PRO-DRUG DEVELOPMENT

Abstract

Pro-drug plays a very essential role in the field of pharmaceutical drug discovery and development, by improving the pharmacokinetic, biopharmaceutical property of the medicinally active agent and produce the desired therapeutic effect at the site of action. The term pro-drug is defined as the derivative of the active drug molecules which are biologically inert and produced the pharmacological effect by in-vivo conversion of the enzymatic and chemical. the main aim of the development of pro-drug in pharmaceutical drug discovery and development to overcome some incompatibility that is effective to produce the desired pharmacological effect that is chemical instability, low solubility, pre systematic toxicity, low target selectivity, etc. in this review we have discussed the concept, classification and some examples of the pro-drug which are used to produce the desired pharmacological effect by binding to the targeted site.

Keywords: Pro-drug, pharmacokinetic, biopharmaceutical.

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I. INTRODUCTION

Prodrugs are chemical substances that are biologically inactive but become active after administration to become drugs. Prodrugs are often developed to address pharmacodynamic challenges including toxicity, side effects, and ineffectiveness as well as pharmacokinetic challenges like limited solubility and absorption, active first-pass metabolism, or quick excretion.

Prodrugs can occasionally be activated through chemical (inter- or intra-molecular) processes including chemical reaction and oxidation or protein processes like those caused by hemoprotein enzymes, esterases, and amidases. Numerous prodrugs have had clinical success treating a variety of acute and chronic diseases [1]. Prodrugs developed for the treatment of cardiovascular illness, such as ACEIs and angiotensin receptor blockers, are two instances of the industry's growing growth (ARBs).

Others include medications like clopidogrel and prasugrel that are used to prevent thrombocyte aggregation in cases of natural process abnormalities and internal organ occurrences. Sulfasalazine may be a frequently used alternative prodrug for the treatment of Crohn's disease and inflammatory bowel disease.

Even though creating biological treatments like organism antibodies is regarded as a promising method to create novel medications, the prodrug technology is still being researched and new prodrugs are continually being generated. Between 2008 and 2017, the authorities certified 249 novel molecular entities; 31 of those, or 12.4% of all new molecular entities, were prodrugs [2].

The long-term potential of prodrugs as standalone treatments, components of multimodal therapy regimens, or treatments for entirely new indications aside from those for which they have already received approval can, however, raise questions about whether recent clinical studies accurately reflect this potential. A list of the top prodrugs undergoing clinical trials from 2013 to 2018 is rumoured to be in this review [2].

II. HISTORY OF PRO-DRUG

The first substance to fit the requirements for a prodrug was acetanilide, which Cahn and Hepp initially used in medical practise in 1867 as an antipyretic drug. Bioactive acetaminophen is produced by hydroxylating acetanilide [3].

Aspirin, commonly known as acetylsalicylic acid, was first used in medicine by Dreser in 1899 after being developed in 1897 by Felix Hoffman in Bayer, Germany [3].

The prodrug concept was intentionally used for the first time by the Parke-Davis company for modification of chloramphenicol structure in order to improve the antibiotic’s bitter taste and poor solubility in water. Chloramphenicol was created in two prodrug forms: chloramphenicol palmitate, which is used as a suspension in children, and chloramphenicol sodium succinate, which has good water solubility [4].

III. CONCEPT OF PRO-DRUG

The main objective of prodrug design is to conceal unfavourable drug properties, such as presystemic metabolism, toxicity, low target selectivity, unfavourable taste, irritation, or pain after local administration, low solubility in water or lipid membranes, chemical instability, and low target selectivity [5, 6, 7]. Prodrugs are frequently used to reduce unwanted toxicity and increase the parent drug's distribution, metabolism, excretion, and absorption [8]. Prodrugs are chemically and/or enzymatically altered drug molecules that are physiologically inert in order to release the parent drug's pharmacological activity in vivo. The term "prodrug" was created in 1958 by Adrien Albert [9]. Whether the prodrug is absorbed prior to, during, or following the active drug's emergence from its inactive form. Some drugs are not made available until they have achieved their goals [4, 5]. A prodrug should increase the bioavailability and therapeutic potency of a parent medication. Despite the fact that the word "prodrug" is now frequently used, prodrugs have also been referred to as reversible or bio reversible derivatives or boilable drug-carrier conjugates. Testa [7] claims that prodrug research has three primary, interrelated objectives:

