



Derivatization and biological activity studies of 3-chloro-3-chlorosulfenyl spiro tetrahydropyran/tetrahydrothiopyran-4,2'-chroman-4'-one

Mohamed I Hegab^{*a}, Hala E M Tolan^a, Eman M H Morsy^a, Abdelsalam I S^b, Alaa M Saleh^b, Farouk A Gad^a & Farouk M E Abdel-Megeid^a

^aPhotochemistry Department, National Research Centre, Dokki, 12622 Giza, Egypt

^bChemistry of Natural and Microbial Products Department, National Research Centre, Dokki, 12622, Giza, Egypt

E-mail: pmihegab_2010@yahoo.com

Received 29 March 2020; accepted (revised) 17 September 2021

The adducts **4a,b-7a,b** have been obtained either by reducing α -chloro- β -oxosulfenyl chlorides **2a,b** with iodide ion in the presence of dienes namely, 2-methyl-1,3-butadiene (isoprene), 2,3-dimethyl-1,3-butadiene, 1,2,3,4-tetrachlorocyclopentadiene, or 1,3-cyclohexadiene, respectively; or by thermolysis of oxadithiin derivatives **3a,b** in the presence of the same aforementioned dienes presumably *via* the formation of the same intermediate **A** in both cases of compounds **2a,b** and **3a,b**. It is observed that α -chloro- β -oxosulfenyl chlorides **2a,b** undergo straight forward substitution with potassium cyanide to give **8a,b**. Direct oxidation of **2a,b** with H₂O₂/AcOH affords 3,3-dichloropyran-4-ones **9a,b**, while conversion of **2a,b** to the sulfonamides **10a,b** followed by oxidation provides 3-chloropyranones **11a,b**. Antioxidant and antimicrobial evaluation of compounds **4a,b-6a,b** shows moderate activity. MIC of the derivative **6b** reveals a remarkable inhibition of the pathogenic gram positive bacteria (*Staphylococcus aureus*) as well as gram negative *E. coli*.

Keywords: α -Chloro- β -oxosulfenyl chlorides, oxadithiin derivatives, sulfonamides, antioxidant, antimicrobial activity

Some α -oxo-thioketone derivatives can be isolated in pure state in the monomeric form¹⁻⁷. Previously, it was reported that some chromene-derived- α -oxo-thioketones were isolated as dimers with 1,3,4-oxadithiin structure *via* the reaction of α -chloro- α -chlorothiocabonyl compounds with potassium iodide or tertiary phosphanes⁸⁻¹⁰. [4+2] Cycloaddition reactions of some 3-thioxo-benzopyran-4-ones (generated *in situ* *via* reduction of the corresponding α -chloro-sulfenylchlorides with potassium iodide) with 2,3-dimethyl-1,3-butadiene was reported¹¹. Also, the thermolysis of spirobenzopyran-3',2-[1,3,4]oxadithiino[5,6-*c*]benzopyran-4'-ones in the presence of 2,3-dimethyl-1,3-butadiene, 1,3-cyclohexadiene, and isoprene was reported¹². Herein we report the investigation of such reactions with newly synthesized spiro tetrahydropyran/ tetrahydrothiopyran-4,2'-chroman-4'-ones and the evaluation of the antioxidant and antimicrobial activities of some of the newly synthesized compounds.

