Green Chemistry Metrics Applied to Benzocaine and Procaine Syntheses: Evaluation with GAPI and AGREE

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Introduction: Local anesthetics [1], including benzocaine and procaine, are essential in modern medical and dental practice, but traditional synthetic methods often rely on hazardous reagents, require high energy input, and employ solvent-intensive procedures that conflict with green chemistry principles. Recent advances have introduced quantitative assessment tools [2], such as the Green Analytical Procedure Index (GAPI) and Analytical GREEnness (AGREE), which systematically evaluate solvent use, energy consumption, and overall sustainability of chemical processes [3,4]. **Objectives:** This study compares literature-reported synthetic routes for benzocaine and procaine, assessing their sustainability and environmental impact with GAPI and AGREE to identify efficient and reproducible protocols suitable for small-scale academic use. **Methods:** A narrative literature review was conducted in May 2025 using PubMed, ScienceDirect and Google Scholar. Studies describing benzocaine synthesis via Fischer esterification or sustainable procaine syntheses were considered eligible. The selected protocols were evaluated for yield, experimental complexity, and environmental performance using AGREE and GAPI metrics according to their original guidelines, assuming a colour scale and a maximum greenness score of 1.00 for each. **Results:** Three synthesis protocols for each anesthetic were identified and evaluated using AGREE and GAPI. AGREE diagrams showed that for benzocaine, the conventional Fischer esterification protocol (A) achieved the lowest score (0,29), whereas alternative protocols (B and C) obtained higher scores of 0,38 and 0,49. GAPI pictograms showed that benzocaine Synthesis A contained more red fields, B was dominated by yellow fields, and C displayed several green fields. For procaine, Synthesis X also showed more red fields, while Y and Z were characterized predominantly by green fields. **Conclusions:** These results confirm that recent protocols employing continuous-flow (C), metal-free (Z), or microwave-assisted (Y) steps thus offer greener options for the synthesis of ester-type local anesthetics. However, despite the environmental benefits, equipment costs can be a barrier to their use, especially in teaching laboratories.

Keywords: benzocaine; procaine; green chemistry synthesis; GAPI; AGREE

Acknowledgments
This work received financial support from the PT national funds (FCT/MECI, Fundação para a Ciência e Tecnologia and Ministério da Educação, Ciência e Inovação) through the projects UID/50006 -Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos.

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