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Regioselective formation of new 3-*S*-alkylated-1,2,4-triazole-quinolones

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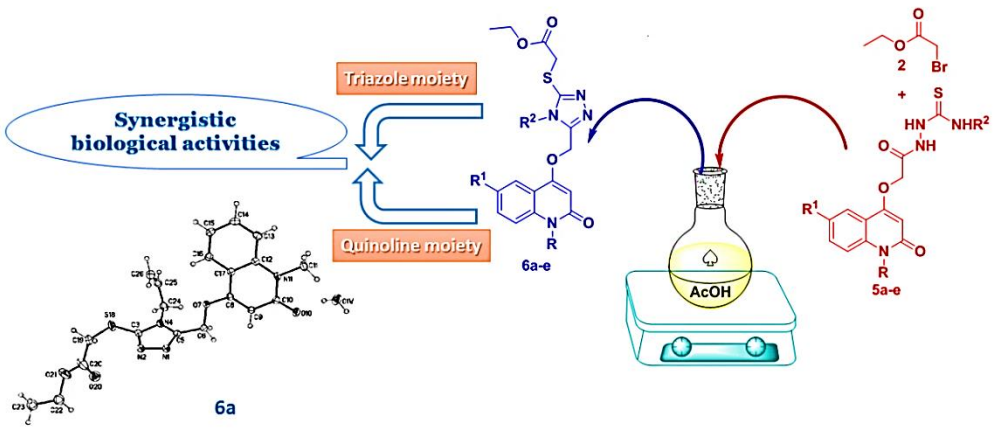

Abstract: Regioselective synthesis of quinolone-1,2,4-triazoles was established starting from 4-hydroxyquinol-2-ones. The strategy started by the reaction of ethyl bromoacetate with 4-hydroxyquinoline to give the corresponding ethyl oxoquinolinyl acetates, which reacted with hydrazine hydrate to afford the hydrazide derivatives. Subsequently, hydrazides reacted with isothiocyanate derivatives to give the corresponding acyl thiosemicarbazides. Finally, subjecting the thiosemicarbazide derivatives with ethyl bromoacetate, reaction underwent internal cyclization and alkylation processes. Alkylation occurred regioselectivity to sulfur atom of thione group and not to amino group. Thus 3-*S*-1,2,4-triazole-quinolones were obtained in good yields. The structure of the obtained

compounds was proved by different spectroscopic together with elemental analysis and X-ray crystallography.

Keywords: Thiosemicarbazides, 3-*S*-alkylated-1,2,4-triazole-quinolones, 2-*N*-alkylated-1,3,4-thiadiazole-quinolones.

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Highlights

- Synthesis of novel quinoline-2-one/1,2,4-triazole hybrids in four steps.
- NMR, IR and mass spectra together with elemental analysis and X-ray crystallography proved the structure of 3-*S*-alkylated-1,2,4-triazole-quinolones and excluded the formation of 2-*N*-alkylated-1,3,4-thiadiazole-quinolones.
- Plausible mechanism for the formation of the targeted compounds was suggested.

1. Introduction

Quinoline moiety is found in many in many of synthetic and naturally occurring biologically active compounds [1, 2]. Heterocycles contains quinolines shed the attention of many researchers due to their wide spectrum of pharmaceutical and biological activities such as antibacterial, anthelmintic, antimalarial, antifungal, cardiotonic, anticonvulsant, analgesic, and anti-inflammatory agents [3].

Annually, around 700,000 drug-resistant pathogens-related deaths are occurred, and therefore the number of these drugs would be increased to millions in case of that current of trends continue [4, 5]. Accordingly, searching and synthesizing of new drugs would be the aim of a numerous researchers.

Interestingly, quinoline-based molecules have shown as anti-inflammatory activity targeting several pharmacological targets such as Phosphodiesterase 4 (PDE4), Transient Receptor Potential Vanilloid 1 (TRPV1), TNF-α converting enzyme (TACE) and Cyclooxygenase (COX). Structure Activity Relationship (SAR) of quinlones has been affected the pharmacological activities [6].

Among the common pharmacophores, 1,2,4-triazole molecule constitutes the active molecule in numerous drugs [7]. In addition, 1,2,4-triazole derivatives possess a varied of pharmaceutical activities such as anti-tubercular [8], antifungal [9], anti-tumor [10], and anti-bacterial agents [11]. The former is due to the presence of the non-covalent interactions of 1,2,4-triazole moiety that can improve the solubility and the ability of binding to biomolecular targets [12]. Fluconazole and ribavirin are interesting known drugs containing 1,2,4-triazole molecule [12]. Thus, 1,2,4-triazole derivatives display a prospective role in the development of new drugs [13].

Previously it was reported that triazoles exhibited *in vitro* an antibacterial activity using the agar dilution technique [14]. Six of these compounds showed potential activity against Gram-positive bacteria (minimal inhibitory concentration [MIC] = 15.63-500 μg/mL). Other showed good activity especially against *Bacillus subtilis* ATCC 6633 (MIC = 15.63-

250 μg/mL), *Staphylococcus aureus* ATCC 25923 (MIC = 31.25-250 μg/mL), and *Micrococcus luteus* ATCC 10240 (MIC = 125-250 μg/mL) [14].

Triazoles and quinolones occupy an important in medicinal chemistry most likely as pharmacophores, consequently they have shown interesting and various biological activities. In addition hybridization of these two molecules would provide more effective candidates that might capable to prevent drug resistance [15]. 1,2,4-Triazole molecule could exhibit good interactions with DNA, enzymes, and receptors *via* hydrogen bonds, coordination, ion-dipole, π–π stacking, hydrophobic effect and/or van der Waals force, etc [16]. A number of 1,4-disubstituted 1,2,3-triazoles having quinolinylmethylene at *N*-1 and 1,2-dihydroquinolinyl methylene at C-4 with different substituents showed cytotoxic effects against various cancer cells [17]. Quinolones linked to 1,2,4-triazoles were synthesized successfully *via* a one pot multistep method using the copper(I)-catalyzed [3+2]-azide-alkyne cycloaddition (CuAAC) reaction. All these compounds revealed inhibitory *in vitro* effects on the growth of four cancer cell lines. Some of these compounds also showed *in vitro* good cytotoxic effects against lung cancer cells and inhibition of PDE4 [18].

Interestingly, hybridization of quinolone ring with 1,2,4-triazole ring hybrid **I** afforded diverse biological properties and pharmacological activities, such as inhibition of the growth of Gram-positive strains including methicillin-sensitive *S. aureus*/MSSA and methicillin-resistant *S. aureus*/MRSA [19-21]. Whereas, ciprofloxacin-1,2,4-triazole hybrids **II** showed moderate to excellent anti-cancer activities against L1210, HL60, and CHO cancer cells in the MTT assay (Figure 1) [8, 22, 23]. Cui and his group [24] prepared a series of quinolone–1,2,4-triazole hybrids **III** which exhibited strong antibacterial and antifungal activities against the tested strains in comparison with reference drugs such as Norfloxacin, Chloramphenicol, and Fluconazole (Figure 1) [24].