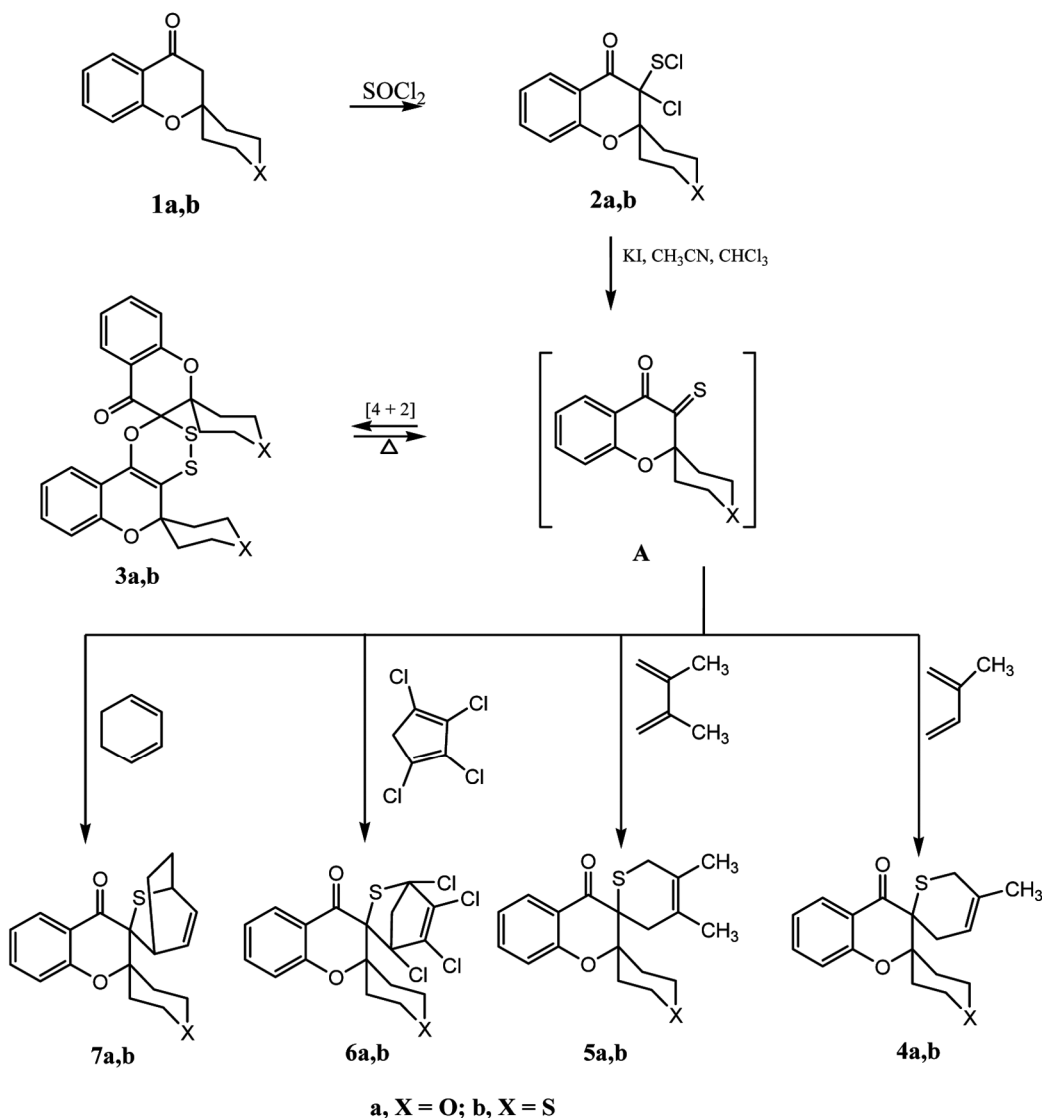
Results and Discussion

Chemistry

α -Oxo-thioketone intermediate **A** presumably can be formed through the reaction of compounds **2a,b**

with potassium iodide in acetonitrile as intermediate step in the formation of compounds **3a,b** or can be generated *in situ* by thermal cleavage of the oxadithiin derivatives **3a,b** in a retro Diels-Alder reaction in dry benzene. So, the reaction of compounds **2a,b** with potassium iodide in acetonitrile in the presence of appropriate diene gave the same products upon thermolysis of compounds **3a,b** in the presence of the same appropriate diene *via* formation of α -Oxo-thioketone intermediate **A**. The obtained results are in accordance with previous reports¹¹⁻¹³.

Accordingly, when the α -oxo-thioketone intermediate **A** (produced from compounds **2a,b** or compounds **3a,b**) was reacted with isoprene, it gave 3-methyl-dispiro(tetrahydropyran/ tetrahydrothiopyran - 4'',2'-chroman-3',6- Δ^3 -thiapyran]-4'-one **4a,b**. The ¹H NMR of these formed products showed a characteristic -CH signal as a multiplet at δ 5.65 ppm in compound **4a**, and at δ 5.62 in compound **4b** (Scheme I). While reaction of intermediate **A** with 2,3-dimethyl-1,3-butadiene and also with 1,2,3,4-tetrachloro-1,3-cyclopentadiene afforded 3,4-dimethyldispiro [tetrahydropyran/tetrahydrothiopyran-4'',2'-chroman-3',6- Δ^3 -thiapyran]-4'-one (**5a,b**) and 1,4,5,6-tetrachloro dispiro [tetrahydropyran/



Scheme I

tetrahydrothiapyran-4'',2'-chroman-3',3'-(2-thiabicyclo [2.2.1]hept-5-ene)]-4'-one (**6a,b**), respectively. Their structures were confirmed by spectral data, where the $^1\text{H NMR}$ of compound **5a** showed a characteristic $2\text{-CH}^a\text{H}^b$ as a doublet at $\delta = 2.71$ ppm, $2\text{-CH}^a\text{H}^b$ as a doublet at $\delta = 2.89$ ppm, and $^1\text{H NMR}$ of compounds **6a,b** showed a characteristic -CH_2 signal as a singlet at $\delta 2.78$ ppm and at $\delta 2.68$ ppm, respectively.

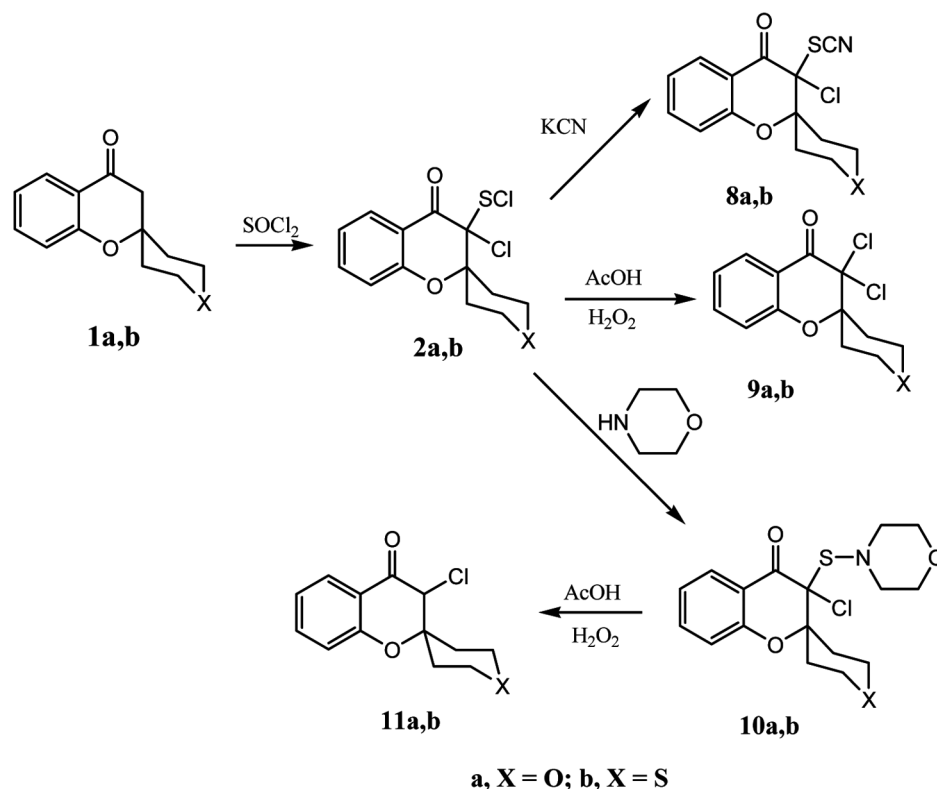
The reaction of intermediate **A** with 1, 3-cyclohexadiene gave dispiro [tetrahydropyran/tetrahydrothiapyran-4'',2'-chroman-3',3'-(2-thiabicyclo [2.2.2]oct-5-ene)]-4'-one **7a,b**. The $^1\text{H NMR}$ showed a characteristic two -CH signals as triplet at $\delta 6.23$ and $\delta 6.43$ ppm in compound **6a**, and at $\delta 6.34$ and $\delta 6.52$ ppm in compound **6b** (Scheme I).

