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SYNTHESIS OF TETRAAZOLO[1,5-A]QUINOLIN ANALOGUES CONTAINING PYRIMIDINE AND THIAZOLIDINONE AS ANTIMICROBIAL AGENTS

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ABSTRACT

A series of new 2-(aryl)-3-(4-phenyl-6-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-2-pyrimidinyl)-1,3-thiazolan-4-one **15(a-j)**has been synthesized by incorporating tetrazole, pyrimidine and thiazolidinone rings in one molecule for intensifying biological activity. Further, all the newly synthesized compounds have been assayed for their antimicrobial activity against Gram-positive bacteria *viz*. *Bacillus subtilis*, *Bacillus sphaericus* and *Staphylococcus aureus*, and Gram-negative bacteria *viz*. *Pseudomonas aeruginosa*, *Klebsiella aerogenes*, *Chromobacterium violaceum*and fungal organisms *viz*. *Candida albicans*, *Aspergillus fumigatus*, *Trichophyton rubrum* and *Trichophyton mentagrophytes.* The antimicrobial assay revealed that the compound containing 4-chlorophenyl **15b**, 4-fluorophenyl **15e** on thiazolidionone ring are found to be the most active against bacterial strains and compound containing 4-nitrophenyl **15c** is highly active against all the fungal organisms.

INTRODUCTION

The invention and manufacture of novel, potent medications as well as their successful implementation in practical fields are the primary goals of progressive and prospective pharmaceutical chemistry research. Every research project's primary goal is to create novel, potent, and unique pharmaceutical compounds and preparations that can outperform known drugs in terms of accuracy. Both quantitative and qualitative effects may result from the preparation and development of these medications; the lack of unwanted side effects, reduced toxicity, increased stability, or cheaper cost are preferred.

A notable five-membered aromatic heterocyclic molecule with a planar structure and a high concentration of poly nitrogen electrons is tetrazole. Through weak interactions including van der Waals, ionic, hydrogen, and coordination bonds, among others, tetrazole molecules can easily bind with various receptors or enzymes in organisms. They are therefore significant to the pharmaceutical industry and exhibit a range of biological functions (Koldobskii 1981, Rajeswari 2025, Lamie 2019, Masood 2023). Tetrazole rings are attractive linkers that can be used to join or stabilize different pharmacophore fragments to produce distinctive functionalized molecules. Tetrazole containing molecules, such as the antibiotics Flomoxef **1**, antihypertensives Lorsartan **2**, Valsartan **3**, and antinociceptive Alfentanil **4**, have been successfully synthesized and widely utilized as clinical drugs to treat a variety of illnesses.

Similarly, compounds which contain pyrimidine ring have therapeutic properties such as antiallergic (Ban 1998), antioxidant (Myriagkou 2023, Tylinska 2024), antiviral (Farghaly 2023), antihistaminic (Song 2015), cytostatic immunomodulating (Weinreich 2012), herbicidal (Wu 2022), anticonvulsant (Wang 2015) fungicidal (Li 2024), antitoxoplasma (Hortua Triana 2012) antimalarial (Gonzalez Cabrera 2015), antibacterial (Ding 2022), antifilarial (Bhoj 2020) and antileishmanial (Lopes 2022). Pyrimidine containing drugs Broxuridine **5** used as antiviral, Brodimoprim **6** used for treatment of respiratory tract and ear infections, Flucytosine **7** for fungal infections, Orotic acid **8** for liver disorder. Pyrimidines comprise important interesting group of antibacterial drugs, which have made a major impact on the field of antibacterial chemotherapy particularly in the past few years. Pyrimidine nucleus act as chemotherapeutic agents and exhibit anticancer activities (El-Kalyoubi2020).

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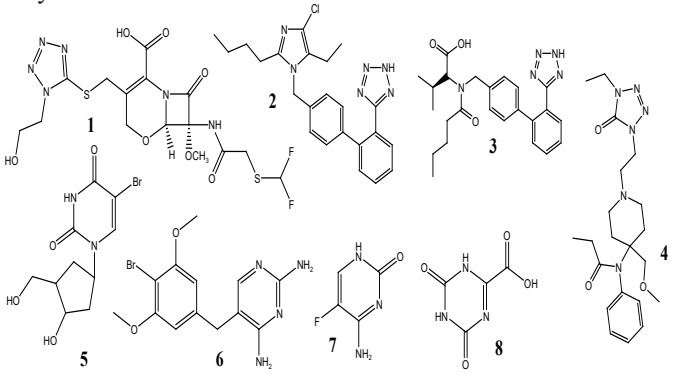
Further, the thiazolidinone is regarded as an essential anchor for the creation of novel therapeutic medicines due to its wide range of biological activities, as a result, the thiazolidinone nucleus has been investigated in organic, pharmaceutical, and photochemical fields. Antibiofilm (Chadha2015), hypoglycaemic (Jain 2012), antimicrobial (Verma 2008) analgesic (Doran1938), antipyretic (Halimehjani 2012), anti-inflammatory activities (Nitsche 2012), anticonvulsant (Singh 2013), antihistaminic (Umesh 2011), anti-HIV (Rawa 2007), cardioprotective (Markovic 2005), and antinociceptive (Pawar 2004) are just a few examples of physiologically active substances. It has been widely documented that the inclusion of arylazo, sulfamoyl phenyl, or phenylhydrazone moiety at different positions of the thiazolidinone ring enhances antimicrobial action. Its inhibitory action on the enzyme Mur B, a precursor involved in the biosynthesis of peptidoglycan, may be the source of its antibacterial effect.



