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A Decade of Development of Ethylidenethiosemicarbazides as Building Blocks for Synthesis of Azoles and Azines (A Review)

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ABSTRACT

This review represents the synthesis of ethylidenethiosemicarbazides, with aryl or heterocyclic moieties, and its utility as building blocks for construction of different heterocyclic compounds such as; thiazoles, thiazolidinones, [1,3,4]thiadiazoles, [1,3,4]triazoles, [1,3]thiazines, pyrimidines, thiazolo[5,4-*b*]quinoxalines, *bis*-thiazoles, and *bis*-pyrazoles. Also, the pharmaceutical applications of ethylidenethiosemicarbazides have been demonstrated.

Keywords: Thiosemicarbazones, Azoles, Azines, Cyclocondensation, Biological Activity.

INTRODUCTION

Ethylidenethiosemicarbazides [(ethylidene) hydrazine carbothioamides) are a class of organic compounds with general structure $[Ar(CH_3)C=N-NH-CS-NH_2]$. Variation of substituents on thioamide nitrogen (A), sulfur atom (B), and hydrazone nitrogen (C) led to developing an array of ethylidenethiosemicarbazides with structural diversity and broad spectrum of biological activities (Figure 1).

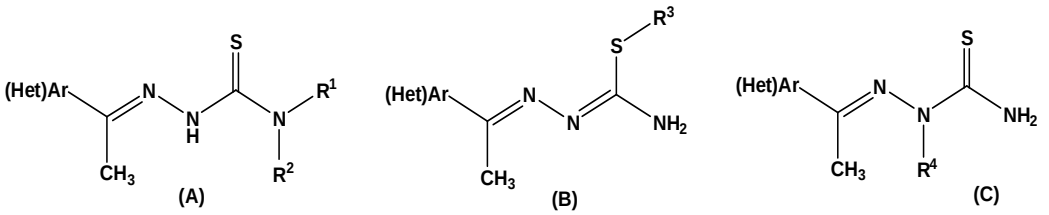
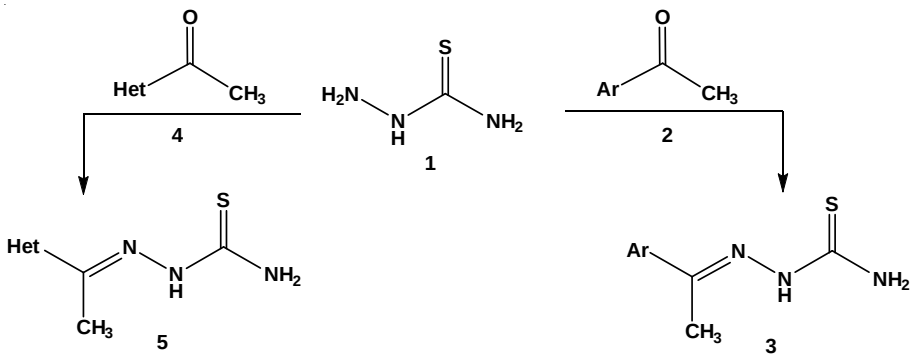


Fig. 1. Representative derivatives of ethylidenethiosemicarbazides

Recently, ethylidenethiosemicarbazides have been used as effective pharmacophoric agents in medicinal chemistry such as; antitumor[1], anti-tubercular[2], anti-amoebic[3], anti-fungal[4], antiviral[5], antimicrobial[6], antioxidant[7], anticonvulsant[8], and anti-trypanosomal[9,10]. Also, these compounds were prescribed for treatment of hypertension as calcium channel blockers[11]. The biological activity of ethylidenethiosemicarbazides is related to their chelating ability with metal ion through either thione or thiolate sulfur and one of the hydrazone-nitrogen atoms[12]. Furthermore, ethylidenethiosemicarbazides have been used as a reactive building blocks for synthesis of different azoles such as, *bis*-thiazoles[13], [1,3,4]thiadiazoles[14], [1,3,4]oxadiazoles[15], thiazolidin-4-ones[16], imidazolinones[17], and thiazoles[18,19]. In this survey, we represent three approaches about ethylidenethiosemicarbazides, with different aryl or heterocyclic moieties, including synthesis, reactivity, and their biological activities.

Synthesis of ethylidenethiosemicarbazides

Ethylidenethiosemicarbazides with aryl group (compound 3) or heterocyclic moiety (compound 5) were prepared through condensation reactions of thiosemicarbazide (1) with acetylarene 2 or heterocyclic ethanone4, respectively [Scheme 1 and Tables 1,2].



Scheme 1. Synthesis of ethylidenethiosemicarbazides

Table 1: 1-(1-arylethylidene)thiosemicarbazide derivatives

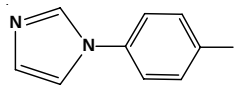
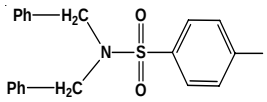
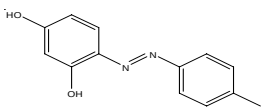
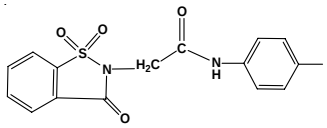
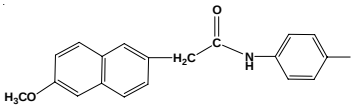
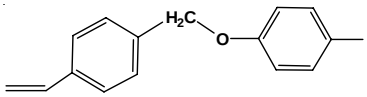
Ar	Ref.	Ar	Ref.
	[4]	3,4-$F_2C_6H_3$	[25]
	[6]	4-BrC_6H_4	[26]
3,4-$Cl_2C_6H_3$	[9]	4-$CH_3OC_6H_4$	[27]
4-$CH_3C_6H_4$	[13]	2-(OH)-4-$(CH_3O)C_6H_3$	[28]
4-$[C(CH_3)_3]C_6H_4$	[16]	4-(*iso*-butyl)C_6H_4	[29]
4-PhC_6H_4			
3-$CF_3C_6H_4$			
3,4-$(OH)_2C_6H_3$			
3-(CH_3O)-4-$(OH)C_6H_3$			
3,4-$(CH_3)_2C_6H_3$			
	[19]	4-$NO_2C_6H_4$	[30]
		3,4-$(CH_3O)_2C_6H_3$	

Table 1(continued)

C_6H_5	[20-22]	2-(OH)-5-$(CH_3O)C_6H_3$	[31]
4-FC_6H_4		2-(OH)-5-BrC_6H_3	[32]
4-ClC_6H_4			[33]
2,4-$Cl_2C_6H_3$			[34]
4-OHC_6H_4	[23]		
4-$NH_2C_6H_4$	[24]		
3-$NH_2C_6H_4$			[35]
3-$NO_2C_6H_4$			

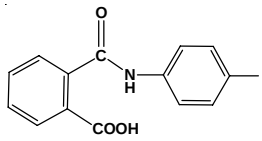
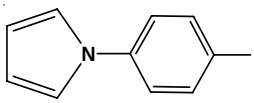
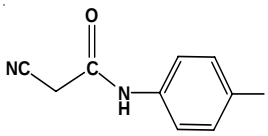
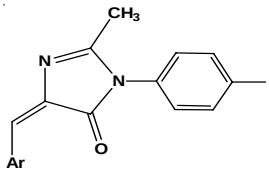
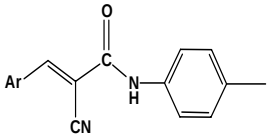
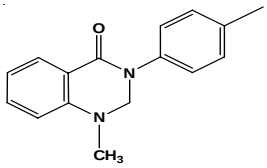
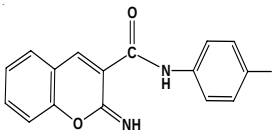
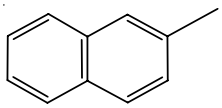
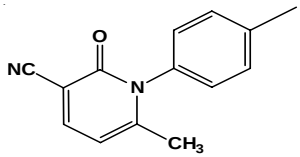
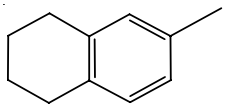
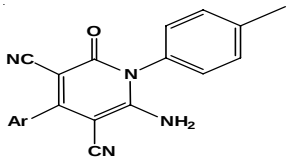
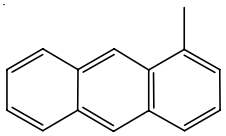
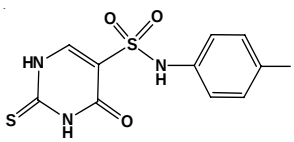
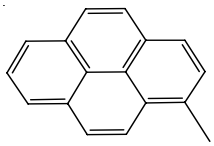
Ar	Ref.	Ar	Ref.
	[36]		[39]
	[37]		[40]
	[37]		[41]
	[37]		[21,42]
	[37]		[43]
	[37]		[44]
	[38]		[45]

Table 1(continued)

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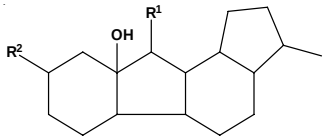
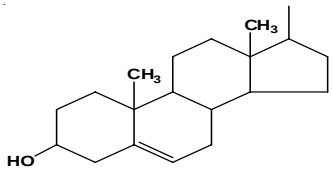
	[46,47]		[48]

Table 2: Ethylidenethiosemicarbazides with heterocyclic moiety

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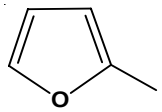
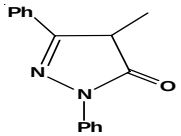
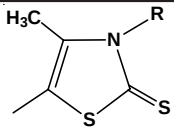
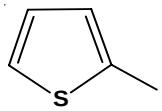
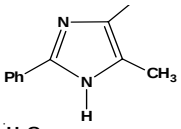
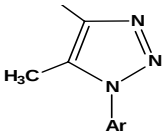
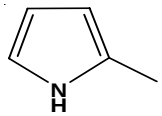
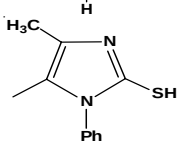
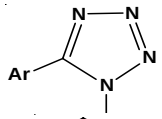
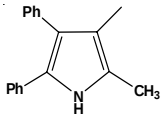
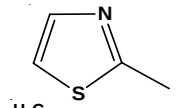
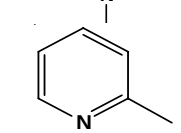
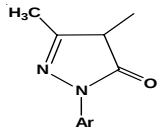
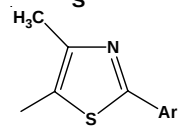
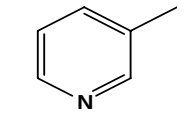
	[21,49]		[56]		[58]
	[20-22,50]		[7]		[14,59,60]
	[51]		[57]		[61]
	[18,52]		[21]		[20-22,62]
	[53-55]		[2]		[20-22,63]

Table 2(continued)

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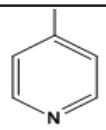
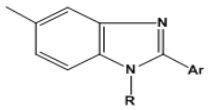
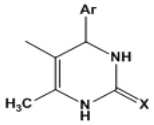
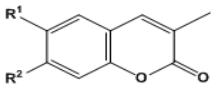
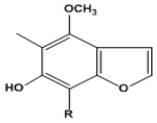
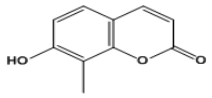
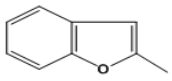
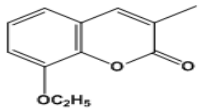
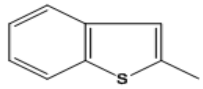
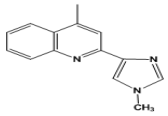
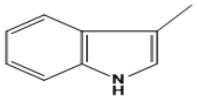
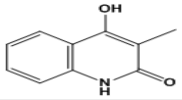
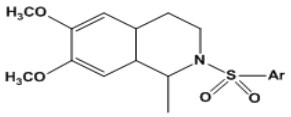
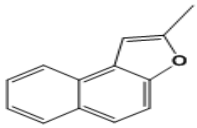
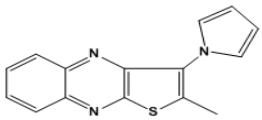
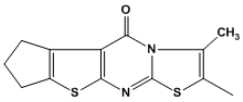
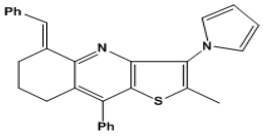
	[20-22]		[5]
	[64-67]		[21,23,70,71]
	[8,68]		[3]
	[51]		[72]

