Published in final edited form as:
Bioorg Med Chem. 2007 December 1; 15(23): 7288–7300. doi:10.1016/j.bmc.2007.08.035.

Direct Diazo-Transfer Reaction on β-lactam: Synthesis and Preliminary Biological Activities of 6-Triazolylpenicillanic Acids

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Abstract

In this study we report the first example of a direct diazo-transfer reaction on readily available 6-aminopenicillanates to give 6-azidopenicillanates in high yield. Subsequent Cu(I)-catalyzed Huisgen cycloaddition between these 6-azidopenicillanates and assorted terminal alkynes facilely furnished 6-triazolylpenicillanic acids was. Preliminary biological screening indicates that these triazolylpenicillanic acids possess low to moderate antibacterial activities.

Introduction

β-lactam antibiotics such as penicillin and cephalosporins are the most commonly prescribed antibacterial agents. Their antibacterial efficacy derives from ability to acylate a serine residue at the penicillin binding proteins (PBPs) active site.[1, 2] Serine acylation inhibits the enzymatic activities of PBPs, thus interfering with the essential polymerization and cross-linking of the peptidoglycan components of the bacterial cell wall.[1] However, the emergence of multi-drug resistant bacteria strains such as *Staphylococcus aureus* is threatening the clinical effectiveness of β-lactam antibiotics.[3] The common resistance mechanism in gram-negative bacteria is the cellular expression of β-lactamases (or penicillinase), which hydrolyze the β-lactam ring and thus inactivate the antibiotics.[4–7] Therapeutic agents targeting β-lactamase resistance include clavulanate, sulbactam, and tazobactam. These are generally administered in combination with β-lactamase susceptible β-lactams.[8, 9] However, the emergence of multi-strains β-lactamase has reduced the efficacy of some of these β-lactamase inhibitors.[10, 11]

There are also other intracellular factors that attenuate the antibacterial activities of β-lactams. For example, the N-5 amide moiety in penicillins is highly reactive and has been proposed to facilitate the hydrolysis of the β-lactam ring in acidic media (Figure 1).[12] Incorporation of electron-withdrawing groups and steric bulk at the N-acyl side chain has been shown to reduce the acid sensitivity of penicillins.[13, 14]

Another shortcoming to the effectiveness of β-lactamase antibiotics is the bacterial outer membrane, which is a formidable barrier in gram negative organisms. In addition, the bacterial membrane could acquire efflux pumps that facilitate active elimination of drug from the bacterial cytosol.[15, 16] All these changes could prevent the intracellular accumulation of

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Supporting Information Available: Proton and carbon NMR spectra for all compounds described in the experimental section. This material is available free of charge via the Internet at http://pubs.acs.org.

pharmacologically relevant concentrations of the β-lactam antibiotics. One clever strategy to facilitate β-lactams diffusion across membrane is to covalently link them to membrane penetrating groups such as sideophores and peptides.[1–3, 17] However, the synthesis of such β-lactam conjugates often involve long synthetic schemes and complicated compound purifications protocols.[2b–e]

One of the most fruitful β-lactam SAR studies has been the modification of the N-acyl groups. These studies have led to the discovery of β-lactam analogs with superior antibacterial activity.[16, 18–20] Much recent studies have shown that attachment of N-acyl groups incorporating the structural feature of peptidoglycan result in PBP specific β-lactams and cephalosporins.[3, 17, 21] PBPs can also tolerate an assorted variety of non-amide groups at the C-6 and C-7 positions of penicillins and cephalosporins, respectively.[20] Some of these non-amide β-lactam analogs, in addition to possessing potent antibacterial activity, have differential affinity for PBP isoforms (Figure 3). For example, mecillinam (amdinocillin), a β-lactam analog with an unusual 6-formylimido moiety, derives its antibacterial activity from its specific interaction with PBP-2.[22] Very few β-lactams with traditional amide bond isosteres have been reported to date. One such example is the sulfonamide derivatives. A subset of these compounds have been synthesized and tested. However these compounds are still prone to chemical degradation and hydrolysis by β-lactamases.[23]

We proposed that 1,4-disubstituted-1,2,3-triazoles could serve as an isostere for the N-acyl group of penicillins and cephalosporins. Due to the similarities between some of its bond characteristics with an amide moeity, the triazole group is commonly used as an amide bond isostere.[24, 25] Unlike amide bond, the triazole moiety is not susceptible to hydrolysis.[24] Replacement of the reactive β-lactam acyl bond with a triazole ring may lead to β-lactams that are more stable in acidic environment. In addition, the triazole ring could in principle facilitate facile conjugation of β-lactams to assorted cell permeable peptides and peptoids for promoted uptake of β-lactams into bacterial cell. Here, we report our efforts on the design, synthesis, and preliminary biological activities of 6-triazolylpenicillanic acid.

Results and Discussion

The key intermediate in the synthesis of the proposed 6-triazolylpenicillanic acids **1** is the 6-azidopenicillanates **2.** It is anticipated that Cu(I)-catalyzed cycloaddition between **2** and appropriate alkynes (Sharpless Click Chemistry)[26] followed by deprotection of the ester protection group will furnish the desired triazolylpenicillanic acid **1** (scheme 1). The synthesis of protected 6-azidopenicillanates similar to **2a–c** has been described in the literature.[27–30] These compounds are generally synthesized, in moderate yields, using multi-step reactions. For example, Barrett and Sakadarat described the synthesis of benzyl protected 6-azidopecillanate, the final intermediate in their total synthesis of 6-aminopenicillanic acid (6-APA), in a six-step reaction scheme with a total yield of about 15%.[30] For the synthesis of 6-triazolylpenicillanates, we desired a more general and mild synthetic strategy to 6-azidopenicillanates.

Synthesis of 6-Azidopenicillanic Acid by Diazo-Transfer Reaction

As a new general alternative, we envisioned that azidopenicillanic acid could be obtained from commercially available 6-aminopenicillanic acids through a diazo-transfer reaction. The diazo-transfer reaction is a mild, high yielding reaction that has been used to effect direct conversion of assorted amines to azides.[31] In addition, a recent observation from our lab has extended the scope of this versatile reaction to include azide functionalization of amine-coated solid supports under heterogeneous reaction conditions.[32] However, our initial efforts at initiating diazo-transfer reaction on unprotected 6-aminopenicillanic acid were unsuccessful. To thoroughly probe the feasibility of this reaction on β-lactam moiety, we decided to investigate various

carboxyl protected 6-aminopenicillanates. The requisite carboxyl protected aminopenicillanates **3a–c** were synthesized adapting literature protocols.[21, 33–37] Using the PNB protected compound **3a,** we initiated diazo-transfer reaction with freshly prepared triflyl azide under basic conditions in the classic CH_2Cl_2/MeOH/H_2O solvent mixture.[31b–e] These conditions, however, gave a complex mixture from which we only isolated a minute amount of the ring-opened methyl ester azide **4.** This product was presumably obtained from Et_3N promoted methanolysis of compound **3a** in addition to the desired diazo-transfer reaction. The reaction was repeated in anhydrous CH_2Cl_2 and Et_3N. Gratifyingly, we obtained the desired azide **5a** in yields of 50–68% within 2 to 2.5 h of reaction, though other uncharacterized degradation products persisted. Because of the potential hazard of handling triflyl azide in halogenated solvent, we investigated the compatibility of this reaction with non-halogenated solvents. The reaction worked equally well when CH_2Cl_2 was replaced with toluene, yielding azide **5a** in 70% yields. Similarly, azides **5b** and **5c** were obtained from amines **2b** and **2c** in moderate to good yields (scheme 2). The β orientation of the azide group in **5a–c** was authenticated by ^{1}H NMR ($J_{5,6}$ coupling constant = 4 Hz),[29] thereby confirming that the reaction occurred with the characteristic retention of configuration.[31b,e]

Cu(I)-catalyzed Cycloaddition Reaction between 6-Azidopenicillanates and Terminal Alkynes

To identify optimum conditions for Cu(I)-catalyzed cycloaddition reaction, we investigated the reaction of azides **5b** and **5c** with 3-phenyl-1-propyne **6** and 2-ethynyl-1,3-dimethoxybenzene **7.** Our choice of terminal alkynes **6** and **7** is partly informed by the possibility that cycloaddition between these alkynes and azides **5** will respectively furnish triazolyl isosteres of penicillin G and methicillin, two historically useful penicillin derivatives. Cu(I)-catalyzed reaction of azide **5b** or **5c** with alkyne **6** resulted in triazoles **8a** and **8b** in excellent yield. Subsequent TFA deprotection of the PMB and the BzD group furnished the desired penicillanic acid **9a** in excellent yield. Similarly, the reaction of azide **5c** with alkyne **7** followed by deprotection of the BzD group gave penicillanic acid **9** in 72% overall yield (scheme 3). Because of the rapidity of deprotection of the BzD group and the product quality, we focused much of our attention on the reactivity of azide **5c.**

We turned to investigate the reactivity of azide **5c** with assorted terminal alkynes in order to probe the scope of this reaction. We selected a subset of terminal alkynes whose closely related carboxylic acid analogs have been shown to support the antimicrobial activities of β-lactams.[38–40] Alkynes such as **7, 10h, 10i,** and **10k** that we could not obtain from commercial sources were synthesized from the corresponding carboxylic acid, through the intermediacy of aldehyde, using the Bestmann-Ohira reagent.[41–43] Hydroxyl alkyne **10f** and **10l** were obtained by a direct Grignard reaction of ethynylmagnesium bromide with the appropriate aldehydes. Detailed protocols for the synthesis of these alkynes are reported in the experimental section.

Cu(I)-catalyzed reaction of alkynes **10a–l** with azidopenicillanate **5b** or **5c** proceeded smoothly at ambient temperature, leading to uneventful formation of triazole **11a–l** in good to excellent yields. Subsequent carbonyl group deprotection furnished the desired 6-triazolylpenicillanic acid **12a–l** (scheme 4).

Biological Evaluation

The synthesized 6-triazolylpenicillanic acids were screened at the National Institute of Allergy and Infectious Disease (NIAID) through the *In vitro* and Animal Models for Emerging Infectious Diseases and Biodefense Screening Program. Compounds were screened following the procedures recommended by the Clinical Laboratory Standard Institute (CLSI). Compound **9a, 12e, 12g,** and **12l** exhibited some antibacterial activity against the Gram-positive bacteria strain *S. pneumoniae* with MIC value of 4 to 8 μg/mL. Similarly, compound **12l** showed a

moderate activity (MIC ≈ 8 μg/mL) against *B. anthracis*. Other compounds listed in Table 1 displayed comparatively poor antibacterial activity (MIC > 8μg/mL).

Conclusion

We have reported a convenient route for the synthesis of 6-triazolyl-penicillanic acid. Preliminary biological evaluations of compounds described in this report demonstrated that they possess low to moderate antibacterial activity. The triazole ring lacks the H-bonding donating N-H group which could act as an additional recognition feature in the binding of some β-lactams to the PBPs. This may partly explain the relatively low antimicrobial activities of these 6-triazolyl-penicillanic acids. Currently, we are investigating the SAR of the lead compounds in order to identify 6-triazolylpenicillanic acid with improved antibacterial activity against drug resistant bacterial strains.

Experimental Section

6-aminopenicillanoic acid (6-APA) was purchased from Sigma Aldrich. Anhydrous solvents and other reagents were purchased and used without further purification. Analtech silica gel plates (60 F_{254}) were used for analytical TLC, and uv light was used to examine the spots. 200–400 Mesh silica gel was used in column chromatography. NMR spectra were recorded on a Varian-Gemini 400 magnetic resonance spectrometer. ^{1}H NMR spectra are recorded in parts per million (ppm) relative to the peak of $CDCl_3$, (7.24 ppm), acetone-d_6 (2.09 ppm), or DMSO-d_6 (2.49 ppm). ^{13}C spectra were recorded relative to the central peak of the $CDCl_3$ triplet (77.0 ppm), acetone-d_6 (205.8 ppm), or the DMSO-d_6 septet (39.7 ppm), and were recorded with complete hetero-decoupling. High-resolution mass spectra were recorded at the Georgia Institute of Technology mass spectrometry facility in Atlanta. Triflyl azide was prepared as described before and used without storage.[31h, 31i] The Bestmann-Ohira reagent was prepared as described by Ghosh *et al*[42] while diphenyldiazomethane was prepared by using the procedure described by Ko *et al*.[37] 6-Aminopenicillanates **3a–c** were synthesized adapting literature procedures.[21, 33–37]

Representative Procedure for the Alkyne Transformation Reaction. 2-Ethynyl-1,3-dimethoxybenzene (7)

2,6-dimethoxybenzaldehyde (0.45 g, 2.71 mmol) was first dissolved in anhydrous MeOH (25 mL) and stirred under argon at room temperature. Anhydrous K_2CO_3 (1.12 g, 8.12 mmol) and Bestmann-Ohira reagent (1.03 g, 5.42 mmol) were added to the reaction mixture and stirring continued for 24 h at room temperature. Solvent was evaporated off, and the remaining residue was dissolved in CH_2Cl_2 (25 mL) and washed with saturated NH_4Cl (3 × 20 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 5:1 Hexane/EtOAc) to give 220 mg (50%) of **7** as a white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 3.55 (1H, s), 3.88 (6H, s), 6.53 (2H, d, J = 8.4 Hz), 7.24 (1H, t, 7.4 Hz); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 56.0, 76.2, 85.7, 100.0, 103.5, 130.3, 162.0.

4-(4-Ethynylphenyl)pyridine (10k)

Reaction of 4-(4-formylphenyl)pyridine (0.3 g, 1.64 mmol) and Bestmann-Ohira reagent (0.627 g, 3.27 mmol) within 24 h as described for the synthesis of compound **7** followed by flash chromatography (silica gel, 2:1 Hexane/EtOAc) gave 261 mg (89%) of **10k** as a white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 3.16 (1H, s), 7.47 (2H, d, J = 6.4 Hz), 7.59 (4H, s), 8.66 (2H, d, J = 6.4Hz). HRMS (EI) calc for [$C_{13}H_9N$] 179.0735, found 179.0746.

2-Ethnylbiphenyl (10i)

The required Biphenyl-2-carbaldehyde was synthesized from the corresponding carboxylic acid through $NaBH_4/BF_3$:OEt_2 reduction to the primary alcohol.[43] Subsequent PDC oxidation of the primary alcohol furnished Biphenyl-2-carbaldehyde. Reaction of biphenyl-2-carbaldehyde (0.66 g, 3.63 mmol) and Bestmann-Ohira reagent (1.72 g, 7.27 mmol) within 24 h followed by flash chromatography (silica gel, 5:1 Hexane/EtOAc) yielded 523 mg (81%) of **10i** as a colorless oil. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 3.03 (1H, s), 7.28–7.32 (1H, m), 7.36–7.45 (5H, m), 7.57–7.63 (3H, m).

3-Ethynylbiphenyl (10h)

The required Biphenyl-3-carbaldehyde was synthesized from the corresponding carboxylic acid through $NaBH_4/BF_3$:OEt_2 reduction to the primary alcohol.[43] Subsequent PDC oxidation of the primary alcohol furnished Biphenyl-3-carbaldehyde. Reaction of biphenyl-3-carbaldehyde (0.87 g, 4.78 mmol) and Bestmann-Ohira reagent (1.72 g, 9.56 mmol) within 24 h followed by flash chromatography (silica gel, 5:1 Hexane/EtOAc) gave 850 mg (100%) of **10h** as a reddish oil. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 3.03 (1H, s), 7.33–7.47 (5H, m), 7.55–7.57 (3H, m), 7.72 (1H, s). HRMS(EI) calc for [$C_{14}H_{10}$] 178.0782, found 178.0797.

