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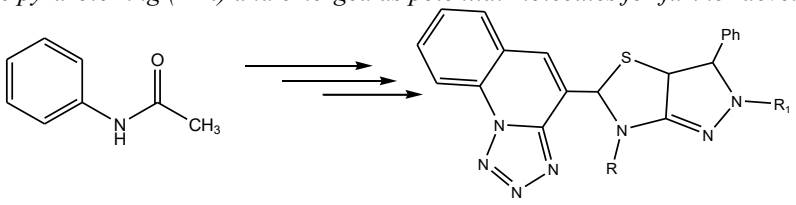
Synthesis and Antibacterial Activity of Tetrazolo[1,5-a]quinoline Analogues Linked with Pyrazolo[3,4-d][1,3]thiazole

*Nagaraj, P., Rakesh, G., and Raghaveer, S.
Department of Chemistry, Telangana University, Nizamabad, Telangana-503322 India

Abstract:
*A new series of 6-(aryl)-2-(alkyl/aryl)-3-phenyl-5-[1,2,3,4]tetraazolo[1,5-a]quinolin-4-yl-3,3a, 5,6-tetrahydro-2H-pyrazolo[3,4-d][1,3]thiazole **11(a-o)** were synthesized by the reaction of 3-(aryl)-5-[(Z)-1-phenylmethylidene]-2-[1,2,3,4]tetraazolo[1,5-a]quinolin-4-yl-1,3-thiazolan-4-one **10(a-c)** with aryl/alkyl hydrazines, and evaluated for their antibacterial activity against four human pathogenic bacteria: Escherichia coli, Klebsiella pneumoniae, Shigella dysenteriae, and Shigella flexneri. Compounds (**11b**), (**11i**), and (**11l**) demonstrated strong antibacterial screening against all the organisms tested. The zone of inhibition of compound **11g** is close to that of the common medication streptomycin, and it is quite effective against K. pneumoniae and S. flexneri. E. coli was effectively inhibited by compound with 4-nitrophenyl on the thiazole ring and isopropyl on the pyrazole ring (**11n**) and emerged as potential molecules for further development.*



***Keywords**: Tetrazole, Quinolin, Pyrazole, Thiazole, Antibacterial Activity.*

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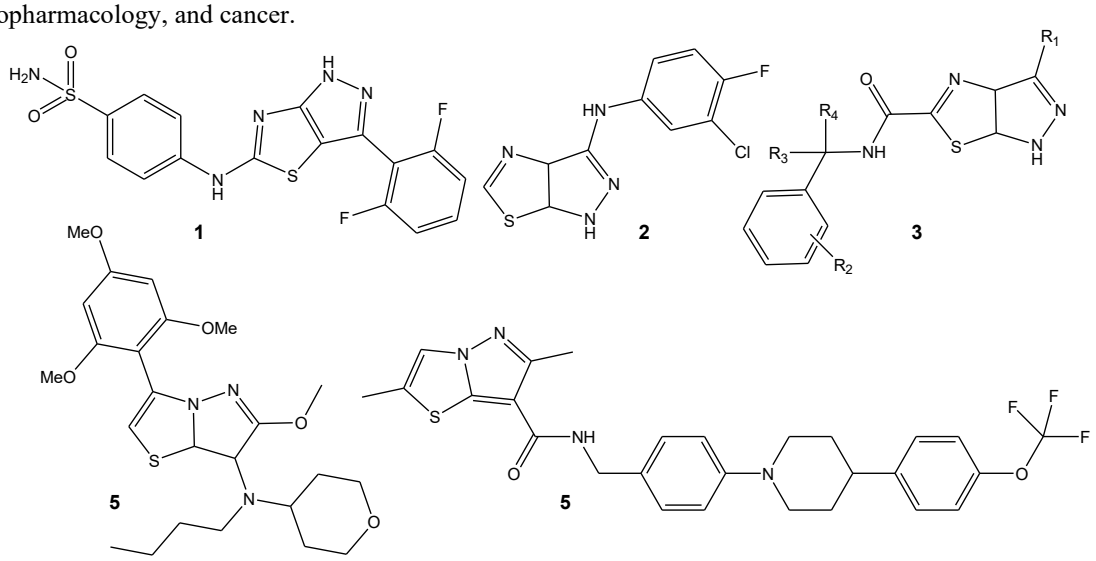
I. INTRODUCTION

Because of their extensive spectrum of pharmacological actions and structural diversity, heterocyclic compounds hold a major place in medicinal chemistry. Among these, pyrazole and thiazole rings are acknowledged as special scaffolds for creating compounds with biological activity. While the thiazole ring is commonly found in natural products and clinically relevant medications, the pyrazole nucleus is linked to anticancer, anti-inflammatory, antiviral, antibacterial, and insecticidal effects. An efficient method to improve biological activity, selectivity, and target affinity is the molecular hybridization of these two pharmacophores into a single framework that forms pyrazole-coupled thiazole derivatives. Thiazole-based heterocycles have been shown in recent studies to have strong antibacterial and anticancer properties [1-3].

Additionally, pyrazolo-thiazole hybrids have been investigated as HIV-1 non-nucleoside reverse transcriptase (NNRT) inhibitors. Thiazolyl-pyrazole conjugates have garnered significant interest in the field of oncology because of their exceptional anticancer characteristics. According to several studies, they have strong antiproliferative action against a variety of cancer cell lines by blocking important molecular targets like EGFR and HER2 kinases [4-10]. The anticancer efficacy of compounds that incorporate extra pharmacophores such naphthalene, quinoline, or curcumin moieties into the pyrazole-thiazole framework has been further improved [11,12]. Strong binding interactions with cancer-related targets have been established by molecular docking studies and structure-based drug design techniques [13].

