

RECENTLY DEVELOPED PRODRUGS AND THEIR INSIGHTS

Abstract

The most popular and successful method for addressing the pharmacokinetic and pharmacodynamic limitations of active medications is the design and manufacture of prodrugs. Throughout history, a substantial number of prodrugs have entered the market for pharmaceuticals, and in recent years, their use as a substitute for parent medications for the effective treatment of a variety of illnesses has increased significantly. Methods: Prodrugs that have recently been approved or that are currently being developed were searched for. Results: According to their target systems, a few prodrugs were reported on and categorized. Conclusions: The prodrug technique has demonstrated numerous achievements and continues to be a practical and efficient method of delivering novel active drugs. The most recent approved prescription medications and the analysis of clinical are clearly stated in this chapter.

Keywords: Prodrug, Clinical Trial, Baloxavir Marboxil; Evofosfamide; Fostemsavir; Ixazomib; Pretomanid; Selexipag.

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I. INTRODUCTION

Prodrugs are chemical substances that are biologically inactive but become active after administration to become drugs. Prodrugs are frequently designed to get past pharmacodynamic obstacles including toxicity, side effects, and poor efficacy as well as pharmacokinetic obstacles like low solubility and absorption, extensive first-pass metabolism, or quick excretion. Prodrugs are often activated either through chemical (inter- or intra-molecular) reactions like hydrolysis and oxidation or enzymatic processes like those carried out by cytochrome enzymes, esterases, and amidases. Numerous prodrugs have had clinical success treating a variety of acute and chronic diseases [1]. The prodrugs developed for the management of hypertension, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), are among the successful examples. Others include clopidogrel and prasugrel, which are used to prevent platelet aggregation in conditions like clotting disorders and cardiac events. Sulfasalazine is a frequently used prescription medication for the treatment of Crohn's disease and ulcerative colitis. The most popular and successful method for addressing the pharmacokinetic and pharmacodynamic limitations of active medications is the design and production of prodrugs. Throughout history, a substantial number of prodrugs have entered the market for pharmaceuticals, and in recent years, their use as a substitute for parent medications for the effective treatment of a variety of illnesses has increased significantly. The prodrug strategy has had several successes and is still a workable and efficient way to introduce novel active drugs. The analysis of clinical trials completed between 2013 and 2018 and the most recent licensed pharmaceuticals both lend weight to this conclusion. The development of novel prodrugs is currently ongoing, even if the synthesis of biological remedies like monoclonal antibodies is seen as a promising method to create new medications. Prodrugs made up 31 out of 249 new molecular entities that the FDA approved between 2008 and 2017 (12.4% of all new molecular entities). However, one can question whether recent clinical studies accurately reflect the future of prodrugs as novel therapies, components of combination therapy regimens, or therapies for novel purposes outside of those already covered by their approved indications. In the present chapter newly designed prodrugs and their benefits are discussed

II. CARDIOVASCULAR SYSTEM

1. Simvastatin: One of the oldest and best-known prodrugs on the market is simvastatin. Its 6-membered lactone ring is hydrolyzed *in vivo* to produce the beta, delta-dihydroxy acid, and an active metabolite with structural similarities to HMG-CoA (hydroxymethylglutaryl CoA), which is how it works. Simvastatin's hydrolysis metabolite competes with HMG-CoA for HMG-CoA reductase, an enzyme that catalyzes the conversion of HMG-CoA to mevalonate, a rate-limiting process in cholesterol production. Nevertheless, from 2013 to 2018, numerous clinical trials examined the effects of statins alone or in combination. The majority of the studies examined simvastatin's interactions with illnesses or conditions to see whether it was safe and whether it was better than other statins in specific situations. However, several trials haven't yet released their findings because they only employed simvastatin in their research. These include NCT03131726, which examined the effectiveness of simvastatin in the treatment of Graves' ophthalmopathy, and NCT03387670, which is a phase 3 trial of simvastatin in multiple sclerosis known as MS-STAT2. NCT03011931 evaluated simvastatin metabolism as a diagnostic for celiac disease activity. The latter was carried

out in response to MS-STAT1 findings indicating patients using simvastatin saw less neuronal death than those taking a placebo [1].

