



Convenient Synthesis of Some New Bi-heterocycles Containing 3-Aminoquinazolin-4(3H)-one and 1,2,4-Triazole Moieties

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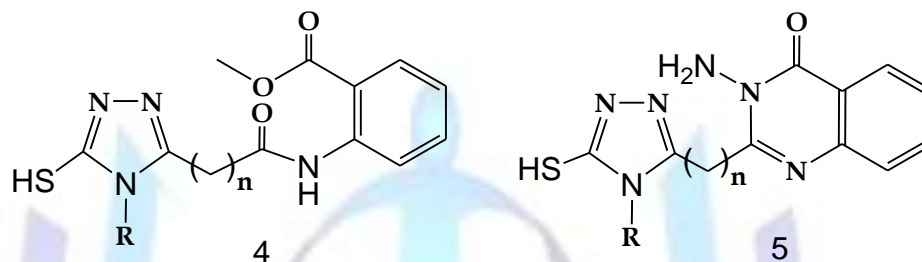
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GRAPHICAL ABSTRACT:



Dicarboxylic acids, thiosemicarbazides and methylantranilate were reacted to give methyl-2-(3-(5-mercapto-4-s-1,2,4-triazol-3-yl)-3-oxoalkylamino)benzoates **4**. The latters, have been cyclized with hydrazine hydrate to give 3-amino-2-((5-mercapto-4-s-1,2,4-triazol-3-yl)alkyl)quinazolin-4(3H)-ones **5** which expected to have biological effects.

Keywords: Thiocarbohydrazides; methylantranilate; methyl-2-(3-(5-mercapto-4-s-1,2,4-triazol-3-yl)-3-oxoalkylamino)benzoates and 3-amino-2-((5-mercapto-4-s-1,2,4-triazol-3-yl)alkyl)quinazolin-4(3H)-ones.

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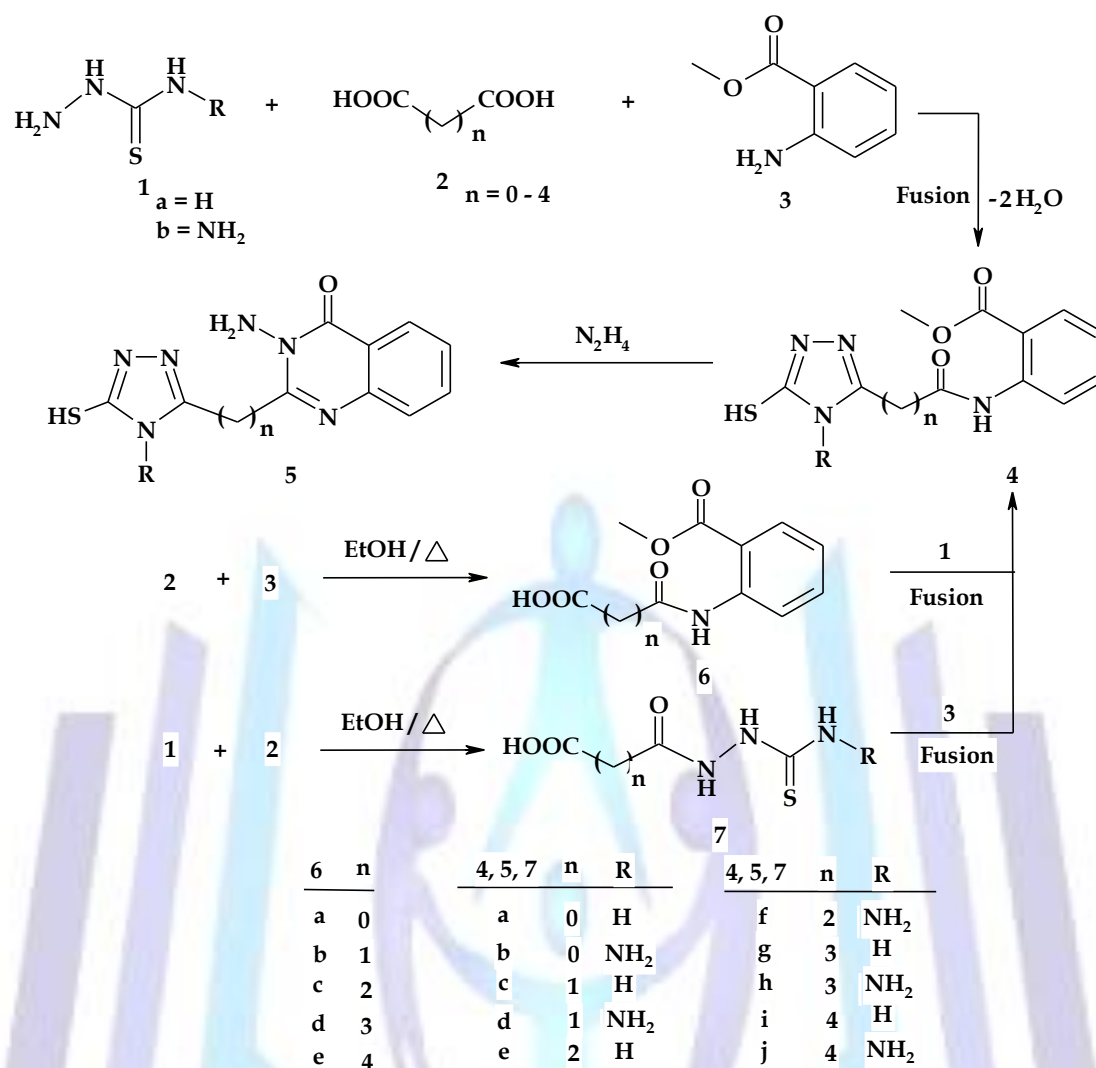


