Benzo- and naphthoimidazoxadiazolediene, naphthobisthiazole as well as naphthothiazine derivatives from 1-acylthiosemicarbazides

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Abstract

1-Acylthiosemicarbazides **1a-d** reacted with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (**2a**), 2,3,5,6-tetrachloro-1,4-benzoquinone (**2b**), 2,3-dichloro-1,4-naphthoquinone (**3a**) and 2,3-dicyano-1,4-naphthoquinone (**3b**) in ethyl acetate with admission of air to form benzo- and naphtho-imidazoxadiazoles **(5, 6, 11)**, naphthobisthiazoles **(12a-d)**, naphthothiadiazines **(13a-d)** as well as 2,3,7,8-tetrachlorothianthrene-1,4,6,9-tetraone **(7)**. Rationales for the observed conversions are presented.

Keywords: Benzo- and naphthoquinones, Cyclocondensation, Fused heterocyclic compounds

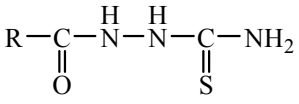
Introduction

The chemistry of quinones is of considerable interest since this class of compounds includes many natural products and numerous important synthetic products[1,2]. Addition of nitrogen nucleophiles to benzo- and naphthoquinones represents a common synthetic route to many fused heterocyclic rings which have been used as synthetic intermediates in medicinal chemistry[3-6] and for dyestuffs[7-16].

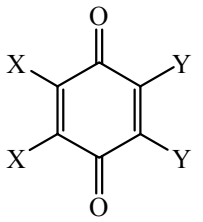
2,3,5,6-Tetrachloro-1,4-benzoquinone (**2b**) and 2,3-dichloro-1,4-naphthoquinone (**3a**) reacted with N^1,N^2-diarylamidines to give benzimidazole and indole derivatives[17,18]. A series of benzo- and naphthothiazolediones have been synthesized by reaction of *N*-substituted thioureas with **2a**, **2b** and **3a**[19]. Indazole, thiadiazine and naphothiadiazine derivatives were isolated from the reaction of thiosemicarbazide with **2b** and **3a**[10]. The reaction of *N,N`*-disubstituted hydrazinecarbothioamides with **2b** and **3a** afforded thiadiazole and thiadiazine derivatives[20]. In contrast, quinoxaline and thiadiazepane derivatives were obtained from the reaction of substituted thioureidoethylthioureas with **2b**[20].

Recently, we have reported that 4-substituted thiosemicarbazides reacted with **2a**, **2b** and **3a** in ethyl acetate with admission of air to form derivatives of 1,5,2,3-oxathiadiazole, indazole, thiadiazine-6-one, 1,3,4-thiadiazaphenanthrenone and naphtho[1,2-*e*`:4,3-*e*`]bis[1,3,4]-

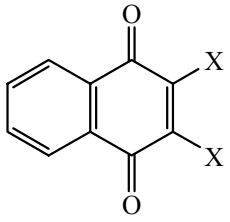
thiadiazine[21]. This unique reactivity has no precedence and warrants further investigation. Therefore, we undertook to prepare electron poorer examples such as 1-acylthiosemicarbazides **1a-d**, and to investigate their behaviour towards benzo- as well as naphthoquinones **2a,b** and **3a,b** (Fig. 1).



1a-d



2: **a**, X = CN, Y = Cl (**DDQ**)
b, X = Y = Cl (**CHL**)



3: **a**, X = Cl (**DCHNQ**)
b, X = CN (**DCNQ**)

1	**a**	**b**	**c**	**d**
R	CH_3	C_6H_5	4-HO-C_6H_4	4-Br-C_6H_4-CH_2

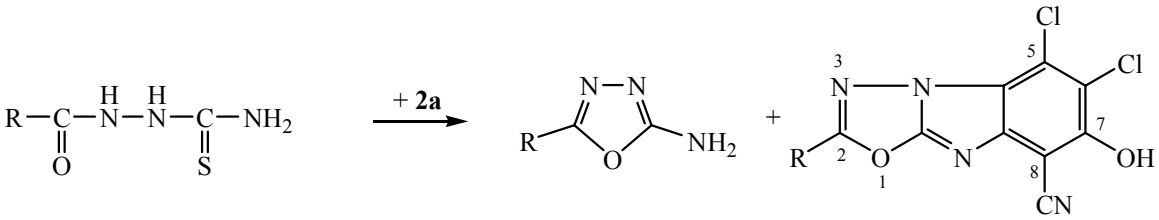
Figure 1

Results and Discussion

Mixing of two-fold molar amounts of **2a** with one mole each of the donors **1a-d** in ethyl acetate with admission of air gives a blue colour (λ_{max} = 573-591 nm). This colour changes gradually to brown with the formation of a solid product. This behaviour is explained as being due to initial formation of an unstable charge-transfer complex (CTC) followed by a chemical reaction which yields substituted benzimidazoxadiazole **5a-d** *via* the reaction of dihydrobenzoquinone (**2a**-H_2) with **4** and elimination one molecule of HCN and another of H_2O (Scheme 1). The structures of the well known compounds **4a-c** were confirmed on the basis of spectral data and mixed melting points. The structural assignments for the benzimidazoxadiazole derivatives **5a-d** are based on the following spectral data: the IR spectrum of **5a** showed characteristic absorption for the hydroxyl group at ν 3440 cm^{-1} and at 2220 cm^{-1} for the cyano group. The ^{1}H-NMR spectrum showed a broad signal at 9.53 ppm due to the OH in addition to the methyl group at 2.33 ppm. The decoupled ^{13}C-NMR spectrum showed signals at δ 164.82, 156.22 and 150.71 for C-2, C-9a and C-8a, respectively. Also, the ^{13}C-NMR clearly indicates the presence of one cyano group at 118.77 ppm beside the aromatic carbons.

