An Overview of Highly Optically Pure Chloramphenicol Bases: Applications and Modifications

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Abstract: Chloramphenicol (CAP) is a widely used broad-spectrum antibiotic. As the precursor of CAP, chloramphenicol bases are stereochemically pure agents and could be used as resolution agents, chiral catalysts and so on. This review summarizes these applications and discusses the structural modifications of chloramphenicol bases.

Key Words: Applications, chloramphenicol bases, structural modifications.

INTRODUCTION

Chloramphenicol (CAP) (**1**) is the first broad-spectrum antibiotic isolated from aerobic broth cultures of an actinomycete, *Steptomyces venezuelae* [1]. It has been widely used for the treatment of numerous microbial infections for nearly sixty years, particularly in developing countries due to its low cost for patients [2]. As the key intermediate for preparing CAP, 2-amino-1-(4-nitrophenyl) propane -1,3-diol (ANP), is also known as chloramphenicol base or *p*-nitrophenylserinol. This compound contains two chiral centers and consists of four isomers, which include *threo*-racemate ANP ((1R,2R) or (1S, 2S) isomers) and *erythro*-racemate ANP ((1R,2S) or (1S,2R) isomers), respectively. Pharmacological studies have confirmed that only (1R, 2R) isomer (**2**) exhibit antibacterial activities after introducing the dichloroacetyl group [3]. (1R, 2R)-ANP is obtained *via* resolution of *threo*-racemate ANP, which leaves (1S, 2S)-ANP (**3**) as chiral waste in the production (Fig. **1**) [4]. Therefore, both enantiomers of *thero*-ANP are commercially available in optically pure form.

Up to now, CAP is chemically available in large quantity amount. This leads to the accumulation of key intermediate (1R, 2R)-ANP and by-product (1S,2S)-ANP in the manufacture of CAP. Therefore, exploitation and utilization of these two synthetic materials would offer many opportunities.

On the other hand, there is no doubt that the stereochemistry of agents plays an important role in their pharmacological activities, delivery properties and metabolism. As a result, the pharmaceutical industry has focused on chiral drug development in recent decades. Consequently, new chiral separation methods are very useful to the development of new pharmaceutical agents.

Currently, chiral ANP ((1R,2R) or (1S,2S)) are useful chiral reagents due to its low cost and availability in large quantity. In addition, it is easy to do structural modifications of ANP because of its polyfunctional group structures. For these reasons, a number of investigations have been done on the applications of chiral ANP. This paper gives a briefly review of the development of chiral ANP, especially in the fields of its structural modifications for biological research and new drug discovery.

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APPLICATIONS OF CHLORAMPHENICOL BASES

1. Applications of Chloramphenicol Base as an Efficient Resolution Agent

Crystallization is one of the most widely used approaches to separate stereoisomers. It is an important strategy in pharmaceutical industry that the racemic mixtures can be separated with resolution *via* diastereoisomeric salt formation. This strategy are generally used when a racemate contains a basic or an acidic group, which can easily form diastereoisomeric salts. However, many resolving agents are expensive and hard to get. Optically pure enantiomers of ANP, (1R,2R)-ANP and (1S,2S)-ANP, contain a basic group and are easily obtained from commercial CAP synthesis. Therefore, both enantiomers are frequently used as resolution agents in the pharmaceutical industry.

1.1. Applications in Resolution of Amino Acids

The earliest application of chiral ANP was to resolve racemic amino acids in peptide synthesis. Leon and coworkers previously reported that *N,N*-dibenzyl derivates of α-amino acids could be resolved with the help of (1R,2R)-ANP or (1S,2S)-ANP. Optically pure amino acids were obtained through hydrolysis and hydrogenolysis from their diastereoisomeric *threo*-dibenzyl salts [5]. Similarly, DL-*p*-tosylserine [6], DL-*threo*-β- phenylserine [7], DL-*N*-methylvalines [8], DL-*threo*- β-phenylserine [9], and *N*-benzoylation of (2RS,3SR) -2-amino-3- hydroxy-3-phenyl propanoic acid [10] were resolved by fractional crystallization of their salts with optically active ANP.

1.2. Applications in Resolution of Other Acids

The resolutions of compounds with carboxylic acids were explored in many studies. The optical resolution of racemic

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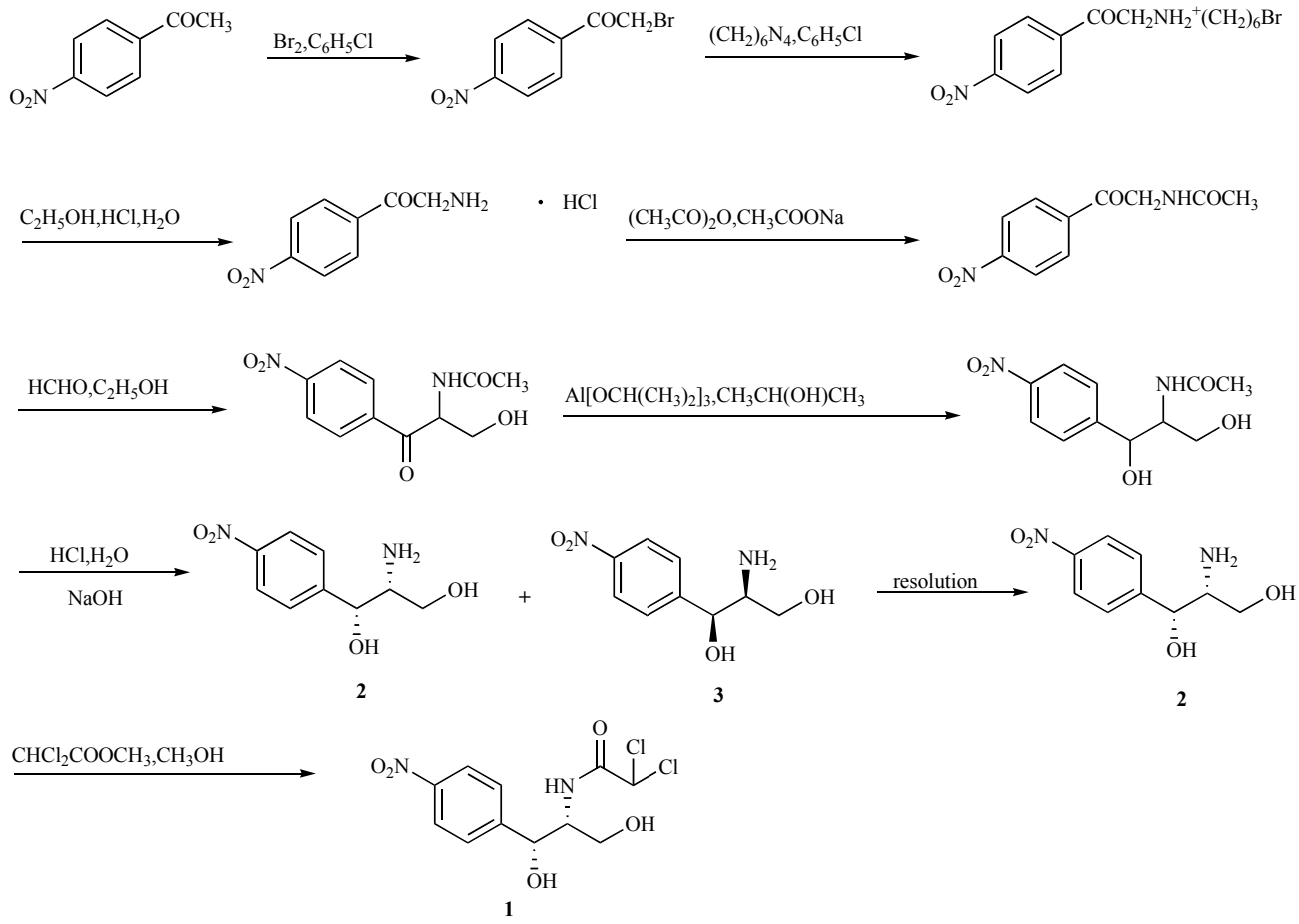


Fig. (1). The synthetic route of chloramphenicol.

