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Vitamin Drug conjugate: a systematic review of pharmacological potential

Cancer is a chronic disease which can cause death. In traditional chemotherapy cytotoxic drugs are used to kill proliferating cancer cells. The cytotoxic agent exhibits less specificity, less biological activity, causes systemic toxicity and undesirable side effects. Each year, about 1.8 million of the population are infected and die due to tuberculosis infection. An increase of drug resistance during the tuberculosis treatment is a significant concern. So, it is necessary to develop a new approach or therapies to resolve drug resistance, drug selectivity in tuberculosis infection and the reduction of the side effects of cytotoxic agents and anti-tubercular drugs. This review describes the newly emerging concept of «vitamin drug conjugate». Vitamin-drug conjugate is a specifically carried drug toward the target site, is one of the promising ways to treat chronic diseases like cancer and tuberculosis and enhance the therapeutic outcome. The purpose of this review is to explore vitamin as a targeting moiety for new anticancer and anti-tubercular drug to overcome challenges, such as non-selectivity, systemic toxicity and multidrug resistance. This approach is beneficial in the treatment of life-threatening disease like cancer, tuberculosis and also in many viral infections.

Keywords: Cancer, Tuberculosis, Vitamin-Drug conjugate, Vitamin B12 conjugate, Folic acid conjugate, Biotin conjugate, Vitamin-E conjugate, Lipid drug conjugate.

Content

List of abbreviations

WHO: World Health Organization
FRA: Folate Receptor Alpha
B_{12}-Co-III-CN-M: Heterodinuclear derivative
MCF7: Human Breast cells
A2780: Human Ovary Cancer Cells
B12-Co-III-CN-Pt-II: Vitamin B_{12}-Platinum conjugate
N_4PY: Pentadentate Nitrogen ligand
N_4PY-S-S-FA: Redox sensitive cleavable linker
FRP: Folate Receptor Positive
AG: Arabinogalactan
FR-AG-GFCG-MTX: Folate receptor Arabinogalactan endosomal cleavable peptide of methotrexate
MTX: Methotrexate
GFLG: Endosomal cleavable peptide
PLGA-PEG-FOL: Polylactideco-glycolide-polyethylene glycol-folate
$SKOV_3$: Folate receptor positive malignant cells
PEG: Polyethylene glycol

PA-PEG-DSPE: Lipopolymer
mPEG-DTP-DSPE: Lipopolymer
FA: Folic acid
PLGA: Polylactic –Co-glycolic acid
FU: 5-Fluorouracil
GG-NP: Guar gum loaded nanoparticles
MTX-FR-GGNP: Guar gum loaded methotrexate folic acid conjugated NP's
G_5-MTX: Pentadentate dendrimer-MTX adduct
5BT-1214: New generation taxoid
TPG5: α-Tocophenyl polyethylene glycol succinate
ɤ-T_3-Tocotrienol
CoQ_{10}: Ubiquinol
$CoQ_{10}H_2$-PEG5000-Vit E: Ubiquinol-Polyethylene glycol-Vit- E Conjugate
SiRNA: Small interfering RNA
RNAi: RNA interference
TPGS: α-Tocopheryl polyethylene glycol succinate
Aa-Su-Saq: Ascorbyl succinic-Saquinavir conjugate
CYP3A4: Cytochrome P_{450} metabolizing enzyme
MTX-PGA: Methotrexate-poly(glycerol adipate)
ATRA-g-PBEA: Docetaxel loaded trans-retinoic acid with poly-β-amino ester
HPMA: N-(2-Hydroxypropyl) methyl acrylamide
MA-Gly-Gly-NHN-Dex: Dexamethasone containing monomer

Review Plan

Inclusion and Exclusion Criteria: The present review is focused on vitamin drug conjugate, its synthetic methodology and its pharmacological screening.

The review data are based on the publication of the last 15 years and in English. Only articles in the relevant area were searched and analyzed from the sources like Scopus, Web of Science along with other online scientific search engines. The keywords used for the search were, 'Vitamin Drug Conjugate', 'anticancer activity, 'anti-tubercular activity', 'pharmacological screening', etc. The resultant data are described in this article. No statistical methods were used in this review.

Introduction

Cancer is an abnormal growth of the cells which tends to proliferate in an uncontrolled way and in some cases to metastasize [1]. There are many methods treating cancer, the most commonly applied one is chemotherapy, but the problem associated with that is non-selectivity in treatment. Severe, often life-threatening, side effects arise in cytotoxic chemotherapy because of the toxicity to susceptible normal cells as the treatment is not selective for tumor cells [2]. In the case of traditional chemotherapy, the most challenging step is to deliver a cytotoxic agent which kills proliferating cancer cells. [3]. The limitation of the used cytotoxic agents, such as doxorubicin, cisplatin, paclitaxel etc., is that these drugs cannot differentiate between tumor cells and normal healthy cells. In other words, non-specificity leads to systemic toxicity causing undesirable adverse effects like hair fall, kidney damage, lung and bone marrow [4, 5]. Thereby it is challenging to deliver the anticancer drug to the tumor site. Thus, by this reason there is a need in urgent requirement to develop a targeted drug delivery system for the selective action of drugs toward the growing cancerous cells with minimum side effects. [5]. It is expected that marked medicines specifically taken up by target cells, can significantly improve the effectiveness of cancer therapy. In recent years, drugs containing different targeting ligands like polysaccharides, folate and peptides are tested to increase antitumor activity [6–10].

In order to eliminate such toxicities the methods have been developed under which the therapeutic agent is targeted by conjugation to a tumor-cell-specific small-molecule linker, thereby minimizing exposure to healthy cells and related side toxicity [11]. Delivering of the therapeutic agent with no affinity for normal cells but a strong affinity for abnormal cells with a targeting ligand is the best approach to improve safety and effectiveness of the drug. There are many advantages of targeted medications over their non-targeted equivalents. Besides, the targeted drugs can specifically distribute their medicinal payloads into the cancer cell, thus preventing non-specific absorption and related normal cell toxicity [12, 13]. In order to achieve effective tumor-targeting drug delivery, it should consists of tumor recognizing moiety and chemotherapeutic

agent which directly connected through a linker. As a result conjugate acting 'prodrug' is formed which upon incorporated in cancer cell readily undergoes to splitting and regenerate the activity of cytotoxic agent [14].

All living cells need vitamins for survival and whereas the main physiological characteristic of cancer cell is an increased appetite for crucial vitamins because of their fast growth [15, 16]. Thus, the receptor involved for the absorption of vitamins will be overexpressed on the surface of cancer cells. Crucial vitamins like Folic acid, biotin, Vitamin B12, and riboflavin are required for tumors rapid growth. One of the approaches is to combine the drugs with vitamins that detect tumor-associated antigens, which raise the sensitivity of cancerous cells to ligand-targeted therapeutics and decrease the exposure of healthy cells to drugs [2]. Recently, it is observed that the folate receptors are more overexpressed in the cancer cells in comparision to normal healthy cells. So, it is accepted that folate receptors may act as excellent biomarkers [16–20]. Folate receptor alpha (FRA) is overexpressed on the surface of multiple types of tumors, including cancer of the pancreas, liver, breast and ovary. Folate can bound to anticancer drugs. The best approach is targeting the FRA-positive tumor cells with several therapeutic probes using folic acid conjugates. Folate conjugates can achieve cancer-specific drug delivery with minimal toxicity [21–23]. Biotin acts as a growth promoter especially in the tumor, as compared to normal cells. Recently it has been reported that biotin receptors are also more overexpressed in the cancer cells like breast, lung, renal, ovarian in contrast to folate as well as vit. B12 receptors [15, 16]. Combination of the anticancer drug with any particular vitamin gives vitamin-anticancer drug conjugate. Conjugation of anticancer agents with vitamin, has proven a novel prodrug approach, improving specificity with minimum side effects. The conjugation scaffold can improve potency as well as bioavailability of cytotoxic agents. The vitamin drug conjugate provides a high dose of a cytotoxic drug to the targeted cancer cell, so the essential vitamins like biotin, vitamin B12, folic acid, riboflavin may act as targeting moiety towards cancer cells. Most commonly, vitamin B12 and folic acid suggested as a targeting agent to tumor cell. Vitamin drug conjugate like folic acid -drug conjugate, Vit.B12–drug conjugate, biotin -drug conjugate and Vit.E–drug conjugate, as well as vitamin C–drug conjugate are listed in this review.

Other than cancer, tuberculosis is also one of the chronic illness, so there is an urgent need to find an effective treatment against chronic tuberculosis infection. Mycobacterium tuberculosis is the pathogen agent causing the infectious disease tuberculosis. Tuberculosis is one of the terrible human diseases which infects about 9 million of the population, including 1.5 million deaths in 2013 as per the WHO survey [24]. Drugs used for the treatment of TB are categorized into two groups; first-line drug and second-line drugs. The most commonly used first-line drugs for the treatment of tuberculosis are Isoniazid, Rifampicin, Ethambutol and pyrazinamide [25]. These drugs develop multidrug resistance because of the lengthy period of treatment, mostly 12–18 months or more [26]. Thereby there is a need of searching for a new anti-tubercular agent or other supportive therapy [27]. Vitamins also play a crucial role to prevent the spread of this chronic illness. Any bacteria like mycobacterium tuberculosis needs essential vitamins like biotin, thiamin to fulfil their requirement and to initiate their infection. Vitamin C, for instance, has antimycobacterial property. Vitamins act as a promising agent to change life cycle as well as the biology of mycobacterium tuberculosis and helps to stop the spread of infection [27]. Lipid drug conjugate improving the bioavailability of the anti-tubercular drug by incorporation of short lipid chain is discussed in this review. Limitations associated with the anti-tubercular drugs like Isoniazid, Rifampicin, Ethambutol and pyrazinamide is liphophilicity issue resulting poor blood-brain barrier penetration. Lipid-antitubercular drug conjugate is also a new approach having potential to enhance efficacy, bioavailability, with reduction in drug resistance.

Vitamin drug conjugate is the novel term that provides selective delivery of cytotoxic agent towards cancer cells with desirable therapeutic effect. This review focuses on the requirements that must be met to achieve the necessary therapeutic efficacy with minimal side effects during the design of vitamin drug conjugate. This review also emphasises on various vitamin drug conjugate reported to date with its synthetic methodology and pharmacological evaluation. Vitamin drug conjugates like folic acid drug conjugate, vitamin B12, biotin, vitamin E, vitamin C–conjugates are listed in this review. All these conjugates were studied to find out the best fit conjugate in terms of its clinical applicability.

1 Vitamin-Drug conjugate

Vitamin-Drug conjugate is considered as a targeted drug delivery system for tumors. It generally consists of the drug connected directly or through a linker to the targeted moiety to form an active pharmacological object, i.e the 'vitamin-Drug conjugate' (Fig. 1). The benefits of vitamin drug conjugate are nontoxic and

it must be stable in circulation and do not harm to normal cells. Upon entry of this conjugate into the cancer cells, it should effectively release the anticancer drug without losing biological activity [5, 28].

Figure 1 Vitamin-drug conjugate

1.1 Vitamin B12- drug conjugate [30].

1.1.1 Vit-B_{12}-metal conjugate

The cancer cells need vitamin B12 and more cellular uptake, so it can be concluded that on conjugation with vit. B12 increases tumor selectivity and enhance therapeutic outcomes. This type of conjugate consists of an anticancer drug with tumor imaging metal-containing compound [31]. A variety of vitamin B12 metal analogues are identified to date, but some provide a promising proof of concept promoting the use of cobalamins in targeted chemotherapy and diagnosis as metal-based medicine and imaging drug carriers [31, 32]. There are number of studies on platinum and other metal-based anticancer agents, but on other hand the clinically established anticancer drug cisplatin has some disadvantages, like low bioavailability, water-solubility, lack of tumor selectivity and undesirable side effects proved. In spite of its harmfulness the platinum complex was clinically approved and accepted because of its pharmacological activity with less side effects [31, 33–34].

