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Development of Aminoglycoside Antibiotics by Carbohydrate Chemistry

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Abstract: With the development of glycomics, more and more carbohydrate mimetics were used to investigate the interactions between carbohydrate-proteins, especially in physiological and pathological processes, molecular recognition, signal transduction, cell communication, cell differentiation and developmental events. Recently, because of the drug-resistance of microorganisms and the development of antibiotics, the interactions between carbohydrate mimetics and RNAs are becoming hot issue. Aminoglycosides, one family of important antibiotics, can bind with 30S subunits of rRNA to prevent the normal translations of proteins, inhibit the proteins involving in the drug-resistance. In this review, the latest advances in development and applications of aminoglycosides are summarized and the detailed descriptions on the SAR study (Structure-activity relationship) of aminoglycoside derivatives are discussed.

Keywords: Carbohydrate mimetic, aminoglycoside antibiotics, rRNA, structure-activity relationship, enzymatic modification, inhibitor, glycochemistry.

INTRODUCTION

Recently, sugar derivatives have emerged as a challenging research area at the interface of biology and chemistry. In fact, glycomics have been widely used as potential pharmaceuticals for the prevention of infection, the neutralization of toxins, and the immunotherapy of cancer. Therefore, further growth in research on the biological functions of the varied carbohydrate mimetics will be closely tied to the availability of bioactive carbohydrates. Saccharides derivatives are highly diverse in structure and biological functions. They are essential for many fields of research, for example, biochemical studies in glycobiology, as potential drugs directed to enzymes or receptors involved in their function and metabolism, and as advanced materials due to their biocompatibility, structure-forming capacity, and environmentally benign properties [1-5]. In the last few years, both chemical and enzymatic synthesis have experienced notable advances in producing either polysaccharides resembling the natural products or novel polysaccharide mimics for biomedical applications and biomaterials development.

As a kind of carbohydrate mimetics, aminoglycosides which bearing carbohydrate scaffolds are important broad-spectrum antibiotics. The first aminoglycoside antibiotic, streptomycin (Fig. **1**), firstly introduced by Waksman in 1944, was used as an effective agent against *Mycobacterium tuberculosis* [6]. Subsequently, other related compounds such as neomycins, paramomycins, kanamycins, gentamicins [7] and tobramycins, [8] as well as semi-synthetic derivatives like amikamycins, [9] dibekacins, sisomicins and netilmicins [10] were discovered during the 1970s [11]. Because of the oto- and nephro- toxicity and drug-resistance, many groups have put focus on designing new semi-synthetic derivatives over the past decades. The development of novel semisynthetic aminoglycoside antibiotics could be achieved via carbohydrate chemistry [12]. Some new biological applications of these antibiotics have already been discovered. Aminoglycosides as potential antiviral agents were reported recently. The development of new anti-HIV entities is one of the representative areas [13]. In this review, we will outline the latest advances in development and applications of this kind of carbohydrate mimetics and discuss the detailed SAR study (Structure-Activity Relationship) of aminoglycoside derivatives as potential antibiotics.

STRUCTURE OF CLINICALLY USEFUL AMINO-GLYCOSIDES ANTIBIOTICS

Diaminocyclitols from natural products bear the common scaffolds of aminoglycoside antibiotics. Based on the structure of diaminocyclitol, aminoglycoside antibiotics are divided into different families (Fig. **1**). 2-Deoxystreptamine (2-DOS) is the core structure of 1, 3-diaminocyclitols (Fig. **1a**). According to the substitution pattern of the 2-DOS ring, the aminoglycosides can be categorized as 4, 5- and 4, 6-linked antibiotics (Fig. **1b**, **c**). These antibiotics show potent bactericidal activities against Gram-negative bacteria [14]. In addition to the 1, 3-diaminocyclitol derivatives families, the aminoglycosides which own 1, 4-diaminocyclitol scaffolds have also been characterized, as shown in Fig. **1d**. Interestingly, they have significant bactericidal activities against both Gram-positive and Gram-negative bacteria, including many aminoglycoside-resistant ones [14].

