Indian Journal of Chemistry
Vol. 62, March 2023, pp. 230-236
DOI: 10.56042/ijc.v62i3.72064

Chemical studies of chromanone-thiadiazole, pyridazine and thiosulfin hybrid

Mohamed I Hegab*, Hala E M Tolan, Farouk A Gad & Farouk M E Abdel-Megeid
Photochemistry Department, National Research Centre, Dokki, 12622 Giza, Egypt
*E-mail: pmihegab_2010@yahoo.com

Received 7 November 2021; accepted (revised) 16 December 2022

3-Chlorochromanon derivatives **4a,b** are reacted with hydrazine hydrate to afford 3-hydrazino-2-tetrahydro(pyran or thiopyran)chroman-4-ones **5a,b**. Then compound **5a,b** is reacted with carbon disulfide and acetylacetone to give 5'-thiolo -2-tetrahydro(pyrane or thiopyran)- spiro[chroman-3,2'- [1,3,4]-thiadiazole]-4-one **6a,b** and 3', 5'-dimethyl- 2-tetrahydro(pyran or thiopyran) spiro [chroman-3,2'- piprazine]-4-one **7a,b**, respectively. α-Chlorosulfenyl chlorides **2a,b** are treated with thioacetic acid to form α-chloroalkyl disulfides **8a,b**, the latter compounds **8a,b** were treated with morpholine to furnish a mixture of 1,3,4-oxadithiins **9a,b**, 1,3,4,5,6-oxatetrathiocins **10a,b**, 1,2,4-trithiolanes **11a,b** (*cis*- and *trans*-), 1,2,4,5-tetrathiins (*cis*- and *trans*-) **12a,b**. The formation of the new compounds are confirmed by spectral (IR, ^{1}H NMR, and MS) analysis.

Keywords: Chromanone, 1,3,4-thiadiazole, Piprazine, 1,3,4-Oxadithiin, 1,3,4,5,6-Oxatetrathiapin, 1,2,4-Trithiolane, 1,2,4,5-Tetrathiin

Chromone moiety is an important component of pharmacophores of a number of biologically active molecules of synthetic as well as natural origin[1]. Chromanones constitute an important class of naturally occurring substances[2-4] and draw the attention of many researchers due to their well-known properties as antiinflammatory[5], antiallergic[6], antibacterial[7], neuroprotective[8], anti HIV[9], antioxidant[10], antifungal[11] etc. They also display spasmolytic, cardiotonic, antiarrhythmic[12] and anticancer properties.[13] Other 4-chromanone derivatives have also been found useful in the treatment of bronchial asthma.[14] There are different methods have been developed for the synthesis of 4-chromanone derivatives.[15-17] Several studies have been reported on 1,3,4- thiadiazole and their derivatives because of their wide range of therapeutic activities. Many drugs containing thiadiazole derivatives are available in market such as acetazolamide, methazolamide, sulphamethazole, cefazoline[18-22].

Sugimura *et al*., reported a highly regioselective method for the preparation of pyridazine derivatives *via* the aza-Diels–Alder reaction of 1,2,3-triazines with 1-propynylamines under neutral conditions.[23] The pyridazine ring is thus a part of the structures of some therapeutic agents available on the market like cadralazine[24], minaprine[25], hydralazine[26], pipofezine[27], Azelastine (antiasthmatic, antiallergic, antihistaminic) [28], Lynparza (anticancer)[29], Emorfazone (Anti-inflammatory, analgesic)[30]. Moreover, a number of pesticides such as Diclomezine, Flufenpyr, Pyridaben are derivatives of pyridazin-3(2H)-ones[31]. Thiosulfines/dithiranes are the compounds attracting much objective attention[32,33]. The generation of thiosulfines/dithiranes from α-chloroalkanesulfenyl chloride *via* acetyl α-chloroalkyl disulfides is an appropriate and credible preparative method[34-36].

Experimental Details

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**,[22] **2a,b**,[22] **3a,b**,[37] and **4a,b**[37] were prepared as reported in the literature.

Reaction of 3-chlorochromanones4a,b with hydrazine hydrate

To a solution of 3-chlorochromamone **4a** or **4b** (0.01 mol) in ethanol (10 mL), hydrazine hydrate (20 mL) was added and refluxed for 4 h. The reaction mixture was concentrated. The precipitate was filtered off and crystallized from ethanol.

3-Hydrazinyl-2',3',5',6'-tetrahydrospiro[chromane-2,4'-pyran]-4-one (5a, $C_{13}H_{16}N_2O_3$)

From **4a**: Grey oil with yield 62%; Rf : 0.47; IR: ν 3268 cm^{-1} NH, 3167, 3150 cm^{-1} NH_2 1690 cm^{-1}(C=O); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.15-2.82 (m, 4H, C-$(CH_2)_2$), 3.12- 3.71 (m, 4H, O-$(CH_2)_2$, 3.39 (br s, 2H, NH_2), 4.45 (s, 1H, 3-CH), 6.12 (br s, 1H, NH), 6.96- 7.88 (m, 4H, Ar-H). MS: m/z (%) = 248 (M^+, 0.98), 216 (0.24), 57 (100).

