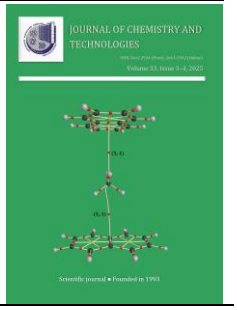
Journal of Chemistry and Technologies, 2025, *33*(3), 911-919

Journal of Chemistry and Technologies

pISSN 2663-2934 (Print), ISSN 2663-2942 (Online).

journal homepage: http://chemistry.dnu.dp.ua
editorial e-mail: chem.dnu@gmail.com



UDC 547.791; 615.27

SYNTHESIS OF NOVEL *N*-BENZYL AND RELATED *1H*-1,2,3-TRIAZOLE-4-CARBOXAMIDES AND THEIR ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES

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Received 24 July 2025; accepted 11 August 2025; available online 25 December 2025

Abstract

A series of novel *N*-benzyl and related *1H*-1,2,3-triazole-4-carboxamides was synthesized and investigated as potential antibacterial and antifungal agents. The new amides were obtained via a convenient synthetic route involving the cyclocondensation of aryl azides with *β*-ketoesters to form *1H*-1,2,3-triazole-4-carboxylic acids, followed by their conversion into amides through the reaction of the corresponding acid chlorides with appropriate amines. A preliminary antimicrobial screening at a concentration of 32 μg/mL was conducted against a panel of bacterial strains, including *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, as well as fungal pathogens *Candida albicans* and *Cryptococcus neoformans*. Several compounds demonstrated selective or broad-spectrum inhibitory activity, with compound 5m showing the most consistent effectiveness across all tested strains. Notable antibacterial activity was observed for compound 5n (20.20 % inhibition of *A. baumannii*), while compounds 5a (22.35 % inhibition of *C. neoformans*) and 5h (17.70 % inhibition of *C. albicans*) exhibited pronounced antifungal activity. Compound 7a showed a promising dual action profile, inhibiting *A. baumannii* by 21.05 % and *C. albicans* by 13.20 %. Among all the tested microorganisms, A. baumannii and C. albicans were the most sensitive to the studied compounds. The results indicate that specific structural features of these 1,2,3-triazole-4-carboxamides contribute significantly to their biological activity and highlight their potential as scaffolds for the development of new antimicrobial agents.

Keywords: *1H*-1,2,3-triazole-4-carboxamides; azides; *β*-ketoesters; cyclocondensation; antimicrobial action.

СИНТЕЗ НОВИХ N-БЕНЗИЛ ТА СПОРІДНЕНИХ 1H-1,2,3-ТРИАЗОЛ-4-КАРБОКСАМІДІВ ТА ЇХ АНТИБАКТЕРІАЛЬНА ТА ПРОТИГРИБКОВА АКТИВНІСТЬ

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Анотація

Серію нових *N*-бензильних і споріднених 1*H*-1,2,3-триазол-4-карбоксамідів синтезовано та досліджено як потенційні антибактеріальні та протигрибкові агенти. Нові аміди одержано за зручною синтетичною схемою з використанням циклоконденсації арилазидів з *β*-кетоестерами з утворенням *1H*-1,2,3-триазол-4-карбонових кислот та подальшим перетворенням їх в аміди шляхом реакції хлорангідридів кислот із відповідними амінами. Попередній антимікробний скринінг при концентрації 32 мкг/мл було проведено проти панелі бактеріальних штамів, включаючи *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* та *Acinetobacter baumannii*, а також грибкових патогенів *Candida albicans* і *Cryptococcus neoformans*. Кілька сполук продемонстрували селективну або широкоспектрову інгібуючу активність, причому сполука 5m показала найбільш стабільну ефективність серед усіх протестованих штамів. Помітну антибактеріальну активність виявлено для 5n (20.20 % інгібування *A. baumannii*), а протигрибкову – для 5a (22.35 % інгібування *C. neoformans*) і 5h (17.70 % інгібування *C. albicans*). Сполука 7a продемонструвала перспективний профіль подвійної дії – 21.05 % інгібування *A. baumannii* та 13.20 % інгібування *C. albicans*. Найбільш чутливими до дії досліджуваних сполук виявилися штами *A. baumannii* та *C. albicans*. Отримані дані свідчать про те, що специфічні структурні особливості цих 1,2,3-триазол-4-карбоксамідів сприяють їхній біологічній активності та підкреслюють їхній потенціал як основи для створення нових антимікробних засобів.

Ключові слова: *1H*-1,2,3-триазол-4-карбоксаміди; азиди; *β*-кетоестери; циклоконденсація; протимікробна дія.

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doi: 10.15421/jchemtech.v33i4.336132

Journal of Chemistry and Technologies, 2025, *33*(3), 911-919

Introduction

With the widespread use and sometimes even abuse of antibiotics, the problem of bacterial resistance to antibiotics has become very serious, and it is posing a great threat to global health [1–4]. The war in Ukraine has significantly disrupted healthcare infrastructure, surveillance systems, and infection control measures, contributing to a rise in antimicrobial resistance [5]. Overcrowded hospitals, limited access to diagnostics, and widespread empirical use of broad-spectrum antibiotics in wounded patients have accelerated the emergence and spread of resistant bacteria [6]. Additionally, forced migration and the breakdown of antimicrobial resistance reporting across borders may undermine coordinated international efforts to monitor and contain resistance [7]. Therefore, development of new antibiotics is imperative urgent task.

Triazoles are five-membered, nitrogen-containing aromatic heterocyclic scaffolds, with two isomeric forms, i. e. 1,2,3-triazole and 1,2,4-triazole. Triazole-containing compounds have a wide range of biological activities such as antibacterial, antifungal, anticancer, antioxidant, antitubercular, antimalarial, anti-HIV, anticonvulsant, anti-inflammatory, antiulcer, analgesic, and etc [8–11]. The bioactivities and the diversity of triazole-containing drugs have attracted wide interest in these heterocycles. Various antibiotic triazole hybrids have been developed, and most of which have shown potent antimicrobial activities summarized the recent reviews [12–14].