2-ethynyl-2-phenylglycolic acid using (1S,2S)-ANP was previously reported by Issei [11]. DL-Phenyllactic acid was later resolved using (1S,2S)-ANP to give diastereoisomeric salts, and then acidified with HCl to give free L-phenyllactic acid [12].

Using (1R,2R)-ANP, compounds such as L-camphor-10-sulfonic acid [13], D-malic acid [14], and the phthalic acid monoester of (S)1-(4-chloro-phenyl)-2-propanol [15] were successfully separated from their corresponding racemic acids. Optical isomers of racemic 4-oxo-6-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a] pyrimidine-3-carboxylic acid were also separated using chiral ANP and the approach of "mutual- resolution" by Elemer [16].

1.3. Applications in Resolution of Drug Intermediates

Resolution of racemic drug intermediates is another important application of chiral ANP. For example, (R)-*o*-chloromandelic acid [17], (R)-(-)-2-hydroxy-2-(2-chlorophenyl) acetic acid [18], α-(2-chloro-phenyl)-6,7-dihydrothieno [3,2-c] pyridine-5(4H)-acetic acid [19] are intermediates for the synthesis of clopidogrel. These chiral intermediates were successfully obtained from their corresponding racemates using chiral ANP as the resolving agents. The resolving process has the advantages of high optical purity, high yield and low cost compared with the method using expensive alkaloid as the resolving agents.

Many other optical intermediates have been purified using (1R,2R)- ANP as the resolution regent in pharmaceutical industry [20-22]. For example, (R)-2-hydroxy-4-phenyl butyric acid has been optically resolved using ANP. This compound is useful as intermediates for certain antihypertensives, agrochem growth regulators, and insect repellents.

1.4. Applications in Resolution Using ANP Derivatives

In order to increase the resolution activity, the ANP structure has been modified for the resolution of some specific compounds. There are numbers of studies performed on the applications of ANP derivatives.

(R)-2-hydroxy-4-oxo-4-phenylbutanoic acid is an important intermediate of an angiotensin converting enzyme (ACE) inhibitor. It has been reported that this enantiomerically pure acid can be easily prepared using the *N,N*-dimethyl derivative of (1R,2R)-ANP (**4**) as a resolution agent [23]. *Threo*-(1S,2S)-*N*-benzyl-*N,N*-dimethyl-[1,3-dihydroxyl-1-(4'-nitrophenyl)]-2-propylammonium chloride (BDDNPAC) (**5**) [24] and the condensation product (CHANP) (**6**) of (1S,2S)-ANP and cyclohexanone [25] were prepared using (1S,2S)-ANP as a chiral starting material. These two chiral regents have been successfully applied to the resolution of racemic 1,1′-bi-2-naphthols (BINOLs). Enantiomerically pure BINOLs possessing a *C*2-symmetric axis and their derivatives are very important chiral ligands and auxiliaries, and have been

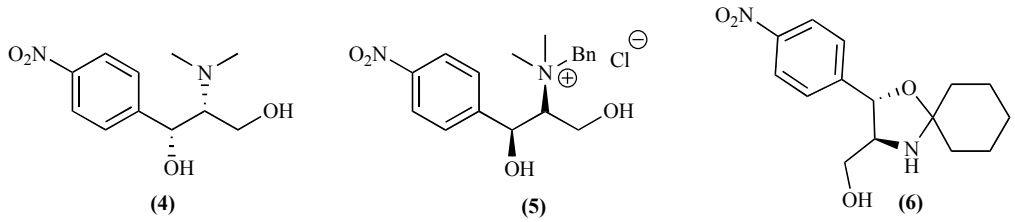


Fig. (2).

extensively used in catalytic and stoichiometric asymmetric synthesis.

2. Applications of Chloramphenicol Base as a Chiral Catalyst

As described above, chiral ANPs used as resolution reagents were extensively applied in many studies. In addition, chiral ANPs and their derivatives also act as chiral catalyst and chiral auxiliary in many asymmetric reactions.

2.1. Used as Chiral Catalyst

2.1.1. Used as Schiff Base Catalyst

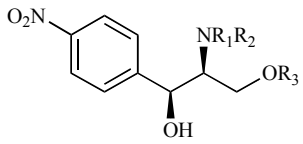
It was reported that a cheap chiral copper Schiff base complex (**7**) could be derived from (1S,2S)-ANP and 3,5-di-*tert*-butyl-2-hydroxy benzaldehyde. This complex is used as chiral catalyst in the reaction of 2,5-dimethyl-2,4-hexadiene (DMHDE) with $N_2CHCOOMe$ to produce R-*trans* isomer of cyclopropane carboxylate, which is an important intermediate in the synthesis of pyrethroid [26].

Recently, a new polystyrene-supported chiral Schiff base ligand (**8**) derived from salicylic aldehyde and optically active (1R, 2R)-ANP was reported by Barbarini [27]. This heterogeneous ligand was complexed with $VO(acac)_2$ and employed to catalyze the enantioselective oxidation of sulfides to sulfoxides using hydrogen peroxide as an environmentally acceptable oxidant. The procedure affords the sulfoxides in good yield and with moderate *e.e.* (enantiomeric excess) values comparable to the homogeneous counterparts.

Other similar literature reports also found that oxidation of methyl *p*-tolyl sulfide with hydrogen peroxide catalyzed by $VO(acac)_2$ and Schiff base derived from (1R,2R)-ANP) afforded R-(+)-methyl *p*-tolyl sulfoxide resulted in high yield and with 43% *e.e.* [28]. A new chiral Schiff base ligand was synthesized starting from (1S,2S)-ANP and salicyl aldehyde, which was used in asymmetric ring-opening of cyclohexene oxide with mercaptan (thiophenols). Moderate enantioselectivity was obtained in this Schiff base/$Ti(OPr\text{-}i)_4$ catalyzed ring-opening reaction [29].

2.1.2. Used as Chiral Amino Ether Catalyst

Compound **9a** was easily prepared from commercially available (1S,2S)-ANP and used as a chiral oxazaborolidine catalyst by Chen and co-workers [30]. This compound can catalyze an efficient enantioselective reduction of *meso*-cyclic imide to yield (3aS,6R,6aR)-hydroxylactam with enantioselectivity of 98% as determined by chiral HPLC analysis.