The mass spectra of products **4-7** showed the molecular ion peak of each compound.

When the sulfonyl compounds **2a,b** were reacted with potassium cyanide, they gave 3'-chloro-3'-thiocyanatospiro(tetrahydropyran/tetrahydrothiapyran-4,2'-chroman)-4'-one (**8a,b**) (Scheme II) and the results are in accordance with previous reports^{10,14}.

The IR spectra of the formed products **8a,b** showed a characteristic absorption band at $\nu 2165\text{ cm}^{-1}$ and at $\nu 2198\text{ cm}^{-1}$, respectively corresponding to the -CN group.

When compounds **2a,b** were reacted with hydrogen peroxide in glacial acetic acid 3',3'-dichlorospiro (tetrahydropyran-4,2'-chroman)-4'-one (**9a,b**) were obtained, and the $^1\text{H NMR}$ spectra of these



Scheme II

compounds agree with the assigned structures (Scheme II).

The conversion of compounds **2a,b** to the corresponding 3'-chloro-3'-morpholinosulfenylspiro(tetrahydropyran/tetrahydrothiapyrane-4,2'-chroman)-4'-one (**10a,b**) (Scheme II) was achieved upon treatment with morpholine. The structures of compounds **10a,b** were confirmed by spectral data ($^1\text{H NMR}$ and MS). Where the $^1\text{H NMR}$ of compound **10a,b** showed the presence of protons of morpholine ring as multiplet at δ 2.89-4.30 ppm. When the sulfonamides **10a,b** were oxidized with hydrogen peroxide in glacial acetic acid, they gave 3'-chlorospiro(tetrahydropyran-4,2'-chroman)-4'-one (**11a,b**). The $^1\text{H NMR}$ showed a signal of 3'-CH in compound **11a** and **11b** as a singlet at δ 5.38, and at δ 5.29 ppm respectively (Scheme II). Formation of compounds **8-11**, is in accordance with previous reports^{10,13}.

Biological activity

Antioxidant activity

Six samples were tested for their antioxidant activity through their scavenging activity against DPPH free radical. All the samples showed weak

Table I — Scavenging activity of different samples for DPPH free radical at concentration 1 mg/mL. Data are presented as mean \pm SD

Sample	DPPH scavenging activity (%)
4a	1.5 \pm 0.01
4b	11.79 \pm 0.04
5a	17.75 \pm 0.02
5b	9.08 \pm 0.1
6a	25.84 \pm 0.02
6b	32.58 \pm 0.01
Ascorbic acid	97 \pm 1.00

scavenging activity compared to the reference ascorbic acid, where the highest scavenging % was 32.58 \pm 0.01 obtained by **6b** at concentration 1mg/mL (Table I).

DPPH scavenging assay is commonly used for screening antioxidant activity. This is due to its efficiency, simplicity and being relatively quick and inexpensive¹⁴. Antioxidant activity of a compound depends on the number of active groups, either proton or electron donating groups, and their position on the aromatic ring where *ortho* position is the most active due to its ability to form intra molecular hydrogen bonding followed by *para* position then *meta* position^{15,16}.

Accordingly, amide derivatives obtained from combining two 2-amino-1,3,4-thiadiazoles containing phenolic hydroxyl groups with different carboxylic acid chlorides showed good DPPH scavenging activity. This can be related to their ability to release hydrogen atoms, either from nitrogen or oxygen that leads to stabilization of the obtained radical by resonance¹⁷.

To confirm whether the protocatechuic acid shows better scavenging activity than its derivatives, a series of esters and amides were synthesized and screened for their antioxidant potential. The obtained results suggest that the slow DPPH scavenging activity of the protocatechuic acid compared with its derivatives is due to the dissociation of the carboxyl group since it decreases the electron-withdrawing property of the substituent; this leads to low susceptibility of the formed quinone toward a nucleophilic attack by a solvent molecule. Better radical scavenging activity of phenolic acid derivatives containing 1,2,4-triazole and 1,3,4-oxadiazole in comparison with parent acids was recently determined and attributed to the participation of the heterocyclic scaffold in resonance stabilization of the formed radical after homolytic cleavage of the OAH and NAH bonds by the DPPH radical, as it was previously demonstrated by DFT calculations for 1,2,4-triazole derivatives^{17,18}.

Similarly, antioxidant capacity of 1,3,4-thiadiazoles derived from phenolic acids is related to their ability to release hydrogen atoms, either from nitrogen or oxygen; this leads to resonance stabilization of the obtained radical. The resulting

phenoxy or nitrogen radical can be highly stabilized through resonance since the unpaired electron may be additionally delocalized across 1,3,4-thiadiazole ring. The nature of the R-substituents, reasonably selected to cover electron-donating, electron-withdrawing and steric properties, strongly influenced DPPH¹⁹.

Minimum inhibitory concentration (MIC)

The investigation of the MIC of the tested compound **6b** was evaluated to determine the optimal concentration at which the maximum inhibition was achieved¹⁶. The study was achieved by using different conc. Range from (50, 100, 150, 200, 250, and 300 ug/mL) of the compound under investigation. The results represented in Figure 1, Table II and Table III indicated that the tested compound varied in its effects on the tested microorganisms. The MIC for *Staphylococcus* and *E.coli* was 150 ug/mL. On the other hand, MIC for the other tested yeast (*Candida albicans*) was 100 ug/mL) and for *A. niger* 200

