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Reactivity of Cyanothioformamides and 3-(4-Bromophenyl)-5-imino-4-oxazolidinethione Toward Ortho-Substituted Nucleophiles

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ABSTRACT: *The substituted benzoazoles* **4** *and* **5a,b** *were obtained by the reaction of cyanothioformamides* **1d** *and* **1b** *or* **1c** *with o-substituted aromatic amines* **2b** *and* **2c**, *respectively. Fused pyrimidinones* **10, 12**, *and* **14** *were synthesized by the reaction of oxazolidinethione (***9***) with 2-amino aromatic and heteroaromatic carboxylic acids. The structures of the synthesized compounds were established based on elemental analysis and spectral data studies.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:611–616, 2002; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10042

INTRODUCTION

A literature survey reveals that cyanothioformamides, which contain a potentially nucleophilic nitrogen atom α to a cyano function α group, are versatile reagents which have been extensively utilized in heterocyclic synthesis [1–3]. The present contribution represents an extension of our recent work [4–7] on cyanothioformamides **1** and deals with their reactivity toward ortho-substituted anilines to furnish fused heterocycles. In addition, the reactivity of oxazolidinethione (**9**) toward similar reagents was investigated.

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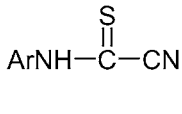
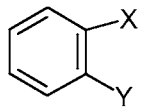


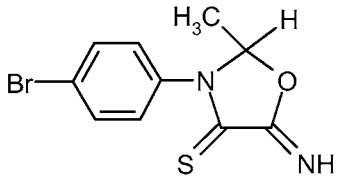
1a-d



2a-f

1a; Ar = $C_6H_4CH_3$-p
b; Ar = C_6H_4Cl-p
c; Ar = C_6H_4Br-p
d; Ar = C_6H_5 NHC_6H_4-p

2a; X = Y = NH_2
b; X = NH_2, Y = OH
c; X = NH_2, Y = Cl
d; X = OH , Y = Cl
e; X = NH_2 , Y = COOH
f; X = Y = OH



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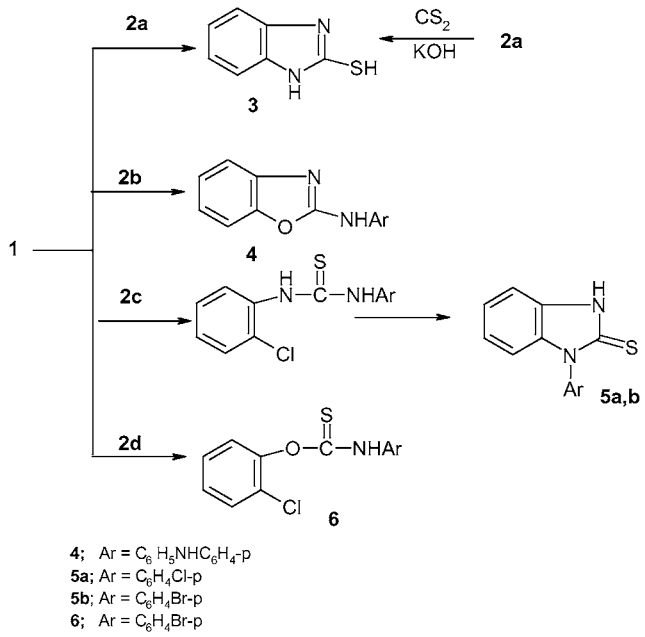
RESULTS AND DISCUSSION

