Design, Synthesis and Biological Evaluation of Benzodiazepines Analogues as Anti-Tubuling Agents

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Introduction: The naturally occurring combretastatin (CA-4) and its analogue phenstatin are reference molecules in the search of new antitumor agents (Fig. 1), They block the polymerization of tubulin, interacting at the colchicine binding site displaying a high degree of cytotoxicity on several cancer cell lines and antiangiogenic and vascular disrupting activities.[1]

In this communication we report a class of compounds with a 1,4-benzodiazepine-2-one nucleus (Fig. 2). These compounds combine structures of phenstatin with benzodiazepines, and could be a novel class of antitubulin agents, showing better pharmacokinetic profile.

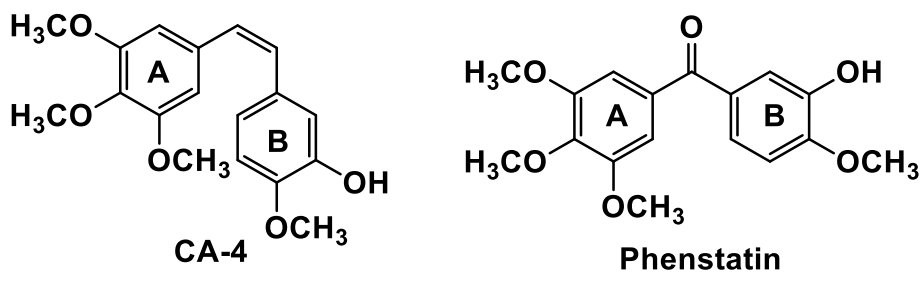


Figure 1. CA-4 and phenstatin

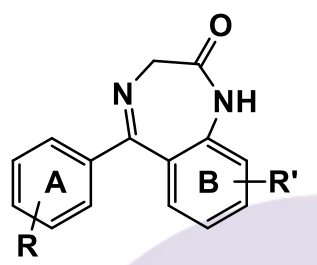
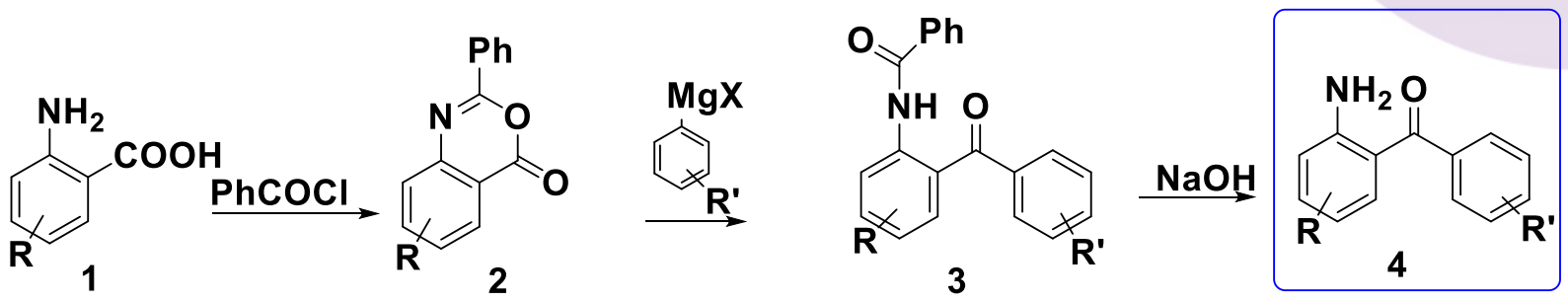


Figure 2. Analogue scaffold

Chemistry: The synthesis of these analogues was carried out from 2-aminobenzophenones.

