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**RESEARCH ARTICLE**

# Synthesis and derivatization of angular 3-chloro-3-chlorosulfenyl naphtho[1,2-*b*]pyran(4*H*)-4-ones with evaluation of antiviral activity

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Angular 2,3-dihydronaphtho[1,2-*b*]pyran(4*H*)-4-ones **1a**,**b** react with an excess of thionyl chloride to give the $\alpha$-chlorosulfenyl chlorides **2a**,**b**, which are reduced by iodide ion to give the corresponding 1,3,4-oxadithiino derivatives **3a**,**b**. However, the aducts **4a**,**b** and **5a**,**b** were obtained by reduced **2a**,**b** with iodide ion in the presence of 2,3-dimethyl-1,3-butadiene and 1,3-cyclohexadiene, respectively. Direct oxidation of **2a**,**b** afford 3,3-dichloronaphthopyran-4-ones **6a**,**b**, whilst conversion to the sulfenamides **7a**,**b** prior to oxidation provides 3-chloronaphthopyranones **8a**,**b**. While $\alpha$-chloro $\beta$-oxo sulfenyl chlorides **2a**,**b** undergo straight forward substitution with 1-methylpiperazine and with potassium cyanide to give **9a**,**b** and **10a**,**b**, respectively. Some of the prepared products were selected and tested for their antiviral activity against herpes simplex virus type-1 (HSV-1). Plaque reduction infectivity assay was used to determine virus count reduction as a result of treatment with test compounds. Compound **5a** showed moderate effect against HSV-1.

*Keywords*: Angular 2,3-dihydronaphtho[1,2-*b*]pyran(4*H*)-4-ones; $\alpha$-Chlorosulfenyl chlorides; 1,3,4-Oxadithiino derivatives; 3,3-Dichloronaphthopyran-4-ones; 3-Chloronaphthopyranones; Herpes simplex virus type-1

## 1. Introduction

Naphtho[1,2-*b*]pyrans like mollugin [1], dihydrolapachenole [2], lapachenole [3] and their 6-demethoxy derivatives [4] have been isolated from natural sources.

The $\alpha$-chloro-$\alpha$-chlorosulfenylketones are versatile intermediates for the formation of $\alpha$-chlorosulfenamides [5, 6], 1,2-diketones [7], $\alpha$-ketothiones [8], $\alpha$-iminoketones [9], thione *S*-imides [10, 11], thione S-ylides [12], thiosulfins/dithirans [13], and thiadiazoles [14].

Some of 3-thiooxo[1]benzopyran-4-ones can be isolated in the dimeric state [15, 16]. In previous paper we have reported a cycloaddition reactions of some 3-thiooxo[1]benzopyran-4-ones, *in situ*, with 2,3-dimethyl-1,3-butadiene and furan [17]. So, we are interested to investigate such reactions, nucleophilic substitution and oxidation reactions with naturally

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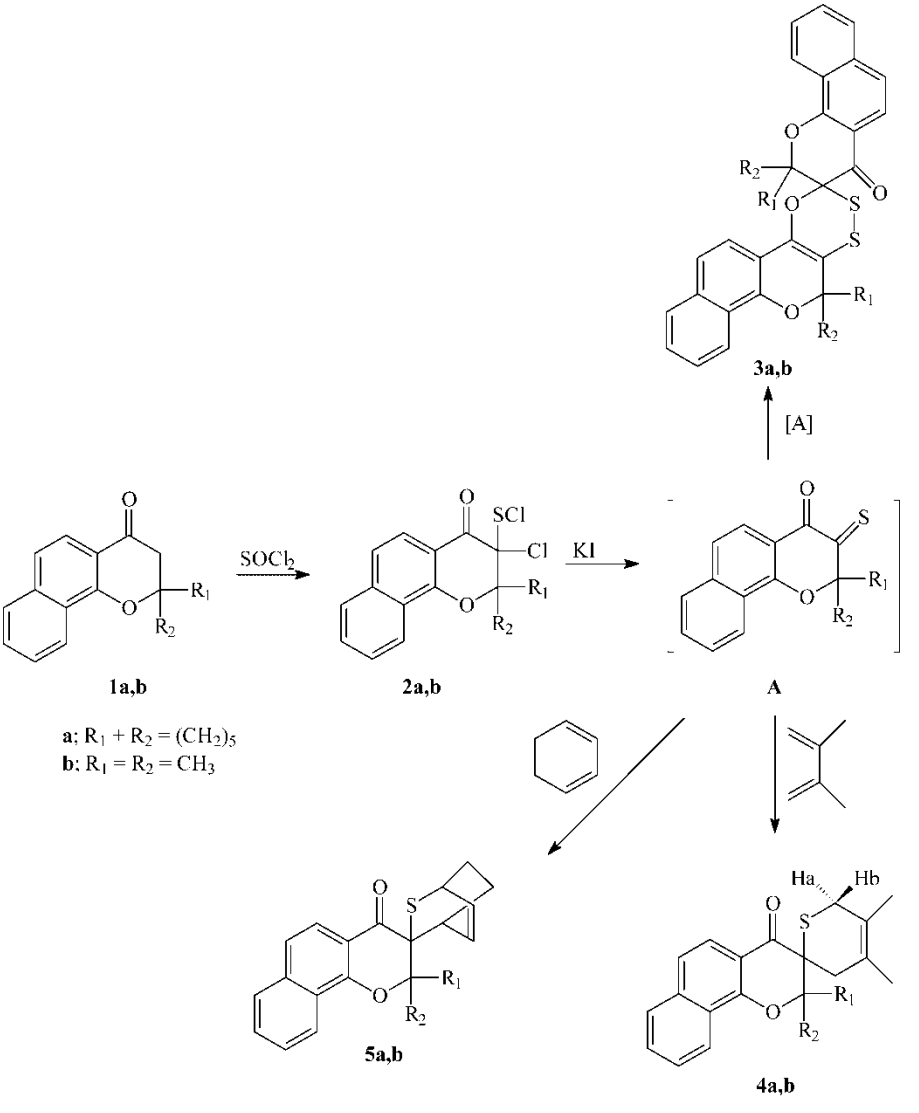
occuring angular naphthopyranones not only to get new derivatives but, also to evaluate the antiviral activity of some new products.

2,3-Dihydronaphtho[1,2-*b*]pyran(4*H*)-4-ones **1a**,**b** have been previously reported [18,19]. Stirring a solution of 2,3-dihydronaphtho[1,2-*b*]pyran(4*H*)-4-ones **1a**,**b** overnight in an excess of thionyl chloride gave, on removal of the unreacted $SOCl_2$, the $\alpha$-chlorosulfenyl chlorides **2a**,**b** in high yield (scheme 1).




