

Anticancer Agents: VTA or VDA

Paul R. Sebahar, J. Adam Willardsen and Mark B. Anderson*

Department of Chemistry, Myriad Pharmaceuticals, Inc. 320 Wakara Way Salt Lake City, Utah 84108, USA

Abstract: The tumor vasculature is quite an attractive target for anti-cancer/anti-tumor therapy because the blood vessels provide the route for nutrient/waste and oxygen/carbon dioxide exchanges as well as a convenient route for tumor metastatic spread. The complex interplay of the tumor with the local blood vasculature is intriguing. Targeting the vasculature in an effort to control the tumor life cycle is therefore very complex yet enticing as a treatment option. In reviewing the literature discussing vascular targeting/disrupting agents, it is sometimes less than clear as to what exactly defines or differentiates a vascular targeting agent (VTA; antiangiogenic or stopping tumors from producing new blood vessels) from a vascular disrupting agent (VDA; disrupting the "established" tumor vasculature). Although, there appears to be differences between these two strategies of modifying the tumor vasculature including differences in the administration schedules. The use of the VTA/VDA terms in scientific reports is not always clear since some agents may also exhibit activities attributed to a VTA and/or a VDA. However these agents are defined, the important goal is to severely cripple and/or "shut-down" the tumor's ability to maintain viability and to subsequently become metastatic and hence are important in the armamentarium of anti-tumor/anti-cancer treatment strategies. This brief review of selected literature reports attempts to summarize some of the chemical structural elements associated with these types of agents and asks the question "Are there common chemical structural features emerging that may assist in a differentiating theme?"

Keywords: Vascular disrupting, vascular targeting, tubulin, oncology, angiogenesis, inhibitor.

INTRODUCTION

The tumor vasculature is quite an attractive target for anti-cancer/anti-tumor therapy because the blood vessels provide the route for tumor development through nutrient/waste and oxygen/carbon dioxide exchanges as well as a convenient route for tumor metastatic spread. The interplay of the tumor with the local blood vasculature is complex [1] and presents challenges as a means of controlling the tumor life cycle but offers promise as an approach for the development of new anticancer therapeutics. Two promising strategies involve the administration of a vascular targeting agent (VTA; antiangiogenic or stopping tumors from producing new blood vessels) or a vascular disrupting agent (VDA; disrupting the "established" tumor vasculature). During tumor progression, neovascularization and sustainment of a functioning network of blood vessels can be occurring simultaneously, yet VTA's and VDA's represent separate targets and therefore have evolved into two individual classes of chemotherapeutics. As the fields have gained considerable attention and more agents have been disclosed, the distinction between the two classes has become less apparent as agents have exhibited properties attributed to both a VTA and/or a VDA. However, examination of the chemical structural elements associated with these types of agents can expose obscure relationships. It is through chemical structural categorization, comparison and analysis of these agents that enables one skilled in the art the opportunity for new insight and to derive novel and/or systematic drug design possibilities.

Categorizations and depictions of a chemical series are at the heart of drug discovery as they form the basis for the initial structure activity relationships (SAR). However, there are many ways to envision a chemical structural series. One concept is the idea of "privileged structures", where certain substructures are generally noted as molecular substructures capable of binding to multiple receptors with high affinity. The substructures can also represent a molecule's core element, which makes up a significant portion of its total mass. For example, the indole substructure is a basic element for a variety of biologically active natural and synthetic products. Likewise, quinazolines have been referred to as privileged structures in constructing a library of agents for the destabilization of tubulin polymerization [2]. Another way to envision a chemical series or 3-dimension array of critical structural features is *via* a pharmacophore model. This depiction focuses on a set of essential elements or core chemical structural features involved in the agents binding to a receptor or a protein. Hence, the pharmacophore is derived from a molecular framework containing the essential chemical structural features needed for the observed biological activity [3] and includes those features recognized by a receptor site [4]. This explanation of a pharmacophore is also illustrated by the IUPAC definition.¹ There are also well-known chemical structure analyses by fingerprint profiling and chemical similarity [5]. Finally, during discussions of the common chemical core structures and 3-D chemical structural elements necessary for exhibiting VDA and VTA effects, Lipkus *et al.* [6] published a timely review of the structural diversity in the CAS registry. The authors indicate that a "scaffold" of a particular molecule is a framework or a linked ring system and revealed that only

*Address for correspondence to this author at the Department of Chemistry, Myriad Pharmaceuticals, Inc. 320 Wakara Way Salt Lake City, Utah 84108, USA; Tel: (801) 584-1166; Fax: (801) 883-3213; E-mail: manderso@myriad.com

¹ <http://www.chem.qmul.ac.uk/iupac/medchem/>

143 framework shapes are contained within the CAS registry. Categorizations and analyses such as these can serve as valuable guides in the development of new scaffolds and eventually lead to the discovery of novel drugs.

We categorized agents first by their reported VDA or VTA effects, followed by organizing the chemical structures according to what appeared to be their essential core scaffold. Compounds were selected based on either having demonstrated clinic relevance or having potency suitable for projected development. For the VTA's, this includes numerous marketed drugs including Taxol[®], Taxotere[®], Ixempra[®], Tarceva[®], Iressa[®], Tykerb[®], Sprycel[®], Gleeevec[®], Tasigna[®], Sutent[®], Nexavar[®], Revlimid[®] and Thalomid[®]. For the less established VDA's, only the vinca alkaloids are approved as anticancer chemotherapeutics, although several other compounds are in the late stages of clinical development including CA4P, AVE8062 and the vadimezan. The result is this brief review of agents reported as VDA's and/or VTA's and some interesting agents that were "close" structural analogs as appropriate. The tables and chemical structure figures gives one a perspective on what has already been reported as VDA's and/or VTA's in addition to an opportunity to derive new insights for novel and/or systematic drug design possibilities. When possible, we indicate the trade names, generic names and/or code numbers to facilitate locating and/or tracking these agents for related assay methods, structure-activity-relationships, mechanism of action studies, and pharmacology and pharmacodynamic effects as this information is released into the public domain.

VASCULAR DISRUPTING AGENTS

Vascular disrupting agents are characterized by their ability to cause a rapid and pronounced shutdown of blood flow to solid tumors by causing the endothelial cells, the cells that line the inside of blood vessels, to change shape and collapse. This results in the tumor cells undergoing extensive necrosis and secondary cell death while the normal tissues remains relatively intact, as blood flow to host tissues are uninterrupted. This phenotypic response is best represented by the classical tubulin-binding agent colchicine, and the structurally similar combretastatins, which competitively bind within the same site on β -tubulin. These small molecule VDA's have an effect on endothelial cells through their ability to depolymerize microtubules. This is possible due to the fact that the blood vasculature surrounding a tumor is abnormal in gross structure and vascular integrity [7]. Selectivity over normal tissue can arise from the difference between the rapidly proliferating nature of the cancer cells and their dependence on tubulin for maintaining the cellular integrity [8]. Unfortunately, both colchicines and combretastatins are marked by their side effects and dose-limiting toxicity [9]. While this therapeutic selectivity is an obvious concern for both current and future development studies, off target activity may not always be detrimental. As one may suspect, some agents may be proapoptotic molecules and mitotic inhibitors at low nanomolar concentrations while exhibiting vascular disruption effects at a different drug concentration. Flavone acetic acid (FAA) and 5,6-dimethylxanthenone-4-acetic acid (DMXAA), derived from FAA structure-activity-relationship studies [10], can be considered to exhibit pleiotropic effects

due to their antivasular actions and the induction of cytokines. Therefore, understanding the selectivity and mechanism of action of VDA's and VTA's is critical for the development of new treatment strategies and viable drugs for the treatment of cancer.

Most of the small molecule VDA's found in the literature [11] are members of the tubulin inhibitor class of compounds. [12] Examples of agents reported as VDA's Fig. (1) that can be grouped according to their core-types Table (1) include colchicine [13] and the combretastatins [14] (CA4P [15], ZD6126 [16], AVE8062 [17] (ombrabulin), OXi-4503 [18], BNC-105²), the vinca alkaloids [19] (vincristine, [20] vinblastine, [20] vindesine, [21] vinorelbine, [22] vinflunine [23]) and the flavonoids (FAA [24] and DMXAA [25] (vadimezan)), ABT-751, [26] TZT-1027 [27] (soblidotin), MPC-6827 [28] (Azixa), CYT997³, NPI-2358, [29] MN-029 [30] (denibulin), ENMD-1198, [31] EPC2407 (detailed at ASCO meeting 2008)⁴, ADH-1[32] (Exherin), and patupilone. [33] Compounds that have not yet been disclosed as VDA's but bind tubulin in a similar fashion as colchicine [34] and may be capable of exhibiting similar vascular disrupting properties Table (2) are: 2ME2 (panzem), [35, 36] AEZS-1125, rosabulin (detailed at AACR meeting 2004)⁶, ZIO-301 [37] (indibulin), dolastatin 10, [38] tasidotin, [39], E-7070[40] BPR0L075, [41] eribulin [42] (E7389) and the hemiasterlins [43] (taltobulin [44] and E7974 (detailed at *Journal of Clinical Oncology* ASCO Annual Meeting Proceedings 2005).⁷ In addition to the compounds cited herein, the literature contains numerous reports of SAR studies focused on new VDA's with efforts directed at colchicine and combretastatin A4 analogs being the most prominent topics [45-50].

VDA's have shown good antitumor efficacy in animal models, and in combination with established anticancer agents and have shown promising results in clinic trials [51]. The vinca alkaloids represent the most established class of VDA's and have resulted in several marketed drugs including Oncovin[®], Velban[®], Eldesine[®] and Navelbine[®]. These are contrasted to the colchine/combretastatin class of VDA's, which do not contain any approved drugs for the use of cancer but have shown promise and have drawn recent interest and resources from various groups. Numerous clinical trials⁸ are currently ongoing for this class as well as the other VDA's listed. Notably, combretastatin analogs

² <http://www.bionomics.com.au/page.php?section=103>

³ <http://www.cytopia.com>

⁴ Anthony, S.P., Read, W., Rosen, P.J., Tibes, R., Park, D. Everton, D., Tseng, B., Whisnant, J., Von Hoff, D. D. (2008) Initial results of a first-in-man phase I study of EPC2407, a novel small molecule microtubule inhibitor anticancer agent with tumor vascular endothelial disrupting activity. Initial results of a first-in-man phase I study of EPC2407, a novel small molecule microtubule inhibitor anticancer agent with tumor vascular endothelial disrupting activity. *J. Clin. Oncol.* **26**, 2531.

⁵ <http://www.aeterna.com/en/page.php?p=31&prod=19>

⁶ Koya, Keizo, Sun, Lijun, Li, Hao, James, David, Tatsuta, Noriaki, Korbut, Timothy, Zhou, Dan, Liang, Guiqing, Wu, Yaming, Du, Zhenjian, Chen, Shoujun, Barsoum, James, Dahl, Thomas A., Ono, Mitsunori, Chen, Lan Bo. (2004) STA-5312, a novel tubulin inhibitor, demonstrates the anticancer activity against chemotherapy-resistant cancers. *Proc. Amer. Assoc. Cancer. Res.* **45**, 1250-a.

⁷ Agoulnik, S., Kuznetsov, G., Tendyke, K., Parent, L.A., Marsh, J.P., Twine, N., Renshaw, F.G., Silberman, S., Littlefield, B.A. (2005) Sensitivity to halichondrin analog E7389 and hemiasterlin analog E7974 correlates with β III tubulin isotype expression in human breast cancer cell lines. *J. Clin. Oncol.* **23**, 2012.

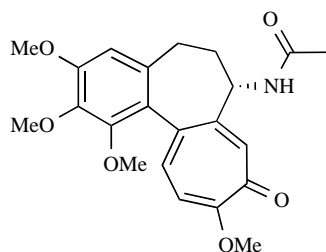
⁸ <http://clinicaltrials.gov>

Zybrestat[®] and AVE8062 (ombrabulin) and flavonoid DMXAA (vadimezan) are the most advanced in terms of their clinical development (Phase III).

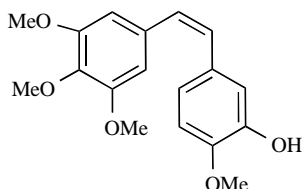
VASCULAR TARGETING AGENTS

The development of vascular targeting agents has typically concentrated on anti-angiogenic approaches such as inhibition of specific protein tyrosine kinases involved in

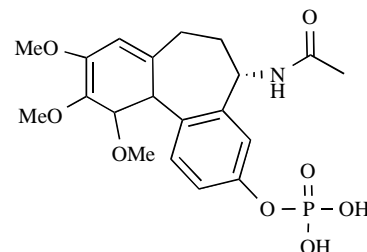
tumor neovascularization. VTA's can also result in tumor-cell necrosis and secondary tumor-cell death, however the observed effects may not be as rapid as with a VDA. Small molecule inhibitors of the VEGF receptor have drawn a lot of investigation and the result of which have yielded several marketed drugs. Other less investigated field of VTA's is focused around the understanding that copper may be critically involved in angiogenesis. This information has led to the evaluation of metal chelators as VTA's and has



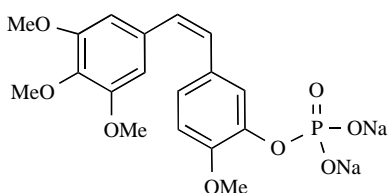
Colchicine



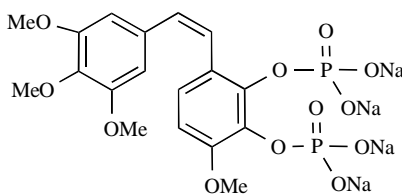
Combretastatin A4



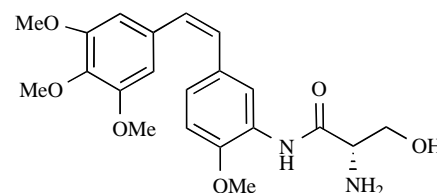
ZD6126



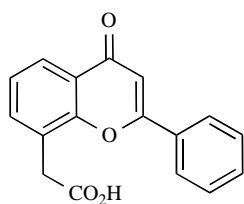
CA4P



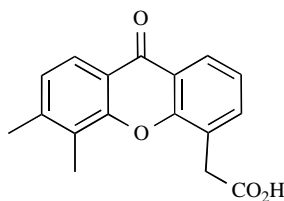
CA1P / OXi4503



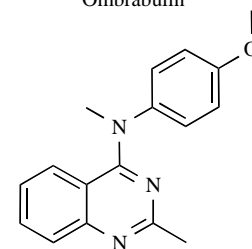
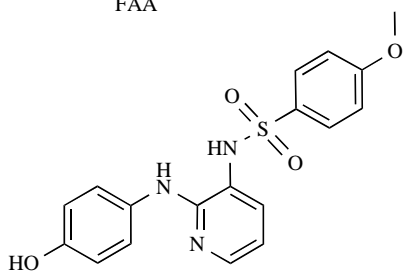
Ombrabulin



