

Synthesis of Novel Quinazoline Derivatives as Antimicrobial Agents

ALY, A. A. *

Department of Chemistry, Faculty of Science, Benha University, Benha, Egypt

Quinazoline isothiocyanate **1** reacts with various nucleophiles (nitrogen nucleophiles, oxygen nucleophiles and sulphur nucleophiles) to afford heterocyclic systems **2**–**13**. Also, the [4+2] cycloaddition reaction of **1** with phenyl isocyanate, benzylidene aryl amine and cinnamic acid derivatives gave novel heterocyclic compounds **14**–**16**. Moreover, the reaction of **1** with active methylene compounds under Michael reaction conditions also was investigated to yield **17** and **18** and it was found that all these reactions proceeded via isothiocyanate heterocyclization to furnish non-condensed heterocyclic compounds. Some of the newly synthesized compounds were tested for their antimicrobial activities.

Keywords quinazoline congeners, quinazoline isothiocyanate, antimicrobial activity

Introduction

Quinazoline derivatives are biologically interesting and their chemistry is now receiving considerable attention due to their applications in medicine for uses as anticonvulsant,¹ anti-inflammatory² and anticancer^{3,4} agents. Like wise triazoles, oxazoles and thiazoles have been the subject of chemical and biological studies on account of their diverse physiological activities.^{5,6}

In view of the aforesaid versatile benefits and in conjunction with our previous work,^{7,8} I have investigated possible utility of quinazoline isothiocyanate **1** for the synthesis of different otherwise not readily accessible heterocyclic compounds containing quinazoline moiety of potential interest, as agrochemical, pharmaceutical or dye intermediates.

Results and discussion

In the present investigation quinazoline moiety was introduced in acrylic acid molecule with a view to find out its effect on the isothiocyanate stability and on the mode of reaction with acidic and basic reagents. The key precursor 3-oxo-3-(4-oxo-3, 4-dihydroquinazolin-2-yl) propenyl isothiocyanate (**1**) was synthesized from the reaction of 3-oxo-3-(4-oxo-3, 4-dihydroquinazolin-2-yl) propenyl chloride in dry acetone with ammonium thiocyanate^{9,10} and the solution obtained was used *in situ* to prevent its decomposition.

The reaction of hydrazine or its derivatives with isothio-

cyanate serves as a key intermediate in the preparation of triazoles,¹¹ thus the reaction of isothiocyanate **1** with phenylhydrazine in dry acetone gave 2-[2-(2-phenyl-5-thioxo-2, 5-dihydro-1*H*-[1, 2, 4] triazol-3-yl) ethenyl]-3*H*-quinazolin-4-one (**2**). Similarly compound **1** reacted with acetylhydrazine and benzoylhydrazine in dry acetone affording *N*-(*N'*-acetyl/benzoylhydrazinocarbothioyl)-3-(4-oxo-3, 4-dihydroquinazolin-2-yl)acrylamide (**3a**, **3b**) respectively.

Treatment of **3a**, **3b** with polyphosphoric acid (PPA) or acetic anhydride afforded the cyclized product¹² 2-[3-oxo-3-(3-methyl/phenyl-5-thioxo-1, 5-dihydro-[1, 2, 4] triazol-4-yl) propenyl]-3*H*-quinazolin-4-one (**4a**, **4b**).

The hitherto-unknown reaction of amino acids¹³ with isothiocyanate was investigated via the reaction of **1** with glycine in the presence of pyridine as a base to yield the azalactone derivative **5**. Moreover, compound **1** reacted with hippuric acid in the presence of aromatic aldehydes (*viz.* benzaldehyde or 3-nitrobenzaldehyde) in dry acetone affording thiourea derivatives **6a**, **6b** which were readily cyclized to give the corresponding imidazole derivatives **7a**, **7b** upon treatment with boiling acetic anhydride.