SCHEME 1

The $^1H$ and $^{13}C$ NMR spectra of compounds **2** are markedly different from those of the naphthopyranones **1**. The unsymmetrical substitution at C-3 confers diastereotopic properties on the geminal methyl groups of **2b** which appear as individual signals shifted slightly downfield at $\delta$ 1.5 and $\delta$ 1.7, of course the signals for C-3 methylene protons are absent in $\alpha$-chlorosulfenyl chlorides **2a**,**b**. $^{13}C$ NMR spectra of the $\alpha$-chlorosulfenyl chlorides **2a**,**b** is

considerable downfield shift of the C-3 signal, which now resonates at $\delta$ 87.89 and $\delta$ 86.83, respectively. MS spectra of the $\alpha$-chlorosulfenyl chlorides **2a**,**b** show the prominent ion peak at $m/z$ 296 (M–$Cl_2$, 29), and $m/z$ 256 (M–$Cl_2$, 20), respectively.

Treatment of **2a** and of **2b** with potassium iodide lead to the corresponding oxo thioketones **A** which dimerized in an unsymmetrical Diels Alder fashion to afford **3a** and **3b** (scheme 1). The $^{13}$C NMR of 1,3,4-oxadithiin **3b** showed 79.55 (C-2′), 83.81 (C-5), 90.55 (C-2), 107.59 (C-4a), 181.98 (C-4′). These data exclude the formation of the possible 1,3-dithiatanes resulting from dimerization across the C=S bond of thioketones **A**. The mass spectrum of **3b**, as an example, shows a prominent ion peak at $m/z$ at 256 (M/2, 18).

The treatment of $\alpha$-chlorosulfenyl chlorides **2a**,**b** with potassium iodide in the presence of 2,3-dimethyl-1,3-butadiene gave thiapyran derivatives **4a**,**b** through highly active $\alpha$-oxo thioketones (**A**). Also, this reaction was carried out in the presence of 1,3-cyclohexadiene to give the bicyclothiapyran adducts **5a**,**b** (scheme 1). The $^1$H NMR spectra of **4a**,**b** showed 5-$CH_2$ protons as a multiplet at $\delta$ 2.05–2.41 and two doublets at $\delta$ 2.56, 2.66 and at $\delta$ 2.80, 2.83 ($J$ = 13.5−15.0 Hz) corresponding to 2-CHaHb protons. $^{13}$C NMR spectrum of **4b** shows 83.60 (C-2′), 113.95 (C-4), 117.20 (C-3), 187.31 (C-4′). $^1$H NMR spectra of **5a**,**b** show 4-$CH_{sp3}$ protons as a multiplet at $\delta$ 3.41–3.55, 1-$CH_{sp3}$ protons as a multiplet at $\delta$ 4.10–4.35, and 5-$CH_{sp2}$ protons as a doublet of doublet at $\delta$ 6.00, 6.01 ($J$ = 6.3, 6.1 Hz), 6-$CH_{sp2}$ protons as a doublet of doublet at $\delta$ 6.20 ($J$ = 6.3, 6.1 Hz). $^{13}$C NMR spectrum of **5b** showed 53.51 (C-4), 54.25 (C-1), 57.15 (C-3), 82.18 (C-2′), 187.15 (C-4′). The mass spectrum of **5b** showed the prominent ion peak at 336 (M, 95).

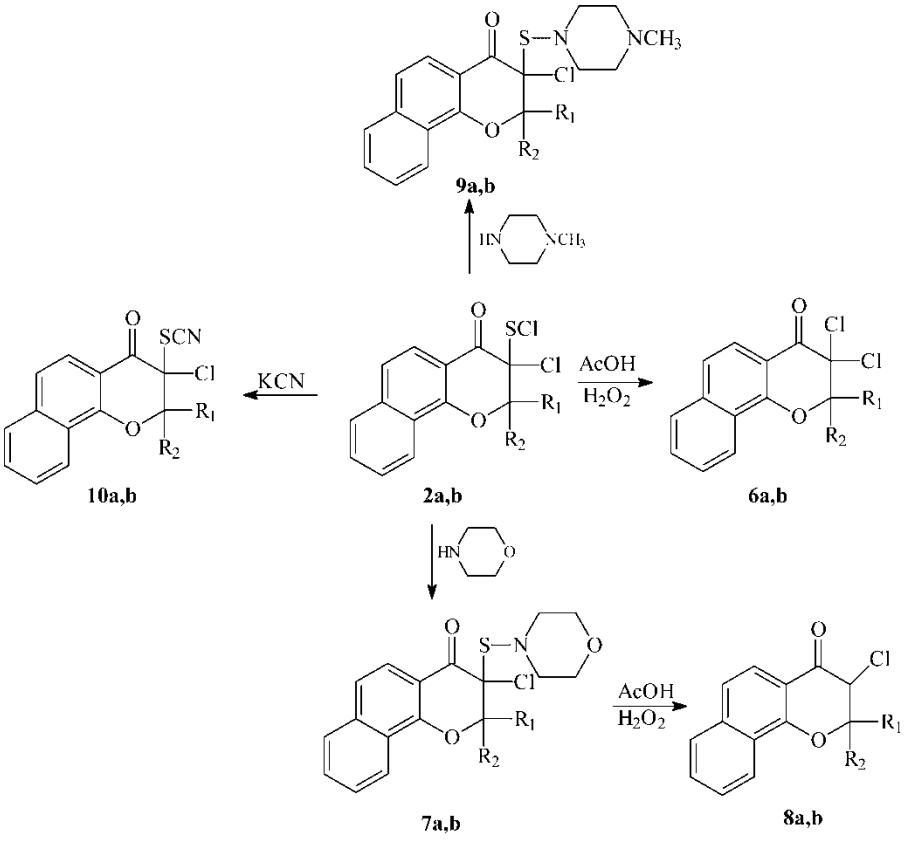
The oxidation of the $\alpha$-chlorosulfenyl chlorides **2a**,**b** was accomplished using an excess of hydrogen peroxide in glacial acetic acid at 50 °C afforded 3,3-dichloro-2,3-dihydronaphtopyran(4*H*)-ones **6a**,**b** (scheme 2). The $^1$H NMR spectrum showed the geminal methyl groups of **6b** as equivalent at $\delta$ 1.68 whereas the mass spectra of **6a**,**b** showed the prominent ion peak at $m/z$ 264 (M–$Cl_2$, 55) and at $m/z$ 224 (M–$Cl_2$, 65), respectively.

Treatment a solution of the $\alpha$-chlorosulfenyl chlorides **2a**,**b** in toluene with two equivalents of morpholine gave the sulfenamides **7a**,**b**, respectively (scheme 2). The $^1$H NMR spectra of **7a**,**b** compare favorably with those of the starting $\alpha$-chlorosulfenyl chlorides **2a**,**b**, though with the obvious presence of signals associated with the morpholine function. The mass spectra of **7a**,**b** showed the prominent ion peak at $m/z$ 381 (M–HCl), and at $m/z$ 341 (M–HCl), respectively.

