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Use of 2-{[5-(2-Amino-4-oxoquinazolin-3(4*H*)-yl)-1,3,4-thiadiazol-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione in the Synthesis of Novel Quinazolinone Derivatives

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Abstract

The 2-{[5-(2-Amino-4-oxoquinazolin-3(4*H*)-yl)-1,3,4-thiadiazol-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione **1** was synthesized and allowed to react with each of *p*-methoxybenzaldehyde, *p*-methoxyacetophenone and chloroacetyl chloride to produce the Schiff bases **2** and **3** and 2-chloro-*N*-(3-{5-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-1,3,4-thiadiazol-2-yl}-4-oxo-3,4-dihydroquinazolin-2-yl)acetamide **6**, respectively. The products **2** and **3** were reacted with phenyl isothiocyanate to afford **4** and **5**. Derivative **6** was reacted with various nucleophiles, namely: thioglycolic acid, ethyl glycinate and 2-aminoethanol giving **7-9** respectively. In turn, the derivative **8** was reacted with α-bromoglucose tetraacetate affording product **8a** whereas **9** was reacted with *p*-acetylaminobenzenesulfonyl chloride affording derivative **9a**. Moreover, the reactions of the derivative **6** with potassium thiocyanate, potassium cyanate, malonitrile, ethyl cyanoacetate and ammonium acetate gave derivatives **10-15**, respectively. All the synthesized derivatives were confirmed by the IR, mass, ^{1}H-NMR and elemental analysis.

Key words: Quinazolinyl thiazolidine, thioxodiazetidinyl quinazoline, piperazinyl quinazolinone, thiomorpholine and triazinoquinazoline.

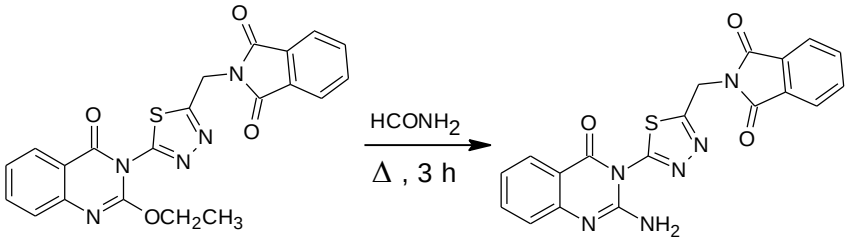
1. Introduction

In recent years there has been an increasing interest in the chemistry of the 4(3*H*)-quinazolinone derivatives because of their biological importance. Many of them show antifungal (Partoli *et al* 1998), antibacterial (Abdel-Hamid *et al* 1997), anticancer (Barker 1995), anti-inflammatory (Bakhit *et al* 1998), anticonvulsant (Gursoy *et al* 1995), immunotropic (Nawrocka *et al* 1997), hypolipidemic (Kuroji *et al* 1996), antitumor (Hame *et al* 1996), antiulcer (Terashima *et al* 1995), analgesic (Hemalatha *et al* 2011), antiproliferative (Raffa *et al* 1999) activities and inhibitory effects for the thymidylate synthase and poly (ADP-ribose) polymerase (PARP) (Baek *et al* 1998). Some of 4-anilinoquinazolines have been found to be potential and highly selective inhibitors of human immunoglobulin E (Berger *et al* 2001) and epidermal growth factor receptor tyrosine kinase (Bridges 2001) which regulates the cell growth and proliferation, so they can work as potent anti-allergic and anti-cancer agents respectively.

2. Results and Discussion

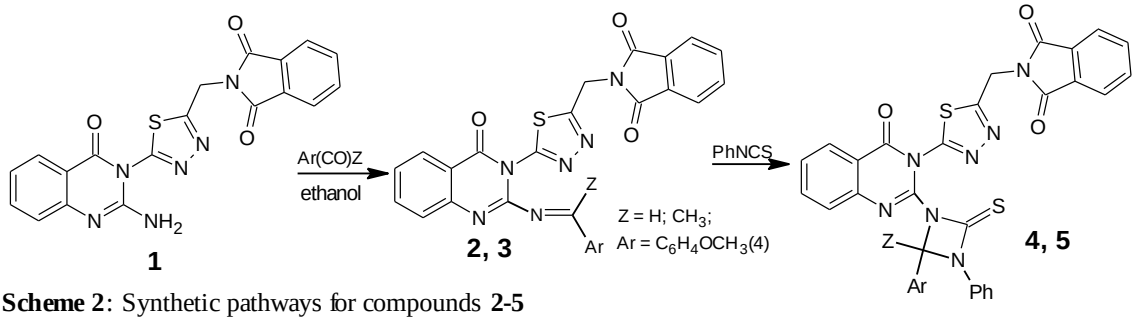
In a continuation of our previous work (El-Hashash *et al*, 2011), novel 2-{[5-(2-amino-4-quinazolin-3(4*H*)-yl)-1,3,4-thiadiazol-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione **1** was first synthesized from our previously

synthesized 2-{[5-(2-ethoxy-4-oxoquinazolin-3(4*H*)-yl)-1,3,4-thiadiazol-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione as the starting material (Scheme 1).



