SYNTHESIS AND β-LACTAMASE INHIBITORY ACTIVITY OF 6-[(1-HETEROARYLTHIOETHYL-1,2,3-TRIAZOL-4-YL)-METHYLENE]PENAM SULFONES

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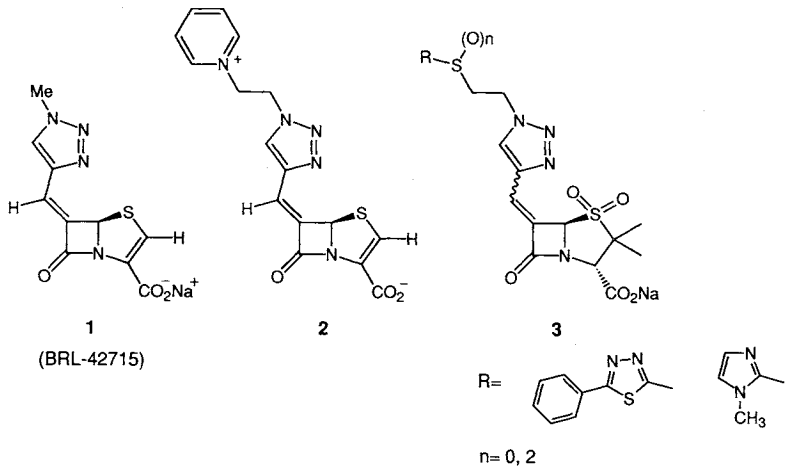
The synthesis of β-lactamase inhibitory activity of a series of sodium 6-[(1-heteroarylthioethyl-1,2,3-triazol-4-yl)methylene]penicillanate 1,1-dioxides are described. Their activity was compared with tazobactam and sulbactam. The *Z*-isomers were more active than the *E*-isomers. The *in vitro* activity of the *Z*-isomers of the phenylthiadiazole derivatives (**13a** and **15a**) was better than sulbactam against the tested β-lactamases and comparable to tazobactam especially against TEM-2 and cephalosporinase. But their synergistic activity with five antibiotics was inferior to tazobactam.

A successful approach to overcoming the bacterial resistance to β-lactam antibiotics caused by β-lactamase production is to develop agents that can inhibit the action of the β-lactamase. The success of clavulanic acid[1)] stimulated extensive research leading to the discovery of other β-lactamase inhibitors such as sulbactam[2)] and tazobactam[3)]. A number of 6-(substituted methylene)penams have been reported in the literature[4,5)] as potent inhibitors of cell free β-lactamases, but were ineffective in synergistic antibacterial tests probably because of poor penetration through the bacterial cell wall. More recently, 6-triazolylmethylenepenem (**1**)[6,7)], BRL-42715, has been shown to be a very potent inhibitor of most bacterial β-lactamases including the class I β-lactamase, which is resistant to other β-lactamase inhibitors.



Although this compound, BRL-42715, was discovered several years ago, there is little information about its pharmacological properties and no clinical efficacy has been documented till today. The N1-position of the 6-triazolylmethylenepenem was modified further (**2**)[8] to improve its β-lactamase inhibitory activity and also its pharmacological properties, but there is little further information reported about this compound.

In our continuous search for potent β-lactamase inhibitors based on the penam sulfone skeleton, we have prepared a series of 6-(substituted methylene)penam sulfones and in this paper we wish to report the synthesis and β-lactamase inhibitory activities of both the *Z*- and *E*-isomers of 6-triazolylmethylenepenicillanic acid sulfones (**3**) containing a 5-membered heteroarylthioethyl side chain at the N1-position of the triazole moiety.

Chemistry

Bromoethanol on treatment with sodium azide in a mixture of acetone and water gave 2-azidoethanol[9] which underwent a cycloaddition reaction with propargyl aldehyde[10] to give 1-(2-hydroxyethyl)-1,2,3-triazole-4-carbaldehyde (**4**) as the major isomer. Further chemical modification of the hydroxy group led to the synthesis of 1-(heteroarylthioethyl)-1,2,3-triazole-4-carbaldehyde (**5a** and **5b**). (Scheme 1)

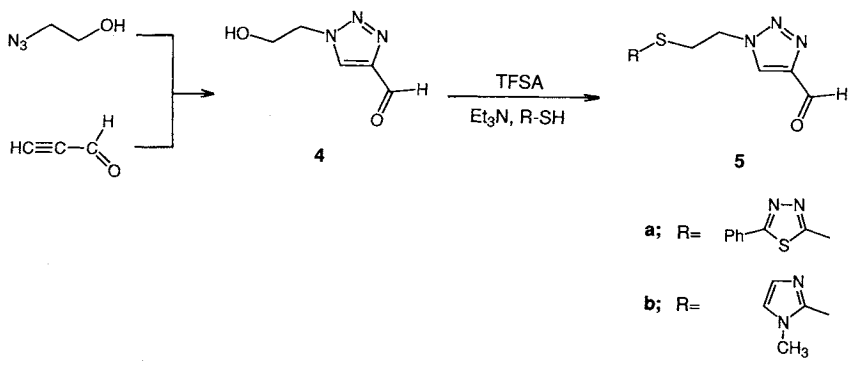
By using the literature procedure, 6-aminopenicillanic acid (6-APA) was converted to the 6α-bromopenicillanic acid[11] which was converted to the *p*-methoxybenzyl ester by using cyanuric chloride[12] (Scheme 2). Oxidation of the ester with peracetic acid[11] gave the corresponding sulfone **6**.

Treatment of 6α-bromopenicillanate 1,1-dioxide (**6**) with methylmagnesium bromide in THF at −78°C, followed by 1-(heteroarylthioethyl)-1,2,3-triazole-4-carbaldehyde (**5**) gave a diastereomeric mixture of the hydroxy derivatives **7** which were acylated by acetic anhydride[5]. All these compounds (**7a**, **8a**, **7b** and **8b**) have the 6*S* stereochemistry which was evident from the coupling constants of 1.8, 1.7, 1.8, and 1.9 Hz, respectively, indicating a *trans* relationship between the 5-H and 6-H *i.e.*, 5α-H and 6β-H.

