New *N*-(Aryl)-5-((quinolin-8-yloxy)methyl)-1,3,4-oxa/Thiadiazol-2-amines and 4-Aryl-5-((quinolin-8-yloxy)methyl)-2*H*-1,2,4-triazole-3(4*H*)-thiones, Synthesis and Characterization

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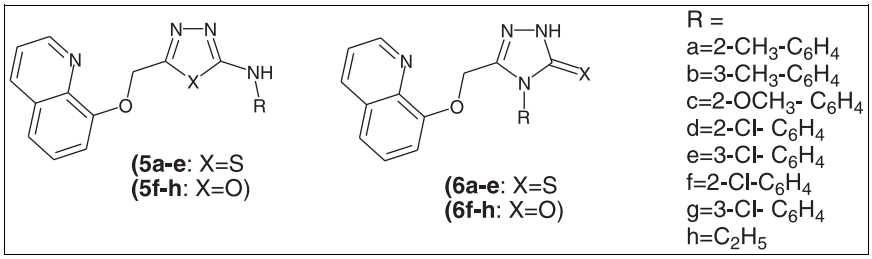
Received May 29, 2012
DOI 10.1002/jhet.1817
Published online 17 March 2014 in Wiley Online Library (wileyonlinelibrary.com).



In this study, methyl 2-(quinolin-8-yloxy) acetate (**2**) obtained by reaction of 8-hydroxyquinoline (**1**) with methyl chloroacetate was condensed with hydrazine hydrate to afford the carbohydrazide (**3**). Thio/semicarbazide derivatives (**4a–g**) were obtained by treatment of the **3** with substituted phenyl iso/thioisocyanates. The **4a–g** on acidic and basic intramolecular cyclization led to *N*-(aryl)-5-((quinolin-8-yloxy)methyl)-1,3,4-oxa/thiadiazol-2-amines (**5a–g**) and 4-aryl-5-((quinolin-8-yloxy)methyl)-2*H*-1,2,4-triazole-3(4*H*)-thiones (**6a–g**), respectively. All the synthesized compounds were characterized by spectroscopic techniques and elemental analyses. The thiosemicarbazide (**4c**) was also confirmed by X-ray crystallography.

J. Heterocyclic Chem., **51**, 1357 (2014).

INTRODUCTION

The synthesis of new compounds and evaluation of their biological and pharmacological activities are the major goals of drug improvement projects. Quinoline alkaloids are extensively distributed in nature and exhibit significant biological activities [1,2]. Compounds containing quinoline nucleus are the key building blocks for synthesis of a huge variety of compounds of vital importance in drug industry; therefore, structural modifications in this structural motif leading to the molecular diversity is important in drug designing [3–5]. The quinoline derivatives have been used as immuno-suppressive [6], hypocholesterolemic [7], and nonnucleoside anti-Hepatitis B virus agents [8]. Effect of a natural quinoline alkaloid, skimmianine, in histamine release from rat mast cells has been studied [9], and 2-mercapto/2-selenobenzoquinoline-3-carbaldehydes have shown wound healing, antibacterial, DNA binding, and *in vitro* antioxidant activities [10].

Similarly, oxa/thiosemicarbazides are the key intermediate for the synthesis of a number of heterocyclic systems such as diazoles, triazoles, and imino thiazolidinones [11,12].

Oxa/thiadiazole is another versatile heterocyclic scaffold of tremendous interest because of its significant contribution in the biological and pharmaceutical fields [13,14] with prominent potential as antituberculosis [15], antidepressant, [16] and antiproliferative agents [17]. The Cefozopran, a fourth-generation cephalosporin, shows remarkable activity against Gram negative and Gram positive bacteria [18]. The inhibitory effect of benzoyl thiadiazole derivatives on C-steel has been studied by electrochemical measurements such as open circuit potential, Tafel polarization, and electrochemical impedance spectroscopy [19]. A number of methods are available for synthesis of oxadiazoles/thiadiazoles including the solid-phase synthesis of substituted 1,3,4-thiadiazoles through resin-bound thiosemicarbazide synthesis [20]. A green protocol has been reported for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles from thiobenzamides using *N*-benzyl-DABCO-tribromide in aqueous media [21].

