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Synthesis and screening of 1, 3, 4-oxadiazinoindolinone and *s*-triazole derivatives of pyranobenzopyran

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3-Formyl-4- hydroxycoumarin is treated with malonic acid in the presence of zinc chloride catalyst to give 2*H*, 5*H*-2,5-dioxo-3-pyrano[3, 2-*c*]benzopyranoic acids **1a-d** which on treatment with methanol in the presence of thionyl chloride give methyl 2*H*, 5*H*-2,5-dioxopyrano[3, 2-*c*]benzopyran-3-oates **2a-d**. Compounds **2a-d** were converted into their acid hydrazides **3a-d**. **3a-d** on treatment with isatin yield 1*H*, 2*H*-3-(2*H*, 5*H*-2,5-dioxopyrano[3, 2-*c*]benzopyran-3-carboxyhydrazono)-2-indolinones **4a-d** which on cyclisation with conc. H_2SO_4 afford 3-[1, 3, 4-oxadiazino[5, 6-*b*]indol-2-yl]-2,5-dioxopyrano[3,2-c]benzopyrans **5a-d**. Acid hydrazides **3a-d** on treatment with carbon disulfide in 10% KOH at room temperature followed by treatment with ortho-chlorobenzoic acid hydrazide furnish 3-(2*H*, 5*H*-2, 5-dioxopyrano[3, 2-*c*]benzopyran-3-yl)-4-{N-2′-chlorophenylcarboxamido]-5-mercapto-1,2,4-triazoles **6a-d**.

Keywords: 3-Formyl-4-hydroxycoumarin, zinc chloride, benzopyronic acids, thionyl chloide, 1,3,4-oxadiazinoindolinone, s-triazole derivatives, pyranobenzopyran, antimicrobial activity

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Pyranobenzopyran and triazole are reported to possess various biological activities[1-10] such as antibacterial, antifungal, CNS depressant, antiviral, ulcer inhibitor etc. Similarly, indoles and 1,3,4-oxadiazino derivatives have their own class of important drug and drug intermediate. It was, therefore, thought of synthesizing first pyranobezopyran derivative and then introducing traizole ring at 3-position of pyranobenzopyran ring, which may have some of the above activities.

For this purpose 3-formyl-4-hydroxyhydroxy-coumarin[12] was treated with malonic acid in the presence of zinc chloride catalyst to give 2*H*, 5*H*-2,5-dioxo-3-pyrano[3,2-*c*]benzopyranoic acids **1a-d**. The same compounds have also been synthesized by using ionic liquid in very low yield. The structures of the compounds have been confirmed by mix melting point and super imposable IR. The IR spectrum of 2*H*, 5*H*-2,5-dioxo-3-pyrano[3,2-*c*]benzopyranoic acid showed absence of band at 2720 cm^{-1} which was due to aldehydic group. ^{1}H NMR spectrum showed singlet at δ 5.75 for C_4-H and singlet at δ 11.80 for hydroxyl proton of carboxylic acid, which is D_2O exchangeable. This compound dissolves with effervescence in sodium bicarbonate solution.

