

# [Antimitotic prodrugs advantages and disadvantages](https://assignbuster.com/antimitotic-prodrugs-advantages-and-disadvantages/)

## Abstract

The intricate prodrug therapy has made possible the synthesis and identification of novel drug discovery that have significant structural modifications or intermediate derivatives which may facilitated and enhanced therapeutic parameter during in vitro and in vivo studies. Along with improved target delivery of prodrugs provides the capability to not only overcome certain limitation of antimitotic drugs, but to increases the chances to undergo clinical phase trial studies to get in to action. Development of these new prodrugs as improved alternatives gone through from significant challenges; nevertheless these potential therapies also use to analysed and give suggestion about their further development by clinical studies.

## Introduction

Cancer is diseases in which the body’s cells become abnormal and split without control. Cancer cells may show aggression nearby tissues. They may spread through the bloodstream and lymphatic system to other parts of the body. [1, 2, 3]. Now the days there are mainly three types of treatments are in use surgery, radiation and chemotherapy. Among these, surgery and radiotherapy are to be employed for specific treating are and chemotherapy employed during the systemic treatment of metastases in local as well as regional cancer cells. Chemotherapeutic drugs can be divided in to alkylating agents, antimetabolites plant alkaloids (antimitotics), topoisomerase inhibitors, and other antitumor agents. All of these drugs affect the cell division or DNA synthesis and translation, and function in other ways. The proliferation rate is the play the key role in for the effects of these drugs thus; they are not much selective of tumours. Chemotherapy is treatment with drugs that kill cancer cells and make them less active. It is the treatment of disease by chemicals, especially by killing micro-organisms or cancerous cells. In popular usage, it refers to antineoplastic drugs used to treat cancer or the combination of these drugs into cytotoxic standardized treatment regimen. In its non-oncological use, the term may also refer to antibiotics, long time use of chemotherapy consequences natural cell deaths in the treatments of tumour [4]. Sometime these agents produce remission and re-growth which result in proliferation of cancer cells along with resistance of drugs. Although, intense researches have been conducted in the field of cancer, there are some pioneering ideas need to come in this field to decrease toxicities, physicochemical properties and therapeutic index [5].

The use of prodrug is generally established as a strategy to improve the physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically potent agents, and thereby increase the develop ability and usefulness of a potential drug [6, 7]. The aim of the prodrug establishment is to improve (i) physicochemical properties like solubility, chemical stability, taste and odour etc. (ii) selectivity; (iii) pharmacokinetic and pharmacodynamic problems and (iv) therapeutic index. Thus; by these improvements, we can overcome the formulation’s challenges of the drugs [8, 9].

The most of the antimitotic prodrugs developed with conjugating prodrug molecules to low to high molecular weight molecules like sugars, enzymes, vitamins, antibodies, polymers and nanoparticals. These are the carriers which transport prodrug in to tumour and drug release with conjugating the drug to the carrier through a spacer that include particular point which make the specific targeting of the drug. These carriers are very complicated in the structure and demand very hard work to make carries linked prodrugs. Hetrogenecity, biodistribution, expression of multidrug resistance, interstitial pressure and amount of the drug reaching to the target site, are the problems which make the task more difficult. Along with that targeting properties will preserved or not with structural changes are major problems in the formulation of carrier liked prodrug molecules.

Here I provide an overview of recent developments in targeted antimitotic prodrug and conjugate design. These are examples which, illustrating the salient features of different targeting strategies. I have focused on prodrug and conjugate examples in

priclinical trials or advanced preclinical studies with advantages and disadvantages associated to each strategy are also discussed.

