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Review Article

Fluorophenyl-1,2,4-Triazole Derivatives: Synthesis, Structural Analysis, Chemotype Clustering and Antimicrobial Screening

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Abstract

A series of novel fluorophenyl-substituted 1,2,4-triazole derivatives were synthesized and characterized via NMR spectroscopy. The synthetic pathway involved key transformations including hydrazinolysis, isocyanate coupling, and cyclization reactions. The structural elucidation confirmed the successful formation of target compounds through spectral analyses.

The antimicrobial activity of the synthesized compounds was evaluated against Gram-positive bacteria (*Staphylococcus aureus, Bacillus subtilis*), Gram-negative bacteria (*Escherichia coli, Salmonella typhimurium*) and fungal strains (*Candida* spp.) using the Minimum Inhibitory Concentration (MIC) method. Among the tested derivatives, compounds 6a–6f exhibited significant antimicrobial potency, with MIC values as low as 6.25 µg/mL against *E. coli* and *S. aureus*. In contrast, earlier-stage intermediates (4a–5c) demonstrated moderate to weak activity, indicating that structural modifications such as fluorophenyl-triazole hybridization enhanced biological efficacy.

To further analyze the structure-activity relationship, chemotype clustering was performed, categorizing the synthesized derivatives based on their core scaffolds and functional groups. This clustering approach provided insights into the impact of different substituents on antimicrobial efficacy, highlighting key structural features contributing to bioactivity.

The most active compounds, 6a–6f, displayed promising antibacterial activity comparable to standard antibiotics (tetracycline and ampicillin) and exhibited moderate antifungal effects.

These findings suggest that fluorophenyl-triazole hybrids are potential candidates for antimicrobial drug development. Further studies, including *in vivo* evaluations, mechanism of action investigations, and expanded chemotype clustering analyses, are warranted to explore their full therapeutic potential.

Introduction

The rise of Multi-drug Resistant (MDR) pathogens presents a serious challenge to global public health, necessitating the search for novel antimicrobial agents with broad-spectrum activity [1,2]. The continuous emergence of resistant bacterial and fungal strains has diminished the effectiveness of conventional antibiotics and antifungal agents, creating an urgent need for the development of new molecular scaffolds with improved therapeutic potential [3]. Triazoles, especially the 1,2,4-triazole core, play a crucial role in medicinal chemistry due to their high metabolic stability, bioavailability, and ability to form strong interactions with biological targets [4,5]. The 1,2,4-triazole moiety is widely incorporated into clinically used antifungal agents such as fluconazole, voriconazole, and posaconazole, which act by inhibiting ergosterol biosynthesis, a critical component of fungal cell membranes [6]. Beyond their antifungal activity, triazole derivatives have also demonstrated potent antibacterial, antiviral, anti-inflammatory, and anticancer properties [7]. Their ability to act as hydrogen bond

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donors and acceptors, engage in π–π stacking interactions, and modulate enzyme activity makes them valuable scaffolds for drug discovery.

Furthermore, the introduction of bioactive functional groups into the triazole ring has been shown to significantly enhance antimicrobial efficacy [8,9]. Particularly, hybridizing triazole derivatives with other pharmacologically active scaffolds has emerged as a powerful strategy to improve drug efficacy and selectivity. In recent years, triazole-fluoroquinolone hybrid compounds have drawn increasing interest as promising antimicrobial candidates, owing to their combined biological advantages [10-12].

Fluoroquinolones, including ciprofloxacin, norfloxacin, and levofloxacin, are among the most widely prescribed synthetic antibiotics due to their potent activity against Gram-positive and Gram-negative bacteria. Their antibacterial mechanism involves inhibition of DNA gyrase and topoisomerase IV, essential enzymes required for bacterial DNA replication and transcription. This mechanism leads to rapid bacterial cell death, making fluoroquinolones effective against a wide range of infections [13-15].

In the pursuit of designing more effective antimicrobial agents, chemotype clustering has emerged as a powerful strategy to classify compounds based on their core structural features and biological activity profiles. By grouping compounds according to shared pharmacophoric elements, chemotype clustering enables a deeper understanding of Structure-activity Relationships (SARs), facilitating the identification of key molecular modifications that enhance biological potency [16,17].

Applying chemotype clustering to fluorophenyl-triazole derivatives allows for a systematic exploration of how different substituents and functional groups influence antimicrobial activity. By analyzing these clusters, it becomes possible to pinpoint structural motifs that contribute to increased bacterial and fungal inhibition, thereby guiding rational drug design.

In this study, we report the synthesis, structural characterization, and antimicrobial evaluation of a new series of fluorophenyl-triazole derivatives. The synthetic strategy involved multiple key transformations, including hydrazinolysis, isocyanate coupling, and cyclization reactions, leading to structurally diverse compounds. Their antibacterial and antifungal activities were assessed against clinically relevant Gram-positive and Gram-negative bacterial strains (*S. aureus, B. subtilis, E. coli, and S. typhimurium*) and fungal pathogens (*C. albicans, C. glabrata, C. parapsilosis, and C. krusei*) using the Minimum Inhibitory Concentration (MIC) method.

Additionally, chemotype clustering was employed to categorize the synthesized derivatives based on their core scaffolds and pharmacophoric elements. This classification helped to identify structure-activity trends, highlighting key modifications that contribute to enhanced antimicrobial efficacy. The findings from this study provide valuable insights into the rational design of next-generation antimicrobial agents, paving the way for further *in vivo* evaluations and mechanistic studies to explore their full therapeutic potential.

Experimental section

Chemistry

All reagents and solvents used in this study were purchased from commercial suppliers and used without further purification unless otherwise stated. Reactions were monitored by Thin-layer Chromatography (TLC) on silica gel plates, and spots were visualized using Ultraviolet (UV) light at 254 nm and 365 nm. The final products were purified by recrystallization or column chromatography using appropriate solvent systems. Melting points were recorded using a digital melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded in DMSO-d_6 on a Bruker 400 MHz spectrometer, and chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard.

