PROGRESS IN THE DISCOVERY OF NEW β-LACTAMASE INHIBITORS AND NATURALLY OCCURRING β-LACTAMS

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During studies on the preparation and purification of penicillin for chemotherapeutic evaluation, Abraham and Chain[1] recognised that bacteria produced an enzyme capable of destroying penicillin. Since then it has been shown that the production of various types of β-lactamases by a variety of important pathogenic bacteria is the principal mechanism whereby bacteria develop resistance to β-lactam antibiotic therapy. The effect of β-lactamase on a penicillin and an analogous cephalosporin is indicated in Scheme 1.

The wide spread use of penicillin after World War II led to the emergence of resistant strains of Staphylococcus aureus. Following the isolation, however, of the penicillin precursor, 6-aminopenicillanic acid (1; 6-APA), from Penicillium chrysogenum in 1957 Beecham workers developed penicillins, e.g. (2)-(4), capable of overcoming these resistant staphylococcal strains.[2] After these advances in penicillin therapy, a range of cephalosporins, e.g. (6)-(8), were introduced as a result of the discovery of cephalosporin C (5) from Cephalosporium acremonium by Abraham and co-workers at Oxford in the mid 1950's.[3]

A major discovery in new naturally occurring β-lactams was reported in the early 1970's when the Lilly and Merck groups identified the cephamycins (9)-(11) from a number of Streptomyces spp.[4] These compounds were novel in that they possessed a 7α-methoxy substituent and this feature was responsible for their increased β-lactamase stability relative to that of the early penicillins and cephalosporins. Chemical introduction of a methoxy group at C-7 in a cephalosporin and C-6 in a penicillin led to the preparation of the clinically useful compounds cefoxitin (12)[5] and temocillin (13).[6] These β-lactams have good activity against a wide range of Gram-negative bacteria and pronounced stability

to a variety of β-lactamases. Synthetic analogues, of the cephamycins [such as latamoxef (14)], were also modelled on the cephamycins, by application of the structure activity relationships learnt from the earlier penicillin and cephalosporin work, and the advances in the general chemical transformation of intermediates such as penicillin G or 6-APA.[7]

1976 was a remarkable year in the discovery of new β-lactam antibiotics with the announcement of the structures and properties of three new families based on clavulanic acid (15),[8,9] thienamycin (16)[10] and nocardicin A (17)[11]; the olivanic acid (18) group of metabolites,[8,12] related to thienamycin was also reported at that time.

In the late 1960's a screening programme to detect microbial metabolites with β-lactamase inhibitory properties was initiated within Beecham laboratories. The screen[8] used was designed to detect compounds which would potentiate the activity of penicillin G against the β-lactamase producing bacterium, Klebsiella aerogenes. By screening about 1000 microorganisms, mainly actinomycetes, certain strains of Streptomyces olivaceus and the culture S.clavuligerus were found to produce β-lactamase inhibitory compounds. The metabolites obtained from S.olivaceus were subsequently shown[12] to be the olivanic acids MM 4550 (19), MM 13902 (20), and MM 17880 (21), while the inhibitory product from S.clavuligerus was identified[9,13] as the novel β-lactam, clavulanic acid (15). Patent applications on clavulanic acid on a world-wide basis were made in the Spring of 1974.

Relative to the general structural features of penicillin and cephalosporin antibiotics, clavulanic acid was novel because it was the first reported naturally occurring example of a β-lactam with an oxygen

atom at position 1. In addition, it lacked an acylamino function at C-6, though it did possess weak broad spectrum antibacterial activity. It also contains a β-hydroxyethylidene substituent at C-2, a unit not present in penicillins but perhaps reminiscent of a feature within the cephalosporin nucleus. The parent ring system has been called a clavam (22), by comparison with nomenclature for penam (23), penem (24), carbapenem (25) and cephem (26); alternatively clavulanic acid (15) can be desribed as a derivative of the 4-oxa-1-azabicyclo[3.2.0]heptane ring system.

The β-lactamases produced by bacteria have been divided[14] into various classes or types and clavulanic acid (15) has been found to be a potent inhibitor of most of the major representatives of these classes.[15] Table 1 shows clavulanic acid to effectively inhibit the Class II (produced by Proteus mirabilis), and Class IV (produced by Klebsiella aerogenes) β-lactamases as well as the Class III and V types, which are plasmid mediated and are further subdivided into TEM, OXA and PSE types. β-Lactamases of the TEM type (e.g. produced by E.coli) are the main group responsible for resistance problems involving Gram-negative populations. The β-lactamases produced by Staphylococcus aureus and most Bacillus spp. are readily inhibited by clavulanic acid. Clavulanic acid is a relatively poor inhibitor of Class I type β-lactamases (sometimes referred to as cephalosporinases) produced by, for example, genera of Enterobacter, Citrobacter and Pseudomonas aeruginosa.

In combination with a penicillin, such as amoxycillin (27), and ticarcillin (28), which shows some instability towards β-lactamases, clavulanic acid produces pronounced synergistic effects against many organisms producing plasmid-mediated β-lactamases, e.g. strains of

Staphylococcus aureus, Klebsiella pneumoniae (aerogenes), Proteus mirabilis, P.vulgaris, Branhamella catarrhalis, Bacteroides fragilis, Escherichia coli, Haemophilis influenzae, and Neisseria gonorrhoeae[16]. (see Tables 2 and 3). Synergy can also be demonstrated with clavulanic acid and first-generation cephalosporins such as cephaloridine, but more recently developed β-lactamase stable cephalosproins, such as cefuroxime (29) and the cephamycin, cefoxitin (12), do not show synergy with the inhibitor (15).

Following extensive in vitro and in vivo studies, coupled with detailed toxicological and drug metabolism experiments in a number of animals species and in man, as well as therapeutic trials in humans, clavulanic acid, as its potassium salt, is marketed, and in clinical use, in conjunction with amoxycillin (27) and with ticarcilin (28), as the products Augmentin*[17] and Timentin*[18] respectively. The oral form of Augmentin is now available on a world-wide basis in many countries including Spain.