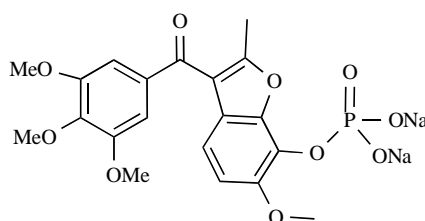
FAA



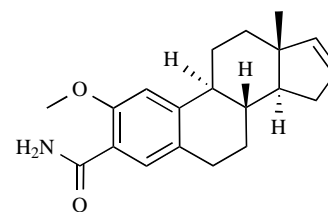
Vadimezan

MPC-6827/
Azixa

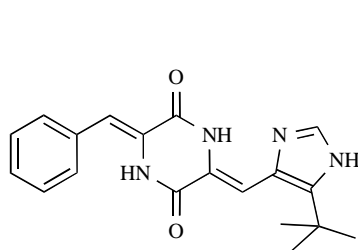
ABT751



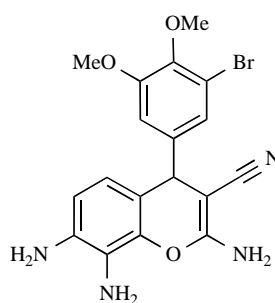
BNC-105



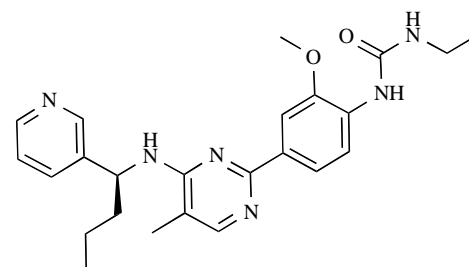
ENMD-1198



NPI-2358

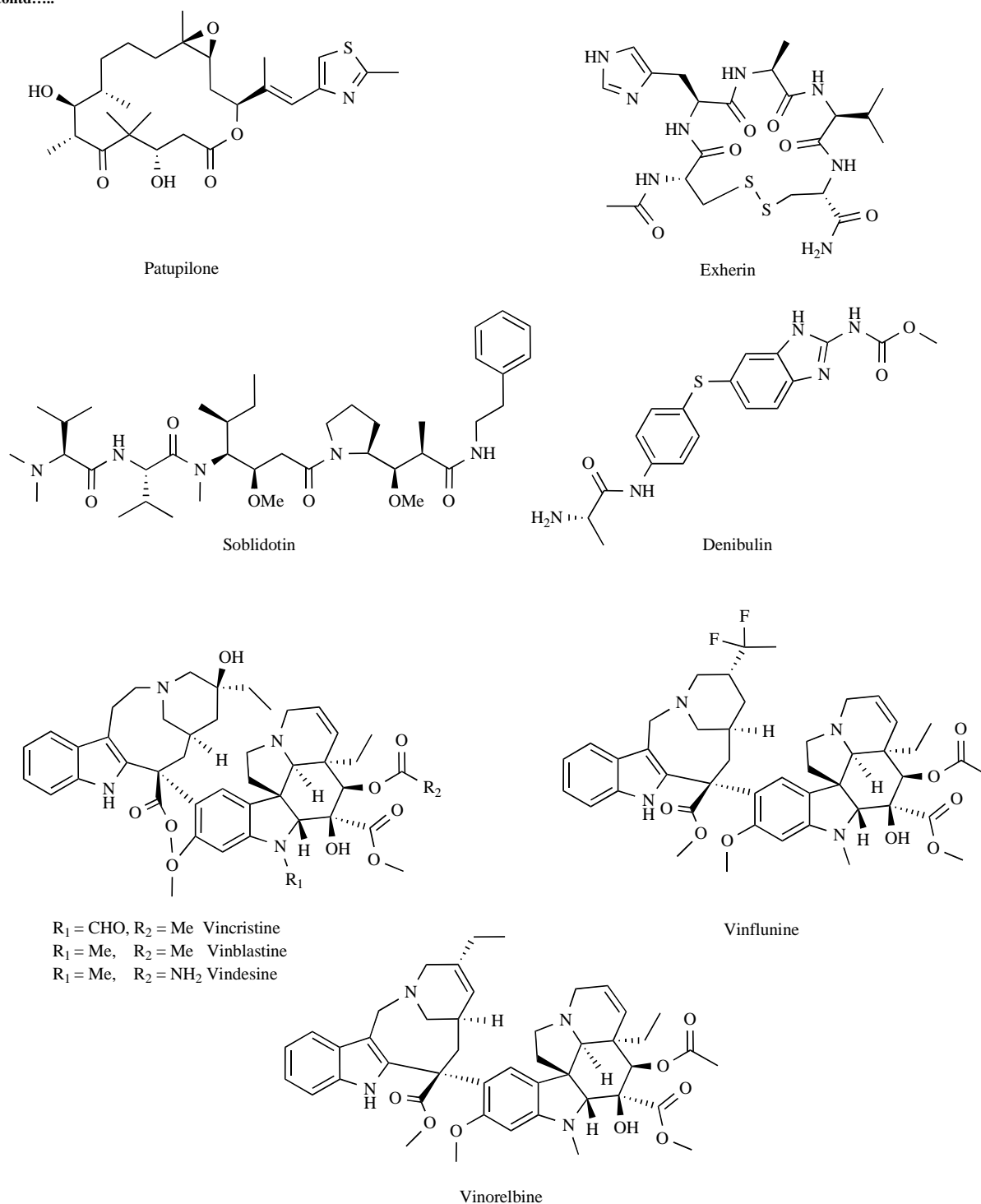


EPC-2407



CYT-997

(Fig. 1). contd.....

**Fig. (1).** Reported vascular disrupting agents.

resulted in the study of compounds such as Coprexa (tetrathiomolybdate) [52].

Arguably, the most prominent class of VTA's Fig. (3) are the taxanes, several of which are approved by the FDA [53, 54] and include: Taxol[®] [55] Taxotere[®], [56] larotaxel (XRP9881), [53] ortataxel (IDN-5109, BAY 59-8862), [57] milataxel (MAC-321, TI00139) [54], IDN-5390 [58],

tesetaxel (DJ-927) [59] and TPI 287⁹. This class also includes various formulations with improved pharmacokinetic and physicochemical properties [60]. Another prominent class of VTA's are the epothilones [61] which are represented by: sagopilone (ZK-EPO) [62], patupilone [63], ABJ879 [64], KOS-862 [65], fludelone [66], BMS-317505,

⁹ <http://www.tapestrypharma.com/news/press/>

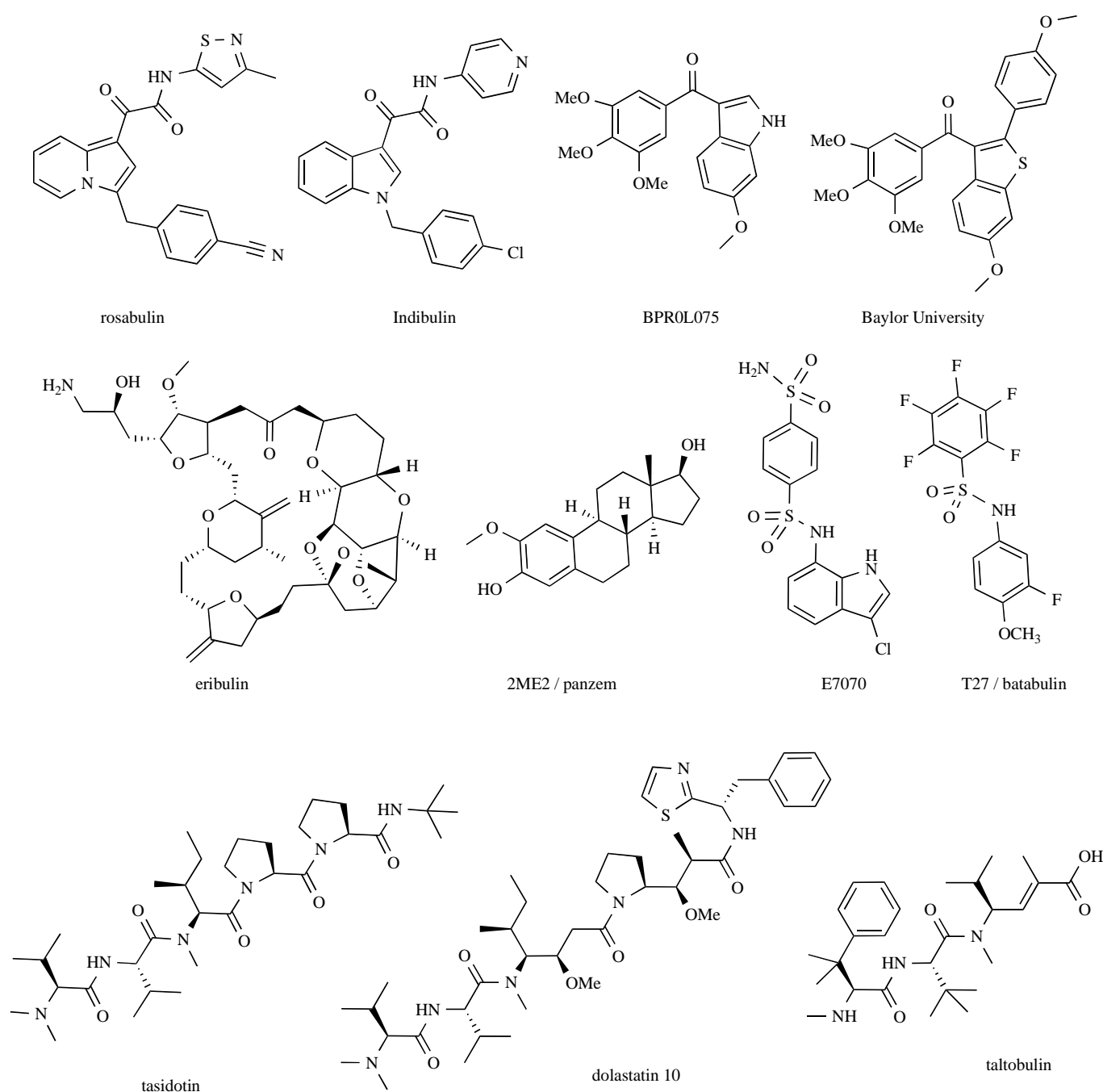


Fig. (2). Possible vascular disrupting agents.

[64] Ixempra[®], [67] and KOS1584. [61] Other core-types include the quinazolines and similar compounds (Zactima[®], canertinib, [68] Tarceva[®], Iressa[®], brivanib, Tykerb[®], tandutinib, Recentin[®], CP-724714), [69-72] the quinolines (bosutinib [73], pelitinib [74], neratinib [75] and E-7080 [76]), the pyrimidines and heterocyclic pyrimidines (Sprycel[®], Gleevec[®], Tassigna[®], pazopanib, CYC-116, [77] PKI166, AEE788 and TTI-237) [71, 78-80], the oxindoles (Tsu-68 [81], semaxanib and Sutent[®]) [82, 83] and the urea and thioureas (sorafenib [84], MGCD-265 [85], ABT-869 [86]). Still other VTA's classified into separate categories include the fumagillins (TNP-470 [87] and CKD-732 [88]), the phthalimides (Revelmid[®], apremilast, Thalidomid[®], pomalidomide) [89, 90], the peptidics (celengetide [91] and tryprostatin A [92]) and the staurosporins (enzastaurin, [93]

lestaurtinib, [94] MKC-1¹⁰ and midostaurin [95]). Others that do not fall into a simple category based on core-type include: vatalanib, [96] motesanib, [97] axitinib, [98] TTI-237, [78] fenretinide, [99] murbitrinib, [100] E-7820, [101] PF-2431066, [102] and tasquinimod. [103] Monoclonal antibodies [104] that have been reported to have antiangiogenic properties include: Alacizumab, Vitaxin[®], Lucentis[®] volociximab, Erbitux[®], Vectibix[™], matuzumab Herceptin [105] and the largely successful Avastin[®]. [106] The aptamer Macugen[®] has also been shown to be a VTA. [107] Matrix metalloproteinases (Marimastat, [108] prinomastat [109] and neovastat [110]) are also reported as vascular targeting agents. Lastly, there are several copper

