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Review On Prodrug : An Advance Approach for The Drug Design to Enhance the Therapeutic Efficacy

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Abstract: *Prodrugs are derivatives of drug molecules that are pharmacologically inactive but require either chemical or enzymatic transformation to release the active drug in vivo in order to exert a pharmacological effect. Prodrugs have better delivery properties that surpass the parent drug molecule. Prodrug concept is justified because it enables the active drug to overcome the barrier that would impede it from reaching the site of action to exert the required pharmacological activity.Some of the barriers that the prodrug approach helps to surmount are as follows, low bioavailability due to poor aqueous solubility (corticosteroids); poor permeability or absorption (ampicillin); high first pass metabolism (propranolol); metabolic instability leading to short half- life, (dopamine); poorsite specificity (anticancer agents); incomplete absorption (epinephrine); unfavorable organoleptic properties (chloramphenicol); difficulties during formulation and adverse effects and toxicity. The prodrug approach is rapidly becoming a crucial part in the stratagem of delivery of drugs. The prodrug strategy implementation in the last 20 y has led to a steady advancement in the biopharmaceutical, physicochemical and/or pharmacokinetic attributes of the pharmacologically active compounds.*

Keywords: *Prodrugs*

I. INTRODUCTION

The success of the prodrug approach can be measured by examining how many prodrugs are currently on the market. Around 10 % of marketed medicines can be categorized as prodrugs currently, and also that during 2008, 33 % of approved small molecular weight drugs were prodrugs, The objective of this review is to provide the researchers with compilation of which carriers would be suitable for prodrug synthesis and what would be their benefits. The prodrug approach is one of the efficient methods of modern research to develop more potent therapeutic agents in the field of medicinal chemistry. A prodrugrefers to a dormant masked form of active drug, which is steered to an activated form after a chemical or enzymatic reaction, once it has been administered into the body

II. CLASSIFICATION

Based on type of carrier moiety

Prodrugs are classified into two broad categories: **the carrier-linked prodrugs** and **bioprecusors**. The carrier-linked prodrug consists of the attachment of a carrier group to the active drug to alter its physicochemical properties and then subsequent enzymatic or nonenzymatic mechanism to release the active drug moiety. Thus the carrier-linked prodrugs are drugs with covalent linkage with specialized nontoxic protective groups or carriers or promoieties in a transient manner to alter or eliminate undesirable properties in the parent molecule. Depending upon the nature of carrier used, the carrier-linked prodrug may further be classified into the followings:

Double prodrugs, pro-prodrugs or cascade-latentiated prodrugs

Where a prodrug is further derivatized in a fashion such that only enzymatic conversion to prodrug ispossible before the latter can cleave to release the active drug.

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Macromolecular prodrugs

Where macromolecules like polysaccharides, dextrans, cyclodextrins, proteins, peptides and polymers are used as carrier.

Site-specific prodrugs

Where a carrier acts as a transporter of the active drug to a specific targeted site.Shaifali et al. World Journal of Pharmaceutical Research

Mutual prodrug

Where the carrier used is another biologically active drug instead of some inert molecule. A mutual prodrug consists of two pharmacologically active agents coupled together so that each acts as a promoiety for the other agent and vice versa. The carrier selected may have the same biological action as that of the parent drug and thus might give synergistic action, or the carrier may have some additional biological action that is lacking in the parent drug, thus ensuring someadditional benefit. The carrier may also be a drug that might help to target the parent drug to a specific site or organ or cells or may improve site specificity of a drug and overcome some side effects of the parent drugs as well.] The candidate drugs selected for mutual prodrug synthesis can be from one therapeutic category or from different therapeutic categories. Similarly, the constituent drugs of a mutual prodrug can act on the same biological target with similar mechanism of action or act on different biological targets with different mechanisms of action. Mutual prodrug of diclofenac with antioxidants is an example of this type. Decreased gastrointestinal irritation with synergistic analgesic action was found for benorylate, a mutual prodrug of aspirin and paracetamol linked through ester linkage. Mutual prodrugs of tolmetin with paracetamol and aspirin with salicylamide have been evaluated with the aim of abolishing the gastrointestinal toxicity of these drugs]Novel mutual pro-drugs by coupling of ibuprofen (NSAID) with sulfa drugs are interesting example to be understood where sulfa drug such as sulfanilide, sulfacetamide, sulfamethoxazole and sulfisoxazole used to overcome drawback of gastrointestinal (GI) irritation and ulceration produced due to free carboxylic group of ibuprofen by converting it into amide linkage

