthetic organic chemistry as excellent catalysts due to their complex structure. Cobalt phthalocyanine (CoPc) was reported to be the first alternative fuel-cell cathode catalyst to the noble metals in the seminal work by Jasinski.\(^{33, 34}\) The origin of catalytic activity was reported to be arises from the binding ability of its cobalt centre towards oxygen.\(^{35, 36, 37}\) Similarly manganese and iron phthalocyanines have
been reported to catalyze a 4-electron reduction of O\textsubscript{2} to produce water.\textsuperscript{38} Chauhan et al. have utilized CoPc for the selective reduction of flavones and isoflavones with sodium borohydride as reducing agent.\textsuperscript{40} Similarly, Jain \textit{et al.} have reported the use of MPcs in the aziridination of olefins.\textsuperscript{39, 40} Recently Kumar \textit{et al.} have studied the catalytic activity of Cobalt (II)phthalocyanine for the reductive amination of carbonyl compounds.\textsuperscript{41} Kumar \textit{et al.} employed phthalocyanine complexes of Fe, Co, Cu and Zn for chemo- and regio-selective reduction of nitroarenes to corresponding amines tolerating a large range of reducible functional groups such as acid, amide, ester, halogen, lactone, nitrile, N-benzyl, O-benzyl, hydroxy and heterocycles.\textsuperscript{42} These astonishing catalytic activity of metallophthalocyanine is likely due to the increased electron withdrawing nature of phthalocyanine ligands ,which results in a more electrophilic metal centre . Other examples of catalytic applications of MPcs include AlPc catalyzed cyanosilylation of aldehydes and ketones \textsuperscript{43} and PdPc catalyzed Suzuki and Heck coupling reactions.\textsuperscript{44}

Based on these reports, we decided to explore the utility of various metallophthalocyanines for the synthesis of alkyne functionalized amido ketones as structural scaffolds.

3.2 Results and Discussion

3.2a Determination of optimum catalyst concentration and reaction conditions for the synthesis of β- amido ketones.

The studies were initiated by screening different metallophthalocyanines for its efficiency in the synthesis of β-acetamido ketones. Copper (II) phthalocyanine (CuPc), zinc phthalocyanine (ZnPc) and aluminium phthalocyanine chloride (AlPcCl) were systematically screened in various concentration and conditions. In a typical experiment, synthesis of the β-acetamido ketone derivative \textbf{3b.1} (Table 3.1) was carried out by heating para propargylated benzaldehyde, acetophenone and acetyl chloride with catalytic amount of CuPc in acetonitrile at 70°C. The progress of the reaction was monitored by TLC analysis. The reaction was found to complete in 3.5 h and analytically pure \textbf{3b.1} was obtained by aqueous work up of the reaction mixture after the removal of the catalyst. The structure of the product was
confirmed by \textsuperscript{1}H NMR, \textsuperscript{13}C NMR, FT-IR and mass spectral analysis. As shown in Table 3.1, CuPc was found to be slightly more efficient than other MPcs and 3 mol\% of catalyst was found to be enough for the completion of reaction. We have also carried out the reactions at room temperature, but the yield obtained was significantly low. Control reactions were done in the absence of catalyst at conditions described for the reactions in the presence of catalyst. No product formation was observed in the absence of catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst (mol %)</th>
<th>time (h)</th>
<th>Yield (%)\textsuperscript{a} at 70 °C</th>
<th>Yield (%)\textsuperscript{a} at rt</th>
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<tr>
<td>1</td>
<td>ZnPc</td>
<td>10</td>
<td>6.0</td>
<td>62</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>AlPcCl</td>
<td>10</td>
<td>6.0</td>
<td>63</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>CuPc</td>
<td>10</td>
<td>6.0</td>
<td>69</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>CuPc</td>
<td>7</td>
<td>6.0</td>
<td>70</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>CuPc</td>
<td>3</td>
<td>6.0</td>
<td>70</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>CuPc</td>
<td>3</td>
<td>3.5</td>
<td>70</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>CuPc</td>
<td>3</td>
<td>16.0</td>
<td>70</td>
<td>6</td>
</tr>
<tr>
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<td>-</td>
<td>16.0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\textsuperscript{a}) Based on the weight of the isolated pure products.