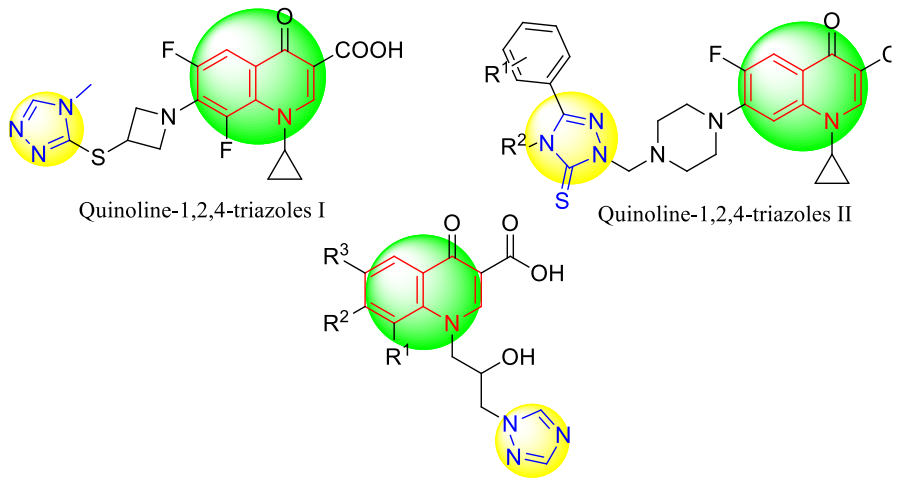


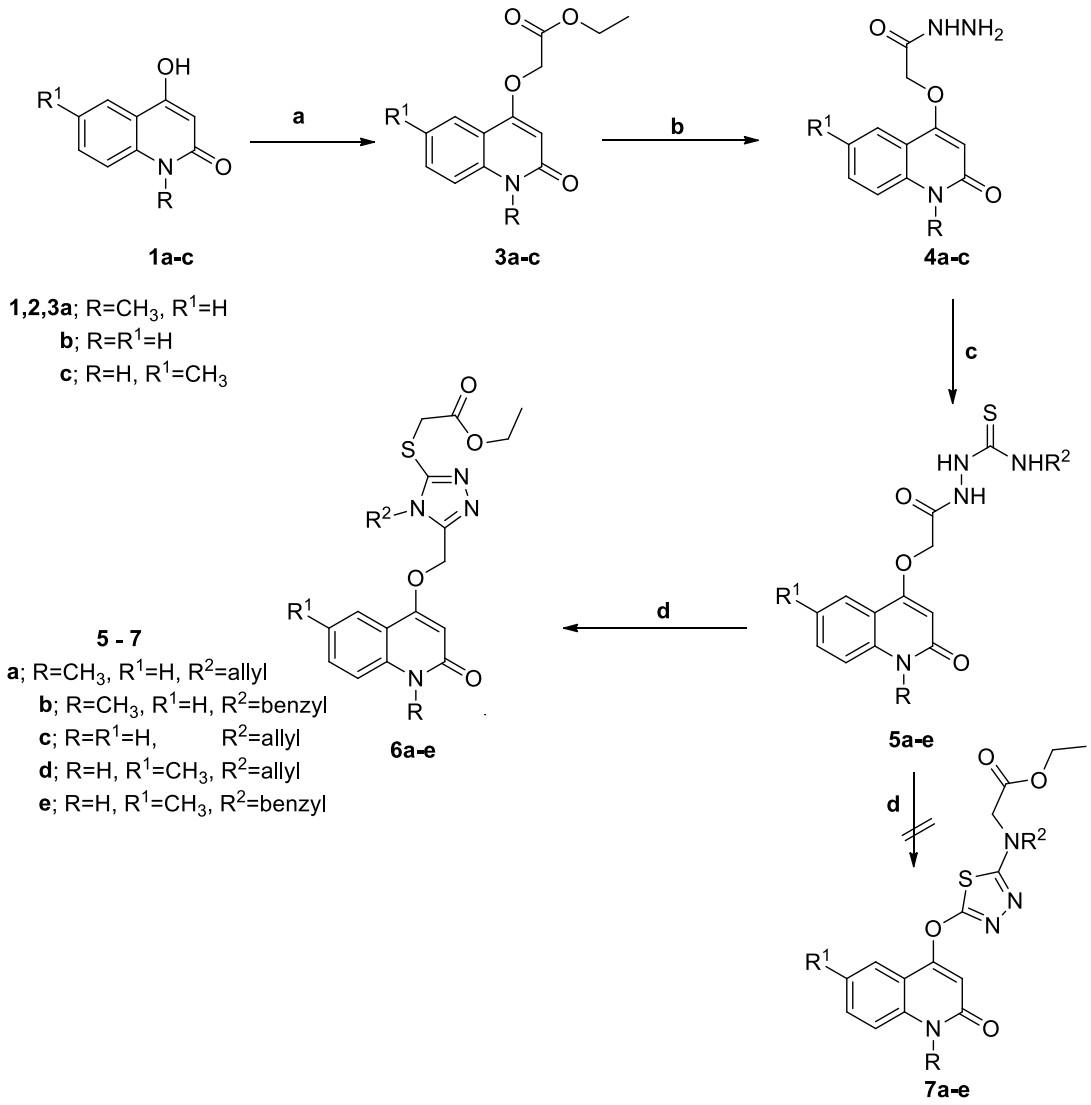
Figure 1. Representative examples of some 1,2,4-triazole-quinolines

Various reports illustrated on the synthesis of triazole-3-thiols from the internal cyclization of acyl hydrazinecarbothioamides in presence of a base [25-27]. *Aly et al* [28] reported on a general method for the synthesis of 1,3,5-trisubstituted 1,2,4-triazoles from the reaction of equal equivalents of amidrazones with ethyl azodicarboxylate and Et_3N (Mitsunobu reagent) [28]. Under acidic condition, *N*-acylthiosemicarbazides underwent internal cyclization into 2-amino-1,3,4-thiadiazole [29].

From the above-mentioned facts, we herein report the synthesis of certain novel 1,2,4-triazole-3-thione derived by quinolin-2-one.

2. Results and Discussion

The reaction sequences for the synthesis of 1,2,4-triazole-quinolone hybrids **6a-e** starting from 4-hydroxyquinoline are outlined in Scheme 1. The synthesis of ethyl 2-((2-oxo-1,2-dihydroquinolin-4-yl)oxy)acetate derivatives **3a-c** were obtained by refluxing ethyl bromoacetate (**2**) with 4-hydroxyquinoline **1a-c** in dry acetone in the presence of anhydrous potassium carbonate. All the newly synthesized compounds gave satisfactory analyses for the proposed structures, which were confirmed based on their IR, ^1H NMR and mass spectra as well as elemental analyses.



Reagents and Conditions: (a) ethyl bromoacetate (**2**), anhydrous K_2CO_3, dry acetone, reflux 7-9 h; (**b**) hydrazine hydrate, EtOH, reflux 12-14 h; (**c**) isothiocyanate derivatives, EtOH, reflux, 4-6 h; (**d**) **2**, AcOH, sodium acetate, reflux, 10-12 h.

Scheme 1. Synthesis of 1,2,4-triazole- quinolones **6a-e**

The structure of compounds **3a-c** was confirmed from the IR, NMR, MS, and elemental analysis, the ester C=O appeared at 1732 cm^{-1}. Moreover, the ethyl pattern appeared at δ_H 1.24 and 4.22 and their attached carbons at δ_c 13.99 and 60.90 ppm respectively. As a representative example for this series, the FT-IR spectrum of compound **3b**, showed a characteristic absorption band at 1732-1729 cm^{-1} corresponding to ester C=O. Moreover, the ^1H NMR spectrum of compound **3b** exhibited a singlet at δ_N 144.5 ppm assigned for N-1; its attached proton appears at δ_H 11.44. *N*-1 gives HMBC correlation with a doublet at δ_H 7.30 and a 1H singlet at 5.85 ppm assigned as H-8 and H-3, respectively; their attached carbons appear at δ_C 115.19 (C-8) and 97.76 (C-3). Also, the spectrum showed a distinctive quartet signal at δ_H 4.22 assigned for H-4d: their attached carbon is distinctive at δ_C 60.90.

H-4e appeared triplet at δ_H 1.24; their attached carbon appears at δ_C 13.99 ppm, H-4e also gives HMBC correlation with carbon at δ_C 60.90 ppm. Distinctive carbons and are shown in Figure 2.

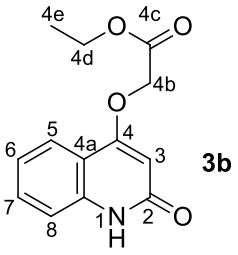


Figure 2. Structure of compound **3b**

Furthermore, the reaction of **3a-c** with hydrazine hydrate in refluxing ethanol, afforded the hydrazide derivatives **4a-c** in good yields. Evidence for the formation of the hydrazide **4b** comes from its IR spectrum where there are absorption bands at 3318 and 3258 cm^{-1} (hydrazide NH-NH_2), also, the hydrazide structure was confirmed by a broad band at 1658-1660 cm^{-1} due to (–C=O) of amide and disappearance of an ester frequency (1732-1729 cm^{-1}). In the ^{1}H NMR spectrum of compound **4b**, the 2H singlet at δ_H 4.68 is distinctive, and is assigned as H-4c; their attached carbon appears at δ_C 66.48. The assignments of N-4e and N-1 are confirmed by their HMBC correlations with H-4c and H-3 respectively. Distinctive carbons and hydrogens for compound **4b** is shown in Figure 3.

