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Review

Vascular disrupting agents

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Abstract—A clear definition for vascular targeting agents (VTAs) and vascular disrupting agents (VDAs) has separated the two as distinct methods of cancer treatment. VDAs differ from VTAs (antiangiogenesis drugs) in their mechanism of action. VTAs attempt to keep new blood vessels from forming and do not act on blood vessels that already feed existing tumors. In contrast, VDAs cause the vascular structure inside a solid tumor to collapse, depriving the tumor of blood and oxygen it needs to survive. Therefore, VDAs are an attractive way to approach the cancer problem by combating developed tumors. The following review discusses six small molecule VDAs, namely DMXAA, ZD6126, TZT1027, CA4P, AVE8062, and Oxi4503, their synthesis, biological mechanism of action, and current clinical status.

Contents

1. Introduction

The concepts behind VTAs as cancer therapeutics were described by Juliana Denekamp in the early 1980s.[1–3] The observation that the physical obstruction of the blood vessels of solid tumors led to tumor regressions in mice resulted in the proposal that VTAs might be created that pharmacologically cause occlusion of tumor vessels.[1–3] This proposal was later validated when it was shown that a toxin targeted by an antibody specific for tumor blood vessels caused tumor regressions in mice[1,4–6] and that antitubulin drugs have inherent VTA activity.[1,7,8]

Abbreviations: VTA, vascular targeting agent; VDA, vascular disrupting agent; TNF-α, tumor necrosis factor α; IFN, interferon; MTD, maximum tolerated dose; PK, pharmacokinetics; PD, pharmacodynamics; TBA, tubulin-binding agent; RhoA, ras homolog gene family (member A); GTP, guanosine triphosphate; GDP, guanosine diphosphate; GEF-H1, guanine exchange factor-H1; SAPK2, stress-activated protein kinase 2; mDia, diaphanous-related formins; GAPs, GTPase-accelerating proteins; GEFs, guanosine nucleotide exchange factors; MT, microtubule; CDI, *N*,*N*′-carbonydiimidazole; DEPC, diethyl phosphorocyanidate; DLT, dose-limiting toxicities; CL, clearance; AUC, area under the curve; Z, benzyloxycarbonyl.

Keywords: Vascular targeting agents; Vascular disrupting agents; Anticancer; Tubulin-binding agents.

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In recent years, a clear division has developed between VTAs and VDAs.[9–13] Two distinct groups of vascular-targeted therapies have evolved: antiangiogenic agents and vascular-disrupting approaches.[9] These differ in three key aspects: their physiologic target, the type or extent of disease that is likely to be susceptible, and the treatment scheduling.[9] Inhibitors of angiogenesis (VTAs) interfere with new vessel formation and therefore have a preventative action, require chronic administration, and are likely to be of particular benefit in early stage or asymptomatic metastatic disease.[9] VDAs target the established tumor blood vessels, resulting in tumor ischemia and necrosis.[9] These agents are therefore given acutely, show immediate effects, and may have particular efficacy against advanced disease.[9] It is therefore important to thoroughly understand the vascular targeting therapy being used to address the disease model.[9–13] VDAs operate by destroying the endothelium of solid tumors resulting in the death of tumor cells from lack of oxygen and nutrients leading to the occlusion of blood-transporting vessels as well as the capillary sprouts.[1,9] This halts blood flow in most of the vessels in the tumor, resulting in widespread necrosis of established tumors.[1,9] The topic of VDAs has been previously reviewed in various formats throughout the literature.[9–13]

VTAs have been divided into two types, small molecule and ligand-directed VTAs.[1] Today, it is accepted that six small molecules, initially classified as VTAs and currently in preclinical or clinical development, behave as VDAs.[9–13] The focus of this review will be on the synthesis, biological mechanism of action, and current clinical status of these six small molecule VDAs which include DMXAA, ZD6126, CA4P, AVE8062, TZT1027, and Oxi4503.

2. Small molecule vascular disrupting agents

VDAs differ from antiangiogenesis drugs (VTAs) in their mechanism of action. VTAs attempt to keep new blood vessels from forming and do not act on blood vessels that already feed existing tumors. In contrast, VDAs cause the vascular structure inside a solid tumor to collapse, depriving the tumor of blood and oxygen it needs to survive.[14]

It is well established that the blood vessels in tumors proliferate more rapidly than those in normal tissues.[15] Thus, simply targeting features of proliferating endothelium, or even newly formed vasculature, could achieve some selectivity for cancer treatment in adults.[15] It is believed that the reason newly formed endothelial cells are more sensitive than more mature cells is that the latter have a more highly developed actin cytoskeleton, which maintains the cell shape despite depolymerization of the tubulin cytoskeleton.[15,16] Clearly, rapid changes in endothelial cell shape in vivo will dramatically alter capillary blood flow, expose basement membrane, and, as a result, induce hemorrhage and coagulation.[15]

With the realization that the tumor vascular supply is extremely important for both maintaining tumor growth and controlling the tumor environment, and thus influencing tumor response to nonsurgical treatments, there has been a reemergence of the concept of specifically targeting the tumor vasculature for therapy.[17–19] A number of new drug-based VDAs have been developed that are believed to be more efficient, less toxic, and several of them are currently undergoing clinical testing.[9–13,17,21–25]

Extensive preclinical testing of these new agents has demonstrated that they can induce substantial reductions in tumor blood flow in a variety of transplanted and spontaneous murine solid tumors, and that these reductions are maintained for sufficient time periods to significantly increase tumor necrosis.[12,16–20]

