β-Lactams in the New Millennium. Part-I: Monobactams and Carbapenems

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Abstract: β-lactam ring-containing compounds such as penicillins, ampicillin, amoxicillin, cephalosporins and carbapenem are among the most famous antibiotics. This article reviews the recent developments in the study of such compounds. The introductory paragraph, which highlights the significance of the subject and cites most of the leading references of the previous century, is followed by an overview of β-lactams and some novel methodologies for the synthesis of bi-, tri- and polycyclic derivatives. The rest of the sections deal with design, synthesis and biological activity of monobactams and carbapenems. Many of them have potential antibacterial activity, even against some resistant strains, and enzyme inhibitory activity.

Keywords: β-Lactam, carbapenem, Staudinger reaction, amino acid cyclization, antimicrobials, cholesterol absorption inhibitors, enzyme inhibitors, anticancer.

1. INTRODUCTION

Natural, semisynthetic and synthetic β-lactam derivatives occupy a central place in medicinal chemistry due to their diverse and interesting antibiotic activities [1-9]. They are classified into different groups such as monobactams, penams, penems, carbapenems, cephems, oxacephems and sulbactams, etc., depending on the ring system present in them. Even though they have a long history of development starting from the discovery of penicillin in 1928, quest for new synthetic methods and refinement of those already known remains appealing, as does research into the application of these in synthesizing novel biologically active β-lactam derivatives. The success of these compounds is due to their excellent bactericidal activity, good pharmacokinetics, low host toxicity and their synergy with other classes of antibiotics such as aminoglycosides. The emergence of various resistant strains of pathogens, however, is of great concern worldwide, and necessitates the design of new molecules with broader activity and least side effects. Furthermore, the utility of β-lactams as building blocks for various biologically active compounds, as well as their recognition as inhibitors of cholesterol absorption [15-18] and certain enzymes [19-20], has given impetus to the researches leading to the synthesis of novel bioactive β-lactam compounds [10-14]. In the late nineties, several groups reported novel methodologies for the synthesis of β-lactams and new β-lactams of potential biological activities by structural modifications [15-24].

This article aims to review the development in synthetic and biological studies of monobactams and carbapenems during the last three years (July 1999 to June 2002). Cephalosporins (cephems) and others will be described in the second part of this review.

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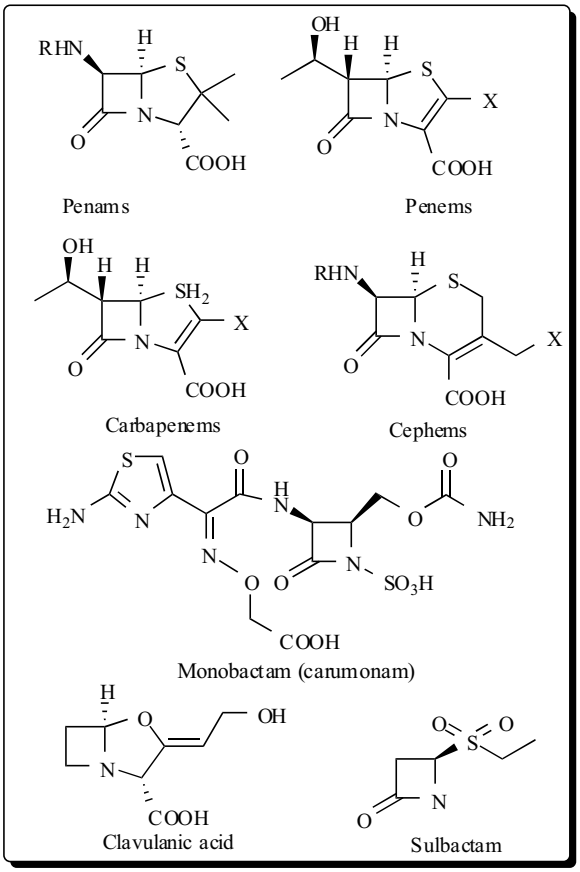
2. SYNTHESIS AND BIOLOGICAL ACTIVITY OF β-LACTAMS: AN OVERVIEW

2.1 Synthesis

The most important aspect of the synthesis of β-lactams has been the construction of the β-lactam ring. The classical methods of its formation can be classified as (i) Staudinger's ketene-imine reaction, an overall [2+2] cycloaddition, (ii)



cyclization reactions of β-amino acids and esters, and (iii) carbene insertion. [2+2] Cycloadditions are the most common convergent route to the formation of the β-lactam

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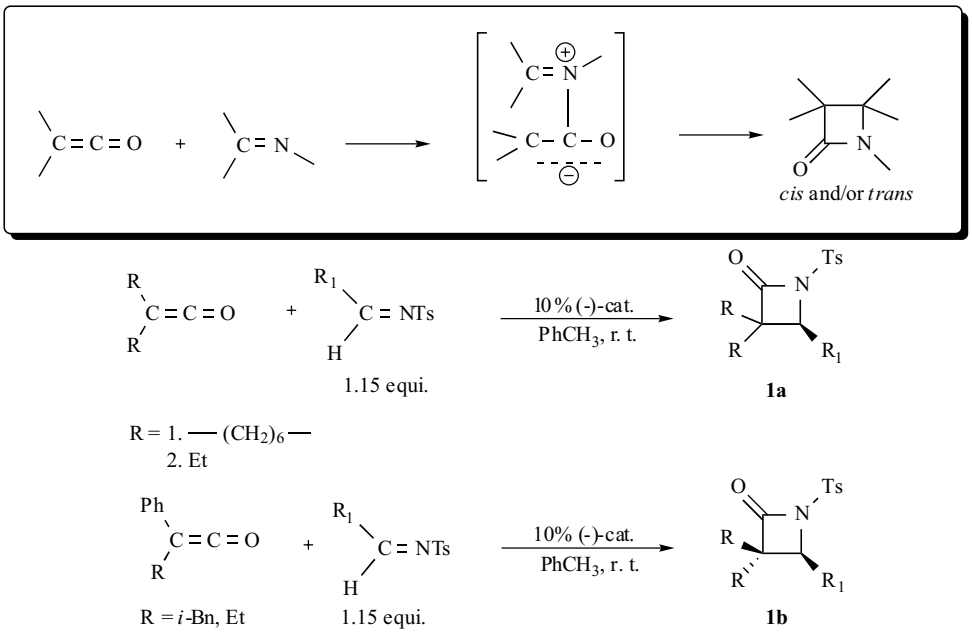
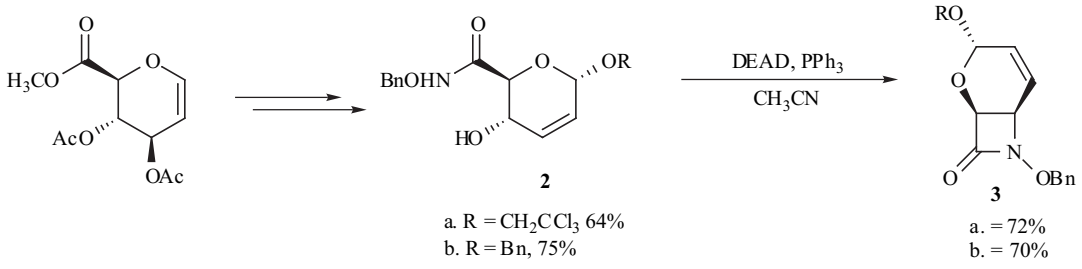


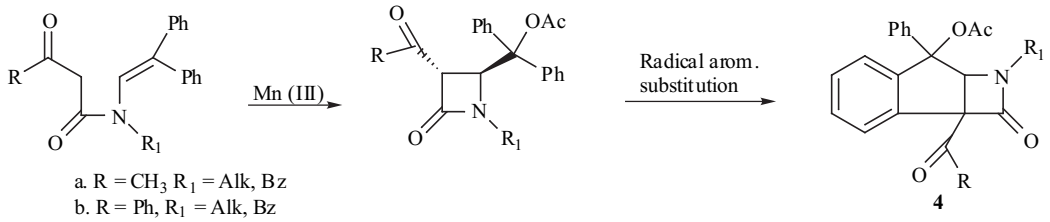
Scheme 1.

ring [25]. Staudinger's reaction has been reviewed recently by Palomo and coworkers [23]. Although commonly called a [2 + 2] cycloaddition, it is generally accepted that the reaction is, in fact, stepwise. The first step of the reaction involves a nucleophilic attack of imino nitrogen on the *sp*-hybridized carbon of ketene to form a *zwitterionic* intermediate which cyclizes to form the azetidinone ring. The stereochemistry of the resulting azetidinone can be *cis, trans* or a mixture of both depending on a number of factors [26-28]. This reaction is still being investigated extensively both from the synthetic and mechanistic points of view, to achieve stereo- and enantiocontrol and explain the stereochemical outcome. Some computer–assisted theoretical calculations have been published to explain stereoselectivity of the reaction [29-31]. A number of chiral auxiliary-based asymmetric Staudinger reactions have been reported [23]. As an important advancement in the area, Fu and Hodous have reported a catalytic enantioselective synthesis of some β-lactams, and its tentative mechanism [32]. They have reacted various symmetrical and unsymmetrical ketenes with imines, derived from aromatic, α, β-unsaturated and aliphatic aldehydes, in the presence of the 4-(pyrrolidino)pyridine derivative as a chiral catalyst (**Scheme 1**). The yields of the products **1a** and **1b** are in the range of 76-98 % while *ee* is 82-98.

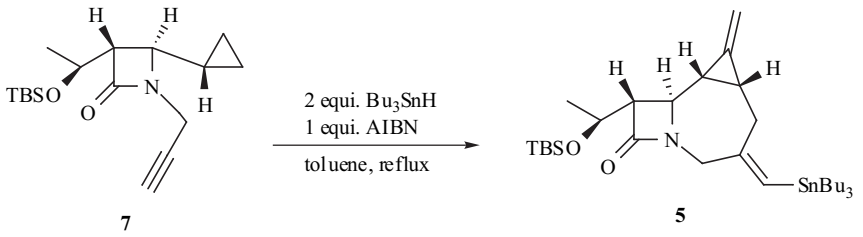
Numerous other monocyclic, fused bi-, tri-, and polycyclic β-lactam derivatives have been synthesized by chemical transformations of the β-lactams synthesized by these classical methods. Alcaide and coworkers have reviewed the synthesis of bi-, tri-, and polycyclic β-lactams using 4-oxazetidin-2-carbaxaldehydes as synthons [33]. Since most of the biologically active β-lactams in clinical use are fused bicyclic compounds, it would be useful to describe some recently discovered new methodologies for the synthesis of such compounds.



Scheme 2.

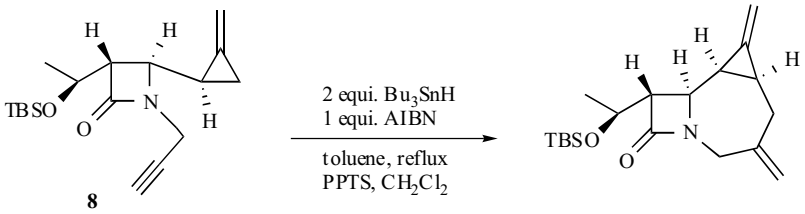


Scheme 3.



7 **5**

Scheme 4.



8 **6**

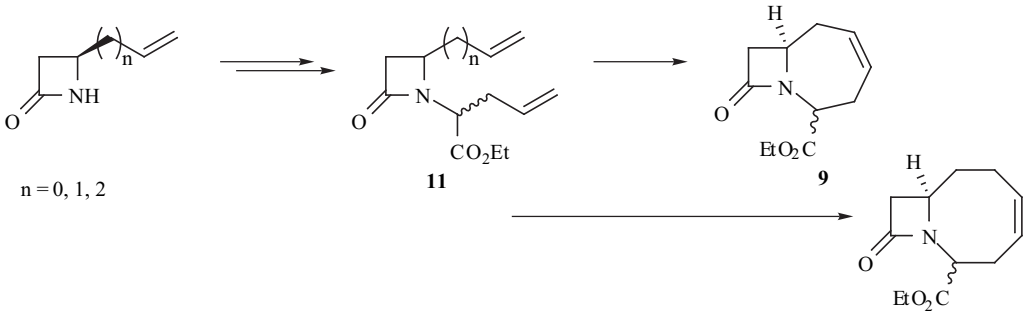
Scheme 5.

Durham and Miller have used carbohydrate template, glucuronic acid glycosides **2** to prepare novel fused bicyclic azetidinones **3** (**Scheme 2**) [34]. Their strategy involves N1 – C4 bond closure of β-hydroxy hydroxamates.

A novel synthesis of fused – tricyclic hydrindene – azetidinones **4** from 2-acyl-*N*-(2,2-diphenyl-1-ethyl)-*N*-alkylacetamides (**Scheme 3**) has been reported by Cerreti and co-workers [35]. The substrates undergo a 4-*exo-trig* radical cyclization followed by ring closure of the resulting azetidinone *via* a radical aromatic substitution in the presence of Mn (III) to afford the product.

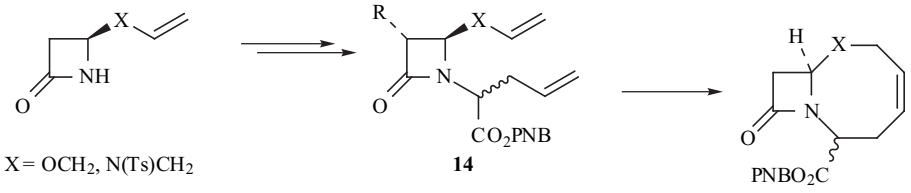
Kilburn and his group have published synthesis of novel fused – tricyclic azetidinones **5** and **6** by radical cyclization in suitably substituted azetidinones **7** (**Scheme 4**) and **8** (**Scheme 5**), respectively [36].

Barrett and co-workers have reported the method for synthesis of novel fused bicyclic azetidinone carboxylic esters **9** and **10** from 4-alkenyl-2-azetidinones **11** *via* Ireland–



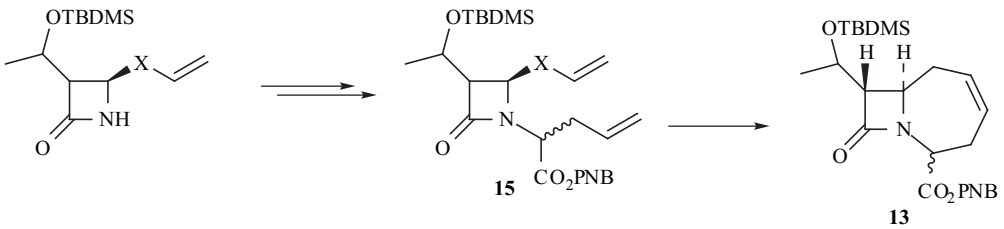
11 **9** **10**

Scheme 6.



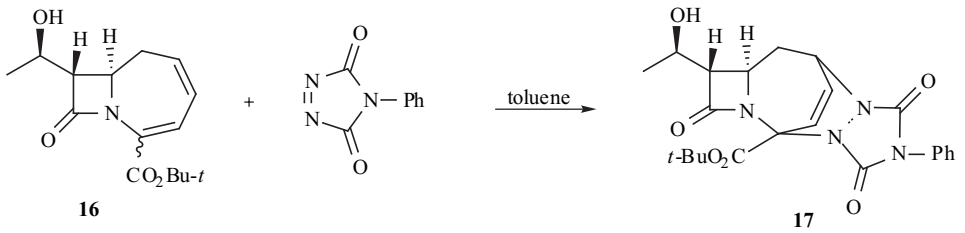
14 **12**

Scheme 7.



15 **13**

Scheme 8.



Scheme 9.