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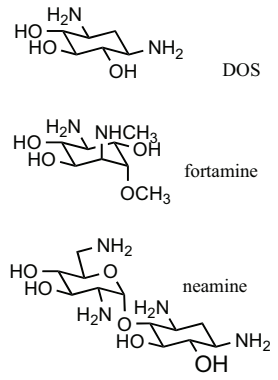
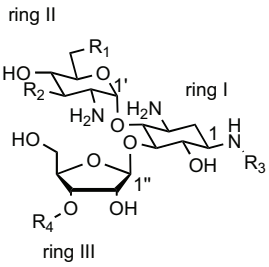


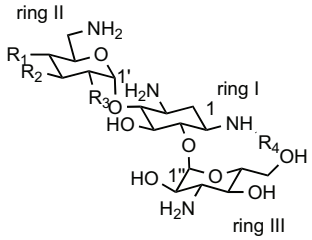
a



	R_1	R_2	R_3	R_4
neomycin:	NH_2	OH	H	DAG[i]
lividomycin:	OH	H	H	a-Man(1, 4)-DAG
paromomycin 1:	OH	OH	H	DAG
butiromycin:	NH_2	OH	AHB[ii]	H
ribostamycin:	NH_2	OH	H	H

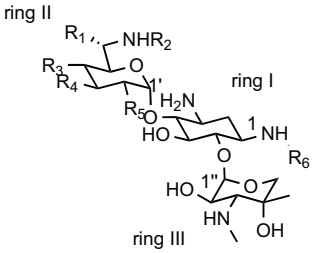
4,5-2- DOS: neomycin class

b



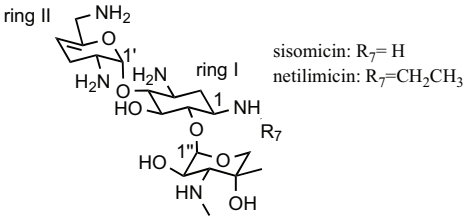
4,6- 2- DOS:kanamycin class

	R_1	R_2	R_3	R_4
kanamycin A:	OH	OH	OH	H
kanamycin B:	OH	OH	NH_2	H
tobramycin:	OH	H	NH_2	H
dibekacin:	H	H	NH_2	H
arbekacin:	H	H	NH_2	AHB
armikacin:	OH	OH	OH	AHB



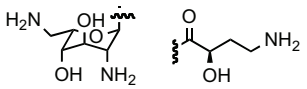
4,6- 2- DOS:gentamicin class

	R_1	R_2	R_3	R_4	R_5	R_6
gentamicin B:	H	H	OH	OH	OH	H
gentamicin C1A:	H	H	H	H	NH_2	H
gentamicin C2:	CH_3	H	H	H	NH_2	H
gentamicin C1:	CH_3	CH_3	H	H	NH_2	H
isepamicin:	H	H	OH	OH	OH	AHB

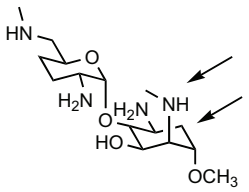


4,6- 2- DOS:gentamicin class

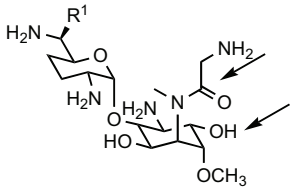
i. DAG: 2,6- diamino- 2,6- dideoxy- b- L- glucopyranosyl
ii. (S)- 4- amino-2- hydroxylbutyryl



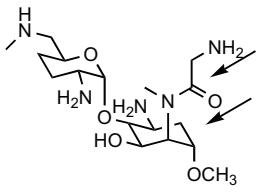
c



sannamycin B



fortimicin A: R_1=Me
fortimicin D: R_1=H



sannamycin A

d

Fig. (1). Structures of clinically useful typical aminoglycosides antibiotics: a. core structures of 2-deoxystreptamine (2-DOS) and neamine; b. 4,5-disubstituted deoxystreptamine aminoglycosides antibiotis; c. 4,6-disubstituted deoxystreptamine aminoglycosides antibiotics; d. structures of 1,4-diaminocyclitol atypical aminoglycosides.

THE MECHANISM OF AMINOGLYCOSIDE ANTIBIOTICS AND DRUG-RESISTANCE

Through a drug-induced process caused by disruption of Mg^{2+} bridges between the lipopolysaccharide molecules, the antibiotics penetrate the outer membranes of Gram-negative bacteria [15] Since aminoglycosides are full of positive charge because of amino groups which are protonated at physiological pH, they show a binding affinity for nucleic acids which are full of negative charge. The primary target of aminoglycosides is 30S rRNA which is the small ribosomal subunits of bacteria. Aminoglycosides binding to 30S rRNA small subunit is accomplished through their interaction with the decoding-site (A-site) of 16S rRNA [16,17] and disruption of the mRNA-decoding fidelity [18,19]. In this way the translation process could be inhibited and disrupted by causing misreading and hindering the translation steps which result in producing abnormal proteins. These aberrant proteins produce membranes with irreversible semi- permeability which increase the passive spread of small molecules resulting in high intracellular drug concentration. This process leads to the loss of the proteins which are important to the survival of microorganism.

