Indian Journal of Chemistry
Vol. 60B, November 2021, pp. 1502-1510

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

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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 (isoperene), 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 H_2O_2/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 activiy. 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

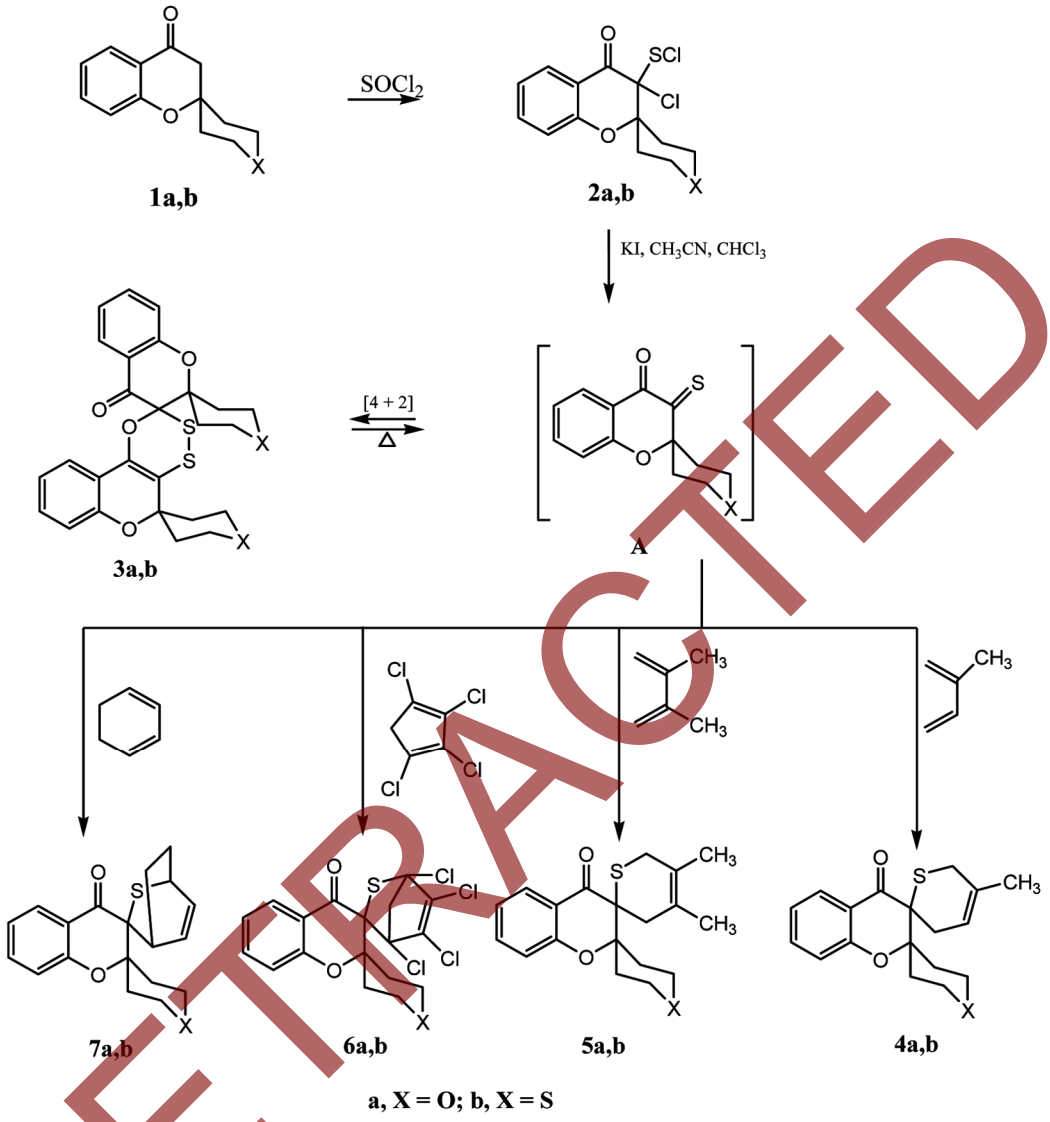
Some α-oxo-thioketone derivatives can be isolated in pure state in the monomericform[1–7]. Previously, it was reported that some chromene-derived-α-oxo-thioketones were isolated as dimers with 1,3,4-oxadithiin structure *via* the reaction of α-chloro-α-chlorothiocarbonyl compounds with potassium iodide or tertiary phosphanes[8–10]. [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 reported[11]. 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 reported[12]. Herein we report the investigation of such reactions with newly synthesized spirotetrahydropyran/ 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 reports[11-13].

