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CAMPTOTHECIN AND ITS ANALOGUES: A REVIEW ON THEIR CHEMOTHERAPEUTIC POTENTIAL

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ABSTRACT

Camptothecin (CPT), a cytotoxic quinoline alkaloid originally isolated from *Camptotheca acuminata*, has gained significant attention for its potent anticancer properties. Its mechanism of action involves the inhibition of DNA topoisomerase I, an essential enzyme for DNA replication and transcription. Despite its promising activity, native camptothecin suffers from poor solubility, instability of its lactone ring at physiological pH, and severe side effects, which limit its clinical application. To overcome these limitations, extensive research has led to the development of various CPT analogues with improved pharmacokinetic profiles and reduced toxicity. Among these, topotecan and irinotecan have been successfully introduced into clinical practice, demonstrating efficacy against a broad spectrum of cancers, including ovarian, colorectal, and small-cell lung cancers. Other novel analogues, such as belotecan and exatecan, are currently under investigation, showing enhanced therapeutic indices and tumor selectivity. Structural modifications of the A and B rings, and substitutions at position 7 and 10 of the CPT molecule, have been particularly effective in enhancing activity and overcoming resistance mechanisms. This review summarizes the current understanding of camptothecin and its analogues, focusing on their mechanisms of action, structure-activity relationships, pharmacological advancements, and clinical relevance. The continual evolution of CPT derivatives underscores their enduring role as valuable chemotherapeutic agents and highlights the importance of rational drug design in optimizing anticancer therapy.

INTRODUCTION

Wall and colleagues discovered Camptothecin (Figure 1), a heterocyclic ring containing alkaloid, from preparations of *Camptotheca acuminata*, a Chinese plant, in 1966 (0). Camptothecin was evaluated in the laboratory after positive reinforcement in lab animals as an

anticancer drug. Unaltered CPT's medicinal value is hampered by its limited water solubility, severe cytotoxicity, and quick deactivation by lactone ring breakdown at physiological pH. Lactone breakdown in acidic environments results in a hydrophilic carboxylate. The last is inert and quickly adheres to protein albumin in serum,

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preventing cellular absorption. However, the Na salt is removed mostly by renal and produces hemorrhagic nephritis and myelotoxicity, resulting in the studies being halted(2).

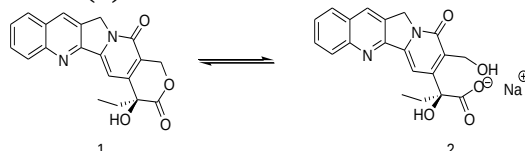


Fig (1): Structures of camptothecin (1) and water soluble sodium salt (2)

The revelation that CPT's principal biological objective is DNA topoisomerase I (topo I) rekindled curiosity in the drug and resulted in the creation of additional hydrophilic analogs. Irinotecan (Camptosar, 3) and Topotecan (Hycamtin, 4) (Figure 2) were granted FDA approval for the treatment of tumors, lung tumors as well as resistant colorectal malignancies, respectively (3).

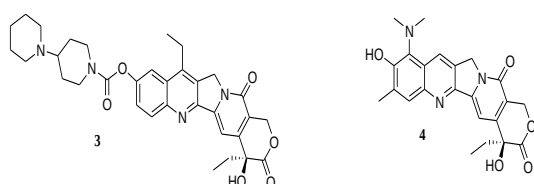


Fig (2): Structure of Irinotecan (3), Topotecan (4)

SYNTHETIC SCIENTIFIC STUDIES:

CPTs and their analogs have created a fertile ground for the advancement of concurrent complete synthesis techniques. Camptothecin and its analogs are currently the subject of various synthetic techniques. Also, there are various semi-synthetic ways of producing CPT analogs. Considering the framework of CPT, several synthetic techniques employing a variety of methodologies have been described. Stork

and Schultz published the very first effective complete preparation of the substance's chiral state in 1971(4). Additional 20(S)-CPT syntheses have indeed been reported ever since. Tagawa *et al.*, published the very first non-symmetric preparation of 20(S)-CPT around 1989, using an N-tosyl-Rproline analog as such asymmetric adjunct to promote the stereoscopic guided building of something like the single chiral center. Comins and Nolan's quickest asymmetrical preparation of CPT so far entails the production of something like the C-ring through an N-alkylation as well as a critical intra-molecular Heck moiety closing reaction (Figure 3, A), Curran *et al.*, devised an intriguing method in which properly modified A- and D/E-rings (Figure 3, B) engage inside a free-radical sequence, resulting in the production of something like the CPT's B- and C-rings (5). Fortunak described a different concurrent development of both the B- and C-rings. Researchers employed an effective intra-molecular Diels-Alder process (Figure 3, C), that is currently financially viable. Blagg and Boger proposed a novel preparation of 20(S)-CPT premised upon the Diels-Alder coupling reaction of such electron-less diene molecule N-sulfonyl-1-aza-1, 3-butadiene along with electron excess molecule dienophile again for construction of the precursor for CPT (Figure 3, D). The major aspects of Bosch's creative technique (6) were intramolecular reactive cyclization to generate the C-ring, succeeded by asymmetrical E-ring production utilizing enolate synthesis (Figure 3, E). again for D-ring synthesis of CPT, Ciufolini and Chavan used intermolecular (Figure 3, F) or intramolecular (7) (Figure 3, G) Michael addition processes, correspondingly. Henegar *et al.* presented a new chemically

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synthesized approach for 20(S)-CPT that is predicated upon that traditional Friedlander reaction of 2-aminobenzoate-aldehyde (A-ring) well with compiled C/D/E ring structure (Figure 3, H) again for CPT B-ring (8).

