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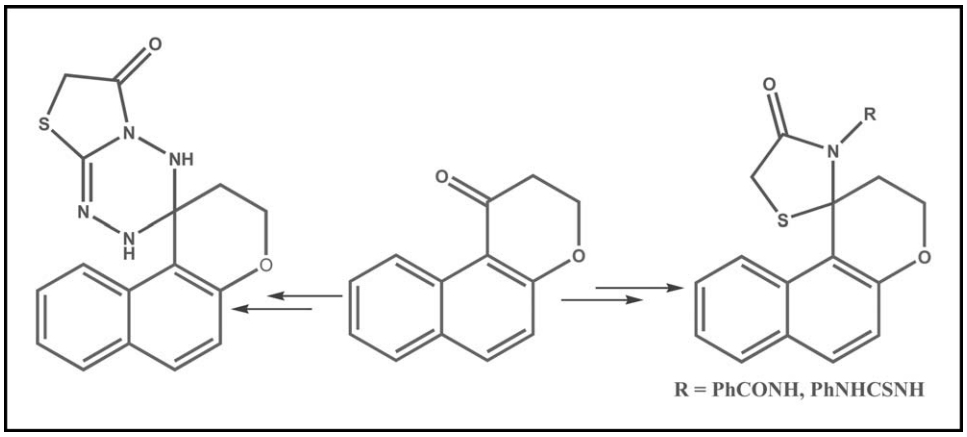

The syntheses of an important class of hitherto unreported spiro derivatives containing benzo[*f*]chromanone moiety involving very simple cyclocondensation reactions are described. Installation of pharmacologically active moieties like thiazolidine and thiazolidinone is achieved by taking simple reagents like ethylchloroacetate, 1, 2-dibromo ethane and thioglycollic acid.

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INTRODUCTION

Proliferation of research in spiro chemistry has now attained considerable height, right from the unprecedented synthesis of spiro hydrocarbon by Bayer [1]. Spiro heterocycles in particular fused at a central carbon atom display diverse biological and pharmaceutical [2–7] activities due to their interesting conformational features and structural implications. The presence of the sterically constrained spiro structure in various natural products also generates interest in the investigation on spiro compound [8,9]. During the last few decades, several papers have been published on spiro compounds, which have been reviewed in depth by Sanigrahi [10] and Pradhan *et al*. [11].

Recently various spirochromane derivatives have been reported to exhibit ACC inhibiting activity in low nanomolar range [12]. The antibiotics β-rubromycine and γ-rubromycine containing spirochromane unit are potent inhibition of human telomerase and are active against the reverse transcriptase of human immunodeficiency virus [13].

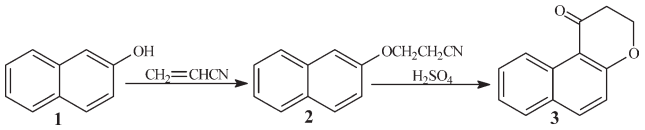
The above reports gave us an impetus to develop simple synthetic strategy for preparing new spiroheterocycles efficiently from benzochromanone. In continuance of our interest in the spirochemistry [14], herein we describe our endeavor towards the synthesis of spiro[benzo[*f*]chroman-4,6′-tetrazine] and spiro[benzo[*f*]-chroman-4,2′-thiazolidinone] derivatives.

RESULTS AND DISCUSSION

Benzo[*f*]chromanone was prepared by the base-catalyzed nucleophilic addition reaction of β-naphthol (**1**) to acrylonitrile followed by the hydrolysis of cyanoethylether (**2**) and subsequent dehydration reaction (Scheme 1) [15].

Spiro-s-tetrazine derivative (**4**) of benzo[*f*]chroman-4-one was prepared by the reaction of benzo[*f*]chroman-4-one with thiocarbohydrazide as per the procedure of Lamon [16] (Scheme 2). The absence of carbonyl absorption along with the appearance of bands at 3294 and 1195 cm^{-1} assignable to ν(N—H) and ν(C=S), respectively, support the formation of the spiro tetrazine product **4**. In its PMR spectrum, an upfield shift of the triplet from δ 4.74 (in case of benzochromanone **3**) to δ 4.36 with *J*-value 6.4 Hz, due to the absence of the long-range anisotropic effect of the carbonyl group has been observed. In addition, a two-proton broad singlet at δ 10.06 assignable to two NH protons and two one proton broad singlets at δ 10.70 and δ 10.89, may be due