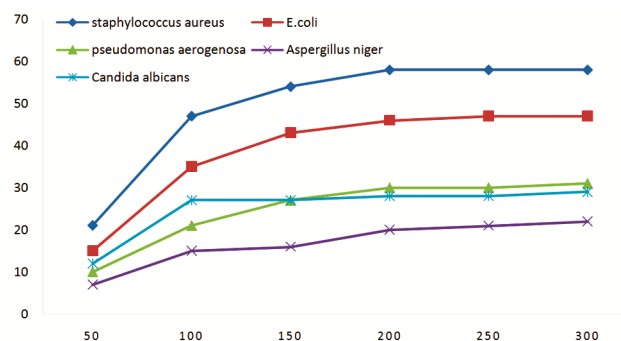


Figure 1 — Minimum inhibitory concentration of sample **6b**

Table II — Antimicrobial activity of the compounds

Sample	Growth Reduction (%)				
	<i>Staphylococcus aureus</i> (g+)	<i>E. coli</i> (g-)	<i>Pseudomonas aeruginosa</i>	<i>Aspergillus niger</i>	<i>Candida albicans</i>
4a	15	10	10	7	17
4b	20	23	15	5	10
5a	44	50	35	22	31
5b	30	21	12	—	7
6a	35	26	—	5	—
6b	47	35	21	15	27

Table III — Minimum inhibitory concentration of sample **6b**

Conc. (ppm)	Growth Reduction (%)				
	<i>Staphylococcus aureus</i> (g+)	<i>E. coli</i> (g-)	<i>Pseudomonas aeruginosa</i>	<i>Aspergillus niger</i>	<i>Candida albicans</i>
50	21	15	10	7	12
100	47	35	21	15	27
150	54	43	27	16	27
200	58	46	30	20	28
250	58	47	30	21	28
300	58	47	31	22	29

ug/mL. These results showed the priority of using this compound as antibacterial as well as antifungal agent²⁰.

Antibacterial activity of the prepared sample as anti Gram-positive (*S aureus*) is greater than antibacterial activity against Gram-negative (*E coli*), this is most probably due to the fact that Gram-positive bacterial cell walls consist of a single layer, whereas Gram-negative cell wall is a multi-layered structure bounded by an outer cell membrane²¹.

Materials and Methods

Chemistry

Melting Points were taken on a digital melting point apparatus and they are uncorrected. Infrared spectra (KBr for solid or neat for liquid) were measured on a Bruker-Vector 22, Germany (Cairo university, Faculty of Science) and Mass spectra were measured on Hewlett-Packard 5988 A (1000 Hz) instrument, Shimadzu GCMS-QP-1000EX mass spectrometer at 70 eV (Cairo University, Faculty of Science). ¹H and ¹³C NMR spectra were obtained by using a JEOL EX-500 MHz (National Research Center, Central Services Laboratory) spectrometers and (CDCl₃) with TMS as internal standard. Chemical shifts were quoted in δ and were related to that of the solvents. Splitting patterns were designated as follow: s singlet; m multiplet. Elemental analyses were operated using Mario Elementar apparatus, Organic Microanalysis Unit, National Research Center, Cairo, Egypt. All reactions were monitored by TLC. Compounds **1a,b**, **2a,b**, and **3a,b** were prepared as reported in the literature²².

Reaction of compounds 2 or 3 with dienes

General procedure

Reaction with **2**: A solution of KI (0.1 mmol) in 20 mL acetonitrile was added to a mixture of compound **2a** or **2b** (0.1 mmol) and 0.1 mmol of the appropriate diene in 10 mL CHCl₃ with stirring for 2h. The reaction mixture was added to a solution of sodium thiosulphate, the organic layer was separated by separating funnel and then the solvent was evaporated to give a residue which was purified by column chromatography with an eluent (chloroform/ethyl acetate 1:3) and silica gel (Merk silica gel 60, particle size 0.040-0.063 mm)¹³.

Reaction with **3**: A mixture of **3a** or **3b** (3 mmol) and appropriate diene (0.6 mL, 6 mmol) in dry benzene (20 mL) was boiled under reflux for 1-3 h. the reaction mixture was evaporated under reduced

pressure to dryness and the residue was treated as mentioned above.

3-Methyl-dispiro(tetrahydropyran-4'',2'-chroman-3',6-Δ³-thiapyran]-4'-one (**4a**, C₁₈H₂₀O₃S)

From isoprene with **2a** or **3a**: Pink oil with yield (34% from **2a**, 60% from **3a**). R_f: 0.32; IR (neat): 1701 (C=O), 1592 cm⁻¹(C=C); ¹H NMR (CDCl₃, 500 MHz): δ 1.53 (s, 3H, CH₃), 1.91-2.60 (m, 6H, 2 C-(CH₂)₂+ 5-CH₂), 3.01 (d, J= 7.4 Hz, 1H, 2-CH^aH^b), 3.18 (d, J= 7.4 Hz, 1H, 2-CH^aH^b), 3.32- 3.57 (m, 4H, O-(CH₂)₂), 5.55-5.95 (m, 1H, 4-CH), 6.90- 7.92 (m, 4H, Ar-H); ¹³C NMR (CDCl₃): δ 21.14 (CH₃), 30.32 (1-CH₂), 34.72 (2-CH), 38.74 (C-1), 64.10 (2-CH₂), 74.62 (C-5), 79.62 (C-2), 117.30, 121.52, 127.43, 132.80, 134.31, 136.69, 156.13 (arom. C), 189.52 (C=O). Anal.C₁₈H₂₀O₃S (316): Calcd. C, 68.33; H, 6.37. Found: C, 68.74; H, 6.18; MS: m/z (%) 316 (16.22) [M⁺], 284 (11.75), 78 (100).

