Regioselective Synthesis, Antitumor and Antioxidant Activities of Some 1,2,4-Triazole Derivatives Based on 4-Phenyl-5-(quinolin-8-yloxy)methyl-4*H*-1,2,4-triazole-3-thiol

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ABSTRACT

Regioselective synthesis of some triazole derivatives **4-19** was achieved from the versatile, readily accessible 4-phenyl-5-(quinolin-8-yloxy)methyl-4*H*-1,2,4-triazole-3-thiol/thione **3.** The structures of the newly synthesized products were confirmed and characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral studies. Most of the synthesized compounds were evaluated for their antitumor and antioxidant activities and demonstrated potent to weak activities.

Keywords: Quinoline; triazole; pyrazole; thiazole; antitumor; antioxidant

INTRODUCTION

In recent years considerable attention has been devoted to the synthesis of triazole and its thione derivatives, as they possess such diverse pharmacological properties and industrial applications. A number of these derivatives showed antimicrobial,[1-5] anti-inflamatory,[6] antioxidant,[7] anticancer,[8, 9] and anticonvulsant activity.[10] In addition, quinolines are well known natural and synthetic products occur in several natural compounds and pharmacologically active substances displaying a broad range of biological activity. Quinoline has been found to possess anticancer,[11,12] antibacterial,[13,14] anti-tuberculosis,[15] antimalarial.[16,17]

In continuation to our research program about the synthesis of heterocyclic compounds having biological interest,[18-21] we report herein the synthesis, antitumor and antioxidant activities of some

novel structures incorporating both triazole and quinoline heterocycles. This work was suggested by our group to investigate the effect of such combination on the anticipated pharmaceutical applications of molecules including both triazole and quinoline moieties.

RESULTS AND DISCUSSION

The synthetic routes adopted for the synthesis of target structures are depicted in (Schemes 1-5). Treatment of acid hydrazide **1** (prepared from hydrazinolysis of ethyl 2-(quinolin-8-yloxy)acetate)[3] with phenyl isothiocyanate in ethanol afforded compound **2**. Heating of the latter with sodium hydroxide (2M) furnished 4-phenyl-5-((quinolin-8-yloxy)methyl)-4*H*-1,2,4-triazole-3-thiol **(3)** (Scheme 1)**.** Triazole **3** can exist in two tautomeric forms, thiol **3a** and its tautomeric thione **3b** on the basis of its spectral data.[22] ^{1}H NMR spectrum showed singlet signals (exchangeable) at 12.81 and 6.33 ppm corresponding to NH and SH respectively. Also, IR spectrum displayed absorption bands at 3204, 2615 and 1321 cm^{-1} corresponding to absorptions of NH, SH and C=S respectively.

Triazole **3** is used as reactive key precursors for synthesis of a number of substituted 1,2,4-triazole derivatives of expected biological activity through its reactivity towards variety of electrophilic reagents depending on the reaction conditions. Thus, treatment of triazole **3** with chloroacetic acid or ethylchloroacetate in absolute ethanol in the presence of potassium hydroxide afforded 2-((4-phenyl-5-((quinolin-8-yloxy)methyl)-*4H*-1,2,4-triazol-3-yl)thio) ethanoic acid **(4a)** and ethyl 2-((4-phenyl-5-((quinolin-8-yloxy)methyl)-*4H*-1,2,4-triazol-3-yl)thio) ethanoate **(4b)** respectively *via* thiol toutomer **3a**. In addition, the reaction of triazole **3a** with methyl iodide

in the presence of sodium ethoxide gives 8-((5-(methylthio)-4-phenyl-4*H*-1,2,4-triazol-3-yl)methoxy) quinoline **(5)** (Scheme 2)**.**

On the other hand, the treatment of triazole **3** with formaldehyde in ethanol furnished 2-(hydroxymethyl)-4-phenyl-5-((quinolin-8-yloxy)methyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **(6)** *via* thione toutomer **3b**. Also, N, 4 –diphenyl -3-((quinolin-5-yloxy)methyl) -5-thioxo -4,5-dihydro -1*H*-1,2,4-triazole-1-carbothioamide **(7)** was obtained *via* the reaction of compound **3b** with phenyl isothiocyanate.

Furthermore, the reaction of compound **3b** with ethylchloroacetate in boiling pyridine as a weak base furnished ethyl 2-(4-phenyl-3-((quinolin-8-yloxy)methyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)acetate **(8)** (Scheme 3) .

Mannich base derivatives are one of the most important compounds that have potent applications in pharmaceutical chemistry. Thus, treatment of 1,2,4-triazole derivative **3b** with several amines namely, piperidine, *p*-toludine, morpholine and *p*-aminobenzoic acid in the presence of formaldehyde afforded new Mannich base derivatives **9a-d** in moderate to good yields (Scheme 3)**.**

An extension of this synthetic approach, ethyl 2-((4-phenyl-5-((quinolin-8-yloxy)methyl)-*4H*-1,2,4-triazol-3-yl)thio) ethanoate (**4b)** reacted with hydrazine hydrate in boiling ethanol to furnish hydrazide **10** which was used as reactive starting material to construct a series of heterocyclic systems as potential antimicrobial agents. Thus, treatment of hydrazide **10** with carbon disulfide,

in ethanol containing potassium hydroxide afforded 5-(((4-phenyl-5-((quinolin-8-yloxy)methyl)-4*H*-1,2,4-triazol-3-yl)thio)methyl)-1,3,4-oxadiazole-2-thiol **(11).**

Also, the reaction of hydrazide **10** with phenyl isothiocyanate in dry benzene containing few drops of triethylamine afforded 4-phenyl-5-(((4-phenyl-8-((quinolin-5-yloxy)methyl)-4*H*-1,2,4-triazol-3-yl)thio) methyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **(12)** (Scheme 4).

The biological activity of pyrazoles as antibacterials, antifungals, and anticancers,[23-25] prompted us to utilize the amino functionality of hydrazide **10** in the design of new heterocyclic systems incorporating pyrazole nucleus. Thus, hydrazide derivative **10** has been allowed to react with acetylacetone to afford pyrazole derivative **13**. On the other hand, heating of hydrazide **10** with glacial acetic acid afforded monoacetyl derivative **14** (Scheme 4**).**

Moreover, the triazole derivative **15** was synthesized through refluxing hydrazide **10** with phthalic anhydride in glacial acetic acid, whereas Schiff base **16** was prepared by condensation of **10** with benzaldehyde in ethanol (Scheme 5).

