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Synthesis and Investigation of Mass Spectra and Antimicrobial Activity of Some Azoles and Azines Based on (QUINOLINE-8-YLOXY) ACETOHYDRAZIDE

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Abstract: A new Azoles and Azines as pyrazole, thiazole, oxadiazole, triazole, thiadiazole, pyridazine and phthalazine based on quinolone moiety efficiently synthesized via simple and efficient chemical reactions of quinoline-8-yloxy acetohydrazide and quinolone-8-yloxy methyl oxadiazole acetohydrazide with electrophilic reagents in base medium using simple techniques and reagents. The structures of the new synthesized products were deduced based on their analytical, spectral data and by using the fragmentation pattern as a tool for supporting the chemical structures. In addition, the biological activity of the synthesized compounds as antimicrobial and antifungal were screened.

Keyboard: quinoline, 8-yloxy acetohydrazide, quinoline-8-yloxy methyl oxadiazole acetohydrazide, thiazole, oxazole, triazole, pyridazine, phthalazine and antimicrobial activity.

1 Introduction

Quinoline or benzo[b]pyridine is an azaheterocyclic aromatic compound and a weak tertiary base that can undergo both nucleophilic and electrophilic substitution reactions. The quinoline moiety is nontoxic to humans on oral absorption and inhalation and therefore occurs in several pharmacologically active compounds, displaying a wide range of biological activities. In particular, quinoline derivatives have been found to exhibit antimalarial, [1-4] antibacterial, [5-7] antiprotozoal, [8-11] anti-HIV, [12-14] anticancer [15-17] and antifungal activity, [18-20] pointing to their versatility as templates in drug discovery. In addition, among heterocyclic compounds, 1,3,4-Oxadiazole is apparently among the most significant heterocyclic cores. The 1,3,4-oxadiazole derivatives may act as ester and amide bioisosteres and hence are of interest in pharmaceutical and agrochemical fields. [21] The wide range of biological activities associated with 1,3,4-oxadiazoles include anti-viral, [22] antimicrobials, [23] antineoplastic, [24] fungicidal, [25] inhibitions of tyrosinase [26] and cathepsin K. [27] In addition, much attention has been focused on the oxadiazole core P-systems as electron-transporting and hole-blocking materials in the area of organic light-emitting diodes.[28] Further 1,3,4-oxadiazole heterocycles can contribute substantially in increasing the pharmacological activity by participating in hydrogen bonding interactions with the receptors. [29] In continuation to our research program about the synthesis of some azoles and azines of biological interest, [30-34] we reported herein the synthesis of some oxadiazole derivatives based on quinoline moiety.

2 Results and Disccussion

8-hydroxyquinoline was reacted with ethylchloroacetate in acetone/KOH and afforded ethyl-2-(quinoline-8-yloxy) acetate **(1)**, addition of hydrazine hydrate to the ester **(1)** produced quinoline acetohydrazide **(2)**, which was used as a good precursor to synthesize some azoles and azines.

Treatment of quinolineyloxy aetohydrazide **(2)** with carbon disulfide in the presence of alcoholic potassium hydroxide afforded the starting material 5-((quinolin-8-yloxy)methyl)-1,3,4-oxadiazole-2(3H)-thione **(3)**. IR spectrum of the oxadiazole **(3)** showed disappearance of carbonyl group and showed absorption bands at 3243, 1621 and 1121 due to ν NH, ν C=N and ν C=S and the mass spectrum showed molecular ion peak at $M^{\cdot+}$ (m/z) =260,73% and its

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fragmentation pattern of the mass spectrum supported the prepared compound (Fig. 1). ^{1}H NMR showed the signal of (exchangeable NH) at 6.4 and (CH2) at 2.37ppm besides the other signals.

Triazoles **(4a, b)**, and **(5)** were obtained by the treatment of oxadiazole **(3)** with primary amines as *p*-toluidine, *p*-anisidine and hydroxylamine hydrochloride in pyridine, respectively. IR spectrum of compounds **(4a, b)** showed the characteristic absorption bands of the molecule, while ^{1}H NMR spectrum of **(4a)** showed δ's of (exchangeable NH) at 5.30, and (CH_3) at 2.21 ppm. Also, ^{1}H NMR of **(4b)** showed δ's of (exchangeable NH) at 5.97 and (CH_3) at3.44 ppm.

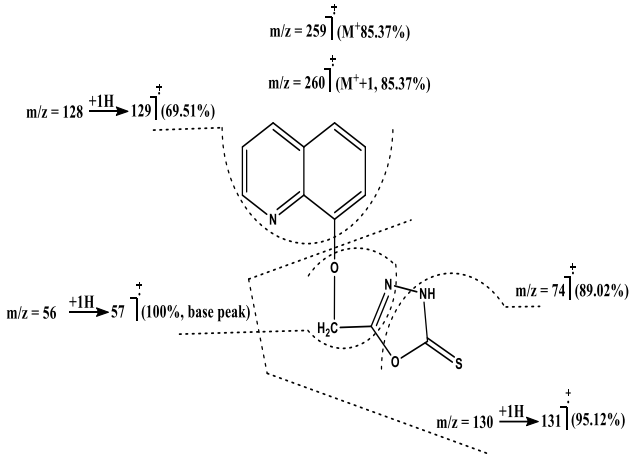


Fig. (1): Mass fragmentation pattern of compound (3)

4-hydroxy-5-((quinolin-8-yloxy)methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione **(5)** showed characteristic bands of (OH), (NH) and (C=S) at 3450, 3300, 1033 cm^{-1} ,respectively and ^{1}H NMR spectrum showed the exchangeable singlet of (OH) and (NH) at 10.52 and 6.11 ppm. besides the other proton signals.

