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DISULFIDE BRIDGING: A POTENT STRATEGY FOR ANTI-TUMOR DRUG DELIVERY

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ABSTRACT: To increase the efficacy of present anti-tumor agents, tumor-targeting can be proved as a successful approach for effective and safer drug delivery with less toxicity. According to researchers, for an effective tumor targeting module, disulfide linkage plays an important role in providing a medium for conjugating an anti-tumor drug with a carrier like vitamins and fatty acids. Disulfide bonds with unique chemical and biophysical properties can be used as cleavable linkers to deliver chemotherapeutic drugs. From the literature review, it has been observed that a disulfide bond acts as a self-immolating linker, which gets cleaved inside the body in the presence of intracellular glutathione; otherwise, it is stable in blood circulation. In this review, we discussed various strategies available in literature using disulfide as a linker in potent tumor targeting agents. Various successful conjugates are described here, which are currently under clinical trials.

INTRODUCTION: In drug development, one of the most promising strategies which are currently being employed is tumor-targeting drug design. Among the various fatal diseases, the second major cause for the death is cancer. Even after different progressive approaches and discovering new technologies for cancer treatment, researchers are still unable to discover an indefinite treatment to eradicate this malignant condition. Another major problem in chemotherapy is a deficiency of tumor cell specificity. A cytotoxic agent can kill fast-growing tumor cells, and traditional chemotherapy relies on this premise. But these cytotoxic agents lack specificity and results in systemic toxicity, which in return causes severe side effects that are undesirable like hair loss, liver damage, kidneys, and bone marrow dysfunction. In order to overcome these issues from the past three decades, drug delivery protocols and systems are being explored. A tumor-targeting drug delivery system is developed in the form of a conjugate, and this conjugate is generated by connecting cytotoxic agents directly or *via* a suitable linker to tumor recognition moiety. The conjugate must be non-toxic hence;, the linker should be stable in blood circulation and only gets cleaved inside cancer cells. Active cytotoxic agent gets regenerated when conjugate gets cleaved upon cell internalization into cancer cells. Linkers are most frequently classified into three classes, *i.e.*, a) hydrazine linker, b) peptide linker c) disulfide linker.

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The requirement of cytotoxic agents and type of cancer helps in the selection of an appropriate linker. Each of the linkers has several advantages and disadvantages and is universal in nature [1]. The disulfide linkers have attracted a lot of attention in the past few years. These disulfide linkers can be cleaved at a higher concentration of glutathione. Because the concentration of glutathione is much

higher in tumor cells than normal cells, the use of disulfide linkers is of keen interest for researchers nowadays for synthesizing disulfide-linked anti-tumor conjugates. Efficacy of disulfide linkers as compare to other linkers against several tumor xenografts in pre-clinical models has been proved [2]. In various chemical and biological agents that show potent reactivity or possess pharmacological activities like anti-tumor activities, disulfide bond (-S-S-) is an extremely valuable functional group [3, 9]. It has already been detected that various proteins, oxidized glutathione, and numerous naturally obtained products, including some drugs *i.e.*, Mitomycin, leinamycin consists of disulfide bond [10, 11]. In this review, we focused on the benefits of using disulfide linkage in tumor-targeting agents. Disulfide bond can degrade inside the human body by different mechanisms, which are briefly explained. This review can be helpful in a comprehensive understanding of this bond, its various merits and how it can be employed in tumor targeting by serving as a linker.

Principles Underlying Disulfide Linkage: Being a biodegradable linker disulfide has gained the keen interest of researchers in the past years and can be employed in controlled drug release medications. Also, disulfide is easy to prepare in the lab, better tolerated by blood plasma and possesses higher sensitivity inside the tumor environment, and these properties contribute into the importance of this bond as in tumor-targeting agents. Recently, it has been reported that drugs can be released in a spatially controlled manner using stimuli-responsive drug delivery systems. Unique microenvironment properties like acidic pH values, high concentration of certain enzymes of tumor tissues, and a more reductive environment of these tissues can be used to design stimuli-responsive drug delivery systems. Intracellular glutathione concentration is in millimolar range (1-10mM) inside the human body, [12] but outside cells in common fluids it is at (20-40 µM) levels, [13, 15] like plasma, except respiratory tract lower part fluid lining. To act as an interface between extracellular space and cellular membrane, glutathione (GSH) can be translocated to the surface of cells [16, 19]. Interestingly, inside cancer cells, GSH concentration is on higher level than that of normal cells. This important fact can be employed to develop anti-tumor drug delivery systems (DDS) [20, 24]. Two thiols can result in the formation of a disulfide bond upon oxidation. Under mild oxidative and physiological pH, the disulfide bond is stable but is susceptible for disulfide-thiol exchange reaction [25] and can only be reduced in the presence of GSH [26].

Thus, research is ongoing on reduction responsive drug delivery systems based on these theoretical facts that extracellular GSH concentration is substantially lower than the intracellular glutathione (GSH) concentration [27] and additionally, due to several times higher GSH concentration in tumor tissue than that in normal tissues made this environment more reductive [28]. Also, in the extracellular space of proteins, disulfide bonds present are oxidative, but due to the abundance of free thiols inside cells, these disulfide bonds get cleaved, *e.g.*, glutathione (which is most abundant). Glutathione disulfide (GSSG) is another main biological disulfide compound that is formed by oxidation of GSH **Fig. 1** [29]. The oxidized GSSG can get reduced back due to the presence of NADPH-dependent enzyme glutathione reductase, and it helps in maintaining cellular redox homeostasis [30, 32].

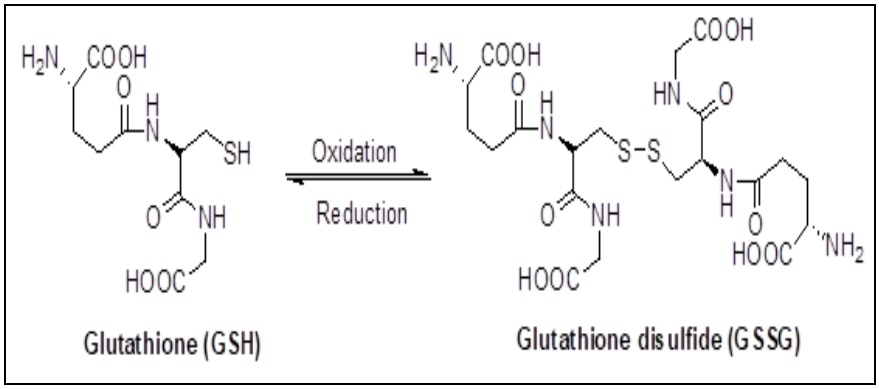


FIG. 1: INTERCONVERSION OF GLUTATHIONE (GSH) AND GLUTATHIONE DISULFIDE (GSSG)

From the literature it has been also seen that this covalent disulfide bond can be cleaved under the presence of reducing agents like dithiothreitol (DTT), mercaptoethanol and tris-(2-carboxyethyl)-phosphine (TCEP) [33, 34]. But, even under harsh extracellular conditions, disulfide bond is relatively stable [35, 36]. This disulfide bond can get cleaved reversibly inside cells through a thiol-disulfide exchange reaction and it can be described as [37].

$$2R\text{-}SH + R'\text{-}SS\text{-}R' \leftrightarrow R\text{-}SS\text{-}R + 2R'SH$$

This reaction is an SN2 type nucleophilic reaction. Sulfur gets attached by a deprotonated thiolate anion which acts as nucleophile [38]. Disulfide bond also plays an important role in protein folding and enhancing their stability as disulfide bond results in a reduction of entropy of denatured state [39, 40]. They play a key role in the transformation of molecular oxygen into reactive oxygen species (ROS), which are part of many biological processes [41].

Some other reviews about disulfide focused on it as therapeutic gene delivery system and thus worked on its evaluation for therapeutic efficacies [42, 47]. Recently, disulfide linkers are now being used for intracellular drug release as drug delivery systems [48, 52].

Mechanism of Drug Release *via* Disulfide Bond: In targeted anti-tumor agents, disulfide bonds act as primary linkers, which help in the conjugation of the drug. It is known that other linkers like amide, ester and hydrazine get cleaved through hydrolytic cleavage, but unlike them, disulfide gets cleaved via electrochemical reduction reaction by yielding respective thiol or through thiol-disulfide exchange reaction [53, 55]. Endogenous thiol molecules like cysteine, homocysteine, N-acetylcysteine, glutathione (L-γ-glutamyl-L-cysteinyl-L-glycine; GSH), other cysteine-containing peptides, and thioglycolic acid trigger a chemical mechanism which initiates cleavage reaction [56].

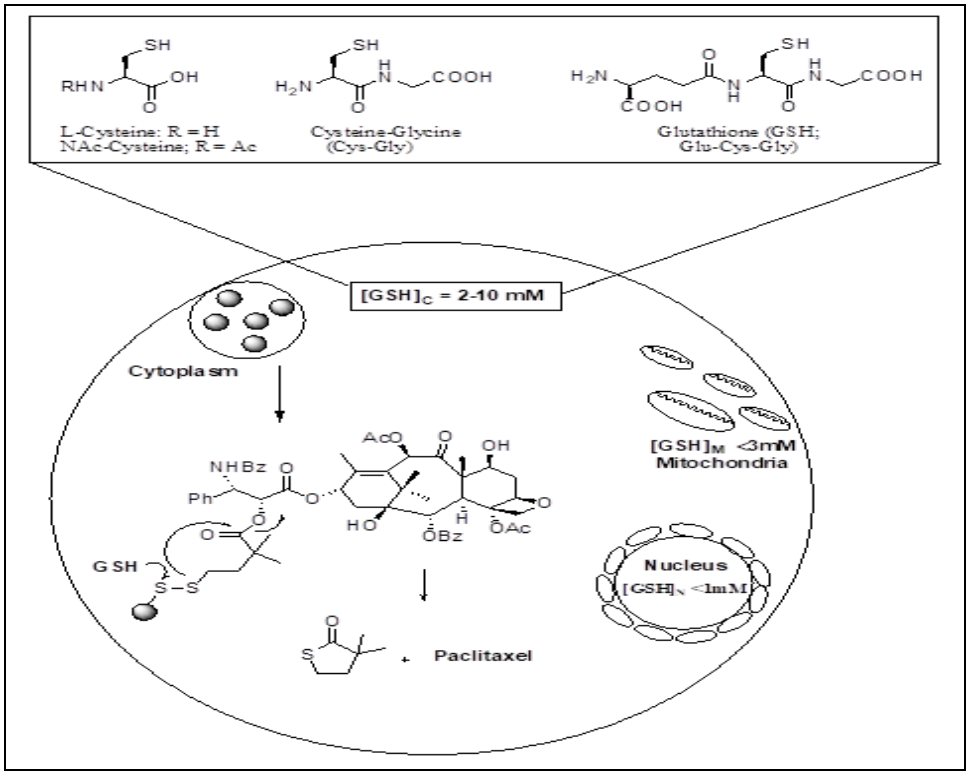


FIG. 2: REPRESENTATIVE ENDOGENOUS THIOLS THAT ARE INVOLVED IN DISULFIDE EXCHANGE REACTIONS FOR DRUG RELEASE IN THE CYTOPLASM VIA DISULFIDE CLEAVAGE.

