



# Synthesis of Novel Azetidinone and Thiazolidinones Derivatives and Evaluation of Their Antimicrobial Efficacy

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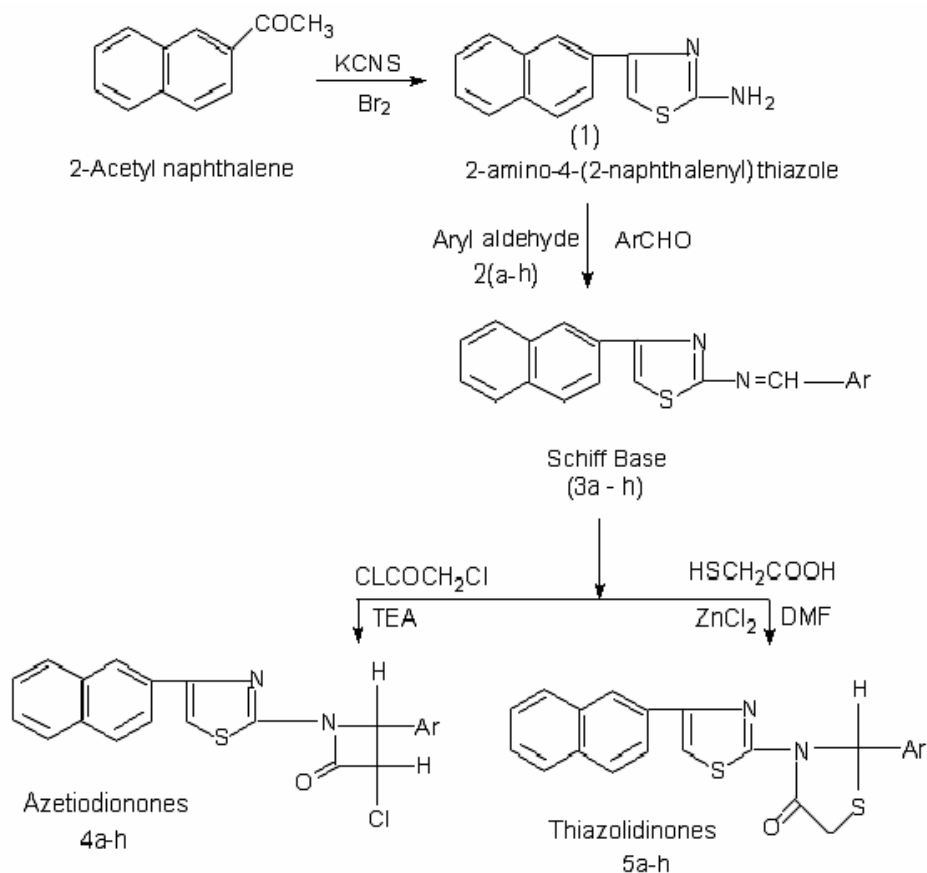
**Abstract:** 2-Amino-4-(2-naphthalenyl) thiazole (**1**) was prepared from 2-acetylnaphthalene. This amine on facile condensation with aromatic aldehydes afford Schiff Base/anils/azomethines(**2a-h**). These anils on cyclocondensation reaction with chloro acetyl chloride and thio glycolic acid (*i.e.* mercapto acetic acid) yields 2-azetidinones and 4-thiazolidinones respectively. The prepared compounds have been screened on some stains of bacteria.

**Key words:** 2-Azetidinones, 4-thiazolidinones, cyclo-condensation reaction, spectral studies antibacterial action.

## Introduction

Thiazoles are one of the most intensively investigated classes of aromatic five membered heterocycles. Thiazole derivatives find new a variety of applications ranging from bacteriostatics, antibiotics, CNS regulants of high selling diuretics<sup>1-5</sup>. All these facts were driving force to develop novel thiazole derivatives with wide structural variation<sup>6</sup>. Thus thiazole derivatives plays pivotal role in medicinal chemistry.

As part of interest in heterocycles that have been explored for developing pharmaceutically important molecules, 4-thiazolidinones<sup>7-9</sup> and 2-azetidinones<sup>10-13</sup> have played an important role in medicinal chemistry. Moreover they have been studied extensively because of their ready accessibility, diverse chemical reactivity and broad spectrum of biological activity. The area in which the transformation of 2-amino-4-(2-naphthalenyl) thiazole into azetidinones and thiazolidinones has not reported so far. Hence it was thought interesting to study such type of moieties shown in **scheme-1**.