(9a): R_1=H; R_2=H; R_3=Tr
(9b): R_1=Me; R_2=Me; R_3=TBDMS
(9c): R_1=Me; R_2=Me; R_3=Tr
(9d): R_1=Me; R_2=Me; R_3=t-Bu
(9e): R_1=Me; R_2=Bn; R_3=Tr
(9f): R_1=Me; R_2=Bn; R_3=TBDMS
(9g): R_1=Bn; R_2=Bn; R_3=TBDMS

Fig. (4).

According to Jiang's preliminary studies, compound **9b** could be a chiral ligand from the modification of (1S, 2S)-ANP. This ligand was used in an enantioselective alkynylation of aldehydes to yield propargylic alcohols with zinc salt and tertiary amine [31,32]. Later, this chiral catalyst was used to catalyze asymmetric addition of terminal alkynes to α-keto ester in the presence of $Zn(OTf)_2$. The corresponding product tertiary propargylic alcohols were obtained in high yields with up to 94% *e.e.* [33].

In further investigations, a series of (1S,2S)-ANP derivatives (**9a-9g**) were synthesized and evaluated for their ability to catalyze enantioselective alkynylations. According to the results, substitution of amino and hydroxyl in (1S,2S)-ANP greatly affected the enantioselectivity of the reaction. For example, compound **9** gave excellent enantioselectivities and yields. When one of the amino substituents was changed to benzyl, the enantioselectivity decreased. The best result was obtained by using **9d** as the ligand, which was used in the asymmetric alkynylation of chloral in high yield with excellent enantiomeric excess (up to 98%) [34]. This inexpensive yet effective chiral ligand and its (1R,2R)-enantiomer gave

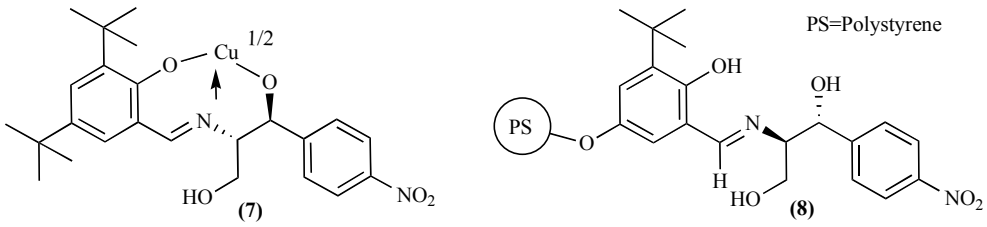


Fig. (3).

excellent enantioselectivities in the alkynylation reactions of cyclic *N*-acyl ketimine [35].

2.1.3. Used as a Chiral Iminium Salt Catalyst

Compounds **10** and **11** were synthesized by Hua and co-workers [36-37]. These two phase transfer catalysts were obtained through *tert*-aminolation and quaterization starting with (1S,2S)-ANP. They showed good catalytic and certain asymmetric induction effects in the α-methylation of phenylacetonitrile and the addition reaction of benzaldehyde with chloroform.

There were two epoxidation catalysts derived from (1S,2S)-ANP, a dihydroisoquinolinium salt (**12**) and a dibenzazepinium salt (**13**) described by Philip [38]. The enantio-controlling asymmetric centers are located in the exocyclic substituent at the nitrogen atom of the catalysts. These iminium salts were employed in the catalytic asymmetric epoxidation of simple alkenes, which only gave low *e.e.* (about 41%).

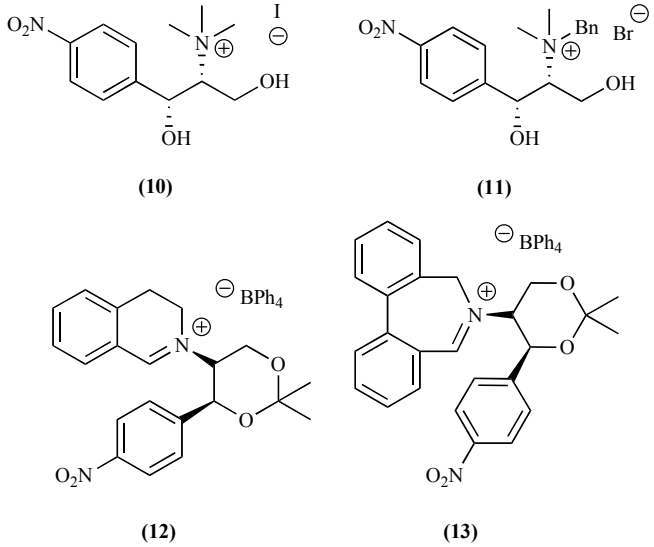


Fig. (5).

2.2. Used as a Chiral Auxiliary

A chiral auxiliary is a chemical compound or unit that is temporarily incorporated into an organic synthesis, so that it can be carried out asymmetrically with the selective formation of one of two enantiomers. Chiral auxiliaries are optically active compounds and introduce additional chirality in otherwise racemic or achiral compounds. The temporary stereo-center then forces the asymmetric control of a newly formed stereo-center using steric hindrance or directing groups to determine chirality. After the creation of a new stereo-center, the original auxiliary can be removed in a third step and recycled.

The ANP was first regarded to promising useful chiral auxiliariy by Sztaricskai. In previous communication, an optically active ANP is reported as a chiral amine component *via* chiral Staudinger reactions in the preparation of *cis*-lactams (**14**). The *cis*-*α/β*-ratio of the two products depended on the protection groups of the ANP diol moiety used. High diastereoselectivity was reached only with a large silyl protecting group. It was always in favor of the configuration of type **14a**, starting from (1S,2S)-ANP [39]. Subsequently, compounds **14** obtained in optically pure form from the modified process were transformed to the *N*-deprotected derivatives (**15**), by means of a two-step oxidative procedure. Compounds **15a** and **15b** are versatile intermediates for the synthesis of novel monobactam derivatives [40]. In addition, several hydroxyl protective groups were introduced by Sztaricskai. The results indicated that *cis*-*α/β*-ratio could be influenced by the protective groups of the diol moiety of ANP and removal of the *N*-auxiliary moiety could be accomplished by direct oxidation [41].

Stereoselectivity of the addition reaction of *o*-toluamides, using (1S,2S)-ANP as chiral auxiliary, was studied. Addition products (**16**), diastereomerically enriched, were obtained after column chromatography separation and further transformed to (R)-(+)-8-oxoberbines (**17**) with *e.e.* of up to 97% [42].

3. Applications of Chloramphenicol Base as a Building Block in Synthetic Chemistry

Since chiral ANP is available in great amount and high enantiomeric purity from the production of CAP, it seemed that the modification of chiral ANP and its derivatives is of practical significance for developing new kinds of inexpensive chiral materials. This non-racemic chiral amino alcohol has been extensively used as a starting material in chemical reaction studies. The various derivatives of chiral ANP were synthesized and their stereochemistry was studied. These new derivatives are of particular interest as intermediates for organic synthesis of more elaborated molecules. Various chemical reactions of ANP were also explored.