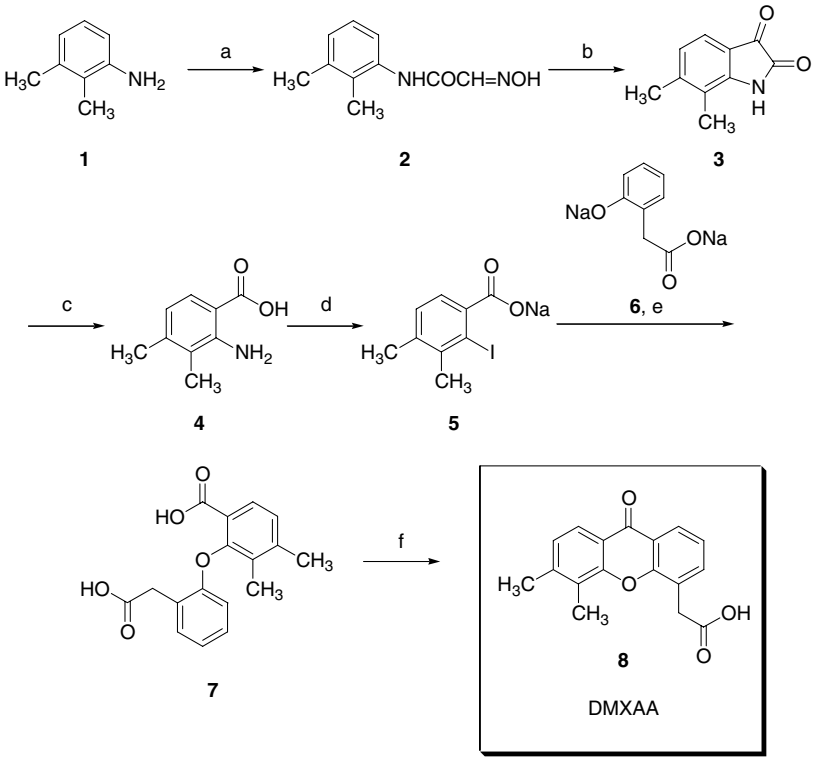
2.1. Flavonoids (DMXAA)

The synthesis of DMXAA (**8**) is shown in Scheme 1.[26]

DMXAA (**8**) induces cytokines [especially tumor necrosis factor α (TNF-α)] in humans.[26] TNF is a natural body protein with anticancer effects.[27] It is produced in the body in response to the presence of toxic substances.[27] Unfortunately, the inherent toxicity of TNF-α in normal tissue has precluded its systemic administration.[28] One strategy to improve its antitumor selectivity, although clearly limited, is to deliver TNF-α directly to the tumor.[28] An alternative approach would be to induce the synthesis of TNF-α in tumors.[23] DMXAA (**8**) induces a shutdown of the tumor vasculature similar to that seen after exposure to TNF-α, suggesting a possible mechanistic link to the cytokine.[28] Several derivatives of this flavone have been synthesized and biologically evaluated.[29]

Amplification of DMXAA (**8**) activity by second signals present in the tumor microenvironment may explain its selectivity for tumor vasculature.[1,30] Several studies have implicated the induction of IFN (interferon)-inducible protein 10,[1,31] serotonin,[1,32] and nitric oxide,[1,33] in the antitumor effects of DMXAA (**8**).[1] In spite of the positive vascular targeting effects of DMXAA (**8**), some tumor cells can survive following treatment and can be a source of tumor regrowth.[34] This suggests that the effective application or administration of DMXAA (**8**) would be useful when combined with other anticancer treatments.[34] DMXAA (**8**) indeed has also been shown to augment the antitumor effects of melphalan,[1,35] cisplatin,[1,36] cyclophosphamide,[1,36] paclitaxel,[1,37] radioimmunotherapy,[1,38] radiation,[1,39,40] immunotherapy,[1,41] and hyperthermia.[1,42,43]

A Phase I clinical trial was conducted to examine the toxicity, maximum tolerated dose (MTD), pharmacokinetics (PK), and pharmacodynamics (PD) of DMXAA (**8**). A secondary objective were to assess its antitumor efficacy. A total of 63 patients received 161 courses of DMXAA (**8**) over 19 dose levels ranging from 6 to 4900 mg/m^2. DMXAA (**8**) was well-tolerated at lower doses and no drug-related myelosuppression was seen. Rapidly reversible dose-limiting toxicities were observed at 4900 mg/m^2, including confusion, tremor, slurred speech, visual disturbance, anxiety, urinary incontinence, and possible left ventricular failure. Transient



Scheme 1. Reagents: (a) $Cl_3CCH(OH)_2$, Na_2SO_4, H_2O, $(NH_2OH)_2{\cdot}H_2SO_4$; (b) H_3CSO_3H; (c) H_2O_2, KCl, KOH; (d) $NaNO_2$, KI; (e) tris[2-(2-methoxyethoxy)ethyl] amine, CuCl; (f) H_2SO_4.

prolongation of the corrected cardiac QT interval was seen in 13 patients evaluated at doses of 2000 mg/m^2 and above. A patient with metastatic cervical carcinoma achieved an unconfirmed partial response at 1100 mg/m^2, progressing after eight courses. These results indicate that DMXAA (**8**) has antitumor activity at well-tolerated doses.[44]