Pyrazole-thiazole compounds have shown broad-spectrum antibacterial, antifungal, antimycobacterial, and antioxidant activity in addition to antiviral and anticancer uses [14-22]. In combined computational and preclinical studies, certain derivatives demonstrated promising activity against breast cancer, while others demonstrated efficacy against multidrug-resistant (MDR) infections by inhibition of the MurA enzyme. Because of their wide range of biological activities, pyrazolo-thiazoles have become preferred scaffolds in medicinal chemistry. Additionally, its fused-ring system provides conformational rigidity and encourages favourable π–stacking interactions, both of which are essential for effective target binding. There have been

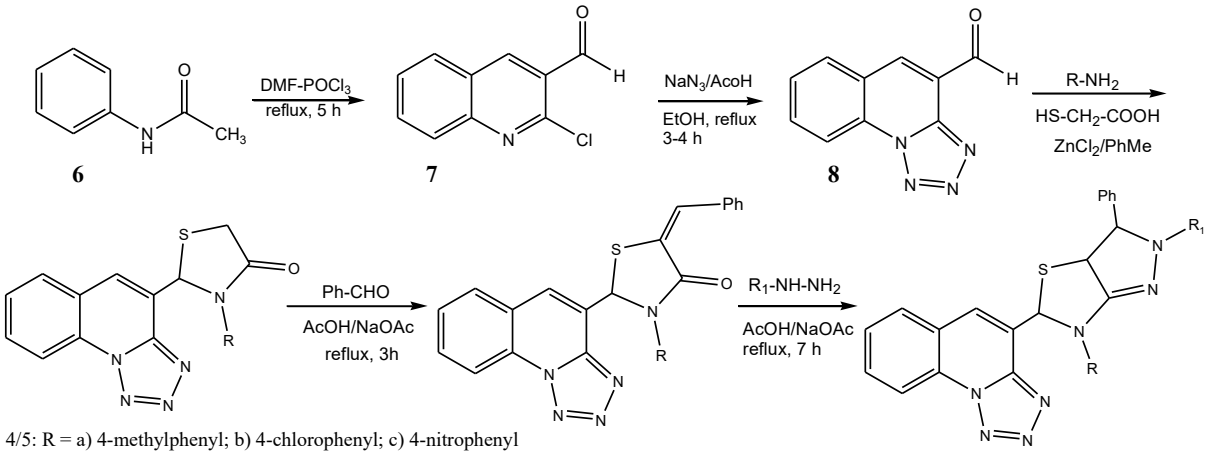
reports of a number of biologically active pyrazolo-thiazole derivatives with a variety of pharmacological characteristics. For example, **1** function as a cyclin-dependent kinase inhibitor [23], **2** as a mGluR4 receptor modulator [24], **3** as a generic protein kinase inhibitor scaffold [25], **4** as a strong corticotropin-releasing factor 1 (CRF1) receptor antagonist, and **5** showing strong suppressant activity against the *Mycobacterium tuberculosis* H37Ra strain [26]. When taken as a whole, these instances demonstrate the structural variety and important therapeutic value of pyrazolo-thiazole frameworks in the treatment of infectious diseases, neuropharmacology, and cancer.



As part of our ongoing research on the synthesis of novel heterocycles, it was thought to be interesting to combine all of these heterocyclic rings into a single molecule in order to create new heterocyclic compounds with potential antimicrobial activity because tetrazole, pyrazolo, thiazole, and their derivatives have a wide range of bioactivities. This study aims to synthesize novel 6-(aryl)-2-(alkyl/aryl)-3-phenyl-5-[1,2,3,4]tetraazolo[1,5-a]quinolin-4-yl-3,3a,5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole **11(a-o)** and evaluate their *in vitro* antibacterial activity.

II. RESULTS AND DISCUSSION

Acetanilide **6** was heterocyclized with dimethylformamide (DMF) in the presence of $POCl_3$ under reflux for 5 hours, yielding 2-chloro-3-quinolinecarbaldehyde **7** in 67% of yields. This was followed by a reaction with sodium azide in the presence of acetic acid to replace the chlorine group with N_3, and then 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 **8** in 59% of yields. 3-aryl-2[1,2,3,4]tetraazolo[1,5-a]quinolin-4-yl-1,3-thiazolan-4-one **9(a-c)** was synthesized in one pot using a condensation-cyclization reaction between compound **8**, the corresponding aromatic amine, and mercapto acetic acid in the presence of $ZnCl_2$ under reflux or microwave irradiation conditions in a yield of 63-72%. In glacial acetic acid at reflux temperature, the corresponding molecule **9(a-c)** interacted with benzaldehyde in the presence of anhydrous NaOAc to produce 3-(aryl)-5-[(Z)-1-phenylmethylidene]-2-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-1,3-thia- zolan-4-one **10(a-c)** in a yield of 62-77%. Furthermore, compound **10** was cyclocondensed with aryl/alkyl hydrazines in the presence of anhydrous NaOAc in glacial acetic acid at reflux temperature for 8 hours, yielding 6-(aryl)-2-(alkyl/aryl)-3-phenyl-5[1,2,3,4]tetraazolo[1,5-a]quinolin-4-yl-3,3a,5,6-tetrahydro-2H-pyrazo- lo[3,4-*d*][1,3]thiazole **11(a-o)** in 44-63% yields (**Scheme 1**). The compounds' structures were validated using IR, ^1H, ^{13}C NMR, and MS spectral analysis, and the spectroscopic dates were completely consistent with those predicted.



