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Synthetic and biological studies on mono- and bis-methylene-bridged heterocyclic sulfides and sulfones of carbostyrils

Rajesh G. Kalkhambkar[a], Geeta M. Kulkarni[a]*, H. Shivkumar[b], R. Nagendra Rao[b], Chandrappa M. Kamanavalli[a] and Jagannath C. Kadakol[a]

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A series of new sulfides and sulfones of carbostyrils were synthesized and tested for their *in vitro* antimicrobial and *in vivo* analgesic activities. The results of a bioassay showed that these newly synthesized compounds exhibit potential antibacterial and antifungal activities. The chloro substitution at C-6 and C-7 positions of carbostyrils was found to enhance the antimicrobial activity. Similarly, halogen-substituted sulfones were found to possess potent analgesic activities. All the newly synthesized compounds were characterized by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, ESI-MS and FAB-MS.

Keywords: sulfides; sulfones; carbostyrils; antimicrobial; analgesic

1. Introduction

Carbostyril is a class of lactams, which is an indispensable heterocyclic unit to both chemists and biochemists. This system has been reviewed recently for its natural occurrence, antimicrobial, analgesic, anti-inflammatory, anticancer, anti-HIV and other miscellaneous properties (*1*). Carbostyril derivatives, which ultimately metabolize as the corresponding 8-hydroxy coumarins in the biological system, are therefore found to be very good anti-inflammatory and analgesic agents (*2*). Interest in carbostyrils as antibiotics is due to the recent observation that they are a potent inhibitor of bacterial DNA gyrase that is involved in the cell growth (*3*, *4*). Many carbostyril derivatives, with a variety of substituents at 4-position and with very good antibacterial activity have been reported in our laboratory (*5*, *6*).

Methylene-bridged sulfides derived from 4-bromomethylcoumarins and 2-mercaptouracil have resulted in fluorescent compounds employed for detection of low DNA concentrations. N-substituted benzimidazole conjugates derived from 3-chloromethyl coumarins and 2-mercapto benzimidazole have recently been reported as antiviral agents. The synthesis and preliminary

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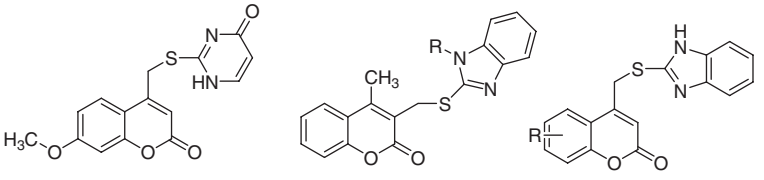


Figure 1. Biologically active methylene-bridged heterocyclic sulfides.

biological evaluation of 2-mercaptobenzimidazole-linked thioethers of various 4-bromomethyl coumarins (*7*, *8*) and 4-thiophenoxymethyl coumarins have been carried out (*9*) in our laboratory. Synthesis and antitubercular activity of aryl sulfides derived from pyranobenzopyrandiones have also been reported recently (*10*) (Figure 1).

In view of the various biological properties associated with methylene-bridged sulfides of coumarin, carbostyril, benzimidazole and uracil, it was thought to be of interest to synthesize some sulfides and sulfones of carbostyrils associated with the aforementioned nuclei. During the present investigation, a variety of heteroaryl sulfides have been synthesized, starting from 4-bromomethyl carbostyrils.

2. Results and discussion

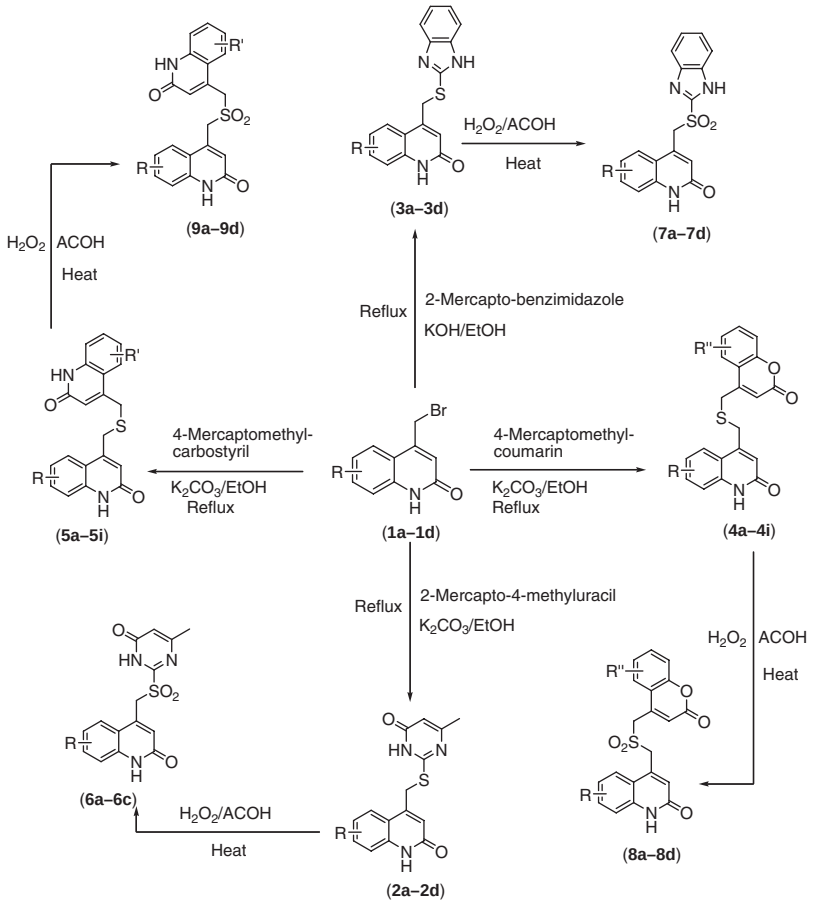
The basic synthetic route employed for the construction of various sulfides and sulfones is outlined in Scheme 1. Various 4-bromomethyl carbostyrils (*11*) (**1a**–**1d**) required for the construction of the target molecules were synthesized by the bromination of acetoacetanilides and cyclization of the intermediate ω-bromoacetoacetanilides in sulfuric acid. The thioethers of carbostyrils with uracil (**2a**–**2d**) and benzimidazole (**3a**–**3d**) were synthesized by the base-catalyzed reaction of 4-bromomethyl carbostyrils (**1a**–**1d**) and anhydrous K_2CO_3 in dry alcohol with 2-mercapto-4-methyl-uracil and 2-mercapto-benzimidazole, respectively, at water bath temperature. Similarly, the thioethers of carbostyrils with coumarins (**4a**–**4i**) and carbostyrils (**5a**–**5i**) were prepared by the reaction of **1a**–**1d** with various substituted 4-mercaptomethyl coumarins and various substituted 4-mercaptomethyl carbostyrils, respectively, in the presence of anhydrous K_2CO_3 and dry alcohol.

By another sequence of reactions, sulfones (**6a**–**6c**), (**7a**–**7d**), (**8a**–**8d**) and (**9a**–**9d**), have been synthesized by the treatment of corresponding thioethers (**2a**–**2c**), (**3a**–**3d**), (**4a**–**4d**) and (**5a**–**5d**), respectively, with 30% H_2O_2 in glacial acetic acid at water bath temperature. All the products gave satisfactory analytical and spectroscopic data, which are in complete agreement with their assigned structures.

