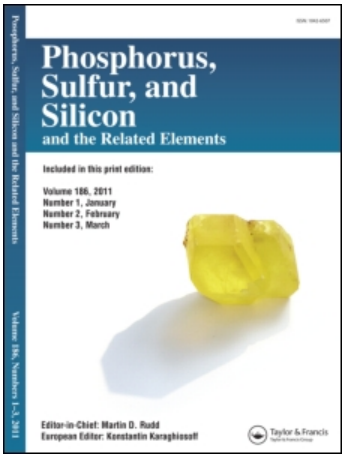

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A Facile One-Step Synthesis of New Types of 8-Thiazolyl and 8-Thiadiazinyl Coumarins

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A Facile One-Step Synthesis of New Types of 8-Thiazolyl and 8-Thiadiazinyl Coumarins

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*N-[4-(7-Methoxy-4-methyl-2-oxo-2H-chromen-8-yl)-thiazol-2-yl]-guanidine (**2**) has been prepared by the condensation of 4-methyl-7-methoxy-8-(2-bromoacetyl)coumarin (**1**) with guanylthiourea. 4-Methyl-7-methoxy-8-[2-(N′-(1-phenylethylideneisopropylidene)-hydrazino]-thiazol-4-yl]chromen-2-ones (**3**, **4**, and **5**) have been prepared by reaction of 4-methyl-7-methoxy-8-(2-bromoacetyl) coumarin (**1**) and thiosemicarbazide in presence of acetophenone or acetone without any solvent. The formation of these compounds was further confirmed by the condensation of acetophenone/acetone thiosemicarbazones with 4-methyl-7-methoxy-8-(2-bromoacetyl)coumarin (**1**) in anhydrous ethanol in a two-step process. Similarly 8-[2-[N′-(benzylidene)hydrazine]-thiazol-4-yl]-7-methoxy-4-methyl-chromen-2-ones (**6**, **7**, and **8**) have been prepared by the condensation of 4-methyl-7-methoxy-8-(2-bromoacetyl)chromen-2-one with thiosemicarbazide and various aromatic aldehydes in a single step without any solvent. The formation of these compounds was further confirmed by the condensation of appropriately substituted benzaldehyde thiosemicarbazones with 4-methyl-7-methoxy-8-(2-bromoacetyl)coumarin in anhydrous ethanol. 4-Methyl-7-methoxy-8-(2-bromoacetyl) chromen-2-one (1) upon condensation with 3,5-dimercapto-4-amino-s-triazole in anhydrous ethanol resulted in the formation of 8-(3-mercapto-3H-[1,2,4]triazolo[3,4-b]thiadiazin-6-yl)-7-methoxy-4-methyl chromen-2-one (9). This compound (**9**) on reaction with various alkyl and phenacyl halides in anhydrous ethanol gave corresponding 4-methyl-7-methoxy-8-[3-(2-oxo-substituted sulphanyl)-7H-[1,2,4]triazolo[3,4-b]thiadiazin-6-yl]chromen-2-ones (**10** to **18**). The structures of newly prepared compounds have been confirmed from analytical and spectral data.*

Keywords Coumarin; thiadiazine; thiadiazole; thiazolyl coumarin

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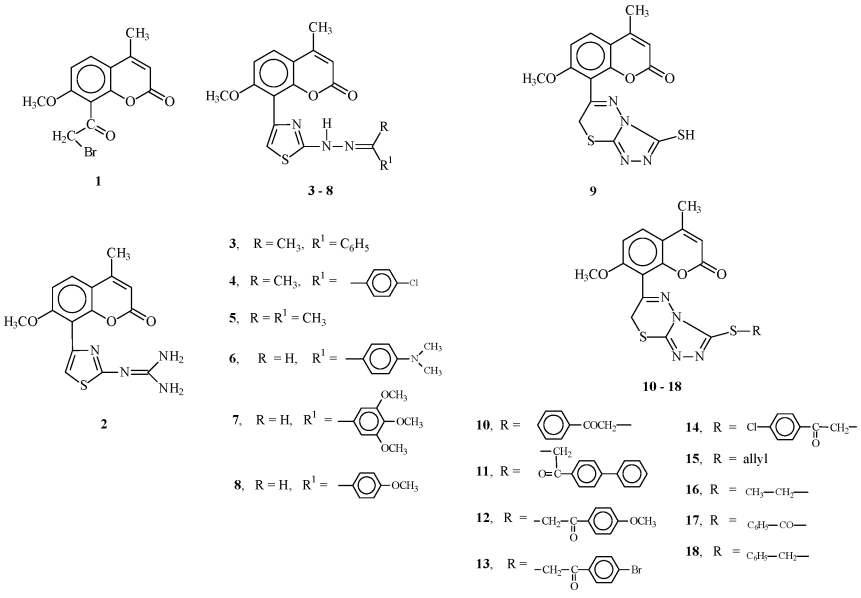
INTRODUCTION