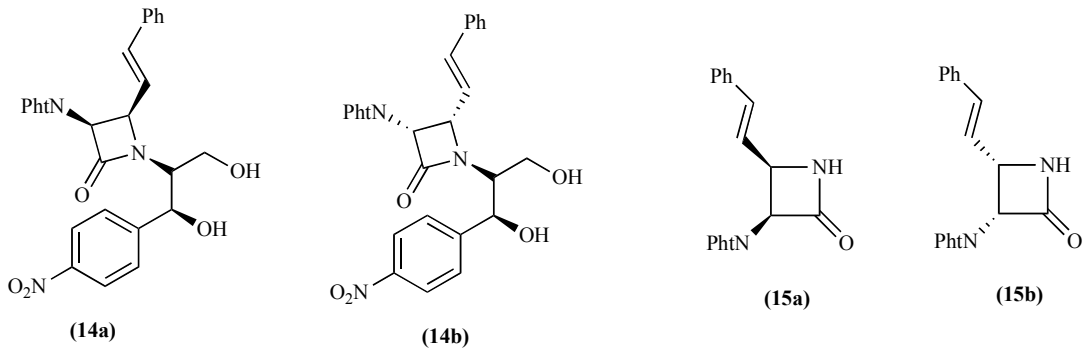
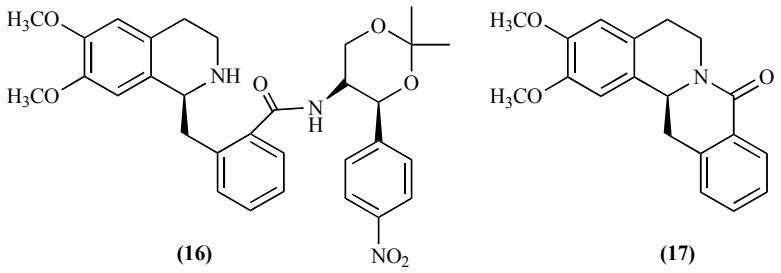


Fig. (6).



(16) **(17)**

Fig. (7).

3.1. Applications in Condensation Reactions

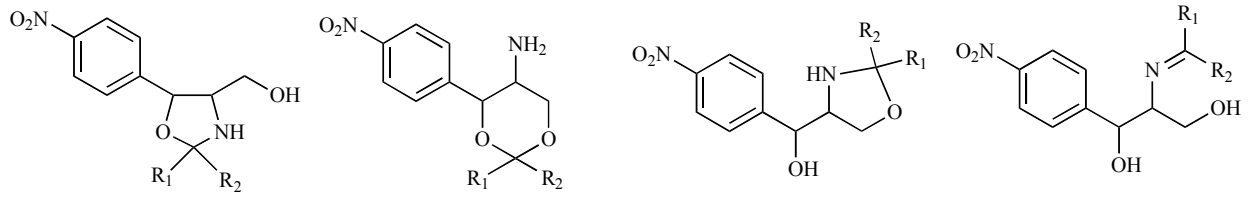
Chiral ANP has a primary amine group and two free hydroxyl groups. Studies found that when they reacted with a carbonyl compound, e.g., acyl halide, their polyfunctional group structures led to formation of mixtures of several derivatives.

It is also reported that (1R,2R)-ANP, (1S,2S)-ANP, or racemic *threo*-ANP reacts with a given carbonyl compound under different experimental conditions to give condensates with different structures (1,2-, 1,3-, or 2,3- cyclocondensation, Schiff bases products) (**18-21**). In most case, the product is a mixture (more than one structural isomer) [43]. Recently, Shan and coworkers reported that condensations of (1S,2S)-ANP with cyclohexanone, acetone, butanone, and pentan-3-one in toluene or xylene by azeotropic distillation in the absence of catalyst afforded almost quantitatively 1,2-cyclocondensation derivatives *via* a highly efficient chemoselectivity [44]. These derivatives partially isomerize to the 2,3-cyclo- condensation derivatives in $CDCl_3$ at ambient temperature. The ring-ring tautomerism is first reported in 2-aminopropane-1,3-diol chemistry [45].

Fourteen Schiff bases (**22**) were synthesized from the (1S,2S)-ANP skeleton and reacted with substituted benzaldehyde and their high resolution ^{1}H-NMR spectra were studied by Darabantu [46]. The ring chain tautomerism of these compounds is described as an essential premise and concept as well for the synthesis of its saturated heterocyclic derivatives. Stereochemical implications about the versatile reactivity of (1S,2S)-ANP are also discussed. In subsequent investigations, Darabantu described total diasteroselective synthesis of compound **23** at *C*1 and *C*8 as well as details concerning their stereochemistry [47]. They recently reported some preliminary data on 1,3-dioxanic Schiff bases (**24**), as a result of the versatile reactivity of (1S,2S)-ANP and considered it of interest to studying this area from both synthetic and stereochemical points of view [48].

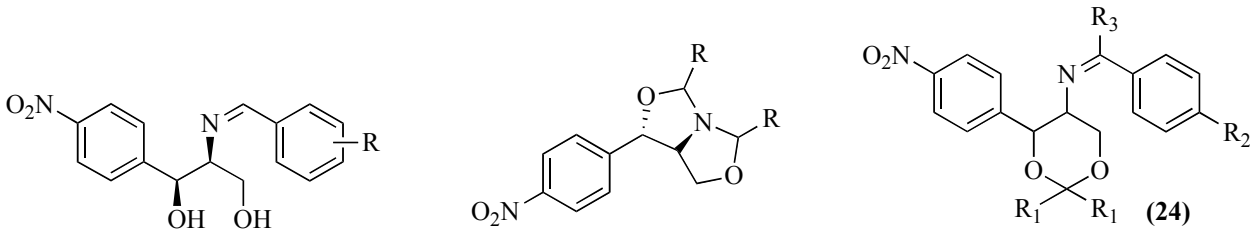
Hu's group has described a concise, highly stereoselective synthesis of some cyclic compounds from (1S,2S)-ANP, such as compounds **25, 26** and **27** [49-51].

The ring-closing reaction of one the (1S,2S)-ANP derivates, (1S,2S)-3-acetoxy-1-(4-nitrophenyl)-2-(*p*- toluenesulfonamido)-1-propanol, was carried out with Mitsunobu



(18) **(19)** R_1=R_2=alkyl group **(20)** **(21)**

Fig. (8).



R: akyl, (substituented)aryl, (hetero)aromatic ring.
(22)

R:H,alkyl,(substiueted)aryl
(23)

R_1: H or Me
R_2: H or Me
R_3: H,Br,NO_2
(24)

Fig. (9).

