Pergamon

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Design, Synthesis and Biological Activity of Novel Enediynyl Monocyclic β-Lactams

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Abstract: Monocyclic β-lactams 1-3 substituted at C-4 with enediyne moiety have been synthesized via Pd(0) mediated coupling reaction. Their antibacterial activity against ampicillin-resistant E. coli have been tested.
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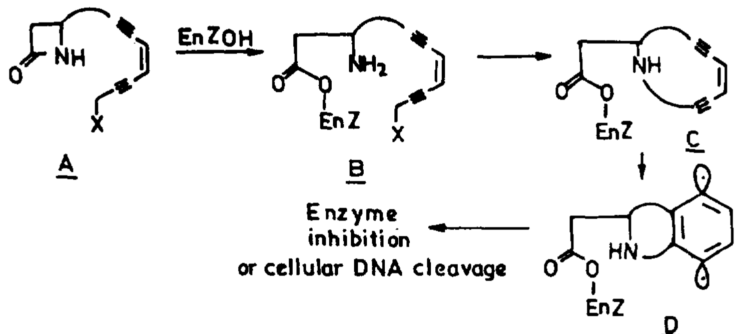
β-Lactam functionality is the key structural element present in various antibiotics with bicyclic framework e.g. penicillins, cephalosporins and carbapenems[1]. Quite a few monocyclic β-lactams are also known to possess antibiotic activity like the nocardicins[2] and monobactams[3]. In many cases the activity of these classes of antibiotics may be severely restricted through their destruction by β-lactamase-producing microorganisms[4]. Herein we report the design and synthesis of novel mechanism-based inhibitors **1-3** having monocyclic β-lactam units substituted at C-4 with enediyne moiety. Their activity against ampicillin-resistant E. coli is also presented.

In our design we have taken two important factors into consideration. Firstly, the antibacterial activity or the bacterial resistance (in most cases) both involve, as a first step, β-lactam ring opening by a serine hydroxyl nucleophile present in transpeptidase[5] or β-lactamase[6]. Secondly, monocyclic enediynes with a ring size of 9 or 10 undergo spontaneous cycloaromatization[7] to generate the lethal benzene-1,4- diradical[8]. Our molecules (general structure **A**) are so designed that opening of β-lactam ring (by transpeptidase or β-lactamase inside the cell will lead to a highly nucleophilic primary amine that will undergo intramolecular N-alkylation to generate the cyclic enediyne represented by structure B. These, in turn, will form the diradicals that are expected to cause damage to the cellular enzymes or more importantly the cellular DNA[9] (Scheme 1), leading to cell death. Thus the molecules (A) will really act as prodrugs.



SCHEME 1

The synthesis of the target molecules 1-3 was accomplished starting from 4-substituted β-lactams 5, 7 and 9 which were prepared from 4-phenyl sulphonylazetidinone (4) by literature methods[10-12]. Attempted coupling of 6, 7 and 9 with 5-chloropent-4-ene-2-yne-1-ol (13) in the presence of Pd(0) catalyst[13] and excess Et_3N failed to produce any desired product. However, when Et_3N was replaced by n-$BuNH_2$, smooth coupling took place and the desired enediyne alcohols 10-12 were obtained in good yields. Interestingly, contrary to our apprehension the β-lactam ring remained intact in the presence of a large excess of n-$BuNH_2$. The alcohols 10-12 were finally directly converted to the chlorides 1-3 by treatment with tosyl chloride and dimethylaminopyridine (DMAP)[14]. The highly reactive *in situ* generated propargylic tosylate evidently underwent displacement by the chloride ion. The entire synthesis is shown in Scheme 2. All the three enediyne chlorides 1-3 are quite stable at room temperature; however, their iodo analogues, prepared via NaI/acetone and presumably more suitable for N-alkylation, were extremely unstable; trace of moisture converted them back to the starting alcohols 10-12 thus making them unsuitable for the current study. All the compounds are well characterized by high field nmr, ir and mass spectral data[15].

The compounds 1-3 were then tested for their antibacterial activity against ampicillin-resistant E. coli. At similar concentrations, the β-lactams 1 and 2 showed stronger activity against the microorganism when compared with oxytetracycline. Compound 3 was, however, weakly active under the same conditions either because of the stability of the 11-membered enediyne at room temperature or due to elimination of the acyclic enediyne moiety after ring opening. The exact mechanism of the antibacterial action of 1 and 2 are currently under investigation.

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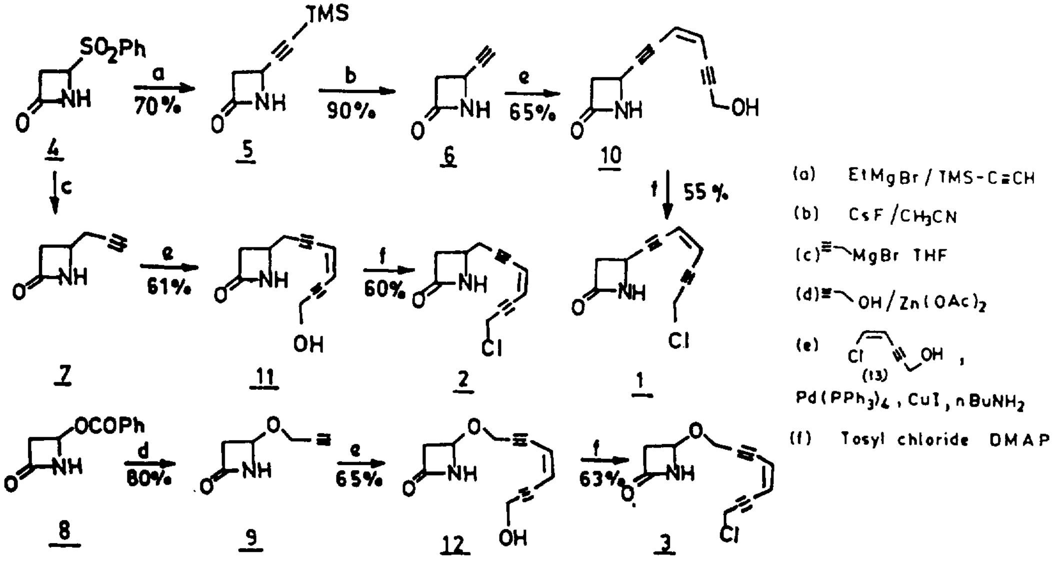

