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Research article

1,2,3-Triazole β-lactam conjugates as antimicrobial agents

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ABSTRACT

A convenient and efficient synthesis of new triazole β-lactam conjugates using click chemistry is described. β-lactam **15** and **16** were prepared using cycloaddition strategy and propargylated at *N*-1 to afford compounds **17** and **18**. Cu-catalyzed click reaction of these β-lactams **17** and **18** with different aryl azides provided 1,2,3-triazole conjugates **6** and **7**, respectively. The products were fully characterized spectroscopically and tested against Gram-(+) and Gram-(-) bacteria. Compound **7a** and **7c** were found to be most active.

1. Introduction

Preantibiotic era diminished its effect by the discovery of penicillin in 1928 [1]. Different classes of antibiotics such as carbapenem, cephalosporin, monobactams have resulted from the modifications of the azetidin-2-one core [2]. Suitable modifications of key motif azetidin-2-one (monocyclic β-lactams) have displayed many pharmacological activities [3, 4] *viz* antimalarial [5], anticholesterolemic [6], anti-inflammatory, and antimicrobial [7, 8] activities. As the structural core, monocyclic β-lactam displays a broad spectrum of antimicrobial activity with low toxicity and high efficacy. The main mechanism of the antibacterial action showed an inhibitory effect on essential structural components of bacterial cell wall biosynthesis [9, 10, 11]. Monocyclic β-lactam is the only class of β-lactams that has not become the victim of β-lactamase [12, 13, 14, 15]. Aztreonam and carumonam [16] are two monobactams known for their antimicrobial activity. Aztreonam is the first clinically used synthetic monocyclic β-lactam drug (Figure 1) [17]. 1,2,3-Triazole derivatives have shown promising biological activity, including inhibitory effect against different bacteria [18, 19, 20, 21]. With these inspirations, new 1,2,3-triazole β-lactam conjugates **5** were envisioned.

In the prevailing literature, the 1,2,3-triazole attached with *β*-lactam core has been reported to exhibit various pharmaceutical properties [22, 23, 24, 25]. For example, β-lactam core with triazole at *C*-3 position *i.e.* 3-(1,2,3-triazol-1-yl)-*β*-lactams showed anti-plasmodial activity [22]. Ferrocenylchalcone-*β*-lactam conjugates were active against *Plasmodium falciparum* [23]. 1,2,3-Triazole tethered *β*-lactam-chalcone bifunctional hybrids showed anticancer activity [24]. Monocyclic *β*-lactam with triazole ring at position *C*-4 *i.e.* 2-((4-((2-Chloro-5-(trifluoromethyl) benzamido) methyl)-1*H*-1,2,3-triazol-1-yl)methyl)-4-oxoazetidin-1-yl 4-methyl benzenesulfonate displayed antimicrobial activity [25]. In our best of knowledge, there is no report on the synthesis of triazole ring at position 1 of the *β*-lactam ring. *i.e.,* at position *N*-1. In our present work, generation of triazole ring at the nitrogen of the *β*-lactam ring is discussed (Figure 2).

The primary mode of action of *β*-lactams to kill bacteria is inhibition of transpeptidases, which form peptidoglycan by cross-linking the peptides. Absence of cross-linking causes the disruption of the cell wall [11]. Lipophilicity is directly relating the biological activities due to its dependency upon solubility, toxicity, permeability, and protein binding [26]. Lipophilicity plays a vital role in antimicrobial activity due to drug bioavailability (how much molecule permeable to the cell wall). Therefore, a molecule with high lipophilicity would easily penetrate through the cell wall and display the biological effect. Compounds with short alkyl chains are effective against yeast and fungi, whereas bacteria (gram-negative organisms) have susceptible to the compounds with long alkyl chains [27]. Thus, the correlation between activity with lipophilicity can be used to design new molecules or to modify others. Based on these facts, new β-lactams were intended to incorporate long alkyl chains to improve the lipophilicity of the molecule.

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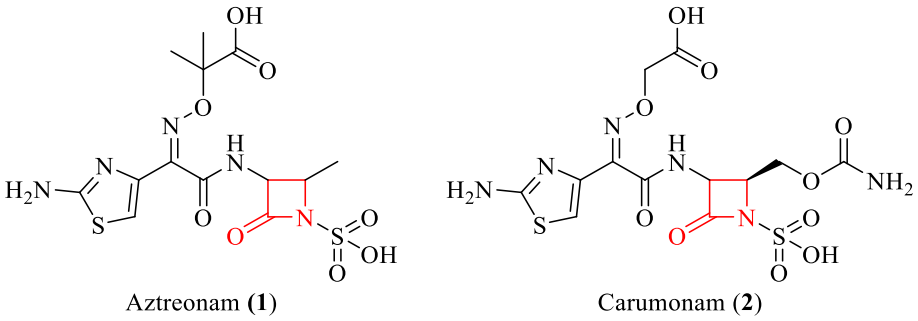


Figure 1. Representative examples of monocyclic β-lactam antimicrobials.