The mode of action[19] of clavulanic acid as a β-lactamase inhibitor has been examined in considerable detail and is illustrated in the sequence shown in Scheme 2. Clavulanic acid is considered to interact with a serine residue in the active site of the β-lactamase and then three subsequent reactions can occur; firstly (15) acts as a substrate and the β-lactam ring is cleaved hydrolytically; secondly a transient intermediate is formed which can slowly break down to regenerate free enzyme, and thirdly an irreversible inactivation occurs by further interaction with species such as lysine residues. With the E.coli RTEM-2 β-lactamase, 115 turnovers of clavulanic acid occur for each irreversible inactivation of enzyme.

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* Trademark of Beecham Group p.l.c.

The chemistry of clavulanic acid has been thoroughly explored by Beecham chemists and has been reviewed in a number of papers.[20,21] In general terms (15) can be readily esterified, reduced, isomerised and oxidised to form esters (30), dihydro derivatives (31), derivatives of isoclavulanic acid (32), epoxides (33), aldehydes (34), and the lactone (35). The reactivity at C-3, and C-6 has also been studied involving oxidative decarboxylation and alkylation to yield compounds such as (36) and (37) respectively, while the C-7 β-lactam carbonyl function underwent a Wittig reaction with azetidine (38) formation. In general all these modifications gave products with poor β-lactamase inhibitory properties.

Transformation of the allylic hydroxyl function did, however, result in a large number of derivatives with significant β-lactamase inhibitory activity, such as acyl (39), ether (40), thioether (41), amine (42), deoxy (43), tetrazole (44), and triazole[22] (45) derivatives. The β-lactamase inhibitory activity of representative derivatives is given in Table 4[23,24] Two homologues (46) of clavulanic acid have been prepared and the chemistry of the vinyl clavam (47) and the diene (48) studied. In addition (15) has been converted into the oxacephem ring system (49) and the 4,7-fused β-lactams system (50).[25]

A study of the stability of clavulanic acid over a range of pH values indicated that the major degradation product is the aminoketone (51), with subsequent formation of small amounts of the pyrazines (52).[26] The compound (51) and the reduced pyrrole (53) have been described as the major metabolites of (15) in man.[27] Trifluoroacetic acid treatment of methyl clavulanate resulted in the 2,8-dioxa-6-azabicycli[3.2.1]octane-7-carboxylic acid derivative (54).[28] Benzyl clavulanate can be isomersised into the clavem (55; R_2 = OH) which is then converted into

the pyrroles (57) on acid treatment.[29] The clavem (55; R_2 = H) has been prepared from clavulanic acid via betaine (58) formation and the betaine (58) can be manipulated to yield the penem (56).[30] Clavulanic acid and a range of clavam derivatives have also been obtained by total synthesis.[31]

The production of clavulanic acid by other Streptomyces spp e.g. S.jumonjinensis, S.katsurahamanus has been noted.[32] Further clavam compounds (59)-(61) have been reported to be produced by S.clavuligerus and other Streptomyces spp., however all these metabolites have been found to possess the opposite stereochemistry to clavulanic acid at C-5.[33] Details of the biosynthesis of clavulanic acid have been described and experiments to identify precursors are the subject of study by Elson and his colleagues within Beecham and by Townsend in the USA.[34,35] The β-lactam carbon atoms (i.e. C-5, -6 and -7) are derived from a three carbon unit via glycerol or glycerate, while the other carbon atoms come from glutamate via ornithine. Recent developments[34] in the identification of precurors implicate the azetidinone, proclavaminic acid (62) and the amine, clavaminic acid (63) (Scheme 3). Note the 5S stereochemistry at C-5 in the putative intermediate (63). Proclavaminic acid (62) is converted into clavaminic acid (63) by an iron dependent dioxygenase. Cell free preparations of S.clavuligerus with added pyridoxal phosphate, pyruvate and NADPH transform clavaminic acid (63) into (15). Further details of the conversion of glycerol and glutamate derivatives into (62), (63) and hence (15) are under study.

As soon as clavulanic acid was identified, attempts were made to obtain strains of S.clavuligerus which produced increased titres of clavulanic acid. In addition, extensive fermentation development studies were undertaken. Currently clavulanic acid is produced in 100,000 and

200,000 litre fermenters using high yielding strains of S.clavuligerus. Complementary programmes, to the more classic strain improvement procedures, using recombinant DNA techniques have been used by Beecham since 1980. Using a number of vectors, chromosomal DNA fragments have been cloned into non-producing strains of S.clavuligerus with a resultant restoration of clavulanic acid production.[36] Much detail is now known on the regions of the chromosome involved with clavulanic acid production and this technology is being used to develop new improved production strains.

The novelty of the structure of clavulanic acid, plus a knowledge of its mode of action is a β-lactamase inhibitor, prompted the preparation of many analogues based on the related penam ring system, usually starting from penicillin G or 6-APA. For example the compounds illustrated in structures (64)-(72) have been shown to the "mechanism based inhibitors" of β-lactamase.[37] Of these inhibitors the penicillanic acid sulphone, sulbactam (64), has been developed and is combined with cefoperazone (73).[38] The mutual pro-drug (sultamicillin) formed by linking sulbactam (64) and ampicillin (74) via their C-3 ester functions has also been examined in some depth.[39] The β-lactamase inhibitory activities of the penicillanic acid derivatives (64)-(67) are shown in Table 5. Some penem analogues (75) also show potent inhibitory activity.[40,41]

Initially the Beecham screen for β-lactamase inhibitors highlighted the olivanic acids[12] (19)-(21) and the related compounds[42] (76)-(79) from Streptomyces olivaceus strains. While these carbapenems demonstrated potent β-lactamase inhibitory properties, they were of greater interest as potential antibiotics.[43] In the same year that the olivanic acids

were reported Merck scientists described[10] thienamycin (16) and its derivatives (80) and (81) from Streptomyces cattleya. Thienamycin (16) was detected via a screen for inhibitors of cell wall synthesis. Later, they also reported[44] the carbapanems (76)-(79) from Streptomyces flavogriseus. To date over 40 naturally occurring carbapenems have been reported from Streptomyces spp. The parent ring system (82) is produced by bacterial species from the genera Serratia, Erwinia and Spirilla.[45]

Like clavulanic acid, the various carbapenems show marked variations in structural features relative to the penicillins and cephalosporins. A $-CH_2-$ unit replaces the -S- atom; an acylamino-function is lacking, an endocyclic double bond is present; sulphur is present but as an amino-ethylthio or related side chain at C-2; the protons at C-6/C-5 can be cis- or trans- orientated (in the penicillin and cephalosporin β-lactam systems for antibacterial activity a cis- relationship was essential).