**Scheme-1**

Where Ar: (a) Phenyl, (b) 4-Methoxy Phenyl (c) 4-Hydroxy Phenyl (d) 2-Hydroxy Phenyl (e) 4-Methyl Phenyl (f) 3,4-Methylenedioxy Phenyl (g) 4-Hydroxy-3-Methoxy Phenyl (h) 3,4-Diethoxy Phenyl

## Experimental

### Materials

2-Amino-4-(2-naphthalenyl) thiazole was prepared according to method reported<sup>14</sup>. The aromatic benzaldehydes (**2a-h**) viz; a: benzaldehyde, b: 4-methoxy benzaldehyde, c: 4-hydroxy benzaldehyde, d: 2-hydroxybenzaldehyde, e: 4-methyl benzaldehyde, f: 4-bromobenzaldehyde, g: 3,4-ethylenedioxy benzaldehyde, h: 4-hydroxy-3-methoxy benzaldehyde and i: 3,4-dimethoxy benzaldehyde were obtained from local dealer. All other chemicals used were of laboratory grade.

### Measurements

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBR pellets on a nicollet 760D spectrophotometer and <sup>1</sup>H NMR spectra in CDCl<sub>3</sub> on Perkin Elmar NMR spectrometer using TMS as an internal standard.

Antimicrobial activity of all the compounds were studied against Gram positive bacteria (*Bacillus Subtillies* and *staphyococcus aureus*) and Gram negative bacteria (*E.Coli* and *salmonella typhi*) at a concentration of 50 $\mu$ g/ml by agar cup method<sup>15</sup>. Methanol system was used as control in the method. Under similar conditions using penicillin and sulfanilamide as a standard comparison carried at control experiment. The area of inhibition of zone is measured in percentage

#### *Preparation of Schiff base (3a-h)*

A mixture of equiolar amount (0.01) of 2-amino-4-(2-naphthalenyl) thiazole (1) benzaldehyde derivative (**2a-h**) in ethanol (40 ml) and piperidine (0.3 ml) was refluxed for 5 hrs on water bath. The reaction mixture was concentrated, cooled and poured in water; the solid obtained was filtered and recrystallised from ethanol to give Schiff base (**3a-h**). It was obtained in 60-65% yield.

#### *Preparation of 2-Azetidinones (4a-h)*

A mixture of Schiff base (3a-h) (0.002 mmol) and triethyl amine [TEA] (0.004 mmol) was dissolved in 1,4-dioxane (50 ml), cooled and stirred. To this well-stirred cooled solution chloro acetyl chloride (0.004 mmol) was added drop wise with in a period of 20 min. The reaction mixture was then stirred for an additional 3 hrs and left at room temperature for 48 hrs. The resultant mixture was concentrated, cooled, poured in to ice cold water, filter and then dried. The product thus obtained was purified by column chromatography over silica gel using 30% ethyl acetate: 70% benzene as an eluent. Recrystallization from either / n-Hexane gave 2-azetidinones (**4a-h**), which were obtained in 55-60% yield.

#### *Preparation of 2-Thiazolidinones (5a-h)*

A mixture of Schiff base (**3a-h**) (0.01 mmol) in THF (30 ml) and mercapto acetic acid (0.01 mmol) with a pinch of anhydrous ZnCl<sub>2</sub> was then refluxed to at a residue, which was dissolved in 1,4-dioxane passed through a column of silica gel using benzene : chloroform (8:2 , v/v) mixture as an eluent. The eluent was concentrated and the product recrystallized 4-thiazolidinones (**5a-h**) from ethanol: 1,4-dioxane (1:1) mixture 50-60% yield. The analytical data of all the compounds **4a -i** and **5a-i** are furnished in **Tables 1** and **2**.

## **Results and Discussion**

The 2-Amino-4-(2-naphthalenyl)thiazole(2) was dissolved in ethanol and was reacted with aeromatic aldehyde in the presence of piperidine to yield Schiff bases (**3a-h**). This Schiff bases (**3a-h**) were then characterized by the elemental analysis, IR spectral studies and NMR spectral studies. The IR spectra of Schiff bases show the prominent band at 1630 cm<sup>-1</sup> for the azomethine group<sup>16, 17</sup>.

