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Articles

Structure–Activity Relationship within a Series of Pyrazolidinone Antibacterial Agents. 1. Effect of Nuclear Modification on *In Vitro* Activity

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The synthesis and biological evaluation of a series of pyrazolidinone-containing mono- and bicyclic compounds are described. The results of this investigation indicate that the [3.3.0] ring system bearing strongly electron-withdrawing groups in the 3-position provides the optimal arrangement for antibacterial activity. Two highly potent derivatives, LY193239 and LY255262, have been selected for further preclinical evaluation.

The β-lactam containing antibacterial agents have become an integral part of the chemotherapeutic arsenal available to today's medical practitioners. Although the variety and number of existing agents is quite extensive, the search for better and more effective drugs continues. The medicinal chemical approach to this search has throughout the years focused on synthetic modifications about the β-lactam ring. These efforts have led to the development of several significant classes of therapeutic agents includng the penicillins, cephalosporins,[1] monobactams, carbapenems,[2] and most recently the carbacephalosporins.[3] Several years ago, we initiated a program designed to discover and develop new chemical scaffolding which could serve to replace the β-lactam ring as a structural feature supporting useful antibacterial activity. This work led to the discovery of the pyrazolidinone class of antibacterial agents in which the key feature was the presence of an aza-γ-lactam (pyrazolidinone) moiety in place of the β-lactam ring.[4] These initial discoveries prompted us to develop a program to probe the structure–activity relationship of the pyrazolidinone-based antibacterials with the intent of improving potency and spectrum of activity. In this account, we describe our efforts to define the optimal pyrazolidinone nucleus which would support potent *in vitro* antibacterial activity.

Our strategy was based upon the assumption that the pyrazolidinone antibactrials' mode of action was the same as that exhibited by the β-lactams. That is, the pyrazolidinones were assumed to exert their antibacterial effect via inhibition of one or more of the bacterial transpeptidase enzymes known as "penicillin binding proteins" (PBPs). Indeed, early studies clearly demonstrated that the [3.3.0] pyrazolidinones effectively compete with penicillin for binding to these enzymes, especially PBP-3.[5] Assuming this PPB–enzyme interaction to be the crucial mechanism by which the pyrazolidinones exert their lethal activity on bacteria, our plans in developing structure–activity relationships (SAR) were keyed on improving the interaction of these compounds with this group of enzymes. Due to the "suicide" nature of the lactam inhibitors, there are two aspects of enzyme–substrate interaction that need to be addressed. As depicted in Scheme I, the first step involved with PBP inactivation involves a noncovalent association of the inhibitor with the enzyme. The formation of this complex is reversible and can be kinetically defined by k_{on}/k_{off}. The second step of the process involves a kinetically "irreversible" step in which an appropriately disposed serine residue in the enzyme's active site is acylated with concomitant lactam ring opening. In order to improve the effectiveness of a particular inhibitor, one can focus on modulating either (or both) of these two steps. Thus, if the affinity of the inhibitor for the enzyme is improved (improved "fit"), an increase in k_{on}/k_{off} (of the

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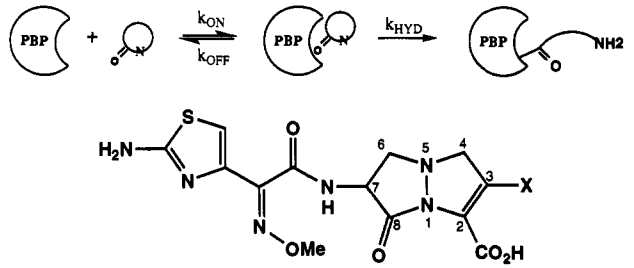
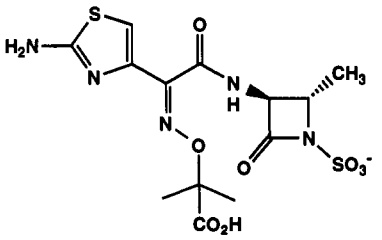
Scheme I



Compound	X
1 (LY173013)	-CO_2Me
2 (LY186826)	-COMe

Figure 1.