3-Methyl-dispiro(tetrahydrothiapyran-4'',2'-chroman-3',6-Δ³-thiapyran]-4'-one (**4b**, C₁₈H₂₀O₂S₂)

From isoprene with **2b** or **3b**: Pale red oil with yield (49% from **2a**, 63% from **3a**). R_f: 0.44; IR (neat): 1683 (C=O), 1634 cm⁻¹ (C=C); ¹H NMR (CDCl₃, 500 MHz): δ 1.65 (s, 3H, CH₃), 1.79-2.90 (m, 6H, 2 C-(CH₂)₂ + 5-CH₂), 2.44-2.73 (m, 4H, S-(CH₂)₂), 3.24 (d, J= 3.7 Hz, 1H, 2-CH^aH^b), 3.24 (d, J= 3.7 Hz, 1H, 2-CH^aH^b), 5.62 (s, 1H, 4-CH), 7.02- 7.98 (m, 4H, Ar-H); ¹³C NMR (CDCl₃): δ 22.22 (CH₃), 24.02 (1-CH₂), 35.16 (2-CH), 39.94 (C-1), 41.11 (2-CH₂), 73.01 (C-5), 81.03 (C-2), 116.36, 120.67, 121.32, 126.56, 127.78, 129.52, 133.92, 136.47, 158.42 (arom. C), 192.02 (C=O). Anal.C₁₈H₂₀O₂S₂ (332): Calcd. C, 65.02; H, 6.06; S, 19.29. Found: C, 65.39; H, 6.30; S, 19.04; MS: m/z (%) 332 (0.70) [M⁺], 287 (2.83), 192 (4.41), 70 (100).

3,4-Dimethyl-dispiro(tetrahydropyran-4'',2'-chroman-3',6-Δ³-thiapyran]-4'-one (**5a**, C₁₉H₂₂O₃S)

From 2,3-dimethyl-1,3-butadiene with **2a** or **3a**: Dark red oil with yield (53% from **2a**, 70% from **3a**). R_f: 0.62; IR (neat): 1703 (C=O), 1601 cm⁻¹ (C=C); ¹H NMR (CDCl₃, 500 MHz): δ 1.70-2.56 (m, 10H, C-(CH₂)₂+ 2CH₃), 2.62 (s, 2H, 5-CH₂), 2.71 (d, J= 5 Hz, 1H, 2-CH^aH^b), 2.78 (d, J= 5 Hz, 1H, 2-CH^aH^b), 3.52- 3.91 (m, 4H, O-(CH₂)₂), 7.01- 7.83 (m, 4H, Ar-H); ¹³C NMR (CDCl₃): δ 23.01 (2-CH₃), 29.72 (1-CH₂), 31.32 (C-4), 34.16 (C-1), 72.01 (2-CH₂), 74.21 (C-5), 78.11 (C-2), 117.31, 120.23,

124.50, 125.48, 127.19, 129.57, 132.28, 133.92, 134.56, 159.46 (arom. C), 191.30 (C=O). Anal. C₁₉H₂₂O₃S (331): Calcd. C, 69.06; H, 6.71. Found: C, 68.83; H, 6.42; MS: *m/z* (%) 331 (1.38) [M⁺], 237 (3.95), 218 (15.34), 121 (100).

3,4-Dimethyl-dispiro(tetrahydrothiapyran-4'',2'-chroman-3',6-Δ³-thiapyran)-4'-one (5b, C₁₉H₂₂O₂S₂)

From 2,3-dimethyl-1,3-butadiene with **2b** or **3b**: Yellow oil with yield (55% from **2a**, 77% from **3a**). *R_f*: 0.48; IR (neat): 1689 (C=O), 1587 cm⁻¹ (C=C); ¹H NMR (CDCl₃, 500 MHz): δ 1.78-2.39 (m, 10H, 2 C-(CH₂)+2CH₃), 2.48- 2.56 (m, 4H, S-(CH₂)₂), 2.59 (s, 2H, 5-CH₂), 2.69 (d, 1H, J= 4.2 Hz, 2-CH^aH^b), 2.79 (d, 1H, J= 4.2 Hz, 2-CH^aH^b), 7.11- 7.95 (m, 4H, Ar-H); ¹³C NMR (CDCl₃): δ 21.72 (1-CH₂), 22.21 (2-CH₃), 30.11 (C-4), 33.24 (C-1), 42.01 (2-CH₂), 72.43 (C-5), 81.04 (C-2), 115.37, 121.53, 125.51, 127.19, 129.31, 133.71, 134.40, 161.01 (arom. C), 192.12 (C=O). Anal. C₁₉H₂₂O₂S₂ (346): Calcd. C, 65.86; H, 6.40. Found: C, 65.49; H, 6.42; MS: *m/z* (%) 346 (9.07) [M⁺], 328 (7.12), 217 (7.92), 57 (100).

1,4,5,6-Tetrachloro-dispiro[tetrahydropyran-4'',2'-chroman-3',3-(2-thiabicyclo[2.2.1]hept-5-ene)]-4'-one (6a, C₁₈H₁₄Cl₄O₃S)

From 1,2,3,4-tetrachloro-1,3-cyclopentadiene with **2a** or **3a**: Pink oil with yield (60% from **2a**, 72% from **3a**). *R_f*: 0.36; IR (neat): 1698 (C=O), 1560 cm⁻¹ (C=C); ¹H NMR (CDCl₃, 500 MHz): δ 1.62-2.50 (m, 4H, C-(CH₂)₂), 2.78 (s, 1H, 7-CH₂), 3.63- 4.21 (m, 4H, O-(CH₂)₂), 6.83- 7.88 (m, 4H, Ar-H). Anal. C₁₈H₁₄Cl₄O₃S (452): Calcd. C, 47.81; H, 3.12. Found: C, 47.49; H, 3.40; MS: *m/z* (%) 452 (0.85) [M⁺], 454 (0.91), 458 (0.80), 72 (100).

1,4,5,6-Tetrachloro-dispiro[tetrahydrothiapyran-4'',2'-chroman-3',3-(2-thiabicyclo[2.2.1]hept-5-ene)]-4'-one (6b, C₁₈H₁₄Cl₄O₂S₂)

From 1,2,3,4-tetrachloro-1,3-cyclopentadiene with **2b** or **3b**: Dark red oil with yield (52% from **2a**, 65% from **3a**). *R_f*: 0.29; IR (neat): 1703 (C=O), 1564 cm⁻¹ (C=C); ¹H NMR (CDCl₃, 500 MHz): δ 1.87-2.52 (m, 4H, C-(CH₂)₂), 2.49- 2.63 (m, 4H, S-(CH₂)₂), 2.68 (s, 2H, 7-CH₂), 7.01- 7.98 (m, 4H, Ar-H). Anal. C₁₈H₁₄Cl₄O₂S₂ (465): Calcd. C, 46.17; H, 3.01; S, 13.70. Found: C, 46.49; H, 3.31; S, 13.34; MS: *m/z* (%) 466 (0.55) [M⁺ + 1], 474 (0.90), 478 (0.60), 122 (100).

