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Direct diazo-transfer reaction on β-lactam: Synthesis and preliminary biological activities of 6-triazolylpenicillanic acids

Po C. Chen, Rebekah E. Wharton, Pratiq A. Patel and Adegboyega K. Oyelere*

*School of Chemistry and Biochemistry, Parker H. Petit Institute for Bioengineering and Biosciences,
Georgia Institute of Technology, Atlanta, GA 30332-0400, USA*

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. Preliminary biological screening indicates that these triazolylpenicillanic acids possess low to moderate antibacterial activities.
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1. 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 (Fig. 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 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 involves long synthetic schemes and complicated compound purification 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 (Fig. 2).[16,18–20] Much recent studies have shown that attachment of *N*-acyl groups incorporating the structural feature of peptidoglycan results 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
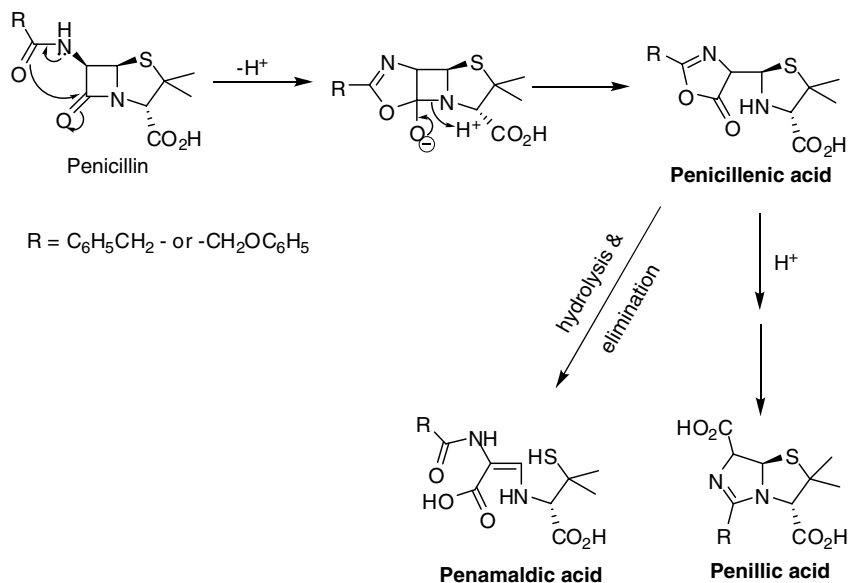
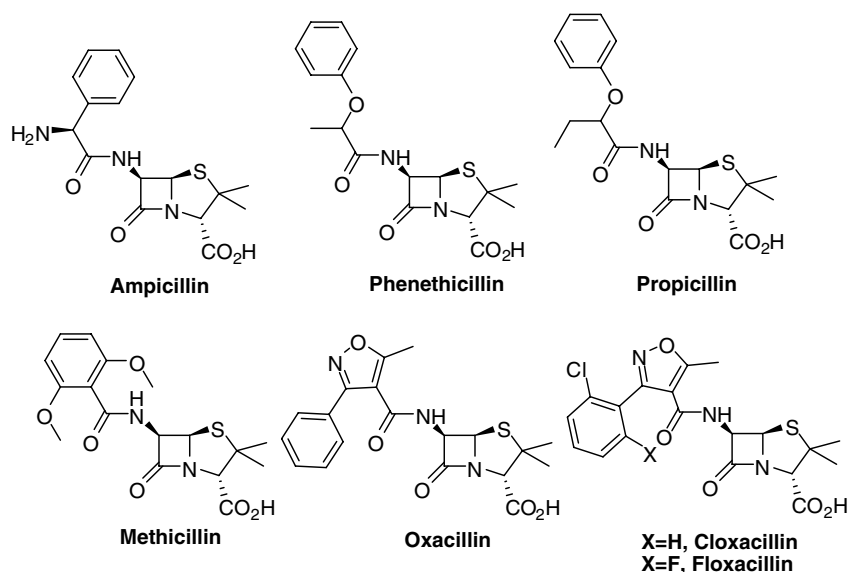**Figure 1.** Self-induced acid hydrolysis of penicillin.

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

β-lactam analogs, in addition to possessing potent antibacterial activity, have differential affinity for PBP isoforms (Fig. 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 moiety, the triazole group is commonly used as an amide bond isostere.[24,25] Unlike an 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.

