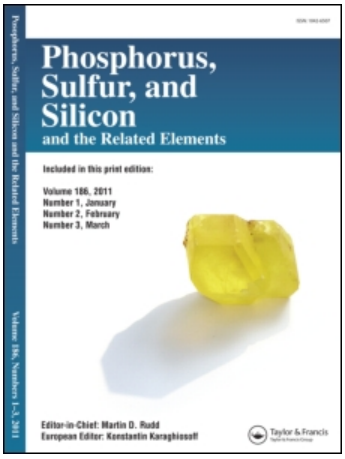

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

1,4-PHENYLENEDIISOTHIOCYANATE IN THE SYNTHESIS OF BIS-(THIOUREA, BENZOTHIAZOLE, QUINAZOLINE, 1,3-BENZOXAZINE AND IMIDAZOLIDINEIMINOTHIONES) DERIVATIVES

A. M. Sh. El-Sharief[a]; Y. A. Ammar[a]; M. A. Zahran[a]; H. Kh. Sabet[a]
[a] Al-Azhar University, Nasr City, Cairo, Egypt

Online publication date: 11 August 2010

To cite this Article El-Sharief, A. M. Sh. , Ammar, Y. A. , Zahran, M. A. and Sabet, H. Kh.(2004) '1,4-PHENYLENEDIISOTHIOCYANATE IN THE SYNTHESIS OF BIS-(THIOUREA, BENZOTHIAZOLE, QUINAZOLINE, 1,3-BENZOXAZINE AND IMIDAZOLIDINEIMINOTHIONES) DERIVATIVES', Phosphorus, Sulfur, and Silicon and the Related Elements, 179: 2, 267 — 275
To link to this Article: DOI: 10.1080/10426500490274682
URL: http://dx.doi.org/10.1080/10426500490274682

Phosphorus, Sulfur, and Silicon, 179:267–275, 2004

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500490274682

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1,4-PHENYLENEDIISOTHIOCYANATE IN THE SYNTHESIS OF BIS-(THIOUREA, BENZOTHIAZOLE, QUINAZOLINE, 1,3-BENZOXAZINE AND IMIDAZOLIDINEIMINOTHIONES) DERIVATIVES

A. M. Sh. El-Sharief, Y. A. Ammar, M. A. Zahran, and H. Kh. Sabet
Al-Azhar University, Nasr City, Cairo, Egypt

(Received August 29, 2002; accepted July 29, 2003)

Interaction of 1,4-phenylenediisothiocyanate ***1*** *with aromatic amines and o-phenylenediamine furnished the novel bisthiourea derivatives* ***2a–c*** *and* ***7****. Hydrazines or o-aminothiophenol reacted with* ***1*** *to produce bis-(thiosemicarbazide* ***4a,b*** *or benzothiazole* ***9****) derivatives. Bisquinazolines* ***12a,b*** *and bisthienopyrimidines* ***13a,b*** *were synthesized through interaction of* ***1*** *with anthranilic acids* ***10a,b*** *and aminothiophenes* ***11a,b****. Interaction of* ***1*** *with two moles of either salicylic acid or N-(4-substituted-phenyl)cyanothioformamide yielded the corresponding bis(1,3-benzoxazine* ***14*** *or imidazolidineiminothiones* ***16****) derivatives.*

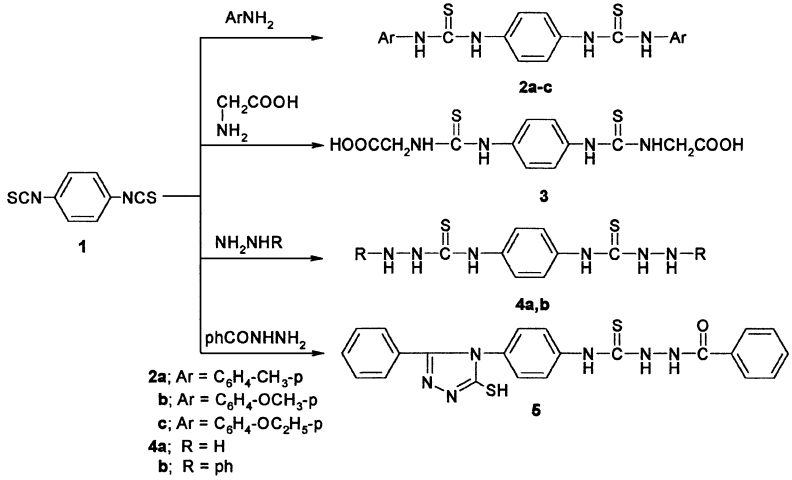
Keywords: 1,4-Phenylenediisothiocyanate; bis-benzothiazole; bis-quinazoline; bis-1,3-benzoxazine