We focused on the study of 1,2,3-triazole-4-carboxamides as an antitumor [15] and antimicrobial [16] agent. It should be noted that among 1,2,3-triazole-4-carboxamide and related compounds, a number of higly active atimicrobe derivatives were founds. For example, 1,2,3-triazole-4-carboxamide **A** exhibited strong fungicidal activity against *Sclerotinia sclerotiorum* by inhibiting succinate dehydrogenase, indicating its potential as a novel pesticide [17]. Other study reported that novel 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamides with a piperazine moiety (Figure, **B**) exhibited broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative bacteria, as well as several fungal strains [18]. A related compound **C** showed notable antimicrobial activity, with MIC values of 2.8–6.2 μg/mL against Gram-positive and 4.0–5.2 μg/mL against Gram-negative bacteria, and demonstrated strong bactericidal effects against *Bacillus subtilis* and *Staphylococcus aureus*, outperforming standard drugs in some cases [19]. Additionally, compound **C** exhibited potent antibiofilm activity against *Staphylococcus aureus*, and molecular docking revealed strong binding of compound 2x to PBPs and DNA gyrase B via hydrogen bonds with Arg136 and Asp73 [17]. In our previous studies, among the compounds that exhibited antimicrobial activity [16], we did not observe significant structure–activity relationships when varying the substituents at positions 1 and 5 (compounds **D** and **E**). However, we noted the importance of the C4 chain lenghts within the amide fragment for biological activity. In particular, in our most recent work published in this journal, compounds containing an acetophenone fragment (compound **F**) demonstrated notable activity [20]. Based on these findings, we decided to synthesize and evaluate structurally related derivatives for their antimicrobial potential.

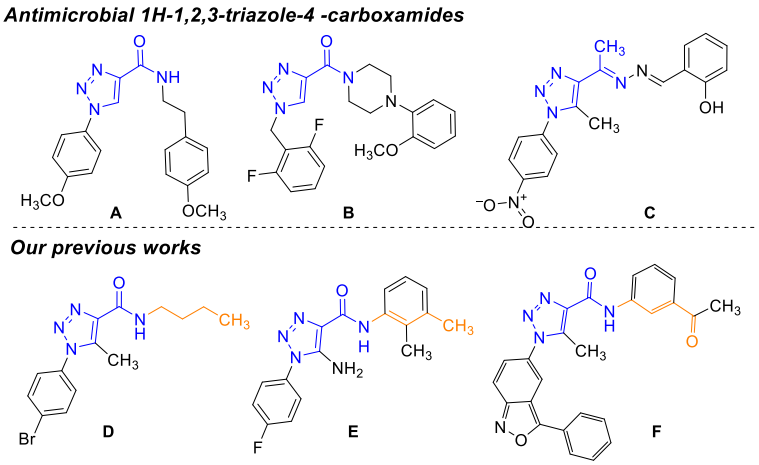


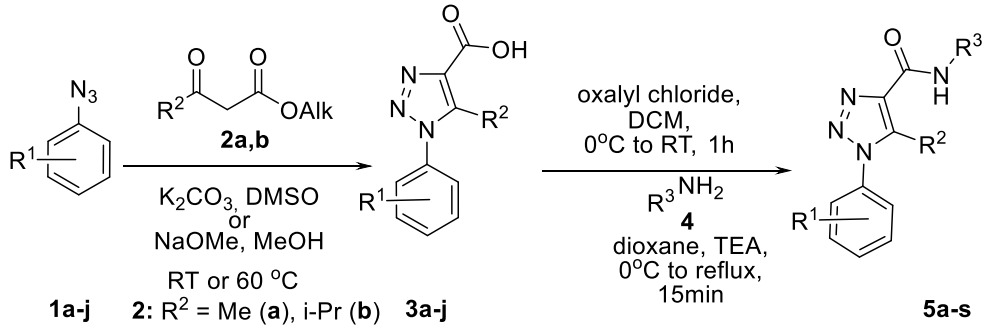
Figure. Antimicrobial 1-aryl-1H-1,2,3-triazole-4-carboxamides

Results and discussion

Chemistry. The compounds presented in the article were obtained in a convenient synthetic path (Scheme) starting from organic azides **1**. In the initial stage, 1-aryl-5-R^1-1*H*-1,2,3-triazole-4-carboxylic acids **3** were synthesized using the

Dimroth method, which involves base-catalyzed cyclocondensation of aryl azide **1** with *β*-ketoesters **2**. Notably, the Dimroth approach enables the efficient preparation of structurally diverse 1*H*-1,2,3-triazole-4-carboxylic acids bearing various substituents at positions 1 and 5, owing to the broad availability of azides and *β*-ketoesters [21]. This reaction proceeds with high yields under both mild (e.g., K_2CO_3, [22; 23]) and strong (e. g., NaOMe [24; 25]) basic conditions, depending on the steric and electronic nature of the substituents.

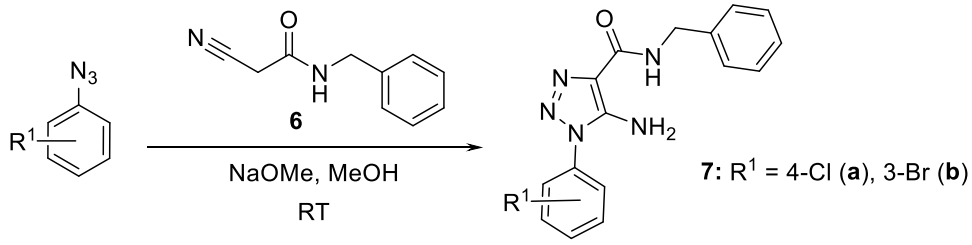
The structure and purity of the compounds are proved by ^{1}H NMR and LCMS methods.



