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SYNTHESIS OF SOME NEW 2-[2,4'-DIOXO SPIRO INDOLE -3,2'- THIAZOLIDIN-3'-YL] ALKANOIC ACIDS AS POTENTIAL FUNGICIDAL AGENTS

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ABSTRACT

2-[2, 4'-dioxo spiro indole -3, 2'- thiazolidin-3'-yl] alkanoic acids (2) have been prepared by refluxing 2-indolone-3-yl imino alkanoic acid (1) with mercapto acetic acid in 1, 4-dioxan. The compounds prepared were screened for their fungicidal activity against *Pyricularia oryzae, Puccinia graminis, Alternaria solani* and *Phytopthora infestans*.

KEY WORDS: Alkanoic acid, fungicidal activity

Indoles have been found to possess a variety of biological activities such as anti-inflamatory (Sondhi et al., 2006 and Radwan et al., 2007), anti cancer (Cao et al., 2004), anti depressant (Kar and Fattah ,1991), anti bacterial (Tiwari et al., 2004 and Cinhana et al 2011), antifungal (ElSawy et al., 2006), antiviral (Gawad et al., 2010) and herbicidal (Wentao et al., 2009) activities.

When indole ring is coupled with another heterocyclic system having a spiro carbon, compounds with increased spectrum of biological activities are obtained such as 1-benzyl-3-heterocyclic indoles which shows anti cancer and anti microbial activity (Eslam et al., 2010) and anti inflammatory activity (Mandour et al., 2010). In the present investigation the effort has been made to synthesize compounds in which indole were clubbed with other heterocyclic system and screened them for fungicidal activity against *Pyricularia oryzae, Puccina graminis ,Alternaria solani* and *Phytopthora infestans*.

MATERIALS AND METHOD

Melting points of all synthesized compounds were determined in open capillary and uncorrected. IR spectra were recorded on Perkin-Elmer Spectrometer in the range 400-4000cm^{-1} . ^{1}HNMR spectra were recorded with TMS as internal standard using DMSO- d_6.Purity of the compounds were checked by TLC on Silica gelG plates with layer thickness of 0.3 mm. All compounds gave satisfactory C, H, N and S elemental analysis.

Synthesis of 2-indolone-3-yl imino alkanoic acid (1)

It was prepared by the method of (Nizamuddin et al.,1999). A mixture of isatin (0.1M), glycin (0.1M) and sodium hydroxide (0.1M) were refluxed in methanol for 4 hours. The solvent was removed and water is poured into the residue to precipitate the desired product which was washed with water dried and recrystallised from ethanol.m.p.180-182^{0}C ; yield 72 %: Significant bands :IR(KBr cm^{-1}) 3475 (NH-Stretching);3208 (OH-Stretching);1750,1720(>C=O-Stretching);1650 (>C=N-Stretching); 1548,1518,1508 (Aromatic ring stretching).Other compounds thus prepared are recorded in table 1.

Synthesis of 2-[2, 4'-dioxo spiro indole -3, 2'- thiazolidin-3'-yl] alkanoic acids (2)

It was prepared by refluxing 2-indolone-3-yl imino alkanoic acid (1) (0.01M) with mercapto acetic acid (0.01M) in 1, 4-dioxan for 4 hours. The solvent was removed and water is poured into the residue to precipitate the desired product which was washed with water dried and recrystallised from ethanol. m.p. 160^{0}C ; yield (64%). Significant bands: IR(KBr cm^{-1}) 3468 (NH-Stretching) ,3213 (OH-Stretching);1748,1728,1688(>C=O-Stretching); 1570,1558,1477(Aromatic ring stretching); 1200(C-S-C Stretching); 1109(C-N-C Stretching): ^{1}H NMR data (DMSO- d_6) δ: 3.3 (s,2H,-NHCH$_2$CO) ;3.7 (s,2H,-S-CH$_2$-CO);6.8-8.0(m,4H+1H,Ar-H+NH) .Other compounds thus prepared are recorded in table 1. The synthesis of these compounds has been given in scheme-I.