Ethyl 2-((4-fluorophenyl)amino)acetate (2)

Ethyl bromoacetate (1 mmol) and 4-fluoroaniline (1 mmol) are dissolved in dry Tetrahydrofuran (THF). Triethylamine (TEA) is added as a base. The reaction mixture is stirred continuously at room temperature using a magnetic stirrer for 24 hours. Upon completion of the reaction, the mixture is filtered under vacuum to separate solid residues. The filtrate is extracted with ethyl acetate. The combined organic phases are dried over sodium sulfate, and the solvent is removed using a rotary evaporator. The crude product is purified by recrystallization. (0.205 g, 82% yield). FT-IR (υ_{max}, cm^{-1}): 3382 (NH), 3050 (aromatik CH), 1723 (C=O). ^{1}H NMR (DMSO-d6, δ ppm): 1.38 (3H, t, J = 7.2 Hz, CH_3), 4.14 (2H, q, J = 7.2 Hz, CH_2), 6.53–6.88 (4H, m, ArCH). ^{13}C NMR (DMSO-d_6, δ ppm): 14.58 (CH_3), 45.62 (CH_2), 60.71 (CH_2), arC: [113.35 (CH), 113.42 (CH), 115.54 (CH), 115.76 (CH), 145.26 (C), 156.20 (C)], 171.71 (C=O). EI MS *m/z* (%): 123.47 (100), 198.50 ([M+1]$^+$, 83), 203.79 (78), 397.45 (65), 409.45 (50).

2-((4-fluorophenyl)amino)acetohydrazide (3)

Compound 1 (1 mmol) and hydrazine hydrate (2.5 mmol) are dissolved in ethanol under a reflux condenser setup. The mixture is heated under reflux conditions for 10 hours using a magnetic stirrer. Upon completion of the reaction, the mixture is cooled to room temperature, and the solvent is removed under vacuum. The crude product is washed with water and extracted with ethyl acetate. The combined organic phases are dried over sodium sulfate, and the solvent is evaporated. The obtained product is purified by crystallization. (0.192 g, 84% yield). FT-IR (υmax, cm-1): 3397 (NH_2), 3302 (NH), 3043 (aromatic CH), 1649 (C=O).^{1}H NMR (DMSO-d6, δ ppm): 2.37 (2H, s, CH_2), 3.86-3.87 (2H, m, NH_2), 4.49 (1H, s, NH), 6.53–6.88 (4H, m, ArCH). ^{13}C NMR (DMSO-d_6, δ ppm): 44.24 (CH_2), 46.27 (CH_2), arC: [113.46 (CH), 113.52 (CH), 115.52 (CH), 115.74 (CH), 145.45 (C), 153.95 (C)], 169.92 (C=O). EI MS *m/z* (%):184.75 ([M+1]$^+$, 100), 200.01 (85), 155.45 (71), 307.45 (60), 489.42 (51).

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General synthesis procedure for 4a, 4b, and 4c

Compound 3 (0.200 g, 1.0 mmol) was dissolved in 10 mL of dry dichloromethane (DCM) in a 50 mL round-bottom flask. To this solution, phenyl isothiocyanate (4a) (0.137 g, 1.0 mmol), benzyl isothiocyanate (4b) (0.165 g, 1.0 mmol), or phenyl isocyanate (4c) (0.119 g, 1.0 mmol) was added dropwise under stirring at room temperature. The reaction mixture was stirred continuously with a magnetic stirrer for 24 hours at ambient temperature (~25 °C).

Upon completion, the precipitated solid was collected by vacuum filtration, washed thoroughly with cold distilled water (3 × 5 mL), and dried under vacuum at room temperature to afford the corresponding urea/thio-urea derivatives 4a–c.

2-(2-((4-fluorophenyl)amino)acetyl)-N-phenylhydrazinecarbothioamide (4a)

Light yellow solid (0.281 g, 89% yield). FT-IR (υmax, cm-1): 3440, 3337 and 3205 (4NH), 3106 (aromatic CH), 1688 (C=O), 1189 (C=S). ^{1}H NMR (DMSO-d6, δ ppm): 4.10 (2H, q, J = 7.2 Hz, CH_2), 6.50–6.88 (4H, m, ArCH), 7.11–7.31 (5H, m, ArCH), 8.02 (2H, s, 2NH), 8.76 (2H, s, 2NH). ^{13}C NMR (DMSO-d_6, δ ppm): 46.13 (CH_2), arC: [113.74 (CH), 113.81 (CH), 115.55 (CH), 115.77 (CH), 117.28 (CH), 121.53 (CH), 128.59 (CH), 129.44 (CH), 130.16 (CH), 139.51 (C), 141.63 (C), 145.31 (C)], 154.21 (C=O), 156.17 (C=S). EI MS *m/z* (%): 319.45 ([M+1]$^+$, 100), 303.79 (85), 247.43 (70), 200.76 (65), 178.12 (54), 373.45 (45).

N-benzyl-2-(2-((4-fluorophenyl)amino)acetyl)hydrazinecarbothioamide (4b)

White solid (0.295 g, 91% yield). FT-IR (υ_{max}, cm^{-1}): 3287 ve 3218 (4NH), 3091 (aromatic CH), 1668 (C=O), 1239 (C=S). ^{1}H NMR (DMSO-d6, δ ppm): 3.73 (2H, s, CH_2), 4.10 (2H, q, J = 7.2 Hz, CH_2), 4.72 (1H, s, NH), 4.90 (1H, s, NH), 4.96 (1H, s, NH), 6.56–6.90 (4H, m, ArCH), 7.30–7.32 (5H, m, ArCH). ^{13}C NMR (DMSO-d_6, δ ppm): 45.99 (CH_2), 47.12 (CH_2), arC: [113.60 (CH), 113.67 (CH), 115.51 (CH), 127.09 (CH), 127.40 (CH), 127.82 (CH), 128.01 (CH), 128.53 (CH), 139.66 (C), 145.38 (C), 153.93 (C)], 156.23 (C=O), 170.46 (C=S). EI MS *m/z* (%): 207.45 (100), 289.63 (88), 333.41 ([M+1]$^+$, 79), 310.96 (70), 410.52 (61), 379.20 (45).

