Hydrazinecarbothioamide group in the synthesis of heterocycles

Ashraf A. Aly,a,* Alan B. Brown,b Talaatt I. El-Emary,c Ashraf M. Mohamed Ewas,d and Mohamed Ramadane

cChemistry Department, Faculty of Science, El-Minia University, 61519-El-Minia, Egypt
bChemistry Department, Florida Institute of Technology, Melbourne, FL 32901, U.S.A.
cChemistry Department, Faculty of Science, Assiut University, Assiut, Egypt
dApplied Organic Chemistry Department, National Research Centre, Dokki, Cairo-12622, Egypt
eMedicinal Chemistry Department, Faculty of Pharmacy, El-Minia University, 61519-El-Minia, Egypt

E-mail: ashrafaly63@yahoo.com

Abstract
The review summarizes recent literatures dealing with hydrazinecarbothioamide group in thiocarbohydrazides and other derivatives including their physical and chemical properties along with their applications in the synthesis of heterocycles.

Keywords: Hydrazinecarbothioamides, heterocycles

Contents

Introduction

1. Synthesis of thiocarbohydrazides
   1.1. Hydrazinolysis of thiophosgene
   1.2. Hydrazinolysis of carbon disulfide
   1.3. Hydrazinolysis of dialkyl xanthates
   1.4. General procedure for the preparation of 1,5-diacyl thiocarbohydrazides
   1.5. From acid hydrazides
   1.6. By phase-transfer catalysis
   1.7. From 1,3,4-oxadiazole-2-thione
   1.8. Action of periodic acid

2. Biological activities of thiocarbohydrazide derivatives

3. Reactions of thiocarbohydrazides
   3.1. Thermolysis of thiocarbohydrazides
3.2. Reactions of thiocarbohydrazides with acetylenic compounds
4. Thiocarbohydrazides in synthesis of heterocycles
5. Reactions of thio(semi)carbohydrazides with π-acceptors p-CHL, DCHNQ, CNIND, TCNE, DDQ, DCNQ, DEM and DECF
6. Heterocycles via metal complexation

References

**Introduction**

Carbohydrazide and thiocarbohydrazide are hydrazine derivatives of carbonic and thiocarbonic acids. Although in general thiocarbohydrazides are more widely used in heterocyclic synthesis than thioureas, both types contain the functional group RNHCSNHR. Substituted thiobiureas (RNHCONHNHCSNHR) are key to the synthesis of many organic heterocyclic ring systems. Several authors have investigated under various conditions the heterocyclization of 1-acylthiobiurea,1 1,6-disubstituted 2,5-dithiobiureas,2 and 1-aryl/alkyl-2-thiobiureas.3 Also, the heterocyclization of compounds having an extended urea-like chain such as 1,4- and 2,4-disubstituted thiosemicarbazides have been reported.4,5 Thiocarbohydrazide derivatives have attracted much attention in recent years due to their applications in the synthesis of heterocyclic compounds,6 synthesis of transition metal complexes,7,8 and pharmacological studies.3 Moreover, carbohydrazide derivatives were widely used as an oxygen scavenger (metal passivator) for water treatment systems, particularly for boiler-feed systems.9 The chemistry of carbohydrazides has grown fast, and has not been reviewed in more than three decades. Accordingly, it is important to shed more light on the recent literature dealing with that chemistry, especially in the field of heterocycles.

**1. Synthesis of Thiocarbohydrazides**

Syntheses of carbohydrazide and thiocarbohydrazide of preparative value are exclusively variations of one basic reaction, viz. the hydrazinolysis of carbonic and thiocarbonic acid derivatives. The individual variants of this general synthesis differ from one another in their applicability and relative merit and are discussed separately below.

**1.1. Hydrazinolysis of thiophosgene**

Reaction of thiophosgene (1) with hydrazine afforded directly thiocarbohydrazide (2) as shown in Scheme 1.10
1.2. Hydrazinolysis of carbon disulfide
The reaction of hydrazine with carbon disulfide is no doubt the cheapest and most useful method for the preparation of thiocarbohydrazide (2) in quantity.\(^\text{11}\)
\[
\text{CS}_2 + 2\text{NH}_2\text{NH}_2 \rightarrow \text{NH}_2\text{NHCSNHNH}_2 \text{ (2)} + \text{H}_2\text{S}
\]

1.3. Hydrazinolysis of dialkyl xanthates
The hydrazinolysis of dialkyl xanthates 3 is a possible route to thiocarbohydrazide (2). By warming the two reactants, high yields of thiocarbohydrazide are claimed to be obtainable; the effluent gases, ethanol and ethanethiol, are ignited as they leave the reaction vessel (Scheme 2).\(^\text{12,13}\)

\[
\text{RO}_\text{S} + 2\text{NH}_2\text{NH}_2 + \text{ROH} + \text{RSH} \rightarrow 2 + \text{ROH} + \text{RSH}
\]

1.4. General procedure for the preparation of 1,5-diacyl thiocarbohydrazides
Thiocarbohydrazide (2) was dissolved in aqueous NaOH solution, which was added dropwise to a solution of acid chloride in tetrahydrofuran at 0-5 \(^\circ\)C. The reaction mixture was then stirred at room temperature for 2 h to give products 4 in 71-80\% yield (Scheme 3).\(^\text{14}\)

\[
\text{2} + 2 + \text{aq NaOH} \rightarrow \text{4}
\]

1.5. From acid hydrazides
Varma\(^\text{15}\) reported the synthesis of benzamidothiosemicarbazides (N-aroyl thiocarbohydrazides) 5 by treating successively the acid hydrazides prepared by the hydrazinolysis of the acid methyl ester with carbon disulphide, sodium monochloroacetate and hydrazine hydrate (Scheme 4).\(^\text{15}\)
1.6. By phase-transfer catalysis
1,5-Diacyl thiocarbohydrazides 4 were efficiently synthesized in high yield (89-95%) by the reactions of thiocarbohydrazide 2 with a variety of aroyl chlorides at room temperature using PEG-400 as a phase-transfer catalyst (Scheme 5).\(^{16}\)

\[
\begin{align*}
\text{ArCOOCH}_3 + \text{NH}_2\text{NH}_2 & \rightarrow \text{ArCONNH}_2 \\
\text{Ar} & \quad \text{CH}_2\text{OH} \\
\text{O} & \quad \text{ArCONNH}_2 \\
\text{N} & \quad \text{ArCONNH}_2 \\
\text{N} & \quad \text{ArCONNH}_2
\end{align*}
\]

Scheme 4

1.7. From 1,3,4-oxadiazole-2-thione
The reaction of 5-(2-hydroxyphenyl)-1,3,4-oxadiazole-2(3\(H\))-thione (6) and salicyloyl hydrazide (7) led to the formation of disalicyloyl thiocarbohydrazide (8) (Scheme 6).\(^{17}\)

\[
\begin{align*}
\text{O} & \quad \text{Ar} \\
\text{Cl} & \quad \text{Ar} \\
\text{N} & \quad \text{Ar} \\
\text{O} & \quad \text{Ar}
\end{align*}
\]

