IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 3, December 2024

Basic Concepts and Application of Prodrug Design

Vaishnavi R Wankhade[1] and Pranita S Dudhe[2]
Student, Vardhaman College of Pharmacy, Karanja (Lad), Maharashtra, India[1]
Assistant Professor and Guide, Vardhaman College of Pharmacy, Karanja (Lad), Maharashtra, India[2]

Abstract: *Prodrug are bio reversible derivatives of drug molecules that undergo an enzymatic and or chemical transformation in vivo to release the active parent drug ,which can then exert desired pharmacological effect this approach has several Advantages over conventional drug administration Prodrug designs is a widely known molecular modification strategy that aims to optimize the physicochemical and pharmacological properties of drug to improve their solubility and pharmacokinetic features and decrease their toxicity .this review aims to describe recent advances in the improvements of solubility via the prodrug approach the main chemical carries and examples of successful strategies will be discussed, highlighting the advance of this field in the last ten years*

Keywords: Solubility, water soluble prodrug, prodrug

I. INTRODUCTION

A prodrug is a pharmacologically inactive compound that is converted into it's active drug by a metabolic bio transformation prodrug enhanced the use fullness of various therapeutic agent by altering their physicochemical properties, pharmacokinetic and biopharmaceutical properties prodrug might alter the tissue distribution, efficacy and toxicity of parent drug.

Below are some reason why prodrug approach should be used in drug designs

- Improved aqueous solubility
- Improved absorption and distribution
- Site specificity
- Improved stability of drugs
- For prolonged release
- To reduced toxicity
- In poor patient acceptability
- In formulation problems

History of Prodrug

Albert has first introduced the enunciation "prodrug" in 1958 actually " predrug" is such an inaccurate term, however the origin version was used to widely to be changed this concept has been used before Albert's publication .[3][23]

The first compound fulfilling the classical criteria of a prodrug was acetanilide, introduced into the medical practice by Cahn and Hepp in 1867 .as an antipyretic agent acetanilide ishydroxylated to biologically active acetaminophen [5]

Another historical prodrug is aspirin (acetylsalicylic acid), synthesized in 1897 by.Felix Hoffman (Bayer, Germany) and introduced into medicine by dresser in 1899 [6]

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 antibiotics bitter tasteand poor solubility in water.[3]

Two prodrug forms of chloramphenicol were synthesized Chloramphenicol sodium succinate with a good water solubility and chloramphenicol palpitate used In the form of suspension in children.[5]

Concept of prodrug :

The awareness that the onset, intensity and duration of drug action are greatly affected bythe while overcoming various physical, chemical and social barrier is certainly the utilization of the prodrug approach physicochemical properties of drug has promoted the emergency of various prodrug.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 3, December 2024

Most of the limitations can be overcome by prodrug approach, but after overcoming the various barriers, the prodrug should rapidly convert into active moiety after reaching the target site.

The design of an efficient, stable, safe, acceptable and aesthetic way to target a drug to its site of action while overcoming various physical, chemical and social barrier is certainly the utilization of the prodrug approach hold great potential.

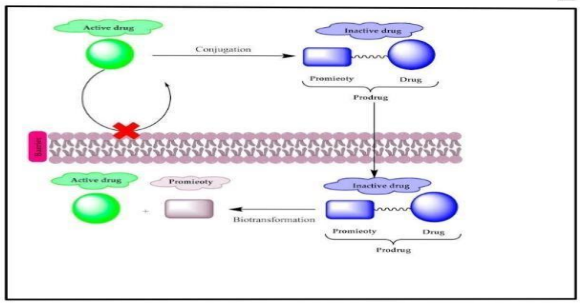


Fig : A simplified illustration of prodrug concepts

Objective of prodrug design :

1. Pharmaceutical objectives:

- To improve solubility e.g. corticosteroids
- To improve chemical stability e.g. dopamine
- To improve organoleptic properties (e.g.choloramphenicol palpitate is sparingly soluble prodrug of chloramphenicol, which is practically tasteless due to its low aqueous solubilityas well as it is hydrolyzed to active chloramphenicol by the action of pancreatic lipase)
- To decrease irritation and pain.

