# SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NOVEL 1,2,3-TRIAZOLYL BENZIMIDAZOLE–BENZOXAZOLE HYBRIDS

**Anja Rakas[1], Jurja Vukovinski[1], Dajana Kučić Grgić[2], Tatjana Gazivoda Kraljević[1]**

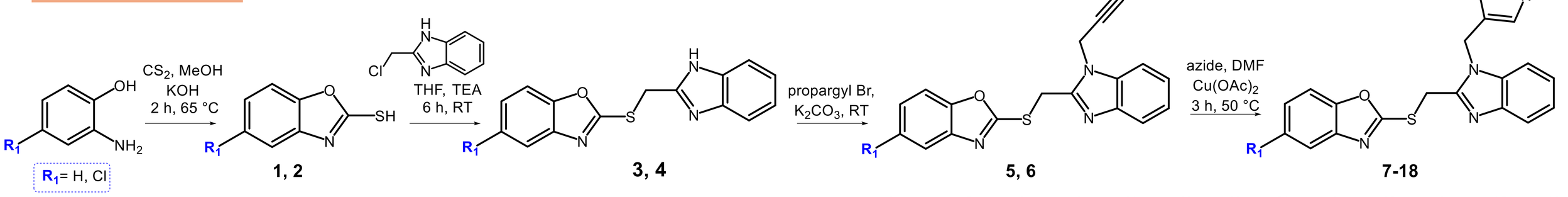
University of Zagreb Faculty of Chemical Engineering and Technology, Department of Organic Chemistry, Marulićev trg 20, 10000 Zagreb, Croatia

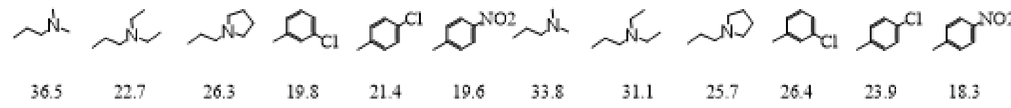
University of Zagreb Faculty of Chemical Engineering and Technology, Department of Industrial Ecology, Marulićev trg 19, 10000 Zagreb, Croatia

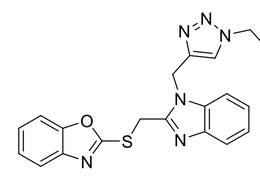
## BACKGROUND

**Benzoxazole and benzimidazole derivatives are recognized for their diversity in the synthesis of biologically active molecules, possessing a wide array of pharmacological activities. These compounds exhibit antimicrobial, anti-inflammatory, antituberculosis, antioxidant and antidepressant properties. Due to their diverse biological activities, benzoxazole and benzimidazole derivatives serve as crucial pharmacophores and substructures in numerous medicinal compounds.[1] They are integral components of several market-available drugs, such as flunoxaprofen, chlorzoxazone, tiabendazole, ciclobendazole, underscoring their importance in pharmaceutical research and development.[2] 1,2,3-triazoles and their derivatives have gained significant attention as potent pharmacophores due to their notable chemotherapeutic properties. Herein, we present the synthesis of benzoxazole and benzimidazole derivatives, which are substituted with a 1,2,3-triazole ring using a copper(I) catalyzed click reaction.[3]**

## CHEMISTRY




| Compd. | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $R_1$ | H | H | H | H | H | H | Cl | Cl | Cl | Cl | Cl | Cl |
| $R_2$ |  | | | | | | | | | | | |
| Yield (%) | 36.5 | 22.7 | 26.3 | 19.8 | 21.4 | 19.6 | 33.8 | 31.1 | 25.7 | 26.4 | 23.9 | 18.3 |



