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UTILITIES OF CYANOTHIOFORMAMIDES AND IMIDAZOLIDINEIMINO-THIONES IN THE SYNTHESIS OF NEW TYPES OF OXADIAZOLE, TRIAZOLTHIONE, BENZOTHIAZOLOQUINAZOLINONE, PYRROLO[2,3-B] PYRROLE AND IMIDAZOTRIAZINE DERIVATIVES OF BIOLOGICAL INTEREST.

F. MAHMOUD
Chemistry Department, Faculty of Science, Al-Azhar University (for Girls), Cairo, Egypt

N. TAHA
Chemistry Department, Faculty of Science, Al-Azhar University (for Girls), Cairo, Egypt

A. EL-SHARIEF
Chemistry Department, Faculty of Science, Al-Azhar University (for Boys), Cairo, Egypt

E. AHMED
Chemistry Department, Faculty of Science, Al-Azhar University (for Girls), Cairo, Egypt

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UTILITIES OF CYANOTHIOFORMAMIDES AND IMIDAZOLIDINEIMINO-THIONES IN THE SYNTHESIS OF NEW TYPES OF OXADIAZOLE, TRIAZOLTHIONE, BENZOTHIAZOLOQUINAZOLINONE, PYRROLO[2,3-B] PYRROLE AND IMIDAZOTRIAZINE DERIVATIVES OF BIOLOGICAL INTEREST.

F.F. MAHMOUD[a] , N.M. TAHA[a] A.M.SH. EL-SHARIEF[b] AND E. M. AHMED[a]

[a] *Chemistry Department, Faculty of Science, Al-Azhar University (for Girls), Cairo, Egypt*

[b] *Chemistry Department, Faculty of Science, Al-Azhar University (for Boys), Cairo, Egypt*

Abstract

Cyanothioformamides were reacted with benzoyl hydrazine, acetyl hydrazine and anthranilic acid to afford oxadiazole (4), triazolthione (5) and benzothiazoloquinazolinone derivatives (6) respectively. They also reacted with thiocarbohydrazide, semicarbazide, thiosemicarbazide and active methylene compounds to produce 3-hydrazino-1,2-,4-triazol-5-thione (8), thiocarbamoylsemicarbazide (9), triazolidinedithione (10). Treatment of imidazolidine iminothiones with different nucleophilic reagents gave imidazotriazines besides other imidazolidine derivatives. Some of the newly synthestized derivatives were screened for antibacterial and antifungal activity and showed prononced antimicrobial activity.

Introduction

Azole derivatives are useful structure elements in medicinal chemistry. They are well known for their antifungal activity and also have found application in drug development for the treatment of allergies, hypertension, inflammation and HIV infections[1-4].

A variety of heterocylic ring closure reactions with cyanothioformamides[5-7] give rise to imidazoles[8], oxazoles[9], thiazoles[10] and other heterocycles[11-22]. Substituted cyanothioformamides are useful as insecticides, fungicides, bactericides, herbicides and acericides[23,24].

Results and discussion

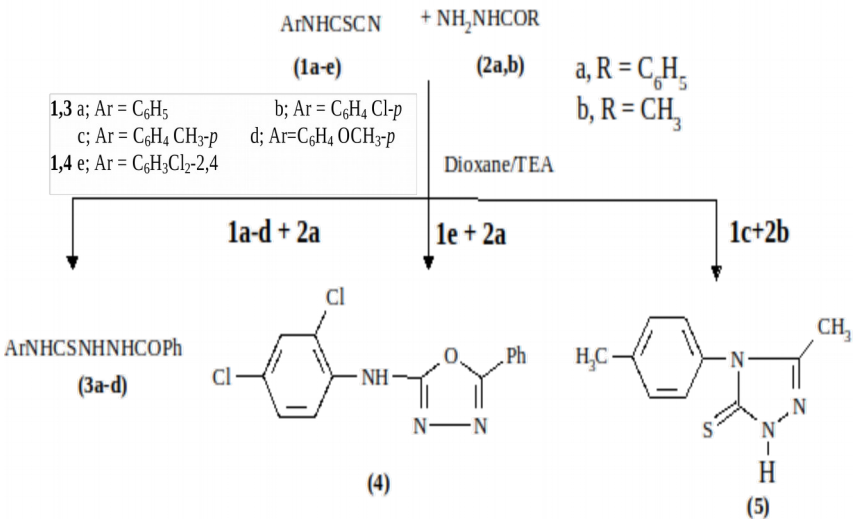
In the present investigation we are interested to study the behaviour of cyanothioformamides (**1)** toward hydrazine derivatives.

Thus, condensation of **1** with benzoyl hydrazine **(2)** in dioxane under reflux in the presence of a catalytic amount of triethylamine afforded the novel (1,2-disubstitutedhydrazines**(3a-d)**, while treatment of N-(2,4-dichlorophenyl-

cyanothioformamide **(1e)** with benzoyl hydrazine **(2a)** in dioxane/TEA under reflux gave 1,3,4-oxadizole derivative **(4)**[23]**.**

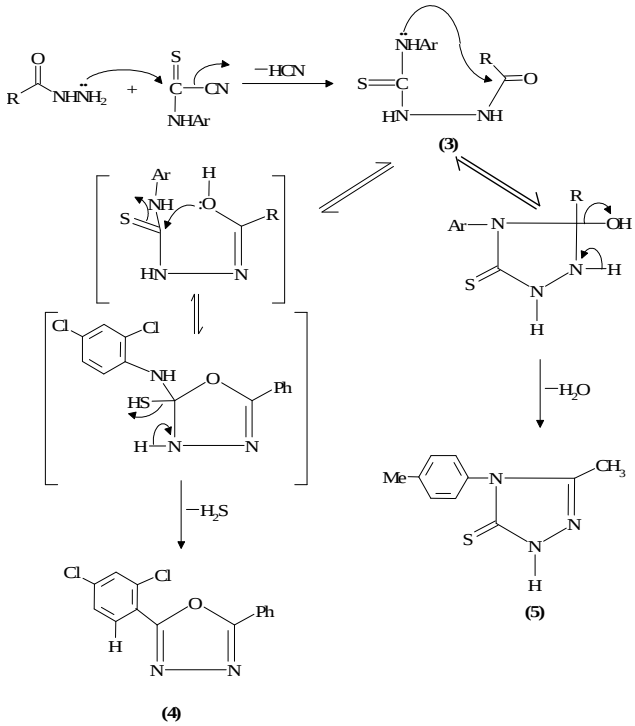
Cyclocondensation of **1c** with acetyl hydrazine **(2b)** in refluxing dioxane – TEA led to the formation of 1,2,4-triazole derivative **(5)**[23].

The structure of the products **3a-d, 4,5** were established by elemental and spectral data (scheme 1).



