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Original paper

Synthesis and biological evaluation of new C (4) heterofunctionalized monocyclic β-lactams derived from penicillin G

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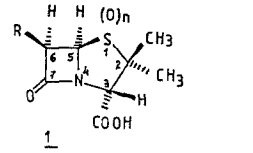
Summary — A simple and practical methodology has been developed for the preparation of monocyclic β-lactams **6** derived from penicillin G, possessing a thiocarbonyl **(6a)** or a sulfonyl **(6b)** substituent at C(4) as potentially good leaving groups. Two phthalidyl ester pro-drugs, **34f** (L = SO_2CH_2Ph) and **40f** (L = SO_2CH_2COOH), exhibited very weak antibacterial properties *in vitro*. However, no activity as β-lactamase inhibitors was detected for the two families of **6**.

Résumé — **Synthèse et évaluation biologique de nouveaux β-lactames monocycliques hétérofonctionnalisés en C(4), dérivés de la pénicilline G.** *Une méthode simple et efficace a été développée pour la préparation de β-lactames monocycliques* **6** *dérivés de la pénicilline G, possédant en C(4) un substituant thioacétyle* ***(6a)*** *ou sulfonyle* ***(6b)*** *en tant que groupes nucléofuges potentiels. Deux esters biodégradables phthalidyles,* ***34f*** *(L = SO_2CH_2Ph) et* ***40f*** *(L = SO_2CH_2COOH), ont manifesté une faible activité antibiotique* in vitro. *Aucune inhibition de β-lactamases n'a été observée dans les deux familles de composés.*

antibiotic / monocyclic β-lactam / penem / sulfone / suicide-inhibition

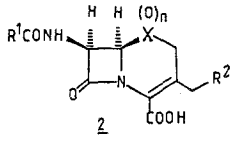
Introduction

Penicillins **1a** and cephalosporins **2a**, the most popular drugs (for a review, see [1]) for the treatment of infections, are powerful inhibitors of the bacterial cell-wall D-D-peptidases (for a review, see [2]). They are characterized by a number of common structural features: a β-lactam ring bearing an acylamino side chain, fused with a sulfur containing heterocycle possessing an acidic residue. Recently, other related classes of interesting active bicyclic β-lactams have been discovered or synthetized, for instance, the carbapenems (thienamycin **3** [3]), the penems **4a** [4—11] and the 1-oxacephems **2d** [12, 13]. However, some monocyclic β-lactams also exhibit excellent bactericidal properties, as illustrated by the naturally occurring nocardicins **5a** [14] and monobactams **5b** [15] and the synthetic oxamazins **5c** [16]. This last discovery stimulated a growing interest in the preparation of new functionalized monocyclic β-



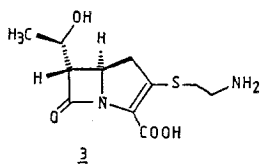
1

1a R = R^1CONH, n = 0
b R = R^1CONH, n = 1
c R = R^1CONH, n = 2
d R = H, n = 2

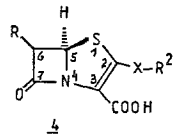


2

2a X = S, n = 0
b X = S, n = 1
c X = S, n = 2
d X = O, n = 0



3
(thienamycin)

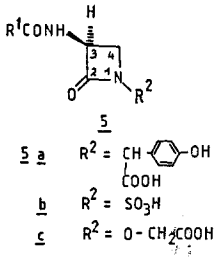


4

4a R = $CH_3(OH)CH$—, X = S, O
b R = R^1CONH—, X = S, O, NR

**Author to whom correspondence should be addressed.*
Abbreviations: **ALL:** allyl; **PNB:** *para*-nitrobenzyl; **TCE:** trichloroethyl; **PIV:** pivaloyloxymethyl; **TAL:** phthalidyl; **G:** phenylacetamido side chain; **DMF:** dimethylformamide; **MCPBA:** *meta*-chloroperbenzoic acid; **eq:** equivalent; **cpd:** compound; **sh:** sharp; **br:** broad.

lactams as potential antibiotics. The chemical activation, necessary for biological activity [17], is usually obtained by placing different electron-withdrawing functional groups at the N(1) position [17—26]. Less attention has been devoted to the C(4) substituents. We therefore decided to investigate a series of chiral monocyclic β-lactams **6** bearing the appendages required for the enzymatic recognition at C(3) and N(1) and, moreover, possessing a heterofunctionalized group at C(4) in the *cis*-stereochemical relationship with regard to the C(3) side chain. This last functional group was designed to play an important role, not only as an electron-withdrawing—activating substituent, but moreover as a potential nucleofugal moiety. Indeed, the general structure **6** could represent the simplest model for a suicide-type inhibition of the bacterial D-D-peptidases (serine enzymes [2]), following the mechanism outlined in Scheme 1 and related to that of the classical β-lactamase inhibitors [27—28].

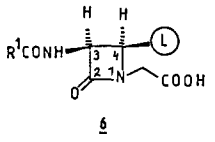


5

5a R^2 = CH(COOH)-C$_6$H$_4$-OH

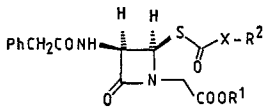
b $R^2 = SO_3H$

c R^2 = O-CH_2COOH



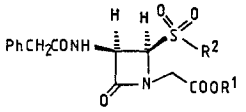
6

L = leaving group



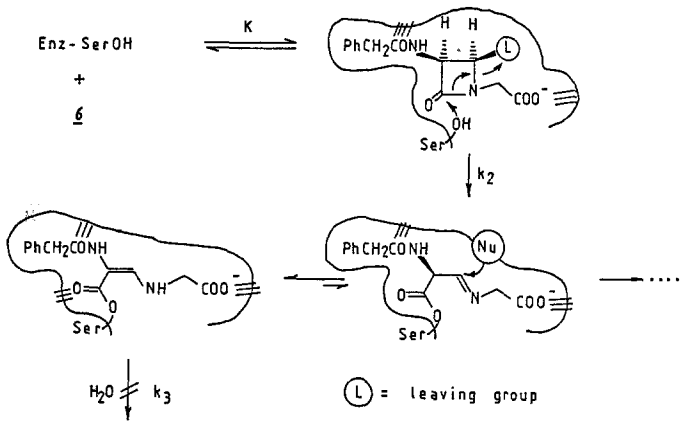
6a

(X = O, S, NR)



6b

In this paper, we report the preparation and biological evaluation of two classes of compounds **6**, the thiocarbonyl-**6a** and the sulfonyl derivatives **6b**. The former can be considered as unstrained topological analogues of the C(2) heterosubstituted penems **4b** [29—32], in which the presence of an acylamino residue at C(6) dramatically enhances the chemical instability [33, 34], reducing their potential therapeutic applications. All the important pharmacophoric groups are maintained if one replaces the endocyclic (C2)—C(3) double bond in **4b** by an exocyclic carbonyl bond in **6a**, but the bicyclic strain is obviously lost. In the second class of compounds **6b**, the sulfur atom at C(4) has been oxidized. It is known that such an oxidation in penam or cephem derivatives can provide new biologically active materials. For instance, sulbactam **1d** [35] is a weak antibiotic but a powerful β-lactamase inhibitor. Some sulfones **1c** derived from penicillins are also active [36] against β-lactamases, whereas the *(R)*-sulfoxide **1b** of hetacillin [37] is reported to behave as an antibiotic. Similarly, the *(R)*- and *(S)*-sulfoxides **2b** [38, 39] and the sulfone



Scheme 1.

2c [39] derived from some cephalosporins exhibit good anti-bacterial properties.

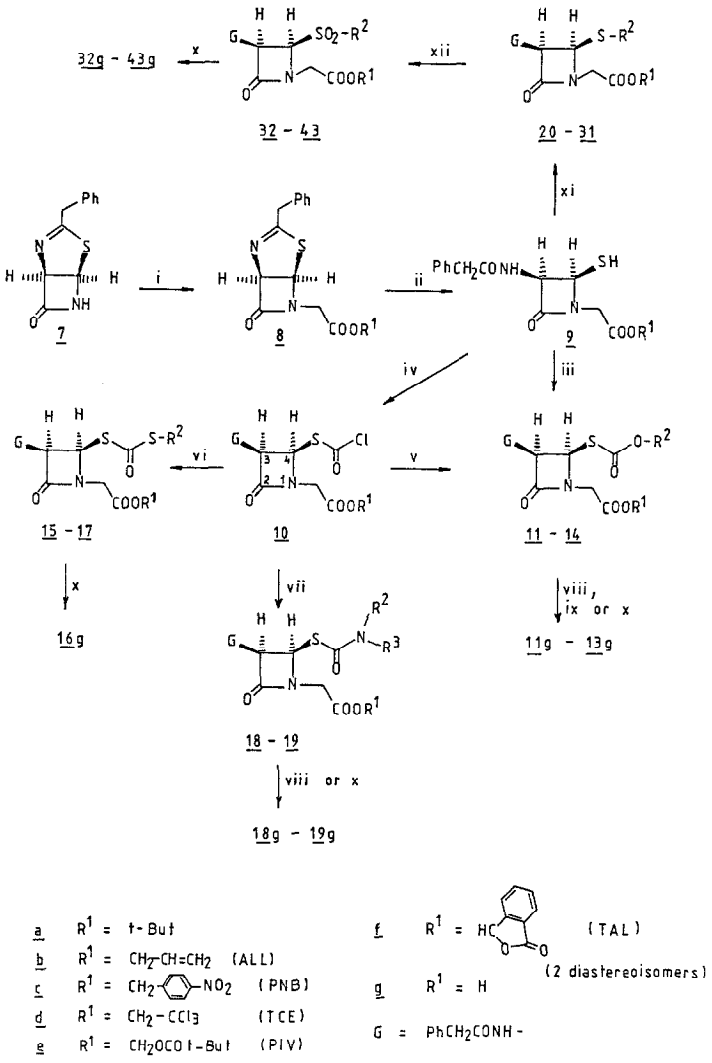
As a synthetic strategy, we planned to use penicillin G (**1a**, $R^1 = PhCH_2$) as a cheap and optically active starting material for the preparation of the β-lactams **6a, b**. Indeed, selective transformations of the thiazolidine ring can be achieved without destruction of the β-lactam moiety or alteration of the C(5)—C(6) stereochemistry.

Chemistry and Results

The thiazoline-azetidinone **7** (Scheme 2) is a useful chiral synthon derived from natural penicillin G by way of well-established methodologies [40—44]. Its *N*-alkylation with bromoacetic acid derivatives, leading to a variety of β-lactams **8**, has already been described [30]. Mild acid hydrolysis of **8** liberated the G side chain and the thiol group to furnish the compounds **9** as common precursors for the two families **6a** and **6b** (Scheme 2). Indeed, the thiol function could be readily acylated. For instance, reaction with ethylchloroformate [45], in the presence of triethylamine, gave the thiocarbonates **11** in good yield (Table I; **6a**, X = O). Attempts to deprotect the *t*-butyl ester **11a** under standard conditions [46] failed, giving rise to degradation of the small ring. The allyl ester **11b** could be cleaved [47] in the presence of Pd°—triphenylphosphine complex and 2-ethylhexanoic acid (or its K^+ salt). However, we were unable to extract pure acid **11g** from the reaction mixture. Hydrogenolysis of the *p*-nitrobenzyl ester **11c** with palladium on charcoal [33] gave the acid **11g** in moderate yield and required large amounts of catalyst. Finally, deprotection of the trichloroethyl ester **11d** with zinc dust in acetic acid and dimethylformamide [48] was found to be the best method for producing the expected acid **11g** with good yield and reasonable purity as ascertained from the ^1H NMR analysis (see Experimental protocols).

Similarly, acylation of the thiol **9** with benzylchloroformate produced the thiocarbonates **12** (Table I). Once again, the free acid was more conveniently prepared from the TCE ester **12d** than from the ALL ester **12b**.

