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EDITORIAL



## The prodrug approach in the era of drug design

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### 1. Introduction

Prodrugs are inactive precursors of an active drug designed to be bioconverted (activated) post administration with the main aim of improving the pharmacokinetic properties of the parent drug. Prodrugs have been successful for a longtime. Sulfasalazine, one of the earliest prodrugs, reaches the colon and is metabolized by bacteria into two active metabolites: sulfapyridine and 5-aminosalicylic acid (5-ASA). Sulfasalazine was approved for use in the USA in 1950 and still is considered first-line treatment in autoimmune conditions such as Crohn's disease and ulcerative colitis [1]. It has been demonstrated that the prodrug approach has reached vast success in the past few years. It is estimated that around 10% of all marketed drugs are prodrugs, 20% of small molecular weight drugs approved between 2000 and 2008 were prodrugs, and between 2008 and 2017 the share of prodrugs in the drug market was 12% [2].

Various strategies are employed in the prodrug approach. The most common of which is making a prodrug susceptible to abundant enzymes by functionalization with a group that can be cleaved to produce the active form of the drug. The prodrug approach to drug optimization offers chemical stability such as an inactive oral prodrug can be stable in the gastrointestinal tract and only be bioconverted by CYP450 in the liver, plasma, or GIT mucosal esterase, or other enzymes. Examples of this include phosphate groups which are susceptible to alkaline phosphatase, ester groups which are susceptible to esterases, and carbamates or amidine groups which are susceptible to amidases. Newer strategies include pegylation, which is used to increase cellular uptake, and dimer prodrugs, which are cleaved to two active moieties.

Also, prodrugs can be used as precursors in biological conversion pathways, as is the case with L-dopa, a prodrug of dopamine. L-dopa crosses the blood-brain barrier through L-type amino acid transporter-1 and is metabolized by aromatic amino acid decarboxylase to active dopamine in the CNS. Targeted prodrugs have also been explored in oncology in order to minimize side effects and improve the tolerability of chemotherapy [3].

Prodrugs are also used to increase the duration of action of medicines, acting as chemical sustained release forms. Lisdexamfetamine dimesylate is an inactive prodrug of

amphetamine used mainly in the treatment of attention deficit hyperactivity disorder (ADHD). The prodrug is hydrolyzed by red blood cells to L-lysine and active d-amphetamine. The duration of action of lisdexamfetamine is 12 h [4] compared to that of instant release amphetamine, which is 3–6 h.

In cardiovascular medicine, prodrugs have been successful. Older prodrugs such as angiotensin-converting enzyme inhibitors (ACEi) are considered cornerstones in the management of hypertension. ACE inhibitors are dicarboxyl ester prodrugs converted to their active -rilat form by liver esterase (such as enalapril and enalaprilat). The exceptions for this are lisinopril and captopril which are not prodrugs, and fosinopril, which is a phosphonic acid prodrug hydrolyzed by liver and GIT mucosa esterases. Newer prodrugs, such as dabigatran etexilate and prasugrel (Table 1), are anticoagulants indicated for the treatment and prevention of blood clotting.

Prodrugs of nucleoside analogs are used to improve pharmacokinetic properties such as intestinal permeability and oral absorption [15]. For instance, valacyclovir and valganciclovir are valine ester prodrugs of acyclovir and ganciclovir, respectively, target intestinal oligopeptide transporter aiming to improve the oral absorption of the parent drug.

### 2. Continued need for prodrugs

During the years 2008–2017, a total of 249 new molecular entities were approved, 31 of which were prodrugs. With the exception of 2016, which had no novel drug approvals of prodrugs, and 2012, which had one, each year at least 2 approvals of prodrugs were reported. Table 1 summarizes novel prodrugs granted FDA approval during 2008–2018.

While the majority of the prodrugs mentioned above are hydrolyzed by esterases; romidepsin, sofosbuvir, benznidazole, and secnidazole reach the intracellular environment as inactive entities. Romidepsin is a novel anticancer agent. It is activated by intracellular glutathione by cleavage of a disulfide bond and producing a thiol group. This group then binds to a zinc atom in Zn-dependent histone deacetylase.