2.1. *Pharmacology*

2.1.1. *Antimicrobial assay*

The *in vitro* antimicrobial activity of the test compounds was tested against the two bacterial microorganisms *Escherichia coli* (Gram negative) and *Bacillus cirrosis* (Gram positive) and the two fungal microorganisms *Aspergillus niger* and *Rhizoctonia bataticola*. DMF was used as a solvent control, and the reference drugs used were norfloxacin and gresofulvin. The tests were carried out by cup plate method (*12–14*), at a concentration of 100, 50 and 25 μg ml^{-1}. After 48 h of incubation at 37°C, the zone of inhibition was measured in millimeters. The percentage inhibition of the test compounds was related to the standard, whose zone of inhibition was taken as 100%.



Where R = R'' =H, 6-Cl, 7-Cl, 8-CH_3

R'' = 6-Cl, 6-CH_3, 5,6-benz, 7,8-benz

Scheme 1. Synthesis of sulfides and sulfones of carbostyrils.

The results of antibacterial activities of sulfides (Table 1) showed that the compounds **2a** and **2b** showed up to 52% activity for both the bacteria at 100 $\mu g\,ml^{-1}$ concentration. The same compounds were active even at 25 $\mu g\,ml^{-1}$ concentration. Similarly, the compounds **3b**, **3c**, **4a**–**4c**, **4f**, **5c**, **5e**, **5g** and **5h** showed a very good activity of 60–65% at 100 $\mu g\,ml^{-1}$ concentration. The same compounds were active even at 25 $\mu g\,ml^{-1}$ concentration and showed 30–45% activity.

The results of antibacterial activity of sulfones (Table 2) showed that almost all the compounds showed up to 60% activity at 100 $\mu g\,ml^{-1}$ concentration, and up to 30% activity at 25 $\mu g\,ml^{-1}$ concentration. From the above results, it is observed that the sulfones showed better antibacterial activity than the corresponding sulfides.

The results of the antifungal activity (Table 3) showed a similar trend. The compounds **2b**, **2c**, **3b**, **3c**, **5e** and **5g** showed a maximum of up to 80% activity for both the bacteria at 100 $\mu g\,ml^{-1}$ concentration and up to 55–60% activity at 25 $\mu g\,ml^{-1}$ concentration. Most of the compounds in this series showed a very good antifungal activity at 25 $\mu g\,ml^{-1}$ concentration.

Similarly, in the results of antifungal activity of sulfones (Table 4), it is observed that all the compounds showed very good antifungal activity at 100 $\mu g\,ml^{-1}$ concentration and up to 55–60%

Table 1. Antibacterial activity of selected sulfides.

	Zone of inhibition											
	E. coli (Gram negative)						*B. cirrosis* (Gram positive)					
Compounds	mm	%	mm	%	mm	%	mm	%	mm	%	mm	%
2a	90	31	50	16	–	–	100	33	58	19	–	–
2b	140	54	82	34	48	20	152	55	94	37	52	21
2c	134	51	74	30	39	13	148	53	81	30	46	17
2d	102	37	55	19	–	–	112	38	63	21	–	–
3a	108	40	67	26	–	–	122	42	73	26	–	–
3b	158	62	98	43	61	28	166	60	108	44	70	33
3c	167	66	112	51	74	38	173	63	119	49	78	38
3d	98	35	51	17	–	–	108	36	60	20	–	–
4a	162	64	102	45	73	37	168	61	112	46	70	33
4b	155	61	98	43	66	32	160	58	100	40	66	30
4c	160	63	100	44	70	35	175	64	120	50	80	40
4e	138	53	71	28	–	–	142	50	78	29	44	16
4f	152	60	95	41	60	28	166	60	108	54	66	30
5b	150	59	92	40	58	27	160	58	98	39	64	29
5c	140	64	74	30	35	10	140	50	70	25	–	–
5e	173	69	121	56	88	48	180	66	122	51	88	45
5f	138	53	70	27	–	–	140	50	66	23	–	–
5g	170	68	119	55	82	44	177	65	118	49	79	39
5h	154	61	88	37	44	17	153	55	70	25	–	–
5i	141	55	74	30	30	7	158	57	74	27	–	–
Standard	240	100	200	100	160	100	260	100	220	100	170	100
Control	20	–	20	–	20	–	20	–	20	–	20	–
Concentration	100 $\mu g\,ml^{-1}$		50 $\mu g\,ml^{-1}$		25 $\mu g\,ml^{-1}$		100 $\mu g\,ml^{-1}$		50 $\mu g\,ml^{-1}$		25 $\mu g\,ml^{-1}$	

Notes: Standards used: norfloxacin, 100% inhibition at each concentration; control: DMF.

Table 2. Antifungal activity of selected sulfides.

	Zone of inhibition											
	A. niger						*R. bataticola*					
Compounds	mm	%	mm	%	mm	%	mm	%	mm	%	mm	%
2a	160	63	102	45	74	38	172	63	110	45	64	29
2b	182	73	128	60	92	51	192	71	132	56	80	40
2c	177	71	120	55	80	42	188	70	128	54	74	36
2d	160	63	109	49	71	36	169	62	108	44	58	25
3a	178	70	125	58	88	48	174	64	108	44	60	26
3b	194	79	140	66	94	52	218	82	148	64	94	49
3c	196	80	150	72	105	60	212	80	142	61	90	46
3d	155	61	96	43	69	35	166	60	100	40	52	21
4a	190	77	140	66	93	52	210	79	142	61	−88	45
4b	188	76	132	62	88	48	202	75	138	59	80	40
4c	194	79	145	69	98	55	220	83	158	69	104	56
4e	170	68	112	51	70	36	170	62	98	39	40	18
4f	180	72	118	54	78	41	192	70	132	56	80	40
5b	177	71	119	55	78	41	182	67	110	45	62	28
5c	158	62	98	53	69	35	162	59	98	39	–	–
5e	202	82	160	77	106	60	228	86	164	72	110	60
5f	150	59	90	38	61	29	159	57	88	34	–	–
5g	206	84	166	81	110	64	222	84	168	74	110	60
5h	152	60	98	43	68	34	160	58	88	34	–	–
5i	144	56	78	32	52	22	154	55	80	30	–	–
Standard	240	100	200	100	160	100	260	100	220	100	170	100
Control	20	–	20	–	20	–	20	–	20	–	20	–
Concentration	100 $\mu g\,ml^{-1}$		50 $\mu g\,ml^{-1}$		25 $\mu g\,ml^{-1}$		100 $\mu g\,ml^{-1}$		50 $\mu g\,ml^{-1}$		25 $\mu g\,ml^{-1}$	

Notes: Standards used: gresofulvin, 100% inhibition at each concentration; control: DMF.

Table 3. Antibacterial activity of selected sulfones.

	Zone of inhibition											
	E. coli (Gram negative)						*B. cirrosis* (Gram positive)					
Compounds	mm	%	mm	%	mm	%	mm	%	mm	%	mm	%
6b	152	60	95	41	60	28	166	60	108	54	66	30
6c	150	59	92	40	58	27	160	58	98	39	64	29
7b	170	68	119	55	82	44	177	65	118	49	79	39
7c	154	61	88	37	44	17	153	55	70	25	–	–
7d	108	40	67	26	–	–	122	42	73	26	–	–
8b	158	62	98	43	61	28	166	60	108	44	70	33
8c	167	66	112	51	74	38	173	63	119	49	78	38
8d	98	35	51	17	–	–	108	36	60	20	–	–
9c	155	61	98	43	66	32	160	58	100	40	66	30
9d	162	64	102	45	73	37	168	61	112	46	70	33
Standard	240	100	200	100	160	100	260	100	220	100	170	100
Control	20	–	20	–	20	–	20	–	20	–	20	–
Concentration	100 $\mu g\,ml^{-1}$		50 $\mu g\,ml^{-1}$		25 $\mu g\,ml^{-1}$		100 $\mu g\,ml^{-1}$		50 $\mu g\,ml^{-1}$		25 $\mu g\,ml^{-1}$	

Notes: Standards used: norfloxacin, 100% inhibition at each concentration; control: DMF.