The molecular formulae for **5a-d** (Scheme 1) are supported by elemental analyses and mass spectra, which gave the expected molecular ion peaks. The semi-micropreparative scale reaction of **1a** with **2a** gave **5a**, as established from the comparison of its IR spectrum and mp with those

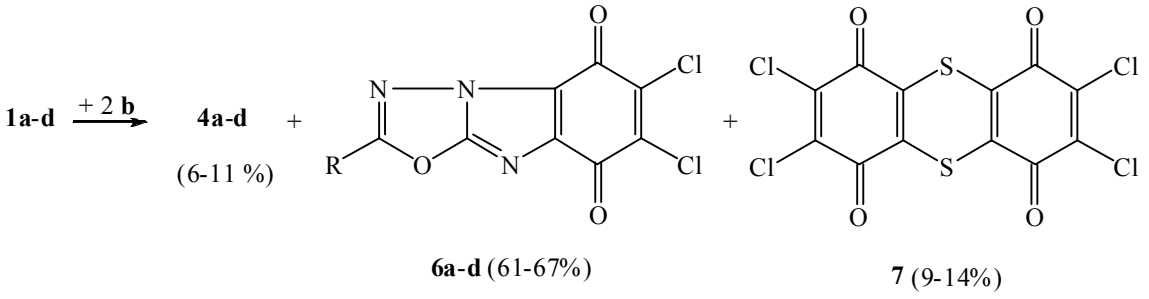
of an authentic sample. In addition, small quantities of numerous coloured, unidentifiable byproducts were observed.



1, 4, 5	a	b	c	d
R	CH_3	C_6H_5	4-HO-C_6H_4	4-Br-C_6H_4-CH_2

Scheme 1

On the other hand, mixing of a two fold molar excess of **2b** with one mole of 1-acylthiosemicarbazides **1a-d** leads to the formation of an initial CTC (λ_{max} = 506-518 nm) followed by formation (complete after three days) of the products, benzimidazoxadiazolediones **6a-d**, oxadiazoles **4a-d** and 2,3,7,8-tetrachlorothianthrene-1,4,6,9- tetraone **7** (Scheme 2).

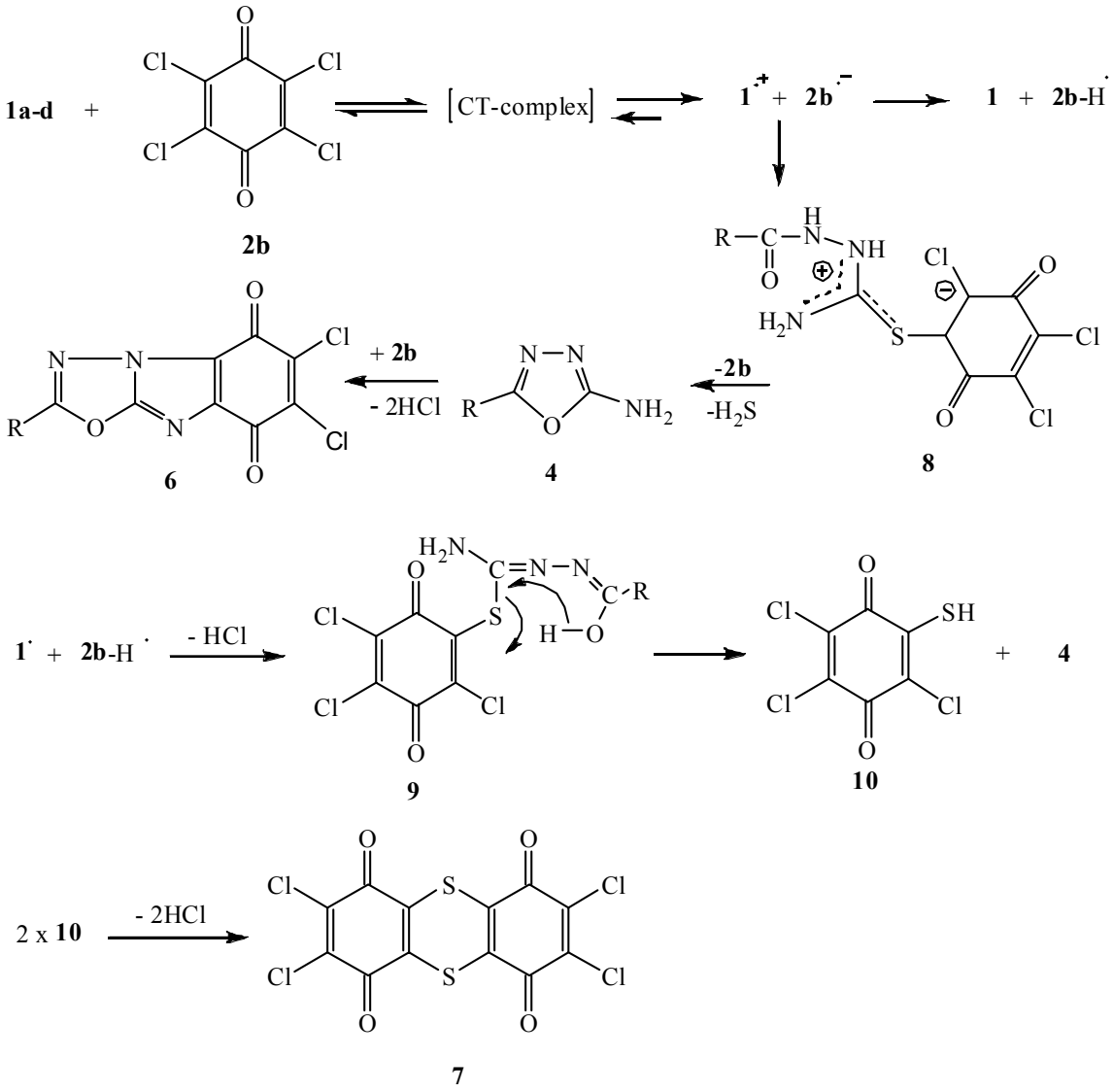


1, 4, 6	a	b	c	d
R	CH_3	C_6H_5	4-HO-C_6H_4	4-Br-C_6H_4-CH_2

Scheme 2

The IR spectrum of **6b** showed a sharp band at 1695 cm^{-1} for the carbonyl group of the quinone system. The ^{1}H-NMR spectrum revealed a multiplet at 7.19-7.66 ppm, which is characteristic of phenyl protons. The ^{13}C-NMR spectrum showed the characteristic absorption signals of the carbonyl carbon atoms of **2b** at 170.72 and 171.83[22]. Other signals were observed in the ^{13}C-NMR of **6b**, clearly indicating the presence of C=N, N=C-O, Cl-C=C=Cl groups

(experimental part). The formation of **6b** was further confirmed by mass spectrometry. Besides the molecular ion at 331/335, the characteristic fragment ion patterns of substituted dichloro compounds were observed[23].