INTRODUCTION:

Attention has been increasingly paid to the synthesis of bis-heterocyclic compounds, which exhibit various biological activities more than heterocyclic ones. These activities include antibacterial, fungicidal, tuberculostatic and plant growth regulative properties [1-6]. Also, it has been indicated in several reports that biquinazolinones have a wide range of applications in synthesis and as chiral building blocks [7, 8]. 4(3*H*)-Quinazolinones are known for more than a century [9]. Molecules based on quinazoline and quinazolinone exhibit multitude of interesting pharmacological activities [10], including anticonvulsant, antibacterial and antidiabetic activity [11, 12]. The important natural and synthetic 4(3*H*)-quinazolinones include *l*-vasicinone [13], chrysogine [14], methaquinolin [15], a sedative piriqualone [16-18], Febrifugine and *iso* febrifugine which possess this ring system were known as potent but toxic antimalarial agents long for than initial isolation [19] and recent chemical studies [20-23]. On the other hand, 1,2,4-triazole derivatives may exhibit different pharmacological activities such as anti-inflammatory, anti-fungal, anti-bacterial, and anti-viral. Some other 1,2,4-triazole derivatives have been reported to possess tuberculostatic, herbicidal and plant growth regulator activities [24-27]. In view of this the chemistry of bis-quinazolinones [28-31], and bis-4-amino-s-triazoles [32,33] was judicious to investigate the synthesis of asymmetric bis-heterocyclic compounds which have been unreported hitherto and are expected to possess biological activity [34-37].

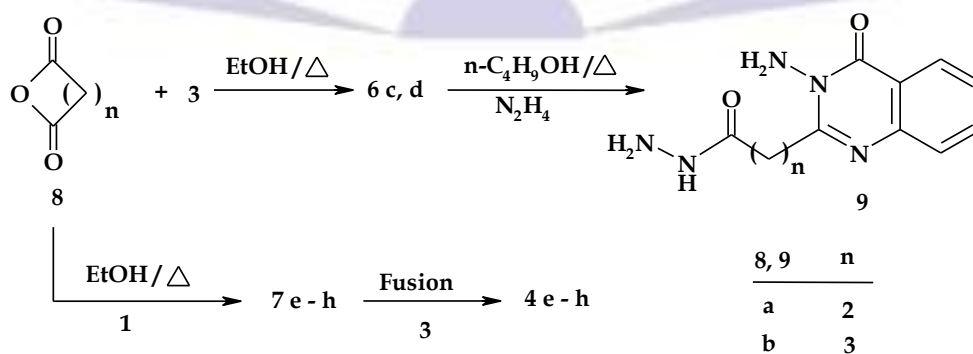
RESULTS AND DISCUSSION:

