Nature-Inspired Antibacterial Agents: Derivatization of Eugenol toward promising anti-*H. pylori* agents

Ilaria D'Agostino,[1] Alessandra Ammazzalorso,[2] Simone Carradori,[2] Damiano Tanini,[3] Francesco Melfi,[1] Noemi Mencarelli,[2] Antonella Capperucci,[2] Francesca Sisto[4]

[1]Department of Pharmacy, University of Pisa, Via Bonanno 6, 56126 Pisa, Italy
[2]Department of Pharmacy, "G. d'Annunzio" University of Chieti-Pescara, Via dei Vestini 31, 66100 Chieti, Italy
[3]Department of Chemistry ''Ugo Schiff'', University of Florence, Via della Lastruccia 3–13, 50019 Sesto Fiorentino, Italy
[4]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Via Pascal 36, 20133 Milan, Italy

Bacterial resistance dramatically affects the effectiveness of current antibiotics, being considered a big concern for Public Health. Also, some bacterial survival capabilities in harsh conditions and invasiveness can cause infection recrudescence and failure in its eradication, as often occurs with *Helicobacter pylori*, recognized as an important risk factor for the development of gastric adenocarcinoma. The search for new antibacterial agents led us to explore the activity of Eugenol (**Figure 1**), an essential oil component known for its polypharmacology and, in particular, broad-spectrum antimicrobial[1,2] and anti-*H. pylori* activity *in vitro*.[3]

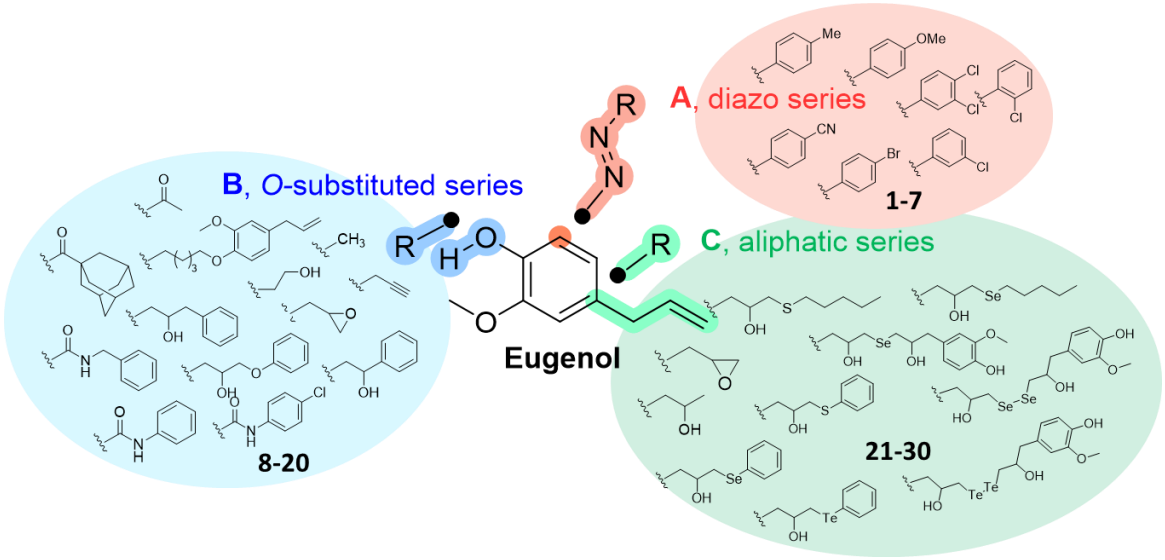

Figure 1. Chemical structures of **Eugenol** and **A-C** series.

Thus, we performed chemical modifications on the **Eugenol** scaffold, generating three different series of derivatives: in series ***A***, a diazo function was added in the *ortho* position; in *B*, the phenolic group was alkylated or incorporated into a carbamate or ester moiety; in ***C***, the allylic portion was replaced by a differently substituted tail, including an epoxide ring, alcohol or chalcogen-bearing chains (**Figure 1**). The antibacterial susceptibility of *H. pylori* strains for these compounds was evaluated on the reference NCTC 11637 strain and three drug-resistant clinical isolates. Interestingly, some of the derivatives showed lower minimal inhibitory concentration (MIC) values on *H. pylori* NCTC 11637 (MICs ranging from 8 to 16 µg/mL) than the parent compound (Eugenol, MIC = 32 µg/mL). They also maintained their antibacterial activity on the resistant strains, exerting a bactericidal effect.[4]

1. Kamatou, G. P.; Vermaak, I.; Viljoen, A. M. Molecules. 2012, 17, 6953-6981.

2. Marchese, A.; Barbieri, R.; Coppo, E.; Orhan, I. E.; Daglia, M.; Nabavi, S. F.; Izadi, M.; Abdollahi, M.; Nabavi, S. M.; Ajami, M. Crit. Rev. Microbiol. 2017, 43, 668-689.
3. Ali, S.M.; Khan, A. A.; Ahmed, I.; Musaddiq, M.; Ahmed, K. S.; Polasa, H.; Rao, L. V.; Habibullah, C. M.; Sechi, L. A.; Ahmed, N. Ann. Clin. Microbiol. Antimicrob. 2005, 4-20.
4. Carradori, S.; Ammazzalorso, A.; Niccolai, S.; Tanini, D.; D'Agostino, I.; Melfi, F.; Capperucci, A.; Grande, R.; Sisto, F.. Pharmaceuticals. 2023 Sep 18;16(9):1317.