Of the naturally occurring carbapenems, thienyamycin is the most potent antibacterial.[46] All carbapenems are in general stable to β-lactamases with the exception of the zinc containing type (e.g. β-lactamase II from Bacillus cereus). All carbapenems are very rapidly degraded/metabolised via the kidney in various animal species including man. This instability is due to the action of a zinc containing enzyme called dehydropeptidase I (DHP-I). Thienamycin is also unstable in concentrated solution. To overcome these problems Merck workers developed the compound imipenem (83), an N-formimidoyl derivative,[47] which has greater chemical stability than (16), and derived the DHP-I inhibitor cilastatin[48] (84). A combination of imipenem (83) and cilastatin (84) is now in clinical use as Primaxin. More recently the carbapenem (85), containing a 1β-methyl substituent, which has pronounced

stability to DHP-I and which retains good chemotherapeutical properties has evolved from an extensive synthetic analogue programme as a possible replacement for imipenem (83).[49]

In addition to clavulanic acid, thienamycin and the olivanic acids, 1976 also heralded the discovery of the nocardicin family of β-lactams - or azetidinones. Despite a concentrated effort though no analogue of nocardicin A (17) was worthy of development.[50]

Nocardicin A was detected using a strain of E.coli highly susceptible to β-lactam antibiotics in conjunction with a β-lactamase sensitivty test.[11] In 1981 Takeda workers reported the application of a similar assay,[51] but based on a super-sensitive strain of Pseudomonas aeruginosa; this led to the identification of the monobactam group of mono-cyclic β-lactams with the characterisation of sulfazecin (86) and isosulfazecin (87) from Pseudomonas acidophila and Pseudomonas mesoacidophila.[52]

Simultaneously the Squibb company disclosed their studies on screening bacteria for β-lactam antibiotics via a β-lactamase induction assay using a strain of Bacillus licheniformis.[53] In addition to sulfazecin (86), the simple metabolite (88) and a number of compounds based on the general structure (89) were isolated from species of Pseudomonas, Gluconobacter, Agrobacterium, Chromobacterium, and Flexibacter.[54] Other examples of naturally occurring monobactams are MM 42842 (90) from Pseudomonas concovenenans[55] and PB-5266 A, B and C (91)-(93) from Cytophaga johnsonae.[56] Intensive chemical synthesis programmes have given monobactam products such as aztreonam (94),[57] tigemonan (95),[58] and carumonan (96).[59]

Recently further application of super-sensitive strains of bacteria as screening organisms has given the formamido cephalosporins, such as (97)-(99) and related cephamycin and cephalosporins,[60] as well as the formamidonocardicins (100)-(103).[61] Non β-lactam metabolites have also been highlighted by such assays and positives include the structures (104)-(108).[62,63]

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Table 1: β-Lactamases; their classification and inhibition by clavulanic acid

β-Lactamase	Class/ Type	Example	Amoxycillin hydrolysis rate (Pen G = 100)	Effect of clavulanic acid	I_{50}* (µg/ml)
Chromosomal cephalosporinase	I	*Enterobacter cloacae* P99	5	-	110
		Pseudomonas aeruginosa A	10	-	
		Escherichia coli JT410	2	-	
		Bacteroides fragilis	>100	+	
Chromosomal penicillinase	II	*Proteus mirabilis* C889	142	+	0.015
Chromosomal broad spectrum	IV	*Klebsiella penumoniae* E70	127	+	0.007
		Branhamella catarrhalis 1908	120	+	
Plasmid mediated	III	TEM-1 and 2; *E.coli* JT4	86	+	0.06
		SHV	126		
	V	OXA type e.g. OXA-2	162	+	
		PSE type e.g. PSE-4	92	+	
		Pseudomonas aeruginosa Dalgleish			
Gram-positive penicillinase		*Staphylococcus aureus* Russell	168	+	0.03

Table 2

Effect of Clavulanic Acid (CA) on the Activity of Amoxycillin against β-Lactamase Producing Organisms (MIC Values, μg/ml)[a]

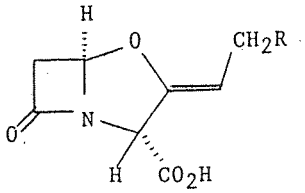
Organism[b]	Amoxycillin + CA (μg/ml)			CA alone
	0	1.0	5.0	
Bacteroides fragilis (28)	33	0.48	0.14	13.1
Escherichia coli[c] (100)	>5000	94.5	13.2	24.8
Haemophilus influenzae[c] (15)	150	0.72	0.44	36.8
Klebsiella aerogenes (45)	315	1.75	0.89	33.2
Klebsiella aerogenes[c] (32)	>5000	126	20	33.6
Neisseria gonorrhoeae[c] (6)	>40	0.18	-	5.6
Proteus species (23)	433	11.6	4.2	62.9
Staphylococcus aureus (35)	106	0.72	0.17	17.1

Table 3

Antibacterial Activity of ticarcillin alone and in the presence of clavulanic acid against a variety of β-lactamase-producing organisms[d]

Organism	MIC (mg/l)					
	MIC ticarcillin + CA (mg/l)					
	0	1	5	10	20	CA alone
Bacteroides fragilis B72	>80	2.5	1.25	-	-	31
Citrobacter freundii E8	16	16	16	16	-	31
Citrobacter diversus	500	8	4	2	-	31
Enterobacter cloacae N1	16	16	16	16	-	62
Escherichia coli JT410[a]	31	31	31	31	-	31
Escherichia coli JT39 R_{TEM}[b]	>2000	125	31	8	-	31
Klebsiella aerogenes E70[a]	500	10	5	2	-	31
Klebsiella aerogenes Ba95[a,b]	2000	500	62	16	-	31
Proteus mirabilis C889	500	62	16	8	-	125
Providentia alcalifaciens Hd[a,b]	>1000	16	4	2	-	62
Pseudomonas aeruginosa A[c]	16	-	16	16	16	250
Pseudomonas aeruginosa Dalgleish	>4000	-	62	-	31	125
Pseudomonas aeruginosa 1822	>4000	-	125	-	31	250
Pseudomonas cepacia	1000	125	31	-	1.0	31
Pseudomonas pseudomallei	500	31	8	-	1.0	250
Serratia marcescens US20[a]	16	16	16	16	-	62
Serratia marcescens US39[a,b]	2000	125	62	31	-	31
Staphylococcus aureus Russell	62	4	2	1	-	15