3-hydrazinyl-2',3',5',6'-tetrahydrospiro[chromane-2,4'-thiopyran]-4-one (5b, $C_{13}H_{16}N_2O_2S$)

From **4b**: Pale pink oil with yield 68%; Rf : 0.30; IR: ν 3269 cm^{-1}NH, 3168, 3154 cm^{-1} NH_2, 1698 cm^{-1}(C=O); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.11-2.51 (m, 4H, C-$(CH_2)_2$), 2.61- 2.85 (m, 4H, S-$(CH_2)_2$), 3.41 (br s, 2H, NH_2), 4.65 (s, 1H, 3-CH), 6.14(br s, 1H, NH), 7.01-7.99 (m, 4H, Ar-H). MS: m/z (%) = 264 (M^+, 18.16), 167 (15.86), 70 (100).

Reaction of 3-hydrazzinochromanones 5a,b with carbon disulphide

Alcoholic potassium hydroxide solution (0.01 mol) in ethanol (7 mL)-water (3 mL) was added to a mixture of 3-hydrazinochromanone **5a** or **5b** (0.01 mol), ethanol (50 mL) and carbon disulfide (0.01 mol) with stirring. The reaction mixture was refluxed until the hydrogen sulfide ceased (~ 20 h). The reaction mixture was concentrated, cooled to room temperature (r.t.), poured into an ice-water mixture (100 mL) and acidified with concentrated hydrochloric acid. The precipitate was filtered off and crystallized from dioxane to give the product.

5''-mercapto-2,3,5,6-tetrahydro-5''H-dispiro[pyran-4,2'-chromane-3',2''-[1,3,4]thiadiazol]-4'-one (6a, $C_{14}H_{14}N_2O_3S_2$)

From **5a**: White powder with yield 81%, m.p = 221-223°C; Rf : 0.52; IR: ν 1697 cm^{-1} (C=O), 1624 cm^{-1}(N=N). 1H NMR ($CDCl_3$, 500 MHz): δ = 2.12-2.76 (m, 4H, C-$(CH_2)_2$), 2.97- 3.52 (m, 4H, O-$(CH_2)_2$), 3.60 (s, 1H, 5"-CH), 6.89- 7.78 (m, 4H, Ar-H), 14.01 (br s, 1H, SH). MS: m/z (%) = 322 (M^+, 15.88), 270 (23.96), 63 (100).

5''-mercapto-2,3,5,6-tetrahydro-5''H-dispiro[thiopy ran-4,2'-chromane-3',2''-[1,3,4]thiadiazol]-4'-one (6b, $C_{14}H_{14}N_2O_2S_3$)

From **5a**: Yellow powder with yield 88%, m.p = 240-242°C; Rf : 0.33. IR: ν 1699 cm^{-1}(C=O), 1630 cm-1(N=N). 1H NMR ($CDCl_3$, 500 MHz): δ = 2.01-2.42 (m, 4H, C-$(CH_2)_2$), 2.56- 2.87 (m, 4H, S-$(CH_2)_2$), 3.62 (s, 1H, 5"-CH), 7.12- 7.96 (m, 4H, Ar-H), 12.10 (br s, 1H, SH). MS: m/z (%) = 338(M^+, 15.71), 253 (16.57), 198 (18.01), 57 (100).

Reaction of 3-hydrazzinochromanones 5a,b with acetylacetone

Acetylacetone (0.01 mol) was added to a solution of hydrazinochromanone **5a** or **5b** (0.01mol) in dioxane (20 mL) and few drops of TEA. The reaction mixture was refluxed for 4 h, cooled to room temperature and the precipitate was filtered off and crystallized from the appropriate solvent to give the crude product.

3'-(3'',6''-dimethylpyridazin-1''(2H)-yl)-2,3,5,6-tetrahydrospiro-[chromane-2',4-pyran]-4'-one (7a, $C_{19}H_{22}N_2O_3$)

From **5a**: Dark red oil with yield 60%; Rf : 0.28; IR: ν 3168 cm^{-1} NH, 1689 cm^{-1}(C=O); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.85 (s, 1H, CH_3), 2.01 (s, 1H, CH_3), 2.14-2.61 (m, 4H, C-$(CH_2)_2$), 2.88-3.11 (m, 4H, O-$(CH_2)_2$), 4.60 (s, 1H, 3'-CH), 4.98 (m, 2H, 4"-CH + 5"-CH), 6.98- 7.89 (m, 4H, Ar-H), 9.18 (br s, 1H, NH). MS: m/z (%) = 326(M^+, 1.66), 266 (4.10), 215 (21.95), 97 (100).