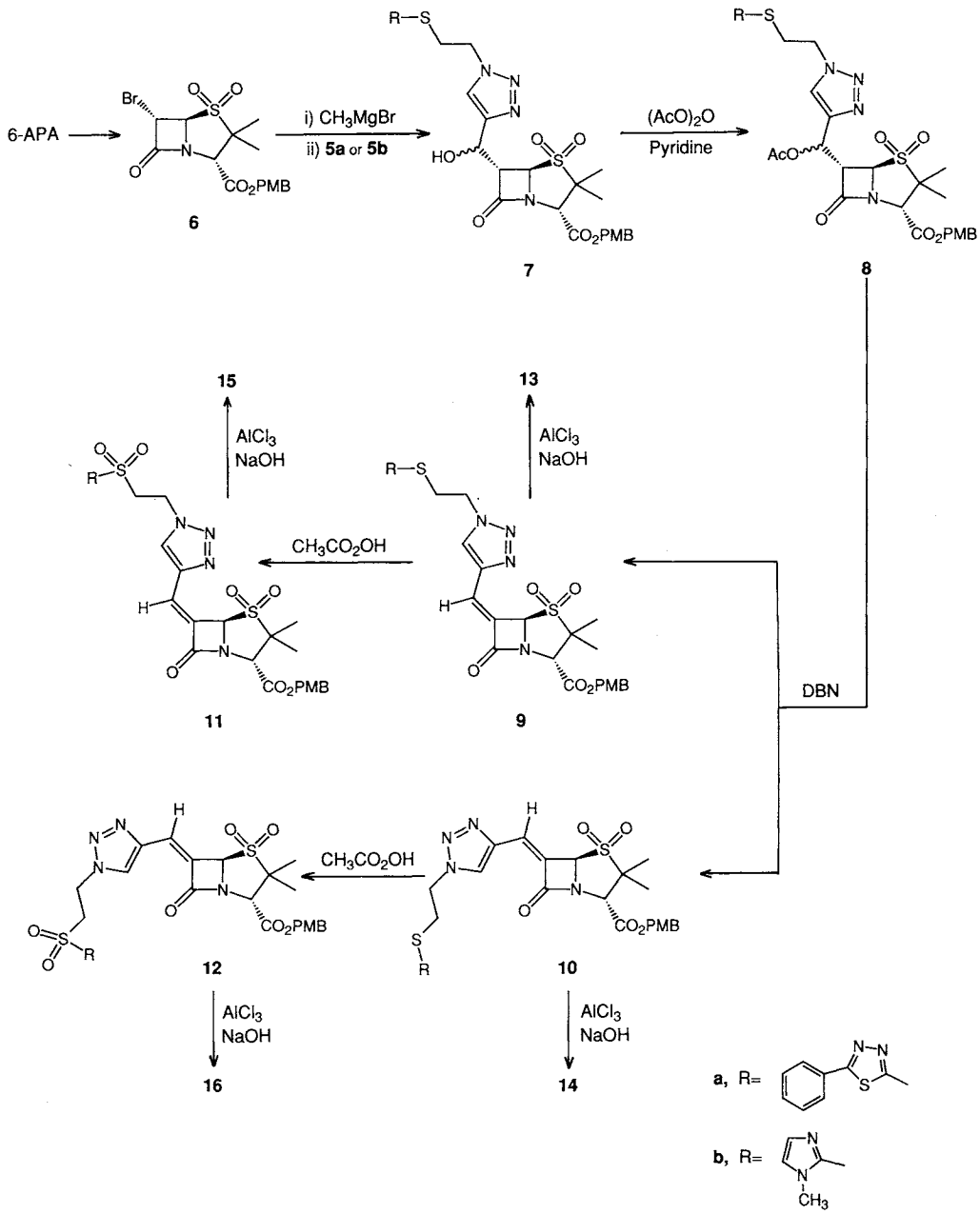
Treatment of the acetate derivatives **8** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) at low temperature gave a mixture of the *Z*-isomers and *E*-isomers (**9** and **10**) which were separated by column chromatography[5]. Each isomer was subjected to oxidation by using peracetic acid to give the corresponding sulfones **11** and **12**.

The *p*-methoxybenzyl groups of the *Z*- and *E*-isomers of the compounds (**9**, **10**, **11**, and **12**) were removed by treatment with aluminum chloride in a mixture of dichloromethane and anisole at −40 ~ −45°C

Scheme 1.



Scheme 2.



followed by treatment with 0.1 N NaOH[8]. The resulting sodium salts were purified by reverse phase chromatography on Prepex 49~63 C18 and collected as homogeneous solids after freeze-drying. (Scheme 2)

Results and Discussion

The β-lactamase inhibitory activity against cell free enzymes is given in Table 1. This activity was

determined by spectrophotometrically measuring the hydrolysis of the substrates (benzyl penicillin or cephaloridine) in the presence and absence of the β-lactamase inhibitors[13,14].

The *Z*-isomers (**13** and **15**) were more active than the *E*-isomers (**14** and **16**) against TEM-2 and cephalosporinase. Except **13a** and **15a**, all the synthesized compounds had poor inhibitory activity against penicillinase. The possible explanation for the reduced inhibitory activity of the *E*-isomers is that the side chain in the *E*-isomers is close to the carbonyl group of the β-lactam ring and thus prevents the active site of the enzyme to interact with the carbonyl group. The oxidation of the sulfur in the side chain of the more active *Z*-isomer (*i.e.*, **15a** and **15b**) generally increased inhibitory activity particularly against cephalosporinase, although the effect was more significant in the phenylthiadiazole derivative **15a** than the methylimidazole derivative **15b**. The *in vitro* activity of the *Z*-isomers of the phenylthiadiazole derivatives (**13a** and **15a**) was better than sulbactam against the tested enzymes and comparable to tazobactam especially against TEM-2 and cephalosporinase. So, these two compounds **13a** and **15a** were selected further for synergism studies[3] with several antibiotics such as ampicillin (ABPC), piperacillin (PIPC), ceftazidime (CAZ), cefotaxime (CTX), and ceftriaxone (CTRX) against whole cells (Table 2). The synergistic effects[3] with these antibiotics against clinical isolates are given in Table 3. None of these compounds showed synergistic activity with any of the tested antibiotics and overall, they were still inferior to tazobactam against most of the organisms.

Table 1. β-Lactamase inhibitory activity of compounds **13**, **14**, **15** and **16** on isolated enzymes; IC_{50}[a] values (μM).

Compounds	Penicillinase[b]	TEM-2[b]	Cephalosporinase[c]
13a	5.5	0.05	0.40
14a	>20	1.63	16.4
15a	4.6	0.30	0.07
16a	>20	>20	13.5
13b	>20	0.47	0.38
14b	>20	>20	19.6
15b	>20	1.08	0.24
16b	>20	>20	>20
Tazobactam	0.31	0.02	2.4
Sulbactam	23	0.7	20

[a] Spectrophotometric assay method; see ref 13, 14.
[b] Substrate concentration (benzylpenicillin), 0.2 mM.
[c] Substrate concentration (cephaloridine), 0.1 mM.