Table 4: β-Lactamase inhibitory activity of selected clavulanic acid derivatives[a]



	Inhibitory activity, I_{50} (μg/ml); β-lactamase from				
	Staphylococcus aureus Russell	*Escherichia coli* JT4 III (TEM)	*Klebsiella aerogenes* E70 II	*Proteus mirabilis* C889 IV	*Citrobacter freundii* Mantio I
Clavulanic acid; R = OH	0.06	0.07	0.03	0.03	10
Deoxyclavulanic acid; R = H	0.12	0.09	0.05	-	5
Isoclavulanic acid	0.6	1.0	0.45	-	5
Acetate; R = $OCOCH_3$	0.04	-	>0.4	-	0.4
Carbamate; R = $OCONHCH_3$	1.5	2.5	2.5	-	0.45
Methyl ether; R = OMe	0.05	0.18	0.07	0.01	8.5
Benzyl ether; R = OCH_2Ph	0.005	0.1	0.04	0.02	4.4
Thioether; R = SMe	0.11	0.04	0.13	0.01	>>10[b]
Amine; R = $N(CH_2Ph)_2$	0.002	0.04	0.08	0.01	0.62

Table 5: β-Lactamase Inhibitory Activity of Penicillanic Acid Derivatives

Inhibitor	I_{50} (μg/ml)* against β-lactamases from		
	Staph. aureus Russell	*E.coli* JT4 (TEM-1)	*Ent. cloacae* P99
(64)	1.6	1.4	6
(65)	1.5	0.15	1.5
(66)	0.7	0.06	5.5
(67)	50	13	>50

Footnotes for Tables

Table 1: * Amount required to give 50% protection of nitrocefin (at 250µg/ml) substrate after a 5 min. preincubation of clavulanic acid with β-lactamase; adapated from Ref. 15.

Table 2: [a] From Ref. 16.

[b] Numbers in parentheses indicate number of strains tested.

[c] Strains producing a plasmid-mediated β-lactamase.

Table 3: [a] Producing a chromosomally mediated β-lactamase.

[b] Plasmid carrying (R+) strain.

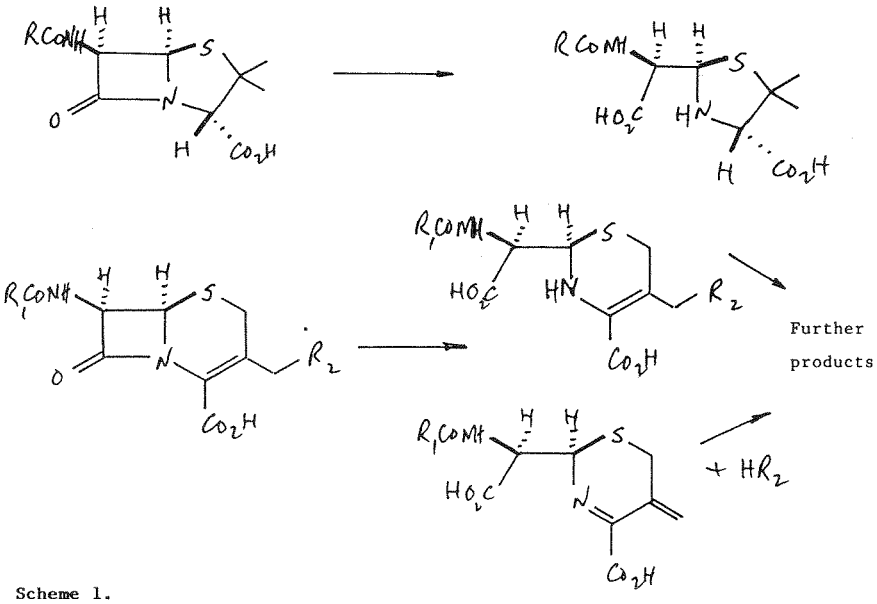
[c] Carbenicillin-sensitive strain producing Sabath enzyme only.

[d] From Ref. 16.

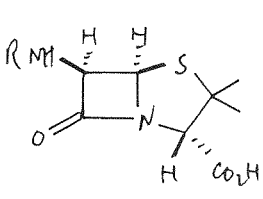
Table 4: [a] From Ref. 23.

[b] β-Lactamase from *Enterobacter cloacae* P99.

Table 5: * See footnote after Table 1; adapated from Ref. 24.

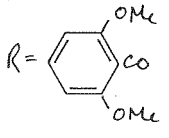


Scheme 1.
Effect of ß-Lactamase on Penicillins and Cephalosporins

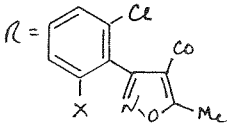


(1) 6-APA; R = H

(2) Methicillin;



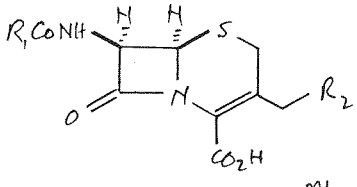
(3) Cloxacillin;



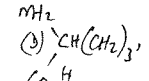
X = H

(4) Flucloxacillin;

X = F

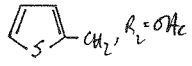


(5) Cephalosporin C;

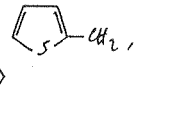


R_2 = OAc

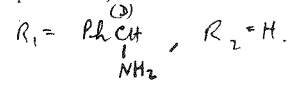
(6) Cephalothin;

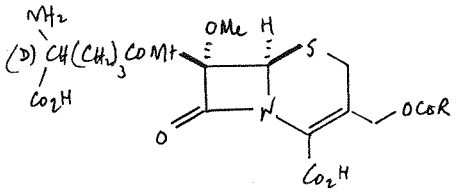


(7) Cephaloridine;