2. 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 be-
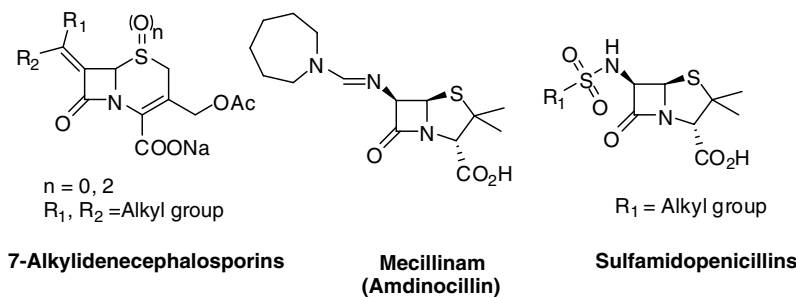
Figure 3. Structure of amide isosteric β-lactams.

tween **2** and appropriate alkynes (Sharpless Click Chemistry)[26] followed by deprotection of the ester 6-azidopenicillanate 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-azidopenicillanate, 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.
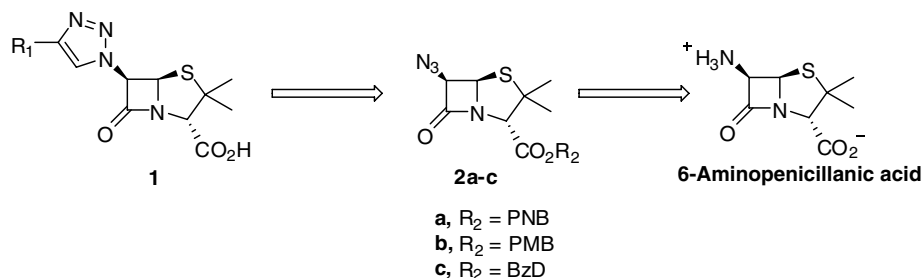
2.1. Synthesis of 6-azidopenicillanic acid by diazo-transfer reaction

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-trans-

fer 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 2–2.5 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]

2.2. 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

Scheme 1. Synthetic approach to 6-triazolylpenicillanic acids. *Abbreviations:* PNB, *para*-nitrobenzyl; PMB, *para*-methoxylbenzyl; BzD, benzhydryl.
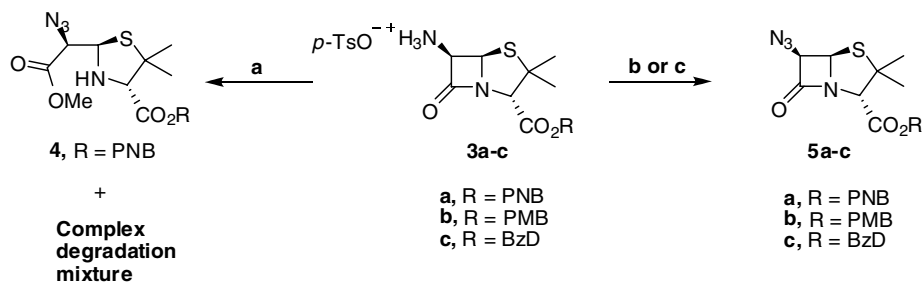
Scheme 2. Synthesis of protected 6-azidopenicillanic acid. Reagents and conditions: (a) TfN$_3$, Et$_3$N, CH$_2$Cl$_2$/MeOH/H$_2$O, rt; (b) TfN$_3$, Et$_3$N, DMAP, rt, 2–2.5 h; (c) TfN$_3$, Et$_3$N, toluene, rt, 1.5–2.5 h.

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 **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 alkynes **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 Section 4.

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).

2.3. Biological evaluation

The synthesized 6-triazolylpenicillanic acids were screened at the National Institute of Allergy and Infec-

tious 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). Compounds **9a**, **12e**, **12g**, and **12l** exhibited some antibacterial activity against the Gram-positive bacteria strain *Streptococcus pneumoniae* with MIC value of 4–8 μg/mL. Similarly, compound **12l** showed a moderate activity (MIC ≈8 μg/mL) against *Bacillus anthracis*. Other compounds listed in Table 1 displayed comparatively poor antibacterial activity (MIC >8 μg/mL).

3. Conclusion

We have reported a convenient route for the synthesis of 6-triazolylpenicillanic 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.