Compound **1a** reacted with an equimolar amount of *o*-phenylenediamine (**2a**) in absolute ethanol in the presence of a catalytic amount of triethylamine under reflux to yield 2-mercaptobenzimidazole (**3**). The assigned structure for compound **3** was based on microanalytical and spectral data. The IR spectrum displays a lack of absorption of the C≡N group and the presence of an NH band at 3150 cm^{-1}. Also, compound **3** was synthesized by treatment of **2a** with carbon disulfide in ethanol in the

presence of potassium hydroxide [8]. Formation of **3** from **1a** is assumed to take place via elimination of hydrogen cyanide and 4-methylaniline. Treatment of compound **1d** with *o*-aminophenol (**2b**) in *N*,*N*-dimethylformamide catalyzed by piperidine produced the benzoxazole derivative **4**. Analytical and spectral data are consistent with the proposed structure. The mass spectrum of **4** shows a molecular ion peak at $m/z = 301$ (100%) corresponding to the molecular formula $C_{19}H_{15}N_3O$ (Fig. 1). The formation of **4** is assumed to proceed via elimination of hydrogen cyanide and hydrogen sulfide. Cyclocondensation of **1b** and **1c** with *o*-chloroaniline (**2c**) in dioxane/TEA furnished the benzimidazole derivatives **5a,b**. Microanalytical and spectroscopic data for **5a** and **5b** are consistent with the assigned structure. Thus, the IR spectra exhibit absorption bands corresponding to the NH group, but not to the C≡N group. The formation of **5** is assumed to proceed through initial elimination of hydrogen cyanide followed by loss of hydrogen chloride [9]. On the other hand, reaction of **1c** with *o*-chlorophenol (**2d**) yielded the thiocarbamate **6**, via elimination of hydrogen cyanide (Scheme 1).

Quinazolinones **7a,b** were obtained by refluxing anthranilic acid (**2e**) with compounds **1c** and **1d** in ethanol containing triethylamine. The formation of quinazolinones **7a,b** is believed to proceed via thiourea formation followed by loss of water. Compounds **7a** and **7b** were also obtained by an independent synthetic route by treatment of **2e** with the appropriate aryl isothiocyanate in refluxing ethanol/TEA [10]. On refluxing compounds



SCHEME 1

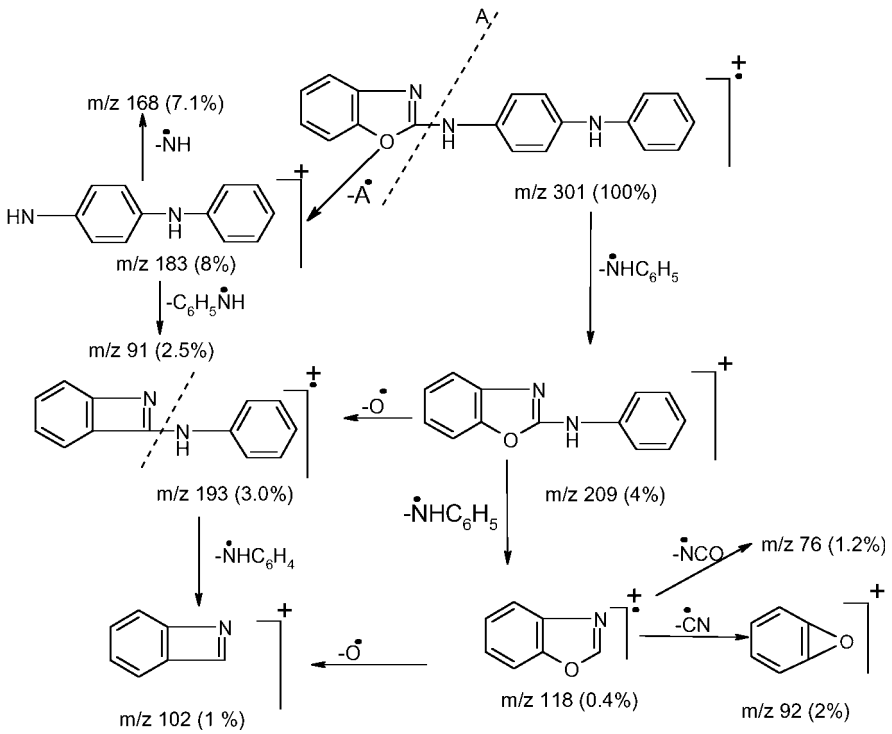
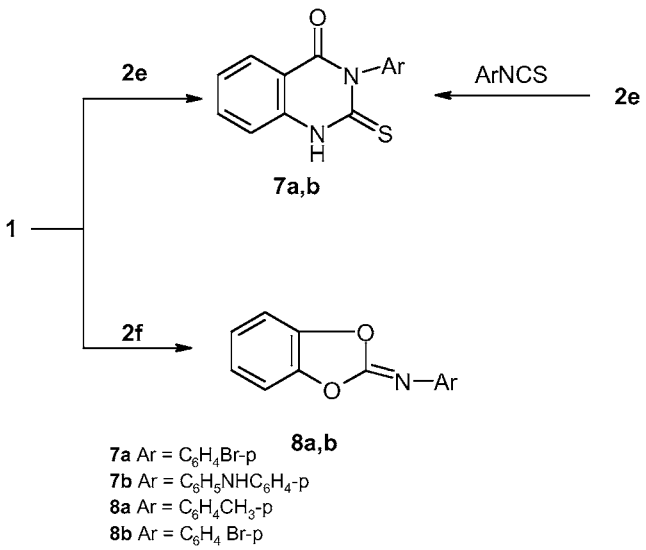


