Chemical Characterization of Emerging Synthetic Opioids (Nitazenes) with High Toxicological Potential

Ferreira, Daniela R.[a,b,c*] ; Neng, Nuno R.[a,b]; Quintas, Alexandre[b]; Gaspar, Helena[c]

[a]Centro de Química Estrutural, Institute of Molecular Sciences, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Lisbon, Lisbon, Portugal.

[b]Laboratório de Ciências Forenses e Psicológicas Egas Moniz, Egas Moniz Center for Interdisciplinary Research, Egas Moniz School of Health & Science, Caparica, Portugal.

[c]BioISI-Biosystems & Integrative Sciences Institute, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Lisbon, Lisbon, Portugal.

* fc64813@alunos.fc.ul.pt

INTRODUCTION

New Psychoactive Substances (NPS) are substances that are not controlled under the **1961 United Nations Single Convention on Narcotic Drugs** or the **1971 United Nations Convention on Psychotropic Substances** [1]. To date, over **1,350 NPS** have been reported worldwide [1], with **synthetic opioids** representing one of the **most dangerous** categories [1]. Between 2009 and 2024, **88 new synthetic opioids** were detected in Europe [2,3]. In recent years, particular attention has been given to the **Nitazene** class. In 2023, 6 out of 7 newly identified synthetic opioids were Nitazenes, compounds linked to **overdose deaths and serious public health** concerns [2,3]. In 2024, all 7 new opioids reported in Europe also belonged to this highly potent class. To date, **22 Nitazenes derivatives** have been identified across **Europe**.

AIMS

- **Synthesis of Nitazene derivatives** based on Nitazene core scaffold.
- Explore chemical diversity via **substitutions two key positions**.
- **Evaluate toxicity** of the synthesized compounds.

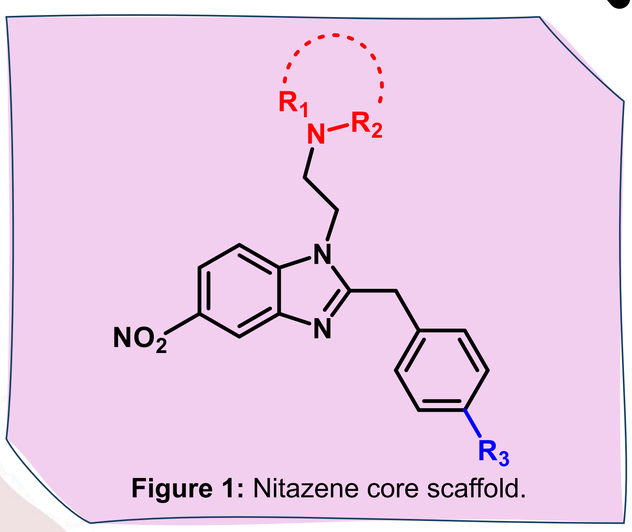


Figure 1: Nitazene core scaffold.

