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Synthesis and Evaluation of Some 2–Aryl–3–[substituted pyridin–2–yl]-amino/methylamino thiazolidin-4-ones

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ABSTRACT

A series of compounds incorporating thiazolidinone moiety has been synthesized and screened for their antifungal activity. 2-Aryl-3-[substituted pyridin-2-yl]-amino/methylamino thiazolidin-4-ones have been synthesized by cyclocondensation of [substituted pyridin-2-yl]-araldehydehydrazone and N-Methyl [substituted pyridin-2-yl]-araldehydehydrazone with mercapto acetic acid in dioxane. The initial reactants required for the synthesis were obtained by refluxing 2-hydrazino substituted pyridine and 2-[N-methylhydrazino]-substituted pyridine with different substituted aldehydes. These newly synthesized compounds were then screened for their fungicidal activity against *Rhizoctina solani* and *Fusarium oxysporum*. Structures of all these compounds were confirmed by ^{1}H NMR, IR and mass spectrum analysis. Some compounds exhibited excellent fungicidal properties.

Keywords: Thiazolidinones, Fungicidal activity, *Rhizoctina solani*, *Fusarium oxysporum*.

INTRODUCTION

The pyridine ring is associated with diverse biological activities viz: antibacterial,herbicidal, fungicidal and plant growth regulators[1-7]. Union of pyridine ring with N-containing heterocycles provide compounds of enhanced herbicidal activity[8]. The investigations of new pyrazine and pyridine derivatives showing antimicrobial activities have been carried out. They appeared to be of elevated activity towards the aerobes[9]. At 100 mgL^{-1}, bioassays indicated that some multi-substituted pyridine derivatives have good herbicidal activity on the roots of oilseed rape and barnyard grass[10].

The thiazolidine ring by virtue of presence of toxophoric - N=C-S linkage and a cyclic >C=O function in the five membered ring is associated with diverse biological activities[11-16]. Reports pertaining to the pesticidal activities to the ring have also been reported[17-19]. Coumarin, thiazole and their respective derivatives have been reported to exhibit significant biological activity and are used as pharmaceuticals[20,21]. They are capable of imparting antimicrobial properties[22]. Amino and urea substituted thiazoles exhibited *in vivo* activity on duckweed (*Lemna paucicostata*)[23].

Keeping all the above facts it was worth interesting to synthesize compounds by incorporating pyridine ring with thiazolidinone ring in view to obtain the compound of better bioactivity.

EXPERIMENTAL

All the chemicals used were of analytical grade either BDH or E. Merck or Fluka and were used as received. The solvents were used after distillation. Melting points were taken in open glass capillaries and were uncorrected. IR spectra were recorded in KBr on a Perkin Elmer 881 spectrophotometer. ^{1}H NMR spectra were recorded on a Perkin-Elmer R-32 [90 MHz] spectrometer in $CDCl_3$ or DMSO-$_{d6}$.

These analyses were carried out at RSIC, CDRI, Lucknow and at BHU Varanasi. The antifungal activities of the synthesized compound were evaluated against *Rhizoctina solani* and *Fusarium oxysporum* by filter paper disc method at 100ppm and 10ppm concentrations. The standard fungicide carbendazim was also tested under similar conditions for comparison.

Synthesis

2-Aryl-3- [substituted pyridin-2-yl]- amino thiazolidin-4-one (II)

The synthesis of this compound involves two steps. In step-I substituted pyridine hydrazide reacts with different substituted benzaldehyde in equimolar ratio to form intermediate hydrazones (I) which in step-II undergoes cyclocondensation with mercapto acetic acid to obtain the desired product. (II).

Step I: N-[substituted pyridine-2-yl] araldehyde hydrazone (I)

A mixture of 2-hydrazino-5-triflouromethyl pyridine (1.77 g; 0.01M) and 2,4-dichlorobenzaldehyde (1.75 g; 0.01M) was refluxed in methanol for 1 hour. The reaction mixture was cooled and poured into ice-cold water. The compound (I) thus separated out was filtered, washed and crystallized from aqueous ethanol.

