

# Synthesis of novel $\beta$ -lactams and *in vitro* evaluation against the human malaria parasite *Plasmodium falciparum*

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## Abstract

The use of three-component four-center Ugi reactions to afford the synthesis of novel  $\beta$ -lactams is described. Three series of compounds have been made using this reaction in combination with the Mannich reaction. All compounds formed are racemic mixtures and were tested against the chloroquine sensitive D10 strain of *Plasmodium falciparum* in an *in vitro* assay. All compounds showed low to moderate microMolar range activity with the most active compounds 2.6 and 3.1 showing IC<sub>50</sub> values 16  $\mu$ M and 15  $\mu$ M respectively

**Keywords:** Ugi reaction, Mannich reaction,  $\beta$ -lactam, antiplasmodial

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## Introduction

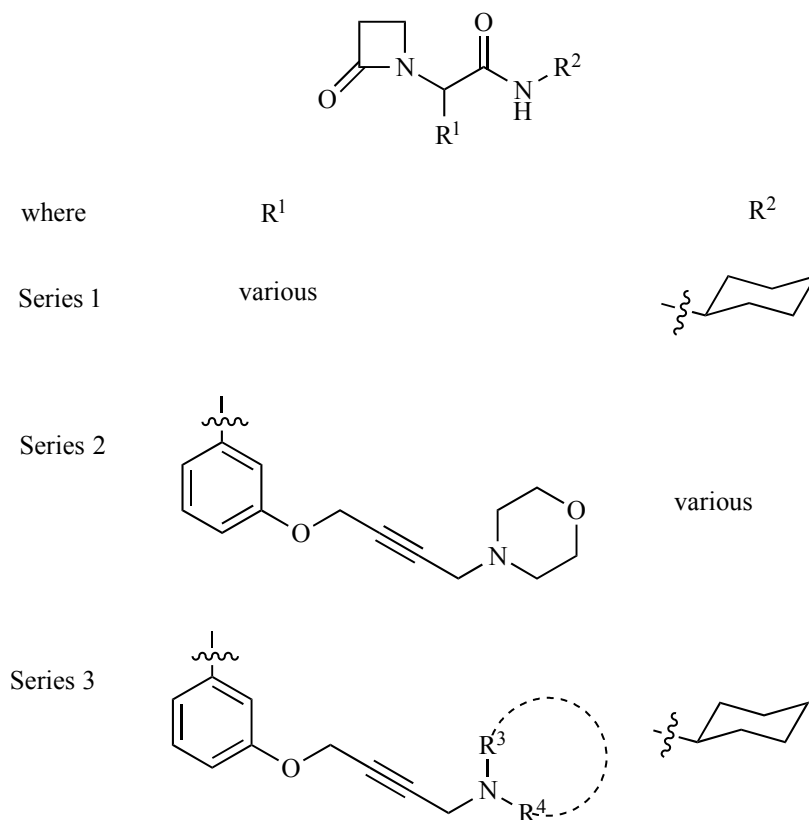
Malaria continues to be a major blight with almost half the world's population at risk.<sup>1</sup> Whilst the disease is currently primarily endemic in Third World countries, the socio-economic impact of this disease is felt worldwide. Each year an approximated 5% of the world's population succumbs to infection by parasites of the genus *Plasmodium*. The level of drug resistance continues to rise. Most recently the emergence of resistance to artemisinin based therapies is of grave concern.<sup>2</sup> The result is an urgent need for new pharmacophores to bypass these resistance mechanisms. Modern medicinal chemistry research is driven by the need to identify, develop and optimise lead compounds in the most cost-effective and efficient way possible. The use of multicomponent reactions (MCRs) which utilise at least three different starting materials in a

one-pot synthesis is an important synthetic strategy in this environment.<sup>3</sup> MCRs give rise to a wide variety of structural diversity via simple methodology.<sup>4</sup>

Ever since the structure of penicillin was elucidated, the  $\beta$ -lactam moiety has been of interest.<sup>5</sup> In recent years there has been an increasing focus on  $\beta$ -lactams and their application to a wide variety of infectious diseases.<sup>6</sup> The exploration of the application of  $\beta$ -lactams in the treatment of malaria is an area of serious research interest. The fact that  $\beta$ -lactams are easily accessed via a three-component four-centre (3C-4CR) Ugi type reaction makes this class of compounds attractive.<sup>4</sup>

We have therefore synthesised a series of  $\beta$ -lactams, using a 3C-4CR protocol, from commercially available starting materials in order to lay a foundation of structure-activity information which will allow a more focused second phase of synthesis and biological evaluation. We report herein, the synthesis and antiplasmodial activity of these  $\beta$ -lactams.

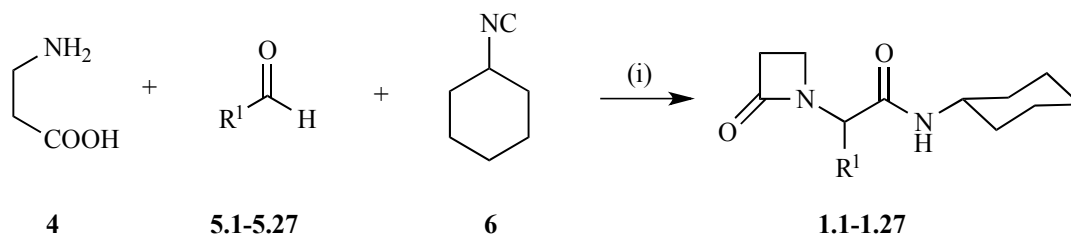
Three series of novel  $\beta$ -lactams have been synthesised and general structures are shown in Figure 1. Series 1:  $R^2$  was a cyclohexyl group and  $R^1$  was varied. In most cases  $R^1$  was a substituted phenyl ring, but there are some exceptions. Series 2:  $R^1$  was kept constant and the starting isocyanide was varied. Series 3:  $R^1$  was varied at the terminal tertiary amine and  $R^2$  was again a cyclohexyl group. The basic backbone formed from the Ugi reaction was preserved.



**Figure 1.** General structure of the three series of novel  $\beta$ -lactams synthesised.

## Results and Discussion

Series 1 was synthesized from  $\beta$ -alanine, cyclohexyl isocyanide and the chosen aldehyde, Scheme 1. Reactions were carried out in methanol at 25 °C. The reaction time varied from 48-72 hours and good yields were obtained. Reactions were carried out in a small volume of solvent in order to maximize yields and minimize reaction times. The use of low molecular weight alcohols or aprotic polar solvents has been shown to be advantageous in Ugi methodology hence the choice of methanol as the solvent.<sup>7</sup> Pirrung and Das Sarma noted that biphasic systems using aqueous media accelerate this type of reactions.<sup>8</sup> This was attempted, but we found that the convenience of removal of the methanol and immediate addition to the silica gel column for purification outweighed any advantage to the use of a biphasic system.

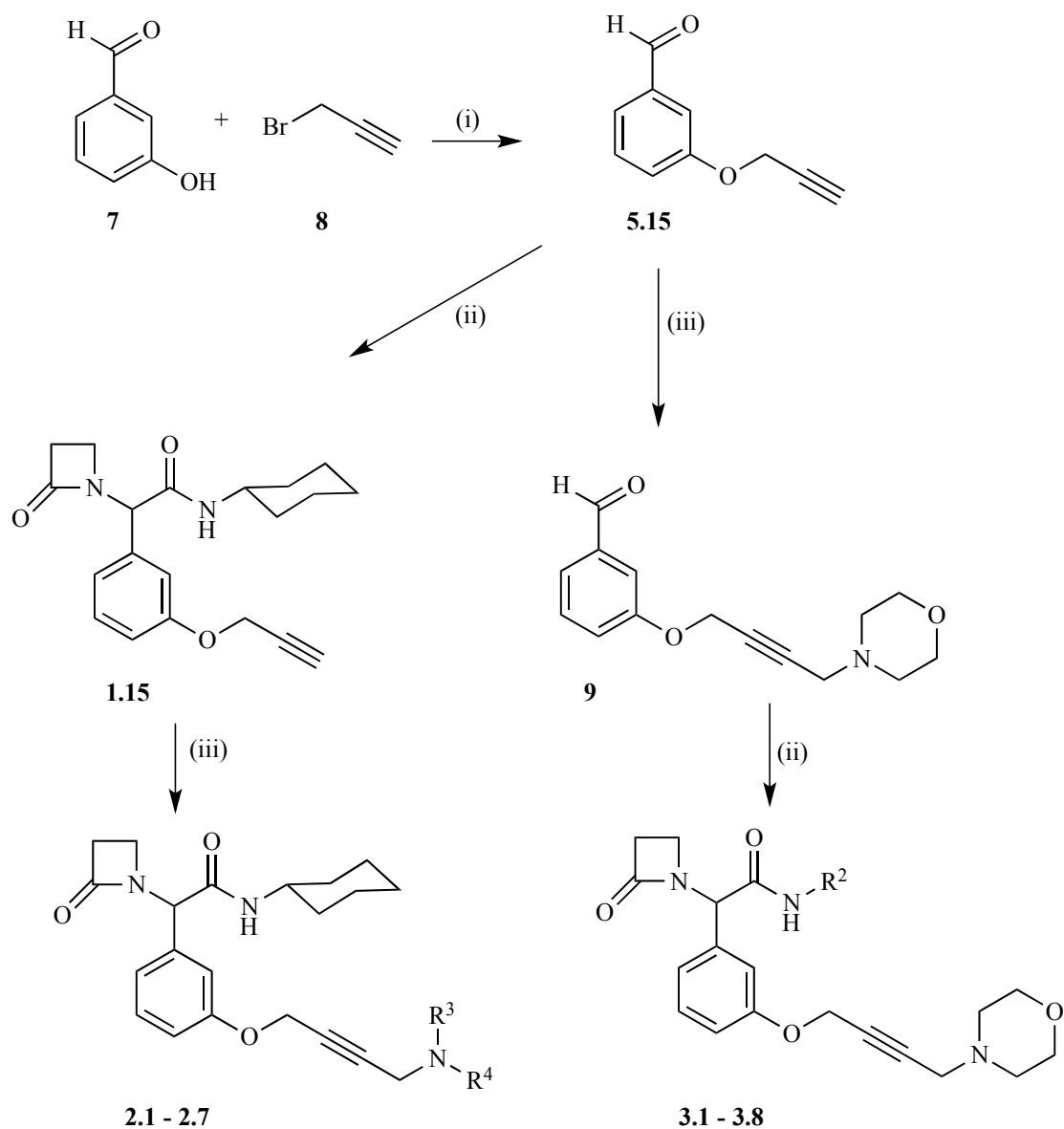


**Scheme 1.** Synthesis of series 1 via the Ugi reaction (i) methanol, 25 °C, 48 – 72 h.

Series 2 and 3 (compounds 2.1 – 2.7 and 3.1 – 3.8 respectively) were synthesised from 3-(prop-2-ynoxy)benzaldehyde 5.15. This was prepared from 3-hydroxybenzaldehyde, 7, and propargyl bromide 6 following the procedure described by Pitlik and Townsend.<sup>9</sup> Propargyl bromide was added dropwise to a mixture of the benzaldehyde in anhydrous DMF at 25 °C and potassium carbonate was used as the base. The reaction was stirred for 18 hours and gave the product in excellent yield.

In series 2, compounds 2.1 – 2.7, cyclohexyl isocyanide was used throughout the series, so the Ugi reaction to form the  $\beta$ -lactam was performed first using the same conditions described for series 1. Thus  $\beta$ -alanine 4, cyclohexyl isocyanide 6 and 3-(prop-2-ynoxy)benzaldehyde 5.15 were mixed together in methanol at room temperature and allowed to stir for 48 – 72 hours. Compound 1.15 was isolated as a white crystalline solid in 81% yield after purification by column chromatography.

Compound 1.15 was then used as a reagent in the Mannich reaction. The terminal acetylene 1.15 was reacted with aqueous formaldehyde, and a series of different amines (1.2 eq) in the presence of a catalytic amount of copper(I) iodide in DMSO. The reaction was allowed to stir at 25 °C for 2 hours before the reaction was quenched with aqueous base. Compounds 2.1 – 2.7 were isolated in good to excellent yields.



**Scheme 2.** Synthesis of series **2** and **3** via Ugi and Mannich reactions (i)  $\text{K}_2\text{CO}_3$ , anhydrous DMF, 25 °C, 18 h; (ii) methanol, 25 °C, 48 – 72 h; (iii) aqueous formaldehyde, Cu(I) iodide, DMSO, 25 °C, 2 h.

The synthetic strategy was reversed in pursuit of series **3** where the Mannich reaction was performed using 3-(prop-2-ynoxy)benzaldehyde **5.15**, morpholine and aqueous formaldehyde to form compound **9**. Compound **9** was then reacted with β-alanine and a series of isocyanides to give compounds **3.1** – **3.9** in good to excellent yields.