The severe disability in MS patients is caused by the secondary progressive MS stage (SPMS). There are currently relatively few medications that can effectively treat SPMS patients or stop the progression of their disabilities. Simvastatin, a prodrug currently used to treat vascular illness and high cholesterol levels, may be employed as an effective therapy for the treatment of SPMS, according to the results of the MS-STAT2 trial. This is because the prodrug may have immunomodulatory and neuroprotective effects. Thienopyridines, particularly clopidogrel and prasugrel, have been shown to be excellent platelet aggregation inhibitors and are still among the first choices in the treatment of clotting problems increased in cardiovascular event therapy. This family of medications primarily inhibits platelets by inhibiting their P2Y₁₂ receptors. Additionally, research revealed that clopidogrel suppresses platelet aggregation caused by collagen and thrombin (for clopidogrel's activation pathway and mode of action).

Most recent clopidogrel and prasugrel clinical trials aimed to determine the optimal dosages, treatment plans, and interactions with other common chronic illnesses like diabetes. However, no fresh signs were being looked into. Therefore, it is anticipated that these most recent clinical trials will contribute to the creation of future guidelines for ailments like acute coronary syndrome, angina, heart failure, atrial fibrillation, and others. It is important to note that the studies with clopidogrel and prasugrel prodrugs when administered with other medications meant to treat different illnesses should be carefully considered. These medications have the potential to prevent the prodrugs from being activated, which would halt the patient's recovery.

- 2. ACT-281959:** ACT-24647 is a new, powerful P2Y₁₂ receptor inhibitor that is being developed for subcutaneous injection for early intervention, in contrast to thienopyridines like clopidogrel and prasugrel. The oral prodrug of ACT-24647, ACT-281959, is activated by hydrolyzing the two ester chains attached to its phosphonic acid. One clinical trial with the NCT01954615 number was carried out to Analyse the ACT-281959's pharmacokinetics, pharmacodynamics, tolerability, and safety. The trial showed that the prodrug produced dose-dependent quantities of the active form and was well tolerated. There were no incidences of bleeding or dyspnea reported, and headaches were the only prevalent side effect. In patients with coronary artery disease, the prodrug merits additional research [2].
- 3. Valsartan with Sacubitril:** The neprilysin inhibitor sacubitril is a prodrug of LBQ657, which was authorized in 2015. An endopeptidase called neprilysin cleaves the c-type, atrial, and brain natriuretic peptides, which ordinarily cause diuresis, natriuresis, and vasodilation. The administration of sacubitril in conjunction with valsartan results in the buildup of natriuretic peptides and the suppression of angiotensin II, which causes vasodilation and a reduction in vascular resistance. In the medicine Entresto, sacubitril is typically combined with valsartan. The effectiveness and safety of the aforementioned prodrugs are the subject of current research. The utilization of the combination in the presence of comorbidities like thyroid cancer, breast cancer, and diabetes is the subject of more recent studies. The precise mechanism of action of this combination is the subject of a postmarketing study. Clinical trials including this combination, whether there are

comorbidities present or not, should examine the fact that nearly all cardiovascular disorders are caused by a variety of contributing factors.

- 4. Selexipag:** The FDA approved Selexipag in 2015 for the management of pulmonary arterial hypertension. They are prostacyclin receptor agonists that, along with their active metabolite ACT-333679, improve pulmonary circulation vasodilation and hence lessen pulmonary arterial hypertension [3]. For Selexipag, sixteen clinical investigations were reported between 2013 and 2018. Bioavailability, dosage response, interactions with clopidogrel (NCT03496506), and drug-drug interactions with gemfibrozil and rifampicin (NCT02770222) were all examined in healthy volunteers. The use of selexipag in individuals with chronic thromboembolic pulmonary hypertension and children with pulmonary arterial hypertension is the topic of ongoing clinical trials (NCT03492177 and NCT03689244, respectively). Selexipag is acceptable and pharmacokinetically and clinically successful, according to preliminary results of trials that have published the results of their trials.
- 5. Dabigatran Etexilate:** A synthetic, reversible direct inhibitor of thrombin is dabigatran etexilate. The clotting process is interfered with as a result of this inhibition, which causes lower levels of fibrin. The liver and plasma esterases activate dabigatran by hydrolysis to produce its active form. The benefit of employing this prodrug over medications like warfarin is that it does not require ongoing lab testing [4]. There are still just a small number of patients receiving dabigatran, according to recent observations. Dabigatran use in the clinic has decreased as a result of the availability of newer, more powerful medications like oral factor Xa inhibitors.