The synthesis of more complex derivatives required the development of a new class of key-intermediates, the 4-



Scheme 2. Synthesis of the C(4)thiofunctionalized β-lactams **6**. Conditions and reagents: i: see [30]; ii: 1 N HCl, DMF, 0—20°C, 1 h; iii: $ClCOOR^2$ (1 eq), Et_3N (1 eq), CH_2Cl_2, —60—20°C; iv: $COCl_2$ (1 eq), Et_3N (1 eq), CH_2Cl_2, —60—20°C; v: R^2OH (1 eq), Et_3N (1 eq), CH_2Cl_2, —60—20°C; vi: R^2SH (1 eq), Et_3N (1 eq), CH_2Cl_2, —60—20°C; vii: R^2R^3NH (2 or 1 eq), Et_3N (0 or 1 eq), CH_2Cl_2, —60—20°C; viii: R^1 = ALL: Pd^0 $(Ph_3P)_4$, 2-ethylhexanoic acid, 20°C; ix: R^1 = PNB: H_2, Pd-C, 20°C; x: R^1 = TCE: Zn, HOAc-DMF, 0°C; xi: R^2-X (1—10 eq), Et_3N (1 eq), DMF, 0—20°C; xii: MCPBA (2—3 eq), CH_2Cl_2, 0—20°C.

thiochlorocarbonyl azetidinones **10**. These were easily prepared [49] by acylation of the thiols **9** with phosgene (Scheme 2). Reaction of **10** with *m*-acetamidophenol or 2-(α-pyridyl)ethanol afforded the thiocarbonates **13** and **14**, respectively, (Table I). From a practical point of view, it was not necessary to isolate the reactive intermediates **10**. Successive treatment of the thiols **9** with equimolar amounts of phosgene and triethylamine, followed by the appropriate alcohol and triethylamine, in a one-pot process, gave the 4-thiocarbonate azetidinones in moderate yield. Deprotection of the TCE esters furnished the acids **13g** and **14g**, of which the latter was found to be slightly stable.

The two other types of 4-thiofunctionalized β-lactams, the dithiocarbonates (Table I; **6a**, X = S) and the thiocarbamates (Table I; **6a**, X = NR), were prepared from the same key synthons **10**, using α-pyridylthiol **(15)**, *p*-methoxybenzylthiol **(16)** or methyl thiolacetate **(17)** as nucleophiles, on the one hand, and diethylamine **(18)** or β-phenylethylamine **(19)**, on the other. In all cases, reaction of the TCE esters with zinc was the best way to furnish the corresponding free acids.

Several attempts to react isolated **10a** with bifunctional nucleophiles (*N*-(diethyl)ethylamine, ethanolamine, *o*-aminophenol, *m*-aminophenol, *p*-aminopyridine and 3-aminotriazole) gave untractable complex mixtures.

The direct precursors of the second class of target molecules, the sulfones **6b**, were obtained by alkylation of the thiols **9** (Scheme 2). Only a few examples of alkylation of a thiol function on β-lactam derivatives have been described in the literature [50—53]. We found that this reaction could be realized at 0°C or room temperature, with a variety of functionalized alkylhalides in dimethylformamide, as a polar solvent, and in the presence of triethylamine.

Table I. Yields of the C(4)thiocarbonyl β-lactams **6a**.

X-R^2	R^1	method (scheme 2)	cpd	yield(%)
O-C_2H_5	t-But	iii	11a	64[b]
	ALL	iii	11b	73[a]
	PNB	iii	11c	93[b]
	TCE	iii	11d	82[b]
	PIV	iii	11e	79[a]
	TAL	iii	11f	71[b]
	H	viii,ix,x	11g	72[c],58[b],83[b]
O-CH_2-Ph	ALL	iii	12b	79[a]
	TCE	iii	12d	86[b]
	PIV	iii	12e	77[a]
	TAL	iii	12f	89[b]
	H	viii,x	12g	74[c],82[b]
O-(NHAc)	TCE	iv+v	13d	31[a]
	TAL	iv+v	13f	67[b]
	H	x	13g	42[b]
O-$(CH_2)_2$-(N)	TCE	iv+v	14d	47[a]
	TAL	iv+v	14f	30[a]
S-(N)	TCE	iv+vi	15d	38[a]
	TAL	iv+vi	15f	40[a]
	H	x	15g	28[b]
S-CH_2-(p-OCH_3)	TCE	iv+vi	16d	59[a]
	TAL	iv+vi	16f	66[b]
	H	x	16g	65[b]
S-CH_2COOCH_3	TAL	iv+vi	17f	26[a]
$N(C_2H_5)_2$	ALL	iv+vii	18b	56[a]
	TCE	iv+vii	18d	52[a]
	TAL	iv+vii	18f	67[b]
	H	viii,x	18g	64[c],76[b]
NH$(CH_2)_2$-Ph	TCE	iv+vii	19d	33[a]
	H	x	19g	56[b]

[a]After chromatography on silica gel.
[b]After precipitation from ether or CH_2Cl_2—ether.
[c]Impure crude product.

The yields of pure isolated products **20**—**31** were moderate to good (Table II). Treatment of the sulfide precursors with a slight excess ($\geqslant$2 eq) of *m*-chloroperbenzoic acid in dichloromethane, at room temperature, afforded the corresponding sulfones **32**—**43** (Table II), which were separated from the *m*-chlorobenzoic acid by washing with bicarbonate solution and chromatography on silica gel or by fractional crystallization from ether. In one case (**40d**, $R^2 = CH_2COOH$), we were unable to achieve this last purification. All the protected sulfones ($R^1 \neq H$) are stable compounds, except the cyanomethyl derivative **43f** which decomposes slowly at room temperature.

The chemical cleavage of the trichloroethyl ester on the N(1) acetyl chain was achieved by treatment with zinc. Under these experimental conditions, the nitro group on the compound **35d** was also reduced and hence the *p*-aminobenzyl sulfone **35g'** ($R^2 = CH_2—C_6H_4—NH_2$) was recovered. In the case of **39d** ($R^2 = CH_2—COOTCE$), cleavage of the two ester functions furnished the acid **40g** ($R^2 = CH_2—COOH$) which was not directly accessible from **40d**. In one case (**42g**, $R^2 = CH_2—CONH_2$), the final deprotection led to some degradation of the β-lactam ring.

All the new compounds prepared were optically active materials possessing the penicillin's *cis*-relationship between the protons on the β-lactam ring as shown by the value of their coupling constant in the ^1H NMR spectra (J = 4—5 Hz, see Experimental protocols). Moreover, the high frequency stretching absorption of the β-lactam carbonyl, near 1785 cm^{-1} for **6a** and 1800 cm^{-1} for **6b**, in the IR spectra was similar to the values found in the penam or penem families.

The free acids and the biodegradable pivaloyloxymethyl (PIV) and phthalidyl (TAL) esters [54] were tested for biological activity against representative Gram-positive and Gram-negative bacterial strains. The acids **11g**—**13g**, **15g**—**16g**, **18g**—**19g**, **32g**—**43g** and the esters **11e**—**12e**, **11f**—**18f**, **32f**, **35f**—**38f**, **41f**—**43f**, did not show any significant bacteriostatic activity, even at high concentrations (100—200 μM). Two pro-drugs exhibited a very weak anti-bacterial effect: **34f** ($L = SO_2CH_2Ph$) was found to be active against *Staphylococcus aureus* (*MIC*: 150 μM; *MBC*: 200 μM) and *Streptococcus pyogenes* (*MIC*: 75 μM; *MBC*: 150 μM) and **40f** ($L = SO_2CH_2COOH$) against *S. aureus* (*MIC*: 100 μM; *MBC*: 100 μM). We have also established that their sulfide precursors **22f** ($L = SCH_2Ph$) and **28f** ($L = SCH_2COOH$) are devoid of anti-bacterial properties.

Since we had a series of new functionalized β-lactams on hand, it was of interest to test these compounds for activity as β-lactamase inhibitors. The acids **11g**—**13g**, **16g**, **18g**—**19g**, **34g**—**38g**, **40g**—**41g**, **43g** and the esters **11e**—**12e**, **34f**, **40f** were thus evaluated against three representative β-lactamases, one of each class A, B and C. No activity was detected at final concentrations of up to 100 μM.

Table II. Yields of the C(4)thioalkyl precursors and the C(4)sulphonyl β-lactams **6b**.

R^2	R^1	sulphides		sulphones	
		cpd	%	cpd	%
CH_3	TCE	20d	63[a]	32d	84[b]
	TAL	20f	79[b]	32f	86[b]
	H			32g	57[b]
nC_3H_7	TCE	21d	38[a]	33d	59[a]
	TAL	21f	10[a]		
	H			33g	68[b]
CH_2-Ph	TCE	22d	75[a]	34d	89[a]
	TAL	22f	77[b]	34f	92[b]
	H			34g	60[b]
CH_2-Ph-NO_2	TCE	23d	55[a]	35d	78[b]
	TAL	23f	75[b]	35f	79[b]
	H			35g'	82[b,d]
CH_2-CH=CH_2	TCE	24d	60[a]	36d	56[a]
	TAL	24f	43[a]	36f	93[b]
	H			36g	53[b]
CH_2-C≡CH	TCE	25d	73[a]	37d	76[a]
	TAL	25f	77[b]	37f	95[b]
	H			37g	71[b]
CH_2-$COOC_2H_5$	TCE	26d	65[a]	38d	73[a]
	TAL	26f	73[b]	38f	86[b]
	H			38g	63[b]
CH_2-COOTCE	TCE	27d	29[a]	39d	82[a]
	H			40g[c]	82[b]
CH_2-COOH	TCE	28d	81[b]	40d	not isolated
	TAL	28f	90[b]	40f	84[b]
CH_2-$CONH(CH_2)_2$-Ph	TCE	29d	79[b]	41d	83[b]
	TAL	29f	85[b]	41f	95[b]
	H			41g	82[b]
CH_2-$CONH_2$	TCE	30d	71[b]	42d	81[a]
	TAL	30f	80[b]	42f	81[b]
	H			42g	degradation
CH_2-C≡N	TCE	31d	82[b]	43d	79[a]
	TAL	31f	92[b]	43f	83[b,e]
	H			43g	67[b]

[a]After chromatography on silica gel.
[b]After precipitation from ether.
[c]Deprotection of the two TCE ester functions.
[d]Reduction of the nitro group; $R^2 = CH_2—C_6H_4—NH_2$.
[e]Impure material.

Conclusion

A simple and practical synthetic scheme has allowed the preparation of a series of monocyclic β-lactams **6**, functionalized at N(1) by an acetyl residue and at C(3) and C(4), respectively, by an acylamino side chain and a thiocarbonyl or sulfonyl moiety in a *cis*-stereochemical relationship. Thus, these compounds possess the minimum basic structural features of penicillins **1a** and cephalosporins **2a**, combined with the presence of a potentially good nucleofugal group at C(4) resulting from the acylation or oxidation of the sulfur atom. This latter substituent was designed to allow irreversible inhibition of the target enzymes of the classical bicyclic β-lactam antibiotics and, hence, to confer improved antibiotic properties on the monocyclic β-lactams **6**. Obviously, this assumption assumes that the enzymatic recognition process is similar for both **6** and the bicyclic β-lactams.

As expected, the compounds in the first class **6a** (L = $SCOXR^2$) are more stable than their corresponding bicyclic topological analogues, the penems **4b**. Indeed, we were able to deprotect the ester functional group on the N(1) acetyl chain in **6a** without destruction of the β-lactam ring, although this was not the case for the C(3) ester substituent in the C(2) heterosubstituted penems bearing a C(6) acylamino side chain [30]. Disappointingly, none of the new compounds **6a** prepared exhibited biological activity *in vitro*, neither as antibiotics nor as β-lactamase inhibitors. The β-lactams in the second class **6b** (L = SO_2R^2) are also stable under the usual conditions of TCE ester deprotection. Two of them showed a definite but very low bactericidal activity *in vitro* against the Gram-positive strains. None of the compounds **6b** were found to be active against β-lactamases.

The biological activity of the penicillins is generally correlated with the chemical reactivity of their β-lactam function [1]. Examination of the IR frequency absorption [55] of the β-lactam carbonyl stretch in the new compounds **6** suggests that **6a** and particularly **6b** should possess the same chemical activation upon nucleophilic attack as the classic antibiotics, due to the presence of a strong electron-withdrawing substituent at C(4). We have thus compared the relative stability in the presence of hydroxylamine of one representative of each class of the β-lactams **6** and of one sulfide precursor as models of inactivated compounds (0.01 M solution of β-lactam, CH_3OH, excess H_2NOH, 20°C). **11a** (L = SCOOEt) and **34d** (L = SO_2CH_2Ph) were found to react with half-lives of 285 and 2.5 min, respectively, whereas the sulfide **22d** (L = SCH_2Ph) was practically unreacted ($t_{1/2}$ » 10 h). Under the same experimental conditions, the penicillin **1a** (R^1 = $PhCH_2$, Me ester) and the cephalosporin **2a** (R^1 = $PhCH_2$, R^2 = H, TCE ester [48]) had half-lives of 5.8 and 7.9 min, respectively. Hence, the thiocarbonyl derivatives **6a** can be considered as slightly activated β-lactams and the sulfones **6b** as strongly activated ones. Nevertheless, the loss of skeletal rigidity in **6**, as a result of opening the fused ring which is characteristic of the classical antibiotics, appears to dramatically handicap the biological properties. Variation of the acylamino chain at C(3) in the two weakly active compounds (**34f** and **40f**) is currently under investigation in order to confirm and eventually improve the bactericidal effect.