All compounds in series **1**, **2** and **3** were isolated as racemic mixtures. The chiral carbon is adjacent to the β-lactam ring. The final products were all characterized fully. Several definitive elements of characterization were identified. As a result of the presence of chiral carbon atom, in

the  $^1\text{H}$  NMR spectra, the four protons on the  $\beta$ -lactam ring give rise to two doublet of triplets (at approximately 3.6 and 3.1 ppm) and two doublet of doublet of doublets (at approximately 2.9 and 2.8 ppm). These signals act as a fingerprint for the desired product. The presence of the carbonyl carbons is clear in both the  $^{13}\text{C}$  NMR spectra and in the IR spectra lending further support to the formation of the desired product. All characterisation data is consistent with the given structures proposed including high resolution mass spectrometry and elemental analysis. No attempt was made to separate the two enantiomers and all testing and characterisation was carried out on the racemic mixtures.

A number of the newly synthesised  $\beta$ -lactams showed moderate activity against the chloroquine sensitive D10 of *P. falciparum*, Table 1. The compounds in series **2** and **3** were generally more active than the compounds of series **1**.

**Table 1.** Results of *in vitro* testing against CQ sensitive D10 of *P. falciparum*

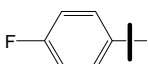

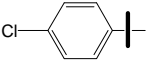

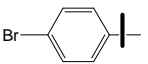

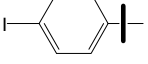

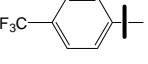

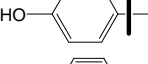

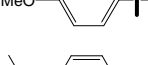
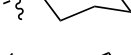
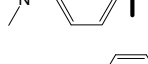

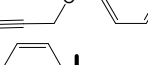

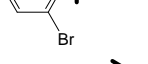

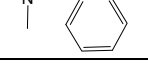
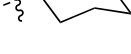
| Cpd No <sup>a</sup> | R <sup>1</sup>  | R <sup>2</sup>  | IC <sub>50</sub> $\mu\text{M}$<br>D10 |
|---------------------|---|---|---------------------------------------|
| CQ                  | -   | -   | 0.032                                 |
| <b>1.1</b>          |   |    | 281                                   |
| <b>1.2</b>          |  |  | 35                                    |
| <b>1.3</b>          |  |  | 58                                    |
| <b>1.4</b>          |  |  | 187                                   |
| <b>1.5</b>          |  |  | 80                                    |
| <b>1.6</b>          |  |  | >331                                  |
| <b>1.7</b>          |  |  | >316                                  |
| <b>1.8</b>          |  |  | 246                                   |
| <b>1.9</b>          |  |  | >294                                  |
| <b>1.10</b>         |  |  | >274                                  |
| <b>1.11</b>         |  |  | 251                                   |

Table 1. Continues

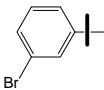

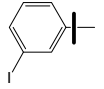

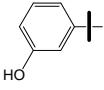

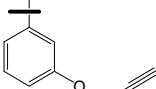

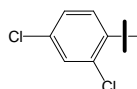

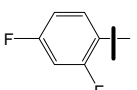

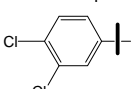

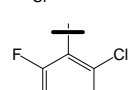

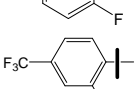

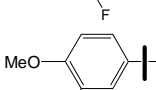
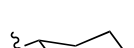
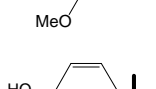

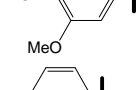

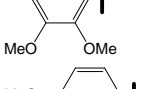

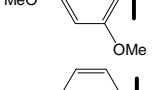

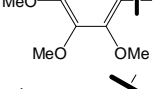

| Cpd Noa | R1  | R2  | IC50 $\mu$ M<br>D10 |
|---------|---|---|---------------------|
| 1.12    |    |    | 200                 |
| 1.13    |    |    | >243                |
| 1.14    |    |    | >331                |
| 1.15    |    |    | 48                  |
| 1.16    |    |    | 192                 |
| 1.17    |    |    | 143                 |
| 1.18    |   |    | 88                  |
| 1.19    |  |  | 27                  |
| 1.20    |  |  | 174                 |
| 1.21    |  |  | >289                |
| 1.22    |  |  | >301                |
| 1.23    |  |  | >289                |
| 1.24    |  |  | >289                |
| 1.25    |  |  | >266                |
| 1.26    |  |  | >254                |

Table 1. Continues

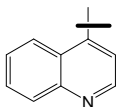

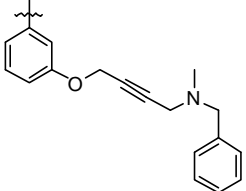

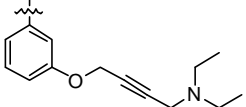

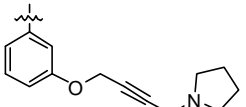
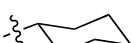
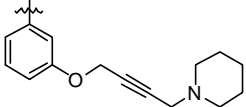

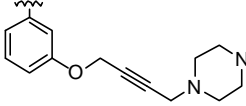

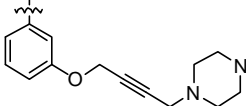

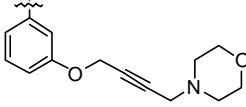

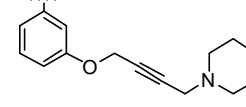
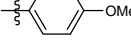
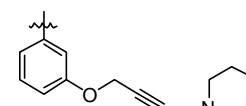

| Cpd Noa | R1  | R2  | IC50 $\mu$ M<br>D10 |
|---------|---|---|---------------------|
| 1.27    |    |    | 235                 |
| 2.1     |    |    | 16                  |
| 2.2     |    |    | 40                  |
| 2.3     |    |    | 65                  |
| 2.4     |   |   | 26                  |
| 2.5     |  |  | 28                  |
| 2.6     |  |  | 28                  |
| 2.7     |  |  | 81                  |
| 3.1     |  |  | 82                  |
| 3.2     |  |  | 57                  |

Table 1. Continues

| Cpd Noa | R1 | R2 | IC <sub>50</sub> μM<br>D10 |
|---------|----|----|----------------------------|
| 3.3     |    |    | 104                        |
| 3.4     |    |    | 38                         |
| 3.5     |    |    | 29                         |
| 3.6     |    |    | 73                         |
| 3.7     |    |    | 15                         |

## Conclusions

In series 1, compounds **1.19** (IC<sub>50</sub> 27 μM), **1.2** (IC<sub>50</sub> 35 μM) and **1.15** (IC<sub>50</sub> 48 μM) were the most efficacious. The data shows that, in general, for series 1, the presence of an electron-withdrawing group on the aromatic group results in compounds that are more active than those which have an electron-donating group. Clearly the pattern of activity is complex, but it is generally true that those compounds with an electron-withdrawing group in the *para* position are more active than those bearing electron-withdrawing groups at other positions. When there are several substituents on the aromatic ring no clear pattern is evident. It was also evident that hydroxyl and methoxy substitution had a detrimental impact on efficacy regardless of position on the phenyl ring.

Compound **1.15** which had shown relatively good efficacy against the D10 strain of *P. falciparum* was selected as the basis for the series 2 and 3. In series 2 there is a smaller variation in efficacy relative to series 1. The nature of the terminal amine group is significant. The



methylbenzyl terminal amine present in **2.1** ( $IC_{50}$  15.7  $\mu$ M) shows greatest efficacy, whilst the morpholine group shows least efficacy. In series **3**, the variation of  $R^2$  had some observable impact on the efficacy against the D10 strain. The most active was the benzotriazole compound, **3.7** and the least efficacious was the compound bearing the monobranched alkyl side-chain, **3.3**.

The addition of a terminal amine group appears to have the overall effect of improving efficacy. However, the efficacy achieved by this class of compounds is moderate at best. Once the target of these molecules has been elucidated, further modification using rational design may prove useful.

## Experimental Section

**General.** All chemicals were used as supplied by Aldrich.  $^1H$  and  $^{13}C$  spectra were recorded at room temperature on Varian EM 400 or 300 MHz spectrometers. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT IR spectrometer. Melting points were performed on a Kofler hot stage microscope (Reichert Thermovar). Elemental analyses were performed using a Carlo Erba EA1108 elemental analyser in the microanalytical laboratory of the University of Cape Town.

Compounds were tested in duplicate on one occasion against chloroquine sensitive (CQS) strain of *Plasmodium falciparum* (D10). Continuous in vitro cultures of asexual erythrocyte stages of *P. falciparum* were maintained using the modified method of Trager and Jensen.<sup>10</sup> Quantitative assessment of antiplasmodial activity in vitro was determined via the parasite lactate dehydrogenase assay using the modified method described by Makler.<sup>11</sup> The samples were prepared to a 2 mg/mL stock solution in 10% DMSO or 10% methanol and were sonicated to enhance solubility. Samples were tested as a suspension if not completely dissolved. Stock solutions were stored at -20 °C. Further dilutions were prepared on the day of the experiment. Chloroquine (CQ) was used as the reference drug in all experiments. A full dose-response was performed for all compounds to determine the concentration inhibiting 50% of parasite growth ( $IC_{50}$  – value). Test samples were tested at a starting concentration of 100  $\mu$ g/mL, which was then serially diluted two-fold in complete medium to give 10 concentrations; with the lowest concentration being 0.2  $\mu$ g/mL. The same dilution technique was used for all samples. CQ was tested at a starting concentration of 100 ng/mL. The highest concentration of solvent to which the parasites were exposed had no measurable effect on the parasite viability (data not shown). The  $IC_{50}$ -values were obtained using a non-linear dose-response curve fitting analysis via Graph Pad Prism v.4.0 software.

**3-(Prop-2-ynyloxy)benzaldehyde (5.15).** Propargyl bromide (3.2 mL, 80% w/w solution in toluene, 28.9 mmol) was added dropwise to a mixture of 3-hydroxybenzaldehyde (3.0 g, 24.1 mmol) and  $K_2CO_3$  (4.99 g, 36.1 mmol) in anhydrous DMF (30 mL) at rt, and stirred for 18 h. The reaction mixture was then diluted with  $H_2O$  (100 mL), and extracted with EtOAc (4 x 50

mL), washed with H<sub>2</sub>O (4 x 200 mL) and brine (150 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and solvent removed to yield the crude product. The crude product was purified via column chromatography, eluting with EtOAc/hexane (1:9) to yield the pure product as a yellow oil (3.54 g, 93%);<sup>12</sup> R<sub>f</sub> (EtOAc/hexane, 2:8) 0.48. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 30 °C): δ<sub>H</sub> 9.97 (s, 1H), 7.49 (m, 3H), 7.25 (m, 1H), 4.75 (d, *J* 2.4 Hz, 2H), 2.54 (t, *J* 2.4Hz, 1H).

**General synthesis for β-lactams.** β-Alanine (1.1 equiv), cyclohexyl isocyanide (1.0 equiv) and the appropriate aldehyde (1.0 equiv) were added to MeOH and allowed to stir at 25 °C for 48-72 h. The reaction was monitored by TLC (1:1 EtOAc/hexane). Once the aldehyde spot had disappeared the reaction was deemed complete. The solvent was removed from the reaction mixture under reduced pressure. The crude mixture was purified using silica gel chromatography eluting with 1:1 EtOAc/hexane. This method is a slight variation on the method described by Pitlik and Townsend.<sup>9</sup>

***N*-Cyclohexyl-2-(4-fluorophenyl)-2-(2-oxoazetidin-1-yl)acetamide (1.1).** White crystalline solid; Yield 74%; mp 126-127 °C (EtOAc/hexane); IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>) 3276s, 2931s, 2855m, 1739vs, 1651vs, 1510s, 1225s, 1161m, 808m; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz, 30 °C): δ<sub>H</sub> 7.34 (m, 2H), 7.05 (m, 2H), 6.25 (d, *J* 7.5Hz, 1H), 5.33 (s, 1H), 3.76 (m, 1H), 3.60 (td, *J* 5.6, 5.6, 2.8Hz, 1H), 3.16 (td, *J* 5.6, 5.6, 2.8Hz, 1H), 2.98 (ddd, *J* 14.8, 5.5, 2.8Hz, 1H) 2.85 (ddd, *J* 14.8, 5.5, 2.8Hz, 1H); 1.86 (m, 2H), 1.62 (m, 3H), 1.32 (m, 2H), 1.12 (m, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, 30 °C): δ<sub>c</sub> 167.9 (IV), 167.5 (IV), 164.0 (IV), 161.5 (IV), 130.9 (IV), 130.9, 130.0, 116.1, 115.9, 50.3, 48.5, 39.0, 36.2, 32.7, 25.5, 24.7, 24.7; HRMS *m/z* 304.1587 [M<sup>+</sup>, C<sub>17</sub>H<sub>21</sub>FN<sub>2</sub>O<sub>2</sub> requires 304.1587]; Anal. Calcd for C<sub>17</sub>H<sub>21</sub>FN<sub>2</sub>O<sub>2</sub>: C, 67.09; H, 6.95; N, 9.20. Found: C, 66.72; H, 6.59; N, 9.30.

