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Synthesis and Biological Evaluation of Some Novel Quinoline-Tetrazole Schiff Base Hybrids as Antimicrobial Agents

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ABSTRACT: Quinoline-tetrazole Schiff base hybrids were synthesized by reaction of substituted 2-chloro-3-formylquinoline with various 1,5-di substituted tetrazole containing anilines under ambient reaction conditions. All compounds were characterized by FTIR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. The in vitro antimicrobial activity of the synthesized compounds was evaluated against two gram negative and three gram positive bacteria, and three fungal strains. Compounds **3a**, **3e** and **3i** showed good antibacterial activity while compounds **3b** and **3e** showed good antifungal activity. All the newly synthesized compounds exhibited low to moderate activity against all pathogens tested.

KEYWORDS: Antimicrobial, Quinoline, Schiff base, Tetrazole.

I. INTRODUCTION

Quinoline, structurally 1-aza-napthalene or benzo[b]pyridine, is a nitrogen containing heterocyclic aromatic compound consist of benzene ring fused with pyridine. It is one of the most privileged N-containing motifs, found in various natural products, the most common being the cinchona alkaloids, which are used in the treatment of malaria.[1] Second, camptothecin, isolated from the Chinese plant Camptotheca acuminata in the early 1960s, is the most important and well-known quinoline alkaloid from an anticancer perspective.[2] Since then, numerous quinoline derivatives have been isolated from natural sources or obtained synthetically due to their wide range of biological activities such as antitumor,[3] antimalarial,[4] antibacterial,[5] antifungal,[6] antiparasitic[7] and insecticidal,[8] antiviral,[9,10] anti-inflammatory,[11] and antiplatelet[12] etc.

Nowadays, quinoline ring containing various drugs are used to treat systemic lupus erythematosus, rheumatoid arthritis, and rheumatic disorders such as graft versus host disease,[13] as well as amoebiasis. Quinolone derivatives such as chloroquine, mefloquine and quinine are used to treat malaria.[14] Ciprofloxacin,[15] a qulinoline containing broad-spectrum antibiotic, is used to treat many bacterial infections such as uncomplicated urinary tract infections where other antibiotics are not appropriate, conjunctivitis, pneumonia, and skin and bone infections. Bedaquiline[16] is a diarylquinoline that inhibits mycobacterial ATP-synthase. Brexpiprazole[17] is used to treat the symptoms of schizophrenia. Dovitinib[18] exhibits potent inhibitory activity against multiple RTKs involved in tumor growth and angiogenesis while Mavorixafor[19] is a selective allosteric antagonist of the CXCR4 receptor on HIV. Gemifloxacin[20] is used to treat acute bacterial exacerbations of chronic bronchitis and mild to moderate community-acquired pneumonia caused by susceptible bacteria.

Tetrazole, a nitrogen-rich multi-electron conjugated system,[21,22] is an important heterocyclic compound due to its wide spectrum of biological applications such as antimicrobial,[23-25] anticonvulsant,[26] antihypertensive,[27,28] analgesic,[29] antiinflammatory,[30-32] and anticancer[33-35]. It acts as a bioisostere of the cis-amide and carboxylic acid group due to close pKa values. As it does not have acidic properties like carboxylic acids, it helps in reducing the noxious properties of drugs.[36]

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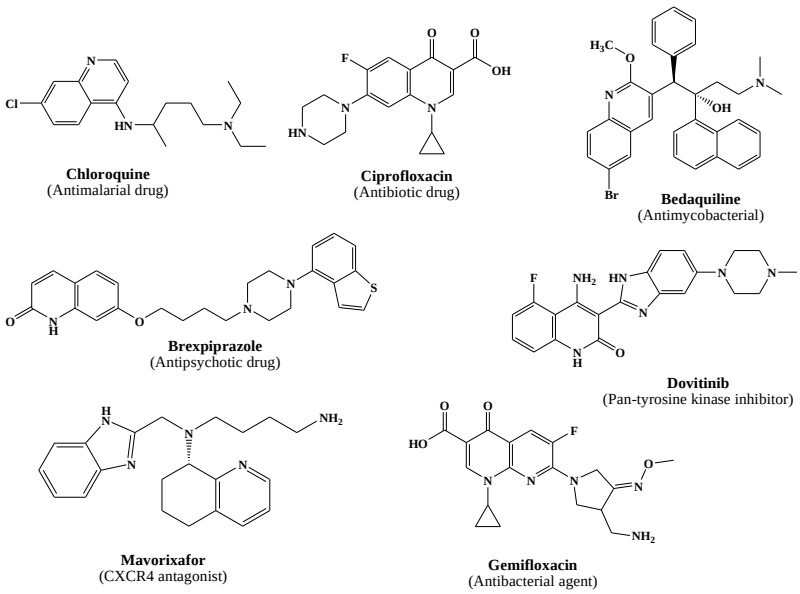
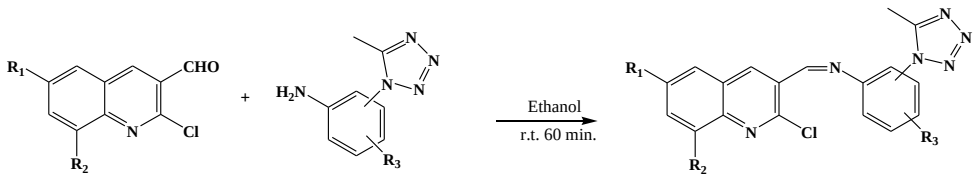


Fig. 1 Drugs containing quinoline scaffolds

With the aim of designing more effective and efficient bioactive compounds, many heterocyclic moieties have been constructed in a single structure as hybrid molecule. In this view, the synthesis of Schiff bases containing nitrogen-rich tetrazole and quinoline rings in a single framework appears to be a promising approach for hybrid molecules with high pharmacological properties. In continuation of our previous work on tetrazole scaffolds, here, we have synthesized a new series of hybrid quinoline-tetrazole Schiff bases for their enhanced antimicrobial activity.



