Citation: Ashraf, M. S., Rehman, I., Fatima, U., & Rehman, M. (2020). Approaches of Prodrug Designing to Treat Cancer, Neurodegenerative Disorders and Viral Diseases. *Global Drug Design & Development Review (GDDDR)*, *V*(I), 33-46. https://doi.org/10.31703/gdddr.2020(V-I).04

GDDDR GLOBAL DRUG DESIGN & DEVELOPMENT REVIEW

Pages: 33 – 46 | **Vol.** V, **No.** I (2020)

Approaches of Prodrug Designing to Treat Cancer, Neurodegenerative Disorders and Viral Diseases

Muhammad Shehzeb Ashraf [a]

Iqra Rehman [b]

Urooj Fatima [c]

Mubashar Rehman [d]

Abstract *Classical prodrug design is a sweeping approach to throw away futile side effects related to drug therapy. The main purpose of prodrug designing is to ameliorate physicochemical, pharmaceutical, and pharmacokinetic characteristics of particular compounds to resolve issues like formulation, delivery to the target site, and toxicity limitations. To fabricate the pharmacological action in CNS, drugs must cross the blood-brain barrier (BBB). Therefore, prodrug strategies are designed which include lipidization and the use of carriers and transporters. In this article, we have reviewed different anticancer, neuroprotective, and antiviral prodrugs. Flurbiprofen prodrugs, glycosylated prodrugs, resveratrol prodrugs, levodopa, etc., are mapped out for neurodegenerative disorders in CNS. Due to the poor oral pharmacokinetic properties of antiviral agents, drug design methods are performed by combining the parent drug molecule with a number of active components such as dipeptide esters, amino acids, nucleosides, and macromolecular-based prodrugs.*

Key Words: Cytochrome P450, Doxorubicin, Drug Delivery, Blood-Brain Barrier, Prodrug Design, Levodopa

Introduction

Prodrugs are entrenched notions to prevail over barriers of drug's usefulness. In Germany, 7% of the marketed drugs can be categorized as prodrugs. The term prodrug was commenced in 1958 by Adrien Albert to elucidate those compounds that encounter biotransformation prior to generating their required pharmacological effect (Ettmayer et al., 2004).

Sulfasalazine was the earliest prodrug and was accepted for use in the USA in 1950 and it is still in use there. Prodrugs have gained success in the past few years as 10% of drugs used in the market are prodrugs. Between 2000 and 2008, 20% of drugs having lesser molecular weight were recognized as prodrugs (Najjar & Karaman, 2019).

Approaches on Prodrug Designing

Prodrugs are the byproducts that are chemically inactive, and they are transmuted to their active configurations

by enzymatic or non-enzymatic reactions (Han & Amidon, 2000) (Järvinen et al., 2005). This phrase was manipulated by Albert to describe that the compound/molecule/moiety that is inactive and after entering the body it becomes pharmaceutically active.

[a] Undergraduate Students, Department of Pharmacy, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan.

[b] Undergraduate Final year students, Department of Pharmacy, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan.

[c] Undergraduate Final year students, Department of Pharmacy, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan.

[d] Assistant Professor, Department of Pharmacy, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan. Email: mrehman@qau.edu.pk

It is used to boost the bioavailability for the poorly absorbed drug. It enters the body in an inactive form and after binding with an enzyme, a reaction takes place and it converts to its active metabolite (Rasheed & Kumar, 2008). The prodrug strategy is mainly based on the type of target and its positioning in the body. We can convert the active metabolite to its prodrug by increasing lipidization or attaching the alkyl or glycosyl group to them to optimize the prodrug (Rautio et al., 2018).

By following different techniques, we can develop advanced drugs that are more potent pharmacologically but their physical, chemical, and biopharmaceutical properties are inefficient so it will lead to poor drug-like properties (Jana, Mandlekar, & Marathe, 2010). There are a lot of approaches we can apply to control substandard properties of the drug and how they are delivered to their target, one of them is designing the dosage form in the best manner, other is prodrug designing. Currently, prodrug designing and its related research are involved in the optimization of lead in drug discovery procedures (Järvinen et al., 2005). Prodrug designing has become an important part of drug delivery standards in large pharmaceutical companies and several small-scale biotech companies are also interested in prodrug designing applications to enhance drug functioning (Psimadas et al., 2012).

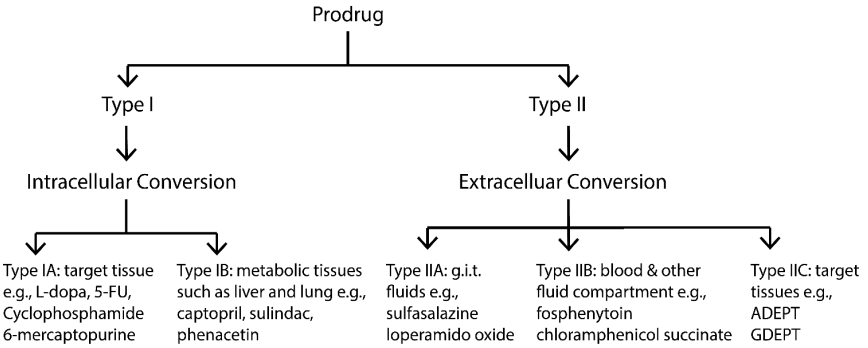

Figure 1: Categorization of Prodrug

In the prodrug designing approach, there is a technique of targeted prodrug design. It has two classes:

1. Targeting particular enzymes
2. Targeting certain membrane transporters

In the first class, enzymes are acknowledged as pre-systemic metabolic sites and are used to enhance oral drug absorption. In the second-class prodrug approach utilizes transporters for the transport of certain polar nutrients like amino acids and peptides. So, this strategy is important when prodrugs are polar or charged (Denny, 2004). Prodrugs are categorized as Intracellular (where conversion takes place inside the cell and Extracellular (where conversion takes place outside of the cell).

Prodrug Designing in Cancer Therapy

Classical Prodrug design is a non-specified approach based on chemical properties that are linked with masking the drug properties that are not required for example, limited bioavailability, lesser site-specificity and chemical instability issues (Han & Amidon, 2000).

In cancer treatment, we apply an approach which utilizes less toxic prodrug forms that are activated when coming in contact with tumor tissues, so these prodrugs are called "tumor activated prodrugs". Prodrugs can also be activated when we deliver exogenous enzymes to tumor cells by using Monoclonal antibodies (Denny, 2004). Various cytotoxins and chemotherapeutic drugs are used for the medication of cancer, but the drawback is that they also target healthy cells rather than cancerous cells, so this factor reduces their clinical efficiency. We require advanced drug designs where there is enhanced selectivity of destroying tumor cells. This design involves two units, the trigger unit, and the effector unit. The trigger unit is linked with the selectivity of the tumor while the effector unit is linked with the required level of killing of cells when the trigger unit is activated (Denny & Wilson, 1998).

A newer approach to prodrug designing is based on the molecular targets that are accountable for cell transformation (Huttunen et al., 2008). Nanomedicine therapy has played a vital role in many diseases and cancer. Nanomedicine based chemoimmunotherapy

has great potential. However, this approach has a number of drawbacks including limited entrance of such drugs into a solid tumor. So, a newer approach namely tumor microenvironment activable therapeutic peptide conjugated prodrugs were designed that led to increased tumor penetration(Zhu et al., 2020). The active form of prodrug must reside in tumor tissue for a time period that induces the cell death of the tumor (Huang & Oliff, 2001).