## Antimitotics

In the process of mitosis eukaryotic cell isolate the chromosome in its cell nucleus into two the same sets which are divided in two nuclei. In cancer the single cell start converts from normal cell to cancerous cells by the process of mitosis. The mitosis inhibitors contain certain different cancer drugs. They are different in mechanism of action from the other classes of cancer drugs [12]. They mainly interfere with cell proliferation of cell rather than alter DNA structure and function. Mitosis includes DNA replication which divides the cells in to two new cells. Spindle fibers separate newly replicates chromosomes and convert them in to two forming cells. The fibres which are produce microtubules which fix with the replicated chromosomes. Now chromosomes pull one of this copy to each side of the cell which includes spindle fibers, without that cell cannot divide. Antimitotics inhibit this earlier uncertain spindle function during cell cycle. Spindle fibers form of long chains of smaller subunit of tubuline protein. In the process of polymerisation tubuline subunits can add to microtubule. Some types of antimitotics stop the process of forming of tubuline monomers which inhibits the microtubule. In this process they arrest movement of chromosomes as well as spindle tubule [13].

Examples of mitotic inhibitors include Taxanes, paclitaxel (Taxol) and docetaxel (Taxotere), Epothilones like ixabepilone (Ixempra), and Vinca alkaloids: vinblastine (Velban), vincristine (Oncovin), and vinorelbine (Navelbine), estramustine (Emcyt) and Colchicines.

Vinca alkaloids and colchicines are those who have more over same mechanism of action. Vinblastine inhibiting the formation spindle fibers which are responsible for position of chromosome and the separation of the chromosomes during anaphase. It also inhibits the formation of microtubules which are responsible for the formation of cell division. Vinca alkaloids have many side effects like others [14]. Vincristine also binds to the tubuline monomers and arrests the formation of spindle microtubules. As result of this, it blocks the movements of chromosome during cell division. Speficity is the major problem with vincristine because it also affects the healthy cells with cancer cells during cell division. Vindesine is another Vinca alkaloid who binds to the microtubules. It has target specificity problem which makes them less potent [15]. Texel is natural antimitotic drug and different in mechanism of action from Vinca alkaloids. Paclitaxal and docetaxel are the two important analogues. Paclitaxel inhibits microtubuline assembly rather than monomers. It binds to microtubules and prevent this breakdown because these two processes, polymerisation and breakdown, both are requiring for movement of replicated chromosomes. The prevention of chromosome’s breakdown inhibits them to move to opposite direction of dividing cells. Reduction in bone marrow function which may result in anaemia, blood in stools or black stools, fast or irregular heart beat, are common side effects associated with paclitaxel [16]. Docetaxel has same mechanism of action as paclitaxel but if the drug is give with combination it will cause major side effects than paclitaxel [17]. Epothilones is microtubule function inhibitor. It binds to beta-tubuline subunit on microtubules and preventing polymerization during cell division and eventually causes cell death. Mainly peripheral neuropathy, mylosuppersion with white blood cells and hypersensitivity reactions are the side effects which cause by Epothilones [18]. Colchicines are antimitotics which have same mechanism of action as Vinca alkaloids. It also binds to tubuline and inhibits polymerization of microtubules. Tubuline availability is necessary for mitosis process and colchicines are inhibiting these tubules as spindle poison. Cancer cell have nature to proliferate most and this make them more susceptible to Colchicines drugs [19].

These are natural anitimitotics and their analogues. Their mechanism of action is mainly on tubuline and sometime called antitubuline agents. But they have their own challenges like insolubility, bioavability, pharmacokinetic and pharmacodynemics, and toxicities problems. Tubuline plays a key role in their effects to bind mitosis but to overcome these challenges, proteins which are involve in the mitosis, are founded. They are presently under process to develop the capacity of clinical efficacy that those drugs have established [20].

