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Medicinal chemistry of amine prodrugs

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Abstract

Amine Prodrugs are being used since the beginning of the 19th century in medicines. Their Chemistry, Biological activity and Pharmacodynamic Characters has been revealed better in the 20th century. Most of the drugs that are invented in the recent century are prodrugs of amines, which show their importance in medical field. The purpose of this review is to focus on various aspects of amine prodrugs like its chemistry, types, uses and future scope in medical field. This review summarizes studies spanning the whole history of amine prodrugs, but emphasizes recent findings and several hypotheses which have been recently introduced to explain in detail how amine prodrugs function at the target site. Understanding the role of amine prodrugs in drug delivery will increase our information on molecules having amine linkages and their potential uses. It is now generally accepted that amine prodrugs have important role(s) in drug targeting; that they are the initial molecules that deliver the drug to target site in stable form. The amine prodrugs are classified on basis of the molecular linkage of nitrogen atom to the nearby atoms, example, -N=H-, -N=N-, -H-N-H-, etc. Various types of molecules having amine linkages are briefly focused to on basis of their mechanism by which they release basic drug molecule at the site.

Keywords: Prodrugs, Absorption, Barrier Transport, Bioactivation, Chemical activation

1. Introduction

The absorption of a drug may often be enhanced by structural modifications (Zambitoet al., 2008) that serve to alter the relative lipophilicity e.g. aminification of a water-soluble acid. The design of an active drug to prodrug is also referred to as drug latentation (Zuluaga et al., 2012). An Amine moiety containing prodrug is inactive and must be converted into an active species within the biological system. There is a variety of mechanisms by which this may be accomplished. The conversion occurs enzymatically by metabolizing enzymes or ch-

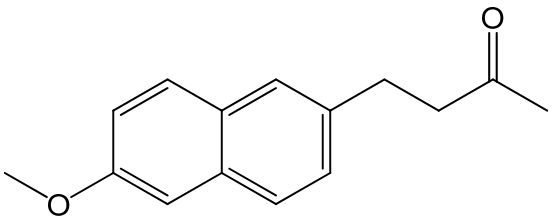

Figure:1. Structure of Nabumetone.

emically by hydrolysis. Prodrugs can be conveniently grouped into two types Carrier-linked prodrugs and Bioprecursors. Carrier-linked prodrugs are the ones where the active drug is covalently linked to an inert carrier or transport moiety. They are generally esters or amides such prodrugs have greater lipophilicity then parent drug due to the attached carrier. Bioprecursors prodrugs are inert molecules obtained by chemical modification of the active drug but do not contain a carrier. Such a moiety has almost the same lipophilicity as the parent drug. It is bioactivated generally by redox biotransformation, only enzymatically, i.e, oxidation, reduction, phosphorylation etc. Nabumetone and Nonsteroidal anti-inflammatory drug is a prodrug which releases CH3 and converts to active drug (Testa et al., 2009).

1.1 Pharmacokinetic barriers

Absorption, distribution, metabolism and excretion of drug substances are influenced by the physicochemical properties of the drug molecule. In order to overcome, the problems associated with these processes, the prodrug approach has been used to improve absorption or poor membrane permeability, avoid presystemic degradation or metabolism thus improved bioavailability. In addition, prodrug approach is used to achieve sustained action, reduce toxicity and achieve site-specific delivery.

1.2 Absorption properties

The most successful area of prodrug research has been the improvement of passive drug permeation through different epithelial cell membranes (Linnankoski et al., 2010). A large number of prodrugs have been developed to improve absorption from the GI tract. The prodrug approach has been used to improve absorption following oral (Gupta et al., 2011), buccal (Lalanne et al., 2009), transdermal (Heather et al., 2005) and ocular (Yi et al., 2012) administration.

1.3 Intestinal absorption

For drug substances with poor water solubilities, the dissolution in the GI tract is frequently the rate-limiting step for absorption, and the bioavailability of such drug substances is often low, unpredictable, and highly dependent on the particle size of the drug. Increasing the aqueous solubility of such drugs with the help of the prodrug approach may improve the absorption from the GI tract (Gong et al., 2012). However, in contrast to the parenteral dosage forms, only few clinical relevant examples exist, where the prodrug principle has been used to increase water solubility in order to improve GI absorption. An example is sulindac, a prodrug of the nonsteroidal anti-inflammatory drug sulindac sulfide (Wang et al., 2011). Because of increased solubility, absorption following oral administration has been im-

proved. It should be emphasized, however, that an increased aqueous solubility does not necessarily result in an improved bioavailability. In order to be able to permeate the lipophilic epithelial cell membranes lining the GI tract, a drug molecule must possess lipophilic properties. Thus, for highly polar compounds, administration of less polar, more lipophilic prodrugs may improve absorption, since for these substances the limiting step in the absorption process is the permeation through the epithelial cell membranes.

In order to improve bioavailability after oral administration, formation of lipophilic prodrugs of polar substances has been successfully applied to the antibiotics clindamycin (Stella rt al., 2007), erythromycin, and ampicillin (Rautio etal., 2008). The ampicillin is a highly polar molecule, and at GI pH, it is present in a zwitterionic form (Zimnitsky et al., 2004). The bioavailability after oral administration is low, ranging from 20 to 60%. Therefore, large doses are required to obtain adequate tissue concentrations, resulting in large amounts reaching the colon and modifying the colinic flora, causing diarrhea. Addition of ester group to the carboxylic terminal of ampicillin inactivates the drug and makes it more lipophilic. Examples of ester prodrugs are bacampicillin, pivampicillin and talampicillin (Ringman et al., 2012). These esters are efficiently absorbed and the bioavailability is superior to that of ampicillin itself. Furthermore, most esters hydrolyze after absorption, usuall in the mucosal cells, and the ampicillin remaining in the gut is present as the inactive ester and is less likely to cause diarrhea; toxicity is also reduced.