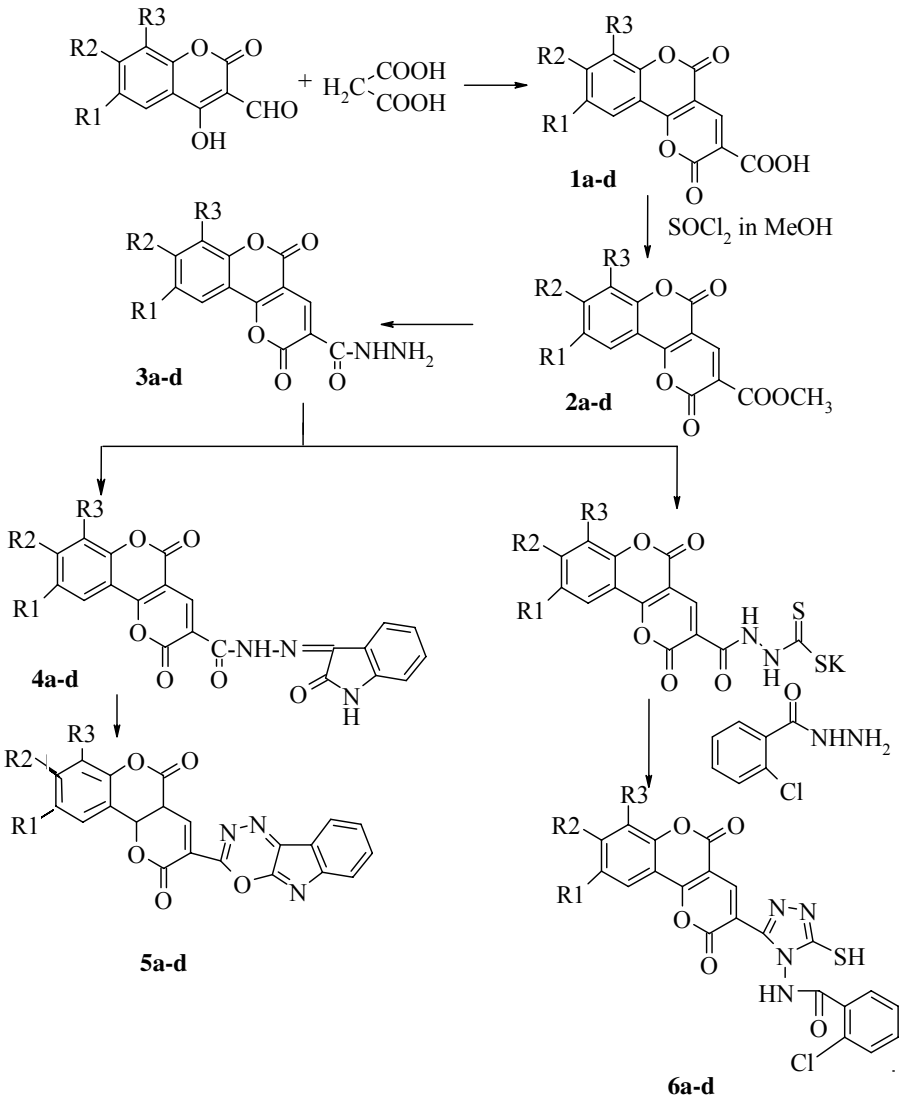
The methyl ester of compound **1** was prepared by using methanol in the presence of thionyl chloride to give 2*H*, 5*H*-2,5-dioxo-3-pyrano[3, 2-*c*]benzopyranoic acids **1a-d** which on treatment with methanol in the presence of thionyl chloride furnished methyl 2*H*, 5*H*-2,5-dioxopyrano[3,2-*c*]benzopyran-3-oates **2a-d**. The compounds **2a-d** were converted into its acid hydrazides **3a-d** which showed the presence of band at 3401, 3219 cm^{-1} for NH in IR spectrum. ^{1}H NMR showed presence of two singlets at δ 4.15 and 8.8 for two NH_2 protons and one NH proton respectively, which were D_2O exchangeable. The acid hydrazides **3a-d** on treatment with carbon disulfide in 10% KOH at room temperature followed by treatment with ortho-chlorobenzoic acid hydrazide gave 3-(2*H*, 5*H*-2,5-dioxopyrano[3,2-*c*]-benzopyran-3-yl)-4-[N-2′-chlorophenylcarboxamido]-5-mercapto-1,2,4-triazoles **6a-d** (**Scheme I**).

3a-d on treatment with isatin gave 1*H*, 2*H*-3-(2*H*, 5*H*-2,5-dioxopyrano[3,2-*c*]benzopyran-3-carboxyhydra-zono)-2-indolinones **4a-d**, which on cyclisation with conc. H_2SO_4 yielded 3-[1,3,4-oxadiazino[5,6-*b*]indol-2-yl]-2,5-dioxopyrano[3,2-*c*]benzopyrans **5a-d**.

The structures of above compounds were in agreement with analytical data (**Tables I** and **II**) and were screened for their antimicrobial activity against bacterial strains (**Table III**).

