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Syntheses of Some Novel Imidazolidinethiones and Condensed Imidazoles Containing Arylazo Moieties Starting from Cyanothioformamides

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ABSTRACT: *Cyclocondensation of cyanothioformamides (**1**) with arylhydrazonomalononitriles (**2**) afforded the novel imidazole derivatives (**4a–e**) in good yields. Isothiocyanatoazobenzene (**6**) was allowed to react with potassium cyanide and gave the new cyanothioformamide (**7**) which was reacted with 4-chlorophenyl isocyanate to yield imidazolidinethione (**8**). Compound (**8**) was subjected to react with hydrochloric acid, o-phenylenediamine, 4-methylaniline, and hydrogen sulfide and furnished compounds (**10**), (**11**), (**12**), and (**15**), respectively. Also, the reactivity of thiohydantoin (**15**) toward some electrophilic reagents such as N,N-dimethylformamide-dimethylacetal and arylidene-malononitriles was investigated. The structure of the synthesized compounds was established by analytical and spectral data.* © 2005Wiley Periodicals, Inc. Heteroatom Chem 16:218–225, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20113

INTRODUCTION

Imidazoles and their fused derivatives are key components of a great many bioactive compounds of both natural and synthetic origin [1]. Hydantoin derivatives are used in therapy as anticonvulsants and chemotherapeutics [2]. Antimicrobial activity was stated among derivatives possessing aromatic substituents at the imidazole nitrogen e.g. *N*-acyl and 5-arylidene derivatives of hydantoin and 4-thiohydantoin [3–5]. Moreover, previous reports demonstrated that synthetic imidazoles act either as inhibitors of α-adrenoceptor mediated events in platelets [6] or inducers of platelets activation [7]. Also, in the literature it is well documented that azo compounds have been widely utilized as dyes and analytical reagents [8]. They can also be used as materials for nonlinear optics and for storage of optical information in laser disks [9]. As an extension to our interest [10–16] on the chemistry of cyanothioformamides **1**, we report herein the synthesis of novel imidazolidinethione and condensed imidazole derivatives containing arylazo moieties.

RESULTS AND DISCUSSION

Cyclocondensation of cyanothioformamides **1** with arylhydrazonomalono-nitriles **2** in ether in the presence of triethylamine at room temperature afforded the novel imidazolidinethiones **4a–e** in good yields (68–82%) (Scheme 1). The structures of compounds **4a–e** have been confirmed by elemental analysis, IR, ^{1}H NMR, and mass spectra. The infrared

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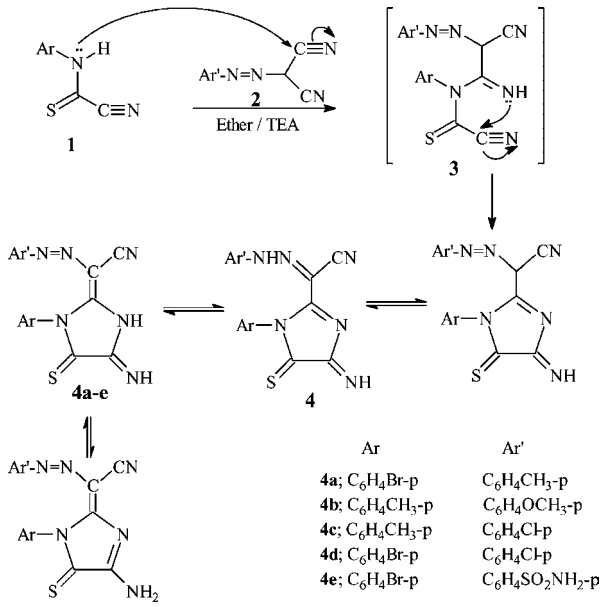


SCHEME 1

spectra of these compounds revealed absorption bands characteristic for NH, C≡N, C=N, and C=S functional groups. On the basis of ^{1}H NMR spectra, these compounds exist in azo form **4a–e** rather than hydrazo form **4** (Scheme 1). The ^{1}H NMR spectrum of compound **4b** for example exhibited two singlets at $\delta = 8.40$ ppm (C=NH) and 9.50 ppm (NH imidazole ring) along with two singlets at $\delta = 2.47$ ppm (CH_3) and 3.84 ppm (OCH_3) in addition to aromatic protons. The final elucidation of the structure **4b** was carried out by its mass spectrum that showed a molecular ion peak at *m/z* 376 (6.10%) together with a base peak at *m/z* 108, and its fragmentation pattern is illustrated in Chart 1. The reaction mechanism was assumed to proceed through a nucleophilic attack of the nitrogen atom of the cyanothioformamide moiety **1** to the *Sp* carbon of the cyano in **2** to form **3** followed by the addition of the imino group to the cyano group to yield the cyclized product **4** (Scheme 1).