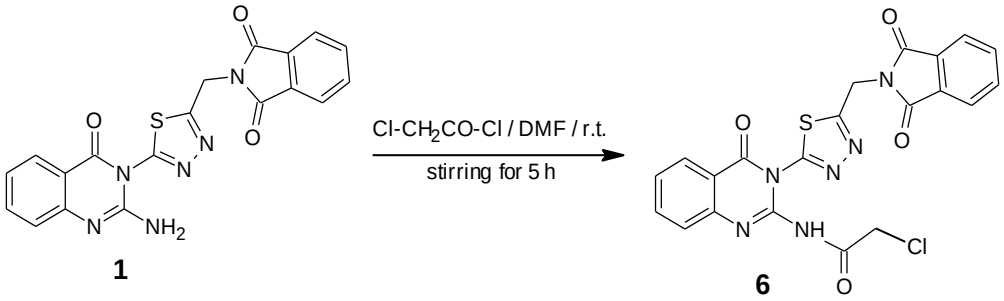
Scheme 1: Synthetic pathways for compound **1**

Therefore, we first discuss and report the behavior of compound **1** towards two selected aldehyde and ketone and chloroacetyl chloride to give the Schiff bases **2** and **3** and 2-chloro-*N*-(3-{5-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl) methyl]-1,3,4-thiadiazol-2-yl}-4-oxo-3,4-dihydroquinazolin-2-yl) acetamide **6**, respectively. Similarly, we report and interpret the behavior of **6** towards various *N*-, *O*- or *S*-nucleophiles in synthesis of new cyclic and acyclic derivatives, with the aim of obtaining more precise information about the course of the reaction. It was noticed that all the pathways assigned for the synthesis of these derivatives are always terminated by a cyclization step caused by elevation in the reaction temperature giving larger stable products. Moreover, it was also noticed that the exocyclic amino nitrogen atom at the 2-position of the quinazolinone became a member of the newly attached five-membered or six-membered heterocyclic ring (e.g. piperazine, pyrrolidine, thiazolidine, diazetidine, oxazolidine, triazine, thiomorpholine and others). The large number of products explored in this way enhances the structure-to-property relationship. In the synthesis of Schiff bases, the reaction of compound **1** with *p*-methoxyacetophenone or *p*-methoxy- benzaldehyde in absolute ethanol gave the Schiff bases **2** and **3** respectively (Scheme 2). Thereafter, **2** and **3** were reacted with phenyl-isothiocyanate in refluxing toluene to give 2-(4-thioxo1,3-diazetidin-1-yl)-3-phthalimidomethylthiadiazolo-quinazolin-4(3*H*)-one products **4** and **5**, respectively. The ^{1}H-NMR spectra of **2** and **3** any band for the NH_2 group of compound **1**. Moreover, the IR spectra of **4** and **5** showed absorption bands in the range 1319-1322 attributable for υ_{max} of C=S.



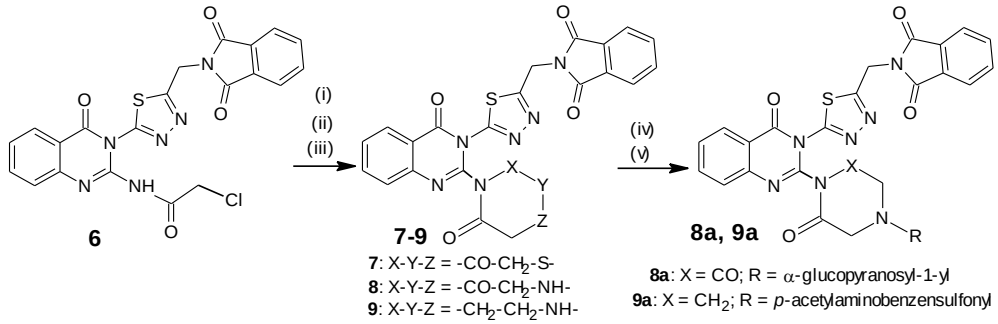
Scheme 2: Synthetic pathways for compounds **2-5**

Compound **1**, on the other hand, was reacted with chloroacetyl chloride, in DMF and at room temperature, to give 3-chloroacetylamino-2-ethoxyquinazolinone **6** (Scheme 3). The IR spectrum showed an absorption 1694 attributable for υ_{max} of C=O group attached to *sec*-NH. The ^{1}H-NMR showed singlets at δ 4.60 which is attributed to CH_2Cl and at 8.0 attributable to *sec*-NH group. The mass spectrum showed a molecular ion peak for the parent product at *m/z* 480.5, 482.5.



