NOVEL METHOD OF SYNTHESIS AND ANTIMICROBIAL EVALUATION OF 2-AROYL-6-HYDROXY/CHLORO/HYDRAZINO/CARBOXYMETHOXY - 3(2H)-PYRADAZINONES.

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ABSTRACT :

Maleoylchloride on cyclocondensation with aromaticacidhydrazides yields 2-aroyl-6-hydroxy-3(2H)-pyridazinones (1a-o). Compounds (1a-o) on chlorination with $POCl_3$ followed by the action of hydrazine hydrate affords corresponding 2-aroyl-6-chloro-3(2H)-pyradazinones (2a-o) and 2-aroyl-6-hydrazino-3(2H)-pyradazinones (3a-o). Compounds (1a-o) on reaction with monochloroaceticacid in aq.NaOH furnishes 2-aroyl-6-carboxymethoxy-3(2H)-pyradazinones (4a-o). The constitution of the products (1 to 4) have been elucidated by elemental analyses and spectral data. The products have been assayed for their antimicrobial activities.

INTRODUCTION :

3(2H)-Pyradazinones substituents in literature[1-3] have been found to exhibit wide spectrum of biodynamic as well as agrochemical agents. Taking into consideration of well known drug "Hydralazin" (Antihypertensive drug)[4] and (analgesics and antipyretics)[5] activity. Such as Along with 3(2H)-pyradazinones derivatives are known to possess plant growth regulators[6-9], herbicidal[10-11] and fungicidal[12-13] activities play a vital role largely due to the wide ranging in agrochemical agents.Encouraged by this properties present article reports by the synthesis of 2,6-disubstituted pyridazinone, likes 2-aroyl-6-hydroxy-3(2H)-pyradazinones (1a-o), 2-aroyl-6-chloro-3(2H)-pyradazinones (2a-o), 2-aroyl-6-hydrazino-3(2H)-pyradazinones (3a-o) and 2-aroyl-6-carboxymethoxy-3(2H)-pyradazinones (4a-o) to secure substituted heterocycle of enhanced biological activity.

The key intermediate maleoylchloride was prepared by the reaction of thionyl chloride. The maleoylchloride is react with different aromaticacidhydrazides followed by chemo selective cyclization gives 2-aroyl-6-hydroxy-3(2H)-pyradazinones (1a-o), compound (1a-o) on treatment with POCl3 yielded 2-aroyl-6-chloro-3(2H)-pyradazinones (2a-o) which on hydrazinolysis with refluxing hydrazine hydrate furnished 2-aroyl-6-hydrazino-3(2H)-pyradazinones (3a-o). Compounds (1a-o) condensed with aq. sodium hydroxide and monochloroaceticacid respectively, led to the formation of 2-aroyl-6-carboxymethoxy-3(2H)-pyradazinones (4a-o). The constitution of the products have been delineated by spectral data. The products have been evaluated for their antimicrobial screening.

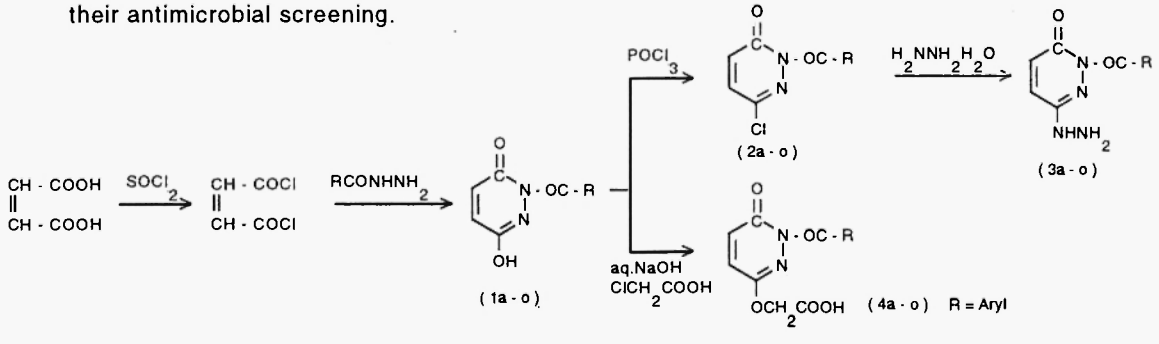

Table - I : The physical data and antimicrobial activity of compounds [1a-o, 2a-o, 3a-o, 4a-o]