A series of new penicillanic acid sulfones having a (1-heteroarylthioethyl-1,2,3-triazol-4-yl)methylene group at the C6 position was synthesized and their β-lactamase inhibitory activity was evaluated. The *in vitro* activity of the *Z*-isomers was better than the *E*-isomers especially against TEM-2 and cephalosporinase. In the phenylthiadiazole series, the *Z*-isomers were much better than sulbactam and equivalent or comparable to tazobactam particularly against TEM-2 and cephalosporinase. However, the synergistic effects were inferior to tazobactam, thus suggesting poor penetration into the bacterial cell wall.

Experimental

The following three enzymes were used for testing the β-lactamase inhibitory activity: Penicillinase (β-lactamase class II[15] from *Bacillus cereus*, purchased from Sigma); Cephalosporinase (β-lactamase class I from *Enterobacter cloacae*, purchased from Sigma); Broad spectrum TEM-2 enzyme (β-lactamase class III from *Escherichia coli*, purchased from Boehringer).

Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were taken on a Shimadzu IR-460 spectrometer. ^{1}H NMR spectra were recorded on a Bruker AC-200-F spectrometer using TMS as an internal standard. High resolution mass spectra (HRMS) were measured with a Kratos MS-50 (direct probe) and fast atom bombardment mass spectra (FAB-MS) were recorded with a Kratos AEI-MS-9 (modified) mass spectrometer in the Department of Chemistry, University of Alberta. Microanalysis were performed with a CHN EA1108 Elemental Analyzer in SynPhar laboratory. The reverse phase column chromatography was performed with a Prepex 40~63 C18 from Phenomenex.

Table 2. Antibacterial activity (MIC μg/ml) of antibiotics

Test organism	ABPC				PIPC			
	Alone	+YTR	+**13a**	+**15a**	Alone	+YTR	+**13a**	+**15a**
S. aureus CT-10	25	3.13	12.5	12.5	100	25	100	100
S. aureus HL-1185	50	0.78	25	25	200	6.25	200	200
S. aureus 54K	3.13	≤0.1	1.56	1.56	12.5	0.78	3.13	3.13
S. aureus 80K	3.13	≤0.1	1.56	1.56	12.5	0.39	3.13	3.13
E. coli TEM-1	>200	1.56	>200	>200	200	0.39	12.5	25
E. coli OXA-1	>200	50	>200	200	12.5	3.13	6.25	12.5
E. coli OXA-3	50	1.56	50	25	1.56	0.39	1.56	1.56
E. coli SHV-1	>200	3.13	>200	>200	50	1.56	25	25
K. pneumoniae 336L	>200	6.25	>200	>200	100	3.13	50	50
K. pneumoniae CTX-1	>200	6.25	>200	>200	>200	6.25	200	200
S. marcescens 200L	>200	50	>200	>200	200	0.78	12.5	12.5
S. marcescens CT-98	>200	>200	>200	>200	>200	100	200	200
P. vulgaris CT-106	>200	25	>200	>200	200	1.56	200	200
C. freundii 2046E	>200	0.39	>200	>200	200	0.39	25	100
C. freundii CT-76	>200	>200	>200	>200	>200	25	>200	>200
E. cloacae P99	>200	100	>200	>200	50	12.5	50	50
E. cloacae 212L	>200	12.5	>200	>200	>200	1.56	200	200
A. calcoaceticus 450L	>200	(−)	>200	>200	>200	(−)	200	>200
A. calcoaceticus 553L	>200	(−)	>200	>200	>200	(−)	100	100
P. aeruginosa CT-122	>200	>200	>200	>200	200	200	200	100
P. aeruginosa CT-137	>200	>200	>200	>200	200	200	200	200
P. aeruginosa CT-144	>200	>200	>200	>200	200	200	200	200
P. aeruginosa PSE-1	>200	>200	>200	>200	3.13	1.56	3.13	3.13
P. aeruginosa PSE-2	>200	>200	>200	>200	25	25	50	50
P. aeruginosa PSE-3	>200	>200	>200	>200	50	6.25	50	50
P. aeruginosa PSE-4	>200	>200	>200	>200	200	25	100	100

YTR=tazobactam, ABPC=ampicillin, PIPC=piperacillin, CAZ=ceftazidime, CTX=cefotaxime, CTRX=

Table 3. Antibacterial activity (MIC μg/ml) of antibiotics

Test organism	ABPC				PIPC			
	Alone	+YTR	+**13a**	+**15a**	Alone	+YTR	+**13a**	+**15a**
E. cloacae 40002	>200	200	>200	>200	25	6.25	50	25
E. cloacae 40011	>200	200	>200	>200	25	6.25	25	25
E. cloacae 40015	>200	>200	>200	>200	25	12.5	50	25
E. cloacae 40018	>200	>200	>200	>200	25	12.5	12.5	12.5
E. aerogenes 41001	>200	200	200	>200	6.25	3.13	3.13	3.13
E. aerogenes 41002	>200	>200	>200	>200	25	12.5	25	25
E. aerogenes 41003	>200	>200	>200	>200	25	25	12.5	25
E. aerogenes 41004	>200	>200	>200	>200	25	25	12.5	25
E. aerogenes 41006	>200	>200	>200	>200	200	100	100	50
S. marcescens 42001	>200	>200	>200	>200	>200	>200	>200	>200
S. marcescens 42002	200	200	50	100	3.13	3.13	0.78	1.56
S. marcescens 42005	>200	>200	>200	>200	>200	100	200	200
S. marcescens 42006	>200	>200	>200	>200	>200	50	50	50
S. marcescens 42008	>200	>200	>200	>200	>200	50	100	200
P. aeruginosa 46001	>200	>200	>200	>200	3.13	3.13	3.13	1.56
P. aeruginosa 46002	>200	200	200	200	1.56	3.13	3.13	3.13
P. aeruginosa 46012	>200	>200	>200	>200	>200	200	200	200
P. aeruginosa 46017	>200	>200	>200	>200	>200	200	200	>200
P. aeruginosa 46025	>200	200	>200	>200	0.78	0.39	0.78	0.39
M. morganii 36010	>200	100	>200	>200	200	6.25	>200	200
M. morganii 36014	>200	6.25	>200	>200	50	0.2	25	12.5
M. morganii 36030	>200	3.13	200	200	50	0.39	25	12.5
C. freundii 44001	>200	>200	>200	>200	>200	100	200	>200
C. freundii 44032	>200	>200	>200	>200	200	50	100	200
C. freundii 44034	>200	>200	>200	>200	>200	100	>200	>200

YTR=tazobactam, ABPC=ampicillin, PIPC=piperacillin, CAZ=ceftazidime, CTX=cefotaxime, CTRX=

alone and in combination with **13a** or **15a**.