Owing to the immense importance and varied bioactivities exhibited by tetrazole, pyrimidine and thiazolidinone derivatives, in continuation of our ongoing research on the synthesis of novel heterocycles, it was thought of interest to incorporate all these heterocyclic rings in one molecule to synthesize new heterocyclic compounds with potential antimicrobial activity. In this article, we wish to report the synthesis of new tetrazolo-quinolin analogues 2-(aryl)-3-(4-phenyl-6-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-2-pyrimidinyl)-1,3-thiazolan-4-one**15(a-j)**and evaluation of their *in vitro* antimicrobial activity.

MATARIALS AND METHODS

Commercial grade reagents were used as supplied. Solvents except analytical reagent grade were dried and purified according to the literature when necessary. Reaction progress and purity of the compounds were checked by thin-layer chromatography (TLC) on pre-coated silica gel F_{254} plates from Merck and compounds visualized either by exposure to UV light. Silica gel chromatographic columns (70–230 mesh) were used for separations. Melting points were determined on a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded as KBr disks on a Perkin–Elmer FTIR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts are reported as δ ppm against TMS as an internal standard and coupling constants (*J*) are reported in Hz units. Mass spectra were recorded on a VG micro mass 7070H spectrometer.

Synthesis of 2-chloro-3-quinolinecarbaldehyde (10): DMF (1 mol) was cooled at 0 °C in a round flask equipped with a drying tube and $POCl_3$ (1.5 mol) was added slowly and the mixture was stirred for 2 h keeping the temperature below 0 °C, then a solution of compound **9** (0.01 mol) in DMF (5 mL) was added dropwise and the reaction mixture was heated under reflux and stirring for 5 h. The resulted mixture was cooled to 0°C and the solution was poured slowly into ice-water and stirring for ten minutes, obtaining a yellow solid which was filtered, washed several times with cold water and dried under vacuum and recrystalized from ethyl acetate to give pure compound **10** in 49% of yields. IR (KBr)ν_{max}: 3089, 2870, 1716, 1590, 781 cm^{-1}; ^{1}H NMR (DMSO-d_6,300 MHz): **δ** 7.49 (d, *J* = 8.3 Hz, 1H, ArH), 7.90-8.00 (m, 3H, ArH), 8.57 (s, 1H, ArH), 10.32 (s, 1H, CHO); ^{13}C NMR (DMSO-d_6, 75 MHz): **δ**114.1, 125.6, 128.0, 129.9, 130.2, 132.0, 133.5, 144.9, 151.8, 189.1; MS: *m/z* 191 (M^+).

Synthesis of [1,2,3,4]tetraazolo[1,5-*a*]quinoline-4-carbaldehyde (11): Compound **10** (0.01 mol), sodium azide (0.02 mol), acetic acid (2 mL), and ethanol (10 mL) were charged in a round bottom flask with mechanical stirrer and condenser. The reaction mixture refluxed for 3-4 h. After the completion of reaction (checked by TLC), the separated compound was filtered and washed with ethanol. The further purification was carried out by leaching in equal volume ratio of chloroform and methanol (10:10 mL) to obtain the pure compound **11** in 54% of yields. IR (KBr)ν_{max}: 3077, 2869, 1719, 1620, 1595, 1329 cm^{-1}; ^{1}H NMR (DMSO-d_6,300 MHz): **δ**7.90-8.00 (m, 4H, ArH), 8.72 (d, *J* = 8.6 Hz, 1H, ArH), 10.34 (s, 1H, CHO); ^{13}C NMR (DMSO-d_6, 75 MHz): **δ**119.5, 123.2, 127.0, 128.1, 134.1, 136.4, 138.9, 139.2, 141.3, 181.9; MS: *m/z* 198 (M^+)