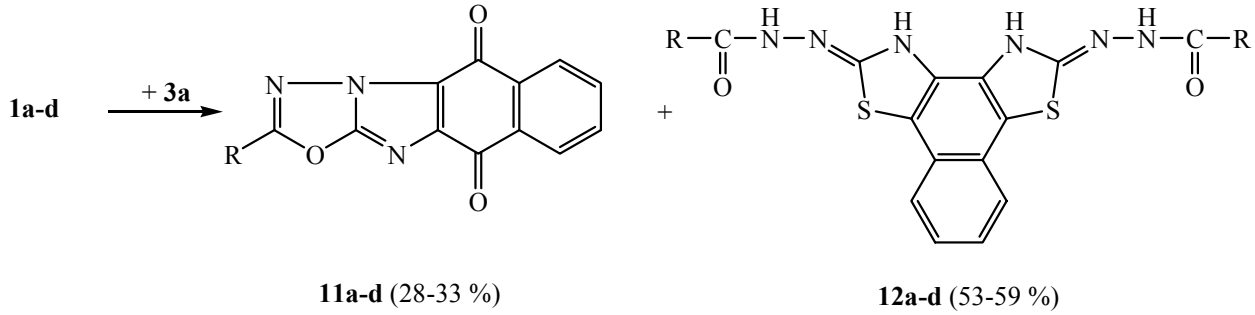


Scheme 3

Formation of products **4**, **6** and **7** may be rationalized by the mechanism shown in Scheme 3. An unstable CTC is formed followed by the formation of radical **1**· and **2b**-H·.

Two routes can be suggested for the formation of compounds **4**, **6** and **7**. The first one is the cyclization of **1a-d** and formation of the oxadiazoles **4a-d** during intramolecular nucleophilic attacks on the thiocarbonyl group. After cyclization, **2b** is released with the liberation of H_2S (Scheme 3). Recombination of **4** and **2b** with elimination of two molecules of HCl would afford

the benzimidazoxodiazolediones **6a-d**. The second possible route is the elimination of one molecule of HCl from (**1** + **2b-H**) to give the intermediate **9**. Nucleophilic attack by the OH group on C=N and detachment of the HS-moiety would afford the intermediate **10** along with oxadiazoles **4a-d**. Then, the tetrachlorothianthrenetetraone **7** could be formed *via* the reaction of two molecules of **10** with the elimination of two molecules of HCl (Scheme 3).



11a-d (28-33 %) **12a-d** (53-59 %)

1, 11, 12	**a**	**b**	**c**	**d**
R	CH_3	C_6H_5	4-HO-C_6H_4	4-Br-C_6H_4-CH_2

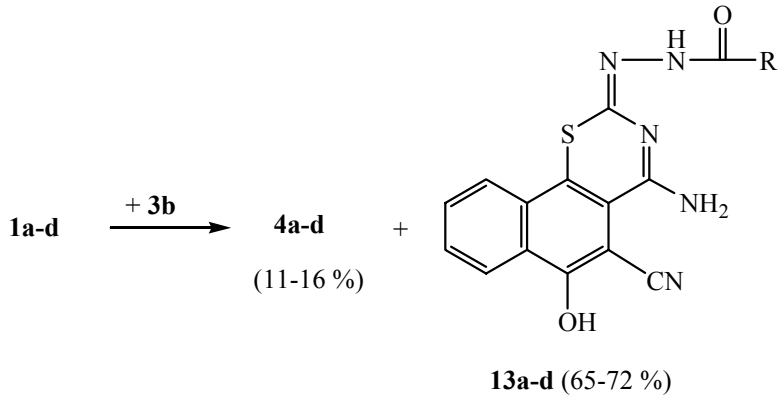
Scheme 4

By mixing equimolar amounts of 1-acylthiosemicarbazides **1a-d** and **3a** in ethyl acetate the colour of the reaction mixture remains unchanged. Obviously, there is no donor-acceptor interaction between these two molecules, which is mainly due to the low electron affinity of **3a** compared with **2b**[24]. Heating of this mixture for 5 hours and chromatographic separation of the residue after concentration gave numerous coloured zones, from which naphthoimidazoxadiazoles **11a-d** and naphthobisthiazoles **12a-d** could be isolated (Scheme 4).

The structures of **11a-d** were delineated from their spectroscopic properties and gross compositions. The major products **12a-d** were found to be formed from one molecule of **3a**-H_2 and two molecules of **1a-d** by loss of two molecules of H_2O and HCl.

The IR spectrum of **12d** showed absorption characteristic of NH groups at 3385, 3225 cm^{-1} and a strong carbonyl group absorption at 1670 cm^{-1}. The ^{1}H-NMR spectrum of **12d** clearly indicates the presence of two different broad signals centered at 10.65 and 11.17 ppm due to thiazole-NH and amide-NH, respectively. In addition, the benzylic-CH_2 as well as aromatic protons were observed (see experimental part). The ^{13}C-NMR of **12d** showed a carbonyl signal at δ_C = 171.48 corresponding to the amide group. Also, the ^{13}C-NMR clearly indicates the presence of signals at 52.28 and 163.26 due to benzylic-CH_2 and thiazole-C_2, respectively. The elemental analysis of **12d** suggested a gross formula $C_{28}H_{20}Br_2N_6O_2S_2$ and this was confirmed by the mass spectrum, which exhibited the molecular ion at m/z 698/694 (17 %). It should be noted also that the mass spectra of compounds **12a-d** show the loss of an acyl group from the molecular ions.

In contrast to the situation with **3a**, on addition of **1a-d** to **3b**, the initial formation of CT complexes (λ_{max} = 523-532 nm) is followed by the formation of naphthothiazine derivatives **13a-d** in addition to oxadiazoles **4a-d** (Scheme 5).



13a-d (65-72 %)

1, 4, 13	a	b	c	d
R	CH_3	C_6H_5	4-HO-C_6H_4	4-Br-C_6H_4-CH_2

Scheme 5

For compound **13b**, the gross formula $C_{20}H_{13}N_5O_2S$ is supported by mass spectroscopy, which clearly demonstrates the loss of a benzoyl group. The ^{13}C NMR spectrum reveals the absence of the C=S signal and the presence of an amide C=O signal (171.56) and only one CN resonance (118.11 ppm). In addition to an OH group, both a NH_2 (δ_H = 7.12 ppm) and a low field amide-NH (δ_H = 11.15 ppm) are present. The IR spectrum of **13b** showed bands at 3445, 3370-3250, 2220 and 1675 cm^{-1} due to OH, (NH and NH_2), CN and amide C=O groups, respectively.