Scheme 1



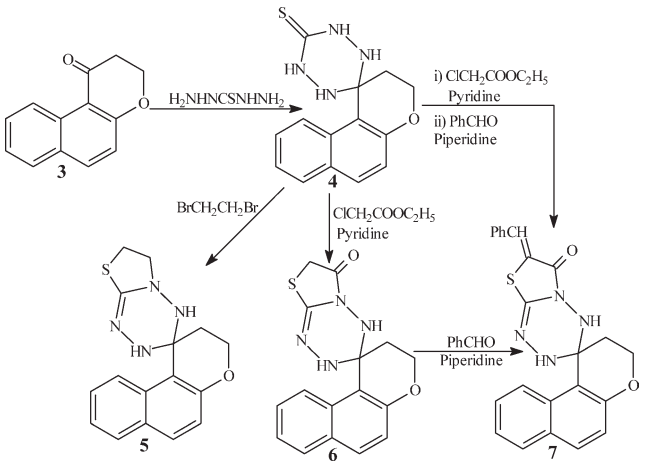
to the two CSNH protons were observed. The cyclocondensation of spiro-s-tetrazine derivative (**4**) with ethylchloroacetate in presence of pyridine gives the corresponding thiazolidinone derivative (**6**) (Scheme 2). The absence of chlorine and —COOH group in the chemical analysis of the compound and the appearance of carbonyl stretching frequency at 1728 cm^{-1} in its IR spectrum along with a prominent peak at 1616 cm^{-1} assignable to C=N stretching suggests the formation of the expected product **6**. In the PMR spectrum of the product appearance of a two proton singlet at δ 3.97 due to the —CH_2- group of the thiazolidinone ring along with a two proton broad singlet (exchangeable with D_2O) at δ 9.70 due to the two NH protons confirms the structure of the spiro thiazolo-s-tetrazine as **6**. The spiro [thiazole-s-tetrazine] derivative was condensed with benzaldehyde in presence of piperidine in ethanol to form benzylidine derivative (**7**) (Scheme 2). The bathocromic shift of the carbonyl stretching frequency from 1728 cm^{-1} to 1705 cm^{-1} due to conjugation with the exocyclic double bond confirms the formation of the benzylidene derivative (**7**). The one pot reaction of tetrazine derivative (**4**), ethylchloroacetate and benzaldehyde in presence of bases pyridine and piperidine in a sequential manner yields the same benzylidene derivative (**7**) (Scheme 2).The IR and PMR spectra of the product formed in both the routes are completely super imposable. Spiro-s-tetrazine derivative (**4**) on condensation with 1, 2-dibromo ethane gives dihydrospiro thiazolo-s-tetrazine derivatives (**5**) (Scheme 2). The appearance of a prominent peak at 1618 cm^{-1} due to the C=N stretching in the IR spectrum and two proton triplets at δ 2.90, 2.99, 4.36, and 4.61 with *J*-value 6 Hz in the PMR spectrum of (**5**) in addition to all other peaks as observed in the PMR spectrum of **4** support the proposed structure **5**.

Hydrazone and thiosemicarbazone derivatives (**8**) of benzochromanone **3** were prepared by the acid catalyzed condensation of benzochromanone with benzoyl hydrazine/4-phenyl thiosemicarbazone (Scheme 3).

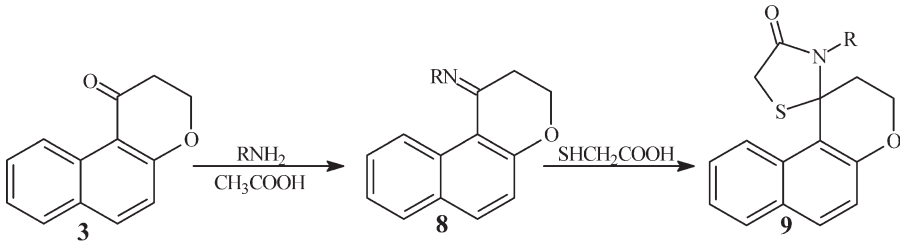
In the IR spectrum of compound **8a**, the shifting of the carbonyl stretching frequency from 1670 cm^{-1} to 1660 cm^{-1} along with the appearance of two bands at 3209 and 1633 cm^{-1} assignable to $\nu(N—H)_{str}$ and $\nu(C=N)_{str}$ confirms the condensation of the carbonyl group with benzoyl hydrazine. In the PMR spectrum of compound 8a, the appearance of a broad singlet at δ 9.75 assignable to the NH proton along with the two triplets at δ 4.37 and δ 3.00 with *J*-value 6 Hz assignable to the two CH_2 group of the chromane moiety confirms the formation of the product as **8a**.