3'-(3'',6''-dimethylpyridazin-1''(2H)-yl)-2,3,5,6-tetrahydrospiro-[chromane-2',4-thiapyran]-4'-one (7b, $C_{19}H_{22}N_2O_2S$)

From **5b**: Yellow oil with yield 65%. Rf : 0.40. IR: ν 3165 cm^{-1} NH, 1697 cm^{-1}(C=O). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.77 (s, 1H, CH_3), 1.95 (s, 1H, CH_3), 2.21-2.57 (m, 4H, C-$(CH_2)_2$), 2.61- 2.86 (m, 4H, S-$(CH_2)_2$), 4.62 (s, 1H, 3'-CH), 4.80 (m, 2H, 4"-CH + 5"-CH), 7.12- 7.97 (m, 4H, Ar-H), 9.20 (br s, 1H, NH). MS: m/z (%) = 342(M^+, 4.85), 272 (14.24), 218 (17.48), 109 (100).

Reaction of α-chlorosulfenyl chloride (2) with thioacetic acid

Thioacetic acid (0.8 ml, 0.01 mol) was added to a solution of 0.01 mol of α-chlorosulfenyl chloride **2a** or **2b**in 30 mL $CC1_4$ and the reaction mixture kept at 50-60 °C until completion of the reaction as judged by TLC (3h). The solvent was evaporated to give the corresponding product.

(RS)-3'-(Acetyldithio)-3'-chloro-2,3,5,6-tetrahydrospiro[chrom-an-2',4-pyran]-4'-one (8a, $C_{15}H_{15}ClO_4S_2$)

From **2a**: Grey oil with yield 62%; Rf : 0.22; IR: ν 1708 cm^{-1}(C=O), 1696 cm^{-1}(CO-CH_3); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.24-2.27 (m, 4H, C-$(CH_2)_2$), 2.48 (s, 3H, CH_3), 3.42- 3.64 (m, 4H, O-$(CH_2)_2$), 7.12-7.97 (m, 4H, Ar-H). MS: m/z (%) = 358 (M^+,

32.98), 326 (9.84). 291 (29.26), 248 (39.36), 220 (30.32), 172 (35.11), 78 (100).

(RS)-3'-(Acetyldithio)-3'-chloro-2,3,5,6-tetrahydrospiro[chroman-2',4-thiapyran]-4'-one(8b, $C_{15}H_{15}ClO_3S_3$)

From 2b: Yellow oil with yield 68%; Rf : 0.38; IR: ν 1710 cm^{-1}(C=O), 1698 cm^{-1}(CO-CH3); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.81-2.26 (m, 4H, C-$(CH_2)_2$), 2.40 (s, 3H, CH_3), 2.66- 2.82 (m, 4H, S-$(CH_2)_2$), 6.97 - 7.67 (m, 4H, Ar-H). MS: m/z (%) = 374 (M^+, 61.80), 376 (70.97), 69 (100).

Reaction of disulfides 8a,b with morpholine

Disulfide **8a** or **8b** (7 mmol) was dissolved in 50 mL ether and treated, with stirring, with 6.0 ml (60 mmol) morpholine, dissolved in 30 ml ether. The rate of the addition is adjusted so as to avoid any appreciable rise of the temperature. The reaction mixture was then extracted three times with water, dried over anhydrous $CaCl_2$, and evaporated *in vacuo*. The oily residue was separated by column chromatography (silica gel, Merck 90, particle size 0.063-0.200 mm, ether-hexane 1:5 as an eluent) to give **9a,b**, **10a,b**, **11a,b** and **12a,b**.

2,2''',3,3''',5,5''',6,6'''-octahydrotrispiro[pyran-4,2'-chromane-3',2''-[1,3,4]oxadithiino[5,6-c]chromene-5'',4'''-pyran]-4'-one (9a, $C_{26}H_{24}O_6S_3$)

From **8a**: Yellow oil, yield 30% IR: ν 1698 cm^{-1} (C=O), 1607 cm^{-1}(C=C); ^{1}H NMR($CDCl_3$, 500 MHz): δ = 1.84 -2.16 (m, 8H, 2C-$(CH_2)_2$), 3.52–4.15 (m, 8H, 2O-$(CH_2)_2$), 6.91–7.98 (m, 8H, Ar-H). MS: m/z (%)= 496 [M^+, 19.12], 406 (15.93), 254 (5.46), 69 (100).[37].

2,2''',3,3''',5,5''',6,6'''-octahydrotrispiro[pyran-4,2'-chromane-3',2''-[1,3,4,5,6]oxatetrathiocino[7,8-c]chromene-7'',4'''-pyran]-4'-one (10a, $C_{26}H_{24}O_6S_4$)

From **8a**: Dark yellow oil with yield 27%; Rf : 0.53; IR: ν 1694 cm^{-1}(C=O), 1601 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ =1.78-2.06 (m, 8H, 2 C-$(CH_2)_2$), 3.01- 3.51 (m, 8H, 2 O-$(CH_2)_2$), 6.88- 7.97 (m, 8H, Ar-H). MS: m/z (%) = 560 (M^+, 0.05), 496 (25.13), 432 (15.25), 216 (100).

cis- and trans-(3'R,5''S)(3'S,5''R)-2,2'''', 3,3'''',5,5'''',6,6''''-octahydrotetraspiro[pyran-4,2'-chromane-3',3''-[1,2,4]trithiolane-5'',3'''-chroane-2''',4''''-pyran]-4',4'''-dione (11a, $C_{26}H_{24}O_6S_3$)

