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SYNTHESIS AND BIOLOGICAL STUDIES OF SOME NOVEL THIAZOLIDINONES

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ABSTRACT

Pyridine-3-carboxylic acid hydrazide on condensation with substituted aromatic aldehydes yielded the benzylidine–arylidine acetohydrazido pyridine derivatives, **(3a-3l)** which on cyclization with thioglycolic acid in presence of anhyd. Zinc chloride as catalyst afforded phenyl -3-(Nicotinyl amino)-1, 3-thiazolidin-4-one derivatives **(4a-4l)**. The structures of the newly synthesized compounds have been established on the basis of IR, MASS and ^{1}H NMR spectral data. These compounds have also been screened for their biological activity.

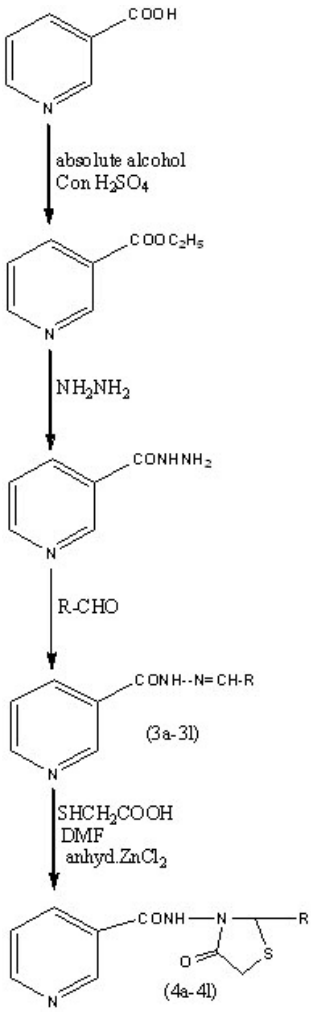
Keywords: *Pyridine; 4-thiazolidinone; Antibacterial; Antifungal.*

INTRODUCTION

Pyridine, a heterocyclic nucleus, plays a vital role in the field of heterocyclic chemistry. A number of pyridine derivatives are known for their varied biological and pharmacological activities. It is seen form the literature that pyridine compounds were associated with different biological properties like pesticidal[1], insecticidal[2] and fungicidal[3] activity. 4-thiazolidinones and its derivatives are known to posses a variety of physiological properties viz. antitubercular[4], antifungal[5] antimicrobial[6], pesticidal[7], nematicidal[8] , antitumor[9] activities.

Prompted by these reports, it was contemplated to design and synthesize some novel pyridine derivatives bearing thiazolidinone moiety and to screen the new synthesized products for their antibacterial and antifungal properties. Results of such studies are discussed in this paper.

The starting material, Pyridine-3-carboxylic acid ethyl ester was prepared by the esterification of Pyridine-3-carboxylic acid with absolute ethanol in presence of conc. H_2SO_4. Pyridine-3-carboxylic acid hydrazide was prepared by the condensation of hydrazine hydrate with the ester in presence of alcohol. The hydrazide upon reaction with substituted aromatic aldehydes in presence of few drops of glacial acetic acid yielded the benzylidine–arylidine acetohydrazido pyridine derivatives**(3a-3l)**. The later compounds upon cyclization with thioglycolic acid in presence of anhyd. Zinc chloride as catalyst afforded the phenyl -3-(Nicotinyl amino)-1,3-thiazolidin-4-one derivatives **(4a-4l)**. The final synthesized compounds were characterized on the basis of IR, MASS and ^{1}H NMR spectral data. The sequence of reactions is as shown in **Scheme-1.**



Scheme-1

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EXPERIMENTAL

Melting points were determined using open capillary tube method and are uncorrected. Thin layer chromatography [silica gel G (E.Merck) plates] was used to monitor the reactions and purity of the newly synthesized compounds. IR spectra were recorded using KBr disk on a Shimadzu Perkin-Elmer 8201 FT-IR. The PMR spectra were recorded on BRUKER AVANCE II 400 NMR SPECTROMETER in $CDCl_3$ and DMSO-d_6 using TMS as internal reference. The FAB mass spectra were recorded on JEOL SX-102/DA-6000 Mass spectrometer operating at 70eV.