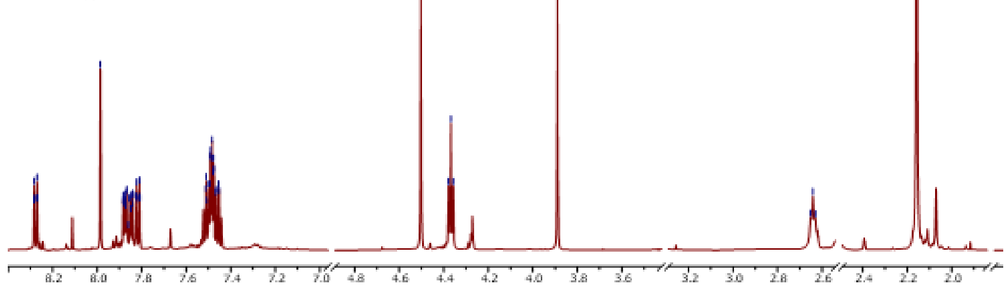



Figure 1. $^1$H NMR spectrum of compund **7**

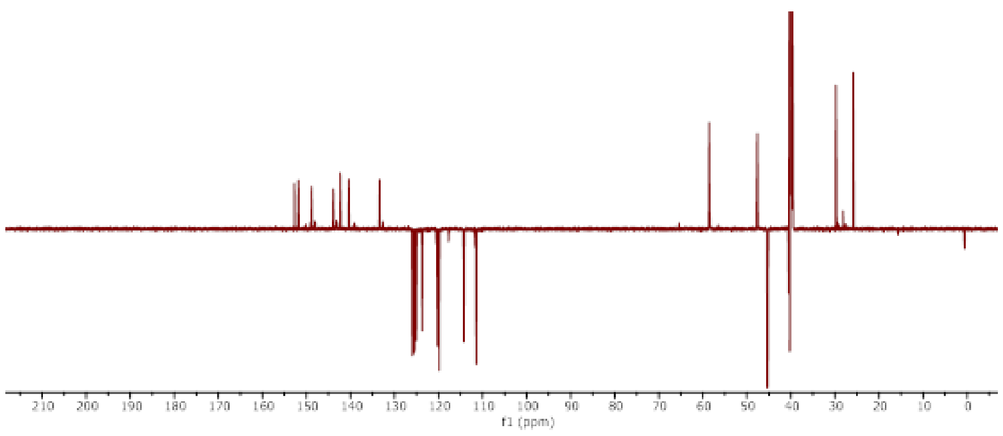



Figure 2. $^{13}$C NMR spectrum of compund **7**

## ANTIBACTERIAL ACTIVITY EVALUATION

**Antibacterial activity *in vitro* of newly prepared 1,2,3-triazolyl benzoxazole –benzimidzole hybrids (7–18) was evaluated against Gram-negative (*Escheirichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*) and Gram-positive (*Staphylococcus aureus, Enterococcus faecalis*) bacterial strains.**

| compd | MIC (μg/mL) | | | | |
|---|---|---|---|---|---|
| | Gram-negative bacteria | | | Gram-positive bacteria | |
| | *E. coli* | *K. pneumoniae* | *P. aeruginosa* | *S. aureus* | *E. faecalis* |
| **7** | >256 | >256 | >256 | >256 | >256 |
| **8** | >256 | >256 | >256 | >256 | >256 |
| **9** | >256 | >256 | >256 | >256 | >256 |
| **10** | >256 | >256 | >256 | >256 | >256 |
| **11** | >256 | >256 | >256 | >256 | >256 |
| **12** | >256 | >256 | >256 | >256 | >256 |
| **13** | >256 | 32 | >256 | >256 | >256 |
| **14** | >256 | >256 | >256 | >256 | >256 |
| **15** | >256 | >256 | >256 | >256 | >256 |
| **16** | >256 | >256 | >256 | >256 | >256 |
| **17** | >256 | >256 | >256 | >256 | >256 |
| **18** | >256 | >256 | >256 | >256 | >256 |

## CONCLUSION

**1,2,3-Triazolyl benzimidazole–benzoxazole hybrids (7–18) were prepared by multistep synthesis including in the first step cyclocondensation raction to benzoxazole derivatives (1, 2) which were then condesed with 2-chloromethylbenzimidazole to yield hybrids of benzimidazole and benzoxazole bridged by a thiomethylene linker (3, 4). *N*-propargylated derivatives (5,6) were converted by Cu(I) catalyzed click reaction with corresponding azides to target 1,2,3-triazolyl benzimidazole–benzoxazole hybrids. Of all the evaluated compounds, 5-chlorobenzoxazole-benzimidazole hybrid with *N,N*-dimethylethyl substituent linked to 1,2,3-triazole moiety (13) showed moderate antibacterial activity against Gram-negative bacterium *Klebsiella pneumoniae*.**

## REFERENCES

1. S. Pal, B. Manjunath, S. Ghorai, S. Sasmal, Academic Press, **79** (2018) 72-75.
2. S. Kakkar, S. Tahlan, S. M. Lim, K. Ramasamy, V. Mani, S. Adnan, B.Narasimhan, *Chem. Cent. J.*, **12** (2018) 1-15.
3. S. G. Agalave, S. R. Maujan, S. Vandana, *Chem. Asian J.*, **6** (2011) 2718.

20 međunarodni znanstveno-stručni skup Ružičkini dani
DANAS ZNANOST – SUTRA INDUSTRIJA
18. – 20. rujna 2024. I Vukovar, Hrvatska

## ACKNOWLEDGEMENT

Financial support from the Croatian Science Foundation under the project IP-2022-10-2420