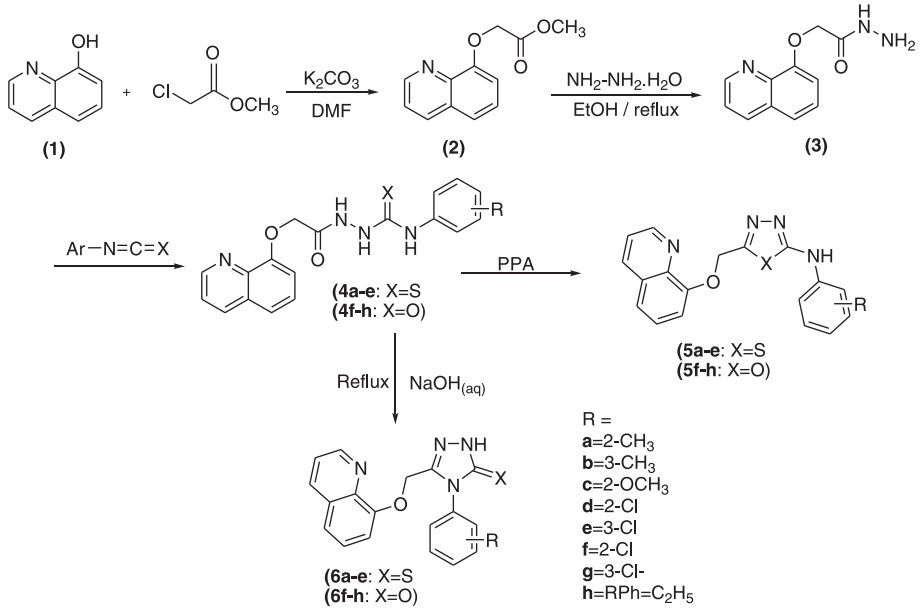
The triazole ring existing in 1,2,3-triazole and 1,2,4-triazole isomeric forms [22] is found in a number of antifungal drugs such as isavuconazole [23], voriconazole [24], and plants protection fungicides such as paclobutrazol [25], epoxiconazole, tebuconazole, flusilazole, propiconazole, and cyproconazole [22].

Taking the drug-like properties and synthetic accessibility of individual heterocyles into account, some hybrid structures of 1,3,4-oxa/thiadiazol-2-amines and 1,2,4-triazole-3(4*H*)-thiones with quinoline were prepared and reported in this article.

RESULTS AND DISCUSSION

As shown in Scheme 1, commercially available quinolin-8-ol (**1**) was treated with methyl chloroacetate using K_2CO_3 in DMF to afford methyl 2-(quinolin-8-yloxy)acetate (**2**)

Scheme 1. Synthetic route to quinolinyloxy 1,3,4-oxa/thiadiazol amines and 1,2,4-triazolone/thiones.



that was smoothly converted into 2-(quinolin-8-yloxy) acetohydrazide (**3**) by refluxing with hydrazine hydrate in ethanol. Treatment of **3** with ethanolic solutions of arylisocyanates or aryl isothiocyanates at reflux afforded quinolinyloxythiosemicarbazides (**4a–4e**) and quinolinyloxy semicarbazides (**4f–4h**), respectively, in excellent yields. In the FTIR spectrum of a typical thiasemicarbazide (**4c**), appearance of peaks for NH stretchings in the range 3332–3257, C-H stretching of methylenic group at 2948 cm^{-1}, and carbonyl and thiocarbonyl at 1688 and 1232 cm^{-1}, respectively, was observed. In ^1H NMR, the NH peaks appeared at 14.35, 10.12, and 9.45 ppm, aromatic protons in the range of 8.85–7.79, and singlets for methylenic and methoxy protons at 4.88 ppm and 3.91 ppm. In ^{13}C NMR, the thiocarbonyl and carbonyl carbons were noted at 174.8 and 167.6 ppm, respectively, whereas the methylenic and the methoxy carbons appeared at 68.2 and 55.4 ppm. In GC–MS, the molecular ion peak was observed at *m/z* 382 and base peak at *m/z* 145, whereas the other important peaks appeared at *m/z* 107, 77, and 31. The structure was finally confirmed unambiguously by X-ray crystallography. The crystal structure of 1-(2-(quinolin-8-yloxy)acetyl)-4-(2-methoxyphenyl)thiosemicarbazide (**4c**) is shown in Figure 1. It crystallizes in the monoclinic space group P $2_1/n$ with unit cell dimensions at a = 8.1506(4) Å, α = 90°, b = 13.8190(4), β = 101.669(4), c = 19.2381(10) Å, γ = 90°. Data were collected on a STOE IPDS II two-circle diffractometer with graphite-monochromated MoKα radiation. An empirical absorption correction was performed using the MULABS [26] option in PLATON [27]. The structure was solved by direct methods using the program SHELXS [28] and refined against F^2 with full-matrix least-squares techniques using the program SHELXL-97 [29]. There were 26,385 reflections measured, 1548 unique (R_{int} = 0.0660) that were used in all calculations. Final R values: $R1 = 0.0452$, $wR(F^2) = 0.1176$ ($I > 2$ (I)); $R1 = 0.0524$, wR (F^2) = 0.1219 (all data). The molecular conformation is stabilized by an N-H. . .O hydrogen bond. An ethanol molecule is bonded to **4c** by an N-H. . .O and an O-H. . .N hydrogen bonds. Molecules of **4c** form centrosymmetric dimers connected by N-H. . .O hydrogen bonds [30].

