Synthesis of novel 1,3-thiazole-, 1,2,4-triazole- thione and triazepine derivatives

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Reaction of the cyanoacetic hydrazide derivatives **1a–e** with isothiocyanates gave the hydrazinocarboxamide and thioamide derivatives **2a–g** and 1,2,4-triazole-3-thiones **3.** Upon reacting **1b–d** with ethyl bromoacetate followed by isothiocyanates; the 1,3-thiazole-5-carbohydrazides **5** were afforded. Cyclisation of products **1b–e** with triethylorthoformate furnished the unexpected ethyl cyanoacetylhydrazonoformate **6**; rather than the expected triazolethiones of type **7**. A mechanism for the formation of product **6** was suggested and discussed. Upon heating product **6** with some arylamines in acetonitrile, the 5-aminotriazepin-7-ones **9** were afforded.

Keywords: novel 1,3-thiazole-, 1,2,4-triazole-thione, triazepine derivatives

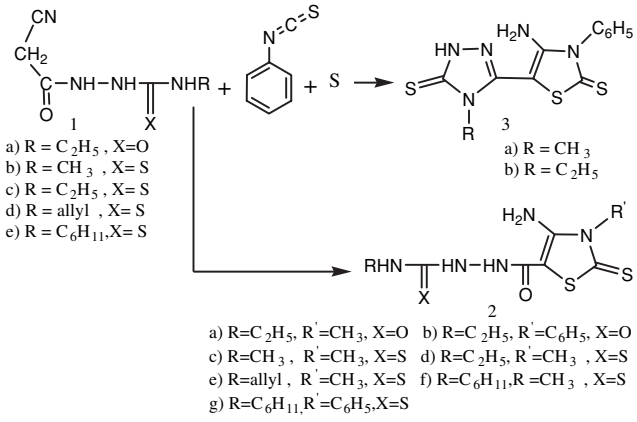
The cyclisation of suitable linear compounds is one of the most common and popular methods for preparing heterocyclic compounds. Unsymmetrical ureas have been cyclised to produce several heterocycles such as 1,3,4-thiadiazoles, 1,2,4-triazoles and 1,3,5-thiazines.[1,2]

Chlorocarbonylsulfenyl chloride when reacted with alkyl- and arylidene- phenylthiosemicarbazenes gave 1,2,4-triazolines and 1,2,4-dithiazolidines.[3] 2,4-Disubstituted thiosemicarbazides were cyclised to 1,2,4-triazoline-3-thiones and 1,3-thiadiazolines when treated with acyl isothiocyanates.[4]

Oxidative cyclisation of substituted aldehyde thiosemicarbazones, induced by different metallic salts, led to 1,2,4-triazoline derivatives.[5-7] On the other hand, the interaction of thiosemicarbazides with the π-acceptors tetracyanoethene afforded substituted 1,3,4-thiadiazepine derivatives.[8] Recently, some newer biologically active fused mesoionic 1,2,4-triazolo[1,5-*a*] pyrimidinium-2-thiolate derivatives were synthesised by reacting thiosemicarbazides with some α –cyano-acrylonitriles and acrylate esters in a one step reaction.[9]

Moreover, drugs containing 1,2,4-triazole moiety *e.g.* triazolam,[10] alparazolam,[11] etizolam,[12] furacrylin[13] and drugs containing 1,3,4-thiadiazole group *e.g.* acetazolamide,[14] benzolamide,[15] methazolamide[16] and furidiazine[17] are well known and find their way for useful application.