1. **Pharmaceutical:** to improve the solubility, chemical stability, and organoleptic properties; to diminish localised pain and/or itch; and to reduce problems with the pharmaceutical technology of the active ingredient.

2. **Pharmacokinetic:** to enhance time profile, increase oral and nonoral absorption, minimise presystemic metabolism, and improve organ/tissue-specific distribution of the active ingredient.Create single chemical entities that combine two pharmaceuticals to lessen toxicity and boost therapeutic index (co-drugs strategy).

   It should be highlighted that the most significant advancements in prodrug design over the past ten years have been methods to increase oral bioavailability and achieve brain- and tumor-specific targeting.

3. Pro-drug is classified into two different groups are

Carrier–linked pro-drugs
Bio precursor pro-drug

- **Carrier–linked pro-drugs:** By establishing a covalent bond between the inert carrier and the active ingredient, this boosted the drug's lipophilicity. They are composed of the carrier group and the drug connected to it. and the method—whether enzymatic or not—by which the active drug is administered. Additionally, carrier-linked pro-drugs can be classified as: - Double prodrugs or cascade-latentialed pro-drugs, where the drug can only be released through enzymatic conversion.

  - **Macromolecular pro-drug:** In this case, the drug is delivered to the active site using macromolecules as carriers.
  - **Location-specific pro-drugs:** deliver the medication to the desired active site
  - **Mutual pro-drug:** This type of drug links two pharmacologically active substances together rather than using inert molecules to create the desired pharmacological effect [10].

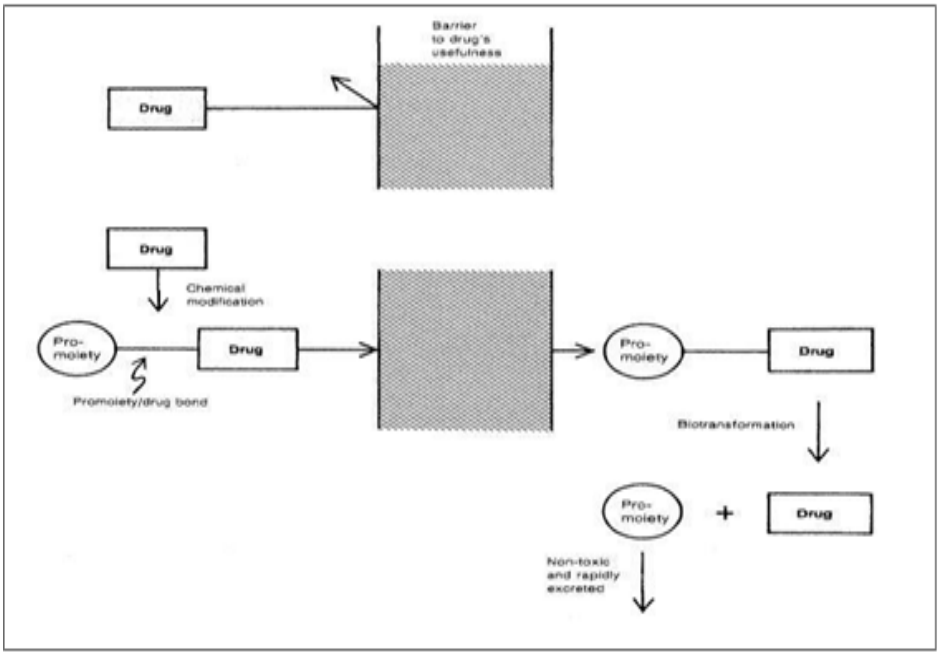
- **Bio precursor pro-drug**: This kind of pro-drug is already active and will transform into an active substance once it has been metabolised and has had an impact on the site of action.