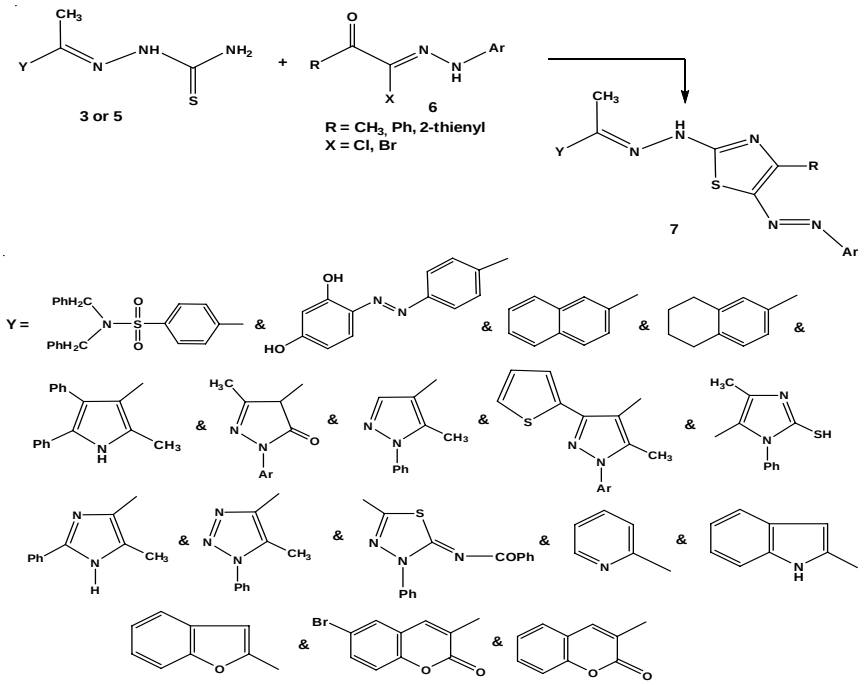
Table 2(continued)

	[51]		[73]
	[69]		[74]
Het	Ref.	Het	Ref.
	[75]		[78]
	[76]		[79]
	[77]		

Reactions of ethylidenethiosemicarbazides

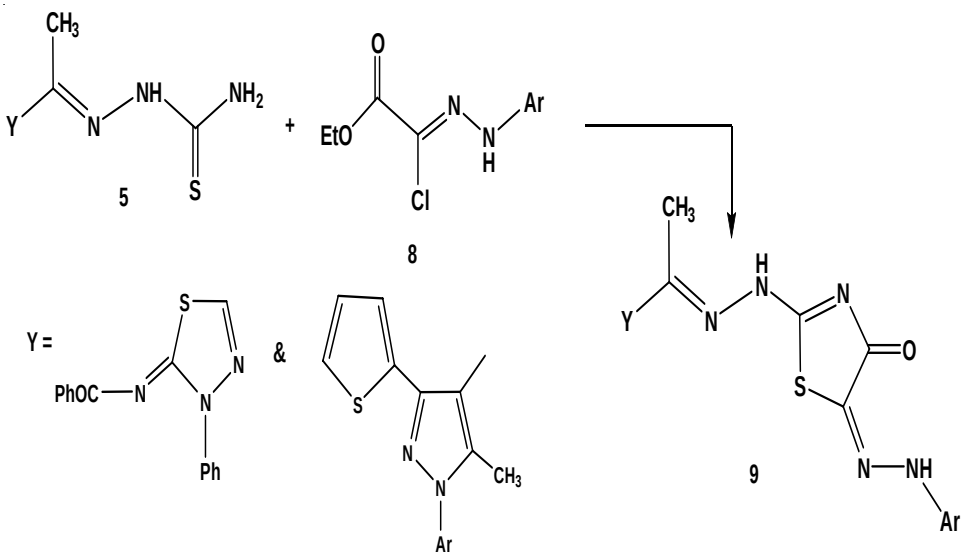
Reaction with α-ketohydrazonoyl halides

5-Arylazothiazoles 7 were synthesizedvia reactions of ethylidenehydrazine-1-carbothioamides3 or 5 with α-ketohydrazonoyl halides 6[*N*-aryl 2-oxopropanehydrazonoyl chlorides or *N*-aryl 2-substituted-acetohydrazonoyl bromides] under thermal conditions[6,7,18,19,42,43,53,57,70,80-86](Scheme 2).



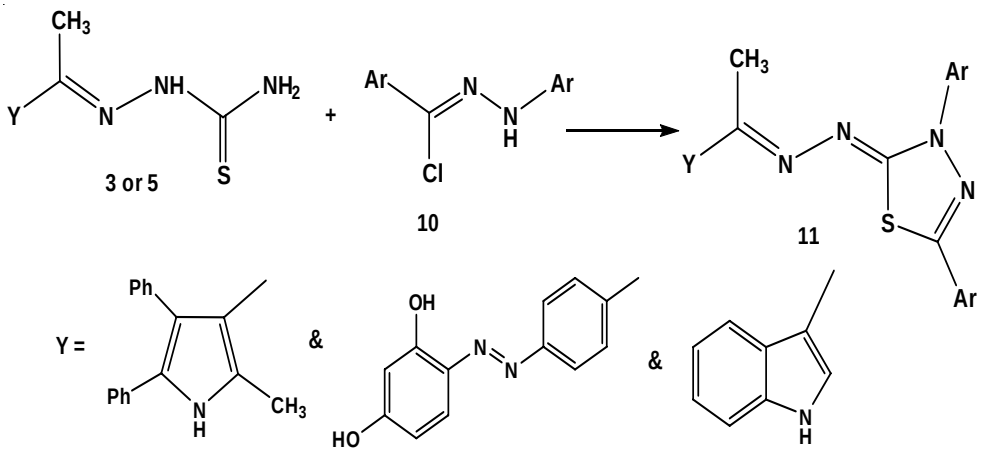
Scheme 2. Reaction of ethylidenehydrazine-1-carbothioamides with α-ketohydrazonoyl halides

By analogous method, ethylidenehydrazine-1-carbothioamides3 or 5reacted with ethyl *N*-aryl-2-chloro-2-hydrazono acetate 8 under reflux conditions in dioxane, containing catalytic amount of triethyl amine and afforded arylhydrazothiazolone[81,85] derivatives 9(Scheme 3).



Scheme 3. Reaction of ethylidenehydrazine-1-carbothioamides with ethyl*N*-aryl-2-chloro-2-hydrazono acetate

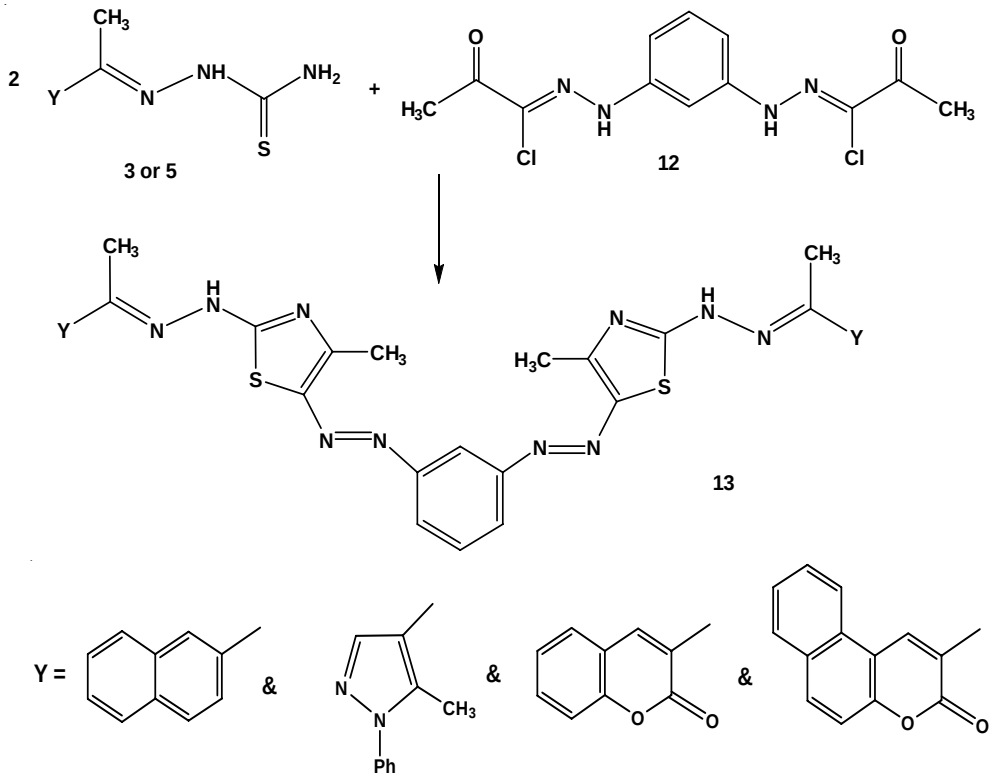
The reactivity of thiosemicarbazones 3 or 5 towards *N*-aryl carbohydrazonoyl chlorides 10, without keto group, has been reported[18,19,84] under thermal[19,84] or microwave irradiation and using grafted chitosan[18] or triethylamine[19,84] as basic catalyst. These reactions have been established to give [1,3,4]thiadiazoles11 (Scheme 4).



Scheme 4. Reaction of thiosemicarbazones with *N*-aryl carbohydrazonoyl chlorides

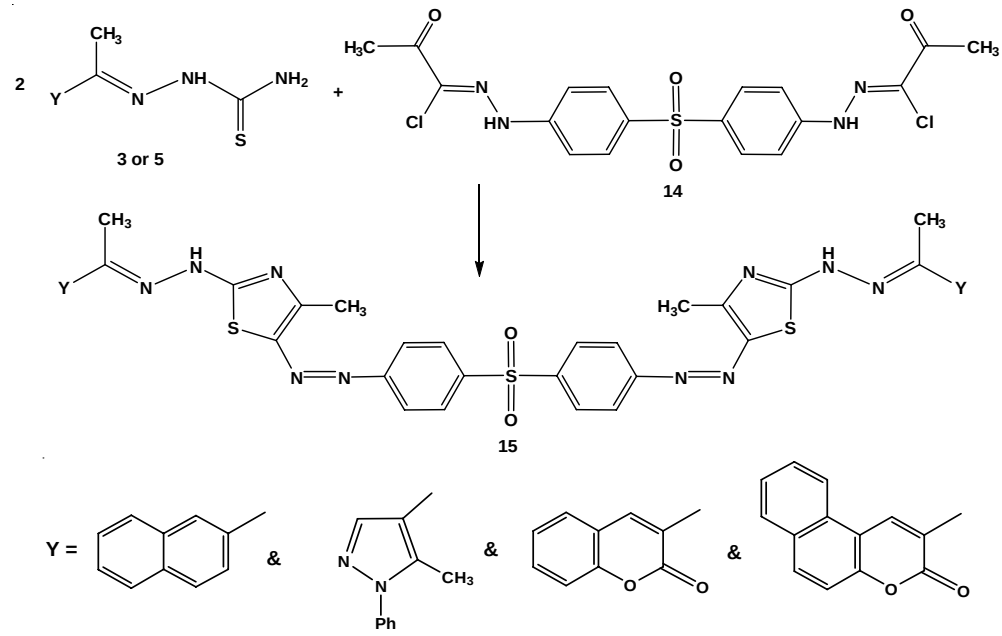
Reaction with *bis*-hydrazonoyl chlorides

Two equivalents of thiosemicarbazones 3 or 5 were reacted with *bis*-[α-ketohydrazonoyl chlorides]12 in dioxane, in the presence of catalytic amount of triethylamine, to furnish the corresponding *bis*-(hydrazonothiazoles)[87]13 (Scheme 5).



