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 biologically inactive compounds that area unit activated post-administration to their pharmacologically active forms. Typically, prodrugs area unit developed to beat pharmacokinetic barriers like poor solubility and absorption, intensive first-pass metabolism, or fast excretion, and pharmacodynamics barriers like toxicity, facet effects, and poor effectualness.

The activation of prodrugs is sometimes via either protein processes like that by hemoprotein enzymes, esterase's and amidases or chemical processes (inter or intra-molecular) like chemical reaction and oxidization. Many prodrugs have enjoyed clinical success in treating varied chronic and acute conditions [1]. Among the booming examples are the prodrugs indented for the management of cardiovascular disease like the angiotonin-converting protein inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). Others area unit those accustomed inhibit thrombocyte aggregation within the cases of natural process disorders and internal organ incidents like clopidogrel and prasugrel. Sulfasalazine may be a common alternative prodrug for the management of inflammatory bowel {disease} and Crohn's disease.

Although the assembly of biological treatments like organism antibodies is taken into account as a promising strategy to create new medicines, the prodrug approach continues to be being explored and novel prodrugs are still being developed. throughout the years 2008–2017, 12.4% of all new molecular entities approved by the authority were prodrugs (31 out of 249) [2].

However, one would possibly ponder whether recent clinical trials mirror the longer term of prodrugs as new treatments, elements of combined treatment regimens, or treatments for brand spanking new indications aside from their already approved ones. during this review, a outline of elite prodrugs in clinical trials throughout the years 2013–2018 is rumored [2]

II. HISTORY OF PRO-DRUG

The first substance that met the traditional requirements of a prodrug was acetanilide, which Cahn and Hepp brought as an antipyretic medication into medical practise in 1867. Bioactive acetaminophen is produced by hydroxylating acetanilide [3].

Acetylsalicylic acid, also known as aspirin, was created in 1897 by Felix Hoffman in Bayer, Germany, and was first used in medicine by Dreser in 1899 [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

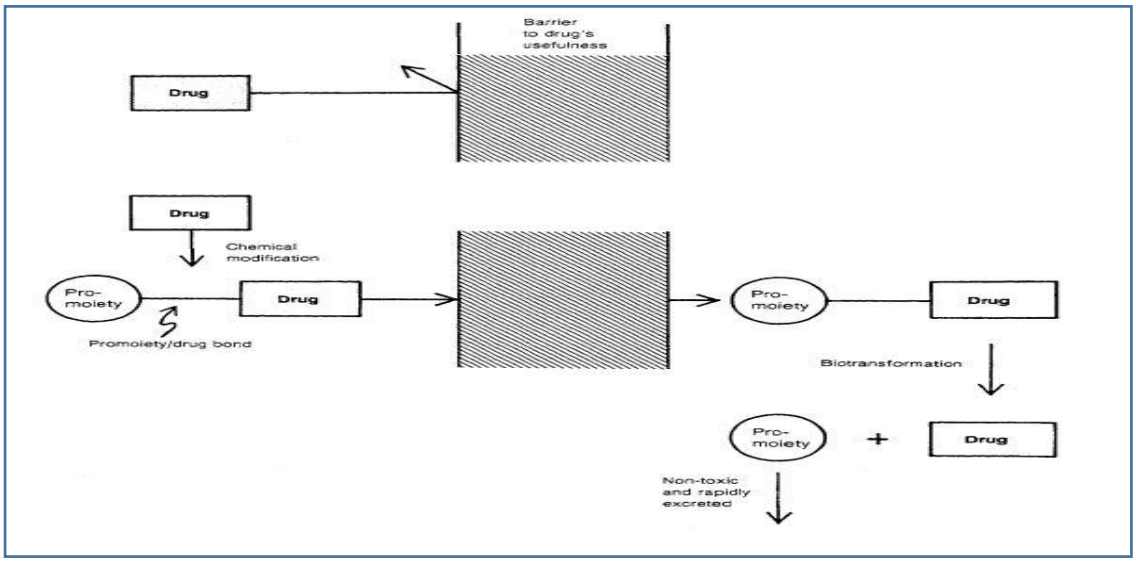
water. Chloramphenicol was created in two prodrug forms: chloramphenicol palmitate, which is used as a suspension in children, and chloramphenicol sodium succinate, which has good water solubility [4].