2-(2-((4-fluorophenyl)amino)acetyl)-N-phenylhydrazinecarboxamide (4c)

Off-white solid (0.277 g, 87% yield). FT-IR (υmax, cm-1): 3421, 3371 and 3158 (4NH), 1682 (C=O), 1615 (C=O). ^{1}H NMR (DMSO-d6, δ ppm): 3.73 (2H, s, CH_2), 6.60 (1H, s, ArCH), 6.91 (3H, d, *J*= 8.0 Hz, ArCH), 7.28 (4H, d, *J*= 4.0 Hz, ArCH), 7.79 (1H, s, ArCH), 7.93 (1H, s, NH), 8.24 (1H, s, NH), 9.16 (1H, s, NH), 9.70 (1H, s, NH).^{13}C NMR (DMSO-d_6, δ ppm): 46.05 (CH_2), arC: [113.61 (CH), 113.68 (CH), 115.52 (CH), 115.74 (CH), 127.00 (CH), 127.35 (CH), 127.50 (CH), 128.54 (CH), 128.58 (CH), 140.92 (C), 145.44 (C), 153.95 (C)], 158.63 (C=O), 170.69 (C=O). EI MS *m/z* (%): 303.70 ([M+1]$^+$, 100), 345.20 (86), 395.45 (80), 406.12 (75), 207.89 (70), 211.53 (65).

General synthesis method (for 5a, 5b and 5c)

Compound 4a (0.250 g, 0.85 mmol), 4b (0.265 g, 0.90 mmol), or 4c (0.260 g, 0.88 mmol) was dissolved in a mixture of 2N NaOH aqueous solution (10 mL) and absolute ethanol (10 mL) in a 100 mL round-bottom flask. The mixture was stirred until a homogeneous solution was obtained, then refluxed under a condenser at 78 °C for 6 hours. After the reaction was complete (monitored by TLC), the reaction mixture was allowed to cool to room temperature. Then, 1N HCl was added dropwise with constant stirring until the pH reached 4–5. During the acidification, a solid precipitate formed, which was collected by vacuum filtration, washed with cold distilled water (2 × 5 mL), and dried under reduced pressure. The crude products were recrystallized from ethanol-water (1:1) to afford the pure compounds 5a–5c.

5-(((4-fluorophenyl)amino)methyl)-4-phenyl-4H-1,2,4-triazole-3-thiol (5a)

Yellow powder (0.238 g, 85% yield). FT-IR (υmax, cm-1): 3393 (NH), 3084 and 3034 (aromatic CH), 1552 (C=N), 2849 (SH). ^{1}H NMR (DMSO-d6, δ ppm): 4.08 (CH_2), 7.40-7.44 (4H, m, ArCH), 7.51-7.60 (5H, m, ArCH), 13.34 (1H, s, NH), 13.83 (1H, s, SH). ^{13}C NMR (DMSO-d_6, δ ppm): 46.17 (CH_2), arC: [113.67 (CH), 113.75 (CH), 115.58 (CH), 115.80 (CH), 123.98 (CH), 124.06 (CH), 127.58 (CH), 128.21 (CH), 129.10 (CH),144.65 (C), 150.69 (C), 154.13 (C)], 156.44 (triazol C), 168.34 (triazol C). EI MS *m/z* (%): 323.79 ([M+Na]$^+$, 100), 298.41 (97), 301.53 (85), 246.45 (71), 200.63 (67), 197.41 (61), 178.10 (53).

4-benzyl-5-(((4-fluorophenyl)amino)methyl)-4H-1,2,4-triazole-3-thiol (5b)

Pale solid (0.254 g, 87% yield). FT-IR (υ_{max}, cm^{-1}): 3361 (NH), 3063 and 3032 (aromatic CH), 2531 (SH), 1571 (C=N).^{1}H NMR (DMSO-d6, δ ppm): 4.18 (2H, s, CH_2), 5.35 (2H, s, CH_2), 6.94-6.52 (2H, m, ArCH), 6.87-6.92 (2H, m, ArCH), 7.29-7.36 (5H, m, ArCH), 10.51 (1H, s, NH), 13.82 (1H, s, SH). ^{13}C NMR (DMSO-d_6, δ ppm): 51.48 (CH_2), 66.72 (CH_2), arC: [114.07 (CH), 119.76 (CH), 119.80 (CH), 126.92 (CH), 127.48 (CH), 127.57 (CH), 128.52 (CH), 128.76 (2CH), 141.04 (C), 154.17 (C), 155.62 (C)], 156.58 (triazol C), 159.23 (triazol C). EI MS *m/z* (%): 315.70 ([M+1]$^+$, 100), 303.70 (89), 298.76 (75), 230.45 (69), 200.73 (55), 186.43 (40).

3-(((4-fluorophenyl)amino)methyl)-4-phenyl-1H-1,2,4-triazol-5(4H)-one (5c)

White crystalline solid (0.246 g, 84% yield). FT-IR (υ_{max}, cm^{-1}): 3382 (NH), 3082 and 3026 (aromatic CH), 1602 (C=O), 1574 (C=N). ^{1}H NMR (DMSO-d6, δ ppm): 3.34 (2H, s, CH_2), 6.94-6.97 (4H, m, ArCH), 7.24-7.50 (5H, m, ArCH), 7.99 (1H, s, NH), 8.80 (1H, s, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 52.84 (CH_2), arC: [117.27 (CH), 118.28 (CH), 118.52 (CH), 121.45 (CH), 121.87 (CH), 122.16 (CH), 123.88 (CH), 124.76 (CH), 128.60 (CH), 141.73 (C), 148.75 (C), 149.62 (C)], 153.16 (triazol C), 156.21 (triazol C). EI MS *m/z* (%): 285.10 ([M+1]$^+$, 100), 378.45 (91), 300.12 (85), 256.43 (73), 241.10 (65).

General synthesis method (6a-f)

Compound 5a–c (0.200 g, 0.65 mmol) was dissolved in 10 mL of dry dimethylformamide (DMF) in a 50 mL round-bottom flask. Then, norfloxacin or ciprofloxacin (0.219 g, 0.65

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mmol) and formaldehyde solution (37%, 0.060 mL, 0.80 mmol) were added to the reaction flask. The mixture was stirred magnetically at room temperature (~25 °C) for 24 hours.

After completion (monitored by TLC), 20 mL of distilled water was added dropwise into the reaction mixture with continuous stirring, leading to the formation of a precipitate. The resulting solid was collected by vacuum filtration, washed with cold water (2 × 5 mL), and dried under reduced pressure. The crude products were recrystallized from ethanol (10 mL) to obtain pure compounds 6a–6f, which were then prepared for analytical studies.