Treatment of oxadiazole **(3)** with chloroacetic acid in the presence of potassium hydroxide yielded 1,3,4-oxadiazol-2-yl)thio)acetic acid **(6)** in a good yield. IR spectrum exhibited the presence of acid carbonyl at 1690, and (OH) at 3418 cm^{-1} besides the other characteristic bands of the compound. Its mass spectrum showed molecular ion peak ($M^{\cdot+}$+1) at 318 (50.93%), ($M^{\cdot+}$) at 317 (50.93%), the base peak at 174 (100%) and its fragmentation pattern supported the structure (Fig. 2).

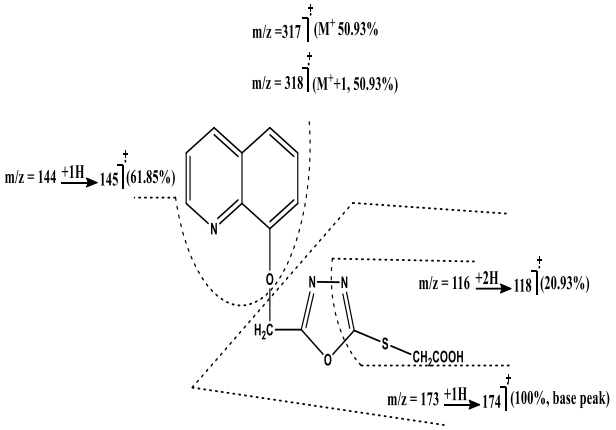


Fig. (2): Mass fragmentation pattern of compound (6)

Methylation of 1,3,4-oxadiazole-thione **(3),** was achieved using methyl iodide in the presence of catalytic amount of potassium hydroxide. IR spectrum of compound **(7)** showed disappearance of NH and C=S frequencies of 1,3,4-oxadiazole, and the mass spectrum showed molecular ion peak ($M^{\cdot+}$+1) at 274 (38.27%), ($M^{\cdot+}$) at 273.05 (39.51%), and the base peak at 158 (100%) and the mass fragmentation pattern supported the structure (Fig. 3).

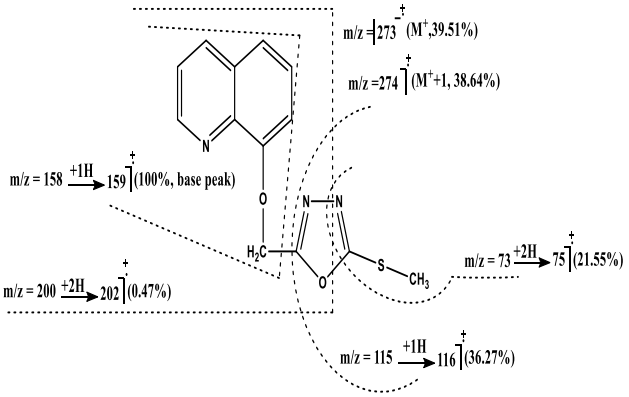


Fig. (3): Mass fragmentation pattern of compound (7)

1,2-bis((5-((quinolin-8-yloxy)methyl)-1,3,4-oxadiazol-2-yl)thio)ethane **(8)** was obtained in good yield via reaction of 1,3,4-oxadiazole-thione **(3)** with 1,2-dibromoethane in presence of a base such as sodium hydroxide. IR spectrum of **(8)** showed all the characteristic absorption bands of the compound, while mass spectrum showed molecular ion peak ($M^{\cdot+}$+1) at 545 (47.69%), ($M^{\cdot+}$) at 544 (74.62%), and the base peak at 159 (100%) and its fragmentation pattern supported the structure (Fig.4).

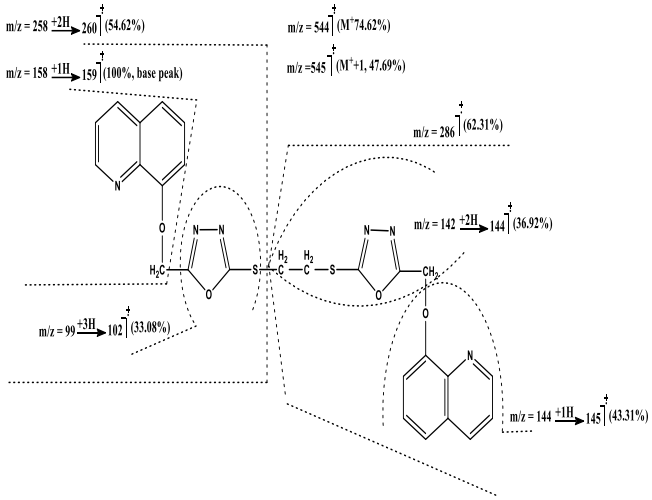


Fig. (4): Mass fragmentation pattern of compound (8)

Addition of ethylchloroacetate to 5-((quinolin-8-yloxy) methyl)-1,3,4-oxadiazole-2(3H)-thione **(3)** produced the ester derivative **(9)**, which was converted to the hydrazide **(10)** by refluxing with hydrazine hydrate in an alcoholic solution. IR spectrum of compound **(9)** showed the characteristic absorption band of carbonyl ester at 1746 cm^{-1} and IR spectrum of the hydrazide **(10)** showed two characteristic bands of ($NH^{\cdot s}$) at 3324 and 3225 cm^{-1} beside $(C=O)_{hydrazide}$ at 1672 cm^{-1} .^{1}H NMR spectrum showed exchangeable singlet at 9.0 ppm for (exchangeable NH) proton and at 5.87 ppm for (NH_2) protons.

