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Review Article

Pro-Drug Development

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ABSTRACT

Prodrugs can provide a flexible approach to enhance the efficacy or safety profile, as well as the poor pharmaceutical and pharmacokinetic features of potential therapeutic candidates as well as, in some situations, clinically authorized drugs. As the prodrugs are inactive form of the drugs which undergoes the metabolism it gives the formation of active compounds which is responsible for the therapeutic activity of drug. Right now the prodrug has more attention in the drug discovery and development. The current article focuses on the overview study of prodrugs like the definition, classification, benefits and types of prodrug design, the various applications of the prodrug as it has vital role in the potential therapeutic activity like cardiovascular disorder, Immunomodulator, antitubercular activity, Anticancer activity, GIT problems, Ocular drug delivery, List of Prodrugs with their uses.

INTRODUCTION

Utilizing prodrug tactics has numerous advantages. Prodrugs can provide a flexible approach to enhance the efficacy or safety profile, as well as the poor pharmaceutical and pharmacokinetic features of potential therapeutic candidates as well as, in some situations, clinically authorized drugs. However, significant resources have historically been invested in structure-activity optimization and formulation strategies to overcome such challenging constraints. However, the prodrug technique frequently poses a comparably lesser hurdle and is more realistic than the alternative of looking for a new candidate with the best attributes or adopting herculean formulation approaches. As a result, the prodrug strategy should be taken into account during the first stages of lead optimisation and used in conjunction with other strategies[1]. Given that several recently approved medications used prodrug techniques, it is obvious that this paradigm shift has attracted some attention. Between 2010 and 2014, a five-year span, the FDA approved 127 medicines with tiny molecular weights. 13 of these, or 10.2%, are unmistakably prodrugs.

Prodrug:

Prodrug is pharmacologically inactive and is transformed into active form by using an enzyme catalyzed by the liver. Adrian Albert first recognized prodrug methods in 1958 although they actually date back to the early 20th century, as

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demonstrated by methenamine, phenacetin, and prontosil7-9. Prodrugs are compounds with little or no pharmacological activity on their own but with an inherent structural lability that enables bioconversion in vivo, whether by chance or design. A combination of the two, as well as a chemical or enzymatic mechanism, might cause this change[2]. Prodrug, the soft drugs and the mutual drugs are designed for the different objectives of mind and once the soft drugs are administered either it is converted into the pharmacologically active compound or converted into the completely inactive compound. The soft drugs are usually used for the specific tissue targets such as tissue and eye. Clevidipine butyrate (Cleviprex) is an ultra-short acting calcium channel blocker it is administered through the intravenous route of administration by the hypertension patient individual. it is rapidly hydrolysed to gives the inactive metabolite furthermore once it is administered by the patient the drug produces the desired effect. Codrugs in contrast, prodrug in that they are composed of pharmacologically active drugs, but they differ in that two chemicals are joined together and one of them serves as the promoiety for the other. The US Food & Drug Administration (FDA) approved at least 30 prodrugs between 2008 and 2017 accounting for more than 12% of all small-molecule novel chemical entities (NCEs) and almost 10% of all approved drugs (which includes both biologics and NCEs).

BENEFITS OF PRODRUG

Aqueous solubility for parenteral drug delivery: The solubility of drug is essential for the intravenous and paracentral drug dosing. The partly soluble drugs are soluble in liquid with variety of formulation strategies. Mostly for the parenteral dosing the ionized and the polar drugs are used in in order to increase the aqueous solubility of drug. Whereas the non-ionized drugs used when the drugs with the polar functional group moiety.

a) ***Prolonged the duration of action*:** The controlled drug release formulations are widely used like suspension and polymeric metrics. The controlled drug release has advantages like it improved the patient compliance and reduces the dosing frequency. The prodrug used to formulate the controlled release of drug by improving the solubility of drug and dissolution rate. The prodrug also used in the development of sustained release formulation and intravenous injections.

b) For example, the most recent intramuscularly administered prodrug with an extended duration of action to receive FDA approval is aripiprazole lauroxil. It is used to treat adults with schizophrenia. It is a dodecanoic acid-acylated N-acyloxymethyl prodrug of aripiprazole, which features a particularly lipophilic N-hydroxymethyl group. Sorbitan monolaurate and polysorbate 20 are solubilizing components in the aripiprazole lauroxil suspension for intramuscular injection. Aripiprazole lauroxil is expected to be hydrolyzed by enzymes after being injected into the body, forming the N-hydroxymethyl intermediate, which is then vulnerable to non-enzymatic breakdown, releasing aripiprazole and formaldehyde.