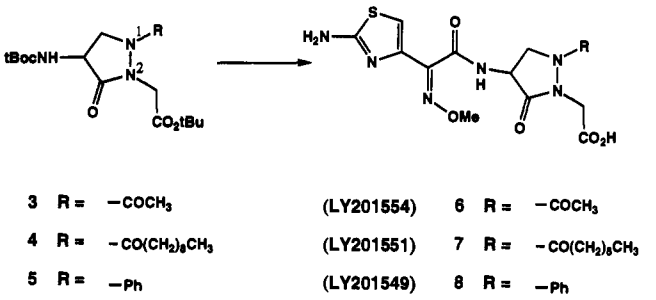
2a Aztreonam

Figure 2.

first step) would be anticipated. The resulting longer residence time of the inhibitor in the active site would provide greater opportunity for the second "irreversible" acylation to occur. On the other hand, if the acylating ability of the inhibitor is increased, one would anticipate a greater k_{hyd} of the second step, resulting in improved efficiency in enzyme inactivation. Thus, one can in principle improve an inhibitor's potency by improving its affinity for the enzyme or by increasing its reactivity. Typically, one must consider both of these aspects of the enzyme–inhibitor interaction while proceeding through a developing SAR. Parenthetically, it should be noted that our ultimate success in preparing more potent antibacterials will be judged on the ability of the new compounds to inhibit growth of bacteria rather than merely an improved ability to deactivate the target enzyme. Thus, in the whole-cell systems that will be used for compound evaluation, one must consider other parameters such as permeability of the cell wall towards the inhibitor and the ability of the inhibitor to evade the bacterial defensive enzymes.

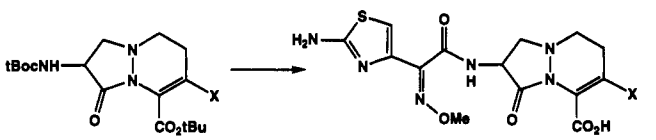
Our first approach to this challenge was to examine the effect of modifying (in a rather dramatic way) the basic pyrazolidinone-containing nuclei in order to determine the range of configurations that would support antibacterial activity. The [3.3.0] bicyclic nucleus of the initial lead compounds LY173013 (1) and LY186826 (2) (Figure 1) had already demonstrated an ability to support biological activity.[6] Assuming that the aza-γ-lactam contained within these compounds was serving as a biological surrogate of the β-lactam ring, it seemed appropraite to substitute this five-membered ring lactam for the β-lactam of the major classes of known antibacterials. We began by investigating monocyclic derivatives due to the β-lactam analogy provided by the monobactams (such as aztreonam, **2a**; Figure 2). Thus, the pyrazolidinones **3–5**[7] were deblocked and acylated under modified Schotten–Baumann conditions to provide compounds **6–8** (Scheme II)

Scheme II



3	R = $-COCH_3$	(LY201554)	6	R = $-COCH_3$
4	R = $-CO(CH_2)_6CH_3$	(LY201551)	7	R = $-CO(CH_2)_6CH_3$
5	R = $-Ph$	(LY201549)	8	R = $-Ph$

Scheme III



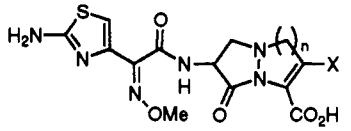
9	X = -CO_2Me	(LY253837)	11 X = -CO_2Me
10	X = -COMe	(LY227953)	12 X = -COMe

suitable for biological evaluation. Unfortunately, none of these monocyclic derivatives exhibited any antibacterial activity (against either Gram-positive or -negative organisms) when tested to a maximum concentration of 128 μg/mL. Our attempts to prepare the N_2-sulfonated derivatives of the monocyclic pyrazolidinones (in analogy to azethreonam **2a**) were unsuccessful, presumably due to the lability of the N_2–sulfonate bond.

The reason for the lack of activity in these monocyclic compounds is not known. Certainly, the overall molecular geometry is much different than the known active bicyclic pyrazolidinones (**1** and **2**). Also, one would anticipate the reactivity of the lactam ring to be less than that of the bicyclic system due to the absence of additional ring strain. In any case, although this investigation into the monocyclic pyrazolidinones as potential antibacterials was rather limited, the initial discouraging results led us to divert our attention to bicyclic structures containing the aza-γ-lactam ring.