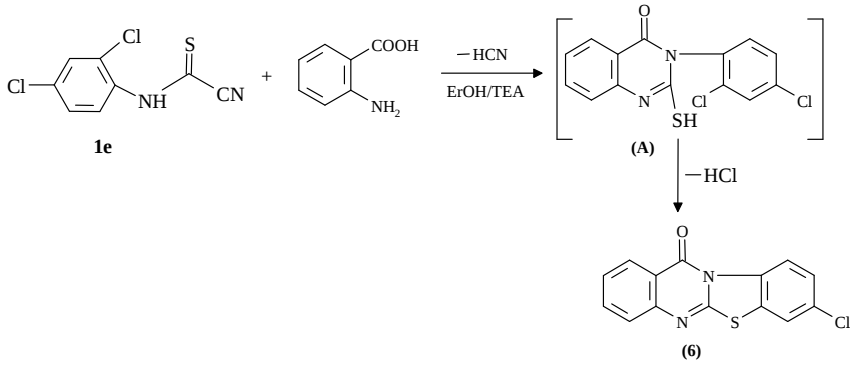
Scheme (1)

The formation of **3** can be explained by assuming that addition of NH_2 group to C=S is followed by HCN eliminaton; In case of Ar=$C_6H_3Cl_2$-2,4 ring closure through nucleophilic attack by enolic hydroxyl to electrophilic carbon of thione with the loss of hydrogen sulphide occurs to give **4.** But in case of Ar=$C_6H_4CH_3$-p, R=CH_3, nucleophilic addition of aryl -N to the carbonyl carbon followed by elimination of water molecule takes place to give **5** (Scheme 2).



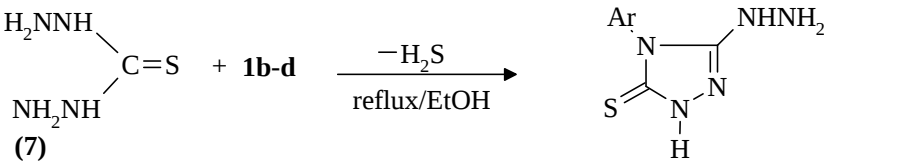
Scheme (2)

Cyclocondensation reaction between compound **(1e)** and anthranilic acid under reflux in ethanol in the presence of triethylamine afforded benzo[4,5]thiazolo[2,3-b] quinazolinone **(6)**. The formation of **6** is belived to take place by elimination of HCN molecule followed by formation of the intermediate N-(2,4-dichlorophenyl)-2-mercaptoquinazolinone [A] which undergoes aromatic nucleophilic substitution of o-Cl by s-nucleophile (scheme 3).



Scheme (3)

Treatment of compound **1b-d** with thiocarbohydrazide **(7)** in ethanol and a few drops of piperidine at reflux temperature gave the 1,2,4-triazole[23] derivative **(8a-c)**. The assignment of structure 8 is based on analytical and spectral data (Scheme 4).



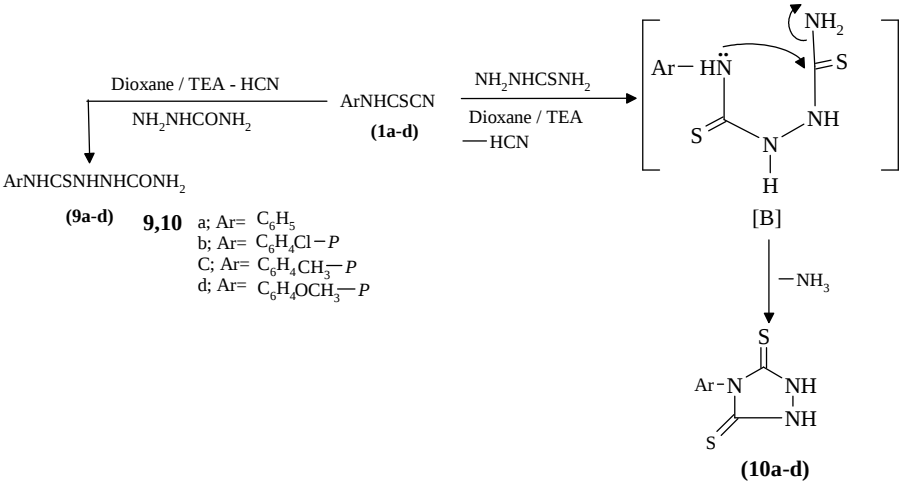
8 a, Ar = C_6H_4Cl-p

b, Ar = $C_6H_4CH_3-p$

c, Ar = $C_6H_4OCH_3-P$

(Scheme 4)

The thiocarbamoyl semicarbazide **(9a-d)** were achieved upon treatment of compounds **(la-d)** with semicarbazide in dioxane/triethylamine through elimination of hydrogen cyanide; while the reaction of thiosemicarbazide with compounds **(la-d)** afforded the corresponding 1,2,4-triazolidine-3,5-dithione[23] derivatives **(10a-d)** under same reaction condition. The structures of compounds **(9,10)** have been confirmed by elemental analyses, infrared, 'HNMR and mass spectra. Formation of **10** was rationalized by the formation of thiocarbamayl thiosemicarbazide as intermediate [B] which was cyclized to give 10 with the loss of ammonia molecule (Scheme 5)



9,10 a; Ar= C_6H_5
b; Ar= C_6H_4Cl-P
C; Ar= $C_6H_4CH_3-P$
d; Ar= $C_6H_4OCH_3-P$

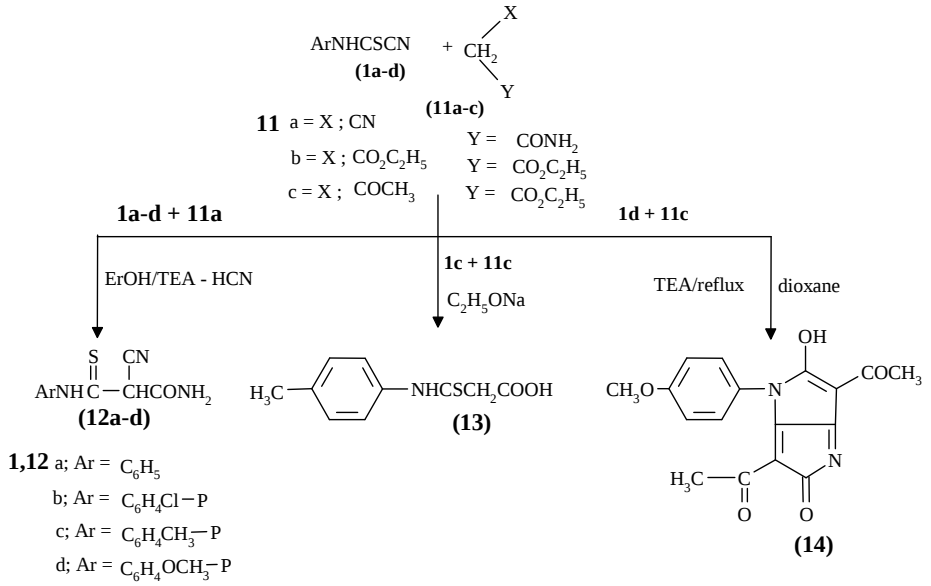
(Scheme 5)

Our investigation was extended to study the reactions of cyanothioformamide **(1)** with active methylene compounds.

