

Medicinal Chemistry of ureido derivatives as Antiinfectives[§]

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Abstract- Ureides are compounds, which essentially incorporate urea as a substructural component either in open or cyclic form. Ureido derivatives are one of the oldest classes of bioactives, widely used as antiinfective agents. Several of these compounds, including aminoquinuride, aminocarbalide, imidurea, cloflucarban, nitrofurazone, urosulfan, viomycin are used in clinical situations. One of the ureides, the triclocarban is compulsorily used as antibacterial agent in cleansing and disinfecting solutions in hospital, household, cosmetics, toys, textile and plastics. It disables the activity of ENR, an enzyme vital for building the cell wall of the bacteria and fungus. Besides, the ureido-penicillins in clinical use there have been several ureido-lactam derivatives which have been reported to exhibit significant antibacterial activity. A urea containing dipeptide TAN-1057A isolated from *Flexibacter* spp. has potent bioactivity against MRSA. The metal complexes of sulphonyl ureido derivatives are effective antifungal agents by inhibiting the activity of phosphomannose isomerase, a key enzyme in the biosynthesis of yeast cell walls. There have been number of ureides including the cyclic ureas which are potent HIV protease inhibitors and display significant anti-HIV activity. The urea derivative, merimepodip that has been derived using structure based design, is potent inhibitor of IMPDH and is active against Hepatitis-C infection. This review will primarily focus on the significant work reported for this class of compounds including design, synthesis and biological activity.

Introduction

The ureides are compounds which essentially incorporate urea as substructure unit either in open or cyclic form. These are an important class of compounds since out of the five nucleobases, the three pyrimidine bases cytosine, thymine and uracil incorporates urea as a substructural component. The ureides per say have been associated with several bioactivities as evident from the MDDR database which incorporates more than 6000 compounds having urea scaffold [1]. Some of the important pharmacological activities ascribed to ureides are antiinfectives, antitumor, anticancer and for various metabolic disorders including diabetes and hyperlipidemia. In this review we will primarily focus on the antibacterial, antifungal and antiviral activities including anti-HIV activity shown by several urea derivatives.

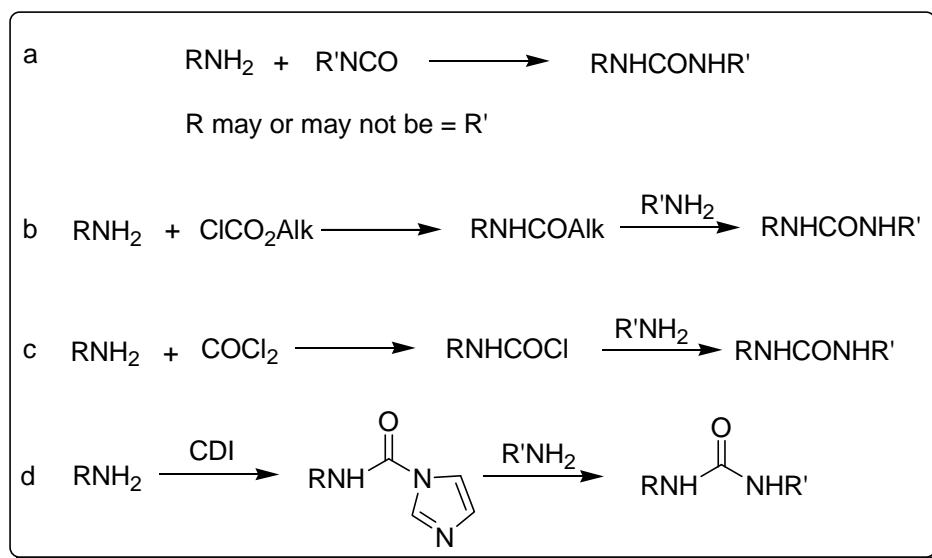
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Scope

The main objective of the present review article is to highlight the importance of ureides for the antiinfective activity. Therefore, this article does not cover the total literature and it is likely that certain important references may have been left out. A SciFinder search for the subject "urea" result in more than 2.6 lacs hits. This review article will include references obtained from SciFinder (Scholar) searches using following keywords a) ureides and antibacterials, b) urea and antibacterials, c) ureides and antiviral, d) urea and antivirals, e) ureides and antifungal, f) urea and antifungal and g) ureides and HIV. The complete literature for some of the ureides mentioned in the Chemical Abstracts was not available; therefore corresponding details will not be highlighted though references will be made to these reports.

General syntheses of Ureides

The syntheses of urea and ureides have been recently reviewed by Sartori and Maggi [2]. Some of the commonly employed method to obtain this class of compounds are a) Reaction of an amino derivative with an isocyanate to yield urea derivative; b) Reaction of an amino compound with alkyl chloroformate followed by reaction with another amine to give urea derivative c) Reaction of carbonyl chloride with amino derivative to obtain symmetrical urea derivative and d) Reaction of amine with CDI (carbonyldiimidazole) followed by reaction with another amine to yield urea derivative. Recently, new methods of the preparation of urea derivatives have also been reported, but they too qualify within these groups. [3-4]. More recently, Larhed et al. described cobalt carbonyl-assisted superfast synthesis of symmetrical ureas under microwave condition [5].



Antibacterial agents

The ureides are one of the most simple and commonly used antibacterial agents. The urea per say has antibacterial activity which was discovered during early part of the nineteenth century and since then urea and its derivatives have been extensively used as non-medicinal disinfectants in clinical situations. Urea and its derivatives have been reported to exert a

bacteriostatic and bactericidal action on gram negative bacteria, and to a lesser extent on the gram positive organisms [6]. Since they were found to antagonize sulfonamide inhibitors and increase the solubility of sulfonamide drugs, they were speculated to be of valuable importance to treat gram negative infections in human subjects [7].

The aryl ureas are one of the simplest of all the chemicals to be used in clinics. In studies reported in the middle of the last century, Beaver et al described the synthesis and antibacterial activity of several diaryl ureas [8]. These ureides were prepared in one step utilizing the isocyanate method. A number of these diaryl ureas displayed significant antibacterial activity though triclocarban (**1**) was developed for the clinical use. In present times, triclocarban is compulsorily used in the cleansing and disinfecting solutions in hospitals, households, cosmetics, toys, textiles and plastics. It is active against gram positive bacteria and certain fungi, but less so against gram negative bacteria. It is now known that triclocarban disables the activity of ENR (enoyl-acyl carrier-protein reductase), an enzyme vital for building the cell wall of the bacteria and fungus [9]. Another analogous urea derivative the cloflucarban (**2**) has been reported to have similar antibacterial properties and commercial utility.

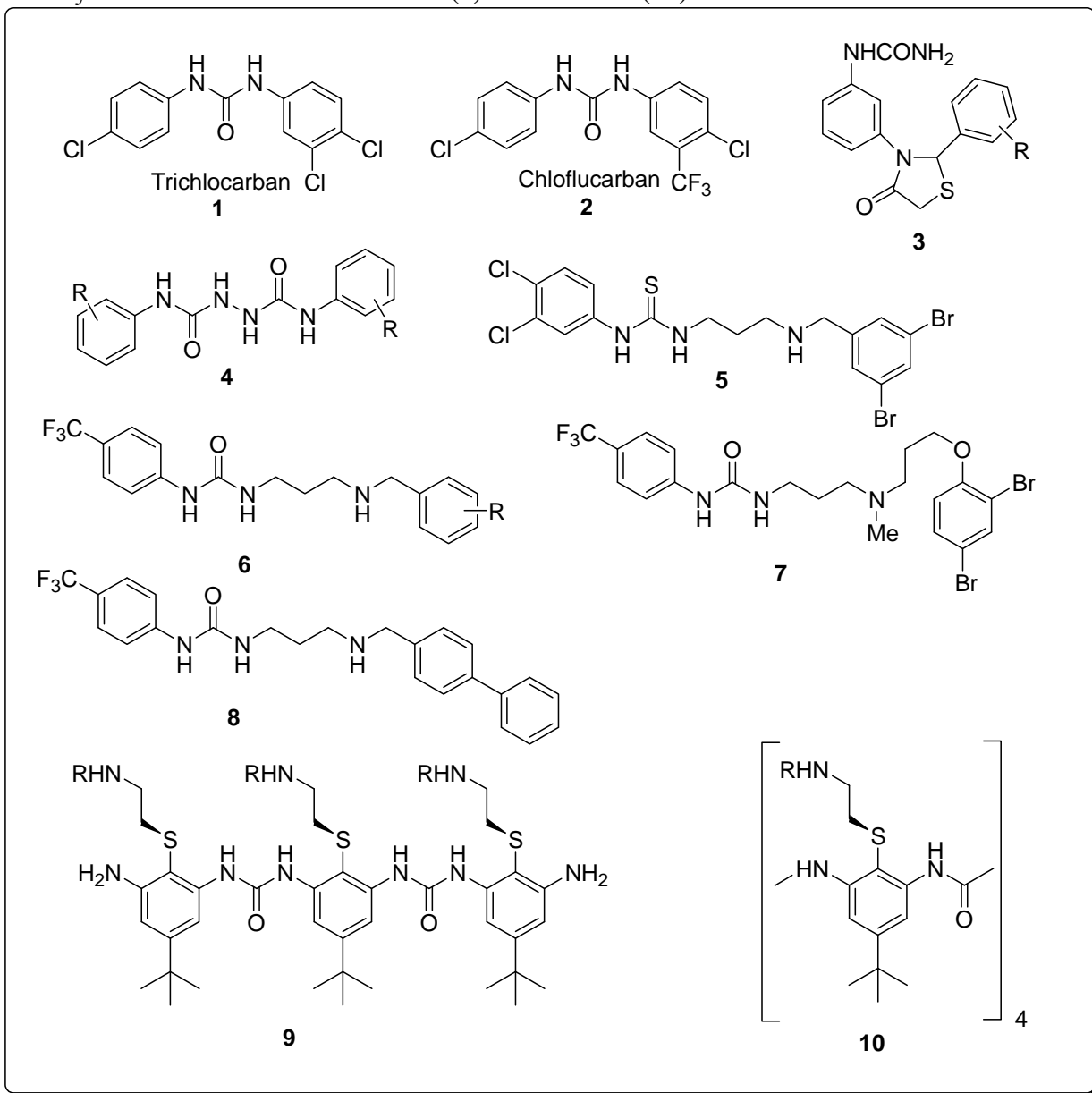
The aryl urea present on the thiazolidinones (**3**) were synthesized and evaluated for their antibacterial activity against *S. aureus* and *E. coli* [10]. However these compounds showed moderate activity only.

The biarylamides were discovered to inhibit the synthesis of peptidoglycans in *S. aureus* in an *in vitro* screening through high throughput assay [11]. This effort led to the identification of a series of biaryl amides (**4**) and related compounds that demonstrated *in vitro* antibacterial activity against wide range of antibiotic resistant and sensitive bacterial pathogen [12]. The activities of these compounds were attributed to their ability to inhibit peptidoglycan synthesis. In the attempt to discover broad spectrum activity against organisms of interest, this program was later extended to evaluation against several gram positive and gram negative strains. However, it was observed that these compounds display only sporadic activity against some of the gram negative organisms. Recently, the QSAR model was developed based on these biarylamides which provided the details regarding how the changes in the molecules affect the antibacterial activity. It was further reported that the hydrophobicity at the ends of the molecule was the primary driving force, with trifluoromethyl groups providing the largest observed effect. [13].

Recently Seth et al. have described the synthesis of several aryl urea analogs (**6** and **7**) based on the thiourea derivative (**5**) discovered during inhouse screening for discovery of new structure for antibacterial activity [14]. The optimization of the lead structure was carried out with a view to obtain a broad spectrum antibacterial agent which is active *in vivo* too. Additionally, their objective was to identify substances which would reduce the hydrophobicity and maintain the antibacterial activity. The isocyanate method was adopted to synthesize these ureides. Several analogs were found to be equipotent to the Linezolid that was used as a standard in the bioassay. During detailed evaluation of the selected analogs, few were found to display low micromolar activity against *S. aureus*, *S. pyrogens* and *E. faecalis* but were found to be inactive against *P. aeruginosa*. Further, it was observed that the antibacterial activity is reduced in the presence of bovine serum which was attributed to the high serum protein binding of this class of compounds. The analysis of the SAR reflected that increasing the hydrophobicity improved the activity which led to the conclusion that these urea analogs are binding in a very lipophilic pocket. However, the two urea derivatives **7** and **8** selected for the *in vivo* studies were not as

potent as the standard vancomycin at the dose they were evaluated. Higher doses of these compounds led to toxic effects on the animals.

Recently, the antibacterial activity of novel urea oligomers has been described by Tew and coworkers [15]. The inspiration for the synthesis of such urea oligomers was derived from the antibacterial activity of aryl ureas. These urea oligomers were synthesized in one pot and had internal NH---S hydrogen bonding to limit their conformational flexibility. Though most of these oligomers were reported to be potent antimicrobials against *E. coli* and *B. subtilis*, the activity was concentrated in the trimer (**9**) and tetramer (**10**).



