

# **Role of plants in anticancer drug discovery**

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## **Highlights**

- Cancer is second deadly disease after cardiovascular diseases.
- There is a tremendous need to discover novel safer and more effective anticancer agents.
- Plants serve as a basis for promising therapeutic agents for cancer treatment.
- Important plant derived anticancer agents have been discussed here.
- Some potential plant derived lead molecules have also been discussed.

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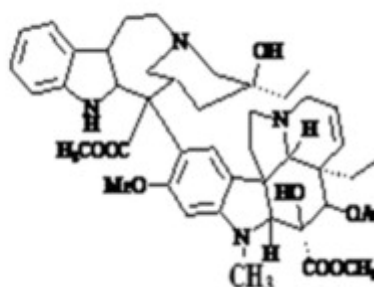
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## Abstract

Cancer is one of the major causes of death and the number of new cases, as well as the number of individuals living with cancer, is expanding continuously. Worldwide the alarming rise in mortality rate due to cancer has fuelled the pursuit for effective anticancer agents to combat this disease. Finding novel and efficient compounds of natural origin has been a major point of concern for research in the pharmaceutical sciences. Plants have been seen to possess the potential to be excellent lead structures and to serve as a basis of promising therapeutic agents for cancer treatment. Many successful anti-cancer drugs currently in use or their analogues are plant derived and many more are under clinical trials. This review aims to highlight the invaluable role that plants have played, and continue to play, in the discovery of anticancer agents.

## Graphical abstract

*Catharanthus roseus* → Vinblastine (anticancer drug)



**Keywords** cancer, drugs, natural products, plant derived anticancer drugs.

## **1. Introduction**

Cancer is a multifaceted disease that represents one of the leading causes of mortality in developed countries. Worldwide, one in eight deaths is due to cancer and it is the second most common cause of death in the US, exceeded only by heart disease, accounting for nearly one of every four deaths (<http://www.cancer.org>). The World Health Organization (WHO) projects that without immediate action, the global number of deaths from cancer will increase by nearly 80% by 2030, with most occurring in low- and middle-income countries. External factors (such as tobacco, infectious organisms, chemicals, and radiation) and internal factors (inherited mutations, hormones, immune conditions, and mutations that occur from metabolism) are mostly responsible for cancer. These causal factors may act together or in sequence to initiate or promote the development of cancer (<http://www.state.nj.us/health/cancer/causes.shtml>).

While tremendous efforts have been made over the past decades to improve the available therapeutic options, and a large number of potent chemotherapeutic anticancer agents have been identified and successfully used in clinical practice, cancer still remains a major cause of disease and death in most countries. New therapeutic options to treat cancer are a high priority for most of the pharmaceutical companies and independent research organisations worldwide. Considerable research activity is devoted to the discovery of more potent treatments, while minimising their toxic side effects. However, most anticancer agents display a narrow therapeutic window due to their lack of selectivity against cancer cells (Shengquan et al., 2013; Kratz et al., 2008). The ultimate goal of cancer chemotherapy is the development of selective drugs that can kill malignant tumor cells or render them benign without affecting normal cells. Thus, there is an overwhelming need to develop new chemopreventative agents that are both effective and safe (Sporn and Liby, 2005). One practical approach to this problem is the use of terrestrial plants as a platform for drug development.

Plants have played a dominant role in the development of sophisticated traditional medicine systems. The WHO estimates that approximately 80 % of the population in some Asian and African countries depend on traditional medicine for primary health care. Plant products, however, also play an important secondary role in the health care sectors of developed countries, with 70% to 80% of populations of developed countries having used some form of alternative or complementary medicine (e.g. acupuncture). Herbal treatments are the most popular form of traditional medicine, and are highly lucrative in the international marketplace. The global market for herbal products is expected to reach \$5 Trillion by 2050 (Anand and Neetu, 2011).

Plants products have a long history of use in the treatment of cancer. Hartwell in his review of plants used against cancer lists more than 3000 plant species (Kaur et al., 2011). Plant based drug discovery has resulted in the development of many anticancer drugs currently in clinical use. Besides this it also provides a platform for design of novel and safe drugs through proper understanding of the complex synergistic interaction of various constituents of anticancer herbs (Larkin, 1983; Saxe, 1987)

There are four major structural classifications of plant-derived anticancerous compounds, namely vinca alkaloids, epipodophyllotoxin lignans, taxane diterpenoids and camptothecin quinoline alkaloid derivatives. These substances embrace some of the most exciting new chemotherapeutic agents currently available for use in a clinical setting.

## **2. Vinca alkaloids and its semisynthetic analogues**

The era of using plant material as anticancer agents started with the isolation of two alkaloids vinblastine (**1**) and vincristine (**2**) from the Madagascar periwinkle, *Catharanthus roseus* G. Don (Apocynaceae) (Verma and Singh, 2010). These two drugs have been used in clinical oncology for almost 50 years and work by blocking the polymerization of tubulin molecules into microtubules, preventing the formation of the mitotic spindle which result in metaphase arrest and apoptosis (Jordan et al, 1991). A series of semisynthetic analogues of these two important drug molecules have been developed. The first semisynthetic vinca alkaloid to enter into human clinical trials was vindesine (eldisine, **3**) in which the C(23) acetyl group in vinblastine was changed to an amido group (Jordan and Wilson, 2004). Vindesine is primarily used to treat acute lymphocytic leukemia (ALL). Less frequently, it is prescribed for use in breast cancer, blast crisis of chronic myelocytic leukemia (CML), colorectal cancer, non-small cell lung cancer (NSCLC), and renal cell cancer (kidney cancer). Vindesine is used in countries such as Britain, South Africa, and several European countries, but it is not approved by the FDA, and is thus not commercially available in the U.S. Eli Lilly discontinued Eldisine in Canada in 1998 to make way for newer, more effective vinca alkaloid drugs (<http://www.encyclopedia.com/topic/Vindesine.aspx>).

Vinorelbine (Navelbine, **4**), is another semisynthetic derivative of vinblastine in which the bridge linking the indole ring to the piperidine nitrogen has been shortened by one carbon and water has been eliminated from the piperidine ring. The drug was approved in France in 1989 under the brand name Navelbine for the treatment of NSCLC (<http://www.pierre-fabre.com/en>). It gained approval to treat metastatic breast cancer (MBC) in 1991. Vinorelbine received approval by the FDA in December 1994 sponsored by Burroughs

Wellcome Company. Pierre Fabre Group now markets Navelbine in the U.S (Smith, 1995; <http://www.drugs.com/pro/vinorelbine.html>).

Vinflunine (**5**), a dihydro-fluoro derivative of vinorelbine was approved by the European medical agency (EMA) in 2009 as second line chemotherapy in metastatic urothelial cancer (Bachner and De Santis, 2008; Mamtani and Vaughn, 2011).