CAZ				CTX				CTRX			
Alone	+YTR	+**13a**	+**15a**	Alone	+YTR	+**13a**	+**15a**	Alone	+YTR	+**13a**	+**15a**
12.5	25	25	25	3.13	12.5	3.13	3.13	6.25	12.5	12.5	12.5
100	25	50	50	3.13	1.56	3.13	3.13	6.25	3.13	6.25	6.25
12.5	6.25	12.5	6.25	1.56	0.78	1.56	1.56	3.13	1.56	3.13	3.13
6.25	3.13	6.25	6.25	0.78	0.39	0.78	0.78	1.56	0.78	1.56	1.56
≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1
0.2	0.2	0.2	0.2	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1
≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1
0.39	0.2	0.2	0.2	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1
0.39	0.2	0.2	0.39	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1
50	0.39	25	12.5	25	0.2	6.25	6.25	50	≤0.1	6.25	6.25
≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1
12.5	6.25	6.25	6.25	50	50	25	50	50	25	25	12.5
25	0.78	12.5	12.5	100	0.2	50	100	50	≤0.1	25	25
0.2	≤0.1	0.2	0.2	1.56	<0.1	0.78	1.56	25	≤0.1	1.56	3.13
100	25	50	50	25	6.25	12.5	12.5	25	12.5	25	25
100	3.13	50	50	50	6.25	50	50	100	12.5	100	100
0.39	0.2	0.2	0.39	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1
6.25	(−)	6.25	3.13	6.25	(−)	6.25	6.25	6.25	(−)	12.5	12.5
6.25	(−)	6.25	6.25	6.25	(−)	6.25	12.5	12.5	(−)	12.5	12.5
50	50	50	50	>200	>200	>200	>200	>200	>200	>200	>200
25	25	25	12.5	>200	>200	>200	>200	>200	>200	>200	>200
50	50	50	50	>200	>200	>200	>200	>200	>200	>200	>200
3.13	3.13	3.13	1.56	25	25	25	25	50	25	100	50
1.56	1.56	1.56	1.56	12.5	12.5	12.5	12.5	50	25	25	50
1.56	1.56	1.56	1.56	12.5	25	25	12.5	100	25	50	50
1.56	1.56	1.56	1.56	12.5	12.5	12.5	12.5	50	25	50	25

ceftriaxone, Inoculum size, 10^6 cfu/ml. Concentration of the inhibitors, 10 μg/ml.

alone and in combination with **13a** or **15a**.

CAZ				CTX				CTRX			
Alone	+YTR	+**13a**	+**15a**	Alone	+YTR	+**13a**	+**15a**	Alone	+YTR	+**13a**	+**15a**
25	1.56	25	25	50	6.25	50	25	100	3.13	50	100
12.5	1.56	12.5	12.5	50	6.25	50	25	50	3.13	50	50
200	50	100	100	100	50	100	100	200	100	100	100
50	50	50	50	25	25	12.5	25	50	25	25	50
0.78	3.13	3.13	6.25	0.39	0.39	0.2	0.39	1.56	1.56	1.56	0.78
25	25	25	50	6.25	3.13	6.25	6.25	12.5	6.25	12.5	12.5
25	25	50	25	6.25	3.13	3.13	6.25	12.5	6.25	12.5	12.5
25	25	25	25	3.13	6.25	6.25	6.25	3.13	6.25	12.5	12.5
200	100	100	100	25	25	25	25	50	50	50	50
1.56	1.56	1.56	1.56	0.78	0.78	0.78	0.39	1.56	0.78	0.78	0.78
0.78	0.78	0.78	0.78	0.78	1.56	0.78	1.56	1.56	0.78	0.39	0.39
1.56	1.56	1.56	1.56	0.78	0.78	0.78	0.78	1.56	0.78	0.78	0.39
0.78	0.78	0.78	0.39	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
0.78	0.78	0.78	0.78	0.39	0.39	0.2	0.2	0.39	0.39	0.39	0.2
1.56	1.56	1.56	1.56	12.5	12.5	12.5	12.5	12.5	12.5	1.25	25
0.78	0.78	0.78	0.78	6.25	12.5	12.5	12.5	3.13	3.13	3.13	3.13
100	50	100	100	>200	>200	>200	>200	>200	>200	>200	>200
100	100	100	100	>200	>200	>200	>200	>200	>200	>200	>200
0.39	0.39	0.39	0.39	3.13	0.39	1.56	0.78	12.5	0.78	6.25	3.13
>200	6.25	>200	>200	>200	3.13	>200	>200	100	0.78	100	50
25	≤0.1	25	12.5	6.25	≤0.1	6.25	3.13	3.13	≤0.1	1.56	0.78
12.5	≤0.1	12.5	6.25	6.25	≤0.1	3.13	3.13	1.56	≤0.1	0.39	0.39
200	50	100	100	50	25	25	25	50	50	100	50
200	50	200	200	50	12.5	50	25	100	12.5	100	50
200	100	200	200	50	25	50	50	100	25	100	50

ceftriaxone, Inoculum size, 10^6 cfu/ml. Concentration of the inhibitors, 10 μg/ml.

1-(2-Hydroxyethyl)-1,2,3-triazole-4-carbaldehyde (**4**)

Propargyl aldehyde[10] (18.99 g, 0.35 mol) was added to an ice-cooled solution of 2-azidoethanol[9] (25.50 g, 0.29 mol) in dichloromethane (100 ml). The mixture was stirred at room temperature for 20 hours, then washed sequentially with water and brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified on a silica gel column using a mixture of hexane - ethyl acetate, 1 : 3 (v/v) as eluant to give **4** (28.65 g, 69%) as a solid: mp 74~75°C; IR ($CHCl_3$) cm^{-1}: 1696 and 1521; ^1H NMR (200 MHz, $CDCl_3$) δ 2.46 (1H, br s), 4.07~4.17 (2H, m), 4.60 (2H, t, J=4.9 Hz), 8.28 (1H, s), 10.13 (1H, s); MS m/z 141.0532 (M^+, $C_5H_7N_3O_2$ requires M, 141.0537).