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SCHEME-I

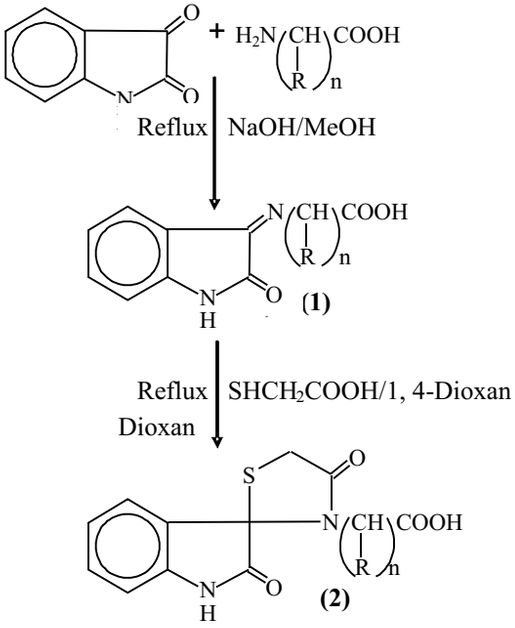

Table 1: Details of compounds synthesized

S.No.	R	n	m.p. (^{0}C)	Yield (%)	Molecular Formula	Analysis			
						Nitrogen (%)		Sulphur (%)	
						Found	Calc.	Found	Calc.
1a	H	1	182	72	$C_{10}H_8O_3N_2$	14.03	13.72	-	-
1b	CH_3	1	195	71	$C_{11}H_{10}O_3N_2$	13.34	12.84	-	-
1c	$CH(CH_3)_2$	1	165	70	$C_{13}H_{14}O_3N_2$	11.69	11.38	-	-
1d	CH_2OH	1	178	68	$C_{11}H_{10}O_4N_2$	11.04	11.96	-	-
1e	CH_2SH	1	169	71	$C_{11}H_{10}O_3N_2S$	11.73	11.20	13.11	12.80
1f	CH_2COOH	1	148	70	$C_{12}H_{10}O_5N_2$	11.03	10.69	-	-
1g	CH_2CH_2COOH	1	157	64	$C_{13}H_{12}O_5N_2$	10.77	10.14	-	-
1h	CH_2CONH_2	1	164	62	$C_{12}H_{11}O_3N_4$	22.31	21.62	-	-
1i	$CH_2CH_2CONH_2$	1	143	68	$C_{13}H_{13}O_4N_3$	14.09	15.27	-	-
1j	CH_2 $CH(CH_2)_2$	1	155	65	$C_{14}H_{14}O_3N_2$	11.31	10.85	-	-
2a	H	1	162	64	$C_{12}H_{11}O_3N_2S$	11.01	10.65	12.81	12.17
2b	CH_3	1	168	55	$C_{13}H_{14}O_3N_2S$	9.79	10.07	12.11	11.51
2c	$CH(CH_3)_2$	1	148	70	$C_{15}H_{17}O_3N_2S$	9.23	9.18	11.12	10.49
2d	CH_2OH	1	151	72	$C_{13}H_{14}O_4N_2S$	9.94	9.52	11.49	10.88
2e	CH_2SH	1	141	71	$C_{13}H_{14}O_3N_2S_2$	9.92	9.03	21.01	20.64
2f	CH_2COOH	1	126	69	$C_{14}H_{14}O_5N_2S$	8.12	8.69	10.22	9.94
2g	CH_2CH_2COOH	1	113	70	$C_{15}H_{16}O_5N_2S$	8.98	8.33	8.99	9.52
2h	CH_2CONH_2	1	139	68	$C_{14}H_{15}O_4N_2S$	9.48	9.12	11.02	10.42
2i	$CH_2CH_2CONH_2$	1	119	65	$C_{15}H_{17}O_4N_3S$	12.99	12.54	9.98	9.55
2j	CH_2 $CH(CH_2)_2$	1	129	62	$C_{16}H_{18}O_3N_3S$	13.01	12.65	10.10	9.64

Evaluation of Fungicidal Activity

The anti fungal activity was evaluated by agar plate technique against *Pyricularia oryzae, Puccina graminis, Alternaria solani* and *Phytopthora infestans* at concentrations 1000 ppm, 100 ppm and 10 ppm. The number of replications in each case was three. On the basis of growth recorded on 7th day of incubation the fungicidal activity of test compounds was calculated in terms of present inhibition of mycelial growth using the following formula.

Present inhibition of mycelial growth $= \frac{dc - dt}{dc} \times 100$

Where

dc = Average diameter growth of the colony in control sets on 7th day of incubation.

dt = Average diameter growth of the colony in treatment set on 7th day of incubation.

Diameter growth=apparent diameter of the colonydiameter of colony of the inoculums

The percentage inhibitions of various compounds are recorded in table -2

RESULTS AND DISCUSSION

It is evident from the activity data that the all of the tested compounds have significant fungitoxicity at 1000 ppm against all the fungi but their toxicity decreased considerably at lower concentration, although compounds having serial number 2d, 2e, 2f, 2g, 2h, 2i and 2j show greater fungitoxicity against all the organisms but the result are not very spectacular except for compounds 2h, 2i and 2j.

It is also evident from the fungicidal screening data that these compounds are more active on *P. graminis* and *A. solani* than *P. oryzae* and *P. infestans.* It is also observed from the result that introduction of polar substituents like-NH_2 group enhances the fungicidal activity.

Table 2: Fungicidal activity of compounds synthesized

S.No.	Average % inhibition after 7 days											
	Pyricularia oryzae			*Puccinia graminis*			*Alternaria solani*			*Phytophthora infestans*		
	1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm
2a	62	45	26	63	46	27	64	47	28	62	46	27
2b	64	47	27	65	48	28	65	47	28	66	48	29
2c	68	49	29	69	50	29	69	51	29	67	48	27
2d	72	51	31	73	52	32	71	50	30	73	52	32
2e	74	52	32	75	53	33	74	51	31	76	54	34
2f	73	52	31	72	50	30	73	52	31	74	51	32
2g	66	48	28	67	46	26	68	46	26	67	47	29
2h	82	58	35	84	60	36	86	61	37	84	61	37
2i	80	56	32	79	65	31	80	56	32	81	57	31
2j	76	53	32	78	54	33	77	53	32	78	54	33
Carbendazim	100	78	54	100	79	55	100	78	54	100	78	55

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