Oxadiazole acetohydrazide **(10)** was utilized to prepare thiazolidine with different aryl groups via reaction with different aldehydes as benzaldehyde and 4-chlorobenzaldehyde gave the schiff's bases **(11a, b)**. IR spectrum of compound **(11a)** showed the characteristic absorption bands of carboxylic (OH) at 3323 cm^{-1}, (NH) at 3229 cm^{-1} and (C=O) at 1672 cm^{-1}. Its ^{1}H NMR spectrum showed the characteristic δ at 5.87 for (exchangeable NH). IR spectrum of **(11b)** showed the absorption bands of (OH, NH and C=O) groups at 3428, 3225 and 1682 cm^{-1} respectively, while its ^{1}HNMR showed the singlet *δ of* (exchangeable NH) at 6.25 ppm. These synthesized Schiff's bases were then cyclized using thioglycolic acid in ethanol and produced the target thiazolidine compounds **(12a, b)**. IR spectrum of compound **(12a)** showed two characteristic carbonyl groups at 1684 and 1643 cm^{-1} for the thiazolidine ring and amide, respectively. ^{1}H NMR spectrum of **(12a)** showed three methylene groups at 3.5, 3.7, 4.7 ppm. for thiazolidine ring and the singlet (exchangeable NH) at 11.2 ppm. IR spectrum of **(12b)** showed characteristic bands of (NH-OH) at 3414-3283 cm^{-1} besides the $(C=O)_{thiazolidine}$ at 1682 cm^{-1} and (C=O) of amide at 1625 cm^{-1}. The mass spectrum showed molecular ion peak at (m/z) = 528(6.07%), 529.9 (4.3%) and its mass fragmentation pattern confirmed the suggested structure (Fig. 5).

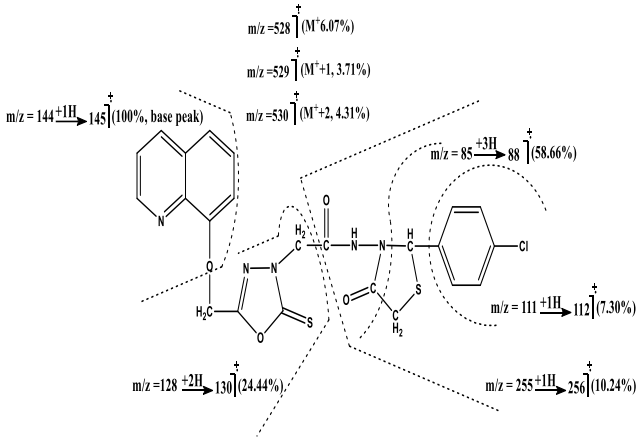


Fig. (5): Mass fragmentation pattern of compound (12b)

In addition, the acetohydazide **(10)** was utilized to prepare some azines such as phthalazines **(13)**, pyridazines **(14)**, and dihydro pyridazine **(15)**. 2-(2-(5-((quinolin-8-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetyl) -2,3-dihydrophthalazine-1,4-dione **(13)** was prepared by refluxing acetohydrazide **(10)** and phthalic anhydride in n-butanol. IR spectrum of compound **(13)** showed the characteristic absorption bands of the molecule and its mass spectrum showed molecular ion peak at (m/z) = 461.39 (38.64%) and the mass fragmentation pattern supported the suggested structure (Fig. 6).

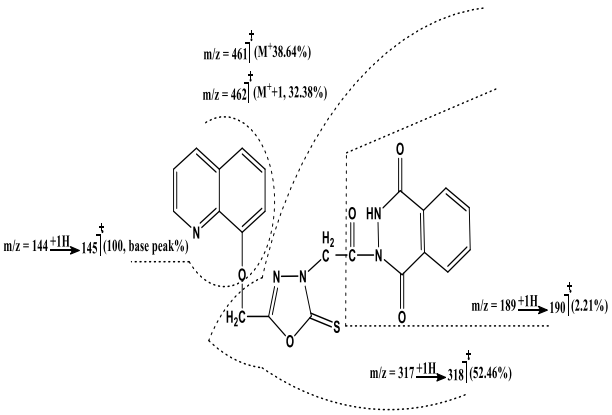


Fig. (6): Mass fragmentation pattern of compound (12b)

By the same way, the 1,2-dihydropyridazine-3,6-dione **(14)** and tetrahydropyridazine-3,6-dione **(15)** were synthesized *via* reaction of succinic anhydride and/or maleic anhydride with acetohydrazide **(10)** in n-butanol, respectively. IR spectrum of compound **(14)** showed the absorption bands of (NH) at 3226 and 1674 - 1655 cm^{-1} attributed to ν C=O's and its mass spectrum showed molecular ion peak at 412, (13.15%) related to ($M^{\cdot+}$+1), the base peak at 145 (100%) and the mass fragmentation pattern supported the suggested structure (Fig. 7). Also, IR spectrum of compound **(15)** reveals the presence of two different carbonyl groups, (C=O) of acetyl at 1671 cm^{-1} and the other (C=O) of pyrazolone at 1654 cm^{-1} and ^{1}H NMR spectrum showed the signal of (exchangeable NH) at 6.33 ppm.

