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Synthesis and antimicrobial screening of N-[coumarin-6-ylamino]thiazolidinone and spiro indolo-thiazolidinone derivatives

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Condensation of N-[coumarin-6-yl]hydrazonoarylmethanes **3a-h** obtained from the condensation of the coumarin-6-ylhydrazine hydrochloride **2a-d** and aromatic aldehydes, on treatment with mercaptoacetic acid in dry 1,4-dioxane in the presence of catalytic amount of anhydrous zinc chloride yields N-[coumarin-6-ylamino]-2-arylthiazolidin-4(*H*)-ones **4a-h**. While, coumarin-6-ylhydrazine hydrochloride **2a-d** on condensation with isatin *in situ* yields corresponding 1,2-dihydro-3-[coumarin-6-ylhydrazono]indol-2-ones **5a-d**. Compound **5a-d** on treatment with mercaptoacetic acid in dry 1,4-dioxane in the presence of catalytic amount of anhydrous zinc chloride affords N-[coumarin-6-ylamino]spiro-[3*H*-indole-(1*H*,2*H*)-3,2-(4*H*)-thiazolidine]-2,4-diones **6a-d**. The structures of the compounds **3**, **4**, and **6** have been confirmed on the basis of their spectral and analytical data. The above compounds are screened for their antimicrobial activities and have been found to exhibit significant antibacterial and antifungal activities.

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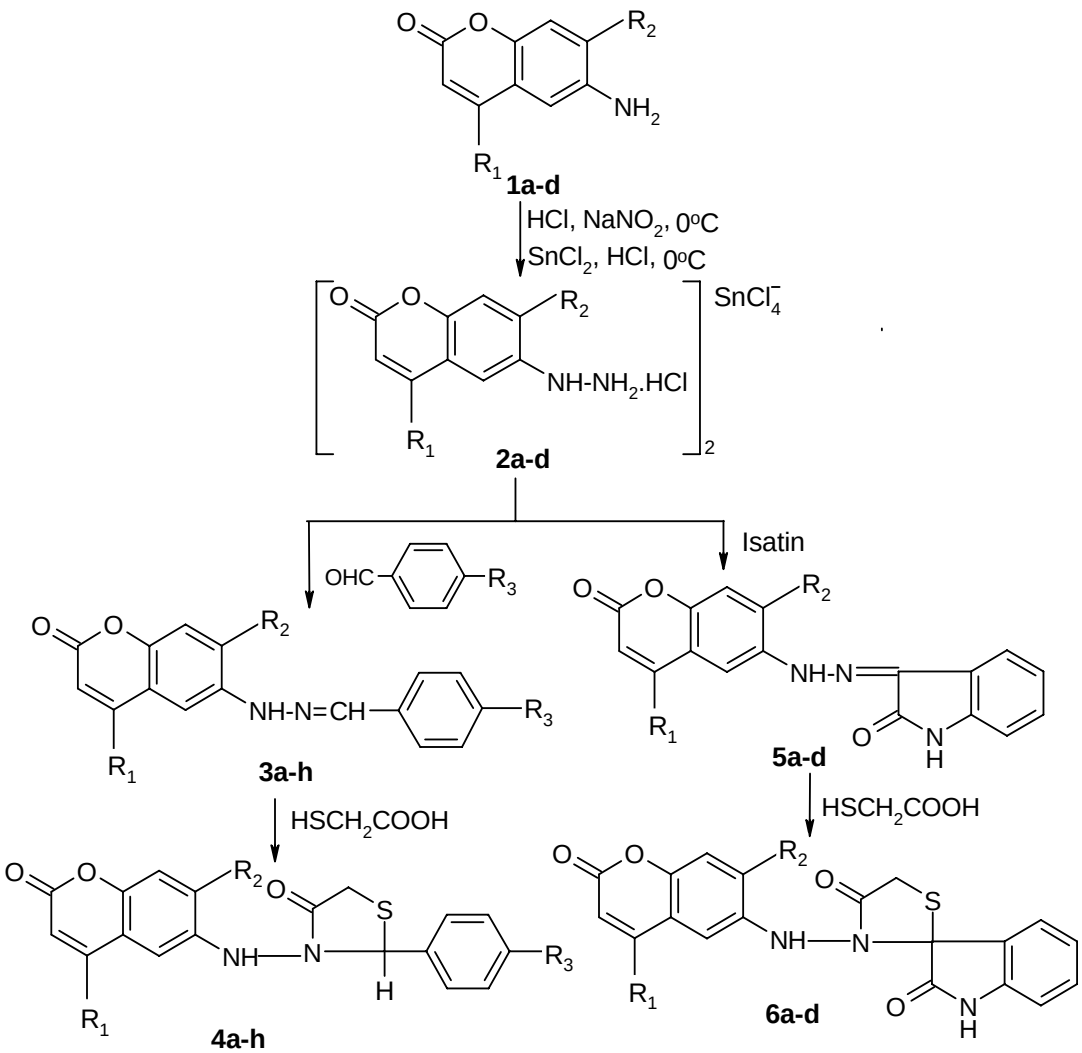
The chemistry of coumarin derivatives continues to draw attention of synthetic organic chemists due to their varied biological activities[1-4]. Several nitrogen mustards synthesized from 6-aminocoumarins exhibit carcinogenic activity[5] and are known to possess antiviral activity and especially effective against HIV1[6]. Thiazolidin-4-ones are known to possess wide range of pharmaceutical activities[7]. Various indole derivatives show a wide range of biochemical properties[8]. It has been reported[9] that, if the indole ring is joined to other heterocyclic compounds through a spiro-carbon atom, the resulting compounds show increased spectrum of biological activities. By observing the importance of the above compounds, we planned to synthesize such compounds in which the 6-aminocoumarin ring is joined to the thiazolidin-4-one ring system and to the spiro-indolothiazolidin-4-one ring system, which may possess some of the above biological activity.