Experimental protocols

Chemistry

mps (Leitz microscope) are uncorrected. The rotations were determined (±1°) on a Perkin—Elmer 241 MC polarimeter and the IR spectra on a Perkin—Elmer 681 spectrometer (calibration with polystyrene) with CH_2Cl_2 as the solvent, unless otherwise stated. The ^1H NMR spectra (ppm) were recorded ($CDCl_3$, unless otherwise stated, with tetramethylsilane (TMS) as the internal standard) on a Varian T60 (or XL200) instrument. Column chromatographies were performed with Merck silica gel 60 (70—230 mesh ASTM). CH_2Cl_2, DMF and EtOAc were dried over P_2O_5 then distilled. Ether was dried over $LiAlH_4$ and Et_3N on KOH. Elemental analyses were carried out by the Continental Pharma Co. (Belgium). The results indicated by the symbols of the elements were within ±0.4% of the theoretical values. The physical parameters of the compounds are summarized in Table III.

2-[3-benzyl-6-oxo-2-thia-4,7-diaza-(1R, 5R)-bicyclo-[3,2,0]-hept-3-en-7-yl]-alkyl acetates ***8***

8a, **8b**, **8c**, **8d** and **8g** were prepared according to reference [30]. Similarly, **8e** and **8f** were obtained from esterification of **8g** with chloromethyl-pivalate or 2-carboxybenzaldehyde.

8e: 65%; IR: 1780 (br) cm^{-1}; ^1H NMR (200 MHz) δ: 1.22 (s, 9), 3.76 (ABd, 1, *J* = 18.3 Hz), 3.82 (ABd, 1, *J* = 15.1 Hz), 3.98 (ABd, 1, *J* = 15.1 Hz), 4.30 (ABd, 1, *J* = 18.3 Hz), 5.74 (d, 1, *J* = 4 Hz), 5.76 (s, 2), 6.05 (d, 1, *J* = 4 Hz), 7.30 (sh m, 5); Anal. $C_{19}H_{22}O_5N_2S$ (C, H, N).

8f: 66%; IR: 1785 (br) cm^{-1}; ^1H NMR δ: 3.84 (two ABd, 1, *J* = 18 Hz), 3.90 (br s, 2), 4.39 (ABd, 1, *J* = 18 Hz), 5.77 (two d, 1, *J* = 4 Hz), 6.06 (sh m, 1), 7.30 (s, 5), 7.40 (s, 1), 7.50—8.06 (m, 4); Anal. $C_{21}H_{16}O_5N_2S$ (C, H, N).

2-[3-Phenylacetamido-2-thiol-(3R, 4R)-azetidin-2-on-1-yl]-alkyl acetates ***9***

8 in DMF solution (1 g/20 ml) was treated at 0°C with 1.2 N aq HCl (10 ml/g of **8**). After 1 h of stirring at room temp., the mixture was poured into cold water. The precipitate of **9** was filtered off or extracted with EtOAc, then dried as usual.

9a: 84%; IR: 3420 (NH), 2550 (SH), 1775, 1738, 1687, 1510 cm^{-1}; ^1H NMR δ: 1.46 (s, 9), 1.90 (d, 1, *J* = 10 Hz, SH), 3.65 (s, 2), 3.66 (ABd, 1, *J* = 18 Hz), 4.10 (ABd, 1, *J* = 18 Hz), 5.03—5.66 (m, 2), 7.10 (d, 1, *J* = 8 Hz, NH), 7.30 (s, 5).

9b: 73%; IR: 3420, 2560, 1777, 1748, 1682, 1605, 1510 cm^{-1}; ^1H NMR δ: 1.93 (d, 1, *J* = 10 Hz), 3.66 (s, 2), 3.79 (ABd, 1, *J* = 18 Hz), 4.26 (ABd, 1, *J* = 18 Hz), 4.66 (br d, 2, *J* = 5 Hz), 5.06—6.33 (m, 6), 7.15 (br d, 1, *J* = 8.5 Hz), 7.33 (s, 5).

9c: 87%; IR (KBr): 3280, 2540, 1763, 1738, 1655, 1610, 1645—20 cm^{-1}; ^1H NMR ($CDCl_3$—DMSO-d_6, 5:1) δ: 2.78 (d, 1, *J* = 9.5 Hz), 3.55 (s, 2), 3.91 and 4.33 (two ABd, 2, *J* = 18 Hz), 4.86—5.63 and 5.30 (m + s, 4), 7.26 (s, 5), 7.60 (d, 2, *J* = 9 Hz), 8.16 (d, 2, *J* = 9 Hz), 8.82 (br d, 1, *J* = 8 Hz).

9d: 80%; IR: 3420, 2550, 1780, 1765, 1687, 1510 cm^{-1}; ^1H NMR (200 MHz, CD_3COCD_3) δ: 2.82 (d, 1, *J* = 8 Hz), 3.65 (s, 2), 4.06 (ABd, 1, *J* = 18 Hz), 4.38 (ABd, 1, *J* = 18 Hz), 4.90 (sh m, 3), 5.45 (d×d, 1, *J* = 4.8 and 8.5 Hz), 7.30 (sh m, 5), 8.02 (br d, 1, *J* = 8.5 Hz).

9e: 76%; IR: 3420, 2555, 1775 (br), 1680, 1610, 1512 cm^{-1}; ^1H NMR ($CDCl_3$ + 5% DMF) δ: 1.23 (s, 9), 1.90 (d, 1, *J* = 10 Hz), 3.63 (s, 2), 3.80 and 4.20 (two ABd, 2, *J* = 18 Hz), 4.90—5.63 (m, 2), 5.80 (s, 2), 7.06 (br d, 1, *J* = 8 Hz), 7.30 (s, 5).

9f: 92%; IR (KBr): 3275, 2535, 1795—65 (br), 1650, 1607, 1543 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 3.54 (s, 2), 4.04 (m, 1), 4.34 (br ABd, 1, *J* = 18 Hz), 5.38 (m, 1), 5.82 (m, 1), 7.30 (br s, 5), 7.50 (s, 1), 7.66—8.00 (m, 4).

2-[3-Phenylacetamido-2-thiochlorocarbonyl-(3R,4R)-azetidin-2-on-1-yl]-alkyl acetates ***10***

To a solution of **9** (1 eq) in dry CH_2Cl_2 (1 g/20 ml), stirred at −60°C under argon, phosgene (20% in toluene, 1.1 eq) and then Et_3N (1.1 eq) were added dropwise with a syringe, through a rubber stopper. The mixture was allowed to reach room temp. slowly and stirring was continued for 2—3 h. Washing rapidly with cold 0.05 N HCl, extraction with CH_2Cl_2, drying of the organic phases ($CaCl_2$), concentration under vacuum and precipitation with dry ether, afforded crude **10** which was directly used for further reactions or storred in dry ice.

10a: 88%; IR: 3420, 1788, 1758, 1740, 1687, 1510, 840 cm^{-1}; ^1H NMR δ: 1.49 (s, 9), 3.60 (ABd, 1, *J* = 18 Hz), 3.65 (s, 2), 4.20 (ABd, 1, *J* = 18 Hz), 5.38 (d×d, 1, *J* = 5 and 8 Hz), 5.75 (d, 1, *J* = 5 Hz), 6.63 (br d, 1, *J* = 8 Hz), 7.33 (s, 5).

10b: 68%; IR: 3420, 1790, 1755, 1687, 1510, 840 cm^{-1}; ^1H NMR δ: 3.66 (s, 2), 3.76 (ABd, 1, *J* = 18 Hz), 4.35 (ABd, 1, *J* = 18 Hz), 4.70 (br d, 2, *J* = 5.5 Hz), 5.16—5.57 (m, 3), 5.66—6.20 and 5.80 (m + d, 2, *J* = 5 Hz), 6.83 (br d, 1, *J* = 8 Hz), 7.35 (s, 5).

10d: 85%; IR: 3420, 1790, 1768, 1688, 1605, 1508, 840 cm^{-1}; ^1H NMR δ: 3.63 (s, 2), 3.86 (ABd, 1, *J* = 18.5 Hz), 4.45 (ABd, 1, *J* = 18.5 Hz), 4.80 (s, 2), 5.33 (d×d, 1, *J* = 5 and 7.5 Hz), 5.78 (d, 1, *J* = 5 Hz), 6.70 (br d, 1, *J* = 7.5 Hz), 7.33 (s, 5).

10e: 71%; IR: 3420, 1790, 1763, 1687, 1510, 840 cm^{-1}; ^1H NMR δ: 1.21 (s, 9), 3.63 (s, 2), 3.75 (ABd, 1, *J* = 18 Hz), 4.31 (ABd, 1,

Table III. Physical parameters of the β-lactams.

Cpd	m.p(°C)	$[\alpha]_D$(°) $CHCl_3$,c(%)	R_F CH_2Cl_2-EtOAc(v:v)
8e	85-6	-58.6 (0.435)	0.50 (70:30)[a]
8f	156-9	-48.0 (1.59)	0.41 (80:20)
11a	143-6	+31.8 (0.56)	0.30 (65:35)[a]
11b	155-6	+32.2 (0.345)	0.44 (75:25)
11c	144-7	+19.0 (0.185)	0.35 (70:30)
11d	133-5	+30.4 (0.44)	0.56 (70:30)
11e	70-3	+34.6 (0.625)	0.26 (70:30)[a]
11f	200-9	+24.4 (0.255)	
12b	127-8	+28.1 (0.265)	0.46 (75:25)
12d	125-6	+27.3 (0.62)	0.50 (70:30)
12e	71-2	+35.1 (0.24)	0.26 (80:20)[a]
12f	173-5	+21.2 (0.36)	
13d	74-8	+14.6 (0.185)	0.23 (60:40)
13f	167-9	+18.2 (0.245)	0.21 (60:40)
14d	25-8	+27.7 (0.435)	0.26 (60:40)
14f	72-6	+28.6 (0.44)	0.22 (40:60)
15d	135-9	+45.8 (0.12)	0.51 (60:40)
15f	113-8	+56.0 (0.36)	0.42 (40:60)
16d	116-9	+50.9 (0.925)	0.33 (80:20)
16f	178-81	+48.7 (0.19)	0.45 (60:40)
17f	107-13	+25.2 (0.235)	0.47 (60:40)
18b	134-6	+73.7 (0.24)	0.54 (40:60)[a]
18d	99-100	+57.4 (0.20)	0.70 (40:60)
18f	192-5	+56.4 (0.26)	0.34 (50:50)
19d	44-7	+47.7 (0.21)	0.52 (70:30)
20d	107-9	-43.2 (0.575)	0.54 (70:30)
20f	176-80	-35.8 (0.150)	0.56 (70:30)
22d	148-9	-109.4 (0.43)	0.45 (80:20)
22f	195-7	-46.9 (0.265)[b]	0.43 (60:40)
23d	136-8	-105.4 (0.255)	0.36 (80:20)
23f	198-202	-36.4 (0.30)[b]	
24d	(foam)	-108.2 (0.20)	0.43 (80:20)
24f	150-3	-39.2 (0.56)	0.32 (70:30)
25d	112-4	-53.0 (1.21)	0.33 (80:20)
25f	180-5	-21.6 (0.29)[b]	0.35 (60:40)
26d	141-3	-52.1 (0.555)	0.58 (80:20)
26f	172-8	-27.6 (0.655)[b]	0.35 (60:40)
27d	153-5	-44.0 (1.10)	0.39 (80:20)
28d	117-20	-34.5 (0.76)[b]	
28f	93-9	-25.4 (0.66)[b]	
29d	151-5	-32.2 (0.35)[b]	0.34 (60:40)
29f	172-6	-21.9 (0.38)[b]	0.22 (40:60)
30d	135-40	-29.5 (0.255)[b]	
30f	195-8	-27.7 (0.24)[b]	
31d	153-4	-32.5 (0.50)[b]	
31f	125-30	-27.6 (0.405)[b]	0.39 (40:60)
32d	129-30	-9.6 (0.25)	
32f	237-40	+15.3 (0.40)[b]	
34d	150-2	-92.2 (0.335)	0.54 (80:20)
34f	261-9	-16.9 (0.62)[b]	
35d	204-8	-68.6 (0.53)	
35f	189-94	-33.8 (0.51)[b]	
36d	49-54	-14.2 (0.085)	0.44 (80:20)
36f	194-9	+1.4 (0.53)[b]	
37d	88-93	-57.7 (0.28)	0.58 (70:30)
37f	158-68	+4.2 (0.365)[b]	
38d	75-103	-42.7 (0.135)	0.65 (80:20)
38f	193-9	-4.0 (0.715)[b]	
39d	46-9	-27.4 (0.395)	0.60 (80:20)
40f	110-9	-3.2 (0.72)[b]	
41d	166-8	-0.03 (0.21)[b]	
41f	208-17	+21.3 (0.27)[b]	
42d	117-21	-16.8 (0.255)	0.59 (0:100)
42f	205-10	+16.0 (0.79)[b]	
43d	155-8	-10.8 (0.695)[b]	0.51 (70:30)

[a]Benzene—EtOAc.
[b]DMF.

