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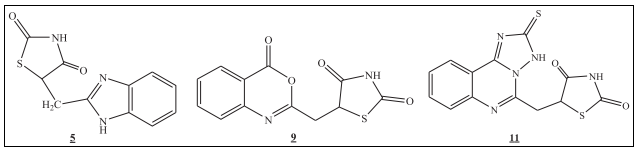

2-(2,4-Dioxothiazolidin-5-yl)acetic acid **1** and its chloride derivative **2** were allowed to react with different aromatic amines such as *o*-phenylenediamine, *o*-aminothiophenol, *p*-aminoacetophenone, and anthranilic acid to give the biologically active nuclei such as imidazoles, thiazoles, benzoxazines, and quinazolines incorporated with the thiazolidindione nucleus. The antimicrobial activity of five of the synthesized compounds was examined against one gram positive bacteria (*Staphylococcus aureus*), one gram negative bacteria (*Escherichia coli*), and two fungi (*Aspergillus flavus* and *Candida albicans*). Four compounds showed moderate antibacterial and antifungal activities.

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INTRODUCTION

Small ring heterocycles containing nitrogen, oxygen, and sulfur have been under investigation for a long time because of their important medicinal properties. Among these types of molecules, imidazoles, thiazoles, and thiazolidinones have been shown to have various important biological activities such as antibacterial, antifungal, antiviral, diuretic, antitubercular, anti-HIV, antihistaminic, anticancer, anticonvulsant, anti-inflammatory, and analgesic properties [1–10]. Oxazines are known to be biologically active as antimalarial, antianginal, antihypertensive, anti-H_5N_1, and potent antirheumatic agents [11,12]. Oxazines are an important group of organic dyes that are generally π-conjugated systems, with interesting photo-physical and lasing properties [13]. In addition, quinazoline derivatives have been identified as a new class of cancer chemotherapeutic agents with significant therapeutic efficiency against solid tumors [14–16]. It is well known that quinazoline derivatives are potent inhibitors of epidermal growth factor receptor [17–25]. The biological significance of these classes of compounds initiated our interest to incorporate thiazolidindiones, imidazoles, benzoxazines, and quinazolines in one framework with a view to obtain compounds of high biological activity.

RESULTS AND DISCUSSION

With the aim of obtaining more precise information about the course of the reaction and some interesting pharmaceutical compounds, we reported herein the action of different amines on the thiazolidindione derivatives **1** and **2** to obtain new heterocyclic compounds with expected biological activity.

The thiazolidindione derivatives **1** and **2** were previously prepared [26] via treatment of thiourea with maleic anhydride in concentrated hydrochloric acid followed by the reaction with thionyl chloride in case of **2**.

The key intermediate **1** was allowed to react with *o*-phenylenediamine and/or *o*-aminothiophenol in boiling ethanol to yield the amide derivative **3** and thioester **4**, respectively. The infrared spectra of these products showed the new characteristic absorption bands for the amide $\gamma_{C=O}$ at 1640 and thioester $\gamma_{C=O}$ at 1727 cm^{-1}, and the disappearance of $\gamma_{C=O}$ and γ_{OH} of the acid.

Heating of amide **3** or thioester **4** with HCl/ACOH mixture afforded **5** or **6** with the construction of imidazole or thiazole ring linked to the thiazolidindione nucleus.

The structures of **5** and **6** were confirmed authentically via the treatment of the acid **1** with *o*-phenylenediamine and/or *o*-aminothiophenol in the presence of $POCl_3$ and/or treatment of the acid chloride **2** with *o*-phenylenediamine and/or *o*-aminothiophenol in presence of triethylamine.

