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# Synthesis and Antimicrobial Evaluation of Some 4-Thiazolidinone Derivatives Containing Polynuclear Hydrocarbon

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Some 4-thiazolidinone derivatives have also been known to be associated with several biological activities thus can be utilized as promising scaffold for developing analogues. Aryl aldehydes were treated with naphthylamine to yield corresponding Schiff's bases. The Schiff's bases were treated with thioacetic acid in the presence of anhydrous $ZnCl_2$ to afford 4-thiazolidinone derivatives then all the compounds were characterized and evaluated for antibacterial and antifungal activity. Compounds having methoxy group at *meta*- and *para*-position, dimethylamino and hydroxyl group at *para*-position was found to be biologically active.

**Keywords: 4-Thiazolidinone, Schiff's bases, Antimicrobial, Polynuclear hydrocarbon.**

## INTRODUCTION

Chemical transformation of known active molecule involves the use of already known principle on reported active molecule for the search of new molecules, which could have an increased potency, a better activity profile and improved safety [1]. Imines have been reported to possess biological activity [2]. Some 4-thiazolidinone derivatives have also been known to be associated with several biological activities such as antibacterial, antifungal anticonvulsant, antiviral, sedative, hypnotic, antitubercular, anthelmentic, anticonvulsant, antihistaminic, anticancer and antiinflamatory activity thus can be utilized as promising scaffold for developing analogues [3]. It has been reported that groups like hydroxyl, methoxy, ethoxy, chloro in the phenyl ring increases the activity of parent compound [4,5]. So far no systematic attempt has been made to study the effect of polynuclear hydrocarbon on the antimicrobial activity. So keeping in view the present work involves the synthesis, characterization and evaluation of antibacterial activity of some novel 4-thiazolidinone derivatives containing polynuclear hydrocarbons.

## EXPERIMENTAL

General synthetic procedure involves the two step synthesis proceed *via* imine formation in the first step followed by attack of sulphur nucleophile on the imine carbon followed by attack of nitrogen on the carboxylic moiety and finally intramolecular cyclization with elimination of water involve an amine, a carbonyl compound and a mercaptoacetic acid yield 4-thiazolidinone. The water formed during cyclization is removed by using anhydrous zinc or sodium sulphate as a dessicant (Fig. 1).

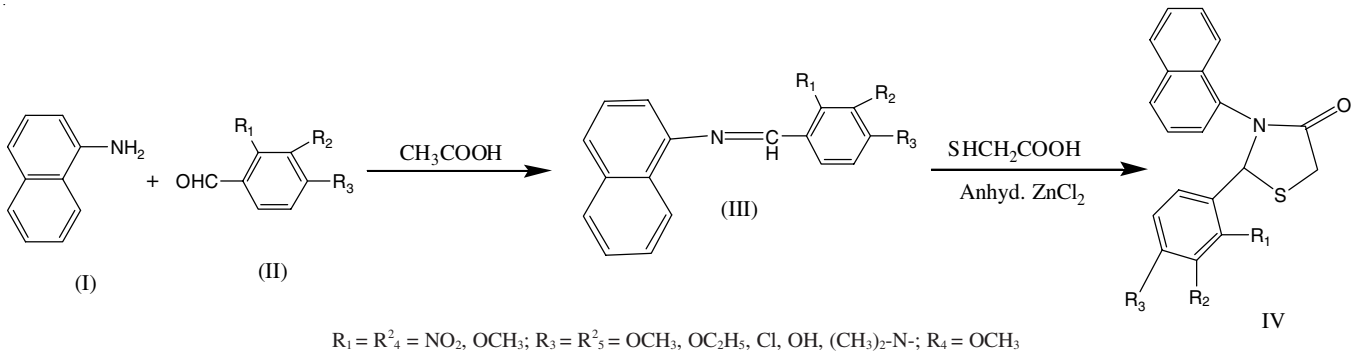
### Synthesis of Schiff's bases

**Naphthalene-1-yl-(2-nitro-benzylidene)amine:** A mixture of α-naphthylamine (3 mmol) and benzaldehyde derivatives (3 mmol) in methanol (30 mL) containing 3-4 drops of glacial acetic acid was refluxed for 3 h. Thin layer chromatography was monitored to check the completion of the reaction. Thereafter reaction mixture was cooled to room temperature. The solid was filtered, washed with cold ethanol, dried and recrystallized using a mixture of hexane and acetone (9:1) [6].

**Synthesis of 4-thiazolidinone derivatives:** A mixture of Schiff's bases (3 mmol) and mercaptoacetic acid (3 mmol) in anhydrous 1:4-dioxane (30 mL) was refluxed for 8 h. The progress of the reaction was monitored by thin layer chromatography. The mixture was cooled and the residue was filtered, dried and washed with cold water. The pure product was isolated by column chromatography using chloroform and hexane (8:2) as eluent and silica (100-120) as adsorbent [7].