## Present scenario in antimitotics drug development (Specific druggable protein targets)

The targeted proteins with specific function of new generation of anti mitotics are identified with molecularly targeted drug discovery. These new agents play important role in the unique way to provide the significant effects, which take beyond the certain limitations of drugs as well as extend the scope of their clinical efficacy of current antitubuline drugs. Although, they are facing some considerable challenges, but molecular mechanism of action of mitotic-checkpoint plays important role in mitosis [21]. Antitubuline drugs have complex chemical structure and are complicated to isolate and synthesised from their natural sources. Neurotoxicity and insolubities are the major problems with Vinca alkaloids and Taxanes. They also interfere in function of microtubules in axons, which provoke the neuronal vesicle motility. The non-structural components of mitosis as potential drug targets are one of the solution for therapy. They have unique effects in morphological stages during the mitosis which is bring mitotic Kinesins, Aurora kinases and polo-like kinases (PLKs), as druggable protein target classes [22]. Targeting these proteins is well known as mitotics kinesin, kinesin spindle protein (KSP) are requires for the proliferation from prophase to prometaphase and Centromeric protein E (CENPE) is required during prometaphase to metaphase and also have effects in mitotic checkpoint [23, 24].

These protein targets are only finds in dividing cells so non-dividing cells are not effected. This showed that, this kind of target inhibition have potential and improved therapeutic index compare to tubuline target anti mitotic drugs. Although, proteins inhibitors might not enough effects on both the mitotic spindle and cytoskeleton but they have some significant role out side the mitosis. Moreover, to support these new agents, the role played by them in the mitosis, cause target inhibition to be connected with tumour growth inhibition. By the using pharmacodynemic marker, significant effective dose during drug development founded. These doses were affected instead of maximally tolerated dose, might also caused improved therapeutics index. The mechanism of action of these agents by which they inhibits tumour cells undergo cell death was not properly defined but they have many positive effects on these proteins. Activation of caspace 3 (significant effectors) has been identified in studies of protein target drugs, along with that mitotic catastrophe has also been founded [25, 26, 27]. Actually, catastrophe is cell death occurs from metaphase of mitosis against the drugs that produce DNA damage because of in this stage the caspace 2 is involved rather than caspase 3 which produces many morphological and therapeutic aspects of cell death. On the other hand, mitotic check point as effectors of cell death against protein inhibitors was contentious. It was suggested that KSP inhibitors needed mitotic checkpoint. In contrast to that, role of checkpoint studies involved that; this signalling might cause cell death with mitotic damage [28, 29, 30]. This mechanism might supported by Aurora B inhibitors [31]. Eventually, the mechanism of action of these new protein inhibitors became more understandable that, they are more involved in killing cell by unique mechanism but also, different genetic alterations, which may produce during cancer, play the important role during inhibition by these agents. Although, this studies is unfinished so it’s hard to get these new agent in action because they needed further more researches.

KSP Inhibitors:

Ispinesib was first KSP inhibitor and studied in clinic to check the therapeutic effects. Small molecules of KSP ATPase were targeting by this drug but it was not involved in effecting ATP and ADP. In terms of specificity, it was 40, 000 times more selective as compare to other kinesins. Firstly it was studied intravenously and results founded that during different number of days, the cumulative dose delivery was same and dose limiting toxicity on both occasion was neutropenia as well as haematopoietic lineages, along with that nausea, vomiting and diarrhoea also observed. Raise in the dose also increases the amounts of phosphor-histones-H3 in tumour which involved inhibition of proliferation of tumour cells with dose. As consequence, the pharmacodynamic activities also increased. In earlier, the renal cell, hepatocellular and colorectal cancers are not responding to anti tubuline agents, but this KSP inhibitor extend the time duration of stability for more than 6 months. This agent also needed following treatments of natural anti tubuline agents [32].

The next KSP ATPase inhibitor is same to Ispinesib, and during clinical evaluation it came from the chemical synthesis [33]. It has more efficacious than first one. During the studies it is connected with dose limiting toxicities that is neutropenia and hyperbilirubinaemia [34, 35]. For cholangiocarcinoma, it gives some positive effect and two more cancers extend as stable diseases for more than six months.

Third potent KSP inhibitor is MK-0731. It is more selective about more than 20, 000 fold and associated with increased activity of hepatic transaminases and neutropenia [36].