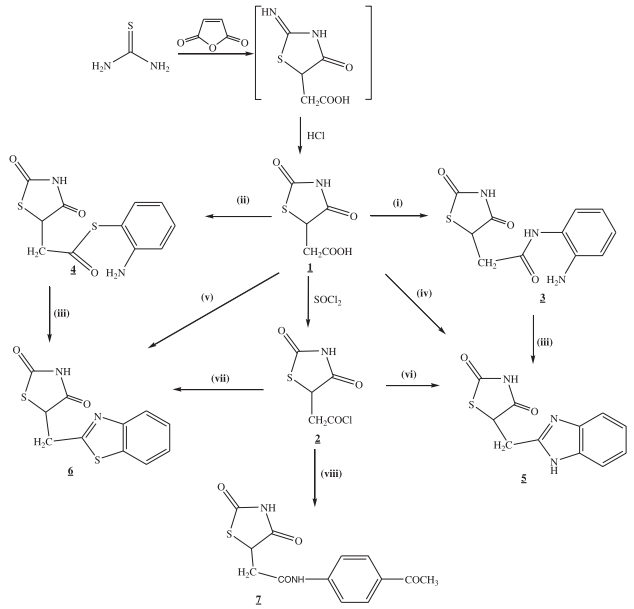
Treatment of **2** with *p*-aminoacetophenone in the presence of triethylamine afforded the amide derivative *N*-(4-acetylphenyl)-2-(2,4-dioxothiazolidin-5-yl)acetamide **7** (cf. Scheme 1).

The structures of **3–7** were confirmed from the correct analytical and spectroscopic data (cf. Experimental).

When the acid chloride **2** was allowed to react with anthranilic acid in refluxing toluene in the presence of pyridine, 2-[2-(2,4-dioxothiazolidin-5-yl)acetamido]benzoic acid **8** was formed.

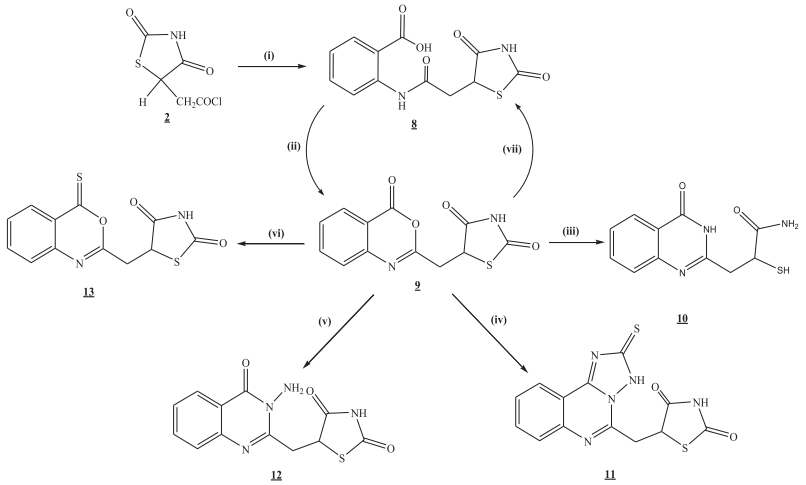
The infrared spectra of **8** showed the new characteristic absorption bands for the $\gamma_{C=O}$ amide and acid at 1657and 1699 cm^{-1}, as well as γ_{OH} acid in the range 3241–3350 cm^{-1} (cf. Scheme 2).

Scheme 1 (i) *o*-Phenylenediamine/ethanol; (ii) *o*-aminothiophenol/ethanol; (iii) HCl/Acetic acid; (iv) *o*-phenylenediamine/$POCl_3$; (v) *o*-aminothiophenol/$POCl_3$; (vi) *o*-phenylenediamine/Et_3N/dioxane; (vii) *o*-aminothiophenol/Et_3N/dioxane; (viii) *p*-aminoacetophenone/Et_3N/dioxane.



(i) *o*-phenylenediamine / Ethanol ; (ii) *o*-aminothiophenol / Ethanol ; (iii) HCl /Acetic acid ; (iv) *o*-phenylenediamine / $POCl_3$; (v) *o*-aminothiophenol / $POCl_3$; (vi) *o*-phenylenediamine / Et_3N / dioxane ; (vii) *o*-aminothiophenol / Et_3N / dioxane ; (viii) *p*-aminoacetophenone / Et_3N / dioxane.

Scheme 2 (i) Anthranilic acid/pyridine/toluene; (ii) acetic anhydride/Δ; (iii) ammonium acetate/fusion; (iv) $NH_2NHCSNH_2$/pyridine; (v) $NH_2NH_2.H_2O$; (vi) P_2S_5/pyridine; (vii) $Br_2/CHCl_3$.