Because of the worldwide abuse of antibiotics, microbial resistance has become a rapid and global problem against antibiotics in general, including aminoglycosides. Mutational strains can reduce the intake of drugs by changing the membrane proteins of mutants, increase the efflux of drugs with the help of microorganism's drug transporters and modify the drugs by some modifying-enzymes (Fig. **2**) to make them inactive or decrease the intracellular effective drug concentration. Some strains can also modify the drugs' targets to make the molecular inactive. Enzymatic modification of the aminoglycoside antibiotics is one of the most important mechanisms of resistance. The major enzymes include aminoglycoside phosphotransferases (APH), aminoglycoside nucleotidyl-transferases (ANTs), and acetyltransferases (AAC). Based on the difference of the modification sites of the antibiotics, each kind of enzymes can be divided into several families [20-22].

STRUCTURE-ACTIVITY RELATIONSHIP (SAR)

Comparing natural aminoglycosides with semi-synthetic ones and discovering the sites inactivated by bacterial enzymes are the simple and direct methods to study the structure-activity relationships [23]. According to the mechanisms of molecular action and drug-resistant, the effectiveness of antibiotics is closely related to the amount of charge and the modifying sites (Fig. **2a**, **b**) of the antibiotic molecular. The amount of the charge depends on the number of amino groups. Aminoglycosides with a higher number of amino groups can bind more strongly to RNA than analogs with reduced charged groups [15]. Ring I is also the main target of inactivating bacterial enzymes, and ring III seems to be less sensitive to structural modifications than rings II and I (Fig. **2**). Changing of C-3' or C-4' hydroxyl groups or both can protect the antibiotics from APH and ANT to keep the activity of molecules [23]. Some former reviews have summarized details of the SARs [21, 23, 24].

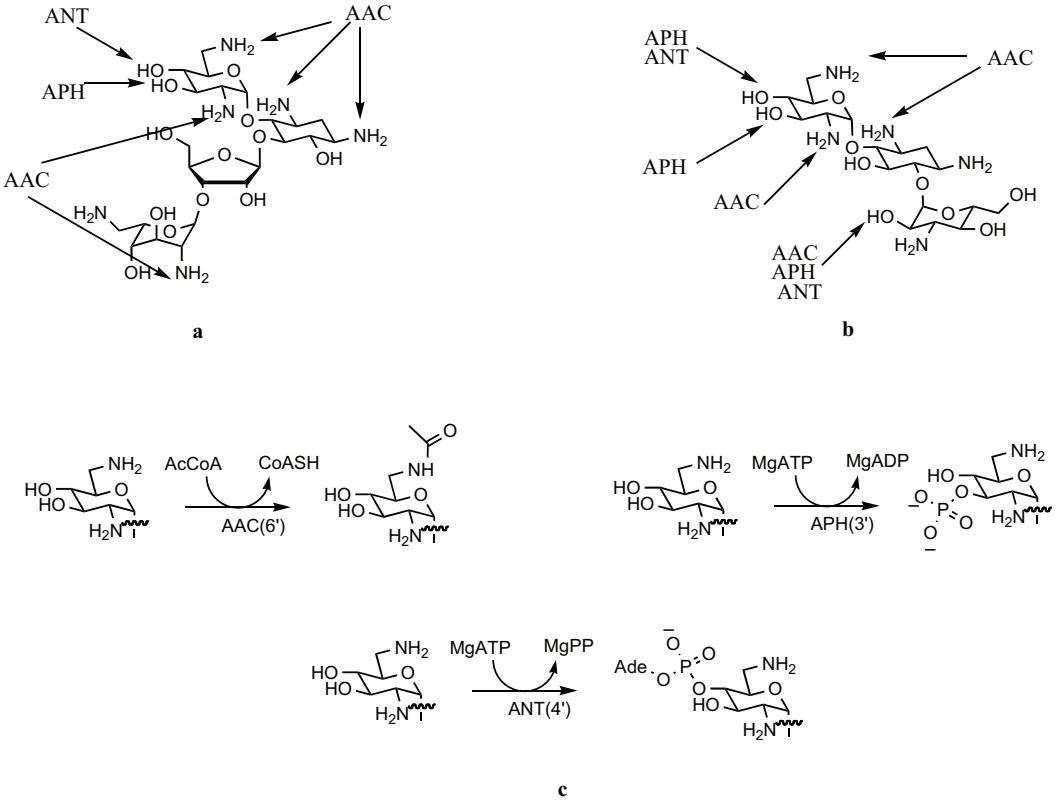


Fig. (2). The modifying enzyme and their mechanism of action a. enzymatic modified sites of neomycin; b. enzymatic modified sites of kanamycin A; c. the action mechanism of modifying enzyme.