Due to the stability of disulfide linker in intracellular space, targeted drug delivery agent linked with it gets easily taken up because after the endocytosis in the cytoplasm, primarily, a disulfide cleavage occurs. Furthermore, redox machinery present on the cellular surface does not contribute to drug release *via* disulfide linker cleavage unless otherwise modified, but instead of that, it gets cleaved by thiol triggered intracellular mechanism [53]. The mechanism involved in disulfide exchange reactions for drug release in the cytoplasm *via* disulfide cleavage is explained in **Fig. 2.**

There was another study about the reduction of disulfide bonds inside the cells, and that serves as a mechanism of disulfide reduction [57]. One of the reasons for the reduction of many protein disulfide bonds can be thioredoxin (Trx). The reduction occurs via the formation of intermediate mixed disulfide and Trx-sulfate attack on the N-terminal of Trx-Cys. This occurred via the nucleophilic reaction mechanism on the Sulfur group of the terminal, which is related to the mixed disulfide bond. AS there is the supply of NADPH, thioredoxins reductase (TrxR) helps in recycling of Trx **Fig. 3A.** Glutaredoxin (Grx) catalytically reduces glutathionylated protein thiols *via* a nucleophilic attack on the G sulfur by Grx N-terminal Cys transfer of protein-bound glutathione to Grx occurs. The catalyzed reduction by NADPH with the help of glutathione oxidoreductase (GOR), the oxidized glutathione (GSSG) is recycled **Fig. 3B** by following dithiol mechanism protein disulfides are reduced by Grx by attacking on Cys presented on the N-terminal of Grx substituted on disulfide group, which in turn gave rise to a mixed disulfide after nucleophilic attack.

Same as that of the intramolecular procedure followed for Trx, C-terminal Grx Cys also reduced mixed disulfide **Fig. 3C** [58].

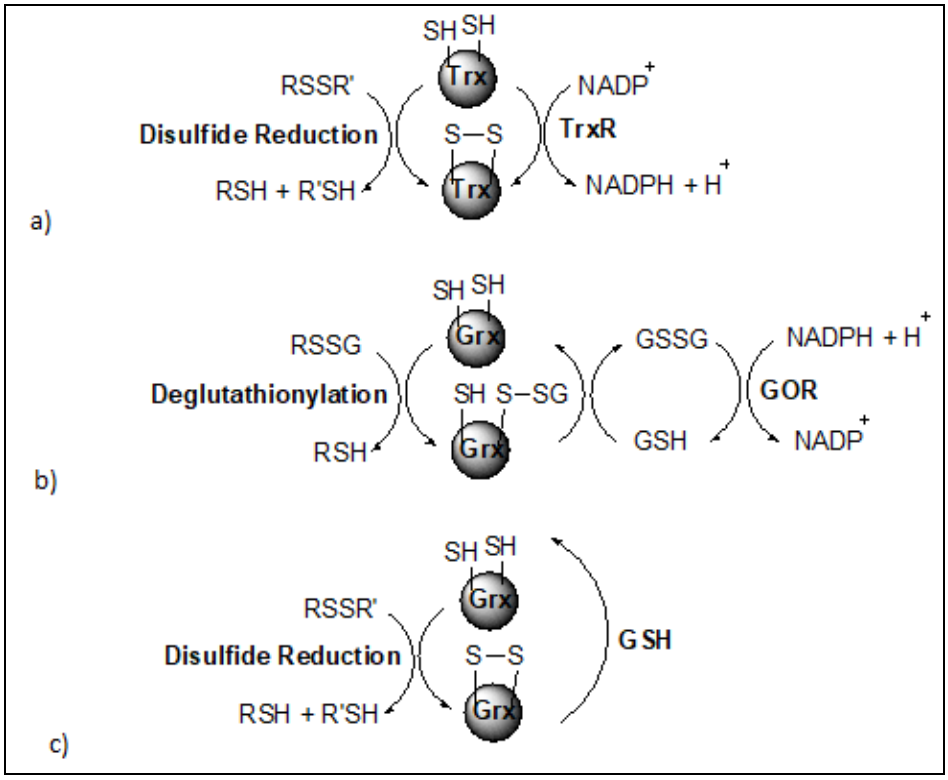


FIG. 3: GENERAL MECHANISM FOR DISULFIDE REDUCTION

Disulfide Linkage-Employing Tumor-Targeting Drug Delivery:

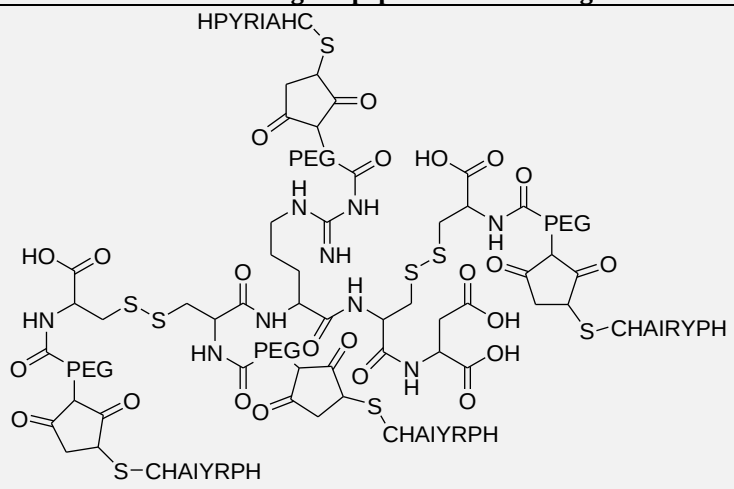
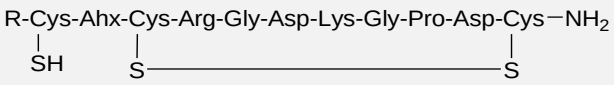
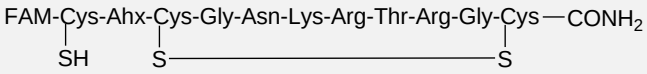
Disulfide Linkage in Peptide-Based Strategies for Tumor Treatment: Genetic mutations and epigenetic alterations are being considered as one of the causes of cancer.

On the basis of this theory, Lu *et al.* have explored on Peptide T7-modified polypeptide with disulfide bonds for targeted delivery of plasmid DNA for gene therapy of prostate cancer by targeting plasmid DNA (pDNA). They employed a cationic gene vector for tumor targeting, called as disulfide crosslinked arginine-aspartic acid peptide modified by HAIYPRH (T7) peptide (CRD-PEG-T7).

The results showed that nanosized positively charged CRD-PEG-T7-plasmid DNA complex **Table 1** have efficient cellular efficacy, minimum cellular toxicity and in comparison to CRD-PEG plasmid DNA complex have dual targeting effect. This new modified drug delivery agent had four times higher capacity to target over expressed transferrin receptor (TfR) on tumor cells in comparison with non-modified system. These results ensured that CRD-PEG-T7-plasmid DNA

may act as significant gene delivery system by targeting metastatic cancer [59]. Kotamraju *et al.* proposed an idea that efficacy of targeted gene cancer therapy can be increased by delivering an anti-tumor agent to the tumor interior using tumor-homing peptides which have properties to penetrate tissues. LyP-1 (CGNKRTRGC) and iRGD (CRGDKGPDC) were used by them for formation of this type of peptides. Conjugation of these peptides with a tumor targeting agent can be done by forming the cyclizing disulfide bond with cysteines presented in lipid structure. LyP-1, iRGD and CRGDC (GACRGDCLGA) peptides with a cysteine or maleimidohexanoic acid added externally at N-terminus of the sequences had been synthesized by them, with retaining tumor-homing properties of the peptide and the biological activity, subsequent conjugation to payloads yielded stable compounds. The expected results were obtained by performing studies on nude mice bearing orthotropic 22Rv1 tumors, Mice bearing MCF10 Ca1A human breast cancer xenograft tumors and intracellular oligonucleotide delivery to HeLa cells which determined that conjugates have the desired activities and efficacies. These conjugates can act as a powerful tool for disulfide-bridged peptide-mediated imaging, targeted drug delivery, and other applications [60].

TABLE 1: DISULFIDE AS A LINKER IN PEPTIDE BASED STRATEGIES FOR ANTI-TUMOR PROPERTIES

S. no.	Disulfide Linkage in peptide based strategies	Ref.
1	 1	59
2	 Ahx = 6-Aminohexanoic acid R =5(6)-Carboxyflurescein or Ac 2 (iRGD peptide with a third cysteine)  Ahx = 6-Aminohexanoic acid R = 5(6)-Carboxyfluorescein 3 (LyP-1 peptide)	60

Versatile Disulfide Bond in Nanoparticle-Based Strategies for Tumor Treatment: The development of strategies for the functionalization of nanoparticles is crucial for future clinical use to improve anti-cancer therapies but biological barriers (extracellular and intracellular) can cause hindrance in the delivery of active anti-tumor agents by using this strategy. To explore this angle Wen *et al.*, (2014) researched and stated that to overcome biological barriers (extracellular and intracellular), targeted drug delivery systems are required so that they can deliver the therapeutic drug to a specific biological site. This study showed that extracellular barriers could be

overcome by highly stable vehicles, have sustained drug release in the blood circulation, and accumulate at the site of action.

Intracellular barriers determine effective cellular internalization, controllable release, and endosomal escape. Thus, in case to develop a comprehensive targeted drug delivery system, both extracellular and intracellular barriers are critically important.

As the structures of nanoparticles (NPs) can be tailored to release the therapeutic drug at the action site by overcoming the biological barriers, nanoparticles (NPs) based drug and gene delivery systems can be prepared. Wang *et al.*, (2014) prepared newly self-assembled nanomedicines through entirely different mechanisms and explored another prospect of this field.

According to previous studies, stable nanoparticles cannot be prepared by using hydrophobic molecules as they can't self-assemble themselves; thus, amphiphilic or ionic materials were required for their functionality and stability *in-vivo*.