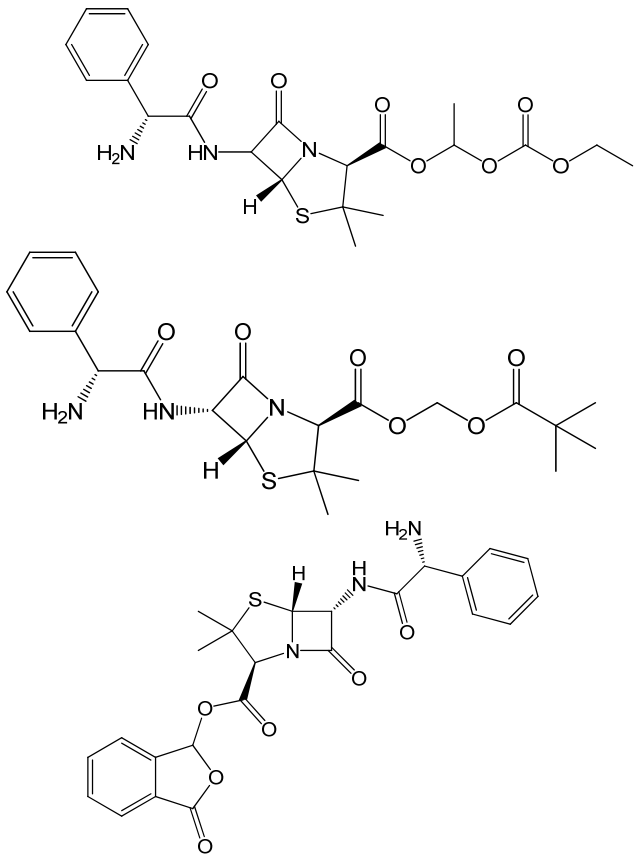

Figure:2. Structure of Bacampicillin (top), Pivampicillin (middle), and Talampicillin (bottom).

1.4 Buccal absorption

Bioavailability of high clearance drugs can often be substantially improved by buccal administration. First-pass metabolism can be avoided by this route, since the veins in the oral cavity drain directly to the systemic circulation and bypass the liver. However, to avoid first-pass metabolism and drug must be rapidly absorbed trough the buccal mucosa and not be swallowed, dissolved or suspended in saliva. Few drug substances have the physicochemical properties needed for both rapid dissolution in saliva and rapid permeation through the buccal mucosa. The narcotic and gastric ketobemidone is and example of a high clearance drug which is too hydrophilic to pass the buccal mucosa at a sufficient rate. The possibility of improving the permeation of ketobemidone through buccal mucosa, and thereby increasing bioavailability via the prodrug approach, has been investigated. (Fernández et al., 2012) They found that by esterification of the phenolic group in the ketobemidone molecule, it was possible to enhance the permeation of ketobemidone through porcine buccal mucosa in vivo studies on rats confirmed the results of the in vitro studies. In addition, it was proved that the cleavage of the prodrugs by saliva enzymes proceeded too slowly to be of significant clinical relevance. Similarly improved buccal delivery of nalbuphine, naloxone and naltrexone prodrugs following buccal administration to rats has also been studied (Lalanne et al., 2009).

1.5 Dermal and transdermal absorption

Like buccal administration, transdermal administration of drugs offers the possibility of avoiding firs-pass metabolism. Furthermore, a sustained action of the drug may be achieved (Lehman et al., 2012). However, only few drugs when applied to the skin for systemic (transdermal delivery) or topical (dermal delivery) use are able to permeate the skin barrier at a sufficiently high rate and in sufficient amounts to obtain a therapeutic effect. For most drug substances, the main barrier function of the epidermis resides in the outermost layer, the stratum corneum, which consists of dead keratinized epithelial cells. In order to permeate this layer, a substance must exhibit optimal physicochemical properties, it must be soluble in both water and lipids.

In recent years prodrugs have been investigated to solve the problems associated with poor permeability of drugs into and through the skin, and to improve the treatment of skin diseases such as eczema, herpes simplex and psoriasis. The drugs substances considered included nalidixic acid, acyclovir, fluorocytosine, mitomycin C, aspirin, indomethacin, cromoglycic acid, theophylline, 5-fluorouracil, hydrocortisone, purine analogs, dithranol, metronidazole, nicorandil, lonapalene and vidarabine. These studies demonstrated that it is possible to improve the permeation properties of drugs substances with the help of prodrugs. For example, a 180-fold enhanced flux of the purine analogue 6-mercaptopurine through hairless mouse skin was seen when the diethyl N-Mannich base was applied as a suspension in isopropyl myristate compared to 6-mercaptopurine itself (Kumar et al., 2012).

The prodrug approach has been evaluated for drug substances intended to act systemically following abs option through the skin, unfavorable physicochemical properties of morphine impair its ability to permeate skin. The in-vitro permeation rates of a series of morphine esters have been investigated and compared with the rates of the parent compound. Study demonstrates that the buccal delivery of morphine can be markedly improved by using ester

prodrugs with higher lipophilicity than morphine itself (Zeppetella et al., 2011). With isopropyl myristate even greater enhancement was reached. Similarly, it has been demonstrated that it is possible to improve the transdermal permeation properties of the narcotic analgesic ketobemidone by using the prodrug approach.

1.6 Ocular Delivery

A major problem in ocular therapy is the attainment of an optimal drug concentration at the site of action within the eye. The difficulty is largely due to precorneal factors such as solution drainage, tear turnover and conjuctival absorption. Most of the topically applied drugs used in ophthalmology were originally developed for systemic application, and are not well suited for ocular delivery, i.e., corneal absorption. Thus the main goal of developing prodrugs, intended for topical ocular administration has been to increase corneal drug absorption to enhance efficacy, reduce the incidence of systemic side effects by lowering the required dose, prolong the duration of action, and thereby improve patient compliance.

The prodrug approach has been successfully applied to steroidal ophthalmic drugs. Acetate and phosphate esters of dexamethasone and prednisolone are being used clinically. The phosphate esters increase the water solubility of the readily soluble steroids (Vollmann et al., 2008). Clear solutions are often preferred over suspensions for ophthalmic administration, partly to overcome problems associated with the pharmaceutical formulation but also to improve patient compliance and dosing reproducibility. The acetate esters were developed to improve corneal permeation. In vitro permeation studies have shown that the acetate esters permeate the intact cornea more readily than the parent drugs.