III. CONCEPT OF PRO-DRUG

Prodrug design's main goal is to hide undesirable drug properties like presystemic metabolism, toxicity, low target selectivity, undesirable 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 typically used to improve the parent drugs' absorption, distribution, metabolism, excretion, and undesired toxicity [8]. Prodrugs are biologically inert derivatives of drug molecules that undergo an enzymatic and/or chemical conversion in vivo to release the pharmacologically active parent drug. Adrien Albert coined the word "prodrug" in 1958 [9]. Whether the prodrug is absorbed before, during, or after the release of the active drug from its inactive state. Some medications are not released until they have completed their intended actions [4, 5]. The bioavailability and therapeutic potency of a parent medicine should be improved by a prodrug. Prodrugs have also been referred to as reversible or bio reversible derivatives or boilable drug-carrier conjugates, despite the fact that the term "prodrug" is now widely used. According to Testa [7], prodrug research has three mains, overlapping goals:

- Pharmaceutical: to enhance the solubility, chemical stability, and organoleptic qualities; to lessen localized discomfort and/or irritation; and to lessen issues with the active agent's pharmaceutical technology.
- Pharmacokinetic: to boost organ/tissue-specific distribution of the active substance, increase oral and non-oral absorption, decrease presystemic metabolism, and improve time profile.
- To reduce toxicity and increase therapeutic index, create single chemical entities that combine two medications (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 PRO-DRUGS

Pro-drug is classified into two different groups are.

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

A. Carrier–Linked Pro-Drugs

This increased the drug's lipophilicity by covalently linking the inert carrier to the active ingredient. They are made up of the medication being attached to the carrier group. and the process by which the active medication is delivered, whether it be enzymatic or not. Additionally, carrier-linked pro-drugs are divided into:- Double pro-drug or cascade-latentialed pro-drug: in this case, only enzymatic conversion allows the drug to be released.

- 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 medications are manufactured with an efficient pharmacological action and are used to treat a variety of serious diseases, but their use is discouraged due to their toxicity and other factors that do not meet standard criteria. These types of medications are used to treat a variety of diseases by maximizing a drug's physicochemical and pharmacokinetic properties after pro-drug design.
- Deliver the medication to the spot where it is needed by encapsulating it in a carrier that the barrier will allow to pass through and enter the pro-drug.
- Enhance the drug's kinetics.

VI. SPECIFIC PRODRUGS IN PHARMACOLOGY

A. 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 that resembles HMG-CoA in structure (hydroxymethylglutaryl CoA). Simvastatin's hydrolysis metabolite competes with HMG-CoA for HMG-CoA reductase, an enzyme that catalysis 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 bulk of them studies evaluated simvastatin's safety and capacity to be preferred over other statins in certain circumstances by examining how it interacts with various illnesses and diseases. 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 [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**

Adenosine diphosphate (Figure 1) receptor blockers, especially thienopyridines, are proven excellent platelet aggregation inhibitors and remain of the first choices in the prevention of clotting disorders and follow up treatment of cardiovascular incidents. Platelet inhibition of this class of drugs is mainly achieved through blocking P2Y12 receptors of platelets. Furthermore, studies reported that clopidogrel (Figure 1) inhibits collagen and thrombin-induced platelet aggregation (for activation pathway and mechanism of action of clopidogrel see Scheme 1) [13]