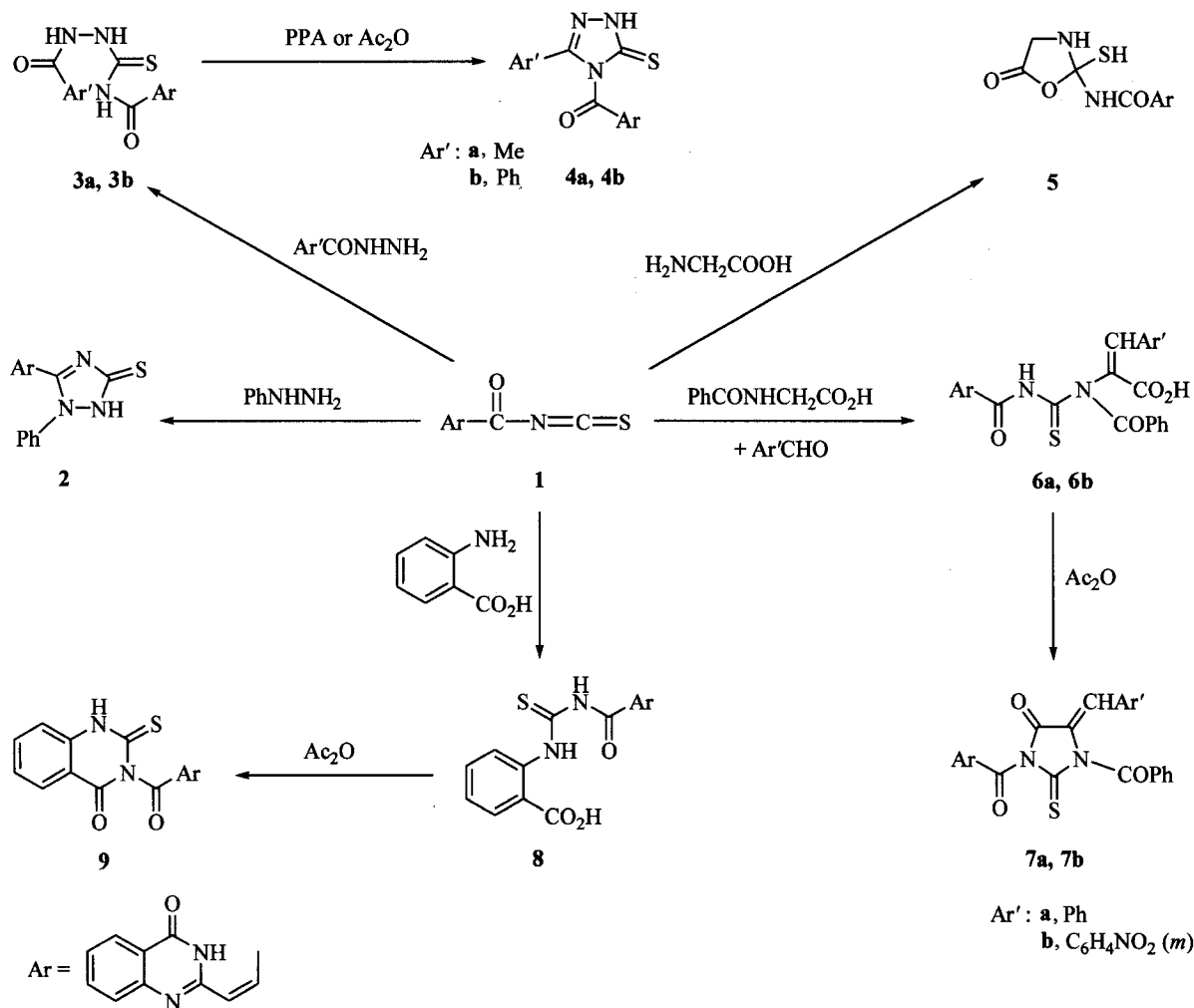
An even more convenient access to the synthesis of heterocyclic compounds of biological interest was established, by treatment of isothiocyanate **1** with anthranilic acid to yield thiourea derivative **8**, which cyclized by acetic anhydride to give 2-[3-oxo-3-(4-oxo-2-thioxo-1, 4-dihydro-2*H*-quinazolin-3-yl) propenyl]-3*H*-quinazolin-4-one (**9**) (Scheme 1)

Compound **1** reacted with thioglycolic acid as a sulphur nucleophile in dry acetone to afford the adduct **10**, and cyclization of **10** by acetic anhydride^{14,15} afforded thiazolidine derivative **11**. Also, when compound **1** was allowed to react with *o*-aminophenol as amphoteric nucleophile afforded thiourea derivative **12**, which yielded the cyclized benzooxazole derivative **13**, via the evolution of H₂S gas when heated above its melting point.

Similar to the reported behaviour of isothiocyanate derivatives¹⁶, the cycloaddition reaction of **1** with phenyl isocyanate gave oxadiazine derivative **14**. Moreover, the cycloaddition reaction of isothiocyanate was extended to react with benzylidene arylamine to afford 2-[2-(5-phenyl/(*p*-carboxyphenyl)-6-phenyl-4-thioxo-5, 6-dihydro-4*H*-[1, 3, 5]-oxadiazin-2-yl) ethenyl]-3*H*-quinazolin-4-one (**15a**, **15b**) which

* E-mail: alymaboud@hotmail.com

Scheme 1



illustrated that the reaction occurs via [4 + 2] π -electron cycloaddition.¹⁷ Also, other cycloaddition reactions employing cinnamic acid derivatives were recently reported,¹⁸ thus **1** reacted with cinnamic acid derivatives to give the corresponding oxazine derivatives **16a**–**16c**.