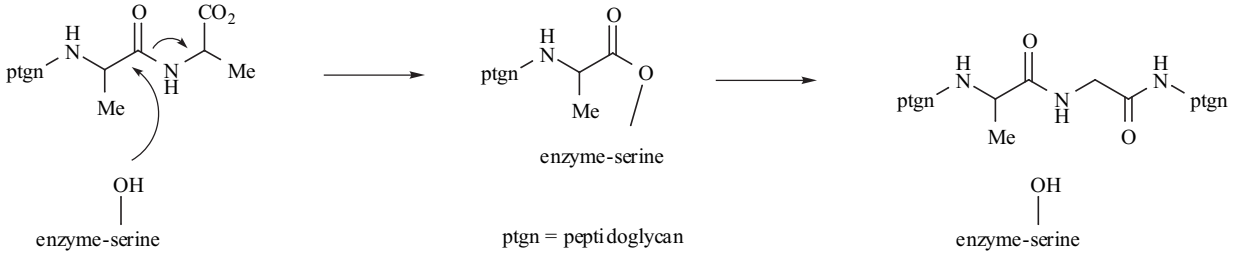
Claisen rearrangement and subsequent metathesis employing molybdenum carbene or ruthenium carbene catalysts (**Scheme 6**) [37]. Azetidinones **12** and **13** have been synthesized using the same method from azetidinones **14** (**Scheme 7**) and **15** (**Scheme 8**), respectively. A fused bicyclic azetidinone **16** with diene function in the other ring, synthesized by this methodology, has been transformed to a fused tetracyclic azetidinone **17** (**Scheme 9**).

2.2 Antibacterial Activity

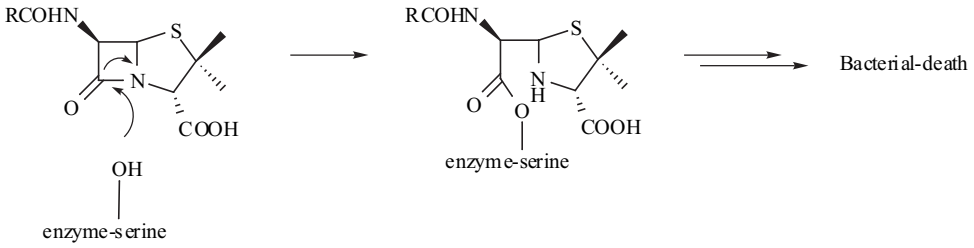
The β-lactam antibacterials act on bacteria by inhibiting the final step of the bacterial cell wall biosynthesis. Although several mechanisms might be operating in this inhibition, the most important is probably the inhibition of the terminal peptidoglycan cross-linking. Bacteria have a cytoplasmic membrane similar to that of eukaryotes. This membrane is surrounded by a periplasmic space, which is in turn enclosed by a peptidoglycan layer, and finally the outer membrane. The peptidoglycan layer is a cross-linked polymer that forms a net-like structure, which provides structural rigidity to the organism, and allows it to survive in mediums to which it may be strongly hypertonic. As a bacterium grows, a series of covalent cross-links must be formed between adjoining peptidoglycan strands in the cell wall. These cross-links are stitched together by transpeptidase enzymes in the cell membrane through the replacement of a terminal D-alanine unit on one peptidoglycan strand with a glycine residue on a neighboring peptidoglycan strand. The initial cleavage of the D-alanine residue by transpeptidase occurs by a nucleophilic addition of an active site serine onto the amide functionality, as shown in **Scheme 10**. In a subsequent amidation step, the resulting enzyme-linked peptidoglycan is converted to the cross-linked material, which releases serine for further catalysis.

Penicillins, cephalosporins and related β-lactam drugs possess an unusual ability to interrupt this crucial cross-linking process by an irreversible acylation of the hydroxy group of the catalytic serine unit within the enzyme active site resulting in the formation of a catalytically inactive stable enzyme-drug adduct (**Scheme 11**). The net result is decrease in the number of cross-linked residues within the cell wall making it weak and prone to rupture. Inhibition of the transpeptidase thus inhibits the bacterial growth. The sequences leading to cidal action are still not clearly understood. Nicks may be produced at the growth site of the cell wall. If these nicks are sufficiently severe, the protoplast may protrude into the medium and burst resulting in bacterial death.

The major limitation to the potentials of β-lactam antibacterials is the ability of bacteria to produce a family of enzymes called β-lactamases. These enzymes hydrolyze the β-lactam ring which is required for antibacterial activity. There are different types of β-lactamases and their efficacy in hydrolyzing the ring varies widely. There are four distinct classes of β-lactamases, of which class A enzymes are the most common. In order to counter the hydrolysis by β-lactamases, some antibiotics are administered in



Scheme 10.



Scheme 11.

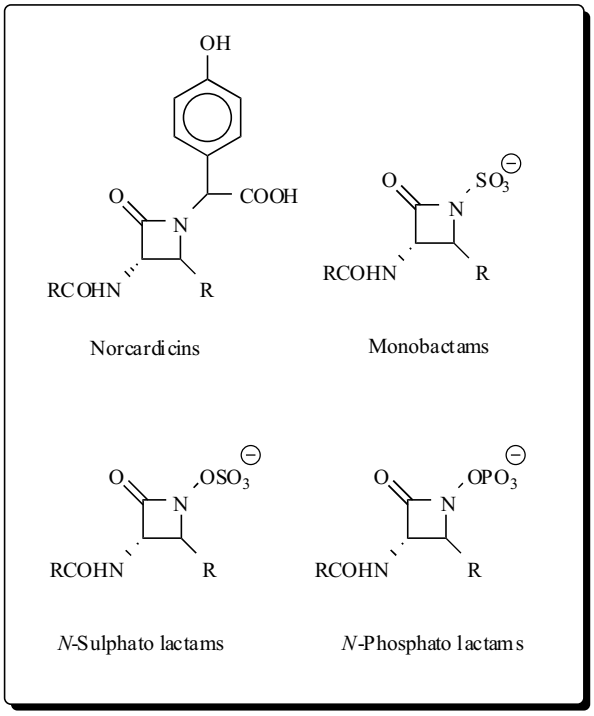
combination with a β-lactamase inhibitor drug. For example, amoxicillin is administered in combination with clavulanic acid. However, the discovery of new variants of β-lactamases, which are resistant to known β-lactamase inhibitors, has caused great concern worldwide.

The major thrust areas in research on β-lactams have been the development of new stereoselective methodologies to construct the β-lactam ring, and structural modifications in compounds, especially carbapenems and cephems with known activity, to design and develop new molecules with i) a broad spectrum of activity, specially against resistant strains and ii) least side effects. A recently emerging interest is in the study of enzyme inhibition activity of β-lactams, which is justified as several compounds with appreciable activity against various enzymes have been reported.

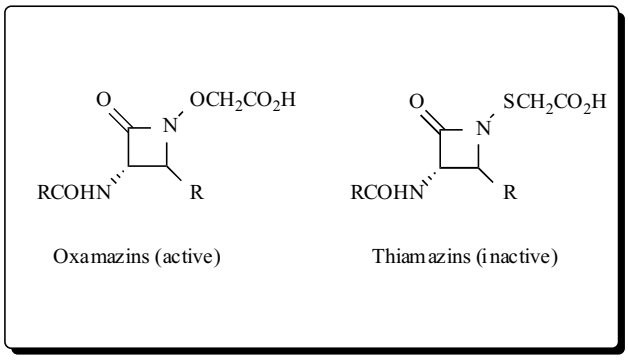
3. SYNTHESIS AND BIOLOGICAL ACTIVITY OF MONOCYCLIC β-LACTAMS

3.1 Antimicrobial Agents

The first classes of monocyclic β-lactam antibacterial agents were isolated from natural sources in the late 1970s and early 1980s. The discovery of the nocardicins and monobactams demonstrated for the first time that a conformationally constrained bicyclic structure was not necessary for antibacterial activity of β-lactams [38-41]. These reports led to investigations on monocyclic lactams having various types of anionic heterosubstituents on the nitrogen center [42]. These synthetic analogues had a broad spectrum of activity against aerobic Gram-(-) bacteria but little or no activity against Gram-(+) bacteria such as *S. aureus*. Aztreonam is the first monobactam to have clinical applications. .

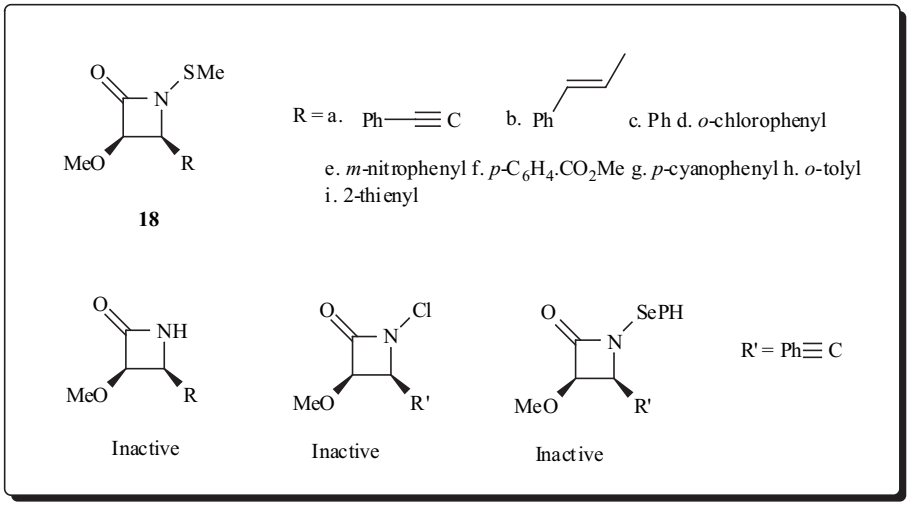


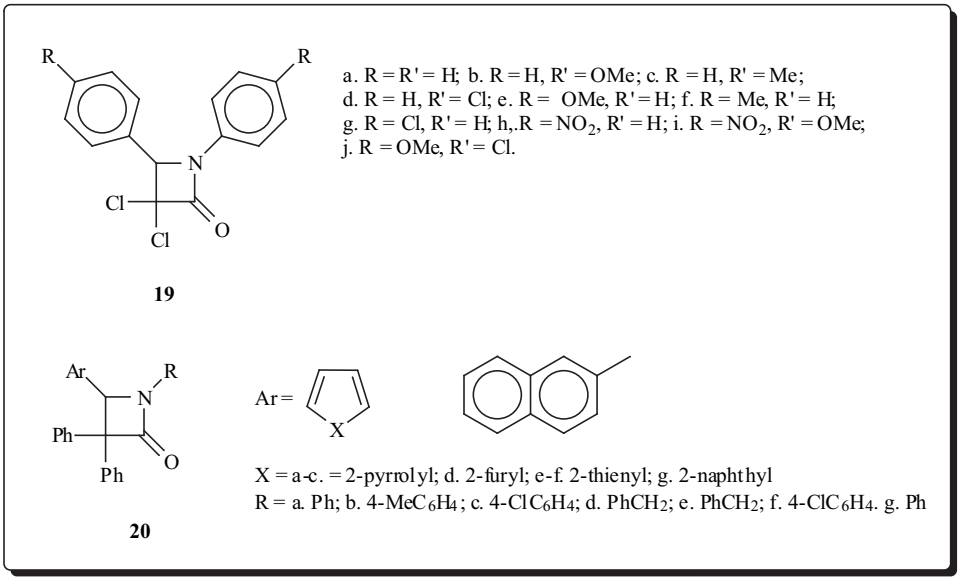
Miller and coworkers compared the antibacterial activity of the oxamazins, having a N-O linkage, to their sulfur analogue, thiamazins [43,44]. While the oxamazins were strongly antimicrobial, the thiamazins lacked antibacterial activity, probably due to the longer N-S bond compared to the N-O bond of the oxamazins, which prevented a proper fit of the thiamazin lactam within the active site of the transpeptidase enzyme.



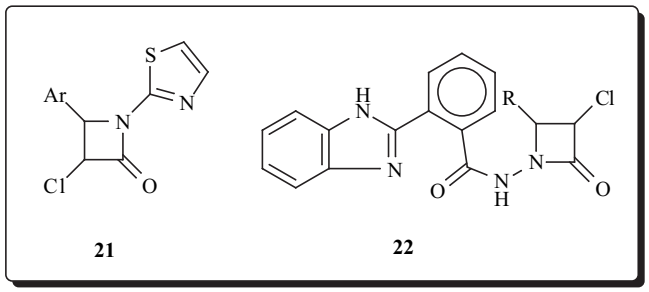
Contrary to the observations of Miller's laboratory, Turos and coworkers have reported several *N*-thiolated β-lactams **18** with potent antibacterial activity against *Staphylococcus* and *Micrococcus* bacteria [45,46]. However, these compounds have weak activity against *N. gonorhoeae, B. fragalis, and H. influenzae*. Also, they showed no activity *against K. pneumoniae, L. monocytogenes, V. cholorae, S. pyrogenes, S. agalactiae, S. marcessens, S. typhimurium, P. aeruginosa, P. mirabilis, M. smegmatis, E. cloacae or E. coli*. Thus, these lactams exhibited a narrow spectrum of antibacterial activity with high selectivity for *Staphylococcus* species. The most active analogue is **18d** (MIC = 15 μg/mL for *S. aureus* and 5-10 μg/mL for MRSA strains). From the study of structure – activity relationship of a number of *N*-thiolated- and *N*-unsubstituted lactams with different groups on C-4, they have shown that the presence of N-S linkage is necessary for the antibacterial activity. These β-lactams are atypical in the sense that they are lipophilic and devoid of the typical acidic ring required for recognition by the penicillin binding proteins. It indicates that the mechanism of action for these lactams is different from all previous classes of β-lactams.

Guner and coworkers have synthesized a series of ten *N*-aryl substituted 3,3-dichloro-4-aryl-2-azetidinones **19** by the Staudinger reaction [25] and evaluated them for antibacterial and antifungal activity [47]. The MIC of these compounds for *E. coli* is 250 μg/mL while for *S. aureus* and *B. subtilis* it is more than 250 μg/mL. The activity is particularly interesting against *P. aeruginosa* (MIC = 125 μg/mL). These compounds have significant activity against fungi *C. albican* and *C. glabrata* (MIC = 125 μg/mL) which is independent of substituents on the aryl ring. Thus, these compounds exhibit better activity against Gram-(-) bacteria than Gram-(+) bacteria. A similar report was published earlier by Naik and coworkers [48]. A series of *N*-aryl substituted 3,3-diphenyl-4-heteroaryl/(2-naphthyl)-2-azetidinones **20** exhibited better activity against fungi and Gram-(-) bacteria *E. coli* (MIC = 10-25 μg/mL) in comparison to activity against Gram-(+) *S. aureus* (MIC = 15-75) μg/mL). Also, all these β-lactams were inactive against *K. pneumoniae*. The most active compound in the series was *N*-phenyl-3,3-diphenyl-4-(2-naphthyl)-2-azetidinone (**20d**) (MIC = 10 μg/mL against *E. coli* and 15 μg/mL against *S. aureus*).





Parikh and coworkers have reported the antibacterial and antifungal activity of the azetidinones **21** bearing a thiazole ring on the nitrogen of azetidinones and differently substituted phenyl rings on C-4 [49]. These compounds have been synthesized by the Staudinger method using suitable imine and chloroketene [25]. *In vitro* antibacterial assay against *B. megaterium*, *B. subtilis* and *E. coli*, and antifungal activity against *A. niger*, carried out using cup-plate agar diffusion method by measuring the zone of inhibition, showed a zone of inhibition in the range of 18-25 mm at 50 μg dose.

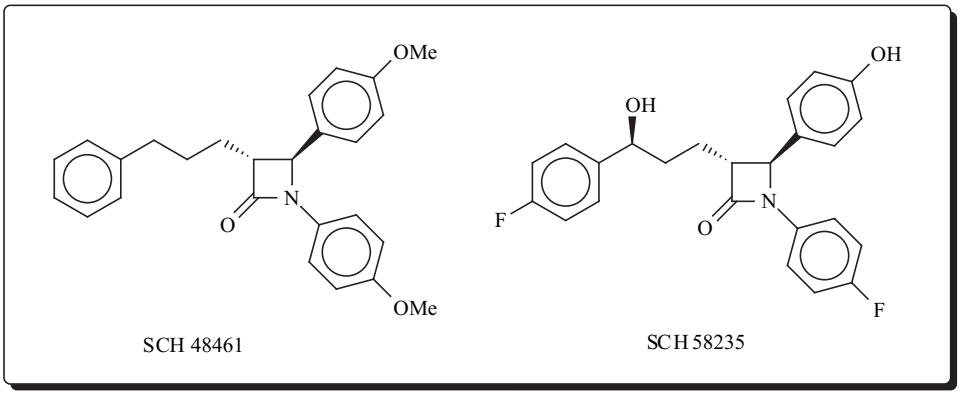


3.2 Antitubercular Compounds

Some of the β-lactams synthesized by Parikh and coworkers have been evaluated for *in vitro* antitubercular activity against *M. tuberculosis* H37Rv strains at TAACF, USA [49,50]. Many compounds with thiazole moiety showed > 50% inhibition in primary screening at a dose level of 12 μg/mL. The compounds **22** with benzimidazolylbenzoylhydrazine moiety on N-1 and R = phenyl/4-chlorophenyl/2,4-dichlorophenyl moieties inhibited 97% of the strain at the same dose level [50].