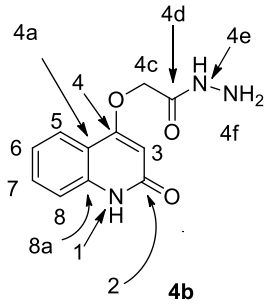


Figure 3. Structure of compound **4b**

For the synthesis of new quinolone-triazole hybrids **6a-e**, we planned to prepare the key intermediates **5a-e** as new precursors for functionalized triazole derivatives. To approach these targets, the reaction of compounds **4a-c** and isothiocyanate derivatives in refluxing ethanol was carried out yielding the hydrazinecarbothioamides **5a-e**. Elemental analyses, IR, and NMR in addition to mass spectra were in good agreement with the assigned product structures. As a representative example for this series, the ^{1}H NMR spectrum of **5a** as an example showed distinctive are the allyl signals: H-4i (2H doublet at δ_H 4.72), H-4j (1H

double-double-triplet at δ_H 5.88), H-4k (two 1H doublets at δ_H 5.11 and 5.02), C-4i (δ_C 45.46), C-4j (δ_C 131.17), and C-4k (δ_C 117.80). ^{15}N NMR spectrum revealed singlet at δ_N 137.9 ppm assigned for N-1. N-1 gives HMBC correlation with a singlet at δ_H 6.26, assigned as H-3; its attached carbon appears at δ_C 97.85. Distinctive carbons are as shown in Figure 4.

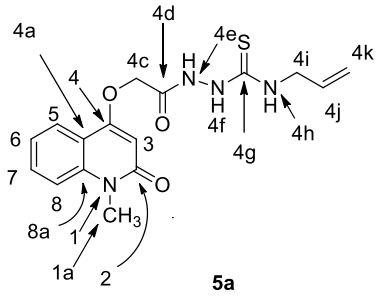


Figure 4. Structure of compound **5a**

Interestingly, heterocyclization of the triazole moiety **6a-e** can take place when hydrazinecarbothioamides **5a-e** are treated with **2** in refluxing glacial acetic acid and sodium acetate for 10-12 h. The structure of the target compounds was confirmed by IR, ^{1}H NMR, elemental analyses, MS, and X-ray crystallography.
The structures of **6a** and **6b** were determined by single crystal X-ray diffraction (**Figures 5-8**). Compounds **6a** and **6b** crystallized in a triclinic system and P-1 space group with Z = 2 (two molecular formula per asymmetric unit).

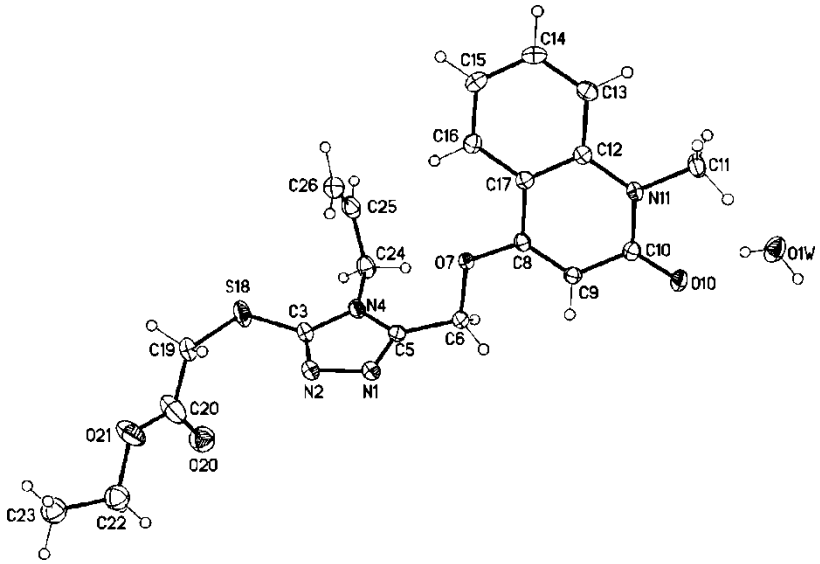


Figure 5. The molecular structure of compound **6a** (displacement parameters are drawn at 50% probability level).

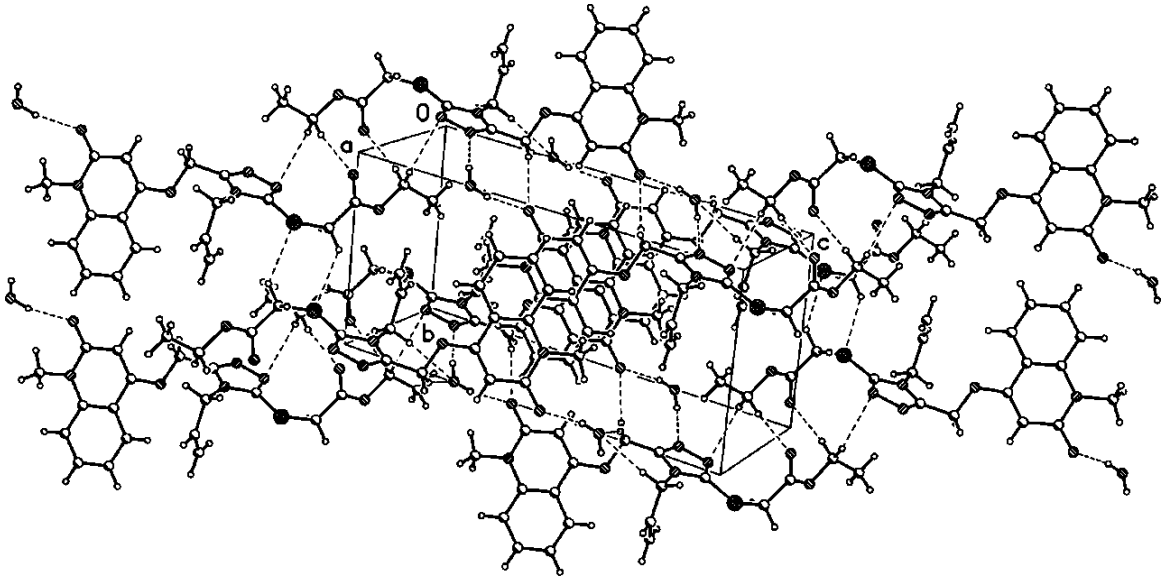


Figure 6. The molecular packing of the compound **6a**.

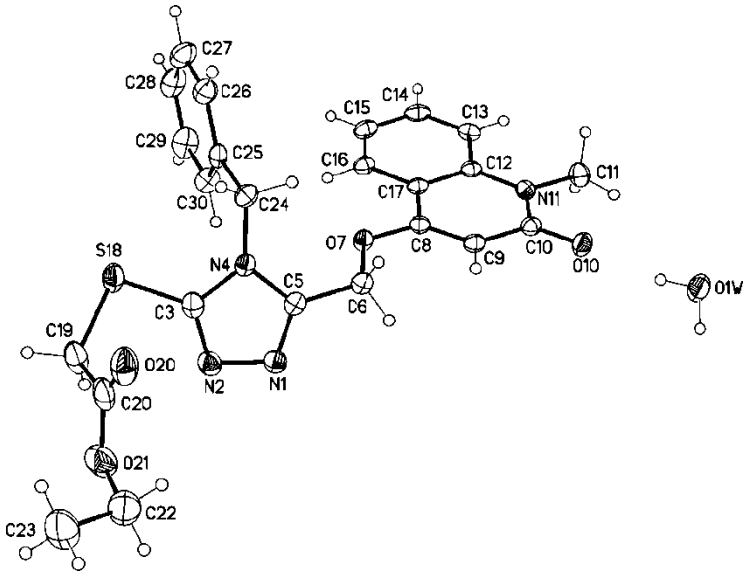


Figure 7. The molecular structure of compound **6b** (displacement parameters are drawn at 50% probability level).

