ANTICANCER AGENTS FROM DIVERSE NATURAL SOURCES

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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. Natural products 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 are natural products or their analogues and many more are under clinical trials. This review aims to highlight the invaluable role that natural products have played, and continue to play, in the discovery of anticancer agents and also summarizes the recently launched natural product-derived anticancer drugs and new natural product templates in clinical pipeline.

Keywords cancer, drugs, endophytes, marine organisms, 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 [1]. The World Health Organization (WHO) projects that without immediate action, the global number of deaths from cancer will increase to 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 [2].

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 [3-4]. 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 chemo-preventative agents that are both effective and safe [5]. One practical approach to this problem is the use of natural products as a platform for drug development.

Nature is an excellent source of potential chemotherapeutic agents and lead compounds that have provided the basis and insight for the semi-synthesis or total synthesis of several effective new drugs. To date, approximately half of the drugs currently used in clinical natural product (NP) or NP based [6-7]. In 2010, ten of 20 small molecules that were launched against different diseases, half of these were either NPs or directly derived from them, with the majority being in the antitumor class [8]. A total of nine natural-product based drugs were approved by Food and Drug Administration (FDA) during the two year period from 2011-2012, that are classified as 4 NPs and 5 NP derived drugs (Table 1). It is noteworthy that all the tyrosine kinase inhibitors described in table 1 fall under synthetic natural product mimic category (S/NM), showing competitive inhibition of NP substrate.

Nature is an attractive source of new therapeutic candidate compounds as tremendous chemical diversity is found in millions of species of plants, animals, marine organisms and microorganisms. There is a strong biological and ecological rationale for natural sources to produce novel bioactive secondary metabolites [9]. These organisms have evolved a complex chemical defense system, which involves the production of large numbers of chemically diverse compounds. The genes that are responsible for the chemical compounds obtained from various natural sources can frequently be exchanged. *De novo* synthesis of bioactive molecules, using combinatorial chemistry is unlikely to replace the millions of years of evolution and natural selection available to living organisms, and thus, natural products, are still the most promising source for new drug discovery [10, 6].

Since the 1940s, a large variety of compounds isolated from natural sources have been found to show anti-tumorigenic properties [11]. A large number of anti-tumor drugs derived from plant, microorganism and marine organisms have been identified and approved against cancer during the last 60 years (Table 1-2). To date, out of 236 new chemical entities (NCEs) that have been launched as anticancer drugs, approximately 80% are NP derived or inspired by NPs (Figure 1**)**. The total number of approved anticancer drugs, and their sources for a time period of 30 years from 1983 to 2012 with a sharp increase from 2010-2012 are dipicted in Figures 2 and 3. Therefore, this review highlights the invaluable role played by natural sources in the discovery of anticancer agents.

2. Terrestrial plants as a source of anticancer agents

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 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 [12].

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 [13]. 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 [14-15].

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.

2.1 Vinca alkaloids and its semi-synthetic 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) [16]. 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. This results in metaphase arrest and apoptosis [17]. A series of semi-synthetic analogues of these two important drug molecules have been developed. The first semi synthetic 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 [18]. 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 [19].

Vinorelbine (Navelbine, **4)**, is another semi synthetic 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 [20]. 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 [21-22].

Vinflunine (**5),** a dihydro-fluoro derivative of vinorelbine was approved by European medical agency (EMEA) in 2009 as second line chemotherapy in metastatic urothelial cancer [22-23]. Similar to other members in the vinca alkaloid class, vinflunine binds to the tubulin molecules, causing microtubule depolymerization and the formation of tubulin paracrystals [25-28]. This interaction then leads to G_2/M phase arrest [25, 28-30] and apoptosis results [29-30]. 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 [31].

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 [32].

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(2) [33], but Keryx discontinued its further development in 2005 but trials may still be ongoing by Prescient Neuropharma [34]. The clinical trial website shows its 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 vinglycinate (**7**) and vintripol **(8)**, that are structural analogues of vindesine. Vinglycinate substituted by glycinate residue at the vindoline C-4 position entered phase I clinical trials in 1967, but concluded with toxicity [35-36]. Although many other semi synthetic compounds have been developed from vinblastine and vincristine, none of these have exerted marked benefits in clinical evaluation.

2.2 Taxol and its semi-synthetic 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 [37]. A number of its semisynthetic derivatives have been developed. The first to reach clinical use was docetaxel (**10)** [38] which have shown

significant clinical activity in a wide range of tumors and a different toxicity pattern than the parent compound [39-40]. 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 phosphor-glyco protein (PGP) efflux pump [41-42], which is highly expressed in the BBB [43]. 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 [44-45]. Cabazitaxel binds to and stabilizes tubulin, resulting in the inhibition of microtubule depolymerization and cell division, cell cycle arrest in the G_2/M phase, and the inhibition of tumor cell proliferation [45]. 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 [46] 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 [47].

The approval of nanoparticle based formulation abraxane shows that improved formulation can have a dramatic effect [48]. 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 the treatment of breast cancer. 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 [49].

Novel taxanes in development are being designed to improve the pharmacology and therapeutic index, and replace paclitaxel and docetaxel as standard treatments in NSCLC [50]. 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 [51]. 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 [52-53]. 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 [54]. 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 NSCLCs. But despite the low objective response rate, treatment was associated with survival comparable to that seen with standard platinum-based combination chemotherapy [55]. The clinical trials database shows its 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 NSCLCs has been reported and this combination was showing modest activity in chemotherapy-naïve patients with advanced/metastatic NSCLC [56]. 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 [57]. The clinical trials data-base is showing its 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).

Ortataxel (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, ortataxel showed encouraging activity and clinical benefit in breast cancer patients who are resistant to paclitaxel or docetaxel combinations [58]. The clinical trials data-base is showing its 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 [59-60]. 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^2 [61]. 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 [62-63]. 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 [64]. 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 [65]. 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 [66]. 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 [67]. Several other taxane derivatives are in clinical development and include albumin-bound paclitaxel, albumin-bound docetaxel, paclitaxel microspheres and many others [68].

2.3 Phodophylotoxin and its semi-synthetic analogues

Phodophyllotoxin (**22),** obtained from *Podophyllum peltatum,* is another important anti-cancer compound [69]. Some 30 years after its discovery, it was demonstrated that this compound binds irreversibly to tubulin [70] and therefore had potential as an anticancer agent. Etoposide (**23)** and teniposide (**24)** are the two key analogs of podophylotoxin. 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 [71-72]. The impressive potency and clinical efficacy of the two analogues has prompted extensive structure activity studies based on the podophylotoxin prototype and numerous podophylotoxin analogues have been synthesised and evaluated since 1950s to overcome the problems such as poor water solubility, acquired drug resistance and metabolic inactivation met by parent molecule. Several semi synthetic analogues like NK 611, GL-331, azatoxin, Top-52, etoposide phosphate and tafluposide have been produced as either clinical drugs or novel clinical trial candidates for various cancers [73-80].

2.4 Camptothecin and its semi-synthetic analogues

Camptothecin (CPT) (**25)**, a quinoline alkaloid with topoisomerase-I inhibitor activity isolated from *Camptotheca acuminate,* induces cell death by DNA damage [81]. 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 [82].

Another semi-synthetic CPT derivatives 9-amino camptothecin (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 myelosupression 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 [83-84]. 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 [85]. Karenitecin (BNP-1350, **30**), another semi synthetic analogue of CPT has been used in phase II trials against malignant melanoma [86-87] 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 [88]. 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 [89].

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 [90] and phase II for the treatment of recurrent epithelial ovarian and fallopian tube cancers, previously treated with platinum and taxanes [91]. 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 [92]. DRF-1042 (**34)** a novel, orally active camptothecin analogue, has completed phase I clinical trials by Dr Reddys Laboratories [93]. Exatecan mesylate (**35)** has been in phase II trials for the treatment of gastric cancers [94], and the treatment of children with relapsed or refractory rhabdomyosarcoma [95]. 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 [96]. Rubitecan did however show promising activity against pancreatic cancer, and as such was taken for further development and is currently in the last phases of clinical trials -prior to FDA approval against refractory pancreatic cancer [97].

Besides this, various conjugated CPT analogues have been developed by conjugating small molecules at 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 [98].TP-300 (**38)** is undergoing phase I trials against advanced solid tumours [99]. EZN-2208 (**39)** is undergoing phase I studies in patients with advanced malignancies [100].

Co-polymers have also been used as prodrugs of CPTs. MAG-CPT is a copolymer linked to CPT through a glycylaminohexanoyl-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 [101]. 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 [102]. CRLX-101 is a nanopharmaceutical comprised of the chemotherapeutic camptothecin (CPT) conjugated to a linear, cyclodextrin-based polymer. CRLX101 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 CRLX101 when administered intravenously to subjects with advanced solid tumors [103]. 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. The liposome encapsulated formulation of irinotecan has been developed by Neo Pharma and Pharma engine; it is an oncology drug product consisting of the active metabolite of irinotecan (CPT-11), a known anticancer drug, encapsulated in a liposome. The irinotecan liposome formulation is currently in phase I trials in the treatment of advanced cancers [104]. 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.

2.5 Combrestatin and its analogues

Combretastatins have been isolated from the bark of the South African tree *Combretum caffrum* Kuntze (Combretaceae). Combretastatin (**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 β-tubulin are among the most active of the natural products isolated from *C. Caffrum* [105]. 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 [106]. 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 anapalstic thyroid cancer [107].

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 [108]. OXiGENE, announced that OXi4503 has been granted orphan designation by the US FDA for the treatment of AML [109].

2.6 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 [110]. It interacts with the ribosomal A-site and prevents the correct positioning of amino acid side chains of incoming aminoacyl-tRNAs (**Table 1**).

2.7 Ingenol mebutate (ingenol-3-angelate **44**, trade name Picato) is a substance found in the sap of the plant *Euphorbia peplus* [111]. 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 (**Table 1).** In addition to these well known anticancer compounds, a number of other plant secondary metabolites have been discovered and are in clinical pipeline (**Table 3).**

3. Microorganisms as a source of anticancer agents

Microorganisms are a plentiful source of structurally diverse bioactive substances, and have provided important contributions to the discovery of antibacterial agents. The success of several medicinal drugs from microbial origin such as penicillins (from *Penicillium* species), cephalosporins (from *Cephalosporium acremonium*), cyclosporine (from *Trichoderma* and *Tolypocladium* species), griseofulvin (from *Penicillium griseofulvum* fungus), mevastatin (compactin; from *Penicillium* species) and lovastatin (from *Aspergillus* species); ivermectins

(from *Streptomyces* species) and *β*-lactam antibiotics from various fungal taxa, has shifted the focus of drug discovery from plants to microorganisms [168].