Scheme 5. Reaction of thiosemicarbazones with *bis*-[*a*-ketohydrazonoyl chlorides]

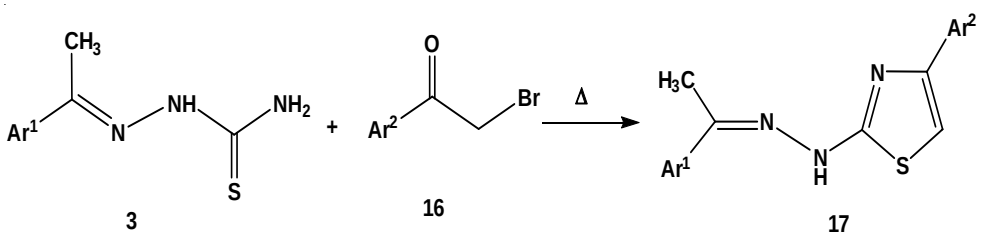
By the same manner, *bis*-hydrazonothiazoles 15, containing sulfonyl group, were synthesized *via* reaction of thiosemicarbazones 3 or 5 with sulfonyl*bis*-[α-ketohydrazonoyl chlorides]14 in a molar ratio (2:1), respectively[87](Scheme 6).



Scheme 6. Reaction of thiosemicarbazones with sulfonyl*bis*-[*a*-ketohydrazonoyl chlorides]

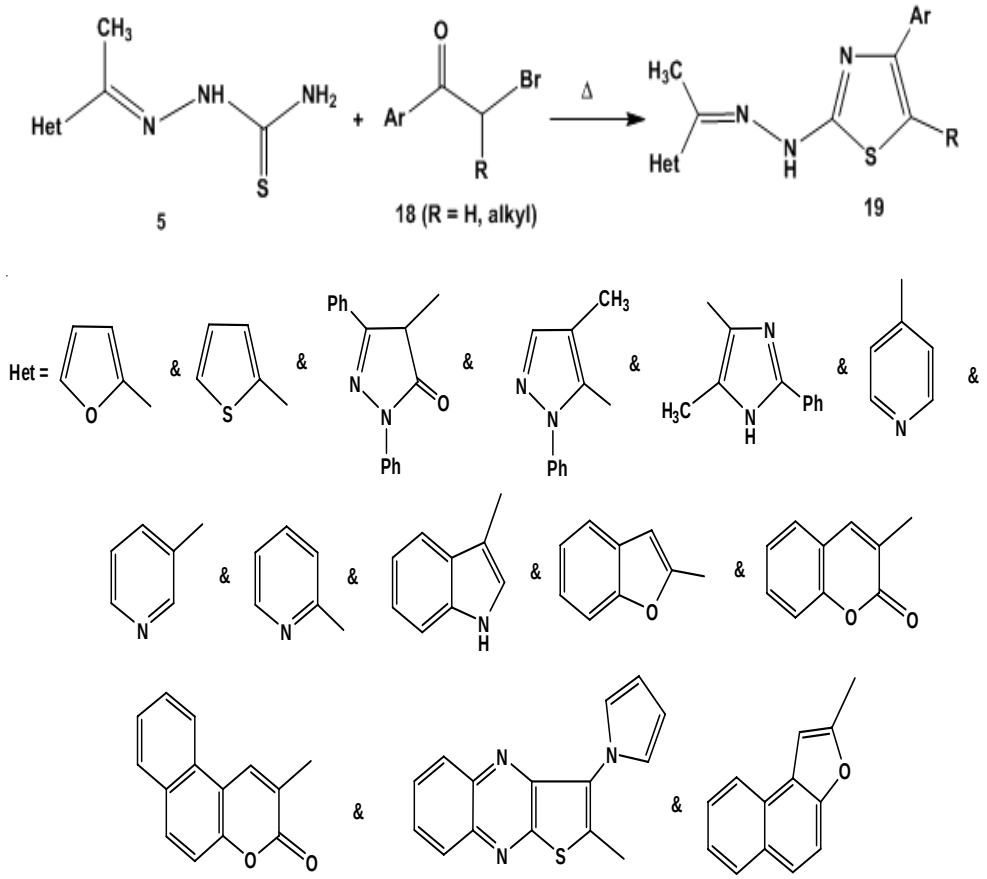
Reaction with α-halocarbonyl compounds

Treatment of 2-[(1-arylethylidene) hydrazine]-1-carbothioamides3 with 1-aryl-2-bromoethanone 16 under thermal conditions gave the respective 2-[2-(1-arylethylidene)hydrazono]-4-arylthiazoles[6,10,19,21,29,42,43,49,83,88-90]17(Scheme 7).



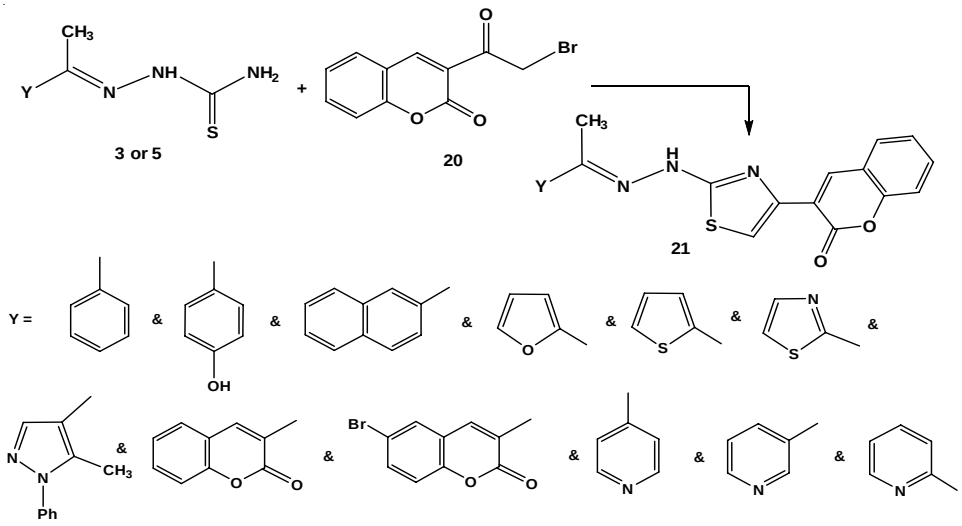
Scheme 7.Reaction of arylethylidenehydrazine-1-carbothioamides with 1-aryl-2-bromoethanone

Also, refluxing of thiosemicarbazones 5, with heterocyclic moiety, with 1-aryl-2-substituted (unsubstituted)-2-bromoethanone 18 afforded 2-hydrazono-4-arylthiazoles[49,52,55,74,76,80,84,88-93]19 (Scheme 8).



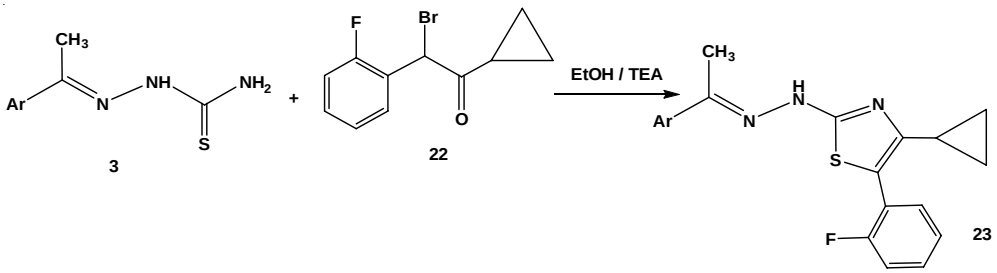
Scheme 8.Reaction of thiosemicarbazones with 1-aryl-2-substituted (unsubstituted)-2-bromoethanone

Conversion of ethylidenehydrazine-1-carbothioamides3 or 5 into 2-hydrazonothiazoles with coumarin moiety21 was achieved through their reactions with 3-(2-bromoacetyl) -2*H*-chromen-2-one(20) inethanol [7,21,23,71,84,86,94,95] (Scheme 9).



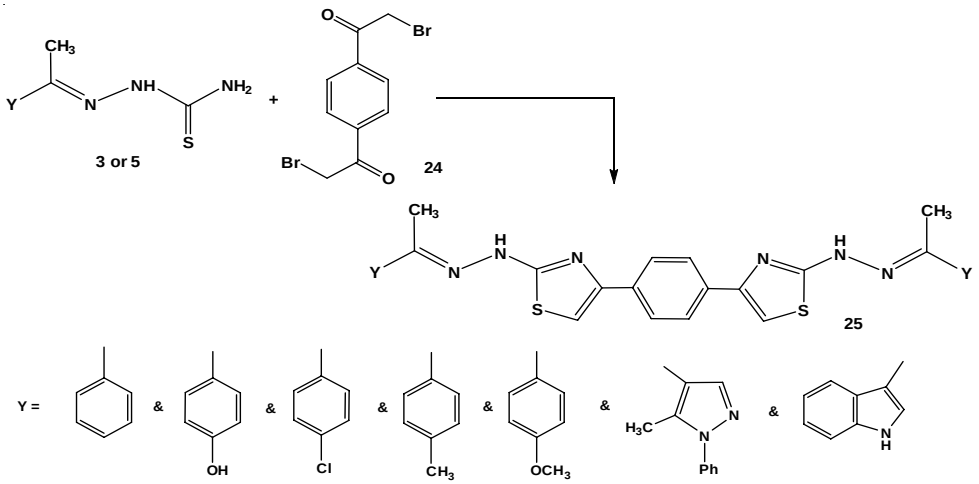
Scheme 9. Synthesis of 4-(coumarin-3-yl)-2-hydrazonothiazoles

2-Arylhydrazono-5-(2-fluorophenyl) thiazoles23 were synthesized from the reaction of 1-(1-arylethylidene)thiosemicarbazides 3 with *a*-bromoketone 22 in ethanolic solution containing triethylamine as a basic catalyst[30] (Scheme 10)



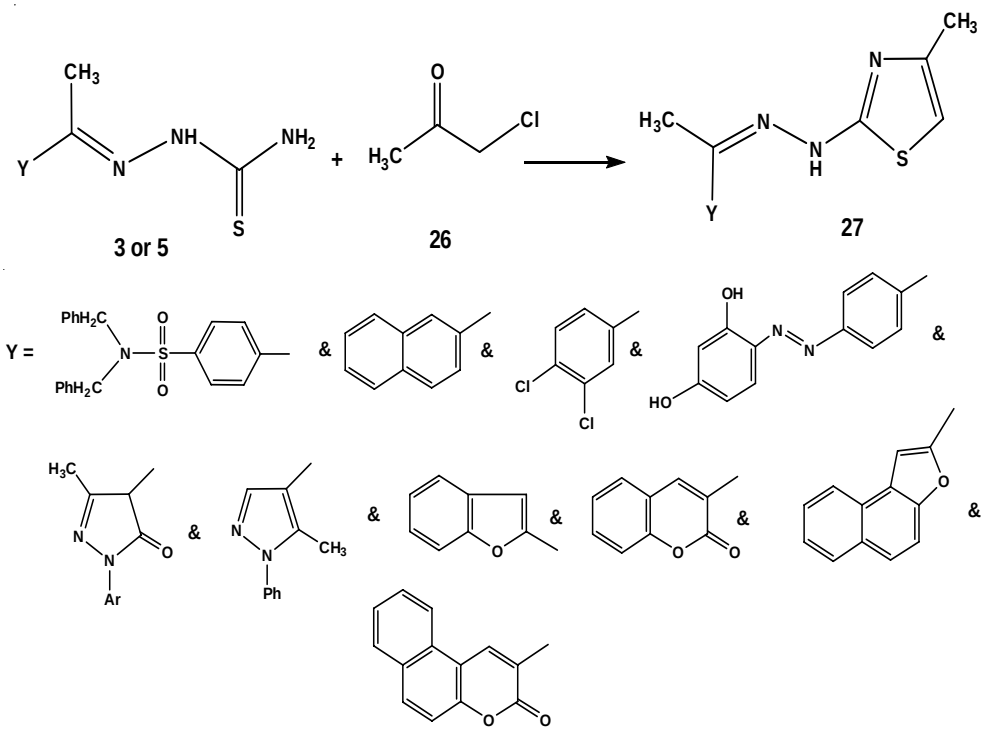
Scheme 10. Reaction of arylethylidenethiosemicarbazides with α-bromoketone

Thiosemicarbazones 3 or 5 were reacted with1,4-*bis*-(2-bromoacetyl)benzene (24) under thermal condition to give 1,4-phenylene-*bis*-thiazolyl derivatives[13]25 (Scheme 11).