Representative Procedure for the Alkyne Transformation via Grignard Reaction. 1-phenylprop-2-yn-1-ol (10f)

To a solution of benzaldehyde (0.5 g, 4.71 mmol) in anhydrous THF (2 mL) was added ethynylmagnesium bromide (14.0 mL, 0.5M in THF) at room temperature under argon. The reaction mixture was stirred for 1 h and quenched with distilled water. The reaction mixture was partitioned between CH_2Cl_2 (10 mL) and water (15 mL), and the two layers separated. The organic layer was washed in succession with distilled water (2 × 10 mL) and saturated brine (2 × 10 mL), and dried over Na_2SO_4. Solvent was evaporated off to give 0.626g (100%) of **10f** as a brownish oil. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 2.66 (1H, d, J = 2.4 Hz), 5.45 (1H, d, J = 4.0 Hz), 7.30–7.40 (3H, m), 7.54 (2H, d, J = 7.2 Hz); HRMS (FAB, thioglycerol) calc for [C_9H_8O] 132.0575, found 132.0566.

1-(4-(pyrdin-4-yl)prop-2-yn-1-ol (10l)

To a solution of benzaldehyde (0.5 g, 2.73 mmol) in anhydrous THF (2 mL) was added ethynylmagnesium bromide (8.2 mL, 0.5M in THF) at room temperature under argon. The reaction mixture was stirred for 1 h and quenched with distilled water. The reaction mixture was partitioned between CH_2Cl_2 (10 mL) and water (15 mL), and the two layers separated. The organic layer was washed in succession with distilled water (2 × 10 mL) and saturated brine (2 × 10 mL), and dried over Na_2SO_4. Solvent was evaporated off to give 0.491 (86%) of **10l** as a brownish solid. ^{1}H-NMR (CD_3OD, 400MHz) δ 3.05 (1H, s), 5.46 (1H, s), 7.66–7.78 (6H, m), 8.56 (2H, d, J = 9.2 Hz); HRMS (FAB, thioglycerol) calc for [$C_{14}H_{11}NO$ + H]$^+$ 210.0918, found 210.0909.

Representative Procedures for Diazo-transfer Reaction. Method A: *p*-Nitrobenzyl 6-azidopenicillanate (5a)

4-Nitrobenzyl 6-aminopenicillanate salt **3a** (5.0 g, 9.5 mmol) was suspended in EtOAc (40 mL) and washed with saturated $NaHCO_3$ (2 × 30 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give pure 4-nitrobenzyl 6-aminopenicillanate. To a solution of 4-nitrobenzyl 6-aminopenicillanate in anhydrous CH_2Cl_2 (10 mL) was added triflyl azide solution (25 mmol) in CH_2Cl_2 (25 mL), and Et_3N (2.1 mL, 15.0 mmol). The reaction mixture was stirred at room temperature for 2 h. Solvent was evaporated off and the residue was directly purified by flash chromatography (silica, gradient 4:1; 3:1 Hexane/EtOAc) to give 2.35 g (68%) of **5a** as a colorless gel. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.38 (3H, s), 1.61 (3H,

s), 4.49 (1H, s), 4.92 (1H, d, *J* = 4.0 Hz), 5.23 (2H, q, *J* =24.0, 12.0 Hz), 5.43 (1H, d, *J* = 4.0 Hz), 7.50 (2H, d, *J* = 8.8 Hz), 8.17 (2H, d, *J* = 8.8 Hz); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 26.4, 31.5, 64.3, 65.7, 66.5, 67.6, 70.0, 123.7, 128.0, 141.5, 147.9, 167.0, 169.8;

Method B: Benzhydryl 6-azidopenicillanate (5c)

Benzhydryl 6-aminopenicillanate salt **3c** (3.5 g, 6.32 mmol) was suspended in EtOAc (60 mL) and washed with saturated $NaHCO_3$ (3 × 40 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give 2.4 g of pure benzhydryl 6-aminopenicillanate. To a solution of benzhydryl 6-aminopenicillanate in anhydrous CH_2Cl_2 (15 mL) was added triflyl azide solution (14 mmol) in CH_2Cl_2 (35 mL), DMAP (1.15 g, 9.24 mmol), and Et_3N (0.1 mL). The reaction mixture was stirred at room temperature for 1.5 h and solvent was evaporated off. The residue was directly purified by flash chromatography (silica, gradient 1:0; 5:1 Hexane/EtOAc) to give 1.38 g (54%) of **5c** as a colorless gel. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.26 (3H, s), 1.64 (3H, s), 4.57 (1H, s), 4.89 (1H, d, *J* = 4.0 Hz), 5.47 (1H, d, *J* = 4.0 Hz), 6.93 (1H, s), 7.28–7.35 (10H, m); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 26.2, 31.9, 64.7, 66.6, 67.8, 70.2, 78.4, 126.8, 127.5, 128.1, 128.4, 128.5, 138.8, 166.5, 169.8; HRMS (FAB, mnba) calc for $[C_{21}H_{20}N_4O_3S + H]^+$ 409.1334, found 409.1357.

Method C: *p*-Nitrobenzyl 6-azidopenicillanate (5a)

4-Nitrobenzyl 6-aminopenicillanate salt **3a** (0.75 g, 1.4 mmol) was suspended in EtOAc (30 mL) and washed with saturated $NaHCO_3$ (2 × 20 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give pure 4-nitrobenzyl 6-aminopenicillanate. To a solution of pure 4-nitrobenzyl 6-aminopenicillanate in anhydrous toluene (5 mL) was added triflyl azide solution (2.97 mmol) in toluene (25 mL), and Et_3N (0.3 mL, 2.1 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction was diluted with EtOAc (10 mL) and washed with 1N HCl (20 mL), distilled water (2 × 20 mL), and saturated brine (20 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give 361 mg (70%) of **5a** as a yellowish solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.42 (3H, s), 1.66 (3H, s), 4.52 (1H, s), 4.92 (1H, d, *J* = 4.0 Hz), 5.26 (2H, q, *J* = 24.0, 12.0 Hz), 5.46 (1H, d, *J* = 4.0 Hz), 7.53 (2H, d, *J* = 8.8 Hz), 8.24 (2H, d, *J* = 8.8 Hz).

p-Methoxybenzyl 6-azidopenicillanate (5b)

6-azidopenicillanate **5b** was prepared from *p*-Methoxybenzyl 6-aminopenicillanate **3b** (4.0 g, 7.9 mmol) and triflyl azide (25 mmol) in CH_2Cl_2 (total volume = 25 mL), and Et_3N (1.44 mL, 10.3 mmol) using **method A.** The reaction mixture was stirred at room temperature for 2 h. Purification of the crude product by flash chromatography (silica, gradient 4:1; 3:1 Hexane/EtOAc) afforded 1.40 g (49%) of **5b** as a colorless gel. ^{1}H-NMR ($CDCl_3$, 100MHz) δ 1.36 (3H, s), 1.61 (3H, s), 3.79 (3H, s), 4.45 (1H, s), 4.88 (1H, d, *J* = 4.0 Hz), 5.10 (2H, app. q, *J* = 24.0, 12.0 Hz), 5.44 (1H, d, *J* = 4.0 Hz), 6.87 (2H, d, *J* = 8.8 Hz), 7.27 (2H, d, *J* = 8.8 Hz); ^{13}C-NMR ($CDCl_3$, 400MHz) δ 26.6, 31.7, 55.3, 64.6, 66.5, 67.4, 67.7, 70.2, 113.9, 126.5, 130.4, 159.7, 167.2, 169, 7; HRMS (FAB, mnba) calc for $[C_{16}H_{18}N_4O_4S + H]^+$ 363.1127, found 363.1151.

Representative Procedure for Cu(I)-Catalyzed Cycloaddition Reaction. *p*-Methoxybenzyl benzyl-6-triazolylpenicillanate (8a)

p-Methoxybenzyl 6-azidopenicillanate **5b** (0.27g, 0.635 mmol) and 3-phenyl-1-propyne **6** (0.17 mL, 1.39 mmol) were dissolved in anhydrous THF (8 mL) and stirred under argon at room temperature. Copper (I) iodide (0.011 g, 0.06 mmol), and Hunig's base (0.1 mL) were then added to the reaction mixture, and stirring was continued for 2 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with 1:4 NH_4OH/saturated NH_4Cl (3 × 30 mL) and again with saturated NH_4Cl (30 mL). The organic layer was dried over Na_2SO_4 and

concentrated *in vacuo*. The crude product was purified by flash chromatography (silica, gradient 3:1; 2:1; 3:2 Hexane/EtOAc) to give 246 mg (71%) of **8a** as a white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.35 (3H, s), 1.57 (3H, s), 3.79 (3H, s), 4.08 (2H, s), 4.47 (1H, s), 5.12 (2H, app. q, *J* = 24.0, 12.0 Hz), 5.69 (1H, d, *J* = 4.0 Hz), 6.27 (1H, d, *J* = 4.4 Hz), 6.88 (2H, d, *J* = 8.8 Hz), 7.20–7.30 (7H, m), 7.42 (1H, s); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 26.9, 30.9, 32.0, 55.2, 65.3, 66.2, 67.3, 67.5, 70.5, 114.0, 122.4, 126.5, 128.5, 128.6, 130.6, 138.5, 147.2, 160.0, 167.1, 168.1; HRMS (FAB, thioglycerol) calc for $[C_{25}H_{26}N_4O_4S + H]^+$ 479.1753, found 479.1756.

Benzhydryl benzyl-6-triazolylpenicillanate (8b)

Reaction of benzhydryl 6-azidopenicillanate **5c** (0.270 g, 0.661 mmol) and 3-phenyl-1-propyne **6** (0.17 mL, 1.39 mmol) within 2.5 h followed by flash chromatography (silica, gradient 3:1; 2:1; 3:2 Hexane/EtOAc) gave 246 mg (71%) of **8b** as a white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.61 (3H, s), 1.57 (3H, s), 4.09 (2H, s), 4.59 (1H, s), 5.73 (1H, d, *J* = 4.0 Hz), 6.29 (1H, d, *J* = 4.4 Hz), 6.94 (1H, s), 7.21–7.35 (15H, m), 7.43 (1H, s); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 26.7, 31.2, 32.0, 65.4, 66.3, 67.4, 70.6, 78.6, 122.4, 126.5, 126.9, 127.6, 128.3, 128.5, 128.6, 128.7, 138.5, 138.7, 138.8, 147.3, 166.3, 168.1; HRMS (FAB, mnba) calc for $[C_{30}H_{28}N_4O_3S + H]^+$ 525.1956, found 525.1960.

Benzhydryl 2,6-dimethoxyphenyl-6-triazolylpenicillanate (8c)

Reaction of benzhydryl 6-azidopenicillanate **5c** (0.227 g, 0.555 mmol) and 2-Ethynyl-1,3-dimethoxybenzene **7** (0.06 g, 0.37 mmol) within 4 h followed by flash chromatography (silica gel, 1:1 Hexane/EtOAc) gave 120 mg (57%) of **8c** as a white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.26 (3H, s), 1.69 (3H, s), 3.78 (6H, s), 4.64 (1H, s), 5.80 (1H, d, *J* = 4.8 Hz), 6.42 (1H, d, *J* = 4.4 Hz), 6.62 (2H, d, *J* = 8.4 Hz), 6.96 (1H, s), 7.26–7.35 (11H, m), 7.95 (1H, s); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 26.7, 31.4, 56.0, 65.2, 66.4, 67.7, 70.6, 78.6, 104.1, 125.2, 126.9, 127.6, 128.3, 128.5, 128.6, 128.7, 129.9, 138.9, 139.9, 158.3, 166.4, 168.6; HRMS (FAB, thioglycerol) calcd for $[C_{31}H_{30}N_4O_5S + H]^+$ 571.2015, found 571.2049.

Benzhydryl 4-pyridyl-6-triazolylpenicillanate (11a)

4-Ethynylpyridyl hydrochloride (0.06 g, 0.414 mmol) was suspended in EtOAc (30 mL) and washed with saturated $NaHCO_3$ (1 × 30 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give 4-ethynylpyridine **10a** as white brown solid. The reaction of benzhydryl 6-azidopenicillanate **5c** (0.15 g, 0.367 mmol) and **10a** (0.076 g, 0.734 mmol) within 3 h followed by flash chromatography (silica gel, gradient 1:1; 1:4 Hexane/EtOAc) gave 166 mg (74%) of **11a** as a white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.26 (3H, s), 1.69 (3H, s), 4.65 (1H, s), 5.80 (1H, d, *J* = 4.0 Hz), 6.39 (1H, d, *J* = 4.0 Hz), 6.96 (1H, s), 7.32–7.36 (10H, m), 7.77 (2H, d, *J* = 5.20 Hz), 8.19 (1H, s), 9.03(2H, d, *J* = 5.20 Hz); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 26.8, 31.1, 65.7, 66.2, 67.2, 70.8, 78.8, 120.1, 122.1, 126.7, 127.5, 128.2, 128.4, 128.5, 138.6, 138.6, 144.5, 149.2, 165.9, 167.5; HRMS (FAB, thioglycerol) calc for $[C_{28}H_{25}N_5O_3S + H]^+$ 512.1756, found 512.1763.

Benzhydryl 3-pyridyl-6-triazolylpenicillanate (11b)

The reaction of benzhydryl 6-azidopenicillanate **5c** (0.15 g, 0.441 mmol) and 3-ethynylpyridine **10b** (0.068 g, 0.661 mmol) within 3 h followed by flash chromatography (silica gel, gradient 1:1; 1:3 Hexane/EtOAc) gave 170 mg (76%) of **11b** as a white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.26 (3H, s), 1.70 (3H, s), 4.66 (1H, s), 5.80 (1H, d, *J* = 4.0 Hz), 6.40 (1H, d, *J* = 4.0 Hz), 6.96 (1H, s), 7.32–7.36 (10H, m), 8.13 (1H, s), 8.26 (1H, d, *J* = 8.24 Hz), 8.58 (1H, br s), 9.03(1H, br s); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 26.9, 31.1, 65.7, 66.3, 67.3, 70.7, 78.7, 120.8, 126.7, 127.5, 128, 2, 128, 4, 128, 5, 133.8, 138.5, 138.6, 138.6, 144.0, 146.1, 148.3,

166.0, 167.6; HRMS (FAB, thioglycerol) calc for $[C_{28}H_{25}N_5O_3S + H]^+$ 512.1756, found 512.1773.

Benzhydryl 2-pyridyl-6-triazolylpenicillanate (11c)

The reaction of benzhyldryl 6-azidopenicillanate **5c** (0.15 g, 0.367 mmol) and 2-ethynylpyridine **10c** (0.06 mL, 0.55 mmol) within 6 h followed by flash chromatography (silica gel, gradient 4:1; 2:1; 1:2; Hexane/EtOAc) gave 145 mg (64%) of **11c** as a white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.25 (3H, s), 1.71 (3H, s), 4.64 (1H, s), 5.78 (1H, d, *J* = 4.0 Hz), 6.39 (1H, d, *J* = 4.0 Hz), 6.96 (1H, s), 7.32–7.36 (10H, m), 7.78 (1H, m), 8.18 (1H, d, *J* = 7.69 Hz), 8.45 (1H, s), 8.58 (1H, d, *J* = 4.39 Hz); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 26.9, 31.3, 65.7, 66.5, 67.4, 70.8, 78.7, 120.5, 123.0, 126.8, 127.5, 128.2, 128.4, 128.5, 128.6, 138.6, 138.7, 166.1, 167.8; HRMS (FAB, thioglycerol) calc for $[C_{28}H_{25}N_5O_3S + H]^+$ 512.1756, found 512.1765.