Synthesis of (*E*)-1-phenyl-3-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-2-propen-1-one (13): A solution of compound **11** (0.01 mol) and the acetophenone **12** (0.01 mol) in ethanol (50 mL) was treated with pyridine (1 mL). The reaction mixture was refluxed for 8 h. After completion of the reaction it was cooled to room temperature, filtered the solid thus separated and washed with water and alcohol o afford pure compounds **13** in 64% of yields. IR (KBr) ν_{max}: 3091, 1698, 1626, 1610, 1589, 1154 cm^{-1}; ^{1}H NMR (DMSO-d_6,300 MHz): δ 6.61 (d, *J* = 15.8 Hz, 1H, CH=CH), 6.95 (s, 1H, ArH), 7.60-7.70 (m, 8H, ArH), 8.32 (d, *J* = 15.8 Hz, 1H, CH=CH), 8.67 (d, *J* = 8.5 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6,300 MHz): δ119.7, 120.6, 122.5, 127.2, 128.5, 129.4, 130.1, 130.9, 131.5, 132.0, 133.4, 135.2, 136.7, 137.8, 141.3, 185.4; MS: *m/z* 301 (M^++1).

Synthesis of 4-phenyl-6-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-2-pyrimidinamine (14): A solution of compound **13** (0.01 mol) and guanidine hydrochloride (0.015 mol) in ethanol (25 mL) was treated with 5 mL of aqueous NaOH (0.01 mol). The reaction mixture was refluxed. TLC (EtOAc: Petroleum-ether, 2:1) showed that the reaction was complete in 8 h. The reaction mixture was poured in 50 mL of 10% cold HCl solution and the precipitate was filtered, washed with water, until free from acid and on recrystallization from benzene-ethanol gave compound **14** in 56% of yield. IR (KBr) ν_{max}: 3477, 3087, 1621, 1602, 1582, 1512, 1177 cm^{-1}; ^{1}H NMR (DMSO-d_6,300 MHz): δ 5.12 (s, 2H, NH_2), 7.15 (s, 1H, ArH), 7.50-7.60 (m, 8H, ArH), 8.07 (s, 1H, ArH), 8.71 (d, *J* = 8.6 Hz, 1H, ArH);

^{13}C NMR (DMSO-d_6,300 MHz): δ 110.8, 118.9, 124.0, 126.9, 127.9, 128.9, 129.7, 130.9, 131.3, 133.2, 135.7, 136.4, 138.9, 140.6, 159.7, 163.5, 172.2; MS: *m/z* 339 (M^+).

General procedure for the synthesis of 2-(aryl)-3-(4-phenyl-6-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-2-pyrimidinyl)-1,3-thiazolan-4-one 15(a-j): To a stirred mixture of compound **14** (0.01 mol), aryl aldehyde (0.01 mol) and thioglycolic acid (0.015 mol) in dry toluene (20 mL), $ZnCl_2$ (0.02 mol) was added and refluxed for 6 h at 110 °C. After cooling, the filtrate was concentrated to dryness under reduced pressure and the residue was taken-up in ethyl acetate. The ethyl acetate layer was washed with brine, 5 % sodium bicarbonate solution and finally with brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness at reduced pressure; the crude product thus obtained was purified by column chromatography on silica gel with hexane-ethyl acetate as eluent to get the corresponding pure compounds **15(a-j)** in 45-69 % of yields.

2-(4-methylphenyl)-3-(4-phenyl-6-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-2-pyrimidinyl)-1,3-thiazolan-4-one (15a): IR (KBr) ν_{max}: 3097, 1702, 1620, 1601, 1584, 1489, 1177, 914 cm^{-1}; ^{1}H NMR (DMSO-d_6,300 MHz): δ 2.12 (s, 3H, CH_3), 3.61 (s, 2H, CH_2-S), 5.81 (s, 1H, CH-S), 7.20-7.30 (m, 5H, ArH), 7.50-7.60 (m, 8H, ArH), 8.23 (s, 1H, ArH), 8.51 (d, *J* = 8.5 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6,300 MHz): δ 27.1, 38.9, 71.2, 118.9, 122.8, 123.2, 124.8, 125.6, 126.6, 127.4, 127.9, 128.7, 129.7, 131.8, 134.2, 134.9, 135.0, 135.4, 136.3, 139.1, 140.5, 159.8, 161.1, 174.4, 175.2; MS: *m/z* 516 (M^++1).

2-(4-chlorophenyl)-3-(4-phenyl-6-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-2-pyrimidinyl)-1,3-thiazolan-4-one (15b): IR (KBr) ν_{max}: 3112, 1707, 1616, 1611, 1582, 1485, 1172, 921, 788 cm^{-1}; ^{1}H NMR (DMSO-d_6,300 MHz): δ 3.57 (s, 2H, CH_2-S), 5.79 (s, 1H, CH-S), 7.20-7.30 (m, 5H, ArH), 7.50-7.60 (m, 8H, ArH), 8.22 (s, 1H, ArH), 8.49 (d, *J* = 8.5 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6,300 MHz): δ 38.7, 71.1, 118.5, 122.7, 123.0, 124.3, 126.4, 127.1, 127.9, 128.0, 128.6, 129.6, 131.7, 132.8, 134.5, 135.1, 135.9, 136.4, 139.2, 140.4, 159.7, 161.2, 174.0, 175.1; MS: *m/z* 536 (M^+).