Accordingly, when the α-oxo-thioketone intermediate **A** (produced from compounds **2a,b** or compounds **3a,b**) was reacted with isoperene, it gave 3-methyl-dispiro(tetrahydropyran/ tetrahydrothiapyran -4",2'-chroman-3',6-Δ^3-thiapyran]-4'-one **4a,b.** The ^{1}H 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-dimmethyl-1,3-butadiene and also with1,2,3,4-tetrachloro-1,3-cyclopentadiene afforded 3,4-dimethyldispiro [tetrahydropyran/tetrahydrothiapyran-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}H NMR of compound **5a** showed a characteristic 2-C*H*^{a}H^b as a douplet at δ= 2.71ppm, 2-CH^a*H*^{b} as a douplet at δ= 2.89 ppm, and ^{1}H NMR of compounds **6a,b** showed a characteristic –CH_2 signal as a singlet at δ 2.78 ppm and at δ 2.68 ppm, respectively.

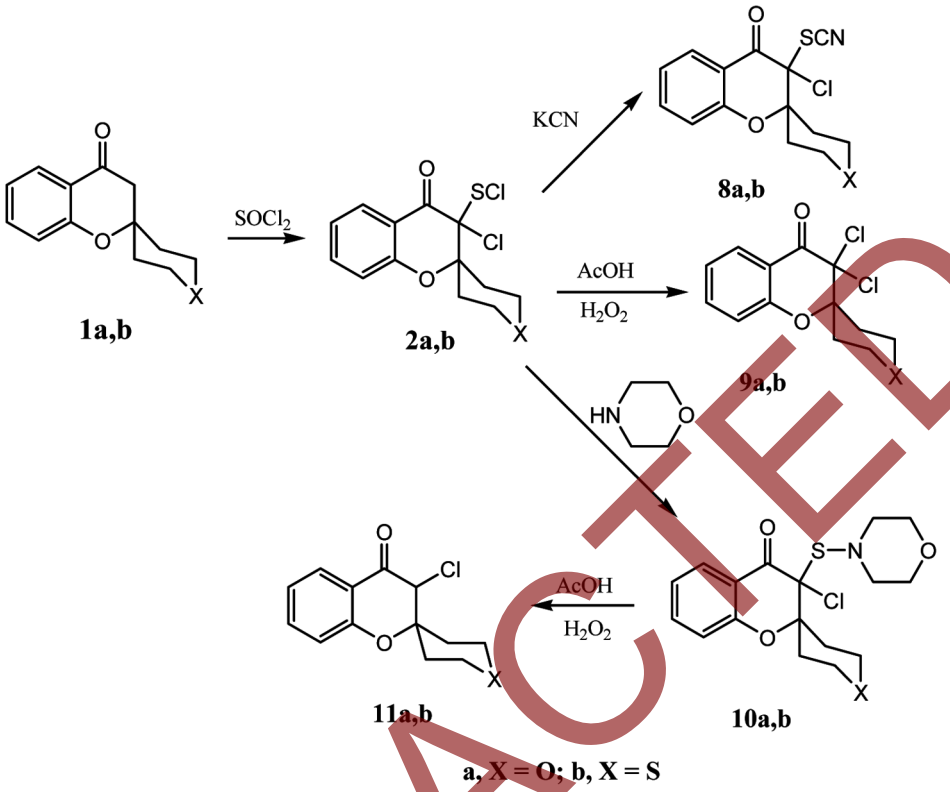
The reaction of intermediate **A** with 1, 3-cyclohexadiene gave dispiro [tetrahydropyran/ tetrahydrothiapyran-4",2'-chroman-3',3-(2-thiabicyclo [2.2.2]oct-5-ene)]-4'-one **7a,b**. The ^{1}H NMR showed a characteristic two –CH signals as triplet at δ 6.23 and δ 6.43 ppm in compound **6a**, and at δ 6.34 and δ 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 sulfenyl 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 ν 2165 cm^{-1} and at ν 2198 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}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}H NMR and MS). Where the ^{1}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}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 scavenging activity compared to the reference ascorbic acid, where the highest scavenging % was 32.58±0.01 obtained by **6b** at concentration 1mg/mL (Table I).