Various new types of bis-heterocycles are having both 3-aminoquinazolinone and 1,2,4-triazole moieties were established through the synthesis of these research work via different routes. In the first route, the synthesis of 3-amino-2-((5-mercapto-4 substituted-1,2,4-triazol-3-yl)alkyl)quinazolin-4(3*H*)-ones **5a-j** took place via two steps: Firstly, the one pot reaction of thiohydrazide **1a,b**, the dicarboxylic acid **2** and methylanthranilate **3** under fusion conditions afforded the corresponding methyl-2-(3-(5-mercapto-4-substitued-1,2,4-triazol-3-yl)-3-oxoalkylamino)benzoates **4a-j**. Secondly, refluxing of the mono amide intermediates **4a-j** with excess amount of hydrazine hydrate in *n*-butanol for 3-5 hours gave the target compound **5a-j** in a good yield. In the second route, the dicarboxylic acids **2** were refluxed with methyl anthranilate **3** in absolute ethanol to give methyl anthraniloyl mono carboxylates **6a-e** analogously, interaction of **6a-e** with thiocarbhydrazides **1a,b** under fusion conditions to give the corresponding mono amides **4a-j** which refluxed with hydrazine hydrate to afford **5a-j**. In the third route, the dicarboxylic acids **2** were refluxed with thiocarbhydrazides **1a,b** in absolute ethanol to give substituted-(4-methylthiosemicarbazido)-3-oxocarboxylic acids **7a-j** was interacted with methyl anthranilate **3** under fusion conditions to give the corresponding mono amides **4a-j**. The latters were refluxed with hydrazine hydrate to afford **5a-j** as mentioned above. Characterization of the newly synthesized compounds was elucidated owing to their spectral data IR, mass and ¹H NMR in addition to elemental analysis. (Scheme 1)



Scheme 1

In the fourth route, substituted-(4-methylthiosemicarbazido)-3-oxocarboxylic acids **7e-h** could be obtained from boiling of dicarboxylic acid anhydrides **8a,b** with thiocarbonylhydrazides **1a,b**. The fusion of **7e-h** with methyl anthranilate **3** gave 2-(3-(5-mercapto-4-substitued-1,2,4-triazol-3-yl))-3-oxoalkylamino)benzoates **4e-h**. Finally, dicarboxylic acid anhydrides **8a,b** were refluxed with methyl anthranilate **3** to afford methyl anthraniloyl mono carboxylates **6c,d** which gave 3-(3,4-dihydro-3-amino-4-oxoquinazolin-2-yl)alkanehydrazides **9a,b** up on treatment with hydrazine hydrate. (Scheme 2)



Scheme 2



EXPERIMENTAL

All melting points were uncorrected. IR spectra were recorded (KBr disc) on a Shimadzu FT-IR 8201 PC Spectrophotometer. ¹H-NMR spectra were recorded in CDCl₃ or (CD₃)₂SO on a Varian Gemini 200 MHz Spectrometer and chemical shifts were expressed in units using TMS as an internal reference. Elemental analyses were carried out at the Microanalytical Center, Cairo University, Giza, Egypt, and National Research Centre.

Methyl-2-(3-(5-mercapto-4-s-1,2,4-triazol-3-yl)-3-oxoalkylamino) benzoates 4a-j:

Method (A): A mixture of semicarbazide or thiocarbonylhydrazide (0.005 mol) **1a,b**, dicarboxylic acids **2** (0.01 mol) and methylantranilate **3** (0.005 mol) was heated in an oil bath at 170 °C for 30 min., the resulting solid was collected and recrystallized from ethanol to give the respective amides **4a-j**.

Method (B): The semicarbazide or thiocarbonylhydrazide (0.01 mol) and mono amides **6a-e** (0.01 mol), were heated in an oil bath at 170 °C for 30 min. the resulting solid was collected and recrystallized from ethanol to give the respective amides **4a-j**.

Method (C): The carboxylic acid derivatives **7a-j** (0.01 mol) and methylantranilate (0.01 mol) were heated in an oil bath at 170 °C for 30 min. the resulting solid was collected and recrystallized from ethanol to give the respective amides **4a-j**.