New classification: Based on cellular site of bioactivation

Prodrugs can be classified into two major types, based on their cellular sites of bioactivationinto the final active drug form (Table 1.1) with Type I being those that are bioactivated intracellularly(e.g., anti-viral nucleoside analogs, lipidlowering statins) and Type II being those that are bioactivated extracellularly, especially in digestive fluids or the systemic circulation (e.g., etoposide phosphate, valganciclovir, fosamprenavir, antibody-, gene- or virus-directed enzyme prodrugs [ADEP/GDEP/VDEP] for chemotherapy or immunotherapy).

Both types can be further categorized into Subtypes, i.e. Type IA, IB and Type IIA, IIB and IIC based on whether or not the intracellular bio activating location is also the site of therapeutic action, or the bio activation occurs in the gastrointestinal (GI) fluids or systemic circulations

III. NEWER ASPECTS

Cyclization-activated prodrugs

Oligopeptides are promising carriers for cyclization-activated prodrugs, as they are generally nontoxic, non-immunogenic, specifically targeted at epithelial transporters such as hPEPT1 or hPEPT2 and provide chemical diversity through their side chains so that drug release rates can be finely tuned. Further, their di- or tri-functionality offers a wide span of chemical routes for both prodrug synthesis and intramolecular activation. Oligopeptides can be attached to a drug through their amino groups, hence offering the C-terminal carboxyl group as nucleophile to promote intramolecular activation. Conversely, if the drug attached the peptide"s carboxyl, the N-terminal amino group will become available to eventually engage in a cyclization-elimination for prodrug activate.

Carrier based Classification :- According to Wermuth prodrugs can be divided into two main categories, bioprecusors and carrierlinked prodrugs. Bioprecursors do not have a promoiety or carrier but yield the active compound upon biotransformation. A bioprecursor prodrug is transformed chemically through hydration (for example, lactones such as some statins), reduction(for example, sulindac, platinum (IV) complexes) or oxidation (for example, dexpanthenol,

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nabumetone) or metabolically to the active agent .Carrier-linked prodrugs are for drugs with major drawbacks, which are linked to a nontoxic carrier or promoiety through covalent linkage tochange or get rid of their undesirable physicochemical properties. These prodrugs subsequently undergo enzymatic or non-enzymatic cleavage to release the active drug moiety . The main groups of carrierlinked prodrugs are amides and esters. Other groups include carbamates, phosphates, oximes, carbonates, N-Mannich and imines bases.Based on the essential characteristics of the carrier that is used, the carrier-linked prodrug can be classified further into, double prodrugs and mutual prodrugs. Double prodrug is derivatized further in a manner that only enzymatic conversion to prodrug is possible before the latter is able to cleave and releasethe active drug. A number of benzodiazepines are insoluble in water and therefore prodrugs which are water soluble are required for injections. Double prodrugs of benzodiazepines are prepared in which rate of cyclisation is influenced by the nature of amino acid carrier group . Macromolecules such as proteins, polymers, peptides, dextrans, polysaccharides, and cyclodextrins (CDs) can be employed as carriers in order to form macromolecular prodrugs. Site-specific prodrugs, where a carrier transport an active drug to a given targeted site

