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2-Phenylaminonaphthoquinones and related compounds: Synthesis, trypanocidal and cytotoxic activities

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ABSTRACT

A series of new 2-aminonaphthoquinones and related compounds were synthesized and evaluated in vitro as trypanocidal and cytotoxic agents. Some tested compounds inhibited epimastigote growth and trypomastigote viability. Several compounds showed similar or higher activity and selectivity as compared with current trypanocidal drug, nifurtimox. Compound **4l** exhibit higher selectivity than nifurtimox against *Trypanosoma cruzi* in comparison with Vero cells. Some of the synthesized quinones were tested against cancer cells and normal fibroblasts, showing that certain chemical modifications on the naphthoquinone moiety induce and excellent increase the selectivity index of the cytotoxicity (**4g** and **10**). The results presented here show that the anti-*T. cruzi* activity of 2-aminonaphthoquinones derivatives can be improved by the replacement of the benzene ring by a pyridine moiety. Interestingly, the presence of a chlorine atom at C-3 and a highly lipophilic alkyl group or aromatic ring are newly observed elements that should lead to the discovery of more selective cytotoxic and trypanocidal compounds.

1. Introduction

Infectious diseases and cancer are responsible for a large number of worldwide mortality. Cancer is one of the top ten leading causes of death. It is estimated that 7.6 million people died of cancer in 2008[1,2] and, if current trends continue, this number will rise to 9 million people by 2015.[3] On the other hand, infectious diseases still constitute a global health problem, causing the death of 8.8 million people in 2008.[1] Several neglected diseases are encountered among those with the highest economic burden. A specific parasitosis, Chagas disease (American trypanosomiasis, caused by *Trypanosoma cruzi*), affects more than 8 million people in Latin America, and causes approximately 10,000 deaths annually, which in the Americas is a higher figure than for malaria, and it is responsible for 89% of deaths from tropical-clustered diseases in the region.[1] In addition, Chagas disease causes over US$1.2 billion/year of productivity loss in seven of the countries where it is endemic.[4] Although both cancer and Chagas disease have different etiologies, they share metabolic and pathophysiological features such as glutathione metabolism, some signal transduction pathways, tissue invasion mechanisms and immune evasion strategies. Thus, the information obtained from a therapeutic target in any one of these cell types can be a useful tool for drug research in the other. As a result, several reports describe the effect of various compounds from natural extracts or new synthetic molecules against both *T. cruzi* and cancer cells.[5–12] On the order hand, a considerable number of natural and synthetic quinones (Fig. 1), have shown interesting biological properties, such as such as antimalarial (calothrixin A and B),[13–16] antibacterial (cribostatin I and streptonigrin),[17,18] antitumor (streptonigrin, calothrixin A and B and griffithazanone A),[19–22] and fungicidal activities.[23] These compounds have some important structural features, such as the 2-aminonaphthoquinone moiety (**1**), or 2-aminoquinoline- and isoquinoline-5,8-diones, or a substituted phenylamino group at C-2 (Fig. 1). It is known that the presence of the nitrogen atom, allows modulation of the

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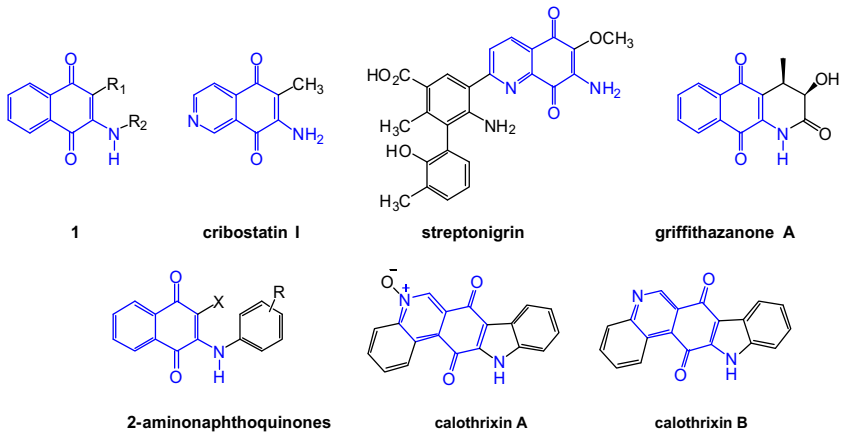


Figure 1. Structures of representative 2-amino-1,4-napthoquinone-type compounds with biological activities.

substituent's effects on the electronic properties of the quinone system, as well as modification of the geometry of the quinone molecules and their reduction intermediates.