As nanocarriers deliver the loaded drug to tumor tissues more efficiently, but it also has the drawback that few nanocarriers have substandard loading ability so they need more shots to attain curative effect, which ultimately can lead to systemic toxicity and inflammation. Now in this case prodrug nanoparticles represent a more effective drug delivery system because they only get activated at target sites (Y. Zhang et al., 2016).

Another approach namely enzyme directed immunostimulant (EDI) prodrug concept. In this approach activation of immune cells takes place resulting in immunogenicity. In this method, prodrug is injected into active immunostimulants by cancer cells. A study was conducted in which it was examined that how EDI metabolism occurs in three distinct cancer lines i.e., B16 melanoma, TC2 prostate, and 4T1 breast cancer. B16 melanoma cell lines induced the highest immunogenicity (>95%) while TC2 and 4T1 cells produced 40% and 30% immunogenicity respectively (Ryan et al., 2020).

The development of prodrugs in cancer treatment has a strategy to improve various properties like biopharmaceutical properties, physicochemical properties, and pharmaceutical properties of potent and selective drugs. One type of powerful drug is bio precursors, which do not have bio transformed in vivo carriers for various enzymes (Jana et al., 2010).

Targeted prodrug schemes are being exercised to augment tumor selectivity and to lessen the aftereffects. The enzyme is first delivered to the target site and when we are sure that enzyme concentration in blood is zero, the prodrug would be administered that would be converted to its active form, so efficacy would be enhanced, and systemic toxicity would be decreased (Hou & Liu, 2020).

Carriers for enzymes to deliver them to the target site include ADEPT, VDEPT, and LEAPT. But a few restrictions of carriers include loss of enzyme activity, poor delivery progress, and uncontrollable phagocytosis. Several prodrugs are initiated by the enzyme beta-glucosidase, which activates the hydrolysis of the glycosidic bond of amygdalin and releases hydrogen cyanide, which lowers tumor cells by inhibiting cytochrome C oxide (Zhou et al., 2013).

Cytochrome p450 is involved in bioconversion of prodrugs to their active form of the drug. The role of CYP enzymes in prodrugs has promising advantages in cancer therapy. Although CYP enzymes are majorly present in the liver, it also targets prodrugs when in extrahepatic tissues, because of the large superfamily of CYP enzymes (Huttunen et al., 2008).

The General Concept of ADEPT and GDEPT

In this process, the antitumor antibody is conjoined with the enzyme, and is inhibited in this tumor by IV infusion. After the enzyme is inactive in the bloodstream, prodrug is given which can be stimulated by that enzyme conjugate. In GDEPT, certain genes encode prodrug activating enzymes, these are localized to tumor tissues. However, the gene having the prodrug activating enzyme will hold both normal and tumor cells (Han & Amidon, 2000). The gene involved in GDEPT is also called a "suicide gene". This suicide gene therapy is involved in both GDEPT and VDEPT (Lee et al., 2002).

Table 1. Prodrugs for Cancer

S. No	Prodrug	The active form of drug	MOA	CYP forms that are involved in the activation of prodrugs
1	Cyclophosphamide	Phophoramide mustard	Hydroxylation	CYP2B6 CYP2C9
2	Ifosfamide	Ifosfamide mustard	Hydroxylation	CYP2B6 CYP3A4
3	Dacarbazine (DTIC)	MTIC	Hydroxylation	CYP1A1 CYP1A2
4	Tamoxifen	4-Hydroxy-tamoxifen Endoxifen	Hydroxylation N-Demethylation	CYP2D6 CYP3A4

Doxorubicin Prodrug

In a study, the PEG-DOX-CUV prodrug was designed for its higher drug-carrying property and lesser unwanted effects. This prodrug is in the form of nanoparticles in which doxorubicin (DOX) and curcumin (cur) would deliver simultaneously to treat cancer as combination therapy. When PEG-DOX-CUV NPS would be incorporated by the tumor, the Schiff's base linker joining DOX and PEG would be scattered in an acidic medium, and doxorubicin and curcumin would release into the nucleus and cytoplasm of tumors with enhanced anti-tumor activity (Huang & Oliff, 2001).

Albumin binding prodrugs having doxorubicin complexes have shown anti-tumor activity. In this strategy, Albumin's binding prodrugs of doxorubicin are synthesized by an anti-prostate antigen, a serine protease indirectly expressed in prostate cancer. Various oligopeptides e.g., hexapeptides, decapeptides show more substrate specificity towards Human PSA, so there are incorporated in Albumin binding doxorubicin prodrugs (Kratz et al., 2005).

Carboplatin Prodrug

Platinum-based drugs e.g., carboplatin, cisplatin and oxaliplatin have a very wide scope in cancer therapy but they have more side effects and drug resistance, so carboplatin is loaded with Fe3O4 nanoparticles to make it a prodrug for its efficient Anti-tumor activity. Carboplatin-filled nanoparticles have a great potential for delivery, well-received by ovarian cancer cell lines through endocytosis (Song et al., 2019). Paclitaxel and cisplatin are widely used in combined chemotherapy for treating lung cancer, but it has a lot of systemic toxic side effects. Now to overcome these side effects, cisplatin/paclitaxel nanoparticles as a prodrug are developed that are efficacious in lung cancer. It works by exhibiting efficient cytotoxicity of tumor cells and effectively inhibiting tumor growth in-vivo (W. Zhang et al., 2016).

Platinum complexes act as prodrugs and they would be activated when they would reduce to platinum analogs. To improve the antitumor activities of carboplatin, the platinum complex was developed in a manner featuring equatorial ligand sphere of carboplatin and lipophilic axial carboxylate ligands (Varbanov et al., 2012).

Tamoxifen Prodrug

Tamoxifen is the front-line treatment for estrogen receptor-positive (ER+) breast cancer. CYP2D6 enzymatic activity is required for the conversion of tamoxifen to its active form that is 4-hydroxy-tamoxifen and endoxifen. Around 8% of breast cancer patients are resistant to tamoxifen because they lack the enzyme CYP2D6 (Jiang et al., 2012). A genetic variation in CYP2D6 is found in recent studies, as persons who lack CYP2D6 enzyme will have difficulty in tamoxifen conversion to its active form. Besides this, CYP2C9 and CYP3A4 also have a role in the metabolism of tamoxifen. Polymorphism in CYP2C9 will lead to enzyme inefficacy and it will ultimately lead to adverse drug reactions (Manish, Lynn, & Mishra, 2020). Tamoxifen is a selective estrogen receptor modulator (SERM) that hinders the binding of estrogen to its receptor and is productive in premenopausal as well as postmenopausal women (Hong et al., 2020).

Tamoxifen employs its pre-emptive effects by seizing cell proliferation and bringing about Apoptosis. In accordance to a study, taking tamoxifen treatment 5 years consecutively can reduce the death rate by 31% (Chang, Pan, & Lee, 2018).

