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SYNTHESIS AND ANTIMICROBIAL SCREENING OF NOVEL 3-ARYL-2(4-(PYRROLIDIN-1-YL) PHENYL) THIAZOLIDIN-4-ONES

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A series of novel 3-aryl-2(4-(pyrrolidin-1-yl) phenyl) thiazolidin-4-ones has been synthesized and screened for antibacterial activity. From the synthesized compounds **4a**, **4d** and **4f** show moderate antibacterial activity.

4-Thiazolidinones, one of the members of sulfur and nitrogen containing heterocycles are the core structure of a number of biologically important compounds[1]. These are reported to exhibit bioactivities like anticonvulsant[2], antimicrobial[3], anti-diarrheal[4], antidiabetic[5], anti HIV[6], anticancer[7], antihistamine[8], antifungal[9], antioxidant[10], anti YFV (Yellow Fever Virus)[11], antitubercular[12], analgesic, anti-inflammatory[13] activities.

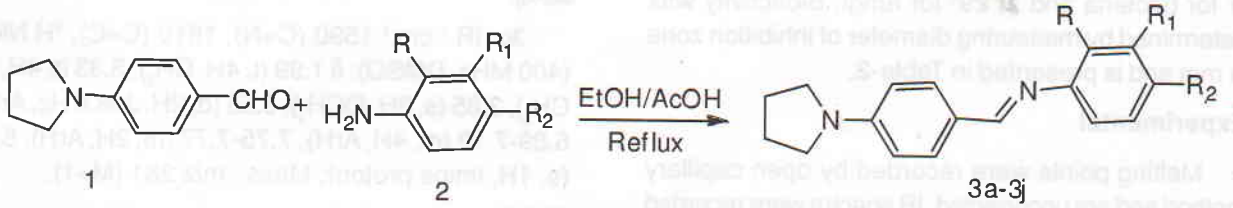
Five member heterocyclic compounds and their derivatives have been reported to show important biological properties[14]. One of the member from this i.e. Pyrrolidine ring act as an intermediate for many pharmaceuticals[15], food, pesticide[16], paints, textile and polymer materials[17]. Pyrrolidine derivatives have been reported to show different important biological activities like anticancer[18].

So present study was undertaken to synthesise 4-thiazolidinone containing pyrrolidine moiety by reacting Schiff base with mercapto acetic acid.

In the present work Schiff bases (imines) **3a-3j** were prepared by reacting aldehyde and various aromatic amines. The 4-thiazolidinones **4a-4j** were prepared by reacting imines with mercapto acetic acid using toluene or dioxan as solvent, in both solvent system the yield is nearly same only the time consumption is different.

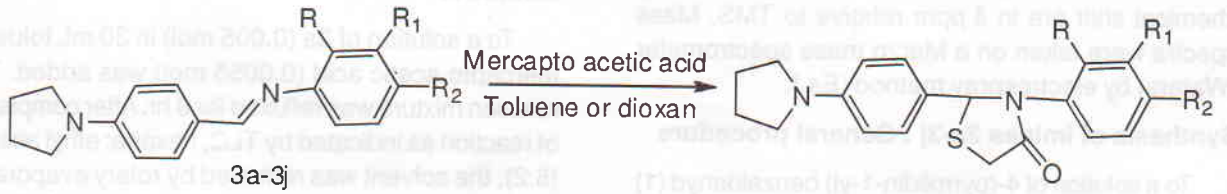
Antimicrobial activity

Compounds **3a-3j** and **4a-4j** were screened for in vitro antimicrobial activity against *Pseudomonas aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 25923), *E. Coli* (ATCC25922) and *Candida sp.*, using disc diffusion method. Each compound was dissolved in DMSO to get concentration of 50µg/mL. Discs of Whatmann filter paper no. 41 (6 mm) were



1 2 3a-3j

SCHEME-1



3a-3j 4a-4j

SCHEME-2

Table-1
Physical data of compounds **3a-3j** and **4a-4j**

Compd	R	R_1	R_2	Yield (%)	M.P. (°C)
3a	H	H	F	63	150-151
3b	H	H	H	58	140-141
3c	OCH_3	H	H	61	117-118
3d	CH_3	H	CH_3	60	125-127
3e	CH_3	H	H	59	98-100
3f	H	H	Br	64	125-128
3g	H	H	OCH_3	61	120-121
3h	H	OCH_3	H	60	114-116
3i	H	H	CH_3	58	119-120
3j	H	CH_3	H	59	118-121
4a	H	H	F	55	108-110
4b	H	H	H	48	115-119
4c	OCH_3	H	H	51	121-123
4d	CH_3	H	CH_3	40	105-107
4e	CH_3	H	H	55	106-108
4f	H	H	Br	59	131-132
4g	H	H	OCH_3	45	126-128
4h	H	OCH_3	H	40	111-117
4i	H	H	CH_3	45	115-117
4j	H	CH_3	H	44	105-106

