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SYNTHESIS OF SOME THIADIAZOLES, SELENADIAZOLES AND SPIROHETEROCYCLIC COMPOUNDS FROM THEIR 2,2-DIMETHYL-BENZOPYRAN PRECURSORS

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New series of 4,4-dimethylbenzopyrano[4,3-d]-1,2,3-selenadiazoles and 4,4-dimethylbenzopyrano-[4,3-d]-1,2,3-thiadiazoles have been synthesized from semicarbazones of chroman-4-one precursors. Some 4-acetyl-2'-acetylamino-2,2-dimethylspiro[chroman-4,5'-Δ^2-1,3,4-thiadiazolines] have been synthesized by cyclization of thiosemicarbazones of 2,2-dimethylchroman-4-ones using acetic anhydride. The selected compounds were tested for Phosphotyrosine phosphatase 1B inhibition.

Keywords: chromanone, *Phosphotyrosine phosphatase 1B*, selenadiazole, spiroheterocyclic compounds, thiadiazole.

Substituted chroman-4-ones, a class of oxygen heterocycles, are common among natural products and are extensively used as synthetic intermediates [1]. They have been used to prepare various fused heterocyclic ring systems and tested for a wide range of pharmacological activity. Some chroman-4-ones with medical use are khellin, a coronary vasodilator, chroman-4-one-2-carboxylic acids, spasmolytic agents, and disodium chromoglycate, an antiallergenic drug [2, 3].

On the other hand, it is well known that a number of heterocyclic compounds containing nitrogen and sulfur exhibit a wide variety of biological activities. However, reports about selenium-containing heterocycles are relatively scarce, although some of them are used as chemotherapeutic agents; also some 1,3,4- and 1,2,3-selena/thiadiazoles were found to possess significant antibacterial and antiviral activities [4-8].

The fused ring systems of chroman-4-ones are found to possess enhanced biological activities and the synthesis of selenadiazoles and thiadiazoles fused to carbocyclic/heterocyclic rings is of growing interest [9-17].

Aldehyde thiosemicarbazones on oxidation with $NaOH/K_3[Fe(CN)_6]$ give 1,3,4-thiadiazolines [18]. The synthesis of a spiro-fused Δ^2-1,3,4-thiadiazoline from 5α-cholestan-3-one thiosemicarbazone has been reported [19]. A relatively recent method of conversion of unsubstituted aldehyde thiosemicarbazones into 1,3,4-thiadiazolines involves acetylation of thiosemicarbazones [20, 21]. Spiro-1,3,4-thiadiazolines were shown to be potent medicinally active compounds [22, 23]. Taking into account the activities associated with chromone and the spirothiadiazoline nucleus and as a continuation of our work on the chromone nucleus [24-26], it was thought worthwhile to synthesize 1,2,3-selena/thiadiazoles fused to chroman-4-ones and some Δ^2-1,3,4-thiadiazoline derivatives spiro-fused with chroman-4-ones.