To balance the competition between intermolecular forces involved in nanomedicines self-assembly, they developed disulfide-induced nano-medicines (DSINMs) by inserting a single disulfide bond in hydrophobic molecules that improved their stability.

A number of first-line chemotherapy drugs (doxorubicin, paclitaxel, gemcitabine, and fluorouracil), derivatives of small-molecule natural products, and fluorescent probes were developed by using this strategy [62]. Lattore *et al.* in 2014, carried out a study which was a general approach for the controlled and selective release of targeted drugs by multi-functionalization of magnetic nanoparticles (MNPs) using anti-cancer drugs (Gemcitabine and Doxorubicin) and targeting moieties. By the formation of disulfide bonds between MNPs and drugs derivatives, functionalization was achieved.

Their strategy was to introduce a pyridyl disulfide group to the anti-cancer drugs, which can react with -SH groups of already activated MNPs.

Under a highly reducing intracellular environment, the drugs get released without any chemical modification by cleavage of the linker. In the intracellular conditions, the release occurred within 5-8 h, while in extracellular conditions, a negligible percentage of release was observed.

This approach can be further used for nanoparticle functionalization in several types of anti-cancer and targeting agents [63].

In bladder cancer, there has been no significant improvement over the last three decades as the drugs associated with it have moderate efficacy but more toxicity. Pan *et al.* developed nanometer-scale micelles loaded with paclitaxel (PTX) which were found to be bladder cancer-specific and were estimated its anti-cancer activity and toxicity.

Bladder cancer-specific targeting micelles were synthesized that are cross-linked with disulfide bonds to remain stable during blood circulation and coated with PLZ4 bladder cancer targeting ligand for cancer-specific drug delivery.

DC-PNM-PTX showed stability in sodium docecyl sulfate (SDS) solution, but after the addition of glutathione got dissolved within 5 min at a physiological intracellular concentration of 10 mM.

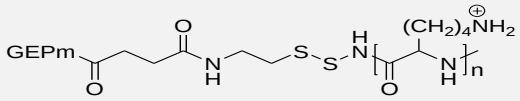
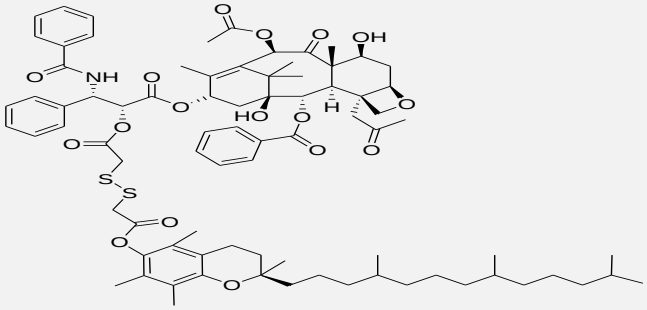
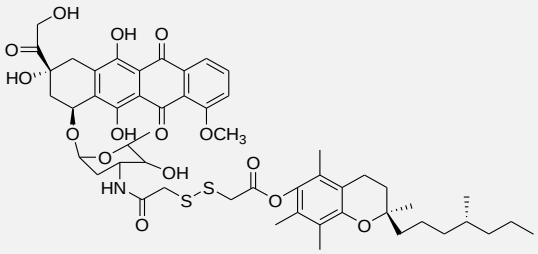
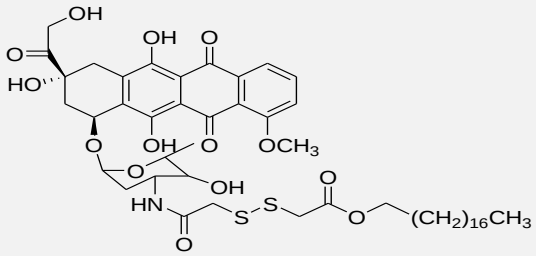
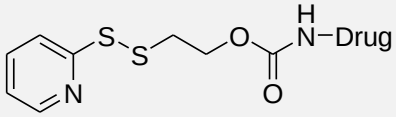
Patient-derived bladder cancer xenografts (PDXs) were used for *in-vivo* targeting and anti-cancer activity using immunodeficient mice. DC-PNM (disulfide-cross linked PLZ4-nanomicelle) specifically delivered a higher drug load to patient-derived bladder cancer xenografts than to lung cancer xenografts in the same mice after intravenous administration.

At the same dose, DC-PNM-PTX (disulfide-cross linked PLZ4-nanomicelle loaded with paclitaxel) was more effective than free PTX in prolonging the progression-free survival as well as the survival of mice carrying patient-derived xenografts.

The study was also helpful to show that cisplatin resistance was overcome by DC-PNM loaded with PTX and median survival got improved to 69.5days in comparison to 55 days of free PTX [64].

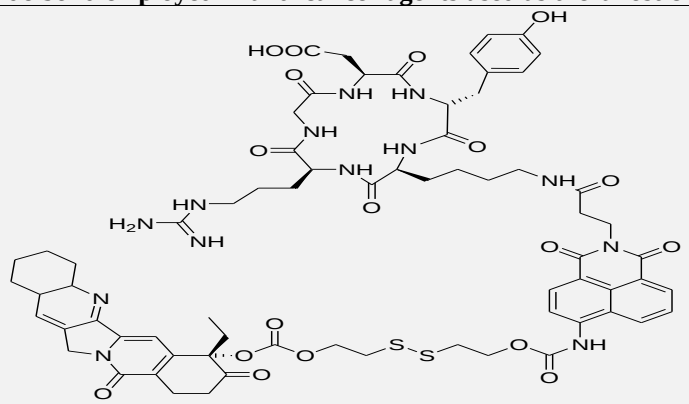
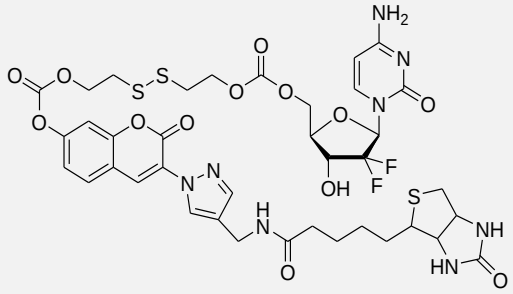
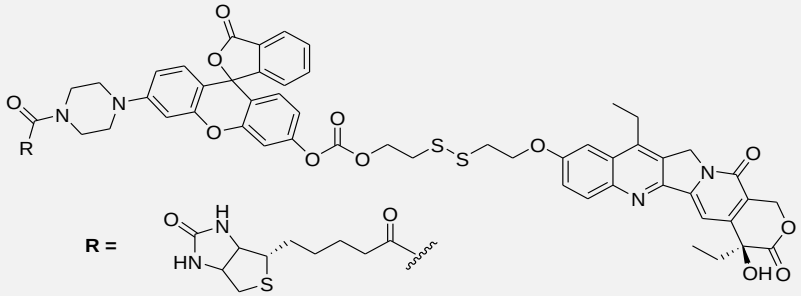
The various examples of a versatile disulfide bond in nanoparticle-based strategies are described in **Table 2.**

TABLE 2: VERSATILE DISULFIDE BOND IN NANOPARTICLE-BASED STRATEGIES

S. no.	Disulfide Linkage in nanoparticle-based strategies	Ref.
1	 4 (mPEG-SS-PLL)	61
2	 5 (PTX-SS-VE)  6 (DOX-SS-VE)  7 (DOX-SS-SA)	62
3	 8, 9 (Drug = DOX or GEM)	63

Disulfide Bond Employed in Anticancer Agents used as the agnostic Agents: The agnostics refer to an appealing new approach to drug development wherein the therapeutic modalities are combined with those associated with diagnostic imaging, and it can be extended to the subcellular level by enhancing efficacy while facilitating imaging. This type of drug delivery system contains both an active drug (for efficacy) and a fluorophore (for ease of monitoring uptake and delivery). In principle, this approach would permit drug delivery and release to be monitored directly. In 2012, Lee *et al.*, with emphasis on this study, synthesized RGD peptide-appended naphthalimide pro-camptothecin (CPT) conjugate using disulfide bond as a cleavable linker, naphthalimide moiety for fluorescence, RGD cyclic peptide for tumor targeting, and CPT as an active tumor agent. Within the endoplasmic reticulum of U87 cells, CPT payload was released *via* RGD-dependent endocytosis mechanisms as it was revealed by fluorescence-based colocalization under endoplasmic reticulum-selective dye [65]. In the same way, Maiti *et al.* in 2013 formed a conjugate in which biotin was used as a cancer-targeting unit, Gemcitabine (GMC), as a model active drug a coumarin moiety as a fluorescent reporter, and a thiol-specific cleavable disulfide bond. Studies were conducted on A549 cells, and the conjugate was released in the lysosome.

TABLE 3: EXAMPLES OF DISULFIDE BOND EMPLOYED IN ANTI-CANCER AGENTS USED AS THERAGNOSTIC AGENTS

S. no.	Disulfide bond employed in anti-cancer agents used as theranostic agents	Ref.
1	 10	65
2	 11	66
3	 12	67

The thiol-induced disulfide cleavage of conjugate occurred based on the mechanism of receptor-mediated endocytosis [66]. Bhuniya *et al.* (2014) explored the self-immolative cleavage of disulfide on exposure to biological thiols using this same principle of "all in one" prodrug and pharmacological studies for biotinylated piperazine-rhodol conjugate was performed in which anti-cancer drug SN-38 was used as the active agent.

The viability of the design was tested under controlled chemical conditions, and *in-vitro* and in-vivo studies were used to monitor the release and delivery of the SN-38 payload and mice xenografts [67]. The various disulfide bond employed anti-cancer agents used as theragnostic agents are shown in **Table 3.**

Disulfide Linkage in Copolymer Based Strategy for Tumor Treatment: By using disulfide linkage, a copolymer-paclitaxel conjugate was synthesized and a novel controlled drug delivery system developed by Chen *et al.* in 2012.

Acrylate derivatives were radically polymerized using copolymer-like polyethylene glycol (PEG), and for developing a structural backbone, carboxyl groups were used, which were further followed by conversion of tert-butyl into carboxyl groups on hydrolyzing **Fig. 4.**

Carboxyl group presented on paclitaxel was used as an active site for reaction, employing disulfide bond that was covalently linked to backbone of a copolymer and 32 wt% of paclitaxel was loaded.

