SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF NEW CEPHALOSPORINS WITH AMINOIMIDAZOLES AT C-7

EFFECT OF THE *pK*a OF THE C-7 AMINOIMIDAZOLE ON ANTIBACTERIAL SPECTRUM AND β-LACTAMASE STABILITY

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Cephalosporins with new aminoimidazole heterocycles at C-7 have been synthesized by reaction of *anti*-α-aminooximes with C-7 dihaloisocyanocephalosporins esters or by direct condensation of 2-fluoroimidazoles with C-7 aminocephalosporins esters. These compounds combine a broad spectrum of antibacterial activity, including Gram-negative and Gram-positive organisms with a good β-lactamase stability. Activity is discussed in terms of its relationship to the *pK*a of the C-7 aminoimidazole heterocycle, basic C-7 aminoimidazole residues gave cephalosporins with the best β-lactamase stability but the poorest activity against Gram-positive organisms. An additional interesting property of the C-7 imidazolylaminocephalosporins is the oral activity present in some compounds of this series.

In a recent paper, we described the synthesis and antibacterial properties of cephalosporins substituted at C-7 by aminobenzimidazole and aminoimidazoline residues[1]. These compounds possessed high antibacterial activity against a broad spectrum of organisms. This study also showed that the *pK*a of the C-7 heterocycle influences both the spectrum (broad for the benzimidazoles, narrow for the imidazolines) and the lactamase stability (moderate for the benzimidazoles, excellent for the imidazolines). We wish now to report the synthesis and antibacterial properties of the undescribed member of this family of compounds, namely the C-7 imidazolylaminocephalosporins, and discuss the influence of small variations of the *pK*a of the C-7 substituent on the spectrum and β-lactamase stability of these compounds.

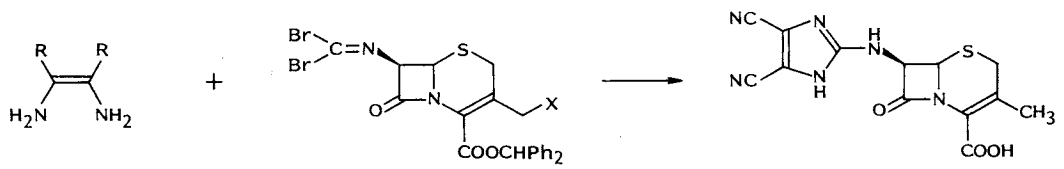
Chemistry

Isocyanide Dihalide Chemistry

The isocyanide dihalides **1** are valuable intermediates in the synthesis of C-7 benzimidazolyl and imidazolinylaminocephalosporins[1,2]. However, the instability of the dienamine of general structure **2a** precludes their use as key intermediates for condensation with the isocyanide dihalides **1** to give directly C-7 imidazolylaminocephalosporins.

Dienamine **2b** substituted with electron withdrawing groups is an exception and this compound could be condensed successfully with **1a** to give the desired cephalosporin **3** (Scheme 1).

Scheme 1.

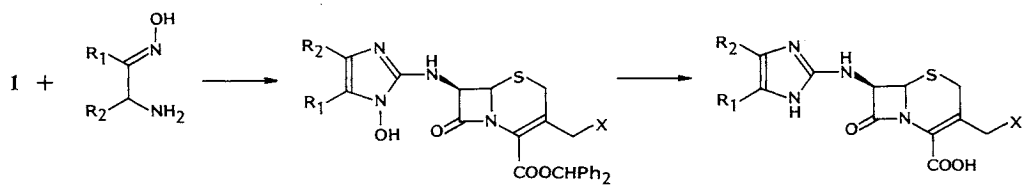


2a R=alkyl, aryl
2b R=CN

1a X=H
1b X=OAc
1c X=STdz

3

Scheme 2.



4

	R_1	R_2
4a	CH_3	H
4b	CH_3	CH_3
4c	Ph	H
4d	Bz	H
4e	PNB	H
4f	CH_2OH	H

5

6

7~14

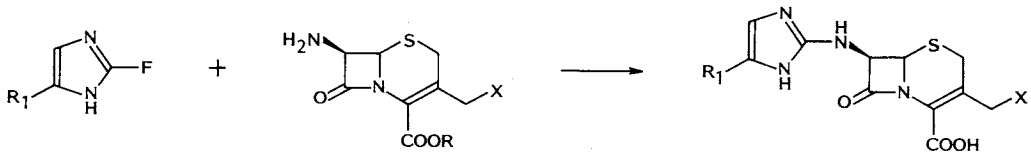
	R_1	R_2	X
7	H	CH_3	H
8	H	CH_3	OAc
9	CH_3	CH_3	H
10	CH_3	CH_3	STdz
11	Ph	H	OAc
12	Bz	H	OAc
13	PNB	H	OAc
14	CH_2OH	H	OAc

To avoid the difficulties due to the instability of the dienamines of more general structure **2a**, we looked at *anti*-α-aminooximes **4**, a readily available class of compounds which can be considered as masked stable dienamine equivalents. The utility of this class of compounds in the synthesis of a variety of heterocycles has been demonstrated[3~5]. We found that these molecules (**4a~4f**) can be condensed with isocyanide dibromides in THF at low temperature (<0°C) to give *N*-hydroxy aminoimidazoles **5**, which can be reduced using mild reducing agents[6] to the desired aminoimidazoles **7~14** or deprotected to give *N*-hydroxyaminoimidazole **6**, free acid. The overall sequence is thus equivalent to the reaction of an unstable dienamine **2a** with the isocyanide dibromide **1**[2] (Scheme 2).

2-Fluoroimidazole Chemistry

Imidazoles substituted at the 2 position by different leaving groups (Cl, I, ...)[7~9] could not be condensed with aminocephalosporin esters under various conditions. In contrast, it has been possible to condense 2-fluoroimidazole[10] under acid catalysis with 7-aminocephalosporin esters to give directly the desired 7-imidazolylaminocephalosporins **17~23**, after deprotection of the carboxylic acid (Scheme 3). Moreover the anion of *N*-trityl-2-fluoroimidazole can be easily generated at low temperature, and reacted

Scheme 3.

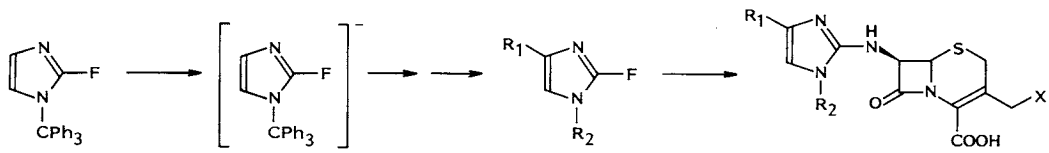


15 16 17~23

	R	X
16a	*t*-Bu	H
16b	*t*-Bu	OAc
16c	*t*-Bu	(STdz)
16d	$CHPh_2$	(STz)
16e	$CHPh_2$	(STrz)
16f	*t*-Bu	(SiTdz)

	R_1	X
17	H	H
18	H	OAc
19	H	STz
20	H	STdz
21	CH_3	STdz
22	H	STrz
23	H	SiTdz

Scheme 4.



24 25~43

	R_1	R_2	X
25	$(CH_2)_2NO_2$	H	OAc
26	$(CH_2)_2CN$	H	OAc
27	$(CH_2)_2NHAc$	H	OAc
28	$(CH_2)_3NHSO_2CH_3$	H	OAc
29	$(CH_2)_3SOEt$	H	STz
30	$(CH_2)_3SO_2Et$	H	STz
31	$(CH_2)_3NHCONH_2$	H	STz
32	$(CH_2)_2COOH$	H	STz
33	SCH_3	H	OAc
34	$CONHCH_3$	H	OAc
35	COOEt	H	OAc
36	H	$(CH_2)_3NH_2$	OAc
37	H	$CH_2CH=CH_2$	OAc
38	COOH	H	OAc
39	NHCOEt	H	OAc
40	$(CH_2)_2CH_3$	H	OAc
41	CH_2NH_2	H	OAc
42	CH_2OCH_3	H	OAc
43	CH_2SCH_3	H	OAc

with a variety of electrophiles leading to 4-substituted fluoroimidazoles **24**. These could be condensed with 7-aminocephalosporin esters to give, after deprotection, the imidazole ring substituted 7-imidazolylaminocephalosporanic acids (**25**~**43**) (Scheme 4). This route permitted, on a small scale, a convergent, short and efficient access to a variety of unsubstituted and monosubstituted 7-imidazolylaminocephalosporins, and was therefore preferred for this class of compounds[11].

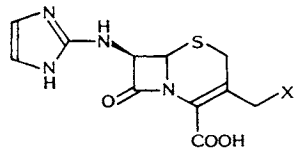
Antibacterial Properties, Structure-activity Discussion

In Vitro Activity

Spectrum

The antibacterial properties of some representative examples of the compounds synthesized are shown

Table 1. Antibacterial activity and β-lactamase stability of unsubstituted C-7 imidazolyl aminocephalosporins.

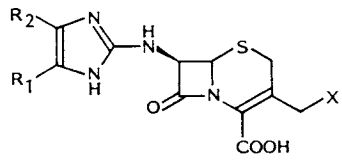


Organism[a]	Compound (free acid)							
	17 X H	**18** OAc	**19** STz	**20** STdz	**22** STrz	**23** SiTdz	Cefotaxime	Mecillinam
Streptococcus pyogenes A1	256	16	2	4	16	1	0.03	16
Staphylococcus aureus A6	>256	32	16	16	32	1	4	16
S. aureus A4[h]	>256	128	32	128	256	2	32	>256
Escherichia coli A8	1	0.12	0.06	0.03	0.06	0.03	0.25	0.06
Klebsiella pneumoniae A24	8	0.12	0.03	0.03	0.03	0.016	0.06	0.03
Enterobacter cloacae A13	32	>32	1	128	16	4	256	0.25
Serratia marcescens A16	>256	>32	8	8	0.5	16	0.25	128
Proteus mirabilis A18	64	32	1	8	16	4	0.06	32
P. vulgaris Pv9	>256	32	2	16	128	16	0.5	64
Pseudomonas aeruginosa A21	256	>32	>256	>256	256	>128	128	>256
E. cloacae P99^{+}[b,c]	4	8	1	4	2	2	32	0.03
E. cloacae P99^{-}[b]	1	0.12	0.016	0.06	0.06	0.016	0.03	0.06
E. coli TEM X3[b,d]	0.5	0.06	0.016	0.03	0.03	0.016	0.06	1
E. coli X4[b,f]	0.5	0.06	0.016	0.03	0.03	0.016	0.06	0.03
K. aerogenes X5L[b,e]	1	2	1	8	0.25	1	4	4
K. aerogenes X6[b,f]	1	0.12	0.06	0.06	0.06	0.03	0.06	0.12
E. coli DC0[b,f]	0.5	0.06	0.016	0.03	0.06	0.016	0.03	0.03
E. coli DC2[b,g]	—	0.016	0.004	0.008	0.03	0.004	0.002	0.004

[a] MIC in μg/ml, Jewell and Permain growth medium, inoculum 10^5 cfu per spot.
[b] Inoculum 10^4 cfu per spot.
[c] Constitutive type I lactamase producer.
[d] TEM I type lactamase producer.
[e] Type IV lactamase producer.
[f] Parent organism.
[g] Permeability mutant.
[h] Lactamase producer.

in Tables 1~4. Imidazole ring unsubstituted cephalosporins have a high level of activity against most Gram-negative organisms, with the exception of *Pseudomonas aeruginosa* and in this respect are equivalent to cefotaxime. As mecillinam, they are inferior to cefotaxime against Gram-positive organisms, especially *Streptococcus pyogenes* (Table 1). The nature of the C-3′ substituent influences the spectrum and the potency; as in the C-7 amidic series, the most potent compounds have heterocyclic residues at C-3′[7]. Mono and disubstituted imidazolylamino-cephalosporins (Tables 2 and 3) share with the unsubstituted series a high level of activity against Gram-negative bacteria. Their activity against Gram-positive organisms tends to be inferior to the unsubstituted derivatives. The introduction of lipophilic residues on the imidazole ring (**11**~**13**, Table 2) does not improve this activity, as is usually seen in the C-7 amidic series[12~15]. Substitution of the imidazole heterocycle can also lead to compounds with better activity against *Serratia*

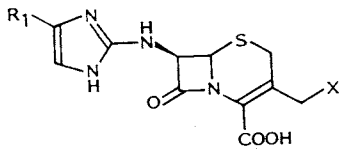
Table 2. Antibacterial activity and β-lactamase stability of alkyl and aryl substituted C-7 imidazolyl aminocephalosporins.