Antimicrobial activity

All the above synthesized compounds were screened *in vitro* for their antimicrobial activity against variety of bacterial strains such as *S.aureus*, *S.typhi* and *E.coli*. The minimum inhibition concentration



1a-6a : R_1, R_2, R_3 = H

1b-6b : R_1 = CH_3, R_2, R_3 = H

1c-6c : R_1, R_3 = H, R_2 = CH_3

1d-6d : R_1, R_2 = H, R_3 = CH_3

Scheme I

(MIC) was determined using Tube Dilution technique according to standard procedure[11] (**Table II**). The standard drugs used for comparison were ciprofloxacin, cloxacillin and gentamycin. By visualizing the antimicrobial data it could be observed that many of the compounds possess significant activity.

Experimental Section

General. Melting points were taken in open capillaries and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 257 spectrometer using KBr; ^{1}H NMR and ^{13}C NMR spectra in DMSO-d_6 were recorded on VXR-300 MHz using TMS as internal standard; and mass spectra on a Shimadzu GC-MS. The homogeneity of the compounds was described by TLC on silica gel plates. The spots are developed in iodine chamber.

2*H*,5*H*-2,5-Dioxo-3-pyrano[3, 2-*c*]benzopyranoic acids 1a-d. General procedure. Method A — A mixture of 3-formyl-4-hydroxycoumarin[12] (0.01 mole),

Table I — Characterization data of compound **1 a-d**, **2a-d**, **3a-d**, **4a-d**, **5a-d** and **6a-d**

Compd	Mol. formula	R_1	R_2	R_3	m. p. °C	Yield (%)	Found (Calcd) (%) C	H	N	S	Cl
1a	$C_{13}H_6O_6$	H	H	H	291	A=12	60.36	2.31	—	—	—
						B=19	(60.46	2.32	—	—	—)
1b	$C_{14}H_8O_6$	CH_3	H	H	305	A=10	61.56	2.65	—	—	—
						B=18	(61.76	2.94	—	—	—)
1c	$C_{14}H_8O_6$	H	CH_3	H	308	A=10	61.54	2.68	—	—	—
						B=18	(61.76	2.94	—	—	—)
1d	$C_{14}H_8O_6$	H	H	CH_3	298	A=10	61.65	2.52	—	—	—
						B=18	(61.76	2.94	—	—	—)
2a	$C_{14}H_8O_6$	H	H	H	267	75	61.48	2.48	—	—	—
							(61.76	2.94	—	—	—)
2b	$C_{15}H_{10}O_6$	CH_3	H	H	270	72	62.58	3.15	—	—	—
							(62.94	3.49	—	—	—)
2c	$C_{15}H_{10}O_6$	H	CH_3	H	264	74	62.84	3.41	—	—	—
							(62.94	3.49	—	—	—)
2d	$C_{15}H_{10}O_6$	H	H	CH_3	271	70	62.51	3.24	—	—	—
							(62.94	3.49	—	—	—)
3a	$C_{13}H_8O_5N_2$	H	H	H	163	68	57.14	2.59	10.15	—	—
							(57.35	2.94	10.29	—	—)
3b	$C_{14}H_{10}O_5N_2$	CH_3	H	H	160	62	58.45	3.14	9.45	—	—
							(58.74	3.49	9.79	—	—)
3c	$C_{14}H_{10}O_5N_2$	H	CH_3	H	154	59	58.35	3.15	9.57	—	—
							(58.74	3.49	9.79	—	—)
3d	$C_{14}H_{10}O_5N_2$	H	H	CH_3	165	62	58.58	3.25	9.41	—	—
							(58.74	3.49	9.79	—	—)
4a	$C_{21}H_{11}O_6N_3$	H	H	H	307	73	62.54	2.58	10.16	—	—
							(62.84	2.74	10.47	—	—)
4b	$C_{22}H_{13}O_6N_3$	CH_3	H	H	319	70	63.41	2.94	9.88	—	—
							(63.62	3.13	10.12	—	—)
4c	$C_{22}H_{13}O_6N_3$	H	CH_3	H	301	73	63.32	2.86	9.82	—	—
							(63.62	3.13	10.12	—	—)
4d	$C_{22}H_{13}O_6N_3$	H	H	CH_3	296	69	63.48	2.99	9.96	—	—
							(63.62	3.13	10.12	—	—)
5a	$C_{21}H_9O_5N_3$	H	H	H	297	78	65.45	2.12	10.81	—	—
							(65.79	2.34	10.96	—	—)
5b	$C_{22}H_{11}O_5N_3$	CH_3	H	H	290	76	66.27	2.47	10.34	—	—
							(66.49	2.77	10.58	—	—)
5c	$C_{22}H_{11}O_5N_3$	H	CH_3	H	286	78	66.63	2.68	10.48	—	—
							(66.49	2.77	10.58	—	—)
5d	$C_{22}H_{11}O_5N_3$	H	H	CH_3	291	80	66.47	2.54	10.42	—	—
							(66.49	2.77	10.58	—	—)
6a	$C_{21}H_{11}O_5N_4SCl$	H	H	H	134	60	53.87	2.26	11.84	6.67	7.41
							(54.07	2.36	12.01	6.86	7.51)
6b	$C_{22}H_{11}O_5N_4SCl$	CH_3	H	H	130	58	54.87	2.26	11.42	6.67	7.12
							(55.00	2.29	11.66	6.66)	7.29
6c	$C_{22}H_{11}O_5N_4SCl$	H	CH_3	H	131	61	54.76	2.13	11.24	6.45	7.18
							(55.00	2.29	11.66	6.66	7.29)
6d	$C_{22}H_{11}O_5N_4SCl$	H	H	CH_3	128	56	54.67	2.24	11.28	6.52	7.21
							(55.00	2.29	11.66	6.66	7.29)