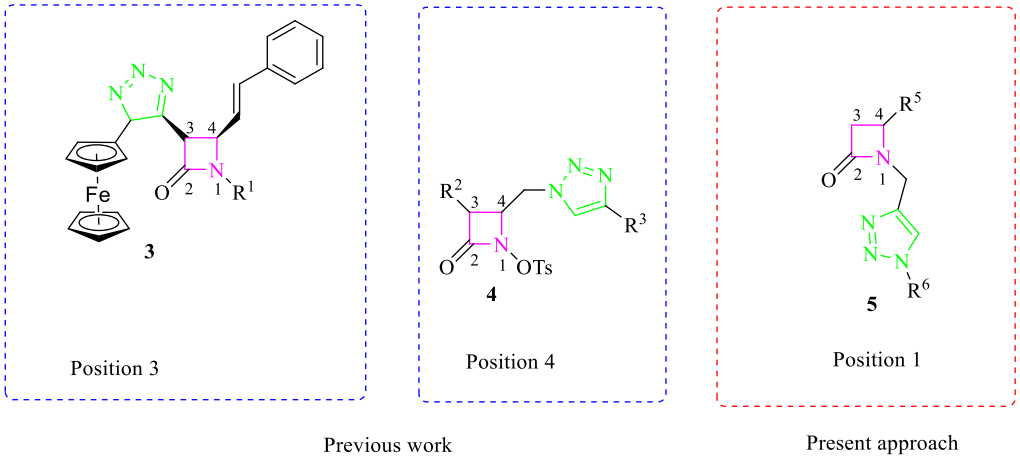


Figure 2. Generation of 1,2,3-triazole on different positions of the *β*-lactam ring.

The current methodology provides two points to enhance lipophilicity in the scaffolds shown in Figure 3. These molecules could be prepared by generating a triazole linker using Copper(I)-catalyzed Azide-Alkyne Cycloaddition (CuAAC) reaction between alkyne **9** and aryl azides **10**. The compound **9** could be obtained by propargylation of azetidin-2-one **11** (Scheme 1).

2. Results and discussion

Among various reported methods [4, 28, 29, 30] for the preparation of azetidin-2-ones, the cycloaddition of chlorosulphonyl isocyanate (**13**, CSI) with alkene provides an efficient and one-pot procedure to produce 4-substituted azetidin-2-one derivatives [31]. Under anhydrous and dry reaction conditions, chlorosulphonyl isocyanate **13** undergoes cycloaddition reaction with alkene **14** (n = 1 or 2) to produce azetidin-2-one derivative **15** (n = 1) or **16** (n = 2). Lower yields could be attributed to high reactivity and moisture sensitivity of CSI. Azetidin-2-ones (**15** and **16**) thus formed were subjected to propargylation using standard propargylation reaction conditions [32, 33] to yield compound **17** and **18** in good yields. These new products were fully characterized spectroscopically. In compound **15** and **16**, NH proton appears as a broad singlet at δ 5.85 ppm. The NH broad singlet disappeared in proton NMR of compounds **17** and **18**, and characteristics peaks of the acetylenic proton were observed at δ 2.26 (t, 1H, J = 2.56 Hz) ppm. These observations confirm the formation and structure of **17** and **18**.

Next, azides **10** were prepared using the literature method from corresponding substituted anilines [34]. These azides were used as ethyl acetate solution without further purification. The ethyl acetate solution of azide can be stored in a refrigerator overnight without loss of reactivity or yield. Having prepared azides and propargyl derivatives **17** and **18**, copper-catalyzed Huisgen 1,3-dipolar cycloaddition was tested. Aryl azides **10** were reacted with β-lactam **17** in the presence of Cu(I) catalyst

