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Chemoselective Knoevenagel reaction as a novel route for the synthesis of biscoumarinyl methylsulphones and 4+1, 1+4 approach synthesis of aminooxadiazolyl and N-(2,5-dimethyl)pyrrolylcoumarins

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4-Bromomethylcoumarins **1** on reaction with thiourea gives 4-mercaptomethyl coumarins **2**, which on further reaction with ethyl chloroacetate afford the corresponding sulphide esters **3a-c**. The sulphone esters **3d-f** which are obtained upon oxidation of compounds **3a-c**, undergo cyclisation with salals through Knoevenagel reaction to furnish biscoumarins **4** in good yield. Also esters **3a-f** on reaction with hydrazine hydrate (99.9%) give the corresponding carbohydrazides **5**. Compounds **5** when reacted separately with cyanogen bromide and acetonyl acetone yield aminooxadiazolyl **6** and N-(2,5-dimethyl)pyrrolylcoumarins **7**, respectively. The compounds have been characterized by elemental analysis, IR, ^{1}H NMR, mass and 2D-HOMO COSY data. All the newly synthesized compounds have been screened for antimicrobial activity against gram-ve bacterium *Escherishia coli*, gram+ve bacterium *Bacillus staphylococci* and fungi *penicillium* and *Aspergillus*.

Keywords: Knoevenagel reaction, bromomethylcoumarins, cyanogen bromide, acetonyl acetone, antimicrobial activity

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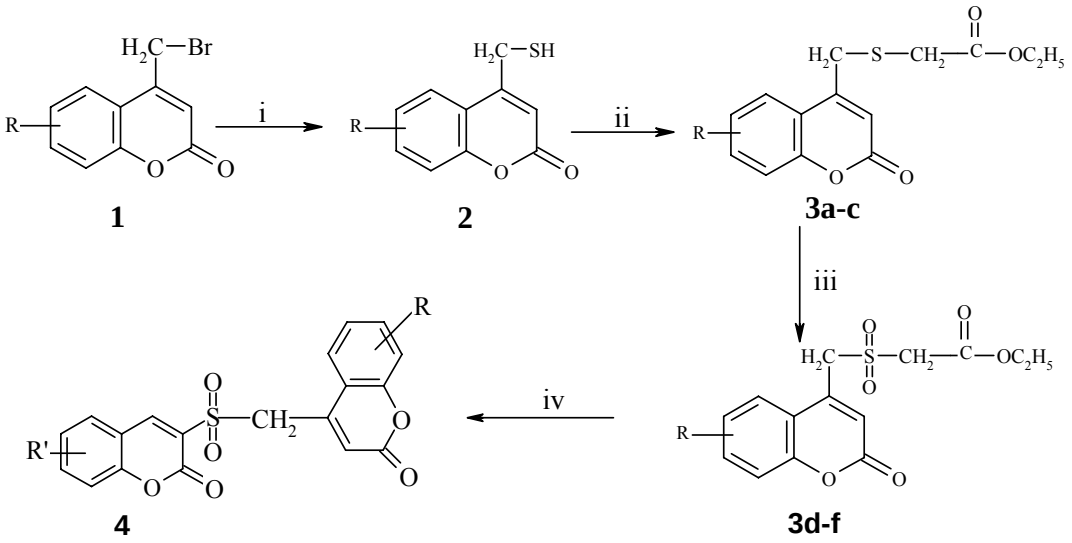
Compounds containing two coumarin moieties have been found to be extremely useful as anticoagulants, antimicrobials[1] and triplet sensitisers[2]. Bhattacharya *et. al.*[3] have isolated biscoumarinyl ether "Lasiocephalin[4]" from the roots of *Lasiocephonerio-cephalus*, the structure of which was deduced by Vishwanath *et. al*[5]. An important feature of this compound is the presence of an aryl ether linkage between C_7 and C_6 position of the two moieties. On the other hand oxadiazoles and pyrroles have been found to exhibit wide ranging pharmacological properties[6-9]. The present communication reports the multi-step synthesis of biscoumarins linked by C_4 and C_3 position of the two coumarin moieties via methylene sulphone bridge and in continuation of our work on 4-sulphonamidomethyl[10-14] and 4-dichloroacetamidomethyl[15] coumarins, it was thought of considerable interest to synthesise the title compounds.

The required 4-bromomethylcoumarin **1** has been systhesised by the Pechmann cyclisation of various phenols with γ-bromoethylacetoacetate. Compounds **1** on reaction with thiourea resulted in the formation of 4-mercaptomethylcoumarins **2**, which on further reaction with ethyl chloroacetate gave the corresponding sulphide esters **3a-c**.

The attempted cyclisation of sulphide esters **3a-c** with salals did not result in the formation of biscoumarinyl methyl sulphides, this is due to the poor reactivity of two methylene groups. The sulphone esters **3d-f** which are obtained upon oxidation of compounds **3a-c**, undergo cyclisation with salals through Knoevenagel reaction to furnish biscoumarins **4** in good yield (**Scheme I, Table I**). The synthetic potential of resulting sulphanyl/-sulphonyl acetic acid hydrazide derivatives **5** has been utilized in two ways. In one case cyanogen bromide has been used as a source of single carbon and carbohydrazide acts as a source of four atoms reacting through its enol form generating the amino oxadiazole derivatives **6**. In the second case double electrophilic character of acetonyl acetone and the enhanced nucleophilicity of the ^{1}N-nitrogen of the carbo-hydrazide have been used to synthesise 2,5-dimethyl-pyrroles **7 (Scheme II, Table II)**. The newly synthe-sised compounds were characterised by analytical (**Tables I** and **II**) and spectral data (**Tables III** and **IV**). The results of antimicrobial screening revealed