After a single intramuscular injection of the prodrug, aripiprazole enters the body within 5–6 days, and its high plasma levels last for an additional 36 days.

c) ***Improved the metabolic stability*:** The metabolic instability mostly attributed the hepatic metabolism moreover the intestine is the major site for the metabolism of drug. The instability of drug may reduce the total amount of drug reaches to the systemic circulation. The prodrug is protecting the drug against the first pass metabolism by masking the pharmacological moiety like phenol hence it reduces the rate of metabolism this strategy is explained by considering example like bambuterol and terbutaline. Dimethylcarbamate promoters like bambuterol protect the two phenol moieties on terbutaline that are prone to rapid and

extensive first-pass metabolism in the stomach and liver. But once the bambuterol administered by the patient its slowly converted into the terbutaline and further monocarbamate metabolite by butyrocholinesterase enzyme present outside of lungs.

d) Amino acid promoeities in drug design and development [4]

***Advantages of amino acid as promoeities*:**

1. Well established prodrug chemistry
2. Large structural diversity
3. Availability of commercially successful amino acid
4. Used to improve the Pharmaceutical properties of marketed drugs

The majority of amino acid prodrugs are either esters or amides, in which parent functional groups (hydroxyl, amine, and carboxyl) are joined to the -amine or -carboxylic group of the amino acid. A parent medication can also be linked to an amino acid, amino or -carboxylic group via carbamate and carbonate linkages. The usage of amino acid side chains as prodrug handles offers a multitude of functional group opportunities, including amine, carboxylic acid, alcohol, and thiol. Although amino acids are typically directly conjugated to parent medications in most circumstances, bifunctional linkers have been utilized to further improve structural diversity and broaden the types of parent drugs that could be linked.

Prodrugs for better oral drug delivery:

Dealing with inadequate aqueous solubility, In development for the treatment of hepatocellular carcinoma and colorectal cancer, brivanib alaninate (BMS-582664) is an investigational amino acid ester prodrug of brivanib (BMS-540215), a selective dual inhibitor of vascular endothelial growth factor receptor 2 (VEGFR-2) and fibroblast growth factor receptor 1 (FGFR-1).[4] Brivanib has an extremely low solubility in aqueous solution (b1 g/ml at pH 6.5), which is thought to be a factor in its solubility/dissolution rate-limited oral bioavailability (22-88% in mice, rats, dogs, and monkeys), especially The rapid and full conversion of brivanib alaninat e to brivanib by several esterases, most likely duri ng absorption makes it an ideal oral delivery meth od for brivanib A selective nonpeptide NK1 neur okinin receptor antagonist that is utilised as an ant idepressant, antiemetic, and anxiolytic, CAM-4562 is a dimethyl glycine ester of CAM-4451. Due to low solubility CAM4451 has limited oral bioavailability.

CLASSIFICATION OF PRODRUG[15,16]

The prodrug is classified into different subclasses like intentional and fortuitous prodrug. The intentional prodrugs are designed for the modification of known active moiety and for the change in the structure of the active moiety. These prodrugs are used to improve the physical and pharmacokinetic properties of drugs. Fortuitous prodrug is prontosil The prodrugs are designed by two ways as prodhoc and adhoc.

According to the Newer classification the prodrugs are divided into two classes

Type I and type II (site of extracellular and site of intracellular) it is further divided into different classes type I (Type IA, Type IB) Type II- (Type IIA Type IIB, type II C) Prodrugs that fall under several categories are known as mixed-type prodrugs. This kind is one that undergoes conversion at several locations concurrently or sequentially. Type IA/IB prodrugs, such as HMG Co-A reductase inhibitors, are examples of prodrugs that are simultaneously converted in target cells and metabolic organs. A prodrug is referred to be a Type IIA/IA prodrug (for example, tenofovir disoproxil fumarate) when it undergoes sequential conversion, such as initially in GI fluids and subsequently systemically within the target cells. Prodrugs can also be categorized according to how they are activated, for as through oxidation, reduction, or hydrolysis.