4/5: R = a) 4-methylphenyl; b) 4-chlorophenyl; c) 4-nitrophenyl

9(a-c)			10(a-c)			11(a-o)		
11	**R**	**R'**	**11**	**R**	**R'**	**11**	**R**	**R'**
a	4-Me-C_6H_4-	C_6H_5-	**f**	4-Cl-C_6H_4-	C_6H_5-	**k**	4-NO_2-C_6H_4-	C_6H_5-
b	4-Me-C_6H_4-	4-Cl-C_6H_4-	**g**	4-Cl-C_6H_4-	4-Cl-C_6H_4-	**l**	4-NO_2-C_6H_4-	4-Cl-C_6H_4-
c	4-Me-C_6H_4-	C_6H_5-CH_2-	**h**	4-Cl-C_6H_4-	C_6H_5-CH_2-	**m**	4-NO_2-C_6H_4-	C_6H_5-CH_2-
d	4-Me-C_6H_4-	$(CH_3)_2$-CH-	**i**	4-Cl-C_6H_4-	$(CH_3)_2$-CH-	**n**	4-NO_2-C_6H_4-	$(CH_3)_2$-CH-
e	4-Me-C_6H_4-	CH_3-	**j**	4-Cl-C_6H_4-	CH_3-	**o**	4-NO_2-C_6H_4-	CH_3-

Scheme 1

Compound **7** infrared spectra showed stretching frequencies for the aldehyde group (CHO) at 2870, the carbonyl (C=O) at 1716, and the distinctive C-Cl stretching at 781 (C-Cl) cm^{-1}. In its proton NMR spectra, the aldehyde proton signal was detected at δ 10.32 ppm as a singlet, the aromatic proton signals appeared at δ 7.49 ppm as a 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 the proton of C-4 appeared as a singlet at δ 857 ppm. Compound **8** infrared spectra showed stretching frequencies for the aldehyde group (CHO) at 2869, the carbonyl (C=O) at 1719, and the distinctive N=N and C=N stretching at 1595 and 1620 cm^{-1}. In its proton NMR spectra, the aldehyde proton signal was detected at δ 10.32 ppm as a singlet, the aromatic proton signal at δ 8.72 ppm as a doublet with coupling constant (*J*) = 8.6 Hz for one proton, and the other at δ 7.90-8.00 ppm as a multiplet for four protons. In its ^{13}C NMR spectra, the tetrazole ring carbon signal was detected at δ 139.2 ppm, the quinoline ring carbon signal at δ 138.9 ppm and 141.3 ppm, the carbonyl carbon signal at δ 181.9 ppm, and the other carbon signals appeared in accordance with the structure.

The development of the thiazolidinone ring was indicated by the presence of C=O and N-C-S absorption bands at 1715 and 1171 cm^{-1} in the infrared spectra of compound **9a**; further absorption bands were seen at 1593 (N=N) and 1639 (C=N) cm^{-1}. The protons of the thiazolidinone ring were detected at δ 3.37 ppm as singlet for two protons, which was assigned to CH_2-C=O, and at δ 5.92 as singlet for one proton, which was assigned to N-CH-S. The other aromatic proton signals were detected at δ 6.90-7.00 as singlet for three protons, at δ 7.50-7.60 ppm as multiplet for five protons, and at δ 8.47 ppm as a doublet with coupling constant *J* = 8.4 Hz for one proton. In its ^{13}C NMR spectra, the tetrazole ring carbon signal was detected at δ 142.2 ppm, the quinoline ring carbon signals at δ 124.2 ppm and 142.7 ppm, and the thiazolidinone ring carbon signals at δ 46.2, 68.7, and 170.1 ppm. According to its molecular makeup, the molecular ion peak in its mass spectrum emerged at m/z: 361 amu.

Compound **10a** infrared spectra showed absorption frequencies at 1696 and 1612 cm^{-1} that corresponded to the thiazolidinone ring's C=O and C=C. The tetrazole ring's N=N, C=N, and C-N stretching frequencies were observed at 1602, 1563, and 1131 cm^{-1}. The other aromatic proton signals were detected at δ 7.10-7.25 ppm as multiplet for four protons, at δ 7.40-7.90 ppm as multiplet for ten protons, and at δ 8.51 ppm as doublet with coupling constant 8.7 Hz for one proton. Its proton NMR spectrum revealed the thiazolidinone ring signals at δ 6.41 ppm as singlet with one proton for S-CH-N. In its carbon NMR spectra, the quinoline ring's strong signals were found at δ 125.1, 139.2 ppm, the tetrazole ring's carbon at δ 142.9 ppm, and the

thiazolidinone ring's carbons at δ 66.9, 132.7, and 161.8 ppm. At δ 133, the methylidine carbon signal was detected. The molecular ion signal at m/z 450 amu was visible in its mass spectrum.