IV. OBJECTIVES OF PRO-DRUG

1. The majority of pharmaceuticals are produced with effective pharmacological action and are used to treat a wide range of serious disorders, but their use is contraindicated owing to their toxicity and other elements that do not adhere to accepted standards. These sorts of drugs work to enhance a drug's physicochemical and pharmacokinetic qualities following pro-drug design, and they are used to treat a number of ailments.

2. By encapsulating the medication in a carrier that the barrier will permit to pass through and enter the pro-drug, you can deliver the medication to the area where it is needed.

3. Improve the kinetics of the medication.



V. SPECIFIC PRODRUGS IN PHARMACOLOGY

1. In cardiovascular system

- **Simvastatin:** One of the oldest and best-known prodrugs on the market is simvastatin (Figure 1). 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). Simvastatin's hydrolysis metabolite competes with HMG-CoA for HMG-CoA reductase, an enzyme that catalyses the conversion of HMG-CoA to mevalonate, a rate-limiting step in cholesterol biosynthesis.

Nevertheless, from 2013 to 2018, numerous clinical trials examined the effects of statins alone or in combination.

The majority of them 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, some trials haven't yet released their findings because they only used 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 [11,12].

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.

- **Clopidogrel and prasugrel:** Thienopyridines in particular, which have been shown to be good platelet aggregation inhibitors, continue to be one of the primary options in the treatment of cardiovascular accidents after they have occurred as well as in the prevention of clotting disorders. This family of medications primarily inhibits platelets by inhibiting their P2Y12 receptors. Most recent clopidogrel and prasugrel clinical trials (Figure 1) focused on determining the optimum 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 trials with clopidogrel and prasugrel pro-drugs 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. Molecules 2019, 3 accomplished by inhibiting platelet P2Y12 receptors. Additionally, investigations revealed that clopidogrel (Figure 1) suppresses platelet aggregation caused by collagen and thrombin (for clopidogrel's activation pathway and mechanism of action) [13].

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- **Selexipag:** The FDA approved Selexipag (Figure 1) in 2015 for the management of pulmonary arterial hypertension. They are prostacyclin receptor agonists that lower pulmonary arterial hypertension and promote pulmonary circulation vasodilation, along with its active metabolite ACT-333679 [14]. Sixteen clinical investigations on selexipag were reported between 2013 and 2018. Tests on bioavailability, dosage response, interactions with clopidogrel, and drug-drug interactions involving gemfibrozil and rifampicin were performed on healthy volunteers (NCT02770222). Currently, selexipag is being used in clinical trials for adults with chronic thromboembolic pulmonary hypertension and children with pulmonary arterial hypertension (NCT03492177 and NCT03689244, respectively). Selexipag is acceptable, pharmacokinetically efficient, and clinically successful, according to preliminary findings of trials the results of which have been published.

- **Dabigatran:** Etexilate A synthetic, reversible direct thrombin inhibitor is dabigatran etexilate (Figure 1). This inhibition disrupts the clotting process, causing fibrin levels to drop. The liver and plasma esterases hydrolyze dabigatran to produce its active form. The fact that this prodrug does not require continuing lab monitoring gives it an edge over medications like warfarin [15]. Recent data indicate that there are still just a small number of patients receiving dabigatran. The usage of dabigatran in clinical settings has decreased since more recent, powerful medications, like oral factor Xa inhibitors, are now more widely available.