III. NERVOUS SYSTEM

- 1. ANAVEX 2-73:** A small molecule orphan medication called ANAVEX 2-73, also known as blarcamesine, was created by Anavex Life Sciences Corp. to stimulate sigma-1 receptors in neurons. Through preventing or reducing protein misfolding, cellular stress, mitochondrial malfunction, and oxidative stress, this activation modifies pathways related to neurodegeneration. An aminotetrahydrofuran called ANAVEX 2-73 is activated by the demethylation of its tertiary amine group [5]. Rett syndrome and Alzheimer's disease are the two main conditions that ANAVEX 2-73 is being tested on. ANAVEX2-73-RS-001, also known as NCT03758924, is the only phase 2 trial that has received FDA approval. This medication seems promising, either in terms of its therapy potential or its potential as a lead compound from the few results that are available and are only available on the manufacturing company's website.
- 2. Deutetrabenazine and Valbenazine:** The fast-acting hydrolysis of the L-valine ester of [+]--dihydrotrabenazine (DTBZ) results in the prodrug valbenazine. Valbenazine was made possible by 2017, the FDA authorised the use of NBI-98854 to treat Tardive Dyskinesia. The reversible inhibition of VMAT2 in the treatment of TD is the mechanism of action of valbenazine. VMAT2 is in charge of moving and recycling neurotransmitters across synapse and is specifically found in the central nervous system. Dopamine in particular is depleted from the presynaptic neurotransmitter pool as a result of VMAT2 inhibition, which also accelerates neurotransmitter breakdown. The active metabolite of valbenazine, DTBZ, also inhibits vesicular transporter 2 for monoamines. Similarly,

deutetrabenazine, which is metabolised to a-dihydrotetrabenazine, was also approved in 2017. Due to reduced hepatic metabolism, both prodrugs showed good selectivity for vesicular monoamine transporter 2 and permitted once-daily dosing. Neurotransmitter uptake, particularly dopamine uptake, is lowered as a result of this inhibition. Dopaminergic neurons are less abundant in patients with Parkinson's disease and tardive dyskinesia. As a result of the inhibition, dopamine concentrations at neuron synapses might be increased, which reduces symptoms [6]. Recent clinical trials evaluated the efficacy and safety of both prodrugs in the treatment of various diseases. Tourette syndrome and chorea. Although the results have not yet been made public, the studies' prompt completion seems optimistic.

- 3. Aripiprazole, 3.2.3 Lauroxil:** Aripiprazole lauroxil is a long-acting injectable prodrug that has been approved for the treatment of bipolar disorder and schizophrenia [7]. The prodrug is hydrolyzed after intramuscular injection to produce N-hydroxymethyl-aripiprazole, which then experiences spontaneous cleavage to produce aripiprazole. The agonism of dopaminic and 5-HT_{1A} receptors as well as alpha-adrenergic 5-HT_{2A} receptors is the mechanism of action of the active metabolite. Aripiprazole's binding profile is understood, however it is still unclear how the drug actually works to produce its antipsychotic effects. However, adverse effects including orthostatic hypertension are connected to alpha-adrenergic receptor antagonism. The prodrug's key benefit is that it is an extended release dose form of the active substance. Patients who struggle to take their prescriptions as prescribed benefit from better adherence as a result [8].
- 4. Acetate of Eslicarbazepine:** During first-pass metabolism, the prodrug of eslicarbazepine acetate is hydrolyzed to produce eslicarbazepine. Patients with epilepsy can utilise the metabolite, eslicarbazepine, as an anticonvulsant to treat partial-onset episodes. The metabolite's mode of action is still not fully known. Studies revealed that the medication has minimal adverse effects and rather modest activity. The primary goal of this prodrug is to prevent eslicarbazepine epoxide from forming before it enters the systemic circulation [9]. When using this medication, precautions should be exercised because its administration may result in suicidal events. When using this medication, precautions should be exercised because its administration may result in suicidal events.