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

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

DPPH scavenging assay is commonly used for screening antioxidant activity. This is due to its efficiency, simplicity and being relatively quick and inexpensive[14]. 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 resonance[17].

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 phenoxyl 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 DPPH[19].

Minimum inhibitory concertation (MIC)

The investigation of the MIC of the tested compound **6b** was evaluated to determine the optimal concentration at which the maximum inhibition was achieved[16]. 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

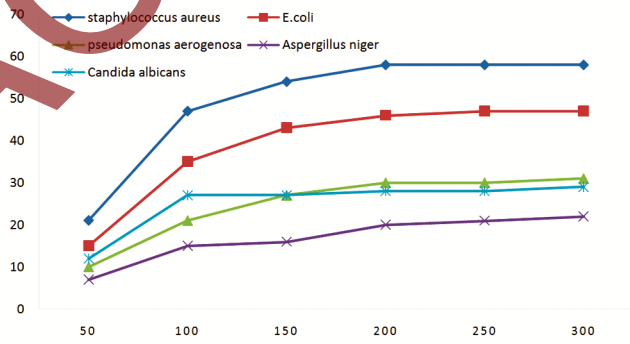


Figure 1 — Minimum inhibitory concentration of sample **6b**

Table II — Antimicrobial activity of the compounds

Sample	Growth Reduction (%)				
	Staphylococcus aureus (g+)	*E. coli (g −)*	*Pesudomonas aeroginosa*	*Aspergillus niger*	*Candida albicans*
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 (%)				
	Staphylococcus aureus (g+)	*E. coli (g -)*	*Pesudomonas aeroginosa*	*Aspergillus niger*	*Candida albicans*
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 agent[20].

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 membrane[21].

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). ^{1}H and ^{13}C NMR spectra were obtained by using a JEOL EX-500 MHz (National Research Center, Central Services Laboratory) spectrometers and ($CDCl_3$) 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 literature[22].

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 $CHCl_3$ 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-Δ^3-thiapyran]-4'-one (4a, $C_{18}H_{20}O_3S$)

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); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.53 (s, 3H, CH_3), 1.91-2.60 (m, 6H, 2 C-(CH_2)+ 5-CH_2), 3.01 (d, J= 7.4 Hz, 1H, 2-C*H*^{a}Hb), 3.18 (d, J= 7.4 Hz, 1H, 2-CH^a*H*^{b}), 3.32- 3.57 (m, 4H, O-$(CH_2)_2$), 5.55-5.95 (m, 1H, 4-CH), 6.90- 7.92 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 21.14 (CH_3), 30.32 (1-CH_2), 34.72 (2-CH), 38.74 (C-1), 64.10 (2-CH_2), 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.$C_{18}H_{20}O_3S$ (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-Δ^3-thiapyran]-4'-one (4b, $C_{18}H_{20}O_2S_2$)

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); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.65 (s, 3H, CH_3), 1.79-2.90 (m, 6H, 2 C-(CH_2) + 5-CH_2), 2.44-2.73 (m, 4H, S-$(CH_2)_2$), 3.24 (d, J= 3.7 Hz, 1H, 2-*CH*^{a}H^b), 3.24 (d, J= 3.7 Hz, 1H, 2-*C*H^a*H*^{b}), 5.62 (s, 1H, 4-CH), 7.02- 7.98 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 22.22 (CH_3), 24.02 (1-CH_2), 35.16 (2-CH), 39.94 (C-1), 41.11 (2-CH_2), 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.$C_{18}H_{20}O_2S_2$ (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-Δ^3-thiapyran]-4'-one (5a, $C_{19}H_{22}O_3S$)

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); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.70-2.56 (m, 10H,C-$(CH_2)_2$+ 2CH_3), 2.62 (s, 2H, 5-CH_2), 2.71 (d, J= 5 Hz, 1H, 2-C*H*^{a}H^b), 2.78 (d, J= 5 Hz, 1H, 2-CH^a*H*^{b}), 3.52- 3.91 (m, 4H,O-$(CH_2)_2$), 7.01- 7.83 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 23.01 (2-CH_3), 29.72 (1-CH_2), 31.32 (C-4), 34.16 (C-1), 72.01 (2-CH_2), 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. $C_{19}H_{22}O_3S$ (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-Δ^3-thiapyran]-4'-one (5b, $C_{19}H_{22}O_2S_2$)