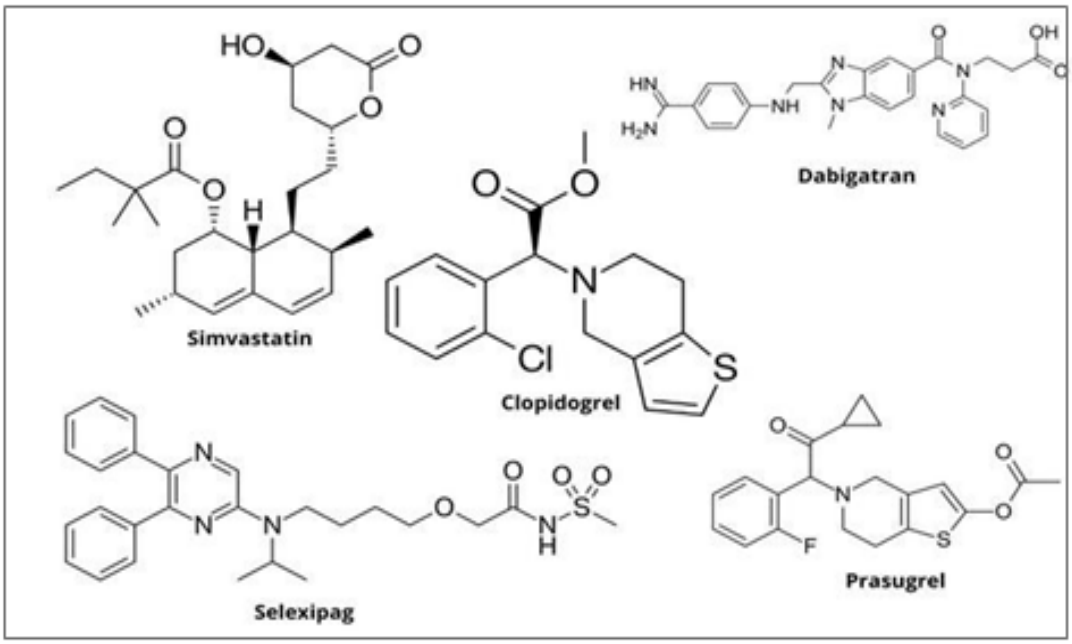

Figure 1: Structure of Different Cardiovascular Pro-Drugs

2. Nervous System

- **Blarcamesine:** ANAVEX Life Sciences Corp. created the orphan drug blarcamesine (ANAVEX 2-73) to stimulate sigma-1 receptors in neurons. Through the prevention or reduction of protein misfolding, cellular stress, mitochondrial dysfunction, and oxidative stress, this activation modifies the pathways underlying neurodegenerative diseases [16]. The demethylation of its tertiary amine group activates an aminotetrahydrofuran known as ANAVEX 2-73 [17].

  Rett syndrome and Alzheimer's disease are the main conditions that ANAVEX 2-73 (Figure 2) is being tested on. The FDA has approved ANAVEX2-73-RS-001, also known as NCT03758924, as the only phase 2 trial. This medicine appears promising in terms of both its medicinal potential and its potential as a lead chemical from which stronger sigma receptor agonists might be inspired, despite the fact that information is restricted and limited to the website of the manufacturing company.

- **Valbenazine and deutetrabenazine:** The L-valine organic component of [+]—dihydrotetrabenazine (DTBZ), known as valbenazine (Figure 2) prodrug, undergoes a rapid chemical reaction to become its active drug, DTBZ. In 2017, the office authorised the use of valbenazine, also known by the trade name NBI-98854, for the treatment of dyskinesia. The reversible suppression of VMAT2 during the therapy of TD is the mechanism of action of valbenazine. VMAT2 is responsible for the utilisation of neurotransmitters at the junction and its preference for the central nervous system. The depletion of presynaptic neurochemicals, particularly Dopastat, is caused by the inhibition of VMAT2, which also speeds up neurochemical breakdown. Sac aminoalkane transporter 2 is actively inhibited by each valbenazine and its active ingredient, DTBZ.

  For dopaminergic neurons, similarly. The inhibition enables larger Dopastat concentrations in the somatic cell synapses, which reduces symptoms [19].

