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Synthesis of 3-Phenyl-4[4-(*m*-nitrophenyl)-*N*-2-(2'-aryluroido / arylthiouroido-4'-*N*-morpholino-*s*-triazin)-benzo-[6,7]-coumarins and their Applications

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Abstract Several 3 – phenyl – 4 [4-(*m* – nitrophenyl) – *N* – 2 - (2'-aryluroido / arylthiouroido - 4' - *N* -morpholino-*s*-triazin)-benzo-(6,7)-coumarins were prepared using 2-(*m*-nitrophenyl)-3-hydroxy naphthalene, cyanuric chloride, morpholine and various aryl – ureas / aryl – thioureas derivatives to give desired compound. The structures of the compounds were confirmed by elemental analysis and spectral analysis. The antibacterial activities of these compounds have been screened and were also applied as Fluorescent Brighteners on Polyester fabrics.

Keywords: Benzo – coumarins, Antibacterial activity, Fluorescent Brighteners.

Introduction

The chemistry of coumarins and *s* – triazine have been extensively studied because many drugs include the ring. Many derivatives of coumarin have been used as therapeutic agents¹⁻⁴. Similarly a number of *s*-triazine derivatives have shown various biological activities⁵⁻⁹. Furthermore, urea¹⁰ and thiourea¹¹ derivatives also possess wide therapeutic activities.

Also coumarins have played an important role in textile chemistry and subsequently emerged as fluorephore¹²⁻¹⁵. The coumarin ring system substituted by (hetero) aromatic residues or electro-attracting substituents are characterized by their high light stability. The present study reports the synthesis, application, absorption, characteristics and fastness properties and important biological activities displayed by triazinyl amino coumarin derivatives having following structure.

Experimental

All the melting points are taken in open capillaries and are uncorrected. Absorption and fluorescence emission spectra were recorded on a Hitach U – 320 spectrometer and Jobin Yvon JY 3CS spectrophotofluorometer respectively., IR spectra were recorded on Perkin Elmer 377 – spectrometer, while ^1H NMR spectra on a Varian 60 MHz instrument EM – 360 – L using TMS as internal standard and $\text{CDCl}_3 + \text{DMSO} - d_6$ as solvent. Elemental analysis was performed on Carlo – Erba 1108 analyzer.

Arylureas and arylthioureas

The starting compounds arylureas¹⁷ and arylthioureas¹⁸ are prepared by the known methods.

2-Phenyl-2-(m-nitrophenyl)-3-naphthylacetate

A mixture of 2-(*m*-nitroanilide)-3-hydroxynaphthalene (0.01 mol) and phenylacetic acid (0.01 mol) was stirred with pyridine (20 mL) for an hour to get a clear solution. Phosphorous oxychloride (2.5 mL) was then added in about 15 min. at such a rate that the temperature of the mixture did not rise above 50°C. the mixture was stirred for an hour and diluted with hydrochloric acid. The solid obtained was filtered, washed first with water, then with sodium bicarbonate solution (10% W/V) and again with water, dried and crystallized from acetone to get light pink crystals, yield 84%, m.p.142°C.

3-Phenyl-4-(m-nitroanilide)-benzo-(6,7-b)coumarin

The above compound (0.01 mol) synthesized was added to pulverized potassium hydroxide (1.5 gm) containing pyridine (15 mL) and the mixture was stirred for an hour. It was then decomposed with conc. Hydrochloric acid (10 mL). The resulting mixture was filtered, washed first with water, then with sodium bicarbonate (10% W/V) and again with water, dried and crystallized from chloroform-DMF(4:1) to get brown crystals yield 76%, m.p. 182°C.