4. Experimental

6-Aminopenicillanoic acid (6-APA) was purchased from Sigma Aldrich. Anhydrous solvents and other reagents were purchased and used without further purification.
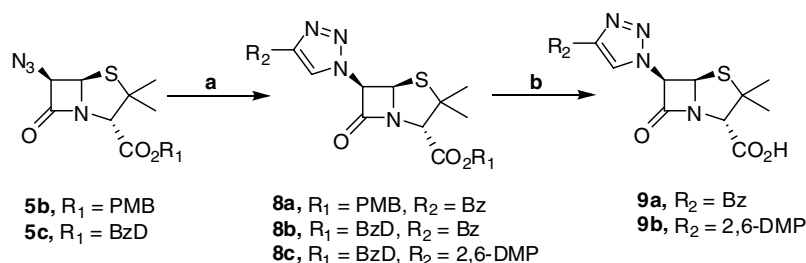
Scheme 3. Cu(I)-catalyzed cycloaddition reaction between 6-azidopenicillanates and representative terminal alkynes. Reagents and conditions: (a) CuI, Hunig's base, alkynes **6** or **7**, THF, rt; (b) TFA, anisole, CH$_2$Cl$_2$, −5 °C.
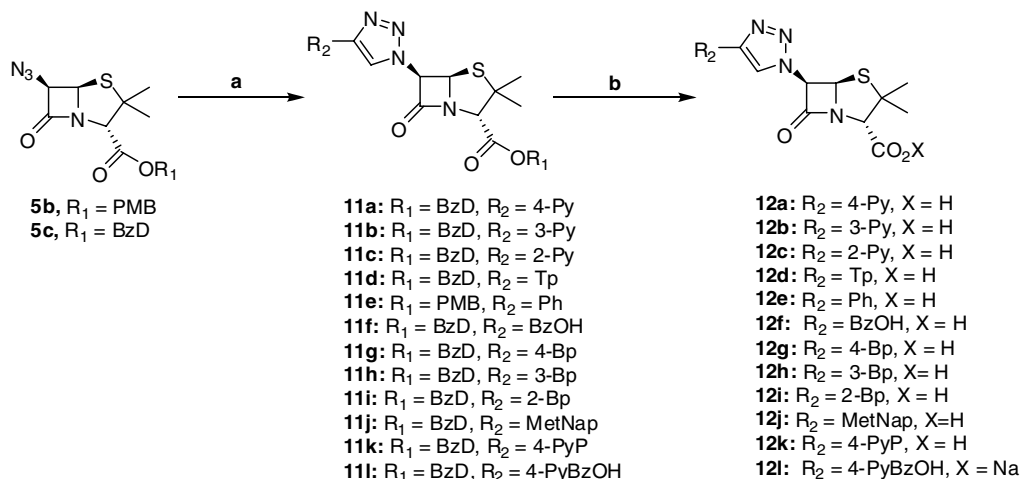
Scheme 4. Scope of Cu(I)-catalyzed cycloaddition between 6-azidopenicillanate and terminal alkynes. Reagents and conditions: (a) CuI, Hunig's base, alkynes **10**, THF, rt; (b) TFA, anisole CH$_2$Cl$_2$, −5 °C.

Analtech silica gel plates (60 F$_{254}$) were used for analytical TLC, and UV light was used to examine the spots. Two hundred to four hundred 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,i] The Bestmann-Ohira reagent was prepared as described by Ghosh et al.[42] while diphenyldiazomethane was prepared by using the procedure described by Ko and Kim.[37] 6-Aminopenicillanates **3a–c** were synthesized adapting literature procedures.[21,33–37]

4.1. Representative procedure for the alkyne transformation reaction

4.1.1. 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$_2$CO$_3$ (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$_2$Cl$_2$ (25 mL) and washed with saturated NH$_4$Cl (3 × 20 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, 5:1 hexane/EtOAc) to give 220 mg (50%) of **7** as a white solid. ^{1}H NMR (CDCl$_3$, 400 MHz) 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$_3$, 100 MHz) δ 56.0, 76.2, 85.7, 100.0, 103.5, 130.3, 162.0.

4.1.2. 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 **10 k** as a white solid. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 3.16 (1H, s), 7.47 (2H, d, J = 6.4 Hz), 7.59 (4H, s), 8.66 (2H, d, J = 6.4 Hz). HRMS (EI) calcd for [C$_{13}$H$_9$N] 179.0735, found 179.0746.
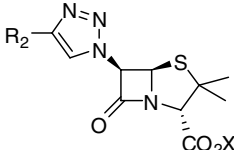
4.1.3. 2-Ethynylbiphenyl (10i). The required biphenyl-2-carbaldehyde was synthesized from the corresponding carboxylic acid through NaBH$_4$/BF$_3$:OEt$_2$ reduction to the primary alcohol.[43] Subsequent PDC oxidation of the primary alcohol furnished biphenyl-2-carbaldehyde. Reaction of biphenyl-2-carbaldehyde (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$_3$, 400 MHz) δ 3.03 (1H, s), 7.28–7.32 (1H, m), 7.36–7.45 (5H, m), 7.57–7.63 (3H, m).