Table 4. Antifungal activity of selected sulfones.

	Zone of inhibition											
	A. niger						*R. bataticola*					
Compounds	mm	%	mm	%	mm	%	mm	%	mm	%	mm	%
6b	180	72	118	54	78	41	192	70	132	56	80	40
6c	177	71	119	55	78	41	182	67	110	45	62	28
7b	177	71	120	55	80	42	188	70	128	54	74	36
7c	160	63	109	49	71	36	169	62	108	44	58	25
7d	178	70	125	58	88	48	174	64	108	44	60	26
8b	206	84	166	81	110	64	222	84	168	74	110	60
8c	202	82	160	77	106	60	228	86	164	72	110	60
8d	180	72	118	54	78	41	192	70	132	56	80	40
9c	190	77	140	66	93	52	210	79	142	61	−88	45
9d	188	76	132	62	88	48	202	75	138	59	80	40
Standard	240	100	200	100	160	100	260	100	220	100	170	100
Control	20	–	20	–	20	–	20	–	20	–	20	–
Concentration	100 $\mu g\,ml^{-1}$		50 $\mu g\,ml^{-1}$		25 $\mu g\,ml^{-1}$		100 $\mu g\,ml^{-1}$		50 $\mu g\,ml^{-1}$		25 $\mu g\,ml^{-1}$	

Notes: Standards used: gresofulvin, 100% inhibition at each concentration; control: DMF.

activity at 25 $\mu g\,ml^{-1}$. From the results, it is observed that sulfones are better antifungal agents than the corresponding sulfides.

2.1.2. *Analgesic activity*

The analgesic activity of the test compounds was carried out *in vivo* by acetic-acid-induced writhing method (*15*). Albino mice of either sex were divided into control, standard and different test groups of six mice each (20–25 g). Control group received 2 ml kg^{-1} of 2% aqueous gum acacia, p.o. standard, was treated with aspirin at a dose level of 100 mg kg^{-1} and the test compounds were administered p.o. at a dose level of 100 mg kg^{-1} body weights in 2% aqueous acacia. One hour after the administration, all the groups received acetic acid (0.6% v/v in distilled water) i.p. at a dose level of 1 ml/100 g, and 10 min after i.p. the number of writhes per animal was recorded for 20 min. The analgesic activity was expressed as percentage of protection (Table 5).

Table 5. Analgesic activity of selected sulfides and sulfones.

Compounds	No. of writhes	Percentage of protection
2c	0.983 ± 0.79*	78.22
3b	15.83 ± 1.25*	64.96
3c	6.50 ± 0.56*	62.73
4b	13.45 ± 0.98	49.60
4c	15.80 ± 1.24*	65.91
4f	0.973 ± 0.80*	78.20
5e	15.83 ± 1.25*	64.96
5g	6.88 ± 0.70*	84.20
6b	6.16 ± 0.60*	35.50
7b	14.98 ± 1.27*	63.56
8d	13.33 ± 0.95*	48.70
9d	6.10 ± 0.60*	35.54
Control	45.10 ± 0.90	
Standard	8.30 ± 0.40	81.55

Notes: The values are expressed as mean ± SEM. The results are analyzed by using one-way ANOVA ($F = 76.782$) followed by Tukey's multiple comparative test. P-values of <0.05, <0.01 and <0.001 were considered statistically significant. *$P < 0.001$ vs. control.

The results of analgesic activities (Table 3) showed that, among the tested compounds, **2c**, **3b**, **3c**, **5e** and **5g** significantly inhibited the acetic-acid-induced writhing (up to 78–84%) and the other compounds **4b**, **4c** and **4f** in the range 49–78% when compared to the standard. The analgesic activity was expressed as percentage of protection, the results of which are summarized in Table 5.

3. Conclusion

A series of new sulfides and sulfones of carbostyrils were synthesized. These newly synthesized compounds exhibit potential antibacterial and antifungal activities. The chloro substitution at C-6 and C-7 positions of carbostyrils was found to enhance the antimicrobial activity. Similarly, halogen-substituted sulfones were found to possess potent analgesic activities. Further studies are required to study their exact mechanism of action.

4. Experimental

Melting points of the products were determined by open capillaries on a Buchi apparatus and are uncorrected. The IR spectra were recorded on a Nicolet Impact-410 FT-IR spectrophotometer, using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-300F 300 MHz spectrometer in $CDCl_3$ using TMS as an internal standard with ^{1}H resonant frequency of 300 MHz and ^{13}C resonant frequency of 75 MHz. D_2O exchange was applied to confirm the assignment of the signals of NH protons. The mass spectra were recorded on FAB-MS, and electron spray ionization mass spectra (ESI-MS) were recorded on a Quattro LCZ (Walters-Micromass, Manchester, UK). The elemental analysis was carried out by using Heraus CHN rapid analyzer. C, H and N analyses of all the compounds resulted within ±0.4% of the theoretical values. The homogeneity of the compounds was described by TLC on aluminum silica gel 60 F_{254} (Merck) detected by UV light (254 nm), iodine vapor, LCMS (MPS-SCIEX-API-2000) and HPLC (Aligent 1100 Series). Nomenclature was made using ChemDraw software. All the reagents were of analytical reagent grade or chemically pure. All solvents were dried, deoxygenated and redistilled before use.

4.1. *General procedure for the preparation of compounds 2a–2d*

A mixture of substituted 4-bromomethyl carbostyril (**1a**–**1d**) (4 mmol), 2-mercapto-4-methyl-uracil (4 mmol) and powdered anhydrous potassium carbonate (4 mmol) in super dry alcohol (20 ml) was refluxed on a water bath for 10 h. After completion of the reaction, the separated solid was filtered off, washed with 20% HCl and with excess of cold water, dried and crystallized from suitable solvent.

4.1.1. *4-[4′-Methyl-6-oxo-1,4-dihydropyridin-2-yl-sulfanylmethyl]-carbostyril (**2a**)*

Yield: 85%; Colorless crystals (acetic acid); m.p. 254–256 °C; IR (KBr): 3434, 1658, 1611, 1577 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.52 (s, 3H, C4′−CH_3 of uracil), 4.79 (s, 2H, C4−CH_2 of carbostyril), 6.51 (s, 1H, C3–H of carbostyril), 6.68 (s, 1H, C5′−H of uracil), 7.25–7.89 (m, 4H, Ar−H), 11.85 (s, 1H, −N*H*CO), 12.24 (s, 1H, −N*H*CO of uracil); ^{13}C NMR (75 MHz $CDCl_3$ + TFA, δ ppm): 168.50, 162.44, 158.28, 156.34, 154.28, 136.89, 133.48, 132.80, 127.08, 124.60, 119.40, 116.30, 109.10, 35.98, 22.30; FAB-MS: m/z 300 (M + H); Anal. Calcd for $C_{15}H_{13}N_3O_2S$: C, 60.18; H, 4.38; N, 14.04; found: C, 59.98; H, 4.14; N, 13.88%.