1-cyclopropyl-6-fluoro-7-(4-((3-(((4-fluorophenyl) amino)methyl)-4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)methyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (6a)

White powder (0.412 g, 76% yield). FT-IR (υ_{max}, cm^{-1}): 3058 (aromatic CH), 1720 (C=O), 1671 (C=O), 1541 (C=N). ^{1}H NMR (DMSO-d6, δ ppm): 1.16 (2H, s, CH_2), 1.32 (2H, s, CH_2), 2.74 (2H, s, CH_2), 2.89 (2H, s, CH2), 2.95 (2H, s, CH_2), 3.06 (2H, s, CH_2), 4.17 (2H, d, *J*=4.0 Hz, CH_2), 5.18 (2H, d, *J*=8.0 Hz, CH_2), 6.79-7.27 (3H, m, ArCH), 7.47 (4H, m, ArCH), 7.82-7.96 (4H, m, ArCH), 8.62 (1H, s, NH), 15.18 (1H, s, OH). ^{13}C NMR (DMSO-d_6, δ ppm): 8.04 (CH_2), 31.24 (CH_2), 36.24 (CH_2), 49.95 (2CH_2), 50.12 (2CH_2), 68.78 (CH_2), arC: [111.23 (CH), 111.46 (CH), 113.70 (CH), 113.78 (CH), 115.42 (CH), 115.64 (CH), 118.51 (CH), 118.79 (CH), 118.96 (CH), 119.04 (CH), 122.15 (CH), 144.63 (C), 145.52 (C), 145.62 (C), 147.68 (C), 149.47 (C), 152.19 (C), 154.04 (C), 154.67 (C)], 148.33 (CH), 156.34 (CH), 162.77 (triazol C), 166.94 (triazol C), 169.68 (C=O), 176.77 (C=O). EI MS *m/z* (%): 578.12 (100), 644.43 ([M+1]$^+$, 89), 600.76 (85), 598.12 (76), 521.12 (71), 498.12 (69), 483.12 (65), 403.65 (51).

1-ethyl-6-fluoro-7-(4-((3-(((4-fluorophenyl)amino) methyl)-4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)methyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (6b)

Yellow solid (0.425 g, 78% yield). FT-IR (υ_{max}, cm^{-1}): 3067 (aromatic CH), 1720 (C=O), 1669 (C=O), 1541 (C=N). ^{1}H NMR (DMSO-d6, δ ppm): 1.41 (2H, s, CH_2), 2.74 (2H, s, CH_2), 2.90 (2H, s, CH_2), 3.04 (2H, s, CH_2), 3.34 (3H, s, CH_3), 4.16 (2H, s, CH_2), 4.58 (2H, s, CH_2), 5.17 (2H, s, CH_2), 6.49 (1H, s, ArCH), 6.82 (1H, s, ArCH), 6.94 (1H, s, ArCH), 7.17 (1H, s, ArCH), 7.25 (1H, s, ArCH), 7.49 (2H, s, ArCH), 7.58 (2H, s, ArCH), 7.90 (1H, s, ArCH), 7.96 (1H, s, ArCH), 8.47 (1H, s, CH), 8.93 (1H, s, NH), 15.34 (1H, s, OH). ^{13}C NMR (DMSO-d_6, δ ppm): 14.78 (CH_2), 31.24 (CH_2), 36.25 (CH_3), 49.52 (CH_2), 49.94 (CH_2), 50.04 (CH_2), 50.16 (CH_2), 68.77 (CH_2), arC: [106.36 (CH), 111.50 (CH), 111.72 (CH), 113.70 (CH), 113.78 (CH), 115.44 (CH), 118.49 (CH), 122.14 (CH), 129.12 (CH), 129.55 (CH), 144.63 (C), 145.83 (C), 147.67 (C), 149.47 (C), 152.06 (C), 154.04 (C)], 148.88 (CH), 166.58 (triazol C), 166.91 (triazol C), 169.65 (C=O), 176.60 (C=O). EI MS *m/z* (%): 600.12 (100), 654.78 ([M+Na]$^+$, 81), 576.15 (79), 550.36 (74), 491.10 (69), 398.12 (57), 312.45 (48).

7-(4-((4-benzyl-3-(((4-fluorophenyl)amino)methyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)methyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (6c)

Off-white powder (0.439 g, 74% yield). FT-IR (υ_{max}, cm^{-1}): 3045 (aromatic CH), 1728 (C=O), 1627 (C=O), 1551 (C=N). ^{1}H NMR (DMSO-d6, δ ppm): 1.15 (2H, s, CH_2), 1.32 (2H, s, CH_2), 2.26 (2H, s, CH_2), 2.74 (2H, s, CH_2), 2.90 (2H, s, CH_2), 4.70 (2H, s, CH_2), 5.01 (2H, s, CH_2), 5.26 (2H, s, CH_2), 5.32 (2H, s, CH_2), 7.31-7.51 (11H, s, ArCH), 7.80 (1H, s, CH), 7.96 (1H, s, CH), 8.61 (1H, s, NH), 15.31 (1H, s, OH). ^{13}C NMR (DMSO-d_6, δ ppm): 8.02 (CH_2), 11.58 (CH_2), 31.23 (CH_2), 36.24 (CH_2), 45.67 (CH_2), 46.02 (CH_2), 47.33 (CH_2), 49.88 (CH_2), 50.10 (CH_2), 106.66 (CH), arC: [106.82 (C), 117.17 (CH), 111.39 (CH), 119.00 (C), 127.27 (CH), 127.46 (CH), 127.68 (CH), 127.78 (CH), 128.48 (CH), 128.69 (CH), 128.82 (2CH), 129.91 (2CH), 135.95 (C), 139.28 (C), 139.47 (C), 145.55 (C), 149.02 (C), 152.12 (C)], 148.20 (kinolon CH), 154.60 (triazol C), 166.32 (triazol C), 168.73 (C=O), 176.68 (C=O). EI MS *m/z* (%): 658.23 ([M+1]$^+$, 100), 599.12 (87), 600.42 (76), 503.34 (69), 485.10 (51), 431.19 (49), 317.43 (39).