Also, treatment of hydrazide derivative **10** with benzoic acid in the presence of phosphorous oxychloride furnished oxadiazole derivative **17.** Oxadiazole **17** can be prepared also by refluxing benzoylchloride in pyridine, the melting point and IR spectra of the products are consistent. Finally, treatment of hydrazide derivative **10** with *D*-glucose in ethanol containing few drops of acetic acid furnished glucosazone **18** (Scheme 5).

Antitumor Activity

Treatment of cell lines, hepatocellular carcinoma (HePG-2), mammary gland (MCF-7), Colorectal carcinoma (HCT-116) and Human prostate cancer cell line (PC3) with some of the synthesized products using MTT assay showed different cytotoxic effect as shown in (Table S 1, Supplemental Materials). It was observed that, triazolethione **7** showed the most potent cytotoxic effect against Colorectal carcinoma (HCT-116) and mammary gland (MCF-7) concluded from their IC50 values 8.4 and 7.7 µg/mL and strong activity against the other two cell lines. Also, Mannich base **9b** showed very strong activity against hepatocellular carcinoma (HePG-2) and Human prostate cancer cell line (PC3) (IC50 = 9.1, 8.8 µg/mL). The rest of compounds showed moderate activity against all cell lines while triazole derivative **17** showed weak cytotoxicty.

Antioxidant Activity

Antioxidant activity of the synthesized products and their ability to inhibit oxidation in rat brain and kidney homogenates were evaluated using (ABTS) inhibition. It was observed from data in (Table S 2, Supplemental Materials) that most of the tested compounds showed potent antioxidant activities especially triazoles **7** and **9d** showed higher activity in comparison to the standard ascorbic acid.

CONCLUSION

We used 4-phenyl-5-(quinolin-8-yloxy)methyl-4*H*-1,2,4-triazole-3-thiol/thione **3** as a reactive starting material to synthesize a novel series of triazole derivatives through its reactions with variety of chemical reagents. Most of the synthesized products were evaluated for their antitumor and antioxidant activities and exhibited potent to moderate activity.

EXPERIMENTAL

Melting points were determined on a capillary point apparatus equipped with a digital thermometer and Gallen Kamp melting point apparatus and are uncorrected. IR-Spectra (KBr disk) were recorded on FT/IR-BRUKER, Vector 22. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 with TMS for (300 and 50 MHz) as an internal reference. Mass spectrometry was done on Thermo Finnegan (San Jose, CA) LCQ spectrophotometer with electro spray ionization (ESI) and on Shimadzu GCMS-QP-1000EX mass spectrophotometer at 70 e.v. Elemental analyses were performed on a Carlo Erba-1106 instrument. The pharmaceutical applications of the products were carried out at Faculty of Pharmacy, Mansura University, Egypt. The Supplemental Materials contains sample IR, mass and ^{1}H NMR spectra of the products (Figures S 1 – S 24)

Synthesis of N-phenyl-2-(2-(quinolin-8-yloxy)acetyl)hydrazine-1-carbothioamide (2)

A mixture of hydrazide **1** [prepared from the reaction of ethyl 2-(quinolin-8-yloxy)acetate with hydrazine hydrate in ethanol according to reported procedures][3] (0.01 mol) and phenyl isothiocyanate (0.01 mol) in absolute ethanol (30 mL) was refluxed for 4 h then cooled to room temperature. The product solid was collected by filtration, dried and crystallized from ethanol. Yield, 79 %; Pale yellow, m.p. 195-197 °C. IR (KBr, ν cm^{-1}), 3320-3190 (NH), 1677 (CO), 1315 (CS); ^{1}H NMR (DMSO-d_6, δ ppm): 10.42, 9.74, 5.31 (3S, 3H, 3NH exchangeable) , 8.91 (d,1H,C-2 quin.), 8.32 (d, 1H, C-4 quin.), 7.61 – 7.13 (m, 9H, 1H C-3 quin., and 8H Ar-H) , 4.92 (s, 2H, OCH_2); ^{13}C NMR δ: 198.3 (C=S), 168.3 (C=O), 155.1, 148.2, 142.4, 140.3, 136.2, 130.3, 128.5, 128.2, 127.1, 125.7, 120.5, 118.3, 108.2, (aromatic carbons), 65.8 (CH_2); Anal. calcd. for $C_{18}H_{16}N_4O_2S$ (352.41) :C, 61.35; H, 4.58; N, 15.90 Found:C, 61.24; H, 4.35; N, 15.76.

Synthesis of 4-phenyl-5-((quinolin-8-yloxy)methyl)-4*H*-1,2,4-triazole-3-thiol/ thione (3) [26]

A mixture of compound **2** (0.01 mol) and 10% sodium hydroxide solution (20 mL) was refluxed for 3 h, cooled to room temperature, poured over crushed ice and acidified with conc. HCl to pH 5. The precipitate was collected by filtration, washed with water, dried and crystallized from ethanol to afford triazole **3**. Yield, 85%, Pale yellow, m.p. 219-221 °C. IR spectrum (KBr, ν, cm^{-1}): 3204 (NH), 2615 (SH), 1637 (C=N), 1321(C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 12.82 (s, 1H, SH or NH exchangeable), 7.17-8.37 (m, 11H, Ar-H), 6.33 (s, 1H, SH, exchangeable) 4.91 (s, 2H, OCH_2); ^{13}C NMR δ: 169.2 (C=S), 156.3, 155.2, 148.3, 141.2, 134.8, 133.7, 132.5, 128.4, 128.1, 127.2, 125.5, 120.2, 116.3, 106.1(aromatic carbons), 73.2 (CH_2); MS: *m/z* 334 (M^+,18.67%), 336 ((M^{+2}, 11.32%), 145 (100%). Anal. calcd. for $C_{18}H_{14}N_4OS$ (334.09): C, 64.65; H, 4.22; N, 16.75 Found: C, 64.89; H, 4.36; N, 16.70 .

Synthesis of 2-(4-phenyl-5-((quinolin-8-yloxy)methyl)-4*H*-1,2,4-triazol-3-yl)thio) acetic acid (4a)

A mixture of compound **3** (0.01 mol) and chloroacetic acid (0.01 mol) was dissolved in ethanol (20 mL) containing potassium hydroxide (0.015 mol). The mixture was heated at reflux on water bath for 6 h. The crude solid product that deposited was collected, dried and recrystallized from ethanol to afford crystalline solid **4a**. Yield, 88%, Yellow, m.p. 178-180 °C. IR spectrum (KBr, ν, cm^{-1}): 3422 (OH), 2915, 2850 (CH aliphatic)**,** 1701(C=O), 1598(C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 11.23 (s, 1H, OH, exchangeable), 8.42-7.02 (m, 11H, Ar-H), 4.89 (s, 2H, OCH_2), 4.20 (s, 2H, SCH_2); ^{13}C NMR δ 173.5 (C=O), 155.8, 152.8, 148.2, 142.3, 134.2, 132.9, 132.2, 128.8, 128.3, 127.5, 126.2, 121.1, 117.2, 107.3, (aromatic carbons), 68.2 (OCH_2), 42.6 (SCH_2); MS: *m/z* 392 (M^+, 7.65 %), 77 (100%). Anal. calcd. for $C_{20}H_{16}N_4O_3S$ (392.43): C, 61.21; H, 4.11; N, 14.28 Found: C, 61.17; H, 4.01; N, 14.22.