4.1.4. 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$_3$, 400 MHz) δ 3.03 (1H, s), 7.33–7.47 (5H, m), 7.55–7.57 (3H, m), 7.72 (1H, s). HRMS(EI) calcd for [C$_{14}$H$_{10}$] 178.0782, found 178.0797.
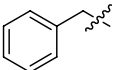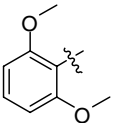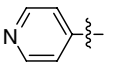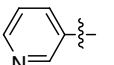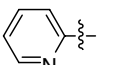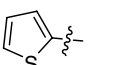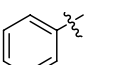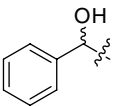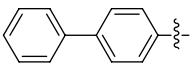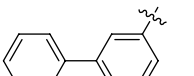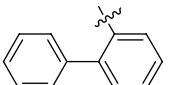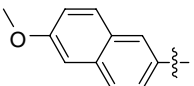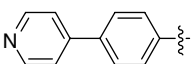
4.2. Representative procedure for the alkyne transformation via Grignard reaction

4.2.1. 1-Phenylprop-2-yn-1-ol (10f). To a solution of benzaldehyde (0.5 g, 4.71 mmol) in anhydrous THF

Table 1. Minimal inhibitory concentration (MIC) of 6-triazolylpenicillanic acids in µg/mL: each MIC value was obtained from an average of three independent experiments
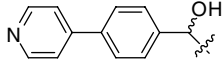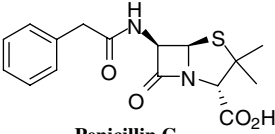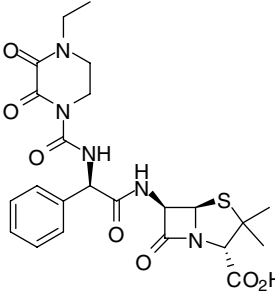
X = H, Na

Compound	R₂	S. aureus ATCC 29213 (µg/mL)	Escherichia coli ATCC 25922 (µg/mL)	S. pneumoniae ATCC 49619 (µg/mL)	B. anthracis AMES (µg/mL)
9a		>8	>8	4	>8
9b		>8	>8	>8	>8
12a		>8	>8	>8	>8
12b		>8	>8	>8	>8
12c		>8	>8	>8	>8
12d		>8	>8	8	>8
12e		>8	>8	4	>8
12f		>8	>8	>8	>8
12g		>8	>8	≥8[b]	>8
12h		>8	>8	>8	>8
12i		>8	>8	>8	>8
12j		>8	>8	>8	>8
12k		>8	>8	>8	>8

Table 1 (*continued*)

Compound	R₂	*S. aureus* ATCC 29213 (µg/mL)	*Escherichia coli* ATCC 25922 (µg/mL)	*S. pneumoniae* ATCC 49619 (µg/mL)	*B. anthracis* AMES (µg/mL)
12l[a]		>8	>8	≥8[b]	≥8[b]
	Penicillin G	1	>2	ND[c]	≤0.125
	Piperacillin	2	4	ND[c]	1

[a] X = Na.
[b] Denotes that one of the 3 replicates had MIC value of 8 µg/mL.
[c] No data.

(2 mL) was added ethynylmagnesium bromide (14.0 mL, 0.5 M 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 0.626 g (100%) of **10f** as a brownish oil. ^1H NMR (CDCl₃, 400 MHz) 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) calcd for [C_9H_8O] 132.0575, found 132.0566.

4.2.2. 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, 0.5 M 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. ^1H NMR (CD₃OD, 400 MHz) 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) calcd for [$C_{14}H_{11}NO+H$]⁺ 210.0918, found 210.0909.

4.3. Representative procedures for diazo-transfer reaction

4.3.1. 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) were 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. ^1H NMR (CDCl₃, 400 MHz) 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 (CDCl₃, 100 MHz) 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.

4.3.2. 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) were 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. ^1H NMR (CDCl₃, 400 MHz) 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$_3$, 100 MHz) 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) calcd for [C$_{21}$H$_{20}$N$_4$O$_3$S+H]$^+$ 409.1334, found 409.1357.