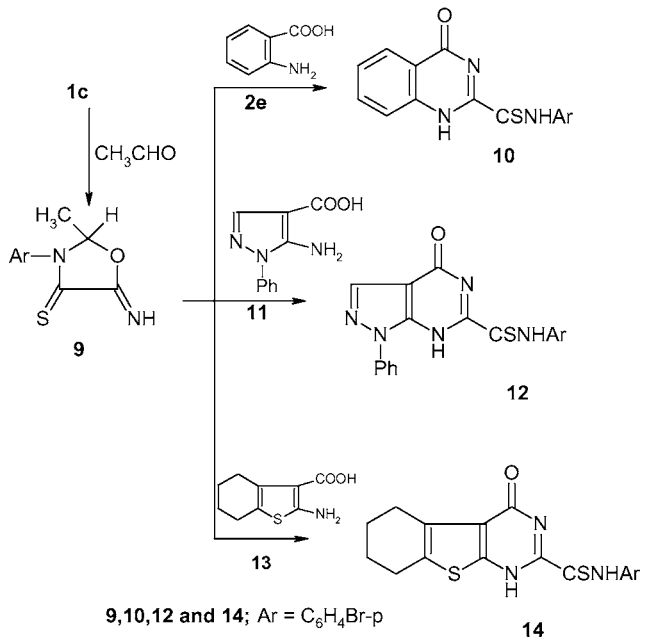
FIGURE 1 Fragmentation pattern of compound **4**.

1a and **1c** with an equimolar amount of catechol (**2f**) in dimethylformamide in the presence of triethylamine,1,3-benzodioxole derivatives **8a,b** were obtained. Formation of **8** is assumed to proceed by elimination of hydrogen cyanide and hydrogen sulfide (Scheme 2).

Oxazolidine (**9**) was synthesized by the reaction of cyanothioformamide (**1c**) with acetaldehyde in the ether in the presence of triethylamine at room temperature. The reactivity of **9** toward compounds containing an amino group with a vicinal carboxyl group was investigated. Thus, refluxing of **9** with anthranilic acid (**2e**) in absolute ethanol containing triethylamine furnished a yellow product which is formulated as the quinazolinone derivative **10**. The structure of **10** was established by microanalytical and spectral data. The IR spectrum of **10** exhibit characteristic bands for NH and C=O functional groups. The ^{1}H NMR spectrum of **10** (DMSO-d_6) show signals at 11.40 and 12.10 ppm assigned to 2 NH protons and a multiplet at 6.77–7.74 ppm assigned to aromatic protons. Also, the mass spectrum of **10** contains a molecular ion peak at $m/z = 360$ (79%), which is in agreement with the proposed formula $C_{15}H_{10}BrN_3OS$. Presumably, the formation of **10** takes place by nucleophilic attack of the amino group of anthranilic acid on the imino group of compound **9** with loss of acetaldehyde [5], followed by cyclization with elimination of water (Scheme 3). In a similar manner, compound **9** was treated with the heterocyclic ortho-amino carboxylic acids 5-amino-1-phenylpyrazole-4-carboxylic acid (**11**) and 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (**13**)