Oxidation of the sulfenamides **7a**,**b** was achieved using an identical procedure to that described for the oxidation of the $\alpha$-chlorosulfenyl chlorides **2** (scheme 2). The only isolable materials, 3-chloro-2,3-dihydropyran(4*H*)-4-ones **8a**,**b**, were obtained in good yield after crystallization from petroleum ether 40–60 °C. The unsymmetrical substitution of C-3 in these chloroketones **8a**,**b** confers diastereotopic properties on the C-2 substituents. In the $^1$H NMR spectra the geminal methyl groups of **2b** affords signals at $\delta$ 1.53 and $\delta$ 1.60. H-3 appears as a singlet at $\delta$ 4.32 for **8a** and at $\delta$ 4.45 for **8b**. MS spectra of **8a**,**b** showed the prominent ion peak at $m/z$ 300 (M, 30), and at $m/z$ 260 (M, 15), respectively.

The conversion of **2a**,**b** with *N*-methylpiperazine, using an identical procedure to that descibed for the reaction of the $\alpha$-chlorosulfenyl chlorides **2** with morpholine, to the corresponding sulfenamides **9a**,**b** (scheme 2). The $^1$H NMR spectra of **9a**,**b** showed the presence of signals associated with the piperazine function as a multiplet at $\delta$ 2.61–2.84 (CH3−N($CH_2$)$_2$−), and at $\delta$ 3.11–3.45 (−N($CH_2$)$_2$−) and the mass spectra showed the prominent ion peak at $m/z$ 394 (M−HCl), and at $m/z$ 354 (M−HCl), respectively.

Also, with the $\alpha$-chlorosulfenyl chlorides **2a**,**b**, a smooth reaction potassium cyanide could be observed and the corresponding thiocyanates **10a**,**b** were obtained (scheme 2). The structures of **10a**,**b** were established by spectral data. IR spectra of **10a**,**b** show CN stretching at $\nu$ 2152 and at $\nu$ 2154, respectively. The $^1$H NMR spectra of thiocyanates **10a**,**b** are similar to




SCHEME 2

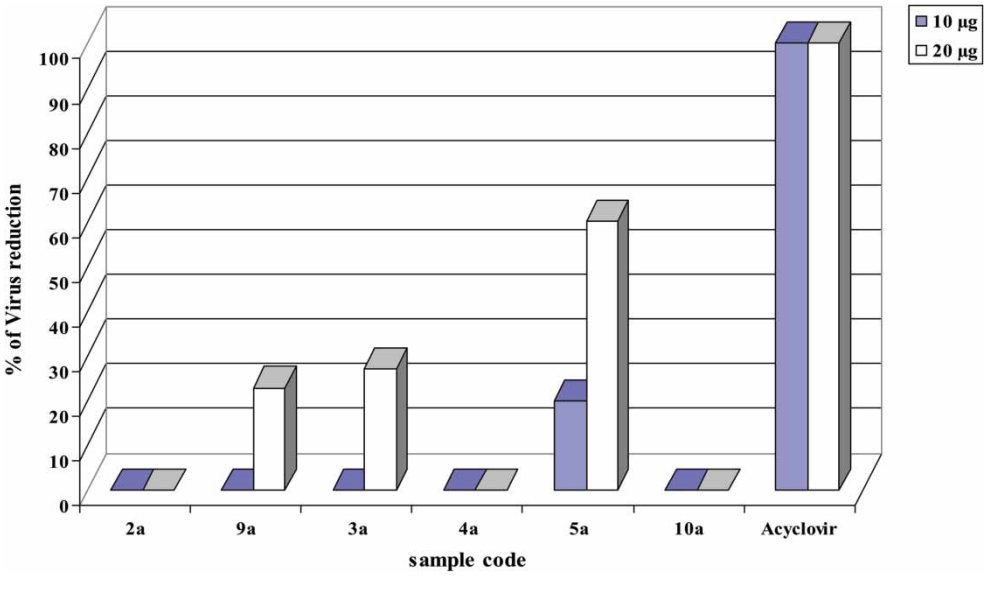



Figure 1. Effect of novel derivatives on HSV-1.

those of **2a**,**b** and the mass spectra of thiocyanates **10a**,**b** showed the prominent ion peaks at $m/z$ 357 (M, 50), and at $m/z$ 317 (M, 35), respectively.

The plaque infectivity assay was carried out to test compounds **2a**, **3a**, **4a**, **5a**, **9a** and **10a** for antiviral activity. The test was performed to include the three possibilities for antiviral activity; virucidal effect, virus adsorption, and effect on virus replication for HSV-1. The results of antiviral bioassay are summarized in figure 1. The six tested compounds showed percentage of inhibition of virus propagation ranged from 0 to 60 percentages, but the highest activity was observed when HSV-1 was treated with compound **5a**. The percent of reduction was increased three times when the compound concentration increase from 10 to 20 μg. Since the cytotoxicity assay showed very low level, then the antiviral activity of compound **5a** will be proportional with compound concentration. The results were revealed that compound **5a** may be anti-HSV-1 promising material when compared with the same concentrations of acyclovir as a standard anti-HSV drug.

## 2. Experimental

### 2.1 *Chemistry*



Melting points were determined on open glass capillary using Electrothermal IA 9000 SERIES digital melting point apparatus (Electrothermal, Essex, UK) and are uncorrected. Microanalyses were performed with all final compounds on Elementar-Vario EL, Microanalytical Unit, Central Services Laboratory, National Research Centre, Cairo, Egypt. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. $^1$H NMR spectra were run at 300 MHz and $^{13}$C NMR spectra were run at 75.46 MHz in $CDCl_3$ as solvent. Chemical shifts are quoted in $\delta$ and were related to that of the solvents (Cairo University, Faculty of Science). Splitting patterns were designated as follow: s singlet; d doublet; t triplet; m multiplet. Mass specra were recorded on Schimadzu GCMS-QP 1000EX (EI, 70 eV) spectrometers. IR spectra were obtained with Bruker-Vector 22 for neat samples (for liquids) or KBr wafers (for solid) (Micro-analytical Center of Cairo University). Compounds **1a** [18], **1b** [19] were prepared according to the literature procedures.

**2.1.1 2,3-Dihydrospiro[naphtho[1,2-b]pyran(4H)-2,1′-cyclohexane]-4-one (1a).** Yield 70% from petroleum ether 40–60 °C, m.p. 100–102 °C (lit. m.p. 97–98 °C) [18].

**2.1.2 2,3-Dihydro-2,2-dimethylnaphtho[1,2-b]pyran(4H)-4-one (1b).** Yield 75% from petroleum ether 40–60 °C, m.p. 73–75 °C (lit. oil) [19].

### 2.2 *General procedure for the preparation of α-chlorosulfenyl chlorides 2*

The naphthopyranones **1** (20 mmol) was disolved in thionyl chloride (150 mmol) and stirred overnight. Removal of the excess thionyl chloride afforded $\alpha$-chlorosulfenyl chlorides **2**.