2. Pharmacokinetic Objectives

- To improve oral absorption or permeability and thus increase bioavailability (ampicillin,epinephrine).
- To decrease first pass metabolism (propranolol)
- To improve absorption by non oral routes.
- To provide organ or tissue selective delivery of active agent

3. Pharmacodynamics Objectives

- To avoid adverse effects or toxicities
- To mask reactive species to improve it's therapeutic index
- To improve site specificity (i.e. That the site of action of an active drug is rather nonspecificsuch as anticancer agents).

Classification of prodrug:

Based on type of carrier moiety:

Prodrug are classified into two broad categories : the carrier linked prodrug and bioprecusors. Thecarrier -linked prodrug consist of the attachment of a carrier group to the active drug to alter its physicochemical properties and then subsequent enzymatic or nonenzymatic mechanism to releasethe active drug moiety. Thus the carrier linked prodrugs are drugs with covalent linkage with specialised nontoxic protective group or carriers or Promoities in a transient manner to alter or eliminate undesirable properties in the parent molecule .Depending upon the nature of carrier used, the carrier linked prodrug may further be classified into the followings[1]

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 3, December 2024

1. Double prodrugs, pro-prodrugs cascade- latentiated prodrug:
Where a prodrug is further derivatized in a fashion such that only enzymatic conversation to prodrug is possible before the latter can cleave to release the active drug.[8]

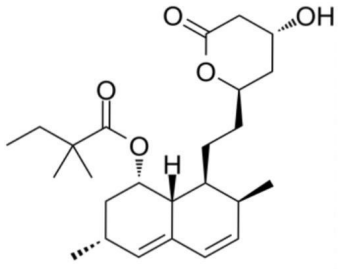
2. Macromolecular prodrugs:
When macromolecules like polysaccharides, dextrans, cyclodextrins, proteins, peptides and polymers are used as carrier.[8]

3. Site-specific prodrugs:
Where a carrier acts as a transporter of the active drug to a specific targeted site. [8]

4. Mutual prodrug:
It consists of two pharmacologically active drugs joined with each other. They are taken togetherwith the aim to mask the side effects of active drug and give the synergistic action. For example Estramustine has a phosphorylated steroid (17- α- estradiol) coupled to Nor-mustard which has carbamate linkage.[7]

New classification : Based on cellular site of bioactivation:
Prodrug can be classified into major type, based on their cellular site of bioactivation into the finalactive drug form with type I being those that are bioactivated intracellur- aly (e.g.,anti-viral nucleotide analogies, lipid – lowering statins) and type II being those that are bioactivated extracellularly, especially in digestive fluids or the systemic circulation (e.g.,.Etoposide phosphate, valganciclovir, fosamprenavir ,antibody -,gene -or virus -directed enzyme prodrug (ADEP/GDEP/VDEP) for chemotherapy or immunotherapy).both type can be further categorized into subtypes ,i.e. Type IA,IB and Type IIA, IIB and IIC based on whether or not the intracellularbioactivation location is also the site of therapeutic action, or the bioactivation occurs in the gastrointestinal (GI) fluids or systematic circulation.[1]

Selected Prodrugs:
Cardiovascular System:
Simvastatin:
Simvastatin is amongst the oldest and best-known prodrug available on the market. Its w of action involves in vivo hydrolysis of its 6-membered lactone ring to yield the beta, delta-dihydroxy acid, and an active metabolite that is similarin structure to HMG-CoA (hydroxymethylglutaryl CoA). The hydrolysis metabolite of simvastatin competes with HMG-CoA for HMG-CoA reductase, which catalyzes the transformation of HMG-CoA to mevalonate, a rate-limiting step in cholesterol biosynthesis. However, many clinical trials were investigating the e_ects of statins in combinationor as sole treatments during 2013–2018.[13]

