SEPTEMBER 23-27 2024
19BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
BENTO GONÇALVES, RS - BRAZIL

Modeling and synthesis of 6-imidazolylquinazoline-2,4-diones as potential SARS-CoV-2 M^{pro} inhibitors

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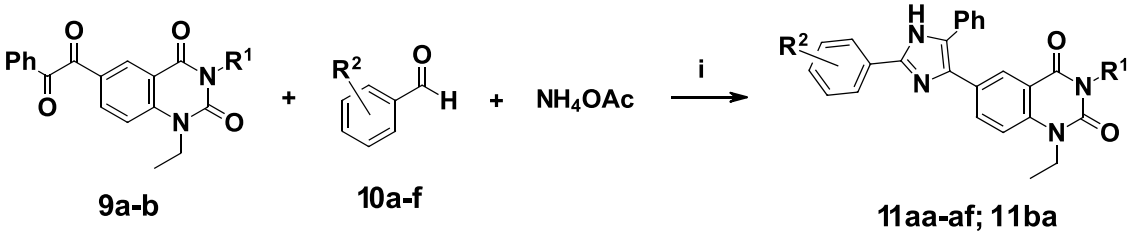
Keywords: *Imidazoles, quinazolines, molecular modeling.*

ABSTRACT

Given the importance of the *N*-heterocycles imidazole[1] and quinazoline[2] in Medicinal and Synthetic Chemistry, we modeled a series of potential inhibitors of SARS-CoV-2 Main Protease with the aid of Molecular Docking and Semi-empirical Quantum Mechanics (SQM). Initially, PM6-optimized structural models of the proposed M^{pro} inhibitors were docked into the enzyme's active site.[3-4] The three highest-ranked different positions were submitted to a further PM6-D3H4X/COSMO optimization in a protein globular model.[5] Debus-Radziszewski imidazole synthesis by reacting quinazolinylethanediones with ammonium acetate and aldeydes in acetic acid at 100 °C for 2 h[6] furnished the final products in good to excellent yields (65 - >95 %) after extraction and recrystallization. The obtained compounds were predicted to favorably bind to the enzyme, while quinazoline core and diarylimidazole moiety both fitted within its active site. Anti-SARS-CoV-2 assays are being carried out in collaboration with partner research groups at our institution.

* Synthesis
* Molecular Docking
* Semiempirical Quantum Mechanics



R^1 = *i*-Pr, Ph. R^2 = H, 2-OCH_3, 2-Cl, 4-OCH_3, 4-Cl, 1-Naph (-C_4H_4-).
i) Acetic acid, 100 ºC, 2 h.

ACKNOWLEDGEMENTS

We gratefully acknowledge CNPQ, CAPES and FAPERGS for financial support.

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