### 3.2b Synthesis of N-substituted alkyne functionalized amido carbonyl compounds.

We then turned our attention towards the synthesis of alkyne functionalized amido ketones. A two-step strategy was designed for this purpose. In the initial step, we have synthesized certain propargylated aldehydes and ketones (Scheme 3.3) and the propargylated fragments were then introduced in the β-amido ketones by following a MPC catalyzed
procedure. The typical procedure for the synthesis of propargylated aldehydes and ketones involves the stirring of an equivalent amount of 4-hydroxybenzaldehyde in DMF with 3 equivalents of K$_2$CO$_3$ in 50°C for 0.5h, after cooling the reaction mixture to room temperature an equivalent amount of propargyl bromide was added, and the reaction mixture was stirred in room temperature for 4h. After completion of the reaction, the mixture was poured into ice cold water and the resulting propargylated aldehyde was filtered washed and dried (Scheme 3.3.). The reaction was clean and high yielding (>90%). Similar procedure was followed for the conversion of 2-hydroxy aldehyde and 2- & 4-hydroxy ketones to their corresponding aromatic propargylated ketones. The newly synthesized propargylated aldehydes and ketones are used as such in the synthesis of amido ketones.

Scheme 3.3 Synthesis of alkyne functionalized aldehydes and Ketones

The β-acetamidoketones with alkyne functionalities were synthesized by a one-pot three component reaction between the propargylated aldehyde and an enolizable propargylated or nonpropargylated ketone in acetonitrile in the presence of acetyl chloride and catalytic amount of CuPc at 70°C. Refluxing of acetophenone, para propargylated benzaldehyde and acetyl chloride with catalytic amount of CuPc in acetonitrile gave N-(3-oxo-3-phenyl-1-(4-(prop-2-ynyloxy)phenyl)propyl)acetamide 3b.1 (Scheme 3.4) as a white solid. The β-acetamido ketone derivative was characterized by $^1$H NMR, $^{13}$C NMR, FT-IR and MS.
Good results obtained in our initial studies with CuPc prompted us to examine the scope of CuPc assisted reactions with different substituted aldehydes, ketones and nitrile component. As shown in table 3.2, a series of substituted aldehydes and ketones were screened under identical condition and all the reactions resulted in the formation of the desired product in good to excellent yield. The product formation was accelerated slightly by the introduction of electron-withdrawing group like bromine at the ortho position of the aldehyde compared to unsubstituted compound \(3b.5\) (Table 3.2). Also product formation was accelerated slightly by the introduction of electron-withdrawing group like chlorine or bromine at the para-position of the enolisable ketones compared to the corresponding compound prepared using acetophenone as enolizable ketone \(3b.1\) (Table 3.2). Eventhough the yield of the compounds prepared using ortho-propargylated aldehydes are comparatively less than the same obtained from para-propargylated aldehydes, their yield was increased by the introduction of electron-withdrawing group like chlorine at the para position of the ketone (Table 3.2).

We have also examined the reaction with bromopropionitrile as the nitrile source, and the reaction resulted in the formation of \(\beta\)-bromopropionamido ketones with moderate yield (Scheme 3.5 and Table 3.2). The yield of compounds \(3b.11\) and \(3b.12\) are less compared to the products obtained using acetonitrile as the nitrile component (Table 3.2). In general electron deficient substrates were reacted faster than electron rich substrates. Thus an array of 12 Männich type alkyne functionalized small peptides were synthesized (Table 3.3).
**Scheme 3.5** CuPc catalysed synthesis of $\beta$-bromopropionamido alkynes