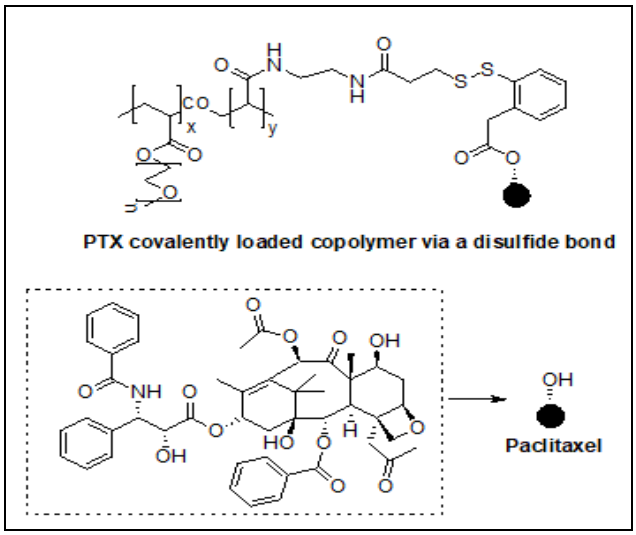


FIG. 4: DEVELOPMENT OF PACLITAXEL LOADED COPOLYMER VIA DISULFIDE BOND

This drug-loaded copolymer complex in an aqueous solution gets self-assembled into spherical micelle, in which the core represented hydrophobic drug while the shell was hydrophilic PEG. Optical techniques were used to measure the mean diameter of micelles, including transmission electron microscopy and dynamic light scattering, and it was found to be 60 nm. Biocompatibility and suitability to use copolymers as a drug carrier were proved by in vitro cytotoxicity studies.

The synthesized copolymer was proven to be chemotherapeutic towards kidney tumor cells, *i.e.*, OS-CR-2 cells but had not shown any toxicity towards normal human cells. This result showed stability of disulfide inside normal cells but readily cleavable in cancer cells. These properties showed that these copolymers could be proved favorable as they were less toxic and have reduced drug side effects [68].

Versatile Disulfide Linkage in Antibody-Drug Conjugates: Disulfide bonds have a bio activating connection in imaging as well as in tumor management therapy.

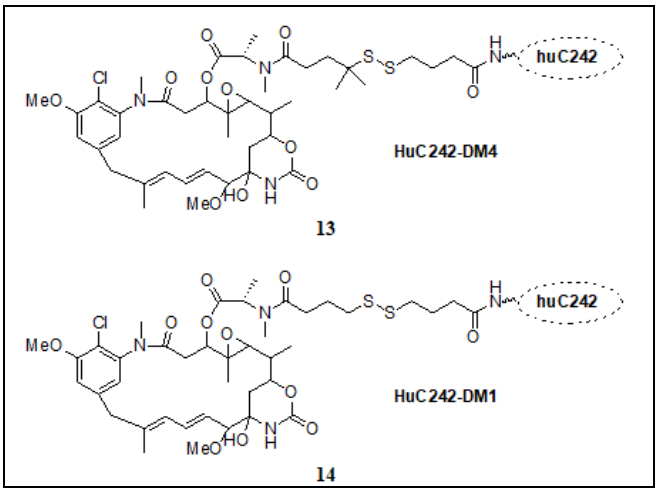


FIG. 5: ANTIBODY-DRUG CONJUGATES HUC242-DM4 AND HUC242-DM1

The first successful cases of disulfide Linkage in antibody-drug conjugates were reported by Chari *et al.*, including two conjugates Hu C242-DM1 and HuC242-DM4 **Fig. 5.** Against the antigen-expressing COLO 205 cells during the *in-vitro* evaluation of both conjugates, it was demonstrated that the conjugates possess tumor-targeting potency, and it was about 1000-fold less cytotoxic toward the antigen-negative human melanoma A-375 cell line while the maytansinoid conjugate HuC242-DM4, bearing a sterically hindered disulfide, was about 2-fold more potent than HuC242-DM1. Based on the promising efficacy, HuC242-DM1 (Cantuzumabmertansine) and HuC242–DM4 was further administered to clinical evaluation in cancer patients [69].

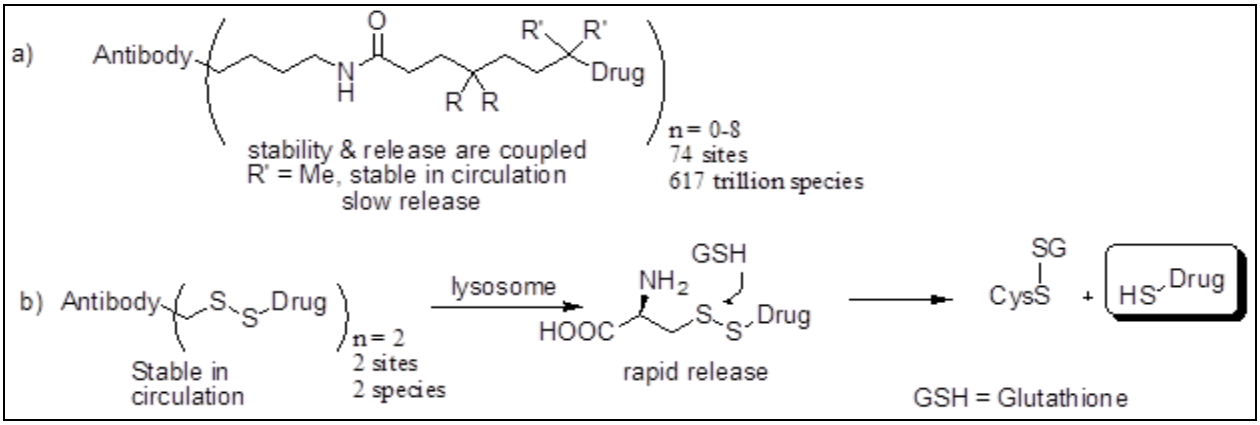


FIG. 6: ANTIBODY-DISULFIDE CONJUGATES A) HETEROGENEOUS LYS CONJUGATES, B) DECOUPLING STABILITY AND RELEASE

Disulfides have circulation stability and intracellular release, but in addition, their higher stability caused a corresponding decrease in bond cleavage and release of payload. But, an antibody can make it reversibly stable.

Pillow *et al.* (2017) examined that by attachment of small molecule in an antibody with unhindered disulfide was stable in circulation yet internalization inside cell and catabolism of antibody generated a rapidly reducible disulfide catabolite **Fig. 6**. This property can be used for the stable and facile release of payload, and also reversible nature offers an improved way for targeting delivery and therapeutic effects [70].

Innovative Disulfide Linkage in Biotin-Anticancer Drug Conjugate: Chen *et al.* (2010) developed a tumor-targeted advanced drug delivery approach on the basis of mechanism and specificity that will target a particular tumor using receptor-mediated endocytosis according to the vitamin used in conjugate developed. This developed conjugate was made tumor-specific using biotin as a vitamin linked to a taxoid, *i.e.,* SB-T-1214 *via* cleavable disulfide linker **Table 4.**

Receptors for biotin were over-expressed on the surface of tumor cells on which site-specific conjugate attacked. The drug was released via glutathione-triggered self-immolated cleavage of disulfide following receptor-mediated endocytosis upon cell internalization. To monitor all the above processes, confocal fluorescence microscopy (CFM) and flow cytometry were done using L1210FR leukemia cells.

Cell specificity was examined using biotin-linked-taxoid-fluorescein on three different cell lines, *i.e.,* a) for which did not have any overexpressed biotin receptors (L1210 cell lines), b) in which negative biotin receptor and healthy mammalian lung fibroblast present (W138 cells), and c) in which overexpressed biotin receptors are present (L1210FR cell lines) and results showed that this molecular probe was highly specific only for L1210FR cells. The anti-tumor activity of the molecular probe was examined against these three cell lines to find the correlation with cell-specific drug delivery. In the same way cell toxicity and specificity for conjugate *i.e.* biotin-linker-SB-T-1214, was determined against the same three cell lines, and excellent results were obtained [71]. Such strategic design of disulfide linkers can be readily applicable to a range of tumor-targeting drug conjugates. In 2014, another tumor-targeting DDS was developed by Ojima's group on the basis of 1,3,5-triazine center, and there are three side chains on it, from which one is connected with biotin and the other two connected with two anti-cancer agents bearing a cleavable linker *i.e.* camptothecin and SBT- 1214 (having different anti-tumor mechanisms).

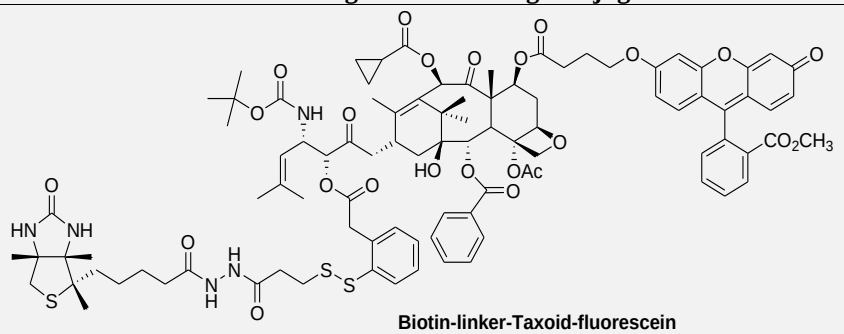
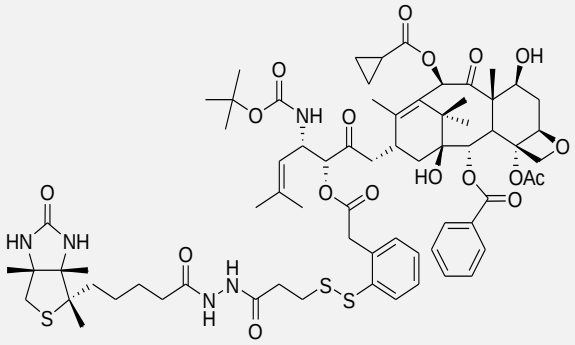
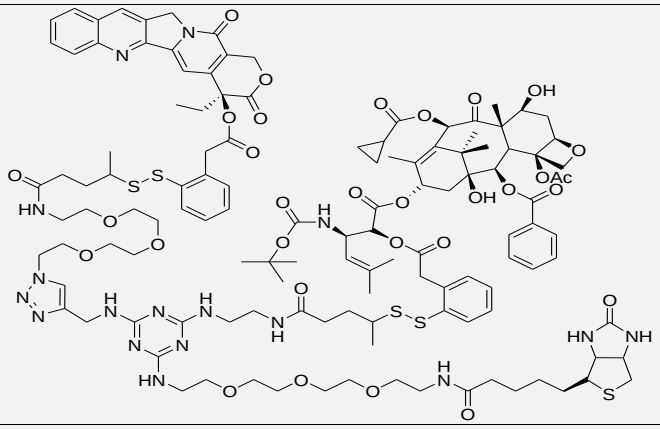
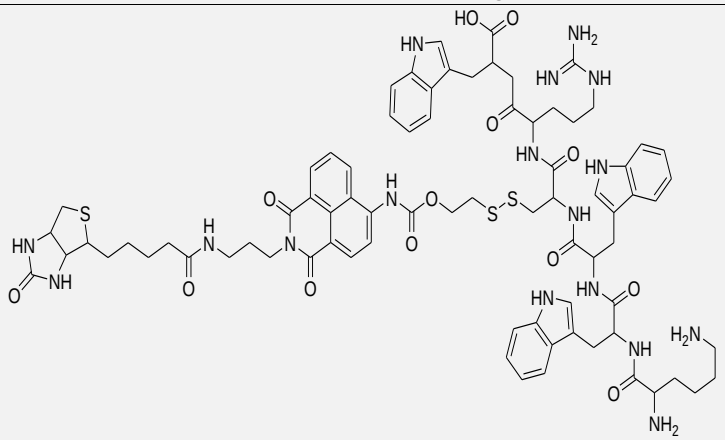
Usage of two drugs produces synergistic effects and helps in increasing the pharmacological effects of the conjugate. Conjugate gave positive responses towards MX-1, MCF-7, ID8, L1210FR, LCC6-WT, LCC6-MDR, MDA-MB 231, and SkBr3 when examined by CFM and Flow cytometry tests. It also showed impressively low IC_{50} values (3.22-9.80 nM) for biotin receptor-positive cancer cell lines while high IC_{50} values (705 nM) in a normal cell line (WI38) during cytotoxicity experiments [72]. Peptides may have extre