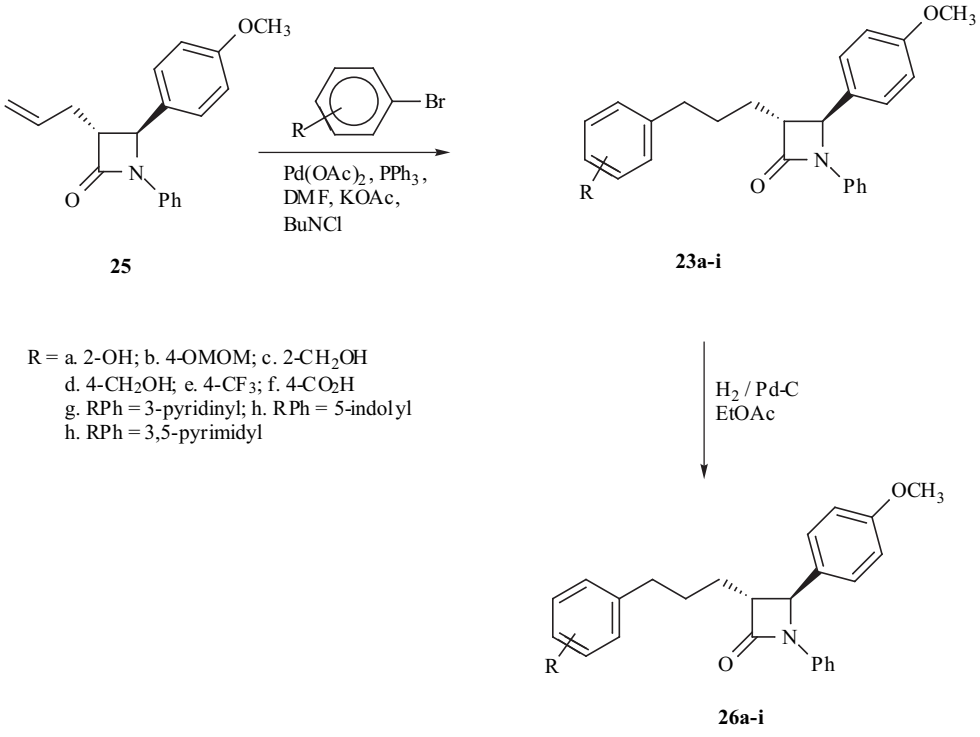
3.3 Cholesterol Absorption Inhibitors

The scientists at Schering-Plough Research Institute at Kenilworth, NJ, are working towards the development of monocyclic β-lactams as cholesterol absorption inhibitors (CAI). In 1994, Miller and coworkers reported SCH 48461, a 3-(3'-phenylpropyl)-2-azetidinone as a potent CAI [51]. Later, Rosenblum and coworkers discovered SCH 58235 as a potent orally active CAI (ED_{50} = 0.04 mg/kg in a 7-day cholesterol-fed hamster model), which is a clinical candidate for the treatment of hypercholesterolemia [52]. This group, in order to study the effect of conformationally restricted C-3 side chains on CAI activity, has reported the synthesis and

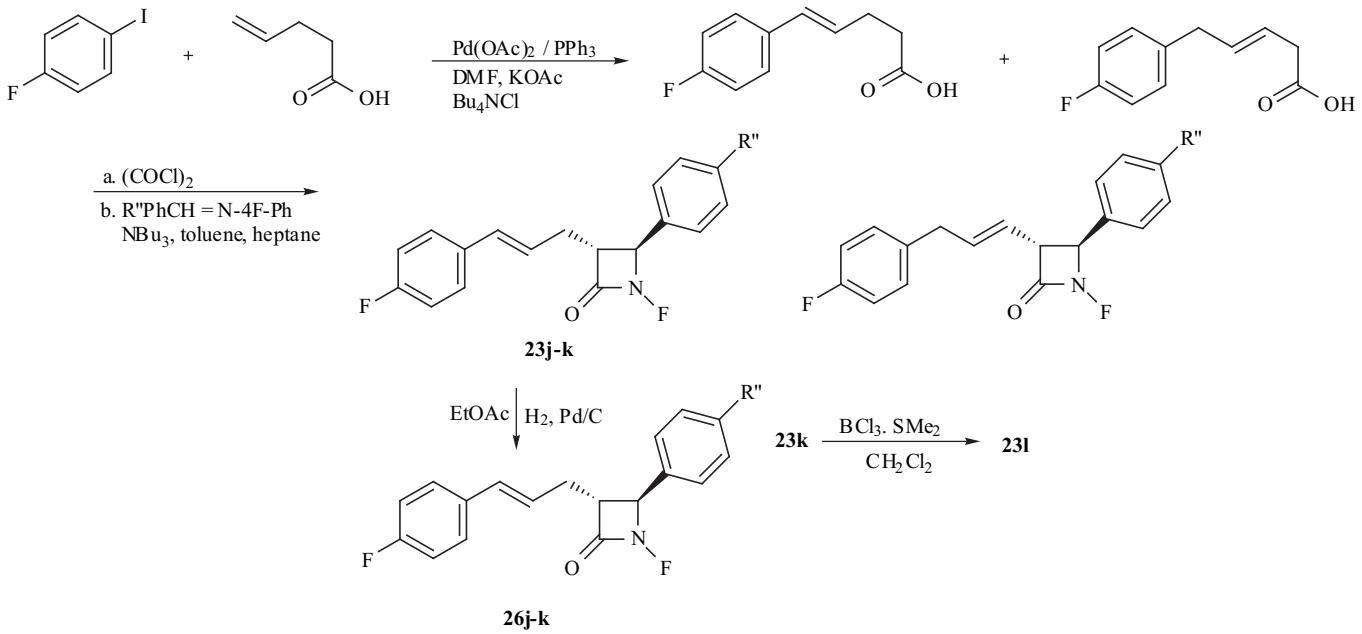


CAI activity of a series of 2-azetidinones **23** with 3-(3'-arylpropenyl) and **24** with 3-(3'-arylpropynyl) substituents [53]. The compounds have been synthesized either by a palladium–catalyzed arylation of suitable azetidinones **25** (**Scheme 12**) or directly by Staudinger reaction (**Scheme 13,14**) [25]. The catalytic hydrogenation of **23** and **24** has led to the formation of their saturated analogues, **26** and **27**, respectively. The CAI study in liver cholesterol esters in a 7-day cholesterol-fed hamster model showed low activity of **25** (<10% reduction of CE @ 10mpK) suggesting the requirement of a carbon spacer with pendant phenyl residue for CAI activity. The CAI activity of the C-3 side chain unsaturated analogue **23** (0 - -95% reduction of CE @ 10mpK) and **24** (0 - -64% reduction of CE @ 10mpK) was similar to their corresponding saturated analogues **26** and **27**. The CAI activity favored small lipophilic substitution on the pendent C-3 aromatic side chain. Based on these studies, authors have suggested that side chain restricted analogs, which explore similar conformation space as **24** will not show significant CAI activity.

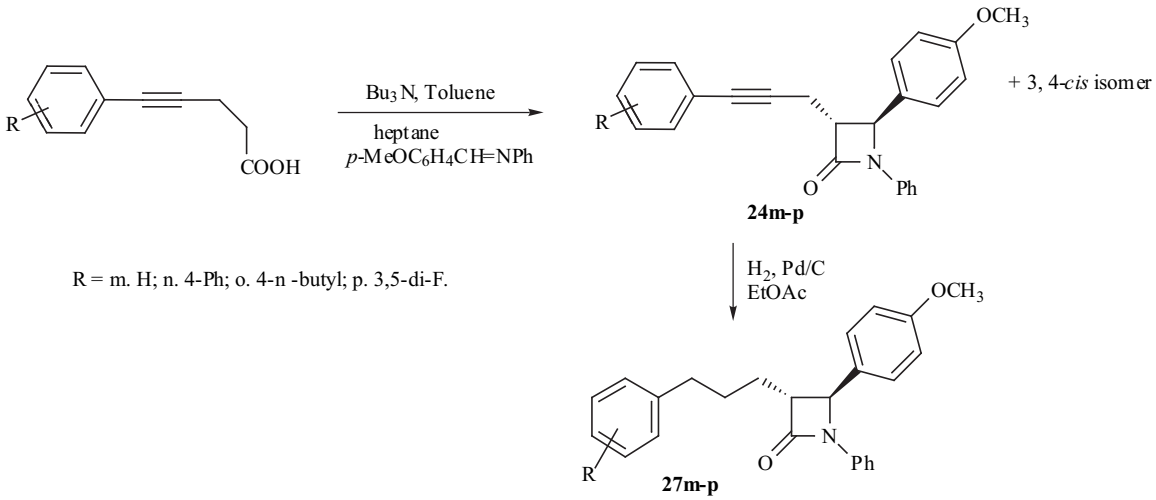
In order to identify the molecular target of these compounds and understand the precise mechanism of their action, Burnett and coworkers have designated a cholesterol absorption inhibition binding protein (CAIBP) and prepared a number of biochemical tools which include high affinity radioactive or fluorescent analogues for binding/affinity applications, cross linking reagents, photo-affinity labeling experiments, and biotinylated derivatives for affinity chromatography applications. In continuation of these studies, they have reported the synthesis and CAI activity of iodinated analogues **28**, **29**, **31**, **31a** and **32** of Sch 48461 and Sch 58235 [54]. Schemes **15-17** show the synthesis of compounds **28**, **31** and **31a,** and **32**, respectively, whereas analogue **29** was synthesized by the Staudinger method [25]. *In vivo* CAI activity in a cholesterol-fed hamster model is shown in **Table 1**. It is evident from the data in **Table 1** that the compounds **31** and **32** are the most active in the series. The *N*-iodophenyl analogue **31** is slightly more potent than the pendant iodophenyl analogue **31a**.



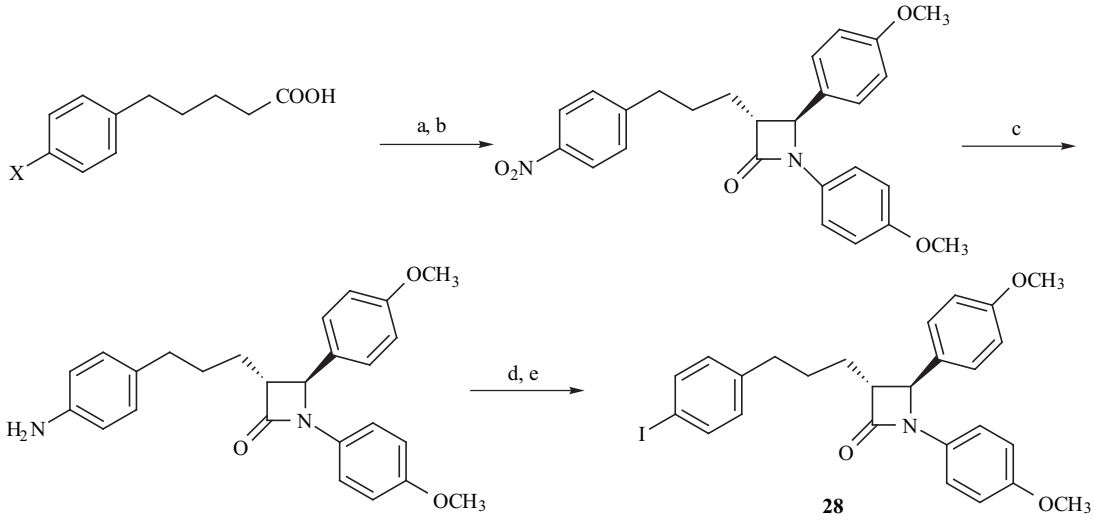
Scheme 12.



Scheme 13.

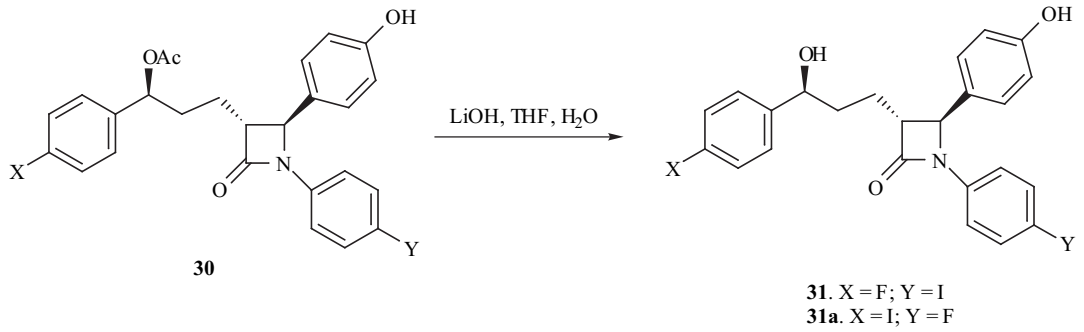


Scheme 14.



Reagents and conditions: a. HNO_3, H_2SO_4, -10°C; b. i) $(COCl)_2$ ii) ArCH=NAr, Bu_3N, tol, reflux; c. H_2, Pd/C; d. AcOH, $NaNO_2$, H_2O e. K1

Scheme 15.



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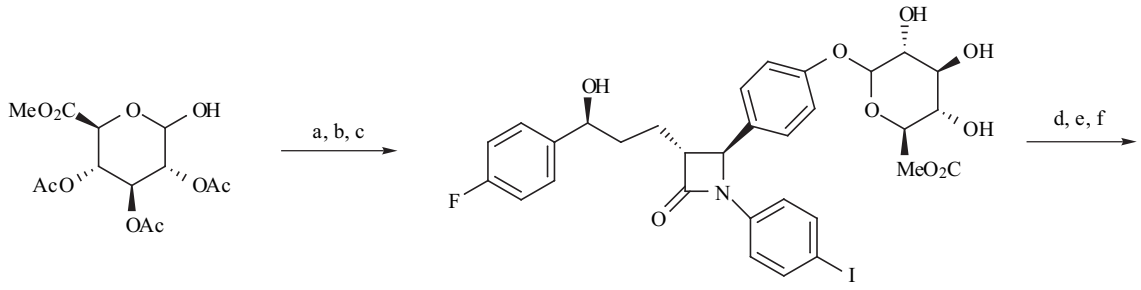
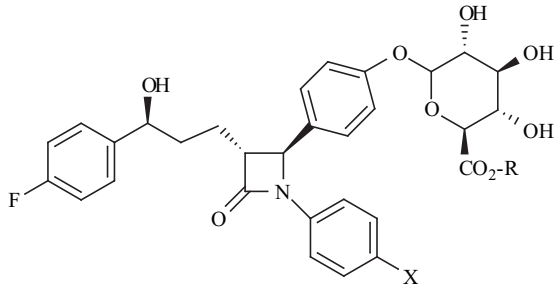
31. X = F; Y = I
31a. X = I; Y = F

Scheme 16.



a. Cs_2CO_3, Cl_3CCN, CH_2Cl_2; b. **28**, BF_3-Et_2O, CH_2Cl_2
c. KCN, MeOH; d. Bu_3SnBu_3, $Pd(Ph_3P)_4$, toluene, reflux
e. NaI, Iodogen TM, 10: 1 EtOAc / AcOH; f. MeOH, Et_3N,. H_2O 1: 2: 7.



32. X = I; R = H

Scheme 17.