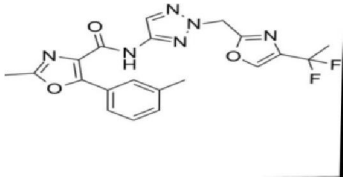


Structure : Simvastatin

ACT-281959:
In contrast pyridines such as clopidogrel and prasugrel, ACT-24647 is a novel potent P2Y12 receptor inhibitor that is being developed for early intervention through subcutaneous injection. ACT-281959 is the oral prodrug of ACT-24647 which is activated through hydrolysis of the two ester chains on its phosphonic acid [18]. One clinical trial coded

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 3, December 2024

NCT01954615was conducted to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ACT-281959.

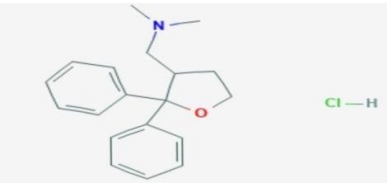


Structure :ACT 281659

Nervous System:

ANAVEX 2-73:

ANAVEX 2-73 or Blarcamesine is a small molecule orphan drug, developed by Anavex Life Sciences Corp., which activates sigma-1 receptors in neurons. This activation modulates processesrelated to neurodegeneration by preventing or decreasing protein misfolding, cellular stress, mitochondrial dysfunction, and oxidative stress[20] . ANAVEX 2-73 is an amino- tetrahydrofuranwhich is activated through demethylation of its tertiary amine group[21].

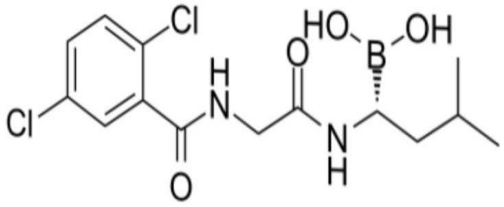


Structure : AVAVEX 2-73

Oncology

Ixazomib

The ester prodrug of Ixazomib, ixazomib citrate is used in the cases of multiple myeloma. The prodrug undergoes into its parent drug via hydrolysis. Ixazomib's mechanism of action involves areversible inhibition of the beta 5 subunit of the 20S proteasome. Ixazomib was first approved by the FDA in 2015 in combination with lenalidomide and dexamethasone. It is currently marketed by Takeda Pharmaceuticals under the brand name Ninlaro as ixazomib citrate. A total of 34 NCTsstudied ixazomib as a sole therapy or in combination during the start of 2013 till the end of 2018.The earliest NCTs revolved around the pharmacokinetics, safety, e_cacy, and tolerability of ixazomibin mainly multiple myeloma patients in 2011–2012. Newer NCTs are now focused on the ect of ixazomib in multiple sclerosis, lymphoma, sarcoma, and leukaemia.[13]

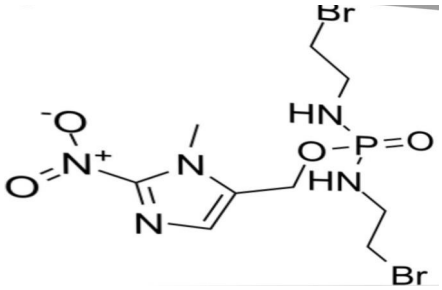


Structure : Ixazomib

Evofosfamide:

Evofosfamide (previously known as TH-302), a hypoxia-activated prodrug(HAP) has been designed to penetrate tohypoxic regions of tumors. Evofosfamide is reduced at thenitroimadazole site of the prodrug by intracellular reductasesand when exposed to hypoxic conditions, leads to therelease ofthe alkylating agent bromoisophosphoramide mustard (Br-IPM). Br-IPM can then act asa DNA crosslinking agent at thetumor hypoxic region and may diffuse to adjacentnormoxicregions via a bystander effect [10]