mely diverse sequences, and peptide-based drugs can be designed to have enhanced target selectivity with fewer side effects in various physiological and pathological processes. Considering this into fact, Kim *et al.* (2014) proposed a work conjugating a peptide with biotin through a disulfide linker. Holliday junction (HJ) inhibitor peptide 2 (KWWCRW) has limited pharmaceutical applications as it has poor membrane permeability, low bioavailability, and metabolic instability.

By cross-linking the peptide to a biotinylated naphthalimide conjugate with a cleavable disulfide linker. Biotin helps increase the bioavailability of the conjugate as it can directly transport biotin-targeting units into tumor cells via a biotin-selective uptake system. HepG2 and WI-38 cell lines were used to check the stability and selectivity of the conjugate.

Also, it was confirmed by dose-dependent cytotoxicity experiments that this conjugate produced a higher anti-tumor effect than the HJ inhibitor peptide-2 itself. 73The structures of disulfide-linked biotin-anticancer drug conjugates are mentioned in **Table 4.**

TABLE 4: DISULFIDE LINKAGE IN BIOTIN-ANTICANCER DRUG CONJUGATES

S. no.	Disulfide Linkage in Biotin-drug Conjugates	Ref.
1.	 **Biotin-linker-Taxoid-fluorescein**  **Biotin-linker-SB-T-1214 conjugate**	71
2.		72
3.		73

Innovative Disulfide Linkage in Folate-Drug Conjugates: Like biotin, folic acid (FA) is another essential vitamin that can be used for synthesizing tumor-targeting agents. Because FA-linked molecules are efficiently bound and internalized by FR-expressing cells, there is the possibility of using FA to target a small molecule drug to FR-over-expressed tumors. On concentrating this concept,

Leamon *et al.* (2005) designed and evaluated a conjugate in which folate was linked with mitomycin C via disulfide linkage, named EC72, and FR-positive cells were used to examine its anti-tumor efficacy. On the coupling of folic acid-γcysteine with 7-N-modified MMC through a cleavable disulfide bond, EC72 was synthesized. This conjugate expressed dose-dependent activity against folate receptor (FR)-positive cell lines *in-vitro* and also retained higher affinity towards FR-positive cells.

Two reasons that can be considered for EC72's targeted and specific activity for the FR can be (i) biological activity blockage due to excess folic acid and (ii) unresponsiveness of this drug towards FR-negative cell lines. EC72's activity was confirmed initially by *in-vivo* tests in xenograft models. No evidence of myelosuppression or toxicity was observed even on 30 consecutive days of daily dosing of the conjugate to major organs, including the FR-positive kidneys, which made these results significant [74].

Reddy *et al.* in 2006 further carried out investigations on this compound and found that it exhibited no toxicity, but the therapeutic effect was clearly seen against M109 tumors; even Fr-positive kidneys were free from any harmful effects. By comparing this conjugate with EC110 (a folate-MMC conjugate in which amide bond was used for conjugation), they also provided an example of how bearing a cleavable bond like disulfide is important, as EC110 was not able to produce M109 tumor activity.

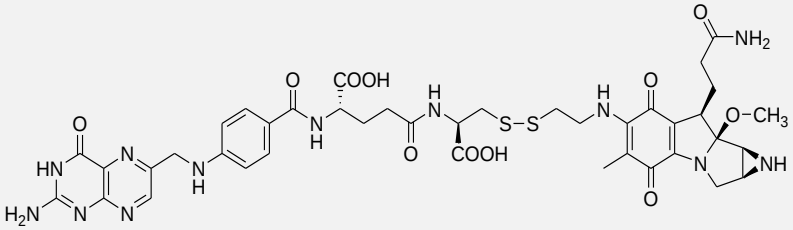
They also revealed that with an increase in the size of the subcutaneous tumor, the therapeutic potential of EC72 gets decreased. They tried combination therapy using paclitaxel to overcome this limitation, which helped enhance anti-tumor efficacy and decrease toxicity and well-tolerated dose levels. Another more advanced folate-MMC conjugate, named EC118, was also developed bearing two linkers, i.e., disulfide bond, which is reducible, and hydrazone bond, which is acid labile. This resulted in more significant results towards a large number of tumor regressions in the case of M109 tumors, which was apparently less in EC72 [75].

In 2007, Leamon *et al.* worked on another strategy by developing a molecule by using two different active anti-tumor agents with a different mechanism of action, but attached to the same ligand. It was a new type of tumor-targeted agent. This folate receptor (FR)-targeted agent was named as EC0225 and represented the "first in class" multidrug. It was constructed using a single folate molecule, extended by a hydrophilic peptide-based spacer, which was further connected to Mitomycin and Vincaalkaloid units through two separate disulfide linkers.

In-vitro studies of conjugate showed potent, dose-responsive activity and on the administration of well-tolerated dosing regimens produced curative activity against FR-positive xenograft tumors. It was observed that EC0225 can even cure tumors as large as 750 mm^3 in volume when used to treat mice [76]. In the same year, Reddy et al. developed another molecule EC131, a new folate receptor (FR)-targeted drug conjugate, using potent microtubule-inhibiting agent maytansinoid DM1 and combining it with folic acid (FA) *via* an intramolecular disulfide bond.

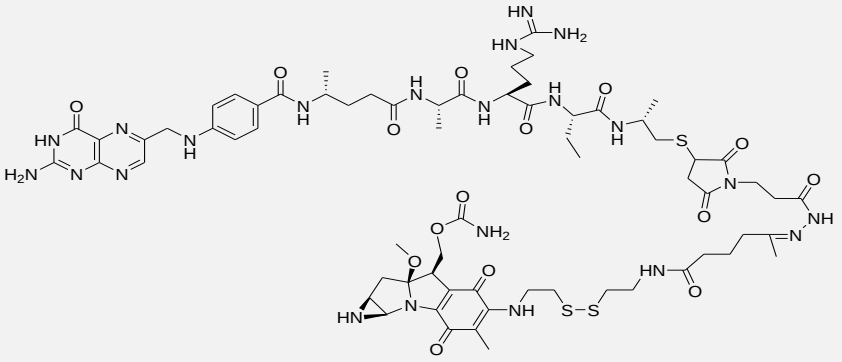
EC131 retained its efficacy towards FR-positive cells when tested on cells in culture and gave FR-specific cytotoxicity having IC_{50} value in the low nanomolar range [77]. The structures of disulfide-linked folate-anticancer drug conjugates are mentioned in **Table 5.**

TABLE 5: DISULFIDE LINKAGE IN FOLATE-ANTICANCER DRUG CONJUGATES

S. no.	Disulfide Linkage in Folate-drug Conjugates	Ref.
1.		74

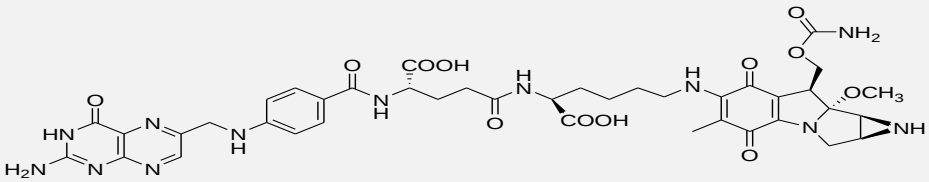
19 (EC72)

2. [75]



EC118

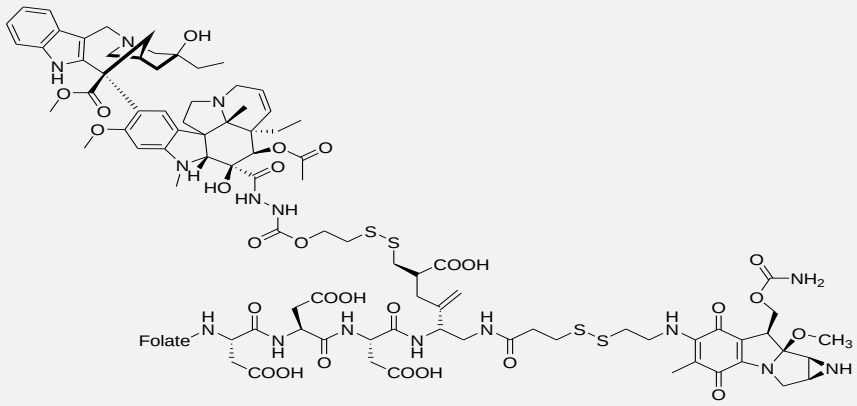
20



EC110 (Folate-Lys-MMC)

21

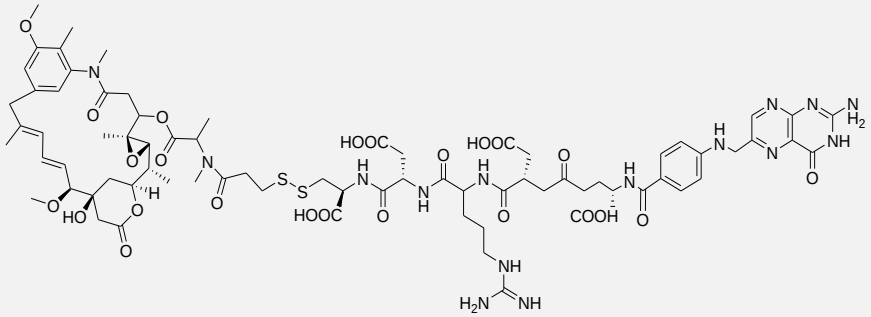
[76]



EC0225

22

[77]



EC131

23

Steric Effects of Disulfide Bond: Reactions that proceed through SN2 type mechanism, steric factors play a major role in their kinetics because of a crowded transition state structure. For the best orientation of their molecular orbitals, middle and leaving moieties should have linear conformation [78, 80]. Bulky functional groups can hinder access to attacking thiol, and it increases activation energy. Furthermore, the binding of a substrate can be stabilized by steric interactions [81, 82]. Moreover, it has also been seen that steric factors can make disulfide linkage more labile by accelerating their interchange reactions due to increased strain development on disulfide bond [83]. When an

external -SH group is substituted into a disulfide structure, an SN2 mechanism is preferred theoretically. The rate of disulfide cleavage can be diminished by an increase in steric blockage. Sterics formed by groups adjacent to disulfide bonds affect the drug's biological and non-biological therapeutic effect conjugates [84].