The majority of the recent clinical trials on clopidogrel and prasugrel (Figure 1) were to further establish the best doses of the drugs, their regimens and their interactions with other common chronic conditions such as

diabetes. However, no new indications were being explored. Thus, it is expected that those recent clinical trials will aid in the development of future guidelines for conditions such as acute coronary syndrome, angina, heart failure, atrial fibrillation, and others. It is worth noting that careful consideration should be taken into consideration in the trials with clopidogrel and prasugrel pro-drugs when given with other medicines intended to treat other ailments. These medicines have the potential to interfere with the prodrugs' activation of the prodrug resulting in reversing the patient's recovery. Molecules 2019, 3 achieved through blocking P2Y12 receptors of platelets. Furthermore, studies reported that clopidogrel (Figure 1) inhibits collagen and thrombin-induced platelet aggregation (for activation pathway and mechanism of action of clopidogrel) [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, along with its active metabolite ACT-333679, improve pulmonary circulation vasodilation and hence lessen pulmonary arterial hypertension [14]. 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 findings of studies whose results have been published.

- **Dabigatran**

Etexilate A synthetic, reversible direct inhibitor of thrombin is dabigatran etexilate (Figure 1). 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 [15]. 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.

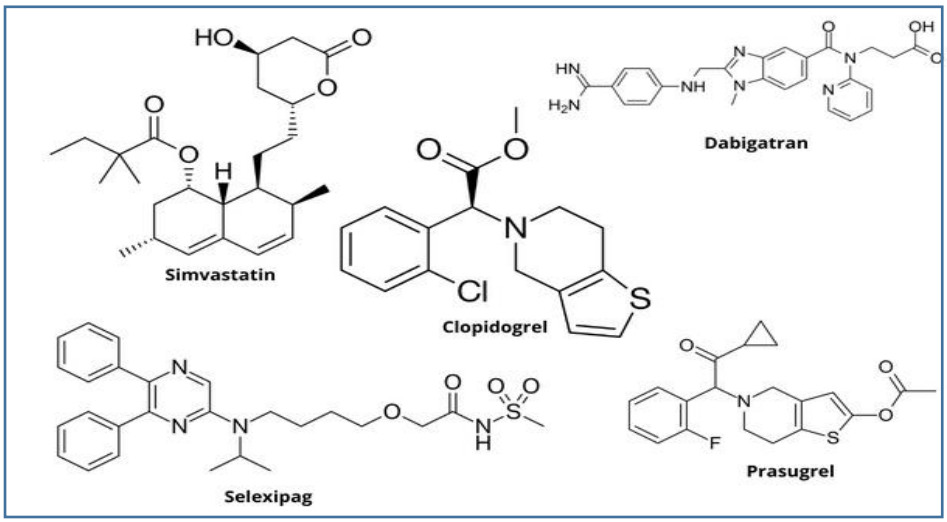

Figure 1: -Structure of different Cardiovascular pro-drugs

B. Nervous System

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

A small molecule orphan drug called ANAVEX 2-73, also known as blarcamesine (Figure 2), was created by ANAVEX Life Sciences Corp. to stimulate sigma-1 receptors in neurons. By preventing or reducing protein misfolding, cellular stress, mitochondrial dysfunction, and oxidative stress, this activation modifies processes related to neurodegeneration [16]. ANAVEX 2-73 is an aminotetrahydrofuran which is activated through demethylation of its tertiary amine group [17].

Rett syndrome and Alzheimer's disease are the two main conditions that ANAVEX 2-73 (Figure 2) is being tested on. ANAVEX2-73-RS-001, also known as NCT03758924, is the only phase 2 trial that has received FDA approval. This medicine seems promising, either in terms of its therapeutic potential or in terms of its potential as a lead molecule from which stronger sigma receptor agonists can be inspired, even though data are scant and limited to the manufacturing company's website.