Platinum

Cisplatin is also platinum-based drug with anticancer activity. However there are some disadvantages of this drug, such as nephrotoxicity, neurotoxicity, phototoxicity, nausea etc. Alberto et al. developed a method to overcome the problem associated with anticancer drug cisplatin and its side effects. Conjugation of cisplatin with cobalamine (vit B12) increases tumor selectivity and enhance the clinical output [31, 35, 36]. Metal containing scaffolds is attached to the nitrogen atom to the cyano group on vit B12, producing a derivative (B12-Co-III-CN-M) where vitamin is functioning as a ligand. A further step is vitamin B12 converted to its cofactor (either methylcobalamine or adenosylcobalamin) required for reduction of Co (III) to Co (II) by removing bioactive molecule Vit.B12 Co III. CN is mixed with metal. The formed cyano metal fragment (CN-M) release directly inside the cell. This cyanocobalamine metal conjugate (Figure 2) considered as prodrug, which shows the clinical endpoint [31, 36].

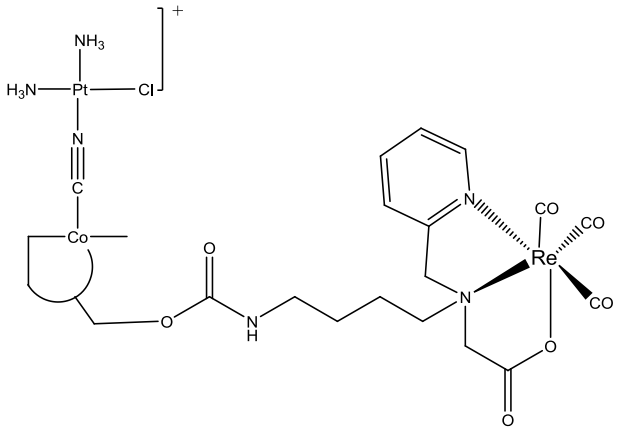


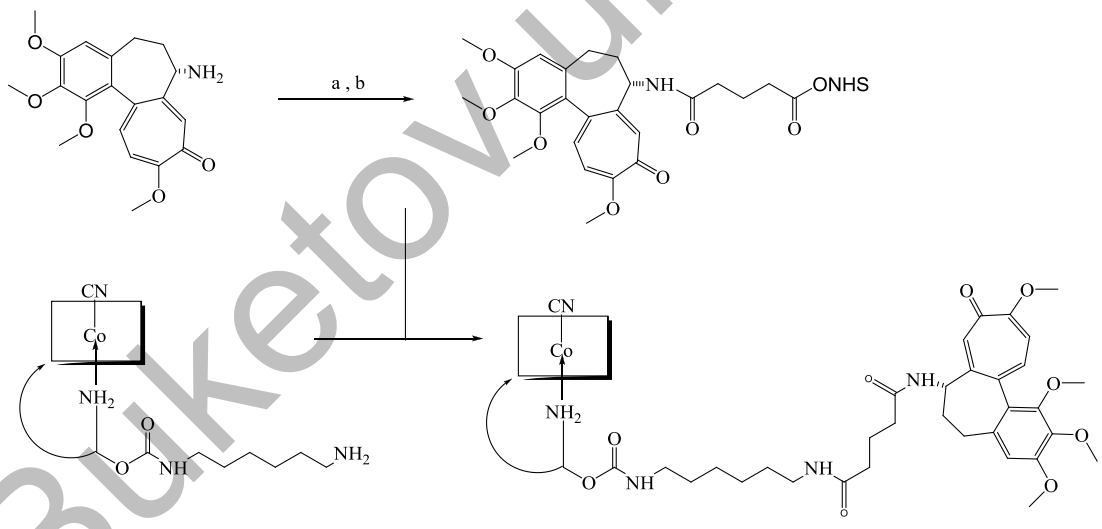
Figure 2. Vitamin B12-Platinum Conjugate

In vitro cytotoxicity experimental investigation on adenocarcinoma of human breast cells (MCF7) and adenocarcinoma of cells of human ovary(A2780) demonstrated that differentiated Pt (II-Cyano complexes exhibited antitumor action equivalent to that seen in cisplatin, suggesting that (B12-CoIII-CN-PtII) analogue should be considered as an active drug because they have an affinity to generate Pt-II containing antitumor drug quickly in the body effectively. Unfortunately, this theory was not compatible with the data that the original analogues were less carcinogenic than cisplatin [31, 37].

1.1.2 Colchicine- Cobalamins conjugate

Colchicine functions as a spindle toxin with a mode of action close to that of taxanes, and it also acts as a cytotoxic agent. Colchicine inhibits the polymerization of tubulin and prevents cancer cell proliferation at metaphase in mitosis. But colchicine has not proven effective for cancer therapy to date because of its overbearing toxic effects that cause undesirable side effects at endovenously medication [38–40]. Using the cobalamin leads to selective delivery of colchicine to tumor cells, the side effects associated with colchicine can decrease drastically [38].

Joshua et al., developed colchicine-cobalamin conjugate (Fig. 3). By substitution at the C7 position of colchicine by p-alkoxy-acetophenone and bonded with cobalamin via hydrazone, which has acid sensitive nature. Malignant cells are more likely prone to cellular absorption of this scaffold. Upon interaction of this scaffold with cancer cells occurs hydrolysis of the acid liable hydrazone linker inside the lysosome. Colchicine behaves as a powerful antineoplastic agent, helps to balance the microtubule as well as shows cellular apoptosis. This scaffold is highly stable at pH 7 and in the cellular medium, is more susceptible to hydrolysis at pH 4.5, having a half-life of 138 min. This scaffold display LC50 values in nanomolar across the variety of cancer cell such as brain, breast and melanoma in cellular medium. The increase of the drug's bioavailability by overcoming the undesirable side effects associated with tubulin can be achived by adding colchicine to cobalamin. The in vitro cytotoxicity of this bioconjugate is equivalent to that of existing chemotherapy medications such as paclitaxel and docetaxel. However, bioconjugate is highly soluble in water and considerably inexpensive than paclitaxel or docetaxel [38, 41–43].



(a) Glutaric anhydride in DMSO : (b) EDCI , NHS in DMSO (34% yield, 3 steps)

Figure 3. Synthesis of colchicine cobalamine conjugate

2 Folic acid-drug conjugate

Folic acid is one of the essential vitamins, and folate receptors act as a target for the cancer treatment [44]. The folate receptors are recently emerged as a promising theragnostic target due to their great functional flexibility in multiple solid tumors [45]. The major problem is the delivery of anticancer drug due to non-selectivity, which result in toxicity because having an inability to distinguish between cancer and normal healthy cells. This problem can be resolved by conjugating anticancer drug with folic acid. Folic acid acts as a targeting ligand to deliver many therapeutic agents towards growing tumors tissues. Folic is used as a tar-

get because it easy conjugate with therapeutic, as well as diagnostic agent and also shows a high affinity towards the folate receptor. Most important that folate receptor is limitly distributed in the normal cell, but overexpressed in cancer cells [46]. This foremost approach involves linking FA to the anticancer drug forming small molecule drug compound to get effectual clinical output. Folate conjugate attached to folate receptor by means of endocytosis process, which is overexpressed in cancer cells and attached drug shows its therapeutic output after cellular administration. [44].

2.1 Folic acid- Bleomycin conjugate

Most challenging step in cancer therapy is to deliver anticancer drug due to their non-selectivity and systemic toxicity [47]. Bleomycin acts as an anticancer antibiotic. The problem associated with bleomycin is short half-life, less clinical output and more undesirable side effect. Due to this problem, there is limited use of bleomycin as a therapeutic agent in cancer therapy [48].

Geersing et al., developed a method which shows that bleomycin imitates conjugate of folic acid (Fig. 4) where folic acid conjugate with pentadentate nitrogen ligand(N4Py) through a cleavable di-sulphide linker. This conjugate exibits promising efficacy and selective delivery of the anticancer drug in cancer cells which are overexpressed toward folate receptor. This conjugate also increases potency as well as selectivity of cytotoxic anticancer agent. A significant effect was seen by the MTS assay conducted in KB cells on N4Py-S-S-FA metabolic function after 48 h, which is enhanced after 72 hours. Pentadentate iron ligand conjugated with folic acid can induce selective apoptosis of FR (+) cancerous cells in contrast with a minimum effect observed for FR (−) cells. Enhanced efficacy is observed after a duration of 72 hrs due to the existence of a disulphide bond-containing cleavable linker moiety. These observations demonstrate the strength of therapeutics targeted by ligands, with strong potency and improved selectivity relative to compounds without targeted moiety [47, 49–51].

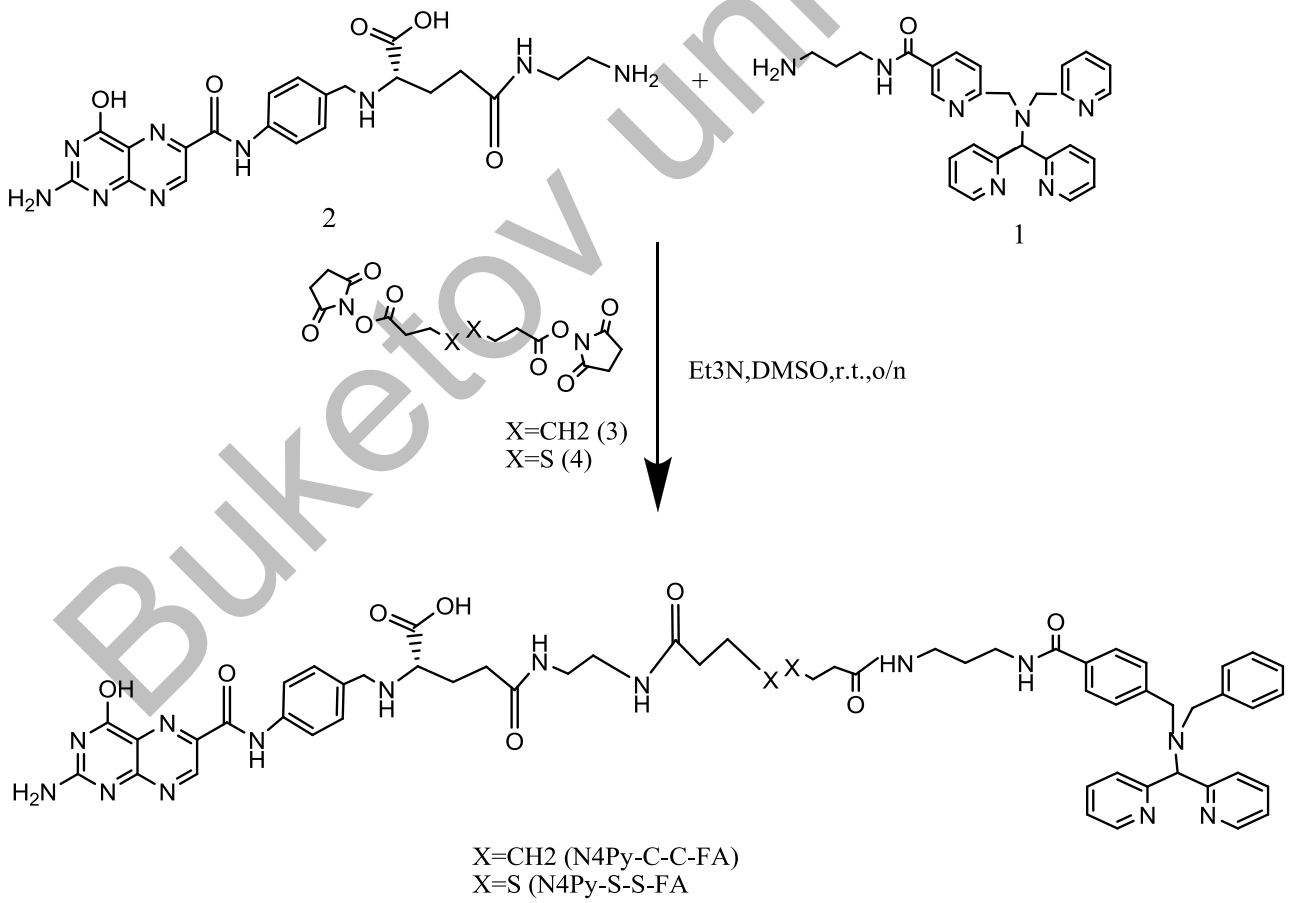


Figure 4. Synthesis of N4Py-C-C-FA and N4Py-S-S-FA

2.2 Arabinogalactan-folic acid-methotrexate conjugate

Folic acid exibits a high affinity toward the folate receptor (FR). We proposed a new selective delivery mechanism based on the naturally occurring polymer AG for anticancer drugs and characterized their ability to detect, penetrate and kill tumor cells with overexpression of folate receptor [52].