Scheme 5

1.8. Action of periodic acid
1,5-Diacyl thiocarbohydrazides 4 were expeditiously transformed into the corresponding 1,5-diacyl carbohydrazides 9 with periodic acid by room temperature grinding under solvent free conditions. This protocol has the advantages of mild conditions, fast reaction rate, high yield, and simple work-up procedure (Scheme 7).\(^{18}\)
Scheme 7

2. Biological activities of thiocarbohydrazide derivatives

Thiocarbohydrazide is the closest structural analog of thiosemicarbazide, derivatives of which are recommended as effective antitubercular\textsuperscript{18,19} and antiviral preparations\textsuperscript{20}. Thiocarbazides of the aromatic series also exhibit high antiviral\textsuperscript{21} and antimicrobial activity\textsuperscript{22}. Macrocycles synthesized in the reactions of thiocarbohydrazide (2) with polycarbonyl compounds and their complexes with the salts of divalent metals are effective fungistatic agents\textsuperscript{23}, while the cytotoxicity of the carbohydrazones and thiocarbohydrazones of some ketones is commensurable with or even exceeds the cytotoxicity of the well-known product melphalan\textsuperscript{24}.

3. Reactions of thiocarbohydrazides

3.1. Thermolysis of thiocarbohydrazides

Thermolysis of dithiocarbohydrazides offers monomeric and dimeric aliphatic and aromatic $N$-isothiocyanatoamines. An example is shown in Scheme 8\textsuperscript{25}.

Scheme 8

3.2. Reactions of thiocarbohydrazides with acetylenic compounds

1-Benzoyl-2-phenylacetylene (10a) and 1-(2-thienoyl)-2-phenylacetylene (10b) with thiocarbohydrazides in acetic acid/water or ethanol/water, with the reagents in an equimolar ratio, led to the formation of the corresponding 1-carbothiohydrazinoyl-5-hydroxy-3-phenyl-5-$R$-2-pyrazolines 11 with yields of 60-88\% (Scheme 9)\textsuperscript{26}.
The structure of the compounds 11 so obtained demonstrated that the process takes place selectively through the intermediate formation of the enamine A, which is in tautomeric equilibrium with the hydrazone form B; at the second stage of the reaction attack by the amide nitrogen atom on the electron-deficient carbonyl carbon atom is accompanied by closure of the pyrazoline ring (Scheme 9).\textsuperscript{26} By contrast, 1-acetyl-2-phenylacetylene 10c reacted with thiocarbohydrazide (2) in (i) DMSO or (ii) AcOH at room temperature only through the carbonyl moiety to furnish \( N^2-(Z\text{-}trans) \) - and \( N^3-(Z\text{-}cis) \)-bis(1-methyl-3-phenyl-2-propynylidene)-carbonothioic dihydrazides 12 in 76 or 92% yield, respectively (Scheme 10).\textsuperscript{27}

**Scheme 10**

**4. Thiocarbohydrazides in the synthesis of heterocycles**

**4.1. Synthesis of pyrazoles**

As previously mentioned, 1-benzoyl-2-phenylacetylene (10a) and 1-(2-thenoyl)-2-phenylacetylene (10b) reacted with thiocarbohydrazides to give 1-carbothiohydrazinoyl-5-hydroxy-3-phenyl-5-\( R \)-2-pyrazolines 11 with yields of 60-88% (Scheme 9).\textsuperscript{26} The reaction of ketene dithioacetals 13a,b with thiocarbohydrazide (2) in hot ethanol afforded the corresponding pyrazole derivatives 14a,b, respectively (Scheme 11).\textsuperscript{28a} The reaction of \( \alpha,\beta \)-acetylenic \( \gamma-
hydroxy nitriles with thiosemicarbazide, under mild conditions (rt, no catalyst, in 1:1 aqueous ethanol, 4–14 h), proceeds chemo-, regio- and stereoselectively to give hitherto inaccessible tri-functionalized (amino, hydroxylalkyl and thioamide groups) pyrazoles 15 in 53–91% yields. The hydroxyl function is easily protected by using the corresponding acetals of the starting acetylenic hydroxynitriles (Scheme 11).\textsuperscript{28b}

![Scheme 11](image)

**Scheme 11**

Reaction of 2,4,6-triphenylpyrylium tetrafluoroborate with 2 at room temperature in ethanol in the presence of triethylamine gave 5-(2-oxo-2-phenylethyl)-3,5-diphenylethyl)-3,5-diphenyl-4,5-dihydro-1H-pyrazole-1-carbothiohydrazide (16, Scheme 12).\textsuperscript{29}

![Scheme 12](image)

**Scheme 12**

Heating of 3-methyl-5-oxo-1-phenyl-∆\textsuperscript{2}-pyrazoline-4-thiocarbohydrazide (17) with phenyl isothiocyanate in absolute ethanol afforded ∆\textsuperscript{1}-(4,5-dihydro-3-methyl-5-oxo-1-phenylpyrazol-4-yl)thiocarbonyl-∆\textsuperscript{1}-phenylthiosemicarbazide (18, Scheme 13).\textsuperscript{30} Treatment of 17 with sodium nitrite in acetic acid yielded 4-azidothiocarbonyl-3-methyl-1-phenyl-∆\textsuperscript{2}-pyrazolin-5-one (19). Compound 17 underwent facile condensation with cyclohexanone and benzaldehyde in absolute ethanol giving ∆\textsuperscript{1}-cyclohexyldine-3,4-dihydro-3-methyl-5-oxo-1-phenylpyrazole-4-thiocarbohydrazide (20) and ∆\textsuperscript{1}-benzylidine-3,4-dihydro-3-methyl-1-phenylpyrazole-4-
thiocarbohydrazide (21), respectively (Scheme 13). Compound 17 reacted with CS$_2$ in KOH to give 4-(4,5-dihydro-5-thioxo-1,3,4-thiadiazol-2-yl)-3-methyl-1-phenyl-$\Delta^2$-pyrazolin-5-one (22, Scheme 13).$^{31}$

![Scheme 13](image)

**Scheme 13**

### 4.2. Synthesis of thiazoles and thiazolidines

Reaction of 2 with aryl isothiocyanates gave 1,5-di(arylamidothiocarbo)-thiocarbohydrazides 23 (Scheme 14). Oxidation of 23 with potassium ferrocyanide afforded symmetrical bis-benzothiazoles (24, Scheme 14).$^{31}$ Surprisingly, reaction proceeds via migration of alkyl substituent to form the thionylated product 24 (Scheme 14).$^{13}$

![Scheme 14](image)