In the IR spectra of compounds **11a**, the disappearance of the amide carbonyl (C=O) absorption band at about 1696 cm^{-1}, which was present in compounds, confirmed the cyclization of the involvement of the α,β-unsaturated carbonyl system. The bands around 1331 cm^{-1} characteristic for N-C-S bending vibration provided confirmatory evidence for ring closure. In addition, absorption bands corresponding to the pyrazole moiety's C=N were identified at around 1565 cm^{-1}. Further confirmation was found from the ^{1}H NMR spectra, which showed the N-CH-S protons of the thiazole ring at 7.00-7.20 ppm as a singlet, 5-CH fused protons at 4.38 ppm, and CH-N-R_2 protons of the pyrazole ring at 5.47 ppm. These signs indicate that the cyclization phase has occurred. The significant signals in the ^{13}C NMR spectra corresponding to the carbons of the pyrazolo-thiazole ring in all the compounds detected nearly at 27.3, 57.9, 65.8, and 144.5 ppm, provide further confirmation of their structures. In conclusion, all of the synthesized compounds produced satisfactory spectrum data compatible with their structures.

ANTIBACTERIAL ACTIVITY

All compounds **11(a-o)** were evaluated for antibacterial activity against four human pathogenic bacteria: *Escherichia coli, Klebsiella pneumoniae, Shigella dysenteriae*, and *Shigella flexneri*. The cup plate method was used to estimate the zone of inhibition (in mm) at a dose of 100 µg/mL[53]. To conduct the antibacterial assay, standard inoculums (1-2 × 107 c.f.u/mL 0.5 Mc Farland standards) were applied to sterile agar plates using a sterilized glass spreader. The discs, measuring 6.26 mm in diameter, were made from Whatman no. 1 filter paper and sterilized with dry heat at 140 °C for 1 hour. The sterile discs had previously been soaked in a known concentration of the test substances and were put in a nutrient agar medium. The plates were inverted and incubated at 37 degrees Celsius for 24 hours. **Table 1** shows the findings of measuring the inhibition zones and comparing them to the standard drugs streptomycin.

Table 1: Antibacterial Activity of Compounds 11(a-o)

Compound	Zone of inhibition (mm) at 100 *µ*g/mL			
	E. coli	***K. pneumoniae***	***S. dysenteriae***	***S. flexneri***
11a	11	12	9	6
11b	22	20	24	25
11c	16	12	10	7
11d	6	13	11	9
11e	15	13	18	11
11f	9	12	15	12
11g	10	26	14	25
11h	11	17	14	13
11i	20	19	21	24
11j	12	15	13	9
11k	14	9	12	15
11l	23	21	22	26
11m	9	12	7	16
11n	26	17	16	11
11o	9	6	12	15
Streptomycin	30	30	30	30

Compounds **11(a–o)** that contained 4-methylphenyl on the thiazole ring, 4-chlorophenyl on the pyrazole ring (**11b**), 4-chlorophenyl on the thiazole, isopropyl group on the pyrazole ring (**11i**), and 4-nitrophenyl on the thiazole ring, 4-chlorophenyl on the pyrazole ring (**11l**) demonstrated strong antibacterial screening data against all the organisms tested. The zone of inhibition of compound **11g** is close to that of the common medication streptomycin, and it is quite effective against *K. pneumoniae* and *S. flexneri*. *E. coli* was effectively inhibited by compound with 4-nitrophenyl on the thiazole ring and isopropyl on the pyrazole ring (**11n**). Other substances shown good to moderate efficacy against the used organisms.

III. MATARIALS AND METHODS

All reagents are commercial grade and were used as supplied. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel F254 plates from Merck, and compounds visualized by exposure to UV light. Chromatographic columns 70–230 mesh silica gel for separations were used. IR spectra were recorded using KBr disk 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 in δ ppm units with respect to TMS as 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 (7): DMF (1 mol) was cooled to 0 °C in a round flask equipped with a drying tube, and $POCl_3$ (1.5 mol) was slowly added to the mixture, which was stirred for 2 hours while keeping the temperature below 0 °C. A solution of compound **6** (0.01 mol) in DMF (5 mL) was then added dropwise, and the reaction mixture was heated under reflux and stirring for 5 hours. The resulting combination was cooled to 0 °C before being gently poured into ice water and stirred for ten minutes to produce a yellow solid that was filtered, washed several times with cold water, dried under vacuum, and recrystallized from ethyl acetate to yield pure compound **7** in 67% of yield. 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 (8): Compound **7** (0.01 mol), sodium azide (0.02 mol), acetic acid (2 mL), and ethanol (10 mL) were charged into a round bottom flask equipped with a mechanical stirrer and condenser. The reaction mixture refluxed for 3-4 hours. After the reaction was complete (as determined by TLC), the isolated chemical was filtered and washed with ethanol. To get the pure chemical **8**, further purification was performed by leaching in an equal volume ratio of chloroform and methanol (10:10 mL). Yield 59%; 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^+).

General procedure for the synthesis of 3-aryl-2[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-1,3-thiazolan-4-one 9(a-c): $ZnCl_2$ (0.001 mol) was added after two minutes to a stirred mixture of compound **8** (0.001 mol), aromatic amine (0.0014 mol), and thioglycolic acid (0.015 mol) in dry toluene (5 mL). The mixture was then exposed to microwave radiation at 280 W for four to seven minutes at 110 °C. Following cooling, the solvent was extracted using ethyl acetate, and the crude product was refined using column chromatography on silica gel with hexane ethyl acetate (4:6), yielding pure compounds **9(a-c)** in 63-72% of yields.

