NEW HYBRID PIPERAZINES-NAPHTHOQUINONES DERIVATIVES AS POSSIBLE ANTI-*MYCOBACTERIUM* AGENTS

Bicalho, A.K.S. [1]; Pacheco, F.S.[1]; Carvalho, A.S.[1*]; Ferreira, V.F.[1]

[1]*Universidade Federal Fluminense/Faculdade de Farmácia, Laboratório de Inovação em Química e Tecnologia Farmacêutica*
R. Dr. Mario Vianna, 523 - Santa Rosa, Niterói, Rio de Janeiro, Brasil
**alcionecarvalho@id.uff.br*

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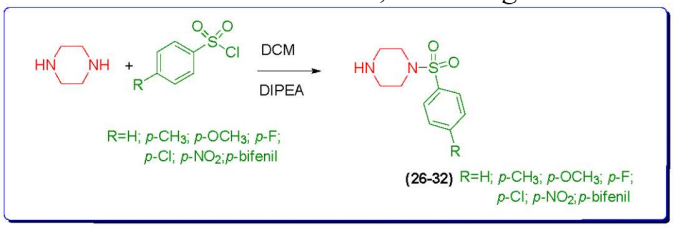
Introduction

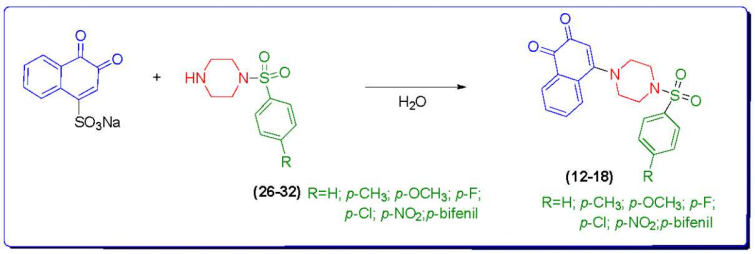
Tuberculosis (TB) is a treatable and curable disease. However, it can be fatal if left untreated. According to the WHO Global Tuberculosis Report 2023, there has been an increase in cases of multidrug resistant, and extensively resistant strains of *M. tuberculosis*, resulting in a 3% increase between 2020 and 2021 with 450,000 new cases of the disease resistant to the rifampicin drug in 2021.[1] According to the WHO, this is the first time in years that an increase has been reported in the number of people who fall ill with tuberculosis (TB).[2] Due to this enormous problem, one of the goals of our research laboratory is to synthesize new substances as possible anti-TB agents. The substances proposed in this work were designed to explore molecular hybridization as a medicinal chemistry strategy. In this study, the two pharmacophoric fragments chosen as the new potent derivatives were the naphthalene-1,2-dione nucleus present in our molecules with good anti-TB activity and the piperazine presents in the substance PBTZ 169 (study in phase II), on a nanomolar scale against multiresistant MDR-TB bacteria.[1]

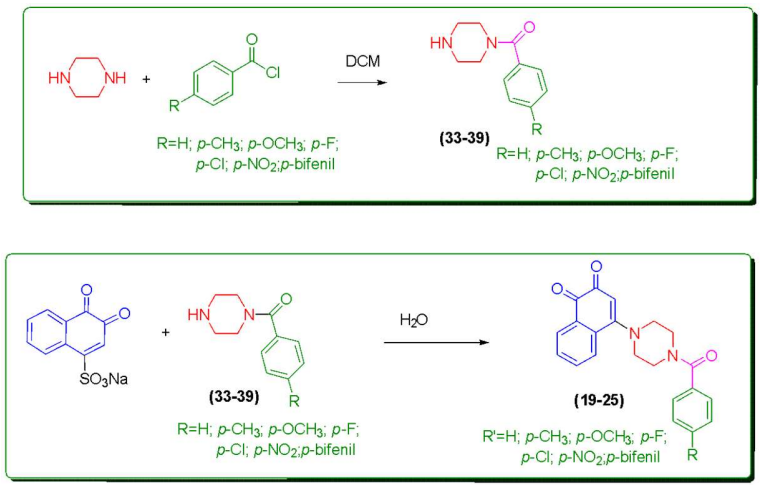
Material and Methods

The new R-piperazin-1-yl-naphthalene-1,2-dione derivatives (**1-10**) were prepared in two steps: The first reaction was the sulfonation of piperazine with the respective sulfonyl chlorides in dichloromethane at room temperature, with yields ranging from 62 to 81%. The second step was the substitution reaction on sodium 3,4-dioxo-3,4-dihydronaphthalene-1-sulfonate with the respective 1-R-(phenylsulfonyl)piperazine in methanol and water at room temperature.

The derivatives obtained were sent for testing at the Evandro Chagas Clinical Research Institute - IPEC/Fiocruz under the supervision of researcher Maria Cristina da Silva Lourenço. The antimycobacterial activity against Mycobacterium tuberculosis is being tested on the H37Rv ATCC 27294 strain using the Alamar Blue Assay microplate dilution colorimetric method, according to Franzblau.







Scheme 1. Synthesis route of new naphthoquinones derivatives (12-25).

Results and Discussion

The products were obtained in median yields of 50 to 78%. After purification and characterization of all products.

Conclusion

The synthesis route of the new candidates proved to be economical and effective, obtaining the products in two steps. Tests for anti-*Mycobacterium* are underway. It is expected that by monitoring the biological evaluation of the new naphthoquinone compounds we will be able to arrive at a new alternative prototype against *M. tuberculosis*.

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