1a-j **2:** R^2 = Me (**a**), i-Pr (**b**) **3a-j** **5a-s**

Alk = Me or Et

5: R^1 = 4-Br, R^2 = Me, R^3 = Bn (**a**)
R^1 = 4-F, R^2 = Me, R^3 = 2-Cl-C_6H_4-CH_2 (**b**)
R^1 = H, R^2 = Me, R^3 = 4-Cl-C_6H_4-CH_2 (**c**)
R^1 = H, R^2 = i-Pr, R^3 = 2-MeO-C_6H_4-CH_2 (**d**)
R^1 = 4-F, R^2 = Me, R^3 = Ph-CH-Me (**e**)
R^1 = 4-Me, R^2 = Me, R^3 = 4-F-C_6H_4-CH-Me (**f**)
R^1 = H, R^2 = Me, R^3 = 4-MeO-C_6H_4-CH-Me (**g**)
R^1 = 4-F, R^2 = Me, R^3 = 4-MeO-C_6H_4-CH-Me (**h**)
R^1 = 3-Me, R^2 = Me, R^3 = 2-Py-CH_2 (**i**)
R^1 = 4-Me, R^2 = Me, R^3 = 2-Py-CH_2 (**j**)
R^1 = 2,4-Me_2, R^2 = Me, R^3 = 2-Py-CH_2 (**k**)
R^1 = 3-Cl, R^2 = Me, R^3 = 2-Py-CH_2 (**l**)
R^1 = 4-Me, R^2 = Me, R^3 = 3-Py-CH_2 (**m**)
R^1 = 3,5-Me_2, R^2 = Me, R^3 = 3-Py-CH_2 (**n**)
R^1 = 2-Me, R^2 = Me, R^3 = 3-MeCH(OH)-C_6H_4 (**o**)
R^1 = 3-Me, R^2 = Me, R^3 = 3-MeCH(OH)-C_6H_4 (**p**)
R^1 = 4-Me, R^2 = Me, R^3 = 3-MeCH(OH)-C_6H_4 (**q**)
R^1 = 3,4-Me_2, R^2 = Me, R^3 = 3-MeCH(OH)-C_6H_4 (**r**)
R^1 = 4-MeO, R^2 = Me, R^3 = 3-Ac-C_6H_4 (**s**)



1a-j **7a,b**

Scheme. Synthetic routes to the target compounds

Biological activity. Antimicrobial screening. The results of the preliminary screening (two parallel trials) of the newly synthesized compounds in concentration 32 μg/mL (~100 μM) on seven pathogens (*S. aureus, E. coli, K. pneumoniae, P. aeruginosa, A. baumannii, C. albicans* and *C. neoformans*) are presented in Table.

The preliminary screening of the selected 1,2,3-triazole-4-carboxamide at a concentration of 32 μg/mL demonstrated a broad range of antimicrobial and antifungal activities, with significant variation depending on the specific compound and microbial strain. Among the compounds tested, **5m** exhibited the most consistent and promising broad-spectrum effect, inhibiting the growth of *Staphylococcus aureus* by 9.00 %, *Escherichia coli* by 8.15 %, *Klebsiella pneumoniae* by 8.90 %, *Pseudomonas aeruginosa* by 4.85 %, and *Acinetobacter baumannii* by 10.45 %. It also showed moderate antifungal activity with 6.10 % inhibition of *Candida albicans* and 2.20 % against *Cryptococcus neoformans*. Another compound of note is **5s**, which inhibited *K. pneumoniae* by 6.45 %, *P. aeruginosa* by 8.25 %, *A. baumannii* by 9.30 %, and also demonstrated notable antifungal effects, particularly 8.55 % against *C. albicans* and 15.05 % against *C. neoformans*. Compound **5j** showed high activity against *S. aureus* (11.20 %), *K. pneumoniae* (6.60 %), and *A. baumannii* (10.25 %), although its antifungal effects were lower, with only 5.70 % inhibition of *C. albicans* and a slightly negative

effect on *C. neoformans* (–3.05 %). **5l** was similarly active against *S. aureus* (11.40 %) and moderately active against *K. pneumoniae* (5.90 %) and *A. baumannii* (2.20 %), with limited antifungal effects. **5a** stood out for its selective and antifungal activity, particularly 22.35 % inhibition of *C. neoformans*—the highest value observed in the entire study—alongside 14.20 % inhibition of *A. baumannii* and 9.30 % of *C. albicans*, although its antibacterial effects against other strains were minimal or negative. Compound **7a** also showed remarkable inhibition of *A. baumannii* (21.05 %) and antifungal activity against *C. albicans* (13.20 %), while maintaining mild to moderate antibacterial activity. A few compounds such as **5d**, **5e**, and **5h** exhibited pronounced antifungal activity, with *C. albicans* inhibition values of 15.25 %, 11.85 %, and 17.70 %, respectively, despite being largely inactive or slightly stimulatory toward bacterial strains. On the other hand, several compounds demonstrated poor or even negative activity across most strains, notably **5f**, which consistently reduced growth inhibition with negative values such as –17.85 % (*S. aureus*), –13.05 % (*E. coli*), and –20.95 % (*A. baumannii*), suggesting potential microbial stimulation or a lack of efficacy. Similarly, **5r** had a strong negative impact on *C. neoformans* (–59.20%), representing a possible toxic or growth-promoting effect. Overall, the results highlight several candidates with selective or broad antimicrobial potential, particularly **5m**, **5s**, **5j**, and **7a**, which demonstrated moderate to inhibitory effects and merit further investigation as potential antimicrobial agents.