Other compounds of this type were synthesized similarly by taking aldehydes of different R^1.

Yield: 2.4g (72%); m.p.:196^{0}C
Analysis for $C_{13}H_8F_3Cl_2$ Found: C = 46.00; H = 2.48; N = 12.30
(Calculated): C = 46.71; H = 2.39; N = 12.51
1R (KBr) V_{MAX} cm^{-1}: 3205 (-NH); 1622 (C=N); 1555,1511, 1474 (C=C); 750 (C-Cl)

(a) R' = H (1.04g)
(b) R' = 2-Cl (1.39g)
(c) R' = 4-Cl (1.39g)
(d) R'= 2-OH (1.21g)
(e) R' = 4-OH (1.21g)
(f) R' = 4-F (1.23g)
(g) R'= 4-CH_3 (1.85g)
(h) R'= 4-OCH_3 (2.01g)
(i) R' = 3,4- $(OCH_3)_2$ (2.32g)
(j) R' = 3-OCH_3, 4-OH (1.52g)
(k) R' = 3-NO_2 (1.60g)
(l) R'=4-N $(CH_3)_2$ (1.58g)
(m) R' = 2-COOH (1.50g)

The analytical data of these compounds are recorded in Table 1.

Step-II: 2-Aryl-3- [substituted pyridin-2-yl]- amino thiazolidin-4-one (II)

A mixture of 5-[triflouromethylpyridin-2-yl]-2,4-dichlorobenzaldehyde hydrazone (3.34g, 0.01M) and mercapto acetic (0.92 g, 0.01M) was refluxed for 5 h in dioxane (30 ml). Excess of solvent was removed and the residue was poured into ice-cold water and neutralized by sodium bicarbonate solution. The compound thus obtained was filtered, washed, dried and recrystallized from aqueous ethanol.

Yield: 2.74g(72%);m.p.: 185^{0}C

Analysis for $C_{15}H_{10}ON_3SF_3Cl_2$) C = 44.00; H = 2.36; N = 10.01
Found: (Calculated): (C = 44.12); (H = 2.45); (N = 10.29)
IR (KBr)cm^{-1}: 3194(NH); 1678(C=O);
1591,1552, 1477 (C=C)
1240, 1121 (C-S-C); 751 (C-Cl)
^{1}H NMR ($CDCl_3$) δ ppm: 2.31 (s, 1H, N-CH-S)
3.60 (s, 2H, O=C CH-CH_2-S)
7.00 - 7.80 (m, 6H, Ar-H)

Table 1: Analytical data of synthesized compounds (I a – Im)

Compd No.	R	R'	Molecular formula (Formula weight)%	Yield	m.p. (°C)	C Exp.	C Cal.	H Exp.	H Cal.	N Exp.	N Cal.
Ia	5-CF3	H	$C_{13}H_{10}N_3F_3$(265)75		192	58.6	-58.87	3.8	-3.77	15.93	-15.85
Ib	"	2-Cl	$C_{13}H_9N_3F_3Cl$ (299.5)	72	163	52	-52.09	3.07	-3	14.22	-14.02
Ic	"	4-Cl	$C_{13}H_9N_3F_3Cl$ (299.5)	69	190	51.96	-52.09	2.87	-3	14.19	-14.02
Id	"	2-OH	$C_{13}H_{10}N_3F_3O$(281)	65	199	55.6	-55.57	3.31	-3.2	14.85	-14.95
Ie	"	4-OH	$C_{13}H_{10}N_3F_3O$ (281)	68	205	55.62	-55.51	3.1	-3.2	14.73	-14.95
If	"	4-F	$C_{13}H_{10}N_3F_3O$ (281)	64	215	55.2	-55.13	3.2	-3.18	19.81	-19.78
Ig	"	4-Me	$C_{14}H_{12}N_3F_3$ (279)	70	143	60	-60.22	3.15	-3.02	15.25	-15.05
Ih	"	4-OMe	$C_{14}H_{12}N_3F_3$ (279)	68	165	56.73	-56.95	3.08	-3.05	14	-14.24
Ii	"	3,4-(OMe)2	$C_{15}H_{14}N_3F_3O$ (325)	72	130	55.4	-55.38	4.25	-4.31	12.8	-12.92
Ij	"	3-OMe,4-OH	$C_{14}H_{12}N_3F_3O_2$ (311)	67	143	54	-54.02	3.75	-3.86	13.26	-13.56
Ik	"	3-NO_2	$C_{13}H_9N_4F_3O_2$ (310)	64	187	50.12	-50.32	2.8	-2.9	18.13	-18.06
Il	"	4-N(Me)$_2$	$C_{15}H_{15}N_4F_3$ (308)	65	204	58.21	-58.44	4.95	-4.87	14.7	-14.84
Im	"	2-COOH	$C_{14}H_{10}N_3F_3O_2$ (309)	68	172	54.21	-54.37	3.03	-3.24	13.4	-13.59