Pinhasi et al., developed a method, in this FR-AG-GFLG-MTX (Folate receptor Arabinogalactan endosomal cleavable peptide of methotrexate) (Figure5) is the conjugate which delivers a cytotoxic agent in FR overexpressing cells. In this conjugate, folic acid and methotrexate are bond to arabinogalactan (AG) via endosomal cleavable peptide (GFLG). The formed conjugate FR-AG-GFLG-MTX shows 6.3-fold increase in the cytotoxic activity. This research produces a new FA bound anticancer agent conjugate to deliver methotrexate to the overexpressed cancer cells in FR [40–42]. An important potential benefit of this drug delivery mechanism is that it exibits effective therapy for malignant cells and multidrug-resistant tumor cells [52, 55].

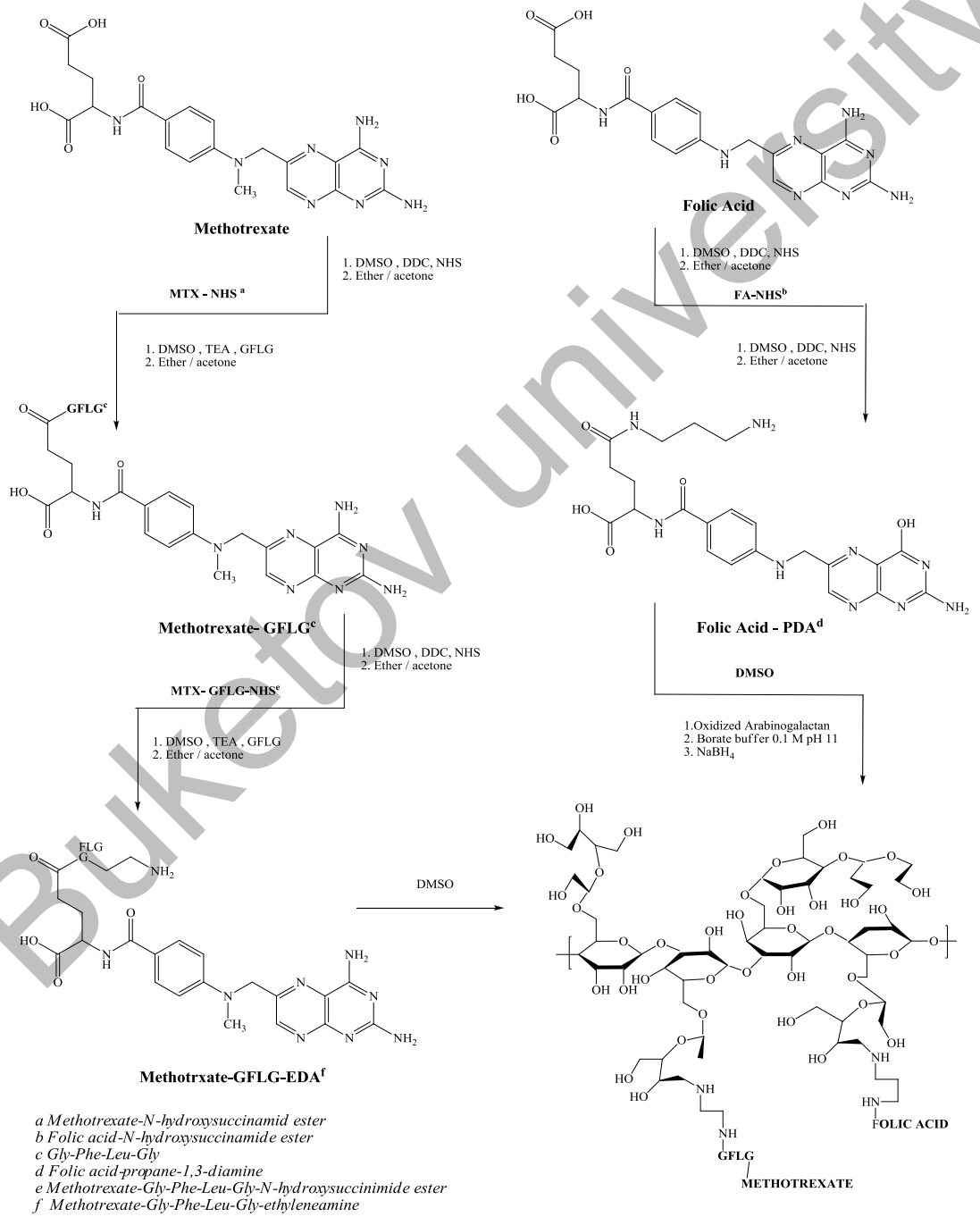


Figure 5. Synthetic scheme of FA-AG-GFLG-MTX Conjugate

2.3 Docetaxel loaded -PLGA-PEG Folate conjugated nanoparticles

Nanoparticulate formulations incorporating anticancer drugs have recently gained much interest due to their accumulation the tumor cells [56, 57]. Esmaeilli et al., reported a method, in which Docetaxel nanoparticles were developed for folate receptor-targeted cancer therapeutics using polylactideco-glycolide-polyethylene glycol-folate (PLGA-PEG-FOL) conjugate (Fig. 6). The FOL-coupled di-block co-polymer was obtained by the reaction of active Folic acid with the co-polymer of the PLGA-PEG-NH_2 di-block, where the folate ligands were supposed to be revealed on the micellar layer. The docetaxel loaded folate conjugate was formed by an emulsification process, with an overall size of 200 nm in diameter.

In contrast with the non-targeted nanoparticles, the folate targeted ones exibited a higher degree of intracellular absorption via Folate receptor-mediated endocytosis process, which plays an essential role in the absorption of nanoparticles in Folate receptor-positive malignant cells (SKOV3). These studies indicate Docetaxel loaded-folate targeted nanoparticles are a highly beneficial drug delivery system for the tumor cells that are folate receptor-positive and which contribute to increased cytotoxicity [56, 58–60].

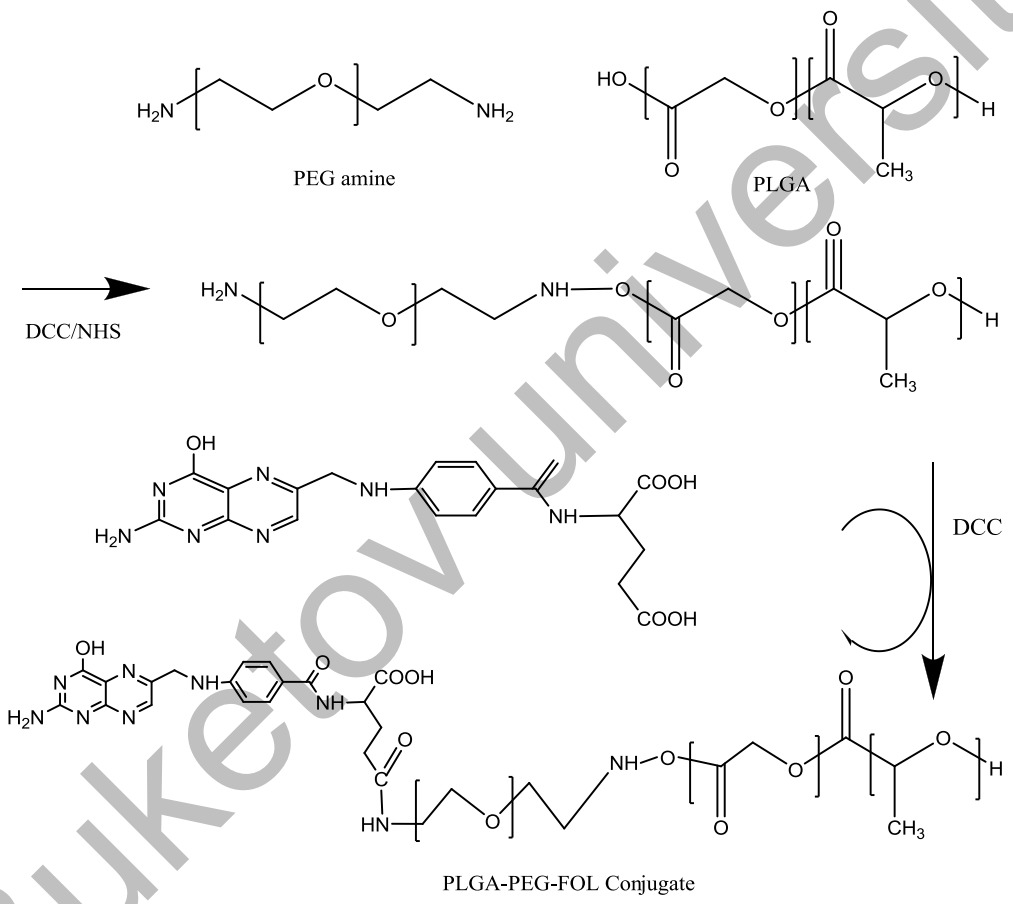
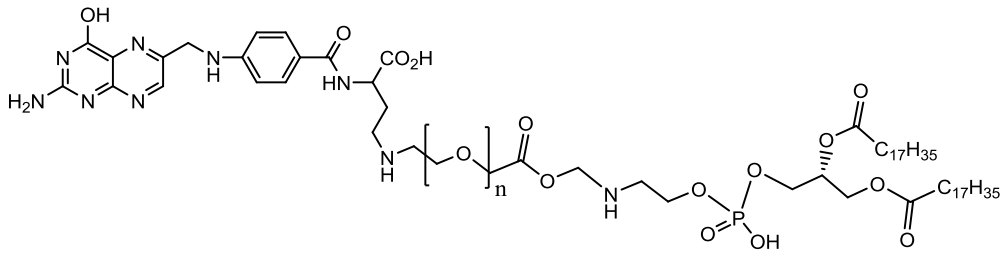


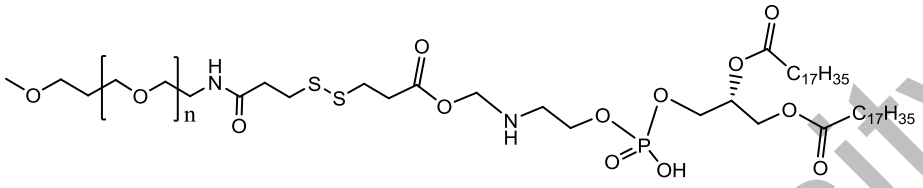
Figure 6. Synthetic scheme of PLGA-PEG-FOL conjugate

2.4 Folic acid-PEG conjugate

Folate bond polyethylene glycol (PEG) liposome are obtained for effective cancer therapy because they have an affinity to accumulate into the tumors due to increased permeability [61, 62]. Folic acid phospholipid conjugation (Fig. 7) is the best approach to transfer chemotherapeutic agent to folate receptor (FR) expressing tumor. In this case is used polyethylene glycol (PEG) liposome with folate linked to the outer end of phospholipid attached PEG molecule. It seems to be a suitable way for liposome deposition in tumor and binding of liposome to FR on cancer cells and release anticancer drug via receptor-mediated endocytosis process. [61, 63]. In vitro studies demonstrate that increase in the antitumor activity of liposomal agents occurs via folate targeting in the FR expressing malignant cells [61, 64, 65].



