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RESEARCH ARTICLE

Halogenated, alkylated and new types of imidazolidine, pyrrolidine, imidazotriazine and thienoimidazole derivatives with biological and antitumor activities

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New types of halogenated, alkylated and (bis)cyanothio-formamides were prepared and reacted with iso(thio)cyanates, aldehydes and dibenzylideneacetone to produce (bis)imidazolidine-imino(di)thiones and (oxazolidine and bispyrrolidine)iminothiones, respectively. Imidazolidineiminothiones were reacted with H_2S/TEA to give thiohydantoin which reacted with p-chlorobenzaldehyde to achieve the corresponding thienoimidazole derivative. Most of the synthesized products exhibited antibacterial, antifungal and antitumor activities.

Keywords: Biscyanothioformamide; Bisimidazolidineiminothiones; Bispyrrolidineiminothiones; Imidazotriazine; Thienoimidazole

1. Introduction

A variety of heterocyclic ring closure reactions of cyanothioformamides [1–3] gave rise to imidazole [4], oxazole [5], thiazole [6, 7] and other heterocycles [8–11]. Our interest in the chemistry of cyanothioformamide [12–16] led us to synthesize various types of cyanothioformamides containing aliphatic, aromatic and heterocyclic [17] moieties as well as sulpha derivatives [18]. Various fused heterocycles [19, 20] starting from cyanothioformamides were synthesized and comparative studies between the latter and related compounds [21, 22] were carried out. El-Sharief *et al.* [20, 23] reacted different types of cyanothioformamides and o-chlorocyanothioformanilide with various electrophilic, nucleophilic and o-substituted nucleophilic reagents. The same authors [24] synthesized biscyanothioformamide derived from 1,4-bisisothiocyanatobenzene and reacted it with different reagents, also they [25, 26] treated activated nitriles and 2,4-diisocyanatotoluene with various cyanothioformamides to produce new (imidazolidine and bisimidazolidine)-iminothione derivatives, respectively. In the present investigation, halogenated cyanothioformamides, other types of biscyanothioformamides derived from 2,4-bis(isothiocyanato)toluene and new types of

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bisimidazolidineiminothiones are synthesized to discuss and compare their chemistry. Some halogenated oxazolidineiminothiones and imidazotriazines have been also prepared.

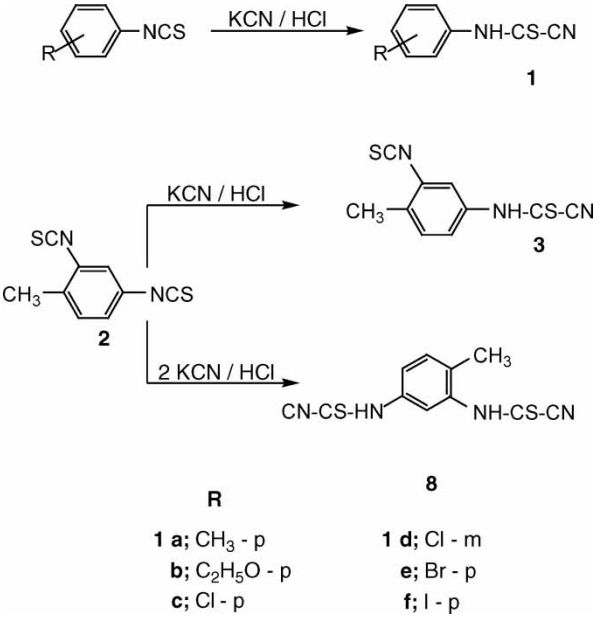
Thus, several cyanothioformamides containing (p-methyl-, p-ethoxy-, p-chloro- and m-chloro-) phenyl **1a–d** [20] were prepared. p-Bromo- and p-iodocyanothioformanilides **1e**,**f** (scheme 1) are similarly prepared.

Another different type of cyanothioformanilides derived from 2,4-bis(isothiocyanato)-toluene have been also prepared. Thus, interaction of equimolar amounts of 2,4-bis(isothiocyanato)toluene **2** [27] and potassium cyanide at room temperature [3] furnished a product which its elemental and spectral data were compatible with structure **3** (scheme 1) as 4-methyl-3-isothiocyanatocyanothio-formanilide.

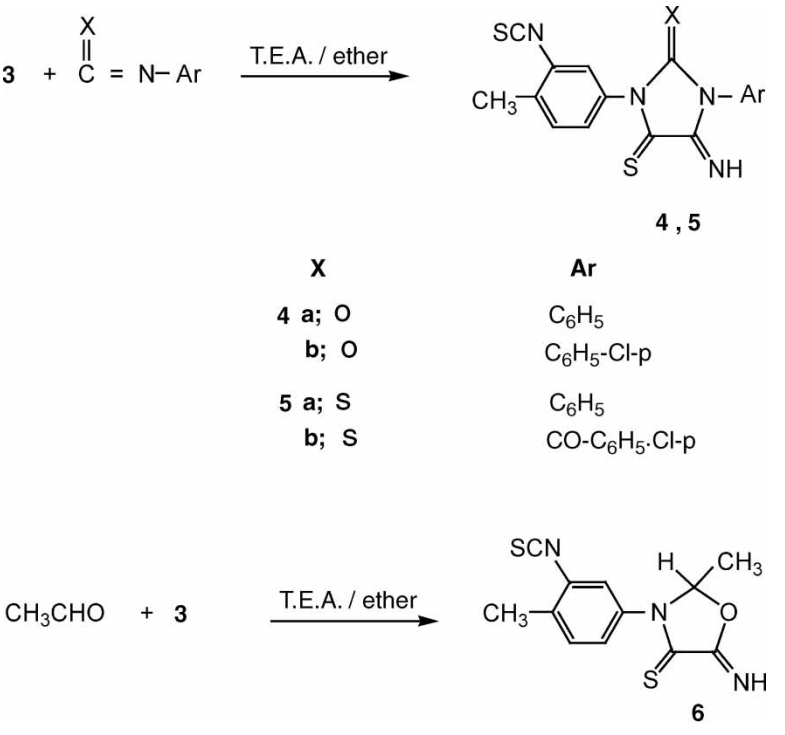
IR measurements showed bands characteristic of NH, −C≡N, −NCS and −C(S)−N functionalities. The ^{1}H NMR spectrum exhibited CH_3−Ar, 3 Ar−H and an NH which disappeared on addition of D_2O. Formation of **3** could be rationalized on basis that the isothiocyanate group in the para position to the methyl group is more active than that at ortho position. 4-Methyl-3-isothiocyanatocyanothioformanilide **3** was allowed to react with some electrophiles. Thus, when **3** was reacted with (phenyl and p-chlorophenyl)isocyanate in the presence of triethylamine as a catalyst, an apparent cycloaddition reaction occurred to afford one product, in each case, which were compatible with structures **4a**,**b** (scheme 2) as 1-aryl-3-(3-isothiocyanato-4-methylphenyl)-4-thioxo-5-imino-2-imidazolidinones.

Similarly, 2,4-dithioxoimidazolidine **5** (scheme 2) could be achieved on reaction of **3** with phenylisothiocyanate and with p-chlorobenzoylisothiocyanate under the same conditions to produce 1-(phenyl and p-chlorobenzoyl)-3-(3-isothiocyanato-4-methylphenyl)-5-imino-2,4-dithioxoimidazolidines **5a,b**, respectively.

The imidazolidine structures **4a**,**b** and **5a**,**b** were demonstrated by IR, ^{1}H NMR, mass spectra and elemental analyses. IR measurements of these products (table 5) exhibited the absence of νCN and the presence of νNH, νNCS and νCS−N−. Compounds **4a**,**b** and **5b** showed νCO around 1690 cm^{-1}. ^{1}H NMR spectra revealed the presence of CH_3−Ar and Ar−H protons and



SCHEME 1



SCHEME 2

the variable hydrogen NH which disappeared on addition of D_2O. Mass spectra of **4a** showed M^+ at m/z 352 (100%, base peak); **4b**, M^+ at m/z 386 (100%, base peak), which shed some light on their stabilities and m/z at 388 (37.8%) *i.e.* (M+2 due to chlorine atom).

