Benzo- and naphthoimidazoxadiazole Dieni, 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 products1,2. 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 chemistry3,6 and for dyestuffs7-16.

2,3,5,6-Tetrachloro-1,4-benzoquinone (2b) and 2,3-dichloro-1,4-naphthoquinone (3a) reacted with N,N'-diarylamidines to give benzimidazole and indole derivatives17,18. A series of benzo- and naphthothiazolenediones have been synthesized by reaction of N-substituted thioureas with 2a, 2b and 3a19. Indazole, thiadiazine and naphthothiadiazine derivatives were isolated from the reaction of thiosemicarbazide 2b and 3a10. The reaction of N,N`-disubstituted hydrazinecarbothioamides with 2b and 3a afforded thiaazole and thiadiazine derivatives20. In contrast, quinoxaline and thiadiazepane derivatives were obtained from the reaction of substituted thioureidoethylthioureas with 2b20.

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\textsuperscript{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).

\[
\begin{array}{c}
\text{RC} & \text{N} & \text{H} \\
\text{O} & \text{N} & \text{H} \\
\text{S} & \text{NH}_2
\end{array}
\quad
\begin{array}{c}
\text{X} & \text{Y} \\
\text{O} & \text{Y} \\
\text{X} & \text{X} \\
\text{O} & \text{X}
\end{array}
\]

\begin{tabular}{|c|c|c|c|}
\hline
\textbf{R} & \textbf{a} & \textbf{b} & \textbf{c} & \textbf{d} \\
\hline
\text{CH}_3 & \text{C}_6\text{H}_5 & 4-\text{HO-C}_6\text{H}_4 & 4-\text{Br-C}_6\text{H}_4-\text{CH}_2 \\
\hline
\end{tabular}

\textbf{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 ($\lambda_{\text{max}} = 573\text{-}591$ 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\textsubscript{2}) with 4 and elimination one molecule of HCN and another of H\textsubscript{2}O (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 $\nu = 3440$ cm\textsuperscript{-1} and at 2220 cm\textsuperscript{-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 $\delta = 164.82$, 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.

$$\text{R} - \text{C} - \text{N} - \text{N} - \text{C} - \text{NH}_2 + 2\text{a} \rightarrow \text{R} - \text{N} - \text{N} - \text{C} - \text{NH}_2 + 3\text{a}$$

1a-d 4a-d (17-22 %) 5a-d (65-73 %)

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<tr>
<td>R</td>
<td>CH$_3$</td>
<td>C$_6$H$_5$</td>
<td>4-HO-C$_6$H$_4$</td>
<td>4-Br-C$_6$H$_4$-CH$_2$</td>
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**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 ($\lambda_{\text{max}} = 506$-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).

$$\text{1a-d} + 2\text{b} \rightarrow 4\text{a-d} + 6\text{a-d} (61-67\%) + 7 (9-14\%)$$

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**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.

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 radicals 1⁻ and 2b⁻⁻⁻.

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 H₂S (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).

![Scheme 3](image)

1a-d + 3a → 11a-d (28-33 %)

12a-d (53-59 %)

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. Heating of this mixture for 5 hours and chromatographic separation of the residue after concentration gave numerous coloured zones, from which naphthimidazoxadiazoles 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 and two molecules of 1a-d by loss of two molecules of H2O 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 ¹H-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-CH₂ as well as aromatic protons were observed (see experimental part). The ¹³C-NMR of 12d showed a carbonyl signal at δC = 171.48 corresponding to the amide group. Also, the ¹³C-NMR clearly indicates the presence of signals at 52.28 and 163.26 due to benzylic-CH₂ and thiazole-C₂, respectively. The elemental analysis of 12d suggested a gross formula C₂₈H₂₀Br₂N₆O₂S₂ 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\text{max} = 523-532 nm) is followed by the formation of naphthothiazine derivatives 13a-d in addition to oxadiazoles 4a-d (Scheme 5).

For compound 13b, the gross formula C_{20}H_{13}N_{5}O_{2}S 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$_2$ ($\delta$H = 7.12 ppm) and a low field amide-NH ($\delta$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.