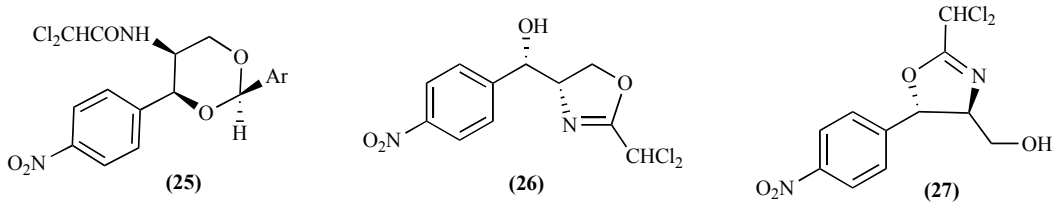


Fig. (10).

reagent (PPh_3-diethylazodi- carboxylate). Compound **28** was obtained in 45% yield. This reaction is stereospecific and results in an expected configuration inversion at the α-carbon atom of the benzyl group [52]. By cyclization of the (1S,2S)-ANP derivate, (1S,2S)-2-(4-methylphenyl- sulfonylamino) -1-(4-nitrophenyl) propan-1,3-diol, it was to get compound **29**. This ring-closing reaction product was reduced to give (1S,2S)-1-(4-nitro phenyl)-2-(4-methylphenylsulfonylamino) propan-1- ol, and if *via* aza-Payne rearrangement, followed by reduction to give (1S)-3-(4-methylphenylsulfonylamino)-1-(4-nitrophenyl)propan-1-ol. This product was attracted interest as possible intermediate product in the synthesis of fluoxetine, a drug for the treatment of depressions and other disorders [53].

There are also other reactions about ANP. A series of isomeric 2-oxazolidinones (**30a, 30b**) was synthesized from (1S,2S)-ANP and ethyl chloroformate [54]. These 2-oxazolidinones can be explained by their high biological activities The synthesis of a new type boron-containing multifunction derivatives, the tetracoordinated spiroborate complexes (**31**) [55] and the diastereomeric β-enaminones (**32**) have been prepared from racemic ANP and (+)-3-carene- derived β-chlorovinylketone. The (1R,2R) diastereomer (**32a**) was obtained from crystallization in MeCN. This phenomenon demonstrates a new possibility for the resolution of racemic amines [56]. The first convergent and non-protective synthesis of a G-2-s-triazine-based dendrimer having enantiomerically pure (1S,2S)-ANP as peripheral group and piperazine as linker is described by Darabantu [57,58].

3.2. Applications in Oxidation Reactions

There have been some investigations of the oxidation of ANP and its derivatives. Because the structure of ANP has a benzyl hydroxyl group and a primary hydroxyl group, it can be easily oxidized. A part of the *C*(1)-*C*(2) bond underwent cleavage, to give 4-nitrobenzaldehyde (**33**) or 4-nitrobenzoic acid (**34**). It was reported that (1S,2S)-ANP was oxidized by $Na_2H_3IO_6$ (H_2SO_4) to generate 4-nitrobenzaldehyde in 96% yield. Oxidation of (1S, 2S)-ANP with a 717 anion-exchange resin-supported bromine gave compound **35** [59]. This compound was obtained by generating 4-nitrobenzoic acid cyclocondensed with unchanged (1S,2S)-ANP in the reaction system. The conversion of (1R,2R)-ANP to (1R,2R)-α-amino-β-hydroxy acid (**36**) by oxidation of the primary hydroxyl group mediated by homogeneous and heterogeneous 2,2,6,6-tetramethyl piperidine 1-oxyl radical (TEMPO) was reported by Pagliaroa [60]. Studies showed that heterogeneous TEMPO (the hybrid organic-inorganic silica sol-gel catalysts) is a selective mediator of the oxidation of benzylic amino diols.

The *N*-acetylated (1S,2S)-ANP derivative was oxidized by NaOCl in HOAc to give compound **37** [61]. However, when it was oxidized by $KMnO_4(H_2SO_4)^6$ and $KBrO_3$

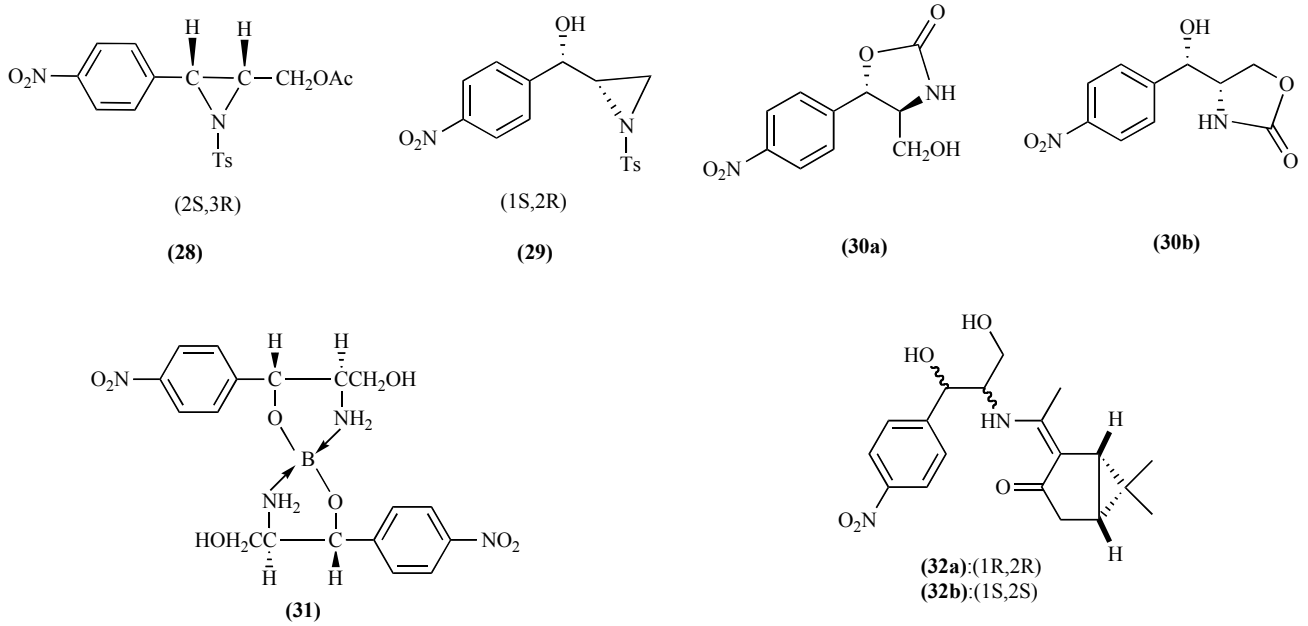


Fig. (11).

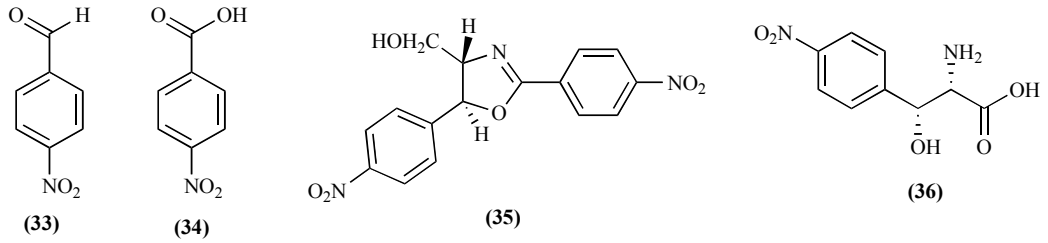


Fig. (12).

(H_2SO_4)[7], compound **38** and compound **39** were obtained, respectively, in high yield [62]. Oxidation of this derivative with a 717 anion-exchange resin-supported bromine gave compound **40**. While oxidation of its 2-dimethyl-amino derivative, under similar conditions, gave compound **41**.