Mutual prodrugs are those in which, another active drug is utilized as a carrier rather than some inert molecules. It comprises of coupling two pharmacologically active agents in such a way that each active agent behaves as a promoiety for the other active agent and vice versa.The mutual prodrug carrier selected would have additional biological action that might be absent in the parent drug or both carrier and the parent drug might have the same biological action, which ensures synergistic action or some additional benefit (e.g. sulfadimidine, a mutual prodrug of ampicillin and sulbactam)

. The carrier can also serve as a drug that helps to target the parent drug to a given site or cells or organ or can improve a drug‟s site specificity (e.g. sulfasalazine, mutual prodrug of 5-aminosalicylicacid (5-ASA) and sulfapyridine . It can also be utilized to subdue the parent drug‟s side effects too (e.g. benorilate, mutual prodrug of paracetamol and aspirin) .The benefits of carrier-linked prodrugs include, an increase in absorption; pain relief on the injection site; reduction of GI irritation; masking of unpleasant taste; lowering toxicity; reduction of metabolic inactivation; increasing chemical stability and prolongation or shortening of the duration of action.

Criteria for carrier-linked prodrugs:

Certain criteria need to be satisfied for a carrier-linked prodrug to be a welldesigned A covalent bond binds the carrier to the drug. The prodrug needs to be inactive or rather less activecompared to the parent drug. The link ought to be bioreversible. To make sure that the site of action has effective drug levels, the active form generation must occur with rapid kinetics. The carrier and prodrug released after nonenzymatic or enzymatic hydrolysis must be nontoxic. A carrierlinked prodrug bioavailability is modulated through the use of a transient moiety. In case of carrier prodrugs, lipophilicity is a subject oextensive changes of the parent molecule. The bioactivation process is exclusively hydrolytic, although at times, it is a redox system.

Carriers or promoieties : The carrier or promoiety changes the drug‟s physical attributes to increase fat or water solubility or provide site-directed delivery. The choice of which carrier to use is dependent on the prodrug‟s purpose, the parent drug‟s available functional groups, the prodrug‟s enzymatic and chemical conversion mechanisms to parent drug, the carrier‟s safety, and the ease of manufacturing . Correct choice of a carrier is the most important part of prodrug design. It should be carried out with respect to the state of the disease, the dosage, and the therapy duration. As single parent drug can be derivatized to several prodrugs, this change is due only to the change in nature of promoiety.

This difference in the promoiety varies the cleavage of drug and promoiety bond .

Criteria for carriers:

In an ideal situation, the carrier should not have intrinsic toxicity. The carrier should also be nonantigenic and non-immunogenic, and should not accumulate in the body. Instead, the carrier should have satisfactory functional groups for adequate loading capacity and drug attachment. It should also be relatively easy to produce at a low cost. A carrier must remain stable under prodrug administration conditions, chemical manipulation and autoclaving. It should undergo biodegradation to inactive metabolites. Its characterization should be easy, and it needs to mask the liganded drug‟s

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activity until the active agent released at the desired action site. The carrier isexpected to have some biological activity of its own in relation to a mutual prodrug approach.

Lipids as prodrug carriers: Lipidic prodrugs, also known as drug-lipid conjugates, have the lipid moiety covalently bound to a drug. Drug-lipid conjugates are prepared so as to exploit the advantage of the metabolic pathway of the lipid biochemistry, and thus allow for targeting of organs or overcome delivery problems. Pharmacological half-life and pharmacokinetics of the drug can be improved by using lipid carriers, thus allowing for reduced dosing frequency. Lipids have other advantages such as an increase in absorption through intestines in regards to oral drugabsorption and to the central nervous system for brain delivery. In addition, drug targeting maybe enhanced usingthe lipid delivery systems. To target the liver, lipids are bound with endogenous proteins in the blood, which carries the lipids to the organ . Various natural lipid carriers are commonly used in the design of lipid prodrugs, including glycerides, fatty acids, and phospholipids. In designing the fatty acid-linked conjugates, the drugs are linked either to the ω- position at the end of the carbon chain orto the free carboxylate group (figure 3a). In case of conjugation to a carboxylate group, a drug containing an amino group or alcohol is linked to the fatty acid, which results in an ester or amide- linked conjugate, respectively. These conjugation strategies generally involve the use of an activating agent, such as N,N′-carbonyldiimidazole or carbodiimide, to convert the poor –OH leaving group to a better one, followed by the addition of an amine-or alcohol-containing drug ,This approach is the most common method of linking fatty acids and has been utilized for many parent drugs including non-steroidal antiinflammatory drugs (NSAIDs, ketorolac), angiotensinconverting enzyme inhibitors (enalapril), nucleosides (zidovudine) and testosterone Conjugation to the ω-position is preferable in cases where increased albumin binding and cell membrane transporter properties are preferred. For this method, an ω-modified fatty acid, such as amino or thiol.analogue,is utilized to link to the parent drug.