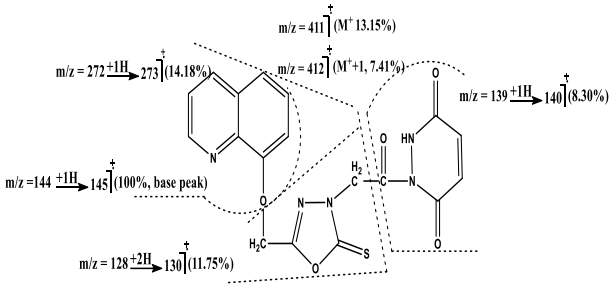


Fig. (7): Mass fragmentation pattern of compound (14)

3 Biological Activity

The antimicrobial activity of the synthesized compounds was evaluated ***in vitro*** using filter paper disk method [35]against two bacterial species namely Escherichia coli **EC** and Streptococus aureus **SA**, and against two fungal species, namely Aspergillus Niger, and Pencillium and the results are listed in (Table 1)**.**

The screening of antibacterial and antifungal activity showed that, all of the tested compounds showed from moderate to good inhibition against the tested antibacterial and antifungal pathogenic strains.

Table (1): Biological activity of the synthesized compounds

Cpd.	*Escherichia coli*	*Streptococcus*	*Aspergillus Niger*	*Penicillium*
4a	+++	+++	+++	+++
4b	+++	+++	+++	+++
5	++	++	++	+
6	+++	+++	+++	+++
7	+++	+++	+++	+++
8	++	++	++	+
9	+++	+++	++	++
10	+++	+++	++	++
11a	+++	++	++	++
11b	+++	++	+	++
12a	+++	++	++	++
12b	+++	++	++	++
13	+++	++	+	+
14	++	++	++	+
15	++	++	++	+

Compounds **(4a-15)** showed comparatively good activity against the two tested bacterial species Escherichia coli **EC** and Streptococcus aureus **SA**, while, compounds **(4a), (4b), (6), (7), (9), (10), (11a), (11b), (12a), (12b)** and **(13)** are the most active compounds against both fungal species Aspergillus Niger, and Pencillium.

On the other hand, compounds **(5), (8), (14),** and **(15)** exhibited moderate activity towards both bacterial and fungal species.

The good activity of some tested compounds as may be attributed to the presence of pharmacologically active, S-CH_2COOH and SH, NH, C=S, C=N and S-CH_3 groups and presence of quinolone and oxadiazole nucleolus.

4 Experimental

All 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 spectra were recorded in $CDCl_3$ or DMSO-d6 with TMS for 1H (300 MHz) an internal reference. Mass spectrometry was done on Thermo–Finnigan (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 biological evaluation of the products was carried out at Botany Department, Benha University, Benha, Egypt.

Synthesis of 5-((quinolin-8-yloxy)methyl)-1,3,4-oxadiazole-2(3H)-thione (3):

1,3,4-oxadiazole **3)** was synthesized *via* the reaction of ester **(1)** with hydrazine hydrate to produce hydrazide derivative **(2) (Scheme 1)** which further cyclized using carbon disulfide in presence of potassium hydroxide to afford 1,3,4-oxadiazole-2-thione **(3) (Scheme 2)**, (79%), mp 253–255 °C. IR (ν cm^{-1}) showed the following absorption bands at 3243, 3030, 2821, 1621 and 1121 due to ν NH, ν CH aromatic, ν CH aliphatic, ν C=N and ν C=S groups. Mass spectrum showed molecular ion peak ($M^{\cdot+}$+1) at 260 (73.17%) and the base peak at 57 (100%). ^{1}H NMR showed the signals of (Ar-H) at 8.83-7.61 ppm, (exchangeable NH) at 6.4 and (CH2) at 2.37ppm. Anal. Calcd for **$C_{12}H_9N_3O_2S$**: C, 55.59; H, 3.50; N, 16.21; S, 12.36 Found: C, 55.55%; H, 3.35%; N, 16.34%; S, 12.28%.

Synthesis of 5-((quinolin-8-yloxy)methyl)-4-(p-tolyl/p-methoxy)-4H-1,2,4-triazole-3-thione (4a) and/ or (4b):

An equimolar ratio of oxadiazole **(3)**, and p-toluidine and/ or p-anisidine (0.01 mole) were refluxed for 4 hrs. in ethanol (20 mL), concentrated and left to cool. The solid obtained filtered off, washed with ethanol and recrystallized from ethanol **(Scheme 2)**, (75%) yield, mp 235–237 °C. IR (ν cm^{-1}) showed the following absorption bands at 3053, 2987, 1621 due to ν CH aromatic, ν CH aliphatic, and ν C=N groups. ^{1}H NMR ($CDCl_3$) δ 's at 8.28 (d, 2H, Ar-H), 8.25 (d, 2H, Ar-H), 7.60-6.97 (m, 6H, Ar-H), 5.30 (s, 1H, NH), 3.74(s, 2H, OCH2), and 2.21(s, 3H, CH3). Anal. Calcd for **$C_{19}H_{16}N_4OS$**: C, 65.50; H, 4.63; N, 16.08; S, 9.20 Found: C, 65.32; H, 4.44; N, 16.10; S, 9.35.

