International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 13, Issue 6, 2021

Review Article

LATENTIATED PRODRUG APPROACH OF DRUGS: AN OVERVIEW

DHARUN P. R.[1], ISMAIL Y.[2*], VIJAYA VARA PRASAD M.[3]

[1,2,3]Crescent School of Pharmacy, B. S Abdur Rahman Crescent Institute of Science and Technology, Chennai, Tamil Nadu 600048, India
*Email: ismailcsp@crescent.education

Received: 29 Jul 2021, Revised and Accepted: 31 Aug 2021

ABSTRACT

Prodrugs, with their capability of declining the adverse events and elevating the bioavailability of certain drugs, have captured enormous attention throughout the world since the 20th century. The versatility of the prodrugs that are inert and after administration releasing the parent moiety for the desired effect has become a major criterion for the scientists to incorporate this to alleviate the undesired effects of a conventional drug. About 10% of the prevailing drugs are prodrugs and their usage is being amplified owing to its critical application in cancer therapy, toxicity alleviation, and specificity. The purpose of this review is to understand the prodrugs, strategies incorporated in designing the prodrugs, applications, their crucial benefits in targeted action at a specific site of the body, their advantageous effects in chemotherapy. Also, to be acknowledged with the ongoing clinical trials and researches on prodrugs and some notable marketed prodrugs in a depth manner.

Keywords: Prodrug, Carriers, Enzymes, Strategies, Specificity, Chemotherapy

DOI: https://dx.doi.org/10.22159/ijap.2021v13i6.42794. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Adrian Albert coined the word 'prodrug' or 'pro-agent' in 1958, implying that this technique might temporarily adjust the properties of drugs in order to improve their effectiveness and/or to reduce concomitant toxicity. Prodrugs are bio-reversible derivatives of drug molecules that are used to circumvent some of the parent drug's limitations. The name 'prodrug' refers to substances that exert their pharmacological or therapeutic action only after making some chemical modifications in their structures. There are plenty of prodrugs that are clinically useful. For instance, Hexamine (methenamine) and aspirin are prodrugs of formaldehyde and salicylic acid, respectively, and were formulated as early as the Prodrugs in Clinical Practice in the late nineteenth century. Prodrugs are a pharmacologically inactive form of a drug that undergoes a transition *in vivo* to release the parent drug molecule. They are intended to address therapeutic and/or pharmacokinetic issues with the parent drug molecule that would otherwise limit the drug's clinical usefulness [1]. Bio-precursor prodrugs are prodrugs that undergo structural alterations [2].

It's easy to get confused between prodrugs, soft drugs (also known as ante drugs), and codrugs (also known as mutual drugs), but each category is structured with different purposes in mind. Soft drugs, unlike prodrugs, are pharmacologically active molecules that are quickly transformed to a less pharmacologically active or even fully inactive type once administered. Soft drug therapies are often used to target particular tissues (such as the eye, skin, or lungs) in order to reduce overall systemic exposure and Adverse Drug Reactions (ADRs) [3]. By modulating physicochemical properties that influence absorption or targeting particular enzymes or membrane transporters, the prodrug approach has been commonly used to enhance drug delivery to their site of action [4]. To be translated into the parent drug, most of the prodrugs currently in clinical use need enzymatic catalysis. The prodrugs that are intended to release the parent drug into the bloodstream after GI absorption comes under this category. These are especially ester derivatives of drugs with carboxyl or hydroxyl groups that are easily converted to the parent drug by hydrolysis with the help of the enzyme esterase [5]. Prodrugs are physiologically inactive analogues of parent drug that needs a chemical or enzymatic modification within the body to liberate the active drug and have better delivery than the parent moiety [6]. Typically, enzymatic or non-enzymatic cleavage occurs to cleave the pro-moiety bonds. Fig. 1 elucidates the concept of the prodrug. High chemical reactivity that hinders the regeneration of the parent drug occurs while incorporating the process of enzymatic cleavage. So, an unconventional approach of non-enzymatic cleavage has been emerged to regenerate the parent drug in which the prodrug activation is not induced by inter and intra-individual variability rather by the process of cyclization [7].

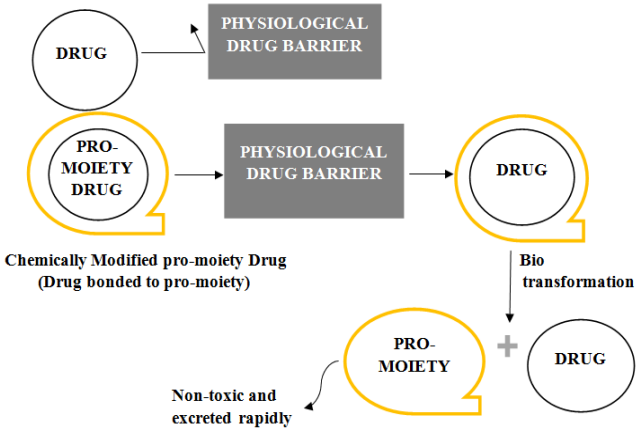

Fig. 1: Schematic depiction of prodrug concept [1]

Cahn and Hepp introduced acetanilide (as Antifebrin) into medical practice in 1867 as an antipyretic agent, and it was the first compound to meet the classical norms of a prodrug. Acetaminophen (paracetamol), a biologically active compound with antipyretic and analgesic properties is produced by the hydroxylation (aromatic hydroxylation) of acetanilide. The Parke-Davis company used the prodrug term for the first time in the middle of the twentieth century during experiments on changing the structure of chloramphenicol to overcome the antibiotic's bitter taste and poor water solubility. Chloramphenicol sodium succinate, which has a better water solubility, and chloramphenicol palmitate, which is used in the form of a suspension in children, were the two prodrug forms of chloramphenicol formulated as a result of this research [8].

Prodrug classification

Prodrugs are divided into two categories:

(a.) 'Carrier linked prodrugs'

(b.) 'Bio precursor prodrugs'

Carrier-linked prodrugs involve a bio-reversible covalent linkage between the active molecule (the drug) and a carrier molecule (also known as a pro-the-moiety). Once *in vivo*, the parent drug and the carrier molecules are released due to the biotransformation of the carrier linked prodrug. The carrier should ideally be nonimmunogenic, simple to synthesize at a low cost, stable under prodrug administration conditions, and biodegrade to nonactive metabolites [9]. Whereas, in co-drugs, two pharmacologically active agents that act a pro-moiety of each other bind together into a single molecule to form a prodrug. Sulphapyridine–5-aminosalicylic acid, indomethacin–paracetamol, and Levodopa (L-DOPA)–entacapone are some examples of co-drugs [10]. The prodrugs can be further divided into two classes based on the site of conversion into the pharmacologically active agent:

• Type I–Metabolized within cells. Especially, Type IA prodrugs metabolize at the cellular targets of their therapeutic actions. Acyclovir, cyclophosphamide, 5-fluorouracil, L-DOPA, and zidovudine are some of the examples of Type IA prodrugs and Type IB prodrugs such as carbamazepine, captopril, molsidomine, primidone involve the metabolic tissue (liver) to get converted to the parent drug molecule. Some prodrugs, known as mixed-type prodrugs, belong to several classes.

• Type II–Metabolized outside the cells. Particularly, Type IIA prodrugs are metabolized in GI's milieu. Whereas the Type IIB are metabolized inside the circulatory system and/or other fluid compartments. Type IIC prodrugs are metabolized within the target cells, such as Antibody Directed Enzyme Prodrug Therapy (ADEPT) and Gene Directed Enzyme Prodrug Therapy (GDEPT) [8]. Mixed-type prodrugs are prodrugs that belong to more than one class [11]. Nearly half of the prodrugs that are currently available are activated by ubiquitous esterases such as acetylcholinesterase, butyrylcholinesterases, carboxylesterases, and arylesterases, which are found all over the body [9].

Bio precursors v/s carrier prodrugs

The following conclusions were made after establishing a comparative balance sheet for the two prodrug approaches.

• A transient transport moiety is used to modulate the bioavailability of carrier prodrugs; however, no such linkage is inferred for bio precursors, which arise from a molecular alteration of the active principle itself.

• In the case of carrier prodrugs, the lipophilicity of the parent molecule is significantly altered, while it is remarkably unchanged in the case of bio precursors.

• For carrier prodrugs, the bioactivation mechanism is entirely hydrolytic; for bio precursors, it mostly incorporates redox systems.

• For carrier prodrugs, the catalysis that leads to the active principle is hydrolytic (either through general catalysis or through extra-hepatic enzymes). Whereas it appears to be limited to Phase I metabolizing enzymes for bio precursors. Esters and amides are the major groups of carrier-linked prodrugs; Phosphates, carbamates, carbonates, oximes, imines, and Nitrogen containing mannich bases (N-Mannich bases) are some of the other groups of carrier-linked prodrugs [8].

Prodrug modification strategies

To reduce the number of proposed candidates while increasing the explored space of physicochemical and pharmacokinetic properties, careful prodrug design is crucial. In rational prodrug design, the ability to predict target properties is critical [12]. Modifying an active drug's Absorption, Distribution, Metabolism, and Excretion (ADME) properties necessitates a thorough understanding of the drug candidate's physicochemical and biological nature. This involves a thorough assessment of drug-likeness, as well as the determination of ADME properties. Data obtained from in vitro and in vivo analysis and computational approaches such as Quantitative Structure-Activity Relationship (QSAR) and molecular docking can get in hand with the assessment of these properties. The overall objective is to design a well permeable drug (absorption) that is metabolically stable (metabolism) enough to reach its target efficiently (distribution) and that could eliminate in an appropriate time (elimination) [13].

Certain questions related to the issue with a drug/bioactive compound must be addressed before the rational design of a prodrug.

- What is the most suitable prodrug category that could be used to solve the problem?
- What are functional groups available in drugs/bioactive compounds for forming a labile linkage?
- Which carrier is the best to use (not for bio precursors)?
- Which linkage is the most appropriate to use?
- What are the enzymes and chemical processes involved in the release of a drug compound? [14].

Problems that need concern can be categorized into three categories based on their pharmaceutical, pharmacokinetic and pharmacodynamic nature [15]. Prodrugs can alter the parent drug's tissue distribution, efficacy, and toxicity of the parent drug. So, the design consideration at the early stage of preclinical development is critical. When designing a prodrug structure, several important factors should be considered, including:

• Parent drug: What are the functional groups that are amenable to chemical prodrug derivatization in a parent drug?

• Pro-moiety: The disease state, dosage, and length of therapy should all be taken into account when selecting a pro-moiety.

• Parent molecule and prodrug: ADME and pharmacokinetic properties must be made clear.

• Degradation by-products: These factors contribute to the development of new degradation products by having an effect on chemical and physical stability [2].