Sofosbuvir is a novel and promising antiviral medication indicated for the treatment of hepatitis C and is used heavily in combination therapy. Sofosbuvir is a substrate for cathepsin A and carboxylesterase 1, which metabolize it by removing its

**Table 1.** Chemical structures of prodrugs to gain FDA approval during 2008–2018. Some of the listed prodrugs were cited in reference [2].

Year	Tradename	Prodrug	Active form	Activation mechanism	Prodrug strategy/gain	Indication/use
2008 [5]	Toviaz	Fesoterodine fumarate	5-hydroxymethyl tolterodine	Hydrolysis by nonspecific esterase	<ul style="list-style-type: none"> <li>Avoid variability in CYP2D6 activity.</li> </ul>	Overactive bladder
	Lusedra	Fospropofol disodium	Propofol	Conversion by alkaline phosphatase	<ul style="list-style-type: none"> <li>Increased aqueous solubility for IV injection by phosphorylation</li> </ul>	Anaesthesia
	Emend	Fosaprepitant dimeglumine	Aprepitant	Dephosphorylation by phosphatase	<ul style="list-style-type: none"> <li>Increased aqueous solubility by phosphorylation.</li> </ul>	Prevention of chemotherapy induced nausea and vomiting
2009 [6]	Effient	Prasugrel	R-138727	2 steps: (1) Hydrolysis by esterase. (2) CYP450 metabolism	<ul style="list-style-type: none"> <li>Faster and more efficient conversion of parent molecule compared to Clopidogrel.</li> <li>Increased potency.</li> </ul>	Prevention and reduction of thrombotic and cardiovascular events
	Istodax	Romidepsin	Metabolite with free thiol group	Activation by intracellular glutathione	-	Cutaneous T-cell lymphoma
2010 [7]	Gilenya	Fingolimod	fingolimod-phosphate	Phosphorylation by sphingosine kinase	<ul style="list-style-type: none"> <li>Structure activity relationship based design to optimize activity.</li> </ul>	Multiple sclerosis
	Pradaxa	Dabigatran etexilate	Dabigatran	Hydrolysis by esterase	<ul style="list-style-type: none"> <li>Structure activity relationship based design to optimize activity.</li> </ul>	Thromboembolism
	Teflaro	Ceftaroline fosamil	Ceftaroline	Plasma phosphatase	<ul style="list-style-type: none"> <li>N-phosphono-prodrug to improve aqueous solubility.</li> </ul>	Acute bacterial skin and skin structure infections and community acquired pneumonia
2011 [8]	Edarbi	Azilsartan medoxomil	Azilsartan	Hydrolysis by esterase during absorption	-	Hypertension
	Horizant	Gabapentin enacarbil	Gabapentin	Hydrolysis by esterase	<ul style="list-style-type: none"> <li>Transport by intestinal monocarboxylate transporter type 1 and sodium dependent multivitamin transporter.</li> <li>Hydrolysis in tissues.</li> </ul>	Restless leg syndrome and post-herpetic neuralgia
	Zytiga	Abiraterone acetate	Abiraterone sulfate and N-oxide abiraterone sulfate	2 steps: (1) Hydrolysis by esterase (2) Metabolism CYP3A4 and SULT2A1	-	Hormone refractory prostate cancer
2012 [9]	Zioptan	Tafluprost	Tafluprost acid	Hydrolysis by esterase	<ul style="list-style-type: none"> <li>Good corneal penetration.</li> <li>Better activity</li> <li>Lesser pigmentation</li> </ul>	Glaucoma
2013 [10]	Tecfidera	Dimethyl fumarate	Monomethyl fumarate	Hydrolysis by esterase	-	Multiple sclerosis
	Sovaldi	Sofosbuvir	GS-461203	Intracellular metabolism by: (1) Cathepsin-Acarboxylesterase 1 (2) Histidine triade nucleotide-binding protein 1 (3) Uridine monophosphate-cytidine monophosphate kinase.	<ul style="list-style-type: none"> <li>Phosphoramidate prodrug to bypass first step phosphorylation required by nucleoside analogs.</li> </ul>	Hepatitis C infection
	Aptiom	Eslicarbazepine acetate	Eslicarbazepine	Hydrolysis during first pass metabolism	<ul style="list-style-type: none"> <li>Avoid the formation of epoxide following metabolism.</li> </ul>	Epilepsy

(Continued)

Table 1. (Continued).