1

1a R_1, R_2 = CH_3
1b R_1 = CH_3, R_2 = H

2

2a R_3 = H, 3-Tet
2b R_3 = H, 4-Tet
2c R_3 = H, 2-Tet
2d R_3 = 3-CH_3, 4-Tet
2e R_3 = 4-CH_3, 3-Tet

3a-i

Scheme 1. Synthesis of compound **3a-i**

II. MATERIALS AND METHODS

2.1 Reagents and instruments

All the chemicals (AR grade) were purchased from Aldrich Chemical Co. and used without further purification. The progress of reaction and purity of the product were monitored by thin layer chromatography using precoated Silica 60/UV254 (SDFCL). IR spectra were recorded (KBr) on a Perkin Elmer 1650 spectrophotometer and reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were carried out on 400 MHz Varian Mercury plus 400 MHz FT NMR spectrometer using TMS as an internal standard and chemical shifts were recorded in ppm on δ scale using $CDCl_3$ as a solvent. Chemical shifts are expressed as δ ppm scale relative to TMS (δ = 0.00 ppm). Melting points were obtained using melting points apparatus (Model MP-96) and are uncorrected.

2.2 Synthesis

2.2.1 General procedure for the synthesis of compounds **3a-i**

To a solution of compound **1** (2 g, 0.1 mmol) in 20 mL ethanol were added compound **2**

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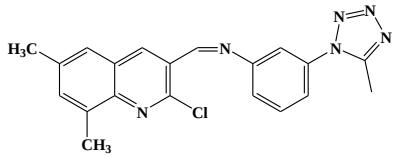
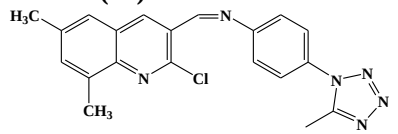
(0.1 mmol) and catalytic amount of piperidine (2-3 drops). Then mixture was stirred at room temperature for 30 min. and poured into ice cold water. The solid separated was filtered, dried and crystallized from ethanol/water (1:2) to give compound **3a-i**.

(ZE)-N-((2-chloro-6,8-dimethylquinolin-3-yl)methylene)-3-(5-methyl-1H-tetrazol-1-yl)benzenamine **(3a)**



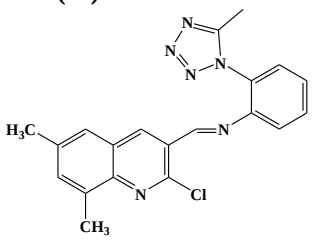
2-chloro-6,8-dimethylquinoline-3-carbaldehyde **1a** reacts with 3-(5-methyl-1H-tetrazol-1-yl)benzenamine **2a** by following the above procedure to give compound **3a**. Pale yellow solid; (3.02 g, 88%) yield; mp 231–232 ºC; IR (KBr, vmax, cm^{-1}): 1611 (C=N azomethine), 1576 (C=N tetrazole ring), 1469 (N=N tetrazole ring), 1091 and 990 (N-N=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.53 (s, 3H, CH_3-tetrazole); 2.71 (s, 3H, CH_3- quinoline); 2.77 (s, 3H, CH_3- quinoline); 7.40-7.41 (dd, 2H, quinoline H-5, H-7); 7.42-7.43 (dd, 2H, Ar-H); 7.48-7.57 (m, 1H, Ar-H); 7.66-7.70 (m, 1H, Ar-H); 8.93 (s, 1H, quinoline H-4); 9.04 (s, 1H, N=CH); ^{13}C NMR: δ ppm: 9.93 (CH_3-tetrazole), 17.65 (CH_3-quinoline, C-8), 21.58 (CH_3-Quinoline, C-6), 117.77 (C, tetrazole), 122.15 (1C), 122.46 (1C), 125.61 (1C), 126.39 (1C), 127.2 (1C), 130.81 (1C),134.72 (1C), 134.96 (1C), 136.35 (1C), 137.63 (1C), 137.73 (1C), 146.81 (1C), 148.25 (Ar C-1), 151.56 (quinoline C-2), 153.13 (quinoline C-9), 158.53 (N=CH); MS (ESI) m/z: 377.04 $(M+1)^+$. Anal. calcd. (%) for $C_{20}H_{17}ClN_6$: C, 63.74; H, 4.55; Cl, 9.41; N, 22.30; Found: C, 63.91; H, 4.56; Cl, 9.43; N, 22.26.

2.2.2 (ZE)-N-((2-chloro-6,8-dimethylquinolin-3-yl)methylene)-4-(5-methyl-1H-tetrazol-1-yl)benzenamine **(3b)**