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 3, December 2024



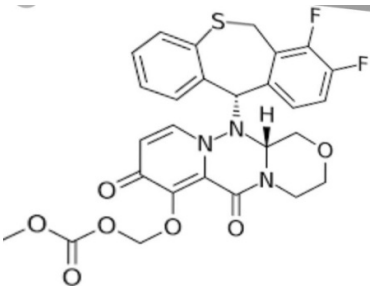
Structure :Evofosphamide

Antivirals

Baloxavir Marboxil

Baloxavir marboxil is a prodrug that is hydrolyzed to its active metabolite, baloxavir. Being the first new antiviral agent for influenza in nearly 20 years, baloxavir marboxil made headlines following its approval in 2018.

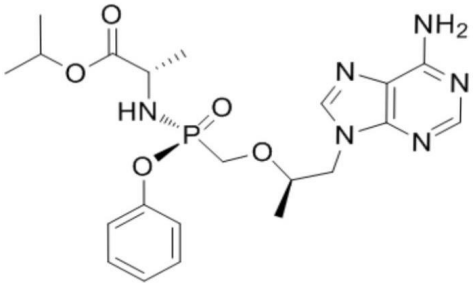
The prodrug is administered in the first 48 hours following symptoms of influenza and decreases viral shedding by inhibiting viral CAP endonuclease. During 2013–2018 only 5 clinical trials reported the prodrug in their intervention three of which have been completed and were aimed at comparing it to placebo and oseltamivir and assessing its safety and e_cacy. Currently, baloxavir marboxil is indicated for patients over the age of 12 but one clinical trial NCT03653364 was aimedto assess the safety and eficacy of the treatment in infants less than 1-year-old. If the results of thistrial are positive, the drug could be indicated for younger patients signaling a better and narrowerepidemiological future of influenza worldwide.[13]



Structure : Baloxavir Marboxil

Tenofovir Alafenamide

Tenofovir alfenamide is an acyclic analog of dAMP; it is phosphorylated to its active form, Tenofovir diphosphate, by AMP kinase. The active form of the prodrug inhibits HIV reverse transcriptase . Currently, tenofovir alfenamide is indicated for the treatment of chronic hepatitis B in patients with compensated liver disease . and HIV-1 infections in combination with emtricitabine. When compared to its prodrug counterpart tenfovir disoproxil, tenofovir alfenamide has been shown to produce lower systemic levels and higher intracellular levels producing better delivery and potency .[13]



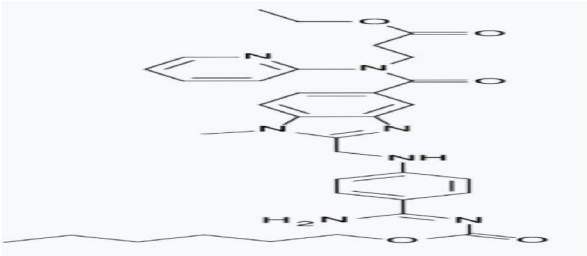
Structure : Tenofovir Alfinamide

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 3, December 2024

Recent Prodrug;

Dabigatran:

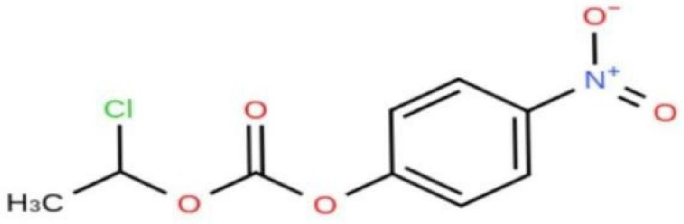
In 2010, the United States food and drug administration approved dabigatran,the first new oral anticoagulant to be approved in the United States of America in 50 years. Dabigatran is a reversiblecompetitive direct thrombine inhibitors [14].the first oral direct thrombine inhibitors was ximelagatran which showed antithrombotic efficacy and safety is compared with warfarin both preclinically and clinically. [22]



