Synthesis of quinazoline derivatives as potential antimicrobial agents

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Abstract:

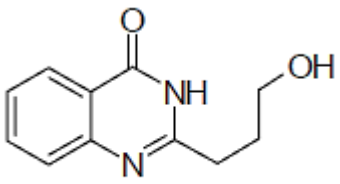
An efficient synthesis of substituted quinazoline derivatives was achieved from the reaction of 2-((1,1-dioxido-3-oxobenzo[d]isothiazol-2(3*H*)-yl)methyl)-4*H*-benzo[d][1,3] oxazin-4-one **(3)** as a reactive starting material with variety of nucleophilic reagents. The Structural formula of all derivatives were confirmed and characterized by elemental analysis and spectral data. Some of the synthesized compounds were also screened for their antibacterial and antifungal activities and compared with standard drugs. Most of the tested compounds showed potent to weak antimicrobial activities.

Keywords:

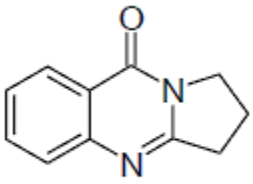
Benzoxazinone, quinazolinone, amino acids, antimicrobial activity.

Introduction

Large numbers of quinazolinone alkaloids have been isolated from a number of plants, animals & microorganisms and synthesized in view of their well-established pharmacological activities[1-3]. Pegamine, [2-(3-hydroxypropyl)-quinazolin-4(1*H*)-one (**I**), Deoxyvasicinone, [2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one, (**II**) and (–)-Vasicinone, [2,3-dihydro- 3(*S*)-hydroxypyrrolo[2,1-*b*]quinazolin-9(1*H*)-one, (**III**) have been isolated as bioactive natural products. Pegamine **I** has been isolated from *Peganum harmala* and exhibits cytotoxic activity[4]. Deoxyvasicinone **II** and (–)-Vasicinone **III** have been isolated from the aerial parts of an evergreen subherbaceous bush *Adhatoda vasica*[5]. Deoxyvasicinone **II** possesses antimicrobial and anti-inflammatory acitivities[6]. (–)-Vasicinone **III** exhibits antitumor[7] and hypotensive[8] activities.



I



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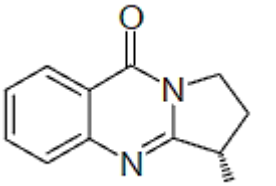
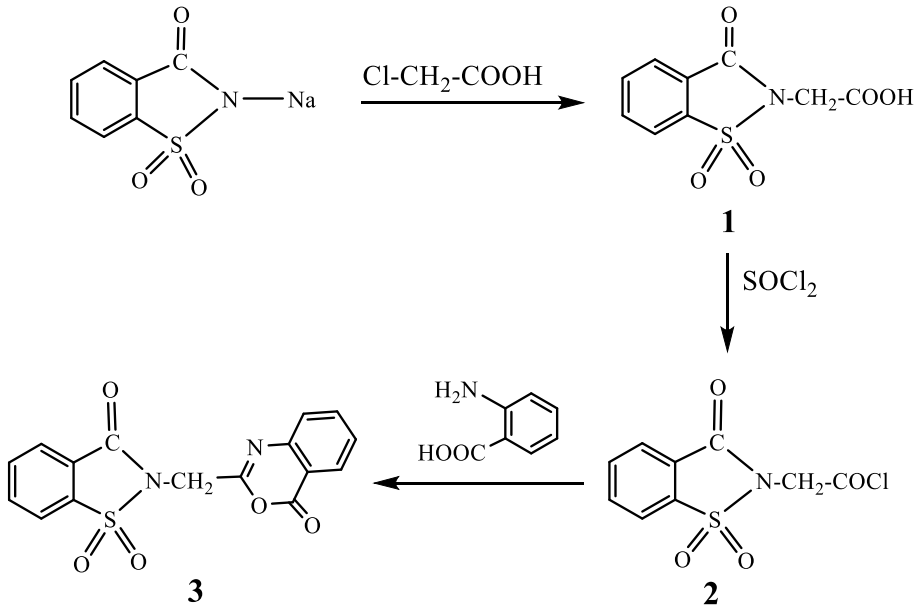


III

In addition, quinazolines and quinazolin-4-ones are an important group of heterocyclic compounds that possess wide range of pharmacological properties, which include their uses as anticonvulsant[9,10], antitumor[11,12], anticancer[13], anti-inflammatory[14,15], analgesics[16], cytotoxicity[17,18], herbicidal[19], antileishmanial[20], anticoccidial[21], antioxidant[22], antibacterial, antifungal[23-29] and several other useful and interesting properties. Considering the above reports in conjunction with our previous work on the synthesis of heterocyclic derivatives as antimicrobial agents. The present study plans to synthesize some new quinazolinone derivatives followed by evaluation of their antimicrobial activities.

