Heteroatom Chemistry
Volume 17, Number 7, 2006

Synthesis of Some Novel Imidazolidine Derivatives and Their Metal Complexes with Biological and Antitumor Activity

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Received 20 June 2005; revised 19 December 2005

ABSTRACT: *Halogenated imidazo(pyrazine,[1,4]-diazocine and quinoxaline), 9,10-anthraquinone-[6,7-e], phenanthroline[5,6-e] {imidazo[4,5-b]-pyrazine}, and naphtho[1,8-ef]imidazo[4,5-b][1,4] diazipen were obtained through interaction of imidazolidineiminothiones with the corresponding diamino compounds. Imidazo[4,5-e] triazine and pyrrolo[2,3-d]imidazole were prepared when the iminothiones were reacted with thiocarbohydrazide and with ethylphenyl acetate, separately. Some of the synthesized compounds exhibited better biological and antitumor activities.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:634–647, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20244

INTRODUCTION

A variety of heterocyclic ring closure reactions with cyanothioformamides [1–3] give rise to imidazole [4], oxazole [5], and thiazole [6,7]. Our interest in the chemistry of cyanothioformamides [8–16] led us to use them in the synthesis of various fused heterocyclic systems [17–26].

Since imidazoles and their fused derivatives are key in many bioactive compounds of both natural and synthetic origins [27] such as histidine, purines, biotin, and hydrantoin; thus, in this investigation different types of fused imidazoles such as imidazo(pyrazine, [1,4]diazocine, quinoxaline, and triazine), naphtho[1,8-*ef*]imidazo[4,5-*b*][1,4] diazipen-9-one, and pyrrolo[2,3-*d*] imidazoles have been synthesized.

Thus cyanothioformamides **I** were prepared [1,20] and reacted by cycloaddition with phenyl and *p*-chlorophenyl isocyanate to produce 1-(phenyl and 4-chlorophenyl)-3-aryl-5-imino-4-thioxoimidazolidine-2-one **II** (Scheme 1).

The imidazolidines **II** contain adjacent imino and thione function in the 4 and 5 positions, which have been shown to be reactive in a number of subsequent ring closure reactions.

Thus, interaction of **IIe,g** with ethylenediamine in boiling ethanol took place easily through elimination of H_2S and NH_3 to afford a product that was expected to have structure **III** (Scheme 2).

However, the infrared spectrum showed the presence of N—H stretching at 3300 cm^{-1}, and the ^1H NMR spectrum of **IVb** revealed the absence of aliphatic protons while **IVa** showed in the aliphatic region the triplet and quartet of C_2H_5—O group only which led to postulate the tautomeric structure **IV** as 1,3-diaryl-4,7-dihydroimidazo[4,5-*b*] pyrazine-2-one. Mass spectrum of **IVb**: at *m/z*, 360, (0.4%), M + 1; 358, (3.4%), M − 1; 127 (100%) base peak, *p*-$Cl{\cdot}C_6H_4{\cdot}NH_2$, 129 (33%) (127:129; 3:1 due to chlorine atoms).

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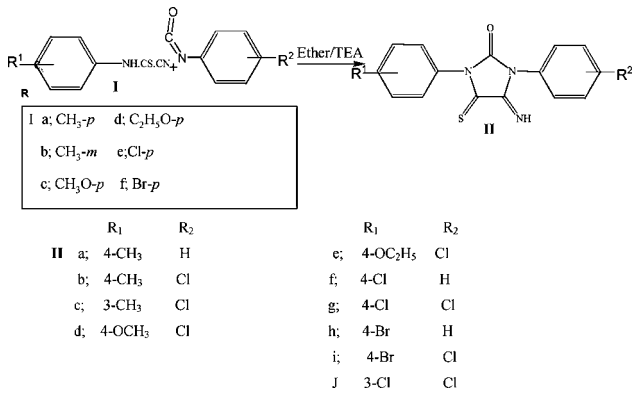
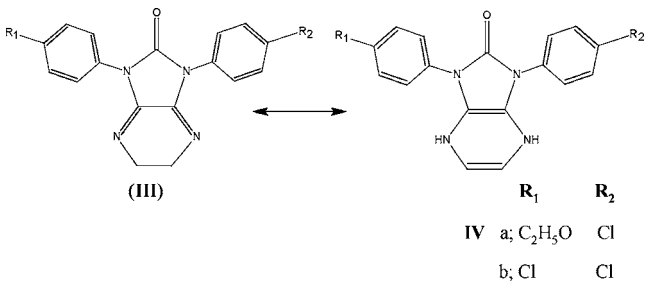


SCHEME 1



SCHEME 2

Similarly, 1,4-diaminobutane was reacted successfully with the iminothiones **IIg** to give **V** as 1,3-di(4-chlorophenyl)-4,5,8,9-tetrahydro-1H-imidazo[4,5-*b*][1,4] diazocin-2-(3H)-one (Fig. 1).

IR spectrum of **V** revealed the presence of the NH stretching at 3300 cm^{-1}. The ^1H NMR spectrum showed broad singlet at 8.9 ppm assigned to NH protons, which disappeared by D_2O. Eight aromatic protons appeared as quartet at 7.3 and 7.5 ppm. Six protons (4 aliphatic, $2 \times CH_2$ and 2 olifinic, —CH=CH—) appeared as multiplet at 3.55–5.35 ppm. Mass spectra of **V** showed at *m/z*, 352, (3.3%), M − Cl.

The authors also studied the reaction between imidazolidineiminothiones **II** and diaminomaleinonitrile where various products could be isolated. Thus, the reaction between equimolar amount of **IIa** and diaminomaleinonitrile was proceeded easily through elimination of H_2S (which could be easily detected) to produce a product that was expected to have structure **VIa** (Fig. 1).

Unfortunately, IR spectra exhibited the absence of νC≡N (which exclude structure **VIa**) and the presence of a broadband at 3300–3100 (νNH, NH_2) and 1710 cm^{-1} (νCO). ^1H NMR of this product exhibited at $\delta = 2.1$ (3H, s, CH_3), 6.7–6.9 (9H, m, Ar H), 8.3 (3H, hump, NH, NH_2), and 8.9 (2H, s, $CONH_2$), both NH, NH_2 and $CONH_2$ were disappeared by D_2O. Mass spectrum revealed M^+ at $m/z = 369$ (3%, $M - H_2O$), 133 (8.5%, *p*-$CH_3 \cdot C_6H_4 \cdot CNO$), 119 (4.9%, C_6H_5NCO), and 127 (100%). These data with elemental analyses demonstrated structure **VIb** for this product.

5-Imino-1,3-di(4-chlorophenyl)imidazolidine-4-thione **IIg** was reacted with diaminomaleinonitrile to produce two products. One of them showed the absence of νC≡N and exhibited elemental and spectral data compatible with **VIc**. The other revealed νC≡N (2225) and νNH (3330) cm^{-1} and was given structure **VII**, which was demonstrated by IR, ^1H NMR, mass spectra, and elemental analyses.

^1H NMR of (**VII**) (δ, ppm): at $\delta = 7.1$–7.3 (8H, q, Ar H), 8.7, 9.1 (3H, 2H; hump, s; NH, NH_2 and $CONH_2$; disappeared by D_2O) and mass spectrum of (**VII**) exhibited at *m/z* 442 (2.5%, M + 1).

The mechanism of formation of **VIb,c** could be rationaled on bases that H_2S and NH_3, which evolved during the reaction, could be added to the cyano groups. In compound **VII**, the thione group was reacted only with one amino group (Fig. 2).

Also, 1,2-diamino-4,5-dibromobenzene, 3,4-diaminotoluene, and 3,4-diaminobenzoic acid were

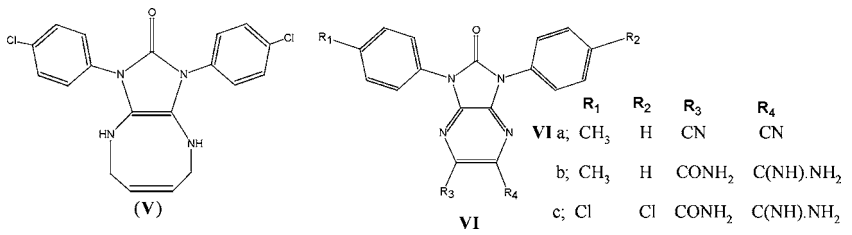


FIGURE 1 Structure of **V** and **VI**.