**2.2.1 (RS)-3-Chloro-3-chlorosulfenylspiro[2,3-dihydronaphtho[1,2-b]pyran(4H)-2,1′-cyclohexane]-4-one (2a).** From **1a**, yield 95% as yellow crystals from petroleum ether 40–60 °C; m.p. 130–133 °C. IR: $\nu_{CO}$ 1709 cm$^{-1}$; $^1$H NMR: $\delta$ 1.28–2.43 (10H, m, $-(CH_2)_5-$), 7.51 (1H, d, $J$ = 8.7 Hz, ArH), 7.56–7.69 (2H, m, ArH), 7.84 (1H, d, $J$ = 8.1 Hz, ArH), 7.94

(1H, d, $J = 8.7$ Hz, ArH), 8.33 (1H, d, $J = 8.4$ Hz, ArH); $^{13}$C NMR: $\delta$ 21.77 (C-4′), 25.01 (C-3′), 27.83 (C-5′), 29.68 (C-2′), 31.81 (C-6′), 86.98 (C-2), 87.89 (C-3), 113.12 (C-8), 122.64 (C-9), 123.51 (C-7), 124.76 (C-10), 125.85 (C-6), 127.53 (C-5), 129.93 (C-6a), 130.90 (C-10a), 137.89 (C-4a), 154.64 (C-10b), 180.14 (C-4); MS (EI): $m/z$ (%) 296 (M–$Cl_2$, 29), 263 (12), 253 (9), 235 (12), 223 (5), 170 (84), 126 (100). Calcd for $C_{18}H_{16}Cl_2O_2S$ (367.22): C, 58.86; H, 4.39; Cl, 19.30; S, 8.73%. Found: C, 58.75; H, 4.29; Cl, 19.11; S, 8.60%.

**2.2.2 (RS)-3-Chloro-3-chlorosulfenyl-2,2-dimethyl-2,3-dihydronaphtho[1,2-b]pyran (4H)-4-one (2b).** From **1b**, yield 90% as yellow crystals from petroleum ether 40–60 °C; m.p. 78–80 °C. IR: $\nu_{CO}$ 1707 cm$^{-1}$; $^1$H NMR: $\delta$ 1.50 (3H, s, $CH_3$), 1.75 (3H, s, $CH_3$), 7.50 (1H, d, $J = 8.7$ Hz, ArH), 7.53–7.65 (2H, m, ArH), 7.85 (1H, d, $J = 8.1$ Hz, ArH), 7.94 (1H, d, $J = 8.7$ Hz, ArH), 8.33 (1H, d, $J = 8.4$ Hz, ArH); $^{13}$C NMR: $\delta$ 22.55 (2-*C*$H_3$), 24.35 (2-*C*$H_3$), 85.82 (C-2), 86.83 (C-3), 113.15 (C-8), 122.62 (C-9), 123.51 (C-7), 124.75 (C-10), 125.85 (C-6), 127.55 (C-5), 129.91 (C-6a), 130.92 (C-10a), 137.83 (C-4a), 154.65 (C-10b), 180.20 (C-4); MS (EI): $m/z$ (%) 256 (M–$Cl_2$, 20), 244 (12), 214 (10), 195 (15), 170 (86), 126 (100). Calcd for $C_{15}H_{12}Cl_2O_2S$ (327.22): C, 55.05; H, 3.69; Cl, 21.67; S, 9.79%. Found: C, 54.97; H, 3.59; Cl, 21.45; S, 9.60%.



### 2.3 *Reaction of α-chlorosulfenyl chlorides 2 with potassium iodide*

A solution of KI (0.8 g, 5 mmol) in $CH_3CN$ (30 ml) was added to a solution **2** (5 mmol) in $CHCl_3$ (10 ml) under stirring. After another 1 h of stirring the reaction mixture was treated with aqueous $Na_2S_2O_3$. The organic phase was separated and dried over $Na_2SO_4$. After evaporation of the solvent *in vacuo* the solid residue was triturated with petroleum ether 60–80 °C to give **3**.

**2.3.1 Trispiro[cyclohexane-1‴,2″-(2″H,3″H)naphtho[1,2-b] pyran(4″H)cyclohexane-1,5′-(2′H,5′H)naphtho[1,2-b]pyrano[3,4-e][1,3,4]oxadithiin]-4″-one (3a).** From **2a**, yield 74% as yellow crystals from petroleum ether 40–60 °C; m.p. 182–185 °C. IR: $\nu_{CO}$ 1693 cm$^{-1}$; $^1$H NMR: $\delta$ 1.15–2.24 (20H, m, 2 $-(CH_2)_5-$), 7.11–7.22 (2H, m, ArH), 7.45–7.81 (8H, m, ArH), 8.25–8.56 (2H, m, ArH); $^{13}$C NMR: $\delta$ 20.69 (C-4‴), 21.25 (C-4), 21.30 (C-3‴), 21.44 (C-3), 24.94 (C-5‴), 25.39 (C-5), 27.26 (C-2‴), 30.47 (C-2), 33.01 (C-6‴), 33.50 (C-6), 79.84 (C-2″), 84.62 (C-5′), 91.00 (C-2′), 108.42 (C-4a′), 113.15 (C-8″), 113.20 (C-7″), 122.17 (C-7′), 122.30 (C-10′), 123.11 (C-10″), 123.28 (C-9′), 124.76 (C-6″), 124.85 (C-11′), 125.15 (C-5″), 126.09 (C-12″), 127.53 (C-9″), 127.80 (C-8′), 129.59 (C-6a″), 129.95 (C-10a″), 135.87 (C-10a″), 137.89 (C-6b′), 144.67 (C-12a′), 151.98 (C-4a″), 154.64 (C-12b′), 156.71 (C-10b″), 157.01 (C-6a″), 181.80 (C-4″); MS (EI): $m/z$ (%) 296 (M/2, 21), 264 (15), 251 (8), 222 (20), 171 (100), 126 (52), 114 (50). Calcd for $C_{36}H_{32}O_4S_2$ (592.74): C, 72.94; H, 5.44; S, 10.82%. Found: C, 72.84; H, 5.42; S, 10.72%.