A literature survey reveals that, attention has been increasingly paid to the synthesis of bisheterocyclic compounds, which exhibit various biological activities[1–4] including antibacterial, fungicidal, tuberculostatic, and plant growth regulative properties. Earlier work[5] revealed that bisheterocyclic compounds displayed much better antibacterial activity than heterocyclic compounds. As an extension of our efforts directed toward the development of convenient synthetic approaches for the synthesis of heterocyclic compounds[6–10] with an expected broad spectrum of biological activity, in this article we report on the synthesis of bis-(thiourea, quinazoline, 1,3-Benzoxazine and imidazolidineiminothiones) starting with 1,4-phenylenediisothiocyanate. The starting material **1** was prepared according to the reported method.[11]

Address correspondence to A. M. Sh. El-Sharief, Chemistry Department, College of Science, King Abdul-Aziz University, Madinah Munawwara, PO Box 344, Kingdom of Saudi Arabia.

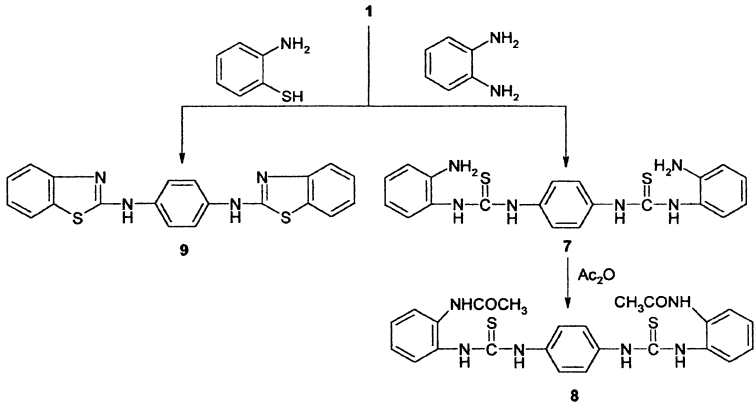
RESULTS AND DISCUSSION

The behavior of **1** toward some mono and binucleophilic reagents was discussed. Thus, treatment of 1,4-phenylenediisothiocyanate **1** with aromatic amines yielded the novel bisthiourea derivatives **2a–c.** The elemental and spectroscopic data of **2a–c** are consistent with the assigned structure. Thus, a representive example, ^{1}H NMR spectrum of **2b** in DMSO-d6 revealed a singlet at δ 3.76 assigned to two OCH_3 groups and a multiplet at δ 6.9–7.74 assigned to the aromatic protons and broad at δ 9.57 assigned to NH groups. Also, when **1** was treated with glycine as another nucleophile the corresponding {3-[4-(3-carboxymethylthioureido)phenyl]-thioureido}-acetic acid **3** was obtained. In addition, 1,4-phenylenediisothiocyanate **1** was treated with hydrazine hydrate and phenyl hydrazine as binucleophile, and furnished upon heating in dioxane under reflux products that could be formulated as the bisthiosemicarbazides **4a,b**. The structures of compounds **4a,b** were established on the basis of their elemental analyses and spectral data (IR, ^{1}H NMR, mass spectra). Mass spectrum of **4a** exhibited a molecular ion peak corresponding to the formula $C_8H_{12}N_6S_2$ ($M^+ = 256$). On the other hand, when **1** was reacted with benzoyl hydrazine the corresponding 4-(4-(2-benzoylhydrazino-thiocarbonylaminophenyl)-5-phenyl-2,4-dihydro-[1,2,4]triazole-3-thione **5** was obtained. The mass spectrum of **5** showed the molecular ion peak at m/z 446 corresponding to the formula $C_{22}H_{18}ON_6S_2$ (Scheme 1).