1-[2-(2-Phenyl-1,3,4-thiadiazol-5-yl)thioethyl]-1,2,3-triazole-4-carbaldehyde (**5a**)

To a stirred mixture of **4** (10.00 g, 70.86 mmol) and triethylamine (7.17 g, 70.86 mmol) in dry dichloromethane (250 ml), was added trifluoromethanesulfonic anhydride (20.00 g, 70.86 mmol) at −15~−20°C and the resulting mixture was stirred for 3.5 hours under a nitrogen atmosphere. A mixture of 2-phenyl-1,3,4-thiadiazole-5-thiol (13.77 g, 70.86 mmol) and triethylamine (7.17 g, 70.86 mmol) in dry dichloromethane (130 ml) was added to the reaction mixture dropwise at −15~−20°C for 40 minutes and stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and washed successively with 20% sodium bicarbonate solution and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was chromatographed on a silica gel column with a mixture of dichloromethane - ethyl acetate, 4 : 1 (v/v) as eluant to give **5a** (7.87 g, 35%) as a solid: mp 160~162°C; IR ($CHCl_3$) cm^{-1}: 1699 and 1523; ^1H NMR (200 MHz, $CDCl_3$) δ 3.89 (2H, t, J=6.3 Hz), 5.02 (2H, t, J=6.3 Hz), 7.49~7.92 (5H, m), 8.23 (1H, s), 10.16 (1H, s).

Anal Calcd for $C_{13}H_{11}N_5OS_2$: C 49.19, H 3.49, N 22.07.
Found: C 49.05, H 3.22, N 21.84.

1-[2-(1-Methylimidazol-2-yl)thioethyl]-1,2,3-triazole-4-carbaldehyde (**5b**)

Compound **5b** was prepared from 2-mercapto-1-methylimidazole (8.09 g, 70.86 mmol), by the same method described for **5a**, in 51% yield as a solid: mp 135~136°C; IR ($CHCl_3$) cm^{-1}: 1697 and 1529; ^1H NMR (200 MHz, $CDCl_3$) δ 3.51 (2H, t, J=6.3 Hz), 3.60 (3H, s), 4.86 (2H, t, J=6.3 Hz), 6.96 (1H, d, J=1.3 Hz), 7.07 (1H, d, J=1.3 Hz), 8.34 (1H, s), 10.15 (1H, s).

Anal Calcd for $C_9H_{11}N_5OS$: C 45.55, H 4.67, N 29.52.
Found: C 45.58, H 4.58, N 29.33.

p-Methoxybenzyl (3*S*,5*R*,6*S*)-6-[(1*RS*)-1-Hydroxy-1-[1-[2-(2-phenyl-1,3,4-thiadiazol-5-yl)thioethyl]-1,2,3-triazol-4-yl]methyl]penicillanate 1,1-Dioxide (**7a**)

To a solution of *p*-methoxybenzyl (3*S*,5*R*,6*S*)-6-bromopenam-3-carboxylate 1,1-dioxide (**6**) (1.00 g, 2.31 mmol) in dry THF (25 ml) was added CH_3MgBr (0.93 ml, 2.78 mmol) and the mixture was stirred at −78°C for 15 minutes under a nitrogen atmosphere. To this reaction mixture, a solution of **5a** (0.73 g, 2.31 mmol) in dry dichloromethane (40 ml) was added and the mixture was stirred at −78°C for 10 hours. The reaction was quenched by adding saturated NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on a silica gel column with $CHCl_3$ - ethyl acetate, 1 : 1 (v/v) as eluant to give the stereoisomeric mixture of **7a** (0.90 g, 58%) as a foam: IR ($CHCl_3$) cm^{-1}: 1784, 1748, and 1314; ^1H NMR (200 MHz, $CDCl_3$) δ 1.24 (3H, s), 1.52 (3H, s), 2.32 (1H, br s), 3.81 (3H, s), 3.85~3.89 (2H, m), 4.13 (1H, dd, J_1=1.8 Hz, J_2=4.4 Hz), 4.38 (1H, s), 4.81 (1H, d, J_1=1.8 Hz), 4.90 (2H, t, J=6.3 Hz), 5.07 and 5.23 (2H, two d, J=11.7 Hz), 5.41 (1H, d, J_2=4.4 Hz), 6.86~7.32 (4H, m), 7.47~7.90 (5H, m), 7.95 (1H, s).

Anal Calcd for $C_{29}H_{30}N_6O_7S_3$: C 51.92, H 4.51, N 12.53.
Found: C 51.53, H 4.22, N 12.50.

p-Methoxybenzyl (3*S*,5*R*,6*S*)-6-[(1*RS*)-1-Hydroxy-1-[1-[2-(1-methylimidazol-2-yl)thioethyl]-1,2,3-triazol-4-yl]methyl]penicillanate 1,1-Dioxide (**7b**)

Following the process described for **7a**, the stereoisomeric mixture of **7b** was obtained from **6** (2.50 g, 5.78 mmol) and **5b** (1.37 g, 5.78 mmol) in 59% yield as a foam: IR ($CHCl_3$) cm^{-1}: 1791, 1752, and 1324; ^1H NMR (200 MHz, $CDCl_3$) δ 1.23 and 1.25 (3H, two s), 1.52 (3H, s), 1.72 (1H, br s), 3.48 (2H, m), 3.59

and 3.60 (3H, two s), 3.81 (3H, s), 4.12 and 4.21 (1H, two dd, $J_1=1.8$ Hz, $J_2=4.6$ Hz), 4.38 and 4.46 (1H, two s), 4.68 (2H, t, $J=6.3$ Hz), 4.81 and 4.85 (1H, two d, $J_1=1.8$ Hz), 5.08 and 5.23 (2H, two d, $J=11.7$ Hz), 5.41 and 5.48 (1H, two d, $J_2=4.6$ Hz), 6.87~7.32 (4H, m), 6.93 (1H, d, $J=1.1$ Hz), 7.03 (1H, d, $J=1.1$ Hz), 7.89 and 7.98 (1H, two s); FAB-MS m/z 591 (M+H).

p-Methoxybenzyl (3*S*,5*R*,6*S*)-6-[(1*RS*)-1-Acetoxy-1-[1-[2-(2-phenyl-1,3,4-thiadiazol-5-yl)thioethyl]-1,2,3-triazol-4-yl)methyl]penicillanate 1,1-Dioxide (**8a**)

Acetic anhydride (2.34 g, 22.96 mmol) was added to a solution of **7a** (1.54 g, 2.30 mmol) and pyridine (2.18 g, 27.55 mmol) in THF (50 ml) and the mixture was stirred overnight at room temperature. The reaction mixture was extracted with dichloromethane and washed sequentially with 1 N HCl, 5% $NaHCO_3$ solution, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a silica gel column using hexane-ethyl acetate, 1:1 (v/v) as eluant to give the stereoisomeric mixture of **8a** (1.53 g, 93%) as a foam: IR ($CHCl_3$) cm^{-1}: 1798, 1746, and 1319; ^1H NMR (200 MHz, $CDCl_3$) δ 1.24 (3H, s), 1.53 (3H, s), 2.10 (3H, s), 3.81 (3H, s), 3.85 (2H, t, $J=6.4$ Hz), 4.31 (1H, dd, $J_1=1.7$ Hz, $J_2=5.0$ Hz), 4.38 (1H, s), 4.76 (1H, d, $J_1=1.7$ Hz), 4.91 (2H, t, $J=6.4$ Hz), 5.08 and 5.20 (2H, two d, $J=11.7$ Hz), 6.50 (1H, d, $J_2=5.0$ Hz), 6.87~7.31 (4H, m), 7.46~7.92 (5H, m), 7.87 (1H, s).