Scheme 3: Synthesis of compound **6**

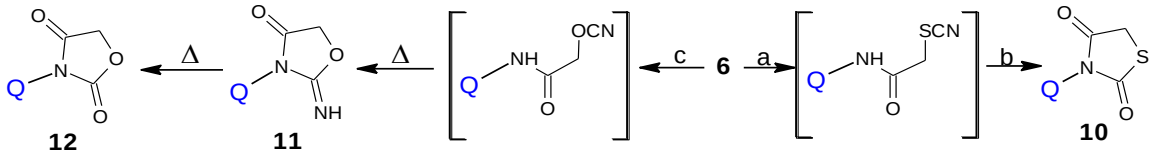
Compound **1** reacted with thioglycolic acid, ethyl glycinate in boiling pyridine, and with 2-aminoethanol in boiling ethanol, affording the products **7-9** with thiomorpholine or piperazine ring at 2-position respectively (Scheme 4). Products **7-9** were produced via ring closure. Their IR spectra showed absorptions in the ranges 1668-1671, 1735-1737 and 1772-1778 attributable for υ_{max} of C=O groups in each of the quinazolinone, the thiomorpholino or piperazino and the phthalimidomethyl moieties, respectively. In addition, the IR spectra of all **7-9** devoid any band for *sec*-NH group. Treating derivative **8** with α-bromoglucose tetraacetate in 1,4-dioxane, followed by a deacetylation step of the product by methanolic sodium carbonate, afforded product **8a**. Similarly, treatment of derivative **9** with *p*-acetylaminobenzenesulfonyl chloride in dry pyridine gave product **9a**. The IR spectrum of **8a** showed absorption bands at 3236, 3400 attributable for υ_{max} of OH groups of the sugar moiety, and the ^{1}H-NMR spectrum devoid any band of NH group. The IR spectrum of product **9a** showed absorptions at 1160 and 3371 which are attributable for υ_{max} of S=O and NH groups of the *p*-acetylaminobenzenesulfonyl moiety. Also, the ^{1}H-NMR showed a singlet at δ 7.23 for the referred NH.



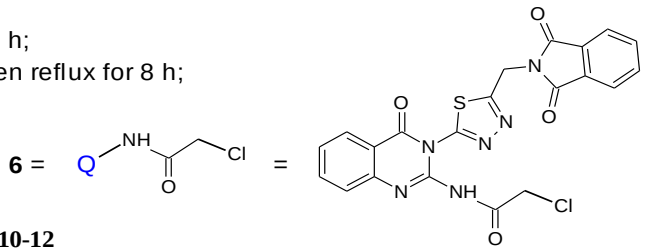
(i) HS-CH_2COOH / pyridine / 8 h (ii) H_2NCH_2COOEt / pyridine / 8 h
(iii) H_2NCH_2CH_2OH / ethanol / 6 h.
(iv) a-bromoglucose tetraacetate then Na_2CO_3/CH_3OH/r.t. 4 h;
(v) p-acetylaminobenzenesulfonyl chloride/pyridine.

Scheme 4 : Synthetic pathways for compounds **7-9**

The derivative **6** and potassium thiocyanate were stirred in DMF at room temperature giving the open chain structure, which on reflux with few drops of pyridine and ethanol gave derivative **10** (Scheme 5). Repeating this procedure with potassium cyanate in ethanol afforded the open structure which on reflux gave the 2-(2-imino-1,3-oxazolidinyl) quinazolinone **11**, which on further heating oxidized to afford the more stable 1,3-oxazolidine-2,4-dione derivative **12**.

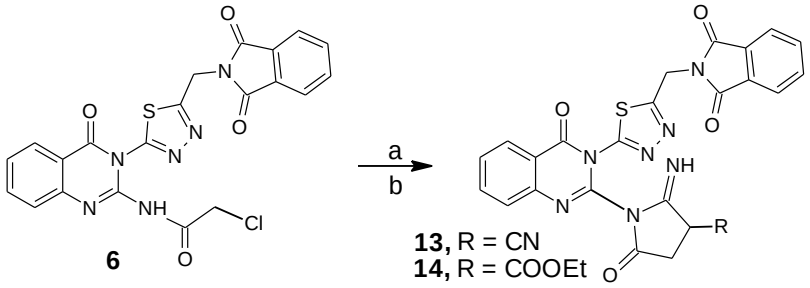


(a) KSCN / DMF / r.t. stirring 8 h
(b) drops of pyridine / ethanol / reflux for 15 h;
(c) KOCN / ethanol / stirring at r.t. for 4 h then reflux for 8 h;



