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PRODRUGS: A REVIEW

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ABSTRACT

Prodrugs are bioreversible derivatives of drug molecules that undergo an enzymatic and/or chemical transformation *in vivo* to release the active parent drug, which can then exert the desired pharmacological effect. This approach has several advantages over conventional drug administration. Prodrugs are with altered physicochemical, biopharmaceutical or pharmacokinetic properties of drugs so the efficiency of drugs gets improved with specific target delivery. This article includes classification, effect of prodrug on solubility, chemical stability, bioavailability, long duration of action and site targeted challenge with examples of prodrug illustrating the role of produg as a better way for the more effective treatment of different diseases.

KEY WORDS: Biopharmaceutical, Bioreversible, Physicochemical, Prodrug.

1.INTRODUCTION

The term “prodrug” or “pro-agent” was first introduced in 1958. Prodrugs are useful formulation with alteration of the physiochemical properties of drugs to render them pharmacologically inactive until metabolized in the body to the active drug moiety.[1] By definition, a prodrug is a compound that undergoes biotransformation before exhibiting its therapeutic effect.[2] Actually these are bioreversible derivatives of drug molecules that undergo an enzymatic and/or chemical transformation *in vivo* to release the active parent drug, which can then exert the desired pharmacological effect.[3] In these there is attachment of active moiety with inactive moiety which must be broken in body by action of enzyme. It is important that the inactive moiety should be non-toxic and preferably rapidly eliminated from the body.[4] Itself prodrugs are inactive compounds which are metabolized either chemically or enzymatically in a controlled or predictable manner to the parent active drug

inside the body. These can enhance the therapeutic efficacy and/or reduce adverse effects via different mechanisms, including increased solubility, improved permeability and bioavailability, prolonged half-life, and tissue-targeted delivery. Strategies to improve the oral bioavailability and achieve tumor-specific targeting have been the most important developments in prodrug design during the last 5 years.[5] With advancement there are many multistep activated prodrug are being produced as capecitabine (Xeloda) which is a prodrug having reduced gastrointestinal toxicity and high tumour selectivity. It undergoes multistep activation involves cleavage of the ester bond of the carbamate by carboxylesterases 1 and 2 followed by a fast, spontaneous decarboxylation reaction resulting in formation of 5'-deoxy-5-fluorocytidine (5'-dFCyd) on which cytidine deaminase (CDA) act to convert it into 5'-dFCyd to 5'-deoxyuridine (5'-dFUrd) that produce active drug 5'-fluorouracil in tumours by the action of thymidine phosphorylase.[6]

2. CLASSIFICATION OF PRODRUGS

2.1 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 specialised 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:

2.1.1. Double prodrugs, pro-prodrugs or cascade-latentiated prodrugs

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

2.1.2. Macromolecular prodrugs

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

2.1.3. Site-specific prodrugs

Where a carrier acts as a transporter of the active drug to a specific targeted site.

2.1.4. 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 some additional 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. [7] 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.[8] Mutual prodrug of diclofenac with antioxidantis is an example of this type.[9] Decreased gastrointestinal irritation with synergistic analgesic action was found for benorylate,[10] 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.[11] 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.[12]

2.2 New classification: Based on cellular site of bioactivation

Prodrugs can be classified into two major types, based on their cellular sites of bioactivation into the final active drug form (Table 1.1) with Type I being those that are bioactivated intracellularly (e.g., anti-viral nucleoside analogs, lipid-lowering 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 bioactivating location is also the site of therapeutic action, or the bioactivation occurs in the gastrointestinal (GI) fluids or systemic circulation.[13]

3. NEWER ASPECTS

3.1 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 is attached to the peptide's carboxyl, the *N*-terminal amino group will become available to eventually engage in a cyclization-elimination for prodrug activation.[14]

Table 1.1 Classification of prodrug based on site of conversion

Prodrug Types	Site of conversion	Subtypes	Tissue Location of Conversion	Examples
Type I	Intracellular	A	Therapeutic Target Tissue Cells	**Type: IA** Acyclovir 5-flurouracil Cyclophoshphamide L-Dopa
		B	Metabolic Tissues (liver, GI mucosal cell, lung, etc.)	**Type: IB** Carbamazepine Captopril Sulindac Heroin
Type II	Extracellular	A	GI Fluids	**Type: IIA** Sulfasalazine Oxyphenisatin
		B	Systemic Circulation and Other Extracellular Fluid Compartments	**Type: IIB** Acetylsalicylate Bacampicillin Chloremphenicol Succinate Fosphenytoin
		C	Therapeutic Target Tissue Cells	**Type: IIC** ADEPs GDEPs VDEPs

3.2 NO releasing prodrugs (NO-prodrgs)

The general structural features of NO–NSAIDs (nitric oxide releasing) enable a large number of variations within the linking spacer and the NO-donating moiety. Owing to the ease of

formation of these nitrate esters, several derivatives could be prepared for a given spacer. Two NO-releasing aspirins are 3-(nitroxymethyl) phenyl 2-acetoxybenzoate (NCX-4016) (Fig. 1) and 4-nitroxybutyl 2- acetoxybenzoate (NCX-4215) (Fig. 2).[15]