3-(4-methylphenyl)-2-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-1,3-thiazolan-4-one (9a): Yield 63%; IR (KBr)ν_{max}: 3094, 1715, 1639, 1593, 1421, 1329, 1171, 917 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.48 (s, 3H, CH_3), 3.37 (s, CH_2-S), 5.92 (s, 1H, N-CH-S), 6.90-7.00 (s, 3H, ArH), 7.50-7.60 (m, 5H, ArH), 8.47 (d, J = 8.4 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 25.1, 46.2, 68.7, 114.9, 115.3, 119.0, 123.1, 126.6, 128.7, 130.8, 131.5, 133.2, 136.5, 137.4, 142.2, 144.7, 170.1; MS: *m/z* 361 (M^+).

3-(4-chlorophenyl)-2-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-1,3-thiazolan-4-one (9b):
Yield 72%; IR (KBr)ν_{max}: 3062, 1702, 1622, 1597, 1429, 1331, 1167, 698 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.24 (s, CH_2-S), 5.68 (s, 1H, N-CH-S), 7.05 (s, 1H, ArH), 7.50-7.70 (m, 7H, ArH), 8.41 (d, J = 8.6 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 46.2, 68.4, 114.9, 120.5, 123.1, 125.7, 126.0, 128.4, 130.1, 131.8, 133.9, 134.02, 136.7, 141.2, 144.6, 169.9; MS: *m/z* 381 (M^+).

3-(4-nitrophenyl)-2-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-1,3-thiazolan-4-one (9c):
Yield 68%; IR (KBr) ν_{max}: 3098, 1712, 1627, 1589, 1420, 1375, 1159, 923 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.29 (s, CH_2-S), 5.77 (s, 1H, N-CH-S), 7.00 (s, 1H, ArH), 7.50-7.60 (m, 5H, ArH), 8.17 (d, J = 9.0 Hz, 2H, ArH), 8.42 (d, J = 8.6 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 46.7, 68.2, 115.1, 120.2, 123.4, 126.5, 127.0. 129.1, 130.1, 133.3, 134.0, 136.6, 142.3, 143.2, 144.2, 170.1; MS: *m/z* 392 (M^+).

General procedure for the synthesis of 3-(aryl)-5-[(*Z*)-1-phenylmethylidene]-2-[1,2,3,4] tetraazolo[1,5-*a*]quinolin-4-yl-1,3-thiazolan-4-one 10(a-c): Compound **9** (0.001 mol), benzaldehyde (0.002 mol), and sodium acetate (0.002 mol) were combined with anhydrous glacial acetic acid (20 mL) and refluxed for five hours. After

concentrating the reaction mixture and pouring it into ice-cold water, the solid was separated, filtered, and cleaned with water. The resulting crude product was then purified using column chromatography on silica gel using hexane–ethyl acetate as the eluent, yielding pure compounds **10(a-c)** in 62-77% of yields.

3-(4-methylphenyl)-5-[(*Z*)-1-phenylmethylidene]-2-[1,2,3,4]tetraazolo[1,5-*a*]-quinolin-4-yl-1,3-thiazolan-4-one (10a): Yield 77%; IR (KBr) ν_{max}: 3025, 1696, 1612, 1602, 1563, 1412, 1331, 822 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.21 (s, 3H, CH_3), 6.41 (s, 1H, S-CH-N), 7.10-7.25 (m, 4H, ArH), 7.40-7.90 (m, 10H, ArH & CH=C), 8.51 (d, J = 8.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 27.8, 66.9, 113.3, 115.9, 120.8, 123.7, 125.1, 128.2, 129.2, 130.1, 131.4, 131.9, 132.7, 133.1, 134.6, 135.2, 136.2, 137.0, 139.2, 140.3, 142.9, 161.8; MS: *m/z* 450 (M^++1).

3-(4-chlorophenyl)-5-[(*Z*)-1-phenylmethylidene]-2-[1,2,3,4]tetraazolo[1,5-*a*] quinolin-4-yl-1,3-thiazolan-4-one (10b): Yield 62%; IR (KBr) ν_{max}: 3032, 1702, 1622, 1610, 1569, 1417, 1328, 821, 687 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 6.38 (s, 1H, S-CH-N), 7.15-7.30 (m, 4H, ArH), 7.40-7.90 (m, 10H, ArH & CH=C), 8.53 (d, J = 8.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 66.1, 115.2, 120.5, 123.6, 125.4, 128.1, 128.5, 129.7, 130.2, 130.4, 130.9, 131.9, 132.3, 133.1, 134.5, 135.1, 136.3, 139.4, 141.1, 142.4, 161.2; MS: *m/z* 469 (M^+).

3-(4-nitrophenyl)-5-[(*Z*)-1-phenylmethylidene]-2-[1,2,3,4]tetraazolo[1,5-*a*] quinolin-4-yl-1,3-thiazolan-4-one (10c): Yield 66%; IR (KBr) ν_{max}: 3037, 1701, 1623, 1614, 1577, 1557, 1411, 1323, 827 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 6.44 (s, 1H, S-CH-N), 7.10 (s, 1H, ArH), 7.29 (m, 1H, ArH), 7.40-7.90 (m, 10H, ArH & CH=C), 8.12 (d, J = 9.01 Hz, 2H, ArH), 8.52 (d, J = 8.5 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 66.9, 115.9, 120.8, 123.7, 125.1, 128.2, 129.0, 129.9, 130.1, 131.2, 131.5, 132.7, 134.6, 134.9, 135.2, 136.2, 139.2, 140.3, 142.9, 143.8, 161.8; MS: *m/z* 481 (M^++1).