Scheme 11. Reaction of thiosemicarbazones with 1,4-*bis*-(2-bromoacetyl)benzene

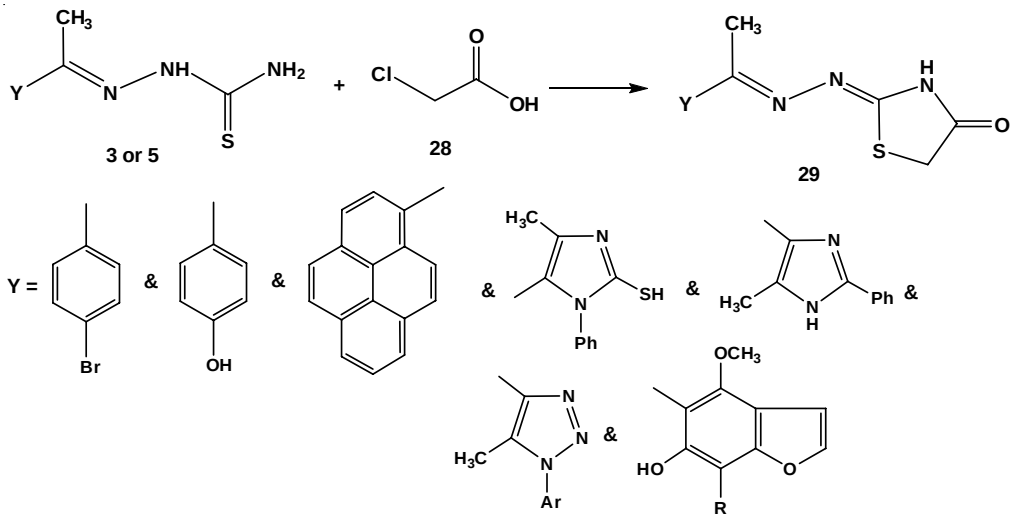
The reactivity of thiosemicarbazones 3 or 5 towards other *a*-haloketones was investigated. Thus, treatment of 3 or 5 with chloroacetone 26furnished the corresponding 4-methyl-2-hydrazonothiazoles 27[6,10,19,42,53,78,80,83] (Scheme 12).



Scheme 12. Reaction of thiosemicarbazones with chloroacetone

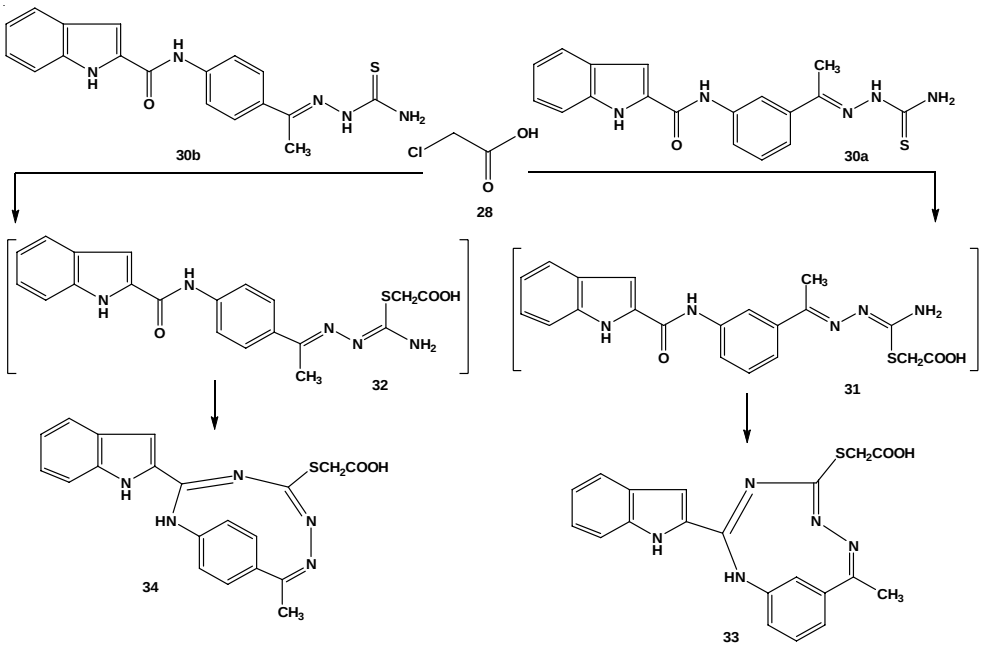
Reaction with chloroethanoic acidor ethyl *α*-haloalkanoate

Cyclocondensation of ethylidenehydrazine-1-carbothiamides3 or 5 with chloroethanoic acid (28) in ethanolic solution, containing anhydrous sodium acetate afforded thiazole-4(5*H*)-one derivatives[7,8,26,45,57,60]29 (Scheme 13).



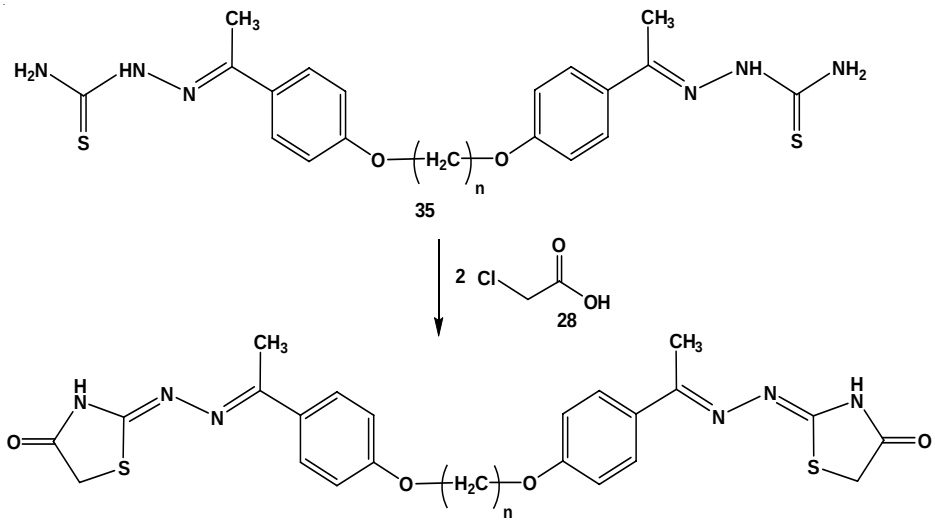
Scheme 13. Synthesis of thiazole-4(5*H*)-one derivatives

Refluxing of chloroethanoic acid (28) with ethylidenehydrazine-1-carbothiamides30aor30b, in ethanolic solution containing sodium acetate, led to formation of tricyclic compounds [2,4,6,7-tetraazabicyclo[7.3.1]trideca-1(13),3,5,7,9,11-hexaen-5-yl]thioethanoic acid (33) or [2,4,6,7-tetraazabicyclo[7.2.2]trideca-1(11),3,5,7,9,12-hexaen-5-yl]thioethanoic acid (34), respectively[96] (Scheme 14). The reactions proceeded by nucleophilic substitution and intramolecular condensation of amino group of thiourea residue and carbonyl of amide linkage.



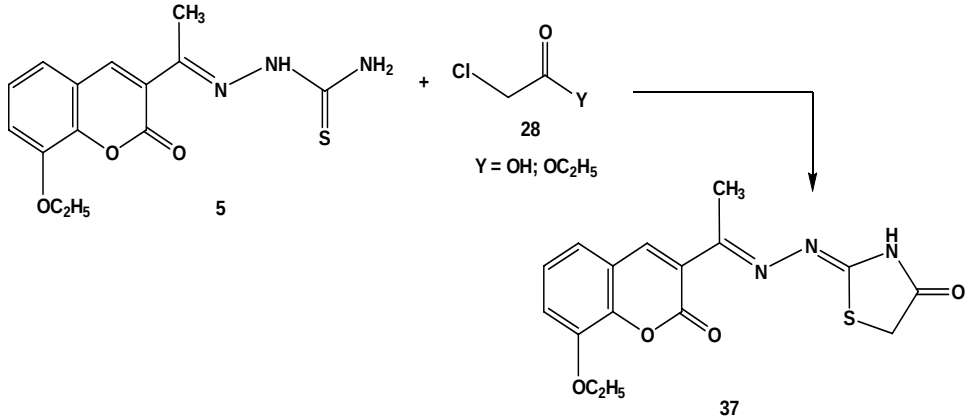
Scheme 14. Synthesis of tricyclic compounds from ethylidenehydrazine-1-carbothiamides

Cyclocondensation of *bis*-oxyphenyl-thiosemicarbazones 35 with two equivalent of chloroethanoic acid (28) gave the respective *bis*-[2-(4-oxybenzylidene)hydrazono)-thiazol-4(5*H*)-one][26]36 (Scheme 15).



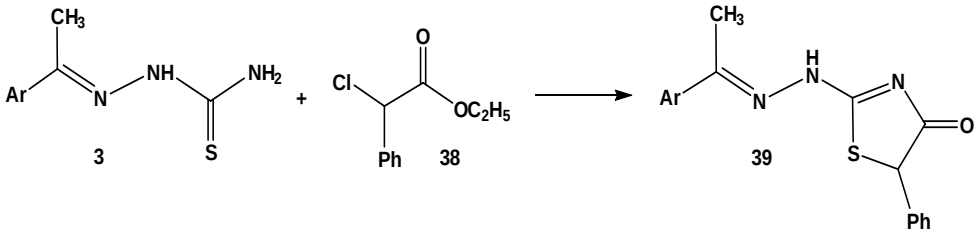
Scheme 15. Synthesis of *bis*-thiazol-4(5*H*)-one derivatives

Treatment of ethylidenehydrazine-1-carbothioamide 5 with chloroethanoic acid or ethyl chloroethanoategave 2-hydrazonothiazolidin-4-one[72] (37) (Scheme 16).