Structure :Dabigatran

Gabapentin enacarbil:

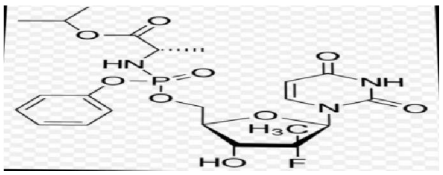
Gabapentin enacarbil extended release tablets received FDA approval in April 2011 for the treatment of moderate to severe primary restless legs syndrome in adult Gabapentine imidiate release was first approved by the FDA in 1994 for the adjunct treatment of partial seizures and is also FDA approved for the treatment of post herpetic – neuralgia Gabapentine immediate release has also been used for many off label indications, including treatment of migraine, headaches, fibromyalgia,and neuropathic pain, and anxiety. [17]



Structure : Gabapentin enacarbil

Sofobuvir:

Originally termed PSI-7977, sofosbuvir is a prodrug of a uridine nucleotide analogue inhibitor of the targets the catalytic site of NS5B and serves as a non-obligate chain terminator**[15]** following treatment with sofosbuvir plus ribavirin, levels of the triphosphate well above the inhibition level have been found in human livers.**[16]**



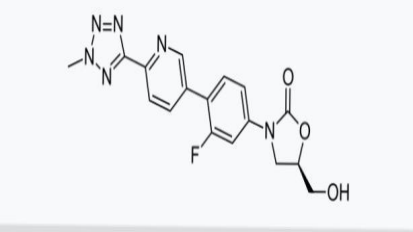
Structure : sofobuvir

Tedizolid:

Tedizolid (formerly torezolid, trade name Sivextro), is an oxazolidinone-class antibiotic. Tedizolid phosphate is a phosphate ester prodrug of the active compound tedizolid. It was developed by Cubist Pharmaceuticals, following acquisition of Trius Therapeutics (originator: Dong-A Pharmaceuticals), and is marketed for the treatment of acute bacterial skin and skin structure infections (also known as complicated skin and skin-structure infections (cSSSIs))[11]..

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 3, December 2024

According to in vitro studies , tedizolid is a bacteriostatic against gram positive organism through some animal models suggest bactericidal activity in vivo [12].similar to line zolid tedizolid exerts it's activity by binding to the 23S ribosomal RNA to the 50S subunit , there by preventing the formation of 70S initiation complex and thus inhibiting protein synthesis [11].



Structure :Tedizolid

Application of prodrug :

Anticancer agent:

Chemotherapeutic agent paclitaxel was attached to poly (hydroxyl ethyl aspartamide) via a succinic spacer arm by a two-step protocol: synthesis of 2'-O- succinyl -paclitaxel; and synthesisof PHEA-2'-o-succinyl paclitaxel. Investigation carried out using murine myeloid cell line showedthat the polymeric prodrug maintain partial pharmacological activity of paclitaxel. The conjugate disappeared from the bloodstream much more quickly as compared to both free drug and naked polymer

In GIT problem : colon targeting:

For e.g. sulphasalazine which is formed by coupling of diazotized sulphanilanide pyridine With 5-amino salicylic acid. On oral administration intact sulphasalazine reaches the colon. The azo reductase associated with colonic microflora convert sulphasalazine to its constituents entities, the active species 5ASA available for absorption in colon, while precolonic adsorption responsible forside effects is reduced.

Immunomodulaters:

Leflunomide is a novel immunomodulat-ary agent which exhibits a strong anti- inflammatory action. It is potent therap-eutic agent in autoimmune disease, graft rejection, and tumour therapy. It is isoxazole derivative as a prodrug and is completely converted to its active meta- bolite which blocks the dihydroorotate dehydrogenase, a key enzyme of the pyrimidine de novo synthesis.