4.3.3. 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$_2$SO$_4$ 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) were added triflyl azide solution (2.97 mmol) in toluene (25 mL), and Et$_3$N (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 1 N HCl (20 mL), distilled water (2 × 20 mL), and saturated brine (20 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo to give 361 mg (70%) of **5a** as a yellowish solid. ^{1}H NMR (CDCl$_3$, 400 MHz) 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).

4.3.4. *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$_2$Cl$_2$ (total volume = 25 mL), and Et$_3$N (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$_3$, 100 MHz) 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$_3$, 400 MHz) 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) calcd for [C$_{16}$H$_{18}$N$_4$O$_4$S+H]$^+$ 363.1127, found 363.1151.

4.4. Representative procedure for Cu(I)-catalyzed cycloaddition reaction

4.4.1. *p*-Methoxybenzyl benzyl-6-triazolylpenicillanate (8a).

p-Methoxybenzyl 6-azidopenicillanate **5b** (0.27 g, 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$_2$Cl$_2$ (40 mL) and washed with 1:4 NH$_4$OH/saturated NH$_4$Cl (3 × 30 mL) and again with saturated NH$_4$Cl (30 mL). The organic layer was dried over Na$_2$SO$_4$ 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$_3$,

400 MHz) 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$_3$, 100 MHz) 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) calcd for [C$_{25}$H$_{26}$N$_4$O$_4$S+H]$^+$ 479.1753, found 479.1756.

4.4.2. 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$_3$, 400 MHz) 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$_3$, 100 MHz) 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) calcd for [C$_{30}$H$_{28}$N$_4$O$_3$S+H]$^+$ 525.1956, found 525.1960.

4.4.3. 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$_3$, 400 MHz) 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$_3$, 100 MHz) 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$_4$O$_5$S+H]$^+$ 571.2015, found 571.2049.

4.4.4. 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$_2$SO$_4$ and concentrated in vacuo to give 4-ethynylpyridine **10a** as a 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$_3$, 400 MHz) 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$_3$, 100 MHz) 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) calcd for [C$_{28}$H$_{25}$N$_5$O$_3$S+H]$^+$ 512.1756, found 512.1763.

4.4.5. 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$_3$, 400 MHz) 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$_3$, 100 MHz) 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) calcd for [C$_{28}$H$_{25}$N$_5$O$_3$S+H]$^+$ 512.1756, found 512.1773.

4.4.6. 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$_3$, 400 MHz) 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$_3$, 100 MHz) 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) calcd for [C$_{28}$H$_{25}$N$_5$O$_3$S+H]$^+$ 512.1756, found 512.1765.

4.4.7. 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$_3$, 400 MHz) 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$_3$, 100 MHz) 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) calcd for [C$_{27}$H$_{24}$N$_4$O$_3$S$_2$+H]$^+$ 517.1368, found 517.1374.

4.4.8. *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$_3$, 400 MHz) 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$_3$, 100 MHz) 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) calcd for [C$_{24}$H$_{24}$N$_4$O$_4$S+H]$^+$ 465.1596, found 465.1571.

4.4.9. 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$_3$, 400 MHz) 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$_3$, 100 MHz) 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) calcd for [C$_{30}$H$_{28}$N$_4$O$_4$S+H]$^+$ 541.1909, found 541.1936.

4.4.10. 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, 400 MHz) 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).

4.4.11. 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$_3$, 400 MHz) 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$_3$, 100 MHz) 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) calcd for [C$_{35}$H$_{30}$N$_4$O$_3$S+H]$^+$ 587.2116, found 587.2143.

4.4.12. 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$_3$, 400 MHz) 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$_3$, 100 MHz) 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, thio-

glycerol) calcd for $[C_{35}H_{30}N_4O_3S+H]^+$ 587.2116, found 587.2143.

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

Reaction of benzhydryl 6-azidopenicillanate **5c** (0.15 g, 0.367 mmol) and 2-ethynyl-6-methoxylnaphthalene (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$_3$, 400 MHz) 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$_3$, 100 MHz) 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) calcd for $[C_{34}H_{30}N_4O_4S+H]^+$ 591.2066, found 591.2061.

4.4.14. 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 **11 k** as a white solid. ^{1}H NMR (CDCl$_3$, 400 MHz) 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$_3$, 100 MHz) 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) calcd for $[C_{34}H_{29}N_5O_3S+H]^+$ 588.2069, found 588.2100.

