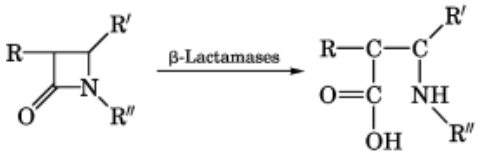
Kirk-Othmer Encyclopedia of Chemical Technology.

β-LACTAMASE INHIBITORS

The antibacterial effectiveness of penicillins, cephalosporins and other β-lactam antibiotics depends upon selective acylation and consequently, inactivation, of transpeptidases involved in bacterial cell wall synthesis. This acylating ability is a result of the reactivity of the β-lactam ring (**1**). Bacteria that are resistant to β-lactam antibiotics often produce enzymes called β-lactamases that inactivate the antibiotics by catalyzing the hydrolytic opening of the β-lactam ring to give products (**2**) devoid of antibacterial activity.



(**1**) active (**2**) inactive

A book (1) and several general reviews (2–4) on β-lactamases have been published. Based on sequence data, it has been suggested that β-lactamases evolved from the enzymes involved in bacterial cell wall synthesis (5–7).

One approach to combating antibiotic resistance caused by β-lactamase is to inhibit the enzyme (see Enzyme inhibition). Effective combinations of enzyme inhibitors with β-lactam antibiotics such as penicillins or cephalosporins, result in a synergistic response, lowering the minimal inhibitory concentration (MIC) by a factor of four or more for each component. However, inhibition of β-lactamases alone is not sufficient. Pharmacokinetics, stability, ability to penetrate bacteria, cost, and other factors are also important in determining whether an inhibitor is suitable for therapeutic use. Almost any class of β-lactam is capable of producing β-lactamase inhibitors. Several reviews have been published on β-lactamase inhibitors, detection, and properties (8–15).

1. Classification and Occurrence

Several classification schemes for β-lactamases have been used to describe the activity of β-lactamase inhibitors (3, 16, 17). The β-lactamases from gram-positive *Staphylococcal* organisms have been divided into four types A, B, C, D on the basis of serological data and are referred to in general as penicillinases or penases. Gram-negative bacteria produce a much greater diversity of β-lactamases and therefore require a more complex classification scheme. The Richmond-Sykes system (18) is most frequently used to describe the activity of β-lactamase inhibitors. This system defines five classes (I–V) of β-lactamases; a sixth (VI) has been added for the β-lactamases produced by *Bacteroides* species (19). The many plasmid-derived β-lactamases of gram-negative

Table 1. *β-Lactamase* Producing Bacteria[a]

Organism	β-Lactamase producers, %[b]	Enzyme origin %		Richmond-Sykes classification
		Chromosomal	Plasmid	
Gram-positive				
Staphylococcus aureus	80		penase	
Staphylococcus epidermidis	80		penase	
Gram-negative				
Escherichia coli	25 (16–76)	15	TEM 80; OXA-1, 7.5	I,III,V
Haemophilus influenzae	25–60		TEM, 92; ROB-1, 8	III
Neisseria gonorrhea	1–10		TEM, 100	III
Salmonella	6		TEM, 100	III
Shigella			TEM	III
Klebsiella pneumoniae	60–90		TEM, 24; SHV-1, 76	III,IV
Enterobacter	25–30	73	TEM, 27	I,III
Citrobacter	20–50	77	TEM, 23	I,III
Pseudomones aeruginosa	23	44	TEM, 9; PSE, 10; others	I,III
Bacillus catarrhalis	87	90^{+}	BRO-1	
Bacillus fragilis	87	∼100		VI

[a]Refs. (16, 19–21).
[b]Clinically resistant bacteria, virtually 100% of the *Enterobacteriaceae*, produce a low level of chromosomal enzyme that can clinically be selected for higher levels.

bacteria have been separated by isoelectric focusing. They have been given names depending on plasmid origin. The clinically most important plasmid-derived β-lactamases and their prevalence, indicated in parenthesis, are (19): TEM-1 (75%), TEM-2 (3%), OXA-1 (5%), OXA-2 (3%), OXA-3 (2%), SHV-1 (2%), and others (10%). The TEM-1 enzyme stands out as an important target for a β-lactamase inhibitor.

Table 1 shows the clinically most important bacteria that produce β-lactamases, separated into gram-positive and gram-negative organisms. The prevalence of β-lactamase is indicated as is the origin and Richmond-Sykes classification. Based on these data the most important β-lactamases to inhibit clinically are the gram-positive penases, the gram-negative TEM, which are Richmond-Sykes type III, and the gram-negative chromosomal cephalosporinases–cephases which are Richmond-Sykes type I. These enzymes are subsequently referred to as penase, TEM(III), and cephase(I).

1.1. Mechanistic Aspects of β-Lactamase Inhibition

The clinically important β-lactamases, eg, the penases, TEM(III), and cephases(I), are serine proteases that form an acyl enzyme intermediate with β-lactam substrates and β-lactam derived β-lactamase inhibitors (22–25). Mechanistic studies using several *β-lactamase* inhibitors have been extensively reviewed (6, 26, 27) and a general inhibition scheme is illustrated in Figure 1. Following Michaelis complex formation (**3**), the enzyme's serine hydroxyl reacts with the β-lactam carbonyl, forming an acyl enzyme intermediate (**4**), the structure of which depends on the inhibitor. This acyl enzyme can then follow Route B and hydrolyze to products and active enzyme, react further to give an irreversibly inactivated enzyme (Route A) or a transiently inactivated enzyme species (Route C). The transient inhibition can result from a conformational change in the enzyme or formation of a species resistant to hydrolysis. In the latter case, amino acrylatelike esters are commonly encountered. A suitably long-lived transient species can occupy the β-lactamase and protect a β-lactam from hydrolysis resulting in a synergistic effect. The transiently inhibited species can then hydrolyze to products, revert to acyl enzyme, or react further to give irreversibly inactivated enzyme. β-Lactamase inhibitors that branch away from

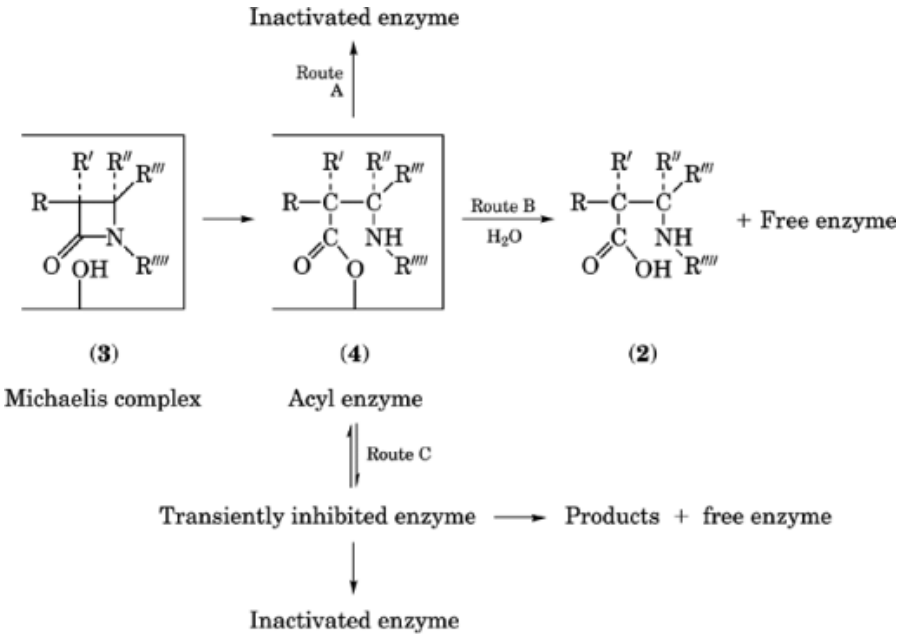


Fig. 1. Scheme for the interaction of β-lactamase inhibitor s and β-lactamases where the enzyme is presented by 

acyl enzyme (**4**) formation have been termed branched pathway inhibitors. The exact mechanistic pathway is dependent on both the enzyme and the inhibitor.