The following are some examples of how prodrug design can be used:

(1) In enhancing the solubility, bioavailability, dissolution as it is the rate-limiting step for absorption

(2) In enhancing the membrane permeability since it has an effect on drug efficacy.

(3) In modifying the distribution profile before the predetermined effect [16].

Prodrugs for the treatment of diseases like myelodysplastic syndromes, Parkinson's, malaria, hypertension, psoriasis, and osteoporosis were successfully synthesized. Enhanced dissolution, penetration, and bioavailability of the corresponding drugs were the results obtained on *in vitro* kinetic analysis [17]. Both drug and prodrug designs can be made by computational methods. Prodrug design is limited to resolving only pharmacokinetic issues relevant to a drug candidate, while drug design requires multi-step procedures to overcome challenges arising from pharmacodynamic and pharmacokinetic characteristics [18]. Since one can optimize all

of the ADMET properties while also extending the commercial life cycle of potential drug candidates, the prodrug approach is a very flexible technique for increasing the use of pharmacologically active compounds. Prodrugs usually have an apparent carrier or pro-moiety that is eliminated by enzymatic or chemical reaction(s), but certain prodrugs release their active drugs after molecular modification, which is certainly referred to as bio precursor prodrugs (e. g., after oxidation or reduction reaction). Where the target prodrug moiety cannot be connected directly to the parent molecule due to steric hindrance or functional properties, typical carrier-linked prodrugs have a synthetic handle, a spacer or linker, between the active drug and the pro-moiety. After the enzymatic or chemical decomposition of the prodrug bond between the pro-moiety and spacer, the spacers cleave conventionally [19]. Prior to the designing of prodrugs, two strategies must be considered.

Solubility enhancing strategy

When the parent drug's low intestinal solubility or dissolution rate is a barrier to bioavailability but not hepatic metabolism, a solubility-enhancing strategy can be used:

• Parent is a Biopharmaceutical Classification System (BCS) Class II drug (low solubility and high permeability).

• High dose/solubility ratio, i.e., over a pH range of1–7.5, the highest targeted parent drug dose will only dissolve in volumes>>250 ml.

• Poor or moderate hepatic clearance (Clh) in preclinical species.

• Hepatic extraction ratio (Eh)<0.5.

• *In vitro* assays showing great permeability

• Fraction of dose absorbed (Fa) after oral administration, measured, is low (<25%) [2].

To exemplify, Carbamazepine (CBZ) is an efficient anticonvulsant drug that produces less sedation and cognitive impairment when compared with other anticonvulsants; nevertheless, its aqueous solubility is 120g/ml, forbidding the Intravenous (IV) [20]. To tackle this problem, CBZ prodrugs were synthesized with an enhanced solubility profile. A Cyclooxygenase-2 (COX-2) inhibitor prodrug of a drug named PC407 for parenteral administration was also developed using the sulphonamide group. The prodrug's solubility increased dramatically, from 1.6g/ml to 20.3 mg/ml. Prodrug exhibited in vivo analgesic activity and aqueous stability, making it a promising candidate as an injectable formulation for COX-2 inhibition [21]. As evidenced by numerous publications that show up to 400,000-fold increased solubility compared to the parent drug, the prodrug method has been an effective tool for enhancing water solubility. The type of linkage (e. g., ester, amide, carbamate, and phosphate) and the appropriate pro-moiety may decide the prodrug specificity, toxic effects, and ideal bioconversion profile [22].

Permeability-enhancing strategy

When the parent drug's low intestinal solubility or dissolution rate is a barrier to bioavailability but not hepatic metabolism, a permeability-enhancing strategy can be used:

• Parent belongs to Class III of BCS classification (low permeability, high solubility).

• Poor or average Clh in preclinical species.

• Eh<0.5.

• *In vitro* assays showing low permeability

• Fa<25% [2].

Secondary pro-moiety which is cleaved by a dissimilar mechanism combines with the primary pro-moiety of the parent drug to form a so-called double prodrug which is an alternate way of preparing prodrugs. Double prodrug and bifunctional prodrugs are completely different and shouldn't be confused since bifunctional prodrug involves the modification of prodrug at two functional groups. Another form which is named co-drugs exists, where two pharmacologically active drugs that act as a pro-moiety of each other are coupled together. Prodrugs that undergo metabolic bioconversion to the active parent drug by functionally efficient and diversity-resistant hydrolases namely the phosphatases, peptidases, and especially the carboxylesterases are the most common targets for prodrug design [9]. Determining the bioconversion rates, which is regulated by age, health conditions and gender factors, hydrolysis rate, pharmacological and toxicological effects are the key limitations in the design of the prodrug [23].

Utilization of prodrugs

The novel formulation of a chemical compound with the intended pharmacological benefits must be chemically stable and should be free from taste and odour problems [1]. In prodrug analysis, the three fundamental objectives stated by Testa are:

• Pharmaceutical objective: To enhance the solubility, chemical stability, and organoleptic properties of the active agent and to minimize the irritation and/or pain after local administration; and to solve problems associated with the active agent's pharmaceutical technology.

• Pharmacokinetic objective: to enhance the absorption, time profile, organ/tissue-selective delivery, and to reduce the pre-systemic metabolism of the active agent.

• Pharmacodynamic objective: to enhance the therapeutic index, reduce toxicity, and to design codrugs [24].

Masking the taste

Extremely bitter compounds like chloramphenicol are limited for administration to the pediatrics. So, chloramphenicol palmitate, a prodrug of chloramphenicol that possess low aqueous solubility, was formulated to counter the bitter taste [25]. Drug/prodrug must possess a satisfactory aqueous solubility to interact with the taste receptors by being solubilized in the saliva. Hence, the bitter taste of the drug was counteracted by decreasing the aqueous solubility. Table 1 lists out some of the prodrugs that are designed to mask the taste.

Table 1: List of some prodrugs used to mask the taste.

Parent drug	Pro-drug	References
Chloramphenicol	Palmitate	[25]
Clindamycin	Palmitate	[26]
Erythromycin	Ethyl succinate Ethyl carbonate	[1, 27]
Oleandomycin	Acyl ester and N-oxide	[28]
Lincomycin	Phosphate ester Carbonate ester	[26, 29, 30]
Sulphafurazole (sulfisoxazole)	N'-Acetyl	[31]
Dextropropoxyphene	Napsylate	[31]

Toxicity reduction

All the therapeutic agents are desired to possess negligible or no clinical toxicity. Prodrug designing has made it easier for researchers to achieve this no-toxicity level. An ample number of examples exist to support this development. One of which is Sulindac, a clinically pertinent prodrug with enhanced absorption and reduced Gastrointestinal (GI) toxicity [1].

Prolongation of drug action

Prodrugs can be used to control the release of an active drug by altering its aqueous solubility and dissolution properties that regulate the active drug's release rate, absorption rate, and tissue distribution. Development of a number of subcutaneous or intramuscular sustained-release depot injections, which keep therapeutic plasma levels of a parent drug stable for weeks to

months has been an application of the prodrug concept. Prodrugs with a long duration of action may be due to sustained bioconversion after oral administration. Prodrug bonds, such as amides, are commonly used in sustained release strategies because they are relatively resistant to bioconversion. Lisdexamfetamine (Vyvanse) is an example of a Levo lysine (L-lysine) amino acid amide prodrug of dextroamphetamine that has been on the market since 2007 [3]. To maintain adequate plasma concentrations of a drug that is rapidly cleared from the body, frequent dosing with conventional dosage forms is required. Patient compliance is also low due to the repeated dosing of short half-life medications, which results in sharp plasma concentration-time profiles. Such challenges are resolved by the sustained or prolonged release of a drug. Traditional formulation approaches are often efficient but are limited to the sustained release, which on the other hand, could be facilitated by the combination of prodrug with a suitable delivery system.

Sinkula in 1978 summarised various methods for prolonged drug action by altering the physicochemical properties of the drug in the form of a prodrug. The made alterations were:

- The Absorption rate and degree
- The extent and rate of prodrug activation
- Protein or tissue binding process time and their extent
- The extent to which tissue or organs are localized, distributed, and then released from those centres.

The inability to rationally predict the impact of the prodrug structural alteration on the subsequent pharmacokinetics has generally prevented the production of prodrugs for the prolongation of therapeutic action [1].

Alteration of drug solubility

Poor aqueous solubility is a major issue that restricts the clinical use of many medications and drug molecules. The prodrug strategy is one of the many methods used to solve this flaw. Because of the ionic existence of the phosphate group, using esters and amides of phosphoric acid to improve a drug's aqueous solubility is a common practice. It's worth noting that phosphate derivatives have excellent chemical stability, sometimes surpassing that of the parent compound. Esterification of amino acids is another way to improve aqueous solubility [8]. To increase aqueous solubility, several prodrugs have been designed [20]. Even for prodrugs that are designed to promote membrane penetrability, stability, and other such therapeutic characteristics, optimal aqueous solubility is required to facilitate oral uptake and for parenteral. Isavuconazonium sulphate, which was recently licensed, used a novel prodrug technique to increase aqueous solubility [3]. Depending on the drug's ultimate application, the prodrug strategy can be used to significantly alter the solubility of a particular compound. Although the palmitate ester of chloramphenicol has proven to be effective in oral formulations, chloramphenicol sodium succinate, a much more water-soluble type that is converted into free chloramphenicol by esterases has been formulated for parenteral delivery [32]. Another type of compound with low water solubility is steroids. Sodium succinate water-soluble prodrugs are available for glucocorticoids such as betamethasone [1].

Reduction of pain at injection sites

Precipitation of drug due to cell lysis and corrosive function of the drug, effects in pain and irritation. Clindamycin 2-phosphate, a prodrug of antibiotic clindamycin with a solubility of>150 mg/ml, triggers no irritation or pain upon Intramuscular (IM) administration, unlike the parent drug itself, which has the solubility of 3 mg/ml [33, 34]. Inside the body, Phosphatase enzymes convert the resulting prodrug, which has no inherent antibacterial function, into clindamycin with a half-life (t1/2) of 10 min [35].

Enhancement of chemical stability

Chemical stability over a suitable period of time is a critical prerequisite for all drug products. If formulation methods can't lend a hand in overcoming the stability problem, prodrug strategy comes into action. This involves the chemical modification of the functional groups that causes the instability and the physical modification that ensures less interaction between the drug and the unstable media [1]. For instance, auto-amino lysis of aqueous sodium ampicillin causes instability [36]. The reaction of ampicillin with acetone produces hetacillin, which is a prodrug of ampicillin and could easily dissociate into ampicillin and acetone when IV dilution 20 mg/ml is carried out. Yet, only the partial dissociation of hetacillin takes place while using concentrated solutions since auto amino lysis is hindered due to the bond between ampicillin and acetone but could easily dissociate *in vivo*. This leads to the expected stability of the compound [1].