From **8a**: colorless oil with yield 37%; Rf : 0.53; IR: ν 1694, 1690 cm^{-1}(2 C=O), 1601 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ =1.76-2.03 (m, 8H, 2 C-$(CH_2)_2$), 3.01- 3.48 (m, 8H, 2 O-$(CH_2)_2$), 6.86- 7.955 (m, 8H, Ar-H). MS: m/z (%) = 528 (M^+, 3.05), 464 (15.28), 432 (10.19), 216 (100).

cis- and trans-2,2'''',3,3'''',5,5'''',6,6''''-octahydrotetraspiro[pyran-4,2'-chromane-3',3''-[1,2,4,5]tetrathiane-6'', 3'''-chromane-2''',4''''-pyran]-4',4'''-dione (12a, $C_{26}H_{24}O_4S_4$)

From **8a**: Dark red oil with yield 20%; Rf : 0.39; IR: ν 1697, 1693 cm^{-1}(C=O), 1611 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.89-2.41 (m, 8H, 2 C-$(CH_2)_2$), 2.61-2.83 (m, 8H, 2 S-$(CH_2)_2$), 7.12- 7.99 (m, 8H, Ar-H). MS: m/z (%) = 560 (M^+, 5.63)496 (35.13), 432 (25.25), 216 (100).

2,2''',3,3''',5,5''',6,6'''-octahydrotrispiro[thiapyran-4,2'-chromane-3',2''-[1,3,4]oxadithiino[5,6-c]chromne-5'',4'''-thiapyran]-4'-one (9b, $C_{26}H_{24}O_6S_3$)

From **8b**: Dark pink oil, yield 28% IR: ν 1699 cm^{-1} (C=O), 1610 cm^{-1}(C=C); ^{1}H NMR: δ = 1.55–2.82 (m, 16H,2C-$(CH_2)_2$+ 2S-$(CH_2)_2$), 7.01–7.98 (m, 8H, Ar-H); MS: m/z (%), 52 [M^+, 0.04], 464 (0.07),267 (0.67), 147 (100).[37]].

2,2''',3,3''',5,5''',6,6'''-octahydrotrispiro[thiapyran-4,2'-chromane-3',2''-[1,3,4,5,6]oxatetrathiocino[7,8-c]chromene-7'',4'''-thiapyran]-4'-one (10b, $C_{26}H_{24}O_4S_6$)

From **8b**: Dark yellow oil with yield 28%; Rf : 0.53; IR: ν 1694 cm^{-1}(C=O), 1601 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ =1.78-2.06 (m, 8H, 2 C-$(CH_2)_2$), 3.01- 3.51 (m, 8H, 2 O-$(CH_2)_2$), 6.88- 7.97 (m, 8H, Ar-H). MS: m/z (%) = 592 (M^+, 1.05), 528 (25.13), 464 (15.25), 248 (100).

cis- and trans- (3'R,5''S)(3'S,5''R)-2,2'''', 3,3'''',5,5'''',6,6''''-octahydrotetraspiro[thiapyran-4,2'-chromane-3',3''-[1,2,4] trithiolane-5'',3'''-chromane-2''',4''''-thiapyran]-4',4'''-dione (11b, $C_{26}H_{24}O_4S_5$)

From **8b**: colorless oil with yield 38%; Rf : 0.53; IR: ν 1694, 1690 cm^{-1}(2 C=O), 1601 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ =1.76-2.03 (m, 8H, 2 C-$(CH_2)_2$), 3.01- 3.48 (m, 8H, 2 O-$(CH_2)_2$), 6.86- 7.955 (m, 8H, Ar-H). MS: m/z (%) = 560 (M^+, 3.05), 496 (15.28), 464 (10.19), 248 (100).

cis- and trans-2,2'''',3,3'''',5,5'''',6,6''''-octahydrotetraspiro[thiapyran-4,2'-chromane-3',3''-[1,2,4,5] tetrathiane-6'',3'''-chromane-2''',4''''-thiapyran]-4',4'''-dione (12b, $C_{26}H_{24}O_2S_6$)

From **8b**: Dark red oil with yield 20%; Rf : 0.39; IR: ν 1697, 1693 cm^{-1}(C=O), 1611 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.89-2.41 (m, 8H, 2 C-$(CH_2)_2$), 2.61-2.83 (m, 8H, 2 S-$(CH_2)_2$), 7.12- 7.99 (m, 8H, Ar-H). MS: m/z (%) = 592 (M^+, 5.63),528 (35.13), 464 (25.25), 248 (100).