With this intention, N-[coumarin-6-yl]hydrazono-1-arylmethanes[10] **3a-h** were refluxed with mercapto-acetic acid in the presence of catalytic amount of anhydrous zinc chloride in dry 1,4-dioxane for 7 hr to yield the corresponding N-[coumarin-6-ylamino]-2-arylthiazolidin-4(*H*)-ones **4a-h**. The IR spectrum of **4f** in KBr showed band at 3424 cm^{-1} for N-H stretching, 3073, at 2925 for –CH stretching, at 1722 for the carbonyl group, etc. ^{1}H NMR spectrum in DMSO-d_6 showed a sharp singlet at δ 2.40 ppm for the three protons of the methyl group and a singlet at δ 3.60 for the two protons of -S-CH_2-. A singlet appeared at δ 3.65 for the proton of >N-CH<, also a singlet was seen at δ 3.80 for the three protons of -OCH_3. A singlet appeared at δ 11.12 for >NH which was D_2O exchangeable. Its ^{13}C NMR spectrum showed signals at δ 17.50 ppm for the methyl carbon, at 43.50 for the carbon of >N-CH<, at 55.60 for the methoxy carbon, at 66.00 the carbon of -S-CH_2-, at 161.00 for the carbonyl carbon of the coumarin ring and at 181.50 for the carbonyl carbon of the thiazolidinone ring, etc. The mass spectrum showed molecular ion peak at M^+ 382 (36) along with the other peaks at m/z (%) 308 (31), 174 (61), 147 (42), 146 (15), etc.

While, the coumarin-6-ylhydrazine hydro-chlorides[11] **2a-d** were condensed with isatin *in situ* in boiling ethanol containing a few drops of glacial acetic acid for 3 hr to yield 1,2-dihydro-3-[coumarin-6-ylhydrazono]indol-2-ones **5a-d** (**Scheme** I). The IR spectrum of **5b** in KBr showed bands at 3441 cm^{-1} for the N-H stretching, at 3050 for C-H stretching, at 1700 for the carbonyl group, etc. ^{1}H NMR in DMSO-d_6 showed a sharp singlet at δ 2.36 ppm for the three protons of the methyl group. A singlet appeared at δ