Scheme I

Table I — Physical and analytical data of compounds **2a-c**, **3a-f** and **4a-l**

Compd	R	R'	m.p. ºC	Yield (%)	Mol.formula	Found (Calcd) %		
						C	H	N
2a	6-CH_3	-	132	89	$C_{11}H_{10}O_2S$	64.05 (64.07	4.83 4.85	- -)
2b	7-CH_3	-	179	86	$C_{11}H_{10}O_2S$	64.06 (64.07	4.84 4.85	- -)
2c	7,8-Benzo	-	165	95	$C_{14}H_{10}O_2S$	69.41 (69.42	4.11 4.13	- -)
3a	6-CH_3	-	95	84	$C_{15}H_{16}O_4S$	61.66 (61.64	5.46 5.47	- -)
3b	7-CH_3	-	88	82	$C_{15}H_{16}O_4S$	61.66 (61.64	5.47 5.47	- -)
3c	7,8-Benzo	-	99	85	$C_{18}H_{16}O_4S$	65.86 (65.85	4.88 4.87	- -)
3d	6-CH_3	-	171	90	$C_{15}H_{16}O_6S$	55.54 (55.55	4.90 4.93	- -)`
3e	7-CH_3	-	160	88	$C_{15}H_{16}O_6S$	55.54 (55.55	4.90 4.93	- -)
3f	7,8-Benzo	-	205	95	$C_{18}H_{16}O_6S$	59.99 (60.00	4.43 4.44	- -)
4a	6-CH_3	H	225	80	$C_{20}H_{14}O_6S$	62.80 (62.82	3.64 3.66	- -)
4b	6-CH_3	7-$N(C_2H_5)_2$	235	71	$C_{24}H_{23}N_3O_6S$	63.55 (63.57	5.04 5.07	3.07 3.09)

— Contd

Table I — Physical and analytical data of compounds **2a-c**, **3a-f** and **4a-l** — *Contd*

Compd	R	R'	m.p. ºC	Yield (%)	Mol.formula	Found (Calcd) % C	H	N
4c	6-CH_3	5,6-Benzo	285	85	$C_{24}H_{16}O_6S$	66.64 (66.66	3.69 3.70	- -)
4d	6-CH_3	6-CH_3	290	82	$C_{21}H_{16}O_6S$	63.60 (63.63	4.02 4.04	- -)
4e	7-CH_3	H	260	83	$C_{20}H_{14}O_6S$	62.81 (62.82	3.65 3.66	- -)
4f	7-CH_3	7-$N(C_2H_5)_2$	220	74	$C_{24}H_{23}NO_6S$	63.54 (63.57	5.05 5.07	3.06 3.09)
4g	7-CH_3	5,6-Benzo	270	83	$C_{24}H_{16}O_6S$	66.65 (66.66	3.69 3.70	- -)
4h	7-CH_3	6-CH_3	250	80	$C_{21}H_{16}O_6S$	63.61 (63.63	4.01 4.04	- -)
4i	7,8-Benzo	H	260	80	$C_{23}H_{14}O_6S$	66.00 (66.02	3.32 3.34	- -)
4j	7,8-Benzo	7-$N(C_2H_5)_2$	265	71	$C_{27}H_{23}NO_6S$	66.23 (66.25	4.69 4.70	2.82 2.80)
4k	7,8-Benzo	5,6-Benzo	>300	82	$C_{27}H_{16}O_6S$	69.21 (69.23	3.39 3.41	- -)
4l	7,8-Benzo	6-CH_3	270	79	$C_{24}H_{16}O_6S$	66.65 (66.66	3.68 3.70	- -)

*Compounds **2** and **4** were recrystallised from ethanol dioxan mixture whereas compound **3** were recrystallised from benzene pet.ether mixture

that majority of the newly synthesised biscoumarins exhibited moderate activity compared to the standard.

Results and Discussion

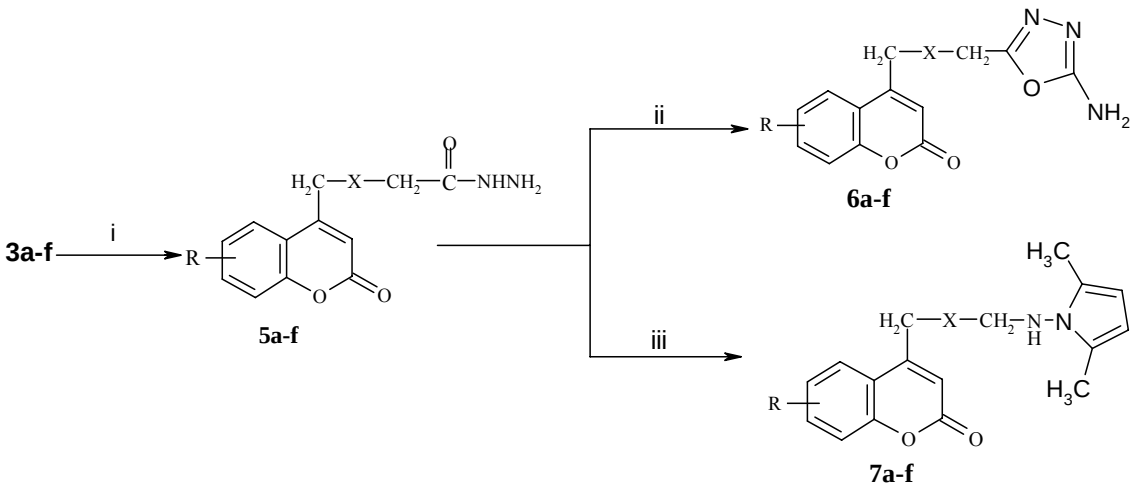
The IR spectrum of compound **2a** (R = 6-CH_3) exhibited characteristic lactone carbonyl stretching vibration of coumarin at 1716 cm^{-1} and stretching vibrations of –SH, C=C and C-O-C were observed at 2568, 1574 and 1192 cm^{-1}, respectively. The ^{1}H NMR spectrum of **2a** displayed a triplet at δ 1.89 due to –SH (D_2O exchangeable), doublet at δ 3.81 due to C_4-CH_2 of coumarin and singlet was observed at δ 3.81. The 6-CH_3, C_3-H, C_5-H, C_7-H and C_8-H protons of coumarin were found to resonate at δ 2.44, 6.46, 7.42, 7.35 and 7.25, respectively (**Table III**).