FA-PEG-DSPE

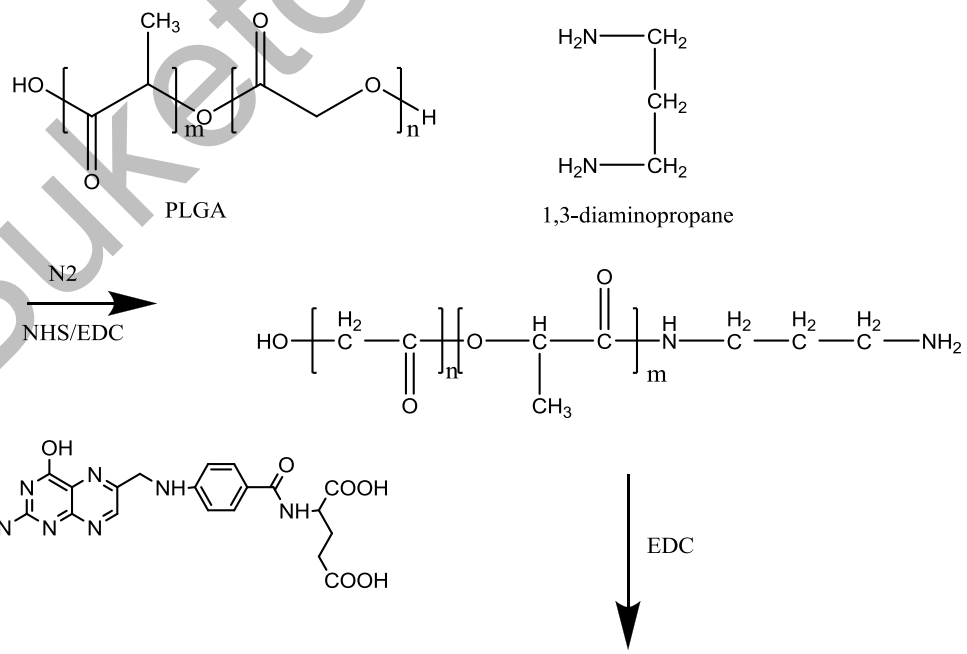


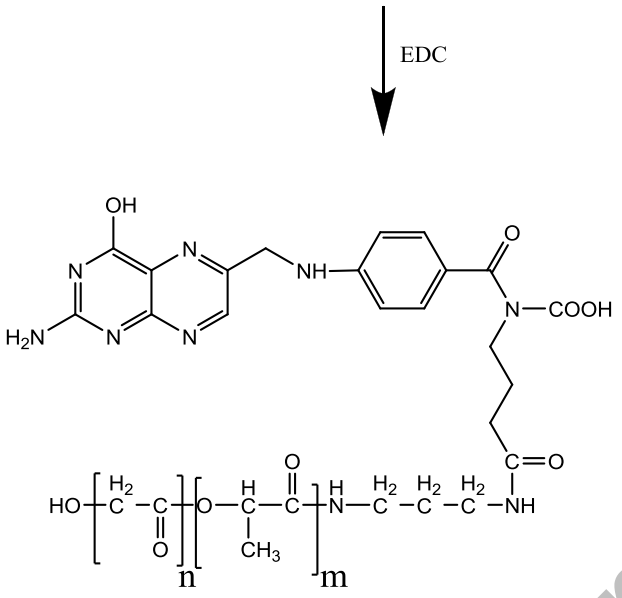
mPEG-DTP-DSPE

Figure 7. Folate-PEG Conjugate

2.5 Folic acid-5-flurouracil conjugated nanoparticles

Wanget al., developed a method in which folic acid (FA) shows the low target efficiency, low conjugation ratios at loading as a carrier in PLGA drug delivery system. They used 1,3-diaminopropane as a crosslinker in FA conjugated PLGA system to reach high conjugation ratio of 46.7 %(mol/mol). The prepared PLGA (Polylactic-co-glycolic acid) [66, 67] was used to encapsulated drug 5-flurouracil (5-HT) into nanoparticles on HT-29, cancer cells were observed to be 5–69 μg/ml in-vitro. In the experiment the value IC50 is smaller for 5-FU and 5-FU loaded PLGA nanoparticles which is 22.9 and 14.17 μg/mL, respectively. The fluorescent microscopy image showed that targeting nanoparticles have a high affinity for cancer cells and nanoparticles with FA. This is more significant amount taken up by cancer cells of HT-29 than the pure drug and untreated nanoparticles. 1,3 di-aminopropane forms a new polymer by facilitating conjugation of FA to PLGA. This FU loaded PLGA-1,3-diaminopropane folic acid nanoparticles (Fig. 8) are one of the efficient approaches to transfer the drug to tumor cells [66, 68, 69].





PLGA 1,3-diaminopropane folic acid

Figure 8. Synthetic scheme of PLGA-1,3 diaminopropane-folic acid

2.6 Guar gum loaded methotrexate-folic acid conjugated nanoparticles

Prepared nanoparticles have excellent properties for drug delivery, such as small size, including the use of biodegradable polymers, and advantages over other innovative drug delivery systems and provide protection, increased stability. Nanoparticles can easily accumulate into the tumor cells due to their small size and provide effective cancer treatment [70–72].

This nanoparticles are developed to target colon cancer. Sharma et al. developed guar gum nanoparticles (GG-NP) with methotrexate (MTX) loaded folic acid. Emulsion cross-linking methods are used to prepare the MTX charged folic acid biocompatible guar gum nanoparticles. The formed conjugate MTX-FR-GGNP shows promising release anticancer drug methotrexate to overexpressed folate receptor and treating colorectal carcinoma. This formulation has dual benefits tend to release the drug in the colon and case of carcinoma [70, 73, 74].

2.7 Methotrexate-dendrimer-folic acid conjugate

Thomas et al., demonstrated that conjugating Folic acid and methotrexate with 5th generation dendrimer [75–77] increases the therapeutic index of Methotrexate (MTX) comparing with methotrexate administered alone [75, 78, 79]. Batch to batch discrepancies in the number of methotrexate (MTX) and folic acid molecules associated with each dendrimer, mainly while scale up processing resulted in differing the therapeutic action of conjugated batches [80, 81].

The biological differences might arise from the enzymatic activity of serum esterase enzyme and result in differences in bioavailability of selected conjugate because methotrexate is bonded through an ester bond [75, 78]. In this study, they attempted a new methodology to generate specialized G5-MTXn adduct via a selective synthesis process by linking MTX to the pentavalent dendrimer using an esterase-stable amide coupling. Synthesized G5-MTX adduct bind to the folic acid receptor via pentavalent coupling that displays 4300-fold more significant activity than free MTX, it was demonstrated by the results of surface plasmon resonance linking studies. This adducts resist enzyme dihydrofolate reductase and also promote cytotoxic effect in FR-expressing KB cells lines via the FR-specific cellular interaction process and by coupling of MTX with pentavalent dendrimer, which plays a significant role as an anticancer agent and also a targeting molecule. The G5-MTXn adduct acts as a promising FR-selective, cytotoxic agent for the treatment of cancer [75, 78, 79, 82].

3 Biotin Drug conjugate

Biotin is one of the essential vitamins and acts as a promising targeting agent. Vitamin drug conjugate is an approach to deliver a high dose of the targeted drug to cancer cells [83]. Biotin is an essential vitamin and is transported through sodium-dependent multivitamin transporter, which is more expressed in many cancers cell lines like colon, breast, lung cancer cell line. Biotin shows overexpression in folate receptor, so growing tumors more need for biotin than normal cells.

It is reported that the conjugation of biotin with many organic molecules and protein shows selective delivery of a cytotoxic agent to cancer cells [84].

3.1 Biotin-taxoid conjugate

Yang et al., developed conjugate in which biotin is combined with new generation taxoids 5BT-1214 [83]. The approach of this invention is simple for tumour-targeted drug delivery system. The use of biotin 5BT-1214 conjugate (Fig. 9) exploits the biotin receptor's upregulation on the cancer cells. The invented process involved the drug delivery via endocytosis mediated by vitamin receptor [16, 83].

The testing result of biotin 5BT-1214 fluorescence conjugate showed the biotin drug conjugate easily incorporate into tumor cell and shows reduced toxicity against normal cells and also shows well systematic stability. Therefore it is one of the best novel targeted drug delivery system for tumor cells [83]. The findings suggest that only the biocompatible biotin-dendrimer adduct may be a successful nano-platform towards cancer treatment and cancer detection [85].

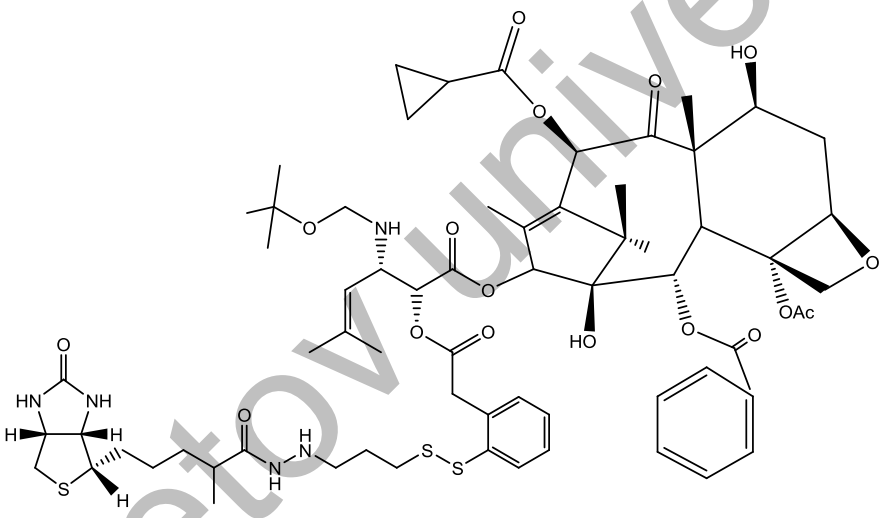


Figure 9. Chemical structure of Biotin-SBT-1214 conjugate

3.2 Gemcitabine-Coumarin-Biotin conjugate

Maiti et al., developed target-specific anticancer prodrug moiety Gemcitabine-Coumarin-biotin conjugate (Fig. 10) to treat various cancers [16, 86]. In this method, they proposed the formulation, development, spectroscopic analysis, and in vitro biological evaluation of Gemcitabine-coumarin-biotin conjugate. This conjugate is a multipurpose molecule mainly consisting of a splittable disulphide bond with a thiol group, fluorescent coumarin moiety, therapeutic action given by gemcitabine and biotin is serve as a cancer-targeting component. Breakdown of the disulphide bond occurs when a free thiol group are added, which is exceptionally high in cancerous cells and also release of therapeutic agent gemcitabine, as well as concurrently rise in fluorescence intensity [86, 87].