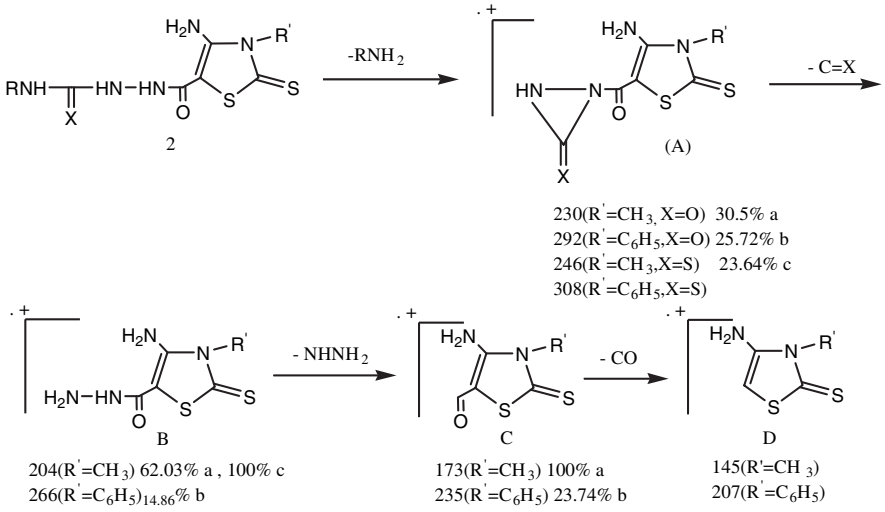
Therefore, in the present work, the synthesis of some 1,3-thiazole-, 1,2,4-triazole-thiones and triazepine derivatives from their thiosemicarbazide derivatives was attempted for their expected biological properties.



Scheme 1

Results and discussion

Upon reacting the 2-cyanoacetic hydrazide derivatives[9] (semi- and thiosemicarbazides) **1a–e** with methyl- or phenyl- isothiocyanate and elemental sulfur in the presence of triethylamine as catalyst, the 2-[(4-amino-3-substituted-2-thioxo-2,3-dihydro-1,3-thiazol-5-yl)carbonyl]-*N*-substitutedhydrazinecarboxamides **2a,b** and *N*-substituted hydrazine-carbothioamides **2c–g ;** were afforded in all cases of reacting **1a–d** with methyl isothiocyanate and in cases of reacting **1a** and **e** with phenyl isothiocyanate but the 5-(4-amino-3-phenyl-2-thioxo-2,3-



Scheme 2 Fragmentation pattern of products **2.**

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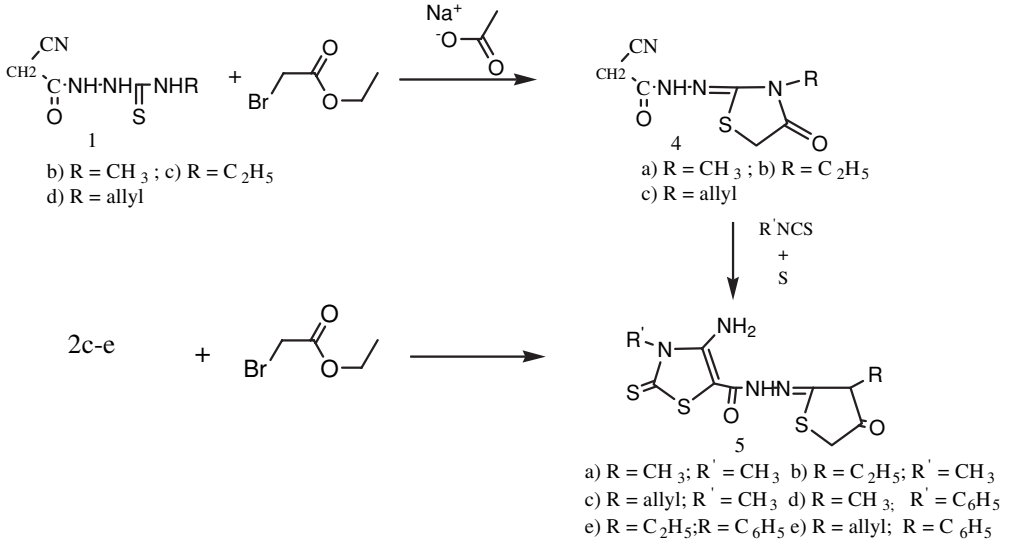


Scheme 3

dihydro-1,3-thiazol-5-yl)-4-substituted-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones **3** were obtained in cases of reacting **1a** and **b** with phenyl isothiocyanate (Scheme 1).