***Oxidative bio activation*:**

A non- peptide angiotensin II receptor antagonist called losartan is used to treat hypertension. In vivo, the primary alcoholic function is converted into carboxylic acid functionality, which reflects

the true active moiety. Hence it can also be thought of as a bioprecursor prodrug. The bioactivation of the cytotoxic, antiproliferative, and non-specific to the cell cycle drug cyclophosphamide is thought to involve an initial oxidative dealkylation, followed by a spontaneous or phosphoramidase-catalyzed hydrolysis to the parent nitrogen mustard.

Reductive bioactivation:

The selectivity of many traditional anticancer medications for cancerous cells is generally weak, and radiation and chemotherapy are particularly ineffective against solid tumors. Solid tumors do, however, have some micro environmental characteristics such low pH, food restriction, and localized hypoxia. Antibacterial and antiparasitic nitroarenes like metronidazole have a well-known mode of action that includes in situ activation to hazardous chemicals. The strategy gives the recommencement of the discovery of various bio reductive prodrug and especially the drug is activated by reduction in the targeted tissues and low oxygen concentration. In such condition favor the reduction reaction. The antitubercular nitroimidazooxazine PA-824, which is now undergoing clinical trials provides bio reductive antimicrobial prodrugs. PA-824 is functional in its reduced form. Glucose-6-phosphate dehydrogenase, which is dependent on the flavin-containing cofactor 420 (F420), catalyzes the reduction of an aromatic nitro group in PA-824. There is evidence to suggest that the nitrenium cation, a potent and extremely reactive electrophile, is the active species in antimicrobial nitroarenes. The search for more selective anticancer drugs has used this idea. Different chemical techniques are being investigated to create bioprecursors activated by reductive enzymes to lethal chemicals, such as platinum (IV) complexes or N-oxides, as tumor cells have a greater potential for reductive activity than normal.

***Carrier linked prodrugs*:**

The majority of carrier-linked prodrugs are esters that have been activated by hydrolysis, either enzymatically or non-enzymatically. Adefovir dipivoxil, tenofovir disoproxil, pradefovir mesylate, and ester prodrugs have been employed to conceal carboxylate groups, phosphate groups, acidic tetrazolate groups, and alcoholic or phenolic functionalities. The various promoieties have been used in the carrier linked prodrug for example alkyl groups, aryl groups, simple or complex carboxylic acids, amino acids, and carbonic acid ester. The amide is the major functional group for the preparation of carrier linked prodrug. The amide consists of amine and carboxylic acid as an active agent. The mannich bases and imines have been derived to be used as prodrug of amine. The carrier linked prodrug must be converted into the active form for the effective drug delivery system at the site of action. Prodrug design is taking into the consideration the criteria found in case of orally active ampicillin derivative but the ampicillin is a broad spectrum antibiotic. This is poorly absorbed when administered through the oral route. The two drugs of the ampicillin have been derived by the esterification of carboxylic acid with lipid loving drug. Once the absorption is carried out it releases the carbon dioxide, formaldehyde and alcohol, pivalic acid from the pivacillin and the carbon dioxide, ethanol are released from the bicampicillin as a carrier drug molecule. These are considered as the natural metabolite present in the human body furthermore these are safer as it is confirmed from the clinical trial.

***Schiff base prodrug*:**

Enamines and imines can be efficient precursors to first amines. They are kept in place by hydrogen bonds. Typically, imines (Schiff bases) are too readily for use as amine prodrugs, materials must be hydrolyzed. Then again in some instances, they could be surprisingly stable and beneficial because they boost the parent's lipophilicity decrease the pKa values and amine. The tranquilizer GABA's aminobutyric acid (GABA) was created as a prodrug in the form of progabide hence it crosses the blood rain barrier and converted into the amino butiramaide and GABA and further it is trapped into the rain.

OBJECTIVES OF PRODRUG DESIGN[3]

***Pharmaceutical*:**

To make a substance more soluble (like corticosteroids).

To increase the stability of chemicals (like dopamine).

To enhance organoleptic qualities (for instance, chloramphenicol palmitate is a sparingly soluble precursor to chloramphenicol, which is hydrolyzed to active chloramphenicol by the action of pancreatic lipase and is essentially tasteless due to its low water solubility).

To lessen irritability and discomfort.