The mass spectrum by electron ionisation (EI) has been recorded for the compound **2a**, the molecular ion peak was observed at m/z 206 (83%) and base peak at m/z 145 (100%).

The IR spectrum of compound **3a** (R = 6-CH_3) exhibited two carbonyl stretching vibrations at 1727 and 1705 cm^{-1} due to ester carbonyl and lactone carbonyl of coumarin whereas stretching vibrations of C=C and C-O-C were observed at 1574 and 1170 cm^{-1}, respectively (**Table III**). The ^{1}H NMR spectrum of **3a** displayed triplet at δ 1.31 due to ester-CH_3 and quartet at δ 4.22 due to -OCH_2, whereas three singlets at δ 2.44, 3.20 and 3.96 due to 6-CH_3, S-CH_2 and C_4-CH_2 of coumarin, respectively. The C_3-H, C_5-H, C_7-H and C_8-H protons of coumarin were found to resonate at δ 6.42, 7.48, 7.37 and 7.26, respectively (**Table III**).

The IR spectrum of compound **3d** (R = 6-CH_3) exhibited lactone carbonyl stretching vibration of coumarin at 1732 cm^{-1} whereas stretching vibrations of C=C, C-O-C and SO_2 were observed at 1569, 1153 and 1317 cm^1, respectively (**Table III**). The ^{1}H NMR spectrum **3d** displayed triplet at δ 1.38 due to ester-CH_3 and quartet at δ 4.36 due to –OCH_2, whereas three singlets at δ 2.45, 4.08 and 4.79 due to 6-CH_3, SO_2-CH_2 and C_4-CH_2 of coumarin, respectively. The C_3-H, C_8-H, C_7-H and C_5-H of coumarin were found to resonate at δ 6.68, 7.28, 7.41 and 7.59, respectively (**Table III**).

The IR spectrum of compound **4h** exhibited the characteristic lactone carbonyl stretching vibration of



i. $N_2H_4.H_2O$ (99.9%)/EtOH, ii. CNBr/CH_3OH/60°C, iii $(CH_3COCH_2)_2$/EtOH
R = 6-CH_3, 7-CH_3 and 7,8-Benzo; X = S, SO_2

Scheme II

Table II — Physical and analytical data of compounds **5a-f**, **6a-f** and **7a-f**

Compd	R	m.p. ºC	Yield (%)	Mol.formula	Found (Calcd) % C	H	N
5a	6-CH_3	155	60	$C_{13}H_{14}N_2O_3S$	56.09 (56.11	5.01 5.03	10.05 10.07)
5b	7-CH_3	150	62	$C_{13}H_{14}N_2O_3S$	56.12 (56.11	5.02 5.03	10.06 10.07)
5c	7,8-Benzo	190	65	$C_{16}H_{14}N_2O_3S$	61.15 (61.12	4.44 4.45	10.91 9.93)
5d	6-CH_3	240	92	$C_{13}H_{14}N_2O_5S$	50.30 (50.32	4.53 4.51	8.89 8.91)
5e	7-CH_3	228	93	$C_{13}H_{14}N_2O_5S$	50.30 (50.32	4.52 4.52	8.90 8.91)
5f	7,8-Benzo	248	95	$C_{16}H_{14}N_2O_5S$	55.47 (55.49	4.02 4.04	9.03 9.03)
6a	6-CH_3	210	87	$C_{14}H_{13}N_3O_3S$	55.42 (55.44	4.02 4.02	8.07 8.09)
6b	7-CH_3	205	86	$C_{14}H_{13}N_3O_3S$	55.43 (55.44	4.00 4.02	8.08 8.09)
6c	7,8-Benzo	228	87	$C_{17}H_{13}N_3O_3S$	50.16 (50.17	3.80 3.83	13.83 13.86)
6d	6-CH_3	230	80	$C_{14}H_{13}N_3O_5S$	50.13 (50.14	3.86 3.88	12.36 12.38)
6e	7-CH_3	213	78	$C_{14}H_{13}N_3O_5S$	50.12 (50.14	3.87 3.88	12.37 12.38)
6f	7,8-Benzo	237	80	$C_{17}H_{13}N_3O_5S$	54.96 (54.98	3.49 3.50	11.31 11.32)
7a	6-CH_3	190	70	$C_{19}H_{20}N_2O_3S$	64.02 (64.04	5.61 5.61	7.85 7.86)
7b	7-CH_3	128	73	$C_{19}H_{20}N_2O_3S$	64.03 (64.04	5.60 5.61	7.86 7.86)

— *Contd*

Table II — Physical and analytical data of compounds **5a-f**, **6a-f** and **7a-f** — *Contd*

Compd	R	m.p. ºC	Yield (%)	Mol.formula	Found (Calcd) % C	H	N
7c	7,8-Benzo	145	80	$C_{20}H_{20}N_2O_3S$	67.32 (67.34	5.09 5.10	7.13 7.14)
7d	6-CH_3	150	85	$C_{19}H_{20}N_2O_5S$	58.54 (58.56	5.14 5.15	7.19 7.21)
7e	7-CH_3	135	83	$C_{19}H_{20}N_2O_5S$	58.75 (58.76	5.13 5.15	7.20 7.21)
7f	7,8-Benzo	198	87	$C_{22}H_{20}N_2O_5S$	62.25 (62.26	4.70 4.71	6.59 6.60)

*All the above compounds were recrystallised from 1:1 ethanol-dioxan mixture.