Other compounds of the series were prepared similarly using different substituents R'.

(IIa) R' = H (IIe) R' = 4-OH (IIi)R' = 3,4-(OMe)$_2$
(IIb) R'= 2-Cl (IIf)R' = 4F (IIj)R' = 3-OCH_3-4-OH
(IIc)R' = 4-Cl (IIg)R' = 4-Me (IIk) R' = 3-NO_2
(IId)R' = 2-OH (IIh) R' = 4-OMe (III)R' = 4-N (Me)$_2$
(IIm) R'= 2-COOH

The analytical data of these compounds are recorded in Table 2.

2-Aryl-3- [substituted pyridine-2-yl] methylamino thiazolidin -4-ones

In the synthesis of this series of compounds two steps were involved. Step -I involves the reaction of substituted pyridine hydrazide with different substituted benzaldehydes in equimolar ratio to an intermediate hydrazone (III) which in step-II undergoes cyclocondensation with mercapto acetic acid to form the desired product (IV).

Table 2: Analytical data of synthesizedcompounds (IIa–IIm)

Compd. No.	R	R'	Molecular Formula (Molecular Weight)	Yield %	m.p. °C	Carbon Exp.	Carbon Cal.	Hydrogen Exp.	Hydrogen Cal.	Nitrogen Exp.	Nitrogen Cal.	Sulfur Exp.	Sulfur Cal.
IIa	5-CF3	H	$C_{15}H_{12}N_2OSF_3$ (339)	69	120	53	-53.1	3.6	-3.64	12.53	-12.39	9.38	-9.44
IIb	"	2-Cl	$C_{15}H_{11}N_3OSF_3Cl$ (373.3)	68	200	48.25	-48.19	2.75	-2.95	11.3	-11.24	8.49	-8.57
IIc	"	4-Cl	$C_{15}H_{11}N_3OSF_3Cl$ (373.3)	67	165	48.11	-48.19	2.78	-2.95	11.15	-11.24	8.38	-8.57
IId	"	2-OH	$C_{15}H_{12}N_3O_2SF_3$ (355)	68	210	50.5	-50.7	3.46	-3.38	11.75	-11.83	8.92	-9.01
IIe	"	4-OH	$C_{15}H_{12}N_3O_2SF_3$ (355)	65	145	50.89	-50.7	3.3	-3.38	11.65	-11.85	8.89	-9.01
IIf	"	4-F	$C_{15}H_{11}N_3OSF_4$ (357)	61	205	50.22	-50.42	3	-3.38	11.5	-11.76	8.73	-8.96
IIg	"	4-Me	$C_{16}H_{14}N_3OSF_3$ (353)	69	165	54.09	-54.39	3.79	-3.97	11.75	-11.9	9.11	-9.06
IIh	"	4-OMe	$C_{16}H_{14}N_3O_2SF_3$ (369)	70	178	52.98	-53.03	3.88	-3.79	11.4	-11.38	8.5	-8.67
IIi	"	3,4-(OMe)$_2$	$C_{17}H_{16}N_3O_3SF_3$ (399)	75	151	51	-51.13	4.25	-4.01	10.61	-10.53	7.87	-8.02
IIj	"	3-OMe,4-OH	$C_{16}H_{14}N_3O_3SF_3$ (385)	64	158	49.67	-49.87	3.52	-3.64	10.8	-10.91	8.12	-8.31
IIk	"	3-NO_2	$C_{15}H_{11}N_4O_3SF_3$ (384)	65	175	46.67	-46.87	2.7	-2.86	11.29	-11.58	8.21	-8.33
III	"	4-NMe_2	$C_{17}H_{17}N_4OSF_3$ (382)	69	192	53.2	-53.4	4.65	(4.450	14.3	-14.66	8.19	-8.38
IIm	"	2-COOH	$C_{16}H_{12}N_3O_3SF_3$ (383)	71	108	50.22	-50	3.41	-3.13	10.76	-10.97	8.2	-8.36