Year	Tradename	Prodrug	Active form	Activation mechanism	Prodrug strategy/gain	Indication/use
2014 [11]	Northera	Droxidopa	Norepinephrine	Decarboxylation by L-aromatic-amino-acid decarboxylase	-	Neurogenic orthostatic hypotension and intradialytic hypotension Parkinson's disease (off-label)
	Sivextro	Tedizolid phosphate	Tedizolid	Dephosphorylation by plasma phosphatase	Structure activity relationship design. <ul style="list-style-type: none"> <li>• Increased monoamine oxidase inhibitory profile.</li> <li>• Improved aqueous solubility.</li> <li>• Improved bioavailability</li> </ul>	Acute bacterial skin and skin infections
2015 [12]	Aristada	Aripiprazole lauroxil	Aripiprazole	2 steps: (1) Hydrolysis by esterase (2) Non-enzymatic hydrolysis	<ul style="list-style-type: none"> <li>• Increase lipid solubility</li> <li>• Prolonged action for IM injection.</li> </ul>	Schizophrenia
	Xuriden	Uridine triacetate	Uridine	Deacetylation by esterase	<ul style="list-style-type: none"> <li>• Catabolism resistance</li> <li>• Enhanced absorption</li> </ul>	Hereditary orotic aciduria
	Entresto	Sacubitril	LBQ657	De-ethylation by liver carboxylesterase 1	-	Heart failure
	Ninlaro	Ixazomib citrate	Active boronic form	Rapid hydrolysis post administration	<ul style="list-style-type: none"> <li>• Improved affinity</li> </ul>	Multiple myeloma
	Cresemba	Isavuconazonium sulfate	Isavuconazole	2 steps: (1) Hydrolysis by esterase (2) Intramolecular cyclization leading to N-dealkylation	<ul style="list-style-type: none"> <li>• Improved aqueous solubility</li> </ul>	Invasive aspergillosis and invasive mucormycosis
	Genvoya Odefsey Descovy	Tenofovir alafenamide	Tenofovir	Hydrolysis by lysosomal protective protein or liver carboxylesterase 1	<ul style="list-style-type: none"> <li>• Phosphoramidate prodrug.</li> <li>• Increased lipophilicity</li> </ul>	HIV
	Uptravi	Selexipag	ACT-333679 (MRE-269)	Hydrolysis by carboxylesterase	<ul style="list-style-type: none"> <li>• Improved bioavailability</li> </ul>	Pulmonary arterial hypertension
2016 [13]	Emflaza	Deflazacort	21-desacetyldeflazacort	Hydrolysis by esterase	-	Duchenne muscular dystrophy
	Xermelo	Telotristat ethyl	Lp-778902	Hydrolysis by carboxylesterase	<ul style="list-style-type: none"> <li>• Improved bioavailability</li> </ul>	Carcinoid syndrome diarrhoea
2017 [14]	Austedo	Deutetrabenazine	Mainly $\alpha$ -dihydrotrabenazine and $\beta$ -dihydrotrabenazine	CYP450 metabolism	<ul style="list-style-type: none"> <li>• Deuterated to retard hepatic metabolism</li> </ul>	Tardive dyskinesia
	Ingrezza	Valbenazine tosylate	Mainly $\alpha$ -dihydrotrabenazine	CYP450 metabolism	<ul style="list-style-type: none"> <li>• Improved pharmacokinetics</li> </ul>	Tardive dyskinesia
	Benznidazole	Benznidazole	Various electrophilic metabolites	Reduction by <i>Trypanosoma cruzi</i> nitroreductase	-	Chagas disease
	Solosec	Secnidazole	(Active metabolite)	Reduction by bacterial nitroreductase	-	Bacterial vaginosis
	Vyzulta	Latanoprostene bunod	Latanoprost acid Butanediol mononitrate	Hydrolysis by corneal esterase	<ul style="list-style-type: none"> <li>• Good corneal penetration</li> <li>• Delivery of NO releasing species</li> </ul>	Glaucoma
2018	Xofluza	Baloxavir marboxil	S-033447	Hydrolysis by esterase	-	Influenza A and B
	Krintafel Akynzeo	Tafenoquine Fosnetupitant	5,6 ortho-quinone tafenoquine netupitant	Bioconversion by CYP2D6 Dephosphorylation by plasma phosphatase	<ul style="list-style-type: none"> <li>• Phosphorylation for IV injection</li> </ul>	Malaria Chemotherapy induced nausea and vomiting