(i) anthranilic acid / pyridine/ toluene ; (ii) Acetic anhydride / Δ ; (iii) Ammonium acetate / fusion ; (iv) $NH_2NHCSNH_2$ / pyridine ; (v) $NH_2NH_2.H_2O$; (vi) P_2S_5 / pyridine ; (vii) Br_2 / $CHCl_3$.

Ring closure of the later by refluxing in acetic anhydride led to the construction of a new benzoxazine ring linked to the thiazolidindione nucleus with the formation of 5-((4-oxo-4*H*-benzo[*d*][3,1]oxazin-2-yl)methyl)thiazolidine-2,4-dione **9**. The infrared spectra of **9** showed the characteristic absorption bands for the $\gamma_{C=O}$ benzoxazinone at 1751 cm^1 and the disappearance of $\gamma_{C=O}$ and γ_{OH} of the acid.

Fusion of **9** with ammonium acetate led to the ring opening of both thiazolidindione and oxazinone rings with the formation of the quinazolinone derivative **10** as the sole product in fairly good yield. The infrared spectra of **10** showed the absence of coupling pattern of $\gamma_{C=O}$ thiazolidindione. The structure of **10** was strongly confirmed from the correct analytical and spectroscopic data. (cf. Experimental.) The

reaction seems to proceed through the following pathway (Scheme 3).

When **9** was allowed to react with thiosemicarbazide in boiling pyridine, the triazoloquinazoline derivative **11** was obtained. The infrared spectra of **11** showed the disappearance of $\gamma_{C=O}$ of benzoxazinone.

The aminoquinazoline derivative **12** has been obtained by treatment of **9** with hydrazine hydrate at room temperature via ring opening of the benzoxazinone **9** followed by ring closure of the hydrazide intermediate. The infrared spectra of **12** showed the characteristic absorption bands of the $\gamma_{C=O}$ and γ_{NH2} at 1650, 3207, and 3322 cm^{-1}, respectively, and the disappearance of $\gamma_{C=O}$ of benzoxazinone.

Treatment of **9** with P_2S_5 gave the corresponding benzoxazinethione derivative **13**. The infrared spectra of **13** showed the characteristic absorption bands for the $\gamma_{C=S}$ at 1275 cm^{-1} and the disappearance of $\gamma_{C=O}$ benzoxazinone.

Bromination of **9** afforded the open structure **8** instead of the unsaturated derivative of **9**. The product was shown by direct comparison (mp, mixed mp, and TLC) to be the thiazolidindione derivative **8** (cf. Scheme 3).

The conversion of **9** to **8** using $Br_2/CHCl_3$ can be visualized to proceed via bromination of **9** followed by elimination of HBr that concurrently opens the oxazinone ring to give [A] [27–29] (not isolated); which was then reduced [29] by the unreacted **9** to afford **8** (cf. Scheme 4).

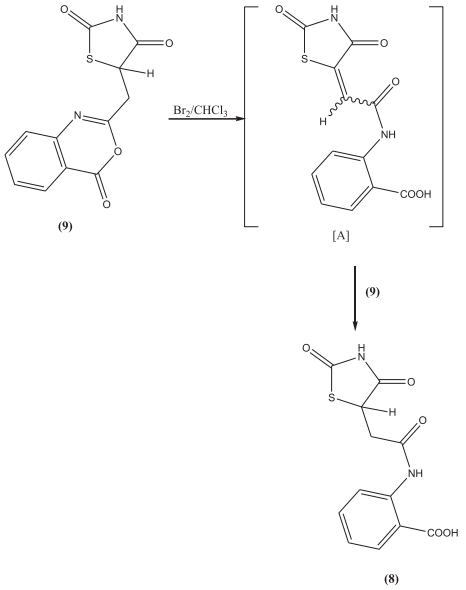
Structures **8–13** were substantiated from their analytical and spectroscopic data (cf. Experimental).

Antimicrobial evaluation. The antibiotic resistance is a growing problem; this is due to the overuse of antibiotics in human and the use of antibiotics as growth promoters in food of animals, so there is a growing demand for new antibiotics.