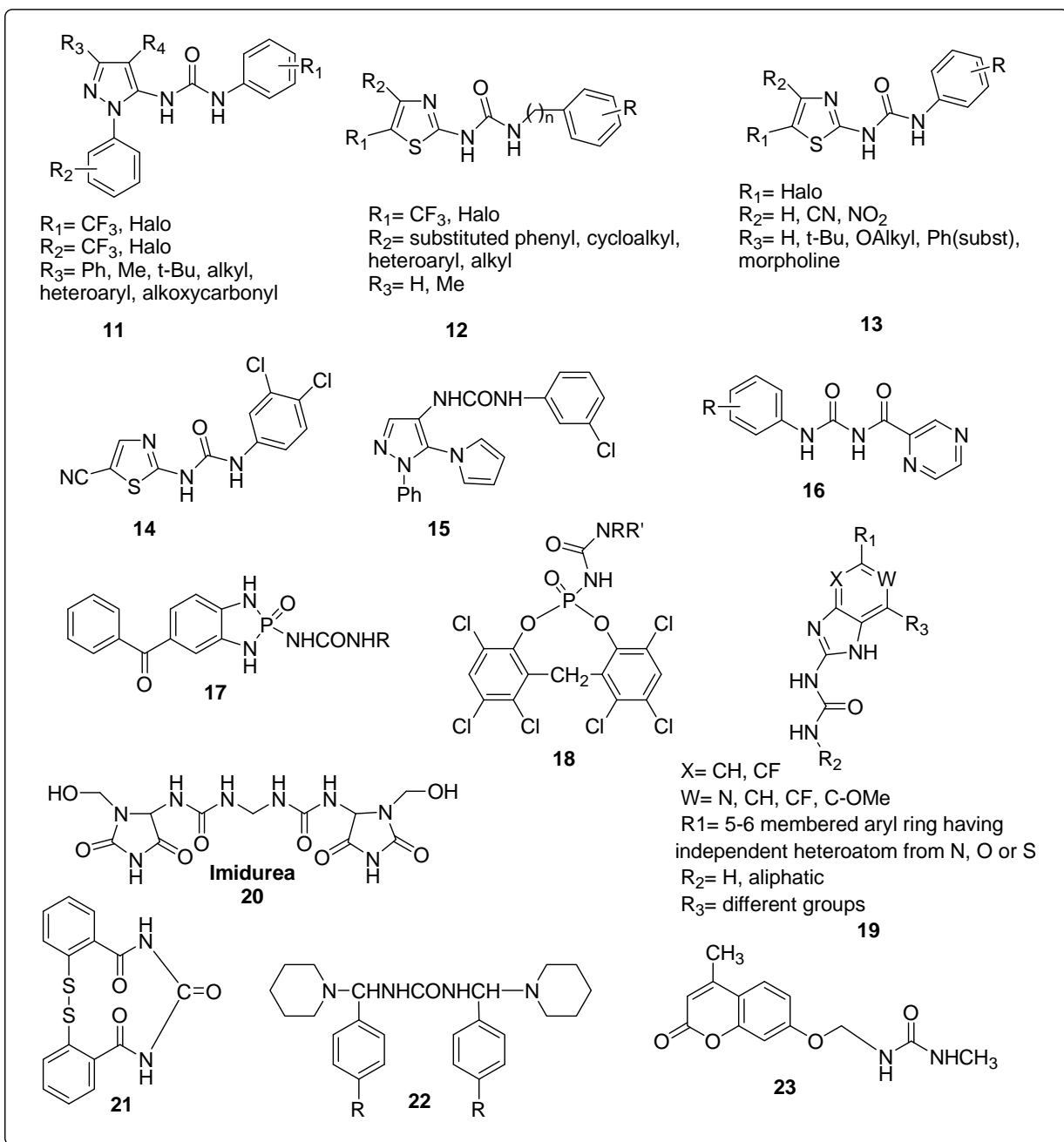
Several diverse aryl ureides derivatives of heterocyclic compounds have been reported. The aryl ureides of 5-aminopyrazole and 2-aminothiazole (**11** and **12**) have been prepared and evaluated for their antibacterial activity [16]. The urea moiety was generated either through the

isocyanate or the chloroformate method. In the SAR described for the pyrazole series that was evaluated against methicillin sensitive *S. aureus*, it was observed that the disubstituted urea is necessary for activity. In order to probe the SAR for substitution of the N-substituent opposite to the pyrazole, it was reported that the active compound required N-aryl substituent preferably 3,4 or 3,5-disubstituted with halogen atom or the trifluoromethyl group. Of the preferred substitution on the heterocyclic ring, the phenyl group having halogen or trifluoromethyl was found to be useful. The SAR of the thiazole compounds was similar to that of pyrazole group though here the urea moiety could have either N-aryl or N-benzyl substituents. The preferred substitution on the phenyl ring here too was the halogen or the trifluoromethyl. Unlike pyrazoles, this series could accommodate more substitution on the phenyl ring. Perhaps, a number of compounds from both the series were subjected to *in vivo* antibacterial evaluation, but none of the compounds could rescue the animals completely as compared to the control vancomycin. The inactivity of such compounds was attributed to their marginal bioavailability and relatively higher MlogP.

Simultaneously, phenyl thiazolyl urea derivatives (**13**) were also reported as inhibitors of MurA and MurB, the enzymes essential for peptidoglycan biosynthesis [17]. These compounds were prepared by the reaction between the substituted thiazoles and isocyanates. The 3,4-dichlorophenyl thiazolyl derivative (**14**) demonstrated an IC₅₀ of 20 µg/mL and displayed potent activity against gram positive strains including methicillin resistant *S. aureus* (MRSA), vancomycin resistant *Enterococcus* and penicillin resistant *S. pneumoniae*. Based on this compound other urea derivatives were generated. The presence of a cyano group at 5-position increased the activity by 2-4 fold and also increased the IC₅₀ against MurA and MurB. Since the antibacterial activity of compounds decreased considerably in the presence of bovine serum, new analogs with increased polarity were prepared in order to minimize the serum protein binding. The compound with 3,4-difluorophenyl moiety demonstrated better activity profile against both the gram positive and gram negative bacteria even in the presence of bovine serum. The docking studies of these compounds with MurB crystal structure have also been reported. These ureides were considered good leads for further studies since some of the derivatives showed better activity than the standard vancomycin.

Recently, out of several new pyrazole derivatives, which have been synthesized and evaluated for their antibacterial activity, only the aryl urea derivative **15** was found to have pronounced activity against *B. cereus* and *S. aureus* and moderate activity against *E. coli* [18]. The 2-[N-(aryluroid)carbonyl]-pyrazines (**16**) prepared in two steps from pyrazine 2-carboxylic acid have been reported to show mild antibacterial activity [19]. Reddy et al. reported potent antibacterial activity in N-(substituted)-N'-(2,3-dihydro-2-oxido-5-benzoyl-1H-1,3,2-benzodiazaphosphol-2-yl) ureas (**17**) against *E. coli* and *S. aureus* [20]. Later these workers extended their study to N-(substituted)-N'-[1,2,4,8,10,11-hexachloro-6-oxido-12H-dibenzo(*d,g*)(1,3,2)dioxaphosphocin-6-yl]ureas (**18**) which were prepared by the reaction between 2'-methylenebis[3,4,6-trichlorophenol] (hexachlorophene) and carbamidophosphoric acid dichlorides. These compounds have also been reported to possess good antimicrobial activity [21].

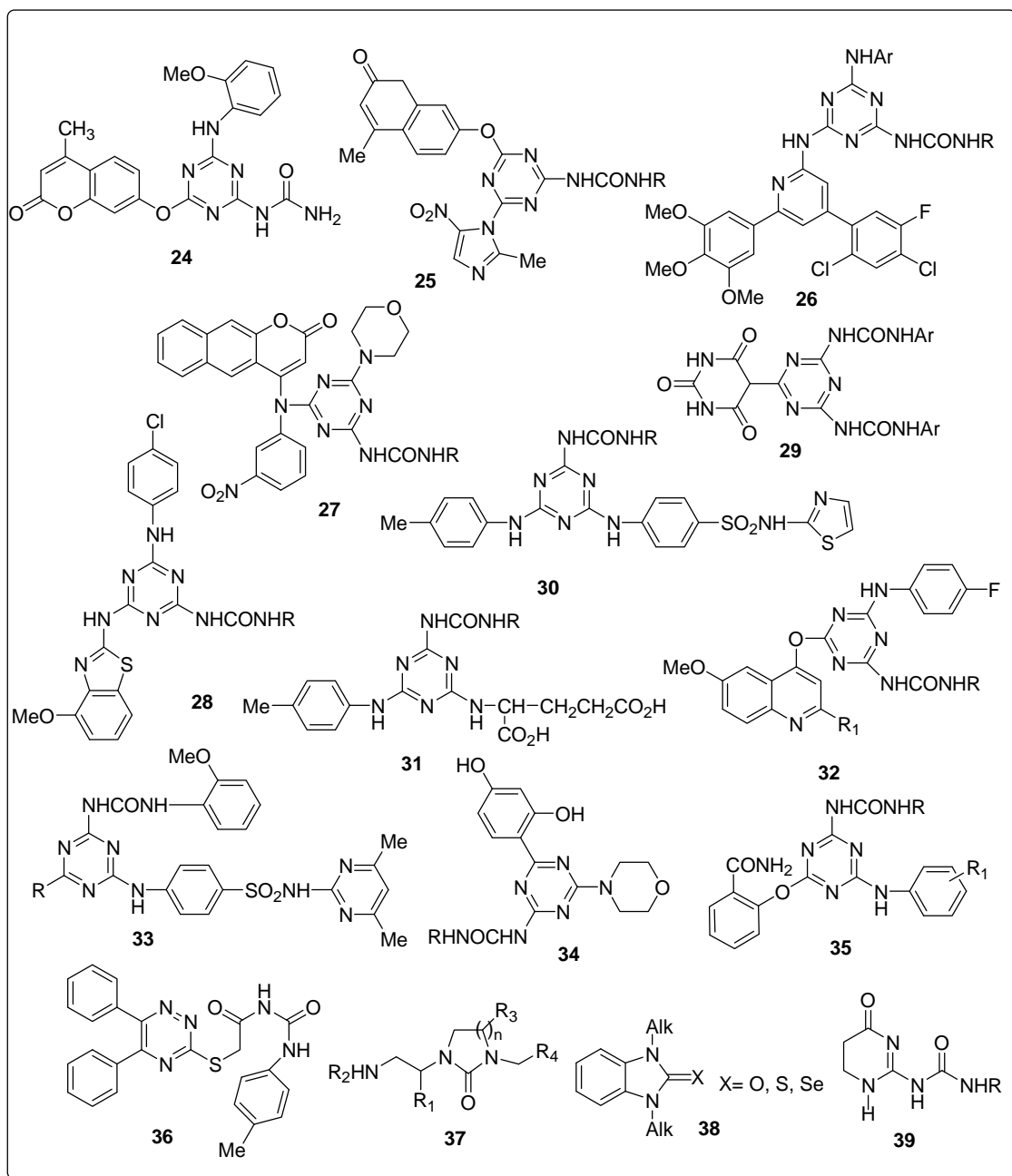
The 2-ureido-6-heteroaryl-3*H*-benzimidazole-4-carboxylic acid derivatives (**19**) and related compounds prepared by the reaction between *N*'-ethyl-*N*-cyanourea and methyl-2,3-diamino-5-(3'-pyridyl)benzoate in water they have been patented as gyrase and topoisomerase IV inhibitors for the treatment of bacterial infections [22]. These compounds show potent antibacterial activity against *S. aureus* with MIC of 0.5µg/mL. *N,N'*-Methylenebis(*N*'-3'(hydroxymethyl)-



2,5-dioxo-4-imidazolidinyl)urea), also known as imidurea (**20**) is on approved list of acceptable non-medicinal ingredient (0.3 to 0.05 w/w) to be used as antimicrobial preservative in topical applications which are for external use only [23].

The 2,2'-dithiobis(benzamide) urea (**21**) prepared for the antibacterial activity were found to be inactive [24]. The aminobenzylated Mannich bases (**22**) of urea prepared by condensing piperidine and urea with substituted benzaldehydes were evaluated against gram positive and gram negative bacteria but the details are unknown [25].

The urea analogs (**23**) of heterocyclic compounds containing coumarin moiety were screened as antibacterial agents by Fattah [26]. These ureides were prepared by the treatment of substituted amines with the acid azide which in turn was obtained from 4-methyl-2-oxo-2H-benzopyran-7-yloxyhydrazine. It was reported that the disubstituted urea showed good biological response against *S. aureus*, though details of the activity were not provided. In continuation, with his studies on ureido derivatives of coumarins, he reported the synthesis of 2-[(methylcoumarinyl)-7-oxy]-4-(2-methoxyanilino)-6-(aryluroido)-s-triazines (**24**) which were found to show no significant antibacterial activity [27]. Several other substituted ureido-triazines have been synthesized as antibacterials by Desai and coworkers [28-38]. These include 2-(4-Me-coumarin-7-yl-oxy)-4-(2-methyl-5-nitro-imidazol-1-yl)-6-(aryl ureido)-s-triazine (**25**), 2-phenyl amino-4-(aryl thio ureido/aryl ureido)-6-[(4'-(2",4"-dichloro-5"-fluoro phenyl)-6'-(3",4",5"-trimethoxy phenyl) pyrimidine-2'-yl)amino]-s-triazine (**26**), 3-phenyl-4-(4-*m*-nitrophenyl)-N-2-(2-aryluroido/arylthiouroido-4'-N-morpholino-s-triazine)-benzo-[6,7]-coumarins (**27**), 2-(4'-methoxybenzothiazol-2'-yl-amino)-4-(4'-chlorophenylureido)-6-(aryluroido)-s-triazine (**28**), 5-(2,4-diaryluroido-s-triazin-6-yl)barbituric acids (**29**), 2-[N4-{N1-(2'-thiazolyl) sulfanilamido}]-4-(4'-methylanilino)-6-(aryluroido)-s-triazines (**30**), 2-(4-methylanilino)-4-(β -aminoglutaric acid)-6-(substituted phenyl ureido)-s-triazine (**31**), 2-(6-methoxy-2-methylstyrylquinolin-4-oxy)-4-(4-fluorophenyl)amino-6-aryluroido-s-triazines (**32**) and other (**33-35**). These have been evaluated mainly against *E. coli* and *S. aureus*. However since no data is available it is apparent that they show



mild to moderate antibacterial activity. Some 1-aryl-3-(5,6-diphenyl-1,2,4-

triazin-3-yl-mercaptoacetyl)ureas (**36**) have also been evaluated for antibacterial activity against *B. subtilis* and *B. pumilus* [39] wherein the compound with bromo group in the ureido phenyl ring was the most active derivative.

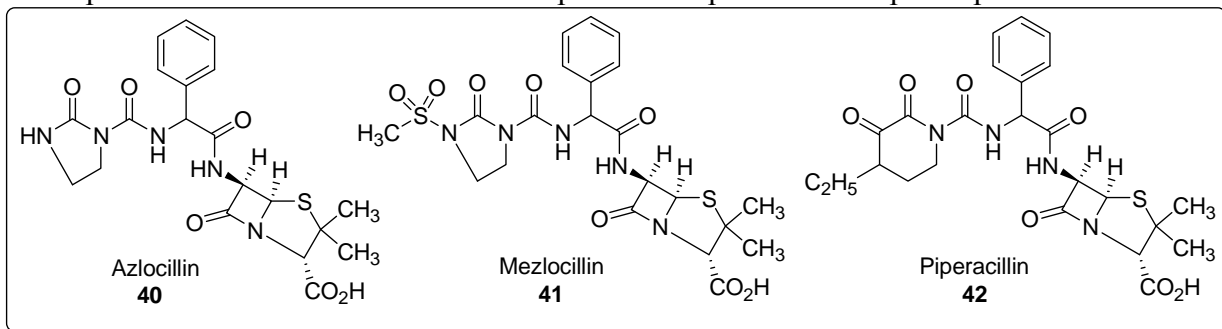
The combinatorial libraries of cyclic ureas (**37**) prepared by Houghten et al. have been patented for their antibacterial activity [40]. Another group has also reported the moderate *in vitro* antimicrobial efficacy against gram positive bacteria of electron rich olefin derived cyclic urea (**38**) of all group 16 elements containing imidazolidine and benzimidazole [41]. Swayze

and Sprankle have utilized combinatorial methods toward the synthesis of cyclic amines. Several compounds bearing a urea group showed potent bactericidal activity by acting upon the phospholipases A2 [42]. The azaindolizine gave >95% inhibition of several strains of bacteria. The 4-oxo-2-ureido-1,4,5,6-tetrahydropyrimidine derivatives (**39**) have been reported to exhibit potent antibacterial activity [43].

Several of the urea derivatives are also potent inhibitors of peptide deformylase, the bacterial metalloenzyme that deformylates the N-formylmethionine of newly synthesised bacterial polypeptides. Since these examples have been discussed in a recent review article by Clement et al. they are not being discussed separately [44].

The β -lactam class of antibiotics include penicillins, cephalosporins, penems, carbanepenems and trinems. β -Lactam antibiotics normally inactivate PBPs (penicillin binding proteins) and interfere with the process of transpeptidation by forming an ester bond between the active site serine and the carbonyl carbon of the β -lactam. Hence, β -lactams mimic the acyl-D-Ala-D-Ala of the bacterial cell wall in their interactions with transpeptidases [45]. These compounds have been the subject of several excellent recently published review articles [46-50]. Hence, herein reference will be made only to few examples of these basic structures containing the ureido group.