4.1.2. *4-[4′-Methyl-6-oxo-1,4-dihydropyridin-2-yl-sulfanylmethyl]-6-chloro-carbostyril (**2b**)*

Yield: 78%; Colorless crystals (acetic acid); m.p. 284–286 °C; IR (KBr): 3400, 1666, 1609, 1578 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.48 (s, 3H, C4′−CH_3 of uracil), 4.60 (s, 2H, C4−CH_2 of carbostyril), 6.52 (s, 1H, C3−H of carbostyril), 6.72 (s, 1H, C5′−H of uracil), 7.30–7.98 (m, 3H, Ar−H), 11.74 (s, 1H, −N*H*CO), 12.14 (s, 1H, −N*H*CO of uracil); ^{13}C NMR (75 MHz $CDCl_3$ + TFA, δ ppm): 167.76, 161.40, 157.18, 155.34, 153.28, 135.89, 133.48, 132.80, 127.08, 124.60, 119.40, 116.30, 110.10, 38.20, 20.38; FAB-MS: m/z 334.5 (M + H); Anal. Calcd for $C_{15}H_{12}ClN_3O_2S$: C, 53.97; H, 3.62; N, 12.59; found: C, 53.80; H, 3.40; N, 12.28%.

4.1.3. *4-[4′-Methyl-6-oxo-1,4-dihydropyridin-2-yl-sulfanylmethyl]-7-chloro-carbostyril (**2c**)*

Yield: 76%; Colorless crystals (acetic acid); m.p. 270–272 °C; IR (KBr): 3435, 1662, 1606, 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.50 (s, 3H, C4′−CH_3 of uracil), 4.59 (s, 2H, C4−CH_2 of carbostyril), 6.48 (s, 1H, C3–H of carbostyril), 6.69 (s, 1H, C5′−H of uracil), 7.25–7.89 (m, 3H, Ar−H), 11.85 (s, 1H, −N*H*CO), 12.20 (s, 1H, −N*H*CO of uracil); ^{13}C NMR (75 MHz $CDCl_3$ + TFA, δ ppm): 166.78, 160.80, 158.18, 156.34, 154.28, 136.89, 133.48, 132.80, 127.08, 124.60, 119.40, 116.30, 110.10, 40.11, 21.38; FAB-MS: m/z 334.5 (M + H); Anal. Calcd for $C_{15}H_{12}ClN_3O_2S$: C, 53.97; H, 3.62; N, 12.59; found: C, 53.69; H, 3.48; N, 12.34%.

4.1.4. *4-[4′-Methyl-6-oxo-1,4-dihydropyridin-2-yl-sulfanylmethyl]-8-methyl-carbostyril (**2d**)*

Yield: 88%; Colorless crystals (acetic acid); m.p. 280–282 °C; IR (KBr): 3424, 1663, 1620, 1572 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.50 (s, 3H, C4′−CH_3 of uracil), 2.62 (s, 3H, C8−CH_3 of carbostyril), 4.60 (s, 2H, C4−CH_2 of carbostyril), 6.60 (s, 1H, C3−H of carbostyril), 6.68 (s, 1H, C5′−H of uracil), 7.29–7.90 (m, 3H, Ar−H), 11.78 (s, 1H, −N*H*CO), 12.18 (s, 1H, −N*H*CO of uracil); ^{13}C NMR (75 MHz $CDCl_3$ + TFA, δ ppm): 168.08, 162.18, 156.18, 155.34, 154.28, 136.89, 133.48, 132.80, 127.08, 124.60, 119.40, 116.30, 109.10, 39.10, 22.18, 18.80; FAB-MS: m/z 314 (M + H); Anal. Calcd for $C_{16}H_{15}N_3O_2S$: C, 61.32; H, 4.82; N, 13.41; found: C, 61.12; H, 4.48; N, 13.22%.

4.2. *General procedure for the preparation of compounds 3a–3d*

A mixture of substituted 4-bromomethyl carbostyril (**1a**–**1d**) (4 mmol), 2-mercapto-benzimidazol (4 mmol) and anhydrous potassium hydroxide (4 mmol) in super dry alcohol (20 ml) was refluxed on a water bath for 10 h. After completion of the reaction, the separated solid was filtered off, washed with 20% HCl and with excess of cold water, dried and crystallized from suitable solvent.

4.2.1. *4-[1H-Benzimidazol-2-yl-sulfanylmethyl]-carbostyril (**3a**)*

Yield: 68%; Colorless crystals (ethanol); m.p. 160–162 °C; IR (KBr): 3430, 1663, 1606, 1551 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 5.12 (s, 2H, C4−CH_2 of carbostyril), 7.48–7.80 (m, 9H, Ar−H), 12.28 (s, 1H, −NH); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA, δ ppm): 163.50, 158.28, 156.34, 155.50, 154.28, 138.34, 136.89, 133.48, 132.80, 127.08, 124.60, 120.20, 119.40, 116.30, 109.10, 36.08; FAB-MS: m/z 308 (M + H); Anal. Calcd for $C_{17}H_{13}N_3OS$: C, 66.43; H, 4.26; N, 13.67; found: C, 66.28; H, 4.04; N, 13.58%.

4.2.2. *6-Chloro-4-[1H-benzimidazole-2-yl-sulfanylmethyl]-carbostyril (**3b**)*

Yield: 70%; Colorless crystals (DMF); m.p. 290–292 °C; IR (KBr): 3439, 1655, 1607, 1555 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 4.85 (s, 2H, C4−CH_2 of carbostyril), 7.43–7.80 (m, 8H, Ar−H), 12.31 (s, 1H, −NH); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA, δ ppm): 162.50, 158.28, 157.34, 155.50, 153.28, 138.34, 137.89, 133.48, 131.80, 127.08, 123.60, 120.20, 118.40, 116.30, 108.10, 35.98; FAB-MS: m/z 342.5 (M + H); Anal. Calcd for $C_{17}H_{12}ClN_3OS$: C, 59.73; H, 3.54; N, 12.29; found: C, 59.40; H, 3.30; N, 12.18%.

4.2.3. *7-Chloro-4-[1H-benzimidazol-2-yl-sulfanylmethyl]-carbostyril (**3c**)*

Yield: 65%; Colorless crystals (acetic acid); m.p. 280–282 °C; IR (KBr): 3450, 1660, 1620, 1541 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 4.78 (s, 2H, C4−CH_2 of carbostyril), 6.60 (s, 1H, C3–H of carbostyril), 7.18–7.94 (m, 7H, Ar−H), 11.98 (s, 1H, −NH exchangeable with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 163.50, 159.28, 158.34, 154.50, 152.28, 138.34, 137.89, 133.48, 131.80, 127.08, 123.60, 121.20, 119.40, 116.30, 109.10, 34.56; FAB-MS: m/z 342.5 (M + H); Anal. Calcd for $C_{17}H_{12}ClN_3OS$: C, 59.73; H, 3.54; N, 12.29; found: C, 59.46; H, 3.36; N, 12.16%.