Confocal microscopic studies demonstrate that instead of W138 cells, this scaffold is selectively absorbed by A549 cells. Fluorescence-based colocalization experiments utilizing specific lysosome and endoplasmic reticulum additives indicate that splitting of thiol-containing disulphide bond of the conjugate can occur in the lysosome by receptor-mediated endocytosis process. This is latest approach with a therapeutic and diagnostic tool that provides both therapeutic benefit, and drug absorption at the cellular level is effectively controlled by fluorescence imaging [86, 88, 89].

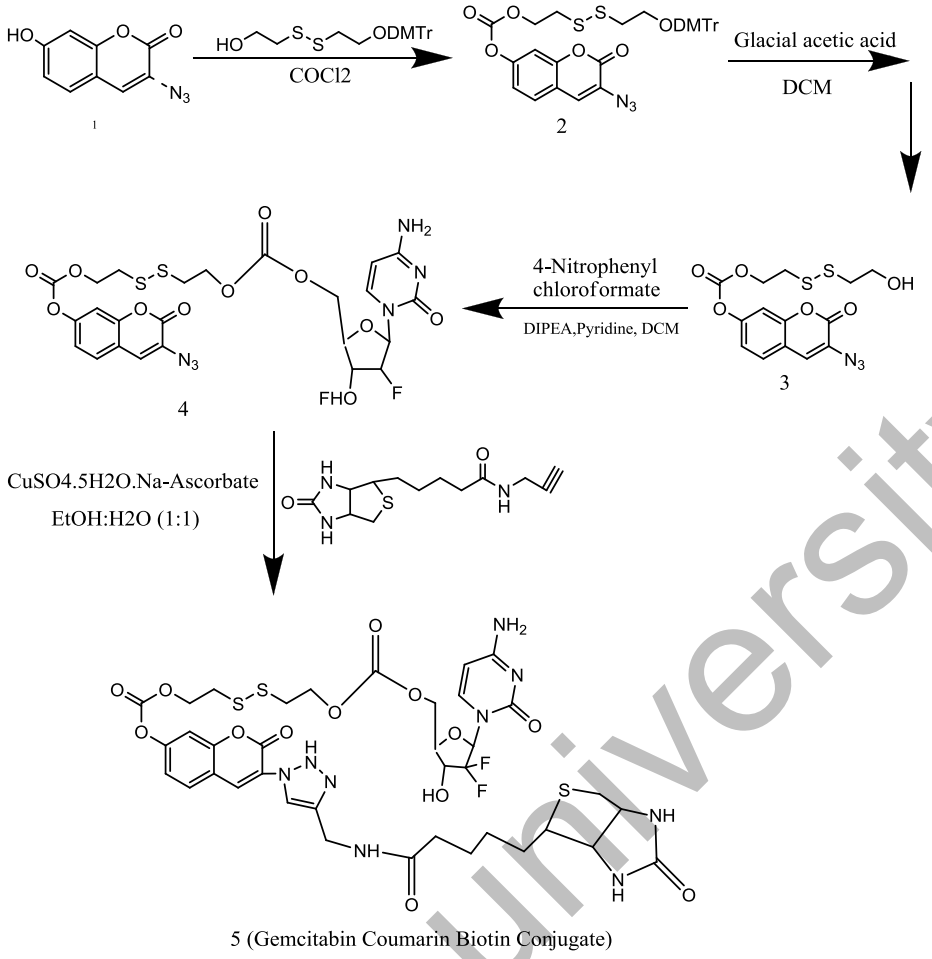


Figure 10. Synthetic scheme of Gemcitabin Coumarin Biotin Conjugate

4 Vit-E-drug conjugate

Vitamin-E and α-tocopherol analogues have a pro-apoptotic property and can kill cancerous cells, also helps in the prevention of cancer without any undesirable effects [90]. Vitamin-E and tocopherol analogues are used in drug delivery system because of their many excellent advantages like drug solubility, biocompatibility and antitumor activity. Upon esterification of vitamin-E succinate, the formation of non-ionic amphiphile known as α-Tocopheryl polyethylene glycol succinate (TPGS) shows the ability to cluster formation behaviour with other organic molecules. Hence it is helpful to develop many drug formulations which show properties like increase bioavailability and targetability of many anticancer drugs [91].

4.1 Gemcitabine-Vit E Conjugate

The main aim of this study is to test in vitro anticancer activity of gemcitabine conjugate to the tocotrienol isomer of vitamin-E (Fig. 11) against pancreatic tumor cells [92, 93]. Abu-Fayyad et al., reported that the free tocotrienol isomer of vit E shows the anticancer activity of gemcitabine. By using 1H NMR and mass spectrometry analysis technique, the conjugate was identified and tested for deamination sensitivity. The anticancer activity of gemcitabine was studied in vitro for pancreatic cancer cells BX-PC3 and PNAC-1 in which [92, 94].

ɤ-T3 conjugation of gemcitabine studied in vitro for enzymatic deamination showed that it was least affected comparing with free and conjugated gemcitabine in solution by deamination deactivation reaction. In vitro cytotoxicity studies indicate that an increase of anticancer activity by entrapping gemcitabine lipid conjugate into a nano-emulsion compared to a free drug is observed. It was concluded that for effective delivery of gemcitabine, conjugation with ɤ-T3 isomer is one of the feasible options [92, 93, 95].

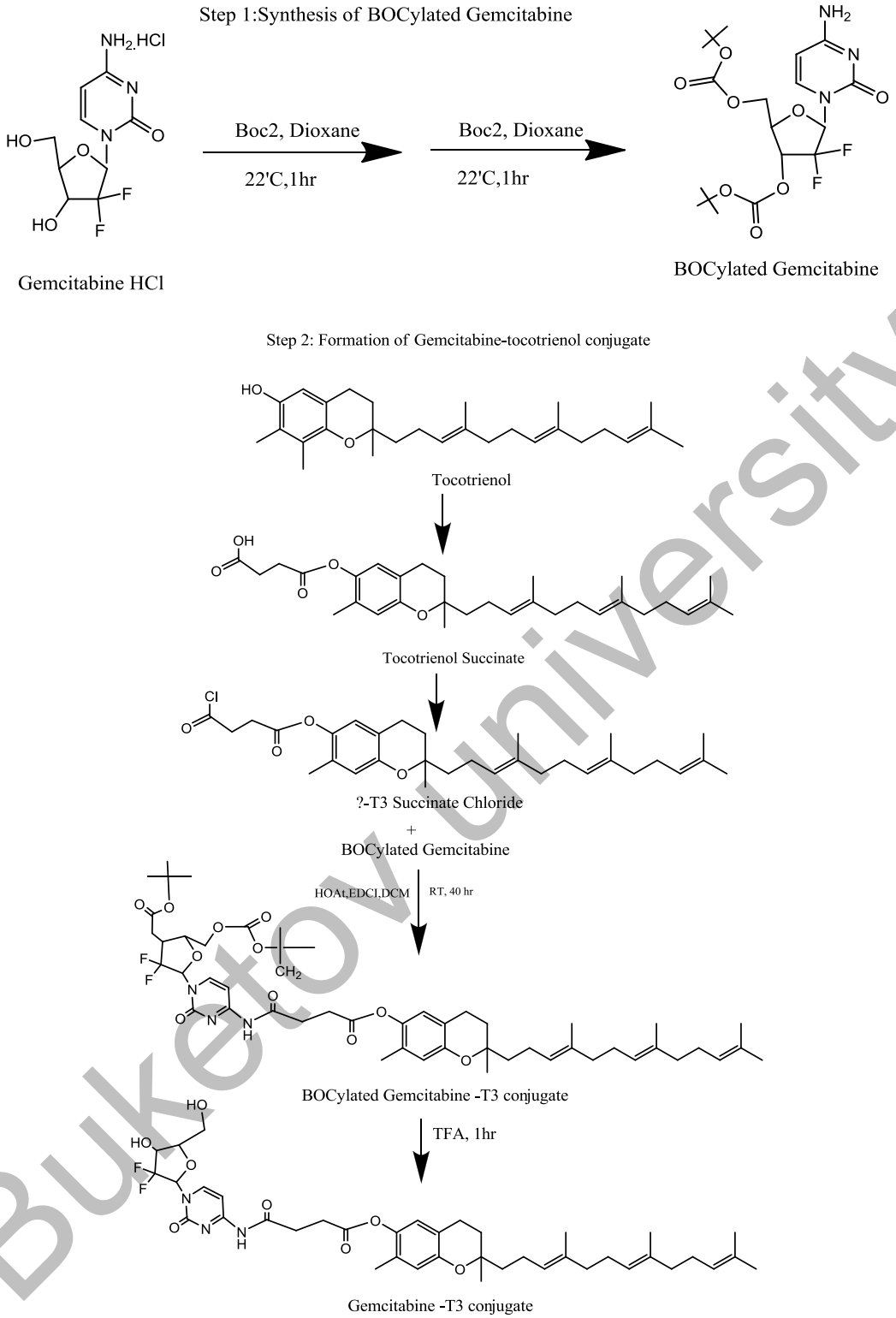


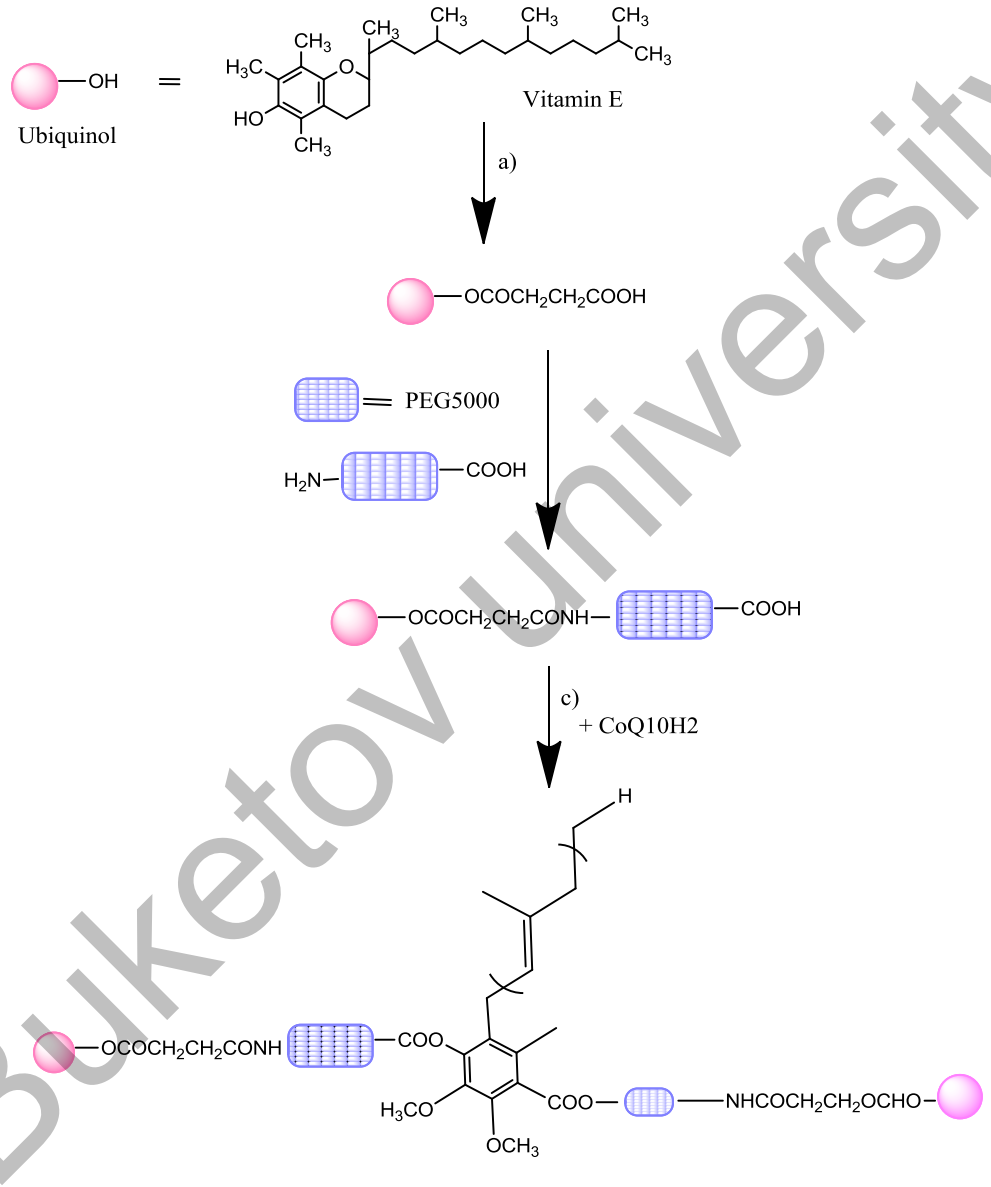
Figure 11. Synthetic scheme of Gemcitabine Vitamin E (Tocotrienol) Conjugate