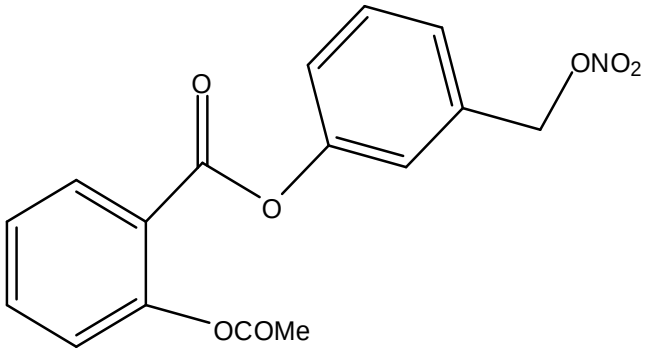

Figure 1: 3-(nitroxymethyl) phenyl 2-acetoxybenzoate

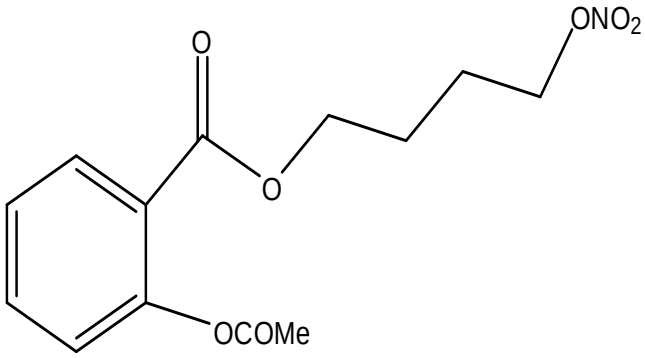

Figure 2: 4-nitroxybutyl 2- acetoxybenzoate

NCX-4016, a stable compound otherwise, requires enzymatic hydrolysis to liberate NO at a constant rate. Following intragastric administration of NCX-4016, levels of NO are elevated both in gastric contents and plasma. NCX-4016 was shown to possess greater anti-inflammatory and analgesic activities than aspirin. It also exhibited antithrombotic activity in several platelet dependent and independent animal models. NCX-4215 did not produce macroscopically visible histological damages in the rat stomach when administered up to 300 mg/kg, whereas 100 mg/kg aspirin produced widespread hemorrhagic damage.[11]

4. WHY TO USE PRODRUG?

Several pharmacokinetic reasons exist for developing prodrugs:

a) To achieve more complete or predictable absorption of the drug.

b) To reduce incomplete and variable systemic bioavailability by preventing extensive presystemic metabolism.

c) To improve access to the site of action, e.g. penetration of the blood-brain barrier.

d) To activate selectively a drug in the intended target tissue, thus avoiding undesirable systemic effects.

e) To optimize either the rate of onset or duration of action of a drug by improving absorption, distribution or elimination characteristics.[16]

f) Improve patient acceptability (decrease pain on injection).[17]

5. ADVANTAGES

Prodrugs are designed to overcome pharmaceutical, pharmacokinetic, or pharmacodynamic barriers such as insufficient chemical stability, poor solubility, unacceptable taste or odor, irritation or pain, insufficient oral absorption, inadequate blood-brain barrier permeability, marked pre-systemic metabolism and toxicity. Furthermore, attachment of a pro-moiety to the active moiety provides a way to overcome the barriers that hamper the optimal use of the active principle.[18]

5.1 **Aqeuous solubility**

Transscleral retinal delivery of celecoxib, an anti-inflammatory and anti-VEGF agent is restricted by its poor solubility and binding to the melanin pigment in choroid-RPE. So for this need the three amide prodrugs of celecoxib were synthesized celecoxib succinamidic acid (CSA) (Fig. 3), celecoxib maleamidic acid (CMA) (Fig. 4), and celecoxib acetamide (CAA) (Fig. 5). These showed lesser melanin binding affinity and capacity with aqueous solubility of CSA, CMA, and CAA were 300-, 182- and 76-fold higher, respectively than celecoxib. The celecoxib succinamidic acid was the soluble prodrug of celecoxib with reduced melanin binding which enhances transscleral retinal delivery of celecoxib.[19]

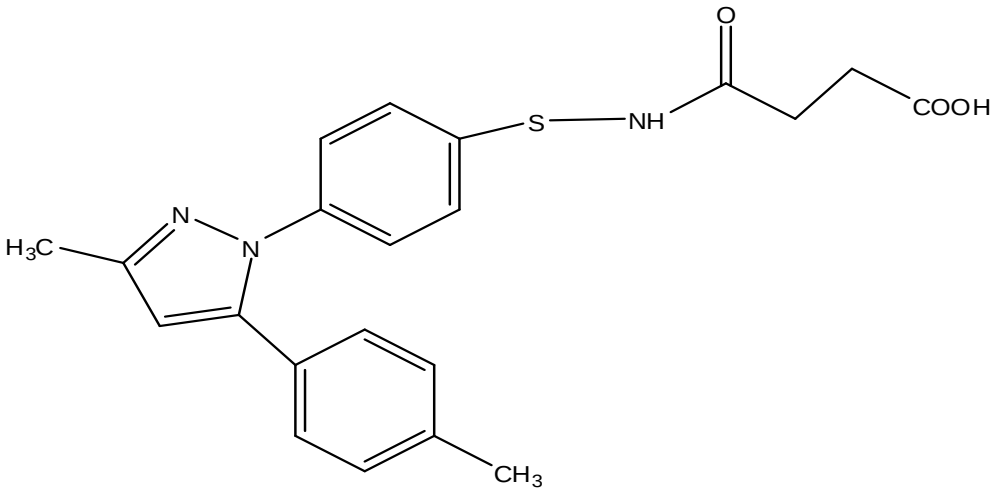

Figure 3: celecoxib succinamidic acid (CSA)