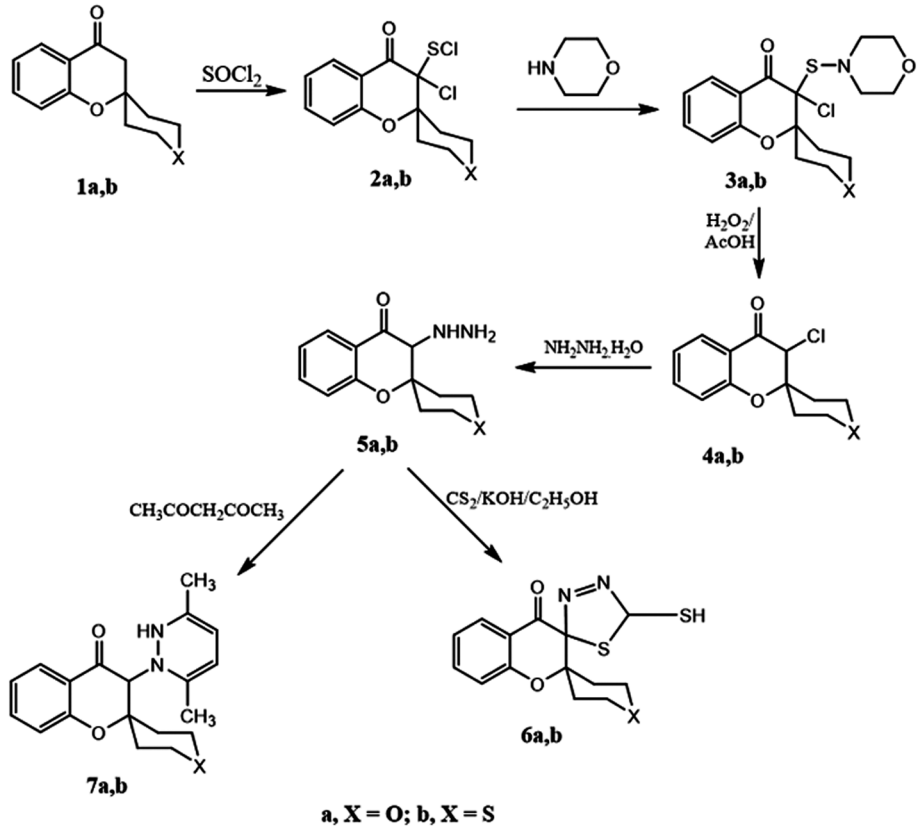
Results and Discussion

The chloro derivatives **4a,b** were reacted with hydrazine hydrate and gave the corresponding 3-

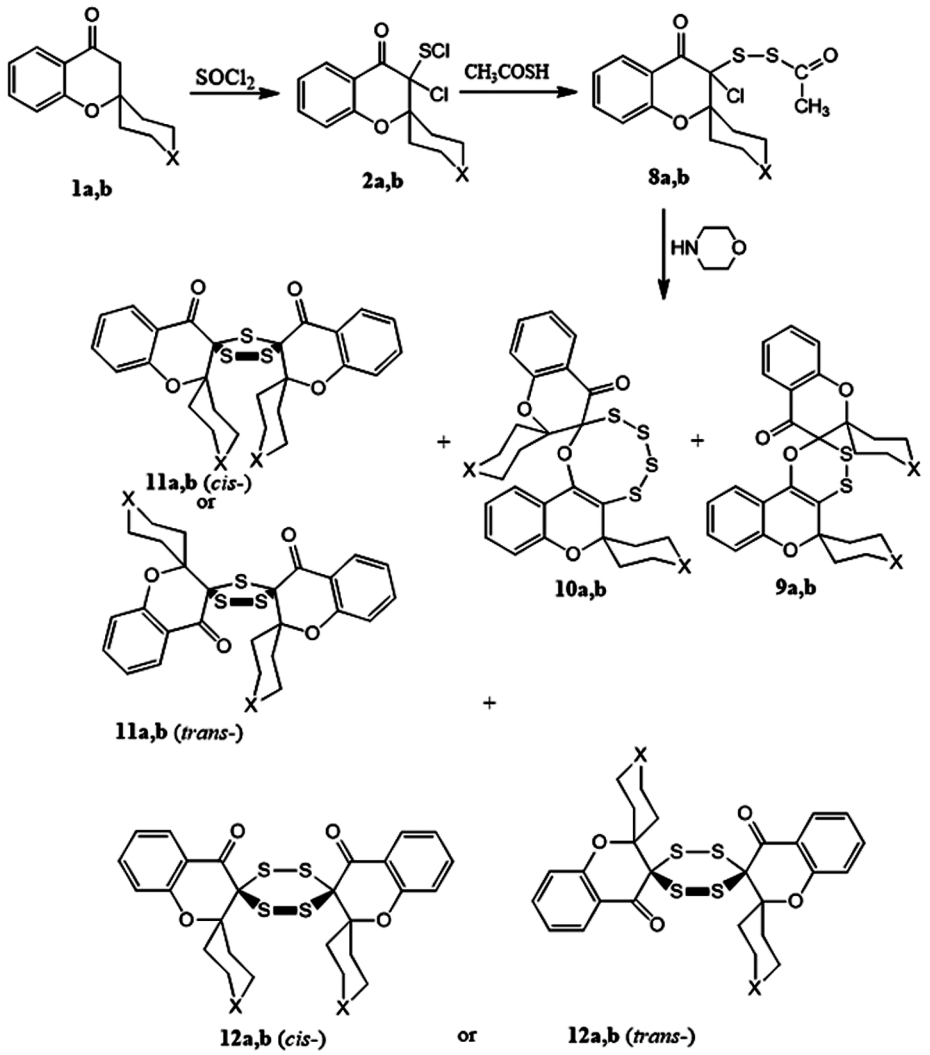
hydrazino-2-tetrahydro(pyrane orthiopyrane) chroman -4-ones **5a,b** according to Scheme 1. The IR spectra of these formed compounds showed a characteristic absorption bands at *v*3265 and (3167-3150) cm^{-1}, at *v* 3269 and (3168-3154) cm^{-1}, respectively corresponding to the amino groups NH & NH_2, respectively. The ^1H NMR spectra showed the NH group as singlet at δ6.12 ppm of compound **5a** and at δ6.14 ppm of compound **5b** in addition to the other protons of these compounds. 5"-mercapto-2,3,5,6-tetrahydro-5"H-dispiro[pyran/thiapyran-4,2'-chromane-3',2"-[1,3,4] thiadiazol]-4'-one **6a,b** were furnished from the reaction of 3-hydrazino-2-tetrahydro(pyrane or thiapyran) chroman-4-ones **5a,b** with carbon disulphide in ethanolic potassium hydroxide (Scheme 1).The desired products were characterized by physical and spectral data. Thus, IR spectra of compounds **6a,b** showed a characteristic absorption band at *v* 1624 cm^{-1}, at *v* 1630 cm^{-1} respectively which corresponding to the amide group (N=N). The ^1H NMR spectra of compounds **6a,b** showed the singlet signal at δ 14.01 ppm and at δ 12.10 ppm, respectively corresponding to the SH group in addition to the protons of these compounds.

