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Synthesis and antibacterial activity of novel 1,2,3-triazole derivatives of benzoxazole

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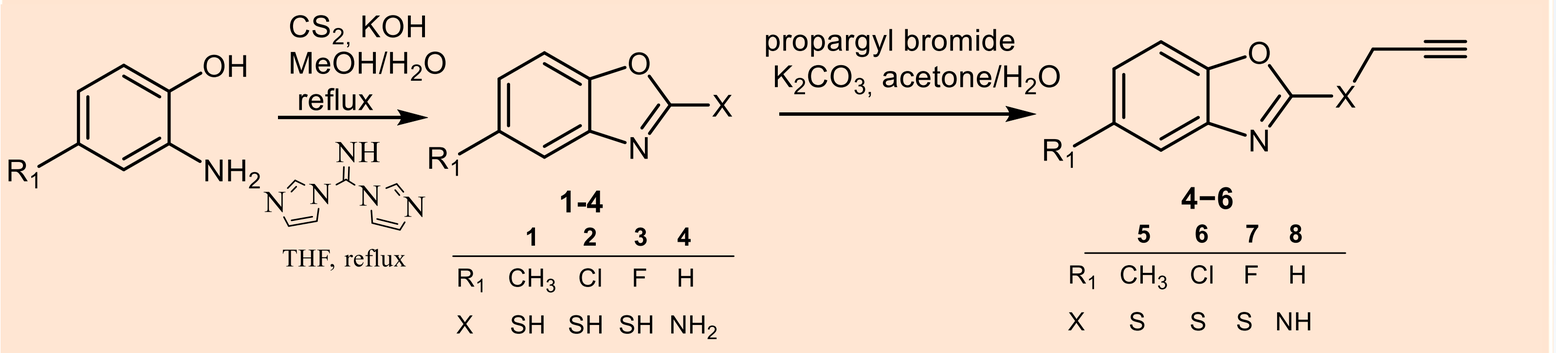
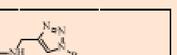
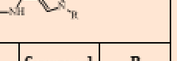
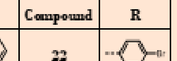
Background

- Recently, the overuse of antibiotics in humans, animals, and agriculture has led to a growing number of bacterial strains developing resistance to commercial antibiotics. Consequently, a significant number of deaths are occurring worldwide, and clinicians are facing a shortage of effective treatments. Because of that there is an increased demand to develop new, potent antibacterial agents. Benzoxazoles are structural isosteres of natural nucleotides and represent an important class of heterocyclic compounds exhibiting exceptional biological activities such as anticancer, antibacterial, anti-inflammatory and antiviral. [1,2]
- In order to evaluate their i*n vitro* antibacterial activity against Gram-positive and Gram-negative bacteria, novel derivatives of benzoxazole containing 1,2,3-triazole ring as a pharmacophore were prepared. Propargylated 2-thiobenzoxazoles were synthesized in a two-step reaction including cyclization reaction of 2-aminophenol using carbon disulfide, and subsequent alkylation reaction with propargyl bromide. 2-thiobenzoxazole derivatives with 1,2,3-triazole moiety were synthesized by Cu(I) catalyzed click reaction of 2-propargylated benzoxazole derivatives with corresponding azides. The structures of synthesized benzoxazole derivatives were confirmed by ^{1}H- and ^{13}C-NMR spectroscopy and mass spectrometry as well.

Results

Chemistry



Compound	R	Compound	R
19		22	
20		23	
21		24	

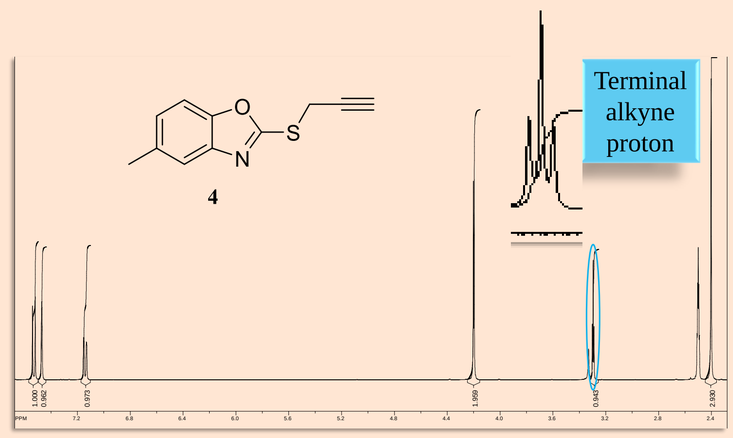
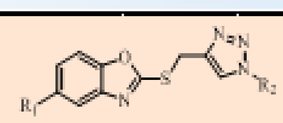


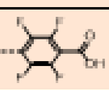
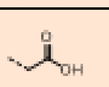
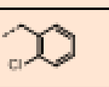
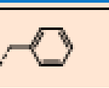
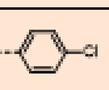
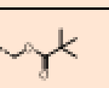
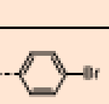
Figure 1. ^{1}H-NMR spectrum of compound 4

Figure 2. ^{1}H-NMR spectrum of compound 12

Formation of the triazole ring is confirmed by the disappereance of the triplet at ~3.2 ppm of the terminal alkyne proton in ^{1}H-NMR spectrum of compound 4 (Figure 1.) and the appereance of the siglet of the triazole ring proton at ~9 ppm in ^{1}H-NMR spectrum of compounds 9–24 (Figure 2.).

Antibacterial activity of 1,2,3-triazole derivatives of 2-thiobenzoxazole (9–18)



Compound	R1	R2	MIC/ mg L^{-1}				
			E.coli	E.faecalis	K.pneumoniae	P.aeruginosa	S.aureus
9	Me		4	4	8	64	32
10	Me		32	256	128	16	128
11	Me		128	>256	256	>256	128
12	Me		>256	>256	>256	>256	>256
13	Me		16	8	2	1	1
14	Me		16	>256	>256	256	>256
15	Cl		>256	256	>256	>256	>256
16	Cl		8	16	32	64	256
17	Cl		16	32	64	8	8
18	F		256	>256	>256	>256	>256

Conclusion

- Novel 1,2,3-triazole derivatives of 2-thiobenzoxazole (9–18) and 2-aminobenzoxazole (19 –24) have been prepared utilizing click chemistry
- 1,2,3-triazole derivative of benzoxazole with methyl(trimethylsilyl) group (13) showed the most pronounced antibacterial activity against Gram-negative bacteria *Klebsiella pneumoniae* (MIC= 2 mgL^{-1}) and *Pseudomonas aeruginosa* (MIC= 1 mgL^{-1}) and against Gram-positive *Staphylococcus aureus* (MIC= 1 mgL^{-1}).

References

[1] C. P. Kaushik, M. Chahal, .*J. Chem. Sci*,. 2020 (132) 142

[2] A. Parate, L. K. Soni, R. Malviya, *Der Pharmacia Sinica* 2013 (4) 130

Acknowledgements

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