METHODS

➢ **Synthesis of Nitazene derivatives [4,5]:**

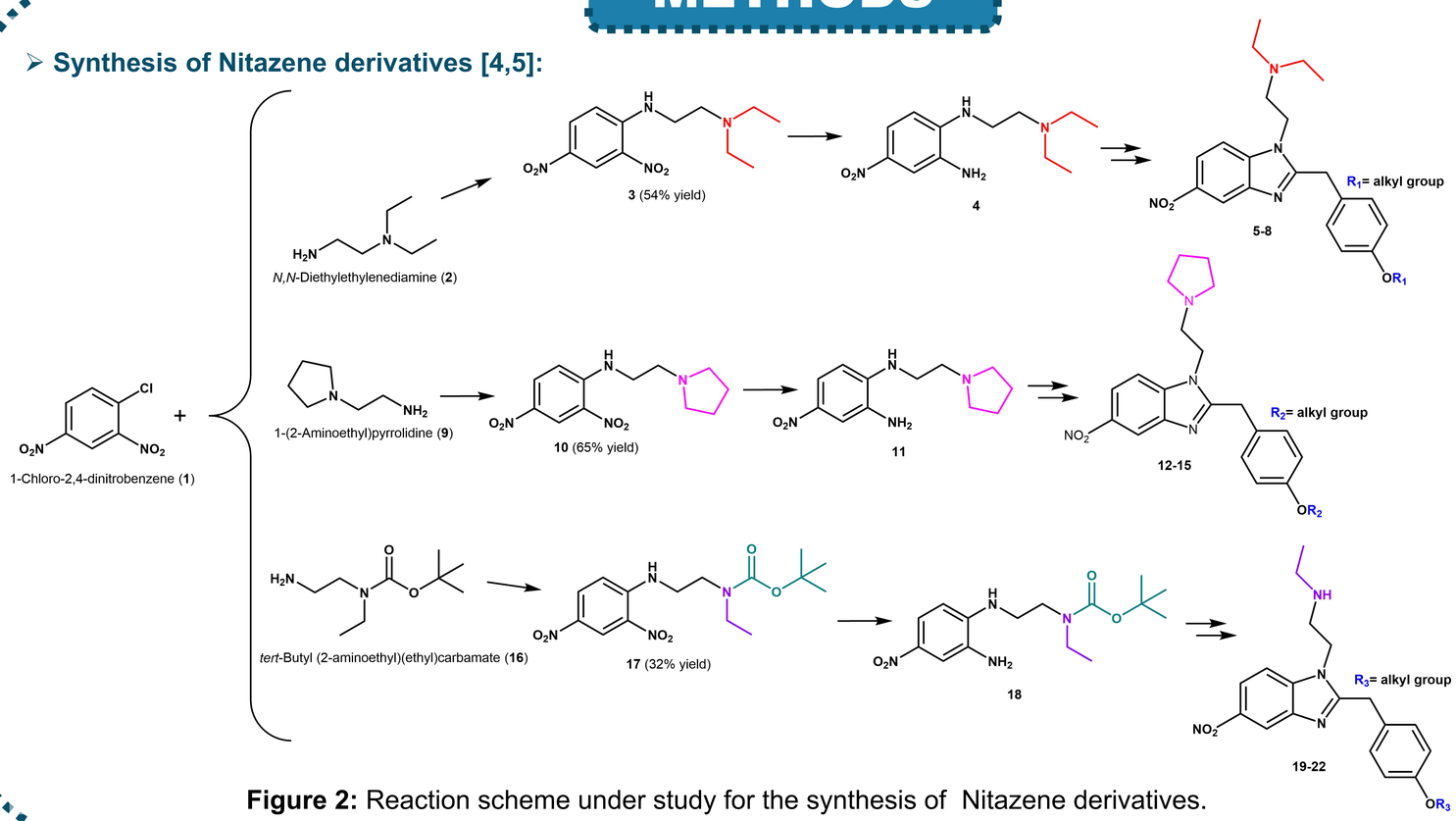
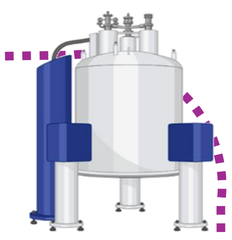


Figure 2: Reaction scheme under study for the synthesis of Nitazene derivatives.