The cephalosporin and carbacephalosporin bicyclic nuclei consist of a β-lactam fused to a six-membered ring. If a pyrazolidinone ring is substituted for the β-lactam ring present in these antibacterials, one arrives at [4.3.0]-fused pyrazolidinones. It appeared very important to us to investigate this class of compounds carefully. In particular, we set out to prepare the exact homologues of the known active compounds **1** and **2**. In this way, the effect of the size of the ring fused to the pyrazolidinone on the antibacterial activity could be precisely determind. Thus, [4.3.0] derivatives **11** (LY253837) and **12** (LY227953) were prepared from precursors **9** and **10** as shown in Scheme III.[7,8] Unfortunately, neither compound demonstrated any inhibition of Gram-positive or -negative growth when tested to a maximum concentration of 128 μg/mL. These results are in stark contrast to the inhibition displayed by the lower homologues **1** and **2** (Table I). Clearly, the overall geometry of the [4.3.0] systems represented by **11** and **12** are different from that of **1** and **2**. Although this would likely impact the initial association step of the enzyme inhibition (Scheme I), it is not clear from examination of molecular models that the geometric differences would be significant enough to explain such disparity in antibacterial activity. However, PBP binding studies have indicated that compounds **11** and **12** do not

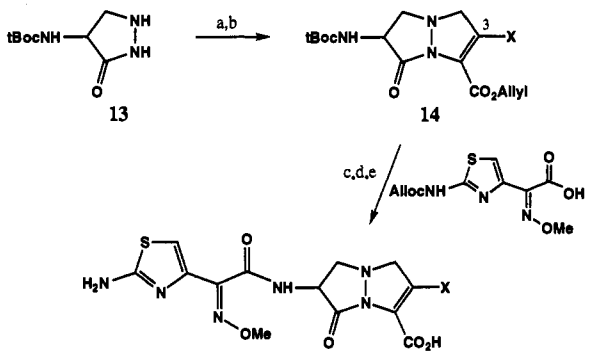
Table I



				MIC (μg/mL)[a]							
no.	code	X	*n*	*S. au* X1.1	*S. Pn.* PARK	*H. in.* C.L.	*E. co* EC14	*Kleb.* X26	*E. ae.* C32	*Pseu.* X239	*Serr.* X99
1	LY173013	CO_2Me	1	>128	8	32	8	8	16	>128	8
2	LY186826	COMe	1	32	1	8	2	1	2	>128	4
11	LY253837	CO_2Me	2	>128	>128	>128	>128	>128	>128	>128	>128
12	LY227953	COMe	2	>128	>128	>128	>128	>128	>128	>128	>128
15	LY243005	CO_2Et	1	>128	8	32	16	8	32	>128	16
16	LY243004	CO_2Pr	1	>128	8	32	32	8	64	>128	32
17	LY228260	CO_2Bn	1	128	64	64	64	64	64	>128	64
18	LY228261	COEt	1	64	2	8	4	2	8	>128	4
19	LY267021	CN	1	64	0.5	1	0.5	0.5	2	>128	2
20	LY255693	SO_2Me	1	64	0.25	2	0.125	0.25	0.25	>128	0.25

[a] *S. au* = *Staphylococcus aureus*, *S. pn.* = *Streptococcus pneumoniae*, *H. in.* = *Haemophilus influenza*, *E. co.* = *E. coli*, *Kleb.* = *Klebsiella*, *E. ae.* = *Enterobacter aerogenes*, *Pseu.* = *Pseudomonas*, *Serr.* = *Serratia*.

Scheme IV[a]



[a] (a) $(R_2O_3P)(X)=CH_2$; (b) $ClCOCO_2$-allyl, iPr_2NEt; (c) HCl, HOAc; (d) $POCl_3$, *N*-methylmorpholine; (e) $Pd(PPh_3)_4$, triethylsilane.

have sufficient affinity for the PBP's of *Escherichia coli* to compete effectively with penicillin-V for binding (i.e., $IC_{50} > 128$ for **11** and **12** using radiolabeled pen-V for the assay).[9a] The other factor contributing to biological activity is the reactivity of the lactam ring (vida supra). Indeed, hydrolysis studies showed LY227953 (**12**) to be nearly 1 order of magnitude less reactive than its homologue LY186826 (**2**).[9b] We attribute the lack of activity in this case to be most likely due to the inability of the [4.3.0] pyrazolidinones to acylate appropriate amino acid residues in the PBP active site.