4.4.15. 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$_3$, 400 MHz) 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$_3$, 100 MHz) δ 26.7, 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) calcd for $[C_{35}H_{31}N_5O_4S+H]^+$ 618.2175, found 618.2180.

4.5. Representative procedure for deprotection of carboxyl protecting group

4.5.1. Benzyl-6-triazolylpenicillanic acid (9a).

p-Methoxybenzyl benzyl-6-triazolylpenicillanate **8a** (0.13 g, 0.26 mmol) was dissolved and stirred in anhydrous CH$_2$Cl$_2$ (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$_2$O (10 mL), and the solvent was evaporated off in an ice bath. The residue was concentrated in vacuo on an ice bath for 15 min and redissolved in THF (5 mL) and 1/2 saturated NaHCO$_3$ (15 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 15 min 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 1 N HCl and extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo to give 89 mg (100%) of **9a** as a white solid. ^{1}H NMR (acetone-d_6, 400 MHz) 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, 100 MHz) 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) calcd for $[C_{17}H_{18}N_4O_3S+H]^+$ 359.1177, found 359.1177.

4.5.2. 2,6-Dimethoxyphenyl-6-triazolylpenicillanic acid (9b).

The reaction of a CH$_2$Cl$_2$ 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, 400 MHz) 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, 400 MHz) 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) calcd for $[C_{18}H_{20}N_4O_5S+H]^+$ 405.1232, found 405.1214.

4.5.3. 4-Pyridyl-6-triazolylpenicillanic acid (12a).

The reaction of a CH$_2$Cl$_2$ 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, 400 MHz) 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, 100 MHz) 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) calcd for $C_{15}H_{15}N_5O_3S+H]^+$ 346.0973, found 346.0972.

4.5.4. 3-Pyridyl-6-triazolylpenicillanic acid (12b).

The reaction of a CH$_2$Cl$_2$ 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, 400 MHz) 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) calcd for $[C_{15}H_{15}N_5O_3S+H]^+$ 346.0973, found 346.0972.

4.5.5. 2-Pyridyl-6-triazolylpenicillanic acid (12c).

The reaction of a CH$_2$Cl$_2$ 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, 400 MHz) 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, 100 MHz) 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) calcd for $[C_{15}H_{15}N_5O_3S+H]^+$ 346.0973, found 346.0974.

4.5.6. 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, 400 MHz) 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, 100 MHz) 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) calcd for $[C_{14}H_{14}N_4O_3S_2+H]^+$ 351.0585, found 351.0577.

4.5.7. 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, 400 MHz) 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, 100 MHz) 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) calcd for $[C_{16}H_{16}N_4O_3S+H]^+$ 345.1021, found 345.1015.

4.5.8. 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, 400 MHz) δ 1.53 (3H, s), 1.67 (3H, s), 3.37 (1H, s), 4.55 (1H, s), 5.84 (1H, br s), 5.97 (1H, s), 6.55 (1H, br s), 7.22–7.43 (4H, m), 7.80 (1H, s); HRMS (FAB, thioglycerol) calcd for $[C_{17}H_{18}N_4O_4S+H]^+$ 375.1127, found 375.1192.

4.5.9. 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, 400 MHz) 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) calcd for $[C_{22}H_{20}N_4O_3S+H]^+$ 421.1334, found 421.1333.

4.5.10. 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, 400 MHz) 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, 100 MHz) 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) calcd for $[C_{22}H_{20}N_4O_3S+H]^+$ 421.1329, found 421.1312.

4.5.11. 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, 400 MHz) 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) calcd for $[C_{22}H_{20}N_4O_3S + H]^+$ 421.1329, found 421.1359.

4.5.12. 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, 400 MHz) 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, 100 MHz) 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) calcd for $[C_{21}H_{20}N_4O_4S+H]^+$ 425.1283, found 425.1264.

4.5.13. 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, 400 MHz) 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) calcd for $[C_{21}H_{19}N_5O_3S+H]^+$ 422.1287, found 422.1301.

4.5.14. 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 min and redissolved in aqueous NaHCO₃ (0.018 g, 0.21 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 15 min 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, 400 MHz) 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) calcd for $[C_{22}H_{20}N_5NaO_4S+H]^+$ 474.1212, found 474.1234.

Acknowledgments

Supplementary data

Proton and carbon NMR spectra for all compounds described in Section 4. This material is available free of charge via the Internet at http://pubs.acs.org. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2007.08.035.

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