4-Isothiocyanatoazobenzene **6** was synthesized by treatment of 4-aminoazobenzene **5** with thiophosgene in 1:1 mixture of dichloromethane and chloroform [17]. Compound **6** was allowed to react with potassium cyanide in aqueous medium at room temperature and gave the novel azo derivative **7**. Cyclocondensation of compound **7** with 4-chlorophenyl isocyanate in tetrahydrofuran in the presence of triethylamine afforded the new imidazolidinethione derivative **8** in good yield. Also, in a similar manner isothiocyanate **6** was cyclized

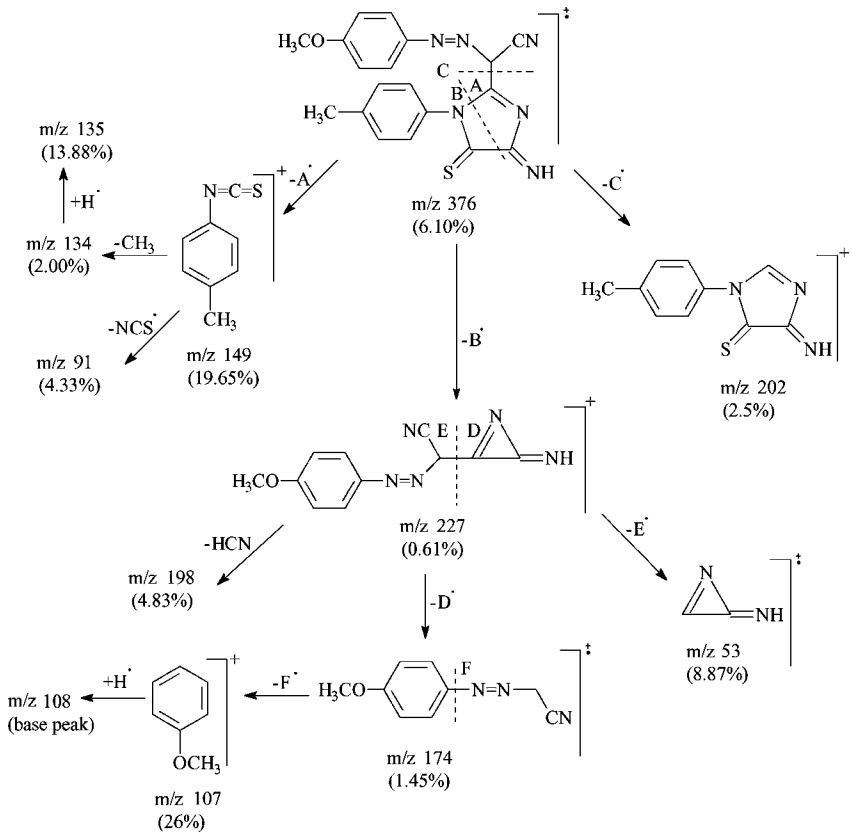
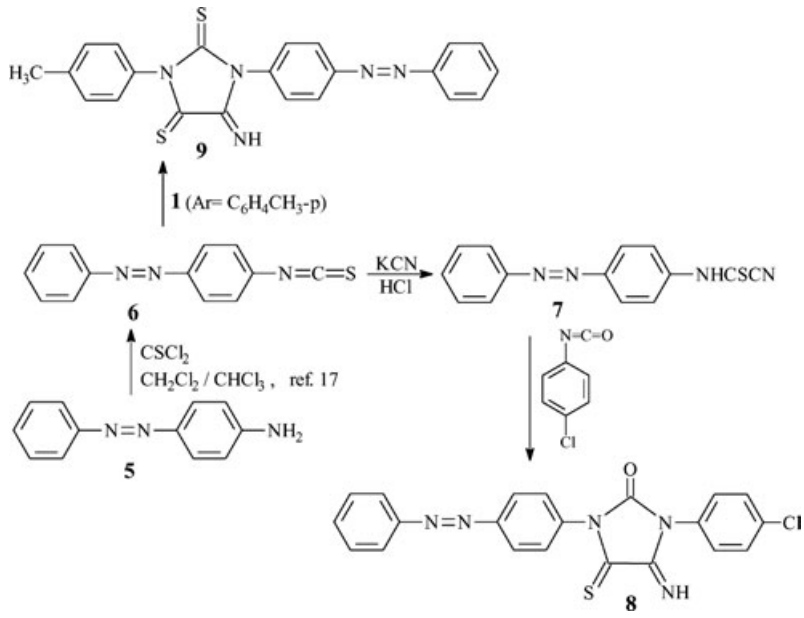