Similar to other members in the vinca alkaloid class, vinflunine binds to the tubulin molecules, inhibiting microtubule polymerization and the formation of tubulin paracrystals (Bennouna et al., 2008; Kruczyński et al., 1998; Pourroy et al., 2004; Simoens et al., 2006). This interaction then leads to G<sub>2</sub>/M phase arrest and apoptosis results (Lobert and Puozzo, 2008; Kruczyński et al., 2002). It has broad *in vitro* and *in vivo* activities against many different malignant cell lines. Vinflunine is actively being studied in patients with advanced stage diseases especially MBC, and NSCLC in phase II/III clinical trials. More phase I/II trials are also being organized to evaluate its efficacy in other advanced solid tumours (Ng, 2011).

In August 2012, the FDA approved vincristine sulphate liposome injection (Marqibo, Talon Therapeutics, Inc.) for the treatment of adult patients with Philadelphia chromosome-negative (Ph-) (ALL) in second or greater relapse or whose disease had progressed following two or more anti-leukaemia therapies. It is a new, targeted, nanoparticle-encapsulated, cancer therapeutic agent specifically designed to improve patient outcomes by combining the potential for enhanced efficacy with the potential for reduced toxicity. (<http://www.marqibo.com>).

Besides these approved vinca alkaloid drugs, many other derivatives are undergoing clinical trials including anhydrovinblastine (Hydravin, **6**) which differs from vinblastine in having a 3'4' double bond in the catharanthine moiety a property it shares with vinorelbine (Navelbine). It entered the clinical trials in 1999 for the treatment of metastatic sarcoma of the lungs. As of 2003 it has been undergoing phase I trials to determine its maximum tolerated dose (MTD), dose-limiting toxicities (DLT) and pharmacokinetics given as a 1-h intravenous infusion once every 3 weeks in patients with advanced refractory solid tumours. The recommended phase II dose was found as 21 mg/ml (Ramnath et al., 2003), but Keryx discontinued its further development in 2005, but trials may still be ongoing by Prescient Neuropharma (Butler, 2008). The clinical trial website ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) shows phase I (NCT00003882) trials for the treatment of advanced recurrent solid tumours. In addition to this, chemists have also grafted amino acid derivatives onto vinblastine, so as to facilitate transport of these large molecules into cell membranes. This work led to the synthesis of molecules with interesting

pharmacological properties, namely vinyglycinate (**7**) and vintripol (**8**), that are structural analogues of vindesine. Vinyglycinate substituted by glycinate residue at the vindoline C-4 position entered phase I clinical trials in 1967, but concluded with toxicity (Armstrong et al., 1967; Budman, 1992). Although many other semi synthetic compounds have been developed from vinblastine and vincristine, none of these have exerted marked benefits in clinical evaluation.

### **3. Taxol and its semisynthetic analogues**

The discovery of paclitaxel (Taxol, **9**) from the bark of the Pacific Yew, *Taxus brevifolia* Nutt (Taxaceae) provides further evidence for the success of natural product drug discovery. No naturally occurring anticancer agent has made a bigger impact on cancer treatment than paclitaxel. Paclitaxel was the first compound discovered to promote microtubule formation and has been used in the treatment of several types of cancers particularly ovarian and breast cancers as well as NSCLC (Kinghorn and Seo, 1996). A number of its semisynthetic derivatives have been developed. The first to reach clinical use was docetaxel (**10**) which have shown significant clinical activity in a wide range of tumors and a different toxicity pattern than the parent compound (<http://www.drugbank.ca/drugs/DB01248>; Bissery et al., 1995; Gelmon, 1994) . However, both of the approved taxanes carry certain limitations, which scientists are still trying to overcome through synthesis of modified analogues. Modifications in the structures of these compounds have been made in an effort to discover novel agents with improved cytotoxicity in resistant tumours, decreased toxicity, and improved solubility. Also the lack of brain penetration of paclitaxel precluded further investigations of this compound in mouse models. The limited ability of paclitaxel and docetaxel to diffuse across the blood brain barrier (BBB) is believed to be caused at least in part by the P-glycoprotein (PGP) efflux pump (Kemper et al., 2003; Fellner et al., 2003) which is highly expressed in the BBB (Beaulieu et al., 1997). Thus, taxane analogues capable of overcoming PGP-mediated transport may result in improved brain penetration.

Cabazitaxel (**11**), an FDA approved semi-synthetic taxane was launched in 2010 for use in combination with prednisone for the treatment of prostate and hormone refractory prostate cancers (<http://www.drugbank.ca/drugs/DB06772>; Channing et al., 2011) . Cabazitaxel binds to and stabilizes tubulin, resulting in the inhibition of microtubule depolymerization and cell division, cell cycle arrest in the G<sub>2</sub>/M phase, and the inhibition of tumor cell proliferation (Channing et al., 2011). Unlike other taxane compounds, this agent is a poor substrate for the membrane-associated, multidrug resistance (PGP) efflux pump and may be useful for treating

MDR tumours. In addition, cabazitaxel penetrates the BBB (<http://www.medkoo.com/Anticancer-trials/Cabazitaxel.htm>) and in combination with prednisone significantly extends overall survival in men with hormone-refractory prostate cancer previously treated with a docetaxel-containing regimen and also improves disease control (<http://www.medicalnewstoday.com/articles/220304.php>).

The approval of nanoparticle based formulation abraxane shows that improved formulation can have a dramatic effect (<http://www.drugbank.ca/drugs/DB01229>). Abraxane (ABI-007) is albumin-bound, 130-nm particle formulation of paclitaxel, free from any kind of solvent. It was first approved in the US in 2005 for its use as a breast cancer treatment. In 2012 it was approved for first-line treatment of metastatic NSCLC among patients who could not receive radiation therapy or curative therapy. Abraxane is a first in its class of drugs using nanoparticle albumin-bound (NAB) technology, acting as a mitotic inhibitor. Abraxane made sales of close to \$386 million in 2011 for its use as breast cancer treatment and was marketed by Celgene (<http://www.medicalnewstoday.com/articles/255388.php>).

Novel taxanes in development are being designed to improve the pharmacology and therapeutic index, and replace paclitaxel and docetaxel as standard treatments in NSCLC (Bao and Pokman, 2011). Several semi-synthetic agents have completed phase I/II clinical trials and are in phase III testing like paclitaxel poliglumex (CT-2103; Xyotax **12**), which is an innovative macromolecular taxane designed to increase the therapeutic index of paclitaxel (Singer et al., 2005). It was reported to be undergoing phase III clinical trials for the treatment of NSCLC, and is positioned to be the first of its class to reach the market (Stewart et al., 2006; Haag and Kratz, 2006). It is also undergoing phase III trial in combination with carboplatin in the treatment of performance status (PS 2) patients with chemotherapy-naïve advanced NSCLC. When compared to paclitaxel/carboplatin combination, paclitaxel poliglumex (PPX) and carboplatin failed to provide superior survival in the first-line treatment of PS 2 patients with NSCLC, but the results with respect to progression-free survival and overall survival were comparable and the PPX regimen was more convenient (Langer et al., 2008). In the clinical trials database, four phase II trials are shown. Two involve the treatment of patients with recurrent or persistent ovarian epithelial cancer or peritoneal cancer (NCT00045682) and fallopian tube cancer (NCT00017017). The other two are in the treatment of MBC (NCT00148707) and in ovarian cancer (NCT0006990).