Table 1. CAI Activity of Iodinated Analogues 28-32

Compd.	% Redn of HCE @ dose (mg/kg/day)	ED_{50} (mg/kg/day)
Sch 48461 (-)	-93@10	2.2
Sch 58235 (-)	-100@1	0.04
28	-56@50	na
29	-82@50	na
30	-54@1	na
31	-63@1	0.49
32	-54@1	na

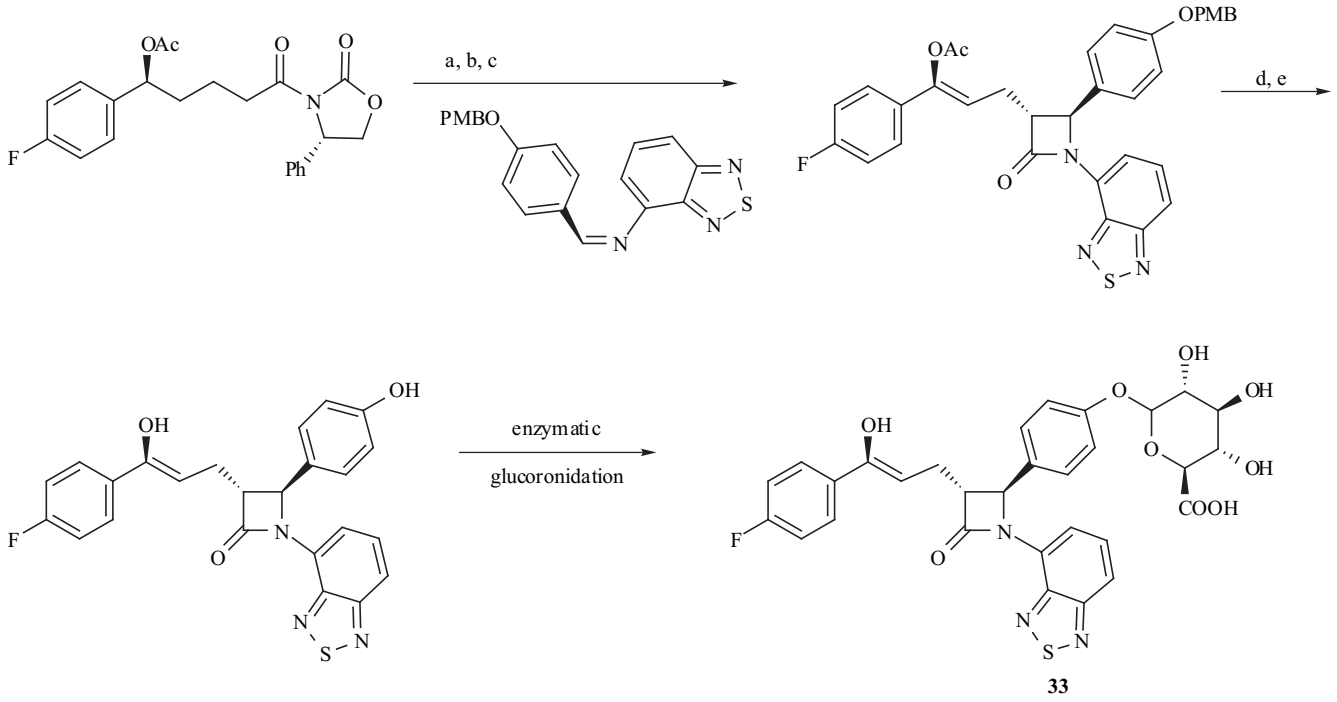
In another communication, they have reported the synthesis (**Schemes 18,20**) and CAI activity (**Table 2**) of fluorescent analogues **33-35** of Sch 58235 at different doses [55]. Scheme **19** shows the synthesis of fluorescent alkynes required for the synthesis of **34** and **35**. All of the compounds exhibited potent CAI activity in a rapid cholesterol absorption assay and are suitable for use as a biological tool for the investigation of the mechanism of action of this class of compounds.

Table 2. CAI Activity of Fluorescent Analogues 33-35

Compd.	Dose (mg/kg)	% inhibition of ^{14}C-cholesterol absorption into plasma
33	10	66
33	30	83
33	100	85
34	30	85
34	56	79
34	186	88
35	30	58
35	100	80
35	300	92

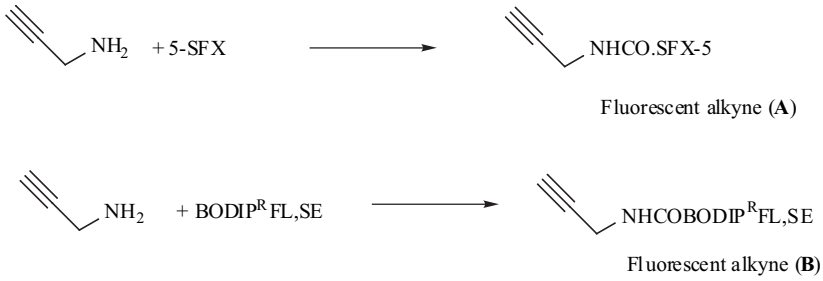
3.4 Enzyme Inhibitors

Bulychev and coworkers have reported the synthesis of *N*-sulfonyloxy β-lactams **36** (**Scheme 21**) as potent β-lactamase inhibitors [56]. The sulfonate moiety serves as a surrogate for the invariant carboxylate β-lactams in

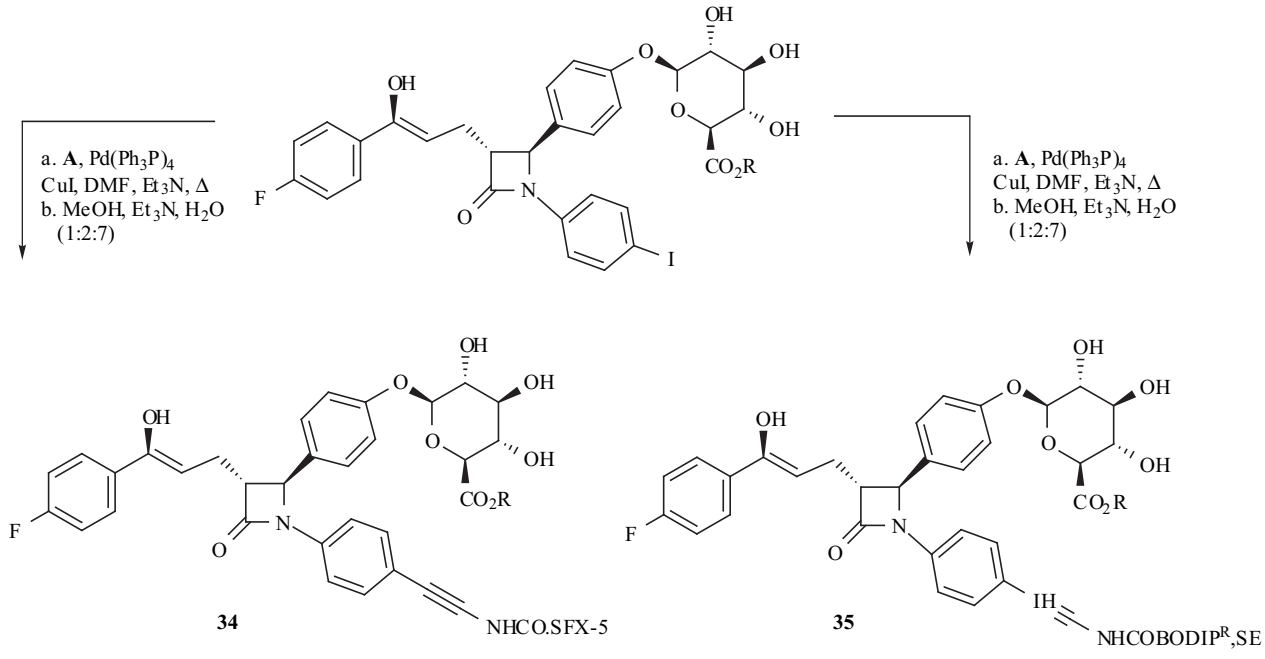


Reagents and conditions: a. imine, $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2; b. BSA, toluene,; c. TBAF (cat); d. MeOH, Et_3N, H_2O; e. BCl_3, CH_2Cl_2

Scheme 18.

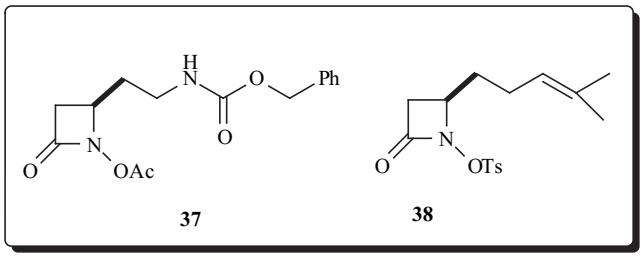


Scheme 19.



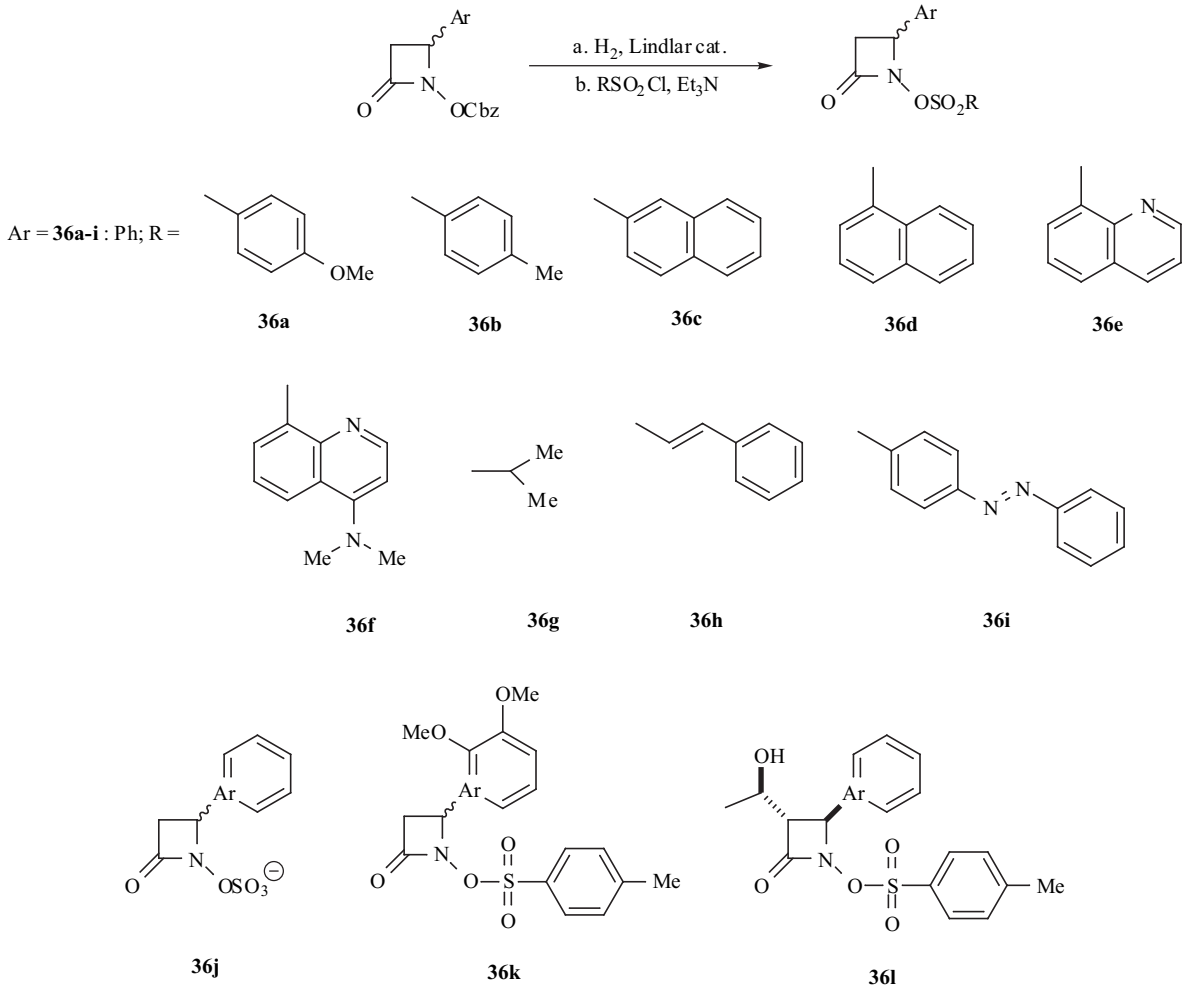
Scheme 20.

recognition by the enzyme [57]. Compounds that lack it, as in *N*-alkoxy or *N*-carbonate derivatives, are recognized by the enzyme either poorly or not at all. The analysis of kinetic data has indicated the strong preference for a hydrophobic moiety at the sulfonate position for inactivation of the class A TEM-1 β-lactamase. Compound **36j** failed to inactivate the enzyme, whereas compound **34c** inactivated the enzyme most favorably (k_{inact}/K_I = 72.5 $M^{-1}s^{-1}X10^{-3}$). The TEM-1 β-lactamase also showed preference for the phenyl ring at C-4. The change of phenyl to methyl at this position reduced the efficiency of inactivation process (lower k_{inact}/K_I, and higher partition ratio) [57]. Compounds **37** and **38,** lacking the phenyl group at position C-4, did not inactivate the enzyme TEM-1 β-lactamase but were able to inhibit the other enzyme Q908R (K_I = 38-52 and 18-36 μM, respectively).



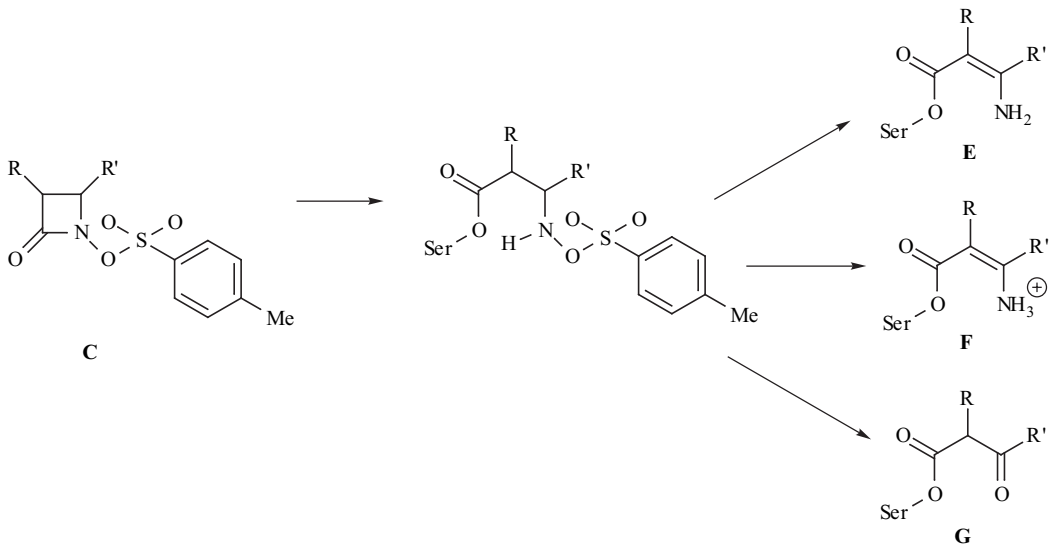
The mechanism of inhibition of a class A β-lactamase by a class of monobactam, exemplified by compound **C**, is shown in **Scheme 22**. The active site serine of the enzyme is acylated by the inhibitor. On acylation of the active site, the tosylate is released from species **D**. The final structure of the inhibited enzymes may differ. Bulychev and coworkers have documented for structures **E-G**.