From these investigations of the monocyclic and [4.3.0] bicyclic pyrazolidinones, it was evident that the aza-γ-lactam would not substitute for the β-lactam ring in all cases. For this reason, we focused our attention on the [3.3.0] fused pyrazolidinone framework wherein the original antibacterial activity was discovered. As previously reported, a newly-devised synthetic route to the [3.3.0] pyrazolidinone nucleus (**14**, Scheme IV) provided access to a number of substituted derivatives.[7,10] Utilizing this chemistry, we were readily able to explore the effect of nuclear substitution on *in vitro* antibacterial activity within this series. Our SAR studies with the [3.3.0] pyrazolidinone were specifically directed toward modifications of the substitutent at the C-3 position of the bicyclic nucleus. Functionality at an equivalent position in the penicillins and cephalosporins (i.e. vinylogously tethered to the carboxylic acid and lactam nitrogen) is known to have a dramatic effect on the antibacterial activity of these β-lactam-containing compounds. In these cases not only are the steric considerations important but the electron

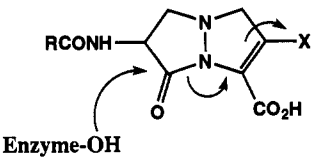


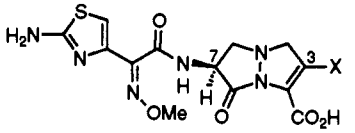
Figure 3.

withdrawing ability of this substituent also directly affects the reactivity of the lactam bond by virtue of its through-conjugated orientation (i.e., its ability to stabilize the products of lactam cleavage). We anticipated that similar factors would be operative with the pyrazolidinone antibacterials (Figure 3).

Our efforts sought to define the steric requirements of the C-3 group (X). In order to achieve interpretable information from this study, we chose to decouple the electron-withdrawing effect (related to k_{hyd}) from size considerations (related to k_{on}/k_{off}). Thus, increasing the size and lipophilicity of the C-3 ester present in LY173013 (**1**) would be expected to have minimal effect on lactam reactivity and hence would most likely influence the specific enzyme binding characteristics of the compound. Thus, utilizing the chemistry outline in Scheme IV, the ethyl ester (LY243005, **15**) propyl ester (LY243004, **16**), and benzyl ester (LY228260, **17**) were prepared, and the *in vitro* microbiological activity was compared to that of LY173013 (**1**) (Table I). As can be seen from the data, the biological activity decreased as the size and lipophilicity of the ester functionality increased. Since the electron-withdrawing ability of these esters would be assumed to be about the same, we concluded that an increase in size and or lipophilicity at the 3-position is deleterious to the antibacterial activity in the [3.3.0] pyrazolidinones. This is presumed to be due to decreased affinity for the target enzyme (assuming their cellular permeability and lactamase susceptibility to be similar). This assumption was further supported in the ketone series with the preparation and evaluation of LY228261 (**18**). This 3-ethyl ketone exhibits diminished *in vitro* activity when compared to its methyl ketone analogue LY186826 (**2**) (Table I).

Our next plan was to study the effect of the electron-withdrawing capability of the 3-substituent on antibacterial activity. At the outset, we anticipated that an increase in this capability would result in a more labile lactam bond thereby increasing k_{hyd} (Scheme I) and potentially providing a more potent antibacterial. This

Table II



21

no.	code	X	MIC (μg/mL)[a]							
			S. au. X1.1	*S. pn.* PARK	*H. in.* C. L.	*E. co.* EC14	*Kleb.* X26	*E. ae.* C32	*Pseu.* X239	*Serr.* X99
21a	LY255262	CN	64	0.25	0.5	0.25	0.25	1	>128	1
21b	LY193239	SO_2Me	32	0.25	0.5	0.06	0.125	0.25	>128	0.125
21c	LY248407	SO_2Et	32	0.125	0.5	0.125	0.125	0.25	>128	0.25
21d	LY203632	SO_2Ph	32	0.125	0.5	0.5	0.125	1	>128	1

[a] See footnote *a* of Table I.

prediction had been verified for the initial lead compounds **1** and **2**. Thus the greater electron-withdrawing potential of the 3-methyl ketone present in **2** as compared with the 3-methyl ester of **1** provided for a more reactive compound (to basic hydrolysis)[11] and a more potent antibacterial (Table I).