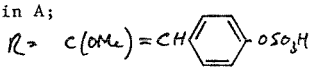


(8) Cephalexin;

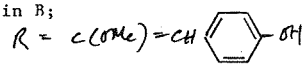




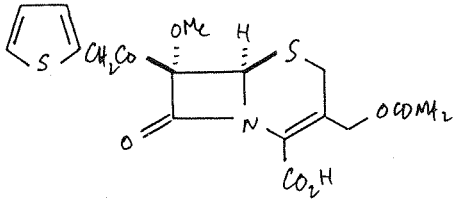
(11) Cephamycin A;



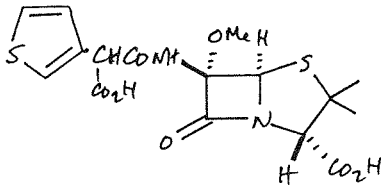
(10) Cephamycin B;



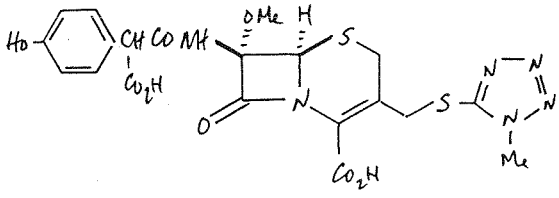
(11) Cephamycin C; $R = NH_2$



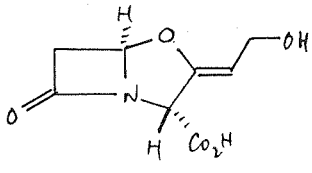
(12) Cefoxitin



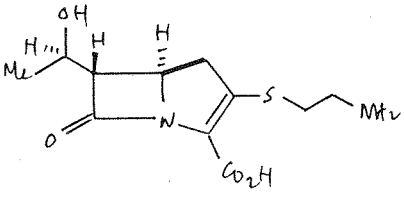
(13) Temocillin



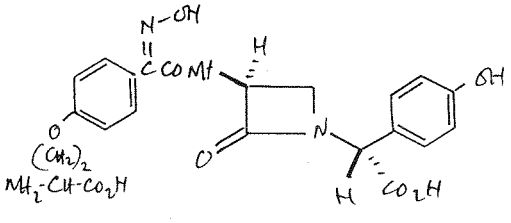
(14) Latamoxef



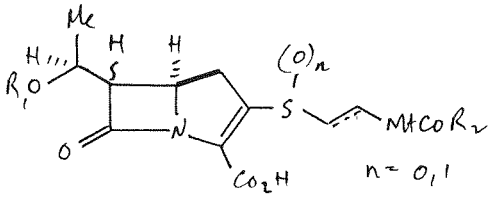
(15) Clavulanic acid



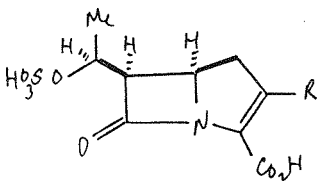
(16) Thienamycin

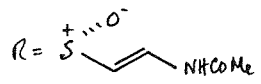


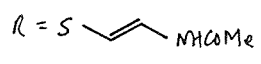
(17) Nocardicin A

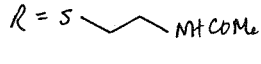


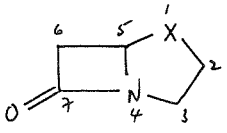
(18) Olivanic acids

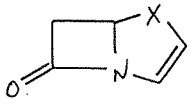


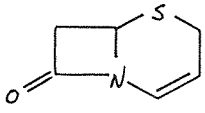
(19) MM 4550; 

(20) MM 13902; 

(21) MM 17880; 

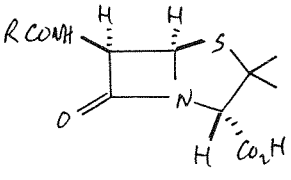


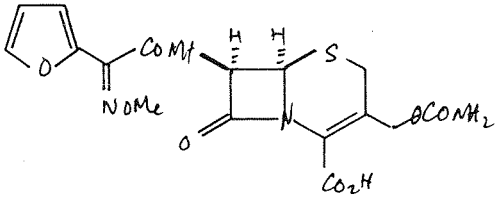




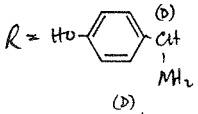
(22) Clavam; X = O (24) Penem; X = S (26) Cephem

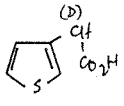
(23) Penam; X = S (25) Carbapenem; X = CH_2

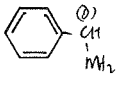


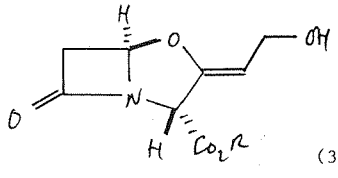


(29) Cefuroxime

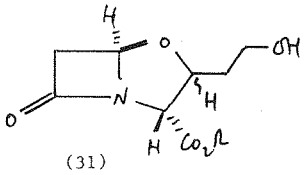
(27) Amoxycillin; 

(28) Ticarcillin; 

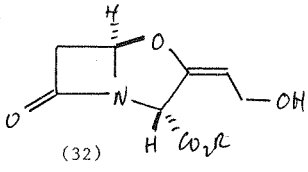
(74) Ampicillin; 



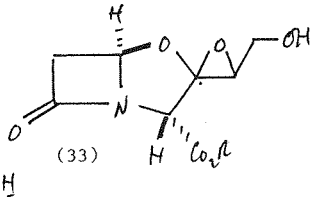
(30)



(31)



(32)



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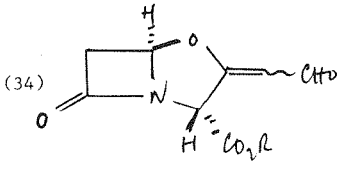

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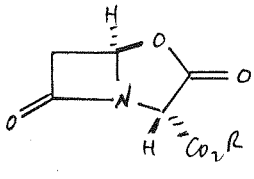