**2-(4-Chlorophenyl)-*N*-cyclohexyl-2-(2-oxoazetidin-1-yl)acetamide (1.2).** White crystalline solid; Yield 77%; mp 127-129 °C (EtOAc/hexane); IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>) 3285m, 2933m, 1739vs, 1651vs, 1539m, 1429m, 1257m, 1091m; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 30 °C): δ<sub>H</sub> 7.38 (d, *J* 8.4Hz, 2H), 7.33 (d, *J* 8.4Hz, 2H), 6.06 (d, *J* 7.7Hz, 1H), 5.26 (s, 1H), 3.82 (m, 1H), 3.61 (td, *J* 5.5, 5.5, 2.6Hz, 1H), 3.20 (td, *J* 5.5, 5.5, 2.6Hz, 1H), 3.06 (ddd, *J* 14.8, 5.5, 2.6Hz, 1H), 2.93 (ddd, *J* 14.8, 5.5, 2.6Hz, 1H); 1.93 (m, 2H), 1.74 (m, 3H), 1.42 (m, 2H), 1.22 (m, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, 30 °C): δ<sub>c</sub> 167.9 (IV), 167.2 (IV), 137.8, 134.7, 133.5, 129.5, 129.2, 70.7, 59.6, 48.7, 39.0, 36.0, 32.8, 25.4, 24.7, 24.7; HRMS *m/z* 320.1290 [M<sup>+</sup>, C<sub>17</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>2</sub> requires 320.1292]; Anal. Calcd for C<sub>17</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>2</sub>: C, 63.64; H, 6.60; N, 8.73. Found: C, 63.30; H, 6.53; N, 8.67.

**2-(4-Bromophenyl)-*N*-cyclohexyl-2-(2-oxoazetidin-1-yl)acetamide (1.3).** White crystalline solid, Yield: 84%; mp 94-95 °C (EtOAc/hexane); IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>) 3304m, 2931s, 2854m, 1741vs, 1657vs, 1644m, 1488m, 1012m; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 30 °C): δ<sub>H</sub> 7.52 (d, *J* 8.8Hz, 2H), 7.26 (d, *J* 8.8Hz, 2H), 6.33 (br d, *J* 7.7Hz, 1H), 5.32 (s, 1H), 3.80 (m, 1H), 3.628 (td, *J* 5.8, 5.8, 2.7Hz, 1H), 3.20 (td, *J* 5.8, 5.8, 2.7Hz, 1H), 3.02 (ddd, *J* 14.8, 5.8, 2.7Hz, 1H), 2.90 (ddd, *J* 14.8, 5.8, 2.7Hz, 1H), 1.90 (m, 2H), 1.71 (m, 3H), 1.40 (m, 2H), 1.19 (m, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100MHz, 30 °C): δ<sub>c</sub> 167.9 (IV), 167.2 (IV), 134.0, 132.2, 129.8, 122.8, 95.0, 70.7, 48.7,

39.7, 36.3, 32.7, 25.4, 24.7, 24.6; HRMS  $m/z$  364.0785 [ $M^+$ ,  $C_{17}H_{21}BrN_2O_2$  requires 364.0786]; Anal. Calcd for  $C_{17}H_{21}BrN_2O_2$ : C, 55.90; H, 5.79; N, 7.67. Found: C, 55.70; H, 5.80; N, 7.56.

***N*-Cyclohexyl-2-(4-iodophenyl)-2-(2-oxoazetidin-1-yl)acetamide (1.4).** White crystalline solid, Yield: 84%; mp 127-129 °C (EtOAc/hexane); IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ) 3288s, 2931s, 1743vs, 1651vs, 1561s, 1486m, 1249m, 1008m;  $^1H$  NMR ( $CDCl_3$ , 400 MHz, 30 °C):  $\delta_H$  7.69 (d,  $J$  8.4Hz, 2H), 7.09 (d,  $J$  8.4Hz, 2H), 6.07 (d,  $J$  8.0Hz, 1H), 5.20 (s, 1H), 3.78 (m, 1H), 3.57 (td,  $J$  5.5, 5.5, 2.6Hz, 1H) 3.16 (td,  $J$  5.5, 5.5, 2.6Hz, 1H), 3.00 (ddd,  $J$  14.6, 5.5, 2.6Hz, 1H), 2.88 (ddd,  $J$  14.6, 5.5, 2.6Hz, 1H), 1.88 (m, 2H), 1.69 (m, 3H), 1.37 (m, 2H), 1.19 (m, 3H);  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz, 30 °C):  $\delta_c$  167.8 (IV), 167.1 (IV), 138.0 (2C), 134.7 (IV), 129.8 (2C), 94.2 (IV), 58.9, 48.5, 39.1, 36.2, 32.5, 25.3, 24.6, 24.5; HRMS  $m/z$  412.0469 [ $M^+$ ,  $C_{17}H_{21}IN_2O_2$  requires 412.0468]; Anal. Calcd for  $C_{17}H_{21}IN_2O_2$ : C, 49.53; H, 5.13; N, 6.79. Found: C, 49.52; H, 5.14; N, 6.47.

***N*-Cyclohexyl-2-(2-oxoazetidin-1-yl)-2-(4-(trifluoromethyl)phenyl)acetamide (1.5).** Yellow crystalline solid; Yield 64%; mp 115-116 °C (EtOAc/hexane); IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ) 3278s, 2930s, 2856m, 1746vs, 1646vs, 1330vs, 1127vs, 703m;  $^1H$  NMR ( $CDCl_3$ , 400 MHz, 30 °C):  $\delta_H$  7.61 (m, 4H), 6.42 (br d,  $J$  6.4Hz, 1H), 5.43 (s, 1H), 3.79 (m, 1H), 3.64 (td,  $J$  5.5, 5.5, 2.9Hz, 1H), 3.21 (td,  $J$  5.5, 5.5, 2.9Hz, 1H), 3.03 (ddd,  $J$  15.0, 5.5, 2.7Hz, 1H), 2.91 (ddd,  $J$  15.0, 5.5, 2.7Hz, 1H), 1.88 (m, 2H), 1.62 (m, 3H), 1.37 (m, 2H), 1.18 (m, 3H);  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz, 30 °C):  $\delta_c$  168.0 (IV), 166.9 (IV), 136.1 (IV), 131.4, 129.5, 125.4, 125.4, 124.9, 59.6, 48.8, 39.2, 36.4, 32.7, 32.7, 25.4, 24.7, 24.6; HRMS  $m/z$  354.1557 [ $M^+$ ,  $C_{18}H_{21}F_3N_2O_2$  requires 354.1555]; Anal. Calcd for  $C_{18}H_{21}F_3N_2O_2$ : C, 61.01; H, 5.97; N, 7.91. Found: C, 60.80; H, 6.27; N, 7.55.

***N*-Cyclohexyl-2-(4-hydroxyphenyl)-2-(2-oxoazetidin-1-yl)acetamide (1.6).** White crystalline solid, Yield: 80%; mp 176-177 °C (EtOAc/hexane); IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ) 3321s, 2931m, 1716vs, 1655vs, 1544m, 1515s, 1227s;  $^1H$  NMR ( $CDCl_3$ , 300 MHz, 30 °C):  $\delta_H$  7.26 (d,  $J$  8.8Hz, 2H), 6.78 (d,  $J$  8.8Hz, 2H), 5.30 (s, 1H), 4.80 (s, 2H), 3.66 (m, 1H), 3.52 (td,  $J$  5.5, 5.5, 2.8Hz, 1H), 3.06 (td,  $J$  5.5, 5.5, 2.8Hz, 1H), 2.92 (ddd,  $J$  14.7, 5.5, 2.8Hz, 1H), 2.79 (ddd,  $J$  14.7, 5.5, 2.8Hz, 1H), 1.73 (m, 5H), 1.19 (m, 5H);  $^{13}C$  NMR ( $CDCl_3$ , 300 MHz, 30 °C):  $\delta_c$  170.5 (IV), 170.0 (IV), 130.6 (2C), 126.6 (IV), 116.6 (2C), 59.6, 50.0, 39.9, 36.1, 33.6, 33.5; HRMS  $m/z$  302.1633 [ $M^+$ ,  $C_{17}H_{22}N_2O_3$  requires 302.1630]; Anal. Calcd for  $C_{17}H_{22}N_2O_3$ : C, 67.53; H, 7.33; N, 9.26. Found: C, 67.20; H, 7.23; N, 9.30.

***N*-Cyclohexyl-2-(4-methoxyphenyl)-2-(2-oxoazetidin-1-yl)acetamide (1.7).** White crystalline solid, Yield: 72%; mp 114-115 °C (EtOAc/hexane); IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ) 3318s, 2930s, 2853m, 1741vs, 1645vs, 1548s, 1512s, 1250s, 1024m, 802m;  $^1H$  NMR ( $CDCl_3$ , 400 MHz, 30 °C):  $\delta_H$  7.28 (d,  $J$  8.8Hz, 2H), 7.26 (d,  $J$  8.8Hz, 2H), 6.27 (br d,  $J$  7.7Hz, 1H), 5.33 (s, 1H), 3.79 (s, 3H), 3.76 (m, 1H), 3.62 (td,  $J$  5.8, 5.8, 2.8Hz, 1H), 3.15 (td,  $J$  5.8, 5.8, 2.8Hz, 1H), 2.98 (ddd,  $J$  14.6, 5.7, 2.8Hz, 1H), 2.83 (ddd,  $J$  14.6, 5.7, 2.8Hz, 1H), 1.88 (m, 2H), 1.69 (m, 3H), 1.38 (m, 2H), 1.18 (m, 3H);  $^{13}C$  NMR ( $CDCl_3$ , 100MHz, 30 °C):  $\delta_c$  168.0 (IV), 167.8 (IV), 159.7 (IV), 129.4 (2C), 127.1 (IV), 114.4 (2C), 59.2, 55.3, 48.6, 38.8, 36.1, 32.7, 25.5, 24.7, 24.7; HRMS  $m/z$  316.1788 [ $M^+$ ,  $C_{18}H_{24}N_2O_3$  requires 316.1787]; Anal. Calcd for  $C_{18}H_{24}N_2O_3$ : C, 68.33; H, 7.65; N, 8.85. Found: C, 67.95; H, 7.50; N, 8.98.

***N*-Cyclohexyl-2-(4-(dimethylamino)phenyl)-2-(2-oxoazetidin-1-yl)acetamide (1.8).** Yellow crystalline solid; Yield 64%; mp 122-125 °C (EtOAc/hexane); IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ) 3275s, 2930s, 1740vs, 1650vs, 1560m, 1523s, 1384m, 1203m, 800m;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, 30 °C):  $\delta_{\text{H}}$  7.25 (d,  $J$  8.8Hz, 2H), 6.82 (d,  $J$  8.8Hz, 2H), 6.00 (d,  $J$  8.0Hz, 1H), 5.27 (s, 1H), 3.81 (m, 1H), 3.610 (td,  $J$  5.5, 5.5, 2.9Hz, 1H), 3.15 (td,  $J$  5.5, 5.5, 2.9Hz, 1H), 2.99 (s, 6H), 2.97 (m, 1H), 2.87 (ddd,  $J$  14.9, 5.5, 2.9Hz, 1H), 1.92 (m, 2H), 1.72 (m, 3H), 1.37 (m, 2H), 1.18 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, 30 °C):  $\delta_{\text{C}}$  168.2 (IV), 167.9 (IV), 149.7, 129.3, 123.9, 113.6, 59.4, 48.7, 41.1, 38.7, 36.1, 32.8, 25.5, 24.8, 24.7; HRMS  $m/z$  343.2258 [ $\text{M}^+$ ,  $\text{C}_{20}\text{H}_{29}\text{N}_3\text{O}_2$  requires 343.2260]; Anal. Calcd for  $\text{C}_{20}\text{H}_{29}\text{N}_3\text{O}_2$ : C, 69.94; H, 8.51; N, 12.23. Found: C, 69.84; H, 8.53; N, 12.51.

***N*-Cyclohexyl-2-(2-oxoazetidin-1-yl)-2-(4-(prop-2-ynyloxy)phenyl)acetamide (1.9).** White crystalline solid; Yield 81%; IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ) 3327s, 2934m, 1731vs, 1671vs, 1553m, 1508s, 1222s, 1024m;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, 30 °C):  $\delta_{\text{H}}$  7.30 (d,  $J$  8.5Hz, 2H), 6.98 (d,  $J$  8.5Hz, 2H), 6.04 (br s, 1H), 5.29 (s, 1H), 4.70 (d,  $J$  2.4Hz, 2H), 3.78 (m, 1H), 3.60 (td,  $J$  5.6, 5.6, 2.7Hz, 1H), 3.15 (td,  $J$  5.6, 5.6, 2.7Hz, 1H), 2.97 (ddd,  $J$  14.0, 5.6, 2.7 Hz, 1H), 2.86 (ddd,  $J$  14.0, 5.6, 2.7 Hz, 1H), 2.54 (t,  $J$  2.4Hz, 1H), 1.88 (m, 2H), 1.67 (m, 3H), 1.33 (m, 2H), 1.16 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100MHz, 30 °C):  $\delta_{\text{C}}$  167.9 (IV), 167.8 (IV), 157.7 (IV), 129.5, 128.0 (IV), 115.4, 78.3 (IV), 75.8 (IV), 59.5, 55.9, 48.7, 38.8, 36.2, 32.8, 25.4, 24.7, 24.7; HRMS  $m/z$  340.1788 [ $\text{M}^+$ ,  $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3$  requires 340.1787]; Anal. Calcd for  $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3$ : C, 70.56; H, 7.11; N, 8.23. Found: C, 70.42; H, 7.31; N, 8.27.