IV. ONCOLOGY

- 1. Ixazomib:** In situations of multiple myeloma, the ester prodrug of ixazomib, ixazomib citrate, is utilised. The prodrug is hydrolyzed into its parent drug. The 20S proteasome's beta 5 subunit is reversibly inhibited as part of ixazomib's mechanism of action. The FDA initially authorised ixazomib in 2015 when it was used in conjunction with lenalidomide and dexamethasone. Ixazomib citrate is now marketed by Takeda Pharmaceuticals under the trade name Ninlaro®. 34 NCTs in all investigated ixazomib as a stand-alone treatment or in combination from the beginning of 2013 to the end of 2018. The early NCTs focused mostly on multiple myeloma patients in 2011–2012 and focused on the pharmacokinetics, safety, efficacy, and tolerability of ixazomibin. The effects of ixazomib in multiple sclerosis, lymphoma, sarcoma, and leukaemia are the current focus of more recent NCTs.

The pharmacokinetics and safety of ixazomib were assessed in patients with advanced solid tumours and relapsed/refractory multiple myeloma in a phase 1 study by Takeda Pharmaceuticals (NCT01830816). According to a research released in June 2019, ixazomib was less well tolerated and had more negative side effects in patients with impaired renal function. A combination therapy consisting of ixazomib plus cyclophosphamide and low-dose dexamethasone was assessed in patients who were ineligible for transplant in a randomised phase 2 study, NCT02046070. The study showed that this treatment plan has manageable toxicity and is tolerated. Additionally, toxicity rates were higher in patients getting 400 mg/m² of cyclophosphamide than in patients receiving the combination at 300 mg/m², indicating that the latter dose is more tolerated.

Ixazomib is currently being studied in patients with peripheral T-cell lymphoma (NCT03547700), mantle cell lymphoma (NCT04047797 and NCT03616782), B-cell lymphoma (NCT02898259), HIV (NCT02946047), multiple myeloma (NCT03608501 and NCT03770260), and triple-negative breast cancer (NCT02993094).

- 2. Evofosfamide:** Evofosfamide, commonly known as TH-302, is a brominated isophosphoramidate mustard prodrug that is hypoxia-activated. An effective DNA alkylator, more active one. The effectiveness of TH-302 is also investigated in a number of cancers, including solid tumours, soft tissue sarcomas, and pancreatic and oesophageal cancers. However, a large number of the clinical trials were halted because of insufficient enrollment, ineffectiveness, and inability to achieve endpoints. However, recently released studies continue to demonstrate benefits and tremendous promise in using the prodrug [10, 11]. This discrepancy in the reports may allow for more research into the drug or the use of hypoxia-activated prodrugs.
- 3. Aldoxorubicin:** Anthracyclines in general and doxorubicin in particular continue to be essential components of sarcoma treatment.

Their considerable toxicities, particularly heart toxicity, and dose-dependent adverse effects, however, severely restrict their prospective usage. Because doxorubicin may be conjugated to albumin to create aldoxorubicin, doxorubicin plasma concentrations could be reduced and less side effects could result. When the compound builds up in tumour cells, liposomes break it into doxorubicin and albumin. Stronger tumour inhibition is possible with greater doses thanks to studies that demonstrate fewer adverse effects [12]. Aldoxorubicin's first human trial was published in 2006, but it is not the only medication used to treat sarcomas; rather, it is a component of a treatment regimen. A review of aldoxorubicin clinical trials, however, revealed that many of the studies were not sufficiently well planned because of the extremely broad definition of "sarcoma". It is important to note that earlier preclinical evidence showed that aldoxorubicin was superior to doxorubicin, at least in terms of toxicity. As a result, it is reasonable to expect that aldoxorubicin merits additional, more carefully planned clinical trials to demonstrate its potential as a superior alternative to doxorubicin as long as it is one of the preferred treatment options.