SCHEME 2



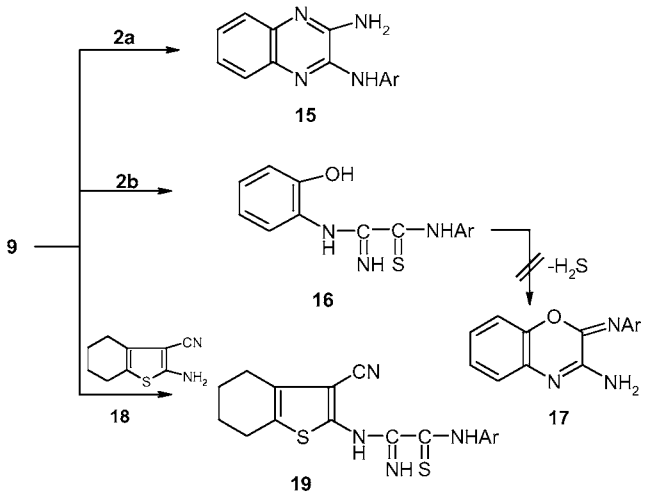
SCHEME 3

to yield the novel condensed pyrimidines **12** and **14**, respectively (Scheme 3).

This investigation was extended to include a study of the reactivity of compound **9** toward binucleophiles. Thus, compound **9** was treated with an equimolar amount of *o*-phenylenediamine (**2a**) in absolute ethanol, in the presence of a catalytic amount of triethylamine, to yield the quinoxaline derivative **15**. Compound **15** is probably formed through nucleophilic attack by a molecule of **2a** on the imino group of **9** with loss of acetaldehyde [5], followed by cyclization with elimination of hydrogen sulfide. On the other hand, when compound **9** was allowed to react with *o*-aminophenol (**2b**) as the binucleophile, the thioamide derivative **16** was obtained. The other possible structure (**17**) for this product was excluded on the basis of microanalytical and spectral data. Similarly, 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (**18**) reacted with compound **9** to give the novel thioamide **19** (Scheme 4).

EXPERIMENTAL

All melting points are uncorrected and were determined on a digital Gallen-Kamp MFB-595 instrument. IR spectra (KBr) were measured on a Shimadzu 440 spectrometer ^{1}H NMR spectra were obtained in dimethylsulfoxide on a Varian Gemini 200 MHz spectrometer using TMS as an internal standard; chemical shifts are reported as δ units. Mass spectra were obtained on a GC MS-QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses



15,16 and 19; Ar = C_6H_4Br-p

SCHEME 4

were carried out at the Microanalytical Center of Cairo University. Physical and analytical data for the synthesized compounds are given in Table 1. The spectral data are collected in Table 2.

The starting compounds **1a–d** [11], **11** [12], **13** [13], and **18** [14] were prepared according to previously reported procedures.

*2-Mercaptobenzimidazole (**3**)*

A mixture of cyanothioformamide (**1a**) (0.01 mol), *o*-phenylenediamine (**2a**) (0.01 mol), and triethylamine (0.5 ml) in absolute ethanol (30 ml) was refluxed for 3 h. The resulting solid obtained was recrystallized from ethanol. MS (%): 150 (M^+; 100), 151 (M + 1; 10), 149 (M − 1; 8.8), 65 (18.1), and 52 (10.8).