Compd	R	Molecular formula	M.P. oC	Yield %	Nitrogen (%)		Antibacterial activity Zone of inhibition in m.m.			Antifungal activity Zone of inhibition in in m.m.	
					Calcd	Found	B.mega	B.substilis	E.Coli	p.fluore-scens	A.awamori
1a	C_6H_5	$C_{11}H_8O_3N_2$	115	78.46	12.96	12.91	16	13	14	18	18
1b	2-Cl.C_6H_4	$C_{11}H_7O_3N_2Cl$	136	79.30	11.17	11.08	18	12	16	20	20
1c	3-Cl.C_6H_4	$C_{11}H_7O_3N_2Cl$	149	83.19	11.17	11.12	22	18	15	22	23
1d	4-Cl.C_6H_4	$C_{11}H_7O_3N_2Cl$	155	80.74	11.17	11.10	20	19	21	26	21
1e	2-$CH_3C_6H_4$	$C_{12}H_{10}O_3N_2$	95	75.45	12.17	12.13	13	14	15	16	17
1f	3-$CH_3C_6H_4$	$C_{12}H_{10}O_3N_2$	117	78.62	12.17	12.11	15	15	17	18	18
1g	4-$CH_3C_6H_4$	$C_{12}H_{10}O_3N_2$	142	72.48	1217	12.08	17	17	18	14	19
1h	2-$OCH_3C_6H_4$	$C_{12}H_{10}O_4N_2$	152	80.06	11.38	11.32	18	14	20	20	21
1i	3-$OCH_3C_6H_4$	$C_{12}H_{10}O_4N_2$	175	72.54	11.38	11.29	20	15	21	23	20
1j	4-$OCH_3C_6H_4$	$C_{12}H_{10}O_4N_2$	192	70.85	11.38	11.30	22	20	19	19	17
1k	2-$NO_2C_6H_4$	$C_{11}H_7O_5N_3$	210	75.00	16.09	16.01	14	14	16	15	21
1l	3-$NO_2C_6H_4$	$C_{11}H_7O_5N_3$	225	71.13	16.09	15.99	18	13	17	17	24
1m	4-$NO_2C_6H_4$	$C_{11}H_7O_5N_3$	252(d)	69.92	16.09	16.03	21	11	18	20	21
1n	4-OHC_6H_4	$C_{11}H_8O_4N_2$	201	61.79	12.06	12.02	13	15	14	14	23
1o	-CH=CHC_6H_5	$C_{13}H_{10}O_4N_2$	249	78.10	10.85	10.78	15	12	13	20	18
2a	C_6H_5	$C_{11}H_7O_2N_2Cl$	195	62.14	11.94	11.88	16	14	13	17	19
2b	2-Cl.C_6H_4	$C_{11}H_6O_2N_2Cl_2$	182	65.98	10.40	10.34	19	16	15	21	24
2c	3-Cl.C_6H_4	$C_{11}H_6O_2N_2Cl_2$	210	70.32	10.40	10.30	20	18	17	18	22
2d	4-Cl.C_6H_4	$C_{11}H_6O_2N_2Cl_2$	198	65.10	10.40	10.37	18	14	16	27	18
2e	2-$CH_3C_6H_4$	$C_{12}H_9O_2N_2Cl$	187	73.82	11.26	11.19	15	13	14	17	19
2l	3-$CH_3C_6H_4$	$C_{12}H_9O_2N_2Cl$	206	69.60	11.26	11.23	14	12	13	19	17
2g	4-$CH_3C_6H_4$	$C_{12}H_9O_2N_2Cl$	195	62.08	11.26	11.15	17	11	15	16	21
2h	2-$OCH_3C_6H_4$	$C_{12}H_9O_3N_2Cl$	209	65.73	10.58	10.49	18	16	14	15	20
2i	3-$OCH_3C_5H_4$	$C_{12}H_9O_3N_2Cl$	273	62.11	10.58	10.53	20	18	21	18	18
2j	4-$OCH_3C_5H_4$	$C_{12}H_9O_3N_2Cl$	201	59.32	10.58	10.46	19	23	17	22	17
2k	2-$NO_2C_6H_4$	$C_{11}H_6O_4N_3Cl$	216	68.96	15.02	14.99	21	12	18	20	24
2l	3-$NO_2C_6H_4$	$C_{11}H_6O_4N_3Cl$	243	70.93	15.02	15.00	24	14	16	16	21
2m	4-$NO_2C_6H_4$	$C_{11}H_6O_4N_3Cl$	260	72.49	15.02	14.98	20	15	13	15	23
2n	4-OHC_6H_4	$C_{11}H_7O_3N_2Cl$	242	58.82	11.17	1.12	18	13	14	17	18
2o	-CH=CHC_6H_5	$C_{13}H_9O_3N_2Cl$	>300	56.18	10.12	10.07	16	14	15	13	17
3a	C_6H_5	$C_{11}H_{10}O_2N_4$	103	62.44	24.34	24.29	15	12	13	19	16
3b	2-Cl.C_6H_4	$C_{11}H_9O_2N_4Cl$	143	74.65	21.17	21.15	18	15	17	18	18
3c	3-Cl.C_6H_4	$C_{11}H_9O_2N_4Cl$	188	69.93	21.17	21.09	17	17	21	25	20
3d	4-Cl.C_6H_4	$C_{11}H_9O_2N_4Cl$	215	71.14	21.17	21.12	23	19	16	23	19
3e	2-$CH_3C_6H_4$	$C_{12}H_{12}O_2N_4$	153	80.19	22.95	22.89	15	12	14	19	23
3l	3-$CH_3C_6H_4$	$C_{12}H_{12}O_2N_4$	187	78.42	22.95	22.94	17	14	13	20	20
3g	4-$CH_3C_6H_4$	$C_{12}H_{12}O_2N_4$	199	76.00	22.95	22.90	19	17	18	18	17