  In a number of recent clinical trials, it was determined whether deutetrabenazine (Figure 2), which was also licenced in 2017 and is also converted to a-di-hydro-tetrabenazine, was safe and effective for treating chorea and Gilles de la Tourette's disease. Each prodrug allowed once-daily dosing due to decreased internal organ metabolism and an undeniably high sac aminoalkane transporter 2 property [18]. This inhibition leads to a reduction in the absorption of dopastat, which is the primary neurotransmitter. Patients with dyskinesia and Parkinson's disease display a milder variation of Tourette syndrome. Results have not yet been made public, but early completion of the trials seems to be a good thing.

- **Aripiprazole lauroxil:** The long-acting injectable prodrug of aripiprazole known as aripirazole lauroxil (Figure 2) has been approved for the treatment of schizophrenia and bipolar disorder [20,21]. The prodrug is hydrolyzed after intramuscular injection to produce N-hydroxymethyl-aripiprazole, which then spontaneously cleaves to produce aripiprazole. The agonism of dopaminic and 5-HT1A receptors, as well as alpha-adrenergic 5-HT2A receptors, is the method of action of the active metabolite [22]. Aripiprazole's binding profile is well studied, however it is still unclear how the

drug actually works to produce its antipsychotic effects. However, alpha-adrenergic receptor antagonists have been associated to side effects such orthostatic hypertension. One of the key benefits of the prodrug is that the active ingredient is in an extended release dose form. Better adherence results as a result for patients who have trouble taking their medications as directed [23].

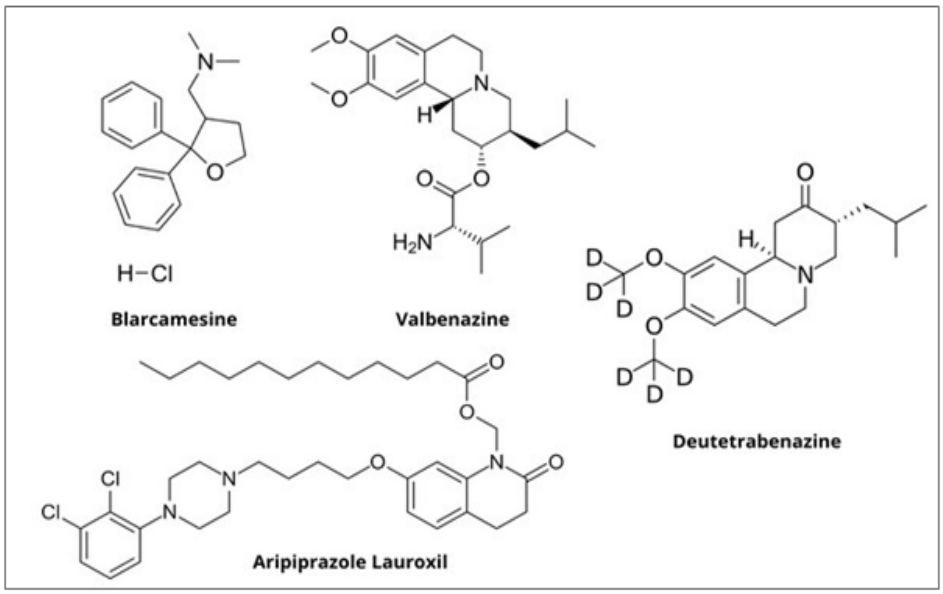

Figure 2: Structure of Different Nervous System Pro-drugs

3. In Antiviral

- **Baloxavir Marboxil:** The active metabolite baloxavir is created by hydrolyzing the prodrug baloxavir marboxil (Figure 3). After being licenced in 2018 as the first brand-new antiviral therapy for influenza in nearly 20 years, baloxavir marboxil attracted attention. Baloxavir works by preventing CAP endonuclease from functioning [27]. The prodrug, which is administered within 48 hours after the onset of influenza symptoms, inhibits viral CAP endonuclease to limit viral shedding. Between 2013 and 2018, only five clinical trials including the prodrug were disclosed, three of which are now finished. In these trials, the prodrug's safety and effectiveness were assessed by contrasting it with a placebo and oseltamivir.