A coumarin ring is found in a variety of natural products, which exhibit various pharmacological effects. Derivatives of coumarin are also important in drugs having varied properties. There are excellent monographs and review articles[1–5] describing the structure, synthetic reactions, and properties of coumarins. Numerous reports have appeared in the literature that describe antimicrobial,[6,7] antiradiation,[8,9] and antiparasitic[10] properties of the thiazole ring. Various 1,2,4-triazoles and N-bridged heterocycles derived from them are found to be associated with diverse pharmacological activities.[11–16]



SCHEME 1

Prompted by the above observations, and in continuation of our search for biologically active nitrogen- and sulfur-containing heterocycles,[17–20] we decided to synthesize these heterocyclic coumarins.

RESULTS AND DISCUSSION

Synthesis of N-[4-(7-methoxy-4-methyl-2-oxo-2H-chromen-8-yl)-thiazolo-2-yl]-guanidine (**2**) has been achieved by the condensation of 4-methyl-7-methoxy-8-(2-bromoacetyl)coumarin (**1**) with guanylthiourea

in anhydrous ethanol. 4-Methyl-7-methoxy-8-[2-(N′-(1-phenyl-ethylidene/isopropylidine)hydrazino]thiazol-4-yl]chromen-2-ones (**3**, **4**, and **5**) have been obtained by the reaction of 4-methyl-7-methoxy-8-(2-bromoacetyl)coumarin (**1**) thiosemicarbazide, acetophenones, and acetone in a single step under solvent free conditions. Alternatively, these compounds were synthesized in a two-step process involving condensation of thiosemicarbazones, acetophenones, and acetone with **1** in anhydrous ethanol. Similarly, condensation of **1** with thiosemicarbazide and appropriately substituted aromatic aldehydes in a single step gave the corresponding thiazoles (**6**, **7**, and **8**). The structures of these compounds were further confirmed by the condensation of **1** with aromatic aldehyde thiosemicarbazones in anhydrous ethanol. This is a two step process. The compounds obtained by both methods are identical (by mixed mp measurements, TLC, and IR spectra). All the hydrazino thiazolyl coumarins (**3–8**) displayed characteristic absorption bands due to –C=N and lactone –C=O at 1611 and 1738 cm^{-1}. The ^1H NMR spectra of **5** exhibited a characteristic singlet for thiazole and coumarin C_3-protons at δ 7.68 and 6.15, respectively. The remaining protons are observed in the usual region (Table I).

The 8-(3-mercapto-7H-[1,2,4]triazolo[3,4-b]thiadiazin-6-yl)-7-methoxy-4-methyl chromen-2-one (**9**) was synthesized by condensing 3,5-dimercapto-4-amino-s-triazole with 4-methyl-7-methoxy-8-(2-bromoacetyl)chromen-2-one in anhydrous ethanol. The compound (**9**) upon condensation with various alkyl and phenacyl halides in anhydrous ethanol gave corresponding 4-methyl-7-methoxy-8-[3-(2-oxo substituted sulphanyl)-7H-[1,2,4]triazolo[3,4-b]thiadiazin-6-yl]chromen-2-ones (**10–18**). All the compounds displayed strong absorption bands due to –C=N- and lactone carbonyl of coumarin at 1603–1615 and 1726–1738. The ^1H NMR spectrum of **14** exhibited a characteristic singlet for –S-CH_2 of thiadiazine at δ 3.9. The –CH_2-S- appeared as singlet at δ 4.9. The remaining protons were observed in the expected region (Table I).