3-Hydrazino-2-tetrahydro(pyrane orthiapyran)-chroman-4-ones **5a,b** also, reacted with acetylacetone to yield 3'-(3",6"-dimethylpyridazin-1"(2H)-yl)-2,3,5,6-tetrahydrospiro[chromane-2',4-pyran/thiapyran]-4'-one**7a,b** (Scheme 1), which confirmed *via* IR, ^1H NMR, and MS spectra. Whereas, IR of compound **7a** showed a characteristic absorption band at *v* 3168 cm^{-1}(NH), 1689 cm^{-1}(C=O). and of compound **7b** showed at *v* 3165 cm^{-1}(NH),1697 cm^{-1}(C=O). The ^1H-NMR spectrum of compound **7a** showed the singlet signals, at δ 1.85 and at δ = 2.01 ppm for the 2 CH_3 groups, 4.60 (s, 1H, 3'-CH), 4.98 (m, 2H, 4"-CH + 5"-CH), 9.18 ppm (br s, 1H, NH). in addition to the protons of the compound. While the ^1H-NMR spectrum of compound **7b** showed the singlet signals, at δ1.77, 1.95 (s, 2H, 2 CH_3), 4.62 (s, 1H, 3'-CH), 4.80 (m, 2H, 4"-CH + 5"-CH), 9.20 ppm (br s, 1H, NH) besides the other protons of the compound.

The compounds α-chlorosulfenyl chloride **2a,b** were treated with thioacetic acid in CCl_4 at 50 °C to give α-chloroalkyl disulfides **8a,b** according to Scheme 2, and the formed compounds were confirmed by spectral data (IR, ^1H NMR, MS). Where, IR spectrum of compound **8a** showed a



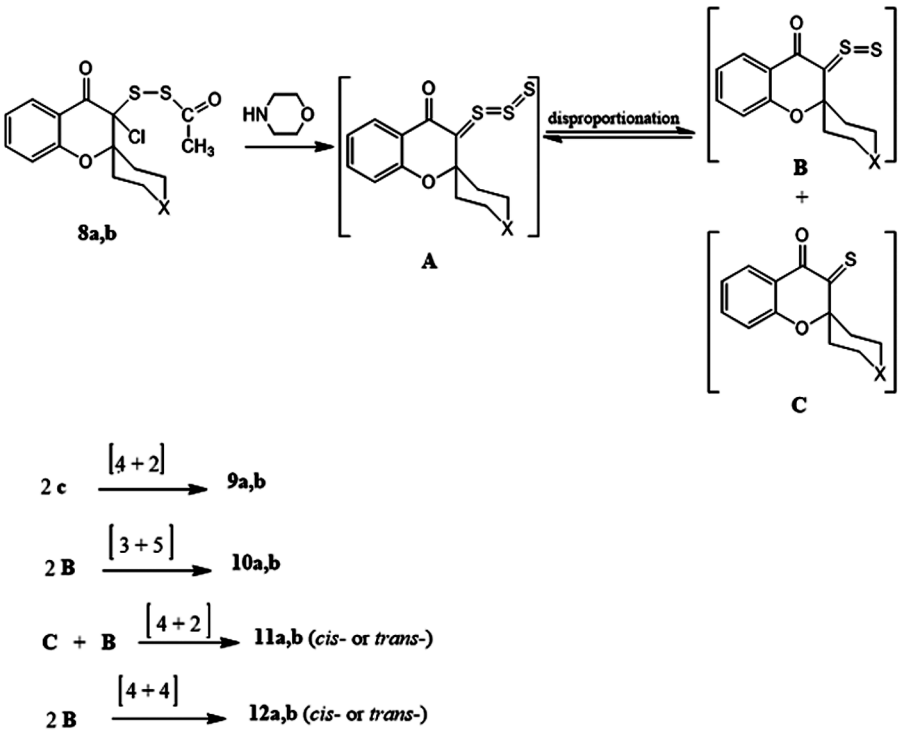
Scheme 1 — Synthesis of compounds **5-7**