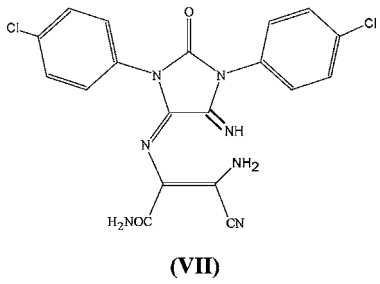


FIGURE 2 Structure of **VII**.

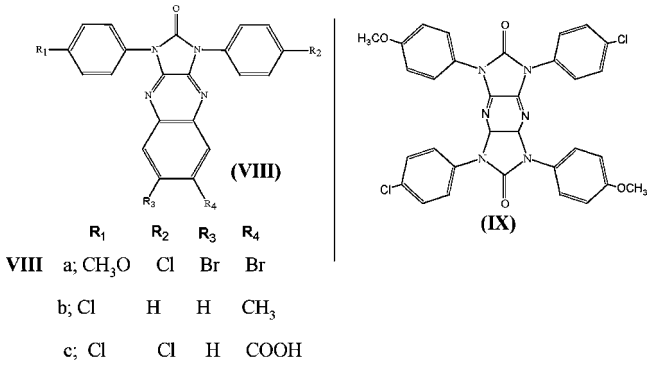


FIGURE 3 Structure of **VIII** and **IX**.

reacted successfully with the iminothiones **IId,f**, and **g**, respectively, through elimination of H_2S and ammonia to yield 2-oxo-1,3-diaryl-1,3-dihydro-2H-imidazo[4,5-*b*]quinoxalines **VIIIa–c**, respectively (Fig. 3).

Mass spectrum of **VIIIa** exhibited M^+ at *m/z* 560 (100% base peak), ^1H NMR spectrum of **VIIIb** showed the expected singlet assigned to the methyl protons, and the 12 aromatic protons appeared as multiplet at 6.5–6.9 ppm. Besides **VIIIa**, a by-product could be isolated which structure was assigned to **IX** as diimidazo [4,5-*b*: 4′,5′-*e*]pyrazine derivative (Fig. 3). The product **IX** could be produced through desulfurization of the iminothione under the reaction conditions to give the corresponding iminocarbene, which then dimerized to produce **IX**. ^1H NMR, at $\delta = 3.85$ (6H, s, 2 × OCH_3), $\delta =$ 6.9–7.3 (16H, 2q, Ar H), and mass spectrum, showed M^+ at *m/z* 624 (1.3%). Formation of **IX** is in complete agreement with the previous findings obtained by Khattak et al. [6] and recently by El-Sharief et al. [14].

In a similar fashion, 1,2-diaminoanthraquinone was reacted with (**IIa, d**, and **e**) to produce 7,9-diaryl-7H,9H,{[9,10]anthraquinone}[6,7-*e*]imidazo[4,5-*b*] pyrazine-8-one **X** (Fig. 4). H_2S could be easily detected throughout the reaction period.

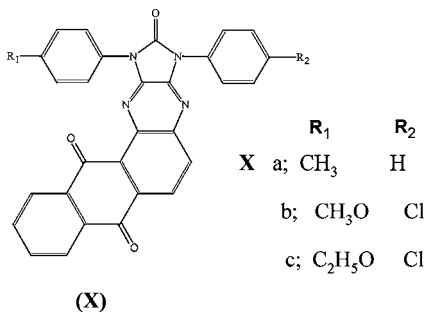


FIGURE 4 Structure of **X**, **XI**, and **XII**.

These products **Xa–c** are sulphur-free and the IR spectra revealed the absence of NH stretching. The ^1H NMR of **Xa** showed the expected singlet peak at 2.3 ppm assigned to the methyl protons. The spectrum of the aromatic protons appeared as a complex pattern between 6.7 and 7.1 ppm. Mass spectrum of **Xb** showed a molecular ion peak at *m/z* 421, 1.2% (M − *p*-Cl·C_6H_4—) with a base peak at *m/z* 238, 100%, 1,2-diaminoanthraquinone; 153, 3.47% *p*-Cl·C_6H_4·NCO, and 149, 0.3% *p*-CH_3O·C_6H_4·NCO.

Similarly, 5,6-diamino-1,10-phenanthroline reacted successfully with the imidazolidineiminothione **IIf** through elimination of H_2S and NH_3 to produce 6-(4-chlorophenyl)-8-phenyl-6H,8H-{[1,10] phenanthrolino}[5,6-*e*]imidazo[4,5-*b*]pyrazine-7-one **XI** (Fig. 5).

The IR measurements of this product showed the absence of NH stretching. Mass spectra of **XI** exhibited M^+ at *m/z* 474(2.47%), 153, 100% (base peak); *p*-Cl·C_6H_4·NCO); 155, 32.9% (3:1) due to the chlorine atom.

A new type of fused imidazoles was achieved by interaction of various imidazolidineiminothiones **II** with 1,8-diaminonaphthalene, which proceeded easily through evolution of H_2S and elimination of NH_3 followed by precipitation of solid.

All of these experiments were found to yield two products, one of them which was precipitated during refluxing was analyzed for structure **XII** as 8,10-diaryl-8H,10H-naphtho[1,8-*ef*]imidazo[4,5-*b*][1,4]diazepin-9-one **XIIa–d** (Fig. 5). IR (no νNH & NH_2; νC=O at 1690, νC=N at 1620 cm^{-1}). Mass spectrum: **XIIa**, at *m/z* 402 (100%, M^+, base peak); **XIIb**, *m/z* = 436 (100%, M^+, base peak).

Fragmentation pattern for mass spectrum of **XIIc** is illustrated in Chart 1; **XIId**, *m/z* = 422 (100%, M^+, base peak). It is obvious that most of these products exhibited a molecular ion peak as base peak through some light on their higher stability. Also, most of the chlorinated compounds showed the percent (3:1) and gave fragments up to M + 5.

The other product was obtained when the reaction mixture was concentrated, which showed analytical and spectral data compatible with the intermediate **XIII** (Fig. 6).

IR measurements of **XIII** exhibited NH stretching underneath the NH_2 stretching at 3360 and 3280 cm^{-1}. ^1H NMR of **XIIId** showed the aromatic protons peak at 6.9–7.3 ppm, whereas the variable NH and NH_2 protons appeared as hump and overlap with the aromatic protons at 7.0–7.3 ppm, which disappeared by D_2O. Mass spectra of **XIIIb**: 453 (1.1% M^+).

All the above-mentioned fused imidazoles were obtained through interaction of the corresponding

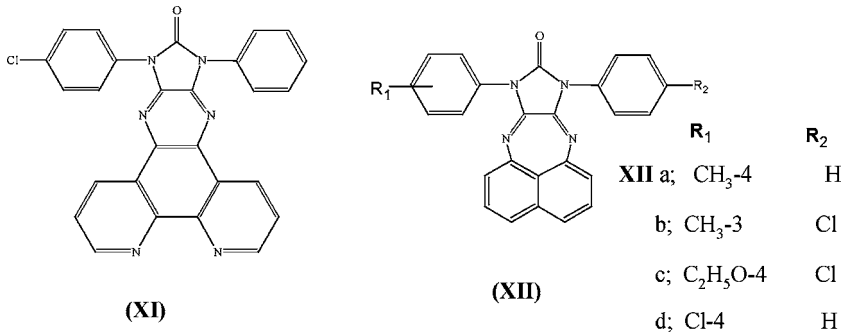


FIGURE 5 Structure **XI** and **XII**.