Amino acids as prodrug carriers: Amino acids do have proven record of being successfully used as promoieties in synthesis of prodrugs. In recent times, a hot field in regards to drug delivery research has concentrated on developing amino acid prodrugs for different active transporter targeted delivery goals. Most of amino acid prodrugs are either esters or amides, in which amine or carboxylic group of amino acid is attached to hydroxyl, amine or carboxyl group of drug moiety. Amino acids are biocompatible and easily ionisable. The amino acid prodrugs improve oral delivery of drugs, which have poor permeability and solubility. When an amino acid is introduced, be it a derivative or natural, to a parent drug, it normally rises the solubility in water by multiplier magnitudes via an ammonium cation or an ionized carboxylate anion. In addition, numerous transporters required for absorbing oligopeptides and amino acids are expressed in the epithelial cells of the intestinal brush- border membranes and have been discovered to play a substantial role in absorbing various amino acid prodrugs [38]. For instance, the enhanced oral bioavailability of valganciclovir and valacyclovir, amino acid ester prodrugs of ganciclovir and acyclovir, respectively, are ascribed to their enhanced intestinal transport through the H+- coupled peptide transporter 1 (PEPT1) In recent times, prodrugs of amino acid have ensured controlled drug release in the kind of lisdexamfetamine dimesylate, which is a L-lysine amino acid amide prodrug of D-amphetamine.Benefits of amino acids as promoieties include, large structural diversity; they are normal dietary constituents and are nontoxic in moderate doses as compared to other promoieties; a broad range of functional groups like hydroxyl, amine, or carboxylic acid group, which can be attached to parent drug; well established prodrug chemistry; commercial availability; fewer safety concerns; substrates for variousdifferent intestinal influx transporters; they have gastroprotective action; the availability of amino acid prodrugs those are commercially successful; utilized for the improvement of pharmaceutical attributes of difficult compounds or marketed drugs. All α-amino acids contain a chiral α-carbon with the exception of glycine, and are available in two optical isomers, D- and L-form. The L-form exists naturally. Assuch, the prodrugs prepared by using these amino acids are normally activated by enzymes that occur naturally. The L- and D-amino acid prodrugs have similar physicochemical attributes; however, the latter is stable against hydrolysis due to enzymes that occur naturally. This amino acid characteristic is frequently used by medicinal chemists to create stable prodrugs of aminoacid.

Furthermore, the large arrays of di-/tripeptides and synthetic amino acids like Damino acids, homo amino acids, beta-homo amino acids, N-methyl amino acids, α-methyl amino acids are commercially available as promoieties for medicinal chemists in addition to natural amino acids.When amino acids are promoieties, they offer the largest expanse and structural diversity of physicochemical

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properties. By selection of the proper amino acid, polarity, solubility profile and acid base properties of a given drug molecule can be altered. Few examples of prodrugs that are reported using amino acids as promoieties and the advantage .