SCHEME 1

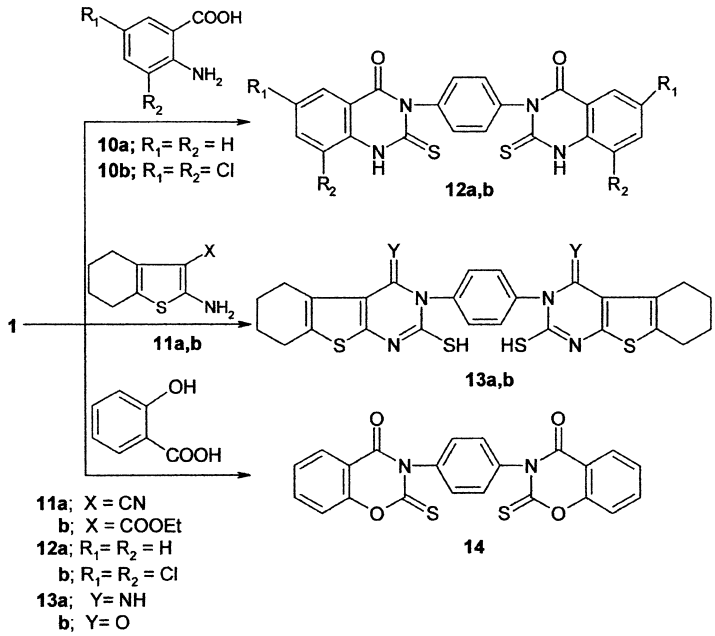
Next, we moved to investigate the behavior of isothiocyanate **1** toward some 1,2-binucleophiles. Thus, compound **1** reacted with o-phenylenediamine in refluxing dioxane/TEA to yield a single product with analytical and spectral data indicated that two moles of the reagent were consumed without elimination of H_2S. Consequently, we assigned the thiourea derivative **7** to this reaction product. Mass spectrum of **7** reveals a molecular ion peak at m/z 408 (38.46%) corresponding to the molecular formula $C_{20}H_{20}N_6S_2$. The structure of **7** also was confirmed through its acylation with acetic anhydride to give the acetanilide derivative **8**. Its ^1H NMR spectrum in DMSO-d_6 revealed a singlet at δ 3.01 assigned to two $COCH_3$ groups and a multiplet at δ 7.18–7.32 assigned to the aromatic protons and singlet at δ 7.50, 7.51, 7.99, 8.03, and 13.7 assigned to NH groups. On the other hand, the reaction of **1** with o-aminothiophenol afforded the corresponding N,N′-Bis-(benzothiazole-2-yl)-benzene-1,4-diamine **9** which elucidated by elemental and spectral data. (Scheme 2).



SCHEME 2

Quinazoline and thienopyrimidine derivatives proved to be a good CAMP phosphodiesterase inhibitor with an excellent antianxiety profile in animals.[12] Other derivatives showed antipyretic,[13] antitumor,[14] and herbicidal activities.[15] Encouraged by such properties, we planned to synthesize bisquinazoline and thienopyrimidine derivatives. Thus, interaction of **1** with anthranilic acids **10a,b** in dioxane/TEA caused cyclocondensation to furnish the corresponding bisquinazolinone derivatives **12a,b** in acceptable yield.

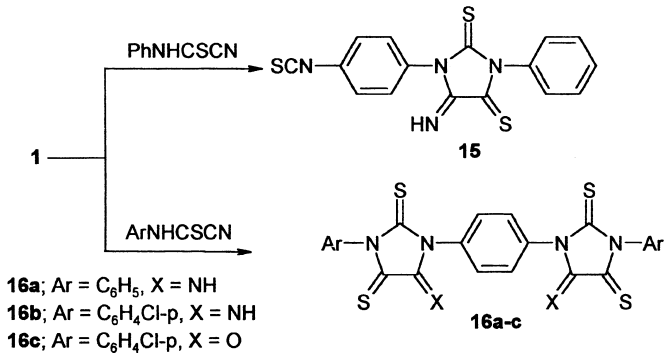
Compound **12a** was found to be identical in every respect to the compound prepared according to the reported method.[16] Compounds **12a,b** resulted from a competitive nucleophilic attack