*2-[N-(4-phenylaminophenyl)]benzoxazolamine (**4**)*

A mixture of cyanothioformamide (**1d**) (0.01 mol), *o*-aminophenol (**2b**) (0.01 mol), and triethylamine (0.5 ml) in *N*,*N*-dimethylformamide (10 ml) was refluxed for 3 h, then allowed to cool, and poured into cold water (50 ml). Its acidification with HCl yielded a solid product which was recrystallized from ethanol. MS (%): 301 (M^+; 100), 302 (M + 2; 21.8), 300 (7.1), 22b (1.6), 208 (3.7), 193 (3.0), 169 (13.5), 150 (6.0), 128 (2.7), 77 (8.6), and 76 (1.5).

TABLE 1 Melting Points, Yields, and Analytical Data of the Synthesized Compounds

				Elemental Analyses (Calcd./Found)		
Compd. No.	*M.p. (°C)*	*Yield (%)*	*Formula (Mol. Wt)*	*C*	*H*	*N*
4	112–114	60	$C_{19}H_{15}N_3O$ (301)	75.75 75.60	5.02 5.00	13.95 14.10
5a	90–91	72	$C_{13}H_9ClN_2S$ (260.5)	59.88 59.80	3.45 3.50	10.74 10.60
5b	140–142	70	$C_{13}H_9BrN_2S$ (305)	51.14 51.20	2.95 2.90	9.18 9.00
6	>300	68	$C_{13}H_9BrClNOS$ (342.5)	45.54 45.60	2.62 2.60	4.08 4.10
7a	300–301	84	$C_{14}H_9BrN_2OS$ (333)	50.45 50.20	2.70 2.80	8.40 8.50
7b	300–302	90	$C_{20}H_{15}N_3OS$ (345)	69.56 69.50	4.34 4.30	12.17 12.20
8a	182–182	74	$C_{14}H_{11}NO_2$ (225)	74.67 74.50	4.89 4.90	6.22 6.10
8b	180–181	80	$C_{13}H_8BrNO_2$ (290)	53.80 53.70	2.76 2.80	4.82 4.90
9	118–119	84	$C_{10}H_9BrN_2OS$ (285)	42.10 42.20	3.15 3.10	9.82 9.70
10	190–191	87	$C_{15}H_{10}BrN_3OS$(360)	50.00 50.10	2.77 2.60	11.66 11.70
12	120–122	81	$C_{18}H_{12}BrN_5OS$ (426)	50.72 50.72	2.81 2.80	16.43 16.50
14	125–126	83	$C_{17}H_{14}BrN_3OS_2$ (420)	48.57 48.70	3.33 3.40	10.00 10.00
15	150–151	67	$C_{14}H_{11}BrN_4$ (315)	53.33 53.20	3.50 3.49	17.78 17.60
16	100–101	65	$C_{14}H_{12}BrN_3OS$ (350)	48.00 48.10	3.42 3.40	12.00 12.00
19	110–111	64	$C_{17}H_{15}BrN_4S_2$ (419)	48.69 48.70	3.58 3.50	13.37 13.40