Organism[a]	Compound (free acid)						
	7	**8**	**9**	**11**	**12**	**13**	**40**
	X H	OAc	H	OAc	OAc	OAc	OAc
	R_1 H	H	CH_3	Ph	Benzyl	4-NO_2-benzyl	$-(CH_2)_2CH_3$
	R_2 CH_3	CH_3	CH_3	H	H	H	H
Streptococcus pyogenes A1	>256	128	256	8	—	16	32
Staphylococcus aureus A6	>256	128	>256	4	32	16	64
S. aureus A4[h]	>256	>256	>256	64	128	64	256
Escherichia coli A8	1	0.12	2	32	0.25	0.5	0.06
Klebsiella pneumoniae A24	1	1	8	64	32	0.5	0.06
Enterobacter cloacae A13	8	32	64	>256	128	—	32
Serratia marcescens A16	4	4	32	>256	64	8	128
Proteus mirabilis A18	>256	64	>256	256	32	16	32
P. vulgaris Pv9	>256	32	>256	256	256	128	64
Pseudomonas aeruginosa A21	>256	>256	>256	>256	>256	>256	>256
E. cloacae P99^{+}[b,c]	4	2	4	>256	8	8	4
E. cloacae P99^{-}[b]	1	0.06	4	64	0.5	2	0.06
E. coli TEM X3[b,d]	0.5	0.06	2	64	0.5	0.5	0.03
E. coli X4[b,f]	0.5	0.06	1	8	0.25	0.5	0.016
K. aerogenes X5L[b,e]	1	0.25	4	256	4	8	0.25
K. aerogenes X6[b,f]	1	0.25	4	64	0.5	1	0.03
E. coli DC0[b,f]	1	0.12	2	16	0.25	0.25	0.016
E. coli DC2[b,g]	0.5	<0.03	1	0.5	0.06	0.016	<0.002

[a] MIC in μg/ml, Jewell and Permain growth medium, inoculum 10^5 cfu per spot.
[b] Inoculum 10^4 cfu per spot.
[c] Constitutive type I lactamase producer.
[d] TEM I type lactamase producer.
[e] Type IV lactamase producer.
[f] Parent organism.
[g] Permeability mutant.
[h] Lactamase producer.

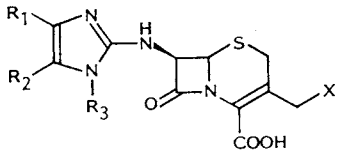
Table 3. Antibacterial activity and β-lactamase stability of functionalized alkyl substituted C-7 imidazolyl aminocephalosporins.



Organism[a]	Compound (free acid)											
	14	**41**	**42**	**43**	**25**	**26**	**27**	**32**	**28**	**29**	**30**	**31**
	X OAc	OAc	OAc	OAc	OAc	OAc	OAc	STz	OAc	STz	STz	STz
	R_1 $-CH_2-OH$	$-CH_2-NH_2$	$-CH_2-OCH_3$	$-CH_2-SCH_3$	$-(CH_2)_2-NO_2$	$-(CH_2)_2-CN$	$-(CH_2)_2-NHAc$	$-(CH_2)_2-COOH$	$-(CH_2)_3-NHSO_2CH_3$	$-(CH_2)_3-SOEt$	$-(CH_2)_3-SO_2Et$	$-(CH_2)_3-NHCONH_2$
Streptococcus pyogenes A1	32	32	32	16	16	32	64	128	32	8	8	32
Staphylococcus aureus A6	32	32	32	32	16	32	>64	>128	32	32	16	64
S. aureus A4[h]	256	256	256	128	128	128	>64	>128	>64	>32	>32	256
Escherichia coli A8	0.06	0.06	0.25	0.06	0.03	0.12	0.06	0.12	0.016	0.06	0.03	0.06
Klebsiella pneumonia A24	2	0.06	0.25	0.06	0.03	0.12	0.12	0.12	0.03	0.03	0.03	0.06
Enterobacter cloacae A13	256	0.5	64	2	>128	128	8	8	2	32	32	32
Serratia marcescens A16	128	32	64	32	0.5	8	64	4	>64	0.25	1	0.5
Proteus mirabilis A18	32	32	16	8	0.25	16	16	2	4	0.25	0.25	2
P. vulgaris Pv9	32	64	32	32	8	32	32	4	8	4	4	8
Pseudomonas aeruginosa A21	>256	>256	>256	>256	>128	>128	>64	>128	>64	>128	>32	256
E. cloacae P99^{+}[b,c]	4	1	64	32	8	16	8	32	4	2	2	2
E. cloacae P99^{-}[b]	0.06	0.06	0.12	0.06	0.03	0.03	0.06	0.12	0.016	0.016	0.03	0.03
E. coli TEM X3[b,d]	0.06	0.06	0.12	0.06	0.03	0.03	0.06	0.12	0.016	0.016	0.03	0.03
E. coli X4[b,f]	<0.03	0.06	0.12	0.06	0.03	0.03	0.06	0.12	0.016	0.016	0.03	0.016
K. aerogenes X5L[b,e]	0.25	0.5	4	2	0.5	2	1	0.5	0.5	0.5	0.5	0.5
K. aerogenes X6[b,f]	0.06	0.25	0.05	0.12	0.06	0.012	0.12	0.25	0.03	0.03	0.03	0.06
E. coli DC0[b,f]	0.06	0.06	0.12	0.06	0.03	0.03	0.06	0.12	0.016	0.016	0.03	0.03
E. coli DC2[b,g]	<0.03	0.03	0.06	0.016	0.008	0.03	0.008	0.03	0.004	0.008	0.008	0.008

[a] MIC μg/ml, Jewell and Permain growth medium, inoculum 10^5 cfu per spot. [b] Inoculum 10^4 cfu per spot. [c] Constitutive type I lactamase producer. [d] TEM I type lactamase producer. [e] Type IV lactamase producer. [f] Parent organism. [g] Permeability mutant. [h] Lactamase producer.

Table 4. Antibacterial spectrum and β-lactamase stability of electron withdrawing groups and nitrogen substituted C-7 imidazolyl aminocephalosporins.



Organism[a]	Compound (free acid)								
		3	**33**	**35**	**38**	**34**	**39**	**6**	**37**	**36**
	X	H	OAc	OAc	OAc	OAc	OAc	H	OAc	OAc
	R_1	CN	H	H	H	H	H	H	H	H
	R_2	CN	SCH_3	COOEt	COOH	$CONHCH_3$	NHCOEt	CH_3	H	H
	R_3	H	H	H	H	H	H	OH	$-CH_2CH=CH_2$	$-(CH_2)_3NH_2$
Streptococcus pyogenes A1		>256	64	4	64	32	64	256	32	128
Staphylococcus aureus A6		64	64	4	64	32	128	>256	16	>128
S. aureus A4[h]		>256	>256	16	256	64	256	>256	>256	>128
Escherichia coli A8		>256	4	4	0.5	2	64	64	2	0.12
Klebsiella pneumoniae A24		>256	16	2	0.5	2	64	128	1	0.12
Enterobacter cloacae A13		>256	64	≥256	>256	>256	>256	>256	64	16
Serratia marcescens A16		>256	256	64	2	64	>256	256	256	64
Proteus mirabilis A18		>256	64	8	64	4	64	256	256	128
P. vulgaris Pv9		—	128	≥256	64	64	>256	>256	256	>128
Pseudomonas aeruginosa A21		>256	≥256	≥256	≥256	>256	>256	>256	>256	>128
E. cloacae P99^{+}[b,c]		>256	128	≥256	16	256	>256	256	128	0.25
E. cloacae P99^{-}[b]		>256	4	8	0.5	2	64	64	4	0.12
E. coli TEM X3[b,d]		>256	4	4	0.25	2	64	64	2	0.12
E. coli X4[b,f]		>256	2	2	0.25	1	64	64	1	0.12
K. aerogenes X5L[b,e]		>256	32	64	4	32	256	128	64	4
K. aerogenes X6[b,f]		>256	4	4	1	4	128	128	8	0.5
E. coli DC0[b,f]		>256	4	4	0.5	2	64	64	1	0.12
E. coli DC2[b,g]		>256	2	1	0.12	—	16	32	0.25	0.06

[a] MIC in μg/ml, Jewell and Permain growth medium, inoculum 10^5 cfu per spot. [b] Inoculum 10^4 cfu per spot. [c] Constitutive type I lactamase producer. [d] TEM type lactamase producer. [e] Type IV lactamase producer. [f] Parent organism. [g] Permeability mutant. [h] Lactamase producer.

marcescens and *Proteus mirabilis* strains (**25**, **29**, **30**, Table 3).

The substitution of the imidazole ring by electron withdrawing groups leads to much less potent compounds (Table 4). The substitution of the nitrogen of the imidazole heterocycle is also detrimental to activity (**6**, **36**, **37**, Table 4).

Except for the most lipophilic compounds, **11**, **13** (Table 2) the penetration of these compounds through the outer membrane of *Escherichia coli* is good, as can be seen by comparing their activity against *E. coli* DC0 with their activity against the permeability mutant *E. coli* DC2 (Tables 1~4). The nature of the imidazole substituent seems to have little influence on the intrinsic activity against the *E. coli* DC2 organism, except for the phenyl substituted compound **11** (Tables 2, 3). However it is interesting to note that the low activity of imidazolylaminocephalosporins substituted by electron withdrawing groups is primarily due to their low intrinsic activity against Gram-negative organisms, as can be seen in the case of *E. coli* DC2 (Table 4). The positively charged C-7 substituent therefore plays an essential role in the interaction of these compounds with their target enzyme, PBP2[1].