SCHEME 3

of the COOH group on the intermediate thiourea where H_2O was eliminated. Similarly, interaction of **1** with 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene **11a** and ethyl-2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate **11b** yielded the corresponding bisthienopyrimidine derivatives **13a,b** (Scheme 3). Structure **13a,b** was established on elemental analyses and spectroscopic studies. The mass spectrum of **13a** revealed a molecular ion peak at 550 which in agreement with the proposed formula $C_{26}H_{22}N_4O_2S_4$. On the other hand, refluxing of diisothiocyanate **1** with salicylic acid in dioxane caused cyclization to produce the 3,3′-(1,4-phenylene)bis(2-thioxo-2,3-dihydro-benzo[e][1,3]oxazine-4-one **14** through elimination of H_2O (Scheme 3). Its mass spectrum assigned a molecular ion peak at m/z 432 (28.26%).

Finally, this investigation was extended to cover the behavior of **1** toward cyanothioformanilides. Thus, compound **1** reacted with N-phenyl-cyanothioformamide, where 1 mmol was consumed and yielded 5-imino-(4-isothiocyanato-phenyl)-3-phenyl-imidazolidine-2,4-dithione **15** (Scheme 4). While, on refluxing of 1,4-phenylenediisothiocyanate **1** with N-(4-substituted phenyl)cyanothioformamide in THF in the presence of TEA two moles were consumed and afforded



SCHEME 4

1,1′-(1,4-phenylene)bis[3-(4-substituted phenyl)-5-imino-imidazolidine-2,4-dithiones] **16a,b**. Imine hydrolysis of **16b** using DMF/HCl afforded 1,1′-(1,4-phenylene)bis[3-(4-chloro-phenyl)-5-oxo-imidazolidine-2,4-dithione] **16c** (Scheme 4).

EXPERIMENTAL

All melting points are uncorrected. IR spectra(KBr)were measured on shimadzu 440 spectrometer, ^{1}H NMR spectra were obtained in DMSO on a Varian Gemini 200 MHz spectrometer using TMS as internal standard; chemical shifts are reported as (ppm). Mass spectra were obtained on GC MS\QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center, Faculty of Science (Cairo University, Egypt). The characteristics data for prpared compounds are given in Table I.

The starting compound 1,4-phenylenediisothiocyanate **1** was prepared according to the reported method.[12]

1,4-Bisthioureas 2a–c: A mixture of **1** (0.01 mmol) in dioxane (30 ml), primary amine (0.02 mmol), and triethylamine (0.5 ml) was refluxed for 6 h. The solid that obtained on heating was boiled with dioxane to give **2a–c**. IR (**2a**): 3224 (NH), 3016 (CH-arom.), 1550 and 1018 (C=S). IR (**2b**): 3224 (NH), 1512 and 1242 (C=S). ^{1}H NMR (**2b**; DMSO-d_6): 3.76(s, 3H, 2OCH_3), 6.9–7.45 (m, 12H, Ar-H), 9.57 (br, 4H, 4NH, D_2O-exchangeable). ^{1}H NMR (**2c**; DMSO-d_6): 1.32 (t, 6H, 2CH_3), 4.02 (q, 4H, 2OCH_2), 6.87–744 (m, 12H, Ar-H), 9.5 (s, 4H, 4NH; D_2O-exchangeable).

{3-[4-(3-Carboxymethylthioureido)phenyl]thioureido}acetic acid 3: A mixture of **1** (0.01 mmol) in THF (30 ml), glycine (0.02 mmol)