Five classes of microorganism (cyanophytes, marine microbes, extremophiles, microbial symbionts and plant endophytes) are now known to produce secondary metabolites against abdominal environments and for self-protection [169-174]. Micro-organisms are a prolific source of structurally diverse bioactive metabolites and have yielded some of the most important products of the pharmaceutical industry. Secondary metabolites from microorganisms with potential anti-tumor activities have been discovered in recent years. Antitumor antibiotics are among the most important of the cancer chemotherapeutic agents. Recently approved microbial derived anticancer drugs include everolimus (RAD-001, **45**). It is a 40-*O*-(2-hydroxyethyl) derivative of a macrolide, sirolimus (**46**) isolated from *Streptomyces hygroscopicus* [175] acts as an inhibitor of mammalian target of rapamycin (mTOR) and marketed under the trade name Afinitor by Novartis. It was approved by FDA in May 2011 for the treatment of advanced pancreatic neuroendocrine tumours. Then in April 2012, it was approved by FDA for the treatment of renal angiomyolypoma with tuberous sclerosis complex, and in July 2012 was approved for the treatment of hormone receptor-positive, HER2-negative breast cancer.

Carfilzomib (CFZ, tradename Kyprolis, **47**) is a tetrapeptide epoxyketone and a selective proteasome inhibitor. The US FDA approved its use on 20 July 2012 for relapsed and refractory multiple myeloma patients who have received at least two prior therapies, including bortezomib and an immunomodulatory agent. It is an analog of epoxomicin **(48**), a potent anti-tumor agent isolated from an unidentified *Actinomycetes* strain, No Q996-17 [176]. It is used as a selective and irreversible inhibitor of the 20S proteasome and is marketed by Onyx Pharmaceuticals.

At present microorganisms are considered as the most promising sources of natural anti-tumor drugs owing to their wide distribution and diversity among all organisms on earth. Additionally, microorganisms that can survive in abdominal environments secrete metabolites of potential medical applications. An exciting “pipeline” of new anticancer clinical and preclinical agents have emerged from intense efforts over the past decade to more effectively explore the rich chemical diversity offered by the micro-organisms (Table 4).

To date, majority of the anticancer drugs are developed either from plants or bacteria but no fungal metabolites or their derivatives have been approved as anticancer drugs. Fungal metabolites and derivatives thereof are much less investigated for their potential in cancer therapy but last decade has shown a fabulous increase in the number of anticancer fungal

derived compounds in clinical pipeline. Fungi are known for producing many novel metabolites showing wide range of different bioactivities with a large number reported to possess cytotoxic properties [235-242]. More than 1500 fungal metabolites had been reported to show anti-tumor and antibiotic activity. Some of them have entered clinical trials while others serve as lead structures in the search for clinically applicable antitumor drugs [243]. More than 30% of isolated metabolites from fungi are from *Aspergillus* and *Penicillium* spp. [244].

One of the best evaluated fungal metabolites in anticancer area is fumagillin (**49**) which arises from a mixed sesquiterpenoid (C15-nucleus) and polyketide (C10 side chain) biosynthesis of the fungus *Aspergillus fumigatus* [245]. Many semi-synthetic analogues of fumagillin have been synthesized in order to increase potency and at the same time decrease toxicity. The most potent of these includes TNP-470 (**50**) and CKD-732 (**51**). TNP-470 has been shown to inhibit angiogenesis *in vitro* and *in vivo*. In 1992, TNP-470 entered clinical development for cancer as an anti-angiogenic agent for the treatment of breast, prostate, and brain cancer, as well as Kaposi sarcoma [246]. TNP-470 stunted the growth of every malignancy it touched-animal tumours, human tumours, and spreading tumours. It suppressed tumours of the ovaries, colon, prostate, and breasts. In some cases the tumours shrank; in others, they disappeared [247]. However some patients, whose malignancies were repressed, or even eliminated, started showing unacceptable side effects - problems with motor coordination, seizures, and malaise [248].

CKD-732 [6-O-(4-dimethylaminoethoxy) cinnamoyl fumagillol hemioxalate] has also entered clinical trials, being even more potent and less toxic than TNP-470 [249-251]. Phase I clinical trials were done to evaluate the safety, tolerability, and pharmacokinetics (PK) of CKD-732 in combination with capecitabine and oxaliplatin (XELOX) in nine metastatic colorectal cancer patients who had progressed on irinotecan-based chemotherapy. The phase II trials recommended dose of CKD-732 was determined to be 5 mg/m^2/d, and this dose was safely combined with conventional doses of capecitabine and oxaliplatin in this patient population. Further studies on the effects of CKD-732 in combination with xelox and other chemotherapies using a larger study population are warranted [252].

Another anticancer lead compound of fungal origin is the sesquiterpene illudin S (**52),** first isolated from the basidiomycete *Omphalotus illudens* [253]. Many semi-synthetic analogues of illudin S have been synthesised, most promising of which is the alkylating agent irofulven (**53**). Irofulven has a significantly superior therapeutic index in comparison to the parent natural product showing more selectively towards human tumor cells [254].

In 2001, the FDA granted fast track status to the novel anti-tumor drug-candidate irofulven (also known as hydroxymethylacylfulvene, HMAF, and MGI-114). It is a DNA-alkylating agent that has an unusual mechanism. In phase I and phase II clinical trials, conducted by MGI Pharma and the National Cancer Institute, irofulven exhibited particularly promising results in shrinking malignant solid tumours, including those of drug-resistant cancers [255]. It demonstrated remarkable results on patients with pancreatic cancer that had stopped responding to drugs, offering new hope for patients with this deadly disease. Based on these favourable results, a phase III clinical trial of irofulven for the treatment of pancreatic cancer was started [256]. Furthemore, a multi-center phase II trial was conducted by the Gynecologic Oncology Group to evaluate the activity and safety of irofulven in patients with recurrent epithelial ovarian cancer [557]

Plinabulin (NPI-2358, **54**), another compound of fungal origin, was isolated from cultures of the marine-derived fungus *Aspergillus ustus* [258]. Its structure is based on the diketopiperazine phenylahistin (also known as halimide). It acts as a tumor vascular disrupting agent by inducing rapid depolymerisation of existing microtubules in the highly proliferating tumor vascular endothelial cells and is reported to be undergoing two phase I trials [259-260]. Preclinical data indicate plinabulin has favourable safety and antitumor activity profiles, leading to initiation of phase I clinical trial to determine the recommended phase 2 dose (RP2D) and assess the safety, pharmacokinetics, and biologic activity of plinabulin in patients with advanced malignancies. At the RP2D of 30 mg/m², plinabulin showed a favourable safety profile, while eliciting biological effects as evidenced by decrease in tumor blood flow, tumor pain, and other mechanistically relevant adverse effects. On the basis of these results additional clinical trials were initiated with plinabulin in combination with standard chemotherapy agents [261]. In combination with docetaxel plinabulin is at present in phase II clinical studies against advanced NSCLC [262]. Besides these many other fungal compounds are showing promising anticancer activitities which makes them interesting candidates for preclinical and clinical studies (Table 4).

4. Marine derived anticancer agents

Marine organisms comprise approximately half of the total biodiversity on earth and are the greatest source to discover novel therapeutics. Because of the physical and chemical conditions in the marine environment, almost every class of marine organism exhibits a variety of molecules with unique structural features. The efforts to extract drugs from the sea started in the late 1960s. However, the systematic investigation began in the mid-1970s. It was Bergman who first isolated two compounds from sponges namely, spongouridine (**55)**

and spongothymidine (**56)** in the early 1950s from the Caribbean sponge *Tethya crypta* [263-265]. These are considered as the precursors of all nucleoside drugs [266]. Recently, much attention has been focussed on marine organisms due to their extensive biodiversity [267]. Structurally unique secondary metabolites have been isolated and identified from marine organisms and many of the candidates have shown prominent biological activities [268-270].

To date, eight marine drugs have been approved by the FDA or EMEA, out of which four are anticancer drugs, cytarabine (**57)** , a synthetic analogue of **48** was approved by the FDA in 1969 in the treatment of cancers of white blood cells such as AML and non-Hodgkin lymphoma [271], ecteinascidin 743 (**58)**, isolated from *Ecteinascidia turbinata* was approved by the EMEA in 2007 for use in Europe, Russia and South Korea for the treatment of advanced soft tissue sarcoma. [272-273], eribulin mesylate (Halaven™, **59**) a synthetic macrocyclic ketone analogue of the marine sponge natural product halichondrin B, gained FDA approval in November 2010 for MBC [274]. Brentuximab vedotin (SGN-35, **60**) another marine derived drug was approved by US FDA on Aug 9, 2011 to treat anaplastic large cell lymphoma (ALCL) and Hodgkin lymphoma. The compound consists of the chimeric monoclonal antibody brentuximab (which targets the cell-membrane protein CD30) linked to three to five units of the antimitotic agent monomethyl auristatin E (MMAE, reflected by the 'vedotin' in the drug's name). The antibody portion of the drug attaches to CD30 on the surface of malignant cells, delivering MMAE which is responsible for the anti-tumour activity [275]. MMAE is a synthetic derivative of dolastatin 10, a natural cytostatic pseudopeptide originally isolated from the marine shell-less mollusk *Dorabella auricularia* [276].

These success stories have had to overcome difficulties inherent to marine natural products-derived drugs, such as sustainable sources and issues related to structural complexity. Many other factors, particularly the cytotoxicity that they show on normal human cell lines, render the compounds unfit for use as medicinal supplements, but despite their failures, the past decade has seen a dramatic resurgence in the number of preclinical anticancer lead compounds from diverse marine life entering human clinical trials. So far more than 10,000 bioactive compounds have been discovered from marine sources, and hundreds of new compounds are discovered every year [277]. Most of these come from marine animals, including sponges, sea cucumbers, bryozoans, tunicates, sea hares, and sharks with largest numbers from sponges. As an important source of anticancer drugs, in recent years, marine-derived anticancer agents have been widely investigated. According to BCC reports global market for marine derived drugs by type was around $ 4.8 billion in 2011 and is forecasted to

reach $ 8.6 billion by 2016. In 2010 the market for sponges was $ 3 billion and BCC has forecasted that this market will reach $4 billion by 2016. Molluscs are the fastest growing market and are expected to grow from $ 69.4 million in 2011 to $490.1 million by 2016 at a compound annual growth rate of 47.8%.