EXPERIMENTAL

All melting points were determined in open capillary tubes using a sulfuric acid bath and were uncorrected. IR spectra (ν max, cm^{-1}) were recorded on a Perkin Elmer instrument. The ^1H NMR spectra were recorded on a Varian 200 MHz spectrometer using tetramethyl silane (TMS) as internal standard. Chemical shift values are expressed δ ppm. Mass spectra were scanned on Perkin-Elmer, SCIEX-API-2000, ESI,

TABLE I Spectral Data of Compounds

Compd.	IR (ν max$_{cm}^{-1}$) -C=N	lactone –C=O	NH_2 or other	^{1}H NMR (δ ppm)[a]	Mass spectrum
2	1607	1726	3307	2.51 (s, CH, C_4-CH_3), 3.96 (s, 3H, -OCH_3), 6.29 (s, 1H, C_3 of coumarin), 7.24 and 7.83 (d, $J = 9$ Hz, aromatic AB protons) 7.47 (s, 1H, C_5' of thiazole) and 8.22–8.26 (s, broad, 2H, 2 × NH_2, D_2O exchangeable)	M^+ 330
3	1607	1744	—	2.52 (s, 3H, CH_3), 2.53 (s, 3H, N=C-CH_3), 4.11 (s, 2H, OCH_3), 6.17 (s, 1H, C_3 of coumarin) 7.39–7.44 (m, 5H, Ar-H), 7.68 (s, 1H, C_5' of thiazole) 7.78–7.82 (doublets, 2H, aromatic protons) and 8.18 (1H, NH, D_2O exchangeable).	M^+ 406
4	1605	1730	—	2.50 (s, 6H, 2 × CH_3), 3.91 (s, 3H, OCH_3), 4.36 (s, 1H, NH, D_2O exchangeable), 6.26 (s, 1H, C_3), 7.23 (d, 2H, C_3' and C_5' of p-chlorophenyl), 7.48 (d, 2H, C_2'' and C_6'' of p-chlorophenyl), 7.79 (d, 2H, Ar-H) and 8.40 (s, C_5' of thiazole)	—
5	1620	1735 (lactone –C=O)	—	2.1 (s, 6H, 2 × $N(CH_3)_2$), 2.6 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 4.05 (s, 1H, -NH-), 6.2 (s, 1H, C_3 of coumarin), 7.8 (d, 1H, Ar-H), 7.95 (d, 1H, Ar-H) and 8.3 (s, 1H, C_5 of thiazole)	—
6	1615 (-C=N-)	1734 (lactone –C=O)	—	2.2 (s, 6H, 2 × $N(CH_3)_2$), 4.1 (s, 3H, OCH_3), 6.2 (s, C_3 of coumarin), 6.8 (d, 2H, $J = 8$ Hz, C_3'' and C_5'' of p-N,N-dimethylaminophenyl), 7.3 (s, 1H, C_5' of thiazole), 7.5 (d′, 2H, $J = 8$Hz, C_2' and C_6' of p-N,N-dimethylamino) 7.00 (s, 1H, azomethine) 8.0-8.3 (H, unresolved doublets, C_5 and C_6 Ar-H) and 11.2 (s, 1H, NH)	—

(*Continued on Next Page*)

TABLE I Spectral Data of Compounds *(Continued)*

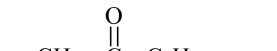
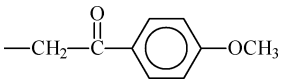
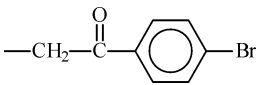
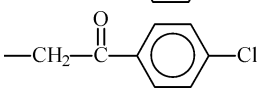
Compd.	IR (ν max$^{-1}_{cm}$) -C=N	lactone –C=O	NH_2 or other	^{1}H NMR (δ ppm)[a]	Mass spectrum
7	1615	1739 (lactone –C=O)	—	2.51 (s 3H, C_4-CH_3), 3.9 (s, 3H, OCH_3), 4.10 (s, 9H, 3 × OCH_3), 6.1 (s, 3H, C_3 of coumarin), 6.9–7.1 (m, 4H, Ar-H), 7.3 (s, 1H, azomethine), 7.8 (s, 1H, C_5' of thiazole) and 11.39 (s, 1H, -NH-, D_2O exchangeable)	—
8	1615	1730 (lactone –C=O)	—	2.5 (s, 3H, CH_3), 4.1 (s, 6H, 2 × OCH_3), 6.15 (s, 1H, C_3 of coumarin), 7.00 (s, 1H, azomethine), 7.3–7.4 (m, 4H, Ar-H), 7.65–7.75 (m, 2H, Ar-H), 8.1 (s, 1H, C_5' of thiazole) and 8.35 (s, 1H, NH D_2O exchangeable)	—
9	1611	1738 (lactone –C=O)		2.4 (s, 3H, CH_3), 4.09 (3H, OCH_3), 3.95 (s, 5H, 3H of OCH_3 and s, 2H, -SCH_2-), 6.15 (s, 1H, C_3 of coumarin), 7.25 (d, 1H, Ar-H) 7.95 (d, 1H, Ar-H) and 14.00 (s, 1H, SH)	—
10	1606	1729	1684 (ketone C=O)	2.5 (s, 3H, CH_3), 3.9 (s, 2H, S-CH_2), 4.1 (s, 3H, OCH_3), 4.9 (s, 2H, -S-CH_2), 6.1 (s, 1H, C_3 of coumarin), 7.18–7.3 (m, 5H, Ar-H), 7.65 (d, 1H, Ar-H of coumarin), 7.85 (d, 1H, Ar-H of coumarin)	—
11	1606	1720	1680 (-C=O)	2.20 (s, 3H, CH_3), 4.00 (s, 3H, OCH_3), 4.40 (s, 2H, SCH_2), 5.00 (s, 2H, SCH_2), 6.20 (s, 1H, C_3 of coumarin), 7.38–8.20 (m, 11H, Ar-H of coumarin and biphenyl ring)	—
18	1610	1724		2.55 (s, 3H, CH_3), 4.00 (s, 3H, OCH_3), 4.10 (s, 2H, -SCH_2-), 4.90 (s, 2H, -SCH_2), 6.25 (1H, C_3 of coumarin), 7.25–7.40 (m, 1H, Ar-H) and 7.65–8.00 (m, 6H, Ar-H)	—