Prodrug Designing in Neuro-Degenerative Disorder

The blood-brain barrier is the crucial hurdle for the drug to show its pharmacological action. Some drug might
have large molecular weight or other are highly hydrophilic (Henderson & Piquette-Miller, 2015) (Li, Boado, & Pardridge, 2001). With the development of science and technology, different designs are being proposed in which one is a prodrug (Pardridge, 2002). Prodrug easily penetrates through BBB (blood-brain barrier) and after entering the blood-brain barrier it gets separated from its parent active moiety and the drug exhibits its effect. Another approach is to reduce the molecular weight of the drug and use different transporter for diffusing the drug across the BBB. If the lipophilicity of the drug molecule is increased it can easily cross the blood-brain barrier (Banks, 2009). But the main drawback is that it is highly absorbed in the brain. It is unable to move back and gets trapped so prodrug is the good candidate for lipidization but there are limited prodrugs e.g. ester prodrug candidate. Another approach is through a chemical drug delivery system which involves the chemical modification of drug molecules. Therefore, it can easily cross the blood-brain barrier and shows its effect. Different transporters are used for prodrug delivery the most common is LAT-1 (Large amino acid transporter 1) (Gynther et al., 2008) (Peura et al.,

2011).To LAT-1 meta substituted phenylalanine prodrug (Valproic acid) had greater affinity as compared to the para-substituted derivative (Gynther et al., 2008). LAT-1 antagonist can minimize the binding of LAT-1 to prodrug (Peura et al., 2011) (Montaser et al., 2020). The main strategy of the prodrug is that they bind to FAAH (fatty acid amide hydrolase) and this enzyme clears the prodrug in the brain and the drug produces their pharmacological effect. So we should design such prodrugs or nuclear receptor modulators which are the better substrate of FAAH enzyme (Meinig et al., 2019) (Ferrara & Scanlan, 2020) .

Table 2. Prodrugs for Neurodegenerative Disorders

S. No	Prodrug	Active form	Enzyme involved	MOA
1	Levodopa	Dopamine	Dopamine decarboxylase	It crosses BBB and converted to dopamine
2	Flurbiprofen axetil	Flurbiprofen	Carboxylesterase	After crossing BBB, it gets separated and the drug was released in lysosome mimicking medium
3	Triacetyl resveratrol	Resveratrol	Deacetylase	Increases BCL-2 expression and decreases BAK expression

Flurbiprofen Prodrugs

Flurbiprofen prodrugs are used against the prolifertion of the neurodegenerative disorder. The physicochemical properties of the drug can be found by molinspiration, ADME software, etc. The carboxylic group of flurbiprofen has a very important role in transport as it combines with amide moiety to form a prodrug which can easily be crossed by the blood-brain barrier (Ferrara & Scanlan, 2020) (Najjar & Karaman, 2019) (Investigation & Hepatotoxicity, 2011). The docking score shows the efficiency of the prodrug of flurbiprofen to cross the BBB. Examples of amide prodrug are Dicyclohexylcarbimide. (Investigation & Hepatotoxicity, 2011)(Perioli et al., 2004).

HCT-1026 is another prodrug i.e. R-Flurbiprofen in which no carrier is present, and it helps in increasing the safety profile and pharmacological action. These prodrugs help to restore cognitive function by NO/cGMP signaling and in this way they treat dementia (Abdul-Hay et al., 2009)(Bondì et al., 2013). Flurbiprofen also binds to nano base drug transporter e.g. ε Lysine and can be transported across BBB through AMT (adsorption mediated transcytosis). After entering the carrier gets separated and the drug was released in a lysosome mimicking medium and shows its pharmacological action (Al-Azzawi et al., 2020). This is used as a medication for Alzheimer's disease by increasing the hydrophobicity of the drug as it binds to the carrier (Al-Azzawi et al., 2020)(Perioli et al., 2004). The complex structure can be found by FTIR (Fourier transform infrared) spectroscopy (Investigation & Hepatotoxicity, 2011) (Al-Azzawi et al., 2020).

Glycosylated Prodrugs

Microglia's dysfunction may lead to neuroinflammation and accumulation of the Aβ pathway, DAPPD (N, N diacetyl-p-phenylenediamine) suppress NLRP3 by NFK β pathway and also reduces aggregation of Aβ (Kim et al., 2020).

Another prodrug called as hydroxy pyridinones is a prodrug and has metal chelation action and assists in the detachment of Aβ, any drug concerning metal ions is very favorable for the management of the neurodegenerative disorder, Glycosylation intensifies the action of the drug. The glycosylated complex has better cytotoxic, anti-oxidant, and can chelate metal for properties (Scott et al., 2011).

Ros Responsive Prodrug

Many Alzheimer disease drugs were being suggested but the major drawback is that all the drug targets one pathway (Oliveri, 2015) (Toublet et al., 2020) but ROS responsive prodrug is a multi-targeted directed ligand which shows anti-inflammatory activity and also inhibits the acetylcholinesterase enzyme. The ROS responsive prodrug therapy is the most advanced

treatment for neurodegenerative disorder (Oliveri, 2015).

Pleiotropic Prodrug

All the patients having neurodegenerative disorder are treated with acetylcholinesterase inhibitor but recent studies have shown that butyl cholinesterase is also responsible for the disease, so MTDL drug class named Pleiotropic prodrug was designed which targets more than one pathway (Toublet et al., 2020) (Christophe & Patrick, 2018). These are butyl cholinesterase inhibitor as well as 5HT6 receptor antagonist and the prodrug is pleiotropic carbamate (Toublet et al., 2020). Another novel drug name Revastigmine, a pleiotropic prodrug that inhibits acetylcholinesterase as well as also targets 5HT receptor mainly 5HT4 receptor.

Resveratrol Prodrug

Due to the recent development in nanotechnology different prodrugs entered into the body through nanoparticle carrier. Microglia is responsible for removing the microbes and pathogen; continuous exposure may harm microglia (Zhao et al., 2020).

Resveratrol is the drug for Parkinson's disease, but it is not extensively distributed because of its limited ability to cross BBB hence bioavailability is less. So its prodrug is formulated i.e., alkylated, glycosylic prodrug which shows antioxidant and anti-inflammatory, neuro-protective effect and they can easily cross BBB (Peñalver et al., 2018) (Wang et al., 2020). Resveratrol is used to treat Huntington's disease with its eighth derivative. (Peñalver et al., 2018). Another study shows that resveratrol had a high affinity toward hub genes including AKT1, MPK3, TNF, etc and it increases the BCL-2 and decreases manifestation of BAK. Moreover, it also stops glutamate-induced apoptosis. In this way, it targets more than one receptor or gene and shows its neuroprotective function (Wang et al., 2020).

Levo-dopa Prodrug

In Parkinson's neurodegenerative disorder dopamine was administered earlier but the limitation is that it cannot cross the BBB. So nowadays levodopa is administered but it also had downsides such as extensive metabolism, so its pharmacological action is less. So nano-carrier is used for administration of levodopa (Gray et al., 2014). The clinical trial is being conducted in which levodopa is compared with that of controlled release levodopa. Outcomes of a double-blinded study show that controlled-release levodopa controls the symptoms and does not originates dyskinesia (Juncos et al., 1987). Besides the controlled release of levodopa another approach has been designed in which microparticles are being coated with Chitosan coated hydroxypropyl methylcellulose microparticles which increase the plasma concentration of levodopa. Moreover, it also increases the contact time of levodopa (Dankyi et al., 2020). Decreased efficacy is the untoward effect of levodopa because dopamine receptors are continuously degraded so dopamine receptor (D1) agonist bromocriptine was given but it did not control the symptom, so dihydrexidine was proposed which dramatically treated the disease and lessen the symptoms (Mailman, Yang, & Huang, 2021).