**2-(2-Bromophenyl)-*N*-cyclohexyl-2-(2-oxoazetidin-1-yl)acetamide (1.10).** White crystalline solid, Yield: 79%; mp 145-147 °C (EtOAc/hexane); IR (KBr,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ) 3316s, 2934m, 1730vs, 1678vs, 1540s, 1400m, 1356m, 1246m, 1026m, 727m;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz, 30 °C):  $\delta_{\text{H}}$  7.62 (dd,  $J$  8.0, 1.1Hz, 1H), 7.48 (dd,  $J$  8.0, 1.5Hz, 1H), 7.33 (td,  $J$  7.6, 7.6, 1.1Hz, 1H), 7.22 (td,  $J$  7.6, 7.6, 1.5Hz, 1H), 6.05 (br d,  $J$  7.7Hz, 1H), 5.73 (s, 1H), 3.79 (m, 1H), 3.58 (td,  $J$  5.5, 5.5, 2.6Hz, 1H), 3.08 (td,  $J$  5.5, 5.5, 2.6Hz, 1H), 2.98 (ddd,  $J$  14.6, 5.5, 2.6Hz, 1H), 2.88 (ddd,  $J$  14.6, 5.5, 2.6Hz, 1H), 1.90 (m, 2H), 1.63 (m, 3H), 1.35 (m, 2H), 1.26 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, 30 °C):  $\delta_{\text{C}}$  167.6 (IV), 167.8 (IV), 134.4 (IV), 133.4, 130.2, 129.8, 127.9, 124.67 (IV), 59.4, 48.8, 39.2, 36.3, 32.8, 32.7, 25.4, 24.7, 24.7; HRMS  $m/z$  364.0789 [ $\text{M}^+$ ,  $\text{C}_{17}\text{H}_{21}\text{BrN}_2\text{O}_2$  requires 364.0786]; Anal. Calcd for  $\text{C}_{17}\text{H}_{21}\text{BrN}_2\text{O}_2$ : C, 55.90; H, 5.79; N, 7.67. Found: C, 55.76; H, 5.60; N, 7.63.

***N*-Cyclohexyl-2-(2-((dimethylamino)methyl)phenyl)-2-(2-oxoazetidin-1-yl)acetamide (1.11).** Pale yellow crystalline solid; Yield 77%;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz, 30 °C):  $\delta_{\text{H}}$  7.77 (d,  $J$  6.0Hz, 1H), 7.50 (dd,  $J$  8.2, 2.1Hz, 1H), 7.32 (m, 1H), 7.17 (m, 2H), 5.78 (s, 1H), 4.20 (d,  $J$  14.0Hz, 1H), 4.18 (td,  $J$  5.5, 5.5, 2.6Hz, 1H), 3.50 (m, 2H), 2.98 (ddd,  $J$  14.6, 5.5, 2.6Hz, 1H), 2.93 (d,  $J$  14.0Hz, 1H), 2.77 (ddd,  $J$  14.6, 5.5, 2.6Hz, 1H), 2.24 (s, 6H), 1.90 (m, 2H), 1.58 (m, 3H), 1.25 (m, 2H), 1.00 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz, 30 °C):  $\delta_{\text{C}}$  169.0 (IV), 167.5 (IV), 136.6 (IV), 131.3, 128.4, 127.7, 127.6, 62.9, 52.0, 47.8, 44.8 (2C), 40.5, 36.4, 33.2, 32.9, 25.5, 24.9, 24.7; HRMS  $m/z$  343.2263 [ $\text{M}^+$ ,  $\text{C}_{20}\text{H}_{29}\text{N}_3\text{O}_2$  requires 343.2260]; Anal. Calcd for  $\text{C}_{20}\text{H}_{29}\text{N}_3\text{O}_2$ : C, 69.94; H, 8.51; N, 12.23. Found: C, 70.01; H, 8.56; N, 12.03.

**2-(3-Bromophenyl)-N-cyclohexyl-2-(2-oxoazetid-1-yl)acetamide (1.12).** White crystalline solid, Yield: 84%;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz, 30 °C):  $\delta_{\text{H}}$  7.50 (m, 2H); 7.33 (m, 1H), 7.25 (m, 1H), 6.31 (br d,  $J$  7.6Hz, 1H), 3.78 (td,  $J$  5.6, 5.6, 2.8Hz, 1H), 3.20 (td,  $J$  5.6, 5.6, 2.8Hz, 1H), 3.01 (ddd,  $J$  14.6, 5.6, 2.8Hz, 1H), 2.90 (ddd,  $J$  14.6, 5.6, 2.8Hz, 1H), 1.90 (m, 2H), 1.65 (m, 3H), 1.35 (m, 2H), 1.15 (m, 3H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz, 30 °C):  $\delta_{\text{C}}$  168.0 (IV), 167.0 (IV), 137.2 (IV), 131.7, 131.2, 130.6, 126.7, 123.0 (IV), 59.5, 48.8, 39.2, 36.4, 32.7, 32.7, 25.4, 24.7, 24.7; HRMS  $m/z$  364.0786 [ $\text{M}^+$ ,  $\text{C}_{17}\text{H}_{21}\text{BrN}_2\text{O}_2$  requires 364.0786]; Anal. Calcd for  $\text{C}_{17}\text{H}_{21}\text{BrN}_2\text{O}_2$ : C, 55.90; H, 5.79; N, 7.67. Found: C, 55.67; H, 5.83; N, 7.78.

**N-Cyclohexyl-2-(3-iodophenyl)-2-(2-oxoazetid-1-yl)acetamide (1.13).** White crystalline solid, Yield: 76%; mp 106-107 °C (EtOAc/hexane); IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 3266s, 2929s, 2852m, 1744vs, 1651vs, 1564s, 1248m;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300MHz, 30 °C):  $\delta_{\text{H}}$  7.67 (m, 2H), 7.33 (d,  $J$  7.8Hz, 1H), 7.10 (t,  $J$  7.8Hz, 1H), 6.33 (br d,  $J$  7.8Hz, 1H), 5.29 (s, 1H), 3.75 (m, 1H), 3.63 (td,  $J$  5.8, 5.8, 2.9Hz, 1H), 3.20 (td,  $J$  5.8, 5.8, 2.9Hz, 1H), 3.00 (ddd,  $J$  14.6, 5.8, 2.9Hz, 1H), 2.88 (ddd,  $J$  14.6, 5.8, 2.9Hz, 1H), 1.86 (m, 2H), 1.62 (m, 3H), 1.32 (m, 2H), 1.13 (m, 3H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 75.5 MHz, 30 °C):  $\delta_{\text{C}}$  167.9 (IV), 166.9 (IV), 137.6, 137.2, 127.0, 130.6, 127.2, 94.7, 59.2, 48.7, 39.1, 36.3, 32.6, 25.4, 24.7, 24.6; HRMS  $m/z$  412.0465 [ $\text{M}^+$ ,  $\text{C}_{17}\text{H}_{21}\text{IN}_2\text{O}_2$  requires 412.0468]; Anal. Calcd for  $\text{C}_{17}\text{H}_{21}\text{IN}_2\text{O}_2$ : C, 49.53; H, 5.13; N, 6.79. Found: C, 49.74; H, 5.17; N, 6.40.

**N-Cyclohexyl-2-(3-hydroxyphenyl)-2-(2-oxoazetid-1-yl)acetamide (1.14).** White crystalline solid, Yield: 79%; mp 158-160 °C (EtOAc/hexane); IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 3246br, 2934s, 1726vs, 1658vs, 1598s, 1555m, 1457s, 1247m, 1237m, 735m;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz, 30 °C):  $\delta_{\text{H}}$  8.19 (br s, 1H), 7.20 (t,  $J$  7.9Hz, 1H), 6.89 (m, 1H), 6.83 (m, 1H), 6.50 (d,  $J$  7.9Hz, 1H), 5.31 (s, 1H), 3.71 (m, 1H), 3.62 (td,  $J$  5.5, 5.5, 2.7Hz, 1H), 3.17 (td,  $J$  5.5, 5.5, 2.7Hz, 1H), 2.92 (ddd,  $J$  14.7, 5.5, 2.7Hz, 1H), 2.79 (ddd,  $J$  14.7, 5.5, 2.7Hz, 1H), 1.83 (m, 2H), 1.59 (m, 3H), 1.26 (m, 2H), 1.11 (m, 3H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 75.5 MHz, 30 °C):  $\delta_{\text{C}}$  168.1 (IV), 157.4 (IV), 135.7, 130.3, 130.2, 119.2, 116.2, 115.3, 58.7, 48.9, 39.2, 35.9, 33.6, 25.4, 24.7, 24.6, 24.6; HRMS  $m/z$  302.1632 [ $\text{M}^+$ ,  $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_3$  requires 302.1630]; Anal. Calcd for  $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_3$ : C, 67.53; H, 7.33; N, 9.26. Found: C, 67.42; H, 7.19; N, 9.36.

**N-Cyclohexyl-2-(2-oxoazetid-1-yl)-2-(3-(prop-2-ynyloxy)phenyl)acetamide (1.15).** White crystalline solid; Yield 81%; mp 128-129 °C (EtOAc/hexane); IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 3264s, 3216m, 2931s, 2852m, 1738vs, 1648vs, 1602m, 1269m, 1035m, 775m;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz, 30 °C):  $\delta_{\text{H}}$  7.28 (t,  $J$  7.5Hz, 1H), 6.95 (m, 3H), 6.18 (d,  $J$  7.7Hz, 1H), 4.67 (d,  $J$  2.4Hz, 2H), 3.75 (m, 1H), 3.62 (td,  $J$  5.6, 5.6, 2.8Hz, 1H), 3.19 (td,  $J$  5.6, 5.6, 2.8Hz, 1H), 2.97 (ddd,  $J$  14.7, 5.6, 2.8Hz, 1H), 2.84 (ddd,  $J$  14.7, 5.6, 2.8Hz, 1H), 2.51 (t,  $J$  2.4Hz, 1H), 1.85 (m, 2H), 1.62 (m, 3H), 1.30 (m, 2H), 1.11 (m, 3H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 75.5 MHz, 30 °C):  $\delta_{\text{C}}$  167.8 (IV), 167.3 (IV), 157.9 (IV), 135.5, 130.1, 121.2, 114.9, 114.7, 78.3 (IV), 75.7, 59.8, 55.8, 48.6, 39.0, 36.21, 32.7, 25.4, 24.7, 24.6; HRMS  $m/z$  302.163340.1783 [ $\text{M}^+$ ,  $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3$  requires 340.1787]; Anal. Calcd for  $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3$ : C, 70.23; H, 7.00; N, 7.90. Found: C, 70.42; H, 7.31; N, 8.27.

**N-Cyclohexyl-2-(2,4-dichlorophenyl)-2-(2-oxoazetid-1-yl)acetamide (1.16).** White crystalline solid; Yield 77%; mp 156-157 °C (EtOAc/hexane); IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 3292m, 2933s,

1741vs, 1647vs, 1553s, 1473m, 1252m, 812m, 569m;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, 30 °C):  $\delta_{\text{H}}$  7.46 (m, 2H), 7.29 (m, 1H), 6.30 (br d,  $J$  7.7Hz, 1H), 5.72 (s, 1H), 3.82 (m, 1H), 3.60 (td,  $J$  5.5, 5.5, 2.8Hz, 1H), 3.12 (td,  $J$  5.5, 5.5, 2.8Hz, 1H), 3.02 (ddd,  $J$  14.6, 5.5, 2.6Hz), 2.92 (ddd,  $J$  14.6, 5.5, 2.6Hz), 1.92 (m, 2H), 1.73 (m, 3H), 1.41 (m, 2H), 1.21 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, 30 °C):  $\delta_{\text{C}}$  167.7 (IV), 166.7 (IV), 135.4, 135.9, 131.3, 129.9, 127.6, 70.7, 56.4, 48.8, 39.2, 36.2, 32.7, 32.7, 25.4, 24.7, 24.7; HRMS  $m/z$  354.0904 [ $\text{M}^+$ ,  $\text{C}_{17}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_2$  requires 354.0902]; Anal. Calcd for  $\text{C}_{17}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_2$ : C, 57.47; H, 5.67; N, 7.89. Found: C, 57.10; H, 5.71; N, 7.91.