The novel 2,4-dioxothiazolidinylbenzoxazinone derivatives were evaluated for their *in vitro* antimicrobial activity against two strains of bacteria and two fungus strains; tetracycline was used as standard drug for bacteria, and amphotericin was used as standard drug for fungi. Preliminary screening of 2,4-dioxothiazolidinylbenzoxazinone derivatives and standard drugs were performed at fixed concentration 20 mg/mL; inhibition was recorded by measuring the diameter of the inhibition zone at the end of 18 h for bacteria.

On the basis of the results of the inhibition zone, data in Table 1 revealed that 20 mg/mL was the potent concentration of the 2,4-dioxothiazolidinyl benzoxazinone derivatives and the standard drugs, compounds **6**, **8**, **9**, **11** exhibited moderate antibacterial and antifungal activities compared with the standard drugs. Compound **5** exhibited no antimicrobial activity.

Scheme 4



EXPERIMENTAL

Melting points were measured on an electrothermal melting point apparatus. Elemental analyses and antimicrobial activity were carried out at the microanalytical unit, Cairo University, Giza, Egypt. The IR spectra were measured on a Unicam SP-1200 spectrometer (Pye Unicam limited U.K.) using KBr wafer technique. The ^1H NMR spectra were measured in

Scheme 3

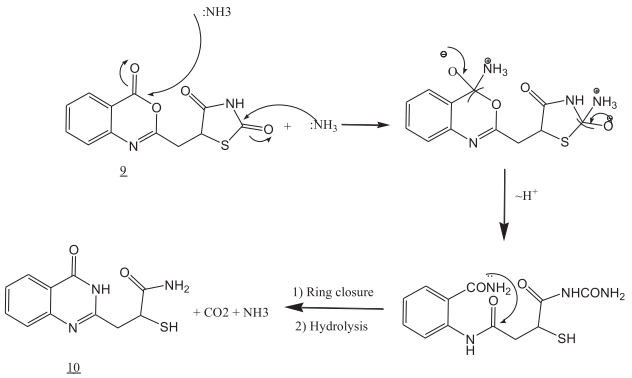


Table 1

Antibacterial and antifungal activity (as inhibition zone in mm diameter).

Sample	*Escherichia coli* (G^-)	*Staphylococcus aureus* (G^+)	*Aspergillus flavus* (fungus)	*Candida albicans* (fungus)
Control: DMSO	0	0	0	0
Tetracycline antibacterial agent	30	28	—	—
Amphotericin B antifungal agent	—	—	16	19
5	0	0	0	0
6	12	11	0	11
8	12	11	0	9
9	13	13	9	11
11	12	12	11	10

G: Gram reaction. 0.0: no activity (inhibition zone less than 7 mm). 7–10: weak activity.
Solvent: DMSO. 11–15: moderate activity. More than 15: strong activity.

DMSO-d_6 on a Varian plus instrument (300 MHz). Mass spectra were recorded on a Shimadzu GC–MS QP-1000EX instrument (SHIMADZU USA) operating at 70 ev.

General procedure for the synthesis of *N*-(2-aminophenyl)-2-(2,4-dioxothiazolidin-5-yl)acetamide (3) and *S*-(2-amino phenyl)-2-(2,4-dioxothiazolidin-5-yl)ethanethioate (4). A mixture of **1** (0.875 g, 5 mmol) and *o*-phenylenediamine (0.54 g, 5 mmol) or *o*-aminothiophenol (0.625 g, 5 mmol) in 20 mL of absolute ethanol was refluxed for 2 h. The reaction mixture was evaporated under vacuum. The residue was recrystallized from the appropriate solvent.

