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Note

Novel method for synthesis and antimicrobial activity of 2-arylsulpho-6-hydroxy/chloro/hydrazino/carboxy-methoxy-3(2*H*)-pyridazinones

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The title compounds 2-arylsulpho-6-hydroxy/chloro/hydrazino/carboxymethoxy-3(2*H*)-pyridazinones **1-4** have been synthesised. The chemoselective cyclocondensation of maleoyl chloride with arylsulphonyl hydrazides gives **1a-o**. Compounds **1a-o** on chlorination with $POCl_3$ give **2a-o** which on reaction with hydrazine hydrate give **3a-o**. Compounds **1a-o** on reaction with $ClCH_2COOH$ in aq. NaOH furnish **4a-o**. The structures of the products have been delineated by elemental analyses and spectral data. Antimicrobial activities have also been studied.

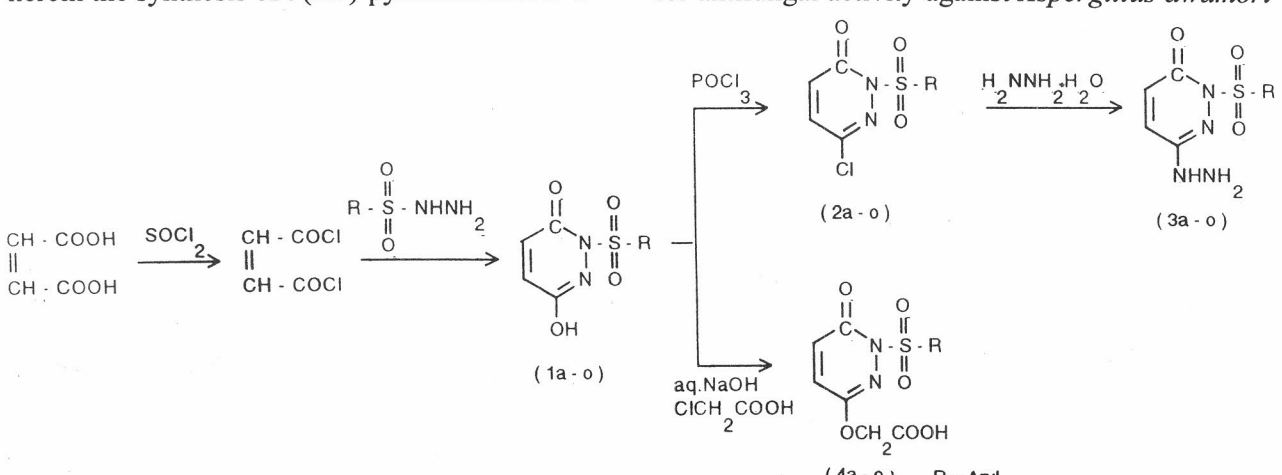
A number of 3(2*H*)-pyridazinones have been reported to be associated with different biological activities[1-3], and have been used as agrochemical agents, such as plant growth regulator[4-7], herbicides[8,9] and fungicides[10,11]. "Hydralazine[12] is a well known drug in medicinal chemistry employed as an antihypertensive drug. With a view to synthesize diverse biodynamic derivatives associated with 3(2*H*)-pyridazinone derivatives, we report herein the synthesis of 3(2*H*)-pyridazinones **1-4**.

The literature survey reveals that 3(2*H*)-pyridazinones are synthesised by the old conventional method involving condensation of maleic anhydride with hydrazine hydrate[13], whereas our present method required cyclocondensation of maleoyl chloride with arylsulphonyl hydrazide.

The starting compound maleoyl chloride, prepared by the reaction of maleic acid with thionyl chloride, on chemoselective cyclization with arylsulphonyl hydrazides in the presence of pyridine yielded 2-arylsulpho-6-hydroxy 3(2*H*)-pyridazinones **1a-o** (**Scheme I**). Compounds **1a-o**, on chlorination with $POCl_3$ furnished 2-arylsulpho-6-chloro-3(2*H*)-pyridazinones **2a-o** which underwent hydrazinolysis by refluxing with hydrazine hydrate to afford 2-arylsulpho-6-hydra-zino-3(2*H*)-pyridazinones **3a-o**.

Compounds **1a-o** also underwent condensation with chloroacetic acid in aq. NaOH, to form 2-arylsulpho-6-carboxymethoxy-3(2*H*)-pyridazinones **4a-o**. The formation of these products has been delineated by spectral study. All the products synthesised were evaluated for their antimicrobial activity against different strains of bacteria and fungi (**Table I**).