***Pharmacokinetic:*[10]**

1. Ampicillin, epinephrine, and propanolol are examples of drugs whose bioavailability can be increased by improving oral absorption or permeability.
2. To enhance absorption via extraoral methods.
3. To deliver an active drug with organ or tissue specificity.

***Pharmacodynamics*:**

To prevent negative consequences or toxicities.

To hide reactive species in order to raise its therapeutic effectiveness.

To increase site specificity, which refers to the fact that the location of action of an active medicine, such as an anticancer agent, is generally nonspecific.

Functional Group compliance for prodrug design:

Ester group[11]

Carboxylic, hydroxyl, amine, phosphate/phosphonate, and carbonyl groups are typical functional groups suitable for prodrug design. Prodrugs are frequently created by altering these groups, such as esters, carbonates, oximes, oximes, carbamates, and amides Amines can be converted into Mannich bases, enamines, and imines.

A drug's carboxylic or hydroxyl group may bind to an active site via ionic or hydrogen bonding and play a significant role in its action. At physiological pH, it is ionic, making it incapable of crossing the g.i.t. membrane. Most frequently, ester prodrugs are utilized to improve the liophilicity of drug and membrane permeability of polar drug by masking the hydroxyl and carboxylic group. Ester is the common functional group used in the design of prodrug. More than 50 % of marketed preparations, they are undergoes the activation by enzymatic ester hydrolysis. The ester is susceptible to hydrolysis and the most common enzymes are responsible for the hydrolysis like acetylcholine esterase, carboxyesterase, butyrylcholinesterase. An ester prodrug can frequently synthesizes by following the approach. Once within the body, common esterases quickly hydrolyze the ester link. Several alkyl and aryl ester prodrugs, including ACE inhibitors can be synthesize successfully. The enzymatic hydrolysis of prodrug is different from the non-enzymatic hydrolysis in the electronic steric requirement in the starting material.

The enzyme-catalyzed ester hydrolysis is influenced by both the aryl and alcohol region close to the cleavable ester bond. Direct ester synthesis with the existing functional group may occasionally fail to yield a prodrug that is sufficiently labile in vivo due to steric hindrance in the active drug. This issue can be overcome by employing -acyloxyalkyl (e.g., cefuroxime axetil) or alkoxy-carbamoyloxyalkyl esters (e.g., candesartan cilexetil) esters in cascade prodrugs containing double esters, where terminal ester group is accessible for enzymatic cleavage. The introduction of a double ester prodrug, which requires enzymatic breakdown and then releases the parent drug through a spontaneous chemical reaction, has led to faster bio activation. When synthesizing oral acyloxyalkyl drugs, the double ester prodrug technique has been the method of preference. e g Beta lactam antibiotics

Phosphate Group containing the amine, hydroxyl group:[11,12,13,14]

In order to improve the poorly water-soluble medicines' aqueous solubility, phosphate ester prodrugs are often created for the hydroxyl and amine functions. The aqueous solubility often increases in the presence of the dianionic

phosphate promoiety. When phosphatases are present at the intestinal brush border or in the liver, phosphate prodrugs often exhibit adequate chemical stability and quick bioconversion to the parent drug. Phosphate esters are frequently hydrolyzed by alkaline phosphatases, as opposed to carboxylic acid esters.

Only a small number of phosphate prodrugs for oral administration have been commercialized, despite the fact that there are numerous successful instances of parenteral phosphate prodrugs.

Oxime as a derivative:[12]

As derivatives of ketones, amidines, and guanidines, oximes (such as ketoximes, amidoximes, and guanidoximes) offer the chance to change molecules that don't have hydroxyl, amine, or carboxyl functionalities. The adaptable microsomal cytochrome P450 (CYP450) enzymes33, 34, also known as xenobiotic metabolizing enzymes35, 36, hydrolyze oximes. Oximes, particularly strongly basic amidines and guanidoximes, can be utilized to increase a parent drug's membrane permeability and absorption.

Improved the permeability:[8]

The main goal of prodrug derivatization of polar substances is to increase lipophilicity while maintaining an appropriate level of solubility in order to improve passive transcellular absorption. As a result, the design entails using the proper promoters to mask ionizable or hydrogen-bonding groups. This approach has typically proven effective, and several prodrugs in this category are currently being used in clinical trial. When the parent drug's low intestinal permeability poses a significant obstacle to bioavailability such as in the case of BCS Class III medicines (high solubility, low permeability) with low or moderate, permeability-enhancing strategies can be used. Several examples of prodrugs like angiotensin converting enzyme inhibitor and ampicillin antibiotics.