Scheme 2 — Synthesis of compounds **8**-**12**

characteristic absorption band at ν1708 cm^{-1}(C=O), 1696 cm^{-1}(CO-CH_3) and of compound **8b** showed at ν1710 cm^{-1}(C=O), 1698 cm^{-1}(CO-CH3). The ^{1}H-NMR spectra showed a characteristic singlet signal at δ 2.48 and δ 2.40 ppm corresponding to the CO-CH_3 group of compound **8a** and **8b,** respectively.

However, α-chloroalkyl disulfides **8a,b** were treated with morpholin in ether at 50°C, according to reported procedure,[35,36] to afford four components: 2,2''',3,3''',5,5''',6,6'''-octahydrotrispiro[pyran-4,2'-chromane-3',2''-[1,3,4]oxadithiino[5,6-c]chromene-5'',4'''-pyran]-4'-one (**9a,b**) (as known compounds)[22], 2,2''',3,3''',5,5''',6,6'''-octahydrotrispiro[pyran-4,2'-chromane-3',2''-[1,3,4,5,6]oxatetrathiocino[7,8-c]-chromene-7'',4'''-pyran]-4'-one (**10a,b**), cis- and trans-(3'R,5''S)(3'S,5''R)-2,2''',3,3''',5,5''',6,6'''-octahydr otetraspiro[pyran-4,2'-chromane-3',3''-[1,2,4]trith iola ne-5'',3'''-chromane-2''',4'''-pyran]-4',4'''-dione (**11a,b**), and cis- and trans-2,2''',3,3''',5,5''',6,6'''-octahydrotetraspiro[pyran-4,2'-chromane-3',3''-[1,2,4,5]tetrathiane-6'',3'''-chromane-2''',4'''-pyran]-4',4'''-dione (**12a,b**) which are separated by column chromatography (silica gel, Merck 90, particle size 0.063-0.200 mm, ether-hexane 1:5 as an eluent) (Scheme 2). IR spectrum of compound **10a** showed a characteristic absorption band at ν1694 cm^{-1}(C=O) and of compound **10b** showed at ν1694 cm^{-1}(C=O). The ^{1}H-NMR spectra showed the signals corresponding to the protons of the compounds**10a** and **10b**, whereas the MS spectra of compounds **10a,b** shows the molecular ion peak at *m/z* 560, 592, respectively.IR spectra of compounds **11a,b** showed a characteristic absorption



Scheme 3 — Synthesis of compounds **9-12**

band at *v*1694, 1690 cm^{-1} (2 C=O). The ^{1}H-NMR spectra showed the signals corresponding to the protons of the compounds **11a** and **11b**, whereas the MS spectra of compounds **11a,b** shows the molecular ion peak at *m/z* 528, 560, respectively. However the compounds **12a,b** were confirmed by spectral data (IR, ^{1}H NMR, MS). Where, IR spectra showed a characteristic absorption band at *v*1697, 1693 cm^{-1} (2 C=O), The ^{1}H NMR spectra showed the signals corresponding to the protons of the compounds **12a** and **12b**, whereas the MS spectra of compounds **12a,b** shows the molecular ion peak at *m/z*560, 592, respectively. The formation of the four compounds **9-12** could be explained via Scheme 3.

Conclusion

3-Chlorochromanon derivatives were treated with hydrazine hydrate afforded 3-hydrazino-2-tetrahydro(pyran or thiopyran)chroman-4-oneswhich reacted with carbon disulfide and with acetylacetone to give 5'-thiolo - 2-tetrahydro(pyrane or thiopyran)-spiro[chroman-3,2'- [1,3,4]-thiadiazole]-4-one and 3', 5'-dimethyl- 2-tetrahydro(pyran or thiopyran) spiro [chroman-3,2'-piprazine]-4-one,respectively. α-Chlorosulfenyl chlorides were treated with thioacetic acid to form α-chloroalkyl disulfides, the latter compounds were reacted with morpholine to yield a mixture of 1,3,4-oxadithiins, 1,3,4,5,6-oxatetrathiocins, 1,2,4-trithiolanes (*cis*- and *trans*-), 1,2,4,5-tetrathiins (*cis*- and *trans*-), which are separated via column chromatography.