Active site directed β-lactam-derived inhibitors have a competitive component of inhibition, but once in the active site they form an acyl enzyme species which follows one or more of the pathways outlined in Figure 1. Compounds that follow Route C and form a transiently inhibited enzyme species and are subsequently hydrolyzed to products have been termed inhibitory substrates or competitive substrates. Inhibitors that give irreversibly inactivated β-lactamase (Route A) are called suicide inactivators or irreversible inhibitors. The term progressive inhibitor has also been used. An excellent review has appeared on inhibitor interactions with β-lactamases (28).

The activity of β-lactamase inhibitors is often expressed as an IC_{50} value, which is defined as the concentration of inhibitor that causes 50% inhibition of enzyme activity for a given set of conditions. IC_{50} values, which vary widely according to substrate, time of incubation, and other factors, are presented herein solely to give an indication of potency and enzyme inhibitor specificity. Values that decrease with preincubation are indicative of irreversible inhibitors.

1.2. β-Lactam-Based Inhibitors

1.2.1. Penicillins, Cephalosporins, and Monobactams

Early attempts at inhibiting β-lactamases using inorganics or penicillin fragments were not successful (29, 30). The use of reactive penicillin species, such as diazo species from 6-aminopenicillanic acid (6-APA) or ampicillin (31) and penicillin isocyanates (32), was successful, but not practical because of the reactivity of the molecules. The discovery that cephalosporin C (33) and methicillin (34) inhibited β-lactamases resulted in the screening of numerous antibiotics and a number of β-lactamase-resistant penicillins and cephalosporins were found to be β-lactamase inhibitors. These compounds act by forming a transiently inhibited acyl enzyme species as a

(6)
Acyl enzyme

(7)
Transient inhibition

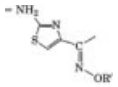
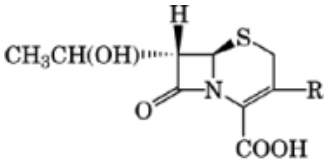


Fig. 2. Transiently inhibited species for cephalosporins bound to β-lactamase. R, an aminothiazole oxime,

result of conformational change (35–37) and are inhibitory substrates (Fig. 1, Route C). No clinically useful inhibitors have been identified from this class. These efforts have been extensively reviewed (8, 10, 13, 14, 37).

Modern β-lactamase-resistant cephalosporins, primarily of the aminothiazole oxime structural type shown in Figure 2, have been reported to be inhibitors of type I cephases (38–42). β-Lactamase inhibition occurs through the transiently inhibited enzyme species (**7**), which requires a good C-3 leaving group. Cephalosporins without a leaving group at C-3 are poor inhibitors (43, 44). None of the aminothiazole oxime structural types is an effective synergist.

A series of activated cephalosporins having electron withdrawing groups at C-3, such as [128474-86-2] (**8**, R = CHO), $C_{10}H_{11}NO_5S$, and [123036-47-5] (**8**, R = CN), $C_{10}H_{10}N_2O_4S$, were prepared in an attempt to increase β-lactamase inhibition (45, 46). These compounds inhibited type I cephases and synergy was demonstrated (**8**, R = CN) with ceftizoxime. A series of 7-β-[2-(1,3-dithiolan-2-ylidene)acetamido] cephalosporins represented by [71908-34-4] (**9**), $C_{18}H_{20}N_5O_6S_4$, are potent inhibitors of type I cephase and give synergy with cephaloridine (47). Several monobactams have been reported to be inhibitory substrates for type I cephases (48–51). Interesting exceptions are the monophosphams such as represented by [120020-34-0] (**10**), $C_{12}H_{15}N_5O_8PS$, and some oligopeptide monobactams which are reported to be irreversible inhibitors (Fig. 1, Route A) (52, 53). The monocyclic β-lactam [123039-89-4] (**11**), $C_9H_8N_2O_2$, inhibits a broad range of β-lactamases, but is too unstable for practical use (54).



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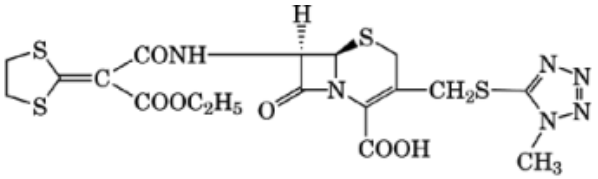

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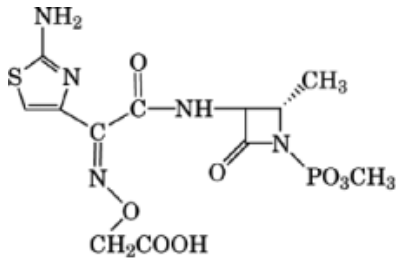

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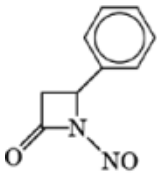
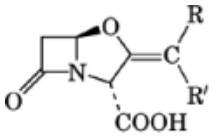


(11)

1.2.2. Clavulanic Acid Class of β-Lactamase Inhibitors

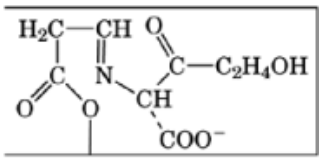
The discovery of clavulanic acid [58001-44-8] (**12**, R = CH_2OH, R′ = H), $C_8H_9NO_5$, in 1976 marked a turning point in β-lactamase inhibitor research (55). This natural product isolated from *Streptomyces clavuligerus*, ATCC 27064, using a cleverly designed screen, had an unusual β-lactam structure compared to classical penicillins and cephalosporins. The nucleus has the trivial name clavam: an oxygen replaces the ring sulfur and there is no C-6 substituent. The x-ray structure of clavulanic acid, the chemical name of which is [2(*R*)-(2α,3(*Z*),5α)]-3-(2-hydroxy-ethylidine)-7-oxo-4-oxa-1-azabicyclo[3.2.0.]heptane-2-carboxylic acid, has been published (56).