Results and discussion

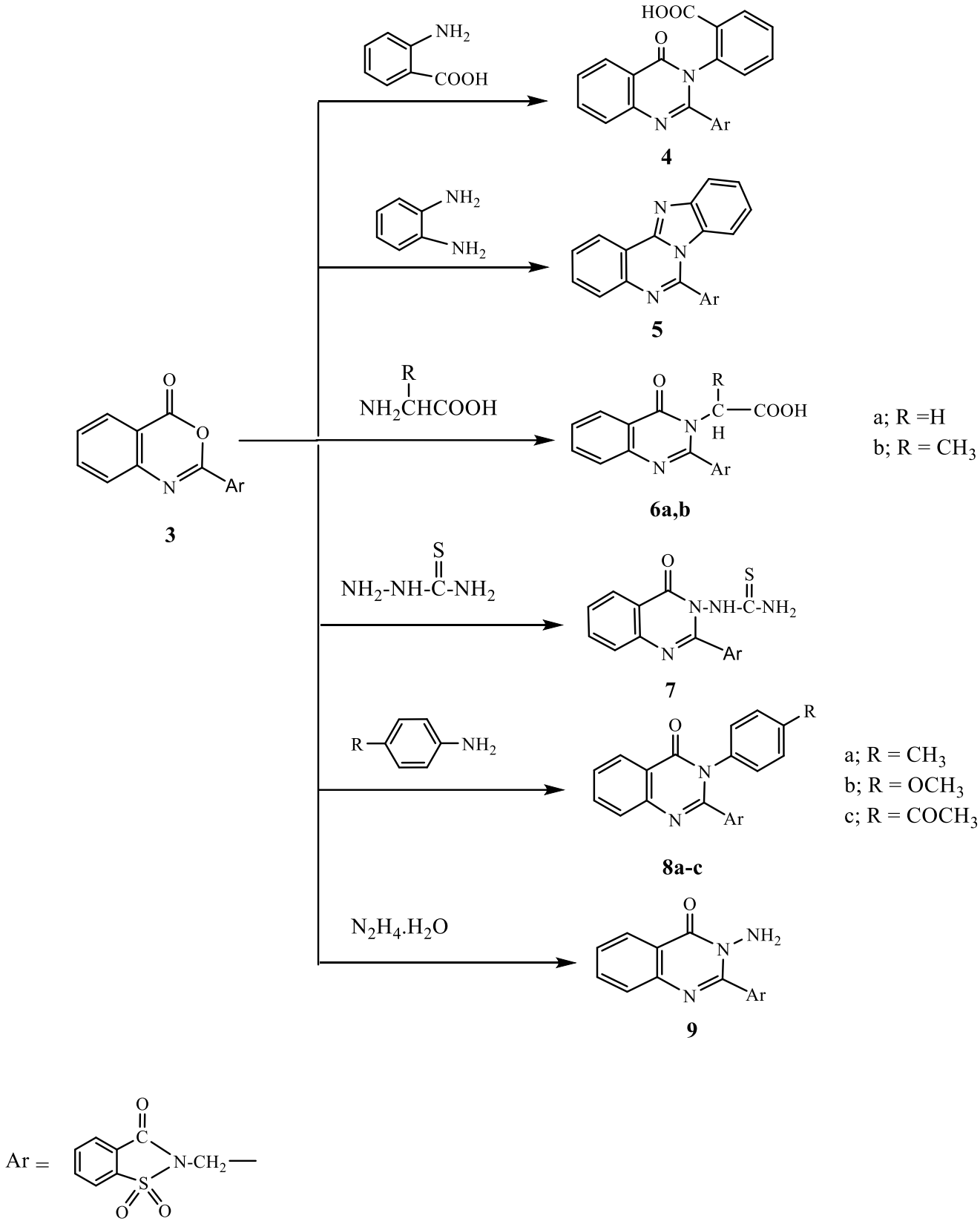
As shown in **Scheme 1**, 2-(1,1-dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)acetic acid **(1)** was synthesized by treatment of sod-saccharine with chloro acetic acid in dry xylene[30]. Reaction of acid **1** with thionyl chloride gave acid chloride **2**, which upon reaction with anthranilic acid in pyridine yielded 2-((1,1-dioxido-3-oxobenzo[d]isothiazol-2(3*H*)-yl)methyl)-4*H*-benzo[d][1,3]oxazin-4-one **(3),** which is used as a reactive key precursor for synthesizing a number of substituted quinazolinone derivatives of expected antimicrobial activity. The structure of benzoxazinone **3** was confirmed on the basis of its spectral data and elemental analysis where IR spectrum showed absorption bands at 2923, 2850 cm^{-1}, 1734-1745 cm^{-1}, 1606 cm^{-1}, 1335 cm^{-1} corresponding to (CH_2, CO, C=N and S=O) and ^{1}HNMR showed signals at 4.47-4.63 and 7.16-8.56 ppm corresponding to CH_2, and Ar-H protons, respectively.