Table

Preliminary screening of selected 1,2,3-triazole-4-carboxamide

	The percentage of growth inhibition (GI) in concentration 32 μg/mL, % [a]						
	Bacteria					**Fungal**	
N	*S. aureus ATCC 43300*	*E. coli ATCC 25922*	*K. pneumoniae ATCC 700603*	*P. aeruginosa ATCC 27853*	*A. baumannii ATCC 19606*	*C. albicans ATCC 90028*	*C. neoformans ATCC 208821*
5a	–2.65 ± 2.05	2.85 ± 3.32	1.90 ± 5.80	8.30 ± 0.14	**14.20 ± 2.97**	9.30 ± 4.67	**22.35 ± 10.96**
5b	–3.25 ± 1.20	0.70 ± 1.98	–8.65 ± 6.72	2.15 ± 1.48	–2.85 ± 3.89	7.90 ± 2.69	3.35 ± 10.68
5c	9.55 ± 2.33	0.90 ± 0.85	–0.05 ± 1.63	1.80 ± 0.85	6.35 ± 0.49	3.65 ± 0.64	–3.10 ± 3.39
5d	–7.85 ± 2.76	0.45 ± 2.47	0.05 ± 4.17	2.75 ± 2.47	–2.20 ± 8.63	**15.25 ± 4.88**	5.80 ± 6.51
5e	–4.55 ± 2.76	–6.55 ± 2.76	–2.90 ± 0.00	–6.25 ± 0.21	–3.30 ± 10.75	**11.85 ± 1.06**	–12.55 ± 7.28
5f	–17.85 ± 1.20	–13.05 ± 3.46	–12.25 ± 1.06	–9.20 ± 1.13	–20.95 ± 3.46	**10.25 ± 0.35**	–5.25 ± 8.56
5g	–0.90 ± 3.11	–3.20 ± 9.05	–4.05 ± 0.21	–0.55 ± 1.48	–9.40 ± 0.71	7.45 ± 6.15	–2.50 ± 0.99
5h	–4.80 ± 2.12	–5.75 ± 8.98	–9.35 ± 6.43	–2.85 ± 1.77	–12.70 ± 6.36	**17.70 ± 12.73**	–3.65 ± 1.34
5i	0.60 ± 0.14	–6.30 ± 1.98	–0.50 ± 2.97	–2.00 ± 1.13	–4.70 ± 4.38	1.60 ± 2.12	–0.55 ± 0.92
5j	**11.20 ± 1.56**	0.45 ± 5.87	6.60 ± 1.13	–0.90 ± 2.55	**10.25 ± 5.30**	5.70 ± 1.56	–3.05 ± 7.42
7k	8.15 ± 4.31	0.00 ± 7.35	4.65 ± 3.46	0.65 ± 4.03	4.00 ± 6.36	2.75 ± 3.89	–5.75 ± 8.98
5l	**11.40 ± 1.41**	–1.50 ± 6.08	5.90 ± 0.99	0.15 ± 0.07	2.20 ± 2.55	2.40 ± 4.38	–6.75 ± 0.21
5m	9.00 ± 4.53	8.15 ± 1.77	8.90 ± 1.98	4.85 ± 1.06	**10.45 ± 3.32**	6.10 ± 0.14	2.20 ± 3.54
5n	0.80 ± 5.23	3.90 ± 1.41	0.45 ± 6.15	4.30 ± 2.97	**20.20 ± 17.11**	7.00 ± 1.70	–5.95 ± 14.50
5o	–8.80 ± 5.37	2.05 ± 0.92	1.15 ± 2.47	**13.70 ± 5.52**	4.25 ± 6.43	7.50 ± 4.95	**10.00 ± 0.85**
5p	7.15 ± 17.89	0.95 ± 2.47	–0.15 ± 12.66	6.75 ± 5.30	7.25 ± 0.07	7.75 ± 1.63	–1.15 ± 7.00
5q	3.65 ± 3.04	–3.05 ± 0.64	1.20 ± 4.53	–4.55 ± 2.19	0.75 ± 5.73	7.10 ± 2.55	–8.70 ± 6.51
5r	5.25 ± 4.17	–2.30 ± 0.99	2.55 ± 5.73	0.55 ± 3.61	5.15 ± 8.56	7.60 ± 2.12	–59.20 ± 24.32
5s	–15.95 ± 12.37	4.70 ± 2.97	6.45 ± 4.03	8.25 ± 0.49	9.30 ± 5.80	8.55 ± 0.07	**15.05 ± 10.82**
7a	2.75 ± 6.29	0.15 ± 1.63	2.65 ± 11.38	3.80 ± 2.97	**21.05 ± 13.36**	**13.20 ± 3.68**	–7.45 ± 11.38
7b	–7.70 ± 6.36	3.60 ± 0.85	–1.95 ± 13.22	–2.20 ± 5.80	–7.95 ± 17.32	6.60 ± 2.40	2.00 ± 3.68

Comment: Data are presented as M ± SD calculated from two parallel trials [a].

Experimental Section

All chemicals used were of laboratory grade and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on Varian Unity Plus 400 (400 MHz) spectrometers in DMSO-d_6 solutions using TMS or the deuterated solvent as internal reference. Mass spectral analyses were performed using an Agilent 1100 series LC/MSD with API-ES/APCI mode (200 eV). Elemental analyses were accomplished using a Carlo Erba 1106 instrument. Melting points were determined on a Boetius melting point apparatus. The starting 1*H*-1,2,3-triazole 4-carboxylic acids **3** were synthesized according to previously described synthetic procedures [16].

*General procedure for synthesis of compounds **5***

The appropriate 1,2,3-triazole-4-carboxylic acids **3** (1 mmol, 1 eq.) was dissolved in dry DCM (30 mL) and cooled in an ice bath. Oxalyl chloride (173 μL, 2 mmol, 2 eq.) was added, followed by 1 drop of the DMF, and the reaction was stirred for 1 h at room temperature. Evaporation of the volatiles under reduced pressure afforded crude acid chloride, which was immediately carried onto the next step. The acid chloride was added to the solution of appropriate amine **4** (1 mmol, 1 eq.) and TEA (140 μL, 1 mmol, 1 eq.) in dioxane (10 mL)

under ice bath cooling. It was left for 1 h at room temperature, then heated to reflux and reflux for 1 min. Then the mixture was cooled to room temperature and diluted with water (50 mL). Crude product **5** was collected by filtration and recrystallized from ethanol with a small addition of the DMF. Finally, the compounds **5** were dried at 60°C under vacuum to yield pure products.