(12)

Clavulanic acid has only weak antibacterial activity, but is a potent irreversible inhibitor for many clinically important β-lactamases (10–14, 57, 58) including penases, and Richmond-Sykes types II, III, IV, V, VI (*Bacteroides*). Type I cephases are poorly inhibited. Clavulanic acid synergizes the activity of many penicillins and cephalosporins against resistant strains. The chemistry (59–63), microbiology (64, 65), structure activity relationships (10, 13, 60–62, 66), biosynthesis (67–69), and mechanism of action (6, 26, 27, 67) have been reviewed.

Mechanistic studies (6, 26, 27, 67) have shown that the acyl enzyme species is the ring opened compound (**13**), which can tautomerize to the transiently inhibited amino acrylate (**14**), and both of these species can react further to give irreversibly inactivated enzyme. Three inactivated forms of the enzyme have been detected. Two, according to labeling studies, retain the complete clavulanate skeleton and the other retains only the carbon chain of the β-lactam ring. Structure (**15**) has been suggested as one possible inactivated form.



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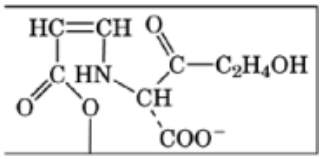

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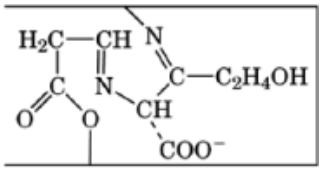
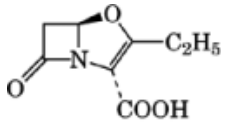


(15)

Consistent with the proposed mechanism is the finding that deoxyclavulanate [69779-62-0] (**12**, R = CH_3, R′ = H), $C_8H_9NO_4$, and the oxapenem [78808-19-2] (**16**) $C_8H_9NO_4$, are potent inhibitors whereas the dihydroclavulanic acid [59897-36-2] (**17**), $C_8H_{11}NO_5$, is devoid of useful activity. The oxapenem (**16**) is a more potent inhibitor than clavulanic acid (**12**, R = CH_2OH, R′ = H) but (**16**) is unstable.



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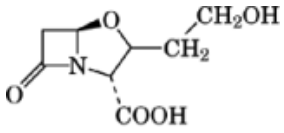
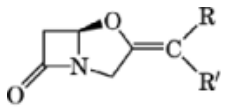


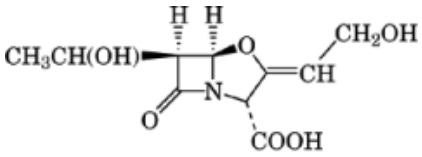
(17)

Analogues of clavulanic acid have been reviewed (10, 11, 13, 60–62, 66). Inhibitory activity for selected compounds is given in Table 2. A number of clavulanic acid analogues are more potent than the parent compound. Additionally, the natural (*Z*)-isomer (**12**, R = CH_2OH, R′ = H) is more potent than the (*E*)-isomer (**12**, R = H, R′ = CH_2OH) which is a general trend. One surprising feature is that the carboxyl group of clavulanic acid is not required for potent inhibition of β-lactamase (10, 13, 62, 70, 71). For antibacterial activity β-lactam antibiotics normally require an analogously positioned carboxylic acid or other acidic group. Descarboxy

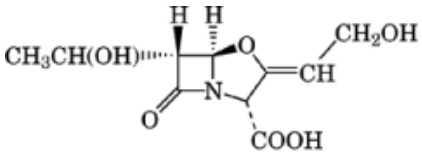
compounds [86408-58-4] (**18**, R = H, R′ = SC_6H_5), $C_{12}H_{11}NO_2S$, and [79908-54-6] (**18**, R = $COOCH_3$, R′ = H), $C_8H_8NO_4$, demonstrate β-lactamase inhibition. Few derivatives have been reported that have substitution at C-6. The hydroxyalkyl compounds [66825-93-2] (**19**) and (**20**), $C_{10}H_{13}NO_6$, have been disclosed as β-lactamase inhibitors (13) where the cis epimer (**19**) is more active than the trans (**20**).



(**18**)



(**19**)

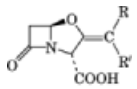


(**20**)

1.2.3. Carbapenem β-Lactamase Inhibitors

Carbapenems are another class of natural product β-lactamase inhibitors discovered about the same time as clavulanic acid. Over forty naturally occurring carbapenems have been identified; many are potent β-lactamase inhibitors. Carbapenem is the trivial name for the 1-azabicyclo[3.2.0]hept-2-ene ring system (**21**) shown in Table 3. The synthesis (74), biosynthesis (75), and β-lactamase inhibitory properties (13, 14, 66) of carbapenems have been reviewed. Carbapenems are often more potent than clavulanic acid and include type I cephases in the spectrum of inhibition. Table 3 lists the available β-lactamase inhibition data. Synergy is frequently difficult to demonstrate because the compounds are often potent antibacterials.

The mechanism of β-lactamase inhibition has been studied (6, 26, 27, 83). Reversible inhibition is believed to result from the Δ^1-pyrroline (**22**). Certain sulfate ester containing compounds, such as SF-2103A (**21**, R = R″ = SO_3H, R′ = H), give long-lived transiently inhibited species suggesting possible conformational changes or additional ionic bonds to the enzyme (6, 83, 86, 89)). MM-22381 (**21**, R = H, R′ = CH_3, R″ = $SCH_2CH_2NHCOCH_3$) and MM-22383 (**21**, R = R′ = H, R″ = $SCHCHNHCOCH_3$), are the only compounds having trans β-lactam stereochemistry for which IC_{50} data are available. Other trans compounds, such as thienamycin, imipenem, and the PS-5 series, have been reported to be β-lactamase inhibitors (90–97), but only limited data have been published. Several totally synthetic carbapenems have also been reported to be potent β-lactamase inhibitors (98, 99). Asparenomycin [76466-24-5] (**23**), $C_{14}H_{16}N_2O_6S$, and its analogues are reported to be irreversible inhibitors (14, 100). These compounds have functionality at C-6 that could react further in a Michael fashion. However, no commercial β-lactamase inhibitor product has been developed from this class of compounds, in part because of low fermentation titers (high synthetic cost), poor stability (82, 84, 87), short half-life in humans (101), and degradation by renal dipeptidase (102–106).