DMXAA (**8**) is currently in Phase II clinical trials in the United States for the treatment of prostate cancer (sponsored by Antisoma Research; AS1404).[45] In this trial a DMXAA/docetaxel regimen is being compared with docetaxel alone.[45] Furthermore, DMXAA (**8**) is undergoing three additional Phase II clinical trials in combination with carboplatin and paclitaxel for the treatment of lung, ovarian, and prostate cancer.[46] Both of these trials are being carried out in Europe, Australia, and New Zealand.[46]

2.2. Tubulin-binding agents

Tubulin-binding agents (TBAs) which bind to either the colchicine or vinblastine sites cause microtubule depolymerization. The TBA-induced depolymerization of microtubules activates the small guanosine nucleotide triphosphatase, RhoA, which is an intracellular coordinator of the cytoskeletal rearrangement of microtubules and actin.[12,47] RhoA-GDP is activated by guanosine nucleotide exchange factors (GEFs) that promote the exchange of GTP for GDP. While the exact mechanism by which microtubule depolymerization activates RhoA has not yet been established, binding to microtubules inhibits a number of proteins such as GEF-H1. Upon dissociation from microtubules, GEF-H1 can activate RhoA.[12,48,49] RhoA-GTP in turn can activate a number of downstream effectors such as RhoA kinase which is able to phosphorylate myosin resulting in increased actinomyosin contractility.[12,50,51] (Fig. 1).

2.2.1. ZD6126. The synthesis of ZD6126 (**12**) from colchicine is shown in Scheme 2.[52,53]

ZD6126 (**12**) is a phosphate prodrug of the tubulin-binding agent *N*-acetylcholchinol (NAC), an inhibitor of tubulin polymerization.[52] After administration of ZD6126 (**12**) and release of NAC by phosphatases, NAC binds to and destabilizes tubulin, leading to selective contraction (rounding up) of the proliferating, immature endothelial cells lining the tumor blood vessels.[52] This results in disruption of the endothelial cell monolayer lining the tumor vessels and leads to blood vessel congestion, loss of blood flow, and consequent tumor cell death due to nutrient deprivation and buildup of toxic waste products.[52]

Despite a large reduction in vascular volume, induction of extensive necrosis in tumors, and a reduced tumor cell yield in a clonal excision assay observed after a single dose treatment of ZD6126 (**12**), a thin viable rim of tumor cells remained adjacent to normal tissue.[52,54] The surviving tumor cells are problematic and can result in regeneration of the tumor, however combining ZD6126 (**12**) with cisplatin,[55] taxol,[56] or radiation[57] has been shown to eliminate the viable tumor rim and