3.3. Applications in Reduction Reactions

Direct reductions of ANP to form aniline derivatives had not been reported in previous literatures. However, it was reported that nitroso compounds could be the electrochemically reduced from (1S, 2S)-ANP derivatives in a ''redox'' flow cell equipped with two consecutive porous electrodes of opposite polarities. Considering the electrophilic or dipolar reactivity of nitroso compounds, these species could be key products in the synthesis of more sophisticated molecules having biological activities [63,64].

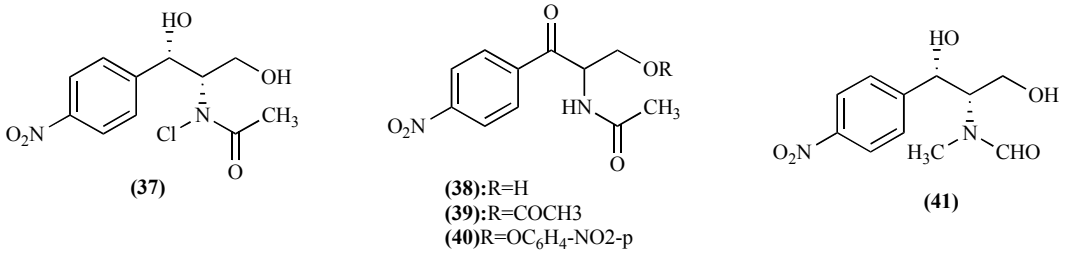


Fig. (13).

Subsequent studies found that hydroxylamine derivatives could be electrochemically prepared in a batch cell from the (1S,2S)-ANP derivatives. These electro-reduction hydroxylamine derivatives could be key products in the synthesis of various species with possible biological activities [65,66].

4. Structural Modification of Cloramphenicol Base to Obtain Biologically Active Compounds

Since the structure of ANP has multiple functional groups, it indicates that this compound may possess potential biological activities. Its pharmacological functions were studied in many papers. Early studies found that (1R,2R)-ANP, the hydrolytic product of chloramphenicol, inhibited smooth muscles contraction *in vitro* [67]. (1R,2R)-ANP showed a strong inhibitory effect on rat liver mitochondria monoamine oxidase. The inhibition by this compound was noncompetitive and reversible [68].

Moreover, (1R,2R)-ANP inhibited the growth of enterobacteria, Staphylococcus aureus, and Candida albicans at 0.5-1.0% concentration. At lower concentration (0.001-0.005%), however, it stimulated microbial growth. So this compound may be used as growth regulator for pathogenic microorganisms, especially in the preparation of culture media [69]. The activity of *N*-dialkyl-substituted derivatives of racemic ANP as plant-growth regulators were reported [70]. Substituted s-triazines having pure enantiomeric (1S,2S)-ANP or its amino-1,3-dioxanes derivatives as peripheral fragments showed a preliminary herbicidal activities [71-73].

Because of their potential biological activities and polyfunctional reactivities, chiral ANP also became of interest for structural modifications to improving pharmacological application. Many derivatives have been synthesized and their biological activities have been extensively tested.

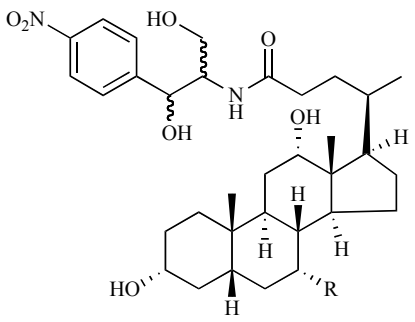
4.1. For Preparing Novel Antimicrobial and Antifungal Agents

In the development of cationic peptide antibiotic mimics, which disrupt or permeabilise the bacterial membrane and sensitize these organisms to hydrophobic antibiotics, Thakura disclosed the synthesis of eight new amides (**42**) derived from chiral ANP and cholic acid or deoxycholic acid. The antibacterial and antifungal activities of these novel amides were also tested. These easily accessible amides showed moderate antibacterial and antifungal activities. Particularly the amide (R=H, (1S,2S)) obtained from deoxycholic acid and (1S,2S)-ANP was found to be potent against various Gram-positive bacteria. The inhibitory concentrations (IC_{50}) of compound against pathogenic bacteria are in a range of 4.9~27 mg/mL [74].

A series of phosphorylated derivatives of racemic ANP and their physiological activities were studies by Kudrya [75]. Of all the compounds prepared, compound **43** had the greatest insecticidal and nematocidal activities, which might lead to the development of new drugs.

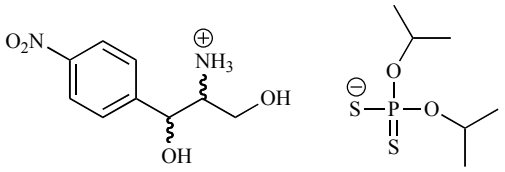
4.2. For Preparing Bacterial Ribosome Inhibitors

The antibiotic CAP inhibits protein synthesis by binding to the peptidyl transferase region of the ribosome. Its clinical



R=H,OH; (1R,2R)or(1S,2S)

(42)



(1R,2R)or(1S,2S)

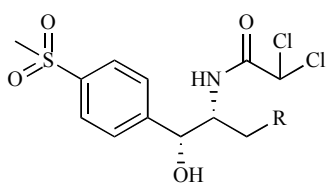
(43)

Fig. (14).

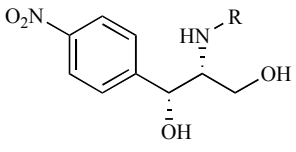
use is limited because of toxic site effects and drug resistance. Chloramphenicol has been derivatized in many ways in order to define its essential functional groups and to improve its drug properties.

The CAP molecule can be subdivided into two parts: (1) key structure ANP comprised of the nitro group substituted aromatic ring system and the propanediol moiety and (2) the acyl side chain. Wide variations are permitted for the aryl moiety and the propanediol moiety whereas the acyl side chain is essential for activities. Replacing the nitro group on the phenyl ring with methylsulfonyl group was to give thiamphenicol (TAP) (**44a**). This compound has been wildly used as veterinary drug. The terminal hydroxy group of TAP was replaced by a fluorine atom to give florfenicol (FF) (**44b**). FF does not carry the risk of inducing human aplastic anemia that is associated with chloramphenicol. It also has activity against some chloramphenicol resistant strains of bacteria, possibly because it is less affected by the major enzyme produced in plasmid-mediated bacterial resistance against chloramphenicol and thiamphenicol.

The dichloroacetyl group of chloramphenicol was replaced by alternative amino acid or dipeptide groups give aminoacyl analogs and one peptidyl analog were reported by Drainas [76]. These are (L-Phe-ANP) (**45a**), (Gly-ANP) (**45b**), and (L-Phe-Gly-ANP) (**45c**). The kinetics of inhibition of peptide bond formation by these analogs were examined in a cell-free system, which was derived from *E. coli*. The following *Ki* values have been determined: 18.0 μM for **45a**, 5.5μM for **45b**, 1.5μM for **45c**. These analogs were assumed to behave as classical competitive inhibitors. It is suggested that as compared with chloramphenicol, the two aminoacyl analogs and the dipeptidyl analog increase structural similarity to the 3'-terminus of aminoacyl-tRNA or of peptidyl-tRNA and that this similarity results in a more pronounced competitive inhibition.