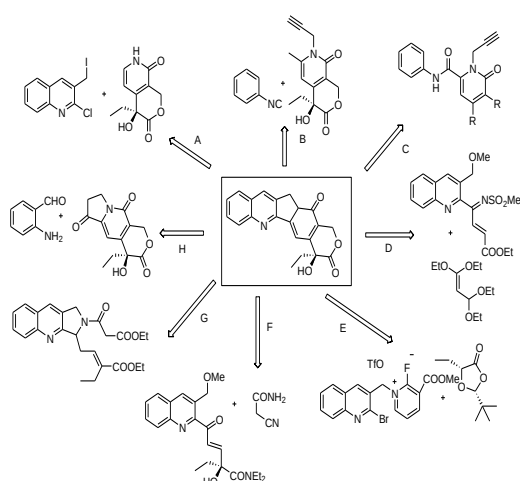


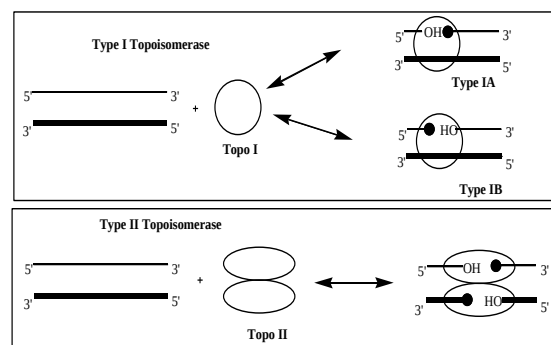
Fig (3): Selected strategies for the synthesis of camptothecin.

MODE OF ACTION:

The complete response is described as follows, by the CPT underlying mechanism: CPTs cause tissue damage during the S-phase in such cytoskeleton by attaching towards the TOPO- I-DNA pair and creating a buildup of breaks in DNA strands at the time of replication. This same structure is typically a temporary auxiliary responsible for DNA relaxation throughout a variety of essential biological processes and it is typically quickly recoverable in the absence of CPT (910). Topoisomerases are crucial nuclear proteins that change the topographical state of DNA by introducing transitory breaches in the phosphodiester framework (1112). They are capable of relieving torsional strain in helical structure DNAs and resolving topologically complicated DNA molecules.

Topoisomerases play critical roles in fundamental biological functions such as

transcription and replication (13,14). This represents the fundamental process catalyzed by topoisomerases. These enzymes were first categorized as type I or type -II enzymes based on whether they catalyzed their processes by creating temporary single-stranded DNA or intermittent dual-stranded DNA, as illustrated in (Figure 4). This molecular explanation is still valid, despite the recent revelation of additional members of both the topoisomerase group (15); it has grown significantly more difficult. Type I molecules are further subdivided into two separate subcategories without any structural similarity, Category I A (which includes bacterial type I topoisomerases) as well as Category I B (which includes eukaryotes kind I topoisomerases) (Figure 4). Category I. A processors, which demand magnesium like a coenzyme, target a single-stranded sequence of DNA to form a temporary covalently complex in which the catalyst is connected towards the 5'-end of the snipped strand and then relaxes only slightly. Topo I B, on the other hand, does not demand metallic ions or even a single-stranded area to produce a temporary DNA-(3'-phospho-tyrosyl)-enzyme phase and may release either negative or positive superhelicals (16). Furthermore, topoisomerases-II requires ATP but Topoisomerases- I must not.



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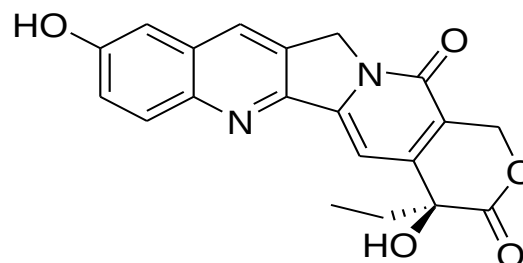
Fig (4): Type I topoisomerases make single strand DNA cuts and type II topoisomerases make double strand DNA cuts.

CAMPTOTHECIN MODIFICATIONS:

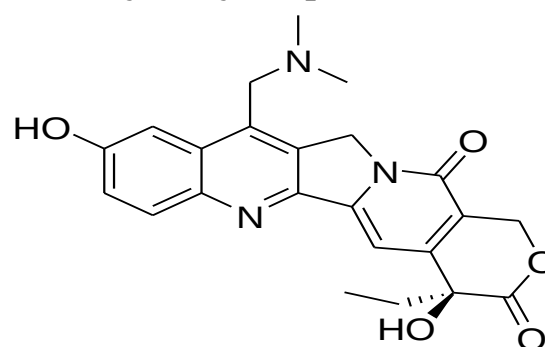
Camptothecin alterations have sparked a lot of interest in an attempt to enhance the parent substance's therapeutic efficacy. Soon after the development and preliminary studies with CPT, several semi-synthetic compounds were created to overcome the dissolution and stability difficulties with CPT. Many additional analogs were synthesized, like folate conjugate, esters conjugates, or amine conjugates.