J = 18 Hz), 5.35 (d×d, 1, J = 5 and 7.5 Hz), 5.73 (d, 1, J = 5 Hz), 5.80 (s, 2), 6.88 (br d, 1, J = 7.5 Hz), 7.33 (s, 5).

10f: 89%; IR: 3420, 1795—60 (br), 1686, 1605, 1510, 840 cm^{-1}; ^1H NMR δ: 3.62 (s, 2), 3.86 (br ABd, 1, J = 18.5 Hz), 4.43 (ABd, 1, J = 18.5 Hz), 5.13—5.50 (m, 1), 5.77 (br d, 1, J = 5 Hz), 7.10 (br d, 1), 7.30 (s, 5), 7.38 (br s, 1), 7.50—8.03 (m, 4).

2-[3-Phenylacetamido-2-ethylthiocarbonate-(3R,4R)-azetidin-2-on-1-yl]-alkyl acetates ***11***

To a solution of **9** (1 eq) in dry CH_2Cl_2 (1 g/20 ml), stirred at −60°C under argon, ethylchloroformate (1.1 eq) and then Et_3N (1.1 eq) were added dropwise with a syringe. The mixture was allowed to reach room temp. slowly and stirring was continued for 2 h. Washing with 0.05 N HCl, extraction with CH_2Cl_2, drying ($CaCl_2$) and concentration gave a crude product which was purified by column chromatography on silica gel or (and) precipitation from dry ether.

11a: IR: 3420, 1780, 1740, 1725, 1695, 1510 cm^{-1}; ^1H NMR δ: 1.26 (t, 3, J = 7 Hz), 1.46 (s, 9), 3.54 (ABd, 1, J = 18 Hz), 3.60 (s, 2), 4.13 (ABd, 1, J = 18 Hz), 4.23 (q, 2, J = 7 Hz), 5.53—5.76 (ABXm, 2), 6.74 (d, 1, J = 8 Hz), 7.30 (s, 5) after D_2O exchange, 5.60 (sh ABq, 2, J = 5 Hz); Anal. $C_{20}H_{26}O_6N_2S$ (C, H, N).

11b: IR: 3418, 1782, 1750, 1722, 1695, 1508 cm^{-1}; ^1H NMR δ: 1.28 (t, 3, J = 7 Hz), 3.64 (s, 2), 3.71 (ABd, 1, J = 18 Hz), 4.30 (ABd, 1, J = 18 Hz), 4.25 (q, 2, J = 7 Hz), 4.68 (br d, 2, J = 5 Hz), 5.13—6.00 (m, 5), 6.50 (br d, 1), 7.35 (s, 5); Anal. $C_{19}H_{22}O_6N_2S$ (C, H, N).

11c: IR: 3420, 1783, 1758, 1720, 1695, 1610, 1528, 1510 cm^{-1}; ^1H NMR δ: 1.28 (t, 3, J = 7 Hz), 3.63 (s, 2), 3.80 (ABd, 1, J = 18 Hz), 4.23 (q, 2, J = 7 Hz), 4.33 (ABd, 1, J = 18 Hz), 5.30 (s, 2), 5.40—5.76 (ABXm, 2), 6.46 (br d, 1, J = 7.5 Hz), 7.33 (s, 5), 7.55 (d, 2, J = 8.5 Hz), 8.28 (d, 2, J = 8.5 Hz); Anal. $C_{23}H_{23}O_8N_3S$ (C, H, N).

11d: IR: 3420, 1786, 1770, 1720, 1695, 1505 cm^{-1}; ^1H NMR δ: 1.28 (t, 3, J = 7 Hz), 3.64 (s, 2), 3.85 (ABd, 1, J = 18 Hz), 4.25 (q, 2, J = 7 Hz), 4.43 (ABd, 1, J = 18 Hz), 4.81 (s, 2), 5.40—5.83 (ABXm, 2), 6.45 (br d, 1, J = 7.5 Hz), 7.33 (s, 5); Anal. $C_{18}H_{19}O_6N_2SCl_3$ (C, H, N).

11e: IR: 3420, 1785, 1675, 1722, 1695, 1508 cm^{-1}; ^1H NMR δ: 1.23 (s, 9), 1.30 (t, 3, J = 7 Hz), 3.64 (s, 2), 3.76 (ABd, 1, J = 19 Hz), 4.30 (ABd, 1, J = 19 Hz), 4.26 (q, 2, J = 7 Hz), 5.45—5.80 (ABXm, 2), 5.83 (s, 2), 6.60 (br d, 1, J = 8 Hz), 7.33 (s, 5); Anal. $C_{22}H_{28}O_8N_2S$ (C, H, N).

11f: IR: 3410, 1788 (br), 1720, 1696, 1608, 1505 cm^{-1}; ^1H NMR (CD_3COCD_3) δ: 1.29 (t, 3, J = 7 Hz), 3.65 (s, 2), 3.80—4.50 (m, 4), 5.36—5.90 (ABXm, 2), 7.33 (s, 5), 7.54 (s, 1), 7.88 (m, 4); Anal. $C_{24}H_{22}O_8N_2S$ (C, H, N).

11g: *General procedure for TCE deprotection.* The TCE ester in DMF—HOAc (3:1) solution (100 mg/ml) was treated at 0°C with zinc dust (large excess) for 4 h under vigorous stirring. After dilution with EtOAc, the mixture was filtered and the solid residue washed twice with EtOAc. The filtrates were washed with 0.05 N HCl and the aqueous phase extracted with EtOAc. The collected organic phases were washed with brine, dried ($CaCl_2$) and concentrated under vacuum at 25°C. Precipitation from ether at 0°C gave the acid as a very hygroscopic white solid; IR (KBr): 3265, 3100—2900, 2600—2300, 1775, 1720—1710, 1658, 1530, 1417 cm^{-1}; ^1H NMR ($CDCl_3$ + 5% DMSO-d_6) δ: 1.30 (t, 3, J = 7 Hz), 3.63 (s, 2), 3.69 (ABd, 1, J = 18 Hz), 4.23 (ABd, 1, J = 18 Hz), 4.25 (q, 2, J = 7 Hz), 5.36—5.80 (ABXm, 2), 7.00 (br d, 1, J = 7.5 Hz), 7.32 (s, 5), 8.10 (sh m, 1); ^1H NMR ($CDCl_3$—DMSO-d_6, 1:1) δ: 5.43 (d×d, 1, J = 5 and 8 Hz) and 5.70 (d, 1, J = 5 Hz).

2-[3-Phenylacetamido-2-benzylthiocarbonate-(3R,4R)-azetidin-2-on-1-yl]-alkyl acetates ***12***

Using benzylchloroformate as the reagent, the procedure described for **11** was applied.

12b: IR: 3418, 1783, 1750, 1715, 1687, 1508 cm^{-1}; ^1H NMR δ: 3.61 (s, 2), 3.70 (ABd, 1, J = 18 Hz), 4.30 (ABd, 1, J = 18 Hz), 4.67 (br d, 2, J = 5 Hz), 5.22 (s, 2), 5.10—6.00 (m, 5), 6.45 (br d, 1, J = 8 Hz), 7.33 (s, 5), 7.40 (s, 5); Anal. $C_{24}H_{24}O_6N_2S$ (C, H, N).

12d: IR: 3420, 1784, 1770, 1715, 1690, 1508 cm^{-1}; ^1H NMR δ: 3.62 (s, 2), 3.85 (ABd, 1, J = 18 Hz), 4.43 (ABd, 1, J = 18 Hz), 4.79 (s, 2), 5.23 (s, 2), 5.43—5.86 (ABXm, 2), 6.50 (br d, 1, J = 8 Hz), 7.33 (s, 5), 7.41 (s, 5); Anal. $C_{23}H_{21}O_6N_2SCl_3$ (C, H, N).

12e: IR: 3420, 1785, 1765, 1714, 1690, 1505 cm^{-1}; ^1H NMR δ: 1.21 (s, 9), 3.58 (s, 2), 3.71 (ABd, 1, J = 18 Hz), 4.28 (ABd, 1, J = 18 Hz), 5.20 (s, 2), 5.40—5.75 (ABXm, 2), 5.78 (s, 2), 6.63 (br d, 1, J = 8 Hz), 7.28 and 7.35 (s, 5); Anal. $C_{27}H_{30}O_8N_2S$ (C, H, N).

12f: IR: 3420, 1788 (br), 1712, 1687, 1605, 1503 cm^{-1}; ^1H NMR (CD_3COCD_3) δ: 3.63 (s, 2), 3.96 (br ABd, 1, J = 19 Hz), 4.43 (ABd, 1, J = 19 Hz), 5.28 (s, 2), 5.40—5.87 (ABXm, 2), 7.32 (s, 5), 7.40 (s, 5), 7.52 (s, 1), 7.83 (sh m, 4); Anal. $C_{29}H_{24}O_8N_2S$ (C, H, N).

12g: IR: 3420, 1780, 1720, 1680, 1650, 1610, 1510 cm^{-1}; ^1H NMR ($CDCl_3$ + 10% DMF) δ: 3.60 (s, 2), 3.70 (ABd, 1, J = 18 Hz), 4.25 (ABd, 1, J = 18 Hz), 5.17 (s, 2), 5.43—5.83 (ABXm, 2), 6.93 (br d, 1, J = 7.5 Hz), 7.30 (s, 5), 7.40 (s, 5), 8.08 (sh m, 1).

2-[3-Phenylacetamido-2-(m-acetamido)phenylthiocarbonate-(3R,4R)-azetidin-2-on-1-yl]-alkyl acetates ***13***

To a solution of **10** (1 eq) in dry CH_2Cl_2 (1 g/20 ml), stirred at —60°C under argon, solid *m*-acetamidophenol (1 eq) and then Et_3N (1 eq) were added successively. The mixture was allowed to reach 20°C slowly and stirring continued for 2 h. Washing with 0.01 N HCl, extraction with CH_2Cl_2, drying ($CaCl_2$) and concentration gave a crude product which was purified by column chromatography on silica gel and (or) precipitation from ether.

13d: IR: 3427, 3330, 1787, 1770, 1730, 1690 (br), 1611, 1602, 1520 (br), 1492 cm^{-1}; ^1H NMR ($CDCl_3$ + 10% DMSO-d_6) δ: 2.11 (s, 3), 3.63 (s, 2), 4.00 (ABd, 1, J = 18.5 Hz), 4.50 (ABd, 1, J = 18.5 Hz), 4.83 (s, 2), 5.51 (d×d, 1, J = 5 and 7.5 Hz), 5.83 (d, 1, J = 5 Hz), 6.83 (m, 1), 7.33 (br s, 7), 7.66 (sh m, 1), 8.76 (d, 1, J = 7.5 Hz), 9.66 (br s, 1); Anal. $C_{24}H_{22}O_7SN_3Cl_3$ (C:46.01, H, N).

13f: IR: 3420, 3360, 1785 (br), 1725, 1695 (br), 1605, 1520 cm^{-1}; ^1H NMR ($CDCl_3$ + 20% DMSO-d_6) δ: 2.03 and 2.11 (two s, 3), 3.63 (br s, 2), 3.80—4.60 (m, 2), 5.53 (m, 1), 5.80 (br d, 1, J = 4 Hz), 6.83 (m, 1), 7.10—8.10 (m), 7.33 (s, 5), 7.50 (s, 1), 9.03 (br d, 1, J = 8 Hz), 9.83 (br s, 1); Anal. $C_{30}H_{25}O_9SN_3$ (C, H, N).

13g: IR (KBr): 3340, 3280, 1775, 1730, 1660, 1604, 1540, 1487, 1420 cm^{-1}; ^1H NMR ($CDCl_3$—DMSO-d_6, 1:1) δ: 2.08 (s, 3), 3.61 (s, 2), 4.00 (br m, 2), 5.48 (m, 1), 5.80 (d, 1, J = 5 Hz), 6.83 (m, 1), 7.33 (sh m, 7), 7.63 (br s, 1), 7.94 (br d, 1, J = 8 Hz).