¹⁰ <http://www.entremed.com/science/mkc-1/>

Table 1. Reported and Possible Vascular Disrupting Agents

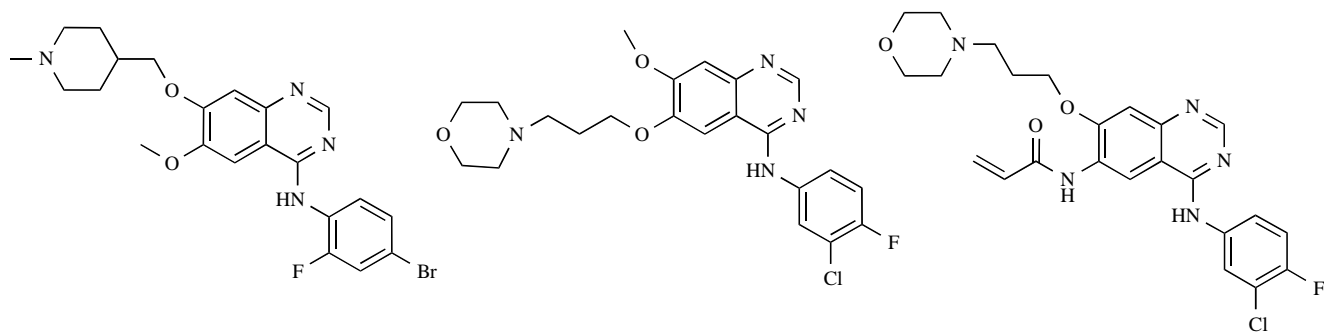
Compound or Generic Name	Trade Name	Manufacturer	Core-Type
colchicine	Colchicine®	Watson Labs	Colchicine
CA4P/ Combrestatin	Zybrestat®	OxiGene	Colchicine/ Combrestatin
CA1P/ Oxi4503		OxiGene	Colchicine/ Combrestatin
ZD6126		AstraZeneca/ Angiogene	Colchicine/ Combrestatin
Ombrabulin/ AVE8062		Anjinomoto/ Sanofi-Aventis	Colchicine/ Combrestatin
BPR0L075		Taiwan National Health Research Institutes	Colchicine & Combrestatin
		Baylor Univ.	Colchicine & Combrestatin
BNC-105		Bionomics	Colchicine & Combrestatin
FAA		National Cancer Institute	Flavonoid
Vadimezan/ DMXAA		Antisoma/ Novartis	Flavonoid
vincristine	Oncovin®	Pierre Fabre	Vinca/Indole
vinblastine	Velban®	Eli-Lilly	Vinca/Indole
vindesine	Eldesine®	Eli-Lilly	Vinca/Indole
vinorelbine	Navelbine®	Pierre Fabre/ GlaxoSmithKline	Vinca/Indole
vinflunine	Javlor®	Pierre Fabre/ Bristol-Myers Squibb	Vinca/Indole
Patupilone/ epothilone B/ EPO906		Novartis	Epothilones
ABT-751/ E7010		Eisai/ Abbott	Amino-pyridine
MPC-6827	Azixa®	Myriad Pharmaceuticals	Quinazoline
CYT-997		Cytopia Ltd	Pyrimidine
NPI-2358		Nereus Pharmaceuticals	Diketopiperazine
Denibulin/ MN-029		Angiogene/ MediciNova	Aminoimidazole
ENMD-1198		EntreMed	Steroid
EC2407		Maxim Pharmaceuticals/ Epicept Corp	Benzopyran
Taltobulin		Wyeth	Dolastatin
AS2O3	Trisenox®	Cephalon	Inorganic
Batabulin/ T27/		Amgen	Aryl sulphonamide
E7070		Eisai	Aryl sulphonamide
Panzem/ 2ME2		EntreMed	Steroid
AEZS-112		AeternaZentaris	Indole
Indibulin/ ZIO-301		Ziopharm Oncology /Baxter	Indole
Rosabulin/ STA-5312		Synta Pharma	Indolizine
Eribulin/ E7389		Eisai	Halichondrin
E7974		Eisai	Hemasterlin

chelating agents¹¹ that have been investigated as VTA's or anti-angiogenesis agents including Coprexa (TTM, Tetra-

thiomolybdate) [111]¹², ATN-224 [112], Penicillamine [113] and Trientine [114].

¹¹ http://medgadget.com/archives/2007/02/studying_copper.html

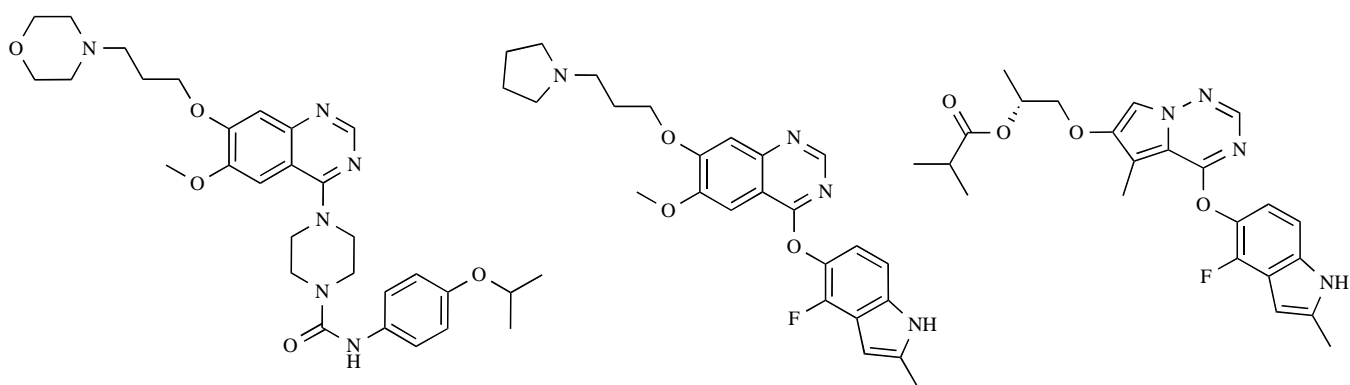
¹² The current status of Coprexa is unknown as sources have suggested the development has been discontinued. http://www.mlive.com/businessreview/annarbor/index.ssf/2008/07/afer_fda_rejects_coprexa_futur.html



Vandetanib

Gefitinib

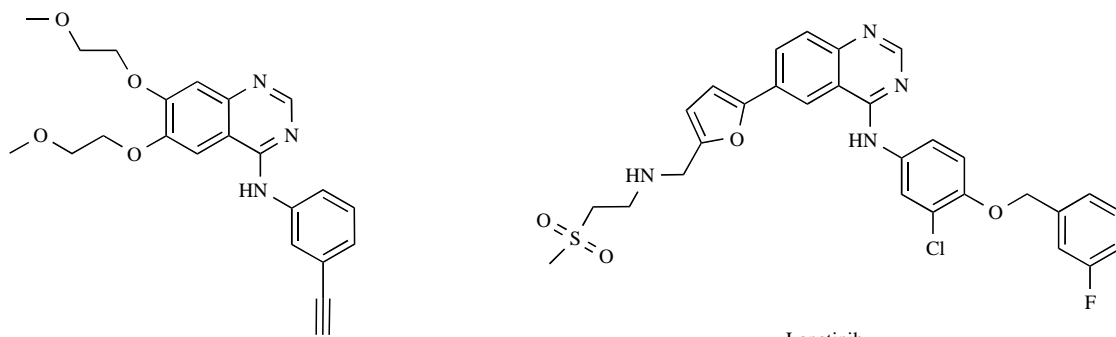
Canertinib



Tandutinib

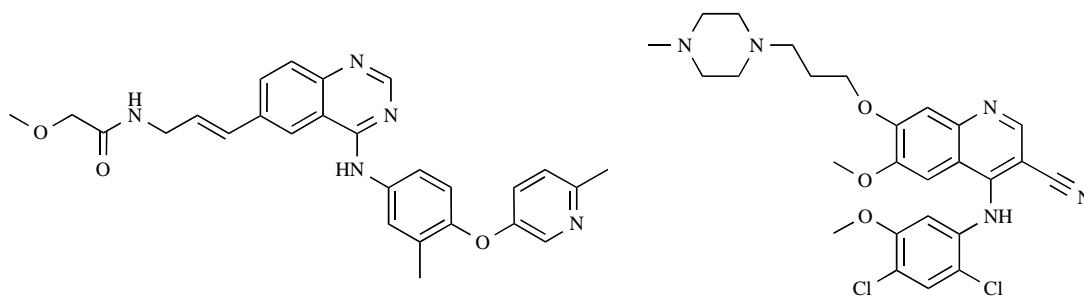
Cediranib

Brivanib



Erlotinib

Lapatinib



CP-724714

Bosutinib

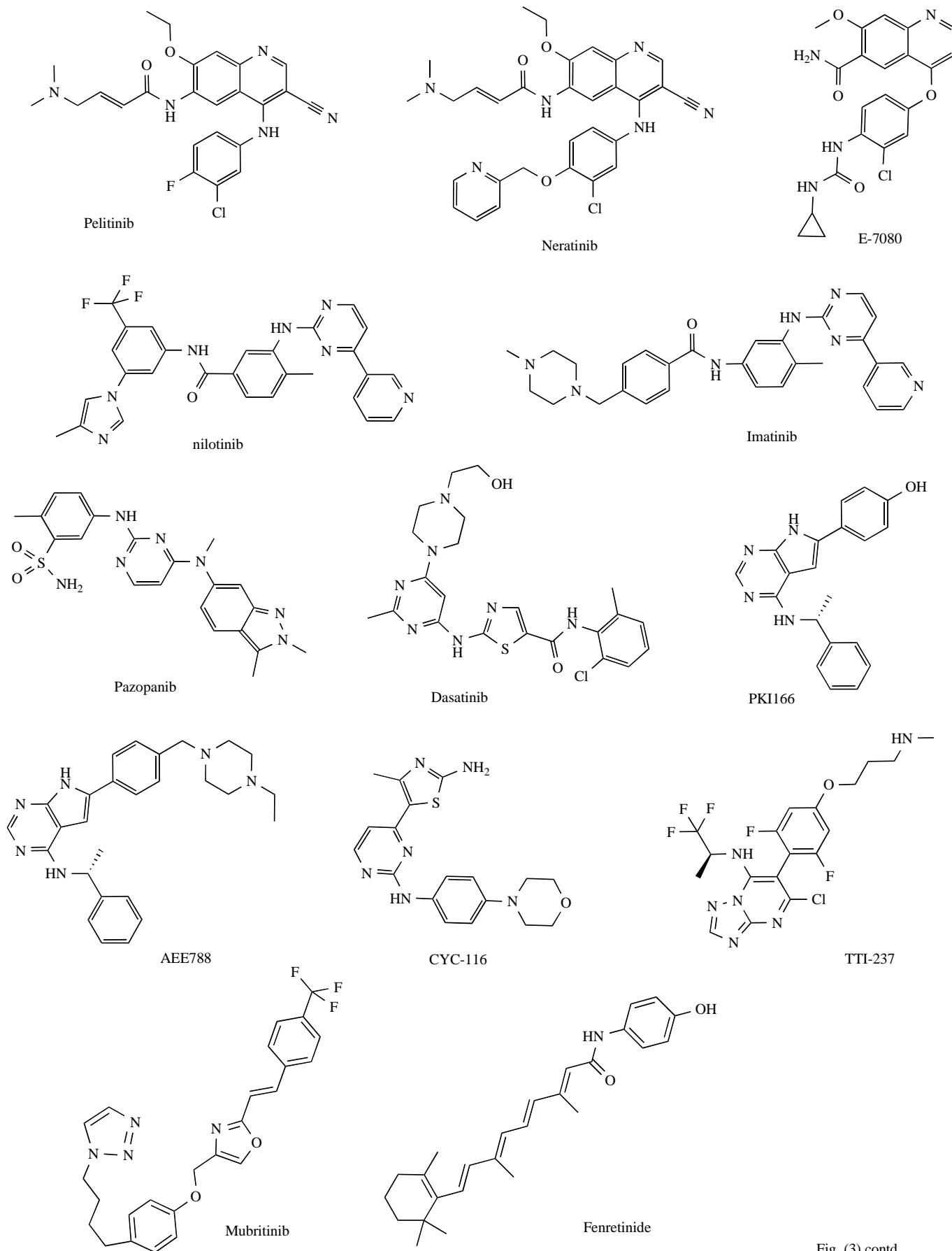
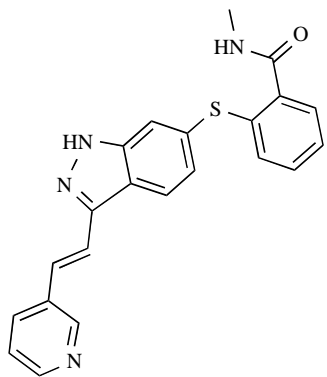
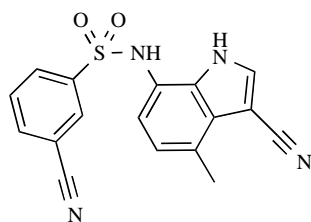


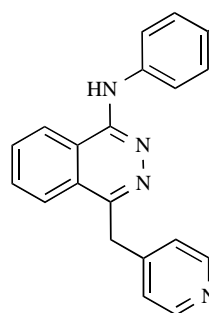
Fig. (3) contd....



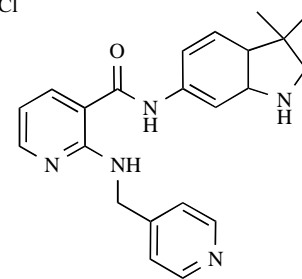
Axitinib



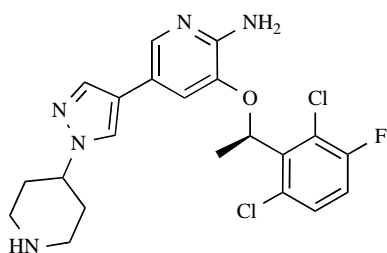
E-7820



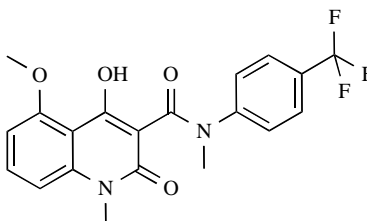
Vatalanib



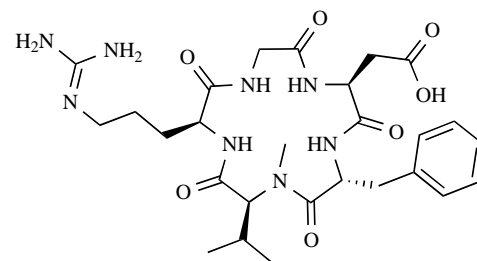
Motesanib



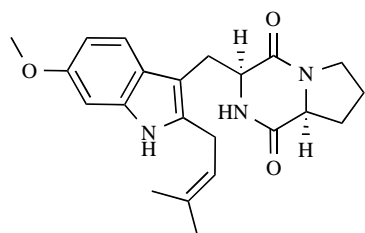
PF-2341066



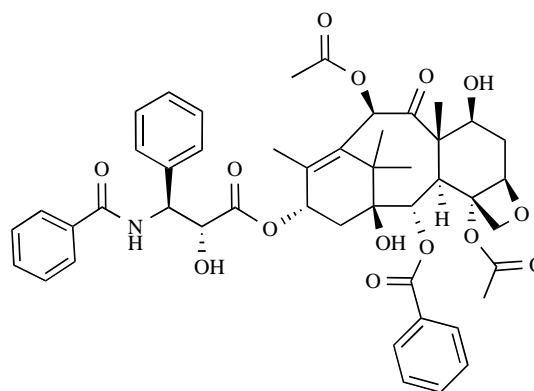
Tasquinimod



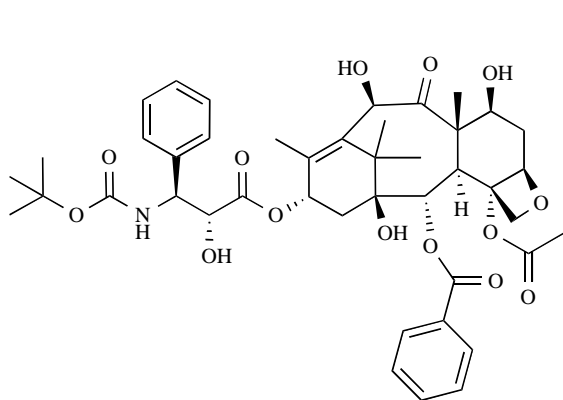
Cilengitide



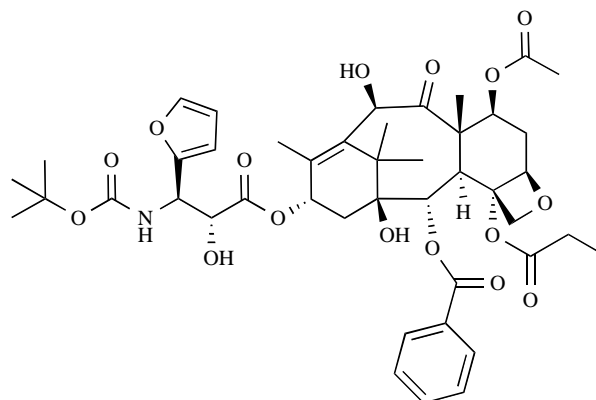
Tryprostatin A



Paclitaxel



Docetaxel



Milataxel

Fig. (3) contd.....