Conclusions

Novel and interesting structures are presented here from the reactions between the electron donor 1-acylthiosemicarbazides **1a-d** and electron acceptors; benzo- as well as naphthoquinones **2a,b** and **3a,b**. In a fairly complex, multistep process, three interesting kinds of fused heterocyclic compounds (benzo- and naphthoimidazoxadiazoles, naphthobisthiazole and naphthothiazine derivatives) are formed, in addition to the oxadiazole ring. Thus, benzo- and naphthoquinones may act either as mediators or as building blocks in heterocyclization of acylthiosemicarbazides. The results reported also supplement the chemistry of nucleophilic substitution of halogenated *p*-quinones, which continues to be of interest for the synthesis of many heterocycles.

Experimental Section

General Procedures: The uncorrected melting points were determined on a Gallenkamp melting point apparatus, IR spectra were recorded using KBr disks on Shimadzu 408 or Bruker Vector 22 FT-IR instruments. ^{1}H 300 MHz and ^{13}C-NMR 75 MHz spectra were recorded on a Bruker WM300 instrument, 500 MHz ^{1}H and 125 MHz ^{13}C-NMR spectra on a Bruker DRX 500 spectrometer. Chemical shifts are expresses as δ [ppm] with reference to tetramethylsilane as an internal standard, s = singlet d = doublet, m = multiplet. The ^{13}C signals were assigned on the basis of DEPT 135/90 spectra. The mass spectra (70 ev, electron impact mode) were recorded on an AMD 604 instrument. The UV-VIS spectra were recorded on a Perkin-Elmer Lambda 2 spectrophotometer. Combustion analysis was carried out at the Microanalytical center, Cairo University, Egypt. Preparative layer chromatography (plc) was carried out using air dried 1.0 mm thick layers of a slurry of silica gel (Merck PF_{254}) applied on 48 cm wide and 20 cm high glass plates using cyclohexane/ ethyl acetate as developing solvent. Zones were detected by their colour or by quenching of indicator fluorescence upon exposure to 254 nm light and extracted out with acetone.

Materials: 1-Acylthiosemicarbazides **1a-c** were prepared according to the literature[25-27]. The ^{1}H-NMR spectral data of 1-acetylthiosemicarbazide (**1a**)[25], 1-benzoylthiosemicarbazide (**1b**)[26], and 1-(4-hydroxyphenyl)thiosemicarbazide (**1c**)[27] were in full accord with the published data.

1-(4-Bromophenylaceto)thiosemicarbazide (1d). To a stirred solution of thiosemicarbazide (0.91 g, 10 mmol) in 50 ml dry acetone, *p*-bromophenylactic acid (2.15 g, 10 mmol) was added and the mixture was refluxed for 3 hours. A white precipitate was formed and recrystallized from ethanol to give colourless crystals (2.84 g, 85 %), mp = 96-98 °C.

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (**2a**, Aldrich) was recrystallized from benzene/-chloroform (2:3). 2,3,5,6-Tetrachloro-1,4-benzoquinone (**2b**, Aldrich) was recrystallized from benzene before use. 2,3-Dicyano-1,4-naphthoquinone (**3b**) was prepared from 2,3-dichloro-1,4-naphthoquinone (**3a**) according to Badni[28] and recrystallized from dichloromethane.

Reaction of 1-acylthiosemicarbazides 1a-d with 2a

To a solution of 454 mg of **2a** (2 mmoles) in 20 ml of dry ethyl acetate, were added the acylthiosemicarbazides **1a-d** (1 mmol) in 15 ml of dry ethyl acetate dropwise with stirring at room temperature. Thereafter, the mixture was stirred for 24 h, filtered, and the precipitate was washed with a small amount of cold ethyl acetate. The filtrate was concentrated and the residue chromatographed on thin-layer plates (silica gel Pf_{254}) using cyclohexane/ethyl acetate (5:1) to give only one zone containing the oxadiazole derivatives **4a-d**. Recrystallization of the isolated products from suitable solvents afforded the pure compounds **4a-d** and **5a-d**.

2-Amino-5-methyloxadiazole (4a). Yield 17 mg (17 %) mp 233-235 °C (lit. 232-234 °C)[29].

2-Amino-5-phenyloxadiazole (4b). Yield 19 mg (19 %) mp 252-54 °C (lit. 250 °C)[30,31].

2-Amino-5-(4-hydroxyphenyl))oxadiazole (4c). Yield 22 mg (19 %) mp 286-288 °C (lit. 288-290 °C)[30,31].

2-Amino-5-(4-bromobenzyl))oxadiazole (4d). Colourless crystals (21 mg, 21 %), mp 185-187 °C (ethanol). IR (KBr): ν 3410 (NH_2), 1630 (C=N), 1595 (aryl), 1085 (C-O-C) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 4.21 (s, 2H, CH_2), 6.88 (br, 2H, NH_2), 7.14-7.69 (m, 4H, aryl-H). MS m/z (%): 255/253 (M^+, 33), 211 (21), 131 (36), 90 (87), 77 (100). Anal. Calcd. for $C_9H_8N_3BrO$: C, 42.54; H, 3.17; N, 16.54. Found: C, 42.78; H, 2.98; N, 16.29.

2-Methyl-5,6-dichloro-8-cyano-7-hydroxy[4,5]benzimidazo[2,1-*b*][1,3,4]oxadiazole (5a). Brown crystals (193 mg, 68 %), mp 135-137 °C (methanol). IR (KBr): ν 3440 (OH), 2220 (CN), 1625 (C=N), 1600 (aryl), 1090 (C-O-C) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.33 (s, 3H, CH_3), 9.53 (br, 2H, OH). ^{13}C-NMR (DMSO-d6): δ 16.68 (CH_3), 118.77 (CN), 121.44, 121.88 (C-5, C-6), 142.44 (C-8), 150.22 (C-4a), 150.71 (C-8a), 152.98 (C-7), 156.22 (C-9a), 164.82 (C-2). MS m/z (%): 286/282 (M^+, 18), 239 (22), 169 (29), 139 (12), 113 (45), 43 (100). Anal. Calcd. for $C_{10}H_4Cl_2N_4O_2$: C, 42.43; H, 1.42; N, 19.79; Cl, 25.05. Found: C, 43.62; H, 1.67; N, 19.57; Cl, 25.17.