### Spectral characterization of 4-thiazolidine derivatives

**2-(2-Nitrophenyl)-3-(naphthalene-1-yl)thiazolidin-4-one (1a):** m.f.: $C_{19}H_{14}N_2O_3S$, yield: 43 %, PMR ($CDCl_3$, δ in ppm): 3.6 (s, 1H, -CH-thiazolidine ring), 5.8 (m, 1H, -CH-thiazolidine ring), 7.15 (s, 2H, $-CH_2$-naphthalene ring), 7.23




$R_1 = R^2_4 = NO_2, OCH_3$; $R_3 = R^2_5 = OCH_3, OC_2H_5$, Cl, OH, $(CH_3)_2$-N-; $R_4 = OCH_3$

Fig. 1

(s, 1H, CH-benzene), 8.1 (s, 1H, CH-benzene). IR (KBr, $\nu_{max}$, $cm^{-1}$): 1724 (CO- cyclic), 2950 ($CH_2$-S- cyclic), 1680 (CON- cyclic), 668-602 (C-S-C), 1140 (CO- cyclic), $M^{+1}$ Peak- 360.30.

**2-(4-Hydroxyphenyl)-3-(naphthalene-1-yl)thiazolidin-4-one (1b):** m.f.: $C_{19}H_{15}NO_2S$, yield: 43 %, PMR ($CDCl_3$, δ in ppm): 3.6 (s, 1H, -CH-thiazolidine ring), 5.8 (m, 1H, -CH-thiazolidine ring), 7.15 (s, 2H, -$CH_2$-naphthalene ring), 7.23 (s, 1H, CH-benzene), 5.8 (s, 1H- OH-benzene). IR (KBr, $\nu_{max}$, $cm^{-1}$): 1724 (CO- cyclic), 2950 ($CH_2$-S- cyclic), 1680 (CON- cyclic), 668-602 (C-S-C), 1140 (CO- cyclic), $M^{+1}$ Peak- 331.39.

**2-(4-Dimethylaminophenyl)-3-(naphthalene-1-yl)-thiazolidin-4-one (1c):** m.f.: $C_{21}H_{20}N_2OS$, yield: 43 %, PMR ($CDCl_3$, δ in ppm): 3.6 (s, 1H, -CH-thiazolidine ring), 5.8 (m, 1H, -CH-thiazolidine ring), 7.15 (s, 2H, -$CH_2$-naphthalene ring), 7.23 (s, 1H, CH-benzene), 2.78 (s, 3H- $CH_3$-benzene). IR (KBr, $\nu_{max}$, $cm^{-1}$): 1724 (CO- cyclic), 2950 ($CH_2$-S- cyclic), 1680 (CON- cyclic), 668-602 (C-S-C), 1140 (CO- cyclic), $M^{+1}$ Peak- 359.50.

**2-(4-Methoxyphenyl)-3-(naphthalene-1-yl)thiazolidin-4-one (1d):** m.f.: $C_{20}H_{17}NO_2S$ yield: 43 %, PMR ($CDCl_3$, δ in ppm): 3.6 (s, 1H, -CH-thiazolidine ring), 5.8 (m, 1H, -CH-thiazolidine ring), 7.15 (s, 2H, -$CH_2$-naphthalene ring), 7.23 (s, 1H, CH-benzene), 3.68 (s, 3H- $CH_3$-benzene). IR (KBr, $\nu_{max}$, $cm^{-1}$): 1724 (CO- cyclic), 2950 ($CH_2$-S- cyclic), 1680 (CON- cyclic), 668-602 (C-S-C), 1140 (CO- cyclic), $M^{+1}$ Peak- 345.50.

**2-(3,4-Dimethoxyphenyl)-3-(naphthalene-1-yl)thiazolidin-4-one (1e):** m.f.: $C_{22}H_{23}NO_2S$, yield: 43 %, PMR ($CDCl_3$, δ in ppm): 3.6 (s, 1H, -CH-thiazolidine ring), 5.8 (m, 1H, -CH-thiazolidine ring), 7.15 (s, 2H, -$CH_2$-naphthalene ring), 7.23 (s, 1H, CH-benzene), 3.71 (s, 3H-, $CH_3$-benzene). IR (KBr, $\nu_{max}$, $cm^{-1}$): 1724 (CO- cyclic), 2950 ($CH_2$-S- cyclic), 1680 (CON- cyclic), 668-602 (C-S-C), 1140 (CO- cyclic), $M^{+1}$ Peak- 375.49.