Table II — Spectral data of compounds **1b-6b**

Compd	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)	Mass m/z (%)
1b	2.4(s, 3H, CH_3), 5.75(s, 1H, C_4-H), 7.04(d, 1H, C_7-H, *J*=7.5Hz), 7.2(d, 1H, C_8-H, *J*=7.5 Hz), 7.45(s, 1H, C_{10}-H), 11.80(s, 1H, D_2O exchangeable).	22(CH_3), 101.4(C_4), 102.1(C_3), 114.9(C_{10a}), 118(C_7), 118.2(C_{4a}), 125(C_{10}), 129.8(C_9), 131.5(C_8), 151(C_{6a}), 151.8(C_{11}), 161.7(C_2), 162.4(C_5), 182(COOH).	272 (M^+), 244, 228, 200, 175, 172, 149, 144, 116, 91, 77,etc.
2b	2.25(s,3H,CH_3), 4.20(s, 3H, OCH_3), 6.10 (s, 1H, C_4-H), 7.10 (d, 1H, C_8-H, *J*=7.5 Hz), 7.25 (d, 1H, C_7-H, *J*=7.5 Hz), 7.40(s, 1H, C_{10}-H)	20(CH_3), 68(OCH_3), 101.5(C_4), 102.6(C_3), 115.5(C_{10a}), 118.1(C_7), 121(C_{4a}), 124.4(C_{10}), 130(C_9), 131(C_8), 150(C_{6a}), 151(C_{11}), 162(C_2), 162.5(C_5), 171($COOCH_3$).	286(M^+), 256, 228, 200, 172, 144, 116, 91, 77 etc.
3b	2.30(s, 3H, CH_3), 4.15 (s, 2H, NH_2 D_2O exchangeable), 6.35 (s, 1H, C_4-H), 7.05 (d, 1H, C_8-H, *J*=7 Hz), 7.20 (d, 1H, C_7-H, *J*=7 Hz), 7.40 (s, 1H, C_{10}-H), 8.80 (s, 1H, D_2O exchangeable).	22(CH_3), 100.3(C_4), 102(C_3), 116(C_{10a}), 118.2(C_7), 119.4(C_{4a}), 124.3(C_{10}), 129(C_9), 130.8(C_8), 149.4(C_{6a}), 150(C_{11}), 160(CONH), 162(C_2), 163(C_5).	286(M^+), 271, 256, 255, 228, 227, 200, 175, 172, 146, 144, 118, 91, 90, 89, 77 etc.
4b	2.30 (s, 3H, CH_3), 6.20 (s, 1H,C_4-H), 7.08 (d, 1H, C_4'-H, *J*=7.0 Hz), 7.27 (d, 1H, C_8-H, *J*=7.5 Hz), 7.40 (t, 2H, C_5'& C_6' H), 7.58(s, 1H, C_{10}-H, *J* = 7.0 Hz), 7.70(d, 1H, C_7-H, *J*=7.5Hz), 7.91(d, 1H, C_7' H, *J*=7.0Hz), 8.25 (s, 1H, NHCO, D_2O exchangeable), 8.70 (s, 1H, N-NH–C, D_2O exchangeable).	