2. Amine prodrugs

Amine moiety is commonly found in many of the popular prodrugs. New researches are also in progress on amine prodrug due to their specific physical and chemical properties. Amine containing prodrug are basically classified as on basis of basic functional groups and linkages as, amide prodrugs, azo linkage prodrugs, lipid peptides prodrugs, etc.

2.1 Classification

There are a variety of Amine prodrugs and they not only differ from each other due to presence of carrier linkage or precursor, but also in differ from the type of functional groups or moieties present. The functional groups present in a prodrug can increase or decrease the absorption, distribution, metabolism and excretion of drug. In case of prodrugs it is necessary that the functional group attached to the active drug should increase or maintain the lipophilicity of the prodrug. The major type of Amine prodrug are grouped according to functional group and in the case of the bioprecursor drugs, grouped according to type of metabolic activation are discussed briefly below: -

2.1.1 Amides

Derivatization of amines (Simplicio et al., 2007, March et al., 2012, Stathopoulou et al., 2012) to give amides has not been widely used as prodrug strategy due to high chemical

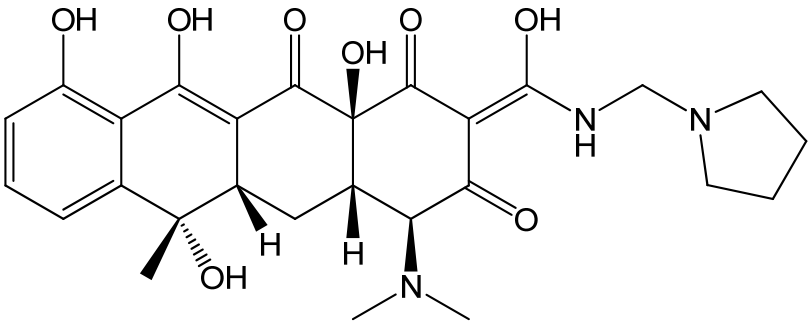

Figure: 3. Structure of Rolitertracycline

stability of amide linkages and the lack of amidase enzymes necessary for hydrolysis. A more common approach has been to utilize Mannich's bases as a prodrug form of the amines. Mannish's base results from the reaction of two amines with an aldehydes or ketone. As seen hetacillin the effect of forming the Mannich base (Pospisil et al., 2007) is to lower the basicity of the amine and thereby increases lipophilicity and absorption, i.e. hetacillin is a prodrug of Ampicillin with amide linkage. When nitrogen is present in an amide linkage it is some times desirable to utilize the amide nitrogen as one of amines necessary to form a Mannich base. This approach has been utilized in the antibiotic tetracycline, in which the amide nitrogen was allowed to react with formaldehyde and pyrrolidine to give the Mannich's base rolitertracycline. In this case, additional ionizable functionality and increases the water solubility of the parent drug. Hydrolysis of the Mannich's base occurs completely and rapidly in aqueous media to give active tetracycline.

A number of different functionalities have been evaluated as prodrug derivatives of carbonyl (Simplicio et al., 2007, Petersson et al., 2004) e.g. aldehydes and ketones, although this approach has not found wide clinical utility. These have generally involved derivatives in which the sp2 hybridized carbonyl carbon is converted to a sp3-hybridized carbon attached to two heteroatoms such as oxygen, nitrogen or sulfur. Under hydrolysis, these functionalities are reconverted slowly to the carbonyl compounds i.e., methamine or hexamine is a prodrug of the urinary tract antiseptic, formaldehyde. After oral absorption, hexamine remains inert and stable in blood at pH 7.4. When excreted in urine, the prodrug decomposes in the acidic pH to generate active formaldehyde, which exerts its antibacterial action in the urinary tract. By utilizing a prodrug approach, the systemic release of formaldehyde is prevented and the toxicity is reduced. Other prodrug approaches have involved the use of oximes, imines and enol esters, although these types of compounds have not been used clinically. There are a number of agents that contain imine and oxime linkages such as many of the third generation cepholosporins (Kannasani et al., 2012, Idani et al., 2012) e.g. cefolaxime and deftizoxime, but these are not prodrugs, but are drugs containing oxime linkages in the cephalosporin ring structure.

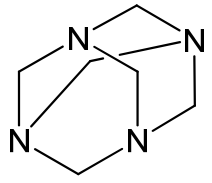

Figure: 4. Structure of Hexamine

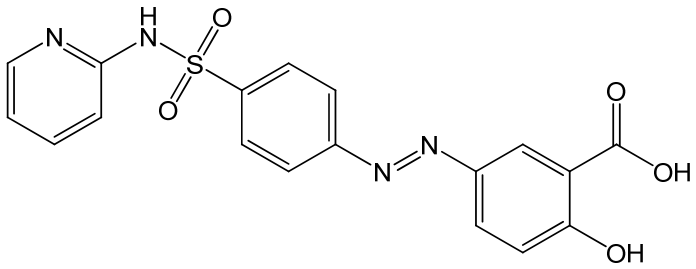

Figure: 5. Structure of sulfasalazine

2.1.2 Azo linkages

Amines have occasionally been incorporated into an azo linkage for the purpose of producing a prodrug. In fact, it was an azo dye prontosil, which led to discovery of the sulfonamides, the first antibacterial used to treat systemic infections. While prontosil was itself inactive in vitro, it was active in vivo, where it was converted by azo redutase enzymes in the gut to sulfanilamide, the active species, i.e. sulfasalazine is a prodrug used in anti-inflammatory bowel disease.

Mesalamine (Mesalazine) is a drug for breaking inflammation of ulcerative colitis, since it is not absorbed into the systemic circulation. However, following oral administration, the drug is inactivated before reaching the lower intestine, the site of action. Covalent binding of this agent to sulfapyridine yield the prodrug sulfasalazine an azo compound. This prodrug reaches the colon intact where cleavage by the bacterial enzyme azo reductase rel-eases the active mesalamine for local action.