**Scheme 14**
Allowing compound 25 to react with α-halocarbonyl compounds such as phenacyl bromide, chloroacetone, 2-bromomethyl propionate, chloroacetic acid, and bromo-diethylmalonate afforded the thiazolines 26a-c and thiazolidinones 27a,b, respectively (Scheme 15).32

Scheme 15

When thiocarbohydrazide (2) was treated with an equivalent of α-bromo-γ-butyrolactone (28) in boiling ethanol, a 1,3-thiazolidine dimer (29) was provided in low yield (Scheme 16).33

Scheme 16

4.3. Synthesis of 1,2,4-triazolethiones
4-Amino-3-substituted-l,2,4-triazol-5-thiones have proven to possess high cytotoxicity in vitro against thymocytes.34a 1-Acyl thiocarbohydrazides 5 were cyclized with aqueous NaOH to 4-amino-3-aryl(H)-l,2,4-triazol-5-thione (30, Scheme 17).34b Several derivatives of compound 5
have been similarly cyclized by aqueous NaOH. Additional syntheses of bis-[4-N-amino-5-mercaptop-1,2,4-triazol-3-yl]alkanes were reported. Moreover, 4-amino-5-mercaptop-5-[(1H-indol-3-yl)methyl]-1,2,4-triazole has been synthesized by heating thiocarbohydrazide with 1H-indol-3-acetic acid.

![Scheme 17](image1)

**Scheme 17**

Reactions of 2-methyl-4-phenylthiosemicarbazide with ethyl orthoformate in boiling xylene led to the formation of 2-methyl-4-phenyl-1,2,4-triazolium-5-thiolate (31) and 1-methyl-4-phenyl-1,2,4-triazoline-5-thione (32, Scheme 18). The formation of these mesoionic compounds resulted from the rearrangements of 2,4-disubstituted thiosemicarbazides to 1,4-derivatives, which helped to depict the structure quite convincingly.

![Scheme 18](image2)

**Scheme 18**

Hydrazine reacted with acetylhydrazine-carbothioamide to afford 4-amino-3-methyl-Δ²-1,2,4-triazoline-5-thione (33), whereas two molecules of 2 reacted together in presence of hydrazine to form 4-amino-3-hydrazino-Δ²-1,2,4-triazoline-5-thione (34, Scheme 19).

![Scheme 19](image3)

**Scheme 19**
N-Methyl hydrazinecarbothioamide reacted with phenyl isocyanide to yield only 4-methyl-$\Delta^2$-1,2,4-triazoline-5-thione (35), whereas $N$-phenyl-hydrazine-carbothioamide afforded 2-phenylamino-1,3,4-thiadiazole (36) in addition to 4-phenyl-$\Delta^2$-1,2,4-triazoline-5-thione (37, Scheme 20).37

![Scheme 20](image_url)

Scheme 20

Reactions of $N$-phenyl-hydrazine-carbothioamide with ethylphenylimidate hydrochloride at pH > 7 illustrated the formation of 3,4-diphenyl-$\Delta^2$-1,2,4-triazoline-5-thione (38, Scheme 21).38

![Scheme 21](image_url)

Scheme 21

Compound 2 reacted with two equivalents of diphenylcarbodiimide in DMF to yield 3-anilino-4-(N,N’-diphenylguanidino)-$\Delta^2$-1,2,4-triazoline-5-thione (39, Scheme 22).39 On the contrary, 1-phenylthiocarbohydrazide reacted with one equivalent of diphenylcarbodiimide in DMF to yield 3,4-bis(phenylamino)-$\Delta^2$-1,2,4-triazoline-5-thione (40, Scheme 22).40

![Scheme 22](image_url)
Similarly, Kurzer and Secker reported the formation of 3-hydroxy-$\Delta^2$-1,2,4-triazoline-5-thione (41) from 1,4-bis(ethoxycarbonyl) thiosemicarbazide under alkaline conditions (Scheme 23).41

\[
\text{SNH}_{2} \cdot \text{COOEt} \rightarrow \text{HN} \cdots \text{N} \cdots \text{S} \cdots \text{OH} \\
\text{41}
\]

Scheme 23

Compounds like 3-(2,6-difluorophenyl)-1-phenyl-$\Delta^2$-1,2,4-triazoline-5-thiones 43 having insecticidal properties were prepared by heating thiosemicarbazones 42 in ethanolic hydrochloric acid (Scheme 24).42

\[
\text{R} = \text{2,6-F}_2\text{C}_6\text{H}_3; \text{R}_1 = \text{Ph}; \text{R}_2,\text{R}_3 = \text{Me} \\
\text{42: EtOH, } \Delta, \text{1h} \\
\text{HCl} \\
\text{R}_1 \\
\text{EtOH, } \Delta, \text{1h} \\
\text{43} \\
\]

Scheme 24

Equimolar quantities of thiocarbohydrazide (2) and aryl isothiocyanates reacted in DMF at room temperature, affording excellent yields of the monoadducts, i.e. l-amino-thiocarbamoyl-4-aryl-3-thiosemicarbazides (44, $R = \text{C}_6\text{H}_5$, $p$-$\text{ClC}_6\text{H}_4$, or $p$-$\text{MeOC}_6\text{H}_4$, Scheme 25).43 The action of two moles of benzoyl isothiocyanate readily gave the linear di-adduct, e.g. (45; $R = R' = \text{Ph}$). Boiling of compound 44 in alkali gave rise to cyclization, forming 3-mercapto-5-phenyl-1,2,4-triazole ($R = \text{C}_6\text{H}_5$) as shown in Scheme 25.43

\[
\text{NH}_2\text{.NH.CS.NH.NH}_2 \rightarrow \text{RCONCS} \\
\text{RCONCS} \rightarrow \text{RCONHCSNHCHSNHCSNHCO} \\
\text{RCONCS} \rightarrow \text{RCONHCSNHCHSNHCSNHCO} \\
\text{44} \\
\text{45} \\
\]

Scheme 25
4-Methylthiophenyl acetonitrile (46) was converted into 4-methylthiophenyl acetic acid (47) by alkaline hydrolysis (Scheme 26). The acid 47 was fused with thiocarbohydrazide (2) to get 4-amino-5-(4-methylthio)benzyl)-4H-1,2,4-triazole-3-thiol (48) as illustrated in Scheme 26. In this procedure, an equimolar mixture of 47 and 2 was heated in an oil bath till the contents melted. The reaction mixture was maintained at this temperature for 3 h. Then it was allowed to cool and treated with dilute sodium bicarbonate solution in order to remove any unreacted acid. The solid was filtered, washed with water, dried and recrystallized from ethanol to obtain the pure triazole.

![Scheme 26](image)

Various 4-amino-2,3-dihydro-4H-triazoles with aromatic, aliphatic and heterocyclic substituents at the C(5) positions were synthesized from corresponding acids 49 and/or acid esters 50 and thiocarbohydrazide (2, Scheme 27). This method allows the synthesis of these heterocycles in a short time and at reduced expense.