SCHEME 2

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15. All the nmr spectra were recorded in $CDCl_3$ at 200 MHz. Selected Spectral Data: For **10**: ν_{max} 3296, 2932, 1763, 1600, 1369, 1256, 1079, 838; δ_H 6.93 (1H, *bs*, NH), 5.91 (1H, *dt*, J = 1.6, 10.9 Hz), 5.81 (1H, *dd*, J = 1.3, 10.9 Hz) 4.45 (3H, *m*), 3.37 (1H, *ddd*, J = 0.8, 5.2, 14.7 Hz), 3.11 (1H, *dt*, J = 1.9, 14.7 Hz); δ_c 167.64, 120.71, 118.73, 96.09, 94.47, 82.30, 51.28, 46.57, 37.78; Mass (EI) 175 (M^+). For **1**: ν_{max} 3256, 2922, 2336, 2096, 1758, 1637, 1541, 1513, 1340, 1262, 1183, 1159, 1121, 1038, 753, 689; δ_H 6.2 (1H, *bs*, NH), 5.89 (2H, *m*), 4.47 (1H, *ddd*, J = 1.2, 2.8, 5.3 Hz), 4.34 (2H, *d*, J = 1.4 Hz), 3.39 (1H, *ddd*, J = 1.5, 5.3, 14.7 Hz) 3.15 (1H, *ddd*, J = 1.7, 2.6, 14.6 Hz); δ_c ($CDCl_3$, 200 MHz) 166.66, 119.92, 119.88, 94.85, 91.71, 83.13, 81.77, 46.92, 37.62, 30.85; Mass (EI) 151 (M^+-42). For **11**: ν_{max} 3276, 2924, 2368, 2338, 2216, 1738, 1513, 1437, 1413, 1360, 1305, 1221, 1160, 1118, 1020, 751, 724, 695. δ_H 6.96 (1H, *bs*, NH), 5.84 (1H, *dt*, J = 1.4, 10.9 Hz), 5.76 (1H, *dt*, J = 1.5, 10.9 Hz), 4.40 (2H, *bs*), 3.86 (1H, *m*) 3.07 (1H, *ddd*, J = 1.4, 4.5, 14.8 Hz), 2.94 (1H, *ddd*, J = 1.7, 2.9, 14.8 Hz), 2.87 (1H, *ddd*, J = 1.4, 3.8, 18 Hz), 2.68 (1H, *ddd*, J = 1.4, 5.0, 18 Hz); δ_c 168.65, 119.16 (2C), 95.59, 92.02, 81.90, 80.56, 50.68, 45.65, 41.75, 25.11; Mass (EI) 189 (M^+). For **2**: ν_{max} 3279, 2927, 2369, 2319, 1765, 1740, 1363, 1263, 1182, 752, 690; δ_H 6.07 (1H, *bs*, NH), 5.84 (2H, *bs*), 4.37 (2H, *s*), 3.87 (1H, *m*), 3.13 (1H, *ddd*, J = 2.0, 4.9, 14.9 Hz), 2.87-2.65 (3H, *m*); δ_c 167.2, 120.81, 118.45, 93.23, 90.9, 88.8, 83.4, 80.07, 46.0, 42.9, 26.04; Mass (EI) 165 (M^+-42). For **12**: ν_{max} 3279, 2930, 1769, 1436, 1360, 1172, 1122, 1082, 1027, 946; δ_H 7.67 (1H, *bs*, NH), 5.92 (1H, *d*, J = 10.9 Hz), 5.81 (1H, *dt*, J = 1.5, 11.1 Hz), 5.20 (1H, *dd*, J = 1.5, 3.9 Hz), 4.62 (1H, *dd*, J = 1.7, 17 Hz), 4.43 (2H, *s*), 4.39 (1H, *dd*, J = 1.0, 17 Hz), 3.22 (1H, *ddd*, J = 2.6, 3.9, 15.1 Hz), 2.98 (1H, *dt*, J = 1.2, 15.1 Hz); δ_c 167.85, 120.01, 118.26, 96.95, 91.85, 84.77, 82.02, 79.02, 57.51, 50.65, 45.65; Mass (EI) 205(M^+). For **3**: ν_{max} 3335, 2928, 2357, 2310, 2086, 1774, 1668, 1618, 1538, 1449, 1400, 1353, 1264, 1167, 1131, 1077, 949, 882; δ_H 6.77 (1H, *bs*, NH), 5.9 (2H, *m*), 5.27 (1H, *dd*, J = 1.5, 3.9 Hz), 4.47 (2H, *dd*, J = 0.9, 2.7 Hz), 4.38 (2H, *d*, J = 1.1 Hz) 3.19 (1H, *ddd*, J = 2.7, 3.9, 15.1 Hz), 2.96 (1H, *dd*, J = 1.2, 15.1 Hz); δ_c 166.39, 119.73, 119.58, 92.29, 91.80, 84.17, 82.6, 78.26, 56.85, 45.88, 30.78; Mass (EI) 181 (M^+-42).

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