Acid-catalyzed intramolecular cyclization of quinolinyloxy thiosemicarbazide (**4a–4e**) and quinolinyloxy semicarbazides (**4f–4h**) using polyphosphoric acid afforded quinolinyloxy 1,3,4-oxadiazole amines (**5a–4e**) and 1,3,4-thiadiazole amines (**5f–5h**), respectively. The absorption bands associated with different functional groups appeared in the expected regions. Considering compound (**5g**), the structure was supported by FTIR with stretching for NH group at 3292 and methylenic

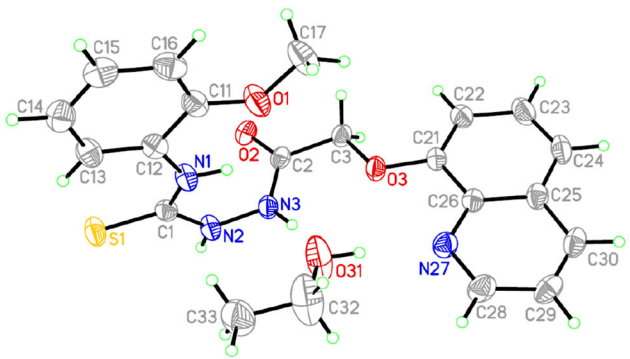


Figure 1. Crystal structure of 1-(2-(quinolin-8-yloxy)acetyl)-4-(2-methoxyphenyl)thiosemicarbazide (**4c**). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

CH_2 at 2930 cm^{-1}. In ^1H NMR spectrum, one NH signal at 10.88 ppm instead of three NH protons was noted besides the singlet for methylenic protons at 5.84 ppm. In ^{13}C NMR, the methylenic carbon appeared at 65.3 ppm, and disappearance of carbonyl carbon was noted.

The intramolecular cyclization in basic medium led to the synthesis of quinolinyloxy1,2,4-triazolones (**6a–6e**) or 1,2,4-thiones derivatives (**6f–6h**). In FTIR spectrum of **6b**, appearance of NH stretching at 3258 cm^{-1}, CH stretching at 2929 cm^{-1}, and thiocarbonyl stretching at 1254 cm^{-1} was observed. ^1H NMR signals at 5.57 ppm, and 2.36 ppm signal was assigned to methylenic and aromatic methyl protons. Furthermore, disappearance of two NH signals and presence of only one NH signal at 9.75 ppm was observed. ^{13}C NMR spectrum indicated thiocarbonyl at 168.4, and methylenic and methyl carbon at 67.9 and 21.4 ppm, respectively.

EXPERIMENTAL

Melting points of all synthesized compounds were determined in open capillary using a digital Gallenkamp (SANYO) model MPD BM 3.5 apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were determined at 300 MHz using a Bruker AM-300 spectrophotometer. FTIR spectra were measured on FTS 3000 MX spectrophotometer and mass spectra (EI, 70 eV) on a GC–MS instrument.

Synthesis of methyl 2-(quinolin-8-yloxy) acetate (2). To a solution of 8-hydroxyquinoline (1.0 mmol) in DMF, methyl chloroacetate (1.2 mmol) was added dropwise using K_2CO_3 (1.2 mmol) as the base. The reaction was heated on a water bath for 8 h. The reaction mixture was cooled to room temperature and poured onto ice cold water. The product was precipitated out, filtered, washed with cold water, and recrystallized by aqueous ethanol afford (**2**). Yield: 85%; mp 70–71°C; IR: 2928 (CH_2), 1715 (C═O), cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.77–8.64 (m, 1H, ArH), 8.458–8.31 (m, 1H, ArH), 7.71–7.55 (m, 3H, ArH), 7.20–7.12 (m, 1H, ArH), 5.04 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3).

Synthesis of 2-(quinolin-8-yloxy)acetohydrazide (3). Hydrazine hydrate (1.7 mmol) was added to the suspension of methyl 2-(quinolin-8-yloxy)acetate (1 mmol) in ethanol and refluxed for 14 h. The reaction mixture was cooled to room temperature and concentrated under vacuum. The product was precipitated out and recrystallized from ethanol. mp 140–142°C. IR (cm^{-1}): 3326–3257 (N-H, $NHNH_2$), 1062 (C-OC), 1185 (N-N); ^1H NMR (DMSO-d_6): 8.09 (s, IH, CONH), 7.72–7.47 (m, 6H, ArH), 4.88 (s, 2H, OCH_2), 4.45 (s, 2H, NH_2); *Anal*. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.72; H, 5.00; N, 19.29. Found: C, 60.69; H, 5.09; N, 19.41%.

Synthesis of 1-(2-(quinolin-8-yloxy)acetyl)-4-substituted semicarbazides (4a–e) and thiosemicarbazides (4f–4h): general procedure. To a stirred solution of 2-(quinolin-8-yloxy) acetohydrazide (0.461 mmol) in methanol, suitably substituted isothiocyanate or isocyanate (0.461 mmol) was added slowly with continuous stirring and refluxed for 10–12 h. The completion of reaction was monitored by TLC. Reaction mixture was cooled to room temperature, and methanol was evaporated under vacuum, crude product washed with distilled water, and recrystallized by aqueous ethanol or petroleum ether ethyl acetate (8:2) mixture.

Synthesis of *N*-(substituted phenyl)-5-((quinolin-8-yloxy) methyl)-1,3,4-oxadiazolamines (5a–e) and 1,3,4-thiadiazolamines (**5f–h**): general procedure. Semicarbazides (**4a–e**) or thiosemicarbazides (**4f–4h**) (0.88 mmol) was stirred at 90°C with polyphosporic acid (2.65 g) for 24 h in a water bath. After completion, the reaction mixture was poured on crushed ice and stirred for 10 min. The reaction mixture was extracted with ethyl acetate two times, and the combined extract was thoroughly washed with sodium hydrogen carbonate (5%). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The products (**4a–h**) were recrystallized from ethanol.