APPLICATIONS OF PRODRUG[9,16]

Anticancer agent:[17]

Chemotherapeutic Agent a two-step approach involving the manufacture of 2′-O-succinylpaclitaxel and PHEA-2′-O-succinylpaclitaxel was used to link paclitaxel to poly (hydroxyl ethyl aspartamide) via a succinic spacer arm. According to research involving murine myeloid cell lines, paclitaxel's partial pharmacological action is maintained by the polymeric prodrug. Compared to the free drug and naked polymer, the conjugation cleared the bloodstream at faster rate.

Development in prodrug design: Aldoxorubicin Anthracyclines in general and doxorubicin in particular continue to be essential components of sarcoma treatment. Their considerable toxicities, particularly heart toxicity, and dose-dependent adverse effects, however, severely restrict their prospective usage. By conjugating doxorubicin to albumin, aldoxorubicin was created, allowing for lower plasma concentrations of the drug and fewer adverse effects. When the compound builds up in tumor cells, liposomes break it into doxorubicin and albumin. According to studies, greater doses can be delivered with fewer adverse effects, which results in stronger tumor inhibition. Aldoxorubicin's first human trial was published in 2006, but it is not the only medication used to treat sarcomas; rather, it is a component of a treatment regimen. It is important to note that earlier preclinical evidence showed that aldoxorubicin was superior to doxorubicin, at least in terms of toxicity. As a result, it is reasonable to expect that aldoxorubicin merits additional, more carefully planned clinical trials to demonstrate its potential as a superior alternative to doxorubicin as long as it is one of the preferred treatment options.

GIT Problem:

For e.g. sulphasalazine which is formed by coupling of diazotized sulphanilamide pyridine with 5-amino salicylic acid. On oral administration intact sulphasalazine reaches the colon. The azo reductase associated with colonic microflora convert sulphasalazin to its constituent’s entities, the active species 5ASA available for absorption in colon, while precolonic absorption responsible for side effects is reduced.

Immunomodulatory:

Leflunomide is a novel immunomodulatory agent which exhibits a strong anti-inflammatory action. It is potent therapeutic agent in autoimmune diseases, graft rejection, and tumour therapy. It is isoxazole derivative as a prodrug and is completely converted to its active metabolite which blocks the dihydroorotate dehydrogenase, a key enzyme of the pyrimidine de novo synthesis.

Antitubercular agent:[7]

Three effective antitubercular drugs—ethambutol (EB), isoniazid (INH), and p-amino salicylic acid (PAS)—have a variety of side effects brought on by the development of poisonous metabolites. We created and described mutual prodrugs of EB with PAS (PE), PAS with PAS (PP), and INH with PAS (PI). These mutual prodrug conjugates, according to in vitro hydrolysis investigations in SGF and SIF, do not hydrolyze significantly and are absorbed unable to hydrolyzed. According to in vivo investigations, isoniazid concentrations were higher overall, with the exception of PP, and serum levels of EB, PAS, and INH were higher than when given alone. Mutual prodrugs PE and PI effectively remove the issues of rapid metabolism, toxicity, local irritation, and therapeutic dose reduction.

CNS delivery

L-dopa is the only prodrug that is clinically utilized to reach the brain primarily through LAT1-mediated transport. Due to its hydrophilic nature, the neurotransmitter dopamine is unable to cross the BBB. However, the brain can absorb dopamine via LAT1 because dopamine is converted into its -amino acid, L-dopa. In the brain tissue as well as the peripheral circulation, L-amino acid decarboxylase converts L-Dopa into dopamine. Although the peripheral tissues metabolize around 95% of L-dopa to dopamine, the remaining L-dopa has been therapeutically effective enough to use this method in clinical practice for more than 30 years.

Ocular delivery:

Pilocarpine was changed into one of its ester prodrug forms. In comparison to pilocarpine, the prodrug solution of pilocarpic acid diester and monoester demonstrated significant biological activity and a longer half-life. Bunod Latanoprostene The prodrug latiprostene bunod contains the two active moieties latiprostene acid and butanediol mononitrate, which together produce NO and are delivered in a 1:1 ratio. By hydrolyzing the prodrug, corneal esterase produces active drugs. Given that both of the active ingredients lower intraocular pressure, it is recommended for the treatment of glaucoma.