Ayoma and coworkers have reported the design, synthesis and human chymase inhibitory activity of 3-benzylazetidin-2-ones [58]. Human chymase is a chymotrypsin-like serine protease, which is thought to play an important role in cardiovascular diseases and chronic inflammation following fibrosis, such as cardiac, renal, and pulmonary fibrosis. They deduced from their earlier studies of 1-oxacephems and 1,3-diazetidin-2,4-diones that the 7β-phenyl ring and *N*-benzyl substituent, respectively, present in them were essential for inhibition of human chymase [59]. Accordingly, they envisioned 3-benzylazetidin-2-ones as potential human chymase inhibitors and synthesized compounds **39a-d** starting from D-aspartic acid and **40a,b** starting from L- aspartic acid [58]. Of these six compounds, **39b** was the best from activity and stability point of view (IC_{50} = 0.17 nM and $t_{1/2}$ = 0.9 h). However, its stereoselective preparation was difficult, and so they selected **39a** (IC_{50} = 0.46 nM and $t_{1/2}$ = 1.0 h) for further enhancement of the stability in human plasma by modifying

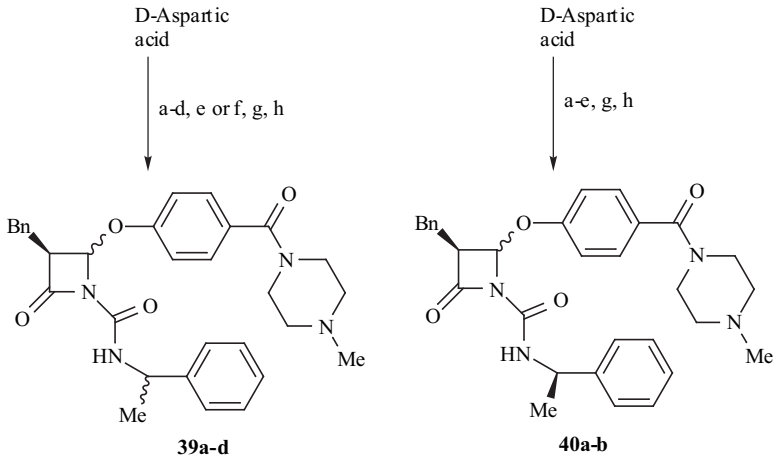


Scheme 21.

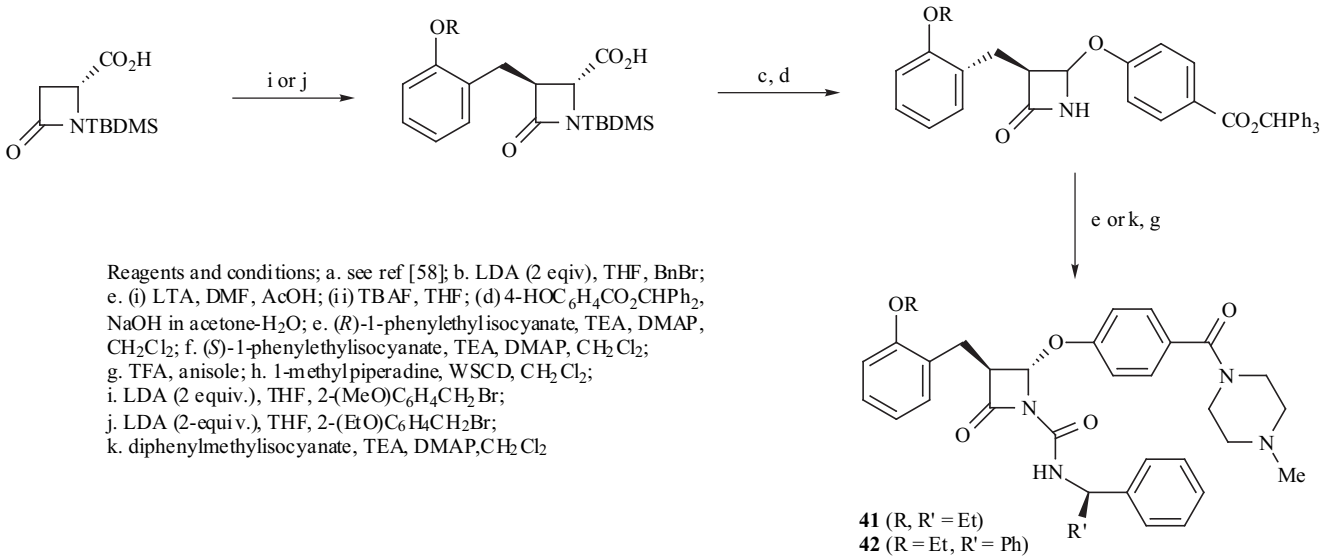
its 1'-, 3- and 4-positions. Compounds **41** and **42**, synthesized as shown in **Scheme 24**, possessed sufficient activity against chymase (IC_{50} = 2.1 and 3.1 nM, respectively) and stability in human plasma ($t_{1/2}$ = 5.0 and 6.0 h, respectively). Steric hindrance at 1- and 3-positions has been proposed to prevent the attack of a variety of nucleophiles in the human plasma on the carbonyl group of β-lactam, thus enhancing the stability of the later in human plasma.



Scheme 22.



Scheme 23.



Reagents and conditions; a. see ref [58]; b. LDA (2 eqiv), THF, BnBr; e. (i) LTA, DMF, AcOH; (ii) TBAF, THF; (d) 4-$HOC_6H_4CO_2CHPh_2$, NaOH in acetone-H_2O; e. (*R*)-1-phenylethylisocyanate, TEA, DMAP, CH_2Cl_2; f. (*S*)-1-phenylethylisocyanate, TEA, DMAP, CH_2Cl_2; g. TFA, anisole; h. 1-methylpiperadine, WSCD, CH_2Cl_2; i. LDA (2 equiv.), THF, 2-$(MeO)C_6H_4CH_2Br$; j. LDA (2-equiv.), THF, 2-$(EtO)C_6H_4CH_2Br$; k. diphenylmethylisocyanate, TEA, DMAP, CH_2Cl_2

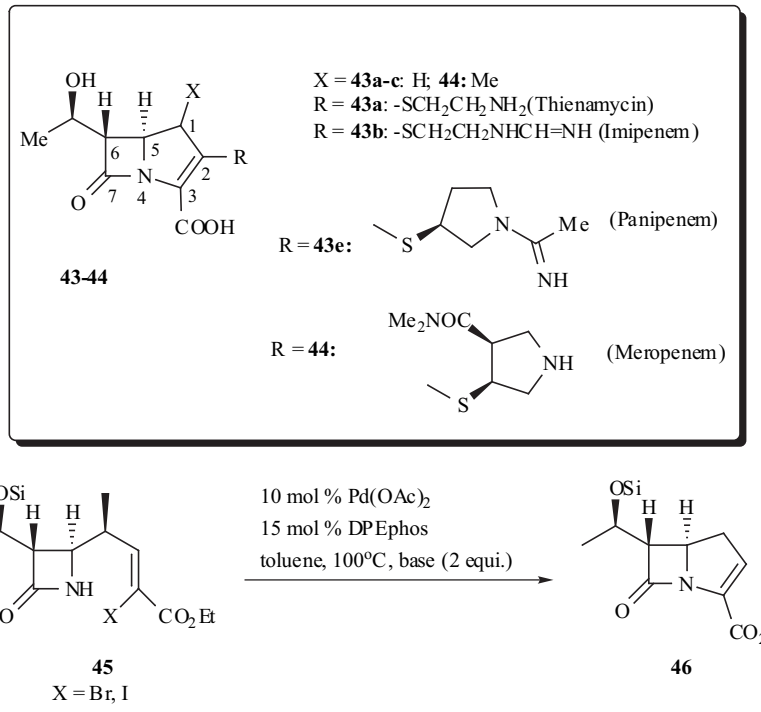
Scheme 24.

4. SYNTHESIS AND BIOLOGICAL ACTIVITY OF CARBAPENEMS

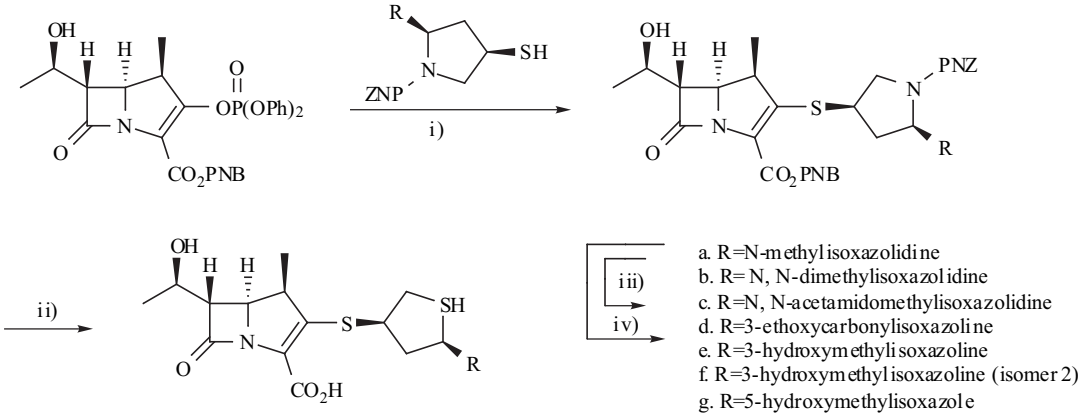
Since the discovery of thienamycin (**43a**), several carbapenem derivatives have been synthesized and evaluated for their antibacterial activity. Currently, two 1-H carbapenems, imipenem (**43b**) and panipenem (**43c**), and one β-methyl carbapenem, meropenem (**44**) are available in the market for clinical use [60-62]. Carbapenems have a broad antimicrobial spectrum and potent bactericidal activity [63]. However, most of them have some limitations from the viewpoint of clinical application. For example, imipenem is unstable to the renal dehydropeptidase-I (DHP-I) and has epileptic side effect. Meropenem has good stability to DHP-I due to steric hindrance of the β-methyl group at C-1 and an excellent spectrum against Gram-(-) bacteria, but it is relatively less active against Gram-(+) bacteria than imipenem. Edward and Betts have described the development of carbapenems from thienamycin to the prodrug, faropenem [64]. They have discussed the scope and limitations of developmental strategies for synthetic design. The design of a molecule with broader spectrum is a challenging task as it requires balancing opposing physical properties like lipophilicity (which in a broader sense favors activity against Gram-(+) organisms) and hydrophilicity (which in a broader sense favors activity against Gram-(-) organisms). Evaluation of meropenem and imipenem against different strains is still going on. For example, Christenson and coworkers studied their effect on *P. aeruginosa,* isolated from cystic fibrosis patients at the Children's Medical Center in Salt Lake City, UT, USA, and found that carbapenems were more effective (92.5 % isolates were susceptible) than cephalosporins like cefepime and ceftazidime (77.6 % strains were susceptible) [65]. Rebuck and coworkers found that imipenem and meropenem were also more active (MIC = 0.0625-0.25 mg/L) than the cephem drug, cefime (MIC = 2.0-8.0 mg/L) against SHV- and TEM-derived extended spectrum β-lactamases [66]. Imipenem has been compared with doxycycline and amikacin against *A. baumannii*, a common cause of nosocomial pneumonia, and found better (MIC = 0.12 mg/L) than them [67]. With regard to neurotoxic effects, Norby has concluded in his study that all carbapenems are not alike [68]. Imipenem and ritipenem have been observed as ten times more toxic than benzyl penicillin in a rat model. However, meropenem has proven to be less neurotoxic in animal studies and seems to be associated with fewer risks of seizures in patients. Furthermore, meropenem, in contrast to imipenem, can be used for the treatment of bacterial meningitis.

Mori and Kozawa are actively engaged in developing new methods for construction of the carbapenem skeleton [69,70]. A new method involving palladium – catalyzed C-N bond forming reaction (**Scheme 25**) in azetidinone **45** leading to the synthesis of carbapenem **46** with a carboxylic group on C-3 of the five–membered ring has been reported by them [71].

The studies on carbapenems from a pharmaceutical point of view in the previous decade have been devoted mainly to the synthesis and evaluation of 1β-methylcarbapenem derivatives as antibacterials. Kang, Kim, Shin and coworkers have reported a series of works on synthesis, antibacterial activity and stability to porcine renal DHP-I of 1β-methylcarbapenems [72-74]. Kang and coworkers synthesized **47a-g** containing 5'-isoxazolopyrrolidin-3'-ylthio derivatives as C-2 side chain (**Scheme 26**) [72]. Most compounds exhibited potent antibacterial activities against a wide range of Gram-(+) and Gram-(-) bacteria and high stability to DHP-I comparable to that of meropenem. Isoxazoline derivative **47e** exhibited the most potent antibacterial activity (MIC = 0.013 - 0.391μg/mL) and



Scheme 25.



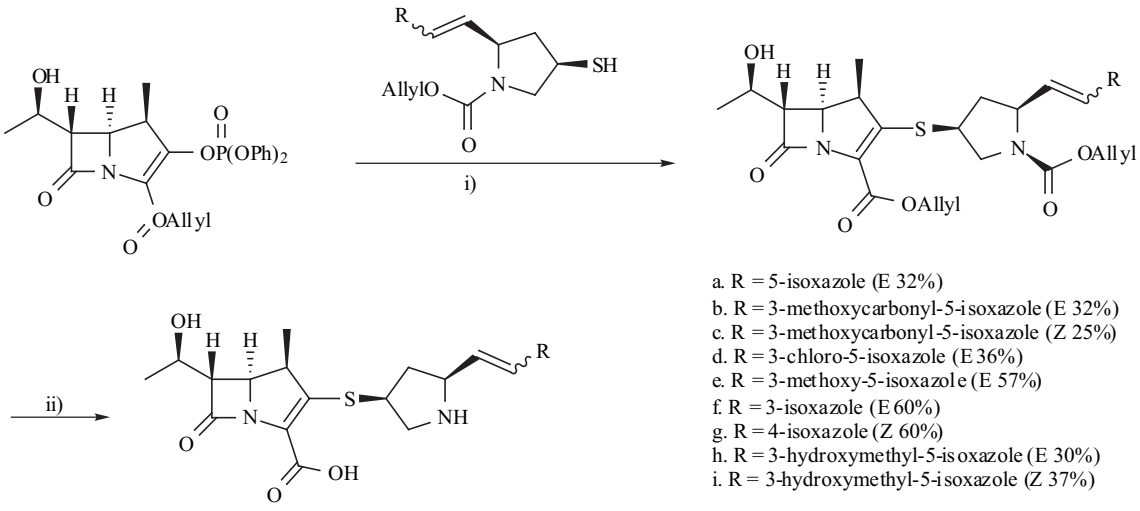
47a-g

Reagents and conditions: i) DIPEA, CH_3CN, r.t.., 1 h; ii) Zn, phosphate buffer (pH 6.0), THF, r. t. Dianion HP-iii) iodomethane, acetone, r. t. iv) iodoacetamide, acetone, r. t.

Scheme 26.

quaternized isoxazolidine **47c** possessed the best stability to DHP-I (0.78). Although there was no significant difference among the antibacterial activities of isoxazolidines **47a-c**, isoxazolines **47d-f** and isoxazole **47g** series, **47d-f** showed slightly better activity against Gram-(-) bacteria except *P. aeruginosa* isolates. Isoxazolines **47a-c** showed slightly better anti-pseudomonal activities than those of **47d-g**.