![Scheme 27](image)

Reaction of carboxylic acids 51 with thiocarbohydrazide (2) at melting temperature afforded 4-amino-5-mercapto-3-aryloxymethyl/anilinomethyl-1,2,4-triazoles 52 (Scheme 28).
Scheme 28

Different dicarboxylic acids 53 were fused with 2 to obtain bis-[4-amino-5-mercapto-1,2,4-triazol-3-yl]alkanes (54, Scheme 29).47

Scheme 29

As an extension to the former work, fusing 2,3,5-trichlorobenzoic acid (55) with 2 afforded the corresponding 3-(2,3,5-trichlorophenyl)-4-amino-1,2,4-triazole-5-thione (56, Scheme 30).48 Synthesized triazolethiols were screened for their antimicrobial and anti-inflammatory activities such as against Escherichia coli (ATTC-25922), Staphylococcus aureus (ATTC-25923), Pseudomonas aeruginosa (ATCC-27853) and Klebsiella pneumoniae. Some of the compounds exhibited promising antimicrobial and anti-inflammatory activities.48

Scheme 30

The biologically active 1-(6-methoxy-2-naphthyl)-1-(5-amino-4-mercapto-s-triazol-3-yl)ethane (58) was synthesized by the fusion of 2-(6-methoxy-2-naphthyl)-propanoic acid (57, Naproxen) and thiocarbohydrazide (2) as shown in Scheme 31.49 Heterocyclic compound 58 exhibited a remarkable antifungal activity compared with the standard fungicide Mycostatine.
Radiosterilization of 58 in the dry state proves to be applicable (retaining their structures unchanged up to 40 kGy). 49

The s-triazolosulfonamide derivatives 60 were obtained in good yields by fusion of the tosyl amino acid derivatives 59 with 2 in an oil bath at 180 °C (Scheme 32). 50

Scheme 31

Scheme 32
Scheme 33

Fusion of 2 with 2-chlorohippuric acid (61) afforded the corresponding triazole derivative 62. In the reaction of 2 with 4-chlorohippuric acid (63), double cyclization occurred to give the triazolotriazine (64) via the expected triazole derivative (Scheme 33), while fusion of bis-phenoxycetic acids 65 with thiocarbohydrazide (2) afforded 1,4-bis-[4-amino-5-mercapto-1,2,4-triazol-3-ylmethoxy]-phenylenes 66 in good yields (Scheme 34).

Scheme 34

4.3.1. Glycosides of triazolethiols. Refluxing of equimolar amounts of D-glucono- and D-galactono-1,5-lactones (67 and 68) with thiocarbohydrazide (2) in pyridine for 4 h gave the respective 4-amino-3-mercaptopo-1,2,4-triazoles 69 and 70 in good yields. However, under
microwave irradiation (MW) compounds 69 and 70 were obtained with improved yields (88%) and shorter reaction times (5-6 min; Scheme 35).52

Scheme 35

The synthesis of (1R,2S)-1,2-bis(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)ethane-1,2-diol (72) has been achieved by the dehydrative cyclization of L-tartaric acid (71) with thiocarbohydrazide (2) (Scheme 36).53

Scheme 36

4.4. Synthesis of thiadiazoles, thiadiazolines and thiadiazolidines
Glotova et al synthesized 1,3,4-thiadiazole derivatives 74 from 1-benzylidene-thiocarbohydrazides and 3-bromo-1-phenylprop-2-yn-1-one (73) in acetic acid (Scheme 37).54,55

Scheme 37
Solvents affect the cyclized products resulting from the reaction of thiocarbohydrazide (2) with carbon disulfide. In pyridine, reaction of 2 with carbon disulfide afforded the salts 75 and 76. In DMF, compound 2 reacted with carbon disulfide and KOH to afford the salt 77 which can be cyclized on warming to give the corresponding 1,3,4-thiadiazoline-2-thione (Scheme 38).

\[
\begin{align*}
2 & \xrightarrow{CS_2} \text{75} \quad \text{76} \\
2 & \xrightarrow{CS_2, KOH/ DMF} \text{77}
\end{align*}
\]

**Scheme 38**

Several 2-phenylimino-1,5-diacyl- and/or-1,5-diaryl-hydrazine-1,3,4-thiadiazolidines 80 were synthesized by the reaction of 1,5-diaryl- and/or 1,5-diacyl-3-thiocarbohydrazides 4 with N-phenyl isocyanodichloride (78). The products 79 obtained on basification with dilute ammonium hydroxide afforded the free bases 80, which were acetylated using a mixture of acetic acid and acetic anhydride in 1:1 ratio to afford monoacetyl derivatives 81 (Scheme 39).

\[
\begin{align*}
\text{4} & + \text{78} \xrightarrow{\text{CHCl}_3, -\text{HCl}} \text{80} \\
\text{79} & \xrightarrow{\text{dil NH}_2\text{OH}} \text{81}
\end{align*}
\]

**Scheme 39**
4.5. Synthesis of dithiazolidines
Choudhari and Berad reported the synthesis of several 3-phenylimino-4-arylidineamino-5-arylidinehydrazino-1,2,4-dithiazolidines 84 by one step condensation of bis-1,5-arylidine-3-thiocarbohydrazides 82 and \( N \)-phenyl-S-chloro-isothiocarbamoyl chloride (83), followed by basification of the first-formed hydrochloride salts (Scheme 40).58

\[
\text{Scheme 40}
\]

4.6. Synthesis of pyridazines
The reaction of 2-benzylidene-1,2,3,4-tetrahydrocarbazol-1-ones 85 with thiocarbohydrazide (2) yielded pyridazinocarbazoles 86 and not the thiol-substituted pyrazinocarbazoles as expected (Scheme 41).59,60

\[
\text{Scheme 41}
\]

4.7. Synthesis of thiazines
Aly et al recently demonstrated that 1,4-diphenylbut-2-yn-1,4-dione (87) reacted with \( N \)-substituted hydrazinocarbothioamides to form the corresponding \( N'\)-[(2\(E\))-6-benzyol-4-phenyl-2\(H\)-1,3-thiazin-2-ylidene]-substituted hydrazides 88a-e (Scheme 42).61
Scheme 42

4.8. Synthesis of triazines

A facile synthetic route to triazinones 90 is outlined in Scheme 43. The reaction mixture of 2 and oxazolones 89 was refluxed for nearly 2 h and the products separated upon cooling were collected by filtration.