2.1.3 Lipid peptides

The α-amino acids with long hydrocarbon side chains the so called lipoidic amino acids and their homo-oligomers, the lipoidic peptides (Krauss et al., 2005, Cho et al., 2012, Marsman et al., 2011) represent a class of compounds which combine standard features of lipids with those of amino acids. Several uses of lipoidic amino acids (Patel et al., 2005, Blanchfield et al., 2005, Mencarelli et al., 2011, Braun et al., 2005) and peptides have been proposed particular interest is their potential use as a drug delivery system. The lipoidic amino acids and peptides could be covalently conjugated to or incorporated into poorly absorbed peptides and drugs to enhance the passage of the pharmacologically active compounds across biological membranes. Because of their bifunctional nature, the lipid amino acid and peptides have the capacity to be chemically conjugated to drugs with a wide variety of functional group. The linkage between drugs and lipoidic unit may either be biologically stable or possess biological or chemical instability. In either case, the resulting conjugate would be expected to possess a high degree of membrane like character, which may be sufficient to facilitate their passage across membrane. The long alkyl side chains may also have the additional effect of protecting a liable parent drug from enzymatic attack, there by enhancing metabolic activity.

3. Various amine prodrug approaches to improve absorption

Mucus is a viscoelastic and adhesive gel that protects the lung airways, gastrointestinal (GI) tract, vagina, eye and other mucosal surfaces. Most foreign particulates, including

conventional particle-based drug delivery systems, are efficiently trapped in human mucus layers by steric obstruction and/or adhesion. Trapped particles are typically removed from the mucosal tissue within seconds to a few hours depending on anatomical location, thereby strongly limiting the duration of sustained drug delivery locally (Lai et al., 2009).

3.1 Amides and simple carbamates

In vivo corneal absorption of the amino acid prodrugs of acyclovir (ACV) was observed by the Katragadda S. et al (Katragadda et al., 2008) using a topical well model and microdialysis in rabbits. The L-alanine–ACV (AACV), L-serine–ACV (SACV), L-isoleucine–ACV (IACV), γ-glutamate–ACV (EACV) and L-valine–ACV (VACV) prodrugs were synthesized and evaluated in various ocular tissues. SACV and VACV exhibited approximately two-fold increase in area under the curve (AUC) relative to ACV ($p < 0.05$). It can be concluded as the amino acid ester prodrug seems to be a promising candidate for the treatment of ocular infections. (Katragadda et al., 2008)

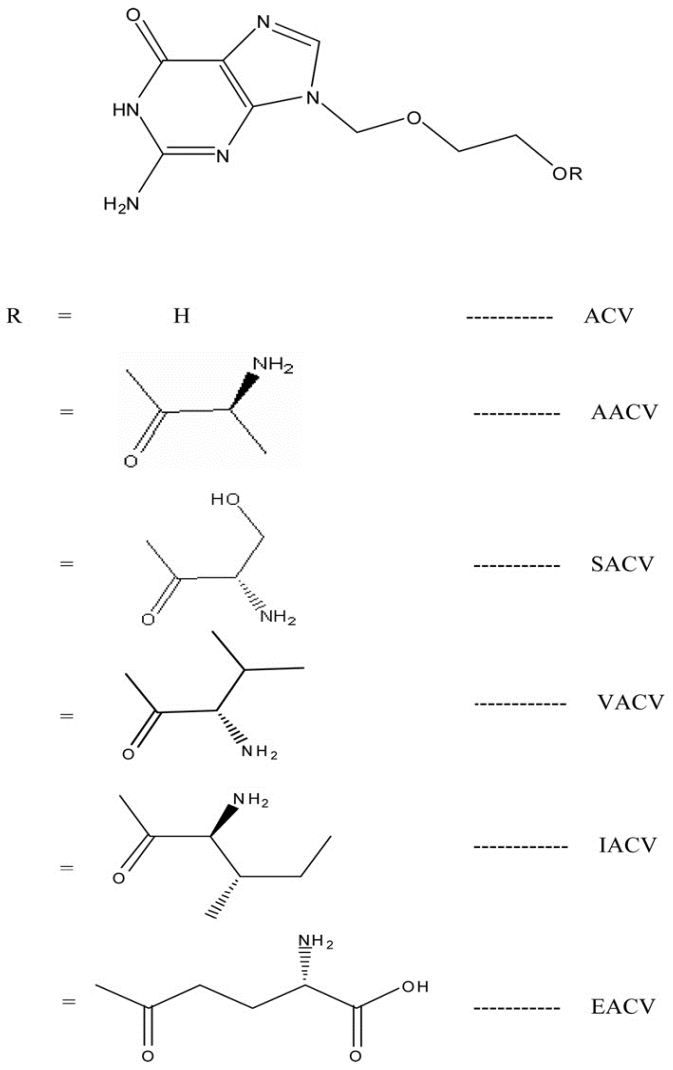

Figure: 6. Structure of amino acid prodrug of acyclovir

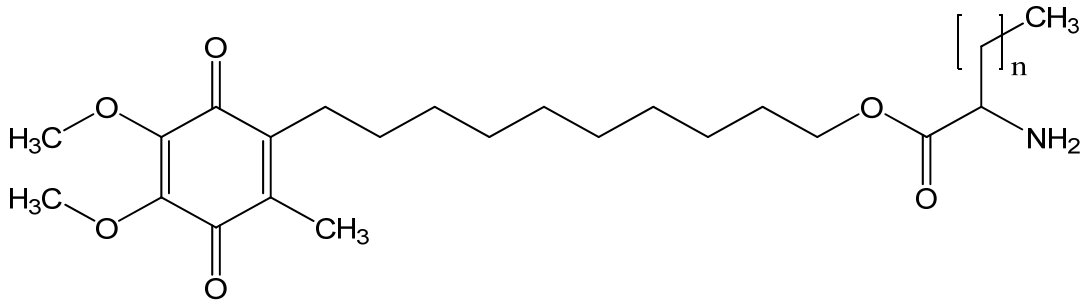

Figure: 7. Structure of prodrug of idebenone

Pignatello R. et al. (Pignatello et al., 2009) using Lipoamino acids (LAA) to modifying the physico-chemical properties of drugs, namely the lipophilicity and amphiphilicity. To show the role of amphiphilicity with respect to lipophilicity in the interaction of drugs with biomembranes, they evaluated the mode of such an interaction of lipophilic conjugates of LAA with the antioxidant drug idebenone (IDE). DSC analysis and transfer kinetic studies were carried out using dimyristoylphosphatidylcholine (DMPC) multilamellar liposomes (MLVs) as a model (biomembrane model). A progressive penetration inside the vesicles was observed upon incubation of IDE–LAA compounds with empty liposomes. The enhanced amphiphilicity of the drug due to the LAA moieties caused more complex interactions with DMPC bilayers, compared to those registered with the native drug or IDE alkanoate esters. The lipophilic antioxidant drug idebenone was converted into amphiphilic prodrugs by means of conjugation with short-chain 2-alkylamino acids.