prepared, discs were placed on the surface of inoculated agar plate and 10µL of each dissolved compound was loaded on disc. The compound was allowed to diffuse for 10 min. DMSO was used as control. The Petri dishes were incubated at 37° for 24 hr for bacteria and at 29° for fungi. Bioactivity was determined by measuring diameter of inhibition zone in mm and is presented in Table-2.

Experimental

Melting points were recorded by open capillary method and are uncorrected. IR spectra were recorded in KBr disc on Shimadzu IR Affinity 1 spectrophotometer. ^{1}H NMR were recorded on a Varian As 400 MHz spectrophotometer in $CDCl_3$/DMSO-d_6, chemical shift are in δ ppm relative to TMS. Mass spectra were taken on a Macro mass spectrometer (Waters) by electrospray method (Es.).

Synthesis of imines 3a-3j : General procedure

To a solution of 4-(pyrrolidin-1-yl) benzaldehyd (**1**) (0.010 mol) in 50 mL ethanol, various aromatic amines (**2**) (0.015 mol) were added. The reaction mixture was made acidic by adding 1-2 drops of gl acetic acid and refluxed for 4 hr. After completion of reaction as indicated by TLC, hexane: ethyl acetate (8:2), the solvent was removed by rotary evaporator, the residue was recrystallised from ethanol to give compounds **3a-3j**.

3c: IR : cm^{-1} 1590 (C=N), 1610 (C=C), ^{1}H NMR (400 MHz, DMSO): δ 1.99 (t, 4H, CH_2), 3.33 (t, 4H, N-CH_2), 3.85 (s, 3H, OCH_3), 6.55 (d, 2H, J=8.8 Hz, ArH), 6.89-7.13 (m, 4H, ArH), 7.75-7.77 (m, 2H, ArH), 8.19 (s, 1H, imine proton); Mass : m/z 281 (M+1).

Synthesis of thiazolidinones 4a-4j : General procedure

Method A

To a solution of **3a** (0.005 mol) in 30 mL toluene, mercapto acetic acid (0.0055 mol) was added. The reaction mixture was refluxed for 8 hr. After completion of reaction as indicated by TLC, hexane: ethyl acetate (8:2), the solvent was removed by rotary evaporator, the residue was treated with saturated solution of $NaHCO_3$, extracted with ethyl acetate, dried over

Table-2
Antimicrobial activity data of **4a-4j**

Compd	*Pseudomonas aeruginosa* (ATCC27853)	*Staphylococcus aureus* (ATCC 25923)	*E. coli* (ATCC25922)	*Candida sp*
4a	12mm	12mm	18mm	–
4b	–	–	–	–
4c	–	–	–	–
4d	10mm	10mm	–	–
4e	–	–	–	–
4f	12mm	10mm	16mm	–
4g	–	–	–	–
4h	–	–	–	–
4i	–	–	–	–
4j	–	–	–	–
Gentamycin	24mm	21mm	27mm	–
Nystatin	–	–	–	23 mm

anhyd. Na_2SO_4 and solvent was distilled off. The residue was recrystallised from ethanol to give compound **4**a. Similarly **4**b-**4**j were prepared.

Method B

To a solution of **3**a (0.005 mol) in 30 mL dioxan, mercapto acetic acid (0.0055 mol) was added. To the resulting solution pinch of $ZnCl_2$ was added. The reaction mixture was refluxed for 16 hr. After completion of reaction as indicated by TLC, hexane: ethyl acetate (8:2), the solvent was removed by rotary evaporator, the residue was treated with saturated solution of $NaHCO_3$, extracted with ethyl acetate, dried with Na_2SO_4 and solvent was distilled off. The residue was recrystallised from ethanol to give compound **4**a. Similarly **4**b-**4**j were prepared.

4d : IR : 1680 (CO), 1532 (aromatic): ^{1}H NMR (400 MHz, DMSO): 2.02 (t, 8.60 Hz, 4H, CH_2), 2.31 (s, 6H, Ar-CH_3), 3.35 (t, 8.6 Hz, 4H, CH_2), 4.12-4.19 (m, 2H, CH_2), 5.92 (s, 1H, CH), 6.51-7.76 (m, 7H, ArH). Mass : m/z 353 (M+1).

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