TABLE I Characteristics Data for the Prepared Compounds

Compd. No.	m.p. [°C]	Yield (%)	Mol Formula (mol.wt.)	Elemental analyses Calcd./Found			
				C	H	N	S
2a	260	90	$C_{22}H_{22}N_4S_2$	64.99	5.45	13.78	15.77
			(406)	64.90	5.40	13.70	15.70
2b	274	95	$C_{22}H_{22}N_4O_2S_2$	60.25	5.06	12.77	14.62
			(438)	60.20	5.10	12.70	14.60
2c	245	95	$C_{24}H_{26}N_4O_2S_2$	61.78	5.62	12.01	13.74
			(466)	61.70	5.60	12.10	13.80
3	280	70	$C_{12}H_{14}N_4O_4S_2$	42.10	4.12	16.36	18.73
			(342)	42.00	4.10	16.30	18.70
4a	185	86	$C_8H_{12}N_6S_2$	37.48	4.72	32.78	25.02
			(256)	37.40	4.60	32.70	24.90
4b	210	76	$C_{20}H_{20}N_6S_2$	58.80	4.93	20.57	15.70
			(408)	58.70	4.90	20.50	15.60
5	>300	53	$C_{22}H_{18}N_6OS_2$	59.17	4.06	18.82	14.36
			(446)	59.10	4.10	18.70	14.30
7	185	78	$C_{20}H_{20}N_6S_2$	58.80	4.93	20.57	15.70
			(408)	58.80	4.80	20.50	15.60
8	260	56	$C_{24}H_{24}N_6O_2S_2$	58.52	4.91	17.06	13.02
			(492)	58.50	4.80	16.90	12.90
9	>300	84	$C_{20}H_{18}N_4S_4$	64.15	3.77	14.96	17.12
			(374)	64.10	3.70	14.90	17.10
12a	>300	67	$C_{22}H_{14}N_4O_2S_2$	61.38	3.28	13.01	14.90
			(430)	61.30	3.20	13.10	14.80
12b	>300	56	$C_{22}H_{14}N_4O_2S_2Cl_4$	46.50	1.77	9.86	11.28
			(568)	46.50	1.70	9.80	11.20
13a	200	68	$C_{26}H_{24}N_6S_4$	56.91	4.41	15.31	23.37
			(548)	56.80	4.30	15.20	23.30
13b	>300	77	$C_{26}H_{22}N_4O_2S_4$	56.70	4.03	10.17	23.29
			(550)	56.60	4.10	10.10	23.20
14	>300	66	$C_{22}H_{12}N_2O_4S_2$	61.10	2.80	6.48	14.83
			(432)	61.10	2.70	6.40	14.80
15	260	49	$C_{16}H_{10}N_4S_3$	54.21	2.84	15.81	27.14
			(354)	54.10	2.80	15.80	27.10
16a	>300	75	$C_{24}H_{16}N_6S_4$	55.79	3.12	16.27	24.82
			(516)	55.70	3.00	16.20	24.80
16b	>300	54	$C_{24}H_{14}N_6S_4Cl_2$	49.23	2.41	14.35	21.90
			(584)	49.20	2.30	14.30	21.80
16c	280	76	$C_{24}H_{12}N_4S_4O_2Cl_2$	49.06	2.06	9.54	21.83
			(586)	48.90	1.95	9.50	21.80

in NaOH (10 ml) was stirred at room temperature for 2 h; the product was precipitated with dilute HCl, filtered, washed with water, dried, then recrystallized from dioxane to give **3**. IR: 3324, 3242 (NH), 2862 (CH-aliph.), 1719 (C=O), 1534 and 1244 (C=S). ^{1}H NMR (DMSO-d_6):

4.2 (s, 6H, $2CH_2$ + 2NH), 7.2–7.4 (q, 4H, A-B system), 7.8 (s, 2H, 2NH), 9.7 (s, 2H, 2COOH).

Bisthiosemicarbazide derivatives 4a,b: A solution of **1** (0.01 mmol) and hydrazine hydrate or phenyl hydrazine (0.02 mmol) in dioxane (30 ml) was refluxed for 3 h; the solid which formed on heating was collected and washed with dioxane to give **4a,b**. IR (**4a**): 3295, 3223 (NH_2), (NH), 1507 and 1270 (C=S). MS (**4a**; %): 256 (M^+; 9.53), 257 (M + 1; 6), 224 (35), 192 (25), 150 (100). ^{1}H NMR (**4b**; DMSO-d_6): 6.76–7.44 (m, 14H, Ar-H), 7.97, 9.58, 9.71 (s, 6H, 6NH; D_2O-exchangeable).