2-[3-Phenylacetamido-2-β(α-pyridyl)ethylthiocarbonate-(3R,4R)-azetidin-2-on-1-yl]-alkyl acetates ***14***

General one-pot procedure from ***9***. A solution of thiol **9** (1 eq) in CH_2Cl_2 was treated at —60°C with phosgene (1 eq) and Et_3N (1 eq) as described previously. After 2 h at 20°C, the crude mixture was cooled again at —60°C. β-Pyridylethanol (1 eq) and Et_3N (1 eq) were added successively. The next work-up was conducted as described for compounds **13**.

14d: IR: 3415, 1788, 1770, 1710, 1687, 1594, 1510 cm^{-1}; ^1H NMR δ: 3.13 (t, 2, J = 7 Hz), 3.63 (s, 2), 3.82 (ABd, 1, J = 18 Hz), 4.41 (ABd, 1, J = 18 Hz), 4.60 (t, 2, J = 7 Hz), 4.80 (s, 2), 5.36—5.80 (ABXm, 2), 6.46 (d, 1, J = 7 Hz), 7.30 and 7.03—8.06 (s + m, 8), 8.57 (m, 1); Anal. $C_{23}H_{22}O_6SN_3Cl_3$ (C: 47.57, H, N).

14f: IR: 3420, 1790 (br), 1710, 1688, 1600, 1503, 1410 cm^{-1}; ^1H NMR δ: 3.11 (t, 2, J = 7 Hz), 3.61 (s, 2), 3.76 (ABd, 1, J = 19 Hz), 4.36 (ABd, 1, J = 19 Hz), 4.58 (t, 2, J = 7 Hz), 5.30—5.80 (ABXm, 2), 6.53 (br d, 1), 6.96—8.10 (m), 7.28 (s, 5), 7.40 (s, 1), 8.50 (m, 1); Anal. $C_{29}H_{25}O_8SN_3$ (C, H, N).

2-[3-Phenylacetamido-2-(α-pyridyl)dithiocarbonate-(3R,4R)-azetidin-2-on-1-yl]-alkyl acetates ***15***

The one-pot procedure described for **14** was applied using α-pyridylthiol as the reagent.

15d: IR: 3415, 1788, 1770, 1688 (br), 1640, 1575, 1510, 1450 cm^{-1}; ^1H NMR ($CDCl_3$—DMSO-d_6, 1:1) δ: 3.56 (s, 2), 3.97 (ABd, 1, J = 19 Hz), 4.46 (ABd, 1, J = 19 Hz), 4.86 (s, 2), 5.50 (d×d, 1, J = 5 and 7.5 Hz), 5.91 (d, 1, J = 5 Hz), 7.32 (s, 5), 7.43—8.10 (m, 3), 8.66 (m, 1), 9.00 (br d, 1, J = 7.5 Hz); Anal. $C_{21}H_{18}O_5S_2N_3Cl_3$ (C, H, N).

15f: IR: 3418, 1790 (br), 1689, 1640, 1607, 1575, 1508, 1415 cm^{-1}; ^1H NMR δ: 3.61 (s, 2), 3.78 (ABd, 1, J = 19 Hz), 4.36 (ABd, 1, J = 19 Hz), 5.43 (d×d, 1, J = 5 and 7 Hz), 5.83 (d, 1, J = 5 Hz), 6.60—7.30 (m, 4), 7.27 (s, 5), 7.36 (s, 1), 7.45—8.00 (m, 4), 8.54 (m, 1); Anal. $C_{27}H_{21}O_7S_2N_3$ (C, H, N).

15g: IR (KBr): 3400—3200, 1775, 1730, 1662, 1530, 1452, 1420 cm^{-1}; ^1H NMR ($CDCl_3$—DMSO-d_6, 5:1) δ: 3.60 (s, 2), 3.63 (ABd, 1, J = 18 Hz), 4.20 (ABd, 1, J = 18 Hz), 5.50 (d×d, 1, J = 5 and 8 Hz), 5.85 (d, 1, J = 5 Hz), 7.30 (sh m), 7.53—8.13 (m), 8.56 (br d, 1, J = 8 Hz).

2-[3-Phenylacetamido-2-(p-methoxybenzyl)dithiocarbonate-(3R,4R)-azetidin-2-on-1-yl]-alkyl acetates ***16***

The one-pot procedure described for **14** was applied using *p*-methoxybenzylthiol as the reagent.

16d: IR: 3420, 1785, 1770, 1687, 1642, 1610, 1511, 1495 cm^{-1}; ^1H NMR δ: 3.61 (s, 2), 3.80 (s, 3), 3.78 (ABd, 1, J = 19 Hz), 4.16 (s, 2), 4.43 (ABd, 1, J = 19 Hz), 4.81 (s, 2), 5.55 (d×d, 1, J = 5 and 8 Hz), 5.88 (d, 1, J = 5 Hz), 6.42 (d, 1, J = 8 Hz), 6.86 (d, 2, J = 9 Hz), 7.23 (d, 2, J = 9 Hz), 7.33 (s, 5); Anal. $C_{24}H_{23}O_6S_2N_2Cl_3$ (C, H, N).

16f: IR: 3418, 1787 (br), 1685, 1640, 1610, 1510 cm^{-1}; ^1H NMR ($CDCl_3$ + 10% DMSO-d_6) δ: 3.61 (s, 2), 3.80 (s, 3), 3.86 (br ABd, 1, J = 18.5 Hz), 4.20 (br s, 2), 4.46 (ABd, 1, J = 18.5 Hz), 5.53 (m, 1), 5.93 (br d, 1, J = 4.5 Hz), 6.86 (br d, 2, J = 9 Hz), 7.06—8.06 (m), 7.33 (s, 5), 8.33 (m, 1); Anal. $C_{30}H_{26}O_8S_2N_2$ (C, H, N).

16g: IR (KBr): 3600—2800, 1770, 1740, 1660, 1640, 1610, 1512, 1415 cm^{-1}; ^1H NMR ($CDCl_3$—DMSO-d_6, 5:1) δ: 3.58 (s, 2), 3.63 (ABd, 1, J = 18 Hz), 3.80 (s, 3), 4.18 (s, 2), 4.23 (ABd, 1, J = 18 Hz), 5.50 (d×d, 1, J = 5 and 8 Hz), 5.95 (d, 1, J = 5 Hz), 6.85 (d, 2, J = 9 Hz), 7.25 (d, 2, J = 9 Hz), 7.32 (s, 5), 8.56 (br d, 1, J = 8 Hz); Anal. $C_{22}H_{22}O_6S_2N_2$ (C, N, H).

2-[3-Phenylacetamido-2-(methylacetate)dithiocarbonate-(3R,4R)-azetidin-2-on-1-yl]-alkyl acetate ***17***

The procedure described for **13** was applied using thiol-methylacetate as the reagent.

17f: IR: 3420, 1788 (br), 1745, 1688, 1655, 1500 cm^{-1}; ^1H NMR δ: 3.63 (s, 2), 3.76 (br s, 5), 3.80 (ABd, 1, J = 18 Hz), 4.40 (ABd, 1, J = 18 Hz), 5.50 (m, 1), 5.86 (br d, 1, J = 5 Hz), 6.50 (m, 1), 7.30 (s, 5), 7.40 (s, 1), 7.47—8.00 (m, 4); Anal. $C_{25}H_{22}O_9S_2N_2$ (C, H, N).

2-[3-Phenylacetamido-2-(N-diethyl)thiocarbamate-(3R,4R)-azetidin-2-on-1-yl]-alkyl acetates ***18***

The procedure described for **13** was applied using diethylamine (2 eq) as the reagent and base.

18b: IR: 3420, 1778, 1750, 1685, 1650, 1510, 1412 cm^{-1}; ^1H NMR δ: 1.13 (t, 6, J = 7 Hz), 3.33 (br q, 4, J = 7 Hz), 3.65 (s, 2), 3.76 (ABd, 1, J = 18 Hz), 4.31 (ABd, 1, J = 18 Hz), 4.68 (br d, 2, J = 6 Hz), 5.10—6.00 (m, 5), 6.70 (m, 1), 7.33 (s, 5); Anal. $C_{21}H_{27}O_5N_3S$ (C, H, N).

18d: IR: 3420, 1782, 1768, 1688, 1650, 1510, 1412 cm^{-1}; ^1H NMR δ: 1.13 (t, 6, J = 7 Hz), 3.30 (br q, 4, J = 7 Hz), 3.65 (s, 2), 3.86 (ABd, 1, J = 18 Hz), 4.43 (ABd, 1, J = 18 Hz), 4.81 (s, 2), 5.43—5.83 (m, 2), 6.50 (br d, 1, J = 8 Hz), 7.33 (s, 5); Anal. $C_{20}H_{24}O_5N_3SCl_3$ (C, H, N).

18f: IR: 3418, 1795—1770 (br), 1686, 1650, 1508, 1411, 980 cm^{-1}; Anal. $C_{26}H_{27}O_7SN_3$ (C, H, N).

18g: IR (KBr): 3280, 1775, 1743, 1714, 1660, 1623, 1528, 1415, 1260 cm^{-1}; ^1H NMR ($CDCl_3$ + 5% DMF) δ: 1.10 (m, 6), 3.26 (m, 4), 3.64 (s, 2), 3.76 (ABd, 1, J = 18 Hz), 4.33 (ABd, 1, J = 18 Hz), 5.43—5.96 (m, 2), 7.30 (br s, 6 + 1), 8.00 (m, 1).

2-[3-Phenylacetamido-2-N(β-phenylethyl)thiocarbamate-(3R,4R)-azetidin-2-on-1-yl]-alkyl acetates ***19***

The procedure described for **13** was applied using β-phenylethylamine as the reagent.

19d: IR: 3420, 3340, 1783, 1768, 1685, 1500, 1412 cm^{-1}; ^1H NMR δ: 2.76 (br t, 2, J = 7 Hz), 3.46 (m, 2), 3.60 (s, 2), 3.80 (ABd, 1, J = 18 Hz), 4.38 (ABd, 1, J = 18 Hz), 4.78 (s, 2), 5.43—5.86 (m, 3), 6.66 (m, 1), 7.30 (br s, 10); Anal. $C_{24}H_{24}O_5N_3SCl_3$ (C, H, N).

19g: IR (KBr): 3280, 1765 (br), 1660 (br), 1605, 1525 (br), 1495, 1220, 1200 cm^{-1}; ^1H NMR ($CDCl_3$ + 5% DMF) δ: 2.7 (m, 2),

3.36 (m, 2), 3.50 (s, 2), 3.63 (ABd, 1, J = 18 Hz), 4.11 (ABd, 1, J = 18 Hz), 5.26—5.70 (m, 2), 6.43 (m, 1), 7.03 (br s, 10), 8.00 (m, 1).

2-[3-Phenylacetamido-2-thioalkyl-(3R,4R)-azetidin-2-on-1-yl]-alkyl acetates

A solution of the thiol **9** (1 eq) in dry DMF (100 mg/ml) was treated at 0°C with the alkylating reagent (1—10 eq) and then with triethylamine (dropwise addition, with a syringe, through a rubber stopper, 1 eq in all cases except 2 eq with iodoacetic acid). The mixture was stirred for 1 h at 0°C and 6—7 h at 20°C. After dilution with EtOAc, the solution was washed with 0.05 N HCl and the aqueous phase extracted twice with EtOAc. The organic layers were washed with brine, dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by column chromatography on silica gel or (and) precipitation from dry ether.

Methyliodide (10 eq)

20d: IR: 3420, 1780, 1765, 1684, 1510 cm^{-1}; ^{1}H NMR δ: 1.89 (s, 3), 3.66 (s, 2), 3.86 (ABd, 1, J = 18 Hz), 4.41 (ABd, 1, J = 18 Hz), 4.80 (s, 2), 5.03 (d, 1, J = 4.5 Hz), 5.56 (d×d, 1, J = 4.5 and 9 Hz), 6.50 (br d, 1, J = 9 Hz), 7.33 (s, 5); Anal. $C_{16}H_{17}O_4N_2SCl_3$ (C, H, N).