Scheme 5 : Synthetic pathways for compounds **10-12**

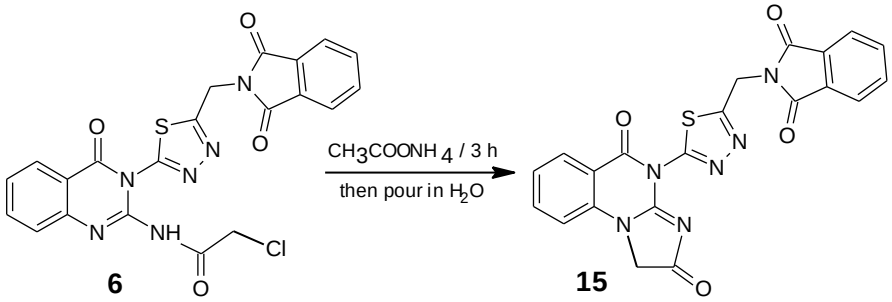
On the other hand, product **6** was heated under reflux with malonitrile and ethyl cyanoacetate in dry pyridine affording products **13** and **14** respectively (Scheme 6). The IR spectra of products **10-14** showed appearance of the absorption bands in the ranges 1668-1671 and 1726-1734 and 1777-1779 attributable for υ_{max} of C=O of the quinazolinone and the five-membered ring at 2-position and disappearance of band of C-Cl bond. The the IR spectra of **13** and **14** showed absorptions in the range 3105-3330 attributable for υ_{max} of =NH groups.



(a) $NCCH_2CN$/pyridine/3 h; (b) $NCCH_2COOEt$/pyridine/3 h.

Scheme 6 : Synthetic pathways for compounds **13** and **14**

The derivative **6** was also fused with ammonium acetate affording the annelated quinazoline **15** (Scheme 6). The IR spectrum for product **15** showed disappearance of C=O band at 1694 which was previously assigned in the IR spectrum of product **6**.



Scheme 7 : Synthetic pathway for compound **15**

3. Experimental

General

All melting points recorded are uncorrected. The IR spectra were recorded on a Pye Unicam SP1200 spectrophotometer using the KBr wafer technique. The ^{1}H-NMR spectra were determined on a Varian FT-200, or Bruker AC-200 MHz instrument using TMS as an internal standard. Chemical shifts (δ) are expressed in ppm. The mass spectra were determined using MP model NS-5988 and Shimadzu single focusing mass spectrometer (70 eV). All solvents used were of HPLC/AnalaR grade. All reagents were used as received from Alfa Aesar.

Synthesis of the starting material 2-{[5-(2-amino-4-oxoquinazolin-3(4H)-yl)-1,3,4-thiadiazol-2-yl] methyl}-1H-isoindole-1,3(2H)-dione **(1)**:

2-{[5-(2-Ethoxy-4-oxoquinazolin-3(4*H*)-yl)-1,3,4-thiadiazol-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione was heated under reflux with formamide (0.01 mol each) for 3h. The mixture was poured onto ice/water mixture with stirring leaving a white gum to separate out which began to solidify forming. This material was washed with water, filtered and recrystallized from ethanol as off-white needles of **1**, yield 68 %, m.p. 272-273 ℃. Anal. for $C_{19}H_{12}N_6O_3S$ (m.w. 404); Found: C, 56.49; H, 2.99; N, 20.83; S, 7.95; Calcd: C, 56.44; H, 2.97; N, 20.79; S, 7.92; IR υ (cm^{-1}) 1671, 1730, 1790 (3xC=O), 1528 (C=N); 3389 (NH); 3443 (CH); MS: *m/z* (int. %) $[M+H]^+$ 404 (78.3); ^{1}H-NMR (DMSO-d_6) δ 7.29-8.19 (m, 4H; ArH), 2.0 (s, NH, amine).

Synthesis of Schiff bases **(2, 3)***:*

Heating a mixture of compound **1** (0.01 mol) and *p*-methoxybenzaldehyde or *p*-methoxyacetophenone (0.01 mol) in absolute ethanol (10 mL) in a water bath for 30 min then leaving it to cool in ice -water gave a solid material which was filtered, washed with 2 % HCl then water and crystallized from ethanol to give products **2** and **3** respectively.

2-[(5-{2-[(1E)-(4-Methoxyphenylideneamino)]-4-oxoquinazolin-3(4H)-yl}-1,3,4-thiadiazol-2-yl)methyl]-1H-isoindole-1,3(2H)-dione **(2)**: White crystals from ethanol; m.p. 251-252 ℃, yield 48 %. Anal. for $C_{27}H_{18}N_6O_4S$ (m.w. 522); Found: C, 62.12; H, 3.48; N, 16.13; S, 6.16; Calcd: C, 62.07; H, 3.45; N, 16.09; S, 6.13; IR υ (cm^{-1}) 1514 (N=CH), 1631 (C=N), 1670, 1727, 1786 (3xC=O) 2720, 2820 (CH); MS: *m/z* (int. %) $[M+H]^+$ 522 (55.7); ^{1}H-NMR (DMSO-d_6) δ 3.93 (s, 3H, O*CH*$_3$), 5.17 (s, 2H, *CH*$_2$), 6.91-7.59 (m, 4H, Ph-H), 7.88-7.96 (m, 4H, phthalimide moiety), 7.40-8.13 (m, 4H, quinazolinone), 8.58 (s, 1H, N=C*H*).