**Table 3.2** List of amido ketone alkynes prepared for the triazole ligation studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction components</th>
<th>Amido ketones</th>
<th>% yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldehyde</td>
<td>Ketone</td>
<td>Nitrile</td>
<td>3b.1</td>
</tr>
<tr>
<td>1</td>
<td>CHO</td>
<td>O</td>
<td>CN</td>
</tr>
<tr>
<td>2</td>
<td>CHO</td>
<td>O</td>
<td>CN</td>
</tr>
<tr>
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<td>CHO</td>
<td>O</td>
<td>CN</td>
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<tr>
<td>4</td>
<td>CHO</td>
<td>O</td>
<td>CN</td>
</tr>
<tr>
<td>5</td>
<td>CHO</td>
<td>O</td>
<td>CN</td>
</tr>
</tbody>
</table>

$^a$Isolated yield
Table 3.2 Continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction components</th>
<th>2-amido ketones</th>
<th>% yielda</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aldehyde</td>
<td>Ketone</td>
<td>Nitrile</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>7</td>
<td>8</td>
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<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

aIsolated yield

3.2c Recyclability of the catalyst

The recyclability of the catalyst was examined by performing the reactions with recovered catalyst. For this, the catalyst recovered from the
reaction mixture was purified by repeated washing with acetone and subjected to vacuum drying in an air oven at 80°C for 2h. The performance of the purified catalyst was examined by conducting the reactions up to 5 cycles (Table 3.4). The recovered catalyst was found to be effective for converting the substrates to products. All the reactions yielded almost same amount of the product.

Table 3.4 Result of the recycling reactions with CuPc

3.2d Structure elucidation by Spectroscopy

Structure identification of β-acetamido carbonyl derivatives:

![Figure 3.5.](image)

For the general discussion, the compound 3b.1 taken as the representative example of the β-acetamidoketone alkyne prepared from propargylated aldehydes and acetophenone. The molecule is numbered as shown in figure 3.5. The FT-IR spectrum of the compound gave major absorption at 3264.9, 3084.6, 2128.1, 1677.8, 1637.3 and 1558.2 cm⁻¹.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b.1</td>
<td>N-(3-oxo-3-phenyl-1-(4-(prop-2ynyloxy)phenyl)propyl)acetamide</td>
<td>88</td>
</tr>
<tr>
<td>3b.2</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>3b.3</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>3b.4</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>3b.5</td>
<td>91</td>
<td></td>
</tr>
</tbody>
</table>

1 cycle
The band observed at 3264.9 cm$^{-1}$ due to NH stretching vibration. The amide band, i.e., band due to the C=O stretching vibration occurs at 1637.3 cm$^{-1}$ and the amide 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 1558.2 cm$^{-1}$. The absorption at 1677.8 cm$^{-1}$ is due to the keto carbonyl group.

**Figure 3.6** IR spectrum of compound 3b.1

**Figure 3.7** $^1$H NMR spectrum of compound 3b.1
The $^1$H NMR spectrum of 3b.1 is given in figure 3.7. In the $^1$H NMR, the downfield signals from $\delta$ 7.95-6.89 are due to the aromatic protons of the two benzene rings and the -NH proton comes at $\delta$ 8.27-8.25. The two protons on C5 are in different chemical environments due to the presence of the adjacent chiral carbon C4. In the $^1$H NMR spectrum, these two proton signals are observed between $\delta$ 3.49-3.47. The CH proton at position C4 is observed as multiplet between $\delta$ 5.34-5.29. The methyl proton on C1 is observed at $\delta$ 1.77 and the protons at C20 are observed at $\delta$ 4.75 & 3.53 respectively.

![Figure 3.8 $^{13}$C NMR spectrum of compound 3b.1](image)

The $^{13}$C NMR spectrum of 3b.1 is given in figure 3.8. The ketonic carbon at C6 and the amide carbon at C2 are observed at their characteristic regions in the $^{13}$C NMR spectrum, i.e., at $\delta$ 197.2 and 168.2 respectively. The signals at $\delta$ 138.8, 136.6, 135.7, 133.2, 128.7, 127.9, 127.8, and 114.5 are due to the aromatic carbons. The other up field resonances observed at, $\delta$ 48.4 & 22.6 are due to C4 & C1 respectively and the peaks at $\delta$ 79.3 & 78.1 are due to C21 & C22 and the peaks at $\delta$ 57.7 and 55.3 are due to C20 & C5 respectively.
The structure was further confirmed by mass spectral analysis. The mass spectrum of \textbf{3b.1} is given in figure 3.9, which shows molecular ion peak at m/z 322.2, which is well in agreement with the calculated values.