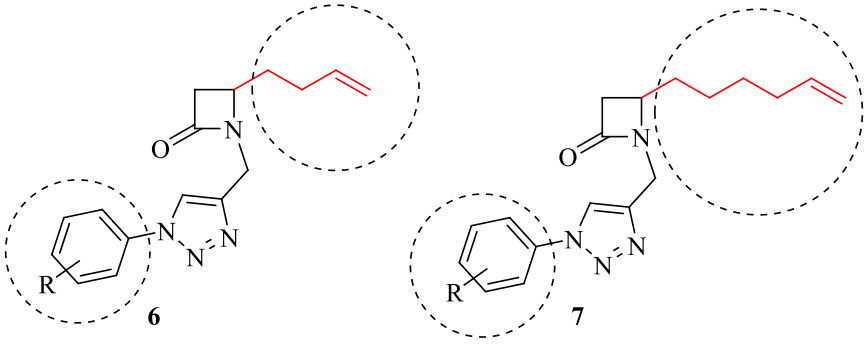
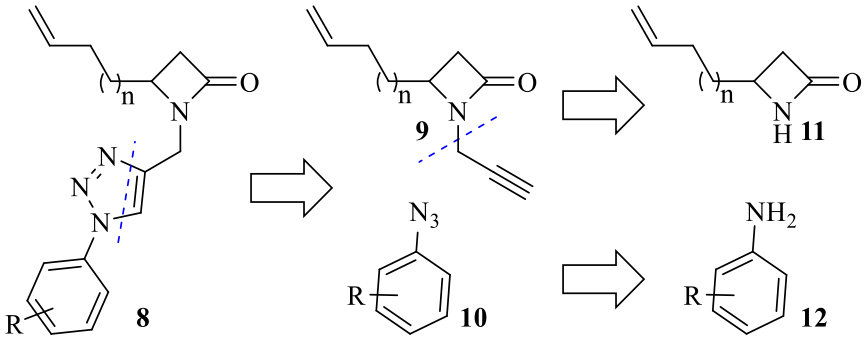


Figure 3. Synthetic approach to improve lipophilicity.



Scheme 1. Synthetic strategy.

to yield respective cycloadducts **6** in moderate to good yield (Scheme 2). All newly synthesized compounds were fully characterized spectroscopically. In the IR spectrum of the cycloadduct **6a**, the absorption bands in the region 1716.68 cm^{-1} for C=O group, two absorption bands in the region 1519.7, 1338.19 $cm^{-1}$for NO_2 while 1458 cm^{-1} were observed and the presence of these signals revealed the formation of triazole ring. ^{1}H NMR and ^{13}C NMR spectroscopic data satisfy the structure of these compounds. The triazole ring consists of one proton, which appeared as a singlet at δ 8.13 ppm. The triazole ring is connected with the β-lactam ring by methylene. These protons have appeared as two doublets of doublets at δ 4.71 and 4.45 (J = 15.88 Hz) ppm. Two double doublets at δ 2.63, 3.02 (J = 14.64 Hz), and one multiplet at δ 3.73–3.68 were assigned to protons present in the β-lactam ring. Aromatic protons were appeared as multiplets at δ 8.33–8.30, 8.16–8.14, triplet 8.63 (J = 2.21 Hz) and 7.76 (J = 8.2 Hz) ppm. Protons for the aliphatic chain attached at C-4 of the β-lactam ring showed multiplets at δ 5.82–5.75 ppm and δ 5.02–4.96 ppm for vinylic protons. Other remaining protons of the aliphatic chain appeared as multiplets on δ 2.15–1.51 ppm. ^{13}C NMR spectral data further supported the formation of these cycloadducts. A signal due to the carbonyl carbon of the β-lactam ring appeared at δ 167.14 ppm. Two carbons present in newly formed 1,2,3-triazole ring carbon appeared at δ144.81, 120.55 ppm, while carbon connecting 1,2, 3-triazole with β-lactam ring showed the signal at δ 52.02 ppm. These spectroscopic data confirms the formation of the triazole ring and the structure.