2-[(5-{2-[(1Z)-1-(4-Methoxyphenyl)ethylideneamino]-4-oxoquinazolin-3(4H)-yl}-1,3,4-thiadiazol-2-yl)methyl]-1H-isoindole-1,3(2H)-dione **(3)**: White crystals from ethanol, m.p. 261-263 ℃, yield 68 %. Anal. for $C_{28}H_{20}N_6O_4S$ (m.w. 536); Found: C, 62.72; H, 3.76; N, 15.69; S, 5.99; Calcd: C, 62.69; H, 3.73; N, 15.67; S, 5.97; IR υ (cm^{-1}) 1628 (C=N), 1668, 1730, 1782 (3C=O), 3447 (CH); MS: *m/z* (int. %) $[M+H]^+$ 536 (61.3); ^{1}H-NMR (DMSO-d_6) δ 2.37 (s, 3H, *CH*$_3$), 3.93 (s, 3H, O*CH*$_3$), 5.17(s, 2H, *CH*$_2$), 7.30-7.60 (m, 4H, PhH), 7.88-8.04 (m, 4H, phthalimido moiety), 7.51-8.13 (m, 4H, quinazolinone).

Synthesis of Compounds **4** and **5**:

Equimolar amounts of **3** or **4** (0.01 mol) and phenyl isothiocyanat in 25 mL toluene was refluxed for 6 h. The solvent was distilled off, the residue was washed with ethanol followed by water and then the product was crystallized from ethanol as yellow crystals.

2-({5-[4-Oxo-2-(4-(4-methoxyphenyl)-3-phenyl-2-thioxo-1,3-diazetidin-1-yl)quinazolin-3(4H)-yl]-1,3,4-thia-diazol-2-yl}methyl)-1H-isoindole-1,3(2H)-dione **(4)**: M.p. 298-300 ℃, yield 68 %. Anal. for $C_{34}H_{23}N_7O_4S_2$ (m.w. 657); Found: C, 62.41; H, 3.77; N, 14.97; S, 9.81; Calcd: C, 62.10 ; H, 3.50; N, 14.92; S, 9.74; IR υ (cm^{-1}) 1519 (N=C), 1671, 1728, 1777 (3xC=O), 3443 (CH); 1319 (C=S); MS: *m/z* (int. %) $[M+H]^+$ 657 (59.1); ^{1}H-NMR (DMSO-d_6) δ 3.74 (s, 3H, -O*CH*$_3$), 4.59 (d, 1H, N-*CH*), 5.17 (s, 2H, *CH*$_2$), 5.30 (d, 1H, *CH*Ph), 7.03-7.20 (m, 4H, -*C*$_6$*H*$_4$OCH$_3$), 7.25-7.29 (m, 5H, -*C*$_6$*H*$_5$), 7.03-8.06 (m, 4H, quinazolinone), 7.88-8.05 (m, 4H, phthalimido moiety).

2-({5-[4-Oxo-2-(4-methyl-4-(4-methoxyphenyl)-3-phenyl-2-thioxo-1,3-diazetidin-1-yl)quinazolin-3(4H)-yl]-1,3,4-thia-diazol-2-yl}methyl)-1H-isoindole-1,3(2H)-dione **(5)**: M.p. > 300 ℃, yield 72 %. Anal. for $C_{35}H_{25}N_7O_4S_2$ (m.w. 671); Found: C, 62.66; H, 3.80; N, 14.63; S, 9.58; Calcd: C, 62.59; H, 3.73; N, 14.60; S, 9.54; IR υ (cm^{-1}) 1522 (N=C), 1670, 1730, 1774 (3xC=O), 3327, 3433 (CH); 1322 (C=S); MS: *m/z* (int. %) $[M+H]^+$ 671 (66.3); ^{1}H-NMR (DMSO-d_6) δ 1.64 (s, 3H, -*CH*$_3$), 3.75 (s, 3H, -O*CH*$_3$), 4.49 (s, 1H, *CH*Ph), 5.17 (s, 2H, *CH*$_2$), 6.84-7.32 (m, 4H, -*C*$_6$*H*$_4$OCH$_3$), 7.28-7.30 (m, 5H, *C*$_6$*H*$_5$), 7.19-7.99 (m, 4H, quinazolinone), 7.85-8.05 (m, 4H, phthalimido moiety).

*Synthesis of compound **(6)**:*

Compound **1** (0.01 mol) was dissolved in 50 mL of dry toluene and cooled to 15 ℃. To this solution was added drop wise an equimolar amount of chloroacetyl chloride with frequent stirring. The temperature of the reaction was brought slowly to room temperature and then the solution was heated under reflux for 4 h. The excess toluene was distilled off and the resultant precipitate was filtered, washed repeatedly with dry toluene, dried and crystallized from aqueous dioxane.