Synthesis of 4-(substituted phenyl)-5-((quinolin-8-yloxy) methyl)-2*H*-1,2,4- triazolones (6a–e) and 1,2,4-thiones (**6f–6h**): general procedure. 1-(2-(Quinolin-8-yloxy)acetyl)-4-substituted semicarbazides (**4a–e**) or thiosemicarbazides (**4f–4h**) (0.51 mmol) was refluxed in aqueous sodium hydroxide solution (4 N, 5 mL). The reaction progress was monitor by TLC. After completion, the reaction mixture was cooled to room temperature and filtered. The filtrate was neutralized by hydrochloric acid (4 N) to precipitate out the product, filtered, washed with distilled water, and recrystallized by aqueous ethanol.

1-(2-(Quinolin-8-yloxy)acetyl)-4-o-tolylthiosemicarbazide (4a). Yield: 65%; mp 253–255°C; IR: 3335–3219 (NH), 2958 (CH_2), 1738, (C═O), 1238 (C═S), 1178 (C-N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 14.35, 10.26, 9.45 (3NH), 8.75–8.69 (m, 1H, ArH), 8.45–8.26 (m, 1H, ArH), 7.76–7.45 (m, 4H, ArH), 7.33–7.25 (m, 4H, ArH), 4.91 (s, 2H, CH_2), 2.74 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 166.5, 155.4, 151.4, 147.6, 139.3, 138.2, 133.8, 131.4, 129.3, 129.0, 128.2, 126.9, 125.2, 122.6, 122.2, 121.3, 67.9, 21.4. *Anal*. Calcd for $C_{19}H_{18}N_4O_2S$: C, 62.28; H, 4.95; N, 15.29; S, 8.75. Found: C, 62.15; H, 4.77; N, 15.18; S, 8.90.

1-(2-(Quinolin-8-yloxy)acetyl)-4-m-tolylthiosemicarbazide (4b). Yield: 63%; mp 142–144°C; IR: 3392–3271 (NH), 2945 (CH_2), 1687 (C═O), 1258 (C═S), 1184 (C-N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 14.11, 10.44, 9.69 (3NH), 8.89–8.88 (m, 2H, ArH), 8.37–8.31 (m, 1H, ArH), 7.61–7.41 (m, 5H, ArH), 7.34–6.97 (m, 2H, ArH), 4.91 (s, 2H, CH_2), 2.03 (s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 167.1, 154.3, 153.3, 148.6, 139.4, 139.0, 133.5, 130.4, 129.2, 129.0, 127.1, 126.9, 125.7, 122.4, 121.7, 121.4, 68.2, 21.4. *Anal*. Calcd for $C_{19}H_{18}N_4O_2S$: C, 62.28; H, 4.95; N, 15.29; S, 8.75. Found: C, 62.33; H, 4.81; N, 15.19; S, 8.61.

1-(2-(Quinolin-8-yloxy)acetyl)-4-(2-methoxyphenyl) thiosemicarbazide (4c). Yield: 70%; mp 250–253°C; IR: 3332–3257 (NH), 2948 (CH_2), 1688 (C═O), 1232 (C═S), 1185 (C-N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 14.35, 10.12, 9.74 (3NH), 8.85–8.61 (m, 2H, ArH), 7.86–7.69 (m, 3H, ArH), 7.66–7.41 (m, 4H, ArH), 7.31–7.19 (m, 1H, ArH), 4.88 (s, 2H, CH_2), 3.91 (OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8, 167.6, 151.4, 149.2, 139.3, 135.4, 133.9, 133.2, 130.6, 129.7, 128.5, 127.4, 126.5, 124.3, 123.7, 123.0, 121.8, 68.2, 55.4. *Anal*. Calcd for $C_{19}H_{18}N_4O_3S$: C, 59.67; H, 4.74; N, 14.65; S, 8.38. Found: C, 59.74; H, 4.79; N, 14.78; S, 8.48.

1-(2-(Quinolin-8-yloxy)acetyl)-4-(2-chlorophenyl) thiosemicarbazide (4d). Yield: 60%; mp 120–122°C; IR: 3368–3172 (NH), 2951 (CH_2), 1683 (C═O), 1244 (C═S), 1182 (C-N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 14.34, 10.67, 9.68 (3NH), 8.56–8.41 (m, 1H, ArH), 8.32–8.11 (m, 1H, ArH), 7.78–7.42 (m, 6H, ArH), 7.33–7.25 (m, 2H, ArH), 4.87 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.6, 162.8, 150.3, 148.5, 147.2, 138.6, 138.1, 131.6, 129.7, 129.2, 128.6, 128.2,

127.4, 126.5, 124.4, 123.3, 115.3, 68.2. *Anal*. Calcd for $C_{18}H_{15}ClN_4O_2S$: C, 55.88; H, 3.91; N, 14.48; S, 8.29. Found: C, 55.84; H, 3.74; N, 14; S, 8.51.