4-(4-(2-Benzoylhydrazino-thiocarbonylaminophenyl)-5-phenyl-4H-[1,2,4]triazole-3-thiol 5: A solution of **1** (0.01 mmol) and benzoyl hydrazine (0.02 mmol) in dioxane (30 ml) was refluxed for 24 h; the reaction mixture was allowed to cool and poured into cold water (50 ml). The product was collected and recrystallized from dioxane to give **5**. IR: 3225 (NH), 1650 (C=O), 1510 and 1224 (C=S). MS (**5**; %): 446 (M^+; 10), 382 (10), 343 (10), 258 (10), 134 (27), 103 (20), 75 (26), and 52 (100).

1-(-Amino-phenyl)-3-{4-[3-(2-amino-phenyl)thioureido]-phenyl}thiourea 7: A mixture of **1** (0.01 mmol), o-phenylenediamine (0.02 mmol), and triethylamine (0.5 ml) in dioxane (30 ml) was refluxed for 6 h; the solid product which produced on heating was collected and boiled with dioxane to give **7**. IR: 3355, 3271 (NH_2), (NH), 1531 and 1271 (C=S). MS (**7**; %): 408 (M^+; 38), 365 (42), 327 (42), 296 (50), 257 (38), 249 (69), 229 (62), 209 (53), 195 (84), and 128 (100).

N-[2-(3-{4-[3-(2-Acetylaminophenyl)thioureido]-phenyl}thioureido)-phenyl] acetamide 8: Compound **7** (0.01 mmol) was refluxed with acetic anhydride (10 ml) for 3 h then allowed to cool. The solid product was collected then recrystallized from ethanol to give **8**. IR: 3153, 3109 (NH), 2993 (CH-aliph.), 1716 (C=O), 1458 and 1177 (C=S). ^{1}H NMR (DMSO-d_6): 3.01 (s, 6H, $2COCH_3$), 7.18–7.32 (m, 12H, Ar-H), 7.50, 7.51, 7.99, 8.03 (4H, 4NH; D_2O-exchangeable), 13.7 (s, 2H, 2NH-$COCH_3$; D_2O-exchangeable).

N,N′-Bis-(benzothiazole-2-yl)-benzene-1,4-diamine 9: A mixture of **1** (0.01 mmol), o-aminothiophenol (0.02 mmol), and triethylamine (0.5 ml) in DMF (30 ml) was refluxed for 12 h then allowed to cool and poured into cold water (50 ml). Acidification with HCl yielded a solid product which was recrystallized from dioxane to give **9**. IR: 3213 (NH), 3048 (CH-arom.), 1601 (C=N). ^{1}H-NMR (DMSO-d_6): 7.36–8.26 (m, 12H, Ar-H) and 12.5 (s, 2H, 2NH; exchangeable with D_2O) MS (**9**; %): 374 (M^+; 19), 375 (M+1; 19), 358 (35), 338 (47), 337 (100), 307(41), 296 (72), 239 (47) and 158 (59).

3,3′-(1,4-phenylene)bis(2-thioxo-4-oxo-2,3-dihydro-1H-quinazoline derivatives 12a,b: A mixture of **1** (0.01 mmol) and

anthranilic acid derivatives **10a,b** (0.02 mmol) in dioxane (30 ml) and triethylamine (0.5 ml) was refluxed for 3 h; the solid product which produced on heating was collected and boiled with dioxane to give **12a,b**. IR (**12a**): 3213 (NH), 1662 (C=O), 1532 and 1195 (C=S). IR (**12b**): 3376 (NH), 1681 (C=O), 1508 and 1222 (C=S). MS (**12a**; %): 430 (M^+; 48), 364 (44), 339 (64), 323 (48), 278 (100), 254 (56), 246 (68), 215 (100), 152 (76). MS (**12b**; %): 568 (M^+; 71), 569 (M+1; 56), 570 (M+2; 48), 571 (M+3; 26), 567 (100), 565 (65), 552 (20), 380 (27), 364 (22), 320 (44), 232 (36), 192 (2), 159 (35), 97 (22).