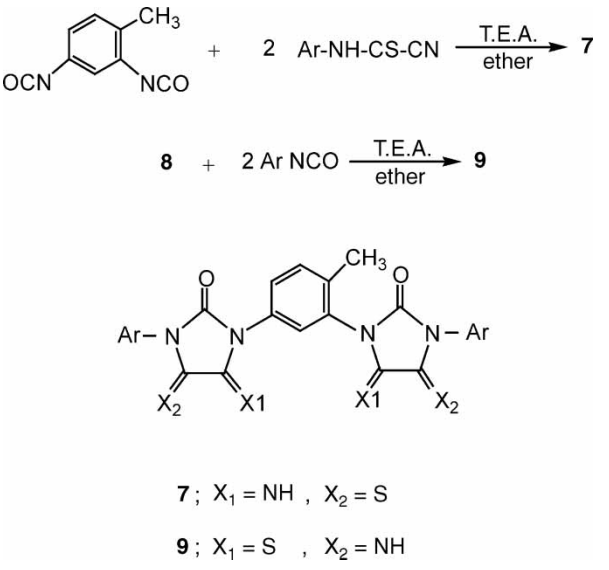
Cyanothioformamide **3** could be also reacted easily with acetaldehyde in the presence of triethylamine under the same conditions where cycloaddition reaction took place to produce 2-methyl-3-(3-isothiocyanato-4-methylphenyl)-5-imino-4-thioxo-oxazolidine **6** (scheme 2). This structure **6** was confirmed by elemental analysis and spectral data.

In one of our recent publications [26], the authors reacted 2,4-dithiocyanatotoluene with cyanothioformanilides where one molecule of the former reacted with two molecules of the latter to produce the corresponding bisimidazolidineiminothiones **7** (scheme 3).

In this investigation, the authors decided to synthesize the isomer of this bisimidazole **7**. Thus, 2,4-bis (cyanothioformamido)-toluene **8** (scheme 1) could be synthesized through the interaction of 2,4-bis(isothiocyanato)toluene **2** with two equivalents of potassium cyanide in dimethylformamide. IR measurements of **8** exhibited the absence of νNCS and the presence of νNH, νC≡N, and νCS−N<. ^{1}H NMR and MS also fit the proposed structure.

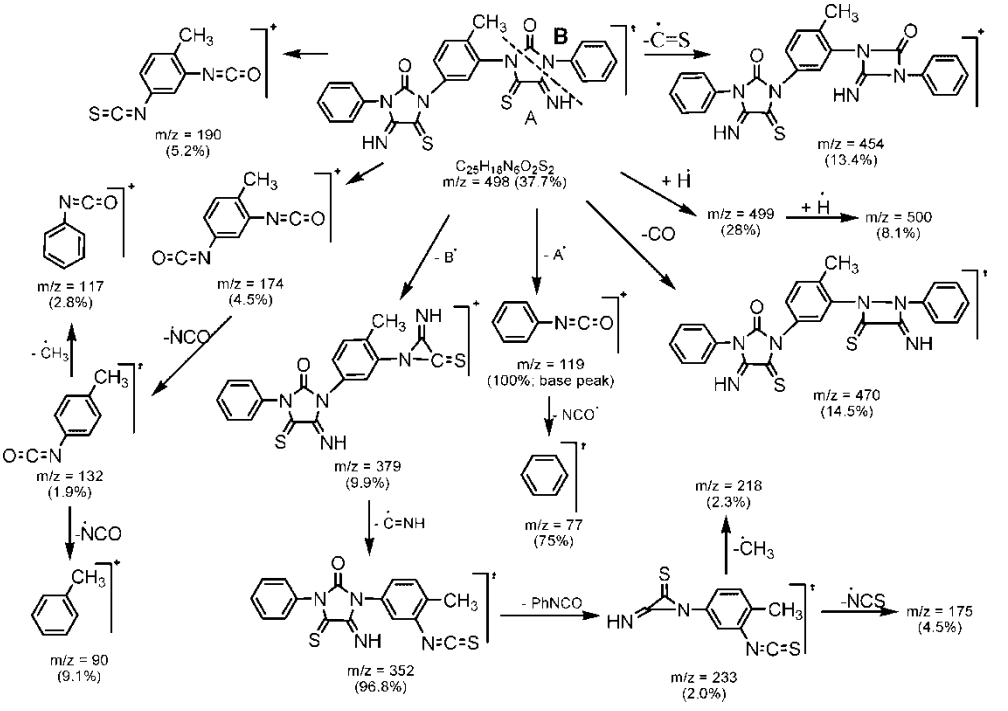
Interaction of **8** with phenyl- and with p-chlorophenyl-isocyanate in the presence of triethylamine caused the apparent cycloaddition reaction to produce, in each case, one product which revealed elemental and spectral data compatible with **9a**,**b** (scheme 3) respectively. IR spectrum of **9** exhibited the disappearance of νC≡N and the appearance of νNH, νCO and νCS−N< while ^{1}H NMR of **9b** showed the respective signals for the aliphatic, aromatic and variable hydrogens. The ms fragmentation pattern of **9a** is illustrated in scheme 4.

Various halogenated and alkylated imidazolidineiminothiones **10** (scheme 5) were obtained through interaction of the corresponding cyanothioformamides with phenyl- and

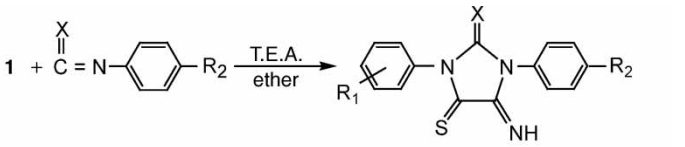


SCHEME 3

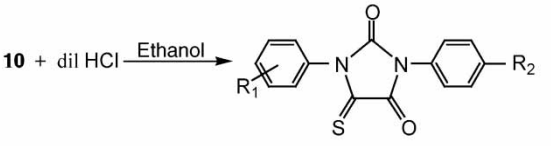
p-chlorophenylisocyanates. Some examples of heterocycles **10** were exposed to hydrolytic dil. HCl to furnish the respective chloro-, bromo-, iodo- and ethoxy- 4-thioxoimidazolidine-2,5-diones **11** (scheme 5), wherein IR revealed the disappearance of νNH.



SCHEME 4 Fragmentation pattern of compound **(9a)**.



10 ; X = O
12 ; X = S, R = H



11

	R_1	R_2
10 a ;	H	H
b ;	Cl-p	H
c ;	Cl-p	Cl
d ;	Cl-m	Cl
e ;	Br-p	H
f ;	Br-p	Cl
g ;	I-p	H
h ;	I-p	Cl
i ;	C_2H_5O-p	Cl

	R_1	R_2
11 a ;	Cl-p	Cl
b ;	Cl-m	Cl
c ;	Br-p	H
d ;	Br-p	Cl
e ;	I-p	Cl
f ;	C_2H_5O-p	Cl

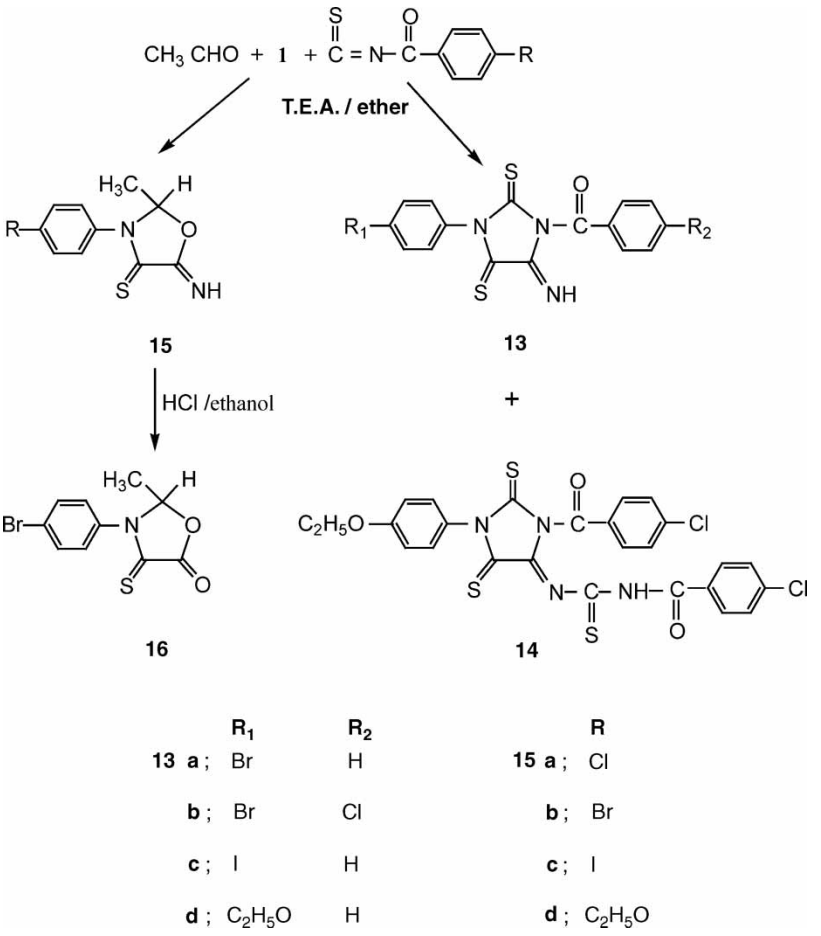
	R_1
12 a ;	H
b ;	Cl-p
c ;	Br-p
d ;	I -p

SCHEME 5

Bromo- and iodoimidazolidinedithiones **12** (scheme 5) were synthesized by reacting the corresponding cyanothioformamides with phenylisothiocyanate with evidence of the reaction shown by IR (absence of $\nu C{\equiv}N$ and presence of νNH). Another type of halogenated imidazolidinedithione **13** (scheme 6) could be accessed when the respective cyanothioformamides were reacted with benzoyl- and p-chlorobenzoylisothiocyanate. An additional product could be isolated from the reaction of p-ethoxy-cyanothioformanilide **1b** and p-chlorobenzoylisothiocyanate which exhibited elemental analysis and spectral data compatible with structure **14** (scheme 6).