4-(4-methoxyphenyl)-5-((quinolin-8-yloxy)methyl)-4H-1,2,4-triazole-3-thiol (4b):

Yield (77%), mp 210–212 °C. IR (ν cm^{-1}) showed the following absorption bands at 3050, 2995, 1625 cm^{-1} due to ν CH aromatic, ν CH aliphatic, and ν C=N group. ^{1}H NMR ($CDCl_3$) δ's at 8.78-6.99 (m, Ar-H), 5.97 (s, 1H, NH), 5.2(s, 2H, OCH_2), and 3.44 (s, 3H, CH_3). Anal. Calcd for Anal. Calcd for **$C_{19}H_{16}N_4OS$**: C, 62.62; H, 4.43; N, 15.37; S, 8.80 Found: C, 62.83; H, 4.46; N, 15.42; S, 8.85.

Synthesis of 4-hydroxy-5-((quinolin-8-yloxy)methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (5):

To a solution of **(3)** (0.01 mole) in pyridine, $NH_2OH.HCl$ (0.012 mole) was added, and then left to reflux for 5 hrs. and then poured on ice/H_2O and gave a solid product, which filtered off and crystallized from ethanol to yield hydroxyl triazole **(5) (Scheme 2),** (82%) yield, mp. 290–292 °C. IR (ν cm^{-1}) showed the following absorption bands at 3450, 3300, 3050, 2918, 1634, 1033 cm^{-1} due to ν OH, NH , ν CH aromatic, ν CH aliphatic, ν C=N, and ν C=S groups. ^{1}H NMR ($CDCl_3$) δ 10.52 (s, 1H, OH), 7.61-7.37 (m, 6H, Ar-H), 6.11 (s, 1H, NH) and 4.7(s, 2H, OCH2). Anal. Calcd for **$C_{12}H_{10}N_4O_2S$**: C, 59.50; H, 4.16; N, 23.13 Found: C, 59.41; H, 4.27; N, 23.24.

Synthesis of 2-((5-((quinolin-8-yloxy)methyl)-1,3,4-oxadiazol-2-yl)thio) acetic acid (6):

A solution of **(3)** (0.01 mole) in ethanol (15 mL) containing Potassium hydroxide (0.3 g) and was treated with chloroacetic acid (0.01 mole) in 5 ml ethanol. The reaction mixture was refluxed for 4 hrs. and the solvent was allowed to evaporate. The residue obtained was treated with H_2O (10 ml), acidified with dilute Hydrochloric acid to PH= 5, the precipitate was collected by filtration, and recrystallized by ethanol **(Scheme 2)**, IR spectrum of compound **(6)** exhibited the presence of carbonyl stretching vibration band at 1690, and (OH) of carboxylic group content at 3418 cm^{-1} besides the other characteristic bands of the compound**.** Mass spectrum of compound **(6)** showed molecular ion peak ($M^{\cdot+}$) at 317 (50.93%) ($M^{\cdot+}$+1) at 318 (50.93%), and the base peak at 174 (100%) and the fragmentation pattern supported the prepared structure. Anal. Calcd for **$C_{14}H_{11}N_3O_4S$**: C, 52.99; H, 3.49; N, 13.24; S, 10.10 Found: C, 52.78; H, 3.38; N, 13.42; S, 10.13.

Synthesis of 2-(methylthio)-5-((quinolin-8-yloxy)methyl)-1,3,4-oxadiazole (7):

Compound **(3)** (0.01 mole) was dissolved in ethanol (20 ml), Sodium hydroxide (*1N*) (2 ml) and methyl iodide (0.2 ml) were added, then the mixture was stirred at ambient temperature for 5 hrs., the excess of solvent was evaporated, H_2O (5 ml) was added, cooled down and the precipitate was collected by filtration and recrystallized from ethanol **(Scheme 2)**, IR spectrum of compound **(7)** showed absorption bands at 3205, 2907, 1623, 1115 due to ν NH_2, ν CH aliphatic, ν C=N, and ν C=S groups, its mass spectrum showed molecular ion peak ($M^{\cdot+}$) at 378 (83.95%), ($M^{\cdot+}$+1) at 379 (74.07%), base peak at 144 (100%) and the fragmentation pattern of this compound supported the suggested structure. Anal. Calcd for **$C_{13}H_{11}N_3O_2S$**: C, 57.13; H, 4.06; N, 15.37; S, 11.73 Found: C, 57.25; H, 4.10; N, 15.42; S, 11.91.