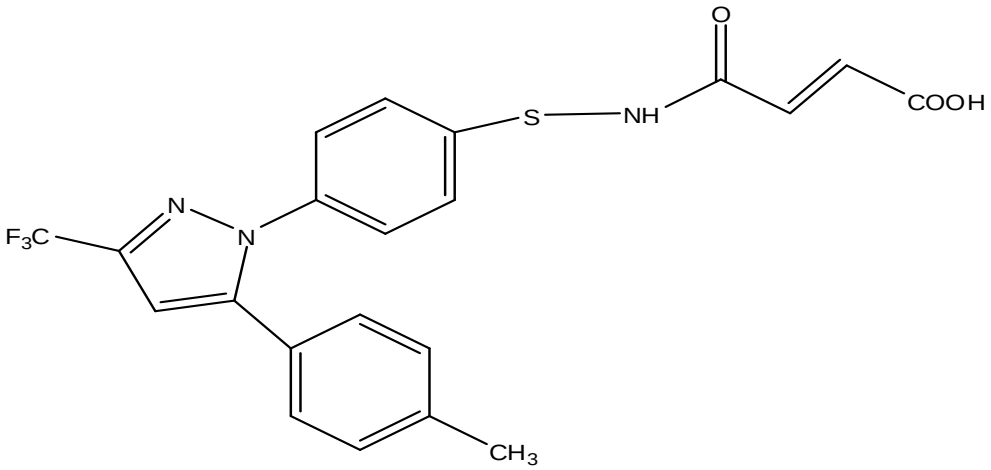

Figure 4: celecoxib maleamidic acid (CMA)

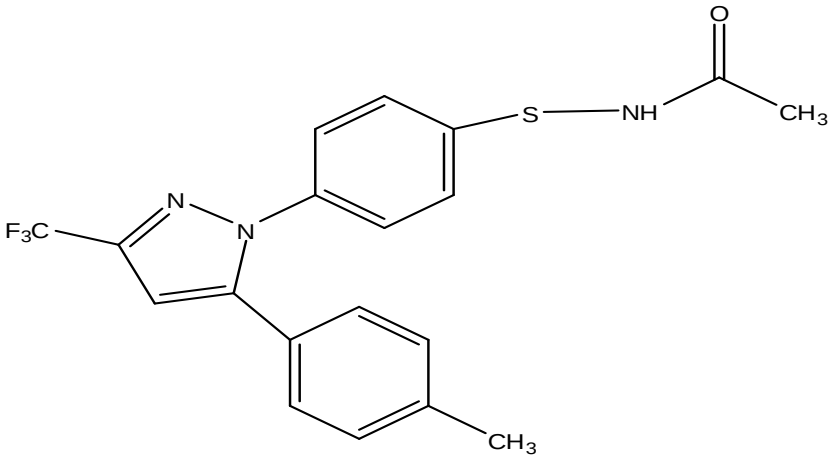

Figure 5: celecoxib acetamide (CAA)

Several other examples are as Miproxifene phosphate, TAT-59 (anticancer), phosphate ester of miproxifene/DP-TAT-59 and sulindac (non steroidal anti-inflammatory), oxide prodrugs of sulindac sulphide etc.[20] The lactol derivative of a lactone cyclooxygenase-2 inhibitor, DFU was found to be 10 to 20 times more soluble than DFU in a variety of aqueous vehicles. [21]

5.2 Oral bioavailability

Gabapentin is an anticonvulsant used for the treatment of epilepsy and post-herpetic neuralgia, but suffers from suboptimal pharmacokinetic properties including saturable absorption. XP-13512 was developed as an oral prodrug. XP-13512 is a substrate of MCT-1, a monocarboxylate transporter (MCT) which is highly expressed in all segments of the colon as well as upper GI. Oral bioavailability increased from 25% for gabapentin to 85% for XP-13512 in monkeys. XP-13512 is currently in two phase IIa clinical trials for post-herpetic neuralgia and restless leg syndrome.[22] Another such an example could be peptidomimetic

prodrugs of didanosine (DDI) that show improve oral bioavailability via targeting intestinal oligopeptide transporter (PepT1) and enhancing chemical stability like 5'-O-L-valyl ester prodrug of DDI demonstrated the highest membrane permeability and inhibited uptake of glycylsarcosine (Gly-Sar, a typical substrate of PepT1) by Caco-2 cells (Fig. 6).[23]