3-Amino-2-[3-(4-amino-5-mercapto-4H-[1,2,4]triazol-3-yl)-alkyl]-3H-quinazolin-4-ones (5a-j):

The corresponding amides **4a-j** (0.01 mol) and 95% hydrazine hydrate (0.05 mol) were dissolved in n- butanol (30 ml) and refluxed for 6-8 hours. Cooling the reaction mixture in ice gave the crude product, which was filtered off and recrystallized to give compounds **5a-j**.

Methyl anthraniloyl mono carboxylates (6):

Method (A):

A mixture of the dicarboxylic acids **2** (0.01 mol) and methylantranilate **3** (0.01 mol) was dissolved in ethanol and refluxed for 3-4 hours. After cooling, the precipitate so formed was filtered and recrystallized from the appropriate solvent to give **6a-e**.

Method (B):

A mixture of the acid anhydride **8a,b** (0.01 mol) and methylantranilate **3** (0.01 mol) was dissolved in ethanol and refluxed for 3-4 hours. After cooling the precipitate so formed was filtered and recrystallized from the appropriate solvent to give **6c,d**.

Substituted-(4-methylthiosemicarbazido)-3-oxocarboxylic acids (7):

Method (A):

A mixture of the dicarboxylic acids **2** (0.01 mol) and semicarbazide or thiocarbonylhydrazide (0.01 mol), was dissolved in ethanol (30 ml) and refluxed for 4-5 hours. After cooling, the precipitate so formed was filtered and recrystallized from the appropriate solvent to give **7a-j**.

Method (B):

A mixture of the acid anhydride **8a,b** (0.01 mol) and semicarbazide or thiocarbonylhydrazide (0.01 mol), was dissolved in ethanol (30 ml) and refluxed for 4-5 hours. After cooling, the precipitate so formed was filtered and recrystallized from the appropriate solvent to give **7e-h**.

3-(3,4-dihydro-3-amino-4-oxoquinazolin-2-yl)alkanehydrazides (9a,b):

The corresponding amides **6a,b** (0.01 mol) and 95% hydrazine hydrate (0.05 mol) were dissolved in n- butanol (30 ml) and refluxed for 6-8 hours. Cooling in ice gave the crude product which was filtered off and recrystallized to give compounds **9a,b**.