2-(4-nitrophenyl)-3-(4-phenyl-6-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-2-pyrimidinyl)-1,3-thiazolan-4-one (15c): IR (KBr) ν_{max}: 3067, 1712, 1618, 1611, 1572, 1482, 1354, 1168, 912 cm^{-1}; ^{1}H NMR (DMSO-d_6,300 MHz): δ 3.63 (s, 2H, CH_2-S), 5.80 (s, 1H, CH-S), 7.22 (s, 1H, ArH), 7.50-7.60 (m, 10H, ArH), 7.76 (d, *J* = 8.4 Hz, 2H, ArH), 8.27 (s, 1H, ArH), 8.53 (d, *J* = 8.5 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6,300 MHz): δ 38.5, 71.0, 118.2, 122.5, 123.3, 123.9, 124.7, 126.7, 127.5, 128.6, 128.9, 129.2, 131.1, 134.5, 135.3, 136.2, 139.7, 140.4, 141.5, 144.7, 159.1, 160.2, 173.5, 175.4; MS: *m/z* 547 (M^++1).

2-(3-nitrophenyl)-3-(4-phenyl-6-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-2-pyrimidinyl)-1,3-thiazolan-4-one (15d): IR (KBr) ν_{max}: 3087, 1705, 1619, 1603, 1581, 1482, 1174, 919 cm^{-1}; ^{1}H NMR (DMSO-d_6,300 MHz): δ 3.58 (s, 2H, CH_2-S), 5.78 (s, 1H, CH-S), 7.22 (s, 1H, ArH), 7.50-7.60 (m, 10H, ArH), 8.15-8.20 (m, 3H, ArH), 8.49 (d, *J* = 8.5 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6,300 MHz): δ 38.1, 71.5, 118.4, 119.8, 122.6, 123.5, 123.9, 124.7, 126.3, 127.2, 128.4, 129.9, 130.5, 131.1, 132.5, 134.6, 135.2, 136.1, 138.0, 139.0, 140.1, 147.5, 159.7, 161.3, 174.1, 175.0; MS: *m/z* 546 (M^+).

2-(4-hydroxyphenyl)-3-(4-phenyl-6-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-2-pyrimidin- yl)-1,3-thiazolan-4-one (15e): IR (KBr) ν_{max}: 3444, 3065, 1711, 1617, 1602, 1577, 1481, 1175, 917 cm^{-1}; ^{1}H NMR (DMSO-d_6,300 MHz): δ 3.62 (s, 2H, CH_2-S), 5.13 (s, 1H, OH), 5.84 (s, 1H, CH-S), 6.97 (d, *J* = 8.4 Hz, 2H, ArH), 7.20-7.25 (m, 3H, ArH), 7.50-7.60 (m, 8H, ArH), 8.24 (s, 1H, ArH), 8.53 (d, *J* = 8.5 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6,300 MHz): δ38.1, 71.3, 115.3, 118.4, 122.0, 123.7, 124.2, 125.4, 126.1, 127.5, 128.6, 129.8, 130.2, 131.9, 134.4, 135.5, 136.6, 139.2, 140.6, 156.7, 159.5, 161.3, 174.1, 175.0; MS: *m/z* 517 (M^+).

2-(2-hydroxyphenyl)-3-(4-phenyl-6-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-2-pyrimidin- yl)-1,3-thiazolan-4-one (15f): IR (KBr) ν_{max}: 3412, 3082, 1701, 1615, 1603, 1587, 1487, 1172, 917 cm^{-1}; ^{1}H NMR (DMSO-d_6,300 MHz): δ 3.57 (s, 2H, CH_2-S), 5.78 (s, 1H, CH-S), 6.59 (s, 1H, OH), 6.80-6.90 (m, 2H, ArH), 7.15-7.25 (m, 3H, ArH), 7.50-7.60 (m, 8H, ArH), 8.27 (s, 1H, ArH), 8.55 (d, *J* = 8.5 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6,300 MHz): δ 38.7, 71.5, 115.8, 118.0, 120.9, 121.4, 122.3, 123.1, 124.5, 125.8, 126.7, 127.9, 128.2, 128.9, 129.0, 131.2, 134.3, 135.7, 136.4, 139.2, 140.3, 154.3, 158.1, 161.3, 173.5, 174.7; MS: *m/z* 518 (M^++1).