Synthesis of pyridyl-3-carbohydrazide[10]

A mixture of Pyridine-3-carboxylic acid ethyl ester[10] (0.1 mol), and hydrazine hydrate (99%) (0.1 mol), in absolute alcohol (50ml) was refluxed for about 4hrs. The excess of solvent was removed and the residue was poured into ice cold water (125ml). The solid which is obtained was recrystallized from ethanol to get white crystalline product. Yield-82%, Mp 162 ^{O}C, IR (KBr): 1612 (C=N), 1670(C=O), 3048 (-CH of pyridyl).

Synthesis of benzylidine–arylidine acetohydrazido pyridine (3a-3l).

The hydrazide (0.01 mol) was dissolved in 30 ml of ethanol containing few drops of glacial acetic acid. The appropriate aromatic aldehydes (0.01 mol) were added and the reaction mixture was refluxed for about 6 hrs. The reaction mixture was cooled and poured into crushed ice and the solid which is obtained was filtered, washed with water and recrystallized from alcohol. The physical data of the compounds **(3a -3l)** is given in Table 1.

Table: 1 *Physical data of compounds (**3a-3l**)*

Compound	R-CHO	% yield	Melting point (^{O}C)
3a	C_6H_5	68	148
3b	4-OCH_3	66	107
3c	3,4,5- $(OCH_3)_3$	70	187
3d	4- $(CH_3)_2N$	68	138
3e	Furfural	64	156
3f	3-OH ,4-OCH_3	70	114
3g	4-Cl	66	165
3h	4-NO_2	70	175
3i	3,4- $(OCH_3)_2$	69	132
3j	2,4-$(Cl)_2$	72	144
3k	2-OH	66	115
3l	4-CH_3	67	98

3k: IR (KBr) (cm^{-1}): 3059(CH-Ar), 2904 (C-H), 1656(C=O), 1601(C=C). ^{1}H-NMR ($CDCl_3$) ä ppm: 6.8-9.1 (m, 9H, Ar-H, Ar-CH), 11.4(s, 1H, OH) 12.0 (s, 1H, CONH). MS: m/z: 241 [M^+] (58) , 153 (100).

3i: IR (KBr) (cm^{-1}): 3218(CH-Ar), 3061 (C-H), 1676 (C=O), 1593(C=C). ^{1}H-NMR ($CDCl_3$) ä ppm: 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.87-9.1 (m, 9H, Ar-H, Ar-CH), 11.86 (s, 1H, CONH).MS: m/z: 286[M^+] (67), 198 (100)

Synthesis of phenyl-3-(Nicotinyl amino)-1, 3-thiazolidin-4-one derivatives (4a-4l).

A mixture of Schiff base (0.01 mol) and thioglycolic acid (0.01 mol) in DMF (15 ml) containing a pinch of anhyd. Zinc chloride was refluxed for 8-11 hrs. The reaction mixture was cooled and poured into crushed ice. The solid thus obtained was filtered, washed with water and recrystallized from suitable solvents. The physical data of the compounds **(4a-4l)** is given in Table 2.

Table: 2 *Physical data of compounds (**4a-4l**)*

Compound	R-CHO	% yield	Melting point (^{O}C)
4a	C_6H_5	60	165
4b	4-OCH_3	62	187
4c	3,4,5- $(OCH_3)_3$	66	176
4d	4- $(CH_3)_2N$	58	187
4e	Furfural	54	149
4f	3-OH,4-OCH_3	64	213
4g	4-Cl	56	264
4h	4-NO_2	60	211
4i	3,4- $(OCH_3)_2$	59	196
4j	2,4-$(Cl)_2$	69	236
4k	2-OH	61	219
4l	4-CH_3	60	238

4a: IR (KBr) (cm^{-1}): 3080(CH-Ar), 2988 (C-H), 1720 (C=O), 1580(C=N). ^{1}H-NMR ($CDCl_3$) ä ppm: 3.6(s, 1H, CH), 4.7 (s, 2H, S-CH_2), 7.6-8.2 (m, 9H, Ar-H), 8.7 (s, 1H, CONH).MS: m/z: 309[M^+] (43) , 221 (32), 178(100)

4b: IR (KBr) (cm^{-1}): 3105(CH Ar), 2965 (C-H), 1708 (C=O), 1590(C=N), 1520 & 1337 (NO_2). ^{1}H-NMR ($CDCl_3$) ä ppm: 3.8(s, 3H, OCH_3), 3.5(s, 1H, CH), 4.8 (s, 2H, S-CH_2), 7.4-8.0 (m, 8H, Ar-H), 9.1 (s, 1H, CONH). MS: m/z: 329 [M^+] (61), 241(100), 198 (76).