**Scheme 5**

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 $\delta$ [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 Pr$_{254}$) 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 (NH₂), 1630 (C=N), 1595 (aryl), 1085 (C-O-C) cm⁻¹. ¹H-NMR (DMSO-d₆): δ 4.21 (s, 2H, CH₂), 6.88 (br, 2H, NH₂), 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 C₉H₈N₃BrO: 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. ¹H-NMR (DMSO-d₆): δ 2.33 (s, 3H, CH₃), 9.53 (br, 2H, OH). ¹³C-NMR (DMSO-d₆): δ 16.68 (CH₃), 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), 164.88 (C-2). MS m/z (%): 286/282 (M⁺, 18), 239 (22), 169 (29), 139 (12), 113 (45), 43 (100). Anal. Calcd. for C₁₀H₄Cl₂N₄O₂: 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), 1090 (aryl), 1080 (C-O-C) cm⁻¹. ¹H-NMR (DMSO-d₆): δ 7.18-7.55 (m, 5H, aryl), 9.49 (br, 1H, OH). ¹³C-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 C₁₅H₆Cl₂N₄O₂: 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), 2215 (CN), 1610 (C=N), 1090 (aryl), 1080 (C-O-C) cm⁻¹. ¹H-NMR (DMSO-d₆): δ 6.96-7.4 (m, 4H, aryl), 9.38 (br, 1H, OH). ¹³C-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 C₁₅H₆Cl₂N₄O₃: 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. ¹H-NMR (DMSO-d₆): δ 4.73 (s, 2H, CH₂), 6.98-7.43 (m, 4H, aryl), 9.48 (br, 1H, OH). ¹³C-NMR (DMSO-d₆): δ 52.71 (CH₂), 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 C₁₆H₁₂BrCl₂N₄O₂: 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 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, Rf = 0.146, contained the oxadiazoles 4a-d, and the second zone, Rf = 0.096 (characterized by its green colour) contained benzimidazoxadiazoleediones 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): v 2960 (Al-CH), 1690 (C=O), 1620 (C=N), 1086 (C-O-C) cm⁻¹. ¹H-NMR (DMSO-d₆): δ 2.36 (s, 3H, CH₃). ¹³C-NMR (DMSO-d₆): δ 15.83, 142.12, 150.84, 150.93, 154.12, 164.87, 170.66, 171.76. MS m/z (%): 273/269 (M⁺, 27), 228 (31), 157 (24), 129 (18), 101 (2), 43 (100). Anal. Calcd. for C₉H₃Cl₂N₃O₃: 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): v 1695 (C=O), 1625 (C=N), 1595 (aryl), 1088 (C-O-C) cm⁻¹. ¹H-NMR (DMSO-d₆): δ 7.19-7.66 (m, 5H, aryl). ¹³C-NMR (DMSO-d₆): δ 127.94, 129.11, 151.26, 151.64, 157.52, 165.11, 170.66, 171.76. MS m/z (%): 351/347 (M⁺, 23), 228 (16), 129 (16), 121 (100), 93 (81), 77 (62). Anal. Calcd. for C₁₄H₅Cl₂N₃O₄: 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-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): v 3460 (OH), 1695 (C=O), 1625 (C=N), 1088 (C-O-C) cm⁻¹. ¹H-NMR (DMSO-d₆): δ 6.87-7.48 (m, 4H, aryl), 9.46 (br, 1H, OH). ¹³C-NMR (DMSO-d₆): δ 126.93, 129.11, 157.52, 170.66, 171.76 (C=O, C-8). MS m/z (%): 351/347 (M⁺, 23), 228 (16), 129 (16), 121 (100), 93 (81), 77 (62). Anal. Calcd. for C₁₄H₅Cl₂N₃O₄: 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): v 2975 (Ali-CH), 1690 (C=O), 1620 (C=N), 170.66 (C=O), 171.76 (C=O, C-8). MS m/z (%): 351/347 (M⁺, 23), 228 (16), 129 (16), 121 (100), 93 (81), 77 (62). Anal. Calcd. for C₁₄H₅Cl₂N₃O₄: 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.
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 C₁₅H₆BrCl₂N₃O₃: 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 (lit²⁰ 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 Rₐ = 0.192 contained naphthimidazoxadiazole-dione 11a-d, the second zone Rₐ = 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. ¹H-NMR (DMSO-d₆): δ 2.35 (s, 3H, CH₃), 7.24-7.86 (m, 4H, aryl). ¹³C-NMR (DMSO-d₆): δ 15.83 (CH₃), 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 C₁₃H₇N₃O₃: 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), 1078 (C-O-C) cm⁻¹. ¹H-NMR (DMSO-d₆): δ 2.35 (s, 3H, CH₃), 7.24-7.86 (m, 4H, aryl). ¹³C-NMR (DMSO-d₆): 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), 173.38 (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 C₁₈H₉N₃O₃: 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. ¹H-NMR (DMSO-d₆): δ 9.09 (br, 1H, OH). ¹³C-NMR (DMSO-d₆): 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 C₁₈H₉N₃O₄: 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\(^{-1}\). \(^{13}\)C-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\(_3\)O\(_3\): 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)acetyldihydrazide (12a). Blue crystals (212 mg, 55 %), mp 200-202 °C (acetonitrile). IR (KBr): ν 3390, 3215 (NH), 1670 (C=O), 1610 (aryl) cm\(^{-1}\). \(^{13}\)C-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\(_6\)O\(_2\)S\(_2\): 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\(^{-1}\). \(^{13}\)C-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\(_6\)O\(_2\)S\(_2\): 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), 1610 (aryl) cm\(^{-1}\). \(^{13}\)C-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\(_6\)O\(_4\)S\(_2\): 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)acycthydrazide (12d). Blue crystals (368 mg, 53 %), mp 214-216 °C (acetonitrile). IR (KBr): ν 3385, 3225 (NH), 1670 (C=O), 1595 (aryl) cm\(^{-1}\). \(^{13}\)C-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\(_2\)N\(_6\)O\(_2\)S\(_2\): 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-2H-naphtho[2,1-e][1,3]thiazine-2-ylimine)acetohydrazide (13a). Orange crystals (218 mg, 67 %), mp 214-216 ºC (methanol). IR (KBr): ν 3440, 3260 (OH, NH, NH2), 2215 (CN), 1670 (C=O), 1625 (C=N), 1595 (aryl) cm⁻¹. ¹H-NMR (DMSO-d₆): δ 2.37 (s, 3H, CH₃), 7.16 (br, 2H, NH₂), 7.35-7.84 (m, 4H, aryl), 9.62 (br, 1H, OH), 11.18 (br, 1H, amide-NH). ¹³C-NMR (DMSO-d₆): δ 22.34 (CH₃), 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 C₁₅H₁₁N₅O₂S: 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-2H-naphtho[2,1-e][1,3]thiazine-2-ylimine)benzohydrazide (13b). Orange crystals (279 mg, 72 %), mp 228-230 ºC (acetonitrile). IR (KBr): ν 3445, 3370-3250 (OH, NH, NH₂), 2220 (CN), 1675 (C=O), 1620 (C=N), 1600 (aryl) cm⁻¹. ¹H-NMR (DMSO-d₆): δ 7.12 (br, 2H, NH₂), 7.31-7.95 (m, 9H, aryl), 9.57 (br, 1H, OH), 11.15 (br, 1H, amide-NH). ¹³C-NMR (DMSO-d₆): 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), 238 (11), 175 (12), 105 (100), 77 (53), 65 (41). Anal. Calcd. for C₂₀H₁₃N₅O₂S: C, 55.78; H, 3.43; N, 18.08; S, 8.45. Found: C, 61.78; H, 3.56; N, 17.89; S, 8.05.