1a- 6a : R_1= H, R_2= H, R_3=H
1b- 6b : R_1= H, R_2= CH_3, R_3= H
1c- 6c : R_1= CH_3, R_2= CH_3, R_3= H
1d- 6d : R_1= CH_3, R_2= OCH_3, R_3= H
3e, 4e : R_1= H, R_2= H, R_3= OCH_3
3f, 4f : R_1= H, R_2= CH_3, R_3= OCH_3
3g, 4g : R_1= CH_3, R_2= CH_3, R_3= OCH_3
3h, 4h : R_1= CH_3, R_2= OCH_3, R_3= OCH_3

Scheme I

11.12 for the >NH proton and a singlet was observed at δ 12.92 for the >NH of the indole ring; both the singlets were D_2O exchangeable. Its ^{13}C NMR showed signals at δ 17.00 ppm for the methyl carbon atom, at 160.00 for >C=N-, at 162.20 for the carbonyl carbon of the coumarin ring, and at 175.10 for the carbonyl carbon of the indole ring, etc.

Compounds **5a-d** on refluxing with mercaptoacetic acid in 1,4-dioxane for 6 hr in the presence of catalytic amount of anhydrous zinc chloride afforded N-[coumarin-6-ylamino]spiro-[3*H*-indole-(1*H*,2*H*)-3,2-(4*H*)-thiazolidine]-2,4-diones **6a-d** (**Scheme I**). The IR spectrum of **6b** in KBr showed bands at 3427 cm^{-1} for the N-H stretching, at 2922 and 2853 for the C-H stretching, at 1720 for the carbonyl group, etc. ^1H NMR in DMSO-d_6 showed a sharp singlet at δ 2.40 ppm for the three protons of the methyl group and a singlet at δ 3.60 for the two protons of -S–CH_2-. A singlet was observed at δ 11.12 for the >NH proton and a singlet at δ 12.92 for the >NH of the indole

ring; both the singlets were D_2O exchangeable. Its ^{13}C NMR showed signals at δ 17.00 ppm for the methyl carbon, at 42.00 for the spiro carbon atom, at 66.00 for the methylene carbon of the -S-CH_2- group, at 162.20 for the carbonyl of the coumarin ring, at 175.10 for the carbonyl of the indole ring and at 182.10 for the carbonyl of the thiazolidinone ring, etc. Its mass spectrum showed molecular ion peak M^+ 393 (52) along with the other peaks at m/z (%) 319 (32), 174 (51), 147 (39), 146 (15), etc.

Antimicrobial activity

All the above compounds **4a-h**, **5a-d**, and **6a-d** were screened for their antibacterial activity against *S. aureus,* and *S. typhi* and antifungal activity against *A. niger* and *C. albicans* (**Table I**). The minimum inhibitory concentration (MIC) was determined using tube dilution method according to the standard procedure[12]. DMF was used as a solvent and blank. Ciprofloxacin and Miconazole were used as the antibacterial and antifungal standards respectively. An examination of result reveals that all the compounds showed antimicrobial activity ranging from 50 μgm/ mL to 200 μgm/mL.

The presence of the methoxy group at the C-7 position and the methyl group at C-4 position of the coumarin ring such as in compound **5d** was found to be more effective at the concentration of 50 μgm/ mL against *S. typhi, A. niger* and *C. albicans* compared to the other compounds (**4a** to **6d**) of the same series. Similarly, the spiro compounds generally exhibit enhanced activity and thus compound **6d** showed activity at 50 μgm/ mL against *S. aureus, S. typhi, A. niger* and *C. albicans*.

Table I — Antimicrobial activity data (MIC μgm/mL) of compounds **4a-h, 5a-d,** and **6a-h**

Compd	Antibacterial activity		Antifungal activity	
	S.aureus	*S. typhi*	*A.niger*	*C.albicans*
4a	+	+	-	+
4b	+	+	-	++
4c	+++	+++	+	++
4d	+++	+++	++	+++
4e	++	+	-	-
4f	+++	+++	++	++
4g	+++	+++	+++	+++
4h	+++	+++	+++	+++
5a	++	+	++	++
5b	++	++	+++	++
5c	+++	+++	++++	++++
5d	+++	++++	++++	++++
6a	++	++	++	++
6b	++	+++	+++	+++
6c	+++	++++	++++	+++
6d	++++	++++	++++	++++
Ciprofloxacin	*	*		
Miconazole			*	*

Note: 200 μgm/mL = +, 150 μgm/mL =++, 100 μgm/mL = +++, 50 μgm/mL = ++++, - = Not active up to 200 μgm/mL, * = 5 μgm/mL.