***N*-(2-Aminophenyl)-2-(2,4-dioxothiazolidin-5-yl)acetamide (3).** Gray crystals; mp: 136–138°C, (ethanol) yield 60%. IR (KBr) (ν_{max}, cm^{-1}): 3401, 3342, 3283 (NH, NH2), 1749, 1703 (C═O thiazolidindione), 1640(C═O amide). ^{1}H NMR (DMSO-d_6): δ_H (ppm) 3.84 (m, 2H, CH_2), 4.98 (dd, 1H, CH, J = 3.9 and 4.8 Hz), 4.71 (br.s, 2H, NH_2, exchangeable with D_2O), 6.78–7.13 (m, 4H, Ar.H), 10.43 (s, 1H, NH, exchangeable with D_2O), 12.83 (br.s, 1H, $NH_{thiazolidindione}$, exchangeable with D_2O). MS, *m*/*z* (%) 265 (M^+, 7), 210 (27), 149 (50),105 (63), 60 (100). *Anal*. Calcd for $C_{11}H_{11}N_3O_3S$ (265): C, 49.80; H, 4.18; N, 15.84; S, 12.09. Found: C, 49.62; H, 4.33; N, 15.76; S, 11.93.

***S*-2-Amino phenyl 2-(2,4-dioxo thiazolidin-5-yl)ethanethioate (4).** Yellow crystals; mp: 76–78°C, (petroleum ether 60–80/benzene) yield 70%. IR (KBr) (ν_{max}, cm^{-1}): 3377, 3175(NH), 1747, 1652 (C═O thiazolidindione), 1727(C═O thioester). ^{1}H NMR (DMSO-d_6): δ_H (ppm) 3.90 (m, 2H, CH_2), 4.74 (dd, 1H, CH, J = 4.1 and 4.8 Hz), 4.34(br.s, 2H, NH_2, exchangeable with D_2O), 6.57–7.27 (m, 4H, Ar.H), 12.63 (br.s, 1H, $NH_{thiazolidindione}$, exchangeable with D_2O). MS, *m*/*z* (%) 282 (M^+, 5), 248 (33), 124 (100), 97 (11), 80 (52), 52 (17). *Anal*. Calcd for $C_{11}H_{10}N_2O_3S_2$ (282): C, 46.79; H, 3.57; N, 9.92; S, 22.71. Found: C, 47.92; H, 4.01; N, 10.26; S, 22.49.

General procedure for the synthesis of 5-((1*H*-benzo[*d*]imidazol-2-yl)methyl)thiazolidine-2,4-dione (5) and 5-(benzo[*d*]thiazol-2-ylmethyl)thiazolidin-2,4-dione (6).

Method 1: A mixture of **1** (0.875 g, 5 mmol) and *o*-phenylenediamine (0.54 g, 5 mmol) or *o*-minothiophenol (0.625 g, 5 mmol) in 15 mL of phosphorous oxychloride was refluxed for 18 h on water bath. The excess of $POCl_3$ was evaporated under vacuum and then poured into crushed ice with vigorous stirring; the resulted solid was filtered off and recrystallized from the appropriate solvent.

Method 2: To a solution of *o*-phenylenediamine (0.54 g, 5 mmol) or *o*-aminothiophenol (0.625 g, 5 mmol) and 0.5 mL of triethylamine in 10 mL of dry dioxane was added dropwise a solution of **2** (0.965 g, 5 mmol) in 5 mL of the same solvent. The reaction mixture was stirred for ~20 min and then poured into 100 mL of cold water; the precipitated solid was filtered off and recrystallized from the appropriate solvent.

5-((1H-Benzo[d]imidazol-2-yl)methyl)thiazolidin-2,4-dione (5). White powder, mp: 244–246°C, (acetic acid) yield = 67%. IR (KBr) (ν_{max}, cm^{-1}): 3226, 3120 (NH), 1757, 1692 (C═O thiazolidindione). ^{1}H NMR (DMSO-d_6): δ_H (ppm) 3.82–3.90 (m, 2H, CH_2), 5.13 (dd, 1H, CH, J = 4.1 and 4.3 Hz), 5.87(s, 1H, $NH_{imidazole}$, exchangeable with D_2O), 7.26–7.70 (m, 4H, Ar.H), 12.13 (s, 1H, $NH_{thiazolidindione}$, exchangeable with D_2O). MS, *m*/*z* (%) 249 (M^+ + 2, 7), 247 (M^+, 40), 188 (18), 105 (25), 87 (14), 73 (20), 60 (100), 54 (20). *Anal*. Calcd for $C_{11}H_9N_3O_2S$ (247): C, 53.43; H, 3.67; N, 16.99; S, 12.97. Found: C, 53.72; H, 4.03; N, 16.56; S, 12.57.