QUINOLINE MODIFICATIONS

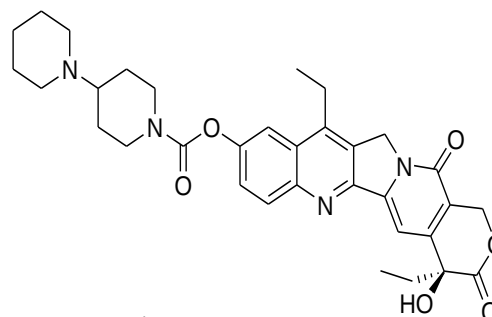
The most typically changed area of Camptothecin seems to be the quinoline ring. These compounds have better bioavailability, lactone stability, and anticancer action. Amongst some of the various derivatives are the FDA-approved therapies topotecan and irinotecan (17). Figure 5 illustrates each of the quinoline-modified derivatives.



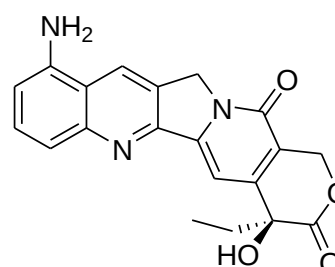
10-hydroxycamptothecin



Topotecan

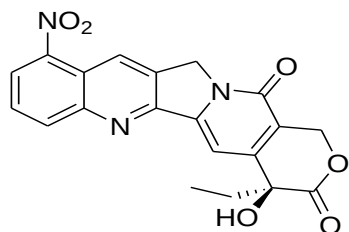


Irinotecan

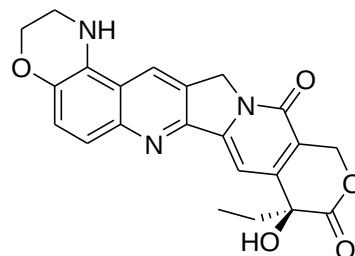


9-aminocamptothecin

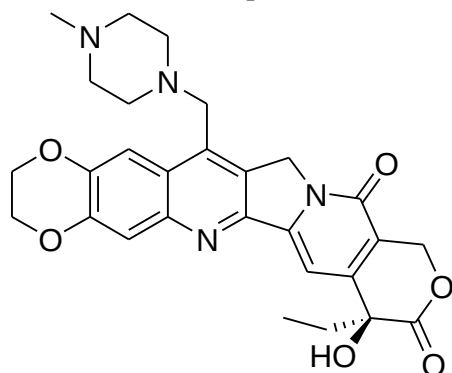
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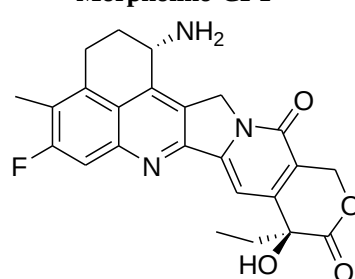
9-nitrocamptothecin



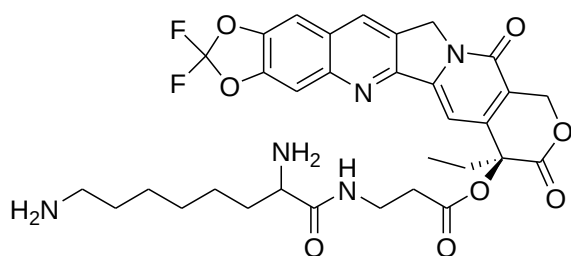
Morpholino-CPT



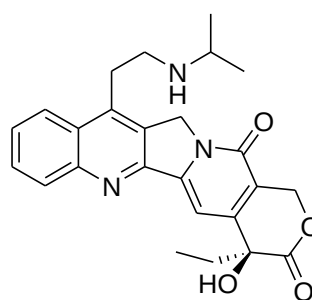
Lurtotecan



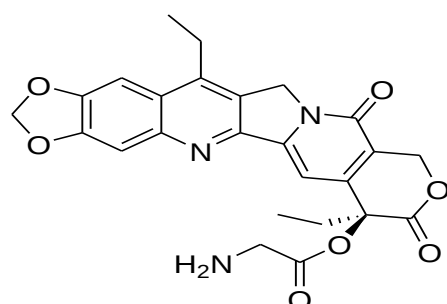
Exatecan



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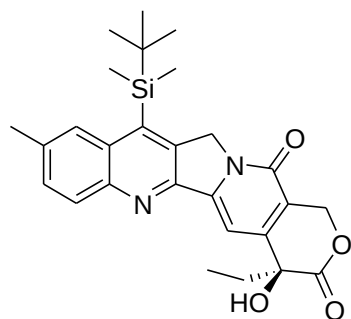