Enhancement of oral absorption

Bioavailability after oral administration is always dissolution rate-limited if a drug is more water-insoluble. The absorption rate of highly polar compounds is limited by GI mucosa. The degree of lipophilicity is necessary for the drugs that are absorbed by passive diffusion through the GI tract. Enhanced lipophilicity in the prodrug design of polar compounds is ideal for its GI absorption. Several penicillin derivatives use this strategy [1].

Improving metabolism

The following are the methods used to enhance drug metabolism

(i) Steric shields: Chemical and enzymatic degradation affect some functional groups more than others. Esters and amides, for instance, tend to hydrolyze more than carbamates and oximes, where steric shields could prevent this by increasing their stability. Steric shields were created to prevent a nucleophile or a nucleophilic centre on an enzyme from approaching the susceptible group.

(ii) Electronic effects of bio-isosteres: Through this strategy, some labile functional groups are protected via electronic stabilization. For instance, a more stable ester functional group urethane is formed by the replacement of a methyl group with an amine group in an ester. The methyl and the amine group have the same size and valance but differ with the varying electronic properties as they can donate electrons to the carbonyl group through their inductive effect, lowering the electrophilicity of the carbonyl carbon and thus preventing hydrolysis by stabilizing it.

(iii) Stereo electronic modification: Labile groups are stabilized by the combination of steric hindrance and electronic stabilization.

(iv) Metabolic blockers: By the introduction of some polar group at some specific site, the metabolism of certain drugs takes place. For instance, replacing the hydrogen group with a methyl group at the 6th position of the megestrol acetate, which is an oral contraceptive, metabolism of the drug gets prevented and thus extending the duration of action.

(v) Exclusion of susceptible metabolic groups: Some chemical molecules are labile to metabolic enzymes. For instance, a methyl group on an aromatic ring undergoes frequent oxidation to form carboxylic acid results in rapid elimination of the drug.

(vi) Group shifts: If the metabolically vulnerable group is not involved in essential binding interactions within the active site of the receptor or enzyme, it is possible to remove or replace it. Masking of the vulnerable group using prodrug or shifting the group is done if the said group is crucial. This method was used to create salbutamol from its analogue neurotransmitter, norepinephrine, in 1969. Catechol Ortho-methyl transferase (O-methyl transferase) metabolizes norepinephrine by methylating one of its phenolic groups.

(vii) Ring variation: Altering the rings enhances the metabolic stability since some of the ring systems can be amendable to metabolism. For instance, Stability is enhanced while replacing the imidazole ring with a 1,2,4-triazole ring [13].

To enhance permeability

Increasing lipophilicity in order to improve passive transcellular absorption while maintaining a standard level of solubility becomes the primary goal of prodrug derivatization of polar compounds [39]. When the parent drug's low intestinal permeability is a significant barrier to bioavailability, a permeability-enhancing strategy can be used [40].

Selective delivery nature of prodrugs

To resolve various undesirable drug properties, prodrugs can be engineered to target particular enzymes or carriers by including enzyme or carrier-substrate specificity. Targeted-prodrug design necessitates a thorough understanding of specific enzymes or carrier systems and their characteristics [39]. Drug aiming for specific tissues, locations, enzymes, and other factors accounts for a significant portion of drug-related experiments around the world. One strategy being vigorously sought is the use of prodrugs to achieve site-specificity with minimal side effects [1, 4]. For a site-specific delivery, the configuration of at least 3 factors needs to be made by using the prodrug strategy.

- The prodrug uptake must be rapid and the perfusion rate must be effectively minimal for the easy targeted action.
- The cleavage of prodrugs to the active drug must be performed once at the site of action
- The retainment of the active drug must be performed by the tissues after the generation of the active drug [41, 42].

The targeted drug release depends on the enzymes present in the target organ. After a thorough understanding of the cleavage produced by that specific enzyme, the design of the corresponding prodrug is altered [43]. Site selectivity is the most prominent feature that a prodrug could offer that can be accomplished in four distinct ways: by passive supplementation of the drug into the organ, transporter facilitated delivery, selective enzymatic metabolism, antigen targeting [44].

Prodrugs for CNS delivery

The Blood-brain barrier (BBB) which is formed by endothelial cells, has become a permeability factor for Central Nervous system (CNS) acting drugs. It maintains the chemical environment suitable for brain function and facilitates the transport of nutrients but prevents the entry of blood-borne and neurotoxic drugs into the brain [8]. Also, the CNS neurotransmitters and neuromodulators are restricted to reach the circulatory system [45]. Having known the transport mechanisms and enzyme activity at BBB, significant improvement in CNS-specific delivery could be achieved. For instance, levodopa is a prodrug of dopamine. It is converted back to dopamine and exhibits its pharmacodynamic activities since dopamine is a hydrophilic molecule [2]. Enhancing the lipophilicity of the parent drug has conventionally been used to increase CNS drug concentration. The prodrug must easily reach the tissue of the brain, must easily convert back to the parent drug, must be more site-specific, and the parent drug should have prolonged retention within the tissue of the brain for this strategy to be effective [46]. To ease the transportation of drugs into CNS, three methodologies have been used:

a) Involving lipidization of molecules to boost passive diffusion.

b) Improving carrier or receptor-mediated transport via BBB

c) Lowering the drug's active efflux from the brain into the blood. To achieve the intended therapeutic effect in CNS, the bioconversion of prodrug should be extended in peripheral tissues but must be rapid in the tissues of the brain, especially the bioconversion must be limited to specific brain areas due to its anatomical complexity [47, 48].

Prodrugs that can use carried-mediated transport pathways make for interesting targets in drug development. Levodopa, with its L-type amino acid transporter 1, is one best example of this since it crosses the BBB and could treat Parkinson's, unlike the hydrophilic dopamine. Despite this, more developed carrier-mediated prodrugs have been designed to facilitate intestinal absorption after oral administration. Intestinal peptide transporter 1 lends a hand in improving the oral absorption of numerous amino acid prodrugs [3].

Prodrugs for hepatic delivery

The liver, which is the major metabolizing organ, may have enormous potential for organ-specific delivery of drugs since it contains a wide range of liver-specific metabolizing enzymes sufficient for prodrug activation [51]. Hep-Direct prodrugs are a new type of Cytochrome P (CYP)-activated prodrug that is designed to target the liver [52]. Hepatic-direct prodrugs get arrested in blood and other tissues except for the liver due to resistant activity towards the esterase cleavage. Certain drugs could benefit from this prodrug strategy, which could increase their efficacy and safety. Adefovir dipivoxil, a prodrug of adefovir, is developed to enhance the oral bioavailability. Yet, adefovir dipivoxil caused nephrotoxicity. As a result, a hep direct prodrug pradefovir, designed to overcome that nephrotoxicity and to enhance the anti-hepatitis B virus (HBV) action. The CYP3A4 isozyme hydroxylates pradefovir at the Carbon (4)-methine site in the liver, then enacts a rapid ring opening followed by a b-elimination response to produce adefovir and aryl vinyl ketone [53]. Nucleotide kinases transform adefovir to adefovir diphosphate, whereas the aryl vinyl ketone generates a glutathione conjugate. Preclinical studies which involved rats and monkeys show that the pradefovir produced a substantial increase in adefovir and its mono-and diphosphates exposure in the liver compared to the kidney, implying that pradefovir has strong liver targeting properties and may have a lower risk of nephrotoxicity [54]. Pradefovir mesylate, adefovir that is being used for hepatitis B therapy. Pradefovir is oxidised primarily in the liver's hepatocytes and is catalysed by CYP450 enzyme. Pradefovir has shown better effectiveness with low systemic adefovir levels in Phase II trials in hepatitis B patients, which contributes to the affirmations for liver targeting [2]. Pradefovirs became the most effective redirect prodrug for hepatic delivery of adefovir. The application of hepatic-directed prodrugs includes the designing of cytarabine 50-monophosphate and lamivudine for liver tumour and HBV, respectively [55]. Chronic HBV, Hepatitis-C virus (HCV) and hepatocellular carcinoma patients have been promisingly benefited by the Hep-Direct prodrugs [53].

Prodrugs for colonic drug delivery

Various anti-inflammatory agents and other drug molecules are intended for colon specific delivery to treat Inflammatory bowel disease (IBD) with the help of this prodrug strategy. Coating with biodegradable and pH sensitive polymers, and the formation of biodegradable complexes are just a few of the options for this type of delivery. All these methodologies tend to reduce the release and absorption in the stomach thereby making the effective delivery to the colon [56]. Amino salicylates, immunosuppressants and corticosteroids are the only medications used to treat IBD. When making prodrugs, the carrier of choice is determined by the functional group on the drug compound that can be conjugated with the carrier [41, 57]. As colon-targeted drug delivery compounds, various forms of prodrugs linked to different carriers have been prepared and evaluated. Absorption and stability in the upper GI tract, hydrolysis selectivity, and the concentration of the drug regenerated in the colon are among the parameters assessed. Some of the conjugates tested for colon-specific delivery include amino-acid, glucuronide, glycoside, azo, cyclodextrin and dextran. A prodrug is generally active as a colon drug carrier if it is hydrophilic and rigid to reduce absorption from the upper GI tract, and is converted into a more lipophilic compound in the colon for absorption [56].

Prodrugs for transdermal drug delivery

Amino acid and ester prodrugs have sparked interest in the field of transdermal drug delivery science and are the widely used prodrugs [58]. One of the prodrug applications in transdermal delivery is that the absorption rate of the drug can be enhanced by the modification of the skin permeability through physical and chemical alterations, which are achieved by manipulating the interaction between the drug-skin and drug vehicle [59]. If the parent drug has a low affinity for the skin, a prodrug strategy comes in handy to enhance the drug permeation and is readily converted back to the parent drug inside the skin with the aid of certain metabolic processes and enzymes. This drug's partitioning behavior can be enhanced by modifying it chemically to develop a hydrophilic or lipophilic prodrug, depending on the vehicle used [60]. Amino acids have been frequently utilized as pro-moieties in designing prodrugs since they are safe on *in vivo* and are readily ionizable [61]. Ester prodrugs are designed by utilizing a carboxylic acid group with an alcohol group, whereas amide prodrugs are designed by combining an amine and a

carboxylic acid group [58]. Transdermal phenol delivery has significant clinical benefits, particularly in the fields of narcotic analgesics and in therapies involving hormone replacement [62].

Prodrugs for tissue targeting

The majority of antitumor and antiviral drugs are cytotoxic and have a variety of side effects. Tissue-specific drug delivery has a lot of promise in terms of both safety and efficacy.

To target tissue delivery, multiple prodrug methods have been studied, including:

(a) Enzymatic activation of the prodrug with the aid of enzymes localized at the target site.

(b) Tissue-specific transporters deliver prodrugs to their target tissues.

(c) Drug and molecule conjugates that are uniquely coupled to target tissues [53].