Antimicrobial activity. All the compounds were tested for their antimicrobial activity under identical conditions. Antibacterial activity against *Bacillus megaterium, Bacillus substilis, Escherichia coli* and *Psudonomus fluorescens* and for antifungal activity against *Aspergillus awamori*



Scheme I

Table I—The physical data and antimicrobial activity of compounds **1-4**

Compd	R	mp °C	Yield (%)	Mol. formula	Nitrogen (%)		Antibacterial activity*			Antifungal activity*	
					Calcd	Found	*B. mega*	*B. substilis*	*E. coli*	*P. fluorescens*	*A. awamori*
1a	C_6H_5	174	68.12	$C_{10}H_8O_4N_2S$	11.11	11.09	16	14	14	16	16
1b	3-$COOHC_6H_4$	187	73.96	$C_{11}H_8O_6N_2S$	9.45	9.39	19	13	16	18	18
1c	4-(CH=CHCOOH)C_6H_4	215	76.08	$C_{13}H_{10}O_6N_2S$	8.69	8.60	23	15	18	20	17
1d	4-Cl,3-$COOHC_6H_3$	183	71.29	$C_{11}H_7O_6N_2SCl$	8.47	8.41	20	18	19	21	23
1e	2-Cl,5-$COOHC_6H_3$	198	75.36	$C_{11}H_7O_6N_2SCl$	8.47	8.39	16	16	14	26	20
1f	3-COOH,4-OHC_6H_3	226	67.53	$C_{11}H_8O_7N_2S$	8.97	8.90	14	14	13	20	21
1g	3-COOH,2-$OCH_3C_6H_3$	138	78.88	$C_{12}H_{10}O_7N_2S$	8.58	8.52	18	12	18	17	24
1h	2-COOH,4-$OCH_3C_6H_3$	154	70.45	$C_{12}H_{10}O_7N_2S$	8.58	8.50	22	15	20	19	19
1i	3-COOH,6-$OCH_3C_6H_3$	189	69.81	$C_{12}H_{10}O_7N_2S$	8.58	8.53	19	13	19	23	21
1j	3-COOH,4-$CH_3C_6H_3$	210	73.42	$C_{12}H_{10}O_6N_2S$	9.03	9.00	14	11	16	17	22
1k	3-COOH,6-$CH_3C_6H_3$	231	77.00	$C_{12}H_{10}O_6N_2S$	9.03	8.99	17	13	15	19	18
1l	4-ClC_6H_4	107	83.77	$C_{10}H_7O_4N_2SCl$	9.77	9.71	19	18	14	24	21
1m	4-BrC_6H_4	285(d)	85.99	$C_{10}H_7O_4N_2SBr$	8.45	8.41	17	14	13	20	17
1n	4-$NHCOCH_3C_6H_4$	229	79.04	$C_{12}H_{11}O_5N_3S$	13.59	13.52	12	12	12	19	19
1o	4-$NHCOCH_3$,3-COOH-C_6H_3	253	82.40	$C_{13}H_{11}O_7N_3S$	11.89	11.84	14	11	15	17	20
2a	C_6H_5	142	65.19	$C_{10}H_7O_3N_2SCl$	10.35	10.29	16	11	14	17	15
2b	3-$COOHC_6H_4$	158	56.38	$C_{11}H_7O_5N_2SCl$	8.90	8.83	18	13	13	19	18
2c	4-(CH=CHCOOH)C_6H_4	245	59.94	$C_{13}H_9O_5N_2SCl$	8.22	8.17	17	15	16	21	15
2d	4-Cl,3-$COOHC_6H_3$	138	62.68	$C_{11}H_6O_5N_2SCl_2$	8.02	7.99	20	17	24	19	19
2e	2-Cl,5-$COOHC_6H_3$	175	65.32	$C_{11}H_6O_5N_2SCl_2$	8.02	8.01	23	15	19	24	23
2f	3-COOH,4-OHC_6H_3	273	60.00	$C_{11}H_7O_6N_2SCl$	8.47	8.42	19	14	16	18	18
2g	3-COOH,2-$OCH_3C_6H_3$	106	63.08	$C_{12}H_9O_6N_2SCl$	8.12	8.05	21	16	15	20	21
2h	2-COOH,4-$OCH_3C_6H_3$	143	64.37	$C_{12}H_9O_6N_2SCl$	8.12	8.10	18	12	17	25	19
2i	3-COOH,6-$OCH_3C_6H_3$	213	65.65	$C_{12}H_9O_6N_2SCl$	8.12	8.07	17	14	13	19	17
2j	3-COOH,4-$CH_3C_6H_3$	273	62.80	$C_{12}H_9O_5N_2SCl$	8.52	8.49	15	16	18	16	16
2k	3-COOH,6-$CH_3C_6H_3$	275	70.01	$C_{12}H_9O_5N_2SCl$	8.52	8.48	18	17	20	18	18
2l	4-ClC_6H_4	184	63.14	$C_{10}H_6O_3N_2SCl_2$	9.18	9.14	24	19	25	16	24
2m	4-BrC_6H_4	>300	69.29	$C_{10}H_6O_3N_2SClBr$	8.01	7.99	16	12	21	14	20
2n	4-$NHCOCH_3C_6H_4$	271	71.74	$C_{12}H_{10}O_4N_3SCl$	12.82	12.78	12	14	15	19	17
2o	4-$NHCOCH_3$,3-COOH-C_6H_3	239	75.93	$C_{13}H_{10}O_6N_3SCl$	11.30	11.26	15	17	14	21	19
3a	C_6H_5	187	63.18	$C_{10}H_{10}O_3N_4S$	21.05	20.99	14	13	16	18	15
3b	3-$COOHC_6H_4$	216	74.31	$C_{11}H_{10}O_5N_4S$	18.05	18.04	17	11	13	14	12
3c	4-(CH=CHCOOH)C_6H_4	203	65.96	$C_{13}H_{12}O_5N_4S$	16.66	16.59	19	14	15	17	14
3d	4-Cl,3-$COOHC_6H_3$	115	61.18	$C_{11}H_9O_5N_4SCl$	16.25	16.20	26	15	18	20	19
3e	2-Cl,5-$COOHC_6H_3$	98	59.73	$C_{11}H_9O_5N_4SCl$	16.25	16.23	21	13	17	18	21
3f	3-COOH,4-OHC_6H_3	242	62.49	$C_{11}H_{10}O_6N_4S$	17.17	17.11	19	14	12	15	15