Structure of products **2** and **3** was elucidated by elemental analyses and spectroscopic determinations. Mass spectra of products **2** were characterised by the presence of ion peaks (A) at 230 (R' = CH_3, X = O), 292 (R' = C_6H_5, X = O), 246 (R' = CH_3, X = S) and 308 (R' = C_6H_5, X = S) which indicated the splitting of RNH_2 moieties in the mass spectrometer, splitting of C=X group from fragment (A) giving the ion peak fragments (B) at *m/e* 204 (R' = CH_3) and 266 (R' = C_6H_5), which leave a hydrazine to form fragments (C) at *m/e* 173 (R' = CH_3) and 235 (R' = C_6H_5) as shown in Scheme 2.

Furthermore, when compounds **1b–d** were reacted with ethyl bromoacetate in the presence of sodium acetate; 2-cyano-*N*-(3-substituted-4-oxo-1, 3-thiazolidin-2-ylidene)acetohydrazides **4** were afforded in excellent yield. Reaction of the latter products with methyl or phenyl isothiocyanate gave the 4-amino-3-substituted-*N*-(3-substituted-4-oxo-1,3-thiazolidin-2-ylidene)-2-thioxo-2,3-dihydro-1,3-thiazole-5-carbohydrazides **5** (Scheme 3). Products **5a–c** were obtained, also, by reacting **2c–e** with ethyl bromoacetate (m.p. and mixed m.p. no depression).

Spectral determinations of products **4** and **5** accorded well their proposed structures. Thus, IR spectra of products **4** revealed the presence of ν_{CN} and $\nu_{C=O}$ at 2257-2260 and 1700-1705 cm^{-1} regions respectively. The spectra of products **5** lack nitrile absorptions and showed $\nu_{C=O}$ at 1697-1721 cm^{-1} region.

^{1}H NMR spectra of products **4** showed the presence of CH_2CN and CH_2-thiazolidine moieties at δ: 3.75–3.77 and 4.06–4.11 ppm regions respectively.

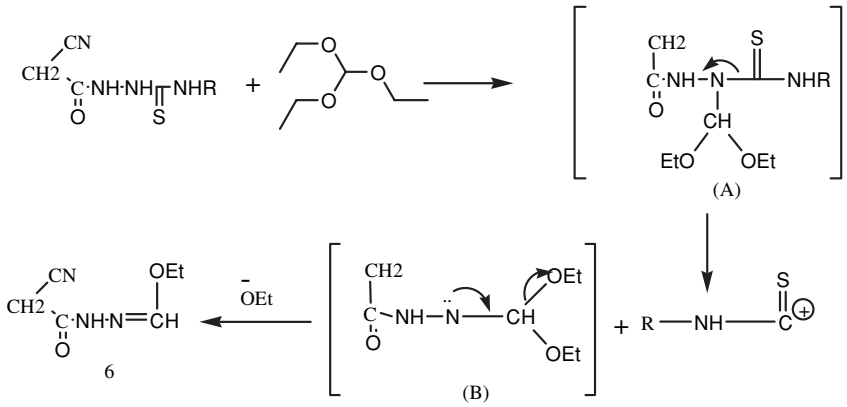
Moreover, mass spectra of products **4** and **5** accorded well their proposed structures. (Table 2).

Furthermore, cyclisation of products **1b–c** with triethyl orthoformate in dry xylene afforded unexpectedly ethyl cyanoacetylhydrazonoformate of type **6** in all cases rather than the expected triazole–thione derivatives **7** (Scheme 4).

