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Novel anthraquinone based chalcone analogues containing an imine fragment: Synthesis, cytotoxicity and anti-angiogenic activity

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ABSTRACT

A new class of imine derivatives of hybrid chalcone analogues containing anthraquinone scaffold was synthesized and evaluated for their in vitro cytotoxic activity against HeLa, LS174, and A549 cancer cells. The compound **5n** with furan ring linked to imino group showed potent activity against all target cells with IC_{50} values ranging from 1.76 to 6.11 μM. A mode of action study suggested that compounds induced changes typical for apoptosis in HeLa cells. The most active compounds inhibited tubulogenesis and **5h** was found to exhibit a strong anti-angiogenic effect.

Natural and synthetic chalcones are known cytotoxic pharmacophores that act by disruption of the cell cycle, inhibition of angiogenesis, binding MDM2 human oncoprotein and induction of apoptosis.[1] During the last years, a number of pharmacologically interesting hybrid chalcone analogues were synthesized involving structural modification to improve their anticancer potential and chemoprotective properties. The examples of these transformations are introduction of different substituents on aromatic rings, replacement of phenyl rings A or B with heterocyclic, polyaromatic or organometallic structures and substitution on enone part of chalcone. Some new classes of hybrid chalcone compounds with pronounced activity against various types of cancer cell lines contain Mannich bases of heterocyclic chalcones,[2] dihydrobenzofuran,[3] imidazopyridine/pyrimidine,[4] 3-arylquinoline,[5] quinoline-2-one,[6] naphthalene,[7] indole,[8,9] pyrazole,[10] quinoxaline,[11] amidobenzothiazole,[12] and ferrocene.[13]

Tumor angiogenesis is a physiological process that is involved in the formation of a network of blood capillaries supplying cancerous growths with oxygen and nutritients.[14] Chalcone analogues exhibit antitumor activities through various mechanisms and inhibition of angiogenesis is one of them.[15] The natural chalcone, xanthohumol and its synthetic derivatives inhibit angiogenesis by suppressing vascular endothelial growth factor (VEGF),[16] while the flavonoid precursor 4-hydroxychalcone inhibits this process by affecting both VEGF and basic fibroblast growth factor (bFGF) intracellular signaling pathways.[17] The chalcone derivatives bearing furan and thiophene heterocycles demonstrated strong anti-angiogenic activity[18] as well as quinolil-thienyl chalcones in the role of VEGFR-2 kinase inhibitors.[19]

On the other hand, some natural anthraquinones like aloe-emodin, emodin and rhein displayed anti-angiogenic effects in the zebrafish model. Contrary, chrysophanol with no substitution and physcion with the substituted methoxy group did not show any anti-angiogenic activity. Emodin was the most potent anti-angiogenic compound inhibiting endothelial cell proliferation, migration and tube formation in a dose-dependent manner.[20,21] Some representative chalcone and anthraquinone-based structures are presented in Figure 1.

In continuation with our current interest toward synthesis of bioactive anthraquinone compounds,[22] in this work we explored the possibility to combine the potential synergic anticarcinogenic effects of chalcone moiety and anthraquinone scaffold. To the best of our knowledge, there is no literature data on preparation and biological activity of anthraquinone based chalcone analogues. Thus, we designed and synthesized a new class of chalcones with anthraquinone as A-ring and different arylimino or alkylimino substituents in *para*-position of B-ring, together with an evaluation of their antiproliferative and anti-angiogenic potential.