Spectroscopic characterisation of bipropargylated $\beta$-acetamidoketones:

![Mass spectrum of compound 3b.1](image)

**Figure 3.9** Mass spectrum of compound 3b.1

For the general discussion of bipropargylated $\beta$-acetamido ketones, the compound \textbf{3b.8} is taken as the representative one. The molecule is numbered as shown in figure 3.10. The FT-IR spectrum of the compound gave major
absorption at 3322.8, 3302.5, 3271.6, 3073.9, 2924.5, 2122.3, 1664.3, 1637.3, 1603.5, 1551.5, and 1024.7 cm\(^{-1}\).

**Figure 3.11** IR spectrum of compound 3b.8

The bands at 3271.6 cm\(^{-1}\), 3322.8 cm\(^{-1}\) are due to NH and \(\equiv \) stretching vibration. The amide band, i.e. band due to the C=O stretching vibration occurs at 1637.3 cm\(^{-1}\) and the amide 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 1551.5 cm\(^{-1}\). The absorption at 1664.3 cm\(^{-1}\) is due to the keto carbonyl group.

**Figure 3.12** \(^1\)H NMR spectrum of compound 3b.8
The $^1$H NMR spectrum of 3b.8 is given in figure 3.12. In the $^1$H NMR, the downfield signals from $\delta$ 7.95-6.84 are due to the aromatic protons of the two benzene rings and the NH proton comes at $\delta$ 8.24-8.22. The two protons on C5 are in different chemical environments due to the presence of the adjacent chiral carbon C4. In the $^1$H NMR spectrum, these two proton signals are observed between $\delta$ 3.62-3.52. The CH proton on C5 carbon is observed as multiplet between $\delta$ 5.33-5.27. The methyl proton on C1 is observed at $\delta$ 1.77 and the protons at C13 and C20 are observed at $\delta$ 4.91-4.75.

![Figure 3.13 13C NMR spectrum of compound 3b.8](image)

The structure of 3b.8 was further confirmed by $^{13}$C NMR spectrum (figure 3.13). The ketonic carbon at C6 and the amide carbon at C2 are observed at their characteristic regions in the $^{13}$C NMR spectrum, i.e., at $\delta$ 195.9 and 156.0 respectively. The signals at $\delta$ 114.4-130.2 are due to the aromatic carbons. The other up field resonances at $\delta$ 64.0, 55.6, 55.2, 44.2, and 22.6 are due to C5, C13, C20, C4 and C1 respectively and the peaks at 78.1-79.3 are due to C14, C15, C21 and C22.
3.2e Mechanistic interpretation for the CuPc catalyzed multicomponent synthesis of β-amido ketones:

A catalytic cycle that accounts the stereoselective product formation is given in scheme 3.6. The Lewis acid catalysis by the copper ion of the metallophthalocyanine initiates the reaction by the formation of a copper enolate a of the ketonic substrate. The addition of aldehyde moiety to a followed by the acylation with acid chloride in the subsequent steps forms the β-acyloxy ketone intermediate b. The acyloxy group of b then replaced by more nuleophilic nitrogen of the nitrile to form a stable cation intermediate c. This intermediate on further reaction with water or other reactive intermediates like HOCl formed during the reaction may lead to the formation of β-amido ketone derivative 1. The observed diastereoselectivity may be due to the blocking of the attack of the incoming aldehyde carbocation moiety from the more hindered face by the bulky metal binding isoindol units of CuPc and closes the catalytic cycle with enhanced formation of the anti-diastereomer.

Scheme 3.6 The possible catalytic cycle for the CuPc assisted synthesis of β-amido ketone derivatives
3.3 Conclusion

In summary, we have developed a metallophthalocyanines mediated one pot stereoselective process for the synthesis of a wide array of alkyne functionalised Mannich type $\beta$-amido ketone derivatives using a regenerable and recyclable metallophthalocyanine. The process has following merits:

- Efficiency of the catalyst: Copper phthalocyanine (CuPc) is the more efficient catalyst compared to other metallophthalocyanines (ZnPc, AlPcCl) for the synthesis of $\beta$-amido ketone derivatives.