2-[4-(dimethylamino)phenyl]-3-(4-phenyl-6-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-2-pyrimidinyl)-1,3-thiazolan-4-one (15g): IR (KBr) ν_{max}: 3064, 1698, 1621, 1604, 1587, 1477, 1167, 911 cm^{-1}; ^{1}H NMR (DMSO-d_6,300 MHz): δ 2.96 (s, 6H, CH_3), 3.63 (s, 2H, CH_2-S), 5.82 (s, 1H, CH-S), 6.71 (d, *J* = 8.3 Hz, 2H, ArH), 7.20-7.25 (m, 3H, ArH), 7.50-7.60 (m, 8H, ArH), 8.24 (s, 1H, ArH), 8.49 (d, *J* = 8.5 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6,300 MHz): δ 38.4, 45.6, 70.9, 113.2, 118.2, 122.1, 123.7, 124.3, 126.5, 127.1, 128.5, 128.9, 129.3, 131.0, 131.9, 134.6, 135.9, 136.1, 139.3, 140.4, 141.3, 159.2, 161.3, 174.1, 174.9; MS: *m/z* 544 (M^+).

2-(4-hydroxy-3-methoxyphenyl)-3-(4-phenyl-6-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-2-pyrimidinyl)-1,3-thiazolan-4-one (15h): IR (KBr) ν_{max}: 3413, 3089, 1701, 1612, 1602, 1576, 1478, 1172, 1072, 919 cm^{-1}; ^{1}H NMR (DMSO-d_6,300 MHz): δ 3.57 (s, 2H, CH_2-S), 3.94 (s, 3H, CH_3), 4.87 (s, 1H, OH), 5.78 (s, 1H, CH-S), 6.91 (s, 1H, ArH), 7.15-7.20 (m, 3H, ArH), 7.50-7.60 (m, 8H, ArH), 8.21 (s, 1H, ArH), 8.52 (d, *J* = 8.5 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6,300 MHz): δ 37.8, 58.4, 71.4, 112.1, 117.8, 118.0, 119.8, 122.3, 123.4, 124.0, 126.1, 127.5, 128.2, 129.8, 131.1, 133.2, 134.3, 135.5, 136.9, 139.7, 140.8, 146.5, 148.7, 159.2, 160.5, 174.2, 175.9; MS: *m/z* 548 (M^++1).

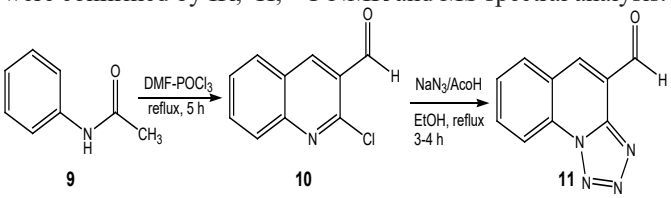
2-(2-furyl)-3-(4-phenyl-6-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-2-pyrimidinyl)-1,3-thiazolan-4-one (15i): IR (KBr) ν_{max}: 3113, 1713, 1627, 1610, 1578, 1487, 1172, 911 cm^{-1}; ^{1}H NMR (DMSO-d_6,300 MHz): δ 3.62 (s, 2H, CH_2-S), 5.79 (s, 1H, CH-S), 6.20-6.30 (m, 2H, ArH), 7.17 (s, 1H, ArH), 7.50-7.60 (m, 9H, ArH), 8.19 (s, 1H, ArH), 8.53 (d, *J* = 8.5 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6,300 MHz): δ 38.2, 71.4, 118.3, 121.7, 122.4, 123.7, 124.2, 125.3, 126.1, 127.3, 127.9, 128.4, 129.9, 130.2, 131.9, 133.2, 135.5, 136.7, 138.4, 140.7, 159.1, 161.2, 174.0, 175.6; MS: *m/z* 491 (M^+).

2(1,3-benzodioxol-5-yl)-3-(4-phenyl-6-[1,2,3,4]

tetraazolo[1,5-*a*]quinolin-4-yl-2-pyrimidinyl)-1,3-thiazolan-4-one (15j): IR (KBr) ν_{max}: 3054, 1699, 1612, 1600, 1583, 1481, 1176, 1031, 918 cm^{-1}; ^1H NMR (DMSO-d_6,300 MHz): δ 3.67 (s, 2H, CH_2-S), 5.88 (s, 1H, CH-S), 6.01 (s, 2H, O-CH_2-O), 6.85-6.90 (m, 2H, ArH), 7.10-7.20 (m, 2H, ArH), 7.50-7.60 (m, 8H, ArH), 8.25 (s, 1H, ArH), 8.53 (d, *J* = 8.5 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6,300 MHz): δ 37.4, 71.7, 102.4, 108.1, 111.2, 117.4, 121.4, 122.1, 123.4, 124.1, 126.4, 127.2, 128.0, 129.5, 131.4, 133.0, 134.6, 135.8, 136.1, 139.2, 140.5, 145.1, 147.2, 158.1, 160.3, 173.5, 175.1; MS: *m/z* 545 (M^+).