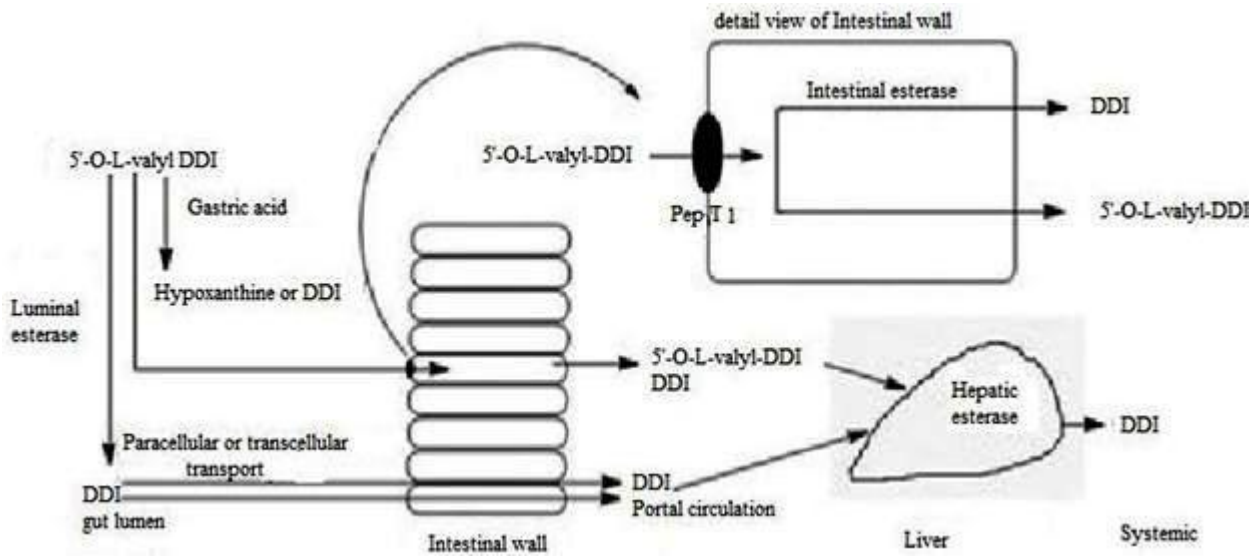

Figure 6: The prodrug is passed through gastrointestinal region where get cleaved with the esterase enzyme and transported via intestinal PepT1 in Caco-2 cells.

5.3 Chemical instability improvement

Potassium tricycle [5.2.1.$0^{2,6}$]-decan-8-yl dithiocarbonate (D609) is a selective antitumor agent, potent antioxidant, and cytoprotectant. It has dual therapeutic benefits against cancer, e.g., enhancing tumor cell death while protecting normal tissues from damage but it contains a dithiocarbonate (xanthate) group [O-C(=S)S^-/O-C(=S)SH], which is chemically unstable, being readily oxidized to form a disulfide bond so a series of S-(alkoxyacyl) D609 prodrugs (with varying the steric bulkiness of the acyl group) was developed by connecting the xanthate group of D609 to an ester via a self-immolative methyleneoxyl group which undergoes esterase-catalyzed hydrolysis of the acyl ester bond followed by conversion of the resulting hydroxymethyl D609 to formaldehyde and D609. These prodrugs are stable to ambient conditions, but readily get hydrolyzed by esterases to liberate D609 in a controlled manner. More importantly, the lead prodrug methyleneoxybutyryl D609 is biologically more effective than D609 in inhibiting sphingomyelin synthase, thereby increasing the level of ceramide and inducing apoptosis in U937 leukemia cells. Prodrug modification of the xanthate moiety with an alkoxyacyl group can improve D609 oxidative stability and enhance its antitumor activity.[24]

5.4 Long-duration of action

An example is the novel depots of buprenorphine esters prodrugs: buprenorphine propionate, enanthate and decanoate. These produced a long-acting antinociceptive effect after IM injection in rats.[25]

5.5 Improvement of absorption

Antibiotic prodrugs comprise the largest group of prodrugs developed to improve oral absorption. Pivampicillin (Fig. 7), talampicillin (Fig. 8) and bacampicillin (Fig. 9) are prodrugs of ampicillin. All these were resulting from the esterification of the polar carboxylate group to form lipophilic, enzymatically labile esters. The absorption of these prodrugs was found to be nearly complete (98–99%), whereas that of ampicillin is <50.[26]