Table III – IR and ^{1}H NMR data of compounds **2a-c, 3a-f** and **4a- 4l**

Compd	R	R'	$\upsilon_{C=O}$ cm^{-1} Lactone	υ_{SO2} cm^{-1}	^{1}H NMR (δ, ppm, 300 MHz)
2a	6-CH_3	-	1716	-	1.89 (t, *J*=7.1Hz, 1H, -SH), 2.44 (s, 3H, 6-CH_3), 3.81 (d, *J*=7.2 Hz, 2H, C_4-CH_2), 6.46 (s, 1H, C_3-H), 7.42 (s, 1H, C_5-H), 7.35 (dd, *J*=8.4 1.4 Hz, 1H, C_7-H), 7.25 (d, *J*=8.7 Hz, 1H, C_8-H).
2b	7-CH_3	-	1727	-	1.89 (t, *J*=7.1 Hz, 1H, -SH), 2.46 (s, 3H, 7-CH_3), 3.82 (d, *J*=7.2 Hz, 2H, C_4-CH_2), 6.42 (s, 1H, C_3-H), 7.54 (d, *J*=7.8 Hz, 1H, C_5-H), 7.15 (d, *J*=8.1 Hz, 1H, C_6-H), 7.43 (s, 1H, C_8-H).
2c	7,8-Benzo	-	1705	-	2.06 (t, *J*=7.1 Hz, 1H, -SH), 4.26 (d, *J*=7.2 Hz, 2H, C_4-CH_2), 6.61(s, 1H, C_3-H), 7.28-8.46 (m, 6H, Ar-H).
3a	6-CH_3	-	1705 & 1727	-	1.31 (t, *J*=7.1 Hz, 3H, est-CH_3), 2.44 (s, 3H, 6-CH_3), 3.20 (s, 2H, S-CH_2), 3.96 (s, 2H, C_4-CH_2), 4.22 (q, *J*=7.1 Hz, 2H, -OCH_2), 6.42 (s, 1H, C_3-H), 7.48 (s, 1H, C_5-H), 7.37 (d, *J*=8.4 Hz, 1H, C_7-H), 7.26 (d, *J*=8.4 Hz, C_8-H).
3b	7-CH_3	-	1705 & 1732	-	1.38 (t, *J*=7.1 Hz, 3H, est-CH_3), 2.46 (s, 3H, 7-CH_3), 3.29 (s, 2H, S-CH_2), 3.94 (s, 2H, C_4-CH_2), 4.24 (q, *J*=7.1 Hz, 2H, -OCH_2), 6.42 (s, 1H, C_3-H), 7.59 (d, *J*=8.1 Hz, 1H, C_5-H), 7.13 (d, *J*=7.8 Hz, 1H, C_6-H), 7.16 (s, 1H, C_8-H).
3c	7,8-Benzo	-	1711	-	1.32 (t, *J*=7.1 Hz, 3H, est-CH_3) 3.22 (s, 2H, S-CH_2), 4.05 (s, 2H, C_4-CH_2), 4.23 (q, *J*=7.1 Hz, 2H, -OCH_2), 6.51 (s, 1H, C_3-H), 7.64-8.59 (m, 6H, Ar-H).
3d	6-CH_3	-	1732	1317	1.38 (t, 3H, est.-CH_3, *J*=7.1 Hz), 2.45 (s, 3H, 6-CH_3), 4.08 (s, 2H, SO_2-CH_2), 4.26 (q, 2H, -OCH_2), 4.79 (s, 2H, C_4-CH_2), 6.68 (s, 1H, C_3-H), 7.59 (s, 1H, C_5-H), 7.41 (d, *J*=8.1 Hz, 1H, C_7-H), 7.28 (d, *J*=7.8 Hz, 1H, C_8-H).
3e	7-CH_3	-	1732 & 1711	1328	1.36 (t, 3H, est.-CH_3, *J*=7.1 Hz), 2.47 (s, 3H, 7-CH_3), 4.07 (s, 2H, SO_2-CH_2), 4.31 (q, *J* =7.1 Hz, 2H, -OCH_2), 4.79 (s, 2H, C_4-CH_2), 6.67 (s, 1H, C_3-H), 7.88 (d, *J*=8.1 Hz, 1H, C_5-H), 7.30 (s, 1H, C_8-H), 7.28 (d, *J*=7.8 Hz, 1H, C_6-H).
3f	7,8-Benzo	-	1705	1323	1.40 (t, *J*=7.1 Hz, 3H, est.-CH_3), 4.26 (q, *J*=7.1 Hz, 2H, O-CH_2), 4.68 (s, 2H, SO_2-CH_2), 5.13 (s, 2H, C_4-CH_2), 6.68 (s, 1H, C_3-H), 7.73-8.39 (m, 3H, Ar-H).
4a	6-CH_3	H	1738	1317	2.46 (s, 3H, 6-CH_3), 4.97 (s, 2H, C_4-CH_2), 6.48 (s, 1H, C_3-H), 8.58 (s, 1H C_4-H), 7.22-7.78 (m, 7H, Ar-H).
4b	6-CH_3	7-N(C_2H_5)$_2$	1716	1339	1.26 (t, *J*=7.1 Hz, 6H, two -CH_3), 2.44 (s, 3H, 6-CH_3), 3.51 (q, *J* =7.1 Hz, 4H, N-CH_2), 4.92 (s, 2H, C_4-CH_2), 6.46 (s, 1H, C_3-H), 8.31 (s, 1H, C_4-H), 7.19-7.72 (m, 6H, Ar-H).