Finally, clinical experience of KSP inhibitors showed that these agents associated with common dose limiting toxicities like neutropenia, increased activity of hepatic transaminases which are also observed with tubulin inhibitors. Although, some of toxicities like alopecia, mucositis and neuropathy, are not often seen. Nausea and vomiting have seen uncommonly with these protein targeting inhibitors.

AURORA and PLK inhibitors

One of the potent drug called as VX-680 also know as MK0457 as ATP competitive inhibits Aurora A, B and C to inhibit the cell differentiation in cell culture [37]. It’s mechanism of action is to inhibit the FMS-related tyrosine kinase 3 and imatinib-resistant mutants forms of Abelson tyrosine (ABL) kinase. Imatinib and dasatinib are the resistant to those agents. During the studies, cancer cell from different patients, were tested against intravenous infusions. As results, neutropenia was mostly observed dose limiting toxicity and when the dose increased the some pharmacodynemic effects in skin was also observed. To evaluate that, phospho-histone-H3, Ki67 (antigen) and cycline B1 expressions are being checked before and after these studies. In the skin biopsies, there was no strong evidence observed, which showed the mitotic arrest or decrease in cell proliferation in the skin, during clinical studies. There was strong proof about the effects on cell proliferation which are haematopoietic, but it was not case with skin biopsies. Mitotic inhibition, aneuploidy, was expected from the pan-Aurora but only delay in the mitotic progression observed during studies. Moreover, these agents inhibit the Aurora B and decrease the PHH3 levels when other anti-mitotic agent increases this biomarker. To overcome this limitation, the assays procedures developed which are capable to find out the decrease in the level of PHH3. Skin was not responding to these drugs. Extended stable disease for more than 6 months observed [21].

Another ATP-competitive Aurora B inhibitor is AZD1152 with significant IC50 cellular proliferation. This inhibitor evaluated in two schedules. In the both schedules, neutropenia observed as dose limiting toxicity for intravenous infusion. Moreover, next assessments reached in phase I and II studies for cancer like leukaemia [38].

BI 2536 is first ATP-competitive inhibitor of PLK1. There were three different partitions to evaluate this small molecule inhibitor. Every partition was evaluated by intravenous infusion and as result of that, same toxicity and dose delivery were obtained. Thrombocytopenia and neitropaenia were major dose limiting toxicities in every partition [39].

The second ATP non-competitive inhibitor of PLK1 is ON 01910. It may support PLK, to bind the substrates. It is currently under trail for two different doses because it has low potency to FLT1 and platelet derived growth factor receptor (PDGFR). Increased activity of hepatic enzymes, anaemia, leucopoenia and gastrointestinal symptoms, are the adverse effects with this inhibitor [40].

All over, neutropaenia without significant neuropathy was major dose limiting toxicity with these inhibitors.

Challenges and Developments in New Antimtotic Drugs

Although, these novel antimitotic drugs have very significant role in inhibition of mitosis, they are facing many problems during their developments. Their appropriate ways, potential to reduce toxicities, activities, safety profile, and efficacy are some promising questions are yet to be solved. These agents have reduced risk of neurotoxicity, which is proved in clinic, but they also have dose limiting toxicities like neutropenia with relative sparing of the other haematopoietic lineages. So it will be difficult to tell yet that they have potential [41].

Another challenge was that, there was no clear perceptive between inhibition of respective mitotic target and cell death. Because they have mechanism of action is to arrest mitosis but whether this mitosis arrest initiate by activating by mitotic checkpoint or it is followed by mitotic slippage for further cell death. To identify the patients who are best responding to these agents is also a challenge in developments in theses agents. In addition to that, during clinical development, it is difficult to develop surrogate tissue to check the pharmacodynemic responses of these drugs because targets of these agent, was absent in most of them [42].

Along with pharmacodynemic effects, duration of such effect both is also crucial determinants for apoptosis. Therapeutic window can be calculated by evaluation of tumour markers at maximum tolerated dose (MTD) or below the MTD if possible but this might be achieved by incorporation of serial tumour biopsies was uniquely challenging. In addition to, which schedules would be sufficiently discover pharmacodynemic and pharmacokinetic data was difficult [43].