3,3′-(1,4-Phenylene)bis(4-Imino-3,4,5,6,7,8-hexahydro-1H-benzo-[4,5]-thieno-[2,3-d]-pyrimidine-2-thione 13a and 3,3′-(1,4-phenylene)bis(2-thioxo-2,3,5,6,7,8-hexahydro-1H-benzo[4,5]-thieno-[2,3-d]-pyrimidin-4-one 13b: To a suspension of **1** (0.01 mmol) and **11a** or **11b** (0.02 mmol) in dioxane (30 ml), triethylamine (0.5 ml) was added. The reaction mixture was heated under reflux for 3 h; the solid product which produced on heating was collected and washed with hot dioxane to give **13a,b**. IR (**13a**): 3267, 3157 (NH), 2932 (CH-aliph), 1556 and 1258 (C=S). IR (**13b**): 3197 (NH), 2932 (CH-aliph), 1663 (C=O), 1509 and 1228 (C=S).^{1}H NMR (**13a**): 1.77, 2.79 (m, 16H, $8CH_2$), 3.57 (s, 2H, 2SH), 5.8 (humb, 2H, 2NH), 7.07–7.44 (m, 4H, Ar-H). MS (**13a**; %): 548 (M^+; 22.45), 549 (M+1; 29), 534 (46), 473 (38), 458 (63), 446 (32), 391 (57), 379 (46), 329 (59), 266 (85), and 225 (100). MS (**13b**; %): 550 (M^+; 32), 551 (M+1; 30), 533 (55), 402 (53), 360 (62), 343 (46), 308 (69), 301 (32), 287 (32), 246 (37), 228 (55), and 182 (100).

3,3′-(1,4-Phenylene)bis(4-oxo-2-thioxo-2,3-dihydro-benzo[e]-[1,3]-oxazine 14: A mixture of **2** (0.01 mmol), salicylic acid (0.02 mmol), and triethylamine (0.5 ml) in DMF (30 ml) was refluxed for 24 h. The obtained solid was recrystallized from dioxane to give **15**. IR (**15**): 1677 (C=O) and 1515 and 1124 (CS-N). MS (**15**; %): 432 (M^+; 28), 398 (44), 369 (44), 339 (54), 223 (46), 199 (54), 164 (48), 130 (50), 126 (70), and 86 (100).

5-Imino-(4-isothiocyanato-phenyl)-3-phenyl-imidazolidine-2,4-dithione 15: A solution of **1** (0.01 mmol) in THF (30 ml), N-phenylcyanothio-formamide (0.02 mmol) and few drops of triethylamine was stirred at room temperature for 0.5 h; the solid obtained was recrystallized from chloroform/pet. ether to give **15**. IR (**15**): 3350 (NH), 2100 (-NCS), 1515 and 1198 (C=S). MS (**15**): 354 (M^+; 11.3), 355 (M+1; 9.2), 356 (M+3; 5.8), 339 (9.4), 313 (2.3), 192 (25), 176 (26), 162 (7.5), 135 (48), 77 (100).

1,1′-(1,4-Phenylene)bis[3-(4-substituted-phenyl)-5-imino-imidazolidine-2,4-dithiones] 16a,b: A solution of **1** (0.01 mmol), N-(4-substituted-phenyl)cyanothio-formamide (0.02 mmol), and

triethylamine (0.5 ml) in THF (20 ml) was refluxed for 3 h. The solid which formed on heating was collected and washed with hot dioxane to give **16a,b**. IR (**16b**): 3221 (NH), 1512 and 1280 (C=S). ^{1}H NMR (**16**b; DMSO-d_6): 7.22–7.85 (m, 12H, Ar-H), 9.96 (s, 2H, 2NH; D_2O-exchangeable). MS (**16a**; %) : 516 (M^+; 2), 354 (60), 283 (7), 224 (5), 192 (53), 161 (17), 135 (89), 90 (30), 77 (100).

Hydrolysis of 16b: To a solution of **16b** (0.01 mmol) in boiling DMF (20 ml), conc. HCl (5 ml) was added. The obtained product was recrystallized from dioxane to give **16c**. IR (**16c**): 3062 (CH-arom.), 1756 (C=O), 1513 and 1089 (C=S).

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