Arylamino-naphthoquinones as new synthetic platforms to produce anticancer drugs

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Introduction

Cancer is one of the world's most important diseases, causing millions of deaths every year [1]. In addition to the health and socio-economic impacts, the problems related to the drugs currently used, such as low selectivity against healthy cells, side effects and resistance developed by tumors, make it increasingly necessary to research, develop and produce new drugs that provide more effective treatments [2]. In this scenario, 4-arylamino-1,2-naphthoquinones and 1,2,3-triazoles have been attracting attention for their anticancer properties, individually or in hybrid substances [3]. The limitations of producing 4-arylamino-1,2-naphthoquinone-triazole hybrids via alkylation with propargyl bromide or direct insertion of triazole rings are challenging. For example, the alkylation of the oxygen atom in position 2 of the naphthoquinonic ring with propargyl bromide is frequently reported, forming 4-arylimino derivatives as the main products [4]. This work aims to develop the synthesis of 4-arylamino-1,2-naphthoquinone-triazole hybrids by exploiting the reaction between arylamines and the naphthoquinone derivative, to develop prototype candidates for new drugs against cancer.

Material and Methods

To evaluate the hypotheses developed and achieve the objectives of this work, three approaches were developed: **a)** rational design for the substances of interest and development of viable synthetic methodology (Figure 1); **b)** bibliographic research seeking the best available methods, for synthesis and **c)** synthetic laboratory study to evaluate the methodologie viability found. The methodologies applied to the present work consist of **1)** *N*-propargilation of anilines [5]; **2)** the formation of arylaminonaphtoquinones, an adaptation of the method described by Hatfield *et al.* [6] and **3)** the 1,2,3-triazoles synthesis by Cu(I)-catalyzed 1,3-dipole cycloaddition [7].

Anilines, sodium azide, and 4-Amino-3-hydroxy-1-naphthalenesulfonic acid used as reagents were acquired from Merck Inc. The solvents used were obtained from BioScie. The characterization of the prepared substances was carried out through melting point range, proton nuclear magnetic resonance (^{1}H NMR) and carbon-13 nuclear magnetic resonance (^{13}C/APT), infrared spectroscopy (IR), and low-resolution mass spectrometry (LRMS). The infrared spectra were obtained using the Varian 660-IR FT-IR Spectrometer, and the absorption values were recorded in wave numbers, with the unit being reciprocal centimeters (cm^{-1}). The nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were obtained on Varian VNMRS (500 MHz) or Bruker Ascend (500 MHz) spectrometers. Thin layer chromatography analyses were performed using silica gel on aluminum TLC plates obtained from Merck Inc. Column purifications of the flash type were conducted using Flash Silica (40-63 μm; 230-400 mesh).

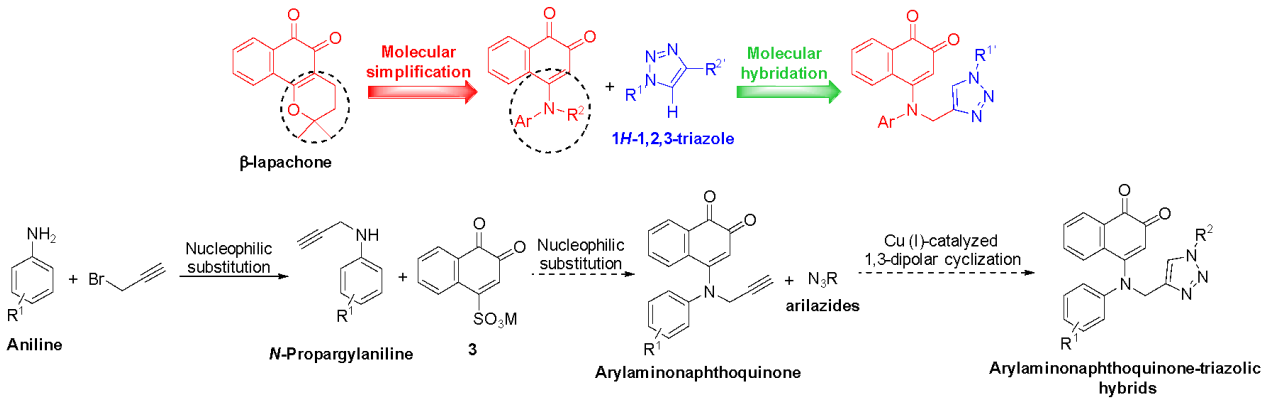
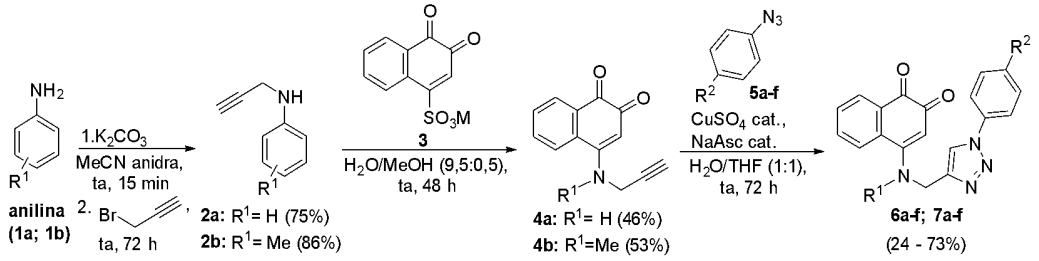


Figure 1. Proposed synthesis for 4-arylamino-1,2-naphthoquinone-triazole hybrids.

Results and Discussion

The synthetic methodology chosen for the hybrid synthesis is a three-step synthesis (Scheme 2). The first stage involved the alkylation of commercial anilines (**1a**; **1b**) with propargyl bromide to provide the *N*-propargylanilines (**2a**; **2b**). To carry out the second stage, different methods were studied to promote the nucleophilic substitution reaction most efficiently between the *N*-propargylated anilines and the 4-sulfonic-1,2-naphthoquinone sodium or potassium salt (**3**), the critical step. After finding the best condition, the 4-arylamino-1,2-naphthoquinone products were obtained in yields of between 46% and 53% to compounds **4a** and **4b**, respectively. In the third step, the triazole synthesis was carried out between the 4-arylamino-1,2-naphthoquinones and the arylazide to provide the hybrids **6** and **7** types in 24-73% yields.



6a: R^1= R^2= H (38%) **6b:** R^1= H; R^2= Me (40%) **6c:** R^1= H; R^2= Cl (47%) **6d:** R^1= H; R^2= OMe (59%) **6e:** R^1= H; R^2= NO_2 (64%) **6f:** R^1= H; R^2= F (58%)
7a: R^1= Me; R^2= H (56%) **7b:** R^1= R^2= Me (24%) **7c:** R^1= Me; R^2= Cl (39%) **7d:** R^1= Me; R^2= OMe (67%) **7e:** R^1= Me; R^2= NO_2 (48%) **7f:** R^1= Me; R^2= F (73%)

Scheme 1. Synthesis of 4-arylamino-1,2-naphthoquinone-triazole hybrids

Conclusion

The synthesis of hybrids was shown to be effective for a variety of molecules, with satisfactory yields and simple purification processes. Tests for biological activity and optimization of the process are going to be made.

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