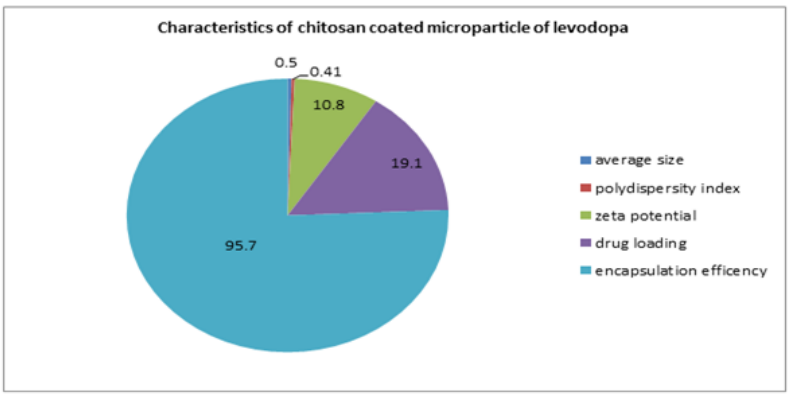

Figure 2: Chitosan coated hydroxyl propyl methyl cellulose microparticles of levodopa which helps in controlled release of levodopa (Dankyi et al., 2020)

Fosmetpantothenate Prodrug

PANK2 genes are found on chromosome 20. Mutations in PANK 2 genes lead to the decrease production of PPA that is phosphopantetheine acid which ultimately decreases the level of coenzyme A in CNS and causes a neurodegenerative disorder that is (PKAN). Fosmetpantotenate prodrug was administered which activates coenzyme synthesis regeneration (Auciello et al., 2020).

DNP and Perforin Inhibitor Prodrug

In neurodegenerative disorder, dopaminergic neurons are constantly being relapsed so a drug that is 2,4 Dinitrophenol was administered but it is not effectual so the prodrug of DNP that is MP-201 was given which shows that it refurbishes the motor function in the brain (Kishimoto et al., 2020). Another drug named perforin inhibitor is used for the treatment of disease they bind to LAT-1 and show their pharmacological effect including a decrease in lipopolysaccharide-induced neuro inflammation and Alzheimer's disease. Perforin inhibitor also reduces oxidative stress and neural apoptosis. (Tampio et al., 2020).

In neurodegenerative disorder, dopaminergic neurons are constantly being relapsed so a drug that is 2,4 Dinitrophenol was administered but it is not effectual so the prodrug of DNP that is MP-201 was given which shows that it refurbishes the motor function in the brain (Kishimoto et al., 2020). Another drug named perforin inhibitor is used for the treatment of disease they bind to LAT-1 and show their pharmacological effect including a decrease in lipopolysaccharide-induced neuro inflammation and Alzheimer's disease. Perforin inhibitor also reduces oxidative stress and neural apoptosis. (Tampio et al., 2020).

Prodrug Approaches for Viral Diseases

Different anti-viral stratagems have been employed for the provision of the drug at the location of action. Prodrug plays an important role in the optimization of effect (Choudhary et al., 2020). For example, HIV infection has become a chronic disease due to the disproportionate use of anti-viral medicines so the drugs are given in combination e.g. three drugs are given, in which two are the reverse transcriptase inhibitors and one is the nucleoside inhibitor (Back & Marzolini, 2020). All the HIV infections have solubility and absorption problems, for example, tamasavir, so to overcome these issues its prodrug Fostemsavir was proposed (Meanwell et al., 2018). Strategies of the prodrug include the targeted delivery, for example, the targeted delivery in the retina in anti-viral prodrug nanomicelle i.e. HCO-40/OC-4O (Mandal et al., 2017). Types of the prodrugs decide which strategy have to be employed e.g. the most astonishing prodrug macro micelle follows the envelope mediated and the receptor-mediated disruption (Sinokrot et al., 2017). Macromolecule prodrug controls the release of the drug so that the drug can be released for a prolonged period (Neeraj et al., 2011).

Table 3. Prodrugs for Viral Diseases

S. No	Prodrug	Active form	Derivative of Prodrug	Enzymes Involved
1	Valacyclovir	Acyclovir	Amino-acid ester	Adenosine deaminase
2	Penciclovir	Famciclovir	Guanine nucleoside	Xanthine oxidase
3	Valganciclovir	Ganciclovir	Valine ester	Esterase valacyclovirase

Acyclovir Prodrugs

Acyclovir is used as the drug of choice for herpes simplex infection. Because of its reduced solubility and invasion among tissues, the transporter targeted delivery approach is a favorable method to enhance the cellular permeability of acyclovir (Talluri et al., 2008). Water-soluble dipeptide esters of ACV are thought to be extremely effective in the case of herpetic viruses. The dipeptide-based strategy is extremely fortuitous for bioactive agents which includes functional moieties as thiol, phenol, and amines. The main function of amino acids and dipeptide esters as prodrugs of acyclovir is because of their high-water solubility and remarkable transepithelial permeabilities that lifts the oral pharmacokinetics. Therefore, dipeptide based prodrugs can be used as an approach for targeting the peptide membrane transporters (Santos et al., 2009). The valine ester prodrug of acyclovir known as Valacyclovir enhances the oral bioavailability by three to five times of the parent drug by translocation of prodrug caused by the peptide transporters (PEPT). To enhance the absorption of acyclovir, novel enzymatically stable stereoisomeric prodrugs such as l-Valine-l-valine and l-valine-d-valine-acyclovir, etc are formulated. Therefore the metabolic activity can be

amplified by assimilating a di-isomer into the peptide chain at a specific position (Talluri et al., 2008) (Santos et al., 2009). Ten amino acid ester prodrugs were considered by computing the urinary retrieval of acyclovir. The results endorsed that L-amino acid prodrugs are superior prodrugs because of the participation of stereoselective transporter as compared to D-isomers as shown in figure 2. Two analogs of acyclovir with fluctuations in the 6th substitute of the purine ring were proposed to attain plasma levels of drug equivalent to intravenous dosing (Tolle-Sander et al., 2004).

The amino-acid–based prodrug valganciclovir is enchanted by the Na+ /Cl− coupled amino acid transporter. This transporter proved to be an efficient delivery method for amino acid-based prodrugs. Secondly, Ganciclovir, an antiviral drug, is not acknowledged as a substrate by amino acid transporter.

However, if we attach a carboxyl group of valine by an ester linkage, valganciclovir, the resulting prodrug, sets of as a magnificent substrate for the transporters. The coupling of the neutral amino acid

substrates in the form of an ester with the carboxyl group of amino acid will enhance the delivery of the therapeutically active agents (Umapathy, Ganapathy, & Ganapathy, 2004). The oral bioavailability of acyclovir can be improved by employing the human apical sodium-dependent bile acid transporter (hASBT). A study was performed in which Acyclovir valylchenodeoxycholate was given orally to rats which led to the idea that to augment the oral bioavailability of acyclovir, a bile acid prodrug approach can be employed. The four bile acid prodrugs of acyclovir are chenodeoxycholate, deoxycholate, cholate, and ursodeoxycholate attached by valine linkers to the parent drug (Beauchamp et al., 1992).

For a nucleoside to work efficiently as an inhibitor of viral polymerase it must be altered to its relevant nucleoside triphosphates. Three distinct kinases are required for carrying out this process. The process of phosphorylation highly affects the activity of nucleosides as viral polymerase inhibitors. The utilization of these prodrug approaches has led to the production of a variety of compelling inhibitors of HCV replication. The amalgamation of a nucleotide prodrug and a direct-acting antiviral agent provides an interferon-free therapy for HCV patients (Sofia, 2013). Hepdirect prodrugs are an advanced class of phosphates and phosphonate prodrugs that provides high plasma and tissue stability and are primarily used for delivering the nucleoside based prodrugs to the liver (Erion et al., 2004).