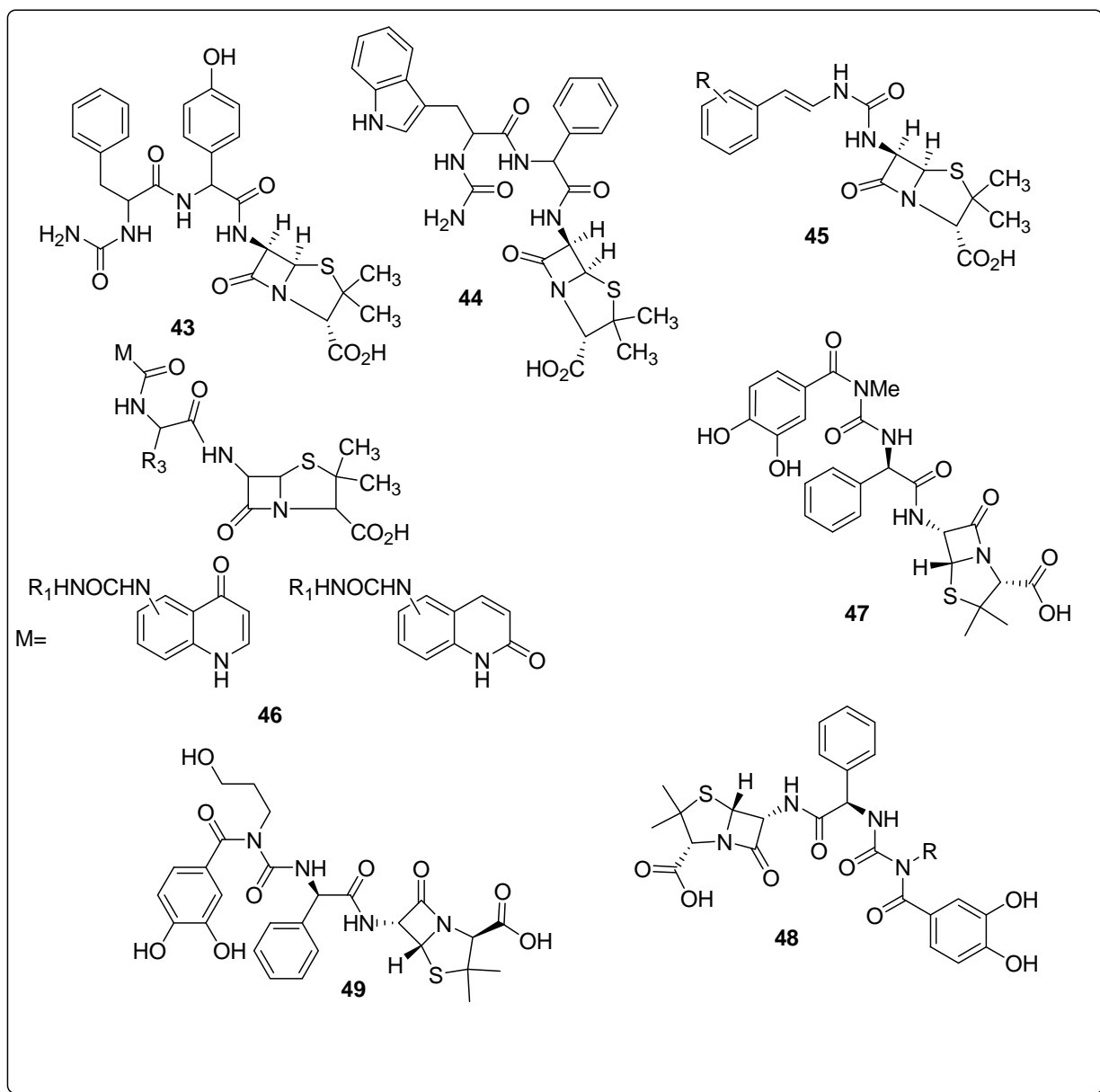
The ureido penicillins exhibit a broad spectrum antibacterial activity which includes many anaerobes, the gram positive streptococci (including enterococci) and gram negative bacilli including *P. aeruginosa*. The three most widely used and extensively studied ureidopenicillins include Azlocillin (**40**), Mezlocillin (**41**) and Piperacillin (**42**). These ureidopenicillins are more tolerated as compared to ampicillin and cephalosporins.



Nathwani and Wood reviewed the clinical pharmacology and therapeutic uses of penicillins class of drugs including the acylureidopenicillin [51]. These three penicillins are given parenterally as they are not absorbed after the oral administration. Especially, piperacillin is highly effective in biliary tract infections where the initial therapy includes the support for the electrolyte displacement, correction of the metabolic imbalances and antibacterial therapy. During randomized clinical trials including patients with acute cholangitis and acute cholecystitis, it has been observed that piperacillin is as efficacious as ampicillin plus tobramycin [52]. However in acute cases, where a substantial risk of *P. aeruginosa* and *Enterobacter spp.* is involved, clinical studies have justified the use of combination of aminoglycoside with the ureido penicillin. These ureidopenicillins have been discussed in detail in another review article published recently [53].

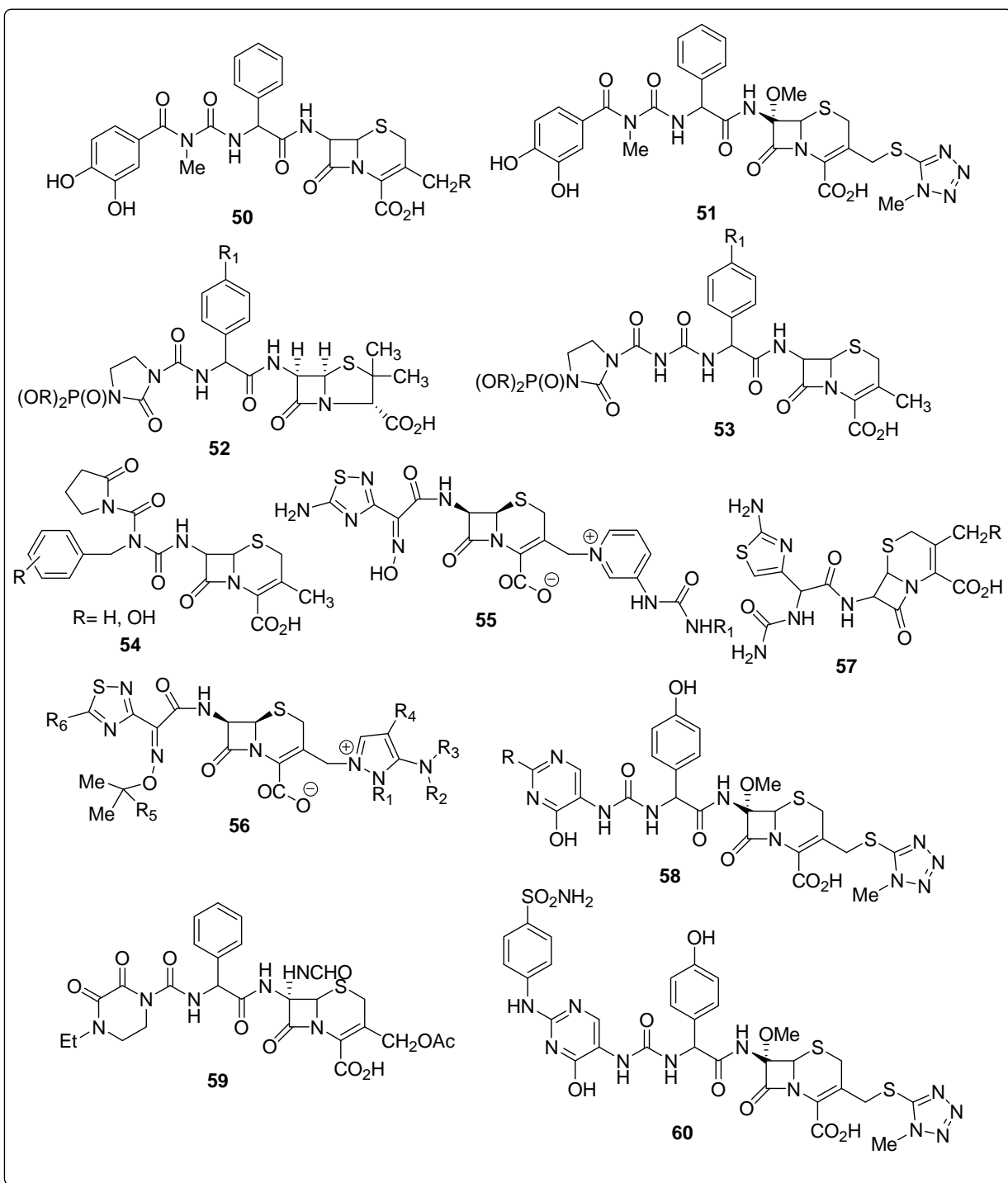
Several modifications to the ureidopenicillin group of compounds have been attempted. A detailed structure-activity relationship of the stereochemistry and various alkyl, aryl, aralkyl and heterocyclic substituents at the two chiral centres in the dipeptide side-chain of a new series of 6-[alpha-(alpha'-ureido-acylamino) acylamino] penicillanic acids was disclosed by Ferres and coworkers [54]. It was reported that effect of these changes had a pronounced influence on the degree of activity against gram positive and especially gram negative bacteria. Further, it was emphasized that the size, shape and spatial disposition of a substituent were the parameters of importance in influencing antibacterial activity, rather than its lipophilic or electronic character. The 6-[D-alpha(alpha'-ureidoacyl-amino)acylamino]penicillanic acids were discovered to have carbenicillin-like profile, with improvements against *P. aeruginosa*, *K. aerogenes*, sensitive and beta-lactamase-producing gram positive cocci. The two most active compounds discovered during the study were **43** and **44**. A series of vinyl ureidopenicillins (**45**) were prepared by reacting 8-aminopenicillanic acid and vinyl isocyanate and cyanates [55]. These ureidopenicillins were initially evaluated against lactic acid production. The active compounds were also screened for their antibacterial activity against 12 pathogenic strains, but no compound shows any prominent activity though among themselves the vinylureido derivatives were less potent than the ureido derivatives. The N[ureidodihydro-oxo-3-quinolinylcarbonyl]penicillins (**46**) were patented for their use as antibacterials [56]. They were prepared either through reaction of the free amino acid of the appropriate penicillin or acid or salt with a reactive derivative of corresponding ureido-dihydro-oxy-3-quinolinecarboxylic acid or reacting a free amino acid, the 6-aminopenicillanic acid with a reactive derivative of the corresponding D-N-[ureidodihydro-oxo-3-quinolincarboxyl]-2-substituted glycine. These compounds were found to be effective against several bacterial strains including *S. aureus*, *P. ruegosa*, *E. coli*, *K. pneumoniae*, *Enterococcus*, *P. vulgaris*.

Ohi and coworkers have reported the synthesis and antibacterial activity of several semisynthetic β -lactam antibiotics. A new series of ureidopenicillins having catechol moiety in the 6-acyl side chain was found to exhibit significant activities against *P. aeruginosa*. Amongst, several derivatives, 6-[(R)-2-[3-(3,4-dihydroxybenzoyl acetamido)] penicillanic acid (**47**) had the most potent *in vitro* activity against gram negative bacteria, its activity being approximately 60-fold greater than that of piperacillin [57]. Furthermore they studied the relationship between *in vitro* and *in vivo* activities of 6-[(R)-2-[3-(3,4-dihydroxybenzoyl)-3-R-1-ureido]-2-phenylacetamido] penicillanic acids (**48**) having C₂ as alkyl or substituted alkyl groups. In this series, [(R)-2-[3-(3,4-dihydroxybenzoyl)-3-(3-hydroxypropyl)-1-ureido] -2-phenylacetamido] penicillanic acid (**49**) showed the most potent protective effect on mice in experimental *P. aeruginosa* infections [58]. These catechol containing ureidopenicillins were readily metabolized by the enzyme catechol-O-methyl-transferase.-3-methyl-1-ureido]-2-phenyl-. Therefore, in an attempt to increase the resistance towards the metabolism through this enzyme, the effect of several substituents on the catechol moiety was evaluated. It was observed that the presence of a chloro substituent resists the metabolism of these penicillins by the catechol-O-methyl-transferase. This modification led to enhancement in the *in vivo* activity against *P. aeruginosa* and *E. coli* infections despite no change in the *in vitro* activity [59]. Additionally, they reported a new series of ureidocephalosporin (**50**) and ureidocephamycin (**51**) derivatives for antibacterial activity against two species of gram positive and seven species of gram negative strains of bacteria and their activities were compared to cefoperazone and ceftazidime [60].



The substituent on the ureido group affected the activity of compounds against gram negative bacteria. The methyl analogs were found to have high activity. In case of cephamycin the presence of a tetrazole-5-thiol group as the substituent was potent against *E. coli* and *S. marcescens*. It was also strongly active against the *P. aeruginosa* with almost 8-32 fold increase in activity as compared to cefoperazone and 4 fold compared with ceftazidime. Antibacterial evaluation of new ureido-β-lactam derivatives having dialkyloxy-phosphoryl-2-oxo-imidazolidinyl moieties (**52** and **53**) showed that these compounds had bactericidal effect against gram positive bacteria [61].