Thus, the condensation of compounds **(la-d)** with cyanoacetamide **(11a)** by refluxing in ethanol/TEA led to formation of thiocarbamylcyanoacetamide derivatives **(12a-d),** through the elimination of hydrogen cyanide. Structures of compounds **12a-d** were identified based on elemental and spectral data.

Treatment of compound **(1c)** with diethyl malonate **(11b)** in the presence of sodium ethoxide led to the formation of novel thiocarbamoyl acetic acid derivative **(13).**

When compound **(Id)** was refluxed with ethyl acetoacetate **(11c)** in dioxane in the presence of triethylamine, double cyclization was occurred and produced the novel pyrrolo [2,3-b] pyrrole derivative **(14)** on the basis of analytical and spectral data (Scheme 6).

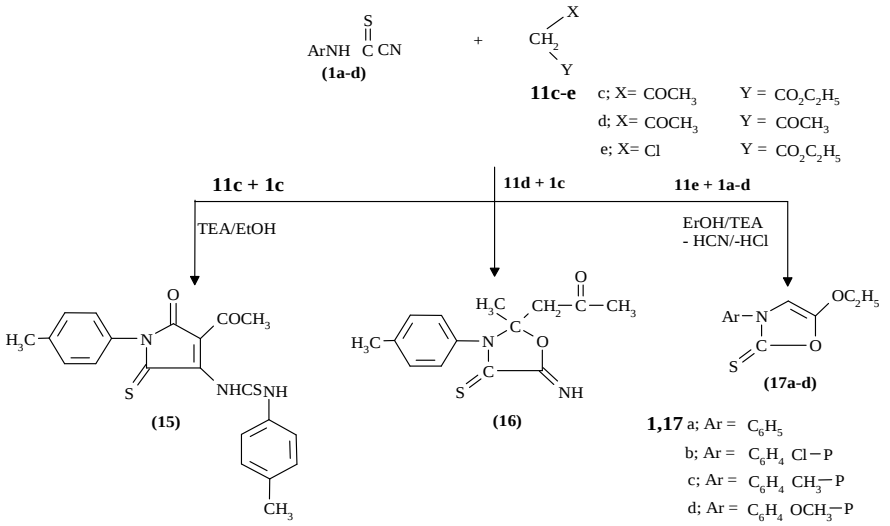


Scheme (6)

Also, cyclocondansatoin of compound **(Ic)** with ethyl acetoacetate **(11c)** in refluxing ethanol in the presence of triethylamine furnished the novel pyrrole derivatives **(15)** while, cyclocondensation of compound **(Ic)** with acetyl acetone **(11d)** at room temperature in ether in the presence of triethylamine yielded the

corresponding oxazolidinethione **(16)** Structure of compound **(16)** was identified based on elemental and spectral data.

Cycloalkylation of compounds (la-d) with ethyl chloroacetate (**11e)** in the presence of an equimolar amount of triethylamine in ethanol under reflux afforded the novel oxazole derivatives **(17a-d).** Structures of compounds **(17a-d)** were identified based on elemental and spectral data (Scheme 7).

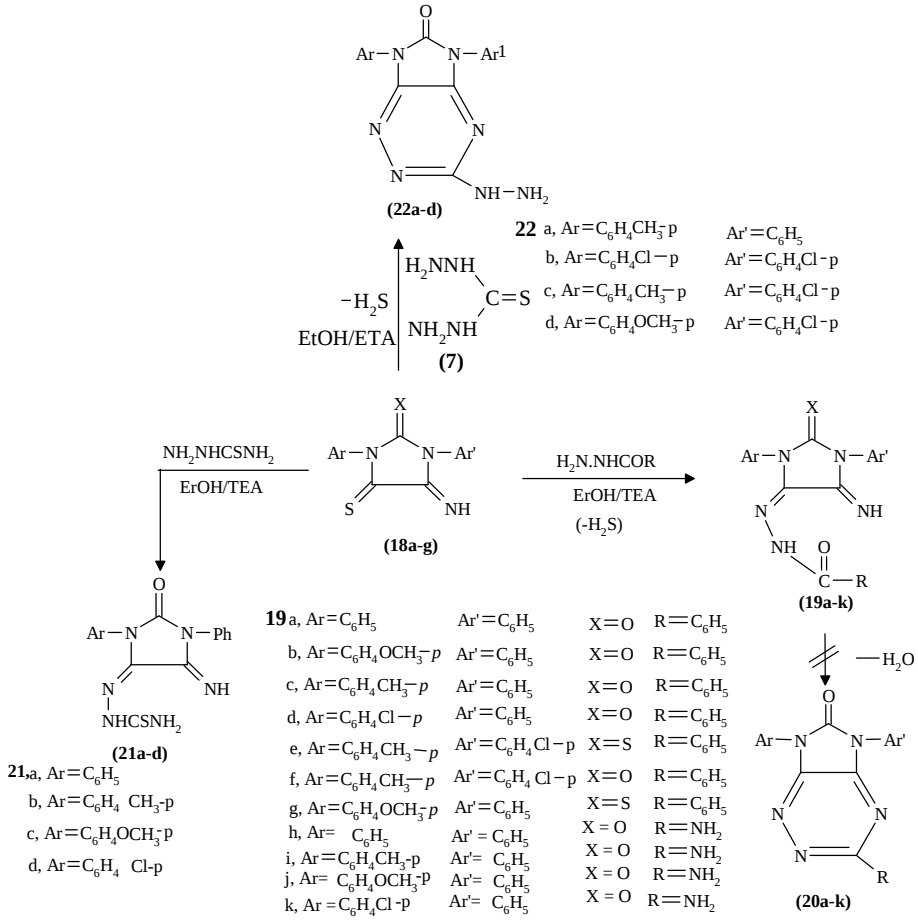


Scheme (7)

The reactivity of imidazolidineiminothiones **(18)**, which was obtained through interaction of **(1)** with isocyanate[25-27], towards hydrazines was investigated. Thus, reaction of imidazoldines **(18)** with benzoyl hydrazine **(2a)** in ethanol in the presence of triethylamine at reflux temperature, gave the hydrazones **(19a-g)** and the cyclized products **20** were not produced.