***N*-Cyclohexyl-2-(2,4-difluorophenyl)-2-(2-oxoazetidin-1-yl)acetamide (1.17).** White crystalline solid; Yield 84%; mp 147-150 °C (EtOAc/hexane); IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 3315s, 2932s, 2855m, 1748vs, 1673vs, 1531s, 1505s, 1392m, 1248m, 1141m;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400MHz, 30 °C):  $\delta_{\text{H}}$  7.45 (dd,  $J$  14.7, 8.4Hz, 1H), 6.88 (dt,  $J$  11.2, 5.7Hz, 2H), 6.27 (br d,  $J$  7.2Hz, 1H), 5.56 (s, 1H), 3.77 (m, 1H), 3.59 (m, 1H), 3.17 (m, 1H), 3.00 (ddd,  $J$  14.8, 5.6, 2.8Hz, 1H), 2.90 (ddd,  $J$  14.8, 5.6, 2.8Hz, 1H), 1.85 (m, 2H), 1.64 (m, 3H), 1.35 (m, 2H), 1.15 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 400MHz, 30 °C):  $\delta_{\text{C}}$  167.8 (IV), 166.6 (IV), 131.2, 130.1, 112.0, 111.8, 104.7, 104.4, 53.6, 48.8, 39.2, 36.4, 32.7, 25.4, 24.7, 24.7; HRMS  $m/z$  322.1491 [ $\text{M}^+$ ,  $\text{C}_{17}\text{H}_{20}\text{F}_2\text{N}_2\text{O}_2$  requires 322.1493]; Anal. Calcd for  $\text{C}_{17}\text{H}_{20}\text{F}_2\text{N}_2\text{O}_2$ : C, 63.34; H, 6.25; N, 8.69. Found: C, 63.00; H, 6.33; N, 8.71.

***N*-Cyclohexyl-2-(3,4-dichlorophenyl)-2-(2-oxoazetidin-1-yl)acetamide (1.18).** White crystalline solid; Yield 84%; mp 117-118 °C (EtOAc/hexane); IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 3303s, 2932s, 2854m, 1741vs, 1656vs, 1542m, 1032m;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400MHz, 30 °C):  $\delta_{\text{H}}$  7.43 (d,  $J$  2.0Hz, 1H), 7.41 (d,  $J$  7.8Hz, 1H), 7.21 (d,  $J$  7.8Hz, 1H), 6.85 (br s, 1H), 5.41 (s, 1H), 3.70 (m, 2H), 3.24 (td,  $J$  5.5, 5.5, 2.6Hz, 1H), 3.00 (ddd,  $J$  14.5, 5.5, 2.6Hz, 1H), 2.90 (ddd,  $J$  14.5, 5.5, 2.6Hz, 1H), 2.29 (m, 1H), 1.89 (m, 2H), 1.69 (m, 3H), 1.39 (m, 2H), 1.16 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100MHz, 30 °C):  $\delta_{\text{C}}$  168.0 (IV), 166.8 (IV), 135.4, 133.1, 132.8, 130.9, 130.0, 127.3, 58.3, 58.2, 48.7, 39.3, 32.6, 25.4, 24.7, 23.6; HRMS  $m/z$  354.0900 [ $\text{M}^+$ ,  $\text{C}_{17}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_2$  requires 354.0902]; Anal. Calcd for  $\text{C}_{17}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_2$ : C, 57.47; H, 5.67; N, 7.89. Found: C, 57.77; H, 5.90; N, 7.53.

**2-(2-Chloro-3,6-difluorophenyl)-*N*-cyclohexyl-2-(2-oxoazetidin-1-yl)acetamide (1.19).** White crystalline solid; Yield 79%; mp 182-184 °C (EtOAc/hexane); IR (KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 3339m, 2933m, 1751vs, 1667vs, 1529s, 1470s, 1388m, 1257m, 1228m, 821m;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz, 30 °C):  $\delta_{\text{H}}$  7.21 (m, 1H), 7.07 (m, 1H), 6.00 (s, 1H), 5.98 (d,  $J$  6.8Hz, 1H), 3.88 (m, 1H), 3.59 (td,  $J$  5.5, 5.5, 2.6Hz, 1H), 3.14 (m, 2H), 2.94 (ddd,  $J$  14.5, 5.5, 2.6Hz, 1H), 1.96 (m, 2H), 1.72 (m, 3H), 1.40 (m, 2H), 1.23 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz, 30 °C):  $\delta_{\text{C}}$  168.2 (IV), 165.5 (IV), 117.3, 117.0, 115.2, 115.1, 114.9, 114.8, 53.1, 48.9, 39.4, 36.8, 32.9, 32.7, 25.5, 24.7; HRMS  $m/z$  356.1100 [ $\text{M}^+$ ,  $\text{C}_{17}\text{H}_{19}\text{ClF}_2\text{N}_2\text{O}_2$  requires 356.1103]; Anal. Calcd for  $\text{C}_{17}\text{H}_{19}\text{ClF}_2\text{N}_2\text{O}_2$ : C, 57.23; H, 5.37; N, 7.85. Found: C, 57.13; H, 5.59; N, 7.87.

***N*-Cyclohexyl-2-(2-fluoro-4-(trifluoromethyl)phenyl)-2-(2-oxoazetidin-1-yl)acetamide (1.20).** White crystalline solid; Yield 74%; mp 108-109 °C (EtOAc/hexane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz, 30 °C):  $\delta_{\text{H}}$  7.57 (t,  $J$  7.6Hz, 1H), 7.44 (d,  $J$  8.2Hz, 1H), 7.37 (d,  $J$  9.9Hz, 1H), 6.12 (d,  $J$  7.9Hz, 1H), 5.55 (s, 1H), 3.82 (m, 1H), 3.58 (td,  $J$  5.7, 5.7, 3.0Hz, 1H), 3.22 (td,  $J$  5.7, 5.7, 3.0Hz, 1H), 3.03 (ddd,  $J$  14.8, 5.7, 3.0Hz, 1H), 2.94 (ddd,  $J$  14.8, 5.7, 3.0Hz, 1H), 2.01 (m, 2H),

1.70 (m, 3H), 1.36 (m, 2H), 1.21 (m, 3H); HRMS  $m/z$  372.1460 [ $M^+$ ,  $C_{18}H_{20}F_4N_2O_2$  requires 372.1461]; Anal. Calcd for  $C_{18}H_{20}F_4N_2O_2$ : C, 58.06; H, 5.41; N, 7.52. Found: C, 57.93; H, 5.47; N, 7.72.

***N*-Cyclohexyl-2-(3,4-dimethoxyphenyl)-2-(2-oxoazetidin-1-yl)acetamide (1.21).** White crystalline solid; Yield 73%; mp 140-141 °C (EtOAc/hexane); IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ) 3275s, 2924s, 2853m, 1752vs, 1644s, 1517s, 1260s, 1250s, 1145m, 1027m;  $^1H$  NMR ( $CDCl_3$ , 300 MHz, 30 °C):  $\delta_H$  6.89 (m, 3H), 5.89 (d,  $J$  7.8Hz, 1H), 5.22 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.80 (m, 1H), 3.62 (td,  $J$  5.8, 5.8, 2.7Hz, 1H), 3.16 (td,  $J$  5.8, 5.8, 2.7Hz, 1H), 3.04 (ddd,  $J$  14.6, 5.8, 2.7Hz, 1H), 2.89 (ddd,  $J$  14.6, 5.8, 2.7Hz, 1H), 1.93 (m, 2H), 1.71 (m, 3H), 1.43 (m, 2H), 1.19 (m, 3H);  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz, 30 °C):  $\delta_C$  167.3 (IV), 162.8 (IV), 127.3 (IV), 120.7, 111.5, 111.3, 60.0, 56.0, 56.0, 48.7, 38.8, 36.2, 32.8, 25.5, 24.7; HRMS  $m/z$  346.1895 [ $M^+$ ,  $C_{19}H_{26}N_2O_4$  requires 346.1893]; Anal. Calcd for  $C_{19}H_{26}N_2O_4$ : C, 65.87; H, 7.56; N, 8.09. Found: C, 65.55; H, 7.35; N, 8.02.

***N*-Cyclohexyl-2-(4-hydroxy-3-methoxyphenyl)-2-(2-oxoazetidin-1-yl)acetamide (1.22).** White crystalline solid, Yield: 76%; mp 178-180 °C (EtOAc/hex); (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ) 3489s, 3283m, 2938m, 1741vs, 1647vs, 1519m, 1270m, 1263m, 1251m, 1032m;  $^1H$  NMR ( $CDCl_3$ , 300 MHz, 30 °C):  $\delta_H$  6.92 (m, 3H), 5.86 (d,  $J$  7.8Hz, 1H), 5.70 (s, 1H), 5.20 (s, 1H), 3.88 (s, 3H), 3.82 (m, 1H), 3.61 (td,  $J$  5.8, 5.8, 2.8Hz, 1H), 3.16 (td,  $J$  5.8, 5.8, 2.8Hz, 1H), 3.03 (ddd,  $J$  14.6, 5.8, 2.9Hz, 1H), 2.89 (ddd,  $J$  14.6, 5.8, 2.9Hz, 1H), 1.91 (m, 2H), 1.71 (m, 3H), 1.42 (m, 2H), 1.21 (m, 3H);  $^{13}C$  NMR ( $CDCl_3$ , 75.5 MHz, 30 °C):  $\delta_C$  167.9 (IV), 167.8 (IV), 146.9 (IV), 146.0 (IV), 126.6 (IV), 121.3, 114.8, 110.8, 59.7, 56.0, 48.6, 38.8, 36.0, 32.6 (2C), 25.4, 24.7, 24.6; IR HRMS  $m/z$  332.1739 [ $M^+$ ,  $C_{18}H_{24}N_2O_4$  requires 332.1736]; Anal. Calcd for  $C_{18}H_{24}N_2O_4$ : C, 65.04; H, 7.28; N, 8.43. Found: C, 64.87; H, 7.22; N, 8.25.

***N*-Cyclohexyl-2-(2,3-dimethoxyphenyl)-2-(2-oxoazetidin-1-yl)acetamide (1.23).** White crystalline solid, Yield: 72%; mp 148-149 °C (EtOAc/hex); IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ) 3255s, 2930s, 2852m, 1747vs, 1650vs, 1557s, 1483s, 1274s, 1068s, 742m;  $^1H$  NMR ( $CDCl_3$ , 400 MHz, 30 °C):  $\delta_H$  7.06 (t,  $J$  8.0Hz, 1H), 6.96 (d,  $J$  8.0Hz, 1H), 6.92 (d,  $J$  8.0Hz, 1H), 5.85 (br s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.73 (m, 1H), 3.67 (td,  $J$  5.6, 5.6, 2.8Hz, 1H), 3.23 (td,  $J$  5.6, 5.6, 2.8Hz, 1H), 2.98 (ddd,  $J$  14.0, 5.6, 2.8Hz, 1H), 2.85 (ddd,  $J$  14.0, 5.6, 2.8Hz, 1H), 1.85 (m, 2H), 1.63 (m, 3H), 1.33 (m, 2H), 1.08 (m, 3H);  $^{13}C$  NMR ( $CDCl_3$ , 75.5 MHz, 30 °C):  $\delta_C$  168.0 (IV, CO), 167.9 (IV, CO), 152.8, 146.8, 129.2, 120.7, 112.8, 61.0, 55.8, 54.1, 48.6, 39.5, 32.9, 32.7, 25.5, 24.8, 24.9; HRMS  $m/z$  346.1891 [ $M^+$ ,  $C_{19}H_{26}N_2O_4$  requires 346.1893]; Anal. Calcd for  $C_{19}H_{26}N_2O_4$ : C, 65.87; H, 7.56; N, 8.09. Found: C, 65.65; H, 7.54; N, 8.07.

***N*-Cyclohexyl-2-(2,4-dimethoxyphenyl)-2-(2-oxoazetidin-1-yl)acetamide (1.24).** White crystalline solid; Yield 82%; mp 103-105 °C (EtOAc/hexane); IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ) 3287s, 2934s, 1748vs, 1651vs, 1615s, 1506s, 1209s, 1039m;  $^1H$  NMR ( $CDCl_3$ , 400 MHz, 30 °C):  $\delta_H$  7.25 (d,  $J$  8.0 Hz, 1H), 6.49 (m, 2H), 5.71 (d,  $J$  8.0 Hz, 1H), 5.55 (s, 1H), 3.81 (s, 3H), 3.81 (s, 3H), 3.78 (m, 1H), 3.61 (td,  $J$  5.6, 5.6, 2.8 Hz, 1H), 3.13 (td,  $J$  5.6, 5.6, 2.8 Hz, 1H), 2.98 (ddd,  $J$  14.6, 5.7, 2.7 Hz, 1H), 2.85 (ddd,  $J$  14.6, 5.7, 2.7 Hz, 1H), 1.91 (m, 2H), 1.72 (m, 3H), 1.4 (m, 2H), 1.19 (m, 3H);  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz, 30 °C):  $\delta_C$  168.2 (IV), 168.0 (IV), 161.3 (IV), 158.1 (IV),

130.5, 115.9 (IV), 104.7, 98.9, 55.4, 55.4, 54.3, 48.4, 39.2, 36.1, 32.9, 32.8, 25.5, 24.7, 24.7; HRMS  $m/z$  346.1894 [ $M^+$ ,  $C_{19}H_{26}N_2O_4$  requires 346.1893]; Anal. Calcd for  $C_{19}H_{26}N_2O_4$ : C, 65.87; H, 7.56; N, 8.09. Found: C, 65.5; H, 7.56; N, 8.26.