21(CH_3), 101.8(C_4), 102(C_3), 115(C_{10a}), 117.6(C_7), 119(C_{4a}), 120(C_5'), 121.5(C_6'), 124(C_4'), 125(C_{10}), 126(C_7'), 127($C_3'_a$), 129(C_9), 131.4(C_8), 135(C_7'a), 139(C_3'), 151(C_6a), 152(C_{11}), 157(C_1'), 159(CONH), 161(C_2), 162.5(C_5).	415(M^+), 270, 255, 227, 200, 172, 146, 145, 118, 117, 91, 77 etc.
5b	2.48(s, 3H, CH_3), 6.30(s, 1H, C_4-H), 6.90(d, 1H, C_5'-H *J*=7 Hz), 7.15 (d, 1H, C_8-H, *J*=7.5 Hz), 7.25(t, 2H, C_6' & C_7'-H), 7.55(d, 1H, C_7-H *J* = 7.5 Hz), 7.40(s, 1H, C_{10}-H), 7.80 (d, H, C_8'-H, *J* = 7.0 Hz).	20 (CH_3), 100.1(C_3), 101.5(C_4), 101.5(C_{10a}), 118(C_7), 120(C_{4a}), 121(C_6'), 122.5(C_7'), 124 (C_5'), 124.5(C_{10}), 126.5($C_4'_b$), 128(C_8'), 130(C_9), 131(C_8), 136(C_8'a), 138(C_4'a), 150 (C_6a), 152(C_{11}), 156($C_9'_a$), 160 (C_2'), 162 (C_2), 162.5(C_5).	397(M^+), 375, 357, 344, 342, 227, 213, 199, 175, 144, 134, 133, 125, 105, 90, 84, 83, 77, 68, 57 etc.
6b	2.4 (s, 3H, CH_3), 3.15(s, 1H, SH, D_2O exchangeable), 6.65(s, 1H, C_4-H), 7.15 (d, 1H, C_8-H, *J*=7 .5 Hz), 7.25(t, 2H, C_4' & C_5' H), 7.50 (d, 1H, C_7-H, *J* = 7.5 Hz), 7.70 (d, 1H, C_6' H *J*=7 Hz), 7.85(s, 1H, C_{10}-H), 7.95(d, 1H, C_3' H, *J* = 7.0 Hz), 8.50(s, 1H, -NH, D_2O exchangeable).	22 (CH_3), 100.0 (C_3), 102.0 (C_4), 110.0 (C_{10a}), 118 (C_7), 120 (C_{4a}), 121 (C_4'), 124 (C_5'), 125 (C_{10}), 127.0 (C_3'), 129.0(C_9), 131 (C_8), 135 (C_6'), 137 (C_1'a), 141(C_2'), 150.0 (C_{6a}), 152.0 (C_{11}), 156.0 (C_3, N-C= N), 159 (CONH), 162 (C_2), 163.0 (C_5), 165 (C_5 N=C (SH)-N)	480(M^+), 482(M^{+2}), 403, 393, 384, 296, 279, 229, 214, 190, 177, 162, 161, 149, 147, 136, 119, 104, 92, 77 etc

Table III — Antibacterial activity of compounds **1a-d**, **2a-d**, **3a-d**, **4a-d**, **5a-d** and **6a-d**