Synthesis of 1,2-bis((5-((quinolin-8-yloxy)methyl)-1,3,4-oxadiazol-2- yl)thio) ethane (8):

Oxadiazole **(3)** (0.025 mole) of dissolved in DMSO (10 mL), (0.5 mL) of 30% NaOH and 1,2-dibromoethane (0.2 mL) were added. The mixture stirred at 60 ˚C for 2 hrs., then H_2O (10 ml) was added, the precipitate formed was collected by filtration and crystallized with ethanol **(Scheme 2)**, IR of compound **(8)** showed frequencies at 2984, and 1619 due to ν CH aliphatic, and ν C= N groups, besides the other characteristic peaks of the compound (Chart 11), its mass spectrum showed molecular ion peak ($M^{\cdot+}$) at 544 (74.62%), ($M^{\cdot+}$+1) at 545 (74.69%), base peak at 159 (100%) and the fragmentation pattern supported this structure**.** Anal. Calcd for **$C_{26}H_{20}N_6O_4S_2$** :C, 62.62; H, 4.43; N, 15.37; S, 8.80 Found: C, 62.44; H, 4.26; N, 15.55; S, 8.92.

Synthesis of Ethyl 2-(5-((quinolin-8-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol3(2H)-yl)acetate (9)

An equimolar ratio of **(3)** (0.01) and ethylchloroacetate (0.01mole) in dry acetone (40 mL) and in presence of dry K_2CO_3 (0.04 mole), were allowed to reflux for 5 hrs., concentrated and cooled and then poured into H2O to give a solid product, which filtered off, dried, and crystallized from ethanol **(Scheme 2)**, (83%) yield, mp. 76–78 °C. IR (ν cm^{-1}) showed the following absorption bands at 3051, 2978, 1746, 1156, 1112, 1021 due to ν CH aromatic, ν CH aliphatic, ν C=O, ν C=S and ν C-O-C groups. Mass spectrum showed molecular ion peak ($M^{\cdot+}$+1) at 346 (15.4%), ($M^{\cdot+}$) at 345 (15.98%), and the base peak at 187 (100%). Anal. Calcd for **$C_{16}H_{15}N_3O_4S$**: C, 55.64; H, 4.38; N, 12.17; S, 9.28 Found: C, 55.77; H, 4.59; N, 12.28; S, 9.35.

Synthesis of 2-(5-((quinolin-8-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetohydrazide (10)

A solution of **(9)** (0.01 mole) in ethanol (20 ml) and hydrazine hydrate (0.01 mole) was refluxed for 6 hrs. After

cooling, the solid separated washed with water, dried and recrystallized from ethanol **(Scheme 3)**. (80%), mp 144–146 °C. Anal. Calcd for **$C_{14}H_{13}N_5O_3S$**: C, 50.75; H, 3.95; N, 21.14; S, 9.68 Found: C, 50.92; H, 3.84; N, 21.28; S, 9.78, (80%), mp. 144–146 °C. IR (ν cm^{-1}) showed the following absorption bands at 3324-3225, 3056, 2922, 1672, 1143 due to ν $NHNH_2$, ν CH aromatic, ν CH aliphatic, ν C=O, ν C=S, and ν C-O-C groups. ^{1}H NMR (DMSO) δ 9.0 (s, NH), 8.88-7.37 (m, Ar-H), 5.87 (br, 1H, NH_2), 4.87 (s, 2H, OCH2), 4.02 (s, 2H, CH2CO). Anal. Calcd for **$C_{14}H_{13}N_5O_3S$**: C, 50.75; H, 3.95; N, 21.14; S, 9.68 Found: C, 50.92; H, 3.84; N, 21.28; S, 9.78.

Synthesis of N'-benzylidene-2-(5-((quinolin-8-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetohydrazide (11a)

A mixture of the hydrazide **(10)** (0.01 mole) and benzaldehyde (0.01 mole) in ethanol (20 mL) and in presence 2-3 drops of glacial acetic acid was refluxed for 4 hrs. After completion of the reaction, the solvent evaporated and residue recrystallized from ethanol **(Scheme 3)**, (78%), mp 83–85°C. IR (ν cm^{-1}) showed the following absorption bands at 3229, 3052, 2923, 1672, 1624 and 1140 due to ν NH, ν CH aromatic, ν CH aliphatic, ν C=O, ν C=N and ν C=S groups. ^{1}H NMR (DMSO) δ8.83-7.43 (m, Ar-H), 5.87 (s, 1H, NH) 4.71 (s, 2H, OCH2), 4.01 (s, 2H, CH2CO). Anal. Calcd for **$C_{21}H_{17}N_5O_3S$**:C, 60. 13; H, 4.09; N, 16.70, S, 7.64 Found: C, 60. 25; H, 4.12, N, 16.90, S, 7.85.

N'-(4-chlorobenzylidene)-2-(5-((quinolin-8-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetohydrazide (11b)

Compound **(10)** (0.01 mole) was treated with 4-chlorobenzaldehyde (0.01 mole) in ethanol (20 mL) and in presence of 2-3 drops of glacial acetic acid refluxed for 4 hrs. After completion of the reaction, the solvent evaporated and the filtered solid was collected by filtration and crystallized by ethanol **(Scheme 3)**, (74%) yield, mp. 97–99 °C. IR (ν cm^{-1}) showed the following absorption bands at 3225, 2915 and 1682due to ν NH, ν CH aliphatic and ν C=O. ^{1}H NMR (DMSO) δ 8.75-7.45 (m, Ar-H), 6.25 (s, 1H, NH), 5.43 (s, 2H, OCH2), 4.46 (s, 2H, CH2CO), 4.13 (s, 2H, CH2). Anal. Calcd for **$C_{21}H_{16}ClN_5O_3S$**: C, 55.57; H, 3.55; N, 15.43; S, 7.06 Found: C, 55.62; H, 3.78; N, 15.63; S, 7.30.