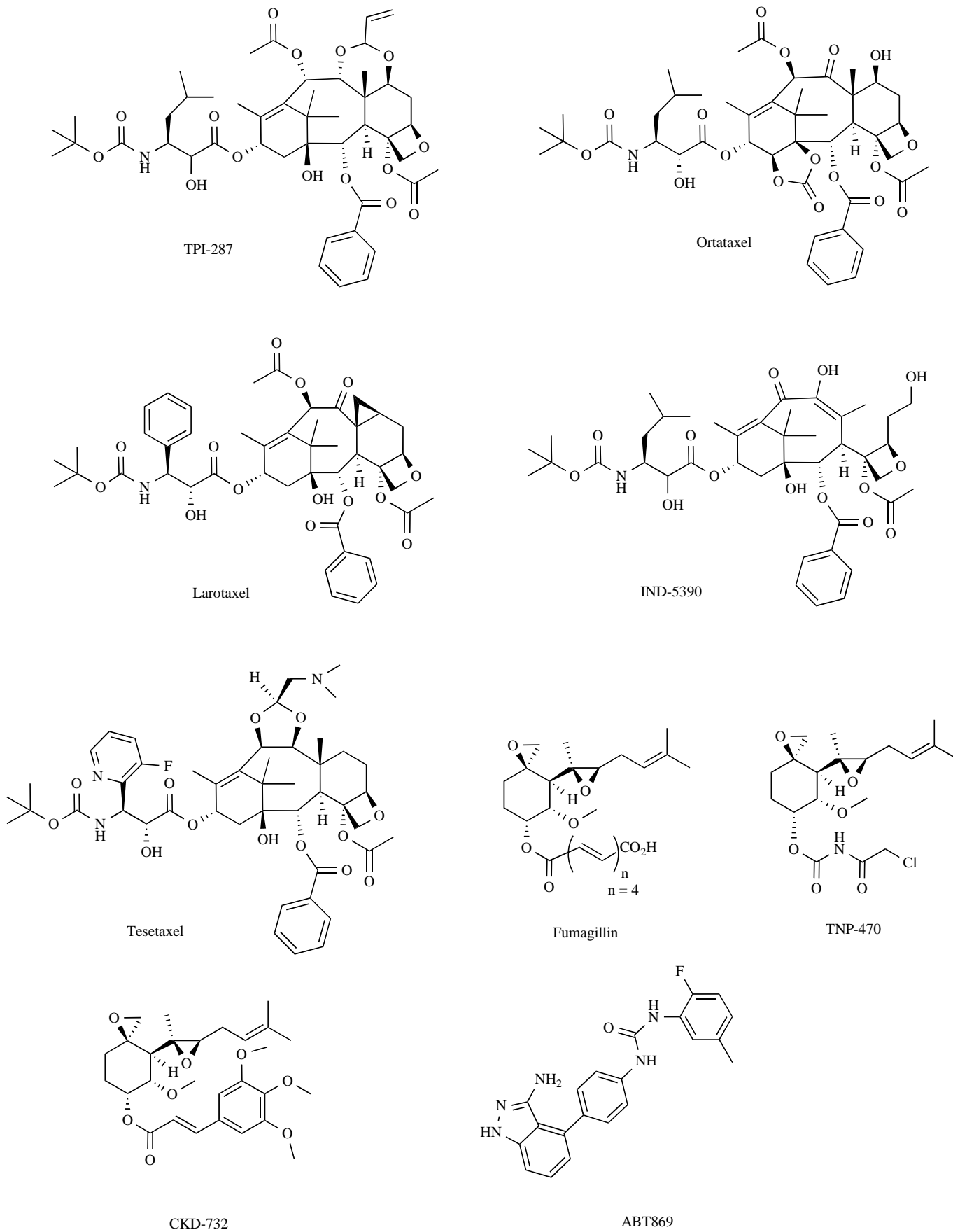


Fig. (3) contd.....

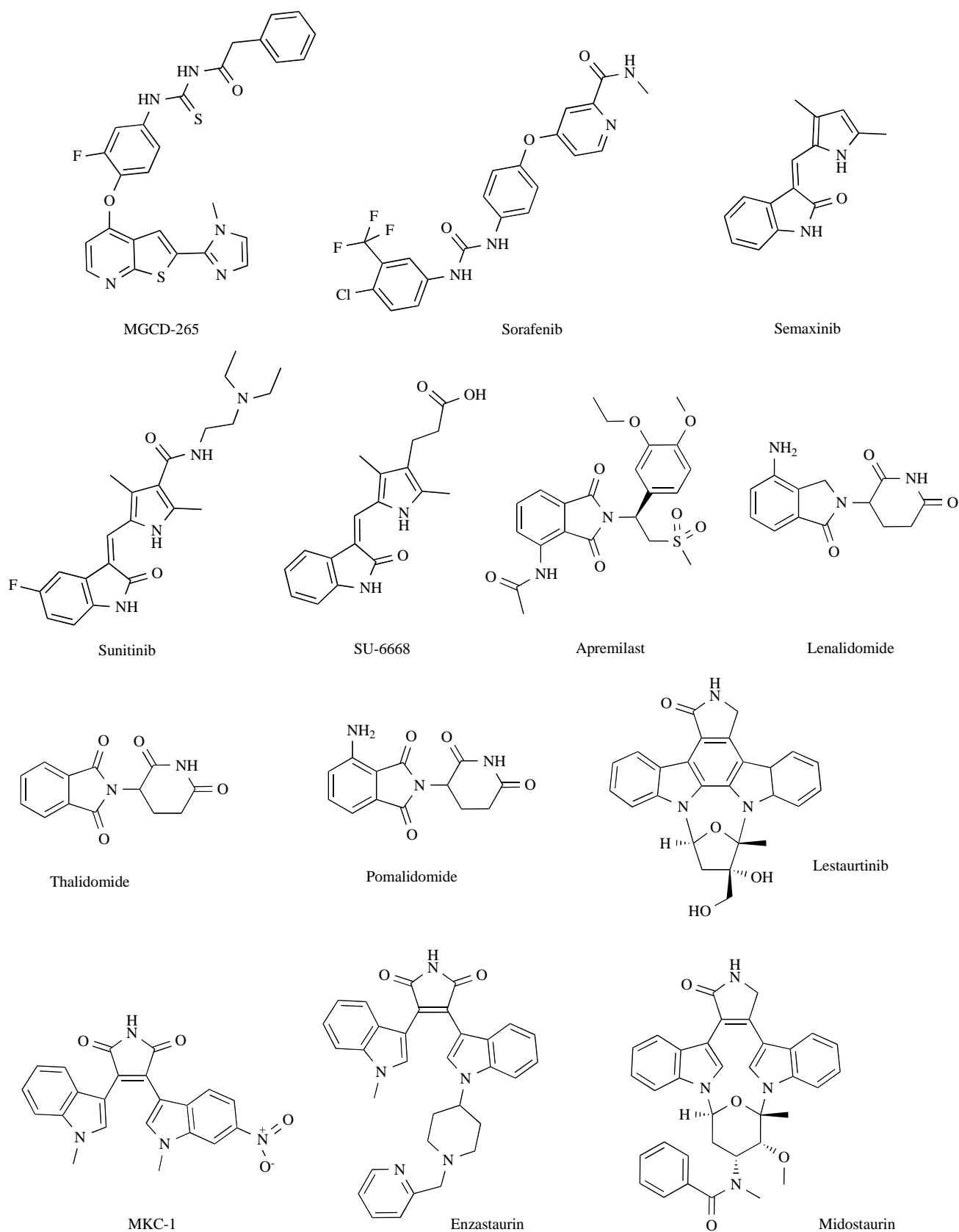


Fig. (3). Reported vascular targeting agents.

Given the breadth of compounds in the clinic, the individual status of all vascular targeting agents is not

covered here; rather the reader is referred to the U.S. National Institutes website for the current status of clinical

Table 2. Reported Vascular Targeting Agents

Compound or Generic Name	Trade Name	Manufacturer	Core-Type
Paclitaxel	Taxol®	BMS	Taxane
DHA-paclitaxel	Taxoprexin®	Luitpold Pharmaceutical	Taxane
Paclitaxel polyglumex/ CT-2103	Opaxio®	Cell Therapeutics	Taxane
<i>nab</i> paclitaxel/ ABI-007	Abraxane®	Abraxis Oncology	Taxane
Larotaxel/ XRP9881		Sanofi-Aventis	Taxane
Docetaxel	Taxotere®	Sanofi-Aventis	Taxane
Milataxel/ MAC-321, T100139		Wyeth-Ayerst / Taxalog	Taxane
Tesetaxel/ DJ-927		Daiichi Sankyo/ Genta	Taxane
Orataxel/ IDN-5109, BAY 59-8862		Indena/ Spectrum/ Bayer	Taxane
TPI-287		Tapestry	Taxane
IDN-5390		Indena	Taxane
Ixabepilone	Ixempra®	BMS	Epothilones
Patupilone/ epothilone B/ EPO906		Novartis	Epothilones
Sagopilone		Bayer Schering Pharma	Epothilones
ABJ879		Novartis	Epothilones
KOS-862		BMS / Kosan/Roche	Epothilones
KOS-864		BMS / Kosan	Epothilones
Fludelone/ KOS-1591		BMS	Epothilones
BMS-31705		BMS	Epothilones
Vandetanib/ ZD6474	Zactima®	AstraZeneca	Quinazoline
Canertinib/ CI-1033, PD183805		Pfizer	Quinazoline
Erlotinib/ OSI-774	Tarceva®	Genentech/OSI and Roche	Quinazoline
Gefitinib/ ZD1839	Iressa®	AstraZeneca	Quinazoline
Lapatinib/ GW572016	Tykerb®	GlaxoSmithKline	Quinazoline
Tandutinib/ MLN518		Millenium	Quinazoline
Cediranib/ AZD2171	Recentin®	AstraZeneca	Quinazoline
CP-724714		Pfizer	Quinazoline
Brivanib/ BMS582664		BMS	Pyrrolotriazine
Bosutinib/ SKI-606		Wyeth-Ayerst	Quinoline
Pelitinib/ EKB-569		Wyeth-Ayerst	Quinoline
Neratinib/ HKI272		Wyeth-Ayerst	Quinoline
E-7080		Eisai	Quinoline
Dasatinib/ BMS-354825	Sprycel®	BMS	Pyrimidine
Imatinib/ STI571	Gleevec®	Novartis	Pyrimidine
Nilotinib/ AMN107	Tasigna®	Novartis	Pyrimidine
Pazopanib/ GW786034		GSK	Pyrimidine
CYC-116		Cyclacel	Pyrimidine
Vatalanib/ PTK787, ZK222584		Novartis	Phthalazine
Axitinib/ AG-013736		Pfizer	Indazole
E-7820		Eisai	Indole
TSU/ SU6668		Pharmacia/Pfizer	Oxindole

(Table 2) contd.....

Compound or Generic Name	Trade Name	Manufacturer	Core-Type
Semaxanib/ SU5416		Pharmacia/Pfizer	Oxindole
Sunitinib/ SU11248	Sutent®	Pfizer	Oxindole
PKI166/ CGP-75166		Novartis	Pyrrolopyrimidine
AEE788		Novartis	Pyrrolopyrimidine
TTI-237		Wyeth-Ayerst	Triazolopyrimidine
Lestaurtinib/ CEP701		Cephalon	Staurosporine
MKC-1		Hoffman-La Roche	Staurosporine
Enzastaurin/ LY317615		Eli-Lilly	Staurosporine
Midostaurin/ PKC412A		Novartis	Staurosporine
Mubritinib/ TAK-165		Takeda	Oxazole
Motesanib/ AMG706		Amgen/ Takeda	Pyridine
PF-2341066		Pfizer	Pyridine
Sorafenib/ BAY43-9006	Nexavar®	Bayer/Onyx	Urea
ABT-869		Abbott/ Genentech	Urea
MGCD-265		MethylGene	Thiourea
Celengitide		Merck KGaA	Peptide
Tryprostatin A			Peptide
Tasquinimod		Active Biotech	Oxoquinoline
Fenretinide/ ST-602		McNeil	Retinoid
Lenalidomide/ CC-5013	Revelmid®	Celgene	Phthalimide
Apremilast/ CC-10004		Celgene	Phthalimide
Thalidomide	Thalomid®	Celgene	Phthalimide
Pomalidomide		Celgene/ Entremed	Phthalimide
Fumagillin			Fumagillin
TNP-470/ AGM-1470		Takeda	Fumagillin
CKD-732		Chong Kun Dang Pharmaceutical	Fumagillin
Tertathiomolybdate (TM)	Coprexa™	Pipex	Tertathiomolybdate
ATN-224		Attenuon	Tertathiomolybdate
Penicillamine	Cuprimine®	Merck	Amino acid
Trientine	Syprine®	Merck	Polyamine
Marimastat/ BB2516		British Biotech	Matrix-metalloproteinase
Prinomastat		Pfizer	Matrix-metalloproteinase
Neovastat (AE-941)		Aeterna	Matrix-metalloproteinase
Alacizumab		UCB Celltech	mAb
Bevacizumab	Avastin®	Genentech	mAb
Ranibizumab	Lucentis™	Genentech	mAb
Vitaxin	Vitaxin™	Ixsys	mAb
Volociximab		Eos Biotechnology	mAb
CNTO-95		Centocor	mAb
TRC-093		Cell Matrix	mAb
Pegaptanib	Macugen®	Pfizer/ Eyetech Pharmaceutical	Aptamer

trials for compounds listed¹³. Additionally, a general review for the clinical advancement of antiangiogenesis inhibitors [115] as well as for the recent progress of taxanes [116] and epothilones [117] have been reported.