Anal Calcd for $C_{31}H_{32}N_6O_8S_3$: C 52.23, H 4.53, N 11.79.
Found: C 52.30, H 4.41, N 11.68.

p-Methoxylbenzyl (3*S*,5*R*,6*S*)-6-[(1*RS*)-1-Acetoxy-1-[1-[2-(1-methylimidazol-2-yl)thioethyl]-1,2,3-triazol-4-yl]methyl]penicillanate 1,1-Dioxide (**8b**)

Compound **8b** was obtained in 90% yield as a foam from **7b** (0.61 g, 1.03 mmol), using the procedure described for **8a**: IR ($CHCl_3$) cm^{-1}: 1796, 1749, and 1326; ^1H NMR (200 MHz, $CDCl_3$) δ 1.24 and 1.31 (3H, two s), 1.53 and 1.55 (3H, two s), 2.05 and 2.10 (3H, two s), 3.50 (2H, t, $J=6.4$ Hz), 3.58 (3H, s), 3.82 (3H, s), 4.28 (1H, dd, $J_1=1.9$ Hz, $J_2=4.9$ Hz), 4.38 and 4.40 (1H, two s), 4.73 (2H, t, $J=6.4$ Hz), 4.76 (1H, d, $J_1=1.9$ Hz), 5.08 and 5.20 (2H, two d, $J=11.7$ Hz), 6.34 and 6.48 (1H, two d, $J_2=4.9$Hz), 6.87~7.32 (4H, m), 6.95 (1H, d, $J=1.0$ Hz), 7.04 and 7.06 (1H, two d, $J=1.0$ Hz), 7.75 and 7.85 (1H, two s).

Anal Calcd for $C_{27}H_{32}N_6O_8S_2$: C 51.25, H 5.10, N 13.28.
Found: C 51.21, H 4.68, N 13.17.

p-Methoxybenzyl (3*S*,5*R*,6*Z*)-6-[1-[1-[2-(2-Phenyl-1,3,4-thiadiazol-5-yl)thioethyl]-1,2,3-triazol-4-yl]methylene]penicillanate 1,1-Dioxide (**9a**) and *p*-Methoxybenzyl (3*S*,5*R*,6*E*)-6-[1-[1-[2-(2-Phenyl-1,3,4-thiadiazol-5-yl)thioethyl]-1,2,3-triazol-4-yl]methylene]penicillanate 1,1-Dioxide (**10a**)

1,5-Diazabicyclo[4.3.0]non-5-ene (95%, 1.34 g, 10.27 mmol) was added to a solution of **8a** (7.32 g, 10.27 mmol) in dichloromethane (100 ml) at −70°C under a nitrogen atmosphere and the reaction mixture was stirred for 20 minutes. The reaction was quenched by adding water and extracted with dichloromethane. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified on a silica gel column using $CHCl_3$-ethyl acetate-hexane, 1:3:2 (v/v) as eluant to give the *Z*-isomer (**9a**) (3.35 g) and *E*-isomer (**10a**) (2.35 g) as a solid.

Z-Isomer (**9a**): 50% yield; mp 153~154°C (EtOAc-Hexane); IR ($CHCl_3$) cm^{-1}: 1777, 1746, and 1318; ^1H NMR (200 MHz, $CDCl_3$) δ 1.32 (3H, s), 1.53 (3H, s), 3.82 (3H, s), 3.86 (2H, t, $J=6.4$ Hz), 4.44 (1H, s), 4.94 (2H, t, $J=6.4$ Hz), 5.12 and 5.28 (2H, two d, $J=11.7$ Hz), 5.63 (1H, d, $J=1.3$ Hz), 7.30 (1H, d, $J=1.3$ Hz), 6.89~7.35 (4H, m), 7.48~7.91 (5H, m), 7.89 (1H, s).

Anal Calcd for $C_{29}H_{28}N_6O_6S_3$: C 53.36, H 4.32, N 12.88.
Found: C 53.32, H 4.30, N 12.98.

E-Isomer (**10a**): 35% yield; mp 174~176°C (EtOAc-Hexane); IR ($CHCl_3$) cm^{-1}: 1766, 1747, and 1318; ^1H NMR (200 MHz, $CDCl_3$) δ 1.30 (3H, s), 1.53 (3H, s), 3.82 (3H, s), 3.91 (2H, t, $J=6.2$ Hz), 4.42 (1H, s), 4.96 (2H, t, $J=6.2$ Hz), 5.12 and 5.28 (2H, two d, $J=11.7$ Hz), 5.15 (1H, s), 7.10 (1H, s), 6.88~7.35 (4H, m), 7.47~7.92 (5H, m), 8.75 (1H, s).

Anal Calcd for $C_{29}H_{28}N_6O_6S_3$: C 53.36, H 4.32, N 12.88.
Found: C 53.25, H 4.15, N 12.76.

p-Methoxybenzyl (3*S*,5*R*,6*Z*)-6-[1-[1-[2-(1-Methylimidazol-2-yl)thioethyl]-1,2,3-triazol-4-yl]methylene]penicillanate 1,1-Dioxide (**9b**) and *p*-Methoxybenzyl (3*S*,5*R*,6*E*)-6-[1-[1-[2-(1-Methylimidazol-2-yl)thioethyl]-1,2,3-triazol-4-yl]methylene]penicillanate 1,1-Dioxide (**10b**)

Compounds **9b** and **10b** were prepared from **8b** (6.23 g, 9.85 mmol) by the same method as described for **9a** and **10a**.

Z-Isomer (**9b**): 42% yield; mp 65~67°C (EtOAc-Hexane); IR ($CHCl_3$) cm^{-1}: 1776, 1750, and 1324; ^1H NMR (200 MHz, $CDCl_3$) δ 1.33 (3H, s), 1.54 (3H, s), 3.44~3.52 (2H, m), 3.56 (3H, s), 3.82 (3H, s), 4.44 (1H, s), 4.75 (2H, t, J=6.1 Hz), 5.12 and 5.28 (2H, two d, J=11.7 Hz), 5.64 (1H, d, J=1.3 Hz), 6.87~7.35 (4H, m), 6.93 (1H, d, J=1.2 Hz), 7.03 (1H, d, J=1.2 Hz), 7.26 (1H, d, J=1.3 Hz), 7.91 (1H, s); FAB-MS *m/z* 573 (M+H).