2-Chloro-6,8-dimethylquinoline-3-carbaldehyde **1a** reacts with 4-(5-methyl-1H-tetrazol-1-yl)benzenamine **2b** by following the above procedure to give compound **3b**. Yellow solid; (3.08 g, 90%) yield; mp 222–223 ºC; IR (KBr, vmax, cm^{-1}): 1603 (C=N azomethine), 1582 (C=N tetrazole ring), 1501, 1456 (N=N tetrazole ring), 1073 and 917 (N-N=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.52 (s, 3H, CH_3-tetrazole); 2.68 (s, 3H, CH_3-quinoline); 2.77 (s, 3H, CH_3-quinoline); 7.47 (dd, 2H, Ar-H); 7.52 (m, 1H, quinoline-H); 7.57 (m, 1H, quinoline-H); 8.61 (dd, 2H, Ar-H); 8.93 (s, 1H, quinoline H-4); 9.03 (s, 1H, N=CH); ^{13}C NMR: δ ppm: 10.06 (CH_3-tetrazole), 17.66 (CH_3-quinoline, C-8), 21.51 (CH_3-Quinoline, C-6), 122.46 (C, tetrazole), 124.69 (2C), 126.49 (1C), 127.20 (2C), 131.83 (1C), 134.93 (1C), 136.4 (1C),137.7 (1C), 139.71 (1C), 146.76 (1C), 147.47 (1C), 148.25 (Ar C-1), 151.59 (quinoline C-2), 153.22 (quinoline C-9), 158.33 (N=CH); MS (ESI) m/z: 377.16 $(M+1)^+$. Anal. calcd. (%) for $C_{20}H_{17}ClN_6$: C, 63.74; H, 4.55; Cl, 9.41; N, 22.30; Found: C, 63.82; H, 4.55; Cl, 9.46; N, 22.29.

2.2.3 (ZE)-N-((2-chloro-6,8-dimethylquinolin-3-yl)methylene)-2-(5-methyl-1H-tetrazol-1-yl)benzenamine **(3c)**



2-Chloro-6,8-dimethylquinoline-3-carbaldehyde **1a** reacts with 2-(5-methyl-1H-tetrazol-1-yl)benzenamine **2c** by following the above procedure to give compound **3c**. Pale yellow solid; (2.81 g, 82% yield); mp 207–208 ºC; IR (KBr, vmax, cm^{-1}): 1623 (C=N azomethine), 1588 (C=N tetrazole ring), 1491, 1446 (N=N tetrazole ring), 1003 and 976 (N-N=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.5 (s, 3H, CH_3-tetrazole); 2.57 (s, 3H, CH_3-quinoline); 2.77 (s, 3H, CH_3-quinoline); 7.46-7.53 (m, 4H, Ar-H); 7.55-7.57 (m, 1H, quinoline-H); 7.69-7.73 (m, 1H, quinoline-H); 8.42 (s, 1H, quinoline H-4); 9.06 (s, 1H, N=CH); ^{13}C NMR: δ ppm: 10.06 (CH_3-tetrazole), 17.66 (CH_3-quinoline, C-8), 21.51 (CH_3-Quinoline, C-6), 119.41 (C, tetrazole), 125.9 (1C), 126.26 (1C), 126.75 (1C), 127.03 (1C), 127.72 (1C), 128.3 (1C), 132.23 (1C), 135.14 (1C),136.19 (1C), 137.78 (1C), 139.72 (1C), 146.72 (1C), 147.51 (Ar C-1), 148.19 (quinoline C-2), 153.21 (quinoline C-9), 158.95 (N=CH); MS (ESI) m/z: 376.99 $(M+1)^+$. Anal. calcd. (%) for $C_{20}H_{17}ClN_6$: C, 63.74; H, 4.55; Cl, 9.41; N, 22.30; Found: C, 63.72; H, 4.56; Cl, 9.43; N, 22.33.

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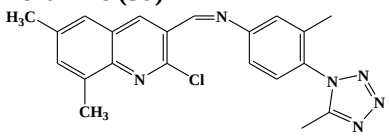
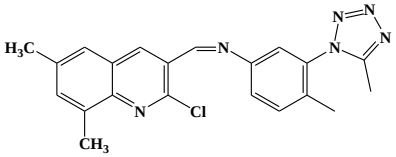
2.2.4 (ZE)-N-((2-chloro-6,8-dimethylquinolin-3-yl)methylene)-3-methyl-4-(5-methyl-1H-tetrazol-1-yl)benzenamine **(3d)**



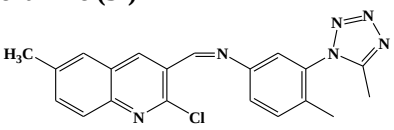
2-Chloro-6,8-dimethylquinoline-3-carbaldehyde **1a** reacts with 3-methyl-4-(5-methyl-1H-tetrazol-1-yl)benzenamine **2d** by following the above procedure to give compound **3d**. Off white solid; (3.31 g, 93%) yield; mp 217–218 ºC; IR (KBr, νmax, cm^{-1}): 1591 (C=N azomethine), 1493 (C=N tetrazole ring), 1421 (N=N tetrazole ring), 1073 and 1012 (N-N=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.12 (s, 3H, CH_3-tetrazole); 2.52 (s, 3H, CH_3-Ar); 2.54 (s, 3H, CH_3-quinoline); 2.76 (s, 3H, CH_3-quinoline); 7.21 (d, 1H); 7.46-7.55 (M, 4H); 8.88 (s, 1H, quinoline H-4); 9.02 (s, 1H, N=CH); ^{13}C NMR: δ ppm: 9.12 (CH_3-tetrazole), 16.98 (CH_3-Ar, C-4), 17.66 (CH_3-quinoline, C-8), 21.59 (CH_3-Quinoline, C-6), 119.99 (C, tetrazole), 123.39 (1C), 125.57 (1C), 126.47 (1C), 127.20 (1C), 132.53 (1C), 133.26 (1C), 133.35 (1C), 134.86 (1C), 136.29 (1C), 137.54 (1C), 137.57 (1C), 146.70 (1C), 148.22 (Ar C-1), 150.57 (quinoline C-2), 152.52 (quinoline C-9), 157.70 (N=CH); MS (ESI) m/z: 391.53 $(M+1)^+$. Anal. calcd. (%) for $C_{21}H_{19}ClN_6$: C, 64.53; H, 4.90; Cl, 9.07; N, 21.50; Found: C, 64.42; H, 4.86; Cl, 9.14; N, 21.56.