Benzhydryl 2-thiopyl-6-triazolylpenicillanate (11d)

Reaction of benzhydryl 6-azidopenicillanate **5c** (0.15 g, 0.367 mmol) and 3-ethynylthiopene **10d** (0.06 g, 0.55 mmol) within 5 h followed by flash chromatography (silica gel, gradient 1:0; 5:1; 3:1 Hexane/EtOAc) gave 150 mg (79%) of **11d** as a white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.25 (3H, s), 1.69 (3H, s), 4.64 (1H, s), 5.78 (1H, d, *J* = 4.4 Hz), 6.36 (1H, d, *J* = 4.0 Hz), 6.96 (1H, s), 7.30–7.38 (11H, m), 7.44 (1H, dd, *J* =4.0, 1.2 Hz), 7.70 (1H, dd, *J* = 2.0, 1.2 Hz), 7.90 (1H, s); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 26.7, 30.9, 66.1, 67.3, 70.8, 78.7, 120.1, 121.6, 125.7, 126.4, 126.9, 127.6, 128.3, 128.6, 128.7, 131.1, 138.7, 138.8, 143.8, 166.3, 168.2; HRMS (FAB, thioglycerol) calc for $[C_{27}H_{24}N_4O_3S_2 + H]^+$ 517.1368, found 517.1374.

p-Methoxybenzyl phenyl-6-triazolylpenicillanate (11e)

Reaction of *p*-methoxybenzyl-6-azidopenicillanate **5b** (0.15 g, 0.414 mmol) and phenylacetylene **10e** (0.14 mL, 1.24 mmol) within 2 h followed by flash chromatography (silica gel, gradient 3:1; 3:2 Hexane/EtOAc) gave 165 mg (86%) of **11e** as a white foam. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.38 (3H, s), 1.66 (3H, s), 3.80 (3H, s), 4.54 (1H, s), 5.14 (2H, app. q, *J* = 24.0, 12.0 Hz), 5.75 (1H, d, *J* = 4.0 Hz), 6.37 (1H, d, *J* = 4.0 Hz), 6.89 (2H, d, *J* = 8.8 Hz), 7.29–7.35 (3H, m), 7.39–7.42 (2H, m), 7.82 (2H, m), 7.99 (1H, s); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 27.0, 30.8, 55.2, 65.4, 66.1, 67.2, 67.6, 70.7, 114.0, 120.3, 125.8, 126.5, 128.4, 128.8, 129.9, 130.6, 147.5, 160.0, 167.1, 168.2; HRMS (FAB, thioglycerol) calc for $[C_{24}H_{24}N_4O_4S + H]^+$ 465.1596, found 465.1571.

Benzhydryl α-hydroxylbenzyl-6-triazolylpenicillanate (11f)

Reaction of benzhydryl 6-azidopenicillanate **5c** (0.2 g, 0.49 mmol) and 1-phenylprop-2-yn-1-ol **10f** (0.13 g, 0.985 mmol) within 2 h followed by flash chromatography (silica gel, 2:1 Hexane/EtOAc) gave 191 mg (72%) of **11f** as a white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.23 (3H, d, *J* = 12 Hz), 1.59 (3H, d, *J* = 8.0 Hz), 4.61 (1H, s), 5.71 (1H, d, *J* = 4.4 Hz), 5.99 (1H, d, *J* = 5.2 Hz), 6.23 (1H, dd, *J* = 4.0, 1.6 Hz), 6.95 (1H, s), 7.24–7.42 (15H, m), 7.57 (1H, s). ^{13}C-NMR ($CDCl_3$, 100MHz) δ 26.6, 31.2, 31.3, 65.3, 65.3, 66.3, 66.4, 67.3, 67.4, 68.7, 68.9, 70.4, 70.5, 78.5, 122.0, 122.1, 126.1, 126.2, 126.3, 126.4, 126.6, 126.7, 127.1, 127.3, 127.6, 127.7, 128.0, 128.2, 128.3, 128.4, 138.5, 138.6, 141.5, 150.9, 166.0, 167.4, 167.5; HRMS (FAB, thioglycerol) calc for $[C_{30}H_{28}N_4O_4S + H]^+$ 541.1909, found 541.1936.

Benzhydryl 4-biphenyl-6-triazolylpenicillanate (11g)

Reaction of benzhydryl 6-azidopenicillanate **5c** (0.15 g, 0.367 mmol) and 4-ethynylbiphenyl **10g** (0.098 g, 0.55 mmol) within 5 h followed by flash chromatography (silica gel, gradient 1:0; 5:1; 3:1 Hexane/EtOAc) gave 158 mg (73%) of **11g** as a white solid. ^{1}H-NMR (DMSO-d_6, 400MHz) δ 1.26 (3H, s), 1.69 (3H, s), 4.92 (1H, s), 5.88 (1H, d, *J* = 2.0 Hz), 6.81 (1H, d,

J = 2.0 Hz), 6.96 (1H, s), 7.32 (2H, d, *J* = 8.0 Hz), 7.38 (5H, t, *J* = 7.2 Hz), 7.47 (5H, t, *J* = 6.8 Hz), 7.52 (2H, d, *J* = 8.0 Hz), 7.77 (2H, d, *J* = 8.0 Hz), 7.90 (2H, d, *J* = 8.0 Hz), 8.66 (1H, s)

Benzhydryl 3-biphenyl-6-triazolylpenicillanate (11h)

Reaction of benzhydryl 6-azidopenicillanate **5c** (0.15 g, 0.367 mmol) and 3-ethynylbiphenyl **10h** (0.098 g, 0.55 mmol) within 5 h followed by flash chromatography (silica gel, gradient 1:0; 5:1; 3:1 Hexane/EtOAc) gave 215 mg (100%) of **11h** as a white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.14 (3H, s), 1.58 (3H, s), 4.54 (1H, s), 5.68 (1H, d, *J* = 4.4 Hz), 6.28 (1H, d, *J* = 4.0 Hz), 6.86 (1H, s), 7.12 (1H, s), 7.19–7.24 (10H, m), 7.31–7.39 (3H, m), 7.45 (1H, d, *J* = 8.0 Hz), 7.52 (2H, d, *J* = 8.0 Hz), 7.69 (2H, d, *J* = 8.0 Hz), 7.95 (1H, s); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 26.7, 30.9, 65.5, 66.2, 67.3, 70.7, 78.7, 120.5, 124.6, 124.7, 126.9, 127.2, 127.5, 127.6, 128.3, 128.5, 128.6, 128.7, 129.3, 130.4, 138.7, 138.8, 140.6, 141.9, 147.5, 166.3, 168.2; HRMS (FAB, thioglycerol) calc for $[C_{35}H_{30}N_4O_3S + H]^+$ 587.2116, found 587.2143.

Benzhydryl 2-biphenyl-6-triazolylpenicillanate (11i)

Reaction of benzhydryl 6-azidopenicillanate **5c** (0.15 g, 0.367 mmol) and 2-ethynylbiphenyl **10i** (0.098 g, 0.55 mmol) within 5 h followed by flash chromatography (silica gel, gradient 1:0; 5:1; 3:1 Hexane/EtOAc) gave 150 mg (70%) of **11i** as a white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.20 (3H, s), 1.47 (3H, s), 4.47 (1H, s), 5.63 (1H, d, *J* = 4.0 Hz), 6.26 (1H, d, *J* = 4.4 Hz), 6.80 (1H, s), 6.93 (1H, s), 7.22–7.45 (18H, m), 8.15 (1H, d, *J* = 8.0 Hz); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 26.7, 31.3, 65.4, 66.3, 67.4, 70.4, 78.6, 123.0, 126.9, 127.2, 127.5, 127.8, 128.1, 128.2, 128.5, 128.6, 128.6, 128.7, 128.8, 129.2, 130.3, 138.8, 140.2, 141.5, 166.3, 167.0; HRMS (FAB, thioglycerol) calc for $[C_{35}H_{30}N_4O_3S + H]^+$ 587.2116, found 587.2143.

Benzhydryl 6-methoxynapthalyl-6-triazolylpenicillanate (11j)

Reaction of benzhydryl 6-azidopenicillanate **5c** (0.15 g, 0.367 mmol) and 2-ethynyl-6-methoxylnapthalene (0.067 g, 0.37 mmol) within 5 h followed by flash chromatography (silica gel, gradient 1:0; 5:1; 3:1 Hexane/EtOAc) gave 175 mg (81%) of **11j** as a white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.27 (3H, s), 1.72 (3H, s), 3.91 (3H, s), 4.67 (1H, s), 5.80 (1H, d, *J* = 4.4 Hz), 6.41 (1H, d, *J* = 4.4 Hz), 6.97 (1H, s), 7.13–7.16 (2H, m), 7.31–7.35 (10H, m), 7.77 (2H, dd, *J* = 6.4, 2.8 Hz), 7.88 (1H, dd, *J* = 6.4, 1.6 Hz), 8.08 (1H, s), 8.26 (1H, s); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 26.7, 31.0, 55.3, 65.5, 66.2, 67.3, 70.8, 78.7, 119.3, 120.2, 124.3, 124.6, 125.1, 126.9, 127.4, 127.6, 128.3, 128.6, 128.7, 128.9, 129.7, 134.4, 138.7, 138.8, 147.7, 158.0, 166.3, 168.2; HRMS (FAB, mnba) calc for $[C_{34}H_{30}N_4O_4S + H]^+$ 591.2066, found 591.2061.

Benzhydryl 4-pyridylphenyl-6-triazolylpenicillanate (11k)

Reaction of benzhydryl 6-azidopenicillanate **5c** (0.15 g, 0.367 mmol) and 4-(4-ethynylphenyl) pyridine **10k** (0.098 g, 0.55 mmol) within 5 h followed by flash chromatography (silica gel, gradient 1:1; 1:2; 1:4 Hexane/EtOAc) gave 202 mg (94%) of **11k** as a white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.27 (3H, s), 1.71 (3H, s), 4.66 (1H, s), 5.80 (1H, d, *J* = 4.0 Hz), 6.40 (1H, d, *J* = 4.0 Hz), 6.97 (1H, s), 7.31–7.35 (12H, m), 7.61 (2H, br s), 7.72 (2H, d, *J* = 8.0 Hz), 7.97 (2H, d, *J* = 8.0 Hz), 8.09 (1H, s); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 26.7, 30.9, 65.6, 66.2, 67.3, 70.7, 78.7, 120.8, 126.5, 126.9, 127.5, 127.6, 128.3, 128.6, 128.7, 131.2, 137.3, 138.7, 138.8, 146.6, 148.8, 148.9166.3, 168.1; HRMS (FAB, thioglycerol) calc for $[C_{34}H_{29}N_5O_3S + H]^+$ 588.2069, found 588.2100.

Benzhydryl 4-pyridylbenzylhydroxyl-6-triazolylpenicillanate (11l)

Reaction of benzhydryl 6-azidopenicillanate **5c** (0.15 g, 0.367 mmol) and 1-(4-(pyrdin-4-yl) prop-2-yn-1-ol **10l** (0.115 g, 0.55 mmol) within 2 h followed by flash chromatography (silica gel, gradient 1:2; 1:3 Hexane/EtOAc) gave 190 mg (84%) of **11l** as a white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.22 (3H, d, *J* = 12 Hz), 1.60 (3H, d, *J* = 5.6 Hz), 4.58 (1H, s), 5.72 (1H,

d, J = 4.4 Hz), 6.08 (1H, s), 6.28 (1H, d, J = 4.4 Hz), 6.92 (1H, s), 7.24–7.32 (10H, m), 7.44 (2H, dd, J = 6.0, 1.6 Hz) 7.52–7.58 (4H, m), 7.67 (1H, s), 8.53 (2H, dd, J = 6.4, 1.6 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ26.7, 30.6, 31.1, 31.2, 64.3, 65.4, 66.2, 66.3, 67.3, 68.4, 68.5, 70.5, 78.6, 121.4, 122.0, 126.6, 126.9, 127.1, 127.4, 128.1, 128.3, 128.4, 128.5, 137.1, 137.2, 138.5, 142.9, 147.8, 149.6, 150.8, 150.9, 166.0, 167.5, 167.6; HRMS (FAB, thioglycerol) calc for $[C_{35}H_{31}N_5O_4S + H]^+$ 618.2175, found 618.2180

Representative Procedure for Deprotection of Carboxyl Protecting Group. Benzyl-6-triazolylpenicillanic acid (9a)

p-Methoxybenzyl benzyl-6-triazolylpenicillanate **8a** (0.13 g, 0.26 mmol) was dissolved and stirred in anhydrous CH_2Cl_2 (1 mL) at −5°C. Anhydrous anisole (0.2 mL, 1.83 mmol) and trifluoroacetic acid (0.5 mL, 6.49 mmol) were added, and the reaction mixture stirred for 2 h. The reaction mixture was diluted with cold Et_2O (10 mL), and the solvent was evaporated off in an ice bath. The residue was concentrated *in vacuo* on an ice bath for 15 minutes, and redissolved in THF (5 mL) and ½ saturated $NaHCO_3$ (15 mL) at 0°C. The resulting mixture was stirred at 0°C for 15 minutes and partitioned between deionized water (5 mL) and EtOAc (20 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The aqueous layer was acidified to pH 3 in an ice bath with 1N HCl and extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give 89 mg (100%) of **9a** as a white solid. ^{1}H-NMR (acetone-d_6, 400MHz) δ 1.55 (3H, s), 1.70 (3H, s), 4.07 (2H, s), 4.55 (1H, s), 5.85 (1H, d, J = 4.4 Hz), 6.58 (1H, d, J = 4.4 Hz), 7.26–7.28 (5H, m), 7.79 (1H, s); ^{13}C-NMR (acetone-d_6, 100MHz) δ 26.8, 31.0, 31.8, 65.1, 67.0, 67.8, 70.7, 123.2, 126.7, 128.8, 128.9, 129.0, 139.9, 168.4, 168.5; HRMS (FAB, mnba) calc for $[C_{17}H_{18}N_4O_3S + H]^+$ 359.1177, found 359.1177.

2,6-Dimethoxyphenyl-6-triazolylpenicillanic acid (9b)

The reaction of a CH_2Cl_2 solution of **8c** with anisole and TFA within 2 h, as described for the synthesis of **9a** from **8a**, afforded 85 mg (100%) of **9b** as a white solid. ^{1}H-NMR (acetone-d_6, 400MHz) δ 1.59 (3H, s), 1.77 (3H, s), 3.77 (6H, s), 4.62 (1H, s), 5.93 (1H, d, J = 4.4 Hz), 6.73 (1H, d, J = 4.4 Hz), 6.74 (2H, d, J = 8.4 Hz), 7.35 (1H, t, J = 8.4 Hz), 8.15 (1H, s); ^{13}C-NMR (acetone-d_6, 400MHz) δ 26.9, 31.2, 55.9, 65.2, 67.2, 68.0, 70.7, 104.6, 126.2, 131.0, 158.7, 168.6; HRMS (FAB, mnba) calc for $[C_{18}H_{20}N_4O_5S + H]^+$ 405.1232, found 405.1214.

4-pyridyl-6-triazolylpenicillanic acid (12a)

The reaction of a CH_2Cl_2 solution of **11a** with anisole and TFA within 0.5 h, as described for the synthesis of **9a** from **8a**, afforded 80 mg (100%) of **12a** as a white solid. ^{1}H-NMR (acetone-d_6, 400MHz) δ 1.56 (3H, s), 1.73 (3H, s), 4.60 (1H, s), 5.95 (1H, d, J = 4.0 Hz), 6.78 (1H, d, J = 4.0 Hz), 8.57 (2H, br s), 9.01 (2H, br s), 9.07 (1H, s); ^{13}C-NMR (acetone-d_6, 100MHz) δ 27.1, 31.6, 65.7, 67.7, 68.0, 71.4, 122.8, 126.8, 142.8, 143.6, 146.6, 167.5, 170.7; HRMS (FAB, mnba) calc for $C_{15}H_{15}N_5O_3S + H]^+$ 346.0973, found 346.0972.

3-pyridyl-6-triazolylpenicillanic acid (12b)

The reaction of a CH_2Cl_2 solution of **11b** with anisole and TFA within 0.5 h, as described for the synthesis of **9a** from **8a**, afforded 80 mg (100%) of **12b** as a reddish white solid. ^{1}H-NMR (acetone-d_6, 400MHz) δ 1.57 (3H, s), 1.74 (3H, s), 4.60 (1H, s), 5.95 (1H, d, J = 4.0 Hz), 6.76 (1H, d, J = 4.0 Hz), 8.15 (1H, br s), 8.84 (1H, s), 8.92 (2H, m), 9.41 (1H, br s); HRMS (FAB, mnba) calc for $[C_{15}H_{15}N_5O_3S + H]^+$ 346.0973, found 346.0972.

