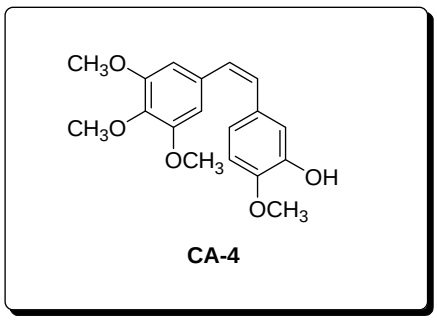
# Novel B-Ring Modified Combretastatin A-4 Analogues: Synthesis and Cytotoxic Activity

Mariana Gerova[1], Lyudmila Ivanova[2], Boris Chivachev[3], Margarita Apostolova[2] and Ognyan Petrov[1]

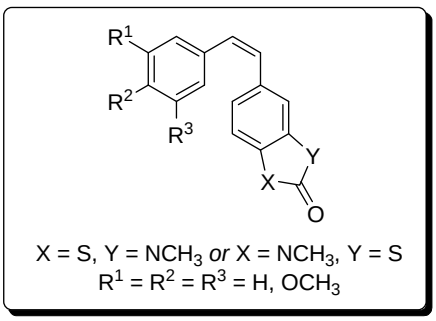
[1] Faculty of Chemistry, University of Sofia, 1126 Sofia, Bulgaria.
*E-mail:* mgerova@chem.uni-sofia.bg
[2] Institute of Molecular Biology, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria.
[3] Central Laboratory for Mineralogy and Crystallography, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria.

Combretastatins are a group of compounds with antimitotic activity isolated from the bark of the South African tree Combretum caffrum. The most promising of these natural products is combretastatin A-4 (CA-4). The CA-4 is a very attractive compound because of its simple structure and high cytotoxic activity against a variety of human cancer cell lines. The stilbene CA-4 is a potent anti-cancer drug and represents a new class of therapeutic compounds known as vascular disrupting agents.

We designed and synthesized 12 novel heterocyclic analogues of CA-4 containing benzothiazolone moiety, which could have important pharmacological properties. Compounds with general structure (**I**) were obtained in good yields and were evaluated for their cell growth inhibition activity on different human cell lines (HepG2, K562 and EA hy.926). The 3-methyl-6-(3,4,5-trimethoxystyryl)-2(3*H*)-benzothiazolone displayed potent cytotoxic activity against HepG2 cells with $IC_{50}$ values in the nanomolar range. The ability of benzothiazolones to inhibit tubulin polymerization has been evaluated by fluorescent microscopy and flow-cytometry. The results showed that HepG2 were arrested at a pro-metaphase stage, with formation of condensed chromosomes and unnormal spindle formation. The arrest of cell cycle at G2/M phase also triggered the apoptotic cell death in HepG2 line. The heterocyclic analogues of CA-4 showed a potent antitumor activity and it is important because new anticancer therapeutics may emerge from these efforts.




**CA-4**




X = S, Y = $NCH_3$ *or* X = $NCH_3$, Y = S
$R^1 = R^2 = R^3$ = H, $OCH_3$

**General structure I**