2.2.5 (ZE)-N-((2-chloro-6,8-dimethylquinolin-3-yl)methylene)-4-methyl-3-(5-methyl-1H-tetrazol-1-yl)benzenamine **(3e)**



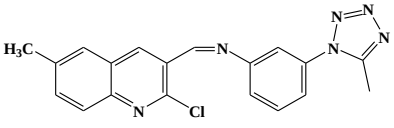
2-Chloro-6,8-dimethylquinoline-3-carbaldehyde **1a** reacts with 4-methyl-3-(5-methyl-1H-tetrazol-1-yl)benzenamine **2e** by following the above procedure to give compound **3e**. Off white solid; (3.10 g, 87%) yield; mp 205–206 ºC; IR (KBr, νmax, cm^{-1}): 1622 (C=N azomethine), 1509 (C=N tetrazole ring), 1433 (N=N tetrazole ring), 1081 and 1003 (N-N=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.14 (s, 3H, CH_3-tetrazole); 2.51 (s, 3H, CH_3-Ar); 2.56 (s, 3H, CH_3-quinoline); 2.79 (s, 3H, CH_3-quinoline); 7.23 (m, 2H); 7.44-7.52 (M, 3H); 8.84 (s, 1H, quinoline H-4); 8.99 (s, 1H, N=CH); ^{13}C NMR: δ ppm: 9.27 (CH_3-tetrazole), 16.59 (CH_3-Ar, C-4), 17.63 (CH_3-quinoline, C-8), 22.39 (CH_3-Quinoline, C-6), 120.71 (C, tetrazole), 123.32 (1C), 125.48 (1C), 126.26 (1C), 127.37 (1C), 132.35 (1C), 133.62 (1C), 133.99 (1C), 135.06 (1C), 136.32 (1C), 137.45 (1C), 137.75 (1C), 145.90 (1C), 149.20 (Ar C-1), 150.98 (quinoline C-2), 152.56 (quinoline C-9), 158.78 (N=CH); MS (ESI) m/z: 391.58 $(M+1)^+$. Anal. calcd. (%) for $C_{21}H_{19}ClN_6$: C, 64.53; H, 4.90; Cl, 9.07; N, 21.50; Found: C, 64.40; H, 4.83; Cl, 9.16; N, 21.58.

2.2.6 (ZE)-N-((2-chloro-6-methylquinolin-3-yl)methylene)-4-methyl-3-(5-methyl-1H-tetrazol-1-yl)benzenamine **(3f)**



2-Chloro-6-methylquinoline-3-carbaldehyde **1b** reacts with 4-methyl-3-(5-methyl-1H-tetrazol-1-yl)benzenamine **2e** by following the above procedure to give compound **3f**. Pale yellow solid; (3.26 g, 89%) yield; mp 196–197 ºC; IR (KBr, νmax, cm^{-1}): 1572 (C=N azomethine), 1486 (C=N tetrazole ring), 1341 (N=N tetrazole ring), 1049 and 903 (N-N=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.10 (s, 3H, CH_3-tetrazole); 2.52 (s, 3H, CH_3-Ar); 2.55 (s, 3H, CH_3-quinoline); 7.20-7.21 (d, 1H); 7.44-7.52 (m, 2H); 7.62-7.69 (m, 2H); 7.91-7.93 (d, 1H); 8.91 (s, 1H, quinoline H-4); 8.99 (s, 1H, N=CH); ^{13}C NMR: δ ppm: 9.11 (CH_3-tetrazole), 16.99 (CH_3-Ar, C-4), 21.62 (CH_3-Quinoline, C-6), 120.04 (C, tetrazole), 123.35 (1C), 126.79 (1C), 127.05 (1C), 127.66 (1C), 128.07 (1C), 132.55 (1C), 133.25 (1C), 133.45 (1C), 134.71 (1C), 137.36 (1C), 138.00 (1C), 147.37 (1C), 149.23 (Ar C-1), 150.42 (quinoline C-9), 152.52 (quinoline C-2), 157.31 (N=CH); MS (ESI) m/z: 377.33 $(M+1)^+$. Anal. calcd. (%) for $C_{20}H_{17}ClN_6$: C, 63.74; H, 4.55; Cl, 9.41; N, 22.30; Found: C, 63.79; H, 4.51; Cl, 9.43; N, 22.34.

2.2.7 (ZE)-N-((2-chloro-6-methylquinolin-3-yl)methylene)-3-(5-methyl-1H-tetrazol-1-yl)benzenamine **(3g)**