2-Phenyl-5,6-dichloro-8-cyano-7-hydroxy[4,5]benzimidazo[2,1-*b*][1,3,4]oxadiazole (5b). Brown crystals (252 mg, 73 %), mp 206-208 °C (acetonitrile). IR (KBr): ν 3430 (OH), 2215 (CN), 1610 (C=N), 1590 (aryl), 1080 (C-O-C) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 7.18-7.55 (m, 5H, aryl), 9.49 (br, 1H, OH). ^{13}C-NMR (DMSO-d6): δ 118.74 (CN), 121.64, 122.18 (C-5, C-6), 127.66, 128.86, 129.38 (aryl-CH), 131.12 (aryl-C), 141.96 (C-8), 150.67 (C-4a), 150.88 (C-8a), 153.11 (C-7), 156.18 (C-9a), 164.88 (C-2). MS m/z (%): 348/344 (M^+, 16), 239 (29), 169 (18), 139 (22), 105 (100), 65 (33). Anal. Calcd. for $C_{15}H_6Cl_2N_4O_2$: C, 52.20; H, 1.75; N, 16.23; Cl, 20.54. Found: C, 52.38; H, 1.91; N, 16.05; Cl, 20.62.

2-(4-Hydroxyphenyl)-5,6-dichloro-8-cyano-7-hydroxy[4,5]benzimidazo[2,1-*b*][1,3,4]oxadiazole (5c). Brown crystals (253 mg, 70 %), mp 155-157 °C (acetonitrile). IR (KBr): ν 3450 (OH), 2220 (CN), 1625 (C=N), 1600 (aryl), 1090 (C-O-C) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 6.96-7.4 (m, 4H, aryl), 9.38 (br, 1H, OH), 9.52 (br, 1H, OH). ^{13}C-NMR (DMSO-d6): δ 118.69 (CN), 121.53, 122.10 (C-5, C-6), 126.12, 129.16 (aryl-CH), 130.08, 142.12 (C-8), 150.52 (C-4a), 151.10 (C-8a), 153.35 (C-7), 156.53 (aryl-C), 165.02 (C-2). MS m/z (%): 364/360 (M^+, 21), 239 (32), 169 (15), 121 (96), 105 (88), 93 (100), 77 (82), 65 (44). Anal. Calcd. for $C_{15}H_6Cl_2N_4O_3$: C, 49.89; H, 1.67; N, 15.51; Cl, 19.63. Found: C, 50.06; H, 1.45; N, 15.73; Cl, 19.44.

2(4-Bromobenzyl)-5,6-dichloro-8-cyano-7-hydroxy[4,5]benzimidazo[2,1-*b*][1,3,4]oxadiazole (5d). Brown crystals (285 mg, 65 %), mp 220-222 °C (ethanol). IR (KBr): ν 3435 (OH), 2220 (CN), 1620 (C=N), 1595 (aryl), 1086 (C-O-C) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 4.73 (s, 2H, CH_2), 6.98-7.43 (m, 4H, aryl), 9.48(br, 1H, OH). ^{13}C-NMR (DMSO-d6): δ 52.71 (CH_2), 118.69 (CN), 121.62, 121.98 (C-5, C-6), 126.66 (aryl-C),128.33, 129.64 (aryl-CH),134.32 (aryl-C),142.11 (C-8), 150.72 (C-4a), 150.86 (C-8a), 153.14 (C-7),156.14 (C-9a), 164.76 (C-2). MS m/z (%): 442/436 (M^+, 22), 356 (29), 239 (6), 189 (77), 142 (15), 91 (88), 77 (100), 65 (54). Anal. Calcd. for $C_{16}H_7BrCl_2N_4O_2$: C, 43.87; H, 1.61; N, 12.79; Cl, 16.19. Found: C, 44.02; H, 1.54; N, 12.93; Cl, 16.03.

Reaction of 1-acylthiosemicarbazides 1a-d with 2b

To a stirred solution of 492 mg (2 mmmols) of **2b** in 30 ml of dry ethyl acetate, were added acylthiosemicarbazides **1a-d** (1 mmol) in 15 ml dry ethyl acetate dropwise at room temperature. The colour of the reaction mixture changed gradually from reddish brown to pale blue. The mixture was stirred for another 72 h and then filtered off. The blue precipitate which contained compound **7**[20] was washed with cold ethyl acetate. The filtrate was concentrated and the residue was then separated by preparative layer chromatography (plc) using a suitable eluent (cyclohexane/ ethyl acetate, 5:1 for the reaction of **2b** with **1a** and **1d**; 3:1 for the reaction of **2b** with **1b** and **1c**) to give numerous coloured zones, two of which (with high intensity) were removed and extracted. The faster migrating one, R_f = 0.146, contained the oxadiazoles **4a-d**, and the second zone, R_f = 0.096 (characterized by its green colour) contained benzimidazoxadiazolediones **6a-d**. Extraction of the zones with acetone, and concentration, gave a residue which was rechromatographed to separate the pure compounds.

2-Methyl-6,7-dichloro-benzo[4,5]imidazo[2,1-*b*][1,3,4]oxadiazole-5,8-dione (6a). Pale green crystals (171 mg, 63 %), mp 190-192 °C (ethanol). IR (KBr): ν 2960 (Ali-CH), 1690 (C=O), 1620 (C=N), 1086 (C-O-C) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.36 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6): δ 15.83 (CH_3), 142.12 (C-6, C-7), 150.84, 150.93 (C-4a, C-8a), 154.12 (C-9a), 164.87 (C-2), 170.66, 171.76 (C-5, C-8). MS m/z (%): 273/269 (M^+, 27), 228 (31), 157 (24), 129 (18), 101 (32), 43 (100). Anal. Calcd. for $C_9H_3Cl_2N_3O_3$: C, 39.73; H, 1.11; N, 15.17; Cl, 26.06. Found: C, 40.01; H, 1.26; N, 15.28; Cl, 25.79.