Compd	Antibacterial activity			Compd	Antibacterial activity		
	S.aureus	*S.typhi*	*E.coli*		*S.aureus*	*S.typhi*	*E.coli*
1a	-	-	-	**4a**	-	150	145
1b	-	-	-	**4b**	-	-	150
1c	-	-	-	**4c**	-	-	140
1d	-	-	-	**4d**	140	100	95
2a	-	-	-	**5a**	85	90	110
2b	-	150	150	**5b**	90	120	100
2c	-	-	-	**5c**	80	80	65
2d	-	150	150	**5d**	95	70	80
3a	145	130	95	**6a**	100	115	85
3b	150	145	100	**6b**	90	120	80
3c	90	125	95	**6c**	85	85	90
3d	80	80	105	**6d**	50	70	65

- =Not active up to 150 µg/mL

malonic acid (0.01 mole) and anhydrous zinc chloride (0.02 mole) were fused at 120°C for 30 min. The mixture was poured into ice-water and filtered. The solid obtained was dissolved in sodium bicarbonate, filtered and the filtrate was acidified with conc. HCl to get **1a-d**, which were recrystallised from methanol.

Method B — To a mixture of 3-formyl-4-hydroxy-coumarin (0.001 mole) and malonic acid (0.001 mole), the ionic liquid[bmim] $Cl.AlCl_3$ N = 0.50-0.67 was added in an inert atmosphere and the reaction mixture was heated for 15 min. The reaction mixture was quenched by adding 6 *M* HCl in cold condition. It was then extracted with ethyl acetate. The organic layer was dried using anhydrous sodium sulphate and evaporated to yield the compounds **1a-d**.

Methyl 2*H*,5*H*-2,5-dioxopyrano[3,2-*c*]benzopyran-3-oates 2a-d. General procedure. Thionyl chloride (0.01 mole) was added dropwise into the cold solution of **1a-d** (0.002 mole) and methanol (10 mL). The mixture was stirred at room temperature for 3 hr and poured into water. The solid obtained was filtered and washed with solution of sodium bicarbonate and water. The product was recrystallised from ethanol.

2*H*,5*H*-2,5-Dioxopyrano[3,2-*c*]benzopyranoic acid hydrazide 3a-d. General procedure. A mixture of **2a-d** (0.001 mole), hydrazine hydrate (0.001 mole), 10 mL ethanol and 2 drops of acetic acid was refluxed for 5 hr. The solution was concentrated, cooled and poured into ice-water. The solid product thus obtained was filtered under suction and dried. The product was recrystallized from methanol.

1*H*,2*H*-3-(2*H*,5*H*-2,5-Dioxopyrano[3,2-*c*]benzopyran-3-carboxyhydrazono)-2-indolinones 4a-d. General procedure. A mixture of **3a-d** (0.001 mole), isatin (0.001 mole), 20 mL of ethanol and 2 drops of glacial acetic acid was refluxed for 1 hr. It was then left overnight at room temperature. The solution was poured into ice-water. The solid obtained was filtered, dried and recrystallised from methanol.

3-[1,3,4-Oxadiazino[5,6-*b*] indol-2-yl]-2*H*,5*H*, 2,5-dioxopyrano[3,2-*c*]benzopyran-2,5-diones 5a-d. General procedure. The hydrazone **4a-d** (0.001 mole) was dissolved with cooling in conc. H_2SO_4 (10 mL). The reaction mixture was stirred for 15 min and further kept for 4 hr at room temperature. It was then poured into crushed ice and neutralized with ammonia solution. The precipitate thus obtained was filtered, washed with water and recrystallized from ethanol to obtain **5a-d**.

3-(2*H*,5*H*-2,5-Dioxopyrano[3,2-*c*]benzopyran-3-yl)-4-[N-2′-chlorophenyl carboxamido]-5-mercapto-1,2,4-triazoles 6a-d. General procedure. To a solution of potassium hydroxide (0.05 mole) in absolute ethanol (10 mL), **3a-d** (0.01 mole) and carbon disulfide (0.015 mole) were added and the mixture was stirred for 16 hr. To this ortho-chlorobenzoic acid hydrazide was added and heated for 6 hr. The reaction mixture was cooled and poured into ice. On acidification the compounds **6a-d** were obtained, which were filtered, washed with water and crystallized from aqueous ethanol.

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