Table – Contd

Table I—The physical data and antimicrobial activity of compounds **1-4** (Contd.)

Compd	R	mp °C	Yield (%)	Mol. formula	Nitrogen (%)		Antibacterial activity*			Antifungal activity*	
					Calcd	Found	*B. mega*	*B. substilis*	*E. coli*	*P. fluorescens*	*A. awamori*
3g	3-COOH,2-$OCH_3C_6H_3$	197	57.04	$C_{12}H_{12}O_6N_4S$	16.47	16.42	17	16	14	12	14
3h	2-COOH,4-$OCH_3C_6H_3$	240	58.19	$C_{12}H_{12}O_6N_4S$	16.47	16.40	13	14	17	25	17
3i	3-COOH,6-$OCH_3C_6H_3$	281	60.40	$C_{12}H_{12}O_6N_4S$	16.47	16.35	14	18	19	19	19
3j	3-COOH,4-$CH_3C_6H_3$	148	54.85	$C_{12}H_{12}O_6N_4S$	17.28	17.23	17	13	13	17	20
3k	3-COOH,6-$CH_3C_6H_3$	205	57.77	$C_{12}H_{12}O_5N_4S$	17.28	17.19	19	15	18	20	18
3l	4-ClC_6H_4	192	65.85	$C_{10}H_9O_3N_4SCl$	18.63	18.58	20	17	21	23	25
3m	4-BrC_6H_4	285(d)	70.93	$C_{10}H_9O_3N_4SBr$	16.23	16.21	18	16	19	18	22
3n	4-$NHCOCH_3C_6H_4$	133	68.18	$C_{12}H_{13}O_4N_5S$	21.67	21.63	21	12	16	17	18
3o	4-$NHCOCH_3$,3-COOH-C_6H_3	214	75.35	$C_{13}H_{13}O_6N_5S$	19.07	19.02	17	14	18	21	19
4a	C_6H_5	189	81.93	$C_{12}H_{10}O_6N_2S$	9.03	8.97	17	14	14	19	17
4b	3-$COOHC_6H_4$	209	80.00	$C_{13}H_{10}O_8N_2S$	7.90	7.81	19	17	16	21	18
4c	4-(CH=COOH)C_6H_4	236	78.21	$C_{15}H_{12}O_8N_2S$	7.36	7.28	21	20	18	23	18
4d	4-Cl,3-$COOHC_6H_3$	198	75.48	$C_{13}H_9O_8N_2SCl$	7.20	7.11	20	18	20	27	24
4e	2-Cl,5-$COOHC_6H_3$	240	78.73	$C_{13}H_9O_8N_2SCl$	7.20	7.09	23	16	21	22	21
4f	3-COOH,4-OHC_6H_3	151	69.04	$C_{13}H_{10}O_9N_2S$	7.56	7.50	17	15	14	18	20
4g	3-COOH,2-$OCH_3C_6H_3$	168	78.97	$C_{14}H_{12}O_9N_2S$	7.29	7.22	15	14	18	17	24
4h	2-COOH,4-$OCH_3C_6H_3$	202	75.19	$C_{14}H_{12}O_9N_2S$	7.29	7.19	20	17	16	21	18
4i	3-COOH,6-$OCH_3C_6H_3$	247	74.22	$C_{14}H_{12}O_9N_2S$	7.29	7.15	23	18	15	24	20
4j	3-COOH,4-$CH_3C_6H_3$	232	80.45	$C_{14}H_{12}O_8N_2S$	7.60	7.54	15	14	12	20	23
4k	3-COOH,6-$CH_3C_6H_3$	255	82.13	$C_{14}H_{12}O_8N_2S$	7.60	7.49	13	12	17	18	17
4l	4-ClC_6H_4	119	84.78	$C_{12}H_9O_6N_2SCl$	8.12	8.03	18	16	16	22	22
4m	4-BrC_6H_4	>300	81.06	$C_{12}H_9O_6N_2SBr$	7.19	7.12	17	13	15	17	18
4n	4-$NHCOCH_3C_6H_4$	262	79.65	$C_{14}H_{13}O_7N_3S$	11.44	11.36	14	12	18	14	20
4o	4-$NHCOCH_3$,3-COOH-C_6H_3	274	82.81	$C_{15}H_{13}O_9N_3S$	10.21	10.14	19	15	14	19	23