FXai, a direct inhibitor of the clotting factor Xa, provides high water solubility but poor membrane permeability due to multiple sites of ionization and a molecular weight exceeding 500 Da, making it a Class III drug according to the Biopharmaceutics Classification System. To overcome the ionization problem and increase the transcellular permeability Bruesewitz. et al. (Bruesewitz et al., 2006) used various ester and hydroxyamidine prodrugs exhibiting a reduced number of ionization sites which were studied in the Caco-2 monolayer model for intestinal permeation. FXai has an apparent permeability (Papp) of about 1 nm/s, which is generally regarded as very low. The butylester-hydroxyamidine double-prodrug was found to provide a markedly increased permeability (40.4 nm/s) as did the co-application of chitosan (43.3 nm/s).

Pyrazinamide (PZA) is active against M. tuberculosis and is a first line agent for the treatment of human tuberculosis. PZA is itself a prodrug that requires activation by a pyrazinamidase to form its active metabolite pyrazinoic acid (POA). Since the specificity of cleavage is dependent on a single bacterial enzyme, resistance to PZA is often found in tuberculosis patients. Esters of POA have been proposed in the past as alternatives to PZA however the most promising compounds were rapidly degraded in the presence of serum. In order to obtain compounds that could survive during the transport phase, Simões M.F. et al. (Simoes et al., 2009) synthesized lipophilic ester and amide POA derivatives and due to their lipophilicity these cross the membrane easily.

Katragadda S. et al. (Katragadda et al., 2006) 1-Valine ester of acyclovir, valacyclovir (VACV) and l-glycine-valine ester of acyclovir, gly-val-acyclovir (GVACV) were used as model compounds, to study the transport across the cornea. Transport studies were conducted

with isolated rabbit corneas at 34 °C. Complete inhibition of VACV hydrolysis was observed in the presence of Pefabloc SC (4-(2-aminoethyl)-benzenesulfonyl-fluoride) and PCMB (p-chloromercuribenzoic acid). Similar trend was also observed with GVACV in the presence of bestatin. Transport of VACV and GVACV across cornea showed decreased metabolic rate and modulation of transport in presence of PCMB and bestain respectively. The principle enzyme classes responsible for the hydrolysis of VACV and GVACV were carboxylesterases and aminopeptidases respectively. This study shows the utility of enzyme inhibitors to modulate transport and metabolism of prodrugs appears to be a promising strategy for enhancing drug transport across cornea.

New peptidic self-cleavable spacers were synthesized that released a parent drug via succinimide formation and the oligoarginine-based cargo-transporter (OACT) system. These novel self-cleavable spacers are promising for developments of the OACT system as means to potentially enhance intestinal absorption of parent drugs (Hayashi et al., 2007).

The synthesis and evaluation are described as prodrugs of four cyclic cidofovir dipeptide conjugates in which the free pOH of 2 is esterified by the Ser side chain alcohol group of an X-L-Ser(OMe) dipeptide: 3 (X= L-Ala), 4 (X = L-Val), 5 (X = L-Leu), and 6 (X = L-Phe). Perfusion studies in the rat established that the mesenteric permeability to 4 is more than 30-fold greater than to cidofovir, and the bioavailability of 4 is increased 8-fold relative to cidofovir in an in vivo murine model (Eriksson et al., 2008).

Percutaneous absorption were studied of tolterodine (TOL) using O-acylmenthol derivatives were studied by Zhao L. et al. (Zhao et al., 2009) The in vitro permeation studies of TOL were conducted in isopropyl myristate (IPM) solution or from patches in side-by-side diffusion cells. Topical application of patches without enhancer or with L-menthol and (E)-2-isopropyl-5-methylcyclohexyl octadec-9-enoate (M-OA) as enhancers in rats were used. The in vitro permeation studies indicated that M-OA was the most promising enhancer for transdermal delivery, as 2-isopropyl-5-methylcyclohexyl 2-hydroxypanoate (M-LA) was merely effective in IPM solution. The mean steady-state plasma concentrations after applying patches without enhancer or with l-menthol and M-OA as enhancers were 0.89, 0.84 and 1.47 μg/mL, respectively.

Bupropion (BUP) is an aminoketone used as an antidepressant and non-nicotine aid to smoking cessation (Mitrouska et al., 2007). However, in addition to side effects such as nausea and vomiting, there are reported cases of seizures due to BUP overdoses or unintentional exposure (Shepherd et al., 2004, Segraves et al., 2000). To address the dose-related risk of seizures associated with high peak concentration of the drug following oral administration, BUP HCl is administered in divided doses. In chronic cases, tablets are given three times a day (Lipka et al., 2009, Wang et al., 2006). To overcome this problem of side effect, reduced metabolism in the gut wall and first pass effect, the transdermal system of bupropion is prepared, but the stability of hydroxybupropion (BUPOH) is more than the bupropion which make it suitable candidate for this purpose. The problem with BUPOH is its poor permeability across the membrane. Alternatively, the prodrug But-BUPOH (carbamates hydroxyl-bupropion) was found to be stable, and also provided a 2.7-fold increase in the transdermal flux of BUPOH across human skin in vitro. Thus, But-BUPOH provides a viable option for the transdermal delivery of BUPOH (Kiptoo et al., 2009).