The facile synthesis of spirothiazolidinone derivative (**9**) was achieved by the condensation of thioglycollic acid with hydrazone/phenylthiosemicarbazone derivatives of benzochromanone (Scheme 3). The absence of the —COOH group in the chemical analysis of compound (**9a**) and the appearance of two carbonyl stretching frequencies, one at 1708 cm^{-1} and another at 1664 cm^{-1} along with the disappearance of the ν $(C=N)_{str}$ in

Scheme 2



Scheme 3



R = a) PhCONH; b) PhNHCSNH

the IR spectrum suggests the formation of the product. In the PMR spectrum the appearance of a two proton singlet at δ 3.70 due to the —CH_2 protons of the thiazolidinone ring along with all other peaks as observed for compound (**8a**) confirms the formation of spirothiazolidinone product (**9a**). Similarly the structures of **8b** and **9b** have also been established.

CONCLUSIONS

In conclusion, we have described efficient and simple methods for the synthesis of spiro[benzochroman-4,6′-tetrazine] and spiro[benzochroman-4,2′-thiazolidinone] derivatives whose structures have been established on the basis of their IR and PMR spectral data. Taking into consideration the literature reports on the biological activities of the benzo[*f*]chromanone, tetrazine, and thiazolidinone moieties, the spiro compounds containing these moieties can be expected as the potent antimicrobial agents. Thus, the biological study is in progress.

EXPERIMENTAL

The melting points were determined in open capillaries on a sulfuric acid bath and are uncorrected. Purity of the products was checked by TLC on silica gel G (BDH) using toluene-ethylacetate (4:1) as eluent. IR spectra were recorded on a Shimadzu FT-IR Prestige-21 spectrophotometer using KBr as background and under DRS technique. NMR spectra were recorded on Varian 200 and 400 MHz FT NMR spectrometer and were recorded in $CDCl_3$, unless otherwise stated. Mass spectra were recorded on a LCMS spectrometer, model HP-5899A. Elemental analyses were performed on Flash 2000 elemental analyzer, and results were within ±0.4% of calculated values. All other reagents and solvents were obtained from commercial sources and used without further purification.

Spiro [Benzo[f]chroman-4,6′-hexahydro-s-tetrazine] -3-thione (4). To a solution of thiocarbohydrazide (1.06 g, 0.01 mole) in hot water (20 mL), benzochromanone (**3**) (1.98 g, 0.01 mole) in ethanol (5 mL) was added drop wise under stirring. The product began to precipitate during the course of addition. Then the reaction mixture was kept overnight in refrigerator and the resultant pale yellow solid was filtered, washed well with hot water and ethanol and finally recrystallized from acetic acid to get compound **4**.Yield 72%, mp 200°C. IR (KBr) (ν_{max}/cm^{-1}): 1269 (C=S), 3294 (N—H). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H (ppm): 3.14 (2H, t, $J_{3,2}$ 6.4 Hz, H-3), 4.36 (2H, t, $J_{2,3}$ 6.4 Hz, H-2), 7.07–7.82 (4H, m, ArH), 9.12 (1H, d, *J* 7.6 Hz, ArH), 9.38 (1H, d, *J* 8.4 Hz, ArH),10.06 (2H, br s, NH),10.70 (1H, s, CSNH), 10.89 (1H, s, CSNH). MS (CI): *m/z* 287 $[M+H]^+$. Anal. Calcd for $C_{14}H_{14}N_4OS$: C, 58.74; H, 4.90; N, 19.58. Found: C, 58.43; H, 4.56; N, 19.21.