In choosing appropriate substituents, for this study we targeted small, nonlipophilic groups (based on our earlier studies) with electron-withdrawing capabilities greater than esters or ketones. To gauge the relative withdrawing capabilities we consulted Hammond σ_p values for various substituents.[12] The σ_p value for CO_2Me is 0.39 and that of COMe is 0.50. From these values, and considerations of size and lipophilicity, we chose the cyano functionality (σ_p = 0.66) as the next substituent to incorporate on the [3.3.0] pyrazolidinone framework. The 3-cyano nucleus (**14**; X = CN) was prepared as previously described.[7] Deblocking and side-chain addition as depicted in Scheme IV provided LY267021 (**19**). To our delight, this compound proved to be more active *in vitro* than the original lead antibacterial agents LY173013 (**1**) and LY186826 (**2**) (Table I). Encouraged by this result, we continued along the same lines of reasoning and prepared the 3-methyl sulfone (σ_p = 0.68) derivative LY255693 (**20**). Biological evaluation revealed an even more potent antibacterial agent (Table I). Clearly, in proceeding from methyl ketone to cyano to methyl sulfone we have not only changed the reactivity of the lactam contained within these constructs but have also made changes with respect to size and lipophilicity. Thus, the influence of these steric effects must also be considered in our analysis. Indeed, the reactivity differences measured for the nitrile **19** (k = 17.3 h^{-1}) and sulfone **20** (k = 14.8 h^{-1})[11] toward base hydrolysis at pH 10 (35 °C) do not account for the observed difference in antimicrobial activity. The effect of the size and lipophilicity of the sulfone was also investigated and will be presented in our discussion of nonracemic derivatives (*vida post*).

Further extension of the lactam reactivity versus antibacterial activity SAR led us to attempt to prepare substituted pyrazolidinones which would be predicted to be more labile toward lactam ring opening than the nitrile **19** or sulfone **20**. Unfortunately our attempts to prepare a 3-$COCF_3$ derivatives were unsuccessful as all attempts to deblock and acylate the nucleus (**14**; X = $COCF_3$) resulted in destruction of the lactam ring. It is our assumption that these derivatives are too labile to be considered as potentially useful antibacterial agents. These limitations not withstanding, our progress in improving the *in vitro* activity of the pyrazolidinone-based agents has been dramatic.

All of the compounds discussed to this point have been racemic and as such would not be appropriate for clinical evaluation. Thus, utilizing the chemistry of Scheme IV beginning with chiral **13** (derived from L-serine)[13] we prepared the optically active 3-cyano (LY255262; **21a**) and 3-methyl sulfone (LY193239; **21b**). These single isomers (distinguished by the *S* configuration at C-7) exhibited approximately twice the antibacterial activity of their racemic counterparts (Table II).

As a final study of the effect of nuclear modification on *in vitro* activity of the pyrazolidinone antibacterials, we prepared the ethyl sulfone LY248407 (**21c**) and phenyl sulfone LY203632 (**21d**). Consistent with our previous findings, these larger and more lipophilic substituents resulted in an overall modest decrease in potency when compared with the parent sulfone LY193239 (**21b**) (Table 2).

In summary, our studies of the effect of nuclear modification on *in vitro* activity of pyrazolidinone-containing antibacterial agents has led us to the discovery of the 3-methyl sulfone substituted [3.3.0] pyrazolidinone LY193239 (**21b**). This highly potent γ-lactam antibacterial is viewed as having potential in treating infectious diseases caused by various Gram-positive and -negative organisms. Investigations into the effect of side-chain substitution (at position 7) on the activity of these novel antibacterials became the next important area of SAR development. The results of these studies will be presented in a future publication.

Experimental Section

All reactions described herein were performed under an inert atmosphere of dry nitrogen in flame-dried glassware unless otherwise noted. All reagents were used as supplied unless stated otherwise. Melting points were recorded on a Thomas-Hoover apparatus and are uncorrected. ^1H NMR spectra were recorded at 300 MHz with a General Electric QE-300 instrument, at 270 MHz with a Brucker W-M instrument and at 90 MHz with a Jeol FX-90 instrument. Chemical shifts are recorded in parts per million (δ) relative to tetramethylsilane. IR spectra were recordedon a Nicolet MX-1 FT-IR, optical rotations were measured on a Perkin-Elmer 241 spectrometer, and UV spectra were obtained on a Cary 219. The mass spectral data were obtained on either a CEC-21-140 or a Varian MAT-731 spectrometer. All MPLC separations were conducted on Merck Lobar columns (LiChroprep RP-18) with the help of a Fluid Metering Inc. pump. Analytical HPLC separations were performed on a Varian chromatographic system utilizing a MicroPak MCH-5N-cap 15 cm × 4 mm column and a variable-wavelength UV detector set to record at 254 nm.