***N*-Cyclohexyl-2-(2-oxoazetidin-1-yl)-2-(2,3,4-trimethoxyphenyl)acetamide (1.25).** White crystalline solid, Yield: 75%; mp 125–127 °C (EtOAc/hex); IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ) 3255m, 2926s, 2852m, 1745vs, 1643vs, 1494s, 1468s, 1096vs, 1040s;  $^1H$  NMR ( $CDCl_3$ , 400 MHz, 30 °C):  $\delta_H$  7.06 (d,  $J$  9 Hz, 1H), 6.67 (d,  $J$  9 Hz, 1H), 5.85 (d,  $J$  9 Hz, 1H), 5.56 (s, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.87 (s, 3H), 3.80 (m, 1H), 3.64 (td,  $J$  5.7, 5.7, 2.7 Hz, 1H), 3.21 (td,  $J$  5.7, 5.7, 2.7 Hz, 1H), 3.01 (ddd,  $J$  14.6, 5.6, 2.6 Hz, 1H), 2.87 (ddd,  $J$  14.6, 5.6, 2.6 Hz, 1H), 1.93 (m, 2H), 1.73 (m, 3H), 1.39 (m, 2H), 1.22 (m, 3H);  $^{13}C$  NMR ( $CDCl_3$ , 75.5 MHz, 30 °C):  $\delta_C$  168.0 (IV), 167.8 (IV), 154.1 (IV), 151.5 (IV), 142.0 (IV), 123.6, 121.0 (IV), 107.2, 61.0, 60.6, 55.8, 54.3, 48.4, 39.2, 36.0, 32.8, 32.6, 25.3, 24.6, 24.6; HRMS  $m/z$  376.1999 [ $M^+$ ,  $C_{20}H_{28}N_2O_5$  requires 376.1998]; Anal. Calcd for  $C_{20}H_{28}N_2O_5$ : C, 63.21; H, 7.5; N, 7.44. Found: C, 63.81; H, 7.3; N, 7.46.

***N*-Cyclohexyl-2-(2-oxoazetidin-1-yl)-2-(ferrocenyl)acetamide (1.26).** Orange crystalline solid; Yield 67%; mp 145–146 °C (EtOAc/hexane); IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ) 3332s, 2930s, 2853m, 1736vs, 1671vs, 1544s, 1396m, 1229m, 486s;  $^1H$  NMR ( $CDCl_3$ , 400 MHz, 30 °C):  $\delta_H$  6.43 (br d,  $J$  7.2 Hz, 1H), 5.10 (s, 1H), 4.38 (s, 1H), 4.19 (m, 7H), 3.80 (m, 1H), 3.23 (td,  $J$  5.6, 5.6, 2.8 Hz, 1H), 2.94 (td,  $J$  5.6, 5.6, 2.8 Hz, 1H), 2.87 (ddd,  $J$  14.6, 5.6, 2.8 Hz, 1H), 1.96 (m, 2H), 1.66 (m, 2H), 1.38 (m, 2H), 1.21 (m, 3H);  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz, 30 °C):  $\delta_C$  167.3 (IV), 166.9 (IV), 82.8 (IV), 69.1 (5C), 58.6, 68.3, 67.8, 55.9, 48.6, 38.8, 36.7, 33.0, 32.9, 28.2; HRMS  $m/z$  395.1422 [ $M^+$ ,  $C_{21}H_{27}N_2O_2Fe$  requires 395.1422]; Anal. Calcd for  $C_{21}H_{27}N_2O_2Fe$ : C, 63.81; H, 6.88; N, 7.09. Found: C, 63.70; H, 6.61; N, 7.05.

***N*-Cyclohexyl-2-(2-oxoazetidin-1-yl)-2-(quinolin-4-yl)acetamide (1.27).** White crystalline solid; Yield 69%; mp 197–199 °C (EtOAc/hexane); IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ) 3280s, 2928s, 1747vs, 1650vs, 766s;  $^1H$  NMR ( $CDCl_3$ , 400 MHz, 30 °C):  $\delta_H$  8.93 (d,  $J$  4.4 Hz, 1H), 8.19 (d,  $J$  8.3 Hz, 1H), 8.12 (d,  $J$  7.8 Hz, 1H), 7.80 (t,  $J$  7.5 Hz, 1H), 7.69 (t,  $J$  7.8 Hz, 1H), 7.49 (d,  $J$  4.4 Hz, 1H), 6.06 (s, 1H), 5.89 (d,  $J$  8.7 Hz, 1H), 3.90 (m, 1H), 3.68 (td,  $J$  5.6, 5.6, 2.6 Hz, 1H), 3.06 (ddd,  $J$  14.1, 5.4, 2.4 Hz, 1H), 2.920 (td,  $J$  5.6, 5.6, 2.6 Hz, 1H), 2.85 (ddd,  $J$  14.1, 5.4, 2.4 Hz, 1H), 1.93 (m, 2H), 1.70 (m, 3H), 1.39 (m, 2H), 1.19 (m, 3H);  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz, 30 °C):  $\delta_C$  167.8 (IV), 166.9 (IV), 150.1, 148.7, 139.8, 130.5, 129.8, 127.7, 126.1 (IV), 122.8, 120.5, 55.0, 48.9, 39.0, 36.4, 32.7, 32.6, 25.3, 24.7, 24.6; HRMS  $m/z$  337.1793 [ $M^+$ ,  $C_{20}H_{23}N_3O_2$  requires 337.1790]; Anal. Calcd for  $C_{20}H_{23}N_3O_2$ : C, 71.19; H, 6.87; N, 12.45. Found: C, 71.37; H, 6.89; N, 12.65.

**General procedure for Mannich Reactions.** The terminal acetylene (1.0 equiv), aqueous formaldehyde (5.0 equiv), amine (1.2 eq) and copper(I) iodide (0.02 equiv) were stirred in commercial DMSO at 25 °C for 2 h.  $H_2O$  was added to the reaction mixture, which was basified to pH 8. The mixture was extracted with EtOAc, washed with brine, dried ( $Na_2SO_4$ ) and solvent evaporated to yield the crude products.



***N*-Cyclohexyl-2-[3-({4-[benzyl(methyl)amino]but-2-ynyl}oxy)phenyl]-2-(2-oxoazetidin-1-yl)acetamide (2.1).** Crude residue was purified via column chromatography, eluting with MeOH/DCM (0.5:9.5) to yield the product as a white powder, (75.1 mg, 72%); mp 88 – 91 °C;  $R_f$  (MeOH/DCM, 0.5:9.5) 0.33; IR (DCM,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ) 2312w, 1742s, 1672s, 1249s and 1025m;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz, 30 °C):  $\delta_{\text{H}}$  7.26 (m, 6H), 6.98 (m, 3H), 5.90 (d,  $J$  7.5Hz, 1H), 5.24 (s, 1H), 4.76 (t,  $J$  1.8Hz, 2H), 3.73 (m, 1H), 3.56 (td,  $J$  5.7, 5.7, 2.7Hz, 1H), 3.50 (s, 2H), 3.31 (t,  $J$  1.8Hz, 2H, H7), 3.11 (td,  $J$  5.7, 5.7, 2.7Hz, 1H), 2.95 (ddd,  $J$  14.7, 5.7, 2.7Hz, 1H), 2.79 (ddd,  $J$  14.7, 5.7, 2.7Hz, 1H), 2.29 (s, 3H), 2.0 – 0.8 (m, 10H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz, 30 °C):  $\delta_{\text{C}}$  167.9 (IV), 167.4 (IV), 158.1 (IV), 138.1 (IV), 136.4 (IV), 130.0, 129.1 (2C), 128.3 (2C), 127.1, 121.0, 115.1, 114.9, 82.8 (IV), 80.0 (IV), 60.1, 59.9, 56.2, 48.6, 45.1, 41.9, 39.0, 36.2, 32.7, 29.6, 25.4, 24.7 and 24.6; HRMS  $m/z$  473.6162 ( $\text{M}^+$ ,  $\text{C}_{29}\text{H}_{35}\text{N}_3\text{O}_3$  requires 473.6152); Anal. Calcd for  $\text{C}_{29}\text{H}_{35}\text{N}_3\text{O}_3$ : C, 73.54; H, 7.45; N, 8.87. Found: C, 73.24; H, 7.57; N, 8.80.

***N*-Cyclohexyl-2-(3-{{4-(diethylamino)but-2-ynyl}oxy}phenyl)-2-(2-oxoazetidin-1-yl)-acetamide (2.2).** Crude residue was purified via column chromatography, eluting with MeOH/EtOAc (0.1:9.9 to 1:9) to yield the product as a white powder, (83.0 mg, 89%); mp 102 – 105 °C;  $R_f$  (EtOAc) 0.12; IR (DCM,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ) 2305w, 1741s, 1672s, 1248s and 1022m;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz, 30 °C):  $\delta_{\text{H}}$  7.29 (m, 1H), 6.96 (m, 3H), 5.94 (d,  $J$  7.8Hz, 1H), 5.25 (s, 1H), 4.71 (t,  $J$  2.1Hz, 2H), 3.76 (m, 1H), 3.60 (td,  $J$  6.0, 6.0, 2.4Hz, 1H), 3.44 (t,  $J$  2.1Hz, 2H), 3.17 (td,  $J$  6.0, 6.0, 2.4Hz, 1H), 2.99 (ddd,  $J$  14.7, 6.0, 2.4Hz, 1H), 2.86 (ddd,  $J$  14.7, 6.0, 2.4Hz, 1H), 2.51 (q,  $J$  7.5Hz, 4H), 2.0 – 1.1 (m, 10H), 1.03 (t,  $J$  7.5Hz, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, 30 °C):  $\delta_{\text{C}}$  167.9 (IV), 167.4 (IV), 158.2 (IV), 136.3 (IV), 130.0, 120.9, 115.1, 114.8, 82.9 (IV), 79.2 (IV), 60.1, 56.3, 48.7, 47.2 (2C), 41.0, 39.0, 36.3, 32.8, 32.7, 25.4, 24.7, 24.6 and 12.5 (2C); HRMS  $m/z$  425.5715 ( $\text{M}^+$   $\text{C}_{25}\text{H}_{35}\text{N}_3\text{O}_3$  requires M, 425.5712); Anal. Calcd for  $\text{C}_{25}\text{H}_{35}\text{N}_3\text{O}_3$ : C, 70.56; H, 8.29; N, 9.87; Found: C, 70.41; H, 7.98; N, 9.85.

***N*-Cyclohexyl-2-(2-oxoazetidin-1-yl)-2-{{3-[(4-pyrrolidin-1-yl)but-2-ynyl]oxy}phenyl}acetamide (2.3).** Crude residue was purified via column chromatography, eluting with MeOH/EtOAc (0.3:9.7 to 1:9) to yield the product as a white powder, (74.2 mg, 80%); mp 89 – 91 °C;  $R_f$  (MeOH/EtOAc, 0.3:9.7) 0.11; IR (DCM,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ) 2305w, 1742s, 1672s, 1245s and 1022m;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz, 30 °C):  $\delta_{\text{H}}$  7.26 (m, 1H), 6.97 (m, 3H), 6.00 (d,  $J$  7.8Hz, 1H), 5.26 (s, 1H), 4.71 (t,  $J$  2.1Hz, 2H), 3.76 (m, 1H), 3.61 (td,  $J$  6.0, 6.0, 2.4Hz, 1H), 3.44 (t,  $J$  2.1Hz, 2H), 3.17 (td,  $J$  6.0, 6.0, 2.4Hz, 1H), 2.99 (ddd,  $J$  14.7, 6.0, 2.4Hz, 1H), 2.86 (ddd,  $J$  14.7, 6.0, 2.4Hz, 1H), 2.59 (m, 4H), 1.78 (m, 4H), 2.1 – 1.0 (m, 10H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, 30 °C):  $\delta_{\text{C}}$  167.9 (IV), 167.4 (IV), 158.2 (IV), 136.4 (IV), 130.0, 121.0, 115.1, 114.9, 83.7 (IV), 78.8 (IV), 60.0, 56.3, 52.6 (2C), 48.7, 43.3, 39.0, 36.3, 32.7, 32.6, 25.4, 24.7, 24.6 and 23.8 (2C); HRMS  $m/z$  423.5558 ( $\text{M}^+$   $\text{C}_{25}\text{H}_{33}\text{N}_3\text{O}_3$  requires 423.5553); Anal. Calcd for  $\text{C}_{25}\text{H}_{33}\text{N}_3\text{O}_3$ : C, 70.89; H, 7.85; N, 9.92%. Found: C, 70.67; H, 7.81; N, 9.75.