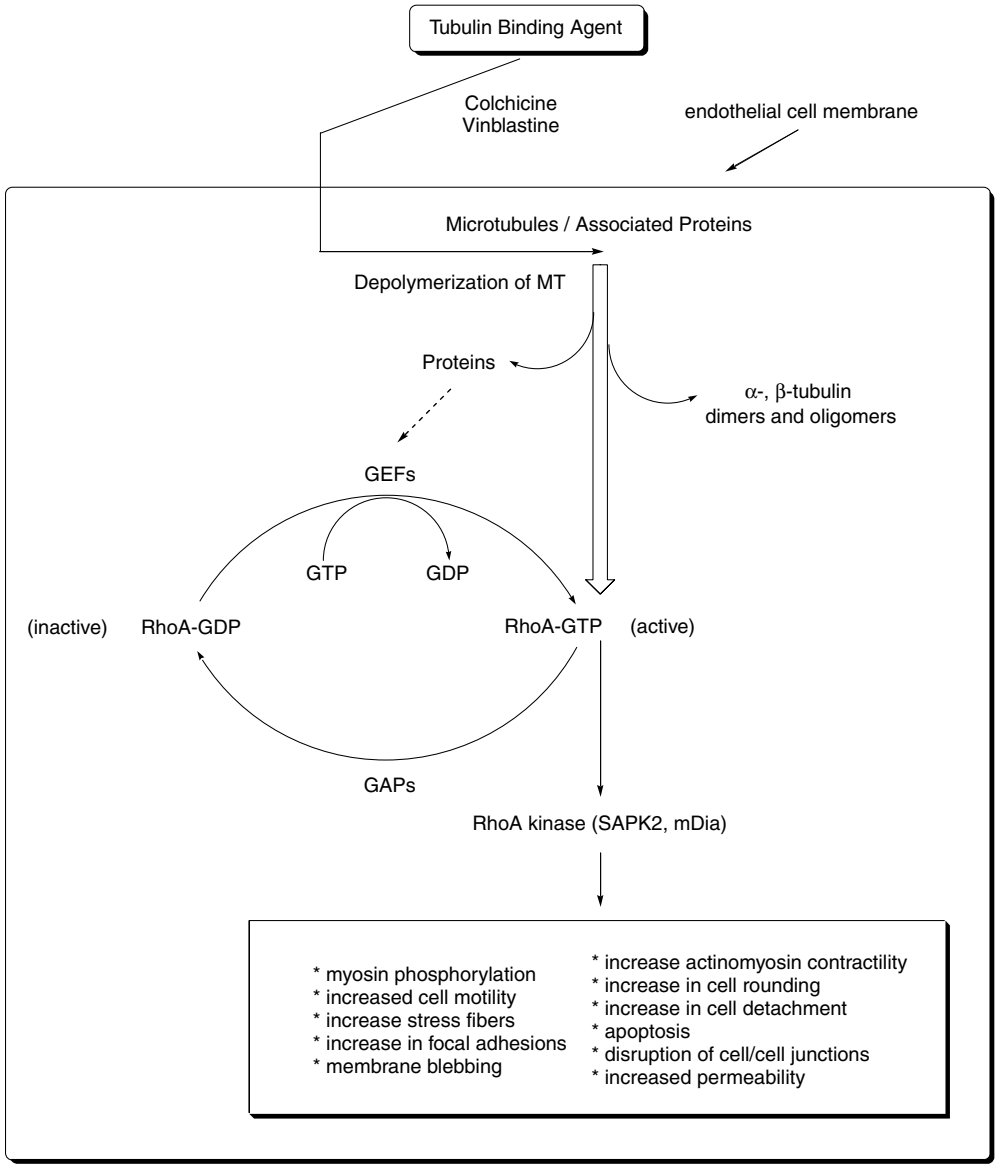


Figure 1. Proposed mechanism of vascular disruption by tubulin-binding agents. Microtubule (MT) depolymerization results in the release of microtubule-associated proteins leading to activation of RhoA and its downstream effectors such as RhoA kinase. The resulting cytoskeletal rearrangements lead to rapid vascular shutdown.[12]

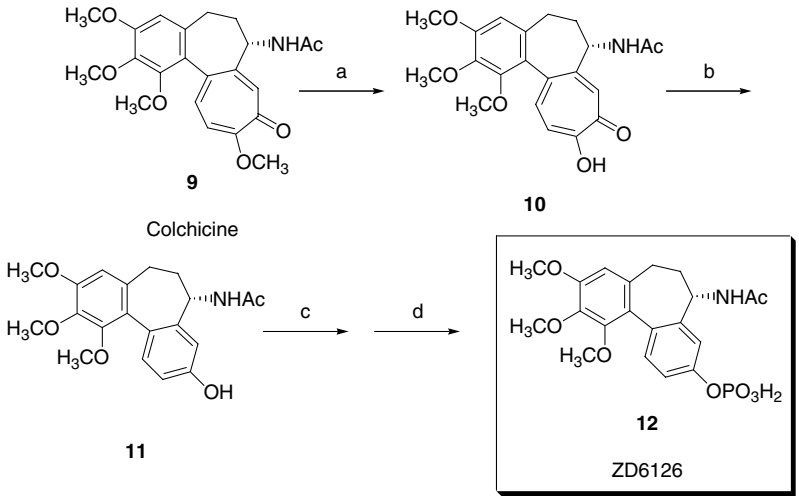
significantly enhance the activity of ZD6126 (**12**), resulting in tumor regression.[58]

In a Phase I clinical trial, 27 patients were treated with 5–112 mg/m^2 ZD6126 (**12**). In this study, ZD6126 (**12**) was converted to the ZD6126-phenol (**11**). The $t_{1/2}$ was 2–3 h and the AUC and C_{max} levels were dependent on ZD6126 (**12**) dose. Adverse events (10% of the patients) were anorexia, constipation, dyspnea, fatigue, headache, nausea, pain, and vomiting. Adverse effects did not appear to be dose related.[59]

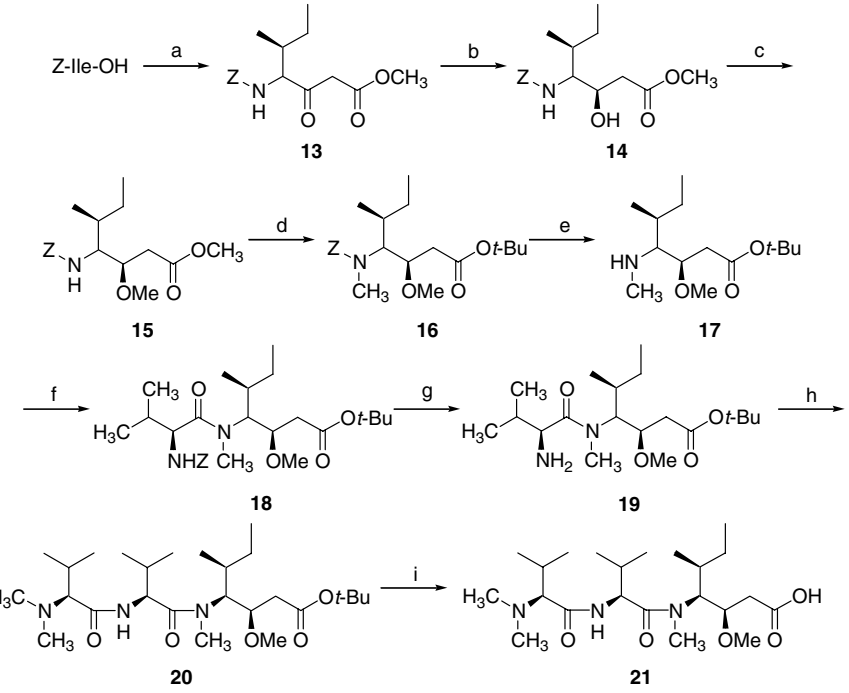
ZD6126 (**12**) was in Phase II clinical trials in the United States for the treatment of metastatic renal cell carcinoma (sponsored by AstraZeneca),[60] and an additional separate trial incorporating combination therapy with oxaliplatin, 5-fluorouracil, and leucovorin in subjects with metastatic colorectal cancer.[61] Recent developments have halted these trials, due to toxicity problems (cardiac events) with ZD6126 (**12**).[62]