General procedure for the synthesis of 6-(aryl)-2-(alkyl/aryl)-3-phenyl-5-[1,2,3,4]tetra- azolo[1,5-*a*]quinolin-4-yl-3,3a,5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole 11(a-o): In glacial acetic acid (20 mL), a combination of corresponding compound **10** (0.001 mol), aryl/alkyl hydrazine (0.0015 mol), and anhydrous sodium acetate (0.0015 mol) was refluxed for eight hours. After the reaction mixture was concentrated and allowed to cool to room temperature, the separated solid was filtered and thoroughly cleaned with water. The resulting crude product was then purified using column chromatography on silica gel using hexane-ethyl acetate as an eluent, yielding pure compounds **11(a-o)** in good yields of 44-63%.

6-(4-methylphenyl)-2,3-diphenyl-5-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-3,3a,5,6-tetra- hydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole (11a): yield 57%; IR (KBr) ν_{max}: 3062, 1610, 1565, 1540, 1232, 1035, 810 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.62 (s, 3H, CH_3), 4.38 (s, 1H, CH), 5.47 (s, 1H, CH), 6.89 (s, 1H, ArH), 7.00-7.20 (m, 10H, ArH & S-CH-N), 7.50-7.80 (m, 7H, ArH), 8.12 (d, J = 7.9 Hz, 1H, ArH), 8.61 (d, J = 8.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 27.3, 57.9, 65.8, 67.4, 115.2, 117.5, 118.0, 122.7, 123.0, 125.9, 126.9, 127.4, 128.1, 128.9, 129.5, 130.7, 131.9, 132.7, 133.1, 136.0, 137.8, 139.8, 140.5, 141.1, 144.5, 149.2; MS: *m/z* 539 (M^+).

2-(4-chlorophenyl)-6-(4-methylphenyl)-3-phenyl-5-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-3,3a,5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole (11b): yield 63%; IR (KBr) ν_{max}: 3047, 1612, 1567, 1532, 1229, 1030, 812, 688 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.64 (s, 3H, CH_3), 4.32 (s, 1H, CH), 5.46 (s, 1H, CH), 6.90 (s, 1H, ArH), 7.00-7.20 (m, 7H, ArH & S-CH-N), 7.50-7.80 (m, 9H, ArH), 8.14 (d, J = 7.9 Hz, 1H, ArH), 8.65 (d, J = 8.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 27.8, 57.1, 65.3, 66.9, 117.4, 122.9, 123.2, 124.5, 125.4, 126.5, 127.7, 128.5, 129.7, 130.2, 13.4, 130.9, 131.5, 132.1, 133.6, 136.2, 137.4, 139.2, 140.2, 141.6, 145.4, 148.3; MS: *m/z* 575 (M^++1).

2-benzyl-6-(4-methylphenyl)-3-phenyl-5-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-3,3a,5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole (11c): yield 61%; IR (KBr) ν_{max}: 3057, 2978, 1614, 1567, 1542, 1235, 1037, 819 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.59 (s, 3H, CH_3), 3.72 (s, 2H, CH_2), 4.34 (s, 1H, CH), 5.42 (s, 1H, CH), 6.88 (s, 1H, ArH), 7.10-7.30 (m, 10H, ArH & S-CH-N), 7.50-7.80 (m, 7H, ArH), 8.14 (d, J = 7.9 Hz, 1H, ArH), 8.68 (d, J = 8.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 27.4, 57.3, 59.0, 65.5, 67.8, 117.4, 122.5, 123.4, 125.7, 126.0, 127.1, 127.9, 128.0, 128.9, 129.3, 129.0, 130.9, 131.5, 132.3, 133.4, 135.9, 136.8, 137.1, 139.4, 140.1, 140.9, 149.4; MS: *m/z* 554 (M^++1).

2-isopropyl-6-(4-methylphenyl)-3-phenyl-5-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-3,3a, 5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole (11d): yield 44%; IR (KBr) ν_{max}: 3033, 2981, 1614, 1563, 1547, 1228, 1031,

799 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.41 (d, J = 6.21 Hz, 6H, CH_3), 2.64 (s, 3H, CH_3), 3.29 (m, 1H, CH), 4.33 (s, 1H, CH), 5.42 (s, 1H, CH), 6.82 (s, 1H, ArH), 7.00-7.15 (m, 5H, ArH & S-CH-N), 7.50-7.80 (m, 7H, ArH), 8.11 (d, J = 7.9 Hz, 1H, ArH), 8.62 (d, J = 8.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 24.1, 26.5, 57.4, 60.1, 65.6, 67.5, 117.1, 122.0, 123.5, 125.9, 126.7, 127.6, 128.3, 129.8, 130.7, 131.9, 132.2, 133.5, 136.4, 137.6, 139.5, 140.7, 141.3, 148.9; MS: *m/z* 505 (M^+).

2-methyl-6-(4-methylphenyl)-3-phenyl-5-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-3,3a,5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole (11e): yield 56%; IR (KBr) ν_{max}: 3078, 1605, 1572, 1554, 1229, 1022, 805 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.60 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 4.32 (s, 1H, CH), 5.41 (s, 1H, CH), 6.85 (s, 1H, ArH), 7.00-7.15 (m, 5H, ArH & S-CH-N), 7.50-7.80 (m, 7H, ArH), 8.16 (d, J = 7.9 Hz, 1H, ArH), 8.59 (d, J = 8.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 27.0, 41.1, 57.7, 65.7, 67.1, 117.6, 122.3, 123.7, 125.7, 126.8, 127.9, 128.8, 129.5, 130.2, 131.7, 132.0, 133.7, 136.7, 137.0, 139.6, 140.9, 141.4, 149.5; MS: *m/z* 477 (M^+).