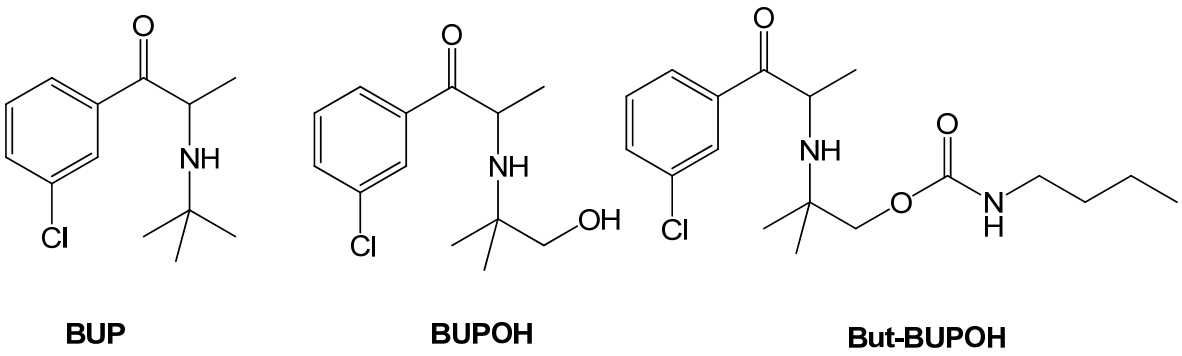

Figure:8. PEG and other macromolecular systems

Dendrimers represent a class of polymers characterised by their well-defined structure, with a high degree of molecular uniformity and low polydispersity. They have found a wide-range of pharmaceutical applications; however, more recently, they have been shown to function as effective intracellular carriers for drugs. In addition, dendrimers have been shown to be capable of bypassing efflux transporters. A new generation of dendrimer-based delivery systems will enable the efficient transport of drugs across cellular barriers (Najlah et al., 2006).

Dendrimer-based prodrugs are also an important approach for the increase in absoption of drugs (naproxen) which shows that poor permeability across the membrane due to its poor solubility. Najlah et al., (2007) Applied such approach to increase the solubility of naproxen by the use of G0 polyamidoamine (PAMAM) dendrimers which conjugate either by an amide bond or an ester bond. In addition, one lauroyl chain (L) was attached to the surface group of G0 PAMAM dendrimer of the diethylene glycol ester conjugate (G0-deg-NAP) to enhance permeability. G0-deg-NAP was hydrolyzed more rapidly in 80% human plasma (t1/2 = 51 min) and was rapidly cleaved in 50% liver homogenate (t1/2 = 4.7 min). Permeability studies showed a significant enhancement in the transport of naproxen when conjugated to dendrimers; L-G0-deg-NAP yielding the highest permeability. Dendrimer-based prodrugs with appropriate linkers have potential as carriers for the oral delivery of low solubility drugs such as naproxen. (Testa et al., 2009) also give their opinion over the use of dendrimers for the better transport of drugs across the cellular barrier, because dendrimers represent a class of polymers characterised by their well-defined structure, with a high degree of molecular uniformity and low polydispersity.

Targeted delivery is possible via targeting ligands conjugated to the dendrimer surface or via the enhanced permeability and retention (EPR) effect. Svenson S. (Svenson et al., 2009) use some dendremers such as poly(amidoamine) (PAMAM), poly(propylene imine) (PPI or DAB) and poly(etherhydroxylamine) (PEHAM) dendrimers, to associate with the many commercial small molecule drugs with anticancer, anti-inflammatory, and antimicrobial either via physical interactions or through chemical bonding (prodrug approach). Cationic surfaces of dendrimers show cytotoxicity; however, derivatization with fatty acid or PEG chains, reducing the overall charge density and minimizing contact between cell surfaces and dendrimers, can reduce toxic effects.

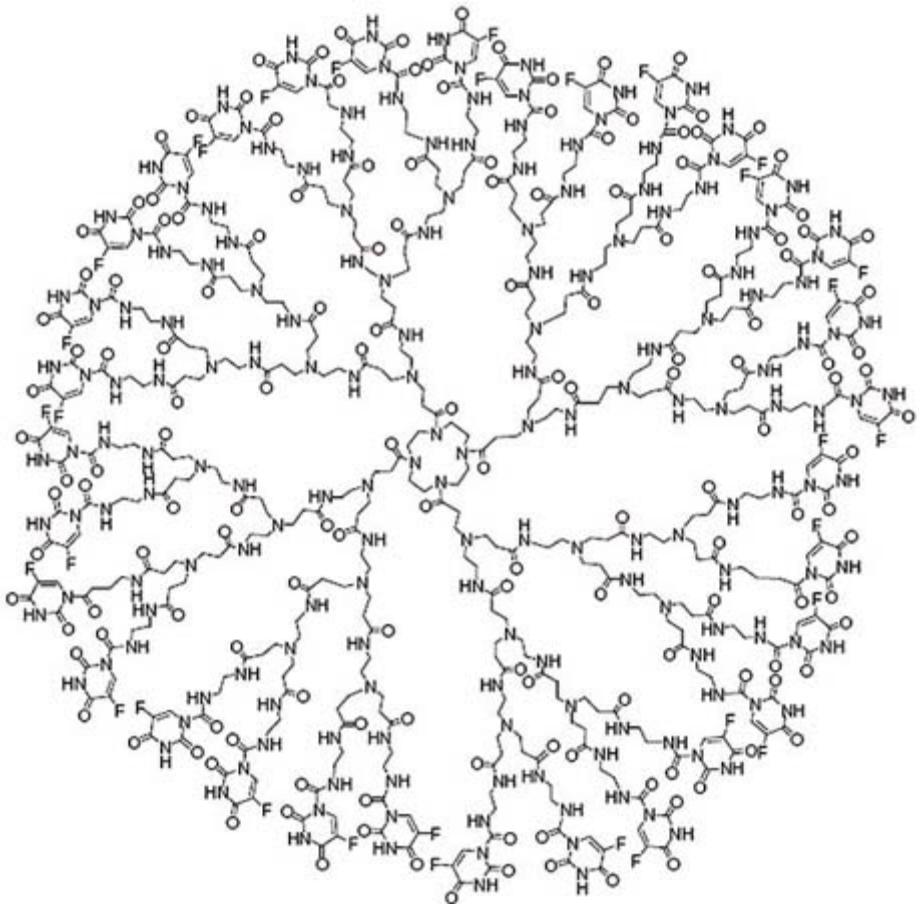

Figure 9. Chemical structure of 5-FU-PAMAM dendrimer conjugate. Reproduced with permission from.