Synthesis of N-(4-oxo-2-phenylthiazolidin-3-yl)-2-(5-((quinolin-8-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetamide (12a)

To a solution of **(11a)** in ethanol, thioglycolic acid (0.01 mole) was added. The reaction mixture refluxed for 3 hrs. After cooling, the product obtained was collected by filtration and recrystallized by ethanol **(Scheme 3)**, (75%) yield, mp 105–107 °C. IR (ν cm^{-1}) showed the following absorption bands at 3296, 2926, 1684, and 1643 due to ν NH, ν CH aliphatic, ν C=O, and ν C=S groups. ^{1}H NMR (DMSO) δ 8.71-7.37 (m, Ar-H), 6.39 (s, 1H, NH), 5.65 (s, 2H, OCH2), 4.73 (s, 2H, CH2CO), 4.1 (s, 2H, CH2). Anal. Calcd for **$C_{23}H_{19}N_5O_4S_2$**: C, 55.97; H, 3.88; N, 14.19; S, 12.99. Found: C, 56.01; H, 3.71; N, 14.23; S, 13.13.

Synthesis of N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-2-(5-((quinolin-8-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl) acetamide (12b)

(0.01 mol) of **(11b)** in ethanol, thioglycolic acid (0.01 mole) was added and the reaction mixture was allowed to reflux for 3 hrs. After that, the mixture cooled and the product obtained filtered off, and recrystallized from ethanol **(Scheme 3)**, (78%) yield, mp. 125–127 °C. IR (ν cm^{-1}) showed the following absorption bands at 3284, 2924, 1683, and 1625 due to ν NH, ν CH aliphatic, ν C=O, and ν C=N groups. Mass spectrum showed molecular ion peak ($M^{\cdot+}$+2) at 530 (4.31%), ($M^{\cdot+}$+1) at 529 (3.7%), ($M^{\cdot+}$) at 528 (6.07%), and the base peak at 145 (100%). Anal. Calcd for **$C_{23}H_{18}ClN_5O_4S_2$**: C, 52.32; H, 3.44; N, 13.26; S, 12.14 Found: C, 52.56; H, 3.65; N, 13.33; S, 12.27.

Synthesis of 2-(2-(5-((quinolin-8-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetyl)-2,3-dihydrophthalazine-1,4-dione(13)

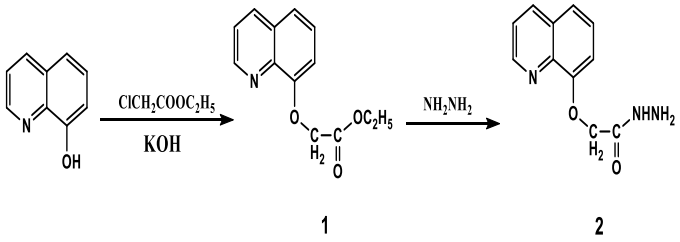
A mixture of hydrazide **(10)** (0.01 mol), and phthalic anhydride (0.01 mole) in n-butanol was refluxed for 6 hrs. After cooling, the solid obtained filtered off, washed, and recrystallized from butanol **(Scheme 3)**, (88%) yield, mp. 92–94 °C. IR (ν cm^{-1}) showed the following absorption bands at 3292, 3050, 2924, 1762, and 1655 cm^{-1} due to ν NH, ν CH aromatic, ν CH aliphatic, and ν C=O's groups. Mass spectrum showed molecular ion peak ($M^{\cdot+}$+1) at 462(32.38%), ($M^{\cdot+}$) at 461(38.64%), and the base peak at 145 (100%). Anal. Calcd for **$C_{22}H_{15}N_5O_5S$**: C, 57.26; H, 3.28; N, 15.18; S, 6.95 Found: C, 57.44 H, 3.51 N, 15.29; S, 7.01.

Synthesis of 1-(2-(5-((quinolin-8-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetyl)-1,2-dihydropyridazine-3,6-dione (14)