- Yield of the products: Excellent yield was observed for all the newly synthesized $\beta$-acetamido ketone derivatives using CuPc catalyst, in a very short reaction time.

- Recyclability of the catalyst: The catalyst, CuPc was recovered and reused for several times, by simple filtration and washing with the solvent. Therefore the synthesis of $\beta$-amido ketone derivatives was an inexpensive and a clean process.

3.4 Experimental:

3.4.1 Materials and methods.

The catalyst CuPc was procured from Sigma-Aldrich Chemicals Pvt. Ltd. (India). All solvents and reagents were procured from Aldrich chemical company, Fluka, or Merck and are used without any further purification. Fourier transform infrared (FT-IR) spectra were recorded on a Jasco FTIR-1400 spectrometer. The $^1$H and $^{13}$C nuclear magnetic resonance (NMR) spectra operating at the frequencies of 400 and 100 MHz respectively were measured with Varian NMR (VNMRS-400) spectrometer and the $^1$H and $^{13}$C nuclear magnetic resonance (NMR) spectra operating at the frequencies of 300 and 75 MHz respectively were measured with Bruker ACF 300 MHz spectrometer in dimethylsulphoxide-$d_6$ (DMSO-$d_6$) or CDCl$_3$. The $^1$H-NMR chemical shifts are reported in parts per million (ppm) relative to TMS as internal standard ($\delta = 0$ ppm). Mass (FAB) spectra were recorded on a JEOL JMS600H spectrometer. The coupling constants are reported in hertz (Hz).
Reactions were monitored by thin-layer chromatography (TLC) using plates prepared with Merck silica gel G. Column chromatography was performed on Merck silica (100 to 200 Mesh). Stereochemistry of the compounds were assigned by comparing the coupling constant (J value) of the methane proton with reported data.

3.4.2 Typical Experimental Procedure for the Synthesis of alkyne 3b.2

To a stirred suspension of CuPc (3 mol% by unit of aldehyde) in acetonitrile (5 ml), an equi-molar amount of propargylated benzaldehyde (1.44g, 0.01mol) and 4-chloro-acetophenone (1.55g, 0.01mol) were taken in an RB flask. To this, dry acetyl chloride (4 ml) was added and the mixture was stirred at room temperature for 4 h. After completion of the reaction (monitored by TLC), the mixture was poured into water and stirred well. The precipitate obtained was washed with distilled water and dried under vacuum. Final washings with petroleum ether (2×20 ml) afforded the alkyne 3b.1 (3g, 90%).

3.4.3 Spectral datas

N-(3-oxo-3-phenyl-1-(4-(prop-2-yn-1-yloxy)phenyl)propyl)acetamide (3b.1): FT-IR, KBr, γmax: 3264.9, 3084.6, 2128.1, 1677.8, 1637.3, 1558.2, 1514.8, 1448.3, 1361.5, 1292.1, 1288.1, 1195.7, 1100.2, 1025.9, 889.9, 824.4, 754.9; ¹H NMR (400 MHz, DMSO-d₆): δ 8.26-8.24 (d, J=8.0 Hz, 1H), 7.95-7.93 (d, J=7.2 Hz, 2H), 7.65-7.61 (t, 1H), 7.53-7.51 (d, J=7.6 Hz, 2H), 7.28-7.26 (d, J=8.4 Hz, 2H), 6.92-6.90 (d, J=8.4 Hz, 2H), 5.34-5.29 (m, 1H), 4.75 (s, 2H), 3.53 (s, 1H), 3.49-3.47 (d, J=8 Hz, 2H), 1.77 (s, 3H); ¹³C NMR (100MHz, DMSO-d₆): δ 197.2, 168.2, 156.0, 138.8, 136.6, 135.7, 133.2, 128.7, 127.9, 927.8, 114.5, 79.3, 78.1, 64.0, 63.9, 57.7, 55.3, 48.4, 44.6, 40.1, 22.6; MS: m/z Calcd for C₂₀H₁₉NO₃, 321.37; Found, 322.2.