Step-I:Synthesis of N-Methyl-N-[substituted pyridine-2yl] araldehyde hydrazones (III)

The title compound was prepared by refluxing a mixture of 2-[N-methylhydrazino]-3-triflouromethylpyridine (1.91g; 0.01M) and 3-methoxy-4-hydroxy benzaldehyde (1.50g; 0.01M) in methanol for two hours. The reaction mixture was cooled and poured into ice cold water. The resultant compound was filtered, washed, dried and recrystallized from aqueous ethanol.

Yield:2.31g (71%); m.p.: 151 ^{0}C
Analysis for $C_{15}H_{14}N_3O_2F_3$ Found: C = 55.18; H = 4.53; N = 12.70
(Calculated): C = 55.38; H = 4.31; N = 12.97
IR (KBr)cm^{-1}: 3294 (O-H); 1605 (C=N); 1579, 1519, 1448 (C=C)

Other compounds of this series were synthesized similarly using different substituents R and R' as given below:

The analytical data are presented in Table 3.

Sept II: 2-Aryl-3-[substituted pyridin-2-yl] methylamino thiazolidin-4-ones (IV)

A mixture of N-Methyl-N-[3-triflouromethy lpyridin-2-yl]-3-methoxy-4-hydroxy benzaldehyde hydrazone (3.25 g, 0.01M) and mercaptoacetic acid (0.92 g, 0.01M) was refluxed in dioxane (30 ml) for 5 hours. Excess of solvent was removed and the residue was poured into ice cold water. This solution was then neutralized from aqueoussodiumbicarbonate solution. The compound thus obtained was filtered, washed, dried and recrystallized from aqueous ethanol.

Other compounds were prepared similarly using various substituents R and R'.

Yield: 2.75g (69%); m.p.:104^{o}C
Analysis for $C_{17}H_{16}N_3O_3F_3$(Found): C = 51.33; H = 4.31; N = 10.30; S=8.20
(Calculated): C = 55.38; H = 4.31; N = 12.90; S=8.02
1R (KBr)cm^{-1}: 3498 (O-H); 1722(C=O); 1579, 1519, 1448 (C=C); 1302 (C-S-C)

R = 3-CF_3 R' = (IVa) 4-Me;(IVb) 4-OMe;(IVc) 4-N (Me)2;(IVd) 3-NO_2
R = 3-$CF_3$5-Cl R' = (IVe) 4-Cl;(IVf) 4-Me;(IVg) 4-OMe;(IVh) 3-OMe, 4-OH;IV(i) 2-NO_2
R = 5-CF_3, 3-Cl R' =(IVj)4-Cl;(IVk) 4-Me; (IVl) 4-OMe; (IVm) 2-NO_2;(IVn) 4-N$(Me)_2$

Table 3: Analytical studies of synthesized compounds (IIIa – IIIn)