In view of the literature report that increasing C-2 side chain lipophilicity enhances anti-MRSA activity, Kim and coworkers extended the study of Kang's group by incorporating the ethenyl group in a new series of compounds **48a-i** as a hydrophobic spacer between pyrrolidine and isoxazole moiety (**Scheme-27**) [73]. Introduction of the ethenyl group significantly improved potency and DHP-I stability. All carbapenems were more stable to DHP-I than reference compounds, meropenem and imipenem. The *E*-isomers, **48b** and **48h** were having greater stability (2.68, 2.01) to DHP-I than the *Z*-isomer **48c** and **48i** (1.35, 1.59), respectively. Further, all the compounds except **48e-g** (MIC = 0.781-25.0 μg/mL) and **48i** (MIC = 3.125 μg/mL) showed comparable or superior activity (0.004-0.195) to those of reference compounds (MIC of imipenem = 0.007-1.563 μg/mL and of meropenem 0.013-0.195 μg/mL) against both Gram-(+) and Gram-(-) bacteria. Focusing on Gram-(-) bacteria including *P. aeruginosa*, **48a-c** (MIC = 0.098-0.195μg/mL) and **48h** (MIC = 0.098-0.195 μg/mL) were better than imipenem (MIC = 0.195-1.563μg/mL) and equivalent to meropenem. In general, 5-isoxazoles **48a-e**, **48h** and **48i** possessed higher *in vitro* potency than 3- and 4-isoxazoles **48g,h**. Among the 5-isoxazoles, **48a**, **48b** and **48h** showed the most potent and well balanced activity, but **48e**, having a methoxy group, displayed lower activity, especially against *P. aeruginosa*. As for configuration of the ethenyl group at C-5 position of the pyrrolidine ring, geometrical isomers **48b** and **48c** were almost equivalent against all tested strains, while *E*-isomer,



48a-i

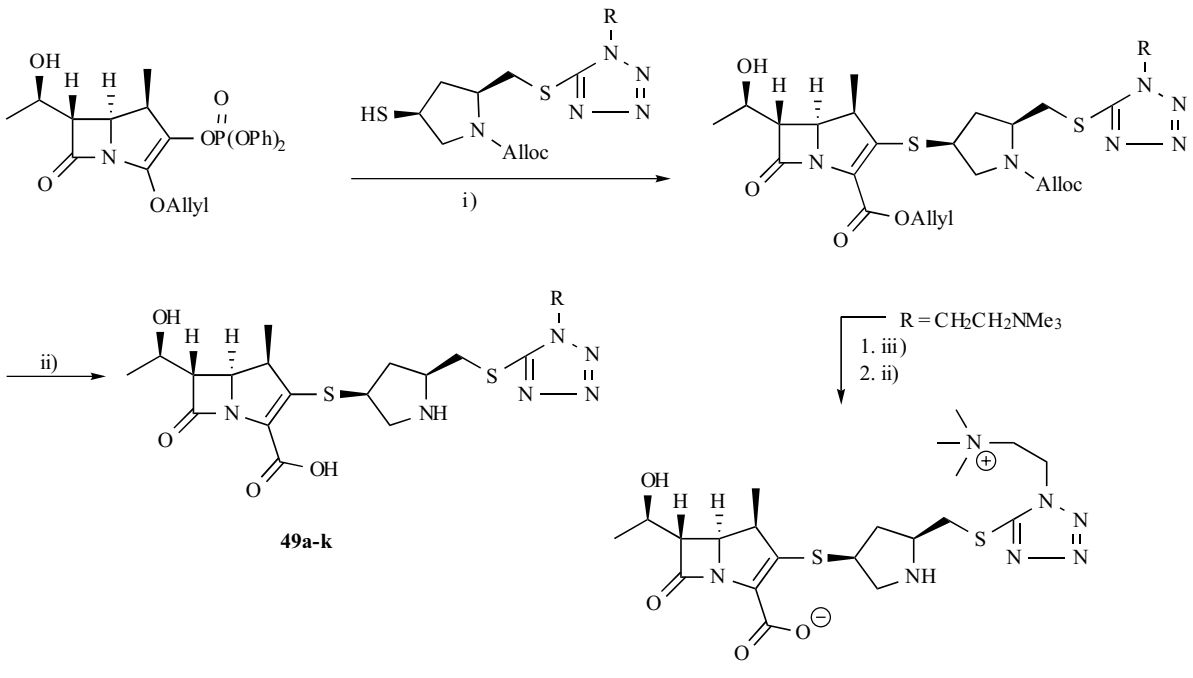
Reagents and conditions: i)*i*-Pr_2NEt, CH_3CN, 0°C; ii) Bu_3SnH, cat. $Pd(PPh_3)_4$, 0°C to rt. 2h.

Scheme 27.

48h possessed several fold better activity than *Z*-isomer, **48i** against Gram-(-) bacteria.

Shin and coworkers incorporated a tetrazolothioether moiety into the C-5 position of the pyrrolidine ring and synthesized **49a-l** (**Scheme 28**) [74]. They envisioned a carbapenem bearing a thioether nucleus as a lipophilic site and tetrazole heterocyclic substituent as a basic part with balanced activity against both Gram-(+) and Gram-(-) strains. Most compounds except for **49a** and **49b** exhibited well-balanced antibacterial activity and good stability to DHP-I. All compounds showed 2-4 fold superior activity against Gram-(+) bacteria. The compound **49c** showed the best antibacterial activity against both Gram-(+) and Gram-(-) bacteria (MIC = 0.004-0.7810 μg/mL). Its half-life (11.02 min) was 3-fold longer than that of imipenem (3.46 min) and meropenem (3.99 min). And, **49c** also displayed approximately three times higher value in AUC and three times lower value in clearance than imipenem and meropenem. Quaternized compound **49l** showed a pronounced activity against *Pseudomonas* and enhanced stability to DHP-I, whereas it had a reduction in activity against Gram-(+) and Gram-(-) bacteria compared to the parent compound **49k**.

Imamura and coworkers at the Banyu Tsukuba Research Institute at Ibaraki, Japan, are involved in exploring the potentials of 1β-methylcarbapenems having pyrrolidinylthio side chains at C-2 position for use against methicillin-resistant strains [75-83]. They established from their structure-activity relationship studies in the late nineties that introduction of an additional basic function onto the pyrrolidine ring was important for enhancing anti-pseudomonal activity and reported the development of the potent carbapenem BO-2727 which exhibited a broad-spectrum activity with good efficacy against *P. aeruginosa* and significant activity but insufficient efficacy against MRSA [84]. On the other hand, they reported a dithiocarbamate, BO-3482, possessing potent anti-MRSA activity, and demonstrated that increased lipophilicity of the C-2 side chain was responsible for enhancement of the anti-MRSA activity [85]. Based on these observations, they have designed and synthesized several 1β-methylcarbapenems with pyrrolidinylthio side chains possessing well-balanced hydrophobicity and basicity [75-83]. A phenyl ring was introduced as a hydrophobic site between the pyrrolidine ring and an aminoalkyl substituent, a basic site [75,76]. Among the compounds with or without several kinds of spacers between the pyrrolidine ring and phenyl ring, J-111,347 (**50**), having a 4-(aminomethyl)phenyl group directly attached to C-5 of the pyrrolidine ring, was found to have excellent activity against MRSA (MIC = 0.006 μg/mL against *S. aureus* 209P NIHJ JC1) and *P. aeruginosa* (MIC = 0.039 μg/mL against *P. aeruginosa* AK 109). However, it showed epileptogenicity in the rat head essay (200 μg/rat-head). With regard to the structure, this compound had an unusual *trans*-(3*S*,5*R*)-stereochemistry while most of the known carbapenems, such as meropenem, BO-2727 and S-4661, had a *cis*-5-substituted-3-pyrrolidinylthio side chain. In order to improve the safety profiles of **50**, they modified its aminomethyl moiety by introducing various types of substituents onto the nitrogen of the primary amino function and on the benzilic carbon adjacent to the amino function and discovered three derivatives, J-111,225 with methylated amino nitrogen (**51** MIC = 0.006 or less μg/mL against *S. aureus* 209P NIHJ JC1 and 0.39 μg/mL against *p. aeruginosa* AK 109), J-114,870 (**52**, MIC = 0.006 or less

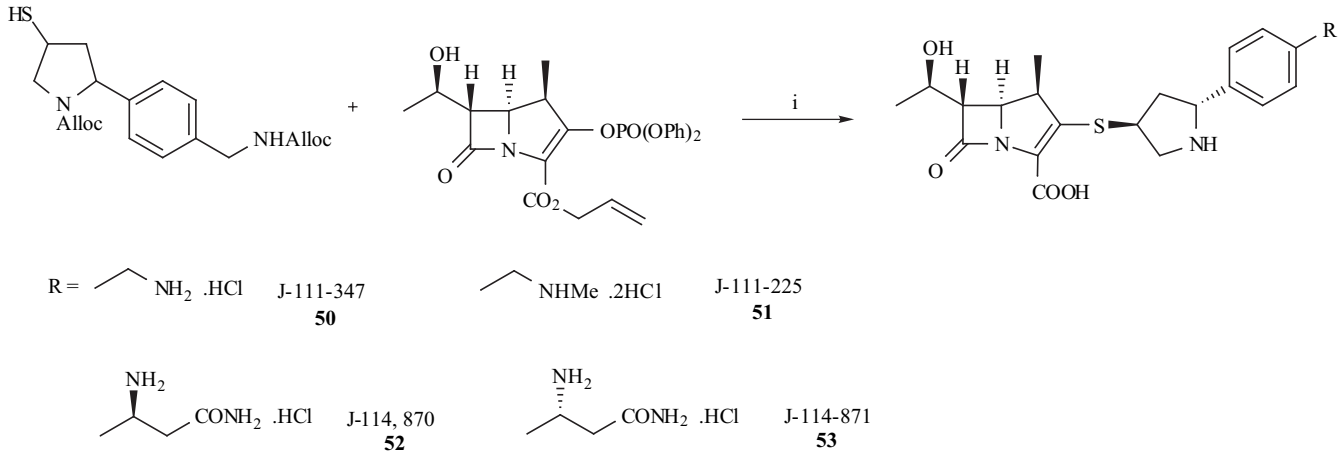


Reagents and conditions: i) *i*-Pr_2NEt, CH_3CN, 0°C, 5h, 45-60%
ii) *n*-Bu_3SnH, cat. $Pd(PPh_3)_4$, CH_2Cl_2, 0°C, 1h, 26-49%; (iii) MeI, acetone, rt, 24h, quant.

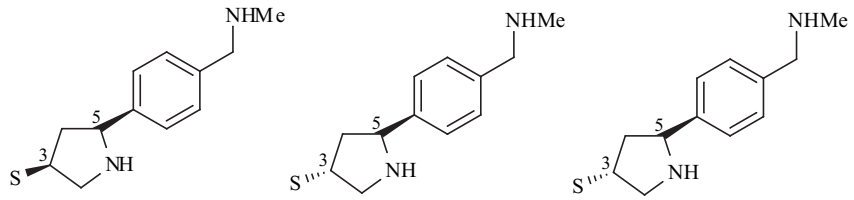
Scheme 28.

μg/mL against *S. aureus* 209P NIHJ JC1 and 0.78 μg/mL against *P. aeruginosa* AK 109), and J-114-871 (**53**, MIC = 0.006 or less μg/mL against *S. aureus* 209P NIHJ JC1 and 1.56 μg/mL against *P. aeruginosa* AK 109), with a carbamoylmethyl group on α-position of the amino function, having good safety profiles and ultra-broad-spectrum, and not much less antibacterial activity covering MRSA and *P. aeruginosa* [75-78]. The compound J-111,225 (**51**) was synthesized by the method reported for the synthesis of J-111,347 (**50**) [72]. An improved method for the synthesis of **51** employing an unprotected C-2 side chain thiol, 4-mercapto-2-[4-(N-methylaminomethyl)phenyl] pyrrolidine is also reported by this group [80]. They have also published a stereoselective synthesis of J-114,870 (**52**) [81]. In order to investigate the influence of C-3 and C-5 stereochemistry of the side chain on biological activity they synthesized J-111,225 (**51**) and its diastereomers (**51a-c**) (**Scheme 29**) and evaluated them for *in vitro* antimicrobial activities against *S. aureus* (including a MRSA strain, pMS520.Smith, a MR-*S. epidermidis* strain MB 5181)), *E. coli* and *P. aeruginosa* as well as their epileptogenicity using imipenem and vancomycin as reference drugs [79]. As for the C-3 configuration, the (3*S*)-isomers, **51** and **51a** were significantly more active (MIC = 0.006 μg/mL against *S. aureus* 209P NIHJJC and 1.0-12.5 μg/mL against *P.aeruginosa* AKR17) than the corresponding (3*R*)-isomers, **51b** and **51c** (MIC = 0.006 μg/mL against *S. aureus* 209P NIHJ JC1 and >25 μg/mL against *P.aeruginosa* AKR17). The reference compounds imipenem and vancomycin had an MIC of 3.13 μg/mL and >100 μg/mL, respectively against *P.aeruginosa* AKR17. Of the two (3*S*)-isomers, the *trans*-(5*R*)-isomer **51** was 4-fold more active (MIC = 0.78 μg/mL against MRSA and 0.39 μg/mL against *P. aeruginosa*) than the *cis*-(5*S*)-isomer **51a** against MRSA (MIC = 3.13 μg/mL) and *P. aeruginosa* (MIC = 1.56 μg/mL). Furthermore, there was no undesired epileptogenecity after intracerebroventricular injection of the *trans*-(3*S*,5*R*)-isomer **51** at a dose of 200 μg/rat, whereas the *cis*-(3*S*,5*S*)-isomer **51a** produced several adverse effects at the same dose.

1β-Methylcarbapenems bearing a doubly quaternized 1,4-diazabicyclooctane (DABCO) substituted dithiocarbamate moiety at the C-2 side chain **54** and **55** (**Scheme 30, 31**) generally showed potent *in vitro* anti-MRSA activity and high affinity to penicillin-binding protein-2' (PBP) [86]. DABCO moiety was effective in enhancing antibacterial activity against the MRSE strain in the case of the phenyl and 1,2,3,6-tetrahydropyridyl derivatives. *In vivo* studies showed ED_{50} value (6.6 and 1.9 mg/kg, respectively) of these two derivatives very low in comparison to original compounds (>50, 7.5 mg/kg) in a mouse systemic infection model suggesting that the DABCO moiety may play a key role in improving *in vivo* anti-MRSA activity. The compound **55a** with a [4-(carbamoylmethyl-1,4-diazabicyclo-[2,2,2]octanediium-1-yl)methyl-1,2,3,6-tetrahydropyridinyl-thiocarbonylthio] moiety was optimal in the series with an excellent anti-MRSA activity (*in vitro* anti-MRSA MIC = 5.36 μg/mL; *in vivo* anti-MRSA MIC = 1.86 μg/mL), favorable DHP-I susceptibility and a good safety profile.



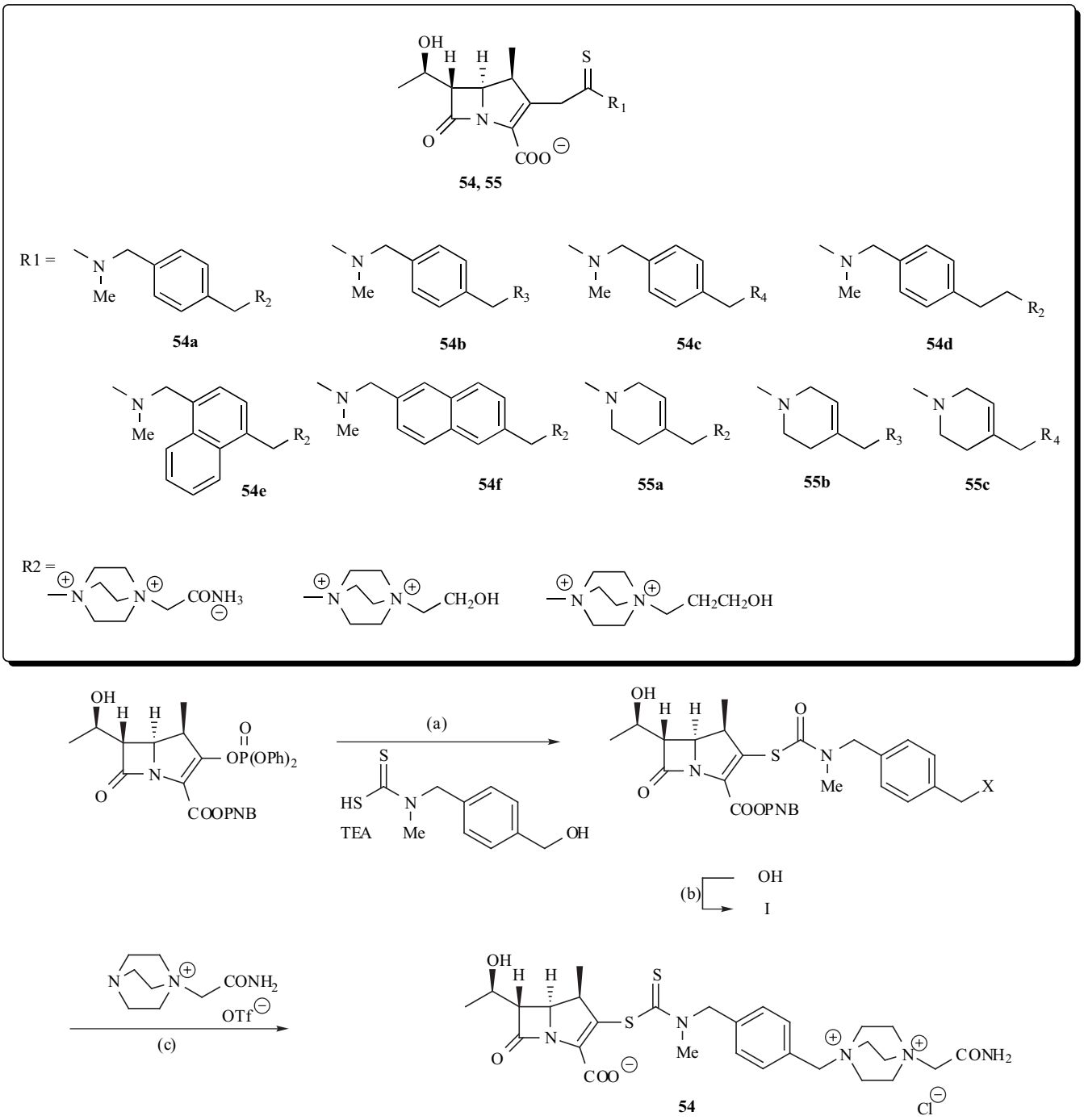
Reagents and conditions: i. a. NaOH, 0°C, b. *i*-Pr_2NEt, MeCN, 0°C, c. $(PPh_3)_2PdCl_2$, *n*-Bu_3SnH, H_2O, CH_2Cl_2.