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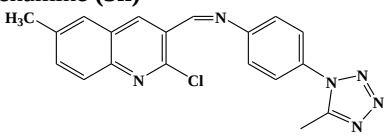
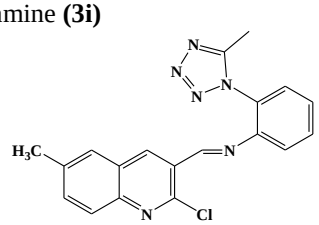
2-Chloro-6-methylquinoline-3-carbaldehyde **1b** reacts with 3-(5-methyl-1H-tetrazol-1-yl)benzenamine **2a** by following the above procedure to give compound **3g**. Pale yellow solid; (3.04 g, 86%) yield; mp 190–191 ºC; IR (KBr, νmax, cm^{-1}): 1572 (C=N azomethine), 1486 (C=N tetrazole ring), 1341 (N=N tetrazole ring), 1049 and 903 (N-N=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.08 (s, 3H, CH_3-tetrazole); 2.53 (s, 3H, CH_3-quinoline); 7.23-7.25 (d, 1H); 7.46-7.53 (m, 3H); 7.57-7.59 (m, 2H); 7.82-7.83 (d, 1H); 8.79 (s, 1H, quinoline H-4); 8.90 (s, 1H, N=CH); ^{13}C NMR: δ ppm: 9.14 (CH_3-tetrazole), 21.53 (CH_3-quinoline, C-6), 118.47 (C, tetrazole), 122.21 (1C), 124.67 (1C), 126.51 (1C), 127.32 (1C), 127.97 (1C), 131.45 (1C), 132.76 (1C), 133.36 (1C), 134.59 (1C), 138.30 (1C), 138.92 (1C), 146.27 (1C), 148.90 (Ar C-1), 150.11 (quinoline C-9), 152.33 (quinoline C-2), 156.58 (N=CH); MS (ESI) m/z: 363.26 $(M+1)^+$. Anal. calcd. (%) for $C_{19}H_{15}ClN_6$: C, 62.90; H, 4.17; Cl, 9.77; N, 23.16; Found: C, 62.87; H, 4.19; Cl, 9.76; N, 22.18.

2.2.8 (ZE)-N-((2-chloro-6-methylquinolin-3-yl)methylene)-4-(5-methyl-1H-tetrazol-1-yl)benzenamine **(3h)**



2-Chloro-6-methylquinoline-3-carbaldehyde **1b** reacts with 4-(5-methyl-1H-tetrazol-1-yl)benzenamine **2b** by following the above procedure to give compound **3h**. Yellow solid; (3.26 g, 92%) yield; mp 217–218 ºC; IR (KBr, νmax, cm^{-1}): 1596 (C=N azomethine), 1501 (C=N tetrazole ring), 1372 (N=N tetrazole ring), 1027 and 926 (N-N=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.23 (s, 3H, CH_3-tetrazole); 2.48 (s, 3H, CH_3-quinoline); 7.23-7.25 (d, 2H); 7.44-7.51 (m, 2H); 7.57-7.59 (d, 2H); 7.72-7.75 (m, 1H); 8.67 (s, 1H, quinoline H-4); 8.96 (s, 1H, N=CH); ^{13}C NMR: δ ppm: 9.67 (CH_3-tetrazole), 21.61 (CH_3-quinoline, C-6), 117.56 (C, tetrazole), 122.23 (1C), 124.57 (2C), 126.48 (1C), 127.36 (2C), 128.32 (1C), 132.69 (1C), 133.96 (1C), 135.53 (1C), 138.12 (1C), 140.32 (1C), 146.81 (Ar C-1), 149.93 (quinoline C-9), 153.01 (quinoline C-2), 159.59 (N=CH); MS (ESI) m/z: 363.19 $(M+1)^+$. Anal. calcd. (%) for $C_{19}H_{15}ClN_6$: C, 62.90; H, 4.17; Cl, 9.77; N, 23.16; Found: C, 62.84; H, 4.18; Cl, 9.78; N, 23.19.

2.2.9 (ZE)-N-((2-chloro-6-methylquinolin-3-yl)methylene)-2-(5-methyl-1H-tetrazol-1-yl)benzenamine **(3i)**



2-Chloro-6-methylquinoline-3-carbaldehyde **1b** reacts with 2-(5-methyl-1H-tetrazol-1-yl)benzenamine **2c** by following the above procedure to give compound **3i**. Yellow solid; (2.88 g, 81%) yield; mp 176–177 ºC; IR (KBr, νmax, cm^{-1}): 1604 (C=N azomethine), 1512 (C=N tetrazole ring), 1382 (N=N tetrazole ring), 1087 and 1013 (N-N=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.13 (s, 3H, CH_3-tetrazole); 2.51 (s, 3H, CH_3-quinoline); 7.21-7.22 (d, 1H); 7.41-7.47 (m, 3H); 7.54-7.57 (m, 1H); 7.74-7.76 (m, 2H); 8.72 (s, 1H, quinoline H-4); 8.89 (s, 1H, N=CH); ^{13}C NMR: δ ppm: 9.07 (CH_3-tetrazole), 19.92 (CH_3-quinoline, C-6), 117.97 (C, tetrazole), 121.34 (1C), 123.57 (1C), 126.56 (1C), 127.51 (1C), 128.17 (1C), 130.42 (1C), 131.72 (1C), 132.96 (1C), 134.45 (1C), 138.08 (1C), 138.97 (1C), 145.97 (1C), 149.00 (Ar C-1), 150.17 (quinoline C-9), 153.03 (quinoline C-2), 157.08 (N=CH); MS (ESI) m/z: 363.26 $(M+1)^+$. Anal. calcd. (%) for $C_{19}H_{15}ClN_6$: C, 62.90; H, 4.17; Cl, 9.77; N, 23.16; Found: C, 62.85; H, 4.21; Cl, 9.75; N, 23.18.

2.3 Antimicrobial activity determination

The antibacterial activity of compounds **3a-i** was tested against five bacterial strains: Escherichia coli, Pseudomonas aeruginosa, Bacillus megaterium, Staphylococcus aureus and Bacillus cereus. Antifungal activity of the synthesized compounds was performed against three fungal species: Candida albicans, Saccharomyces cerevisiae and Aspergillus niger. Their potency was determined by measuring their inhibition zone diameter obtained on agar culture media. The diameter of the inhibition zone on agar culture media was obtained to determine the potential activity of the compounds. The experiments were performed in triplicate to verify the results. Tetracyclin and nystatin were used as positive controls for antibacterial and antifungal studies, respectively.