Prodrugs in cancer therapy

Chemotherapy is a fundamental cancer treatment. Chemotherapy for different cancers has made significant strides over the past few decades. Most of the anticancer drugs currently on the market work by inhibiting cell proliferation or by stopping the cell cycle at a specific phase. Since oncostatic drugs have low selectivity, they affect both neoplastic and rapidly proliferating normal cells, including bone marrow, epithelia, gut, lymphatic cells, hair follicles, and gametes. Anticancer drugs' ineffectiveness and long-term use are hampered by their lack of specificity and related toxicity. As a result, it's unsurprising that there's a serious need to boost their specificity. Prodrug design is one of the most promising approaches to overcome this problem. An anticancer prodrug should be delivered to cancer cells, where recombinant enzymes can convert it to a cytotoxic parent drug [63]. The main objective is to deliver the prodrug to the site of action where it is bio transformed into its parent drug leaving the normal cells undisturbed by causing no toxicity [64]. Identifying compounds that are increasingly successful at destroying tumour cells has been a strong focus for much of the 80 y of modern drug research in oncology. Immunotherapies, Antibody-drug conjugates (ADCs), and Chimeric antigen receptor-T cells (CAR-Ts) all have emerged in the last two decades as exciting new biological therapies that can incredibly kill tumour cells. However, in most cases, high anti-tumour efficacy has been accompanied by high toxicity, limiting the usage of these drugs at their maximum effective levels, over the entire treatment duration, or in large patient populations wherever necessary [65]. Prodrugs are commonly used to transmit cytotoxic agents to cancer cells with specificity. Targeted prodrugs for cancer therapy have achieved a great deal of variety in terms of the target range, activation chemistry, scale, and physicochemical design. The self-assembling macromolecular prodrugs like targeted drug-polymer conjugate, drug-antibody conjugate assembles to form liposomal and micellar nanoparticles that are currently a major trend in Prodrug cancer therapy [66]. Prodrug of 5-fluorouracil which is used in the therapy of solid tumours like breast and colorectal cancers is Capecitabine and is regarded as the forerunner of chemotherapy prodrugs [67, 68]. Capecitabine is quickly and thoroughly absorbed after oral administration and is metabolized by hepatic carboxylesterases. Cytidine deaminase in the liver and tumour tissues converts 5'-deoxy-5-fluorocytidine to 5'-deoxy-5-fluorouridine, which is then converted to highly cytotoxic 5'-fluorouracil by thymidine phosphorylase [69]. Anticancer compounds based on platinum (IV) have a lot of promise for surpassing the limitations of current platinum (II)-based chemotherapies. They are classified as prodrugs because the cytotoxic platinum (II) needs to be activated by bio reduction [70]. Breast cancers that are hormone dependant are prominently cured by tamoxifen, which acts as a selective regulator of estrogen receptors and inhibits the proliferation of tumour cells [71, 72]. Along with the Camptothecin (CPT), which is a novel anticancer prodrug, another prodrug named doxorubicin hydrochloride (DOX ·HCl) is shown to possess the anticancer activity and is included in the prodrug category. The DOX HCl loaded CPT prodrug could simultaneously deliver two anticancer drugs, resulting in collective cytotoxicity against tumour cells, implying that this reduced glutathione (GSH)-responsive mechanism could be a successful carrier to boost the efficacy of drug delivery [73]. Any overexpressed molecules that include enzymes, antigens and peptide transports are targeted for therapeutic action. The use of enzyme-activating prodrugs is a two-step process. The first step involves targeting and expressing a drug-activating enzyme in tumours. Administration of a nontoxic prodrug which is a precursor of the exogenous enzyme is the second step. The outcome is the conversion of the prodrug to the actual parent drug with the anticancer properties within the tumour cells to produce the therapeutic activity. Both enzymes and prodrugs must follow certain criteria in order for this technique to be clinically effective. The enzymes can be either nonhuman or human proteins that are only produced at low levels in normal tissues [74]. The conjugated prodrug remains inactive until it reaches the tumour site and once reached, it undergoes transformation and binds to the surface of tumour cells, releases carrier molecules to restore its efficacy. Drug conjugates can thus be thought of as tumour-activated prodrugs (TAPs). While most of the typical prodrugs are transformed to parent drugs by hydrolysis, restoring TAP activity should preferably depend on interaction with antigens and receptors located on the cancer cells [75]. Exogenous enzymes can be administered to tumour cells with the help of antibodies or genes to broaden the spectrum of tumour responsive enzyme-prodrug cancer therapy [76]. Onco-static drug precursors are used in enzyme activated prodrug strategies (ADEPT, GDEPT). Mitomycin C phosphate, Cyclophosphamide ifosfamide, and Etoposide phosphate are few examples of enzyme-activated prodrugs [77, 78].

Recent approaches and proposals

Since1993, the number of prodrug patents has risen exponentially (by over 2000% in2002), with patents for cancer treatment accounting for 37% of all patents [79]. Prodrugs make up about 10% of all medicines marketed in the world today [8]. Prodrugs are increasingly being used to enhance drug characteristics, and their influence and advancement are projected to increase [80]. The Food and Drug Administration (FDA) approved 30 prodrugs from 2008 to 2017 are listed in table 2.

Table 2: FDA approved prodrugs in the period 2008 to 2017

No	Prodrug	Mechanism of action	Prodrug strategy and improved property	Approval date	Reference
1.	Fosaprepitant (Emend, fosaprepitant dimeglumine)	Prevention of chemotherapy-induced nausea and vomiting (SPR antagonist)	Improved solubility allowing intravenous administration	25 Jan 2008	[81]
2.	Fesoterodine (Toviaz, fesoterodine fumarate)	Overactive bladder (competitive muscarinic receptor antagonist)	Reduced interpatient pharmacokinetic variability	31 Oct 2008	[82]
3.	Fospropofol (Lusedra, fospropofol disodium)	Anaesthetic (sedative–hypnotic agent)	Aqueous solubility property of propofol is enhanced from 150 μg ml^{-1} to ~500 mg ml^{-1}	12 Dec 2008	[83, 84]
4.	Prasugrel (Effient, prasugrel hydrochloride)	Reduction of thrombotic and cardiovascular events (inhibitor of the platelet P2Y12 receptor that is	Bioprecursor prodrug that releases a thiolactone by ester hydrolysis and undergoes further metabolic	7 Oct 2009	[85]

No	Prodrug	Mechanism of action	Prodrug strategy and improved property	Approval date	Reference
		activated by Adenosine di-phosphate ADP)	activation to a form that sulfenylates the platelet P2Y12 receptor		
5.	Romidepsin (Istodax)	Cutaneous T cell lymphoma (zinc-dependent Histone deacetylase (HDAC) inhibitor)	Reduction of the disulfide bond by glutathione results in an active monocyclic dithiol	5 Nov 2009	[87]
6.	Fingolimod (Gilenya, fingolimod hydrochloride)	Multiple sclerosis. Sphingosine-1-phosphate (S1P) agonist.	Hydroxyl form is a more lipophilic prodrug that enables permeation	21 Sept 2010	[87]
7.	Dabigatranetexilate (Pradaxa, dabigatran etexilate mesylate)	Thromboembolism (direct inhibitor of thrombin)	Permeation through increased lipophilicity	19 Oct 2010	[88]
8.	Ceftaroline fosamil (Teflaro, ceftaroline fosamil monoacetate monohydrate)	Pneumonia or skin or skin structure infections (antibacterial; inhibits cell wall synthesis)	Improved solubility (from 2.3 mg ml^{-1} to>100 mg ml^{-1}), thus allowing intravenous administration	29 Oct 2010	[89]
9.	Azilsartan medoxomil (Edarbi, azilsartan medoxomil monopotassium)	Hypertension (angiotensin II antagonist	The absolute bioavailability of azilsartan after oral intake of the prodrug tablet is ~58%	25 Feb 2011	[90]
10.	Gabapentin enacarbil (Horizant)	Restless leg syndrome or postherpetic neuralgia. Gamma-aminobutyric acid (GABA) and calcium-channel modulator.	Increased permeation via gastrointestinal transporters	6 Apr 2011	[91]
11.	Abiraterone acetate (Zytiga)	CYP17A1 inhibitor	Rapid dissolution and subsequent prodrug hydrolysis may generate an intraluminal supersaturated solution of abiraterone, leading to better absorption	28 Apr 2011	[92]
12.	Tafluprost (Zioptan)	Intraocular hypertension (prostaglandin analogue)	Ocular permeation through increased lipophilicity	10 Feb 2012; first approval in Germany on 1 Mar 2008	[93, 94]
13.	Dimethyl fumarate (Tecfidera)	Multiple sclerosis	Increased permeation, probably through increased lipophilicity • Marketed in Germany since the mid-1990s for the treatment of psoriasis	27 Mar 2013	[95]
14.	Eslicarbazepine acetate (Aptiom)	Epilepsy (anticonvulsant; voltage-gated sodium-channel blocker)	Changes the metabolic profile to reduce potential drug interactions, have a more favourable safety profile	8 Nov 2013	[96, 97]
15.	Sofosbuvir (Sovaldi and others)	HCV infection (nucleotide analogue; HCV NS5B polymerase inhibitor)	Improved membrane permeation and targeting to the liver	6 Dec 2013	[98]
16.	Droxidopa (Northera)	Neurogenic orthostatic hypotension or Parkinson disease–off-label (dopamine precursor)	Improved brain permeability267 • Marketed in Japan since 1989	18 Feb 2014	[99]
17.	Tedizolid phosphate (Sivextro)	Acute bacterial skin infections (oxazolidinone of antibacterial class; binds 50S ribosomal subunit)	Improved solubility	20 Jun 2014	[100]
18.	Isavuconazonium (Cresemba, isavuconazonium sulfate)	Invasive aspergillosis or invasive mucormycosis (azole antifungal; inhibits synthesis of ergosterol, a cell wall component)	Improved solubility	6 Mar 2015	[101]
19.	Sacubitril sodium (part of Entresto, which contains anionic forms of sacubitril and valsartan, sodium cations and water)	Heart failure (neprilysin inhibitor)	Likely improved permeability through increased lipophilicity	7 Jul 2015	[102]
20.	Uridine triacetate (Xuriden)	Hereditary orotic aciduria (pyrimidine analogue for uridine replacement)	Improved membrane permeability through increased lipophilicity	4 Sept 2015	[103]
21.	Aripiprazole lauroxil (Aristada)	Schizophrenia (antipsychotic; partially owing to inhibition of the D2 receptor)	Sustained release and prolonged duration of action following intramuscular administration	6 Oct 2015	[104]
22.	Tenofovir alafenamide (Genvoya and other combinations, tenofovir alafenamide hemifumarate)	Human immune deficiency virus (HIV)-1 infection (HIV-1 nucleoside analogue reverse-transcriptase inhibitor)	Increased permeability through increased lipophilicity and enhanced intracellular targeting247,248 • Prodrug targets T cells for HIV-1 but is also cleaved in the liver and thus is also used for HBV infection	5 Nov 2015	[105, 106]
23.	Ixazomib citrate (Ninlaro)	Multiple myeloma (reversible proteasome inhibitor)	Likely increased stability of oxidatively unstable boronic acid	20 Nov 2015	[107]
24.	Selexipag (Uptravi)	Pulmonary hypertension (non-	Prolonged duration of action and	22 Dec 2015	[108, 109]