Considerable steps have already come in to view, to overcome these limitations and evade toxic side effects, produced by these agents. Such steps make two different types of practices; they are prodrugs and drug targeting methods. During these practices both methods led to increase some of biochemical properties along with pharmacokinetic and pharmacodynemic effects.

## Prodrug

Prodrugs are chemically modified versions of pharmacologically active agents that must undergo transformation in vivo to release the active drug. The prodrug is administered in an inactive or significantly less active form. The use of prodrugs is generally established as a strategy to improve the physicochemical, biopharma-ceutical or pharmacokinetic properties of pharmacologically potent agents, and thereby increase the develop ability and usefulness of a potential drug [6].

## Antimitotic Prodrugs which are in Use or Developing

The following are the antimitotic prodrugs which try to develop to overcome these limitation associated with specific antimitotic drugs like Vinca alkaloids, Texans, Cochicines and phodopyllotoxins.

A) Hydrolytically Activated Paclitaxel Prodrug

Paclitaxel is well using in diseases like ovarian cancer, breast cancer and lung cancer but it has limitation like low water solubility, less effective, drug resistance and some effects. At high dose it produces hypersensitive reactions, hematologic toxicity, and neurotoxicity. It also limited by granulocyte colony-stimulating factors dependent neutropenia. It has dose dependent neurotoxicity expressed by loss of sensation [44].

## Adapt from [44]

By masking position7 hydroxyl group of paclitaxel with hydrophilic side chain (\*) and resulted 7-(2″, 3″-dihydroxypropyl carbonoxy) – paclitaxel is biologically inert and is activated at low pH conditions by hydrolytic cleavage of the carbamate linkage, obtaining active paclitaxel, dihydroxy propanol, and CO2 [44].

Following are the results obtained by analysing paclitaxel prodrug.

Figure, (A) Figure, (B)

## Table 1, Figure A and Figure B, Adapt from [44].

Table 1 is hydrolytic activation of paclitaxel prodrug in vivo, indicating decrease in prodrug and increase in active drug. Figure (A), for conversion to active paclitaxel in vivo, indicating peak plasma concentrations were observed at 3 hours for paclitaxel prodrug (P1) and at 6 hours for active paclitaxel (P2), for 1 patient. Figure (B), for activation of paclitaxel in vivo, demonstrates the slow-release mechanism in vivo, for 5 pateints [44].

B) First enzymatically activated Taxotere Prodrugs

Designed for ADEPT (Antibody Directed Enzyme Prodrug Therapy) and PMT (Prodrug Mono Therapy)

Paclitaxel and its semi synthetic analogue docetaxel is essential drugs in the treatment of cancer as antimitotic drugs. There is slight difference between them is substitution at 3′- nitrogen on the side chain and the 10-posititon of the taxoid core. They have high potency to solid tumour but they have number of undesirable side effects and poorer water solubility and also with detergent they initiate hypersensitivity reaction on body. These drug’s delivery have evaluated on enzymatic hydrolysis in ADEPT (Antibody Directed Enzyme Prodrug Therapy) and PMT (Prodrug Mono Therapy). The two docetaxel prodrugs in figure A have synthesised with glucuronic moiety is linked to a double spacer. Para hydroxyl bezyle alcohol connected to diamer tether through a carbamate linkage in this spacer. This complex was shown to be more potent and labrets drugs in the presence of Î²-Dglucuronidase enzyme in ADPET and PMT therapy [45].

Figure A, structure of scheme 2 and scheme 3 (Prodrug 4), scheme 2 and scheme 4 (Prodrug 5) and Prodrug 3

## Adapt from [45]

Following are the results by the comparison of these two drugs.

Both of prodrugs have 24 hr-run of stability and there was no release from the prodrug during this time. Table 1 showed that these two prodrugs have compatible IC 50 values for the ADEPT and PMT strategy. Figure A and figure B showed that, during HPLC detection, prodrug level decreased until finished and spacer and parent drug, docetaxel, reached at area of stability [45].