Requirements for choosing polymers as drug carriers:The availability of suitable functionalgroups such as -OH, -COOH, -NH2, or -SH to covalently bind with drugs, biocompatible, non- immunogenic and nontoxic, biodegradable, molecular weight low enough to limit renal excretion, availability, reproducible manufacture, ease of administration to patients, hydrophilic to ensure aqueous solubility, low polydispersity and final conjugates should have a satisfactory homogeneity [68]. Prodrugs are increasingly becoming an integral component of the drug discovery stratagem. The rising percentage of approved new drug entities which are in fact, prodrugs, is a clear indication of their importance. Proper selection of a carrier is the most important part of prodrug design and synthesis. Selection of promoeity in prodrug research should be done wisely as it will determine the regeneration of active drug in vivo and also the promoeity itself should be nontoxic and excreted soon.

Applications :- 1. *Improving bioavailability when the drug candidate is not drug-like due to unfavorable physical properties as:*

- poor water solubility,
- low lipophilicity,
- chemical instability,
- unacceptable taste or smell,
- local irritation, pain.

Improving bioavailability when the drug candidate is not drug-like, due to pharmacokineticproperties:

- low bioavailability,
- poor penetration through biological membranes,
- increased first-pass metabolism,
- slow absorption by parenteral route,
- rapid absorption/elimination instead of long-lasting effect,
- lack of specificity in certain tissues [23-26].

The specific objective of prodrug design is to optimize unfavorable physicochemical properties, to increase chemical and/or metabolic stability, to achieve planned delivery.Prodrugs with optimized pharmacokinetic properties have the following advantages:

- obtaining parenteral preparations,
- masking unpleasant tastes, odors,
- avoiding injection site irritation or pain,
- preventing rapid administration site inactivation,
- increasing passage through the blood-brain barrier,
- tissue/organ specific drug administration,
- decrease in multidrug resistance,
- side effects - and toxicity profile improved.

Prodrugs with improved lipophilicity :-

In many medications a carboxyl functional group exists as indispensable function for their pharmacological activity. However, its presence causes too high polarity for oral ad-ministration,as in the small intestine at pH 5-7 it is largely ionized, which prevents the passage of molecules through membranes by passive diffusion. Esterification of these groups with short or longaliphatic alcohol is the most widely used method .ACE inhibitors are mostly ethyl ester prodrugs (enalapril, trandolapril,quinapril, benazepril). Ethyl esters considerable increase lipophilicity, thus increasing absorption (figure 2).Methyl ester occurs more rarely, because by hydrolysis toxic methyl alcohol is released. Therefore

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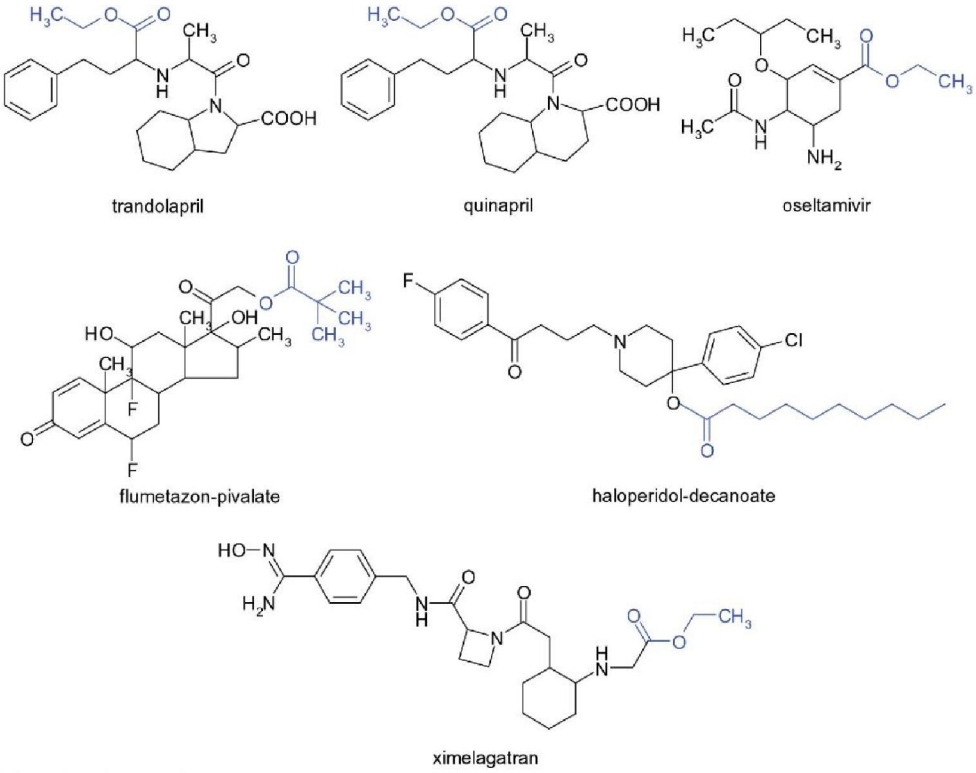
this method of design of prodrugs is used only in case of low dose medicines, respectively in the case of esters with very short duration



