PRO-DRUG DEVELOPMENT

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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.

I.INTRODUCTION

Prodrugs are chemical substances that are biologically inactive but become active after administration to become drugs. Prodrugs are typically created to overcome pharmacokinetic obstacles such as low solubility and absorption, vigorous first-pass metabolism, or rapid excretion, as well as pharmacodynamic obstacles such as toxicity, side effects, and ineffectiveness.

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, esterase's, 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.

The prodrug technique is still being investigated, and new prodrugs are still being produced, even if the construction of biological remedies like organism antibodies is considered to be a promising strategy to build new medicines. 31 out of 249 new molecular entities certified by the authorities between 2008 and 2017—or 12.4% of all new molecular entities—were prodrugs [2].

One can wonder, though, if recent clinical studies accurately reflect the long-term potential of prodrugs as standalone treatments, components of multimodal therapy regimens, or treatments for whole new indications other from those for which they have already received approval. In this review, a list of top prodrugs undergoing clinical trials from 2013 to 2018 is rumored [2].

II. HISTORY OF PRO-DRUG

Acetanilide, introduced into medical practice by Cahn and Hepp in 1867 as an antipyretic medicine, was the first compound to meet the standard criteria for a prodrug. By hydroxylating acetanilide, bioactive acetaminophen is created [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].

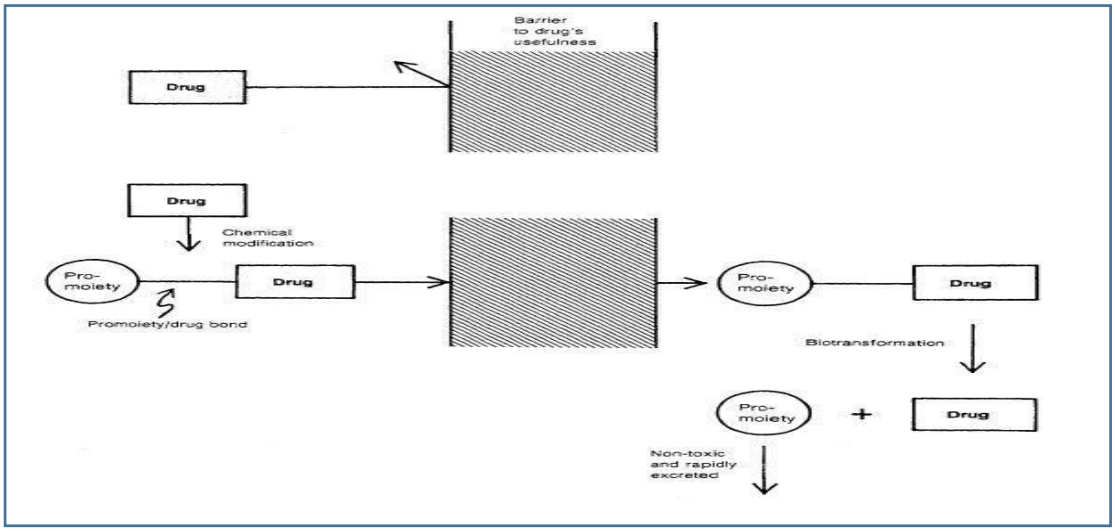
The prodrug concept was intentionally used for the first time by the Parke-Davis company for modification of chloramphenicol structure in order to improve the antibiotic's bitter taste and poor solubility in water. Chloramphenicol was created in two prodrug forms: chloramphenicol palmitate, which is 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 unfavorable drug properties, such as presystolic metabolism, toxicity, low target selectivity, unfavorable 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:

- Pharmaceutical: to improve the solubility, chemical stability, and organoleptic properties; to diminish localized pain and/or itch; and to reduce problems with the pharmaceutical technology of the active ingredient.
- Pharmacokinetic: to enhance time profile, increase oral and nonoral absorption, minimize presystolic 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.



IV. CLASSIFICATION OF THE PRODRUGS

Pro-drug is classified into two different groups are.