**2.3.2 2′,2′,5,5-Tetramethylspiro[2′,3′-dihydronaphtho[1,2-b]pyran(4′H)-3′,2-naphtho [1,2-b]pyrano(5H)[3,4-e][1,3,4]oxadithiin]-4′-one (3b).** From **2b**, yield 60% as yellow crystals from petroleum ether 40–60 °C; m.p. 130–133 °C. IR: $\nu_{CO}$ 1700 cm$^{-1}$; $^1$H NMR: $\delta$ 1.55 (3H, s, $CH_3$), 1.60 (3H, s, $CH_3$), 1.70 (3H, s, $CH_3$), 1.77 (3H, s, $CH_3$), 7.10–7.23 (2H, m, ArH), 7.45–7.80 (8H, m, ArH), 8.21–8.57 (2H, m, ArH); $^{13}$C NMR: $\delta$ 21.51 (2′-$CH_3$), 23.35 (5-$CH_3$), 26.01 (2′-$CH_3$), 26.23 (5-$CH_3$), 79.55 (C-2′), 83.81 (C-5), 90.55 (C-2), 107.59

(C-4a), 113.17 (C-8′), 113.25 (C-7′), 122.17 (C-7), 122.35 (C-10), 123.10 (C-10′), 123.30 (C-9), 124.75 (C-6′), 124.85 (C-11), 125.15 (C-5′), 126.19 (C-12), 127.55 (C-9′), 127.75 (C-8), 129.60 (C-6a′), 130.01 (C-10a), 135.87 (C-10a′), 137.89 (C-6b), 145.00 (C-12a), 151.90 (C-4a′), 154.65 (C-12b), 156.75 (C-10b′), 157.00 (C-6a), 181.98 (C-4′); MS (EI): $m/z$ (%) 256 (M/2, 30), 241 (15), 226 (31), 214 (15), 195 (10), 171 (85), 126 (100). Calcd for $C_{30}H_{24}O_4S_2$ (512.61): C, 70.28; H, 4.71; S, 12.50%. Found: C, 70.11; H, 4.68; S, 12.35%.

### 2.4 *Reaction of α-chlorosulfenyl chlorides 2 with potassium iodide in the presence of 2,3-dimethyl-1,3-butadiene*

A solution of KI (0.8 g, 5 mmol) in $CH_3CN$ (30 ml) was added to a solution **2** (5 mmol) in $CHCl_3$ (10 ml) containing 2,3-dimethyl-1,3-butadiene (5.5 mmol) under stirring. After another 1 h of stirring the reaction mixture was treated with aqueous $Na_2S_2O_3$. The organic phase was separated and dried over $Na_2SO_4$. After evaporation of the solvent *in vacuo* the solid residue was triturated with ethyl alcohol to give **4**.



**2.4.1 3,4-Dimethyldispiro[cyclohexane-1″,2′-(2′H,3′H)naphtho[1,2-b]pyran(4′H)-3′,6-Δ³thiopyrane]-4′-one (4a).** From **2a**, yield 30% as yellow crystals from ethyl alcohol; m.p. 170–173 °C. IR: $\nu_{CO}$ 1683 cm$^{-1}$; $^1$H NMR: $\delta$ 1.30–2.00 (16H, m, $-(CH_2)_5-$ +2 $CH_3$), 2.20–2.41 (2H, m, 5-$CH_2$), 2.66 (1H, d, $J$ = 13.5 Hz, 2-C*Ha*Hb), 2.83 (1H, d, $J$ = 13.5 Hz, 2-CHa*Hb*), 7.19 (1H, d, $J$ = 8.7 Hz, ArH), 7.56–7.68 (2H, m, ArH), 7.85 (1H, d, $J$ = 8.1 Hz, ArH), 7.94 (1H, d, $J$ = 8.7 Hz, ArH), 8.35 (1H, d, $J$ = 8.4 Hz, ArH); MS (EI): $m/z$ (%) 378 (M, 29), 315 (23), 296 (20), 266 (26), 251 (19), 223 (22), 206 (26), 202 (29), 171 (100), 126 (49), 114 (68), 63 (78). Calcd for $C_{24}H_{26}O_2S$ (378.15): C, 76.15; H, 6.92; S, 8.47%. Found: C, 75.98; H, 6.80; S, 8.15%.

**2.4.2 3,4,2′,2′-Tetramethylspiro-2′,3′-dihydronaphtho[1,2-b]pyran(4′H)-3′,6-Δ³thiopyrane-4′-one (4b).** From **2b**, yield 30% as yellow crystals from ethyl alcohol; m.p. 110–113 °C. IR: $\nu_{CO}$ 1685 cm$^{-1}$; $^1$H NMR: $\delta$ 1.28 (3H, s, $CH_3$), 1.57 (3H, s, $CH_3$), 1.62 (3H, s, $CH_3$), 1.70 (3H, s, $CH_3$), 2.05–2.21 (2H, m, 5-$CH_2$), 2.56 (1H, d, $J$ = 15.0 Hz, 2-C*Ha*Hb), 2.80 (1H, d, $J$ = 15.0 Hz, 2-CHa*Hb*), 7.15 (1H, d, $J$ = 8.7 Hz, ArH), 7.55–7.65 (2H, m, ArH), 7.82 (1H, d, $J$ = 8.1 Hz, ArH), 7.94 (1H, d, $J$ = 8.7 Hz, ArH), 8.34 (1H, d, $J$ = 8.4 Hz, ArH); $^{13}$C NMR: $\delta$ 19.19 (3-$CH_3$), 19.88 (4-$CH_3$), 21.11 (2′-$CH_3$), 23.18 (2′-$CH_3$), 28.70 (C-5), 32.45 (C-2), 56.51 (C-6), 83.60 (C-2′), 113.95 (C-4), 117.20 (C-3), 118.75 (C-5′), 119.75 (C-6′), 120.97 (C-7′), 123.20 (C-8′), 124.82(C-9′), 125.39 (C-10′), 127.21(C-4a′), 128.29 (C-6a′), 137.22 (C-10a′), 157.30 (C-10b′), 187.31 (C-4′); MS (EI): $m/z$ (%) 338 (M, 30), 323 (25), 308 (23), 293 (10), 278 (15), 256 (30), 226 (40), 214 (30), 195 (35), 171 (70), 126 (100). Calcd for $C_{21}H_{22}O_2S$ (338.45): C, 74.51; H, 6.55; S, 9.47%. Found: C, 74.29; H, 6.48; S, 9.21%.

### 2.5 *Reaction of α-chlorosulfenyl chlorides 2 with potassium iodide in the presence of 1,3-cyclohexadiene*

A solution of KI (0.8 g, 5 mmol) in $CH_3CN$ (30 ml) was added to a solution **2** (5 mmol) in $CHCl_3$ (10 ml) containing 1,3-cyclohexadiene (5.5 mmol) under stirring. After another 1 h of stirring the reaction mixture was treated with aqueous $Na_2S_2O_3$. The organic phase was separated and dried over $Na_2SO_4$. After evaporation of the solvent *in vacuo* the solid residue was triturated with ethyl alcohol to give **5**.