2-Chloro-N-(3-{5-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1,3,4-thiadiazol-2-yl}-4-oxo-3,4-dihydroquinazolin-2-yl)acetamide **(6)**: White crystals from dioxane; m.p. 179-181 ℃, yield 73 %. Anal. for $C_{21}H_{13}ClN_6O_4S$ (m.w. 480.5); Found: C, 52.48; H, 2.74; Cl, 7.43; N, 14.57; S, 6.71; Calcd: C, 52.44 ; H, 2.71; Cl, 7.39; N, 14.48; S, 6.66; IR υ (cm^{-1}) 3205 (N-H), 3010 (Ar-H), 2935 (CH_2), 1666, 1694, 1776 (CO), 775 (CCl); MS: *m/z* (int. %) $[M+H]^+$ 480.5 (73.4); ^{1}H-NMR (DMSO-d_6) δ 4.60 (s, 2H, *CH*$_2$Cl), 8.00 (s, 1H, *NH*), 7.25-7.85 (m, 4H, quinazolinone), 7.96-8.03 (m, 4H, phthalimido moiety).

*Synthesis of compounds **7** and **8***

Compound **1** (0.01 mol) was heated under reflux with thioglycolic acid or ethyl glycinate (0.01 mol) in 20 mL pyridine for 8h. The mixture was cooled down then poured onto ice-water mixture and stirred allowing the white precipitate to settle down. The precipitate was filtered, washed thoroughly, dried and crystallized from ethanol affording white needles of compounds **7** or **8**.

2-({5-[2-(3,5-Dioxothiomorpholin-4-yl)-4-oxoquinazolin-3(4H)-yl]-1,3,4-thiadiazol-2-yl}methyl)-1H-isoindole-1,3(2H)-dione **(7)**: Yield 54 %; m.p. 299-301 ℃. Anal. for $C_{23}H_{14}N_6O_5S_2$ (m.w. 518); Found: C, 52.69; H, 4.12; N, 13.23; S, 10.10; Calcd: C, 52.66 ; H, 4.08; N, 13.17; S, 10.03; IR υ (cm^{-1}) 1671, 1736, 1776 (C=O), 2829, 2930 (C-H); MS: *m/z* (int. %) $[M+H]^+$ 518 (62.7); ^{1}H-NMR (DMSO-d_6) δ 3.77, 4.12 (4 d, 4H, (*CH*$_2$)$_2$S), 5.17 (s, 2H, *CH*$_2$N), 7.32-7.87 (m, 4H, quinazolinone), 7.94-8.04 (m, 4H, phthalimide).

2-({5-[2-(3,5-Dioxopiperazin-4-yl)-4-oxoquinazolin-3(4H)-yl]-1,3,4-thiadiazol-2-yl}methyl)-1H-isoindole-1,3(2H)-dione **(8)**: Yield 58 %; m.p. 221-223 ℃. Anal. for $C_{23}H_{15}N_7O_5S$ (m.w. 501); Found: C, 55.14; H, 3.03; N, 19.61; S, 6.42; Calcd: C, 55.09; H, 2.99; N, 19.56; S, 6.39; IR υ (cm^{-1}) 1668, 1735, 1772 (C=O), 2808, 2937 (C-H), 3180 (NH); MS: *m/z* (int. %) $[M+H]^+$ 501 (57.3); ^{1}H-NMR (DMSO-d_6) δ 1.91 (s,

1H, *NH*), 3.45, 3.46 (4 d, 4H, $(CH_2)_2S$), 5.17 (s, 2H, CH_2N), 7.32-7.87 (m, 4H, quinazolinone), 7.94-8.04 (m, 4H, phthalimido moiety).

2-({5-[2-(1-(α-glucopyranosyl-1-yl)-3,5-Dioxopiperazin-4-yl)-4-oxoquinazolin-3(4H)-yl]-1,3,4-thiadiazol-2-yl}methyl)-1H-isoindole-1,3(2H)-dione **(8a)**: Yield 42 %; m.p. 288-291 ℃. Anal. for $C_{29}H_{25}N_7O_{10}S$ (m.w. 663); Found: C, 52.53; H, 3.81; N, 14.81; S, 4.87; Calcd: C, 52.49; H, 3.77; N, 14.78; S, 4.83; IR υ (cm^{-1}) 1670, 1737, 1773 (C=O), 3236, 3400 (OH bonded and non-bonded). MS: *m/z* (int. %) $[M+H]^+$ 663 (47.8); ^{1}H-NMR (DMSO-d_6) δ 3.25 (4 d, 4H, $(CH_2)_2S$), 5.17 (s, 2H, CH_2N), 3.30-3.65 (m, 6H, H-2', H-3', H-4', H-5', H-6_a' and H-6_b'), 3.58 (m, 2'-OH, 3'-OH, 4'-OH), 3.65 (s, 6'-OH), 4.20 (dd, 1H, H-1'), 7.88-7.98 (m, 4H, phthalimido moiety), 7.32-8.02 (m, 4H, quinazolinone).