5-(Benzo[d]thiazol-2-ylmethyl)thiazolidin-2,4-dione (6). Yellow powder, mp: 174–176°C (ethanol), yield = 75%. IR (KBr) (ν_{max}, cm^{-1}): 3226, 3112 (NH), 1757, 1684 (C═O thiazolidindione). ^{1}H NMR (DMSO-d_6): δ_H (ppm) 3.85 (dd, 1H, 1H of CH_2, J = 8.7 and 4.2), 3.90 (dd, 1H, 1H of CH_2, J = 8.1 and 3.9), 5.11 (dd, 1H, CH, J = 3.9 and 4.5 Hz), 7.41–7.54 (m, 2H, Ar.H), 7.94 (d, 1H, Ar.H, J = 6.9), 8.08 (d, 1H, Ar.H, J = 8.7), 12.17 (s, 1H, $NH_{thiazolidindione}$, exchangeable with D_2O). MS, *m*/*z* (%) 266 (M^+ + 2, 4), 264(M^+, 37), 221 (23), 193 (42),148 (100), 108 (23), 69 (36). *Anal*. Calcd for $C_{11}H_8N_2O_2S_2$ (264): C, 49.98; H, 3.05; N, 10.60; S, 24.26. Found: C, 49.69; H, 3.23; N, 10.82; S, 23.96.

General procedure for the synthesis of *N*-(4-acetylphenyl)-2-(2,4-dioxothiazolidin-5-yl)acetamide (7). To a solution of *p*-aminoacetophenone (0.675 g, 5 mmol) and 0.5 mL of triethylamine in 10 mL of dry dioxane was added dropwise in a solution of **2** (0.965 g, 5 mmol) in 5 mL of the same solvent. The reaction mixture was left at room temperature for ~20 min and then poured into 100 mL of cold water; the precipitated solid was filtered off and recrystallized from ethanol.

Brown powder, mp: 231–233°C, yield = 60%. IR (KBr) (ν_{max}, cm^{-1}): 3336, 3200 (NH), 1749, 1680 (C═O thiazolidindione), 1707, 1655(C═O ketone and amide). ^{1}H NMR (DMSO-d_6): δ_H

(ppm) 2.65 (s, 3H, CH3), 3.09–3.82 (m, 2H, CH_2), 4.74 (dd, 1H, CH, J = 3.9 and 4.8 Hz), 7.83 (d, 2H, Ar.H, J = 9 Hz), 7.92 (d, 2H, Ar.H, J = 8.4 Hz), 10.52 (s, 1H, NH_{amide} , exchangeable with D_2O) 12.04 (s, 1H, $NH_{thiazolidindione}$, exchangeable with D_2O). MS, *m/z* (%) 292(M^+, 5), 248(13), 233 (24), 199 (36),172 (17), 145 (30), 120 (100), 92 (33), 65 (34), 56 (33). *Anal*. Calcd for $C_{13}H_{12}N_2O_4S$ (292): C, 53.42; H, 4.14; N, 9.58; S, 10.97. Found: C, 53.58; H, 3.98; N, 10.02; S, 10.66.

General procedure for the synthesis of 2-(2-(2,4-dioxothiazolidin-5-yl)acetamido)benzoic acid (8).

Method 1: To a solution of anthranilic acid (6.85 g,0.05 mol) in dry pyridine was added dropwise a solution of **2** (9.65 g, 0.05 mol) in dry ether with stirring for 5 h. The excess of ether was evaporated under vacuum and then poured into ice cold HCl. The resulted solid was filtered off and recrystallized from ethanol. Yield = 58%.

Method 2: A mixture of **2** (9.65 g, 0.05 mol) and anthranilic acid (6.85 g,0.05 mol) in 40 mL of dry toluene in the presence of catalytic amount of pyridine was refluxed for 6 h. Toluene was evaporated under vacuum. The reaction mixture was poured into ice cold HCl. The precipitated solid was separated by filtration and recrystallized from ethanol. Yield = 75%.