— Contd

Table III – IR and ^{1}H NMR data of compounds **2a-c, 3a-f** and **4a- 4l**--*Contd*

Compd	R	R'	$\upsilon_{C=O}$ cm^{-1} Lactone	υ_{SO2} cm^{-1}	^{1}H NMR (δ, ppm, 300 MHz)
4c	6-CH_3	5,6-Benzo	1722	1295	2.45 (s, 3H, 6-CH_3), 5.13 (s, 2H, C_4-CH_2), 6.57 (s, 1H, C_3-H), 9.36 (s, 1H, C_4-H), 7.21-8.47 (m, 9H, Ar-H).
4d	6-CH_3	6-CH_3	1743	1312	2.45 and 2.47 (2s, 6H, Ar-CH_3), 5.06 (s, 2H, C_4-CH_2), 6.72 (s, 1H, C_3-H), 8.67 (s, 1H, C_4-H), 7.32-7.75 (m, 6H, Ar-H).
4e	7-CH_3	H	1732	1312	2.46 (s, 3H, 7-CH_3), 4.96 (s, 2H, C_4-CH_2), 6.43 (s, 1H, C_3-H), 8.57 (s, 1H, C_4-H), 7.15-7.81 (m, 7H, Ar-H).
4f	7-CH_3	7-N(C_2H_5)$_2$	1732	1335	1.26 (t, *J*=7.1 Hz, 6H, two-CH_3), 2.45 (s, 3H, 7-CH_3), 3.50 (q, *J*=7.1 Hz, 4H, N-CH_2), 4.90 (s, 2H, C_4- CH_2), 6.40 (s, 1H, C_3-H), 8.30 (s, 1H, C_4-H), 7.12-7.85 (m, 6H, Ar-H).
4g	7-CH_3	5,6-Benzo	1738	1313	2.46 (s, 3H, 7-CH_3), 5.10 (s, 2H,C_4-CH_2), 6.58 (s, 1H, C_3-H), 9.36 (s, 1H, C_4-H), 7.18-8.49 (m, 9H, Ar-H).
4h	7-CH_3	6-CH_3	1732	1317	2.45 (s, 6H, Ar-CH_3), 5.04 (s, 2H, C_4-CH_2), 6.46 (s, 1H, C_3-H), 8.72 (s, 1H, C_4-H), 7.14-7.85 (m, 6H, Ar-H).
4i	7,8-Benzo	H	1738	1312	5.13 (s, 2H, C_4-CH_2), 6.63 (s, 1H, C_3-H), 8.73 (s, 1H, C_4-H), 7.42-8.53 (m, 10H, Ar-H).
4j	7,8-Benzo	7-N(C_2H_5)$_2$	1727	1306	1.26 (t, *J*=7.1 Hz, 6H two-CH_3), 3.49 (q, *J*=7.1 Hz, 4H, N-CH_2), 5.01 (s, 2H, C_4-CH_2), 6.51(s, 1H, C_3-H), 8.50 (s, 1H, C_4-H), 7.37-8.52 (m, 9H, Ar-H).
4k	7,8-Benzo	5,6-Benzo	1722	1315	5.19 (s, 2H, C_4-CH_2-), 6.53 (s, 1H, C_3-H), 8.60(s, 1H, C_4-H), 7.55-8.59 (m, 12H, Ar-H).
4l	7,8-Benzo	6-CH_3	1732	1312	2.43 (s, 3H, 6-CH_3), 5.14 (s, 2H, C_4-CH_2), 6.63 (s, 1H, C_3-H), 8.70 (s, 1H, C_4-H), 7.35-8.50 (m, 9H, Ar-H).

In compound **2a- c,** SH were D_2O exchanged

coumarin at 1732 cm^{-1} whereas stretching vibrations of C=C, -SO_2 and C-O-C were observed at 1569, 1317 and 1153 cm^{-1}, respectively (**Table III**). The ^{1}H NMR spectrum **4h** displayed two singlets at δ 2.46 and 5.04 due to two aromatic -CH_3 groups and C_4-CH_2 of coumarin, respectively, whereas singlet at δ 6.46 due to C_3-H of coumarin and C_4-H of coumarin were found to resonate to δ 8.72. The aromatic protons were found to resonate in the range δ 7.14-7.85 (**Table III**). Further, the proton-proton coupling has been studied by 2-D HOMO COSY spectrum which displayed two singlets at δ 2.40 and 2.46 due to 6-CH_3 and 7'-CH_3 of coumarin, and another singlet at δ 5.10 due to C_4-CH_2 of coumarin whereas C_3'-H of coumarin at δ 6.50, C_4-H at δ 8.90, doublet at δ 7.24 due to C_8-H and C_8'-H, and another doublet at δ 7.44 due to C_6'-H, doublet of doublet at δ 7.65 due to C_7-H, singlet at δ 7.84 due to C_5-H and doublet at δ 7.87 due to C_5'-H.