These Schiff bases on cyclo-condensation reaction with chloro acetyl chloride afford 2-azetidinone (**4a-h**) and with thio-glycolic acid afford 4-thiazolidinone (**5a-h**) respectively. The structures of both these compounds (**4a-h**) and (**5a-h**), respectively, have been confirmed by elemental analysis, IR spectral studies, and NMR spectral studies. These compounds shows the band at 1690 cm<sup>-1</sup> for cyclic >C=O group<sup>16, 17</sup>. All the compounds show the NMR signals for different kinds of protons at their respective positions. The data are shown in **Tables 1** and **2**. The C, H, N, S analysis of all the compounds of the series are presented in **Table 1** and **2**. The values are consistent with their predicted structure (**Scheme 1**).

**Table 1** Analytical and spectral Data of Commands **4a-h**

Compd	Molecular formula	Mol. Wt	Yield (%)	M.P. (°C)	% Analysis								PMR (̈́ PPM)
					%C		%H		%N		%S		
					Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	
4a	C <sub>12</sub> H <sub>15</sub> ClN <sub>2</sub> OS	390.5	65	182-3	67.6	67.5	3.84	3.9	7.17	7.1	8.19	8.1	9-2 1H d C <sub>3</sub> H 9-2-7-8 (12 H mtd aromatic C <sub>4</sub> H
4b	C <sub>23</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>2</sub> S	420.5	61	178-9	65.5	65.4	4.04	3.9	6.65	6.6	7.60	7.5	8-2-7.8 (11H mtd aromatic & C <sub>4</sub> H, 9.2 (H d. C <sub>3</sub> H) 2.1 (3H <sub>3</sub> CH <sub>3</sub> )
4c	C <sub>22</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>2</sub> S	406.5	55	170-1	64.9	67.8	3.69	3.6	6.88	6.8	7.87	7.8	8-2-9.8 (11H mtd aromatic & C <sub>4</sub> H, 9.2 (H d. C <sub>3</sub> H) 3.9 (H S OH)
4d	C <sub>22</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>2</sub> S	406.5	60	190-1	64.9	64.8	3.69	3.6	6.88	6.8	7.87	7.8	8-2-9.8 (11H mtd aromatic & C <sub>4</sub> H, 9.2 (H d. C <sub>3</sub> H) 3.9 (H S OH)
4e	C <sub>23</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>2</sub> S	406.5	65	103-4	68.2	68.1	4.20	4.1	6.92	6.8	7.91	7.8	8-2-9.8 (11H mtd aromatic & C <sub>4</sub> H, 9.2 (H d. C <sub>3</sub> H) 3.9 (H S OH)
4f	C <sub>23</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>3</sub> S	434.5	56	151-2	63.5	63.4	3.45	4.3	6.44	6.4	7.36	7.2	8-2-7.8 (11H mtd aromatic & C <sub>4</sub> H, 9.2 (H d. C <sub>3</sub> H) 3.9 (H S OH)
4g	C <sub>23</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>2</sub> S	436.5	52	188-9	63.2	63.1	3.89	3.8	6.41	6.3	7.33	7.2	8-2-9.8 (11H mtd aromatic & C <sub>4</sub> H, 9.2 (H d. C <sub>3</sub> H) 3.9 (H S OH)
4h	C <sub>24</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>3</sub> S	450.5	45	169-7	63.9	63.8	4.21	4.1	6.21	6.1	7.10	7.0	8-2-9.8 (11H mtd aromatic & C <sub>4</sub> H, 9.2 (H d. C <sub>3</sub> H) 3.9 (H S OH)