Fig. **1** shows some semi-synthetic aminoglucosides with an (S)-4-amino-2- hydroxybutanoyl (AHB) group at the N-1 position of the 2-deoxystreptamine. The added AHB group has been reported to regain antibacterial activity of aminoglycosides by increasing steric interactions toward the aminoglycoside-modifying enzyme [25]. Recently, there are two works focusing on the structural modifications at N-5 and/or O-6 of N-1 AHB neamine derivatives [26, 27]. These reports showed that the attachment of AHB group at N-1 can also revive the antibacterial activity of pyranmycin against resistant bacteria.

DEVELOPMENT DERIVATIVES BASED ON AMINO-GLYCOSIDES' NATURAL SCAFFOLD

Derivatives Modified at the Enzymatic Modified Sites of the Molecular

To keep the activity of the antibiotics molecules in cell, the derivatives of molecular enzymatic modified sites are selected. Fig. **2** shows that neamine (Fig. **1a**) is the main target of inactivating bacterial enzyme, and the studies on aminoglucosides-RNA complexes have revealed the minimal core structure required for RNA base recognition [28, 29]. Some neamine derivatives have been synthesized to study the SAR.

Yan and coworker used N-6'-acylated aminoglycosides (Fig. **4a**) to develop the inhibitors of AAC (6') [30]. However, no activity was observed and they were not the substrates either. The N-6'-acylated group protected the amino from AAC (6') modifying, **7** and **8** (Fig. **4a**) showed weaker antibacterial activity comparing with the parent compound neamine.

C4'-position on ring I of neamine modified derivatives were synthesized to protect the antibiotics molecular from ANT (4'), APH (4') or APH (3'). With the exception of **1**, most synthetic analogues exhibited excellent antibiotic activity against some typical nondrug-resistant bacteria and drug-resistant bacteria that can express aminoglycoside-modifying enzymes [31]. Among these synthetic analogues, compounds **3** and **6** (Fig. **3**) showed remarkable antibiotic activity against drug-resistant bacteria with a nitrogen atom at the end of substituent, and three carbon-carbon bonds between the end nitrogen atom and carbonyl group.

The Inhibitors of the Modifying Enzyme

Although the former method to develop the inhibitors was failed, [30] the aminoglycoside-CoA bisubstrates strategy achieved the goal of developing the inhibitors of AAC (6'). Gao and coworkers reported amide-linked aminoglycoside-CoA bisubstrates as the inhibitors of the modifying enzymes in 2005 at first [32]. Most of these bisubstrates were nanomolar tight-binding competitive inhibitors of AAC (6')-Ii (an important enzyme leading to antibiotic resistance), especially **9**(Ki =76±25nm) and **10**(Ki =43±23 nm). The high potency of these bisubstrate inhibitors and the crystal structure of complexes suggest that they are good mimics of the enzymatic reaction intermediates. Then they synthesized a second generation of AAC (6') bisubstrates inhibitors containing a sulfonamide, sulfoxide and sulfone, and expected to find better mimics of the intermediate (Fig. **4b**) [32]. However except of **12**(Ki =60±30 nm) and **15**(Ki =90±60 nm), other canditates showed worse activity

Cationic Amphiphile Aminoglycoside Antibiotics Derivetives

Cationic amphiphiles containing positively charged amino always show broad-spectrum antibacterial activity. These compounds can change the permeability of cytoplasmic membrane, resulting in the extravasation of the cytoplasm material, which impede the metabolic of the cell to kill the bacterial. The widely-used Bromo Geramine is one of these antibiotics. Dodine, benzalkonium chlorides, sphingosine, and chlorohexidine are currently used in commercial antiseptics and disinfectants. Amphiphilic aminoglycoside antibiotics could combine the mechanisms of aminoglycoside and amphiphiles antibiotics or own some new mechanisms of action.

In 2008 and 2009, amphiphilic aminoglycosides were achieved by modifying C5"-hydroxyl group in neomycin B via attachment of hydrophobic substituents including lipid chains, aromatic residues, hydrophobic amino acids and steroids (Fig. **5a**) [33, 34, 35].

