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, monobactam 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 -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].

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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 and aryl azides. The compound could be obtained by propargylation of azetidin-2-one (Scheme 1).

2. Results and discussion

Among various reported methods for the preparation of azetidin-2-ones, the cycloaddition of chlorosulphonyl isocyanate (CSI) with alkene provides an efficient and one-pot procedure to produce 4-substituted azetidin-2-one derivatives. Under anhydrous and dry reaction conditions, chlorosulphonyl isocyanate undergoes cycloaddition reaction with alkene to produce azetidin-2-one derivative (n = 1) or (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 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 were prepared using the literature method from corresponding substituted anilines. 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 were reacted with β-lactam in the presence of Cu(I) catalyst.
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 NO₂ while 1458 cm⁻¹ were observed and the presence of these signals revealed the formation of triazole ring. ¹H NMR and ¹³C 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 6.47 and 4.45 (J = 15.88 Hz) ppm. Two 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. ¹³C 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 ring with the β-lactam ring showed the signal at δ 52.02 ppm. All 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 C₁₈H₂₁N₅O₃) showed the molecular ion peak at 356.1717. The IR spectrum displayed vibrations at 1716.39 cm⁻¹ and the presence of these signals revealed the formation of triazole ring. 1H 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 CH₂ = 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 MTCC4441 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 NO₂ and electron releasing OCH₃ 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 1. Synthetic strategy.

Scheme 2. Reagents and conditions: (i) DCM, room temperature, (ii) Propargyl bromide, KOH, TBAB, THF (iii) BuOH:H₂O (1:1), Copper acetate, sodium ascorbate.
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. 1H NMR, and 13C NMR spectra were recorded in deuteron chloroform with Bruker Advance II spectrometer (400 and 100 MHz, 500 and 126 MHz, respectively). 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 (0.47 mmol, 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-propargylated 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 Na2SO4. 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)-1H-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, 1438.9, 1338.19; 1H (400 MHz, CDCl3 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, 2H), 1.58–1.51 (m, 1H), 1H; 13C (100 MHz, CDCl3, ppm) 167.14, 148.97, 144.81, 137.62, 137.01, 131.01, 131.02, 125.82, 123.35, 120.55, 115.66, 115.36, 52.02, 47.90, 35.87, 32.05, 29.72; HRMS (ESI): m/z calcd for C16H18N5O3 (M + H): 328.1410; found 328.1407.

4-(but-3-en-1-yl)-1-(4-(3-nitrophenyl)-1H-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; 1H NMR (400 MHz, CDCl3 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, 2H), 1.53–1.59 (m, 1H); 13C (100 MHz, CDCl3, 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 C16H18N5O2 (M + H): 328.1410; found 328.1407.

Table 1. Physical properties of compound 6 and 7.

| Compound | R     | Color     | Physical State | MP (°C) |
|----------|-------|-----------|----------------|--------|
| 6a       | 3-NO2 | White     | Solid          | 35–37  |
| 6b       | 4-NO2 | White     | Semi-solid     | -      |
| 6c       | 3-Cl  | White     | Semi-solid     | -      |
| 6d       | 4-Cl  | White     | Semi-solid     | -      |
| 6e       | 4-OMe | White     | Semi-solid     | -      |
| 7a       | 3-NO2 | Pale yellow | Semi-solid   | -      |
| 7b       | 4-NO2 | 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) | R. 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-(but-3-en-1-yl)-1-(4-(4-(methylthio)phenyl)-1H,2,3-triazol-1-yl) methylazetidin-2-one (6d) White color, semi solid, Yield: 317 mg, 82%; FTIR (thin film, cm⁻¹): 1660, 1436, 1340, 1272, 1260, 1172, 1102, 1029, 927, 763-7.60 (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, 1H), 1.57-1.49 (m, 4H), 13C (100 MHz, CDCl₃, 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 calc for C₁₄H₁₂N₂O (M + H): 317.1169; found 317.1188.

4-(but-3-en-1-yl)-1-(4-(4-methoxyphenyl)-1H,2,3-triazol-1-yl) methylazetidin-2-one (6e) White color, semi solid, Yield: 468 mg, 64%; FTIR (thin film, cm⁻¹): 1667, 1559, 1520, 1493, 1243, 1194, 1158, 1029, 927 (400 MHz, CDCl₃ ppm): 7.99 (s, 1H), 7.63-7.60 (m, 2H), 7.04-7.00 (m, 2H), 7.62-7.78 (m, 2H), 5.78-6.58 (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), 2.38 (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). 13C (100 MHz, CDCl₃ ppm): 166.91, 143.57, 137.11, 134.41, 129.17, 128.86, 120.88, 122.15, 115.44, 54.28, 51.75, 42.48, 35.89, 31.93, 31.63, 29.63; HRMS (ESI): m/z calc for C₁₄H₁₂N₂O (M + Na): 319.1535; found 319.1538.

1-(1-(1-(3-nitrophenyl)-1H-1,2,3-triazol-1-yl)methyl)-4-(buten-1-yl)azetidine-2-one (6f) White color, semi solid, Yield: 442 mg, 61%; FTIR (thin film, cm⁻¹): 1619, 1406, 1343, 1340, 1292, 1027, 934, 969.10, 668.83, 560.46; 1H (400 MHz, CDCl₃ ppm): 7.44 (s, 1H), 7.39-7.35 (m, 3H), 7.28-7.24 (m, 2H), 7.58-6.58 (m, 1H), 5.50 (m, 2H), 5.01-4.94 (m, 2H), 4.57 (dl, 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). 13C (100 MHz, CDCl₃ ppm): 166.91, 143.57, 137.11, 134.41, 129.17, 128.86, 120.88, 122.15, 115.44, 54.28, 51.75, 42.48, 35.89, 31.93, 31.63, 29.63; HRMS (ESI): m/z calc for C₁₄H₁₂N₂O (M + Na): 319.1535; found 319.1538.

1-(1-(1-(3-chlorophenyl)-1H-1,2,3-triazol-1-yl)methyl)-4-(buten-1-yl)azetidine-2-one (7c) White color, MP: 197-200 °C, Yield: 134 mg, 71%; FTIR (thin film, cm⁻¹): 1661, 1407, 1439, 1311, 1268, 1015, 954; 1H (500 MHz, CDCl₃ ppm): 7.52 (s, 1H, J = 15.88 Hz), 7.67 (d, 2H), 7.59 (d, 2H), 5.78-5.72 (m, 2H), 5.01-4.92 (m, 2H), 4.68 (d, 1H, J = 14.56 Hz), 4.32 (d, 1H, J = 15.88 Hz), 3.95-3.85 (m, 2H), 3.00 (dd, 1H, J = 4.96, 14.96 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). 13C (100 MHz, CDCl₃ ppm): 167.18, 147.32, 144.98, 139.88, 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 calc for C₁₄H₁₄ClN₂ (M + Na): 356.1723; found 356.1717.

Declarations

Author contribution statement

Kuldip 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; 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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