Successful Cases of Disulfide Linked Anticancer Agents: As mentioned in research studies, the efficacy of tumor-targeted drug conjugates is due to its therapeutic warhead, hence according to drug payloads, disulfide-linked tumor-targeting agents are classified.

These highly efficient and potent anti-tumor agents that are used for designing tumor-targeting agents are paclitaxel, vinblastine, epothilone, mitomycin C, tubulysin, and camptothecin derivative SN-38 **Fig. 7.**

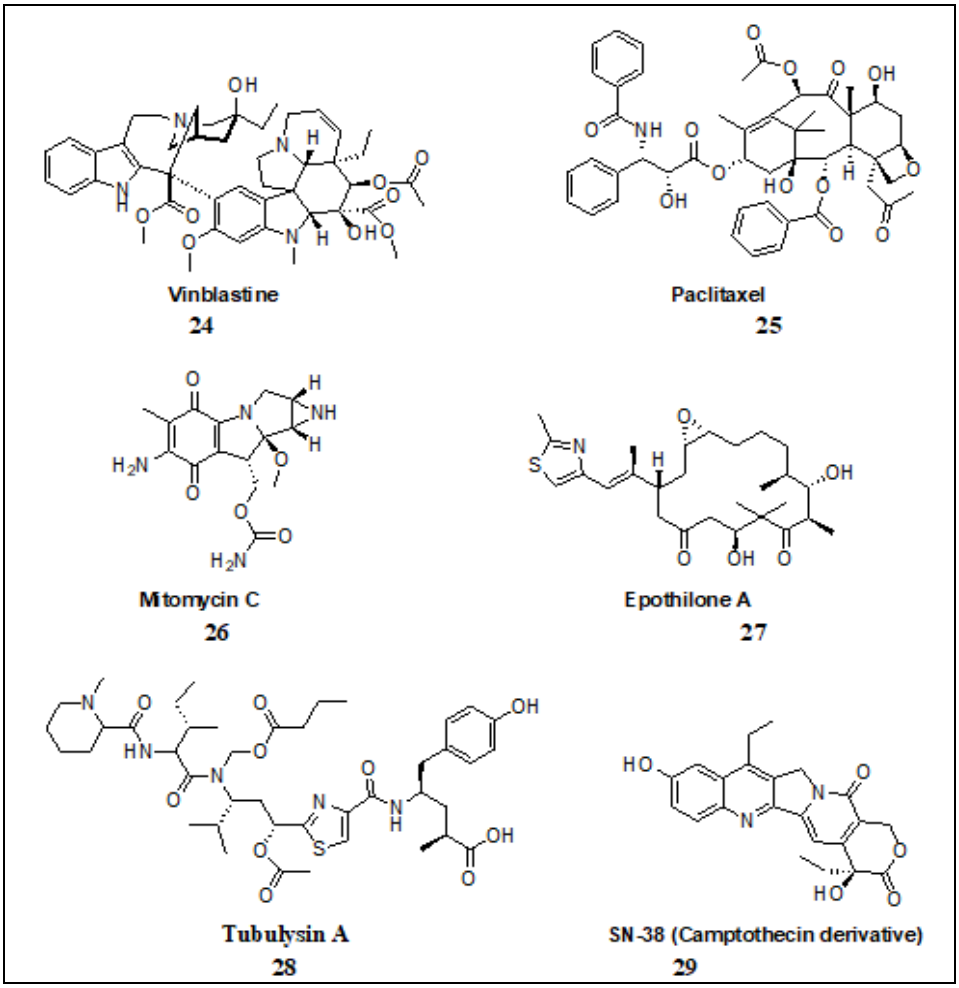


FIG. 7: ANTI-CANCER AGENTS USED IN DESIGNING TUMOR-TARGETING AGENTS HAVING DISULFIDE LINKAGE

By using the above-mentioned active cancer treating agents, till date, many drug conjugates bearing disulfide have been reported that have successfully entered into clinical trials.

Vinblastin: In 1958 it was first isolated from *Catharanthus roseus* and used for the treatment of bladder, non-small cell lung, and brain cancers. 85 By inhibiting the assembly of microtubules and mitotic cell division, vinblastine mechanistically acts as a microtubule-destabilizing agent (MDA). Using the small molecule drug conjugate (SMDC) strategy, it can synthesize highly selective anti-tumor agents that can have lower toxicity for normal human cells. Based on all these theories, some tumor-targeting agents were synthesized like EC0272, EC0265, and EC0276 by the introduction of a methyl group nearby disulfide region.

In comparison to unmodified compounds, these molecular probes have significantly greater stability, and also their rate of disulfide cleavage got decreased. Under reducing conditions, half-lives (t1/2) of EC0265 and EC0272 were 1hour and

0.5 h respectively (8 mM DTT, pH = 7.4, 37 °C). Another derivative, EC0276 (four methyl group-substituted disulfide derivative) have half-life more than 8 h and have stability more than 3 days in the presence of PBS buffer. This stability also affects the cytotoxicity of the compounds. EC195, a derivative synthesized from vinblastine, also proposed that the active molecule will be released by thioquinone-methide-based 1,6-elimination. But by 1,2-elimination, the parent drug was released faster, as in the case of EC145, than that of 1,6-elimination. In GSH and DTT, half-lives were 45 min and less than 5 min respectively and had stability in PBS for over 24 h (pH = 7.4, 37 °C). 86-93

Tubulysin: Antibiotic products "Tubulysins" are from mycobacterial family that possesses anti-angiogenic, anti-cancer, and antiproliferative activities, and they target microtubules [94, 95]. In the picomolar range, IC_{50} values of these agents have cytostatic effects on different cancer cell lines [96]. However, in comparison to their therapeutic potentials, they have a double-edged sword, severe toxicity. To overcome the drawbacks, tubulysin was conjugated with folatevia disulfide linker (EC0305) [97]. Another tubulysin folate conjugate EC0510 has a similar IC_{50} value to EC0305 was synthesized. In KB cellular tumor mouse models, both of these conjugates showed different efficacies. With 80% complete reversion by animals, EC0510 exhibited excellent anti-cancer activity at 0.5 μmol/kg dose. On the other side, at the same dosage, moderate tumor regression was showed by EC0305. But as the dosage increased from 0.5 to 1.0 μmol/kg it showed a promising anti-tumor effect, and in the span of 80 days of study, all mice tumors were disappeared.

Analog of tubulysin B, EC0317, which was also a folate conjugate and methyl- ether analog, was also synthesized using disulfide bond. This conjugate was less active in comparison to EC0305 even at a dose of 2.0 μmol/kg. Even against FR-positive M109 and 4T1-cl2 models, EC0305 possessed better anti-tumor activities than Vinblastine conjugate EC145 [98]. Different spacers were used for modification in tubulysin-folate conjugates. A second-generation spacer was used for conjugate EC1456, which further moved to phase I clinical trials for advanced solid cancer [99]. Without off-target binding 2-[3-(1,3-Dicarboxypropyl) ureido] pentanedioic acid (DUPA), a ligand of prostate-specific membrane antigen (PSMA) can be selectively attached for imaging and therapeutic efficacy against prostate cancer cells. With a limited expression on normal tissues, most prostate cancers (PSMA) are highly expressed. DUPA-TubBH was one such molecule that is used as a PSMA-targeted anti-tumor agent; PSMA-positive LNCaP cells got killed by this conjugate (IC_{50} = 3 nM) and with no loss in body weight and it eliminated almost established tumor xenografts in nude mice [100].

With an undisclosed structure, EC1169 a derivative of DUPA-TubBH, was developed using a releasable disulfide linker in TubBH structure and act as a high-affinity PSMA-targeting ligand which further progressed to phase I clinical trials against prostate cancer [101]. Conjugate CRL-L1-TubBH was also generated by conjugation of Tubulysin B with cholecystokinin 2 receptor (CCK2R) ligand, which specifically inhibits CCK2R-positive tumors and with negligible cytotoxicity against normal cells but have excellent receptor-specific anti-tumor effect [102].

Paclitaxel: Another clinically effective first-line chemotherapeutic agent is Paclitaxel (PTX), which can help treat different types of tumor and also cause promotion of tubulin assembly into microtubules [103]. But several shortcomings like poor solubility in water, less selectivity, and other toxic effects included neurotoxicity, hyper-sensitivity, nephrotoxicity, and cardiotoxicity, limiting its pharmacological applications.

Octreotide as a ligand was used to overcome the above-mentioned drawbacks, which bound explicitly to somatostatin receptors 2 and 5 (SSTR2 and SSTR5) and resulted in higher efficacy towards cancer cells. Thus, a tumor-targeting agent was designed as Octreotide (Phe)-polyethylene glycol–paclitaxel [OCT (Phe)-PEG-PTX] bearing a disulfide bond.

This conjugate had higher cytotoxicity towards NCI-H446 cells (overexpression of SSTR) and less towards WI-38 cells (normal cells without SSTR expression) and also had a pH-dependent profile. Also, *in-vivo* studies showed that OCT (Phe)–

PEG–PTX had better anti-cancer potential (66.3% inhibition in tumor weight) with low systemic toxicity than mPEG-PTX conjugate (43%) and commercially available PTX (Taxol, 54.3%) in an xenograft mouse model of NCI-H446 cancer cells [104].