Other taxol analogues like 7-DHA-Taxol (Taxaprexin **13**, Lutipold pharmaceuticals) made by linking paclitaxel to docosahexaenoic acid (DHA), a fatty acid that is easily taken up by tumor cells. As of 2006 it has been undergoing open-label, non-randomized, multi-

institutional phase II trials to assess the antitumor activity and safety as first-line treatment of patients with advanced NSCLC. It was concluded that as a single-agent, docosahexaenoic acid-paclitaxel has little activity in patients with advanced NSCLC. But despite the low objective response rate, treatment was associated with survival comparable to that seen with standard platinum-based combination chemotherapy (Payne et al., 1998). The clinical trials database shows several phase II and phase III trials alone or in combination therapy. As a single agent, it is undergoing phase III trials against advanced lung cancers (NCT00249262) and phase II trials against advanced eye melanoma (NCT00244816) and advanced skin melanoma (NCT00249262). It is also undergoing phase III trials in combination therapy with carboplatin for the treatment of advanced skin melanoma (NCT00243867).

Larotaxel (XPR9881 **14**, Sanofi-Aventis), a cyclopropyl derivative is undergoing several trials alone or in combination therapy. Its phase I study in combination with carboplatin in chemotherapy-naïve patients with stage IIIB or stage IV NSCLC has been reported and this combination was showing modest activity in chemotherapy-naïve patients with advanced/metastatic NSCLC (Robert et al., 2010). Phase II multicenter study of larotaxel (XRP9881), in patients with MBC who previously received taxane-based therapy concluded its good activity, manageable toxicity, and a favourable therapeutic index in women with taxane-pre-treated MBC (Diéras et al., 2008). The clinical trials database is showing several phase II and phase III trials in combination therapy. These include phase II trials in combination with docetaxel and trastuzumab against breast cancer (NCT00485979) and phase III trials in combination with cisplatin versus gemcitabine/cisplatin in the first line treatment of locally advanced/metastatic urothelial tract or bladder cancer (NCT0062564).

Ortaxel (BAY-59-862, **15**), a new-generation taxane, is active in tumor models resistant to paclitaxel and docetaxel and elicits responses in taxane-resistant NSCLC. In its phase II study against taxane resistant breast cancers, ortaxel showed encouraging activity and clinical benefit in breast cancer patients who are resistant to paclitaxel or docetaxel combinations (Beer and Lenaz, 2008). The clinical trials database is showing three phase II trials, one is for the treatment of NSCLCs (NCT00054314). The other two are in treatment of advanced kidney cancer (NCT00039169) and refractory Non Hodgkin's lymphoma (NCT00039156).

TPI-287 (Tapestry Pharmaceuticals, **16**) is reported to be undergoing phase I/II study in combination with temozolomide for the treatment of melanoma (NCT01067066), phase I/II study for safety and efficacy study in the treatment of neuroblastoma and medulla blastoma (NCT01483820), a randomised efficacy study to treat primary refractory or early relapsed neuroblastoma (NCT01505608) and is also undergoing phase II studies to treat breast cancer



metastatic to the brain (Fitzgerald et al., 2012; <http://www.clinicaltrials.gov/ct2/show/NCT01332630>). Unlike the other taxanes, TPI-287 is permeable through the BBB.

Milataxel (MAC-321 **17**, Taxolog) completed phase II trials for colorectal cancer in 2009, but has been discontinued due to toxicity issues at the dose level 35mg/m<sup>2</sup> (Ramanathan et al., 2008). Tesetaxel (DJ-927, **18**) has been undergoing 14 phase I/II clinical trials alone or in combination therapy with other drugs against various cancer types (<http://clinicaltrialsfeeds.org/clinical-trials/results/?term=Tesetaxel>; Saif et al., 2011). BMS-275183 (**19**), an oral C-4 methyl carbonate analogue of paclitaxel was undergoing phase I studies in order to (i) assess the safety and tolerability of BMS-275183, and (ii) determine a suitable phase II dose of the drug when given on a continuous daily schedule to patients with advanced solid tumours. Unfortunately the lack of evidence showing clinical benefit and the occurrence of two fatal events of neutropenic sepsis, coupled with high drug exposure, led to the discontinuation of its further development (Heath et al., 2011). BMS-275183 is also undergoing randomized, phase II study in patients with pre-treated NSCLC (NCT00099879). Another taxane derivative, BMS-184476 (Bristol-Myers-Squibb, **20**), a 7-methylthiomethyl ether derivative of paclitaxel displays potency superior to paclitaxel against tumor cells in culture and human tumor xenografts. It also inhibits the growth of paclitaxel-resistant human tumor cell lines with multidrug resistance mediated by either P-glycoprotein or mutated tubulin (Plummer et al., 2002). It has been undergoing phase I trials to study its effectiveness in treating patients who have advanced solid tumors. RPR 109881A (**21**) is another taxane derivative containing a cyclopropyl ring. Its activity was assessed in a variety of murine and human tumour lines *in vitro* and *in vivo* and compared with docetaxel, RPR 109881A was active against tumours sensitive to docetaxel (Gelmon et al., 2000). It has been in phase III studies to determine if RPR 109881A is a better treatment than capecitabine (Xeloda) for advanced breast cancer in patients that no longer benefit from docetaxel and/or paclitaxel (<http://www.clinicaltrials.gov/ct2/show/NCT00081796>). Several other taxane derivatives are in clinical development and include albumin-bound paclitaxel, albumin-bound docetaxel, paclitaxel microspheres and many others (Hennenfent and Govindan, 2006).

#### **4. Podophyllotoxin and its semisynthetic analogues**

Podophyllotoxin (**22**), obtained from *Podophyllum peltatum*, is another important anti-cancer compound (Imbert, 1998). Some 30 years after its discovery, it was demonstrated that this compound binds reversibly to tubulin (Wilson et al., 1975) and therefore had potential as an

anticancer agent. Etoposide (**23**) and teniposide (**24**) are the two key analogs of podophyllotoxin. Instead of acting as the microtubule inhibitors in the same manner as the lead compound, these derived drugs exert their anticancer activity by acting as inhibitors of the enzyme topoisomerase II and are, therefore useful in the treatment of various cancers (Srivastava et al., 2005; Odwyer et al., 1985). The impressive potency and clinical efficacy of the two analogues has prompted extensive structure activity studies based on the podophyllotoxin prototype and numerous podophyllotoxin analogues have been synthesised and evaluated since the 1950s to overcome the problems such as poor water solubility, acquired drug resistance and metabolic inactivation met by parent molecule. Several semisynthetic analogues like NK-611, GL-331, azatoxin, Top-53, etoposide phosphate and tafluposide have been produced as either clinical drugs or novel clinical trial candidates for various cancers Hanauske et al., 1995; Mross et al., 1996; Liu et al., 2002; Huang et al., 2000; Cline et al., 1997; Hande, 1998; Zhang and Trissel, 1999; Sargent et al., 2003).