Table 1, measured for L1210 cell lines were (HPLC):

Prodrug, Scheme 2 and scheme 3 : 4. 86 uM

Docetaxel : 14. 4 uM

Spacer: 75. 3uM

Prodrug, Scheme 2 and scheme 4: 2. 69 uM

Spacer: 45. 8uM

Figure A, Comparison of the disappearance of the three prodrugs.

Figure B, Enzymatic cleavage of prodrug 5 Figure 2, Scheme 2 and Scheme 4.

## Table 1, Figure A and Figure B adapt from [45].

C) Zyn-Linked colchicines: Controlled-release lipophilic prodrugs

With enhanced antitumor efficacy

Zyn-linked drug have rapid binding property to cell membrane. These Zyn-linkers prolong their binding and preservation in tissues, make sense to produce Zyn-linkers conjugates those who have better local delivery of therapeutics. Colchicine has chosen for these studies because this drug and its analogues are still under examination. Five Zyn linked colchicine analogues with either cleavable hydrazone or imine bonds, have synthesised and evaluated their stability , cytotoxicity and antitumour activity [46].

Fig. 1. Structures of colchicine and modifications to form the analogues for Zyn-Linking are shown.

Fig. 2. Structures of the Zyn-Linkers modified for attachment of

the colchicine analogues.

Fig. 3. Structures of Zyn-Linker conjugates are shown with the bonds subject to hydrolysis indicated by an arrow: (a) hydrazones conjugates linked at the B-ring of the colchincine moiety, (b) imine conjugate, and (c) hydrazones conjugate linked at the A ring of the colchicine moiety.

## Figure 1, 2 and 3, adapt from [46]

Following are the results for their relationship among different properties.

## Table 1

Table2

Table3

## Table 1, 2 and 3, adapt from [46]

Table 1 showed that, ZYN 162 and PKH 158 at pH 7. 2, are two potential products and out of them one is expected and one is unidentified products. Table 2 showed that, 80% to less than 1%, was range of therapeutic and unhydrolysed conjugated, was inactive. Zyn-linkers had no antimitotic activity; on the other hand, drug or Zyn-linked drugs were active. Table 3 showed that, with 4-formayl group thiocolchicine have reduced their toxicities and enhanced therapeutic activity [46].

D) Preparation, characterization, cytotoxicity and pharmacokinetics

Of liposome containing water-soluble prodrugs of paclitaxel

Paclitaxel have antimitotic effect against the various cancers like breast cancer, ovarian cancer, head and neck cancers. Due to its aqueous insolubility, it was dissolving in the mixture of 50 % Ethanol and 50 % Cremopher EL (caster oil). Neurotoxicity and hypersensitivity are side effects of this Cremopher. So to reduce this side effect and to enhance the drug entrapment in liposome with better aqueous solubility, three prodrugs and prodrugs liposome formulations have synthesised and evaluated their pharmacokinetic parameter, stability and antitumor activity with parent drug [47].

Following are the results obtained during comparison in stability, cytitoxicity and pharmacokinetic property of drug, prodrugs and their prodrug liposome.

1) Stability

## Table1

## Table 2

## Figure 1, 2 and 3, Table 1 and 2, adapt from [47]

Figure 2 and 3 showed that, by the changing the property like diameter, membrane fluidity and charge, liposome containing 2′-mPEG-paclitaxel composed of PC-PG-CHOL 9: 1: 5 showed better stability more than 2 months and good entrapment ability.

Table 1 and 2 showed that, in vitro cytotoxic effects of liposome containing compound 3 and 4 on two cell line, HT-29 and MeWo, maintained, but rapidly hydrolysed and giving free parent drugs, while liposome loaded paclitaxel-2’succinyl had more resistance to hydrolysed. 2′-PEG-paclitaxel also had ability to make difference in pharmacokinetic parameters as compare to free drug [47].