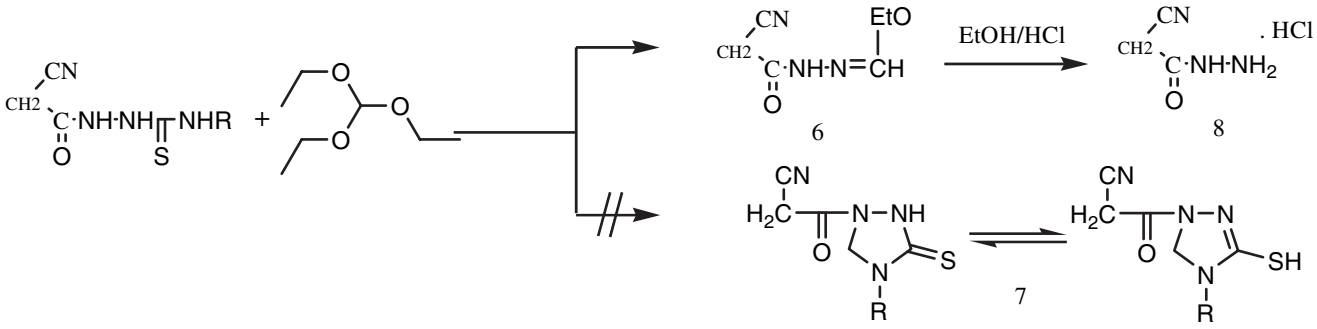
Structure of product **6** was confirmed chemically by heating it in ethanolic hydrochloric acid, the solid product obtained was identified as cyanoacetylhydrazide hydrochloride salt **8** (no depression in m.p. and mixed m.p. with the product obtained from treating cyanoacetyl hydrazide with EtOH/HCl). Also element test for product **6** showed the absence of elemental sulfur.

^{1}H NMR spectrum of **6** was characterised by the presence of ethyl proton signals at δ: 1.33 (t, *J*=7.18 Hz) and 4.16 (q, *J*=7.18 Hz) ppm; due to OC_2H_5 moiety. The spectrum showed also another proton signals at: δ: 3.73, 6.48 and 9.03 (D_2O-exchangeable) ppm for CH_2CN, N = CH and NH respectively.Its mass spectrum accorded well its proposed molecular structure and revealed a molecular ion peak at 155 (100%) characteristic to $M^{+\bullet}$.

The following mechanism can suggest the formation of product **6**:



Product 6

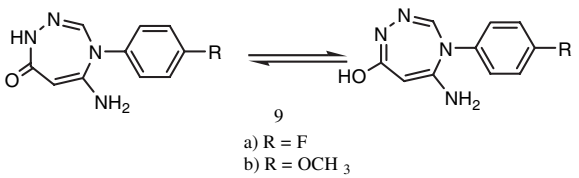


Scheme 4

Table 1 Characterisation of the synthesised products

Compd.	M.p./°C (Solvent)	Yield/%	Mol. formulae (M.Wt.)	Analysis: Calcd / Found			
				C	H	N	S%
2a	259-261	78	$C_8H_{13}N_5O_2S_2$	34.90	4.76	25.44	23.29
	(DMF)		(275.34)	35.00	4.80	25.60	23.10
2b	177-179	65	$C_{13}H_{15}N_5O_2S_2$	46.27	4.48	20.76	19.00
	(EtOH)		(337.41)	46.10	4.50	20.60	19.10
2c	249–251	90	$C_7H_{11}N_5OS_3$	30.31	4.00	25.25	34.68
	(Ac/DMF)		(277.39)	30.56	4.21	25.40	34.50
2d	233–234	78	$C_8H_{13}N_5OS_3$	32.97	4.50	24.03	33.01
	(Acetonitrile)		(291.41)	32.80	4.40	24.00	33.21
2e	222–223	68	$C_9H_{13}N_5OS_3$	35.62	4.32	23.08	31.70
	(Acetonitrile)		(303.42)	34.78	4.80	22.88	33.10
2f	232–233	62	$C_{12}H_{19}N_5OS_3$	41.71	5.54	20.27	27.87
	(Ac/DMF)		(345.50)	41.88	5.19	20.57	27.96
2g	238–240	65	$C_{17}H_{21}N_5OS_3$	50.09	5.19	17.18	23.60
	(Ac/DMF)		(407.57)	50.09	5.25	17.40	23.92
3a	267–269	78	$C_{12}H_{11}N_5S_3$	44.84	3.45	21.79	29.92
	(Acetonitrile)		(321.44)	44.75	3.57	21.99	30.10
3b	275–277	63	$C_{13}H_{13}N_5S_3$	46.54	3.91	20.88	28.67
	(Acetonitrile)		(335.46)	46.68	3.76	20.95	28.65
4a	183–184	81	$C_7H_8N_4O_2S$	39.61	3.80	26.40	15.11
	(EtOH)		(212.23)	39.62	4.00	26.36	15.15
4b	193–194	78	$C_8H_{10}N_4O_2S$	42.47	4.46	24.76	14.17
	(EtOH)		(226.25)	42.26	4.61	24.62	14.32
4c	167–168	93	$C_9H_{10}N_3O_2S$	45.37	4.23	23.52	13.46
	(EtOH)		(238.26)	45.23	4.46	23.59	13.49
5a	249–250	66(A)	$C_9H_{11}N_5O_2S_3$	34.05	3.49	22.07	30.30
	(Ac/DMF)	90(B)	(317.41)	34.03	3.38	21.91	30.68
5b	233–234	64(A)	$C_{10}H_{13}N_5O_2S_3$	36.24	3.95	21.13	29.02
	(Ac/DMF)	95(B)	(331.43)	36.38	4.00	21.13	30.22
5c	237–238	58(A)	$C_{11}H_{13}N_5O_2S_3$	38.47	3.81	20.39	28.01
	(Ac/DMF)	89(B)	(343.44)	38.51	4.03	20.44	27.93
5d	260–261	55	$C_{14}H_{13}N_5O_2S_3$	44.31	3.45	18.46	25.35
	(DMF)		(379.47)	44.25	3.67	18.55	25.51
5e	250–251	52	$C_{15}H_{15}N_5O_2S_3$	45.75	3.84	17.80	24.44
	(Ac/DMF)		(393.50)	45.65	3.85	17.67	24.25
5f	242–243	53	$C_{16}H_{15}N_5O_2S_3$	47.39	3.73	17.27	23.72
	(Ac/DMF)		(405.51)	47.36	3.89	17.40	23.89
6	114–145	80	$C_6H_9N_3O_2$	46.44	5.85	27.08	–
	(pet.ether/ACOEt)		(155.12)	46.67	5.92	27.48	–
9a	165–166	88	$C_{10}H_9FN_4O$	54.54	4.12	25.44	F, 8.63
	(Acetonitrile)		(220.20)	54.66	4.23	25.60	8.66
9b	153–154	81	$C_{11}H_{12}N_4O_2$	56.89	5.21	24.13	–
	(Acetonitrile)		(232.24)	57.00	5.30	24.30	

The present work was extended to probe reactivity of product 6 towards aryl amines. Thus, upon heating product 6 with either *p*-fluoroaniline or *p*-anisidine in acetonitrile, the corresponding 5-amino-4-(aryl)-1,4-dihydro-7*H*-1,2,4-triazepine-7-ones 9a and b were afforded smoothly in good yield.



9

a) R = F
b) R = OCH_3

Product 9

Structure of products 9 was elucidated from their spectral properties. Their IR spectra revealed the absence of nitrile absorptions. ^{1}H NMR spectra lack proton signals due to OC_2H_5 group; instead showed signals at δ: 4.00 and 10.66–10.76 ppm respectively corresponded to amino[18] and imino protons. Moreover, the proposed structure of the triazepines 9a and b were accorded well by mass spectra which showed molecular ion peaks *m/e* (M^+) at 220 and 232 respectively.