N-(3-(4-chlorophenyl)-3-oxo-1-(4-(prop-2-yn-1-yloxy)phenyl)propyl)acetamide (3b.2): FT-IR, KBr, γmax: 3289.0, 3263.9, 3081.7, 2965.9, 2130.9, 1682.5, 1644.9, 1612.2, 1588.1, 1558.2, 1512.8, 1488.7, 1455.9, 1414.5, 1372.1, 1288.2, 1117.5, 1091.5, 1021.1, 990.3, 834.9, 826.6, 772.4, 738.6, 682.7, 643.1, 616.1, 556.4; ¹H NMR (400MHz, DMSO-d₆): δ 8.25-8.23 (d, J=8.0 Hz, 1H), 7.97-7.95 (d, J=8.8 Hz, 2H), 7.59-7.57 (d, J=8.8 Hz, 2H), 7.28-7.26 (d, J=8.4 Hz, 2H), 6.92-6.90 (d, J=8.8 Hz,
2H), 5.32-5.26 (q, 1H), 4.76-4.75 (m, 2H), 3.53 (s, 1H), 3.49-3.38 (m, 2H), 1.76 (s, 3H); $^{13}$C NMR (100MHz, DMSO-d$_6$): $\delta$ 196.3, 168.2, 156.1, 138.1, 138.5, 135.2, 129.9, 128.8, 127.8, 114.5, 79.3, 78.1, 63.9, 57.7, 55.3, 22.6; MS: m/z Calcd for C$_{20}$H$_{18}$ClNO$_3$, 355.81; Found, 356.0.

N-(3-(4-bromophenyl)-3-oxo-1-(4-(prop-2-ynyloxy)phenyl)propyl)acetamide (3b.3): FT-IR, KBr, $\gamma$max: 3271.6, 3062.4, 2119.4, 1671.0, 1641.9, 1604.5, 1577.4, 1544.7, 1417.4, 1372.1, 1300.8, 1223.6, 1180.2, 1011.5, 818.6; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 8.26-8.24 (d, 1H), 7.88-6.50 (m, 8H), 5.27-5.28 (m, 1H), 4.75 (s, 2H), 3.53 (s, 1H), 2.55-2.45 (m, 2H), 1.76 (s, 3H); $^{13}$C NMR (100MHz, DMSO-d$_6$): $\delta$ 206.47, 196.29, 168.19, 156.06, 138.09, 135.50, 135.22, 129.93, 128.78, 127.76, 114.52, 78.34, 78.11, 55.29, 48.33, 44.59, 30.66, 22.60; MS: m/z Calcd for C$_{20}$H$_{18}$BrNO$_3$, 400.27; Found, 399.90.

N-(1-(2-bromophenyl)-3-oxo-3-(4-(prop-2-yn-1-ynyloxy)phenyl)propyl)acetamide (3b.4): FT-IR, KBr, $\gamma$max: 3285.1, 3082.6, 2132.0, 1679.9, 1644.9, 1602.6, 1556.3, 1509.0, 1372.1, 1301.7, 1261.2, 1233.3, 1173.5, 1023.1, 825.4, 758.9; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 8.37-8.35 (d, J=7.2 Hz, 1H), 7.99-7.97 (d, J=8.8 Hz, 2H), 7.56-7.57 (d, J=8.0 Hz, 1H), 7.47-7.45 (d, J=8.0 Hz, 1H), 7.40-7.36 (t, 1H), 7.21-7.17 (t, 1H), 7.09-7.07 (d, J=7.2 Hz, 2H), 5.64-5.59 (m, 1H), 4.91-4.90 (m, 2H), 3.62 (s, 1H), 3.45-3.16 (m, 2H), 1.79 (s, 3H); $^{13}$C NMR (100MHz, DMSO-d$_6$): $\delta$ 194.8, 168.4, 161.0, 142.2, 132.6, 130.3, 129.9, 128.8, 127.9, 127.7, 122.2, 114.7, 78.7, 63.9, 63.9, 63.9, 55.7, 48.7, 42.1, 22.5. MS: m/z Calcd for C$_{20}$H$_{18}$BrNO$_3$, 400.27; Found, 401.90.