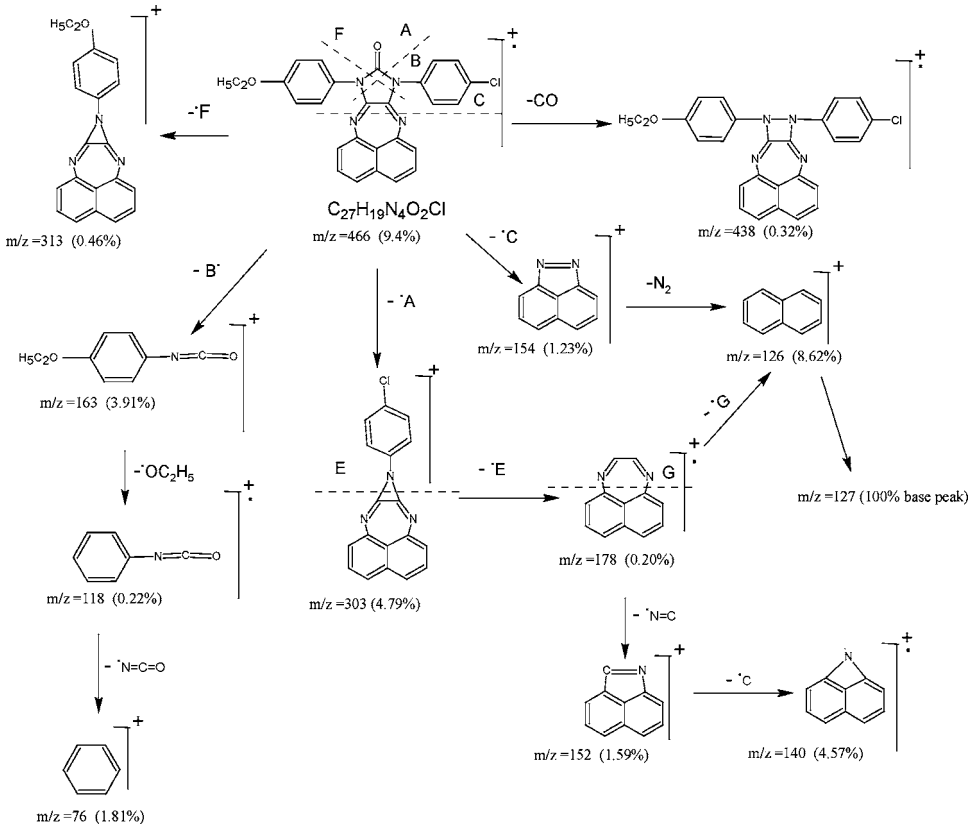


CHART 1 Fragmentation pattern of compound (**XIIc**).

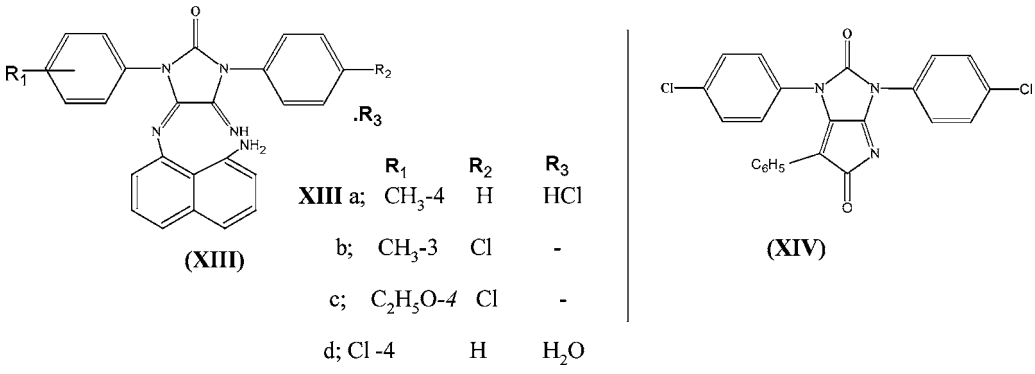


FIGURE 6 Structure of **XIII** and **XIV**.

o-diamino compounds with the iminothione system where the thione group was first reacted and then the imino group to liberate H_2S and NH_3, respectively.

Another type of fused imidazoles could also be synthesized through interaction of the imidazolidinothione with active methylene compounds such as ethyl phenylacetate. The thiocarbonyl group was first reacted with the active methylene group (evolution of H_2S) and then cyclization took place through the imino group.

Thus, interaction of ethyl phenylacetate with imidazolidineiminothiones **IIg** gave a product with elemental and spectral data compatible with structure **XIV** as 1,3-bis(4-chlorophenyl)-6-phenylpyrrolo [2,3-*d*] imidazole-2,5-(1H, 3H) dione. The IR spectrum of **XIV** revealed the absence of NH stretching. The ^{1}H NMR spectrum of the product displayed a multiplet peak at 7.2–7.4 ppm assigned to the aromatic protons. Fragmentation pattern for mass spectrum of **XIV** is illustrated in Chart 2.

Acetyl acetone was selected as another type of active methylene to react with the iminothiones **IIg**, where H_2S could be easily detected throughout the reaction period to give 3-[1,3-bis-(4-chlorphenyl)-5-imino-2-oxo-imidazolidine-4-ylidene]-pentane-2,4-dione **XVa** (Fig. 7). IR (νNH at 3270, νC=O at 1700 and νC=N at 1630 cm^{-1}). The ^{1}H NMR spectrum of the product showed the expected singlet assigned to the two methyl protons. The eight aromatic protons occurred as quartet at 7.1–7.3 ppm. A broad singlet at 8.7 ppm was assigned to the inner NH proton disappeared by D_2O. Mass spectrum of **XVa**: at *m/z* 416 (5.4%, M + 1).

Also, **IIg** was reacted with ethyl cyanoacetate through elimination of H_2S to give **XVb**. The IR spectrum showed the presence of NH stretching at 3300 and CN stretching at 2217 cm^{-1}. The ^{1}H NMR spectrum of **XVb** showed the expected triplet peak assigned to the methyl protons, whereas the methylene protons appeared as quartet at 4.1 ppm. The eight aromatic protons occurred as quartet at 7.3 ppm. A broad singlet at 8.9 ppm was assigned to the inner NH proton disappeared by D_2O.

It is obvious that the thione group in the imine thione system could condense with active methylene in presence of basic catalyst as sodium ethoxide.

Also, cyclization could be achieved with ethyl phenylacetate, and the nonisolation of the cyclic structure with ethyl cyanoacetate may be due to the fact that the authors could not isolate all the products formed in this reaction, but the most isolatable one.

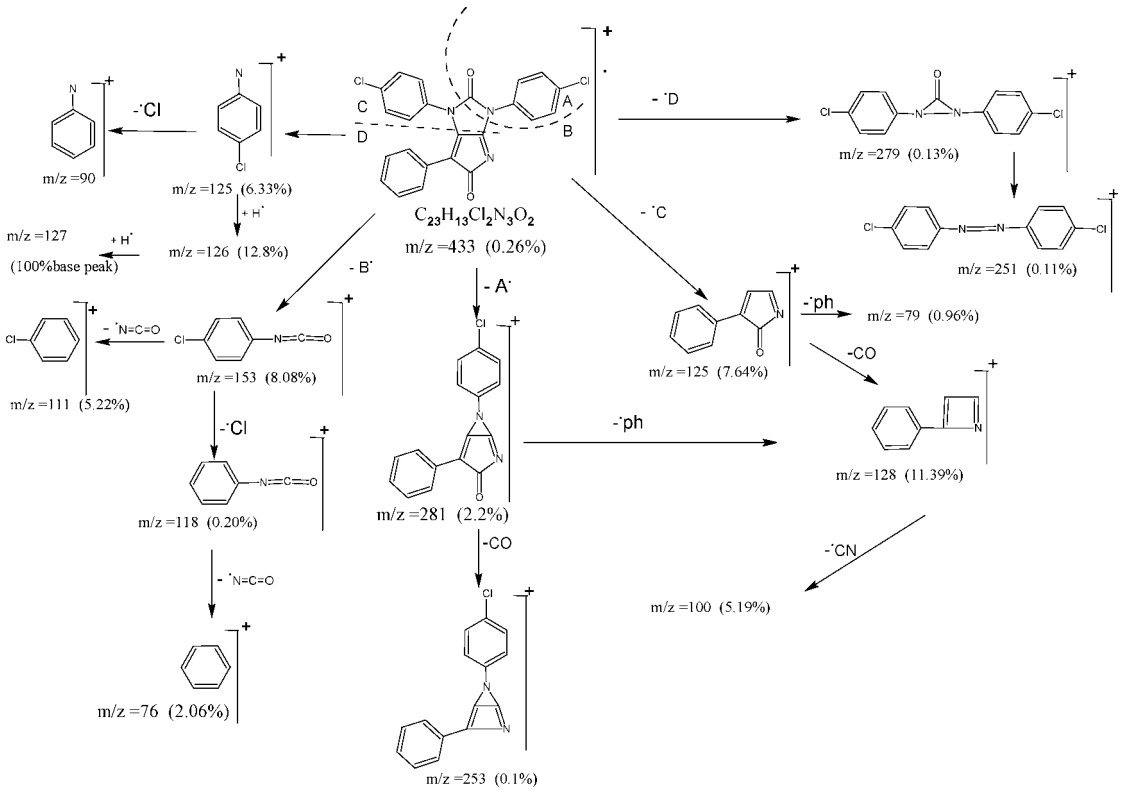


CHART 2 Fragmentation pattern of compound (**XIV**).

