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Synthesis and antimicrobial evaluation of some 4-substituted thiazolidinone derivatives

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Abstract

In the present study 4-substituted thiazolidinones derivatives were synthesized from 2- amino pyridine which was used as a starting material. In this first the pyridyl thiourea was synthesized using ammonium isothiocyanate and conc HCl. And from this (pyridyl thiourea) schiff's bases were formed using different aldehydes and the Schiff's bases obtained were cyclised into 4-substituted thiazolidinones using thioglycolic acid. The compounds obtained were purified by column chromatography using silica jel .The chemical structure of the compounds were confirmed using IR. ^{1}HNMR and synthesized compounds are investigated for their antibacterial and antifungal activity against E.coli and S.aureus and C.albican using cup plate method. Compounds (4a, 4b) and 4d showed good activity.

Key words: Thiazolidinone, Schiff base, pyridyl thiourea.

INTRODUCTION

4-substituted thiazolidinone derivatives reported to show a variety of pharmacological and microbiological activities. Numerous literatures have highlighted its chemistry and use.[1-3] And a comprehensive review have shown that this moiety posses several activities like antibacterial, antifungal, analgesic and antiparkinsonian etc. Thus the biological significance of this class of compounds impelled to synthesize the new thiazolidinone derivatives having different pharmacological properties. Thus the thiazolidinone derivatives were synthesized from 2-amino pyridine.[4] First the pyridyl thiourea was synthesized from 2-amino pyridine using ammonium isothiocyanate and conc HCl and then Schiff's base were formed using different aldehydes and the base obtained is cyclised into 4-substituted thiazolidinone using thioglycolic acid. The compounds obtained were screened for antibacterial activity against bacteria *(E.coli* and *S.aureus)*and antifungal activity against pathogenic fungi *C.albican.* Compounds (3a-3e) were screened for above mentioned micro-organisms by using cup-plate agar method at concentration

100 µg/ml using amoxicillin as an standarad. Screening showed that these compounds were active as anibacterial and antifungal.[5]

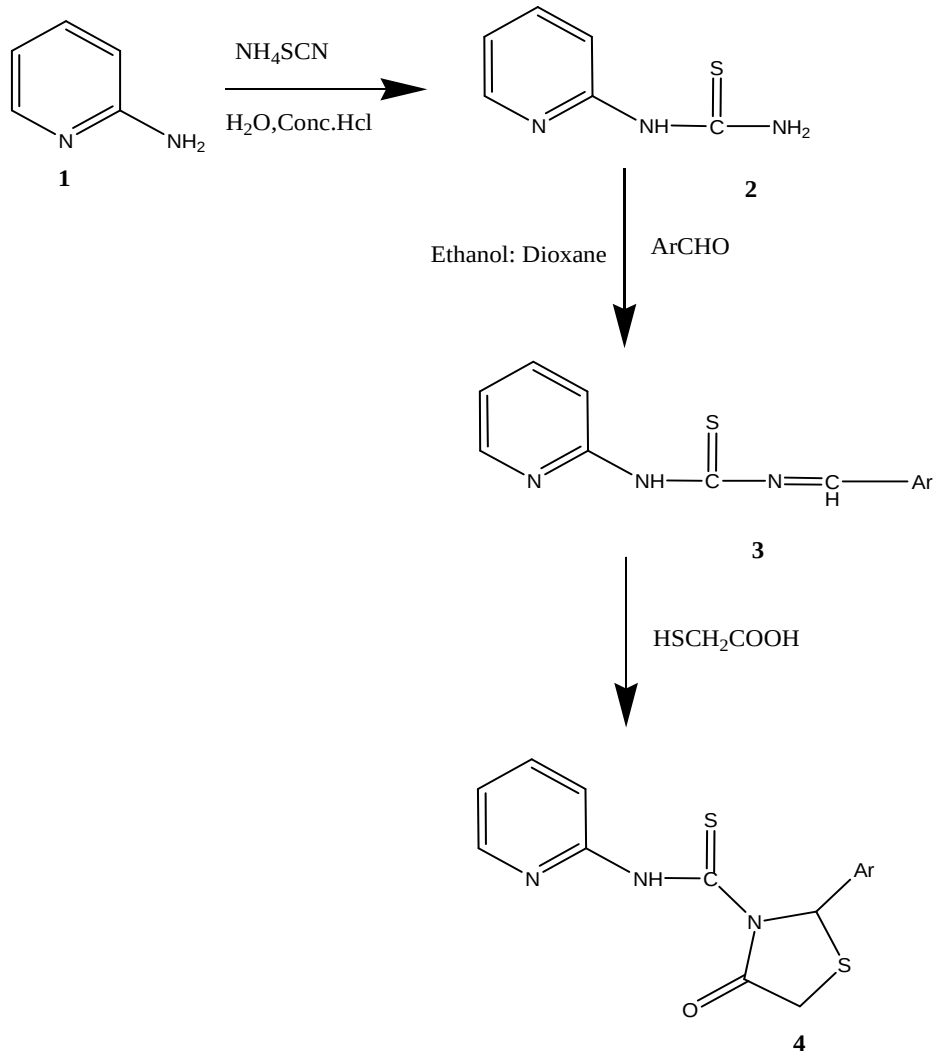
MATERIALS AND METHODS

Melting points are determined in open capillary tube using Veego VMP-1 apparatus and are uncorrected. IR spectra is recorded (in KBr) on Shimadzu FT-IR spectrometer.[1]HNMR spectra is recorded on Bruker DRX-300(300 MHz FT-NMR) using CDCl3 as solvent and TMS as internal standard.TLC using silica gel-G checked the purity of the compounds.