ɟ. 2. Examples of ester prodrugs

Optimization of bioavailability :- The purpose of prodrug synthesis in most cases is increasingbioavailability. They give good permeability, strongly influced by acid base properties.

IV. APPLICATIONS

The prodrug approach has broad range of application as:

In GIT problem: colon targeting Different approaches based on prodrug formulation, pH- sensitivity, time-dependency (lag time)microbial degradation and osmotic pressure etc are designed to formulate the different dosage forms like tablets, capsules, multiparticulates,microspheres, liposomes for colon targeting. Prodrugs that are chemically constructed to target colonic release or are degraded specifically by colonic bacteria can be useful in the treatment of inflammatory bowel disease (IBD). An amino acid (mutual) azo prodrug of 5-ASA was synthesized by coupling L-tryptophan with salicylic acid for targeteddrug delivery to the inflamed colonic tissue in IBD. In vitro kinetic studies in rat fecal matter showed 87.18% release of 5-aminosalicylic acid with a half- life of 140.28 min with first order kinetics. The synthesizedazo conjugate was found to produce comparable mitigating effect as that of sulfasalazine on colitis in rats without the ulcerogenicity of 5- aminosalicylic acid. Omeprazole . is a prodrug of a sulfonamide that exerts its potent anti-ulcer effects by covalently modifying cysteine residues on the luminal side of the proton pump (i.e., H+/K+-ATPase) in the oxyntic mucosa of the stomach. This prodrug only exerts its anti-secretory effect in the acidic environment of the oxyntic mucosa of the stomach

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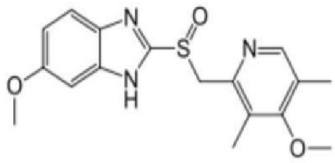

Figure 13: omeprazole

An amide prodrug (FLU-GLY) was synthesized by coupling flurbiprofen with Lglycine. This prodrug was much less toxic and had less ulcerogenicity activity than the parent drug. Selective delivery of drugs to the colon can be useful in terms of reducing the dose administered and reducing undesirable side-effects

Immunomodulators

Leflunomide novel immunomodulatory agent which exhibits a strong antiinflammatory action. It is potent therapeutic agent in autoimmune diseases, graft rejection, and tumors therapy. It is isoxazole derivative as a prodrug is completely converted to its active metabolite A 77 1726 (M1) which blocks the dihydroorotate dehydrogenase, a key enzyme of the pyrimidine de novo synthesis.

Anti-Tubercular agents

Ethambutol (EB), isoniazid (INH) and p-amino salicylic acid (PAS) are potent antitubercular agents having various side effects due to formation of toxic metabolites. Mutual prodrugs of EB with PAS , (PE), PAS with PAS (PP) and INH with PAS (PI) were synthesized and characterized. In vitro hydrolysis studies in SGF and SIF reveal that these mutual prodrug conjugates do not hydrolyze appreciably and are absorbed unhydrolyzed. In vivo studies showed greater serum concentrations of EB, PAS and INH than their concentrations when given alone and isoniazid concentrations were greater except for PP. Mutual prodrugs PI and PE significantly eliminate the problem of fast metabolism, toxicity and local irritation and reduction of therapeutic doses