Compounds of different chemical classes and with different mechanisms of action have been found as potential antitumor lead molecules (**Table 5**). Apratoxin A (**61)** a potent cytotoxin isolated from a marine cyanobacterium *Lyngbya majuscule*, reversibly inhibits the secretory pathway for several cancer-associated receptors by interfering with cotranslational translocation [278]. This was the first report of an anti-tumor compound which acts by this mechanism. Also, the cyclic depsipeptide largazole (**62)**, isolated from a cyanobacterium of the genus *Symploca*, is one of the most potent class I histone deacetylase inhibitors, and is also the first known cyanobacterial secondary metabolite that encloses a thioester [279-280].

4.1 Marine derived compounds in clinical trials

The first anticancer agent derived from marine organism to enter clinical trials was a cyclic depsipeptide didemnin B (**63)** isolated from *Tridemnum solidum* [281]. But severe toxicity shown by this molecule led to the termination of trials by the NCI in 1990 [282]. Since then, many marine derived agents have reached clinical trials but have failed in different stages. Dolastatin 10 (**64**) entered phase I clinical trials in the 1990s through the NCI and progressed to phase II trials but was dropped from clinical trials, as a single agent because of toxic effects [283-285]. However its structural design led to the synthesis of its analogue TZT-1027 (soblidotin, **65**). It was designed with the goal of maintaining the potent antitumor activity while reducing the toxicity of the parent compound. Soblidotin differs from dolastatin 10 in the replacement of the terminal dolaphenine amino acid residue unit with a simple phenylethylamine group. TZT-1027 was found to be a vascular disrupting agent, collapsing the vasculature in the tumours. But it also dropped from phase II due to the lack of the expected therapeutic efficacy [286] and is currently under the auspices of Asaka pharmaceuticals.

Dolastatin 15 (**66**), which could not itself reach clinical trials because of its poor water solubility, prompted the development of various synthetic analogues with enhanced chemical properties, including cemadotin (**67**) and synthadotin (**68**) [286]. Cematodin (LU-103793) underwent six phase I clinical studies, but its phase II evaluations have produced no objective results to date [287-289], as a result the current clinical evaluation of LU-103793 has been discontinued [269]. ILX-651 (Synthadotin) another synthetic dolastatin 15 analogue was orally active and advanced to three phase II clinical trials against a wide range of cancers

initially under Ilex pharmaceuticals. Currently these trials have been ended up and it is now in preclinical trials in the United States under the auspices of Genzyme's. Neovastat extracted from shark cartilage was dropped from phase III due to lack of therapeutic efficacy [290]. Methionine aminopeptidase (MetAPs) inhibitor like LAF389 (**69**) also dropped in either phase I due to the severe toxicities or the lack of positive therapeutic effects [291-292]. Cryptophysin 1(**70**), a group of 27 marine cyanobacteria-derived tubulin binding compounds, were first obtained from the marine cyanobacteria *Nosto*c sp. These are potent cytotoxic and antimitiotic agents whose mechanism of action is ascribed to the destabilisation of microtubules. Cryptophysin 52 (**71**) is the synthetic analogue of cryptophysin 1 which was developed by Eli Lilly to improve hydrolytic stability and formulation. Cryptophysin 52 revealed 40-400 times higher potency than either vinca alkaloids or paclitaxel in *in-vitro* cytotoxicity assays [293-294]. It entered phase I trials in 1990s against refractory solid tumours but results were not favourable in phase II trials involving patients with stage IIIb or IV NSCLC, previously treated with platinum containing chemotherapeutics [295-296]. Currently cryptophysin 52 has been excluded from clinical trials, however novel analogues such as cryptophysin 309 and 249 were found to be promising enough to advance into the clinical trials [297].

Bryostatin-1 (**72**), a polyketide isolated initially from Bryozoa, *Bugula neritina* is now known to be produced by its bacterial symbiont, *Candidatus endobugula sertula* [298]. It works as a PKC isozyme inhibitor [299], and has undergone about 80 separate phase I and phase II clinical trials, alone or in combination therapy, since its introduction in 1993. In more than three dozen clinical trials to fight various forms of the disease, it gave mostly mediocre results, both on its own and in combinations with other cancer-fighting drugs. Its various phase I and phase II clinical trials, alone or in combination with other drugs against various solid tumours are reported in clinical trials website. One is in phase II trials (NCT00032188) against advanced kidney cancer, a second one is in phase I clinical trials against recurrent or refractory HIV related lymphoma. A third one is in phase I trials (NCT00004144) for the treatment of advanced cancers. A Fourth (NCT00004008) and fifth (NCT00005056) one are in phase II trials against ovarian epithelial and progressive kidney cancers respectively. According to the present clinical results, the clinical development of bryostatin-1 is faced with several major challenges, including how to reduce its toxicity (mainly myalgia), increase its therapeutic efficacy (mainly through combination with other anticancer drugs), and develop proper molecular biomarkers for the selection of patients and the therapeutic surveillance.

Plitidepsin (**73**), isolated from mediterranean tunicate *Aplidium albicans* is a cyclic depsipeptide and closely related analogue of didemnum has successfully reached phase II clinical trials for solid and haematological malignant neoplasias like T cell lymphoma and myelofibrosis [300-303], and randomized phase III trial are also ongoing in patients with relapsed/refractory multiple myeloma [304-305]. It is PharmaMar's second most advanced compound and FDA has accepted the proposal made by PharmaMar for the commercial production of the drug. Plitidepsin has been designated an orphan drug by the European Commission (EC) and the FDA for multiple myeloma (MM) [306].

Salinosporamide A (**74**), a proteasome inhibitor isolated from a marine bacterium *Salinispora tropica* [307-309], contains an unusual β-lactone and is undergoing phase I clinical trials for (MM) under the auspices of Nereus Pharmaceuticals [310] San Diego, CA. Squalamine (**75**), an aminosteriod obtained from tissues of the dogfish shark *Squalus acanthias* is under phase II clinical trials to evaluate its safety and effectiveness as a potential treatment for wet age-related macular degeneration (AMD) under the auspices of Ohr Pharmaceutical, Inc [311]. Panobinostat (LBH-589, **76**) is among the most potent HDAC inhibitors [312] and is undergoing extensive phase I and phase II clinical trials [313]**.** The results of phase II trials of panobinostat (LBH-589) against relapsed/refractory Hodgkins lymphoma [314] and phase I trials against primary myelofibrosis (PMF) and post-polycythaemia vera/essential thrombocythaemia myelofibrosis (post-PV/ET MF) demonstrated its antitumor activity [315]. PM00104 (Zalypsis®, **77**), isolated from the mexican sponge *Reniera sp* and the Fijian sponge *Xestospongia caycedoi* [316] and obtained from the skin and mucus of the pacific marine *nudibranch jorunna funebris* [317]. It is a synthetic tetrahydroisoquinoline alkaloid with potent antiproliferative activity against tumor cell lines [318]. It is in phase II trials against solid tumours currently licensed and developed by PharmaMar [319-320].

Lurbinectedin, also known as PM01183 (**78)** is a novel marine-derived covalent DNA binder in clinical development structurally related to ecteinascidins [321-322]. In common with trabectedin, PM01183 contains a pentacyclic skeleton composed of two fused tetrahydroisoquinoline rings (subunits A and B) that is mostly responsible for DNA recognition and binding but the additional module (ring C) in PM01183 is a tetrahydro β-carboline rather than the additional tetrahydroisoquinoline present in trabectedin [323]. This structural difference may confer pharmacokinetic benefits as well as intrinsic activity. It is currently in phase II clinical trials against (BRCA) 1/2-associated or unselected MBC [324].

E7974 (**80**) is a synthetic analogue of the marine sponge natural product hemiasterlin (**79**), which was first reported by Kashman and Co-workers from the marine sponge *Hemiasterella minor* in 1990. It acts via a Tubulin-based antimitotic mechanism. E7974 inhibits polymerization of purified tubulin *in vitro* with IC_{50} values similar to those of vinbalstine. It induces G2-M arrest and marked disruption of mitotic spindle formation characteristic of tubulin-targeted anticancer drugs [325]. Currently it is undergoing phase I trials in treating patients with advanced solid tumours [326].

CDX-011 (glembatumumab vedotin, **81**) is a marine derived antibody-drug conjugate (ADC) that consists of a fully-human monoclonal antibody, CR011, linked to a potent cell-killing drug, monomethyl-auristatin E (MMAE). The ADC technology, comprised of MMAE and a stable linker system for attaching it to CR011, was licensed by Seattle Genetics, Inc. The ADC is designed to be stable in the bloodstream. Following intravenous administration, CDX-011 targets and binds to Transmembrane glycoprotein NMB (GPNMB), a specific protein that is expressed in breast cancer and other tumor types which promotes the migration, invasion and metastasis of breast cancer [327]. Upon internalization into the targeted cell, CDX-011 is designed to release MMAE from CR011 to produce a cell-killing effect. CDX-011 has been shown to be well tolerated and active, with observed objective responses in two positive Phase 1/2 trials in metastatic breast cancer and advanced melanoma. In May 2010, the U.S. FDA granted Fast Track designation to Celldex's CDX-011 for the treatment of advanced, refractory/resistant GPNMB-expressing breast cancer. Celldex Therapeutics, Inc. (Nasdaq: CLDX) has announced its completed randomized phase 2b study evaluating CDX-011 in patients with previously treated metastatic or locally advanced breast cancer [328].

PM060184 (**82)** isolated from Madagascan sponge *Lithoplocamia lithistoides* binds covalently to the minor groove of the DNA, giving rise to double strand breaks and perturbations of the cell cycle inducing cell death [329]. It has shown strong *in vitro* and *in vivo* antitumor activity and a favourable safety profile in preclinical toxicology studies. Currently PM060184 is undergoing Phase Ib trials in combination with capecitabine in treatment of patients advanced solid tumours under the auspices of PharmaMar [330].