N-(3-oxo-1-phenyl-3-(4-(prop-2-yn-1-ynyloxy)phenyl)propyl) acetamide (3b.5): FT-IR, KBr, $\gamma$max: 3279.4, 3083.6, 2134.8, 1682.6, 1644.0, 1601.5, 1566.9, 1508.1, 1374.9, 1302.7, 1255.4, 1227.5, 1172.5, 1032.7, 992.2, 828.3, 751.4, 698.1; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 8.30-8.28 (d, J=8.0 Hz, 1H), 7.95-7.93 (d, J=8.8 Hz, 2H), 7.34-7.28 (m, 4H), 7.22-7.19 (t, 1H), 7.09-7.06 (d, J=8.8 Hz, 2H), 5.36-5.34 (m, 1H), 4.91-4.90 (m, 2H), 3.62 (s, 1H), 3.50-3.35 (m, 2H), 1.78 (s, 3H); $^{13}$C NMR (100MHz, DMSO-d$_6$): $\delta$ 195.5, 168.3, 160.9, 143.0, 130.2, 130.1, 128.2, 126.8, 126.6, 114.7, 78.7, 64.0, 63.9, 55.7, 49.0, 44.2, 22.6. MS: m/z Calcd for C$_{20}$H$_{19}$NO$_3$, 321.37; Found, 322.0.
N-(1-(naphthalen-1-yl)3-oxo-3-(4-prop-2-yn-1-yloxy)propyl)acetamide (3b.6): FT-IR, KBr, γmax: 3309.2, 3068.1, 2920.6, 2124.2, 1671.0, 1643.1, 1688.0, 1576.5, 1542.8, 1508.1, 1419.4, 1370.1, 1265.1, 1183.1, 1180.7, 1022.1, 801.3, 778.1; 1H NMR (400 MHz, DMSO-d6): δ 8.43-8.41 (d, J=8.0 Hz, 1H), 8.10-8.07 (d, J=8.4 Hz, 2H), 7.99-7.93 (m, 3H), 7.84-7.82 (d, J=8.4 Hz, 2H), 7.59-7.46 (m, 4H), 6.22-6.16 (m, 1H), 4.91 (s, 2H), 3.63-3.57 (m, 2H), 3.49-3.44 (m, 1H), 1.80 (s, 3H); 13C NMR (100MHz, DMSO-d6): δ 168.3, 138.5, 130.3, 128.7, 125.6, 122.9, 114.7, 78.7, 55.7, 44.9, 22.6. MS: m/z Calcd for C24H21NO3, 371.43; Found, 372.20.

N-(1-(4-bromophenyl)-3-oxo-3(4-(prop-2-yn-1-yloxy)phenyl)propyl)acetamide (3b.7): FT-IR, KBr, γmax: 3271.6, 3062.4, 2119.4, 1671.0, 1641.9, 1604.5, 1577.4, 1544.7, 1417.4, 1372.1, 1300.8, 1223.6, 1180.2, 1011.5, 818.6; 1H NMR (400 MHz, DMSO-d6): δ 8.38-8.36 (d, 1H), 7.58-7.07 (m, 8H), 5.64-5.59 (m, 1H), 4.90 (s, 2H), 3.61-3.47 (m, 1H), 3.20-2.49 (m, 2H), 1.79 (s, 3H); 13C NMR (100MHz, DMSO-d6): δ 195.2, 168.4, 161.0, 142.6, 131.0, 130.2, 130.0, 128.9, 119.8, 114.7, 78.7, 55.6, 48.5, 43.9, 22.6. MS: m/z Calcd for C20H18BrNO3, 400.27; Found, 401.90.