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III. RESULT AND DISCUSSION

2.4 Synthesis

The desired compounds were obtained by following the route shown in Scheme 1. The compound **1** was synthesized by reacting substituted acetanilides with N,N-dimethylformamide in phosphorus oxychloride.[37] Compound **2** was prepared from substituted nitroanilines by using our previously reported method.[38] The desired compounds **3a-i** were obtained by stirring the mixture of compound 1 with compound 2 in ethanol at room temperature using piperidine as a catalyst. The structures of the desired compounds were also confirmed by infrared, ^{1}H and ^{13}C-NMR, and HRMS analysis. We give the ^{1}H and ^{13}C NMR spectra of compound **3a** in Figure 1. In the ^{1}H NMR spectra of compounds 3a-i, the signal due to CH=N proton was detected in the region 8.89-9.06 ppm. The signal of imine group carbon was observed at 156.58 -159.59 in ^{13}C spectra confirms the formation of Schiff base.

Table 1. Antibacterial activity in mm of compound **3a-i**.

Compounds	Escherichia coli	Pseudomonas aerogenosa	Bacillus megaterium	Staphylococcus aureus	Bacillus cereus
3a	12	12	16	09	11
3b	11	12	08	08	10
3c	10	08	15	14	13
3d	14	17	13	19	12
3e	16	15	18	15	14
3f	11	13	13	14	10
3g	09	21	09	06	11
3h	08	08	06	12	09
3i	17	06	13	13	10
Tetracyclin	20	33	20	30	25

3.2 Antibacterial activity

The in vitro antibacterial activity of compounds 3a-i was examined against two gram negative bacterial strains: Escherichia coli and Pseudomonas aeruginosa and three gram positive bacteria: Bacillus megaterium, Staphylococcus aureus and Bacillus cereus. The results obtained were expressed as area of inhibition and minimum inhibitory concentration (MIC) and compared with the standard drug tetracyclin and were summarized in Table 1. The results showed that compounds **3e** and **3i** exhibited the highest inhibition zone of 16 mm and 17 mm against E. coli, respectively. Compounds **3a** and **3e** displayed good antibacterial activity against B. megaterium with MIC values of 16 mm and 18 mm, respectively. All compounds showed moderate to less activity against the bacterial strains used. Furthermore, the activity of these compounds was found to be less than that of tetracyclin.

Table 2 Antifungal activity in mm of compound **3a-i**.

Compounds	Candida albicans	Saccharomyces cerevisiae	Aspergillus niger
3a	17	14	13
3b	09	05	16
3c	11	12	12
3d	13	11	08
3e	16	15	15
3f	15	13	10
3g	14	11	14
3h	11	10	10
3i	10	14	09
Nystatin	24	20	25

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3.3 Antifungal activity

The in vitro antifungal activity of compounds 3a-i was examined against three fungal species: Candida albicans, Saccharomyces cerevisiae and Aspergillus niger. Table 2 summarizes the results, showing that compound **3e** inhibits all three fungal strains with optimal MIC values of 16 mm, 15 mm and 15 mm against C. albicans, S. cerevisiae and A. niger respectively. The compounds **3b** exhibited the highest inhibition zone of 16 mm against A. niger. All compounds showed moderate to less activity against the fungal strains used. Furthermore, the activity of these compounds was found to be less than that of nystatin.

IV. CONCLUSION

A series of quinoline-linked tetrazole Schiff bases were prepared from substituted 2-chloro-3-formylquinolines and 5-methyl-1H-tetrazolyl substituted anilines. The synthesized compounds were characterized by IR, NMR and mass spectroscopic techniques and evaluated for their antimicrobial activity. Compounds **3e** and **3i** exhibited the highest inhibition zone of 16 mm and 17 mm against E. coli, respectively. Compounds **3a** and **3e** displayed good antibacterial activity against B. megaterium with MIC values of 16 mm and 18 mm, respectively. The antifungal activity of the newly synthesized compounds displayed low to moderate activity against all three fungal strains tested.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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REFERENCES

[1] Kaufman, T.S.; Ruveda, E.A. The quest for quinine: those who won the battles and those who won the war. Angew. Chem. Int. Ed. Engl. **2005**, 44, 854-885.

[2] Wall, M.E. Camptothecin and taxol: Discovery to clinic, Med. Res. Rev. **1998**, 18, 299–314.

[3] Li, S.; Hu, L.; Li, J.; Zhu, J.; Zeng, F.; Huang, Q.; Qiu, L.; Du, R.; Cao, R. Design, synthesis, structure-activity relationships and mechanism of action of new quinoline derivatives as potential antitumor agents. Eur. J. Med. Chem. **2019**, 162, 666-678.

[4] Uddin, A.; Gupta, S.; Shoaib, R.; Aneja, B.; Irfan, I.; Gupta, K.; Rawat, N.; Combrinck, J.; Kumar, B.; Aleem, M.; Hasan, P.; Joshi, M.C.; Chhonker, Y.S.; Zahid, M.; Hussain, A.; Pandey, K.; Alajmi, M.F.; Murry, D.J.; Egan, T.J.; Singh, S.; Abid, M. Blood-stage antimalarial activity, favourable metabolic stability and in vivo toxicity of novel piperazine linked 7-chloroquinoline-triazole conjugates. Eur. J. Med. Chem. **2024**, 264, 115969.

[5] Özcan, E.; Vagolu, S.K.; Gündüz, M.G.; Stevanovic, M.; Kökbudak, Z.; Tønjum, T.; Nikodinovic-Runic, J.; Çetinkaya, Y.; Doğan, Ş.D. Novel quinoline-based thiosemicarbazide derivatives: Synthesis, DFT calculations, and investigation of antitubercular, antibacterial, and antifungal activities. ACS Omega **2023**, 8, 40140-40152.