White powder, mp: 252–254°C. IR (KBr) (ν_{max}, cm^{-1}): 3300 (br., OH), 3240 (NH), 1755, 1699 (C═O thiazolidindione), 1656(C═O amide). ^{1}H NMR (DMSO-d_6): δ_H (ppm) 3.21–3.35 (m, 2H, CH_2), 4.73 (dd, 1H, CH, J = 4.2 and 4.2 Hz), 7.15–8.37 (m, 4H, Ar.H), 11.61 (s, 1H, NH_{amide} , exchangeable with D_2O), 12.04 (s, 1H, $NH_{thiazolidindione}$, exchangeable with D_2O), 13.65 (s, 1H, COOH, exchangeable with D_2O). MS, *m/z* (%) 294 (M^+,20), 276 (11), 217 (14), 165 (11), 137 (70), 119 (100), 90 (28), 59 (26), 55 (19). *Anal*. Calcd for $C_{12}H_{10}N_2O_5S$ (294): C, 48.98; H, 3.43; N, 9.52; S, 10.90. Found: C, 49.12; H, 3.69; N, 9.89; S, 10.38.

General procedure for the synthesis of 5-((4-oxo-4*H*-benzo[*d*][3,1]oxazin-2-yl)methyl)thiazolidin-2,4-dione (9). A solution of **8** (5.88 g, 0.02 mol) in 10 mL of freshly distilled acetic anhydride was refluxed for 2 h. The excess of acetic anhydride was evaporated under vacuum. The residue was recrystallized from ethanol.

White powder, mp: 220–222°C, yield = 80%. IR (KBr) (ν_{max}, cm^{-1}): 3216 (NH), 1750 (br.), 1701 (C═O benzoxazinone and thiazolidindione). ^{1}H NMR (DMSO-d_6): δ_H (ppm) 3.46–3.48 (m, 2H, CH_2), 4.89–4.94 (m, 1H, CH), 7.53–8.13 (m, 4H, Ar. H), 12.18 (s, 1H, $NH_{thiazolidindione}$, exchangeable with D_2O).). MS, *m/z* (%) 276 (M^+,35), 233 (34), 205 (84), 161 (100),146 (62), 118 (28), 90 (87), 64 (24), 50 (28). *Anal*. Calcd for $C_{12}H_8N_2O_4S$ (276): C, 52.17; H, 2.92; N, 10.14; S, 11.61. Found: C, 52.48; H, 3.23; N, 9.92; S, 11.24.

General procedure for the reaction of 9 with ammonium acetate to give 10. A mixture of **9** (0.276 g, 1 mmol) and dry ammonium acetate (0.231 g, 3 mmol) was heated in sand bath at (140–160°C) for 3 h; the reaction mixture was cooled and then poured into water. The resulted solid was filtered off and recrystallized from ethanol.

2-Mercapto-3-(4-oxo-3,4-dihydroquinazolin-2-yl)propanamide (10). Brown powder, mp: 196–198°C. Yield = 84%. IR (KBr) (ν_{max}, cm^{-1}): 3307, 3211 (NH), 1686(C═O quinazolinone), 1652 (C═O amide). ^{1}H NMR (DMSO-d_6): δ_H (ppm) 2.49–2.63 (m, 2H, CH_2), 3.11–3.31 (m, 1H, CH), 3.62 (s, 1H, SH, exchangeable with D_2O) 7.42–8.09 (m, 4H, Ar.H), 9.17 (br.s, 2H, NH_2, exchangeable with D_2O), 10.02 (s, 1H, $NH_{quinazoline}$, exchangeable with D_2O). *Anal*. Calcd for $C_{11}H_{11}N_3O_2S$ (249): C, 53.00; H, 4.45; N, 16.86; S, 12.86. Found: C, 52.82; H, 4.69; N, 16.98; S, 13.08.

General procedure for the reaction of 9 with thiosemicarbazide to give 11. A mixture of **9** (0.552 g, 2 mmol) and thiosemicarbazide (0.182 g, 2 mmol) in 20 mL absolute ethanol in the presence of catalytic amount of pyridine (or in 10 mL of pyridine only) was refluxed for 6 h. The reaction mixture was evaporated under vacuum. The residue was recrystallized from ethanol.