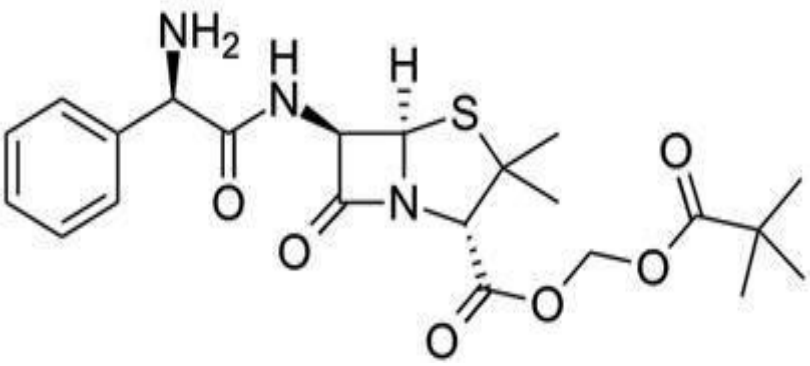

Figure 7: pivampicillin

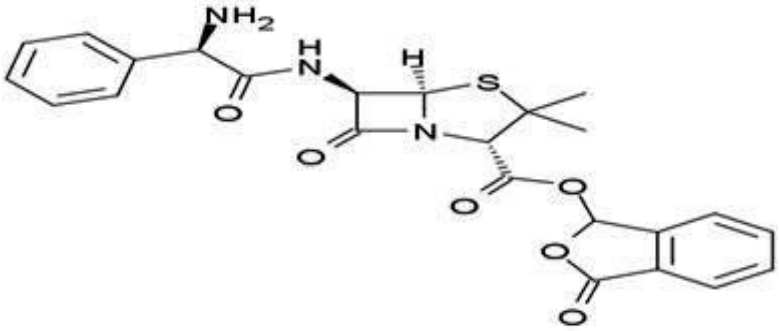

Figure 8: talampicillin

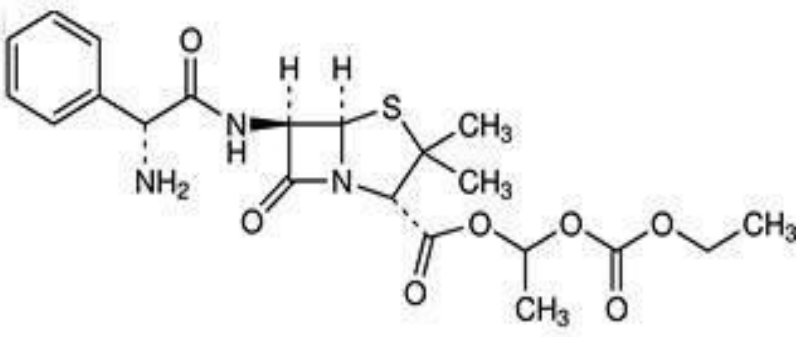

Figure 9: bacampicillin

6. SITE SPECIFICITY IS CENTRAL TO THE PRODRUG DEVELOPMENT

Prodrugs have an important role in site-selective delivery of radiopharmaceuticals. Site-specific prodrugs of diagnostic radiopharmaceuticals are routine in the nuclear medicine applications but the instances of targeting of radiotherapeutic prodrugs are surprisingly rare. Site-selective prodrugs of 5-[125I] iodo-2'-deoxyuridine (125IUdR) are used for cancer radiotherapy. The prodrugs of 125IUdR for targeted delivery include several derivatives with altered permeability like 3',5'-dioctanoyl, 3',5'-dioleoyl, 3'- and 5'-N-alkyl-dihydropyridyl, 3'- and 5'-N-alkyl-dihydroisoquinolyl and 3'- and 5'-N-alkyl-dihydroacridinyl esters of 125IUdR; polymeric and macromolecular prodrugs of 125IUdR for a carrier-mediated or local delivery; metabolically trapped 125IUdR prodrugs and glycoconjugate prodrugs for oral colon-specific delivery of 125IUDR, 125IUDR-5'-beta-d-cellobioside, 125IUDR-5'-beta-D-glucopyranoside, 125IUDR-5'-beta-D-galactopyranoside and 125IUDR-5'-beta-D-glucuronide.[27] With an antigen oriented targeting approach many prodrugs can be converted to its active form (free drug) on specific site like in case of ADC. Actually antibody-directed catalysis (ADC) is a two-step method for the delivery of chemotherapeutic agents in which enzyme-antibody conjugate, prelocalized to antigen-bearing tumor cells, catalyzes the site-specific conversion of prodrug to drug. An ADC system consisting of F(ab')-ÃŸ-lactamase conjugates and a cephalosporin derivative of the oncolytic agent 4-desacetylvinblastine- 3-carboxhydrazide was investigated in LS174T and T380 colon carcinoma xenografts in nude mice. Its activity was compared with that of free drug given alone and with covalent drug-antibody conjugates. Labile covalent drug-antibody conjugates prepared from the same antibodies were less effective than ADC and required much higher antibody doses.[28] Sulfasalazine (Fig. 10) is classic example of colon specific prodrug of 5-ASA and sulfapyridine (Fig. 11), in treatment of ulcerative colitis. This mutual prodrug is having azo linkage which is reduced in colon by azo reductases enzyme secreted by colonic microflora. [7]

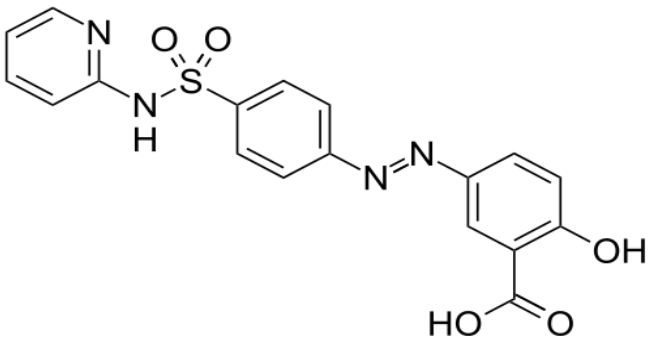

Figure 10: sulfasalazine

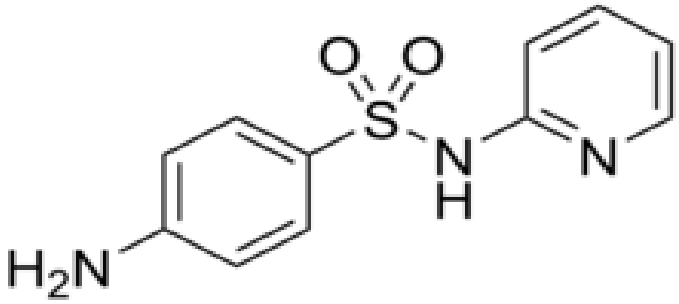

Figure 11: sulfapyridine

7. FUNCTIONAL GROUPS AMENABLE TO PRODRUG DESIGN

Ideally, the design of an appropriate prodrug structure should be considered at the early stages of preclinical development bearing in mind that prodrugs might alter the tissue distribution, efficacy and the toxicity of the parent drug. Several important factors should be carefully examined when designing a prodrug structure, including:

7.1 Parent drug: which functional groups are amenable to chemical prodrug derivatization?

7.2 Promoiety: this should ideally be safe and rapidly excreted from the body. The choice of promoiety should be considered with respect to the disease state, dose and the duration of therapy.