SGN-75 (**83**) is a marine-derived antibody-drug conjugate (ADC) using Seattle Genetics' proprietary technology. SGN-75 is composed of an anti-CD70 antibody h1F6 stably linked to a cytotoxic (cell-killing) agent, monomethyl auristatin F (MMAF). The ADC is designed to be stable in the bloodstream and to release its cytotoxic agent when internalized into CD70-expressing tumor cells. SGN-75 is in phase 1b clinical trial to assess its safety and antitumor

activity in combination with everolimus in patients with CD70-positive metastatic renal cell carcinoma [331].

ASG-5ME is an antibody-drug conjugate (ADC) composed of a fully human monoclonal antibody directed to SLC44A4 (AGS-5), a novel cancer target shown to be expressed in prostate, pancreatic and gastric cancers. The antibody is attached to a potent, synthetic cytotoxic (cell-killing) agent, monomethyl auristatin E (MMAE), via an enzyme-cleavable linker using Seattle Genetics' proprietary ADC technology. ASG-5ME is currently in phase 1 clinical trials to evaluate the safety and antitumor activity in patients with pancreatic, gastric and prostate cancers [332].

In addition, there are many auspicious candidates in the preclinical pipeline, which are continuously feeding the clinical pipeline like depsipeptide (**84)** an HDAC inhibitor [333] was first isolated as a fermentation product from *Chromobacterium violaceum* and shows potential to be a highly efficient anti-cancer agent. Used alone, in preliminary trials it has shown significant effectiveness in the therapy of solid cancers as well as proliferative hematopoietic diseases. When combined with other anti-cancer agents such as 5'- aza-deoxycytidine or PSI/PS-341, it has shown a more powerful capacity to induce apoptosis in cancer cells [334-335]. While, depsipeptide is widely used in the therapy of various kinds of cancers, its anti-cancer mechanism is not well understood.

5. Endophytic fungi as source of anticancer agents

Endophytes refer to the fungi, yeast and bacteria which live inside plant tissue for at least part of their life cycle without causing any disease symptoms in the host [336]. It has been estimated that there may be as many as one million different endophytic fungal taxa [243]. The symptomless nature of endophyte occupation in plant tissue has prompted a focus on symbiotic or mutualistic relationships between endophytes and their hosts [337-338]. In comparison to fungal plant pathogens and fungal soil isolates, relatively few secondary metabolites have been isolated from endophytic fungi. These secondary metabolites of endophytic origin are synthesized via various metabolic pathways and belong to diverse structural groups, i.e., xanthones, steroids, isocumarines, phenols, quinones, furandiones, terpenoids, depsipeptides, and cytochalasines. The majority of the anticancer drugs like taxol, camptothecin, vinca alkaloids, podophylotoxin are from plant origin, as a result the collection of plants from the wild for extraction of natural products has rendered some of the important plant species to become either vulnerable or critically endangered or even extinct. On the other hand high prices of these anticancer products in the clinical market have led to a

widespread research interest around the globe, to develop alternative sources/routes for the production of these compounds.

It was in 1993, when taxol was discovered to be produced in a newly described fungus living in the yew tree [339]. Since, then it has been found in a number of other endophytic fungi, opening the possibility of taxol production by culturing one of these fungal species and thus reducing time and cost for production of the compound [340-341]. Paclitaxel can thus be considered as the first cytotoxic fungal secondary metabolite in clinical use.

The endophytic fungus *Entrophospora infrequens* obtained from *Nothapodytes foetida* was first reported to have the ability to produce CPT. It produces CPT, 9-methoxycamptothecin (**85**), and 10-hydroxycamptothecin (**86**). Compounds **85** and **86** are two important analogues of CPT with lower toxicity and potential anticancer efficacy [342]. Another partially identified fungus (RJMEF001) belonging to the family of Phycomycetes, isolated from the inner bark of *N. foetida*, growing in India, has been reported to produce camptothecin [343]. In addition, studies on *C. roseus* endophytes revealed that *Alternaria* sp. and *Fusarium oxysporum* were isolated from phloem of the plant material and were responsible for production of vinca alkaloids [344].

Similarly the aryltetralignan podophyllotoxin has been reported to be produced by endophytes, namely *Phialocephela fortinii*, isolated from the rhizomes of the host plant *Podophyllum peltatum* [345]. Also *Trametes hirsute*, an endophyte of *P. hexandrum* was reported to produce podophylotoxin.

It has been reported that the active compounds produced by endophytes have structure types that are far beyond those produced by their host plants. Thus improvement of existing drugs by modifying them with endophytes is excellent way of exploiting novel metabolites.

6. Conclusion

The present review demonstrates the potential of nature as a source for anticancer drug discovery. The large number of NP-derived compounds in various stages of clinical development indicates that the use of NP templates is still a viable source of new drug candidates. The quality of lead compounds arising from NP discovery is better and often more bio-friendly, due to their co-evolution with the target sites in biological systems. One prerequisite to natural-product discovery that remains paramount is the range and novelty of molecular diversity. It is widely believed that the earth's pan genome harbours an enormous diversity of natural resources, only a small portion of which have yet been explored. So it can therefore be assumed that natural bio-resources will continue to provide bioactive compounds as leads for the further development of novel and improved drugs.

While the pipeline of potential anticancer agents from plants is promising, the same can be said for interesting new natural product leads to treat cancer from terrestrial microbes and marine organisms. The drug potential of the marine environment remains relatively unexplored, but it is becoming increasingly evident that in future a significant numbers of natural product anticancer drugs/leads can be produced from microbes, marine organisms and/or microbial interactions with the "host from which it was isolated", and therefore this area of natural product research needs to be expanded significantly.

Plant endophytes also offer an exciting new resource, and research continues to reveal that many of the important drugs originally thought to be produced by plants are probably products of an interaction with endophytes residing in the tissues between living plant cells. Laboratory manipulation of endophytic fungi that produce important biological molecules may lead to more reliable supplies of rare anticancer agents and lead compounds of plant origin in the future.

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Figures and Tables

Table **1**. FDA approved anticancer drugs from 2011-2012, their sources, year of approval, originator and mechanism of action

Drug name	Year	Mechanism of action	Source	Originator
Abraxine	2012	Mitotic inhibitor	N	Celgene
Afinator(everolimus)	2012	Mammalian target of rapamycin (mTOR)	ND	Novartis
Afinator(everolimus)	2012	Mammalian target of rapamycin (mTOR)	ND	Novartis
Axitinib	2012	Tyrosine kinase inhibitor	S/NM	Pfizer.
Vismodegib	2012	Cyclopamine-competitive antagonist of the smoothened receptor	S/NM	Genentech,
Pertozumab	2012	Binds to HER2 and inhibits the dimerization of HER2 with other HER receptors	B	Genentech/Roche
Vincristine liposome injection	2012	Microtubule inhibitor	ND	Talon pharmaceuticals
Carfilzomib	2012	Proteasome inhibitor	ND	Onyx pharmaceuticals
Ziv-aflibercept	2012	Vascular endothelial growth factor.	B	Sanofi-Aventis.
Enzalutanide	2012	Androgen receptor antagonist	S/NM	Medivation
Regorafenib	2012	Multi-kinase inhibitor	S/NM	Bayer
Basutinib	2012	Tyrosine kinase inhibitor	S/NM	Pfizer
Omacetaxine mepesuccinate	2012	Tyrosine kinase inhibitors	N	Tova pharmaceuticals
Cabuzantinib	2012	Inhibitor of the tyrosine kinases c-Met and VEGFR2,	S/NM	Exelixis
Ponatinib	2012	Tyrosine-kinase inhibitor.	S/NM	Ariad Pharmaceuticals
Tbo-filgrutism	2012	Stimulate granulocyte proliferation and differentiation.	S	Teva pharmaceuticals
Ingenol mebutate	2012	Protein kinase C activation	N	LEO pharma
Pozopanib	2012	Tyrosine kinase inhibitor	S/NM	Glakso smith kline
Fentanyl sublingual spray	2012	Opioid agonist	S/NM	Insys therapeutics
Fentanyl sublingual tablets	2011	Opioid agonist	S/NM	Prostraka
Brentuximab vedatin	2011	Antibody portion of the drug attaches to CD30 on the surface of malignant cells delivering MMAE	B	Scattle genetics
Asparginase Erwinia	2011	Breaking down of aspariginase	N	Erwa pharma
Fentanyl citrate	2011	Agonist at the μ-opioid receptors	S/NM	Archimedes
Sunitinib malate	2011	Multi-targeted receptor tyrosine kinase (RTK) inhibitor	S/NM	Pfizer
Peginterferon alpha-2b	2011	Bind to its receptor, interferon-alpha receptor 1 and 2 (IFNAR1/2	B	Merck
Vandetanib	2011	Kinase inhibitor	S/NM	Astra zeneca
Crizatinib	2011	Protein kinase inhibitor	S/NM	Pfizer
Ipitimumab	2011	Allows CTLs to continue to destroy the cancer cells	S	Bristol-Myers Squibb
Vemurafenib	2011	B-Raf enzyme inhibitor	S/NM	Roche
Abiraterone acetate	2011	Inhibits 17 ?-hydroxylase/C17,20 lyase (CYP17A1)	ND	Centocor ortho biotech

HER2: Human Epidermal Growth Factor Receptor 2, **VEGFR2**: Vascular Endothelial Growth Factor Receptor 2, **MMAE**: Monomethyl auristatin E**, CTLs:** Cytotoxic T Lymphocyte

Table **2**. Natural product based and natural product inspired anticancer drugs approved from 1950-2012 and their mechanism of action

