Green synthesis of new peptide triazoles with potential activity against protease-activated receptor 2 (PAR2)

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INTRODUCTION

Protease-activated receptor 2 (PAR2) is a member of the G-protein-coupled receptor family that plays a central role in regulating inflammation, pain sensation, and several physiological processes, including wound healing, angiogenesis, epithelial barrier integrity, and itch perception. It is activated by proteases such as pancreatic trypsin, mast cell tryptase, and coagulation factors.

Chronic activation of PAR2 is implicated in various inflammatory and immune-related diseases, such as inflammatory bowel disease (IBD), asthma, arthritis, and skin disorders. Additionally, PAR2 is associated with tumor progression, where it promotes cellular proliferation, angiogenesis, and metastasis in certain cancers.

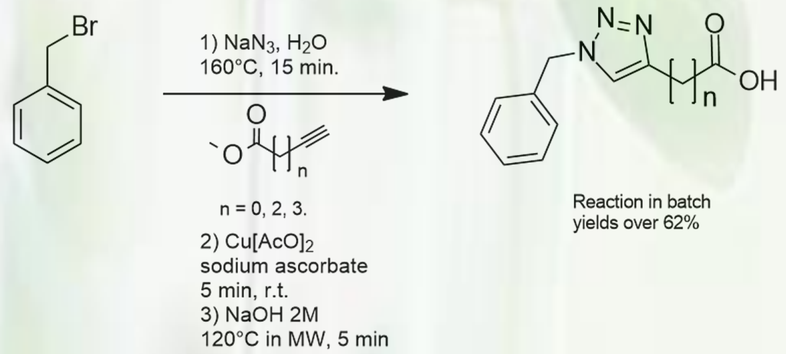
Despite its biological significance and involvement in disease, there are no commercially available drugs that directly target PAR2. While synthesized PAR2 antagonists have been reported, none have advanced to clinical use, underscoring the critical need for the development of effective therapeutic strategies targeting PAR2 to address inflammation-related and other pathological conditions.

OBJETIVE

In this study, we describe the design and synthesis of innovative triazole peptide derivatives with anti-inflammatory properties as PAR2 antagonists. These derivatives were synthesized using environmentally sustainable methodologies, contributing to green chemistry efforts. The findings presented in this work aim to advance the discovery of therapeutic agents targeting PAR2, addressing an unmet need in the treatment of inflammation-driven diseases.

METHODOLOGY

1. Microwave-assisted reaction
2. Biorenewable solvent
3. Earth-abundant metal catalysis
4. Short-time reaction
5. No harsh conditions



Scheme 1: synthesis of triazoles on water.

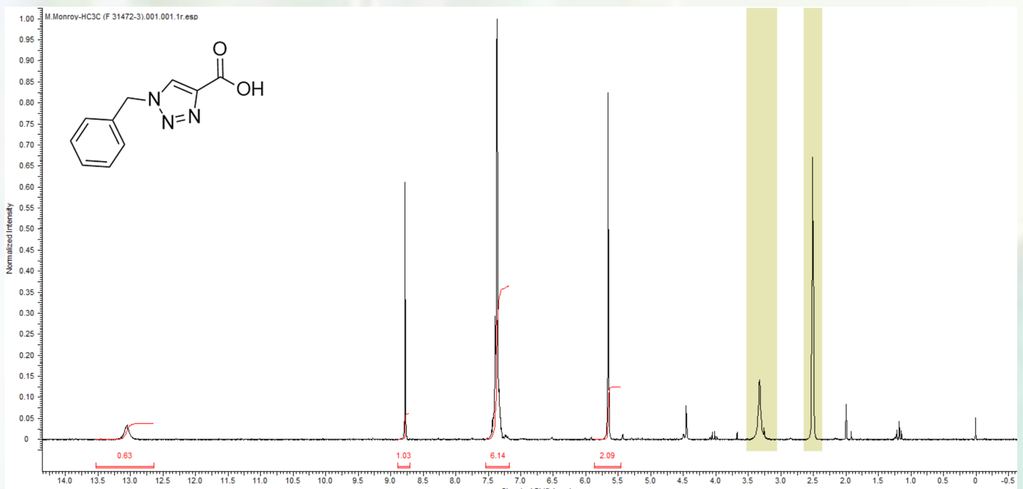
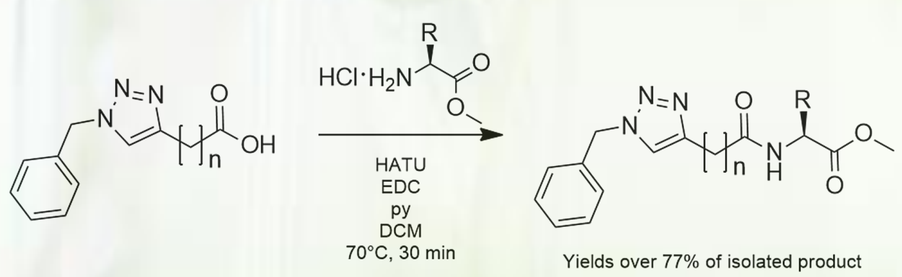


Figure 1: ^{1}H-NMR of the crude reaction mixture from the synthesis of 1-benzyl-1H-1,2,3-triazole-4-carboxylic acid



Scheme 2: Synthesis of amino acid derivatives.

RESULTS

We reduced the synthesis time of benzyl azides from 12 hours (Sun et al.[1]) or 3 hours (Fan et al.[2]) to just 15 minutes using water as a solvent. The subsequent triazole synthesis, previously requiring 12 hours (Mindt and Schibli [3]), was shortened to 5 minutes in water, with no need for prior azide purification. This streamlined process cut the total reaction time from 15 hours to 25 minutes.

Triazole derivatives were obtained with yields over 62%, and peptide-coupled products achieved yields exceeding 77%. Structural confirmation was performed using ^{1}H NMR, ^{13}C NMR, and HR-MS.

FUTURE PERSPECTIVES

Based on the success in the synthesis of these compounds, both in the optimization of the methodology and in the yields, the next steps to follow are:

- cell viability tests
- determine their in vitro activity against PAR2 by means of Ca^{+2} mobilization assays
- 3D-QSAR analysis of structure-activity relationships

ACKNOWLEDGEMENTS

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