Synthesis of ethyl 2-(4-phenyl-5-((quinolin-8-yloxy)methyl)-4*H*-1,2,4-triazol-3-yl)thio)acetate (4b)

A mixture of compound **3** (0.01 mol), ethyl chloroacetate (0.04 mol) and anhydrous potassium carbonate (0.04 mol) in dry acetone (30 mL) was heated under reflux on water bath for 20h. The reaction mixture was allowed to cool, poured into water. The solid so formed was filtered off, washed, dried and crystallized. Yield, 81%, Pale yellow, m.p. 112-114 °C IR spectrum (KBr, ν, cm^{-1}): 2984, 2850 (CH aliphatic)**,** 1742(C=O), 1595 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 8.91-6.86 (m, 11H, Ar-H), 5.05 (s, 2H, OCH_2), 4.104 (s, 2H, SCH_2), 4.18 (q, 2H, CH_2), 1.21 (t, 3H, CH_3). MS: *m/z* 420 (M^+, 24.92 %), 264 (100%). Anal. calcd. for $C_{22}H_{20}N_4O_3S$, (420.13): C, 62.84; H, 4.79; N, 13.32 Found: C, 62.80; H, 4.72; N, 13.27.

Synthesis of 5-((5-(methylthio)-4-phenyl-4*H*-1,2,4-triazol-3-yl)methoxy) quinoline (5)

A compound **3** (0.01 mol) in ethanol (20 mL) containing sodium ethoxide was refluxed for 2h. Methyl iodide (0.01 mol) was then added and the mixture was refluxed for an additional 3h. The solvent was evaporated under reduced pressure, and the solid obtained by adding water was filtered off and recrystallized from ethanol to afford **5.** Yield, 78 %, Pale yellow, m.p. 123-125 °C IR spectrum (KBr, ν, cm^{-1}): 3014(CH aromatic), 2907, 2850 (CH aliphatic) , 1604 (C=N). ^{1}H NMR (DMSO-*d6*, δ ppm): 8.80-6.97 (m, 11H, Ar-H) , 5.25 (s, 2H, OCH_2), 3.87 (s,3H,CH_3); ^{13}C NMR δ 156.3, 152.6, 149.5, 144.6, 133.3, 132.7, 131.5, 127.3, 127.9, 126.8, 126.1, 120.5, 118.5, 110.3, (aromatic carbons), 66.5 (OCH_2), 15.1 (CH_3); Anal. calcd. for $C_{19}H_{16}N_4OS$ (348.42): C, 65.50; H, 4.63; N, 16.08 Found: C, 65.45; H, 4.60; N, 16.15 .

Synthesis of 2-(hydroxymethyl)-4-phenyl-5-((quinolin-8-yloxy)methyl)-2,4-dihydro-3*H*-1,2,4 triazole-3-thione (6)

A mixture of **3** (0.01 mol) and formaldhyde (0.02 mol) in ethanol (20 mL) was refluxed for 5 h. The solid that separated after concentration and cooling was recrystallized from ethanol to give **6**. Yield, 76 %, Yellow, m.p. 134-136 °C. IR spectrum (KBr, ν, cm^{-1}): 3424 (OH), 1598 (C=N) and 1313 (C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 8.92-6.97 (m, 11H, Ar-H) , 5.53, 4.92 (2s, 4H, $2OCH_2$), 4.18 (s, 1H, OH, exchangeable); ^{13}C NMR δ 170.6 (C=S), 156.2, 154.3, 147.5, 142.6, 135.3, 132.6, 131.7, 128.5, 127.3, 126.8, 126.1, 121.6, 118.4, 108.2 (aromatic carbons), 72.2 (OCH_2), 70.3 (OCH_2). Anal. calcd. for $C_{19}H_{16}N_4O_2S$ (364.42): C, 62.62; H, 4.43; N, 15.37 Found: C, 62.45; H, 4.27; N, 15.30.

Synthesis of N,4-diphenyl-3-((quinolin-8-yloxy)methyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazole -1-carbothioamide (7)

To a solution of 4-phenyl-5-((quinolin-5-yloxy)methyl)-4*H*-1,2,4-triazole-3-thiol **3** (0.01 mol) in ethanol (20 mL), phenyl isothiocyanate (0.01 mol) was added. The mixture was refluxed for 3h. The solid product was filtered off, recrystallized from ethanol to afford **7** as a yellow solid**.** Yield, 85 %, Yellow, m.p. 182-184 °C. IR spectrum (KBr, ν, cm^{-1}): 3205 (NH), 2918, 2840 (CH aliphatic), 1597 (C=N), and 1321 (C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 11.03 (s, 1H, NH, exchangeable), 8.90-7.12 (m, 16H, Ar-H), 4.92 (s, 2H, OCH_2); ^{13}C NMR δ 192.3, 185.6 (2C=S) 154.4, 151.2, 148.5, 144.2, 133,7, 132.6, 132.1, 131.5, 130,5, 128.5, 127.2, 127.6, 126.3, 125.7, 122.4, 117.8, 112.5, 108.5, (aromatic carbons), 68.5 (OCH_2); MS: *m/z* 469 (M^+, 13.25 %), 471 (M^{+2}, 7.23 %), 93(100%). Anal. calcd. for $C_{25}H_{19}N_5OS_2$ (469.58): C, 63.95; H, 4.08; N, 14.91 Found: C, 63.87; H, 3.98; N, 14.85.

