XXI Brazilian Meeting on Inorganic Chemistry
X Brazilian Meeting on Rare Earths
III Workshop on Theoretical Bioinorganic Chemistry
Belo Horizonte, September 12 - 15th 2024

Thiones and Dithiones: Precursors in the Synthesis of Thiophenes Obtained via Chan-Lam Coupling with Antitumoral Potential in Colorectal Cancer

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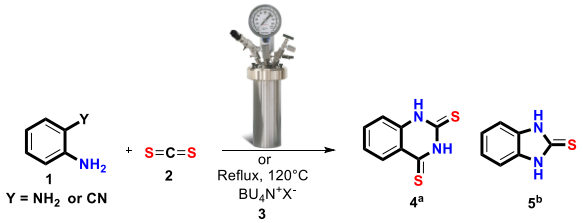
Thematic Area: Biological Inorganic Chemistry

Keywords: Carbon disulfide; Catalysis; Colorectal cancer.

Cancer is a disease of uncontrolled cell growth that spreads throughout the body. In Brazil, 704 thousand new cases are expected annually from 2023 to 2025. The most common cancers are prostate and colorectal in men, and breast and uterine in women. Chemotherapy, the common treatment, has limited efficacy and side effects. Hence, the search for effective drugs is crucial. Quinazolines, versatile compounds used in drugs like Vandetanib, are being explored for this purpose. In the first phase of this work, we synthesized derivatives that incorporate the quinazoline and thione nucleus. CS_2 was utilized as a synthon, and tetrabutylammonium salts (TBAX) were employed as a metal-free phase-transfer catalyst to activate the molecule. During this synthetic process, we used the following reagents: ortho-substituted aniline **1**, sulfur disulfide **2**, and tetrabutylammonium salts **3**, as illustrated in **Scheme 1**. The synthesis resulted in derivative **4** with conversion rates of 78% to 100%, confirmed by ^{1}H NMR. A chromatographic column showed a yield of 51% of product **4**. In the second phase, we utilized Chan-Lam coupling [**1**] to synthesize thiophenyls using dithiones and thiones, phenylboronic acid, and copper (II) acetate. We assessed the cytotoxic activities of these compounds using the MTT (Methyl Thiazol Tetrazolium) method against colorectal cancer (HCT116), triple-negative breast adenocarcinoma (MDA-MB-321), and human lung fibroblast cells (MRC-5). The assay was carried out in triplicate, with concentrations ranging from 10 µM to 200 µM, and incubated for 24 hours. The results indicated that compounds **4** and **5** were not cytotoxic to any of the cell lines. However, the thiophenyl, which was synthesized from compound **5**, showed an IC_{50} of 191 ± 1,8 µM in HCT-116. This indicates that the introduction of phenyl groups to compound **5** increased cytotoxicity. We believe that making structural changes to ring **5** could further enhance this cytotoxicity, and our research group is conducting additional studies to confirm this.

Scheme 1- Synthesis of Thiones and Dithiones using CS_2 as a building block



4: X= Br^-(78%); X= I^- (89%; 51%)[c,d], (100%); X= PF_6^-(97%); X=Cl^-(100%); X= OH^- (100%), 5: X= ClO_4^-(15%).

[a] Conversion determined by ^{1}H NMR spectroscopy analysis of crude reaction mixture (DMSO-d_6, 500 MHz); [b] Yield of the isolated product by chromatographic column in 70-230 mesh silica; [c] Reaction carried out without solvent, at a temperature of 120°C, in the Fischer reactor; [d] Yield of the isolated product by chromatographic column in 70-230 mesh silica doped with NH_4OH.

Acknowledgments: CNPq, FAPEG, UFG, UFCSPA.

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