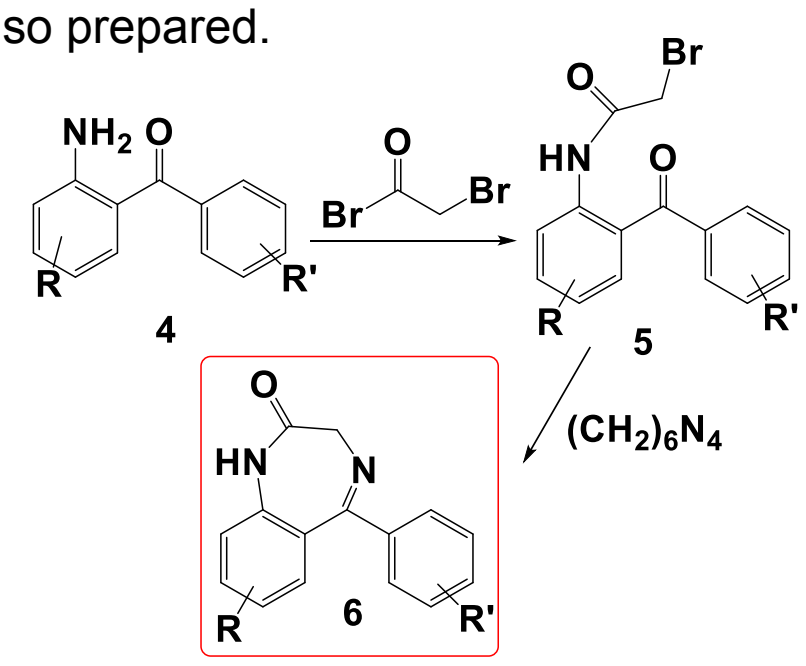
Aminobenzophenones

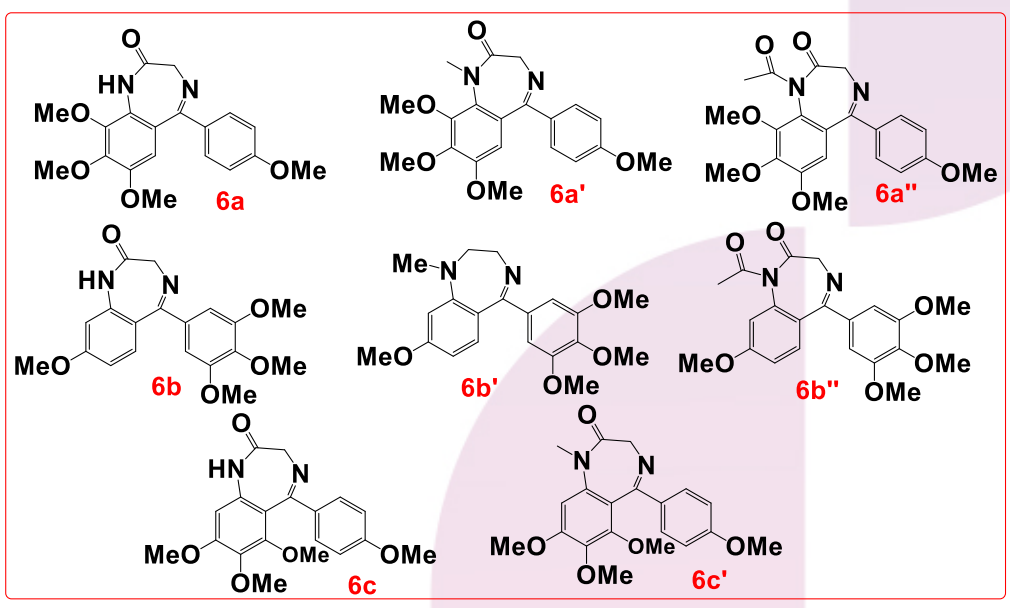
The preparation of the 2-aminobenzophenones starts with a reaction between the appropiate aminoacids (1) and benzoyl bromide to afford the benzoxazinones (2) , that upon reaction with Grignard reagents are converted in the benzamides (3) and finally, by treatment with NaOH, afford the corresponding aminobenzophenones (4).[2]



Benzodiazepines analogues

The amino group was acetylated with bromoacetyl bromide to afford the bromoacetamido benzophenones (5), Finally the 1,4-benzodiazepine-2-one nucleus was obtained using hexamethylentetramine (6).[3] The *N*-1-methylated and the *N*-1-acetylated derivatives were also prepared.





Compound	Conc. (μM)	% (ITP)	Cytotoxicity (HeLa, M)
6a	5	0	
6a'	5	0	
6b	5 10	43 33	
6b'	5	0	$1{,}4 \cdot 10^{-7}$
6b''	5 10	36 23	$8{,}3 \cdot 10^{-8}$

Biological Activity

Inhibition of Tubulin Polymerization (ITP).[4]
Cytotoxicity (HeLa cells).

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References: 1. a) *Med. Res. Rev.* **1998**, *18*, 259-296. b) *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3417-3420. 2. a) *Tetrahedron* **1995**, *51*, 1861-1866. b) *Chin. J. Chem.* **2009**, *27*, 1379-1381. 3. *J. Med. Chem.* **2015**, *58*, 1345-1357. 4. a) *Biochemistry* **1996**, *35*, 4387-4395. b) *J. Med. Chem.* **2005**, *48*, 556−568.