(3*S*-5*S*) **51a** (3*R*-5*R*) **51b** (3*R*-5*S*) **51c**

Diastereomers of J-111, 225 (**51**)

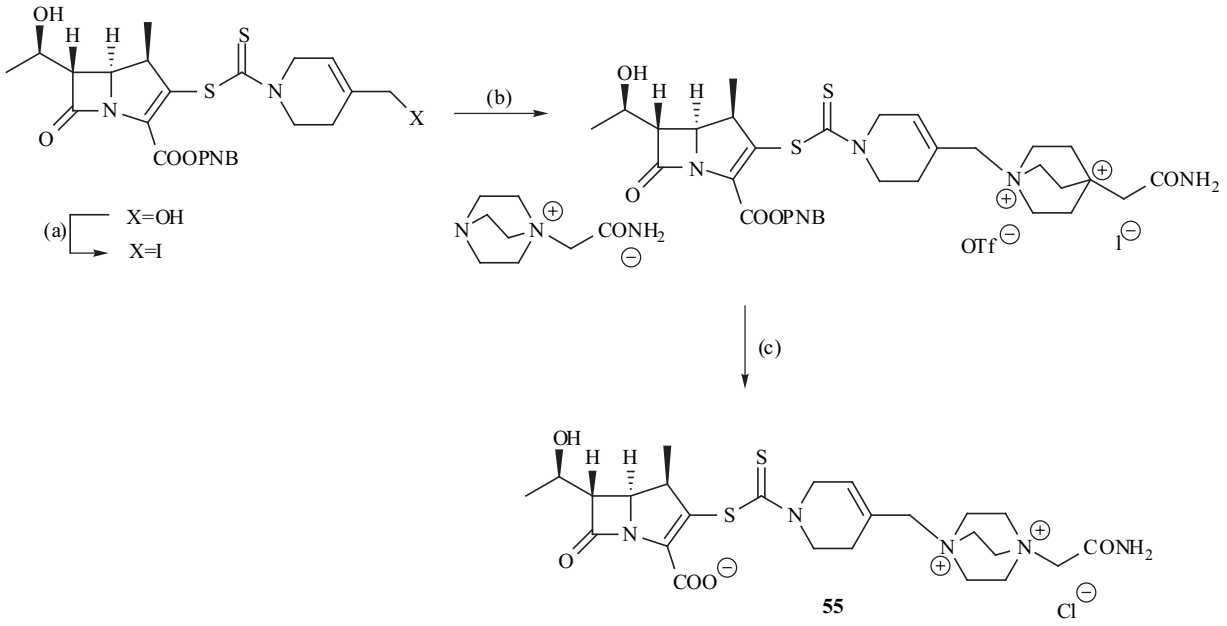
Scheme 29.



Reagents and conditions: (a) (i) *i*-Pr_2NEt, LiCl, THF, rt (b) (i) 1-propanesulfonyl chloride, *i*-Pr_2NEt, THF, 0°C ii) NaI, acetone, 0°C (c) (i) CH_3CN, rt (ii) 10%Pd/C, H_2, THF-H_2O, rt.

Scheme 30.

Nagano and coworkers have reported *in vitro* antibacterial activity of J-111,225 (**51**) against transferable IMP-1 metallo- β-lactamase producers, and its therapeutic efficacy [87,88]. IMP-1 metallo- β-lactamase, which is a class B zinc metallo-enzyme encoded by the transferable *bla*IMP gene, is highly resistant to carbapenems as well as to penicillins and cephalosporins. This compound inhibited seventeen *Serratia marcescens* and two *Pseudomonas aeruginosa* IMP-I producing clinical isolates at a concentration of 32 mg/L (range 4-32 mg/L) and showed synergy with imipenem against IMP-1-producing *S. marcescens*BB5886 and *P. aeruginosa*GN17203 with minimal FIC indices of 0.38 and 0.5, respectively. It was more resistant than imipenem to hydrolysis by class B metallo- β-lactamases. According to their study, the side chain of J-111-225 and the C-5 stereochemistry of the pyrrolidine ring did not appear to contribute to the affinity for the IMP-1 enzyme, while C-3 stereochemistry was important for the inhibitory activity. J-111,225 showed good therapeutic efficacy against methicillin-susceptible *S. aureus*, penicillin-resistant *S.*



Reagents and conditions: (a) (i) 1-propanesulfonyl chloride, *i*-Pr_2NEt, THF, 0°C
ii) NaI, acetone, 0°C (c) (i) CH_3CN, rt (ii) Zn dust, THF, phosphate buffer (pH 6.5) rt.

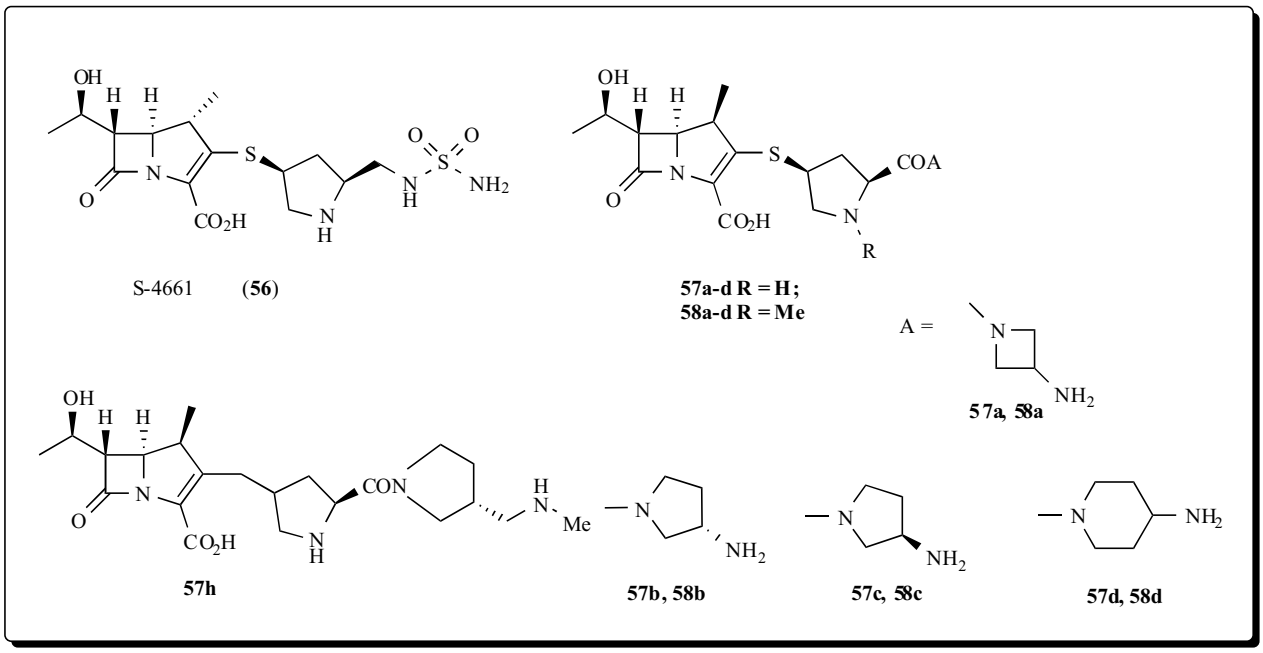
Scheme 31.

pneumoniae, *E. coli*, *K. pneumoniae* and *P. aeruginosa* [88]. In a murine model of systemic infection with MRSA, it showed an ED_{50} value of 5.83 mg/kg, which was comparable to vancomycin (4.84 mg/kg), whereas imipenem failed to cure infected mice (ED_{50} >100 mg/kg). Against a mixed infection caused by MRSA and *P. aeruginosa,* monotherapy with **51** showed an ED_{50} value of 7.23 mg/kg, whereas combined treatment with vancomycin plus imipenem (1:1) had an ED_{50} of 20.86 mg/kg. This result, thus, suggested the suitability of monotherapy with **51** for polymicrobial infections associated with MRSA.

Mikamo and coworkers have reported *in vitro* and *in vivo* antibacterial activity of a 2-(5-substituted pyrrolidin-3-ylthio)-1β-methyl carbapenem, S-4661 (**56**), synthesized earlier by Shionogi, Osaka, Co. Ltd. Japan [89], against *S.agalactiae*, *E. coli*. *P. magnus*, *B. fragilis* and *P. bivia*, which are major pathogens in the fields of obstetrics and gynecology [90]. The MIC_{50} and MIC_{90} of **56** for these strains were 0.25 and 1 mg/L, respectively. An *in vivo* efficacy of **56** was evaluated in a rat model of intrauterine infection, namely pyometra caused by *E. coli* and *B. fragilis*. The accumulation of neutrophils in the uterus in the **56**-treated group was less marked and the number of bacteria significantly lower (*E. coli* 5.67, *B. fragilis* 5.69) than those in the untreated group (*E. coli* 8.00, *B. fragilis* 8.02). Nomura and Nagayama have compared the *in vitro* antibacterial activity of **56** with that of the other carbapenems, i.e., imipenem, meropenem, panipenem and a cephem drug ceftazidime, against 1117 strains of Gram-(+) and Gram-(-) bacteria isolated from the Japanese patients with complicated urinary tract infections [91]. It demonstrated potent and broad-spectrum activity against both Gram-(+)- and Gram-(-) bacteria. These results were in close agreement with the results of Mikamo and coworkers [87].

Kawamoto and coworkers have evaluated the antibacterial and other biological properties of a number of 1β-methyl carbapenems with pyrrolidin-3-ylthio groups substituted with various cyclic amino carbonyl moieties at the C-5 position of the pyrrolidine ring [92]. All of the derivatives with azetidine, pyrrolidine and piperidine showed potent antibacterial activity against a wide range of Gram-(+) and Gram-(-) bacteria. In general, N(H)-carbapenems (**57a-d**) showed greater antipseudomonal activity (MIC = 0.05-0.2 μg/ mL) than N(Me)-carbapenems (**58a-d**) (MIC = 0.4 –1.5 μg/ mL) but the urinary recovery of the former was lower (29.5-65.6 %) than that of the latter (50.4-73.0 %). Although azetidine derivatives **57a** and **58a** had both potent antibacterial activity and excellent urinary recovery, their plasma half-lives were too short to warrant their evaluation for clinical application. The antibacterial activity of four pyrrolidine derivatives (**57b,c** and **58b,c**) was higher than that of piperidine derivatives **57d** and **58d** while their urinary recovery was almost the same. With regard to stereochemistry of the pyrrolidine moiety, compounds **57b** and **58b** containing (*S*)-isomer had slightly better activity than **57c** and **58c** containing (*R*)-isomer. In particular, **57b** had strong antipseudomonal activity (MIC = 0.05 μg/mL) and **58b** had strong antibacterial activity against *S. aureus* 56R (MIC = 0.05 μg/mL), *S. aureus* 535(MRSA) (MIC = 1.5 μg/mL), *E. faecalis* 681 (MIC = 0.2 μg/mL) and *K. pneumoniae* 806 (MIC = 0.01 μg/mL). This group further modified the structure of **57b** and discovered **57h** as the most potent antipseudomonal compound (MIC = 0.05-0.2 μg/mL) with moderate urinary recovery (37.4 %).

2-Alkyl-4-pyrrolydinylthio-β-methylcarbapenems have been explored by Azami and coworkers [93]. They have selected FR21818 as a compound for development. FR21818 exhibited a well balanced spectrum of antibacterial activity, including against *P. aeruginosa* and MRSA,

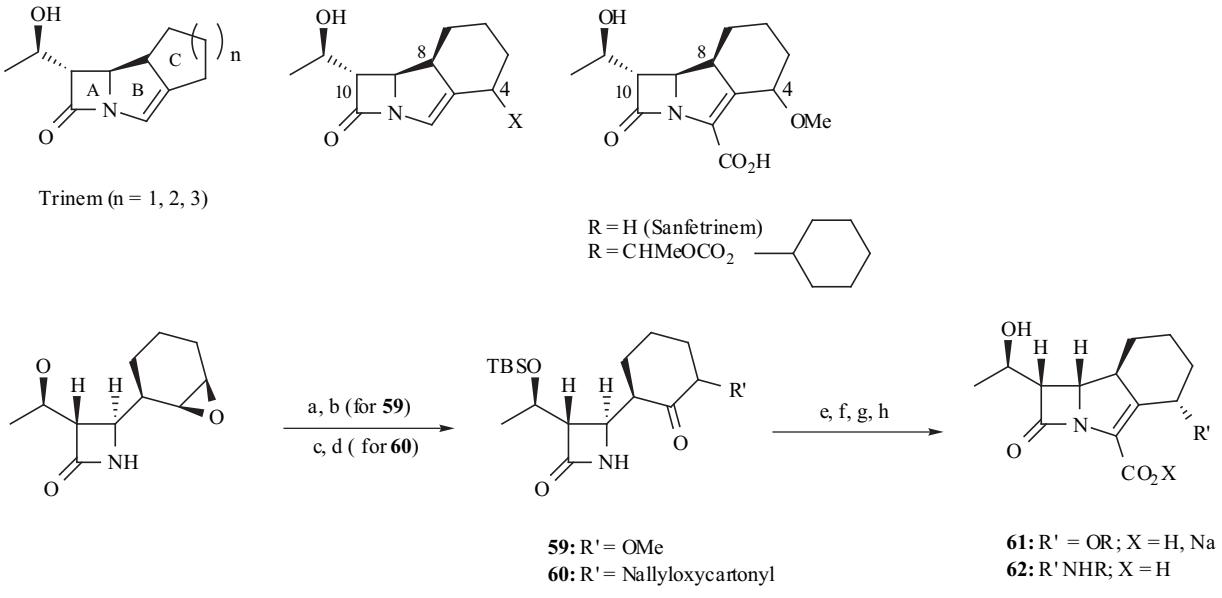


excellent urinary recovery, good stability against renal DHP-I, no antigenicity and mutagenicity, weak toxicity, and good efficacy on mice systemic infection.

Okuda and coworkers have indicated the usefulness of DU-6681a, an oral carbapenem, in cases in which fluoroquinolones are contraindicated [94]. DU-6681 is an active form of oral carbapenem prodrug DZ-2640, synthesized by the Daiichi Pharmaceutical Co., Tokyo, Japan [95]. DZ-2640 administered orally was rapidly absorbed in mice, rats, dogs and monkeys as the active form, DU-6681a [96]. DU-6681 possesses a broad-spectrum and potent *in vitro* antibacterial activity against the majority of Gram-(+) and Gram-(-) bacteria. The activity of DU-6681a against *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* was comparable to or greater than that of R-95867, another oral carbapenem. DU-6681 also showed activity against MRSA and MRSE. The MIC_{90s} of DU-6681a against those strains were four-fold and eight-fold, respectively, lower than those of R-95867.