The IR spectrum of compound **5b** exhibited the characteristic lactone carbonyl stretching band of coumarin at 1710 cm^{-1} and amide carbonyl at 1644 cm^{-1}. The bands at 3342 and 3305 cm^{-1} were due to asymmetric and symmetric stretching vibration of NH_2, whereas stretching vibrations of =C-H and C-O-C were observed at 3049 and 1153 cm^{-1}, respectively (**Table IV)**. Its ^{1}H NMR spectrum displayed three singlets at δ 2.54, 3.14 and 3.97 attributed to 7-CH_3, S-CH_2 and C_4-CH_2 protons of coumarin. The C_3-H of coumarin was found to resonate at δ 6.43 as a singlet, C_5-H at δ 7.60 as a doublet whereas C_6-H and C_8-H at δ 7.13 as a overlapping doublet. The -NH and -NH_2 protons of carbohydrazide were found to resonate at δ 9.10 and 3.52 and have been D_2O exchanged (**Table IV**).

IR spectrum of compound **6a** exhibited the characteristic lactone carbonyl of coumarin at 1719 cm^{-1} and peaks at 3325 and 3127 cm^{-1} due to asymmetric and symmetric stretching vibration of –NH whereas =C-H and C-O-C were observed at 2924 and 1194 cm^{-1}, respectively (**Table IV)**. Its ^{1}H NMR spectrum displayed three singlets at δ 2.43, 3.73 and 3.92 due to 6-CH_3, S-CH_2 and C_4-CH_2 of coumarin. The C_3-H of coumarin was found to resonate at δ 6.49 as a singlet, C_5-H at δ 7.77 as singlet, C_7-H at δ 7.37 as a doublet and C_8-H at δ 7.22 as doublet. The -NH_2 protons of oxadiazole were found to resonate at δ 6.76 as a broad singlet, disappeared on addition of D_2O (**Table IV**).