Synthesis of ethyl 2-(4-phenyl-3-((quinolin-8-yloxy)methyl)-5-thioxo-4,5-dihydro -1*H* 1,2,4-triazol-1-yl)acetate (8)

A mixture of compound **3** (0.01 mol) and ethyl chloroacetate (0.01 mol) in pyridine (15 mL) was refluxed for 4h. After cooling, the reaction mixture was poured into crushed ice and neutralized with dil HCl. The resulting solid product was filtered off and recrystallized from ethanol to give crystals of compound **8**.Yield, 73 %, Pale yellow, m.p.194- 196 °C. IR spectrum (KBr, ν, cm^{-1}): 2987 (CH aliphatic), 1743(C=O), 1641(C=N), 1316(C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 8.08-6.93 (m, 11H, Ar-H) , 5.03 (s, 2H, OCH_2) , 4.99 (s, 2H, CH_2), 4.10 (q, 2H, CH_2), 1.23 (t, 3H, CH_3). ^{13}C NMR δ 190.5 (C=S),172.3 (CO), 155,5, 152.5, 148.3, 144.6, 133.5, 132.2, 131.5, 129.2, 128.5, 126.3, 125.8, 121.5, 117.5, 107.8 (aromatic carbons), 70.5, 67.3 ($2OCH_2$), 48.5 (NCH_2), 16.5 (CH_3). Anal. calcd. for $C_{22}H_{20}N_4O_3S$ (420.13): C, 62.84; H, 4.79; N, 13.32 Found: C, 62.77; H, 4.65; N, 13.21.

General procedure for the synthesis of compounds (9a-d)

A mixture of **3** (0.01 mol) and the corresponding amine (0.02 mol) such as pipredine, *p*-toludine, morpholine, and 4 amino benzoic acid in ethanol (20 mL) was refluxed for 4h in the presence of formaldehyde (37%, 0.02 mol). After cooling and addition of water, the mixture was kept overnight in cold conditions. The solid that separated was collected by filtration and recrystallized from ethanol to yield the target compounds **(9a-d)**.

4-Phenyl-2-(piperidin-1-ylmethyl)-5-((quinolin-5-yloxy)methyl)-2,4 dihydro-3H-1,2,4-triazole-3-thione (9a)

Yield, 72 %, Yellow, m.p. 169 - 171 °C. IR spectrum (KBr, ν, cm^{-1}): 3059 (CH aromatic), 2932-2851 (CH aliphatic), 1617 (C=N), 1315 (C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 8.81-7.02 (m, 11H, Ar-H), 4.85 (s, 2H, OCH_2), 4.23 (s, 2H, NCH_2), 3.65 (t, 4H, CH_2NCH_2), 3.23-3.11 (m, 6H, $3CH_2$); ^{13}C NMR δ 184.5 (C=S), 153.7, 152.2, 144.5, 142.3, 133.3, 132.8, 131.6, 129.4, 127.3, 126.5, 124.2, 122.5, 118.3, 111.5 (aromatic carbons), 69.5, (OCH_2), 56.6, 52.5, 48.5 ($3NCH_2$), 23.5, 22.7 ($3CH_2$);

MS: *m/z* 431 (M^+, 15.21 %), 433, (M^{+2}, 9.10), 98 (100%). Anal. calcd. for $C_{24}H_{25}N_5OS$ (431.56): C, 66.80; H, 5.84; N, 16.23 % Found: C, 66.72; H, 5.77; N, 16.17 %.

4-Phenyl-5-((quinolin-8-yloxy)methyl)-2-((p-tolylamino)methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (9b)

Yield, 74 %, Yellow, m.p. 177- 179 °C. IR spectrum (KBr, ν, cm^{-1}): 3289 (NH) , 2920, 2850 (CH aliphatic), 1616(C=N), 1275(C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 10.93 (s, 1H, NH, exchangeable), (8.36-6.98 (m, 15H, Ar-H), 4.72 (s, 2H, OCH_2), 3.96 (s, 2H, NCH_2). Anal. calcd. for $C_{26}H_{22}N_5OS$ (452.56): C, 68.85; H, 5.11; N, 15.44 Found: C, 68.80; H, 5.05; N, 15.23 %.

2-(Morpholinomethyl)-4-phenyl-5-((quinolin-8-yloxy)methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (9c)

Yield, 71 %, Pale yellow, m.p. 180-182 °C. IR spectrum (KBr, ν, cm^{-1}): 3056 (CH aromatic), 2956, 2850 (CH aliphatic), 1619 (C=N), 1312 (C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 8.87-7.11 (m, 11H, Ar-H), 4.917 (s, 2H, OCH_2), 4.12 (s, 2H, CH_2), 3.88 (t, 4H, CH_2OCH_2), 3.48 (t, 4H, CH_2NCH_2); ^{13}C NMR δ 181.2 (C=S), 154.5, 152.1, 148.4, 142.5, 133.6, 131.5, 131.1, 128,5, 127.8, 125.1, 124.5, 121.2, 117.4, 110.2 (aromatic carbons), 71.5, 69.3 ($3OCH_2$), 52.2, 50.7 ($3NCH_2$); Anal. calcd. for $C_{23}H_{23}N_5O_2S$ (433.53): C, 63.72; H, 5.35; N, 16.15 Found: C, 63.80; H, 5.33; N, 16.09 %

.4-(((4-Phenyl-3-((quinolin-8-yloxy)methyl)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)methyl) amino)benzoic acid (9d)

Yield, 73 %, Pale yellow, m.p. 193-195 °C. IR spectrum (KBr, ν, cm^{-1}): 3422 (OH), 3205 (NH), 1685 (C=O), 1605 (C=N), 1261(C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 12.39 (s, 1H, OH, exchangeable), 8.89 (s, 1H, NH, exchangeable), 8.21-6.98 (m, 15H, Ar-H), 5.20 (s, 2H, OCH_2), 4.92 (s, 2H, CH_2); ^{13}C NMR δ 178.4 (C=S), 169.2 (C=O), 155.3, 152.4, 145.5, 142.3, 136.5, 133.3, 132.5,

131.5, 131.2, 128,2, 127.5, 126.4, 123.4, 121.5, 116.2, 108.5 (aromatic carbons), 68.5 (OCH_2), 48.8 (NCH_2); Anal. calcd. for $C_{26}H_{21}N_5O_3S$ (483.55): C, 64.58; H, 4.38; N, 14.48 Found: C, 64.45; H, 4.30; N, 14.40 % .