TABLE 2 Spectroscopic Data of the Synthesized Compounds

Compd. No.	*IR (KBr, cm^{-1})*	*^1H NMR (ppm) (DMSO-d_6)*
4	3400, 3380 (NH)	6.87–7.91 (m,13H, Ar-H), 8.90, 10.52 (2s, 2H, 2NH; exchangeable upon treatment with D_2O)
5a	3250 (NH)	6.80–8.10 (m, 8H, Ar-H), 12.21 (s, 1H, NH; exchangeable upon treatment with D_2O)
5b	3400 (NH)	6.65–7.79 (m, 8H, Ar-H), 11.91 (s, 1H, NH; exchangeable upon treatment with D_2O)
6	3394 (NH)	7.10–7.86 (m, 8H, Ar-H), 8.51 (s, 1H, NH; exchangeable upon treatment with D_2O)
7a	3250 (NH), 1680 (C═O)	
7b	3400, 3220 (NH), 1670 (C═O)	6.89–7.99 (m, 13H, Ar-H), 8.39, 13.00 (2s, 2H, 2NH; exchangeable upon treatment with D_2O)
8a	1640 (C═N)	2.20 (s, 3H, CH_3), 6.90–7.82 (m, 8H, Ar-H)
8b	1630 (C═N)	6.81–7.90 (m, 8H, Ar-H)
9	3240 (NH) 2950 (CH-aliph) 1580 (C═N)	1.18 (d, 3H, CH_3), 5.22 (q, 1H, CH), 7.58–7.81 (m, 4H, Ar-H), 8.71 (s, 1H, NH; exchangeable upon treatment with D_2O)
10	3280, 3200 (NH), 1680 (C═O)	6.77–7.74 (m, 8H, Ar-H), 11.40, 12.10 (2s, 2H, 2NH; exchangeable upon treatment with D_2O)
12	3290, 3420 (NH), 1690 (C═O)	6.91–7.69 (m, 9H, Ar-H), 7.87 (s, 1H, pyrazole-H), 11.15, 12.14 (2s, 2H, 2NH; exchangeable upon treatment with D_2O)
14	3230, 3190 (NH) 2900 (CH-aliph) 1680 (C═O)	1.73 (m, 8H, $4CH_2$), 7.65–7.90 (m, 4H, Ar-H) 11.18, 12.00 (2s, 2H, 2NH; exchangeable upon treatment with D_2O)
15	3450, 3224 (NH, NH_2)	7.37–8.12 (m, 8H, Ar-H), 9.60 (Hump, 2H, NH_2; exchangeable upon treatment with D_2O), 10.40 (s, 1H, NH; exchangeable upon treatment with D_2O)
16	3420, 3300 (NH), 1640 (C═N)	
19	3460, 3320 (NH), 2900 (CH-aliph), 2200 (C≡N)	1.67 (m, 8H, $4CH_2$), 6.90–7.74 (m, 4H, Ar-H), 9.05, 9.74, 11.31 (3s, 3H, 3NH; exchangeable upon treatment with D_2O)

*1-(4-Substituted phenyl)-2-mercaptobenzimidazoles (**5a,b**)*

A mixture of **1b** or **1c** (0.01 mol), *o*-chloroaniline (**2c**) (0.01 mol), and triethylamine (0.5 ml) in dioxane (20 ml) was heated under reflux for 24 h. Then it was allowed to cool and was poured into cold water (5 ml). The solid product was recrystallized from ethanol. MS (**5b**; %): 304 (M^+; 14), 306 (M + 1; 11.25), 307 (M + 2; 13.75), 264 (11.25), 261 (38), 225 (16), 169 (20), 127 (33), 119 (21.88), 91 (44), 77 (37), 76 (48), and 75 (100).

*2-Chlorophenyl-N-(4-bromophenyl)-thiocarbamate (**6**)*

A mixture of **1c** (0.01 mol), *o*-chlorophenol (**2d**) (0.01 mol), and triethylamine (0.5 ml) was fused at 120°C for 1 h, then cooled and the product was triturated with ethanol (30 ml). The solid product was recrystallized from ethanol.

*Quinazolinones (**7a,b**)*

A mixture of **1c** or **1d** (0.01 mol), anthranilic acid (**2e**) (0.01 mol), and triethylamine (0.5 ml) in absolute ethanol (30 ml) was refluxed for 3 h. The solid product was recrystallized from dioxane. MS (**7a**; %): 332 (M^+; 48), 334 (M + 1; 32), 194 (6.88), 162 (13), 129 (16), 119 (32), 91 (17,13), 77 (19.57), 76 (17.60), and 55 (100).

*2-(4-Substituted phenyl)imino-1,3-benzodioxoles (**8a,b**)*

A mixture of **1a** or **1c** (0.01 mol), catechol (**2f**) (0.01 mol), and a few drops of triethylamine in *N,N*-dimethylformamide (10 ml) was refluxed for 1 h, then allowed to cool. The solid product was collected and recrystallized from dioxane. MS (**8b**; %): 291 (M + 1; 10.88), 292 (M + 2; 7.65), 171 (12), 157 (20), 135 (27), 119 (41), 105 (16), 91 (40.29), 90 (27), 77 (78), 76 (32), and 55 (100).