RESULTS AND DISCUSSION

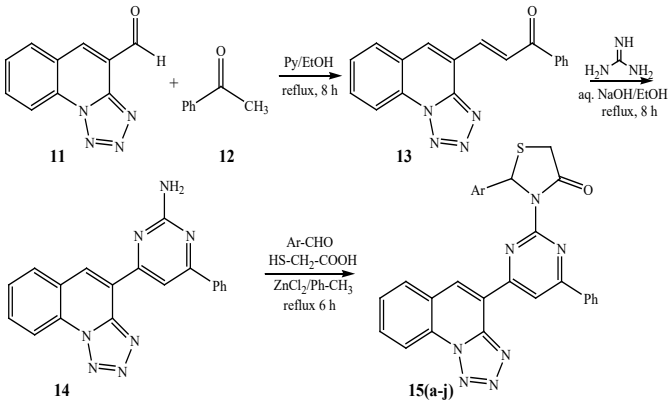
The heterocyclization of acetanilide **9** with dimethylformamide (DMF) in the presence of $POCl_3$ under reflux for 5 h, gave 2-chloro-3-quinolinecarbaldehyde **10** in 49% of yields, which on reaction with sodium azide in the presence of acetic acid for replacement of chlorine group with N_3 followed by heterocyclization in the presence of ethanol under reflux for 3-4 h to give [1,2,3,4]tetraazolo[1,5-*a*]quinoline-4-carbaldehyde **11** in 54% of yields (**Scheme 1**). The structures compounds were confirmed by IR, ^1H, ^{13}C NMR and MS spectral analysis.



Scheme 1: Schematic route for the synthesis of compounds 11

The IR spectrum of compound **10** the stretching frequencies corresponding to the aldehyde group (CHO) observed at 2870 and the carbonyl (C=O) at 1716, and the characteristic C-Cl stretching appeared at 781 (C-Cl) cm^{-1}. Its proton NMR spectra the aromatic proton signals appeared at δ 7.49 ppm as doublet with coupling constant (*J*) = 8.3 Hz for one proton, the other at δ 7.90-8.00 ppm as multiplet for three protons and for a proton of C-4 appeared as singlet at δ 857 ppm, the aldehyde protons signal observed at δ 10.32 ppm as singlet. The IR spectrum of compound **11** the stretching frequencies corresponding to the aldehyde group (CHO) observed at 2869 and the carbonyl (C=O) at 1719, and the characteristic N=N and C=N stretching appeared at 1595 and 1620 cm^{-1}. Its proton NMR spectra the aromatic proton signals appeared at δ 8.72 ppm as doublet with coupling constant (*J*) = 8.6 Hz for one proton, the other at δ 7.90-8.00 ppm as multiplet for four protons, the aldehyde protons signal observed at δ 10.32 ppm as singlet. Its ^{13}C NMR spectra, the signal for carbon of tetrazole ring observed at δ 139.2 ppm, the quinoline ring carbon signals at δ 138.9 ppm and 141.3 ppm, the carbonyl carbon signal appear ar δ 181.9 ppm, the other carbon signals appear according to thestructure. The condensation reaction of compound **11** with acetophenone **12** in the presence of pyridine in ethyl alcohol under reflux temperature for 8 h to afford (*E*)-1-phenyl-3-[1,2,3,4]tetrazolo [1,5-*a*]quinolin-4-yl-2-propen-1-one **13** in 64% of yields. The cyclo-condensation reaction of compound 5 with guanidine hydrochloride in the presence of aqueous sodium hydroxide in ethanol reflux temperature for 8 h to afford 4-phenyl-6-[1,2,3,4] tetraazolo[1,5-*a*]quinolin-4-yl-2-pyrimidinamine **14** in 56% of yield. Further, one-pot cyclo-condensation of compound **14** with corresponding aryl aldehydes and thioglycolic acid in the presence of anhydrous zinc chloride in dry toluene under the reflux for 6 h to give the corresponding compounds 2-(aryl)-3-(4-phenyl-6-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-2-pyrimidinyl)-1,3-thiazolan-4-one **15(a-j)**in 45-69 % of yields (**Scheme 2**). The structures compounds were confirmed by IR, ^1H, ^{13}C NMR and MS spectral analysis.

The IR spectrum of compound **13** the stretching frequencies corresponding to C=O observed at 1698, C=C at 1626 and the characteristic N=N and C=N stretching appeared at 1589 and 1610 cm^{-1}. Its proton NMR spectra the aromatic proton signals appeared at δ 6.95 ppm as singlet for one proton, the other at δ 7.60-7.70 ppm as multiplet for eight protons, at δ 8.67 ppm as doublet with coupling constant *J* = 8.5 for one proton. The alkene protons appear as two doublets at δ 6.61 and 8.32 ppm with coupling constant *J* = 15.8 Hz for one proton in each. Its ^{13}C NMR spectra, the signal for carbon of tetrazole ring observed at δ 137.8 ppm, the quinoline ring carbon signals at δ 136.7 ppm and 141.3 ppm, the carbonyl carbon signal appear at δ 185.4 ppm, the other carbon signals appear according to the structure.