**2-(4-Chlorophenyl)-3-(naphthalene-1-yl)thiazolidin-4-one (1f):** m.f.: $C_{19}H_{14}NOSCl$, yield: 43 %, PMR ($CDCl_3$, δ in ppm): 3.6 (s, 1H, -CH-thiazolidine ring), 5.8 (m, 1H, -CH-thiazolidine ring), 7.15 (s, 2H, -$CH_2$-naphthalene ring), 7.23 (s, 1H- benzene). IR (KBr, $\nu_{max}$, $cm^{-1}$): 1724 (CO- cyclic), 2950 ($CH_2$-S- cyclic), 1680 (CON- cyclic), 668-602 (C-S-C), 1140 (CO- cyclic), $M^{+1}$ Peak- 349.50.

**Evaluation of antimicrobial activity:** Antimicrobial activity of the 4-thiazolidinone derivatives were determined by cup plate method [8] using bacterial strains such as *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeurginosa* and *Bacillus subtilis* and antifungal activity against fungal strain of *Candida albicans* [9,10]. Antibiotic ofloxacin was used as standard drug for determination of antimicrobial activity at concentration of 100 µg/mL [11] and econazole was used as standard drug for determination of antifungal activity at concentration of 100 µg/mL [12] (Table-1).

TABLE-1
ANTIMICROBIAL ACTIVITY OF 4-THIAZOLIDINONE DERIVATIVES

| Compound | Diameters (mm) of zones of inhibition for microorganism | | | | | |
|---|---|---|---|---|---|---|
| | Conc. (µg/mL) | *B. subtilis* | *S. aureus* | *E. coli* | *P. aeurginosa* | *C. albicans* |
| Ofloxacin | 100 | 15.7 | 15.5 | 15.7 | 15.7 | NA |
| Econazole | 100 | NA | NA | NA | NA | 16.5±0.1 |
| **1a** | 100 | 8.6 | 7.9 | 7.5 | 8.5 | – |
| | 150 | 12.8 | 13.3 | 12.7 | 12.7 | – |
| **1b** | 100 | 5.2 | 6.5 | 4.7 | 5.3 | – |
| | 150 | 9.6 | 4.9 | 7.9 | 9.7 | – |
| **1c** | 100 | 9.6 | 9.2 | 8.5 | 9.7 | – |
| | 150 | 12.8 | 15.9 | 15.8 | 16 | – |
| **1d** | 100 | 8.6 | 7.9 | 7.5 | 8.5 | – |
| | 150 | 14.5 | 15.7 | 15.5 | 15.1 | – |
| **1e** | 100 | 6.7 | 5.7 | 5.4 | 5.9 | – |
| | 150 | 11.5 | 10.2 | 11.4 | 15.8 | – |
| **1f** | 100 | 5.8 | 5.7 | 5.2 | 5.9 | – |
| | 150 | 10.5 | 10.2 | 10.5 | 4.8 | – |

*Zone of inhibition were measured as average of triplet; Highly active = Inhibition zone > 12 mm; Moderately active = Inhibition zone 6-12 mm; Slightly active = Inhibition zone < 6 mm; Not active (NA) = Indicate no zone of inhibition.

## RESULTS AND DISCUSSION

All the reactions were carried out in dried glassware. Precoated TLC was used for monitoring the progress of reaction and visualization was done in iodine chamber. The synthesized compounds were purified using recrystallization/column chromatography. After physical characterization, the compounds were subjected to spectral analysis. $^1$H NMR spectra recorded on Brucker WM-300 at 300 spectrometers, chemical shifts are reported in parts per million shift (δ-value) from TMS (δ) as an internal standard. Coupling constant are given in hertz. Mass spectra were recorded on a JEOL-SX-102 instrument using direct analysis in real time (DART). FT-IR spectra were taken on Perkin-Elmer AX-1 spectrometer and values are expressed in $cm^{-1}$. Solubility, melting points, $R_f$ values were determined for each compound.

The synthesized compound 1c was found to be highly active against *S. aureus* and *P. aerugnosa, E. coli* at concentration of 150 µg/mL. Compound **1d** was found to be highly active against *E. coli*, *S. aureus* and *P. aerugnosa* at concentration of 150 µg/mL and moderately active against *B. subtilis* at concentration of 150 µg/mL. Compound **1e** was found to be highly active against *P. aeruginosa* at concentration of 150 µg/mL and moderately active against *E. coli* and *S. aureus* at concentration of 150 µg/mL. Compound 1f was found to be moderatly active against *B. subtilis* and *S. aureus* at concentration of 150 µg/mL. Compound **1a** was found to be slightly active at concentration of 150 µg/mL. Almost all compounds were inactive at concentration of 50 µg/mL.

Econazole was used as standard drug for determination of antifungal activity, which was highly active at concentration of 100 µg/mL. All the compounds were found to be inactive against *C. albicans*. However, compounds having methoxy group at *meta*- and *para*-position, dimethylamino and hydroxyl group at *para*-position of was found to be more active against some microbes.

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