**Table 2** Analytical and spectral Data of Commands Thiazolidinones, **5a-h**

Compd	Molecular formula	Mol. Wt	Yield (%)	M.P. (°C)	% Analysis								PMR (8 PPM)
					%C		%H		%N		%S		
					Cald	Found	Cald	Found	Cald	Found	Cald	Found	
5a	C <sub>22</sub> H <sub>15</sub> N <sub>2</sub> OS <sub>2</sub>	387	65	160-1	68.1	8.1	3.87	3.8	7.23	7.2	16.5	16.4	4.3 (s, 1H C <sub>2</sub> H, C <sub>3</sub> H) 6.2-7-8 (12H mtd aromatic C <sub>4</sub> H), 1.25 (S, 2H, CH <sub>2</sub> )
5b	C <sub>23</sub> H <sub>17</sub> N <sub>2</sub> O <sub>2</sub> S <sub>2</sub>	417	70	165-6	66.1	66.0	4.07	4.0	6.71	6.6	15.3	15.2	8.2-7.8 (11H mtd aromatic C <sub>4</sub> H, 4.6 (1H d. C <sub>3</sub> H), 125 S, 1H, C <sub>2</sub> H, 3.4 (3H SOCH <sub>3</sub> ))
5c	C <sub>22</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub> S <sub>2</sub>	403	63	175-6	65.5	65.4	3.72	3.6	6.94	6.8	15.8	15.38	6.2-7.8 (11H mtd aromatic C <sub>4</sub> H, 4.6 (1H d. C <sub>3</sub> H) 3.4 (3H S OH)
5d	C <sub>22</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub> S <sub>2</sub>	403	71	158-9	65.5	68.4	3.72	3.6	6.94	6.8	15.8	15.7	6.2-7.8 (11H mtd aromatic C <sub>4</sub> H, 4.6 (1H d. C <sub>3</sub> H) 3.4 (3H S OH)
5e	C <sub>23</sub> H <sub>17</sub> N <sub>2</sub> OS <sub>2</sub>	415	60	183-4	66.5	65.4	4.09	4.0	6.74	6.6	15.4	15.3	8.2-7.8 (11H mtd aromatic C <sub>4</sub> H, 4.6 (1H d. C <sub>3</sub> H), 125 S, 1H, C <sub>2</sub> H, 3.4 (3H SOCH <sub>3</sub> ))
5f	C <sub>23</sub> H <sub>15</sub> N <sub>2</sub> O <sub>3</sub> S <sub>2</sub>	431	50	188-9	64.0	66.4	3.48	3.4	6.40	6.3	14.8	14.7	6.2-7.8 (11H mtd aromatic C <sub>4</sub> H, 4.6 (1H d. C <sub>3</sub> H) 3.4 (3H S OH, 2, S, 2H of CH <sub>2</sub> )
5g	C <sub>23</sub> H <sub>17</sub> N <sub>2</sub> O <sub>3</sub> S <sub>2</sub>	433	50	170-1	63.7	63.01	3.92	3.8	6.46	6.3	14.7	14.6	8.2-7.8 (11H mtd aromatic C <sub>4</sub> H, 4.6 (1H d. C <sub>3</sub> H), 125 S, 1H, C <sub>2</sub> H, 3.4 (3H SOCH <sub>3</sub> ))
5h	C <sub>24</sub> H <sub>19</sub> N <sub>2</sub> O <sub>3</sub> S <sub>2</sub>	447	60	180-1	64.4	64.3	4.25	4.2	6.26	6.2	14.3	14.2	8.2-7.8 (11H mtd aromatic C <sub>4</sub> H, 4.6 (1H d. C <sub>3</sub> H), 125 S, 1H, C <sub>2</sub> H, 3.4 (3H SOCH <sub>3</sub> ))

The antibacterial activity of both the series (**4a-h**) and (**5a-h**), respectively, have been carried out against some strain of bacteria. The results (**Table 3 and 4**) show that the prepared compounds are toxic against the bacteria. Compound 4c, 4d, 4b, 5b, 5d and 5f were found more active against the above microbes. The comparison of the antibacterial activity of these compounds with penicillin and sulphanilamide shows that these compounds have almost similar activity.

**Table 3.** Antibacterial Activity of compounds **4a-h**

Compound	% age of zone of inhibition			
	Gram +ve		Gram -ve	
	<i>Bacillus subtilis</i>	<i>Staphyloccous aureus</i>	<i>E.Coli</i>	<i>Salmonella typhi</i>
4a	58	67	44	68
4b	48	76	56	73
4c	75	85	80	65
4d	85	70	70	80
4e	46	67	48	75
4f	70	63	65	50
4g	73	56	70	62
4h	83	73	80	75
Penicillin	85	65	75	75

**Table 4.** Antibacterial Activity of compounds **5a-h**

Compound	Gram +ve		Gram -ve	
	<i>Bacillus subtilis</i>	<i>Staphyloccous aureus</i>	<i>E.Coli</i>	<i>Salmonella typhi</i>
5a	60	72	60	60
5b	85	75	74	72
5c	80	60	60	80
5d	73	80	80	70
5e	70	80	85	83
5f	70	75	80	76
5g	60	65	75	85
5h	75	65	78	70
Sulphanilamide	85	75	70	85

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