β-Lactamase Stability

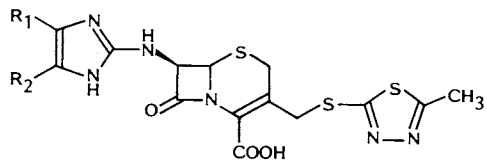
Another interesting feature of these compounds (Tables 1~3) resides in their very good β-lactamase stability against all tested classes of β-lactamases. In this respect they are equivalent or superior to cefotaxime (Table 1).

Influence of the *pK*a of the C-7 Imidazole on Spectrum and Lactamase Stability

The dependence of the antibacterial spectrum and the β-lactamase stability on the *pK*a of the C-7 heterocyclic substituent has been mentioned in our previous paper[1]. The imidazole series now offers the opportunity to fine tune, in the same series, this structure activity finding over a narrow range of *pK*a values (7.1~8.05), by mono and dimethylation of the imidazole ring (Tables 5, 6).

Thus, it is apparent that even a small increase in the percentage of protonated form present at

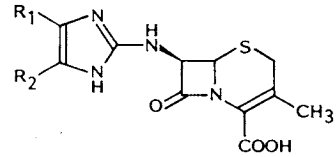
Table 5. Influence on antibacterial spectrum of the *pK*a of 7-imidazolyl aminocephalosporins.



Compound	R_1	R_2	*Streptococcus pyogenes* AO1[a]	*Staphylococcus aureus* A6[a]	*S. aureus* A4[a,c]	*Escherichia coli* DC0[b,d]	*pK*a	% protonated form at pH 7.4	*ΔRm*[e]
20	H	H	2	8	32	0.03	7.1	33	0
21	CH_3	H	16	16	128	0.015	7.4	50	0.24
10	CH_3	CH_3	128	256	>256	0.03	8.05	80	0.40

[a] MIC in μg/ml, Jewell and Permain growth medium, inoculum 10^5 cfu per spot.
[b] Inoculum 10^4 cfu per spot.
[c] Lactamase producer.
[d] Parent organism.
[e] Ref 11.

Table 6. Influence on β-lactamase stability of the *p*Ka of 7-imidazolyl aminocephalosporins.



Compound	R_1	R_2	β-Lactamase type[d]				*p*Ka	% protonated form at pH 7.4
			Ia[a]	Id[a]	IIIa[b]	IVc[c]		
17	H	H	3.8	9	0.27	2.1	7.1	33
7	H	CH_3	2.4	1.14	<0.13	0.8	7.4	50
9	CH_3	CH_3	1.4	<0.15	<0.14	<0.6	8.05	80
Cefotaxime			<0.3	1.7	<0.09	6.0		

[a] Constitutive type I β-lactamase.
[b] TEM I type β-lactamase.
[c] Type IV β-lactamase.
[d] Relative rates of hydrolysis, cephaloridine 100.

physiological pH has a detrimental effect on Gram-positive activity (Table 5). Activity against Gram-negative organisms, as exemplified by *E. coli* DC0, is not influenced by such a small variation of *p*Ka of the C-7 substituent (Table 5). Interestingly the increase in lipophilicity of these compounds, as measured by their ΔRm, is not related with an increased potency against Gram-positive organisms as is usually seen in the amidic series[15] (Table 5) which emphasises further the dominant importance of the *p*Ka of the C-7 aminoimidazole substituent on spectrum in this series.

The β-lactamase stability of 7-imidazolyl aminocephalosporins is also highly dependent on the *p*Ka of the C-7 aminoimidazole substituent. Indeed, even a slight increase of the *p*Ka of the C-7 amino imidazole leads to a measurable corresponding decrease of the rate of hydrolysis by various β-lactamases (Table 6). This result establishes therefore in the imidazole series the correlation existing between β-lactamase stability and positively charged C-7 substituents[1], the most stable compounds having the most basic C-7 aminoimidazole substituent.

In Vivo Activity

Compound **22** has been extensively studied in mouse protection tests, Table 7 shows some of the results obtained, compared to cefaclor, a well established orally active cephalosproin.

Conclusion

The C-7 imidazolylaminocephalosporins are a novel family of highly active antibacterials. The spectrum of activity is broad, but mainly directed towards the Gram-negative organisms. Interesting features of this family of compounds are their good penetration into the periplasmic space of Gram-negative bacteria and their good resistance to hydrolysis by various chromosomally and plasmid mediated β-lactamases. The dependence of the antibacterial spectrum and the β-lactamase stability on the *p*Ka of the C-7 aminoimidazole heterocycle is an interesting feature of this series which emphasises further the findings in the benzimidazole and imidazoline series and constitutes a novel discovery in cephalosporin and penicillin structure-activity relationships.

Table 7. Activity of **22** and cefaclor in mouse protection test[a].

Organism	Compound					
	22			Cefaclor		
	MIC[b]	PO[c]	Sc[d]	MIC[b]	PO[c]	Sc[d]
Staphylococcus aureus A6	32	>100	>100	2	1.83	2.07
Escherichia coli EO18 (Lact.$^+$)	0.25	0.84	1.27	2	4.41	17.8
Salmonella dublin A20	0.008	0.15	0.14	1	1.27	1.93
Enterobacter cloacae F004	0.12	0.76	0.73	8	4.39	4.39
Proteus vulgaris PO15	0.25	<0.39	<0.39	256	15.9	13.4

[a] Group of five mice were challenged intraperitoneally with the test organisms ($10\sim100$ LD_{50} doses) and dosed twice on the day of challenge, the experiments were terminated after four days and PD_{50} were calculated by the Logit Analysis.
[b] MIC in μg/ml, Jewel and Permain agar, inoculum 10^5 cfu per spot.
[c] PD_{50}, oral dosing.
[d] PD_{50}, subcutaneous dosing.

Table 8. Supplementary material (^{1}H NMR data of imidazolyl aminocephalosporins; δ ppm).

6	(90 MHz, DMSO-d_6): 2.04 (s, 6H), 3.44 (s, 2H), 5.04 (d, J=4.5 Hz, 1H), 5.48 (d, J=4.5 Hz, 1H), 6.42 (s, 1H)
8	(60 MHz, DMSO-d_6): 2.1 (s, 3H), 2.2 (s, 3H), 3.7 (s, 2H), 4.9 (d, J=13 Hz, 1H), 5.2 (d, J=13 Hz, 1H), 5.3 (d, J=4.5 Hz, 1H), 5.7 (d, J=4.5 Hz, 1H), 6.8 (s, 1H)
9	(90 MHz, DMSO-d_6-CD_3COOD): 2.05 (s, 6H), 2.1 (s, 3H), 3.4 (d, J=18 Hz, 1H), 3.6 (d, J=18 Hz, 1H), 5.1 (d, J=4.5 Hz, 1H), 5.4 (d, J=4.5 Hz, 1H)
10	(90 MHz, DMSO-d_6-CD_3COOD): 2.04 (s, 6H), 2.67 (s, 3H), 3.6~3.8 (AB, 2H), 4.3~4.55 (AB, 2H), 5.16~5.48 (AB, 2H)
11	(90 MHz, DMSO-d_6): 2.0 (s, 3H), 3.55 (m, 2H), 4.7 (d, J=13 Hz, 1H), 5.0 (d, J=13 Hz, 1H), 5.2 (d, J=4.5 Hz, 1H), 5.8 (d, J=4.5 Hz, 1H), 7.3 (s, 1H), 7.2~7.8 (m, 5H)
12	(60 MHz, DMSO-d_6, TFAd): 2.0 (s, 3H), 3.6 (s, 2H), 3.9 (s, 2H), 4.7 (d, J=13 Hz, 1H), 5.0 (d, J=13 Hz, 1H), 5.2 (d, J=4.5 Hz, 1H), 5.6 (d, J=4.5 Hz, 1H), 6.8 (s, 1H), 7.3 (s, 5H)
13	(90 MHz, DMSO-d_6-CD_3COOD): 2.0 (s, 3H,), 3.5~3.7 (m, 2H), 4.0 (s, 2H), 4.7 (d, J=13 Hz, 1H), 5.0 (d, J=13 Hz, 1H), 5.2 (d, J=4.5 Hz, 1H), 5.6 (d, J=4.5 Hz, 1H), 6.8 (s, 1H), 7.5 (d, J=9 Hz, 2H), 8.2 (d, J=9 Hz, 2H)
14	(90 MHz, DMSO-d_6): 2.0 (s, 3H), 3.5 (m, 2H), 4.3 (s, 2H), 4.75 (d, J=12 Hz, 1H), 5.05 (d, J=12 Hz, 1H), 5.15 (d, J=4.5 Hz, 1H), 5.7 (m, 1H), 6.8 (s, 1H)
17	(90 MHz, TFAd): 2.5 (s, 3H), 3.58 (m, 2H), 5.44 (d, J=4.5 Hz, 1H), 5.6 (m, 1H), 7.0 (s, 2H)
18	(90 MHz, DMSO-d_6): 2.1 (s, 3H), 3.65 (m, 2H), 4.8 (d, J=12 Hz, 1H), 5.15 (d, J=12 Hz, 1H), 5.3 (d, J=4.5 Hz, 1H), 5.7 (dd, J=4.5, 10 Hz, 1H), 7.1 (s, 2H), 9.4 (d, J=10 Hz, 1H)
19	(90 MHz, DMSO-d_6-CD_3COOD): 3.7 (s, 2H), 3.9 (s, 3H), 4.3 (s, 2H), 5.15 (d, J=4.5 Hz, 1H), 5.5 (d, J=4.5 Hz, 1H), 7.0 (s, 2H)
20	(90 MHz, DMSO-d_6): 2.6 (s, 3H), 3.7 (m, 2H), 4.2 (d, J=12 Hz, 1H), 4.5 (d, J=12 Hz, 1H), 5.1 (d, J=4.5 Hz, 1H), 5.5 (m, 1H), 6.9 (s, 2H), 9.2 (m, 1H)
21	(90 MHz, DMSO-d_6): 2.1 (s, 3H), 2.65 (s, 3H), 3.6 (d, J=18 Hz, 1H), 3.8 (d, J=18 Hz, 1H), 4.2 (d, J=13 Hz, 1H), 4.5 (dd, J=13 Hz, 1H), 5.2 (d, J=4.5 Hz, 1H), 5.5 (dd, J=4.5, 7.2 Hz, 1H), 6.7 (s, 1H), 9.2 (d, J=7.2 Hz, 1H)
22	(90 MHz, DMSO-d_6): 3.7 (m, 2H), 4.0 (m, 2H), 5.1 (d, J=4.5 Hz, 1H), 5.5 (dd, J=4.5, 10 Hz, 1H), 7.05 (s, 2H), 7.2 (m, 1H), 7.9 (s, 1H), 9.3 (d, J=10 Hz, 1H)
23	(90 MHz, DMSO-d_6-CD_3COOD): 3.4 (d, J=18 Hz, 1H), 3.65 (d, J=18 Hz, 1H), 4.3 (m, 2H), 5.06 (d, J=4.5 Hz, 1H), 5.54 (d, J=4.5 Hz, 1H), 6.81 (s, 2H), 8.88 (s, 1H)
25	(90 MHz, DMSO-d_6-CD_3COOD): 2.05 (s, 3H), 3.08 (t, J=7.5 Hz, 2H), 3.39 (d, J=18 Hz, 1H), 3.57 (d, J=18 Hz, 1H), 4.68 (d, J=13.2 Hz, 1H), 4.75 (m, 2H), 5.03 (d, J=13.2 Hz, 1H), 5.13 (d, J=4.5 Hz, 1H), 5.59 (d, J=4.5 Hz, 1H), 6.50 (s, 1H)
26	(100 MHz, DMSO-d_6-CD_3COOD): 1.97 (s, 3H), 2.75 (m, 4H), 3.39 (d, J=20.5 Hz, 1H), 3.65 (d, J=20.5 Hz, 1H), 4.72 (d, J=14.3 Hz, 2H), 5.02 (d, J=14.3 Hz, 1H), 5.02 (d, J=4.4 Hz, 1H), 5.59 (d, J=4.4 Hz, 1H), 6.63 (s, 1H)