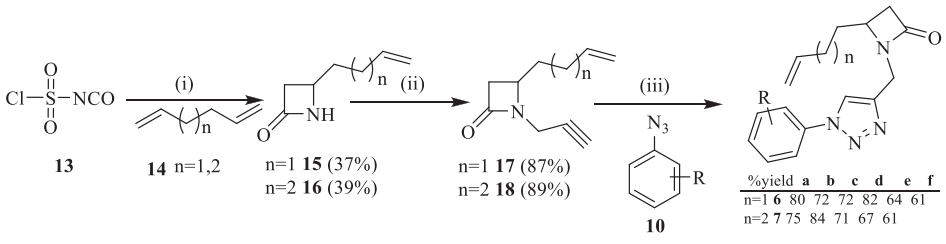
When different azides **10** were treated with compound **18**, the cycloadducts **7** were obtained in moderate to good yield. Mass analysis of **7a** (analyzed for $C_{18}H_{21}N_5O_3$) showed the molecular ion peak at 356.1717. The IR spectrum displayed vibrations at 1717cm^{-1} for C=O, 1519, 1338 cm^{-1} for NO_2 while the presence of a signal at 1438 cm^{-1} revealed the formation of the triazole ring. ^{1}H NMR spectrum of compound **7a** showed characteristic spectral features of the β-lactam ring. Two doublets of doublet at δ 2.60, 3.02 (J = 14.64 Hz) ppm, one multiplet appeared around δ 3.70–3.65 ppm were assigned for the protons of the β-lactam ring. The four protons of the aromatic ring appeared as a set of multiplet at δ 7.76, 8.18, 8.33, and 8.63 ppm. The singlet at δ 8.16 ppm was assigned to proton present at C-5 carbon of 1,2,3-triazole ring. Two doublets at δ 4.43 ppm and 4.71 ppm were due to methylene protons connecting the β-lactam ring with a triazole ring. ^{13}C NMR spectrum showed 18 signals. The signal due to the carbonyl carbon of the β-lactam ring appeared at δ 167.27 ppm. Two carbons of the 1,2,3-triazole ring appeared at δ 144.8, and 120.5 ppm. The carbon linking 1,2,3-triazole with β-lactam ring showed a signal at δ 52.3 ppm. The signals due to carbons in the aliphatic chain appeared in the region δ 42.6–24.8 ppm, while that of CH_2 = CH appeared at 115.3 and 114.7 ppm. Remaining signals in the region between δ148.97–115.3 ppm were attributed to carbons in the aromatic ring attached to the triazole ring. All spectroscopic data confirm the structure of cycloadduct **7a**. The physical properties of synthesized compounds are summarized in Table 1.

2.1. Antimicrobial activity and structure activity relationship

All compounds were screened by spot assay method against *Pseudomonas aeruginosa MTCC1034, Bacillus subtilis* MTCC441 and methicillin-sensitive *S. aureus* (MSSA) ATCC29213 (Table 2). All compounds were inactive against *S. aureus*. Among the synthesized compounds, having electron-withdrawing groups (nitro, chloro) at 3rd-position of benzene ring were found to be active for *P. aeruginosa*, and *B. subtilis*. Compounds with electron-withdrawing group NO_2 and electron releasing OCH_3 at *p*-position was inactive against *P. aeruginosa* but showed moderate activity against *B. subtilis*. *p*-Cl substituted compounds showed moderate activity against *P. aeruginosa*, *B. subtilis*. Overall, substitution at meta-position was found useful. Compounds with a long alkyl chain displayed better activity. Compound **7a** found most active among the series. To conclude it, Compound **7a** could be carried forward to further studies.

3. Conclusion

In conclusion, a methodology to prepare triazole-2-azetidinone conjugates is described. In this methodology, the triazole ring was installed at the *N*-1 of the azetidin-2-one ring using a methylene tether. These final products were fully characterized spectroscopically and tested against Gram-(+) and Gram-(-) bacteria. Compound **7a** and **7c** were found to be most active. Further, compounds **7** are more lipophilic and is more active as compared to compounds **6**, due to the presence of a long side chain.



Scheme 2. Reagents and conditions: (i) DCM, room temperature, (ii) Propargyl bromide, KOH, TBAB, THF (iii) ^{t}BuOH:H_2O (1:1), Copper acetate, sodium ascorbate.

Table 1. Physical properties of compound 6 and 7.

Compound	R	Color	Physical State	MP (°C)
6a	3-NO_2	White	Solid	35–37
6b	4-NO_2	White	Semi-solid	-
6c	3-Cl	White	Semi-solid	-
6d	4-Cl	White	Semi-solid	-
6e	4-OMe	White	Semi-solid	-
6f	Benzyl	White	Semi-solid	-
7a	3-NO_2	Pale yellow	Semi-solid	-
7b	4-NO_2	White	Semi-solid	-
7c	3-Cl	White	Solid	228–230
7d	4-Cl	White	Semi-solid	-
7e	4-OMe	White	Semi-solid	-

Table 2. Antimicrobial activity of synthesized compounds.

Compound	MIC(μg/ml) *B. subtilis*	MIC(μg/ml) *P. aeruginosa*
6a	5	10
6b	20	40
6c	10	5
6d	ND	ND
6e	5	10
6f	20	5
7a	1.25	1.25
7b	ND	ND
7c	1.25	1.25
7d	ND	ND
7e	20	10
Standard drug (ampicillin)	0.5	1

4. Experimental

All chemicals and solvents were purchased from Merck, Spectrochem, and/or S. D. Fine-chem. Melting points were determined by open capillary using the digital melting point apparatus and are uncorrected. ^{1}H NMR, and ^{13}C NMR spectra were recorded in deuteron chloroform with Bruker Advance II spectrometer (400 and 100 MHz, 500 and 126 MHz, respectively) in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard. The chemical shift values are expressed as parts per million downfield from TMS, and *J* values are in hertz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet, dd: double doublet, and br: broad peak. High-resolution mass spectra were recorded on Bruker-micrOTOF-Q II spectrometer. Column chromatography was performed on a silica gel (100–200 mesh). Thin-layer chromatography was used to monitor the progress of the reactions. Spectral data and copies of spectra are available as supplementary content online.