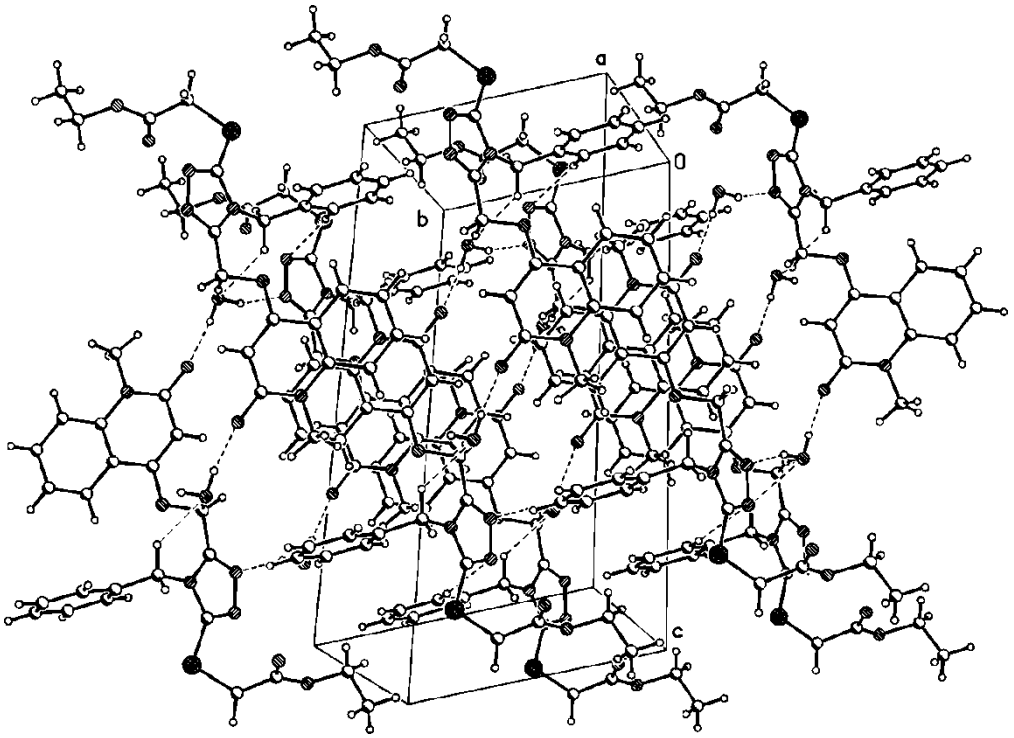
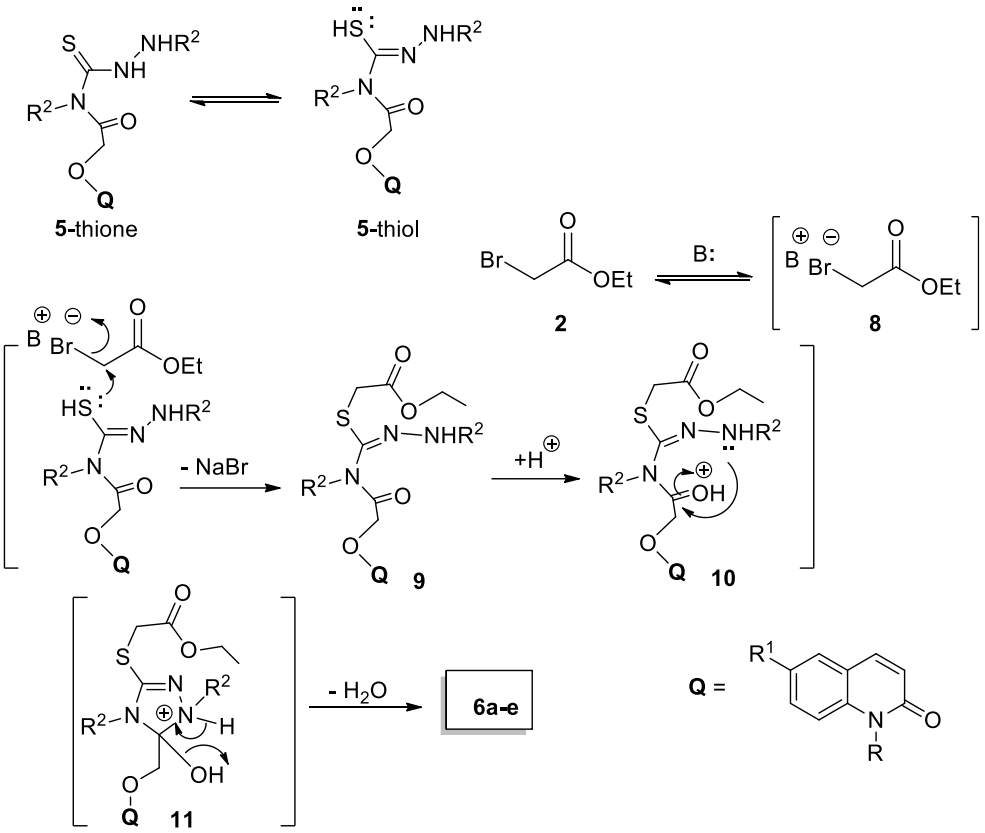


Figure 8. The molecular packing of the compound **6b**.

The IR spectrum of compound **6e** showed an absorption of the carbonyl ester and the NH stretching at υ_{max}/cm^{-1} 3129 and 1715 cm^{-1}, respectively. Both elemental analysis and mass spectroscopy indicated the molecular formula of **6e** as $C_{24}H_{24}N_4O_4S$. The ^1H NMR spectrum of compound **6e** showed the quinolone-NH at δ_H 11.31, whereas the ester protons as triplet and quartet and triplet at δ_H 1.18 and 4.11 (J= 7.1 Hz), respectively.

On the basis that the thiadiazole compounds **7a**-**e** were not formed, the proposed mechanism (Scheme 2) showed that the first step would be as alkylation of the thione group as shown in the intermediate **9**. The intermediate **9** was as due to the combination of NaOAc (as a base) with the halo compound **2** that would form the corresponding salt **8**. Thus the nucleophilic addition of the thiol lone pair to the electrophilic carbon in compound **2** would enhance the facile elimination of NaBr to form the intermediate **9** (Scheme 2). The next step involved the protonation of **9** into intermediate **10**. Internal cyclization of **10** would then give the intermediate **11**. Finally dehydration **11** would give directly compounds **6a-e** (Scheme 2).



Scheme 2. Mechanism describes the formation of compounds **6a-e**

3. Material and Methods

3.1. General Information

All reagents were used as purchased from Merck (St. Louis, MO, USA). Thin-layer chromatography (TLC) was made as Merck alumina-backed TLC plates and visualized under UV light. Spectra were measured in DMSO-d_6 on a Bruker AV-400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, and 40.54 MHz for ^{15}N, in the Chemistry Department, Florida Institute of Technology, 150 W University Blvd, Melbourne, FL 32901, USA. Chemical shifts are expressed in δ (ppm) versus internal tetramethylsilane (TMS) = 0 ppm for ^{1}H and ^{13}C, and external liquid ammonia = 0 ppm for ^{15}N. Coupling constants are stated in Hz. Correlations were established using ^{1}H-^{1}H COSY, and ^{1}H-^{13}C and ^{1}H-^{15}N HSQC and HMBC experiments. All ^{15}N signals were observed indirectly, via HSQC or HMBC experiments. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, and the coupling constants (*J*) are reported in Hertz (Hz). Splitting patterns are denoted as follows: singlet (s), doublet (d), multiplet (m), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), triplet of doublets (td), and doublet of quartet (dq). Melting points (mp) were determined with a Stuart melting point instrument in the Chemistry Department, Florida Institute of Technology, 150 W University Blvd, Melbourne,

FL, USA, and are expressed in °C as well. Mass spectra were recorded on a Finnigan Fab 70 eV at Al-Azhar University, Egypt. Elemental analyses were carried out on a Perkin Elmer device at the Microanalytical Institute of Organic Chemistry, Karlsruhe Institute of Technology, Karlsruhe, Germany.