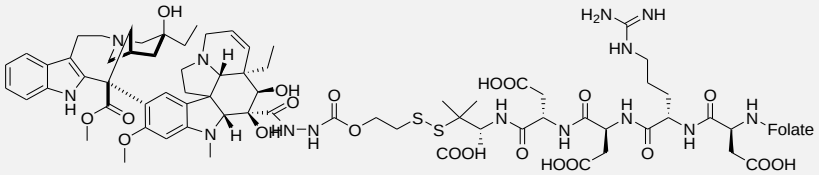
Mitomycin C: An antibiotic Mitomycin is usually known as mitomycin C (MMC), is obtained from the broth of *Streptomyces caespitosus* [105, 106]. This compound has a very wide anti-tumor spectrum and showed its effectiveness towards pancreatic cancer, breast cancer, gastric cancer, cervical cancer, neck, head, and bladder cancer [107]. But fast clearance and cellular toxicity limited its clinical use [108]. EC72 is one of the conjugates which was synthesized by using folic acid as targeting ligand, and it showed an effective dose-response towards FR-positive cell lines in *in-vitro* studies. At the same time, it does not produce any toxicity or pathological degeneration in animals.

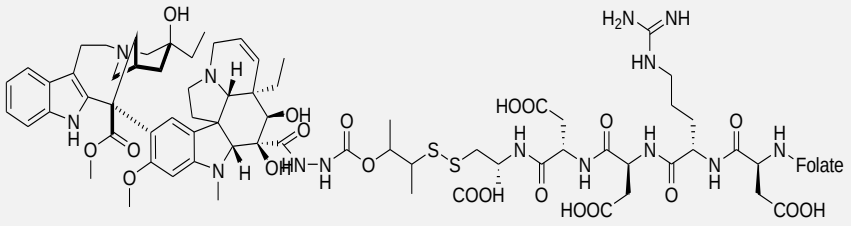
In another research, the disulfide linker of EC72 was changed with carbon chain and a non-releasable conjugate (EC110) was synthesized but it was not able to create any potent anti-tumor effect at same dose like EC72, which proved that disulfide is important for effective drug delivery. But increased in subcutaneous tumor size the therapeutic effect of EC72 also got decreased. 74 One more folate-MMC conjugate (EC118) was also constructed in order to elevate tumor efficacy by the use of two linkers *i.e.*disulfide bond and an acid-labile hydrazone bond. Against subcutaneous M109 tumors, this conjugate showed more potency in comparison to EC72. Also, anti-tumor efficacy improved by using a combination of MMC and paclitaxel [75]. This multidrug approach can result in great deposition of the drug inside tumor mass and for that, EC0225 was synthesized comprising both PTX and MMC and made it FR-expressing tumor-specific [76]. This folate-targeted multidrug conjugate on passing pre-clinical studies initiated towards Phase I clinical trials (CTI: NCT00441870) for patients who have refractory or metastatic tumors and do not get treated by standard therapy.

Others: Another class of anti-cancer drugs that target microtubules isepothilones [109]. Ixabepilone (Ixempra), one of these analogs, got approved in 2007 by the FDA and was used to treat metastatic and breast cancers that weree early not responding towards standard chemotherapies [110]. Endocyte Inc. and Bristol Myers Squibb together developed BMS-753493 conjugate, *i.e.*, Epofolate. By using epothilone, a semi-synthetic analog, Epofolate was constructed as folate conjugate. But due to unknown reasons phase, II clinical trials of the conjugate were terminated.[111]. In another conjugate, conjugation of folic acid was done with Camptothecin using releasable disulfide carbonate linker and hydrophilic peptide spacer.

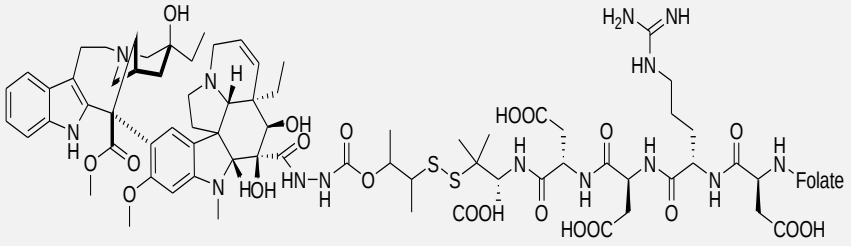
This conjugate proved higher efficacy towards folate receptor-expressing cells and also helped to prevent cell proliferation of KB cells having IC_{50} values of 10 nM [112]. To validate the use of SMDC in targeting tumor-associated phosphatidylserine (PS) in the tumor microenvironment (ZnDPA)-SN38 conjugate was developed [113]. By attaching folic acid to maytansinoid, an anti-microtubule agent, a cleavable disulfide bond EC131 conjugate was designed. With an IC_{50} in the low nanomolar range, this compound has shown a high affinity for FR-positive cells in the pre-clinical investigation. The pre-clinical studies were conducted on BALB/c mice and human KB models in FR-positive M109 cells [77]. Another conjugate was synthesized when HDAC (Histone Deacetylase) inhibitor (NCH-31) *via* a disulfide bond attached to folic acid. Against FR-positive MCF-7 breast cancer cells, the compound showed good growth-inhibitory activity [114].

TABLE 6: SUCCESSFUL CASES OF DISULFIDE-LINKED ANTI-CANCER AGENTS

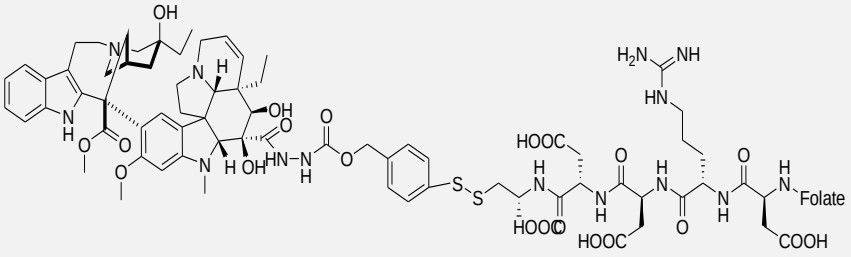
S. no.	Structure with Compound Name	Ref.
1.	**Vinblastine as active drug**	
		86, 93
	EC0265	



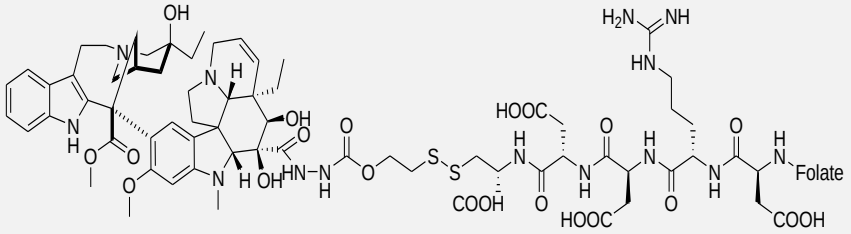
EC0272



EC0276



EC195

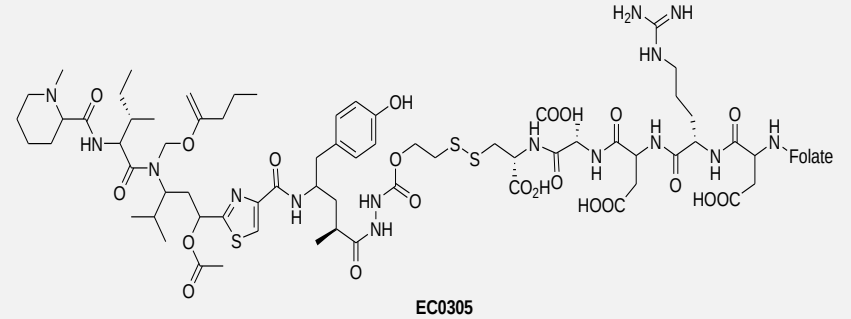


EC145

NCT01170650 (In phase III)

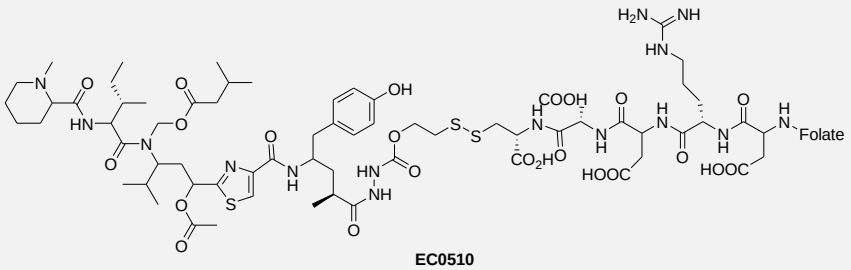
2. **Tubulysin as active agent**

97



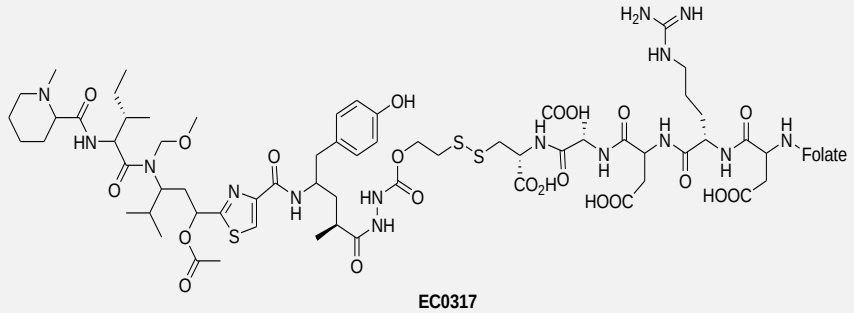
EC0305

98



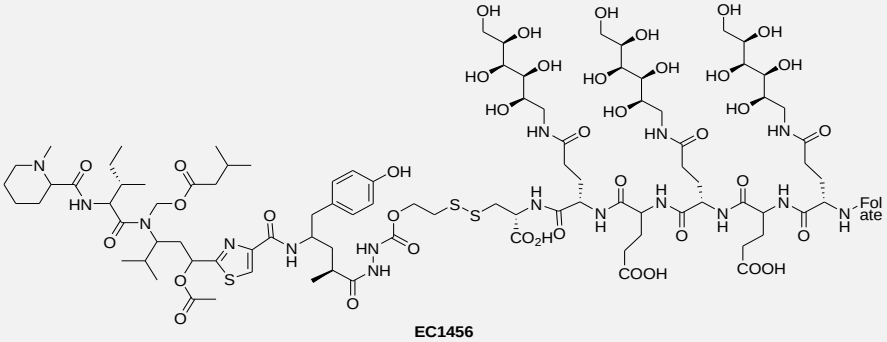
EC0510

98



EC0317

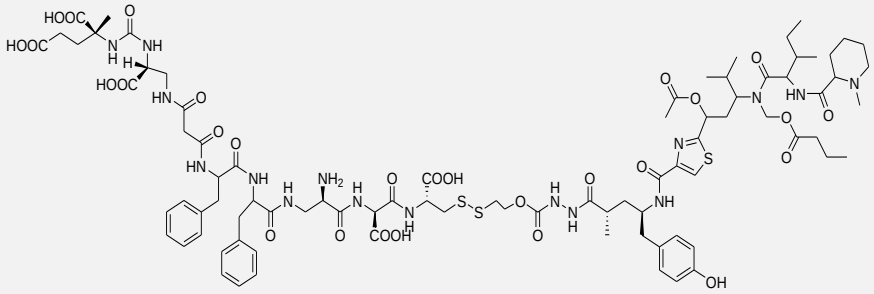
99



EC1456

NCT01999738 (In Phase I)

