SYNTHESIS AND BIOLOGICAL EVALUATION OF HYBRID 1,2,4-TRIAZOLE DERIVATIVES FEATURING A 1,8-NAPHTHALIMIDE CORE

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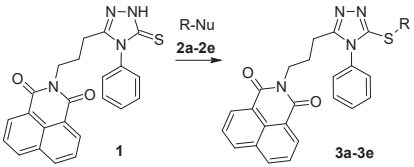
In this work, we set out to broaden the chemical diversity of 1,2,4-triazoles by integrating them with the compelling heterocyclic scaffold, 1,8-naphthalimide. The naphthalimide unit has recently attracted significant attention for its remarkable photophysical properties, DNA-intercalating ability, and demonstrated anticancer and antimicrobial activities [1–4]. By merging these two bioactive frameworks, we aim to develop a novel series of hybrid compounds with potentially synergistic properties.

The target compounds were synthesized via a multi-step process designed for precision and efficiency at every stage. In the initial step, esters 3a–3e of triazolylthioacetic acid were prepared through an alkylation reaction of triazole 1 (Scheme 1).

Scheme 1

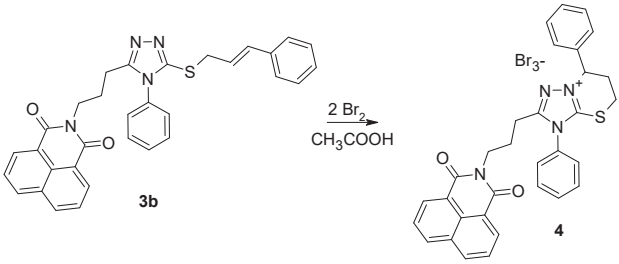


R = K (**2a, 3a**), CH_2-CH=CH-Ph (**2b, 3b**), CH2COOEt (**2c, 3c**), (CH2)3COOEt (**2d, 3d**), *p*-CH_2-Ph-COOMe (**2e, 3e**)

Nu = OH (**2a**), Br (**2b**), Cl (**2c-2e**)

In the second step, ester 3b was transformed into triazolium tribromide 4 (Scheme 2) by reacting the cinnamyl ester with a twofold molar excess of bromine in acetic acid, following a standard electrophilic heterocyclization protocol.

Scheme 2



The target compounds were synthesized via a multi-step process designed for precision and efficiency at each stage. Initially, esters 3a–3e of triazolylthioacetic acid were prepared through an alkylation reaction starting from triazole 1 (Scheme 1).

Subsequently, the series of 1,2,4-triazole derivatives was evaluated for antimicrobial activity. Various pathogenic and opportunistic microorganisms—including both Gram-negative and Gram-positive bacteria, as well as fungi—were exposed to these compounds at specific concentrations. Changes in colony forming units (CFU/ml) were measured to assess efficacy, revealing that although most compounds exhibited limited activity, candidates 3e and 4 significantly reduced microbial counts. All measured results are summarized in Table 1.

Among the tested microorganisms, *Bacillus cereus* ATCC 11778 exhibited the highest resistance. This Gram-positive, facultatively anaerobic, motile, and spore-forming bacterium is widely distributed in environments such as soil, plants, water, and the intestinal tract. Overall,

the results indicated that the hybrid compounds were generally more effective against Gram-negative bacteria (e.g., *Escherichia coli* (lac+), *Klebsiella oxytoca*, *Pseudomonas aeruginosa*, and *Serratia ficaria*) than against Gram-positive species. These findings underscore the potential of the hybrid compounds as promising antimicrobial agents and highlight the need for further studies to elucidate their mechanisms of action, safety profiles, and broader efficacy.

Table 1. Antagonistic activity of organic compounds against test strains of microorganisms

	Tested microorganisms	**Starting concentration м/о**	**Control**	**1**	**3a**	**3b**	**3c**	**3d**	**3e**	**4**
1	*Enterococcus faecalis*	$1{,}5\cdot10^8$	ND	ND	ND	ND	ND	ND	ND	ND
2	*Escherichia coli (lac+)*	$1{,}5\cdot10^8$	ND	ND	ND	ND	ND	ND	ND	ND
3	*Klebsiella oxytoca*	$1{,}5\cdot10^8$	ND	ND	ND	ND	ND	ND	ND	ND
4	*Pseudomonas aeruginosa*	$1{,}5\cdot10^8$	ND	ND	ND	ND	ND	ND	ND	ND
5	*Staphylococcus aureus*	$1{,}5\cdot10^8$	$1\cdot10^6$	ND	ND	ND	ND	ND	$1\cdot10^6$	ND
6	*Bacillus cereus ATCC 11778*	$1{,}5\cdot10^8$	$5\cdot10^8$	$4\cdot10^8$	$2\cdot10^8$	$2\cdot10^8$	$2\cdot10^8$	$1\cdot10^8$	$1\cdot10^8$	$3\cdot10^7$
7	*Geotrihium candidum*	$1{,}5\cdot10^8$	$2{,}4\cdot10^7$	ND	ND	ND	ND	ND	$2{,}4\cdot10^7$	ND
8	*Candida albicans*	$1{,}5\cdot10^8$	ND	ND	ND	ND	ND	ND	ND	ND
9	*Lactobacillus plantarum A*	$1{,}5\cdot10^8$	ND	ND	ND	ND	ND	ND	ND	ND
10	*Serratia ficaria*	$1{,}5\cdot10^8$	ND	ND	ND	ND	ND	ND	ND	ND

Experimental data revealed that compound 3e significantly reduced *Bacillus cereus* concentrations to $1\cdot10^8$ CFU/ml and demonstrated activity against *Staphylococcus aureus* ($1\cdot10^6$ CFU/ml) and *Geotrichum candidum* ($2.4\cdot10^7$ CFU/ml), indicating broad-spectrum efficacy. In contrast, compound 4 exhibited promising yet more selective activity by reducing *Bacillus cereus* levels to $3\cdot10^7$ CFU/ml.

These observations highlight the impact of structural modifications in 1,2,4-triazole derivatives on antimicrobial potency. In particular, compound 3e appears effective against multiple pathogens; its benzoate group may target bacterial esterases or similar enzymes—disrupting metabolic processes—while enhancing lipophilicity and membrane penetration. Meanwhile, the selective activity of compound 4 suggests that variations in functional groups and overall molecular structure can yield distinct antimicrobial profiles.

Collectively, these findings warrant further investigation into the mechanisms of action of these hybrid compounds, as well as comprehensive studies to evaluate their toxicity, pharmacokinetics, and therapeutic potential. Overall, the data underscore the importance of targeted structural modifications in developing effective antimicrobial agents.

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