(4-Amino-5-cyano-6-hydroxy-2H-naphtho[2,1-e][1,3]thiazine-2-ylimine)-4-hydroxybenzohydrazide (13c). Reddish orange crystals (278 mg, 69 %), mp 233-235 ºC (acetonitrile). IR (KBr): ν 3470, 3380-3260 (OH, NH, NH₂), 2220 (CN), 1670 (C=O), 1620 (C=N), 1600 (aryl) cm⁻¹. ¹H-NMR (DMSO-d₆): δ 7.05-7.82 (m, 10H, NH₂ 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 C₂₀H₁₃N₅O₃S: 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-2H-naphtho[2,1-e][1,3]thiazine-2-ylimine)-2-(4-bromo-phenyl)acetohydrazide (13d). Orange crystals (312 mg, 65 %), mp 248-250 ºC (methanol). IR (KBr): ν 3430, 3380-3260 (OH, NH, NH₂), 2220 (CN), 1675 (C=O), 1615 (C=N), 1590 (aryl) cm⁻¹. ¹H-NMR (DMSO-d₆): δ 4.26 (s, 2H, CH₂), 7.05-7.78 (m, 10H, NH₂ and aryl), 9.65 (br, 1H, OH), 11.16 (br, 1H, amide-NH). ¹³C-NMR (DMSO-d₆): δ 52.61 (CH₂), 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 C₂₁H₁₄BrN₅O₂S: 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.

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References