Scheme 43

Reaction of thiocarbohydrazide (2) with dicyandiamides 91 yielded 1-amino-6-hydrazono-4-imino(or arylimino)hexahydro-1,3,5-triazine-2-thiones 92 (Scheme 44).
Scheme 44

4-Amino-6-(aryl-furanylmethyl)-3-mercapto-1,2,4-triazin-5(4H)-ones 94a-f were synthesized by refluxing the corresponding substituted aryl-furanylpicryl acids 93a-f with 2 in ethanolic solution on a steam-bath (Scheme 45).64

Scheme 45

Another class of fused triazines, identified as imidazo[4,5-e]triazine-2-ones 96a,b, were obtained from the interaction of imidazolidineimino-thiones 95a,b with 2 via elimination of both H₂S and NH₃ (Scheme 46).30 The isolated products were investigated as antitumor agents.30

Scheme 46
4.9. Synthesis of thiadiazines

Thiocarbohydrazide (2) reacted with diethyl bromomalonate (DBM) and with 4-bromo-4H-3-substituted-1,3-disubstituted-pyrazol-5-ones 98 in ethanolic pyridine solution affording 2-hydrazino-6-carbethoxy-4H,6H-1,3,4-thiadiazin-5-one (99) and 2-hydrazino-5-substituted-4H-pyrazolo[5,4-e]1,3,4-thiadiazines 100, respectively (Scheme 47). Reaction of 2 with 3-bromo-2-oxoglutaric acid dimethyl ester (101) in methanol gave (2-hydrazino-5-methoxycarbonyl-6H-1,3,4-thiadiazin-6-yl)acetic acid methyl ester hydrobromide (102, Scheme 48).

![Scheme 47](image1)

Scheme 47

![Scheme 48](image2)

Scheme 48

4.10. Synthesis of tetrazinethiones

Interestingly, Mohan and his group demonstrated the synthesis of a series of tetrazinethiones. For example, reaction of 2 with p-chloro-benzaldehyde proceeded to give successfully the tetrazine-3(2H)-thione 103 (Scheme 49).
The reaction of 2 with 2-adamantanone (104) in ethanol gave the spiro-[adamantine-2,3'-s-tetrazine]-6'-thione (105). In the same manner, 1',2',4',5'-tetrahydrospiro[fluorene -9,3')-s-tetrazine]-6'(H)-thione (107) was obtained by the reaction of 9-fluorenone (106) with thiocarbohydrazide (2). Cyclic alkanones such as cyclopentanone (108) reacted with 2 to form the corresponding tetrazinethione 109 (Scheme 49). Isatin (110) reacted with 2 in similar fashion to give 1',2',4',5'-tetrahydro-3H-2-oxospiro[indole-3,3'-s-tetrazine]-6'-thione (112). Reinvestigation of the reaction of 110 with 2 under the same reaction condition (the aqueous solution of thiocarbohydrazide was stirred without further heating and treated dropwise over 15 min with 110 in ethanol) proved that the obtained compound was isatin-β-thiocarbohydrazide (111, Scheme 50).

Scheme 49

Scheme 50
Mohan reported on another tetrazinethione 114 from the reaction of furfural (113) with 2, which was identified as 6-(2-furyl)-1,4,5,6-tetrahydro-s-tetrazine-3(2H)-thione (Scheme 51). 72 3-Methylspiro[indane-1,3'-hexahydro-s-tetrazine]-6'-thione (116) was obtained from the reaction of 3-methylindan-1-one (115) with 2. 73 1,7,7-Trimethyl-bicyclo[2.2.1]-heptan-2-one (117) reacted with 2 in 2N acetic acid to give 1,7,7-trimethyl-spiro[bicycle-[2.2.1]heptane-2,3'-[1,2,4,5]tetrazinane]-6'-thione (118). 74 Treatment of 118 with ethyl chloroacetate and aldehydes in the presence of pyridine afforded 7-arylidenespiro[bicycle-heptane-2'-3(4H)-[2H]-thiazolo[3,2-b]-s-tetrazin]-6-(7H)-ones 119 (Scheme 52). 74 1,4-Dioxo-3,4-dihydro-2(1H)phthalazinecarbothiohydrazide (121) was initially synthesized by reaction of phthalic anhydride (120) with thiocarbohydrazide (2). Heterocycles 122-126, i.e. 4-substituted-1-thioxo-1,2-dihydro[1,2,4,5]tetrazino[1,2-b]-phthalazine-6,11-diones, were subsequently synthesized by cyclocondensation of 121 with trimethyl orthoformate, trimethyl orthoacetate, benzoic anhydride, cyanogen bromide and carbon disulfide, respectively (Scheme 53). 75
4.11. Synthesis of thiaoxadiazines

1,5-Diacyl thiocarbohydrazides 4 were cyclized with iodine to give 1,2,4,5-thiaoxadiazines 127 in 61-80% yields (Scheme 54).\textsuperscript{17} Iodine solution in ethanol was added with continuous stirring; the color of iodine gradually disappeared. The addition of iodine was continued till it was in slight excess indicated by the persistence of its violet color. After keeping the reaction mixture overnight granular solids were obtained; these were identified as dihydroiodo-1,2,4,5-thiaoxadiazines, which on basification with dilute ammonium hydroxide gave the free base (Scheme 54).\textsuperscript{17}
4.12. Synthesis of triazepinothiones

Aly et al. reported the synthesis of 1,2,4-triazepine-3-thiones 129-131. These products were obtained in respective reactions of N1-substituted thiosemicarbazides with dimethyl acetylenedicarboxylate (128, DMAD) and 1,4-diphenylbut-2-yne-1,4-dione (87) under prolonged reflux in DMF (Schemes 55 and 56).

Scheme 55

However, the reaction of the starting materials under microwave irradiation afforded the same products in higher yields within a few minutes. Spectroscopic data excluded the formation of the regio-isomeric heterocycle 132 (Scheme 56).

Scheme 56
4.13. Synthesis of thiadiazepines

\[
\begin{align*}
\text{N-Imidoylthioureas (133, analogous to thiocarbohydrazides) reacted with DMAD (128) to form 1,3,5-thiadiazepines 134a-e (Scheme 57).} \\
\text{The reaction mechanism can be simply described as due to sulfur atoms attacking the triple bond of DMAD in conjugate fashion, followed by proton transfer and nucleophilic attack of the amidine group on the double bond in 128 to form the intermediates 135. Thereafter a nucleophilic attack of the amidine-like nitrogen on the ethylenic-ester would form the salt 136. Aromatization of 136 is accompanied by the extrusion of a hydrogen molecule to produce the stable compounds 134a-e (Scheme 57). A similar observation was reported by Alajarín and his group.}
\end{align*}
\]

Scheme 57. Synthesis of 1,3,5-thiadiazepines 134a-e. a: Ar=4-CH₂OC₆H₄ (84%); b: Ar=4-CH₃C₆H₄ (80%); c: Ar=4-ClC₆H₄ (75%); d: 4-O₂NC₆H₄ (65%); e: Ar=Ph (82%).


Reaction of 2-oxo-2-(3-oxo-5,6-disubstituted-1,2,4-triazin-2(3H)-yl)acetaldehydes 138 with thiocarbohydrazide (2) in a mixture of acetic acid and sodium acetate produced the corresponding 1,2,4,5-tetrazepine-3-thiones (139, Scheme 58).