15: Ar = a) 4-methylphenyl; b) 4-chlorophenyl; c) 4-nitrophenyl; d) 3-nitrophenyl; e) 4-hydroxyphenyl; f) 2-hydroxyphenyl; g) 4-dimethylaminophenyl; h) 4-hydroxy-3-methoxyphenyl; i) 2-furyl; j) 1,3-benzoxole

Scheme 1. Schematic route for the synthesis of compounds 15(a-j)

The IR spectrum of compound **14** the stretching frequencies corresponding to NH_2 observed at 3477, N=N and C=N stretching appeared at 1582 and 1602 cm^{-1}. Its proton NMR spectra the proton of pyrimidine ring appeared at δ 8.07 ppm as singlet for one proton, the other at δ 7.50-7.60 ppm as multiplet for eight protons, at δ 8.71 ppm as doublet with coupling constant *J* = 8.6 for one proton, at δ 7.15 ppm for one proton, the amine proton signals was observed at δ 5.12 as singlet with two proton intensity. Its ^{13}C NMR spectra, the signal for carbon of tetrazole ring observed at δ 136.4 ppm, the quinoline ring carbon signals at δ 135.7 ppm and 140.6 ppm, the pyrimidine ring carbon signals appeared at δ 172.2, 110.8, 163.5 and 159.7 ppm, the other carbon signals appear according to the structure.

The IR spectrum of compound **15a** the absence of absorption band for NH2 and appearance of C=O and N-C-S absorption bands at 1702, 1177 cm-1 indicated the formation of thiazolidinone ring involving the amine group, the other absorption bands were observed at 1585 (N=N), 1601 (C=N) cm^{-1}. Its proton NMR spectra, the signals for the protons of the thiazolidinone ring appeared at δ 3.61 ppm as singlet for two

protons was assigned for CH_2-C=O and at δ 5.81 as singlet for one proton is assigned for N-CH-S, the other aromatic proton signals observed at δ 7.20-7.30 ppm as multiplet for five protons, at δ 7.50-7.60 ppm as multiplet for eight protons, at δ 8.23 ppm as singlet for one proton and a doublet at δ 8.51 ppm as doublet with coupling constant *J* = 8.5 Hz for one proton, Its ^{13}C NMR spectra, the signal for carbon of tetrazole ring observed at δ 135.0 ppm, the quinoline ring carbon signals at δ 136.3 ppm and 140.5 ppm, the pyrimidine ring carbon signals appeared at δ 174.4, 118.9, 161.1 and 159.8 ppm, and the thiazolidinone ring carbon signals appeared at δ 175.2, 38.9 and 71.2 ppm.

ANTIBACTERIAL ACTIVITY

The *in vitro* antibacterial activity of 2-(aryl)-3-(4-pheny l-6-[1,2,3,4]tetraazolo [1,5-*a*] quinolin-4-yl-2-pyrimidinyl)-1,3-thiazolan-4-one **15(a-j)** was assessed against three representative Gram-positive bacteria *viz*. *Bacillus subtilis* (MTCC 441), *Bacillus sphaericus* (MTCC 11) and *Staphylococcus aureus* (MTCC 96), and three Gram-negative bacteria *viz*. *Pseudomonas aeruginosa* (MTCC 741), *Klebsiella aerogenes* (MTCC 39) and *Chromobacterium violaceum* (MTCC 2656) by the broth dilution method (Villanova 1982). Bacteria were grown overnight in Luria Bertani (LB) broth at 37°C, harvested by centrifugation and then washed twice with sterile distilled water. Stock solutions of the series of compounds were prepared in DMSO. Each stock solution was diluted with standard method broth (Difco) to prepare serial two-fold dilutions in the range of 100 to 0.8 **µ**g/mL. Ten microliters of the broth containing about 10^5 colony-forming units (cfu)/mL of test bacteria were added to each well of a 96-well microtiter plate. Culture plates were incubated for 24 h at 37°C, and the growth of bacteria was monitored by visually and spectrophotometrically. Streptomycin was also screened under identical conditions for comparison. The obtained data of compounds **15(a-j)** are presented in **Table 1** as the minimal inhibitory concentration (MIC, µg/mL). It has been observed that the compounds exhibit interesting biological activity, however, with a degree of variation.