Table 2 Spectral properties of the synthesised products

Compd.	IR(KBr) cm^{-1}				^1H NMR (DMSO-d_6)*	Mass
	ν_{NH}	ν_{CN}	$\nu_{C=O}$	$\nu_{C=S}$	δ : ppm	*m/e*(R.I)[b]
2a	3367 3312 3192		1655	1243	1.01(t, 3H, *J*=7.08 Hz, CH_3-ethyl); 3.07(q, 2H, *J*=7.08Hz, CH_2); 3.56(s, 3H, CH_3); 6.51(bs, 1H, HN–ethyl); 7.55(bs, 2H, NH_2); 7.89(bs, 1H, NH); 8.89(bs, 1H, NH).	275 (7.03)
2b	3465 3388 3263		1677	1252	1.05(t, 3H, *J*=7.00Hz, CH_3); 3.10(q, 2H, *J*=7.00Hz, CH_2); 6.60(bs, 1H, NH); 6.94(bs, 2H, NH_2); 7.33(m, 2H, 2CH(Ph.)); 8.00(bs, 1H, NH); 9.00(bs, 1H, NH).	337 (2.77)
2c	3396 3292		1633	1209	2.89(s, 3H, CH_3); 3.56(s, 3H, CH_3); 7.73(bs, 2H, NH_2); 8.39(bs, 1H, NH); 9.39(bs, 2H, 2NH)	277 (2.03)
2d	3375 3270		1637	1201	1.06(t, 3H, *J*=7.02Hz, CH_3-ethyl); 3.45(m, 5H, NCH_3,NCH_2); 7.66(bs, 2H, NH_2); 8.42(bs, 1H, NH); 9.30(bd, 2H, 2NH).	255.7 (29.95)
2e	3383 3278		1632	1203	3.56(s, 3H, CH_3); 4.10(m, 2H, CH_2–allyl); 5.08(m, 2H, CH_2 = C); 5.83 (m, 1H, CH); 7.59(bs, 2H, NH_2); 8.39(bs, 1H, NH); 9.25(bd, 2H, 2NH).	285.1 (2.86)
2f	3360 3278		1637	1202	1.00–2.00(m, 10H, C_6H_{11}); 3.56(s, 3H, CH_3); 4.11(m, 1H, CH); 7.60(bs, 2H, NH_2); 7.85(bs, 1H, NH); 9.18(bs, 2H, 2NH).	345.4 (0.34)
2g	3360 3317		1645	1220	1.00–2.00(m, 10H, C_6H_{11}); 4.15(m, 1H, CH); 6.95(bs, 2H, NH_2); 7.35(m, 2H, CH(Ph)); 7.60(m, 3H, 3CH(Ph)); 8.05(bs, 1H, NH); 9.30(bs, 2H, NH_2).	407.3 (1.51)
3a	3406 3300			1252	3.56(s, 3H, CH_3); 6.22(bs, 2H, NH_2); 7.39(m, 2H, 2CH(Ph)); 7.31(m, 3H, 3CH(Ph)); 13.89(bs, 1H, NH).	321 (100)
3b	3406 3297				1.28(t, 3H, *J*=7.07Hz, CH_3); 4.10(q, 2H, *J*=7.07Hz, CH_2); 6.28(bs, 2H, NH_2); 7.40(m, 2H, 2CH(Ph)); 7.66(m, 3H, 3CH(Ph)); 13.87(bs, 1H, NH).	335.1 (10.10)
4a	3180	2260	1710	1217	3.10(s, 3H, CH_3); 3.76(s, 2H, CH_2CN); 4.06(s, 2H, CH_2-thiazole); 10.59(bs, 1H, NH).	212 (100)