4.1. General procedure for preparation of N-propargylated azetidin-2-one (17 and 18) [31]

Handling of chlorosulphonyl isocyanate [35]: Chlorosulphonyl isocyanate is the most chemically reactive isocyanate known and reacts violently with water (**Danger!**). It can be stored indefinitely in sealed glass ampules, but polyethylene bottles with screw caps are best suited for storage in the laboratory at 4 °C. It should be used in a well ventilated and efficient fumehood. Reaction systems and equipment must be scrupulously dry. Appropriate eye protection, protective gloves, and protective clothing should be used. In case of fire, DO NOT USE WATER! Use dry chemical, dry sand, or carbon dioxide extinguishing media.

Azetidin-2-one (**15** or **16**) was synthesized by reacting chlorosulphonyl isocyanate (0.01 mol) with 1,5-hexadiene or 1,7-octadiene (0.01 mol) using modified literature method [31]. Prepared Azetidin-2-one (2.94 mmol, 1 equiv.) reacted with propargyl bromide (3.23 mmol 1.1 equiv.) in the presence of KOH (3.23 mmol, 1.1 equiv.) and tertiary butyl ammonium bromide (0.47mmol, 0.16 equiv.) in anhydrous THF (5 mL) stirred under nitrogen at room temperature for 3h monitored by TLC. Then, the mixture extracted with ethyl acetate, washed with water to afford the corresponding 4-(but-3-en-1-yl)-1-(-prop-2-yn-1-yl)azetidin-2-one **17** or 4-(hex-5-en-1-yl)azetidin-2-one **18** respectively. Purification with column chromatography (Silica gel, 100–200 mesh; pet ether: ethyl acetate) afforded pure products.

4.2. General procedure for click reaction [36, 37]

To a solution of *N*-propargyated azetidin-2-one **(17** or **18)**, substituted azide **10**, cupric acetate (10 mol%), and sodium ascorbate (20% mol) were added in a solution of water (4 mL) and *tert*-butyl alcohol (4 mL) at room temperature with stirring for 24 h. Upon completion of the reaction (monitored by TLC), the mixture was diluted with water, extracted with ethyl acetate, and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the final compounds were chromatographed (DCM/Methanol) to yield pure products (**6** or **7**).

4-(but-3-en-1-yl)-1-((4-(3-nitrophenyl)-1*H*-1,2,3-triazol-1-yl) methyl)azetidin-2-one (6a) White color, MP:35–37 °C, Yield: 877 mg, 80%, FTIR (thin film, cm^{-1}) 1716.68, 1519.7, 1412.96, 1338.19; ^{1}H (400 MHz, $CDCl_3$, ppm): 8.63 (t, 1H, *J* = 2.08 Hz), 8.33–8.30 (m, 1H), 8.16–8.14 (m, 1H), 8.13 (s, 1H), 7.76 (t, 1H, *J* = 8.2 Hz), 5.84–5.74 (m, 1H), 5.06–4.98 (m, 2H), 4.71 (d, 1H, *J* = 15.84 Hz), 4.45 (d, 1H, *J* = 15.88 Hz) 3.73–3.68 (m, 1H), 3.03 (dd, 1H, *J* = 4.92, 14.68 Hz), 2.63 (dd, 1H, *J* = 2.28, 14.64 Hz), 2.15–2.02 (m, 3H), 1.58–1.51 (m, 1H);^{13}C (100 MHz, $CDCl_3$, ppm) 167.14, 148.97, 144.81, 137.62, 137.01, 131.02, 125.82, 123.35, 120.55, 115.66, 115.36, 52.02, 42.70, 35.87, 32.05, 29.72; HRMS (ESI): *m/z* calcd for $C_{16}H_{18}N_5O_3$ (M + H): 328.1410; found 328.1404.