7-(4-((4-benzyl-3-(((4-fluorophenyl)amino)methyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)methyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (6d)

Pale yellow solid (0.428 g, 76% yield). FT-IR (υ_{max}, cm^{-1}): 3043 (aromatik CH), 1720 (C=O), 1612 (C=O), 1517 (C=N). ^{1}H NMR (DMSO-d6, δ ppm): 1.40 (3H, s, CH_3), 2.18 (2H, s, CH_2), 2.24 (2H, s, CH_2), 2.70 (2H, s, CH_2), 2.74 (2H, s, CH_2), 2.89 (2H, s, CH_2), 2.92 (2H, s, CH_2), 3.07 (4H, s, 2CH_2), 7.14-7.30 (11H, s, ArCH), 7.84 (1H, s, NH), 8.91 (1H, s, CH), 14.90 (1H, s, OH). ^{13}C NMR (DMSO-d_6, δ ppm): 14.73 (CH_3), 45.66 (CH_2), 46.01 (CH_2), 46.18 (CH_2), 47.32 (CH_2), 49.51 (CH_2), 49.89 (CH_2), 50.15 (CH_2), 51.08 (CH_2), 106.18 (CH), arC: [106.31 (CH), 107.53 (C), 111.46 (CH), 111.69 (CH), 119.69 (C), 127.45 (CH), 127.69 (CH), 127.76 (CH), 128.48 (CH), 128.70 (2CH), 129.21 (2CH), 135.96 (C), 136.06 (C), 137.56 (C), 145.75 (C), 145.85 (C), 149.01 (C)], 148.80 (kinolon CH), 166.05 (triazol C), 166.55 (triazol C), 168.72 (C=O), 176.55 (C=O). EI MS *m/z* (%): 646.23 ([M+1]$^+$, 100), 645.23 ([M]$^+$, 88), 586.15 (75), 503.34 (62), 485.10 (55), 431.19 (47), 317.43 (38).

1-cyclopropyl-6-fluoro-7-(4-((3-(((4-fluorophenyl) amino)methyl)-5-oxo-4-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)methyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (6e)

White crystalline solid (0.417 g, 72% yield). FT-IR (υ_{max}, cm^{-1}): 3067 (aromatik CH), 1720 (C=O), 1664 (C=O), 1546 (C=N). ^{1}H NMR (DMSO-d6, δ ppm): 1.19 (2H, s, CH_2), 1.33 (2H, s, CH_2), 2.74 (2H, s, CH_2), 2.84 (2H, s, CH_2), 2.90 (2H, s, CH_2), 3.10 (2H, s, CH_2), 3.36 (2H, s, CH_2), 7.24-7.58 (6H, m, ArCH), 7.88-7.96 (5H, m, ArCH), 8.66 (1H, s, CH), 8.74 (1H, s, CH), 10.56 (1H, s, NH), 14.77 (1H, s, OH). ^{13}C NMR (DMSO-d_6, δ ppm): 8.02 (CH_2), 31.25 (CH_2), 36.25 (CH_2), 36.29 (CH_2), 43.98 (CH_2), 49.95 (CH_2), 50.20 (CH_2), 51.10 (CH_2), arC: [118.77 (CH), 118.94 (CH), 119.90 (CH), 120.13 (CH), 120.31 (CH), 122.32 (CH), 122.49 (CH), 128.81 (CH), 128.90 (CH), 129.08 (CH), 129.18 (CH), 139.65 (C), 140.00 (C), 140.13 (C), 145.22 (C), 145.72 (C), 152.24 (C), 154.72 (C), 154.95 (C)], 148.44 (CH), 155.44 (triazol C-3), 156.50 (triazol

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C-5), 166.45 (C=O), 176.83 (C=O). EI MS *m/z* (%): 628.24 ([M+1]$^+$, 100), 627.24 ([M]$^+$, 85), 568.17 (72), 485.23 (60), 431.12 (48), 317.30 (36), 289.14 (22).

1-ethyl-6-fluoro-7-(4-((3-(((4-fluorophenyl)amino) methyl)-5-oxo-4-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)methyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (6f)

Light brown solid (0.423 g, 73% yield). FT-IR (υ_{max}, cm^{-1}): 3058 (aromatik CH), 1720 (C=O), 1627 (C=O), 1541 (C=N). ^{1}H NMR (DMSO-d6, δ ppm): 1.42 (2H, s, CH_2), 2.70 (2H, s, CH_2), 2.89 (2H, s, CH_2), 3.08 (2H, s, CH_2), 3.08 (2H, s, CH_2), 3.34 (4H, s, 2CH_2), 3.70 (2H, s, CH_2), 4.60 (3H, s, CH_3), 6.95-7.27 (6H, m, ArCH), 7.49-7.97 (5H, m, ArCH), 8.96 (1H, s, CH), 10.59 (1H, s, NH), 15.92 (1H, s, OH). ^{13}C NMR (DMSO-d_6, δ ppm): 14.80 (CH_2), 31.06 (CH_2), 36.40 (CH_3), 48.20 (CH_2), 49.10 (CH_2), 50.89 (CH_2), 51.89 (CH_2), 67.41 (CH_2), arC: [110.02 (CH), 111.01 (CH), 111.95 (CH), 112.74 (CH), 113.03 (CH), 116.70 (CH), 117.67 (CH), 123.41 (CH), 128.50 (CH), 129.01 (CH), 144.09 (C), 145.03 (C), 147.09 (C), 149.53 (C), 153.50 (C), 154.89 (C)], 148.18 (CH), 165.98 (triazol C-3), 166.10 (triazol C-5), 169.03 (C=O), 176.26 (C=O). EI MS *m/z* (%): 616.24 ([M+1]$^+$, 100), 615.24 ([M]$^+$, 83), 556.18 (70), 473.20 (59), 431.10 (45), 317.25 (34), 289.10 (21).

Biological activity evaluation

Microorganisms

Bacterial and fungal cultures used in this study were obtained from various sources, including the USA Agriculture Research Service Culture Collection (NRRL), the American Type Culture Collection (ATCC), and the culture collection of the Department of Pharmacognosy at the Faculty of Pharmacy, Anadolu University, Eskişehir, Turkey.

In vitro antimicrobial activity

The antimicrobial properties of the synthesized compounds were evaluated using the broth microdilution method, as recommended by the Clinical Laboratory Standards Institute (CLSI). Standard antibacterial agents included ampicillin and chloramphenicol, while fluconazole and amphotericin B were used as reference antifungal agents. All experiments were performed in triplicate to ensure accuracy [18].