4.2 Ubiquinol-Polyethylene glycol-Vit E conjugate

Both Ubiquinol and vit E have medicinal value but drawback associated with the Ubiquinol and Vit E, shows low bioavailability, potential toxicity because they have less soluble in aqueous media [96, 97]. Cateniet al., developed a method to overcome the challenge associated with vitamin-E and Ubiquinol. The objective of the present study is to improve the bioavailability of ubiquinol and vit E; the mixed conjugate of Ubiquinol-Polyethylene Glycol-Vitamin E (Fig. 12) was synthesized and characterized. By spectroscopic

methods such as 1H NMR and mass spectroscopy, the synthesized mix conjugate of PEG was characterized. The in vitro release of the conjugate was calculated and evaluation of ubiquinol and vit E also carried out in different pH conditions in human plasma. The obtained result indicates that at pH 7.4. occurs more release of ubiquinol and vit E from PEG conjugate in plasma within 24 hrs. The evaluation of antioxidant activity carried out by DPPH assay and obtained results show that there is no effect on antioxidant activity of ubiquinol and vit-E after esterification with PEG.

The novel CoQ10H2-PEG5000-Vitamin E combined conjugate was obtained and observed an enhancement in water solubility of CoQ10, Vitamin E is predicted by this conjugate. The increase of the beneficial effects and reducing the undesirable side effects of the parent products are observed. [96, 98, 99].



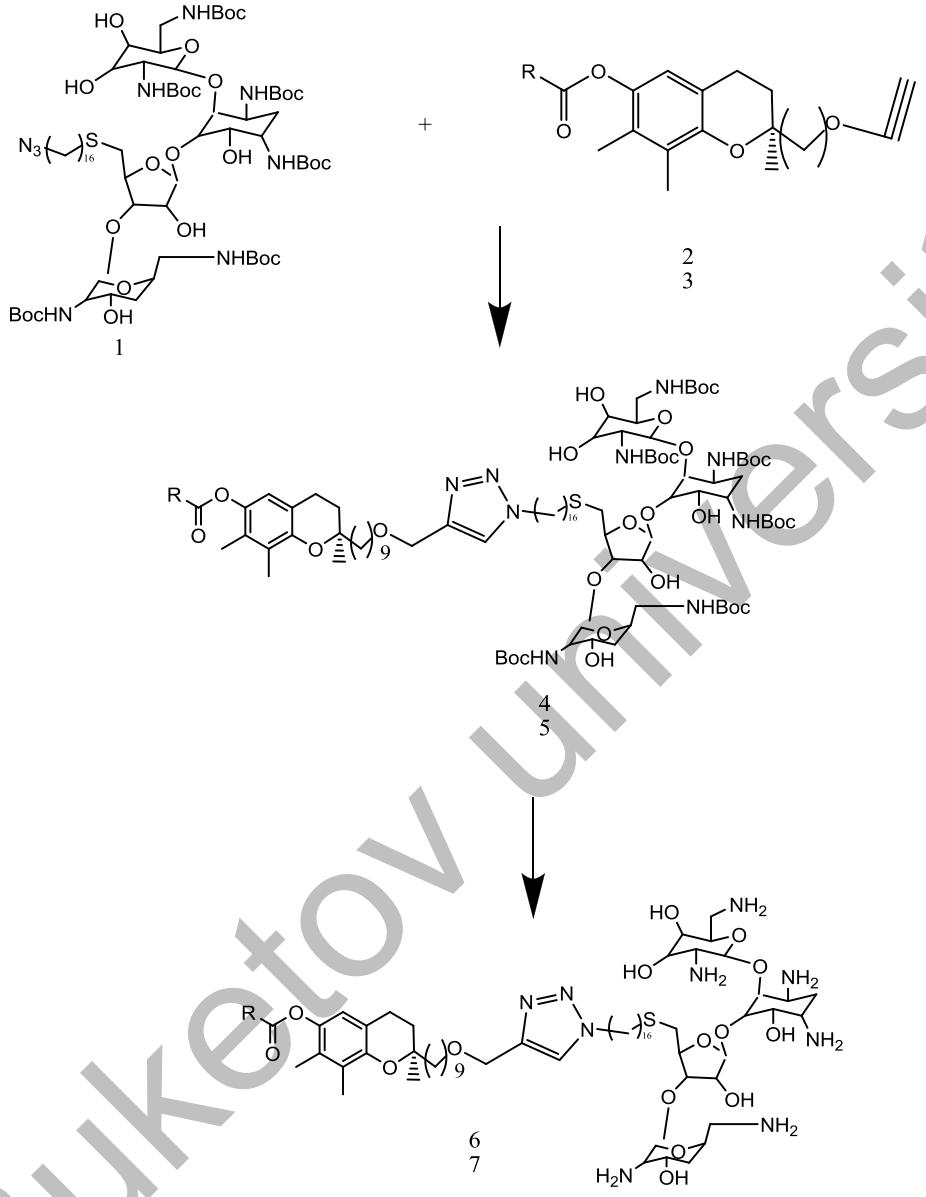
PEGylated derivative of COQ10 and Vit E

a) Succinic anhydride, Toluene Et3N,85?C,9 H; b) Et3N, DCC, HOBT, dry CH2Cl2, Room temperature,24h;c)DCC,DMAP, dry CH2Cl2, Room temperature, under nitrogen 24h.

Figure 12. Synthetic scheme of PEGylated Ubiquinol-Vit E conjugate

4.3 Vit-E-neomycin conjugate

Vit E conjugated neomycin derivative (Fig. 13) is a novel approach to deliver siRNA (small interfering RNSs) to liver cells. In this approach the neomycin derivative exibited RNAi (RNA interference) activity in liver cancer cell [100, 101].



Scheme 1. Synthesis of the prodrug derivatives 6 & 7. Reagents and conditions : (a) Cu powder, t-BuOH-water, 80'C, 4h, 89-97%, (b)Triisopropylsilane, TFA-CH2Cl2, rt, 1h, 79-92%

Figure 13. Synthetic scheme of Vit-E-neomycin conjugate

4.4 Docetaxel loaded Vitamin-E TPGS micelle with cetuximab:

Kutty et al., and Feng et al., developed docetaxel loaded vitamin E TPGS micelle to treat triple-negative breast cancer. For the selective delivery of docetaxel as a design anticancer drug for the treatment of triple-negative breast cancer (TNBC), produced a Cetuximab-conjugated vitamin E TPGS micelles. Hormone progesterone receptor (PR), estrogen receptor (ER) and epidermal growth factor receptor 2 (HER2) [102, 103] are not expressed, therefore their treatment more challenging than positive breast cancer. In docetaxel loaded vitamin E TPGS micelle cetuximab behaves like as targeting ligand. Vitamin E TPGS micelle is designed

with small particle size, have more drug loading capacity, also shows excellent drug release pattern. Micelles are characterized by surface appearance, charge. [102, 104].

TNBC cell lines like MDA MB468, MDA MB 231 and HCC 38 cell line with the expression of epidermal growth factor receptor 2 at a high frequency are used. Moderate and low frequencies are used to check in vitro, anticancer activity, as well as cellular absorption of docetaxel, loaded Vit.E TPGS micelles with cetuximab in contrast to a free drug-like Taxotere. The evaluated IC50 value indicates that the therapeutic agent's concentration can kill 50 % of malignant cells in desired time, like 24 hrs. By comparing the free drug Taxotere, the IC50 value for the micelle is obtained. Thus it was found that docetaxel loaded vitamin E TPGS micelle exibits a 205.6 and 223.8 fold increase in anticancer activity in TNBC compared to free drug Taxotere [102, 105].

5 Vitamin-C Conjugate

5.1 Vitamin C-Saquinavir conjugate (Ascorbyl-succinic-saquinavir)

Luo et al., and Wang et al., developed the ascorbyl-succinic-saquinavir (Aa-Su-Saq) conjugate (Figure14). It was synthesized and evaluated to target sodium-dependent vitamin-C transporter (SVCT) in order to improve the oral absorption of prodrug saquinavir. The affinity of Aa-Su-Saq regarding efflux pump p-glycoprotein(p-gp) and recognition by SVCT of Aa-Su-Saq have also been studied [106, 108].

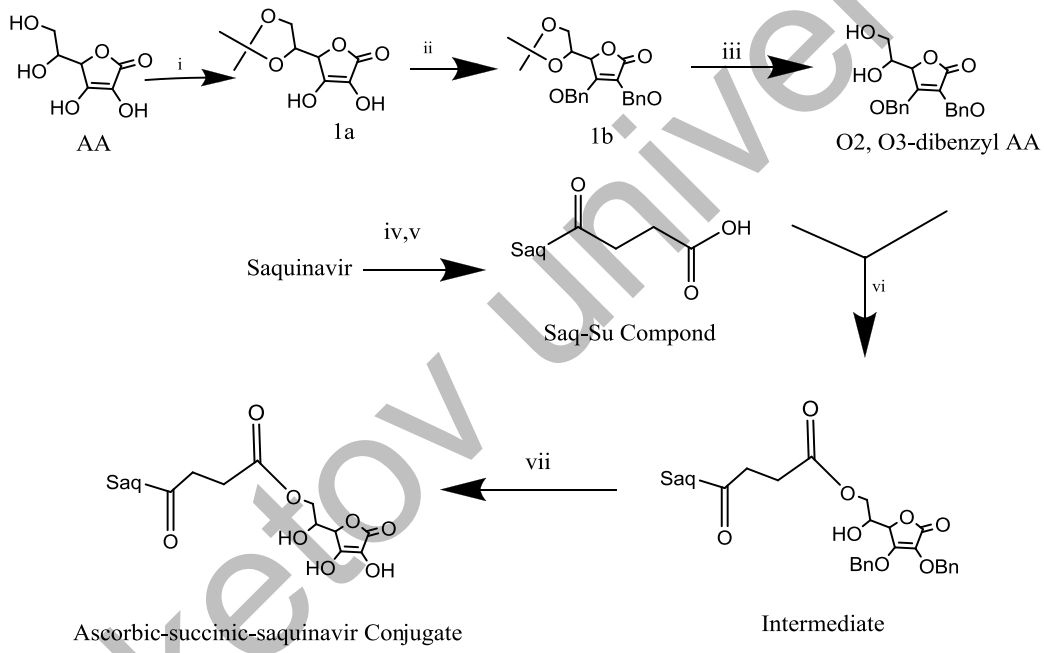


Figure 14. Synthetic scheme of Ascorbic-succinic-saquinavir Conjugate

Polarized MDCK-MDR1 and CaCO-2 cells were taken to determine transepithelial permeability, and rat liver microsomes were used to study the metabolic stability of Aa-Su-Saq. Aa-Su-Saq is stable in DPBS and CaCO-2 cells, having a half-cell life of 9.65 and 5.73 h. In MDCK-MDR1 cells, saquinavir absorption increased by 2.7 and 1.9-fold at the conc. 50μM Saq and Aa-Su-Saq. In MDCK-MDR1 and CaCO-2 cells, cellular accumulation of AA was decreased by 50–70 % compared to control in the presence of 200μM of Aa-Su-Saq. In the presence of 5Mμ ascorbic acid, the uptake of AA-Su-Saq was decreased by about 27 % to 34 %, and absorptive permeability was increased about 4.5-fold. The efflux index was lowered about 13–15-fold in polarized MDCK-MDR and CaCO-2 cells. Aa-Su-Saq not only free from cytotoxicity but also shows an increase in metabolic stability because it shows less affinity toward CYP3A4 [106, 107, 109].