2.2.2. TZT1027. The synthesis of TZT1027 (auristatin PE, soblidotin, **25**) is shown in Schemes 3 and 4.[63,64]

TZT1027 (**25**) is a synthetic derivative of the cytotoxic pentapeptide dolastatin 10, which exhibits inhibitory effects on the growth of human tumor cells in vitro[63] and murine leukemia cells in vivo.[64,65] TZT1027 (**25**) acts by inhibiting tubulin polymerization and has demonstrated potent and broad-spectrum antitumor activity against human tumor xenografts in nude mice, including refractory ovarian, and renal cancers.[65,66] The agent is a mitotic spindle poison, that inhibits microtubule assembly by interacting with tubulin in the Vinca alkaloid-binding domain.[67] More detailed investigation of its mode of action indicated both a high-affinity and a



Scheme 2. Reagents: (a) 1 M HCl; (b) H_2O_2; (c) di-*tert*-butyldiethylphosphoramidite, tetrazole followed by *m*-CPBA; (d) TFA.

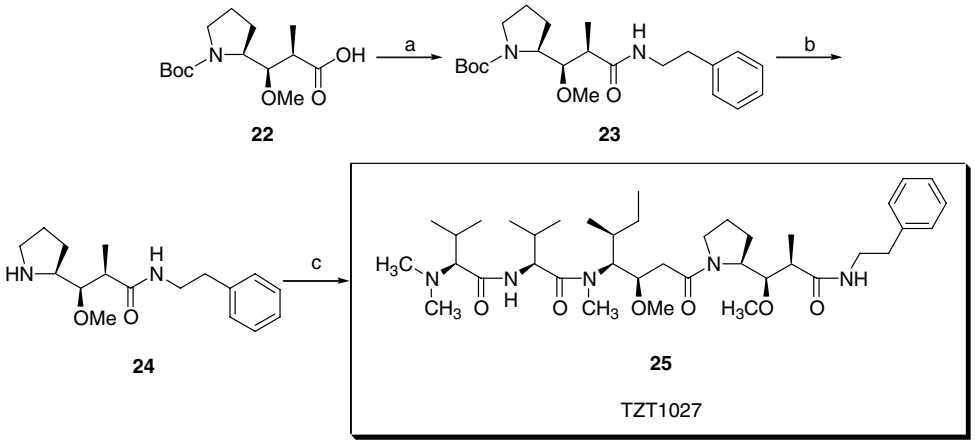


Scheme 3. Reagents: (a) CDI, $MgCl_2$, malonic acid monomethyl ester potassium salt; (b) $NaBH_4$; (c) MeI, Ag_2O; (d) i—NaOH; ii—isobutylene; (e) H_2, Pd/C; (f) Z-Val-OH, DEPC; (g) H_2, Pd/C; (h) *N*,*N*-dimethyl valine, DEPC; (i) CF_3CO_2H.

low-affinity-binding site on tubulin.[65] Further studies into the mode of action of TZT1027 (**25**) have revealed that it induces DNA fragmentation and apoptotic chromatin condensation, and that the tumor cells are arrested in the G_2/M phase of the cell cycle.[68] The induction of apoptosis by TZT1027 (**25**) is independent of the presence or absence of caspase-3 or bcl-2.[68] According to in vitro studies performed with tumor tissue obtained from patients with lung and renal cell cancers, the activity of TZT1027 (**25**) is influenced less by the p53 mutation status than DNA-damaging agents, which may be very relevant for many clinical cancers.[69]

Similar to dolastatin 10, TZT1027 (**25**) seems to have a unique antitumoral vascular activity resulting in the collapse of the tumor vasculature after exposure to the drug that might potentate the direct antitumor effect due to the antimicrotubule activity of the drug.[70,71] TZT1027 (**25**) has been reported to show both potent cytotoxicity against tumor cells and anti-vascular effects.[72] It is these characteristics which make TZT1027 (**25**) effective in single agent administration, unlike some agents which allow for tumor regrowth.[72]

In a Phase I clinical trial 17 patients received a total of >70 courses. The objectives of this trial were to assess the dose-limiting toxicities (DLT), to determine the MTD, and to study the pharacokinetics of TZT1027 (**25**) when given iv over 60 min on day 1 and 8 every 3 weeks to patients with advanced solid tumors. The stopping dose was reached at 2.7 mg/m^2, with neutropenia and infusion arm pain as DLT. Neutropenia was not



Scheme 4. Reagents: (a) 2-phenylethylamine, DEPC; (b) TFA; (c) **21**, DEPC.

complicated by fever. Over all dose levels, eight patients experienced pain in the infusion arm 1 to 2 days after administration of the drug, which seemed ameliorated by adding additional flushing after drug administration. Other side effects included nausea, vomiting, diarrhea, and fatigue. One partial response lasting >54 weeks was observed in an extensively pretreated patient with metastatic liposarcoma. The pharmacokinetics of TZT1027 (**25**) suggested linearity over the dose ranges. No correlation between body surface area and absolute clearance (CL) of TZT1027 (**25**) was established vindicating that a flat dosing regimen might be used in the future. A correlation was observed between the percentage decrease in neutrophil count and the AUC of TZT1027 (**25**).[71]