Chloro-, bromo-, iodo- and ethoxyoxazolidineiminothiones **15** (scheme 6) were obtained through interaction between the corresponding cyanothioformamides and acetaldehyde in the presence of triethylamine. Structures **15** were established by IR, ^{1}H NMR, mass spectra and elemental analyses. 4-Thioxooxazolidine-5-one **16** (scheme 6) could be obtained by hydrolysis of **15** with dil. HCl in boiling ethanol. IR spectrum exhibited disappearance of νNH and appearance of $\nu C{=}O$ (ester) at 1800 cm^{-1}.

Cyanothioformamides were reported by El-Sharief *et al.* [19] to react with α, β-unsaturated ketones (chalcones) to give 3-amino-2-thioxopyrroline derivatives. In this investigation, p-tolylcyanothioformamide **1a** was reacted with dibenzylideneacetone to produce a product whose elemental and spectral data demonstrated that two moles of cyanothioformamide were



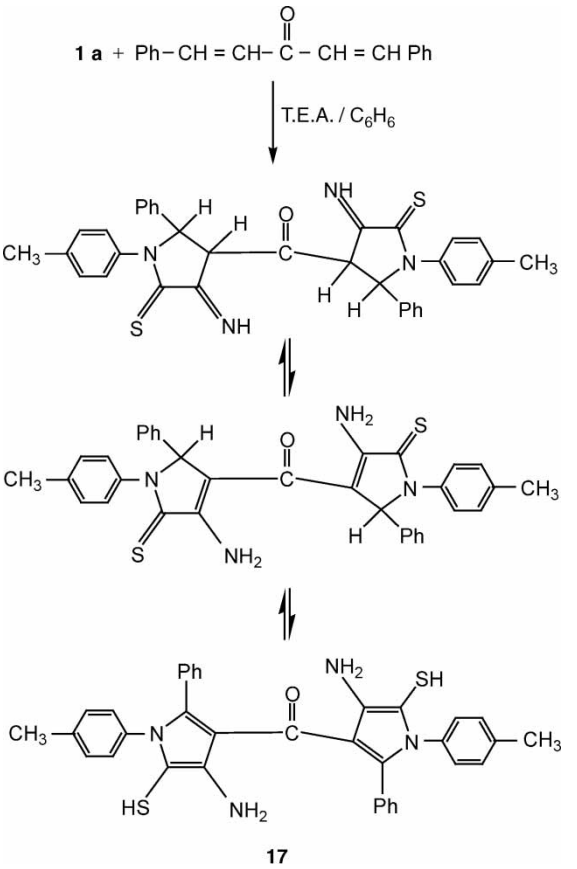
SCHEME 6

consumed with one mole of the dichalcone to give the bispyrrole derivative **17** (scheme 7), as bis(4-amino-5-mercapto-2-phenyl-1-p-tolyl-1H-pyrrol-3-yl)-methanone. This product has another two tautomeric structures, the pyrroline and the pyrrolidine structures (scheme 7).

Cyanothioformamide **1e** could be also reacted successfully with imines in the presence of triethylamine as a catalyst to produce another type of imidazolidineiminothione **18** (scheme 8). IR, ^{1}H NMR and MS are compatible with structure **18**.

p-Bromocyanothioformanilide **1e** was also allowed to react with maleic acid in boiling benzene and in the presence of triethylamine as a catalyst to produce a product which was established to be nitrilodithioacetic acid 1-(4-bromo-phenyl)-3-[3-(4-bromo-phenyl)-thioureido]-1H-pyrrol-2-yl ester **19** (scheme 8).

IR measurements of **19** exhibited the absence of νCO and the presence of νNH, νC≡N and νS=C−N<. The mechanism of formation of **19** could be rationalized as described in (scheme 8). In fact, elimination of HCN and p-bromoaniline could be achieved either from interaction of **1e** with the amino and the thiol groups of the intermediate [**A**] respectively to give **19**, or from the reaction of **1e** with the thiol and the amino groups, respectively, to give **20**. The authors favor structure **19** over the other isomer **20** (scheme 8) on the basis of reasons indicated below and that the former is less sterically hindered than the latter.

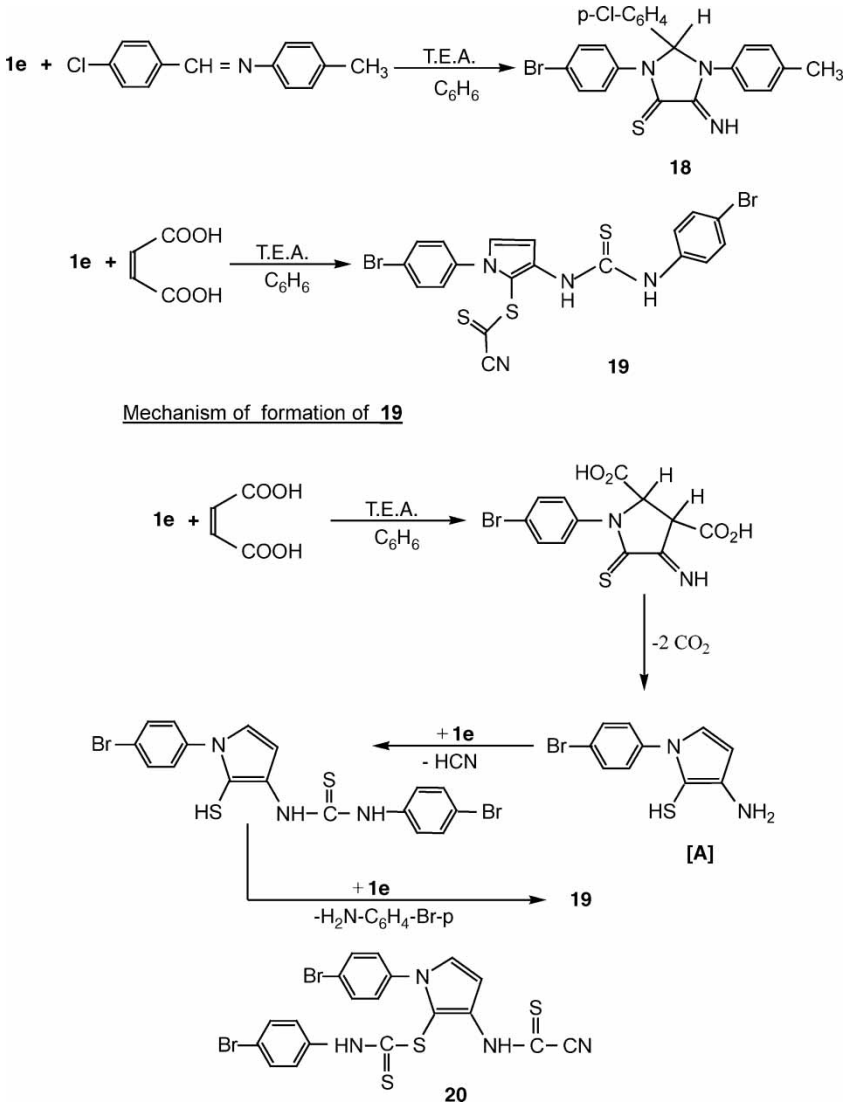


SCHEME 7

It is very difficult to differentiate the two pyrrole structures **19** and **20** using the available analysis such as IR, UV, ^{1}H NMR and ^{13}C NMR. Mass spectrum of the compound exhibited peaks at m/z = 102 (S−CS−CN, 18.6%) and at 103 (HS−CS−CN, 12.1%) characteristic structure **19** and at the same time did not reveal any fragment at m/z = 85 (HN−CS−CN) or at 86 (H_2N−CS−CN) expected for structure **20**. The structure of the pyrrole derivative is also favoured from a molecular modeling study which was carried out by program Chem 3D ultra version 8.03 available from CambridgeSoft. This study showed that structure **19**: nitrilodithioacetic acid 1-(4-bromophenyl)-3-[3-(4-bromophenyl)thioureido]-1H-pyrrol-2-yl ester has less energy E (kcal/mol) = 300.83 and MME = 4.933 than the other isomeric structure **20**, with E = 381.06 kcal/mol and MME = 17.251. These molecular minimization energies (E) indicate a thermodynamic preference for **19** over **20**. These findings are consistent with those obtained by Ragenovic *et al.* [28] and recently by El-Sharief *et al.* [24].