In recent years, we have synthesized several series of 2-aminonaphthoquinone-type compounds such as benzocarbazolequinones, indazolylnaphthoquinones, benzoquinolinequinones, and related heterocyclic compounds.[24–28] Most of these compounds showed micromolar IC_{50} values against several series of tumor cell lines and trypanosome cultures.[25,28] One of the aims of this work was to analyze the influence of the enlargement of the heteropolycyclic system on their trypanocidal and cytotoxic effects. Since no data have been reported regarding the influence of the donor-acceptor and lipophilic properties of 2-phenylaminonaphthoquinones on *T. cruzi* cultures and their cytotoxic activity on normal and cancer cells, we synthesized a variety of these compounds to evaluate their trypanocidal activity and cytotoxic properties against different morphological stages of *T. cruzi* and a panel of four cell lines, including non-tumor dermal human fibroblast (DHF), and three human-derived tumor cell lines, namely PC-3 (prostate), MDA-MB231 and MCF-7 (breast).

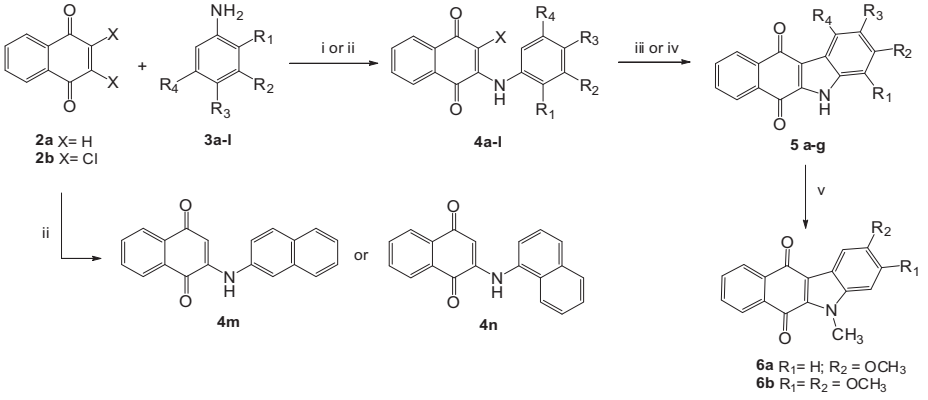
2. Results and discussion

2.1. Chemistry

The synthesis of 2-phenylaminonaphthoquinones (**4a**–**n**) and related 5*H*-benzo[*b*]carbazole-6,11-dione derivatives (**5a**–**d**) followed the general pathway outlined in Scheme 1. The first step was the substitution of the acceptor quinone nucleus (**2a**–**b**) by several aniline derivatives (**3a**–**l**) and 1- or 2-naphthylamine, which were achieved using two different methodologies (*i* or *ii*) reported in the literature.[29–31] Using methodology *ii*, and $CeCl_3{\cdot}7H_2O$ as Lewis acid catalyst, increased yields of the entire series were obtained (Fig. 1 and Table 1). In parallel, to study the importance of the nitrogen atom in the tricyclic system, we decided to obtain several benzocarbazolequinones, because some

Table 1
2-Phenylaminonaphthoquinones prepared by amination of quinones **2a**–**b**

Compound	X	R_1	R_2	R_3	R_4	Yield (%)	
						method i	method ii
4a	H	H	H	H	H	—	89
4b	H	OCH_3	H	H	H	62	67
4c	H	H	OCH_3	H	H	57	100
4d	H	H	H	OCH_3	H	49	78
4e	H	H	OCH_3	OCH_3	H	29	—
4f	H	OCH_3	H	OCH_3	H	65	—
4g	H	OCH_3	H	H	OCH_3	50	81
4h	H	H	H	$O(CH_2)_5CH_3$	H	74	74
4i	H	H	H	OH	H	—	86
4j	H	CH_3	H	CH_3	H	—	99
4k	Cl	OCH_3	H	H	OCH_3	—	83
4l	Cl	H	H	$O(CH_2)_5CH_3$	H	—	92
4m	H	—	—	—	—	—	74
4n	H	—	—	—	—	—	55



Scheme 1. Reagents and conditions: (i) ethanol, rt, 24–72 h; (ii) aniline **3a**–**l** or α- or β-naphthylamine, 0.22 equiv $CeCl_3{\cdot}7H_2O$, ethanol, rt, 12–24 h; (iii) 0.9 equiv $Pd(OAc)_2$, benzoquinone, AcOH, reflux, 12–24 h; (iv) 2–10 mol % $Pd(OAc)_2$, pivalic acid, 140 °C, 12–24 h ; (v) (1) KOH, ethanol, rt, (2) CH_3I, acetone, rt, 6 h (85% of yield for **6a** and 91% for **6b**).