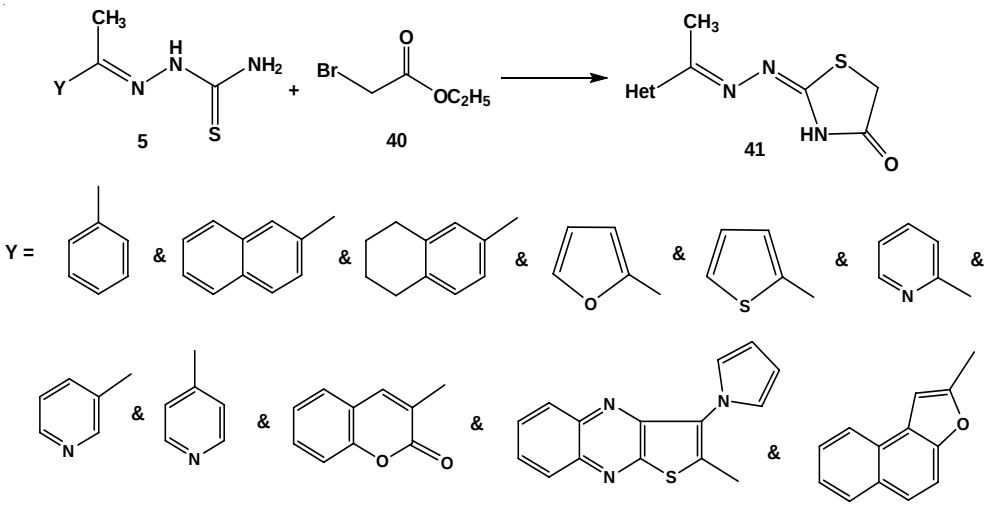
Scheme 16. Reaction of ethylidenehydrazine-1-carbothioamide with chloroethanoic acid or ethyl chloroethanoate

Conduction of 1-(1-arylethylidene) thiosemicarbazides 3 with ethyl 2-chloro-2-phenylacetate (38) under reflux conditions gave the respective 2-[2-(1-arylethylidene) hydrazono]-5-phenyl-thiazol-4(5*H*)-ones[16]39 (Scheme 17).



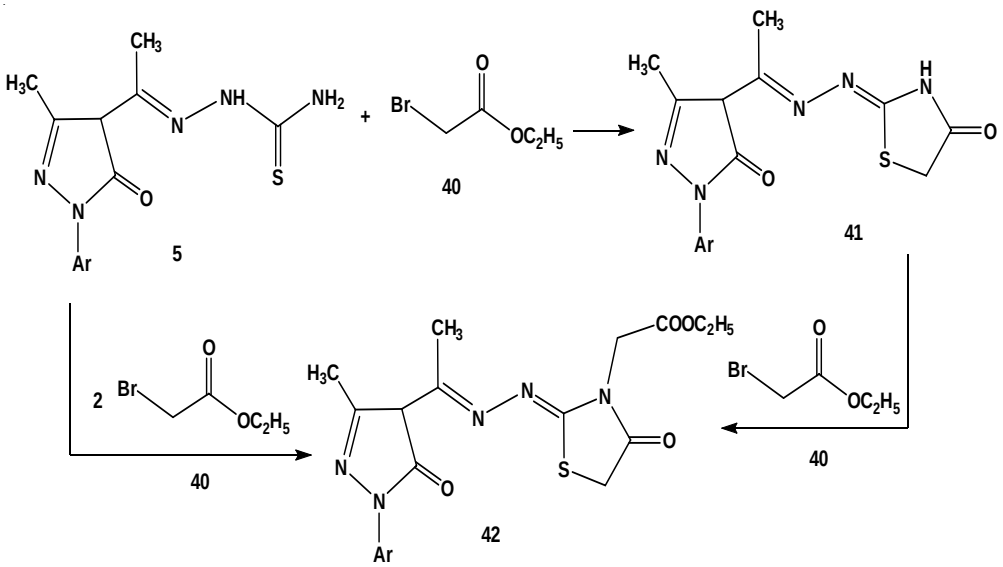
Scheme 17.Synthesis of 5-phenyl-thiazol-4(5*H*)-ones

Similarly, reaction of ethylidenehydrazine-1-carbothioamides3 or 5 with ethyl bromoethanoate(40) under reflux condition in an anhydrous potassium carbonate ethanolic solution afforded 4-thiazolidenones[42,43,76,78,90,97]41(Scheme 18).



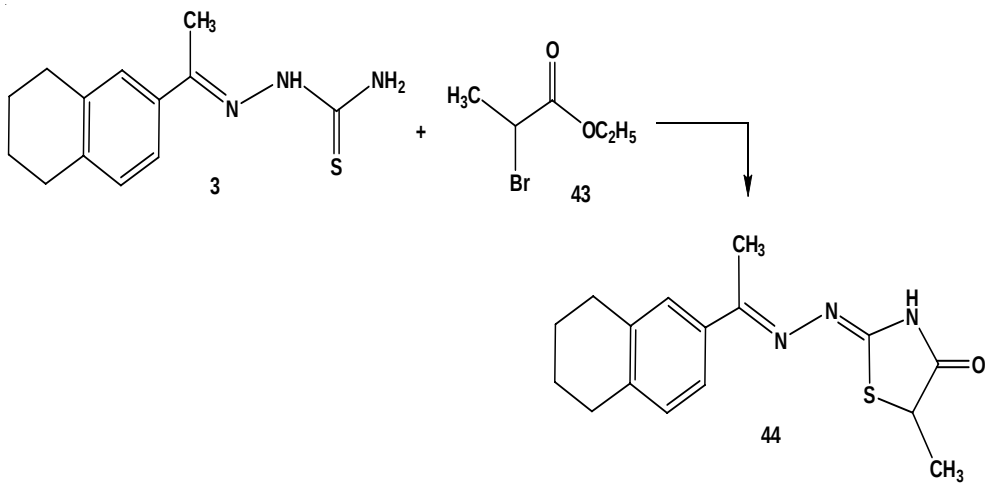
Scheme 18. Synthesis of 2-hydrazono-4-thiazolidenones

Cyclocondensation of ethyli denehydrazine-1-carbothioamide5 with ethyl bromoethanoate(40) in an equal molar ratio, in ethanolic solution containing catalytic amount of fused sodium acetate, afforded thiazole-5(4*H*)-one derivative 41. However, reaction of two moles of ethyl bromoethanoate with one mole of compound 5 gave*N*-ethoxycarbonylthiazole-5(4*H*)-one derivative[6,53,78]42, which was obtained from treatment of 40 with 41 (Scheme 19).



Scheme 19. Reaction of ethylidenehydrazine-1-carbothioamide with ethyl bromoethanoate

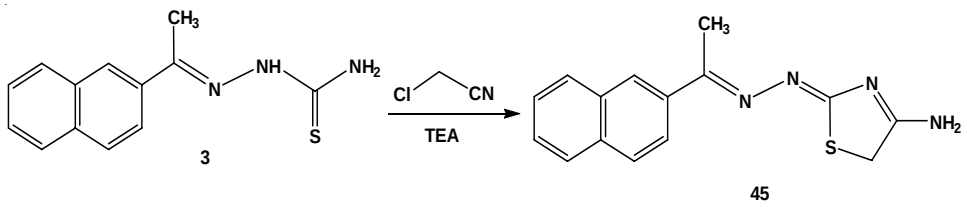
Treatment of arylethylidenethiosemicarbazide 3 with ethyl 2-bromopropanoate (43) under reflux condition in absolute ethanol/piperidine mixturefurnished 5-methyl-4-thiazolidenone[43]44 (Scheme 20).



Scheme 20. Reaction of arylethylidenethiosemicarbazide with ethyl 2-bromopropanoate

Reaction with chloroacetonitrile

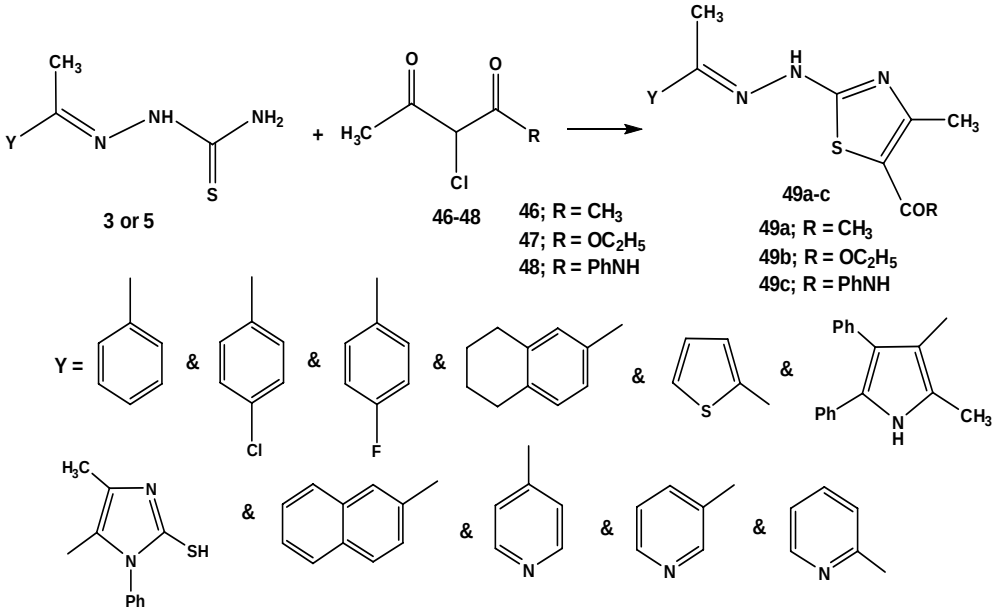
Reaction of chloroacetonitrile with 1-[1-(2-naphthyl)ethylidene]thiosemicarbazide(3) in ethanol/triethylamine mixture, under reflux condition, underwent cyclization to give the respective 2,5-dihydro-4-aminothiazole derivative[42] 45 (Scheme 21).



Scheme 21. Reaction of thiosemicarbazone with chloroacetonitrile

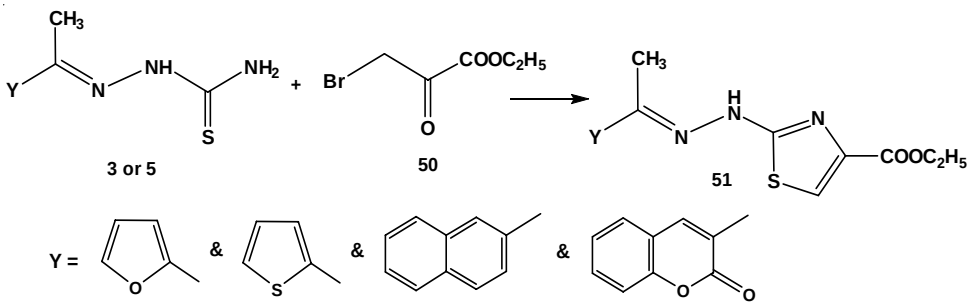
Reaction with α-halo dicarbonyl compounds

Refluxing of ethylidenehydrazine-1-carbothioamides3 or 5 with *a*-halo dicarbonyl compounds such as; chloroacetylacetone (46), ethyl chloroacetoacetate (47), and chloroacetoacetanilide (48) gave the respective 2-hydrazono-4-methylthiazoles[20,42,43,52,57]49 a-c(Scheme 22).



Scheme 22. Reaction of ethylidenehydrazine-1-carbothioamides with *a*-halo dicarbonyl compounds

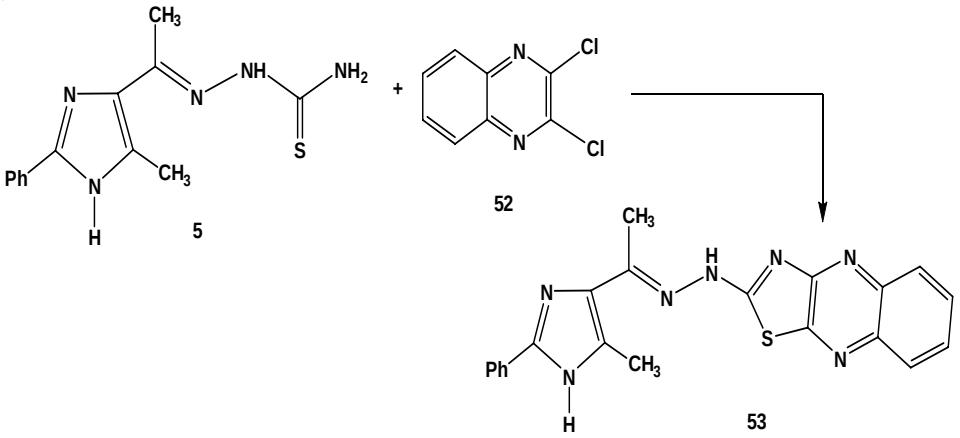
Conventional thermal heating or microwave irradiation of a mixture of ethylidenehydrazine-1-carbothioamides 3 or 5 and ethyl bromopyruvate (50) gave 4-ethoxycarbonylthiazole derivatives[98]51 (Scheme 23).