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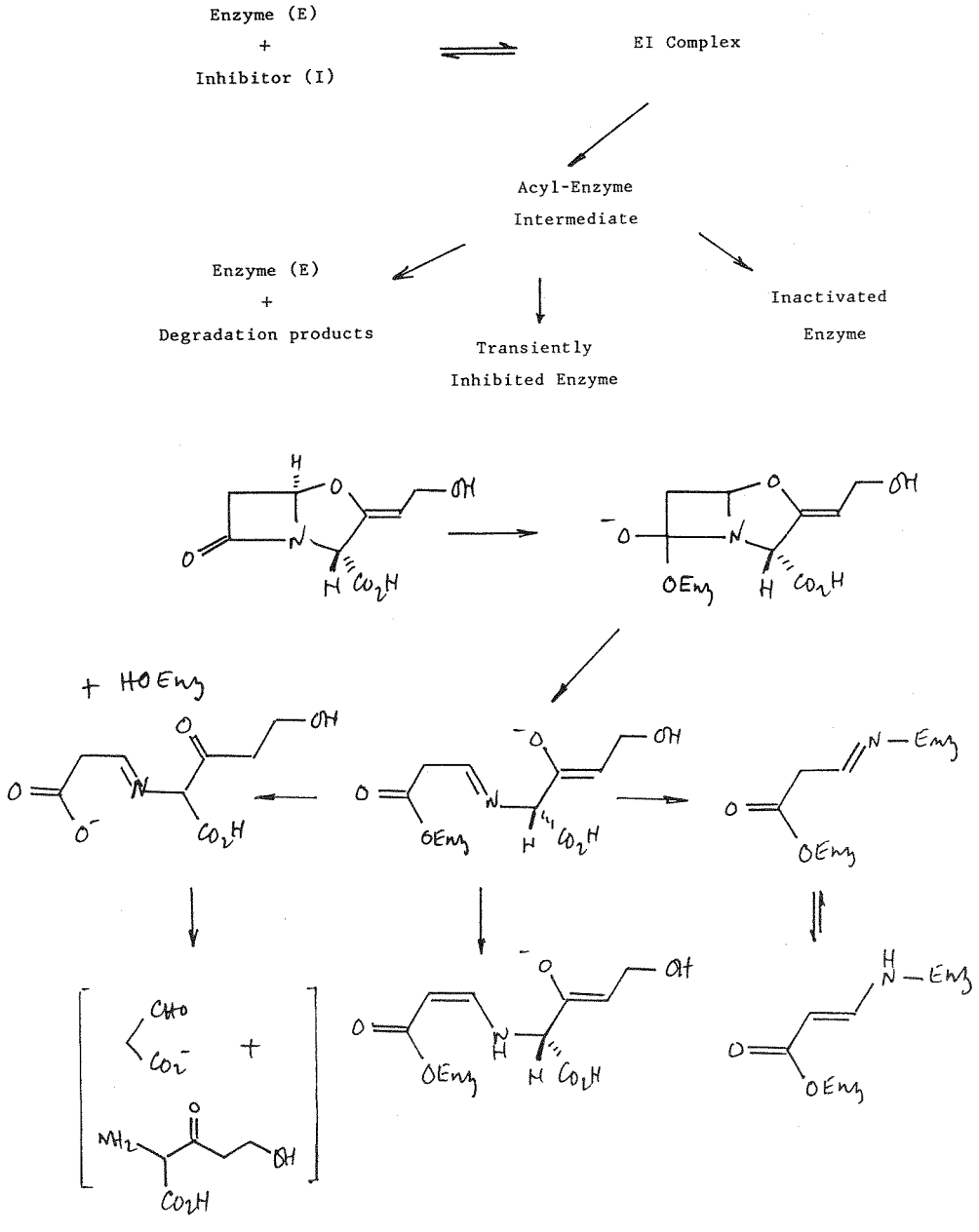
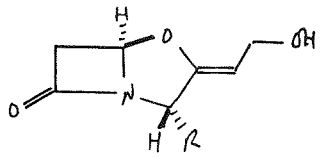
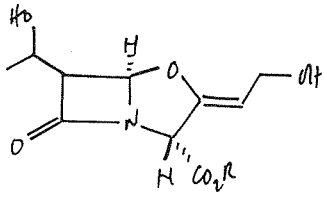


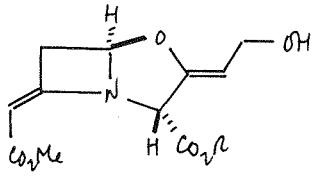
Scheme 2. Inhibition of ß-Lactamase by Clavulanic Acid



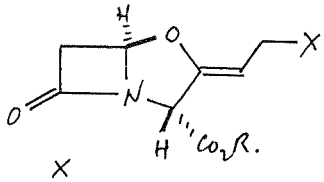
(36) R = OMe or OAc



(37)



(38)



(39) OCOR, $CH(OR_2)$;

(40) OR;

(41) SR, SOR, SO_2R;

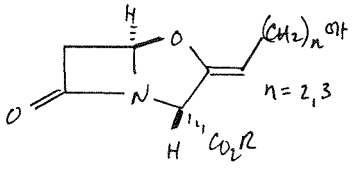
(42) NH_2, NHR, NR_2;

(43) H

(44)

and

(45)



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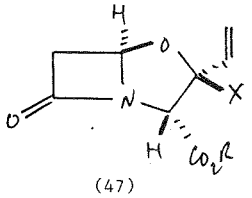
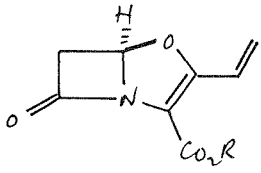
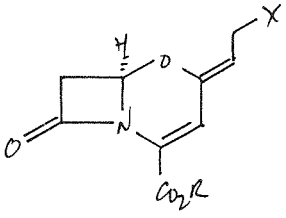


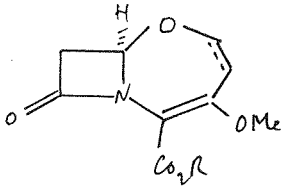
(47)



(48)



(49)



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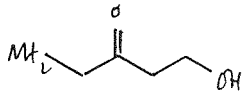
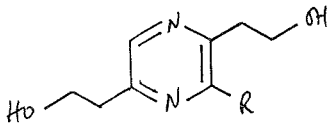
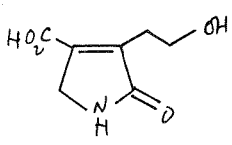