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); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.78-2.39 (m, 10H, 2 C-(CH_2)+2CH_3), 2.48- 2.56 (m, 4H,S-$(CH_2)_2$),2.59 (s, 2H, 5-CH_2), 2.69 (d, 1H, J= 4.2 Hz, 2-C*H*^{a}H^b), 2.79 (d, 1H, J= 4.2 Hz, 2-CH^a*H*^{b}), 7.11- 7.95 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$): δ21.72 (1-CH_2), 22.21 (2-CH_3), 30.11 (C-4), 33.24 (C-1), 42.01 (2-CH_2), 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.$C_{19}H_{22}O_2S_2$ (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, $C_{18}H_{14}Cl_4O_3S$)

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); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.62-2.50 (m, 4H, C-$(CH_2)_2$), 2.78 (s, 1H, 7-CH_2), 3.63- 4.21 (m, 4H, O-$(CH_2)_2$, 6.83- 7.88 (m, 4H, Ar-H). Anal.$C_{18}H_{14}Cl_4O_3S$ (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, $C_{18}H_{14}Cl_4O_2S_2$)

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); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.87-2.52 (m, 4H, C-$(CH_2)_2$), 2.49- 2.63 (m, 4H, S-$(CH_2)_2$), 2.68 (s, 2H, 7-CH_2), 7.01- 7.98 (m, 4H, Ar-H). Anal.$C_{18}H_{14}Cl_4O_2S_2$ (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, $C_{19}H_{20}O_3S$)

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); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.71-2.65 (m, 8H, C-$(CH_2)_2$ +7-CH_2 + 8-CH_2), 2.78-2.89 (m, 1H, 4-CH), 3.04- 3.21 (m, 1H, 1-CH),3.60- 4.01 (m, 4H, O-$(CH_2)_2$), 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); ^{13}C NMR ($CDCl_3$): δ 23.74 (C-7), 26.32 (C-8), 31.92 (C-4), 34.74 (1-CH_2), 35.23 (C-1), 63.17 (C-3), 77.10 (2-CH_2), 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. $C_{19}H_{20}O_3S$ (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, $C_{19}H_{20}O_2S_2$)

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); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.02-2.60 (m , 8H, C-$(CH_2)_2$ +7-CH_2 +8-CH_2), 2.60- 2.76 (m, 4H, S-$(CH_2)_2$), 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); ^{13}C NMR ($CDCl_3$): δ 22.76 (C-7), 27.16 (C-8), 30.91 (C-4), 33.84 (1-CH_2), 37.47 (C-1), 65.88 (C-3), 77.55 (2-CH_2), 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.$C_{19}H_{20}O_2S_2$ (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-chlorosulfenyl 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 $CHC1_3$. The mixture was stirred for 5 min., the organic phase was separated and washed with water (3 times), and dried over $CaCl_2$. The solvent was evaporated *in vacuo* to give **8a** or **8b**.

3'-Chloro-3'-thiocyanatospiro(tetrahydropyran-4,2'-chroman)-4'-one (8a, $C_{14}H_{12}ClNO_3S$).

From **2a**, pink oil with yield 58%. R_f : 0.33 (chloroform/methanol); IR (neat): 1693 (C=O), 2165 cm^{-1} (CN); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.78 (m, 4H, C-$(CH_2)_2$), 3.69 (m, 4H, O-$(CH_2)_2$), 7.01- 7.95 (m, 4H, Ar-H). Anal.$C_{14}H_{12}ClNO_3S$ (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, $C_{14}H_{12}ClNO_2S_2$).

From **2b**, grey oil with yield 60%. R_f : 0.45 (chloroform/methanol); IR (neat): 1697 (C=O), 2198 cm^{-1} (CN); ^1H NMR ($CDCl_3$, 500 MHz): δ 2.02 (m, 4H, C-$(CH_2)_2$), 2.53 (m, 4H, O-$(CH_2)_2$), 7.11- 7.90 (m, 4H, Ar-H).Anal.$C_{14}H_{12}ClNO_2S_2$ (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) wasused 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. $NaHCO_3$ solution (4 × 100 mL). Removal of the deried (Na_2SO_4) solvent gave the crude dichlorochromanones (**9a** or **9b**).