3.2. Starting materials

4-Hydroxyquinoline derivatives **1a-c** were prepared according to the literature [30-32]. Ethyl bromoacetate (**2**) and isothiocyanate derivatives were bought from Aldrich and used as received.

3.3. General procedure

3.3.1. General method for the synthesis of compounds 3a-c

4-Hydroxyquinoline derivatives **1a-c** (1 mmol) were dissolved in 50 ml dry acetone and mixed with anhydrous potassium carbonate (1.1 mmol). This was treated with **2** (0.165 g, 1 mmol) and the mixture was refluxed for 7-9 h under dry condition. After the completion of the reaction (monitored by TLC), the reaction mixture was filtered, and the filtrate was distilled under reduced pressure. The solid thus obtained was subjected to column chromatography using 5% ethyl acetate: petroleum ether to furnish the final products **3a-c**.

3.3.1.1. Ethyl 2-((1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)acetate (3a)

Yield: 0.207 g (79%); mp 130–132 °C, IR (KBr) υ_{max}/cm^{-1} 3188, 1726 [33].

3.3.1.2. Ethyl 2-((2-oxo-1,2-dihydroquinolin-4-yl)oxy)acetate (3b)

Yield: 0.204 g (82%); mp 139–141 °C, IR (KBr) υ_{max}/cm^{-1} 3178, 1732. **^{1}H NMR:** 11.44 (s, 1H; NH-1), 7.83 (d, *J* = 7.8, 1H; H-5), 7.54 (ddd, *J* = 7.3, 7.3, 0.8, 1H; H-7), 7.30 (d, *J* = 8.2, 1H; H-8), 7.20 (dd, *J* = 7.7, 7.5, 1H; H-6), 5.85 (s, 1H; H-3), 4.99 (s, 2H; H-4b), 4.22 (q, *J* = 7.1, 2H; H-4d), 1.24 (t, *J* = 7.1,3H; H-4e). **^{13}C NMR:** 167.58 (C-4c), 162.95 (C-2), 161.36 (C-4), 138.64 (C-8a), 131.09 (C-7), 122.25 (C-5), 121.44 (C-6), 115.19 (C-8), 114.28 (C-4a), 97.76 (C-3), 64.90 (C-4b), 60.90 (C-4d), 13.99 (C-4e). **^{15}N NMR:** 144.5 (N-1). MS m/z (%): 247 (M^+, 6.8), 63 (100), 77 (96), 42 (79). Anal. Calcd. for $C_{13}H_{13}NO_4$ (247.25): C, 63.15; H, 5.30; N, 5.67. Found: C, 63.01; H, 5.51; N, 5.89.

3.3.1.3. Ethyl 2-((6-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)acetate (3c)

Yield: 0.212 g (81%); mp 144–146 °C, IR (KBr) υ_{max}/cm^{-1} 3200, 1715. **^{1}H NMR:** 11.36 (bs, 1H; NH-1), 7.62 (s, 1H; H-5), 7.36 (bd, *J* = 8.4, 1H; H-7), 7.20 (d, *J* = 8.3, 1H; H-8), 5.82 (s, 1H; H-3), 4.98 (s, 2H; H-4b), 4.21 (q, *J* = 7.1, 2H; H-4d), 2.35 (s, 3H; H-6a), 1.24 (t, *J* = 7.1, 3H; H-4e). **^{13}C NMR:** 167.61 (C-4c), 162.83 (C-2), 161.22 (C-4), 136.66 (C-8a), 132.26 (C-7), 130.41 (C-6), 121.70 (C-5), 115.15 (C-8), 114.16 (C-4a), 97.70 (C-3), 64.82 (C-4b), 60.89 (C-4d), 20.49 (C-6a), 13.99 (C-4e). **^{15}N NMR:** 143.7 (N-1). MS m/z (%): 261 (M^+, 26), 77 (100), 65 (44). Anal. Calcd. for $C_{14}H_{15}NO_4$ (261.27): C, 64.36; H, 5.79; N, 5.36. Found: C, 64.65; H, 5.96; N, 5.59.

3.3.2. General method for the synthesis of compounds 4a-c

A mixture of ethyl 2-(2-oxo-1,2-dihydro-quinolin-4-yl)oxy)acetate derivatives **3a-c** (1 mmol) and hydrazine hydrate (1 mmol) in ethanol (40 ml) was heated under reflux for 12-14 h. The reaction mixture was cooled to room temperature and the solid separated was collected by filtration. It was washed with ethanol and recrystallized in methanol to afford the hydrazide derivatives **4a-c** as light yellow solids in good yields.

3.3.2.1. 2-((1-Methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)acetohydrazide (4a)

Yield: 0.211 g (86 %), m.p. 173-175 °C. IR (KBr) υ_{max}/cm^{-1} 3310-3203, 1653 [34]

3.3.2.2. 2-((2-Oxo-1,2-dihydroquinolin-4-yl)oxy)acetohydrazide (4b)

Yield: 0.190 g (81 %), m.p. 179-181 °C. IR (KBr) υ_{max}/cm^{-1} 3318-3258, 1658. **^{1}H NMR:** 11.42 (b, 1H; NH-1), 9.48 (b, 1H; H-4e), 7.98 (d, *J* = 7.9; 1H; H-5), 7.52 (ddd, *J* = 7.2, 7.2, 0.8; 1H; H-7), 7.28 (d, *J* = 8.2; 1H; H-8), 7.18 (dd, *J* = 7.6, 7.6; 1H; H-6), 5.83 (s, 1H; H-3), 4.68 (s, 2H; H-4c), 4.42 (bs, 2H; H-4f). **^{13}C NMR:** 165.47 (C-4d), 163.01 (C-2), 161.75 (C-4), 138.59 (C-8a), 131.02 (C-7), 122.91 (C-5), 121.23 (C-6), 115.04 (C-8), 114.33 (C-4a), 97.77 (C-3), 66.48 (C-4c). **^{15}N NMR:** 144.2 (N-1), 130.3 (N-4e), 54.7 (N-4f). MS m/z (%): 233 (M^+, 100), 168 (50), 97 (24), 40 (23). Anal. Calcd. for $C_{11}H_{11}N_3O_3$ (233.22): C, 56.65; H, 4.75; N, 18.02. Found: C, 56.96; H, 5.01; N, 18.24.

3.3.2.3. 2-((6-Methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)acetohydrazide (4c)

Yield: 0.199 g (80 %), m.p. 180-182 °C. IR (KBr) υ_{max}/cm^{-1} 3322-3279, 1634. **^{1}H NMR:** 11.34 (b, 1H; NH-1), 9.48 (s, 1H; H-4e), 7.79 (bs, 1H; H-8), 7.35 (d, *J* = 8.3; 1H; H-5), 7.19 (d, *J* = 8.3; 1H; H-7), 5.81 (s, 1H; H-3), 4.67 (s, 2H; H-4c), 4.44 (bs, 2H; H-4f), 2.37 (s, 3H; H-6a). **^{13}C NMR:** 166.03 (C-4d), 163.40 (C-2), 162.09 (C-4), 137.10 (C-8a), 132.74 (C-7), 130.81 (C-5), 122.83 (C-6), 115.49 (C-8), 114.69 (C-4a), 98.12 (C-3), 66.68 (C-4c), 20.93 (C-6a). **^{15}N NMR:** 143.6 (N-1), 130.5 (N-4e), 54.6 (N-4f). MS m/z (%): 247 (M^+, 4), 77 (100), 69 (37), 41 (15). Anal. Calcd. for $C_{12}H_{13}N_3O_3$ (247.25): CC, 58.29; H, 5.30; N, 16.99. Found: C, 58.03; H, 5.57; N, 17.16.