Scheme 1: synthetic route for synthesis of 2-((1,1-dioxido-3-oxobenzo[d]isothiazol-2(3*H*)-yl)methyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (**3**).

Benzoxazinone **3** was allowed to react with different nucleophilic reagents such as anthranilic acid, which gave compound **4**, and with orthophenylene diamine produced the fused heterocyclic ring benzo[4,5]imidazo quinazoline **5**.

Treatment of amino acids as glycine and/ or alanine with the benzoxazinone derivative **3** gave compounds **6a** and **6b**, respectively. **(Scheme 2)**.



Scheme 2: Synthesis of quinazolinones 4-9.

On the other hand, quinazolinyl thiourea **7** was obtained by reaction of **3** with thiosemicarbazide, while, compounds **8a-c** were obtained in good yields *via* reaction of **3** with an aromatic amine, namely *p*-toluidine, *p*-anisidine and *p*-aminoacetophenone, respectively.

Finally, amino quinazolinone **9**, was obtained by reaction of benzoxazinone **3** with hydrazine hydrate in boiling ethanol, **(Scheme 2).**

Quinazoline derivatives were reported to have biological activity. In this study, some of the synthesized compounds appear to be promising as potential bio responses which increase their importance towards application in pharmacological, industrial and agriculture fields. Therefore, their effectiveness against a number of microorganisms was tested.

The antimicrobial activity of some of the synthesized compounds was evaluated invitro using cup plate method [30] against two bacterial species namely, *Streptococcus sp.* and *Escherichia Coli*, and against two fungal species namely, *Asperigalleus Niger* and *Penicillium sp.* and results are depicted in (Table **1**):

Table 1: Antimicrobial activities of the synthesized compounds.

Compound No.	***Streptococcus sp.***	***Escherichia Coli***	***A. Niger***	***Penicillium sp.***
4	++	++	++	+
6a	++	++	+	+
6b	++	+++	++	+
7	+++	+++	++	++
8a	++	+++	+++	+
8b	+++	+++	++	++
8c	++	++	+	+
9	++	++	++	+

Signals in table **1** represent the extent of the zone diameter (r mm) inhibition of either fungal growth or bacterial cells for each compound; (+), slightly active; (++), moderately active and (+++), highly active.

The screening of antibacterial and antifungal activity showed that, all of the tested compounds (**4-9**) showed from moderate to good activity at 50 mg/mL against the tested antibacterial and antifungal pathogenic strains.

Compounds (**7**) and (**8b**) showed comparatively good activity against the both tested bacterial strains *Streptococcus sp.* and *Escherichia Coli*, while compound (**8a**) is the most active compounds against the two fungal species *Asperigalleus Niger* and *Penicillium sp.*

Also, compounds (**4**), (**6a**), (**6b**), (**8a**), (**8c**) and (**9**) exhibited moderate activity towards the tested strains.