- 4. Topiramate Dimeglumine:** An aprepitant prodrug is called fosaprepitant dimeglumine. Phosphatase converts it from the inactive state to the active state. Increased water solubility of aprepitant as a result of phosphorylation is a technique employed in

prodrug creation to address solubility problems. It is recommended for the management and primary prevention of nausea brought on by chemotherapy. The prodrug is offered in an IV injectable form, which is a huge benefit for individuals experiencing persistent vomiting. Studies revealed that the prodrug's one-day regimen is equivalent to the three-day standard regimen used today, aprepitant [13]. The greater water solubility of the prodrug results in better bioavailability and a more effective clinical profile, making it superior to its parent drug.

5. **Romidepsin:** The prodrug romidepsin is used to treat and manage peripheral T-cell lymphoma (PTCL). Intracellular glutathione triggers its activation, producing a metabolite with a free thiol group. The metabolite is a strong and focused histone deacetylase inhibitor. As a result of this inhibition, histone acetylation is increased, which affects the cell cycle and causes apoptosis. Despite frequently undergoing rigorous first-line chemotherapy, individuals with PTCL suffer from insufficient responses and a dismal prognosis. In patients with refractory or relapsed/PTCL, the prodrug romidepsin is regarded as a single-agent therapy that produces sustained results. When romidepsin and pralatrexate were administered together, studies have revealed a synergistic effect with tolerable hematologic toxicity. These trials and others imply that romidepsin has additional PTCL indications. Other trials suggested that combining romidepsin with other antineoplastic drugs would enhance the effectiveness of the medication
6. **Telotristat Ethyl:** For the treatment of diarrhoea brought on by carcinoid syndrome, telotristat ethyl was given the all-clear in 2017[14]. The prodrug and somatostatin are both used in the treatment. Serotonin levels rise in the carcinoid syndrome, which causes symptoms like diarrhoea. The prodrug is converted to Lp-778902 by carboxylesterase. The active form selectively inhibits tryptophan hydroxylase to lower serotonin levels throughout the gastrointestinal tract.
7. **Triazoxide of Uridine:** Uridine's acylated prodrug is uridine triacetate. Esterases break it down, producing active uridine. For overdoses of capecitabine and fluorouracil, it serves as an antidote. A prodrug of fluorouracil called capecitabine prevents the conversion of deoxyuridylic acid to thymidylic acid [15]. Due to genetic differences in the enzymes that metabolise fluorouracil or a lack in dihydropyrimidine dehydrogenase, this results in rapidly manifesting toxicity. According to reports, the prodrug uridine triacetate delivers 4 to 6 times as much uridine to the systemic circulation as similar equimolar dosages of uridine alone. This suggests that the prodrug is more effective and bioavailable than its parent medication. This could be as a result of the prodrug's delayed hydrolysis to its

V. ANTIVIRALS

1. **Marboxil Baloxavir:** The prodrug baloxavir marboxil hydrolyzes to produce the active metabolite baloxavir. Baloxavir marboxil gained attention after being approved in 2018 as the first novel antiviral treatment for influenza in nearly 20 years. Baloxavir's mode of action involves inhibiting CAP endonuclease [16]. The prodrug reduces viral shedding by inhibiting viral CAP endonuclease and is given within 48 hours of the onset of influenza symptoms. Only five clinical trials involving the medicine were reported between 2013 and 2018, three of which are now complete. These trials compared the drug to a placebo

and oseltamivir to determine its effectiveness and safety. Baloxavir marboxil is now recommended for patients over the age of 12, although one research trial, NCT03653364, was designed to evaluate the infants younger than one year of age: therapy effectiveness and safety. If the trial's findings are encouraging, the medication might be recommended for younger patients, heralding a more promising and constrained global influenza epidemiological future.