D) Synthesis and evaluation of water-soluble docetaxel prodrugs-

Docetaxel esters of malic acid.

Paclitaxel and docetaxel are semi synthetic analogues widely used for various cancers. But water solubility is major limitation for these drug and to come over from this limitation, at C20, C7 -or/and C10 position several research group introduced solubilising moieties [48].

Figure A

## Figure A, table 1 and table 2, adapt from [48]

Figure A, table 1 and table 2 showed that, 20-DLmalyl docetaxel sodium salt 3a come out with excellent water solubility, more active than docetaxel in vitro and antitumor activity in vivo [48].

E) Synthesis of Water Soluble Prodrugs of the Cytotoxic Agent

Combertastatin A4

Combertastatin A4 has structure similar to colchicine. It is an inhibitor of tubulin polymerisation to stop proliferation of cells. Although, this drug has potential for antimitotic activity, it is soluble in the few pharmaceutically accepted solvents. Synthesis of water soluble glycosides of combertastatin A4, have conducted by make modification by hydroxyl function. To increase the yield, they have reversed the components of the Witting reaction [49].

## Adapt from [49]

The ammonium salt have prepared and converted into potassium salt to make crystal form. This ammonium salt was more stable in buffer solution and degraded slowly in plasma at 37 C when incubated with acid phosphates and alkaline phosphatise [49].

F) Prodrugs of 40-Demethyl-4-deoxypodophyllotoxin: Synthesis and

Evaluation of the Antitumor Activity

4-Deoxypodophyllotoxin (DPT) and 4′-demethyl-4-deoxypodophyllotoxin (DDPT) have comparable in vitro potency against different cell lines but free hydroxyl group at 4′ position in structure of DDPT loss its in vivo antitumor activity against BDF1/3LL model. Replacing this free group by bioreversible functionality might improve in vivo activity. For that series of prodrugs have synthesised and evaluated their cytotoxic and antitumor activities [50].

Following are the results obtained during studies.

## Adapt from [50].

Table showed that 10 and 11 derivatives were properly transferred in to parent drug 2 but weak in vivo activity and 6 derivative showed IR of 95% of antitumor activity. The carbamates and carbonates of two compounds, 6 and 9, showed potent antitumor activity, might be by intermolecular cyclic rearrangements of hydroxyl side chain. Moreover, amino acid prodrugs, 12 to 17, demonstrated better water solubility and potent antitumor activity [50].

## Discussion

Presently the antimitotics prodrugs are novel compounds and hold many promises and may have abilities to improve the drawbacks of anti tubuline or specific protein inhibitors, which are regulating the cell cycle, demonstrated by clinical data. With observations to clinical activity, it is too premature to tell for most of the agents in development. There are number of prodrugs have been developing and some have evaluated in laboratory. Antimitotic prodrugs may improve limitations of these drugs during in vitro and in vivo studies but there are still need more information about clinical phase trails by using number of patients, to these prodrugs.

In particular, hydrolytically activated paclitaxel prodrug has decreases toxicity in vivo and produced better responses in patients with end stage in cancer. Serum half- life also dramatically increased with maximum plasma concentration, in vivo, but more studies require about responses in phase III trails, as it was evaluated in 10 patients. Moreover, information needed about, high concentration expose to tumour tissue for critical time, as significant G2M phase arrest is primary mechanism of action.

First prodrugs of docetaxel have synthesised for the ADPET (Antibody Directed Enzyme Prodrug Therapy) and PMT (Prodrug Mono Therapy) strategies. Spacer have nitro group on the aromatic ring. In the hydrogenesis step it could be preserved which is not seen in the previous paclitaxel prodrugs. This nitro and amino groups containing prodrugs have expressed good kinetics and enzymatic hydrolysis in particular cell line, but more information needed about self immolative spacer for its effects on the paclitaxel on various cell lines. This issue need more clarification prior to clinical trails in malignancy models.

Four conjugates of Zyn-linked colchicine have hydro linkage, imine bond in spacer arms, colchicines moiet