Belotecan

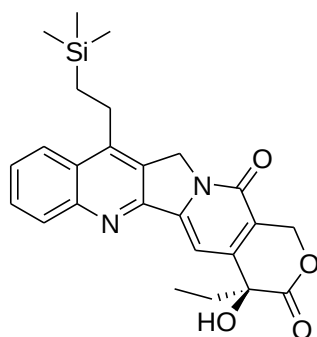


CMMD-Gly

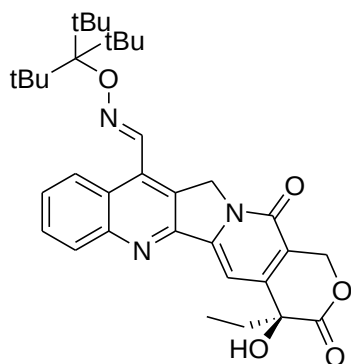
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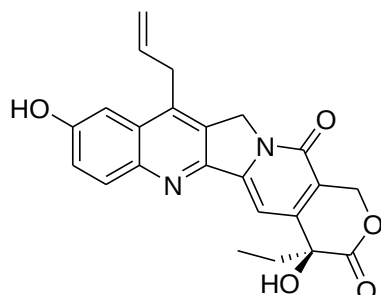
DB-67



Karenitecin



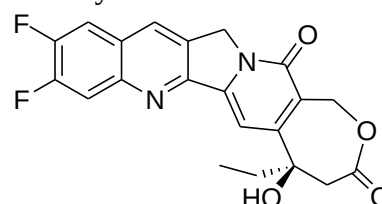
ST1481



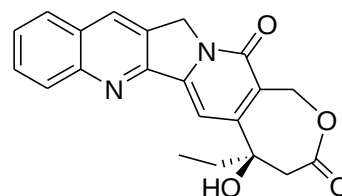
Chimmitecan

E-RING MODIFICATIONS

Changes in the A or B moieties of camptothecin, as initially disclosed, increase dispersion and lactone stability although often keeping, even though not enhancing, potency. Because of the substance's total inactivity, the C or D moieties seem to be the least frequent locations for changes. Because of the low effectiveness of the lactone modification, only a few alterations towards the E-ring were recorded (18). The homocamptothecins depicted in Figure 6 have shown potential in terms of E-ring stability and anti-tumor action.



Diflomotecan



BN80927

Fig (5): Quinoline-modified derivatives

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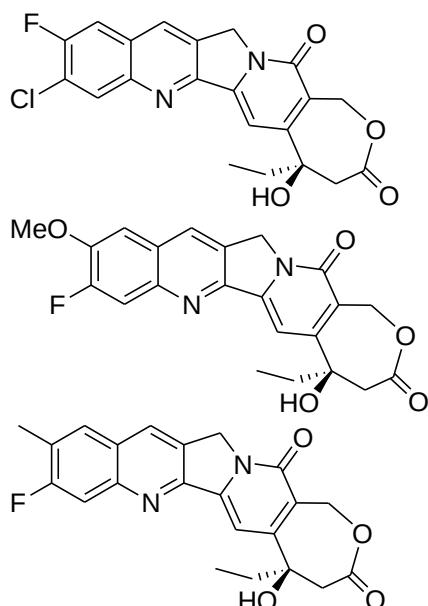


Fig (6): Diflomotecan and related modified camptothecin

20-HYDROXY-LINKED MODIFICATIONS

The stability of lactone has been demonstrated to enhance when the 20-OH group is esterified or alkylated. A 1992 proposal postulated the -OH group as a facilitator of lactone breakdown by activating water via hydrogen bonding (19). While several ester analogs have been created, only a few 20-O-hydroxyl alterations have been evaluated in humans. A few instances of A-ring alterations have previously been explored. The remaining cases are addressed here, and the use of this -OH to covalently attach CPT and its analogs to macromolecular designs will be discussed later.

HYDROPHOBIC ESTERS OF CPT

Cao and colleagues described the synthesis and potential of a variety of camptothecin and 9-NO₂-camptothecin esters (9-NC) (20). The lactone moiety of propanoate of Camptothecin in human serum decreased to 56% after 6 hours, contrasted to just 0.5% after 2 h for Camptothecin. In comparison,

9-NC propionate had increased stability in blood serum, having 64.4% lactone intact at 6 h as well as 5.8% remaining after 51 h, contrasted to just 7% around one hr for 9-NC. Camptothecin propanoate has been studied in CLO-breast tumor and SPA lung tumor murine models using nude mice, whereas 9-NC propanoate has been studied in SQU cells from colon tumors. Under 8 weeks, the magnitude of the breast cancer tumors was determined. In the propanoate-treated mice, the mean size of the tumor ranged from 500 to 100 mm³ at dosages of 5-8 mg/kg, while the average tumor size in the untreated animals was 4500 mm³. In carcinoma xenografts from the SPA and SQU, comparable outcomes were seen. The propanoate and butyrate esters displayed the highest levels of cytotoxicity in HL-60 cells as well as U-937 cells when cultured in a subsequent investigation using 9-NC (21). However, due to the constructs' insufficient solubility, the researchers had to disperse the substances in cottonseed oil along with introducing the resulting mixtures through the gastrointestinal cavity via the anterior portion of the stomach daily for five consecutive days straight each week throughout the research. In vivo results employing Doyle lung carcinoma, BRO-melanoma, SPA lung carcinoma, and BRE stomach tumor xenografts additionally suggested announcing antitumor behavior. Despite the compounds' potential anticancer and lactone stability, the mode of delivery was not the best for long-term therapy (22).