3.3.3. General method for the synthesis of compounds 5a-e

To a suspension of hydrazide derivatives **4a-c** (1 mmol) in absolute ethanol (30 mL), the appropriate isothiocyanate derivatives (1 mmol) were added and the mixture was heated at reflux on a boiling water bath for 4–6 h. The mixture was then left to cool, and the precipitate so formed was collected by filtration, washed with methanol, and recrystallized from ethanol to give the target compounds **5a-e**.

3.3.3.1. N-Allyl-2-(2-((1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)acetyl)-hydrazinecarbothioamide (5a)

Yield: 0.270 g (78 %), m.p. 177-179 °C. IR (KBr) υ_{max}/cm^{-1} 3255, 3100. **^{1}H NMR:** 14.05 (s, 1H; H-4h), 7.85 (d, *J* = 7.8; 1H; H-5), 7.66 (dd, *J* = 7.5, 7.5; 1H; H-7), 7.53 (d, *J* = 8.6; 1H; H-8), 7.26 (dd, *J* = 7.5, 7.5; 1H; H-6), 6.26 (s, 1H; H-3), 5.88 (ddt, J_d = 16.4, 10.9, J_t = 5.6; 1H; H-4j), 5.36 (s, 2H; H-4c), 5.11 (d, *J* = 10.4; 1H; H-4k), 5.02 (d, *J* = 17.2; 1H; H-4k), 4.72 (d, *J* = 5.0; 2H; H-4i), 3.57 (s, 3H; H-1a), 3.45 (b, 1H; H-4e), 3.45 (b, 1H; H-4f). **^{13}C NMR:** 167.87 (C-4g), 161.97 (C-2), 159.80 (C-4), 147.14 (C-4d), 139.43 (C-8a), 131.59 (C-7), 131.17 (C-4j), 122.80 (C-5), 121.62 (C-6), 117.80 (C-4k), 115.02 (C-8), 114.68 (C-4a), 97.85 (C-3), 60.34 (C-4c), 45.46 (C-4i), 28.69 (C-1a). **^{15}N NMR:** 281.4 (N-4e/f), 204.3 (N-4h), 175.3 (N-4f/e), 137.9 (N-1). MS m/z (%): 346 (M^+, 13), 151 (80),139 (100), 80 (56). Anal. Calcd. for $C_{16}H_{18}N_4O_3S$ (346.41): C, 55.48; H, 5.24; N, 16.17. Found: C, 55.79; H, 5.50; N, 16.39.

3.3.3.2. N-Benzyl-2-(2-((1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)acetyl)hydrazine-carbothioamide (5b)

Yield: 0.281 g (71 %), m.p. 190-192 °C. IR (KBr) υ_{max}/cm^{-1} 3249, 3150. **^{1}H NMR:** 10.21 (s, 1H; H-4e), 9.50 (bs, 1H; H-4f), 8.65 (b, 1H; H-4h), 8.18 (dd, *J* = 7.9, 1.0; 1H; H-5), 7.68 (ddd, *J*= 8.5, 7.2, 1.4; 1H; H-7), 7.52 (d, *J* = 8.4; 1H; H-8), 7.31 (m, 5H; H-6, *o, m*), 7.23 (m, 1H; H-*p*), 6.06 (s, 1H; H-3), 4.79 (s, 2H; H-4c), 4.76 (d, *J* = 5.9; 2H; H-4i), 3.57 (s, 3H; H-1a). **^{13}C NMR:** 182.01 (C-4g), 166.23 (C-4d), 162.10 (C-2), 160.33 (C-4), 139.40 (C-8a), 139.17 (C-*i*), 131.56 (C-7), 128.02 (2C-*o*), 126.96 (2C-*m*), 126.59 (C-*p*), 123.49 (C-5), 121.41 (C-6), 115.21 (C-8), 114.54 (C-4a), 97.50 (C-3), 66.38 (C-4c), 46.69 (C-4i), 28.65 (C-1a). **^{15}N NMR:** 137.7 (N-1), 130.1 (N-4e), 118.2 (N-4f), 113.8 (N-4h). MS m/z (%): 396 (M^+, 30), 247 (21), 120 (100), 43 (53). Anal. Calcd. for $C_{20}H_{20}N_4O_3S$ (396.47): C, 60.59; H, 5.08; N, 14.13. Found: C, 60.78; H, 5.36; N, 13.88.

3.3.3.3. N-Allyl-2-(2-((2-oxo-1,2-dihydroquinolin-4-yl)oxy)acetyl)hydrazinecarbothioamide (5c)

Yield: 0.245 g (74 %), m.p. 169-171 °C. IR (KBr) υ_{max}/cm^{-1} 3234, 3120. **^{1}H NMR:** 11.43 (bs, 1H; H-1), 10.13 (b, 1H; H-4e/4f), 9.42 (b, 1H; H-4f/4e), 8.27 (bs, 1H; H-4h), 8.06 (d, *J* = 8.0; 1H; H-5), 7.53 (dd, *J* = 7.6, 7.6; 1H; H-7), 7.29 (d, *J* = 8.2; 1H; H-8), 7.18 (dd, *J* = 7.6, 7.6; 1H; H-6), 5.90 (s, 1H; H-3), 5.84 (ddt, J_d = 16.8, 10.9, J_t = 5.5; 1H; H-4j), 5.15 (d, *J* = 17.2; 1H; H-4k), 5.06 (d, *J* = 10.3; 1H; H-4k), 4.78 (s, 2H; H-4c), 4.13 (bs, 2H; H-4i). **^{13}C NMR:** 181.71 (C-4g), 166.17 (C-4d), 163.00 (C-2), 161.64 (C-4), 138.60 (C-8a), 134.83 (C-4j), 131.06 (C-7), 123.05 (C-5), 121.20 (C-6), 115.30 (C-4k), 115.04 (C-8), 114.26 (C-4a), 97.85 (C-3), 66.35 (C-4c), 45.88 (C-4i). **^{15}N NMR:** 144.4 (N-1), 130.2 (N-4e/4f), 118.0 (N-4f/4e), 110.7 (N-4h). MS m/z (%): 332 (M^+, 30), 273 (74), 90 (100), 42 (33). Anal. Calcd. for $C_{15}H_{16}N_4O_3S$ (332.38): C, 54.20; H, 4.85; N, 16.86 Found: C, 54.48; H, 5.17; N, 17.13.

3.3.3.4. N-Allyl-2-(2-((6-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)acetyl)hydrazine-1-carbothioamide (5d)

Yield: 0.290 g (80 %), m.p. 174-176 °C. IR (KBr) υ_{max}/cm^{-1} 3289, 3165. **^{1}H NMR:** 11.35 (bs, 1H; NH-1), 10.11 (bs, 1H; H-4e), 9.43 (b, 1H; H-4f), 8.28 (b, 1H; H-4h), 7.86 (bs, 1H; H-5), 7.36 (d, *J* = 8.2; 1H; H-7), 7.19 (d, *J* = 8.3, 1H; H-8), 5.87 (s, 1H; H-3), 5.84 (ddt, J_d = 16.0, 10.2, J_t = 5.5; 1H; H-4j), 5.16 (d, *J* = 17.1; 1H; H-4k), 5.06 (d, *J* = 10.2; 1H; H-4k), 4.76 (s, 2H; H-4c), 4.13 (bs, 2H; H-4f), 2.37 (s, 3H; H-6a). **^{13}C NMR:** 181.85 (C-4g), 166.21 (C-4d), 162.88 (C-2), 161.47 (C-4), 136.60 (C-8a), 134.83 (C-4j), 132.22 (C-7), 130.27 (C-6), 122.42 (C-5), 115.30 (C-4k), 114.98 (C-8), 114.13 (C-4a), 97.80 (C-3), 66.32 (C-4c), 45.88 (C-4i), 20.46 (C-6a). **^{15}N NMR:** 143.4 (N-1), 130.4 (N-4e), 118.1 (N-4f), 111.1 (N-4h). MS m/z (%): 346 (M^+, 17), 253 (45), 61(100), 48 (23). Anal. Calcd. for $C_{16}H_{18}N_4O_3S$ (346.41): C, 55.48; H, 5.24; N, 16.17. Found: C, 55.80; H, 5.52; N, 16.39.