N-benzyl-1-(4-bromophenyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide ***5a***

Yield: 94 % as a white solid; mp = 165–167 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (t, *J* = 6.4 Hz, 1H, NH), 7.78 (d, *J* = 8.7 Hz, 2H, 2H^{Ar}), 7.56 (d, *J* = 8.7 Hz, 2H, 2H^{Ar}), 7.35 (d, *J* = 7.1 Hz, 2H, 2H^{Ph}), 7.29 (t, *J* = 7.5 Hz, 2H, 2H^{Ph}), 7.20 (t, *J* = 7.2 Hz, 1H, H^{Ph}), 4.48 (d, *J* = 6.1 Hz, 2H, CH_2), 2.58 (s, *J* = 6.9 Hz, 3H, CH_3). MS (m/z, ES-API) 371, 373 (M^++1); Anal. calcd for $C_{17}H_{15}BrN_4O$: C, 55.00; H, 4.07; N, 15.09; Found: C, 54.89; H, 3.97; N, 15.24.

N-(2-chlorobenzyl)-1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide ***5b***

Yield: 88 % as a white solid; mp = 161–163 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (t, *J* = 6.2 Hz, 1H, NH), 7.68 – 7.62 (m, 2H, 2H^{Ar}), 7.44 – 7.36 (m, 4H, 4H^{Ar}), 7.30 – 7.22 (m, 2H, 2H^{Ar}), 4.57 (d, *J* = 6.2 Hz, 2H, CH_2), 2.56 (s, 3H, CH_3). MS (m/z, ES-API) 345 (M^++1); Anal. calcd for $C_{17}H_{14}ClFN_4O$: C, 59.22; H, 4.09; N, 16.25; Found: C, 59.09; H, 4.20; N, 16.14.

N-(4-chlorobenzyl)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carboxamide ***5c***

Yield: 95 % as a white solid; mp = 154–156 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (t, *J* = 6.3 Hz, 1H, NH), 7.65 – 7.54 (m, 5H, 5H^{Ph}), 7.37 (d, *J* = 8.4 Hz, 2H, 2H^{Ar}), 7.29 (d, *J* = 8.4 Hz, 2H, 2H^{Ar}), 4.46 (d, *J* = 6.3 Hz, 2H, CH_2), 2.57 (s, 3H, CH_3). MS (m/z, ES-API) 327 (M^++1); Anal. calcd for $C_{17}H_{15}ClN_4O$: C, 62.48; H, 4.63; N, 17.15; Found: C, 62.59; H, 4.51; N, 17.26.

5-isopropyl-N-(2-methoxybenzyl)-1-phenyl-1H-1,2,3-triazole-4-carboxamide ***5d***

Yield: 73 % as a white solid; mp = 137–139 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (t, *J* = 6.1 Hz, 1H, NH, NH), 7.67 – 7.60 (m, 3H, 3H^{Ph}), 7.48 – 7.41 (m, 2H, 3H^{Ph}), 7.27 – 7.18 (m, 2H, 2H^{Ar}), 6.94 (d, *J* = 8.1 Hz, 1H, H^{Ar}), 6.88 (t, *J* = 7.4 Hz, 1H, H^{Ar}), 4.51 (d, *J* = 6.1 Hz, 2H, CH_2), 3.90 (s, 3H, CH_3), 3.31 – 3.18 (m, 1H, CH), 1.33 (d, *J* = 7.0 Hz, 6H). MS (m/z, ES-API) 351 (M^++1); Anal. calcd for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99; Found: C, 68.65; H, 6.26; N, 15.78.

1-(4-fluorophenyl)-5-methyl-N-(1-phenylethyl)-1H-1,2,3-triazole-4-carboxamide ***5e***

Yield: 95 % as a white solid; mp = 128–130 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (d, *J* = 8.1 Hz, 1H, NH), 7.61 (dd, *J* = 8.7, 4.8 Hz, 2H, 2H^{Ar}), 7.42 (d, *J* = 8.4 Hz, 2H, 2H^{Ph}), 7.38 (t, *J* = 8.6 Hz, 2H, 2H^{Ar}), 7.32 – 7.26 (m, 3H, 3H^{Ph}), 5.23 – 5.11 (m, 1H, CH), 2.54 (s, 3H, CH_3), 1.53 (d, *J* = 7.1 Hz, 3H, CH_3). MS (m/z, ES-API) 325 (M^++1); Anal. calcd for $C_{18}H_{17}FN_4O$: C, 66.65; H, 5.28; N, 17.27; Found: C, 66.74; H, 5.39; N, 17.11.

N-(1-(4-fluorophenyl)ethyl)-5-methyl-1-(p-tolyl)-1H-1,2,3-triazole-4-carboxamide ***5f***

Yield: 93 % as a white solid; mp = 119–121 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (d, *J* = 8.5 Hz, 1H, NH), 7.46 (dd, *J* = 8.8, 5.4 Hz, 2H, 2H^{Ar}), 7.44 – 7.34 (m, 4H, 4H^{Ar}), 7.04 (t, *J* = 8.8 Hz, 2H, 2H^{Ar}), 5.19 (p, *J* = 7.1 Hz, 1H, CH), 2.53 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 1.55 (d, *J* = 7.1 Hz, 3H, CH_3). MS (m/z, ES-API) 339 (M^++1); Anal. calcd for $C_{19}H_{19}FN_4O$: C, 67.44; H, 5.66; N, 16.56; Found: C, 67.32; H, 5.52; N, 16.73.

N-(1-(4-methoxyphenyl)ethyl)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carboxamide ***5g***

Yield: 92% as a white solid; mp = 97–99 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, *J* = 8.5 Hz, 1H, NH), 7.65 – 7.52 (m, 5H, 5H^{Ph}), 7.34 (d, *J* = 8.6 Hz, 2H, 2H^{Ar}), 6.83 (d, *J* = 8.7 Hz, 2H, 2H^{Ar}), 5.15 (p, *J* = 6.9 Hz, 1H, CH), 3.75 (s, 3H, CH_3O), 2.54 (s, 3H, CH_3), 1.53 (d, *J* = 7.0 Hz, 3H, CH_3). MS (m/z, ES-API) 337 (M^++1); Anal. calcd for : $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16.66; Found: C, 67.73; H, 6.09; N, 16.51.