3-Phenyl -4 [4-(m – nitrophenyl)-N-(2',4'-dichloro-s-triazine-6'yl)-amino]-benzo-(6,7)-coumarin

Finely powdered Cyanuric chloride (0.01 mol) was stirred with acetone (20 mL) for an hour to form a fine suspension. The solution was cooled to 0-5°C in an ice –bath and a solution of sodium carbonate (0.0126 mol) in water (10 mL) were added in about 4 hours to form slurry. To this slurry a solution of 3-phenyl-4-(*m*-nitroanilide)-benzo-[6,7-b]-coumarin (0.01 mol) in acetone (20 mL) was then added at such a rate that the temperature of the mixture did not rise above 4°C. the mixture was stirred for 3-4 hours at 0-5°C, maintaining pH 7.0 by the addition of sodium – carbonate solution (10% W/V)(if necessary). The product was filtered, washed with cold – water, dried and crystallized from benzene to get pale yellow crystals, yield 67%,m.p.125°C.

3 – Phenyl –4 [4-(m – nitrophenyl)-N-2'-chloro-4'-N-morpholino-s-triasin-6'-yl)-amino]-benzo-(6,7)-coumarin

To a stirred solution of 3 – phenyl –4 [N –(m- nitrophenyl)-N-(2',4'-dichloro-s-triazine-6'-yl)-amino]-benzo-(6,7)-coumarin (0.01 mol) in acetone (100 mL) at 25°C was added morpholine(0.015 mol, sp.gr. 1.006). The temperature was then gradually raised to 15°C and the mixture was stirred for 16 hours at 10 – 15°C, maintaining pH 7.0; by the addition of sodium-bicarbonate solution (10%W/V). The mixture was poured on ice (200gm) and the solid separated was filtered, washed with water, dried and crystallized from absolute alcohol to get yellow crystals, yield82%,m.p.195°C.

3 – Phenyl –4 [4-(m – nitro phenyl)-N-2-(2'-arylureido / arylthioureido -4'-N-morpholino-s-triasin)-benzo-(6,7)-coumarins(1 to 26)

A mixture of 3 – phenyl –4 [4-(m – nitro phenyl)-N-2'-chloro-4'-N-morpholino-s-triasin-6'-yl)-amino]-benzo-(6,7)-coumarin(0.01 mol) and various aryl-ureas (0.015 mol) in dioxane (70 mL) was refluxed for 3 hours at 90-95°C; maintaining pH 7.0 by the addition of sodium – carbonate solution(10% W/V). The mixture was then filtered, washed with ice (200 gm) and the solid separated was filtered, washed with water, dried and crystalline from absolute alcohol to get light – yellow orange crystals of Compounds (1-13).

IR-Spectra(cm^{-1} KBr-pellets)

800 cm^{-1} (C_3N_3); 1720 cm^{-1} (C=O, lactonic); 1290 cm^{-1} (C-O-C, morpholino); 1560 cm^{-1} (-NH-); 3310-3340 cm^{-1} (-NHCONH-);1275 cm^{-1} (- NO₂).

¹NMR – Spectra (CDCl_3 – DMSO - D₆) (δ ppm) of a selected compound (1) showed signals at : 2.00(s,8H,-O-CH₂-CH₂-N<); 2.25(s,8H,-O-CH₂-CH₂-N<); 7.31(bs,2H,-NH-); 8.40(s,4H, -NH-CO); 6.90-7.20(m, 16H, ArH); 7.60-8.22(m,6H,ArH, coumarin ring).

Following the same procedure a mixture of 3 – phenyl –4 [4-(m – nitro phenyl)-N-2'-chloro-4'-N-morpholino-s-triasin-6'-yl)-amino]-benzo-(6,7)-coumarin(0.01 mol) and aryl thioureas (0.015 mol) were refluxed to get compounds (14-26).

IR-Spectra(cm^{-1} KBr-pellets)

840 cm^{-1} (C_3N_3); 1725 cm^{-1} (C=O, lactonic); 1295 cm^{-1} (C-O-C, morpholino); 1580 cm^{-1} (-NH-); 1160-1170 cm^{-1} (C=S,thioureido);1280 cm^{-1} (- NO₂).

¹NMR – Spectra (CDCl_3 – DMSO - D₆) (δ ppm) of a selected compound (17) showed signals at : 1.40(s,3H, -CH₃); 2.10(s,8H,-O-CH₂-CH₂-N<); 2.30(s,8H,-O-CH₂-CH₂-N<); 4.00(s,4H,-NHCS-); 7.40(bs,2H, -NH-); 7.10-7.62(m, 15H, ArH); 7.80-8.24(m,6H,ArH, coumarin ring).