4.2.4. *8-Methyl-4-[1H-benzimidazol-2-yl-sulfanylmethyl]-carbostyril (**3d**)*

Yield: 80%; Colorless crystals (acetic acid); m.p. 260–262 °C; IR (KBr): 3450, 1660, 1620, 1541 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.63 (s, 3H, C8−CH_3 of carbostyril), 4.82 (s, 2H, C4−CH_2 of carbostyril), 6.80–7.78 (m, 8H, Ar−H), 11.48 (s, 1H, −NH); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA, δ ppm): 162.50, 158.28, 156.34, 154.50, 152.28, 138.34, 137.89, 133.48, 131.80, 127.08, 123.60, 121.20, 120.40, 116.30, 110.10, 35.06, 18.34; FAB-MS: m/z 322 (M + H); Anal. Calcd for $C_{18}H_{15}N_3OS$: C, 67.27; H, 4.70; N, 13.07; found: C, 67.12; H, 4.48; N, 12.86%.

4.3. *General procedure for the preparation of compounds 4a–4f*

A mixture of substituted 4-bromomethyl carbostyril (**1a**–**1d**) (4 mmol), 4-mercaptomethyl coumarin (4 mmol) and powdered anhydrous potassium carbonate (4 mmol) in super dry alcohol (20 ml) was refluxed on a water bath for 10 h. After completion of the reaction, the separated solid

was filtered off, washed with 20% HCl and with excess of cold water, dried and crystallized from suitable solvent.

4.3.1. *6-Chloro-4-[6-methyl-2-oxo-2H-chromen-4-yl-sulfanylmethyl]-carbostyril (**4a**)*

Yield: 78%; Colorless crystals (acetic acid); m.p. 270–272 °C; IR (KBr): 3419, 1725, 1657, 1570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.48 (s, 3H, C6′−CH_3 of coumarin), 4.12 (s, 2H, C4−CH_2 of carbostyril), 4.28 (s, 2H, C4′−CH_2 of coumarin), 6.61–7.90 (m, 8H, Ar−H), 11.84 (s, 1H, −NH); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA, δ ppm): 163.50, 161.39, 159.90, 158.28, 156.34, 155.50, 154.28, 138.34, 136.89, 133.48, 132.80, 128.45, 127.08, 124.60, 120.20, 116.30, 110.76, 109.10, 46.08, 44.40, 20.56; FAB-MS: m/z 398.5 (M + H); Anal. Calcd for $C_{21}H_{16}SClNO_3$: C, 63.39; H, 4.05; N, 3.52; found: C, 63.33; H, 3.97; N, 3.44%.

4.3.2. *6-Chloro-4-[7-methyl-2-oxo-2H-chromen-4-yl-sulfanylmethyl]-carbostyril (**4b**)*

Yield: 72%; Colorless crystals (acetic acid); m.p. 310–312 °C; IR (KBr): 3431, 1720, 1662, 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.52 (s, 3H, C7′−CH_3 of coumarin), 4.09 (s, 2H, C4−CH_2 of carbostyril), 4.33 (s, 2H, C4′−CH_2 of coumarin), 6.61–7.87 (m, 8H, Ar−H), 11.98 (s, 1H, −NH); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA, δ ppm): 164.00, 161.10, 159.60, 157.28, 156.34, 155.50, 154.28, 139.34, 136.89, 134.48, 132.80, 128.45, 127.08, 124.60, 120.20, 116.30, 111.16, 108.10, 45.08, 43.80, 22.16; FAB-MS: m/z 398.5 (M + H); Anal. Calcd for $C_{21}H_{16}SClNO_3$: C, 63.39; H, 4.05; N, 3.52; found: C, 63.35; H, 3.95; N, 3.45%.

4.3.3. *6-Chloro-4-[7,8-benzo-2-oxo-2H-chromen-4-yl-sulfanylmethyl]-carbostyril (**4c**)*

Yield: 85%; Colorless crystals (DMF); m.p. 322–324 °C; IR (KBr): 3448, 1722, 1657, 1547 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 4.12 (s, 2H, C4−CH_2 of carbostyril), 4.18 (s, 2H, C4′−CH_2 of coumarin), 6.65–8.12 (m, 11H, Ar−H), 11.88 (s, 1H, −NH); FAB-MS: m/z 434.5 (M + H); Anal. Calcd for $C_{24}H_{16}SClNO_3$: C, 66.43; H, 3.72; N, 3.23; found: C, 66.28; H, 3.64; N, 3.12%.

4.3.4. *8-Methyl-4-[7-methyl-2-oxo-2H-chromen-4-yl-sulfanylmethyl]-carbostyril (**4d**)*

Yield: 80%; Colorless crystals (DMF); m.p. 320–323 °C; IR (KBr): 3431, 1720, 1662, 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.57 (s, 3H, C7′−CH_3 of coumarin), 2.62 (s, 3H, C8−CH_3 of carbostyril), 4.01 (s, 2H, C4−CH_2 of carbostyril), 4.12 (s, 2H, C4′−CH_2 of coumarin), 6.66–7.89 (m, 8H, Ar−H), 11.84 (s, 1H, −NH); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA, δ ppm): 163.89, 160.80, 159.60, 157.28, 156.34, 155.50, 154.28, 139.34, 136.89, 134.48, 132.80, 128.45, 127.08, 124.60, 120.20, 116.30, 110.16, 108.10, 47.08, 45.80, 22.16, 20.10; FAB-MS: m/z 378 (M + H); Anal. Calcd for $C_{22}H_{19}SNO_3$: C, 70.00; H, 5.07; N, 3.71; found: C, 69.90; H, 4.86; N, 3.60%.

4.3.5. *4-[7,8-Benzo-2-oxo-2H-chromen-4-yl-sulfanylmethyl]-carbostyril (**4e**)*

Yield: 82%; Colorless crystals (acetic acid); m.p. 262–264 °C; IR (KBr): 3420, 1733, 1644, 1542 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 4.46 (s, 2H, C4−CH_2 of carbostyril), 4.48 (s, 2H, C4′−CH_2 of coumarin), 6.76–8.31 (m, 12H, Ar−H), 12.29 (s, 1H, −NH); FAB-MS: m/z 400 (M + H); Anal. Calcd for $C_{24}H_{17}SNO_3$: C, 72.16; H, 4.29; N, 3.51; found: C, 72.10; H, 4.23; N, 3.30%.

4.3.6. *4-[6-Chloro-2-oxo-2H-chromen-4-yl-sulfanylmethyl]-carbostyril* ***(4f)***

Yield: 84%; Colorless crystals (acetic acid); m.p. 240–242 °C; IR (KBr): 3433, 1724, 1659, 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 4.01 (s, 2H, C4−CH_2 of carbostyril), 4.11 (s, 2H, C4′−CH_2 of coumarin), 6.58–7.89 (m, 9H, Ar−H), 11.94 (s, 1H, −NH); FAB-MS: m/z 384.5 (M + H); Anal. Calcd for $C_{20}H_{14}SClNO_3$: C, 62.58; H, 3.68; N, 3.65; found: C, 62.40; H, 3.43; N, 3.56%.

4.4. *General procedure for the preparation of compounds 5a–5i*

A mixture of substituted 4-bromomethyl carbostyril (**1a**–**1d**) (4 mmol), 4-mercaptomethyl-carbostyril (4 mmol) and powdered anhydrous potassium carbonate (4 mmol) in super dry alcohol (20 ml) was refluxed on a water bath for 10 h. After completion of the reaction, the separated solid was filtered off, washed with 20% HCl and with excess of cold water, dried and crystallized from suitable solvent.