6 Lipid-Drug conjugate

6.1 Stearoyl chloride-Isoniazid conjugate

Isoniazid is the first line anti-tubercular drug in the treatment of tuberculosis. However, there is some limitation associated with its hydrophilic nature, therefore exibits low permeability and have less affinity to cross blood-brain barrier, which results in the low therapeutic output. This problem can be solved by incorporating hydrophobic moiety of the covalently linked lipid-drug conjugate of Isoniazid with a small lipid chain of stearoyl chloride (Fig. 15). Using the method of cold high-pressure homogenization also improves the bioavailability of Isoniazid; lipid-drug conjugate nanoparticles were produced by using an aqueous surfactant. The physicochemical analytical methods like transmission electron microscopy, differential scanning calorimetry, X-ray diffraction method were applied to characterize nanoparticles. In vitro, drug release studies conclude that at pH of 7.4, in phosphate buffer solution shows sustained drug release up to 72 hrs. Higuchi model of diffusion is an attractive one to study the drug release profile of nanoparticle.

This lipid drug conjugate is effective in mycobacterium tuberculosis infection by intracellular trafficking into endosomal and lysosomal vesicles and colocalization with intracellular protein like CD63, LAMP-2, EEA1and Rab11. These nanoparticles exibit affinity to improve effective intracellular absorption of water-soluble drug Isoniazid [110, 111].

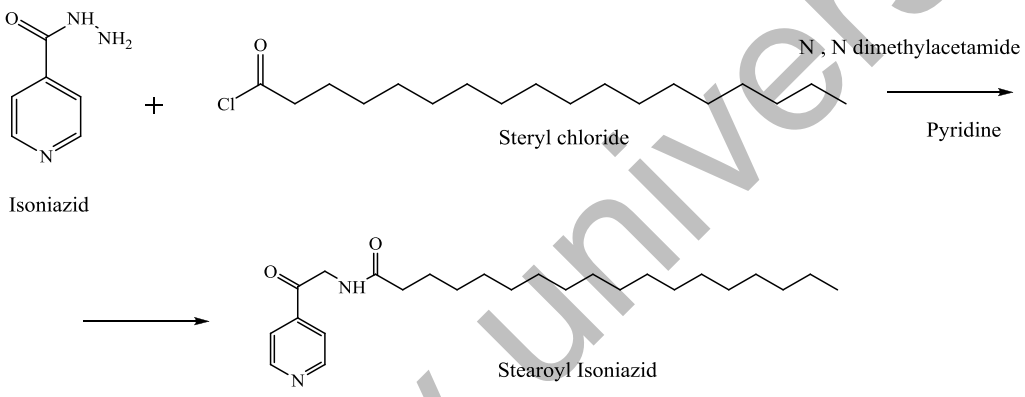


Figure 15. Synthesis of Isoniazid- Stearoyl chloride conjugate

Other approaches for the treatment of cancer and other diseases

7 Polymer drug conjugate

Cancer is considered as chronic illness which responsible for the elevated mortality rate in the world. The effective treatment for the cancer illness is the administration of the chemotherapeutic agent, even though its clinical status is not acceptable. The use of antitumor agent is minimal because it may cause serious complication. Therefore, to protect the normal cells from the severe side effects associated with a chemotherapeutic agent, «Polymer–Drug conjugate» is synthesized.

«Polymer–Drug conjugate» is a drug carrier system that consists of three components like a molecular targeting moiety, solubilizing moiety and active ingredient. Polymer-Drug conjugate in which the active drug is incorporated into the polymeric material. Polymer-Drug conjugate is also regarded as polymeric prodrug [112–114].

7.1 Methotrexate-Poly(glycerol-adipate) conjugate

Polymer drug conjugate is specially designed and intended for cancer therapy. The present study mentions the first polymer-antitumor drug conjugate obtained by cobination of poly-(glycerol adipate) with antitumor agent Methotrexate (Fig. 16). By using carbodiimide mediated reaction, MTX-PGA complex was developed with the reproducible result and with different high MTX molar concentration; the MTX-PGA adduct is self-build into size nanoparticles. The size of the nanoparticles depends on medium pH and the quantity of methotrexate. The change of particle size of NPs resulted in stearic hindrance and build bulkiness within nanoparticles centre and separation of the free functional group of the active agent.

MTX-PGA nanoparticles exibit stability at ionic strength equivalent to 0.15M HCl, in the medium having pH 5–9. They also show chemical stability at pH 7.4 in case of hydrolysis for 30 days, even though it

undergoes enzymatic degradation and release of free drug in unchanged form. In comparison with MTX-PEA NP, earlier reported studies indicated that by conjugating MTX with serum albumin exhibits > 300 times less potent than pure MTX. But MTX-PEA nanoparticles are slightly potent than free MTX in 791T. Along with the studies on enzymatic degradation, these results show that a linker moiety is not a necessary element with a useful biodegradable polymer. Therefore, these quickly produced PGA drug conjugates without a linker moiety can be a practical new approach for polymer-drug conjugate growth [115].

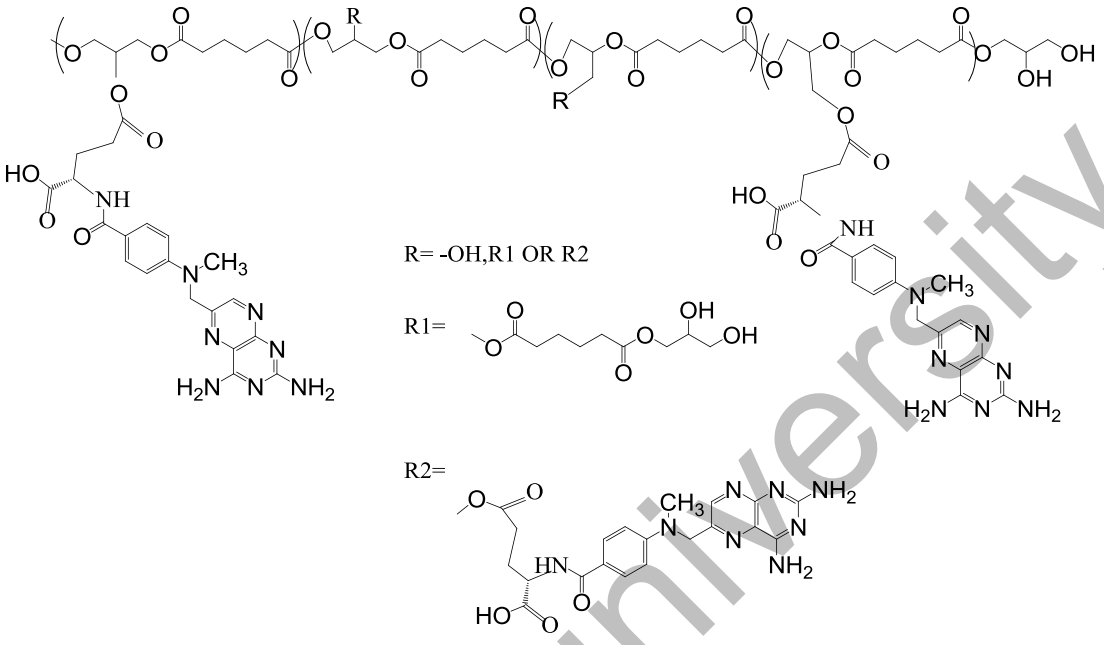


Figure 16. Methotrexate-Poly(glycerol adipate) conjugate

7.2 Docetaxel loaded polymeric nanoparticles

In this study, the drug is conjugated with a polymer producing polymeric nanoparticles to overcome obstacles associated with chemotherapy.

Docetaxel loaded trans-retinoic acid with poly-β-amino ester (ATRA-g-PBEA) nanoparticles is produced by encapsulation. Docetaxel is conjugated with trans-retinoic acid(ATRA) with poly-β-amino ester by the solvent displacement method. Using Zeta-sizer, the size and zeta potential of nanoparticles were measured and the morphology of nanoparticles was evaluated at pH 7.4, and 5.8. with the transmission electron microscopy. The in-vitro drug release study was studied. The cytotoxicity, anti-angiogenic effect and blood compatibility of this controlled release nanoparticles, also studied. The DTX loaded ATRA-g-DBAC nanoparticles show more cytotoxicity and better anti-angiogenic effect compared to free all trans-retinoic acid and docetaxel in chemotherapy. ATRA-g-PBAE nanoparticles are an attractive controlled released system compared to chemotherapy [116].

7.3 HPMA co-polymer-Dexamethasone conjugate

Liu et al., and Quan et al., developed pH-sensitive conjugate of N-(2-Hydroxypropyl) methyl acrylamide (HPMA) containing Dexamethasone polymeric conjugate is able to strengthen the therapy of rheumatoid arthritis. Reversible addition-fragmentation transfer (RAFT) polymerization technique is used to create an unique pH-sensitive and cross-linked Dexamethasone-containing monomer (MA-Gly-Gly-NHN=Dex) with HPMA. The scaffold of Dex-HPMA co-polymer conjugate was studied as well as its biological effectiveness was also tested on rodents with adjuvant-induced arthritis (AIA). Polymeric Dexamethasone conjugate was obtained with poly-dispersity index and with controlled molecular weight. Dexamethasone containing monomer (MA-Gly-Gly-NHN=Dex) regulates feed-in proportion ration Dexamethasone material.

The molecular weight of polymeric Dexamethasone conjugate is 34KDa and PDI is 1.34. at in vivo and in vitro assessment. The release of Dexamethasone from conjugate is caused due to low pH; it is demonstrated by in vitro drug release tests. Polymeric Dexamethasone conjugate has a significant and lengthy anti-inflammatory effect and joint safety. These properties are revealed by the tests such as, endpoint bone miner-

al density and histology grading. Conjugate of Dexamethasone–HPMA co-polymer is obtained with a very well structure is effective against rheumatoid arthritis. In the treatment of rheumatoid arthritis, it also has a specific therapeutic potential [117].