Scheme 23. Reaction of ethylidenehydrazine-1-carbothioamides with ethyl bromopyruvate

Reaction with dihalo compounds

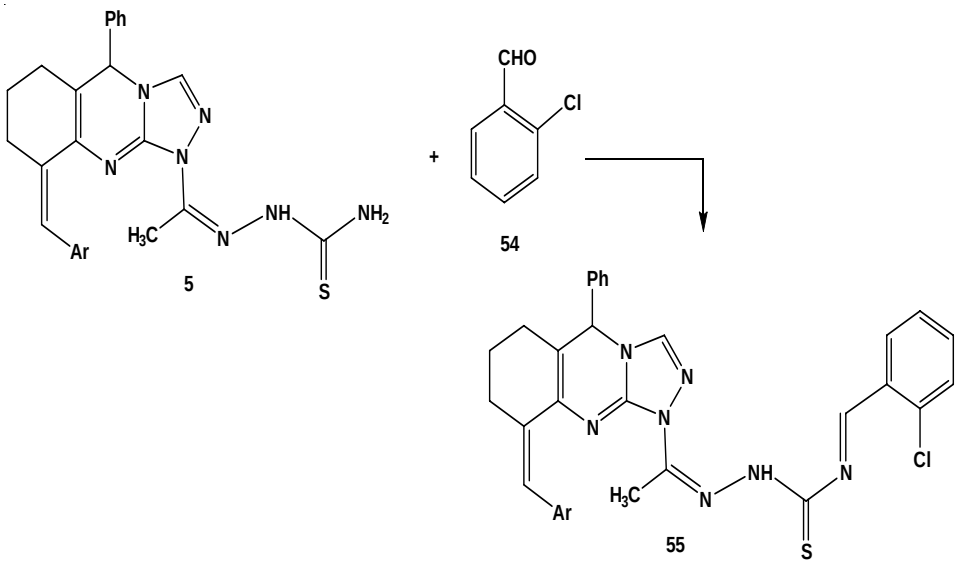
Treatment of ethylidenehydrazine-1-carbothioamide 5with 2,3-dichloroquinoxaline(52) in absolute ethanol, under reflux condition gave ethylidenehydrazonothiazolo[5,4-*b*]quinoxaline[7]53 (Scheme 24).



Scheme 24. Reaction of ethylidenehydrazine-1-carbothioamide with 2,3-dichloroquinoxaline

Reaction with aldehydes

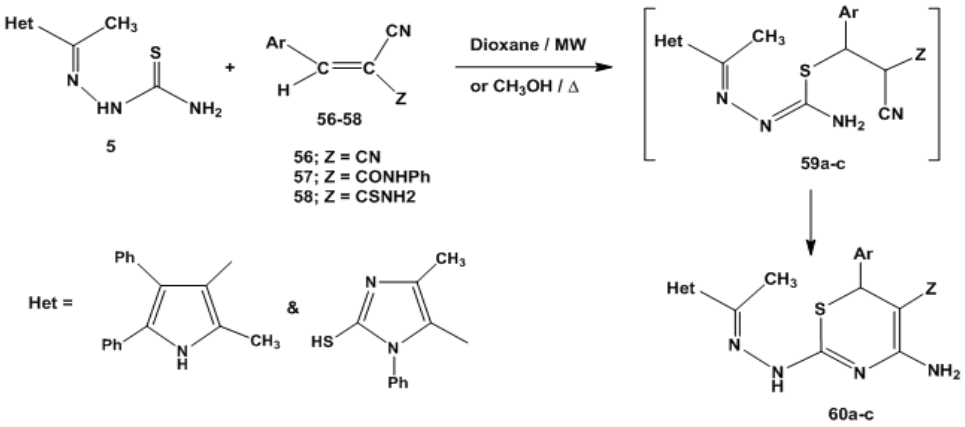
Condensation of 1-[1-(9-arylidene-3-methyl-5-phenyl-6,7,8,9-tetrahydro-[1,2,4] triazolo[3,4-*b*] quinazolin-1(5*H*)-yl) ethylidene] thiosemicarbazide (5) with 2-chlorobezaldehyde (54) gave the respective Schiff's base compound[99] 55 (Scheme 25).



Scheme 25. Preparation of Schiff's base

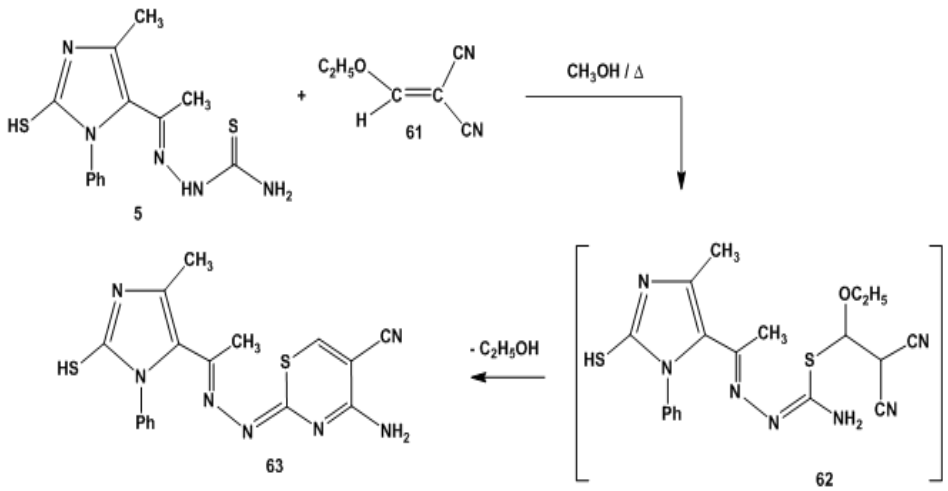
Reaction with *a,b*-unsaturatednitrile compounds

The response of ethylidenehydrazine-1-carbothioamide5 towards different acrylonitrile derivatives was investigated[52,57]. Thus, reaction of5with arylidenemalononitriles 56,2-cyano-*N*,3-diphenylacrylamide (57), and 3-aryl-2-cyano-prop-2-enethioamide (58), in dioxane under microwave irradiation[52] or methanol under thermal conditions[57] furnished the respective 1,3-thiazine derivatives[52,57] 60a-c (Scheme 26).



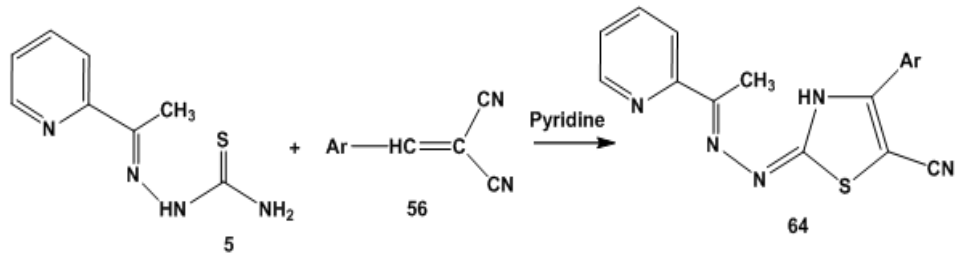
Scheme 26. Reaction of ethylidenehydrazine-1-carbothioamide with acrylonitrile derivatives

Similarly, reaction of ethylidenehydrazine-1-carbothioamide5 with ethoxymethylenemalononitrile (61)in refluxing methanol afforded 4-amino-2-hydrazono-1,3-thiazine-5-carbonitrile[57]63 via non-isolable intermediate 62 (Scheme 27).



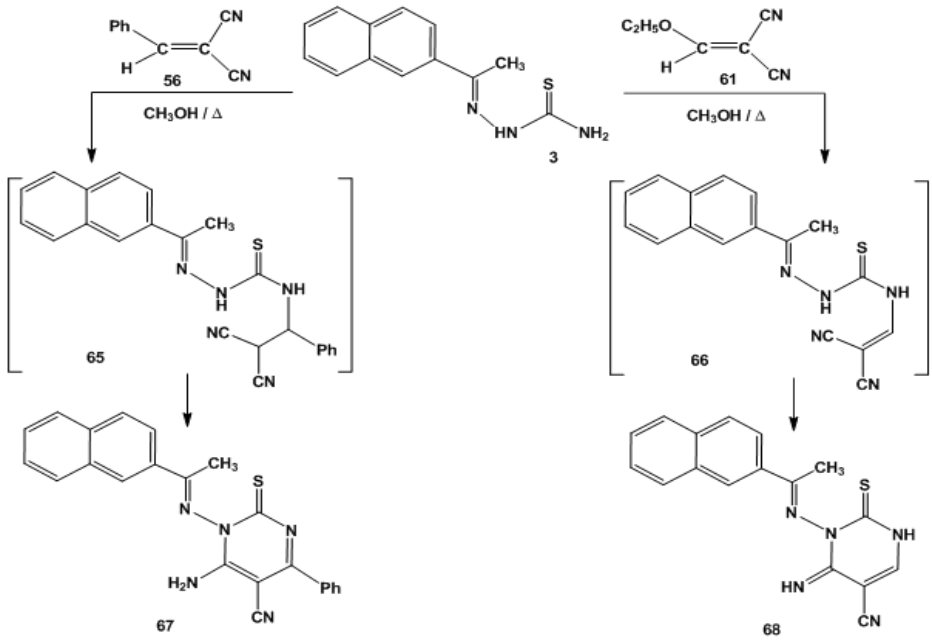
Scheme 27. Reaction of ethylidenehydrazine-1-carbothioamidewith ethoxymethylenemalononitrile

Treatment of an equimolar amounts of 2-[1-(2-pyridyl)ethylidene]hydrazine-1-carbothioamide(5) with arylmethylenemalononitriles 56 in pyridine solution gave 2-hydrazono-4-aryl-2,3 dihydrothiazole-5-carbonitriles[100]64 (Scheme 28).



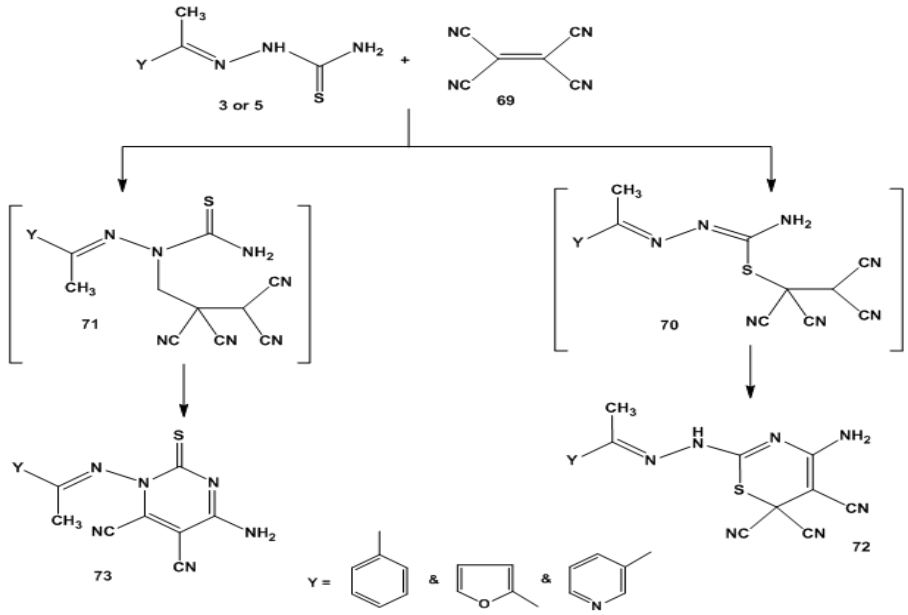
Scheme 28. Synthesis of 2,3-dihydrothiazole-5-carbonitriles

On the other hand, reactions of 1-[1-(2-naphthyl)ethylidene]thiosemicarbazide(3) with benzylidenemalononitrile 56 or ethoxymethylenemalononitrile(61) affordedamino-pyrimidinethione derivative(67) or imino-pyrimidinethione derivative[42](68), respectively (Scheme 29).