No	Prodrug	Mechanism of action	Prodrug strategy and improved property	Approval date	Reference
		prostanoid prostacyclin receptor agonist)	reduced side effects because of the reduction in peak–trough fluctuations		
25.	Deflazacort (Emflaza)	Duchenne muscular dystrophy (corticosteroid)	Likely increased lipophilicity270 • Marketed in Europe since the mid-1980s	9 Feb 2017	[110]
26.	Telotristatetiprate (Xermelo, hippurate salt of telotristat ethyl)	Carcinoid syndrome diarrhoea (tryptophan hydroxylase inhibitor)	Likely improved permeability through increased lipophilicity	28 Feb 2017	[111]
27.	Valbenazine (Ingrezza, valbenazine tosylate)	Tardive dyskinesia	Improved pharmacokinetic profile272	11 Apr 2017	[112]
28.	Benznidazole (Benznidazole)	Chagas disease in children aged 2–12 y (nitroimidazole antimicrobial; inhibits DNA synthesis)	Reduced by nitroreductases into active species149 • Benznidazole been in medical use since 1971	29 Aug 2017	[113]
29.	Secnidazole (Solosec)	Bacterial vaginosis (nitroimidazole antimicrobial)	Reduced by bacterial enzymes into active species	15 Sept 2017	[114, 115]
30.	Latanoprostene bunod (Vyzulta)	High intraocular pressure in patients with open-angle glaucoma or ocular hypertension (prostaglandin analogue)	Hydrolysis by corneal esterases into latanoprost acid and butanediol mononitrate, which is then metabolized to Nitric oxide (NO) and the inactive 1,4-butanediol	2 Nov 2017	[114]

While approximately three prodrugs were approved each year during the ten-year period from 2008 to2017, it is noteworthy to note that drugs accounted for 17% of New chemical entity (NCE) approvals (30% biologics) and the remaining 70 percent of NCEs were prodrugs [3].

Combinatorial chemistry and high throughput screening make it possible to find a new chemical entity with high therapeutic efficacy [116]. These techniques too have limitations due to the undesired physicochemical properties and to surpass this, chemical alterations or new formulation strategies need to be developed to promote the efficacy of the compound [80]. Gorrod had cited four mechanisms causing toxicity in a review of 'potential hazards of the prodrug approach.'

1. A non-parent drug-mediated toxic metabolite formation.

2. During the prodrug activation phase, a vital constituent, for instance, glutathione is consumed. Hepatic cells are protected by l-cysteine since it is needed for glutathione biosynthesis.

3. An "inert" process takes place while a toxic derivative is being formed from a transport moiety.

4. Discharge of pharmacokinetic modifiers [43].

Numerous diseases, whether infectious or caused by normal physiological abnormalities, have benefited from the prodrug approach. Prodrug strategy which is a rational drug design alternative makes a contribution to the recent advancements in the biotech field. Prolongation of action and toxicity reduction had become the primary objective in the prodrug strategy by the incorporation of macromolecules [117]. Antibody prodrugs are a new type of biological strategy in tumour targeting. Prodrugs were used to improve tolerability over a century ago, and at present, almost 10% of all marketed small-molecule drugs can be classified as prodrugs. Pro-body therapeutics are the most advanced antibody prodrugs in development [65]. The modern and traditional prodrug approaches can be differentiated.

The traditional approach of prodrugs

To enhance the permeability of lipophilic groups and the solubility of the parent drug, the involvement of covalent bond formation between the parent and the hydrophilic functional groups is necessary [118, 119]. Although directing the prodrug to a targeted site is difficult in this strategy, it is an effective tool for improving physicochemical and/or biopharmaceutical properties to overcome the *in vivo* limitations of a drug. Modifying the drug kinetics, achieving extended drug release, lowering toxicity, are some of the possible goals of this approach [120].

The molecular revolution in biomedicine

It is a modern strategy in designing the prodrugs where Cellular parameters such as influx and efflux of transporters, protein expressions are considered to enhance the targeting properties of a drug [121-123]. Specific targeting of the enzymes and transporters include the binding of carrier and parent drug. Manipulating the mechanism and site of release becomes a major advantage and a challenge in designing the prodrugs which can be optimized by several computational methods [124, 125]. A research group has developed and tested a novel phospholipid-based prodrug approach [126]. Currently, multiple clinical trials are being performed to assess the effectiveness of prodrugs for various therapeutic purposes. Some of those are listed in table 3. Some of the few notable examples include a study that is ongoing to assess the potency of the anticancer prodrug named NUC-1031, which was developed using Protidic technology, in patients with severe biliary tract cancer [127]. The AKR1C3-activated prodrug OBI-3424 is a prodrug currently being tested in patients with unmanageable T-cell acute lymphoblastic leukaemia [128].

Table 3: Some ongoing clinical trials for prodrugs

Prodrug	Therapeutic uses	Reference
Tenofovir alafenamide	HIV/AIDS and chronic hepatitis B	[129]
Anticancer prodrug 'NUC-1031'	Severe biliary tract cancer	[127, 130]
AKR1C3 activated 'OBI-3424'	Relapse acute lymphoblastic leukaemia, hepatocellular carcinoma, and castrate-resistive prostate cancer	[80, 128]
Baloxavir marboxil	Influenza	[131]
Remdesivir	Coronavirus disease 2019 (covid-19) in adults and adolescents with pneumonia requiring supplemental oxygen	[132]

CONCLUSION

In addition to the beneficiary aspects of prodrugs in reducing ADR, it also plays a role in the target specificity of certain drugs. Multiple studies have shown that prodrugs can positively impact the pharmacokinetic and pharmacodynamics of a drug in many ways, including the targeted delivery, prolongation period, and therapeutic index of specific drugs. Also, the prescription of prodrugs has been widely regarded as the first priority drugs in case of chemotherapy. Hence, prodrug formulations have been considered as one of the vital fields in recent times.

ACKNOWLEDGMENT

The authors are very much thankful to the Crescent School of Pharmacy, B. S. Abdur Rahman Crescent Institute of Science and Technology, Chennai, India for providing essential services to carry out the study.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

We know of no conflict of interest associated with this publication.

REFERENCES

1. Stella VJ, Charman WN, Naringrekar VH. Prodrugs do they have advantages in clinical practice? Drugs. 1985;29(5):455-73. doi: 10.2165/00003495-198529050-00002, PMID 3891303.
2. Rautio J, Kumpulainen H, Heimbach T, Oliyai R, Oh D, Järvinen T, Savolainen J. Prodrugs: design and clinical applications. Nat Rev Drug Discovery. 2008;7(3):255-70. doi: 10.1038/nrd2468, PMID 18219308.
3. Rautio J, Meanwell NA, Di L, Hageman MJ. The expanding role of prodrugs in contemporary drug design and development. Nat Rev Drug Discovery. 2018;17(8):559-87. doi: 10.1038/nrd.2018.46, PMID 29700501.
4. Han HK, Amidon GL. Targeted prodrug design to optimize drug delivery. AAPS PharmSci. 2000;2(1):E6. doi: 10.1208/ps020106, PMID 11741222.
5. Yu LX, Straughn AB, Faustino PJ, Yang Y, Parekh A, Ciavarella AB, Asafu-Adjaye E, Mehta MU, Conner DP, Lesko LJ, Hussain AS. The effect of food on the relative bioavailability of rapidly dissolving immediate-release solid oral products containing highly soluble drugs. Mol Pharm. 2004;1(5):357-62. doi: 10.1021/mp0499407, PMID 16026005.
6. Surendran V, Singh A, Sampathkumar KP. Synthesis and characterization of novel amino acid prodrug of famotidine. Int J Pharm Pharm Sci. 2015;7:403-8.
7. Gomes P, Vale N, Moreira R. Cyclization-activated prodrugs. Molecules. 2007;12(11):2484-506. doi: 10.3390/12112484, PMID 18065953.
8. Zawilska JB, Wojcieszak J, Olejniczak AB. Prodrugs: a challenge for the drug development. Pharmacol Rep. 2013;65(1):1-14. doi: 10.1016/s1734-1140(13)70959-9, PMID 23563019.
9. Huttunen KM, Raunio H, Rautio J. Prodrugs-from serendipity to rational design. Pharmacol Rev. 2011;63(3):750-71. doi: 10.1124/pr.110.003459, PMID 21737530.
10. Das N, Dhanawat M, Dash B, Nagarwal RC, Shrivastava SK. Codrug: an efficient approach for drug optimization. Eur J Pharm Sci. 2010;41(5):571-88. doi: 10.1016/j.ejps.2010.09.014, PMID 20888411.
11. Wu KM. A new classification of prodrugs: regulatory perspectives. Pharmaceuticals (Basel). 2009;2(3):77-81. doi: 10.3390/ph2030077, PMID 27713225.
12. Testa B, Mayer JM, Mayer J. Hydrolysis in drug and prodrug metabolism. John Wiley & Sons; 2003.
13. Karaman R. Prodrugs design based on inter- and intramolecular chemical processes. Chem Biol Drug Des. 2013;82(6):643-68. doi: 10.1111/cbdd.12224, PMID 23998799.
14. Clas SD, Sanchez RI, Nofsinger R. Chemistry-enabled drug delivery (prodrugs): recent progress and challenges. Drug Discovery Today. 2014;19(1):79-87. doi: 10.1016/j.drudis.2013.08.014, PMID 23993918.
15. Lai WF. editor. Systemic delivery technologies in anti-aging medicine: methods and applications. Springer International Publishing; 2020.
16. Karaman R, Fattash B, Qtait A. The future of prodrugs - design by quantum mechanics methods. Expert Opin Drug Delivery. 2013;10(5):713-29. doi: 10.1517/17425247.2013.786699, PMID 23540707.
17. Karaman R. Prodrugs design by computation methods-a new era. Drug Designing. 2013;1:e113.
18. Karaman R. Prodrug Design vs drug design. Drug Des. 2013;02(2):e114. doi: 10.4172/2169-0138.1000e114.
19. Papot S, Tranoy I, Tillequin F, Florent JC, Gesson JP. Design of selectively activated anticancer prodrugs: elimination and cyclization strategies. Curr Med Chem Anticancer Agents. 2002;2(2):155-85. doi: 10.2174/1568011023354173, PMID 12678742.
20. Chen XQ, Venkatesh S. Miniature device for aqueous and non-aqueous solubility measurements during drug discovery. Pharm Res. 2004;21(10):1758-61. doi: 10.1023/b:pham.0000045225.76650.53, PMID 15553219.
21. Liu HF, Wan N, Huan ML, Jia YY, Yuan XF, Zhou SY, Zhang BL. Enhanced water-soluble derivative of PC407 as a novel potential COX-2 inhibitor injectable formulation. Bioorg Med Chem Lett. 2014;24(20):4794-7. doi: 10.1016/j.bmcl.2014.09.007, PMID 25248683.
22. Jornada DH, dos Santos Fernandes GF, Chiba DE, De Melo TR, Dos Santos JL, Chung MC. The prodrug approach: A successful tool for improving drug solubility. Molecules. 2015;21(1):42. doi: 10.3390/molecules21010042, PMID 26729077.
23. Draganov DI, La Du BN. Pharmacogenetics of paraoxonases: a brief review. Naunyn Schmiedebergs Arch Pharmacol. 2004;369(1):78-88. doi: 10.1007/s00210-003-0833-1, PMID 14579013.
24. Testa B. Prodrugs: bridging pharmacodynamic/pharmacokinetic gaps. Curr Opin Chem Biol. 2009;13(3):338-44. doi: 10.1016/j.cbpa.2009.04.620, PMID 19473869.
25. Glazko AJ, Edgerton WH, Dill WA, Lenz WR. Chloromycetin palmitate; a synthetic ester of chloromycetin. Antibiot Chemother (Northfield). 1952;2(5):234-42. PMID 24541898.
26. Sinkula AA, Morozowich W, Rowe EL. Chemical modification of clindamycin: synthesis and evaluation of selected esters. J Pharm Sci. 1973;62(7):1106-11. doi: 10.1002/jps.2600620711, PMID 4714118.
27. Clark Jr RK, Varner EL. New esters of erythromycin. Antibiot Chemother (Northfield). 1957;7(9):487-9. PMID 24544532.
28. Bundy GL. Inventor. 9-deoxy-6, 9α-nitrilo-PGF1. Upjohn Co Assignee Bioprecursors of. United States patent US; 1979 Apr 24. PMID 4151176.
29. Morozowich W, Lamb DJ, Karnes HA, Mackellar FA, Lewis C, Stern KF, Rowe EL. Synthesis and bioactivity of lincomycin-2-phosphate. J Pharm Sci. 1969;58(12):1485-9. doi: 10.1002/jps.2600581213, PMID 5353265.
30. Morozowich W, Sinkula AA, MacKellar FA, Lewis C. Synthesis and bioactivity of lincomycin 2-monoesters. J Pharm Sci. 1973;62(7):1102-5. doi: 10.1002/jps.2600620710, PMID 4714117.
31. Gruber Jr CM, Stephens VC, Terrill PM. Propoxyphene napsylate: chemistry and experimental design. Toxicol Appl Pharmacol. 1971;19(3):423-6. doi: 10.1016/0041-008x(71)90001-9, PMID 4936996.
32. Glazko AJ, Carnes HE, Kazenko A, Wolf LM, Reutner TF. Succinic acid esters of chloramphenicol. Antibiot Annu. 1957-1958;5:792-802. PMID 13521897.
33. Edmondson HT. Parenteral and oral clindamycin therapy in surgical infections: a preliminary report. Ann Surg. 1973;178(5):637-42. doi: 10.1097/00000658-197311000-00014, PMID 4748302.
34. Gray JE, Weaver RN, Moran J, Feenstra ES. The parenteral toxicity of clindamycin 2-phosphate in laboratory animals.