Broth microdilution test for bacteria

The antibacterial activity of the compounds was assessed following the CLSI M100-S16 guidelines. The minimum inhibitory concentration (MIC) values were determined using the broth microdilution method in 96-well microtiter plates (Sigma, Germany). Microbial suspensions grown overnight in double-strength Mueller-Hinton broth (MHB) (Merck, Germany) were adjusted to approximately 10^8 CFU/mL using the MacFarland No: 0.5 standard.

Test compounds were dissolved in a 1:10 mixture of sterile distilled water and DMSO (e.g., for 1000 µL of solution: 100 µL sterile DMSO and 900 µL sterile distilled water). The working concentration range for the compounds was 8000 µg/mL to 0.195 µg/mL. For antibacterial reference compounds (ampicillin and chloramphenicol), the final concentration range was 32 µg/mL to 0.00156 µg/mL. Two-fold serial dilutions of the compounds were prepared in MHB (100 µL per well), and the wells were inoculated with bacterial strains before incubation at 37 °C for 24 hours. Resazurin (Sigma, Germany) was added to confirm MIC values. The MIC endpoint was defined as the lowest concentration with complete (100%) growth inhibition. DMSO was used as the negative control.

For compounds that exhibited significant antibacterial activity, additional experiments were conducted with a lower initial concentration (0.8 mg/mL) and an adjusted first well concentration of 400 µL. The working range for these retests was 400 µg/mL to 0.195 µg/mL [19].

Broth microdilution test for yeasts

The antifungal activity of the compounds was evaluated according to CLSI document M27-A2, using 96-well microtiter plates, RPMI-1640 (Sigma, Germany) medium, and inocula of 0.5–2.5 × 10^3 cells/mL (MacFarland 0.5). The final concentration range for the test compounds was 8000 µg/mL to 0.195 µg/mL, while the antifungal reference agents (fluconazole and amphotericin B) were tested in the range of 16 µg/mL to 0.0078 µg/mL. The microplates were incubated at 37 °C for 24 hours, and MIC values were determined using resazurin as an indicator. The MIC endpoint was recorded as the lowest concentration showing complete (100%) growth inhibition [20].

Chemotype clustering analysis

To explore the Structure-activity Relationships (SARs) of the synthesized fluorophenyl-triazole derivatives, a chemotype clustering approach was implemented. This method allowed for the classification of compounds into distinct chemotypes based on their core scaffolds and functional groups. Molecular descriptors, including Lipophilicity (LogP), Topological Polar Surface Area (TPSA), and hydrogen bond donor/acceptor counts, were calculated to assess their impact on antimicrobial activity. Principal Component Analysis (PCA) and hierarchical clustering were used to visualize compound clustering patterns, providing insights into the most bioactive structural motifs. The clustering results guided further interpretation of Minimum Inhibitory Concentration (MIC) data, helping to correlate key structural features with antimicrobial potency [21].

Results and discussion

Synthesis

A series of fluorophenyl-1,2,4-triazole derivatives were synthesized using a multi-step reaction sequence, as illustrated in Scheme 1. The synthetic pathway involved the preparation of key intermediates, including hydrazides, thiosemicarbazides, and triazole derivatives, which were further coupled with fluoroquinolone-based pharmacophores to enhance antimicrobial activity.

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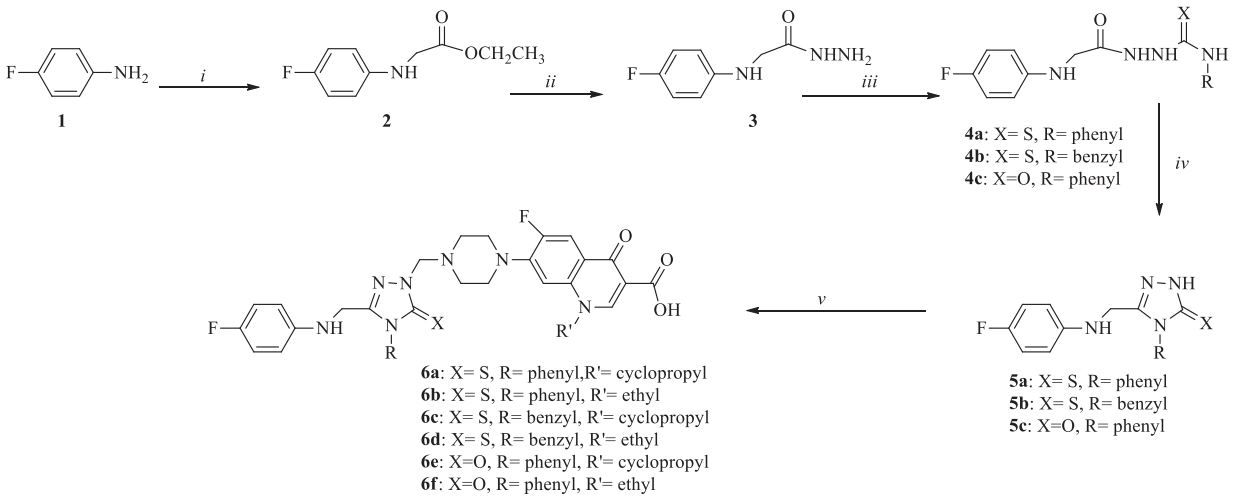

Scheme 1: Reactions and conditions. i: tetrahydrofuran, triethylamine, ethyl bromoacetate, room temperature for 24 h; ii: absolute ethanol, hydrazine hydrate, reflux for 27 h; iii: phenylisosyanate in dichloromethane, room temperature for 24 h; iv: 2 N NaOH in ethanol/water (1:1), reflux for 6h. v: dimethyl formamide, norfloxacin or ciprofloxacin room temperature, 24 h.

The synthesis began with the nucleophilic substitution reaction between ethyl bromoacetate and 4-fluoroaniline in the presence of Tetrahydrofuran (THF) and Triethylamine (TEA), yielding ethyl 2-((4-fluorophenyl)amino)acetate (2). The reaction proceeded efficiently under room temperature conditions for 24 hours.

In the next step, the hydrazinolysis of compound 2 was performed using hydrazine hydrate in absolute ethanol under reflux for 10 hours, affording 2-((4-fluorophenyl)amino) acetohydrazide (3) in high yield. This intermediate served as the key precursor for subsequent modifications.