Cardiovascular system:

One of the oldest and most well-known prodrugs in the market is simvastatin. In order to produce the beta, delta-dihydroxy acid and an active metabolite with a structure comparable to HMG-CoA (hydroxymethylglutaryl CoA), its 6-membered lactone ring must undergo in vivo hydrolysis. Simvastatin's hydrolysis metabolite fights HMG-CoA for the enzyme HMG-CoA reductase, which catalyzes the conversion of HMG-CoA to mevalonate, a rate-limiting step in cholesterol production. Between 2013 and 2018, however, a large number of clinical trials examined the effects of statins alone or in combination.

The majority of them studies examined simvastatin's interactions with illnesses or conditions to see whether it was safe and whether it was better than other statins in specific situations. However, several trials haven't yet released their findings because they only employed simvastatin in their research. These include NCT03131726, which examined the effectiveness of simvastatin in the treatment of Graves' ophthalmopathy, and NCT03387670, which is a phase 3 trial of simvastatin in multiple sclerosis known as MS-STAT2. NCT03011931 evaluated simvastatin metabolism as a diagnostic for celiac disease activity. The latter was carried out in response to MS-STAT1 findings that showed patients on simvastatin saw less death of neurons than those taking a placebo. The secondary progressive MS stage (SPMS), which is the main cause of MS patients' severe impairment. Few medications exist now that can effectively

treat SPMS patients or reduce the course of their disabilities. The MS-STAT2 experiment proved that the prodrug simvastatin, which is already used to treat vascular disease and high cholesterol levels, might also be successfully used to treat SPMS. Adenosine diphosphate receptor blockers like clopidogrel and prasugrel, particularly thienopyridines, have been shown to be good platelet aggregation inhibitors and are still among the top options for preventing clotting problems and treating the effects of cardiovascular occurrences. This family of medications primarily inhibits platelets by inhibiting their P2Y12 receptors. Additionally, research revealed that clopidogrel (Figure 1) suppresses platelet aggregation caused by collagen and thrombin (for clopidogrel's activation pathway and mode of action). Most recent clopidogrel and prasugrel clinical trials aimed to determine the optimal dosages, treatment plans, and interactions with other common chronic illnesses like diabetes. However, no fresh signs were being looked into. Therefore, it is anticipated that these most recent clinical trials will contribute to the creation of future guidelines for ailments like acute coronary syndrome, angina, heart failure, atrial fibrillation, and others. It is important to note that the studies with clopidogrel and prasugrel prodrugs when administered with other medications meant to treat different illnesses should be carefully considered. These medications have the potential to prevent the prodrugs from being activated, which would halt the patient's recovery.

ACT-281959[18]

ACT-281959 A novel, powerful P2Y12 receptor inhibitor called ACT-24647 is being developed for subcutaneous injection as an alternative to thienopyridines like clopidogrel and prasugrel. The two ester chains on the phosphonic acid of ACT-24647's oral prodrug, ACT-281959, are hydrolyzed to activate the drugs . To assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of ACT-281959, one clinical investigation with the NCT01954615 code was completed. The trial showed the prodrug to be well tolerated and to produce dose-dependent quantities of the active form. There were no incidents of bleeding or dyspnea recorded; headache was the main side effect that occurred often. In patients with coronary artery disease, the prodrug merits additional research.

List of the Prodrugs[19]

Table No 1 List Of Prodrugs

Sr No	Name of drugs	Uses
1	Fosphenytoin	Status epileptics
2	Balsalazine	Ulcerative colitis
3	Cefpodoxime	Gonorrhea
4	Candoxatril	Angina
5	Docarpamine	Fever
6	Clopidrogel	Stroke
7	Adefovir	Hepatitis

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CONCLUSION

The Prodrug has attained the more attention in the drug discovery and drug development, improved drug delivery of drugs as it would increases the potential therapeutic activity. The different drugs have been invented for the enhancement of the pharmacokinetic and reduction of dose of drugs. The Prodrug development has a challenge for the formulation study and treatment of various diseases.

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