CHART 1 Fragmentation pattern of compound **4b**.



SCHEME 2

with cyanothioformamide **1** (Ar = $C_6H_4CH_3$-*p*) at room temperature and yielded the 2,4-dithioxo-imidazolidine derivative **9** (Scheme 2). Mass spectrum of compound **9** exhibited a molecular ion peak at *m/z* 415 (18.2%) in addition to a base peak at *m/z* 77 characteristic for phenyl moiety (Chart 2).

Hydrolysis of imino group in compound **8** was achieved by its treatment with hydrochloric acid

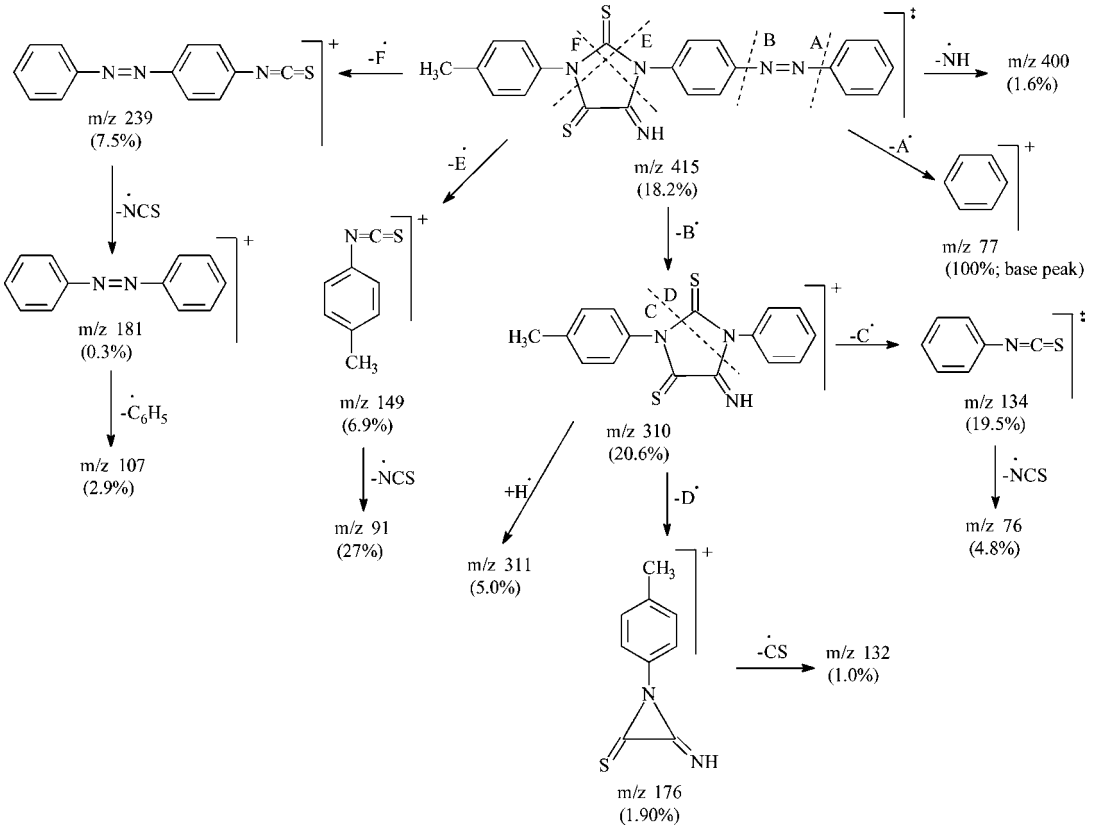
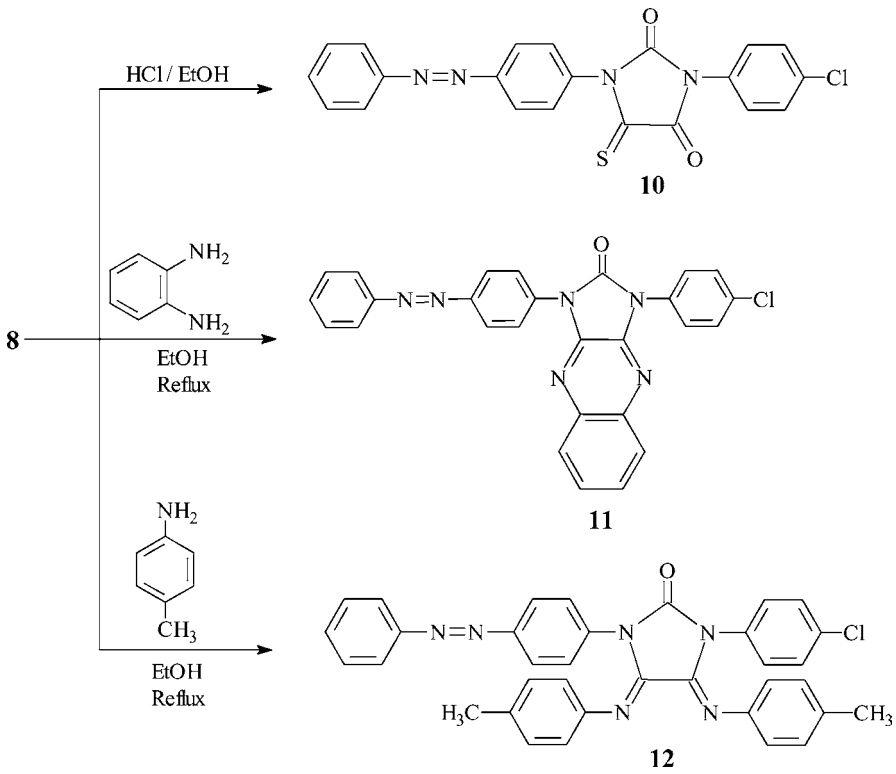