References

1 Siddiqui Z N & Farooq F, *J Chem Sci*, 124 (2012) 1097.
2 Ponce M A, Scervino J M, Erra-Balsells R, Ocampo J A & Godeas A M, *Phytochemistry*, 65 (2004) 3131.
3 Cottiglia F, Dhanapal B, Sticher O & Heilmann J, *J Nat Prod*, 67 (2004) 537.
4 Mutanyatta J, Matapa B, Shushu D D & Abegaz B M, *Phytochemistry*, 62 (2003) 797.
5 Hutter J A, Salman M, Stavinoha W B, Satsangi N, Williams R F, Streeper R T & Weintranb S T, *J Nat Prod*, 59 (1996) 541.
6 Fitzmaerice C & Wragg A H, *Chem Abstr*, 65 (1966) 3444.
7 Deng Y, Lee J P, Ramamonjy M T, Snyder J K, Etages S A, Kanada D, Snyder M P & Turner C J, *J Nat Prod*, 63 (2000) 1082.
8 Larget R, Lockhart B, Renard P & Largeron M, *Biorg Med Chem Lett*, 10 (2000) 835.
9 Groweiss A, Cardellins J H & Boyd M R, *J Nat Prod*, 63 (2000) 1537.
10 Kuroda M, Uchida S, Watanabe K & Mimaki Y, *Phytochemistry*, 70 (2009) 288.
11 Prakash O, Kumar R & Prakash V, *Eur J Med Chem*, 43 (2008) 435.
12 Gabor M & Kallay F, *The Pharmacology of benzopyrone derivatives and related compounds* (Akadémiai Kiadó, Budapest) 1986, p 91.

13 Loa J, Chow P & Zhang K, *Cancer Chem Pharmacol*, 63 (2009) 1007.
14 Ellis G P, *Chemistry of Heterocyclic Compounds: A Series of Monographs*, (John Wiley & Sons, U S A), 1977, p 345.
15 Stankovicova H, Lacova M, Gaplovsky A, Chavanova J & Paranayova N, *Tetrahedron*, 57 (2001) 3455.
16 Kułaczkowska A D & Mazur L, *J Mol Struc,* 985 (2011) 233.
17 Kabbe H J, *Synthesis*, (1978) 886. (https://doi.org/10.1055/s-1978-24924).
18 ShamroukhA H, Hegab M I, *Egypt J Chem*, 63 (2020) 4387.
19 Hegab M I, Girgis A S & Ahmed-Farag I S, *J Heterocyclic Chem*, 43 (2006) 1237.
20 Hafez H N, Hegab M I, Ahmed-Farag I S & El-Gazzar A B A, *Bioorg Med Chem*, 18 (2008) 4538.
21 Hegab M I & El-Shehry M F, *Z Naturforsch*, 69b (2014) 461.
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.
23 Kodama T, Sasaki I & Sugimura H, *J Org Chem*, 86 (2021) 8926.
24 Salvadeo A, Villa G, Segagni S, Piazza V, Picardi L, Romano M & Parini J C, *Arzneim. Forsch*, 35 (1985) 623.
25 Fung M, Thornton A, Mybeck K, Wu J H H Hornbuckle K & Muniz E, *Drug Inf J*, 35 (2001) 293.
26 Imad S, Nisar S, Maqsood Z T, *J Saudi Chem Soc*, 14 (2010) 241.
27 Asif M, *Sop Trans Org Chem*, 1 (2014) 1.
28 McTavish D & Sorkin E M, *Drugs*, 38 (1989) 778.
29 Menear K A, Adcock C, Boulter R, Cockcroft X-L, Copsey L, Cranston A, Dillon K J, Drzewiecki J, Garman S, Gomez S, Javaid H, Kerrigan F, Knights C, Lau A, Loh Jr V M, Matthew I T W, Moore S, O'Connor M J, Smith G C M & Martin N M B, *J Med Chem*, 51 (2008) 6581.
30 Takaya M, Sato M, Terashima K, Tanizawa H & Maki Y, *J Med Chem*, 22 (1979) 53.
31 Lewis K A, Tzilivakis J, Warner D & Green A, *Human and Ecological Risk Assessment: An International Journal*, **22**(4), (2016) 1050 (DOI: 10.1080/10807039.2015.1133242).
32 Huisgen R & Rapp J, *Tetrahedron*, 3 (1997) 939.
33 Fabian J & Senning A, *Sulfur Rep*, 21 (1998) 1.
34 Senning A, Hansen H C, Abdel-Megeed M F & Mazurkiewicz W, *Tetrahedron*, 42 (1986) 793.
35 El-Essawy F A G, Yassin S M, El-SakkaI A, Khattab A F, Støfte I, Møller J & Senning A, *J Org Chem*, 63 (1998) 9840.
36 Hegab M I, Abdel-Megeid F M E, Gad F A, Shiba S A, Møller J & Senning A, *Acta Chem Scand*, 53 (1999) 133.
37 Hegab M I, Tolan H E M, Morsy E M H, Abdelsalam I S, Saleh A M, Gad F A & Abdel-Megeid F M E, *Indian J Chem,* 60B (2021) 1502.