1-(2-(Quinolin-8-yloxy)acetyl)-4-(3-chlorophenyl) thiosemicarbazide (4e). Yield: 59%; mp 193–194°C; IR: 3326–3218 (NH), 2956 (CH_2), 1666 (C═O), 1257 (C═S), 1178 (C-N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 14.14, 10.52, 9.84 (3NH), 8.93–8.86 (m, 1H, ArH), 8.46–8.37 (m, 1H, ArH), 7.65–7.32 (m, 6H, ArH), 7.34–7.22 (m, 2H, ArH), 4.92 (s, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.4, 162.9, 153.7, 149.7, 149.3, 148.5, 138.5, 130.6, 129.6, 129.2, 128.5, 127.5, 122.5, 121.4, 112.4, 68.2. *Anal*. Calcd for $C_{18}H_{15}ClN_4O_2S$: C, 55.88; H, 3.91; N, 14.48; S, 8.29. Found: C, 55.95; H, 3.83; N, 14.40; S, 8.41.

1-(2-(Quinolin-8-yloxy)acetyl)-4-(2-chlorophenyl)semicarbazide (4f). Yield: 66%; mp 204–207°C; IR: 3336–3231 (NH), 2956 (CH_2), 1692, 1650 (C═O), 1183 (C-N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 14.36, 10.87, 9.55 (3NH), 8.69–8.47 (m, 2H, ArH), 7.88–7.65 (m, 5H, ArH), 7.56–7.39 (m, 3H, ArH), 4.87 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 161.4, 150.0, 145.6, 138.4, 131.8, 130.9, 129.0, 128.7, 127.6, 126.4, 124.9, 124.3, 123.6, 122.7, 121.0, 68.2. *Anal*. Calcd for $C_{18}H_{15}ClN_4O_3$: C, 58.31; H, 4.08; N, 15.1. Found: C, 58.44; H, 4.26; N, 15.35.

1-(2-(Quinolin-8-yloxy)acetyl)-4-(3-chlorophenyl)semicarbazide (4g). Yield: 61%; mp 215–217°C; IR: 3309–3221 (NH), 2949 (CH_2), 1699, 1677 (C═O), 1181 (C-N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 14.15, 10.47, 9.68 (3NH), 8.96–8.80 (m, 1H, ArH), 8.28–8.15 (m, 1H, ArH), 7.61–7.31 (m, 5H, ArH), 7.29–7.16 (m, 3H, ArH), 4.92 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 162.7, 154.6, 149.7, 149.1, 148.5, 138.6, 131.4, 130.6, 129.8, 128.1, 127.8, 124.5, 123.3, 121.4, 120.2, 68.3. *Anal*. Calcd for $C_{18}H_{15}ClN_4O_3$: C, 58.31; H, 4.08; N, 15.11. Found: C, 58.48; H, 4.21; N, 15.28.

1-(2-(Quinolin-8-yloxy)acetyl)-4-ethylsemicarbazide (4h). Yield: 57%; mp 262–265°C; IR: 3314–3220 (NH), 2957 (CH_2), 1618, 1580 (C═O), 1195 (C-N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 13.63, 10.32, (2NH), 8.87–8.71 (m, 2H, ArH), 7.88–7.64 (m, 3H, ArH), 7.50–7.42 (m, 1H, ArH), 6.14 (NH), 3.49 (q, 2H, $J = 6.8$ Hz, CH_2), 1.40 (t, 3H, $J = 7.0$ Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 165.0, 150.4, 148.0, 130.3, 128.9, 126.5, 125.4, 123.0, 121.9, 121.1, 67.6, 35.4, 15.0. *Anal*. Calcd for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.43. Found: C, 58.50; H, 5.73; N, 19.52.

N-(2-Methylphenyl)-5-((quinolin-8-yloxy)methyl)-1,3,4-thiadiazol-2-amine (5a). Yield: 75%; mp 163–165°C; IR: 3232 (NH), 2953 (CH_2), 1550, (C═C), 1484 (C═N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.02 (NH), 8.94–8.42 (m, 2H, ArH), 7.71–7.56 (m, 4H, ArH), 7.52–7.32 (m, 3H, ArH), 6.91–6.79 (m, 1H, ArH), 5.55 (s, 2H, CH_2), 2.28 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 155.6, 153.5, 148.8, 140.7, 139.1, 138.8, 137.5, 129.5, 129.4, 126.4, 123.6, 122.5, 121.5, 118.7, 115.2, 111.9, 65.7, 21.8. EIMS *m/z* (%): 348 [M^+] (15), 145 (100%), 106 (55), 91 (47), 85 (21). *Anal*. Calcd for $C_{19}H_{16}N_4OS$: C, 65.50; H, 4.63; N, 16.08; S, 9.20. Found: C, 65.55; H, 4.48; N, 16.23; S, 9.39.