As an extension of this synthetic route, the behaviour of isothiocyanate towards some active methylene compounds under Michael reaction conditions,¹⁹ also was investigated and the reaction of **1** with either acetylacetone or ethyl cyanoacetate in the presence of triethylamine afforded the oxazine derivatives **17** and **18**, respectively (Scheme 2).

Antimicrobial activity

The antimicrobial activities of some synthesized compounds were determined *in vitro* against some of bacteria in addition to a variety of yeast and fungi. Also, a comparison between the activity of our prepared compounds and standard drug was discussed. The tests were carried out using filter paper and hole plate method.²⁰

The tested compounds were dissolved in 10% acetone, and different concentrations were chosen (125, 250, 500 $\mu\text{g}/\text{mL}$). The Gram positive bacteria were *Bacillus cereus*, *Bacillus subtilis*; the Gram negative bacteria were *pseu-*

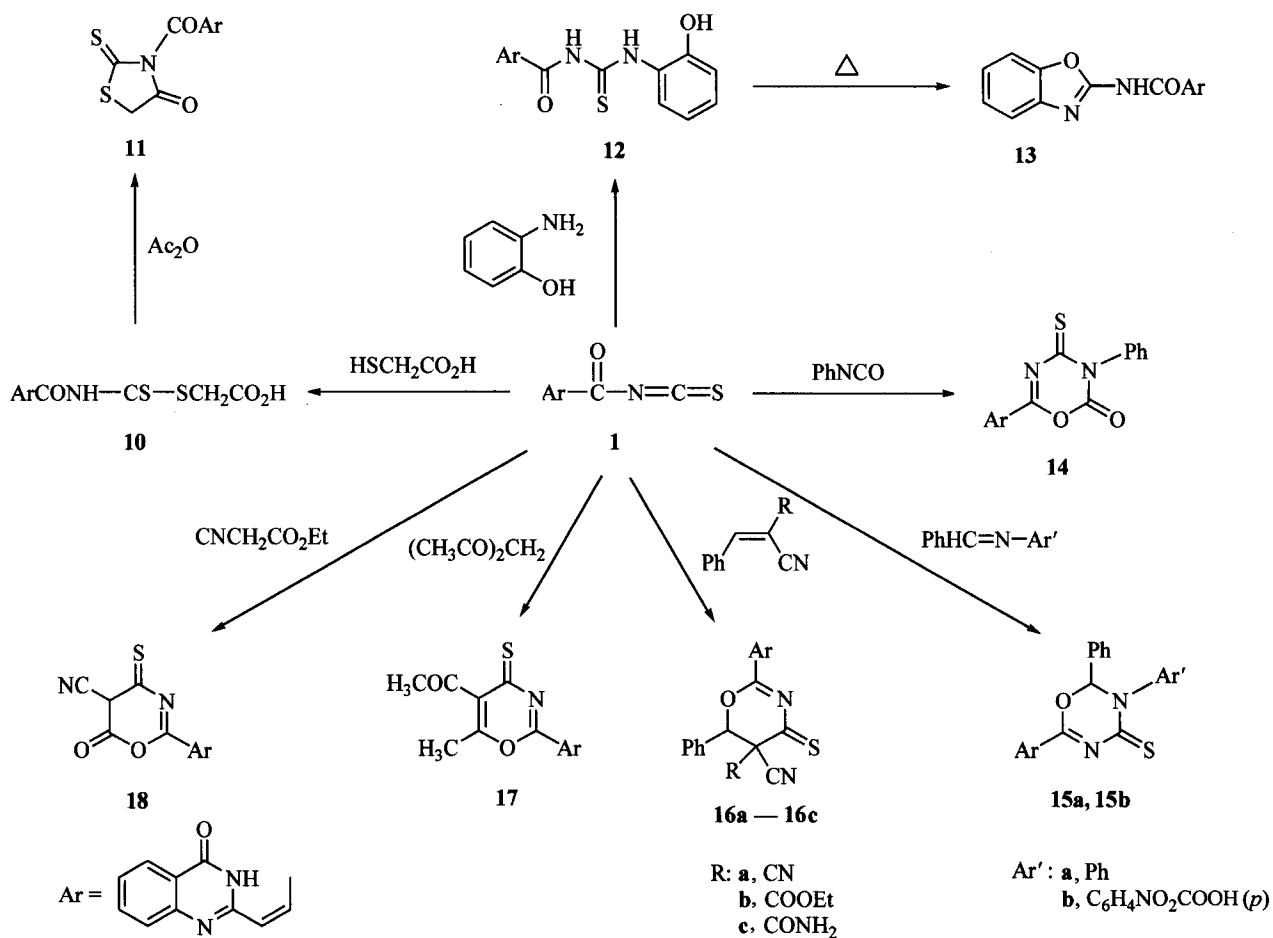
domonas aeruginosa, *Escherichia coli*; the yeast and fungi were *Candida albicans*, *Aspergillus niger* and *Penicillium notatum*. Agar plates were surface inoculated uniformly from fresh broth culture of the Gram positive, Gram negative bacteria, yeast and fungi. The disks were incubated at 5 °C for 1 h to permit good diffusion and then incubated at 28 °C for 24 h. After incubation, the zones of inhibition were measured in mm and the results are shown in Table 1.