The functionalization of compound 3 was achieved via nucleophilic addition with phenylisocyanates or phenylisothiocyanates in dichloromethane (DCM) at room temperature for 24 hours, yielding hydrazinecarbothioamide and hydrazinecarboxamide derivatives (4a–4c). These intermediates were then subjected to cyclization reactions under alkaline conditions (2N NaOH in ethanol/water (1:1), reflux for 6 hours) to afford fluorophenyl-triazole derivatives (5a–5c).

Finally, the fluorophenyl-triazole derivatives (5a–5c) were coupled with norfloxacin or ciprofloxacin using formaldehyde in dimethylformamide (DMF) under room temperature conditions for 24 hours, yielding the final hybrid compounds (6a–6f) with potential antimicrobial activity.

This synthetic strategy successfully led to structurally diverse fluorophenyl-1,2,4-triazole hybrids, integrating fluoroquinolone pharmacophores to enhance biological activity. The synthesis and reaction conditions are summarized in Scheme 1.

Antimicrobial evaluation

The synthesized fluorophenyl-1,2,4-triazole derivatives (6a–6f) were evaluated for their antimicrobial activity against a panel of Gram-positive bacteria, Gram-negative bacteria, and fungal strains using the minimum inhibitory concentration (MIC) method, as shown in Table 1.

The bacterial strains tested included *Escherichia coli* (NRRL 3008), *Staphylococcus aureus* (ATCC 6538), *Bacillus subtilis* (NRRL B-4378), and *Salmonella typhimurium* (ATCC 14028), while the fungal strains comprised *Candida albicans* (ATCC 90028), *Candida glabrata* (ATCC 2001), *Candida parapsilosis* (ATCC 22019), and *Candida krusei* (ATCC 6258). The most active compounds (6a–6f) displayed significant antibacterial activity with MIC values of 6.25 µg/mL against *E. coli* and 12.5 µg/mL against *S. aureus*. In comparison, tetracycline exhibited much lower MIC values of 0.015 µg/mL against both *E. coli* and *S. aureus*, while ampicillin inhibited *E. coli* at 1 µg/mL and *S. aureus* at 0.031 µg/mL. Although the synthesized compounds were less potent than the reference antibiotics, they demonstrated markedly improved activity relative to precursor intermediates (MICs ranging from 1000–8000 µg/mL), highlighting the role of the fluorophenyl-triazole hybridization in enhancing antibacterial efficacy. At this concentration, no clear inhibition zones or observable bacterial growth suppression were recorded, indicating insufficient antibacterial activity under the conditions employed. In contrast, these compounds displayed moderate to strong activity against *B. subtilis* and *S. typhimurium*, with MIC values ranging from 12.5 to 50 µg/mL. Compared to the precursor compounds (4a–5c), the hybrid triazole-fluoroquinolone derivatives demonstrated improved antifungal activity, particularly against *C. albicans* and *C. glabrata*, with MIC values reaching as low as 2000 µg/mL. These findings suggest that the incorporation of the fluorophenyl-triazole moiety contributes more significantly to antifungal rather than antibacterial activity, especially against Gram-negative organisms.

Chemotype clustering and Structure-activity Relationship (SAR) Analysis

To better understand the Structure–activity Relationship (SAR) of the synthesized fluorophenyl-1,2,4-triazole

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Table 1: Antimicrobial activity of synthesized compounds.

	Gram-negative Bacteria		*Gram-positive Bacteria*		*Fungi*			
Compounds	*Escherichia coli NRRL 3008*	*Staphylococcus aureus ATCC 6538*	*Bacillus subtilis NRRL B-4378*	*Staphylococcus typhimurium ATCC 14028*	*Candida albicans ATCC 90028*	*Candida glabrata ATCC 2001*	*Candida parapsilosis ATCC 22019*	*Candida krusei ATCC 6258*
2	1000	8000	4000	8000	-	-	4000	1000
3	4000	8000	1000	4000	-	-	4000	-
4a	8000	-	-	8000	500	1000	-	-
4b	8000	-	-	4000	500	1000	4000	500
4c	8000	2000	1000	4000	-	-	4000	500
5a	2000	-	-	4000	500	1000	-	-
5b	4000	-	-	4000	500	1000	4000	500
5c	2000	2000	8000	8000	-	-	4000	500
6a	6.25	12.5	12.5	50	4000	2000	4000	1000
6b	6.25	12.5	12.5	50	4000	2000	2000	1000
6c	6.25	12.5	12.5	50	4000	2000	2000	1000
6d	6.25	12.5	12.5	50	4000	2000	2000	1000
6e	6.25	12.5	12.5	50	4000	2000	2000	1000
6f	6.25	12.5	12.5	50	4000	2000	2000	1000
Tetra.	0.015	0.015	0.015	0,031				
Amp	1	0,031	0,031	0,16				
Fluk.					0.250	0.125	0.5	0.5
AmB					0.25	0.125	0.5	0.25
DMSO	-	-	-	-	-	-	-	-

Abbreviations: Tetra: Tetracycline; Amp: Ampicillin; Fluc: Fluconazole; AmB: Amphotericin B; DMSO: Dimethyl Sulfoxide.

derivatives, chemotype clustering was performed based on their antimicrobial activity (MIC values). The results, visualized in Figure 1 as a heatmap, suggest notable trends between chemical structure and biological response.

The final hybrid compounds 6a–6f exhibited substantially lower MIC values (6.25–50 µg/mL) against E. coli, S. aureus, and B. subtilis compared to their precursors (2–5c), indicating an improvement in antimicrobial potency. This trend may be associated with the introduction of the fluorophenyl-triazole moiety, which could potentially enhance bacterial membrane permeability and enzyme binding interactions. However, further studies are needed to confirm these mechanisms.

The thiosemicarbazide (4a, 4b) and carboxamide (4c) derivatives showed limited antibacterial activity, suggesting that additional structural modifications were required for improved efficacy. Compounds 5a–5c, which incorporate a triazole ring, displayed slightly enhanced activity relative to earlier intermediates, indicating that triazole cyclization may contribute to bioactivity, although it alone may not be sufficient for potent antimicrobial performance.

The hybrid derivatives (6a–6f) also exhibited moderate antifungal activity, with MIC values ranging from 2000 to 4000 µg/mL against Candida species. When compared to standard antifungal agents such as fluconazole and amphotericin B, the synthesized compounds showed lower efficacy, implying that further structural optimization is necessary to improve antifungal selectivity.

