SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NOVEL BENZOTHIAZOLE DERIVATIVES

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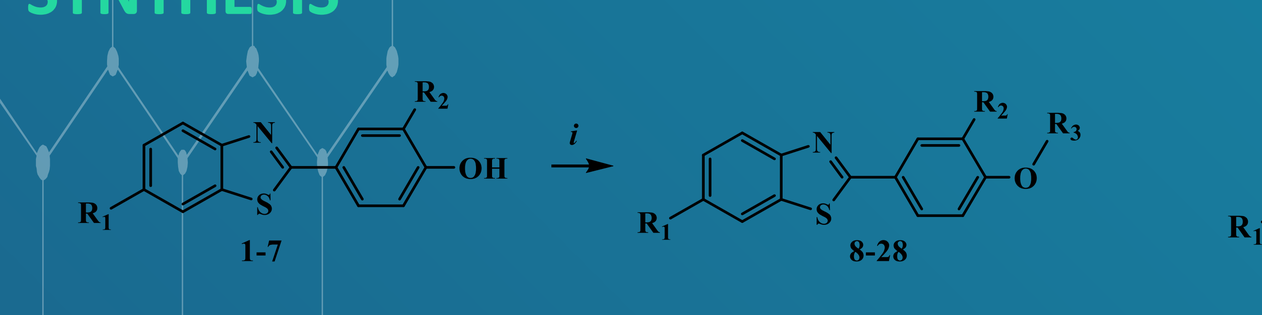
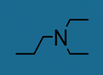
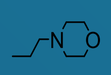
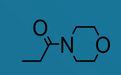
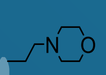
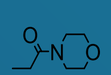
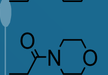
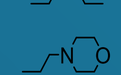
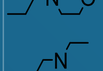
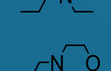
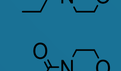
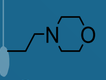
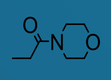
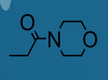
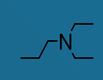
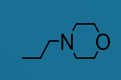
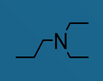
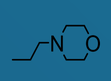
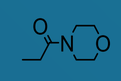
BACKGROUND

Infectious diseases caused by bacteria affect millions of people and represent one of leading causes of death worldwide. On the other side, resistance of pathogenic bacteria to existing antibacterial drugs presents an additional problem. Therefore, the design of new compounds has become one of the most important areas of antibacterial research today. Benzothiazole and their heterocyclic derivatives represent an important class of compounds possessing a wide spectrum of biological activities such as antitumor, antimicrobial, antidiabetic, anti-inflammatory, anticonvulsant, antiviral, antioxidant, antitubercular, antimalarial, photosensitizing, diuretic, analgesic and other activities.[2] Furthermore, benzothiazole–1,2,3-triazole–coumarin hybrid showed anti-*Moraxella catarrhalis* potency (MIC ≤ 0.25 μg/mL) comparable to that of the reference antibiotic azithromycin.[3]

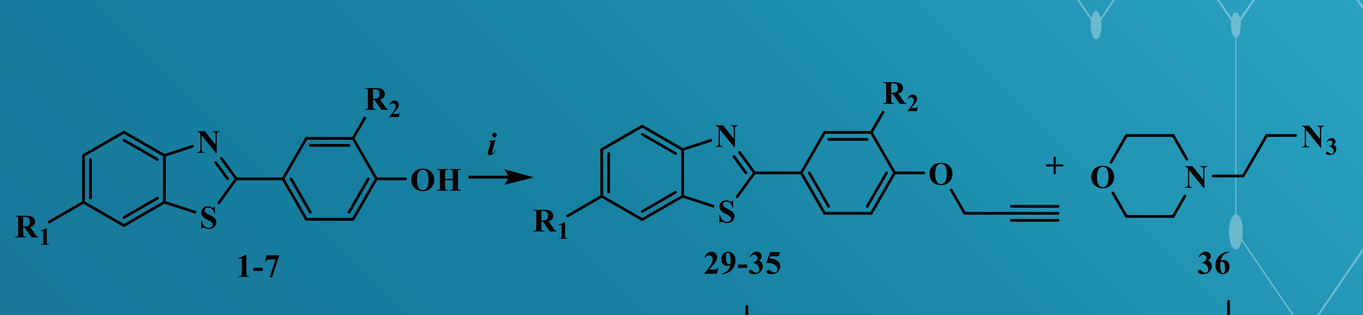
SYNTHESIS



compd	R_1	R_2	compd	R_1	R_2	compd	R_1	R_2
1	H	H	**4**	H	OCH_3	**6**	F	OCH_3
2	Cl	H	**5**	Cl	OCH_3	**7**	Cl	F
3	F	H						

compd	R_1	R_2	R_3	compd	R_1	R_2	R_3	compd	R_1	R_2	R_3
8	H	H		**15**	F	H		**22**	Cl	OCH_3	
9	H	H		**16**	F	H		**23**	F	OCH_3	
10	H	H		**17**	H	OCH_3		**24**	F	OCH_3	
11	Cl	H		**18**	H	OCH_3		**25**	F	OCH_3	
12	Cl	H		**19**	H	OCH_3		**26**	Cl	F	
13	Cl	H		**20**	Cl	OCH_3		**27**	Cl	F	
14	F	H		**21**	Cl	OCH_3		**28**	Cl	F	