Scheme 58
4.15. Synthesis of fused heterocycles

4.15.1. Synthesis of pyrrolo[2,1-b]-1,3,4-oxadiazoles. The Aly group\textsuperscript{80} described the reaction of 2,3-diphenylcyclopropenone (140) with arylidene-N-phenylhydrazine-carbothioamides 141a-e. The formed pyrrolo[2,1-b]-1,3,4-oxadiazoles 142a-e can be described as due to initial [3+2]cycloaddition, followed by further cyclization with loss of H\textsubscript{2}S (Scheme 59).\textsuperscript{80}

\begin{equation}
\text{AcOH} \quad \begin{array}{c}
\text{HN} \\
\text{HN} \\
\text{HN} \\
\text{Ph}
\end{array} + \begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph}
\end{array} \\
\text{R}
\end{equation}

Yield of 127 (%)

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-H\textsubscript{3}CO-C\textsubscript{6}H\textsubscript{4}</td>
<td>76</td>
</tr>
<tr>
<td>4-HO-C\textsubscript{6}H\textsubscript{4}</td>
<td>72</td>
</tr>
<tr>
<td>4-Cl-C\textsubscript{6}H\textsubscript{4}</td>
<td>64</td>
</tr>
<tr>
<td>2-Thienyl</td>
<td>60</td>
</tr>
<tr>
<td>Phenyl</td>
<td>70</td>
</tr>
</tbody>
</table>

Scheme 59

4.15.2. Synthesis of pyrrolo[2,1-b]-1,3,4-oxadiazoles, 1,2,4-triazolo[4,3-b]pyridazine-thiones and pyridazinethiones. Aly et al\textsuperscript{81} have also recently reported that cyclopropenone 140 reacted with two equivalents of either thiosemicarbazide or 1-phenylthiosemicarbazide to afford the corresponding 1,2,4-triazolo[4,3-b]-pyridazinethiones 143-146.\textsuperscript{81} However, the reaction of disubstituted hydrazine-carbothioamides with 140 occurs with stoichiometric amounts of the starting materials to produce pyridazinethiones 147 (Scheme 60). The reaction mechanism, in both cases, was described as a formal [3+3]-cycloaddition.\textsuperscript{81}
4.15.3. Synthesis of fused triazolo-heterocycles. 3-(3,5-Dimethoxyphenyl)-6-(3,4-methylenedioxyphenyl)-7H-[1,2,4]triazolo-[3,4-b][1,3,4]-thiadiazines \(151\) and 6-(3,4-methylenedioxyphenyl)-7,8-dihydro-3-(3,4,5-trimethoxyphenyl)-[1,2,4]triazolo-[4,3-b]-[1,3,4]triazines \(155\) were discovered as activators of caspases and inducers of apoptosis so they may be used to induce cell death in a variety of clinical conditions in which uncontrolled growth and spread of abnormal cells occurs; accordingly, they may be used as therapeutic anti-cancer agents.\(^{82}\)

Reaction of 3,5-dimethoxybenzoic acid (148) with thiocarbohydrazide (2) produced 4-amino-5-(3,5-dimethoxyphenyl)-3-mercapto-(4H)-1,2,4-triazole (149), which reacted with 2-bromo-1-(3,4-methylenedioxyphenyl)ethanone (150) to afford 3-(3,5-dimethoxyphenyl)-6-(3,4-methylene-dioxophenyl)-7H-[1,2,4]triazolo-[3,4-b][1,3,4]thiadiazine (151, Scheme 61).\(^{82}\)
Scheme 61

3-(3,5-Dimethoxyphenyl)-6-(3,4-methylenedioxyphenyl)-7H-[1,2,4]triazolo-[3,4-b][1,3,4]-thiadiazines 151 and 6-(3,4-methylenedioxyphenyl)-7,8-dihydro-3-(3,4,5-trimethoxyphenyl)-(1,2,4)triazolo-[4,3-b]-[1,3,4]triazines 155 were discovered as activators of caspases and inducers of apoptosis so they may be used to induce cell death in a variety of clinical conditions in which uncontrolled growth and spread of abnormal cells occurs; accordingly, they may be used as therapeutic anti-cancer agents.82
On the other hand, reaction of 3,4,5-trimethoxybenzoic acid (152) and thiosemicarbazide produced 5-(3,4,5-trimethoxyphenyl)-1,3,4-thiadiazol-2-amine (153) which reacted with hydrazine hydrate to afford compound 154, which reacted with 2-bromo-1-(3,4-methylenedioxyphenyl)-ethanone (150) to afford 6-(3,4-methylenedioxyphenyl)-7,8-dihydro-3-(3,4,5-trimethoxyphenyl)-[1,2,4]triazolo-[4,3-b][1,3,4]triazine (155, Scheme 62).82

4.15.4. Synthesis of fused 1,3,4-thiadiazines. Bromo rhodanine (156) when treated with thiocarbohydrazide (2) yielded 5H-2-hydrazino-6-thioxo-(1,3)-thiazolo[4,5-e]-1,3,4-thiadiazine (157) which was then condensed with aromatic aldehydes to obtain the Schiff bases 158. Similarly, 156 was reacted with thiosemicarbazide to yield 5H-2-amino-6-thioxo-1,3-thiazolo[4,5-e]-1,3,4-thiadiazine (159). Schiff bases of 159 were also obtained by treating it with aromatic aldehydes (Scheme 63).83
Likewise, 3H,5H-2-iminoamino-7-methyl-(1,2)-pyrazolo[4,5-e]-1,3,4-thiadiazine (162) was formed when 4-bromopyrazole (161) was treated with thiocarbohydrazide (2). This was further allowed to react with aromatic aldehydes to obtain the corresponding Schiff bases 163 (Scheme 64).