Synthesis of 2-(4-phenyl-5-((quinolin-8-yloxy)methyl)-4H-1,2,4-triazol-3-yl)thio) acetohydrazide (10)

To a suspension of **4b** (0.01 mol) in absolute ethanol (30 mL), hydrazine hydrate (0.015 mol) was added and the reaction mixture was refluxed for 6 h. The solution was concentrated and allowed to cool. The resulting solid obtained was filtered after washed with cold water, dried and recrystalized from ethanol to give brown crystals of **10**. Yield, 73 %, Pale yellow, m.p. 197-199 °C. IR spectrum (KBr, ν, cm^{-1}): 3405- 3265 (NH, NH_2), 2924, 2855 (CH aliphatic), 1671 (C=O), 1593 (C=N). ^1H NMR (DMSO-d_6, δ ppm): 9.35 (s, 1H, NH, exchangeable), 8.86-7.01(m, 11H, Ar-H), 5.27 (s, 2H, OCH_2), 4.35 (s, 2H, NH_2, exchangeable), 3.92 (s, 2H, CH_2). MS: *m/z* 406 (M^+, 10.05 %), 407, (M^{+1}, 8.21), 145 (100%). Anal. calcd. for $C_{20}H_{18}N_6O_2S$ (406.46): C, 59.10; H, 4.46; N, 20.68 Found: C, 59.03; H, 4.40; N, 20.59 **%.**

Synthesis of 5-(((4-phenyl-5-((quinolin-8-yloxy)methyl)-4*H*-1,2,4-triazol-3-yl) thio) methyl)-1,3,4-oxadiazole-2-thiol (11)

To a solution of potassium hydroxide (0.15 mol, 1g in 10 mL H_2O) in ethanol (20 mL), hydrazide **10** (0.013 mol) and carbon disulphide (0.06 mol, 5 mL) were added. The mixture was heated at reflux on water bath for 6h. then it was poured into water and neutralized by dilute hydrochloric acid and the precipitated solid was recrystallized from light petroleum ether / benzene to give **11** as yellow

crystals. Yield, 76 %, Yellow, m.p. 122-124 °C. IR spectrum (KBr, ν, cm^{-1}): 2924, 2853 (CH aliphatic), 2613(SH), 1383(C=S), 1595 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 6.91 – 8.36 (m, 11H, Ar-H) , 5.29 (s, 2H, OCH_2), 4.36 (s, 2H, SCH_2), 3.76 (s, 1H, SH). MS: *m/z* 448 (M^+, 15.13 %), 51 (100%). Anal. alcd. for $C_{21}H_{16}N_6O_2S_2$ (448.52): C, 56.24; H, 3.60; N, 18.74 Found: C, 56.17; H, 3.48; N, 18.68 %.

Synthesis of 4-phenyl-5-(((4-phenyl-5-((quinolin-8-yloxy)methyl)-4H-1,2,4-triazol -3-yl)thio) methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (12).

A mixture of hydrazide **10** (0.01 mol) and phenyl isothiocyanate (0.01 mol) in absolute ethanol (30 mL) was refluxed for 6 h and then cooled to room temperature then a mixture of new compound (0.01 mol) and 10% sodium hydroxide solution (20 mL) was refluxed for 5 h, cooled to room temperature, poured over crushed ice and acidified with conc. HCl to pH 5. The precipitate was collected by filtration, washed with water, dried and crystallized from ethanol to give **12**. Yield, 75 %, Pale yellow, m.p. 113-115 °C. IR spectrum (KBr, ν, cm^{-1}): 3286 (NH), 2621(SH), 1598 (C=N), and 1377(C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 9.90 (s, 1H, NH, exchangeable) , 8.84-6.91 (m, 16H, Ar-H) , 5.23(s, 2H, OCH_2), 4.97(s, 1H, SH, exchangeable), and 4.02 (s, 2H, SCH_2). MS: *m/z* 523 (M^+, 10.54 %), 93 (100%). Anal. calcd. for $C_{27}H_{21}N_7OS_2$ (523.63): C, 61.93; H, 4.04; N, 18.72 Found: C, 61.87; H, 3.95; N, 18.66 %.

Synthesis of 1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-((4-phenyl-5-((quinolin-8-yloxy) methyl)-4*H*-1,2,4-triazol-3-yl)thio)ethan-1-one (13)

To a solution of acetohydrazide derivative **10** (0.01 mol) in absolute ethanol (20 mL), acetylacetone (0.01 mol) was added and the reaction mixture was heated at reflux for 8 h, left to cool. The crude solid product that deposited was collected, dried and recrystallized from petroleum ether/ benzene to

afford **13** as a yellow crystalline solid. Yield, 70 %, Yellow, m.p. 121-123 °C. IR spectrum (KBr, ν, cm^{-1}): 1691(C=O), 1592(C=N), and 1361(C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 8.87-7.20 (m, 11H, Ar-H) , 5.26 (s, 2H, OCH_2), 4.36 (s, 2H, SCH_2), 6.45 (s, 1H, pyrazole-H), 2.01, 2.12 (2s, 6H, $2CH_3$). Anal. alcd. for $C_{25}H_{22}N_6O_2S$ (470.55): C, 63.81; H, 4.71; N, 17.86 Found: C, 63.77; H, 4.55; N, 17.70 % .

Synthesis of N'-acetyl-2-((4-phenyl-5-((quinolin-8-yloxy)methyl)-4*H*-1,2,4-triazol-3-yl) thio) acetohydrazide (14).

A solution of acetohydrazide derivative **10** (0.01 mol) in glacial acetic acid (20 mL) was heated at reflux for 5h, left to cool. The crude solid product that deposited was collected and recrystallized from ethanol to afford **14** as yellow crystalline solid. Yield, 77 %, Yellow, m.p. 117-119 °C. IR spectrum (KBr, ν, cm^{-1}): 3246 (NH), 2930, 2845 (CH aliphatic), 1690-1675 (C=O), 1628(C=N), and 1317 (C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 9.86, 6.32 (2s, 2H, 2NH, exchangeable), 8.38-6.90 (m, 11H, Ar-H) , 5.11 (s, 2H, OCH_2), 3.25 (s, 3H, CH_3). MS: *m/z* 448 (M^+, 15.39 %), 145 (100%). Anal. calcd. for $C_{22}H_{20}N_6O_3S$ (448.50): C, 58.92; H, 4.49; N, 18.74 Found: C, 58.72; H, 4.45; N, 18.64 %.

Synthesis of N-(1,3-dioxoisoindolin-2-yl)-2-((4-phenyl-5-((quinolin-8-yloxy) methyl)-4*H*-1,2,4-triazol-3-yl)thio)acetamide (15)

A mixture of **10** (0.01 mol) and phthalic anhydride (0.01 mol) in glacial acetic acid (20 mL) was heated under reflux for 5 h, after cooling, the reaction mixture was poured over ice-water. The separated solid was collected by filtration, washed, dried and recrystallized from glacial acetic acid to give pure product **15**. Yield, 75 %, Pale yellow, m.p. 120-122 °C. IR spectrum (KBr, ν, cm^{-1}): 3236 (NH), 1761-1714 (C=O), 1599 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 11.08 (s, 1H, NH,

exchangeable), 8.87-6.93 (m, 15H, Ar-H), 5.29 (s, 2H, OCH_2), 4.30 (s, 2H, SCH_2); ^{13}C NMR δ 175.4, 168.7, 155.5, 153.3, 148.4, 143.2, 134.7, 133.1, 132.4, 131.5, 129.3, 128.6, 127.3, 126.8, 123.4, 121.6, 118.5, 108.5, 70.2, 48.3. Anal. calcd. for $C_{28}H_{20}N_6O_4S$ (536.57): C, 62.68; H, 3.76; N, 15.66 Found: C, 62.59; H, 3.59; N, 15.52 %.