AMINO ACID ESTERS OF CPT

A set of 20-hydroxyl-associated glucose conjugates of CPT exhibiting superior cellular absorption in tumor cells was created by Lerchen and colleagues at Bayer AG. A set of dipeptides was employed to acylate the compound CPT, and they were

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afterward joined by a thiourea bond to create the carbohydrate-targeting group (p-aminophenyl 3-O-methyl-L-fucopyranoside). It's intriguing to note that valine boosted stabilization in cultured cells whereas glycine reduced it whenever the amino acid next after the CPT was present. Sug-HisVal-CPT was found to comprise the conjugate exhibiting the highest stability in media for culture and the IC₅₀ value that was the smallest in HT29 cells. The treated malignancy development/control group expansion (T/C%) values were found to be 1.8% while intravenously administered to mice containing tumors from breast cancer MX-1 xenografts for three straight days using an MTD of 32 mg/kg, as opposed to 12.7% for topotecan administered on the same regimen at a maximum tolerated daily dosage of 2.5 mg/kg (23). According to fluorescence tests, active transport through lysosomes is how cellular absorption happens in HT29 cells. The pharmacokinetics of this conjugate must be fully analyzed to compare it to the parent drug, even if this work shows a considerable advance in the creation of novel CPTs.

CONJUGATED ANALOGS

In addition to structural modification, conjugation is another important strategy for enhancing the therapeutic benefits of CPT, such as lactone protection, solubility/lipophilicity, tumor cellular identification, and demonstrates specificity of DNA damage. The carbonyl molecule in this particular lactone reacts alongside the 20-OH region of CPT to create intrinsic hydrogen, which speeds up the process of hydrolysis of the normally occurring lactone. As a result, the 20-OH group is now the first conjugation web page. Esterification ranging is the process that is

used frequently by the team, and it is 20-OH. It is important to keep in mind that there are changes between the conjugated and altered esterification, depending on whether or not the prodrug is present. The prodrug in question will undoubtedly be ideal because it is sustained in vivo, significantly less toxic from its parent kind, and specifically targets the microscopic surroundings of tumefaction cells. Giovanella *et al.* presented the evaluation and biosynthesis of many alkyl esters of various sizes (24). In the current research, various s)-O-esters which include 20(S)-O-amides, 20(S)-O-carbonates, as well as carbamates were used for practically every phase of preparation of novel CPT analogies. Furthermore, extra enzymes that are capable of performing intrinsic esterase activity hydrolyze this type of ester prodrug.

Two prodrugs were reported by Shabat *et al.*, to be novel (Figure 7), with all-encompassing defense at pH levels that are normal, compensated back intoxication, and significant solubility. Such CPT drugs (5, 6) can potentially be triggered and hydrolyzed by enzymatic antibody 38C2 (25) or *Escherichia coli* penicillin-G amidase (PGA). Many blood supply systems are currently being developed for handling and distribution which is the focus. Early on, prodrugs that are 20-ester were organized using polyethylene glycol (PEG), leading to the establishment of Prothecan (7) (Figure 7), a medicine that is currently through phase II medical research (26). It was recently revealed by Yokoyama *et al.*, that CPT-loaded is unusual because it is a polymer compound called PEG-P(Asp(Bz-69) block copolymer (PEG-P(ethylene glycol)-poly(benzyl L-aspartate-69) block copolymer (27). It's noteworthy to note that Greenwald *et al.*, documented

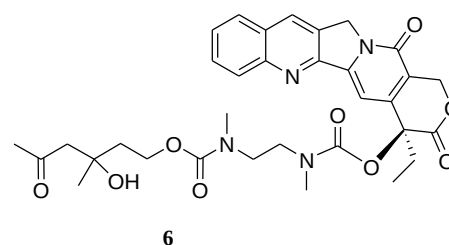
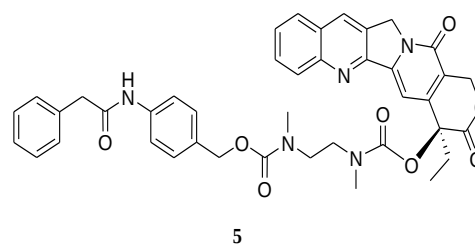
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the binding of two PEG prodrugs using the C-21 capability and the C-17 OH group of CPT hydroxy-amide types (8, 9) (28). The two aforementioned lactone prodrugs, which are easily accessible, are both efficacious and water-soluble in studies using the MX-1 murine xenograft. According to reports, a particular peptide interacts with a drug-glycoconjugate to produce substances with extraordinary in vitro activity (29). For instance, the glycoconjugate (a fucoside with a valine/histidine linker (10) has been shown to avoid cyst production >96% in cancerous tumors related to the female breast xenograft and has therefore already been chosen for health investigations.