Conclusions

Chemotherapy is the golden method to treat a chronic disease like cancer, but there is some complication associated with chemotherapeutic agents causing undesirable side effects with systemic toxicity to the normal cells. Therefore, to avoid this problem, a new approach called «vitamin-drug conjugate» is developed. Many research studies reported various vitamin-drug conjugate like folic acid conjugate, Vitamin B12 conjugate, vitamin-C conjugate, vitamin-E conjugate, Biotin drug conjugate etc. In the case of Lipid drug conjugate, many drugs cannot cross the blood-brain barrier due to their hydrophilic nature. Thus, this problem can be solved by combining hydrophilic drug with short-chain of lipid resulting in new adduct is known as «Lipid-Drug conjugate».

The review describes vitamin drug conjugate which is the newly emerged concept for targeted drug delivery to the cancer cells with achieving desirable clinical output. The recent studies revealed that cancer cells are more overexpressed to vitamins than normal cells, so using the method receptor-mediated endocytosis system can deliver a cytotoxic agent to the cancer cells and may not harm any normal cells. To strengthen this concept, many approaches were studied like conjugation with metals, conjugation with gums and conjugation with vitamins etc. Metal drug conjugate is the clinically approved method as it can deliver both therapeutic and diagnostic agents to the cancer cells with a fewer side effect.

Vit.B12 conjugate, in this cobalamin, is covalently bound to the anticancer drug and produce high biological activity. Therefore the conjugation of drug with vitamin exibits high efficacy and low systemic toxicity. In folic acid conjugate, folate receptor is highly overexpressed on cancer cells compared to normal cells. Thus selective drug delivery of cytotoxic agent toward malignant cells can be achieved by binding with folic acid. That is why it is one of the promising methods that have the potential to treat a variety of cancers in future. α-Tocopherol polyethene glycol succinate is an ester form of vitamin E succinate that shows excellent properties like increase selectivity as well as bioavailability of anticancer drugs. Another preparations like biotin conjugate, Vitamin-C conjugate and vitamin-A conjugate also proved to be useful in cancer therapy and reducing the toxicity. The folic acid drug conjugate was found to be most active and pharmacologically effective amongst all the other conjugates for the treatment of cancer.

Few challenges may arise associated with vitamin drug conjugate, as a synthesis of the conjugate in cobalamin drug conjugate and biotin drug conjugate. Vitamin B12- metal conjugate shows accumulation in non-targeted organs and leads to a severe undesirable side effect. Thus, it is nessessary to design such conjugate that shows increased uptake and selectivity toward tumor in order to avoid accumulation in organs.

Tuberculosis infection treatment drugs develop multidrug resistance due to the more extended treatment period. This problem can be resolved using vitamin as a target molecule to stop the spread of tuberculosis infection. In addition to anti-tubercular therapy, the newer drug is conjugating with vitamins like vitamin-C and vitamin-D are useful and one of the novels approaches against tuberculosis infection in the future.

In future vitamin drug conjugate is an attractive approach of targeted preparation delivery to the many life-threatening disease like cancer, tuberculosis etc.

The summary of these methods and its advantage are shown in the Table.

T a b l e

Vitamin drug Conjugates

Sr. No	Vitamin Drug Conjugate	Advantages
1	2	3
1	Vitamin B12-Metallodrug conjugate	– Vitamin B12-Metal conjugate can overcome the problems associated with anticancer agents. – The increase in tumor selectivity and enhance clinical output by conjugating metal with cobalamin. – In vitro cytotoxicity experiments carried out on adenocarcinoma cells of human ovary and human breast cells demonstrated that Pt-II Cyano complex exhibit antitumor activity and quickly release antitumor drug in the body.

Continuation of Table

1	2	3
2	Colchicine- cobalamin conjugate	– This scaffold is effective against variety of cancers like brain, breast and melanoma. – Colchicine-cobalamin conjugate is one feasible option to resolve the problem associated with tubulin targeted anticancer drug.
3	Folic acid-Bleomycin conjugate	– This conjugate increase potency as well as selectivity of anticancer agents into tumor cells which over expressed toward folate receptor.
4	Arabinogalactan-folic acid-methotrexate conjugate	– Folate targeted arabinogalactan linked methotrexate adduct shows 6–3-fold increase in cytotoxic activity as well selective delivery of antitumor agent into the cancerous cells.
5	Guar gum loaded methotrexate-folic acid conjugated nanoparticles	– These nanoparticles were designed to target colon cancer. – Guar gum loaded methotrexate-folic acid nanoparticles play dual function, it provides robust treatment against the colorectal carcinoma and also show efficacy in case of another carcinoma.
6	Methotrexate-dendrimer-folic acid conjugate	– The coupling of methotrexates with 5th generation dendrimer result in increase of methotrexate therapeutic index comparing to free methotrexate. – This conjugate is not affected by serum esterase enzyme activity because it synthesized by esterase stable amide coupling, so this adduct exibits 4300-fold greater biological activity in contrast with free methotrexate.
7	Docetaxel loaded -PLGA-PEG Folate conjugated nanoparticles	– Folate targeted docetaxel loaded NPs shows displayed a higher degree of intracellular absorption in Folate receptor-positive malignant cells (SKOV3).
8	Folic acid-PEG conjugate	– It is novel approach to deliver anticancer agent to cancerous cells by conjugating folic acid to phospholipid. – Via folate targeted drug delivery system can be increased anticancer activity of liposomal active agent in FR expressing cancerous cells.
9	Folic acid-5-fluorouracil conjugated nanoparticles	– 5-FU conjugated nanoparticles have high affinity toward malignant cells HT-29 compared to pure drug and display the excellent anticancer activity in the 5-HT cells, it is demonstrated by florescent microscopy.
10	Biotin-Taxoid conjugate	– Biotin conjugated with taxoid 5BT-1214, this scaffold is easily integrated into tumor cells and reduce the cytotoxicity of the normal healthy cells. So, it is novel approach and targeted drug delivery of cytotoxic agent to the tumor cells.
11	Gemcitabine-Coumarin-biotin conjugate	– This conjugate is multipurpose molecule, which selectively absorbed by the cancerous cells A549 instead of W138 cells. – This multipurpose scaffold provides both therapeutic benefit and also drug absorption at the cellular level in malignant tumors.
12	Ubiquinol-Polyethylene glycol-Vit E conjugate	– Ubiquinol-PEG-Vit.E conjugate resolved the problem associated with ubiquinol and vit.E like poor bioavailability, potential toxicity. – In vitro study carried out at different pH conditions in human plasma obtained results revealed that at pH 7.4 there is more release of ubiquinol and Vitamin-E from PEG conjugate in plasma within 24hrs.
13	Gemcitabine-vitamin-E conjugate	– In-vitro studies demonstrate that by conjugating gemcitabine with vit.E which is least affected by deamination deactivation reaction compared to free drug. – In-vitro cytotoxicity studies revealed that increase of anticancer activity by entrapping gemcitabine in lipid conjugate compared to free drug is observed.
14	Docetaxel loaded vit-E TPGS micelle with cetuximab	– DTX-loaded vit-E TPGS micelle have small particle size, have high drug loading capacity and excellent drug release pattern. – The TNBC cell lines like MDA-MB468, MDA MB 231 and HCC 38 cell line have been used to check in vitro activity and was found that docetaxel loaded vitamin-E TPGS micelle shows 205.6 and 223.8-fold increase in anticancer activity in TNBC cell line compared to free drug Taxotere.
15	Vitamin-C — Saquinavir conjugate (Aa-Suc-Saq)	– In MDCK-MDR1 cells the absorption permeability of saquinavir is increased about 4–5-fold from Aa-Suc-Saq conjugate. – Aa-Suc-Saq conjugate is free from cytotoxicity and show excellent metabolic stability because it shows less affinity toward CYP314.
16	Stearoyl chloride -Isoniazid conjugate	– Isoniazid-stearoyl chloride conjugate is effective in tuberculosis infection, by intracellular transfer into endosomal and lysosomal vesicles. – The addition of hydrophilic drug isoniazid to short lipid chain stearoyl chloride result into increase of Isoniazid's bioavailability.

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Дәруменді дәрілік конъюгат: фармакологиялық потенциалын жүйелі түрде талдау

Қатерлі ісік өлімге әкелуі мүмкін созылмалы ауру болып табылады. Дәстүрлі химиотерапияда цитотоксикалық препараттар көбейіп бара жатқан қатерлі ісік жасушаларын жою үшін қолданылады. Цитоуытты агенттің талғамдығы төмен болады, биологиялық белсенділік танытпайды, жүйелік уыттылық пен жағымсыз әсер етеді. Жыл сайын халықтың 1,8 миллионға жуығы туберкулез инфекциясын жұқтырып, соның салдарынан қайтыс болады. Туберкулезді емдеу кезінде дәрілік затқа төзімділіктің жоғарылауы маңызды мәселе болып табылады. Сонымен, дәріге тұрақтылықты, туберкулез инфекциясындағы дәрілік селективтілікті және цитоуытты агент пен туберкулезге қарсы препараттардың жанама әсерлерін азайтуды шешудің жаңа әдісін немесе терапиясын жасау өте өзекті мәселе. Бұл шолу мақалада жаңадан пайда болған «дәрумен–дәрілік конъюгаты» тұжырымдамасы сипатталған. Дәрумен–дәрілік конъюгат — бұл мақсатты орынға қарай арнайы жеткізілетін препарат, қатерлі ісік және туберкулез сияқты созылмалы ауруларды емдеудің және терапевтік нәтижелерді жақсартудың перспективалы әдістерінің бірі. Жұмыстың мақсаты — жаңа қатерлі ісікке және туберкулезге қарсы препараттың құрамына кіретін дәруменнің әсерін зерттеуге, селективті емес, жүйелік уыттылық және көп дәрілікке төзімділік сияқты қиындықтарды жеңуге бағытталған. Бұл тәсіл өмірге қауіп төндіретін қатерлі ісік, туберкулез сияқты ауруларды емдеуде және көптеген вирустық инфекцияларда тиімді.

Кілт сөздер: қатерлі ісік, туберкулез, дәрумен–дәрілік конъюгаты, B12 дәрумені конъюгаты, фолий қышқылының конъюгаты, биотин конъюгаты, Е дәрумені конъюгаты, липидті дәрі конъюгаты.

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Конъюгат витамин – лекарственный препарат: систематический обзор фармакологического потенциала

Рак является хроническим заболеванием, которое может привести к смерти. В традиционной химиотерапии цитотоксические препараты используются для уничтожения пролиферирующих раковых клеток. Цитотоксический агент обладает меньшей специфичностью и биологической активностью, также вызывает системную токсичность и нежелательные побочные эффекты. Ежегодно около 1,8 миллиона человек заражаются и умирают от туберкулезной инфекции. Повышение лекарственной устойчивости во время лечения туберкулеза вызывает серьезную озабоченность. Таким образом, необходимо разработать новый подход или методы лечения для устранения лекарственной устойчивости, лекарствен-

ной селективности при туберкулезной инфекции и уменьшения побочных эффектов цитотоксических агентов и противотуберкулезных препаратов. В данной обзорной статье описано недавно появившееся понятие «витаминно-лекарственный конъюгат». Конъюгат витамин–лекарство — препарат, который специально доставляется к месту назначения, и один из многообещающих способов лечения хронических заболеваний, таких как рак и туберкулез, и улучшения терапевтического результата. Цель работы — изучить витамин как целевую составляющую для нового противоопухолевого и противотуберкулезного препарата при преодолении таких проблем, как неселективность, системная токсичность и множественная лекарственная устойчивость. Этот подход полезен и при лечении опасных для жизни заболеваний, таких как вирусные инфекции.

Ключевые слова: рак, туберкулез, конъюгат витамин – лекарство, конъюгат витамина B12, конъюгат фолиевой кислоты, конъюгат биотина, конъюгат витамина E, конъюгат липид – лекарственный препарат.

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