2-pyridyl-6-triazolylpenicillanic acid (12c)

The reaction of a CH_2Cl_2 solution of **11c** with anisole and TFA within 0.5 h, as described for the synthesis of **9a** from **8a**, afforded 80 mg (100%) of **12c** as a white solid. ^{1}H-NMR (acetone-

d_6, 400MHz) δ 1.57 (3H, s), 1.76 (3H, s), 4.63 (1H, s), 5.95 (1H, d, *J* = 4.0 Hz), 6.79 (1H, d, *J* = 4.0 Hz), 7.79 (1H, m), 8.39 (1H, m), 8.48 (1H, m), 8.90 (1H, d, *J* = 5.1 Hz), 8.95 (1H, s); ^{13}C-NMR (acetone-d_6, 100MHz) δ 27.1, 31.5, 65.7, 67.6, 68.0, 71.2, 122.8, 125.3, 125.7, 143.2, 145.9, 146.7, 160.2, 167.8, 168.6; HRMS (FAB, mnba) calc for $[C_{15}H_{15}N_5O_3S + H]^+$ 346.0973, found 346.0974.

2-Thiopyl-6-triazolylpenicillanic acid (12d)

The reaction of a CH_2Cl_2 solution of **11d** with anisole and TFA within 1 h, as described for the synthesis of **9a** from **8a**, afforded 81 mg (100%) of **12d** as a yellowish solid. ^{1}H-NMR (acetone-d_6, 400MHz) δ 1.57 (3H, s), 1.74 (3H, s), 4.59 (1H, s), 5.90 (1H, d, *J* = 4.0 Hz), 6.65 (1H, d, *J* = 4.0 Hz), 7.54 (1H, m), 7.57 (1H, dd, *J* = 3.0, 1.5 Hz), 7.87 (1H, dd, *J* = 3.0, 1.5 Hz), 8.34 (1H, s); ^{13}C-NMR (acetone-d_6, 100MHz) δ 27.1, 31.3, 65.4, 67.3, 68.0, 71.2, 121.4, 121.6, 126.3, 127.1, 132.4, 143.7, 168.3, 168.9; HRMS (FAB, mnba) calc for $[C_{14}H_{14}N_4O_3S_2 + H]^+$ 351.0585, found 351.0577.

Phenyl-6-triazolylpenicillanic acid (12e)

The reaction of a CH_2Cl_2 solution of **11e** with anisole and TFA within 2 h, as described for the synthesis of **9a** from **8a**, afforded 68.5 mg (93%) of **12e** as a white solid. ^{1}H-NMR (acetone-d_6, 400MHz) δ 1.47 (3H, s), 1.67 (3H, s), 4.54 (1H, s), 5.80 (1H, d, *J* = 4.0 Hz), 6.76 (1H, d, *J* = 4.4 Hz), 7.34 (1H, m), 7.44 (2H, m), 7.89 (2H, m), 8.60 (1H, s); ^{13}C-NMR (acetone-d_6, 100MHz) δ 27.2, 31.2, 65.4, 67.3, 68.0, 71.2, 121.6, 126.1, 126.1, 128.6, 129.4, 131.3, 147.3, 168.4; HRMS (FAB, mnba) calc for $[C_{16}H_{16}N_4O_3S + H]^+$ 345.1021, found 345.1015.

α-Hydroxylbenzyyl-6-triazolylpenicillanic acid (12f)

The reaction of a CH_2Cl_2 solution of **11f** with thioanisole and TFA within 0.5 h, as described for the synthesis of **9a** from **8a**, afforded 76 mg (100%) of **12f** as a pale yellowish solid. ^{1}H-NMR (acetone-d_6, 400MHz) δ 1.53 (3H, s), 1.67 (3H, s), 3.37 (1H, s), 4.55 (1H, s), 5.84 (1H, bs), 5.97 (1H, s), 6.55 (1H, bs), 7.22–7.43 (4H, m), 7.80 (1H, s); HRMS (FAB, thioglycerol) calc for $[C_{17}H_{18}N_4O_4S + H]^+$ 375.1127, found 375.1192.

4-Biphenyl-6-triazolylpenicillanic acid (12g)

The reaction of a CH_2Cl_2 solution of **11g** with anisole and TFA within 2 h, as described for the synthesis of **9a** from **8a**, afforded 65 mg (100%) of **12g** as a yellowish solid. ^{1}H-NMR (DMSO-d_6, 400MHz) δ 1.48 (3H, s), 1.65 (3H, s), 4.38 (1H, s), 5.79 (1H, d, *J* = 4.0 Hz), 6.72 (1H, d, *J* = 4.0 Hz), 7.35–7.40 (1H, m), 7.47 (2H, t, *J* = 8.0 Hz), 7.74 (4H, dd, *J* = 11.2, 8.0 Hz), 7.99 (2H, d, *J* = 8.0 Hz), 8.63 (1H, s); HRMS (FAB, mnba) calc for $[C_{22}H_{20}N_4O_3S + H]^+$ 421.1334, found 421.1333.

3-Biphenyl-6-triazolylpenicillanic acid (12h)

The reaction of a CH_2Cl_2 solution of **11h** with anisole and TFA within 2 h, as described for the synthesis of **9a** from **8a**, afforded 54 mg (83%) of **12h** as a white solid. ^{1}H-NMR (acetone-d_6, 400MHz) δ 1.59 (3H, s), 1.77 (3H, s), 4.61 (1H, s), 5.93 (1H, d, *J* = 4.0 Hz), 6.71 (1H, d, *J* = 4.0 Hz), 7.38 (1H, m), δ 7.48 (2H, m), 7.54 (1H, t, *J* = 8.0 Hz), 7.64 (1H, m), 7.72 (2H, m), 7.96 (1H, dt, *J* = 8.0, 1.5 Hz), 8.23 (1H, t, 1.5 Hz), 8.58 (1H, s); ^{13}C-NMR (acetone-d_6, 100MHz) δ 27.2, 31.2, 65.5, 67.3, 68.0, 71.3, 122.0, 124.6, 125.1, 127.2, 127.5, 128.1, 129.4, 130.0, 131.9, 141.1, 142.2, 147.2, 168.4, 168.9; HRMS (ESI, mnba) calc for $[C_{22}H_{20}N_4O_3S + H]^+$ 421.1329, found 421.1312.

2-Biphenyl-6-triazolylpenicillanic acid (12i)

The reaction of a CH_2Cl_2 solution of **11i** with anisole and TFA within 1 h, as described for the synthesis of **9a** from **8a**, afforded 65 mg (100%) of **12i** as a white solid. H-NMR (acetone-d_6, 400MHz) δ 1.53 (3H, s), 1.59 (3H, s), 4.41 (1H, s), 5.78 (1H, d, *J* = 4.0 Hz), 6.55 (1H, d, *J* = 4.0 Hz), 7.00 (1H, s), 7.22–7.25 (2H, m), 7.32–7.52 (6H, m), 8.07 (1H, dd, *J* = 5.8, 1.5 Hz); HRMS (ESI, mnba) calc for $[C_{22}H_{20}N_4O_3S + H\}^+$ 421.1329, found 421.1359.

6-Methoxynaphthalyl-6-triazolylpenicillanic acid (12j)

The reaction of a CH_2Cl_2 solution of **11j** with anisole and TFA within 1 h, as described for the synthesis of **9a** from **8a**, afforded 56 mg (89%) of **12j** as a white foam. ^{1}H-NMR (DMSO-d_6, 400MHz) δ 1.58 (3H, s), 1.78 (3H, s), 3.91 (3H, s), 4.17 (1H, s), 5.80 (1H, d, *J* = 4.0 Hz), 6.62 (1H, d, *J* = 4.0 Hz), 7.16 (1H, dd, *J* = 6.5, 2.2 Hz), 7.30 (1H, m), 7.85 (2H, dd, *J* = 3.0, 5.0 Hz), 7.98 (1H, m), 8.39 (1H, m), 8.55 (1H, s); ^{13}C-NMR (acetone-d_6, 100MHz) δ 26.7, 30.7, 55.1, 65.0, 67.0, 67.6, 70.8, 106.1, 119.5, 121.3, 124.4, 124.5, 126.2, 127.7, 129.3, 129.9, 134.9, 147.4, 158.4, 168.3, 168.4; HRMS (FAB, thioglycerol) calc for $[C_{21}H_{20}N_4O_4S + H]^+$ 425.1283, found 425.1264.

4-Pyridylphenyl-6-triazolylpenicillanic acid (12k)

The reaction of a CH_2Cl_2 solution of **11k** with anisole and TFA within 1 h, as described for the synthesis of **9a** from **8a**, afforded 37 mg (65%) of **12k** as a white foam. ^{1}H-NMR (acetone-d_6, 400MHz) δ 1.58 (3H, s), 1.77 (3H, s), 4.61 (1H, s), 5.94 (1H, d, *J* = 4.0 Hz), 6.74 (1H, d, *J* = 4.0 Hz), 8.17 (4H, m), 8.47 (2H, br s), 8.64 (1H, s), 9.04 (2H, br s); HRMS (FAB, mnba) calc for $[C_{21}H_{19}N_5O_3S + H]^+$ 422.1287, found 422.1301.

4-Pyridylbenzylhydroxyl-6-triazolylpenicillanic acid salt (12l)

Benzhydryl 4-pyridylphenyl-6-triazolylpenicillanate **11l** (0.09 g, 0.14 mmol) was dissolved and stirred in anhydrous CH_2Cl_2 (1 mL) at −5°C. Anhydrous thioanisole (0.2 mL, 1.83 mmol) and TFA (0.5 mL, 6.49 mmol) were added, and the reaction mixture stirred for 0.5 h. The reaction mixture was diluted with cold Et_2O (10 mL), and the solvent was evaporated off in an ice bath. The residue was concentrated *in vacuo* on an ice bath for 15 minutes, and redissolved in aqueous $NaHCO_3$ (0.018 g, 0.21 mmol) at 0°C. The resulting mixture was stirred at 0°C for 15 minutes and partitioned between deionized water (5 mL) and EtOAc (20 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The aqueous layer was frozen in acetone-dry ice bath and concentrated *in vacuo* to give 35 mg (52%) of **12l** as a white solid. ^{1}H-NMR (DMSO-d_6, 400MHz) δ 1.46 (3H, s), 1.61 (3H, m), 4.51 (1H, s), 5.75 (1H, d, *J* = 4.4 Hz), 5.94 (1H, s), 6.67 (1H, d, *J* = 4.0 Hz), 7.57 (2H, d, *J* = 8.0 Hz), 7.86 (4H, m), 8.75 (2H, m); HRMS (FAB, mnba) calc for $[C_{22}H_{20}N_5NaO_4S + H]^+$ 474.1212, found 474.1234.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Professor James Power and Josh Canzoneri for a helpful discussion on the manuscript. This work was financially supported by Georgia Institute of Technology. Compound screening was supported, in part, by the National Institute of Allergy and Infectious Diseases, under contract number N01-AI-30061. C. P. C. is a recipient of a GAANN predoctoral fellowship from the Gatech Center for Drug Design, Development and Delivery. P. A. P. is a Gatech PURA fellow.

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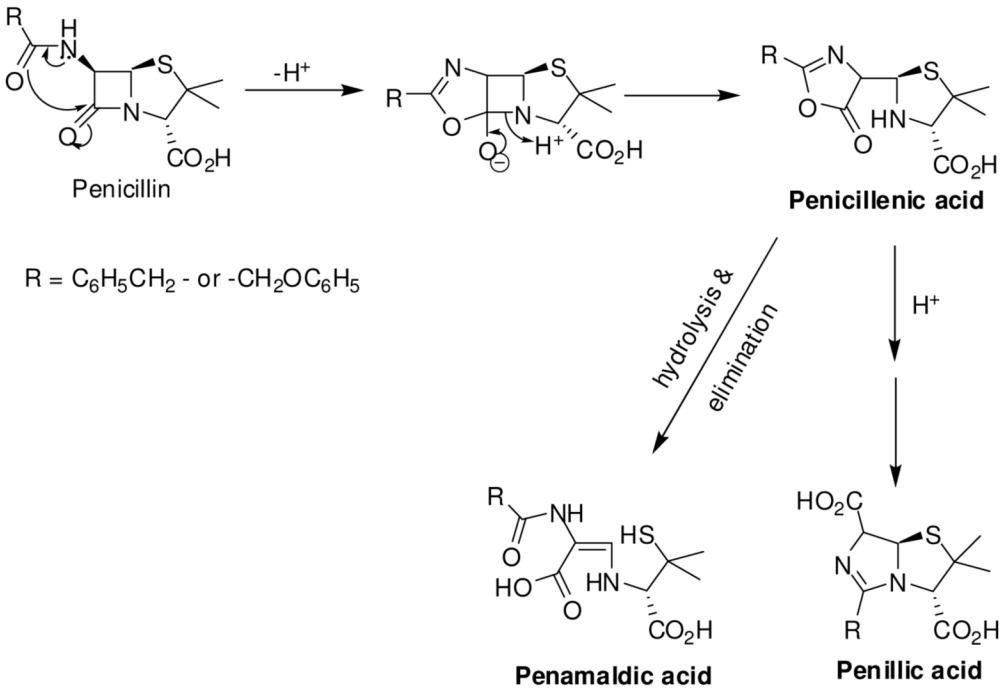


Figure 1.
Self-induced acid hydrolysis of penicillin.

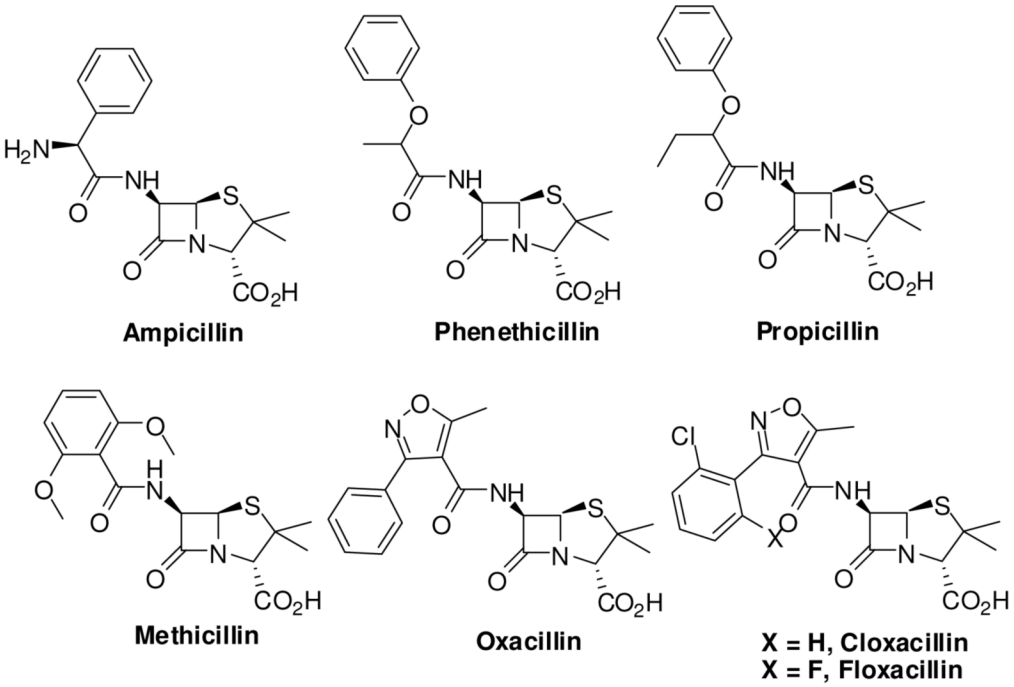


Figure 2.
The structure of some acid- and β-lactamase-resistant penicillins.