2-({5-[2-(2-Oxopiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]-1,3,4-thiadiazol-2-yl}methyl)-1H-isoindole-1,3 (2H)-dione **(9)**: Yield 53 %; m.p. 231-233 ℃. Anal. for $C_{23}H_{17}N_7O_4S$ (m.w. 487); Found: C, 56.73; H, 3.53; N, 20.16; S, 6.61; Calcd: C, 56.67; H, 3.49; N, 20.12; S, 6.57; IR υ (cm^{-1}) 1668, 1737, 1778 (C=O), 2808, 2937 (C-H), 3180 (N-H); MS: *m/z* (int. %) $[M+H]^+$ 487 (78.9); ^{1}H-NMR (DMSO-d_6) δ 2.92-3.84 (4 m, 4H, CH_2CH_2), 3.62, 3.48 (2 d, 2H, COCH_2), 7.25-7.86 (m, 4H, quinazolinone), 7.40-8.02 (m, 4H, phthalimido moiety).

2-({5-[2-(4-(4-Acetylaminobenzensulfonyl)-2-oxopiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]-1,3,4-thiadiazol-2-yl}methyl)-1H-isoindole-1,3 (2H)-dione **(9a)**: Yield 43 %; m.p. 301-302 ℃. Anal. for $C_{31}H_{24}N_8O_7S_2$ (m.w. 684); Found: C, 54.44; H, 3.58; N, 16.48; S, 10.01; Calcd: C, 54.39 ; H, 3.51; N, 16.37; S, 9.36; IR υ (cm^{-1}) 1160 (S=O), 1668, 1712, 1735(C=O), 2808, 2992 (C-H), 3371 (N-H); MS: *m/z* (int. %) $[M+H]^+$ 684 (56.3); ^{1}H-NMR (DMSO-d_6) δ 3.38-3.65 (4 m, 4H, CH_2CH_2), 4.04, 4.29 (2d, 2H, -COCH_2), 7.23 (s, 1H, *NH*), 7.26-7.85 (m, 4H, quinazolinone), 7.98-8.05 (m, 4H, phthalimido moiety), 7.65-8.13 (m, 4H, Ph-H).

Synthesis of compound **(10)**:

A mixture of derivative **6** (0.01 mol) and potassium thiocyanate (0.01 mol) in 25 mL of DMF was stirred at room temperature for 8 h. The mixture was then heated under reflux in 20 mL of ethanol with few drops of pyridine for 15h. The mixture was poured onto dilute ice-water/HCl mixture with continuous stirring where a solid material began to precipitate. The mixture was filtered, washed thoroughly with water, air-dried and crystallized from ethanol affording yellowish white needles of derivative **10**.

2-({5-[2-(2,4-Dioxo-1,3-thiazolidin-3-yl)-4-oxoquinazolin-3(4H)-yl]-1,3,4-thiadiazol-2-yl}methyl)-1H-isoindole-1,3(2H)-dione **(10)**: Yield 37 %; m.p. 144-146 ℃. Anal. for $C_{22}H_{12}N_6O_5S_2$ (m.w. 504); Found: C, 52.44; H, 2.41; N, 16.73; S, 12.82; Calcd: C, 52.38; H, 2.38; N, 16.67; S, 12.70; IR υ (cm^{-1}) 1669, 1734, 1776 (C=O), 2833, 2954 (C-H); MS: *m/z* (int. %) $[M+H]^+$ 504 (77.2); ^{1}H-NMR (DMSO-d_6) δ 3.98 (2d, 2H, CH_2S), 5.17 (s, 2H, CH_2N), 7.32-7.87 (m, 4H, quinazolinone), 7.94-8.04 (m, 4H, phthalimido moiety) .

Synthesis of compounds **11** *and* **12**:

A mixture of compound **6** (0.01 mol) and potassium cyanate (0.01 mol) in 25 mL of ethanol was stirred at room temperature for 4h. The mixture was heated under reflux in 20 mL of ethanol for 8h. The mixture was poured onto ice-water mixture with continuous stirring where a solid material began to precipitate. This was filtered, washed thoroughly with water, dried and crystallized from ethanol to give brownish white needles of derivative **11**. Further heating of product **11** led to its oxidation affording product **12** as light brown crystals.

2-({5-[2-(2-Imino-4-oxo-1,3-oxazolidin-3-yl)-4-oxoquinazolin-3(4H)-yl]-1,3,4-thiadiazol-2-yl}methyl)-1H-isoindole-1,3(2H)-dione **(11)**: Yield 42 %; m.p. 158-160 ℃; Anal. for $C_{22}H_{13}N_7O_5S$ (m.w. 487); Found:

C, 54.28; H, 2.71; N, 20.18; S, 6.60; Calcd: C, 54.21; H, 2.67; N, 20.12; S, 6.57; IR υ (cm^{-1}) 1671, 1731 (C=O), 2954 (CH), 3105 (*NH*); MS: *m/z* (int. %) $[M+H]^+$ 487 (88.2); ^{1}H-NMR (DMSO-d_6) δ 5.17 (s, 2H, CH_2N), 5.37, 5.39 (2d, 2H, CH_2O), 7.32-7.87 (m, 4H, quinazolinone), 7.95-8.04 (m, 4H, phthalimido moiety).