In the present investigation, a new type of halogenated fused imidazoles were obtained through interaction of 3-{4-(chloro-, bromo-, and iodo-)phenyl}-1-(4-chlorophenyl)-4-thioxo-5-imino-2-imidazolidinones **10c**,**f** and **h** with thiocarbohydrazide. The obtained products were the corresponding 5-(4-chlorophenyl)-3-hydrazino-7-(4-halophenyl)-5,7-dihydroimidazo[4,5-e][1,2,4]triazin-6-ones **21a**–**c** (scheme 9) respectively.

In one of our publications [29], we reported a study carried out by National Cancer Institute (Bethesda, Maryland, USA) on one of our compounds derived from a thiohydantoin which contained two chlorine atoms in two different positions and showed remarkable antitumor

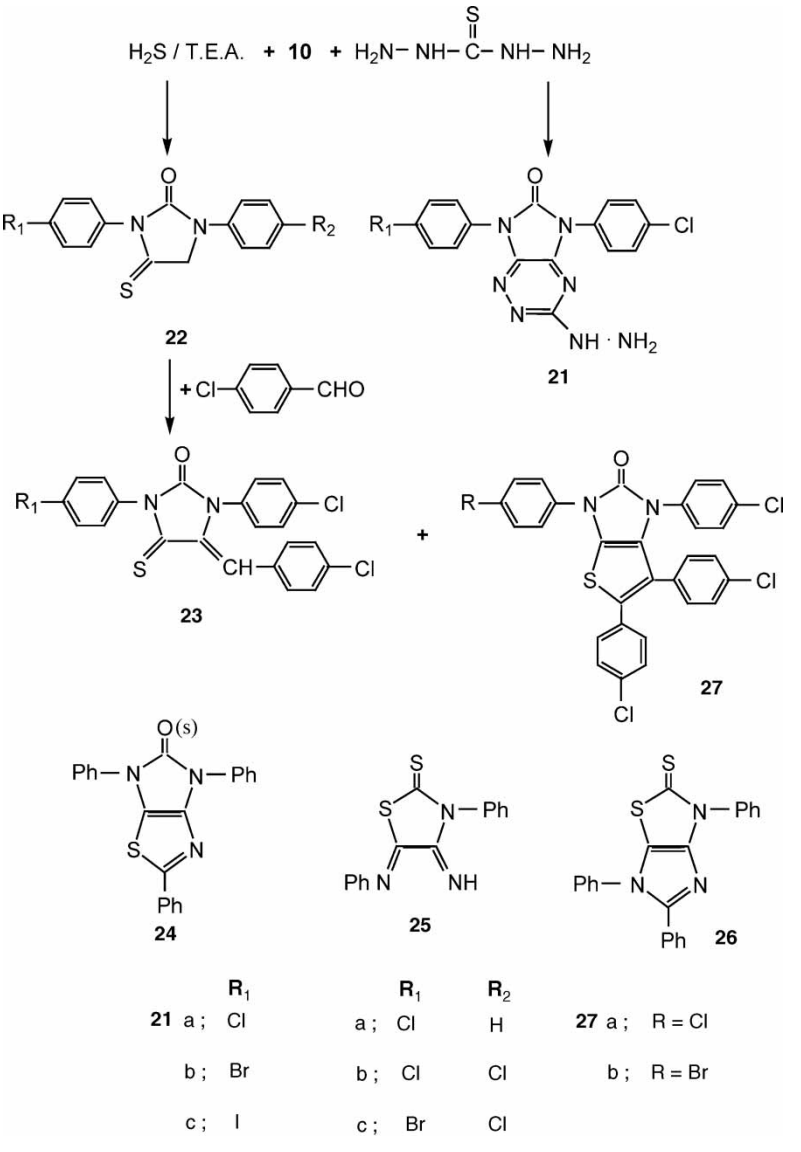


SCHEME 8

activity. This study encouraged us to synthesize, in this investigation, a variety of thiohydantoin derivatives which contain various halogen atoms and reacted them with chlorinated aldehydes. Thus, reduction of some of imidazolidineiminothiones **10** with H_2S in the presence of triethylamine as a catalyst resulted in the formation of 1,3-diaryl-4-thiohydantoin derivatives **22** (scheme 9). IR measurements of **22** exhibited disappearance of νNH which was present in the parent compounds **10**, ^{1}H NMR revealed at 5.5 ppm (2H, s, CH_2) and MS (%) of **20b** at m/z 336 (66.9, M^+) and 139 (100%).

Interaction of the thiohydantoin **22c** with p-chloro-benzaldehyde furnished two products; one of them exhibited elemental and spectral data compatible with 1-(4-bromophenyl)-4-(4-chlorobenzylidene)-3-(4-chlorophenyl)-5-thioxo-midazolidin-2-one **23** (scheme 9).

Ketcham and Schaumann [4] reacted 5-imino-4-thioxoimidazolin-2-one **10a** and 5-imino-2,4-imidazolidinedithione **12a** with benzaldehyde in the presence of BF_3 as a catalyst to

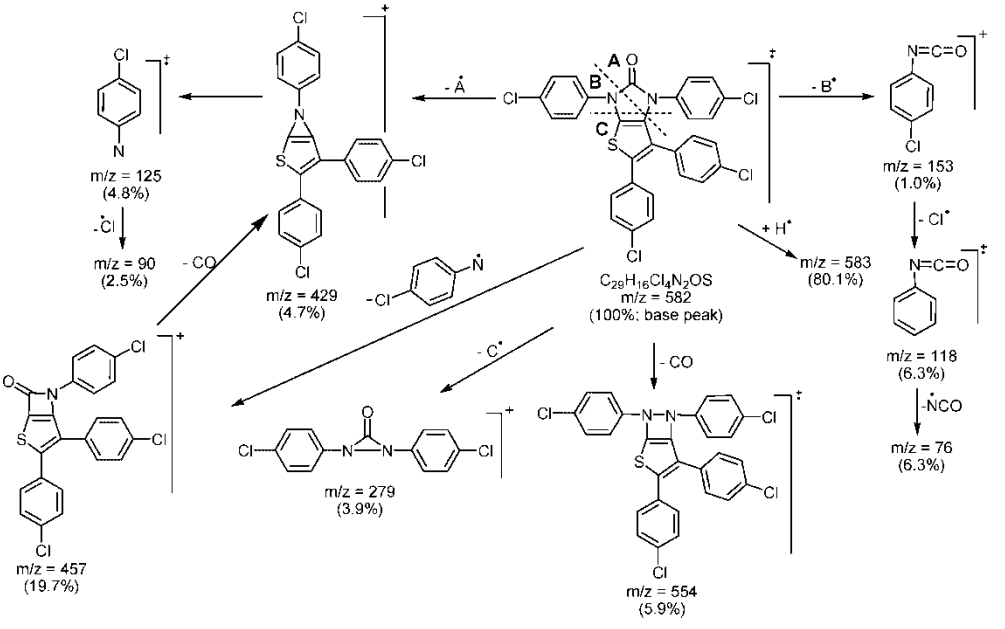


SCHEME 9

produce the imidazo[4,5-d]thiazol-5-one **24** (scheme 9). Also, Kattak *et al.* [6] reacted 4-imino-5-(phenylimino)-2-thiazolidinethione **25** (scheme 9) with benzaldehyde to obtain imidazo[4,5-b]thiazole-2-thione **26** (scheme 9) and they reported that "**26** is best prepared by simply heating the diimine **25** with an excess of benzaldehyde under reflux rather than the BF_3-catalysed reaction".

In this investigation, the thiohydantoin **22c** was reacted with p-chlorobenzaldehyde to give two products as described above. One product was assigned to be **23** whereas the other was assigned the structure as: 3-(4-bromophenyl)-1,5,6-tris-(4-chlorophenyl)-1,3-dihydrothieno-[2,3-d]imidazol-2-one, **27b** (scheme 9).

The mechanism of formation of **27** can be rationalized on basis similar to those described for **24** and **26**, through interaction of **23** with another mole of p-chlorobenzaldehyde as follows:



SCHEME 10 Fragmentation pattern of compound **(27a)**.

Interaction of the thiohydantoin **22b** with p-chlorobenzaldehyde gave directly **27a** as 1,3,5,6-tetrakis-(4-chlorophenyl)-1,3-dihydrothieno[2,3-d]imidazol-2-one. MS (%) of **27a** (scheme 9) exhibited M^+as base peak (100%) at $m/z = 582$ which shed some light on the stability of this product, M+1 (583, 30.1), M+2 (584, 61.1), M−1 (581, 39.6) and M−2 (580, 86.8), fragmentation pattern of **27a** is illustrated in scheme 10. Compound **27b** showed at $m/z = 626$ (8.5, M^+), 627 (3.3, M+1), 628 (5.78, M+2), 625 (1.78, M−1) and 624 (3.78, M−2). ^{1}H NMR spectra of (**a** and **b**) revealed the aromatic protons as a multiplet at $\delta = 7.1$–7.4, also IR spectra of both exhibited νCO at 1690 cm^{-1}.

