Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 1, pp. 11-14, 1997

0960-894X/97 $17.00 + 0.00

PII: S0960-894X(96)00575-6

STUDIES ON PENAM SULFONES III. SYNTHESIS AND β-LACTAMASE INHIBITORY ACTIVITY OF SODIUM (6R)-6-(α-HYDROXYBENZYL)-2β-METHOXYIMINOMETHYL-2α-METHYLPENAM-3α-CARBOXYLATE 1,1-DIOXIDE AND SODIUM 2β-ACYL-2α-METHYLPENAM-3α-CARBOXYLATE 1,1-DIOXIDE

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Abstract: The synthesis and in vitro synergies of (6R)-6-(α-hydroxybenzyl)-2β-methoxyiminomethyl-2α-methylpenam-3α-carboxylate 1,1-dioxide (**4**) and 2β-acyl-2α-methylpenam-3α-carboxylate 1,1-dioxide (**15**) are described. Compound **15** showed good in vitro synergy in combination with piperacillin and ceftazidime against chromosomally mediated class I cephalosporinase producing organisms including TEM, SHV, and OXA-type enzymes producing microorganisms.

After the clinical success of tazobactam (**1**), which was originally synthesized by our group,[1] considerable interest has been directed towards the functionalization of the 2β-methyl group of penicillanic acid.[2,3] While tazobactam and clavulanic acid are highly active against class A enzymes, their activity against class C enzymes is weak. During the course of our further investigation in the penam sulfone area, we identified recently two new series of penam sulfones,[4] 2β-oxyiminomethyl penam sulfones (**2a**) and 2β-hydrazinomethyl penam sulfones (**2b**), respectively. These two classes of compounds showed improved synergy in combination with piperacillin and ceftazidime against class C enzymes (cephalosporinase) producing microorganisms except *Pseudomonas aeruginosa*. In 1985, Sammes et al.[5] reported that (6R)-6-(α-hydroxybenzyl)penam sulfone (**3**) is a powerful inhibitor of class C β-lactamase isolated from *P. aeruginosa*. On the basis of this report, we thought that the introduction of a (6R)-6-(α-hydroxybenzyl) group in the 2β-oxyiminomethyl penam sulfone skeleton might improve the synergy against *P. aeruginosa*. Herein we report the synthesis and in vitro synergy of (6R)-6-(α-hydroxybenzyl)-2β-methoxyiminomethyl-2α-methylpenam-3α-carboxylate-1,1-dioxide (**4**), in a further attempt to obtain a compound with improved activity and synergy against *P. aeruginosa*.

The synergy data (Table 1) indicate that the level of synergy of compound **4** in combination with ceftazidime is very similar to the reference compounds against *E. cloacae* S-11, *E. cloacae* S-65, *E. aerogenes* S-97, *M. morganii* 36014, and *M. morganii* 36030, although against *E. aerogenes* and *M. morganii* compound **4** was not as active as the reference compounds. No synergy was observed against *P. aeruginosa* strains. Thus, the introduction of a (6R)-6-(α-hydroxybenzyl) group in the 2β-methoxyiminomethyl penam sulfone skeleton did not improve synergy particularly against *P. aeruginosa* strains.

Table 1. In vitro synergy of compound **4** with ceftazidime.

Organism	MIC (μg/mL)				
	CAZ	CAZ + **1**	CAZ + **2a** ($R_1 = CH_3$)	CAZ + **3**	CAZ + **4**
E. cloacae S-11	2.0	<0.25	<0.25	<0.25	<0.25
E. cloacae S-65	2.0	<0.25	<0.25	<0.25	<0.25
E. aerogenes S-97	8.0	1.0	0.50	2.0	4.0
M. morganii 36014	>32	<0.25	<0.25	<0.25	2.0
M. morganii 36030	>32	<0.25	<0.25	<0.25	1.0
P. aeruginosa CT-122	32	32	32	32	32
P. aeruginosa CT-137	16	16	16	16	16

In another attempt, sodium salt of 2β-acyl-2α-methylpenam-3α-carboxylate 1,1-dioxide **15** was prepared starting from 2β-carboxy penam sulfone (13)[3a] as shown in Scheme 1. Its in vitro synergy with piperacillin and ceftazidime are shown in the Tables 2 and 3, respectively. In combination with ceftazidime (Table 3) compound **15** showed excellent in vitro synergy against all G(-) organisms, although the synergy against *P. aeruginosa* strains was very weak, possibly due to poor penetration through these strains.