1-(4-fluorophenyl)-N-(1-(4-methoxyphenyl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide ***5h***

Yield: 94 % as a white solid; mp = 135–137 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, *J* = 8.5 Hz, 1H, NH), 7.63 (dd, *J* = 8.6, 4.8 Hz, 2H, 2H^{Ar}), 7.36 (t, *J* = 8.6 Hz, 2H, 2H^{Ar}), 7.34 (d, *J* = 8.6 Hz, 2H, 2H^{Ar}), 6.83 (d, *J* = 8.7 Hz, 2H, 2H^{Ar}), 5.14 (p, *J* = 6.9 Hz, 1H, CH), 3.76 (s, 3H, CH_3O), 2.55 (s, 3H, CH_3), 1.52 (d, *J* = 7.0 Hz, 3H, CH_3). MS (m/z, ES-API) 355 (M^++1); Anal. calcd for : $C_{19}H_{19}FN_4O_2$: C, 64.40; H, 5.40; N, 15.81; Found: C, 64.49; H, 5.27; N, 15.70.

5-methyl-N-(pyridin-2-ylmethyl)-1-(m-tolyl)-1H-1,2,3-triazole-4-carboxamide ***5i***

Yield: 90 % as a white solid; mp = 127–129 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (t, *J* = 5.9 Hz, 1H, NH), 8.52 (dd, *J* = 4.8, 1.7 Hz, 1H, H^{Py-6}), 7.71 (td, *J* = 7.7, 1.8 Hz, 1H, H^{Py-4}), 7.49 (t, *J* = 7.7 Hz, 1H), 7.40 – 7.27 (m, 4H, 3H^{Ar}+H^{Py-3}), 7.23 (dd, *J* = 7.4, 4.9 Hz, 1H, H^{Py-5}), 4.63 (d, *J* = 5.9 Hz, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.46 (s, 3H, CH_3). MS (m/z, ES-API) 308 (M^++1); Anal. calcd for $C_{17}H_{17}N_5O$: C, 66.43; H, 5.58; N, 22.79; Found: C, 66.59; H, 5.44; N, 22.70.

5-methyl-N-(pyridin-2-ylmethyl)-1-(p-tolyl)-1H-1,2,3-triazole-4-carboxamide ***5j***

Yield: 92 % as a white solid; mp = 120–122 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (t, *J* = 5.9 Hz, 1H, NH), 8.52 (dd, *J* = 4.8, 1.7 Hz, 1H, H^{Py-6}), 7.71 (td, *J* = 7.8, 1.8 Hz, 1H, H^{Py-4}), 7.45 – 7.38 (m, 4H, 4H^{Ar}), 7.38 (d, *J* = 7.8 Hz, 1H, H^{Py-3}), 7.20 (dd, *J* = 7.4, 4.9 Hz,

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1H, H^{Py-5}), 4.62 (d, *J* = 5.9 Hz, 2H, CH_2), 2.48 (s, 3H, CH_3) , 2.32 (s, 3H, CH_3). MS (m/z, ES-API) 308 (M^++1); Anal. calcd for $C_{17}H_{17}N_5O$: C, 66.43; H, 5.58; N, 22.79; Found: C, 66.26; H, 5.71; N, 22.87.

1-(2,4-dimethylphenyl)-5-methyl-N-(pyridin-2-ylmethyl)-1H-1,2,3-triazole-4-carboxamide ***5k***

Yield: 87 % as a white solid; mp = 126–128 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (t, *J* = 5.9 Hz, 1H, NH), 8.54 (dd, *J* = 4.8, 1.7 Hz, 1H, H^{Py-6}), 7.70 (td, *J* = 7.7, 1.8 Hz, 1H, H^{Py-4}), 7.39 (d, *J* = 7.8 Hz, 1H, H^{Py-3}), 7.28 – 7.16 (m, 4H, $3H^{Ar}$+H^{Py-5}), 4.63 (d, *J* = 5.9 Hz, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.31 (s, 3H, CH_3). MS (m/z, ES-API) 322 (M^++1); Anal. calcd for $C_{18}H_{19}N_5O$: C, 67.27; H, 5.96; N, 21.79; Found: C, 67.40; H, 5.78; N, 21.90.

1-(3-chlorophenyl)-5-methyl-N-(pyridin-2-ylmethyl)-1H-1,2,3-triazole-4-carboxamide ***5l***

Yield: 89 % as a white solid; mp = 136–138 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (t, *J* = 5.9 Hz, 1H, NH), 8.54 (dd, *J* = 4.8, 1.7 Hz, 1H, H^{Py-6}), 7.71 (td, *J* = 7.7, 1.8 Hz, 1H, H^{Py-4}), 7.68 – 7.53 (m, 4H, $4H^{Ar}$), 7.38 (d, *J* = 7.8 Hz, 1H, H^{Py-3}), 7.24 (dd, *J* = 7.4, 4.9 Hz, 1H, H^{Py-5}), 4.61 (d, *J* = 5.9 Hz, 2H, CH_2), 2.58 (s, 3H, CH_3). MS (m/z, ES-API) 328 (M^++1); Anal. calcd for $C_{16}H_{14}ClN_5O$: C, 58.63; H, 4.31; N, 21.37; Found: C, 58.75; H, 4.14; N, 21.21.