Toxicol Appl Pharmacol. 1974;27(2):308-21. doi: 10.1016/0041-008x(74)90202-6, PMID 4137286.

35. DeHAAN RM, Metzler CM, Schellenberg D, Vandenbosch WD. Pharmacokinetic studies of clindamycin phosphate. J Clin Pharmacol. 1973;13(5):190-209. doi: 10.1002/j.1552-4604.1973.tb00208.x, PMID 4488654.
36. Bundgaard H. Spectrophotometric determination of ampicillin sodium in the presence of its degradation and polymerization products. J Pharm Pharmacol. 1974;26(6):385-92. doi: 10.1111/j.2042-7158.1974.tb09302.x, PMID 4154981.
37. Schwartz MA, Hayton WL. Relative stability of hetacillin and ampicillin in solution. J Pharm Sci. 1972;61(6):906-9. doi: 10.1002/jps.2600610616, PMID 4339954.
38. Ho NF, Park JY, Morozowich W, Higuchi WI. Physical model approach to the design of drugs with improved intestinal absorption. Des Biopharm Prop Prodrugs Analogs. 1977:136-227.
39. Jana S, Mandlekar S, Marathe P. Prodrug design to improve pharmacokinetic and drug delivery properties: challenges to the discovery scientists. Curr Med Chem. 2010;17(32):3874-908. doi: 10.2174/092986710793205426, PMID 20858214.
40. Halen PK, Murumkar PR, Giridhar R, Yadav MR. Prodrug designing of NSAIDs. Mini Rev Med Chem. 2009;9(1):124-39. doi: 10.2174/138955709787001695, PMID 19149665.
41. Friend DR, Chang GW. A colon-specific drug-delivery system based on drug glycosides and the glycosidases of colonic bacteria. J Med Chem. 1984;27(3):261-6. doi: 10.1021/jm00369a005, PMID 6699871.
42. Stella VJ, Himmelstein KJ. Critique of prodrugs and site specific delivery. In: Benzon A, editor. Optimization of drug delivery Symposium Copenhagen: Munksgaard; 1982. p. 134-55.
43. Wermuth CG. Designing prodrugs and bioprecursors. In: The practice of medicinal chemistry. Academic Press; 2008. p. 721-46.
44. Ettmayer P, Amidon GL, Clement B, Testa B. Lessons learned from marketed and investigational prodrugs. J Med Chem. 2004;47(10):2393-404. doi: 10.1021/jm0303812, PMID 15115379.
45. Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood–brain barrier. Neurobiol Disease. 2010;37(1):13-25. doi: 10.1016/j.nbd.2009.07.030, PMID 19664713.
46. Anderson BD. Prodrugs for improved CNS delivery. Adv Drug Delivery Rev. 1996;19(2):171-202. doi: 10.1016/0169-409X(95)00106-H.
47. Pardridge WM. Brain drug development and brain drug targeting. Pharm Res. 2007;24(9):1729-32. doi: 10.1007/s11095-007-9387-0, PMID 17629776.
48. Patel MM, Goyal BR, Bhadada SV, Bhatt JS, Amin AF. Getting into the brain: approaches to enhance brain drug delivery. CNS Drugs. 2009;23(1):35-58. doi: 10.2165/0023210-200923010-00003, PMID 19062774.
49. Warren MS, Rautio J, editors. Prodrugs and targeted delivery. Wiley-VCH Verlag; 2011.
50. Brogden RN, Speight TM, Avery GS. Levodopa: a review of its pharmacological properties and therapeutic use with particular reference to Parkinsonism. Drugs. 1971;2(4):262-400. doi: 10.2165/00003495-197102040-00002, PMID 4340597.
51. Van Montfoort JE, Hagenbuch B, Groothuis GM, Koepsell H, Meier PJ, Meijer DK. Drug uptake systems in liver and kidney. Curr Drug Metabolism. 2003;4(3):185-211. doi: 10.2174/1389200033489460, PMID 12769665.
52. Erion MD, Bullough DA, Lin CC, Hong Z. HepDirect prodrugs for targeting nucleotide-based antiviral drugs to the liver. Curr Opinion Investigational Drugs (London, England: 2000); 2006;7(2):109-17. PMID 16499280.
53. Li F, Maag H, Alfredson T. Prodrugs of nucleoside analogues for improved oral absorption and tissue targeting. J Pharm Sci. 2008;97(3):1109-34. doi: 10.1002/jps.21047, PMID 17696166.
54. Lin CC, Yeh LT, Vitarella D, Hong Z, Erion MD. Remofovir mesylate: a prodrug of PMEA with improved liver-targeting and safety in rats and monkeys. Antiviral Chem Chemotherapy. 2004;15(6):307-17. doi: 10.1177/095632020401500603, PMID 15646644.
55. Reddy KR, Colby TJ, Fujitaki JM, van Poelje PD, Erion MD. Liver targeting of hepatitis-B antiviral lamivudine using the HepDirect prodrug technology. Nucleosides, Nucleotides Nucleic Acids. 2005;24(5-7):375-81. doi: 10.1081/ncn-200059781, PMID 16247954.
56. Sinha VR, Kumria R. Colonic drug delivery: prodrug approach. Pharm Res. 2001;18(5):557-64. doi: 10.1023/a:1011033121528, PMID 11465408.
57. Minami K, Hirayama F, Uekama K. Colon-specific drug delivery based on a cyclodextrin prodrug: release behavior of biphenylylacetic acid from its cyclodextrin conjugates in rat intestinal tracts after oral administration. J Pharm Sci. 1998;87(6):715-20. doi: 10.1021/js9704339, PMID 9607948.
58. Kumar SU, Tyagi DK, Gupta AR. Synthesis, characterization and pharmcological activity of ester prodrugs of naproxen. Asian J Pharm Clin Res. 2010;3:208-11.
59. Valia KH, Tojo K, Chien YW. Long-term permeation kinetics of estradiol: (III) kinetic analyses of the simultaneous skin permeation and bioconversion of estradiol esters. Drug Dev Ind Pharm. 1985;11(6-7):1133-73. doi: 10.3109/03639048509059861.
60. Fang JY, Leu YL. Prodrug strategy for enhancing drug delivery via skin. Curr Drug Discovery Technol. 2006;3(3):211-24. doi: 10.2174/157016306780136772, PMID 17311566.
61. Ar C, Gandhi PM. Synthesis and evaluation of amino acid ester conjugates of hiv protease inhibitor. Asian J Pharm Clin Res. 2019;12:342-6.
62. Devarajan-Ketha H, Sloan KB. N, N′-Dialkylaminoalkylcarbonyl (DAAC) prodrugs and aminoalkylcarbonyl (AAC) prodrugs of 4-hydroxyacetanilide and naltrexone with improved skin permeation properties. Bioorganic Med Chem Lett. 2011;21(13):4078-82. doi: 10.1016/j.bmcl.2011.04.118, PMID 21616664.
63. Mahato R, Tai W, Cheng K. Prodrugs for improving tumor targetability and efficiency. Adv Drug Delivery Rev. 2011;63(8):659-70. doi: 10.1016/j.addr.2011.02.002, PMID 21333700.
64. de Groot FM, Damen EW, Scheeren HW. Anticancer prodrugs for application in monotherapy: targeting hypoxia, tumor-associated enzymes, and receptors. Curr Med Chem. 2001;8(9):1093-122. doi: 10.2174/0929867013372634, PMID 11472243.
65. Kavanaugh WM. Antibody prodrugs for cancer. Expert Opinion Biol Ther. 2020;20(2):163-71. doi: 10.1080/14712598.2020.1699053, PMID 31779489.
66. Giang I, Boland EL, Poon GM. Prodrug applications for targeted cancer therapy. AAPS J. 2014;16(5):899-913. doi: 10.1208/s12248-014-9638-z, PMID 25004822.
67. Johnston PG, Kaye S. Capecitabine: a novel agent for the treatment of solid tumors. Anticancer Drugs. 2001;12(8):639-46. doi: 10.1097/00001813-200109000-00001, PMID 11604550.
68. Koukourakis GV, Kouloulias V, Koukourakis MJ, Zacharias GA, Zabatis H, Kouvaris J. Efficacy of the oral fluorouracil pro-drug capecitabine in cancer treatment: a review. Molecules. 2008;13(8):1897-922. doi: 10.3390/molecules13081897, PMID 18794792.
69. Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, Shimma N, Umeda I, Ishitsuka H. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer. 1998;34(8):1274-81. doi: 10.1016/s0959-8049(98)00058-6, PMID 9849491.
70. Zhang JZ, Bonnitcha P, Wexselblatt E, Klein AV, Najajreh Y, Gibson D, Hambley TW. Facile preparation of mono-, di- and mixed-carboxylato platinum(IV) complexes for versatile anticancer prodrug design. Chemistry. 2013;19(5):1672-6. doi: 10.1002/chem.201203159. PMID 23255183.
71. Hoskins JM, Carey LA, McLeod HL. CYP2D6 and tamoxifen: DNA matters in breast cancer. Nat Rev Cancer. 2009;9(8):576-86. doi: 10.1038/nrc2683, PMID 19629072.
72. Sánchez Sanchez L, Cadena Nava RD, Palomares LA, Ruiz Garcia J, Koay MS, Cornelissen JJ, Vazquez Duhalt R. Chemotherapy pro-drug activation by biocatalytic virus-like nanoparticles containing cytochrome P450. Enzyme Microb Technol. 2014;60:24-31. doi: 10.1016/j.enzmictec.2014.04.003, PMID 24835096.
73. Xu Z, Wang D, Xu S, Liu X, Zhang X, Zhang H. Preparation of a camptothecin prodrug with glutathione-responsive disulfide Linker for anticancer drug delivery. Chem Asian J. 2014;9(1):199-205. doi: 10.1002/asia.201301030, PMID 24136878.