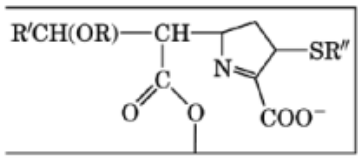


(12)

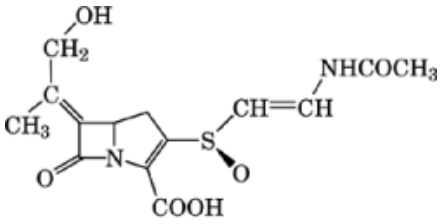
Table 2. β-Lactamase Inhibitory Activity for Clavulanic Acid and Analogues[a]

CAS Registry Number	Molecular formula	R	IC_{50}, μg/mL[b] Penase	TEM(III)	Cephase	Refs.
[58001-44-8]	$C_8H_6NO_5$	CH_2OH	8.2[c]	1.35[c]	10[c]	(60, 66)
			0.03	0.06		13
[69779-62-0]	$C_8H_9NO_4$	H	0.12	0.09	5	66
[78739-05-6]	$C_{10}H_{11}NO_6$	CH_2OOCCH_3	0.04		0.4	(10, 66)
[63617-41-4]	$C_{10}H_{12}N_2O_6$	$CH_2OOCNHCH_3$	1.5	2.5	0.45	(10, 13, 66)
[67529-21-9]	$C_{10}H_{13}NO_5$	$CH_2OC_2H_5$	0.03	0.05	60	13
[130097-27-7]	$C_8H_9NO_8S$	CH_2OSO_3H		3.4		10
[78739-06-7]	$C_9H_{10}NO_4S$	CH_2SCH_3	1.6	1.1[c]		(10, 60, 62, 66)
[64832-72-0]	$C_{10}H_{14}N_2O_4S$	$CH_2SCH_2CH_2NH_2$	0.23[c]	0.05[c]		(10, 60, 62)
[78739-07-8]	$C_9H_9N_2O_4S_2$	$CH_2S_2CNH_2$	3.8[c]	0.08[c]		(10, 60, 62)
[65788-55-8]	$C_8H_{10}N_2O_4$	CH_2NH_2	0.8[c]	0.08[c]		(10, 60, 62, 72)
[75167-01-0]	$C_9H_{12}N_2O_4$	CH_2NHCH_3	0.03	0.007	>50	13
[67065-13-8]	$C_9H_{10}N_2O_5$	CH_2NHCHO	0.04[c]	0.01[c]		(10, 60, 62)
[78739-12-5]	$C_{15}H_{15}N_3O_5$	$CH_2NHCONHC_6H_5$	0.12[c]	0.06[c]		(10, 60)
[78739-15-8]	$C_9H_{12}N_2O_6S$	$CH_2NHSO_2CH_3$	1.15[c]	0.33[c]		(10, 60, 62)
[87131-73-5]	$C_{10}H_{13}NO_5$	$CH_2CH_2CH_2OH$	0.02	0.1		13
[64475-40-7]	$C_{13}H_{11}NO_4$	C_6H_5	<0.08[c]	0.02[c]		(10, 73)
[62319-53-3]	$C_8H_9NO_5$	H[e]	0.6[d]	1[d]		(10, 13, 62)

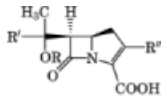
[a] Structure (**12**) where R is defined and R′ is H unless otherwise indicated.
[b] The substrate is nitrocefin unless otherwise indicated.
[c] The substrate is ampicillin.
[d] The substrate is penicillin G.
[e] R′ = CH_2OH.



(**22**)



(**23**)



(21)

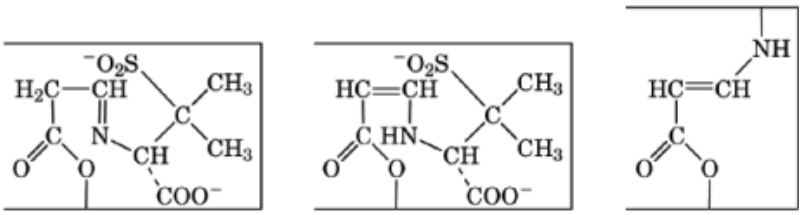
Table 3. Activity of Carbapenem B-Lactamase Inhibitors[a]

Name	CAS Registry Number	Molecular formula	R	R′	R″	IC_{50}, μg/mL[b] Penase	TEM(III)	Cephase(I)	Refs.
trans stereochemistry in side chain R″;									
C-19393S_2	[76025-74-6]	$C_{14}H_{18}N_2O_9S_2$	SO_3H	CH_3	$OSCHCHNHCOCH_3$	0.21	0.00027	0.043	(76–80)
C-19393S_2M	[82795-81-1]	$C_{14}H_{18}N_2O_8S_2$	SO_3H	CH_3	$SCHCHNHCOCH_3$	2.4	0.025	0.0024	(76–78)
MM-4550	[76985-32-5]	$C_{13}H_{16}N_2O_9S_2$	SO_3H	H	$OSCHCHNHCOCH_3$	0.003	0.0004	0.001	(76, 81, 82)
MM-13902	[79057-46-8]	$C_{13}H_{16}N_2O_8S_2$	SO_3H	H	$SCHCHNHCOCH_3$	0.008	0.003	0.0001	(14, 76, 81–83)
C-19393H_2	[83916-44-3]	$C_{14}H_{18}N_2O_6S$	H	CH_3	$OSCHCHNHCOCH_3$	0.004	0.003	0.034	(76, 78–80)
C-19393H_2M_1	[82502-20-3]	$C_{14}H_{18}N_2O_6S$	H	CH_3	$SCHCHNHCOCH_3$	0.6	0.01	0.005	76
C-19393E_5	[83310-72-9]	$C_{13}H_{16}N_2O_6S$	H	H	$OSCHCHNHCOCH_3$	0.0003	0.027	0.015	(76, 84)
epithienamycin B (MM-22382)	[65376-20-7]	$C_{13}H_{16}N_2O_5S$	H	H	$SCHCHNHCOCH_3$	0.012	0.32	0.001	(14, 76, 83)
cis stereochemistry in side chain R″;									
	[83916-46-5]	$C_{14}H_{18}N_2O_6S$	H	CH_3	$OSCHCHNHCOCH_3$	0.59		0.014	79
	[83916-36-3]	$C_{14}H_{18}N_2O_9S_2$	SO_3H	CH_3	$OSCHCHNHCOCH_3$	0.24		0.0005	79
	[83916-40-9]	$C_{13}H_{16}N_2O_9S_2$	SO_3H	H	$OSCHCHNHCOCH_3$	0.003		0.0002	79
	[83916-39-6]	$C_{14}H_{18}N_2O_8S_2$	SO_3H	CH_3	$SCHCHNHCOCH_3$	1		0.004	79
	[83916-42-1]	$C_{13}H_{16}N_2O_8S_2$	SO_3H	H	$SCHCHNHCOCH_3$	0.014		0.004	(79, 85)
	[83916-38-5]	$C_{14}H_{18}N_2O_6S$	H	CH_3	$OSCHCHNHCOCH_3$	0.055		0.001	79
	[83916-41-0]	$C_{13}H_{16}N_2O_6S$	H	H	$OSCHCHNHCOCH_3$	0.0006		0.019	79
	[83916-37-4]	$C_{14}H_{18}N_2O_5S$	H	CH_3	$SCHCHNHCOCH_3$	0.36		0.017	79
	[75443-31-1]	$C_{13}H_{16}N_2O_5S$	H	H	$SCHCHNHCOCH_3$	0.065		1.5	79
no stereochemistry in side chain R″;									
C-19393S_2M_2	[82795-82-2]	$C_{14}H_{20}N_2O_8S_2$	SO_3H	CH_3	$SCH_2CH_2NHCOCH_3$	2.3	0.042	0.006	76
MM-17880	[79057-45-7]	$C_{13}H_{18}N_2O_8S_2$	SO_3H	H	$SCH_2CH_2NHCOCH_3$	0.021	0.005	0.0003	(76, 81, 82)
C-19393H_2M_3	[82889-91-6]	$C_{14}H_{20}N_2O_5S$	H	CH_3	$SCH_2CH_2NHCOCH_3$	0.56	0.0045	0.0054	76
epithienamycin A (MM-22380)	[63582-78-5]	$C_{13}H_{18}N_2O_5S$	H	H	$SCH_2CH_2NHCOCH_3$	0.037	0.69	0.003	76
pluracidomycin A (SF-2103A)	[82138-64-5]	$C_9H_{11}NO_1OS_2$	SO_3H	H	SO_3H	4	0.05	0.0015	(14, 86–88)
trans β-Lactam stereochemistry									
MM-22381	[96193-21-4]	$C_{14}H_{20}N_2O_5S$	H	CH_3	$SCH_2CH_2NHCOCH_3$	5[c]	0.03[c]	0.2	14
MM-22383	[65322-98-7]	$C_{13}H_{16}N_2O_5S$	H	H	$SCHCHNHCOCH_3$	0.04[c]	0.04[c]	10	14