4-(but-3-en-1-yl)-1-((4-(4-nitrophenyl)-1*H*-1,2,3-triazol-1-yl) methyl)azetidin-2-one (6b) White color, semi solid, Yield: 789 mg, 72%; FTIR (thin film, cm^{-1}) 1717.74, 1519.79, 1438.91, 1412.96, 1339.88; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 8.45–8.40 (m, 2H), 8.13 (s, 1H), 8.00–7.96 (m, 2H), 5.82–5.73 (m, 1H), 5.06–4.98 (m, 2H), 4.70 (d, 1H, *J* = 15.88 Hz), 4.45 (d, 1H, *J* = 15.88 Hz), 3.72–3.69 (m, 1H), 3.02 (dd, 1H, *J* = 4.96, 14.68 Hz), 2.62 (dd, 1H, *J* = 2.32, 14.68 Hz), 2.15–2.04 (m, 3H), 1.53–1.59 (m, 1H); ^{13}C (100 MHz, $CDCl_3$, ppm) 167.15, 147.33, 144.93, 141.00, 136.94, 125.60, 120.53, 120.49, 115.68, 52.04, 42.72, 35.84, 32.04, 29.74; HRMS (ESI): *m/z* calcd for $C_{16}H_{18}N_5O_3$ (M + H): 328.1410; found 328.1407.

4-(but-3-en-1-yl)-1-((4-(3-chlorophenyl)-1*H*-1,2,3-triazol-1-yl) methyl)azetidin-2-one (6c) White color, semi solid, Yield: 210 mg, 72%; FTIR (thin film, cm^{-1}): 1663, 1406.56, 1436.31, 1310.89, 1260.86, 1026.51, 953.13, 800.44, 698.83, 668.64, 532.80; ^{1}H (400 MHz, $CDCl_3$, ppm): 8.03 (s, 1H), 7.79 (t, 1H, *J* = 1.92 Hz), 7.64–7.62 (m, 1H),

7.48–7.40 (m, 2H), 5.81–5.72 (m, 1H), 5.05–5.00 (m, 2H), 4.69 (d, 1H, J = 15.8 Hz), 4.42 (d, 1H, J = 15.8 Hz), 3.71–3.67 (m, 1H), 3.01 (dd, 1H, J = 4.92, 14.64 Hz), 2.61 (dd, 1H, J = 2.2, 14.64 Hz), 2.13–2.00 (m, 3H) 1.57–1.51 (m, 1H); ^{13}C (100 MHz, $CDCl_3$, ppm) 167.28, 144.17, 139.27, 137.74, 137.04, 135.68, 130.89, 128.98, 120.60, 115.61, 114.08, 52.00, 42.58, 35.89, 33.82, 28.97; HRMS (ESI): m/z calcd for $C_{16}H_{18}ClN_4O$ (M + H): 317.1169; found 317.1164.

4-(but-3-en-1-yl)-1-((4-(4-chlorophenyl)-1*H*-1,2,3-triazol-1-yl) methyl)azetidin-2-one (6d) White color, semi solid, Yield: 317 mg, 82%; FTIR (thin film, cm^{-1}): 1660, 1436.3, 1405.5,1310.8, 1260.8, 1026.5, 953.1, ^{1}H (400 MHz, $CDCl_3$, ppm): 7.99 (s, 1H), 7.70–7.67 (m, 2H), 7.53–7.49 (m, 2H), 5.81–5.72 (m, 1H), 5.05–4.97 (m, 2H), 4.69 (d, 1H, J = 15.8 Hz), 4.42 (d, 1H, J = 15.8 Hz), 3.70–3.66 (m, 1H), 3.01 (dd, 1H, J = 4.96, 14.64 Hz), 2.61 (dd, 1H, J = 2.28, 14.64 Hz), 2.13–2.02 (m, 3H), 1.57–1.52 (m, 1H); ^{13}C (100 MHz, $CDCl_3$, ppm): 167.09, 144.16, 137.05, 135.36, 134.69, 129.98,121.62, 120.50, 115.58, 51.89, 42.60, 35.83, 31.97, 29.69; HRMS (ESI): m/z calcd for $C_{16}H_{18}ClN_4O$ (M + H): 317.1169; found 317.1188.

4-(but-3-en-1-yl)-1-((4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl) methyl)azetidin-2-one (6e) White color, semi solid, Yield: 468 mg, 64%; FTIR (thin film, cm^{-1}): 1667, 1559, 1520, 1497, 1243, 1194, 1158, 1029, 927; ^{1}H (400 MHz, $CDCl_3$, ppm): 7.90 (s, 1H), 7.63–7.60 (m, 2H), 7.04–7.00 (m, 2H), 5.82–5.72 (m, 1H), 5.05–4.96 (m, 2H), 4.69 (d, 1H, J = 15.72 Hz), 4.40 (d, 1H, J = 15.76 Hz), 3.87 (s, 3H), 3.70–3.65 (m, 1H), 3.00 (dd, 1H, J = 4.96, 14.6 Hz), 2.60 (dd, 1H, J = 2.36, 14.6 Hz), 2.13–2.00 (m, 3H)1.57–1.49 (m, 1H); ^{13}C (100 MHz, $CDCl_3$, ppm) 167.04,159.94, 143.67, 137.11, 130.38, 122.13, 120.65, 115.54, 114.82, 55.64, 51.81, 42.57, 35.88, 31.97, 29.70; HRMS (ESI): m/z calcd for $C_{17}H_{20}N_4NaO_2$ (M + Na): 335.1484; found 335.1478.