5-methyl-N-(pyridin-3-ylmethyl)-1-(p-tolyl)-1H-1,2,3-triazole-4-carboxamide ***5m***

Yield: 91 % as a white solid; mp = 133–135 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (t, *J* = 6.1 Hz, 1H, NH), 8.55 (s, 1H, H^{Py}), 8.40 (dd, *J* = 4.8, 1.5 Hz, 1H, H^{Py}), 7.74 (d, *J* = 7.9 Hz, 1H, H^{Py}), 7.46 – 7.35 (m, 4H, $4H^{Ar}$), 7.32 – 7.23 (m, 1H, H^{Py}), 4.49 (d, *J* = 6.2 Hz, 2H, CH_2), 2.54 (s, 3H, CH_3), 2.46 (s, 3H, CH_3); MS (m/z, ES-API) 308 (M^++1); Anal. calcd for $C_{17}H_{17}N_5O$: C, 66.43; H, 5.58; N, 22.79; Found: C, 66.36; H, 5.49; N, 22.68.

1-(3,5-dimethylphenyl)-5-methyl-N-(pyridin-3-ylmethyl)-1H-1,2,3-triazole-4-carboxamide ***5n***

Yield: 89 % as a white solid; mp = 134–136 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (t, *J* = 6.3 Hz, 1H, NH), 8.55 (s, 1H, H^{Py}), 8.41 (dd, *J* = 4.8, 1.6 Hz, 1H, H^{Py}), 7.74 (d, *J* = 7.9 Hz, 1H, H^{Py}), 7.32 – 7.24 (m, 1H, H^{Py}), 7.19 (s, 1H, $1H^{Ar}$), 7.13 (s, 2H, $2H^{Ar}$), 4.49 (d, *J* = 6.3 Hz, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.41 (s, 6H, $2CH_3$); MS (m/z, ES-API) 322 (M^++1); Anal. calcd for $C_{18}H_{19}N_5O$: C, 67.27; H, 5.96; N, 21.79; Found: C, 67.35; H, 6.03; N, 21.87.

N-(3-(1-hydroxyethyl)phenyl)-5-methyl-1-(o-tolyl)-1H-1,2,3-triazole-4-carboxamide ***5o***

Yield: 88 % as a white solid; mp = 97–99 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H, NH), 7.84 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 4.94 (d, *J* = 3.3 Hz, 1H, OH), 4.75 – 4.63 (m, 1H, CH), 2.43 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 1.36 (d, *J* = 6.4 Hz, 3H, CH_3). MS (m/z, ES-API) 337 (M^++1); Anal. calcd for : $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16.66; Found: C, 67.75; H, 6.10; N, 16.81.

N-(3-(1-hydroxyethyl)phenyl)-5-methyl-1-(m-tolyl)-1H-1,2,3-triazole-4-carboxamide ***5p***

Yield: 90 % as a white solid; mp = 95–97 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H, NH), 7.84 (s, 1H), 7.66 (d, *J* = 8.8 Hz, 1H, $1H^{Ar}$), 7.50 (t, *J* = 8.0 Hz, 1H, $1H^{Ar}$), 7.41 – 7.34 (m, 3H, $3H^{Ar}$), 7.22 (t, *J* = 7.8 Hz, 1H, $1H^{Ar}$), 7.05 (d, *J* = 7.6 Hz, 1H, $1H^{Ar}$), 4.94 (d, *J* = 4.0 Hz, 1H, OH), 4.75 – 4.64 (m, 1H, CH), 2.62 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 1.36 (d, *J* = 6.4 Hz, 3H, CH_3). MS (m/z, ES-API) 337 (M^++1); Anal. calcd for : $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16.66; Found: C, 67.77; H, 5.88; N, 16.54.

N-(3-(1-hydroxyethyl)phenyl)-5-methyl-1-(p-tolyl)-1H-1,2,3-triazole-4-carboxamide ***5q***

Yield: 94 % as a white solid; mp = 169–171 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H, NH), 7.83 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H, $1H^{Ar}$), 7.46 (d, *J* = 8.4 Hz, 2H, $2H^{Ar}$), 7.41 (d, *J* = 8.4 Hz, 2H, $2H^{Ar}$), 7.22 (t, *J* = 7.8 Hz, 1H, $1H^{Ar}$), 7.05 (d, *J* = 7.6 Hz, 1H, $1H^{Ar}$), 4.94 (d, *J* = 4.0 Hz, 1H, OH), 4.78 – 4.58 (m, 1H, CH), 2.60 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 1.36 (d, *J* = 6.4 Hz, 3H, CH_3). MS (m/z, ES-API) 337 (M^++1); Anal. calcd for : $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16.66; Found: C, 67.93; H, 6.06; N, 16.80.

1-(3,4-dimethylphenyl)-N-(3-(1-hydroxyethyl)phenyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide ***5r***

Yield: 92 % as a white solid; mp = 125–127 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H, NH), 7.84 (s, 1H, $1H^{Ar}$), 7.67 (d, *J* = 7.9 Hz, 1H, $1H^{Ar}$), 7.37 – 7.33 (m, 2H, $2H^{Ar}$), 7.26 (dd, *J* = 8.0, 2.0 Hz, 1H, $1H^{Ar}$), 7.23 (t, *J* = 7.9 Hz, 1H, $1H^{Ar}$), 7.05 (d, *J* = 7.6 Hz, 1H, $1H^{Ar}$), 4.95 (d, *J* = 4.0 Hz, 1H, OH), 4.80 – 4.58 (m, 1H, CH), 2.60 (s, 3H, CH_3), 2.36 (s, 6H, $2CH_3$), 1.36 (d, *J* = 6.4 Hz, 3H, CH_3). MS (m/z, ES-API) 351 (M^++1); Anal. calcd for : $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99; Found: C, 68.70; H, 6.26; N, 16.07.

N-(3-acetylphenyl)-1-(4-methoxyphenyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide ***5s***

Yield: 95 % as a white solid; mp = 192–194 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H, NH), 8.54 (s, 1H, $1H^{Ar}$), 8.12 (d, *J* = 8.1 Hz, 1H, $1H^{Ar}$), 7.63 (d, *J* = 7.7 Hz, 1H, $1H^{Ar}$), 7.49 (d, *J* = 9.0 Hz, 2H, $2H^{Ar}$), 7.42 (t, *J* = 7.9 Hz, 1H, $1H^{Ar}$), 7.12 (d, *J* = 9.0 Hz, 2H, $1H^{Ar}$), 3.88 (s, 3H, CH_3O), 2.59 (s, 3H, CH_3), 2.58 (s, 3H, CH_3). MS (m/z, ES-API) 351 (M^++1); Anal. calcd for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99; Found: C, 65.29; H, 5.30; N, 16.08.