Experimental:

Melting points were measured using an electro-thermal digital apparatus and are uncorrected. The IR spectra were recorded as KBr pellets using Buck scientific model 500 IR spectrophotometer. The proton NMR spectra were recorded in DMSO-d6 as solvent at 300 MHz, on Varian Gemini NMR spectrophotometer using TMS as internal standard, chemical shifts are recorded as units (δppm). The chemical shifts are reported as parts per million (ppm). Mass spectra were measured on Shimadzu GCMS-QP 2010 plus Ex mass spectrometer at 70 eV. Microanalyses were performed at the micro-analytical center, Cairo University.

Synthesis 2-(1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)acetic acid (1)

A mixture of sodium 3-oxo-3*H*-benzo[d]isothiazol-2-ide 1,1-dioxide or sodium saccharine (2.05g, 0.01 mole) and chloroacetic acid (0.94 g, 0.01 mole) in dry xylene (40 mL) was refluxed for 8 h. The reaction mixture was filtered off while hot, concentrated and the solid obtained was washed with petroleum ether (40-60), recrystallized from ethanol to give **1**. Yield 40%; m.p. 291-293 ^{o}C; IR spectrum (KBr, ν, cm^{-1}): 3449 (OH), 3097 (CH aromatic), 2922, 2856 (CH_2), 1738-1687 (CO), 1606 (C=N), 1334 (S=O); Anal. calcd. for $C_9H_7NO_5S$ (241.22): C, 44.81; H, 2.93; N, 5.81. Found: C, 44.84; H, 2.99; N, 5.91.

2-(1,1-Dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)acetyl chloride (2)

A mixture of **1** (2.4 g, 0.01 mol) and thionyl chloride (10 ml) was heated on water bath for 2 h. Excess of thionyl chloride was removed by distillation under reduced pressure, a semisolid product **2** was obtained. Yield 90%; m.p. 210-212 ^{o}C; IR spectrum (KBr, ν, cm^{-1}):

3092 (CH aromatic) absorption, 2960 (CH_2), 1738-1716 (CO), 1332 (S=O); Anal. calcd. For $C_9H_6ClNO_4S$ (259.66): C, 41.63; H, 2.33; N, 5.39. Found: C, 41.69; H, 2.25; N, 5.33.

2-((1,1-Dioxido-3-oxobenzo[d]isothiazol-2(3*H*)-yl)methyl)-4*H*-benzo[*d*][1,3] oxazin-4-one (3)

To a solution of anthranilic acid (1.371 g, 0.01 mole) in dry pyridine (30 mL), the acid chloride **2** (5.2 g, 0.02 mole) was added portion wise with stirring at room temperature. The reaction mixture was poured onto cold water (100 mL) and the precipitated solid was filtered off, washed with cold water, dried and recrystallized from ethanol to give benzoxazinone derivative **3**. Yield 70%; m.p. 142-143 ^oC; IR spectrum (KBr, ν, cm^{-1}): 2923, 2850 (CH_2), 1745-1734 (CO), 1606 (C=N), 1335 (S=O); ^{1}HNMR (DMSO-d_6, δ ppm): 4.47, 4.63 (d, 2H, CH_2), 7.16-8.56 (m, 8H, Ar-H); MS: m/z = 342 (M^+, 2 %) Anal. calcd. for $C_{16}H_{10}N_2O_5S$ (342.33): C, 56.14; H, 2.94; N, 8.18. Found: C, 56.10; H, 2.88; N, 8.23.

2-(2-((1,1-Dioxido-3-oxobenzo[d]isothiazol-2(3*H*)-yl)methyl)-4-oxoquinazolin-3(4*H*)-yl)benzoic acid (4)

A mixture of benzoxazinone **3** (3.4 g, 0.01 mol) and anthranilic acid (1.37 g, 0.01 mol) in boiling butanol (30 mL) was refluxed for 6 h. Concentrating the solution gave a solid which was washed, filtered, dried and then crystallized from ethanol affording the quinazolinone **4**. Yield 91%; m.p. 253-255 ^oC; IR spectrum (KBr, ν, cm^{-1}): 3425 (OH), 1737-1674 (CO), 1610 (C=N), 1338 (S=O); ^{1}HNMR (DMSO-d_6, δ ppm): 4.63 (s, 2H, CH_2), 6.5-8.51 (m, 12H, H Ar-H), 11.7 (s, 1H, OH exchangeble); m/z = 461 (M^+, 2 %) Anal. calcd. for $C_{23}H_{15}N_3O_6S$ (461.45): C, 59.87; H, 3.28; N, 9.11. Found: C, 59.84; H, 3.19; N, 9.01.