A Phase II clinical trial has also been completed within the United States, sponsored by Daiichi Pharmaceuticals and the National Cancer Institute for TZT1027 (**25**) which studied the effectiveness of this drug in treating patients who have advanced or metastatic soft tissue sarcoma.[72] Furthermore, TZT1027 (**25**) was in two clinical trials (Phases I and II) within the United States, sponsored by Daiichi Pharmaceuticals. Both trials are now suspended.[73,74] The Phase I trial was studying the side effects and best dose of TZT1027 (**25**) and gemcitabine in treating patients with locally advanced or metastatic solid tumors.[73] The Phase II trial was studying the effectiveness of TZT1027 (**25**) in treating patients who have progressive locally advanced or metastatic non-small cell lung cancer.[74] Teikoku Hormone Manufacturing Company, which holds the rights to TZT1027 (**25**), ended their agreement with Daiichi Pharmaceuticals in May of 2005, and are seeking a new partner for further clinical research.[75,76] In addition, on October 1, 2005 Teikoku Hormone Manufacturing Company and Grelan Pharmaceutical Company merged to form ASKA Pharmaceutical Company.[77,78]

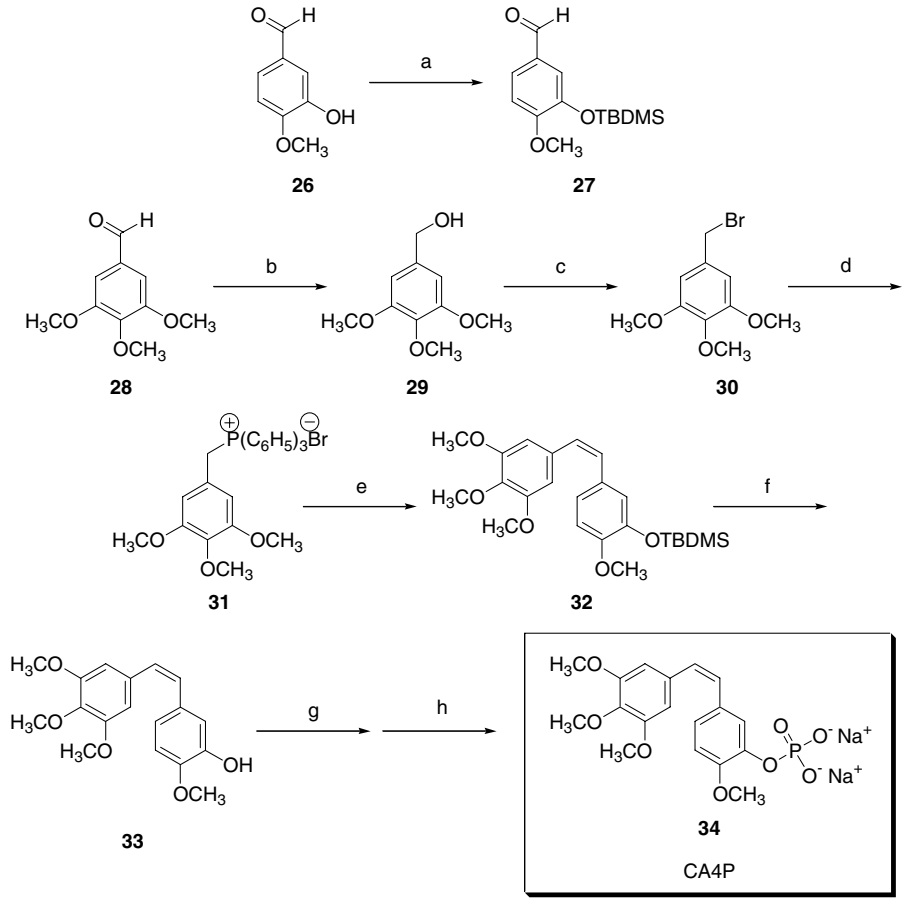
2.2.3. CA4P. The synthesis of the combretastatin A-4 prodrug (Oxi2021, CA4P, **34**) is shown in Scheme 5.[79–81]

CA4P (**34**) is a phosphate prodrug of the tubulin-binding agent combretastatin A-4 (CA4, **33**), an inhibitor of tubulin polymerization.[82] Systemic administration of CA4P (**34**) causes rapid and selective vascular shutdown in a range of human xenografted and rodent tumors.[83] Dephosphorylation of CA4P (**34**) by endogenous phosphatases yields CA4 (**33**), which has a high-affinity for tubulin at or near the colchicine-binding site,[83–85] causing depolymerization of tubulin dimers in the cellular cytoskeleton.[83] The sensitivity of the immature tumor vasculature to CA4P (**34**) probably relates to not only differences between newly formed endothelial cells but also to characteristics of the tumor microcirculation, such as high interstitial fluid pressure, pro-coagulant status, vessel tortuosity, and heterogeneous blood flow distribution.[15,16,86]

CA4P (**34**) significantly reduces vascular function, even at doses down to one-tenth the MTD.[15] It is of interest that, despite the extensive cell kill observed after the vascular shutdown observed with CA4P (**34**), no significant growth retardation is seen.[15] This has been attributed to rapid regrowth from the rim of viable cells surviving at the tumor periphery.[15,87–89] In order to combat these tumor cells which remain CA4P (**34**) has also been studied extensively in combination therapies with conventional chemotherapeutic agents such as cisplatin,[86] taxol,[86] doxorubicin,[90] and 5-fluorouracil,[91] as well as radiation.[92]