DISCUSSION

The selected references used in the writing of this review provide a reasonable initial starting point for the reader to further investigate the various biological and molecular targets underlying this observed VDA or VTA effect. In this regard, a brief examination of one common target, tubulin and microtubules, amongst many of the VTA's and VDA's is warranted. Agents structurally similar to those reported as VDA's or VTA's were selected and included for discussion, however due to the confines of the size of this review it is not possible to be encyclopedic.

Overall, in the case of VDA's and VTA's, the general goal is the same; to disrupt or inhibit the existing or forming blood vasculature surrounding the tumors by obliterating the blood vessel underpinnings that support the viability, growth, replication and potential metastases of tumor cells. Attacking the tumor vasculature is therefore an important member of the armamentarium of anti-tumor/anti-cancer treatment strategies. What remains a challenge is that although VDA treatment can lead to tumor necrosis and death of cancer cells, it can also leave an outer rim of viable cancer cells. This general effect has been observed with colchicine and represents a serious concern for consideration of VDA's as single agent drugs. [118] However, there are reports in the literature indicating that VDA's and VTA's in combination with other anti-cancer agents show promise as a therapeutic regime. [119, 120] Also, the use of VDA's with VTA's represent another potential course of therapy for the treatment of solid tumors. [121] This is a very exciting and evolving field of study with new information discussing possible drug combinations, chemical structure types and sub-structures, clinical utility, and the like being published on a regular basis.

It is important to point out that agents that depolymerize tubulin have been reported to induce disruption of the tumor vasculature while agents stabilizing tubulin polymerization have not shown this same vascular disrupting effect. There are several recent reviews discussing tubulin function and the rich history of tubulin targeting agents. [64, 122-124] Agents not covered here in which the bioactivity is attributed at least in part to their interaction with tubulin include: the phenstatins, indanocine, oncocidine pironetin, spongistatin, spiket P, the cryptophycins, rhizoxin, sarcodictyin, eleutherobin, laulimalide, FR182877, discodermolide and podophyllotoxin. [125] There are three well-known distinct binding sites on β -tubulin commonly referred to as the colchicine, taxol and the vinca alkaloid binding sites. [126] A fourth site has been suggested and reportedly binds tryprostatin A, a specific and novel inhibitor of microtubule assembly. [92] Based on the above references, the data is consistent with the trend that agents which promote tubulin polymerization, and thereby stabilize microtubules bind at the taxane site, while those agents that inhibit tubulin polymerization, and thereby destabilize microtubules, bind at

either at the vinca alkaloid or the colchicine [127, 128] sites. It remains to be seen what the effects of tryprostatin A binding will have on tubulin polymerization and microtubules.

Within the chemical structural core-types of VDA's, there are some interesting similarities and of course marked differences. For example colchicine and the combretastatins, which represent the single largest group, can be considered members derived from a single class, as can the flavonoids FAA and DMXAA. However, if one separates colchicine and the combretastatins into distinct categories further insight is apparent. Clearly, ZD6126 is a colchicine derivative as it preserves the tricyclic ring system and the majority of substituents are identical. Additionally, CA4P, CA1P and ombrabulin are obvious combretastatin A4 analogs due to the common cis-stillbene structural motif and four aryl methoxy substituents. Furthermore, BNC-105, BPR0L075 and the Baylor University compound are recognized as combretastatin A4 derivatives where the stillbene moiety is replaced with a benzophenone linkage. The steroids panzem and ENMD-1198 clearly form a separate class of compounds as do the vinca alkaloids and the dolastatins. The latter group can be further broadened to include Exherin[®] and talatubulin if one classifies these as peptide based rather than their original designation. Other compound such as indibulin and rosabulin, do not fall into the same core-type but are quite similar and probably represent the same pharmacophore. In contrast, the aryl sulphonamides E7070 and baltabulin fall into the same core-type, yet it is not completely evident that the sulphonamide linkage is solely responsible for their activity and indeed they are binding in a like fashion. Other compounds (Azixa[®], ABT751, NPI-2358, EPC-2407, CYT-997, patupilone, denibulin, and eribulin) represent unique classes that fail to be definitively categorized. VDA's as a whole represent a relatively new class of anticancer agents and as research in this area continues, there will be more compounds that fall into these core-types as well as the development of new classes.

VTA's appear to fall into a category of angiogenesis inhibitors *via* a plethora of mechanisms. In the normal cellular environment homeostasis is achieved through a balance of angiogenic mediators *via* interaction with receptors on endothelial cells, the main structural units of blood vessels. Strategies that can affect this pathway represent a validated approach to the treatment of cancers where the balance is shifted toward induction pro-angiogenic events. The most well developed field of which has focused on the correlation between growth factors and the cancer cell's ability to obtain blood supply, proliferate, thrive, and metastasize. For example, growth factor ligands and their respective receptor tyrosine kinases [129, 130] such as fibroblast growth factor receptor (FGFR), vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) [131] have a direct effect on tumor angiogenesis and consequently their inhibition *via* either small molecule or monoclonal antibody inhibitors is an established strategy in anti-tumor/anti-cancer treatment. The epidermal growth factor receptor (EGFR) is another anti-cancer target that is widely expressed in advanced colorectal cancers, and higher levels of EGFR are inversely related to patient survival. [132] Other less

¹³ <http://clinicaltrials.gov>

explored targets include inhibitors of integrin $\alpha V\beta 3$, CDK-2, type 2 methionine aminopeptidase [133] and histone deacetylase (HDAC) [134]. There has also been renewed interest in the use of thalidomide as chemotherapeutic agent due in part to its general anti-angiogenic properties [135]. Additionally anti-angiogenesis can be achieved through the sequestration of metals like copper *via* specific metal targeting agents [136] or through the inhibition of matrix metalloproteinases. As one would suspect, due to the increasing number of anti-angiogenic targets currently being explored for cancer, there are a corresponding large number of different classes of VTA's reported in the literature.

For the VTA's, the list of core-types is more extensive than that of the VDA's and contains several sets which are greater in number as well Table (2). For many of the VTA's this classification enables compounds to be easily placed into groups. These include the taxanes, the epothilones, the thalidomides, the fumagillins, the oxindoles and the staurosporines, which all consist of various analogs of a central core with derivatizations elsewhere on the molecule. This categorization approach also yielded several additional distinct classes including the quinazolines, the pyrimidines, the pyrrolotriazines and the quinolines. However, these groups are part of a larger group of VTA's, the receptor tyrosine kinase inhibitors [137]. If organization is based on the individual pharmacophores, then the number of groups or scaffolds is significantly reduced. For example, the epothilones and the taxanes have been previously unified into one group based on their binding of tubulin [138]. Contrasting cediranib and brivanib, it appears these two compounds, which are in are separated into quinazoline and pyrrolotriazine core-types, respectively can be placed side-by-side. Based on comparison of the overall structure as well as the similarities in substituents, especially with regard to the indole moiety, it is plausible that these compounds would occupy the same relative 3-dimensional space. Arguably, the phthalazine vatalanib and the pyridine motesanib could represent a similar situation. Additionally, many other core-types are characterized as having the same or similar side-chains. For instance, the quinazolines, gefitinib and canertinib, in addition to having the same core-type, both contain identical pendant anilines and tethered morpholines. The quinolines pelitinib and neratinib, have matching cyano, ethoxy and dimethylamino pentenone substituents. Nilotinib and imatinib are both substituted on the pyrimidine core with a 3-pyridyl group and an ortho-methyl aniline. Even compounds of different categories still have overlapping similarities. The quinazoline gefitinib and the quinoline pelitinib both contain the same 3-chloro-4-fluoro aniline moiety. Conversely, ABT869, MGCD-265 and sorafenib are aligned together based on the urea and thiourea functionalities, yet significant differences exists within the rest of the molecule that delineate the three compounds. Celengitide and tryprostatin A are both peptide-based but comparison of the structures shows these compounds lack any further similarities. E-7080 could also be include within the urea core-types however it's more likely that the biological activity is predominately a result of the quinoline moiety and therefore is best represented as a separate category. Still there are several compounds such as TTI-237, murbrinitib, fenretinide, axitinib, E-7820 and tasquinimod where the association with a single group was ambiguous

and were placed into separate groups. While there are both similarities and differences among the listed core-types, their utility has been validated by the approval of several of the compounds shown for the treatment of cancer. VTA's represent an expanding and promising field and it is not surprising that several core-types have been systematically investigated and contain numerous close analogs. Still, there are a large number of smaller groups and some categories only contain a single member and as such, opportunities still exist for the development of new and/or novel VTA's.

Although compounds were segregated based VDA or VTA effects and organized based on chemical structures, one aspect not considered was secondary pharmacology of the agents. Many drugs, even ones that are designed to act specifically on a target protein, bind unintended proteins and can exhibit off-target activity and display dual mechanisms of action or pleiotropism. These effects may be beneficial (e.g. HMG-CoA reductase inhibitors, aka statins, have been reported to have diverse activities in addition to lowering serum cholesterol) [139], neutral (no adverse or beneficial effects), or undesirable (such as side effects or toxicity). It is therefore not surprising that examples exist where VDA's and VTA's exhibit evidence of pleiotropism. As previously mentioned (*vide supra*), the two flavonoid VDA's (FAA and DMXAA) are not limited to just their vascular disrupting properties and have been shown to induce the production of local cytokines such as TNF- α [140] although the observed effects of FAA were absent when studied in human cell lines [141]. Panzem has been recognized as having anti-angiogenic properties in addition to the ability to disrupt the established vasculature of solid tumors [35]. In the case of ABT-751 it is not fully established that the observed effects on tumor vasculature are attributed solely to its cytotoxicity but could be also mediated by its anti-angiogenic properties as well [142]. It is plausible that as with vincristine [143] and patupilone [63], that the antiangiogenic properties of ABT-751 are separate from the vascular disrupting properties and may be intricately dependent on the dose [33]. Similarly, the tubulin stabilizing ability of the vascular targeting agent Taxol[®] is separate from the ability to exhibit antiangiogenic activity at cytostatic concentrations [55].

CONCLUSION

The use of VTA's and VDA's as chemotherapeutics are clearly an important weapon for the fight against cancer and will continue to be an important aspect for oncology drug discovery programs in the future. VDA's represent a much less established class of anti-cancer drugs yet they hold great promise due to their distinct anti-vascular effects. Inspection of the VDA's leads one to recognize the dissimilarity, or greater diversity, in the structures. Aside from the vinca alkaloids, dolastatins and the colchicine/combretastatins, it appears that of the 15 core structures shown that are of clinical significance reported in the literature, there are few members of any class. Consequently a substantial opportunity exists for the development of new VDA's.

The VTA's, which are part of most accepted treatment regimes, represent a larger group of scaffolds and structures. This is in part due to being a more established and validated class of anticancer agents and by the numerous different biological targets that can effect a response. This also means

that the “cores” have been more thoroughly investigated and several analogs exist in many classes. Notably, the taxanes, epothilones and quinazolines have greater than five members in each class and at least one member of which is a marketed drug. If one considers the pharmacophore for the receptor tyrosine kinases as an individual class many more compounds could fall into this category and reduce the overall number of scaffolds listed as VTA's. While both VDA's and VTA's appear beneficial to future of anticancer therapy, it is the potential of the VDA's to augment current strategies that seem to represent the most excitement for the treatment of cancer. As this review has elucidated, there are clearly structural differences between VTA's and VDA's. As interest continues to develop, the separation between these features of the VDA's and VTA's should widen further and their differentiation will become even more apparent.