3.3.3.5. N-Benzyl-2-(2-((6-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)acetyl)hydrazine-carbothioamide (5e)

Yield: 0.297 g (75 %), m.p. 183-185 °C. IR (KBr) υ_{max}/cm^{-1} 3266, 3199. **^{1}H NMR:** 11.35 (s, 1H; NH-1), 10.18 (s, 1H; NH-4d), 9.52 (s, 1H; NH-4g), 8.66 (bs, 1H; NH-4e), 7.86 (s, 1H; H-5), 7.36 (bd, *J* = 8.5, 1H; H-7), 7.32 (m, 4H; H-*o, m*), 7.20 (m, 2H; H-*p,* 8), 5.88 (s, 1H; H-3), 4.76 (s, 4H; H-4b, 4h), 2.37 (s, 3H; H-6a). **^{13}C NMR:** 182.02 (C-4f), 166.28 (C-4c), 162.89 (C-2), 161.47 (C-4), 139.17 (C-*i*), 136.60 (C-8a), 132.23 (C-7), 130.27 (C-6), 128.02 (2C-*m*), 126.98 (2C-*o*), 126.59 (C-*p*), 122.43 (C-5), 114.98 (C-8), 114.12 (C-4a), 97.81 (C-3), 66.35 (C-4b), 46.70 (C-4h), 20.46 (C-6a). **^{15}N NMR:** 143.6 (N-1), 130.2 (N-4d), 118.0 (N-4g), 113.6 (N-4e). MS m/z (%): 396 (M^+, 30), 115 (53), 120 (100), 59 (28). Anal. Calcd. for $C_{20}H_{20}N_4O_3S$ (396.47): C, 60.59; H, 5.08; N, 14.13. Found: C, 60.77; H, 5.33; N, 14.28.

3.3.4. General method for the synthesis of compounds 6a-e

To a suspension of hydrazinecarbothioamide derivatives **5a-e** (1 mmol) in glacial acetic acid (30 mL), sodium acetate (1 mmol), compound **2** (0.165 g, 1 mmol) was added and the mixture was heated at dry condition using $CaCl_2$-guard tube reflux for 10-12 h. The mixture was then left to cool, poured into crushed ice and the precipitate so formed was collected by filtration and recrystallized from ethanol to give the target compounds **6a-e**.

3.3.4.1. Ethyl 2-((4-allyl-5-(((1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)methyl)-4H-1,2,4-triazol-3-yl)thio)acetate (6a)

Yield: 0.311 g (75 %), m.p. 209-211 °C. IR (KBr) υ_{max}/cm^{-1} 1720, 1049. **^{1}H NMR:** 7.80 (bt, *J* = 7.8; 1H; H-7), 7.65 (d, *J* = 8.5; 1H; H-8), 7.52 (d, *J* = 8.0; 1H; H-5), 7.24 (t, *J* = 7.6; 1H; H-6), 6.31 (s, 1H; H-3), 5.91 (ddt, J_d = 17.1, 10.4, J_t = 5.1; 1H; H-4'b), 5.45 (s, 2H; H-4c), 5.16 (d, *J* = 10.4; 1H, H-4'c), 4.94 (d, *J* = 17.2; 1H; H-4'c), 4.73 (d, *J* = 4.7; 2H; H-4'a), 4.13 (s, 2H; H-3'b), 4.11 (q, *J* = 7.1; 2H; H-3'e), 3.56 (s, 3H; H-1a), 1.16 (t, *J* = 7.1; 3H; H-3'f). **^{13}C NMR:** 168.10 (C-3'c), 162.01 (C-2), 159.90 (C-4), 151.24 (C-3'), 150.84 (C-5'), 139.39 (C-8a), 131.79 (C-4'b), 131.54 (C-7), 122.67 (C-5), 121.58 (C-6), 117.70

(C-4a), 115.10 (C-8), 114.70 (C-4'c), 97.87 (C-3), 61.25 (C-3'e), 60.19 (C-4c), 46.02 (C-4'a), 34.44 (C-3'b). 28.66 (C-1a), 13.90 (C-3'f). MS m/z (%): 414 (M^+, 23), 322 (100), 244 (29), 88 (33). Anal. Calcd. for $C_{20}H_{22}N_4O_4S$ (414.48): C, 57.96; H, 5.35; N, 13.52. Found C, 58.18; H, 5.56; N, 13.80.

3.3.4.2. Ethyl 2-((4-benzyl-5-(((1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)methyl)-4H-1,2,4-triazol-3-yl)thio)acetate (6b)

Yield: 0.365 g (78 %), m.p. 221-223 °C. IR (KBr) υ_{max}/cm^{-1} 1726, 1082. **^{1}H NMR:** 7.58 (bt, *J* = 7.8; 1H; H-7), 7.45 (d, *J* = 8.5; 1H; H-8), 7.26 (m, 3H; H-*m, p*), 7.20 (d, *J* = 8.0; 1H; H-5), 7.09 (dd, *J* = 7.7, 1.2; 2H; H-*o*), 7.02 (dd, *J* = 7.6, 7.6; 1H; H-6), 6.28 (s, 1H; H-3), 5.46 (s, 2H; H-4c), 5.37 (s, 2H; H-4'a), 4.13 (s, 2H; H-3'b), 4.11 (q, *J* = 7.1; 2H; H-3'e), 3.54 (s, 3H; H-1a), 1.17 (t, *J* = 7.1; 3H; H-3'f). **^{13}C NMR:** 168.01 (C-3c'), 162.00 (C-2), 159.85 (C-4), 151.24 (C-3'), 151.15 (C-5'), 139.25 (C-8a), 135.18 (C-*i*), 131.34 (C-7), 128.67 (2C-*m*), 127.76 (C-*p*), 126.38 (2C-*o*), 122.54 (C-5), 121.32 (C-6), 114.97 (C-4a), 114.44 (C-8), 97.75 (C-3), 61.27 (C-3'e), 60.18 (C-4c), 46.94 (C-4'a), 34.31 (C-3'b). 28.62 (C-1a), 13.91 (C-3'f). **^{15}N NMR:** 325.7 (N-1'), 171.9 (N-4'), 137.7 (N-1). MS m/z (%): 464 (M^+, 17), 260 (100), 115 (25), 65 (20). Anal. Calcd. for $C_{24}H_{24}N_4O_4S$ (464.54): C, 62.05; H, 5.21; N, 12.06. Found: C, 62.24; H, 5.36; N, 12.22.

3.3.4.3. Ethyl 2-((4-allyl-5-(((2-oxo-1,2-dihydroquinolin-4-yl)oxy)methyl)-4H-1,2,4-triazol-3-yl)thio)acetate (6c)

Yield: 0.305 g (76 %), m.p. 201-203 °C. IR (KBr) υ_{max}/cm^{-1} 3166, 1722. **^{1}H NMR:** 11.46 (s, 1H; H-1), 7.69 (d, *J* = 8.0; 1H; H-5), 7.51 (t, *J* = 7.7; 1H; H-7), 7.29 (d, *J* = 8.2; 1H; H-8), 7.14 (t, *J* = 7.6; 1H; H-6), 6.16 (s, 1H; H-3), 5.91 (ddt, J_d = 17.1, 10.4, J_t = 5.1; 1H; H-4'b), 5.44 (s, 2H; H-4c), 5.17 (d, *J* = 10.4; 1H, H-4'c), 4.94 (d, *J* = 17.2; 1H; H-4'c), 4.74 (d, *J* = 4.7; 2H; H-4'a), 4.12 (s, 2H; H-3'b), 4.10 (q, *J* = 7.1; 2H; H-3'e), 1.17 (t, *J* = 7.1; 3H; H-3'f). **^{13}C NMR:** 168.08 (C-3'c), 162.91 (C-2), 161.22 (C-4), 150.87 (C-3'), 150.77 (C-5'), 138.60 (C-8a), 131.80 (C-4'b), 131.04 (C-7), 122.24 (C-5), 121.36 (C-6), 117.69 (C-4'c), 115.17 (C-8), 114.15 (C-4a), 98.23 (C-3), 61.23 (C-3'e), 60.20 (C-4c), 46.03 (C-4'a), 34.50 (C-3'b), 13.90 (C-3'f). **^{15}N NMR:** 325.4 (N-1'), 170.8 (N-4'), 144.5 (N-1). MS m/z (%): 400 (M^+, 33), 251 (100), 147 (25), 46 (47). Anal. Calcd. for $C_{19}H_{20}N_4O_4S$ (400.45): C, 56.99; H, 5.03; N, 13.99. Found: C, 57.31; H, 5.36; N, 14.27.