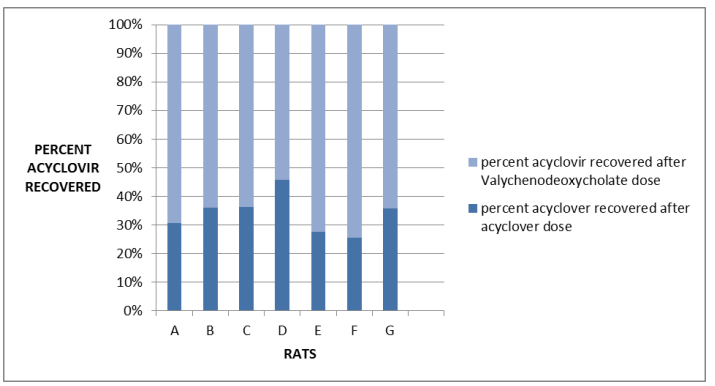

Figure 2. Excretion of acyclovir in urine succeeding the oral administration of acyclovir parent drug and acyclovir prodrug

Vidarabine Prodrug

Vidarabine is an antiviral agent effective against herpes simplex and varicella-zoster viruses. D-and L-amino acid derivatives of vidarabine are referred to as the prodrugs of the parent molecule. The prodrugs of vidarabine are more effective against poxviruses. Currently, prodrugs of vidarabine were studied because of their remarkable activity against the cowpox virus and they are found to be three to five times more potent against vaccinia and cowpox viruses as compared to cidofovir. These prodrugs also enhance the aqueous solubility paralleled to the parent drug (Shen, Kim, Kish, et al., 2009). 5′-O-D-valyl ester derivative of vidarabine is considered a potent

prodrug contender to enhance the oral bioavailability of vidarabine based on its physicochemical properties (Shen, Kim, Mitchell, et al., 2009). The vidarabine ester prodrug has been calculated for its topical delivery by engaging the physicochemical model approach. To study the bioconversion and transport of a drug that is given topically physical model strategy is used. (Ho & Higuchix, 1979).

Ribavirin Prodrug

Macromolecular prodrugs are another type of prodrugs that can be employed as an approach to deliver the chosen drug to the location of the objective. The polymers work as antiviral agents by blocking the entrance of the virus inside the mammalian cell (Smith, Kryger, et al., 2014). Ribavirin is an antiviral drug whose main adverse effect is that it accumulates in the red blood cells. Therefore a prodrug Ribavirin acrylate is synthesized using the chemi-enzymatic approach that reduces the toxicity level in contrast to the parent drug and also maintains the anti-inflammatory activity of the ribavirin (Kryger et al., 2013). Ribavirin (RBV) is a nucleoside congener having commotion against many viruses including influenza, hepatitis C, Lassa fever virus, etc. However, due to its highly adverse PK profile its macromolecular prodrugs are designed. These prodrugs perform their action in the cells where HCV replication takes place (Ruiz-Sanchis et al., 2015). Macromolecular prodrugs of ribavirin are also effective against the treatment of co-infection which are Human immunodeficiency virus (HIV) and Hepatitis C virus (HCV). These prodrugs provide safe and operative treatment along with no accumulation in the erythrocytes and with reduced toxicity levels (Smith et al., 2015). Macromolecular prodrugs are synthesized as entities that provide activity against many viral strains and are used for the inhibition of replication of HIV, Ebola, influenza, measles, etc., viruses (Hinton et al., 2016). Automated parallel polymer synthesis is the technique used for the composition of macromolecular prodrugs of ribavirin (Smith, Wohl, et al., 2014). A study was performed whose main purpose was to synthesize a ribavirin prodrug to acquire liver-specific drug delivery. The main target of this approach was to work on human sodium taurocholate cotransporting polypeptide (NTCP) which is a bile acid transporter located in the liver (Dong et al., 2015).

Sofosbuvir Prodrug

Sofosbuvir, an antiviral prodrug that is used for the treatment of the Hepatitis C virus is proposed to be effective against the replication of SARS-CoV-2, which is a affiliated to the coronavirus family that has triggered a global pandemic emergency .The three-nucleotide congeners such as the triphosphates of sofosbuvir are proposed to be effective for the inhibition of SARS-CoV RNA dependant RNA polymerase (Chien et al., 2020).

Conclusion

The recent development in prodrugs-based drug designing offers a new direction in designing a prodrug that has the most efficacious drug profile. To accomplish the effective concentration of active metabolite at the position of action is a major goal of prodrug therapy. So, a promising strategy should be developed in this regard. Recent advancement in prodrug-based drug designing includes a targeted prodrug approach. In the present era, the research in this area is at a growing stage. As nanomedicine is thought to be the most precise medicine in the developed world but they also have drawbacks including penetration in solid tumor. So, prodrugs are the pre-eminent approach for the actual delivery of drugs to their target site. The above-mentioned strategies of the drug led to the inference that bioavailability and cellular permeability of anti-cancer, neuro protective agents, and antiviral agents can be enhanced by converting the drug of choice into various prodrugs that will perform the function of specific targeted delivery as required. The prodrug approach intensifies the therapeutic effect of the parent molecule.

References

Abdul-Hay, S. O., Luo, J., Ashghodom, R. T., & Thatcher, G. R. J. (2009). NO-flurbiprofen reduces amyloid-β, is neuroprotective in cell culture, and enhances cognition in response to cholinergic blockade. *Journal of Neurochemistry*, *111*(3), 766–776. https://doi.org/10.1111/j.1471-4159.2009.06353.x

Al-Azzawi, S., Masheta, D., Guildford, A., Phillips, G., & Santin, M. (2020). A peptide-based nanocarrier for an enhanced delivery and targeting of flurbiprofen into the brain for the treatment of alzheimer's disease: An in vitro study. *Nanomaterials*, *10*(8), 1–18. https://doi.org/10.3390/nano10081590

Auciello, G., Marco, A. Di, Paz, O. G., Malancona, S., Harper, S., Beconi, M., … Elbaum, D. (2020). *Cyclic Phosphopantothenic Acid Prodrugs for Treatment of Pantothenate Kinase-Associated Neurodegeneration*. https://doi.org/10.1021/acs.jmedchem.0c01531

Back, D., & Marzolini, C. (2020). The challenge of HIV treatment in an era of polypharmacy. *Journal of the International AIDS Society*, *23*(2), 1–12. https://doi.org/10.1002/jia2.25449

Banks, W. A. (2009). Characteristics of compounds that cross the blood-brain barrier. *BMC Neurology*, *9*(SUPPL. 1), 5–9. https://doi.org/10.1186/1471-2377-9-S1-S3

Beauchamp, L. M., Orr, G. F., De Miranda, P., Burnette, T., & Krenitsky, T. A. (1992). Amino acid ester prodrugs of acyclovir. *Antiviral Chemistry and Chemotherapy*, *3*(3), 157–164. https://doi.org/10.1177/095632029200300305

Bondì, M. L., Craparo, E. F., Picone, P., Giammona, G., Di Gesù, R., & Di Carlo, M. (2013). Lipid nanocarriers containing ester prodrugs of flurbiprofen preparation, physical-chemical characterization and biological studies. *Journal of Biomedical Nanotechnology*, *9*(2), 238–246. https://doi.org/10.1166/jbn.2013.1490

Chang, H. T., Pan, H. J., & Lee, C. H. (2018). Prevention of Tamoxifen-related Nonalcoholic Fatty Liver Disease in Breast Cancer Patients. *Clinical Breast Cancer*, *18*(4), e677–e685. https://doi.org/10.1016/j.clbc.2017.11.010

Chien, M., Anderson, T. K., Jockusch, S., Tao, C., Li, X., Kumar, S., … Ju, J. (2020). Nucleotide Analogues as Inhibitors of SARS-CoV-2 Polymerase, a Key Drug Target for COVID-19. *Journal of Proteome Research*, *19*(11), 4690–4697. https://doi.org/10.1021/acs.jproteome.0c00392

Choudhary, D., Goykar, H., Kalyane, D., Sreeharsha, N., & Tekade, R. K. (2020). Prodrug design for improving the biopharmaceutical properties of therapeutic drugs. In *The Future of Pharmaceutical Product Development and Research*. INC. https://doi.org/10.1016/b978-0-12-814455-8.00006-2

Christophe, R., & Patrick, D. (2018). *PLEIOTROPIC PRODRUGS : A NOVEL POLYPHARMACO- LOGY APPROACH TO TREAT NEURODEGENERATIVE*. *87*(supplementum 1), 3187.