Biological Screening

All the compounds were screened for antibacterial activity following disc-agar diffusion method at a concentration of 15 mcg/disc against S.aureus, S.pyogenes (gram-negative bacterial strain) and E.coli and K.pneumoniae (gram - positive bacterial strain). The test organisms were maintained on nutrient agar glant. Nutrient broth was used as the medium for testing. The compounds were vinitially dissolved in 25 % DMF and then dispended in different volumes of sterile nutrients broth contained in tubes. After the compound was mixed, the medium was inoculated with twenty-four old-culture of the test organism. The tubes were then incubated at 37°C up to forty-eight hours and results are summarized in Table 1.

The analytical and characterization data's are represented in Table 1.

Table 1. Analytical and antimicrobial activity data of the compounds 1 – 26.

Compd. No	R	Melting point	Yield%	Nitrogen Found(Calcd).	Antibacterial activity			
					<i>S.Aureus</i>	<i>S.pyogenes</i>	<i>E.Coli</i>	<i>K.pneumonia</i>
1	H	242	65	15.56 (15.86)	2.0	2.5	3.5	0.5
2	2'-CH ₃	240	72	15.51 (15.55)	0.5	1.0	1.0	1.0
3	3'-CH ₃	247	78	15.50 (15.55)	0.5	1.0	0.5	0.5
4	4'-CH ₃	252	68	15.53 (15.55)	0.0	0.5	0.0	0.5
5	2'-NO ₂	239	72	16.72 (16.77)	1.0	0.5	0.1	1.0
6	3'-NO ₂	231	71	16.76 (16.77)	1.0	0.5	1.0	1.0
7	4'-NO ₂	238	70	16.80 (16.77)	0.5	0.5	1.0	0.0
8	2'-Cl	287	64	15.11 (15.12)	1.0	0.5	0.5	0.0
9	3'-Cl	276	78	15.13 (15.12)	0.5	0.5	1.0	0.0
10	4'-Cl	282	79	15.10 (15.12)	0.5	1.0	0.5	0.5
11	2'-OCH ₃	290	62	15.21 (15.21)	1.0	0.5	1.0	1.0
12	3'-OCH ₃	277	58	15.23 (15.21)	1.0	0.5	0.5	0.0
13	4'-OCH ₃	281	63	15.20 (15.21)	0.5	1.0	0.5	0.5
14	H	256	66	15.50 (15.51)	2.5	2.0	4.0	0.5
15	2'-CH ₃	271	66	15.25 (15.21)	2.0	1.0	1.0	0.5
16	3'-CH ₃	261	73	15.19 (15.21)	0.5	0.5	1.0	0.0
17	4'-CH ₃	277	72	15.25 (15.21)	1.5	0.5	1.0	2.0
18	2'-NO ₂	257	74	16.40 (16.42)	2.0	1.5	2.5	0.0
19	3'-NO ₂	263	76	16.45 (16.42)	0.0	0.0	0.5	0.5
20	4'-NO ₂	267	71	16.39 (16.42)	1.0	1.0	2.0	1.0
21	2'-Cl	273	69	14.79 (14.80)	1.0	0.0	1.5	1.0
22	3'-Cl	257	57	14.85 (14.80)	1.0	1.0	2.0	2.0
23	4'-Cl	265	64	14.82 (14.80)	0.5	0.5	1.0	0.0
24	2'-OCH ₃	281	69	14.83 (14.89)	1.0	0.0	1.5	1.0
25	3'-OCH ₃	253	77	14.86 (14.89)	0.0	0.0	0.5	0.5
26	4'-OCH ₃	273	81	14.81 (14.89)	1.0	1.0	2.0	2.0
Standard Drugs				Ampicillin	5.0	--	--	--
				Cephalexin	--	6.0	--	--
				Gentamycin	--	--	6.0	--
				Chloramphenicol	--	--	--	6.0

Dyeing

These compounds were applied to polyester fabrics as fluorescent brighteners using reported procedure¹⁶ and Fastness tests were assessed by the standard methods of testing (BS :1006 – 1978 and IS : 765 – 1979).