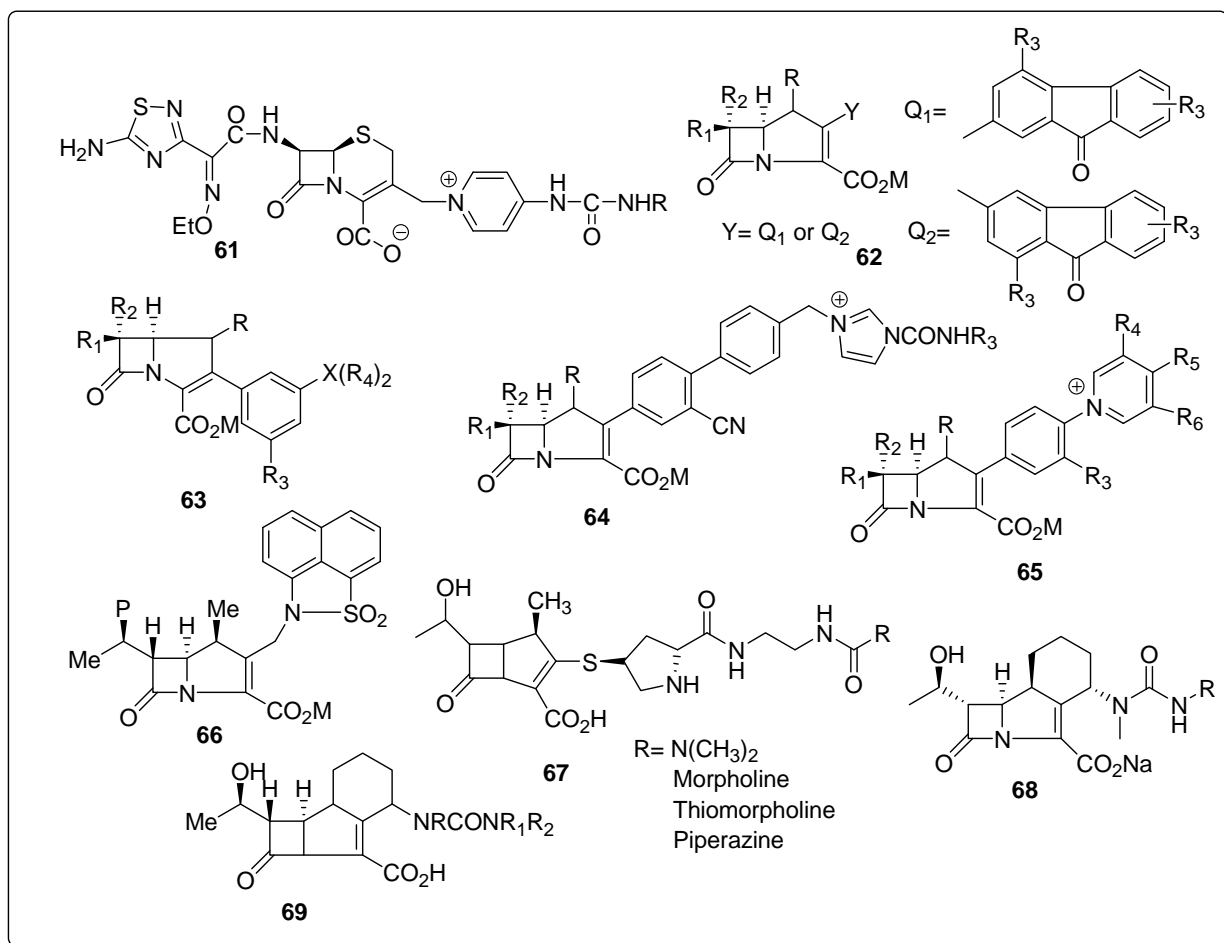
Valcavi et al. prepared and evaluated the antibacterial activity of ureido, acylureido and carbamoylureido derivatives of cephalixin and cefadroxil. Only the 7-[D-α-(imidazolidin-



2-one-1-ylcarbonylamino)-alpha-phenylacetamido]-3-methyl-3-cephem-4-carboxylic acid (**54**) and the 7-[D-alpha-(imidazolidin-2-one-1-ylcarbonylamino)-alpha-p-hydroxyphenylacetamido] -3-methyl-3-cephem-4-carboxylic acid displayed mild antibiotic activity without any improvement against *Pseudomonas* strains [62]. Recently, two new series of quarternized ureido cephem compounds containing ureido pyridine (**55**) and ureido pyrazole (**56**) have been patented for their antibacterial activity with pronounced effect against MRSA [63-64].

The antimicrobial activity, beta-lactamase stability and pharmacokinetics of 7-(alpha-ureido-2-amino-4-thiazolylacetyl)-cephalosporins (**57**) has been reported by Polacek and Stark [65]. These compounds displayed significant activity against gram negative bacteria with L-isomers were more potent than the D-isomers. All compounds exhibited some degree of stability to beta-lactamases. The compounds reached high serum and tissue fluid levels and were excreted unchanged mainly in urine. In the studies directed towards the analysis of structure activity relationship of several of the 7 α -formamidocephalosporins it was observed that the 7 α -formamidocefoperazone (**58**) was more potent than the other ureido and acylamino derivatives [66].

The 7 α -methoxy pyrimidinyl-ureidocephalosporins (**59**) exhibited a broad range of activity against gram positive and gram negative strains [67]. However, one of the compounds having *p*-aminosulfonylanilino substituent (**60**) led to the best results with pronounced activity against gram positive strains especially the MRSA (multi-resistant *S. aureus*). This compound was found to be superior to moxalactam and ceftazidime. The high activity of **60** was confirmed through *in vivo* experiments in mice. The synthesis and bioevaluation of several new broad-spectrum parenteral cephalosporins exhibiting potent activity against both MRSA and *P. aeruginosa* have been recently reported [68]. Among several compounds, the ureido linked pyridinium derivatives (**61**) displayed more potent antibacterial activity. This led to further modification of the aminoalkyl moiety in order to improve the anti-MRSA activity. The results of the SAR led to the conclusion that the anti-MRSA activity could be increased by elongating the carbon chain of the amino-alkyl moiety or by replacing the amino group with other basic group such as guanidine. However these compounds were not pursued for further development due to inferior solubility and acute toxicity detected in the mouse model.



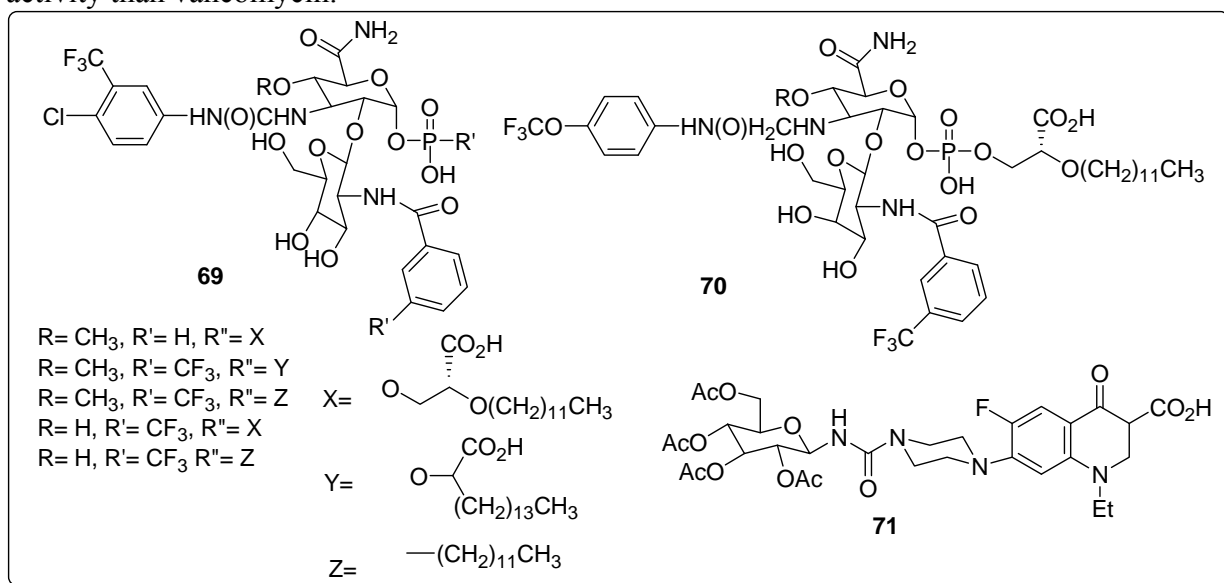
The research groups from Merck have filed several patents for series of carbapenams incorporating urea pharmacophore as antibacterials. These included 2-(9-fluorenyl)carbapenems (**62**), 2-heteroarylphenyl-carbapenem (**63**), 2-biphenylcarbapenem (**64**) and (pyridiniophenyl)carbapenems (**65**) and 2-naphthoiso-thiazole (**66**) [69-73]. These compounds have been evaluated against MRSA, however the details of the activity are not disclosed.

Recently, in order to improve anti-MRSA and antibacterial activity of carbapenem derivatives, Cho et al. described the synthesis and SAR of the 1 β -methylcarbapenems having 5'-substituted aminoethylcarbamoyl pyrrolidine-3'-ylthio group (**67**) [74]. During the study they observed that the piperazine urea derivative exhibited the most potent and well-balanced activity against the gram positive and gram negative bacteria including MRSA as compared to meropenem and imipenem.

A series of novel ureido trinems (**68**) using isocyanate method have been prepared to evaluate their antibacterial activity [75]. These compounds showed promising activity against gram negative bacteria. Another series of ureides of tricyclic carbapenems were also patented as bactericides with significant active against *S. aureus* with MIC of 0.5 $\mu\text{g}/\text{mL}$ [76].

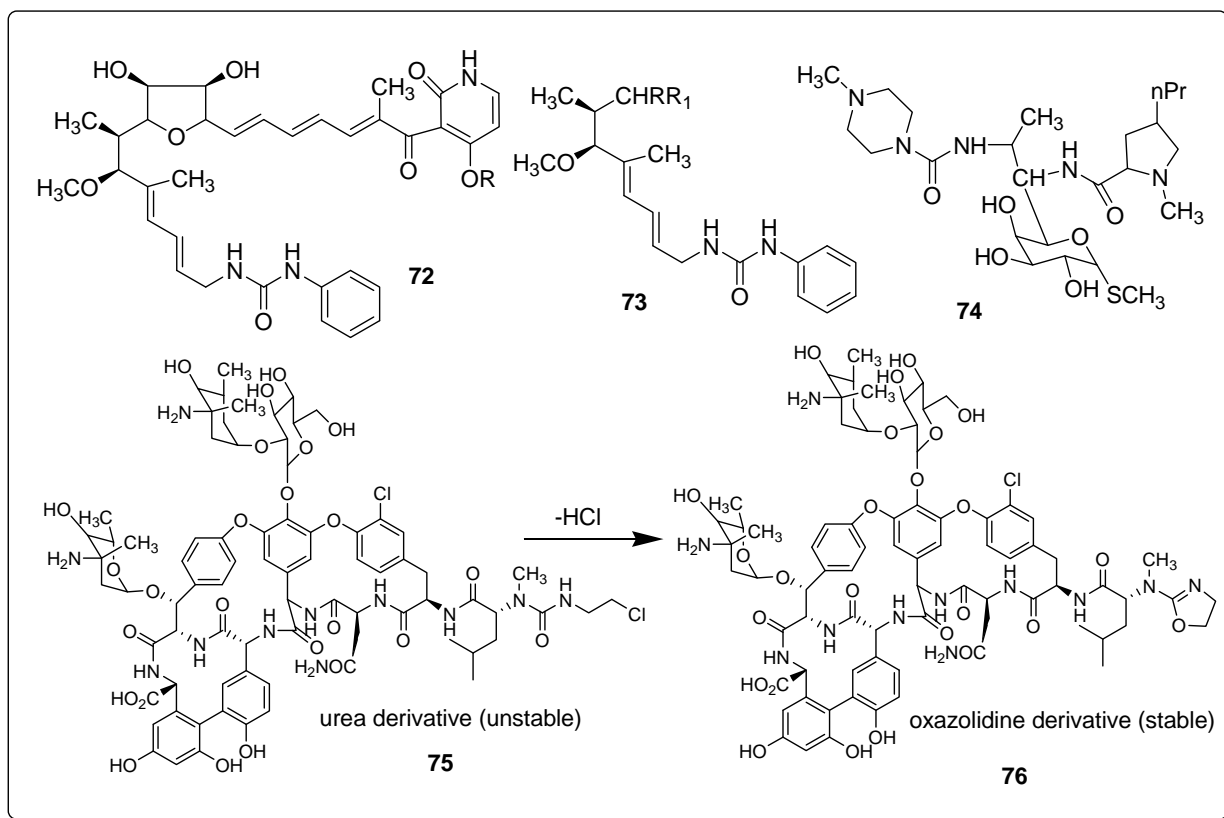
Besides beta lactam, sugar and peptide derivatives obtained from natural sources of prepared through modification of these compounds have been a rich source of useful lead molecules in the area of antibacterials. In an attempt to target the bacterial cell wall synthesis to develop novel antibacterial agents, Sophia et al. have reported a combinatorial library of disaccharides based on moenomycin [77]. In particular these compounds were targeted toward

transglycosylase enzyme activity associated with the PBPs. This library beside other compounds also included ureido derivatives several of which had IC_{50} of below $15\mu\text{g/mL}$ and MIC of $25\mu\text{g/mL}$ (**69-70**). Though these compounds were less active than the moenomycinA for bacterial cell wall synthesis, the authors claimed to have identified simpler disaccharides that inhibit both the cell wall biosynthesis and bacterial growth. These compounds upon purification and reevaluation in comparison to the clinically used antibiotic vancomycin were shown to be equipotent to vancomycin as inhibitors of cell wall biosynthesis. As the experimental results inferred that the lipid II formation was unaffected by the presence of these inhibitors it was concluded that the non-specific perturbations of the cell wall by these compounds are unlikely. The antibacterial activity of these compounds was comparable to that of vancomycin against gram positive bacteria. Additionally against the clinically relevant antibiotic resistant *Enterococcus* organisms, these compounds were shown to have better activity than vancomycin.

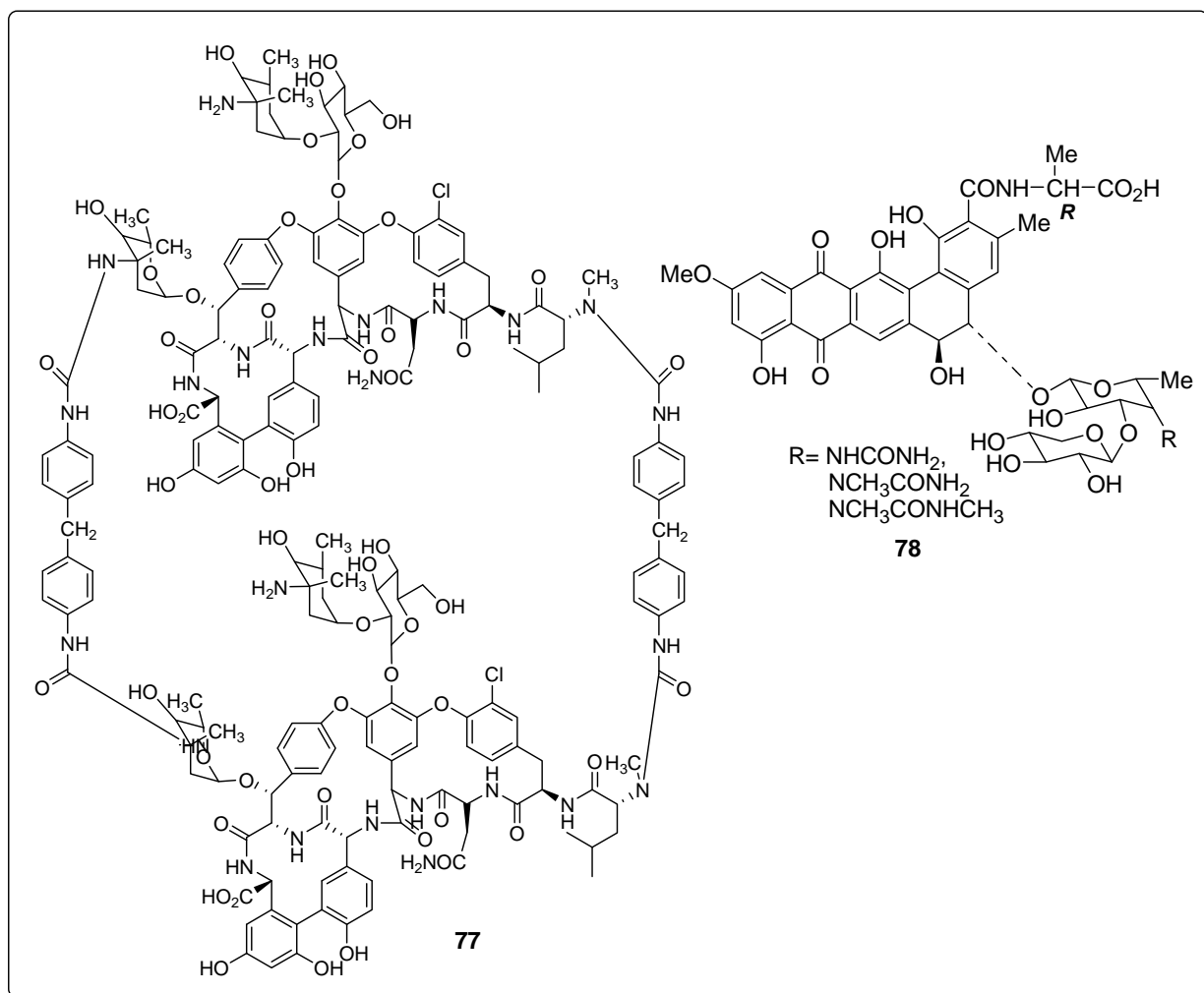


Very recently, the carbohydrate derivative (**71**) of Norfloxacin incorporating urea moiety has been reported [78]. The glycosyl isocyanates were reacted with norfloxacin for the introduction of urea linkage between glycosyl and norfloxacin unit. For the synthesis of unprotected sugar urea compounds, a new synthetic strategy was developed using 1,2-N,O-carbonyl- β -D-glucopyranoses. However the details of the bioactivity are not disclosed.