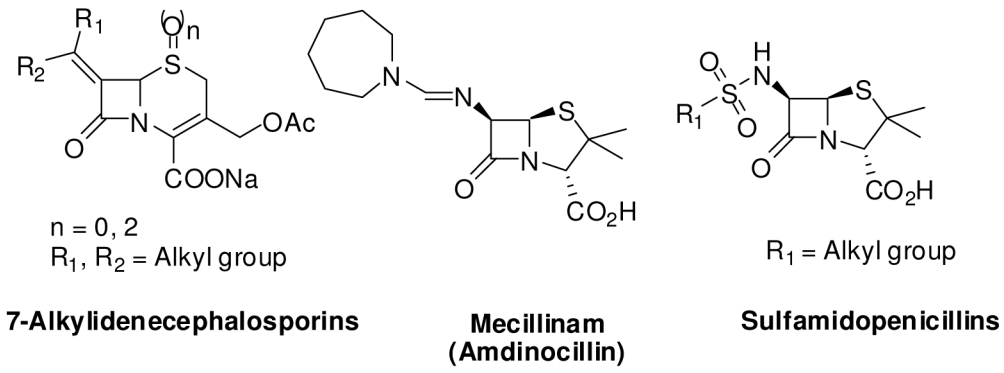
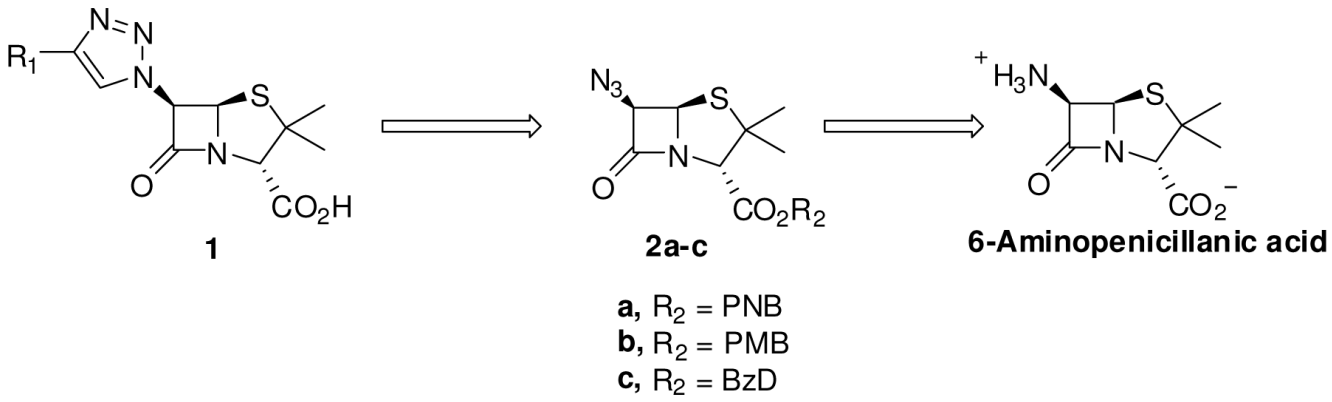
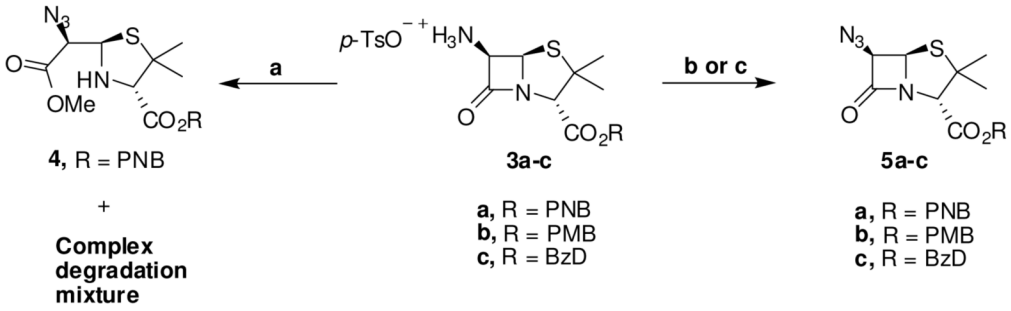


Figure 3.
Structure of amide isosteric β-lactams.



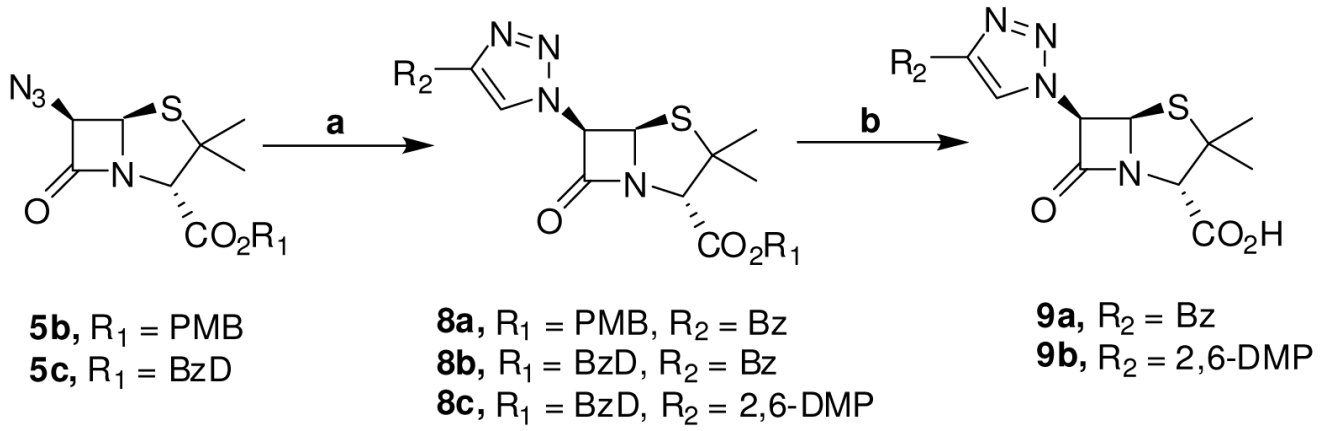
Scheme 1.

Synthetic approach to 6-triazolylpenicillanic acids. Abbreviation: PNB = *para*-nitrobenzyl, PMB = *para*-methoxylbenzyl, BzD = benzhydryl.



Scheme 2.

Synthesis of protected 6-azidopenicillanic acid. Conditions: (a) TfN_3, Et_3N, CH_2Cl_2/MeOH/H_2O, rt, (b) TfN_3, Et_3N, DMAP, rt, 2–2.5 hrs, (c) TfN_3, Et_3N, toluene, rt, 1.5–2.5 hrs.



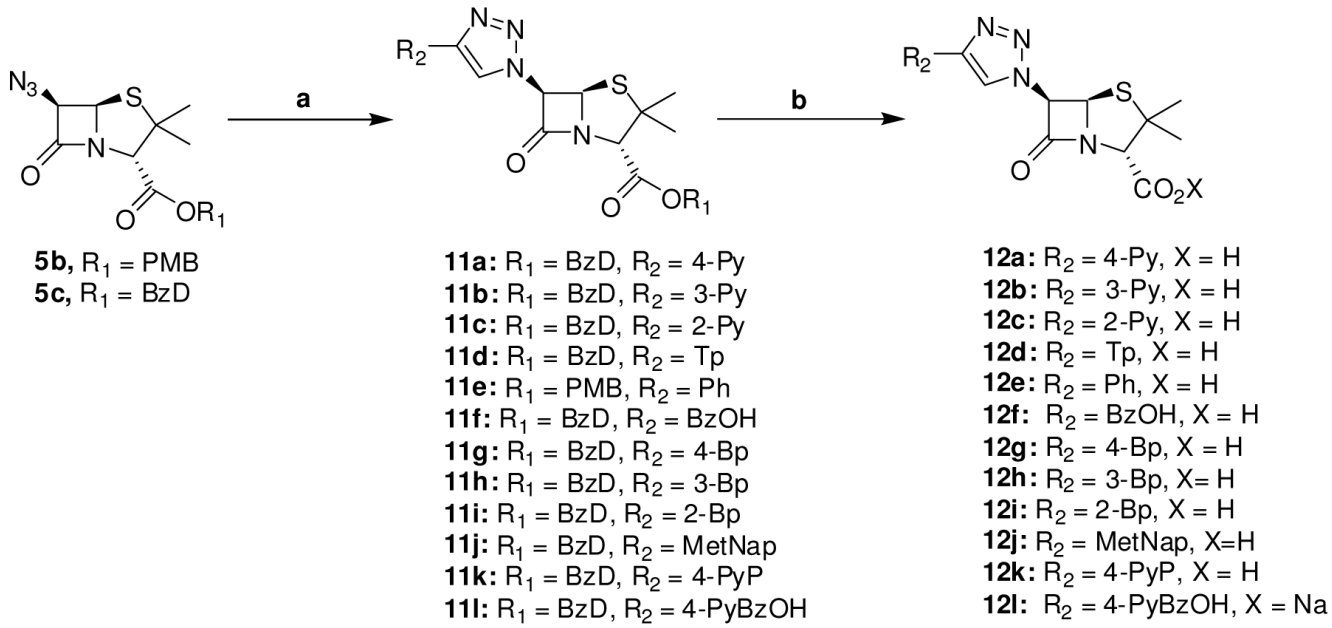
5b, R_1 = PMB
5c, R_1 = BzD

8a, R_1 = PMB, R_2 = Bz
8b, R_1 = BzD, R_2 = Bz
8c, R_1 = BzD, R_2 = 2,6-DMP

9a, R_2 = Bz
9b, R_2 = 2,6-DMP

Scheme 3.

Cu(I)-catalyzed cycloadditions reaction between 6-azidopenicillanates and representative terminal alkynes. Conditions: (a) CuI, Hunig's base, alkynes **6** or **7**, THF, rt, (b) TFA, anisole, CH_2Cl_2, −5°C. Abbreviation: 2,6-DMP = 2,6-dimethoxylphenyl.

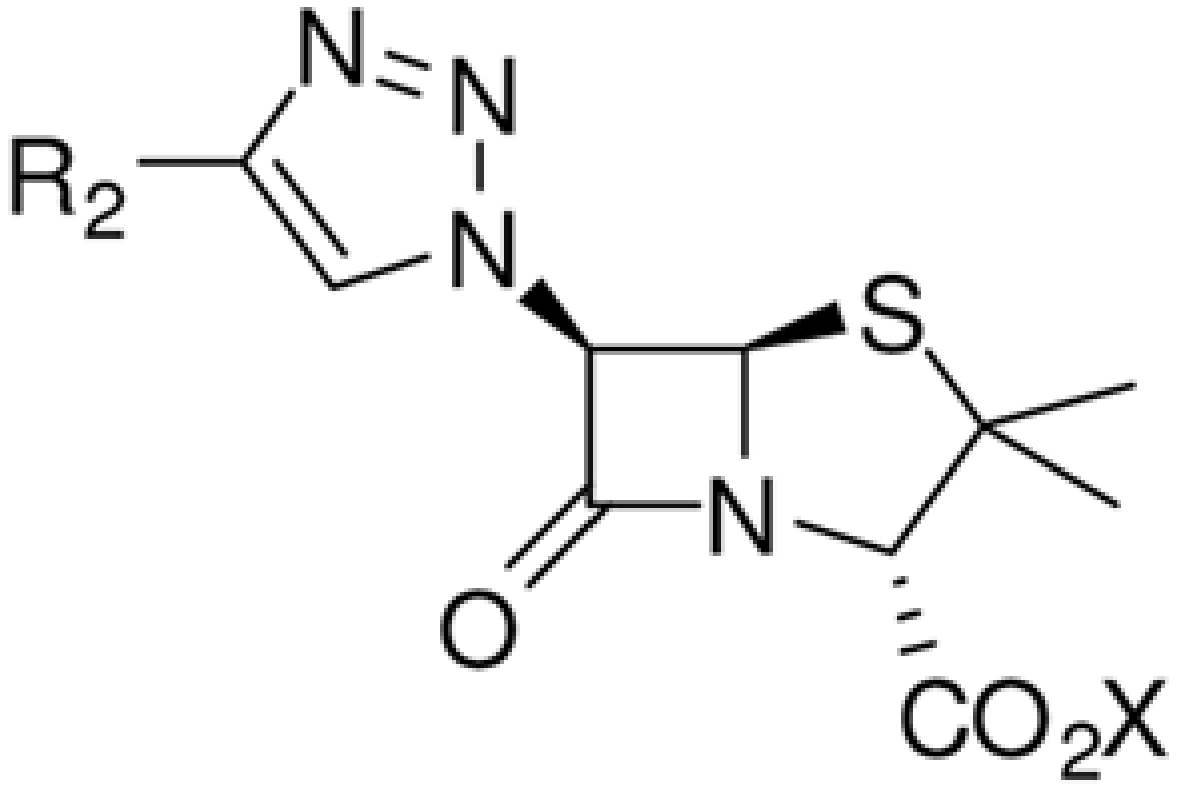


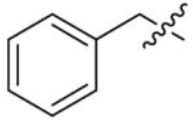
Scheme 4.

Scope of Cu(I)-catalyzed cycloaddition between 6-azidopenicillanate and terminal alkynes. Conditions: a) CuI, Hunig's base, alkynes 10, THF, rt, b) TFA, anisole CH_2Cl_2, −5°C.

Table 1

Minimal Inhibitory Concentration (MIC) of 6-triazolylepenicillanic acids in μg/mL: Each MIC values were obtained from an average of three independent experiments.



Compound	R_2	*S. aureus* ATCC 29213 (μg/mL)	*E. coli* ATCC 25922 (μg/mL)	*S. pneumoniae* ATCC 49619 (μg/mL)	*B. anthracis* AMES (μg/mL)
9a		>8	>8	4	>8

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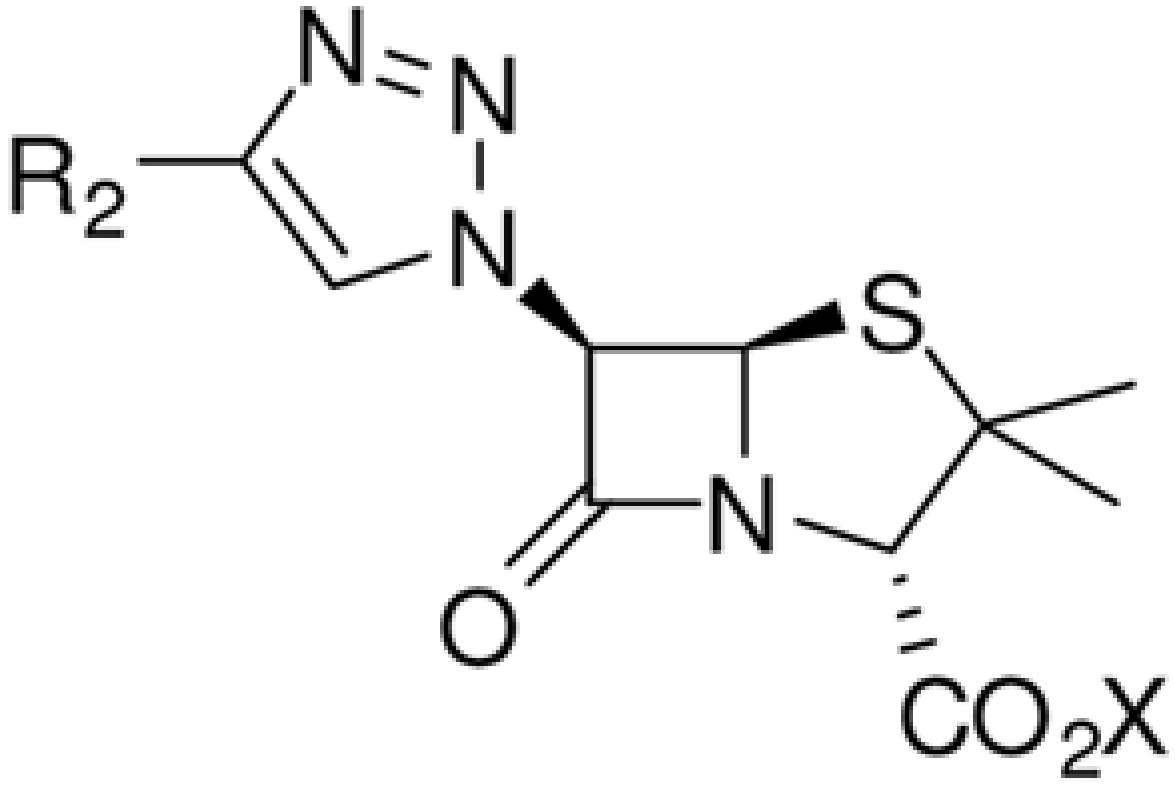
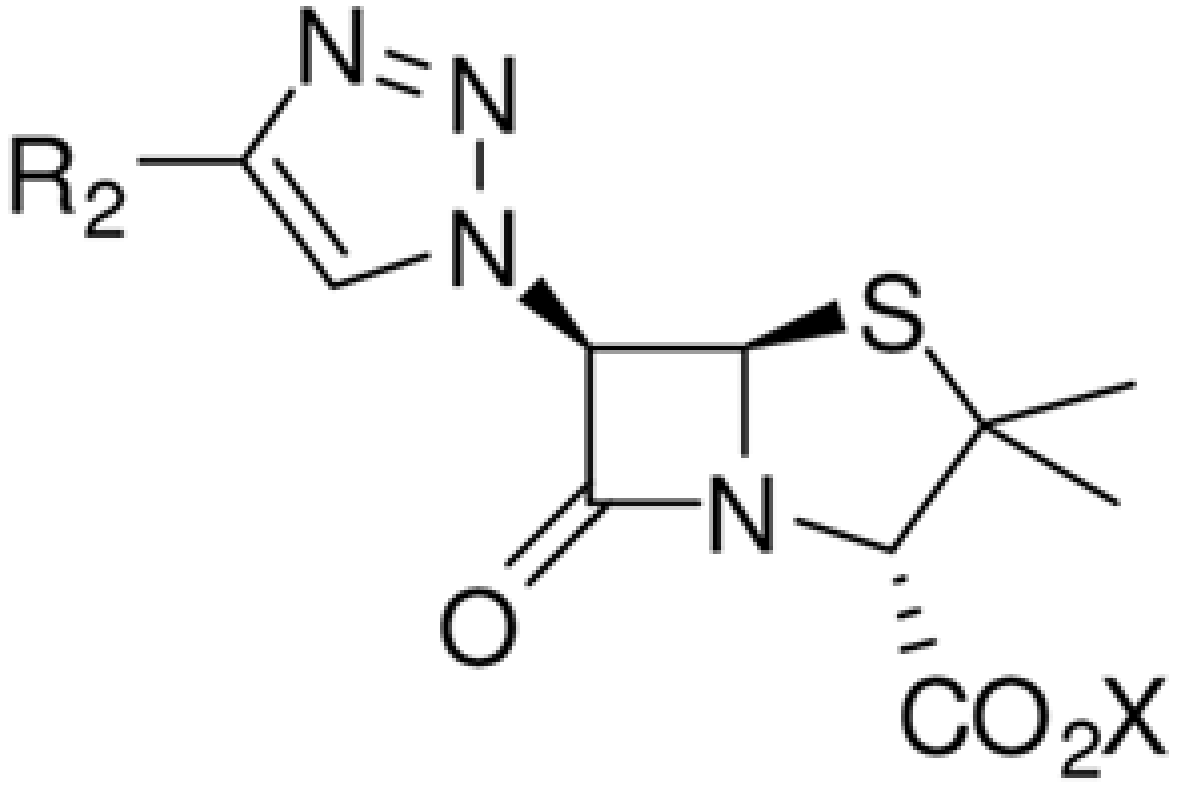
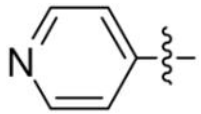