*Zone of inhibition in mm.

Table II—Compounds showing antimicrobial activity comparable with those of known standard drugs

Compd	*B. mega*	*B. substilis*	*E. coli*	*P. flourescens*	*A. awamori*
(1a-o)	**1c, 1h**	**1d, 1l**	**1d, 1h, 1i**	**1e**	**1d, 1g, 1j**
(2a-o)	**2e, 2l**	**2l**	**2d, 2e, 2k, 2l, 2m**	**2h**	**2e, 2l**
(3a-o)	**3d**	**3i**	**3i, 3l, 3m**	**3h**	**3l, 3m**
(4a-o)	**4e, 4i**	**4c, 4d, 4i**	**4d, 4e**	**4d**	**4d, 4j, 4l, 4o**
Activity of standard drugs					
1. Ampicillin (50 μg)	22	18	19	27	–
2. Chloramphanicol (50 μg)	24	19	25	26	–
3. Norfloxacin (50 μg)	24	19	25	26	–
4. Griseofulvin (50 μg)	–	–	–	–	23

using DMF as solvent at 50 μg concentration by Cup-plate method[14]. After 24 hr of incubation at 37°C, the zones of inhibition were measured in mm. The activity was compared with the known antibiotic Ampicillin, Chloramphanicol, Norfloxacin and Griseofulvin at the same concentration.

All the compounds synthesised (**1a-o, 2a-o, 3a-o** and **4a-o**) exhibited moderate to good antimicrobial activity against bacteria and fungi. However, some of the compounds showed remarkable and comparable activity with those of standard drugs at the same concentrations (cf. **Table II**).

Experimental Section

General. Melting points were determined by open capillary method and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were run on a Shimadzu IR-435 spectrophotometer using KBr pellet, and ^1H NMR spectra on a Bruker (300 MHz) spectrometer DMSO-d_6 using TMS as internal standard. Purity of the compounds was routinely checked by TLC using silica gel G.

Maleoyl chloride. A mixture of maleic acid (1.16 g, 0.0 mole) and thionyl chloride (0.02 mole) was refluxed on a water-bath for 4 hr. The excess of thionyl chloride was removed by distillation.