20f: IR: 3420, 1790—1770 (br), 1683, 1510, 1410 cm^{-1}; ^{1}H NMR δ: 1.90 (s, 3), 3.66 (s, 2), 3.83 (ABd, 1, J = 18 Hz), 4.40 (ABd, 1, J = 18 Hz), 5.06 (d, 1, J = 4.5 Hz), 5.60 (d×d, 1, J = 4.5 and 9 Hz), 6.56 (br d, 1, J = 9 Hz), 7.34 (s, 5), 7.56—8.10 (m, 4), 7.45 (s, 1); Anal. $C_{22}H_{20}O_6N_2S$ (C, H, N).

n-*Propyliodide* (10 eq)

21d: IR: 3405, 1775 (br), 1680, 1510, 1495 cm^{-1}; ^{1}H NMR δ: 0.96 (br t, 3), 1.57 (m, 2), 2.40 (m, 2), 3.66 (br s, 2), 4.13 (m, 2), 4.80 (s, 2), 5.10 (d, 1, J = 4.5 Hz), 5.52 (d×d, 1, J = 4.5 and 8 Hz), 6.76 (br d, 1), 7.33 (s, 5).

Benzylbromide (10 eq)

22d: IR: 3420, 1780, 1767, 1685, 1605, 1510 cm^{-1}; ^{1}H NMR δ: 3.43 (ABd, 1, J = 18.5 Hz), 3.58 (s, 2), 3.63 (s, 2), 4.17 (ABd, 1, J = 18.5 Hz), 4.67 (s, 2), 5.03 (d, 1, J = 4.5 Hz), 5.51 (d×d, 1, J = 4.5 and 9 Hz), 6.33 (br d, 1, J = 9 Hz), 7.25 (s, 5), 7.30 (s, 5); Anal. $C_{22}H_{21}O_4N_2SCl_3$ (C, H, N).

22f: IR: 3420, 1790—1770 (br), 1686, 1607, 1512, 1497, 1410 cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ: 3.55 (s, 2), 3.76 (s, 2), 3.53 (ABd, 1, J = 18.5 Hz), 4.26 (ABd, 1, J = 18.5 Hz), 5.06—5.50 (ABXm, 2), 7.30 (br s, 10), 7.50 (s, 1), 7.86 (sh m, 4), 8.96 (br d, 1, J = 7 Hz); Anal. $C_{28}H_{24}O_6N_2S$ (C, H, N).

p-*Nitrobenzylbromide* (1.2 eq)

23d: IR: 3420, 1780, 1765, 1683, 1605, 1520, 1347 cm^{-1}; ^{1}H NMR (CDCl$_3$ + 10% DMSO-d$_6$) δ: 3.70 (s, 4), 3.75 (ABd, 1, J = 18 Hz), 4.36 (ABd, 1, J = 18 Hz), 4.80 (s, 2), 5.08 (d, 1, J = 4.3 Hz), 5.50 (d×d, 1, J = 4.3 and 8 Hz), 7.40 (s, 5), 7.43 (d, 2, J = 9 Hz), 8.06 (br d, 1, J = 8 Hz), 8.20 (d, 2, J = 9 Hz); Anal. $C_{22}H_{20}O_6N_3SCl_3$ (C, H, N).

23f: IR (KBr): 3280, 1775 (br), 1660, 1605, 1540, 1520, 1346 cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ: 3.60 (s, 2), 3.93 (br s, 2), 4.20 (ABq, 2), 5.23 (ABXm, 2), 7.36 (s, 5), 7.53 (s, 1), 7.58 (d, 2, J = 8 Hz), 7.90 (br s, 4), 8.20 (d, 2, J = 8 Hz), 9.06 (br d, 1, J = 7 Hz); Anal. $C_{28}H_{23}O_8N_2S$ (C, H, N).

Allylbromide (10 eq)

24d: IR: 3410, 1780, 1770, 1682, 1510, 1490 cm^{-1}; ^{1}H NMR δ: 3.02 (d, 2, J = 6 Hz), 3.66 (s, 2), 3.85 (ABd, 1, J = 18 Hz), 4.41 (ABd, 1, J = 18 Hz), 4.80 (s, 2), 4.93—5.76 (m, 5), 6.33 (br d, 1), 7.33 (s, 5); Anal. $C_{18}H_{19}O_4N_2SCl_3$ (C, H, N).

24f: IR: 3420, 1790—1770 (br), 1685, 1608, 1510, 1410 cm^{-1}; ^{1}H NMR δ: 3.02 and 3.05 (two d, 2, J = 6 Hz), 3.66 (s, 2), 3.76 and 3.85 (two ABd, 1, J = 18 Hz), 4.33 and 4.38 (two ABd, 1, J = 18 Hz), 4.88—5.33 (m, 3), 5.37—5.83 (m, 2), 6.26 (m, 1), 7.36 (s, 5), 7.41 and 7.43 (two s, 1), 7.56—8.13 (m, 4); Anal. $C_{24}H_{22}O_6N_2S$ (C, H, N).

Propargylbromide (10 eq)

25d: IR: 3420, 3305, 1780, 1765, 1685, 1510, 1410 cm^{-1}; ^{1}H NMR δ: 2.26 (t, 1, J = 2.7 Hz), 3.16 (d, 2, J = 2.7 Hz), 3.66 (s, 2), 3.99 (ABd, 1, J = 19 Hz), 4.48 (ABd, 1, J = 19 Hz), 4.83 (s, 2), 5.33 (d, 1, J = 4.5 Hz), 5.60 (d×d, 1, J = 4.5 and 8 Hz), 6.83 (br d, 1, J = 8 Hz), 7.36 (s, 5); Anal. $C_{18}H_{17}O_4N_2SCl_3$ (C, H, N).

25f: IR: 3420, 3300, 1785 (br), 1685, 1605, 1510, 1410 cm^{-1}; ^{1}H NMR (CD$_3$CN + 15% DMSO-d$_6$) δ: 2.60 (t, 1, J = 2.7 Hz), 3.30 (d, 2, J = 2.7 Hz), 3.60 (s, 2), 4.25 (two sh ABq, 2, J = 18 Hz), 5.36 (ABXm, 2), 7.36 (s, 5), 7.51 (s, 1), 7.90 (sh m, 4), 8.40 (br d, 1); Anal. $C_{24}H_{20}O_6N_2S$ (C, H, N).

(Ethyl)bromoacetate (5 eq)

26d: IR: 3420, 1780, 1765, 1735, 1687, 1610, 1415 cm^{-1}; ^{1}H NMR δ: 1.26 (t, 3, J = 7 Hz), 3.16 (s, 2), 3.66 (s, 2), 4.00 (ABd, 1, J = 18 Hz), 4.20 (q, 2, J = 7 Hz), 4.45 (ABd, 1, J = 18 Hz), 4.81 (s, 2), 5.28 (d, 1, J = 4 Hz), 5.53 (d×d, 1, J = 4 and 8.5 Hz), 6.56 (br d, 1, J = 8.5 Hz), 7.33 (s, 5); Anal. $C_{19}H_{21}O_6N_2SCl_3$ (C, H, N).

26f: IR: 3420, 1785 (br), 1733, 1685, 1607, 1510 cm^{-1}; ^{1}H NMR (CDCl$_3$ + 20% DMSO-d$_6$) δ: 1.26 (t, 3, J = 7 Hz), 3.31 (s, 2), 3.64 (s, 2), 3.86—4.73 (m, 4), 5.16—5.60 (ABXm, 2), 7.40 (s, 5), 7.53 (br s, 1), 7.73—8.10 (sh m, 4), 8.90 (br d, 1, J = 7 Hz); Anal. $C_{25}H_{24}O_8N_2S$ (C, H, N).

(Trichloroethyl)iodoacetate (1.1 eq)

27d: IR: 3420, 1782, 1766, 1685, 1510, 1410 cm^{-1}; ^{1}H NMR δ: 3.23 (s, 2), 3.62 (s, 2), 3.92 (ABd, 1, J = 18 Hz), 4.36 (ABd, 1, J = 18 Hz), 4.70 (s, 2), 4.73 (s, 2), 5.23 (d, 1, J = 4.5 Hz), 5.43 (d×d, 1, J = 4.5 and 8 Hz), 6.10 (m, 1), 7.27 (s, 5); Anal. $C_{19}H_{18}O_6N_2SCl_6$ (C, H, N).

Iodoacetic acid (1.1 eq)

28d: IR (KBr): 3300, 1770, 1756, 1710, 1669, 1537, 1420 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d$_6$) δ: 3.33 (s, 2), 3.53 (s, 2), 4.16 (ABd, 1, J = 18.4 Hz), 4.44 (ABd, 1, J = 18.4 Hz), 4.94 (sh ABq, 2, J = 12 Hz), 5.19 (d, 1, J = 4.6 Hz), 5.27 (d×d, 1, J = 4.6 and 8.2 Hz), 7.28 (sh m, 5), 9.02 (d, 1, J = 8.2 Hz); Anal. $C_{17}H_{17}O_6N_2SCl_3$ (C, H, N).

28f: IR (KBr): 3650—3150, 1780—1720 (br), 1663, 1540, 1410 cm^{-1}; ^{1}H NMR (CDCl$_3$—DMSO-d$_6$, 1:1) δ: 3.23 (s, 2), 3.58 (s, 2), 4.10 (ABd, 1, J = 18 Hz), 4.41 (ABd, 1, J = 18 Hz), 5.13—5.50 (sh m, 2), 7.30 (s, 5), 7.47 (s, 1), 7.80 (sh m, 4), 8.83 (br d, 1, J = 7 Hz); Anal. $C_{23}H_{20}O_8N_2S$ (C: 55.87, H, N).

N-*(Phenylethyl)iodoacetamide* (1 eq)

29d: IR: 3420, 1782, 1768, 1675 (br), 1510, 1410 cm^{-1}; ^{1}H NMR (CDCl$_3$ + 20% DMSO-d$_6$) δ: 2.80 (br t, 2, J = 7 Hz), 3.12 (s, 2), 3.43 (m, 2), 3.63 (s, 2), 4.06 (ABd, 1, J = 18.5 Hz), 4.46 (ABd, 1, J = 18.5 Hz), 4.85 (s, 2), 5.16—5.53 (ABXm, 2), 7.27 (s, 5), 7.33 (s, 5), 7.83 (m, 1), 8.83 (br d, 1); Anal. $C_{25}H_{26}O_5N_3SCl_3$ (C, H, N).

29f: IR: 3420, 3300, 1785 (br), 1675 (br), 1605, 1510, 1410 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d$_6$) δ: 2.70 (br t, 2, J = 7.2 Hz), 3.16 (br s, 2), 3.29 (sh m, 2), 3.54 (s, 2), 4.08 and 4.1 (two ABd, 1, J = 18.2 Hz), 4.40 (br ABd, 1, J = 18.2 Hz), 5.18—5.34 (ABXm, 2), 7.12—7.40 (m, 10), 7.50 and 7.52 (two s, 1), 7.70—7.96 (m, 4), 8.16 (m, 1), 9.00 (d, 1, J = 8 Hz); Anal. $C_{31}H_{29}O_7N_3S$ (C, H, N).

Iodoacetamide (1 eq)

30d: IR (KBr): 3300, 3200, 1775 (br), 1660 (br), 1530 (br), 1410 cm^{-1}; ^{1}H NMR (CDCl$_3$—DMSO-d$_6$, 1:1) δ: 3.16 (s, 2), 3.60 (s, 2), 4.31 (sh ABq, 2), 4.93 (s, 2), 5.36 (ABXm, 2), 7.34 (s, 5), 7.53 (m, 2), 9.00 (br d, 1); Anal. $C_{17}H_{18}O_5N_3SCl_3$ (C: 41.67, H, N).

30f: IR (KBr): 3280, 3210, 1775 (br), 1665 (br), 1610, 1535, 1410 cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ: 3.20 (s, 2), 3.60 (s, 2), 4.33 (sh ABq, 2), 5.33 (ABXm, 2), 7.13 (m, 2), 7.36 (s, 5), 7.60 (s, 1), 7.96 (br s, 4), 9.10 (br d, 1); Anal. $C_{23}H_{21}O_7N_3S$ (C, H, N).

Iodoacetonitrile (1 eq)

31d: IR (KBr): 3420, 2248 (w), 1785, 1765, 1684, 1510, 1410 cm^{-1}; ^{1}H NMR (CDCl$_3$ + 10% DMSO-d$_6$) δ: 3.26 (s, 2), 3.65 (s, 2), 4.06 (ABd, 1, J = 19 Hz), 4.53 (ABd, 1, J = 19 Hz), 4.86 (s, 2), 5.23—5.56 (ABXm, 2), 7.36 (s, 5), 8.70 (br d, 1); Anal. $C_{17}H_{16}O_4N_3SCl_3$ (C, H, N).