[6] Qin, T.-H.; Liu J.-C.; Zhang, J.-Y.; Tang, L.-X.; Ma, Y.-N.; Yang, R. Synthesis and biological evaluation of new 2‑substituted‑4‑amino-quinolines and -quinazoline as potential antifungal agents. Bioorg. Med. Chem. Lett. **2022**, 72, 128877.

[7] Bokosi, F.R.B.; Beteck, R.M.; Laming, D.; Hoppe, H.C.; Tshiwawa, T.; Khanye, S.D. Synthesis of 2-(N-cyclicamino) quinoline combined with methyl (E)-3-(2/3/4-aminophenyl)acrylates as potential antiparasitic agents. Archiv Der Pharmazie **2021**, 354, 2000331.

[8] Ramadan, S.K.; Abd-Rabboh, H.S.M.; Gad, N.M.; Abou-Elmagd, W.S.I.; Haneen D.S.A. Synthesis and characterization of some chitosan-quinoline nanocomposites as potential insecticidal agents, Polycyclic Aromat. Comp. **2023**, 43, 7013-7026.

[9] Li, X.; Li, Y.; Fan, S.; Cao, R.; Li, X.; He, X.; Li, W.; Xu, L.; Cheng, T.; Li, H.; Zhong, W. Discovery and optimization of quinoline analogues as novel potent antivirals against enterovirus D68. J. Med. Chem. **2022**, 65, 14792-14808.

[10] Wang, M.; Zhang, G.; Zhao, J.; Cheng, N.; Wang, Y.; Fu, Y.; Zheng, Y.; Wang, J.; Zhu, M.; Cen, S.; He, J.; Wang, Y. Synthesis and antiviral activity of a series of novel quinoline derivatives as anti-RSV or anti-

IAV agents. Eur. J. Med. Chem. **2021**, 214, 113208.

[11] Ghanim, A.M.; Girgis, A.S.; Kariuki, B.M.; Samir, N.; Said, M.F.; Abdelnaser, A.; Nasr, S.; Bekheit, M.S.; Abdelhameed, M.F.; Almalki, A.J.; Ibrahim, T.S.; Panda, S.S. Design and synthesis of ibuprofen-quinoline conjugates as potential anti-inflammatory and analgesic drug candidates. Bioorg. Chem. **2022**, 119, 105557.

[12] Dandamudi, A.; Seibel, W.; Tourdot, B.; Cancelas, J.A.; Akbar, H.; Zheng, Y. Structure–activity relationship analysis of Rhosin, a RhoA GTPase inhibitor, reveals a new class of antiplatelet agents. Int. J. Mol. Sci. **2023**, 24, 4167.

[13] Rolain, M.J.; Colson Raoult, D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. Int. J. Antimicrob. Agents **2007**, 30, 297-308.

[14] Foley, M.; Tilley, L. Quinoline antimalarials: mechanisms of action and resistance. Int. J. Parasitol. **1997**, 27, 231-240.

[15] Apangu, T.; Griffith, K.; Abaru, J.; Candini, G.; Apio, H.; Okoth, F.; Okello, R.; Kaggwa, J.; Acayo, S.; Ezama, G.; Yockey, B.; Sexton, C.; Schriefer, M.; Mbidde, E.K.; Mead, P. Successful treatment of human plague with oral ciprofloxacin. Emerg. Infect. Dis. **2017**, **23**, 553-555.

[16] Deshkar, A.T.; Shirure, P.A. Bedaquiline: A novel diarylquinoline for multidrug-resistant pulmonary tuberculosis. Cureus **2022**, 14, e28519.

[17] Maeda, K.; Sugino, H.; Akazawa, H.; Amada, N.; Shimada, J.; Futamura T.; Yamashita H.; Ito N.; McQuade, R.D.; Mørk, A.; Pehrson, A.L.; Hentzer, M.; Nielsen, V.; Bundgaard, C.; Arnt, J.; Stensbøl, T.B.; Kikuchi, T. Brexpiprazole I: In vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. J. Pharmacol. Exp. Ther. **2014**, 350, 589-604.

[18] Porta, C.; Giglione, P.; Liguigli, W.; Paglino, C. Dovitinib (CHIR258, TKI258): structure, development and preclinical and clinical activity. Future Oncol. **2015**, 11, 39-50.

[19] Andtbacka R.H.I.; Wang, Y.; Pierce, R.H.; Campbell, J.S.; Yushak, M.; Milhem, M.; Ross, M.; Niland, K.; Arbeit, R.D.; Parasuraman, S.; Bickley, K.; Yeung, C.C.; Aicher, L.D.; Smythe, K.S.; Gan, L. Mavorixafor, an orally bioavailable CXCR4 antagonist, increases immune cell infiltration and inflammatory status of tumor microenvironment in patients with melanoma. Cancer Res. Commun. **2022**, 2, 904-913.

[20] Jivcu, C.; Gotfried, M. Gemifloxacin use in the treatment of acute bacterial exacerbation of chronic bronchitis. Int. J. Chron. Obstruct. Pulmon. Dis. **2009**, 4, 291-300.

[21] Cheng-Xi, W.; Ming, B.; Guo-Hua, G. Tetrazolium compounds: synthesis and applications in medicine. Molecules **2015**, 20, 5528-5553.

[22] Bachar, S.C.; Lahiri, S.C. Synthesis of chloro and bromo substituted 5-(indan-10-yl)tetrazoles and 5-(indan-10-yl)methyltetrazoles as possible analgesic agents. Pharmazie **2004**, 59, 435-438.