2. Biological activity

Biological activity studies of the synthesized compounds were done in Fermentation Biotechnology and Applied Microbiology (Ferm-Ban) Center, Al-Azhar University, Cairo, Egypt.

3. Antimicrobial activity

Compounds **1f**, **3**, **4a**, **4b**, **6**, **8**, **9a**, **9b**, **11e**, **12c**, **14**, **19**, **21b**, **21c** and **22b** were tested for their antimicrobial activity by the diffusion agar technique using the gram positive bacteria *Bacillus subtillus* and *Staphylococcus aureus* and the gram negative bacteria *Escherichia coli* and *Salmonella typhi*. The results are summarized in (table 1).

Most of the synthesized compounds were found to possess various antimicrobial activities toward all the organisms used with minimal inhibitory concentration (MIC). Compounds **1f**, **3**, **4a**, **8**, **11e** and **19** were found to possess high antimicrobial activities against most of the microorganisms used.

Table 1. Antimicrobial screen of the newly synthesized compounds.

Samples	Gram positive						Gram negative					
	Test organism											
	Bacillus subtillus			Staphylococcus aureus			Escherichia coli			Salomonella typhi		
Conc.	1%	2.5%	5%	1%	2.5%	5%	1%	2.5%	5%	1%	2.5%	5%
1f	+++	+++	+++	+++	+++	+++	+++	+++	+++	++	+++	+++
3	++	++	+++	++	+++	+++	++	++	+++	+++	+++	+++
4a	+	++	++	++	++	+++	++	++	++	++	+++	+++
4b	−	−	−	+	+	+	+	+	+	−	−	−
6	−	+	+	+	+	++	+	+	+	++	++	+++
8	+	+	++	++	+++	+++	+	+	++	+++	+++	+++
9a	+	++	++	++	++	++	+	++	++	+	++	++
9b	+	+	+	+	+	+	−	+	+	−	−	+
11e	++	++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
12c	+	++	++	+	+	++	++	++	+++	+	+	++
14	+	+	+	+	+	++	+	+	+	+	+	+
19	+++	+++	+++	+++	+++	+++	+	++	+++	+++	+++	+++
21b	−	−	−	−	−	+	+	−	−	−	−	+
21c	+	+	+	+	+	+	+	+	+	+	+	+
22b	+	++	++	+	++	++	+	+	+	+	+	++

St. = Reference standard; Chloramphenicol was used as standard antibacterial agent
− The test done using the diffusion agar technique.
− Well diameter. 1 cm (100 ul of each conc. Was tested)
− Inhibition values = 0.1 − 0.5 cm beyond control = +; Inhibition values = 0.6 − 1 cm beyond control = ++
− Inhibition values = 1.1 − 1.5 cm beyond control = +++; 0 = not detected.

4. Antifungal activities

The selected compounds were also tested for their antifungal activity using *Aspergillus flavus* and *Aspergillus niger*. Most of the synthesized compounds were found to possess antifungal

Table 2. Antifungal screen of the newly synthesized compounds.

Samples	Test organisms					
	Aspergillus flavus			Aspergillus niger		
Conc.	1%	2.5%	5%	1%	2.5%	5%
1f	++	+++	+++	++	+++	+++
3	+	++	+++	++	++	+++
4a	+	+	++	+	+	++
4b	−	+	+	−	−	+
6	+	+	++	−	+	++
8	+	+	++	−	−	+
9a	+	+	++	+	++	+++
9b	−	−	+	−	−	+
11e	+	++	++	++	+++	+++
12c	−	−	+	−	−	+
14	−	−	+	−	−	+
19	−	+	++	+	++	+++
21b	−	+	+	−	+	+
21c	+	+	+	+	+	++
22b	+	++	++	+	++	++

St. = Reference standard; Grisofluvine was used as standard antifungal agent
− The test done using the diffusion agar technique.
− Well diameter. 1 cm (100 ul of each conc. Was tested)
− Inhibition values = 0.1–0.5 cm beyond control = +; Inhibition values = 0.6 − 1 cm beyond control = ++
− Inhibition values = 1.1–1.5 cm beyond control = +++; 0 = not detected.

activities toward the microorganisms used with minimal inhibitory concentration (MIC), the results are summarized in (table 2).

Compounds; **1f**, **3**, **9a**, **11e**, **19** and **22b** exhibited high antifungal activity against the microorganisms used.

5. Antitumor activity of some of the synthesized compounds

Antitumor activity was done at Cairo University, National Cancer Institute, Cancer Biology Department, Pharmacology Unit.
Antitumor activity: (*In vitro* study)
Reagent:

1. RPMI 1640 medium (Sigma)
2. Ehrlich Ascites Carcinoa cells (EAC) suspension (2.5×10^5/ml)
3. Trypan blue dye
   A stock solution was prepared by dissolving one gram of the dye in (100 ml) distilled water. The working solution was then prepared by diluting (1 ml) of the stock solution with (9 ml) of distilled water. The stain was used then for staining the dead EAC cells.
4. The compounds tested were: **1f**, **3**, **4a**, **8**, **9a**, **11e**, **12c**, **19**, **21a**, **21b** and **22b**.

Procedure:

1. EAC cells were obtained by needle aspiration of ascetic fluid from the preinocculated mice under aseptic conditions [30].
2. The cells tested for viability and contamination by staining certain cell volume of this fluid by an equal volume of the working solution of trypan blue dye [31].
3. The ascetic fluid was diluted to 1 : 10 with saline to contain 2.5×10^6 cells on a hemocytometer.
4. In a set sterile test tubes 0.1 ml of tumor cells suspension, 0.8 ml RPMI 1640 media and 0.1 ml of each tested compound (corresponding to 0.1, 1.0, 10, 10^2, 10^3, 10^4, 10^5 and 10^6 μg) were mixed. The test tube was incubated at 37 °C for 2 hrs. Trypan Blue [31] exclusion test was carried out to calculate the percentage of non viable cells. Compounds producing more than 70% non viable cells are considered active [32].

$$\%\ \text{of non-viable cells} = \frac{\text{No. of non-viable}}{\text{total No. of cells}} \times 100$$

The results are summarized in (table 3).

The results of antitumor activity for the synthesized compounds which are tabulated in table 3, indicated that compounds **3**, **4a**, **8**, **11e**, **12c**, **21a** and **22b** showed a significant activity towards Ehrlich Ascites Carcinoma tumor cells (*in vitro*). The compounds which exhibited the highest antitumor activity are: 2,4-bis(cyanothioformamido)toluene **8**, imidazotriazine **21a** and thiohydantoin **22b** which each of them contain two chlorine atoms in the p-position. Compounds **4a**, which is an imidazolidine containing methyl and isothiocyanato groups, also **3** which is cyanothioformanilide containing the same groups (methyl and isothiocyanate) possess a high antitumor activity. The imidazoli-dinethione and dithione (**11e** and **12c**) having halogen atoms in the p-position also exhibited better antitumor activity.

Table 3. Antitumor Activity of some of the synthesized compounds using (EAC).

	% Inhibition of cell viability		
	μg/ml		
Sample No.	100	50	25
1f	90	70	50
3	90	90	80
4a	100	95	80
8	100	100	100
9a	80	70	60
11e	90	80	70
12c	80	80	70
19	80	70	60
21a	100	100	95
21b	100	70	60
22b	100	100	90

6. Conclusion

Imidazoles and their fused heterocyclic derivatives are key components of a many bioactive compounds of both natural and synthetic origin [33]. Hydantoin derivatives are used in thereby as anticonvulsants [34] and as antitumor [29]. For these activities, the authors, in this investigation, were keen to synthesize many derivatives of these compounds. With respect to antimicrobial, antifungal and antitumor activities; the compounds which possess the higher activities are those of cyanothioformamide, imidazolidine and thiohydatoin derivatives. The presence of a halogen atom, alkyl, isothiocyanate or cyanothioformamido group in the p-position increase this activity.

7. Experimental

Melting points are uncorrected. IR spectra were recorded (KBr) on a Perkin Elmer 1650 spectrophotometer. ^{1}H NMR spectra were recorded on Varian Gemini spectrometer 200 (200 MHz), using DMSO-d_6 as a solvent and TMS as an internal standard. Chemical shifts are expressed as δ ppm units. Mass spectra were recorded on Shimadzu GC-MS QP 100 EX (70 eV). Micro analytical data were obtained from the Micro analytical Center at Cairo University. Found: C, H, N for all compounds were within $\pm$0.3 from the theoretical value. Physical data for the synthesized compounds are given in table 4. Also, the spectral data are collected in table 5.