The results in Table 1 indicated that the presence of quinazoline moiety in the synthesized compounds enhances its antimicrobial activity for gram positive and gram negative bacteria, but has only a slight effect on yeast and fungi as compared with Ampicillin sodium which was used as a standard drug. In summary, I found the access to several interesting heterocyclic compounds, which have interesting biological activities, by utilizing simple reaction sequences starting from 3-oxo-3-(4-oxo-3,4-dihydroquinazolin-2-yl)propenyl isothiocyanate.

Experimental

Melting points were determined on a Gallen kamp apparatus and uncorrected. IR spectra in KBr were recorded on a Perkin Elmer 398 spectrophotometer. ¹H NMR spectra

Scheme 2

Table 1 Antimicrobial activity^a

Tested samples	Organisms						
	<i>A. niger</i>	<i>B. cereus</i>	<i>B. subtilis</i>	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>C. albicans</i>	<i>P. notatum</i>
2	10	15	12	-	-	-	-
4b	12	8	13	10	-	-	-
5	10	10	12	14	-	10	12
7b	12	15	14	0	10	-	-
9	-	10	-	8	-	-	-
11	15	12	13	10	-	15	14
13	12	10	12	NT	-	-	-
14	14	14	-	10	15	NT	NT
15a	-	NT	2	12	-	-	NT
16b	12	10	10	-	-	-	-
17	12	-	10	15	-	10	-
18	-	14	15	10	12	-	-
Ampicillin sodium	25	15	12	10	10	10	NT

^a Diameter of inhibition zones is measured in mm; (-) means no inhibition; NT means not tested.

were recorded on a Varian Gemini, 200 MHz instrument. Mass spectra were obtained on a Shimadzu, GCMS QP 1000 EX mass spectrometer 70 eV EI mode. All reactions were monitored by thin layer chromatography on 0—2 mm silica gel

60F₂₅₄(Merck) plates. The physical data are listed in Table 2. ¹H NMR and mass data of the synthesized compounds are listed in Table 3.