5-((2-Thioxo-2,3-dihydro-[1,2,4]triazolo[1,5-c]quinazolin-5-yl) methyl)thiazolidin-2,4-dione(11). Beige powder, mp: 164–166°C, yield = 74%. IR (KBr) (ν_{max}, cm^{-1}): 3436, 3208 (NH), 1753, 1696 (C═O thiazolidindione), 1266 (C═S). ^{1}H NMR (DMSO-d_6): δ_H (ppm) 3.14–3.35 (m, 2H, CH_2), 4.69–4.73(m, 1H, CH), 7.22 (dd, 1H, Ar.H, J = 7.2 and 7.8 Hz), 7.59 (dd, 1H, Ar.H, J = 6.9 and 8.7 Hz), 7.88 (d, 1H, Ar.H, J = 6.3 Hz), 8.04 (d, 1H, Ar.H, J = 8.1 Hz), 10.61 (s, 1H, NHC═S, exchangeable with D_2O) 12.04 (s, 1H, $NH_{thiazolidindione}$, exchangeable with D_2O). *Anal*. Calcd for $C_{13}H_9N_5O_2S_2$ (331): C, 47.12; H, 2.74; N, 21.13; S, 19.35. Found: C, 47.58; H, 2.98; N, 20.92; S, 19.86.

General procedure for the reaction of 9 with hydrazine hydrate to give 12. To a solution of **9** (0.552 g, 2 mmol) in 20 mL of absolute ethanol was added dropwise hydrazine hydrate (0.1 g, 2 mmol) with stirring at room temperature for 2 h. The reaction mixture was evaporated under vacuum; the residue was recrystallized from ethanol/dioxane.

5-((3-Amino-4-oxo-3,4-dihydroquinazolin-2-yl) methyl) thiazolidin-2,4-dione (12). White powder, mp: 234–236°C, yield = 62%. IR (KBr) (ν_{max}, cm^{-1}): 3437, 3322, 3208 (NH, NH_2), 1754, 1682 (C═O thiazolidindione). ^{1}H NMR (DMSO-d_6): δ_H (ppm) 3.46–3.57 (m, 2H, CH_2), 4.88–4.93 (m, 1H, CH), 5.75 (s, 2H, NH_2, exchangeable with D_2O), 7.51–8.14 (m, 4H, Ar.H), 12.04 (s, 1H, $NH_{thiazolidindione}$, exchangeable with D_2O). MS, *m/z* (%) 290(M^+,20), 276(18), 247 (17), 186 (50),175 (30), 165 (53), 146 (43), 119 (100), 91(37), 59 (33). *Anal*. Calcd for $C_{12}H_{10}N_4O_3S$ (290): C, 49.65; H, 3.47; N, 19.30; S, 11.05. Found: C, 49.38; H, 3.98; N, 20.02; S, 11.49.

General procedure for the synthesis of 5-((4-thioxo-4*H*-benzo[*d*][3,1]oxazin-2-yl)methyl)thiazolidin-2,4-dione (13).
A mixture of **9** (0.276 g, 1 mmol) and 3 or 6 mmol of phosphorous pentasulfide in 10 mL of pyridine was refluxed for 8 h. The reaction mixture was poured into hot water and left overnight. The resulted solid was filtered off and then recrystallized from benzene/ethanol.

Brown powder, mp: 164–166°C, yield = 65%. IR (KBr) (ν_{max}, cm^{-1}): 3321, 3283 (NH), 1753, 1680 (C═O thiazolidindione), 1274 (C═S). MS, *m/z* (%) 292(M^+,47), 249 (65), 221 (39),177 (100), 162 (28), 133 (24), 76 (52), 50(66). *Anal*. Calcd for $C_{12}H_8N_2O_3S_2$ (292): C, 49.30; H, 2.76; N, 9.58; S, 21.94. Found: C, 49.72; H, 2.68; N, 9.23; S, 21.41.

General procedure for the reaction of compound 9 with Br_2 gave compound 8. A mixture of **9** (0.276 g, 1 mmol) and Br_2 (0.158 g, 1 mmol) in 15 mL of chloroform was refluxed for 2 h on water bath. The reaction mixture was evaporated under vacuum. The solid obtained was recrystallized from ethanol to give the opened structure **8** that was confirmed by (mp, mixed mp, and TLC).

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