- Carrier–linked pro-drugs
- Bio precursor pro-drug

A. 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].

B. 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.

V. OBJECTIVES OF PRO-DRUG

- 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.
- 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.
- Improve the kinetics of the medication.
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VI. SPECIFIC PRODRUGS IN PHARMACOLOGY

A. In Cardiovascular System

- **Simvastatin**

Simvastatin is one of the oldest and most well-known pharmaceuticals available (Figure 1). In vivo hydrolysis of its 6-membered lactone ring yields beta, delta-dihydroxy acid and an active metabolite with a structure similar to HMG-CoA. (hydroxymethylglutaryl CoA). HMG-CoA reductase, an enzyme that catalyses the conversion of HMG-CoA to mevalonate, a rate-limiting mechanism in cholesterol production, is in competition with the hydrolysis metabolite of simvastatin with HMG-CoA. Nevertheless, many clinical trials examining the effects of statins alone or in combination were conducted from 2013 to 2018.

By investigating how it interacts with various illnesses and disorders, the majority of these research assessed simvastatin's safety and ability to be preferred above other statins in specific situations. Since simvastatin was the sole medication used in certain trials, the results haven't yet been made public. These include NCT03131726, which investigated simvastatin's efficacy in the treatment of Graves' ophthalmopathy, and NCT03387670, a phase 3 simvastatin trial for multiple sclerosis known as MS-STAT2. Simvastatin metabolism was examined by NCT03011931 as a test for celiac disease activity. This was done in response to MS-STAT1 results showing that simvastatin users experienced less neuronal death than those taking a placebo [11,12].

The secondary progressive MS stage is what causes the significant impairment in MS patients (SPMS). Currently, there aren't many drugs that can effectively treat SPMS patients or halt the development of their problems. According to the outcomes of the MS-STAT2 trial, simvastatin, a prodrug currently used to treat vascular disease and high cholesterol levels, may be used as an effective therapeutic for the treatment of SPMS. This is because the prodrug might have neuroprotective and immunomodulatory properties.

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- **Clopidogrel and Prasugrel**

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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**

In 2015, Selexipag (Figure 1) received FDA approval for the treatment of pulmonary arterial hypertension. Along with its active metabolite ACT-333679, they are prostacyclin receptor agonists that increase pulmonary circulation vasodilation and reduce pulmonary arterial hypertension [14]. Between 2013 and 2018, sixteen clinical studies on selexipag were reported. Healthy volunteers underwent tests on bioavailability, dose response, interactions with clopidogrel (NCT03496506), and drug-drug interactions including gemfibrozil and rifampicin (NCT02770222). Clinical trials involving the use of selexipag in people with chronic thromboembolic pulmonary hypertension and kids with pulmonary arterial hypertension are currently being conducted (NCT03492177 and NCT03689244, respectively). According to preliminary findings of trials whose results have been published, selexipag is tolerable, pharmacokinetically effective, and clinically successful.

- **Dabigatran**

Etexilate Dabigatran etexilate is a synthetic, reversible direct inhibitor of thrombin (Figure 1). This inhibition interferes with the clotting process, resulting in decreased fibrin levels. Dabigatran is hydrolyzed by the liver and plasma esterases to create its active form. This prodrug has an advantage over drugs like warfarin in that it does not need ongoing lab testing [15]. Recent observations suggest that the number of patients receiving dabigatran is still quite limited. Due to the availability of more modern, potent drugs such oral factor Xa inhibitors, dabigatran use in clinical settings has diminished.