terminal ester and phenyl. Finally, phosphorylation by uridine monophosphate-cytidine monophosphate kinase leads to the active GS-461203. While the structures of these drugs do not

resemble those of drugs susceptible to tissue and plasma esterases their affinity to intracellular enzymes made them prime prodrugs exhibiting targeted pharmacological action.

Interestingly, latanoprostene bunod (1 in Figure 1) delivers two active agents in a 1:1 ratio. Upon hydrolysis, the prodrug releases latanoprost acid, a prostaglandin F<sub>2</sub>-alpha analog, and butanediol mononitrate which undergoes further metabolism to NO leading to vascular relaxation. Hence, this prodrug acts via a dual mechanism which leads to lowering of the intraocular pressure.

Although the prodrug approach is advancing and reaching successes in providing effective medications to a variety of diseases it still needs the utilization of the sophisticated computational methods used for the design of drugs. Kinetics and thermodynamics for biological systems (active sites of receptors and enzymes, and etc.) that have biomedical interests have been intensively researched and have been proved to be fruitful. Today, quantum mechanics, such as ab initio, semi-empirical, and density functional theory (DFT), and molecular mechanics (MM) including docking are increasingly being utilized to characterize active sites of receptors and enzymes. These widely used methods have proven as successful tools for providing structure-energy calculations for an accurate prediction of potential drugs [16].

### 3. Expert opinion

The strategies and aims of prodrugs to be approved in the past decade are reported in Table 1. Phosphorylation to improve aqueous solubility was successfully used in the design of fospropofol, fosaprepitant, and fosnetupitant allowing for injections. On the other hand, gabapentin enacarbil was designed to increase the bioavailability of gabapentin by targeting intestinal transporters monocarboxylate transporter type 1 and sodium-dependent multivitamin transporter.

Prodrugs can also be designed to overcome metabolic drawbacks. Tolterodine and fesoterodine are both indicated for overactive bladder disease and both metabolized to 5-hydroxymethyl tolterodine. The bioactivation of tolterodine is highly dependent on CYP2D6 activity which resulted in

interpatient variability. Fesoterodine, on the other hand, is rapidly and completely hydrolyzed by non-specific esterases. Also, eslicarbazepine acetate solved the problem of its predecessors: carbamazepine and oxcarbazepine which produced toxic metabolites such as epoxides.

Taking a leaf from the book of sofosbuvir, the design of prodrugs with the aim of intracellular bioconversion rather than the classical approach to amidase, esterase, or CYP450 activation would be beneficial in the treatment of conditions such as viral infections, cancers, and in the revolution of future antibiotics.

As per November 2018, three prodrugs have been approved; tafenoquine, and fosnetupitant. Baloxavir marboxil (2 in Figure 1) is a novel agent with a novel mechanism of action. It is indicated for the treatment of influenza A and B and given as a single dose during the first 48 h hours of influenza symptoms. It inhibits viral shedding through the inhibition of viral CAP endonuclease. Tafenoquine (3 in Figure 1) is an 8-aminoquinoline analog of primaquine indicated for the treatment of malaria. Fosnetupitant (4 in Figure 1) is the prodrug form of netupitant and one of the active ingredients in Akynzeo, a drug approved for the treatment of acute and delayed nausea due to chemotherapy. It is dephosphorylated by plasma phosphatase to produce the active form.