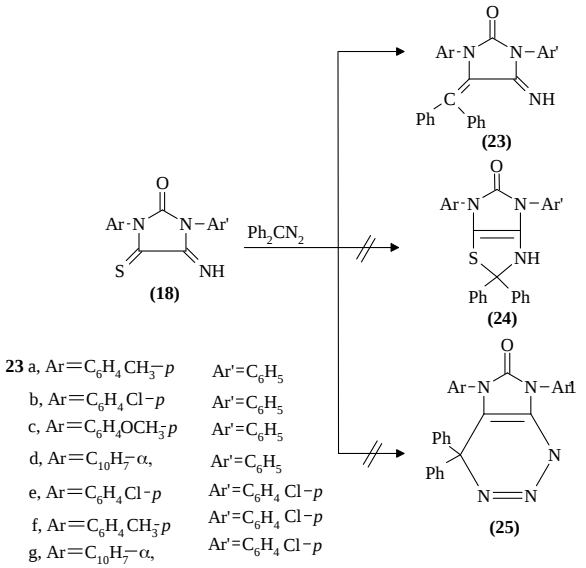
In a similar manner, condensation of compound (**18;**X=O) with semicarbazide furnished the semicarbazones **(19h-k)** and other possible structure **(20)** was discarded on the basis of analytical and spectral data. Also, thiosemicarbazones **(21a-d)** were obtained by treatment of compounds **(18a-d)** with thiosemicarbzide in refluxing ethanol in the presence of triethylamine. The structure of compound 21 was supported by analytical and spectral data (scheme 8).

Cyclocondensation of imidazolidinethiones **(18a-d)** with thiocarbohydrazide **(7)** in refluxing ethanol/TEA led to the formation of imidazotriazine **(22a-d)** . The structure of compound **22** was supported by analytical and spectral data (Scheme 8).



(Scheme 8)

Treatment of **18 (X=O)** with diphenyldiazomethane at room temperature in ether led to the formation of diphenyl methylene derivatives **(23a-g)** and the other possible structures **(24)** and **(25)** were not formed (Scheme 9).



(Scheme 9)

The newly synthesized products were tested for their antimicrobial and antifungal activities. Among them, compounds **3a,4,8c,9,16,23e** exhibit high activity against serratia marescens, *Bacillus cereus, Staphylococcus,* while compounds **16** and **23e** exhibit high activity against *Aspergillus achraceus* Wilhelm *Penicllium chrysogenum thorn.*

Experimental

Melting points were determined on an electrothermal melting point apparatus and were uncorrected. IR (cm^{-1}) spectra were recorded (KBr discs), on a FT-IR 8201 PC Shimadzu spectrophotometer. ^{1}HNMR spectra were obtained on a BRUKER proton NMR-Avance (300 MHz), in DMSO-d_6 and $CDC1_3$ as a solvent, using Tetramethylsilan (IMS) as internal standard. Mass spectra were run on HP model MS- 5988. elemental analyses were performed at the Microanalytical center, Cairo University, Giza, Egypt.

Synthesis of l-benzoyl-2- (substituted aryl) thiocarbamoyl hydrazines (3a-d):

A mixture of N-aryl cyanothioformamide derivates (1) (0.01 mol), benzoyl hydrazine (2a) (0.01 mol) and TEA (0.5 ml) in dioxane (20 ml) was refluxed for 7

hrs. The reaction mixture was then cooled and the obtained product was recrystallized from proper solvent to give (3a-d). The mass spectrum of compound (3b) revealed a molecular ion peak at m/z = 306 (M + l;0.9%) .

The ^{1}H-NMR spectrum of compound (3c) displayed the following signals at δ2.3 (s, 3H, CH_3), 7.1-7.6 (m, 10 H, Ar~ H + NH), 7.9 - 9.7 (2s , 2H, 2NH).

Synthesis of 2-(2,4-dichlorophenyl) amino-5-phenyl – 1,3,4 oxadiazole (4):

A solution of cyanothioformamide (1e) (0.01 mol) in dioxane (30 ml) was treated with benzoyl hydrazine (2a) (0.01 mol) and TEA (0.5 ml). The reaction mixture was refluxed for 6 hr. The product obtained was recrystallized from ethanol to give (4).

The mass spectrum of compound (4) exhibited a molecular ion peak at m/z 304 (M-1, 1.1 %).

Synthesis of 5-methyl-4-(p-tolyl)-2,4-dihydro-l,2,4-triazol-3-thione(5):

A mixture of N-p- tolylcyanothioformamide **(Ic)** (0.01 mol), acetyl hydrazine (2b) (0.01 mol) and triethylamine (0.5 ml) in dioxane (30 ml) was refluxed for 6 hrs. The reaction mixture was then cooled and the obtained product was recrystallized from dioxane to give (5).

The 'H-NMR spectrum of compound (5) exhibited signals at δ 2.3 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 7.2 - 7.5 (m, 5H, Ar - H + NH).

Synthesis of 8-chloro-benzo [4,5] thiazolo [2,3-b] quninazolin -2-one (6):

A mixture of cyanothioformamide (1e) (0.01 mol), anthranilic acid (0.01 mol) in ethanol (25 ml) and TEA (0.5 ml) was heated under reflux for 3 hrs. the obtained product was recrystallized from ethanol to give **(6).**

The mass spectrum of compound **(6)** revealed a molecular ion peak at m/z= 286 (M+1, 8.1 %).

Synthesis of 4-aryl-3-hydrazino-2,4-dihydro-1,2,4-triazol-5-thiones (8a-c):

A mixture of N-substituted cyanothioformamide **(1)** 0.01 mol), thiocarbo-hydrazide **(7)** and (0.5 ml) triethylamine in (50 ml) ethanol was refluxed for 3'hrs. The obtained product was recrystallized from proper solvent to give **(8a-c)**

The mass spectrum of compound **(8c)** showed a molecular ion peak at m/z =. (237, 7.1%).