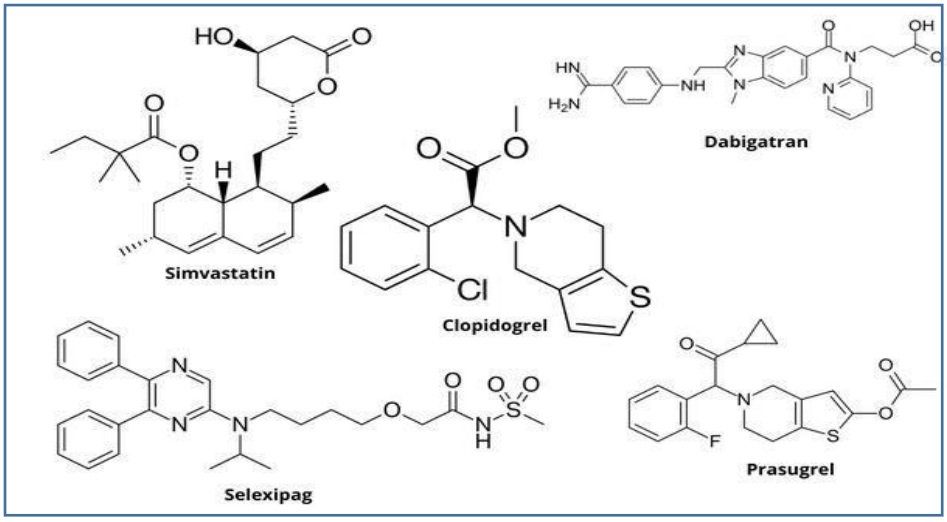

Figure 1: -Structure of different Cardiovascular pro-drugs

B. Nervous System

- **Blarcamesine** (**ANAVEX 2-73)**

Blarcamesine (ANAVEX 2-73), a small molecule orphan medication, was developed by ANAVEX Life Sciences Corp. to activate sigma-1 receptors in neurons. This activation alters the mechanisms involved in neurodegeneration by preventing or decreasing protein misfolding, cellular stress, mitochondrial malfunction, and oxidative stress [16]. An aminotetrahydrofuran called ANAVEX 2-73 is activated by the demethylation of its tertiary amine group [17].

The two main disorders that ANAVEX 2-73 (Figure 2) is being tested on are Rett syndrome and Alzheimer's disease. The only phase 2 trial that has obtained FDA approval is ANAVEX2-73-RS-001, also known as NCT03758924. Even though information is scarce and limited to the website of the manufacturing business, this medication appears promise in terms of both its therapeutic potential and its potential as a lead molecule from which stronger sigma receptor agonists can be inspired.

- **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].

Deutetrabenazine (Figure 2), which was also licenced in 2017 and is also converted to a-dihydrotetrabenazine, was the subject of several recent clinical trials that examined the safety and efficacy of each prodrug in the treatment of chorea and Gilles de la. Due to decreased internal organ metabolism and undeniably high sac aminoalkane transporter 2 property, each prodrug permitted once-daily dosing [18]. Dopastat is the main neurotransmitter whose absorption is decreased as a result of this inhibition. Dyskinesia and Parkinson's disease patients exhibit a more mild form of Tourette syndrome. Results have yet to be published, although timely completion of the studies appears positive.

- **Aripiprazole Lauroxil**

A long-acting injectable prodrug of aripiprazole called aripirazole lauroxil (Figure 2) is 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 experiences spontaneous cleavage to produce aripiprazole. The agonism of dopaminic and 5-HT1A receptors as well as alpha-adrenergic 5-HT2A receptors is the mechanism of action of the active metabolite [22]. Aripiprazole's binding profile is understood, however it is still unclear how the drug actually works to produce its antipsychotic effects. However, the alpha-adrenergic receptor's agonism is associated to adverse outcomes such orthostatic hypertension. 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 [23].