Experimental Section

General. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer using KBr; ^1H NMR and ^{13}C NMR on Bruker AMX500 MHz using TMS as an internal standard (chemical shifts in δ, ppm), and mass spectra on a Shimadzu GC-MS. The homogeneity of the compounds was determined on the silica gel plates. The spots were developed in the iodine chamber. All the compounds gave satisfactory elemental analysis.

N-[7-Methylcoumarin-6-ylamino]-2-(4-methoxyphenyl)thiazolidine-4(*H*)-one 4f. Compound **3f** (0.01 mole, 3.08 g) was refluxed with mercaptoacetic acid (0.01 mole, 0.92 g) in the presence of catalytic amount of anhydrous $ZnCl_2$ in dry 1,4-dioxane (25 mL) for 7 hr. The mixture was then cooled and poured onto crushed ice and water. The product separated was filtered, dried and recrystallised from ethanol. Similarly, compounds **4a-e** and **4g-h** were prepared.

4a: Molecular formula, $C_{18}H_{14}N_2O_3S$, mp 179°C, yield 72%; IR (KBr): 3400, (N-H str.), 3070, 2919 (C-H str.), 1725 (>C=O), 1619, 1552, 1446, 1376, 1300, 1232, 1190, 1112, 1005 cm^{-1}.

4b: Molecular formula, $C_{19}H_{16}N_2O_3S$, mp 258°C, yield 70%; IR (KBr): 3400, (N-H str.), 3069, 2920 (C-H str.), 1721 (>C=O), 1622, 1552, 1446, 1376, 1300, 1232, 1190, 1112, 1005 cm^{-1}.

4c: Molecular formula, $C_{20}H_{18}N_2O_3S$, mp 260°C, yield 69%; IR (KBr): 3400, (N-H str.), 3070, 2921 (C-H str.), 1723 (>C=O), 1617, 1552, 1446, 1376, 1300, 1232, 1190, 1112, 1005 cm^{-1}.

4d: Molecular formula, $C_{20}H_{18}N_2O_4S$, mp 263°C, yield 66%; IR (KBr): 3355, (N-H str.), 3075, 2927 (C-H str.), 1721 (>C=O), 1618, 1525, 1522, 1450, 1373, 1307, 1236, 1127, 1114, 1011 cm^{-1}.

4e: Molecular formula, $C_{19}H_{16}N_2O_4S$, mp 199°C, yield 74%; IR (KBr): 3424, (N-H str.), 3073, 2925 (C-H stretching), 1722 (>C=O), 1616, 1545, 1525, 1451, 1377, 1300, 1261, 1174, 1114, 1012 cm^{-1}.

4f: Molecular formula, $C_{20}H_{18}N_2O_4S$, mp 160°C yield 64%; IR (KBr): 3424, (N-H str.), 3073, 2925 (C-H str.), 1722 (>C=O), 1616, 1545, 1515, 1451 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.40 (s, 3H, -CH_3), 3.60 (s, 2H, -S-CH_2-), 3.65 (s, 1H, >N-CH<), 3.80 (s, 3H, -OCH_3), 6.43 (d, *J*= 9.80Hz, 1H, C_3'-H), 6.90 (d, *J*= 7.50Hz, 2H, C_2'' -H and C_6''-H), 7.32 (s, 1H, C_5'-H), 7.60 (d, *J*= 7.50Hz, 2H, C_3''-H and C_5''-H), 7.90 (s, 1H, C_8'-H), 8.11 (d, *J*= 9.80Hz, 1H, C_4'-H), 11.12 (s, 1H, >NH, D_2O exchangeable); ^{13}C NMR: δ 17.50 (-CH_3), 43.50 (>N-CH<), 55.60 (-OCH_3), 66.00 (-S-CH_2-), 114.00 (C_2'' and C_6''), 116.00 (C_3'), 118.0 0 (C_{4a}'), 129.00 (C_3'' and C_5''), 144.00 (C_4'), 148.18 (C_6'), 153.19 (C_7'), 154.00 (C_{8a}'), 160.00 (C_4''), 161.00 (coumarin >C=O), 181.50 (thiazolidinone >C=O), 120.00 -138.00 (2 Ar-C); Mass (m/z) (%): M^+ 382 (36), 308 (31) (M-CH_2COS), 174 (61) (M-CH_2COS-C_8H_8NO), 147 (42) (M-CH_2COS-C_8H_8NO-HCN), 146 (15) (M-CH_2COS-C_8H_8NO-HCN-H), 134 (53) (M-CH_2COS-$C_{10}H_8NO_2$), 118 (22) (M-CH_2COS-C_8H_8NO-HCN-H-CO), 107 (48) (M-CH_2COS-$C_{10}H_8NO_2$-HCN), 90 (13) (M-CH_2COS-C_8H_8NO-HCN-H-CO-CO), 77 (100) (M-CH_2COS-$C_{10}H_8NO_2$-HCN-HCHO).