Table IV – IR and ^{1}H NMR data of compounds **5a- f, 6a- f** and **7a-f**

Compd	R	$\upsilon_{NH\ cm^{-1}}$ Asym	Sym	$\upsilon_{C=O\ cm^{-1}}$ Lactone	Amide	^{1}H NMR (δ, ppm, 300 MHz)
5a	6-CH_3	3305	3289	1727	1645	2.43 (s, 3H, 6-CH_3), 3.15 (s, 2H, S-CH_2), 3.99 (s, 2H, C_4-CH_2), 6.48 (s, 1H, C_3-H), 7.21 (d, *J*=8.4 Hz, 1H, C_8-H), 7.36 (dd, *J*=1.5 and 9Hz, 1H, C_7-H), 7.52 (d, *J*=1.4 Hz, 1H, C_5-H), 9.16 (br, 1H, CONH), 3.06 (br, 2H, NH_2).
5b	7-CH_3	3305	3290	1710	1644	2.45 (s, 3H, 7-CH_3), 3.15 (s, 2H, S-CH_2), 3.97 (s, 2H, C_4-CH_2) 6.43 (s, 1H, C_3-H), 7.13 (d, *J*=6.3 Hz, 2H, C_6-H and C_8-H), 7.60 (d, *J*=8.4 Hz, 1H, C_5-H), 3.52 (br, 2H, NH_2), 9.10 (br, 1H, $CONH_2$).
5c	7,8-Benzo	3311	3278	1716	1645	3.16 (s, 2H, S-CH_2), 4.09 (s, 2H, C_4-CH_2), 6.58 (s, 1H, C_3-H), 7.61-8.51 (m, 6H, Ar-H), 3.46 (br, 2H, NH_2), 9.20 (br, 1H, -CONH).
5d	6-CH_3	3295	3267	1711	1645	2.46 (s, 3H, 6-CH_3), 4.14 (s, 2H, SO_2-CH_2), 4.95 (s, 2H, C_4-CH_2), 6.63 (s, 1H, C_3-H), 7.25 (d, *J*=8.4 Hz, 1H, C_8-H), 7.35 (d, *J*=8.7 Hz, 1H, C_7-H), 7.50 (s, 1H, C_5-H), 9.80 (br, 1H, -CONH).
5e	7-CH_3	3284	3262	1716	1650	2.45 (s, 3H, 7-CH_3), 4.15 (s, 2H, SO_2-CH_2), 4.96 (s, 2H, C_4-CH_2), 6.62 (s, 1H, C_3-H), 7.1 (d, *J*=9 Hz, 2H, C_6-H and C_8-H), 7.78 (d, *J*=7.8 Hz, C_5-H), 9.70 (s, 1H, -CONH).
5f	7,8-Benzo	3328	3306	1716	1667	4.19 (s, 2H, SO_2-CH_2), 5.09 (s, 2H, C_4-CH_2), 6.80 (s. 1H, C_3-H), 7.66-8.53 (m, 6H, Ar-H), 9.75 (br, 1H, -CONH).
6a	6-CH_3	3325	3127	1719	-	2.43 (s, 3H, 6-CH_3), 3.73 (s, 2H, S-CH_2), 3.92 (s, 2H, C_4-CH_2), 6.49 (s, 1H, C_3-H), 7.77 (s, 1H, C_5-H), 7.37 (d, *J*=8.9 Hz, 1H, C_7-H), 7.22 (d, *J*=8.7 Hz, 1H, C_8-H), 6.76 (s, 2H, NH_2).
6b	7-CH_3	3273	3076	1719	-	2.46 (s, 3H, 7-CH_3), 3.70 (s, 2H, S-CH_2), 3.89 (s, 2H, C_4-CH_2) 6.46 (s, 1H, C_3-H), 7.14 (d, *J*=3.9 Hz, 1H, C_8-H), 7.58 (d, *J*=8.4 Hz, 2H, C_6-H and C_5-H), 6.55 (s, 2H, NH_2).
6c	7,8-Benzo	3331	3311	1721	-	3.86 (s, 2H, S-CH_2), 4.19 (s, 2H, C_4-CH_2), 6.54 (s, 1H, C_3-H), 7.13-7.97 (m, 6H, Ar-H), 6.76 (s, 2H, NH_2).
6d	6-CH_3	3265	3075	1721	-	2.43 (s, 3H, 6-CH_3), 4.89 (s, 2H, SO_2-CH_2), 4.93 (s, 2H, C_4-CH_2), 6.66 (s, 1H, C_3-H), 7.22 (d, *J*=7.5 Hz, 1H, C_8-H), 7.39 (d, *J*=8.1 Hz, C_7-H), 7.68(s, 1H, C_5-H), 7.06 (s, 2H, NH_2).
6e	7-CH_3	3260	3073	1718	-	2.42 (s, 3H, 7-CH_3), 4.86 (s, 2H, SO_2-CH_2), 4.92 (s, 2H, C_4-CH_2), 6.67 (s, 1H, C_3-H), 7.17 (d, *J*=8.7 Hz, 2H, C_6-H and C_7-H), 7.80 (d, *J*=7.8 Hz, 1H, C_5H), 6.95 (s, 2H, NH_2).
6f	7,8-Benzo	3430	3339	1729	-	5.09 (s, 2H, SO_2-CH_2), 5.10 (s, 2H, C_4-CH_2), 6.76 (s, 1H, C_3-H), 7.30-8.63 (m, 6H, Ar-H), 7.20 (s, 2H, NH_2).
7a	6-CH_3	3283		1719	1705	2.14 (s, 6H, two of pyrrole-CH_3), 2.43 (s, 3H, 6-CH_3), 3.34 (s, 2H, S-CH_2), 4.00 (s, 2H, C_4-CH_2), 5.80 (s, 2H, pyrrole C_3 and C_4-H of pyrrole), 6.48(s, 1H, C_3-H), 7.21 (d, *J*=8.1 Hz, 1H, C_7-H), 7.36 (d, *J*=7.8 Hz, 1H, C_8-H), 7.46 (s, 1H, C_5-H), 8.89 (s, 1H, CONH).
7b	7-CH_3	3282		1715	-	2.10 (s, 6H, two of pyrrole-CH_3), 2.45 (s, 3H, 7-CH_3), 3.26 (s, 2H, S-CH_2), 4.05 (s, 2H, C_4-CH_2), 5.73 (s, 2H, C_3 and C_4-H of pyrrole), 6.48 (s, 1H, C_3-H), 7.13 (d, *J*=6.9 Hz, 2H, C_8 and C_6-H of coum), 7.62 (d, *J*=8.7 Hz, 1H, C_5-H of coum), 10.56 (s, 1H, -CONH).
7c	7,8-Benzo	3235		1727	1661	2.13 (s, 6H two of pyrrole-CH_3), 3.53 (s, 2H, S-CH_3), 4.12 (s, 2H, C_4-CH_2), 5.82 (s, 2H pyrrole C_3 and C_4-H), 6.59 (s, 1H, C_3-H), 7.63-8.56 (m, 6H, Ar-H), 10.61 (s, 1H, -CONH).
7d	6-CH_3	3235		1738	1705	2.13 (s, 6H, two of pyrrole-CH_3), 2.41 (s, 3H, 6-CH_3), 4.35 (s, 2H, SO_2-CH_2), 4.92 (s, 2H, C_4-CH_2), 5.77 (s, 2H, pyrrole C_3 and C_4-H), 6.67 (s, 1H, C_3-H), 7.23 (d, *J*=8.1 Hz, 1H, C_8-H of coum), 7.38 (d, *J*=7.8 Hz, 1H, C_7-H), 7.62 (s, 1H, C_5-H), 11.14 (s, 1H, -CONH).
7e	7-CH_3	3278		1727	1672	2.13 (s, 6H two of pyrrole-CH_3), 2.46 (s, 3H, 7-CH_3), 4.32 (s, 2H, SO_2-CH_2), 4.90 (s, 2H, C_4-CH_2), 5.78 (s, 2H, C_3 and C_4-H of pyrrole), 6.64 (s, 1H, C_3-H), 7.14 (d, *J*=6.9 Hz, 2H, C_8 and C_6-H of coum.), 7.71 (d, *J*=8.4 Hz, 1H C_5-H), 11.12 (s, 1H, -CONH).
7f	7,8-Benzo	3289		1727	1678	2.12 (s, 6H two of pyrrole CH_3), 4.55 (s, 2H, -SO_2 CH_2), 5.10 (s, 2H C_4-CH_2), 5.83 (s, 2H, C_3 and C_4-H of pyrrole), 6.60 (s, 1H, C_3-H of), 7.71-8.76 (m, 6H Ar-H), 11.15 (s, 1H, -CONH).

Compound **5a-7c** were D_2O exchanged and **7d-f** were precipitated

In the (EI) mass spectrum of oxadiazole **6a** (R = 6-CH_3). The molecular ion peak was observed at m/z 303 and base peak at m/z 99.