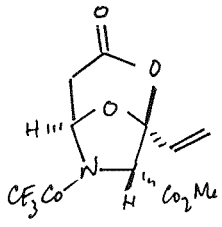
(51)



(52) R = H and Et



(53)



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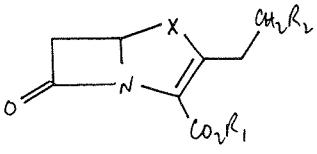
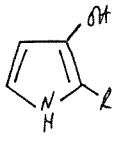
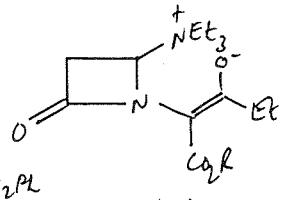


(55) X = O, R_1 = CH_2Ph, R_2 = OH or H

(56) X = S, R_2 = H



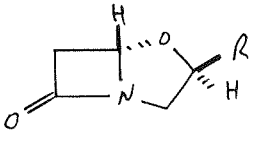
(57) R = CO_2CH_2Ph and R = $COCH_2CH_2OCO_2CH_2Ph$.



(58)

(59) R = CO_2H ; CH_2OH ; CH_2OCHO and CH_2CHCO_2H (NH_2)

ex. S.clavuligerus

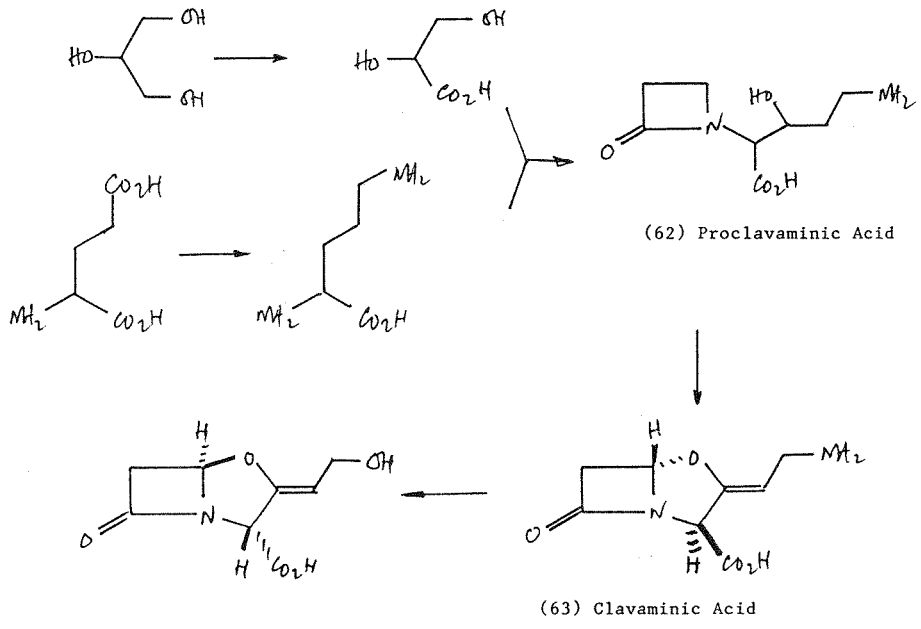


(60) R = CH_2CH_2OH ; $CH_2CH(OH)CHCO_2H$ ($NHCOCH(NH_2)CHMe_2$)

ex. S.antibioticus

(61) R = $CH(NHR_1)CH(OH)CO_2H$; Clavamycins A-F

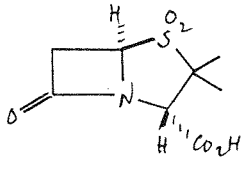
ex. S.hygroscopicus



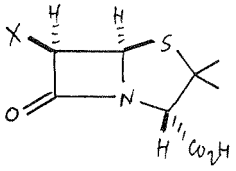
(62) Proclavaminic Acid

(63) Clavaminic Acid

Scheme 3. Biosynthesis of Clavulanic Acid

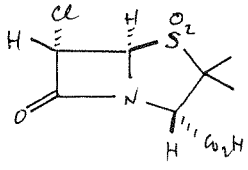


(64) Sulbactam

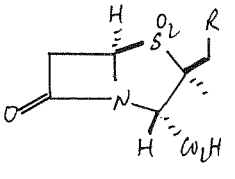


(65) X = Br

(66) X = I

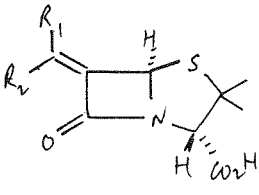


(67)



(68) R = Cl

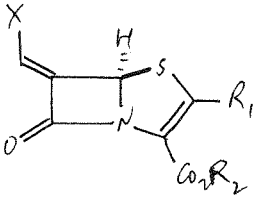
(69) YTR 880; R = 



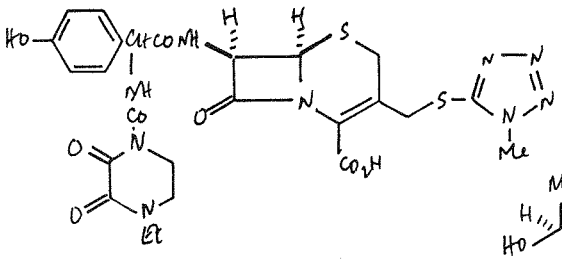
(70) R_1 = COMe, R_2 = H

(71) R_1 = H, R_2 = COMe

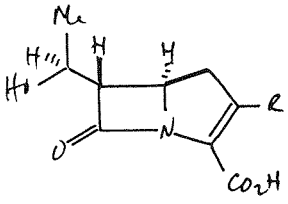
(72) R_1 = OMe, R_2 = H

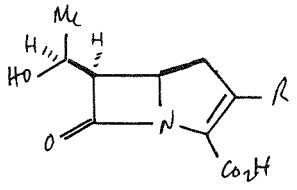


(75) X = alkyl or heterocycle



(73) Cefoperazone





(76) R = S NHCOMe ; MM 22380

Epithienamycin A

(77) R = S NHCOMe ; MM 22381

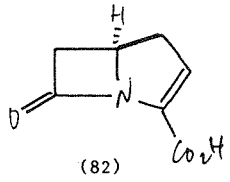
Epithienamycin B

(78) R = S NHCOMe ; MM 22382

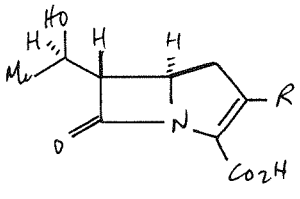
Epithienamycin C

(79) R = S NHCOMe ; MM 22383

Epithienamycin D



(82)