3h	2-$OCH_3C_6H_4$	$C_{12}H_{12}O_3N_4$	186	65.17	21.53	21.48	18	21	16	17	18
3i	3-$OCH_3C_6H_4$	$C_{12}H_{12}O_3N_4$	211	69.87	21.53	21.51	23	18	24	22	18
3j	4-$OCH_3C_6H_4$	$C_{12}H_{12}O_3N_4$	238	72.10	21.53	21.45	19	17	18	26	24
3k	2-$NO_2C_6H_4$	$C_{11}H_9O_4N_5$	173	75.43	25.45	25.39	16	14	18	17	19
3l	3-$NO_2C_6H_4$	$C_{11}H_9O_4N_5$	197	79.77	25.45	25.42	18	16	17	15	23
3m	4-$NO_2C_6H_4$	$C_{11}H_9O_4N_5$	219	73.14	25.45	25.34	19	15	14	16	20
3n	4-OHC_6H_4	$C_{11}H_{10}O_3N_4$	255(d)	65.07	22.76	22.70	14	13	16	12	14
3o	-CH=CHC_6H_5	$C_{13}H_{12}O_3N_4$	278	62.82	20.58	20.49	15	17	12	14	19
4a	C_6H_5	$C_{13}H_{10}O_5N_2$	104	70.11	10.21	10.17	17	12	14	19	19
4b	2-Cl.C_6H_4	$C_{13}H_9O_5N_2Cl$	121	81.65	9.07	9.01	19	14	15	21	20
4c	3-Cl.C_6H_4	$C_{13}H_9O_5N_2Cl$	143	83.48	9.07	8.99	24	16	18	23	24
4d	4-Cl.C_6H_4	$C_{13}H_9O_5N_2Cl$	156	78.86	9.07	9.03	20	18	19	26	23
4e	2-$CH_3.C_6H_4$	$C_{14}H_{12}O_5N_2$	80	81.33	9.72	9.68	13	13	13	14	18
4f	3-$CH_3C_6H_4$	$C_{14}H_{12}O_5N_2$	138	82.97	9.72	9.70	15	12	15	17	17
4g	4-$CH_3.C_6H_4$	$C_{14}H_{12}O_5N_2$	156	85..14	9.72	9.65	14	15	16	19	20
4h	2-$OCH_3.C_6H_4$	$C_{14}H_{12}O_6N_2$	122	78.32	9.21	9.15	18	14	15	16	21
4i	3-$OCH_3.C_6H_4$	$C_{14}H_{12}O_6N_2$	140	80.54	9.21	9.17	17	16	14	20	22
4j	4-$OCH_3.C_6H_4$	$C_{14}H_{12}O_6N_2$	189	75.63	9.21	9.20	22	19	19	23	18
4k	2-$NO_2C_6H_4$	$C_{13}H_9O_7N_3$	193	71.86	13.16	13.11	18	15	16	26	22
4l	3-$NO_2C_6H_4$	$C_{13}H_9O_7N_3$	218	69.08	13.16	13.09	20	13	14	22	25
4m	4-$NO_2C_6H_4$	$C_{13}H_9O_7N_3$	245	73.95	13.16	13.12	23	12	20	19	20
4n	4-OH.C_6H_4	$C_{13}H_{10}O_5N_2$	132	78.13	9.65	9.61	16	14	16	17	24
4o	-CH=CHC_6H_5	$C_{15}H_{12}O_6N_2$	265	78.40	8.86	8.80	18	15	14	18	17