4.1 Trinems (Fused Tricyclic Carbapenems)

Trinems, formerly known as tribactams, are a class of totally synthetic antibiotics. They have a fused tricyclic



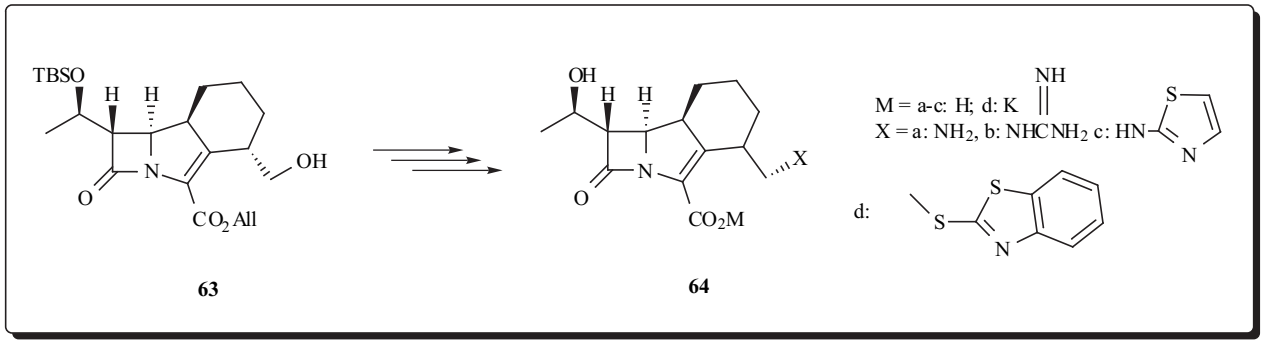
a. ROH, H^+/DCM; b. Swern oxidn.; c. RNH_2. $LiClO_4$/MeCN;
d: AocCl, 2,6-lutidine/DCM; e. Allyl oxalylchloride, Et_3N/DCM; f. $P(OEt)_3$, xylene, reflux;
g. TBAF, AcoOH/THF; h. $Pd(PPh_3)_4$, sodium 2-ethylhexanoate or dimedone/THF.

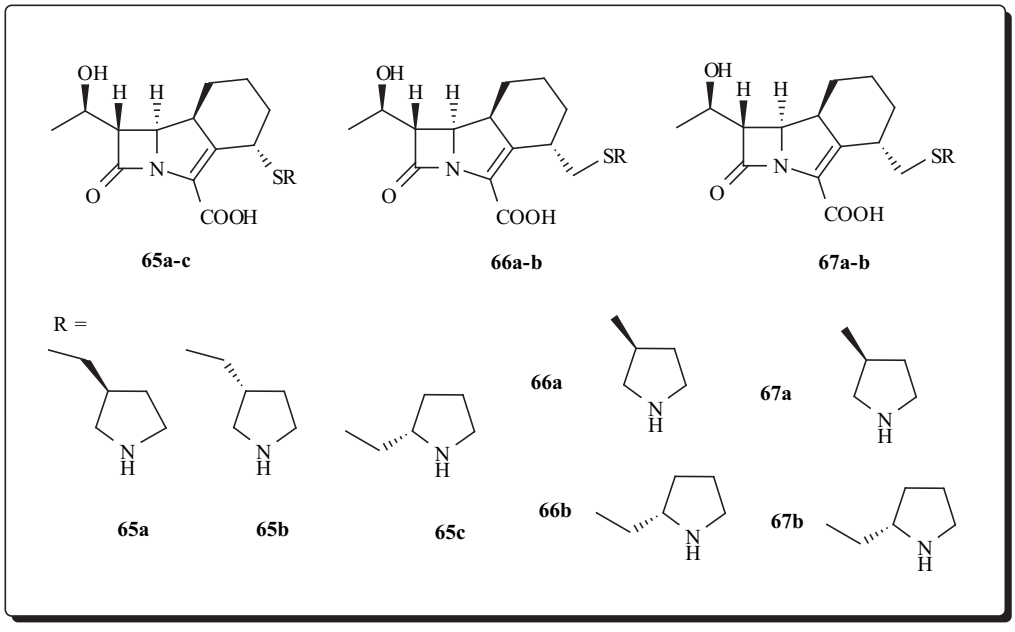
Scheme 32.

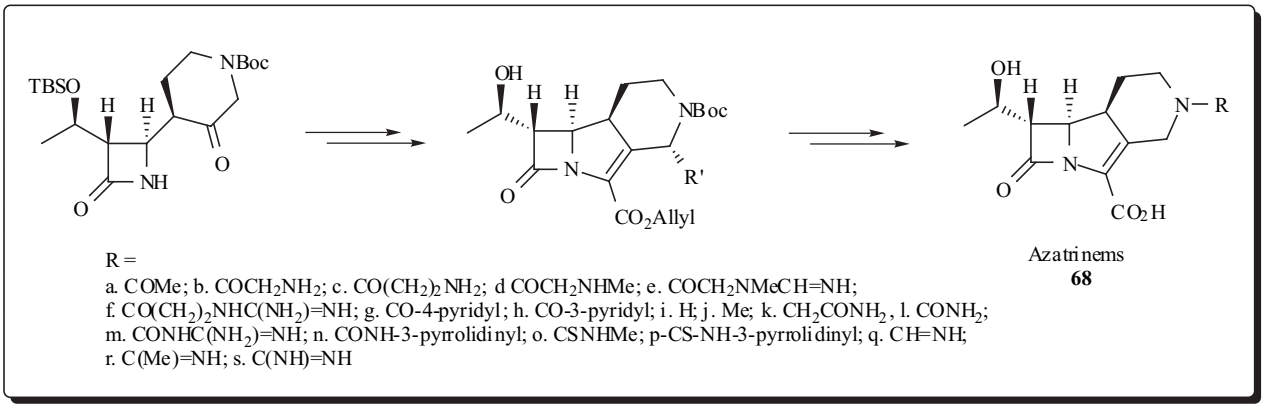
skeleton in which ring C may be 5, 6, or 7-membered and may contain heteroatoms. When ring C is 6-membered as in the structure shown, the C-4 is generally substituted and a hydroxyethyl side chain of defined absolute stereochemistry is present at C-10. Trinems are potent antibacterial agents, with a broad spectrum of activity against both aerobic and anaerobic Gram-(+) and Gram-(-) bacteria, stable to potent β-lactamases and to DHP-I. Sanfetrinem and its biolabile ester cilexetil possessing a fused cyclohexane ring and a 4α-methoxy substituent, reported by the Glaxo Wellcome research group, are promising candidates as the first oral trinems particularly for the treatment of infections caused by penicillin resistant strains [97,98]. Although sanfetrinem can be synthesized using the general method for the trinems synthesis, shown in **Scheme 31**, efforts are going on to simplify its synthesis [99-102]. From the stereochemical viewpoint, (4*S*, 8*S*) configuration of the cyclohexane ring favors a good combination of antimicrobial activity and DHP-I stability in the case of sanfetrinem.

Kanno and coworkers, therefore, opted to study the synthesis and biological study of trinems with similar configuration. They have reported the synthesis of (4*S*)-hydroxymethyltrinem (**63**), a versatile intermediate for the synthesis of such trinems, via stereoselective aldol-type reaction with optically pure (*R*)-2-*t*-butyldimethylsilyl-oxymethylcyclohexanone and converted it into other trinems (**64**) by using the Mitsunobu reaction [103]. The antibacterial activity of these trinems was compared with that of vancomycin. The compounds **64a,b** showed good antibacterial activity against both Gram-(+) and Gram-(-) bacteria (MIC = 0.01-6.2 μg/mL). However, they were less active against *S. aureus* 535, (MRSA) (MIC = **64a**: 25 μg/mL and **64b**: 6.2 μg/mL) and *P. aeruginosa* (MIC = **64a**: 6.2 and **64b**: 50.0 μg/mL). The introduction of an aromatic moiety (**64c,d**) increased the activity against Gram-(+)bacteria including MRSA (MIC = 0.01-3.1 μg/mL). In particular, **64d** showed activity parallel to vancomycin (MIC = 1.56 μg/mL), but **64c** showed therapeutically valuable activity against Gram-(-) bacteria and was selected for further studies.

In another contribution, they have reported the synthesis and antibacterial activity of two types of trinems with pyrrolidinylmethylthio or pyrrolidinylthiomethyl and pyrrolidinylmethylthiomethyl groups at C-4 position [104]. The trinems **65a-c**, **66a,b** and **67a,b** showed potent activity against Gram-(+) bacteria such as *S. aureus 209P*, but weak or moderate activity against Gram-(-)bacteria such as *E. coli NIHJ*, *K. pneumoniae 806* and *S. marcescens 1184*. In spite of having a basic pyrrolidinyl moiety, these trinems rarely showed antipseudomanal activity with the exception of **65a**, which showed very weak activity against *P. aeruginosa 1001*(MIC = 50 μg/mL). (4*R*)-[(*S*)-Pyrrolidin-3-ylthiomethyl]trinem **67a** showed the most potent anti-MRSA activity (MIC = 1.5 μg/mL). Its *in vivo* efficacy



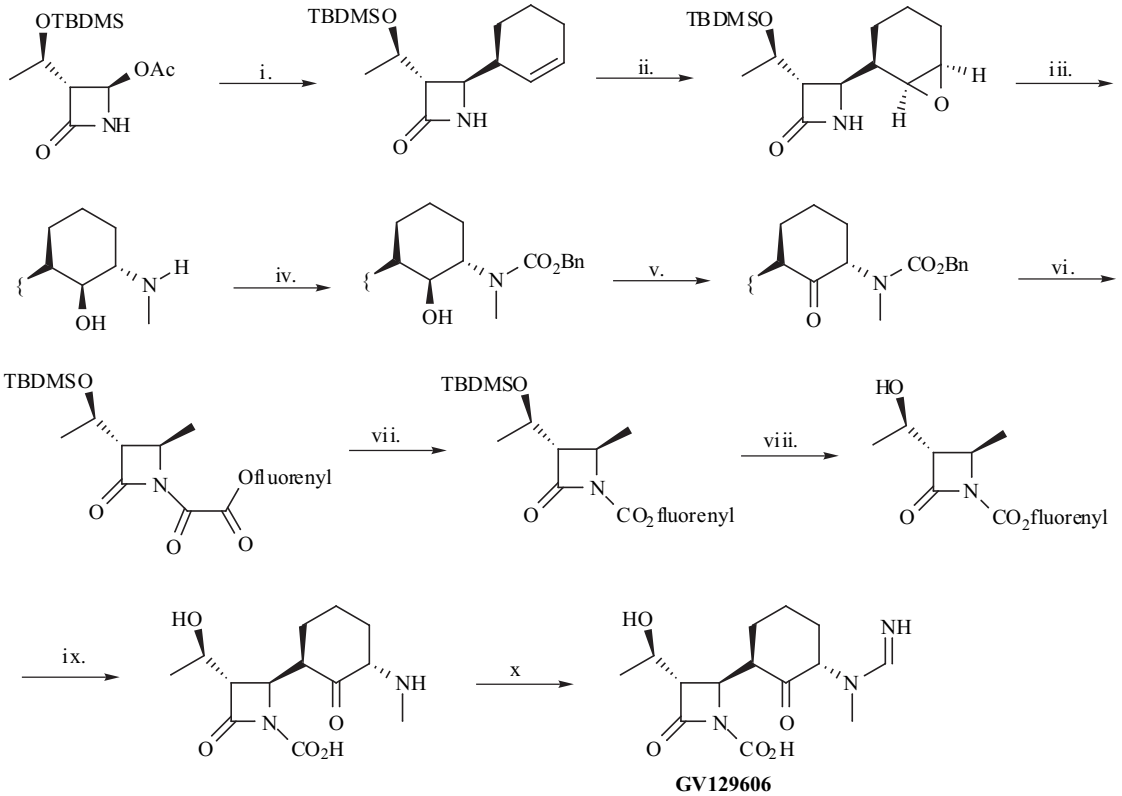




against *S. aureus 507* was comparable to vancomycin and 6-23 times higher than meropenem, panipenem and biapenem.

In the previous decade, synthesis and antibacterial activity of some trinems with an oxa- or thiacyclohaxane ring were reported [105-107]. Mori and coworkers have reported the stereoselctive synthesis and antibacterial activity of trinems with azacyclohexane ring, 5-azatrinems **68** [108]. The amide type compounds **68a-h** had weaker activity than sanfetrinem. In a series of urea and thiourea compounds **68l-p**, the urea **68l** and guanidinocarbonyl derivative **68m** exhibited potent and broad-spectrum activity comparable to sanfetrinem. None of these azatrinems showed any interesting activity against *P. aeruginosa*. The amidine and guanidine derivatives **68q-s** showed good potency against Gram-(+) and Gram-(-) bacteria. In particular, the formamidine **68p** and and guanidine **68s** showed high potency and well-balanced spectrum including activity against *P. aeruginosa*. This antipseudomonal activity supports the hypothesis that a positively charged functional group facilitates the penetration of β-lactam into *Pseudomonas* species [109].

Biondy and coworkers have reported a new, highly diastereoselective synthetic route to a trinem, GV129606 (**Scheme 33**) [110]. The latter which is known to have

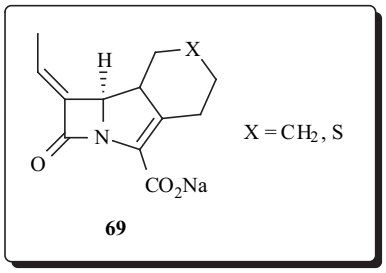


Reagents and conditions: i. B-2-cyclohexanyl-(2-methyleyclohexanyl)$_2$, Et_2Zn, 0°C; ii. Magnesium monoperoxyphthalate, CH_2Cl_2, H_2O, 0°C; iii. $MeNH_2$ (g), $LiClO_4$, MeCN, 60°C; iv. $ClCO_2Bn$, TEA, CH_2Cl_2-v. ClCOCOCL, DMSO, TEA, CH_2Cl_2; vi. $ClCO_2$fluorenyl, TEA, toluene, RT; vii. $P(OEt)_3$, 111°C; viii. Bu_4NBr, KF, AcOH, THF; ix. H_2 1 atm. 5% Pd/C, H_2O/isopropanol; x. benzyloxyformimidate hydrochloride, amberlyst IRA68, H_2O/MeCN, then crystallization from H_2OMeCOMe.

Scheme 33.

activity against difficult strains like *P. aeruginosa* was synthesized earlier in fourteen steps in 0.5 % overall yield [111, 112]. The new route has only ten steps and the overall yield is 7.5 % (**Scheme 33**). The number of purifications by silica gel chromatography has also been limited to 2 instead of the 5 previously reported. Furthermore, this route avoids the use of highly toxic diethylchlorophosphite and the formation of some unstable intermediates.

Copar and coworkers have used theoretical computation and molecular modeling to design biologically active trinems **69** [113]. These compounds have shown considerable inhibitory activity against Class C β-lactamase. The IC_{50} value ranged from 1-5 μM.



69

5. CONCLUSION

The broad spectrum antibiotic activity of azetidinone ring–containing compounds, their effectiveness in cholesterol absorption and enzyme inhibition and their application as synthons for various biologically important compounds make them appealing targets for medicinal chemists. The isolation of various resistant strains of bacteria has caused worldwide concern and efforts are on to discover new β-lactam antibiotics specially carbapenems and cephems to cope with them. The principal strategy in designing the new drugs is the structural modification of known compounds in order to impart appropriate lipophilicity and basicity. In some cases, the stereochemistry of the substituents has been observed to play a role in determining the activity. The structural modifications in them have led to the synthesis of some promising monobactams and carbapenems. Among carbapenems, **47e**, **48a,b** and **48h**, **49c**, J111,225 (**51**), sanfetrinem, **64c** and **67** can be counted as the promising antibacterial drugs for further studies. There is significant enzyme inhibitory activity in some of the compounds among almost all the major classes of β-lactams whereas some of the monobactams synthesized by Burnett and coworkers have shown significant cholesterol absorption inhibition.

I would like to apologize to those scientists whose work may not have appeared either due to limited scope of the review or oversight.

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