SHEME 1. Conditions and reagents: (*i*) K_2CO_3, haloalkylating reagents, acetonitrile, reflux 24 h.



compd	R_1	R_2
29	H	H
30	Cl	H
31	F	H
32	H	OCH_3
33	Cl	OCH_3
34	F	OCH_3
35	Cl	F

compd	R_1	R_2	compd	R_1	R_2	compd	R_1	R_2
37	H	H	**40**	H	OCH_3	**43**	Cl	F
38	Cl	H	**41**	Cl	OCH_3			
39	F	H	**42**	F	OCH_3			

SHEME 2. Conditions and reagents: (*i*) ethanol or acetonitrile, K_2CO_3, 30 min, r.t., propargyl bromide, reflux, over night (*ii*) methanol, azide, copper (II) acetate, 48 h, reflux.

BIOLOGICAL EVALUATION

GRAM-POSITIVE BACTERIA

compd	MIC (μg/ml)				
	Staphylococcus aureus ATCC 25923	*Methicillin-resistant S. aureus* MRSA 11710	*Enterococcus faecalis* ATCC	*Methicillin-resistant S. aureus* MRSA 13276	*Enterococcus faecium* VRE MKB 3019
8	**16**	**32**	**32, 16**	**32**	**16**
9	>128	16, 8	>128	16, 8	>128
10	**8**	**128**	**16**	**8**	**16**
11	**4**	**4**	**4**	**2**	**4**
12	>128	>128	>128	>128	>128
13	**>128**	**128**	**16, 8**	**128**	**16**
14	**16**	**32**	**16**	**32**	**16**
15	>128	>128	>128	>128	>128
16	>128	>128	>128	16	128
17	>128	128	>128	128	>128
18	>128	>128	>128	>128	>128
19	>128	>128	>128	>128	>128
20	**16**	**8**	**16**	**8**	**8**
21	>128	>128	>128	>128	>128
22	>128	>128	>128	32	>128
23	**32**	**16**	**32**	**16**	**32**
24	>128	32	>128	32	>128
25	>128	>128	>128	>128	>128
26	>128	>128	>128	>128	>128
27	**8**	**2**	**16**	**2**	**2**
28-42	>128	>128	>128	>128	>128

GRAM-NEGATIVE BACTERIA

compd	MIC (μg/ml)						
	Escherichia coli ATCC 25922	*Klebsiella pneumoniae* ATCC 700603	*Pseudomonas aeruginosa* ATCC 27853	*Acinetobacter baumannii* ATCC 19606	*Escherichia coli* ESBL 26001	*Klebsiella pneumoniae* ESBL 9350 urin	*Acinetobacter baumanii* 9768
8	>128	>128	>128	128	**64**	>128	128
9	>128	>128	>128	>128	>128	>128	>128
10	>128	>128	>128	>128	>128	>128	>128
11	>128	>128	>128	**16**	**8**	>128	16
12	>128	>128	>128	>128	>128	>128	>128
13	>128	>128	>128	>128	>128	>128	>128
14	>128	>128	>128	>128	**64**	>128	128
15	>128	>128	>128	>128	>128	>128	>128
16	>128	>128	>128	>128	>128	>128	>128
17	>128	>128	>128	>128	>128	>128	>128
18	>128	>128	>128	>128	>128	>128	>128
20	>128	>128	>128	**32**	**16**	>128	**32**
21	>128	>128	>128	>128	>128	>128	>128
22	>128	>128	>128	>128	>128	>128	>128
23	>128	>128	>128	128	128,64	>128	128
24	>128	>128	>128	>128	>128	>128	>128
25	>128	>128	>128	>128	>128	>128	>128
26	>128	>128	>128	>128	>128	>128	>128
27	>128	>128	>128	>128	>128	>128	>128
28-42	>128	>128	>128	>128	>128	>128	>128

CONCLUSION

In order to investigate the antimicrobial activities, new 6-halobenzothiazole derivatives substituted in position 2 with aryl substituents were synthesized. The corresponding 6-halo-2-(4-hydroxyphenyl)benzothiazoles (**1-7**) were converted to 2-(4-alkoxyphenyl)benzothiazole (**8-28**) derivatives by an *O*-alkylation reaction. 1,4-disubstituted 1,2,3-triazole benzothiazole derivatives (**37-42**) were synthesized by copper(I) catalyzed click reaction of the corresponding terminal alkynes (**29-35**) and azide (**36**). Of the all evaluated compounds against Gram-positive bacteria (*Staphylococcus aureus* and *Enterococcus faecalis*) and Gram-negative bacteria (*Klebsiella pneumoniae, Escherichia coli* and *Pseudomonas aeruginosa*) benzothiazole derivatives with *N,N*-diethylamine substituent (**8, 11, 14, 23**) showed the strongest activity against gram-positive clinical strains resistant to antibiotics compared to standard drug amikacin.

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