ANTIMICROBIAL ACTIVITY :

All the compounds reported in Table - I were tested in vitro for their antimicrobial activity under identical conditions. Antibacterial activity against **B. mega, B. Substilis, E. coli** and **P. fluorescens** and for antifungal activity against **A. awamori** using DMF as solvent at 50μg concentration by Cup-plate method[14]. After 24 hrs of incubation at 37°C, the zone of inhibition were measured in mm. The activity was compared with the known antibiotics viz, Ampicillin, Chloramphanicol, Norfloxacin and Griseofulvin at same concentration.

In the case of antibacterial activity and antifungal activity of compounds of types (1 to 4) showed moderate to good and comparable activity with known standard drugs (cf.Table - I).

In case of antimicrobial activity of all the synthesised compounds (1a-o, 2a-o, 3a-o, 4a-o) exhibited moderate, to good activity against each strains of bacteria and fungi. However some of the compounds showed remarkable and comparable activity with known choosen standard drugs at same concentrations which is represented in Table - II.

Table - II :

ANTIMICROBIAL ACTIVITY :
Conclusion
Maximum Antimicrobial activity

Compounds data	B.mega	B.substilis	E.coli	P. flourescens	A. awamori
(1a-o)	1c, 1j,	1c, 1d, 1j,	1c,1d,1i,	1d,	1c,1l,1n
(2a-o)	2l,	2i,2j,	2d,2j,	2d,	2b,2c,2m
(3a-o)	3d,3i	3d,3h,3i,	3c,3i,	3c,3j,	3e,3j,3l
(4a-o)	4c,4j,5m,	4d,4j,	-	4d,4k,	4c,4d,4l,4n
Comparable activity with known standard drugs					
1. Ampicillin (50 mg)	22	18	19	27	-
2. Chloramphanicol (50 mg)	24	19	25	26	-
3. Norfloxacin (50 mg)	24	19	25	26	-
4. Griseofulvin (50 mg)	-	-	-	-	23

EXPERIMENTAL :

Melting points were taken in open capillaries are uncorrected IR absorption spectra (υin cm-1) were recoreded on a shimadzu IR-435 spectrophotometer using KBr pellet and 1HNMR spectra on Br uker (300 MHz) spectrometer in DMS0 using TMS as internal standard. The purity of the compounds were routinely checked by TLC using silical gel G.