6-(4-chlorophenyl)-2,3-diphenyl-5-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-3,3a,5,6-tetra- hydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole (11f): yield 62%; IR (KBr) ν_{max}: 3032, 1617, 1571, 1538, 1230, 1031, 812, 691 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 4.36 (s, 1H, CH), 5.41 (s, 1H, CH), 6.82 (s, 1H, ArH), 7.10-7.20 (m, 8H, ArH & S-CH-N), 7.50-7.80 (m, 9H, ArH), 8.13 (d, J = 7.9 Hz, 1H, ArH), 8.62 (d, J = 8.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 57.8, 65.2, 67.8, 115.6, 117.8, 118.3, 122.7, 123.3, 125.0, 126.0, 127.3, 128.3, 128.9, 130.8, 131.4, 132.6, 133.6, 133.9, 134.2, 135.9, 138.5, 140.3, 141.8, 144.8, 149.8; MS: *m/z* 560 (M^+).

2,6-di(4-chlorophenyl)-3-phenyl-5-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-3,3a,5,6-tetra- hydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole (11g): yield 58%; IR (KBr) ν_{max}: 3058, 1613, 1569, 1536, 1233, 1037, 806, 690 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 4.37 (s, 1H, CH), 5.43 (s, 1H, CH), 6.85 (s, 1H, ArH), 7.10-7.20 (m, 5H, ArH & S-CH-N), 7.50-7.80 (m, 11H, ArH), 8.11 (d, J = 7.9 Hz, 1H, ArH), 8.58 (d, J = 8.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 57.0, 65.4, 67.5, 117.8, 122.6, 123.6, 124.3, 125.4, 126.4, 127.5, 128.5, 130.0, 130.8, 130.9, 131.6, 132.1, 133.0, 133.7, 134.9, 136.1, 138.4, 140.6, 141.0, 145.6, 149.3; MS: *m/z* 595 (M^++1).

2-benzyl-6-(4-chlorophenyl)-3-phenyl-5-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-3,3a,5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole (11h): yield 55%; IR (KBr) ν_{max}: 3054, 2947, 1608, 1556, 1532, 1226, 1031, 807 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.78 (s, 2H, CH_2), 4.35 (s, 1H, CH), 5.42 (s, 1H, CH), 6.87 (s, 1H, ArH), 7.10-7.30 (m, 8H, ArH & S-CH-N), 7.50-7.80 (m, 9H, ArH), 8.13 (d, J = 7.9 Hz, 1H, ArH), 8.64 (d, J = 8.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 57.5, 59.8, 64.9, 67.3, 117.0, 122.5, 123.9, 125.8, 126.8, 127.0, 127.5, 127.9, 128.4, 129.8, 130.5, 131.0, 132.6, 133.3, 133.9, 134.0, 135.6, 136.7, 138.8, 140.7, 141.2, 149.5; MS: *m/z* 574 (M^+).

6-(4-chlorophenyl)-2-isopropyl-3-phenyl-5-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-3,3a, 5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole (11i): yield 49%; IR (KBr) ν_{max}: 3042, 2971, 1605, 1567, 1534, 1233, 1032, 803 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.39 (d, J = 6.18 Hz, 6H, CH_3), 3.24 (m, 1H, CH), 4.32 (s, 1H, CH), 5.41 (s, 1H, CH), 6.80 (s, 1H, ArH), 7.10-7.20 (m, 3H, ArH & S-CH-N), 7.50-7.80 (m, 9H, ArH), 8.13 (d, J = 7.9 Hz, 1H, ArH), 8.60 (d, J = 8.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 24.9, 57.2, 60.5, 65.9, 67.2, 117.3, 122.8, 123.3, 125.3, 126.4, 127.6, 128.5, 130.6, 131.2, 132.0, 133.4, 133.8, 134.5, 136.8, 138.4, 140.21, 141.4, 149.0; MS: *m/z* 498 (M^+).

6-(4-chlorophenyl)-2-methyl-3-phenyl-5-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-3,3a,5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole (11j): yield 61%; IR (KBr) ν_{max}: 3044, 1614, 1561, 1539, 1222, 1041, 798 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.73 (s, 3H, CH_3), 4.31 (s, 1H, CH), 5.40 (s, 1H, CH), 6.84 (s, 1H, ArH), 7.10-7.20 (m, 3H, ArH & S-CH-N), 7.50-7.80 (m, 9H, ArH), 8.17 (d, J = 7.9 Hz, 1H, ArH), 8.59 (d, J = 8.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 41.2, 57.6, 65.0, 67.1, 117.9, 122.5, 123.5, 125.8, 126.5, 127.1, 128.6, 130.8, 131.4, 132.5, 133.5, 133.7, 134.8, 135.4, 138.7, 140.6, 141.6, 149.4; MS: *m/z* 498 (M^+).

6-(4-nitrophenyl)-2,3-diphenyl-5-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-3,3a,5,6-tetra- hydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole (11k): yield 58%; IR (KBr) ν_{max}: 3029, 1612, 1569, 1533, 1377, 1230, 1024, 798 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 4.32 (s, 1H, CH), 5.45 (s, 1H, CH), 6.85 (s, 1H, ArH), 7.10-7.20 (m, 6H, ArH & S-CH-N), 7.50-7.80 (m, 9H, ArH), 8.15 (d, J = 7.9 Hz, 1H, ArH), 8.32 (d, J = 8.9 Hz, 2H, ArH), 8.57 (d, J = 8.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ k) 57.7, 59.3, 65.4, 67.4, 115.8, 117.2, 118.9, 122.8, 123.7, 125.7, 126.2, 127.8, 128.5, 128.8, 130.7, 131.7, 132.2, 133.2, 136.2, 140.8, 141.1, 141.7, 142.3, 144.5, 148.1; MS: *m/z* 571 (M^++1).