CHART 2 Fragmentation pattern of compound **9**.

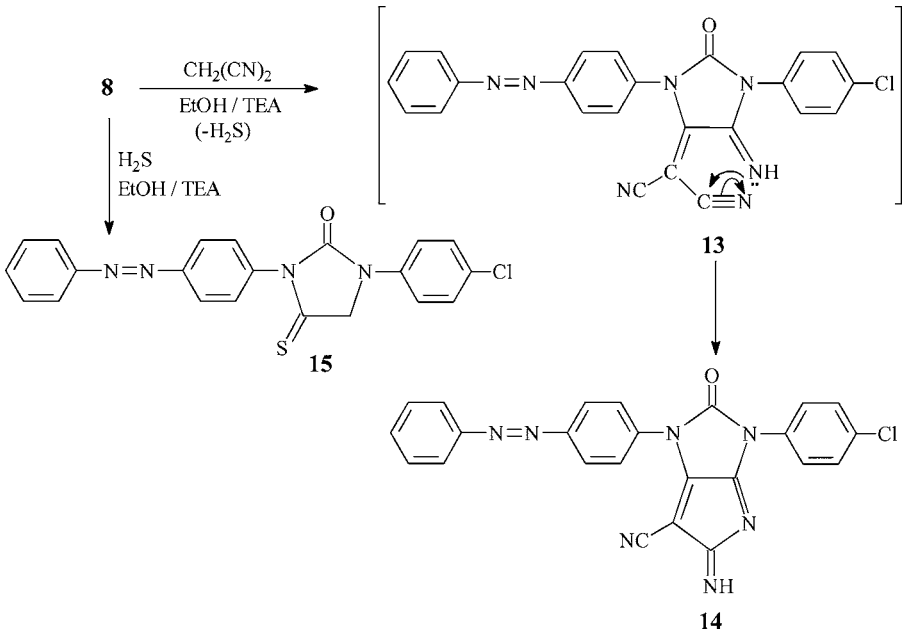


SCHEME 3

in ethanol at room temperature and produced the 2,5-imidazolidinedione derivative **10**. Cyclization of compound **8** with 1,2-phenylenediamine under reflux in ethanol yielded the imidazo[4,5-*b*]quinoxaline derivative **11**, via elimination of hydrogen sulfide and ammonia [15]. Condensation of compound **8** with two molecules of 4-methylaniline furnished the novel di-imine derivative **12** (Scheme 3).

The cyclization of compound **8** with malononitrile in refluxing ethanol in the presence of triethylamine afforded the novel pyrrolo[2,3-*d*]imidazole derivative **14**. The assignment of structure **14** was based on analytical and spectral data. Thus, the infrared spectrum of compound **14** revealed absorption characteristics for NH (3330 cm^{-1}), C≡N (2202 cm^{-1}), and C=O (1725 cm^{-1}). The ^1H NMR spectrum recorded in DMSO-d_6 showed singlet at $\delta = 10.00$ ppm (NH) in addition to aromatic protons (m, 13H). Also, the mass spectrum revealed a molecular ion peak at *m/z* 435 (M-NH; 2.6%) with a base peak at *m/z* 107. This reaction is assumed to proceed via elimination of hydrogen sulfide (lead acetate paper) to form **13** followed by nucleophilic attack by the imino nitrogen on one of cyano groups to give **14** (Scheme 4). The imino functional group in compound **8** was converted into active methylene functional group [15] by treatment with hydrogen sulfide in ethanol in the presence of triethylamine at room temperature (Scheme 4).

Reactivity of thiohydantoin **15** toward some electrophilic reagents was investigated. Thus, *N,N*-dimethylamino derivative **16** was obtained by treatment of methylene function in **15** with dimethylformamide-dimethylacetal (DMF-DMA) as electrophile in dry *m*-xylene under reflux. The ^1H NMR spectrum of compound **16** recorded in DMSO-d_6 revealed the presence of singlet at $\delta = 3.35$ ppm due to *N,N*-dimethylamino moiety and was free methylene function. Thiopyrano[2,3-*d*]imidazol-6-carbonitriles **19a,b** were achieved by cyclocondensation of compound **14** with arylidenemalononitriles **17** in ethanol in the presence of catalytic amount triethylamine under reflux. Structures of compounds **19** were established based on the analytical and spectral data. Thus, the infrared spectra of the synthesized compounds displayed characteristic absorption bands for NH_2, C≡N, C=O, and N=N functional groups. The ^1H NMR spectrum of compound **19a** showed singlet at $\delta = 4.10$ ppm attributed to the presence of thiopyrano proton and the lack of signal due to methylene protons. The formation of thiopyranoimidazole **19** is assumed to proceed via the Michael addition of the nucleophilic carbon atom of methylene on