7.3 Parent and prodrug: the absorption, distribution, metabolism, excretion (ADME) and pharmacokinetic properties need to be comprehensively understood.

7.4 Degradation by-products: these can affect chemical and physical stability and lead to the formation of new degradation products.[3]

8. APPLICATIONS OF PRODRUGS

The prodrug approach has broad range of application as:

8.1 Anticancer agents

8.1.1 Chemotherapeutic agent

Paclitaxel was attached to poly (hydroxyl ethyl aspartamide) via a succinic spacer arm by a two-step protocol: (1) synthesis of 2′-*O*-succinyl-paclitaxel; (2) synthesis of PHEA-2′-*O*-succinyl-paclitaxel. Investigation carried out using murine myeloid cell line showed that the polymeric prodrug maintains partial pharmacological activity of paclitaxel. The conjugate disappeared from the bloodstream much more quickly as compared to both free drug and naked polymer. Massive accumulation of bioconjugate in the liver (80% of the dose) was found to persist throughout 1 week.[29] Many other prodrugs of paclitaxel have been generated such as a series of unsymmetrical polar disulfide prodrugs were designed and

synthesized as reductively activated prodrugs. These compounds behaved as prodrugs *in vitro* on L2987 lung carcinoma cells.[30] A radioactive indium probe in the form of indium-DTPA folate conjugate (111In-DTPA-folate) (Fig. 12) was evaluated in phase I/II clinical studies in 1999 by endocyte and showed great promise in localizing tumor sites.[22] It was appeared to be suitable as a radiopharmaceutical for targeting tumor-associated folate receptors.[31]

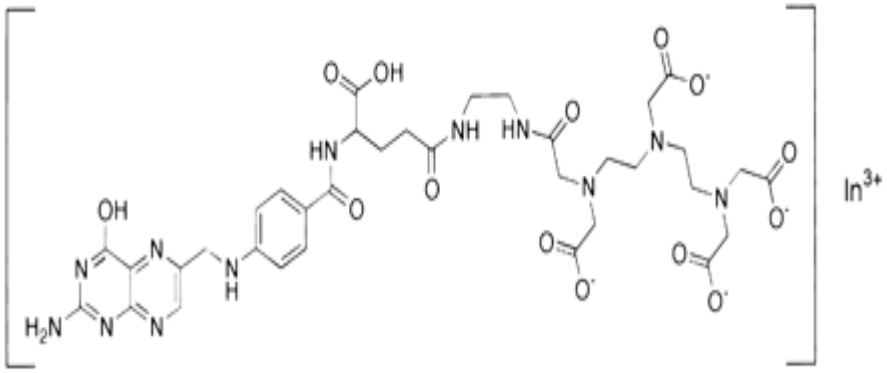

Figure 12: indium-DTPA folate conjugate (111In-DTPA-folate)

8.1.2 Antibody directed enzymes revive anti-cancer prodrugs concept

The approaches are based on the activation of specially designed prodrugs by antibody-enzyme conjugates targeted to tumor-associated antigens (ADEPT) or by enzymes expressed by exogenous genes in tumor cells (GDEPT).[32] For understanding, the example of monoclonal antibodies against tumour-associated antigens can be mentioned here. A fusion protein consisting of a human single chain Fv antibody, C28, against the epithelial cell adhesion molecule and the human enzyme b-glucuronidase was found to be useful in delivery of enzymes selectively to the site of a tumour for activation of a non-toxic prodrug. The prepared fusion was able to convert a non-toxic prodrug of doxorubicin, N-[4-doxorubicin-N-carbonyl(oxymethyl)phenyl]-O-b-glucuronyl carbamate to doxorubicin, resulting in cytotoxicity.[33] 5-fluorouracil-cephalosporin prodrug was used against colorectal and other cancers in antibody and gene-directed therapies**.** The compound was evaluated in the presence of *Enterobacter cloacae* P99 βL (ECl βL) revealing a K_m = 95.4 μM and V_{max} = 3.21 μMol min^{-1} mg^{-1}.[34]

8.2 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.[35] 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 targeted drug 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 synthesized azo conjugate was found to produce comparable mitigating effect as that of sulfasalazine on colitis in rats without the ulcerogenicity of 5-aminosalicylic acid.[36] Omeprazole (Fig. 13) 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.[37]

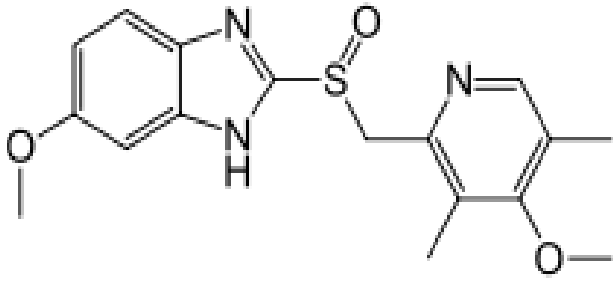

Figure 13: omeprazole

An amide prodrug (FLU-GLY) was synthesized by coupling flurbiprofen with L-glycine. This prodrug was much less toxic and had less ulcerogenic 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.[38]