- **Valbenazine and Deutetrabenazine**

Valbenazine (Figure 2) prodrugis the L-valine organic compound of [+]-α-dihydrotetrabenazine (DTBZ) that undergoes chemical reaction during a quick manner to its active drug, DTBZ. Valbenazine was developed below the name NBI-98854 and was approved by the office for the treatment of dyskinesia in 2017. Valbenazine's mechanism of action is mediate through the reversible inhibition of VMAT2 within the treatment of TD. VMAT2 is selective to the central system and is to blame for the transport and use of neurotransmitters across the junction. The inhibition of VMAT2 augments neurochemical degradation and leads to presynaptic neurochemical depletion, significantly of Dopastat. each valbenazine and its active substance DTBZare active inhibitors of sac aminoalkane transporter two.

Similarly of dopaminergic neurons. The inhibition permits for higher concentrations of Dopastat within the somatic cell synapses resulting in a decrease in symptoms [19].

Several recent clinical trials investigated the security and effectiveness of each prodrug within the treatment of chorea and Gilles de la, deutetrabenazine (Figure 2) was conjointly approved in 2017 and is additionally metabolized to a-dihydrotetrabenazine. each prodrug allowed for once-daily dosing because of diminished internal organ metabolism and incontestable high property for sac aminoalkane transporter two [18]. This inhibition leads to a diminished uptake of neurotransmitters, chiefly Dopastat. Patients having dyskinesia and Parkinson's sickness show a diminished variety Tourette syndrome. Results area unit nevertheless to be printed however timely completion of the trials seems to be promising.

- **Aripiprazole Lauroxil**

Aripirazole lauroxil (Figure 2) is a long-acting injectable prodrug of aripiprazole which is indicated for the management of schizophrenia and bipolar disorder [20,21]. Following intramuscular injection, the prodrug is hydrolyzed to form N-hydroxymethyl-aripiprazole which, in turn, undergoes spontaneous cleavage to aripiprazole. The mechanism of action of the active metabolite is the agonism of dopaminic and 5-HT1A receptors as well as alpha-adrenergic 5-HT2A receptors [22]. However, and while the binding profile of aripiprazole is known, how it exerts its antipsychotic activity is not well established yet. However, side effects such as orthostatic hypertension are linked to agonism of the alpha-adrenergic receptor. The main advantage of the prodrug is that it represents a sustained release dosage form of the active drug. This results in better adherence in patients who have difficulty adhering to their medications [23].