In the series of **15(a-j)**, the compounds containing 4-chlorophenyl (**15b**) and 4-fluorophenyl (**7e**) on thiazolidionone moiety are found to be the most active against Gram-positive bacteria and the Gram-negative bacterial strains. The compound **15j** is highly active against all the three Gram-positive bacteria *B. subtilis, B. sphaericus, S. aureus.* The compounds **15f**, is active against *B. subtilis* under the concentration similar to standard. The remaining compounds showed moderate to good activity against all the organisms employed.

Table 1. Antibacterial activity of compounds 15(a-j)

Compd.	Minimum inhibitory concentration (MIC, µg/mL)					
	B. subtilis	B. sphaericus	S. aureus	P. aeruginosa	K. aerogenes	C. violaceum
15a	25.0	50.0	25.0	>50.0	25.0	>50.0
15b	6.25	12.5	12.5	3.12	3.12	6.25
15c	12.5	50.0	>50.0	50.0	25.0	25.0
15d	50.0	25.0	50.0	25.0	>50.0	25.0
15e	12.5	25.0	12.5	3.12	3.12	12.5
15f	6.25	25.0	25.0	>50.0	50.0	25.0
15g	25.0	50.0	>50.0	25.0	12.5	25.0
15h	12.5	25.0	50.0	50.0	>50.0	50.0
15i	25.0	25.0	50.0	25.0	>50.0	25.0
15j	12.5	12.5	6.25	25.0	50.0	>50.0
Strepto-mycin	6.25	12.5	6.25	1.56	1.56	3.12

ANTIFUNGAL ACTIVITY

The *in vitro* antifungal activity of 2-(aryl)-3-(4-phenyl-6-[1,2,3,4] tetraazolo [1,5-*a*]quino- lin-4-yl-2-pyrimidinyl)-1,3-thiazolan-4-one **15(a-j**) was assessed against four fungal organisms *viz*. *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185) and *Trichophyton mentagrophytes* (IFO 40996)in DMSO by disc diffusion, broth dilution methods (Villanova 1982)**.** *Candida albicans* was grown for 48 h at 28°C in YPD broth (1% yeast extract, 2% peptone and 2% dextrose), harvested by centrifugation, and then washed twice with sterile distilled water. *A. fumigatus*, *T. rubrum* and *T. mentagrophytes* were placed in potato dextrose agar (PDA) (Difco) and incubated at 28 °C for two weeks. Spores were washed three times with sterile distilled water and resuspended in distilled water to obtain initial inoculums of size of 10^5 spores/mL. Ten microliters of the broth containing about 10^3 (for yeast) and 10^4 (for filamentous fungi) cells/mL of test fungi was added to each well of a 96-well microtiter plate. Culture plates were incubated for 48–72 h at 28 °C. The antifungal activity of each compound was compared with the standard drug Amphotericin B. Minimum inhibitory concentration (MIC, µg/mL) was measured and compared with controls. The MIC values of the compounds screened are given in **Table 2**.

In the **15(a-j)** series, the compound containing 4-nitrophenyl (**15c**) is highly active against all the microorganisms employed. The compound with 2-hydroxyphenyl on thiazolidinone also showed good antifungal activity against *C. albicans*, *A. fumigatus* and *T. mentagrophytes,* Similarly the compound **15i** is also highly active against *C. albicans* and *A. fumigatus*. The remaining compounds showed moderate to good activity.

Table 2. Antifungal activity of compounds 15(a-j)

Compd.	Minimum inhibitory concentration (MIC, µg/mL)			
	C. albicans	A. fumigatus	T. rubrum	T. mentagrophytes
15a	25.0	12.5	25.0	50.0
15b	12.5	25.0	50.0	25.0
15c	6.25	6.25	6.25	12.5
15d	25.0	25.0	12.5	25.0
15e	12.5	12.5	25.0	>50.0
15f	12.5	6.25	>50.0	6.25
15g	50.0	50.0	50.0	>50.0
15h	12.5	>50.0	12.5	25.0
15i	6.25	6.25	25.0	50.0
15j	25.0	25.0	25.0	25.0
Amphotericin B	6.25	3.12	3.12	3.12

CONCLUSION

A series of new 2-(aryl)-3-(4-phenyl-6-[1,2,3,4] tetraazolo[1,5-*a*]quinolin-4-yl-2-pyrimidinyl)-1,3-thiazolan-4-one **15(a-j)** has been synthesized by incorporating tetrazole, pyrimidine and thiazolidinone rings in one molecule for intensifying biological activity. Further, all the newly synthesized compounds have been assayed for their antimicrobial activity against Gram-positive bacteria, Gram-negative bacteriaand fungi.The antimicrobial assay revealed that the compound containing 4-chlorophenyl **15b**, 4-fluorophenyl **15e** on thiazolidionone ring are found to be the most active against bacterial strains and compound containing 4-nitrophenyl **15c** is highly active against all the fungal organisms.

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