Table 8. (Continued)

27	(90 MHz, DMSO-d_6-CD_3COOD): 1.82 (s, 3H), 2.02 (s, 3H), 2.65 (m, obscured by solvent, ~2H), 3.27 (t, J=6.6 Hz, 2H), 3.39 (d, J=18.5 Hz, 1H), 3.65 (d, J=18.5 Hz, 1H), 4.75 (d, J=13.2 Hz, 1H), 5.04 (d, J=13.8 Hz, 1H), 5.20 (d, J=4.2 Hz, 1H), 5.56 (d, J=4.2 Hz, 1H), 6.64 (s, 1H)
28	(90 MHz, DMSO-d_6-CD_3COOD): 1.74 (q, obscured by solvent, ~2H), 2.01 (s, 3H), 2.50 (t, obscured by solvent, ~2H), 2.88 (s, 3H), 2.94 (t, J=7.5 Hz, 2H), 3.37 (d, J=21.1 Hz, 1H), 3.64 (d, J=21.1 Hz, 1H), 4.73 (d, J=14.6 Hz, 1H), 5.03 (d, J=14.6 Hz, 1H), 5.08 (d, J=5.0 Hz, 1H), 5.55 (d, J=5.0 Hz, 1H), 6.62 (s, 1H)
29	(90 MHz, DMSO-d_6-CD_3COOD): 1.06 (t, J=7.3 Hz, 3H), 1.80 (m, obscured by solvent, ~2H), 2.4~2.7 (m, obscured by solvent, ~6H), 3.57 (d, J=18 Hz, 1H), 3.68 (d, J=18 Hz, 1H), 3.80 (s, 3H), 4.20 (br s, 2H), 4.98 (d, J=4.9 Hz, 1H), 5.43 (d, J=4.9 Hz, 1H), 6.55 (s, 1H)
30	(90 MHz, DMSO-d_6-CD_3COOD): 1.17 (t, J=7.4 Hz, 3H), 1.85 (m, obscured by solvent, ~2H), 2.50 (t, J=7.5 Hz, obscured by solvent, ~2H), 3.04 (m, 4H), 3.64 (pseudo d, J=9.7 Hz, 2H), 3.91 (s, 3H), 4.30 (br s, 2H), 5.06 (d, J=4.6 Hz, 1H), 5.55 (d, J=4.6 Hz, 1H), 6.59 (s, 1H)
31	(90 MHz, DMSO-d_6-CD_3COOD): 1.63 (q, J=7.0 Hz, 2H), 2.50 (t, obscured by solvent, ~2H), 3.00 (t, J=6.0 Hz, 2H), 3.66 (pseudo d, J=4.5 Hz, 2H), 3.93 (s, 3H), 4.32 (br s, 2H), 5.09 (d, J=4.5 Hz, 1H), 5.54 (d, J=4.5 Hz, 1H), 6.65 (s, 1H)
32	(90 MHz, DMSO-d_6-CD_3COOD): 2.6~2.8 (m, obscured by solvent, 4H), 3.68 (pseudo d, J=4.5 Hz, 2H), 3.95 (s, 3H), 4.34 (br s, 2H), 5.12 (d, J=4.5 Hz, 1H), 5.52 (d, J=4.5 Hz, 1H), 6.66 (s, 1H)
33	(90 MHz, DMSO-d_6-CD_3COOD): 2.08 (s, 3H), 2.28 (s, 3H), 3.40 (d, J=18 Hz, 1H), 3.64 (d, J=18 Hz, 1H), 4.7 (d, J=13 Hz, 1H), 5.05 (d, J=13 Hz, 1H), 5.15 (d, J=4 Hz, 1H), 5.62 (q, J=8, 4 Hz, 1H), 6.60 (s, 1H), 6.95 (d, J=8 Hz, 1H)
34	(90 MHz, DMSO-d_6): 2.03 (s, 3H), 2.73 (s, 3H), 3.37 (d, J=18 Hz, 1H), 3.63 (d, J=18 Hz, 1H), 4.69 (d, J=12.9 Hz, 1H), 5.0 (d, J=12.9 Hz, 1H), 5.14 (d, J=5.1 Hz, 1H), 5.7 (d, J=5.1 Hz, 1H), 7.1 (s, 1H)
35	(90 MHz, DMSO-d_6): 1.20 (t, J=6.4 Hz, 3H), 2.03 (s, 3H), 3.37 (d, J=18 Hz, 1H), 3.6 (d, J=18 Hz, 1H), 4.17 (q, J=6.4 Hz, 2H), 4.66 (d, J=12.9 Hz, 1H), 5.00 (d, J=12.9 Hz, 1H), 5.14 (d, J=5.1 Hz, 1H), 5.63 and 5.74 (dd, J=5.1, 9 Hz, 1H), 7.0 (d, J=9 Hz, 1H), 7.26 (s, 1H)
36	(90 MHz, DMSO-d_6): 1.9 (m, 2H), 2.04 (s, 3H), 2.82 (br t, 2H), 3.48 (d, J=18.4 Hz, 1H), 3.76 (d, J=18.4 Hz, 1H), 4.07 (br t, 2H), 4.73 (d, J=12.9 Hz, 1H), 5.04 (d, J=12.9 Hz, 1H), 5.24 (d, J=4.6 Hz, 1H), 5.65 (d, J=4.6 Hz, 1H), 7.22 (s, 2H)
37	(90 MHz, DMSO-d_6): 1.89 (s, 3H), 3.26 (d, J=18 Hz, 1H), 3.52 (d, J=18 Hz, 1H), 4.37 (d, J=5.1 Hz, 2H), 4.58 (d, J=12.9 Hz, 1H), 4.89 (d, J=12.9 Hz, 1H), 4.90 (m, 3H), 5.49 (d, J=3.9 Hz, 1H), 5.78~6.0 (m, 1H), 6.58 (d, J=1.3 Hz, 1H), 6.63 (d, J=1.3 Hz, 1H)
38	(90 MHz, DMSO-d_6): 2.03 (s, 3H), 3.37 (d, J=18 Hz, 1H), 3.66 (d, J=18 Hz, 1H), 4.69 (d, J=12.9 Hz, 1H), 4.97 (d, J=12.9 Hz, 1H), 5.12 (d, J=5.1 Hz, 1H), 5.60, 5.72 (dd, J=5.1, 9 Hz, 1H), 6.80 (d, J=9 Hz, 1H), 7.20 (s, 1H)
39	(90 MHz, DMSO-d_6): 1.00 (t, J=8 Hz, 3H), 2.04 (s, 3H), 2.12 (q, J=8 Hz, 2H), 3.42 (d, J=16 Hz, 1H), 3.7 (d, J=16 Hz, 1H), 4.7 (d, J=13 Hz, 1H), 5.04 (d, J=13 Hz, 1H), 5.12 (d, J=4 Hz, 1H), 5.60 (d, J=4 Hz, 1H), 6.64 (s, 1H)
40	(90 MHz, DMSO-d_6-CD_3COOD): 0.84 (t, J=7.2 Hz, 3H), 1.5 (q, J=7.2 Hz, 2H), 1.96 (s, 3H), 2.2~2.6 (m, obscured by solvent, 2H), 3.3 (d, J=18 Hz, 1H), 3.58 (d, J=18 Hz, 1H), 4.70 (d, J=12.6 Hz, 1H), 5.0 (d, J=12.6 Hz, 1H), 5.08 (d, J=4.5 Hz, 1H), 5.52 (d, J=4.5 Hz, 1H), 6.52 (s, 1H)
41	(90 MHz, DMSO-d_6): 2.05 (s, 3H), 3.7 (m, 2H), 3.85 (s, 2H), 4.7 (d, J=13 Hz, 1H), 5.1 (d, J=13 Hz, 1H), 5.17 (d, J=4.5 Hz, 1H), 5.68 (d, J=4.5 Hz, 1H), 6.76 (s, 1H)
42	(90 MHz, DMSO-d_6-CD_3COOD): 2.05 (s, 3H), 3.3 (s, 3H), 3.5 (d, J=18 Hz, 1H), 3.7 (d, J=18 Hz, 1H), 4.3 (s, 2H), 4.7 (d, J=13 Hz, 1H), 5.1 (d, J=13 Hz, 1H), 5.2 (d, J=4.5 Hz, 1H), 5.65 (d, J=4.5 Hz, 1H), 7.0 (s, 1H)
43	(90 MHz, DMSO-d_6-CD_3COOD): 2.0 (s, 6H), 3.4 (d, J=19 Hz, 1H), 3.7 (d, J=19 Hz, 1H), 4.7 (d, J=13 Hz, 1H), 5.05 (d, J=13 Hz, 1H), 5.1 (d, J=4.5 Hz, 1H), 5.65 (d, J=4.5 Hz, 1H), 6.75 (s, 1H)

In addition, compound **22** was found to be very well absorbed after oral administration to human volunteers (77% of a 100 mg administered dose was recovered in the urine) which adds further interest to the imidazolylaminocephalosporins.

Experimental

IR spectra (not reported) were recorded as liquid films or KBr pellets on a Perkin-Elmer 781

spectrophotometer and were fully consistent with the assigned structure. ^{1}H NMR spectra were recorded on a 90 MHz JEOL FX90Q, a VARIAN EM390 or BRUKER HX90E spectrometer.

Final cephalosporins of Tables 1~6 were usually hygroscopic solids, which on analysis proved to be mixtures of zwitterion, hydrofluoride or bromide and trifluoroacetate. Meaningful microanalyses were therefore difficult to obtain. IR and ^{1}H NMR have been used to establish the structures of our compounds (Table 8 of supplementary material).

Rm Values Determination:

Rm values[15] were obtained by a reverse phase TLC method using silanised silica gel plates (RP2 Merck) coated with a silicone oil (5% SE30 in ether); the mobile phase consisted of ethanol and Veronal buffer pH 7.2 in the ratio 15:85. The plates were saturated with the solvent before elution and developed in a Camag linear HPTLC developing chamber.