Anti-Tubercular agents:

Ethambutol (EB), isoniazid (INH) and p-amino salicylic acid (PAS) are potent antitubercular agents having various side effects due to formation of toxic metabolites. Mutual prodrugs of EB with PAS (PE), PAS with PAS (PP) and INH with PAS (PI) were synthesized and characterized. In vitro hydrolysis studies in SGF and SIF reveal that these mutual prodrug conjugates do not hydrolyze appreciably and are absorbed unhydrolysed. In vivo studies showed greater serum concentration of EB, PAS and INH than their concentration when given alone and isoniazid concentration were greater except for PP. mutual prodigal PI and PE significantly eliminate the problem of fast metaboplism, toxicity and local irritation and reduction of therapeutic doses

CNS delivery:

The only prodrug that is used clinically for entering the brain predominantly through LAT1- mediated transport is L-dopa. The neurotransmitters dopamine is not able to cross the BBB due to its hydrophilic nature. However, the conversion of dopamine into its alfa-amino acid, L-dopa, enables the brain to uptake dopamine via LAT1. L-dopa is decarboxylated into dopamine by L- amino acid decarboxylase in the brain tissue and also in the peripheral circulation. Although approximately 95% of L-dopa is metabolized to dopamine in the peripheral tissues, the percentageof remaining L-dopa has been therapeutically enough to apply this approach in clinic practice formore than 30 years.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 3, December 2024

Ocular delivery:
The drug pilocarpine was converted to its ester prodrug forms. Pilocarpic acid diester and monoester prodrug solution showed significant biological activity and longer duration of action than pilocarpine.

For treating hypotension:
L-Threo- 3,4-dihydroxyphenylserine (droxidopa) is a norepinephrine (NE) prodrug under development to treat orthostatic hypotention.

Cholesterol – lowering prodrug :
Simvastatin (SV) is a lactone prodrug which undergoes reversible metabolism. In the hydroxy acid from (SVA) it is a potent inhibitors of HMG- CoA reductase.

II. CONCLUSION

The prodrug strategy is one of the most promising approachesto enhance the therapeutic efficacy and/ reduce the adverse effects of the pharmacologically active agents via different mechanisms including increased solubility, stability, improved permeability and bioavailability, prolonged biological half-lifetime, and tissue-targeted delivery. Hence, not surprisingly, prodrugs are becoming an integral part of the drug discovery paradigm. Their importance is supported by the increasing percentage of approved new drug entities that are, in fact, prodrugs. Despite the remarkable progress made in the field of prodrug design, more studies are clearly needed, especially at early stages of the drug discovery, for prodrugs to achieve the desired state of art andtake their place in modern pharmacotherapy.

REFERENCES

[1]. Shaifali Dubey* , Vandana Valecha prodrugs: a review World Journal of Pharmaceutical Research vol. 3, issue 7 , 277-297
[2]. Parajuli Rishi Ram, Pokharel Priyanka,Jouranal of drug delivery and therapeutics. 2015 ; 5(3): 5-9.
[3]. Nada Abedelnasser Elsharif, Review : prodrug concept in drug designs, A journal of pharmaceutical science ISSN : 2229-7006 Volume, 9 Issue 1
[4]. Dr. Ms Rathore, sandeep Kumar, Prodrug designs, international journal of pharmaceutical research. ISSN : 2949-7203Huttunen KM, Raunio H, Rautio J.
[5]. Bertolini A, Ferrari A, Ottani A, et al. Paracetamol: New Vistas of an Old Drug. CNS DrugRev. 2006; 12(3–4): 250–275p.
[6]. Stella VJ, Borchardt RT, Hageman MJ, et Al. Prodrugs Challenges and Rewards:Part 1. New York (NY): Springer; 2007.
[7]. Gennaro, R., Alfanso, W., Remington: The science and Practice of pharmacy, Lippincott Williams & Wilkins, 2003, 20, 1, 913-914.
[8]. Supriya Shirke*, Sheetal Shewale and Manik SatputeDepartment of Pharmaceutics, Satara College of Pharmacy Satara, Maharashtra, India
[9]. Ravindrakumar Gupta, prodrug concept and application, department of pharmaceutical BR Nahata college of pharmacy Mandsour (m. P.)
[10]. Libo Zhang1,2, Paula Marrano2, Bing Wu1,2, Sushil Kumar1,2, Paul Thorner2,4, and Sylvain Baruchel1,3,5 Combined Antitumor Therapy with MetronomicTopotecan andHypoxia-Activated Prodrug,Evofosfamide, in Neuroblastoma andRhabdomyosarcoma Preclinical Models Published OnlineFirst December 30, 2015; DOI: 10.1158/1078- 0432.CCR-15-1853
[11]. Steven D,Burdette and Robin trotman tedizolid:the first once-daily oxazolidine class antibiotics review of anti infective agents.
[12]. Louie A, Liu W, kulawy R, Drysano GL, In vivo pharmacodynamics of torezolid phosphate(TR-701), a new oxazolidinone antibiotic, against methicillin susceptible and methicillin resistant staphylococcus aureus strains in a mous thigh infection model. Antimicrobe agents chemother 2011; 55 : 3353-460