2-(Benzo[4,5]imidazo[1,2-*c*]quinazolin-6-ylmethyl)benzo[d]isothiazol-3(2*H*)-one 1,1-dioxide (5)

A mixture of benzoxazinone **3** (1.02 g, 3 mmol), *o*-phenylenediamine (0.32 g, 3 mmol) and freshly fused sodium acetate (0.2 g) was fused at 180 ^oC for 3 h, the reaction mixture was cooled, washed with dil. HCl. The separated solid product was dried and recrystallized from a mixture of ether-ethanol to give **5**.Yield 61%; m.p. 295-297 ^oC; IR spectrum (KBr, ν, cm^{-1}): 2924, 2850 (CH_2), 1735 (CO), 1630 (C=N), 1336 (S=O); Anal. calcd. for $C_{22}H_{14}N_4O_3S$ (414.44): C, 63.76; H, 3.41; N, 13.52. Found: C, 63.71; H, 3.38; N, 13.46.

General procedures for synthesis of 6a and 6b:

A mixture of benzoxazinone **3** (3.4 g, 0.01 mol) and amino acids *viz* glycine and alanine (0.01 mol) in pyridine (20 ml) was heated under reflux for 5 h. The reaction mixture was poured on ice/HCl, the solid that separated was filtered off and crystallized from methanol to give **6a,6b.**

2-(2-((1,1-Dioxido-3-oxobenzo[d]isothiazol-2(3*H*)-yl)methyl)-4-oxoquinazolin-3(4*H*)-yl)acetic acid (6a)

Yield 81%; m.p. 176-178 ^{o}C; IR spectrum (KBr, ν, cm^{-1}): 3440 (OH), 2930, 2840 (CH_2), 1736-1677 (CO), 1610 (C=N), 1337 (S=O); ^{1}HNMR (DMSO-d_6, δ ppm): 3.82 (s, 2H, N-CH_2), 4.63 (s, 2H, CO-CH_2), 8.50-6.92 (m, 8H, Ar-H), 11.61 (s, 1H, OH, exchangeble); Anal. calcd. for $C_{18}H_{13}N_3O_6S$ (399.38): C, 54.13; H, 3.28; N, 10.52. Found: C, 54.04; H, 3.22; N, 10.49.

2-(2-((1,1-Dioxido-3-oxobenzo[d]isothiazol-2(3*H*)-yl)methyl)-4-oxoquinazolin-3(4*H*)-yl)propanoic acid (6b)

Yield 85%; m.p. 270-272 ^{o}C; IR spectrum (KBr, ν, cm^{-1}): 3442 (OH), 2924, 2860 (CH, CH_3), 1736-1676 (CO), 1615 (C=N), 1334 (S=O); ^{1}HNMR (DMSO-d_6, δ ppm): 1.08 (d, 3H, CH_3), 4.64 (s, 2H, CH_2), 4.86 (q, 1H, CH), 7.07-8.67 (m, 8H, Ar-H), 11.62 (s, 1H, OH, exchangeable); Anal. calcd. for $C_{19}H_{15}N_3O_6S$ (413.40): C, 55.20; H, 3.66; N, 10.16. Found: C, 55.25; H, 3.60; N, 10.07.

1-(2-((1,1-Dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)methyl)-4-oxoquinazolin-3(4*H*)-yl)thiourea (7)

A mixture of benzoxazinone **3** (3.4 g, 0.01 mol) and thiosemicarbazide (0.9 g, 0.01 mol) was refluxed in dry pyridine (30 ml) for 6 hours. The reaction mixture was allowed to cool, treated with ice-cold hydrochloric acid. The separated solid was filtered, washed with water, dried and crystallized from ethanol to give **7.** Yield 78%; m.p. 180-182 ^{o}C; IR spectrum (KBr, ν, cm^{-1}): 3430-3150 (NH_2, NH), 2921-2850 (CH_2), 1737-1676 (CO), 1590 (C=N), 1337 (S=O). ^{1}HNMR (DMSO-d_6, δ ppm): 3.73 (s, 2H, NH_2 exchangeable), 4.64 (s, 2H, CH_2), 7.11-8.51 (m, 8H, Ar-H), 11.62 (s, 1H, NH exchangeable); Anal. calcd. for $C_{17}H_{13}N_5O_4S_2$ (415.44): C, 49.15; H, 3.15; N, 16.86. Found: C, 49.23; H, 3.10; N, 16.81.