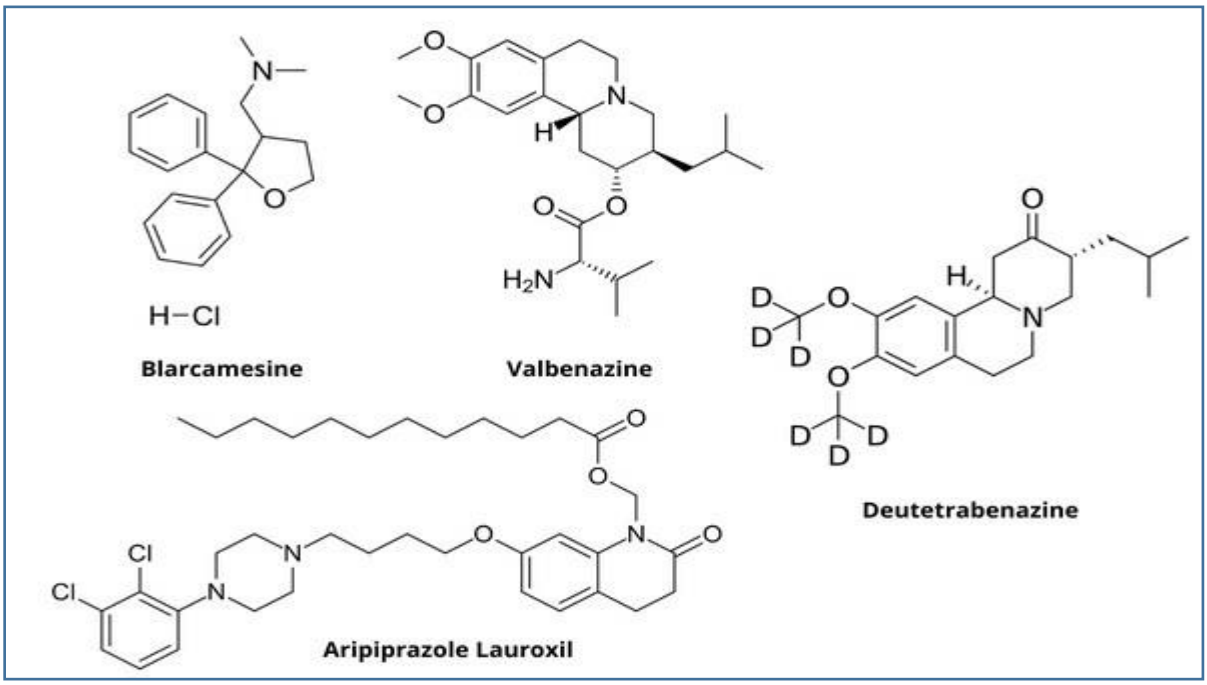

Figure 2:-Structure of different Nervous System Pro-drugs

C. 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.

Baloxavir marboxil is now only advised for people over the age of 12, although a clinical trial NCT03653364 was created to assess the treatment's safety and efficacy in neonates under the age of one. The drug may be advised for younger people if the trial's results are positive, signalling a more optimistic and confined epidemiological future for influenza internationally.

- **Fostemsavir**

The phosphonooxymethyl prodrug of temsavir (BMS-626529), often referred to as fostemsavir or BMS-663068 (Figure 3), works in a special way by binding to the HIV envelope glycoprotein 120 and preventing the virus from attaching to the host CD4 cell surface receptor.

In a phase 2b research involving patients who had already received treatment, fosterimsavir seemed to be well tolerated. Research on [23] is still in its third phase. The majority of the patients who took part in the phase 2b randomised controlled research AI438011, which demonstrated the drug's safety and efficacy, indicated that it was well tolerated [24]. 15 more clinical trials were carried out between 2013 and 2018 to assess the efficacy, pharmacokinetics, interactions, and toxicity of the prodrug. The results of a current phase 3 trial (BRIGHTE or NCT02362503), whose findings are anticipated to be published in 2024, are promising. All studies supported continuing to test the prodrug.

The drug may herald in a new era of HIV-1 treatment, especially for patients who have had several prior treatments and whose virus has grown considerably resistant to conventional therapy [25] if the trial's results are positive.