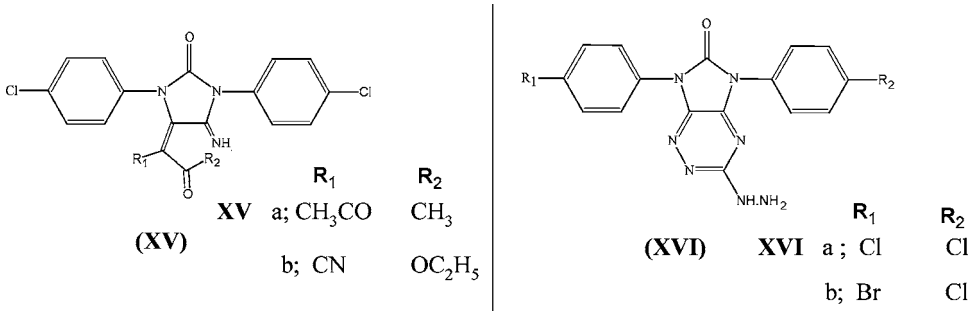


FIGURE 7 Structure of **XV** and **XVI**.

Another type of fused imidazole was obtained from interaction of imidazolidineiminothiones (**IIg** and **i**) with thiocarbohydrazide through elimination of both H_2S and NH_3 to produce 1,3-diaryl-2H-imidazo[4,5-*e*]triazine-2-one **XVIa** and **b** (Fig. 7). IR measurements of the products showed the NH_2 stretching at 3430 and 3350 cm^{-1} and NH stretching at 3200 cm^{-1}. The ^1H NMR spectrum of **XVIa** showed the expected eight aromatic protons as quartet at 7.0–7.3 ppm. A broad singlet occurred at 8.1 ppm assigned to the NH and NH_2 protons, which was disappeared by D_2O. Mass spectra of **XVIb**: at $m/z = 432$ (2.1%, M^+), 153 (100%, base peak *p*-Cl·C_6H_4·NCO).

The authors synthesized some metal complexes from the reaction between imidazolidineiminothiones **II** with metal salts. Thus the reaction of the ligands [**L^1(IId), L^2(IIe)**, and **L^3(IIg)**] with copper(II) and cobalt(II) ions produced a series of mononuclear metal complexes with formulae **[(L)MCl_2]·nH_2O** (Table 1).

The IR spectra (Table 1) of the complexes exhibit a broadband around 3450 cm^{-1} assigned for ν(OH) of water molecules associated with the complexes. Also, IR spectra showed that the absorption of the NH, C=N, and C=S groups in the complexes are shifted to lower frequencies, which indicate that these groups participate in coordinating with Co(II) and Cu(II) cations while the absorption band of the ν(C=O) is not changed.

The magnetic moments of Co(II) complexes, **XVIIa** and **XVIIc** (Table 1), were 4.40 and 4.80 BM, respectively, because of the spin-free value of three unpaired electron, indicating that the Co(II) is high-spin six-coordinate. Also, magnetic moment of Cu(II) complex was 1.82 BM due to the spin one electron.

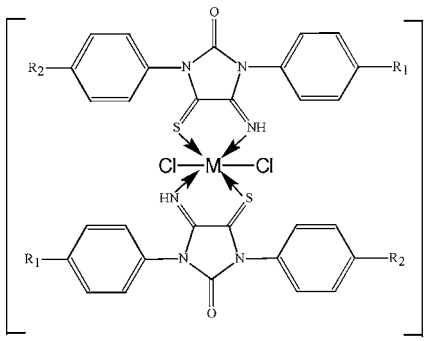
The mass spectral data of the complexes (Table 1) provide good evidence for their molecular formulas. Complexes **XVIIa–c** (Fig. 8) show that the highest mass peak with *m/z*, 844, 855, and 859, respectively, agrees with formula weights of the complexes. The complex **XVIId** shows the highest mass peak with *m/z*, 814, due to formula weight M − 51.5.

On the basis of IR, mass spectral data, and magnetic moments, the suggested structure of the mononuclear complexes **XVII** is shown below.

Reactions of imidazolidineiminothiones **II** with amines and hydrazines (one mole and excess) were studied [15]. In this investigation, another type of (amine, hydrazine, and sulpha) derivatives were selected. Thus α,α-diamino-*p*-xylene was reacted with **IIg** hopping to obtain a bis-imidazol of type **XVIII** (Fig. 9), but instead, equimolar amounts were reacted, followed by oxidation of the terminal amino

TABLE 1 IR, Mass Spectral Data, and Magnetic Moments of **XVII**

Complex	*IR Spectral Band (cm^{-1}) νNH νCO νC=N νC=S*	*Magnetic Moment (BM)*	*Mass Spectral Data (m/z) Found (Calc.)*
XVIIa $[(L^1)_2CoCl_2]3.5H_2O$	3310, 1730, 1520, 1390, 1100 (3350) (1730) (1590) (1450, 1170)	4.40	884 (884)
XVIIb $[(L^1)_2CuCl_2]1.5H_2O$	3360, 1730, 1520, 1380, 1190 (3400) (1730) (1590) (1430, 1150)	1.82	855 (852.5)
XVIIc $[(L^2)_2CoCl_2]0.5H_2O$	3400, 1730, 1500, 1410, 1180 (3450) (1730) (1570) (1460, 1200)	4.80	859 (857.7)
XVIId $[(L^3)_2CuCl_2]$	3260, 1750, 1500, 1420, 1110 (3370) (1725) (1585) (1440, 1170)	–	814(M − 18) (832)



	M	R_1	R_2	n
XVII	a; Co	CH_3O	Cl	3.5 H_2O
	b; Cu	CH_3O	Cl	1.5 H_2O
	c; Co	C_2H_5O	Cl	0.5 H_2O
	d; Cu	Cl	Cl	--

(XVII)

FIGURE 8 Structure **XVII**.

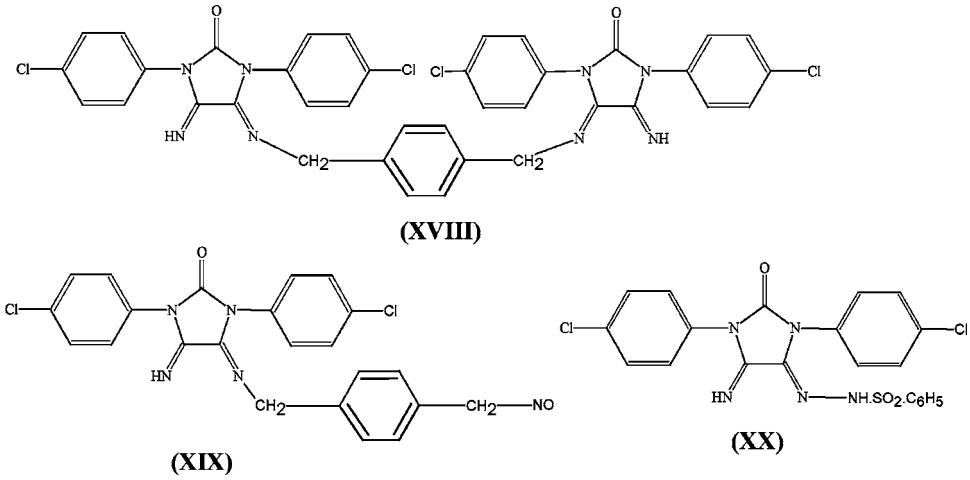
group to produce 1,3-bis-(4-chlorophenyl)-4-imino-5-(4-nitrosomethyl-benzylimino)imidazolidine-2-one **XIX** (Fig. 9).

The ^{1}H NMR spectrum of the product was very informative and proved the structure of the isolated **XIX**. Thus the evidence of the assignment was based on the appearance of the singlet peak at 3.7 ppm corresponding to the two methylene protons α to the nitroso group. There was also another singlet occurred at 3.5 ppm assigned to the other two methylene protons adjacent to the imino group. The NH proton appeared as a hump at 8.9 and disappeared by D_2O and at $\delta = 6.9$–7.1 (12H, m, Ar H). Mass spectrum of **XIX** revealed at $m/z = 483$ (2.4%, $M + H_2O$); 466 (100%, base peak, $M + 1$).