Scheme 29. Synthesis of pyrimidinethione derivatives

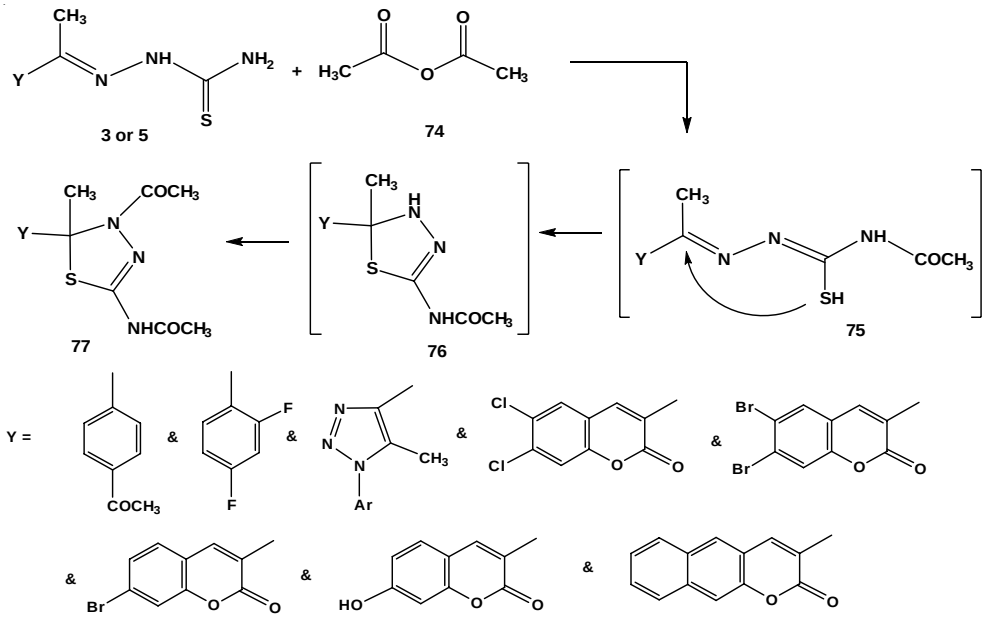
A mixture of 2-arylhydrazono-4-amino-1,3-thiazine-5,6,6-tricarbonitriles 72 and 6-amino-2-thioxo-2,3-dihydropyrimidine-4,5-dicarbonitriles 73 was obtained[101] from the reactions of thiosemicarbazones 3 or 5 with tetracyanoethylene (69) (Scheme 30).



Scheme 30. Reaction of thiosemicarbazone with tetracyanoethylene

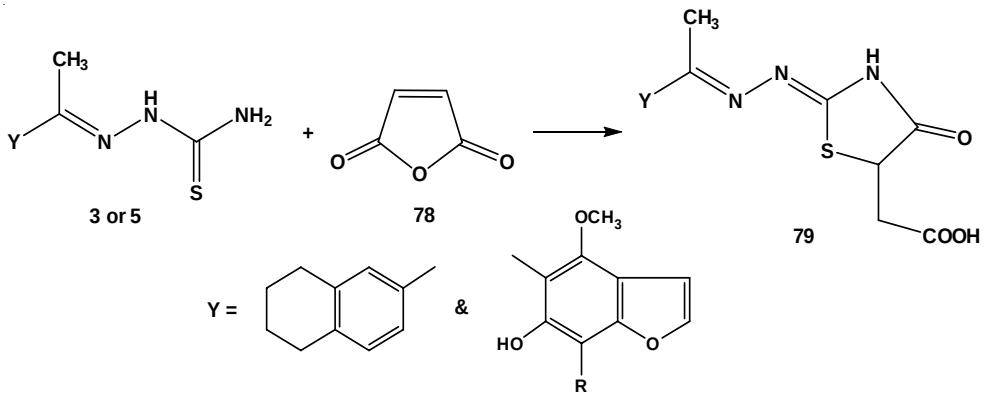
Reaction with anhydrides

Cyclocondensation of ethylidenethiosemicar--bazides 3 or 5 with acetic anhydride (74) led to formation of 3,5-di(*N*-acetylamino)-[1,3,4] thiadiazole derivatives[59,102,103]77. The isolable products were formed *via* acetylation of primary nitrogen of thiourea residue (intermediate 75), intramolecular cyclization of thiol group into imino group (intermediate 76), and acetylation of NH group of [1,3,4]thiadiazole ring (Scheme 31).



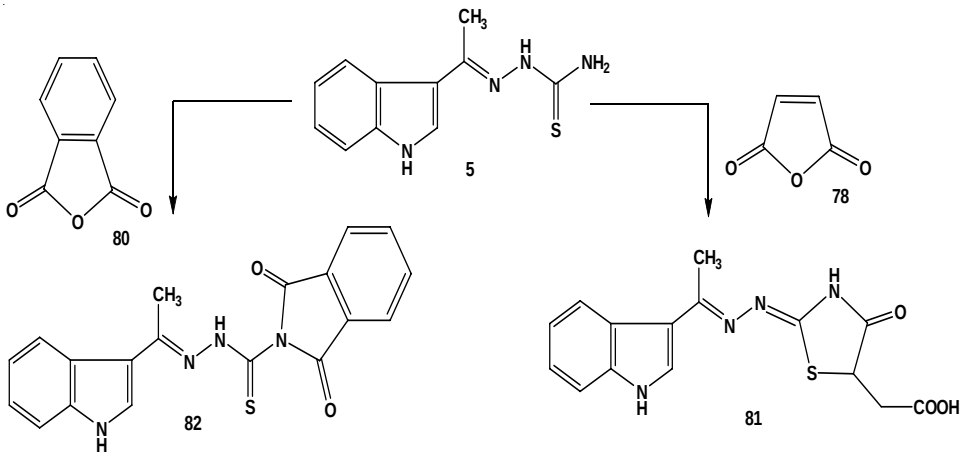
Scheme 31. Reaction of thiosemicarbazone with acetic anhydride

Treatment of ethylidenehydrazine-1-carbothioamides3 or 5 with maleic anhydride (78) gave 2-[2-hydrazono-4-oxo-4,5-dihydrothiazol-5-yl] ethanoic acid derivatives[8,43]79 through thia-Michael reaction(Scheme 32).



Scheme 32. Reaction of ethylidenehydrazine-1-carbothioamides with maleic anhydride

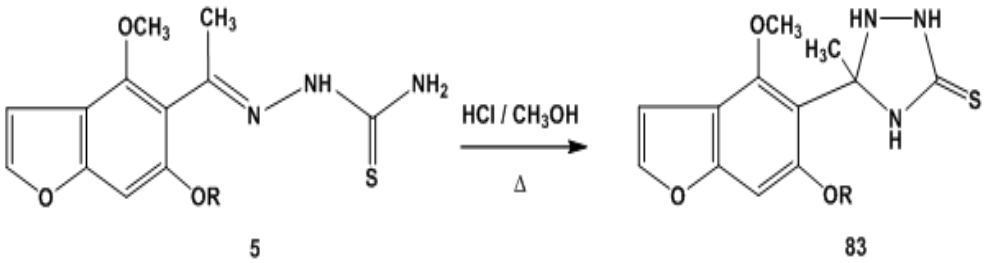
Treatment of thiosemicarbazone (5), containing indole moiety, with maleic anhydride (78) or phthalic anhydride (80) in boiling ethanol gave 2-[2-hydrazono-4-oxo-4,5-dihydrothiazol-5-yl] ethanoic acid derivative (81) or *N*- substituted phthalimide derivative (82), respectively[84] (Scheme 33).



Scheme 33. Reactions of thiosemicarbazone with maleic anhydride and phthalic anhydride

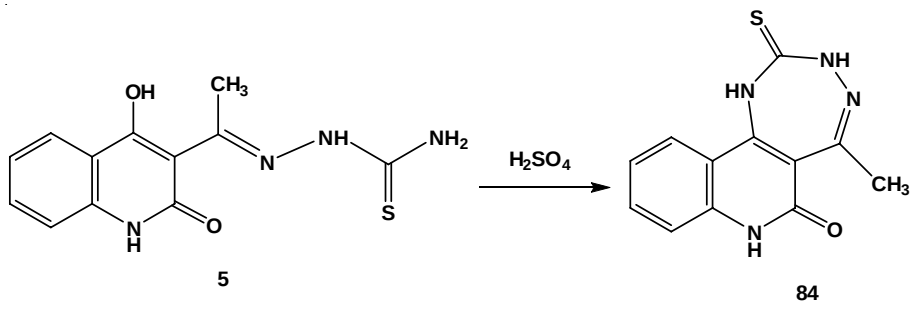
Reaction with hydrochloric and sulfuric acids

Refluxing of thiosemicarbazone (5), containing benzofuran moiety, with methanol/ hydrochloric acid mixture furnished [1,2,4]triazoline-3-thione derivative[68]83 (Scheme 34).



Scheme 34. Reaction of thiosemicarbazone with hydrochloric acid

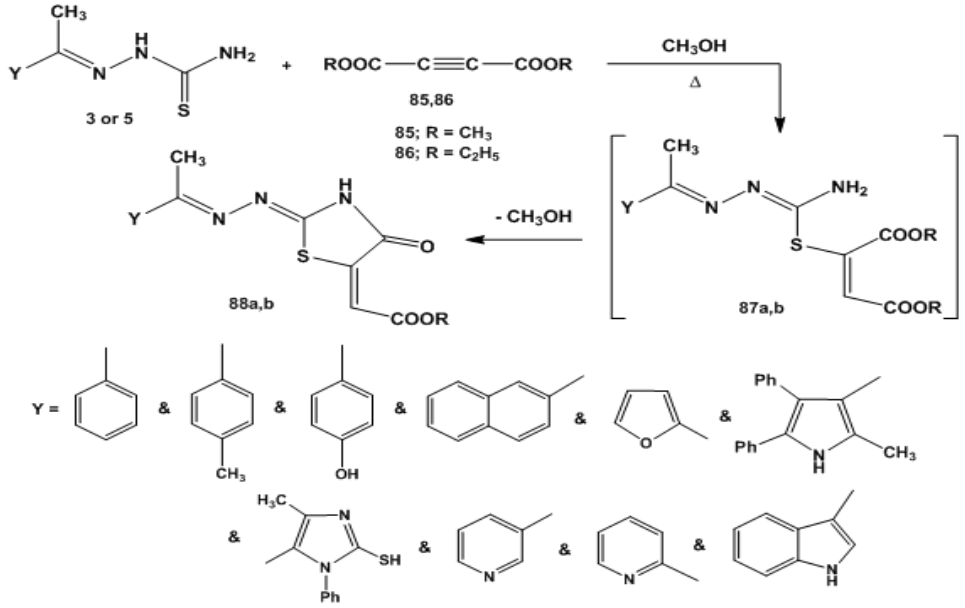
[1,2,4]Triazepino[6,5-*c*]quinolin-6(7*H*)-one (84) was prepared through dehydration of ethylidenehydrazine-1-carbothioamide (5), containing hydroxyquinolone moiety, by sulfuric acid at room temperature[74] (Scheme 35).