Preparation of 4(*R,S*)-[2-(2-aminothiazol-4-yl)-2(*Z*)-(methoxyimino)acetamido]-1-acetyl-2-(carboxymethyl)pyrazolidin-3-one (6). To 4 mL of neat trifluoroacetic acid was added **3** (1.54 g, 4.3 mmol) at room temperature. After stirring for 30

min the solution was concentrated and the residue dissolved in water. After adjusting the pH to 6.0 with 1 N NaOH, the water was removed *in vacuo* and the residue dissolved in 10% aqueous acetonitrile. After cooling in an ice bath, the solid that formed was filtered and dried to yield 804 mg of the crude deprotected material. This material was suspended in 16 mL of a 50:50 water/acetone solution. The pH was adjusted to 7.0 with 40% K_3PO_4 and 1.27 g (4 mmol) of 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetic acid hydroxybenzotriazole active ester[14] was added followed by 20 mL of acetone. The reaction was stirred at room temperature for 6 h while the pH was maintained between 7.0 and 7.3 with 40% K_3PO_4. The acetone was removed *in vacuo* and the pH adjusted to 6.0 with 1 N HCl. The mixture was filtered through Celite and the pH of the filtrate adjusted to 3.5. The resulting precipitate was filtered and the filtrate concentrated. The product was purified via chromatography on HP-20 resin (eluting with water then acetonitrile) followed by crystallization from methanol to yield 350 mg (26%) of **6**: mp 174–177 °C dec; IR (KBr, cm^{-1}) 3312, 1747, 1721, 1688, 1648, 1533, 1410, 1384, 1242, 1042; ^1H NMR (90 MHz, DMSO-d_6) δ 9.18 (d, J = 7.2 Hz, 1H), 7.14 (s, 2H), 6.92 (s, 1H), 5.20–4.80 (m, 1 H), 4.64–4.10 (m, 3H), 4.10–3.60 (m, 1H), 3.80 (s, 3H), 2.08 (s, 3H); MS m/z (M + 1) 385; UV (EtOH) 292 (ϵ = 5669), 233 nm (ϵ = 17 619); HRMS (FAB) m/z (M + 1) calcd for $C_{13}H_{17}N_6O_6S$ 385.0930, found 385.0932.

Compounds **7** and **8** were prepared in a fashion similar to that described for **6** and obtained in yields of 10–30%.

4(*R,S*)-[2-(2-aminothiazol-4-yl)-2(*Z*)-(methoxyimino)acetamido]-1-decanoyl-2-(carboxymethyl)pyrazolidin-3-one (7): mp 201–204 °C; IR (KBr, cm^{-1}) 3420, 2921, 1695, 1672, 1606, 1528, 1386, 1057; ^1H NMR (90 MHz, DMSO-d_6) δ 9.06 (d, J = 7.2 Hz, 1 H), 7.12 (s, 2H), 6.88 (s, 1H), 4.96–4.20 (m, 2H), 4.12–3.68 (m, 3H), 3.76 (s, 3H), 2.44–2.12 (m, 2H), 1.60–1.08 (br s, 14H), 0.88 (t, J = 5.4 Hz, 3H); MS m/z (M + 1) 497; UV (EtOH) 291 (ϵ = 6088), 234 nm (ϵ = 19 129); HRMS (FAB) m/z (M + 1) calcd for $C_{21}H_{33}N_6O_6S$ 497.2179, found 497.2173.

4(*R,S*)-[2-(2-aminothiazol-4-yl)-2(*Z*)-(methoxyimino)acetamido]-1-benzoyl-2-(carboxymethyl)pyrazolidin-3-one (8): mp 231–234 °C; IR (KBr, cm^{-1}) 3396, 3319, 1717, 1659, 1628, 1537, 1385, 1346; ^1H NMR (300 MHz, DMSO-d_6) δ 9.28 (d, J = 9.7 Hz, 1H), 7.60–7.40 (m, 5H), 7.20 (s, 2H), 6.80 (s, 1H), 4.90–4.80 (m, 1H), 4.35–4.20 (m, 1H), 4.00–3.70 (m, 3H), 3.75 (s, 3H); UV (EtOH) 230 nm (ϵ = 19 937); HRMS (FAB) m/z (M + 1) calcd for $C_{18}H_{19}N_6O_6S$ 447.1087, found 447.1077.

The preparation and physical data obtained for compounds **11**, **12**, **15**, **17–20**, and **21b** have been described previously.[7] Compounds **16**, **21a**, **21c** and **21d** were prepared in a manner identical to that reported for **15**, **17–20**, and **21b**.