2-(3′-Carboxy-4′-methylphenylsulpho)-6-hydroxy-3(2*H*)-pyridazinone 1j. A mixture of maleoyl chloride (0.01 mole), 3-carboxy-4-methylphenyl-sulphonyl hydrazide (2.30 g, 0.01 mole) in pyridine and dioxane (25 mL) was refluxed for 4 hr in an oil-bath at 120°C. The cooled reaction mixture was poured into ice-cold water containing conc. HCl to neutralize the excess of pyridine. The product was filtered, dried and crystallised from dioxane, mp 210°C, yield 73.42%. Anal. Calcd for $C_{12}H_{10}O_6N_2S$: C, 50.34; H, 3.49; N, 9.03. Found: C, 50.29; H, 3.47; N, 9.00%; IR (KBr): 2970 (C-H str.), 1700 (C=O), 1675 (C=N), 1210 (C–O–C *asym*), 1305 (S=O str); ^1H NMR: δ 2.41 (s, 3H, $-CH_3$), 7.58-8.25 (s, 5H, Ar-H).

Compounds **1a-o** were prepared similarly and their physical data are given in **Table I**.

2-(3′-Carboxy-4′-methylphenylsulpho)-6-chloro-3(2*H*)-pyridazinone 2j. A mixture of **1j** (3.10 g, 0.01 mole) in $POCl_3$ (10 mL) was refluxed for 1 hr. The reaction mixture was poured gradually onto crushed ice, basified with Na_2CO_3 and extracted with chloroform. The extract was dried over $MgSO_4$ and the solvent evaporated to yield a solid which was crystallised from dioxane to give **2j**, mp 273°C, yield 62.80%. Anal. Calcd for $C_{12}H_9O_5N_2SCl$: C, 43.83; H, 2.73; N, 8.52. Found: C, 43.79; H, 2.70; N, 8.49%; IR (KBr): 2965 (C-H str.), 1700 (C=O), 1580 (C=N), 1250 (C–O–C *asym.*), 1280 (S=O str), 675 (C-Cl str.); ^1H NMR: δ 2.41 (s, 3H, $-CH_3$), 6.7-8.0 (s, 5H, Ar-H).

Compounds **2a-o** were prepared similarly and their physical data are given in **Table I**.

2-(3′-Carboxy-4′-methylphenylsulpho)-6-hydrazino-3(2*H*)-pyridazinone 3j. A mixture of **2j** (3.28 g, 0.01 mole), hydrazine hydrate (0.75 g, 0.015 mole) and pyridine in dioxane (30 mL) was refluxed for 3 hr at 120°C. The reaction mixture was cooled and residual mass poured onto crushed ice containing conc. HCl (5 mL) to neutralize the excess of pyridine. The product was filtered, washed several times with water, dried and recrystallised from dioxane, mp 148°C, yield 54.85%. Anal. Calcd for $C_{12}H_{12}O_5N_4S$: C, 44.44;

H, 3.70; N, 17.28. Found: C, 44.41; H, 3.70; N, 17.23%; IR (KBr): 3400-3200 ($-NHNH_2$), 1700 (C=O), 1580 (C=N), 1570 (NH bending), 1250 (C–O–C *asym.*) and 1280 (S=O str.); ^{1}H NMR: δ 2.41 (s, 3H, $-CH_3$), 6.7-8.4 (m, 5H, NH and Ar-H).

Compounds **3a-o** were prepared similarly and their physical data are given in **Table I**.

2-(3′-Carboxy-4′-methylphenylsulpho)-6-carboxymethoxy-3-(2*H*)-pyridazinone 4j. A mixture of 2-(3′-carboxy-4′-methylphenylsulpho)-6-hydroxy-3(2*H*)-pyridazinone **1j** (3.10 g, 0.01 mole) in aq. NaOH solution and chloroacetic acid (0.01 *M*) was heated on a water-bath for 5 hr. The resulting mixture was poured into ice cold water, acidified the clear solution with 5% HCl, and the isolated product crystallised from dioxane, mp 232°C, yield 80.45%. Found: Anal. Calcd for $C_{14}H_{12}O_8N_2S$: C, 45.52; H, 3.26; N, 7.60. Found: C, 45.61; H, 3.19; N, 7.54%; IR (KBr): 2955 (C-H str.), 1680 (C=O), 1580 (C=N), 1230 (C–O–C *asym.*), 1315 (S=O str); ^{1}H NMR: δ 2.3 (s, 3H, $-CH_3$), 4.9 (s, 2H, CH_2), 7.62-7.87 (m, 5H, Ar-H).

Compounds **4a-o** were prepared similarly and their physical data are given in **Table I**.

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