2. **Fostemsavir or BMS-663068:** The unique method of action of the phosphonooxymethyl prodrug of temsavir (BMS-626529), also known as fostemsavir or BMS-663068, includes binding to the envelope glycoprotein 120 of HIV. This prevents viral attachment to the host CD4 cell surface receptor. Fosterimsavir appeared to be well tolerated in a phase 2b study of patients with prior treatment experience. Phase 3 research is still underway. In the phase 2b randomised controlled study AI438011, which proved the drug's safety and efficacy, the majority of the patients who participated reported that it was well tolerated [17]. An additional 15 clinical trials were conducted between 2013 and 2018 to evaluate the prodrug's efficacy, pharmacokinetics, interactions, and toxicity. All studies favoured continuing to test the prodrug, and a current phase 3 trial (BRIGHT or NCT02362503), whose results are expected to be published in 2024, is showing promise. If the trial's findings are encouraging, the medication may usher in a new age of HIV-1 treatment, particularly for patients who have received numerous previous treatments and whose virus has become significantly resistant to conventional therapy
3. **Tenofovir Alafenamide:** Acyclic dAMP analogue tenofovir alafenamide (is phosphorylated by the help of AMP kinase to tenofovir diphosphate, which is more active. HIV enzyme reverse transcriptase is inhibited by the prodrug's active form [18]. Currently, people with recompensed liver illness can use tenofovir alafenamide to treat their long term hepatitis B emtricitabine combined with HIV-1 infections. Tenofovir and alafenamide were demonstrated to cause least systemic and more cellular (intra) levels than its prodrug analogue, tenofovir disoproxil, leading to superior efficacy and delivery [19].
4. **Sofosbuvir:** A prodrug called sofosbuvir prescribed to treat certain infections like hepatitis C., cathepsin-acarboxylase 1, and uridine monophosphate cytidine monophosphate kinase and Histidine triad nucleotide-binding protein 1 all participate in its three-step intracellular activation. The drug's active form, GS-461203, is produced through the activation of three step route. Sofosbuvir was recommended as the first-line treatment for hepatitis C by the American Association for the Study of Liver Diseases in 2016 [20]. The use of sofosbuvir in conjunction ledipasvir, or with velpatasvir, ribavirin is now more frequently prescribed. Studies on these combinations showed that the regimen was well tolerated, had fewer adverse effects, and had lower dropout rates. The use of sofosbuvir in conjunction with velpatasvir, ledipasvir, or ribavirin is now more frequently prescribed. Studies on these combinations showed that the regimen was well tolerated, had fewer adverse effects, and had lower dropout rates.

VI. BACTERIAL INFECTIONS, MALARIA, AND TUBERCULOSIS

Isoniazid is first prodrugs to enter the market, has long been the preferred treatment for tuberculosis. Bacterial catalase activates it intracellularly to create an enzyme complex of

oxyferrous, which inhibits the production of bacterial cell wall mycolic acid. Isoniazid targets enoyl reductase in Mycobacterium TB and particularly inhibits it. Isoniazid was only mentioned as a component of a combination therapy that also included Moxifloxacin, Prothionamide, Kanamycin, and Isoniazide in recent clinical trial (NCT03057756). Pretomanid, a fresh anti-tuberculosis medication, has been created to be used in conjunction with bedaquiline and linezolid. In comparison to the therapy described in the preceding paragraph, this combination demonstrated more efficacy in treating resistant tuberculosis and required less time for therapy. Following a number of successful clinical trials that demonstrated good pharmacokinetic qualities in healthy patients and combination therapy, Pretomanid was authorised by the FDA in August 2019 [21]. After being reduced to a desnitro derivative, pretomanid increases nitric oxide levels to exert its bactericidal effect. For individuals with advanced HIV-1 infections, newer promising prodrugs show hope. One such treatment is fostemsavir, which has not yet received approval. Additionally, ANAVEX 2-73 may be the first member of a new family of sigma receptor agonists for the treatment of Alzheimer's disease and Rett syndrome. The potential drug appears to have potential and could result in the creation of an entirely new course of medications.