The inclusion of the fluorophenyl group may contribute to increased lipophilicity, cellular uptake, and potential interactions with microbial targets, especially in hybrid compounds. These observations align with literature reports suggesting that fluorine substitution can enhance pharmacokinetic properties and biological activity in triazole derivatives.

Overall, the chemotype clustering analysis supports a correlation between hybrid scaffold integration and increased antibacterial activity. While 6a–6f demonstrated promising antibacterial effects, additional modifications will be explored to optimize antifungal performance. Future studies will focus on SAR-guided analog design, mechanistic evaluations, and *in vivo* validation to better assess the therapeutic potential of these novel compounds.

While the current chemotype clustering analysis reveals useful correlations between chemical modifications and antimicrobial activity, we acknowledge that definitive conclusions regarding mechanisms such as membrane permeability enhancement, enzyme binding affinity, or improved cellular uptake cannot be drawn solely from MIC data. These hypotheses, although supported by trends observed in the heatmap and consistent with literature, require further experimental validation.

In future studies, we intend to perform additional assays such as bacterial membrane permeability tests (e.g., propidium iodide uptake), lipophilicity measurements (e.g.,

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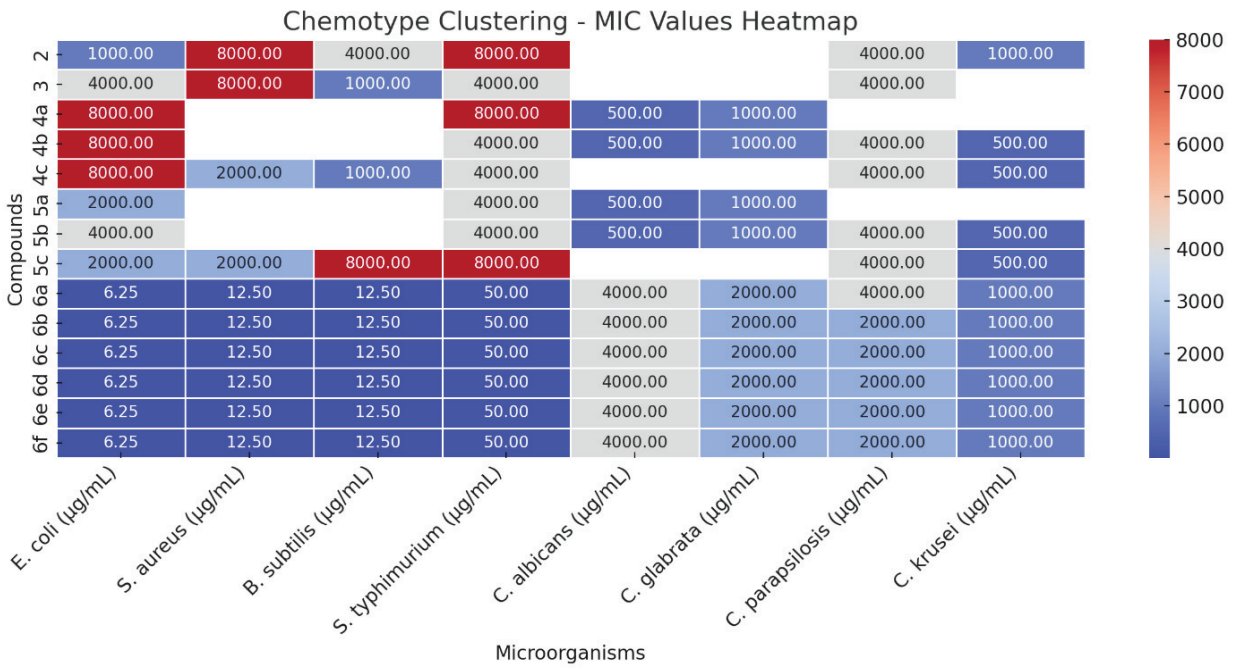

Figure 1: Chemotype Clustering and Structure-activity Relationship.

logP determination), molecular docking and *in vitro* enzyme inhibition studies, as well as fluorescence-based cellular uptake analyses. These approaches will help elucidate the mechanistic basis of the observed activity and confirm the role of the fluorophenyl-triazole scaffold in enhancing antimicrobial efficacy.

Conclusion

In this study, a series of fluorophenyl-1,2,4-triazole derivatives were successfully synthesized and structurally characterized through hydrazinolysis, isocyanate coupling, and cyclization reactions, leading to the development of structurally diverse hybrid compounds. The antimicrobial evaluation revealed that fluorophenyl-triazole-fluoroquinolone hybrids (6a–6f) exhibited significant antibacterial potency, particularly against E. coli, S. aureus, and B. subtilis, with MIC values as low as 6.25 µg/mL, while earlier-stage intermediates (4a–5c) demonstrated only moderate to weak activity, highlighting the role of fluoroquinolone hybridization in enhancing antimicrobial efficacy. Chemotype clustering analysis further provided valuable insights into the structure-activity relationship (SAR), demonstrating that fluorophenyl substitution and fluoroquinolone incorporation played a crucial role in increasing lipophilicity, enzyme binding affinity, and bacterial membrane permeability, ultimately leading to improved antimicrobial activity. The final hybrid compounds (6a–6f) exhibited antibacterial activity with MIC values as low as 6.25 µg/mL against *E. coli* and 12.5 µg/mL against *S. aureus*. By contrast, tetracycline inhibited both strains at 0.015 µg/mL, and ampicillin displayed MIC values of 1 µg/mL against *E. coli* and 0.031 µg/mL against *S. aureus*. These direct comparisons demonstrate that while the new derivatives are less potent than standard antibiotics, they represent a substantial improvement over earlier intermediates, confirming the contribution of fluorophenyl-triazole hybridization to enhanced antimicrobial efficacy. These findings collectively suggest that fluorophenyl-triazole hybrids represent promising candidates for antimicrobial drug development, offering a potential strategy to overcome drug resistance by integrating multiple pharmacophoric features into a single molecular framework. Future research will focus on SAR-guided structural refinements, *in vivo* pharmacokinetic and toxicity assessments, and mechanistic investigations to further explore the therapeutic potential of these novel hybrid molecules and optimize their design for clinical applications.

(Supplementary)

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