Maleoyl chloride

A mixture of maleic acid (1.16 g,0.01 mole) and thionyl chloride (0.02 mole) was condensed for 4 hrs on water bath. The excess of thionylchloride was removed by distillation method.

2-(3'-Methoxy benzoyl)-6-hydroxy-3(2H)-pyradazinone - (1i):

A mixture of maleoylchloride (0.01 mole),3-methoxy benzoyl hydrazide (1.66g, 0.01 mole) in pyridine and dioxane (25 ml) was refluxed for 4 hrs on a oilbath at 120°C temp. The cold reaction mixture was poured into ice cold water. The isoluted product was crystallised from dioxane. m.p. 175°C, Yield : 72.54% (Found : C, 58.45; H, 4.01; N, 11.29; $C_{12}H_{10}O_4N_2$ requires : C, 58.53; H, 4.06; N, 11.38 %) IR (KBr) : 2965 (C-H Str.), 1700 (C=O), 1580 (C=N), 1250 (C-O-C asym), 1HNMR (DMS0) : δ 3.9-4.0 (S,3H,-OCH_3), 7.2-8.1 (s, 6H,-C_6H_4).

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

2-(3'-Methoxy benzoyl)-6-chloro-3-(2H)-pyradazinones - (2i):

A mixture of 1i (2.46g, 0.01 mole) in POCl3 (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 with (MgSO4) and the solvent evaporated to yield a solid which was crystallised from Dioxane to give (2i).m.p. 273°C, Yield : 62.11% (Found : C, 54.35; H, 3.38; N, 10.53; $C_{12}H_9O_3N_2Cl$ requires : C, 54.44; H, 3.40; N, 10.58 %) IR (KBr) : 2965 (C-H

Str.), 1700 (C=O), 1580 (C=N), 1250 (C-O-C asym),760cm $^{-1}$(C-Cl)1HNMR (DMSO) : δ 4.05 (S,3H,-OCH_3), 7.2-8.0 (S,5H Ar-H).

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

2-(3'-Methoxy benzoyl)-6-hydrazino-3-(2H)-pyradazinones - (3i):

A mixture of 2i (2.64g, 0.01 mole) and hydrazine hydrate (0.75g, 0.015 mole) in dioxane (30 ml) was refluxed for 3 hrs. at 120^{o}C temp. The reaction mixture was cooled and residual mass poured onto crushed ice containing HCl (5 ml) to neutralize the excess of pyridine. The product was filtered washed several times with water dried and recrystallised from dioxane.m.p. 211^{o}C, Yield : 69.87% (Found : C, 55.29; H, 4.60; N, 21.51; $C_{12}H_{12}O_3N_4$ requires : C, 55.38; H, 4.61; N, 21.53 %) IR (KBr) : 3400-3200 (-NHNH2), 1700(C=O), 1580 (C=N), 1570 (NH bending), 1250 (C-O-C asym) ; 1HNMR (DMSO) : δ 4.0 (S,3H;-OCH_3), 7.2-8.4 (m;5H,NH and Ar-H).

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

2-(3'-Methoxy benzoyl)-6-Carboxymethoxy-3(2H)-pyradazinone - (4i):

A mixture of 2-(3'-methoxybenzoyl)-6-hydroxy-3(2H)-pyradazinone 1i (2.46g, 0.01 mole) in aq. NaOH solution and chloroacetic acid (0.01 mole) was heated on a water bath for 5 hrs. The resulting mixture was poured into ice cold water, acidify the clear solution with 5% HCl. The isolated products was crystallised from dioxane. m.p. 140^{o}C, Yield : 80.54% (Found : C, 55.18; H, 3.89; N, 9.17; $C_{14}H_{12}O_6N_2$ requires : C, 55.26; H, 3.94; N, 9.21 %) IR (KBr) : 2965 (C-H Str.), 1705 (C=O), 1580 (C=N), 1245 (C-O-C asym),1HNMR (DMSO) : δ 4.7 (S,2H,-CH2),3.8 (S,3H,-OCH_3),6.8-8.2 (m,5H, Ar-H).

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

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