**2.5.1 Dispiro[cyclohexane-1″,2′-(2′H,3′H)naphtho[1,2-b]pyran(4′H)-3′,3(2-thiabicyclo [2,2,2]-oct-5-ene)]-4′-one (5a).** From **2a**, yield 37% as yellow crystals from ethyl alcohol; m.p. 189–192 °C. IR: $\nu_{CO}$ 1684 cm$^{-1}$; $^1$H NMR: $\delta$ 1.18–2.19 (14H, m, $-(CH_2)_5-$ +2 $CH_2$), 3.42–3.65 (1H, m, $CH_{sp3}$), 4.15–4.35 (1H, m, $CH_{sp3}$), 6.00 (1H, dd, $J$ = 6.3, 6.1 Hz, $CH_{sp2}$), 6.20 (1H, dd, $J$ = 6.3, 6.1 Hz, $CH_{sp2}$), 7.15 (1H, d, $J$ = 8.7 Hz, ArH), 7.55–7.67 (2H, m, ArH), 7.82 (1H, d, $J$ = 8.1 Hz, ArH), 7.98 (1H, d, $J$ = 8.7 Hz, ArH), 8.50 (1H, d, $J$ = 8.4 Hz, ArH); MS (EI): $m/z$ (%) 376 (M, 100), 296 (30), 263 (36), 251 (22), 235 (18), 223 (33), 206 (38), 171 (66), 152 (37), 125 (45). Calcd for $C_{24}H_{24}O_2S$ (376.49): C, 76.55; H, 6.42; S, 8.51%. Found: C, 76.45; H, 6.41; S, 8.25%.

**2.5.2 2′,2′-Dimethylspiro-2′,3′-dihydronaphtho[1,2-b]pyran(4′ H)-3′,3-(2-thiabicyclo [2,2,2]-oct-5-ene)-4′-one (5b).** From **2b**, yield 35% as yellow crystals from ethyl alcohol; m.p. 125–128 °C. IR: $\nu_{CO}$ 1695 cm$^{-1}$; $^1$H NMR: $\delta$ 1.45 (3H, s, $CH_3$), 1.61 (3H, s, $CH_3$), 1.89–2.11 (4H, m, 2 $CH_2$), 3.41–3.52 (1H, m, $CH_{sp3}$), 4.10–4.29 (1H, m, $CH_{sp3}$), 6.01 (1H, dd, $J$ = 6.2, 6.1 Hz, $CH_{sp2}$), 6.20 (1H, dd, $J$ = 6.2, 6.1 Hz, $CH_{sp2}$), 7.19 (1H, d, $J$ = 8.7 Hz, ArH), 7.55–7.65 (2H, m, ArH), 7.82 (1H, d, $J$ = 8.1 Hz, ArH), 7.95 (1H, d, $J$ = 8.7 Hz, ArH), 8.52 (1H, d, $J$ = 8.4 Hz, ArH); $^{13}$C NMR: $\delta$ 26.15 (2′-$CH_3$), 27.32 (2′-$CH_3$), 38.45 (C-7), 39.11 (C-8), 53.51 (C-4), 54.25 (C-3), 57.15 (C-1), 82.18 (C-2′), 113.92 (C-5), 117.19 (C-6), 118.72 (C-5′), 119.71 (C-6′), 120.89 (C-7′), 123.19 (C-8′), 124.80 (C-9′), 125.35 (C-10′), 127.23 (C-4a′), 128.30 (C-6a′), 137.18 (C-10a′), 157.39 (C-10b′), 187.15 (C-4′); MS (EI): $m/z$ (%) 336 (M, 95), 321 (100), 306 (45), 278 (10), 228 (5), 184 (75), 126 (80). Calcd for $C_{21}H_{20}O_2S$ (336.43): C, 74.96; H, 5.99; S, 9.52%. Found: C, 74.69; H, 5.90; S, 9.32%.



### 2.6 *Oxidation of α-chlorosulfenyl chlorides 2 with hydrogen peroxide*

Hydrogen peroxide (25%, 50 mmol) was added to a stirred solution of the $\alpha$-chlorosulfenyl chlorides **2** (5 mmol) in glacial acetic acid (30 ml). The reaction mixture was maintained at 50 °C for 3 h. The cold solution was poured into water and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water and aqueous sat. $NaHCO_3$ solution. Removal of the dried solvent gave the crude 3,3-dichloronaphthopyranone **6**.

**2.6.1 3,3-Dichlorospiro[2,3-dihydronaphtho[1,2-b]pyran(4H)-2,1′-cyclohexane] -4-one (6a).** From **2a**, yield 70% as colorless solid from petroleum ether 40–60 °C; m.p. 89–92 °C. IR: $\nu_{CO}$ 1689 cm$^{-1}$; $^1$H NMR: $\delta$ 1.22–2.33 (10H, m, $-(CH_2)_5-$), 7.41 (1H, d, $J$ = 8.7 Hz, ArH), 7.50–7.65 (2H, m, ArH), 7.82 (1H, d, $J$ = 8.1 Hz, ArH), 7.94 (1H, d, $J$ = 8.7 Hz, ArH), 8.35 (1H, d, $J$ = 8.4 Hz, ArH); MS (EI): $m/z$ (%) 264 (M–$Cl_2$, 55), 235 (30), 206 (70), 171 (100), 126 (59). Calcd for $C_{18}H_{16}Cl_2O_2$ (335.22): C, 64.46; H, 4.81; Cl, 21.15%. Found: C, 64.30; H, 4.82; Cl, 20.92%.

**2.6.2 3, 3-Dichloro-2, 2-dimethyl-2, 3-dihydronaphtho[1, 2-b]pyran(4H)-4-one (6b).** From **2b**, yield 69% as colorless solid from petroleum ether 40–60 °C; m.p. 76–78 °C. IR: $\nu_{CO}$ 1691 cm$^{-1}$; $^1$H NMR: $\delta$ 1.68 (6H, s, 2 $CH_3$),7.22 (1H, d, $J$ = 8.7 Hz, ArH), 7.40–7.55 (2H, m, ArH), 7.62 (1H, d, $J$ = 8.1 Hz, ArH), 7.78 (1H, d, $J$ = 8.4 Hz, ArH), 8.20 (1H, d, $J$ = 8.1 Hz, ArH); MS (EI): $m/z$ (%) 224 (M–$Cl_2$, 65), 209 (50), 194 (70), 171 (85), 126 (100). Calcd for $C_{15}H_{12}Cl_2O_2$ (295.16): C, 61.03; H, 4.09; Cl, 24.02%. Found: C, 60.85; H, 3.92; Cl, 23.81%.

### 2.7 *Reaction of α-chlorosulfenyl chlorides 2 with morpholine*

A solution of morpholine (10 mmol) in dry toluene (20 ml) was added dropwise to a vigorously stirred solution of the α-chlorosulfenyl chlorides **2** (5 mmol) in toluene (20 ml). The resulting solution was stirred for 1 h. The formd solid was filtered and the filtrate washed with water, the organic phase separated, and dried over $CaCl_2$. After evaporation of the volatiles *in vacuo* the residue was treated with petroleum ether 40–60 °C to give **7**.