4.4.1. *Compound* ***5a***

Yield: 78%; Colorless crystals (acetic acid); m.p. 304–306 °C; IR (KBr): 3430, 1664, 1551 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 4.00 (s, 2H, C4−CH_2 of carbostyril), 6.52–7.77 (m, 5H, Ar−H), 11.71 (s, 1H, −NH); FAB-MS: m/z 349 (M + H); Anal. Calcd for $C_{20}H_{16}N_2O_2S$: C, 68.94; H, 4.63; N, 8.04; found: C, 68.73; H, 4.57; N, 7.88%.

4.4.2. *Compound* ***5b***

Yield: 72%; Colorless crystals (acetic acid); m.p. 290–292 °C; IR (KBr): 3431, 1662, 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.52 (s, 3H, C8′−CH_3 of carbostyril), 4.08 (s, 2H, C4−CH_2 of carbostyril), 4.10 (s, 2H, C4′−CH_2 of carbostyril), 6.87–7.98 (m, 9H, Ar−H), 11.48 (s, 1H, −NH), 12.02 (s, 1′H, −NH); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA, δ ppm): 162.89, 159.60, 158.34, 157.28, 156.44, 155.50, 154.28, 139.34, 136.89, 134.48, 132.80, 128.45, 127.08, 124.60, 120.20, 116.30, 110.16, 108.10, 39.28, 20.10; FAB-MS: m/z 363 (M + H); Anal. Calcd for $C_{21}H_{18}SN_2O_2$: C, 69.59; H, 5.01; N, 7.73; found: C, 69.30; H, 4.76; N, 7.60%.

4.4.3. *Compound* ***5c***

Yield: 75%; Colorless crystals (acetic acid); m.p. 258–260 °C; IR (KBr): 3432, 1661, 1555 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 4.12 (s, 2H, C4−CH_2 of carbostyril), 6.67–7.78 (m, 4H, Ar−H), 11.83 (s, 1H, −NH); FAB-MS: m/z 418 (M + H); Anal. Calcd for $C_{20}H_{14}Cl_2N_2O_2S$: C, 57.56; H, 3.38; N, 6.71; found: C, 57.24; H, 3.24; N, 6.52%.

4.4.4. *Compound* ***5d***

Yield: 70%; Colorless crystals (acetic acid); m.p. 260–262 °C; IR (KBr): 3425, 1658, 1554 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.59 (s, 3H, C8′−CH_3 of carbostyril), 4.00 (s, 2H, C4−CH_2 of carbostyril), 4.07 (s, 2H, C4′−CH_2 of carbostyril), 6.87–7.98 (m, 8H, Ar−H), 11.58 (s, 1H, −NH), 12.00 (s, 1′H, −NH); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA, δ ppm): 163.80, 159.65, 158.34, 157.28, 156.44, 155.50, 154.28, 139.34, 136.89, 134.48, 132.80, 128.45, 126.08, 124.60, 120.20, 116.30, 110.16, 108.10, 40.28, 22.00; FAB-MS: m/z 398 (M + H); Anal. Calcd for $C_{21}H_{17}ClN_2O_2S$: C, 63.55; H, 4.32; N, 7.06; found: C, 63.38; H, 4.10; N, 6.88%.

4.4.5. *Compound **5e***

Yield: 74%; Colorless crystals (acetic acid); m.p. 277–279 °C; IR (KBr): 3430, 1660, 1552 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.62 (s, 3H, C8′−CH_3 of carbostyril), 4.08 (s, 2H, C4−CH_2 of carbostyril), 4.12 (s, 2H, C4′−CH_2 of carbostyril), 6.73–7.91 (m, 8H, Ar−H), 11.67 (s, 1H, −NH), 12.12 (s, 1H, −NH); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA, δ ppm): 161.20, 158.45, 157.34, 156.28, 155.44, 154.50, 152.28, 139.34, 136.89, 134.48, 132.80, 128.45, 126.08, 124.60, 120.20, 116.30, 110.16, 108.10, 41.18, 20.90; FAB-MS: m/z 397.5 (M + H); Anal. Calcd for $C_{21}H_{17}ClN_2O_2S$: C, 63.55; H, 4.32; N, 7.06; found: C, 63.34; H, 4.14; N, 6.84%.

4.4.6. *Compound **5f***

Yield: 80%; Colorless crystals (acetic acid); m.p. 298–300 °C; IR (KBr): 3435, 1658, 1565 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 2.63 (s, 3H, C8−CH_3 of carbostyril), 4.12 (s, 2H, C4−CH_2 of carbostyril), 6.66–7.82 (m, 4H, Ar−H), 11.08 (s, 1H, −NH); FAB-MS: m/z 377.5 (M + H); Anal. Calcd for $C_{22}H_{20}SN_2O_2$: C, 70.19; H, 5.35; N, 7.44; found: C, 70.10; H, 5.14; N, 7.36%.

4.4.7. *Compound **5g***

Yield: 78%; Colorless crystals (acetic acid); m.p. 272–275 °C; IR (KBr): 3430, 1658, 1559 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 4.10 (s, 2H, C4−CH_2 of carbostyril), 6.60–7.72 (m, 4H, Ar−H), 11.88 (s, 1H, −NH); FAB-MS: m/z 418 (M + H); Anal. Calcd for $C_{20}H_{14}Cl_2N_2O_2S$: C, 57.56; H, 3.38; N, 6.71; found: C, 57.22; H, 3.23; N, 6.50%.

4.4.8. *Compound **5h***

Yield: 70%; Colorless crystals (acetic acid); m.p. 244–246 °C; IR (KBr): 3431, 1660, 1552 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 4.08 (s, 2H, C4−CH_2 of carbostyril), 4.10 (s, 2H, C4′−CH_2 of carbostyril), 6.60–8.44 (m, 9H, Ar−H), 11.50 (s, 1H, −NH), 12.02 (s, 1′H, −NH); FAB-MS: m/z 384 (M + H); Anal. Calcd for $C_{20}H_{15}ClN_2O_2S$: C, 62.68; H, 3.90; N, 7.30; found: C, 62.65; H, 3.85; N, 7.28%.

4.4.9. *Compound **5i***

Yield: 68%; Colorless crystals (acetic acid); m.p. 256–258 °C; IR (KBr): 3428, 1666, 1552 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 4.12 (s, 2H, C4−CH_2 of carbostyril), 4.15 (s, 2H, C4′−CH_2 of carbostyril), 6.68–8.56 (m, 9H, Ar−H), 11.47 (s, 1H, −NH), 12.42 (s, 1′H, −NH); FAB-MS: m/z 384 (M + H); Anal. Calcd for $C_{20}H_{15}ClN_2O_2S$: C, 62.68; H, 3.90; N, 7.30; found: C, 62.60; H, 3.86; N, 7.30%.

4.5. *General procedure for the preparation of compounds 6a–6c*

In a typical reaction, the substituted 4-[4′-methyl-6-oxo-1,4-dihydropyridin-2-yl-sulfanylmethyl]-carbostyril (3 mmol) was suspended in glacial acetic acid (5 ml) and the reaction mixture was cooled to 0 °C. To the cooled suspension, the hydrogen peroxide solution (3 ml, 30%) was added drop-wise and the reaction mixture was stirred for 1 h and heated on a water bath for 3 h. After completion of the reaction, the separated solid was filtered, washed with excess of cold ethanol, dried and recrystallized from suitable solvent.