Isolated Enzyme Studies:

The enzymes used in this assay were crude preparations. The organisms (*Enterobacter cloacae* X1, Ia; *P. aeruginosa* X9, Id; *E. coli* X3, IIIa; *Klebsiella aerogenes* X5L, IVc) were grown with shaking at 37°C overnight in nutrient broth (10 ml). These cultures were then used as the inoculum for prewarmed nutrient broth (200 ml) in 2-liter Erlenmeyer flasks, and were grown with shaking at 37°C for 5~6 hours. The growth was then scraped of the plates and suspended in 0.05 M KH_2PO_4 buffer. The cultures were then centrifuged, washed with 0.05 M KH_2PO_4 buffer pH 7 and resuspended in KH_2PO_4 buffer (pH 7, 0.05 M, 20 ml). The organisms were disrupted by ultrasonication (4×1 minute bursts, the extracts kept cool on ice). The preparation were Gram-stained before and after ultrasonication to ensure good breakage. The preparations were then centrifuged at 18,000 rpm for 2 hours at 0°C and the supernatant dialyzed against 0.05 M KH_2PO_4 buffer pH 7 for 24 hours. The dialyzed extracts were then dispensed in 0.5 ml volumes into wide mouthed universal vials and kept frozen at −20°C. These aliquots were melted for use as required.

The assay was performed using a Cary 15 spectrophotometer at 250 nm in fixed wavelength mode. Two silica cuvettes of 1 cm light path and 1 ml capacity were used. To both were added 0.05 M KH_2PO_4 buffer pH 7 and 20 μl 5×10^{-3} M solution in DMSO of the cephalosporin under test, such that the final volume in the cuvettes after addition of enzyme was 1 ml—this gave a concentration of the cephalosporin in the cuvette of 1×10^{-4} M. The cuvettes were placed in the reference and test light paths of the spectrophotometer. The system was allowed to equilibrate for a minute or so and then the enzyme was added and the rate of increase or decrease in OD was recorded, depending upon the cuvette to which the enzyme was added. The amount of a particular enzyme used was dependent on the amount necessary to produce a change in OD of 0.2~0.4 units/minute when used with cephalosporidine. This enabled rates of (usually) less than 0.1% of the cephaloridine rate to be detected.

7-Imidazolylaminocephalosporins **6~14** *via anti*-α-Aminooximes **4a~4f**: General Procedure A

Isonitrile dibromide **1a~1c**[1] (1 equiv.) was dissolved in THF (1 mmol in 10 ml of THF) at −30°C. *anti*-α-Aminooximes **4a~4f** (3 equiv.) in THF or THF - MeOH (to solubilize the aminooxime, 1 mmol in 3 ml of THF or THF - MeOH) was added to the isonitrile dibromide solution. The progress of the reaction was monitored by TLC and usually took between 0.2 and 2 hours for completion. Two equivalents of TFA were added to the cold solution to protonate any residual free amino group, and the temperature was then allowed to reach ambient. The solvent was evaporated and the crude product was purified by low temperature (−20°C) silica gel chromatography (CH_2Cl_2 - MeOH, 25~70%). **5** ($R_1=CH_3$, $X=R_2=H$): ^{1}H NMR (90 MHz, DMSO-d_6) δ 2.04 (s, 6H), 3.5 (s, 2H), 5.15 (d, J=4.5 Hz, 1H), 5.6 (d, J=4.5 Hz, 1H), 6.25 (s, 1H), 6.8 (s, 1H), 7.15~7.60 (m, 10H).

N-Hydroxy-7-imidazolylaminocephalosporins **5**, 1 equiv., in MeOH (1 mmol in 30 ml of MeOH) were treated with $TiCl_3$[6] (2 equiv.) in MeOH (1 mmol in 1 ml of MeOH) at 40°C for 0.1 to 0.5 hour. The pH of the reaction mixture was then adjusted to 7 with a saturated solution of sodium bicarbonate, the solvents were evaporated under vacuum and the residue purified by low temperature (−20°C) silica gel chromatography (CH_2Cl_2 - MeOH - AcOH) to give the diphenylmethyl 7-imidazolylaminocephalosporanate esters of **7~14** (30~50%). These purified compounds were reacted with a mixture of TFA - anisole, 1:1 (v/v) at room temperature (R.T.) for 0.5 hour. The reagents were evaporated, and the residue dissolved in a

mixture of CH_2Cl_2 - MeOH and precipitated in ether. The solid was recovered by filtration and dried *in vacuo* (60~95%): ^1H NMR in Table 8 of supplementary material. **7** ($R_1=X=H$, $R_2=CH_3$): ^1H NMR (90 MHz, DMSO-d_6) δ 2.08 (s, 3H), 2.1 (s, 3H), 3.35~3.75 (AB, $J=18$ Hz, 2H), 5.1 (d, $J=4.5$ Hz, 1H), 5.5 (d, $J=4.5$ Hz, 1H), 6.55 (s, 1H).

3-Acetoxymethyl-7-[4-(4-nitrobenzyl)imidazole-2-yl]aminoceph-3-em-4-carboxylic Acid **13**

N-Hydroxy-7-imidazolylaminocephalosporin **5** (R_1=PNB, $R_2=H$, X=OAc) was suspended in CH_2Cl_2 (10 ml), and trimethylphosphite (0.8 ml, 6.8 mmol) was added. The mixture was stirred at 45°C for 2 hours, concentrated, and the residue purified by low temperature (−20°C) silica gel chromatography (CH_2Cl_2 - MeOH - AcOH, 98:1:1 (in volume)) to give the aminoimidazole ester (220 mg, 50%). The deprotection to the free carboxylic acid was carried out as in the previous examples, to give **13** (100 mg, 60%): ^1H NMR in Table 7 of supplementary material.

anti-α-Aminooximes **4a**~**4f**: General Procedure B

The synthesis of **4a**~**4c** was carried out according to a literature procedure[16,17], which was adapted to the synthesis of **4d**~**4f**. The precursor bromo ketone (1 equiv.) in toluene (1 mmol in 1 ml toluene), (DMF in case of **4f**) was reacted with potassium phthalimide (1 equiv.) at reflux (R.T. for **4f**) for 4 hours. The solvent was evaporated and the residue purified by silica gel chromatography to give phthalimido ketone (50~70%). The phthalimido ketone was solubilized in a mixture of EtOH - pyridine, 1:1 (v/v) (1 mmol in 1 ml) and treated with hydroxylamine hydrochloride (1.5 equiv.) at R.T. for 24 hours. The solvent was evaporated and the residue purified by silica gel chromatography to give the phthalimido oxime as a mixture of *syn* and *anti* isomers (30~75%). This mixture (1 equiv.) in EtOH (1 mmol in 5 ml EtOH) was treated with hydrazine hydrate (1 equiv.) at 45°C (2 hours) and R.T. (22 hours). Hydrochloric acid (1 N, 1 equiv.) was added with stirring. The mixture was stirred at R.T. for 1 hour, concentrated, washed with water, the solid removed by filtration, the aqueous phase concentrated to give *anti*-α-aminooxime hydrochloride (85~95%). **4d**: ^1H NMR (60 MHz, DMSO-d_6) δ 3.5 (s, 2H), 3.8 (s, 2H), 7.4 (s, 5H).

The free base of *anti*-α-aminooxime **4a**~**4f** was obtained by treating the corresponding hydrochloride with a methanolic solution of potassium hydroxyde (1 equiv.). Precipitated potassium chloride was removed by filtration to give after evaporation of methanol the *anti*-α-aminooxime as a free base which was used directly in the next step.

3-Methyl-7-(4,5-dicyanoimidazol-2-yl)aminoceph-3-em-4-carboxylic Acid **3**

Diaminomaleonitrile (216 mg, 2 equiv.) was solubilized in THF (5 ml) and added to a solution of isocyanide dibromide **1a**[1] (560 mg) in THF (3 ml) at −78°C. The temperature was allowed to reach ambient, the solvent evaporated and the residue purified by silica gel chromatography (AcOEt - CH_2Cl_2, 2:8 (v/v)) to give compound (255 mg, 51%): MP 180~185°C; *Anal* ($C_{26}H_{20}N_6O_3S$) C, H, N. The deprotection of this compound was carried out as described in general procedure A to give **3** (142 mg, 28%): *Anal.* ($C_{13}H_{10}N_6O_3S$) C, H, N; ^1H NMR (90 MHz, CD_3OD) δ 2.15 (s, 3H), 3.25~3.55 (m, 2H), 5.1 (d, $J=4.5$ Hz, 1H), 5.55 (d, $J=4.5$ Hz, 1H).

7-Imidazolylaminocephalosporins **17**~**23**, **41**~**43** *via* 2-Fluoroimidazoles and 7-Aminocephalosporanates: General Procedure C

The appropriate ester **16** (1 equiv.) in DMF (1 mmol in 2 ml DMF) was reacted with the corresponding 2-fluoroimidazole hydrochloride (1 equiv.) at 60°C for 2 hours. The reaction mixture was cooled, the solvent evaporated and the residue purified by silica gel chromatography (CH_2Cl_2 - MeOH - AcOH) to give the corresponding 7-imidazolylaminocephalosporanate (20~45%). These esters were deprotected to the free acids following general procedure A: ^1H NMR in Table 8 of supplementary material.

tert-Butyl-7-(4-azidomethyl-imidazo-2-yl)aminoceph-3-em-4-carboxylate (390 mg, 0.61 mmol) was solubilized in ethanol, 5 drops of TFA were added and the mixture hydrogenated over Pd/C (10%) for 7 hours to give a quantitative yield of reduced product after removal of the catalyst and evaporation of the solvent. This product was deprotected according to general procedure A, and purified by preparative HPLC using an ODS-2 column (H_2O - MeOH - AcOH, 92:8:1 (in volume)) to give compound **41** (71 mg, 17%): ^1H NMR in Table 8 of supplementary material.

7-Imidazolylaminocephalosporins **25**～**40** *via* 2-Fluoroimidazoles and 7-Aminocephalosporanic Acids: General Procedure D

A solution of the substituted 2-fluoro-1-triphenylmethylimidazole (1 mmol) in dry DMF (2 ml) was treated with toluene-4-sulfonic acid monohydrate (1 mmol) and stirred at 85°C for 5 minutes, monitoring the loss of the triphenylmethyl group by HPLC. The appropriate 7-amino-ceph-3-em-4-carboxylic acid (1 mmol) was added, and heating continued for 2.5 hours, again monitoring the progress of the reaction by HPLC. The reaction mixture was then poured into the eluent to be used for purification (10 ml), filtered and purified by preparative HPLC on Whatman "Partisil 10" using a mixture of H_2O - MeOH - AcOH to give the free acids **25**～**40** (5～38%): ^{1}H NMR in Table 8 of supplementary material.

Synthesis of 2-Fluoroimidazole Reagents **15**

The synthesis of the parent 2-fluoroimidazole was carried out according to a published procedure[10].