General Procedure for the Preparation of 5-amino-1-aryl-1H-1,2,3-triazole-4-carboxamides 7

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Sodium (0.023 g, 1 mmol) was added to 2 mL of absolute methanol. The appropriate cyanacetamide **6** (1 mmol) and azide **1** (1 mmol) were slowly added to the obtained sodium methylate solution. The mixture was kept for 30 min. The obtained solid was filtered, washed with water and crystallized from ethanol.

5-amino-N-benzyl-1-(4-chlorophenyl)-1H-1,2,3-triazole-4-carboxamide ***7a***

Yield: 90 % as a white solid; mp = 194–196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (t, *J* = 6.1 Hz, 1H, NH), 7.62 (d, *J* = 9.2 Hz, 2H, 2H^{Ar}), 7.58 (d, *J* = 9.2 Hz, 2H, 2H^{Ar}), 7.34 (d, *J* = 7.1 Hz, 2H, 2H^{Ph}), 7.31 – 7.25 (m, 3H, 3H^{Ph}), 6.30 (s, 2H, NH_2), 4.47 (d, *J* = 6.3 Hz, 2H, CH_2). MS (m/z, ES-API) 328 (M^++1); Anal. calcd for $C_{16}H_{14}ClN_5O$: C, 58.63; H, 4.31; N, 21.37; Found: C, 58.77; H, 4.20; N, 21.28.

5-amino-N-benzyl-1-(3-bromophenyl)-1H-1,2,3-triazole-4-carboxamide ***7b***

Yield: 91 % as a white solid; mp = 178–180 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (t, *J* = 6.2 Hz, 1H, NH), 7.78 (t, *J* = 1.9 Hz, 1H, 1H^{Ar}), 7.62 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H, 1H^{Ar}), 7.54 (t, *J* = 8.0 Hz, 1H, 1H^{Ar}), 7.44 (dd, *J* = 1.8, 0.8 Hz, 1H, 1H^{Ar}), 7.34 (d, *J* = 7.4 Hz, 2H, 2H^{Ph}), 7.28 (t, *J* = 7.5 Hz, 2H, 2H^{Ph}), 7.19 (t, *J* = 7.2 Hz, 1H, 1H^{Ph}), 6.14 (s, 2H, NH_2), 4.46 (d, *J* = 6.3 Hz, 2H, CH_2). MS (m/z, ES-API) 372, 374 (M^++1); Anal. calcd for : $C_{16}H_{14}BrN_5O$: C, 51.63; H, 3.79; N, 18.82; Found: C, 51.57; H, 3.86; N, 18.72.

Antimicrobial assays via CO-ADD [26]

The compounds have been investigated for activity towards one Gram-positive bacteria (*S. aureus* ATCC 43300 MRSA), four Gram-negative bacteria (*E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *K. pneumoniae* ATCC 700603, *A. baumannii* ATCC 19606), and two yeasts (*C. albicans* ATCC 90028 and *C. neoformans* H99 ATCC 208821), and this research was performed by the Community for Open Antimicrobial Drug Discovery (CO-ADD).

Initially, the tests were carried out at a single compound concentration of 32 μg/mL in duplicate, to identify any active compound. All substances were dissolved in DMSO to form a stock concentration of 10 mg/mL. Aliquots were diluted in water and 5 μL were dispensed into empty 384-well plates in duplicate for each strain and cell-assayed. As soon as cells were added to the plates, this gave a final compound concentration of 32 μg/mL, a maximum DMSO concentration of 0.3 %.

All bacteria overnight were cultured in cation-adjusted Q14 Mueller–Hinton broth (CAMHB) at 37 °C. The resultant mid-log phase cultures were added to each well of the compound containing plates (384-well nonbinding surface plates-Corning 3640), giving a cell density of 5×10^5 CFU/mL (colony-forming units/mL). All plates were covered and incubated at 37 °C for 18 h without shaking. Inhibition of bacterial growth was determined by measuring absorbance at 600 nm. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (bacteria without inhibitors) on the same plate as references. Growth inhibition of *C. albicans* was determined by measuring absorbance at 530 nm, while the growth inhibition of *C. neoformans* was determined by measuring the difference in absorbance between 600 and 570 nm, after the addition of resazurin (0.001 % final concentration) and incubation at 35 °C for additional 2 h. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (bacteria without inhibitors) on the same plate as references. Percentage growth inhibition of an individual sample is calculated based on Negative controls (media only) and Positive Controls (bacterial/fungal media without inhibitors). Negative inhibition values indicate that the growth rate (defined in OD = 600 nm) is higher compared to the Negative Control (Bacteria/fungi only, set to 0% inhibition). The growth rates for all bacteria and fungi have a variation of -/+ 10%, which is within the reported normal distribution of bacterial/fungal growth.

Conclusion

The study demonstrated that some 1,2,3-triazole-4-carboxamide can effectively suppress the growth of both bacterial and fungal pathogens. Compounds such as **5m**, **5s**, and **7a** showed the highest biological potential, displaying measurable inhibition across multiple strains. Particularly antifungal properties were observed for **5a**, indicating selective activity against *Cryptococcus neoformans*. In contrast, molecules like **5f** and **5r** lacked efficacy and, in some cases, even promoted microbial growth. These results highlight several promising chemical structures for further optimization in the search for novel antimicrobial agents.

Acknowledgments

The authors are grateful to CO-ADD (The Community for Antimicrobial Drug Discovery), funded by the Wellcome Trust (UK) and The University of Queensland (Australia), for support with antimicrobial screening, and to the 2nd European Chemistry School for Ukrainians for inspiring this work.

Funding

The authors are greatly thankful to the Ministry of Education and Science of Ukraine and Simons Foundation for financial support.

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