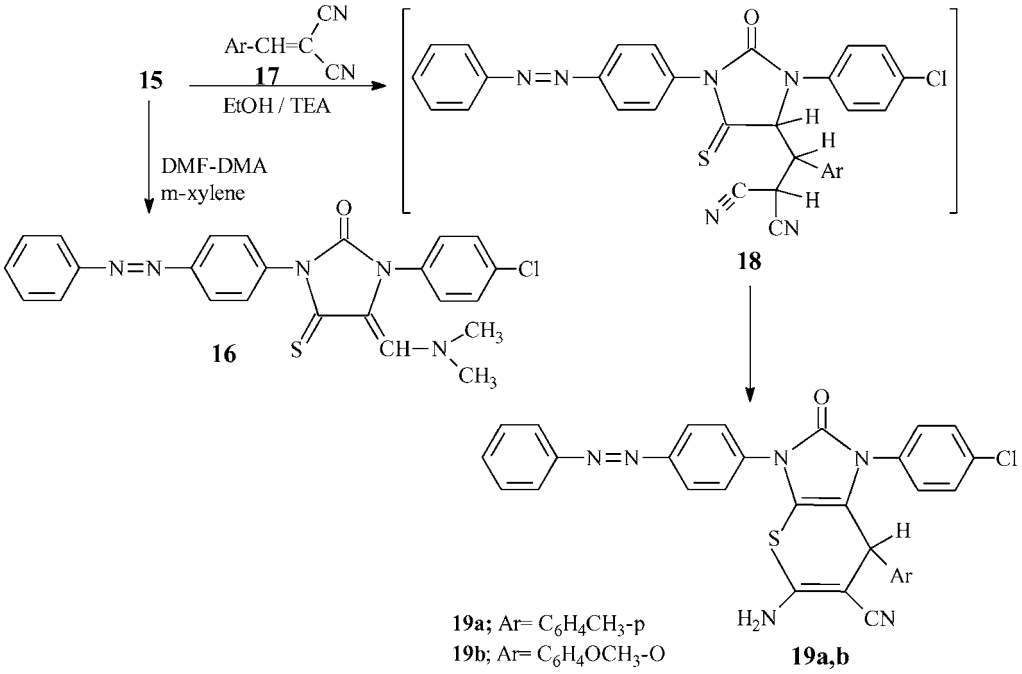


SCHEME 4

benzylidene moiety to give the Michael adduct [15] **18** followed by intramolecular cyclization to form the final product **19** (Scheme 5).

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 internal standard. Chemical shifts are expressed as δ ppm units. Mass spectra were recorded on Shimadzu GC-MS-QP 100 EX (70 eV). Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University. Found: C, H, N for all compounds were within ±0.4% from the



SCHEME 5

theoretical value. Physical data for the synthesized compounds are given in Table 1. Also, the spectral data are collected in Table 2.

*[1-(4-Substituted phenyl)-4-imino-5-thioxo-4,5-dihydro-1H-imidazol-2-yl]- (4-substituted phenylhydrazono)acetonitriles (**4a–e**)*

A mixture of substituted cyanothioformamide **1** (0.01 mole), arylhydrazonomalononitriles **2** (0.01 mole), and triethylamine in ether was stirred at room temperature for 15 h. The solid product was collected and recrystallized from proper solvent to give **4a–e**.

*N-(Azobenzene)cyanothioformamide (**7**)*

A mixture of potassium cyanide (0.01 mole in 10 mL H_2O) and isothiocyanate **6** (0.01 mole) in ethanol was stirred at room temperature for 3 h. The reaction mixture was then poured into ice/HCl (3 mL, 12%), and the obtained product was collected, washed with cold water, and recrystallized from proper solvent to give **7**.

*1-(4-Chlorophenyl)-3-azobenzene-5-imino-4-thioxo-2-imidazolidinone (**8**)*

A mixture of *N*-(azobenzene)cyanothioformamide **7** (0.01 mole), *p*-chlorophenyl isocyanate (0.01 mole), and equivalent amount of triethylamine (0.01 mole) in tetrahydrofuran (25 mL) was stirred at room temperature for 15 min. The product was collected and recrystallized from proper solvent to give **8**.

*1-(Azobenzene)-3-(4-methylphenyl)-5-imino-2,4-imidazoli-dinedithione (**9**)*

Equivalent amounts of **6** (0.01 mole) and cyanothioformamide **1** (Ar=$C_6H_4CH_3$-*p*) (0.01 mole) in 20 mL ether were treated with triethylamine (0.01 mole). After stirring at room temperature for 24 h, the product was collected, washed with *n*-hexane, and recrystallized from proper solvent to give **9**.