X = H, Na

Compound	R_2	*S. aureus* ATCC 29213 (μg/mL)	*E. coli* ATCC 25922 (μg/mL)	*S. pneumoniae* ATCC 49619 (μg/mL)	*B. anthracis* AMES (μg/mL)
9b		>8	>8	>8	>8



X = H, Na

Compound	R_2	*S. aureus* ATCC 29213 (μg/mL)	*E. coli* ATCC 25922 (μg/mL)	*S. pneumoniae* ATCC 49619 (μg/mL)	*B. anthracis* AMES (μg/mL)
12a		>8	>8	>8	>8

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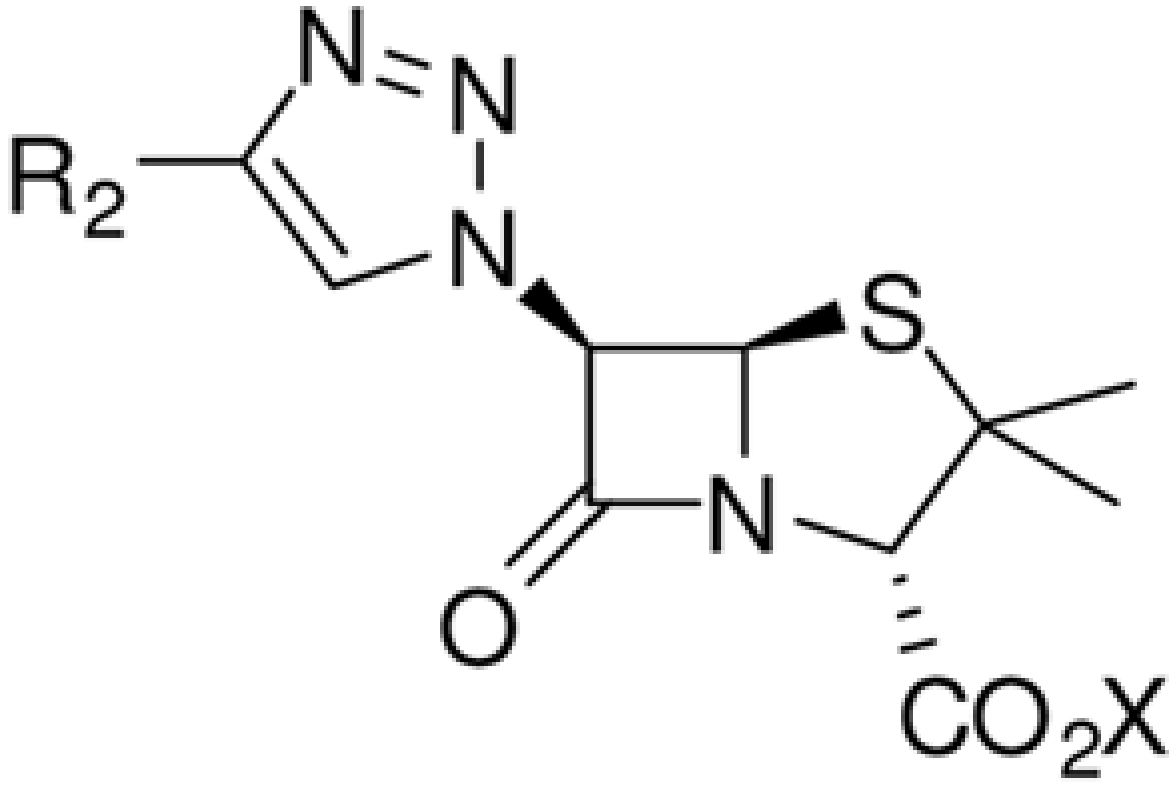
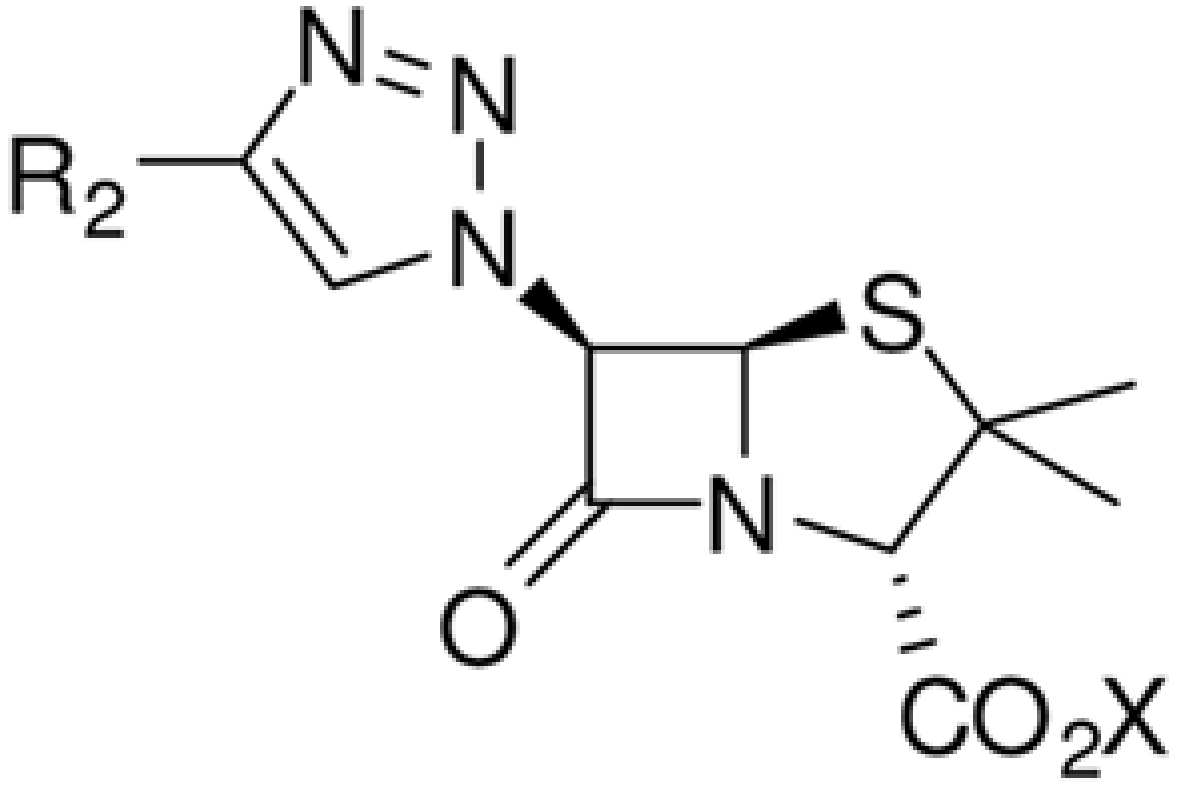


X = H, Na

Compound	R_2	*S. aureus* ATCC 29213 (μg/mL)	*E. coli* ATCC 25922 (μg/mL)	*S. pneumoniae* ATCC 49619 (μg/mL)	*B. anthracis* AMES (μg/mL)
12b		>8	>8	>8	>8



X = H, Na

Compound	R_2	*S. aureus* ATCC 29213 (μg/mL)	*E. coli* ATCC 25922 (μg/mL)	*S. pneumoniae* ATCC 49619 (μg/mL)	*B. anthracis* AMES (μg/mL)
12c		>8	>8	>8	>8

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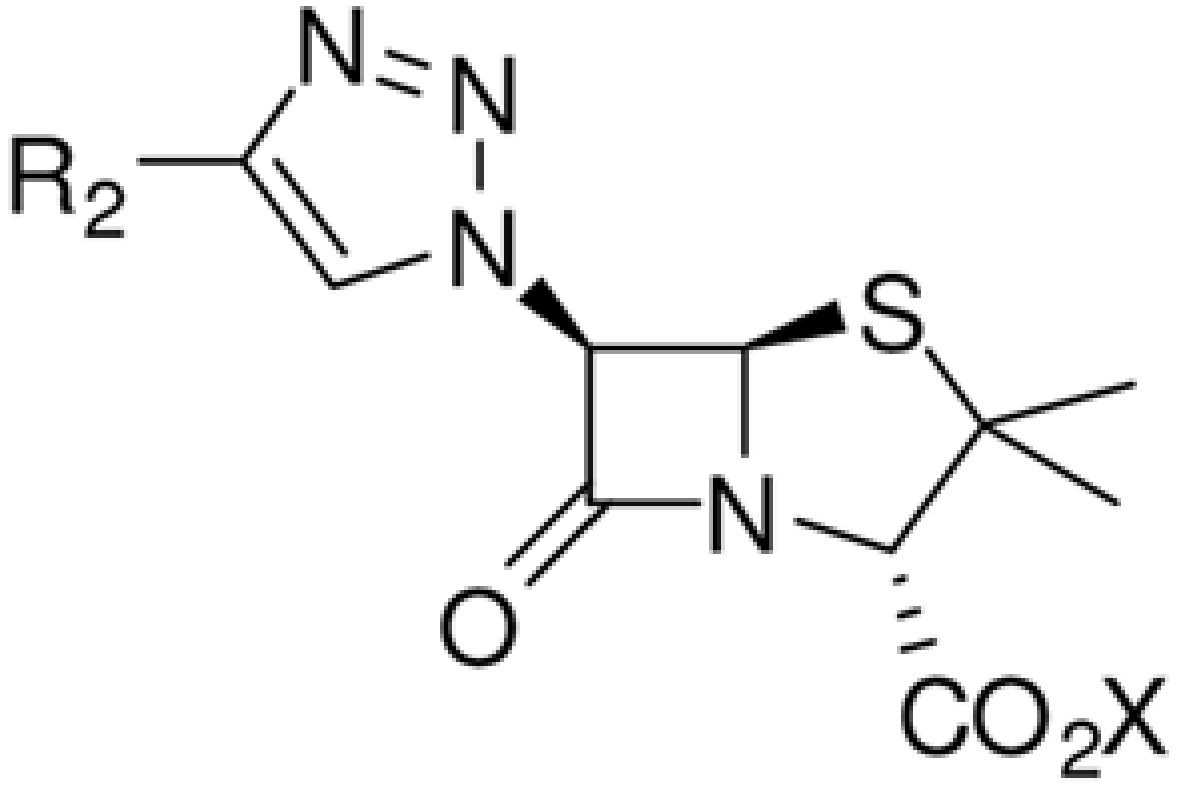

X = H, Na

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Compound	R_2	*S. aureus* ATCC 29213 (μg/mL)	*E. coli* ATCC 25922 (μg/mL)	*S. pneumoniae* ATCC 49619 (μg/mL)	*B. anthracis* AMES (μg/mL)
12d		>8	>8	8	>8