### **5. Camptothecin and its semisynthetic analogues**

Camptothecin (CPT) (**25**), a quinoline alkaloid with topoisomerase-I inhibitor activity isolated from *Camptotheca acuminata*, induces cell death by DNA damage (Hsiang et al., 1985). It was however withdrawn from clinical trials because of its low aqueous solubility and severe toxicity. To overcome these limitations, a number of CPT analogues were synthesized and approved for clinical use such as topotecan (**26**), irinotecan (**27**) and belatecan (**28**) which effectively inhibit DNA topoisomerase-I, a critical enzyme in DNA replication and transcription (Oberlies and Kroll, 2004).

Another semisynthetic CPT derivatives 9-aminocamptothecin (9-AC, **29**), showed potent activity in preclinical studies, but has not demonstrated clinically useful antitumor activity to date. It entered phase I trials in 1993 and demonstrated predictable dose dependent myelosuppression as its major toxicity. However, in subsequent phase II trials, despite showing modest activity in ovarian and malignant lymphoma, the drug was not found to be active against lung cancer or colon cancer on any schedule. Thus it was dropped from further development in 1999 (Pazdur et al., 1997; Vey et al., 1999). However it has been undergoing several phase I/II studies to determine its safety, efficacy and tolerability alone or in combination studies with other drugs (Farray et al., 2006). Karenitecin (BNP-1350, **30**), another semi synthetic analogue of CPT has been used in phase II trials against malignant melanoma (Adil et al., 2005; <http://www.clinicaltrials.gov/ct2/show/NCT00062491>) and in phase II in treatment of patients with brain tumours (NCT00062478). Diflomotecan (BN-

80915, **31**) is an E-ring modified CPT analogue, which possesses greater lactone stability in plasma compared with other topoisomerase I inhibitors and was the first homo CPT to enter into development. As of 2007 it has been undergoing phase I clinical trials against solid tumours (Scott et al., 2007). A phase II open label study investigating the activity of diflomotecan (BN80915) administered at the fixed dose of 7mg as a 20 minute intravenous infusion once every 3 weeks in patients with sensitive small cell lung cancer (SCLC) who have failed first-line treatment with a platinum based regimen has been completed by Ipsen pharmaceuticals (<http://clinicaltrialsfeeds.org/clinical-trials/show/NCT00080015>).

Gimatecan (ST-1481, **32**), an oral topoisomerase I inhibitor, has been reported to be in phase I for the treatment of patients with advanced solid tumours (Zhu et al., 2009) and phase II for the treatment of recurrent epithelial ovarian and fallopian tube cancers, previously treated with platinum and taxanes (Pecorelli et al., 2010). Elomotecan (BN-80927, **33**), an inhibitor of topoisomerase I and II, is in phase I trials against advanced solid tumours by Ipsen and Roche pharmaceuticals (Trocóniz et al., 2012). DRF-1042 (**34**) a novel, orally active camptothecin analogue, has completed phase I clinical trials by Dr Reddys Laboratories (<http://www.evaluategroup.com/Universal/View.aspx?type=Story&id=29649>). Exatecan mesylate (**35**) has been in phase II trials for the treatment of gastric cancers (Ajani et al., 2005), and the treatment of children with relapsed or refractory rhabdomyosarcoma. (<http://clinicaltrialsfeeds.org/clinical-trials/show/NCT00055939>). Rubitecan (**36**) exists as an equilibrium form of 9-nitro-camptothecin (9-NC) and 9-amino-camptothecin (9-AC). It is a metabolite that was thought to be active though it failed in clinical trials showing unsatisfactory activity against a number of other solid tumours in relatively small phase I/II trials (Clark, 2006). Rubitecan did however show promising activity against pancreatic cancer, and was advanced into phase III clinical trials but based on unfavourable results an application for FDA approval by SuperGen, the company developing the drug was withdrawn (<http://www.prnewswire.com/news-releases/supergen-announces-withdrawal-of-orathecintm-nda-53822397.html>).

Besides this, various conjugated CPT analogues have been developed by conjugating small molecules at the C-20 hydroxyl which leads to stabilisation of the lactone ring delaying its opening and reducing affinity to serum albumin. Also the prodrug approach leads to a slow release of the active drug form which can dramatically alter the therapeutic index of CPTs. Various conjugated CPT analogues have been developed and some have reached clinical trials.

CZ-48 (**37**), which is a 20-*O*-alkyl ester of CPT, is currently in phase I for the treatment of solid tumours (<http://stehlin.org/cz48/>). TP-300 (**38**) is undergoing phase I trials against advanced solid tumours (Anthony et al., 2012). EZN-2208 (**39**) is undergoing phase I studies in patients with advanced malignancies (Kurzrock et al., 2012).

Co-polymers have also been used as prodrugs of CPTs. MAG-CPT is a copolymer linked to CPT through a glycylohexanoyl-glycyl spacer which was developed by Pharmacia and Upjohn in an attempt to overcome problems associated with the delivery of CPT. Unfortunately because of toxicity issues, its development was discontinued after phase I (Bissett et al., 2004). XMT-1001 is a prodrug in which CPT is attached to poly (1-hydroxy methyl ethylene hydroxy methyl formyl) and is being evaluated in an ongoing phase 1b clinical trial targeting lung cancers, following successful completion of a phase 1 clinical trial. Phase 2 clinical trials for XMT-1001 are planned for treatment of lung cancers (<http://www.mersana.com/product-pipeline/xmt-1001.php>). CRLX-101 is a nano pharmaceutical comprised of the chemotherapeutic camptothecin (CPT) conjugated to a linear, cyclodextrin-based polymer. CRLX-101 is designed to increase the exposure of tumor cells to CPT while minimizing side effects. Phase I/II trials of this prodrug are being conducted to determine the safety, toxicity, and the maximum tolerated dose (MTD) of CRLX-101 when administered intravenously to subjects with advanced solid tumors (<http://www.clinicaltrials.gov/ct2/show/NCT00333502>). In addition to this, nanoparticle encapsulation and liposomal core loading are being investigated to help optimise the delivery of CPT and some have already reached clinical trials. Irinotecan (CPT-11) encapsulated has been developed by Neo Pharma and Pharma engine; it is an oncology drug product consisting of the active metabolite of irinotecan (CPT-11) encapsulated, a known anticancer drug, encapsulated in a liposome. The irinotecan liposome formulation is currently in phase I trials in the treatment of advanced cancers (<http://www.clinicaltrials.gov/ct2/show/NCT00046540?term=cancer&intr=cpt-11+liposomal&rank=4>). Formulation of relatively insoluble analogues of CPT for their improvement in drug delivery (pharmacodynamic profile) may be obtained with liposomal formulations. Such formulations may lead to improved safety and efficacy profiles, when compared with the pro-drug CPT.