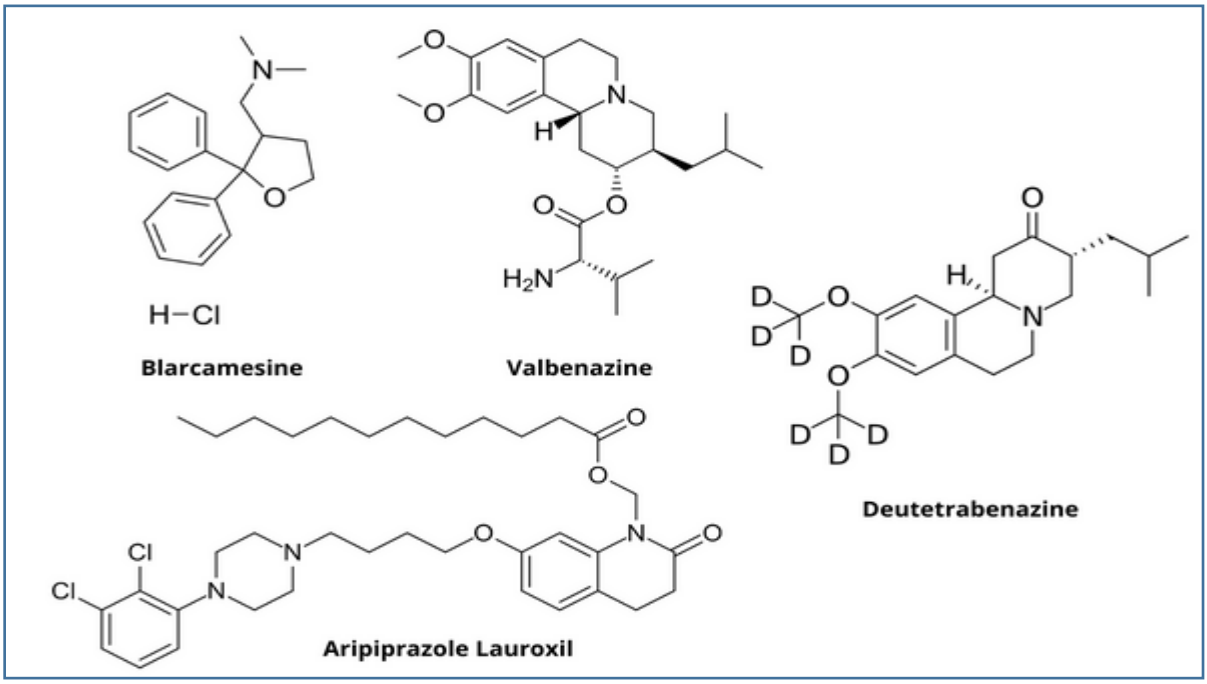

Figure 2:-Structure of different Nervous System Pro-drugs

C. In Antiviral

- **Baloxavir Marboxil**

The prodrug baloxavir marboxil (Figure 3) 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 [27]. 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 including the prodrug were reported between 2013 and 2018, three of which are now complete. These trials evaluated the prodrug's safety and efficacy by comparing it to a placebo and oseltamivir.

Currently, baloxavir marboxil is only recommended for individuals over the age of 12; however, a clinical trial NCT03653364 was designed to evaluate the treatment's safety and effectiveness in newborns younger than one year of age. If the trial's findings are encouraging, the medication might be recommended for younger individuals, heralding a more promising and constrained epidemiological future for influenza globally.

- **Fostemsavir**

The unique mode of action of the phosphonooxymethyl prodrug of temsavir (BMS-626529), also known as fostemsavir or BMS-663068 (Figure 3), involves binding to the HIV envelope glycoprotein 120, which 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 on [23]. In the phase 2b randomised controlled study AI438011, which proved the drug's safety and effectiveness, the majority of the patients who participated reported that it was well tolerated [24]. 15 further clinical trials were conducted between 2013 and 2018 to evaluate the prodrug's effectiveness, pharmacokinetics, interactions, and toxicity. All studies favoured continuing to test the prodrug, and a current phase 3 trial (BRIGHTE 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 [25].