E-Isomer (**10b**): 51% yield; mp 143~144°C (EtOAc-Hexane); IR ($CHCl_3$) cm^{-1}: 1773, 1753, and 1325; ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (3H, s), 1.54 (3H, s), 3.56 (3H, s), 3.57 (2H, t, J=6.3 Hz), 3.82 (3H, s), 4.43 (1H, s), 4.75 (2H, t, J=6.3 Hz), 5.17 (1H, s), 5.12 and 5.29 (2H, two d, J=11.7 Hz), 6.87~7.37 (4H, m), 6.93 (1H, d, J=1.2 Hz), 7.06 (1H, d, J=1.2 Hz), 7.08 (1H, s), 8.70 (1H, s).

Anal Calcd for $C_{25}H_{28}N_6O_6S_2$: C 52.43, H 4.93, N 14.68.
Found: C 52.54, H 4.73, N 14.71.

p-Methoxybenzyl (3*S*,5*R*,6*Z*)-6-[1-[1-[2-(2-Phenyl-1,3,4-thiadiazol-5-yl)sulfonylethyl]-1,2,3-triazol-4-yl]methylene]penicillanate 1,1-Dioxide (**11a**)

Peracetic acid (32%, 0.21 g, 2.76 mmol) was added to a solution of **9a** (0.90 g, 1.38 mmol) in dichloromethane (25 ml) and the mixture was stirred at room temperature overnight. The reaction mixture was extracted with dichloromethane and washed with water, 5% $NaHCO_3$ solution, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a silica gel column using dichloromethane-ethyl acetate, 8:1 (v/v) as eluant to give **11a** (0.83 g, 88%) as a solid: mp 188~189°C (EtOAc-Hexane): IR ($CHCl_3$) cm^{-1}: 1777, 1746, and 1321: ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (3H, s), 1.50 (3H, s), 3.83 (3H, s), 4.33 (2H, t, J=6.4 Hz), 4.40 (1H, s), 5.06 (2H, t, J=6.4 Hz), 5.12 and 5.28 (2H, two d, J=11.7 Hz), 5.51 (1H, d, J=1.1 Hz), 7.25 (1H, d, J=1.1 Hz), 6.89~7.36 (4H, m), 7.51~8.00 (5H, m), 8.11 (1H, s).

Anal Calcd for $C_{29}H_{28}N_6O_8S_3$: C 50.86, H 4.12, N 12.28.
Found: C 50.36, H 3.87, N 12.16.

In a similar manner, the following compounds **12a**, **11b** and **12b** were obtained from the corresponding thio-compounds **10a**, **9b**, and **10b**, respectively.

p-Methoxybenzyl (3*S*,5*R*,6*E*)-6-[1-[1-[2-(2-Phenyl-1,3,4-thiadiazol-5-yl)sulfonylethyl]-1,2-3-triazol-4-yl]methylene]penicillanate 1,1-Dioxide (**12a**)

93% yield; mp 163~164°C (EtOAc-Hexane); IR ($CHCl_3$) cm^{-1}: 1773, 1750, and 1325; ^1H NMR (200 MHz, DMSO-d_6) δ 1.31 (3H, s), 1.45 (3H, s), 3.77 (3H, s), 4.54 (1H, s), 4.55 (2H, t, J=6.2 Hz), 5.07 (2H, t, J=6.2 Hz), 5.15 and 5.28 (2H, two d, J=11.7 Hz), 5.74 (1H, s), 7.25 (1H, s), 6.93~7.41 (4H, m), 7.56~8.09 (5H, m), 8.82 (1H, s); FAB-MS *m/z* 685 (M+H).

p-Methoxybenzyl (3*S*,5*R*,6*Z*)-6-[1-[1-[2-(1-Methylimidazol-2-yl)sulfonylethyl]-1,2,3-triazol-4-yl]methylene]penicillanate 1,1-Dioxide (**11b**)

86% yield; mp 89~91°C (EtOAc-Hexane); IR ($CHCl_3$) cm^{-1}: 1783, 1750, and 1325; ^1H NMR (200 MHz, $CDCl_3$) δ 1.33 (3H, s), 1.54 (3H, s), 3.82 (3H, s), 3.89 (3H, s), 4.09 (2H, t, J=6.1 Hz), 4.44 (1H, s), 4.82~5.04 (2H, m), 5.12 and 5.28 (2H, two d, J=11.7 Hz), 5.63 (1H, d, J=1.1 Hz), 6.89~7.35 (4H, m), 7.00 (1H, s), 7.01 (1H, s), 7.20 (1H, d, J=1.1 Hz), 7.77 (1H, s); FAB-MS *m/z* 605 (M+H).

p-Methoxybenzyl (3*S*,5*R*,6*E*)-6-[1-[1-[2-(1-Methylimidazol-2-yl)sulfonylethyl]-1,2,3-triazol-4-yl]methylene]penicillanate 1,1-Dioxide (**12b**)

67% yield; mp 148~150°C (EtOAc-Hexane); IR ($CHCl_3$) cm^{-1}: 1773, 1751, and 1325; ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (3H, s), 1.55 (3H, s), 3.83 (3H, s), 3.93 (3H, s), 3.99~4.31 (2H, m), 4.43 (1H, s,), 4.99 (2H, t, J=6.6 Hz), 5.16 (1H, s), 5.13 and 5.29 (2H, two d, J=11.7 Hz), 6.89~7.36 (4H, m), 6.95

(1H, s), 7.01 (2H, s), 8.67 (1H, s).

Anal Calcd for $C_{25}H_{28}N_6O_8S_2$: C 49.66, H 4.67, N 13.90.
Found: C 49.68, H 4.49, N 13.62.