## **6. Combretastatin and its analogues**

Combretastatins have been isolated from the bark of the South African tree *Combretum caffrum* Kuntze (Combretaceae). Combretastatin A4 (**40**) is active against colon, lung and

leukaemia cancers. The combrestatin A series is historically known for its remarkable biological activity in terms of inhibition of tubulin assembly and *in vitro* cytotoxicity against human cancer cell lines. CA-4P (**41**) and CA-1P (**42**) which binds at the colchicine site of  $\beta$ -tubulin are among the most active prodrugs of the natural products isolated from *C. cafferum* (Cirla and Mann, 2003). A number of phase I/II trials have been done on CA-4P which focussed on establishing the safety and tolerability of its combination with other treatment regimen like chemotherapy, radiotherapy and antiangiogenic therapies (Nathan et al., 2012). These studies showed that CA-4P can be safely combined with a number of other conventional therapies and has lead to the initiation of phase II studies in NSCLC and anaplastic thyroid cancer (<http://www.clinicaltrials.gov/ct2/show/NCT00653939>).

The phosphate prodrug of combretastatin A-1 (CA-1P, OXi4503) has shown excellent activity in preclinical studies and has entered in 7 clinical trials. Two clinical studies are currently underway using OXi-4503. One is in phase I study evaluating the safety and tolerability in patients with AML (NCT01085656). The second study is in phase IIb to study its safety and efficacy against solid tumour growing in liver (Patterson et al., 2012). OXiGENE announced that OXi4503 has been granted orphan designation by the US FDA for the treatment of AML (<http://www.marketwatch.com/oxigene-announces-oxi4503-granted-orphan-designation-for-treatment-of-acute-myelogenous-leukemia-2012-11-21>).

## 7. Other plant derived anticancer agents

**7.1 Omacetaxine mepesuccinate** (or homoharringtonine **43**, trade name Synribo, made by Teva Pharmaceutical Industries Ltd) is an alkaloid from *Cephalotaxus harringtonia*. On October 26, 2012, the FDA granted accelerated approval to omacetaxine mepesuccinate as subcutaneous use for the treatment of adult patients with chronic- or accelerated-phase CML, with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKIs). Omacetaxine is a protein translation inhibitor. It inhibits protein translation by preventing the initial elongation step of protein synthesis (Wetzler and Segal, 2011). It interacts with the ribosomal A-site and prevents the correct positioning of amino acid side chains of incoming aminoacyl-tRNAs.

**7.2 Ingenol mebutate** (ingenol-3-angelate **44**, trade name Picato) is a substance found in the sap of the plant *Euphorbia peplus* (Fallen et al., 2012). A gel form of the compound was approved for use by the US FDA and EMA in January 2012 for the treatment of acid

keratosis. The substance is an ester of diterpene and angelic acid and is marketed by LEO pharma.

**7.3 Betulinic acid (45)**, a naturally occurring pentacyclic triterpenoid, is a common secondary metabolite of plants, primarily from *Betula* species (Betulaceae) (Cichewitz et al., 2004). Betulinic acid was isolated from *Zizyphus* species, e.g. *Mauritiana rugosa* and *M. oenoplia* (Pisha et al., 1995; Shoeb, 2006) and exhibits various biological activities, such as anti-HIV, anti-inflammatory, antioxidant, antiretroviral and antibacterial properties (Fujioka et al., 1994; Nguemfo et al., 2009; Tzakos et al., 2012; Onwuchekwa and Oluwole, 2011; Yogeewari et al., 2005). Mostly recently, it has been employed as a potential anticancer agent by inhibition of topoisomerase (Chowdhury et al., 2002; Mukherjee et al., 2006; Fulda and Debatin, 2005; Mullauer et al., 2010; Fulda, 2009). A large number of betulinic acid derivatives have been developed to increase its therapeutic activity. But development of betulinic acid derivatives for clinical use has been hampered by adverse pharmacological and physico-chemical characteristics of this class of compounds. One novel, well tolerated BetA derivative is NVX-207, which showed significant anti-tumor activity in clinical studies in canine cancer patients with treatment-resistant malignancies. NVX-207-induced apoptosis was associated with activation of the intrinsic apoptotic pathway via cleavage of caspases -9, -3, -7 and of poly (ADP-ribose) polymerase (PARP). A phase I/II study in dogs suffering from naturally occurring cancer receiving local treatment of NVX-207 (10 mg mL<sup>-1</sup>) showed excellent clinical responses including a complete remission in so far 5/5 treated animals (Willmann et al., 2009).

**7.4 Flavopiridol (46)** is totally synthetic, but its chemical structure is based on identical to a product rohitukine obtained from *Dysoxylum binectariferum*, a plant indigenous to India (Naik et al., 1988). Flavopiridol was one of the over 100 analogs synthesized during structure–activity studies, Its mechanisms of action remain incompletely defined but include targeting of cyclin dependent kinases including the CDK9/cyclin T complex (Chao and Price, 2001; Chao et al., 2000; de Azevedo et al., 2002; Lam et al., 2001) down regulation of Mcl-1 and other antiapoptotic proteins (Gojo et al., 2002; Kitada et al., 2000) induction of mitochondrial permeability changes (Hussain et al., 2008) and other. Originally synthesized and supplied by Hoechst India Limited, flavopiridol is provided to the Division of Cancer Treatment and Diagnosis of the National Cancer Institute (NCI) by Aventis Pharmaceuticals, Inc. Flavopiridol is the first potent inhibitor of cyclin-dependent kinases (cdks) to reach

clinical trial (Geoffrey and Shapiro, 2004). It is currently undergoing several phase I and phase II clinical trials, either alone or in combination with other anticancer agents, against a broad range of tumors, including leukemias, lymphomas and solid tumors.

**7.5 Curcumin (47)** is a polyphenol derived from the *Curcuma longa* plant, commonly known as turmeric. Turmeric contains a class of compounds known as the curcuminoids, comprised of curcumin, demethoxycurcumin and bis-demethoxycurcumin. Curcumin is the principal curcuminoid and comprises approximately 2-5% of turmeric; it is responsible for the yellow color of the spice as well as the majority of turmeric's therapeutic effects (Wilken et al., 2011). It has a variety of therapeutic properties including anti-oxidant, analgesic, anti-inflammatory and antiseptic activity (Akram et al., 2010). More recently curcumin has been found to possess anti-cancer activities via its effect on a variety of biological pathways involved in mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumorigenesis and metastasis (Wilken et al., 2011). Phase IIa clinical trial of curcumin is going on for the prevention of colorectal neoplasia (Carroll et al., 2011). In addition it is also undergoing several phase I and II trials against several solid tumours.

Besides these, a large number of other anticancer agents isolated from plants are listed in Table 1.