Neomycin lipid (Fig. **6a**, **15**-**25**) conjugates depends on the length and nature of the lipid moiety. Shorter aliphatic chains (**25**) or aromatic chains (**24**) resulted in reduced activity. Neomycin C16- and C20-conjugates are particularly active against Gram (+) MDR (Methicillin drug-resistant)

strains including MRSA (Methicillin-resistant *Staphylococcus aureus*) and MRSE (methicillin-resistant *S. epidermidis*). A remarkable 32-fold enhancement against MRSA is observed in compounds **21** and **23** (MIC 8 μg/mL) comparing with neomycin (MIC 256 μg/mL). The result demonstrates that conjugations of neomycin with C16- or C20-lipids induce optimal antibacterial activity against MRSA while shorter lipids (C6- or C12-) result in reduced antibacterial activity comparing with neomycin. For instance, compound **16**

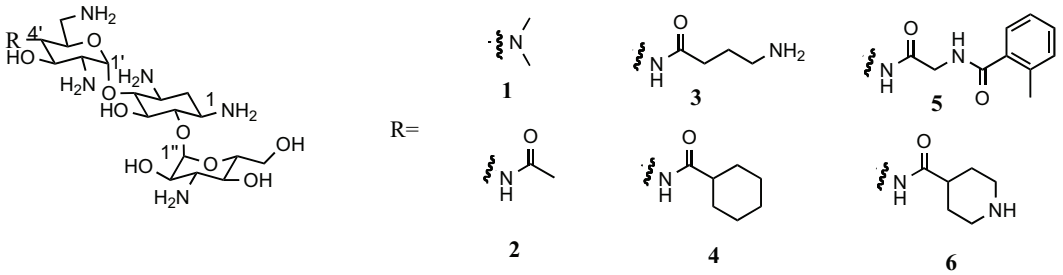


Fig. (3). C4'-position on ring I of neamine modified derivatives.

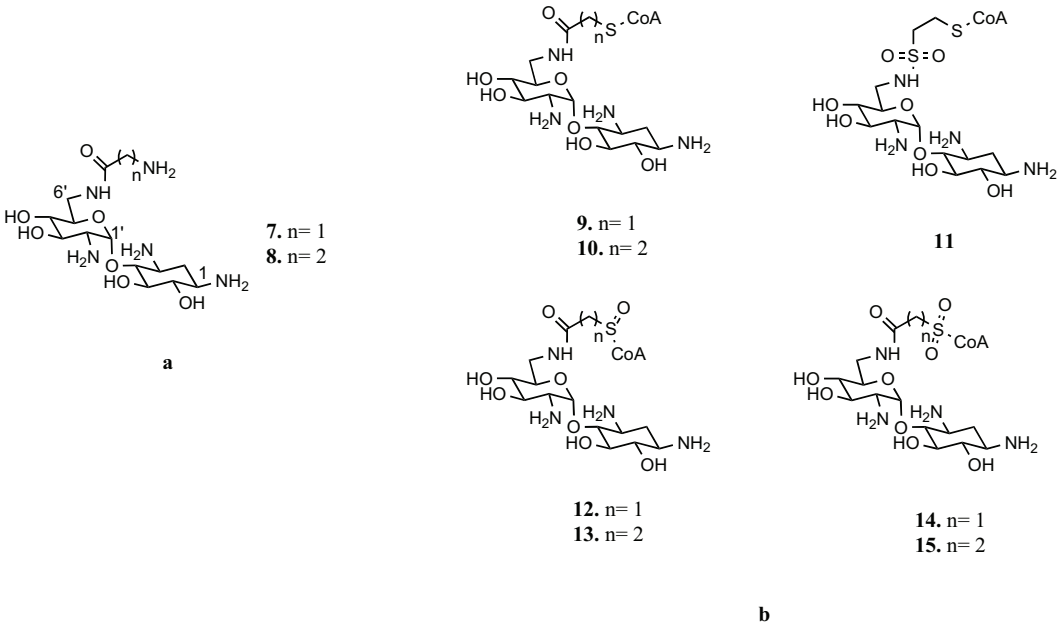


Fig. (4). N-6'-acylated aminoglycoside derivatives.

bearing a C6-lipid chain shows stronger activity against G (-) E. *coli*. and gentamicin-resistant E. *coli* than the C16- or C20-lipid conjugates. In the case of P. *aeruginosa*, C20-lipid conjugate shows optimal antimicrobial activity. None of the compounds show antifungal activity against Candida albicans in growth inhibition assays with MIC > 512 μg/mL [33].