On modified CPT analogs, there might be further use of responsive feasible groups, such as NH₂, OH, and -COOH, alongside the 20-OH moiety. These mixed groups served as a component of the quinoline (A/B) ring structure. In reality, DE-310 (11) is a macromolecular form of DX-8951 (Figure 7), a derivative of camptothecin, or a carboxymethyl dextran polyalcohol structure, that has been covalently linked to a peptidyl spacer. The moiety is released progressively through DE-310 over an extremely lengthy period, providing the topoisomerase inhibitor with the desired prolonged exposure. DE-310 is now undergoing phase II medical studies. Polymer Directed Enzyme Prodrug Therapy (PDEPT) represents a newly created, totally novel approach to chemotherapy that is sensitive (30). This form of therapy is essentially a two-step anticancer treatment whereby the prodrug and the drug are both localized at the exact location of the tumor via a polymer molecule. During the initial stage, a polymer-prodrug conjugated molecule is delivered and captured in tumefaction sites using the EPR (increased permeability and

retention) result. It will nevertheless be discovered that a combination of an HPMA antibody with a copolymer that is catalytic exists (31).

Papisov (32) effectively used a liquid conjugate that is macromolecular and dissolves. The dual-phase, two-step medicine release mechanism used to treat this unique type of toxicity is described as follows. The entire time frame that is particularly hydrolysis, which is to start succinimide ester breakage, which results in drug release from the polymeric substance in the form of a cyclic succinimide glycy-CPT. This happens during the second step within the hydrolysis of a glycy ester, which results in the release of a live drug in vivo. The conjugated compound was put together using the anchor poly (1-hydroxymethylethylene hydroxy-methyl formal) (PHF), which is an extremely hydrophilic and biodegradable polymer.



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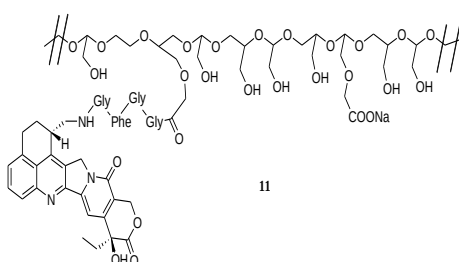
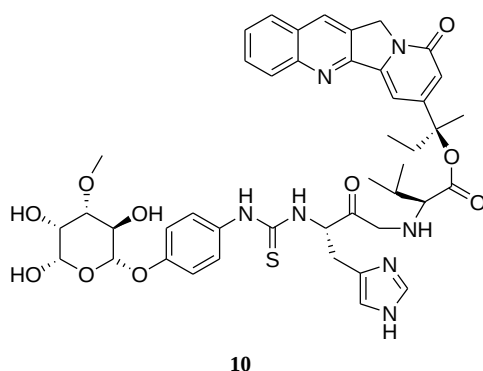
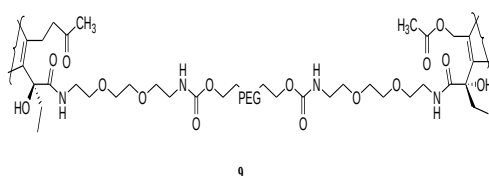
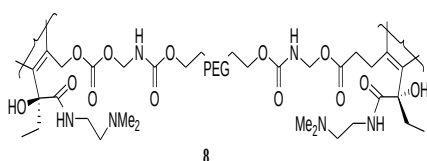
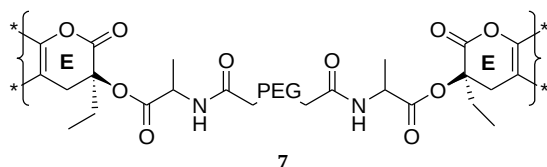


Fig (2.14): CPT Conjugates

Because they frequently qualify for tumor treatment, camptothecin and its conjugates have an antitumor activity that is exceptional. The simple artificial CPT approaches as well as the artificial process that produces semi-synthetic CPT sorts were provided by enormous advances. Additional studies on the CPT derivatives' functioning mechanisms revealed the Topoisomerase enzyme inhibition activity as the cellular part, along with its analogs. The design specifications that CPT uses to form a noncovalent bond with the Topo I-DNA pair are multimodal. The structure-activity interactions reveal a method that is highly practical for CPT's I inhibition and its categories that are typically unique. The suggestion for the therapeutic application of topotecan (Hycamtin) and irinotecan (Camptosar) as well as many analogs that are currently in various stages of studies has extremely exposed an area that is specific in anticancer treatment that is today's advancement. Large goals still concern the upcoming development of anticancer CPTs that are intriguing and unquestionably better.

CONCLUSION

Camptothecin and its analogues represent a vital class of chemotherapeutic agents due to their unique mechanism of inhibiting DNA topoisomerase I. While the parent compound faces challenges such as poor solubility and toxicity, structural modifications have led to the development of clinically effective analogues like topotecan and irinotecan. Continued research into novel derivatives aims to enhance efficacy, reduce resistance, and improve pharmacokinetics. With advancements in targeted delivery and combination therapies, camptothecin-based drugs hold enduring promise in cancer treatment, reinforcing the importance of

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ongoing innovation in anticancer drug development.