  Although a clinical trial NCT03653364 was established to evaluate the medication's safety and effectiveness in newborns under the age of one, baloxavir marboxil is currently only recommended for adults over the age of 12. If the trial's findings are favourable, the medication may be recommended for younger people, portending a more positive and constrained epidemiological future for influenza globally.

- Fostemsavir: In a unique fashion, the phosphonooxymethyl prodrug of temsavir (BMS-626529), also known as fostemsavir or BMS-663068 (Figure 3), prevents the HIV virus from adhering to the host CD4 cell surface receptor by binding to the HIV envelope glycoprotein 120.

Fosterimsavir appeared to be well tolerated in patients who had already undergone treatment in a phase 2b study. Research on [23] is still in its third phase. The vast majority of patients who participated in the phase 2b randomised controlled study AI438011, which proved the drug's safety and effectiveness, said it was well tolerated [24]. Between 2013 and 2018, 15 more clinical trials were conducted to evaluate the prodrug's effectiveness, pharmacokinetics, interactions, and toxicity. A phase 3 trial that is currently underway (BRIGHTE or NCT02362503) and whose findings are expected to be published in 2024 has encouraging results. The prodrug's continued testing was backed by all studies.

If the trial's findings are encouraging, the medication may usher in a new age of HIV-1 treatment, especially for patients who have undergone numerous treatments in the past and whose virus has become significantly resistant to traditional therapy [25].

4. In Neoplastic

- **Ixazomib:** In cases of multiple myeloma, the ester prodrug of ixazomib, ixazomib citrate (Figure 3), is used. The prodrug, the parent medication, is hydrolyzed. The 20S proteasome's beta 5 subunit is reversibly inhibited as part of ixazomib's method of action. In 2015, the FDA granted ixazomib its initial approval when it was coupled with lenalidomide and dexamethasone. Ixazomib citrate is now offered by Takeda Pharmaceuticals under the trade name Ninlaro. 34 NCTs in total, either alone or in combination, investigated ixazomib from the start of 2013 to the end of 2018. Early NCTs mainly focused on multiple myeloma patients' pharmacokinetics, safety, effectiveness, and tolerance between 2011 and 2012.

  The effects of ixazomib on leukaemia, lymphoma, multiple sclerosis, and sarcoma are presently the focus of more recent NCTs. In a phase 1 research, Takeda Pharmaceuticals evaluated the pharmacokinetics and safety of ixazomib in patients with advanced solid tumours and relapsed/refractory multiple myeloma (NCT01830816). Ixazomib was less well tolerated and had higher adverse effects in patients with reduced renal function, according to research published in June 2019. The efficacy of a combination therapy consisting of ixazomib plus cyclophosphamide and low-dose dexamethasone in patients who were ineligible for transplant was assessed in a randomised phase 2 study [26], NCT02046070.

  This therapeutic approach is well tolerated and has manageable toxicity, according to the study. Additionally, people who received the combination at a dose of 300 mg/m2 displayed lower rates of toxicity than people who received cyclophosphamide at a dose of 400 mg/m2, indicating that the latter dose is more well-tolerated. Currently, ixazomib is being studied in trials for peripheral T-cell lymphoma (NCT03547700), mantle cell lymphoma (NCT04047797 and NCT03616782), B-cell lymphoma (NCT02898259), HIV (NCT02946047), multiple myeloma (NCT03608501 and NCT03770260), as well as triple-negative breast cancer (NCT02993094).