74. Xu G, McLeod HL. Strategies for enzyme/prodrug cancer therapy. Clin Cancer Res. 2001;7(11):3314-24. PMID 11705842.
75. Chari RV. Targeted delivery of chemotherapeutics: tumor-activated prodrug therapy. Adv Drug Delivery Rev. 1998;31(1-2):89-104. doi: 10.1016/s0169-409x(97)00095-1, PMID 10837619.
76. Bagshawe KD, Sharma SK, Begent RH. Antibody-directed enzyme prodrug therapy (ADEPT) for cancer. Expert Opin Biol Ther. 2004;4(11):1777-89. doi: 10.1517/14712598.4.11.1777, PMID 15500406.
77. Singh PP, Joshi S, Russell PJ, Verma ND, Wang X, Khatri A. Molecular chemotherapy and chemotherapy: a new front against late-stage hormone-refractory prostate cancer. Clin Cancer Res. 2011;17(12):4006-18. doi: 10.1158/1078-0432.CCR-11-0248, PMID 21531822.
78. Altaner C. Prodrug cancer gene therapy. Cancer Lett. 2008;270(2):191-201. doi: 10.1016/j.canlet.2008.04.023, PMID 18502571.
79. Stella VJ. Prodrugs as therapeutics. Expert Opin Ther Pat. 2004;14(3):277-80. doi: 10.1517/13543776.14.3.277.
80. Markovic M, Ben-Shabat S, Dahan A. Prodrugs for improved drug delivery: lessons learned from recently developed and marketed products. Pharmaceutics. 2020;12(11):1031. doi: 10.3390/pharmaceutics12111031, PMID 33137942.
81. Hale JJ, Mills SG, MacCoss M, Dorn CP, Finke PE, Budhu RJ, Reamer RA, Huskey SE, Luffer-Atlas D, Dean BJ, McGowan EM, Feeney WP, Chiu SH, Cascieri MA, Chicchi GG, Kurtz MM, Sadowski S, Ber E, Tattersall FD, Rupniak NM, Williams AR, Rycroft W, Hargreaves R, Metzger JM, MacIntyre DE. Phosphorylated morpholine acetal human neurokinin-1 receptor antagonists as water-soluble prodrugs. J Med Chem. 2000;43(6):1234-41. doi: 10.1021/jm990617v, PMID 10737756.
82. Michel MC. Fesoterodine: a novel muscarinic receptor antagonist for the treatment of overactive bladder syndrome. Expert Opin Pharmacother. 2008;9(10):1787-96. doi: 10.1517/14656566.9.10.1787, PMID 18570610.
83. Stella VJ, Zygmunt JJ, Georg IG, Safadi MS. Inventors; University of Kansas., assignee. Water soluble prodrugs of hindered alcohols. United States patent US. PMID 6872838; 2005 Mar 29.
84. Kumpulainen H, Jarvinen T, Mannila A, Leppanen J, Nevalainen T, Mantyla A, Vepsalainen J, Rautio J. Synthesis, *in vitro* and *in vivo* characterization of novel ethyl dioxy phosphate prodrug of propofol. Eur J Pharm Sci. 2008;34(2-3):110-7. doi: 10.1016/j.ejps.2008.02.121, PMID 18403185.
85. Dobesh PP. Pharmacokinetics and pharmacodynamics of prasugrel, a thienopyridine P2Y12 inhibitor. Pharmacotherapy. 2009;29(9):1089-102. doi: 10.1592/phco.29.9.1089, PMID 19698014.
86. VanderMolen KM, McCulloch W, Pearce CJ, Oberlies NH. Romidepsin (Istodax, NSC 630176, FR901228, FK228, depsipeptide): a natural product recently approved for cutaneous T-cell lymphoma. J Antibiot (Tokyo). 2011;64(8):525-31. doi: 10.1038/ja.2011.35, PMID 21587264.
87. Adachi K, Chiba K. FTY720 story. Its discovery and the following accelerated development of sphingosine 1-phosphate receptor agonists as immunomodulators based on reverse pharmacology. Perspect Medicin Chem. 2007;1:11-23. doi: 10.1177/1177391X0700100002, PMID 19812733.
88. Stangier J, Rathgen K, Stahle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. Br J Clin Pharmacol. 2007;64(3):292-303. doi: 10.1111/j.1365-2125.2007.02899.x, PMID 17506785.
89. Ishikawa T, Matsunaga N, Tawada H, Kuroda N, Nakayama Y, Ishibashi Y, Tomimoto M, Ikeda Y, Tagawa Y, Iizawa Y, Okonogi K, Hashiguchi S, Miyake A. TAK-599, a novel N-phosphono type prodrug of anti-MRSA cephalosporin T-91825: synthesis, physicochemical and pharmacological properties. Bioorg Med Chem. 2003;11(11):2427-37. doi: 10.1016/s0968-0896(03)00126-3, PMID 12735989.
90. Kurtz TW, Kajiya T. Differential pharmacology and benefit/risk of azilsartan compared to other sartans. Vasc Health Risk Manag. 2012;8:133-43. doi: 10.2147/VHRM.S22595, PMID 22399858.
91. Cundy KC, Branch R, Chernov Rogan T, Dias T, Estrada T, Hold K, Koller K, Liu X, Mann A, Panuwat M, Raillard SP, Upadhyay S, Wu QQ, Xiang JN, Yan H, Zerangue N, Zhou CX, Barrett RW, Gallop MA. XP13512 [(+/-)-1-([(alpha-isobutanoyloxyethoxy)carbonyl] aminomethyl)-1-cyclohexane acetic acid], a novel gabapentin prodrug: I. Design, synthesis, enzymatic conversion to gabapentin, and transport by intestinal solute transporters. J Pharmacol Exp Ther. 2004;311(1):315-23. doi: 10.1124/jpet.104.067934, PMID 15146028.
92. Stappaerts J, Geboers S, Snoeys J, Brouwers J, Tack J, Annaert P, Augustijns P. Rapid conversion of the ester prodrug abiraterone acetate results in intestinal supersaturation and enhanced absorption of abiraterone: *in vitro*, rat in situ and human *in vivo* studies. Eur J Pharm Biopharm. 2015;90:1-7. doi: 10.1016/j.ejpb.2015.01.001, PMID 25592324.
93. Fukano Y, Kawazu K. Disposition and metabolism of a novel prostanoid antiglaucoma medication, tafluprost, following ocular administration to rats. Drug Metab Dispos. 2009;37(8):1622-34. doi: 10.1124/dmd.108.024885, PMID 19477946.
94. Hoy SM. Tafluprost/timolol: a review in open-angle glaucoma or ocular hypertension. Drugs. 2015;75(15):1807-13. doi: 10.1007/s40265-015-0476-9, PMID 26431840.
95. Linker RA, Haghikia A. Dimethyl fumarate in multiple sclerosis: latest developments, evidence and place in therapy. Ther Adv Chronic Dis. 2016;7(4):198-207. doi: 10.1177/2040622316653307, PMID 27433310.
96. Benes J, Parada A, Figueiredo AA, Alves PC, Freitas AP, Learmonth DA, Cunha RA, Garrett J, Soares-da-Silva P. Anticonvulsant and sodium channel-blocking properties of novel 10, 11-dihydro-5 H-dibenz [b, f] azepine-5-carboxamide derivatives. J Med Chem. 1999;42(14):2582-7. doi: 10.1021/jm980627g, PMID 10411478.
97. Ben-Menachem E. Eslicarbazepine acetate: a well-kept secret? Epilepsy Curr. 2010;10(1):7-8. doi: 10.1111/j.1535-7511.2009.01337.x, PMID 20126330.
98. Sofia MJ, Bao D, Chang W, Du J, Nagarathnam D, Rachakonda S, Reddy PG, Ross BS, Wang P, Zhang HR, Bansal S, Espiritu C, Keilman M, Lam AM, Steuer HM, Niu C, Otto MJ, Furman PA. Discovery of a β-d-2′-deoxy-2′-α-fluoro-2′-β-C-methyluridine nucleotide prodrug (PSI-7977) for the treatment of hepatitis C virus. J Med Chem. 2010;53(19):7202-18. doi: 10.1021/jm100863x, PMID 20845908.
99. Goldstein DSdihydroxyphenylserine (L-DOPS): a norepinephrine prodrug. Cardiovasc Drug Rev. 2006;24(3-4):189-203. doi: 10.1111/j.1527-3466.2006.00189.x, PMID 17214596.
100. Vera Cabrera L, Gonzalez E, Rendon A, Ocampo Candiani J, Welsh O, Velazquez Moreno VM, Choi SH, Molina Torres C. *In vitro* activities of DA-7157 and DA-7218 against Mycobacterium tuberculosis and Nocardia brasiliensis. Antimicrob Agents Chemother. 2006;50(9):3170-2. doi: 10.1128/AAC.00571-06, PMID 16940121.
101. Ohwada J, Tsukazaki M, Hayase T, Oikawa N, Isshiki Y, Fukuda H, Mizuguchi E, Sakaitani M, Shiratori Y, Yamazaki T, Ichihara S, Umeda I, Shimma N. Design, synthesis and antifungal activity of a novel water soluble prodrug of antifungal triazole. Bioorg Med Chem Lett. 2003;13(2):191-6. doi: 10.1016/s0960-894x(02)00892-2, PMID 12482421.
102. Ksander GM, Ghai RD, deJesus R, Diefenbacher CG, Yuan A, Berry C, Sakane Y, Trapani A. Dicarboxylic acid dipeptide neutral endopeptidase inhibitors. J Med Chem 1995;38(10):1689-700. doi: 10.1021/jm00010a014, PMID 7752193.
103. Von Borstel RW, Bamat MK. Inventors; Pro-Neuron. inc, assignee. Acylated uridine and cytidine and uses thereof. Patent WO 89/03837; 1989 May 5.
104. Raedler LA. Aripiprazole lauroxil (Aristada): long-acting atypical antipsychotic injection approved for the treatment of patients with schizophrenia. American Health Drug Benefits. 2016;9(Spec Feature):40-3. PMID 27668044.
105. Ballatore C, McGuigan C, De Clercq E, Balzarini J. Synthesis and evaluation of novel aAmidate prodrugs of PMEA and PMPA. Bioorganic Med Chem Lett. 2001;11(8):1053-6. doi: 10.1016/s0960-894x(01)00128-7, PMID 11327587.
106. Eisenberg EJ, He GX, Lee WA. Metabolism of GS-7340, a novel phenyl monophosphoramidate intracellular prodrug of PMPA, in blood. Nucleosides Nucleotides Nucleic Acids. 2001;20(4-7):1091-8. doi: 10.1081/NCN-100002496, PMID 11562963.