- 1. Tafenoquine:** A recently licenced prodrug for the treatment of malaria is tafenoquine. CYP2D6 transforms it into the drug's active form, 5,6 ortho-quinone tafenoquine [22]. The metabolite is ingested by the parasite and converted intracellularly to radicals, which causes toxicity and parasite death. The widespread use of this prodrug is constrained by the substantial risk of hemolysis in patients who are born with G6PD deficiency.
- 2. Tedizolid Phosphate:** The prodrug of tedizolid, tedizolid phosphate, is suggested for the treatment of acute bacterial skin infections. Plasma phosphatases transform tedizolid phosphate into tidezolid, the drug's active parent compound. With regard to gram-positive bacteria, particularly methicillin-resistant *S. aureus*, the latter has demonstrated strong in vitro activity [23]. The prodrug is more effective than its parent medication because it dissolves better in water and dephosphorylates slowly into tidezolid, allowing for once-daily dose with less adverse effects.
- 3. Ceftaroline Fosamil:** Similar to this, an older prodrug called ceftaroline fosamil is phosphorylated to increase its solubility in water and is likewise activated by plasma phosphatase to produce ceftaroline. It is recommended for the treatment of community-acquired pneumonia as well as acute bacterial skin and skin structure infections [24]. The prodrug has an advantage over its parent medication due to its enhanced water solubility, which leads to increased bioavailability and more effective therapeutic effects.
- 4. Latanoprostene Bunod:** The prodrug latiprostene bunod contains the two active substances latiprostene acid and butanediol mononitrate, which together produce NO and are delivered in a 1:1 ratio. The following section.

VII. OPTHALMOLOGY

Bunod Latanoprostene: The prodrug latiprostene bunod contains the two active substances latiprostene acid and butanediol mononitrate, which together produce NO and are delivered in a 1:1 ratio. By hydrolyzing the prodrug, corneal esterase produces active drugs. Due to the fact that both active drugs lower intraocular pressure, it is approved for the treatment of

glaucoma [25]. The capacity of latanoprostene buno to produce NO and the prostaglandin F₂-alpha analogue latanoprost acid metabolite, which causes tissue and cell relaxation, gives it a new dual mode of action. Molecules 24 FOR PEER REVIEW IN 2019 By hydrolyzing the 15 prodrug, corneal esterase produces active drugs. Due to the fact that both active drugs lower intraocular pressure, it is approved for the treatment of glaucoma [26].

VIII. SUMMARY

In the years from 2013 to 2018, a significant number of newly licenced prodrugs were made available. Some of the prodrugs belonged to novel classes, such as sacubitril, while others, like baloxavir marboxil, were groundbreaking. Despite their well-established roles in the clinic, older prodrugs like simvastatin, clopidogrel, and prasugrel are still being examined in clinical trials. Their clinical studies focus mostly on regimen optimisation, investigation of other indications, and delivery to patients with various chronic conditions. For patients with advanced HIV-1 infections, newer prospective prodrugs like fostemsavir, which has not yet received approval, show promise. A novel family of sigma receptor agonists for the treatment of Rett syndrome and Alzheimer's disease may include ANAVEX 2-73 as its first member. The experimental drug appears to have promise and may pave the way for the development of an entirely new class of medications. Even though they have a long history of use in clinical settings, older prodrugs like simvastatin, clopidogrel, and prasugrel are still being examined in trials. Their clinical studies are mostly focused on regimen optimisation, the investigation of other indications, and delivery to patients with various chronic conditions. For individuals with advanced HIV-1 infections, newer promising prodrugs show hope. One such treatment is fostemsavir, which has not yet received approval. Additionally, ANAVEX 2-73 may be the first member of a new family of sigma receptor agonists for the treatment of Alzheimer's disease and Rett syndrome. The potential drug appears to have promise and could result in the creation of an entirely new class of medications.

IX. FINAL REMARKS

Poor pharmacokinetic features, such as poor water solubility, low penetration, short period of action, and also the metabolism by first-pass are primarily blamed for the letdown of a significant number of drug molecules both during and afterward the drug improvement process. Hence role of the drug molecules kinetics in the initial phases of the drug design and development process has been relaxed examined by researchers as a result of this. The prodrug strategy, which aims to overcome the physical, chemical, biological, and organoleptic obstacles of some of the presently marketed medications suffering from low bioavailability and patient noncompliance, is one method for enhancing a drug's pharmacokinetics profile.