Synthesis of (E)-N'-benzylidene-2-((4-phenyl-5-((quinolin-8-yloxy)methyl)-4*H*-1,2,4-triazol-3-yl)thio)acetohydrazide (16)

To a hot solution of acetohydrazide derivative **10** (0.01 mol) in ethanol (20 mL), benzaldehyde (0.01 mol) was added and the reaction mixture was heated under reflux for 6 h., left to cool. The crude solid product that deposited was collected, dried and recrystallized from ethanol to afford **16** as yellow crystals. Yield, 80 %, Yellow, m.p. 130-132 °C. IR spectrum (KBr, ν, cm^{-1}): 3258 (NH), 3058 (CH aliphatic), 1686 (C=O), and 1598 (C=N). ^1H NMR (DMSO-d_6, δ ppm): 10.26 (s, 1H, NH, exchangeable), 9.06 (s, 1H, CH=N), 8.65-6.97 (m, 16H, Ar-H), 5.11 (s, 2H, OCH_2), 4.63 (s, 2H, SCH_2); ^{13}C NMR δ 173.5, 155.3, 154.2, 148.1, 144.4, 142.3, 134.3, 132.9, 132.2, 131.7, 129.5, 127.8, 127.4, 126.2, 125.7, 125.1, 122.6, 121.3, 119.4, 107.2, 69.8, 50.3. MS*: m/z* 494 (M^+, 8.82 %), 145 (100%). Anal. calcd. for $C_{27}H_{22}N_6O_2S$ (494.57): C, 65.57; H, 4.48; N, 16.99 Found: C, 65.32; H, 4.72; N, 16.77 %.

Synthesis of 2-phenyl-5-((4-phenyl-5-((quinolin-8-yloxy)methyl)-4*H*-1,2,4-triazol-3-yl)thio)methyl-1,3,4-oxadiazole (17)

A mixture of **10** (0.01 mol) and benzoic acid (0.01 mol) in phosphorous oxychloride (15 mL) was heated at reflux on water bath for 6 h. left to cool and poured into crushed ice. The solid product that formed was collected, washed with water, dried and recrystallized from light petroleum ether to afford **17** as brown crystals. Yield, 78 %, Brown, m.p. 125-127 °C. IR spectrum (KBr, ν, cm^{-1}):

1600 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 8.86-7.20 (m, 16H, ArH), 5.28 (s, 2H, OCH_2); 4.35 (s, 2H, SCH_2). MS: *m/z* 492 (M^+, 11.17 %), 105 (100%). Anal. calcd. for $C_{27}H_{20}N_6O_2S$ (492.56): C, 65.84; H, 4.09; N, 17.06 Found: C, 65.61; H, 3.98); N, 16.90 %.

Alternative method for synthesis of oxadiazole 17

A mixture of **10** (0.01 mol) and benzoyl chloride (0.03 mol) in pyridine (5 mL) was heated at reflux on water bath for 6 h. left to cool, neutralized by cooled dilute hydrochloric acid. The solid product that formed was collected, washed with water, dried and recrystallized from light petroleum ether to afford **17.**

Synthesis of N'-((2S,3R,4R,5S)-2,3,4,5,6-pentahydroxyhexylidene)-2-((4-phenyl-5-((quinolin-5-yloxy)methyl)-4*H*-1,2,4-triazol-3-yl)thio)acetohydrazide (18)

A mixture of acetohydrazide derivative **10** (0.01 mol) and glucose (0.01 mol) in ethanol (30 mL) was heated under reflux for 4h. The solid product which was separated out after cooling was collected, dried and recrystallized from ethanol to afford hydrazone **18**. Yield, 78 %, Pale yellow, m.p. 170-172 °C. IR spectrum (KBr, ν, cm^{-1}): 3392-3150 (OH, NH), 2850 (CH aliphatic), 1680 (C=O), 1632 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 10.63 (s, 1H, NH, exchangeable), 8.99 (s, 1H, CH=N), 8.52-7.12 (m, 11H, ArH), 5.20 (s, 2H, OCH_2); 4.26 (s, 2H, SCH_2), 4.32-3.68 (brs, 5H, 5OH), 3.43 (m, 2H, CH_2), 3.30-3.15 (m, 4H, 4CH). Anal. calcd. for $C_{26}H_{28}N_6O_7S$ (568.61): C, 54.92; H, 4.96; N, 14.78 Found: C, 54.82; H, 4.77; N, 14.63 %.