Compd No.	R	R'	Molecular Formula (Molecular weight)	Yield %	m.p.	Carbon Exp.	Carbon Cal.	Hydrogen Exp.	Hydrogen Cal.	Nitrogen Exp.	Nitrogen Cal.
IIIa	3-CF_3	4-Me	$C_{15}H_{14}N_3F_3$ (293)	70	72	61	-61.43	4.5	-4.78	14.46	-14.33
IIIb	3-CF_3	4-OMe	$C_{15}H_{14}N_3OF_3$ (309)	69	82	58.41	-58.25	4.71	-4.53	13.03	-13.59
IIIc	3-CF_3	4-N$(Me)_2$	$C_{16}H_{17}N_4F_3$ (322)	62	151	59.4	-59.63	5.35	-5.28	17.28	-17.39
IIId	3-CF_3	3-NO_2	$C_{14}H_{11}N_4O_2F_3$ (324)	59	105	51.6	-51.85	3.29	-3.39	17.1	-17.28
IIIe	3-CF_3,5-Cl	4-Cl	$C_{15}H_{13}N_3F_3Cl$ (327.5)	60	95	48	-48.28	2.91	-2.87	12.32	-12.07
IIIf	3-CF_3,5-Cl	4-Me	$C_{15}H_{13}N_3F_3Cl$ (327.5) 58	58	103	54.85	-54.96	3.79	-3.97	12.59	-12.82
IIIg	3-CF_3,5-Cl	4-OMe	$C_{15}H_{13}N_3OF_3Cl$ (343.5)	64	92	52.4	-52.4	3.86	-3.78	12	-12.23
IIIh	3-CF_3,5-Cl	3-OMe,4-OH	$C_{15}H_{13}N_3O_2F_3Cl$ (359.5)	61	149	50.27	-50.07	3.51	-3.62	11.51	-11.68
IIIi	3-CF_3,5-Cl	2-NO_2	$C_{14}H_{10}N_4O_2F_3Cl$ (358.5)	59	138	46.7	-46.86	2.95	-3.79	15.41	-15.62
IIIj	5-CF_3,3-Cl	4-Cl	$C_{14}H_{10}N_3F_3Cl_2$ (348)	65	174	48.39	-48.28	2.65	-3.87	12.19	-12.07
IIIk	5-CF_3,3-Cl	4-Me	$C_{15}H_{13}N_3F_3Cl$ (327.5) 67	67	148	54.2	-54.96	3.82	-3.97	12.65	-12.82
IIIl	5-CF_3,3-Cl	4-OMe	$C_{15}H_{13}N_3OF_3Cl$ (343.5)	71	140	52.29	-52.2	3.5	-3.78	11.98	-12.23
IIIm	5-CF_3,3-Cl	2-NO_2	$C_{14}H_{10}N_4O_2F_3Cl$ (358.5)	62	158	46.99	-46.86	2.62	-2.79	15.5	-15.62

The analytical data of these compounds are recorded in Table 4. The synthesis of compounds I, II, III and IV is given in Scheme 1.

Antifungal Screening: All the test chemicals were dissolved in acetone and subjected to the following assay. The standard malt agar medium was prepared by dissolving malt (20 g), dextrose (20 g) and agar (20 g) in 1 litre distilled water and sterilizing at 1.5 kg cm^{-2} for 20 minutes. After cooling it to about 40^{0}C, a mixture of penicillium G and streptosulphate (5 mg each) was thoroughly mixed in order to prevent any bacterial contamination. The filter paper discs (5 mm diameter), Whatmann