Table 2 Characterization data of the synthesized compounds

Compd No.	Yield (%)	M. p. (°C)	Mol. formula (M. Wt)	Analysis (%) found/(calcd)			
				C	H	N	S
2	65	120—122	C ₁₈ H ₁₃ N ₅ O ₅ S	62.34	3.79	20.29	9.61
			(347.39)	(62.23)	3.77	20.16	9.23)
3a	64	231—233	C ₁₄ H ₁₃ N ₅ O ₃ S	50.81	3.82	21.25	
			(331.35)	(50.75)	3.95	21.14	—)
3b	60	250—252	C ₁₉ H ₁₅ N ₅ O ₃ S	58.09	3.95	17.71	
			(393.42)	(58.00)	3.84	17.80	—)
4a	59	202—204	C ₁₄ H ₁₁ N ₅ O ₂ S	53.71	3.46	22.46	10.67
			(313.34)	(53.66)	3.54	22.35	10.23)
4b	58	220—222	C ₁₉ H ₁₃ N ₅ O ₂ S	60.89	3.57	18.77	8.21
			(375.41)	(60.79)	3.49	18.66	8.54)
5	71	> 300	C ₁₄ H ₁₂ N ₄ O ₄ S	50.71	3.52	16.93	9.18
			(332.34)	(50.60)	3.64	16.86	9.65)
6a	68	181—183	C ₂₈ H ₂₀ N ₄ O ₅ S	64.20	3.95	10.73	6.47
			(524.55)	(64.11)	3.84	10.68	6.11)
6b	70	196—198	C ₂₈ H ₁₉ N ₅ O ₇ S	59.11	3.24	12.39	
			(569.55)	(59.05)	3.36	12.30	—)
7a	61	140—142	C ₂₈ H ₁₈ N ₄ O ₄ S	66.45	3.45	11.15	
			(506.53)	(66.39)	3.58	11.06	—)
7b	63	156—158	C ₂₈ H ₁₇ N ₅ O ₆ S	60.89	3.01	12.81	
			(551.53)	(60.98)	3.12	12.70	—)
8	84	140—142	C ₁₉ H ₁₄ N ₄ O ₄ S	57.80	3.45	14.3	8.46
			(394.41)	(57.86)	3.58	14.21	8.13)
9	80	171—173	C ₁₉ H ₁₂ N ₄ O ₃ S	60.55	3.28	14.95	
			(376.39)	(60.63)	3.21	14.89	—)
10	71	150—152	C ₁₄ H ₁₁ N ₃ O ₄ S ₂	48.21	3.24	12.15	18.61
			(349.39)	(48.13)	3.17	12.03	18.36)
11	67	106—108	C ₁₄ H ₉ N ₃ O ₃ S ₂	50.86	2.61	12.56	
			(331.37)	(50.74)	2.74	12.68	—)
12	82	230—232	C ₁₈ H ₁₄ N ₄ O ₃ S	59.09	3.96	15.40	
			(366.39)	(59.01)	3.85	15.29	—)
13	79	205—207	C ₁₈ H ₁₂ N ₄ O ₃	65.16	3.70	16.74	
			(332.31)	(65.06)	3.64	16.86	—)
14	86	187—189	C ₁₉ H ₁₂ N ₄ O ₃ S	60.55	3.29	14.96	8.21
			(376.39)	(60.63)	3.21	14.89	8.52)
15a	82	170—172	C ₂₅ H ₁₈ N ₄ O ₂ S	68.38	4.19	12.70	7.69
			(438.50)	(68.48)	4.14	12.78	7.31)
15b	77	201—203	C ₂₆ H ₁₈ N ₄ O ₄ S	64.66	3.65	11.57	
			(482.51)	(64.72)	3.76	11.61	—)
16a	59	160—162	C ₂₂ H ₁₃ N ₅ O ₂ S	64.31	3.19	17.09	7.43
			(411.44)	(64.22)	3.18	17.02	7.79)
16b	58	173—175	C ₂₄ H ₁₈ N ₄ O ₄ S	62.80	3.85	12.32	
			(458.49)	(62.87)	3.96	12.22	—)
16c	61	197—199	C ₂₂ H ₁₅ N ₅ O ₃ S	61.66	3.75	16.39	
			(429.45)	(61.53)	3.52	16.31	—)
17	65	195—197	C ₁₇ H ₁₃ N ₃ O ₃ S	60.25	3.75	12.50	
			(339.37)	(60.17)	3.86	12.38	—)
18	73	270—272	C ₁₅ H ₈ N ₄ O ₃ S	55.45	2.55	17.35	9.53
			(324.32)	(55.55)	2.49	17.28	9.89)