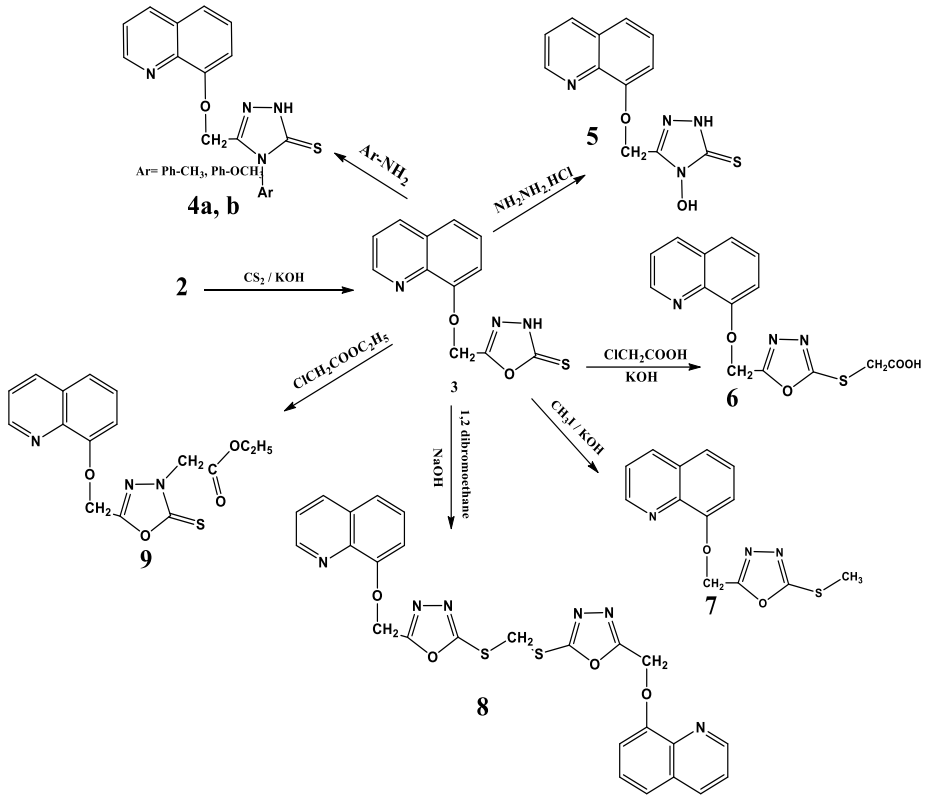
To a solution of (0.01 mole) of compound **(10)** in n-butanol (20 ml), (0.01 mole) of maleic anhydride was added. The mixture was refluxed for 6 hrs. After cooling, the solid product obtained by filtration and recrystallized from ethanol **(Scheme 3)**, (83%), mp. 169–171 °C. IR (ν cm^{-1}) showed the following absorption bands at 3226, 2914, 1674, 1655 and 1114, 950 due to ν NH , ν CH aliphatic, ν C=O's and ν C-O-C group. Mass spectrum showed molecular ion peak ($M^{\cdot+}$+1) at 412 (13.15%), and the base peak at 145 (100%). Anal. Calcd for **$C_{18}H_{13}N_5O_5S$**: C, 52.55; H, 3.19; N, 17.02; S, 7.79 Found: C, 52.74; H, 3.32; N, 17.20; S, 7.99.

Synthesis of 1-(2-(5-((quinolin-8-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetyl) tetrahydropyridazine-3,6-dione (15)

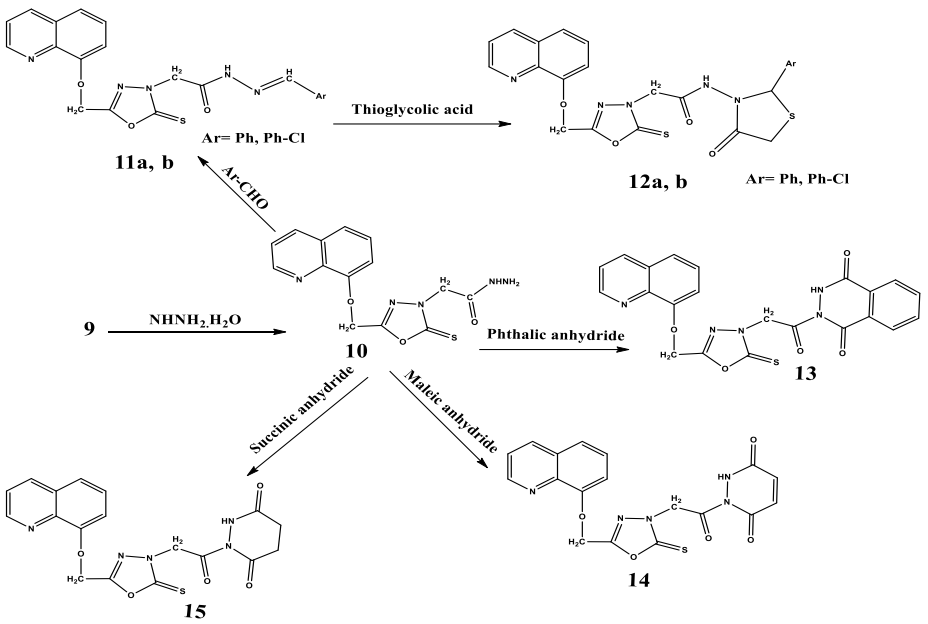
A solution of **(10)** (0.01 mole), and succinic anhydride (0.01 mole) in n-butanol was refluxed for 6 hrs. After cooling, the solid obtained was filtered off, washed, and recrystallized from ethanol **(Scheme 3)**, (86%) yield, mp. 184–186 °C. IR (ν cm^{-1}) showed the following absorption bands at 3294, 2922, 1671, and 1654 cm^{-1}due to ν NH, ν CH aliphatic and ν C=O's. ^{1}H NMR (DMSO) δ 8.86 (t, 2H, Ar-H), 8.36 (t, 2H, Ar-H), 7.6-7.4 (m, Ar-H), 6.33 (s, 1H, NH), 5.85 (s, 2H, OCH_2), 5.43 (s, 2H, CH_2CO). Anal. Calcd for **$C_{18}H_{15}N_5O_5S$**: C, 52.30; H, 3.66; N, 16.94; S, 7.76 Found: C, 52.51; H, 3.89; N, 17.02; S, 7.95.



Scheme 1



Scheme 2



Scheme 3

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