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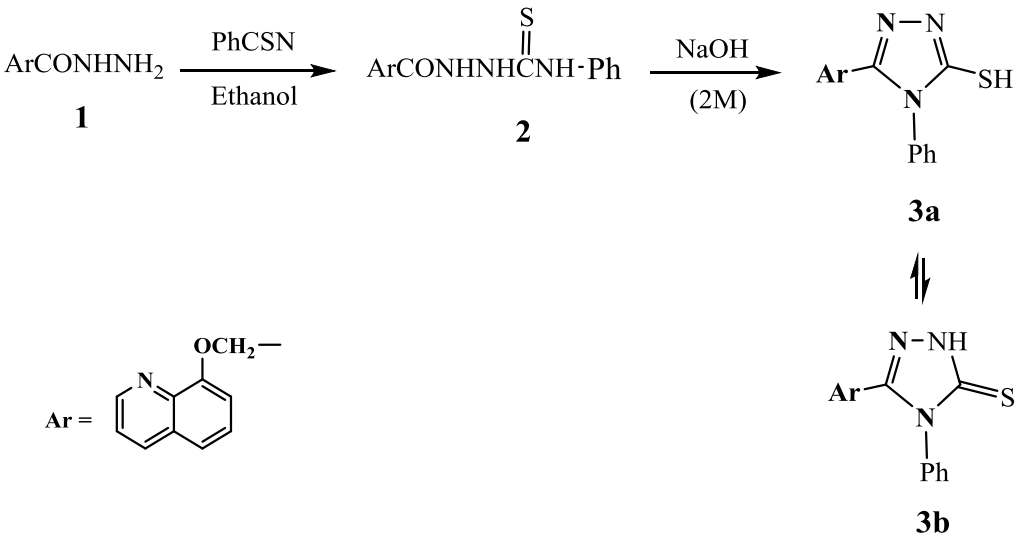
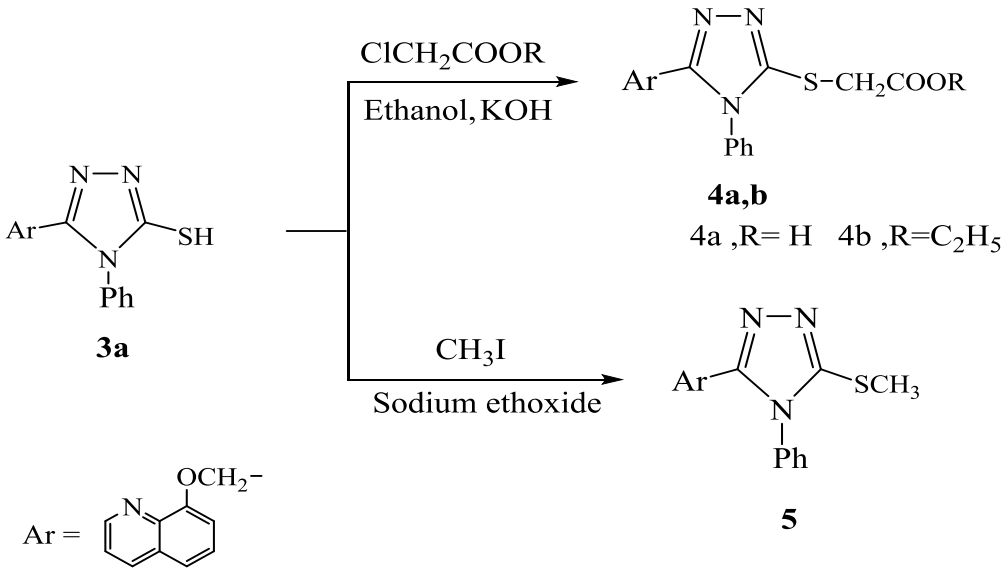
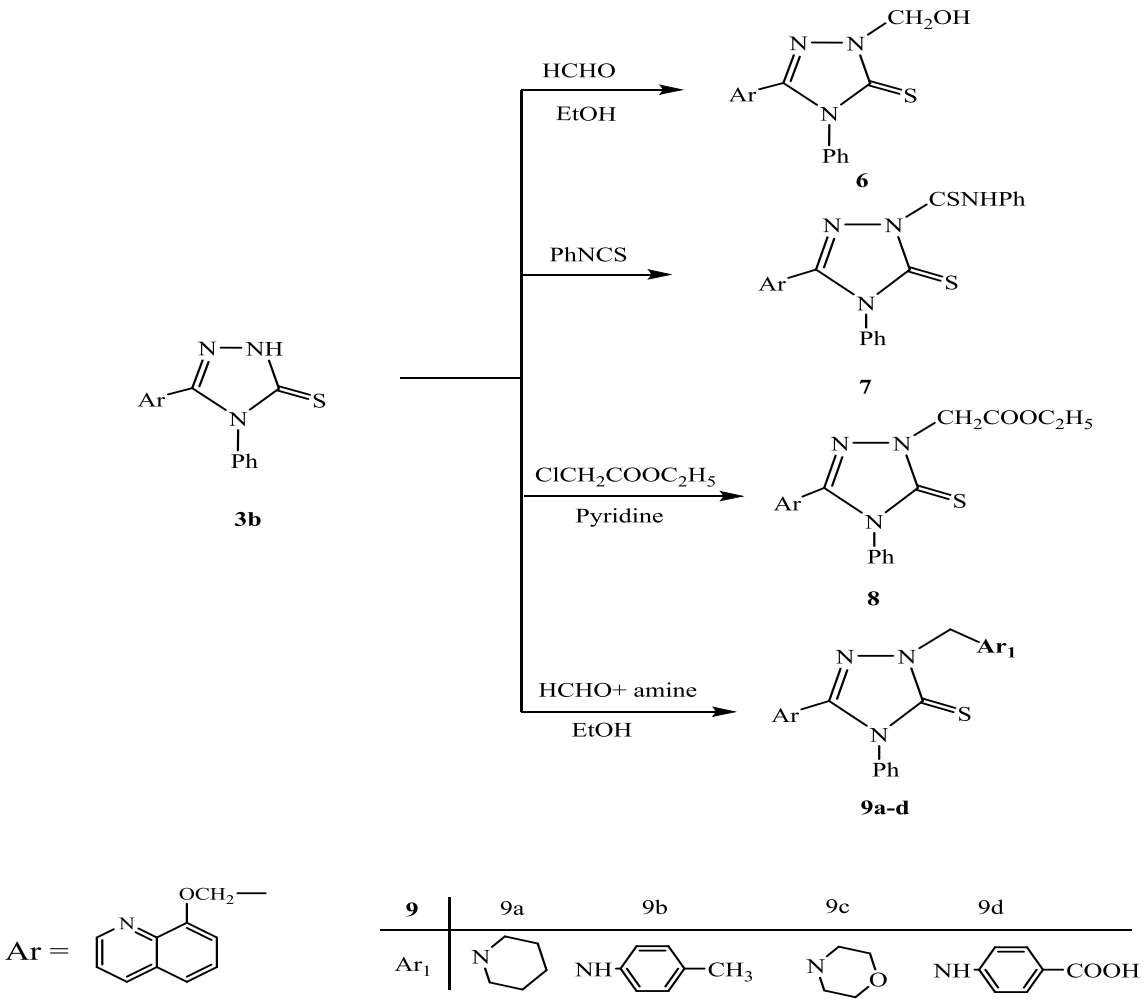