Scheme 1

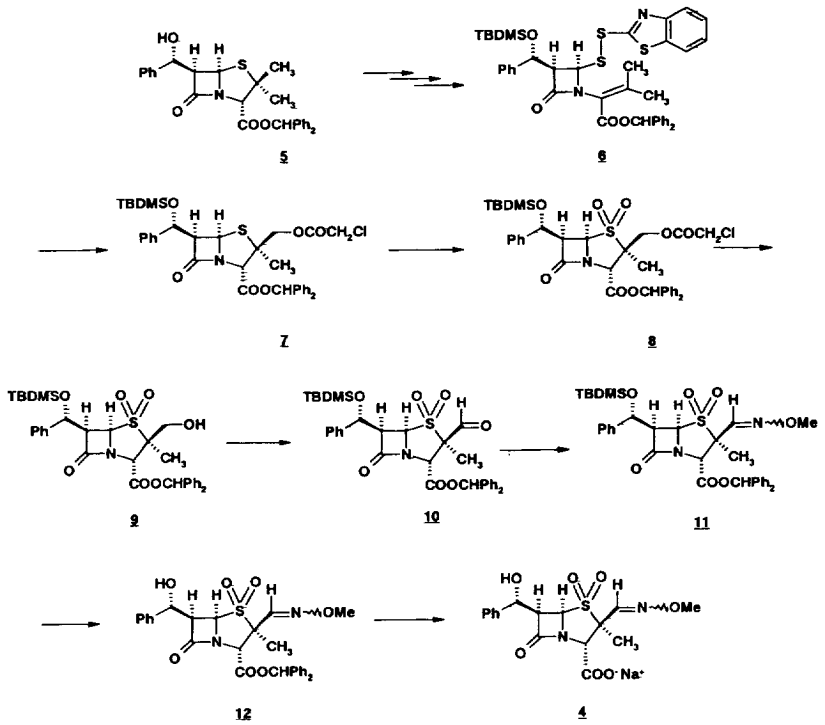


Table 2. In vitro synergy of compound **15** with piperacillin (PIPC).

Organism	MIC (μg/mL)		
	PIPC alone	+ TAZ	+ compound **15**
S. aureus 54K	200	0.78	6.26
S. aureus 80K	50	0.39	3.13
E. coli TEM 3	200	3.13	3.13
E. coli TEM 7	>400	0.78	1.56
E. coli OXA 1	25	3.13	1.56
E. coli OXA 3	3.13	1.56	1.56
E. coli SHV 1	>400	1.56	3.13
E. coli SHV 5	200	≤0.2	1.56
K. pneumoniae CTX 1	>400	6.25	12.5
S. marcescens 200 L	200	0.78	3.13
P. vulgaris CT 106	200	1.56	25
C. freundii 2046E	>400	0.78	1.56
C. freundii 44032	200	200	12.5
P. aeruginosa 46220 (DR-2)	100	12.5	6.25
E. cloacae P99	100	25	12.5
E. cloacae 40011	50	6.25	6.25
E. cloacae 40015	100	50	25
E. aerogenes 41003	12.5	12.5	3.13
E. aerogenes 41004	12.5	12.5	6.25
E. aerogenes 41006	100	100	12.5
M. morganii 36014	50	≤0.2	0.39

Inhibitor conc: 5 μg/mL; TAZ: tazobactam.

Table 3. In vitro synergy of compound **15** with ceftazidime (CAZ).

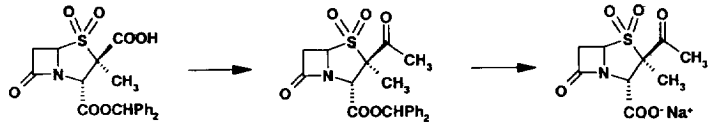
Organism	MIC (μg/mL)		
	CAZ alone	+ TAZ	+ compound **15**
E. coli TEM 3	25	≤0.2	0.39
E. coli TEM 7	12.5	≤0.2	0.39
K. pneumoniae CTX 1	100	0.78	1.56
P. vulgaris CT 106	12.5	0.39	1.56
C. freundii CT 76	50	50	12.5
C. freundii 44032	400	200	12.5
P. aeruginosa 46220 (DR-2)	25	25	6.25
E. cloacae P99	100	12.5	6.25
E. cloacae 40011	25	3.13	1.56
E. cloacae E40002	200	200	12.5
E. aerogenes 41003	12.5	12.5	1.56
E. aerogenes 41004	12.5	12.5	1.56
E. aerogenes 41006	200	100	12.5
M. morganii 36014	25	≤0.2	≤0.2

Inhibitor conc: 5 μg/mL; TAZ: tazobactam.