3-(*n*-Propoxycarbonyl)-7-(*R,S*)-[2-(2-aminothiazol-4-yl)-2(*Z*)-(methoxyimino)acetamido]-8-oxo-1,5-diazabicyclo[3.3.0]-oct-2-ene-2-carboxylic acid (16): mp >150 °C dec; IR (KBr, cm^{-1}) 3191, 1722, 1676, 1620, 1534, 1431, 1391, 1329, 1266; ^1H NMR (300 MHz, DMSO-d_6) δ 9.13 (br d, J = 6 Hz, 1H), 7.23 (br s, 2H), 7.10 (s, 1H), 4.99–4.87 (m, 1H), 3.94 (t, J = 7.5 Hz, 2H), 4.05–2.85 (m, 5H), 3.83 (s, 3H), 1.61–1.49 (m, 2H), 0.89 (t, J = 7.5 Hz, 3H); MS m/z (M + 1) 453; UV (EtOH) 309 (ϵ = 8622), 232 nm (ϵ = 13 722); HRMS (FAB) m/z (M + 1) calcd for $C_{17}H_{21}N_6O_7S$ 453.1192, found 453.1212.

3-Cyano-7(*S*)-[2-(2-aminothiazol-4-yl)-2(*Z*)-(methoxyimino)acetamido]-8-oxo-1,5-diazabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (21a): mp >225 °C dec;, IR (KBr, cm^{-1}) 3320, 2220, 1724, 1642, 1534, 1399, 1047; NMR (300 MHz, DMSO-d_6) δ 9.17 (d, J = 9 Hz, 1H), 7.25 (br s, 2H), 6.96 (s, 1H), 5.10–4.94 (m, 1H), 4.34 and 4.03 (AB q, J = 12 Hz, 2H), 4.00–3.60 (m, 1H), 3.85 (s, 3H), 3.13 (dd, J = 9 and 12 Hz, 1H); MS m/z (M + 1) 392; UV (EtOH) 303 (ϵ = 9307), 230 nm (ϵ = 16 345); $[\alpha]^{25}_{589}$ −383.1° (c = 0.189, MeOH); HRMS (FAB) m/z (M + 1) calcd for $C_{14}H_{14}N_7O_6S$ 392.0777, found 392.0796.

3-(Ethylsulfonyl)-7(*S*)-[2-(2-aminothiazol-4-yl)-2(*Z*)-(methoxyimino)acetamido]-8-oxo-1,5-diazabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (21c): mp >200 °C; IR (KBr, cm^{-1}) 3320, 2940, 1725, 1705, 1530, 1410, 1380, 1310, 1125, 1040; NMR (300 MHz, DMSO-d_6) δ 9.16 (d, J = 10 Hz, 1H), 7.23 (br s, 2H), 6.92 (s, 1H), 5.10–4.94 (m, 1H), 4.05 and 4.33 (AB q, J = 12 Hz, 2H), 3.94 (t, J = 12 Hz, 1H), 3.84 (s, 3H), 3.77–3.10 (m, 3H), 1.22 (t, J = 10 Hz, 3H); MS m/z (M + 1) 459; UV (EtOH) 304 (ϵ = 11 717), 232 nm (ϵ = 14 870); $[\alpha]^{25}_{589}$ −211.6° (c = 0.225, DMSO).

3-(Phenylsulfonyl)-7(*S*)-[2-(2-aminothiazol-4-yl)-2(*Z*)-(methoxyimino)acetamido]-8-oxo-1,5-diazabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (21d): mp >200 °C dec; IR (KBr, cm^{-1}) 3330, 1725, 1645, 1530, 1405, 1150; NMR (300 MHz, DMSO-d_6) δ 9.09 (d, J = 10 Hz, 1H), 8.05–7.60 (m, 5H), 7.21 (br s, 2H), 6.91 (s, 1H), 5.02–4.90 (m, 1H), 3.83 (s, 3H), 4.12 and 3.82 (AB q, J = 12 Hz, 2H), 3.75 (t, J = 10 Hz, 1H), 3.06 (dd, J = 15, 10 Hz, 1H); MS m/z (M + 1) 507; UV (EtOH) 316 (ϵ = 11 587), 228 nm (ϵ = 22 315); $[\alpha]^{25}_{589}$ −82.7° (c = 0.168, DMSO).

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