[a] Structure (**21**) where R, R′, and R″ are as defined.
[b] The substrate is amicillin for penicillinases and cephalothin for cephases unless otherwise indicated.
[c] The substrate is nitrocefin.

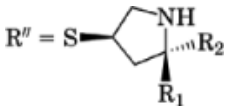
1.2.4. Penem B-Lactamase Inhibitors

The synthesis and antibacterial properties of penems, the trivial name for the 4-thia-1-azabicyclo[3.2.0]hept-2-ene ring system (**24**), have been reviewed (107, 108). Like the closely related carbapenems, many of the penems are potent antibacterials. Additionally, penems are also susceptible to degradation by renal dipeptidase, but to a lesser extent. The limited β-lactamase inhibitory data available for penems are presented in Table 4. SCH-29,482 [77646-83-4] (**24**, R = H, R′ = $CH(OH)CH_3$, R″ = SCH_2H_5), $C_{10}H_{13}NO_4S_2$, is reported to be an inhibitor of type I cephases and the OXA-2 enzyme (109). Compounds [101803-54-7] and [101914-68-5] (**24**, R = H, R′ = $CH_3CH(OH)$,

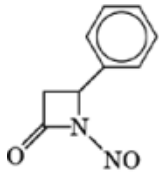


(26) (27) (28)

Fig. 3. Species in the inhibition pathway for sulbactam with β-lactamase.



and [130097-28-8] (**24**, R = R′ = R″ = CH_3) are also reported to inhibit cephase(I) and some TEM inhibition was reported for the first two. 6-Methylene-substituted penems ($R = R_1CH{=}$) are potent, better β-lactamase inhibitors than clavulanic acid, and many of the compounds are potent synergists. No data have been published on the mechanism of β-lactamase inhibition. Comparative data for [102209-75-6] the (*Z*)-isomer of



(11)

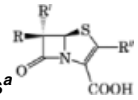
with other other β-lactamase inhibitors (113), and structure activity relationships have been reported (115).

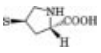
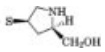
1.2.5. Penam Sulfone B-Lactamase Inhibitors

Natural product discoveries stimulated the rational design of β-lactamase inhibitors based on the readily accessible penicillin nucleus. An early success was penicillanic acid sulfone, (2(*S*)-cis)-3,3-dimethyl-7-oxo-4,4-dioxide-4-thia-1-azabicyclo [3.2.0]heptane-2-carboxylic acid [68373-14-8] (sulbactam) (**25**, R = R′ = H, R″ = R‴ = CH_3), $C_8H_{11}NO_5S$. The synthesis (118), microbiology (119–121), and clinical use (122–124) of sulbactam have been reviewed. Sulbactam, with minor exceptions, is a weak antibacterial, but is a potent irreversible inactivator of many β-lactamases including penases, and Richmond-Sykes type II,III,IV,V; VI(*Bacteroides*) β-lactamases. Sulbactam is better than clavulanic acid against type I cephases and synergy is observed for combinations of many penicillins and cephalosporins. Because sulbactam is not well absorbed orally, prodrug forms have been developed (125–129). Mechanism of action studies (26, 27), including labeling experiments, are consistent with formation of a thiazolidine opened acyl enzyme species 3 that tautomerizes to the transiently inhibited form 3. These intermediates, shown in Figure 3, can react further to give inactivated enzyme species such as 3.

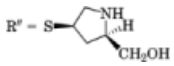
Numerous other penicillin sulfones have been reported to be β-lactamase inhibitors, as illustrated in Table 5. The effect of C-6 substituents has been extensively explored starting with 6-APA sulfone (**25**, R = NH_2, R′ = H, R″ = R‴ = CH_3), which has modest activity. Mechanistic considerations led to preparation of

Table 4. Activity of Penem B-Lactamase Inhibitors[a]



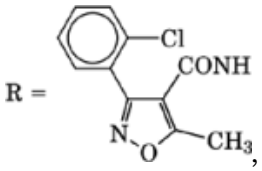
CAS Registry Number	Molecular formula	R	R′	R″	IC_{50}, μg/mL[b] Penase	TEM(III)	Cephase(I)	Refs.
[77646-83-4][c]	$C_{10}H_{13}NO_4S_2$	H	$CH_3CH(OH)$	SC_2H_5			inhib.	109
[101803-54-7]	$C_{13}H_{16}N_2O_6S_2$	H	$CH_3CH(OH)$		no	0.2–1.8[d]	0.07–0.25[d]	110
[101914-68-5]	$C_{13}H_{18}N_2O_5S_2$	H	$CH_3CH(OH)$					
[130097-28-8]	$C_9H_{11}NO_3S$	CH_3	CH_3	CH_3	no	no	inhib.	111
[81519-84-8]	$C_{10}H_9NO_4S$	$CH_3COCH=$	Z isomer	CH_3	claim broad spectrum			112
[102209-75-6]	$C_{10}H_8N_4O_3S$		Z isomer	H	0.016	0.002	0.002	(113, 115)
[81519-81-5]	$C_8H_7NO_3S$	$CH_3CH=$[e]	Z isomer	H	0.6	0.04	1	(115–117)
[128658-07-1]	$C_8H_7NO_3S$	$CH_3CH=$	E isomer	H	3.2	0.2	0.4	(115, 117)
[93853-93-0]	$C_{11}H_7NO_3S_2$	2 – thienyl – CH=[e]	Z isomer	H	0.4	0.008	0.02	116
[93853-93-1]	$C_{11}H_7NO_3S_2$	2 – thienyl – CH=	E isomer	H	>10	3.5	3	116
[93854-02-5]	$C_{11}H_7NO_3S_2$	3 – thienyl – CH=	Z isomer	H	0.012	0.13	0.003	(115, 116)
[93854-42-3]	$C_{11}H_7NO_4S$	2 – furyl – CH=	Z isomer	H	0.013	0.003	0.005	(115, 116)
[93853-72-6]	$C_{11}H_7NO_4S$	3 – furyl – CH=	Z isomer	H	0.4	0.1	0.025	116

[a] Structure (**24**) where R, R′, R″ are as defined.
[b] The substrate is nitrocefin.
[c] Compound SCH-29482.
[d] Data is from a series of compounds where substituents on R″ vary. Best compounds are the one shown and where

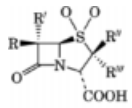


[e] Represents a series of compounds.

sulfones of poor substrates, compounds such as methicillin, cloxacillin, nafacillin, and quinacillin sulfone (**25**, R = an aromatic moiety, R′ = H, and R″ = R‴ = CH_3), which were expected to have a long-lived acyl enzyme species 3 that would react further to give inactivated enzyme. The compounds all act as β-lactamase inhibitors; but they are poor synergists. Aged solutions of cloxacillin sulfone, where

R =  ,

in phosphate buffer gave a product that inhibited *C. freundi* β-lactamase (153, 154). Both the C-6 phthalamido [82087-00-1] and sulfonamido [83053-95-6] compounds, for example, are reported to inhibit *B. cereus* β-lactamase through a conformational change in the enzyme (138).