The scientific community has been inspired to continue employing the prodrug approach, a tried-and-true method for creating new therapeutic entities with better clinical profiles than their parent medications, by the high success rates witnessed in recent years. A drug's ADME (absorption, distribution, metabolism, and elimination) may change if its physicochemical qualities are altered. A thorough knowledge of the parent drug's physicochemical and biological behaviour is necessary for this to be successful. To acquire a thorough understanding of this topic, it is effective to use tissue in vitro-in vivo data, in silico

or computational predictions utilising quantitative structure-activity relationship (QSAR), or molecular modelling.

Additionally, the development of a new class of prodrugs known as "targeted drugs" has been sped up by the use of computational chemistry, molecular biology, and data from enzymes and transporters. As a result, scientists have started using the targeted prodrugs technique instead of their standard methods for synthesising classical prodrugs. This tendency has led to the creation of new drug molecules with superior therapeutic characteristics to those of their parent drugs. In the upcoming years, we think that the targeted prodrug concept made easier, and we anticipate that more than 20% of medicines sold will contain prodrugs. The cornerstone for designing more effective medications is the use of molecular orbital (semi-empirical, *ab initio*, and DFT) and molecular mechanics methods, with or without an x-ray and spectroscopic examination of enzymes and transporters. Without the aid of computational data, the researchers synthesised the majority of the prodrugs discussed in this review using their own chemical or/and biological understanding. However, before engaging in any wet chemistry, a computational design is urgently required to produce more successful and effective prodrugs. In order to comprehend how enzymes catalyse biochemical transformations, we have been researching the mechanisms of various intramolecular events over the past ten years.

The objective was to find a computational technique that produces correlations between estimated kinetic and thermodynamic values and experimental reaction rates, then uses the resulting correlation equations to create novel prodrugs. We investigated the mechanisms of a number of intramolecular events, such as Kirby's acid-catalyzed hydrolysis of N-alkylmaleamic acids and Bruice's cyclization of dicarboxylic semiesters, using DFT and MM approaches and discovered linear relationships between predicted and observed reaction rates. We have created and synthesised several novel prodrugs on the basis of the resulting equations, including prodrugs of dopamine to treat Parkinson's disease, prodrugs of gabapentin to treat convulsions, prodrugs of tranexamic acid to treat bleeding disorders, prodrugs of aza-nucleosides to treat myelodysplastic syndromes, and prodrugs of atovaquone to treat malaria. Additionally, we have utilised this strategy to cover up the harsh taste of regularly used medications like the pain reliever paracetamol. The parent drug's amine or hydroxyl group was linked to a promoiety in the aforementioned prodrugs, causing the prodrug to undergo an intramolecular reaction upon exposure to physiological medium, yielding the parent drug and a non-toxic promoiety at a rate solely based on the chemistry of the inactive promoiety [1]. In light of the aforementioned, an efficient design based on knowledge of the chemistry and biology of enzymes and transporters, along with the application of suitable computational tools, is a critical step for invoking successful prodrugs.

Preclinical testing for linker (promoiety) and prodrug toxicity and cytotoxicity is required. Additionally, the application of the directed enzyme prodrug therapy (DEPT) technique, which makes use of the creation of synthetic enzymes to activate prodrugs at certain places, ought to be expanded. Genes, antibodies, viruses, and clostridial organisms are just a few of the possible targets for DEPT entities. This tactic can greatly enhance the clinical profile of the medicine and the tolerability of the chemotherapeutic regimen. It is important to remember that using albumin as a protein carrier for cancer cells has a lot of promise, as demonstrated by the success of the drug doxorubicin in taking advantage of albumin buildup in solid tumours and their acidic environment. If this approach is successful,

it might be used to deliver a variety of anticancer drugs into tumours. In conclusion, the prodrug technique is still an effective and practical way to create novel active entities. This can be achieved by looking at recently approved prescription medications and the analysis of clinical trials done between 2013 and 2018.

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