Kirromycin, an elfamycin class of antibiotic, produced by fermenting *Streptomyces* spp. and *Actinomyces* spp. strains was degraded to obtain 1-N-desmethyl goldinamine. This amino derivative formed ureido compounds (**72**) by the reaction with isocyanates [79]. The N-Ph ureido derivative of 1-N-desmethyl goldinamine was able to inhibit bacterial protein synthesis in cell-free assay and was active against whole microorganisms, although with lower potency than kirromycin. It was speculated that like other elfamycins, this compound too inhibit bacterial protein synthesis by binding elongation factor Tu to form non-dissociable ribosome-EFTu complex. The ureide was further degraded at the tetrahydrofuran ring yielding and aldehyde (**73**) which was then modified keeping the urea subunit preserved. Only mild antibacterial activity of observed against *E. hirae* and *N. gonorrhoeae*.



Sztaricskai et al. have reported the modifications of lincomycin, wherein they synthesized 7(R)-azido-7-deoxylincomycin that had better antibacterial activity than the parent compound [80]. Towards the objective to improve upon the activity, the azido group was transformed to the ureido group. The transformation was brought about by reducing the azide to amine in the presence of triphenylphosphine followed by reaction with heterocyclic secondary amines in the presence of carbon dioxide. The ureido derivative having N-methyl piperazine (**74**) group was found to possess moderate effect (IC_{50} of $6.2 \mu\text{g/mL}$) against *B. fragilis*. This group also reported the chemical modifications of the glycopeptide antibiotic, eremomycin by reacting it with several isocyanates and isothiocyanates [81]. The reaction of chloroethyl isocyanate led to formation of N-(2-chloroethylureido) derivative (**75**) which under the conditions of isolation transformed into the cyclic oxazoline compound (**76**) in an intramolecular reaction. Though this compound show mild activity against various strains of *S. aureus* it was less potent than the

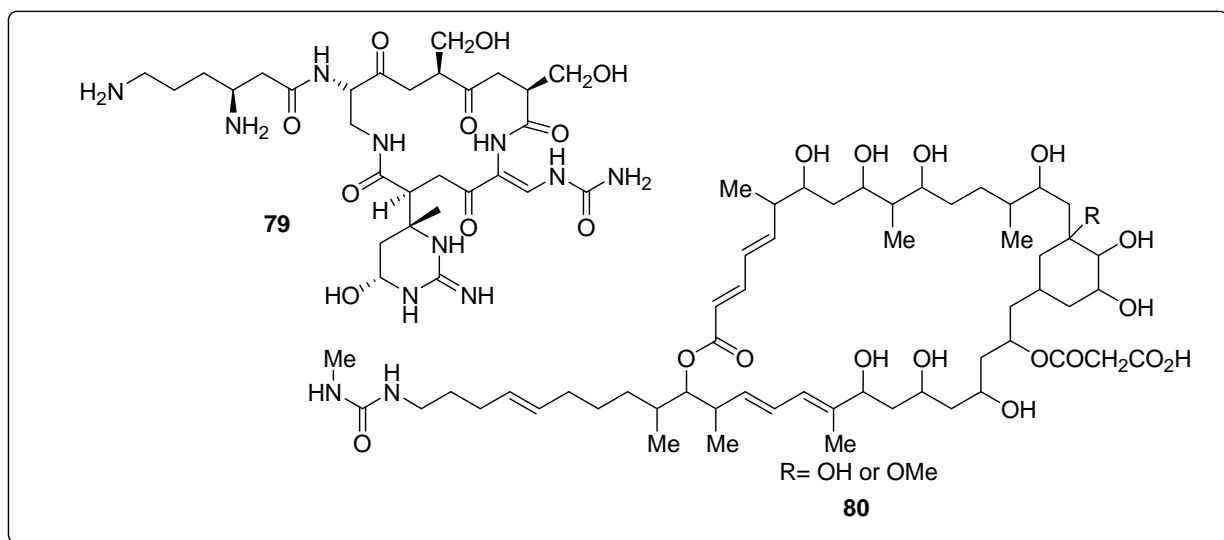


parent eremomycin or vancomycin. The reaction of bisisothiocyanate led to the formation of a mixture of several dimers. However when the reaction was carried out at lower temperature a covalent dimer with ureido-bridge (**77**) was isolated. The rigid structure of this compound however unfavorably influences the binding of the modified antibiotic to the N-acyl-D-Ala-D-Ala unit of peptidoglycan moiety of the bacterial cell wall.

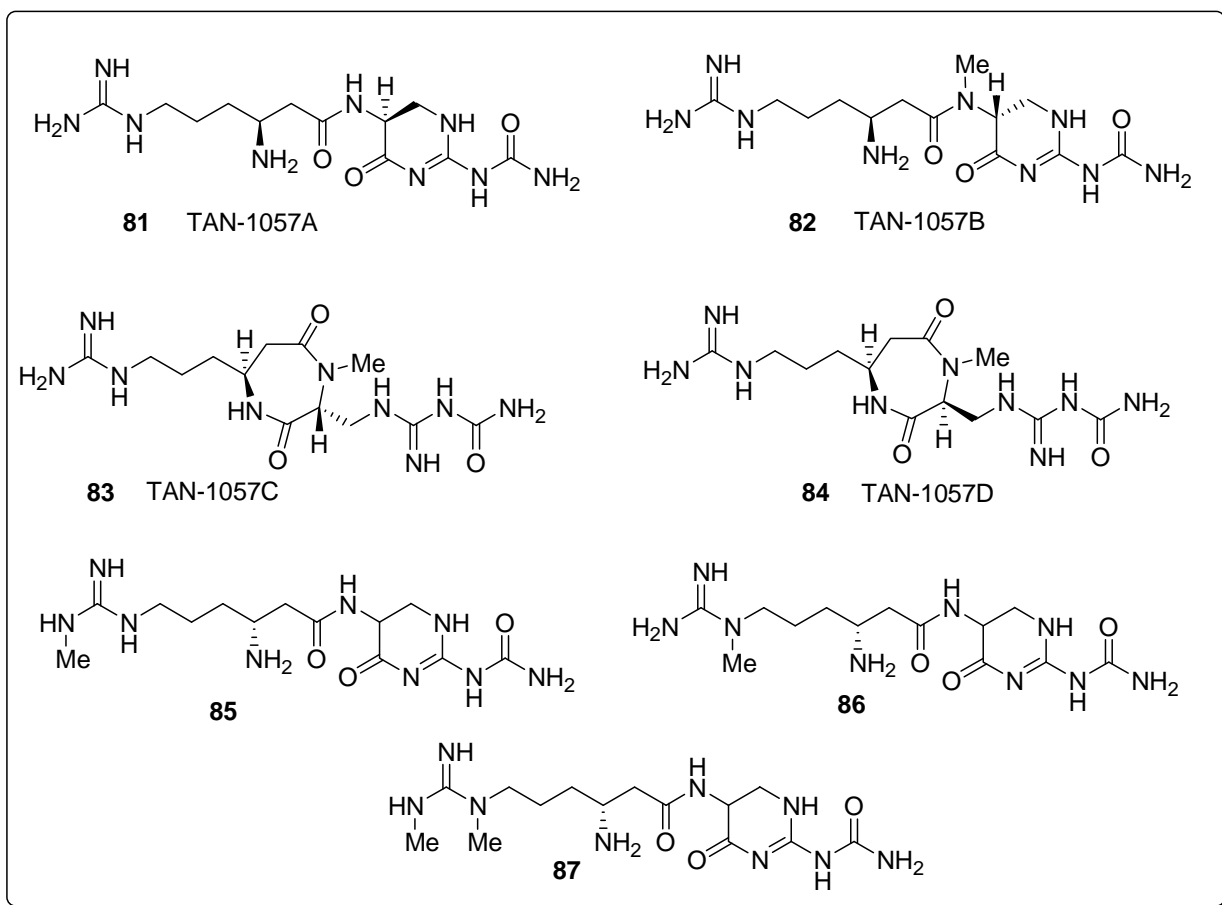
The pradimicins are a family of antibiotics that show antibacterial activity both *in vitro* and *in vivo*. In order to improve the water solubility of this otherwise sparingly soluble compound, Kamachi et al. reported several modifications including the synthesis of ureido derivatives (**78**) [82]. However, these compounds were found to be less active than the parent compound.

Synthetic modifications and antibacterial activity of a ureidohomopentapeptide tuberactomycin (**79**) against *P. multocida*, *E. coli* and MRSA have been reported by Lyssikatos et al [83]. It was observed that the presence of benzyl and phenyl ureas increased the potency of the parent antibiotic.

During the HPLC analysis of the culture filtrate and mycelium of *S. olivaceus* Tu 4018, two urea-containing derivatives (**80**, R=H or OMe) belonging to kanchanamycin group of macrolide antibiotic were detected [84]. Though these compounds were found to have only mild activity against gram positive bacteria they showed distinct activity against *P. fluorescens*.



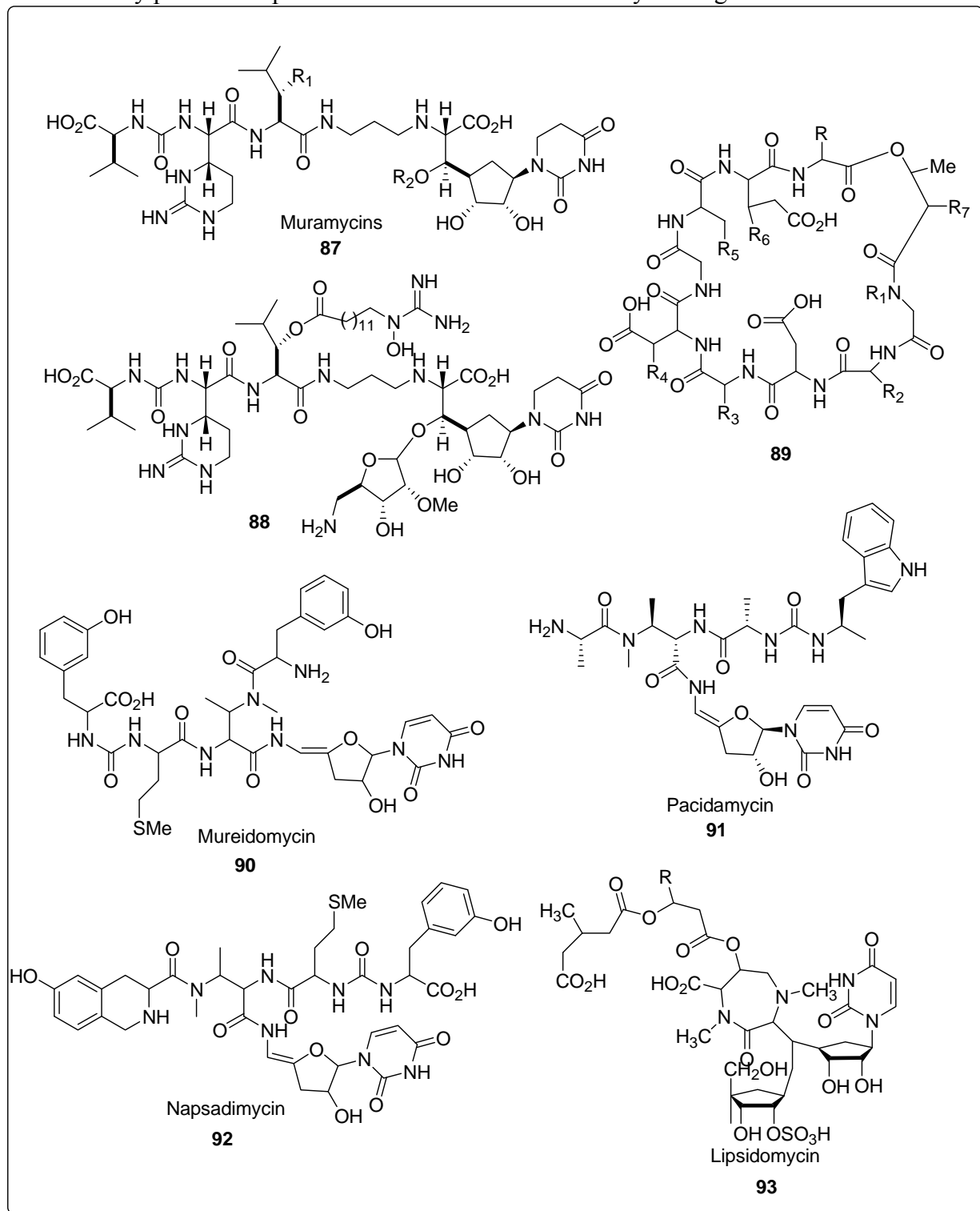
TAN-1057A-D (**81-84**) are dipeptide antibiotic which were isolated from *Flexibacter* sp. PK-74 and PK-176 and have potent activity against MRSA [85]. These compounds were found to display better activity against gram positive bacteria than gram negative bacteria. The TAN-1057-A and D which have the S-configuration in the heterocyclic portion of the molecule were more active than TAN-1057-B and -C which possess R-configuration. TAN-1057A has been found to exhibit potent activity against several MRSA strains and was found to be very similar to vancomycin. The activity of TAN-1057 was affected by the change in the pH of the assay medium. The Tan-1057 has 10 times stronger activity at pH 9 than at pH 7 and the activity against *S. aureus* was superior to those of imipenem and vancomycin. Though the effect of TAN-1057 on cell wall biosynthesis is unknown, but it is believed that the drug interferes with the protein biosynthesis after the formation of aminoacyl-tRNA. Two independent research



groups have achieved the total synthesis of this unique peptide antibiotic [86-87]. In order to further optimize the antibacterial activity of TAN-1057 A and B modifications have been carried out [88]. The study was aimed at developing the chemical analogues of Tan-1057 which are better tolerated and display broader antibacterial activity against gram positive bacteria including *Enterococci* and *Pneumococci*. It was observed that the introduction of a methyl group at the terminal position (**85**) led to enhancement of activity but a larger group such as ethyl or isopropyl decreased the activity. The replacement of the guanidine functionality with amidine group did not have much effect on the activity. In contrast the compound (**86**) with a methyl group on the proximal nitrogen was found to be having better activity than the natural product. It was reported that, in comparison to the natural product, this compound displayed a drastic increase in the *in vitro* potency against *S. pneumoniae*. Further, in the *in vivo* assay using a murine *S. aureus* an excellent $ED_{100} \leq 0.5$ mg/kg was observed, underlining high antibacterial activity. However, presence of methyl group (**87**) on both the nitrogen was not useful.