Dankyi, B. O., Amponsah, S. K., Allotey-Babington, G. L., Adams, I., Goode, N. A., & Nettey, H. (2020). Chitosan-Coated Hydroxypropylmethyl Cellulose Microparticles of Levodopa (and Carbidopa): In Vitro and Rat Model Kinetic Characteristics. *Current Therapeutic Research - Clinical and Experimental*, *93*, 100612. https://doi.org/10.1016/j.curtheres.2020.100612

Denny, W. A. (2004). Tumor-activated prodrugs - A new approach to cancer therapy. *Cancer Investigation*, *22*(4), 604–619. https://doi.org/10.1081/CNV-200027148

Denny, W. A., & Wilson, W. R. (1998). *Therapies **. 387–394.

Dong, Z., Li, Q., Guo, D., Shu, Y., & Polli, J. E. (2015). Synthesis and Evaluation of Bile Acid-Ribavirin Conjugates as Prodrugs to Target the Liver. *Journal of Pharmaceutical Sciences*, *104*(9), 2864–2876. https://doi.org/10.1002/jps.24375

Erion, M. D., Reddy, K. R., Boyer, S. H., Matelich, M. C., Gomez-Galeno, J., Lemus, R. H., … Van Poelje, P. D. (2004). Design, Synthesis, and Characterization of a Series of Cytochrome P 450 3A-Activated Prodrugs (HepDirect Prodrugs) Useful for Targeting Phosph(on)ate-Based Drugs to the Liver. *Journal of the American Chemical Society*, *126*(16), 5154–5163. https://doi.org/10.1021/ja031818y

Ettmayer, P., Amidon, G. L., Clement, B., & Testa, B. (2004). Lessons Learned from Marketed and Investigational Prodrugs. *Journal of Medicinal Chemistry*, *47*(10), 2393–2404. https://doi.org/10.1021/jm0303812

Ferrara, S. J., & Scanlan, T. S. (2020). A CNS-Targeting Prodrug Strategy for Nuclear Receptor Modulators. *Journal of Medicinal Chemistry*,

63(17), 9742–9751. https://doi.org/10.1021/acs.jmedchem.0c00868

Gray, R., Ives, N., Rick, C., Patel, S., Gray, A., Jenkinson, C., … Whittuck, M. (2014). Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): A large, open-label, pragmatic randomised trial. *The Lancet*, *384*(9949), 1196–1205. https://doi.org/10.1016/S0140-6736(14)60683-8

Gynther, M., Laine, K., Ropponen, J., Leppänen, J., Mannila, A., Nevalainen, T., … Rautio, J. (2008). Large neutral amino acid transporter enables brain drug delivery via prodrugs. *Journal of Medicinal Chemistry*, *51*(4), 932–936. https://doi.org/10.1021/jm701175d

Han, H. K., & Amidon, G. L. (2000). Targeted prodrug design to optimize drug delivery. *AAPS PharmSci*, *2*(1), 1–11. https://doi.org/10.1208/ps020106

Henderson, J. T., & Piquette-Miller, M. (2015). Blood-brain barrier: an impediment to neuropharmaceuticals. *Clinical Pharmacology and Therapeutics*, *97*(4), 308–313. https://doi.org/10.1002/cpt.77

Hinton, T. M., Zuwala, K., Deffrasnes, C., Todd, S., Shi, S., Marsh, G. A., … Zelikin, A. N. (2016). Polyanionic Macromolecular Prodrugs of Ribavirin: Antiviral Agents with a Broad Spectrum of Activity. *Advanced Healthcare Materials*, *5*(5), 534–540. https://doi.org/10.1002/adhm.201500841

Ho, N. F. H., & Higuchix, W. I. (1979). *PHARMACEUTICAL SCIENCES @ Physical Model Evaluation of*. *68*(11), 1341–1346.

Hong, J., Huang, J., Shen, L., Zhu, S., Gao, W., Wu, J., … Shen, K. (2020). A prospective, randomized study of Toremifene vs. tamoxifen for the treatment of premenopausal breast cancer: Safety and genital symptom analysis. *BMC Cancer*, *20*(1), 1–10. https://doi.org/10.1186/s12885-020-07156-x

Hou, J., & Liu, Y. (2020). *Magnetically Directed Enzyme / Prodrug Prostate Cancer Therapy Based on β -Glucosidase / Amygdalin*.

Huang, P. S., & Oliff, A. (2001). Drug-targeting strategies in cancer therapy. *Current Opinion in Genetics and Development*, *11*(1), 104–110. https://doi.org/10.1016/S0959-437X(00)00164-7

Huttunen, K. M., Mähönen, N., Raunio, H., & Rautio, J. (2008). *Cytochrome P450-Activated Prodrugs : Targeted Drug Delivery*. 2346–2365.

Investigation, P., & Hepatotoxicity, A. C. I. (2011). *Asian Journal of Pharmaceutical and Health Sciences*. 1–5.

Jana, S., Mandlekar, S., & Marathe, P. (2010). Prodrug Design to Improve Pharmacokinetic and Drug Delivery Properties: Challenges to the Discovery Scientists. *Current Medicinal Chemistry*, *17*(32), 3874–3908. https://doi.org/10.2174/092986710793205426

Järvinen, T., Rautio, J., Masson, M., & Loftsson, T. (2005). Design and Pharmaceutical Applications of Prodrugs. *Drug Discovery Handbook*, 733–796. https://doi.org/10.1002/0471728780.ch17

Jiang, Q., Zhong, Q., Zhang, Q., Zheng, S., & Wang, G. (2012). Boron-based 4-hydroxytamoxifen bioisosteres for treatment of de novo tamoxifen resistant breast cancer. *ACS Medicinal Chemistry Letters*, *3*(5), 392–396. https://doi.org/10.1021/ml3000287

Juncos, J. L., Fabbrini, G., Mouradian, M. M., & Chase, T. N. (1987). Controlled Release Levodopa-Carbidopa (CR-5) in the Management of Parkinsonian Motor Fluctuations. *Archives of Neurology*, *44*(10), 1010–1012. https://doi.org/10.1001/archneur.1987.00520220016008

Kim, M., Park, M. H., Nam, G., Lee, M., Kang, J., Song, I.-S., … Lim, M. H. (2020). A Glycosylated Prodrug to Attenuate Neuroinflammation and Improve Cognitive Deficits in Alzheimer's Disease Transgenic Mice. *Molecular Pharmaceutics*. https://doi.org/10.1021/acs.molpharmaceut.0c00677

Kishimoto, Y., Johnson, J., Fang, W., Halpern, J., Marosi, K., Liu, D., … Mattson, M. P. (2020). A mitochondrial uncoupler prodrug protects dopaminergic neurons and improves functional outcome in a mouse model of Parkinson's disease. *Neurobiology of Aging*, *85*, 123–130. https://doi.org/10.1016/j.neurobiolaging.2019.09.011