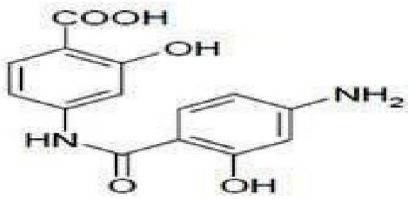

Figure 16: PI

Antiviral activity:-

The first diastereoselective synthesis of aryloxy phosphoramidate prodrugs of 30deoxy-20, 30- didehydrothymidine monophosphate (d4TMP) was reported where (S)-4-isopropylthiazolidine- 2- thione-1 was used as a chiral auxiliary to introduce the stereochemistry at the phosphorus atom. In the last step of the developed reaction sequence, the nucleoside analogue d4T was introduced to a stereochemically pure phosphoramidate which led to the formation of the almost diastereomerically pure phosphoramidate prodrugs 8a-d (g95% de).[41] A purine nucleoside, 2',3'-didehydro-2',3'-dideoxyguanosine (D4G) (Fig. 17) was found to be inactive in cell culture and lack of activity of D4G is primarily due to solution instability. D4G was modified at the 6 position of the purine ring to contain a cyclopropylamino group yielding the prodrug, cyclo-D4G having anti-HIV activity with increased stability, lipophilicity, solubility and decreased toxicity relative D4G

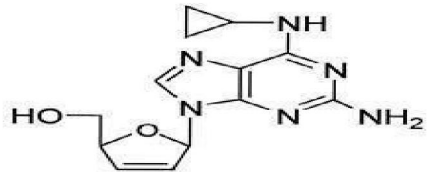

Figure 17: 2',3'-didehydro-2',3'-dideoxyguanosine (D4G)

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Quinidine was observed to be P-gp substrates cum inhibitors.[45] Quinidine, exhibit an uncertain combination of three distinct interactions with P-gp, It was conjugated to valine in the form of an ester to give Val-quinidine which is a good substrate for the aminoacid and peptide transporters present on the cornea. This identifies various amino acid and peptide transporters on the cornea including a Na+-independent large neutral amino acid transporter LAT1, a neutral, cationic amino acid transporter and oligopeptide transport system PepT1. So dipeptideaciclovir conjugate, Val-Val-ACV, was synthesized which was cleaved specifically by the dipeptidases, aminopeptidasesand cholinesterases and shown to be highly permeable across cornea (2.3-fold that of aciclovir). This conjugate showed excellent in vitro antiviral activity against HSV1 and very good in vivo activityagainst HSV1 rabbit epithelial/stromal keratitis.[22] Another drug pilocarpine was converted to its ester prodrug forms.Pilocarpic acid diester and monoesterprodrug solution showed significant biological activity and longer duration of action than pilocarpine.

Cholesterol-lowering prodrug :-

Simvastatin (SV) is a lactone prodrug which undergoes reversible metabolism. In the hydroxy acid form (SVA) it is a potent inhibitor of HMG-CoA reductase

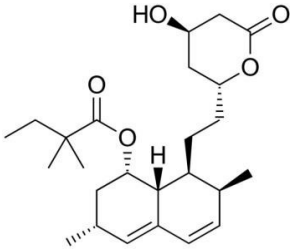

Figure 19: Simvastatin

V. CONCLUSION

By studying the following references the conclusion of my review article study is as “by using the advance techniques/approaches of the drug design we can enhance the efficacy of the drug or particular dosage form and we can make it more effective than the conventional drugs” In future for making the treatment more effective, prodrug development appears to be complementary. With the new discovery of enzymes, microbes and receptors in body, moretarget would be explored that will generate the new era of targetspecific medicines with desired pharmacological, pharmaceutical profile and this will be helpful in achieving best clinical drug application. The application of this prodrug strategyy will lead to the development of morepotent primary drugs with minimal side/toxic effect.

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