**2.7.1 (RS)-3-Chloro-3-morpholinosulfenylspiro[2,3-dihydronaphtho[1,2-b]pyran(4H)-2,1′-cyclohexane]-4-one (7a).** From **2a**, yield 40% as yellow crystals from petroleum ether 40–60 °C; m.p. 76–78 °C. IR: $\nu_{CO}$ 1695 $cm^{-1}$; $^1H$ NMR: $\delta$ 1.22–2.19 (10H, m, $-(CH_2)_5-$), 2.91–3.22 (4H, m, $-N(CH_2)_2-$), 3.53–3.72 (4H, m, $-O(CH_2)_2-$), 7.53 (1H, d, $J = 8.7$ Hz, ArH), 7.60–7.71 (2H, m, ArH), 7.84 (1H, d, $J = 8.1$ Hz, ArH), 7.96 (1H, d, $J = 8.7$ Hz, ArH), 8.32 (1H, d, $J = 8.4$ Hz, ArH); MS (EI): $m/z$ (%) 381 (M–HCl, 25), 296 (90), 266 (30), 251 (25), 235 (20), 206 (30), 171 (90), 126 (100). Calcd for $C_{22}H_{24}ClNO_3S$ (417.92): C, 63.22; H, 5.78; Cl, 8.48; N, 3.34; S, 7.67%. Found: C, 63.01; H, 5.61; Cl, 8.25; N, 3.21; S, 7.35%.



**2.7.2 (RS)-3-Chloro-2,2-dimethyl-3-morpholinosulfenyl-2,3-dihydronaphtho[1,2-b]pyran(4H)-4-one (7b).** From **2b**, yield 30% as yellow crystals from petroleum ether 40–60 °C; m.p. 65–68 °C. IR: $\nu_{CO}$ 1695 $cm^{-1}$; $^1H$ NMR: $\delta$ 1.45 (3H, s, $CH_3$), 1.73 (3H, s, $CH_3$), 2.92–3.22 (4H, m, $-N(CH_2)_2-$), 3.54–3.72 (4H, m, $-O(CH_2)_2-$), 7.50 (1H, d, $J = 8.7$ Hz, ArH), 7.55–7.65 (2H, m, ArH), 7.85 (1H, d, $J = 8.1$ Hz, ArH), 7.94 (1H, d, $J = 8.7$ Hz, ArH), 8.35 (1H, d, $J = 8.4$ Hz, ArH); MS (EI): $m/z$ (%) 341 (M–HCl, 18), 326 (40), 311 (60), 256 (90), 226 (30), 195 (30), 171 (85), 126 (100). Calcd for $C_{19}H_{20}ClNO_3S$ (377.86): C, 60.39; H, 5.33; Cl, 9.38; N, 3.70; S, 8.48%. Found: C, 60.19; H, 5.29; Cl, 9.18; N, 3.65; S, 8.23%.

### 2.8 *Oxidation of α-chlorosulfenamides 7 with hydrogen peroxide*

The procedure that employed for the preparation of 3,3-dichloronaphthopyranones **6** above has been used.

**2.8.1 (RS) 3-Chlorospiro [2,3-dihydronaphtho[1,2-b]pyran(4H)-2,1′-cyclohexane]-4-one (8a).** From **7a**, yield 65% as yellow crystals from petroleum ether 40–60 °C; m.p. 71–73 °C. IR: $\nu_{CO}$ 1701 $cm^{-1}$; $^1H$ NMR: $\delta$ 1.24–2.25 (10H, m, $-(CH_2)_5-$), 4.32 (1H, s, CH), 7.42 (1H, d, $J = 8.7$ Hz, ArH), 7.51–7.60 (2H, m, ArH), 7.83 (1H, d, $J = 8.1$ Hz, ArH), 7.94 (1H, d, $J = 8.7$ Hz, ArH), 8.30 (1H, d, $J = 8.4$ Hz, ArH); MS (EI): $m/z$ (%) 300 (M, 30), 264 (100), 235 (18), 223 (30), 171 (90), 152 (37), 126 (80). Calcd for $C_{18}H_{17}ClO_2$ (300.77): C, 71.87; H, 5.69; Cl, 11.78%. Found: C, 71.70; H, 5.59; Cl, 11.50%.

**2.8.2 (RS) 3-Chloro-2,2-dimethyl-2,3-dihydronaphtho[1,2-b]pyran(4H)-4-one (8b).** From **7b**, yield 50% as oil. IR: $\nu_{CO}$ 1695 $cm^{-1}$; $^1H$ NMR: $\delta$ 1.50 (3H, s, $CH_3$), 1.60 (3H, s, $CH_3$), 4.45 (1H, s, CH), 7.50 (1H, d, $J = 8.7$ Hz, ArH), 7.55–7.65 (2H, m, ArH), 7.83 (1H, d, $J = 8.1$ Hz, ArH), 7.98 (1H, d, $J = 8.7$ Hz, ArH), 8.39 (1H, d, $J = 8.4$ Hz, ArH); MS (EI): $m/z$ (%) 260 (M, 15), 224 (100), 209 (50), 194 (80), 171 (95), 126 (75). Calcd for $C_{15}H_{13}ClO_2$ (260.70): C, 69.10; H, 5.02; Cl, 13.59%. Found: C, 68.89; H, 4.88; Cl, 13.42%.

### 2.9 *Reaction of α-chlorosulfenyl chlorides 2 with N-methylpiperazine*

The procedure that employed for the reaction of **2** with morpholine was used.

**2.9.1 (RS)-3-Chloro-3-(4-methylpiperazino)sulfenylspiro[2,3-dihydronaphtho[1,2-b] pyran(4H)-2,1′-cyclohexane]-4-one (9a).** From **2a**, yield 29% as yellow crystals from ethyl alcohol; m.p. 148–150 °C. IR: $\nu_{CO}$ 1689 cm$^{-1}$; $^1$H NMR: $\delta$ 1.29–2.25 (10H, m, $-(CH_2)_5-$), 2.31 (3H, s, $CH_3$), 2.61–2.83 (4H, m, $CH_3-N(CH_2)_2-$), 3.11–3.45 (4H, m, $-N(CH_2)_2-$), 7.53 (1H, d, $J$ = 8.7 Hz, ArH), 7.60–7.71 (2H, m, ArH), 7.84 (1H, d, $J$ = 8.1 Hz, ArH), 7.95 (1H, d, $J$ = 8.7 Hz, ArH), 8.33 (1H, d, $J$ = 8.4 Hz, ArH); MS (EI): $m/z$ (%) 394 (M–HCl, 11), 380 (15), 296 (25), 235 (15), 171 (85), 126 (100). Calcd for $C_{23}H_{27}ClN_2O_2S$ (430.98): C, 64.09; H, 6.31; Cl, 8.22; N, 6.50; S, 7.45%. Found: C, 63.81; H, 6.21; Cl, 8.00; N, 6.31; S, 7.11%.