3.3.4.4. Ethyl 2-((4-allyl-5-(((6-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)methyl)-4H-1,2,4-triazol-3-yl)thio)acetate (6d)

Yield: 0.320 g (77 %), m.p. 201-203 °C. IR (KBr) υ_{max}/cm^{-1} 3130, 1710. **^{1}H NMR:** 11.36 (bs, 1H; NH-1), 7.48 (bs, 1H; H-5), 7.34 (dd, *J* = 8.3, 1.4, 1H; H-7), 7.19 (d, *J* = 8.3, 1H; H-8), 6.13 (s, 1H; H-3), 5.94 (ddt, J_d = 17.1, 10.3, J_t = 5.1, 1H; H-3b'), 5.42 (s, 2H; H-4b), 5.19 (d, *J* = 10.4, 1H; H-4c'), 4.95 (d, *J* = 17.2, 1H; H-4c'), 4.74 (d, *J* = 4.7, 2H; H-4a'), 4.13 (s, 2H; H-3a'), 4.11 (q, *J* = 7.1, 2H; H-3c'), 2.31 (s, 3H; H-6a), 1.17 (t, *J* = 7.1, 3H; H-3d'). **^{13}C NMR:** 168.09 (C-3b'), 162.81 (C-2), 161.10 (C-4), 150.91 (C-3'), 150.79

(C-5′), 136.61 (C-8a), 132.21 (C-7), 131.87 (C-4b′), 130.38 (C-6), 121.70 (C-5), 117.57 (C-4c′), 115.12 (C-8), 114.04 (C-4a), 98.18 (C-3), 61.24 (C-3c′), 60.18 (C-4b), 46.02 (C-4a′), 34.50 (C-3a′), 20.41 (C-6a), 13.90 (C-3d′). **^{15}N NMR:** 325.1 (N-1'), 170.5 (N-4'), 143.7 (N-1). MS m/z (%): 414 (M^+, 68), 366 (48), 322 (100), 169 (65). Anal. Calcd. for $C_{20}H_{22}N_4O_4S$ (414.48): C, 57.96; H, 5.35; N, 13.52. Found: C, 58.25; H, 5.66; N, 13.20.

3.3.4.5. Ethyl 2-((4-benzyl-5-(((6-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)methyl)-4H-1,2,4-triazol-3-yl)thio)acetate (6e)

Yield: 0.355 g (76 %), m.p. 231-233 °C. IR (KBr) υ_{max}/cm^{-1} 3129, 1715. **^{1}H NMR:** 11.31 (bs, 1H; NH-1), 7.26 (m, 4H; H-7, *m*, *p*), 7.12 (m, 3H; H-8, *o*), 6.99 (bs, 1H; H-5), 6.10 (s, 1H; H-3), 5.44 (s, 2H; H-4b), 5.36 (s, 2H; H-4a′), 4.12 (s, 2H; H-3a′), 4.11 (q, *J* = 7.1, 2H; H-3c′), 2.20 (s, 3H; H-6a), 1.18 (t, *J* = 7.1, 3H; H-3d′). **^{13}C NMR:** 168.01 (C-3b′), 162.77 (C-2), 161.04 (C-4), 151.22 (C-3′), 151.18 (C-5′), 136.45 (C-8a), 135.16 (C-*i*), 132.10 (C-7), 130.12 (C-6), 128.58 (2C-*m*), 127.78 (C-*p*), 126.44 (2C-*o*), 121.51 (C-5), 114.93 (C-8), 113.88 (C-4a), 98.07 (C-3), 61.26 (C-3c′), 60.07 (C-4b), 46.99 (C-4a′), 34.31 (C-3a′), 20.41 (C-6a), 13.92 (C-3d′). **^{15}N NMR:** 325.7 (N-1'), 172.0 (N-4'), 143.3 (N-1); MS m/z (%): 464 (M^+, 45), 312 (100), 212 (44), 72 (40). Anal. Calcd. for $C_{24}H_{24}N_4O_4S$ (464.54): C, 62.05; H, 5.21; N, 12.06. Found: C, 61.75; H, 5.46; N, 12.32.

Crystal Structure Determinations of 6a, and 6b

The single-crystal X-ray diffraction studies were carried out on a Bruker D8 Venture diffractometer with PhotonII detector at 123(2) K using Cu-Kα radiation (λ = 1.54178 Å). Dual space methods (SHELXT) [35] were used for structure solution and refinement was carried out using SHELXL-2014 (full-matrix least-squares on F^2) [36]. Hydrogen atoms were localized by difference electron density determination and refined using a riding model (H(O) free). Semi-empirical absorption corrections were applied. For **6a** an extinction correction was applied). In **5a** the ethyl acetate moiety is disordered (see cif-file for details).

6a-sb1286_hy: colourless crystals, $C_{20}H_{22}N_4O_4S \cdot H_2O$, M_r = 432.49, crystal size 0.20 × 0.16 × 0.08 mm, triclinic, space group *P-1* (No. 2), a = 7.0910(3) Å, b = 8.2169(3) Å, c = 17.7449(7) Å, α = 85.683(1)°, β = 87.765(1)°, γ = 88.624(1)°, V = 1029.98(7) Å^3, Z = 2, ρ = 1.395 Mg/m^{-3}, μ(Cu-K$_\alpha$) = 1.75 mm^{-1}, F(000) = 456, $2\theta_{max}$ = 144.4°, 20322 reflections, of which 4017 were independent (R_{int} = 0.023), 274 parameters, 9 restraints, R_1 = 0.042 (for 3944 I > 2σ(I)), wR_2 = 0.105 (all data), S = 1.02, largest diff. peak / hole = 0.78 / -0.41 e Å^{-3}.

6b-sb1287_hy: colourless crystals, $C_{24}H_{24}N_4O_4S \cdot H_2O$, M_r = 482.55, crystal size 0.18 × 0.14 × 0.04 mm, triclinic, space group *P-1* (No. 2), a = 6.9485(2) Å, b = 8.7826(2) Å, c = 20.5350(5) Å, α = 78.344(1)°, β = 80.966(1)°, γ = 74.199(1)°, V = 1173.97(5) Å^3, Z = 2, ρ = 1.365 Mg/m^{-3}, μ(Cu-K$_\alpha$) = 1.59 mm^{-1}, F(000) = 508, $2\theta_{max}$ = 144.4°, 19113 reflections, of which 4608 were independent (R_{int} = 0.022), 314

parameters, 3 restraints, R_1 = 0.037 (for 4456 I > 2σ(I)), wR_2 = 0.099 (all data), S = 1.05, largest diff. peak / hole = 0.57 / -0.31 e Å^{-3}.

CCDC 2071983 (**6a)**, and 2071984 (**6b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4. Conclusion

A series of regioselective quinoline-2-one/1,2,4-triazole hybrids **6a-e** have been prepared in four steps from 4-hydroxy-2-quinolinones **1a-c**. *O*-alkylation with ethyl bromoacetate is followed by hyrazinolysis to give acylhydrazides **4a-c.** These react with isothiocyanates to afford thiosemicarbazides **5a-e.** Finally, *S*-alkylation of **5a-e** with ethyl bromoacetate triggers ring closure to 1,2,4-triazoles **6a-e.** The structure assignments of the products rest on IR spectroscopy, 1D and 2D NMR spectroscopy of ^{1}H, ^{13}C, and ^{15}N, and X-ray crystallography. We plan to expand the library of quinoline-2-one/1,2,4-triazole hybrids hoping to get prospective biological active compounds.

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