5. Reactions of thiocarbohydrazides with π-acceptors p-CHL, DCHNQ, CNIND, TCNE, DDQ, DCNQ, DECF and DEM

5.1. Reaction of thiocarbohydrazides with 2,3,5,6-tetrachloro-1,4-benzoquinone

Hassan et al reported\textsuperscript{84} that addition of tetrahydrofuran (THF) solutions of substituted thiocarbohydrazides to a solution of 2,3,5,6-tetrachloro-1,4-benzoquinone (p-CHL, 164) in a
ratio of 1:2 in the same solvent formed, after standing for 48 hours at room temperature, substituted imidazothiadiazoleiones 165 as minor products (21-24%) and substituted benzo-bisimidazothiadiazoles 166 as major products (48-54%) (Scheme 65).84

Other work was also undertaken to examine the reactions of thiocarbohydrazides derived from ethylene diamine \( p \)-CHL. Thus, two equivalents of thioureidoethylthiourea derivatives reacted with 164 in THF at room temperature to afford substituted imino-[1,3,6]-thiadiazepane-2-thiones 167 as minor products (14-19%) and trichloro-7-oxo-quinoxaline-1-carbothioamides 168 as major products (41-49%), in addition to the corresponding dihydrobenzoquinone (Scheme 65).85

![Scheme 65](image)

**Scheme 65**

**5.2. Reaction of thiocarbohydrazides with 2,3-dichloro-1,4-naphthoquinone**

Hassan has also reported that substituted naphthimidazothiadiazoleiones 170 and disubstituted naphthobisimidazo-thiadiazoles 171 were obtained from the reaction of substituted thiocarbohydrazides with 2,3-dichloro-1,4-naphthoquinone (DCHNQ, 169, Scheme 66).84

![Scheme 66](image)

**Scheme 66**
5.3. Reaction of thiocarbohydrazides with [1,3-dioxo-2,3-dihydro-1(H)-inden-2-ylidene]propanedinitrile

The reaction of substituted thiocarbohydrazides with (1,3-dioxo-2,3-dihydro-1(H)-inden-2-ylidene)propanedinitrile (CNIND, 172) was carried out in ethyl acetate under reflux, followed by chromatographic separation. The reaction mixture afforded the products 173-175 (Scheme 67), and numerous colored byproducts in very small quantities.84

![Scheme 67](image)

5.4. Reaction of thiosemicarbohydrazides with 1,1,2,2-tetracyanoethylene

The reaction of equimolar quantities of thiocarbohydrazides with 1,1,2,2-tetracyanoethylene (TCNE, 176) afforded the thiadiazoles 177 and thiadiazine derivatives (178, Scheme 68).84

![Scheme 66](image)
Upon addition of doubled molar amounts of 176 to a solution of 4-substituted thiosemicarbazides in ethyl acetate, with the admission of air, the green color of a transient charge-transfer complex is observed, which quickly gives way to a brown and finally to a characteristic reddish orange color. Chromatographic separation of the sublimation residue gave products 179–182 (see Scheme 69).86

![Scheme 69](image)

**Scheme 69**

5.5. Reaction of acyl thiosemicarbohydrazides with \(\pi\)-acceptors

Mixing of two-fold molar amounts of acceptor 164 and/or 2,3-dicyano-5,6-dichloro-1,4-benzoquinone (DDQ, 183) with one mole of acyl thiosemicarbohydrazides in ethyl acetate, with admission of air, gave a blue color (\(\lambda_{\text{max}} = 573-591\) nm).
This behavior is explained as being due to initial formation of an unstable charge-transfer complex (CTC) followed by a chemical reaction which yields substituted oxadiazoles 185 and heterocycles 186-188. Upon reaction of the same acyl thiosemicarbazones with two equivalents of acceptors 169 and/or 2,3-dicyano-1,4-naphthoquinone (DCNQ, 184) in ethyl acetate, the transient CT-complexes underwent conversion into heterocycles 189-191 (Scheme 70). 87

Reactions of acyl thiosemicarbazones with 176 in DMF were found to run smoothly, the conversions of starting materials, in case of phenyl substituent, in chlorobenzene to 192, whereas the other derivatives of the target donors gave with 176, heterocycles 193-195 (Scheme 71). 88
Reaction of N-substituted-hydrazino-carbothioamides with diethyl maleate (DEM, 196) gave mainly the corresponding ethyl 7-oxo-3-substituted-7H-[1,2,4]triazolo[3,4-b][1,3]thiazine-5-carboxylates 200a-e. This reaction can be ascribed to nucleophilic attack of the thiol group on the ester carbon accompanied by elimination of one molecule of ethanol to form the intermediate 197. Thereafter amidine-like nucleophilic attack on the amide is accompanied by water elimination to give 198. Nucleophilic attack of the terminal NH on the π-deficient double-bond produces the corresponding triazolo-dihydrothiazines 199.

\[ \text{Scheme 72. Reaction of } N \text{-substituted-hydrazino-carbothioamides with diethyl maleate (196).} \]

Ultimately, it was proposed that aerial oxidation of 199 gives the stable heterocyclic compounds 200 (Scheme 72).

5.6. Reaction of thiosemicarbazones with selected π-acceptors

Acceptor 172 reacted with formohydrazonohydrazide and N-benzylideneformohydrazonohydrazide to respectively form aminooindenopyrazolo-pyridazinone 202 and phenyl-1,2,3,4-tetraazacyclopenta-fluorene 203 (Scheme 73).

\[ \text{Scheme 73} \]
Addition of methylene chloride solutions of 2-phenylidene-N-substituted-hydrazine-carbothioamides to solutions of 183 in the same solvent resulted in the appearance of a green color, which gradually changed into brown. 5-Substituted N-phenyl-1,3,4-thiadiazole-2-amines 204 (6-11%), together with 3-amino-5,6-dichloro-4,7-dioxo-N-phenyl-4H-indazole-2(7H)-carbothioamide 205 (71%), were isolated by preparative thin layer chromatography (Scheme 74). 88

![Scheme 74](image)

Mixing equimolar amounts of 2-phenylidene-N-substituted-hydrazine-carbothioamides and 169 in ethyl acetate for 72 h led to the formation of substituted benzindazole-4,9-diones 206 as major products and substituted benzophthalazinediones 207 as minor products (Scheme 74). 90 Addition of ethyl acetate solutions of 2-phenylidene-N-substituted-hydrazine-carbothioamides to solutions of 176 in the same solvent resulted in the formation of heterocycles 208-210 (Scheme 75). 91

![Scheme 75](image)

5.6.1. Reaction of thiosemicarbazones with diethyl 2,3-dicyanofumarate. Equimolar solutions of aldehyde 4-phenylthiosemicarbazones and diethyl 2,3-dicyanofumarate (DECF, 211)
in ethyl acetate formed, on warming to reflux temperature for 14–18 h, major (212, 213 in 54–61%) and minor (214, 215 in 22–26%) products in each case (Scheme 76).\textsuperscript{92}

\begin{align*}
\text{Scheme 76}
\end{align*}

5.7. Reaction of N-imidoylthioureas with 1,1,2,2-tetracyanoethylene

Aly et al also reported the reaction of N-imidoylthioureas (analogous to thiocarbohydrazides) with 176 in dry ethyl acetate at room temperature under a stream of N\textsubscript{2}. Addition of electron donors to electron acceptor 176 in dichloromethane at room temperature led to complex formation characterized by CT-bands in the visible region. These CT-complexes gradually disappeared to give the precipitated thiadiazines 216 (Scheme 77).\textsuperscript{93}

\begin{align*}
\text{Scheme 77}
\end{align*}

Aly has also demonstrated a very convenient synthesis of the fused thiazoles 217 (Scheme 78) from the reaction of aroylphenylthioureas (as analogues of thiocarbohydrazides) with \pi-acceptor quinones (CHL-p, DDQ and DCHNQ).\textsuperscript{94}
Scheme 78. Synthesis of fused 1,3-thiazoles.