Spiro [Benzo[f]chroman-4,3′(4H)[2H] thiazolo[3,2-b]-s-tetrazine]-6(7′H)-one (6). A mixture of tetrazine (**4**) (0.001 mole, 0.286 g), ethylchloroacetate (0.001 mole, 0.1 mL) and five drops pyridine in dioxane (15 mL) was heated under reflux for 9 h. Then it was isolated with ice cold water. The precipitate thus obtained was filtered and recrystallized from ethanol to get compound **6**. Yield 60%, mp 255°C. IR (KBr)(ν_{max}/cm^{-1}): 1616 (C=N), 1728 (C=O), 3317 (N—H). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm): 2.96 (2H, t, $J_{3,2}$ 6.4 Hz, H-3), 3.97 (2H, s, CH_2CO), 4.28 (2H, t, $J_{2,3}$ 6.4 Hz, H-2), 7.03–7.78 (m, 3H, ArH), 7.87 (1H, d, *J* 8.4 Hz, ArH), 9.47 (1H, d, *J* 7.6 Hz, ArH), 9.63 (1H, d, *J* 8.4 Hz, ArH), 9.70 (2H, br s, NH). MS (CI): *m/z* 327 $[M+H]^+$. Anal. Calcd for $C_{16}H_{14}N_4O_2S$: C, 58.90; H, 4.29; N, 17.18. Found: C, 58.55; H, 3.92; N, 16.89.

7′-Benzylidene spiro[benzo[f]-chroman-4,3′(4′H)[2H]thiazolo [3,2-b]-s-tetrazine]-6′-one(7). ***Method – A*** To a solution of thiazolidinone (**6**) (0.001mole, 0.33 g) in dioxane (15 mL), benzaldehyde (0.001 mole, 0.1 mL) was added and refluxed for 6 h. The reaction mixture was poured into ice cold water. The brown precipitate thus obtained was filtered, dried and purified by column chromatography using ethyl acetate and toluene as eluent. Yield 58%, mp 225°C. IR(KBr)(ν_{max}/cm^{-1}):1616(C=N), 1705(C=O), 3292(N—H).^{1}H-NMR (400 MHz, $CDCl_3$): δ_H (ppm): 3.10 (2H, t, $J_{3,2}$ 6.4 Hz, H-3), 4.38 (2H, t, $J_{2,3}$ 6.4 Hz, H-2), 7.06–7.77 (m, 8H, ArH), 7.89 (1H, d, *J* 8.4 Hz, ArH), 8.01 (1H, br s, = CHPh), 9.43 (1H, d, *J* 8.8 Hz, ArH), 9.67 (1H, s, NH), 9.69 (1H, d, *J* 8.4 Hz, ArH). MS (CI): *m/z* 415 $[M+H]^+$. Anal. Calcd for $C_{23}H_{18}N_4O_2S$: C, 66.66; H, 4.34; N, 13.53. Found: C, 66.45; H, 3.98; N, 13.4.

Method – B. A mixture of tetrazine (**4**) (0.001 mole, 0.29 g), ethylchloroacetate (0.001 mole 0.1 mL) and pyridine in dioxane was heated under reflux for 4 h. Then to the reaction mixture, benzaldehyde (0.001 mole, 0.1 mL) and few drops of piperidine was added and further refluxed for 5 h. The reaction mixture was cooled and poured into ice cold water. The crude product thus obtained was purified by column chromatography using ethyl acetate and toluene as eluent. Yield 65%, mp 225°C, Mixed mp 225°C. Anal. Calcd for $C_{23}H_{18}N_4O_2S$: C, 66.66; H, 4.34; N, 13.53. Found: C, 66.31; H, 4.11; N, 13.23.

The spectral and analytical data of the product **7** obtained by Method-B is same as the product obtained in Method-A.

6′,7′-Dihydrospiro[benzo[f]chroman-4,3′ (4′H) [2H]thiazolo [3,2-b]-s-tetrazine] (5). A mixture of spiro-s-tetrazine of benzochromanone (**4**) (2.86 g, 0.01 mole) and 1, 2-dibromoethane (0.85 mL, 0.01 mole) in 1, 4-dioxane was refluxed for 6 h in an oil bath. The reaction mixture was cooled to room temperature and then poured into ice cold water. The greenish yellow precipitate thus obtained was filtered, dried and finally recrystallized from methanol. Yield 67%, mp 195°C. IR (KBr) (ν_{max}/cm^{-1}): 1618(C=N), 3338 (N—H). ^{1}H-NMR (200 MHz, $CDCl_3$): δ_H (ppm): 2.90 (2H, t, *J* 6 Hz, S-CH_2), 2.99 (2H, t, *J* 6 Hz, CH_2), 4.36 (t, 2H, *J* = 6 Hz, N-CH_2), 4.61(t, 2H, *J* = 6 Hz,O-CH_2), 7.03–7.78 (m,4H,ArH), 9.29 (d,1H, *J* = 8.8 Hz, ArH), 9.69 (d,1H, *J* = 8.8 Hz, ArH), 10.61(2H, br s, NH). MS (CI): *m/z* 313 $[M+H]^+$. Anal. Calcd for $C_{16}H_{16}N_4OS$: C, 61.54; H, 5.13; N, 17.95. Found: C, 61.35; H, 4.92; N, 17.58.