REFERENCES

- [1] Dome, B.; Hendrix, M. J. C.; Paku, S.; Tovari, J.; Timar, J. (2007) Alternative Vascularization Mechanisms in Cancer: Pathology and Therapeutic Implications. *Am. J. Pathol.*, **170** (1), 1-15.
- [2] Liu, J. F.; Wilson, C. J.; Ye, P.; Sprague, K.; Sargent, K.; Si, Y.; Beletsky, G.; Yohannes, D.; Ng, S. C. (2006) Privileged structure-based quinazolinone natural product-templated libraries: identification of novel tubulin polymerization inhibitors. *Bioorg. Med. Chem. Lett.*, **16** (3), 686-90.
- [3] Ehrlich, P. (1909) *Dtsch. Chem. Ges.*, **42**, 17.
- [4] Gund, P. (1977) *Prog. Mol. Subcell. Biol.*, **5**, 117-143.
- [5] Kubinyi, H., (2002) Chemical Similarity and Biological Activities *J. Brazilian Chem. Soc.*, **13** (6), 717.
- [6] Lipkus, A. H.; Yuan, Q.; Lucas, K. A.; Funk, S. A.; Bartelt, W. F., 3rd; Schenck, R. J.; Trippe, A. J. (2008) Structural diversity of organic chemistry. A scaffold analysis of the CAS registry. *J. Org. Chem.*, **73** (12), 4443-51.
- [7] Fukumura, D.; Jain, R. K. (2007) Tumor microvasculature and microenvironment: targets for anti-angiogenesis and normalization. *Microvasc. Res.*, **74** (2-3), 72-84.
- [8] Thorpe, P. E., (2004) Vascular targeting agents as cancer therapeutics. *Clin. Cancer Res.*, **10** (2), 415-27.
- [9] Folpini, A.; Furfori, P. (1995) Colchicine toxicity--clinical features and treatment. Massive overdose case report. *J. Toxicol. Clin. Toxicol.*, **33** (1), 71-7.
- [10] Rewcastle, G. W.; Atwell, G. J.; Baguley, B. C.; Calveley, S. B.; Denny, W. A. (1989) Potential antitumor agents. 58. Synthesis and structure-activity relationships of substituted xanthenone-4-acetic acids active against the colon 38 tumor *in vivo*. *J. Med. Chem.*, **32** (4), 793-9.
- [11] Carlson, R. O., (2008) New tubulin targeting agents currently in clinical development. *Exp. Opin. Investig. Drugs*, **17** (5), 707-22.
- [12] Cai, S. X. (2007) Small molecule vascular disrupting agents: potential new drugs for cancer treatment. *Recent Patents Anticancer Drug Discov.*, **2** (1), 79-101.
- [13] Brossi, A.; Yeh, H. J.; Chrzanowska, M.; Wolff, J.; Hamel, E.; Lin, C. M.; Quin, F.; Suffness, M.; Silverton, J. (1988) Colchicine and its analogues: recent findings. *Med. Res. Rev.*, **8** (1), 77-94.
- [14] Chaplin, D. J.; Pettit, G. R.; Parkins, C. S.; Hill, S. A. (1996) Antivascular approaches to solid tumour therapy: evaluation of tubulin binding agents. *Br. J. Cancer Suppl.*, **27**, S86-8.
- [15] Griggs, J.; Metcalfe, J. C.; Hesketh, R. (2001) Targeting tumour vasculature: the development of combretastatin A4. *Lancet Oncol.*, **2** (2), 82-7.
- [16] Davis, P. D.; Dougherty, G. J.; Blakey, D. C.; Galbraith, S. M.; Tozer, G. M.; Holder, A. L.; Naylor, M. A.; Nolan, J.; Stratford, M. R.; Chaplin, D. J.; Hill, S. A. (2002) ZD6126: a novel vascular-targeting agent that causes selective destruction of tumor vasculature. *Cancer Res.*, **62** (24), 7247-53.
- [17] Hori, K. (2005) Antineoplastic strategy: irreversible tumor blood flow stasis induced by the combretastatin A-4 derivative AVE8062 (AC7700). *Chemotherapy*, **51** (6), 357-60.
- [18] Hokland, S. L.; Horsman, M. R. (2007) The new vascular disrupting agent combretastatin-A1-disodium-phosphate (OXI4503) enhances tumour response to mild hyperthermia and thermo-radiosensitization. *Int. J. Hyperthermia*, **23** (7), 599-606.
- [19] Lobert, S.; Vulevic, B.; Correia, J. J. (1996) Interaction of vinca alkaloids with tubulin: a comparison of vinblastine, vincristine, and vinorelbine. *Biochemistry*, **35** (21), 6806-14.
- [20] Hill, S. A.; Lonergan, S. J.; Denekamp, J.; Chaplin, D. J. (1993) Vinca alkaloids: anti-vascular effects in a murine tumour. *Eur. J. Cancer*, **29A** (9), 1320-4.
- [21] Door, R., In *Cancer Chemotherapy Handbook*, Fritz, Ed. Elsevier publishing Company Inc.: New York, 1980.
- [22] Holwell, S. E.; Hill, B. T.; Bibby, M. C. (2001) Anti-vascular effects of vinflunine in the MAC 15A transplantable adenocarcinoma model. *Br. J. Cancer*, **84** (2), 290-5.
- [23] Kruczynski, A.; Poli, M.; Dossi, R.; Chazottes, E.; Berrichon, G.; Ricome, C.; Giavazzi, R.; Hill, B. T.; Taraboletti, G. (2006) Anti-angiogenic, vascular-disrupting and anti-metastatic activities of vinflunine, the latest vinca alkaloid in clinical development. *Eur. J. Cancer*, **42** (16), 2821-32.
- [24] Baguley, B. G. S. B. C. Flavones and Xanthenones as Vascular-Disturbing Agents. In *Vascular Targeted Therapies in Oncology*, Siemann, D. W., Ed. 2006; pp 159-178.
- [25] Rustin, G. J.; Bradley, C.; Galbraith, S.; Stratford, M.; Loadman, P.; Waller, S.; Bellenger, K.; Gumbrell, L.; Folkes, L.; Halbert, G. (2003) 5,6-dimethylxanthenone-4-acetic acid (DMXAA), a novel antivascular agent: phase I clinical and pharmacokinetic study. *Br. J. Cancer* **88** (8), 1160-7.
- [26] Segreti, J. A.; Polakowski, J. S.; Koch, K. A.; Marsh, K. C.; Bauch, J. L.; Rosenberg, S. H.; Sham, H. L.; Cox, B. F.; Reinhart, G. A. (2004) Tumor selective antivascular effects of the novel antimetabolic compound ABT-751: an *in vivo* rat regional hemodynamic study. *Cancer Chemother. Pharmacol.*, **54** (3), 273-81.
- [27] Natsume, T.; Watanabe, J.; Ogawa, K.; Yasumura, K.; Kobayashi, M. (2007) Tumor-specific antivascular effect of TZZT-1027 (Soblidotin) elucidated by magnetic resonance imaging and confocal laser scanning microscopy. *Cancer Sci.*, **98** (4), 598-604.
- [28] Kasibhatla, S.; Baichwal, V.; Cai, S. X.; Roth, B.; Skvortsova, I.; Skvortsov, S.; Lukas, P.; English, N. M.; Sirisoma, N.; Drewe, J.; Pervin, A.; Tseng, B.; Carlson, R. O.; Pleiman, C. M., MPC-6827: a small-molecule inhibitor of microtubule formation that is not a substrate for multidrug resistance pumps. *Cancer Res.*, **67** (12), 5865-71.
- [29] Nicholson, B.; Lloyd, G. K.; Miller, B. R.; Palladino, M. A.; Kiso, Y.; Hayashi, Y.; Neuteboom, S. T. (2006) NPI-2358 is a tubulin-depolymerizing agent: *in-vitro* evidence for activity as a tumor vascular-disrupting agent. *Anticancer Drugs*, **17** (1), 25-31.
- [30] Shi, W.; Siemann, D. W. (2005) Preclinical studies of the novel vascular disrupting agent MN-029. *Anticancer Res.*, **25**(6B), 3899-904.
- [31] Moser, C.; Lang, S. A.; Mori, A.; Hellerbrand, C.; Schlitt, H. J.; Geissler, E. K.; Fogler, W. E.; Stoeltzing, O. (2008) ENMD-1198, a novel tubulin-binding agent reduces HIF-1 α and STAT3 activity in human hepatocellular carcinoma(HCC) cells, and inhibits growth and vascularization *in vivo*. *BMC Cancer*, **8**, 206.
- [32] Kelland, L. (2007) Drug evaluation: ADH-1, an N-cadherin antagonist targeting cancer vascularization. *Curr. Opin. Mol. Ther.*, **9**(1), 86-91.
- [33] Ferretti, S.; Allegrini, P. R.; O'Reilly, T.; Schnell, C.; Stumm, M.; Wartmann, M.; Wood, J.; McSheehy, P. M. J. (2005) Patupilone Induced Vascular Disruption in Orthotopic Rodent Tumor Models Detected by Magnetic Resonance Imaging and Interstitial Fluid Pressure. *Clin. Cancer Res.*, **11**(21), 7773-7784.
- [34] ter Haar, E.; Rosenkranz, H. S.; Hamel, E.; Day, B. W. (1996) Computational and molecular modeling evaluation of the structural basis for tubulin polymerization inhibition by colchicine site agents. *Bioorg. Med. Chem.*, **4**(10), 1659-1671.
- [35] Mabjeesh, N. J.; Escuin, D.; LaVallee, T. M.; Pribluda, V. S.; Swartz, G. M.; Johnson, M. S.; Willard, M. T.; Zhong, H.; Simons, J. W.; Giannakakou, P. (2003) 2ME2 inhibits tumor growth and angiogenesis by disrupting microtubules and dysregulating HIF. *Cancer Cell*, **3**(4), 363-75.
- [36] Kamath, K.; Okouneva, T.; Larson, G.; Panda, D.; Wilson, L.; Jordan, M. A. (2006) 2-Methoxyestradiol suppresses microtubule

