Preparation of 1-thiocarbamoyl-3,5-diaryl-4,5-dihydro-1*H*-pyrazoles and cytotoxic evaluation against breast cancer cell line (MCF-7)

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Key-words: *pyrazoles, breast cancer, MTT.*

Abstract

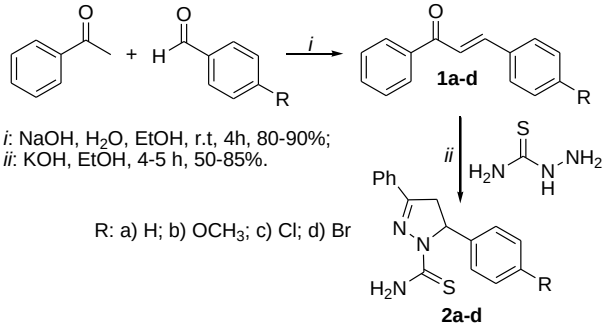
Cytotoxicity of four synthetic pyrazoles was evaluated against breast cancer cell line (MCF-7).

Introduction

Pyrazoles are an important class of heterocyclic compounds that attract attention due to the range of their biological activities, such as anti-inflammatory, antibacterial, antiviral, antimicrobial, antidepressant, anti-obesity and antihypertensive. These molecules generally can be synthesized by reaction of 1,3-dicarbonyl compounds or α,β-unsaturated/doubly unsaturated aldehydes and ketones with hydrazines.[1] Pyrazoles have also been reported as potent anticancer agents.[2] The demand for new, more efficient drugs, that can be administered in low doses to treat cancer, has increased considerably. Also, the search for molecules that can be combined with commercial drugs has been target of several studies.[3] In the recent years, breast cancer has been the major cause of death in women worldwide.[2] According to this propensity, the aims of this work were to synthesize pyrazoles and evaluate their cytotoxicity against the breast cancer cell line MCF-7 and, from that, to continue studies of structure-activity relationship and gene expression with the most promising molecules.

Results and discussions

The target molecules 1-thiocarbamoyl-3,5-diaryl-4,5-dihydro-1*H*-pyrazoles **2a-d** were synthesized based in the methodology reported by Pizzuti *et al*[4], making use of chalcones **1a-d** previously prepared by our research group as starting materials.[5] The reaction scheme is shown in **Figure 1**.



i: NaOH, H_2O, EtOH, r.t, 4h, 80-90%;
ii: KOH, EtOH, 4-5 h, 50-85%.

R: a) H; b) OCH_3; c) Cl; d) Br

Figure 1. Synthetic scheme of molecules **2a-d**.

The cytotoxic activities were evaluated against breast cancer cell line (MCF-7) obtained from the Rio de Janeiro Cell Bank (PABCAM, Federal University of Rio de Janeiro) by measuring the reduction of soluble (MTT) 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide in water insoluble formazan. The cells were treated with different concentrations of pyrazoles (5, 10, 20, 40 and 80 µM) previously dissolved in dimethyl sulfoxide (DMSO) for 24, 48 and 72 hours. All observations were validated by at least two independent experiments in triplicates for each experiment.

Findings of cytotoxicity revealed that pyrazoles **2c** and **2d** demonstrated significant activity against MCF-7 cell line, inhibiting more than 50% of cell growth after 72 hours of exposure in a concentration of 40 µM. In future studies, these molecules will be combined with other drugs in order to try effect improvement.

The results showed that pyrazoles substituted with the atoms chlorine and bromine were most effective to inhibit cell growth. This fact can be assigned to their higher electronegativity, as observed in another work with a series of 1,5-diphenylpyrazoles, in which molecules with chlorine atoms exhibited strong activity.[2]

Conclusions

In sum, the pyrazoles were satisfactorily synthesized and cell viability assay showed that pyrazoles **2c** and **2d** were the most promising molecules to continue gene expression analysis against breast cancer cell line. Also, other molecules may be synthesized in order to complement the research and maybe become an alternative against breast cancer treatment.

Acknowledgments

The authors are grateful to Universidade Federal de Pelotas, Capes, CNPq and Fapergs.

[1]Zora, M.; Kivrak, A. and Yazici, C. *J. Org. Chem*. **2011**, *76*, 6726.
[2]Ewes, W. A. et al. *Heterocycl. Commun*. **2015**, *21*, 367.
[3]Jeon, Y. W. et al. *Tumor Biol.* **2015**, *36*, 6349.
[4]Pizzuti, L. et al. *Ultrason. Sonochem*. **2009**, *16*, 728.
[5]Vasconcelos, A. et al. *Cell Biochem. Funct.* **2013,** *31,* 289.