Muramycins (**88**), a family of nucleoside-lipopeptide antibiotics in its unique core structure incorporates urea. These are cell wall biosynthesis inhibitors with *in vitro* and *in vivo* efficacy. They have been reported to be active against the gram positive bacteria and permeable *E. coli*. They inhibit *MraY*, an enzyme that links UDP-MurNAc-pentapeptide to the C_{55} lipid carrier during bacterial cell wall biosynthesis. Recently, several muramycins analogs have been isolated from a *Streptomyces spp.* out of which the most active ureide was **89** [89]. The closely related uridyl peptides isolated from *Streptomyces spp.* extend to mureidomycins (**90**) [90], pacidamycins (**91**) [91], napsamycins (**92**) [92], lipsidomycins (**93**) [93] which are potent

antibacterial agents. This class of compounds reportedly inhibits the bacterial translocase, an enzyme that play critical role in cell wall synthesis. In order to obtain a compound having better activity profile compared to these standard natural uridyl analogs several modifications



have been reported [94-96]. The preparation of another unique depsipeptide containing a urea moiety (**94**) in the side chain as antibacterial agent was patented by Finn et al. [97]. This ureide was found to have MIC and ED₅₀ values < 1 µg/mL against *S. aureus*.

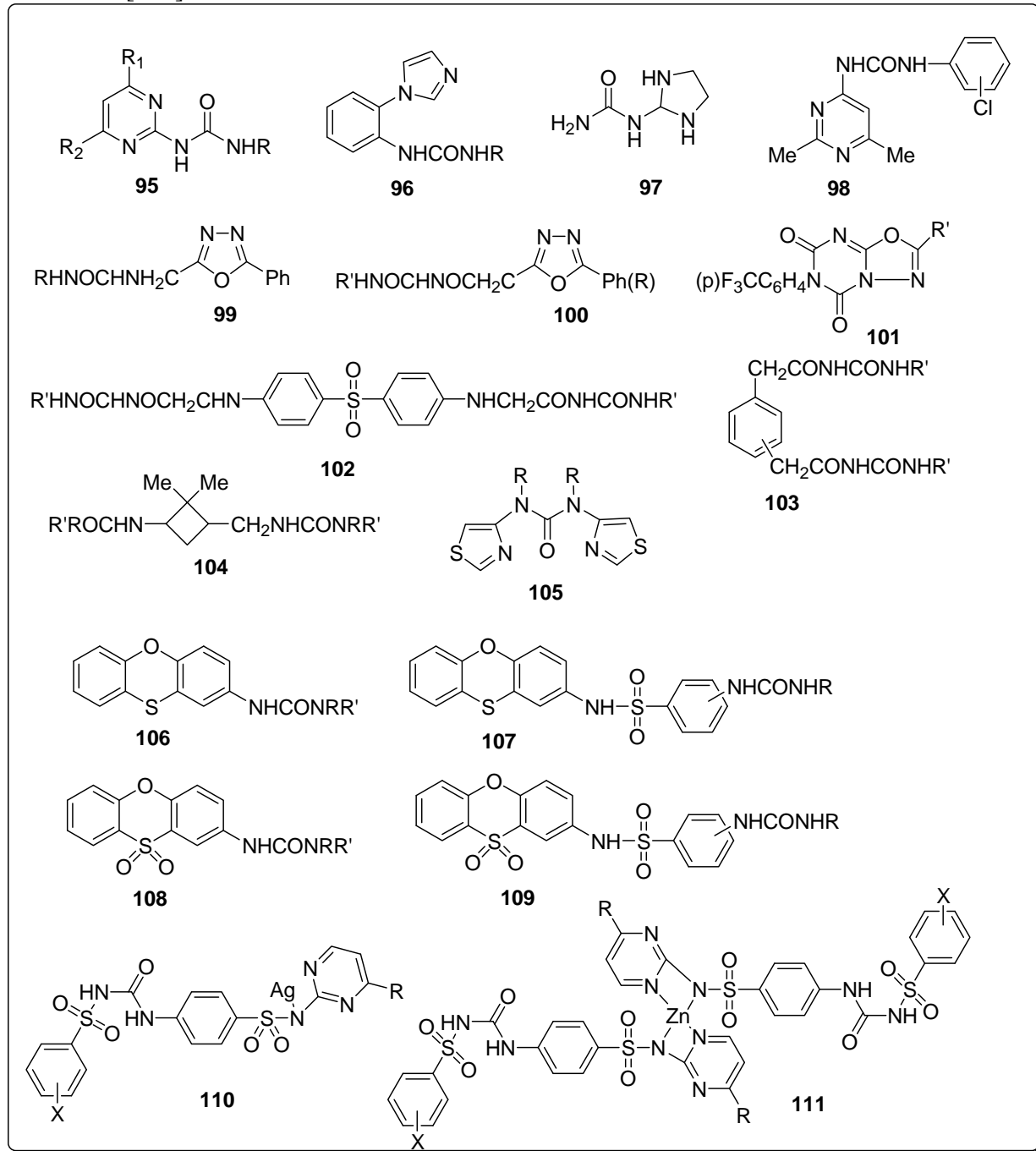
Arg-gingipain (Rgp) is a major cysteine proteinase produced by the oral bacterium *P. gingivalis*, which is a major pathogen of advanced periodontal diseases. This enzyme is important for the bacterium both to exhibit its virulence and to survive in periodontal pockets. In order to provide new therapeutic approach to periodontal diseases, Kadowaki and coworkers reported the development of Rgp inhibitors [98]. Initially they isolated and purified a novel and potent inhibitor of Rgp from the culture supernatant of *Streptomyces* species strain FA-70, now designated as FA-70C1. This compound was found to be an antipain analog composed of phenylalanyl-ureido-citrullinyl-valinyl-cycloarginal. The K_i value was calculated to be 4.5x10⁻⁹ M when benzyloxycarbonyl-phenylalanyl-arginine-4-methyl-coumaryl-7-amide was used as a substrate. This compound also inhibited cathepsins B, L, and H, though their K_i values were much higher than that of Rgp. FA-70C1 had little or no inhibitory activity on Lys-gingipain, another cysteine proteinase of *P. gingivalis*. The Rgp-induced degradation of various human proteins was completely blocked by this inhibitor. Disruption of both the bactericidal activity of polymorphonuclear leukocytes and the viability of human fibroblasts and umbilical vein endothelial cells induced by the culture supernatant of *P. gingivalis* was suppressed by the inhibitor in a dose-dependent manner. The enhancement of vascular permeability induced by *in vivo* administration of the culture supernatant of *P. gingivalis* was strongly inhibited by the inhibitor. Furthermore, the growth of *P. gingivalis* was suppressed by FA-70C1 in a dose-dependent manner.

Antifungal Activity

The urea as such forms one of the ingredients of several topical antifungal ointments beside the usual antifungal agent [99]. Urea is used in the ratio of 10-40% in these applications. It is documented that the use of urea potentiates the antifungal activity of imidazole derivatives present in these preparations [100]. There have been several reports of array of ureides as antifungal and fungicidal agents both for animal and agriculture use. However, we will not be disclosing compounds which have been documented to show activity against fungal infections prevalent in agriculture. Recently an excellent detailed review article on antifungals has been published by Kidwai et al [101].

Most of the ureides that have been reported as antifungal agents are derived from heterocycles. It has been reported that the 2-ureidopyrimidine (**95**) prepared by the condensation reaction between the amidine and active methylene compounds possess mild fungicidal activity though no data has been provided [102]. The ureido derivative (**96**) of imidazole obtained by the addition reaction of substituted isocyanates with 1-(2-aminophenylimidazole) were patented for their use as antifungals [103]. Imidazolidinylurea (**97**) compositions containing pyrithione and (or) pyrithione derivatives have synergistic antimicrobial activity and can be used in cosmetic, pharmaceutical, and food products have also been patented [104]. It has been reported that the imidazolidinylurea-Na pyrithione mixture (0.3 + 0.005%) completely inhibited the growth of *C. albicans*. The 2-chlorophenyl and 3-chlorophenyl pyrimidinylureas (**98**) prepared by the treatment of 6-amino-2,4-dimethylpyrimidine with substituted isocyanates were reported to possess mild fungicidal activity [105]. The urea derivatives of oxadiazoles (**99-100**) obtained by the reaction between acid chloride of oxadiazole acetic acid and urea have been found to display mild activity in their evaluation as antifungal agents [106-107]. The fungitoxicity

of 1,3,4-oxadiazolo[3,2-a]-s-triazine-5,7-diones (**101**) was also reported by Yadav and coworkers [108].



Parekh et al. also reported the fungicidal evaluation of *p,p'*-bis(*N*-aryluroido-carbonylmethylamino)diphenylsulfones (**102**) which were prepared by amidation of acid chlorides of sulphonyl derivative with substituted urea followed by treatment with thionyl chloride [109]. Some of the ureides of benzenediacyc acids (**103**) prepared by the reaction between urea and benzenediacyc dichloride isomers have been reported to show moderate fungicidal activity [110]. Avotins reported the synthesis of 2,2-Dimethyl-3-[*N'*-

alkyl(aryl)ureido]-1-[[N'-alkyl(aryl)ureido]methyl]cyclobutanes (**104**) which were evaluated for several bioactivities including fungicidal but the detail of their results are unknown [111].

The research group of Supuran et al. has reported the evaluation of several ureido derivatives for antifungal activity. The antifungal activity of alkyl ureido derivatives of 2,2'-diamino-4,4'-dithiazole (**105**) which were prepared through isocyanate method show good biological activity against *A. niger* and *C. albicans* but were less potent than the standard itaconazole used in the bioassay [112]. The mechanism of action of these compounds was suggested to involve inhibition of ergosterol biosynthesis and interaction with lanosterol-14- α -demethylase. These authors also reported antifungal activity of similar analogs of 2-aminophenoxathin (**106-107**) [113]. These compounds had comparable activities to ketoconazole and itraconazole against *Aspergilli* but were found to be much less effective against *Candida spp.* In continuation, ureides of 2-aminophenoxathiin-10,10-dioxide (**108-109**) were also prepared and evaluated for antifungal activity against *Aspergillus* and *Candida spp.* [114]. These compounds were found to be equipotent to the standard ketoconazole with MICs in the range of 0.3-0.5 $\mu\text{g/mL}$.

The significant antifungal activity of the silver salt of sulfadiazine is attributed to the inhibition of phosphomannose isomerase, a zinc containing enzyme involved in the biosynthesis of the yeast cell wall. This zinc enzyme has a specific binding for Ag(I) ions which is important for its inhibition by the sulfadiazine silver salt. This rational prompted Supuran et al. to carry out the synthesis of sulfonylureido derivatives of sulfadiazine and sulfamerazine (**110**), including their silver and zinc complexes (**111**) [115]. The compounds were readily synthesized by reactions of sulfadiazine and sulfamerazine with isocyanates followed by metal complex formation. Some of these derivatives exhibited antifungal activity in the micromolar range against *A. flavus*, *A. niger* and *C. albicans*. The complexes of silver showed better activity as compared to the zinc complexes and the halogeno-substituted ligands led to more active antifungal complexes as compared to the phenyl- or tosyl-ureido derivatives, but these compounds were less active than the standard antifungal ketoconazole. Nevertheless it was claimed that the antifungal activity was better than silver sulfadiazine, a known pharmacological agent. As a result of experiments directed toward the elucidation of mechanism of action of these antifungals, it was proposed that similar to many other silver derivatives, these compounds might poison some components of the key respiratory enzymes in the fungal electron system or through interaction with phosphomannose isomerase present in the pathogenic species.

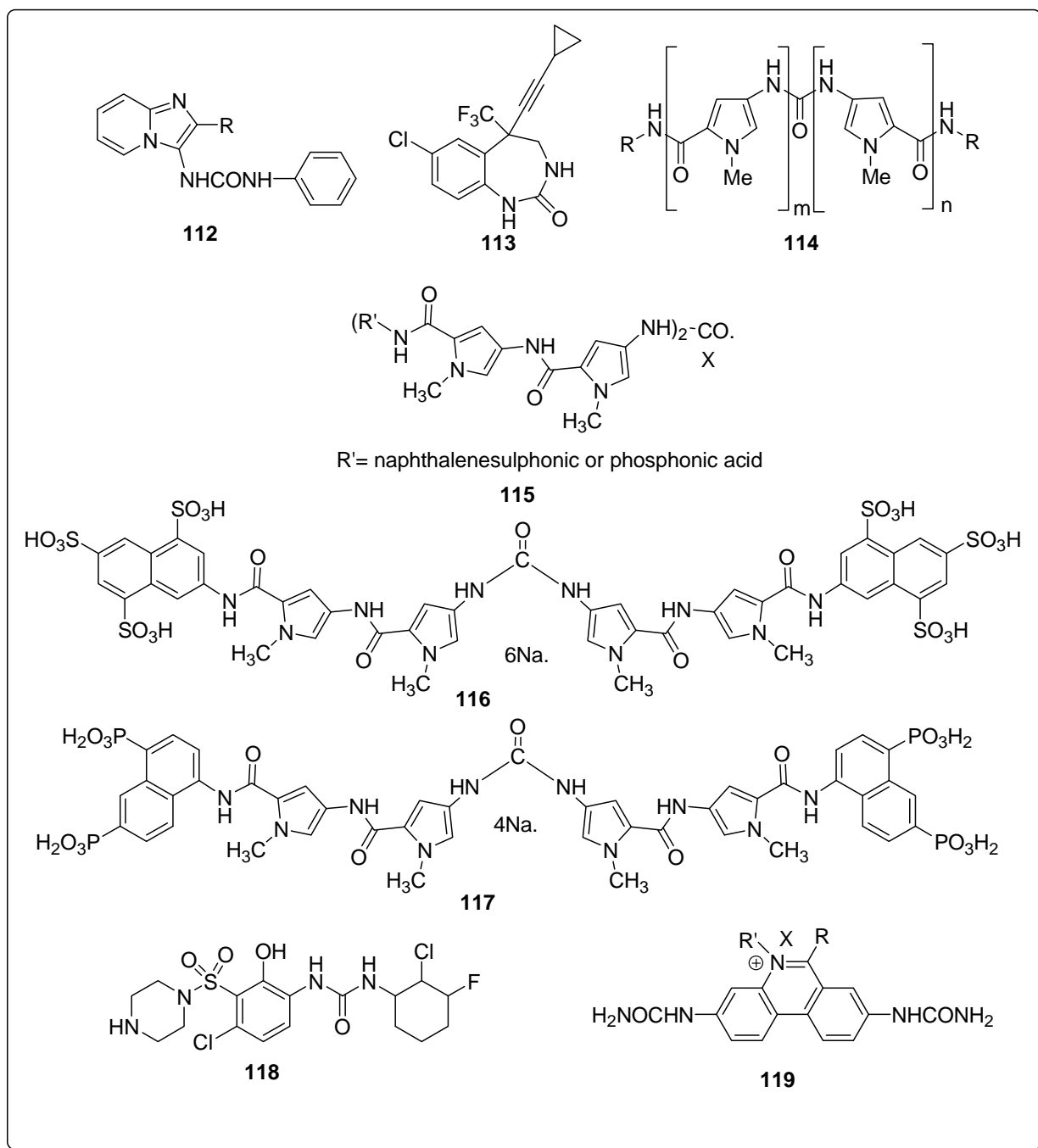
Antiviral Activity

An array of ureides including several peptidomimetics has been reported to display potent antiviral activity including anti-HIV activity. The anti-HIV agents comprises of the nucleosidic reverse transcriptase inhibitors, the HIV-protease inhibitors and the NNRTIs (non-nucleosidic reverse transcriptase inhibitors). Despite several NNRTIs (nevirapine, delavirdine, efavirenz) have been introduced in the market, currently the development of NNRTIs is of high priority as it is one of the most significant enzyme required for virus replication. Since the discovery of the anti-HIV activity of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymidine and tetrahydroimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one and thione as the first NNRTIs, numerous additional compounds have been reported as NNRTIs. Corbett in his review article published recently covered the literature of publications and patents between 1998 and 2001 and cited all peer review articles published on the subject till date [116]. The structural studies of several NNRTIs have shown that these derivatives contain a central hydrophilic part and two hydrophobic moieties, generally an aromatic cycle in a butterfly-like conformation [117]. Significantly, most of these compounds contain an amide, thioamide, urea or thiourea function

in their structure [118]. Based on these considerations, Guieffier and coworkers designed the synthesis of ureidoimidazo[1,2-*a*]pyridine derivatives (**112**) for anti-HIV activity [119]. In order to understand the conformational orientation of the molecule, the crystal structure of these compounds was studied. The bioevaluation against large number of viruses including several HIV strains did not yield the desired results as most of the compounds were inactive, though the ureido derivatives displayed mild activity against HCMV (Human Cytomegalovirus).