N-(3-Methylphenyl)-5-((quinolin-8-yloxy)methyl)-1,3,4-thiadiazol-2-amine (5b). Yield: 72%; mp 142–144°C; IR: 3239 (NH), 2918 (CH_2), 1556 (C═C), 1488 (C═N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.41 (NH), 8.93–8.55 (m, 2H, ArH), 7.69–7.62 (m, 3H, ArH), 7.53–7.38 (m, 3H, ArH), 7.24–7.19 (m, 1H, ArH), 6.83–6.81 (m, 1H, ArH), 5.67 (s, 2H, CH_2), 2.29 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 155.5, 152.2, 148.8, 140.8, 139.1, 138.8, 137.5, 129.7, 129.4, 127.9, 123.2, 122.7, 121.5, 118.4, 115.1, 112.7, 65.7, 21.7. EIMS *m/z* (%): 348 [M^+] (20), 145 (100%), 106 (49), 91 (51) 85 (25). *Anal*. Calcd for $C_{19}H_{16}N_4OS$: C, 65.50; H, 4.63; N, 16.08; S, 9.20. Found: C, 65.37; H, 4.48; N, 16.26; S, 9.07.

N-(2-Methoxyphenyl)-5-((quinolin-8-yloxy)methyl)-1,3,4-thiadiazol-2-amine (5c). Yield: 79%; mp 136–168°C; IR: 3244 (NH), 2929 (CH_2), 1562 (C═C), 1462 (C═N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 11.01 (NH), 8.59–8.42 (m, 2H, ArH), 7.89–7.58 (m, 6H, ArH), 7.45–7.26 (m, 2H, ArH), 5.88 (s, 2H, CH_2), 3.91 (OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 153.3, 148.1, 140.2, 139.2, 138.7, 136.8, 129.7, 129.0, 128.6, 127.8, 125.2, 125.1, 123.9, 123.2, 122.6, 118.4, 65.9, 54.9. EIMS *m/z* (%): 364 [M^+] (22), 206 (11), 145 (100%), 122 (44), 31 (31). *Anal*. Calcd for $C_{19}H_{16}N_4O_2S$: C, 62.62; H, 4.43; N, 15.37; S, 8.80. Found: C, 62.78; H, 4.59; N, 15.30; S, 8.94.

N-(2-Chlorophenyl)-5-((quinolin-8-yloxy)methyl)-1,3,4-thiadiazol-2-amine (5d). Yield: 70%; mp 150–152°C; IR: 3222 (NH), 2919 (CH_2), 1555 (C═C), 1418 (C═N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 11.51 (NH), 8.82–8.51 (m, 2H, ArH), 8.22–8.01 (m, 2H, ArH), 7.70–7.58 (m, 4H, ArH), 7.36–7.21 (m, 2H, ArH), 5.66 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 151.6, 148.2, 140.4, 130.7, 129.2, 128.4, 126.5, 125.2, 124.3, 123.9, 123.1, 122.0, 121.6, 120.9, 120.4, 117.4, 64.4. EIMS *m/z* (%): 368 [M^+] (26), 184 (20), 145 (100%), 111 (33). *Anal*. Calcd for $C_{18}H_{13}ClN_4OS$: C, 58.61; H, 3.55; N, 15.19; S, 8.69. Found: C, 58.70; H, 3.51; N, 15.14; S, 8.71.

N-(3-Chlorophenyl)-5-((quinolin-8-yloxy)methyl)-1,3,4-thiadiazol-2-amine (5e). Yield: 68%; mp 169–171°C; IR: 3232 (NH), 2941 (CH_2), 1548 (C═C), 1444 (C═N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 11.47 (NH), 9.09–8.90 (m, 2H, ArH), 7.94–7.69 (m, 6H, ArH), 7.61–7.42 (m, 2H, ArH), 5.76 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7, 152.1, 148.2, 140.0, 129.2, 126.9, 126.0, 125.6, 124.8, 124.5, 124.0, 123.1, 121.6, 120.6, 120.5, 65.7. EIMS *m/z* (%): 368 [M^+] (21), 145 (100%), 128 (61), 126 (40). *Anal*. Calcd for $C_{18}H_{13}ClN_4OS$: C, 58.61; H, 3.55; N, 15.19; S, 8.69. Found: C, 58.66; H, 3.50; N, 15.25; S, 8.58.

N-(2-Chlorophenyl)-5-((quinolin-8-yloxy)methyl)-1,3,4-oxadiazol-2-amine (5f). Yield: 75%; mp 201–202°C; IR: 3256 (NH), 2959 (CH_2), 1551 (C═C), 1452 (C═N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.26 (NH), 8.42–8.34 (m, 2H, ArH), 7.92–7.61 (m, 6H, ArH), 7.62–7.43 (m, 2H, ArH), 5.66 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 152.3, 148.3, 146.5, 141.5, 138.4, 134.2, 128.2, 126.7, 126.1, 125.3, 124.8, 124.2, 123.8, 121.1, 65.7. EIMS *m/z* (%): 352 [M^+] (19), 145 (100%), 128 (47), 111 (37). *Anal*. Calcd for $C_{18}H_{13}ClN_4O_2$: C, 61.28; H, 3.71; N, 15.88. Found: C, 61.51; H, 3.42; N, 15.64.