2-Phenyl-6,7-dichloro-benzo[4,5]imidazo[2,1-*b*][1,3,4]oxadiazole-5,8-dione (6b). Pale green crystals (216 mg, 65 %), mp 210-212 °C (acetonitrile). IR (KBr): ν 1695 (C=O), 1625 (C=N), 1600 (aryl), 1085 (C-O-C) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 7.19-7.66 (m, 5H, aryl). ^{13}C-NMR (DMSO-d_6): δ 127.94, 128.81, 129.44 (aryl-CH), 131.22 (aryl-C), 142.26 (C-6, C-7), 150.87, 151.11 (C-4a, C-8a), 154.22 (C-9a), 164.96 (C-2), 170.72, 171,83 (C-5, C-8a). MS m/z (%): 335/331 (M^+, 21), 228 (26), 200 (17), 129 (19), 105 (100), 71 (71). Anal. Calcd. for $C_{14}H_5Cl_2N_3O_3$: C, 50.33; H, 1.51; N, 12.58; Cl, 21.58. Found: C, 50.56; H, 1.32; N, 12.37; Cl, 21.37.

2-(4-Hydroxyphenyl)-6,7-dichloro-benzo[4,5]imidazo[2,1-*b*][1,3,4]oxadiazole-5,8-dione (6c). Pale green crystals (234 mg, 67 %), mp 214-216 °C (acetonitrile). IR (KBr): ν 3460 (OH), 1695 (C=O), 1625 (C=N), 1595 (aryl), 1088 (C-O-C) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 6.87-7.48 (m, 4H, aryl), 9.46 (br, 1H, OH). ^{13}C-NMR (DMSO-d6): δ 126.93, 129.11 (aryl-CH), 130.14, 141.87 (C-6, C-7), 151.26, 151.64 (C-4a, C-8a), 154.14 (C-9a), 157.52 (aryl-C), 165.11 (C-2), 170.66, 171.76 (C-5, C-8). MS m/z (%): 351/347 (M^+, 23), 228 (16), 157 (28), 129 (16), 121 (100), 93 (81), 77 (62). Anal. Calcd. for $C_{14}H_5Cl_2N_3O_4$: C, 48.03; H, 1.44; N, 12.00; Cl, 20.25. Found: C, 47.81; H, 1.66; N, 12.28; Cl, 20.47.

2-(4-Bromobenzyl)-6,7-dichloro-benzo[4,5]imidazo[2,1-*b*][1,3,4]oxadiazole-5,8-dione (6d). Pale green crystals (260 mg, 61 %), mp 242-246 °C (ethanol). IR (KBr): ν 2975 (Ali-CH), 1690 (C=O), 1620 (C=N), 1600 (aryl), 1085 (C-O-C) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 4.28 (s, 2H, CH_2), 6.98-7.42 (m, 4H, aryl). ^{13}C-NMR (DMSO-d6): δ 52.64 (CH_2), 126.23 (aryl-CH), 126.24 (aryl-

C), 129.88 (aryl-CH),131.33 (aryl-C), 141.92 (C-6, C-7), 151.11, 151.22 (C-4a, C-8a), 154.33 (C-9a), 164.92 (C-2), 170.74, 171.83 (C-5, C-8). MS m/z (%): 431/425 (M^+, 28), 327 (22), 229 (31), 198 (63), 118 (27), 91 (66), 77 (100). Anal. Calcd. for $C_{15}H_6BrCl_2N_3O_3$: C, 42.19; H, 1.42; N, 9.84; Cl, 16.60. Found: C, 41.92; H, 1.31; N, 10.05; Cl, 16.83.

2,3,7,8-Tetrachlorothianthrene-1,4,6,9-tetraone (7). Yield (with **1a**, 41 mg (10%); **1b**, 50 mg (12 %); **1c**, 58 mg (14 %); **1d**, 37 mg (9 %) mp 342-344 °C (lit[20]. 342-344 °C)

Reaction of 1-acylthiosemicarbazides 1a-d with 3a

A mixture of equimolar amounts of the appropriate 1-acylthiosemicarbazide **1a-d** and **3a** was stirred under reflux in 30 ml of dry ethyl acetate for 3 hours. The mixture was concentrated under vacuum and the residue separated by plc using cyclohexane / ethyl acetate (1:1) as developing solvent to give numerous coloured zones, two of which (with the highest intensity) were extracted and removed. The fastest migrating one R_f = 0.192 contained naphthimidazoxadiazoledione **11a-d**, the second zone R_f = 0.144 (which was always characterized by a blue colour) contained the naphthobisthiazole derivatives **12a-d**. Extraction of the zones with acetone, and concentration gave a residue, which was rechromatographed to separate the pure compounds.

2-Methylnaphtho[4,5]imidazo[2,1-*b*][1,3,4]oxadiazole-5,10-dione (**11a**). Reddish brown crystals (76 mg, 30 %), mp 183-185 °C (acetonitrile). IR (KBr): ν 1670 (C=O), 1625 (C=N), 1590 (aryl), 1085 (C-O-C) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.35 (s, 3H, CH_3), 7.24-7.86 (m, 4H, aryl). ^{13}C-NMR (DMSO-d_6): δ 15.83 (CH_3), 128.66, 129.89 (aryl-CH), 132.14 (aryl-C), 150.87, 151.26 (C-4a, C-10a), 154.14 (C-11a), 164.63 (C-2), 173.38 (C-5, C-10). MS m/z (%): 253 (M^+, 28), 210 (19), 182 (21), 154 (11), 132 (36), 105 (67), 76 (54), 43 (100). Anal. Calcd. for $C_{13}H_7N_3O_3$: C, 61.66; H, 2.79; N, 16.59. Found: C, 61.87; H, 2.61; N, 16.32.

2-Phenylnaphtho[4,5]imidazo[2,1-*b*][1,3,4]oxadiazole-5,10-dione (**11b**). Reddish brown crystals (104 mg, 33 %), mp 222-234 °C (methanol). IR (KBr): ν 1690 (C=O), 1620 (C=N), 1600 (aryl), 1080 (C-O-C) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 7.22-7.89 (m, 9H, aryl). ^{13}C-NMR (DMSO-d_6): δ 127.96, 128.53, 128.84, 129.33, 129.84 (aryl-CH), 132.16, 132.88 (aryl-C), 150.76, 151.14 (C-4a, C-10a), 154.33 (C-11a), 164.42 (C-2), 173.36 (C-5, C-10). MS m/z (%): 315 (M^+, 21), 210 (18), 182 (14), 154 (10), 132 (22), 105 (100), 77 (64), 65 (52). Anal. Calcd. for $C_{18}H_9N_3O_3$: C, 68.57; H, 2.88; N, 13.33. Found: C, 68.81; H, 3.04; N, 13.05.