Derivatives with a 1, 2, 3-triazole linkage (Fig. **5b**) manifest modest antibacterial activities comparing with neomycin B, and **42** and **45** are the most active derivatives among these compounds. Most of the derivatives bearing amide-based linkages (Fig. **6a 26-39**) were less active than the parent neomycin B. The derivatives with amino acids groups manifest similar levels of antibacterial activity with no particular difference between D- and L-amino acids. On average, it appears that these 5"-modified neomycin derivatives are more active against G (+) bacteria (S. *aureus*) than G (-) bacteria (E. *coli*). For example, there is only a 4-fold MIC difference in neomycin B between G (+) and G (-) bacterial [34].

Baussanne and coworkers protected one to four hydroxyl functions of neamine with phenyl, naphthyl, pyridyl, or quinolyl rings [35]. Among sixteen amphiphilic neamine derivatives, six derivatives (Fig. **5d**) appeared to be active against sensitive and resistant Gram (+) bacteria (S. *aureus* strains), especially against MRSA and VRSA (Vancomycin-resistant S. *aureus*), to which neomycin B is totally inactive. When used to test sensitive or resistant bacterial Gram (-) strains, **53** showed better MIC values ranging from 4 up to 16 μg/mL. Only **53** is active on both Gram (+) and Gram (-) bacteria. The replacement of the naphthyl rings with benzyl, pyridyl, or quinolyl rings led to the complete disappearance of the antibiotic activities both on Gram (+) and Gram (-) bacteria. The presence of three 2NM groups is critical for obtaining antimicrobial effects against Gram (+) bacteria and necessary for Gram (-) bacteria. The hydrophobic groups enhance the penetration of the corresponding derivatives in the phospholipid bilayer of bacterial, result in either increased uptake or destabilization of the lipid membrane and give affinity to minor groove binding, and stacking [35].

A similar work was reported that aminoglycoside antibiotics including kanamycin A, amikacin and neamine in which all hydroxyl groups of the polyol are derivatized with hydrophobic polycarbamates or polyethers. (Fig. **5e**) [36]. The results showed that the nature of the polyol modification as well as the nature of the aminoglycoside antibiotics has a strong effect on the antibacterial potency. The most potent antibacterials are polyol-modified neomycin B-based amphiphiles (**5e-1**) containing unsubstituted aromatic rings. These analogues exhibit up to 256-fold enhanced antibacterial activity against resistant strains comparing with neomycin B.

Others

In 2007, Hanessian synthesized C2"-ether analogues of paromomycin (Fig. **6a**). The X-ray cocrystal complexes revealed a new mode of binding in the A-site rRNA, whereby rings I and II adopted the familiar orientation and position previously observed with paromomycin, but rings III and IV were oriented differently [37]. All of these modifications at the C2"-position (**6a-1**) were well tolerated against Gram (+) (S. *aureus*), while the smaller, aliphatic, and polar functionalities seemed to fare better against Gram (-) (E. *coli*). The nonpolar carbon and oxygen analogues (**6a-2**) showed reduced activity, especially for Gram (-) (E. *coli*). The activity results are consistent with the presence of a relatively large pocket about the C2"-side chain in the A-site which was unoccupied. Removal of ring IV of the C2"-substituted analogues (**6a-3**) decrease the activity of the parent compounds, while the paromomycin lacking ring IV is totally inactive. Although the activity of C2" ethers lacking ring IV is slightly reduced compared to that of the parent analogue, the loss of ring IV is not detrimental. Thus,