8.3 Immunomodulators

Leflunomide 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 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.[39]

8.4 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 (Fig. 14) (PE), PAS with PAS (PP) (Fig. 15) and INH with PAS (PI) (Fig. 16)

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.[40]

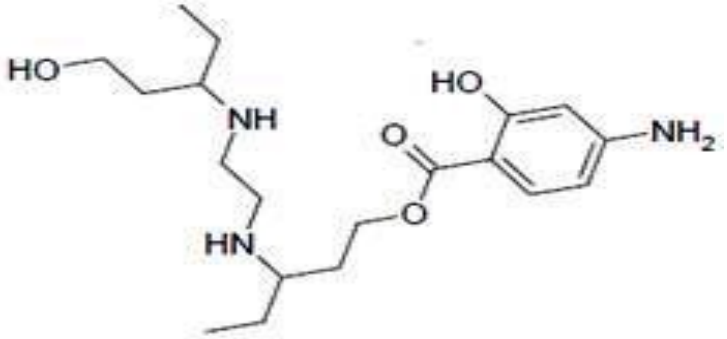

Figure 14: PE

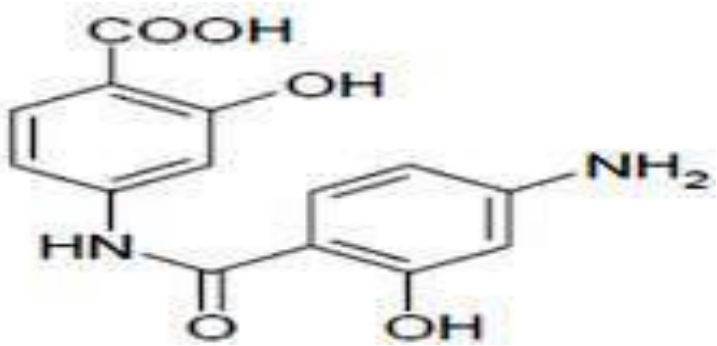

Figure 15: PP

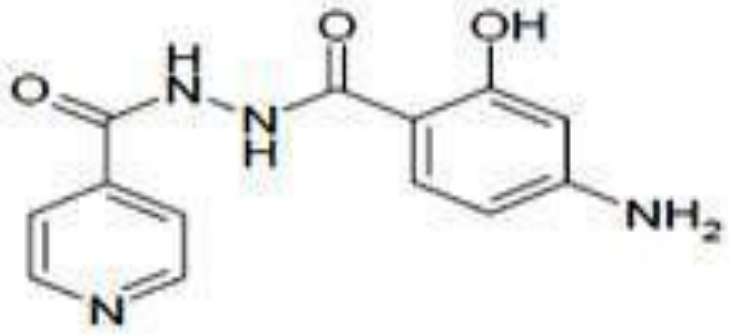

Figure 16: PI

8.5 Antiviral activity

The first diastereoselective synthesis of aryloxy phosphoramidate prodrugs of 30-deoxy-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 phosphordiamidate 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 to D4G.[42]

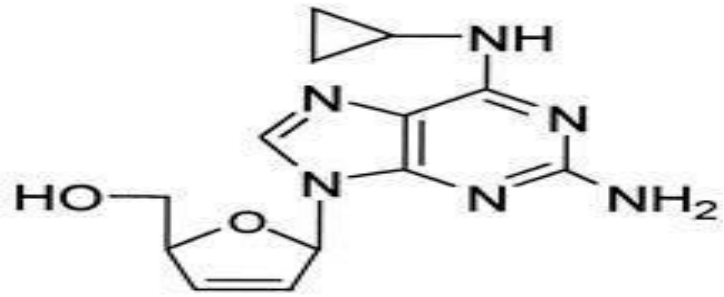

Figure 17: 2',3'-didehydro-2',3'-dideoxyguanosine (D4G)

8.6 Transdermal delivery

An investigation report states skin permeation of three novel mutual prodrugs (MP) in which n-acetyl-glucosamine is coupled with an NSAID, either ketoprofen or ibuprofen. They were evaluated for transdermal permeation. In MP1 and MP2 ibuprofen and ketoprofen were covalently to the amide nitrogen of n-acetyl-glucosamine (NAG) but another compound MP3 covalently links ibuprofen to the amide nitrogen, using a short chain acetyl linker. MP2 permeates shed snakeskin more than three times greater than either ibuprofen derivative.[43] Piperazinyl esters improved skin permeation of naproxen and are promising prodrugs of naproxen for topical drug delivery.[44]

8.7 CNS delivery

The only prodrug that is used clinically for entering the brain predominantly through LAT1-mediated transport is L-dopa. The neurotransmitter dopamine is not able to cross the BBB due to its hydrophilic nature. However, the conversion of dopamine into its α-amino acid, L-dopa, enables the brain to uptake dopamine *via* LAT1. L-Dopa is decarboxylated into dopamine by L-amino acid decarboxylase in the brain tissue and also in the peripheral circulation. Although approximately 95% of L-dopa is metabolized to dopamine in the peripheral tissues, the percentage of remaining L-dopa has been therapeutically enough to

apply this approach in clinic practice for more than 30 years. Another example of LAT1 utilizing prodrug is 4-chlorokynurenine, a prodrug of 7-chlorokynurenic acid.[1]