**Table 1: Other anticancer agents derived from terrestrial plants**

Name	Source	Target	Clinical status	Ref
Berberine	<i>Berberis amarensis</i>	caspase-3-dependent apoptosis	Lead molecule	Liang et al., 2009; Kapoor, 2012
Berberine	<i>Hvdrastris canadensis</i>	-	Lead molecule	Diogo et al., 2011;
Bruceantin	<i>Brucea antidysenterica</i>	Inhibits peptidyl transferase elongation reaction	Clinical development terminated	
Beta Lapachone (ARQ-501)	<i>Tabebuia avellanae</i>	topoisomerase I&II	Phase II	Cragg et al., 2005; Blanco et al, 2011
Colchicine	<i>Colchium automole</i>	anti-mitotic	Lead molecule	Bhattacharyya et al., 2008
Diadzein & Genistein	<i>Lupinus species</i>	inhibits 3A 4-mediated metabolism	Phase II	Jung et al., 2012; Messing et al., 2012
Dimethyl xanthene-9-on-4-acetic acid (DMXAA) analog	<i>Flavone-8-acetic acid</i>	TNF- $\alpha$ induction	Phase I/II	Daniel et al., 2012; Buchanan et al., 2012
Ellipticine	<i>Ochrosia borbonia</i>	topoisomerase II inhibitor	Lead molecule	Iveta et al., 2013; Marie et al., 2012
4-Ipomeanol	<i>Ipomoea batatas</i>	DNA binding	Lead molecule	Lakhanpal et al., 2001
Kanglaite	<i>Coix lachryma-jobi</i>	Inhibits mitosis of tumor cells during G <sub>2</sub> /M phase	Lead molecule	Zhan et al., 2012
Meisoindigo	<i>Indigofera tinctoria</i>	Induces apoptosis by locking Stat 3 signaling	CD terminated	Lee et al., 2010
Phenoxodiol	<i>plant isoflavone genistein</i>	inhibits plasma membrane electron transport & cell proliferation	Phase I	Simon et al., 2012
Perillyl alcohol	<i>Limonene analogue</i>	Activates capase 3 apoptosis	Phase I	Garcia et al., 2010; Farazuddin et al., 2012
Pervilleine A	<i>Erthroxylum porvillei</i>	inhibition of P-glycoprotein	Lead molecule	Mi et al., 2003
Roscovitine (CYC 202)	<i>Olomucine (Raphanus sativus)</i>	CDK inhibitor	Phase II	Slovackova et al., 2012; Foell et al., 2008
Silvestrol	<i>Aglaia foveolata</i>	triggers mitochondrial pathway of apoptosis	Lead molecule	Kim et al., 2007
Santonin	<i>Artemisia maritima</i>	Inhibition of NF-Kb	Lead molecule	Khazir et al., 2013

## **8. Conclusion**

Anticancer agents discovered from plants have played an important role in the treatment of cancer. Compounds derived from plants may not serve directly as drugs, but they provide leads for the development of potential anticancer agents. Plant derived compounds such as paclitaxel, camptothecin, and podophylotoxin have significantly influenced cancer research on many aspects. They have helped the researchers to understand the disease better, provided new and efficient therapies possessing new mechanisms of action, opened new research avenues, and provided new inspiration in the development of new and future anticancer drugs. Plants represent an enormous diversity on earth, but only a small portion of that has been yet explored. So it is anticipated that plants can provide potential bioactive compounds for the development of leads against various diseases indeed far greater than compounds achievable by synthesis.

With the fast recognition of novel proteins having significant regulatory effects on tumor cell cycle progression, and their conversion into targets for high throughput screening, molecules isolated from plants and other natural sources are proving to be an important basis of novel inhibitors of the action of these key proteins, and have the potential for development into selective anti-cancer agents.

## **Acknowledgements**

Authors are thankful to Prof. Egmont Rohwer (Head, Department of Chemistry) and Prof. Don A Cowan (Director, Genomics Research Institute and Centre for Microbial Ecology and Genomics) University of Pretoria for their valuable help and support. Thanks are also due to Dr. Pieter De-Maayer, CMEG for editing the manuscript. We also acknowledge University of Pretoria for Postdoctoral fellowship to JK and BAM.

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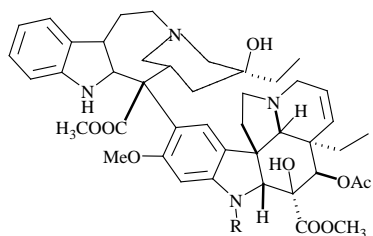
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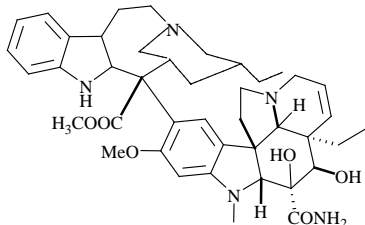
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## Appendix A. Supplementary data

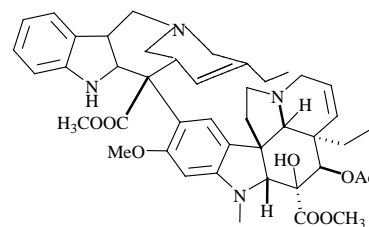
Supplementary Fig. I. Chemical structures of various plant based natural and semisynthetic anticancer natural products.



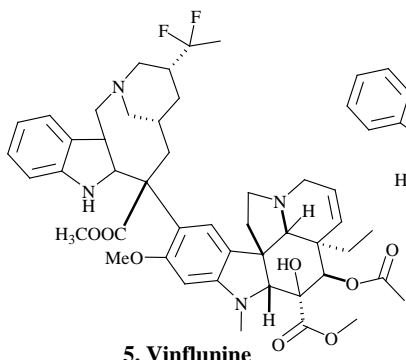
1. Vinblastine R = CH<sub>3</sub>  
2. Vincristine R = CHO