N-(3-oxo-1,3(4-(prop-2-yn-1-yloxy)phenyl)propyl)acetamide (3b.8): FT-IR, KBr, γmax: 3322.8, 3302.5, 3271.6, 3073.9, 2924.5, 2122.3, 1664.3, 1637.3, 1603.5, 1576.5, 1551.5, 1500.0, 1454.1, 1424.2, 1373.1, 1264.1, 1229.4, 1162.2, 1117.6, 1024.7, 1008.3, 834.6; 1H NMR (400 MHz, DMSO-d6): δ 8.24-8.22 (d, J=8 Hz, 1H), 7.95-7.93 (d, J=8.8 Hz, 2H), 7.27-7.25 (d, J=8.8 Hz, 2H), 7.08-7.06 (d, J=9.2 Hz, 2H), 6.92-6.89 (d, J=8.8 Hz, 2H), 5.33-5.27 (m, 1H), 4.90 (s, 2H), 4.75 (s, 2H), 3.61 (s, 1H), 3.53 (s, 1H), 3.47-3.41 (m, 2H), 1.77 (s, 3H); 13C NMR (100MHz, DMSO-d6): δ 195.6, 168.2, 156.0, 130.2, 130.1, 127.8, 114.7, 114.5, 79.4, 78.7, 78.1, 64.1, 55.7, 55.3, 44.2, 22.6.

N-(3-oxo-3-phenyl-1-(2-(prop-2ynyloxy) phenyl)propyl)acetamide (2b.9): FT-IR, KBr, γmax: 3293.8, 3246.5, 2115.5, 1667.4, 1646.9, 1551.4, 1024.9, 752.1. 1H NMR (400 MHz, DMSO-d6): δ 8.27-8.25 (d, 1H), 8.00-6.94 (m, 9H), 5.67-5.61 (m, 1H), 4.85-4.82 (d, 2H), 3.62-3.60 (s, 1H), 2.53-2.45 (m, 1H), 1.815 (s, 3H); 13C NMR (100MHz, DMSO-d6): δ 197.2, 168.3, 153.9,
N-(3-(4-chlorophenyl)-3-oxo-1-(2-(prop-2-ynyloxy) phenyl) propyl) acetamide (2b.10): FT-IR, KBr, \( \gamma \)max: 3203.8, 3080.7, 1684.5, 1650.7, 1556.2, 1494.5, 1240, 1095.3, 818.6, 753; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \( \delta \) 8.28-8.27 (d, 1H), 8.01-6.94 (m,8H), 5.60 (m, 1H), 4.87-4.86 (m, 2H), 3.63-3.62 (m, 2H), 2.50 (s, 1H), 1.78 (s, 3H); \(^{13}\)C NMR (100MHz, DMSO-d\(_6\)): \( \delta \) 196.3, 168.3, 153.8, 138.1, 135.0, 131.1, 19.9, 128.8, 127.9, 126.5, 121.1, 112.2, 79.3, 78.2, 55.7, 44.3, 44.2, 30.6, 22.6; MS: m/z Calcd for C\(_{20}\)H\(_{18}\)ClNO\(_3\), 355.8; Found, 356.0.

3-bromo-N-(3-oxo-3-phenyl-1-(2-(prop-2-ynyloxy) phenyl) propyl) propanamide (2b.12): FT-IR, KBr, \( \gamma \)max: 3292.8, 3235.0, 3097.1, 2921.6, 2109.7, 1685.4, 1647.8, 1563.0, 1487.8, 1213.9, 1028.8, 752.1; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \( \delta \) 8.44-8.42 (d, 1H), 7.99-6.94 (m, 9H), 5.69-5.65 (m, 1H), 4.87-4.86 (d, 2H), 3.72-3.45 (m, 2H), 2.49 (s, 1H), 2.07 (s, 3H); \(^{13}\)C NMR (100MHz, DMSO-d\(_6\)): \( \delta \) 197.1, 168.3, 153.9, 136.3, 133.2, 131.0, 130.9, 128.7, 128.7, 128.0, 128.0, 127.9, 126.5, 121.0, 112.2, 79.3, 78.2, 55.7, 44.6, 44.0, 30.7, 29.3; MS: m/z Calcd for C\(_{20}\)H\(_{18}\)ClNO\(_3\), 414.2; Found, 414.0.
References


3b.