Benzenesulfonyl hydrazide was also allowed to react with the iminothiones **IIg**, where H_2S could be easily detected through the reaction time. The isolated product was analyzed for structure **XX** (Fig. 9) as 4-(phenylsulfonyl)hydrazono-1,3-bis(4-chlorophenyl)-5-iminoimidazolidin-2-one.

Since imidazoles have various activities as mentioned above [27], and sulfonamides have been reported to exhibit antimicrobial, antifungal [28], insulin releasing, carbonic anhydrase inhibitory [29], anti-inflammatory [30], and antitumor properties [31], the authors decided to couple both in one nucleus hopping to obtain products with better activities. Thus, interaction of **II** with sulphadiazine, sulphathiazole, and sulphacetamide-furnished products that revealed elemental and spectral data compatible with structure **XXI** as 4-(1,3-diaryl-5-imino-2-oxoimidazolidin-4-ylideneamino)-benzenesulfonamide derivatives (Fig. 10).

^{1}H NMR spectrum of **XXIc** showed all the expected signals. Thirteen aromatic protons occur as multiplet between 6.9 and 7.2 ppm. Two singlets at 2.3 and 2.5 ppm, each integrating for three protons, were assigned to the methyl attached to phenyl group and methyl in the acetyl group, respectively. Two broad singlets at 8.5 and 9.1 ppm were assigned to

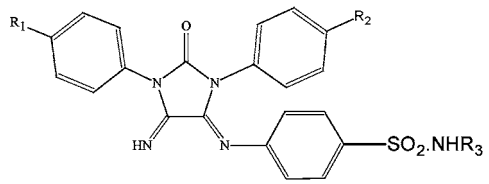


(XVIII)

(XIX)

(XX)

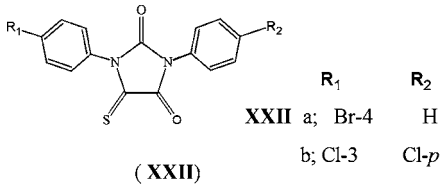
FIGURE 9 Structure of **XVIII**, **XIX**, and **XX**.



(XXI)

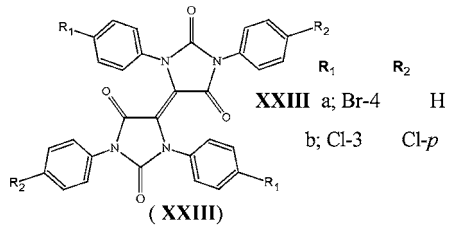
	R_1	R_2	R_3
XXI a;	CH_3	H	2-pyrimidinyl
b;	CH_3	H	2-thiazolyl
c;	CH_3	H	acetyl
d;	Cl	Cl	2-pyrimidinyl

FIGURE 10 Structure of **XXI**.



(**XXII**)

	R_1	R_2
XXII a;	Br-4	H
b;	Cl-3	Cl-*p*



(**XXIII**)

	R_1	R_2
XXIII a;	Br-4	H
b;	Cl-3	Cl-*p*

FIGURE 11 Structure of **XXII** and **XXIII**.

the NH and SO_2NH protons, which were disappeared by D_2O.

Imidazolidine iminothiones **IIh,j** were subjected to imine hydrolysis by dil HCl/EtOH to produce 4-thioxoimidazolidine-2,5-diones **XXIIa,b** (Fig. 11). The IR spectra showed the disappearance of NH stretching.

Interaction of these 4-thioxoimidazolidinones **XXIIa,b** with copper turnings in *p*-xylene furnished copper sulfide with sulfur-free products which their elemental and spectral data were compatible with structure **XXIII** as bis-imidazolidine-2,5-diones.

The IR spectrum showed the presence of C=O and C=C stretching at 1710 and 1600 cm^{-1}, respectively.

BIOLOGICAL ACTIVITY

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

Antimicrobial Activity

Compounds **IVa, V, VIc, VIIIa, XIIa, XIIId, XIV, XVa, XVIIb, XVIId, XX, XXIa,** and **XXIIb** were tested for their antimicrobial activity by the *diffusion agar technique* using the gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus* and the gram-negative bacteria *Escherichia coli* and *Salmonella typhi*. The results are summarized in Table 2.

Most of the synthesized compounds were found to possess various antimicrobial activities toward all the organisms used. Imidazopyrazine **VIc** was found to possess the highest antimicrobial activity against *S. aureus*, *E. coli*, and *S. typhi*. Imidazopyrazine **IVa**, 1,3-bis(4-chlorophenyl)imidazolidine-2-one derivatives **XVa** and **XX**, also **XXIa**, which have sulphadiazine moiety and copper complex **XVIIb**, were found to possess antimicrobial activities against most of the microorganisms used.

Antifungal Activities

The selected compounds were also tested for their antifungal activity using *Aspergillus flavus* and *Aspergillus niger*. Some of the synthesized compounds were found to possess antifungal activities toward the microorganisms used, and the results are summarized in Table 3.

The copper complexes (**XVIIb** and **d**) exhibited higher activities. Imidazolidine containing sulphadiazine **XXIa** or sulphathiazole **XXIb** moieties and imidazopyrazine with two chlorine atoms (**VIc**) showed better activity. Compounds **IVa, VIIIa, XIIId,** and **XVa** were also found to possess antifungal activities against the microorganisms used.

ANTITUMOR ACTIVITY OF SOME OF THE SYNTHESIZED COMPOUNDS

Antitumor activity was estimated at Cairo University, National Cancer Institute, Cancer Biology Department, Pharmacology Unit. The results are summarized in Table 4.

TABLE 2 Antimicrobial Screen of the Newly Synthesized Compounds

	Test Organisms											
	Gram-positive						*Gram-negative*					
	Bacillus subtillus			*Staphylococcus aureus*			*Escherichia coli*			*Salmonella typhi*		
Samples	*1%*	*2.5%*	*5%*	*1%*	*2.5%*	*5%*	*1%*	*2.5%*	*5%*	*1%*	*2.5%*	*5%*
IVa	+	+	++	++	+++	+++	++	++	+++	+	++	+++
V	−	−	−	−	−	−	−	−	−	−	−	−
VIc	++	++	++	+++	+++	+++	++	++	+++	+++	+++	++++
VIIIa	−	−	−	−	−	−	−	−	−	−	−	−
XIIa	−	−	−	−	−	−	−	−	−	−	−	−
XIIId	−	+	+	−	+	+	−	+	+	−	+	+
XIV	+	+	+	+	+	+	+	+	+	+	+	+
XVa	++	++	+++	+	++	++	+	++	++	+	++	++
XVIIb	+	++	++	+	++	++	+	++	++	+	+	++
XVIId	−	−	−	−	−	+	−	−	+	−	+	+
XX	+	+	++	+	++	++	+	++	++	+	+	++
XXIa	+	++	++	+	+	++	−	+	+	+	++	++
XXIb	+	+	+	−	+	+	+	+	+	+	+	++

St. = Reference standard; chloramphenicol was used as standard antibacterial agent. The test was done using the diffusion agar technique. Well diameter. 1 cm. . . (100 μL of each concentration 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.

TABLE 3 Antifungal Screen of the Newly Synthesized Compounds

	Test Organisms					
	Aspergillus flavus			*Aspergillus niger*		
Samples	*1%*	*2.5%*	*5%*	*1%*	*2.5%*	*5%*
IVa	−	−	+	−	+	+
V	−	−	−	−	−	−
VIc	+	+	++	−	+	+
VIIIa	−	+	++	−	−	−
XIIa	−	−	−	−	−	−
XIIId	−	−	+	−	−	−
XIV	−	−	−	−	−	−
XVa	−	−	−	−	+	+
XVIIb	+	+	++	+	+	+
XVIId	+	++	++	+	+	+
XX	−	−	+	−	+	+
XXIa	+	+	++	+	+	+
XXIb	−	−	+	+	+	++

St. = Reference standard; grisofluvine was used as a standard antifungal agent. The test was done using the diffusion agar technique. Well diameter. 1 cm. . . (100 μL of each concentration 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.