Conclusion

All the compounds synthesized were screened for antibacterial activity. For all the tested compounds the zone of inhibition in mm are given in Table 1. Activities of standard drugs are also given for comparison.

Evaluation of bacterial activity reveals that the compound 1 and 14 having phenylureido and phenylthioureido groups respectively in the 4' – position of *s*-triazine ring showed activity

up to 3.5 mm and 4.0 mm respectively. These compounds are nearly 59 – 60% as active as Gentamycin and 43-52% as active as Ampicillin. However, the compound 2-13 and 15-26 having substituted phenylureido and phenylthioureido groups in the 4' – position of *s*-triazine ring showed slight decrease in the activity due to presence of morpholin groups in the 2' – position of *s*-triazine ring and also showed maximum inhibitory zone up to 2.5 mm.

Table 2. Absorption – Emission and Fastness Evaluation Data of the compounds 1 – 26.

Compd. No.	Absorption Emission			Fastness properties						
	λ_{max}	λ_{max}	Log E	Light	Wash	Perspiration		Chlorine	Sublimation	Pick up Value
						Acid	Alkaline			
1	345	463	4.46	5	4	3 -4	4	3 - 4	2 - 3	1 - 2
2	320	446	4.39	4	4	4	3 -4	3	2	1 - 2
3	314	453	4.36	4	4	3 -4	4	4	3	1 - 2
4	319	461	4.56	4	3 - 4	5	5	5	3	2
5	334	452	4.57	4	4 - 5	5	5	5	4	2
6	330	447	4.70	4 - 5	5	5	5	4	4	3
7	342	457	4.80	5	6	5 -6	6	5	4	4
8	338	458	4.63	5	5 -6	6	5 -6	5 - 6	4	3 - 4
9	312	451	4.46	5	6	6	6	6	2 - 3	4
10	305	445	4.34	3	4 -5	4 -5	4 -5	5 - 6	2	4
11	354	444	4.30	4 - 5	4	4	4	3	2	2
12	326	458	4.67	3	3 -4	3 -4	3 -4	3 - 4		1 - 2
13	317	457	4.45	3 - 5	3 -4	4	3	3	2 - 3	2
14	315	454	4.42	4	3 -4	4 -5	4 -5	4	4	2
15	330	465	4.54	4 - 5	4	4	5	4	4	1 - 2
16	333	446	4.37	4 - 5	5	5 -6	5 -6	5 - 6	4	2
17	345	460	4.49	6	5	4 -5	5 -6	5 - 6	4	3
18	310	446	4.35	5 - 6	5	5	4 -5	5	4	2 - 3
19	335	454	4.43	5 - 6	5 -6	5 -6	5 -6	5 - 6	4	4
20	300	432	4.21	3 - 4	4	4	4	5	3	4
21	305	440	4.32	3	4 -5	4 -5	4 -5	5 - 6	2 - 3	4
22	312	450	4.47	5	6	6	6	6	4	4
23	338	460	4.61	5	5 -6	6	5 -6	6	4	3 - 4
24	342	458	4.80	5	6	5 -6	6	5	4	4
25	330	448	4.72	4 - 5	5	5	5	4	4	3
26	334	451	4.56	4	4 -5	5	5	5	3	2 - 3

The compounds when applied to polyester fibres as a fluorescent brighteners (Table 2) showed a whitening effect with bluish fluorescence in the case of compound 5,6,15,16,25,26; greenish – blue fluorescence in the case of compounds 1,2,3,4,11,12,13,14; and bluish – violet fluorescence in the case of 7,8,9,10,17,18,19,21,22,23,24 compounds on assessment, for relative use as fluorescent brighteners could be sub – divided into grades as under:

Compounds	Grade
10,20,21	1
1,2,3,4,11,12,13,14	2
5,6,7,8,9,15,16,17,18,19,22,23,24,25,26	3

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