4-(Benzamido/phenylthiourido)iminobenzo[f]chroman-4-one(8). ***General procedure.*** To a solution of benzochromanone (**3**) (0.005 mole) in methanol (15 mL), benzoic acid hydrazide/4-phenylthiosemicarbazone (0.005 mole) and few drops of glacial acetic acid were added. The mixture was then heated under reflux for 7 h. The precipitate thus obtained was filtered, washed properly with methanol and recrystallized from methanol.

Compound 8a. Yield 56%, mp 185 °C. IR (KBr) (ν_{max}/cm^{-1}): 1633 (C=N), 1660 (C=O), 3209 (N—H). ^{1}H-NMR (200 MHz, $CDCl_3$): δ_H (ppm): 3.00 (2H, t, $J_{3,2}$ 6 Hz, H-3), 4.37 (2H, t, $J_{2,3}$ 6 Hz, H-2), 7.04–7.88 (9H, m, ArH), 8.97–9.06 (2H, m, ArH), 9.75 (1H, br s, NH). MS (CI): *m/z* 317 $[M+H]^+$. Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.95; H, 5.06; N, 8.86. Found: C, 75.57; H, 4.87; N, 8.56.

Compound 8b. Yield 60%, mp 190°C. IR (KBr) (ν_{max}/cm^{-1}): 1370 (C=S), 1642 (C=N), 3240 (N—H). ^{1}H-NMR (200 MHz, $CDCl_3$): δ_H (ppm): 3.21 (2H, t, $J_{3,2}$ 6 Hz, H-3), 4.42 (2H, t, $J_{2,3}$ 6 Hz, H-2), 7.12–7.93 (9H, m, ArH), 8.89–9.23 (2H, m, ArH), 9.42 (1H, br s, NHCS), 9.68 (1H, br s, NHPh). MS (CI): *m/z* 348 $[M+H]^+$. Anal. Calcd. for $C_{20}H_{17}N_3OS$: C, 69.16; H, 4.90; N, 12.10. Found: C, 68.84; H, 4.58; N, 11.78.

Spiro[benzo[f]chroman-4,2′-(3′-(benzamido/phenylthiourido)-4′-thiazolidinone] (9). ***General procedure.*** A mixture of hydrazone derivative (**8**) (0.002 mole) and mercaptoacetic acid (0.006 mole) in 1, 4-dioxane (20 mL) was refluxed for 14 h. Then was cooled to room temperature and saturated solution of $NaHCO_3$ was added to it. The crude precipitate thus obtained was purified by column chromatography using ethyl acetate and toluene as eluent.

Compound 9a. Yield 60%, mp 168°C. IR (KBr) (ν_{max}/cm^{-1}): 1602(C=N),1664(PhC=O),1708(CH_2C=O),3211(N—H). ^{1}H-NMR (200 MHz, $CDCl_3$): δ_H (ppm): 2.99(2H, t, $J_{3,2}$ 6 Hz, H-3), 3.70 (s, 2H, CH_2CO), 4.34 (2H, t, $J_{2,3}$ 6 Hz, H-2), 7.03–7.93 (10H, m, ArH), 9.43–9.47 (1H, m, ArH), 9.73(1H, br s, NH). MS (CI): *m/z* 391 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{18}N_2O_3S$: C, 67.69; H, 4.16; N, 7.18. Found: C, 67.47; H, 3.96; N, 6.85.

Compound 9b. Yield 65%, mp 210°C. IR (KBr) (ν_{max}/cm^{-1}): 1622 (C=N), 1712 (CH_2C=O), 3231(N—H). ^{1}H-NMR (200 MHz, $CDCl_3$): δ_H (ppm): 3.02 (2H, t, $J_{3,2}$ 6 Hz, H-3), 3.85 (s, 2H, CH_2CO), 4.42 (2H, t, $J_{2,3}$ 6 Hz, H-2), 7.23–7.84 (10H, m, ArH), 9.51–9.54 (1H, m, ArH), 9.56(1H, br s, NHCS), 9.72 (1H, br s, NHCSPh). MS (CI): *m/z* 422 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{19}N_3O_2S_2$: C, 62.70; H, 4.51; N, 9.98. Found: C, 62.51; H, 4.26; N, 9.65.

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