Table 3 Spectral data for the synthesized compounds

Compd	¹ H NMR (δ) ^a	MS <i>m/z</i> (R. A)
2	(DMSO- <i>d</i> ₆): 4.88 (br, 1H, NH), 7.22—8.36 (m, 11H, ArH + olefinic protons), 8.51 (br, 1H, NH)	347 (30%)
3a	(DMSO- <i>d</i> ₆): 2.52 (s, 3H, CH ₃), 5.01 (br, 1H, NH), 6.93—7.41 (m, 6H, ArH + olefinic protons), 9.11, 9.32, 9.66 (each s, 3H, 3NH)	—
3b	—	393 (38%)
4a	—	313 (76%)
4b	(CDCl ₃): 4.76 (br, 1H, NH), 7.09—8.1 (m, 11H, ArH + olefinic protons), 8.71 (s, 1H, NH)	—
5	(CDCl ₃): 2.67 (s, 2H, CH ₂), 3.31 (s, 1H, SH), 4.69 (s, 1H, NH), 6.96—7.86 (m, 6H, ArH olefinic protons), 8.12, 8.89 (2s, 2H, 2NH)	—
6a	(DMSO- <i>d</i> ₆): 4.61 (br, 1H, NH), 6.01 (s, 1H, \diagup C=CH), 7.21—8.25 (m, 16H, ArH + olefinic protons), 9.23 (br, 1H, NH), 10.96 (s, 1H, OH)	—
6b	—	569 (41%)
7a	(CDCl ₃): 4.45 (br, 1H, NH), 6.31 (s, 1H, \diagup C=CH), 7.11—8.32 (m, 16H, ArH + olefinic protons)	—
7b	—	551 (77%)
8	—	394 (82%)
9	(CDCl ₃): 4.95 (br, 1H, NH), 7.12—8.11 (m, 10H, ArH + olefinic protons), 8.56 (br, 1H, NH)	376 (59%)
10	(DMSO- <i>d</i> ₆): 3.51 (s, 2H, CH ₂), 4.95 (br, 1H, NH), 7.12—8.23 (6H, ArH + olefinic protons), 9.36 (br, 1H, NH), 11.51 (s, 1H, OH)	349 (46%)
11	—	331 (100%)
12	—	366 (53%)
13	(CDCl ₃): 5.11 (br, 1H, NH), 7.11—8.32 (m, 10H, ArH + olefinic protons), 10.21 (br, 1H, NH)	—
14	(DMSO- <i>d</i> ₆): 5.35 (br, 1H, NH), 7.10—8.23 (m, 11H, ArH + olefinic protons)	376 (82%)
15a	(CDCl ₃): 3.29 (s, 1H, methine proton), 4.96 (br, 1H, NH), 7.01—8.21 (m, 16H, ArH + olefinic protons)	—
15b	—	482 (91%)
16a	—	411 (28%)
16b	(DMSO- <i>d</i> ₆): 1.22 (t, <i>J</i> = 7.1 Hz, 3H, CH ₃), 4.01 (s, 1H, methine proton), 4.21 (q, <i>J</i> = 7.2 Hz, 2H, CH ₂), 4.71 (br, 1H, NH), 7.18—7.94 (m, 11H, ArH + olefinic protons)	458 (91%)
16c	(DMSO- <i>d</i> ₆): 3.99 (s, 1H, methine proton), 4.01 (br, 2H, NH ₂), 5.10 (br, 1H, NH), 6.88—7.94 (m, 11H, ArH + olefinic protons)	—
17	(CDCl ₃): 1.81 (s, 3H, CH ₃), 2.49 (s, 3H, CH ₃ CO), 4.79 (br, 1H, NH), 6.78—7.89 (m, 6H, ArH + olefinic protons)	339 (56%)
18	(CDCl ₃): 3.98 (s, 1H, methine proton), 4.81 (br, 1H, NH), 6.87—7.79 (m, 6H, ArH + olefinic protons)	324 (85%)

^aAll NH, OH and NH₂ signals were exchangeable with D₂O.

3-Oxo-3-(4-oxo-3,4-dihydroquinazolin-2-yl) propenyl isothiocyanate (**1**)

To a stirred solution of 3-oxo-3-(4-oxo-3,4-dihydroquinazolin-2-yl)propenyl chloride (**1**) (8 mmol) in dry acetone (20 mL), solid ammonium thiocyanate (8 mmol) was added. The reaction mixture was stirred for 1 h at room temperature, then filtered off to leave a clear solution of **1** in acetone.

2-[2-(2-Phenyl-5-thioxo-2,5-dihydro-1H-[1,2,4] triazol-3-yl) ethenyl]-3H-quinazolin-4-one (**2**)

A solution of isothiocyanate **1** (7 mmol) and phenylhydrazine (7 mmol) in dry acetone was heated under reflux for 30 min, the reaction mixture was concentrated then left to cool, and crystallization from methanol gave crystals of **2**. IR ν_{\max} : 3347—3280 (NH), 1680 (CO of quinazolinone), 1616 (C = N), 1302 (CS) cm^{-1} beside three characteristic bands for quinazoline moiety²¹ in the region 1630—1615, 1580—1570 and 1515—1480 cm^{-1} .

N-(N'-Acetyl/benzoylhydrazinocarbothioyl)-3-(4-oxo-3,4-dihydroquinazolin-2-yl) acrylamide (**3a**, **3b**)

General procedure The solution of **1** (5 mmol) in dry acetone (25 mL) and the aroylhydrazine namely acetylhydrazine or benzoylhydrazine (5 mmol) was heated under reflux for 1 h. The solid product was filtered off and recrystallized from acetic acid to give **3a**, **3b**. IR ν_{\max} : 3390—3280 (NH), 1691—1680 (CO), 1305 (CS) cm^{-1} .

2-[3-Oxo-3-(3-methyl/phenyl-5-thioxo-1,5-dihydro-[1,2,4] triazol-4-yl) propenyl]-3H-quinazolin-4-one (**4a**, **4b**).