In a Phase I clinical trial 34 patients received 167 infusions of CA4P (**34**) over a four week period. CA4P (**34**) was rapidly converted to CA4 (**33**). CA4P (**34**) was well-tolerated in 14 of 16 patients at 52 or 68 mg/m^2 (doses at which the tumor blood flow reduction has been recorded). The only toxicity that possibly was related to the drug dose up to 40 mg/m^2 was tumor pain. Dose-limiting toxicity was reversible ataxia at 114 mg/m^2, vasovagal syncope and motor neuropathy at 88 mg/m^2, and fatal ischemia in previously irradiated bowel at 52 mg/m^2. Other drug-related toxicities seen in more than one patient were pain, lymphopenia, fatigue, anemia, diarrhea, hypertension, hypotension, vomiting, visual disturbance, and dyspnea.[93]

CA4P (**34**) is currently in three Phase II clinical trials in the United States. The first clinical trial involves the treatment of advanced solid tumors using CA4P (**34**)



Scheme 5. Reagents: (a) TBDMSCl; (b) $LiAlH_4$; (c) PBr_3; (d) $P(PPh_3)_3$; (e) i—*n*-BuLi; ii—**27**; iii—separation of *Z*-isomer; (f) TBAF; (g) $(BnO)_2P(O)H$; (h) i—TMSCl, NaI; ii—$NaOCH_3$.

in combination with the chemotherapy drugs, carboplatin and paclitaxel (sponsored by Oxigene).[94] Furthermore, CA4P (**34**) is also in two Phase II clinical trials under the sponsorship of the National Cancer Institute (NCI) to address both the ability of CA4P (**34**) to stop the growth of anaplastic thyroid cancer by stopping blood flow to the tumor as a single agent,[95] and in combination therapy with doxorubicin, cisplatin, and radiation therapy.[96] To date there have been nine clinical trials involving CA4P (**34**) worldwide, either as a single agent or in combination therapy.[97,98]

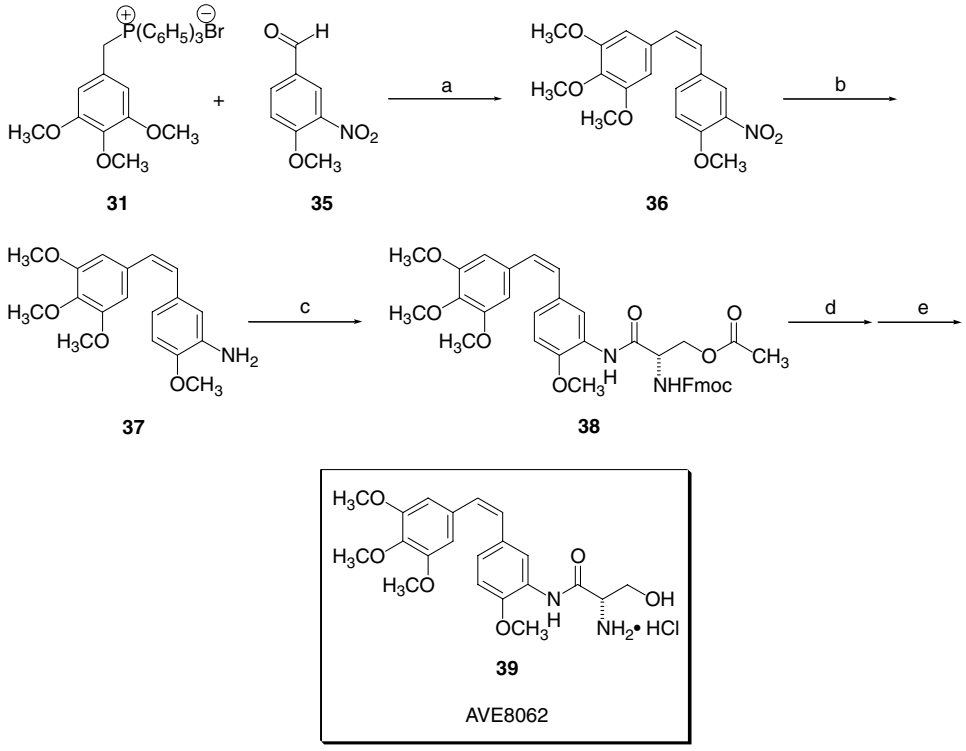
2.2.4. AVE8062. The synthesis of the AVE8062 (AC7700, **39**) is shown in Scheme 6.[99,100]

AVE8062 (**39**) is the serine prodrug of the TBA CA4 (**33**). The parent compound is released upon exposure to amino peptidase.[100] It is interesting to note that AVE8062 (**39**) was found to have more powerful tumor blood flow (TBF) stasis effects[101,102] and antitumor effects compared with CA4P (**34**).[102,103] AVE8062 (**39**) causes shape changes in proliferating endothelial cells, rapid shutdown of tumor blood flow, and extensive necrosis in experimental tumor models.[1,10,104] However, despite the strong tumor-suppressing qualities of AVE8062 (**39**), it does not produce an immediate reduction in tumor size upon administration.[105]