1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-4-(but-3-en-1-yl)azetidin-2-one (6f) White color, semi solid, Yield: 442 mg, 61%; FTIR (thin film, cm^{-1}): 1660.19, 1406.8, 1436.43, 1310.92, 1027.92, 953.4, 699.10, 668.83, 560.46; ^{1}H (400 MHz, $CDCl_3$, ppm): 7.44 (s, 1H), 7.39–7.35 (m, 3H), 7.28–7.24 (m, 2H), 5.78–5.68 (m, 1H), 5.50 (m, 2H), 5.01–4.94 (m, 2H), 4.57 (d, 1H, J = 15.72 Hz), 4.32 (d, 1H, J =15.72 Hz), 3.63–3.58 (m, 1H), 2.95 (dd, 1H, J = 4.96, 14.96 Hz), 2.54 (dd, 1H, J = 2.32, 14.56 Hz), 2.07–2.02 (m, 2H), 1.99–1.92 (m, 1H), 1.50–1.42 (m, 1H). ^{13}C (100 MHz, $CDCl_3$, ppm): 166.91, 143.57, 137.11, 134.41, 129.17, 128.86, 128.08, 122.15, 115.44, 54.28, 51.75, 42.48, 35.89, 31.93, 31.63, 29.63; HRMS (ESI): m/z calcd for $C_{17}H_{20}N_4NaO$ (M + Na): 319.1535; found 319.1538.

4-(hex-5-en-1-yl)-1-((1-(3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl) methyl)azetidin-2-one (7a) pale yellow color, semi solid, Yield: 451 mg, 75%; FTIR (thin film, cm^{-1}): 1717, 1436, 1406, 1313,1018, 952, 889, 669; ^{1}H (400 MHz, $CDCl_3$, ppm): 8.63 (t, 1H, J = 2.08 Hz), 8.33–8.30 (m, 1H), 8.17–8.15 (m, 1H), 8.16 (s, 1H), 7.76 (t, 1H, J = 8.2 Hz), 5.82–5.72 (m, 1H), 5.02–4.92 (m, 2H), 4.71 (d, 1H, J = 15.88 Hz), 4.43(d 1H, J = 15.84 Hz), 3.70–3.65 (m, 1H), 3.02 (dd, 1H, J = 4.92, 14.6 Hz), 2.60 (dd, 1H, J = 2.28, 14.64 Hz), 2.07–1.97 (m, 2H), 1.95–1.90 (m, 1H), 1.51–1.30 (m, 5H); ^{13}C (100 MHz, $CDCl_3$, ppm): 167.27, 148.96, 144.81, 138.41, 137.6, 131.04, 125.82, 123.34, 120.57, 115.33, 114.78, 52.33, 42.63, 35.82, 33.53, 32.66, 28.64, 24.83; HRMS (ESI): m/z calcd for $C_{18}H_{22}N_5O_3$ (M + H): 356.1723; found 356.1717.

4-(hex-5-en-1-yl)-1-((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl) methyl)azetidin-2-one (7b) White color, semi solid, Yield: 505 mg, 84%; FTIR (thin film, cm^{-1}): 1716.7, 1519, 1504,1338, 1232, 1040, 852, 749; ^{1}H (400 MHz, $CDCl_3$, ppm): 8.44–8.40 (m, 2H), 8.13(s. 1H), 7.99–7.95 (m, 2H), 5.80–5.71 (m, 1H), 5.01–4.93 (m, 2H), 4.69 (d, 1H, J = 15.84 Hz), 4.42 (d, 1H, J = 15.84 Hz), 3.68–3.64 (m, 1H), 3.01 (dd, 1H, J = 4.96, 14.64 Hz), 2.59 (dd, 1H, J = 2.24, 14.6 Hz), 2.07–2.02 (m, 2H), 1.95–1.91 (m, 1H), 1.48–1.25 (m, 5H); ^{13}C (100 MHz, $CDCl_3$, ppm): 167.28, 147.32, 144.98, 140.98, 138.52, 125.61, 120.22, 120.48, 114.8, 52.38, 42.65, 35.81, 33.53, 32.68, 28.64, 24.82; HRMS (ESI): m/z calcd for $C_{18}H_{22}N_5O_3$ (M + H): 356.1723; found 356.1728.