4-Methyl-2-fluoro-imidazole was obtained by analogy to the literature method[10]. 4-Methyl-2-aminoimidazole (5.8 g, 40 mmol) was dissolved in 50% fluoroboric acid (200 ml) at −10°C. To this solution was added with stirring a solution of $NaNO_2$ (3.3 g, 48 mmol) in 5 ml water. Nitrogen was passed through the reactor and the mixture was irradiated (Hanovia 450W medium pressure Hg lamp or Philipps 125W medium pressure Hg lamp) for 4 hours. The solution was neutralized (pH 6) with 60% (v/v) sodium hydroxide at 0°C, extracted with ethyl acetate, dried over $MgSO_4$, evaporated, dissolved in ether and treated with a solution of HCl in Et_2O. The hydrochloride was filtered, dried (1.2 g, 22%). MP 130～135°C; ^{1}H NMR (60 MHz, D_2O) δ 2.25 (s, 3H), 6.85 (s, 1H).

2-Fluoro-1-triphenylmethylimidazole

2-Fluoroimidazole (3.2 g, 37 mmol) was dissolved in dry CH_2Cl_2 (100 ml), and triethylamine (5.7 ml, 41 mmol) was added. To the solution was added triphenylmethylchloride (10.4 g, 37 mmol), and the mixture stirred 2 hours. After addition of water (100 ml), the organic layer was separated, dried, and evaporated. Crude product was triturated with MeOH (80 ml) to give title compound (9 g, 73%). MP 176～178°C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.58 (d, J=1.9 Hz, 1H), 6.68 (t, J=1.9 Hz, 1H), 7.0～7.6 (m, 15H).

2-Fluoro-4-formyl-1-triphenylmethylimidazole

2-Fluoro-1-triphenylmethylimidazole (39.9 g, 0.12 mol) was dissolved in dry THF (600 ml), and cooled under argon to −70°C. *tert*-Butyllithium (85 ml, 2.1 M solution in pentane) was added dropwise over 20 minutes, and the mixture stirred 1 hour at −70°C, after which DMF (16.2 ml, 0.18 mol) was added, and the temperature held for a further hour. The temperature was then allowed to rise slowly to ambient, and the reaction quenched with wet Et_2O (1 liter). More water was then added, and the Et_2O layer separated. Evaporation and trituration with MeOH gave title compound (29 g, 67%). MP 182～183°C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.1～7.5 (m, 16H), 9.75 (s, 1H).

2-Fluoro-4-(1-hydroxy-2-nitroethyl)-1-triphenylmethylimidazole

2-Fluoro-4-formyl-1-triphenylmethylimidazole (10.7 g, 30 mmol) and anhydrous K_2CO_3 (91 mg, 0.66 mmol) were added to nitromethane (180 ml), and the mixture stirred 20 hours at ambient temperature. The volume was reduced to about 20 ml, and product filtered and washed with Et_2O to give title compound (10.1 g, 80%): ^{1}H NMR (90 MHz, DMSO-d_6) δ 4.52 (dd, J=9.4, 12.3 Hz, 1H), 4.83 (dd, J=3.7, 12.3 Hz, 1H), 5.10 (m, 1H), 5.85 (br, 1H), 6.57 (s, 1H), 7.0～7.7 (m, 15H).

2-Fluoro-4-(2-nitrovinyl)-1-triphenylmethylimidazole

2-Fluoro-4-(1-hydroxy-2-nitroethyl)-1-triphenylmethylimidazole (10.1 g, 24 mmol) was dissolved in dimethoxyethane (100 ml) and treated with 4-dimethylaminopyridine (150 mg, 1.2 mmol), pyridine (1.9 ml, 2.4 mmol), and acetic anhydride (2.8 ml, 3 mmol). The mixture was stirred at ambient temperature for 16 hours, evaporated, and the residue triturated with Et_2O, to give title compound (8.6 g, 87%): ^{1}H NMR (90 MHz, DMSO-d_6) δ 6.9～7.6 (m, 17H), 8.07 (dd, J=2.5, 12.7 Hz, 1H).

2-Fluoro-4-(2-nitroethyl)-1-triphenylmethylimidazole

2-Fluoro-4-(2-nitrovinyl)-1-triphenylmethylimidazole (1 g, 2.5 mmol) was suspended in EtOH (30 ml),

and $NaBH_4$ (1 g, 26 mmol) added to the stirred mixture. After 30 minutes the mixture was diluted with water, pH adjusted to 4 with acetic acid, and the precipitated product filtered off to give title compound (800 mg, 80%). ^1H NMR (90 MHz, DMSO-d_6) δ 3.02 (t, J=7.5 Hz, 2H), 4.72 (t, J=7.5 Hz, 2H), 6.46 (s, 1H), 6.9~7.5 (m, 15H).

4-(2-Aminoethyl)-2-fluoro-1-triphenylmethylimidazole

2-Fluoro-4-(2-nitroethyl)-1-triphenylmethylimidazole (570 mg, 1.4 mmol), and cobaltous chloride hexahydrate (680 mg, 2.9 mmol) were stirred in EtOH (25 ml), and $NaBH_4$ (540 mg, 14.5 mmol) added in portions, with cooling, over 10 minutes. After a further 20 minutes, the mixture was drowned into water (200 ml), and product extracted into Et_2O. Evaporation gave title compound (410 mg, 79%) as a foam: ^1H NMR (90 MHz, DMSO-d_6) δ 2.38 (t, J=7.4 Hz, obscured by solvent, 2H), 2.65 (t, J=7.4 Hz, obscured by solvent, 2H), 6.29 (s, 1H), 7.0~7.5 (m, 15H).

2-Fluoro-4-(2-acetamidoethyl)-1-triphenylmethylimidazole

4-(2-Aminoethyl)-2-fluoro-1-triphenylmethylimidazole (600 mg, 1.6 mmol) was dissolved in pyridine (10 ml), and acetyl chloride (130 mg, 1.6 mmol) run in solwly. After stirring for 20 minutes, the reaction was drowned into water (100 ml), and product extracted into Et_2O. The combined extracts were washed rapidly with 1 N HCl, dried, and evaporated to give title compound (350 mg, 53%): MP 153~155°C; ^1H NMR (90 MHz, $CDCl_3$) δ 1.94 (s, 3H), 2.57 (t, J=6.5 Hz, 2H), 3.44 (q, J=6.5 Hz, 2H), 6.28 (s, 1H), 7.05~7.45 (m, 15H).

2-Fluoro-4-(2-cyanovinyl)-1-triphenylmethylimidazole

Sodium hydride (1 g, 50% in oil, 20.8 mmol) was suspended in dimethoxyethane (25 ml), and a solution of diethyl cyanomethylphosphonate (3.6 g, 20.3 mmol) in dimethoxyethane (40 ml) was run in. After stirring 30 minutes, solid 2-fluoro-4-formyl-1-triphenylmethylimidazole (6 g, 16.9 mmol) was added and the stirring continued a further 30 minutes. The reaction mixture was poured into water (200 ml), acidified with acetic acid to pH 4, and product extracted into EtOAc. Crude product was chromatographed on silica, eluting with a mixture of CH_2Cl_2 and EtOAc, to give title compound (5.25 g, 82%) as a 4:1 mixture of E:Z isomers: ^1H NMR (90 MHz, $CDCl_3$) δ 5.17 (d, J=12 Hz, 0.2H), 5.87 (d, J=15.6 Hz, 0.8H), 6.69 (s, 0.8H), 6.82 (s, 0.2H), 7.30 (m, 16H).

2-Fluoro-4-(2-cyanoethyl)-1-triphenylmethylimidazole

4-(2-Cyanovinyl)-2-fluoro-1-triphenylmethylimidazole (3.7 g, 9.8 mmol) and magnesium (9 g, 37.5 mmol) were suspended in MeOH (200 ml) and stirred at ambient temperature. After a variable induction period, an exotherm began, and the flask was cooled to maintain the temperature below 40°C. After stirring for 4.5 hours, the mixture was poured into water (200 ml), acidified to pH 4 with acetic acid and, after dissolution of magnesium hydroxide, crude product was extracted into CH_2Cl_2 and purified by chromatography on silica, eluting with a mixture of CH_2Cl_2 and EtOAc, to give title compound (2.48 g, 66%): MP 128~130°C; ^1H NMR (90 MHz, $CDCl_3$) δ 2.71 (t, J=4.5 Hz, 4H), 6.42 (s, 1H), 7.1~7.4 (m, 15H).

2-Fluoro-4-(3-aminopropyl)-1-triphenylmethylimidazole

4-(2-Cyanoethyl)-2-fluoro-1-triphenylmethylimidazole (4 g, 10.5 mmol) and cobaltous chloride hexahydrate (5 g, 21 mmol) were suspended in EtOH (150 ml), and $NaBH_4$ (4 g, 0.1 mol) added in portions over 10 minutes, keeping the temperature below 30°C. After stirring a further 45 minutes, the mixture was drowned into water (500 ml), and the product extracted into Et_2O. Evaporation gave title compound (3.3 g, 82%) as a gum: ^1H NMR (90 MHz, $CDCl_3$) δ 1.87 (quintet, J=7.0 Hz, 2H), 2.49 (t, J=7.0 Hz, 2H), 2.90 (t, J=7.0 Hz, 2H), 5.15 (br, 2H), 6.24 (s, 1H), 7.1~7.3 (m, 15H).

2-Fluoro-4-(3-methanesulfonamidopropyl)-1-triphenylmethylimidazole

4-(3-Aminopropyl)-2-fluoro-1-triphenylmethylimidazole (800 mg, 2.1 mmol) was dissolved in pyridine (25 ml), and methanesulfonylchloride (240 mg, 2.1 mmol) run in at ambient temperature. After stirring 1 hour, the mixture was drowned into water (250 ml), and product extracted into Et_2O. After washing

the Et_2O extracts with 2 N HCl, the product was purified by chromatography, eluting with a mixture of CH_2Cl_2 and EtOAc, to give title compound (260 mg, 27%) as a foam, used without further characterization.

2-Fluoro-1-triphenylmethyl-4-(3-ureidopropyl)imidazole

4-(3-Aminopropyl)-2-fluoro-1-triphenylmethylimidazole (810 mg, 2.1 mmol) was dissolved in THF (50 ml), and a solution of potassium cyanate (168 mg, 2.1 mmol) in water (50 ml) added. The mixture was stirred and the pH adjusted to 6 with 1 N HCl, followed by stirring for a further hour. Organics were then extracted into CH_2Cl_2, and the product purified by chromatography on silica, eluting with CH_2Cl_2 - MeOH, 95 : 5 (v/v), to give title compound (270 mg, 30%): ^{1}H NMR (90 MHz, CH_2Cl_2 - MeOH, DMSO-d_6) δ 1.54 (quintet, J=7.3 Hz, 2H), 2.33 (t, J=7.3 Hz, 2H), 2.92 (q, J=6.3 Hz, 2H), 5.28 (br s, 2H), 5.90 (t, J=6.3 Hz, 1H), 6.28 (s, 1H), 6.95~7.55 (m, 15H).