Synthesis of 4-aryl-thiocarbamoyl- semicarbazides (9a-d):

A mixture of N-aryl cyanothioformamide derivatives (1) (0.01 mol), semicarbazide (0.01 mol) and triethylamine (0.5 ml) in dioxane (30 ml) was refluxed for 6 hrs. The reaction mixture was then cooled and the product obtained was recrystallized from proper solvent to give **(9a-d)**

The mass spectrum of **9a** showed a molecular ion peek at m/z = (228, 3%) and the mass spectrum of compound **9d** raveled a molecular ion peak at m/z. 239 (M-l; 4%). The 'H-NMR spectrum of compound **9d** reveled the signals at δ = 3.8 (s,3H, OCH_3), 6.8., 7.3 (2d, 4H, Ar-H) , 7.5 (s, 1H, NH), 8.0 (s, 2H, 2NH) 9.5 (s. 2H, NH_2)

Synthesis of 4-aryl-1,2,4- triazolidine- 3,5-dithiones (10a-d)

A mixture of N- aryl cyanothioformamide derivatives (1) (0.01 mol), thiosemicarbazide (0.01 mol) and triethylamine (0.5 ml) in dioxane (20 ml) was refluxed for 6 hrs. The reaction mixture was then cooled and the obtained product was recrystallized from proper solvent to give **(10 a-d)**

The mass spectrum of compounds **(10c)** showed molecular ion peak at m/z = (223, 6.3 %) and the mass spectrum of compound **(10d)** reveled a molecular ion peak at m/z: (239, 6.3%). The 'H-NMR spectrum of compound (**10d)** revealed the signals at δ = 3.7 (s, 3H, OCH_3), 6.8, 7.3 (2d, 4H, Ar- H), 8.1 (hump, 1H, NH), 9.4 (s, 1H, NH).

Formation of 2- arylthiocarbamoyl -2-cyanoacetamides (12a-d)

A mixture of N-aryl cyanothioformamide derivatives (1) (0.01 mol), cyanoacetamide **(11a)** (0.01 mol) and triethylamine (0.5 ml) in ethanol (30 ml) was refluxed for 7 hrs. The reaction mixture was then cooled and the obtained product was recrystallized from proper solvent to give **(12a-d)**

The mass spectrum of compound **(12c)** exhibited a molecular ion peak at m/z (233, 33%). The HNMR spectrum of compound **(12c)** revealed the signals at δ 2.2 (s, 3H, CH_3) , 4.3 (hump 2H, NH_2) ,7.1- 7.3 (m , 6 H , ArH+ CH + NH).

Synthesis of 2-(*p*-tolyl thiocarbamoyl) acetic acid (13):

A mixture of *p*-tolyl cyanothioformamide **(Ic)** (0.01 mol), diethyl malonate **(11b)** (0.01 mol) and sodium ethoxide (0.01 mol) in absolute ethanol (30 ml) was refluxed for 6 hrs. the obtained solid was recrystallized from ethanol to give (**13)**.

The mass spectrum of compound **(13)** showed a molecular ion peak at m/z (195,7.5%).

Synthesis of 3,6-diacetyl-5-hydroxy-4-(*p*-methoxy phenyl)-4-pyrrolo[2,3b] pyrrol-2-one (14) :

A mixture of N-(*p*-methoxyphenyl) cyanothioformamide) **(1d)** (0.01 mol), ethyl acetoacetate **(11c)** (0.01 mol) and triethylamine (0.5 ml) in dioxane (30 ml) was refluxed for 8 hrs. The reaction mixture was then cooled and the product obtained was recrystallized from dioxane to give **(14).**

The mass spectrum of compound **(14)** showed a molecular ion peak at m/z (326, 7.6%). The 'H-NMR spectrum of compound **(14)** exhibited a molecular ion peak at δ 3.75 (s, 3H, OCH_3), 3.86 (s, 6H, 2 $COCH_3$) , 4.68 (s, 1H, OH), 6.79 - 7.39 (m, 4H, Ar, H).

Synthesis of 1-[4-acetyl- 5-oxo-2-thioxo-1-(4-tolyl) 2,5-dihydro-lH pyrrol-3-yl]-3-(4- tolyl) thiourea (15):

A mixture of N-(*p*-tolyl) cyanothioformamide **(Ic)** (0.01 mol), ethyl acetoacetate **(11c)** (0.01 mol) and triethylamine (0.5 ml) in ethanol (30 ml) was refluxed for 8 hrs. The reaction mixture was then cooled and the product obtained was recrystallized from benzene to give **(15)** The mass spectrum of compound **(15)** showed a molecular at m/z = 409.7, 8%**.**

The ^{1}H-NMR spectrum of compounds **(15)** showed the signals at δ= 2.3, 2.4 (2s, 6H, $2CH_3$), 2.5 (s,3H, $COCH_3$) , 6.9 - 7.4 (m, 8H, Ar-H), 8.8, 12.9 (2s, 2H, 2NH).

Synthesis of l-[5-imino-2-methyI-4-thioxo-3-(4-toIyl) oxazolidin-2-yl] propan-2-one (16):

A mixture of N-(p-tolyl) cyanothioformamide **(Ic)** (0.01 mol), acetyl acetone **(11d)** (0.01 mol) and triethylamine (0.5 ml) in ether (30 ml) was stirred for 1 hr. The reaction mixture was then concentrated and recrystallized from ethanol to give **(16)**. The mass spectrum of compound **(16)** showed a molecular ion peak at m/z = 276.5, 2.3%.

The ^{1}H-NMR spectrum of compounds **(16)** showed the signals at δ = 2.2, 2.3 (2s, 6H, $2CH_3$), 2.4 (s,2H, CH_2), 2.5 (s, 3H, $COCH_3$) , 7.2 - 7.4 (m, 4H, Ar- H), 8.8 (s, 1H,NH).

Synthesis of 3-aryl-5-ethoxy-3H-oxazole- 2-thiones (17a-d)

A mixture of N-aryl cyanothioformamide derivatives (1) (0.01-mol), ethyl chloracetate **(11c)** (0.01 mol) and TEA (0.5 ml) in ethanol (30 ml) was refluxed for 8 hrs. The reaction mixture was then cooled the obtained product was recrystallized from proper solvent to give **(17a-d)**

The mass spectrum of compounds **(17a)** revealed a molecular ion peak at m/z (221, 5.37%). The 'H-NMR spectrum of compound **(17a)** revealed the signals at δ 1.19 (t, 3H, CH_3), 3.03 (q, 2H, CH_3), 3.37 (s, IH, CH, oxazole), 7.0 - 7.5 (m, 5H, Ar-H).

Synthesis of N(1,3-(diaryl)-5-imino-2-oxo-imidazolidine-4-ylidine) benzo hydrazide (19a-g).

A mixture of (0.01 mol), imdazolidine derivatives **(18)** (0.01 mol) benzoyl hydrazine (2a) and (0.5 ml) triethylamine in (30 ml) ethanol was refluxed for 7 hrs. The product obtained was recrystallized from proper solvent to give **(19a-g).** The mass spectrum of compound **(19d)** exhibited a molecular ion peak at m/z = (417, 1.44%), for compound **(19g)** at m/z = 431, 2.01%) and for compound **(19g)** at m/z (429, 8.1%).

The ^{1}H-NMR spectrum of compound **(19e**) exhibited the following signals at δ 2.3 (s, 3H, CH_3) , 7.3-7.8 (m, 13 H, Ar- H),9.8 , 14.1 (2s, 2H, 2NH). Also, the H-NMR spectrum of compound **(19g)** exhibited the following signals δ 3.8 (s, 3H, OCH_3), 7.2 - 7.8 (m, 14H, Ar-H), 8.2 , 13.5(2s,2H,NH).