3',3'-Dichlorospiro(tetrahydropyran-4,2'-chroman)-4'-one (9a,$C_{13}H_{12}Cl_2O_3$)

From **2a**, colorless oil with yield 33%. R_f : 0.49; IR (neat): 1701 (C=O), 1606 cm^{-1} (C=C); ^1H NMR ($CDCl_3$, 500 MHz): δ 1. 87-2.69 (m, 4H, C-$(CH_2)_2$), 3.41- 3.88 (m, 4H, O-$(CH_2)_2$), 7.01- 7.87 (m, 4H, Ar-H). Anal.$C_{13}H_{12}Cl_2O_3$ (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, $C_{13}H_{12}Cl_2O_2S$)

From **2a**, yellow oil with yield 30%. R_f : 0.53.IR (neat): 1699 (C=O), 1602 cm^{-1} (C=C); ^1H NMR ($CDCl_3$, 500 MHz): δ 2.01-2.47 (m, 4H, C-$(CH_2)_2$), 2.51- 2.85 (m, 4H, S-$(CH_2)_2$), 6.99- 7.98 (m, 4H, Ar-H). Anal.$C_{13}H_{12}Cl_2O_2S$ (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 morphline (10a, 10b)

Method A

A solution of secondary amine (morphline) (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 $CaCl_2$ and evaporated to give the residue, and chloroform was used as an eluent.

3'-Chloro-3'-morphlinosulfenylspiro (tetrahydropyran-4,2'-chroman)-4'-one(10a, $C_{17}H_{20}ClNO_4S$)

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 ($CDCl_3$, 500 MHz): δ 1.92-2.36 (m, 4H, C-$(CH_2)_2$), 2.89-3.23 (m, 4H, N-$(CH_2)_2$), 3.42- 4.30 (m, 8H, pyranoO-$(CH_2)_2$, morphilinoO-$(CH_2)_2$), 6.96- 7.92 (m, 4H, Ar-H). Anal.$C_{17}H_{20}ClNO_4S$ (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, $C_{17}H_{20}ClNO_3S_2$)

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 ($CDCl_3$, 500 MHz): δ 1.97-2.43 (m, 4H, C-$(CH_2)_2$), 2.52-2.88 (m, 4H, S-$(CH_2)_2$), 2.95-3.12 (m, 4H, N-$(CH_2)_2$), 3.54-3.83 (O-$(CH_2)_2$), 7.01- 7.98 (m, 4H, Ar-H). Anal.$C_{17}H_{20}ClNO_3S_2$ (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 morphlino 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, $C_{13}H_{13}ClO_3$)

From **10a**, brown oil with yield 48%. R_f : 0.24; IR (neat): 1694 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 500 MHz): δ 2.01-2.72 (m, 4H, C-$(CH_2)_2$), 3.01- 4.31 (m, 4H, O-$(CH_2)_2$), 5.38 (s, 1H, 3-CH) 6.91- 7.88 (m, 4H, Ar-H). Anal.$C_{13}H_{13}ClO_3$ (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, $C_{13}H_{13}ClO_2S$)

From **10b**, red oil with yield 58%. R_f : 0.51; IR (neat): 1698 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 500 MHz): δ 2.21-2.58 (m, 4H, C-$(CH_2)_2$), 2.61- 2.82 (m, 4H, S-$(CH_2)_2$), 5.29 (s, 1H, 3-CH), 6.81- 7.90 (m, 4H, Ar-H). Anal.$C_{13}H_{13}ClO_2S$ (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. 100µl samples (1mg/mL) were mixed with 900µl 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:

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

Where $\mathbf{A_1}$ was the absorbance of the DPPH solution without sample and $\mathbf{A_2}$ 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 (whatᵔ 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-chloroβ-oxosulfenyl chlorides with iodide ion in the presence of some homodienes or by thermolysis of oxadithiin derivatives in the presence of some homodienes. While α-chloroβ-oxosulfenyl chlorides undergo straight forward substitution with potassium cyanide to give the corresponding thiocyanate. Direct oxidation of α-chloroβ-oxosulfenyl 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.

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