Table 1: Characterization Data of the Newly Synthesized Compounds

Compd. No.	Mp.°C Solvent	Color Yield%	Mol. Formula (mol. Wt.)	Elemental analysis calcd. / found%			
				C	H	N	S
4a	235-36	Colorless	C ₁₁ H ₁₀ N ₄ O ₃ S (278.29)	47.48	3.62	20.13	11.52
	EtOH	77		47.50	3.60	20.11	11.50
4b	174-75	Colorless	C ₁₁ H ₁₁ N ₅ O ₃ S (293.30)	45.04	3.78	23.88	10.93
	EtOH	79		45.08	3.81	23.83	10.97
4c	223-25	Colorless	C ₁₂ H ₁₂ N ₄ O ₃ S (292.31)	49.31	4.14	19.17	10.97
	EtOH	80		49.36	4.16	19.20	10.94
4d	>300	Colorless	C ₁₂ H ₁₃ N ₅ O ₃ S (307.33)	46.90	4.26	22.79	10.43
	EtOH	82		46.93	4.30	22.75	10.49
4e	165-67	Colorless	C ₁₃ H ₁₄ N ₄ O ₃ S (306.34)	50.97	4.61	18.29	10.47
	EtOH	81		51.00	4.63	18.32	10.50
4f	233-35	Colorless	C ₁₃ H ₁₅ N ₅ O ₃ S (321.35)	48.59	4.70	21.79	9.98
	EtOH	83		48.56	4.73	21.81	10.01
4g	172-74	Colorless	C ₁₄ H ₁₆ N ₄ O ₃ S (320.37)	52.49	5.03	17.49	10.01
	EtOH	85		52.51	5.06	17.52	9.98
4h	227-29	Colorless	C ₁₄ H ₁₇ N ₅ O ₃ S (335.38)	50.14	5.11	20.88	9.56
	EtOH	86		50.16	5.13	20.90	9.58
4i	185-87	Colorless	C ₁₅ H ₁₈ N ₄ O ₃ S (334.39)	53.88	5.43	16.75	9.59
	EtOH	82		53.90	5.45	16.77	9.56
4j	244-45	Colorless	C ₁₅ H ₁₉ N ₅ O ₃ S (349.41)	51.56	5.48	20.04	9.18
	EtOH	74		51.59	5.50	20.06	9.15
5a	253-55	Colorless	C ₁₀ H ₈ N ₆ OS (260.28)	46.15	3.10	32.29	12.32
	EtOH	76		46.17	3.13	32.32	12.35
5b	282-84	Colorless	C ₁₀ H ₉ N ₇ OS (275.29)	43.63	3.30	35.62	11.65
	EtOH	69		43.66	3.32	35.59	11.62
5c	>300	Colorless	C ₁₁ H ₁₀ N ₆ OS (274.30)	48.17	3.67	30.64	11.69
	EtOH	73		48.20	3.70	30.61	11.71
5d	>300	Colorless	C ₁₁ H ₁₁ N ₇ OS (289.32)	45.67	3.83	33.89	11.08
	EtOH	76		45.62	3.88	33.91	11.10
5e	295-97	Colorless	C ₁₂ H ₁₂ N ₆ OS (288.33)	49.99	4.19	29.15	11.12
	EtOH	80		50.02	4.22	29.18	11.10
5f	244-46	Colorless	C ₁₂ H ₁₃ N ₇ OS (303.34)	47.51	4.32	32.32	10.57
	EtOH	66		47.53	4.30	32.35	10.53
5g	>300	Colorless	C ₁₃ H ₁₄ N ₆ OS (302.35)	51.64	4.67	27.80	10.61
	EtOH	75		51.66	4.65	27.83	10.63
5h	235-37	Colorless	C ₁₃ H ₁₅ N ₇ OS (317.37)	49.20	4.76	30.89	10.10
	EtOH	81		49.18	4.78	30.91	10.12



5i	>300	Colorless	$C_{14}H_{16}N_6OS$	53.15	5.10	26.56	10.13
	EtOH	78	(316.38)	53.13	5.14	26.53	10.11
5j	288-90	Colorless	$C_{14}H_{17}N_7OS$	50.74	5.17	29.59	9.68
	EtOH	73	(331.40)	50.77	5.19	29.61	9.71
6a	98-100	Colorless	$C_{10}H_9NO_5$	53.82	4.06	6.28	--
	EtOH	73	(223.18)	53.85	4.03	6.26	--
6b	96-98	Colorless	$C_{11}H_{11}NO_5$	55.70	4.67	5.90	--
	EtOH	78	(237.21)	55.73	4.64	5.92	--
6c	95-97	Colorless	$C_{12}H_{13}NO_5$	57.37	5.22	5.58	--
	EtOH	77	(251.24)	57.40	5.24	5.54	--
6d	85-87	Colorless	$C_{13}H_{15}NO_5$	58.86	5.70	5.28	-
	EtOH	66	(265.26)	58.88	5.73	5.31	-
6e	80-83	Colorless	$C_{14}H_{17}NO_5$	60.21	6.14	5.02	-
	EtOH	70	(279.29)	60.24	6.12	5.05	-
7a	186-88	Colorless	$C_3H_5N_3O_3S$	22.08	3.09	25.75	19.65
	EtOH	78	(163.16)	22.07	3.06	25.79	19.68
7b	184-86	Colorless	$C_3H_6N_4O_3S$	20.22	3.39	31.45	18.00
	EtOH	75	(178.17)	20.24	3.37	31.46	18.03
7c	181-83	Colorless	$C_4H_7N_3O_3S$	27.11	3.98	23.72	18.10
	EtOH	77	(177.18)	27.08	3.96	23.74	18.13
7d	179-81	Colorless	$C_4H_8N_4O_3S$	25.00	4.20	29.15	16.68
	EtOH	70	(192.20)	25.03	4.22	29.18	16.65
7e	184-86	Colorless	$C_5H_9N_3O_3S$	31.41	4.74	21.98	16.77
	EtOH	71	(191.21)	31.44	4.75	22.01	16.74
7f	187-89	Colorless	$C_5H_{10}N_4O_3S$	29.12	4.89	27.17	15.55
	EtOH	66	(206.22)	29.15	4.92	27.15	15.57
7g	183-85	Colorless	$C_6H_{11}N_3O_3S$	35.11	5.40	20.47	15.62
	EtOH	68	(205.23)	35.08	5.43	20.50	15.60
7h	173-75	Colorless	$C_6H_{12}N_4O_3S$	32.72	5.49	25.44	14.56
	EtOH	68	(220.25)	32.75	5.51	25.46	14.59
7i	171-73	Colorless	$C_7H_{13}N_3O_3S$	38.34	5.98	19.16	14.62
	EtOH	66	(219.26)	38.31	5.97	19.19	14.65
7j	168-70	Colorless	$C_7H_{14}N_4O_3S$	35.89	6.02	23.91	13.69
	EtOH	69	(234.28)	35.86	6.05	23.93	13.66
9a	171-73	Colorless	$C_{11}H_{13}N_5O_2$	53.43	5.30	28.32	-
	EtOH	63	(247.25)	53.45	5.32	28.35	-
9b	175-77	Colorless	$C_{12}H_{15}N_5O_2$	55.16	5.79	26.80	-
	EtOH	74	(261.28)	55.19	5.82	26.82	-