Scheme 35. Dehydration of ethylidenehydrazine-1-carbothioamide

Reaction with dialkyl but-2-ynedioate

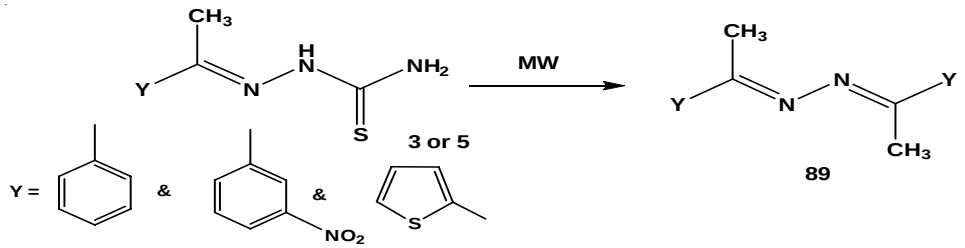
Refluxing of ethylidenehydrazine-1-carbothioamides 3 or 5 with dimethyl but-2-ynedioate or diethyl but-2-ynedioate in methanol afforded the respective alkyl 2-[2-hydrazono-4-oxothiazol-5(4*H*)-ylidene] ethanoate derivatives [42,52,57,84,100,104,105]88a,b (Scheme 36).



Scheme 36. Reaction of ethylidenehydrazine-1-carbothioamides with dialkyl but-2-ynedioate

Self-condensation Reaction

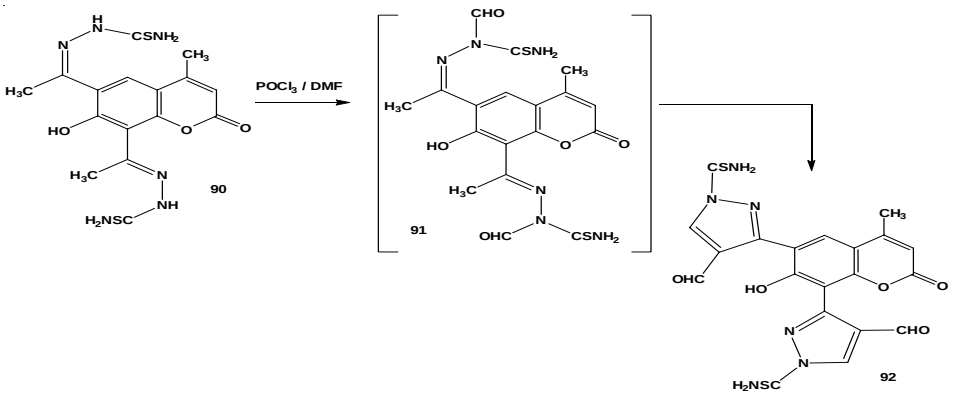
Microwave irradiation of ethylidenehydrazine-1-carbothioamides3 or 5led to self-condensation and give3,4-diazahex-2,4-diene derivatives89[15] (Scheme 37).



Scheme 37. Microwave irradiation of ethylidenehydrazine-1-carbothioamides

Vilsmeier-Haack Reaction

Treatment of *bis*-thiosemicarbazones 90 with Vilsmeier-Haack reagent furnished the respective 6,8-*bis*-pyrazolylcoumarine derivative[106] 92 (Scheme 38).



Scheme 38. Reaction of *bis*-thiosemicarbazone with Vilsmeier-Haack reagent

Biological activity

Antimicrobial activity

Ethylidenethiosemicarbazide 3 or 5 were proclaimed to display a wide range of antibacterial and antifungal activities with different pharmacophore moieties[4,6,7,25,39,58,64,65,67,68,72] (Chart 1).

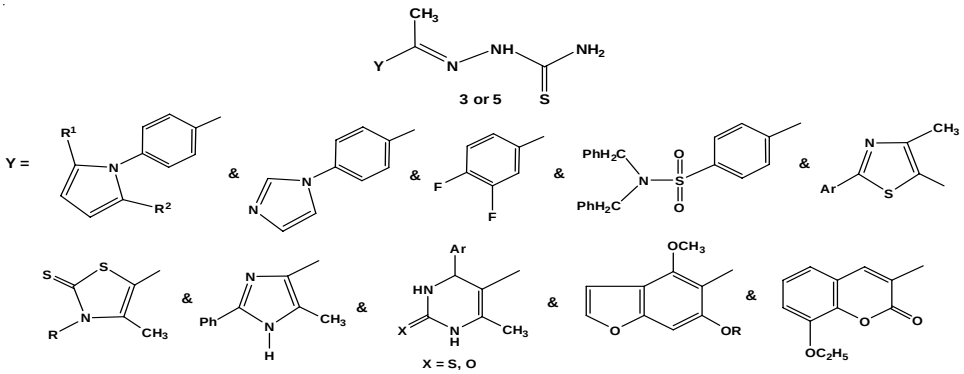


Chart 1. Ethylidenethiosemicarbazide having antimicrobial activity

Antiviral activity

Ethylidenethiosemicarbazide with aryl or benzimidazole substituents were evaluated as antiviral agents and showed moderate activity in most cases[5,33,107,108] (Chart 2).

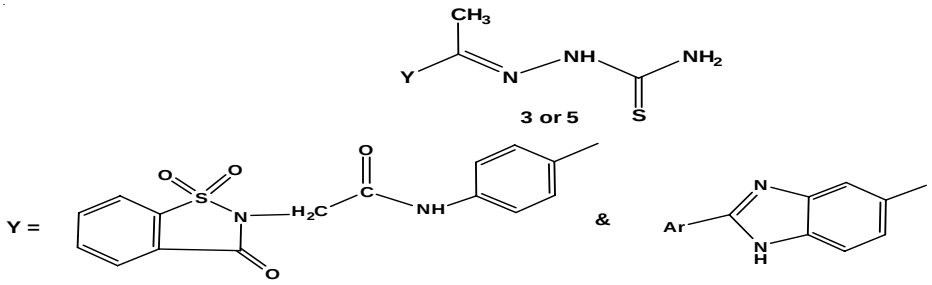


Chart 2. Ethylidenethiosemicarbazide havingantiviral activity

Anticancer activity

Different alicyclic, aryl, or heterocyclic moieties introduced to thiosemicarbazone scaffolds 3 or 5 led to strengthen the anticancer activities against different cell lines[1,7,18,31,47,48,51,73,75,85,96] (Chart 3).

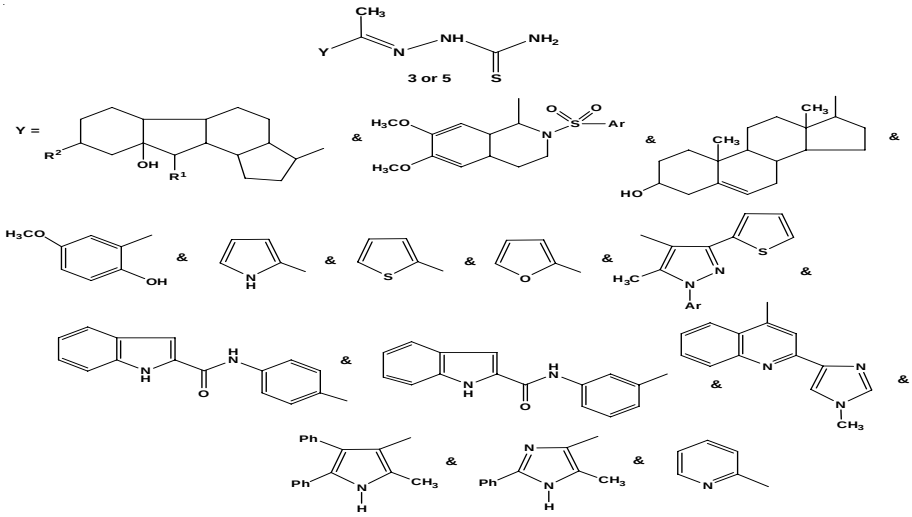


Chart 3. Ethylidenethiosemicarbazide having anticancer activity

Anticonvulsant activity

Thiosemicarbazones are promising anticonvulsant candidates[8] that contain non-polar groups(aryl or heteroaryl) and thiourea residue (polar group which is responsible for hydrogen bonding) (Chart 4).

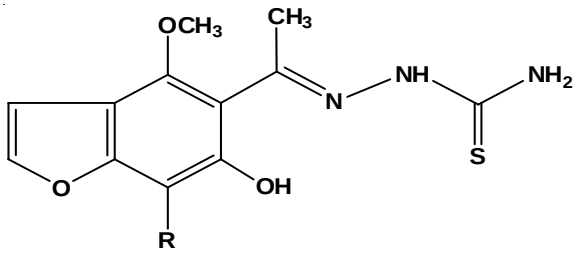


Chart 4. Ethylidenethiosemicarbazide having anticonvulsant activity

Antiparasitic activity

Recent research focuses on developing new drugs for Chagas diseases, caused by the protozoan parasite *Trypanosoma Cruzi*. Ethylidenethiosemicarbazides were evaluated and displayed higher activity against *T. Cruzi*[9,10,24,38] (Chart 5).

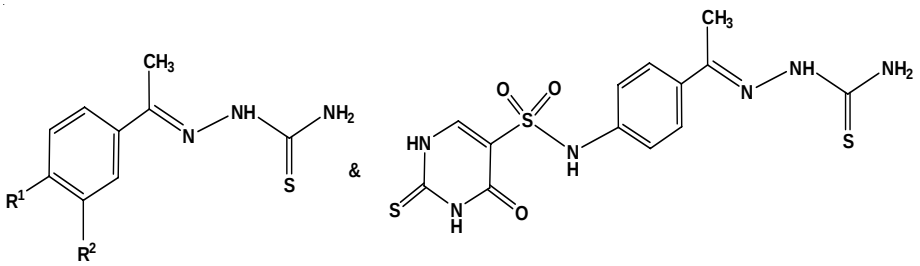


Chart 5. Ethylidenethiosemicarbazide having antiparasitic activity

Miscellaneous

Other pharmaceutical applicationsof ethylidenethiosemicarbazides such as; Tyrosinase inhibitors[51], antihypertensive[66], antioxidant[36], antiamoebic[3], and antitubercular agents[2] have been reported (Chart 6).

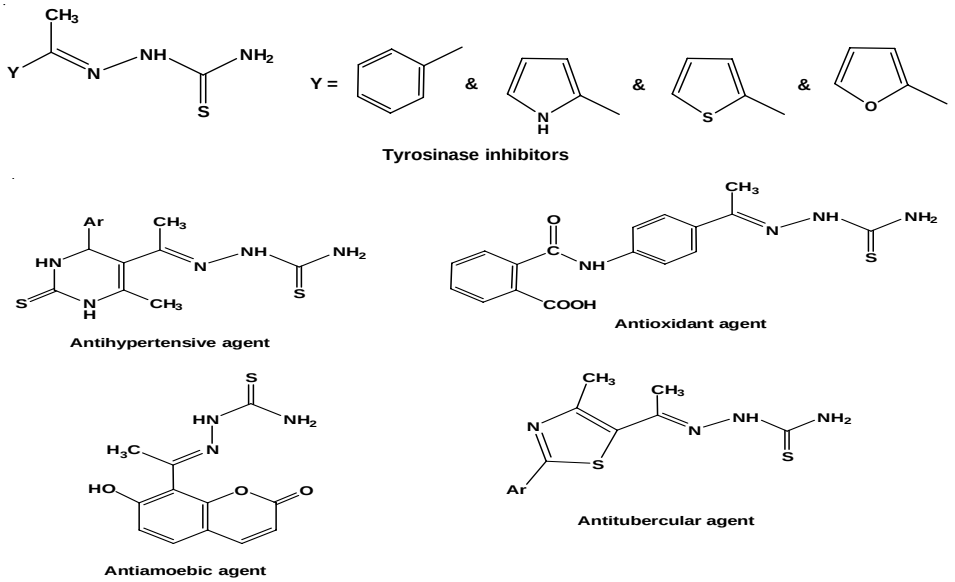


Chart 6. Miscellaneous activities of Ethylidenethiosemicarbazide

CONCLUSION

Ethylidenethiosemicarbazides have been exploited as starting scaffolds for synthesis of different azoles, azines, and fused heterocyclic compounds. Also, ethylidenethiosemicarbazides were associated with a broad spectrum of biological activities.

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