4b	3160	2258	1705	1250	1.14(t, 3H, *J*=7.02 Hz, CH_3); 3.70(q, 2H, *J*=7.02 Hz, N-CH_2); 3.95(m, 4H, CH_2CN); (CH_2-thiazole), 10.67(bs, 1H, NH).	226.1 (100)
4c	3172	2257	1705	1236	3.75((s, 2H, CH_2CN); 4.11(s, 2H, CH_2-thiazole); 4.25(s, 2H, N-CH_2); 5.19 (m, 2H, CH_2 = C); 5.84(m, 1H, CH); 10.70(bs, 1H, NH).	238 (97.90)
5a	3410 3259		1721	1242	3.22(s, 3H, NCH_3); 3.58(s, 3H, N-CH_3); 4.08(s, 2H, CH_2, thiazole); 7.85(bs, 2H, NH_2); 10.14 (bs, 1H, NH).	317 (34.83)
5b	3188		1712	1237	1.22(t, 3H, *J*=7.10 Hz, CH_3-ethyl); 3.58(s, 3H, CH_3); 3.80(q, 2H, *J*=7.10 Hz, CH_2-ethyl); 4.07(s, 2H, CH_2-thiazole); 7.82(bs, 2H, NH_2); 10.04(bs, 1H, NH).	331 (66.71)
5c	3328 3273		1697	1243	3.58(s, 3H, CH_3); 4.12(s, 2H, CH_2-thiazole); 4.38(m, 2H, CH_2-allyl); 5.20 (m, 2H, CH_2 = C); 5.95(m, 1H, CH); 7.74(bs, 2H, NH_2); 9.93(bs, 1H, CH); 7.74(bs, 2H, NH_2); 9.93(bs, 1H, NH).	343 (8.49)
5d	3328 3188		1708	1240	3.24(s, 3H, CH_3); 4.09(s, 2H, CH_2-thiazole); 7.11(bs, 2H, NH_2); 7.37(m, 2H, 2CH(Ph)); 7.66(m, 3H, 3CH(Ph)); 10.14(bs, 1H, NH).	379.1 (6.41)
5e	3402 3396		1713	1241	1.24(t, 3H, *J*=7.08 Hz, CH_3); 3.82(q, 2H, *J*=7.08 Hz, N-CH_2); 4.09(s, 2H, CH_2-thiazole); 7.20(bs, 2H, NH_2); 7.38(m, 2H, 2CH(Ph)); 7.61(m, 3H,	393.1 (36.25)
	3156				3CH(Ph)); 10.16(bs, 1H, NH).	
5f	3422 3281		1709	1241	4.14(s, 2H, CH_2-thiazole); 4.40(m, 2H, CH_2-allyl); 5.24(m, 2H, CH_2 = C); 5.90(m, 1H, CH); 7.20(bs, 2H, NH_2); 7.35(m, 2H, 2CH(Ph)); 7.60(m, 3H, 3CH(Ph)); 1019(bs, 1H, NH).	405.2 (5.58)
6	3187	2261	1685		1.33(t, 3H, *J*=7.18 Hz, CH_3); 3.73(s, 2H, CH_2); 4.16(q, 2H, *J*=7.18 Hz, CH_2); 6.48(s, 1H, CH); 9.03(bs, 1H, NH).	155.1 (13.55)
9a	3390 3364	–	1698	1214	4.00(b,2H,NH_2); 7.40(m,5H,Ar,3-H); 8.00(m,1H,6-H); 10.76(b,1H, NH).	220(M^+) (76.27)
9b	3386 3354	--	1695	1247	3.76(s, 3H, OCH_3); 4.00(b, 2H, NH_2); 6.80–7.40(m, 5H, Ar, 3-H); 8.00(m, 1H, 6-H); 10.66(b, 1H, NH).	232(M^+) (86.83)