RESULTS AND DISCUSSION



NMR

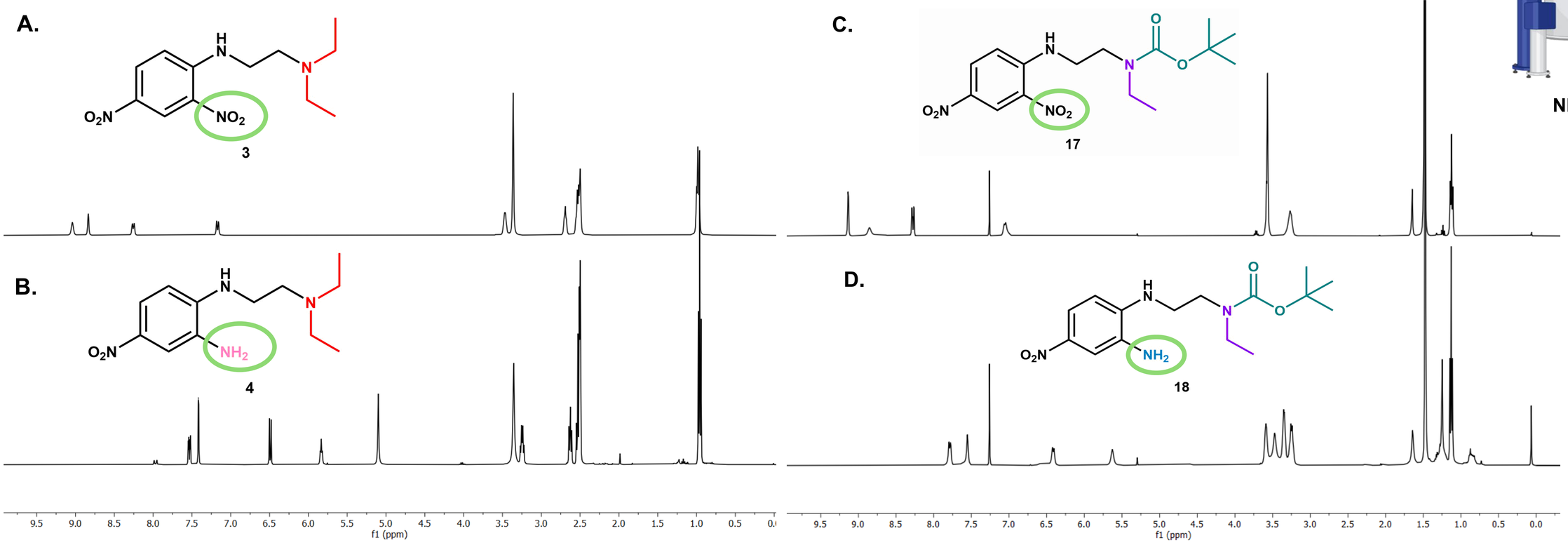


Figure 3: ^{1}H NMR spectra in DMSO-d_6: **A** – intermediate **3**; and **B -** intermediate **4;** ^{1}H NMR spectra in $CDCl_3$: **C** – intermediate **17**; and **D -** intermediate **18.**

CONCLUSIONS AND FUTURE WORK

✓ **Synthesis of intermediates** of Nitazene derivatives with **reasonable yields** (32%-65%).

- **Toxicological evaluation** of Nitazene derivatives on **different cell lines**.
- Contribute to understanding the **health and societal risks** of emerging Nitazenes.

REFERENCES

[1] UNODC, *Early Warning Advisory on New Psychoactive Substances*, https://www.unodc.org/LSS/Home/NPS.

[2] EUDA, *European Drug Report* ***2025***, https://www.euda.europa.eu/publications/european-drug-report/2024/new-psychoactive-substances_en.

[3] UNODC, *International Drug Control Conventions: Scheduling Decisions*, https://www.unodc.org/unodc/en/commissions/CND/Mandate_Functions/Scheduling.html.

[4] Bucha, M. *et al*.; Indian J. Heterocycl. Chem., **2018**, 28, 321–327.

[5] Renton, P. *et al*.; ACS Med. Chem. Lett., **2012**, 3, 227–231.

ACKNOWLEDGMENTS

Daniela R. Ferreira gratefully acknowledges her PhD grant (No. 2024.03215.BDANA) awarded by the Fundação para a Ciência e a Tecnologia (FCT). Centro de Química Estrutural is a Research Unit funded by FCT through projects UIDB/00100/2020 (https://doi.org/10.54499/UIDB/00100/2020) and UIDP/00100/2020 (https://doi.org/10.54499/UIDP/00100/2020). Institute of Molecular Sciences is an Associate Laboratory funded by FCT through project LA/P/0056/2020 (https://doi.org/10.54499/LA/P/0056/2020). BioISI—Biosystems & Integrative Sciences Institute is funded by FCT through the projects UIDB/04046/2020 (https://doi.org/10.54499/UIDB/04046/2020) and UIDP/04046/2020 (https://doi.org/10.54499/UIDP/04046/2020). CiiEM has provided support through Project 10.54499/UIDB/04585/2020, funded by FCT.