6. Heterocycles via Metal Complexation

A series of complexes 218 of the type [M(TML)X2]; where TML is Tetratedant Macroyclic Ligand; M = Co(II), Ni(II), Cu(II), Zn(II) or Cd(II); X = Cl, CH3COO or NO2 have been synthesized by template condensation of glyoxal and compound 2 in the presence of divalent metal salts in methanolic medium (Scheme 79).95 The procedure can be summarized as follows: to a stirring methanolic solution (50 mL) of 2 (10 mmol) was added a divalent cobalt, nickel, copper, zinc or cadmium salt (5 mmol) dissolved in a minimum quantity of methanol (20 mL). The resulting solution was refluxed for 0.5 h. After that glyoxal (10 mmol) dissolved in 20 mL methanol was added to the refluxing mixture and refluxing continued for 6–10 h, depending upon the metal salt. The mixture was concentrated to half of its volume and kept in desiccators for 2 d. The complexes 218 were filtered, washed with methanol, acetone and ether and dried in vacuo: yield 40%. The complexes are soluble in DMF and DMSO, but are insoluble in common organic solvents and water.95

Scheme 79
The triple Cu(II) thiocarbohydrazide-2,3-butanedione system in the Cu(II) hexacyanoferrate gelatin immobilized matrix (219 and 220) has been prepared. The similar process in the nickel(II) hexacyanoferrate(II) matrices does not occur under such conditions (Scheme 80).96

\[
\begin{align*}
\text{Scheme 80}
\end{align*}
\]

Moreover, a series of complexes of the type [M(TML)X\(_2\)]; 221 where TML is a tetradenate macrocyclic ligand, M= Co(II), Ni (II), Cu (II); X= Cl\(^-\), X= CH\(_3\)COO\(^-\) or NO\(_3\)\(^-\) have been synthesized by template condensation of benzil and thiocarbohydraide in the presence of divalent metal salts in methanolic medium (Scheme 81).96

\[
\begin{align*}
\text{Scheme 81}
\end{align*}
\]

Reactions of formylpodands 222 with carbohydrazide (2b) or thiocarbohydrazide (2a) afforded macroheterocycles 223 and 224 with a carbo- or thiocarbohydrazone moiety respectively (Scheme 82).97
Scheme 82

References

86. Hassan, A. A.; Mohamed, N. K.; Shawky, A. M.; Döpp, D. ARKIVOC 2003, (i), 118.

Biographical Sketches

Ashraf Abd El-Moneim Aly Shehata (born 1963). He is a Professor of Organic Chemistry in Chemistry Department, Faculty of Science, Organic Division, El-Minia University, 61519-El-Minia, Egypt. He was awarded with a channel system program to complete his Ph.D. program under the supervision of Prof Dr Henning Hopf, in the field of cyclophane chemistry for two years at TU-Braunschweig, Germany. Awarded with a scientific grant to be a scientific visitor to TU-Braunschweig, Germany from 28 November 1997 until 31 January 1999. He published about 70 papers in sound international journals. Awarded as a visiting Professor in Sultan of Oman. Awarded with “The State’s Encouragement National Prize in Organic Chemistry (2004) from the Academy of Science and Technology, Cairo, Egypt”. Awarded with DAAD scholarship for two months from 12 August 2005 until 12 October 2005 with Prof Dr Henning Hopf. He has been selected on the boards of referees in the following journals: Journal of Organic Chemistry, Journals of Royal Society of Chemistry (RSC), and Arkivoc. Acknowledged by Shoman foundation (in 2006) for his research program and his list of publications. He has joint research with Dr Alan B. Brown, Chemistry Department, University Blvd, Melbourne, Florida, U.S.A. He has a prospective cooperation with Prof. Dr. Shinmyozu Teruo, Department of Applied Molecular Chemistry, Institute for Materials Chemistry and Engineering, Japan. The research group of Professor Ashraf A Aly is working for a long time on the chemistry of cyclophanes and he is interested in study of synthetic approaches to new cyclophanes containing heterocyclic rings. Moreover, his research activity deals with synthesis of heterocycles which may have prospective biological and/or pharmaceutical activities. In 10-2008, he has been invited as a visitor Professor in Saudi Arabia, Al-Jouf University, Faculty of Science, Chemistry Department. E-mail: ashrafaly63@yahoo.com.
Dr Alan B. Brown (born 1957) was awarded a B. A. in chemistry from Middlebury College and a Ph.D. in organic chemistry from the University of Wisconsin - Madison. After an N.I.H. postdoctoral fellowship at Columbia University, he joined Florida Institute of Technology in 1988. His research interests include sensor science, aromaticity, and applied NMR spectroscopy. E-mail: abrown@fit.edu.

Dr. Talaat Ibrahim Aly El-Emary. Ph.D. Assistant Prof. of Organic Chemistry, Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt. Awarded DAAD Grant in Tubingen University, Institute of Organic Chemistry, Germany at 1998 for 2 months July & August 1998. He published 37 papers in sound international journals specialized in organic chemistry and inorganic chemistry journals. E-mail: emary768@hotmail.com.

Dr. Ashraf Metwally Mohamed Ewas was born in 1968, Beni-suef, Egypt. A researcher in National Research Center, Chemical Industries Research Division, Applied Organic Chemistry Department., Giza-Dokki, Egypt. His Research interests on the synthesis of heteroorganic compounds of biological interest, specially as anticancer agents. In 1998, he was awarded many scientific missions to Poland in order to complete his Ph.D. Program (1997-1998) under supervision of Professor Marian Mikolajczyk. Awarded another three scientific missions dated in 1999, 2001 and 2006 to Poland under the same program to elaborate his Post doctoral research. He participated in the research program on the (Synthesis of enantiomerically pure cyclopropylphosphonate derivatives via asymmetric cyclopropanation of chiral α-phosphorylvinyl sulfoxides). Awarded a post doctoral scientific grant for supporting a young researchers (February, 2007) from the Ministry of High Education and Scientific Research in the Faculty of Organic Chemistry, TU-Dresden, Germany. He participated in the research program entitled (New domino reactions with sulfones) with Professor Peter Metz. In 09-2008, he has
been invited as a visitor assistant Professor in Saudi Arabia, Al-Jouf University, Faculty of Science, Chemistry Department. E-mail: ammewas@yahoo.com.

**Mohamed Ramadan Eisa** (born 1978) was awarded a B. Pharm. Sci., from Faculty of Pharmacy, Helwan University in 2000 and a M.Sc., Pharmaceutical Organic Chemistry from Faculty of Pharmacy, El-Minia University in 2005. His research interests the design of novel heterocycles which posses anticancer activity. He registries his Ph.D. under the supervision of Professor Ashraf A. Aly. E-mail: elbashamohammed@yahoo.com.