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 3, December 2024

[13]. Anas Najjar, Abderraman Najjar and Rafik karaman, review newly developed prodrugs and prodrugs in development, an insight of the recent year. YearsMolecules 2020, 25, 884;doi:10.3390/molecules25040884.

[14]. Michael Ganetsky, kavita M. Babu, Steven D salhanick, Roberts brown, Edward W. Boyer,Dabigatran : review of pharmacology and management of bleeding complication of this wovel oral anticoagulant j. Med toxicol (2011) 7:281-287.

[15]. Juif, P.E.; Boehler, M.; Dobrow, M.; Ufer, M.; Dingemanse, J. Clinical Pharmacology ofthe Reversible and Potent P2Y12 Receptor Antagonist ACT-246475 After Single Subcutaneous Administration in Healthy MaleSubjects. J. Clin. Pharmacol. 2019, 59, 123–130

[16]. Hauel NH, Nar H, priepk H, Ries U, Stassen JM wienen W (2002) structure based design of novel potent nonpeptide thrombine inhibitors J Med Chem 45(9) 1757-1766.

[17]. Juif, P.E.; Boehler, M.; Dobrow, M.; Ufer, M.; Dingemanse, J. Clinical Pharmacology ofthe Reversible and Potent P2Y12 Receptor Antagonist ACT-246475 After Single Subcutaneous Administration in Healthy Male

[18]. Hauel NH, Nar H, priepk H, Ries U, Stassen JM wienen W (2002) structure based design of novel potent nonpeptide thrombine inhibitors J Med Chem 45(9) 1757-1766.

[19]. Tesei, A.; Cortesi, M.; Zamagni, A.; Arienti, C.; Pignatta, S.; Zanoni, M.; Paolillo, M.; Curti, D.; Rui, M.;Rossi, D.; et al. Sigma Receptors as Endoplasmic Reticulum Stress"Gatekeepers" and their Modulators asEmerging New Weapons in the Fight AgainstCancer.Front Pharm. 2018, 9, 711.

[20]. Villard, V.; Espallergues, J.; Keller, E.; Vamvakides, A.; Maurice, T. Anti-amnesic and neuroprotective potentialsof the mixed muscarinic receptor/sigma 1 (sigma1) ligand ANAVEX2-73, a novel aminotetrahydrofuranderivative. J. Psychopharmacol. (Oxf. Engl.)2011, 25, 1101–1117

[21]. Wolfgang G Eisert, Norbert Hauel,Joachim stangier, Wolfgang wienen, Andreas Clemens, Joanne Van ryn, Dabigatran :an oral novel potent reversible nonpeptide inhibitors of thrombine DVT : A New Era in Anticoagulant Therapy.

[22]. K M Huttunen, H. Raunio, J.Rautio. Prodrugs from serendipity to rational design. Pharmacol Rev. 2011; 63: 750-771.