N-(3-Chlorophenyl)-5-((quinolin-8-yloxy)methyl)-1,3,4-oxadiazol-2-amine (5g). Yield: 70%; mp 218–220°C; IR: 3292 (NH), 2930 (CH_2), 1568 (C═C), 1474 (C═N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.88 (NH), 8.69–8.57 (m, 2H, ArH), 7.90–7.64 (m, 6H, ArH), 7.60–7.51 (m, 2H, ArH), 5.84 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.2, 152.3, 147.6, 141.1, 131.2, 129.6, 128.2, 126.2, 125.2, 124.6, 123.9, 122.1, 121.4, 120.6, 120.1, 119.8, 115.2, 65.3. EIMS *m/z* (%): 352 [M^+] (14), 184 (11), 145 (100%), 126 (54). *Anal*. Calcd for $C_{18}H_{13}ClN_4O_2$: C, 61.28; H, 3.71; N, 15.88. Found: C, 61.21; H, 3.84; N, 15.80.

N-Ethyl-5-((quinolin-8-yloxy)methyl)-1,3,4-oxadiazol-2-amine (5h). Yield: 77%; mp 145–147°C; IR: 3230 (NH), 2951 (CH_2), 1549 (C═C), 1449 (C═N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$):

δ 9.00 (NH), 8.41–8.11 (m, 2H, ArH), 7.85–7.51 (m, 4H, ArH), 5.53 (s, 2H, CH_2), 3.51 (q, 2H, $J = 6.9$ Hz, CH_2), 0.97 (t, 2H, $J = 6.8$ Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 153.3, 147.5, 140.0, 129.7, 128.2, 128.0, 126.0, 125.2, 124.6, 121.6, 65.6, 36.6, 15.4. EIMS *m/z* (%): 270 [M^+] (15), 184 (17), 145 (100%), 128 (56), 44(19). *Anal*. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.09; H, 5.16; N, 20.79.

4-(2-Methylphenyl)-5-((quinolin-8-yloxy)methyl)-2H-1,2,4-triazole-3(4H)-thione (6a). Yield: 61%; mp 196–198°C; IR: 3266 (NH), 2930 (CH_2), 1574 (C=N), 1250 (C=S) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.89 (bs, 1H, NH), 8.87–8.81 (m, 1H, ArH), 8.35–8.30 (m, 1H, ArH), 7.73–7.65 (m, 3H, ArH), 7.58–7.50 (m, 1H, ArH), 7.47–7.43 (m, 1H, ArH), 7.38–7.11 (m, 3H, ArH), 5.40 (s, 2H, CH_2), 2.35 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 151.3, 140.5, 139.2, 136.1, 135.8, 134.9, 133.8, 132.4, 132.0, 130.2, 129.9, 129.1, 128.3, 128.0, 125.4, 118.1, 67.8, 21.3. EIMS *m/z* (%): 348 [M^+] (10), 145 (100%), 91 (45), 15 (39). *Anal*. Calcd for $C_{19}H_{16}N_4OS$: C, 65.50; H, 4.63; N, 16.08; S, 9.20. Found: C, 65.56; H, 4.69; N, 16.14; S, 9.28.

4-(3-Methylphenyl)-5-((quinolin-8-yloxy)methyl)-2H-1,2,4-triazole-3(4H)-thione (6b). Yield: 60%; mp 175–177°C; IR: 3258 (NH), 2929 (CH_2), 1574 (C=N), 1254 (C=S) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.75 (bs, 1H, NH), 8.86–8.79 (m, 1H, ArH), 8.47–8.35 (m, 1H, ArH), 7.74–7.55 (m, 3H, ArH), 7.50–7.48 (m, 2H, ArH), 7.30–7.11 (m, 3H, ArH), 5.57 (s, 2H, CH_2), 2.36 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4, 151.4, 140.6, 139.5, 137.3, 135.8, 133.6, 132.9, 132.1, 131.0, 130.6, 129.4, 128.4, 128.0, 125.1, 121.5, 118.1, 67.9, 21.4. EIMS *m/z* (%): 348 [M^+] (16), 184 (14), 145 (100%), 91 (37). *Anal*. Calcd for $C_{19}H_{16}N_4OS$: C, 65.50; H, 4.63; N, 16.08; S, 9.20. Found: C, 65.40; H, 4.66; N, 16.13; S, 9.34.

4-(2-Methoxyphenyl)-5-((quinolin-8-yloxy)methyl)-2H-1,2,4-triazole-3(4H)-thione (6c). Yield: 59%; mp 211–213°C; IR: 3269 (NH), 2948 (CH_2), 1579 (C=N), 1256 (C=S) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (bs, 1H, NH), 8.76–8.40 (m, 2H, ArH), 7.82–7.53 (m, 4H, ArH), 7.58–7.36 (m, 4H, ArH), 5.69 (s, 2H, CH_2), 3.91 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 150.6, 141.5, 139.6, 137.3, 135.0, 134.4, 133.6, 132.8, 131.3, 130.4, 129.8, 128.7, 127.0, 125.9, 123.9, 118.1, 67.9, 21.9. EIMS *m/z* (%): 364 [M^+] (14), 145 (100%), 107 (43), 31 (27). *Anal*. Calcd for $C_{19}H_{16}N_4O_2S$: C, 62.62; H, 4.43; N, 15.37; S, 8.80. Found: C, 62.55; H, 4.44; N, 15.21; S, 8.70.