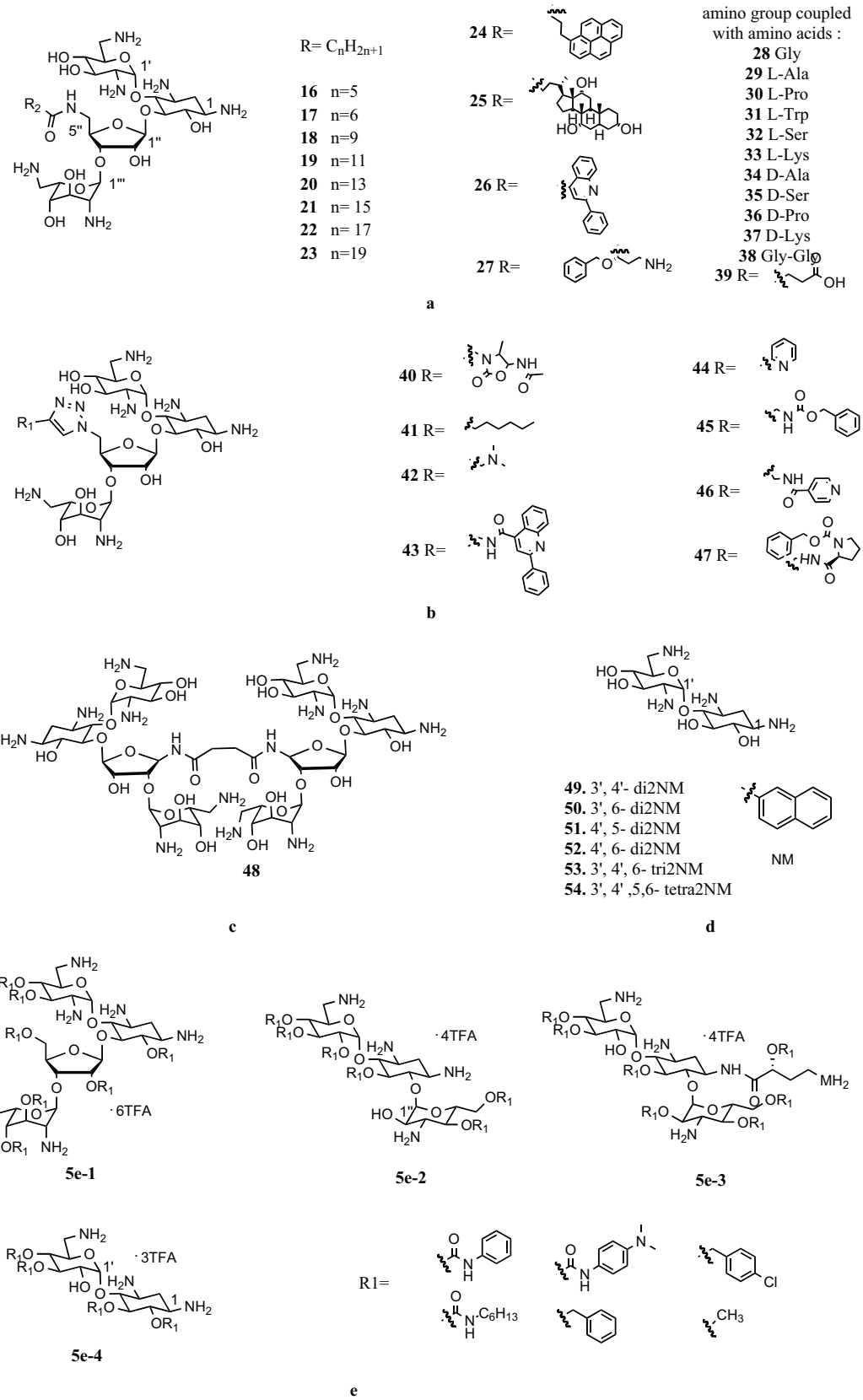
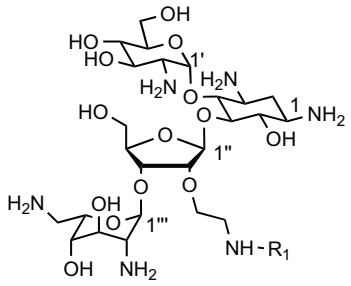
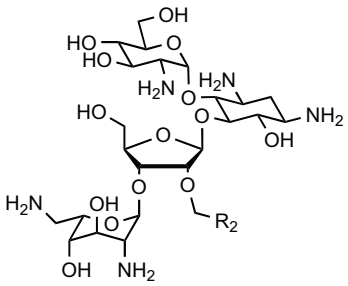


Fig. (5). Cationic amphiphilic aminoglycoside antibiotics: a. C5"-hydroxyl group in neomycin B modified through amide group by hydrophobic substituents including lipid chains, aromatic residues, hydrophobic amino acids; b. C5" of neomycin B derivatives by 1, 2, 3-triazole linkage; c. Di-neomycin B derivative; d. Neamine protected one to four hydroxyl functions with naphthyl; e. All hydroxyl groups of kanamycin A, amikacin, and neamine derivatized with hydrophobic polycarbamates or polyethers.



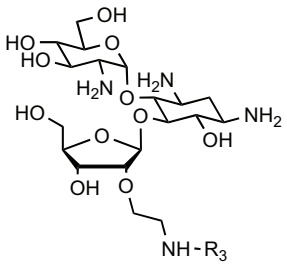
6a-1

R1=all kind of lipophilic and lipophobic as well as aliphatic and aromatic groups.