Screening Test

Antitumor activity: (In Vitro Study). Reagent

1. RPMI 1640 medium (Sigma)
2. Ehrlich Ascites Carcinoma cells (EAC) suspension (2.5×10^5/mL)
3. Trypan blue dye: A stock solution was prepared by dissolving 1 g of the dye in (100-mL) distilled water. The working solution was then prepared by diluting 1 mL of the stock solution with g mL of distilled water. The stain was then used for staining the dead EAC cells.

The compounds tested were **IVb, VIb, VIc, XIIIa, XIIId, XVb, XVIId, XXIa,** and **XXIb**.

Procedure

1. EAC cells were obtained by needle aspiration of ascetic fluid from the preinoculated mice under aseptic conditions [32].
2. The cells were 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 [33].

TABLE 4 Antitumor Activity of Some of the Synthesized Compounds Using (EAC)

	% Inhibition of Cell Viability (μg/mL)		
Sample No.	*100*	*50*	*25*
IVb	60	40	10
VIb	100	90	80
VIc	95	90	80
XIIIa	50	40	20
XIIId	90	80	80
XVb	100	90	70
XVIId	100	100	100
XXIa	50	20	10
XXIb	100	80	70

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 of sterile test tubes, 0.1 mL of tumor cells suspension, 0.8 mL of 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 tubes were incubated at 37 for 2 h. Trypan blue [33] exclusion test was carried out to calculate the percentage of nonviable cells. Compounds producing more than 70% nonviable cells are considered active [34].

$$\%\ \text{of nonviable cells} = \frac{\text{No. of nonviable}}{\text{No. of cells}} \times 100$$

The results of antitumor activity for the synthesized compounds indicated that compounds **VIb, VIc, XIIId, XVb, XVIId**, and **XXIb** showed a significant activity toward Ehrlich ascites carcinoma tumor cells (in vitro). The compound that exhibited the highest activity (**XVIId**) is the one of copper complexes with the ligand (imidazolidine iminothione) having two chlorine atoms. Imidazopyrazine with alkyl group (**VIb**) also showed higher activity. Compounds having chlorine atom (**VIc**), (**XIIId** and **XVb**), or methyl and thiazolyl groups (**XXIb**) were found to have more powerful activity than the other compounds.

EXPERIMENTAL

All melting points are uncorrected and determined on digital Gallen Kamp MFB-595 instrument. IR spectra (KBr) (cm^{-1}) were measured on a Shimadzu 440 spectrometer. ^{1}H NMR spectra (delta, ppm) were obtained in dimethyl sulfoxide on a Varian Gemini 200 (200 MHz) spectrometer, using TMS as an internal standard; chemical shifts are reported as δ units. Mass spectra (m/z, %) were obtained on GC MS-QP 100 Ex mass spectrometer at 70 eV. Elemental analyses were carried out at Micro Analytical Unit, Cairo University, Cairo, Egypt. Found: C, H, N for all compounds were within $\pm$0.4 from the theoretical value.

Cyanothioformamides **(Ia–f)**

Compounds (**Ia–e**) were previously prepared [1,20], and the *p*-bromo derivative (**If**) was similarly prepared. *p*-Bromophenylcyanothioformamide **If**; yellow crystals, m.p. 126°C from (chloroform/*n*-hexane) (55% yield), IR: νNH (3200), νCN (2217); ^{1}H NMR: 6.7 (4H, q, *p*-substituted), 8.3 (1H, hump, NH, disappeared by D_2O).

Imidazolidineimnothiones **(IIa–j)**

Compounds (**IIa–g**) were previously prepared [16], and **IIh–j** were similarly obtained: *1-Phenyl-3-(4-bromophenyl)-5-imino-4-thioxoimidazolidine-2-one* (**IIh**). Pale yellow crystals. m.p. 167°C from ethanol (45%), IR: absence of νC≡N and the presence of νNH (3250), νCO (1700), and νCS·N < (1490.1150); ^{1}H-NMR, 6.8–7.0 (9H, m, Ar H), 8.4 (1H, s, NH, disappeared by D_2O).

1-(4-Chlorophenyl)-3-(4-bromophenyl)-5-imino-4-thioxoimidazolidine-2-one (**IIi**). Pale yellow crystals, m.p. 196°C from ethanol (45%), ^{1}H NMR: 6.9–7.1(8H, q, Ar H), 8.5 (1H, s, NH, disappeared by D_2O).

1-(4-Chlorophenyl)-3-(3-chlorophenyl)-5-imino-4-thioxoimidazolidine-2-one (**IIj**). Pale yellow crystals, m.p. 141°C from ethanol (40%); IR: no νCN and νNH (3300), νCO (1710); MS, M^+ at m/z 349(100%; base peak).

General Procedure for the Reactions Between Imidazolidineiminothiones **(II)** *and the Diamino Compounds*

A mixture of **II** (0.005 mole) and the requisite diamine (0.006 mole) in ethanol (25 mL) was refluxed

for 5 h (till H_2S ceased), and the reaction mixture was then cooled and decomposed on to cold dil HCl.

1. *Ethylenediamine and* **IIe** gave a solid, which recrystallized from ethanol to give **IVa** m.p. 235°C (25%), IR: νNH (3300), νCO (1680); ^{1}H NMR: 1.1 (3H, t, CH_3), 4.1(2H, q, CH_2), 7.2–7.4 (10H, m, Ar H), 8.1 (2H, s, 2NH, disappeared by D_2O). *Ethylenediamine and* **IIg** furnished a product that recrystallized from ethanol: water (1:1) to give **IVb**, m.p. 295°C (15%), IR: νNH (3320), νCO (1690): ^{1}H NMR: 7.3–7.5 (10H, q, 2 *p*-substituted + CH = CH underneath the quartet), MS: 359 (0.4) M + 1, ($C_{17}H_{12}N_4OCl_2$), 358 (3.4) M−1, 127 (100; base peak) *p*-Cl·C_6H_4·NH_2, 129 (33), (127:129 – 3:1 due to chlorine atoms).

2. *1,4-Diaminobutane and* **IIg** gave a solid that crystallized from ethanol:water (1:1) to give **V**, m.p. 280°C (17%), IR: NH (3300), CO (1700); ^{1}H NMR: 3.55–5.35 (6H, m, 2 × CH_2 + —CH=CH—), 7.3–7.5 (8H, q, Ar H), 8.9 (2H, broad singlet, 2NH, disappeared by D_2O), MS: 351 (3.3) M − Cl, ($C_{19}H_{16}N_4OCl_2$) 353 (0.9), 354 (1.3), 153 (6.5) *p*-Cl·C_6H_4·NCO, 127 (100, base peak) *p*-Cl·C_6H_4·NH_2, 129 (30) (127:129 – 3:1 due to chlorine atoms).

3. *Diaminomaleinonitrile and* **IIa** gave a solid that recrystallized from ether/*n*-hexane to give **VIb**, m.p. 280°C decomp. (20%), IR showed the absence of νC≡N and the presence of νNH_2 and NH (3300–3100), νCO (1710), ^{1}H NMR: 2.1 (3H, s, CH_3), 6.7–6.9 (9H, m, Ar H), 8.3 (3H, hump, NH & NH_2), 8.9 (2H, s, CO N H_2), both NH, NH_2, and $CONH_2$ were disappeared by D_2O. MS: 369 (3) M − H_2O, ($C_{20}H_{17}N_7O_2$) 370 (0.3), 368 (8.7), 367 (1.3), 133 (8.5) *p*-CH_3·C_6H_4·NCO, 119 (4.9) C_6H_5NCO and 127 (100) *p*-Cl·C_6H_4·NH_2. *Diaminomaleinonitrile and* **IIg** precipitated a product during reflux, which filtered off and recrystallized from ethanol to give **VIc**, m.p. 280°C decomp. (25%). IR: (no νC≡N) and 3350–3150 (νNH, νNH_2) 1710 (νCO); ^{1}H NMR: 6.9–7.1 (8H, q, Ar H), 8.7 (3H, hump. NH, NH_2), 9.3 (2H, s, CO NH_2), both NH, NH_2, and $CONH_2$ disappeared by D_2O·MS: ($C_{19}H_{13}N_7O_2Cl_2$), 396 (24.1) M − $HCONH_2$, 396 (77.6), 153 (72.1) *p*-Cl·C_6H_4·NCO, 127 (50) *p*-Cl·C_6H_4·NH_2 and 64 (100). Concentration of the alcohol mother liquid furnished a product that recrystallized from ether/*n*-hexane to give **VII**, m.p. 140°C (20%). IR: νC≡N (2225), νNH (3330), ^{1}H NMR, 7.1–7.3 (8H, q, Ar H), 8.7, 9.1 (3H, 2H, 2s, NH, NH_2 and $CONH_2$, disappeared by D_2O), MS: 442 (2.5, M + 1), ($C_{19}H_{13}N_7O_2Cl_2$), 443 (4.7, M + 2), 444 (6.1, M + 3), 153 (18.7, *p*-Cl·C_6H_4·NCO) and 127 (100%, *p*-Cl·C_6H_4·NH_2).

