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## Efficient *N*-arylation and *N*-alkylation of quinazolines using PEG-400 as green solvent

Gabriel de Paula Bueno<sup>1\*</sup>, Luiz Vinícius Santos de Oliveira,<sup>1</sup> Giovanna Preterotto Lourençon<sup>1</sup> and Giuliano Cesar Clososki<sup>1</sup>

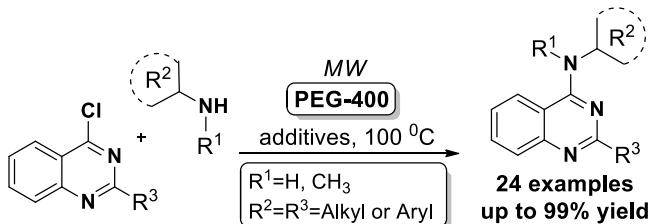
<sup>1)</sup> Department of Biomolecular Sciences, Faculty of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, FCFRP-USP, 14040-903

\*e-mail: gabriel\_bueno@usp.br

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### ABSTRACT

Quinazolines represent a significant class of aromatic *N*-heterocycles.<sup>1</sup> Derivatives of 4-aminoquinazoline are particularly valuable due to their presence in numerous pharmaceuticals, including erlotinib, gefitinib, and prazosin, and their role as antagonists of human adenosine A3 receptors.<sup>2-4</sup> The extensive utilization of this structural motif in biologically active compounds underscores the necessity for developing selective protocols to access functionalized derivatives.<sup>5</sup> Thus, this study presents a green, cost-effective, and efficient method for *N*-arylation and *N*-alkylation employing PEG-400 in a microwave reactor (Scheme 1). This novel synthetic approach holds promise for future applications in multifunctional supramolecular nanosystems<sup>6</sup> and in the development of candidates for cancer therapies, exemplified by the successful synthesis of Verubulin and analogs in high yields.



Scheme 1. Protocol employed in microwave-assisted reaction.

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### REFERENCES

- (1) Heravi, M. M.; Zadsirjan, V. Prescribed Drugs Containing Nitrogen Heterocycles: An Overview. *RSC Adv.* **2020**, 10 (72), 44247–44311. <https://doi.org/10.1039/d0ra09198g>.
- (2) Bansal, R.; Malhotra, A. Therapeutic Progression of Quinazolines as Targeted Chemotherapeutic Agents. *Eur. J. Med. Chem.* **2021**, 211, 113016. <https://doi.org/10.1016/j.ejmech.2020.113016>.
- (3) Banerjee, S.; Arnst, K. E.; Wang, Y.; Kumar, G.; Deng, S.; Yang, L.; Li, G. B.; Yang, J.; White, S. W.; Li, W.; et al. Heterocyclic-Fused Pyrimidines as Novel Tubulin Polymerization Inhibitors Targeting the Colchicine Binding Site: Structural Basis and Antitumor Efficacy. *J. Med. Chem.* **2018**, 61 (4), 1704–1718. <https://doi.org/10.1021/acs.jmedchem.7b01858>.
- (4) Xu, P.; Chu, J.; Li, Y.; Wang, Y.; He, Y.; Qi, C.; Chang, J. Novel Promising 4-Anilinoquinazoline-Based Derivatives as Multi-Target RTKs Inhibitors: Design, Molecular Docking, Synthesis, and Antitumor Activities in Vitro and Vivo. *Bioorganic Med. Chem.* **2019**, 27 (20). <https://doi.org/10.1016/j.bmc.2019.06.001>.
- (5) Nishimura, R. H. V.; Dos Santos, T.; Murie, V. E.; Furtado, L. C.; Costa-Lotufo, L. V.; Clososki, G. C. Efficient *N*-Arylation of 4-Chloroquinazolines En Route to Novel 4-Anilinoquinazolines as Potential Anticancer Agents. *Beilstein J. Org. Chem.* **2021**, 17, 2968–2975. <https://doi.org/10.3762/bjoc.17.206>.
- (6) Davis, M. E.; Chen, Z. G.; Shin, D. M. Nanoparticle Therapeutics: An Emerging Treatment Modality for Cancer. *Nat. Rev. Drug Discov.* **2008**, 7 (09), 771–782. <https://doi.org/10.1038/nrd2614>.