**2.9.2 (RS)-3-Chloro-2,2-dimethyl-3(4-methylpiprazino)sulfenyl-2,3-dihydronaphtho [1,2-b]pyran(4H)-4-one (9b).** From **2b**, yield 25% as yellow crystals from ethyl alcohol; m.p. 118–121 °C. IR: $\nu_{CO}$ 1701 cm$^{-1}$; $^1$H NMR: $\delta$ 1.41 (3H, s, $CH_3$), 1.67 (3H, s, $CH_3$), 2.38 (3H, s, $N-CH_3$), 2.63–2.84 (4H, m, $CH_3-N(CH_2)_2-$), 3.11–3.42 (4H, m, $-N(CH_2)_2-$), 7.50 (1H, d, $J$ = 8.7 Hz, ArH), 7.62–7.73 (2H, m, ArH), 7.83 (1H, d, $J$ = 8.1 Hz, ArH), 7.91 (1H, d, $J$ = 8.7 Hz, ArH), 8.30 (1H, d, $J$ = 8.4 Hz, ArH); MS (EI): $m/z$ (%) 354 (M–HCl, 15), 340 (10), 325 (16), 310 (35), 224 (15), 208 (31), 171 (100), 126 (65). Calcd for $C_{20}H_{23}ClN_2O_2S$ (390.91): C, 61.44; H, 5.92; Cl, 9.06; N, 7.16; S, 8.20%. Found: C, 61.19; H, 5.82; Cl, 8.88; N, 6.98; S, 7.95%.



### 2.10 *Reaction of α-chlorosulfenyl chlorides 2 with potassium cyanide*

To a solution of KCN (5 mmol) in 10 ml ethanol and 10 ml water was added a solution of α-chlorosulfenyl chlorides **2** (5 mmol) in 10 ml $CHCl_3$. The mixture was stirred for 15 min, the organic phase separated and washed with water dried over $CaCl_2$. The solvent was evaporated *in vacuo* to give **10**.

**2.10.1 (RS)-3-Chloro-3-thiocyanatospiro[2,3-dihydronaphtho[1,2-b]pyran(4H)-2,1′-cyclohexane]-4-one (10a).** From **2a**, yield 40% as viscous oil on elution from silica gel with 30% ethyl acetate in petroleum ether 40–60 °C. IR: $\nu_{CO}$ 1709, $\nu_{CN}$ 2151 cm$^{-1}$; $^1$H NMR: $\delta$ 1.15–2.28 (10H, m, $-(CH_2)_5-$), 7.41–7.62 (3H, m, ArH), 7.85 (1H, d, $J$ = 8.1 Hz, ArH), 7.96 (1H, d, $J$ = 8.7 Hz, ArH), 8.36 (1H, d, $J$ = 8.4 Hz, ArH); MS (EI): $m/z$ (%) 357 (M, 50), 322 (42), 296 (20), 266 (26), 251 (20), 223 (18), 206 (30), 171 (80), 126 (100). Calcd for $C_{19}H_{16}ClNO_2S$ (357.83): C, 63.77; H, 4.50; Cl, 9.90; N, 3.91; S, 8.95%. Found: C, 63.55; H, 4.48; Cl, 9.58; N, 3.72; S, 8.71%.

**2.10.2 (RS)-3-Chloro-2,2-dimethyl-3-thiocyanato-2,3-dihydronaphtho[1,2-b]pyran (4H)-4-one (10b).** From **2b**, yield 40% as oil on elution from silica gel with 30% ethyl acetate in petroleum ether 40–60 °C. IR: $\nu_{CO}$ 1710, $\nu_{CN}$ 2154 cm$^{-1}$; $^1$H NMR: $\delta$ 1.35 (3H, s, $CH_3$), 1.68 (3H, s, $CH_3$),7.55 (1H, d, $J$ = 8.7 Hz, ArH), 7.60–7.70 (2H, m, ArH), 7.89 (1H, d, $J$ = 8.1 Hz, ArH), 7.96 (1H, d, $J$ = 8.7 Hz, ArH), 8.35 (1H, d, $J$ = 8.4 Hz, ArH); MS (EI): $m/z$ (%) 317 (M, 35), 282 (25), 267 (30), 256 (5), 252 (40), 224 (10), 194 (60), 171 (95), 126

(100). Calcd for $C_{16}H_{12}ClNO_2S$ (317.77): C, 60.47; H, 3.80; Cl, 11.17; N, 4.40; S, 10.07%. Found: C, 60.17; H, 3.69; Cl, 10.92, N, 4.21; S, 9.83%.

## 3. Antiviral bioassay

### 3.1 *Preparation of synthetic compounds for bioassay*

Tested compounds were dissolved as 100 mg each in 1 ml of 10% DMSO in water. The final concentration was 100 μg/μl (Stock solution). The dissolved stock solutions were decontaminated by addition of 50 μg/ml antibiotic-antimycotic mixture (10,000 U penicillin G sodium, 10,000 μg streptomycin sulfates and 250 μg amphotericin B, PAA Laboratories GmbH, Austria).

### 3.2 *Cell culture*

African green monkey kidney-derived cells (Vero) were used. Cells were propagated in Dulbeccos' Minimal essential medium (DMEM) supplemented with 10% foetal bovine serum, 1% antibiotic-antimycotic mixture. The pH was adjusted at 7.2–7.4 by 7.5% sodium bicarbonate solution. The mixture was sterilized by filtration through 0.2 μm pore size nitrocellulose membrane.



### 3.3 *Viruses*

Herpes Simplex Virus type-1 was obtained from Environmental Virology Lab., Department of Water Pollution Research, National Research Centre.

### 3.4 *Cytotoxicity assay*

Cytotoxicity was assayed for both dimethylsulfoxide (DMSO) and the tested compounds. Serial dilutions were prepared and inoculated on Vero cells grown in 96-well tissue culture plates. The maximum tolerated concentration (MTC) for each compound was determined by both cell morphology and cell viability by staining with tryban blue dye.

### 3.5 *Plaque reduction infectivity assay*

A 6-well plate was cultivated with cell culture ($10^5$ cell/ml) and incubated for 2 days at 37 °C. HSV-1 was diluted to give $10^4$ PFU/ml and mixed with the tested compound at 10 and 20 μg concentrations and incubated overnight at 4 °C. Growth medium was removed from the multiwell plate and virus-compound mixture was inoculated (100 μl/well). After 1 h contact time, the inoculum's was aspirated and 3 ml of MEM with 1% agarose was overlaid the cell sheets. The plates were left to solidify and incubated at 37 °C until the development of virus plaques. Cell sheets were fixed in 10% formalin solution for 2 h and stained with crystal violet stain. Control virus and cells were treated identically without chemical compounds. A standard acyclovir was used at the same concentrations as the tested compounds. Virus plaques were counted and the percentage of reduction was calculated [20].

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