

# The Vascular Disrupting Agent STA-9584 Exhibits Potent Antitumor Activity by Selectively Targeting Microvasculature at Both the Center and Periphery of Tumors

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**Abstract**

Vascular disrupting agents (VDAs) are an emerging class of therapeutics targeting the existing vascular network of solid tumors. However, their clinical progression has been hampered because of limited single-agent efficacy, primarily caused by the persistence of surviving cells at the well perfused “viable rim” of tumors, which allows rapid tumor regrowth to occur. In addition, off-target adverse events, including cardiovascular toxicities, underscore a need for compounds with improved safety profiles. Here, we characterize the mechanism of action, antitumor efficacy, and cardiovascular safety profile of (S)-2-amino-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl)-3-phenylpropanamide hydrochloride (STA-9584), a novel tubulin-binding VDA. In vitro, 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)aniline (STA-9122) (active metabolite of STA-9584) displayed increased potency relative to other tubulin-binding agents and was highly cytotoxic to tumor cells. STA-9584 induced significant tumor regressions in prostate and breast xenograft models in vivo and, in an aggressive syngeneic model, demonstrated superior tumor growth inhibition and a positive therapeutic index relative to combretastatin A-4 phosphate (CA4P). It is noteworthy that histological analysis revealed that STA-9584 disrupted microvasculature at both the center and periphery of tumors. Compared with CA4P, STA-9584 induced a 73% increase in central necrotic area, 77% decrease in microvasculature, and 7-fold increase in tumor cell apoptosis in the remaining viable rim 24 h post-treatment. Ultrasound imaging confirmed that STA-9584 rapidly and efficiently blocked blood flow in highly perfused tumor regions. Moreover, cardiovascular effects were evaluated in the Langendorff assay and telemetered dogs, and cardiovascular toxicity was not predicted to be dose-limiting. This bioactivity profile distinguishes STA-9584 from the combretastatin class and identifies the compound as a promising new therapeutic VDA candidate.

**Footnotes**

- Article, publication date, and citation information can be found at <http://jpet.aspetjournals.org>. <http://dx.doi.org/10.1124/jpet.112.196873>.

-  The online version of this article (available at <http://jpet.aspetjournals.org>) contains supplemental material.

**ABBREVIATIONS:**
**VDA**
*vascular disrupting agent*
**CA4**
*combretastatin A-4*
**CA4P**
*CA4 phosphate*
**ASA404**
*5,6-dimethylxanthenone-4 acetic acid*
**MTD**
*maximal tolerated dose*
**NSCLC**
*non-small-cell lung cancer*
**TUNEL**
*terminal deoxynucleotidyl transferase dUTP nick-end labeling*
**HUVEC**
*human umbilical vein endothelial cell*
**DMSO**
*dimethyl sulfoxide*
**PBMC**
*peripheral blood mononuclear cell*
**SCID**
*severe combined immunodeficient*
**LVP<sub>dev</sub>**
*developed left ventricular pressure*
**QTc**
*corrected QT interval*
**T/C**
*treated/control*
**Oxi4503**
*[3-methoxy-2-phosphonatoxy-6-[(Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl] phosphate*
**AVE8062**
*(2S)-2-amino-3-hydroxy-N-[2-methoxy-5-[(Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl]propanamide*
**AVE8063**
*(Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)aniline*
**MN-029**
*methyl-[5-[[4-[(2S)-2-aminopropanoyl]amino]phenyl]sulfonyl]-1H-benzimidazol-2-yl]carbamate monohydrochloride*
**ZD6126**
*N-acetylcochinel-O-phosphate*
**NPI-2358**
*(3Z,6Z)-3-[[5-(tert-butyl)-1H-imidazol-4-yl]methylene]-6-(phenylmethylene)-2,5-piperazinedione*
**CYT997**
*N-ethyl-N'-[2-methoxy-4-[5-methyl-4-[[[(1S)-1-(3-pyridinyl)butyl]amino]-2-pyrimidinyl]phenyl]urea*
**STA-9122**
*2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)aniline*
**STA-9584**
*(S)-2-amino-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl)-3-phenylpropanamide hydrochloride*
**ZD6216**
*(5S)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5H-dibenzo[a,c]cyclohepten-3-yl dihydrogenphosphate.*
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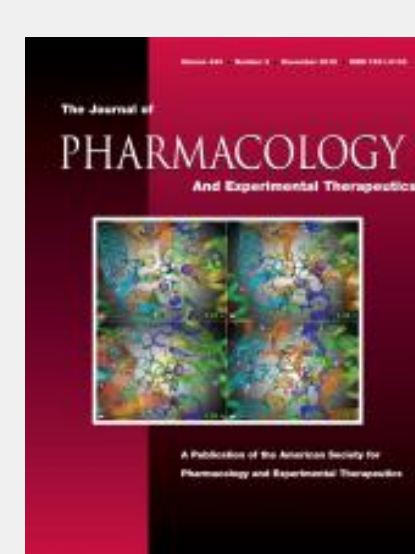
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