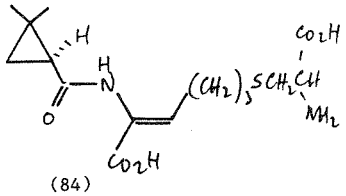


(80) S NHCOMe

N-Acetylthienamycin

(81) S NHCOCH3

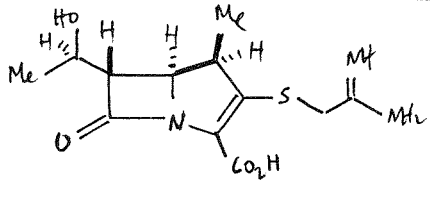
N-Acetyldehydro-thienamycin



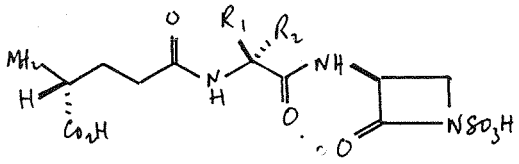
(84)

(83) S NH NH

Imipenem

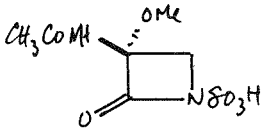


(85)



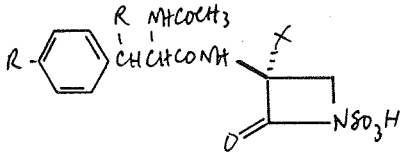
(86) Sulfazecin; $R_1 = H$, $R_2 = Me$

SQ 26,445



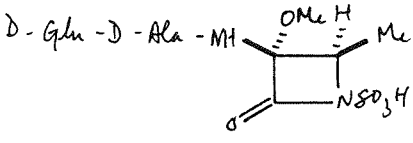
(88) SQ 26,180

(87) Isosulfazecin; $R_1 = Me$, $R_2 = H$

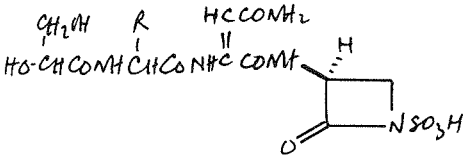


(89) X = H or OMe

R = H, OH or OSO_3H



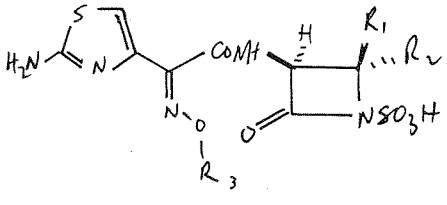
(90) MM 42842



(91) PB-5266 A; R = Me

(92) PB-5266 B; $R = CH_2OH$

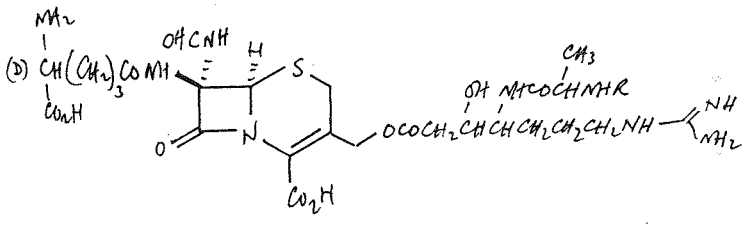
(93) PB-5266 C; R = H



(94) Aztreonam; $R_1 = H$, $R_2 = Me$, $R_3 = CMe_2CO_2H$

(95) Tigemonan; $R_1 = R_2 = Me$, $R_3 = CMe_2CO_2H$

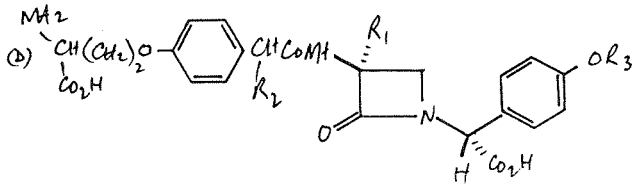
(96) Carumonan; $R_1 = CH_2OCONH_2$, $R_2 = H$, $R_3 = CH_2CO_2H$



(97) Chitinovorin A; $R = H$

(98) Chitinovorin B; R = L-Ala

(99) Cephabicin F_3; R = L-Ala-L-Ala etc.

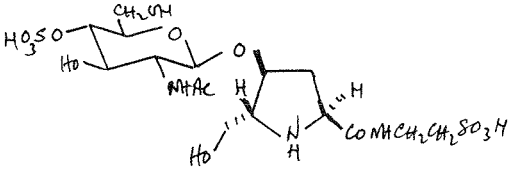


(100) Formadicin A; R_1 = NHCHO, R_2 = OH, R_3 =

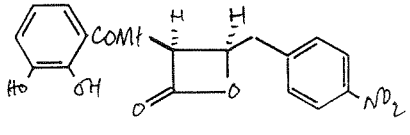
(101) Formadicin B; R_1 = H, R_2 = NHCHO, R_3 =

(102) Formadicin C; R_1 = NHCHO, R_2 = OH, R_3 = H

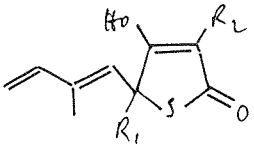
(103) Formadicin D; R_1 = H, R_2 = NHCHO, R_3 = H



(104) Bulgecin A

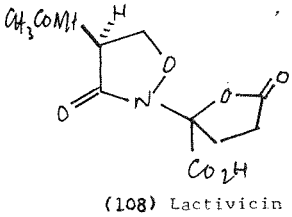


(105) Obafluorin



(106) Thiolactomycins

(107) FR-900148



(108) Lactivicin