Cyanothioformanilides **(1a–e)** were prepared [3,20], 4-iodo- **(1f)** and 3-isothiocyanato-4-methyl **(3)** cyanoathioformanilides and 2,4-bis-(cyanothioformamido)toluene **(8)** were similarly prepared.

7.1 *1-Aryl-3-(3-isothiocyanato-4-methylphenyl)-5-imino-4-thioxo-2-imidazolidinone (4a,b)*

To a solution of (**3**, 0.005 mole) and phenyl/ or p-chloro-phenyl(isothiocyanate) (0.005 mole) in tetrahydrofuran (30 ml) TEA (3 drops) were added and magnetically stirred at room temperature for 15 min. The obtained product was collected and recrystallized to give **4**.

Table 4. Characterization data for newly synthesized compounds.

Compd. No.	M.p. (°C)	Solvent cryst.	(Color)	Yield (%)	Molecular formula (Mol. Wt.)
3	89	C/n-H	Light yellow	50	$C_{10}H_7N_3S_2$ (233)
4a	145	C/n-H	Light orange	75	$C_{17}H_{12}N_4OS_2$ (352)
4b	220	C/n-H	Light orange	83	$C_{17}H_{11}N_4OS_2Cl$ (386)
5a	125	C/n-H	Yellow orange	75	$C_{17}H_{12}N_4S_3$ (368)
5b	184	C/n-H	Orange	80	$C_{18}H_{11}N_4OS_3Cl$ (430)
6	142	C/n-H	Yellow	83	$C_{12}H_{11}N_3OS_2$ (277)
8	129	C/n-H	Yellow	65	$C_{11}H_8N_4S_2$ (260)
9a	187	C/n-H	Orange	75	$C_{25}H_{18}N_6O_2S_2$ (498)
9b	235	C/n-H	Orange	81	$C_{25}H_{16}N_6O_2S_2Cl_2$ (566)
10c	192	C/n-H	Yellow Orange	85	$C_{15}H_9N_3OSCl_2$ (349)
10d	141	C/n-H	Yellow Orange	65	$C_{15}H_9N_3OSCl_2$ (349)
10e	167	C/n-H	Orange	75	$C_{15}H_{10}N_3OSBr$ (359)
10f	196	C/n-H	Orange	85	$C_{15}H_9N_3OSClBr$ (393)
Xg	175	C/n-H	orange	80	$C_{15}H_{10}N_3OSI$ (407)
10h	201	E	Orange	80	$C_{15}H_9N_3OSClI$ (441)
10i	194	E	Orange	85	$C_{17}H_{14}N_3O_2SCl$ (359)
11a	174	E	Light orange	55	$C_{15}H_8N_2O_2SCl_2$ (350)
11b	140	E	Light orange	50	$C_{15}H_8N_2O_2SCl_2$ (350)
11c	108	E	Light orange	53	$C_{15}H_9N_2O_2SBr$ (360)
11d	194	E	Light orange	50	$C_{15}H_8N_2O_2SClBr$ (394)
11e	145	E	Light orange	55	$C_{15}H_8N_2O_2SClI$ (442)
11f	174	E	Light orange	55	$C_{17}H_{13}N_2O_3SCl$ (360)
12c	152	Ether/ n-H.	Yellow orange	50	$C_{15}H_{10}N_3S_2Br$ (375)
12d	135	Ether/n-H.	Yellow orange	35	$C_{15}H_{10}N_3S_2I$ (423)
13a	141	C/n-H	Brown	55	$C_{15}H_{10}N_3OS_2Br$ (403)
13b	103	C/n-H	Brown	50	$C_{16}H_9N_3OS_2ClBr$ (437)
13c	145	C/n-H	Brown	40	$C_{16}H_{10}N_3OS_2I$ (451)
13d	82	C/n-H	Brown	45	$C_{18}H_{15}N_3O_2S_2$ (369)
14	245	E	Yellow	45	$C_{26}H_{18}N_4O_3S_3Cl_2$ (601)
15b	170	E	Yellow	55	$C_{10}H_9N_2OSBr$ (284)
15c	167	E	Yellow	75	$C_{10}H_9N_2OSI$ (332)
15d	92	E	Yellow	70	$C_{12}H_{14}N_2OS$ (234)
16	235	E	Light yellow	50	$C_{10}H_8NO_2SBr$ (285)
17	180	E	Yellow	60	$C_{35}H_{30}N_4OS_2$ (486)
18	170	E	Yellow	55	$C_{22}H_{17}N_3SClBr$ (470.5)
19	115	E	Yellow	50	$C_{19}H_{12}N_4S_3Br_2$ (552)
21c	240	E	Yellow	45	$C_{16}H_{11}N_7OClI$ (479)
22b	189	B	Light yellow	65	$C_{15}H_{10}N_2OSCl_2$ (336)
22c	175	B	Light yellow	60	$C_{15}H_{10}N_2OSClBr$ (382)
23	210	E	Yellow	60	$C_{22}H_{13}N_2OSCl_2Br$ (504)
27a	130	E	Yellow	50	$C_{29}H_{16}N_2OSCl_4$ (582)
27b	150	E	Yellow	55	$C_{29}H_{16}N_2OSCl_3Br$ (626)

C/n-H. = Chloroform/n-hexane, E = Ethanol, B = Benzene

7.2 *1-Aryl-3-(3-isothiocyanato-4-methylphenyl)-5-imino-2,4-imidaz-oilidinedithiones (5a,b)*

To a solution of (**3**, 0.005 mole) and phenyl/ or p-chlorobenzoylisothiocyanate (0.005 mole) in THF (30 ml), TEA (3 drops) were added then reacted and worked as above to give **5**.

7.3 *2-Methyl-3-(3-isothiocyanato-4-methylphenyl)-5-imino-4-thioxo-oxazolidine (6)*

To a solution of (**3**, 0.005 mole) in dry ether (30 ml) acetaldehyde (0.005 mole), & TEA (3 drops) were added then reacted and worked as above to give **6**.

Table 5. Spectral data for newly synthesized compounds.

Compd. No.	IR (ν_{max}) cm^{-1a}	^1H NMR (δ ppm) (DMSO-d_6)	MS (%) (m/z)
1f	3270 (NH), 2240 (C ≡ N), 1475, 1100 (S = C-N<) & 500 (Ar-I).	6.7–7.0 (4H, AB-q, J = 8 Hz, p-substituted), 8.9 (1H, hump, NH).	288 (M^+, 38.0), 261 (M-HCN, 68.2), 203 (C_6H_4-I, 30.2), 161 (C_6H_4.NHCSCN, 24.8), 127 (I, 38.0).
3	3250(NH), 2245 (C ≡ N), 2150 (-NCS) & 1400, 1100 (S = C-N<).	2.3 (3H, s, CH_3), 6.9–7.1 (3H, m, Ar-H) & 9.0 (1H, hump, NH).	233 (M^+, 40.1), 234 (M + 1, 6.5), 235 (M + 2, 4.9), 206 (toluene-2,4-diisothiocyante, 100).
4a	3350 (NH), 3090 (Ar-CH), 2900 (aliph.-CH), 2100 (-NCS), 1770 (C = O), 1650 (C = N), 1500 & 1230 (S = C-N<).	2.3 (3H, s, CH_3), 7.1–7.5 (8H, m, Ar-H) & 8.9(1H, s, NH).	352 (M^+, 100), 206 (toluene-2,4-diisothiocyante, 15.6), 148 (4-isothiocyanatotoluene, 14.3) & 119 (phenylisocyanate, 58.4).
4b	3300 (NH), 1770 (C = O), 1640 (C = N), 1480, 1240 (S = C-N<).	2.3 (3H, s, CH_3), 7.1–7.4 (7H, m, Ar-H) & 8.9 (1H, s, NH).	386 (M^+, 100), 206 (toluene-2,4-diisothiocyante, 70.7), 148 (4-isothiocyanatotoluene, 67.1).
5a	3290 (NH), 3050 (Ar-CH), 2950 (aliph.-CH), 2130 (-NCS), 1490 & 1250 (S = C-N<).	2.3 (3H, s, CH_3), 7.0–7.4 (8H, m, Ar-H), 8.7 (1H, s, NH).	
5b	3300 (NH), 2135 (-NCS), 1500, 1270 (S = C-N<).	2.3 (3H, s, CH_3), 7.3–7.7 (7H, m, Ar-H), 8.7 (1H, s, NH).	352 (M-78, 66.9), 353 (27.6), 206 (59.8), 164 (41.7) & 93 (100).
6	3350 (NH), 3130 (-NCS), 1470, 1270 (S = C-N<).	1.3 (3H, d, J = 6 Hz, CH_3-C), 2.3 (3H, s, CH_3-Ar), 6.1 (1H, q, J = 6 Hz, CH), 7.3–7.5 (3H, m, Ar-H) & 8.9 (1H, s, NH).	280 (M + 3, 55.2), 164 (4-isothiocyanatotoluene, 10.4), 127 (65.7) & 63 (100).
9a	3250 (NH), 3100 (Ar-CH), 2900 (aliph.-CH), 1770 (C = O), 1650 (C = N), 1425 & 1120 (S = C-N<).	2.3 (3H, s, CH_3), 7.5–7.9 (13H, m, Ar-H), 9.7 (2H, broad s, 2NH).	498 (M^+, 37.7), 499 (M + 1, 28.8), 500 (M + 2, 6.1), 501 (M + 3, 11.2), 352 (96.8), 206 (toluene-2,4-diisothiocyante, 15), 119 (C_6H_5NCO, 100), 77 (C_6H_5, 78.2).
9b	3300 (NH), 3080 (Ar-CH), 2900 (aliph.-CH), 1750 (double intense peaks, 2 C = O), 1650 (double intense peaks 2C = N), 1400 & 1100 (S = C-N<).	2.3 (3H, s, CH_3), 7.3–7.7 (8H, AB-q, 2 p-substituted), 7.8–8.0 (3H, m, Ar-H of tolyl) & 8.9 (2H, s, 2NH).	566 (M^+, 24.8), 206 (38.2), 153 (p-ClC_6H_4·NCO, 100).
10h	3300 (NH), 1770 (C = O), 1630 (C = N), 1500 & 1130 (S = C-N<).	7.3–7.6 (8H, AB-q, 2 p-substit-uted) & 8.5 (1H, s, NH).	
12c	3250 (NH), 1640 (C = N), 1470 & 1115 (S = C-N<).	7.2–7.5 (9H, m, Ar-H) & 8.7 (1H, s, NH).	375 (M^+, 27.3), 376 (M + 1, 38.1), 377 (M + 2, 25.3), 378 (M + 3, 8.4), 379 (M + 4, 6.9), 296 (M-Br, 7.4), 213 (p-BrC_6H_4·NCS, 33.7), 77 (C_6H_5, 100).
14	3250 (NH), 3070 (Ar-CH), 2900 (aliph.-CH), 1690 (C = O), 1630 (C = N), 1450 & 1150 (S = C-N<).	1.2 (3H, t, J = 7 Hz, CH_3), 4.3 (2H, q, J = 7 Hz, CH_2), 7.2–7.6 (12H, m, Ar-H), 9.3 (1H, s, NH).	569 (M-S, 53.0), 431 (41.7), 139 (p-ClC_6H_4·CO^+, 100).
15b	3250 (NH), 3080 (Ar-CH), 2900 (aliph.-CH), 1670 (C = N), 1500 & 1270 (S = C-N<).	1.4 (3H, d, J = 6 Hz, CH_3), 6.2 (1H, q, J = 6 Hz, CH), 7.5–7.8 (4H, AB-q, J = 8 Hz, p-substituted) & 8.7 (1H, broad s, NH).	