[a]NH_2, NH are D_2O exchangeable.
[b]R.I. Relative Intensity (%).

Experimental

All melting points are uncorrected. Microanalyses were carried out by the Microanalytical Laboratory, National Research Center, Cairo, Egypt. Infrared Spectra (KBr-disc) were recorded using a Jasco FT/IR-300E spectrophotometer. ^1H NMR spectra were measured in DMSO-d_6 using Varian Mercury 300 MHz and Varian Gemini 200MHz with chemical shift in δ from Me_4Si. Mass spectra were recorded on GC/MS Finnigan SSQ 7000 spectrophotometer.

The physical and analytical details of the products are given in Table 1, and their spectral data are presented in Table 2.

2-[(4-Amino-3-substituted-2-thioxo-2,3-dihydro-1,3-thiazol-5-yl) -carbonyl]-N-substituted hydrazine carboxamides ***2 a, b*** *and 5-(4-Amino-3-phenyl-2-thioxo-2,3-dihydro-1,3-thiazol-5-yl)-4-substituted-2,4-dihydro-3H-1,2,4-triazole-3-thiones* (**3**): *General procedure*: A mixture of **1a–e** (0.01 mol), the desired isothiocyanate (0.012 mol) and elemental sulfur (0.01 mol) in absolute ethanol (50 ml containing few drops of triethylamine) was heated under reflux for 3 h. The solid product obtained (after cooling or after concentration and cooling) was filtered off, washed with cold ethanol, dried and crystallised to give products **2a–g** and **3**.

2-Cyano-N-(3-substituted-4-oxo-1,3-thiazolidin-2-ylidene) acetohydrazides (**4**): *General procedure*: A mixture of **1b–d** (0.01mol), ethyl bromoacetate (0.01 mol) and sodium acetate (0.01 mol) in absolute ethanol (30 ml) was heated under reflux for 3 h. The solid product obtained after cooling the reaction mixture was filtered off, washed with cold ethanol, dried and crystallised to give products **4**.

4-Amino-3-substituted-N-(3-substituted-4-oxo-1,3-thiazolidin-2-ylidene)-2-thioxo-2,3-dihydro-1,3-thiazole-5-carbohydrazides

(**5**): *Method A*: *General Procedure*: A mixture of **2** (0.01 mol), the desired isothiocyanate (0.012 mol) and elemental sulfur (0.01 mol) in absolute ethanol (40 ml), triethyl amine (0.01 mol) was heated under reflux for 3 h. After cooling the reaction mixture; the solid product obtained was filtered, washed with ethanol, dried and crystallised for purification to give products **5**.

Method B: *General Procedure*: To a suspension of **2c,d** or **e** (0.01 mol) in absolute ethanol (50 ml), it was added. ethyl bromo-acetate (0.01 mol) and sodium acetate (0.01 mol). The reaction mixture was heated under reflux for 3h. and left to cool. The solid product obtained was filtered off, washed with ethanol, dried and then crystallised for purification to give products **5a–c** (m.p.s and mixed m.p.s gave depression with the products obtained from compounds **4**).

Ethyl Cyanoacetylhydrazonoformate (**6**): A mixture of **1b–e** (0.01mol) and triethyl orthoformate (0.03 mol) in dry xylene (100 ml) was heated under reflux for 1 h. The reaction mixture was concentrated and left to cool. The solid product obtained was filtered off, dried and crystallised for purification to give product **6**.

Ethyl cyanoacetylhydrazonoformate hydrochloride (**8**): *Method A*: To a solution of **6** (1g) in absolute ethanol (20 ml), conc. hydrochloric acid (3 ml) was added and the relation mixture was heated under reflux for 1 h. then concentrated and left to cool. The obtained solid product was filtered off, washed with cold ethanol, dried and crystallised from absolute ethanol to give **8** (m.p. 201–203°C.).

Method B: A solution of thiosemicarbazide **1**(1g) in absolute ethanol (20 ml) containing conc. hydrochloric acid (3 ml) was heated under reflux for 15 min., concentrated and left to cool. The solid product separated out was filtered off, washed with cold absolute ethanol, dried and crystallised from absolute ethanol to give **8** (m.p. 201–203°C) (m.p. and mixed m.p. with the product obtained from method A gave no depression).

5-Amino-4-aryl-1,4-dihydro-7H-1,2,4-triazepin-7-ones (**9**): A mixture of **6** (0.01 mol) and the desired aryl amine (0.01 mol) in acetonitrile (25 ml) was heated under reflux for 2 h. The solid product obtained after cooling the reaction mixture was filtered off, dried and crystallised from acetonitrile to give the triazepine-ones **9a,b**.

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