Drug name	Year	Mechanism of action	Source	Ref
Leucovorin	1950	Synergistic action with 5-FU, increasing its effectiveness	N	FDA
Mitomycin C	1956	DNA cross linker	N	FDA
Methyl prednisolone	1955	Irreversibly binds with glucocorticoid receptor	ND	FDA
Dexamethasone	1958	Binds to cytoplasmic glucocorticoid receptor	ND	FDA
Medroxyprogesterone acetate	1958	Inhibits secretion of gonadotropins	ND	FDA
Triamcinalone	1958	Binds to glucocorticoids	ND	FDA
Nadralone phenyl propionate	1959	Androgen-receptor agonist	ND	FDA
Chromomycin A3	1961	Inhibition of RNA polymerase	N	Japan antibiotics
Mithramycin	1961	Inhibiting DNA dependent RNA synthesis	N	FDA
Dromastanalone	1961	Potent androgenic effect	ND	FDA
Vincristine	1963	Interaction with tubulin	N	FDA
Actinomycin D	1964	Intercalation to DNA and stabilisation of cleavable complexes of topoisomerase I and II with DNA	N	FDA
Vinblastine	1965	Inhibiting mitosis by destroying the Microtubules of the mitotic apparatus	N	FDA
Bleomycin	1966	Induction of DNA strand breaks	N	FDA
Doxorubicin	1966	Inhibition of topoisomerase II	N	FDA
Daunomycin	1967	Inhibition of DNA polymerase	N	FDA
Teniposide	1967	Inhibition of topoisomerase II	ND	FDA
Testolactone	1969	Inhibition of steroid aromatase activity	ND	FDA
Asparaginase	1969	Breaking down of asparginase	N	FDA
Testosterone	1970	Activation of androgen and estrogen receptors	N	Cole
Ethinyl estradiol	1970	Binding to estrogen receptor	ND	Cole
Prednisone	1970	Irreversibly binds with glucocorticoid receptor	ND	Cole
Fluoxymesterone	1970	Binds to androgen receptor	ND	Cole
Hydroxy progestrone	1970	Interacts with progesterone receptor	ND	Cole
Megestrol acetate	1971	Potent agonist of the progesterone receptor	ND	FDA
Calusterone	1973	activation of androgen and certain estrogen Receptors	ND	FDA
Tamoxifen	1973	competitively binds to estrogen receptors on Tumor cells	S/NM	FDA
Methyl testosterone	1974	activation of androgen and certain estrogen Receptors	ND	FDA
Neocarzinostatin	1976	DNA damage by binding in the minor grove	N	Japan antibiotics
Streptozocin	1977	DNA damage by alkylation	N	Carter
Fosfestrol	1977	Oestrogen agonist	ND	Carter
Prednisalone	1977	Irreversibly bind with glucocorticoid receptors	ND	Carter
Norethindrone acetate	1977	Binds to the progesterone receptor	ND	Carter
Nafoxidine	1977	Antiestrogen	S/NM	Carter
Mitobronitol	1979	Alkylation via induced or derived epoxide groups	ND	FDA
Estramustine	1980	Alkylation of DNA and other cellular components	ND	FDA
Etoposide	1980	Forms ternary complex with DNA and the topoisomerase II enzyme	ND	FDA
Aclarubicin	1981	Inhibits RNA synthesis through intercalation	N	I 090013
Peplomycin	1981	Forms complexes with iron that causes single and double stranded breaks in DNA	N	I 090889
Carmofur	1981	Acid ceramidase inhibitor	S*	I 091100
Elliptinium acetate	1983	Binds covalently to a nucleophillic biological molecule	ND	P091123
Enocitabine	1983	Inhibits TS	S*	ARMC 19 (318)
Epirubicin HCl	1984	Forms complexes with DNA by intercalation between base pairs and inhibits topoisomerase II activity	ND	ARMC 20 (318)
Leuprolide	1984	Acts as agonist at pituitary GnRH receptors	ND	ARMC 20 (319)
Mitoxantrone hci	1984	Topoisomerase II inhibitor	S*	ARMC 20 (321)
Camostat mesylate	1985	Protease inhibitor	S/NM	ARMC 21 (325)
Triptorelin	1986	Forms stable complexes with DNA and interferes with nucleic acid synthesis	ND	I 090485
Goserelin acetate	1987	Inhibitor of pituitary gonadotropin secretion	ND	ARMC 23 (336)
Doxifluridine	1987	Inhibition of kinase activity	S*	ARMC 23 (332)
Pirarubicin	1988	Inhibition of mitosis through interaction with tubulin	ND	ARMC 40 (469)
Vinorelbine	1989	Inhibits topoisomerase II activity	ND	ARMC 25 (320)
Toremifene	1989	Binds to estrogen receptors	S/NM	ARMC 25 (319)
Idarubicin hcl	1990	Potent 5-lipoxygenase inhibitor	ND	ARMC 26 (303)
Fludarabine phosphate	1991	Inhibits kinase activity	S*	ARMC 27 (327)
Masoprocol	1992	Inhibits the enzyme adenosine deaminase	N	ARMC 28 (333)
Pentostatin	1992	Stabilization of microtubules	N	ARMC 28 (334)
Paclitaxel	1993	DNA strand breakage and inhibition of DNA synthesis	N	ARMC 29 (342)
Cladribine	1993	Inhibition of DNA synthesis	ND	ARMC 29(335)
Cytarabine ocfosfate	1993	Steroidal aromatase inhibitor	ND	ARMC 29 (335)
Formestone	1993	Akt inhibitor	ND	ARMC 29 (337)
Miltefosine	1993	AT1-receptor antagonists	ND	ARMC 29 (340)
Angiotensin ii	1994	Inhibits the action of topoisomerase I	N	ARMC 30 (296)
Irinotecan hcl	1994	DNA damage by binding in the minor grove	ND	ARMC 30 (301)
Zinostatin stimalamer	1994	Suppression of microtubule dynamic assembly	ND	ARMC 30 (313)
Docetaxel	1995	Topoisomerase II inhibitor	ND	ARMC 31 (341)
Anastrozole	1995	Inhibits aromatase activity	S/NM	ARMC 31 (338)
Bicalutamide	1995	Competes with androgen for the binding of androgen receptors	S/NM	ARMC 31 (338)
Fadrozole HCl	1995	Aromatase inhibitor	S/NM	ARMC 31 (342)
Gemcitabine HCl	1995	Inhibits TS	S*	ARMC 31 (344)
Etoposide phosphate	1996	Topoisomerase II inhibitor	ND	DNP 10 (13)
Raltiterxed	1996	Inhibits TS	S*/NM	ARMC 32(315)
Letrazole	1996	Non-steroidal competitive inhibitor of the aromatase	S/NM	ARMC 32 (311)
Topetecan hcl	1996	Topoisomerase I inhibitor	ND	ARMC 32 (320)
Capecitabine	1998	Thymidylate synthase inhibition and incorporation into RNA and DNA	S*	ARMC 34 (319)
Arglabin	1999	Inhibitor of farnesyl phosphate	N	ARMC 35 (335)
Alitretinion	1999	Binds to all isoforms of intracellular retinoid X (RXR) & reteniods (RAR) receptors	ND	ARMC 35 (333)

Table 2 Continued

Exemestane	1999	Aromatase inhibitor	ND	DNP 13(46)
Valrubicin	1999	Blocking of SV40 large T antigen helicase	ND	ARMC 35(350)
Temozolomide	1999	Alkylate/methylate DNA	S*/NM	ARMC 35 (350)
Gemtuzumab Ozogamicin	2000	Binds to antigen expressing DNA on AML blast cells	ND	DNP 14(23)
Bexarotene	2000	Binds with and activates retinoid X receptor subtypes	S*/NM	DNP 14 (23)
Imatinib mesilate	2001	Tyrosine kinase inhibitor	S/NM	DNP 15 (38)
Amrubicin hcl	2002	Topoisomerase II inhibitor	ND	ARMC 38 (349)
Fulvestrant	2002	Estrogen antagonist	ND	ARMC 38 (357)
Gefitinib	2002	Inhibits the (EGFR) tyrosine kinase by binding to the ATP binding site of the enzyme	S/NM	ARMC 38 (358)
Bortezomib	2003	Boronate proteasome inhibitor	S/NM	ARMC 39 (345)
Belatecan hcl	2004	Topoisomerase I inhibitor	ND	ARMC 40 (449)
Tataporfin sodium	2004	Photosensitizer	ND	ARMC 40 (469)
Erlotinib hydrochloride	2004	Tyrosine kinase inhibitor	S/NM	ARMC 40 (454)
Pemetrexed disodium	2004	Inhibits (TS), (DHFR) and (GARFT),	S*/NM	ARMC 40 (463)
Abarelix	2004	Inhibitor of gonadotropin secretion.	S*/NM	ARMC 40 (446)
Azacytidine	2004	Inhibition of DNMT	S*	ARMC 40 (447)
Abraxane	2005	Mitotic inhibitor	N	DNP 19 (45)
Tamibarotene	2005	Specific agonist for retinoic acid receptor ?/? with possible binding to RXR	S*/NM	DNP 19 (45)
Clofarabine	2005	Inhibition of DNA synthesis, inhibition of ribonucleotide reductase and direct induction of apoptosis	S*	DNP 20 (27)
Sunitinib malate	2006	Oral multi-kinase inhibitor	S/NM	DNP 19 (44)
Vorinostat	2006	HDACI	S*/NM	DNP 20 (27)
Dasatinib	2006	HDACI	S/NM	DNP 20 (27)
Decitabine	2006	Inhibits DNA or RNA methyltransferases	S*	ARMC 43 (475)
Nelarabine	2006	Ara-GTP competes with endogenous deoxyGTP (dGTP) for incorporation into DNA	S*	DNP 20 (27)
Lapatinib ditosylate	2007	Tyrosine kinase inhibitor	S/NM	ARMC 42 (528)
Nilotinib HCl	2007	Tyrosine kinase inhibitor	S/NM	ARMC 43 (480)
Nanoxel	2007	Mitotic inhibitor	N	I 422122
Temsirolimus	2007	Serine/threonine kinase inhibitor	ND	ARMC 43 (490)
Ixabepilone	2007	Microtubule inhibitor	ND	ARMC 43 (473)
Trabectedin	2007	Alkylation of DNA	N	ARMC 43 (492)
Pralatraxate	2009	DHFR inhibitor	ND	DNP 23 (18)
Degarelix	2009	GnRH antagonists	S*/NM	DNP 22 (16)
Pazopanib	2009	Tyrosine kinase inhibitor	S/NM	DNP 23 (18)
Cabazitaxel	2010	Microtubule inhibitor	ND	I 287186
Eribulin mesylate	2010	Microtubule inhibitor	ND	I 287199
Mifamurtide	2010	Activator of monocytes &macrophages	ND	DNP 23 (18)
Romidepsin	2010	HDACI	N	DNP 23 (18)
Vinflunine	2010	Tubulin inhibitor	ND	I 219585

ARMC (Annual Reports in Medicinal Chemistry); DNP (Drug News and Perspectives); FDA (Food and Drug Administration); I (Identification number in the Prous Integrity Database); values in parenthesis denotes page numbers. The letters represent the various classes of drugs, N = unmodified natural product; ND = modified natural product; S/NM = synthetic compound showing competitive inhibition of the natural product substrate; S* = synthetic compound with a natural product pharmacophore; S*/NM = synthetic compound with a natural product pharmacophore showing competitive inhibition of the natural product substrate. Biologics and vaccines have been not been incorpated within natural product inspired category. **TS**: thymidylate synthase, **DHFR**: dihydrofolate reductase, **GARFT**: glycinamide ribonucleotide formyltransferase, **EGFR**: epidermal growth factor receptor, **AM**L: Acute myeloid leukaemia, **DNMT**: DNA methyltransferase, **HDACI**: Histone deacetylase inhibitor, **GTP**: Gaunosine triphosphte, **5-FU**: 5-fluoro uracil, **GnRH**: gonodotropin receptor hormone.