[a]NMR of all the compounds were recorded in DMSO-d_6.

TABLE II Analytical Data of 2, 3, 4, 6, and 8

Compd. *	R^1	R^2	Mp °C	Elemental Analyses—Calcd. (Found)			
				C	H	N	S
2	—	—	284–286	54.54 (54.52)	4.27 (4.24)	16.96 (16.93)	9.71 (9.68)
3	CH_3	C_6H_5	244–246	65.17 (65.15)	4.68 (4.72)	10.30 10.36	7.88 (7.91)
4	CH_3	-C_6H_4 (*p*-Cl)	270–272	60.07 (60.00)	4.12 (3.98)	9.55 (9.50)	7.29 (7.25)
5	CH_3	CH_3	215–217	58.52 (58.46)	4.30 (4.25)	12.80 (12.74)	9.76 (9.70)
6	H	-C_6H_4 (*p*-NMe_2)	224–226	63.58 (63.53)	5.10 (5.08)	12.89 (12.84)	7.38 (7.33)
7	H	-C_6H_3 (2,3,4-trimethoxy)	208–210	59.86 (59.82)	4.81 (4.76)	8.73 (8.70)	6.66 (6.64)

TABLE III Analytical Data of 5, 8, 9, 10, 15, and 16

Compd. *	R^1	R^2	Mp °C	Elemental Analyses—Calcd. (Found)			
				C	H	N	S
8	H	C_6H_5 (p-OCH_3)	254–258	62.69 (62.60)	4.54 (4.50)	9.97 (10.00)	7.61 (7.58)
9	—	—	235–237	49.99 (49.95)	3.36 (3.32)	15.55 (15.51)	17.79 (17.75)
10			237–239	57.73 (57.70)	3.79 (3.75)	11.71 (11.68)	13.40 (13.36)
11			224–226	62.80 (62.74)	4.00 (3.94)	10.00 (10.10)	11.56 (11.50)
12			242–244	56.68 (56.63)	3.96 (3.92)	11.02 (11.00)	12.61 (12.58)
13			240–242	49.56 (49.51)	3.07 (2.90)	10.05 (9.95)	11.50 (11.46)
14			210–212	53.85 (53.81)	3.34 (3.30)	10.92 (10.88)	12.50 (12.46)
15	Allyl		203–205	53.99 (53.94)	4.03 (3.96)	13.96 (13.94)	16.01 (15.58)
16	Ethyl		187–189	52.56 (52.50)	4.15 (4.00)	14.42 (14.37)	16.51 (16.45)
17	Benzoyl		220–222	56.89 (56.84)	3.47 (3.41)	12.06 (12.14)	13.81 (13.75)
18	$-CH_2-C_6H_5$		162–164	58.65 (58.60)	4.03 (4.00)	12.44 (12.40)	14.23 (14.20)

12.5 eV. The purity of the compounds was monitored by TLC performed on silica gel plates (Merck) using benzene:acetone (3:1) solvent.