Kratz, F., Mansour, A., Soltau, J., Warnecke, A., Fichtner, I., Unger, C., & Drevs, J. (2005). Development of albumin-binding doxorubicin pro-drugs that are cleaved by prostate-specific antigen. *Archiv Der Pharmazie*, *338*(10), 462–472. https://doi.org/10.1002/ardp.200500130

Kryger, M. B. L., Wohl, B. M., Smith, A. A. A., & Zelikin, A. N. (2013). Macromolecular prodrugs of ribavirin combat side effects and toxicity with no

loss of activity of the drug. *Chemical Communications*, *49*(26), 2643–2645. https://doi.org/10.1039/c3cc00315a

Lee, H. J., Cooperwood, J. S., You, Z., Ko, D. H., & Pyoung, H. H. (2002). Prodrug and antedrug: Two diametrical approaches in designing safer drugs. *Archives of Pharmacal Research*, *25*(2), 111–136. https://doi.org/10.1007/BF02976552

Li, J. Y., Boado, R. J., & Pardridge, W. M. (2001). *Blood – Brain Barrier Genomics*. 61–68.

Mailman, R. B., Yang, Y., & Huang, X. (2021). D1 , not D2 , dopamine receptor activation dramatically improves MPTP-induced parkinsonism unresponsive to levodopa. *European Journal of Pharmacology*, *892*(November 2020), 173760. https://doi.org/10.1016/j.ejphar.2020.173760

Mandal, A., Cholkar, K., Khurana, V., Shah, A., Agrahari, V., Bisht, R., … Mitra, A. K. (2017). Topical Formulation of Self-Assembled Antiviral Prodrug Nanomicelles for Targeted Retinal Delivery. *Molecular Pharmaceutics*, *14*(6), 2056–2069. https://doi.org/10.1021/acs.molpharmaceut.7b00128

Manish, M., Lynn, A. M., & Mishra, S. (2020). Cytochrome P450 2C9 polymorphism: Effect of amino acid substitutions on protein flexibility in the presence of tamoxifen. *Computational Biology and Chemistry*, *84*, 107166. https://doi.org/10.1016/j.compbiolchem.2019.107166

Meanwell, N. A., Krystal, M. R., Nowicka-Sans, B., Langley, D. R., Conlon, D. A., Eastgate, M. D., … Kadow, J. F. (2018). Inhibitors of HIV-1 Attachment: The Discovery and Development of Temsavir and its Prodrug Fostemsavir. *Journal of Medicinal Chemistry*, *61*(1), 62–80. https://doi.org/10.1021/acs.jmedchem.7b01337

Meinig, J. M., Ferrara, S. J., Banerji, T., Banerji, T., Sanford-Crane, H. S., Bourdette, D., & Scanlan, T. S. (2019). Structure-Activity Relationships of Central Nervous System Penetration by Fatty Acid Amide Hydrolase (FAAH)-Targeted Thyromimetic Prodrugs. *ACS Medicinal Chemistry Letters*, *10*(1), 111–116. https://doi.org/10.1021/acsmedchemlett.8b00501

Montaser, A. B., Järvinen, J., Löffler, S., Huttunen, J., Auriola, S., Lehtonen, M., … Huttunen, K. M. (2020). L-Type Amino Acid Transporter 1 Enables the Efficient Brain Delivery of Small-Sized Prodrug across the Blood–Brain Barrier and into Human and Mouse Brain Parenchymal Cells. *ACS Chemical Neuroscience*. https://doi.org/10.1021/acschemneuro.0c00564

Najjar, A., & Karaman, R. (2019). The prodrug approach in the era of drug design. *Expert Opinion on Drug Delivery*, *16*(1), 1–5. https://doi.org/10.1080/17425247.2019.1553954

Neeraj, A., Chandrasekar, M. J. N., Sara, U. V. S., & Rohini, A. (2011). Poly(HEMA-Zidovudine) conjugate: A macromolecular pro-drug for improvement in the biopharmaceutical properties of the drug. *Drug Delivery*, *18*(4), 272–280. https://doi.org/10.3109/10717544.2010.536272

Oliveri, V. (2015). New Glycoconjugates for the Treatment of Diseases Related to Metal Dyshomeostasis. *ChemistryOpen*, *4*(6), 792–795. https://doi.org/10.1002/open.201500155

Pardridge, W. M. (2002). Why is the global CNS pharmaceutical market so under-penetrated? *Drug Discovery Today*, *7*(1), 5–7. https://doi.org/10.1016/S1359-6446(01)02082-7

Peñalver, P., Belmonte-Reche, E., Adán, N., Caro, M., Mateos-Martín, M. L., Delgado, M., … Morales, J. C. (2018). Alkylated resveratrol prodrugs and metabolites as potential therapeutics for neurodegenerative diseases. *European Journal of Medicinal Chemistry*, *146*, 123–138. https://doi.org/10.1016/j.ejmech.2018.01.037

Perioli, L., Ambrogi, V., Bernardini, C., Grandolini, G., Ricci, M., Giovagnoli, S., & Rossi, C. (2004). Potential prodrugs of non-steroidal anti-inflammatory agents for targeted drug delivery to the CNS. *European Journal of Medicinal Chemistry*, *39*(8), 715–727. https://doi.org/10.1016/j.ejmech.2004.05.006

Peura, L., Malmioja, K., Laine, K., Leppänen, J., Gynther, M., Isotalo, A., & Rautio, J. (2011). Large amino acid transporter 1 (LAT1) prodrugs of valproic acid: New prodrug design ideas for central nervous system delivery. *Molecular Pharmaceutics*, *8*(5), 1857–1866. https://doi.org/10.1021/mp2001878

Psimadas, D., Georgoulias, P., Valotassiou, V., & Loudos, G. (2012). Molecular Nanomedicine Towards Cancer : *Journal of Pharmaceutical Sciences*, *101*(7), 2271–2280. https://doi.org/10.1002/jps

Rasheed, A., & Kumar, C. K. A. (2008). Novel

approaches on prodrug based drug design. *Pharmaceutical Chemistry Journal*, *42*(12), 677–686. https://doi.org/10.1007/s11094-009-0213-3

Rautio, J., Meanwell, N. A., Di, L., & Hageman, M. J. (2018). The expanding role of prodrugs in contemporary drug design and development. *Nature Reviews Drug Discovery*, *17*(8), 559–587. https://doi.org/10.1038/nrd.2018.46

Ruiz-Sanchis, P., Wohl, B. M., Smith, A. A. A., Zuwala, K., Melchjorsen, J., Tolstrup, M., & Zelikin, A. N. (2015). Highly active macromolecular prodrugs inhibit expression of the hepatitis c virus genome in the host cells. *Advanced Healthcare Materials*, *4*(1), 65–68. https://doi.org/10.1002/adhm.201400307

Ryan, A. T., Pulukuri, A. J., Davaritouchaee, M., Abbasi, A., Hendricksen, A. T., Opp, L. K., … Mancini, R. J. (2020). Comparing the immunogenicity of glycosidase-directed resiquimod prodrugs mediated by cancer cell metabolism. *Acta Pharmacologica Sinica*, *41*(7), 995–1004. https://doi.org/10.1038/s41401-020-0432-4