General procedure

Method A A solution of **3a** or **3b** (5 mmol) in acetic acid (20 mL) and polyphosphoric acid (20 mL) was heated to 150—180 °C for 1 h, then cooled to room temperature. The reaction mixture was poured onto ice/water, the formed precipitate was collected by filtration, dried and crystallized from acetic acid to give **4a**, **4b**. IR ν_{\max} : 3363—3294 (NH), 1690—1680 (CO), 1620—1605 (C = N) and 1290 (CS) cm^{-1} .

Method B Compound **3a** or **3b** (5 mmol) in acetic anhydride (15 mL) was heated on water bath for 30 min. The reaction mixture was cooled. The solid product separated was filtered off and crystallized to give **4a**, **4b**.

N-(2-Mercapto-5-oxo-oxazolidin-2-yl)-3-(4-oxo-3,4-dihydroquinazolin-2-yl) acrylamide (**5**)

To a solution of **1** (5 mmol) in dry acetone (20 mL), glycine (5 mmol) and pyridine (1 mL) were added and the

reaction mixture was refluxed for 1 h, cooled and poured onto ice/HCl. A solid product was filtered off, washed with water and recrystallized from ethanol to give **5**. IR ν_{\max} : 3254—3162 (NH), 2353 (SH), (1715, 1670) (CO) and 1618 (C = N) cm^{-1} .

2-{1-Benzoyl-3-[3-oxo-3-(4-oxo-3,4-dihydroquinazolin-2-yl) propenyl] thioureido}-3-(phenyl/3'-nitrophenyl) acrylic acid (**6a**, **6b**).

General procedure A solution of isothiocyanate **1** (5 mmol) in the dry acetone (20 mL) was added to hippuric acid (5 mmol) and benzaldehyde or 3-nitrobenzaldehyde (5 mmol) in presence of a few drops of pyridine. The reaction mixture was refluxed for 1.5 h, then cooled and poured onto ice/HCl. The precipitate obtained was filtered off, washed with water and recrystallized from benzene to give **6a**, **6b**. IR ν_{\max} : 3480—3310 (OH), 3280, 3215 (NH), 1710, 1670 (CO) cm^{-1} .

2-[3-Oxo-3-(4-arylidene-3-benzoyl-5-oxo-2-thioxoimidazolidin-1-yl) propenyl]-3H-quinazolin-4-one (**7a**, **7b**).

General procedure Compound **6a** or **6b** (10 mmol) in acetic anhydride (10 mL) was heated on water bath for 30 min. The reaction mixture was cooled and poured onto ice-cold water. The solid product separated was filtered and recrystallized from ethanol to give **7a**, **7b**. IR ν_{\max} : 3265—3200 (NH), 1700—1680 (CO), 1306—1292 (CS) cm^{-1} .

2-{3-[3-Oxo-3-(4-oxo-3,4-dihydroquinazolin-2-yl) propenyl] thioureido} benzoic acid (**8**)

A mixture of equimolar amounts of **1** and anthranilic acid (10 mmol) in dry acetone (20 mL) was refluxed for 1 h. The reaction mixture was then allowed to cool to room temperature and the solid product was collected and crystallized from benzene to give **8**. IR ν_{\max} : 3416—3205 (OH, NH), 1695—1670 (CO), 1303 (CS) cm^{-1} .

2-[3-Oxo-3-(4-oxo-2-thioxo-1,4-dihydro-2H-quinazolin-3-yl) propenyl]-3H-quinazolin-4-one (**9**)

A solution of **8** (5 mmol) in acetic anhydride (20 mL) was heated on water bath for 30 min. A solid product was precipitated during the reaction and at the end of reaction period the solid product was filtered off while hot then recrystallized from benzene to give **9**. IR ν_{\max} : 3285—3200 (NH), 1680—1670 (CO), 1630—1615 (C = N) and 1285 (CS) cm^{-1} .

[3-Oxo-3-(4-oxo-3,4-dihydroquinazolin-2-yl) propenylthiocarbamoylsulfanyl] acetic acid (**10**)

To a solution of **1** (10 mmol) in dry acetone (20 mL), thioglycollic acid (10 mmol) was added. The reaction mix-

ture was refluxed for 1 h. After cooling, the precipitate was recrystallized from ethanol to give **10**. IR ν_{\max} : 3485—3345 (OH and NH), 1705, 1690, 1675 (CO), 1318 (CS) cm^{-1} .