4. i. *1,2-Diamino-4,5-dibrombenzene and* **IId** furnished a solid that recrystallized from ethanol to give **VIIIa**, m.p. 225°C (35%). IR: (no νNH, NH_2, or CS), νCO(1690) and νC=N(1630); ^{1}H NMR: 4.1 (3H, s, OCH_3), 6.9 (10H, m, Ar H), MS: 560 (100, M^+, base peak, $C_{22}H_{13}O_2ClBr_2$), 559 (26.4, M − 1), 561 (33.1, M + 1), 562 (52.3, M + 2), 563 (15.9, M + 3), 564 (2.8, M + 4). Concentration of the alcohol mother liquid of experiment (4-i) furnished **IX**, m.p. 270°C from ethanol (15%). ^{1}H NMR, 3.85 (6H, s, 2 × OCH_3), 6.9–7.3 (16H, 2q, Ar H), MS (%): 624 (1.3, M^+, $C_{32}H_{22}N_6O_4Cl_2$), 625 (0.9, M + 1), 626 (2.3, M + 2), 627 (1.8, M + 3), and 457 (100, base peak).

ii. *3,4-Diaminotoluene and* **IIf** gave a product that recrystallized from ethanol to give **VIIIb**, m.p. 215°C (30%). ^{1}H NMR: 2.1 (3H, s, CH_3), 6.5 – 6.9 (12H, m, Ar H); MS: M^+, 386 (7.0), ($C_{22}H_{15}N_4OCl$) and 153 (100. base peak, *p*-ClC_6H_4·NCO).

iii. *3,4-Diaminobenzoic acid and* **IIg** yield a solid that recrystallized from ethanol to give **VIIIc**, m.p. 225°C, (25%). IR: no νNH, NH_2, νOH (COOH) broadband (3100–2500), νCO (1690, 1650) and νC=N (1630) ^{1}H NMR: 9.3 (1H, s, OH, disappeared by D_2O), 6.7–6.9 (11 H, m, Ar H).

5. *1,2-Diaminoanthraquinone and* **IIa** precipitated a solid during reflux, which collected and recrystallized from ethanol to give **Xa**, m.p. 220°C (45%). IR, absence of νNH, NH_2 and the presence of νCO (1720, 1680), νC=N (1630); ^{1}H NMR, 2.3 (3H, s, CH_3), 6.7–7.1 (15H, m, Ar H).

1,2-Diaminoanthraquinone and **IId** precipitated a product during reflex, which was filtered off and recrystallized from ethanol to give **Xb** m.p. 250°C (55%). ^{1}H NMR: 3.9 (3H, s, OCH_3), 6.7–7.2 (14H, m, Ar H), MS: ($C_{30}H_{17}N_4O_4Cl$) at *m/z* 421 (1.2, M − *p*-Cl·C_6H_4), 238 (100, base peak, 1.2-diaminoanthraqunone), 153 (3.5, *p*-Cl·C_6H_4·NCO) and 149 (0.3, *p*-CH_3O·C_6H_4·NCO).

1,2-Diaminoanthraquinone and **IIe** furnished a product that recrystallized from ethanol to give **Xc**, m.p. 260°C (60%). IR: νCO (1730, 1685), νC=N (1630); ^{1}H NMR: 1.2 (3H, t, CH_3), 4.1 (2H, q, CH_2), and 6.6–7.2 (14H, m, Ar H).

6. *5,6-Diamino-1.10-phenanthroline* and **IIf** precipitated a product, which was collected and recrystallized from ethanol to give **XI**, m.p. 245°C (35%). ^{1}H NMR revealed the aromatic protons as multiplet at δ = 7.1–7.4 ppm. MS: 474 (2.47, M^+, $C_{27}H_{15}N_6OCl$), 475 (1.19, M + 1), 476 (1.25, M + 2), 477 (0.71, M + 3), 478 (0.61, M + 4), 153 (100%, base peak, *p*-Cl·C_6H_4·NCO), and 119 (18.41, C_6H_5·NCO).

7. *1,8-Diaminonaphthoquinone and* **IIa** precipitated a product during reflux, which was collected and recrystallized from dioxane to give **XIIa** m.p. >300°C, (25%) IR: showed no νNH or NH_2 and νCO (1690), νC=N (1620), ^{1}H NMR: 2.5 (3H, s, CH_3), 6.7–7.2 (15H, m, Ar H). MS: 402 (100, M^+, base peak, $C_{26}H_{18}N_4O$), 403 (31.9, M + 1), 404 (4.32, M + 2), 405 (0.6, M + 3). Similarly, **XIIb**, m.p. > 300°C from

dioxane (30%), ^{1}H NMR: 2.6 (3H, s, CH_3), 6.9–7.3 (14H, m, Ar H); MS: 436 (100, M^+, base peak, $C_{26}H_{17}N_4OCl$), 437 (33.95, M + 1), 438 (39.8, M + 2), 439 (10, M + 3), 440 (1.6, M + 4). **XIIc**, m.p. > 300°C from dioxane, (33%), ^{1}H NMR: 1.2 (3H, t, CH_3), 4.1 (2H, q, CH_2), 6.9–7.3 (14H, m, Ar H). MS: 466(9.4, M^+, $C_{27}H_{19}N_4O_2Cl$), 127 (100). **XIId**, m.p. > 300°C from dioxane, (25%), MS: 422 (100, M^+, base peak, $C_{25}H_{15}N_4OCl$), 423 (29.9, M + 1), 424 (38.0, M + 2), 425 (10.4, M + 3), 426 (1.3, M + 4), and 427 (0.4, M + 5).

Concentration of the alcohol mother liquid of these experiments then treated with cold dil HCl (if necessary) furnished, **XIIIa**, m.p. >300°C from ethanol (20%), IR: νNH and NH_2 (broadband 3360–3280), νCO (1680) and νC=N (1620); MS: 455(0.93, M + HCl, $C_{26}H_{21}N_5O{\cdot}HCl$), 418(1.7, M − 1), and 334 (100, base peak). **XIIIb**, m.p. > 300°C from ethanol (25%), ^{1}H NMR: 2.3(3H, s, CH_3), 7.0–7.2 (14H, m, Ar H), 8.3–8.4 (3H, broad singlet, NH and NH_2, disappeared by D_2O), MS: 453 (1.1, M^+, $C_{26}H_{20}N_5OCl$), 452 (2.85, M − 1), 454 (0.74, M + 1), 455(0.39, M + 2), 127 (100, base peak). **XIIIc**, m.p. >300°C from ethanol (20%), ^{1}H NMR: 2.2 (3H, t, CH_3), 4.2 (2H, q, CH_2), 7.1–7.3 (14H, m, Ar H), 7.3–7.4 (3H, brood s, NH and NH_2, disappeared by D_2O). MS: 483 (1.15, M^+, $C_{27}H_{22}N_5O_2Cl$), 127 (100). **XIIId**, m.p. >300°C from ethanol (25%); MS: 457 (1.43, M + H_2O, $C_{25}H_{18}N_5OCl{\cdot}H_2O$), 439 (0.29, M^+) 438 (0.89, M − 1), 440 (0.32, M + 1), 166 (100).

Interaction of Imidazolidineiminothions (**IIg** *) with Active Methylene Compounds*

1. *Pyrollo [2.3-d] imidazole derivative* (**XIV**). To a solution of **IIg** (0.005 mole) and ethylphenyl acetate (0.005 mole) in absolute ethanol (30 mL), sodium ethoxide (0.005 mole) was added and the mixture was refluxed for 7 h. Decomposition of the reaction mixture with cold dil HCl furnished a product that crystallized from ethanol to give **XIV**, m.p. 230°C (25%), IR: no ν(NH, CS.N), νCO (1690), νC=N (1635) and νC=C (1600); ^{1}H NMR exhibited the aromatic protons at δ = 7.2–7.4 ppm. MS: 433(0.3, M^+ $C_{23}H_{13}N_3O_2Cl_2$), 434 (0.2, M + 1) 432 (0.7, M − 1), 153 (8, *p*-Cl·C_6H_4·NCO), and 127 (100).