- dynamics and arrests mitosis without depolymerizing microtubules. *Mol. Cancer Ther.*, **5**(9), 2225-33.
- [37] Bacher, G.; Nickel, B.; Emig, P.; Vanhoefer, U.; Seeber, S.; Shandra, A.; Klenner, T.; Beckers, T. (2001) D-24851, a novel synthetic microtubule inhibitor, exerts curative antitumoral activity *in vivo*, shows efficacy toward multidrug-resistant tumor cells, and lacks neurotoxicity. *Cancer Res.*, **61**(1), 392-9.
- [38] von Mehren, M.; Balcerzak, S. P.; Kraft, A. S.; Edmonson, J. H.; Okuno, S. H.; Davey, M.; McLaughlin, S.; Beard, M. T.; Rogatko, A. (2004) Phase II trial of dolastatin-10, a novel anti-tubulin agent, in metastatic soft tissue sarcomas. *Sarcoma*, **8**(4), 107-11.
- [39] Ray, A.; Okouneva, T.; Manna, T.; Miller, H. P.; Schmid, S.; Arthaud, L.; Luduena, R.; Jordan, M. A.; Wilson, L. (2007) Mechanism of action of the microtubule-targeted antimetabolic depsipeptide tasidotin (formerly ILX651) and its major metabolite tasidotin C-carboxylate. *Cancer Res.*, **67**(8), 3767-76.
- [40] Yokoi, A.; Kuromitsu, J.; Kawai, T.; Nagasu, T.; Sugi, N. H.; Yoshimatsu, K.; Yoshino, H.; Owa, T. (2002) Profiling novel sulfonamide antitumor agents with cell-based phenotypic screens and array-based gene expression analysis. *Mol. Cancer Ther.*, **1**(4), 275-86.
- [41] Kuo, C. C.; Hsieh, H. P.; Pan, W. Y.; Chen, C. P.; Liou, J. P.; Lee, S. J.; Chang, Y. L.; Chen, L. T.; Chen, C. T.; Chang, J. Y. (2004) BPROL075, a novel synthetic indole compound with antimetabolic activity in human cancer cells, exerts effective antitumoral activity *in vivo*. *Cancer Res.*, **64**(13), 4621-8.
- [42] Dabydeen, D. A.; Burnett, J. C.; Bai, R.; Verdier-Pinard, P.; Hickford, S. J.; Pettit, G. R.; Blunt, J. W.; Munro, M. H.; Gussio, R.; Hamel, E. (2006) Comparison of the activities of the truncated halichondrin B analog NSC 707389 (E7389) with those of the parent compound and a proposed binding site on tubulin. *Mol. Pharmacol.*, **70**(6), 1866-75.
- [43] Zask, A.; Kaplan, J.; Musto, S.; Loganzo, F. (2005) Hybrids of the hemisterlin analogue taltobulin and the dolastatins are potent antimicrotubule agents. *J. Am. Chem. Soc.*, **127**(50), 17667-71.
- [44] Ayral-Kaloustian, S.; Zask, A.; Taltobulin. Oncolytic drug, Tubulin polymerization inhibitor, Antimetabolic drug. *Drugs Future* **2005**, **30** (3), 254-260.
- [45] Perez-Melero, C.; Maya, A. B.; del Rey, B.; Pelaez, R.; Caballero, E.; Medarde, M., A new family of quinoline and quinoxaline analogues of combretastatins. *Bioorg. Med. Chem. Lett.* **2004**, **14** (14), 3771-4.
- [46] Coggiola, B.; Pagliai, F.; Allegrone, G.; Genazzani, A. A.; Tron, G. C. (2005) Synthesis and biological activity of mustard derivatives of combretastatins. *Bioorg. Med. Chem. Lett.*, **15** (15), 3551-4.
- [47] Alvarez, C.; Alvarez, R.; Corchete, P.; Perez-Melero, C.; Pelaez, R.; Medarde, M. (2007) Synthesis and biological activity of naphthalene analogues of phenstatins: naphthylphenstatins. *Bioorg. Med. Chem. Lett.*, **17**(12), 3417-20.
- [48] Provot, O.; Giraud, A.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. (2005) Synthetic approach to enyne and enediyne analogues of anticancer agents. *Tetrahedron Lett.*, **46**(49), 8547-8550.
- [49] Sun, L.; Vasilevich, N. I.; Fuselier, J. A.; Hocart, S. J.; Coy, D. H. (2004) Examination of the 1,4-disubstituted azetidinone ring system as a template for combretastatin A-4 conformationally restricted analogue design. *Bioorg. Med. Chem. Lett.*, **14**(9), 2041-6.
- [50] Medarde, M.; Ramos, A. C.; Caballero, E.; Pelaez-Lamamie de Clairac, R.; Lopez, J. L.; Gravalos, D. G.; Feliciano, A. S. (1999) Synthesis and pharmacological activity of diarylindole derivatives. Cytotoxic agents based on combretastatins. *Bioorg. Med. Chem. Lett.*, **9**(16), 2303-8.
- [51] Hinnen, P.; Eskens, F. A. (2007) Vascular disrupting agents in clinical development. *Br. J. Cancer*, **96**(8), 1159-65.
- [52] Pan, Q.; Kleer, C. G.; van Golen, K. L.; Irani, J.; Bottema, K. M.; Bias, C.; De Carvalho, M.; Mesri, E. A.; Robins, D. M.; Dick, R. D.; Brewer, G. J.; Merajver, S. D. (2002) Copper deficiency induced by tetrathiomolybdate suppresses tumor growth and angiogenesis. *Cancer Res.*, **62**(17), 4854-9.
- [53] Dieras, V.; Limentani, S.; Romieu, G.; Tubiana-Hulin, M.; Lortholary, A.; Kaufman, P.; Girre, V.; Besenval, M.; Valero, V. (2008) Phase II multicenter study of larotaxel (XRP9881), a novel taxoid, in patients with metastatic breast cancer who previously received taxane-based therapy. *Ann. Oncol.*, **19**(7), 1255-60.
- [54] Sampath, D.; Discifani, C. M.; Loganzo, F.; Beyer, C.; Liu, H.; Tan, X.; Musto, S.; Annable, T.; Gallagher, P.; Rios, C.; Greenberger, L. M. (2003) MAC-321, a novel taxane with greater efficacy than paclitaxel and docetaxel *in vitro* and *in vivo*. *Mol. Cancer Ther.*, **2**(9), 873-84.
- [55] Pasquier, E.; Honore, S.; Pourroy, B.; Jordan, M. A.; Lehmann, M.; Briand, C.; Braguer, D. (2005) Antiangiogenic concentrations of paclitaxel induce an increase in microtubule dynamics in endothelial cells but not in cancer cells. *Cancer Res.*, **65**(6), 2433-40.
- [56] Vacca, A.; Ribatti, D.; Iurlaro, M.; Merchionne, F.; Nico, B.; Ria, R.; Dammacco, F., Docetaxel versus paclitaxel for antiangiogenesis. *J. Hematother. Stem Cell Res.*, **11**(1), 103-18.
- [57] Polizzi, D.; Pratesi, G.; Monestiroli, S.; Tortoreto, M.; Zunino, F.; Bombardelli, E.; Riva, A.; Morazzoni, P.; Colombo, T.; D'Incalci, M.; Zucchetti, M. (2000) Oral efficacy and bioavailability of a novel taxane. *Clin. Cancer Res.*, **6**(5), 2070-4.
- [58] Petrangolini, G.; Cassinelli, G.; Pratesi, G.; Tortoreto, M.; Favini, E.; Supino, R.; Lanzi, C.; Belluco, S.; Zunino, F. (2004) Antitumor and antiangiogenic effects of IDN 5390, a novel C-seco taxane, in a paclitaxel-resistant human ovarian tumour xenograft. *Br. J. Cancer*, **90**(7), 1464-8.
- [59] Roche, M.; Kyriakou, H.; Seiden, M. (2006) Drug evaluation: tesetaxel—an oral semisynthetic taxane derivative. *Curr. Opin. Investig. Drugs*, **7**(12), 1092-9.
- [60] Hennenfent, K. L.; Govindan, R. (2006) Novel formulations of taxanes: a review. Old wine in a new bottle? *Ann. Oncol.* **17**(5), 735-49.
- [61] Fumoleau, P.; Coudert, B.; Isambert, N.; Ferrant, E. (2007) Novel tubulin-targeting agents: anticancer activity and pharmacologic profile of epothilones and related analogues. *Ann. Oncol.*, **18 Suppl 5**, v9-15.
- [62] Hoffmann, J.; Vitale, I.; Buchmann, B.; Galluzzi, L.; Schwede, W.; Senovilla, L.; Skuballa, W.; Vivet, S.; Lichtner, R. B.; Vicencio, J. M.; Panaretakis, T.; Siemeister, G.; Lage, H.; Nanty, L.; Hammer, S.; Mittelstaedt, K.; Winsel, S.; Eschenbrenner, J.; Castedo, M.; Demarche, C.; Klar, U.; Kroemer, G. (2008) Improved cellular pharmacokinetics and pharmacodynamics underlie the wide anticancer activity of sagopilone. *Cancer Res.*, **68**(13), 5301-8.
- [63] James, M. L.; Maxwell, P. J.; Catherine, T. A.; Brian, M. G.; Jessica, L. T.; John, R.; Paul, M.; Yi-Zarn, W.; Eugene, A. W. (2004) Epothilone B is a more potent antiangiogenic than paclitaxel in a human tumor-based angiogenesis model. *J. Am. College Surg.*, **199**(3), 90.
- [64] Altmann, K. H.; Gertsch, J. (2007) Anticancer drugs from nature—natural products as a unique source of new microtubule-stabilizing agents. *Nat. Prod. Rep.*, **24**(2), 327-57.
- [65] Rizvi, N.; Villalona-Calero, M.; Lynch, T.; Yee, L.; Gabrail, N.; Sandler, A.; Cropp, G.; Graham, M.; Palmer, G. (2005) P-565 A Phase II study of KOS-862 (Epothilone D) as second-line therapy in non-small cell lung cancer. *Lung Cancer*, **49**(Supplement 2), S266-S267.
- [66] Cho, Y. S.; Wu, K.-D.; Moore, M. A. S.; Chou, T.-C.; Danishefsky, S. J., Second generation epothilones: Discovery of fludelone and its extraordinary antitumor properties. **2005**, **30** (7), 737.
- [67] Lee, F. Y.; Borzilleri, R.; Fairchild, C. R.; Kim, S. H.; Long, B. H.; Reventos-Suarez, C.; Vite, G. D.; Rose, W. C.; Kramer, R. A. (2001) BMS-247550: a novel epothilone analog with a mode of action similar to paclitaxel but possessing superior antitumor efficacy. *Clin. Cancer Res.*, **7**(5), 1429-37.
- [68] Britten, C. D. (2004) Targeting ErbB receptor signaling: a pan-ErbB approach to cancer. *Mol. Cancer Ther.*, **3**(10), 1335-42.
- [69] Jani, J. P.; Finn, R. S.; Campbell, M.; Coleman, K. G.; Connell, R. D.; Currier, N.; Emerson, E. O.; Floyd, E.; Harriman, S.; Kath, J. C.; Morris, J.; Moyer, J. D.; Pustilnik, L. R.; Rafidi, K.; Ralston, S.; Rossi, A. M.; Steyn, S. J.; Wagner, L.; Winter, S. M.; Bhattacharya, S. K. (2007) Discovery and pharmacologic characterization of CP-724,714, a selective ErbB2 tyrosine kinase inhibitor. *Cancer Res.*, **67**(20), 9887-93.
- [70] Bradley, D. P.; Tessier, J. L.; Checkley, D.; Kuribayashi, H.; Waterton, J. C.; Kendrew, J.; Wedge, S. R. (2008) Effects of AZD2171 and vandetanib (ZD6474, Zactima) on haemodynamic variables in an SW620 human colon tumour model: an investigation using dynamic contrast-enhanced MRI and the rapid

- clearance blood pool contrast agent, P792 (gadomelitol). *NMR Biomed.*, **21**(1), 42-52.
- [71] Rocha-Lima, C. M.; Soares, H. P.; Raez, L. E.; Singal, R. (2007) EGFR targeting of solid tumors. *Cancer Control*, **14**(3), 295-304.
- [72] Ayers, M.; Fargnoli, J.; Lewin, A.; Wu, Q.; Platero, J. S. (2007) Discovery and validation of biomarkers that respond to treatment with brivanib alaninate, a small-molecule VEGFR-2/FGFR-1 antagonist. *Cancer Res.*, **67** (14), 6899-906.
- [73] Vultur, A.; Buettner, R.; Kowolik, C.; Liang, W.; Smith, D.; Boschelli, F.; Jove, R. (2008) SKI-606 (bosutinib), a novel Src kinase inhibitor, suppresses migration and invasion of human breast cancer cells. *Mol. Cancer Ther.*, **7**(5), 1185-94.
- [74] Jefford, M.; Zalberg, J. (2005) Recent Advances in the Systemic Therapy of Metastatic Colorectal Cancer. *Am. J. Cancer*, **4**(1), 14-34.
- [75] Rabindran, S. K.; Discafani, C. M.; Rosfjord, E. C.; Baxter, M.; Floyd, M. B.; Golas, J.; Hallett, W. A.; Johnson, B. D.; Nilakantan, R.; Overbeek, E.; Reich, M. F.; Shen, R.; Shi, X.; Tsou, H. R.; Wang, Y. F.; Wissner, A. (2004) Antitumor activity of HKI-272, an orally active, irreversible inhibitor of the HER-2 tyrosine kinase. *Cancer Res.*, **64**(11), 3958-65.
- [76] Koyama, N.; Magario, N.; Yamamoto, Y.; Matsui, J.; Tsuruoka, A. (2008) [Anti-tumor effect of E7080, a novel angiogenesis inhibitor]. *Nippon Yakurigaku Zasshi*, **132**(2), 100-4.
- [77] Schmidt, M.; Bastians, H. (2007) Mitotic drug targets and the development of novel anti-mitotic anticancer drugs. *Drug Resist. Updat.*, **10**(4-5), 162-81.
- [78] Beyer, C. F.; Zhang, N.; Hernandez, R.; Vitale, D.; Lucas, J.; Nguyen, T.; Discafani, C.; Ayril-Kaloustian, S.; Gibbons, J. J. (2008) TTI-237: a novel microtubule-active compound with *in vivo* antitumor activity. *Cancer Res.*, **68**(7), 2292-300.
- [79] Kling, J. (2006) Bundling next-generation cancer therapies for synergy. *Nat. Biotechnol.*, **24**(8), 871-2.
- [80] Cabebe, E.; Wakelee, H. (2007) Role of anti-angiogenesis agents in treating NSCLC: focus on bevacizumab and VEGFR tyrosine kinase inhibitors. *Curr. Treat Options Oncol.*, **8**(1), 15-27.
- [81] Kamei, S.; Okada, H.; Inoue, Y.; Yoshioka, T.; Ogawa, Y.; Toguchi, H. (1993) Antitumor effects of angiogenesis inhibitor TNP-470 in rabbits bearing VX-2 carcinoma by arterial administration of microspheres and oil solution. *J. Pharmacol. Exp. Ther.*, **264**(1), 469-74.
- [82] Folkman, J. (2007) Angiogenesis: an organizing principle for drug discovery? *Nat. Rev. Drug Discov.*, **6**(4), 273-86.
- [83] Ning, S.; Laird, D.; Cherrington, J. M.; Knox, S. J. (2002) The antiangiogenic agents SU5416 and SU6668 increase the antitumor effects of fractionated irradiation. *Radiat. Res.*, **157** (1), 45-51.
- [84] Kim, S.; Yazici, Y. D.; Calzada, G.; Wang, Z. Y.; Younes, M. N.; Jasser, S. A.; El-Naggar, A. K.; Myers, J. N. (2007) Sorafenib inhibits the angiogenesis and growth of orthotopic anaplastic thyroid carcinoma xenografts in nude mice. *Mol. Cancer Ther.*, **6**(6), 1785-92.
- [85] Liu, X.; Yao, W.; Newton, R. C.; Scherle, P. A. (2008) Targeting the c-MET signaling pathway for cancer therapy. *Exp. Opin. Investig. Drugs*, **17**(7), 997-1011.
- [86] Albert, D. H.; Tapang, P.; Magoc, T. J.; Pease, L. J.; Reuter, D. R.; Wei, R. Q.; Li, J.; Guo, J.; Bousquet, P. F.; Ghoreishi-Haack, N. S.; Wang, B.; Bukofzer, G. T.; Wang, Y. C.; Stavropoulos, J. A.; Hartandi, K.; Niquette, A. L.; Soni, N.; Johnson, E. F.; McCall, J. O.; Bouska, J. J.; Luo, Y.; Donawho, C. K.; Dai, Y.; Marcotte, P. A.; Glaser, K. B.; Michaelides, M. R.; Davidsen, S. K. (2006) Preclinical activity of ABT-869, a multitargeted receptor tyrosine kinase inhibitor. *Mol. Cancer Ther.*, **5**(4), 995-1006.
- [87] Hotz, H. G.; Reber, H. A.; Hotz, B.; Sanghavi, P. C.; Yu, T.; Foitzik, T.; Buhr, H. J.; Hines, O. J. (2001) Angiogenesis inhibitor TNP-470 reduces human pancreatic cancer growth. *J. Gastrointest. Surg.*, **5**(2), 131-8.
- [88] Kim, J. H.; Lee, S. K.; Ki, M. H.; Choi, W. K.; Ahn, S. K.; Shin, H. J.; Hong, C. I. (2004) Development of parenteral formulation for a novel angiogenesis inhibitor, CKD-732 through complexation with hydroxypropyl-beta-cyclodextrin. *Int. J. Pharm.*, **272**(1-2), 79-89.
- [89] Moutouh-de Parseval, L. A.; Verhelle, D.; Glezer, E.; Jensen-Pergakes, K.; Ferguson, G. D.; Corral, L. G.; Morris, C. L.; Muller, G.; Brady, H.; Chan, K. (2008) Pomalidomide and lenalidomide regulate erythropoiesis and fetal hemoglobin production in human CD34+ cells. *J. Clin. Invest.*, **118**(1), 248-58.
- [90] Kumar, S.; Rajkumar, S. V. (2006) Thalidomide and lenalidomide in the treatment of multiple myeloma. *Eur. J. Cancer*, **42**(11), 1612-22.
- [91] Burke, P. A.; DeNardo, S. J.; Miers, L. A.; Lamborn, K. R.; Matzku, S.; DeNardo, G. L. (2002) Cilengitide targeting of alpha (v)beta(3) integrin receptor synergizes with radioimmunotherapy to increase efficacy and apoptosis in breast cancer xenografts. *Cancer Res.*, **62**(15), 4263-72.
- [92] Usui, T.; Kondoh, M.; Cui, C. B.; Mayumi, T.; Osada, H. (1998) Tryprostatin A, a specific and novel inhibitor of microtubule assembly. *Biochem. J.*, **333**(Pt 3), 543-8.
- [93] Graff, J. R.; McNulty, A. M.; Hanna, K. R.; Konicek, B. W.; Lynch, R. L.; Bailey, S. N.; Banks, C.; Capen, A.; Goode, R.; Lewis, J. E.; Sams, L.; Huss, K. L.; Campbell, R. M.; Iversen, P. W.; Neubauer, B. L.; Brown, T. J.; Musib, L.; Geeganage, S.; Thornton, D. (2005) The protein kinase Cbeta-selective inhibitor, Enzastaurin (LY317615.HCl), suppresses signaling through the AKT pathway, induces apoptosis, and suppresses growth of human colon cancer and glioblastoma xenografts. *Cancer Res.*, **65**(16), 7462-9.
- [94] Martiny-Baron, G.; Fabbro, D. (2007) Classical PKC isoforms in cancer. *Pharmacol. Res.*, **55**(6), 477-86.
- [95] Utz, I.; Gekeler, V.; Ise, W.; Beck, J.; Spitaler, M.; Grunicke, H.; Hofmann, J. (1996) Protein kinase C isoenzymes, p53, accumulation of rhodamine 123, glutathione-S-transferase, topoisomerase II and MRP in multidrug resistant cell lines. *Anticancer Res.*, **16**(1), 289-96.
- [96] Sharma, S.; Freeman, B.; Turner, J.; Symanowski, J.; Manno, P.; Berg, W.; Vogelzang, N. (2008) A phase I trial of PTK787/ZK222584 in combination with pemetrexed and cisplatin in patients with advanced solid tumors. *Invest. New Drugs*.
- [97] Sherman, S. I.; Wirth, L. J.; Droz, J. P.; Hofmann, M.; Bastholt, L.; Martins, R. G.; Licitra, L.; Eschenberg, M. J.; Sun, Y. N.; Juan, T.; Stepan, D. E.; Schlumberger, M. J. (2008) Motesanib diphosphate in progressive differentiated thyroid cancer. *N Engl. J. Med.*, **359**(1), 31-42.
- [98] Choueiri, T. K. (2008) Axitinib, a novel anti-angiogenic drug with promising activity in various solid tumors. *Curr. Opin. Investig. Drugs*, **9**(6), 658-71.
- [99] Ribatti, D.; Raffaghello, L.; Marimietri, D.; Cosimo, E.; Montaldo, P. G.; Nico, B.; Vacca, A.; Ponzoni, M. (2003) Fenretinide as an anti-angiogenic agent in neuroblastoma. *Cancer Lett.*, **197**(1-2), 181-4.
- [100] Moasser, M. M. (2007) Targeting the function of the HER2 oncogene in human cancer therapeutics. *Oncogene*, **26**(46), 6577-92.
- [101] Funahashi, Y.; Sugi, N. H.; Semba, T.; Yamamoto, Y.; Hamaoka, S.; Tsukahara-Tamai, N.; Ozawa, Y.; Tsuruoka, A.; Nara, K.; Takahashi, K.; Okabe, T.; Kamata, J.; Owa, T.; Ueda, N.; Haneda, T.; Yonaga, M.; Yoshimatsu, K.; Wakabayashi, T. (2002) Sulfonamide derivative, E7820, is a unique angiogenesis inhibitor suppressing an expression of integrin alpha2 subunit on endothelium. *Cancer Res.*, **62**(21), 6116-23.
- [102] Zou, H. Y.; Li, Q.; Lee, J. H.; Arango, M. E.; McDonnell, S. R.; Yamazaki, S.; Koudriakova, T. B.; Alton, G.; Cui, J. J.; Kung, P. P.; Nambu, M. D.; Los, G.; Bender, S. L.; Mroczkowski, B.; Christensen, J. G. (2007) An orally available small-molecule inhibitor of c-Met, PF-2341066, exhibits cytoreductive antitumor efficacy through antiproliferative and antiangiogenic mechanisms. *Cancer Res.*, **67**(9), 4408-17.
- [103] Dalrymple, S. L.; Becker, R. E.; Isaacs, J. T. (2007) The quinoline-3-carboxamide anti-angiogenic agent, tasquinimod, enhances the anti-prostate cancer efficacy of androgen ablation and taxotere without effecting serum PSA directly in human xenografts. *Prostate*, **67**(7), 790-7.
- [104] Million, R. P. (2008) Therapeutic area crossroads: anti-angiogenesis. *Nat. Rev. Drug Discov.*, **7**(2), 115-116.
- [105] Izumi, Y.; Xu, L.; di Tomaso, E.; Fukumura, D.; Jain, R. K. (2002) Tumour biology: herceptin acts as an anti-angiogenic cocktail. *Nature*, **416**(6878), 279-80.
- [106] Bock, F.; Onderka, J.; Dietrich, T.; Bachmann, B.; Kruse, F. E.; Paschke, M.; Zahn, G.; Cursiefen, C. (2007) Bevacizumab as a