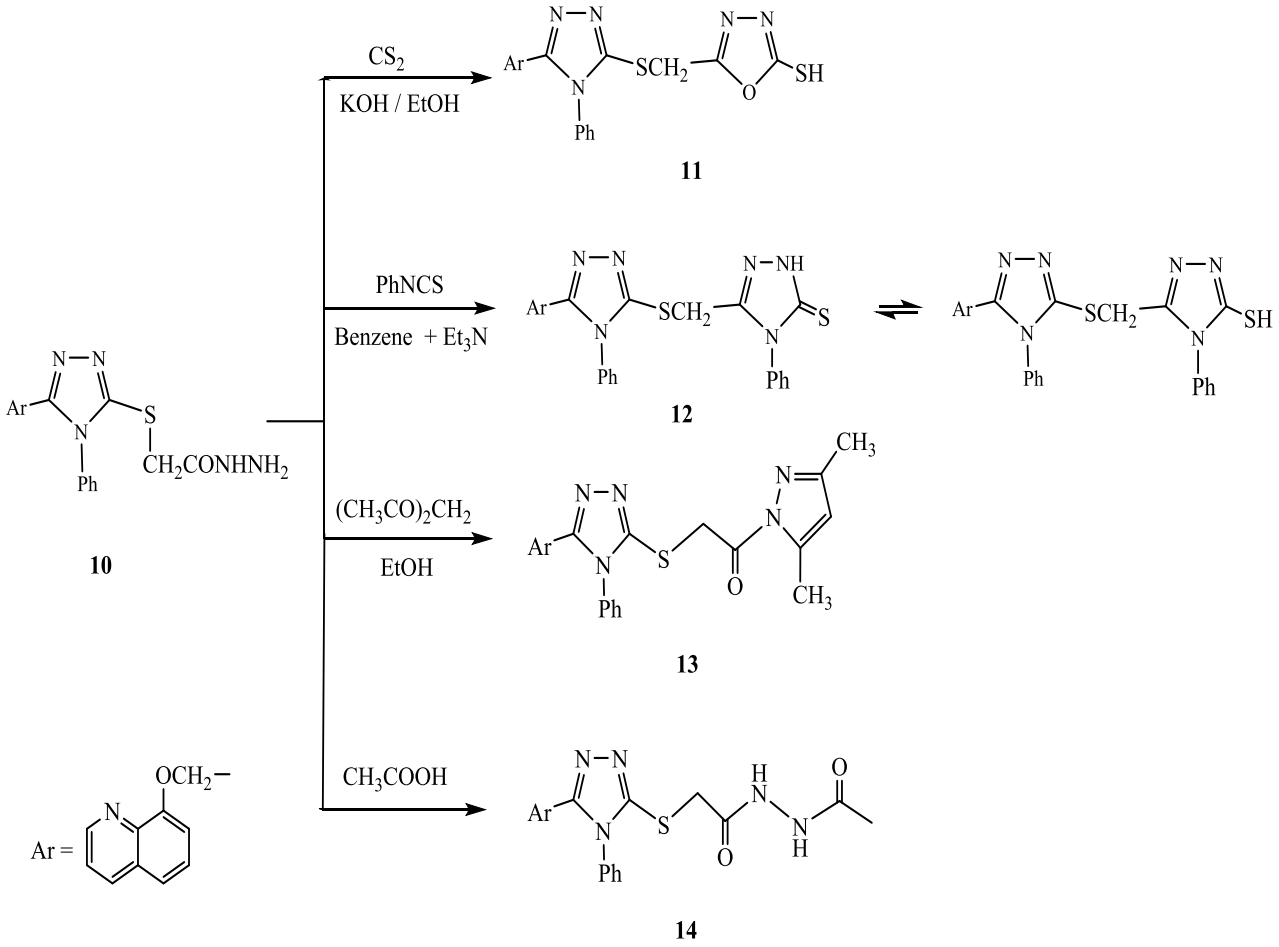
Scheme 1: Synthetic pathway of triazole **3.**



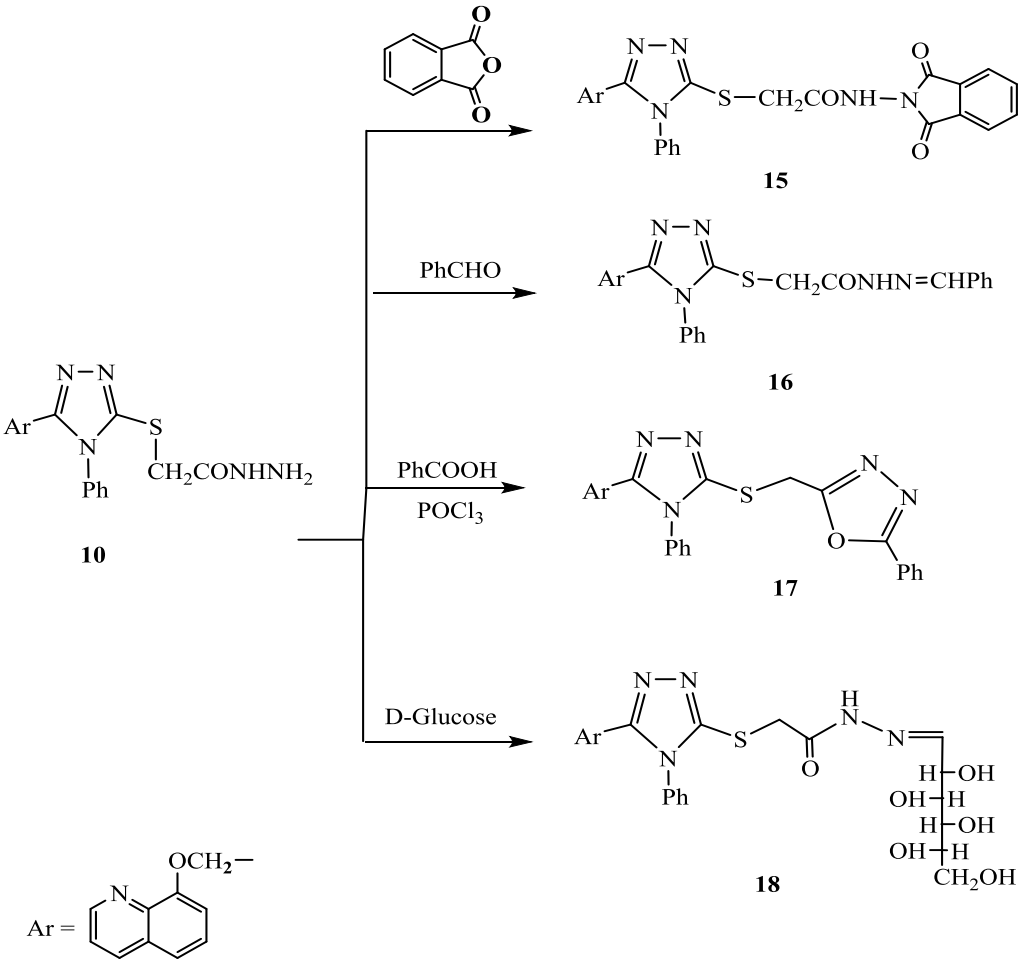
Scheme 2: Synthesis of triazole derivatives **4,5**.



Scheme 3: Synthesis of triazole derivatives **6-9**.



Scheme 4: Synthesis of triazole derivatives **11-14.**



Scheme 5: Synthesis of triazoles derivatives **15.18.**