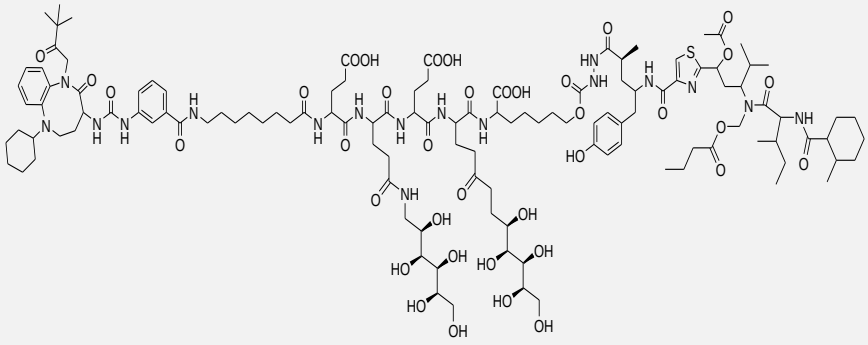
100



EC1169
(DUPA-TubBH

NCT02202447 (In phase I)

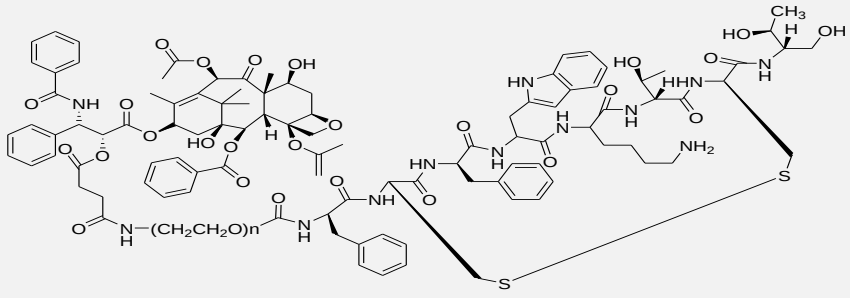
101



CRL-L1-TuBH

3. **Paclitaxel as active agent**

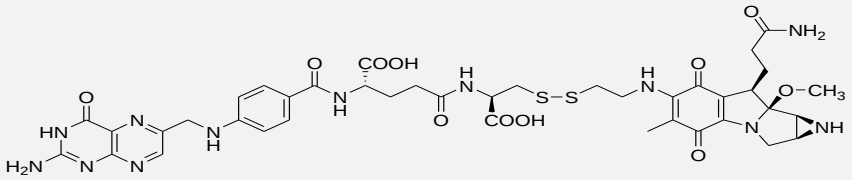
105



OCT(Phe)-PEG-PTX

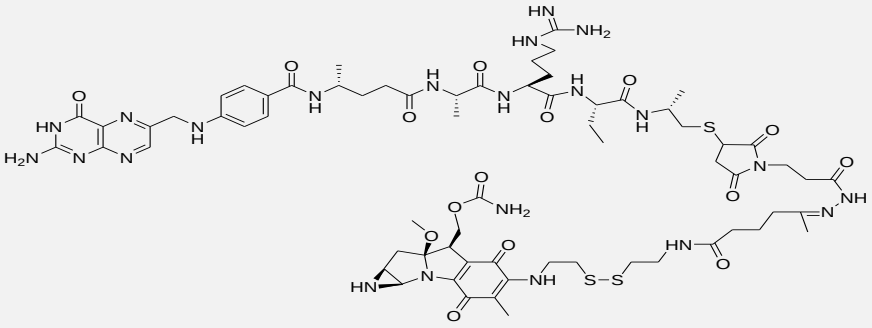
4. **Mitomycin C as active agent**

74



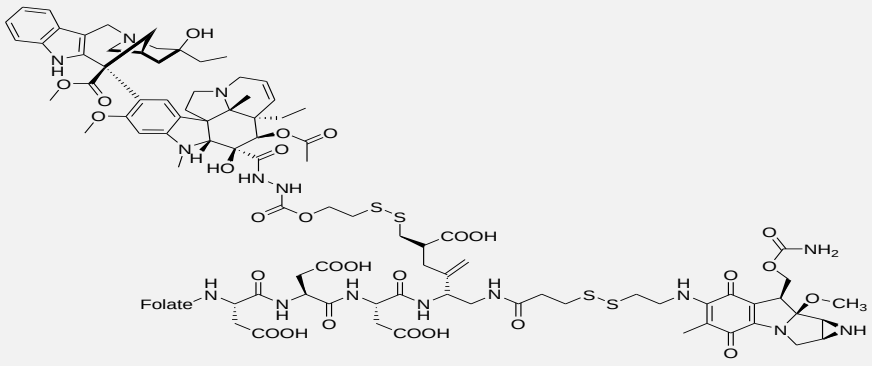
EC72

75



EC118

76

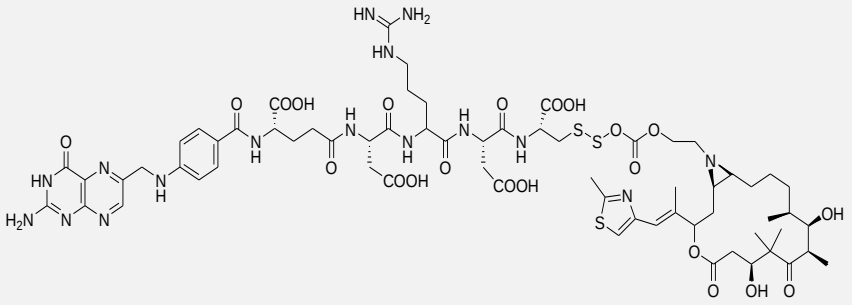


EC0225

NCT00441870 (In phase I)

5. **Others**

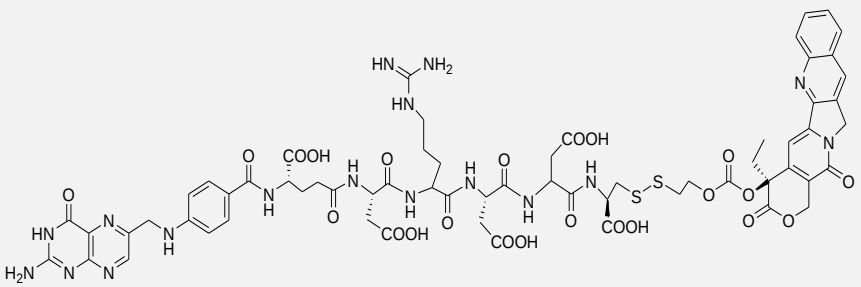
111



Epofolate
(BMS-753493)

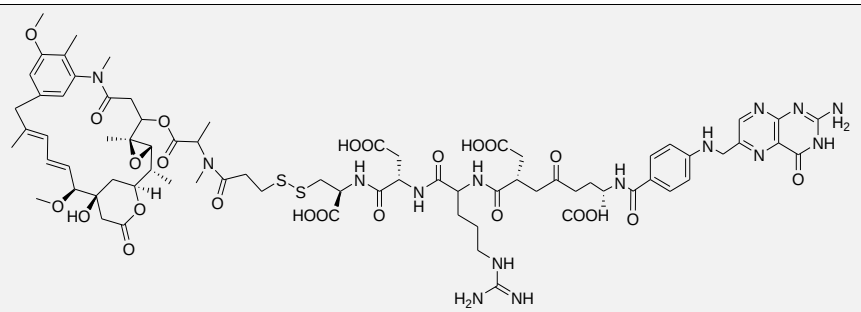
NCT0050017 (In Phase I)

112



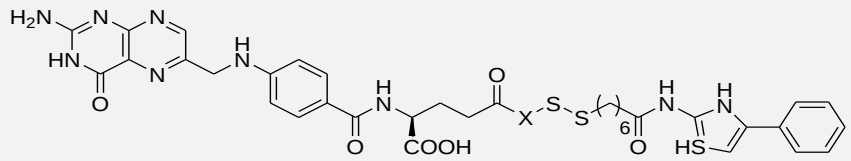
Camptothecin derivative with disulfide linker

77



EC131

114



Folate-NCH-31

1. X = $NHCH_2CH_2^-$
2. X = $NHCH_2CH_2OCH_2CH_2OCH_2CH_2^-$

Conclusion and Future Per-Spectives: Due to the rapid development and expansion of targeted drug design, interest in disulfide-based biodegradable linkers is growing at a faster rate. With improved anti-tumor efficacy, numerous potent conjugates have been presented, which have increased tumor inhibition and reduced side effects and better tumor selectivity. Several more of these targeted conjugates are under clinical or pre-clinical study.

Disulfide linkage-based tumor-targeting conjugates development has definitely opened the gate for a drug delivery system that is more effective and cell-specific. Several strategies can be employed in synthesizing a tumor-targeting conjugate having disulfide linkage with monoclonal antibodies (mAb), glucose, biotin and folic acid. By using disulfide bond linkage, the carrier and chemotherapeutic agent together act as bi-functional conjugate. Even though there are several successful cases of conjugates bearing disulfide bonds and have superiority in targeted drug delivery, much has to be done for further improvements. In conclusion, disulfide bonds have provided significant tumor-targeting conjugates that improve the drug's anti-cancer efficacy with a reduction in side effects. And further investigation on the design of disulfide linkage will bring more progress in the development of targeted tumor drug delivery systems.

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