Rodgers and Cocuzza from DuPont filed patent for 1,3-benzodiazepin-2-ones and 1,3-benzoxazepin-2-ones (**113**) useful as HIV reverse transcriptase inhibitors [120]. They claimed the treatment of HIV infection by coadministration of these compounds with at least one of the HIV-reverse transcriptase inhibitor and/or HIV protease inhibitor. Earlier Mongelli et al. have disclosed the anti-HIV activity of the poly ureido derivatives of pyrrole (**114**) [121].

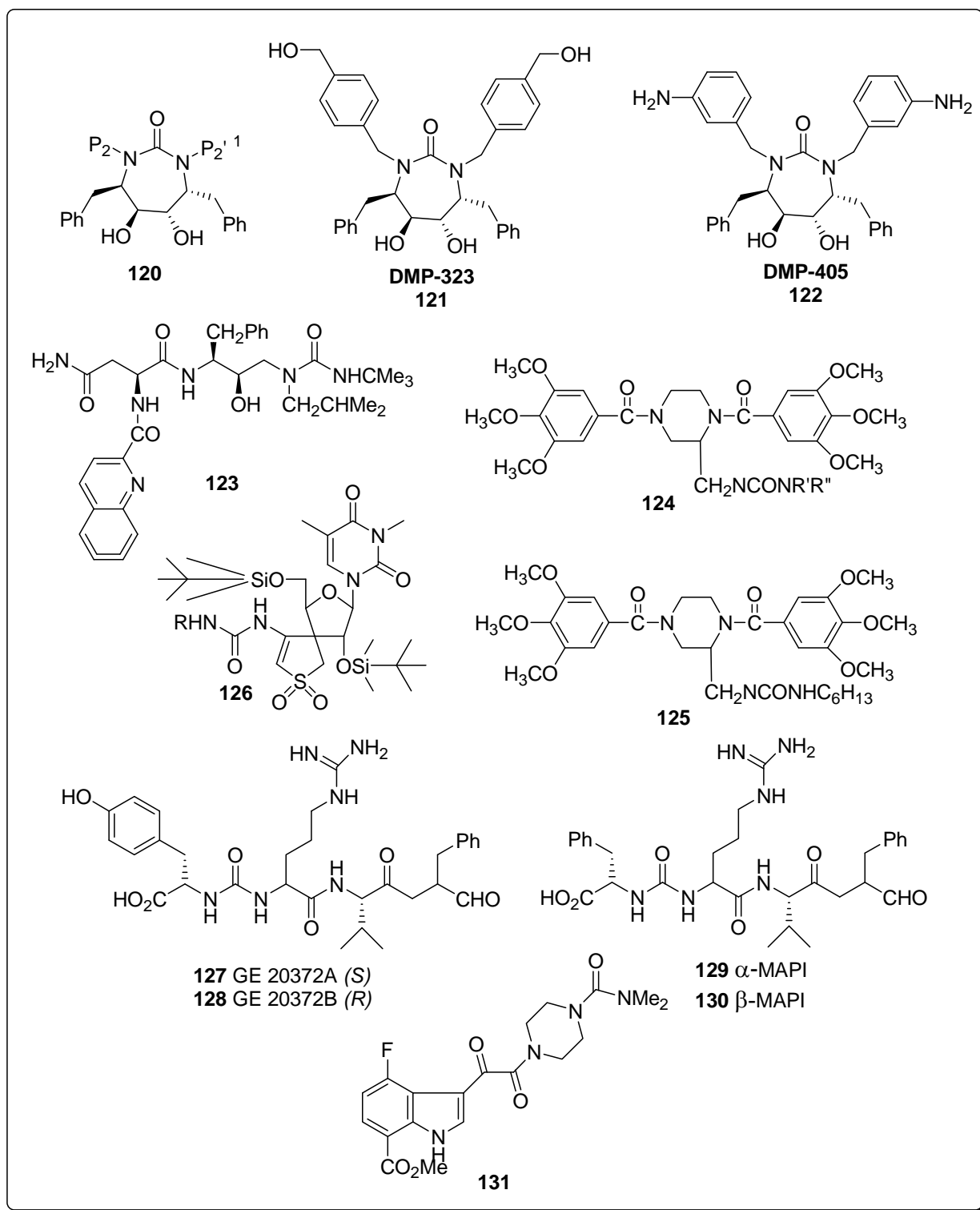
Clanton and coworkers disclosed the biological activity of a series of novel distamycin-related monomeric or dimeric ureido structural classes incorporating the bisamido-N-methylpyrrole-naphthalene-sulfonic acid group, with differences in the number and position of the sulfonic acids on the naphthalene rings [122]. Several compounds were highly potent inhibitors of HIV virus-induced cell killing and viral replication of a wide variety of laboratory isolates, as well as a monocytotropic virus and a clinical isolate in human peripheral blood lymphocytes. These compounds were structurally related to the non-toxic minor groove DNA binder of distamycin and contained aromatic phosphonic acid group which made them different from other sulfonic acid containing compounds reported to be potent inhibitors of the HIV. It was shown that many of the polyanionic sulfonated compounds would bind to serum proteins and that mere changes in the position of the sulfonic acid moieties would alter both protein binding and antiviral activity. In most cases, the antiviral activity of these compounds was attributed to the inhibition of binding/fusion. The most commonly studied compounds, the naphthalenesulfonic acids (**115**), were required to be in bis formation (**116-117**) to retain antiviral activity, although the naphthalene subunit did display anti reverse transcriptase activity. Later the design and synthesis of similar analogs of distamycin that blocks the HIV-1 cell fusion through affecting the specific chemokine receptors was also reported by Howards et al [123]. The compound 2,2'[[4,4'-[[aminocarbonyl] amino]bis[N,4'-di[pyrrole-2-carboxamide-1,1'-dimethyl]]-6,8-naphthalenedisulfonic acid] hexasodium salt (NSC 651016), was shown to inhibit syncytia formation and cell fusion which was not due to interference with binding of HIV-1. Recently patent on the utility of diarylurea derivatives, particularly N-[2-hydroxy-3-(1-piperazinyl-sulfonyl) phenyl]-N'-(halophenyl)ureas (**118**) in the chemokine dependent disease such as HIV has also been filed [124]. Another patent describing the synthesis and use of the phenanthridine derivatives including the ureido analog (**119**) as anti-HIV agent has been filed very recently [125]. In the *in vitro* system, this compound showed the binding affinity to DNA with K_d of 106, μM , IC_{50} of $>1/0 \mu\text{M}$ $\mu\text{g/mL}$ against HIV-1 rev response element, IC_{50} of 15 μM against HIV-1, and exhibited no toxicity against HeLa cells at 10 μM . 126.



Beside NNRT, the other most studied enzymes for the development of anti-HIV agents are the proteases. The advantage with the proteases is that they can be crystallized and thus can be utilized for structure based drug design. One of the most potent and studied class of molecules that show inhibition of HIV proteases are the cyclic ureas (**120**). Several crystal structures of cyclic urea derivatives complexed with HIV-1 protease are available in the PDB (protein data bank). Like NNRTIs, there have been number of excellent review articles which have been published and explicitly describe these compounds in details. Two of the ureides DMP-323 (**121**) and DMP-405 (**122**) were considered as potential drug candidates only to be discontinued due to high blood level variability in humans (DMP-323) [126] and disappointing antiviral potency in the presence of plasma proteins (DMP-405) [127]. Towards the objective to

understand the interactions of this class of molecules with the proteases more publications adopting the molecular modeling approaches have appeared recently. Detailed QSAR approaches for these molecules have been discussed in the review article by Hansch et al [128]. Debnath studied detailed 3-D QSAR on cyclic urea derivatives using COMFA analysis [129]. The substructural molecular fragment method was applied by Solovev and Varnek in order to model the anti-HIV activity of these cyclic ureas [130]. More recently, Parish et al. disclosed that the rigid docking experiments with the proteases indicated that inhibitors with higher binding affinities ie in RSSR, RSRR or RRSR conformations are more precisely oriented for optimal interactions [131]. More recently, Miertus et al reported the design of a small focused virtual library of nonsymmetrically substituted cyclic urea inhibitors of the proteases employing computer-assisted combinatorial chemistry methods [132]. Their design was based on X-ray structure of the protease-inhibitor complex PR-XV-638 as the receptor model. They reported that the nonsymmetrical compounds with decreased peptidic character inhibited the proteases with comparable inhibition potencies as their C2-pseudosymmetric counterparts and possess superior pharmacokinetic properties. N-(3-hydroxy-1-phenyl-4-ureido-2-butyl)asparaginamides (**123**) and analogs which were prepared using isocyanates were patented as retroviral protease inhibitors [133]. It has been described that compound **123** had IC₅₀ of 7 nM against HIV protease *in vit*. It is documented that neurotoxicity induced by HIV-1-infected macrophages can be prevented by PAF-acetylhydrolase, the main enzyme responsible of PAF catabolism [134]. Based on this rational Heyman et al. discovered the antiviral activity in the piperazine derivatives which were originally prepared as PAF antagonists [135]. In their objective to enhance the antiviral activity *ro.* of these compounds, several ureido analogs of the biologically active piperazines (**124**) were designed and reported recently [136]. These compounds showed potent response for anti-HIV activity and were mildly active as PAF antagonist. The significant anti-HIV activity of these compounds was further increased by placing a lipophilic group on the urea pharmacophore (**125**).

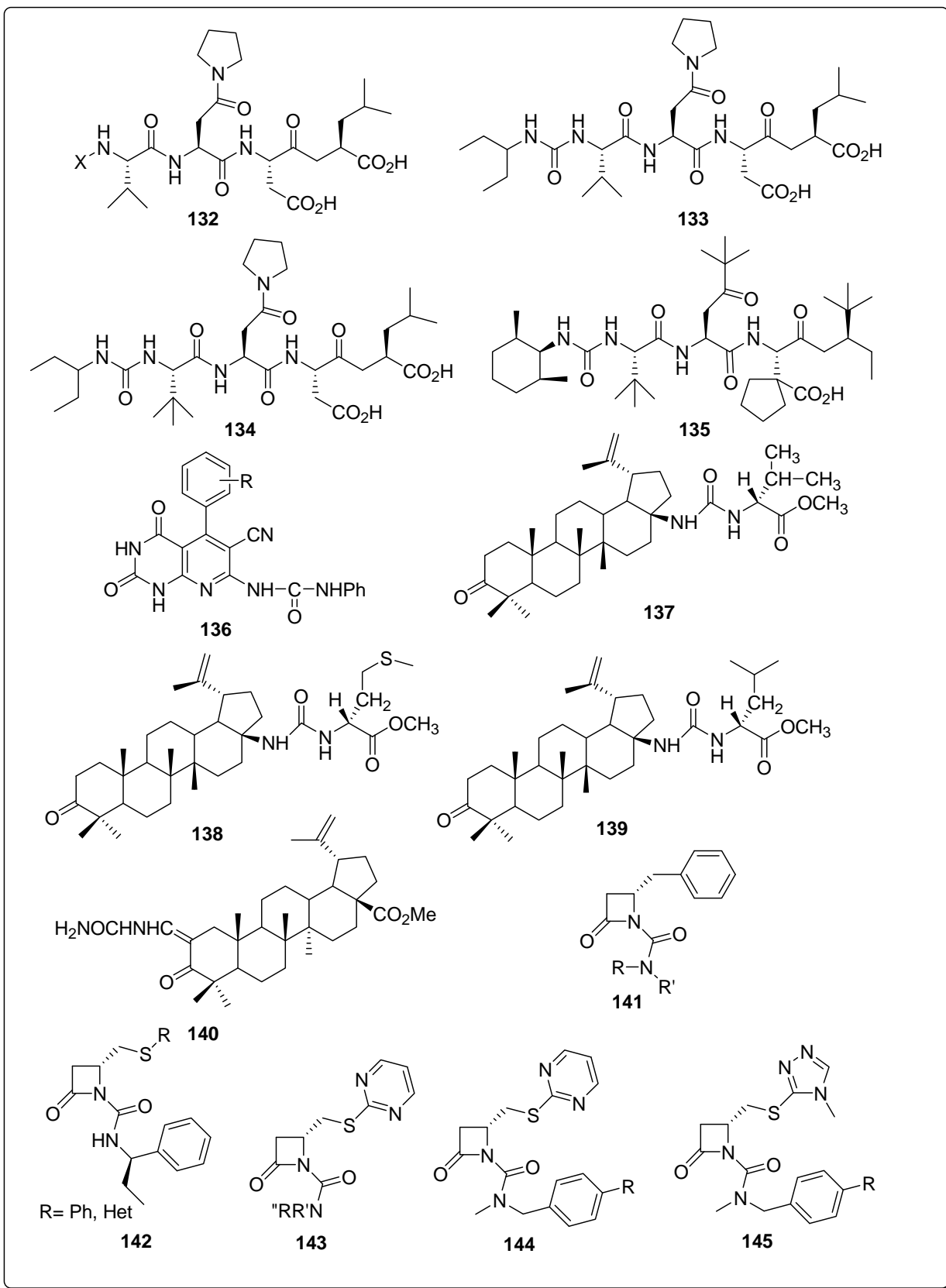
More recently, the design and synthesis of new analogs of [2',5'-bis-*O*-(*tert*-butyldimethylsilyl)- β -D-ribofuranosyl] -3'-spiro-5''-(4''-amino-1'',2''-oxathiole-2'',2''-dioxide) (TSAO) (**126**) substituted at the 4''-amino group of the spiro moiety including the ureido derivatives have been reported [137]. All ureides described in this report were obtained by the reaction of substituted isocyanates. However, it was found that most of these compounds do not elicit the desired anti-HIV effect though some of these derivatives showed good biological response against HCMV at subtoxicity level.