Table 2: Spectral Data of Some Newly Synthesized Compounds:

Comp. no	Spectral data
4f	IR $\bar{\nu}$ (cm ⁻¹): 3273, 3161 (NH ₂); 1655 (C=O); 1621 (C=N) and 1600 (C=C).
4h	IR $\bar{\nu}$ (cm ⁻¹): 3277, 3219 (NH ₂) 1651 (C=O); 1625 (C=N) and 1601 (C=C). Mass (m/z): 335 (100%); 336 (17.0%) and 337 (5.0 %).
4g	Mass (m/z): 320 (100 %); 321 (3.0 %) and 322 (2.0 %).
5b	Mass (m/z): 275 (100 %); 276 (12.0 %) and 277 (3.0 %).
5f	IR $\bar{\nu}$ (cm ⁻¹): 3239, 3123 (NH ₂) 1654 (C=O); 1613 (C=N) and 1602 (C=C). ¹ H NMR δ_{H} (ppm): 3.08-3.49 (m, 4H, CH-aliph.); 5.80-5.64 (s, 4H, 2NH ₂); 8.16-7.50 (m, 4H, ArH's) and 13.48 (s, 1H, NH) Mass (m/z): 303 (100%); 287 (53%), 243 (13%), 186 (48), 146 (14%) and 120 (15 %).
5h	IR $\bar{\nu}$ (cm ⁻¹): 3277, 3219 (NH ₂) 1652 (C=O); 1625 (C=N) and 1601 (C=C).
6c	IR $\bar{\nu}$ (cm ⁻¹): 3252 (NH); 1735, 1691 (CO's); 1629 (C=N) and 1609 (C=C). Mass (m/z): 251 (100.0%); 252 (15.0%) and 253 (1.2%).
6d	IR $\bar{\nu}$ (cm ⁻¹): 3295 (NH); 1721, 1677 (C=O's); 1612 (C=N) and 1601 (C=C). ¹ H NMR δ_{H} (ppm): 1.95 (m, 2H, CH ₂ -aliph.); 2.23 (t, 4H, 2 CH ₂ -aliph); 3.91 (s, 3H, CH ₃) 7.11-7.80 (m, 4H, ArH's) 8.10 (s, 1H, NH) and 10.08 (s, 1H, COOH).
7e	¹ H NMR δ_{H} (ppm): 1.90 (d, 2H, NH ₂); 2.03 (m, 1H, NHC=S); 2.48-2.53 (t, 4H, 2CH ₂) 8.10 (d, 1H, NHC=O) and 10.07 (s, 1H, COOH).
9a	¹ H NMR δ_{H} (ppm): 1.80-2.40 (m, 4H, 2CH ₂); 4.30 (m, 4H, 2NH ₂); 7.52-7.88 (m, 4H, ArH's) and 7.91 (m, 1H, NH).
9b	Mass (m/z): 261 (37%); 188 (100%); 230 (65%); 175 (89 %); 146 (60%); 130 (13%) and 90 (17%).

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