4g: Molecular formula, $C_{21}H_{20}N_2O_4S$, mp 256°C, yield 66%; IR (KBr): 3390, (N-H str.), 3080, 2912 (C-H str.), 1720 (>C=O), 1619, 1551, 1522, 1445, 1382, 1262, 1195, 1107, 1025 cm^{-1}.

4h: Molecular formula, $C_{21}H_{20}N_2O_5S$, mp 265°C, yield 73%; IR (KBr): 3379, (N-H str.), 3080, 2912 (C-H str.), 1719 (>C=O), 1617, 1570, 1495, 1382, 1262, 1221, 1117, 1025 cm^{-1}.

1,2-Dihydro-3-[7-methylcoumarin-6-ylhydrazono]indol-2-one 5b. To the suspension of coumarin-6-ylhydrazine hydrochloride **2b** in ethanol (25 mL) was added isatin (0.01 mole, 1.47 g) and catalytic amount of glacial acetic acid (3-4 drops) and the reaction mixture was refluxed on a water-bath for 3 hr. The mixture was then cooled and poured onto crushed ice and water. The product separated was filtered, dried and recrystallised from ethanol. Similarly, compounds **5a** and **5c-d** were prepared.

5a: Molecular formula, $C_{17}H_{11}N_3O_3$, mp 183°C, yield 82%; IR (KBr): 3400 (N-H str.), 3025 (C-H str.), 1721 (>C=O), 1610, 1552, 1462, 1383, 1290 cm^{-1}.

5b: Molecular formula, $C_{18}H_{13}N_3O_3$, mp 199°C, yield 80%; IR (KBr): 3441, (N-H str.), 3050 (C-H str.), 1700 (>C=O), 1619, 1560, 1455, 1420, 1341 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.36 (s, 3H, -CH_3), 6.44 (d, *J*= 9.80Hz, 1H, C_3'-H), 6.94 (d, *J*= 8.00Hz, 1H, C_4-H), 7.07 (t, 1H, C_5-H), 7.26 (t, 1H, C_6-H), 7.32 (s, 1H, C_5'-H), 7.57 (d, *J*= 8.00Hz, 1H, C_7-H), 7.90 (s, 1H, C_7'-H), 8.11 (d, *J*= 9.80Hz, 1H, C_4'-H), 11.12 (s, 1H, >NH, D_2O exchangeable), 12.92 (s, 1H, indole >NH, D_2O exchangeable); ^{13}C NMR: δ 17.00 (-CH_3), 116.00 (C_3'), 118.01 (C_{4a}'), 144.01 (C_4'), 148.18 (C_6'), 153.19 (C_7'), 154.00 (C_{8a}'), 160.00 (>N=C<), 162.20 (coumarin >C=O), 175.10 (indole >C=O) and 120.00-138.00 (8 Ar-C).

5c: Molecular formula, $C_{19}H_{15}N_3O_3$, mp 186°C, yield 81%; IR (KBr): 3409, (N-H str.), 3050 (C-H str.), 1717 (>C=O), 1613, 1562, 1461, 1395, 1311 cm^{-1}.