2-[3-Oxo-3-(4-oxo-2-thioxothiazolidin-3-yl)propenyl]-3H-quinazolin-4-one (**11**)

A solution of **10** (4 mmol) in acetic anhydride (15 mL) was heated on water bath for 1 h. A solid product was obtained after cooling, recrystallization from benzene-pet. ether (60—80 °C) mixture gave **11**. IR ν_{\max} : 3295 (NH), (1690, 1680) (CO), 1296 (CS) cm^{-1} .

1-(2-Hydroxyphenyl)-3-[3-oxo-3-(4-oxo-3,4-dihydroquinazolin-2-yl)propenyl]thiourea (**12**)

To a solution of **1** (8 mmol) in dry acetone (25 mL), *o*-aminophenol (8 mmol) was added. The reaction mixture was refluxed for 1 h. After cooling, the solid product was filtered and recrystallized from benzene to give **12**. IR ν_{\max} : 3350 (due to bonded OH), 3285—3222 (NH), 1685—1670 (CO), 1322 (CS) cm^{-1} .

N-Benzooxaol-2-yl-3-(4-oxo-3,4-dihydroquinazolin-2-yl)-acrylamide (**13**)

The thiocarbamate **12** (4 mmol) was heated at 250 °C and H_2S gas was liberated during the fusion process. After evolution of all H_2S gases, the reaction mixture was left to cool, a solid product of **13** was obtained, which was crystallized from ethanol to give **13**. IR ν_{\max} : 3290—3235 (NH), 1683—1671 (CO), 1615 (C = N) cm^{-1} .

2-[2-(5-Phenyl-6-oxo-4-thioxo-5,6-dihydro-4H-[1,3,5]-oxadiazin-2-yl)ethenyl]-3H-quinazolin-4-one (**14**)

A solution of **1** (4 mmol) in dry acetone (20 mL) was added to phenyl isocyanate (4 mmol) and the reaction mixture was refluxed for 1 h. The solid product obtained was crystallized from xylene to give **14**. IR ν_{\max} : 3245 (NH), 1695—1670 (CO), 1620 (C = N), 1306 (CS) cm^{-1} .

2-[2-(5-Phenyl/*p*-carboxyphenyl-6-phenyl-4-thioxo-5,6-dihydro-4H-[1,3,5]oxadiazin-2-yl)ethenyl]-3H-quinazolin-4-one (**15a**, **15b**)

General procedure To a solution of benzylidene aryl amine (7 mmol) in dry toluene (20 mL) was added a solution of **1** (7 mmol) in dry acetone (25 mL) and the mixture was heated under reflux for 1.5 h. The reaction mixture was concentrated, allowed to cool and the solid product formed was recrystallized from benzene to give **15a**, **15b**. IR ν_{\max} : 3301—3209 (NH), 1681—1674 (CO), 1621—1611 (C = N), 1286—1273 (CS), 1072—1060 (C—O—C) cm^{-1} .

5-Cyano-5-substituted-2-[2-(4-oxo-3,4-dihydroquinazolin-2-yl)ethenyl]-6-phenyl-4-thioxo-5,6-dihydro-4H-[1,3]-oxazine (**16a**—**16c**)

General procedure Isothiocyanate **1** (5 mmol) in dry acetone (20 mL) was added to the appropriate cinnamic acid derivative (5 mmol) in dry toluene (10 mL). The reaction mixture was heated under reflux for 1.5 h. The solid product formed was filtered off and recrystallized from benzene to give **16a**—**16c**. IR ν_{\max} : 3356—3241 (NH), (1730, 1683—1671) (CO), 1276—1261 (CS) and 2241 (C≡N) of **16a**) cm^{-1} .

2-[2-(5-Acetyl-6-methyl-4-thioxo-4H-[1,3]oxazin-2-yl)ethenyl]-3H-quinazolin-4-one (**17**) and 6-oxo-2-[2-(4-oxo-3,4-dihydroquinazolin-2-yl)ethenyl]-4-thioxo-5,6-dihydro-4H-[1,3]oxazine-5-carbonitrile (**18**)

General procedure To a solution of isothiocyanate **1** (8 mmol) in dry acetone (30 mL), acetylacetone or ethyl cyanoacetate (8 mmol) and triethylamine (1.5 mL) were added and the reaction mixture was refluxed for 3 h. The hot reaction mixture was then poured onto ice and the precipitate obtained was collected and recrystallized from xylene to give **17** and **18**. IR for **17** ν_{\max} : 3222 (NH), 1709, 1671 (CO), 1617 (C = N), 1273 cm^{-1} (C = S); IR for **18**: ν_{\max} 3196 (NH), 2230 (C≡N), 1720, 1678 (CO), 1621 (C = N), 1278 (C = S) cm^{-1} .

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