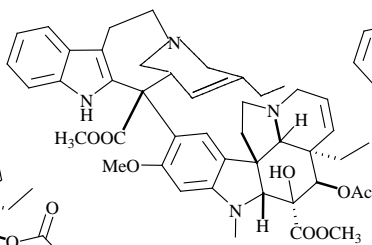
3. Vindesine



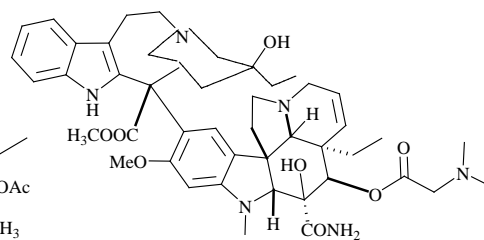
4. Navelbine



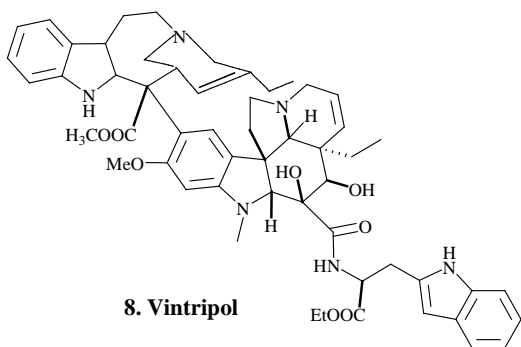
5. Vinflunine



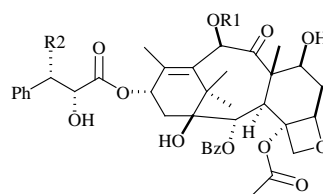
6. Hydravin



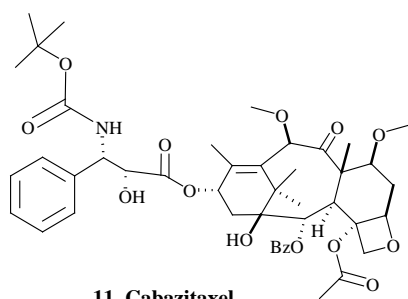
7. vinginglycinat



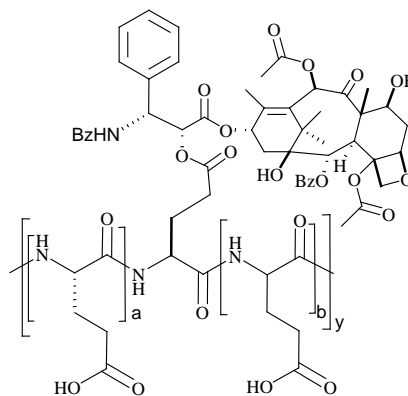
8. Vintripol



9. Taxol: R<sub>1</sub> = COCH<sub>3</sub>, R<sub>2</sub> = HNCOC<sub>6</sub>H<sub>5</sub>  
10. Docetaxol: R<sub>1</sub> = H, R<sub>2</sub> = HNCOC(CH<sub>3</sub>)<sub>3</sub>

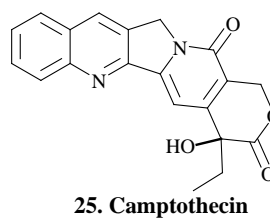
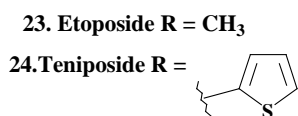
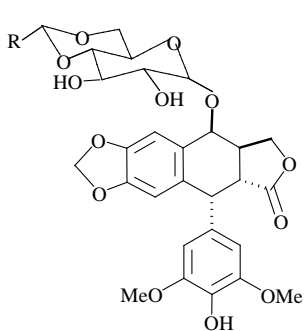
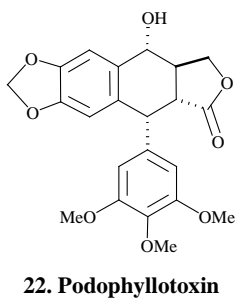
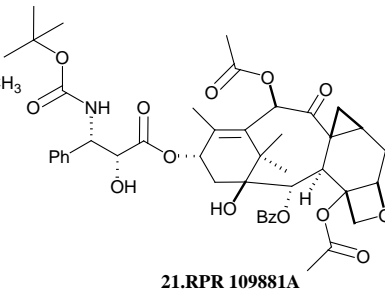
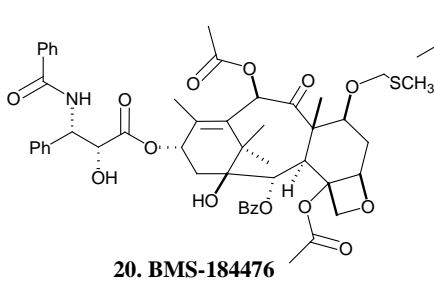
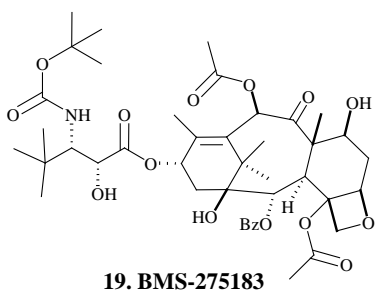
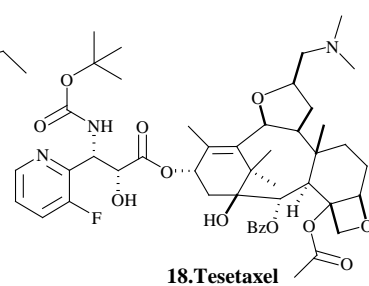
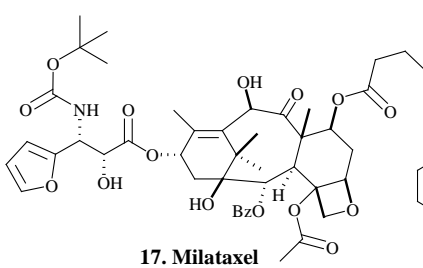
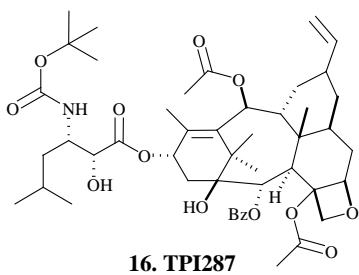
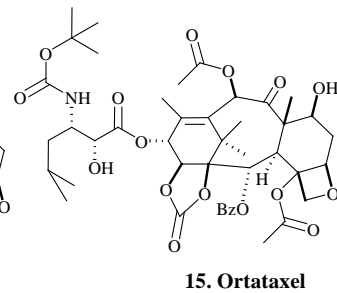
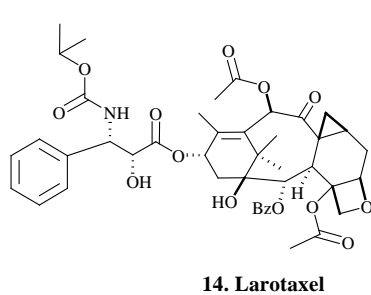
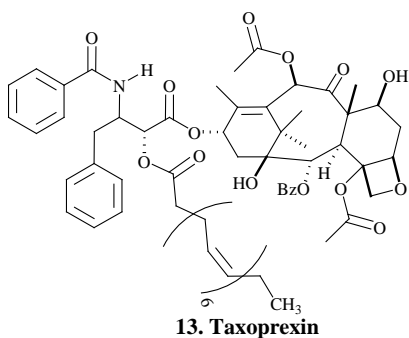