On the investigation of the effect of poly(amidoamine) (PAMAM) dendrimer on skin permeation of 5-fluorouracil (5-FU) it was found that the increased skin partitioning of dendrimer from lipophilic vehicles increased the drug solubility in skin. Pre-treatment with dendrimer increased permeability coefficient of 5-FU by 4-fold in mineral oil and 2.5-fold in isopropyl myristate. Permeation studies were performed using excised porcine skin in a Franz diffusion cell and 14C labelled 5-FU samples were analyzed using liquid scintillation counter (Venuganti et al., 2008).

Inclusion complex of trazodone hydrochloride (TRD) with hydroxypropyl-β-cyclodextrin (HP-βCD) has been investigated by 1H NMR, 13CNMR, 2D NMR, FTIR and UV/visible spectroscopy. It was testified that the inclusion complex was formed between HP-βCD and trazodone Based on the enhancement of the absorbance of trazodone produced through complex formation, a spectrophotometric method for the determination of trazodone in bulk aqueous solution in presence of HP-βCD was developed. The linear relationship between the absorbance and trazodone concentration was obtained in the range of 5–30 μg ml−1 with a correlation coefficient of 0.9998 (Misiuk et al., 2009).

3.2 β-aminoketones

Mannich bases (β-aminoketones) have received rather less attention probably because they are not sufficiently susceptible to elimination at pH encountered in vivo. But Simplício

A.L. et al. (Simplicio et al., 2007) synthesized a series of amino adduct of chalcone and other carbonyl compounds which eliminate at around pH 7.4 (t1/2 < 15 min) releasing the amine and the ketone, which shows the greater lipophilicity than parent amines due to the significantly suppressed ionisation characteristics at biologically relevant pH values.

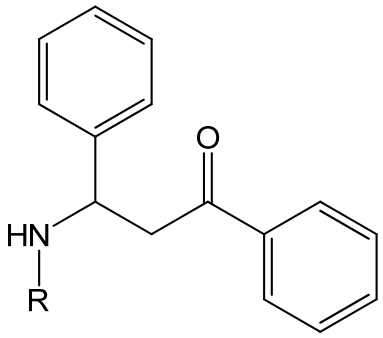

Figure:10. Structure of β-aminoketones

3.3 (Acyloxy)alkyl carbamates

This is another approach for the preparation prodrugs which increases the permeation of parent drug through the biomembrane. Majumdar S. et al. (Majumdar et al., 2006) synthesized N-alkyl-N-alkyloxycarbonylaminomethyl (NANAOCAM) derivatives of substituted phenols, theophylline (Th) and 6-mercaptopurine (6-MP) drugs and examined in in vitro diffusion cell experiments from IPM across hairless mice skins. The prodrug of acetaminophen and 6MP increased permeation across the skin by about 2- and 4-fold, respectively, compared to the parent drug. The ability of N-alkyl-N-alkyloxycarbonylaminomethyl promoiety to act as soft alkylating agent and its influence in increasing membrane permeation for phenols, imides and thiols have been probed.

For slowing down the too fast metabolic velocity and increasing the bioavailability of cordycepin, four N-acyl-(propionyl-, octanoyl-, lauroyl- and stearoyl-) cordycepin derivatives were synthesized chemically and their pharmacokinetic profiles were investigated (Wei et al., 2009). The Tmax, Cmax and AUC of N-octanoyl-cordycepin were nearly 4, 30 and 68 ti-

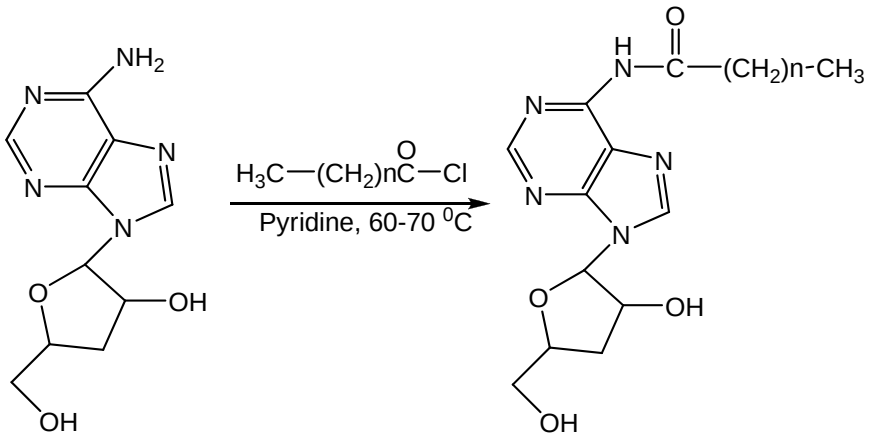

Figure:10. Structure of cordycepin and its prodrug N6-octanoyl-cordycepin.

mes respectively, higher than that of cordycepin. It indicated that N-octanoyl modification could decrease the metabolic velocity and increase the bioavailability of cordycepin to the maximum, thus it might be a promising prodrug of cordycepin.

Transdermal gel formulation for ibuprofen is prepared using Polyoxyethylene cetyl/oleyl ether and ethanol. Skin permeation rates and lag times of ibuprofen were evaluated using the Franz-type diffusion cell in order to optimize the gel formulation. The pharmacokinetic properties of the optimized formulation were compared with those of two marketed products in rats. The relative bioavailability of ibuprofen gel compared to the two marketed products was 228.8% and 181.0% (Rhee et al., 2008).