Synthesis of pyridyl thiourea from aminopyridine- (2)

Fresh Aminopyridine was taken 15.3g (0.1mole) in 250ml microwave flask & was treated with ammonium thiocyanate (0.2 mole) to which water and conc. HCl added and kept under microwave irradication for 7 hr at 7-8 power. There was clear brownish liquid formed which was evaporated gives crude pyridyl thiourea. This reaction was monitored by TLC.

Scheme



Synthesis of Schiffs Bases of Pyridyl thiourea(3a-3h)

Pyridyl thiourea (27.5g, 0.1 mole) was dissolved in ethanol and dioxane (2:1) mixture and to this solution substituted aromatic aldehyde (0.4mole) were added, in presence of catalytic amount of glacial acetic acid (2-3 mL). The reaction mixture was heated under reflux for 10-12 hours and checked TLC for completion of reaction. The reaction mixture was then allowed to cool and poured over crushed ice. Then it was poured into ice cold water to afford the corresponding Schiff's bases.. The precipitated Schiff's bases obtained.[6]

Synthesis of thiazolidinones from schiffs bases(4a-4f)

A homogeneous mixture of schiffs base (0.01 mole) and thioglycollic acid (0.01mole) in 15 mL dioxane was refluxed at 115˚c for 24 hrs.The reaction mixture was triturated with 10% Sodium bicarbonate solution. The neutral solution was poured into crushed ice. The solid obtained was filtered off ,washed with water and dried, then product was recrystallized from chloroform to give 60% yield.[7]

Table- 1

Compounds	Ar	Molecular Formulas
4a	4-Chlorophenyl	$C_{15}H_{12}ClN_3OS_2$
4b	3- Nitrophenyl	$C_{15}H_{12}N_4O_3S_2$
4c	4-Dimethyl amino phenyl	$C_{17}H_{18}N_4OS_2$
4d	3-Methoxy4- Hydroxyphenyl	$C_{16}H_{15}N_3O_3S_2$
4e	4-Hydroxyphenyl	$C_{15}H_{13}N_3O_2S_2$
4f	9-Anthranyl	$C_{23}H_{19}N_3OS_2$

(4a). 2-(4-Chlorophenyl)-4-oxo-N-(pyridin-2-yl)-1,3-thiazolidine-3- carbothioamide

% Yield-72%, m.p-156-158^{0}C, IR (KBr, cm^{-1})-3166(NH str), 1733(C=O), 1140(N-C=S), 1334(C-N). ^{1}H NMR (DMSO-D_6)- 12(s, 1H, NH), 3.39-3.21(2H,s, -CH_2), 5.27(s, 1H, CH) 7.02-7.87 (m, 8H, Phenyl).

(4c).2-[4-(Dimethylamino)phenyl]-4-oxo-N-(pyridin-2-yl)-1,3-thiazolidine-3-carbothioamide

% Yield-74%, m.p.-187-190^{0}C, IR(KBr, cm^{-1})-3402(NH str), 1652(C=O), 1218(N-C=S), 1374(C-N), ^{1}H NMR(DMSO-D_6)-10(s, 1H, NH), 3.71-3.80(2H, s, -CH2), 7.67-7.71(m, Phenyl).

Antimicrobial Evaluation

The antibacterial activity of synthesized compounds is done using gram +ve and gram –ve bacteria (*E. coli and S. aureus)* and antifungal activity against *C. albicans.* Media (Sabouraud dextrose agar medium or Nutrient agar) was sterilized by autoclaving at 15lbs pressure (121°C) for 15 min and poured (15-20 ml) into sterilized petri dishes in sterile environment and allowed to solidify. On the surface of the solidified media microbial suspension were spread with the help of sterile glass spreader or glass Slide.

Table 2 : Zone of inhibition of compounds (3a-3e) against *C. albicans* expressed as inhibition zone diameter (mm)

Compounds	Candida albicans(100µg)
3a	19
3b	22
3c	17
3d	19
3e	25
DMSO	-

Standard (Fluconazole 100µg/ml) – 25 mm

Table 3 : Zone of inhibition of compounds (3a-3e) against *E. coli*, *S. aureus*, and *P. auerogenosae*

Compound	*E. coli*	*S. aureus*	*P.auerogenosae*
3a	12	13	19
3b	20	18	12
3c	20	15	15
3d	15	20	19
3e	17	15	18
DMSO	-	-	-

Standard (Amoxicillin 100 µg/ml) – 22mm

A stainless steel borer (pre-sterilised) was used to bore the cavities. Solutions of the test compounds were placed serially in the cavities with the help of micropipette and allowed to diffuse. DMSO was used as a solvent for all the compounds and as a control. Fluconazole and Amoxicillin were used as a references standard and also screened under Similar conditions for comparison. The plates were then incubated at 370C for 24-48 Hours. The zone of inhibition observed around the cavities after incubation was measured. The results are presented in table below.[8-9]

RESULTS AND DISCUSSION

All the synthesized final compounds were first purified by successive recrystallization using appropriate solvents and some purified by column chromatography. The purity of the synthesized compounds were checked by performing thin layer chromatography and determining melting points .Then the synthesized compounds is subjected to spectral analysis such as IR,^{1}HNMR to confirm the structures.All the analytical details showed the satisfactory results.

Since the titled compounds are known to posses antimicrobial activity, the compounds were screened for their antibacterial and anti-fungal activity by cup plate method. One gram +ve bacteria such as *Staphylococcus aureus* and two gram –ve bacteria such as *Escherichia Coli* and *Pseudomonas auregenosa* and one anti fungal species such as *Candida albicans* are tested for the activities. The concentration of (100µg)/ml of our titled compound has been used. Amoxicillin and Fluconazole is used as an standard. All the compounds have shown mild to moderate activities.[10]

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