2-(4-chlorophenyl)-6-(4-nitrophenyl)-3-phenyl-5-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-3,3a,5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole (11l): yield 59%; IR (KBr) ν_{max}: 3056, 1621, 1545, 1532, 1247, 1029, 810, 697 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 4.32 (s, 1H, CH), 5.41 (s, 1H, CH), 6.84 (s, 1H, ArH), 7.10-7.20 (m, 3H, ArH & S-CH-N), 7.50-7.80 (m, 11H, ArH), 8.13 (d, J = 7.9 Hz, 1H, ArH), 8.32 (d, J = 8.9 Hz, 2H, ArH), 8.57 (d, J = 8.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 57.3, 65.1, 67.9, 117.9, 122.7, 123.4, 124.9, 125.9, 126.3, 127.3, 128.0, 130.1, 130.5, 130.9, 131.2, 132.5, 133.6, 136.3, 140.4, 141.3, 141.8, 142.7, 145.7, 149.8; MS: *m/z* 605 (M^+).

2-benzyl-6-(4-nitrophenyl)-3-phenyl-5-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-3,3a,5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole (11m): yield 54%; IR (KBr) ν_{max}: 3044, 1614, 1566, 1533, 1211, 1039, 799 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.88 (s, 2H, CH_2), 4.35 (s, 1H, CH), 5.42 (s, 1H, CH), 6.84 (s, 1H, ArH), 7.10-7.30 (m, 6H, ArH & S-CH-N), 7.50-7.80 (m, 9H, ArH), 8.08 (d, J = 7.9 Hz, 1H, ArH), 8.32 (d, J = 8.9 Hz, 2H, ArH), 8.57 (d, J = 8.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 57.2, 65.4, 67.0, 117.0, 122.0, 123.6, 125.4, 126.8, 127.0, 127.5, 127.9, 128.4, 129.4, 130.5, 131.9, 132.8, 133.0, 135.9, 136.6, 140.3, 141.2, 141.9, 143.0, 149.2; MS: *m/z* 585 (M^+).

2-isopropyl-6-(4-nitrophenyl)-3-phenyl-5-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-3,3a,5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole (11n): yield 63%; IR (KBr) ν_{max}: 3032, 2971, 1605, 1572, 1542, 1233, 1023, 805 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.39 (d, J = 6.18 Hz, 6H, CH_3), 3.22 (m, 1H, CH),, 4.36 (s, 1H, CH), 5.48 (s, 1H, CH), 6.90 (s, 1H, ArH), 7.03 (s, 1H, S-CH-N), 7.50-7.80 (m, 9H, ArH), 8.10 (d, J = 7.9 Hz, 1H, ArH), 8.32 (d, J = 8.9 Hz, 2H, ArH), 8.57 (d, J = 8.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 24.3, 57.7, 60.7, 65.6, 67.4, 117.7, 122.9, 123.5, 125.4, 126.0, 127.9, 128.3, 130.8, 131.5, 132.5, 133.7, 136.5, 140.5, 141.0, 141.4, 142.5, 149.1; MS: *m/z* 536 (M^+).

2-methyl-6-(4-nitrophenyl)-3-phenyl-5-[1,2,3,4]tetraazolo[1,5-*a*]quinolin-4-yl-3,3a,5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole (11o): yield 56%; IR (KBr) ν_{max}: 3055, 2951, 1614, 1561, 1539, 1234, 1026, 802 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.69 (s, 3H, CH_3), 4.31 (s, 1H, CH), 5.42 (s, 1H, CH), 6.91 (s, 1H, ArH), 7.05 (s, 1H, S-CH-N), 7.50-7.80 (m, 9H, ArH), 8.14 (d, J = 7.9 Hz, 1H, ArH), 8.32 (d, J = 8.9 Hz, 2H, ArH), 8.62 (d, J = 8.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 41.5, 57.4, 65.2, 67.2, 117.3, 122.6, 123.1, 125.7, 126.1, 127.4, 128.1, 130.5, 131.8, 132.4, 133.3, 136.6, 140.3, 141.5, 141.8, 142.9, 149.3; MS: *m/z* 509 (M^++1).

IV. CONCLUSION

In summary, we have described the synthesis of novel 6-(aryl)-2-(alkyl/aryl)-3-phenyl-5-[1,2,3,4]tetraazolo[1,5-a]quinoline-4-yl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d][1,3]thiazole **11(a-o)** and evaluated for their antibacterial activity against four human pathogenic bacteria: *Escherichia coli, Klebsiella pneumoniae, Shigella dysenteriae*, and *Shigella flexneri*. Compounds (**11b**), (**11i**), and (**11l**) demonstrated strong antibacterial screening against all the organisms tested. The zone of inhibition of compound **11g** is close to that of the common medication streptomycin, and it is quite effective against *K. pneumoniae* and *S. flexneri*. *E. coli* was effectively inhibited by compound with 4-nitrophenyl on the thiazole ring and isopropyl on the pyrazole ring (**11n**) and emerged as potential molecules for further development.

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