31f: IR: 3420, 2245 (w), 1785 (br), 1685, 1605, 1510, 1410 cm^{-1}; ^{1}H NMR (CD$_3$CN + 10% DMSO-d$_6$) δ: 3.46 (s, 2), 3.60 (s, 2), 4.05 (ABd, 1, J = 18 Hz), 4.43 (ABd, 1, J = 18 Hz), 5.30 (ABXm, 2), 7.34 (s, 5), 7.46 (s, 1), 7.83 (br s, 4), 8.40 (m, 1); Anal. $C_{23}H_{19}O_6N_3S$ (C, H, N).

2-[3-Phenylacetamido-2-alkylsulfonyl-(3R,4R)-azetidin-2-on-1-yl]-alkyl acetates and acetic acids

A solution of the sulfide precursor (1 eq) in dry CH_2Cl_2 (100 mg/2—5 ml) was treated at 0°C with MCPBA (80% purity, 3 eq; addition

of the solid in small portions). The mixture was stirred for 1 h at 0°C and 2—3 h at 20°C. Work-up A: dilution with CH_2Cl_2, washing with 5% $NaHCO_3$, drying ($CaCl_2$) and concentration under vacuum gave the crude product which was purified by column chromatography on silica gel or (and) precipitation from ether. Work-up B: removal of the solvent under vacuum and precipitation from ether yielded the sulfone which was washed twice with ether.

Methylsulfones

32d: IR: 3410, 1800, 1768, 1693, 1510, 1412 cm^{-1}; ^1H NMR δ: 2.46 (s, 3), 3.65 (s, 2), 4.18 (ABd, 1, J = 18.5 Hz), 4.73 (ABd, 1, J = 18.5 Hz), 4.80 (s, 2), 5.10 (d, 1, J = 4.5 Hz), 5.89 (d×d, 1, J = 4.5 and 9.5 Hz), 7.10 (br d, 1, J = 9.5 Hz), 7.33 (s, 5); Anal. $C_{16}H_{17}O_6N_2SCl_3$ (C, H, N).

32f: IR (KBr): 3320, 1790—1770 (br), 1670, 1535, 1410 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.93 (s, 3), 3.63 (s, 2), 4.46 (sh ABq, 2), 5.16—5.93 (m, 2), 7.33 (s, 5), 7.55 (s, 1), 7.86 (br s, 4); Anal. $C_{22}H_{20}O_8N_2S$ (C, H, N).

32g: IR (KBr): 3305, 1790, 1745, 1676, 1533, 1390 cm^{-1}; ^1H NMR ($CDCl_3$—DMSO-d_6, 3:1) δ: 2.66 (s, 3), 3.60 (s, 2), 3.86 (ABd, 1, J = 18.5 Hz), 4.36 (ABd, 1, J = 18.5 Hz), 5.13 (d, 1, J = 4.5 Hz), 5.67 (d×d, 1, J = 4.5 and 8.5 Hz), 7.30 (s, 5).

n-*Propylsulfones*

33d: IR: 3410, 1795, 1767, 1690, 1510 cm^{-1}; ^1H NMR δ: 0.90 (t, 3, J = 7 Hz), 1.61 (m, 2), 2.50 (m, 2), 3.63 (s, 2), 4.20 (ABd, 1, J = 19 Hz), 4.70 (ABd, 1, J = 19 Hz), 4.78 (s, 2), 5.06 (d, 1, J = 5 Hz), 5.86 (d×d, 1, J = 5 and 9 Hz), 7.00 (br d, 1, J = 9 Hz), 7.33 (s, 5); Anal. $C_{18}H_{21}O_6N_2SCl_3$ (C, H, N).

33g: IR (KBr): 3320, 1789, 1735, 1670, 1532, 1390, 1320, 1288, 1255 cm^{-1}.

Benzylsulfones

34d: IR: 3410, 1800, 1770, 1695, 1605, 1510, 1380 cm^{-1}; ^1H NMR δ: 3.55 (ABd, 1, J = 14 Hz), 3.67 (s, 2), 3.91 (ABd, 1, J = 14 Hz), 4.08 (ABd, 1, J = 19 Hz), 4.65 (ABd, 1, J = 19 Hz), 4.71 (sh ABq, 2), 4.88 (d, 1, J = 5 Hz), 5.86 (d×d, 1, J = 5 and 9 Hz), 7.13 (d, 1, J = 9 Hz), 7.37 (sh m, 10); Anal. $C_{22}H_{21}O_6N_2SCl_3$ (C, H, N).

34f: IR (KBr): 3290, 1798, 1785, 1773, 1672, 1550, 1495 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ: 3.60 (br s, 2), 4.24 (br s, 2), 4.12 and 4.34 (two ABd, 1, J = 18 Hz), 4.34 and 4.53 (two ABd, 1, J = 18 Hz), 5.15 and 5.26 (two d, 1, J = 4.8 Hz), 5.63 and 5.66 (two d×d, 1, J = 4.8 and 8 Hz), 7.10—7.40 (m, 10), 7.46 and 7.48 (two s, 1), 7.70—7.96 (m, 4), 9.13 and 9.18 (two d, 1, J = 8 Hz); Anal. $C_{28}H_{24}O_8N_2S$ (C, H, N).

34g: IR (KBr): 3300, 1790, 1740, 1670, 1530, 1495 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 3.65 (s, 2), 3.85 (ABd, 1, J = 18 Hz), 4.31 (s, 2), 4.36 (ABd, 1, J = 18 Hz), 5.21 (d, 1, J = 5 Hz), 5.70 (d×d, 1, J = 5 and 8.5 Hz), 7.33 (br s, 10), 9.13 (d, 1, J = 8.5 Hz).

p-*Nitrobenzylsulfones*

35d: IR: 3410, 1800, 1768, 1690, 1609, 1529, 1510 cm^{-1}; ^1H NMR (200 MHz) δ: 3.62 (ABd, 1, J = 14 Hz), 3.70 (sh ABq, 2), 3.83 (ABd, 1, J = 14 Hz), 4.12 (ABd, 1, J = 18 Hz), 4.60 (ABd, 1, J = 18 Hz), 4.63 (ABd, 1, J = 12 Hz), 4.80 (ABd, 1, J = 12 Hz), 4.84 (d, 1, J = 4.5 Hz), 5.81 (d×d, 1, J = 4.5 and 8.7 Hz), 6.76 (d, 1, J = 8.7 Hz), 7.34 (s, 5), 7.32 (d, 2, J = 8 Hz), 8.22 (d, 2, J = 8 Hz); Anal. $C_{22}H_{20}O_8N_3SCl_3$ (C, H, N).

35f: IR (KBr): 3280, 1780 (br), 1660, 1610, 1522, 1350 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ: 3.50 (br s, 2), 3.86 and 3.90 (two s, 2), 4.19 (ABd, 1, J = 18 Hz), 4.38 and 4.54 (two ABd, 1, J = 18 Hz), 5.09 and 5.16 (two d, 1, J = 4.6 Hz), 5.27 (d×d, 1, J = 4.6 and 8 Hz), 7.26 (br s, 5), 7.46 and 7.49 (two s, 1), 7.47 and 7.50 (two d, 2, J = 8 Hz), 7.70—7.98 (m, 4), 8.08 and 8.10 (two d, 2, J = 8 Hz), 8.97 and 9.01 (two d, 1, J = 8 Hz); Anal. $C_{28}H_{23}O_{10}N_3S$ (C, H, N).

35g': IR (KBr): 3300, 1775 (br), 1740, 1668 (br), 1613, 1520 (br), 1382 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ: 3.64 (sh ABq, 2, J = 14 Hz), 3.82 (ABd, 1, J = 18.5 Hz), 4.16 (sh ABq, 2, J = 14 Hz), 4.28 (ABd, 1, J = 18.5 Hz), 5.15 (d, 1, J = 5 Hz), 5.64 (d×d, 1, J = 5 and 8.5 Hz), 6.84 (d, 2, J = 8 Hz), 7.03 (d, 2, J = 8 Hz), 7.30 (sh m, 5), 9.17 (d, 1, J = 8.5 Hz).

Allylsulfones

36d: IR: 3412, 1798, 1769, 1690, 1638, 1605, 1510 cm^{-1}; ^1H NMR δ: 3.26 (sh m, 2), 3.65 (s, 2), 4.17 (ABd, 1, J = 19 Hz), 4.71 (ABd, 1, J = 19 Hz), 4.80 (sh ABq, 2), 5.20 (d, 1, J = 4.5 Hz), 5.30—6.10 and 5.85 (m + d×d, 4, J = 4.5 and 9.5 Hz), 7.13 (d, 1, J = 9.5 Hz), 7.36 (s, 5); Anal. $C_{18}H_{19}O_6N_2SCl_3$ (C, H, N).

36f: IR (KBr): 3320, 1805, 1784, 1773, 1672, 1630, 1605, 1535 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ: 3.57 (sh ABq, 2, J = 13.8 Hz), 3.69 and 3.71 (two d, 2, J = 6 Hz), 4.21 and 4.30 (two ABd, 1, J = 18 Hz), 4.50 and 4.59 (two ABd, 1, J = 18 Hz), 5.22 and 5.33 (two d, 1, J = 4.8 Hz), 5.34 (br d×d, 2, J = 14.9 Hz), 5.55—5.78 (m, 2), 7.30 (sh m, 5), 7.50 and 7.52 (two s, 1), 7.70—8.0 (m, 4), 9.06 and 9.08 (two d, 1, J = 8 Hz); Anal. $C_{24}H_{22}O_8N_2S$ (C, H, N).

36g: IR (KBr): 3300, 1790, 1740, 1670, 1640, 1525, 1500 cm^{-1}; ^1H NMR ($CDCl_3$ + 10% DMSO-d_6) δ: 3.35 (br d, 2, J = 6 Hz), 3.67 (s, 2), 3.93 (ABd, 1, J = 19 Hz), 4.48 (ABd, 1, J = 19 Hz), 5.20 (d, 1, J = 4.5 Hz), 5.26—6.0 and 5.78 (m + d×d, 4, J = 4.5 and 9 Hz), 7.40 (s, 5).

Propargylsulfones

37d: IR: 3410, 3300, 1800, 1765, 1692, 1510, 1413 cm^{-1}; ^1H NMR δ: 2.50 (sh m, 1), 3.46 (sh m, 2), 3.65 (s, 2), 4.18 (ABd, 1, J = 19 Hz), 4.70 (ABd, 1, J = 19 Hz), 4.81 (sh ABq, 2), 5.46 (d, 1, J = 5 Hz), 5.97 (d×d, 1, J = 5 and 9.5 Hz), 6.90 (br d, 1, J = 9.5 Hz), 7.36 (s, 5); Anal. $C_{18}H_{17}O_6N_2SCl_3$ (C, H, N).

37f: IR (KBr): 3320, 3280, 1890 (br), 1673, 1610, 1533, 1408 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ: 3.64 (br s, 2), 4.23 (sh m, 2), 4.30—4.67 (m, two ABq, 2, J = 18 Hz), 5.37 and 5.44 (two d, 1, J = 4.5 Hz), 5.69 (m, 1), 7.30 (br s, 5), 7.53 (br s, 1), 7.72—8.00 (m, 4), 9.09 (br d, 1, J = 8 Hz); Anal. $C_{24}H_{20}O_8N_2S$ (C, H, N).

37g: IR (KBr): 3400, 3290, 1787 (br), 1740, 1675, 1525, 1390 cm^{-1}; ^1H NMR ($CDCl_3$ + 10% DMSO-d_6) δ: 2.76 (br s, 1), 3.60 (s, 2), 3.73 (br s, 2), 3.90 (ABd, 1, J = 18 Hz), 4.34 (ABd, 1, J = 18 Hz), 5.33 (d, 1, J = 4 Hz), 5.70 (d×d, 1, J = 4 and 9 Hz), 7.21 (s, 5), 8.53 (d, 1, J = 9 Hz).

Ethoxycarbonyl-methylsulfones

38d: IR: 3410, 1800, 1768, 1745, 1695, 1510, 1415 cm^{-1}; ^1H NMR δ: 1.3 (t, 3, J = 7 Hz), 3.53 (s, 2), 3.66 (s, 2), 4.17 (ABd, 1, J = 18 Hz), 4.26 (q, 2, J = 7 Hz), 4.67 (ABd, 1, J = 18 Hz), 4.81 (s, 2), 5.60 (d, 1, J = 4.5 Hz), 5.93 (d×d, 1, J = 4.5 and 9 Hz), 6.90 (br d, 1, J = 9 Hz), 7.34 (s, 5); Anal. $C_{19}H_{21}O_8N_2SCl_3$ (C, H, N).