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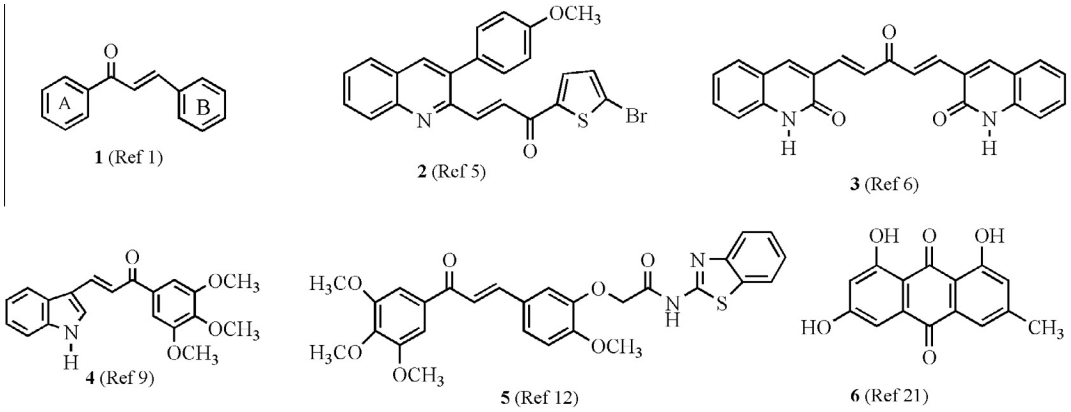
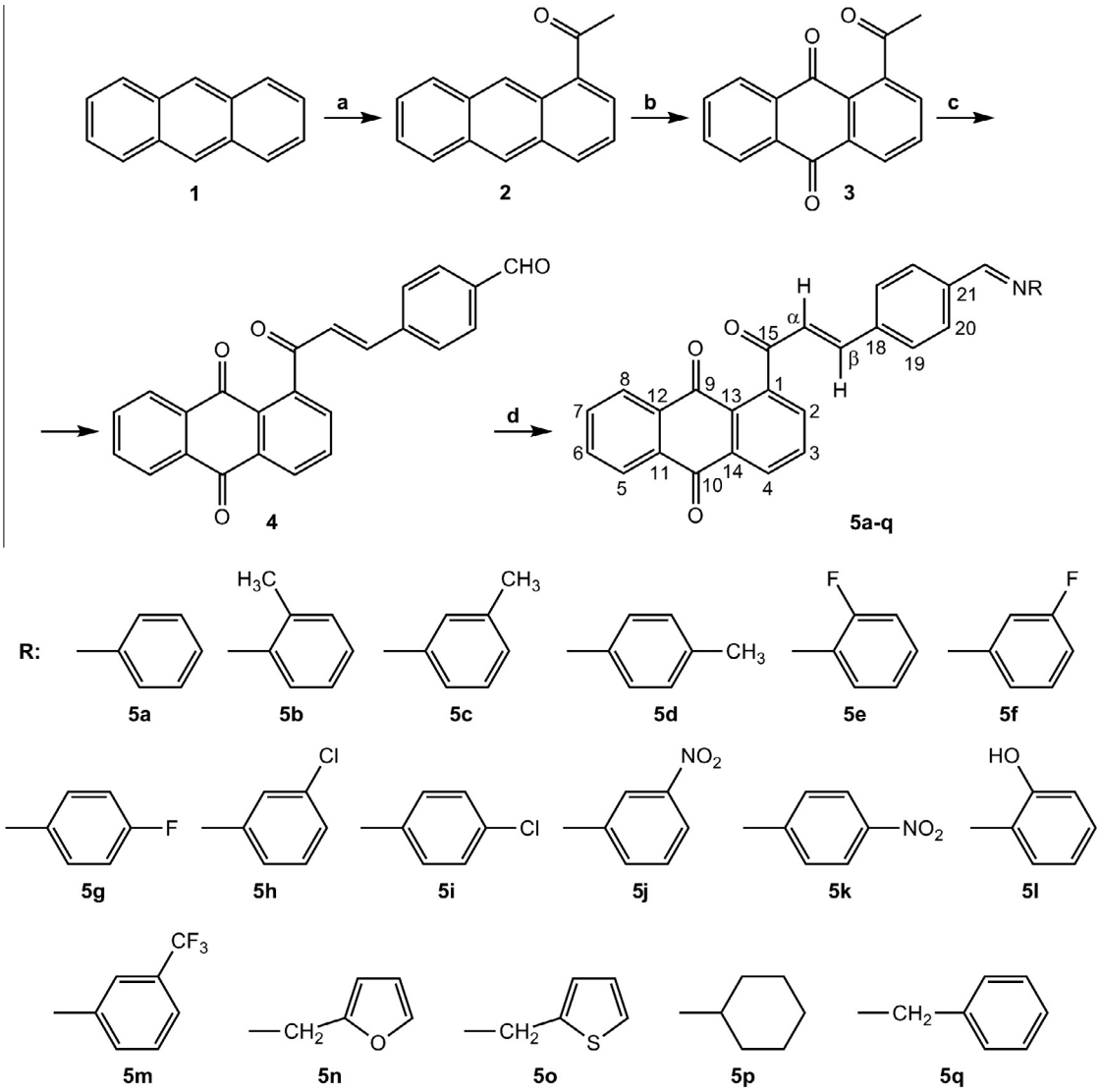


Figure 1. Basic structure of chalcone (**1**) and some representative chalcone and anthraquinone-based derivatives with antitumor properties (**2**–**6**).

Starting aromatic amines were selected to obtain the compounds with a good coverage of polar, steric, electron-donating and electron-withdrawing properties. Our further strategy was based on replacement of the phenyl group by the benzyl one as well as more flexible alkyl group bonded to heterocyclic furan and thiophene rings.



Scheme 1. Reagents and conditions: (a) CH_3COCl, $AlCl_3$, CH_2Cl_2, 2 h, 0 °C, 5 M HCl; (b) CrO_3, CH_3COOH, 5 min reflux, H_2O; (c) terephthalaldehyde, NaOH, MeOH, 5 h, reflux; (d) primary amines, AcOH, dioxane, 12–48 h, reflux.