Sodium (3*S*,5*R*,6*Z*)-6-[1-[1-[2-(2-Phenyl-1,3,4-thiadiazol-5-yl)thioethyl]-1,2,3-triazol-4-yl]methylene]penicillanate 1,1-Dioxide (**13a**)

Anhydrous aluminum chloride (0.31 g, 2.32 mmol) was added to a stirred solution of **9a** (0.60 g, 0.92 mmol) in an anhydrous mixture of dichloromethane (6 ml) and anisole (25 ml) at $-40\sim-45$°C under a nitrogen atmosphere. After 1 hour, the reaction was quenched by adding water and the pH was adjusted to pH 7.1 with 0.1 N NaOH. The mixture was filtered and the aqueous layer was separated by separating funnel. The organic layer was washed with water and the washing was added to the previous aqueous layer. The resulted solution was freeze-dried to give a solid, which was purified by reverse phase chromatography using water-acetonitrile, 10:1 (v/v) as eluant to give **13a** (0.23 g, 45%) as a solid: IR (Nujol) cm^{-1}: 1770; ^1H NMR (200 MHz, DMSO-d_6) δ 1.40 (3H, s), 1.46 (3H, s), 3.87 (1H, s), 3.90 (2H, t, $J=5.9$ Hz), 4.90 (2H, t, $J=5.9$ Hz), 5.78 (1H, s), 7.40 (1H, s), 7.55~7.94 (5H, m), 8.46 (1H, s); FAB-MS *m/z* 555 (M+H).

In an analogous manner, the following compounds **14a**, **15a**, **16a**, **13b**, **14b**, **15b** and **16b** were prepared from the corresponding PMB ester compounds **10a**, **11a**, **12a**, **9b**, **10b**, **11b**, and **12b**, respectively.

Sodium (3*S*,5*R*,6*E*)-6-[1-[1-[2-(2-Phenyl-1,3,4-thiadiazol-5-yl)thioethyl]-1,2,3-triazol-4-yl]methylene]penicillanate 1,1-Dioxide (**14a**)

51% yield; IR (Nujol) cm^{-1}: 1759; ^1H NMR (200 MHz, DMSO-d_6) δ 1.37 (3H, s), 1.46 (3H, s), 3.81 (1H, s), 3.90 (2H, t, $J=6.2$ Hz), 4.95 (2H, t, $J=6.2$ Hz), 5.51 (1H, s), 7.09 (1H, s), 7.56~7.95 (5H, m), 8.83 (1H, s); FAB-MS *m/z* 555 (M+H).

Sodium (3*S*,5*R*,6*Z*)-6-[1-[1-[2-(2-Phenyl-1,3,4-thiadiazol-5-yl)sulfonylethyl]-1,2,3-triazol-4-yl]-methylene]penicillanate 1,1-Dioxide (**15a**)

63% yield; IR (Nujol) cm^{-1}: 1750; ^1H NMR (200 MHz, DMSO-d_6) δ 1.38 (3H, s), 1.45 (3H, s), 3.92 (1H, s), 4.57 (2H, t, $J=6.3$ Hz), 5.01 (2H, t, $J=6.3$ Hz), 5.66 (1H, s), 7.39 (1H, s), 7.62~8.12 (5H, m), 8.45 (1H, s); FAB-MS *m/z* 587 (M+H).

Sodium (3*S*,5*R*,6*E*)-6-[1-[1-[2-(2-Phenyl-1,3,4-thiadiazol-5-yl)sulfonylethyl]-1,2,3-triazol-4-yl]methylene]penicillanate 1,1-Dioxide (**16a**)

48% yield; IR (Nujol) cm^{-1}: 1759; ^1H NMR (200 MHz, DMSO-d_6) δ 1.37 (3H, s), 1.45 (3H, s), 3.80 (1H, s), 4.55 (2H, t, $J=6.2$ Hz), 5.05 (2H, t, $J=6.2$ Hz), 5.46 (1H, s), 7.00 (1H, s), 7.58~8.12 (5H, m), 8.82 (1H, s); FAB-MS *m/z* 587 (M+H).

Sodium (3*S*,5*R*,6*Z*)-6-[1-[1-[2-(1-Methylimidazol-2-yl)thioethyl]-1,2,3-triazol-4-yl]methylene]-penicillanate 1,1-Dioxide (**13b**)

56% yield; IR (Nujol) cm^{-1}: 1769; ^1H NMR (200 MHz, DMSO-d_6) δ 1.38 (3H, s), 1.44 (3H, s), 3.50 (2H, t, $J=6.3$ Hz), 3.53 (3H, s), 3.78 (1H, s), 4.68 (2H, t, $J=6.3$ Hz), 5.73 (1H, d, $J=1.2$ Hz), 6.97 (1H, d, $J=1.0$ Hz), 7.24 (1H, d, $J=1.0$ Hz), 7.35 (1H, d, $J=1.2$ Hz), 8.39 (1H, s,); FAB-MS *m/z* 475 (M+H).

Sodium (3*S*,5*R*,6*E*)-6-[1-[1-[2-(1-Methylimidazol-2-yl)thioethyl]-1,2,3-triazol-4-yl]methylene]-penicillanate, 1,1-Dioxide (**14b**)

53% yield; IR (Nujol) cm^{-1}: 1751; ^1H NMR (200 MHz, DMSO-d_6) δ 1.38 (3H, s), 1.46 (3H, s), 3.51 (2H, t, $J=6.3$ Hz), 3.54 (3H, s), 3.82 (1H, s), 4.73 (2H, t, $J=6.3$ Hz), 5.54 (1H, s), 6.96 (1H, d, $J=1.1$ Hz), 7.10 (1H, s), 7.23 (1H, d, $J=1.1$ Hz), 8.76 (1H, s); FAB-MS *m/z* 475 (M+H).

Sodium (3*S*,5*R*,6*Z*)-6-[1-[1-[2-(1-Methylimidazol-2-yl)sulfonylethyl]-1,2,3-triazol-4-yl]methylene]-penicillanate 1,1-Dioxide (**15b**)

52% yield; IR (Nujol) cm^{-1}: 1764; ^1H NMR (200 MHz, DMSO-d_6) δ 1.38 (3H, s), 1.44 (3H, s), 3.78 (1H, s), 3.86 (3H, s), 4.21 (2H, t, $J=6.4$ Hz), 4.84 (2H, t, $J=6.4$ Hz), 5.69 (1H, d, $J=0.9$ Hz), 7.09 (1H,

s), 7.32 (1H, d, J=0.9 Hz), 7.44 (1H, s), 8.33 (1H, s); FAB-MS m/z 507 (M+H).

Sodium (3*S*,5*R*,6*E*)-6-[1-[1-[2-(1-Methylimidazol-2-yl)sulfonylethyl]-1,2,3-triazol-4-yl]methylene]-penicillanate 1,1-Dioxide (**16b**)

39% yield; IR (Nujol) cm^{-1}: 1760; ^1H NMR (200 MHz, DMSO-d_6) δ 1.38 (3H, s), 1.46 (3H, s), 3.83 (1H, s), 3.87 (3H, s), 4.21 (2H, t, J=6.2 Hz), 4.90 (2H, t, J=6.2 Hz), 5.54 (1H, s), 7.05 (2H, s), 7.44 (1H, s), 8.71 (1H, s); FAB-MS m/z 507 (M+H).

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