REFERENCES

1. Wall ME, Wani MC, Cook CE, Palmer KH, McPhail AT, Sim GA. Plant antitumor agents. I. The isolation and structure of camptothecin, a novel alkaloidal leukemia and tumor inhibitor from *Camptotheca acuminata* 1,2. *J Am Chem Soc.* 1966;88(16):3888- 90. doi: 10.1021/ja00968a057.
2. Moertel CG, Schutt AJ, Reitemeier RJ, Hahn RG. Phase II study of camptothecin (NSC-100880) in the treatment of advanced gastrointestinal cancer. *Cancer Chemother Rep.* 1972;56(1):95-101. PMID 5030811.
3. Fassberg J, Stella VJ. A kinetic and mechanistic study of the hydrolysis of camptothecin and some analogues. *J Pharm Sci.* 1992;81(7):676-84. doi: 10.1002/jps.2600810718, PMID 1403703.
4. Burke TG, Mi Z. Preferential binding of the carboxylate form of camptothecin by human serum albumin. *Anal Biochem.* 1993;212(1):285-7. doi: 10.1006/abio.1993.1325, PMID 8368506.
5. Gottlieb JA, Luce JK. Treatment of malignant melanoma with camptothecin (NSC100880). *Cancer Chemother Rep.* 1972;56(1):103-5. PMID 5030802.
6. Pommier Y, Pourquier P, Fan Y, Strumberg D. Mechanism of action of eukaryotic DNA topoisomerase I and drugs targeted to the enzyme. *Biochim Biophys Acta.* 1998;1400(1-3):83-105. doi: 10.1016/s0167-4781(98)00129-8, PMID 9748515.
7. Kingsbury WD, Boehm JC, Jakas DR, Holden KG, Hecht SM, Gallagher G et al. Synthesis of water-soluble (aminoalkyl)camptothecin analogues: inhibition of topoisomerase I and antitumor activity. *J Med Chem.* 1991;34(1):98-107. doi: 10.1021/jm00105a017, PMID 1846923.
8. Negoro S, Fukuoka M, Masuda N, Takada M, Kusunoki Y, Matsui K et al. Phase I study of weekly intravenous infusions of CPT-11, a new derivative of camptothecin, in the treatment of advanced non-small-cell lung cancer. *J Natl Cancer Inst.* 1991;83(16):1164-8. doi: 10.1093/jnci/83.16.1164, PMID 1653362.
9. Venditto VJ, Simanek EE. Cancer therapies utilizing the camptothecins: a review of the in vivo literature. *Mol Pharm.* 2010;7(2):307-49. doi: 10.1021/mp900243b, PMID 20108971.
10. Liu YQ, Li WQ, Morris-Natschke SL, Qian K, Yang L, Zhu GX et al. Perspectives on biologically active camptothecin derivatives. *Med Res Rev.* 2015;35(4):753-89. doi: 10.1002/med.21342, PMID 25808858.
11. Hinz HR, Harris NJ, Natelson EA, Giovanella BC. Pharmacokinetics of the in vivo and in vitro conversion of 9-nitro-20(S)-camptothecin to 9-amino-20(S)-camptothecin in humans, dogs, and mice. *Cancer Res.* 1994;54(12):3096-100. PMID 8205523.
12. Rajendra R, Gounder MK, Saleem A, Schellens JH, Ross DD, Bates SE et al. Differential effects of the breast cancer resistance protein on the cellular accumulation and cytotoxicity of 9-aminocamptothecin and 9-nitrocamptothecin. *Cancer Res.* 2003;63(12):3228-33. PMID 12810652.