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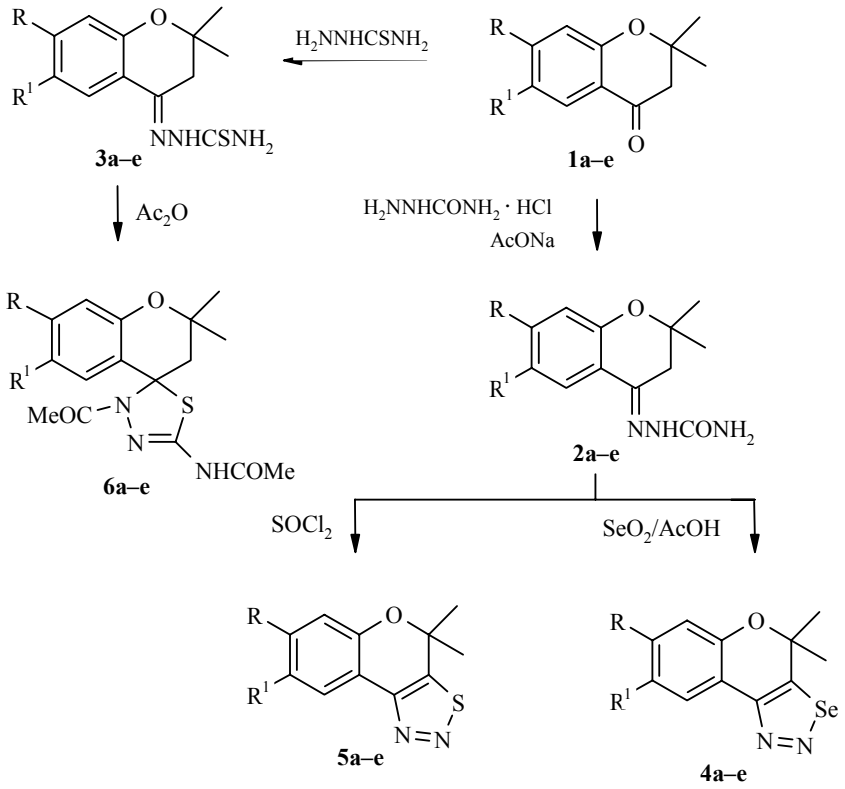
In the present work a number of 2,2-dimethylchroman-4-ones **1** were converted into their semicarbazones **2** and thiosemicarbazones **3**. On treatment with SeO_2/AcOH the semicarbazones gave the corresponding 4,4-dimethylbenzopyrano[4,3-*d*]-1,2,3-selenadiazoles **4,** whereas the same semicarbazones when treated with $SOCl_2$ gave 4,4-dimethylbenzopyrano[4,3-*d*]-1,2,3-thiadiazoles **5**. Thiosemicarbazones **3** when heated with acetic anhydride gave (chroman-4-yl)-5-spiro-4'-acetyl-2'-acetylamino-2,2-dimethylspirochroman-4,5'-Δ^2-1,3,4-thiadiazolines **6**. The structures of the products were confirmed by their spectral data and elemental analysis.



1-6 a-d R = H, **e** R = Me; **a** R^1 = H, **b** R^1 = F, **c** R^1 = Cl, **d** R^1 = Br, **e** R^1 = Cl

The selected compounds from **4-6** were tested for *phosphotyrosine phosphatase 1B* inhibitory activity, which corresponds to antidiabetic (antiobesity) activities. From the results shown in Table 1 it can be concluded that the title compounds show no *phosphotyrosine phosphatase 1B* inhibition.

TABLE 1. Phospotyrosine Phosphatase 1B Inhibition (*in vitro* Assay)*

Compounds	Inhibition, %	Compounds	Inhibition, %
4b	0	**5c**	0
5a	5.7	**5e**	0
5b	0	**6a**	0

* Concentration 30 μM.