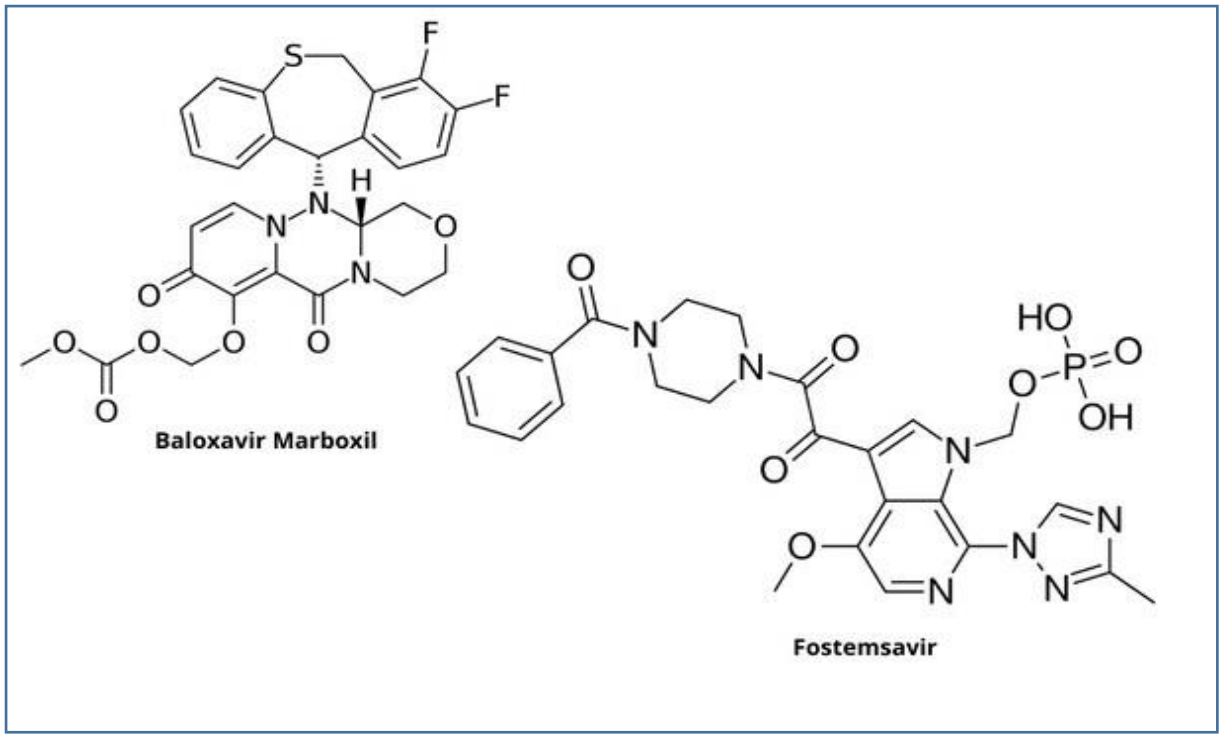

Figure 3:- Structure of different Antiviral Pro-drugs

D. In Neoplastic

- **Ixazomib**

The ester prodrug of ixazomib, ixazomib citrate (Figure 3), is used in multiple myeloma cases. The parent drug, the prodrug, is hydrolyzed. Ixazomib's mode of action includes reversibly inhibiting the beta 5 subunit of the 20S proteasome. Ixazomib was first approved by the FDA in 2015 when it was combined with lenalidomide and dexamethasone. Takeda Pharmaceuticals is now selling ixazomib citrate under the brand name Ninlaro. From the beginning of 2013 to the end of 2018, 34 NCTs in all investigated ixazomib either alone or in combination. Between 2011 and 2012, early NCTs mostly examined the pharmacokinetics, safety, efficacy, and tolerance of patients with multiple myeloma.

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. In a randomised phase 2 research [26], NCT02046070, the effectiveness of a combination therapy comprising of ixazomib plus cyclophosphamide and low-dose dexamethasone was evaluated in patients who were ineligible for transplant.

The study found that this therapeutic strategy is tolerated and has controllable toxicity. Additionally, individuals receiving the combination at 300 mg/m2 showed lower rates of toxicity than those receiving 400 mg/m2 of cyclophosphamide, indicating that the latter dose is better tolerated. There are now active studies looking at ixazomib in people 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).

- **Evofosfamide**

Evofosfamide, also referred to as TH-302(Figure 3), is an isophosphoramide mustard prodrug that is activated by hypoxia. The active form, a powerful DNA alkylator. A variety of cancers, including solid tumours, oesophageal, soft tissue, and pancreatic cancers, are being studied to determine the efficacy of TH-302.Many of the trials, but were dropped due to poor enrolment, inefficiency, and failure to meet goals. However, freshly published trials

continue to show the prodrug's advantages and great promise [21–23]. The disparity in the reports may enable additional investigation of the drug or the strategy of hypoxia-activated prodrugs.

- **Romidepsin**

For the management and therapy of peripheral Tcell lymphoma, romidepsin is a prodrug (Figure 3). (PTCL). Its activation is brought on by intracellular glutathione, which results in a metabolite with a free thiol group. The metabolite is a potent and targeted inhibitor of histone deacetylase. This inhibition induces a rise in histone acetylation, which alters the cell cycle and results in death. People with PTCL usually get aggressive first-line chemotherapy, but their prognoses are poor and their responses are insufficient. The prodrug romidepsin is recognised as a single-agent therapy that delivers long-lasting effects in individuals with refractory or relapsed/PTCL. Studies have shown a synergistic benefit with tolerable hematologic harm when romidepsin and pralatrexate were given simultaneously. Romidepsin may have additional PTCL indications, according to these and other trials. Romidepsin may be more effective when combined with other antineoplastic medications, according to other studies [27].