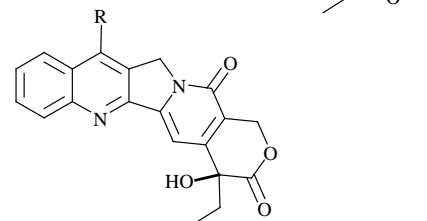
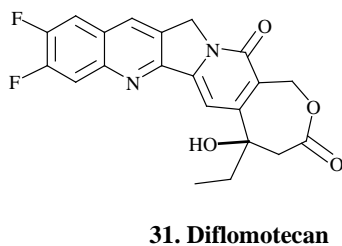
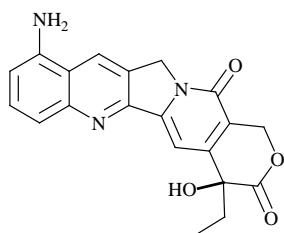
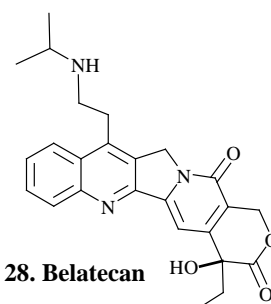
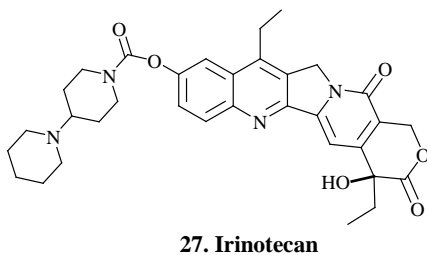
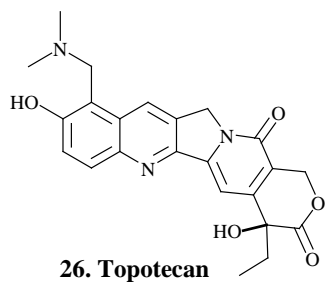
11. Cabazitaxel



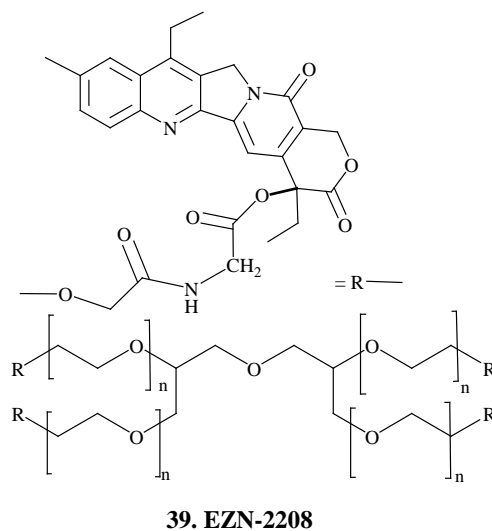
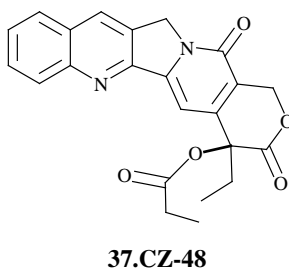
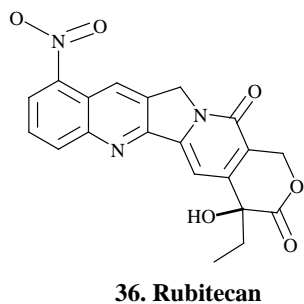
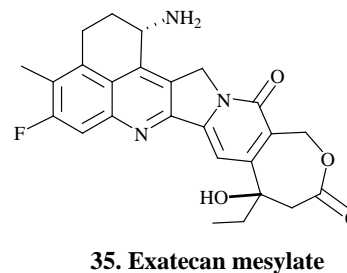
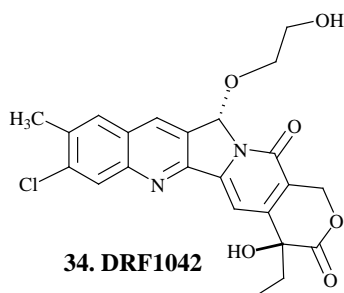
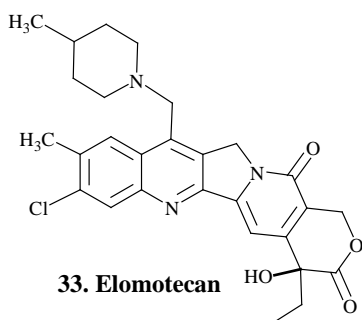
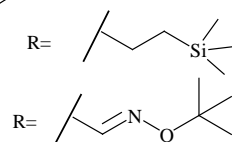
a + b averages 10

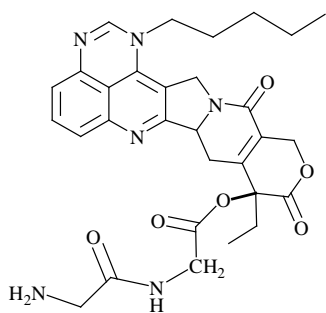
12. Paclitaxel polyglumex



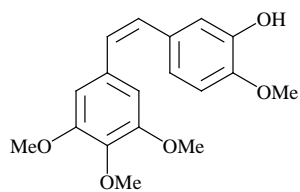


**32. Gimatecan**

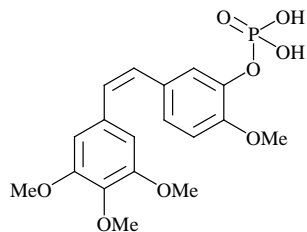




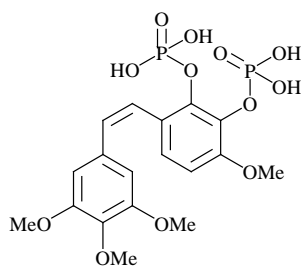
**38.TP-300**



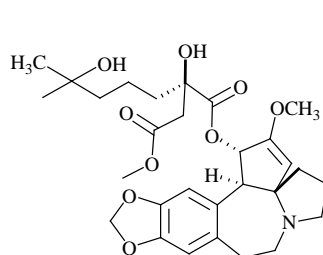
**40. Combrastatin A4**



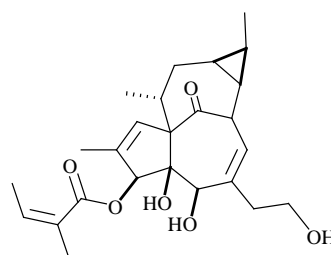
**41. CA-4P**



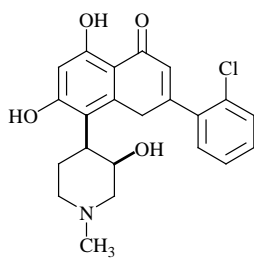
**42. CA-1P**



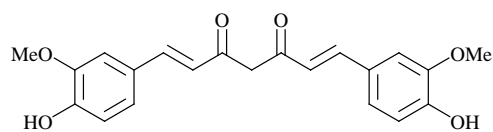
**43. Homoharringtonine**



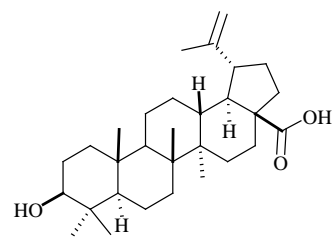
**44. Ingenol-3-O-angelate**



**46. Rohitukine**



**47. Curcumin**



**45. Betulinic acid**