TABLE 2. Characterization Data of Various Compounds Synthesized

Compounds	Empirical-formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_{12}H_{15}N_3O_2$	61.88 / 61.79	6.46 / 6.48	18.05 / 18.01	198	66
2b	$C_{12}H_{14}FN_3O_2$	57.43 / 57.36	5.64 / 5.62	16.69 / 16.72	192	71
2c	$C_{12}H_{14}ClN_3O_2$	53.77 / 53.84	5.26 / 5.27	15.65 / 15.70	205	69
2d	$C_{12}H_{14}BrN_3O_2$	46.26 / 46.17	4.53 / 4.52	13.49 / 13.46	240	61
2e	$C_{13}H_{16}ClN_3O_2$	55.23 / 55.42	5.71 / 5.72	14.87 / 14.91	255	58
3a	$C_{12}H_{15}N_3OS$	57.68 / 57.81	6.04 / 6.06	16.79 / 16.85	210	61
3b	$C_{12}H_{14}FN_3OS$	53.98 / 53.92	5.29 / 5.28	15.66 / 16.72	246	53
3c	$C_{12}H_{14}ClN_3OS$	50.63 / 50.79	4.96 / 4.97	14.85 / 14.81	230	59
3d	$C_{12}H_{14}BrN_3OS$	43.97 / 43.91	4.29 / 4.30	12.77 / 12.80	255	58
3e	$C_{13}H_{16}ClN_3OS$	52.46 / 52.43	5.42 / 5.42	14.00 / 14.11	268	55
4a	$C_{11}H_{10}N_2OSe$	49.68 / 49.82	3.79 / 3.80	10.52 / 10.56	140	49
4b	$C_{11}H_9FN_2OSe$	46.79 / 46.66	3.21 / 3.20	9.90 / 9.89	180	61
4c	$C_{11}H_9ClN_2OSe$	44.21 / 44.10	3.04 / 3.03	9.23 / 9.35	215	60
4d	$C_{11}H_9BrN_2OSe$	38.28 / 38.40	2.65 / 2.64	8.15 / 8.14	220	63
4e	$C_{12}H_{11}ClN_2OSe$	45.81 / 45.95	3.55 / 3.54	8.95 / 8.93	241	65
5a	$C_{11}H_{10}N_2OS$	60.36 / 60.53	4.60 / 4.62	12.86 / 12.83	182	51
5b	$C_{11}H_9FN_2OS$	55.78 / 55.92	3.85 / 3.84	11.82 / 11.86	212	56
5c	$C_{11}H_9ClN_2OS$	52.39 / 52.28	3.57 / 3.59	11.05 / 11.08	190	59
5d	$C_{11}H_9BrN_2OS$	44.29 / 44.46	3.04 / 3.05	9.45 / 9.43	196	58
5e	$C_{12}H_{11}ClN_2OS$	54.19 / 54.03	4.17 / 4.16	10.53 / 10.50	207	60
6a	$C_{16}H_{19}N_3O_3S$	57.47 / 57.64	5.72 / 5.74	12.57 / 12.60	236	48
6b	$C_{16}H_{18}FN_3O_3S$	54.52 / 54.69	5.18 / 5.16	11.99 / 11.96	216	52
6c	$C_{16}H_{18}ClN_3O_3S$	52.43 / 52.24	4.93 / 4.93	11.39 / 11.42	196	57
6d	$C_{16}H_{18}BrN_3O_3S$	46.53 / 46.61	4.41 / 4.40	10.19 / 10.19	224	61
6e	$C_{17}H_{20}ClN_3O_3S$	53.57 / 53.47	5.26 / 5.28	10.97 / 11.00	199	57

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in nujol on a Perkin-Elmer 1420 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian (300 MHz) spectrometer in $CDCl_3$ or DMSO as a solvent with TMS as an internal standard. Mass spectra were recorded on a Kratos MS-80 mass spectrometer.

2,2-Dimethylchroman-4-one Semicarbazone (2a). Semicarbazide hydrochloride (1.33 g, 0.012 mol) and sodium acetate (12.3 g, 0.15 mol) were taken in a conical flask and dissolved in 35 ml of distilled water. To liberate the free base, the content was warmed on a water bath until a clear solution obtained. To this reaction mixture 2,2-dimethylchroman-4-one (1.76 g, 0.01 mol) in ethanol was added dropwise and the content was warmed on a water bath for 30 to 40 min. A white product separated on cooling the content, which was filtered off, dried, and crystallized from ethanol to give **2a.** IR spectrum, ν, cm^{-1}**:** 3494, 3380, 3177, 3035, 1682, 1618, 1578. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.28 (6H, s); 2.72 (2H, s); 6.56 (2H, s, NH_2); 6.78 (1H, d, *J* = 8.3); 6.87 (1H, m); 7.20 (1H, m); 8.09 (1H, d, *J* = 8.7); 9.36 (1H, s, NH).

Compounds 2b-e were prepared similarly (Table 2).

2,2-Dimethylchroman-4-one thiosemicarbazone (3a). To a solution of 2,2-dimethyl- chroman-4-one (1.76 g, 0.01 mol) in ethanol (25 ml) a few drops of conc. HCl and an ethanolic solution of thiosemicarbazide (0.91 g, 0.01 mol) were added dropwise with constant stirring. The reaction mixture was refluxed for 3 h on a water bath. After cooling, the solid product was filtered off and recrystallized from ethanol to give **3a**. IR spectrum, ν, cm^{-1}: 3429, 3282, 3160, 1630, 1594, 1494, 1215. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.29 (6H, s); 2.88 (2H, s); 6.81 (1H, d, *J* = 8.3); 6.87 (1H, m); 7.24 (1H, m); 8.05 (1H, s, NH); 8.22 (1H, d, *J* = 8.7); 8.28 (1H, s, NH); 10.27 (1H, s, NH).

Compounds 3b-e were prepared similarly (Table 2).