Synthesis of l-(5-imino-2-oxo-l-phenyl, 3-aryl-imidazolidine-4-ylidine methyl) urea (19h-k):

A mixture of (0.01 mol), imdazolidine derivatives **(18)** (0.01 mol), semicarbazide and (0.5 ml) triethylamine in (30 ml) ethanol was refluxed for 3 hrs. The product obtained was recrystallized from proper solvent to give **(19h-k).**

The mass spectrum of compound **(19k)** revealed a molecular ion peak at m/z = (374, 2.94%). The 'H-NMR spectrum of compound **(19i)** showed the signals at δ1.6 (s, 3H, CH_3) , 7.1-7.6 (m, 11 H, Ar- H+ +NH_2), 8.4 , 12.7 (2s,2H,NH).

Synthesis of l-[5-imino 2-oxo-l-phenyl-3-aryI-imidazoline-4-yildine methyl)] thiourea (21a-d):

A mixture of (0.01 mol) imidazolidine derivatives **(18)**, (0.01 mol) thiosemicarbazide and (0.5 ml) triethylamine (30 ml) in ethanol was refluxed for 3hrs. The obtained product was crystallized from proper solvent to give **(21a-d).**

The mass spectrum of compound **(21b**) revealed a molecular ion peak at m/z = (352, 1.6 %). Also, the mass spectrum of compound **(21d)** showed a molecular ion peak at m/z = (372, 37%). The 'H-NMR spectrum of compound **(21c)** displayed the following signals at δ 2.9 (s, 3H, OCH_3), 6.2 (s, 2H, NH_2), 6.9-7.6 (m, 9H, Ar-H), 8.1, 12.9 (2s, 2H, 2NH).

Synthesis of 5,7-(diaryl)-3-hydrazonyI-(5H)-imidazo[4.5-e](1,2,4) triazine-6(7H) 6-one (22a-d)

A mixture of (0.01 mol) imdazolidine derivatives **(18)** (0.01 mol), thiocarbohydrazide **(7)** and (0.5 ml) triethylamine in (50 ml) ethanol was refluxed for 3 hrs. The obtained product was recrystallized from proper solvent to give **(22a-d)**.

The mass spectrum of compound **(22a)** showed a molecular ion peak at m/z = (334, 12%), for compound **(22b)** showed a molecular ion peak at m/z (388, 6.7%), for compound **(22e)** showed a molecular ion peak at m/z (367, 11%) and for compound **(22d)** showed a molecular ion peat at m/z (383, 83%).

Synthesis of 4-imino 1,3-diaryl-5-[diphenyl metheline] imidazolidine-2-one (23a-g)

A solution of imidazolidine derivatives **18** (0.01 mol) was added to ethereal solution of diphenyldiazomethane (0.01 mol) in dry ether (50ml). The solution was stirred for 30 min. then concentrated. The obtained product was recrystallized from ethanol to give **(23a-g).**

The mass spectrum of compound **(23a)** showed a molecular ion peak at m/z (429, 35 %), for compound (**23b**) at m/z (449, 35%), for compound **(23c)** at m/z

(445, 33%), for compound **(23d)** at m/z: (464, 100%), for compound **(23e)** at m/z : (482, 100%), for compound **(23f)** at m/z (462, 33%), and for compound **(23g)** at m/z: (498, 100%). The ^{1}H-NHR spectrum of compound **(23f)** exhibited signals at δ 2.2 (s, 3H, CH_3) , 6.7 - 7.70 (m, 9H, Ar-H + NH).

Table 1. Physical Data of the synthesized compounds

Compd. No	Yield (%)	M.P. (°C)	Cryst Solvent	Mol. Formula (Mol. Wt)	Analyses Required/found		
					C	H	N%
3a	80	169-171	Ethanol	$C_{14}H_{13}N_3OS$ (271.33)	61.67 62.04	4.83 4.88	15.49 15.51
3b	75	198-200	Dioxane	$C_{14}H_{12}N_3OSCl$ (305.78)	54.99 55.13	3.95 3.96	13.74 13.78
3c	75	150-151	Ethanol	$C_{15}H_{15}N_3OS$ (285.37)	63.13 63.22	5.97 5.30	14.72 14.75
3d	85	223-225	Dioxane	$C_{15}H_{15}N_3O_2S$ (301.37)	59.78 59.86	5.02 5.02	13.94 13.96
4	65	168-170	Ethanol	$C_{14}H_9N_3OCl_2$ (306.28)	54.89 54.76	2.96 2.95	13.78 13.74
5	75	248-250	Dioxane	$C_{10}H_{11}N_3S$ (205.47)	58.45 58.59	5.39 4.40	20.54 20.59
6	75	237-239	Ethanol	$C_{14}H_7N_2OSCl$ (286.85)	58.62 58.79	2.46 2.47	9.81 9.84
8a	70	180-181	Benzene	$C_8H_8N_5SCl$ (241.59)	39.76 39.86	3.34 3.35	28.99 29.06
8b	60	191-192	Ethanol	$C_9H_{11}N_5S$ (221.10)	48.78 48.91	4.37 5.01	31.71 31.83
8c	65	260-261	Ethanol	$C_9H_{11}N_5OS$ (237.3)	42.55 42.61	4.67 4.68	29.51 29.52
9a	75	152-153	Ethanol	$C_8H_{10}N_4OS.H_2O$ (228.27)	42.09 42.14	5.29 5.30	24.54 24.57
9b	75	180-182	Ethanol	$C_8H_9N_4OSCl$ (244.70)	39.27 39.29	3.71 3.71	22.90 22.92
9c	85	200-201	Dioxane	$C_9H_{12}N_4OS$ (224.28)	48.19 48.25	5.40 5.40	24.98 25.01
9d	75	225-226	Dioxane	$C_9H_{10}N_4O_2S$ (240.28)	44.99 45.23	5.03 5.39	23.32 23.44