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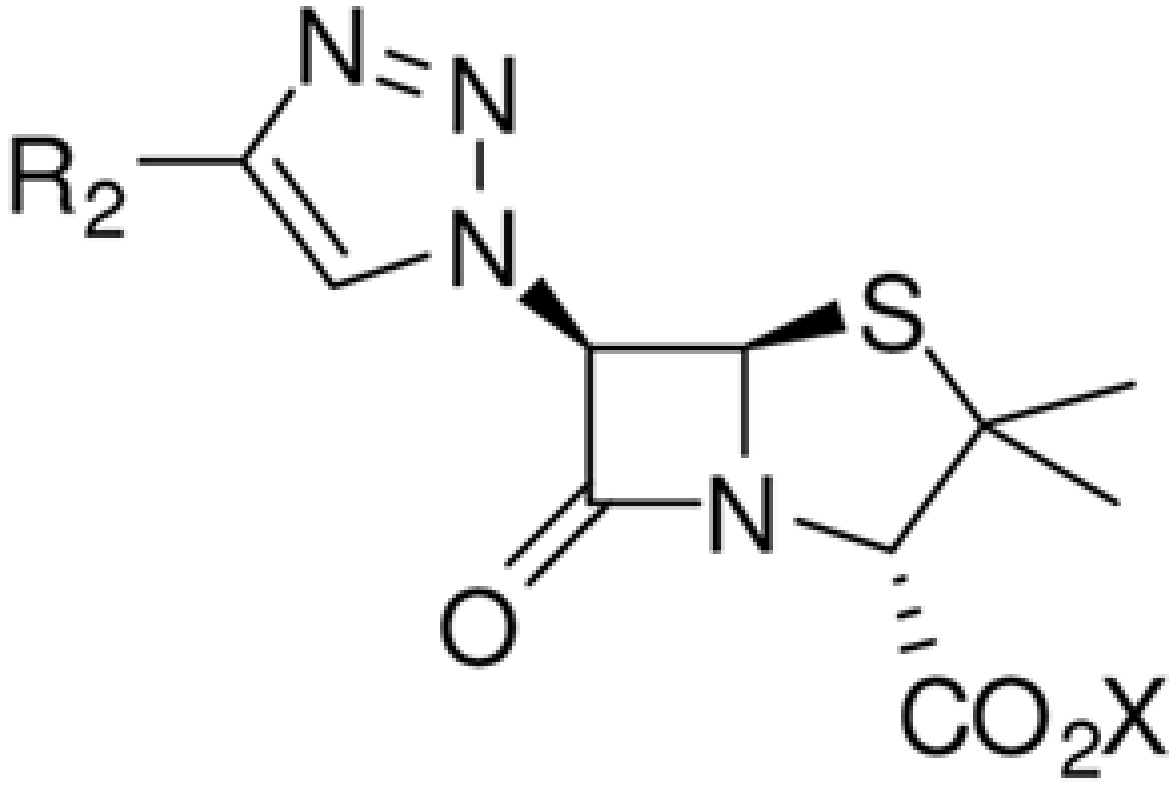
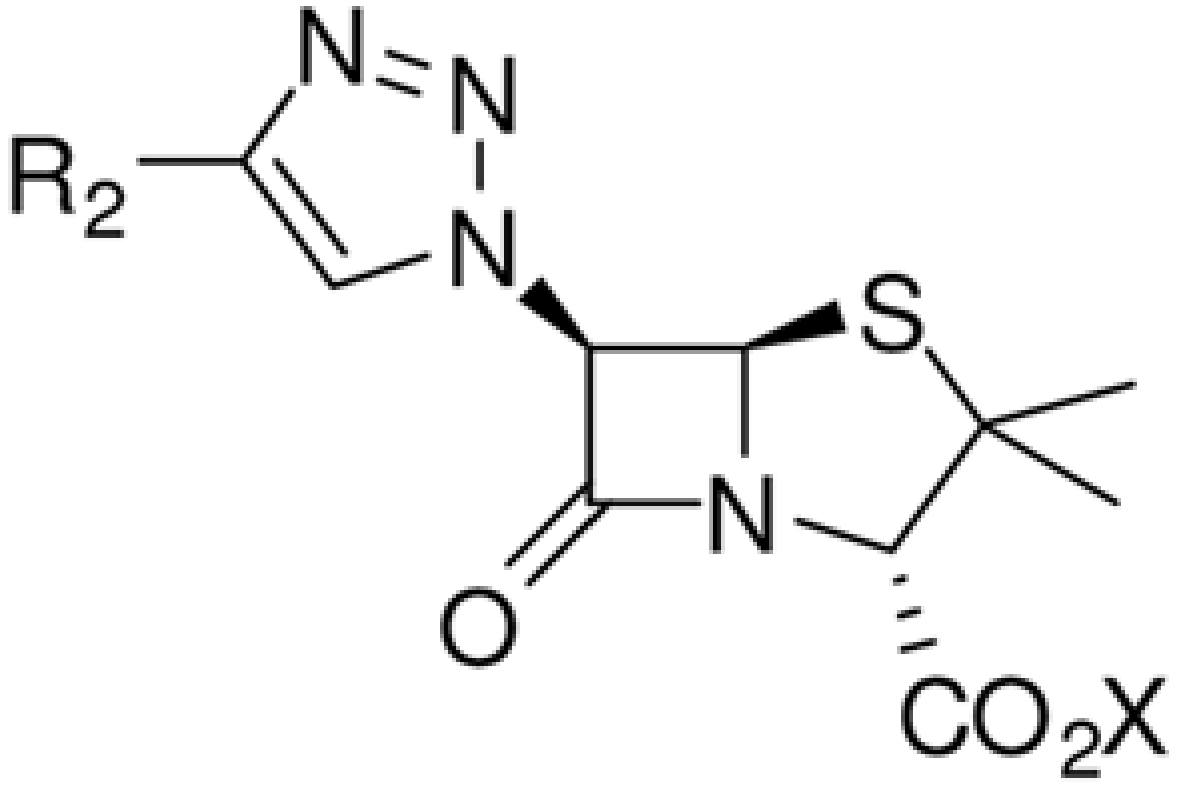
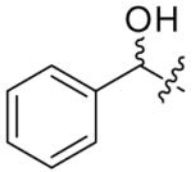


X = H, Na

Compound	R_2	*S. aureus* ATCC 29213 (μg/mL)	*E. coli* ATCC 25922 (μg/mL)	*S. pneumoniae* ATCC 49619 (μg/mL)	*B. anthracis* AMES (μg/mL)
12e		>8	>8	4	>8



X = H, Na

Compound	R_2	*S. aureus* ATCC 29213 (μg/mL)	*E. coli* ATCC 25922 (μg/mL)	*S. pneumoniae* ATCC 49619 (μg/mL)	*B. anthracis* AMES (μg/mL)
12f		>8	>8	>8	>8

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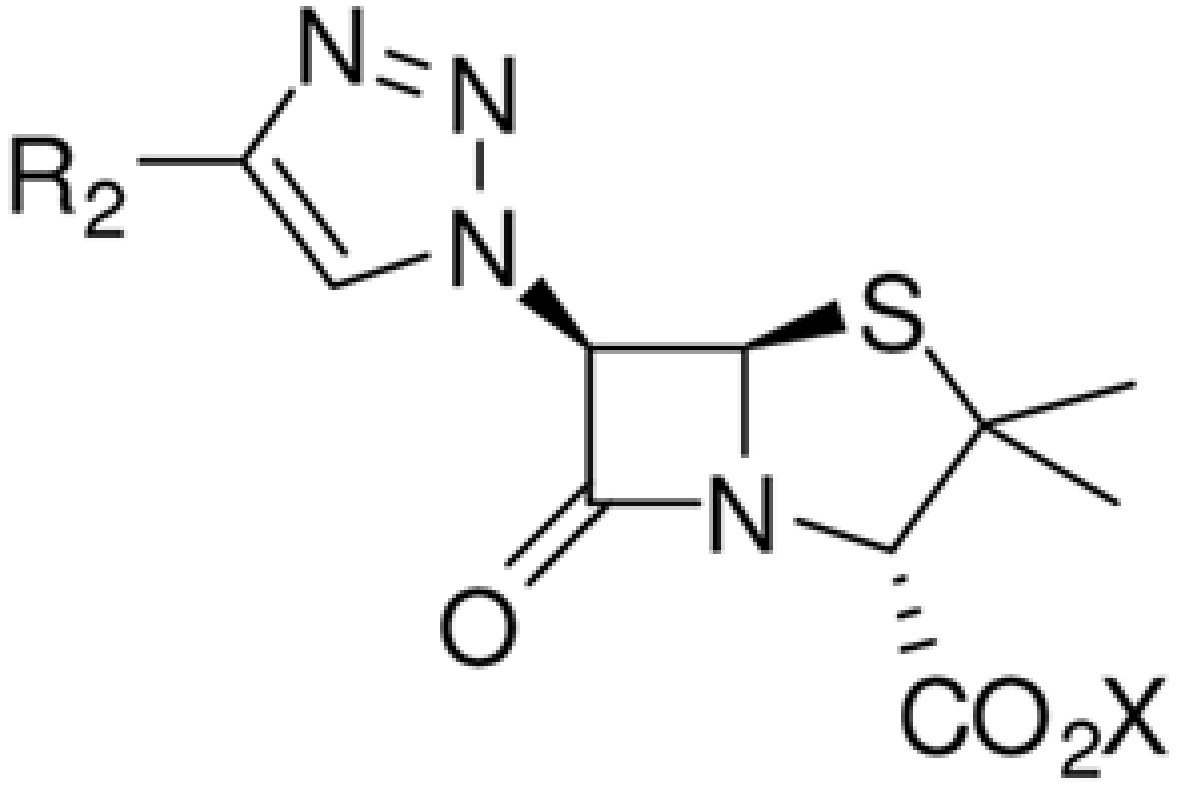
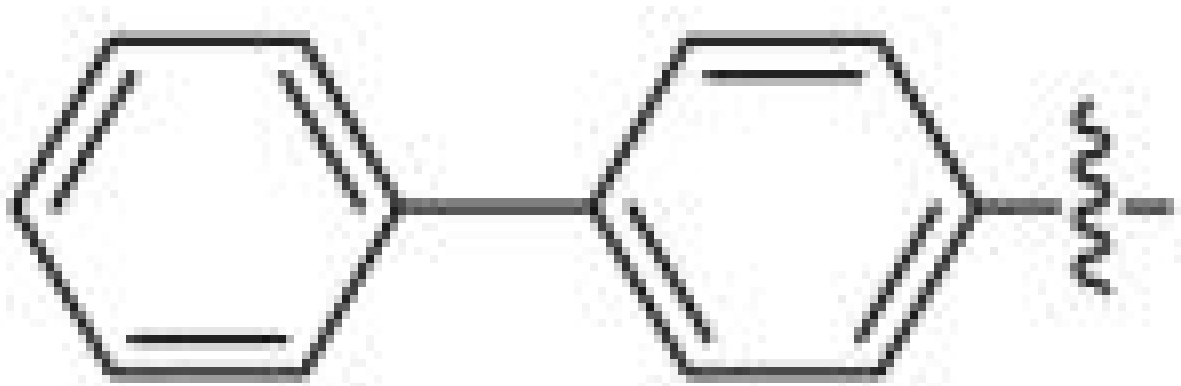


X = H, Na

Compound	R_2	*S. aureus* ATCC 29213 (μg/mL)	*E. coli* ATCC 25922 (μg/mL)	*S. pneumoniae* ATCC 49619 (μg/mL)	*B. anthracis* AMES (μg/mL)
12g		>8	>8	≥8**	>8

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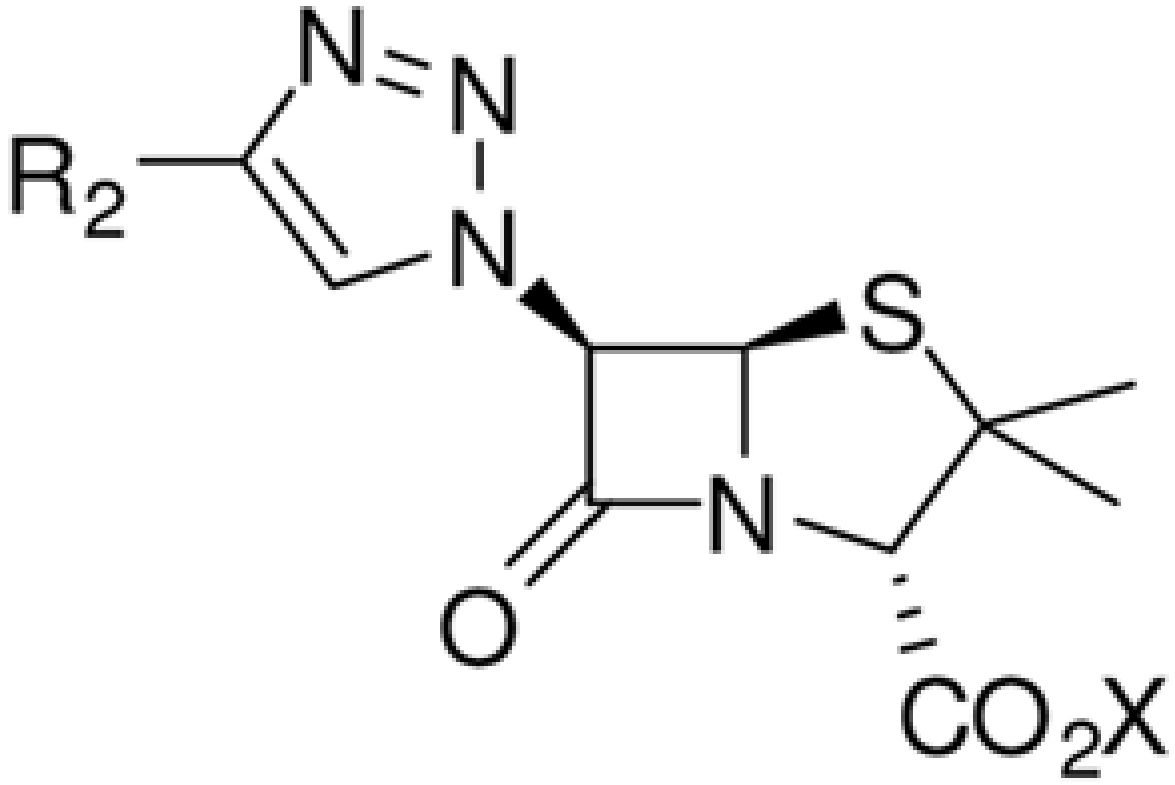
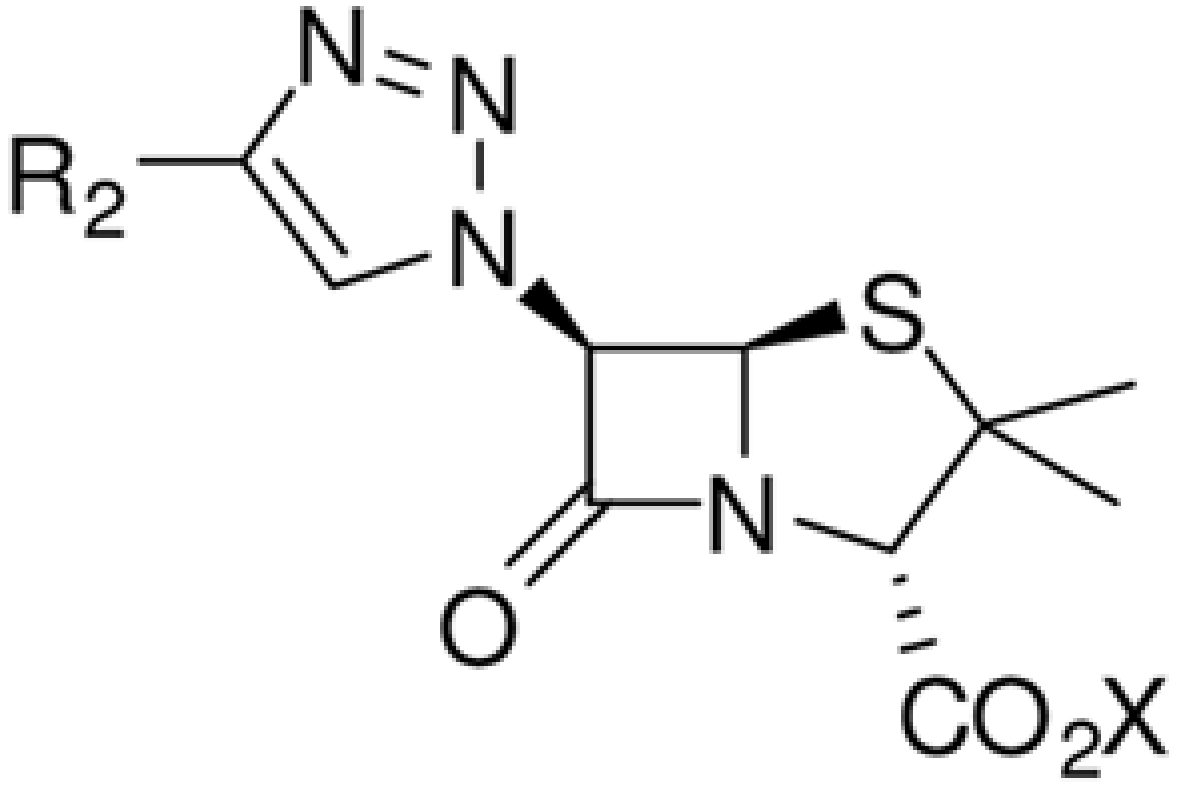
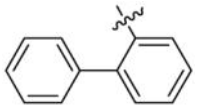


X = H, Na

Compound	R_2	*S. aureus* ATCC 29213 (μg/mL)	*E. coli* ATCC 25922 (μg/mL)	*S. pneumoniae* ATCC 49619 (μg/mL)	*B. anthracis* AMES (μg/mL)
12h		>8	>8	>8	>8



X = H, Na

Compound	R_2	*S. aureus* ATCC 29213 (μg/mL)	*E. coli* ATCC 25922 (μg/mL)	*S. pneumoniae* ATCC 49619 (μg/mL)	*B. anthracis* AMES (μg/mL)
12i		>8	>8	>8	>8