- **Evofosfamide:** The isophosphoramide mustard prodrug evofosfamide, commonly known as TH-302(Figure 3), is activated by hypoxia. the strong DNA alkylator in its active form. To ascertain the effectiveness of TH-302, several cancers, including solid tumours, oesophageal, soft tissue, and pancreatic cancers, are being researched. Many of the trials, however, were abandoned because of low enrollment, ineffectiveness, and failure to achieve objectives. However, recently released trials continue to highlight the benefits and significant promise of the prodrug [21–23]. The discrepancy in the reports may allow for more research into the medication or the hypoxia-activated prodrug method.

- **Romidepsin:** Romidepsin is a prodrug used for the treatment and management of peripheral Tcell lymphoma (Figure 3). (PTCL). Intracellular glutathione triggers its activation, resulting in a metabolite with a free thiol group. The metabolite is a powerful and selective histone deacetylase inhibitor. A spike in histone acetylation is brought on by this inhibition, which changes the cell cycle and causes death. PTCL patients typically receive aggressive first-line chemotherapy, although they have poor prognoses and inadequate responses. In patients with refractory or relapsed/PTCL, the prodrug romidepsin is recognised as a single-agent therapy that produces long-lasting results. Studies have showed that giving romidepsin and pralatrexate at the same time had a synergistic benefit and manageable hematologic side effects. These and subsequent trials suggest that romidepsin may have additional PTCL indications. Other research [27] suggest that romidepsin may be more effective when coupled with additional antineoplastic drugs.

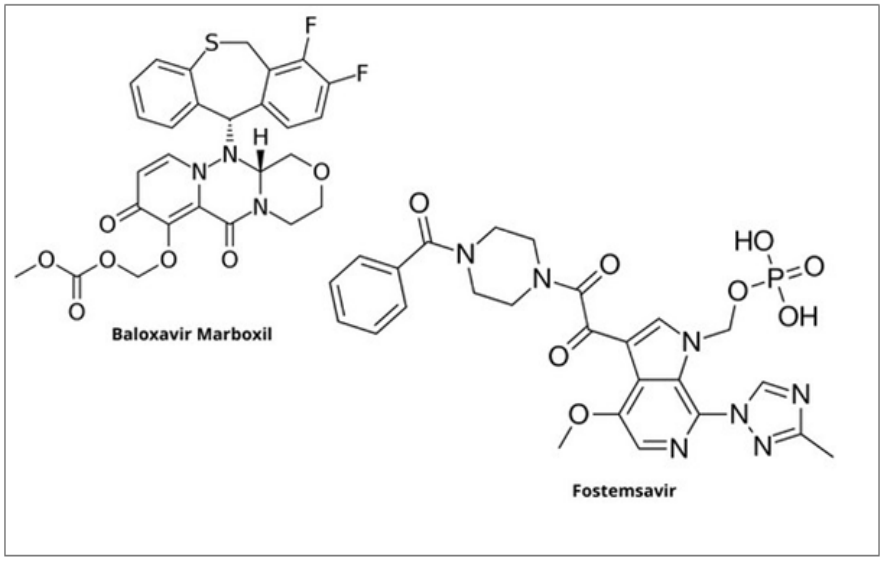

Figure 4: Structure of Different Neoplastic Pro-drugs

VI. APPLICATION OF PRO-DRUG

1. Pro-drugs are used to change a drug's pharmacological effect by enhancing its biological and therapeutic actions.
2. Change the taste—bad taste leads to poor patient compliance. There are two ways to get past bad taste:

- Saliva lessens the drug's ability to dissolve.
- Reduce the drug's attraction to taste receptors.

3. By improving the smell of the medication, patient compliance rose.
4. Change the physicochemical characteristics of the medicine to increase formulation stability.
5. Lessening of GIT irritability: The GIT might get irritated by several drugs. Pro-drugs are used to mitigate the harm the medication causes to the GIT in order to address this issue.
6. The pro-drug makes chemicals more stable.
7. Increasing the drug's lipophilicity, which raised the drug's bioavailability.
8. Halt the metabolism of the precursor.
9. Reduced the dangerous side effects of the potent medication.
10. Delivered the drug to the patient's place of activity.

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