The IR spectrum of **7b** (R = 7-CH_3) exhibited two strong carbonyl stretching bands at 1719 and 1705 cm^{-1} due to lactone carbonyl of coumarin and amide carbonyl, respectively. The –NH, =C-H, and C-O-C stretching vibrations were observed at 3283, 2921 and 1144 cm^{-1}, respectively. The ^{1}H NMR spectrum of **7b** displayed four singlets at δ 2.10, 2.45, 3.26 and 4.05 due to two –CH_3 of pyrrole, 7-CH_3 of coumarin, S-CH_2, and C_4-CH_2 of coumarin, respectively. The C_3-H and C_4-H of pyrrole were found to resonate at δ 5.73 and C_3-H of coumarin resonated at δ 6.48 as singlet, C_5-H as a doublet at δ 7.62 and C_6-H as doublet at δ 7.13 as a singlet at δ 7.13, whereas –NH of amide was found to resonate at δ 10.56 as a singlet and was D_2O exchanged (**Table IV**).

The mass spectrum of **7a** has been recorded by electron ionisation (EI) and the molecular ion peak was observed at m/z 356 which itself is the base peak.

Antimicrobial activity

Newly synthesised compounds have been screened for antimicrobial activity against Gram-negative bacterium *Escherishia coli*, Gram-positive bacterium *Bacillus staphylicocci* using *Norfloxacin* as standard and fungi *Penicillium, Aspergillus* using *Griseofulvin* as standard, nutrient agar was used as culture medium. Test solution was prepared in 1 mL of DMF and 0.1 mL of this solution was used for testing by cup-plate method[16]. The zones of inhibition formed were measured in mm and the results revealed that all the compounds were moderately active against bacteria and fungi.

Experimental Section

Melting points were recorded on a mettler FPI instrument and are uncorrected. IR spectra were recorded on a nicolet impact spectrometer using KBr pellets; and ^{1}H NMR spectra on a Bruker 300 MHz using $CDCl_3$, DMSO-d_6 and D_2O as solvents.

Thiourea, ethylchloroacetate, salicylaldehyde, 4-N, N-dietlylamino salicylaldehyde and naphthylaldehyde were commercial samples and were used after purification.

Synthesis of 4-mercaptomethylchromen-2-ones 2. General procedure. An equimolar mixture of 4-bromomethylcoumarins **1** (0.01 mole) and thiourea (0.01 mole) was stirred in ethanol-ether (1:1) mixture at room temperature for 2 hr and then refluxed on a steam-bath for 4 hr and left overnight. The separated solid was filtered, washed with excess aq. ethanol and dissolved in 5% sodium hydroxide solution (15 mL), filtered and filtrate was re-precipitated with dil. HCl. The separated solid was filtered, washed with excess of water, dried and recrystallised from suitable solvent (**Table I**).

Synthesis of (2-oxo-2*H*-chromen-4-ylmethyl-sulphanyl)acetic acid ethyl esters 3a-c. **General procedure**. Compound **2** (0.01 mole) was refluxed in super dried ethanol in the presence of anhyd. potassium carbonate (0.01 mole) for 10 min then an equimolar quantity of ethyl chloroacetate (0.01 mole) was added from the top of the condenser, attached with calcium chloride guard tube. The heating was continued for 5-6 hr. After cooling, the dark green coloured reaction mixture was poured into crushed ice which was previously concentrated. Separated solid was acidified with dil. HCl, filtered, dried and recrystallised from suitable solvent (**Table I)**.

Synthesis of (2-oxo-2*H*-chromen-4-ylmethyl-sulphonyl)acetic acid ethyl esters 3d-f. General method. Esters **3a-c** (1.5 g) were suspended in gl. acetic acid (7 mL) and hydrogen peroxide solution (5 mL, 30%) was added in portions to the cooled suspension. After the addition was over the reaction mixture was allowed to attain room temperature and heated on a water-bath for 2 hr. The reaction mixture was cooled and the separated solid was filtered and washed with excess ethanol, dried and recrystallised from suitable solvent (**Table I**).

Synthesis of 3-coumarinyl-(4′-coumarino-methyl)sulphones 4. General procedure. A mixture of **3d-f** (0.01 mole) and salals (0.01 mole) was stirred overnight in ethanol in the presence of catalytic amount of piperidine. The separated solid was filtered, washed with excess ethanol, dried and recrystallised from suitable solvent (**Table I**).

Synthesis of (2-oxo-2*H*-chromen-4-ylmethylsul-phanyl)acetic acid hydrazides 5. General procedure. A mixture of **3a-f** (0.01 mole) and hydrazine hydrate (0.02 mole, 99.9%) was refluxed on a water-bath for 4-5 hr in ethanol and was concentrated to half of its original volume and left overnight. The separated solid was filtered, washed with excess ethanol and recrystallised from a suitable solvent (**Table II**).

Synthesis of 4-(5-amino-[1,3,4]oxadiazol-2-yl-methylsulphanyl/sulphonyl-methyl)chromen-2-ones 6. General procedure. A mixture of **5** (0.01 mole) and cyanogen bromide (0.012 mole) in methanol was

heated on an oil-bath for 3 hr at 50-60°C. The resulting clear solution was filtered and the filtrate was neutralised with sodium bicarbonate solution. The separated solid was filtered, washed with excess water, dried and recrystallised from a suitable solvent (**Table II**).

Synthesis of N-(2,5-dimethyl-pyrrol-1-yl)-2-(2-oxo-2*H*-chromen-4-ylmethyl sulphanyl/sulphonyl)-acetamides 7. To a suspension of **5** (0.01 mole) in absolute ethanol, acetonyl acetone (0.02 mole) was added and refluxed on a water-bath for 2 hr in the presence of catalytic amount of acetic acid. The solvent was removed by rotary evaporator and left overnight. The separated solid was washed with excess ethanol, dried and recrystallised from a suitable solvent (**Table II**).

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