(*continued*)

Table 5. Continued.

Compd. No.	IR (ν_{max}) cm^{-1}[a]	^1H NMR (δ ppm) (DMSO-d_6)	MS (%) (m/z)
15c	3270 (NH), 3050 (Ar-CH), 2900 (aliph.-CH), 1680 (C = N), 1500 & 1270 (S = C-N<).	1.5 (3H, d, J = 6 Hz, CH_3), 6.3 (1H, q, J = 6 Hz,CH), 7.3, 7.8 (4H, AB-system, J = 8 Hz, Ar-H), 8.7 (1H, s, NH).	
15d	3250 (NH), 3070 (Ar-CH), 2850-2950 (aliph.-CH), 1650 (C = N), 1500 & 1260 (S = C-N<).	1.4 [3H, t, J = 7 Hz, CH_3 (Et)], 1.6 (3H, d, J = 6 Hz, CH_3-CH), 4.1 (2H, q, J = 7 Hz, CH_2), 6.1 (1H, q, J = 6 Hz, CH), 6.9–7.3 (4H, AB-q, p-substituted) & 8.8 (1H, hump, NH).	
17	3400, 3250 (NH_2), 3080 (Ar-CH), 2930 (aliph.-CH), 1730 (C = O), 1500 & 1130 (S = C-N<).	2.2 (6H, s, 2 CH_3), 5.3 (4H, s, 2 NH_2) & 7.3–7.7 (20 H, m, Ar-H+2CH).	586 (M^+, 13.4), 587 (M + 1, 4.5), 585 (M-1, 27.9), 584 (M-2, 50.0), 509 (M-C_6H_5,14.5), 149 (p-$CH_3C_6H_4$.NCS, 25.7), 91 ($CH_3C_6H_4^+$, 100).
18	3250 (NH), 1490 & 1150 (S = C-N<).	2.3 (3H, s, CH_3), 7.5–7.8 (13 H, m, Ar-H) & 8.7 (1H, s, NH).	455 (M-CH_3, 100), 456 (25.9), 457 (56.5), 213 (p-BrC_6H_4NCS), 240 (p-BrC_6H_4.NH.CS.CN, 5.1), 117 (p-$CH_3C_6H_4NC$, 3.8) & 92 (CH_3-C_6H_5, 3.4).
19	3280, 3120 (2NH), 2220 (C ≡ N), 1490 & 1080 (S = C-N<).		525 (M-HCN, 55.8), 524 (100), 213 (p-BrC_6H_4.NCS, 16.3), 155 ($BrC_6H_4^+$,6.0).
21c	3430, 3350 (NH_2), 3170 (NH) & 1690 (C = O).	7.4–7.7 (8H, m, Ar-H), 8.9 (3H, broad s, NH & NH_2).	480 (M + 1, 7.1), 481 (M + 2, 16.9), 482 (M + 3, 10.7), 483 (M + 4, 11.5), 484 (M + 5, 7.0), 448 (M-NH.NH_2, 3.5), 245 (p-IC_6H_4. NCO, 84.7) & 153 (p-ClC_6H_4NCO, 24.0)
22b	3080 (Ar-CH), 2900 (aliph.-CH), 1750 (C = O), 1500 & 1100 (S = C-N<).	5.5 (2H, s, CH_2), 7.3–7.6 (4H, AB-q, p-substituted).	336 (M^+, 66.9), 337 (M + 1, 13.8), 338 (M + 2, 50.6), 339 (M + 3, 15.8), 340 (M + 4, 12.4), 169 (p-ClC_6H_4- NCS, 4.2), 153 (p-ClC_6H_4NCO, 8.3) & 139 (100).
23	1690 (C = O), 1620 (C = C), 1500 & 1130 (S = C-N<).	6.9–7.3 (13H, m, Ar-H+CH).	504 (M^+, 60.46), 503 (M-1, 100), 505 (M + 1, 60.5), 506 (M + 2, 61.4), 469 (M-Cl, 8.74), 424 (M-Br, 1.1), 214 (p-BrC_6H_4NCS, 1.2), 198 (p-Br C_6H_4NCO, 2.1), 153 (p-ClC_6H_4N-CO, 2.3).

[a]All NH and NH_2 were disappeared on addition of D_2O.

7.4 *2,4-Bis-[1-(4-chlorophenyl)-2-oxo-4-imino-5-thioxoimidazolidin-3-yl]toluene (9a,b)*

To a solution of (**8**, 0.005 mol) and phenyl/ or p-chloro-phenylisocyanate (0.01 mol) in THF (30 ml), TEA (3 drops) were added then reacted and worked as above to give **9a**,**b**.

7.5 *Halogenated and alkylated imidazolidineiminothiones (10a–i)*

To a solution of halogenated and alkylated cyanothioformanilides (**1**, 0.005 mole) and phenyl/ or p-chlorophenylisocyanate (0.005 mole) in dry ether (30 ml), TEA (3 drops) were added then reacted and worked as above to give **10a–i**.

7.6 *4-Thioxoimidazolidine-2,5-diones (11a–f)*

The respective imidazolidineiminothione (**10**, 0.005 mole) in boiling ethanol (30 ml) was treated with dil. HCl during stirring. The obtained product was collected, washed with water and crystallized to give **11a**–**f**.

7.7 *Halogenated 5-imino-2,4-dithioxoimidazolidines (12a–d)*

A mixture of cyanothioformanilide (**1**, 0.005 mole), phenyl isothiocyanate (0.005 mole) and TEA (3 drops) in dry ether (30 ml) was stirred at room temperature for 15 min. The obtained product was collected and crystallized to give **12a**–**d**.

7.8 *1-(Benzoyl/ or p-chlorobenzoyl)-3-aryl-5-iminoimidazolidine-2,4-dithiones (13)*

The respective p-(bromo-, iodo- or ethoxy)cyanothioformanilide (0.005 mole), benzoyl or p-chlorobenzoylisothiocyanate (0.005 mole) and TEA (3 drops) were added then worked as above to give **13a**–**d**.

p-Ethoxycyanothioformanilide (0.005 mole), p-chlorobenzoyl-isothiocyanate (0.01 mole) and TEA (3 drops) were worked as above to produce **14**.