2. *Acetylacetone and* **IIg** gave **XVa**, m.p. 81°C, from ethanol (30%), ^{1}H NMR: 2.4 (3H, s, CH_3-Ar), 2.7 (3H, s, CH_3—CO), 7.1–7.3 (8H, m, Ar H), and 8.7 (1H, broad s, NH, disappeared by D_2O); MS: 416 (3.2, M + 1, $C_{20}H_{15}N_3O_3Cl_2$), 417 (5.4, M + 2), 418 (42.7, M + 3), 419 (29.3, M + 4), and 127 (100, base peak, *p*-Cl·C_6H_4·NH_2).

3. *Ethylcyano acetate and* **IIg** gave **XVb**, m.p. 130°C from ethanol (25%), MS: 275 (36%, M − *p*-Cl·C_6H_4·NCO), 153 (8%, *p*-Cl·C_6H_4·NCO), and 127 (100%, base peak, *p*-Cl·C_6H_4·NH_2).

*Imidazo[4,5- e]triazine-2-one (***XVIa,b***)*

1. A mixture of thiocarbohydrazide (0.005 mole) and **IIg** (0.005 mole) in absolute ethanol (25 mL) was refluxed for 5 h (H_2S must be ceased). The product that precipitated was filtered off, washed with ethanol, and recrystallized from ethanol to give **XVIa**, m.p. 250°C (45%). IR: NH_2(3430, 3350), NH (3200), CO (1690), and C=N (1630); MS: 388 (5.4, M + 1, $C_{16}H_{11}N_7OCl_2$), 389 (19.1, M + 2), 390 (16.2, M + 3), 391 (13.6, M + 4), 392 (10.8, M + 5), and 153 (100, base peak, *p*-Cl·C_6H_4·NCO).

2. In a similar fashion, thiocarbohydrazide and **IIi** gave **XVIb**, m.p. 195°C from ethanol (40%), ^{1}H NMR: 7.1–7.3 (8H, m, Ar H) and 8.3 (3H, hump, NH and NH_2, disappeared by D_2O).

Preparation of Metal Complexes **XVII**

Ethanolic solutions of metal chloride and the ligand were mixed in a molar ratio 2:1 (L:M) and refluxed for 2–3 h. The resulting precipitates were filtered, washed with ethanol and then with ether, and finally air-dried. The complexes are stable in solid state, and soluble in acetone, ethanol, and dimethylformamide.

1,3-Bis(4-chlorophenyl)-4-imino-5-(4-nitrosomethyl benzylimino)imidazolidine-2-one **XIX**. A mixture of α,α-diamino *p*-xylene (0.005 mole) and **IIg** (0.01 mole) was dissolved in absolute ethanol (25 mL) and refluxed for 5 h (H_2S must be ceased). The product that precipitated was filtered off and recrystallized from ethanol to give **XIX**, m.p. 265°C (35%). IR: NH (3250), CO (1690), and C=N (1630), MS (%): 483 (2.4, M + H_2O), 466 (100, base peak, M + 1, $C_{23}H_{17}N_5O_2Cl_2$), 467 (29.19, M + 2), 468 (98.69, M + 3), 469 (27.41, M + 4), 470 (3.75, M + 5), and 153 (3.72, *p*-Cl·C_6H_4·NCO).

4-(Phenylsulphonyl)hydrazono-1,3-bis(4-chlorophenyl)-5-iminoimidazolidine-2-one **XX**. A mixture of benzenesulphonyl hydrazide (0.005 mole) and **IIg** (0.005 mole) was reacted as above to give **XX**, m.p. 240°C from benzene (40%). IR: NH (3250), CO (1695), and SO_2—N (1450, 1170), ^{1}H NMR: 6.1–7.4 (13H, m, Ar H), 8.5 and 8.9 (2H, 2 humps, 2 NH, disappeared by D_2O), MS (%): ($C_{21}H_{15}N_5O_3SCl_2$); 334 (2.16, M − *p*-Cl·C_6H_4·NCO), 153 (42.76, *p*-Cl·C_6H_4·NCO), 157 (7.52, $C_6H_5SO_2NH_2$), and 77 (100, base peak, C_6H_5—).

Interaction of imidazolidineiminothiones **II** *with sulpha derivatives to give* **XXIa–d**. A solution of **IIa** (0.005 mole) and sulphadiazine (0.005 mole) in absolute ethanol (30 mL) was refluxed for 5 h.

The product that precipitated was filtered off and recrystallized from ethanol to give **XXIa**, m.p. 245°C (55%). IR: NH (3300–3250), CO (1690), C=N (1630); ^{1}H NMR: 2.2 (3H, s, CH_3), 6.9–7.1 (16H, m, Ar H), 8.3 (1H, s, NH), and 9.1 (1H, s, SO_2NH), both NH were disappeared by D_2O. MS: ($C_{26}H_{21}N_7O_3S$); 263 (0.3, M-sulphadiazine); 265 (2.04), 250 (5.31, sulphadiazine), 251 (3.98), 149 (100), 133 (34.56, *p*-$CH_3{\cdot}C_6H_4{\cdot}$NCO), and 119 (10.9; C_6H_5NCO).

Sulphathiazole and **IIa** were similarly reacted to produce **XXIb**, m.p. 220°C, from ethanol (35%). ^{1}H NMR: 2.2 (3H, s, CH_3), 6.8–7.1 (15H, m, Ar H), 8.3 (1H, s, NH), and 9.1 (1H, s, SO_2 NH), the last two signals were disappeared by D_2O. MS: ($C_{25}H_{20}N_6O_3S_2$); 438 (0.23, M − C_6H_6); 263 (1.0, M-sulphathiazole), 255 (19.96, sulphathiazole), 191 (100), 133 (1.22, *p*-$CH_3{\cdot}C_6H_4{\cdot}$NCO), and 119 (3.63, $C_6H_5{\cdot}$NCO). Also, sulphacetamide and **IIa** gave **XXIc**; m.p. 110°C, from ethanol, (40%). MS: ($C_{24}H_{21}N_5SO_4$); 295 (100, base peak), 296 (25.9), 297 (8.5), 298 (6.6), 133 (6.4), and 119 (6).

In a similar manner, sulphadiazine and **IIg** gave **XXId**, m.p. 210°C from ethanol, (35%). ^{1}H NMR: 7.0–7.3 (15H, m, Ar H), 8.4, 9.1 (2H, 2 broad signal. NH, SO_2 NH, disappeared by D_2O); MS: 454 (0.2, M − $Cl{\cdot}C_6H_4$), 153 (16.7, *p*-$Cl{\cdot}C_6H_4{\cdot}$NCO), and 127 (100, base peak, *p*-$Cl{\cdot}C_6H_4$ – NH_2).

4-Thioxoimidazlidine-2,5-diones **XXIIa,b**. A solution of **IIh** (0.005 mole) in boiling ethanol (25 mL) was treated with dil HCl (1:1) drop by drop. The obtained product was collected, washed with water, and recrystallized from ethanol to give **XXIIa**, m.p. 140°C (45%), IR spectrum revealed the absence of νNH. Similarly **IIj** gave **XXIIb**, m.p. 108°C, from ethanol (40%); IR: no νNH.

Bis-imidazolidine-2,5-diones **XXIIIa,b**. To a solution of **XXIIa** (0.005 mole) in *p*-xylene (20 mL), copper turnings (0.5 gm; excess) were added. The reaction mixture was refluxed for 3 h. Filteration of xylene (to separate Cu S) gave a product which recrystallized from dioxane to give **XXIIIa**; m.p. >300°C (30%). **XXIIb** similarly gave **XXIIIb**, m.p. >300°C, from dioxane (35%). ^{1}H NMR of **XXIIIb** exhibited the aromatic protons at δ = 7.0–7.3 ppm; MS of **XXIIIa**: 656 (24.8; M^+), 657 (8.4, M + 1), 658 (47.17, M + 2), 659 (15.8, M + 3), 660 (30.0, M + 4), 197 (18.48, *p*-$Br{\cdot}C_6H_4{\cdot}$NCO), 181 (100, base peak, *p*-$Br{\cdot}C_6H_4$NC), and 119 (33.46, $C_6H_5{\cdot}$NCO).

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