2-(4-Hydroxyphenyl)naphtho[4,5]imidazo[2,1-*b*][1,3,4]oxadiazole-5,10-dione (11c). Reddish brown crystals (106 mg, 32 %), mp 259-261 °C (acetonitrile). IR (KBr): ν 3460 (OH), 1695 (C=O), 1625 (C=N), 1590 (aryl), 1085 (C-O-C) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 6.98-7.73 (m, 8H, aryl), 9.09 (br, 1H, OH). ^{13}C-NMR (DMSO-d_6): δ 126.72, 128.66, 128.92, 129.87 (aryl-CH), 131.12, 132.88 (aryl-C), 150.86, 151.33 (C-4a, C-10a), 154.14 (C-11a), 156.12 (aryl-C), 164.52 (C-2), 173.47 (C-5, C-10). MS m/z (%): 331 (M^+, 32), 210 (18), 154 (22), 121 (86), 105 (93), 92 (86), 77 (100), 65 (63). Anal. Calcd. for $C_{18}H_9N_3O_4$: C, 65.26; H, 2.74; N, 12.68. Found: C, 64.97; H, 2.91; N, 12.53.

2-(4-Bromobenzyl)naphtho[4,5]imidazo[2,1-*b*][1,3,4]oxadiazole-5,10-dione (11d). Reddish brown crystals (111 mg, 28 %), mp 195-197 °C (methanol). IR (KBr): ν 2975 (Ali-CH), 1690 (C=O), 1625 (C=N), 1600 (aryl), 1080 (C-O-C) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 4.24 (s, 2H, CH_2), 7.12-7.82 (m, 8H, aryl). ^{13}C-NMR (DMSO-d_6): δ 52.57 (CH_2), 126.88 (aryl-C), 128.57, 129.88, 130.67, 131.12 (aryl-CH), 132.94, 135.37 (aryl-C), 151.27 (C-4a, C-10a), 152.96 (C-11a), 165.12 (C-2), 173.56 (C-5, C-10). MS m/z (%): 394/396 (M^+, 31), 314 (22), 198 (57), 196 (36), 168 (16), 140 (9), 105 (61), 91 (72), 77 (100), 65 (48). Anal. Calcd. for $C_{19}H_{10}BrN_3O_3$: C, 54.71; H, 2.30; N, 10.63. Found: C, 54.96; H, 2.46; N, 10.39.

Naphtho[1,2-*d*:4,3-*d*`]bis(imidazo[2,1-*b*][1,3,4]oxadiazole)acetylhydrazide (12a). Blue crystals (212 mg, 55 %), mp 200-202 °C (acetonitrile). IR (KBr): ν 3390, 3215 (NH), 1670 (C=O), 1600 (aryl) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.36 (s, 6H, CH_3), 7.10-7.48 (m, 4H, aryl), 10.64 (br, 2H, thiazole-NH), 11.12 (br, 2H, amide-NH). ^{13}C-NMR (DMSO-d_6): δ 21.12 (CH_3), 127.93, 128.27 (aryl-CH), 130.26, 134.61, 135.74 (aryl-C), 162.66 (C-2), 171.12 (amide-CO). MS m/z (%): 386 (M^+, 19), 343 (16), 300 (24), 244 (31), 164 (21), 120 (11), 77 (54), 43 (100). Anal. Calcd. for $C_{16}H_{14}N_6O_2S_2$: C, 49.73; H, 3.65; N, 21.75; S, 16.59. Found: C, 49.51; H, 3.81; N, 21.96; S, 16.37.

Naphtho[1,2-*d*:4,3-*d*`]bis(imidazo[2,1-*b*][1,3,4]oxadiazole)benzohydrazide (12b). Blue crystals (301 mg, 59 %), mp 285-287 °C (acetonitrile). IR (KBr): ν 3385, 3220 (NH), 1675 (C=O), 1610 (aryl) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 7.16-7.98 (m, 14H, aryl), 10.52 (br, 2H, thiazole-NH), 11.16 (br, 2H, amide-NH). ^{13}C-NMR (DMSO-d_6): δ 127.84, 127.93, 128.96, 130.36 (aryl-CH), 130.78, 134.66, 135.76 (aryl-C), 163.11 (C-2), 171.37 (amide-CO). MS m/z (%): 510 (M^+, 25), 405 (14), 300 (19), 244 (23), 164 (12), 105 (100), 77 (53). Anal. Calcd. for $C_{26}H_{18}N_6O_2S_2$: C, 61.16; H, 3.55; N, 16.46; S, 12.56. Found: C, 60.93; H, 3.74; N, 16.71; S, 12.32.

Naphtho[1,2-*d*:4,3-*d*`]bis(imidazo[2,1-*b*][1,3,4]oxadiazole)-4-hydroxybenzohydrazide (12c). Blue crystals (309 mg, 57 %), mp 262-264 °C (acetonitrile). IR (KBr): ν 3370, 3240 (OH, NH), 1670 (C=O), 1600 (aryl) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 6.98-7.88 (m, 12H, aryl), 9.58 (br, 1H, OH), 10.63 (br, 2H, thiazole-NH), 11.22 (br, 2H, amide-NH). MS m/z (%): 542 (M^+, 18), 421 (19), 300 (9), 244 (17), 188 (13), 121 (71), 120 (100), 92 (82), 77 (63).. Anal. Calcd. for $C_{26}H_{18}N_6O_4S_2$: C, 57.55; H, 3.34; N, 15.49; S, 11.82. Found: C, 57.77; H, 3.19; N, 15.27; S, 12.08.

Naphtho[1,2-*d*:4,3-*d*`]bis(imidazo[2,1-*b*][1,3,4]oxadiazole)-2-(4-bromophenyl)aceto-hydrazide (12d). Blue crystals (368 mg, 53 %), mp 214-216 °C (acetonitrile). IR (KBr): ν 3385, 3225 (NH), 1670 (C=O), 1595 (aryl) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 4.28 (s, 4H, CH_2), 6.98-7.42 (m, 12H, aryl), 10.65 (br, 2H, thiazole-NH), 11.17 (br, 2H, amide-NH). ^{13}C-NMR (DMSO-d_6): δ 52.28 (CH_2), 128.86, 129.82, 130.96, 131.22 (aryl-CH), 132.12, 134.76 (aryl-C), 163.26 (C-2), 171.48 (amide-CO). MS m/z (%): 698/694 (M^+, 17), 524 (18), 298 (24), 198 (36), 118 (24), 91 (38), 77 (100), 65 (64). Anal. Calcd. for $C_{28}H_{20}Br_2N_6O_2S_2$: C, 48.29; H, 2.89; N, 12.07; S, 9.21. Found: C, 48.41; H, 3.11; N, 11.82; S, 9.47.