(25)

Table 5. Activity of Penam Sulfone B-Lactamase Inhibitors[a]

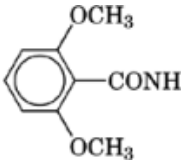
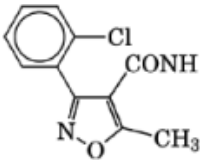
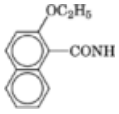
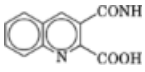
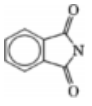
Compound	CAS Registry Number	Molecular formula	R	R″	IC$_{50}$, μg/mL[b,c] Penase	TEM(III)	Cephase(I)	Refs.
sulbactam	[68373-14-8]	$C_8H_{11}NO_5S$	H	CH_3	1.4	1.7	5	(118–120, 130–132)
6-APA sulfone	[36091-15-3]	$C_8H_{12}N_2O_5S$	NH_2	CH_3	0.4	40	50	13
methicillin sulfone	[76350-41-9]	$C_{17}H_{20}N_2O_8S$		CH_3	>50	16	20	(13, 33, 40)
cloxacillin sulfone	[76788-83-5]	$C_{19}H_{18}ClN_3O_7S$		CH_3	+	+	+	(133–135)
nafacillin sulfone	[77724-76-6]	$C_{25}H_{21}N_2O_7S$		CH_3		+		133
quinacillin sulfone	[76788-82-4]	$C_{19}H_{17}N_3O_8S$		CH_3	+	+		(126, 137)
	[82087-00-1]	$C_{16}H_{14}N_2O_7S$		CH_3	+			138

Table 5. ***Continued***

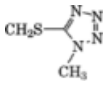
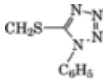
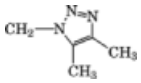
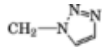
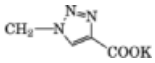
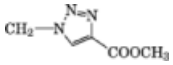
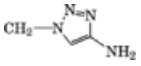
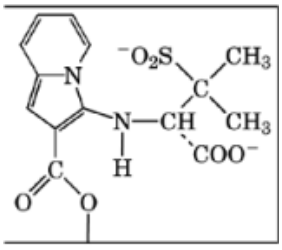
Compound	CAS Registry Number	Molecular formula	R	R″	IC_{50}, μg/mL[b,c] Penase	TEM(III)	Cephase(I)	Refs.
[d]	[83053-95-6]	$C_9H_{11}F_3N_2O_7S_2$	CF_3SO_2NH	CH_3	+	+		(137, 138)
	[76350-36-2]	$C_8H_{10}ClNO_5S$	H	CH_3	50	30	30	(13, 139)
[e]	[76613-60-8]	$C_8H_{10}ClNO_5S$	Cl	CH_3	50	13	>50	13
	[75527-87-6]	$C_8H_{10}BrNO_5S$	Br	CH_3	4	1.5	>50	13
[d, f]	[108636-76-6]	$C_{14}H_{14}N_2O_5S$	2-pyridyl-CH═	CH_3	+	+	+	(140, 141)
[f]	[110088-75-7]	$C_{12}H_{12}N_2O_5S_2$	2-thiazolyl-CH—	CH_3	+	0.0009[g]	+[g]	141
[f]	[123361-44-4]	$C_{11}H_{15}NO_5S$	CH_2CHCH_2	CH_3	claim broad spectrum[c]			142
	[78494-75-4]	$C_{15}H_{17}NO_6S$	$C_6H_5CH(OH)$	CH_3	no[g]		+[g]	142
	[76517-56-1]	$C_9H_{13}NO_6S$	$HOCH_2$	CH_3	+[g]	+[g]	+[g]	143
	[87579-77-9]	$C_8H_9NO_5S$	H	CH_2[h]	1.5	0.25	15.5	144
BLP-2013	[79886-07-0]	$C_8H_{10}ClNO_5S$	H	CH_2Cl	9.6	+		(45, 146, 147)
[i]	[115095-95-9]	$C_8H_{10}ClNO_5S$	H	CH_3	15.3[j]			146
	[95123-11-8]	$C_8H_{10}BrNO_5S$	H	CH_2Br	+[j]	+[j]		147
	[95123-10-7]	$C_8H_{11}NO_6S$	H	CH_2OH	no[j]	+[j]		147
[d]	[95123-06-1]	$C_{15}H_{15}NO_7S$	H	$CH_2OOCC_6H_5$	no[j]	+[j]		147
	[112110-80-2]	$C_9H_{10}N_2O_5S_2$	H	CH_2SCN	2.8[j]	+[j]	+[j]	148
	[89051-51-4]	$C_{10}H_{16}N_5O_5S_2$	H	CH_2N_3	1.1[j]			131
	[112110-81-3]	$C_{10}H_{16}N_5O_5S_2$	H		0.335[j]			148
	[112110-83-5]	$C_{15}H_{15}N_5O_5S_2$	H		0.354[j]			148
[d]	[98382-76-4]	$C_{12}H_{16}N_4O_5S$	H		0.026[j]			149
tazobactam	[89786-04-9]	$C_{10}H_{12}N_4O_5S$	H		0.27	0.04[j]	0.93	(131, 148, 150–152)
[d]	[89785-79-5]	$C_{11}H_{11}N_4O_7SK$	H		0.23[j]			131
	[89786-01-6]	$C_{12}H_{14}N_4O_7S$	H		0.018[f]			131

Table 5. ***Continued***

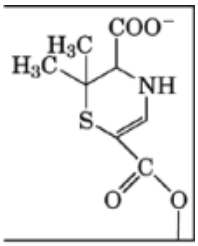
Compound	CAS Registry Number	Molecular formula	R	R″	IC_{50}, μg/mL[b,c] Penase	TEM(III)	Cephase(I)	Refs.
	[98382-75-3]	$C_{10}H_{13}N_5O_5S$	H		0.22[f]			131

[a]Structure (**25**) where R, R″ are as defined, and $R' = H$ and $R''' = CH_3$ unless otherwise indicated.
[b]Substrate is nitrocefin unless otherwise indicated.
[c]+ Indicates enzyme inhibition, but no available IC_{50} data.
[d]Represents series of compounds.
[e]$R' = Cl$.
[f]$R' = (Z) - \text{isomer}$.
[g]Substrate is ampicillin.
[h]Cyclopropane ring bonded also to C-2.
[i]$R''' = CH_2Cl$.
[j]Substrate is ampicillin.