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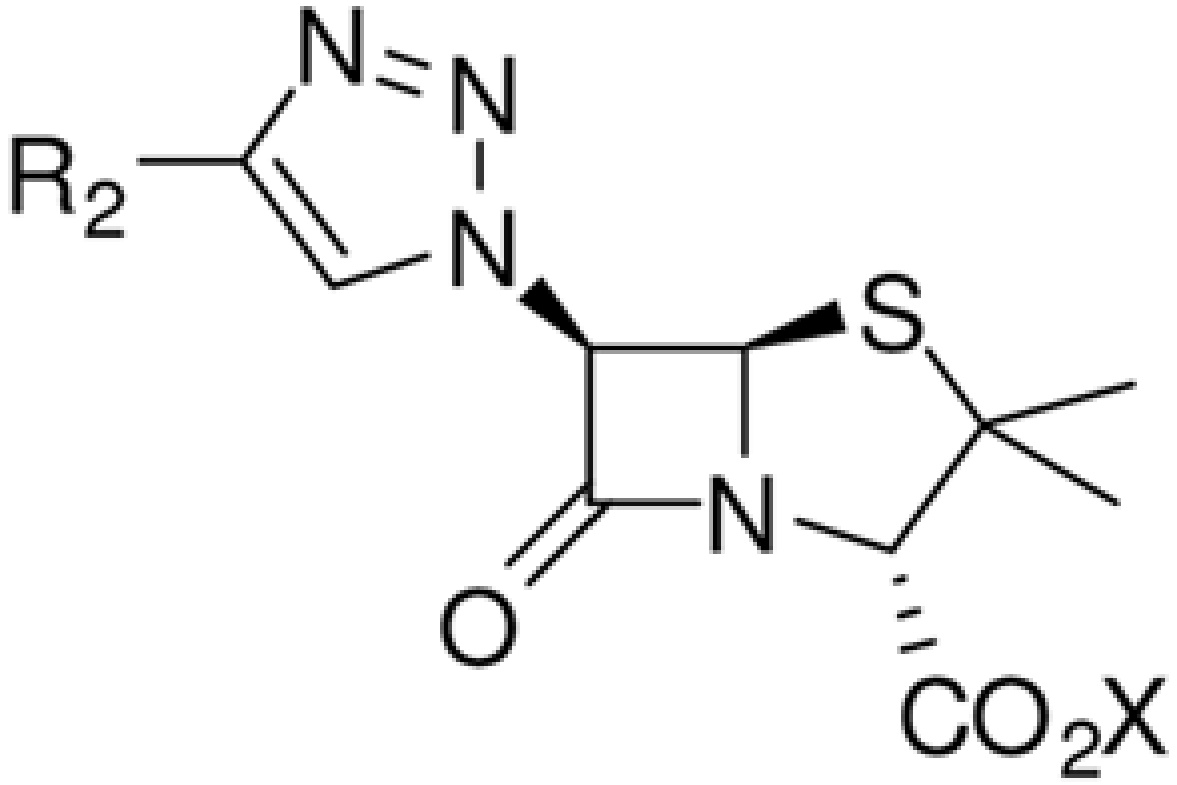
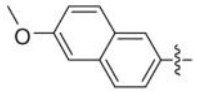
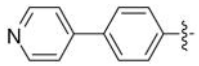


X = H, Na

Compound	R_2	*S. aureus* ATCC 29213 (μg/mL)	*E. coli* ATCC 25922 (μg/mL)	*S. pneumoniae* ATCC 49619 (μg/mL)	*B. anthracis* AMES (μg/mL)
12j		>8	>8	>8	>8
12k		>8	>8	>8	>8

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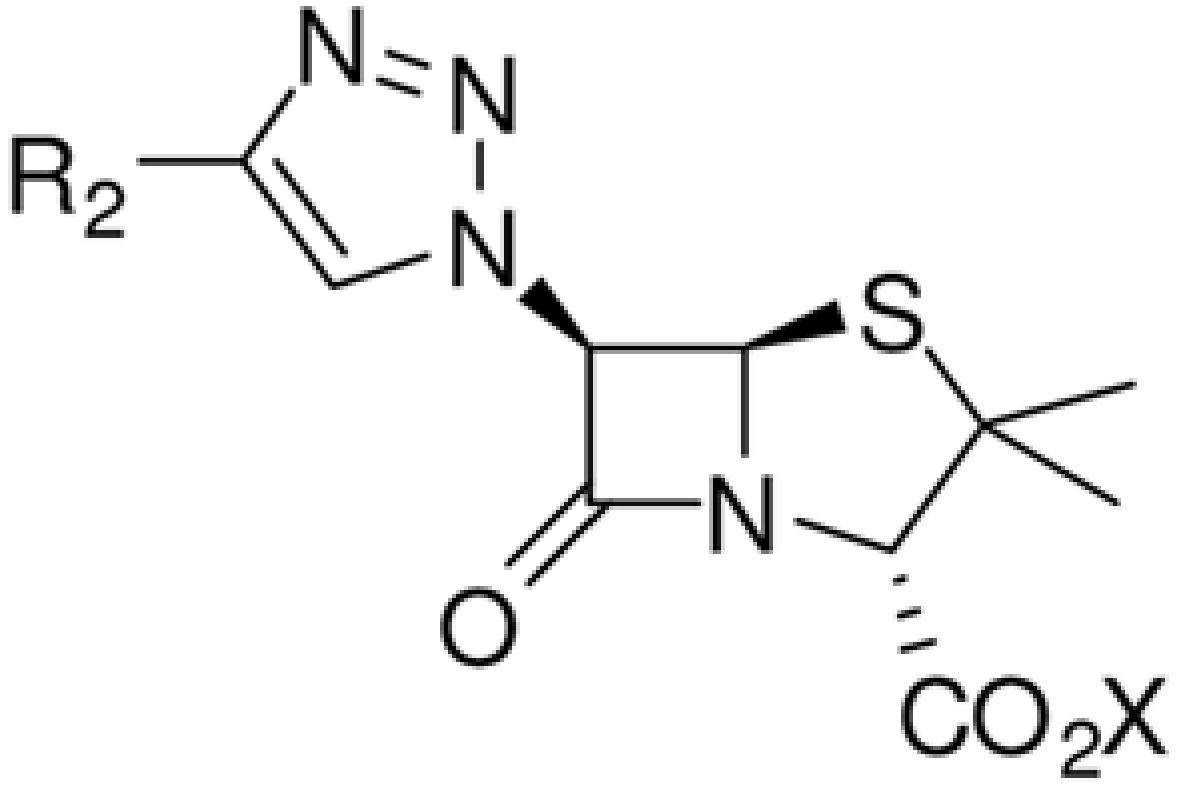
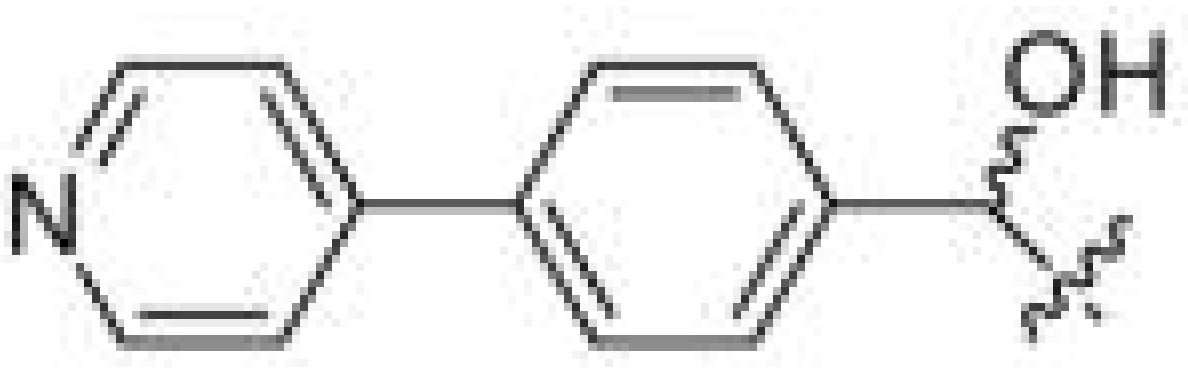


X = H, Na

Compound	R_2	*S. aureus* ATCC 29213 (μg/mL)	*E. coli* ATCC 25922 (μg/mL)	*S. pneumoniae* ATCC 49619 (μg/mL)	*B. anthracis* AMES (μg/mL)
12l*		>8	>8	≥8**	≥8**

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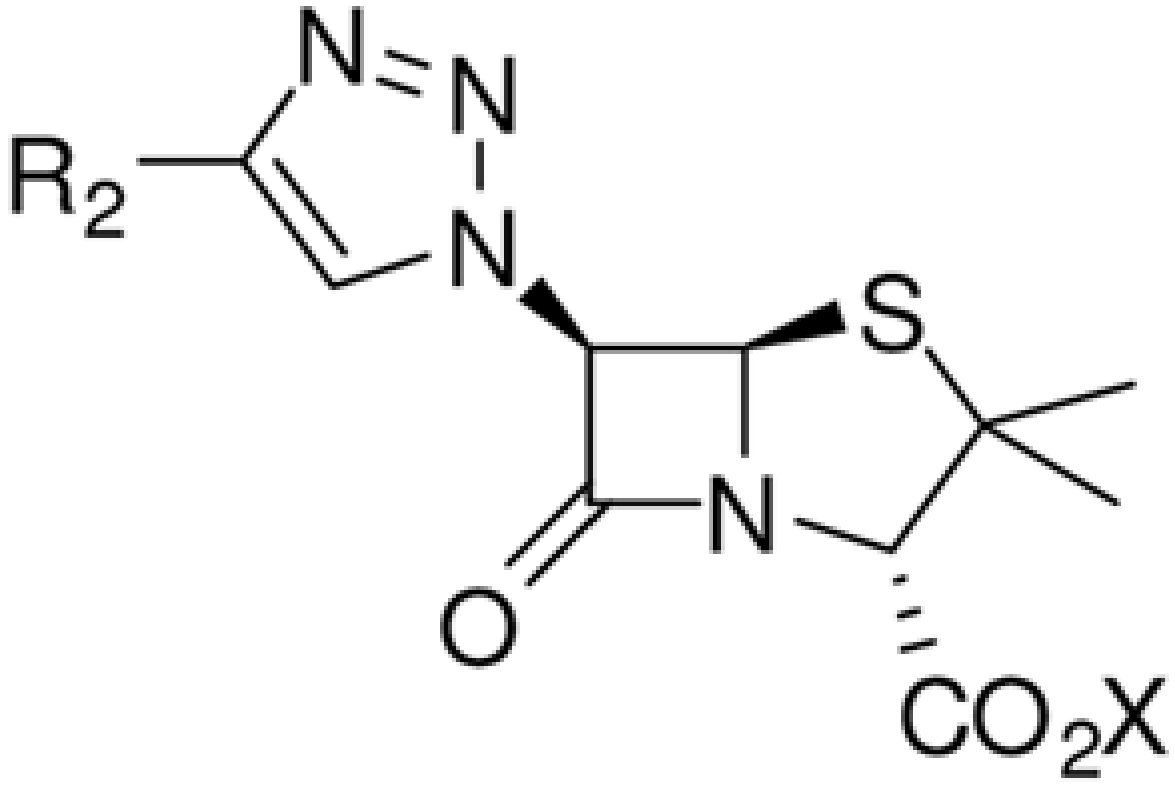
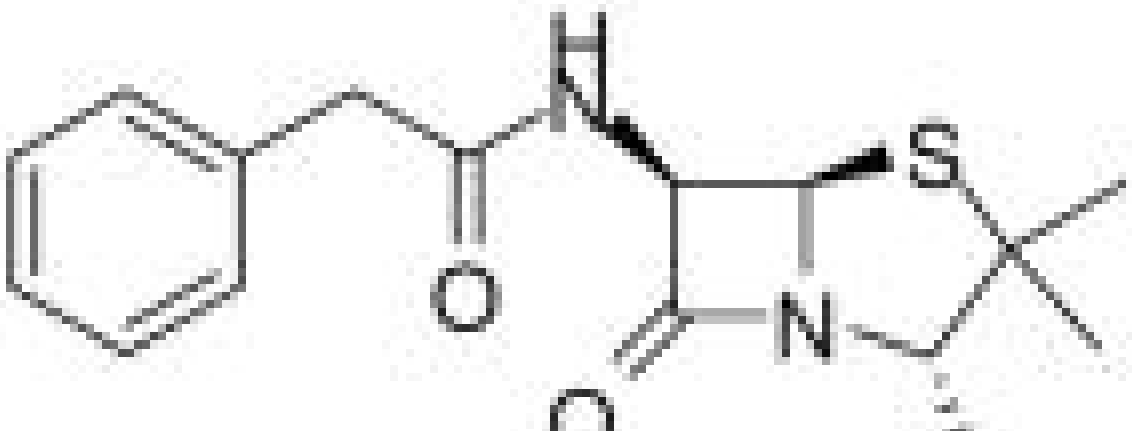


X = H, Na

Compound	R_2	*S. aureus* ATCC 29213 (μg/mL)	*E. coli* ATCC 25922 (μg/mL)	*S. pneumoniae* ATCC 49619 (μg/mL)	*B. anthracis* AMES (μg/mL)
		1	>2	N. D.***	≤0.125

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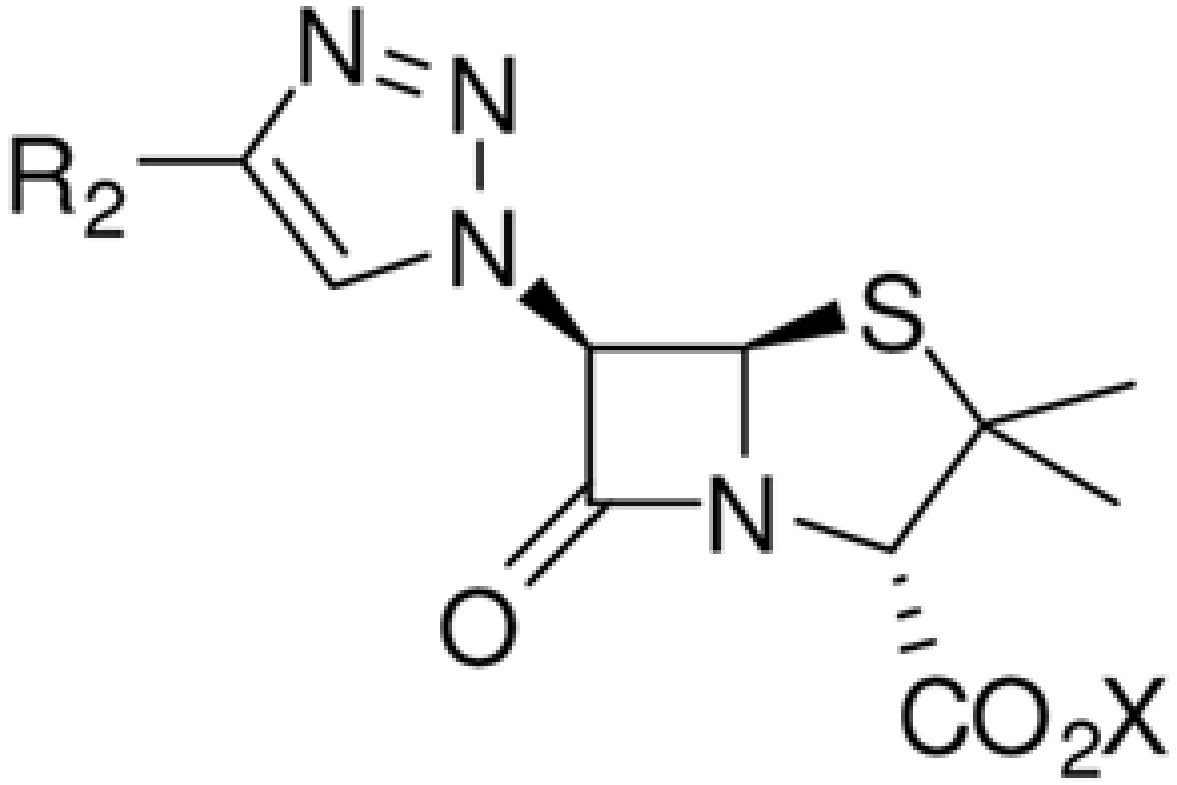
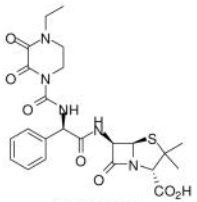


X = H, Na

Compound	R_2	*S. aureus* ATCC 29213 (μg/mL)	*E. coli* ATCC 25922 (μg/mL)	*S. pneumoniae* ATCC 49619 (μg/mL)	*B. anthracis* AMES (μg/mL)
Piperacillin		2	4	N. D.***	1

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* X = Na

** Denotes that one of the 3 replicates had MIC value of 8 μg/mL.

*** No Data