Reaction of 1-acylthiosemicarbazides 1a-d with (3b)

A solution of **1a-d** (1 mmol) in 20 ml of dry ethyl acetate is added dropwise to solution of **3b** (1 mmol) in 10 ml of dry ethyl acetate at room temperature. The reaction mixture becomes green and gradually turns into a reddish brown colour. It was left standing for 48 hours, concentrated *in vacuo* and the residue was subjected to plc using cyclohexane/ethyl acetate (2:1) to give numerous coloured zones, the two intense of which were removed and extracted. The fastest migrating zone which quenched all indicator fluorescence upon exposure to 254 nm UV-light contained oxadiazole derivatives **4a-d** and the slowest migrating zone (which is always characterized by orange colour) contained the naphthothiazine derivatives **13a-d**. Extraction of the zones with acetone and recrystallization afforded the reaction products.

(4-Amino-5-cyano-6-hydroxy-2*H*-naphtho[2,1-*e*][1,3]thiazine-2-ylidene)acetohydrazide (13a). Orange crystals (218 mg, 67 %), mp 214-216 °C (methanol). IR (KBr): ν 3440, 3260 (OH, NH, NH_2), 2215 (CN), 1670 (C=O), 1625 (C=N), 1595 (aryl) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.37 (s, 3H, CH_3), 7.16 (br, 2H, NH_2), 7.35-7.84 (m, 4H, aryl), 9.62 (br, 1H, OH), 11.18 (br, 1H, amide-NH). ^{13}C-NMR (DMSO-d_6): δ 22.34 (CH_3), 117.84 (CN), 126.74, 127.82, 128.35, 129.88 (aryl-CH), 132.14,136.67 (aryl-C), 153.82 (C-6), 154.93 (C-2), 156.76 (C-4), 171.42 (amide-CO). MS m/z (%): 325 (M^+, 31), 282 (24), 254 (18), 238 (11), 175 (19), 76 (32), 43 (100). Anal. Calcd. for $C_{15}H_{11}N_5O_2S$: C, 55.38; H, 3.41; N, 21.53; S, 9.86. Found: C, 55.59; H, 3.63; N, 21.29; S, 10.05.

(4-Amino-5-cyano-6-hydroxy-2*H*-naphtho[2,1-*e*][1,3]thiazine-2-ylidene)benzohydrazide (13b). Orange crystals (279 mg, 72 %), mp 228-230 °C (acetonitrile). IR (KBr): ν 3445, 3370-3250 (OH, NH, NH_2), 2220 (CN), 1675 (C=O), 1620 (C=N), 1600 (aryl) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 7.12 (br, 2H, NH_2), 7.31-7.95 (m, 9H, aryl), 9.57 (br, 1H, OH), 11.15 (br, 1H, amide-NH). ^{13}C-NMR (DMSO-d_6): δ 118.11 (CN), 126.58, 127.12, 127.54, 127.76, 128.24, 128.93, 129.86 (aryl-CH), 130.86, 132.38, 134.76 (aryl-C), 153.65 (C-6), 154.84 (C-2), 156.93 (C-4), 171.56 (amide-CO). MS m/z (%): 387 (M^+, 23), 282 (19), 240 (24), 175 (12), 105 (100), 77 (53), 65 (41). Anal. Calcd. for $C_{20}H_{13}N_5O_2S$: C, 62.00; H, 3.38; N, 18.08; S, 8.28. Found: C, 61.78; H, 3.56; N, 17.89; S, 8.05.

(4-Amino-5-cyano-6-hydroxy-2*H*-naphtho[2,1-*e*][1,3]thiazine-2-ylidene)-4-hydroxybenzohydrazide (13c). Reddish orange crystals (278 mg, 69 %), mp 233-235 °C (acetonitrile). IR (KBr): ν 3470, 3380-3260 (OH, NH, NH_2), 2220 (CN), 1670 (C=O), 1620 (C=N), 1595 (aryl) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 7.05-7.82 (m, 10H, NH_2 and aryl), 9.57 (br, 1H, OH), 9.68 (br, 1H, OH), 11.18 (br, 1H, amide-NH). MS m/z (%): 403 (M^+, 34), 282 (16), 254 (12), 211 (6), 175 (8), 121 (67), 104 (83), 77 (100), 65 (56). Anal. Calcd. for $C_{20}H_{13}N_5O_3S$: C, 59.55; H, 3.25; N, 17.36; S, 7.95. Found: C, 59.31; H, 3.48; N, 17.54; S, 8.19.

(4-Amino-5-cyano-6-hydroxy-2*H*-naphtho[2,1-*e*][1,3]thiazine-2-ylidene)-2-(4-bromophenyl)acetohydrazide (13d). Orange crystals (312 mg, 65 %), mp 248-250 °C (methanol). IR (KBr): ν 3430, 3380-3260 (OH, NH, NH_2), 2220 (CN), 1675 (C=O), 1615 (C=N), 1590 (aryl) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 4.26 (s, 2H, CH_2), 7.05-7.78 (m, 10H, NH_2 and aryl), 9.65 (br, 1H, OH), 11.16 (br, 1H, amide-NH). ^{13}C-NMR (DMSO-d_6): δ 52.61 (CH_2), 126.94, 127.73, 128.26,

129.85, 130.12, 130.63 (aryl-CH), 131.22, 132.36, 134.75 (aryl-C), 153.58 (C-6), 154.68 (C-2), 156.76 (C-4), 171.48 (amide-CO). MS m/z (%): 481/479 (M^+, 27), 400 (12), 282 (19), 254 (6), 228 (7), 198 (28), 118 (68), 77 (100), 65 (74). Anal. Calcd. for $C_{21}H_{14}BrN_5O_2S$: C, 52.51; H, 2.94; N, 14.58; S, 6.68. Found: C, 52.24; H, 3.98; N, 14.76; S, 6.41.

Acknowledgements

A. A. Hassan is indepted to the A. v. Humbodlt- Foundation for the donation of the Shimadzu 408 IR spectrophotometer.

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