Compound **4** was prepared as shown in Scheme 2. Conversion of the compound **5**[5] into the corresponding azetidinone disulfide **6** was achieved by three steps through a ring opening procedure of the sulfoxide as described by Kamiya et al.[6] Stirring of the azetidinone disulfide **6** with chloroacetic acid in presence of silver acetate[7] in methylene chloride at room temperature for 16 h gave the corresponding 2β-chloroacetyloxymethyl-3α-carboxylate **7** as the major product. The mixture was directly subjected to oxidation with $KMnO_4$ in a mixture of acetone-water-glacial acetic acid to afford the corresponding penam sulfone **8** along with the cepham sulfone in a ratio of 2:1. Heating of the mixture with thiourea in ethanol at 60 °C for 70 min gave the 2β-hydroxymethyl penam sulfone **9**. Oxidation of the alcohol **9** with pyridinium chlorochromate in methylene chloride at room temperature for 24 h gave the 2β-carboxaldehyde **10**, which on treatment with

methoxylamine hydrochloride in presence of pyridine in a mixture of methylene chloride and ethanol gave the oxime **11** in about 58% yield. Removal of the *t*-butyldimethylsilyl group by treatment with 48% HF in acetonitrile at room temperature for 1 h afforded the benzhydryl (6R)-6-(α-hydroxybenzyl)-2β-methoxyiminomethyl-3α-carboxylate-1,1-dioxide **12** in 60% yield. Hydrogenation of compound **12** over Pd/C in ethanol at 50 psi for 48 h gave the free acid, which on treatment with $NaHCO_3$ gave the desired compound **4**. For ^{1}H NMR, see Table 4.

Scheme 2



13 **14** **15**

The benzhydryl ester of the 2β-carboxy penicillanic acid sulfone (**13**)[3a] was treated with oxalyl chloride in presence of a catalytic amount of DMF to give the corresponding acyl chloride which was directly reacted with CH_3MgBr in presence of CuI to provide the benzhydryl ester of 2β-acyl penicillanic acid sulfone **14**. Removal of the ester protecting group by TFA/anisole followed by treatment with $NaHCO_3$ gave the corresponding sodium alt **15** in 90% yield. For ^{1}H NMR see Table 4.

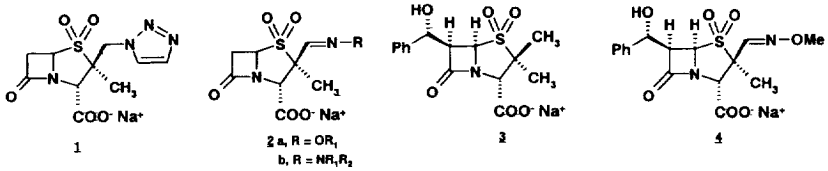


Table 4. ^{1}H NMR data of compounds **4** and **15**.

Compound	^{1}H NMR (DMSO-d_6, δ ppm)
4	7.50 (s, 1H); 7.25-7.43 (m, 5H); 5.75 (br, m, 1H, exchanged with D_2O); 5.30 (d, 1H, J = 10.6 Hz); 4.78 (d, 1H, J = 4.7 Hz); 4.27 (s, 1H); 4.20-4.30 (m, 1H); 3.80 (s, 3H); 1.38 (s, 3H).
15	5.03 (dd, 1H, J = 1.0 and 4.2 Hz); 4.78 (s, 1H); 3.54 (dd, 1H, J = 4.2 and 16.0 Hz); 3.11(dd, 1H, J = 1.0 and 16.0 Hz); 2.40 (s, 3H); 1.58 (s, 3H).

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(*Received in USA* 13 *August* 1996; *accepted* 22 *November* 1996)