[23] Oulous, A.; Harit, T.; Yahyaoui, M.I.; Asehraou, A.; Malek, F. New family of tetrazole-pyrazole compounds: Synthesis, characterization, antimicrobial activity and docking study. Arabian J. Chem. **2023**, 16, 105268.

[24] Bourhou, C.; Benouda, H.; Bellaouchi, R.; Merzouki, M.; Fraj, E.; Harit, T.; Challioui, A.; Asehraou, A.; Touzani, R.; Ozdemir, I.; Bouammali, B. Synthesis of novel tetrazolic derivatives and evaluation of their antimicrobial activity. J. Mol. Struct. **2023**, 1278, 134913.

[25] Abualnaja, M.M.; Alalawy, A.I.; Alatawi, O.M.; Alessa, A.H.; Qarah, A.F.; Alqahtani, A.M.; Bamaga, M.A.; El-Metwaly, N.M. Synthesis of tetrazole hybridized with thiazole, thiophene or thiadiazole derivatives, molecular modelling and antimicrobial activity Saudi Pharm. J. **2024**, 32, 101962.

[26] Rostom, S.A.; Ashour, H.M.; El-Razik, H.A.; El-Fattah, A.H.; El-Din, N.N. Azole antimicrobial pharmacophore-based tetrazoles: synthesis and biological evaluation as potential antimicrobial and anticonvulsant agents. Bioorg. Med. Chem. **2009**, 17, 2410-2422.

[27] Masood, A.; Khan, M.A.; Ahmad, I.; Breena; Raza, A.; Ullah, F.; Shah, S.A. Synthesis, Characterization, and Biological Evaluation of 2-(N-((2′-(2H-tetrazole-5-yl)-[1,1′-biphenyl]-4yl)-methyl)-pentanamido)-3-methyl butanoic acid derivatives. Molecules **2023**, 28, 1908.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1747-1755 www.ijprajournal.com ISSN: 2249-7781

[28] Bayannavar, P.K.; Kamble, R.R.; Joshi, S.D.; Nesaragi, A.R.; Shaikh, S.K.J.; Sudha, B.S.; Dodamani, S.S.; Hoolageri, S.R. Design and synthesis of angiotensin converting enzyme (ACE) inhibitors: Analysis of the role of tetrazole ring appended to biphenyl moiety. **2022**, 7, e202103336.

[29] Asadi, M.; Mohammadi-Khanaposhtani, M.; Hosseini, F.S.; Gholami, M.; Dehpour, A.R.; Amanlou, M. Design, synthesis, and evaluation of novel racecadotril-tetrazole-amino acid derivatives as new potent analgesic agents. Res. Pharm. Sci. **2021**, 16, 341-357.

[30] Lamie, P.F.; Philoppes, J.N.; Azouz A.A.; Safwat, N.M. Novel tetrazole and cyanamide derivatives as inhibitors of cyclooxygenase-2 enzyme: design, synthesis, anti-inflammatory evaluation, ulcerogenic liability and docking study. J. Enzyme inhib. Med. Chem. **2017**, 32, 805-820.

[31] Altıntop, M.D.; Sever, B.; Temel, H.E.; Kaplancıklı, Z.A.; Özdemir, A. Design, synthesis and in vitro COX inhibitory profiles of a new series of tetrazole-based hydrazones. Eur. J. Life Sci. **2022**, 1, 20-27.

[32] Oliveira, L.P.; Florentino, I.F.; Silva, D.P.; Pazini, F.; Carvalho, F.S.; Sanz, G.; Vaz, B.G.; Rocha, F.F.; Fajemiroye, J.O.; Ghedini, P.C.; Lião, L.M.; Menegatti, R.; Costa, E.A.; Oliveira, T.S. Anti-inflammatory, antinociceptive, and vasorelaxant effects of a new pyrazole compound 5-(1-(2-fluorophenyl)-1H-pyrazol-4-yl)-1H-tetrazole: role of NO/cGMP pathway and calcium channels. Canadian J. Physiol. Pharmacol. **2023**, 101, 216-225.

[33] Verma, A.; Kaur, B.; Venugopal, S.; Wadhwa, P.; Sahu, S.; Kaur, P.; Kumar, D.; Sharma, A. Tetrazole: A privileged scaffold for the discovery of anticancer agents. Chem. Biol. Drug Design **2022**, 100, 419-442.

[34] Vanam, N.R.; Anireddy, J.S. Synthesis and biological evaluation of tetrazole fused imidazopyridine derivatives as anticancer agents. Chem. Data Collect. **2023**, 48, 101092.

[35] Hsu, Y.-J.; Shi, W.-X.; Tseng, Y.-C.; Chiu, T.-H.; Cheng, M.-H.; Chen, K.-T. Facile synthesis and anticancer activity of tetrazolyl-benzothiazole derivatives, J. heterocyclic chem. **2023**, 60, 2036-2045.

[36] Nazariy, T.P.; Vasyl, S.M.; Mykola, D.O. New convenient synthesis of 2,3-diaminotheino[2,3-d]pyrimidin-4 (3H)-one derivates from substituted alkyl 2-(1H-tetrazol-1-yl)thiophene-3-carboxylates. Tetrahydron **2008**, 64, 1430-1434.

[37] Meth-Cohn, O.; Narine, B.; Tarnowski, B. A versatile new synthesis of quinolines and related fused pyridines. part 5.' The synthesis of 2-chloroquinoline-3-carbaldehydes. J. Chem. Soc., Perkin Trans. 1. **1981**, 1520-1530.

[38] Vedpathak, S.G.; Momle, R.G.; Kakade, G.K.; Ingle, V.S. An improved and convenient route for the synthesis of 5-methyl-1H-tetrazol-1-yl substituted benzenamines. World J. Pharm. Res. **2016**, 5, 1049-1057.