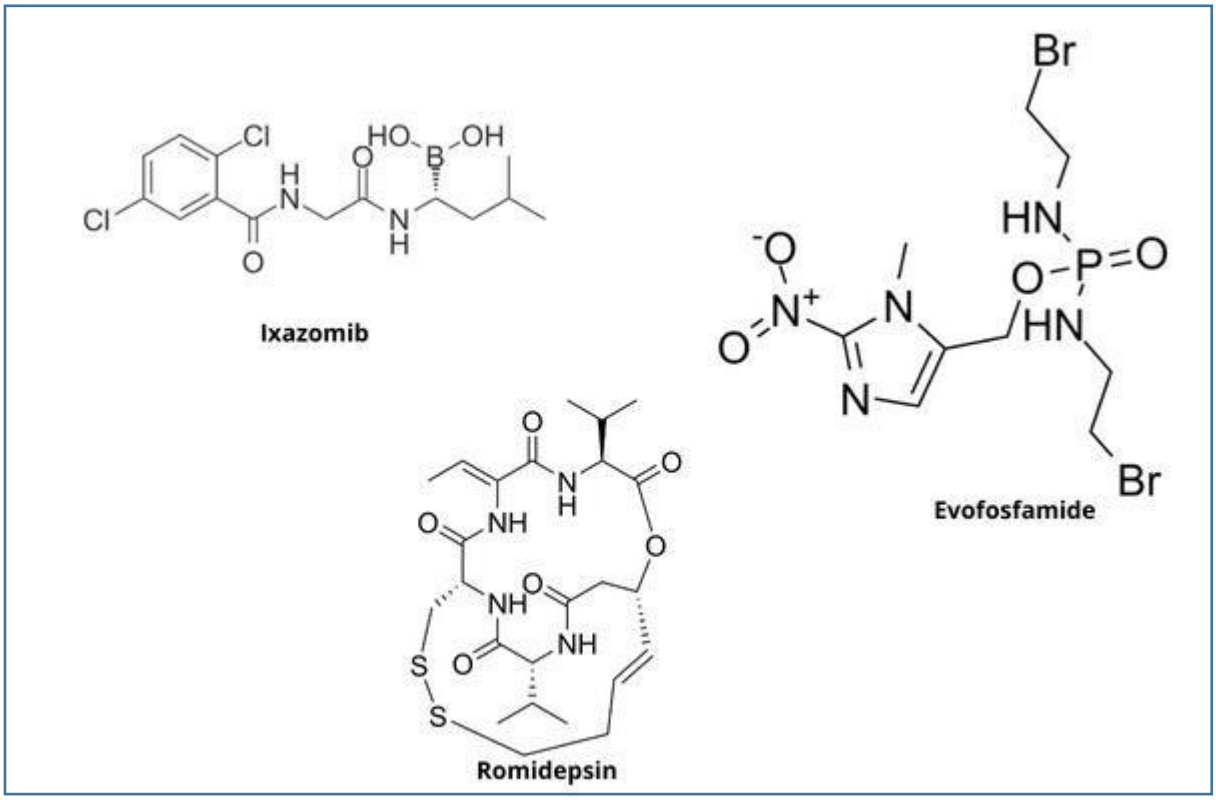

Figure 4: - Structure of different Neoplastic Pro-drugs

VI. APPLICATION OF PRO-DRUG

- Pro-drugs are used to change a drug's pharmacological effect by enhancing its biological and therapeutic actions.
- 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.
- By improving the smell of the medication, patient compliance rose.
- Change the physicochemical characteristics of the medicine to increase formulation stability.
- 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.
- The pro-drug makes chemicals more stable.
- Increasing the drug's lipophilicity, which raised the drug's bioavailability.

- Halt the metabolism of the precursor.
- Reduced the dangerous side effects of the potent medication.
- Delivered the drug to the patient's place of activity.

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