2-Fluoro-4-allyl-1-triphenylmethylimidazole

2-Fluoro-1-triphenylmethylimidazole (50 g, 0.15 mol) was dissolved in THF (700 ml), cooled to -70°C, treated dropwise with *tert*-butyllithium (100 ml of 2.1 M solution in pentane), and stirred at the same temperature for 2 hours. Cuprous iodide (30 g, 0.16 mol) was added, and stirring continued for 2 hours. The resulting red solution was treated with allyl bromide (50 ml, 0.58 mol), maintaining the temperature below -60°C, and then stirred for a further hour at -70°C, before being allowed to come to ambient temperature. The mixture was then poured into Et_2O (3 liters), and the Et_2O layer washed successively with saturated ammonium chloride and brine. Evaporation of the dried solution gave a solid which was triturated with MeOH before being chromatographed on silica, eluting with Et_2O, to give title compound (32.4 g, 60%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.17 (d, J=6.3 Hz, 2H), 5.12 (cd, J=9 Hz, 2H), 5.91 (m, 1H), 6.22 (s, 1H), 7.0~7.4 (m, 15H); MS m/e 368 (M^+).

2-Fluoro-4-(3-hydroxypropyl)-1-triphenylmethylimidazole

4-Allyl-2-fluoro-1-triphenylmethylimidazole (32.4 g, 0.09 mol) in THF (700 ml) was cooled to 0°C and treated with a solution of diborane (300 ml, 1 M solution in THF). After stirring 15 minutes at 0°C, the mixture was allowed to come to ambient temperature overnight. Water (175 ml) was then slowly added, followed by 2 N NaOH solution (175 ml) and 30% hydrogen peroxide (50 ml), after which the mixture was stirred vigorously overnight. The organic layer was separated, and the aqueous layer re-extracted with Et_2O. The combined extracts were evaporated, and the residue purified by chromatography on silica, eluting with Et_2O, to give title compound (11.7 g, 33%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.74 (quintet, J=7.3 Hz, 2H), 2.47 (t, J=7.3 Hz, 2H), 3.54 (t, J=7.3 Hz, 2H), 6.37 (s, 1H), 7.03~7.42 (m, 15H); MS m/e 386 (M^+).

2-Fluoro-4-(3-methanesulfonyloxypropyl)-1-triphenylmethylimidazole

2-Fluoro-4-(3-hydroxypropyl)-1-triphenylmethylimidazole (3.86 g, 10 mmol) was dissolved in pyridine (20 ml), and the stirred solution treated with methanesulfonyl chloride (1 ml, 12.5 mmol). After 2 hours the mixture was poured into water (200 ml) and product extracted into CH_2Cl_2. The dried solution was evaporated, azeotroped with toluene, and triturated with petrol to give title compound (3.95 g, 85%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.02 (quintet, J=6.8 Hz, 2H), 2.53 (t, J=6.8 Hz, 2H), 2.91 (s, 3H), 4.22 (t, J=6.8 Hz, 2H), 6.24 (s, 1H), 7.05~7.40 (m, 15H).

2-Fluoro-4-(3-ethylthiopropyl)-1-triphenylmethylimidazole

A solution of ethanethiol (74 μl, 1 mmol) in DMF (2 ml) was stirred at ambient temperature, and treated with sodium hydride (100 mg, 50% in oil, 2 mmol). After 10 minutes, 2-fluoro-4-(3-methanesulfonyloxypropyl)-1-triphenylmethylimidazole (464 mg, 1 mmol) was added to this solution, and the mixture stirred overnight and poured into water (20 ml). Organics were extracted into CH_2Cl_2 and product purified by chromatography on silica, eluting with CH_2Cl_2 - EtOAc, 98 : 2 (v/v) to give title compound (375 mg, 87%): ^{1}H NMR (90 MHz, DMSO-d_6) δ 1.20 (t, J=7.4 Hz, 3H), 1.85 (quintet, J=7.4 Hz, 2H), 2.37~2.62 (m, 6H), 6.24 (s, 1H), 7.18~7.42 (m, 15H).

2-Fluoro-4-(3-ethanesulfinylpropyl)-1-triphenylmethylimidazole

4-(3-Ethylthiopropyl)-2-fluoro-1-triphenylmethylimidazole (129 mg, 0.3 mmol) was dissolved in CH_2Cl_2 (6 ml), cooled to 0°C, and treated with 3-chloroperoxybenzoic acid (51 mg, 0.3 mmol). After 15 minutes the mixture was washed with 5% $NaHCO_3$ solution, and the organic layer evaporated to give title compound (138 mg, 100%), used with no further purification: ^{1}H NMR (90 MHz, DMSO-d_6) δ 1.28 (t, J=7.5 Hz, 3H), 2.02 (quintet, J=7.5 Hz, 2H), 2.48~2.80 (m, 6H), 6.27 (s, 1H), 7.08~7.42 (m, 15H).

2-Fluoro-4-(3-ethanesulfonylpropyl)-1-triphenylmethylimidazole

2-Fluoro-4-(3-ethylthiopropyl)-1-triphenylmethylimidazole (129 mg, 0.3 mmol) was oxidized as above, using 3-chloroperoxybenzoic acid (102 mg, 0.6 mmol), to give title compound (140 mg, 100%), used with no further purification: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.35 (t, J=7.2 Hz, 3H), 2.09 (quintet, J=7.2 Hz, 2H), 2.58 (t, J=7.2 Hz, 2H), 2.84 (q, J=7.2 Hz, 4H), 6.29 (s, 1H), 7.05~7.42 (m, 15H).

2-Fluoro-4-thiomethyl-1-triphenylmethylimidazole

2-Fluoro-1-triphenylmethylimidazole (328 mg, 1 mmol) in dry THF (3 ml) was treated at −78°C, under an atmosphere of argon, with *tert*-butyllithium (1 ml, 2.1 M solution in pentane, 2 mmol) and stirred at this temperature for 2 hours. The deep-red mixture was then treated with dimethyldisulphide (0.18 ml, 2 mmol). The color was immediately discharged. The mixture was stirred for 30 minutes at −78°C and for 1 hour at −15°C. Diethylether was then added, the mixture washed with brine until the aqueous washings were neutral, and then evaporated to dryness to give title compound (368 mg, MP 142~143°C, 92%): MS (M^+) 374, (M−HF) 354, ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.34 (s, 3H), 6.48 (s, 1H), 7~7.35 (m, 15H).

2-Fluoro-4-azido-1-triphenylmethylimidazole

A stirred solution of 2-fluoro-1-triphenylmethylimidazole (6.56 g, 20 mmol) in dry THF (75 ml), under an atmosphere of argon, was cooled to −70°C and treated dropwise, with a solution of *tert*-butyllithium (20 ml, 2 M solution in pentane, 40 mmol) and stirred for 1 hour at −70°C.

The deep-red solution so produced was treated dropwise, at −70°C, with a solution of tosylazide (20 ml, 1 M solution in toluene, 20 mmol) and the temperature was allowed to rise to 0°C. A yellow solution was produced and this was treated with a solution of sodium pyrophosphate (10 g, 38 mmol) in water (100 ml) before being extracted with CH_2Cl_2 (4 × 30 ml). The combined organic extracts were washed with water, dried over $MgSO_4$, filtered and evaporated to give title compound (8 mg). The product was purified by chromatography on silica eluting with CH_2Cl_2 - hexane, 1 : 1 (v/v) and recrystallization from hexane to give title compound (2.5 g, MP 112~113°C, 34%):

Anal Calcd for $C_{22}H_{16}N_5F$: C 71.5, H 4.3, N 19.0.
Found: C 71.4, H 4.4, N 18.7.

2-Fluoro-4-(triphenylphosphinimino)-1-triphenylmethylimidazole

2-Fluoro-4-azido-1-triphenylmethylimidazole (1.65 g, 4.5 mmol) was dissolved in dry ether (50 ml) at 25°C and treated dropwise with a solution of triphenylphosphine (1.3 g, 5 mmol) in dry ether (50 ml). Nitrogen was evolved and the title compound precipitated. It was filtered off and washed well with ether (2.1 g, MP 182°C decomposition, 78%):

Anal Calcd for $C_{40}H_{31}N_3FP$: C 79.6, H 5.14, N 6.97.
Found: C 79.4, H 5.1, N 6.8.

2-Fluoro-4-ethylcarbamoyl-1-triphenylmethylimidazole

A stirred solution of 2-fluoro-4-(triphenylphosphinimino)-1-triphenylmethylimidazole (1.5 g, 2.5 mmol) in dry EtOAc (100 ml) was treated, at 25°C, with propionylchloride (0.2 ml, 2.7 mmol) and stirred for 10 minutes. Aqueous sodium bicarbonate (200 ml saturated solution) was then added, the mixture stirred for 10 minutes and the organic layer passed through a short silica column. The appropriate fractions were combined, evaporated and the residue so obtained was triturated with ether (20 ml) to give title compound (0.6 g, MP 190~192°C, 60%):

Anal Calcd for $C_{25}H_{22}N_3OF$: C 75.2, H 5.5, N 10.5.
Found: C 75.1, H 5.6, N 10.4.

2-Fluoro-4-bromo-1-triphenylmethylimidazole

A solution of *N*-bromosuccinimide (890 mg, 5 mmol) in DMF (25 ml) was added dropwise to a well-stirred solution of 2-fluoro-1-triphenylmethylimidazole (1.64 g, 5 mmol) in DMF (50 ml). After stirring overnight in an atmosphere of argon, the mixture was slowly poured into water. A fine yellow precipitate was produced which was filtered off, dried under vacuum over P_2O_5, and triturated with ether to give title compound (1.22 g, 60%): MP 166~170°C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.5 (s, 1H), 7~7.5 (m, 15H).

2-Fluoro-4-methylcarbamoyl-1-triphenylmethylimidazole

A stirred solution of 2-fluoro-4-bromo-1-triphenylmethylimidazole (812 mg, 2 mmol) in dry THF (6 ml) was cooled, under argon, to −75°C, and treated dropwise with a solution of *n*-butyllithium (1.3 ml, 1.6 M solution in hexane, 2.08 mmol). After stirring at this temperature for 15 minutes the mixture was treated, dropwise, with methylisocyanate (0.24 ml, 4 mmol), stirred for a further 30 minutes and then, having removed the cooling bath, for a further hour. The mixture was diluted with Et_2O (40 ml), washed with a saturated solution of NH_4Cl (2×40 ml), and the organic phase dried over $MgSO_4$. The dessicant was filtered off and the solvent evaporated to give a yellow foam (731 mg) which was purified by chromatography on silica (Merck ART 9385) using EtOAc-hexane, 2:1 (v/v) to give title compound (290 mg, 37%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.05 (d, J=4.5 Hz, 3H), 6.84 (d, J=4.5 Hz, 1H), 7.1~7.5 (m, 16H).

2-Fluoro-4-carboxy-1-triphenylmethylimidazole

2-Fluoro-4-formyl-1-triphenylmethylimidazole (1.39 g, 3.9 mmol) was dissolved in a mixture of ethanol (20 ml) and CH_2Cl_2 (16 ml) and treated with a solution of $AgNO_3$ (1.48 mg, 8.7 mmol) in water (2 ml) and then with a solution of KOH (20 ml of a solution containing 2.1 g KOH in 35 ml H_2O, 21.6 mmol). A mild exotherm was observed (temperature of mixture 30°C). After stirring overnight the mixture was filtered through a pad of supercell, the pad washed with H_2O (50 ml), and the filtrate washed with ether (2×50 ml). The aqueous solution was cooled in an ice bath, acidified to pH 1 with 2 N HCl, the precipitate so obtained extracted with $CHCl_3$ (3×100 ml), the $CHCl_3$ extracts washed with brine (100 ml), dried over $MgSO_4$, filtered and evaporated to give title compound (1.17 g white solid, 80%): ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.0~7.7 (m, 16H).