General procedures for synthesis of 8a and 8b:

A mixture of benzoxazinone **3** (3.4 g, 0.01 mol), and an aromatic amine, *viz p*-toluidine and *p*-anisidine (0.01 mol), in boiling ethanol (40 mL) was refluxed for 3-6 h. The obtained precipitate was filtered off, washed with water, dried and crystallized from ethanol to give **8a,8b.**

2-((4-Oxo-3-(*p*-tolyl)-3,4-dihydroquinazolin-2yl)methyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (8a)

Yield 85%; m.p. 116-117 ^{o}C; IR spectrum (KBr, ν, cm^{-1}): 2925, 2850 (CH_2), 1739-1680 (CO), 1590 (C=N), 1338 (S=O). Anal. calcd. for $C_{23}H_{17}N_3O_4S$ (431.47): C, 64.03; H, 3.97; N, 9.74. Found: C, 64.12; H, 3.91; N, 9.69.

2-((3-(4-Methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl) benzo[*d*] isothiazol-3(2*H*)-one 1,1-dioxide (8b)

Yield 80%; m.p. 135-137 ^{o}C; IR spectrum (KBr, ν, cm^{-1}): 2924, 2850 (CH_2), 1739-1675 (CO), 1635 (C=N), 1338 (S=O); ^{1}HNMR (DMSO-d_6, δ ppm): 3.74 (s, 3H, OCH_3), 4.84 (s, 2H, CH_2), 6.81-8.51 (m, 12H, Ar-H); Anal. calcd. for $C_{23}H_{17}N_3O_5S$ (447.47): C, 61.74; H, 3.83; N, 9.39. Found: C, 61.69; H, 3.78; N, 9.43.

2-((3-(4-Acetylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)benzo[*d*] isothiazol-3(2*H*)-one 1,1-dioxide (8c)

A mixture of benzoxazinone **3** (3.4 g, 0.01 mol) and 4-aminoacetophenone (1.35 g, 0.01 mol) in ethanol (20 mL) containing few drops of piperidine was heated at 70°C for 7h. The excess solvent was distilled off and the solid that separated after cooling was recrystallized from toleuene to give **8c**. Yield 75%; m.p. 205-206 ^{o}C; IR spectrum (KBr, ν, cm^{-1}): 2925 (CH_2), 1739-1645 (CO), 1590 (C=N), 1338 (S=O); ^{1}HNMR (DMSO-d_6, δ ppm): 3.74 (s, 3H, CH_3), 4.63 (s, 2H, CH_2), 7.17-8.51 (m, 12H, Ar-H); Anal. calcd. for $C_{24}H_{17}N_3O_5S$ (459.48): C, 62.74; H, 3.73; N, 9.15. Found: C, 62.65; H, 3.79; N, 9.21.

2-((3-Amino-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (9)

To a solution of benzoxazinone **3** (3.4 g, 0.01 mol) in 40 mL ethanol, hydrazine monohydrate (0.49 mL, 0.01mol) was added and the solution was heated under reflux for 3 h. The solid that deposited on cooling after distilling off most of the solvent was filtered off and recrystallized from ethanol to yield **9**. Yield 67%; m.p. 157-158 ^{o}C; IR spectrum (KBr, ν, cm^{-1}): 3426 (NH_2), 1740-1673 (CO), 1630 (C=N), 1338 (S=O); ^{1}HNMR (DMSO-d_6, δ ppm): 3.99 (s,

2H, NH_2), 4.43 (s, 2H, CH_2), 6.71-8.51 (m, 8H, Ar-H); Anal. calcd. for $C_{16}H_{12}N_4O_4S$ (356.36): C, 53.93; H, 3.39; N, 15.72. Found: C, 53.89; H, 3.33; N, 15.61.

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