Dispiro[tetrahydropyran-4'',2'-chroman-3',3-(2-thiabicyclo[2.2.2]oct-5-ene)]-4'-one (7a, C₁₉H₂₀O₃S)

From 1,3-cyclohexadiene with **2a** or **3a**: Brown oil with yield (57% from **2a**, 65% from **3a**). *R_f*: 0.54; IR (neat): 1706 (C=O), 1606 cm⁻¹ (C=C); ¹H NMR (CDCl₃, 500 MHz): δ 1.71-2.65 (m, 8H, C-(CH₂)₂ + 7-CH₂ + 8-CH₂), 2.78-2.89 (m, 1H, 4-CH), 3.04- 3.21 (m, 1H, 1-CH), 3.60- 4.01 (m, 4H, O-(CH₂)₂), 6.23(t, J= 6.3 Hz, 1H, 5-CH), 6.43 (t, J= 4.6 Hz, 1H, 6-CH), 7.01- 7.81 (m, 4H, Ar-H); ¹³C NMR (CDCl₃): δ 23.74 (C-7), 26.32 (C-8), 31.92 (C-4), 34.74 (1-CH₂), 35.23 (C-1), 63.17 (C-3), 77.10 (2-CH₂), 83.62 (C-2), 118.36, 120.73, 121.46, 122.04, 126.60, 127.74, 128.80, 130.92, 133.59, 134.22, 136.42, 137.05, 159.06 (arom. C), 193.42 (C=O). Anal. C₁₉H₂₀O₃S (328): Calcd. C, 69.48; H, 6.14. Found: C, 69.69; H, 6.42; MS: *m/z* (%) 328 (61.51) [M⁺], 310 (2.71), 277 (3.26), 57 (100).

Dispiro[tetrahydrothiapyran-4'',2'-chroman-3',3-(2-thiabicyclo[2.2.2]oct-5-ene)]-4'-one (7b, C₁₉H₂₀O₂S₂)

From 1,3-cyclohexadiene with **2b** or **3b**: Pink oil with yield (45% from **2a**, 70% from **3a**). *R_f*: 0.63; IR (neat): 1688 (C=O), 1585 cm⁻¹ (C=C); ¹H NMR (CDCl₃, 500 MHz): δ 2.02-2.60 (m, 8H, C-(CH₂)₂ + 7-CH₂ + 8-CH₂), 2.60- 2.76 (m, 4H, S-(CH₂)₂), 3.01-3.16 (m, 1H, 4-CH), 3.25- 3.47 (m, 1H, 1-CH), 6.34(t, J= 7.2 Hz, 1H, 5-CH), 6.52 (t, J= 5.7 Hz, 1H, 6-CH), 7.01- 7.97 (m, 4H, Ar-H); ¹³C NMR (CDCl₃): δ 22.76 (C-7), 27.16 (C-8), 30.91 (C-4), 33.84 (1-CH₂), 37.47 (C-1), 65.88 (C-3), 77.55 (2-CH₂), 83.46 (C-2), 118.24, 119.39, 122.70, 128.79, 132.71, 134.91, 138.82, 137.05, 156.76 (arom. C), 183.55 (C=O). Anal. C₁₉H₂₀O₂S₂ (344): Calcd. C, 66.24; H, 5.85. Found: C, 66.01; H, 5.58; MS: *m/z* (%) 344 (4.85) [M⁺], 307 (4.85), 267 (5.67), 69 (100).

Reaction of α-chlorosulfonyl chloride **2 with potassium cyanide (**8a**, **8b**)**

General Procedure.

To a solution of potassium cyanide (KCN, 0.01 mol) in 10 mL ethanol and 10 mL water was added a solution of (0.01 mol) compound **2a** or **2b** in 10 mL CHCl₃. The mixture was stirred for 5 min., the organic phase was separated and washed with water (3 times), and dried over CaCl₂. The solvent was evaporated *in vacuo* to give **8a** or **8b**.

3'-Chloro-3'-thiocyanatospiro(tetrahydropyran-4,2'-chroman)-4'-one (8a, C₁₄H₁₂ClNO₃S).

From **2a**, pink oil with yield 58%. R_f : 0.33 (chloroform/methanol); IR (neat): 1693 (C=O), 2165 cm⁻¹ (CN); ¹H NMR (CDCl₃, 500 MHz): δ 1.78 (m, 4H, C-(CH₂)₂), 3.69 (m, 4H, O-(CH₂)₂), 7.01- 7.95 (m, 4H, Ar-H). Anal.C₁₄H₁₂ClNO₃S (309): Calcd. C, 54.28; H, 3.90, N, 4.52. Found: C, 54.49; H, 3.60, N, 4.36; MS: m/z (%) 309 (19.34) [M⁺], 311 (6.23), 280 (19.34), 55 (100).

3'-Chloro-3'-thiocyanatospiro(tetrahydrothiapyran-4,2'-chroman)-4'-one (8b, C₁₄H₁₂ClNO₂S₂).

From **2b**, grey oil with yield 60%. R_f : 0.45 (chloroform/methanol); IR (neat): 1697 (C=O), 2198 cm⁻¹ (CN); ¹H NMR (CDCl₃, 500 MHz): δ 2.02 (m, 4H, C-(CH₂)₂), 2.53 (m, 4H, O-(CH₂)₂), 7.11- 7.90 (m, 4H, Ar-H). Anal.C₁₄H₁₂ClNO₂S₂ (325): Calcd. C, 51.61; H, 3.71, N, 4.30. Found: C, 51.89; H, 3.40, N, 4.56; MS: m/z (%) 325 (23.85) [M⁺], 327 (21.15), 254 (33.08), 57 (100).