3.4 Trimethyl lock and coumarin systems

A novel coumarin-based highly water-soluble photocleavable protective group was used to design photosensitive protecting paclitaxel prodrugs. These novel paclitaxel conjugates demonstrated excellent water solubility, over 100 mg mL−1. Thus, the use of a detergent in the formulation can be omitted completely, even at high doses. (7-[Bis-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]amino]-4-[[3'-N-(2'-O-benzoyl-3'-N-deben-zoylpaclitaxel)] carbonyloxymethyl] coumarin hydrochloride) (Phototaxel) released the parent drug, paclitaxel, quickly and efficiently by minimal tissue-damaging 365 nm UV light irradiation at low power. For such prodrugs, tumor-tissue targeting after administration could be achieved by selective light delivery, similar to that used in photodynamic therapy. In addition, newly designed coumarin derivative 7-[Bis-[2-[[2-(dimethylamino) ethyl] amino]-2-oxoethyl] amino]-4-(hydroxymethyl) coumarin hydrochloride (a) can be applied in organic chemistry as a photosensitive protective group and for the design of caged compounds (Noguchi et al., 2008).

4. Applications of Amine Prodrugs

Amine prodrugs are widely used for the purpose of treatment or therapeutic use. The uses of Amine prodrug are increasing with study of drugs pharmacokinetic and pharmaceutical techniques i.e. computer aided drug designing, in vitro evaluation etc. There are many applications of Amine prodrug.

4.1. Prolongation of duration of action

Frequent dosing is required for drugs having short biological half-lives, this can be overcome by use of both controlled release and prodrug approaches. The two rate controlling steps rate of release of prodrug from the site of application or administration into the systemic circulation and rate of conversion of prodrug into active drug in the blood. Examples include the intramuscular depot injections of ester prodrugs of steroids and antipsychotics. Since testosterone and estriadiol are natural soft drugs their Amine prodrug is sometimes called as prodrug-soft drugs i.e. Testosterone cypionate, Testosterone propionate, Estradiol propionate, etc.

4.2. Bioavailability

Most drugs are absorbed by passive diffusion for which lipophilicity is an important prerequisite. The bioavailabilities of topically administered drugs also depend upon lipid sol-

ubility. Skin penetrability of polar drugs can be improved by esterification to form lipid soluble compounds. One of the best approaches in enhancing topical availability of drugs with carboxyl functions is their esterification with one of the hydroxyl groups of propylene glycol or glycerol. The later are common penetration enhancer components of topical formulations. E.g. glyceryl ester of naproxen (Holmgaard et al., 2010).

4.3. Drug Targeting

The prodrug is converted into its active form only in the target organ/tissue by utilizing either specific enzymes or a pH value different from the normal pH for activation i.e., Dopamine, a neurotransmitter, produces vasodilatation or renal tissue by binding to specific receptors in the kidney and thus can be used to treat renal hypertension. However, the therapeutic index of dopamine is small as it precipitates high blood pressure by interaction with the α-adrenergic receptors. This can be overcome by taking advantage of the fact that the α-glutamyl derivatives of amino acids and peptides selectively accumulate in the kidneys. Such a derivative of dopamine, on reaching the kidneys, is acted upon successively by two enzymes that are present in high concentration in the renal tissues, α-glutamly transpeptidase and L-aromatic amino acid decarboxylase to release the active drug dopamine locally. The increase in dopamine levels produces a marked increase in renal blood flow.

4.4. Administration of antiviral drugs

Another example of site-specific delivery is that of acyclovir, an antiviral drug useful in herpes infections. After entry into the infected cells, the drug is acted upon by the viral enzyme thymidine kinase to form acyclovir monophosphate that cannot diffuse back out of the cell. The monophosphate is further converted to the active triphosphate form by the cellular enzymes. The triphosphate then destroys the viral DNA. Thus, activation of acyclovir occurs only in the cells infected with the virus.

4.5. Targeting urinary tract

Hexamine (methenamine) is a prodrug of the urinary tract antiseptic formaldehyde. After oral absorption, hexamine remains inert and stable in blood at pH 7.4. When excreted in urine, the prodrug decomposes in the acidic pH to generate active formaldehyde, which exerts its antibacterial action in the urinary tract since 10 to 30% of the prodrug decomposes in the stomach and causes gastric distress; it is generally formulated as enteric coated/buffered tablets (Bannwarth et al., 2008).

4.6. Redox System for Drug Delivery to Brain

The high selectivity and poor permeability of the blood-brain barrier limits the delivery of hydrophilic drugs to the brain. A more recent, novel and smart approach for delivery of drugs to brain is use of dihydropyridine (pyridinium salt redox system. The drug to be delivered to the brain is covalently linked to the lipoidal dihydropyridine carrier groups to form a prodrug which will partition across, otherwise highly selective BBB. After administration, the prodrug is rapidly distributed throughout the body as well as in the brain. The reduced or the dihydro form of the carrier prodrug is oxidized by NAD-NADH system, both, in the brain and the body, to form lipid insoluble, polar quaternary pyridinium salt form (which is inacti-

ve). Thus, the drug is preferentially targeted to the brain whereas its systemic concentration is negligible. (Petersson et al., 2004) The Liver is the primary site for metabolism of almost all amide moiety containing prodrugs because of its relative richness in possessing a large variety of enzymes in sufficient amounts. The other organs are lungs, kidney, intestine, placenta, adrenals, skin, brain, muscles etc.

5. Future prospects

There is a wide variance in cytotoxicity between the prodrug and the activated form, i.e., Ganciclovir, 5-FloroUracil, Hexamine, etc. There is a reqirement to study the cytotoxicity caused by parent drug as well as their amine moiety contining prodrugs. Amine prodrug has shown a new way towards synthesis of molecules helpful in targeting. It can be expected that further research in this area will led to the development of prodrugs that can overcome the problems encountered with barriers like solubility, permeability, stability, presystemic metabolism and targeting limitations to the delivery of drug candidates.

6. Conclusion

The concept of prodrug is very interesting with respect to the chemistry involved and its variety of applications. Several amine prodrug approaches has been satisfactory employed to absorption of drugs resulted in improved bioavailability. One advantageous aspect of amine prodrug is that target selectivity can be achieved for antiviral and drugs used for treatment of urinary tract infection.

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Conflict of Interest

There are no financial contributions to the work in this article, which can be potential conflict of interest.

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