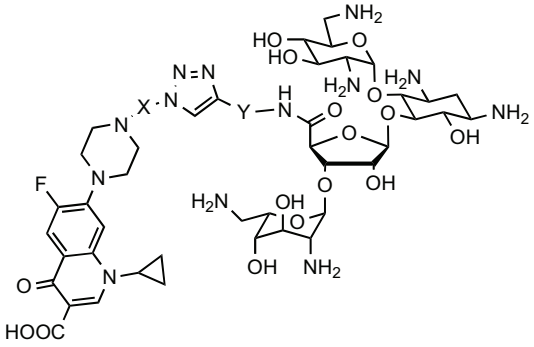
6a-2

R2= nonpolar carbon and oxygen groups

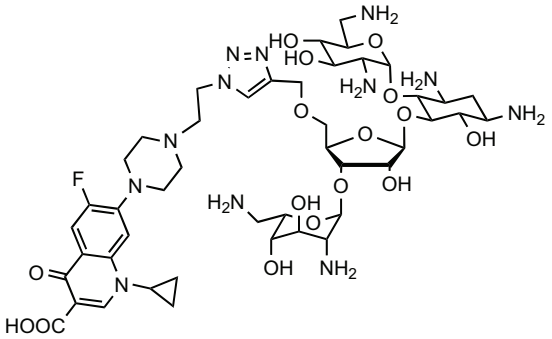


6a-3

a



6b-1



6b-2

b

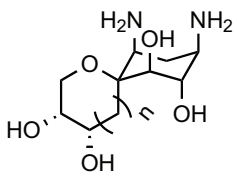
Fig. (6). Derivatives with a new mode of binding with A-site: a. C2''-ether derivatives of paromomycin; b. The structures of ciprofloxacin and neomycin combining.

ring IV appears to be less important for binding in the C2''-ether series.

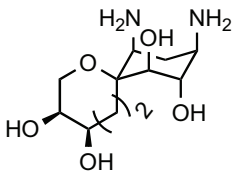
A series of new hybrid structures containing fluoroquinolone (ciprofloxacin) and aminoglycoside (neomycin) antibiotics linked via 1, 2, 3-triazole moiety were designed and synthesized (Fig. **6b**), and their antibacterial activities were determined against both Gram-negative and Gram-positive bacteria, including resistant strains. The nature of spacers in both the ciprofloxacin and neomycin parts greatly influenced the antibacterial activity [38].

DEVELOPMENT OF UNNATURAL SCAFFOLD OF THE AMINOGLYCOSIDE ANTIBIOTICS

In 2009, Ioannis A. reported a new designed RNA-targeted small molecules [39]. Former designment mainly changed some groups of the aminoglycoside and kept the major scaffold, especially aminoglycosidic structure. In this report, by computational methods, they designed and synthesized neamine's analogues, small-molecule rigid spirocyclic scaffolds (Fig. **7**). Although they had only two amino groups embedded in the structure and possessed half the electrostatic load present in neamine (EC_{50} =9.5 mm), they exhibited satisfactory binding affinities for the bacterial decoding center which were directly supported by their potencies as inhibitors of protein production. Especially for **55** (EC_{50}=6.5 mm), but also for **57** (EC_{50}=74 mm). **56** and **57** inhibited protein production in both bacterial and eukaryotic IVT assays in comparison to that of **55**, which appeared to be inactive for the eukaryotic system (EC_{50} >1mm), this specialty and selectivity results may decrease the toxicity of aminoglycoside antibiotics and pave the way for future rational drug-discovery efforts.



55. n= 1
56. n= 2



57

Fig. (7). Unnatural spirocyclic scaffold of the aminoglycoside antibiotics.

DISCUSSION

The toxicity, drug-resistant, and spectrum of antibacterial are the barriers for wide usgaes of aminoglycoside antibiotics. To tackle these problems, the binding between aminoglycoside and RNA to find the affinity and selectivity to different structures should be taken into considerations. Chemical modification through carbohydrate chemistry is widely applied to find the SAR and new antibiotics. The achievement of successful semi-synthetic antibiotics makes it a successful exporation. Adding active groups, protecting the enzymatic modified sites, changing the hydrophobic of the molecule, and synthesizing the inhibitors of the modifying-enzymes are the known strategys to find new antibiotics. With the development of computational chemistry and SAR study, new efficient antibiotics will appear to tackle the problems of the antibacterial process.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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