(44a):R=OH
(44b):R=F



(45a):R=-Gly,
(45b):R=-Phe-L
(45c):R=-Gly-Phe-L

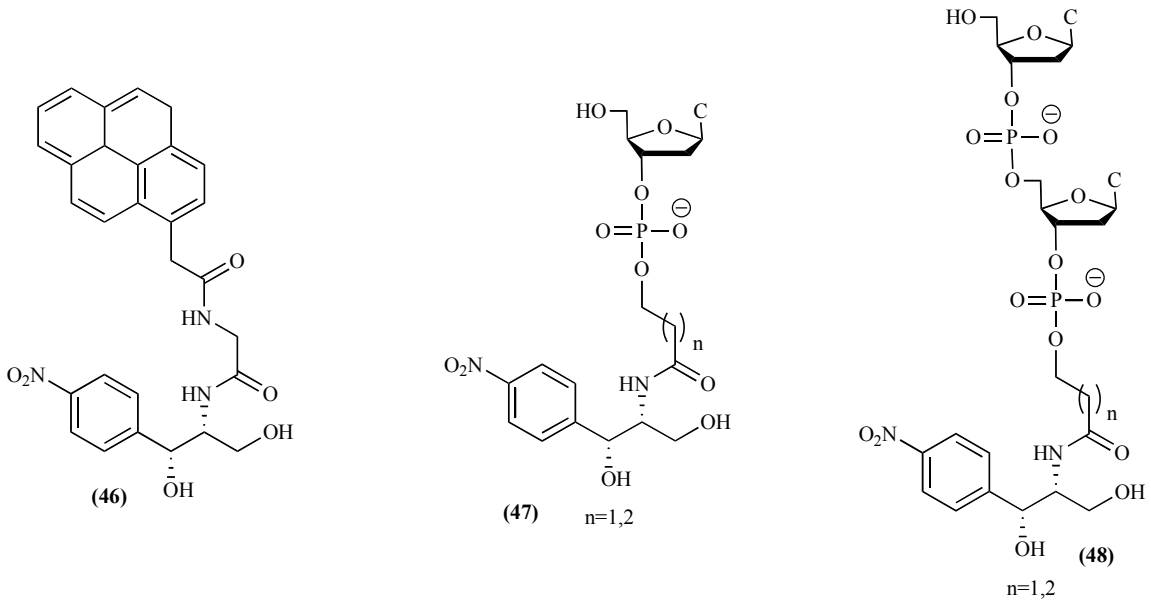
Fig. (15).

Conjugates of (1R,2R)-ANP through appropriate linkers to either a pyrene moiety or to a mono- or dinucleotide moiety were designed by Nielsen [77]. This chemical modification strategy is supposed to improve binding to ribosomes by providing specific interactions in the peptidyl transferase site or to the P-loop in the ribosome. The pyrene chloramphenicol conjugate (**46**) shows enhanced binding to the chloramphenicol binding site compared to the native chloramphenicol, whereas the four nucleotide conjugates (**47, 48**) were shown to bind to the chloramphenicol binding site or to the P-loop.

4.3. For preparing Ceramidase Inhibitors

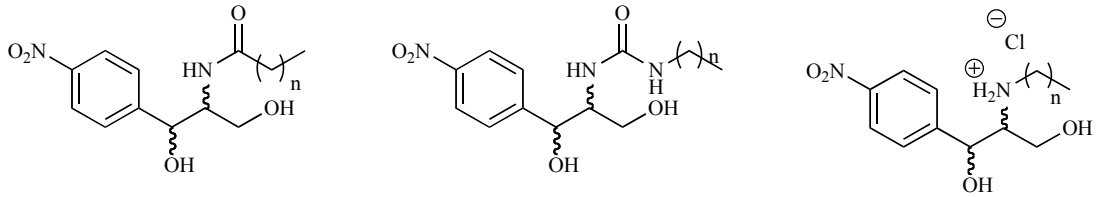
Ceramide (Cer) has emerged as an important modulator of cancer cell growth and apoptosis. Ceramidases (CDases), which play a key role in Cer metabolism, are considered as potential targets for anticancer therapy. A promising approach by introducing Cer analogs as CDases inhibitors has been explored to increase endogenous Cer. The therapeutic use of ceramide analogs is for inhibiting proliferation, preferably in cancer cells, or increased angiogenesis or for modulating apoptosis. Since the similarity between structure of Cer and ANP, many researchers have focused on developing ceramide analogs using ANP as the starting material.

Reaction of (1S,2S)-ANP with caproyl chloride giving hexanoic acid ester derivative (**49**) was reported by Peter [78]. This compound described as an analog of ceramide possesses apoptogenic and antiproliferative properties. It had an antiproliferative IC_{50} equal to 2.4 μM. Another active ceramide analogue B13 (**50**) possessing the phenyl group instead of the alkenyl chain and (1R,2R) configuration instead of (1S,2S) of the natural ceramides was derived from (1R,2R)-ANP [79]. Treatment with B13 caused the release of cytochrome C and induced apoptosis. Biological activity of B13 was also demonstrated in malignant melanoma, colon, and prostate cancer cells, and in animal experiments of *in vivo* cancer growth [80]. In later studies, a series of novel isosteric analogs of B13, urea analogs (**51**) and *N*-alkyl analogs (**52**) were designed, synthesized, and evaluated as potential anticancer agents. The urea analogs of B13 showed comparable or slightly more potent cytotoxic activities as



(46) **(47)** n=1,2 **(48)** n=1,2

Fig. (16).



(49):n=4;(1S,2S)
(50): n=12;(1R,2R)

(51) n=11;(1S,2S) n=11;(1R,2R)

(52) n=13;(1S,2S) n=13;(1R,2R)

Fig. (17).

compared to B13, indicating that urea does appear to serve as a bioisostere of amide. However, all compounds were identified to be promising lead compounds for therapeutic development [81,82].

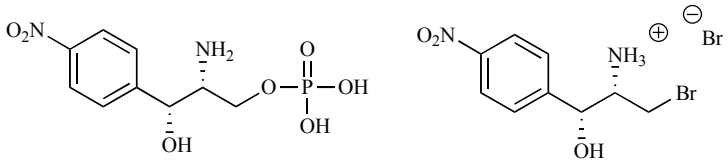
4.4. For Preparing Antagonists of EDG/S-1P Receptors

Recently sphingosine-1-phosphate (S-1P), one the metabolite of sphingolipids, has attracted considerable attention both as an intracellular second messenger and an intercellular mediator. It has been reported that S-1P binds to cell surface receptor EDG, which is coupled *via* plasma membrane G-protein to multiple effector systems. EDG binding to S-1P would affect various biological responses, including mitogenesis, differentiation, proliferation, and apoptosis, and thus is supposed to be involved in a variety of pathological conditions such as angiogenesis, inflammation, and cardiovascular diseases. Therefore, the search for antagonist's activities of novel S-1P analogues toward EDG/S-1P receptors would provide the basis for development of novel therapeutic agents for such diseases.