- potent inhibitor of inflammatory corneal angiogenesis and lymphangiogenesis. *Invest. Ophthalmol. Vis. Sci.*, **48**(6), 2545-52.
- [107] Pegaptanib sodium (Macugen) for macular degeneration. *Med. Lett., Drugs Ther.*, **47** (1212), 55-6.
- [108] Zhu, W. H.; Guo, X.; Villaschi, S.; Francesco Nicosia, R. (2000) Regulation of vascular growth and regression by matrix metalloproteinases in the rat aorta model of angiogenesis. *Lab. Invest.*, **80**(4), 545-55.
- [109] Ferrario, A.; Chantrain, C. F.; von Tiehl, K.; Buckley, S.; Rucker, N.; Shalinsky, D. R.; Shimada, H.; DeClerck, Y. A.; Gomer, C. J. (2004) The matrix metalloproteinase inhibitor prinomastat enhances photodynamic therapy responsiveness in a mouse tumor model. *Cancer Res.*, **64**(7), 2328-32.
- [110] Dupont, E.; Falardeau, P.; Mousa, S. A.; Dimitriadou, V.; Pepin, M. C.; Wang, T.; Alaoui-Jamali, M. A. (2002) Antiangiogenic and antimetastatic properties of Neovastat (AE-941), an orally active extract derived from cartilage tissue. *Clin. Exp. Metastasis*, **19**(2), 145-53.
- [111] Medici, V.; Sturniolo, G. C. (2008) Tetrathiomolybdate, a copper chelator for the treatment of Wilson disease, pulmonary fibrosis and other indications. *IDrugs*, **11**(8), 592-606.
- [112] Juarez, J. C.; Betancourt, O., Jr.; Pirie-Shepherd, S. R.; Guan, X.; Price, M. L.; Shaw, D. E.; Mazar, A. P.; Donate, F. (2006) Copper binding by tetrathiomolybdate attenuates angiogenesis and tumor cell proliferation through the inhibition of superoxide dismutase 1. *Clin. Cancer Res.*, **12**(16), 4974-82.
- [113] Brem, S.; Grossman, S. A.; Carson, K. A.; New, P.; Phuphanich, S.; Alavi, J. B.; Mikkelsen, T.; Fisher, J. D. (2005) Phase 2 trial of copper depletion and penicillamine as antiangiogenesis therapy of glioblastoma. *Neurooncology*, **7**(3), 246-53.
- [114] Moriguchi, M.; Nakajima, T.; Kimura, H.; Watanabe, T.; Takashima, H.; Mitsumoto, Y.; Katagishi, T.; Okanou, T.; Kagawa, K. (2002) The copper chelator trientine has an antiangiogenic effect against hepatocellular carcinoma, possibly through inhibition of interleukin-8 production. *Int. J. Cancer*, **102**(5), 445-52.
- [115] Sparano, J. A.; Gray, R.; Giantonio, B.; O'Dwyer, P.; Comis, R. L. (2004) Evaluating antiangiogenesis agents in the clinic: the eastern cooperative oncology group portfolio of clinical trials. *Clin. Cancer Res.*, **10**(4), 1206-11.
- [116] Ferlini, C.; Gallo, D.; Scambia, G. (2008) New taxanes in development. *Exp. Opin. Investig. Drugs*, **17**(3), 335-47.
- [117] Donovan, D.; Vahdat, L. T. (2008) Etoposides: clinical update and future directions. *Oncology (Williston Park)*, **22**(4), 408-16; discussion 416, 421, 424 passim.
- [118] Gaya, A. M.; Rustin, G. J. (2005) Vascular disrupting agents: a new class of drug in cancer therapy. *Clin. Oncol. (R. Coll. Radiol.)*, **17**(4), 277-90.
- [119] Horsman, M. R.; Siemann, D. W. (2006) Pathophysiologic effects of vascular-targeting agents and the implications for combination with conventional therapies. *Cancer Res.*, **66**(24), 11520-39.
- [120] Siemann, D. W.; Shi, W. (2004) Efficacy of combined antiangiogenic and vascular disrupting agents in treatment of solid tumors. *Int. J. Radiat. Oncol. Biol. Phys.*, **60**(4), 1233-40.
- [121] Cooney, M. M.; van Heeckeren, W.; Bhakta, S.; Ortiz, J.; Remick, S. C. (2006) Drug insight: vascular disrupting agents and angiogenesis--novel approaches for drug delivery. *Nat. Clin. Pract. Oncol.*, **3**(12), 682-92.
- [122] Hait, W. N.; Rubin, E.; Alli, E.; Goodin, S., Tubulin Targeting Agents. **2007**, 2 (1), 1-18.
- [123] Pellegrini, F.; Budman, D. R. (2005) Review: tubulin function, action of antitubulin drugs, and new drug development. *Cancer Invest.*, **23**(3), 264-73.
- [124] Sengupta, S.; Thomas, S. A. (2006) Drug target interaction of tubulin-binding drugs in cancer therapy. *Exp. Rev. Anticancer Ther.*, **6**(10), 1433-47.
- [125] Hadfield, J. A.; Ducki, S.; Hirst, N.; McGown, A. T. (2003) Tubulin and microtubules as targets for anticancer drugs. *Prog. Cell Cycle Res.*, **5**, 309-25.
- [126] Correia, J. J.; Lobert, S. (2001) Physicochemical aspects of tubulin-interacting antimetabolic drugs. *Curr. Pharm. Des.*, **7**(13), 1213-28.
- [127] Tozer, G. M.; Kanthou, C.; Parkins, C. S.; Hill, S. A. (2002) The biology of the combretastatins as tumour vascular targeting agents. *Int. J. Exp. Pathol.*, **83**(1), 21-38.
- [128] Nguyen, T. L.; McGrath, C.; Hermone, A. R.; Burnett, J. C.; Zaharevitz, D. W.; Day, B. W.; Wipf, P.; Hamel, E.; Gussio, R. (2005) A common pharmacophore for a diverse set of colchicine site inhibitors using a structure-based approach. *J. Med. Chem.*, **48**(19), 6107-16.
- [129] Laura K. Shawver, k. E. L., T. Anne T. Fong, Gerald McMahon, Greg D. Plowman, Laurie M. Strawn. *Drug Discov. Today*, **1997**, 2 (2), 50-63.
- [130] Kim, D. W.; Lu, B.; Hallahan, D. E. (2004) Receptor tyrosine kinase inhibitors as anti-angiogenic agents. *Curr. Opin. Investig. Drugs*, **5**(6), 597-604.
- [131] Kerbel, R.; Folkman, J. (2002) Clinical translation of angiogenesis inhibitors. *Nat. Rev. Cancer*, **2**(10), 727-39.
- [132] Nicholson, R. I.; Gee, J. M.; Harper, M. E. (2001) EGFR and cancer prognosis. *Eur. J. Cancer*, **37** Suppl 4, S9-15.
- [133] Eskens, F. A. (2004) Angiogenesis inhibitors in clinical development; where are we now and where are we going? *Br. J. Cancer*, **90**(1), 1-7.
- [134] Qian, D. Z.; Wang, X.; Kachhap, S. K.; Kato, Y.; Wei, Y.; Zhang, L.; Atadja, P.; Pili, R. (2004) The histone deacetylase inhibitor NVP-LAQ824 inhibits angiogenesis and has a greater antitumor effect in combination with the vascular endothelial growth factor receptor tyrosine kinase inhibitor PTK787/ZK222584. *Cancer Res.*, **64**(18), 6626-34.
- [135] Fujita, K.; Asami, Y.; Tanaka, K.; Akita, M.; Merker, H. J. (2004) Anti-angiogenic effects of thalidomide: expression of apoptosis-inducible active-caspase-3 in a three-dimensional collagen gel culture of aorta. *Histochem. Cell Biol.*, **122**(1), 27-33.
- [136] Brewer, G. J. (2001) Copper control as an antiangiogenic anticancer therapy: lessons from treating Wilson's disease. *Exp. Biol. Med. (Maywood)*, **226**(7), 665-73.
- [137] Sun, L.; McMahon, G. (2000) Inhibition of tumor angiogenesis by synthetic receptor tyrosine kinase inhibitors. *Drug Discov. Today*, **5**(8), 344-353.
- [138] Giannakakou, P.; Gussio, R.; Nogales, E.; Downing, K. H.; Zaharevitz, D.; Bollback, B.; Poy, G.; Sackett, D.; Nicolaou, K. C.; Fojo, T. (2000) A common pharmacophore for epothilone and taxanes: molecular basis for drug resistance conferred by tubulin mutations in human cancer cells. *Proc. Natl. Acad. Sci. USA*, **97**(6), 2904-9.
- [139] Waldman, A.; Kritharides, L. (2003) The pleiotropic effects of HMG-CoA reductase inhibitors: their role in osteoporosis and dementia. *Drugs*, **63**(2), 139-52.
- [140] Mahadevan, V.; Malik, S. T.; Meager, A.; Fiers, W.; Lewis, G. P.; Hart, I. R. (1990) Role of tumor necrosis factor in flavone acetic acid-induced tumor vasculature shutdown. *Cancer Res.*, **50**(17), 5537-42.
- [141] Pang, J. H.; Cao, Z.; Joseph, W. R.; Baguley, B. C.; Ching, L. M. (1998) Antitumor activity of the novel immune modulator 5,6-dimethylxanthone-4-acetic acid (DMXAA) in mice lacking the interferon-gamma receptor. *Eur. J. Cancer*, **34**(8), 1282-9.
- [142] Yee, K. W.; Hagey, A.; Verstovsek, S.; Cortes, J.; Garcia-Manero, G.; O'Brien, S. M.; Faderl, S.; Thomas, D.; Wierda, W.; Kornblau, S.; Ferrajoli, A.; Albitar, M.; McKeegan, E.; Grimm, D. R.; Mueller, T.; Holley-Shanks, R. R.; Sahelijo, L.; Gordon, G. B.; Kantarjian, H. M.; Giles, F. J. (2005) Phase 1 study of ABT-751, a novel microtubule inhibitor, in patients with refractory hematologic malignancies. *Clin. Cancer Res.*, **11**(18), 6615-24.
- [143] Vacca, A.; Iurlaro, M.; Ribatti, D.; Minischetti, M.; Nico, B.; Ria, R.; Pellegrino, A.; Dammacco, F. (1999) Antiangiogenesis is produced by nontoxic doses of vinblastine. *Blood*, **94** (12), 4143-55.