A mixture of p-chloro-, p-bromo-, p-iodo- or p-ethoxy-cyanothioformanilide (**1**, 0.005 mole), acetaldehyde (0.005 mole) and TEA (3 drops) was worked as above to give 5-imino-4-thioxooxazolidine **15**.

The oxazolidineiminothione (**15b**, 0.01 mole) in boiling ethanol (30 ml) was treated drop wise with dil. HCl during stirring. The obtained product was collected, washed with water and crystallized to give **16**.

7.9 *Bis-(4-amino-5-mercapto-2-phenyl-1-p-tolyl-1H-pyrrol-3-yl)-methylene (17)*

A mixture of p-tolylcyanothioformamide (**1a**, 0.01 mole), dibenzylideneacetone (0.005 mole) and TEA (3 drops) in benzene (30 ml) was stirred magnetically at 70 °C for 30 min to give a sticky product. The latter was treated several times with light-petroleum (40–60 °C) to produce a solid which crystallized to give **17**.

7.10 *3-(4-Bromophenyl)-2-(4-chlorophenyl)-5-imino-1-(4-tolyl)-imidazolidine-4-thione (18)*

A mixture of (**1b**, 0.005 mole), (4-Chlorobenzylidene)-p-tolyl-amine (0.005 mole) and TEA (3 drops) in benzene (30 ml) was stirred at 70 °C for 30 min and worked as above to give **18**.

7.11 *The pyrrole derivative (19)*

A mixture of (**1e**, 0.005 mole), maleic acid (0.005 mole) and TEA (3 drops) in benzene (30 ml) was worked as above to give **19**.

7.12 *The imidazo[4,5-e]triazine derivative (21c)*

A mixture of (**10h**, 0.005 mole) and thiocarbohydrazide (0.005 mole) in ethanol (30 ml) was refluxed for 5 hrs (H_2S could be detected). The obtained product was crystallized to give **21c**.

7.13 *4-Thiohydantoin derivatives (22)*

The requisite imidazolidineiminothione (**10**, 0.01 mole) was dissolved in dry benzene (50 ml) and TEA (3 drops) was added. H_2S gas was bubbled in this solution till complete precipitation of the corresponding 4-thiohydantoin which was then filtered off, washed with dry benzene and crystallized to give **22**.

7.14 *Reaction of the thiohydantoin 22c with p-chlorobenzaldehyde*

A mixture of (**22c**, 0.005 mole), p-chlorobenzaldehyde (0.005 mole) in absolute ethanol (30 ml) was refluxed for 5 hrs the obtained product was filtered off and crystallized to give **23**.

Concentration of the reaction mixture mother-liquor furnished another product which was crystallized to give **27b**.

7.15 *Thieno[2,3-d]imidazole-2-one (27a)*

A mixture of (**22c**, 0.005 mole) and p-chlorobenzaldehyde (0.005 mole) in ethanol (30 ml) was refluxed for 5 hrs to give **27a**.

References

[1] A. Reissert, K. Bruggemann. *Ber*., **57**, 981 (1924).
[2] W. Water, K.D. Bode. *Leibigs Ann.*, **131**, 698 (1966).
[3] E.P. Papadopoulos. *J. Org. Chem.*, **44**, 3858 (1979).
[4] R. Ketcham, E. Schumann. *J. Org. Chem*., **45**, 3748 (1980).
[5] R. Ketcham, E. Schaumann, T. Niemer. *Synthesis*, 869 (1980).
[6] I. Kattak, R. Ketcham, E. Schaumann, G. Adiwidjaja. *J. Org. Chem*., **50**, 3432 (1985).
[7] J. Huang, M.D. Graves. *J. Heterocycl. Chem*., **24**, 1981 (1987).
[8] A.M. Sh. El-Sharief, R. Ketcham, E. Schaumann. *Phosphorus, Sulfur*, *Silicon*, **46**, 83 (1989).
[9] A.M. Mohamed, A.M. Sh. El-Sharief, Y.A. Ammar, M.M. Aly. *Pharmazie*, **44**, 765 (1989).
[10] Y.A. Mohamed, Y.A. Ammar, A.M. Sh. El-Sharief, M.M. Aly, *J. Chin. Chem. Soc*., **37**, 511 (1990).
[11] A.M. Sh. El-Sharief, Y.A. Ammar, Y.A. Mohamed, M.S.A. El-Gaby, *Phosphorus, Sulfur, Silicon*, **148**, 117 (1999).
[12] A.M. Sh. El-Sharief, Y.A. Ammar, Y.A. Mohamed, M.S.A. El-Gaby. *Phosphorus, Sulfur, Silicon*, **148**, 215 (1999).
[13] Y.A. Ammar, A.M. Sh. El-Sharief, M.M. Aly, Y.A. Mohamed, Sh. I. Mohamed. *Phosphorus, Sulfur, Silicon*, **166**, 173 (2000).
[14] A.M. Sh. El-Sharief, A.A. Atalla, A.M. Hussein, M.S.A. El-Gaby, A.A. Hassan. *Phosphorus, Sulfur, Silicon*, **160**, 141 (2000).
[15] A.M. Sh. El-Sharief, Y.A. Ammar, Y.A. Mohamed, M.M. Aly, M.S.A. El-Gaby, A.S. Ali. *Phosphorus, Sulfur, Silicon*, **173**, 39 (2001).
[16] A.M. Sh. El-Sharief, A.M. Hussein, M.S.A. El-Gaby, A.A. Atalla, A.A. Ahmed. *Phosphorus, Sulfur, Silicon*, **170**, 47 (2001).
[17] A.M. Sh. El-Sharief, Y.A. Ammar, Y.A. Mohamed, M.S.A. El-Gaby. *Heteroat. Chem*., **13**, 291 (2002).
[18] M.S.A. El-Gaby, Y.A. Ammar, A.M. Sh. El-Sharief, M.A. Zahran, A.A. Khames. *Heteroat. Chem*., **13**(7), 611 (2002).
[19] A.M. Sh. El-Sharief, Y.A. Ammar, M.S.A. El-Gaby, M.A. Zahran, A.A. Khames. *Afinidad*, **60**(503), 47 (2003).
[20] A.M. Sh. El-Sharief, M.S.A. El-Gaby, A.A. Atalla, A.A. El-Adasy. *Afinidad*, **60**(507), 475 (2003).
[21] A.M. Sh. El-Sharief, Y.A. Ammar, M.A. Zahran, H. Kh. Sabet. *J. Chem. Res.* (S), 162 (2003).
[22] A.M. Sh. El-Sharief, Y.A. Ammar, M.A. Zahran, H. Kh. Sabet. *Phosphorus, Sulfur, Silicon*, **179**, 267 (2004).
[23] M.S.A. El-Gaby, A.M. Sh. El-Sharief, A.A. Atalla, A.A. El-Adasy. *J. Chin. Chem. Soc*. **51**, 327 (2004).
[24] A.M. Sh. El-Sharief, Y.A. Ammar, M.S.A. El-Gaby. *Afinidad*, **511**, 240 (2004).
[25] A.M. Sh. El-Sharief, F.F. Mahmoud, N.M. Taha. *Phosphorus, Sulfur, Silicon*, **180**, 573 (2005).
[26] A.M. Sh. El-Sharief, M.S.A. El-Gaby, A.A. Atalla, A.A. El-Adasy. *Heteroat. Chem.*, **16**, 218 (2005).
[27] M.P. Graziak, H. Ding. *Acta. Chim. Slov.*, **47**, 1 (2000).
[28] M.S.A. El-Gaby, J.A. Micky, N.M. Taha, A.M. Sh. El-Sharief. *Acta. Chim. Slov.*, **49**, 159 (2002).
[29] C.T. Supuran, A. Scozzafava, B.C. Jurca, M.A. Lies. *Eur. J. Med. Chem.*, **33**, 83 (1998).

[30] J.J. Anderson, D. Li, E.G. Burton, J.N. Cogburn, J.T. Collins, D.J. Garland, S.A. Huang, P.C. Isakson, C.M. Koboldt, E.W. Logusch, M.B. Morton. *J. Med. Chem.*, **38**, 4570 (1995).
[31] H. Yoshino, N. Veda, J. Niijima, H. Sugumi, Y. Kotake, K. Kitoh, *J. Med. Chem*., **35**, 2496 (1992).
[32] M.M. El-Mcrzabani, A.A. El-Aaser, M.A. Attia. *J. Planta Medica*, **36**, 150 (1972).
[33] D.J. Takemoto, C. Dunford, M.M. McMurrary. *Toxicon*., **20**, 593 (1982).
[34] M.M. El-Mcrzabani, A.A. El-Aaser, M.A. Attia, A.K. El-Dueini, A.M. Ghazel. *J. Med. Plant. Res.*, **36**, 150 (1979).