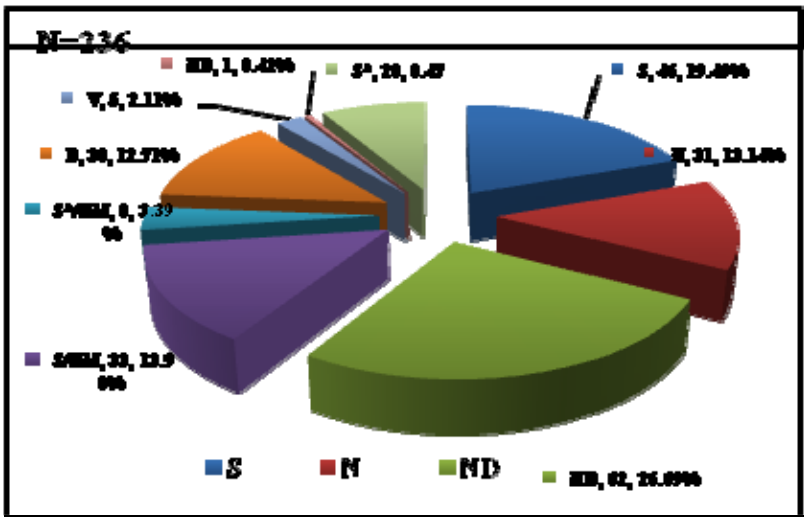


Figure 1 Anticancer drugs approved from 1950-2012 by source. N, unmodified natural product; ND, modified natural product; S, synthetic compound with no natural product conception; S/NM, synthetic compound showing competitive inhibition of the natural product substrate; S*, synthetic compound with a natural product pharmacophore; S*/NM, synthetic compound with a natural product pharmacophore showing competitive inhibition of the natural product substrate; B, Biological; and V, Vaccine.

Table 3. Sources, targets and clinical status of anticancer agents derived from terrestrial plants.

Name	Source	Mechanism of action	Clinical status	Ref
Vinca alkaloids analogues	Catharanthus roseus	Microtubule destabilising agents and binds to tubulin heterodimers		
1. Vinorelbine			Clinical use	12
2. Vinflunine			Clinical use	13
3. Vincristine liposome injection			Clinical use	14
4. Anhydrovinblastine			Phase I	15
Paclitaxel analogues	Taxus brevifolia	Antimitotic agent blocking cells in the metaphase		
1. Docetaxel			Clinical use	16
2. Cabazitaxel			Clinical use	17
3. Abraxane			Clinical use	18
4. Taxoprexin (7-DHA-Taxol)			Phase II/III	19-20
5. Larotaxel (XPR9881)			Phase I	21
6. Ortataxel (BAY-59-862)			Phase II	22-23
7. Milataxel (MAC-321)			Phase II	24
8. TPI-287			Phase II	25-26
9. BMS-275183			Phase I	27
10. Tesetaxel (DJ-927)			Phase I/II	28-29
Camptothecin analogues	Camptotheca acuminate	Topoisomerase I inhibitor		
1. Diflotecan			Phase II	30-31
2. Gimatecan			Phase I/II	32-33
3. Karnetecan			Phase II	34-35
4. 9-Amino CPT			Phase I/II	36
5. Elomotecan			Phase I	37
6. Exetecan mesylate			Phase II	38-39
7. Rubetecan			Phase I/II	40
Podophylotoxin analogues	Podophyllum peltatum	Binding topoisomerase II		
1. NK-611			Phase I	41
2. Tafluposide 105			Phase I	42
3. Etoposide phosphate			Clinical use	43
Combrestatin analogues	Combrestatum caffrum	Inhibitor of colchicine binding site		
1. CA-1P (combrestatin A-4 phosphate)			Phase I	44
2. CA-1P			Phase I	45
Other plant derived anticancer agents				
Betulinic acid	Betula alba	Trigers mitochondrial pathway of apoptosis	Phase I/II	46-47
Berbamine	Berberis amarensis	caspase-3-dependent apoptosis	Lead molecule	48
Beta Lapachone(ARQ-501)	Tabebuia avellanedae	Topoisomerase I&II	Phase II	49-50
Curcumin	Curcumin longa	Inhibits many cell signalling pathways	Lead molecule	51-53
Colchicine	Colchium automole	Anti-mitotic	Lead molecule	54
Diadzein &Genistein	Lupinus species	Inhibits 3A 4-mediated metabolism	Phase II	55-57
DMXAA	Flavone-8-acetic acid analog	TNF-? induction	Phase I/II	58-59
Flavopiridol	Dysoxylum binectariferm	Interferes with CDK and Blocking cell cycle progression	Phase I/II	60-61
Kanglaite	Coix lachryma-jobi	Inhibits mitosis of tumor cells during G2/M phase	Phase II	62
Meisoindigo	Indigofera tinctoria	Induces apoptosis by locking Stat 3 signaling	CD terminated	63-64
Phenoxodiol	plant isoflavone Genistein	Inhibits plasma membrane electron transport &Cell proliferation	Phase I	65-66
Roscovitine (CYC 202)	Raphanus sativus	CDK inhibitor	Phase II	67-68
Silvestrol	Aglaia foveolata	Trigers mitochondrial pathway of apoptosis	Lead molecule	69-70
Santonin	Artemisia sp	NF-kB inhibitor	Lead molecule	71

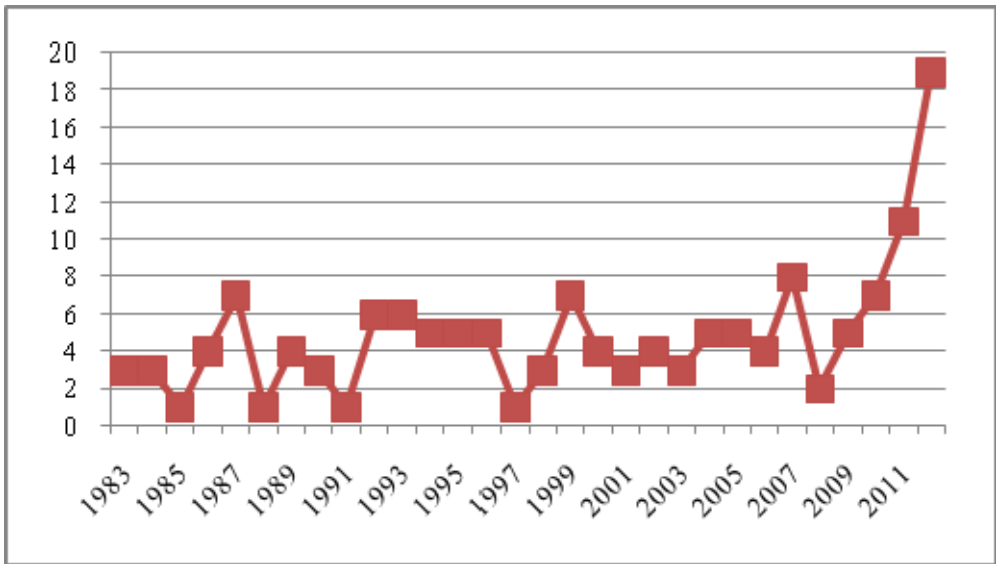
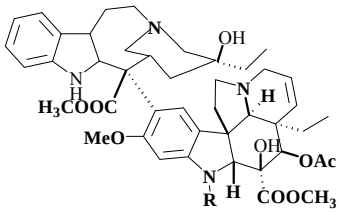
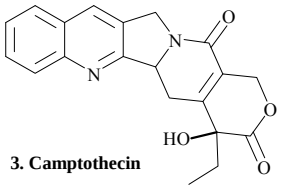


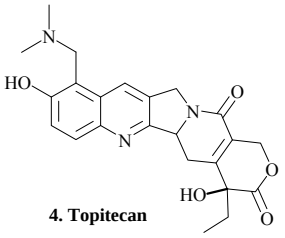
Figure 2 Total number of anticancer drugs by year 1983-2012 with a sharp increase from 2010-2012.