Reaction of α -chlorosulfenyl chloride **2** with hydrogen peroxide/glacial acetic acid (**9a**, **9b**)

General procedure

Hydrogen peroxide (30%, 50 mmol) was added to a stirred solution of the α -chlorosulfenyl chloride **2a** or **2b** (5 mmol) in glacial acetic acid (30 mL). The resulting solution was maintained at 50 °C (CAUTION) for 3 h, and pet.ether/chloroform (3:1) was used as an eluent, the cooled solution was poured into water (400 mL) and extracted with ethyl acetate (5 × 50 mL). The combined ethyl acetate extracts were washed with water (2 × 100 mL) and aq. Sat. NaHCO₃ solution (4 × 100 mL). Removal of the dried (Na₂SO₄) solvent gave the crude dichlorochromanones (**9a** or **9b**).

3',3'-Dichlorospiro(tetrahydropyran-4,2'-chroman)-4'-one (**9a**, C₁₃H₁₂Cl₂O₃)

From **2a**, colorless oil with yield 33%. R_f : 0.49; IR (neat): 1701 (C=O), 1606 cm⁻¹ (C=C); ¹H NMR (CDCl₃, 500 MHz): δ 1.87-2.69 (m, 4H, C-(CH₂)₂), 3.41- 3.88 (m, 4H, O-(CH₂)₂), 7.01- 7.87 (m, 4H, Ar-H). Anal.C₁₃H₁₂Cl₂O₃ (286): Calcd. C, 54.38; H, 4.21. Found: C, 54.69; H, 4.50; MS: m/z (%) 286 (0.57) [M⁺], 288 (1.87), 290 (1.87).

3',3'-Dichloro-spiro(tetrahydrothiapyran-4,2'-chroman)-4'-one (**9b**, C₁₃H₁₂Cl₂O₂S)

From **2a**, yellow oil with yield 30%. R_f : 0.53. IR (neat): 1699 (C=O), 1602 cm⁻¹ (C=C); ¹H NMR

(CDCl₃, 500 MHz): δ 2.01-2.47 (m, 4H, C-(CH₂)₂), 2.51- 2.85 (m, 4H, S-(CH₂)₂), 6.99- 7.98 (m, 4H, Ar-H). Anal.C₁₃H₁₂Cl₂O₂S (301): Calcd. C, 51.50; H, 3.99. Found: C, 51.39; H, 3.69; MS: m/z (%) 301 (0.43) [M⁺], 303 (1.98).

Reaction of α -chlorosulfenyl chloride **2a** or **2b** with morpholine (**10a**, **10b**)

Method A

A solution of secondary amine (morpholine) (20 mmol) in dry toluene (40 mL) was added drop wise over a period of 10 minutes to a vigorously stirred solution of the 3-chloro-3-sulfenyl derivatives (10 mmol) in toluene (50 mL), then cooled to 5 °C. The formed viscous solution was left at RT and was filtered through a celite pad, and pet.ether/chloroform (3:1) was used as an eluent.

Method B

A solution of 3-chloro-3-sulfenyl derivatives **2a** or **2b** (2 mmol) in 10 mL chloroform and (4 mmol) of morpholine was stirred at RT for 10 min. The solid was filtered off and the filtrate washed with water (3 times), and the organic phase dried over CaCl₂ and evaporated to give the residue, and chloroform was used as an eluent.

3'-Chloro-3'-morphlinosulfenylspiro (tetrahydropyran-4,2'-chroman)-4'-one (**10a**, C₁₇H₂₀ClNO₄S)

From **2a**, pink oil with yield (56% from method A; 45% from method B). R_f : 0.52; IR (neat): 1698 cm⁻¹ (C=O); ¹H NMR (CDCl₃, 500 MHz): δ 1.92-2.36 (m, 4H, C-(CH₂)₂), 2.89-3.23 (m, 4H, N-(CH₂)₂), 3.42- 4.30 (m, 8H, pyranoO-(CH₂)₂, morphilinoO-(CH₂)₂), 6.96- 7.92 (m, 4H, Ar-H). Anal.C₁₇H₂₀ClNO₄S (369): Calcd. C, 55.20; H, 5.45, N, 3.79. Found: C, 55.47; H, 5.70; N, 3.89; MS: m/z (%) 369 (0.67) [M⁺], 371 (1.51), 373 (0.66), 121 (100).

3'-Chloro-3'-morphlinosulfenylspiro (tetrahydropyran-4,2'-chroman)-4'-one (**10b**, C₁₇H₂₀ClNO₃S₂)

From **2b**, yellow oil with yield (60% from method A; 50% from method B). R_f : 0.34; IR (neat): 1701 cm⁻¹ (C=O); ¹H NMR (CDCl₃, 500 MHz): δ 1.97- 2.43 (m, 4H, C-(CH₂)₂), 2.52-2.88 (m, 4H, S-(CH₂)₂), 2.95-3.12 (m, 4H, N-(CH₂)₂), 3.54-3.83 (O-(CH₂)₂), 7.01- 7.98 (m, 4H, Ar-H). Anal.C₁₇H₂₀ClNO₃S₂ (385): Calcd. C, 52.91; H, 5.22, N, 3.63. Found: C, 52.69;

H, 5.52; N, 3.36; MS: m/z (%) 385 (0.18) [M^+], 387 (0.85), 389 (0.97), 75 (100).

Reaction of morpholino compound (10a,b) with hydrogen peroxide/glacial acetic acid (to produce 11a, 11b)

The same procedure which was used for preparation of compounds **9a,b**.

3'-Chlorospiro(tetrahydropyran-4,2'-chroman)-4'-one (11a, C₁₃H₁₃ClO₃)

From **10a**, brown oil with yield 48%. R_f : 0.24; IR (neat): 1694 cm^{-1} (C=O); $^1\text{H NMR}$ (CDCl₃, 500 MHz): δ 2.01-2.72 (m, 4H, C-(CH₂)₂), 3.01- 4.31 (m, 4H, O-(CH₂)₂), 5.38 (s, 1H, 3-CH) 6.91- 7.88 (m, 4H, Ar-H). Anal.C₁₃H₁₃ClO₃ (252): Calcd. C, 61.79; H, 5.19. Found: C, 61.51; H, 4.89; MS: m/z (%) 252 (2.30) [M^+], 254 (0.72), 120 (100).