While current trends point toward an age of biological treatments such as antibodies, prodrugs still prove viable products. I believe that the prodrug approach has a strong potential to grow rapidly in such a way that it will provide more than 25% of the marketed therapeutics during the coming decade if the researchers in the field utilize the computational methods used in the drug design and discovery. Computational methods based on quantum mechanics and MM could be used for the design of prodrugs. Prodrugs targeting transporters could be designed with the assistance of computational methods such as docking and etc. In a similar way, prodrugs targeting esterases, amidases and,

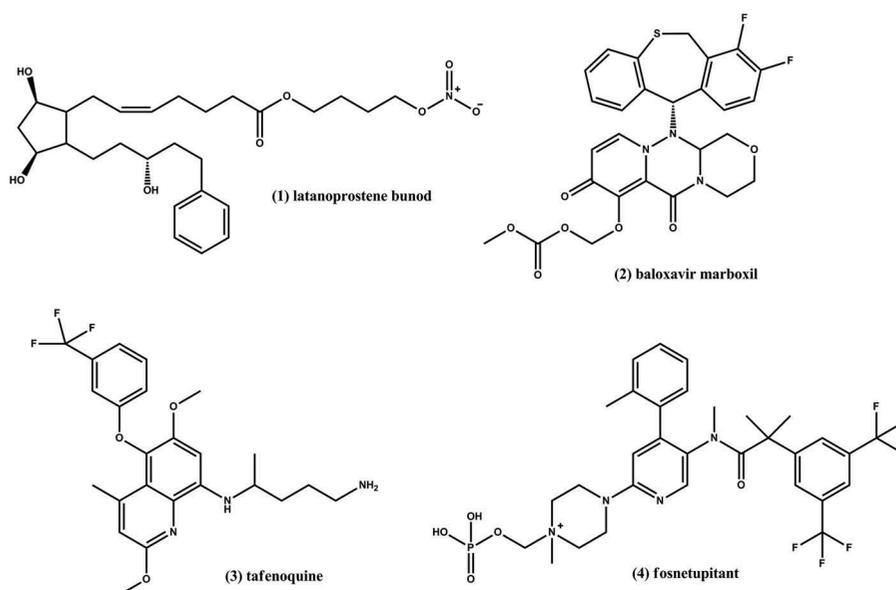


Figure 1. Chemical structures of latanoprostene bunod (1), baloxavir marboxil (2), tafenoquine (3), and fosnetupitant (4).

etc., can be more effective if their design is relied on DFT and ab-initio methods that they have a great ability to predict kinetics of chemical systems. In our group we have used DFT methods for unraveling mechanisms of intramolecular processes that were previously studied in the labs of others to comprehend enzyme catalysis. Our goal was to establish a correlation between experimental and calculated kinetic values and to use the resulting correlation's equation for the design of a number of novel prodrugs [17].

For example, DFT and MM methods we have researched the mechanisms for the intramolecular proton transfer in Kirby's acetals and Bruice's cyclization of dicarboxylic semiesters which led to the design and synthesis of the following novel prodrugs: azanucleosides prodrugs for the treatment for myelodysplastic syndromes, tranexamic acid prodrugs for the treatment of hemorrhage conditions, dopamine prodrugs for Parkinson's disease, atovaquone prodrugs as antimalarial agents, bitterless paracetamol prodrugs as antipyretic and pain killer for pediatrics and geriatrics, and prodrugs of the decongestant phenylephrine. In the above-mentioned examples, the prodrug linker was bound to the amine or hydroxyl group in the parent drug in such a way that the drug-linker entity (prodrug) intraconverts upon an exposure to the physiological environment such as stomach, intestine, and/or blood circulation, with intramolecular reaction rates that are only determined on the chemical structural features of the pharmacologically inactive moiety (linker) [18].

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