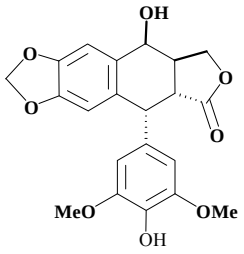
1. Vinblastine R = CH_3
2. Vincristine R = CHO



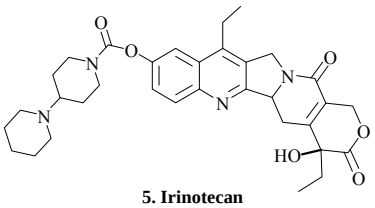
3. Camptothecin



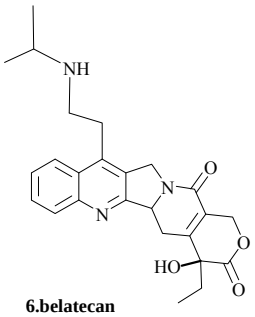
4. Topitecan



7. Podophylotoxin



5. Irinotecan



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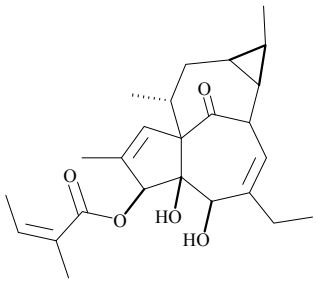
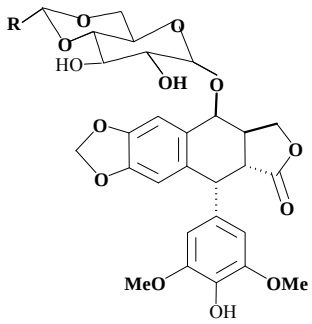
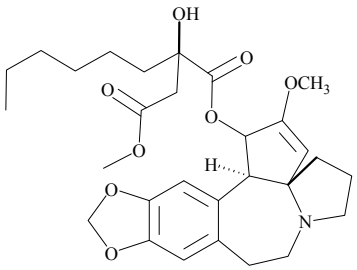


10. Ingenol-3-O-angelate

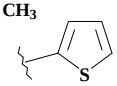


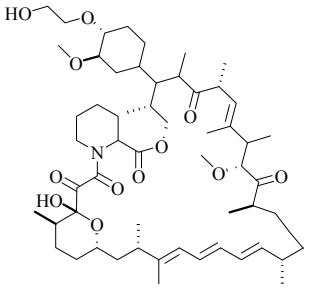
8. Etoposide R = CH_3



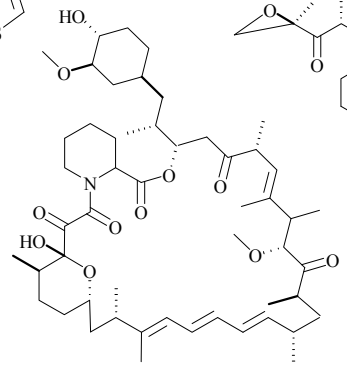
11. Homoharringtonine

9.Teniposide R =

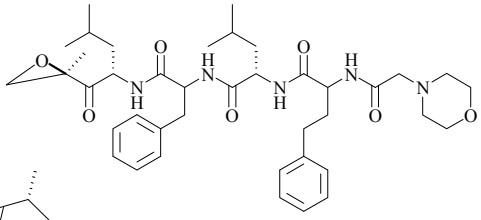




12. Everolimus



13. Sirolimus



14. Carfilzomib

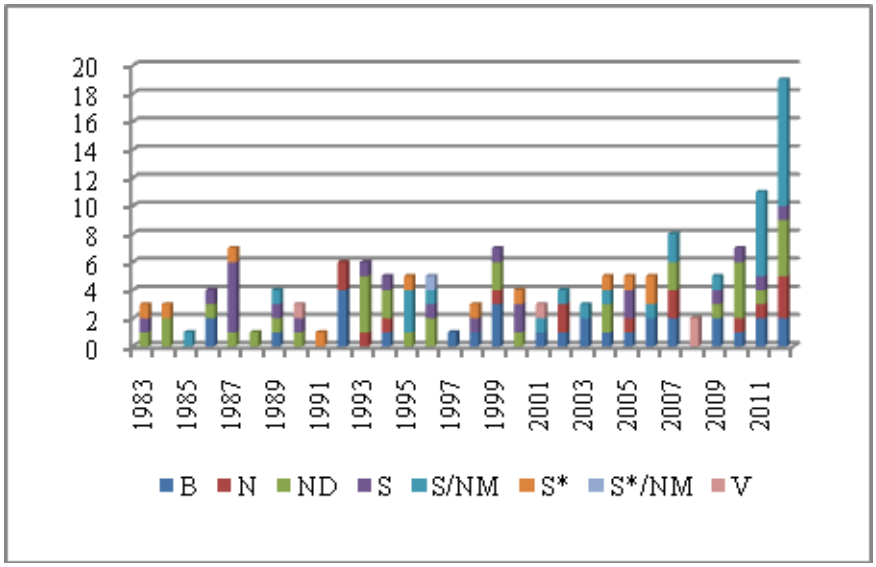
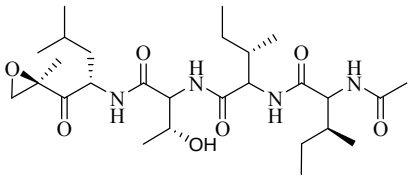


Figure 3 Total number of anticancer drugs by source/year, 1983-2012. N, unmodified natural product; ND, modified natural product; S, synthetic compound with no natural product conception; S/NM, synthetic compound showing competitive inhibition of the natural product substrate; S*, synthetic compound with a natural product pharmacophore; S*/NM, synthetic compound with a natural product pharmacophore showing competitive inhibition of the natural product substrate; B, Biological; and V, Vaccine.

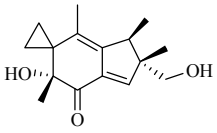
Table **4.** Micro-organism derived anticancer agents, their sources, chemical nature and clinical status.

Name	Source	Class	Clinical status	Ref
Daunomycin	Streptomyces sp.	Anthracycline	Clinical use	80
Doxorubicin	Streptomyces sp.	Anthracycline	Clinical use	81
Epirubicin	Streptomyces sp.	Anthracycline	Clinical use	82
Idarubcin	Streptomyces sp.	Anthracycline	Clinical use	83
L.annamycin	Analog of daoxorubicin	Anthracycline	Phase I/II	84-85
Berubicin hydrochoride	Anolog of berubicin	Anthracycline	Phase II	86
Sabarubicin (MEN-10755)	Analog of daoxorubicin	Anthracycline	Phase II	87-90
Nemorubicin	Analog of daoxorubicin	Anthracycline	Phase II	91-92
Valrubicin	Analog of daoxorubicin	Anthracycline	Clinical use	93
Bleomycin	Streptomyes verticillius	Glycopeptide	Clinical use	94
dactinomycin	Streptomyces sp.	Peptolides	Clinical use	95
Mitomycin	Streptomyces sp.	Mitosnes	Clinical use	96
Distamycin A	Sterptomyces distallcus	Oligopeptide	Lead molecule	97-99
Tanespimycin (17-AAG)	Anolog of geldamycin	CP	Phase II	100-101
Alvespimycin (17-DMAG)	Anolog of geldamycin	CP	Phase I	102
Retaspimycin (IPI-504)	Anolog of geldamycin	CP	Phase Ib/2	103-104
Elsamicin A	Actinomycete strain	Aminoglycoside	Lead molecule	105-106
Chartreusin (U-7257)	Streptomyces chartreusis	Aminoglycoside	Lead molecule	107
Staurosporine(AM-2282)	Streptomyces staurosporeus	Alkaloid	Lead molecule	108-110
7-Oxostaurosporine	Eudistoma vannamei	Alkaloid	Lead molecule	111
UCN-01	Anolog of staurosporine	Alkaloid	Phase I	112
Enzastaurin	Anolog of staurosporine	Alkaloid	Phase III failure	113
Midostaurin	Anolog of staurosporine	Alkaloid	Phase I/II	114-118
Epithilone B	Sorangium cellulosum	PM	Phase II	119
Patupilone(EPO-906)	Anolog of epithilone B	PM	Phase III failure	120
Sagapilone(ZK-EPO)	Anolog of epithilone B	PM	Phase I/II	121-123
Ixaepithilone(BMS-247550)	Anolog of epithilone B	PM	Clinical use	124
Epithilone D	-	PM	Lead molecule	125-126
Pladienolide D	Streptomyces palatensis	Polyketide	Lead molecule	127
E7107	Anolog of pladienolide	Polyketide	Phase I	128-130
Deforolimus	Streptomyces sp.	Rapamycins	phase I/II	131-132
Diazepinomicin	Micromonospora	Alkaloid	Phase II	133
TLN-4601	Anolog of diazepinomicin	Alkaloid	Phase II	134-136
Prodigiosin	Serratia marcescens	Prodiginines	Preclinical trials	137

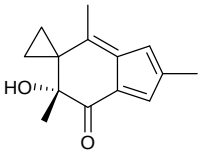
CP: Chaperone protein, **PM**: Polyketide macrolactone



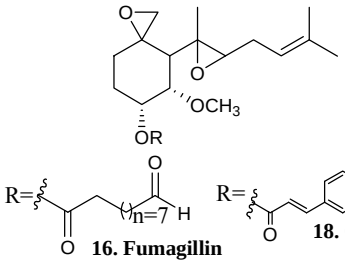
15. epoxomicin



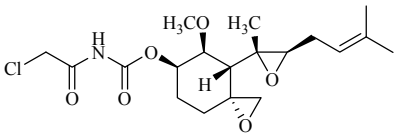
19. Illudin S



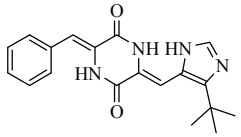
20. Irofulven



16. Fumagillin

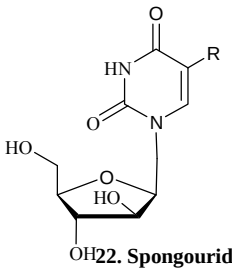


17. TNP-470

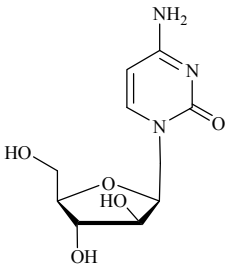


21. Plinabulin

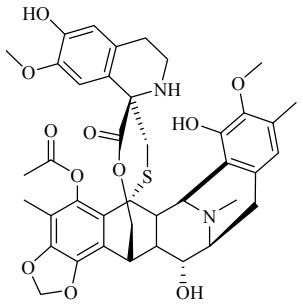
18. CDK-732



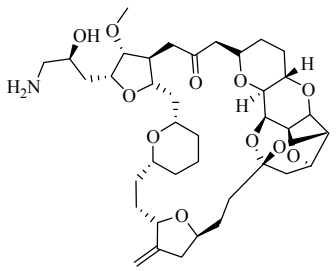
22. Spongouridine R= H
23. Spongothymidine R= CH_3