TABLE 1 Characterization Data for Newly Synthesized Compounds

Compd. No.	*Mp (°C)*	*Solvent Cryst.*	*Color*	*Yield (%)*	*Formula (Mol. Wt.)*
4a	268–270	Dioxan	Violet	82	$C_{18}H_{13}BrN_6S$ (425.31)
4b	252–253	Ethanol	Violet	70	$C_{19}H_{16}N_6OS$ (376.44)
4c	290–291	Ethanol	Violet	74	$C_{18}H_{13}ClN_6S$ (380.5.86)
4d	265–267	Ethanol	Violet	72	$C_{17}H_{10}BrClN_6S$ (445.73)
4e	300–302	Dioxan	Violet	68	$C_{17}H_{12}BrN_7O_2S_2$ (490.36)
7	178–180	Chloroform	Orange	80	$C_{14}H_{10}N_4S_2$ (266.32)
8	216–218	Chloroform	Orange	83	$C_{21}H_{14}ClN_5OS$ (419.90)
9	331–332	Ethanol	Yellow	70	$C_{22}H_{17}N_5S_2$ (415.53)
10	196–197	Dioxan	Red	70	$C_{21}H_{13}ClN_4O_2S$ (420.88)
11	295–297	Ethanol	Yellow	68	$C_{27}H_{17}ClN_6O$ (476.92)
12	192–192	Benzene	Yellow	65	$C_{35}H_{27}ClN_6O$ (583.10)
14	198–200	Ethanol	Brown	67	$C_{24}H_{14}ClN_7O$ (451.87)
15	185–187	Ethanol	Yellow	70	$C_{21}H_{15}ClN_4OS$ (406.90)
16	145–147	Ethanol	Orange	66	$C_{24}H_{20}ClN_5OS$ (461.98)
19a	155–156	Benzene	Yellow	62	$C_{32}H_{23}ClN_6OS$ (575.10)
19b	143–144	Ethanol	Yellow	70	$C_{32}H_{23}ClN_6O_2S$ (591.10)

TABLE 2 Spectral Data of the Synthesized Compounds

Compd No.	*IR(ν_{max}) (cm^{-1})*	*^{1}HNMR (δ(ppm)) (DMSO-d_6)*
4a	3414 (NH), 2235 (C≡N), 1672 (C=N), 1591 (N=N), 1470, 1244 (C=S)	2.30 (s, 3H, CH_3), 6.72, 7.13, 7.24, 7.78 (4d, 8H, Ar-H), 8.54, 9.48 (2s, 2H, two NH)
4b	3405 (NH), 2210 (C≡N), 1675 (C=N), 1590 (N=N), 1420, 1238 (C=S)	2.47 (s, 3H, CH_3), 3.48 (s, 3H, OCH_3), 6.78–7.80 (m, 8H, Ar-H), 8.40, 9.50 (2s, 2H, two NH)