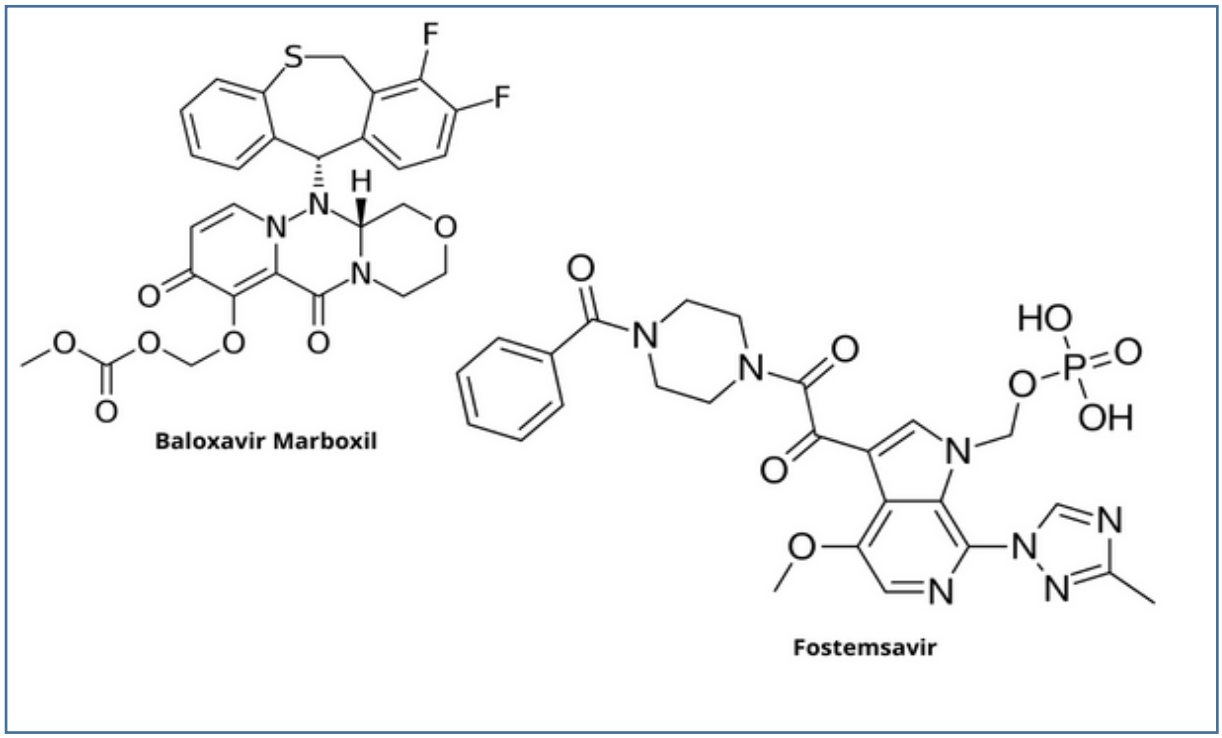

Figure 3:- Structure of different Antiviral Pro-drugs

D. In Neoplastic

- **Ixazomib**

In situations of multiple myeloma, the ester prodrug of ixazomib, ixazomib citrate (Figure 3), is utilized. 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. Early NCTs focused mostly on multiple myeloma patients' pharmacokinetics, safety, effectiveness, and tolerance between 2011 and 2012.

The focus of more recent NCTs is currently on ixazomib's impact on leukaemia, lymphoma, multiple sclerosis, and sarcoma. The pharmacokinetics and safety of ixazomib were assessed in patients with advanced solid malignancies and relapsed/refractory multiple myeloma in a phase 1 study by Takeda Pharmaceuticals (NCT01830816). According to research released in June 2019, ixazomib was less well tolerated and had more 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 [26], 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. Selected trials examining ixazomib 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 are currently ongoing (NCT02993094).

- **Evofosfamide**

Evofosfamide, commonly known as TH-302(Figure 3), is a brominated isophosphoramide mustard prodrug that is hypoxia-activated. An effective DNA alkylator, the active form. The effectiveness of TH-302 is being

investigated in a number of cancers, including solid tumours, oesophageal, soft tissue, and pancreatic cancers. Many of the trials, however, were abandoned because of low enrollment, ineffectiveness, and inability to achieve endpoints. However, recently released studies continue to demonstrate benefits and tremendous promise in using the prodrug [21–23]. This discrepancy in the reports may allow for further research into the drug or the tactic of hypoxia-activated prodrugs.

- **Romidepsin**

A prodrug called romidepsin (Figure 3) is prescribed for the management and treatment of 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 have dismal prognoses and insufficient responses. 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 benefit with tolerable hematologic damage. 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 [27].