Compd. No	Yield (%)	M.P. (°C)	Cryst Solvent	Mol. Formula (Mol. Wt)	Analyses Required/found		
					C	H	N%
10a	70	156-157	Benzene	$C_8H_7N_3S_2$ (209.48)	45.86 45.97	3.36 3.37	20.14 20.19
10b	80	198-200	Ethanol	$C_8H_6N_3S_2Cl$ (243.90)	39.39 39.54	2.47 2.48	17.30 17.37
10c	90	190-191	Ethanol	$C_9H_9N_3S_2$ (223.51)	48.36 48.47	4.05 4.06	24.98 25.01
10d	85	186-187	Ethanol	$C_9H_9N_3OS_2$ (239.51)	45.13 45.22	3.78 3.79	17.62 17.66
12a	65	160-162	Ethanol	$C_{10}H_9N_3OS$ (219.26)	54.78 54.89	4.14 4.14	19.16 19.19
12b	70	125-126	Ethanol	$C_{10}H_8N_3OSCl$ (253.60)	47.36 47.42	3.18 3.19	16.57 16.61
12c	75	170-171	Ethanol	$C_{11}H_{11}N_3OS$ (233.29)	56.63 56.70	4.75 4.76	18.01 18.03
12d	75	198-200	Ethanol	$C_{11}H_{11}N_3O_2S$ (249.29)	53.01 53.06	4.45 4.45	16.86 16.88
13	65	77-78	Ethanol	$C_{10}H_{11}NO_2S$ (209.26)	57.36 57.91	5.30 5.71	6.69 7.22
14	75	180-181	Dioxane	$C_{17}H_{14}N_2O_5$ (326.31)	62.57 62.49	4.32 4.32	8.59 8.57
15	80	222-223	Benzene	$C_{21}H_{19}N_3O_2S_2$ (409.72)	61.56 61.67	4.67 4.68	10.30 10.32
16	75	238-240	Ethanol	$C_{14}H_{16}N_2O_2S$ (276.48)	60.81 60.92	5.83 5.84	10.17 10.19
17a	90	228-230	Dioxane	$C_{11}H_{11}NO_2S$ (221.27)	59.71 59.78	5.01 5.02	6.33 6.34
17b	75	250-251	Benzene	$C_{11}H_{10}NOClS$ (255.76)	51.65 51.81	3.94 3.95	12.51 12.4
17c	85	245-246	Dioxane	$C_{12}H_{13}NO_2S$ (235.29)	61.26 61.33	5.57 5.58	5.95 5.96
17d	85	247-248	Dioxane	$C_{12}H_{13}NO_3S$ (251.29)	57.35 57.42	5.21 5.22	5.57 5.58
19a	80	280-281	Ethanol	$C_{22}H_{17}N_5O_2$ (383.70)	68.86 68.98	4.46 4.47	18.33 18.37
19b	70	268-270	Ethanol	$C_{23}H_{19}N_5O_3$ (413.75)	66.76 66.88	4.63 4.37	17.03 17.03
19c	70	203-204	Dioxane	$C_{23}H_{19}N_5O_2$	69.46	4.81	17.68

Compd. No	Yield (%)	M.P. (°C)	Cryst Solvent	Mol. Formula (Mol. Wt)	Analyses Required/found		
					C	H	N%
				(397.75)	69.58	4.82	17.72
19d	85	259-260	Ethanol	$C_{22}H_{16}N_5O_2Cl$ (417.86)	63.23 63.36	3.86 3.87	16.76 16.79
19e	80	213-215	Ethanol	$C_{23}H_{18}N_5OSCl$ (448.24)	61.63 61.66	4.04 4.05	15.69 15.70
19f	90	218-220	Ethanol	$C_{23}H_{18}N_5O_2Cl$ (431.91)	63.96 64.09	4.20 4.21	16.22 16.25
19g	75	271-272	Dioxane	$C_{23}H_{19}N_5O_2S$ (429.82)	64.27 64.39	4.45 4.46	16.36 16.39
19h	80	236-238	Ethanol	$C_{16}H_{14}N_6O_2$ (322.33)	59.26 59.68	4.37 4.38	26.07 26.10
19i	75	240-242	Ethanol	$C_{17}H_{16}N_6O_2$ (336.35)	60.70 60.76	4.79 4.80	24.98 25.01
19j	75	298-300	Dioxane	$C_{17}H_{16}N_6O_3$ (352.35)	61.35 61.41	4.57 4.58	23.85 23.78
19k	75	302-304	Dioxane	$C_{16}H_{13}N_6O_2ClH_2O$ (374.67)	51.29 51.38	4.03 4.04	22.43 22.47
21a	75	230-232	Ethanol	$C_{16}H_{14}N_6OS$ (338.39)	56.79 56.86	4.16 4.17	24.84 24.86
21b	95	302-305	Dioxane	$C_{17}H_{16}N_6OS$ (352.42)	57.49 57.49	4.57 4.68	23.84 23.88
21c	75	295-297	Dioxane	$C_{17}H_{16}N_6O_2S$ (368.79)	55.42 55.49	4.37 4.38	22.81 22.84
21d	80	248-250	Ethanol	$C_{16}H_{13}N_6OSCl$ (372.73)	51.56 51.66	3.51 3.52	22.54 22.59
22a	85	248-250	Ethanol	$C_{17}H_{15}N_7O$ (333.35)	61.25 60.95	4.45 4.51	29.41 29.27
22b	87	268-270	Acetone	$C_{16}H_{13}N_7OCl_2$ (388.54)	49.45 49.52	2.85 2.86	25.34 25.38
22c	88	298-300	Acetone	$C_{17}H_{14}N_7OCl$ (367.52)	54.18 55.29	3.86 3.82	26.67 26.57
22d	89	240-241	Ethanol	$C_{17}H_{14}N_7O_2Cl$ (383.52)	53.24 53.30	3.67 3.66	25.56 25.46
23a	85	179-180	Ethanol	$C_{29}H_{23}N_3O$ (429.53)	81.09 81.19	5.39 5.40	9.78 9.79
23b	70	205-206	Ethanol	$C_{28}H_{20}N_3OCl$ (449.83)	74.69 74.90	4.48 4.49	9.34 9.36

Compd. No	Yield (%)	M.P. (°C)	Cryst Solvent	Mol. Formula (Mol. Wt)	Analyses Required/found		
					C	H	N%
23c	70	175-176	Ethanol	$C_{29}H_{23}N_3O_2$ (445.52)	78.18 78.27	5.20 5.21	9.43 9.44
23d	65	248-250	Ethanol	$C_{32}H_{23}N_2O$ (465.54)	82.56 82.57	4.97 4.99	9.03 9.04
23e	50	185-186	Ethanol	$C_{28}H_{19}N_3OCl_2$ (484.48)	69.42 69.49	3.95 3.96	8.67 8.68
23f	70	208-210	Ethanol	$C_{29}H_{22}N_3OCl$ (463.86)	75.09 75.23	4.78 4.79	9.06 9.07
23g	60	204-206	Ethanol	$C_{32}H_{22}N_3OCl$ (499.89)	76.89 77.02	4.43 4.49	8.46 8.42