4c	3410 (NH), 2207 (C≡N), 1680 (C=N), 1592 (N=N), 1475, 1235 (C=S)	
4d	3450 (NH), 2250 (C≡N), 1668 (C=N), 1578 (N=N), 1480, 1250 (C=S)	6.76, 7.34, 7.40, 7.79 (4d, 8H, Ar-H), 8.71, 9.65 (2s, 2H, two NH)
4e	3413, 3346, 3257 (NH, NH_2), 2214 (C≡N), 1685 (C=N), 1596 (N=N), 1487, 1251 (C=S)	6.80 (s, 2H, SO_2NH_2), 7.20–7.67 (m, 8H, Ar-H), 8.60, 9.50 (2s, 2H, two NH)
7	3267 (NH), 2233 (C≡N), 1542 (N=N)	7.57–8.16 (m, 9H, Ar-H), 13.60 (Hump, 1H, NH)
8	3365 (NH), 1743 (C=O), 1678 (C=N), 1542 (N=N), 1458, 1214 (C=S)	7.61–8.70 (m, 13H, Ar-H), 10.03 (s, 1H, NH)
9	3220 (NH), 1651 (C=N), 1512 (N=N), 1384, 1280 (C=S)	2.40 (s, 3H, CH_3), 7.37–8.04 (m, 13H, Ar-H), 9.90 (s, 1H, NH)
10	1797, 1743 (C=O), 1542 (N=N), 1384, 1288 (C=S)	7.44–8.08 (m, 13H, Ar-H)
11	1752 (C=O), 1600 (C=N), 1508 (N=N)	7.61–8.17 (m, 17H, Ar-H)
12	1747 (C=O), 1569 (N=N)	2.26, 2.27 (2s, 6H, $2CH_3$), 6.58–8.19 (m, 21H, Ar-H)
14	3330 (NH), 2202 (C≡N), 1725 (C=O), 1620 (C=N), 1542 (N=N)	7.07–7.87 (m, 13H, Ar-H), 10.00 (s, 1H, NH)
15	2929 (CH-aliph), 1747 (C=O), 1542 (N=N), 1432, 1253 (C=S)	4.96 (s, 2H, CH_2), 6.65–7.99 (m, 13H, Ar-H)
16	3060 (CH-arom), 2925 (CH-aliph), 1715 (C=O), 1488 (N=N)	3.35 (s, 6H, $N(CH_3)_2$), 6.91–7.94 (m, 13H, Ar-H), 8.07 (s, 1H, CH)
19a	3332, 3250 (NH_2), 2214 (C≡N), 1743 (C=O), 1596 (N=N)	2.49 (s, 3H, CH_3), 3.45 (s, 2H, NH_2), 4.10 (s, 1H, thiopyran-H), 6.89–8.01 (m, 17H, Ar-H)
19b	3345, 3230 (NH_2), 2220 (C≡N), 1741 (C=O), 1503 (N=N)	3.38 (s, 2H, NH_2), 3.61 (s, 1H, thiopyran), 3.83 (s, 3H, OCH_3), 7.11–7.92 (m, 17H, Ar-H)