4-(2-Chlorophenyl)-5-((quinolin-8-yloxy)methyl)-2H-1,2,4-triazole-3(4H)-thione (6d). Yield: 54%; mp 189–191°C; IR: 3261 (NH), 2932 (CH_2), 1569 (C=N), 1250 (C=S) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.90 (bs, 1H, NH), 8.96–8.46 (m, 2H, ArH), 7.88–7.61 (m, 3H, ArH), 7.59–7.47 (m, 2H, ArH), 7.36–7.23 (m, 3H, ArH), 5.55 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.9, 151.3, 141.6, 139.1, 136.8, 135.5, 133.3, 132.8, 131.5, 130.5, 129.5, 129.0, 128.3, 127.4, 125.4, 123.6, 121.5, 65.3. EIMS *m/z* (%): 368 [M^+] (15), 184 (19), 145 (100%), 128 (59). *Anal*. Calcd for $C_{18}H_{13}ClN_4OS$: C, 58.61; H, 3.55; N, 15.19; S, 8.69. Found: C, 58.56; H, 3.59; N, 15.11; S, 8.78.

4-(3-Chlorophenyl)-5-((quinolin-8-yloxy)methyl)-2H-1,2,4-triazole-3(4H)-thione (6e). Yield: 50%; mp 174–176°C; IR: 3244 (NH), 2926 (CH_2), 1574 (C=N), 1256 (C=S) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.12 (bs, 1H, NH), 8.88–8.63 (m, 3H, ArH), 7.78–7.46 (m, 4H, ArH), 7.30–7.21 (m, 3H, ArH), 5.44 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.5, 151.6, 140.8, 139.6, 137.4, 136.1, 134.4, 133.2, 132.8, 131.5, 130.3, 129.2, 128.6, 126.7, 123.3, 67.8, 14.3. EIMS *m/z* (%): 368 [M^+] (15), 184 (25), 145 (100%), 128 (65). *Anal*. Calcd for $C_{18}H_{13}ClN_4OS$: C, 58.61; H, 3.55; N, 15.19; S, 8.69. Found: C, 58.61; H, 3.54; N, 15.25; S, 8.60.

4-(2-Chlorophenyl)-5-((quinolin-8-yloxy)methyl)-2H-1,2,4-triazol-3(4H)-one (6f). Yield: 54%; mp 180–182°C; IR: 3229 (NH), 2924 (CH_2), 1725 (C=O), 1563 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.86 (bs, 1H, NH), 8.87–8.66 (m, 2H, ArH), 7.78–7.56 (m, 4H, ArH), 7.49–7.34 (m, 3H, ArH), 7.28–7.16 (m, 1H, ArH), 5.34 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 150.5, 141.3, 138.3, 136.1, 135.7, 134.5, 132.1, 128.6, 128.1, 126.6, 124.9, 121.5, 120.3, 118.8, 67.3. EIMS *m/z* (%): 352 [M^+] (18), 184 (20), 158 (10), 145 (100%), 111 (53). *Anal*. Calcd for $C_{18}H_{13}ClN_4O_2$: C, 61.28; H, 3.71; N, 15.88. Found: C, 61.62; H, 3.43; N, 15.60 %.

4-(3-Chlorophenyl)-5-((quinolin-8-yloxy)methyl)-2H-1,2,4-triazol-3(4H)-one (6g). Yield: 56%; mp 225–227°C; IR: 3289 (NH), 2940 (CH_2), 1700 (C=O), 1570 (C=N), 1196 (C-N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.65 (bs, 1H, NH), 8.75–8.39 (m, 2H, ArH), 7.81–7.69 (m, 3H, ArH), 7.57–7.50 (m, 2H, ArH), 7.39–7.13 (m, 3H, ArH), 5.47 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 149.4, 142.0, 139.5, 138.2, 137.4, 135.8, 134.7, 133.5, 132.8, 131.5, 130.2, 129.8, 128.6, 128.1, 125.3, 121.7, 66.7. EIMS *m/z* (%): 352 [M^+] (18), 184 (25), 158 (14), 145 (100%), 111 (44). *Anal*. Calcd for $C_{18}H_{13}ClN_4O_2$: C, 61.28; H, 3.71; N, 15.88. Found: C, 61.33; H, 3.79; N, 15.92.

4-Ethyl-5-((quinolin-8-yloxy)methyl)-2H-1,2,4-triazol-3(4H)-one (6h). Yield: 55%; mp 167–169°C; IR: 3278 (NH), 2934 (CH_2), 1699 (C=O), 1577 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.84 (bs, 1H, NH), 8.83–8.77 (m, 2H, ArH), 7.84–7.65 (m, 2H, ArH), 7.51–7.39 (m, 2H, ArH), 5.42 (s, 2H, CH_2), 4.21 (q, 2H, $J = 6.9$ Hz, CH_2), 0.99 (t, 2H, $J = 6.9$ Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 151.4, 146.4, 141.0, 130.6, 127.3, 126.5, 125.0, 123.6, 122.6, 121.0, 65.5, 36.4, 15.1. EIMS *m/z* (%): 270 [M^+] (10), 145 (100%), 128 (26). *Anal*. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.35; H, 5.41; N, 20.79.

Acknowledgments. NA and AI are grateful to the Higher Education Commission of Pakistan for the financial support for a PhD program.

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