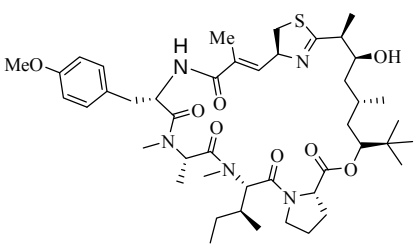
24. cytarabine



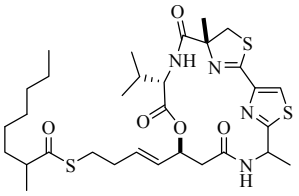
25. ecteinascidin 743



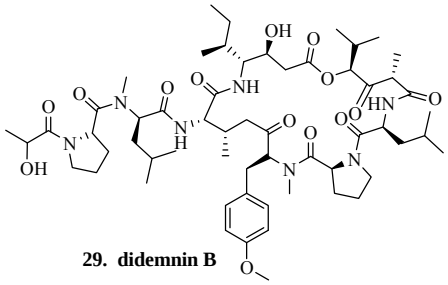
26. eribulin mesylate



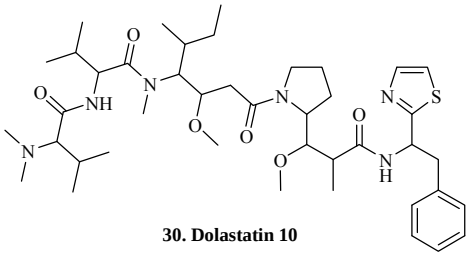
28. Apratoxin A



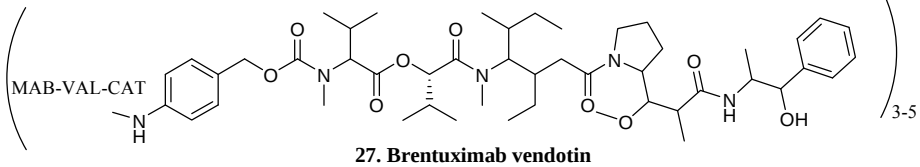
29. Largazole



29. didemnin B



30. Dolastatin 10



27. Brentuximab vendotin

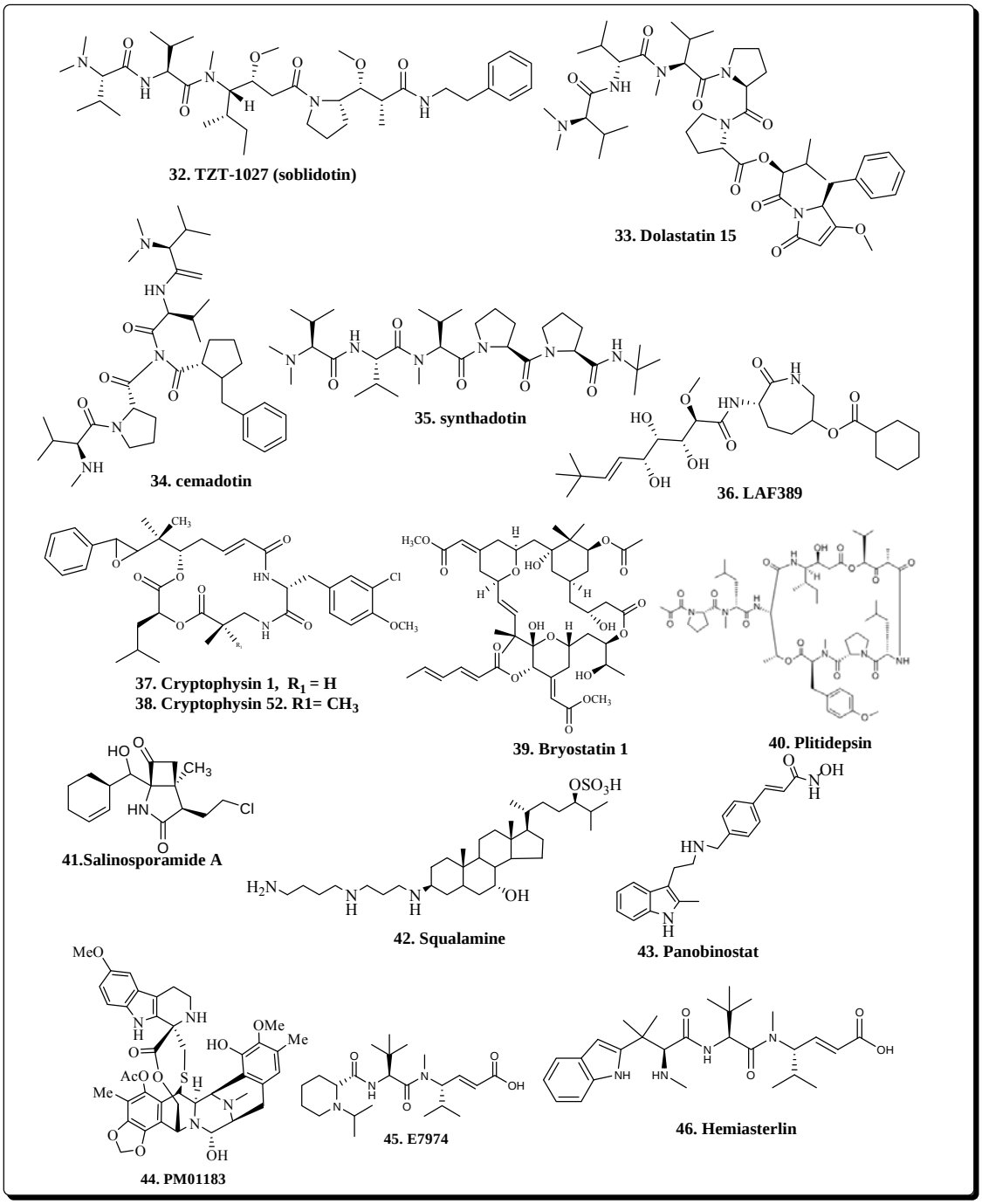


Table **5.** Sources, chemical nature and mechanism of action of marine derived anticancer agents.

Name	Source	Chemical nature	Mechanism of action
Aaptamine	Aaptus suberitoids (sponge)	Alkaloid	Proteosome inhibitor
Alkyl pyridium salt	Haliclona (sponge)	Alkaloid	Inhibit MAC receptors and HDAC enzymes
Asciddemin	Didemnum sp (tunicate)	Alkaloid	Topoisomerase II inhibitor
Trabectedin(ET-745)	Ecteinascidia turbinata (tunicate)	Alkaloid	Cell cycle arrest
Zalypsis	Nudibranch	Alkaloid	Cell cycle arrest
Cortistatin A	Corticium simplex (sponge)	steroidal Alkaloid	CDK inhibitor
Variolus	Krikpatrickia variolosa (archinida)	heterocyclic alkaloid	Topoisomerase inhibitor
Lamellarin D	Lamellaria sp. (sponge)	pyrrole alkaloid	MDR modulator
Agosterol-A	Spongia sp. (sponge)	Steroid	Caspase 9
Cephalostatin 1	Cephalodiscus gilcristi (tunicate)	Steroid	Calcium binding protein
Squalamine	Squalus acanthia (shark)	Amino steroid	Depletes glutathione (GSH)
Aplidine	Alpidium albicans (tunicate)	Depsipeptide	HDACI
Coibamide A	Leptolyngbya sp (cyanobacteria)	Cyclic depsipeptide	Inhibition of protein synthesis
Dehydrodidemnin B	Tridemnum solidum (ascidian)	Cyclic depsipeptide	Inhibiting synthesis of DNA, RNA
Didemnin B	Tridemnum solidum (ascidian)	Cyclic depsipeptide	Tubulin inhibitor
Desmethoxy-majusculamide C	Lyngbya majuscule (cyanobacteria)	Cyclic depsipeptide	DNA polymerase
Thiocoraline	Micromonospora marina (actinomycete)	Depsipeptide	Lysosomatropic
Kahalalide F	Eylsia refescens (sea slug/alga)	Depsipeptide	MDA
Cemadotin	dolastatin derivative (sea hare)	Linear peptide	MDA
Dolastatin 10	Dolabella auricularia (mollusk)	Linear peptide	MDA
Dolastatin 15	Dolabella auricularia (bacteria)	Linear peptide	MDA
Sablidatin	Dolabella auricularia (bacteria)	Linear peptide	Tubulin inhibitor
Diazonamide	Diazona angulata (sea squirt)	Cyclic peptide	Methionine aminopeptidase
LAF-389	Jaspis digonoxea (sponge)	Lactam peptide	Tubulin inhibitor
Vitilevuamide	Didemnim cucliferum (ascidian)	Cyclic peptide	MDA
Hemiasterlin	Hemiasterella minor (sponge)	Tri-peptide	DNA polymerase inhibitor
Depsipeptide	Chromobacterium violaceum (actinomycete)	Bicyclic peptide	HDACI
Bistramide	Lissoclinum bistratum (tunicate)	Polyketide	Protein kinase inhibitor
Salicylihalimide A& B	Halidona sp. (sponge)	Polyketide	Vo-ATPase
Bryostatin-1	Bugula neritina (bryozan)	MCL	Protein kinase inhibitor
Dictyostatin-1	spongia sp. (sponge)	MCL	Tubulin inhibitor
Peloruside A	Mycole hentscheli (sponge)	MCL	Tubulin inhibitor
Laulimalide	Cacospongia mycofijiensis (sponge)	Macrolide	Tubulin inhibitor
Halichondrin B	Halichondria akadia (sponge)	MCP	Mitotic inhibitor
Aplyronine A	Aplysia kudai (sea hare)	Macrolide	Actin inhibitor
eribulin mesylate	sponge	Macrolide	MDA
Scytonemin	Lyngbya aestuarii (cyanobacteria)	Cyclic peptide	Serine/threonine kinase inhibitor
Sarcodictyins	Sarcodictyon reseum (soft coral)	diterpene glycoside	Tubulin inhibitor
Eleutherobin	Erythropodiumcaribaeorum (soft corals)	diterpene glycoside	Tubulin inhibitor
NVP-LAQ824	Psammaplysilla sp. (sponge)	Indolic cinnamyl hydroxymate	HDAC/DNMT
Largazole	Symploca Sp. (cyanobacteria)	Polypeptide	HDAC inhibitor
KRN-7000	Agelas mauritianus (sponge)	Glycosyl ceramide	Immunostimulatory
Discodermolide	Discodermin dissolute (sponge)	Polyketide	MDA
ES-285(Spisulosine)	Maxtromeris polynyma (mollusk)	Alkyl amino alcohol	Cell cycle arrest
Dictyodendrin	Dictyodendrilla verongiformis (sponge)	Pyrralo carbazole	Telomerase II
Plitidepsin	Aplidium albicans (tunicate)	Depsipeptide	Apoptosis inducer

MAC: Muscarinic Acetycholine Receptors, **HDAC**: Histone deacetylase, **MDA**: Microtubule disrupting agents, **DNMT**: DNA methyl transferase, **MCL**: Macrocyclic lactone, **MCP**: Macrocyclic polyether.