1-((1-(3-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-(hex-5-en-1-yl)azetidin-2-one (7c) White color, MP: 228–230 °C, Yield: 134 mg, 71%; FTIR (thin film, cm^{-1}): 1661, 1407, 1439, 1311, 1268, 1015, 954; ^{1}H (500 MHz, $CDCl_3$, ppm): 7.80 (t, 1H, J = 1.92 Hz), 7.65–7.63 (m, 1H), 7.49–7.41 (m, 2H), 8.15 (s, 1H), 5.83–5.75 (m, 1H), 5.01–4.92 (m, 2H), 4.68 (d, 1H, J = 15.8 Hz), 4.43 (d, 1H, J = 15.8 Hz), 3.69–3.63 (m, 1H), 3.01 (dd, 1H, J = 4.92, 14.64 Hz), 2.60 (dd, 1H, J = 2.2, 14.64 Hz), 2.09–2.00 (m, 2H), 1.99–1.93 (m, 2H), 1.49–1.41 (m, 1H), 1.40–1.36 (m, 1H), 1.34–1.24 (m, 2H); ^{13}C (126 MHz, $CDCl_3$, ppm): 167.08, 144.15, 139.05, 137.67, 136.98, 135.27, 130.87, 128.92, 120.52, 115.34, 114.05, 51.81, 42.37, 35.73, 33.42, 32.41, 29.45, 24.81; HRMS (ESI): m/z calcd for $C_{18}H_{22}ClN_4O$ (M + H): 345.1482; found 345.1450.

1-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-(hex-5-en-1-yl)azetidin-2-one (7d) White color, semi solid, Yield: 261 mg, 67%; FTIR (thin film, cm^{-1}): 1735, 1502, 1403, 1239, 1093, 1049, 987, 842; ^{1}H (500 MHz, DMSO, ppm): 8.80 (s, 1H), 7.95 (d, 2H, J = 8.5 Hz), 7.65 (d, 2H, J = 8.5 Hz), 5.75–5.70 (m, 1H), 4.96–4.88 (m, 2H), 4.60 (d, 1H, J = 16 Hz), 4.34 (d, 1H, J = 15.5 Hz), 3.59 (d, 1H, J = 4 Hz), 2.95 (dd, 1H, J = 5, 14.5 Hz), 2.52 (d, 1H, J= 17 Hz), 1.98–1.94 (m, 2H), 1.81–1.76 (m, 1H), 1.41–1.35 (m, 1H), 1.33–1.26 (m, 2H), 1.25–1.20 (m, 2H); ^{13}C (126 MHz, DMSO, ppm): 166.54, 144.3, 138.98, 135.86, 133.37, 130.28, 122.06, 121.9, 115.16, 51.63, 42.38, 35.72, 33.47, 32.38, 28.57, 24.73; HRMS (ESI): m/z calcd for $C_{18}H_{22}ClN_4O$ (M + H): 345.1482; found 345.1456.

4-(hex-5-en-1-yl)-1-((1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl) methyl)azetidin-2-one (7e) White color, semi solid, Yield: 163 mg, 61%; FTIR (thin film, cm^{-1}): 1662,1554, 1518, 1496, 1248, 1197, 1160, 1031, 931; ^{1}H NMR (500 MHz, DMSO, ppm): 8.65 (s, 1H), 7.80 (d, 2H, J = 9 Hz), 7.14 (d, 2H, J = 8.5 Hz), 5.79–5.72 (m, 1H), 4.98–4.90 (m, 2H), 4.58 (d, 1H, J = 16 Hz), 4.32 (d, 1H, J = 15.5 Hz), 3.83 (s, 3H), 3.59–3.37 (m, 1H), 2.96 (dd, 1H, J = 5, 14.6 Hz), 2.59 (dd, 1H, J = 2.28, 14.6 Hz), 2.01–1.96 (m, 2H), 1.83–1.78 (m, 1H), 1.43–1.30 (m, 3H), 1.27–1.22 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$, ppm): 166.55, 159.73, 143.83, 139.04, 130.29, 122.11, 121.81, 115.35, 115.24, 56.05, 51.6, 42.34, 35.74, 33.47, 32.37, 28.57, 24.63; HRMS (ESI): m/z calcd for $C_{19}H_{24}N_4NaO_2$ (M + Na): 363.1797; found 363.1791.

Declarations

Author contribution statement

Kuldeep Singh, Raman Singh: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Rajneesh Kaur: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Antresh Kumar: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Nitin Kumar Singhal, Nitesh Priyadarshi, Satvinder Kaur: Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

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