***N*-Cyclohexyl-2-(2-oxoazetidin-1-yl)-2-{{3-[(4-piperidin-1-yl)but-2-ynyl]oxy}phenyl}acetamide (2.4).** Crude residue was purified via column chromatography, eluting with MeOH/EtOAc (0.3:9.7) to yield the product as a white powder, (70.8 mg, 73%); mp 107 – 109 °C;  $R_f$  (MeOH/EtOAc, 0.3:9.7) 0.24; IR (DCM,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ) 2305w, 1741s, 1672s, 1262s and

1015m;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz, 30 °C):  $\delta_{\text{H}}$  7.29 (m, 1H), 6.96 (m, 3H), 5.92 (d,  $J$  7.8Hz, 1H), 5.25 (s, 1H), 4.71 (t,  $J$  1.8Hz, 2H), 3.78 (m, 1H), 3.60 (td,  $J$  5.7, 5.7, 2.4Hz, 1H), 3.28 (t,  $J$  1.8Hz, 2H), 3.17 (td,  $J$  5.7, 5.7, 2.4Hz, 1H), 3.01 (ddd,  $J$  14.7, 5.7, 2.4Hz, 1H), 2.87 (ddd,  $J$  14.7, 5.7, 2.4Hz, 1H), 2.45 (m, 4H), 1.9 – 1.0 (m, 16H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, 30 °C):  $\delta_{\text{C}}$  167.9 (IV), 167.4 (IV), 158.2 (IV), 136.3 (IV), 130.1, 121.0, 115.1, 114.9, 83.5 (IV), 79.3 (IV), 60.1, 56.4, 53.4 (2C), 48.7, 47.9, 39.0, 36.3, 32.8, 32.7, 25.9 (2C), 25.4, 24.7, 24.6 and 23.8; HRMS  $m/z$  437.5827 ( $\text{M}^+$   $\text{C}_{26}\text{H}_{35}\text{N}_3\text{O}_3$  requires 437.5822); Anal. Calcd for  $\text{C}_{26}\text{H}_{35}\text{N}_3\text{O}_3$ : C, 71.37; H, 8.06; N, 9.60%. Found: C, 71.61; H, 8.14; N, 9.61.

***N*-Cyclohexyl-2-(2-oxoazetidin-1-yl)-2-(3-{[4-(4-isopropylpiperazin-1-yl)but-2-ynyl]oxy}phenyl)acetamide (2.5).** Crude residue was purified via column chromatography, eluting with MeOH/DCM (0.5:9.5) to yield the product as a light yellow oil, (91.0 mg, 86%);  $R_{\text{f}}$  (MeOH/DCM, 0.5:9.5) 0.26; IR (DCM,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 2305w, 1740s, 1675s, 1265s and 1022m;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, 30 °C):  $\delta_{\text{H}}$  7.26 (m, 1H), 6.93 (m, 3H), 6.06 (br s, 1H), 5.25 (s, 1H), 4.67 (t,  $J$  2.0Hz, 2H), 3.73 (m, 1H), 3.59 (td,  $J$  5.6, 5.6, 2.8Hz, 1H), 3.29 (t,  $J$  2.0Hz, 2H), 3.16 (td,  $J$  5.6, 5.6, 2.8Hz, 1H), 2.96 (ddd,  $J$  14.8, 5.6, 2.8Hz, 1H), 2.83 (ddd,  $J$  14.8, 5.6, 2.8Hz, 1H), 2.65 (septet,  $J$  6.4Hz, 1H), 2.56 (br s, 8H), 2.0 – 1.1 (m, 10H), 1.02 (d,  $J$  6.4Hz, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, 30 °C):  $\delta_{\text{C}}$  167.8 (IV), 167.4 (IV), 158.2 (IV), 136.4 (IV), 130.1, 120.9, 115.1, 115.0, 83.0 (IV), 79.7 (IV), 59.9, 56.3 (2C), 54.5, 52.3, 48.7, 48.4 (2C), 47.1, 39.0, 36.3 (2C), 32.8 (2C), 25.4 (2C), 24.7, 18.5;  $m/z$  480.6514 ( $\text{M}^+$   $\text{C}_{28}\text{H}_{40}\text{N}_4\text{O}_3$  requires 480.6506); Anal. Calcd for  $\text{C}_{28}\text{H}_{40}\text{N}_4\text{O}_3$ : C, 69.97; H, 8.39; N, 11.66. Found: C, 70.14; H, 8.20; N, 11.60.

***N*-Cyclohexyl-2-(2-oxoazetidin-1-yl)-2-{3-[(4-piperazin-1-yl)but-2-ynyl]oxy}phenyl}acetamide (2.6).** Crude residue was purified via column chromatography, eluting with MeOH/EtOAc (0.5:9.5) to yield the product as a white powder, (67.4 mg, 65%); mp 115 – 117 °C;  $R_{\text{f}}$  (MeOH/EtOAc, 0.3:9.7) 0.14; IR (DCM,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 2305w, 1741s, 1672s, 1265s and 1025m;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, 30 °C):  $\delta_{\text{H}}$  7.25 (m, 1H), 6.92 (m, 3H), 6.18 (d,  $J$  8.0Hz, 1H), 5.29 (s, 1H), 4.67 (t,  $J$  1.6Hz, 2H), 3.73 (m, 1H), 3.59 (td,  $J$  5.6, 5.6, 2.8Hz, 1H), 3.31 (t,  $J$  1.6Hz, 2H), 3.17 (td,  $J$  5.6, 5.6, 2.8Hz, 1H), 2.95 (ddd,  $J$  14.8, 5.6, 2.8Hz, 1H), 2.83 (ddd,  $J$  14.8, 5.6, 2.8Hz, 1H), 2.56 (br s, 4H), 2.17 (br s, 2H), 1.84 (br s, 4H), 1.7 – 1.1 (m, 8H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, 30 °C):  $\delta_{\text{C}}$  167.9 (IV), 167.4 (IV), 158.1 (IV), 136.4 (IV), 130.1, 120.9, 115.0, 114.9, 82.7 (IV), 80.0 (IV), 59.8, 59.7, 56.3, 51.7 (2C), 48.7, 47.0, 39.1 (2C), 36.3, 32.8 (2C), 25.5, 24.8, 24.7; HRMS  $m/z$  438.5704 ( $\text{M}^+$   $\text{C}_{25}\text{H}_{34}\text{N}_4\text{O}_3$  requires 438.5700); Anal. Calcd for  $\text{C}_{25}\text{H}_{34}\text{N}_4\text{O}_3$ : C, 68.47; H, 7.81; N, 12.77. Found: C, 68.20; H, 7.53; N, 12.59.

***N*-Cyclohexyl-2-{3-[(4-morpholin-4-yl)but-2-ynyl]oxy}phenyl}-2-(2-oxoazetidin-1-yl)acetamide (2.7).** Crude residue was purified via column chromatography, eluting with MeOH/EtOAc (0.1:9.9 to 1:9) to yield the product as a white powder, (74.2mg, 77%); mp 102 – 105 °C;  $R_{\text{f}}$  (EtOAc) 0.17; IR (DCM,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 2305w, 1740s, 1682s, 1263s and 1031m;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz, 30 °C):  $\delta_{\text{H}}$  7.29 (m, 1H), 6.96 (m, 3H), 6.18 (d,  $J$  7.5Hz, 1H), 5.29 (s, 1H), 4.72 (t,  $J$  1.8Hz, 2H), 3.71 (m, 4H), 3.61 (td,  $J$  5.4, 5.4, 2.4Hz, 1H), 3.33 (t,  $J$  1.8Hz, 2H), 3.15 (td,  $J$  5.4, 5.4, 2.4Hz, 1H), 2.99 (ddd,  $J$  14.7, 5.4, 2.4Hz, 1H), 2.85 (ddd,  $J$  14.7, 5.4, 2.4Hz, 1H), 4.50 (m, 4H), 1.9 – 1.0 (m, 10H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, 30 °C):  $\delta_{\text{C}}$  167.8 (IV), 167.4 (IV),

158.1 (IV), 136.4 (IV), 130.0, 120.9, 115.4, 114.9, 82.5 (IV), 80.2 (IV), 66.8 (2C), 59.7, 56.2, 52.1 (2C), 48.7, 47.4, 38.9, 36.3, 32.8, 32.7, 25.5, 24.8 and 24.7; HRMS  $m/z$  439.5552 ( $M^+$   $C_{25}H_{33}N_3O_4$  requires 439.5547); Anal. Calcd for  $C_{25}H_{33}N_3O_4$ : C, 68.31; H, 7.57; N, 9.56. Found: C, 68.45; H, 7.67; N, 9.40.

**3-[(4-Morpholin-4-ylbut-2-ynyl)oxy]benzaldehyde (7).** Crude residue was purified via column chromatography, eluting with MeOH/EtOAc (0.3:9.7) to yield the product as a light-yellow oil, (1.57 g, 88%);  $R_f$  (hexane/EtOAc, 2:8) 0.26; IR (DCM,  $\nu_{max}$ ,  $cm^{-1}$ ) 3058w, 2862w, 2812w, 2312w, 1700s, 1586m, 1478m and 1266s;  $^1H$  NMR ( $CDCl_3$ , 300 MHz, 30 °C):  $\delta_H$  9.97 (s, 1H), 7.48 (m, 3H), 7.23 (m, 1H), 4.78 (t,  $J$  2.0Hz, 2H), 3.69 (m, 4H), 3.31 (t,  $J$  2.0Hz, 2H), 2.49 (m, 4H);  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz, 30 °C):  $\delta_C$  191.8 (IV), 158.2 (IV), 137.8 (IV), 130.1, 124.1, 122.3, 113.5, 83.1 (IV), 79.6 (IV), 66.8 (2C), 56.3, 52.3 (2C) and 47.4; HRMS  $m/z$  259.3053 ( $M^+$   $C_{15}H_{17}NO_3$  requires 259.3049); Anal. Calcd for  $C_{15}H_{17}NO_3$ : C, 69.48; H, 6.61; N, 5.40. Found: C, 69.40; H, 6.30; N, 5.68.

**General synthesis for  $\beta$ -lactams.**  $\beta$ -alanine (1.1 equiv), cyclohexyl isocyanide (1.0 equiv) and the appropriate aldehyde (1.0 equiv) were added to MeOH and allowed to stir at 25 °C for 48-72 hours. The reaction was monitored by TLC (1:1 EtOAc/hexane). Once the aldehyde spot had disappeared the reaction was deemed complete. The solvent was removed from the reaction mixture under reduced pressure. The crude mixture was purified using silica gel chromatography eluting with 1:1 EtOAc/hexane. This method is a slight variation on the method described by Pitlik and Townsend.<sup>9</sup>

***N*-(4-Methoxyphenyl)-2-{3-[(4-morpholin-4-ylbut-2-ynyl)oxy]phenyl}-2-(2-oxoazetidin-1-yl)acetamide (3.1).** Crude residue was purified via column chromatography, eluting with EtOAc to yield the product as a light-brown oil, (0.172 g, 97%);  $R$  (EtOAc) 0.22; IR (DCM,  $\nu_{max}$ ,  $cm^{-1}$ ) 2304w, 1743s, 1282s, 1262s and 1031 m;  $^1H$  NMR ( $CDCl_3$ , 400 MHz, 30 °C):  $\delta_H$  7.39 (d,  $J$  8.8Hz, 2H), 7.27 (m, 1H), 7.04 (m, 2H), 6.93 (m, 1H), 6.80 (d,  $J$  8.8Hz, 2H), 5.51 (s, 1H), 5.26 (s, 1H), 4.70 (s, 2H), 3.74 (s, 3H), 3.67 (m, 5H), 3.28 (s, 2H), 3.19 (td,  $J$  5.6, 5.6, 2.8Hz, 1H), 2.99 (ddd,  $J$  14.8, 5.6, 2.8Hz, 1H), 2.85 (ddd,  $J$  14.8, 5.6, 2.8Hz, 1H), 2.45 (m, 4H);  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz, 30 °C):  $\delta_C$  168.1 (IV), 166.5 (IV), 158.1 (IV), 156.6 (IV), 135.9 (IV), 130.8 (IV), 130.2, 121.7 (2C), 120.9, 115.9, 114.8, 114.1 (2C), 82.6 (IV), 80.3 (IV), 66.8 (2C), 60.2, 56.2, 55.5, 51.9 (2C), 47.3, 39.2 and 36.3; HRMS  $m/z$  463.5340 ( $M^+$   $C_{26}H_{29}N_3O_5$  requires 463.5334); Anal. Calcd for  $C_{26}H_{29}N_3O_5$ : C, 67.37; H, 6.31; N, 9.07. Found: C, 67.41; H, 6.59; N, 9.38.