5d: Molecular formula, $C_{19}H_{15}N_3O_4$, mp 194°C, yield 79%; IR (KBr, cm^{-1}): 3400, (N-H str.), 3063 (C-H str.), 1724 (>C=O), 1615, 1551, 1450, 1377, 1299 cm^{-1}.

N-[7-Methylcoumarin-6-ylamino]spiro-[3*H*-indole-(1*H*,2*H*)-3,2-(4*H*)-thiazolidine]-2,4-dione 6b. Compound **5b** (0.01 mole, 3.19 g) and mercaptoacetic acid (0.01 mole, 1.84 g) were refluxed in the presence of catalytic amount of anhydrous $ZnCl_2$ in dry 1,4-dioxane (25 mL) for 6 hr. The mixture was then cooled and poured onto crushed ice and water. The product separated was filtered, dried and recrystallised from ethanol. Similarly, compounds **6a** and **6c-d** were prepared.

6a: Molecular formula, $C_{19}H_{13}N_3O_4S$, mp 220°C, yield 80%; IR (KBr): 3407, (N-H str.), 2920 and 2850 (C-H str.), 1724 (>C=O), 1612, 1552, 1462, 1405 cm^{-1}.

6b: Molecular formula, $C_{20}H_{15}N_3O_4S$, mp 242°C, yield 77%; IR (KBr): 3427, (N-H str.), 2922 and 2853 (C-H str.), 1720 (>C=O), 1610, 1551, 1458, 1400 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.40 (s, 3H, –CH_3), 3.60 (s, 2H, S–CH_2), 6.44 (d, *J*= 9.80Hz, 1H, C_3'-H), 6.94 (d, *J*= 8.00Hz, 1H, C_4-H), 7.07 (t, 1H, C_5-H), 7.26 (t, 1H, C_6-H), 7.32 (s, 1H, C_5'-H), 7.57 (d, *J*= 8.00Hz, 1H, C_7-H), 7.90 (s, 1H, C_7'-H), 8.11 (d, *J*= 9.80Hz, 1H, C_4'-H), 11.12 (s, 1H, >NH, D_2O exchangeable), 12.92 (s, 1H, indole >NH, D_2O exchangeable); ^{13}C NMR: δ 17.00 (-CH_3), 42.00 (spiro C-atom), 66.00 (-S-CH_2-), 116.00 (C_3'), 118.01 (C_{4a}'), 144.01 (C_4'), 148.18 (C_6'), 153.19 (C_7'), 154.00 (C_{8a}'), 162.20 (coumarin >C=O), 175.10 (indole >C=O), 182.10 for the (thiazolidinone >C=O), 120.00-138.00 (8 Ar-C); Mass (m/z) (%): M^+ 393

(52), 319 (32) (M-CH_2COS), 174 (51) (M-CH_2COS-$C_8H_5N_2O$), 147 (39) (M-CH_2COS-$C_8H_5N_2O$-HCN), 146 (15) (M-CH_2COS-$C_8H_5N_2O$-HCN-H), 145 (22) (M-CH_2COS-$C_{10}H_8NO_2$), 118 (36) (M-CH_2COS-$C_8H_5N_2O$-HCN-H-CO), 102 (17) (M-CH_2COS-$C_{10}H_8NO_2$-HNCO), 90 (44) (M-CH_2COS-$C_8H_5N_2O$-HCN-H-CO-CO), 76 (100) (M-CH_2COS-$C_{10}H_8NO_2$-HNCO-CN).

6c: Molecular formula, $C_{21}H_{17}N_3O_4S$, mp 235°C, yield 83%; IR (KBr): 3355, (N-H str.), 2925 and 2855 (C-H str.), 1718 (>C=O), 1613, 1562, 1460, 1421 cm^{-1}.

6d: Molecular formula, $C_{21}H_{17}N_3O_5S$, mp 213°C, yield 84%; IR (KBr): 3400, (N-H str.), 2921 and 2851 (C-H str.), 1723 (>C=O), 1616, 1567, 1467, 1439 cm^{-1}.

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