2-({5-[2-(2,4-dioxo-1,3-oxazolidin-3-yl)-4-oxoquinazolin-3(4H)-yl]-1,3,4-thiadiazol-2-yl}methyl)-1H-isoindole-1,3(2H)-dione **(12)**: Yield 42 %; m.p. 177-179 ℃; Anal. for $C_{22}H_{12}N_6O_6S$ (m.w. 488); Found: C, 54.18; H, 2.48; N, 17.26; S, 6.59; Calcd: C, 54.10; H, 2.46; N, 17.21; S, 6.56; IR υ (cm^{-1}) 1671, 1731, 1777 (C=O), 2833, 2954 (C-H), 3330 (*NH*); MS: *m/z* (int. %) $[M+H]^+$ 488 (76.3); ^{1}H-NMR (DMSO-d_6) δ 5.17 (m, 2H, CH_2N), 5.36, 5.37 (2d, 2H, CH_2O), 7.34-7.95 (m, 4H, quinazolinone), 7.94-8.04 (m, 4H, phthalimido moiety).

Synthesis of compounds **13** *and* **14**:

A mixture of product **6** (0.01 mol) and malonitrile or ethyl cyanoacetate (0.01 mol) in 25 mL of dry pyridine was heated under reflux for 3h. The mixture was cooled then poured onto ice-water with stirring where a solid began to precipitate. The mixture was filtered, washed with water, air-dried and crystallized from ethanol affording derivatives **13** and **14**.

2-({5-[2-(2-Imino-3-cyano-5-oxopyrrolidin-1-yl)-4-oxoquinazolin -3(4H)-yl]-1,3,4-thiadiazol-2-yl}methyl)-1H-isoindole-1,3(2H)-dione **(13)**: Yield 65 %; m.p. 187-189 ℃; Anal. for $C_{24}H_{14}N_8O_4S$ (m.w. 510); Found: C, 56.53; H, 2.79; N, 21.99; S, 6.31; Calcd: C, 56.47; H, 2.75; N, 21.96; S, 6.27; IR υ (cm^{-1}) 1670, 1734 (CO), 2246 (CN), 2951 (CH), 3105 (*NH*); MS: *m/z* (int. %)$[M+H]^+$ 510 (44.4); ^{1}H-NMR (DMSO-d_6) δ 3.03, 3.10 (2dd, 2H, CH_2), 4.63 (dd, 1H, *CH*CN), 5.17 (s, CH_2, CH_2N), 7.30-7.87 (m, 4H, quinazolinone), 7.98-8.03 (m, 4H, phthalimido moiety).

2-({5-[2-(2-Imino-3-ethoxycarbonyl-5-oxopyrrolidin-1-yl)-4-oxoquinazolin -3(4H)-yl]-1,3,4-thiadiazol-2-yl}methyl)-1H-isoindole-1,3(2H)-dione **(14)**: Yield 65 %; m.p. 139-141 ℃; Anal. for $C_{26}H_{19}N_7O_6S$ (m.w. 557); Found: C, 56.07; H, 3,44; N, 17.66; S, 5.79; Calcd: C, 56.01; H, 3.41; N, 17.59; S, 5.75; IR υ (cm^{-1}) 1117 (C-O), 1668, 1726, 1779 (C=O), 2951 (C-H), 3330 (*NH*); MS: *m/z* (int. %) $[M+H]^+$ 557 (57.3); ^{1}H-NMR (DMSO-d_6) δ 1.17 (t, 3H; OCH_2CH_3), 2.97, 3.04 (2dd, 2H, CH_2), 4.01 (dd, 1H, $CHCH_2$), 4.20 (q, 2H; OCH_2CH_3), 5.17 (s, CH_2, CH_2N), 7.30-7.87 (m, 4H, quinazolone), 7.97-8.03 (m, 4H, phthalimido moiety).

Synthesis of compound **15***:*

A mixture of compound **6** and ammonium acetate (0.01 mol each) was fused on an oil bath at 110 ℃ for 2h. The fused solution was poured onto ice-water with stirring until a white solid was precipitated. The mixture was filtered, washed repeatedly with water, dried and crystallized from ethanol affording off-white needles of derivative **15.**

4-{5-[(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1,3,4-thiadiazol-2-yl}imidazo[1,2-a] quinazoline-2,5 (1H,4H)-dione **(15)**: Yield 78 %; m.p. 182-184 ℃; Anal. for $C_{21}H_{12}N_6O_4S$ (m.w. 444); Found: C, 56.81; H, 2.74; N, 18.96; S, 7.24; Calcd: C, 56.76; H, 2.70; N, 18.92; S, 7.21; IR υ (cm^{-1}) 1668, 1734, 1771 (C=O), 2870, 2980 (C-H), 1605 (C=N); MS: *m/z* (int. %) $[M+H]^+$ 444 (81.7); ^{1}H-NMR (DMSO-d_6) δ 4.26 (2d, 2H, CH_2), 5.17 (s, CH_2, CH_2N), 7.43-7.68 (m, 4H, quinazolinone), 7.73- 8.03 (m, 4H, phthalimido moiety), 8.00 (br s, 1H, *NH*).

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Competing Interests

The authors declare no conflict of interest.

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