8-Fluoro-4,4-dimethylbenzopyrano[4,3-*d*]-1,2,3-selenadiazole (4b). Compound **2b** (1.25 g, 0.05 mol) was dissolved in glacial acetic acid (15 ml) and warmed to 60°C with stirring. To this selenium dioxide (0.55 g, 0.05 mol) was added portionwise during a period of 30 min and the stirring was continued at 60°C for 2-3 h till the evolution of gas ceased. After completion of the reaction, it was filtered to remove the deposited selenium. The filtrate was poured over crushed ice and the solid obtained was filtered, and washed thoroughly with cold water and sodium carbonate and again with water. It was then purified by column chromatography to give pure **4b.** IR spectrum, ν, cm^{-1}: 3045, 1618, 1514, 1487, 1143, 682. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.77 (6H, s); 6.91 to 7.01 (2H, m); 7.81 (1H, m). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm**:** 30.54, 77.03, 80.49, 111.45, 116.72, 118.53, 147.85, 152.64, 156.22, 159.67. Mass spectrum, *m/z*: 284.

Compounds 4a, c-e were prepared similarly (Table 2).

4,4-Dimethylbenzopyrano[4,3-*d*]-1,2,3-thiadiazole (5a). The compound **2a** (2.33 g, 10 mmol) was added portionwise to an excess of freshly distilled thionyl chloride (3 ml) at 0°C. The reaction mixture was then allowed to attain room temperature. After 1 h methylene chloride (15 ml) was added and the resulting mixture was decomposed with saturated sodium carbonate. The methylene chloride layer was washed thoroughly with water and dried over anhydrous Na_2SO_4. Evaporation of solvent gave a syrupy substance, which was purified by crystallization with alcohol followed by column chromatography to give pure **5a.** IR spectrum, ν, cm^{-1}: 1673, 1623, 1588, 1471, 706. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz)**:** 1.76 (6H, s); 7.00 (1H, d, *J* = 8.9); 7.08 (1H, m); 7.33 (1H, m); 8.12 (1H, d, *J* = 8.7). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm**:** 39.72, 77.47, 116.68, 117.50, 122.37, 124.23, 130.81, 149.93, 151.79, 153.73. Mass spectrum, *m/z***:** 218.

Compounds 5b-e were prepared similarly (Table 2).

4'-Acetyl-2'-acetylamino-2,2-dimethylspirochroman-4,5'-Δ^2-1,3,4-thiadiazoline (6a). Compound **3a** (2.0 g, 0.008 mol) was treated with freshly distilled acetic anhydride (20 ml), and the mixture was refluxed for 6-7 h on water bath (90-100°C). After completion of heating the resulting contents were poured over crushed ice with vigorous stirring to give a pale yellow product, which was separated by filtration and recrystallized from ethanol to give **6a**. IR spectrum, ν, cm^{-1}**:** 3175, 1699, 1622, 1582, 1508. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.26 (3H, s); 1.39 (3H, s); 2.04 (3H, s); 2.10 (3H, s); 2.43 (1H, d, *J* = 15, H_a); 3.29 (1H, d, *J* = 15, H_b); 6.70 (1H, d, *J* = 8.9); 6.87 (1H, m); 7.13 (1H, m); 7.26 (1H, d, *J* = 8.8); 11.68 (1H, s, NH). Mass spectrum, *m/z*: 331.

Compound 6b. IR spectrum, ν, cm^{-1}**:** 3177, 1691, 1648, 1625, 1136. ^{1}H NMR spectrum, δ, ppm: 1.26 (3H, s); 1.39 (3H, s); 2.05 (3H, s); 2.12 (3H, s); 2.42 (1H, d, *J* = 16, H_a); 3.17 (1H, d, *J* = 16, H_b), 6.71 to 7.05 (3H, m); 11.27 (1H, s, NH). Mass spectrum, *m/z*: 349.

Compounds 6b-e were prepared similarly (Table 2).

Phosphotyrosine Phosphatases 1B **Inhibition Measurement.** In-house generated human recombinant enzyme: ~35 ng in assay. *para*-Nitrophenyl phosphate (SRL144916): 25 mM. Buffer: Hepes 25 mM, 3 mM DTT, 0.15 M NaOH, 1 mM EDTA, pH 7.4. Dilution buffer (for enzyme): 2 X reaction buffer (3 mM DTT) Test compound in DMSO (DMSO concentration <1% in the assay). Standard used GRC5215. Incubation and continuously monitoring at 30°C for 30 min at 405 nm.

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