C-6 halo-substituted sulfones (**25**, $R =$ H, Cl or Br, $R' =$ Cl or H, $R'' = R''' = CH_3$) have been shown to be weak β-lactamase inhibitors and a series of C-6-heteroarylmethylene derivatives, where $R =$ 2-pyridyl-CH or 2-thiazoyl-CH, are potent suicide β-lactamase inhibitors and synergists that are superior to clavulanic acid. Structure activity relationships are discussed in the literature (141) and based on reactions with methanol, used to mimic the serine hydroxyl of β-lactamases, the acyl enzyme species (**29**) has been suggested as being responsible for inactivation of the enzyme, at least for the $R =$ 2-pyridyl-CH series. Compounds having a leaving group such as acetoxy or fluoro, which can undergo elimination to form the 6-thiazolyl methylene penam sulfone have been reported to be β-lactamase inhibitors and synergists (155). The allyl sulfone (**25**, $R = CH_2CHCH_2$, $R' = H$, $R'' = R''' = CH_3$) was reported to be a potent β-lactamase inhibitor, although no IC_{50} was provided (142). The C-6 hydroxyalkyl sulfones (**25**, $R = C_6H_5CHOH$ or $HOCH_2$, $R' = H$, $R'' = R''' = CH_3$) have been reported as β-lactamase inhibitors. The compound where $R = C_6H_5CHOH$ was primarily active against cephase(I), but the simpler species, $R = HOCH_2$, is reported to be a broad spectrum inhibitor and synergist.

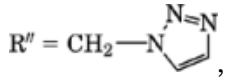


(**29**)



(**30**)

Substitution of the β-methyl group of penicillanic acid sulfone has also been extensively investigated. The cyclopropyl sulfone (**25**, $R = R' = H$, $R'' = CH_2$, $R''' = CH_3$) resembles sulbactam, but is overall a weaker inhibitor. BLP-2013 (**25**, $R = R' = H$, $R'' = CH_2Cl$, $R''' = CH_3$) has activity similar to that of sulbactam (145, 147). The α-chloromethyl analogue (**25**, $R = R' = H$, $R'' = CH_3$, $R''' = CH_2Cl$) is less active. Potent activity has been demonstrated for a series of heteroaryl-substituted methyl sulfones. The compound most studied is tazobactam (YTR-830) (**25**, $R = R' = H$,

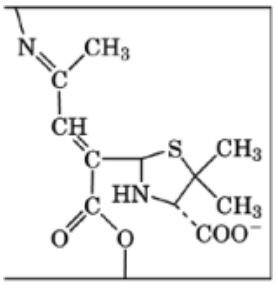


$R''' = CH_3$) which has activity similar to that of clavulanic acid and inhibits many of the type I cephases. The synthesis (156), microbiological activity (152, 156–162), and stability (152) of tazobactam have been reported.

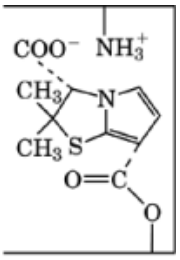
1.2.6. Penam β-Lactamase Inhibitors

Penam is the trivial name given derivatives of the penicillin nucleus (**31**) the chemical name of which is 4-thia-1-azabicyclo[3.2.0]heptane. Table 6 gives activity data for a diverse group of penams. The report that 6-β-bromopenicillanic acid [26631-90-3], [2(*S*)-(2α,5α,6β)]-6-bromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, (**31**, $R = Br$, $R' = H$, $R'' = R''' = CH_3$) is a potent inhibitor led to intense study both of this compound and analogues. The microbiology profile of 6-β-bromopenicillanic acid has been reported (165) and the compound has progressed to clinical trials (6). Mechanistic studies have demonstrated that the dihydrothiazine derivative (30) is responsible for inactivation of β-lactamases (6, 26, 27). The iodo analogue of the bromopenicillinic acid (**31**, $R = I$, $R' = H$, $R'' = R''' = CH_3$) has comparable activity, but the chloro compound (**31**, $R = Cl$, $R' = H$, $R'' = R''' = CH_3$) is substantially less active. Mutual prodrugs of the 6-β-bromo and 6-β-iodo compounds with ampicillin have been reported (189). Analogues of 6-β-bromopenicillanic acid having a substituent in the β-methyl position have been explored, (**31**, $R = Br$, $R' = H$, $R'' = CH_2F$, $R''' = CH_3$) is an example, and in general offer no advantages.

The (*Z*)-isomer f 6-acetylmethylene penicillanic acid, RO 15-1903 [83116-77-2] (**31**, $R = CH_3COCH$, (*Z*)-isomer, $R'' = R''' = CH_3$), [2(*S*)-(2α,5α,6(*Z*))]-3,3-dimethyl-7-oxo-6-(2-oxo-propylidene)-4-thia-1-azabicyclo [3.2.0]-heptane-2-carboxylic acid, has been reported to be a more potent β-lactamase inhibitor than clavulanic acid. Despite excellent β-lactamase inhibition, the compound gave poorer than expected *in vitro* and *in vivo* synergy results (172, 173). This was subsequently attributed to poor uptake of drug by bacteria (172) and instability in serum (177). Mechanistic studies with the TEM enzyme indicate that one molecule of compound inactivates one molecule of enzyme. There is essentially no turnover as substrate. Four inactivated forms of the β-lactamase enzyme have been detected in inhibition studies using RO 15-1903. Structures (**32**) and (**33**) have been implicated in this inactivation. The corresponding (*E*)-isomer (**31**, $R = CH_3COCH$ = (*E*)-isomer, $R'' = R''' = CH_3$) and the related structures, (*Z*)-isomers where $R = CH_3SO_2CH$ or $C_6H_5SO_2CH$, are less potent.



(32)



(33)

The 6-methoxymethylene penicillanic acid [93040-42-7] (**31**, R = CH_3OCH_1 (Z)-isomer, R″ = R‴ = CH_3) was designed to mimic the aminoacrylate species found using clavulanic acid and sulbactam. Upon the reaction of this compound with the enzyme, the potential exists for further Michael addition to inactivate the enzyme. The compound is indeed a β-lactamase inhibitor but no synergy data have been reported. The related imine structure [73707-58-1], R = *p*-$CH_3C_6H_5N$, (Z)-isomer, has also been reported to inhibit type I cephases. The 6-β-[bistrifluoromethane sulfonyl] amidopenicillanic acid [82954-44-7] (**31**, R = $(CF_3SO_2)_2N$), R′ = H, R″ = R‴ = CH_3) was speculated to inhibit the penase from *B. cereus* by triflation or generation of an imine that reacts further with the enzyme. Several C-6 substituted amino penams have been reported to inhibit type I cephases; the complex hydroxyalkyl penicillanic acid derivatives are reported to be potent β-lactamase inhibitors and synergists. In combination with amoxicillin, compound (**31**, R = 1-naphthylCOCH(OH), R′ = H, R″ = R‴ = CH_3) protected animals from infection. Synergy has been reported for the usual penam structures where R involves a 2-naphthylsulfoxide or a 2-naphthylphosphate against a β-lactamase producing strain of *Kleosiella*. An unusual series of ferrocenyl penicillins (190) were reported to inhibit β-lactamases.