3'-Chloro-spiro(tetrahydrothiapyran-4,2'-chroman)-4'-one (11b, C₁₃H₁₃ClO₂S)

From **10b**, red oil with yield 58%. R_f : 0.51; IR (neat): 1698 cm^{-1} (C=O); $^1\text{H NMR}$ (CDCl₃, 500 MHz): δ 2.21-2.58 (m, 4H, C-(CH₂)₂), 2.61- 2.82 (m, 4H, S-(CH₂)₂), 5.29 (s, 1H, 3-CH), 6.81- 7.90 (m, 4H, Ar-H). Anal.C₁₃H₁₃ClO₂S (268): Calcd. C, 58.10; H, 4.88. Found: C, 58.49; H, 4.98; MS: m/z (%) 268 (0.67) [M^+], 270 (1.05), 92 (100).

Biology

Antioxidant (DPPH radical) scavenging ability

The scavenging activity for DPPH free radical was measured according to Zhao *et al.*¹⁸ with some modifications. 100 μl samples (1mg/mL) were mixed with 900 μl of 0.1mM DPPH solution in methanol. The mixture was shaken vigorously and allowed to reach a steady state for 30 min in dark at temperature 37°C. De-colorization of DPPH was determined by measuring the absorbance at 517 nm, and the DPPH radical scavenging was calculated according to the following equation:

$$\% \text{ scavenging rate} = (A_1 - A_2 / A_1) \times 100$$

Where A_1 was the absorbance of the DPPH solution without sample and A_2 was the absorbance of DPPH with the sample. Ascorbic acid was taken as the standard. All the tests were performed in triplicate.

Antimicrobial activity

Nutrient agar (NA) media was used for culturing of the bacterial strains and for the fungal strains potato dextrose agar (PDA) media was used. According the

modified method of Mauny *et al.*¹⁹. where, the tested microorganisms at conc. 1×10^4 cell/mL was used and 0.1 mL of the diluted fluid was then spread on sterilized petri plates in triplicates using the standard spread plate technique, for both bacterial and fungal strain tested. The prepared chemical compounds under investigation were added to the petri dished on paper disc (what man no.3) at concentration (50ug/mL). The (NA) agar plates were then incubated at 37 C for 24 h and the PDA plates were incubated at 27 C for 72 h. After successful growth of microorganisms, the characterized inhibition zone (mm) of each distinct colony was determined in triplicates.

Conclusions

Some adducts were obtained either by reducing α -chloro β -oxosulfonyl chlorides with iodide ion in the presence of some homodienes or by thermolysis of oxadithiin derivatives in the presence of some homodienes. While α -chloro β -oxosulfonyl chlorides undergo straight forward substitution with potassium cyanide to give the corresponding thiocyanate. Direct oxidation of α -chloro β -oxosulfonyl chlorides afforded 3,3-dichloropyran-4-ones, while conversion to the sulfenamides prior to oxidation provides 3-chloropyranones. The results showed that the prepared compounds have slight antioxidant activity and accompanied by major antibacterial activity especially against gram positive bacteria and the tested yeast.

References

- Saville B & Steer M, *J Chem Soc Chem Commun*, 616 (1972).
- Bak C & Praefcke K, *Chem Ber*, 112 (1979) 2744.
- Hahn B, Koepke B & Voss J, *Liebigs Ann Chem*, 10 (1981).
- Bak C & Praefcke K, *J Heterocycl Chem*, 17 (1980) 1655.
- Thimm K & Voss J, *Tetrahedron Lett*, 537 (1975).
- Voss J, Schmueser W & Schlapkohl K, *J Chem Res (S)*, 61 (1977) 144.
- Zehavi U, *J Org Chem*, 42 (1977) 2821.
- El-Essawy F A G, Yassin S M, El-Sakka I A, Khattab A F, Støfte I, Møller J & Senning A, *J Org Chem*, 63 (1998) 9840.
- El-Essawy F A G, Yassin S M, El-Sakka I A, Khattab A F, Støfte I, Møller J & Senning A, *Sulf Lett*, 22 (1998) 19.
- Hegab M I, Abdel-Megeid F M E, Gad F A, Shiba S A, Møller J & Senning A, *Sulf Lett*, 22 (1998) 9.
- Hegab M I, Amr A A & Abdel-Megeid F M E, *Z Naturforsch*, 57b (2002) 922.
- Hegab M I & Moustafa A M, *Z Naturforsch*, 61b (2006) 1413.
- Hegab M I, Rashad A E, Shamroukh A H & Hamza I A, *J Sulfur Chem*, 27 (2006) 213.
- Akar Z, Küçük M & Doğan H, *J Enzyme Inhib Med Chem*, 32 (1) (2017) 640.
- Brewer M S, *Comprehensive reviews in Food Science and Food Safety*, 10(4) (2011) 221.

- 16 Da Silva I P, Brissow E, KellnerFilho L C, Senabio J, de Siqueira K A, VandresenFilho S & Junior P A S, *World J Microbiol Biotechnol*, 33(3) (2017) 62.
- 17 Jakovljević K, Matić I Z, Stanojković T, Krivokuća A, Marković V, Joksović M D & Joksović L, *Bioorg Med Chem Lett*, 27(16) (2017) 3709.
- 18 Zhao G R, Xiang Z J, Ye T X, Yaun J Y & Guo X Z, *Food Chem*, 99 (2006) 767.
- 19 Mauny B, Sadiki M & Ibusaudi K, *J Pharm Analysis*, 6 (2) (2015) 2015.
- 20 Gao Y & Cranston R, *Text Res J*, 78(1) (2008) 60.
- 21 Shtayeh A M S, Yagmour R M, Faidi Y R, Salem K & Al-Nuri M A, *J Enthopharm*, 6 (3) (1998) 267.
- 22 Hegab M I, Morsy E M H, Abd El-Megeid A E, Ali M M, El-Senousy W M, Tolan H E M, Gad F A & Abdel-Megeid F M E, *Phosphorus Sulfur Silicon Relat Elem*, 190 (2015) 1901.