*3-(Azobenzene)-1-(4-chlorophenyl)-4-thioxo-2,5-imidazolidinedione (**10**)*

To a solution of compound **8** (0.01 mole) in boiling dioxane (20 mL), conc. HCl (3 mL) was added. The reaction mixture was allowed overnight. The product was collected, washed with cold water, and recrystallized from proper solvent to give **10**.

*3-(Azobenzene)-1-(4-chlorophenyl)-1H-imidazo[4,5-b]-quinoxalin-2-one (**11**)*

A mixture of compound **8** (0.01 mole), *o*-phenylenediamine (0.01 mole) in absolute ethanol (30 mL) was refluxed until H_2S and NH_3 were evolved. The solid that obtained was recrystallized from proper solvent to give **11**.

*3-(Azobenzene)-1-(4-chlorophenyl)-4,5-bis(4-methylphenyl-imino)-2-imidazolidinone (**12**)*

To a solution of compound **8** (0.01 mole) in 20 mL absolute ethanol was added 4-methylaniline (0.02 mole). The reaction mixture was refluxed until H_2S and NH_3 were evolved, then allowed to cool and poured into water (100 mL) and acidified with hydrochloric acid. The product was collected and recrystallized from proper solvent to give **12**.

*3-(4-Chlorophenyl)-5-imino-2-oxo-1-(4-phenylazophenyl)-1,2,3,5-tetrahydro-pyrrolo[2,3-d]imidazol-6-carbonitrile (**14**)*

A mixture of compound **8** (0.01 mole) and malononitrile (0.01 mole) in 30 mL absolute ethanol in the presence of few drops of triethylamine was refluxed until hydrogen sulfide evolved (18 h). The obtained product was recrystallized from proper solvent to give **14**.

*3-(Azobenzene)-1-(4-chlorophenyl)-4-thiohydantoin (**15**)*

Through a suspension of compound **8** (0.01 mole) in 20 mL absolute ethanol containing triethylamine (0.02 mole) was passed a stream of hydrogen sulfide until the system became clear (0.5 h). The obtained product was collected and washed with ethanol to give **15**.

*3-(Azobenzene)-1-(4-chlorophenyl)-5-(N,N-dimethylamino)-methylidene-4-thioxo-2-imidazolidinone (**16**)*

The *N,N*-dimethylformamide-dimethylacetal (0.02 mole) is added to a solution of the thiohydantoin **15** (0.01 mole) in 30 mL dry *m*-xylene, and the reaction mixture was refluxed for 3 h. The precipitated product was filtered off, washed with ether, and dried. The solid that obtained was recrystallized from proper solvent to give **16**.

*5-Amino-3-(azobenzene)-7-aryl-1-(4-chlorophenyl)-2-oxo-thiopyrano[2,3-d]imidazol-6-carbonitriles (**19a,b**)*

A mixture of thiohydantoin (**15**; 0.01 mole), substituted cinnamonitrile **17** (0.01 mole), and piperidine (0.5 mL) in 30 mL absolute ethanol was refluxed for 6 h. The reaction mixture was then cooled, poured into crushed ice, neutralized with dil HCl (3 mL, 12%) and the obtained product was collected, washed with cold water, and recrystallized from proper solvent to give **19a,b**.

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