38f: IR: 3408, 1798, 1775, 1741, 1690, 1605, 1510 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ: 1.21 (t, 3, J = 7 Hz), 3.57 (s, 2), 4.10—4.42 (q + sh Abq + two ABd, 5), 4.53 and 4.62 (two ABd, 1, J = 17.6 Hz), 5.42 and 5.48 (two d, 1, J = 4.7 Hz), 5.70 (m, 1), 7.30 (br s, 5), 7.53 (br s, 1), 7.72—8.0 (m, 4), 9.08 (br d, 1, J = 8 Hz); Anal. $C_{25}H_{24}O_{10}N_2S$ (C, H, N).

38g: IR (KBr): 3320, 1793, 1743, 1674, 1530, 1395 cm^{-1}; ^1H NMR ($CDCl_3$ + 20% DMSO-d_6) δ: 1.30 (t, 3, J = 7 Hz), 3.63 (s, 2), 3.82 (br s, 2), 3.9—4.54 (q + two ABd, 4), 5.06—6.0 (m, 4), 7.30 (s, 5).

Trichloroethoxycarbonyl-methylsulfone

39d: IR: 3415, 1801, 1768, 1695, 1510, 1380 cm^{-1}; ^1H NMR (200 MHz) δ: 3.49 (ABd, 1, J = 15.2 Hz), 3.59 (ABd, 1, J = 14.6 Hz), 3.61 (ABd, 1, J = 15.2 Hz), 3.70 (ABd, 1, J = 14.6 Hz), 4.18 (ABd, 1, J = 18.8 Hz), 4.63 (ABd, 1, J = 18.8 Hz), 4.71 (ABd, 1, J = 12 Hz), 4.75 (ABd, 1, J = 12 Hz), 4.83 (ABd, 1, J = 12 Hz), 4.86 (ABd, 1, J = 12 Hz), 5.59 (d, 1, J = 4.6 Hz), 5.92 (d×d, 1, J = 4.6 and 9.6 Hz), 6.70 (d, 1, J = 9.6 Hz), 7.32 (sh m, 5); Anal. $C_{19}H_{18}O_8SN_2Cl_6$ (C, H, N).

Hydroxycarbonyl-methylsulfones

40d: ^1H NMR δ: 3.63 (s, 2), 3.83 (sh ABq, 2), 4.16 (ABd, 1, J = 18 Hz), 4.61 (ABd, 1, J = 18 Hz), 4.73 (sh ABq, 2), 5.63 (d, 1, J = 4.5 Hz), 5.92 (d×d, 1, J = 4.5 and 8 Hz).

40f: IR (KBr): 3500—3200, 1785 (br), 1740, 1672, 1530, 1415 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ: 3.56 (br s, 2), 4.13 and 4.16 (two s, 2), 4.25 and 4.31 (two ABd, 1, J = 18.5 Hz), 4.52 and 4.58 (two ABd, 1, J = 18.5 Hz), 5.42 and 5.48 (two d, 1, J = 4.8 Hz), 5.68 (m, 1), 7.30 (br s, 5), 7.52 (s, 1), 7.70—8.00 (m, 4), 9.03 (d, 1, J = 9 Hz); Anal. $C_{23}H_{20}O_{10}SN_2$ (C: 52.10, H, N).

40g (from **39d**): IR (KBr): 3360, 3100—2400 (br), 1810, 1732 (br), 1635 (br), 1533, 1418 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ: 2.73 (s, 3), 2.89 (s, 3), 3.56 (br s, 2), 3.94 (ABd, 1, J = 18.4 Hz), 4.13 (s, 2), 4.34 (ABd, 1, J = 18.4 Hz), 5.40 (d, 1, J = 4.8 Hz), 5.64 (d×d, 1, J = 4.8 and 8.8 Hz), 7.28 (br s, 5), 7.95 (s, 1), 9.02 (d, 1, J = 8.8 Hz) (1:1 complex with DMF).

(β-Phenylethyl)aminocarbonyl-methylsulfones

41d: IR: 3420, 1800, 1768, 1688 (br), 1605, 1510 (br), 1380 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.90 (m, 2), 3.33 (m, 2), 3.60 (s, 2), 3.99 (sh ABq, 2), 4.30 (ABd, 1, J = 18 Hz), 4.69 (ABd, 1, J = 18 Hz), 4.96 (s, 2), 5.50 (d, 1, J = 5 Hz), 5.78 (d×d, 1, J = 5 and 9 Hz), 7.30 (br s, 10), 8.53 (m, 1), 8.90 (br d, 1, J = 9 Hz); Anal. $C_{25}H_{26}O_7N_3SCl_3$ (C, H, N).

41f: IR (KBr): 3400—3300, 1790, 1775, 1670, 1650, 1607, 1530 (br), 1325 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ: 2.74 (t, 2, J = 7 Hz), 3.35 (t, 2, J = 7 Hz), 3.57 (sh ABq, 2, J = 14.5 Hz), 3.85 and 3.88 (two ABd, 1, J = 15 Hz), 4.10 (ABd, 1, J = 15 Hz), 4.31 and 4.35 (two ABd, 1, J = 18.5 Hz), 4.59 and 4.63 (two ABd, 1, J = 18.5 Hz), 5.47 and 5.53 (two d, 1, J = 5 Hz), 5.74 (two d×d, 1, J = 5 and 9 Hz), 7.30 (sh m, 10), 7.56 and 7.58 (two s, 1), 7.76—8.00 (m, 4), 8.57 (m, 1), 8.99 and 9.01 (two d, 1, J = 9 Hz); Anal. $C_{31}H_{29}O_9N_3S$ (C, H, N).

41g: IR (KBr): 3500—3200, 1788, 1735, 1660 (br), 1535 (br), 1325 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.85 (m, 2), 3.30 (m, 2), 3.60 (s, 2), 3.96 (sh ABq, 2), 3.94 (ABd, 1, J = 18 Hz), 4.40 (ABd, 1, J = 18 Hz), 5.45 (d, 1, J = 5 Hz), 5.71 (d×d, 1, J = 5 and 9 Hz), 7.30 (br s, 10), 8.50 (m, 1), 8.90 (d, 1, J = 9 Hz).

Aminocarbonyl-methylsulfones

42d: IR: 3500, 3400, 1800, 1768, 1695 (br), 1600, 1510 cm^{-1}; ^1H NMR (200 MHz) δ: 3.48 (sh ABq, 2, J = 15 Hz), 3.63 (sh ABq, 2, J = 14 Hz), 4.20 (ABd, 1, J = 19 Hz), 4.60 (ABd, 1, J = 19 Hz), 4.78 (sh ABq, 2, J = 12 Hz), 5.45 (d, 1, J = 5 Hz), 5.75 (br s, 1, $CONH_2$), 5.92 (d×d, 1, J = 5 and 9 Hz), 6.35 (br s, 1, $CONH_2$), 6.83 (d, 1, J = 9 Hz), 7.30 (sh m, 5); Anal. $C_{17}H_{18}O_7N_3SCl_3$ (C, H, N).

42f: IR (KBr): 3320, 3200, 1783 (br), 1675 (br), 1610, 1528, 1410 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ: 3.52 (br s, 2), 3.74 and 3.78 (two ABd, 1, J = 14 Hz), 4.03 (ABd, 1, J = 14 Hz), 4.24 and 4.30 (two ABd, 1, J = 18 Hz), 4.52 and 4.58 (two ABd, 1, J = 18 Hz), 5.44 and 5.48 (two d, 1, J = 5 Hz), 5.68 and 5.70 (two d×d, 1, J = 5 and 9 Hz), 7.26 (br s, 5), 7.50 (br s, 1), 7.60—7.96 (m, 4), 8.92 (br d, 1, J = 9 Hz); Anal. $C_{23}H_{21}O_9N_3S$ (C: 52.84, H, N).

Cyanomethylsulfones

43d: IR: 3410, 2260 (w), 1803, 1768, 1690, 1510, 1380 cm^{-1}; ^1H NMR (CD_3CN) δ: 3.60 (s, 2), 4.12 (s, 2), 4.17 (ABd, 1, J = 19 Hz), 4.55 (ABd, 1, J = 19 Hz), 4.85 (s, 2), 5.35 (d, 1, J = 5 Hz), 5.83 (d×d, 1, J = 5 and 9 Hz), 7.23 (br d, 1), 7.30 (s, 5); Anal. $C_{17}H_{16}O_6N_3SCl_3$ (C, H, N).

43g: IR (KBr): 3300, 2260 (w), 1785, 1735, 1670, 1525, 1410 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ: 3.57 (s, 2), 3.96 (ABd, 1, J = 18.5 Hz), 4.32 (ABd, 1, J = 18.5 Hz), 4.98 (br m, 2), 5.51 (d, 1, J = 5 Hz), 5.73 (d×d, 1, J = 5 and 8.5 Hz), 7.30 (sh m, 5), 9.23 (d, 1, J = 8.5 Hz).

Reaction with hydroxylamine

Methanolic solutions of the β-lactam (0.02 M) and of hydroxylamine (0.25 M) were mixed at 20°C (equal volumes). The disappearance of the β-lactam was monitored by high performance liquid chromatography (instruments: Waters Associates, Inc., model 6000A and Absorbance Detector, model 440 (254 nm); Chromatointegrator Merck—Hitachi, model D-2000; column: 150×4.6 mm, packed with Rosil C18 (5 μm); eluant: 60—65% CH_3OH and 40—35% H_2O with a flow-rate of 1.8 ml/min).

Biological methods

The *MIC* of the monocyclic β-lactams (esters and free acids) were measured by microdilution tests in 96-microwell plates (Nunc, Rotkilde, Denmark) as described by Thrupp [56], using a final inoculum of 10^5 CFU/ml and Mueller—Hinton broth (BBL, Microbiological Systems, Cockeyville, PA, U.S.A.). To allow the growth of *Streptococcus*, 5% horse blood (Gibco, Ghent, Belgium) was added to the culture medium. The range of concentrations obtained by 2-fold dilutions were from 200 to 0.006 μM. For water insoluble products, dimethyl sulfoxide was used as solvent, but its concentration never exceeded 2%. Ampicillin and penicillin G TAL or PIV esters (when ester compounds were tested) were included in each experiment as active reference antibiotics. The bacterial strains were obtained from Institut Pasteur (Paris, France): *Escherichia coli* ATCC 25422, *Klebsiella pneumoniae* ATCC 10.031, *Pseudomonas aeruginosa* ATCC 27853, *Proteus mirabilis* NTC 8309, *Serratia marcescens* ATCC 4003, *Salmonella typhimurium* LT2 60.62, *Staphylococcus aureus* ATCC 25923, and *Streptococcus pyogenes* ATCC 8668. *Proteus vulgaris*, a sensitive laboratory strain, was provided by Prof. J. M. Ghuysen (University of Liège, Belgium). Hydrolysis of the TAL and PIV esters (20 mM) was performed by incubation for 120 min at 37°C in the presence of human plasma. Then the solutions were diluted adequately and tested as above [56].

Three β-lactamases, one each of class A, B and C as defined by Ambler [57] and Jaurin and Grundström [58] were chosen for the study. The β-lactamase from *Bacillus licheniformis* 749 (active-serine enzyme, class A) was purified as described by Thatcher [59] and assayed at 30°C using nitrocefin (Glaxo) as the substrate. The enzyme was added to 500 μl of 100 μM nitrocefin in 50 mM sodium phosphate buffer, pH 7.0. The absorbance was monitored at 482 nm during 10 min by means of a Beckman DU-8 spectrophotometer. With 2 ng of enzyme a ΔA of 0.3 was obtained after 10 min of incubation. The β-lactamase from *Bacillus cereus* 5/B/6 (Zn^{++} enzyme, class B) was purified by chromatography on Amberlite CG-50 and CM-Sephadex. The activity was determined using 500 μl of 100 μM cephaloridin (Eli Lilly & Co.) in 100 mM Hepes buffer, pH 7.0, containing 0.5 M NaCl and 20 μM $ZnCl_2$. At 30°C, 0.2 μg of enzyme produced a ΔA of −0.3 at 260 nm in 10 min. The β-lactamase from *Enterobacter cloacae* P99 (active-serine enzyme, class C) was purified as described by Ross [60]. The activity was determined using 500 μl of 100 μM cephaloridin in 50 mM sodium phosphate buffer, pH 7.0. At 30°C, 0.03 μg of enzyme produced a ΔA of −0.3 at 260 nm in 10 min. Before the assays, the stock enzyme solutions (0.5—1.0 mg·ml^{-1}) were diluted in the buffer used for preparing the substrate solutions, supplemented with 0.1 mg/ml of bovine serum albumin. All potential inhibitors and inactivators were tested at final concentrations up to 100 μM.

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