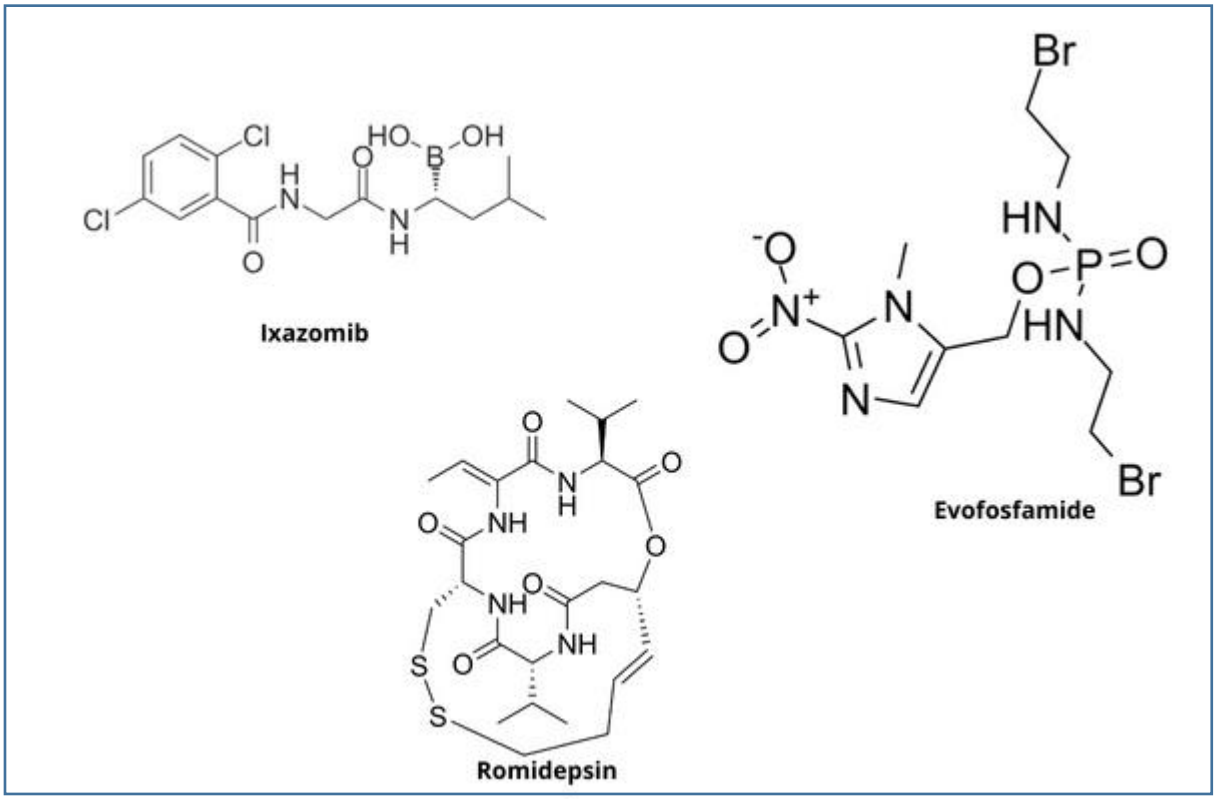

Figure 4: - Structure of different Neoplastic Pro-drugs

VI. APPLICATION OF PRO-DRUG

- Pro-drugs are used to modify the pharmacological action of a medicine by optimising its biopharmaceutical and medicinal activities.
- Alter the taste—poor patient compliance is a result of terrible taste. There are two methods for overcoming poor taste:
  - The drug's solubility decreases in saliva.
  - Decrease the drug's affinity for taste receptors.
- The drug's odour was improved, which increased patient compliance.

- Modify the drug's physical shape to improve formulation stability.
- Reduction in GIT irritation: Certain medications can irritate the GIT. To combat this issue, pro-drugs are utilized to lessen the harm the medication does to the GIT.
- The pro-drug increases chemical stability.
- Enhanced the drug's lipophilicity, which increased the bioavailability of the medication.
- Stop the precursor metabolism.
- Lessened the harmful effects of the powerful medicine.
- Sent the medication to the patient's active location.

VII. ACKNOWLEDGMENTS

This work is supported by ShriRam college of Pharmacy. The authors would like to express their sincere thanks to Dr. Vinay Jain, Mr. Ravindra Mishra and all supporting staff for the valuable contribution to the framing of this work.

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