Table (2). IR spectra of synthesized compounds

Compd. No.	$V_{max}\ (cm^{-1})$
3a	3170(NH), 3058(CH-arom.), 1670 (C=O).
3b	3159(NH), 3039 (CH-arom.), 1651 (C=O), 1531 (C=S).
3c	3124(NH), 2920 (CH-arom.), 1674 (C=O), 1523 (C=S).
3d	3178(NH), 3066 (CH-arom.), 2962, (CH-aliph) (C-aluph), 1670 (C=O).
4	3198(NH) 2837 (CH-aliph).
5	3100(NH), 3093 (CH-arom.), 2920 (CH-aloph), 1496 (C=S).
6	3038 (CH-arom.), 1662 (C=O).
8a	3325, 3209, 3124 (NH, NH_2), 2958 (CH-arom.), 1528 (C=S).
8b	3317, 3209, 3116 (NH, NH_2), 1527 (C=S).
8c	3217, 3116 (NH), 2908 (CH-aliph.), 1527 (C=S).
9a	3352, 3232, 3186 (NH, NH_2), 1523 (C=S).
9b	3355, 3186, 3124 (NH, NH_2), 1527 (C=S).
9c	3355, 3232, 3186, 3132 (NH, NH_2), 1525 (C=S).
10a	3355, 3124 (NH), 1527 (C=S).
10b	3200, 3190 (NH), 3055 (CH-arom.), 1554 (C=S).
10c	3186, 3124 (NH), 2947 (CH-aliph.), 1526 (C=S).
10d	3232, 3186 (NH), 3043 (CH-arom.), 3935 (CH-aliph.) 1523 (C=S).
12a	3417, 3332 (NH), 21941 (C≡N), 1642 (C=O), 1519 (C=S).
12b	3417, 3240 (NH), 3055 (CH-arom.), 2191 (C≡N), 1643 (C=O). 1488 (C=S).
12c	3417, 3325 (NH), 2198 (C≡N),1643 (C=O).
13	3200, 2507 (OH), 1710 (C=O).

Compd. No.	V_{max} (cm^{-1})
14	3400-2495 (OH), 1755, 1618 (C=O), 1620 (C=N).
15	3250, 3156 (NH), 2950 (CH aliph.), 1680 (C=O).
16	3332 (NH), 2970 (CH aliph.), 1743 (C=O), 1651 (C=N).
17a	2977, 2939 (CH aliph.), 1412, 1149 (S=C–N).
17b	2977, 2947 (CH aliph.), 1490, 1120 (S=C–N).
17c	2980, 2939 (CH aliph.), 1492, 1150 (S=C–N).
19a	3274, 3228(NH), 3062 (CH arom.), 1751, 1697 (C=O), 1670 (C=N) .
19b	3355, 3213(NH), 3058 (CH arom.), 1755, 1674 (C=O), 1624 (C=N) .
19c	3363, 3217(NH), 3055 (CH arom.), 1759, 1674 (C=O), 1651 (C=N) .
19h	3448, 3271, 3209, 3147 (NH, NH_2), 1766 (C=O), 1643 (amide).
19i	3440, 3209, 3147, (NH, NH_2), 1774 (C=O), 1643 (amide).
19k	3440, 3209, 3147(NH, NH_2), 1766, 1643 (2C=O).
21a	3440, 3209, 3147(NH, NH_2), 1766, (C=O), 1643 (C=N).
21b	3440, 3271, 3155(NH, NH_2), 1766, (C=O), 1643 (C=N).
21d	3440, 3380, 3155(NH, NH_2), 1766, (C=O), 1643 (C=N).
22a	3479, 3209 (NH), 2923 (CH-aliph.), 1751 (C=O).
22b	3417, 3294 (NH), 3093 (CH arom), 2923 (CH-aliph.), 1759 (C=O).
22c	3425, 3301 (NH_2), 2923 (CH-aliph.), 1759 (C=O).
22d	3440, 3201 (NH_2), 2923 (CH-aliph.), 1751 (C=O).
23b	3332, (NH), 1750 (C=O), 1643 (C=N).
23c	3340, (NH), 1751 (C=O), 1643 (C=N).
23d	3163, (NH), 1751 (C=O), 1666 (C=N).
23f	3332, (NH), 1743 (C=N), 1651 (C=N).
23g	3258, (NH), 1751 (C=O), 1674 (C=N).

Antimicrobial Activity

1. Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against two species of Gram positive bacteria, namely *Staphylococcus aureus* (NCTC-7447), *Bacillus cereus* (ATCC-14579) and two species of Gram negative bacteria *Serratia marcescens* (IMRU 70) and Proteus mirabilis (NTCC-289) using Ampicillin (25 ug) as the reference compound. Table 3 shows the effect of compounds on the microorganisms tested. It was found that all compounds **3a,3c,,4,8c,9d,10a,12c,16,17c,23c** were shown to exhibit an activity

pattern which suggests that they may have a broad spectrum antibacterial effect with a sustained high degree of inhibition, giving almost +++ ratings against all of the test organisms.

2. Antifungal activity

The newly synthesized compounds were screened for their antifungal activity against two species of fungi, *Aspergillius ochraceus* Wilhelm (AUCC-230) and penicillium chrysogemim Thorn (AUCC-530) using the Mycostatin (30ug) as the reference compound. Table 4 showed the effect of compounds **3a,3c,,4,8c,9d,10a,12c,16,17c,23c** on the microorganism tested. It was found that all compounds were shown on exhibit an activity pattern which suggested that they may have broad spectrum of antifungal action with a sustained high degree of inhibition, giving almost ++ ratings against all of the test organisms.

Table 3 : Antimicrobial activity of some prepared compounds:

Comp. No.	Staphylococcus aureus (NCTC-7447)	Bacillus cereus (ATCC-14579)	Serratia marescens (IMRU. 70)	Proteus mirabilis (NTCC-289)
3a	+	++	++	+++
3c	++	+	+	++
4	+++	++	++	+
8c	+++	+++	+++	++
9d	+	+	++	+++
10a	++	+	++	++
12c	++	++	+	+
16	++	++	+	+++
17c	+	++	+	++
23e	++	+++	++	+

\+ : Less active (0.2-0.5 cm)

++ : Moderately active (0.6-1.4 cm)

+++ : Highly active (1.5-3.0 cm)

Standard for Gram positive and Gram negative bacteria : Ampicllin 25 µg.

Table 4 : Antifungal activity of synthesized compounds :

Comp. No.	*Aspergillus ochraceus* Wilhelm (Aucc-230)	*Penicllium chrysogenum* Thorn (Aucc-530)
3a	++	+
3c	+	+
4	++	+
8c	++	++
9d	+	++
10a	+	+
12c	++	++
16	+++	+++
17c	+	+
23e	+++	++

\+ : Less active (0.2-0.5 cm)
++ : Moderately active (0.6-1.4 cm)
+++ : Highly active (1.5-3.0 cm)

Standard for fungi : Mycostatin (30 µg).

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