***N*-(1,1,3,3-Tetramethylbutyl)-2-{3-[(4-morpholin-4-ylbut-2-ynyl)oxy]phenyl}-2-(2-oxoazetidin-1-yl)acetamide (3.2).** Crude residue was purified via column chromatography, eluting with MeOH/EtOAc (0.1:9.9) to yield the product as a white powder, (0.110 g, 62%); mp 86 – 89 °C;  $R_f$  (EtOAc) 0.38; IR (DCM,  $\nu_{max}$ ,  $cm^{-1}$ ) 2305w, 1737s, 1694s, 1266s and 1035m;  $^1H$  NMR ( $CDCl_3$ , 400 MHz, 30 °C):  $\delta_H$  7.27 (m, 1H), 6.93 (m, 3H), 5.93 (s, 1H), 5.19 (s, 1H), 4.69 (s, 2H), 3.69 (m, 4H), 3.59 (td,  $J$  6.0, 6.0, 2.8Hz, 1H), 3.30 (s, 2H), 3.14 (td,  $J$  6.0, 6.0, 2.8Hz, 1H), 2.95 (ddd,  $J$  14.8, 6.0, 2.8Hz, 1H), 2.84 (ddd,  $J$  14.8, 6.0, 2.8Hz, 1H), 2.49 (m, 4H), 1.74 (d,

$J$  14.8Hz, 1H), 1.56 (d,  $J$  14.8Hz, 1H), 1.38 (s, 3H), 1.34 (s, 3H), 0.89 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, 30 °C):  $\delta_{\text{c}}$  168.1 (IV), 167.2 (IV), 155.6 (IV), 136.8 (IV), 130.1, 121.1, 115.2, 115.0, 82.5 (IV), 80.1 (IV), 66.8 (2C), 60.4, 56.2, 52.1 (2C), 52.0, 47.4, 39.0, 36.3, 31.6, 31.5, 31.4, 29.0 and 28.7; HRMS  $m/z$  469.6256 ( $\text{M}^+$   $\text{C}_{27}\text{H}_{39}\text{N}_3\text{O}_4$  requires 469.6244); Anal. Calcd for  $\text{C}_{27}\text{H}_{39}\text{N}_3\text{O}_4$ : C, 69.05; H, 8.37; N, 8.95. Found: C, 69.13; H, 8.54; N, 9.06.

***N*-(1-Methylbutyl)-2-{3-[(4-morpholin-4-ylbut-2-ynyl)oxy]phenyl}-2-(2-oxoazetid-1-yl)acetamide (3.3).** Crude residue was purified via column chromatography, eluting with MeOH/EtOAc (0.1:9.9) to yield the product as a colourless oil, (0.148 g, 91%);  $R_{\text{f}}$  (EtOAc) 0.33; IR (DCM,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 2305w, 1735s, 1695s, 1266s and 1024m;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, 30 °C):  $\delta_{\text{H}}$  7.24 (m, 1H), 6.95 (m, 3H), 6.10 (m, 1H), 5.29 (s, 1H), 4.69 (s, 2H), 3.95 (m, 1H), 3.68 (m, 4H), 3.60 (td,  $J$  5.6, 5.6, 3.2Hz, 1H), 3.30 (s, 2H), 3.12 (td,  $J$  5.6, 5.6, 3.2Hz, 1H), 2.94 (ddd,  $J$  14.8, 5.6, 3.2Hz, 1H), 2.85 (ddd,  $J$  14.8, 5.6, 3.2Hz, 1H), 2.48 (m, 4H), 1.4 – 0.7 (m, 10H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, 30 °C):  $\delta_{\text{c}}$  167.8 (IV), 167.6 (IV), 158.1 (IV), 136.4 (IV), 130.1, 120.9, 115.4, 114.9, 82.5 (IV), 80.2 (IV), 66.8 (2C), 59.7, 56.2, 52.0 (2C), 47.4, 45.5, 38.9, 36.3, 27.3, 20.6, 19.2 and 13.9; HRMS  $m/z$  427.5444 ( $\text{M}^+$   $\text{C}_{24}\text{H}_{33}\text{N}_3\text{O}_4$  requires 427.5437); Anal. Calcd for  $\text{C}_{24}\text{H}_{33}\text{N}_3\text{O}_4$ : C, 67.42; H, 7.78; N, 9.83. Found: C, 67.53; H, 7.96; N, 9.57.

***N*-2-Naphthyl-2-{3-[(4-morpholin-4-ylbut-2-ynyl)oxy]phenyl}-2-(2-oxoazetid-1-yl)acetamide (3.4).** Crude residue was purified via column chromatography, eluting with hexane/EtOAc (3:7) to EtOAc, to yield the product as a light-brown oil, (0.152 g, 82%);  $R_{\text{f}}$  (EtOAc) 0.26; IR (DCM,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 2305w, 1737s, 1694s, 1266s and 1021m;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, 30 °C):  $\delta_{\text{H}}$  7.73 (m, 3H), 7.4 – 7.2 (m, 5H), 7.08 (m, 2H), 6.95 (m, 1H), 5.60 (s, 1H), 5.26 (s, 1H), 4.71 (s, 2H), 3.71 (m, 5H), 3.25 (m, 3H), 3.03 (ddd,  $J$  14.8, 5.6, 2.8Hz, 1H), 2.92 (ddd,  $J$  14.8, 5.6, 2.8Hz, 1H), 2.50-2.42 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, 30 °C):  $\delta_{\text{c}}$  168.3 (IV), 167.0 (IV), 158.1 (IV), 135.7 (IV), 135.2 (IV), 133.8 (IV), 130.8 (IV), 130.2, 128.7, 127.7, 127.5, 126.5, 125.1, 120.9, 119.8, 116.9, 116.0, 114.8, 82.6 (IV), 80.2 (IV), 66.8 (2C), 60.6, 56.2, 51.9 (2C), 47.3, 39.3 and 36.3; HRMS  $m/z$  483.5674 ( $\text{M}^+$   $\text{C}_{29}\text{H}_{29}\text{N}_3\text{O}_4$  requires 483.5670); Anal. Calcd for  $\text{C}_{29}\text{H}_{29}\text{N}_3\text{O}_4$ : C, 72.03; H, 6.04; N, 8.69. Found: C, 72.33; H, 6.27; N, 8.77.

***N*-{[(4-Methoxyphenyl)sulfonyl]methyl}-2-{3-[(4-morpholin-4-ylbut-2-ynyl)oxy]phenyl}-2-(2-oxoazetid-1-yl)acetamide (3.5).** Crude residue was purified via column chromatography, eluting with MeOH/EtOAc (0.1:9.9 to 0.3:9.7), to yield the product as a light-brown oil, (0.143 g, 69%);  $R_{\text{f}}$  (EtOAc) 0.16; IR (DCM,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 2305w, 1745s, 1700s, 1324s, 1266s, 1145s and 1031;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, 30 °C):  $\delta_{\text{H}}$  7.64 (m, 3H), 7.25 (m, 2H), 6.94 (m, 1H), 6.89 (m, 1H), 6.77 (m, 1H), 5.36 (s, 1H), 4.74 (dd,  $J$  14.0, 6.8Hz, 1H), 4.72 (s, 2H), 4.51 (dd,  $J$  14.0, 6.8Hz, 1H), 3.70 (m, 4H), 3.41 (td,  $J$  5.6, 5.6, 2.8Hz, 1H), 3.34 (s, 2H), 3.02 (td,  $J$  5.6, 5.6, 2.8Hz, 1H), 2.90 (ddd,  $J$  14.4, 5.6, 2.8Hz, 1H), 2.81 (ddd,  $J$  14.4, 5.6, 2.8Hz, 1H), 2.51 (m, 4H), 2.41 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, 30 °C):  $\delta_{\text{c}}$  168.3 (IV), 167.7 (IV), 158.0 (IV), 145.3 (IV), 134.9 (IV), 134.0 (IV), 130.1, 130.0 (2C), 128.8 (2C), 121.0, 116.1, 114.9, 82.3 (IV), 80.5 (IV), 66.6 (2C), 60.2, 59.0, 56.1, 51.9 (2C), 47.3, 38.8, 36.3 and 21.7; HRMS  $m/z$  541.6257 ( $\text{M}^+$   $\text{C}_{27}\text{H}_{31}\text{N}_3\text{O}_7\text{S}$  requires 541.6250); Anal. Calcd for  $\text{C}_{27}\text{H}_{31}\text{N}_3\text{O}_7\text{S}$ : C, 59.88; H, 5.77; N, 7.76. Found: C, 60.11; H, 5.94; N, 7.70.

***N*-Benzyl-2-{3-[(4-morpholin-4-ylbut-2-ynyl)oxy]phenyl}-2-(2-oxoazetidin-1-yl)acetamide (3.6).** Crude residue was purified via column chromatography, eluting with MeOH/EtOAc (0.3:9.7), to yield the product as a light-brown oil, (0.168 g, 99%);  $R_f$  (MeOH/EtOAc, 0.3:9.7) 0.26; IR (DCM,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ) 2306w, 1745s, 1683s, 1264s and 1024m;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, 30 °C):  $\delta_{\text{H}}$  7.62 (m, 3H), 7.12 (m, 3H), 6.95 (m, 3H), 6.76 (br s, 1H), 5.37 (s, 1H), 4.67 (m, 2H), 4.43 (dd,  $J$  14.8, 6.0Hz, 1H), 4.38 (dd,  $J$  14.8, 6.0Hz, 1H), 3.60 (m, 5H), 3.28 (s, 2H), 3.12 (td,  $J$  5.6, 5.6, 2.8Hz, 1H), 2.93 (ddd,  $J$  14.8, 5.6, 2.4Hz, 1H), 2.82 (ddd,  $J$  14.8, 5.6, 2.4Hz, 1H), 2.45 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, 30 °C):  $\delta_{\text{C}}$  168.4 (IV), 167.9 (IV), 158.1 (IV), 137.8 (IV), 136.0 (IV), 130.1, 128.7 (2C), 127.7 (2C), 127.5, 121.0, 115.6, 115.0, 82.5 (IV), 80.2 (IV), 66.7 (2C), 59.6, 56.2, 52.0 (2C), 47.3, 43.7, 39.0 and 36.3; HRMS  $m/z$  447.5351 ( $\text{M}^+$   $\text{C}_{26}\text{H}_{29}\text{N}_3\text{O}_4$  requires 447.5340); Anal. Calcd for  $\text{C}_{26}\text{H}_{29}\text{N}_3\text{O}_4$ : C, 69.78; H, 6.53; N, 9.39. Found: C, 69.57; H, 6.41; N, 9.45.

***N*-(1*H*-1,2,3-Benzotriazol-1-ylmethyl)-2-{3-[(4-morpholin-4-ylbut-2-ynyl)oxy]phenyl}-2-(2-oxoazetidin-1-yl)acetamide (3.7).** Crude residue was purified via column chromatography, eluting with EtOAc to yield the product as a brown powder, (0.113 g, 60%); mp 131 – 134 °C;  $R_f$  (MeOH/DCM, 0.5:9.5) 0.21; IR (DCM,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ) 2163m, 1743s, 1705s, 1265s and 1035m;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, 30 °C):  $\delta_{\text{H}}$  8.15 (t,  $J$  6.4Hz, 1H) 7.98 (dt,  $J$  8.4, 2.0, 2.0Hz, 1H), 7.87 (dt,  $J$  8.4, 2.0, 2.0Hz, 1H), 7.48 (td,  $J$  7.6, 7.6, 1.6Hz, 1H), 7.35 (td,  $J$  7.6, 7.6, 1.6Hz, 1H), 7.11 (t,  $J$  8.4Hz, 1H), 6.84 (dd,  $J$  7.6, 1.6Hz, 1H), 6.80 (t,  $J$  2.0Hz, 1H), 6.70 (dd,  $J$  7.6, 1.6Hz, 1H), 6.11 (dd,  $J$  14.0, 6.4Hz, 1H), 5.99 (dd,  $J$  14.0, 6.4Hz, 1H), 5.38 (s, 1H), 4.55 (t,  $J$  1.6Hz, 2H), 3.66 (m, 4H), 3.51 (td,  $J$  5.6, 2.8Hz, 1H), 3.28 (t,  $J$  1.6Hz, 2H), 3.04 (td,  $J$  5.6, 2.8Hz, 1H), 2.91 (ddd,  $J$  14.4, 5.6, 2.8Hz, 1H), 2.80 (ddd,  $J$  =14.4, 5.6, 2.8Hz, 1H), 2.43 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz, 30 °C):  $\delta_{\text{C}}$  169.5 (IV), 169.4 (IV), 167.9 (IV), 158.0 (IV), 146.0 (IV), 135.0 (IV), 130.1, 128.0, 124.0, 120.8, 119.7, 116.1, 114.9, 110.7, 82.5 (IV), 80.2 (IV), 66.8 (2C), 59.2, 56.0, 51.8 (2C), 51.0, 47.3, 38.8 and 36.4; HRMS  $m/z$  488.5468 ( $\text{M}^+$   $\text{C}_{26}\text{H}_{28}\text{N}_6\text{O}_4$  requires 488.5461); Anal. Calcd for  $\text{C}_{26}\text{H}_{28}\text{N}_6\text{O}_4$ : C, 63.92; H, 5.78; N, 17.20. Found: C, 64.28.; H, 6.05; N, 17.29.

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