*3-(4-Bromophenyl)-5-imino-2-methyl-4-oxazolidinethione (**9**)*

A solution of **1c** (0.01 mol) in dry ether (20 ml) was treated with acetaldehyde (0.01 mol) and triethylamine (0.5 ml). The reaction mixture was stirred at room temperature for 0.5 h, then mixed with *n*-hexane to give a solid which was recrystallized from ethanol.

*Formation of 2-[N-(4-Bromophenyl)thiocarbamoyl]-4-(1H)quinazolinone (**10**), 6-[N-(4-Bromophenyl)thiocarbamoyl]-1-phenylpyrazolo[3,4-d]-4-(1H)pyrimidinone (**12**), and 2-[N-(4-Bromophenyl)thiocarbamoyl]-5,6,7,8-tetrahydro[b]thieno-4-(1H)pyrimidinone (**14**)*

A mixture of **9** (0.01 mol), an *o*-amino carboxylic acid derivative (0.01 mol), and triethylamine (0.5 ml) in absolute ethanol (20 ml) was refluxed for 15 min. The solid product formed was collected and recrystallized from dioxane. MS (**10**; %): 360 (M^+; 79), 361 (M + 1; 56), 362 (M + 2; 11.90), 326 (14), 280 (44), 177 (28.25), 119 (100), 91 (33.90), and 71 (9.76). MS (**12**; %): 426 (M^+; 7.14), 371 (7), 296 (10.7), 274 (15), 219 (10.71), 194 (9.52), 186 (26), 153 (47.62), 119 (10.71), 95 (11.90), 78 (3.57), and 64 (100). MS (**14**; %): 420 (M^+; 7.46), 386 (4.48), 305 (11.94), 289 (13), 260 (66.42), 258 (93.66), 236 (10.45), 183 (100), 172 (37.31), 148 (25.75), 118 (53), 90 (17), and 77 (1.12).

*2-[N-(4-Bromophenyl)2,3-quinoxalinediamine (**15**)*

A mixture of **9** (0.01 mol), *o*-phenylenediamine (**2a**) (0.01 mol), triethylamine (0.5 ml), and absolute ethanol (30 ml) was heated under reflux for 3 h, then allowed to cool and poured into cold water (50 ml). The precipitated product was collected and recrystallized from ethanol. MS (**15**; %): 315 (M^+; 20), 316 (M + 1; 4.9), 314 (M − 1; 27), 300 (M − NH; 7.7), 299 (M − NH_2; 45), 284 (1.8), 275 (18.13), 257 (18.1), 234 (15.8), 212 (68.9), 198 (35.7), 183 (25.3), 170 (100), 134 (20), 133 (47), and 129 (10.5).

*N-(4-Bromophenyl)-2-(2-hydroxyphenylamino)-2-iminothioacetamide (**16**)*

A mixture of **9** (0.01 mol), *o*-aminophenol (**2b**) (0.01 mol), triethylamine (0.5 ml), and absolute ethanol (30 ml) was heated under reflux for 24 h, then it was allowed to cool and was poured into cold water (50 ml). The solid product was collected and recrystallized from ethanol.

*N-(4-Bromophenyl)-2-[2-(3-cyano-4,5,6,7-tetrahydro)benzo[b]thienyl]amino-2-iminothioacetamide (**19**)*

A mixture of **9** (0.01 mol), 2-amino-4,5,6,7-tetrahydrobenz[*b*]-3-thiophenecarbonitrile (**18**) (0.01 mol), triethylamine (0.5 ml), and ethanol/DMF (1:1 volume, 20 ml) was heated under reflux for 36 h, then it was allowed to cool and was poured into cold water (100 ml). The solid product was recrystallized from ethanol. MS (%): 418 (M^+; 2.2), 420 (M + 2; 1.3), 397 (1.7), 358 (5.9), 285 (1.3), 273 (16.3), 202 (4.0), 193 (5.1), 192 (41.3), 183 (0.7), and 178 (100).

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