ARTICLE ID: BTS0326022

13. Chen J, Ping Q, Guo J, Chu X, Song M. Pharmacokinetics of lactone, carboxylate and total 9-nitrocamptothecin with different doses and administration routes in rats. *Biopharm Drug Dispos.* 2006;27(2):53-9. doi: 10.1002/bdd.480, PMID 16299828.
14. Kemp KR, Liehr JG, Giovanella B. Combined radiation and 9-nitrocamptothecin (Rubitecan) in the treatment of locally advanced pancreatic cancer. *Ann N Y Acad Sci.* 2000;922:320-3. doi: 10.1111/j.1749-6632.2000.tb07054.x, PMID 11193912.
15. Tagen M, Zhuang Y, Zhang F, Harstead KE, Shen J, Schaiquevich P et al. Pglycoprotein, but not multidrug resistance protein 4, plays a role in the systemic clearance of irinotecan and SN-38 in mice. *Drug Metab Lett.* 2010;4(4):195-201. doi: 10.2174/187231210792928251, PMID 20583968.
16. Filipski E, Berland E, Ozturk N, Guettier C, van der Horst GT, Lévi F et al. Optimization of irinotecan chronotherapy with P-glycoprotein inhibition. *Toxicol Appl Pharmacol.* 2014;274(3):471-9. doi: 10.1016/j.taap.2013.12.018, PMID 24380837.
17. Hendricks CB, Rowinsky EK, Grochow LB, Donehower RC, Kaufmann SH. Effect of P-glycoprotein expression on the accumulation and cytotoxicity of topotecan (SK&F 104864), a new camptothecin analogue. *Cancer Res.* 1992;52(8):2268-78. PMID 1348448.
18. Westover D, Ling X, Lam H, Welch J, Jin C, Gongora C et al. FL118, a novel camptothecin derivative, is insensitive to ABCG2 expression and shows improved efficacy in comparison with irinotecan in colon and lung cancer models with ABCG2-induced resistance. *Mol Cancer.* 2015;14:92. doi: 10.1186/s12943-015-0362-9, PMID 25928015.
19. Nam EJ, Kim JW, Kim JH, Kim S, Kim SW, Jang SY et al. Efficacy and toxicity of Belotecan with and without cisplatin in patients with recurrent ovarian cancer. *Am J Clin Oncol.* 2010;33(3):233-7. doi: 10.1097/COC.0b013e3181a650bc, PMID 19745693.
20. Choi CH, Lee YY, Song TJ, Park HS, Kim MK, Kim TJ et al. Phase II study of Belotecan, a camptothecin analogue, in combination with carboplatin for the treatment of recurrent ovarian cancer. *Cancer.* 2011;117(10):2104-11. doi: 10.1002/cncr.25710, PMID 21523722.
21. Hwang JH, Lim MC, Seo SS, Park SY, Kang S. Phase II study of Belotecan (CKD 602) as a single agent in patients with recurrent or progressive carcinoma of uterine cervix. *Jpn J Clin Oncol.* 2011;41(5):624-9. doi: 10.1093/jjco/hyr017, PMID 21355002.
22. Rhee CK, Lee SH, Kim JS, Kim SJ, Kim SC, Kim YK et al. A multicenter phase II study of belotecan, a new camptothecin analogue, as a second-line therapy in patients with small cell lung cancer. *Lung Cancer.* 2011;72(1):64-7. doi: 10.1016/j.lungcan.2010.07.003, PMID 20832894.
23. Hong J, Jung M, Kim YJ, Sym SJ, Kyung SY, Park J et al. Phase II study of combined Belotecan and cisplatin as first-line chemotherapy in patients with extensive disease of small cell lung cancer. *Cancer Chemother Pharmacol.* 2012;69(1):215-20. doi: 10.1007/s00280-011-1689-6, PMID 21691745.

ARTICLE ID: BTS0326022

24. Zhu AX, Ready N, Clark JW, Safran H, Amato A, Salem N et al. Phase I and pharmacokinetic study of gimatecan given orally once a week for 3 of 4 weeks in patients with advanced solid tumors. *Clin Cancer Res.* 2009;15(1):374-81. doi: 10.1158/1078-0432.CCR-08-1024, PMID 19118068.
25. Frapolli R, Zucchetti M, Sessa C, Marsoni S, Viganò L, Locatelli A et al. Clinical pharmacokinetics of the new oral camptothecin gimatecan: the inter-patient variability is related to alpha1-acid glycoprotein plasma levels. *Eur J Cancer.* 2010;46(3):505-16. doi: 10.1016/j.ejca.2009.11.006, PMID 20007015.
26. Pecorelli S, Ray-Coquard I, Tredan O, Colombo N, Parma G, Tisi G et al. Phase II of oral gimatecan in patients with recurrent epithelial ovarian, fallopian tube or peritoneal cancer, previously treated with platinum and taxanes. *Ann Oncol.* 2010;21(4):759-65. doi: 10.1093/annonc/mdp514, PMID 19906760.
27. Hu J, Wen PY, Abrey LE, Fadul CE, Drappatz J, Salem N et al. A phase II trial of oral gimatecan for recurrent glioblastoma. *J Neurooncol.* 2013;111(3):347-53. doi: 10.1007/s11060-012-1023-0, PMID 23232808.
28. Lansiaux A, Facompré M, Wattez N, Hildebrand MP, Bal C, Demarquay D et al. Apoptosis induced by the homocamptothecin anticancer drug BN80915 in HL-60 cells. *Mol Pharmacol.* 2001;60(3):450-61. PMID 11502875.
29. Sparreboom A, Gelderblom H, Marsh S, Ahluwalia R, Obach R, Principe P et al. Diflomotecan pharmacokinetics in relation to ABCG2 421C>A genotype. *Clin Pharmacol Ther.* 2004;76(1):38-44. doi: 10.1016/j.clpt.2004.03.003, PMID 15229462.
30. Scott L, Soepenberg O, Verweij J, de Jonge MJ, Th Planting AS, McGovern D et al. A multicentre phase I and pharmacokinetic study of BN80915 (diflomotecan) administered daily as a 20-min intravenous infusion for 5 days every 3 weeks to patients with advanced solid tumours. *Ann Oncol.* 2007;18(3):569-75. doi: 10.1093/annonc/mdl439, PMID 17322542.
31. Graham JS, Falk S, Samuel LM, Cendros JM, Evans TR. A multi-centre dose escalation and pharmacokinetic study of diflomotecan in patients with advanced malignancy. *Cancer Chemother Pharmacol.* 2009;63(5):945-52. doi: 10.1007/s00280-008-0795-6, PMID 18654747.
32. Liao Z, Robey RW, Guirouilh-Barbat J, To KK, Polgar O, Bates SE et al. Reduced expression of DNA topoisomerase I in SF295 human glioblastoma cells selected for resistance to homocamptothecin and diflomotecan. *Mol Pharmacol.* 2008;73(2):490-7. doi: 10.1124/mol.107.041178, PMID 17984197.