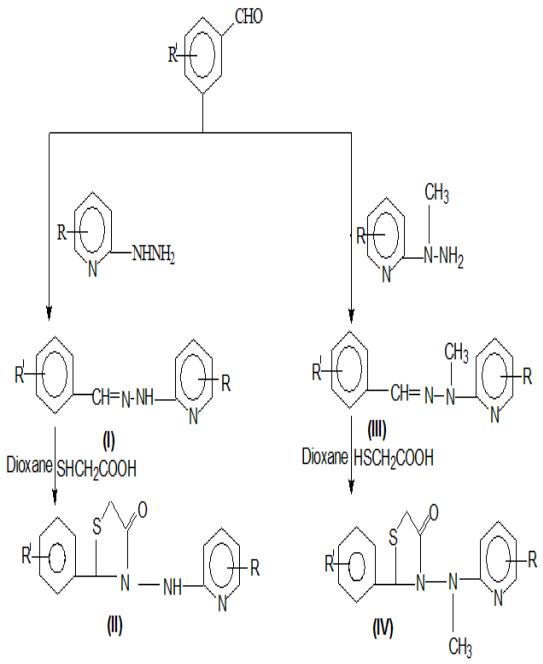
filter paper No. 44 was sterilized in an oven at 120°C for an hour. One mL of the test solution of the toxicant was slowly impregnated on a filter paper disc by evaporating the solvent after each addition with the help of hair dryer. The paper disc for control set was similarly impregnated with one ml of solvent. Each disc was finally dried and aseptically transferred to a petriplate (80 mm diameter) containing 10 mL of the culture medium. Only mycelial disc of the test fungus was inoculated upside down in the centre of assay disc. The plates were incubated at 28+1°C for seven days. The experiment was run in triplicate. After 7 days inhibition in fungal growth was determined as a difference in growth between control plate and those treated with test compound. The percentage inhibition of the mycelial growth was calculated by the following equation:

$$\% \text{ Growth Inhibition} = \frac{C - T}{C} \times 100$$

Where

C = Diameter of fungus colony (in mm) in control plate

T = Diameter of the fungus colony (in mm) in treated plates.



Scheme 1

The percentage of inhibition calculated for selected compounds have been presented in Table 5.

RESULTS AND DISCUSSION

Synthesis

All the synthesized compounds were obtained in good yield. The analytical data of the compounds listed in Tables 1-4 are compatible with the composition of desired product. The spectroscopic results are further in support of the compounds. The IR spectra of the compounds demonstrated well resolved absorption bands for characteristic groups. The appearance of absorption bands at 3200 cm^{-1} and at 1620 cm^{-1} in the IR spectra of intermediate hydrazones are clearly assignable to –NH and C=N stretching vibration respectively. The absorption band at 1680-1720 cm^{-1} in the IR spectra of thiazolidinones is due to carbonyl function and the appearance of characteristic bands of C-S-N toxophore at 1250 cm^{-1} are in further conformity of the formation of thiazolidinones.

Antifungal Activity

All the tested compounds showed moderate to high fungicidal activity at 100 ppm concentration against the test fungi. The compounds II, IIc, IIm and IVb showed greater than 80% activity against *Rhizoctina solani* and *Fusarium oxysporum*. This high activity may be due to the presence of two or more chlorine atoms in the compound and/or due to the methoxy group at para position to the chlorine atom. Although, the compounds bearing hydroxy or carboxylic group also exhibit activity in between 70 to 75% against the fungi but it can be very reasonably concluded that the compounds having combination of –Cl and –OMe at para position exhibit much higher fungicidal activity than any other combination. It was further noticed that neither the replacement of substituent at N- group from –H to $–CH_3$ nor changing the position of –CF3 on pyridine ring from -5 to -3 made any remarkable effect on activity.

Schematic presentation of synthesis of compounds I–IV is given in flow chart (Scheme 1).

CONCLUSION

The antifungal activity of any compound is not the numerical sum of the activity of different toxophores present in the molecule from the results, it has been concluded that compounds II, IIc, IIm and IVb showed strong antifungal activity at 100 ppm concentration. However, compounds IIa, IIe, Iii, IIj and IVa showed good activity against fungus *Rhizoctina solani*. Replacement of –NH by $–NCH_3$ in pyridine ring did not give any remarkable change in antifungal activity.

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