Santos, C. R., Capela, R., Pereira, C. S. G. P., Valente, E., Gouveia, L., Pannecouque, C., … Gomes, P. (2009). Structure-activity relationships for dipeptide prodrugs of acyclovir: Implications for prodrug design. *European Journal of Medicinal Chemistry*, *44*(6), 2339–2346. https://doi.org/10.1016/j.ejmech.2008.08.009

Scott, L. E., Telpoukhovskaia, M., Rodríguez-Rodríguez, C., Merkel, M., Bowen, M. L., Page, B. D. G., … Orvig, C. (2011). N-Aryl-substituted 3-(b-D-glucopyranosyloxy)-2-methyl-4(1H)-pyridinones as agents for Alzheimer's therapy. *Chemical Science*, *2*(4), 642–648. https://doi.org/10.1039/c0sc00544d

Shen, W., Kim, J. S., Kish, P. E., Zhang, J., Mitchell, S., Gentry, B. G., … Hilfinger, J. (2009). Design and synthesis of vidarabine prodrugs as antiviral agents. *Bioorganic and Medicinal Chemistry Letters*, *19*(3), 792–796. https://doi.org/10.1016/j.bmcl.2008.12.031

Shen, W., Kim, J. S., Mitchell, S., Kish, P., Kijek, P., & Hilfinger, J. (2009). 5′-O-D-valyl ara A, a potential prodrug for improving oral bioavailability of the antiviral agent vidarabine. *Nucleosides, Nucleotides and Nucleic Acids*, *28*(1), 43–55. https://doi.org/10.1080/15257770802581757

Sinokrot, H., Smerat, T., Najjar, A., & Karaman, R. (2017). Advanced prodrug strategies in nucleoside and non-nucleoside antiviral agents: A review of the recent five years. *Molecules*, *22*(10). https://doi.org/10.3390/molecules22101736

Smith, A. A. A., Kryger, M. B. L., Wohl, B. M., Ruiz-Sanchis, P., Zuwala, K., Tolstrup, M., & Zelikin, A. N. (2014). Macromolecular (pro)drugs in antiviral research. *Polymer Chemistry*, *5*(22), 6407–6425. https://doi.org/10.1039/c4py00624k

Smith, A. A. A., Wohl, B. M., Kryger, M. B. L., Hedemann, N., Guerrero-Sanchez, C., Postma, A., & Zelikin, A. N. (2014). Macromolecular prodrugs of Ribavirin: Concerted efforts of the carrier and the drug. *Advanced Healthcare Materials*, *3*(9), 1404–1407. https://doi.org/10.1002/adhm.201300637

Smith, A. A. A., Zuwala, K., Kryger, M. B. L., Wohl, B. M., Guerrero-Sanchez, C., Tolstrup, M., … Zelikin, A. N. (2015). Macromolecular prodrugs of ribavirin: Towards a treatment for co-infection with HIV and HCV. *Chemical Science*, *6*(1), 264–269. https://doi.org/10.1039/c4sc02754j

Sofia, M. J. (2013). Nucleotide prodrugs for the treatment of HCV infection. In *Advances in Pharmacology* (1st ed., Vol. 67). Copyright © 2013 Elsevier Inc. All rights reserved. https://doi.org/10.1016/B978-0-12-405880-4.00002-0

Song, H., Quan, F., Yu, Z., Zheng, M., Ma, Y., Xiao, H., & Ding, F. (2019). Carboplatin prodrug conjugated Fe 3 O 4 nanoparticles for magnetically targeted drug delivery in ovarian cancer cells. *Journal of Materials Chemistry B*, *7*(3), 433–442. https://doi.org/10.1039/c8tb02574f

Talluri, R. S., Samanta, S. K., Gaudana, R., & Mitra, A. K. (2008). Synthesis, metabolism and cellular permeability of enzymatically stable dipeptide prodrugs of acyclovir. *International Journal of Pharmaceutics*, *361*(1–2), 118–124. https://doi.org/10.1016/j.ijpharm.2008.05.024

Tampio, J., Huttunen, J., Montaser, A., & Huttunen, K. M. (2020). Targeting of Perforin Inhibitor into the Brain Parenchyma Via a Prodrug Approach Can Decrease Oxidative Stress and Neuroinflammation and Improve Cell Survival. *Molecular Neurobiology*, *57*(11), 4563–4577. https://doi.org/10.1007/s12035-020-02045-7

Tolle-Sander, S., Lentz, K. A., Maeda, D. Y., Coop, A., & Polli, J. E. (2004). Increased acyclovir oral bioavailability via a bile acid conjugate. *Molecular Pharmaceutics*, *1*(1), 40–48.

https://doi.org/10.1021/mp034010t

Toublet, F.-X., Lalut, J., Hatat, B., Lecoutey, C., Davis, A., Since, M., … Rochais, C. (2020). Pleiotropic prodrugs: Design of a dual butyrylcholinesterase inhibitor and 5-HT6 receptor antagonist with therapeutic interest in Alzheimer's disease. *European Journal of Medicinal Chemistry*, *In Press,*. https://doi.org/10.1016/j.ejmech.2020.113059

Umapathy, N. S., Ganapathy, V., & Ganapathy, M. E. (2004). Transport of amino acid esters and the amino-acid-based prodrug valganciclovir by the amino acid transporter ATB 0,+. *Pharmaceutical Research*, *21*(7), 1303–1310. https://doi.org/10.1023/B:PHAM.0000033019.49737.28

Varbanov, H. P., Valiahdi, S. M., Kowol, C. R., Jakupec, M. A., Galanski, M., & Keppler, B. K. (2012). Novel tetracarboxylatoplatinum(iv) complexes as carboplatin prodrugs. *Dalton Transactions*, *41*(47), 14404–14415. https://doi.org/10.1039/c2dt31366a

Wang, W., Wang, S., Liu, T., Ma, Y., Huang, S., Lei, L., … Ding, Y. (2020). Resveratrol: Multi-Targets Mechanism on Neurodegenerative Diseases Based on Network Pharmacology. *Frontiers in Pharmacology*, *11*(May). https://doi.org/10.3389/fphar.2020.00694

Zhang, W., Li, C., Shen, C., Liu, Y., Zhao, X., Liu, Y., … Yue, C. (2016). Prodrug-based nano-drug delivery system for co-encapsulate paclitaxel and carboplatin for lung cancer treatment. *Drug Delivery*, *23*(7), 2575–2580. https://doi.org/10.3109/10717544.2015.1035466

Zhang, Y., Yang, C., Wang, W., Liu, J., Liu, Q., Huang, F., … Liu, J. (2016). Co-delivery of doxorubicin and curcumin by pH-sensitive prodrug nanoparticle for combination therapy of cancer. *Scientific Reports*, *6*(February), 1–12. https://doi.org/10.1038/srep21225

Zhao, N., Francis, N. L., Calvelli, H. R., & Moghe, P. V. (2020). Microglia-targeting nanotherapeutics for neurodegenerative diseases. *APL Bioengineering*, *4*(3). https://doi.org/10.1063/5.0013178

Zhou, J., Zhang, J., David, A. E., & Yang, V. C. (2013). Magnetic tumor targeting of β-glucosidase immobilized iron oxide nanoparticles. *Nanotechnology*, *24*(37). https://doi.org/10.1088/0957-4484/24/37/375102

Zhu, X., Li, C., Lu, Y., Liu, Y., Wan, D., Zhu, D., … Ma, G. (2020). Tumor microenvironment-activated therapeutic peptide-conjugated prodrug nanoparticles for enhanced tumor penetration and local T cell activation in the tumor microenvironment. *Acta Biomaterialia*. https://doi.org/10.1016/j.actbio.2020.11.008