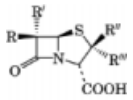
1.2.7. Other Unusual β-Lactam Based Inhibitors

There are a number of other unusual β-lactams reported to have β-lactamase inhibition activity (191–194). In general these compounds are not very potent and are not irreversible inhibitors. Data are also very limited.

1.3. Economic Aspects

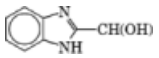
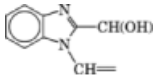
Although a broad range of β-lactamase inhibitors has been discovered, only clavulanic acid and sulbactam have been commercialized. Clavulanic acid (**12**, R = CH_2OH, R′ = H), manufactured by SmithKline Beecham, is sold as an oral and parenteral product in combination with amoxicillin under the trade name Augmentin. A parenteral product in combination with ticarcillin [34787-01-4], $C_{15}H_{16}N_2O_6S$, has the trade name, Timentin. In 1990 worldwide sales of clavulanic acid containing products were about $725 million.

Sulbactam (**25**, R = R′ = H, R″ = R‴ = CH_3) is produced by Pfizer. The oral version of sulbactam in combination with ampicillin is called Unasyn Oral which is the mutual prodrug sultamicillin. Two sulbactam



(31)

Table 6. Activity of Penam-Based β-Lactamase Inhibitors[a]

CAS Registry Number	Molecular formula	R	R′	R″	R‴	IC_{50}, μg/mL[b]			Refs.
						Penase	TEM(III)	Cephase(I)	
[26631-90-3]	$C_8H_{10}BrNO_3S$	Br	H	CH_3	CH_3	1.5/0.005[c]	1.5/0.005[c]	1.5/0.32[c]	(13, 163–168)
[74772-32-0]	$C_8H_{10}INO_3S$	I	H	CH_3	CH_3	0.7	0.06	5.5	(13, 164, 165)
[74326-78-6]	$C_8H_{10}ClNO_3S$	Cl	H	CH_3	CH_3	0.3	50	50	(13, 163, 164, 167, 169, 170)
[108934-65-2]	$C_8H_9BrFNO_3S$	Br	H	CH_2F	CH_3		0.13	0.2	168
[108934-66-3]	$C_8H_9BrN_4O_3S$	Br	H	CH_2N_3	CH_3	0.2	0.04	8.1	168
[105433-74-7]	$C_{10}H_{12}BrNO_3S$	Br	H	$CH_2O_2CCH_3$	CH_3	3.2	0.4	50	168
[105433-78-1]	$C_9H_{12}BrNO_4S$	Br	H	CH_2OCH_3	CH_3	1.3	0.2	6.3	168
[108934-67-4]	$C_{10}H_{14}BrNO_4S$	Br	H	$CH_2OC_2H_5$	CH_3	3.2	0.4	50	168
[105458-19-3]	$C_9H_9BrN_2O_3S_2$	Br	H	CH_2SCN	CH_3	0.4	0.03	50	168
[83116-77-2][g]	$C_{11}H_{13}NO_4S$	CH_3COCH=	Z isomer	CH_3	CH_3	0.00015	0.0002	1.2	(171–177)
[83116-56-7]	$C_{11}H_{13}NO_4S$	CH_3COCH=	E isomer	CH_3	CH_3		0.002	0.012	171
[104127-98-2]	$C_{10}H_{13}NO_5S_2$	CH_3SO_2CH=	Z isomer	CH_3	CH_3	+[d]		+[d]	178
[1041127-97-1]	$C_{15}H_{15}NO_5S_2$	$C_6H_5SO_2CH$=	Z isomer	CH_3	CH_3	+[d]		+[d]	178
[86492-69-5]	$C_{11}H_{14}N_2O_4S$	$CH_3CN(OH)CH$=	Z isomer	CH_3	CH_3		0.2[e]		176
[93040-42-7]	$C_{10}H_{13}NO_4S$	CH_3OCH=	Z isomer	CH_3	CH_3		+[d]		(179, 180)
[73707-58-1]	$C_{15}H_{16}N_2O_3S_2$	*p*-CH_3-C_6H_5S-N=	Z isomer	CH_3	CH_3			0.5	181
[82954-44-7]	$C_{10}H_{10}F_6N_2O_7S_3$	$(CF_3SO_2)_2N$	H	CH_3	CH_3	+[d]			182
[83670-99-9]	$C_8H_{12}N_2O_6S_2$	HO_3SNH	H	CH_3	CH_3			+[d]	183
[89012-63-5]	$C_{12}H_{18}N_2O_5S$	$C_2H_5O_2CCH_2NH$	H	CH_3	CH_3	no[f]	no[f]	0.25[f]	184
[89012-69-1]	$C_{12}H_{20}N_2O_4S$	$CH_3CH(OH)(CH_2)_2NH$	H	CH_3	CH_3	no	no	0.32	184
[89012-67-9]	$C_{12}H_{18}N_2O_4S$	$CH_3CO(CH_2)_2NH$	H	CH_3	CH_3	no	no	0.40	184
[118499-99-3]	$C_{16}H_{17}N_3O_4S$		H	CH_3	CH_3				185
[118498-71-8]	$C_{18}H_{19}N_3O_4S$		H	CH_3	CH_3				185
[113656-11-4]	$C_{17}H_{19}NO_5S$	$C_6H_5CH_2COCH(OH)$	H	CH_3	CH_3	+[f]	+[f]		186
[113656-13-6]	$C_{16}H_{17}NO_5S$	$C_6H_5COCH(OH)$	H	CH_3	CH_3	+	+		186
[109990-44-5]	$C_{20}H_{19}NO_5S$	1-naphthylCOCH(OH)	H	CH_3	CH_3	+	+	+	187
[94723-14-5]	$C_{18}H_{17}NO_6S_2$	2-naphthylSO_2O[f]	H	CH_3	CH_3				188
[94723-16-7]	$C_{24}H_{22}NO_6PS$	2-naphthylOP(C_6H_5)O_2	H	CH_3	CH_3				188
[94723-39-4]	$C_9H_{11}NO_4S$	epoxide		CH_3	CH_3				188
[49628-20-8]	$C_{17}H_{19}NO_5S$	$C_6H_5OCH_2COCH_2$	H	CH_3	CH_3				188

[a] Structure (**30**) where R, R′, R″, and R‴ are defined as indicated.
[b] The substrate is nitrocefin unless otherwise indicated.
[c] These data correspond to set of β-methyl analogues.
[d] Compound is active but no IC_{50} data are available.
[e] Substrate is penicillin G.
[f] Represents a series of compounds.
[g] Compound Ro 15-1903.

parenteral products are sold, a combination product with ampicillin called Unasyn and a combination with cefoperazone [62893-19-0] called Sulperazon. In addition, sulbactam is sold alone for parenteral use with any β-lactam antibiotic as Betamaze. In 1990 worldwide sales of sulbactam containing products were over $280 million.

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