4.5.1. *4-[4′-Methyl-6-oxo-1,4-dihydropyridin-2-yl-sulfonylmethyl]-carbostyril (**6a**)*

Yield: 55%; Colorless crystals (acetic acid); m.p. 250–252 °C; IR (KBr): 3424, 1662, 1609, 1351 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.43 (s, 3H, C4′−CH_3 of uracil), 5.06 (s, 2H, C4−CH_2 of carbostyril), 6.32 (s, 1H, C3–H of carbostyril), 7.18–7.83 (m, 5H, Ar−H), 11.38 (s, 1H, –N*H*CO), 11.38 (s, 1H, –N*H*CO of uracil); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA, δ ppm): 167.89, 163.80, 159.60, 156.34, 155.50, 154.28, 139.34, 136.89, 128.45, 124.60, 116.30, 110.16, 51.08, 22.16; FAB-MS: m/z 332 (M + H); Anal. Calcd for $C_{15}H_{13}N_3O_4S$: C, 54.38; H, 3.92; N, 12.68; found: C, 54.20; H, 3.80; N, 12.44%.

4.5.2. *7-Chloro-4-[4′-methyl-6-oxo-1,4-dihydropyridin-2-yl-sulfonylmethyl]-carbostyril (**6b**)*

Yield: 68%; Colorless crystals (acetic acid); m.p. 288–290 °C; IR (KBr): 3435, 1662, 1606, 1344 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.50 (s, 3H, C6′−CH_3 of uracil), 4.98 (s, 2H, C4−CH_2 of carbostyril), 6.68 (s, 1H, C3–H of carbostyril), 7.25–7.94 (m, 4H, Ar−H), 11.88 (s, 1H, –N*H*CO), 11.88 (s, 1H, –N*H*CO of uracil); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA, δ ppm): 166.80, 162.80, 159.60, 156.44, 155.50, 154.28, 139.34, 136.89, 128.45, 124.60, 115.30, 109.16, 50.22, 20.10; FAB-MS: m/z 366.5 (M + H); Anal. Calcd for $C_{15}H_{12}ClN_3O_4S$: C, 49.31; H, 3.28; N, 11.50; found: C, 49.28; H, 3.12; N, 11.25%.

4.5.3. *8-Methyl-4-[4′-methyl-6-oxo-1,4-dihydropyridin-2-yl-sulfonylmethyl]-carbostyril (**6c**)*

Yield: 66%; Colorless crystals (acetic acid); m.p. 260–262 °C; IR (KBr): 3430, 1663, 1620, 1330 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.49 (s, 3H, C4′−CH_3 of uracil), 2.63 (s, 3H, C8−CH_3 of carbostyril), 5.11 (s, 2H, C4−CH_2 of carbostyril), 6.43 (s, 1H, C3−H of carbostyril), 7.46–7.88 (m, 4H, Ar−H), 11.30 (s, 1H, −N*H*CO), 11.30 (s, 1H, −N*H*CO of uracil); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA, δ ppm): 166.80, 162.80, 159.60, 156.44, 155.50, 154.28, 139.34, 136.89, 128.45, 124.60, 115.30, 109.16, 50.22, 20.10; FAB-MS: m/z 346 (M + H); Anal. Calcd for $C_{16}H_{15}N_3O_4S$: C, 55.65; H, 4.34; N, 12.17; found: C, 55.40; H, 4.28; N, 12.10%.

4.6. *General procedure for the preparation of compounds 7a–7d*

In a typical reaction, the substituted 4-[1*H*-benzimidazole-2-yl-sulfanylmethyl]-carbostyril (3 mmol) was suspended in glacial acetic acid (5 ml) and the reaction mixture was cooled to 0 °C. To the cooled suspension, the hydrogen peroxide solution (3 ml, 30%) was added drop-wise and the reaction mixture was stirred for 1 h and heated on a water bath for 3 h. After completion of the reaction, the separated solid was filtered, washed with excess of cold ethanol, dried and recrystallized from suitable solvent.

4.6.1. *4-[1H-Benzimidazole-2-yl-sulfonylmethyl]-carbostyril (**7a**)*

Yield: 54%; Colorless crystals (acetic acid); m.p. 268–270 °C; IR (KBr): 3429, 1660, 1615, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 4.92 (s, 2H, C4−CH_2 of carbostyril), 7.43–7.88 (m, 9H, Ar−H), 12.34 (s, 1H, −NH); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA, δ ppm): 161.15, 158.28, 156.34, 155.50, 154.22, 138.34, 136.89, 134.48, 132.80, 127.08, 124.66, 120.20, 119.40, 116.30, 110.10, 49.10; FAB-MS: m/z 340 (M + H); Anal. Calcd for $C_{17}H_{13}N_3O_3S$: C, 60.17; H, 3.83; N, 12.38; found: C, 60.08; H, 3.74; N, 12.18%.

4.6.2. *6-Chloro-4-[1H-benzimidazole-2-yl-sulfonylmethyl]-carbostyril (**7b**)*

Yield: 60%; Colorless crystals (acetic acid); m.p. 242–244 °C; IR (KBr): 3439, 1655, 1607, 1338 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 4.98 (s, 2H, C4−CH_2 of carbostyril), 7.40–7.86 (m, 8H, Ar−H), 12.25 (s, 1H, −NH); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA, δ ppm): 161.15, 158.28, 156.34, 155.50, 154.22, 138.34, 136.89, 134.48, 132.80, 127.08, 124.66, 120.20, 119.40, 116.30, 110.10, 49.10; FAB-MS: m/z 374.5 (M + H); Anal. Calcd for $C_{17}H_{12}ClN_3O_3S$: C, 54.69; H, 3.21; N, 11.26; found: C, 54.40; H, 3.10; N, 11.08%.

4.6.3. *7-Chloro-4-[1H-benzimidazole-2-yl-sulfonylmethyl]-carbostyril (**7c**)*

Yield: 52%; Colorless crystals (acetic acid); m.p. 218–220 °C; IR (KBr): 3429, 1660, 1615, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 5.02 (s, 2H, C4−CH_2 of carbostyril), 7.32–7.75 (m, 8H, Ar−H), 12.38 (s, 1H, −NH); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA, δ ppm): 163.15, 159.28, 156.34, 155.50, 154.22, 138.34, 136.89, 134.48, 132.80, 127.08, 124.66, 120.20, 119.40, 116.30, 110.10, 52.70; FAB-MS: m/z 374.5 (M + H); Anal. Calcd for $C_{17}H_{12}ClN_3O_3S$: C, 54.69; H, 3.21; N, 11.26; found: C, 54.45; H, 3.15; N, 11.05%.

4.6.4. *8-Methyl-4-[1H-benzimidazole-2-yl-sulfonylmethyl]-carbostyril (**7d**)*

Yield: 60%; Colorless crystals (acetic acid); m.p. 274–276 °C; IR (KBr): 3440, 1659, 1609, 1328 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.66 (s, 3H, C8−CH_3 of carbostyril), 5.14 (s, 2H, C4−CH_2 of carbostyril), 7.60–7.93 (m, 8H, Ar−H), 12.54 (s, 1H, −NH); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA, δ ppm): 162.10, 159.28, 156.34, 155.50, 154.22, 138.34, 136.89, 134.48, 132.80, 127.08, 124.60, 120.22, 119.44, 116.30, 110.10, 50.10, 21.20; FAB-MS: m/z 354 (M + H); Anal. Calcd for $C_{18}H_{15}N_3O_3S$: C, 61.18; H, 4.24; N, 11.89; found: C, 61.10; H, 4.05; N, 11.78%.