S-1P derivatives such as *threo*-(2S,3S)-analogue (**53**), which is C-3 stereoisomers of natural *erythro*- (2S,3R)-S-1P, was synthesized starting from (1S,2S)-ANP. This compound showed potent inhibitory activities against Ca^{2+} ion mobilization in HL60cells induced by *erythro*-S-1P (IC_{50} =0.015-0.031μM), suggesting that it would compete with cell surface EDG/S1P receptor. The *threo*-(1S,2R)-2-amino-1-aryl-3-bromopropanols (HBr salt) (**54**) was obtained by replacing the terminal phosphate group with bromide. This *threo*-amino-bromide derivative did not loss the inhibitory activities compared with *threo*-(2S,3S)- analogue. Other analogues such as enantiomeric *threo*-(R,R)-analogue and deoxyamino bromide were also synthesized and examined. However, they did not show activities. Their results indicated that the presence and configuration of the amino alcohol moiety appeared to be very important for the antagonist inhibitory effect [83].

4.5. For Preparing Carbonic Anhydrase (CA) Inhibitors

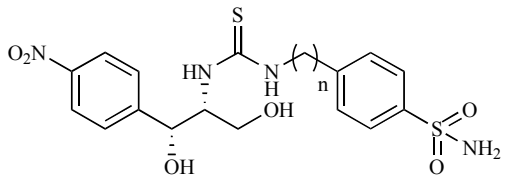
The treatment of glaucoma with inhibitors of the metalloenzyme carbonic anhydrase (CA) is very effective in reducing elevated intraocular pressure (IOP) characteristic of this disease. Two thioureido sulfonamide compounds (**55**), which have been obtained by reaction of isothiocyanate-substituted aromatic sulfonamides with ANP, were reported by Supuran [84]. The new compounds showed good inhibitory properties against three physiologically relevant carbonic anhydrase isozymes, with K_i values of 135 nM and 113 nM against the cytosolic isoform CA I respectively. The inhibition values against the other cytosolic isozymes, CA II and the transmembrane isozyme CA XII, were in a range of 4.9~27 nM. In animal experiments, the new derivatives were also very effective in reducing elevated intraocular pressure in hypertensive rabbits as a glaucoma animal model. Re-



(53) **(54)**

Fig. (18).

cently, the transmembrane isoform CA IX was shown to be a cancer-associated drug target, and it is highly overexpressed in hypoxic tumors with limited distribution in normal tissues. In a study by Nielsen, compound **55** (n=0) has potent inhibitory properties against CA IX with a K_i value of 32 nM and a P_{app} value of 4×10^{-6} cm/s for the absorptive transepithelial transport in Caco-2 cells. The standard, clinically used drugs (dorzolamide DZA, acetazolamide AAZ, methazolamide MZA, ethoxzolamide EZA, and dichlorophenamide DCP) showed K_i values in the range of 25-52nM [85].



(55) n=0 n=2

Fig. (19).

4.6. As Loop-Binding Component of Aminoglycosides Heteroconjugates (RNA Binding Drugs)

Aminoglycosides are well-known natural products that have evolved as inhibitors and modulators of RNA functions. However, most aminoglycosides bind to a variety of RNA targets with moderate affinity due to the nonspecific electrostatic interactions. This lack of selectivity often results in severe toxicity.

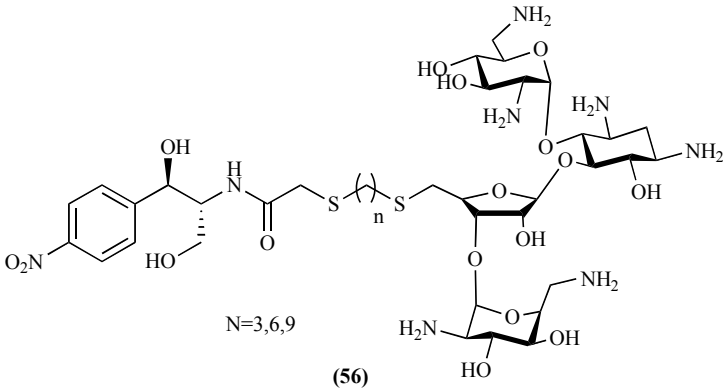
In order to improve specificities of aminoglycosides as a new type of RNA binding drugs, Yu described the design and synthesis of three new heteroconjugates (**56**), which are comprised of an aminoglycoside drug neomycin B(Neo) and (1S,2S)-ANP. (1S,2S)-ANP was selected as the loop-binding moiety because mutation and X-ray crystallographic studies have shown that this substance specifically binds to the central multibranched loop of 23S rRNA. Neo and (1S,2S)-ANP were conjugated with spacers of different lengths to form (NC1, NC2, NC3).

Results in this study showed that Neo-(1S,2S)-ANP conjugates display enhanced, site-selective binding to several RNA targets, and have an enhanced pharmaceutical efficacy and reduced side effects which can be caused by nonspecific drugs. One of the Neo-Cam conjugates, NC2, has a nanomolar (0.022nM) binding constant to the RNA target Rev response element (RRE), a value which is 10 times higher than that of Neo, and binding by the related conjugates, NC2, to trans-activating region (TAR) is 10-fold greater than that of Neo [86].

CONCLUSIONS

(1R,2R)-ANP is the key compound in the industrial synthesis of the CAP, and (1S,2S)-ANP is a the discarded byproduct. Both compounds with high enantionmeric purity have found numerous applications in optical resolutions as resolution regents and in symmetric syntheses as chiral auxiliaries and catalysts. As we know, optically active substances have been more and more commonly used dyestuffs, pharmaceutical products, agricultural chemicals, surfactants and other fields. Asymmetric syntheses and optical resolutions are two main ways to obtain chiral chemicals. So ANP plays an important role in the generation of useful chiral materials and its applications on those two methods will be further explored.

Moreover, chiral ANP has been widely adopted in chemical reaction investigations or organic synthesis as homochiral starting materials and building blocks. Many new kinds of inexpensive chiral materials have been developed.



(56)

Fig. (20).

The stereochemistry and other chemical properties of some possible types of derivatives have been studied. In addition, due to ANP's potential activities, its structure modifications for biological research and drug discovery become more and more popular.

In a word, in order to maximize the utilization of this chiral material and minimize waste disposal, more and more attentions are being paid on chiral ANP for an expanded range of applications. It is believed that this material will have an important future in chemical and pharmaceutical development.

ABBREVIATION

ANP	=	2-amino-1-(4-nitrophenyl)propane-1,3-diol
CA	=	Carbonic anhydrase
CAP	=	Chloramphenicol
Cer	=	Ceramide
EDG	=	Endothelial differentiation gene
ee	=	Enantiomeric excess
FF	=	Florfenicol
Neo	=	Neomycin B
RRE	=	Rev response element
S-1P	=	Sphingosine-1-phosphate
TAP	=	Thiamphenicol
TEMPO	=	2,2,6,6-tetramethylpiperidine-1-oxyl radical
acac	=	2,4 pentanedionate or acetylacetonate

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