2-Fluoro-4-ethoxycarbonyl-1-triphenylmethylimidazole

2-Fluoro-4-carboxy-1-triphenylmethylimidazole (280 mg, 0.75 mmol) was suspended in CH_3CN (0.75 ml), under argon, treated with DBU (0.112 ml, 0.75 mmol) and ethyl iodide (0.069 ml, 0.82 mmol). After stirring at R.T. for 2 hours the reaction mixture was diluted with water and extracted with Et_2O (2×5 ml). The ether extracts were washed with H_2O (2×5 ml), dried over $MgSO_4$, filtered, and the solvent evaporated to give title compound (185 mg, 61%): IR C=O 1720 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.32 (t, J=7.2 Hz, 3H), 4.34 (q, J=7.2 Hz, 2H), 7.0~7.5 (m, 16H).

2-(2-Fluoro-1-triphenylmethylimidazol-4-yl)-(*E*)-propenaldehyde

2-Fluoro-4-formyl-1-triphenylmethylimidazole (1.5 g, 4.2 mmol) was dissolved in dry toluene (70 ml) and treated, under argon, with (triphenylphosphoranylidene)acetaldehyde (4.0 g, 13.1 mmol) and heated at reflux temperature for 4 hours. The reaction mixture was cooled, evaporated to dryness and the residue purified by chromatography on silica (Merck ART 9385) using 40% Et_2O-60% hexane as eluent. The appropriate fractions were combined, evaporated to dryness and the residue crystallized from Et_2O to give title compound (754 mg, 47%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.58~6.75 (dd, J=7.5 Hz, J_E=15 Hz, 1H), 7.0~7.5 (m, 16H), 9.6 (d, J=7.5 Hz, 1H).

2-(2-Fluoro-1-triphenylmethylimidazol-4-yl-(*E*)-propenoic Acid

2-(2-Fluoro-1-triphenylmethylimidazol-4-yl)-(*E*)-propenaldehyde (85 mg, 0.22 mmol) suspended in EtOH (1 ml) was treated, at room temperature with $AgNO_3$ (83 mg, 0.48 mmol, dissolved in the minimum volume of H_2O) and KOH (55 mg, dissolved in 0.2 ml H_2O). After stirring for 45 minutes the reaction mixture was poured into Et_2O (50 ml) and water (50 ml) added. The aqueous phase was separated, acidified to pH 2 with 2 N HCl and the product extracted with ether (2×20 ml). The ether extracts were combined, washed, dried and evaporated to give title compound (59 mg, MP 198~200°C, 66%): IR C=O 1685, C=C

1635 cm^{-1}; ^1H NMR (90 MHz, DMSO-d_6) δ 6.13 (d, J=15 Hz, 1H), 7.0~7.6 (m, 17H).

2-(2-Fluoro-1-triphenylmethylimidazol-4-yl)-propanoic Acid

2-(2-Fluoro-1-triphenylmethylimidazol-4-yl)-(*E*)-propenoic acid (130 mg) was dissolved in EtOAc (40 ml) and shaken in an atmosphere of hydrogen with PtO_2 (50 mg). After 30 minutes the catalyst was removed by filtration and the filtrate evaporated to give the title compound (110 mg) after crystallization from Et_2O: IR C=O 1720 cm^{-1}.

2-Fluoro-4-hydroxymethyl-1-triphenylmethylimidazole

2-Fluoro-4-formyl-1-triphenylmethylimidazole (180 mg, 0.5 mmol) was dissolved in ethanol (20 ml) and treated with sodium borohydride (20 mg, 0.5 mmol) at R.T. for 0.5 hour. The solvent was evaporated, the residue extracted in CH_2Cl_2, concentrated, to give title compound (130 mg, 72%): ^1H NMR (60 MHz, $CDCl_3$) δ 4.5 (s, 2H), 6.6 (s, 1H), 7.1~7.7 (m, 15H).

2-Fluoro-4-hydroxymethylimidazole

2-Fluoro-4-hydroxymethyl-1-triphenylmethylimidazole (1.77 g, 5 mmol) was dissolved in acetone (100 ml). *p*-Toluenesulfonic acid (0.94 g, 5 mmol) was added to the solution, which was stirred at R.T. for 1 hour. The solvent was evaporated, the residue was triturated in ether. The residual oil was dissolved in acetone and treated with sodium bicarbonate (10 mmol), the solid was filtered off, the solvent evaporated and the residue taken up in pentane - CH_2Cl_2 (5 : 1), to give title compound (550 mg, 95%): ^1H NMR (60 MHz, CD_3OD) δ 4.4 (s, 2H), 6.6 (s, 1H).

2-Fluoro-4-methoxymethylimidazole

2-Fluoro-4-hydroxymethylimidazole (232 mg, 2 mmol) was slowly added over 0.1 hour to cold (0°C) thionyl chloride (4 ml). The solution was stirred at 0°C for 1 hour, and thionylchloride was evaporated to give 4-chloromethyl-2-fluoroimidazole, HCl (280 mg, 82%). This compound was treated immediately with anhydrous methanol at R.T. for 1 hour. Powdered $NaHCO_3$ was added to neutralize. The solid was filtered off, the solvent evaporated and the residue taken up into ether. After evaporation of the solvent, the desired compound was obtained as a colorless oil (220 mg, 76%): ^1H NMR (HCl salt) (60 MHz, $CDCl_3$ - CD_3OD) δ 3.35 (s, 3H), 4.35 (s, 2H), 7.05 (s, 1H).

2-Fluoro-4-methylthiomethylimidazole

4-Chloromethyl-2-fluoroimidazole, HCl (220 mg, 1.3 mmol) was added to a solution of methanethiol 2.4 M in THF (1.8 ml, 4 mmol) and triethylamine (0.58 ml, 4 mmol) and stirred at R.T. for 1 hour. The solvent was then evaporated, the residue taken up into ether, filtered and concentrated to give title compound (110 mg, 58%): ^1H NMR (60 MHz, $CDCl_3$) δ 2.05 (s, 3H), 3.6 (s, 2H), 6.55 (s, 1H).

4-Chloromethyl-2-fluoro-1-triphenylmethylimidazole

2-Fluoro-4-hydroxymethyl-1-triphenylmethylimidazole (1.4 g, 4 mmol) was solubilized in methylene chloride (60 ml) at 0°C in presence of triethylamine (0.8 g, 8 mmol). Methane sulfonyl chloride (0.916 g, 8 mmol) was added to the solution and the mixture stirred at R.T. for 3 hours. The reaction mixture was washed with water, dried and concentrated to give title compound (1.5 g, 100%) which was used directly in the next step.

2-Fluoro-4-azidomethyl-1-triphenylmethylimidazole

4-Chloromethyl-2-fluoro-1-triphenylmethylimidazole (1.3 g, 3.5 mmol) was solubilized in tetrahydrofuran (20 ml). Sodium azide (341 mg, 5.3 mmol) in solution in water (5 ml) was added to this solution which was stirred 72 hours at 8°C and 3 hours at 35°C. The reaction mixture was concentrated and the residue purified by silica gel chromatography (CH_2Cl_2 - EtOH, 95 : 5 (v/v)) to give title compound (0.95 g, 71%) which was used directly in the next step.

3-Acetoxymethyl-7-(4-aminomethylimidazol-2-yl)-aminoceph-3-em-4-carboxylic Acid **41**

tert-Butyl-3-acetoxymethyl-7-(4-azidomethylimidazol-2-yl)-aminoceph-3-em-4-carboxylate (390 mg,

0.61 mmol), obtained by condensation of 2-fluoro-4-azidomethyl-1-triphenylmethylimidazole with the appropriate cephalosporin ester following general procedure C, was solubilized in ethanol (10 ml), five drops of TFA were added to the solution. The mixture was hydrogenated over Pd/C (100 mg) at R.T. and atmospheric pressure for 7.5 hours. After evaporation of the solvent the crude product (460 mg) was deprotected according to general procedure A to give, after HPLC purification (ODS2 column) eluent H_2O-MeOH-AcOH, 92:8:1 (in volume), title compound (71 mg, 17%): ^1H NMR in Table 8 of supplementary material.

1-Allyl-2-fluoroimidazole

2-Fluoroimidazole hydrochloride (1.32 g, 10 mmol) was added to a mixture of CH_2Cl_2 (20 ml), allyl bromide (930 μl, 10 mmol), tetra-*n*-butylammonium hydrogen sulfate (170 mg) and 50% w/v aqueous NaOH solution (10 ml) and the mixture was vigorously stirred at R.T. for 3 days. The reaction mixture was diluted with water (20 ml) and extracted with CH_2Cl_2 (2 × 25 ml). The combined organic extracts were washed with 0.1 N HCl (50 ml) and brine (1 × 50 ml) before being dried ($MgSO_4$), filtered and evaporated to give an oil (1.29 g). The oil was purified by chromatography on silica (Merck ART 9385) eluting with EtOAc-petroleum ether (30~40°C), 1:3 (v/v) to give title compound (672 mg, 50%): EI-MS, (M^+) 126; ^1H NMR (90 MHz, $CDCl_3$) δ 4.4 (dt, J=5.6 Hz, J=<1.8 Hz, 2H), 5.15 (m, J_{trans}=16.7 Hz, 1H), 5.31 (m, J_{cis}=10.3 Hz, 1H), 5.94 (ddt, J=5.6, 10.3, 16.7 Hz, 1H), 6.57 (d, J=1.8 Hz, 1H), 6.66 (t, J=1.8 Hz, $J_{H\text{-}F}$=0.9 Hz, 1H).

1-(3-*tert*-Butyloxycarbonylaminopropyl)-2-fluoroimidazole

2-Fluoroimidazole HCl (369 mg, 3 mmol) was added to a mixture of CH_2Cl_2 (6 ml), 50% w/v aqueous NaOH solution (3 ml), tetra-*n*-butylammonium hydrogen sulfate (51 mg) and 1-*tert*-butyloxycarbonylamino-3-bromopropane (1.39 g, 5.84 mmol) and vigorously stirred at R.T. for 3 hours. The mixture was poured into water (5 ml) and extracted with CH_2Cl_2 (2 × 10 ml). The organic extracts were combined, washed with brine (10 ml), dried over $MgSO_4$, filtered and evaporated to give a pale yellow oil (1.39 g). The oil was purified by chromatography on silica (Merck ART 9385) eluting with MeOH-CH_2Cl_2, 1:20 (v/v) to give title compound (170 mg, 23%): ^1H NMR (90 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.95 (m, 2H), 3.15 (q, J=5.8 Hz, 2H), 3.85 (t, J=5.2 Hz, 2H), 4.65 (bt, 1H), 6.6 (s, 1H).

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