4.7. *General procedure for the preparation of compounds 8a–8d*

In a typical reaction, the substituted 4-[6-methyl-2-oxo-2*H*-chromen-4-yl-sulfanylmethyl]-carbostyril (3 mmol) was suspended in glacial acetic acid (5 ml) and the reaction mixture was cooled to 0 °C. To the cooled suspension, the hydrogen peroxide solution (3 ml, 30%) was added drop-wise and the reaction mixture was stirred for 1 h and heated on a water bath for 3 h. After completion of the reaction, the separated solid was filtered, washed with excess of cold ethanol, dried and recrystallized from suitable solvent.

4.7.1. *4-[7,8-Benzo-2-oxo-2H-chromen-4-yl-sulfonylmethyl]-carbostyril (**8a**)*

Yield: 68%; Colorless crystals (acetic acid); m.p. 248–250 °C; IR (KBr): 3426, 1728, 1659, 1322 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 4.90 (s, 2H, C4−CH_2 of carbostyril), 5.10 (s, 2H, C4′−CH_2 of coumarin), 6.66–7.90 (m, 12H, Ar−H), 11.80 (s, 1H, −NH); FAB-MS: m/z 432 (M + H); Anal. Calcd for $C_{24}H_{17}SNO_5$: C, 66.82; H, 3.94; N, 3.24; found: C, 66.56; H, 3.78; N, 3.14%.

4.7.2. *6-Chloro-4-[7-methyl-2-oxo-2H-chromen-4-yl-sulfonylmethyl]-carbostyril (**8b**)*

Yield: 52%; Colorless crystals (acetic acid); m.p. 254–256 °C; IR (KBr): 3444, 1720, 1658, 1348 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.45 (s, 3H, C7′−CH_3 of coumarin),

4.85 (s, 2H, C4−CH_2 of carbostyril), 5.08 (s, 2H, C4′−CH_2 of coumarin), 6.59–7.92 (m, 8H, Ar−H), 12.80 (s, 1H, −NH); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA, δ ppm): 164.55, 161.19, 159.90, 158.28, 156.34, 155.50, 154.28, 138.34, 136.80, 133.40, 132.80, 128.40, 127.00, 124.60, 120.20, 116.30, 110.76, 109.10, 49.18, 53.10, 21.16; FAB-MS: m/z 430.5 (M + H); Anal. Calcd for $C_{21}H_{16}SClNO_5$: C, 58.74; H, 3.72; N, 3.26; found: C, 58.58; H, 3.60; N, 3.18%.

4.7.3. *6-Chloro-4-[7,8-benzo-2-oxo-2H-chromen-4-yl-sulfonylmethyl]-carbostyril (**8c**)*

Yield: 60%; Colorless crystals (acetic acid); m.p. 224–226 °C; IR (KBr): 3446, 1720, 1660, 1342 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 4.90 (s, 2H, C4−CH_2 of carbostyril), 5.10 (s, 2H, C4′−CH_2 of coumarin), 6.66–7.90 (m, 12H, Ar−H), 11.80 (s, 1H, −NH); FAB-MS: m/z 466.5 (M + H); Anal. Calcd for $C_{24}H_{16}SClNO_5$: C, 61.93; H, 3.44; N, 3.00; found: C, 61.60; H, 3.32; N, 2.88%.

4.7.4. *8-Methyl-4-[7,8-benzo-2-oxo-2H-chromen-4-yl-sulfonylmethyl]-carbostyril (**8d**)*

Yield: 68%; Colorless crystals (acetic acid); m.p. 230–232 °C; IR (KBr): 3431, 1721, 1664, 1320 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.44 (s, 3H, C8−CH_3 of carbostyril), 4.91 (s, 2H, C4−CH_2 of carbostyril), 5.10 (s, 2H, C4′−CH_2 of coumarin), 6.63–7.95 (m, 11H, Ar−H), 12.94 (s, 1H, −NH); FAB-MS: m/z 446 (M + H); Anal. Calcd for $C_{25}H_{19}SNO_5$: C, 67.41; H, 4.26; N, 3.14; found: C, 67.30; H, 4.16; N, 3.10%.

4.8. *General procedure for the preparation of compounds 9a–9d*

In a typical reaction, the compounds **5a**–**5d** (3 mmol) were suspended in glacial acetic acid (5 ml) and the reaction mixture was cooled to 0 °C. To the cooled suspension, the hydrogen peroxide solution (3 ml, 30%) was added drop-wise and the reaction mixture was stirred for 1 h and heated on a water bath for 3 h. After completion of the reaction, the separated solid was filtered, washed with excess of cold ethanol, dried and recrystallized from suitable solvent.

4.8.1. *Compound **9a***

Yield: 56%; Colorless crystals (acetic acid); m.p. 311–313 °C; IR (KBr): 3421 1663, 1550, 1315 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 4.92 (s, 2H, C4−CH_2 of carbostyril), 6.58–7.97 (m, 5H, Ar−H), 11.71 (s, 1H, −NH); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 161.80, 158.32, 157.22, 156.42, 155.52, 134.43, 124.60, 120.20, 108.10, 49.28; FAB-MS: m/z 381 (M + H); Anal. Calcd for $C_{20}H_{16}N_2O_4S$: C, 63.15; H, 4.21; N, 7.36; found: C, 63.00; H, 4.10; N, 7.28%.

4.8.2. *Compound **9b***

Yield: 66%; Colorless crystals (acetic acid); m.p. 264–266 °C; IR (KBr): 3425, 1659, 1556, 1315 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.51 (s, 3H, C8′−CH_3 of carbostyril), 4.90 (s, 2H, C4−CH_2 of carbostyril), 5.09 (s, 2H, C4′−CH_2 of carbostyril), 6.55–7.64 (m, 9H, Ar−H), 11.38 (s, 1H, −NH), 12.45 (s, 1′H, −NH); FAB-MS: m/z 430.5 (M + H); Anal. Calcd for $C_{21}H_{18}ClN_2O_4S$: C, 58.73; H, 4.19; N, 6.52; found: C, 58.55; H, 4.00; N, 6.38%.

4.8.3. *Compound **9c***

Yield: 69%; Colorless crystals (acetic acid); m.p. 260–262 °C; IR (KBr): 3420, 1660, 1552, 1313 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.66 (s, 3H, C8′−CH_3 of carbostyril), 4.88 (s, 2H, C4−CH_2 of carbostyril), 5.05 (s, 2H, C4′−CH_2 of carbostyril), 6.66–7.96 (m, 8H, Ar−H), 11.57 (s, 1H, −NH), 12.20 (s, 1H, −NH); FAB-MS: m/z 429.5 (M + H); Anal. Calcd for $C_{21}H_{17}ClN_2O_4S$: C, 54.42; H, 3.67; N, 6.04; found: C, 54.30; H, 3.50; N, 6.00%.

4.8.4. *Compound **9d***

Yield: 70%; Colorless crystals (acetic acid); m.p. 298–300 °C; IR (KBr): 3422, 1666, 1550, 1334 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA, δ ppm): 2.64 (s, 3H, C8−CH_3 of carbostyril), 5.20 (s, 2H, C4−CH_2 of carbostyril), 7.18–7.80 (m, 4H, Ar−H), 11.40 (s, 1H, −NH); FAB-MS: m/z 409 (M + H); Anal. Calcd for $C_{22}H_{20}SN_2O_4$: C, 64.70; H, 4.90; N, 6.86; found: C, 64.50; H, 4.76; N, 6.60%.

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