The 3,5-dimercapto-4-amino-s-triazole[21] and 4-methyl-7- methoxy-8-(2-bromoacetyl)coumarin[22] were prepared according to the literature.

Synthesis of N-[4-(7-Methoxy-4-methyl-2-oxo-2H-chromen -8-yl)-thiazol-2-yl]guanidine (2)

A mixture of 4-methyl-7-methoxy-8-(2-bromo acetyl)chromen-2-one (0.311 g, 0.01 mol) and guanylthiourea (0.103 g, 0.01 mol) in anhydrous ethanol (10 mL) was refluxed for 1 h. The reaction mixture was cooled at room temperature. The solid that separated was filtered, dried, and recrystallized from methanol.

Synthesis of 4-Methyl-7-methoxy-8-[N′-(1-phenyl ethylidene/isopropylidene)-hydrazinothiazol-4-yl]chromen -2-ones (Method 1) (3, 4, 5)

A mixture of 4-methyl-7-methoxy-8-(2-bromo-acetyl-chromen-2-one (0.311 g, 0.01 mol), thiosemicarbazide (0.91 g, 0.01 mol), and acetophenone (0.01 mol) or acetone (0.01 mol) in anhydrous ethanol (10 mL) was refluxed for 0.5 h. The reaction mixture was cooled at room temperature. The solid that separated was filtered, dried, and recrystallized from methanol.

Alternative Synthesis of 4-Methyl-7-methoxy-8-(N′-1-phenyl ethylidene/isopropylidene)hydrazinothiazol-4-yl]chromen -2-ones (Method 2)

A mixture of acetophenone or acetone thiosemicarbazone (0.193 g, 0.01 mol) and 4-methyl-7-methoxy-8-(2-bromoacetyl-chromen-2-one (0.311 g, 0.01 mol) was refluxed in anhydrous ethanol for 30 min. The resulting solid was filtered and recrystallized from a suitable solvent.

8-[2-[N′-(Benzylidene)hydrazine)thiazol-4-yl]-7-methoxy -4-methylchromen-2-ones (Method 1) (6, 7, and 8)

A mixture of 4-methyl-7-methoxy-8-(2-bromo acetyl)chromen-2-one (0.311 g, 0.01 mol), thiosemicarbazide (0.91 g, 0.01 mol), and the appropriate aromatic aldehyde (0.01 mol) in anhydrous ethanol was refluxed for 0.5 h. The reaction mixture was cooled at room temperature.

The solid that separated was filtered, dried, and recrystallized from methanol.

Alternative Synthesis of 8-[2-(N′-(Benzylidene)hydrazine)thiazol-4-yl]-7-methoxy-4 -methylchromen-2-ones (Method 2)

A mixture of 4-methyl-7-methoxy-8-(2-bromoacetyl)chromen-2-one (0.311 g, 0.01 mol) and thiosemicarbazone of the appropriate aromatic aldehyde (0.01 mol) was refluxed in anhydrous ethanol for 30 min. The resulting solid was filtered and recrystallized from a suitable solvent.

8-(3-Mercapto-3H-[1,2,4]triazolo[3,4-b]thiadiazin-6-yl) -7-methoxy-4-methylchromen-2-one (9)

A mixture of 4-methyl-7-methoxy-8-(2-bromoacetyl)chromen-2-one (0.311 g, 0.01 mol) and 2,5-dimercapto-4-amino-1,2,4-triazole (0.148 g, 0.01 mol) was taken in 10 mL of anhydrous ethanol, which was heated to reflux over a period of 3–4 h. Upon cooling at room temperature, the solid separated was filtered, dried, and recrystallized from methanol.

4-Methyl-7-methoxy-8-[3-(2-oxo substituted sulphanyl) -7H-[1,2,4]-triazolo[3,4-b]thiadiazin-6-yl]chromen-2-ones (10–18)

A mixture of 8-(3-mercapto-7H-[1,2,4]triazolo[3,4-b]1,3,4]thiadiazin-6-yl)-methoxy-4-methyl-chromen-2-one (0.360 g, 0.01 mol) and phenacyl bromide (0.01 mol) or the appropriate alkyl halide or acylhalide (0.01 mol) was taken of anhydrous ethanol (10 mL), which was heated to reflux over a period of 4 h Upon cooling at room temperature, the solid that separated was filtered, dried, and recrystallized from methanol.

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