8.8 Ocular delivery

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 amino acid 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 dipeptide-aciclovir conjugate, Val-Val-ACV, was synthesized which was cleaved specifically by the dipeptidases, aminopeptidases and 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* activity against HSV1 rabbit epithelial/stromal keratitis.[22] Another drug pilocarpine was converted to its ester prodrug forms. Pilocarpic acid diester and monoester prodrug solution showed significant biological activity and longer duration of action than pilocarpine.[46]

8.9 For treating hypotension

L-*Threo*-3,4-dihydroxyphenylserine (LDOPS, droxidopa) is a norepinephrine (NE) prodrug under development to treat orthostatic hypotension (Fig. 18).[47]

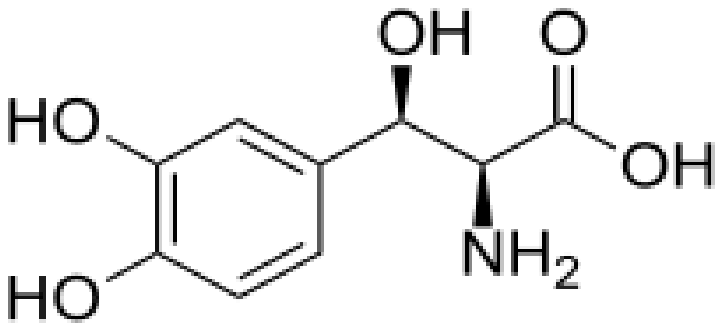

Figure 18: droxidopa

8.10 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 (Fig. 19).[48]

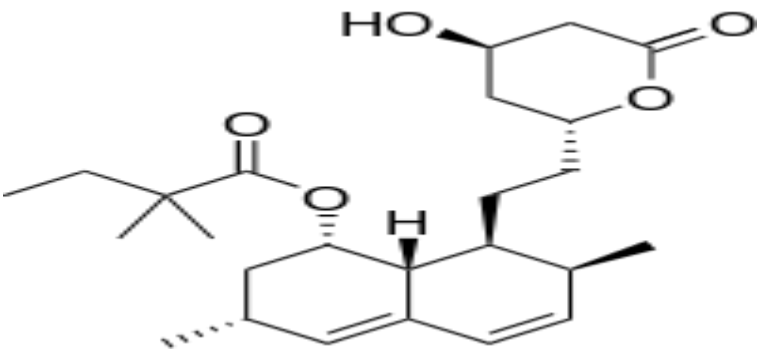

Figure 19: simvastatin

8.11 As new class of stimulants for the treatment of ADHD

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders affecting children. With use of prodrug technology the only developed prodrug stimulant, lisdexamfetamine dimesylate (LDX) (Fig. 20) provide a promising treatment option for ADHD with an improved overdose potential risk profile when compared to d-amphetamine. It is rapidly absorbed from the gastrointestinal tract and converted to d-amphetamine.[2]

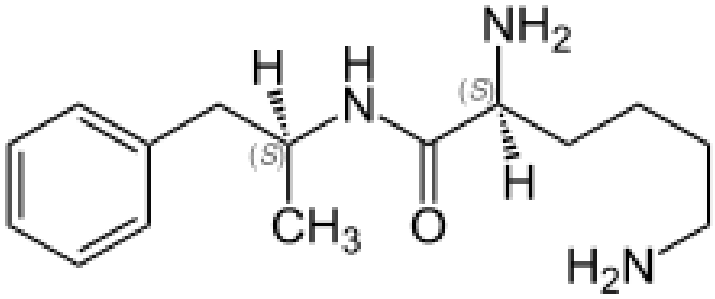

Figure 20: lisdexamfetamine dimesylate

8.12 Thrombolytic agent

Plasminogen activators, include streptokinase, urokinase and tissue-specific plasminogen activator tPA carries the risk of hemorrhage as a major side effect.[49] A heparin/protamine based prodrug system was developed for the controlled delivery of enzyme such as tissue-type plasminogen activator (tPA). This approach termed as antibody targeted, triggered, electrically modified prodrug-type strategy (ATTEMPTS), would permit antibody-directed administration of inactive tPA, and allow a subsequent triggered release of the active tPA at target site.[50] Another delivery system is novel heparin/protamine based enzyme delivery system that can deliver a PA drug without its associated bleeding risk. This system is composed of a large complex made of 2 components linked via a tight but reversible

electrostatic interaction. Therefore, similar to a "prodrug" type approach where the targeting component consisting of an antibody chemically linked with an anionic heparin molecule and drug component consisting of PA derivatized with cationic species. Modified PA would be without proteolytic activity during administration, but when reaches to sites of the clot free PA is released using the triggering agent protamine, which is the clinical heparin antagonist that binds heparin with even stronger affinity than the cationic species.[49]

CONCLUSION

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, more target would be explored that will generate the new era of target-specific medicines with desired pharmacological, pharmaceutical profile and this will be helpful in achieving best clinical drug application. The application of this prodrug strategy will lead to the development of more potent primary drugs with minimal side/toxic effect.

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