4h: IR (KBr) (cm^{-1}): 3088(CH Ar), 2988 (C-H), 1717 (C=O), 1574(C=N). ^{1}H-NMR (CDCl3) ä ppm: 3.5(s, 1H, CH), 4.9 (s, 2H, S-CH_2), 7.9-8.5 (m, 9H, Ar-H), 9.3 (s, 1H, CONH).MS: m/z: 343[M^+](74), 255(100), 212 (51).

BIOLOGICAL ACTIVITY

The MIC determination of the tested compounds was carried out against Gram- positive (*S.aureus, B.subtilis*) and Gram-negative bacteria (*E.coli, P.aeruginosa*) by disc diffusion method[11]. Serial dilutions of the test compounds and reference drugs were prepared in Muller-Hinton agar. The standard drug (10 mg) was dissolved in DMSO (1ml). Further progressive dilutions with melted Muller-Hinton agar were performed to obtain the required concentrations of 1, 2, 4, 8, 16, 31.25, 62.5, 125, 250 and 500 µg/ mL^{-1}. The tubes were inoculated with 10^5 cfu mL^{-1} (colony forming unit/mL) and incubated at 37^{0}C for 24 hr. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC). DMSO was used as a solvent control in all the dilutions. Ciprofloxacin and Griseofulvin were used as standard drugs for antibacterial and antifungal activity respectively.

RESULTS AND DISCUSSION

The main aim of this work was to synthesize various new 4-thiazolidinones (Scheme-1). Initially substituted benzylidine–arylidine acetohydrazido pyridine derivatives, **(3a-3l)** were prepared from the reaction of pyridine-3-carboxylic acid hydrazide (nicotinic hydrazide) with different aromatic aldehydes in presence of few drops of glacial acetic acid. The title compounds **(4a-4l)** were obtained by the cyclization of benzylidine–arylidine acetohydrazido pyridine derivatives, with thioglycolic acid in presence of anhyd. Zinc chloride as catalyst. All the newly synthesized compounds were assigned on the basis of IR, MASS and ^{1}H NMR spectral data.

The final synthesized compounds were screened for their antibacterial and antifungal activity. Perusals of results of antibacterial activity which is expressed as minimum inhibitory concentration (MIC) and they are summarized in Table 3.

Table: 3 *Antimicrobial and antifungal activities of compounds 4a-4l*

Comp	MIC of Thiazolidinones					
	S.aureus	*B.subtilis*	*E.coli*	*P.aeruginosa*	*C.albicans*	*A.niger*
4a	62.5	125	62.5	125	250	31.25
4b	125	250	31.25	125	250	62.5
4c	250	8	125	250	125	62.5
4d	31.25	62.5	125	250	500	125
4e	250	125	250	31.25	500	125
4f	125	250	250	62.5	250	250
4g	500	125	125	125	125	250
4h	500	250	31.25	250	31.25	31.25
4i	125	62.5	8	31.25	62.5	31.25
4j	31.25	31.25	125	62.5	62.5	62.5
4k	62.5	31.25	62.5	125	31.25	125
4l	125	250	250	125	31.25	125
Ciprofloxacin	31.25	31.25	62.5	62.5	-	-
Griseofulvin	-	-	-	-	31.25	62.5
Control(DMSO)	-	-	-	-	-	-

All the newly synthesized compounds were evaluated for their antibacterial and antifungal activity. Compounds showed antimicrobial activity at MIC values of 8-500 µg/ mL. The compound 4i was found to be more active than the other compounds at an MIC value of 8 µg/mL. The synthesized compounds showed antimicrobial activity with MIC values between 31.25 & 500 µg/mL. Amongst the compounds tested for antibacterial activity **4j, 4k** showed good activity against both the gram –ve and gram +ve micro-organisms. The rest of the compounds showed moderate activity against all the organisms. In the antifungal study compounds **4h, 4i, 4j** showed highest activity against both the fungal organisms whereas other compounds showed moderate activity.

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