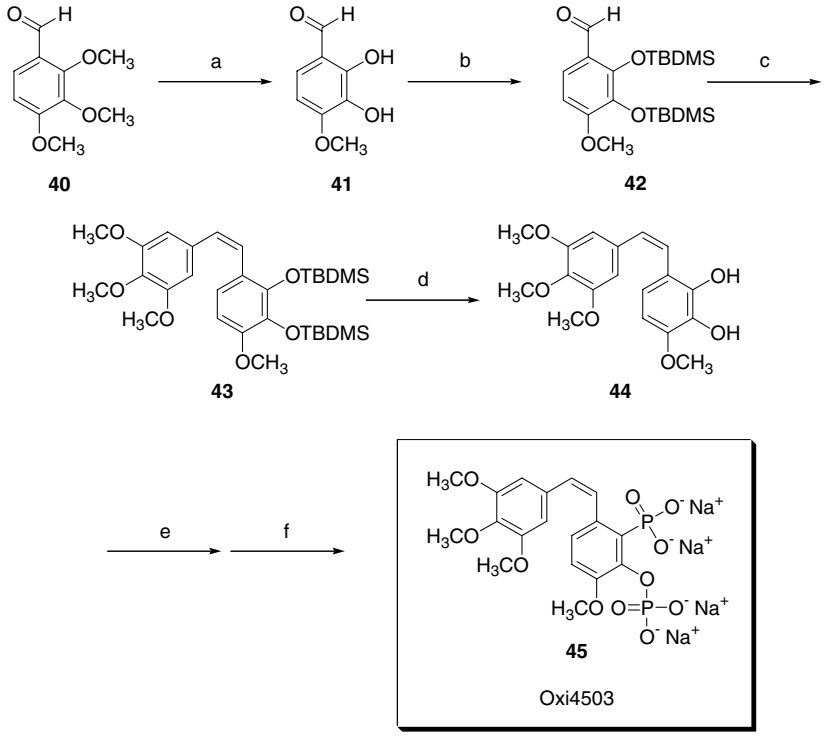
AVE8062 (**39**), licensed from Ajinomoto Co., Inc. in July of 2001 by Aventis Pharma Ltd (Sanofi-Aventis) is currently undergoing Phase I clinical studies in Europe and the United States for patients with solid tumors although no details have been published to date.[106,107]

2.2.5. Oxi4503. The synthesis of the combretastatin A-1 prodrug (Oxi4503, CA1P, **45**) is shown in Scheme 7.[108]

Oxi4503 (**45**), the prodrug of the potent tubulin-binding agent CA1 (**44**)[109], behaves in a similar manner when compared to the CA4P (**34**) regarding its dephosphorylation after administration.[108] However, the preclinical evaluation of Oxi4503 (**35**) shows that not only is it a much more potent agent than CA4P (**34**), but it can also induce tumor growth delays and regressions when used as a single agent. This enhanced activity was unexpected based on the in vitro data for tubulin-binding and for the inhibition of cell proliferation for the active parent drug, CA1 (**44**). As regressions are observed, it indicates that Oxi4503 (**45**), in addition to the vascular effects, is also directly attacking the remaining viable cells at the rim of the tumor mass. One possible explanation for this unanticipated activity is that it is metabolized in vivo to a reactive and cytotoxic *o*-quinone. Supportive evidence has shown that CA1 (**44**) is metabolized by tumor tissue to an agent that covalently



Scheme 6. Reagents and conditions: (a) i—NaH toluene, rt; ii—separation of *Z*-isomer; (b) Zn, AcOH, rt; (c) Fmoc-L-Ser(Ac)-OH, DCC, $HOBt{\cdot}H_2O$, DMF; (d) 2 N NaOH (aq); (e) 4 N HCl/dioxane.



Scheme 7. Reagents: (a) BCl_3; (b) TBDMSCl; (c) i—**31**; ii—**42**; iii—separation of the *Z*-isomer; (d) 48% HBr/KF or TBAF; (e) $(BnO)_2P(O)H$; (f) i—TMSCl, NaI; ii—$NaOCH_3$.

binds to the cellular contents of the tumor.[97,110] Recent positive preclinical reports on Oxi4503 (**45**) have prompted its further evaluation as a VDA.[111]

Oxi4503 (**45**) is currently undergoing Phase I clinical studies for patients with advanced cancer in England (sponsored by Oxigene).[9]

3. Conclusion

This review has provided a summary of six of the small molecule vascular targeting agents currently of interest. It is clear that small molecule VDAs are attractive because of their specific targeting of the tumor vascular system. Of particular interest is the fact that both TZT1027 (**25**) and Oxi4503 (**35**), when compared to the other small molecule VDAs discussed in this review, have the ability to eliminate all of the tumor cells present as a single agent. Future progress including advanced clinical trials will enable these agents to reach cancer patients either as single agents or in combination therapy.

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Biographical sketch

Dr. Lippert was born on March 25, 1972. He received his BA degree in 1994 from the University of Southern Maine in chemistry. Then in 1999 he received his Ph.D in organic chemistry at Arizona State University under the supervision of Professor George R. Pettit, where he worked on the synthesis of natural product anticancer agents at the Cancer Research Institute (CRI). Dr. Lippert was involved in the development of a potent vascular targeting agent, the combretastatin A-1 prodrug, which is now in Phase I clinical trials in England. After a one year postdoctoral assignment at the CRI, where he continued working on the synthesis of anticancer agents, he joined the Medicinal Chemistry Department at Albany Molecular Reseach, Inc. (AMRI) in Albany, NY. While at AMRI, Dr. Lippert has worked mainly on CNS and oncology projects. His research interests include the synthesis of natural products, peptides, peptidomimetics, and biologically active synthetic targets.