Two closely related urea containing tetrapeptide GE 20372 A and B (**127-128**) and (S)- α - and (R)- β -MAPI (microbial alkaline phosphatase inhibitor) (**129-130**), which have been isolated from a culture broth of *Streptomyces spp.* displayed significant activity against HIV [138-139]. The tyrosine analogs were found to be less potent as compared to MAPI.

More recently, Regueiro-Ren and coworkers have filed patent for the use of indolyl-, azaindolyl- and related heterocyclic ureido piperazines (**131**) for treatment of HIV and AIDS [140]. The reaction of 1-(4-fluoro-7-methoxycarbonyl-1H-indol-3-yl)oxoacetyl)piperazine hydrochloride with dimethylcarbonyl chloride yielded compound **131**. The prepared compounds were assayed for inhibition against HIV-1 in HeLa cells.

Besides anti-HIV, ureides have been described to elicit antiviral response against several other viruses including HSV (Herpes Simplex virus), HCMV, HCV (Hepatitis C virus) and others. The ureido-based peptidomimetic inhibitors (**132**) which prevented the association of the two subunits of herpes simplex virus ribonucleotide reductase, an enzyme necessary for efficient replication of viral DNA were designed and developed by Moss et al. [141]. The design of these inhibitors was based on the R2 C-terminal sequence Val-Val-Asn-Asp-Leu, which is the most important functionality for binding to R1 of the HSV. Among several substitutions installed at the N-terminus, it was found that an [(ethylpropyl)amino]carbonyl (ureido derivative) (**133**) increased the inhibitors potency by more than 50 fold. Replacing the ethyl propyl group with simple methyl led to the loss of potency by 2800 folds. This led them to suggest that the NH group of compound (**132**) had significant influence on the lipophilic binding interaction between the inhibitor N-terminus and R1, the strength of which could be augmented by the addition of two methyl groups. It was further suggested that the N-terminal NH of this new ureido-based inhibitor series participate in a hydrogen-bonding interaction with R1 replacement of which with a CH₂ lowers the binding potency. The compound (**134**) wherein the valine is replaced with tert-leucine showed improved inhibitor-binding potency. Their result of the detailed SAR of the ureido series demonstrated that the new ureido-based N-terminus is not influenced by the adjacent inhibitor functionality different than other N-terminal groups. In order to provide the bioactive conformation around the tert-leucine and pyrrolidine-modified asparagines residues of such inhibitors, the NMR experiments were carried out. This was further confirmed by correlating the structure of conformationally restricted inhibitors with inhibitor-binding potency. In the effort to develop a compound that is active *in vivo*, these ureido-peptides were further tailored. On the basis of knowledge generated from the previous



work, modifications on the ureido N-terminus were reported. This finally led to the preparation of BILD 1351 (**135**) which had a stereochemically defined (2,6-dimethylcyclohexyl)amino N-terminus, a bis-ketomethylene derivative as a replacement for the pyrrolidine modified asparagine residue, and a (1-ethylneopentyl)-amino C-terminus and was the most potent anti-herpetic agent in the ureido series described by these workers.

New ureido and thioureido analogs of 7-amino-5-aryl-6-cyanopyrido[2,3-*d*]pyrimidine (**136**) were prepared using isocyanate method for anti-HSV activity [142]. However they show only moderate activity. The SAR analysis indicated that the halogen group at the phenyl position increased the potency of the compounds

The ureides of the lupane terpenoid betulonic acid were prepared by converting the acid group to corresponding isocyanate which was then subjected to reaction with several amines [143]. The ureides of betulonic acid, betulonic acid and betulonic acid 3-oxime (**137-139**) were evaluated for anti-Herpes activity out of which the ureides of betulonic acid were the most active compounds. These compounds were also found to display moderate activity against influenza virus. In continuation, the ureides of another lupine terpenoid (**140**) lupeol were also prepared for their evaluated against HSV, influenza virus, and enterovirus ECHO-6 but none of the compound shows any significant activity [144].

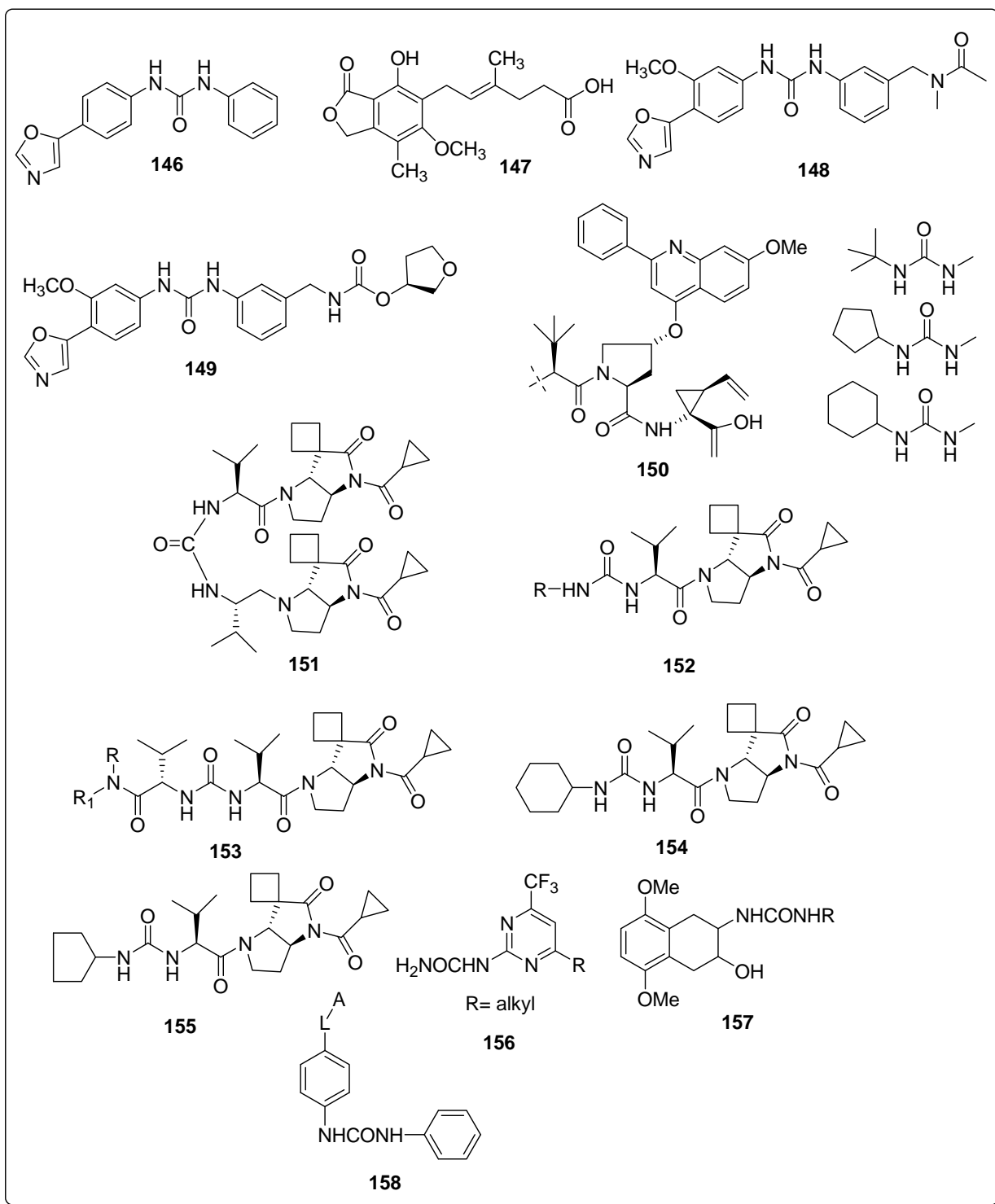
Yoakim and coworkers have described the preparation of novel β -lactams incorporating a carbon side chain at C-4 and a urea function at N-1 (**141**) as inhibitors of HCMV proteases [145]. These compounds were generally prepared by the use of both isocyanate or phenoxycarbamates or carbamoyl chloride methods as required. In the SAR analysis it was disclosed that the substitution at C-3 position of the β -lactam ring increased the enzymatic activity and stability, but a lack of selectivity against other serine proteases were observed. Therefore, most of the studies were performed with azetidinones which did not incorporate substitutions at position-3. The use of trisubstituted and tetrasubstituted urea functionalities gave effective inhibitors of HCMV protease though tetrasubstituted had slight advantage. The benzyl group of the urea moiety was beneficial for bioactivity, particularly when strong electron withdrawing groups were attached to the para position. The preliminary mechanistic investigations carried out by them indicated these compounds to be reversible and competitive inhibitors of HCMV protease and that inhibition involves the formation of acyl-enzyme species. They also reported the synthesis of analogous β -lactam possessing a heterocyclic thiomethyl side chain at C-4 and urea function at N-1 (**142-145**) [146]. The urea derivatives of these compounds were synthesized with the aim to improve the stability in the cell culture for good antiviral activity. The SAR for these compounds described by these workers indicates that changes to the heterocycle did not significantly change the inhibitory activity of these compounds in an enzymatic assay, although improvements in solubility and cell culture activity were noted.

A rapid supply of nucleotides to support DNA and RNA synthesis is required by the rapidly growing cells such as virus. The first step dedicated in the de novo synthesis of guanine nucleotides is conversion of inosinate to XMP catalyzed by inosine monophosphate dehydrogenase. The structure of this enzyme was solved by Vertex pharma [147]. An experimental screen of diverse library of commercially available compounds for inhibitors of IMPDH led to identification of phenyl oxazole (**146**) urea as weak inhibitor. Through the use of computational means (DOCK), the initial inhibitors were built as models into the experimental structure of the crystalline complex of IMPDH, IMP and mycophenolic acid (**147**) [148]. The structure-based drug design led to identification of a urea derivative (**148**) with nanomolar

potency. The comparison between the mycophenolic acid and this compound led to identification of the structural requirements for significant activity. It was postulated that the urea moiety forms a network of hydrogen bonds with an aspartyl carboxylate that is not present in the complex with mycophenolic acid. The X-ray guided further modification of the structure to gain potency in a cell-based assay led to identification of merimepodip ((S)-N-3-[3-(3-methoxy-4-oxazol-5-yl-phenyl)ureido]-benzylcarbamic acid tetrahydrofuran-3-yl-ester, VX-497) (**149**), which was advanced into clinical trials for treatment of Hepatitis C infections [149]. It is a potent, reversible, uncompetitive IMPDH inhibitor which was structurally unrelated to other known IMPDH inhibitors. Markland et al. reported the results of their studies that were performed to compare VX-497 and ribavirin in terms of their cytotoxicities and their efficacies against a variety of viruses [150]. They included DNA viruses (hepatitis B virus [HBV], HCMV, and HSV-1) and RNA viruses (respiratory syncytial virus [RSV], parainfluenza-3 virus, bovine viral diarrhea virus, Venezuelan equine encephalomyelitis virus [VEEV], dengue virus, yellow fever virus, coxsackie B3 virus, encephalo-myocarditis virus [EMCV], and influenza A virus). It was found that VX-497 was 17- to 186-fold more potent than ribavirin against HBV, HCMV, RSV, HSV-1, parainfluenza-3 virus, EMCV, and VEEV infections in cultured cells. The therapeutic index of VX-497 was significantly better than that of ribavirin for HBV and HCMV (14- and 39-fold, respectively). Finally, the antiviral effect of VX-497 in combination with IFN- α was compared to that of ribavirin with IFN- α in the EMCV replication system. Both VX-497 and ribavirin demonstrated additivity when coapplied with IFN- α , with VX-497 again being the more potent in this combination. Recently, Malcolm et al. from Schering Corporation filed the patent for the combination therapy for RNA viral infection involving ribavirin and IMPDH inhibitors with the objective to reduce the detrimental side effects of treatment and to enhance the efficacy [151]. A particular embodiment discloses the use of combination of ribavirin, VX-497 and pegylated interferon-alpha-2b.

In a systematic approach to the optimization of substrate-based inhibitors of the Hepatitis C Virus NS3 Protease discovery of potent and specific tripeptide inhibitors have recently been reported [152]. During the preparation of carbamates but during the optimization process ureido derivatives (**150**) were also prepared isocyanate method and evaluated for their activity. It was disclosed that these urea derivatives led to 2-3 fold increase in the potency in the enzymatic assay though this effect was not translated into the cell based assay. Another series of novel pyrrolidine- β -lactams consisting of ureido group (**151**) which were prepared as HCV NS3/4A protease inhibitors has been reported recently [153]. The ureido function in these new of compounds was introduced either through the isocyanate or the chloroformate methods. During one such synthesis a urea derivative (**152**) was obtained as byproduct which displayed high order of activity. In the light of this observation a series of ureides were prepared and evaluated for their protease inhibiting capability. It was observed that though most of the bis valyl urea containing lactams (**153**) show very low order of activity (IC_{50} of 0.3 μ g/mL), but the compounds **154-155** had best overall activity profile of biochemical and cellular potency. The compound **154** was cocrystallized with the HCV protease to study the binding interactions through X-ray.

The antiviral activity of several other ureides is reported though the details have not been disclosed. The antiviral activity of heterocyclic ureides including that of benzothiazole, benzoxazole, benzthiazole and pyrimidyl has been reported [154]. Trifluoromethyl-2-ureidopyrimidines (**156**), prepared by the cyclocondensation of $H_2NCONHC(:NH)NH_2$ with the appropriate fluorinated β -diketones have been evaluated for their antiviral activity [155].



Chalina et al. have reported the synthesis and antiviral activity of 2-hydroxy-5,8-dimethoxy-3-ureido-1,2,3,4-tetrahydronaphthalenes (**157**) through the isocyanate methodology [156]. The N'-ethyl urea derivative was found to be the most active compound of the series. Ernst et al. have recently patented the several benzyl naphthalene analogs including ureido derivatives (**158**) for their antiviral activity [157]. However they have not provided any biological data.

Conclusions

It is evident that the ureides are an important class of compounds that show significant antibacterial and antiviral activity. The documented research efforts outlined herein indicate that introduction of urea pharmacophore in a mildly active anti-infective enhances its biological activity. Since the incidence of bacterial resistance to antibiotics continues to increase at an alarming rate, there is a clinical need not merely for variants within existing classes of antimicrobial agents, but also for entirely new classes of antibiotics. To combat these phenomena, uridyl peptide derivatives provide an attractive starting point for the development of a novel class of antibacterial drugs, in that they share a bacterial cellular target that has yet to be exploited in the clinical context. Additionally, there may be still many unexplored uridyl heterocycles and glycosyl derivatives that may have not been examined for biological activities in these areas. The anti-HIV activity of cyclic ureas is being actively optimized through molecular modeling and combinatorial chemistry in order to achieve a derivative that is orally active and devoid of side effects encountered with this class of molecules. Presently, the earlier discovered ureides such as aminoquiniride, urosulfan, etc may be of academic interest only in but the ongoing research efforts hold considerable promise to yield new ureide moiety containing clinical candidates.

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