107. Elliott EL, Ferdous AJ, Kaufman MJ, Komar SA, Mazaik DL, McCubbin QJ. Inventors. Boronate ester compounds and pharmaceutical compositions thereof. United States patent US; 2009 Dec 31. p. 12. PMID 485344.
108. Nakamura A, Yamada T, Asaki T. Synthesis and evaluation of N-acylsulfonamide and N-acylsulfonylurea prodrugs of a prostacyclin receptor agonist. Bioorganic Med Chem. 2007;15(24):7720-5. doi: 10.1016/j.bmc.2007.08.052, PMID 17881233.
109. Asaki T, Kuwano K, Morrison K, Gatfield J, Hamamoto T, Clozel M. Selexipag: an oral and selective IP prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. J Med Chem. 2015;58(18):7128-37. doi: 10.1021/acs.jmedchem.5b00698, PMID 26291199.
110. Mollmann H, Hochhaus G, Rohatagi S, Barth J, Derendorf H. Pharmacokinetic/pharmacodynamic evaluation of deflazacort in comparison to methylprednisolone and prednisolone. Pharm Res. 1995;12(7):1096-100. doi: 10.1023/a:1016287104656, PMID 7494809.
111. Liu Q, Yang Q, Sun W, Vogel P, Heydorn W, Yu XQ, Hu Z, Yu W, Jonas B, Pineda R, Calderon-Gay V, Germann M, O'Neill E, Brommage R, Cullinan E, Platt K, Wilson A, Powell D, Sands A, Zambrowicz B, Shi ZC. Discovery and characterization of novel tryptophan hydroxylase inhibitors that selectively inhibit serotonin synthesis in the gastrointestinal tract. J Pharmacol Exp Ther. 2008;325(1):47-55. doi: 10.1124/jpet.107.132670, PMID 18192499.
112. O''Brien CF, Jimenez R, Hauser RA, Factor SA, Burke J, Mandri D, Castro-Gayol JC. NBI98854, a selective monoamine transport inhibitor for the treatment of tardive dyskinesia: a randomized, double-blind, placebo-controlled study. Movement Disorders. 2015;30(12):1681-7. doi: 10.1002/mds.26330, PMID 26346941.
113. Hall BS, Wilkinson SR. Activation of benznidazole by trypanosomal type I nitroreductases results in glyoxal formation. Antimicrobial Agents Chemotherapy. 2012;56(1):115-23. doi: 10.1128/AAC.05135-11, PMID 22037852.
114. Garcia GA, Ngai P, Mosaed S, Lin KY. Critical evaluation of latanoprostene bunod in the treatment of glaucoma. Clinical Ophthalmology (Auckland, NZ) Clin Ophthalmol. 2016;10:2035-50. doi: 10.2147/OPTH.S103985, PMID 27799730.
115. Gillis JC, Wiseman LR. Secnidazole. A review of its antimicrobial activity, pharmacokinetic properties and therapeutic use in the management of protozoal infections and bacterial vaginosis. Drugs. 1996;51(4):621-38. doi: 10.2165/00003495-199651040-00007, PMID 8706597.
116. Sun X, Vilar S, Tatonetti NP. High-throughput methods for combinatorial drug discovery. Sci Transl Med. 2013;5(205);5:205rv1. doi: 10.1126/scitranslmed.3006667, PMID 24089409.
117. de Albuquerque Silva AT, Chung MC, Castro LF, Carvalho Guido RV, Ferreira EISilva AT, Chung MC, Castro LF, Güido RV, Ferreira EI. Advances in prodrug design. Mini Rev Med Chem. 2005;5(10):893-914. doi: 10.2174/138955705774329528, PMID 16250833.
118. Stella VJ, Nti-Addae KW. Prodrug strategies to overcome poor water solubility. Advanced Drug Delivery Rev. 2007;59(7):677-94. doi: 10.1016/j.addr.2007.05.013, PMID 17628203.
119. Stella VJ. Prodrug approaches to enhancing the oral delivery of poorly permeable drugs. In: Prodrugs. Springer; 2007. p. 37-82.
120. Dahan A, Khamis M, Agbaria R, Karaman R. Targeted prodrugs in oral drug delivery: the modern molecular biopharmaceutical approach. Expert Opinion Drug Delivery. 2012;9(8):1001-13. doi: 10.1517/17425247.2012.697055, PMID 22703376.
121. Dahan A, Markovic M, Aponick A, Zimmermann EM, Ben-Shabat S. The prospects of lipidic prodrugs: an old approach with an emerging future. Future Med Chem. 2019;11(19):2563-71. doi: 10.4155/fmc-2019-0155, PMID 31633401.
122. Markovic M, Ben-Shabat S, Aponick A, Zimmermann EM, Dahan A. Lipids and lipid-processing pathways in drug delivery and therapeutics. Int J Mol Sci. 2020;21(9):3248. doi: 10.3390/ijms21093248, PMID 32375338.
123. Markovic M, Ben-Shabat S, Keinan S, Aponick A, Zimmermann EM, Dahan A. Lipidic prodrug approach for improved oral drug delivery and therapy. Med Res Rev. 2019;39(2):579-607. doi: 10.1002/med.21533, PMID 30320896.
124. Markovic M, Ben-Shabat S, Dahan A. Computational simulations to guide enzyme-mediated prodrug activation. Int J Mol Sci. 2020;21(10):3621. doi: 10.3390/ijms21103621, PMID 32443905.
125. Markovic M, Ben-Shabat S, Keinan S, Aponick A, Zimmermann EM, Dahan A. Molecular modeling-guided design of phospholipid-based prodrugs. Int J Mol Sci. 2019;20(9):2210. doi: 10.3390/ijms20092210, PMID 31060339.
126. Markovic M, Dahan A, Keinan S, Kurnikov I, Aponick A, Zimmermann EM, Ben-Shabat S. Phospholipid-based prodrugs for colon-targeted drug delivery: Experimental study and in-silico simulations. Pharmaceutics. 2019;11(4):186. doi: 10.3390/pharmaceutics11040186, PMID 30995772.
127. McNamara MG, Goyal L, Doherty M, Springfeld C, Cosgrove D, Sjoquist KM, Park JO, Verdaguer H, Braconi C, Ross PJ, Gramont A, Zalcberg JR, Palmer DH, Valle JW, Knox JJ. NUC-1031/cisplatin versus gemcitabine/cisplatin in untreated locally advanced/metastatic biliary tract cancer (NuTide: 121). Future Oncol. 2020;16(16):1069-81. doi: 10.2217/fon-2020-0247, PMID 32374623.
128. Evans K, Duan J, Pritchard T, Jones CD, McDermott L, Gu Z, Toscan CE, El-Zein N, Mayoh C, Erickson SW, Guo Y, Meng F, Jung D, Rathi KS, Roberts KG, Mullighan CG, Shia CS, Pearce T, Teicher BA, Smith MA, Lock RB. OBI-3424, a novel AKR1C3-activated prodrug, exhibits potent efficacy against preclinical models of T-ALL. Clin Cancer Res. 2019;25(14):4493-503. doi: 10.1158/1078-0432.CCR-19-0551, PMID 31015346.
129. Alanazi AS, James E, Mehellou Y. The ProTide prodrug technology: where next?. ACS Med Chem Lett. 2019;10(1):2-5. doi: 10.1021/acsmedchemlett.8b00586, PMID 30655934.
130. Arora M, Bogenberger JM, Abdelrahman A, Leiting JL, Chen X, Egan JB, Kasimsetty A, Lenkiewicz E, Malasi S, Uson PLS, Nagalo BM, Zhou Y, Salomao MA, Kosiorek HE, Braggio E, Barrett MT, Truty MJ, Borad MJ. Evaluation of NUC-1031: A first-in-class ProTide in biliary tract cancer. Cancer Chemotherapy Pharmacol. 2020;85(6):1063-78. doi: 10.1007/s00280-020-04079-z, PMID 32440762.
131. Mullard A. FDA drug approvals. Nat Rev Drug Discovery 2018;18:85-9.
132. Hendaus MA. Remdesivir in the treatment of coronavirus disease 2019 (COVID-19): a simplified summary. J Biomol Struct Dyn. 2021;39(10):3787-92. doi: 10.1080/07391102.2020.1767691. PMID 32396771.