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# Synthesis and Antifungal Activity of Azetidinone and Thiazolidinones Derivatives of 2-Amino-6-(2-naphthalenyl)thiazolo[3,2-d]thiadiazole

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**Abstract:** 2-amino-6-(2-naphthalenyl)thiazolo[3,2-d]thiadiazole [1] was prepared by treatment of KCNS and Br<sub>2</sub> on 2-Amino-4-(2-naphthalenyl) thiazole. 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) afford 2-azetidinones and 4-thiazolidinones respectively. The prepared compounds have been screened on some stains of fungi.

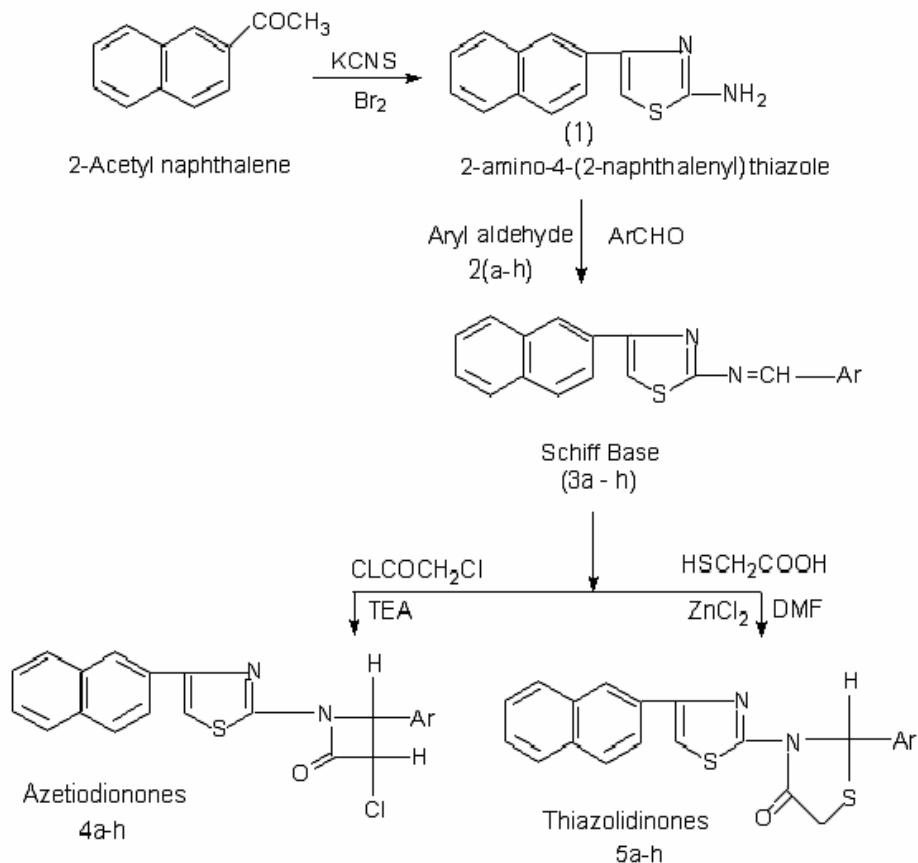
**Keywords:** 2-Azetidinones, 4-thiazolidinones, cyclo-condensation reaction, facile condensation, spectral studies antibacterial action.

## Introduction

Thiazoles are one of the most intensively investigated classes of aromatic five membered heterocycles. Thiazole derivatives find 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 play a 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 azetidionones and thiazolidinones has been reported recently by us<sup>14</sup>. In continuous at this work<sup>14</sup> the present paper comprises the heterocyclization of 2-amino-4-(2-naphthalenyl) thiazole into fused heterocyclic amine and its further transformation into 2-azetidionones and 4-thiazolidinones. The work is scanned 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>15</sup>. The aromatic benzaldehydes (2a-h) viz; a: benzaldehyde, b: 4-methyl benzaldehyde, c: 4-hydroxy benzaldehyde, d: 2-hydroxybenzaldehyde, e: 4-methoxy benzaldehyde, f: 4-bromobenzaldehyde, g: 3,4-ethylenedioxy benzaldehyde, h: 4-hydroxy-3-methoxy benzaldehyde and i: 3,4-diethoxy 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 Nicolet 760D spectrophotometer and <sup>1</sup>H NMR spectra in CDCl<sub>3</sub> on Perkin Elmer NMR spectrometer using TMS as an internal standard. Antifungal activity of all the compounds were studied against various fungi (Tables-3 & 4) at a concentration of 100ppm by agar cup method<sup>16</sup>. Methanol system was used as control in the method. Under similar conditions using penicillin and sulfanilamide as a standard. The comparison carried at control experiment. The area of inhibition of zone is measured as percentage.

*Preparation of 2-amino-6-(2-naphthalenyl)thiazolo[3,2-d]thiadiazole*

In a three necked flask, a solution of 2-amino-4-(2-naphthalenyl) thiazole (0.02 mole) in 1,4-dioxane was placed. Then the flask was kept in an ice-bath. The mechanical stirrer was fitted. The KCNS (0.08 mole) was added gradually into the solution with constant stirring. Finally Br<sub>2</sub> (16 ml) in acetic acid (100 ml) was added slowly with constant stirring. The whole assembly with stirrer was kept in an ice-bath for 6 hrs. The resultant mixture was kept aside until reached room temperature. The product was poured into ice-water, filtered and washed with 1,4-dioxane. The product thus was recrystallized by 1,4-dioxane-ethanol [50:50(v/v)] mixture and checked on TLC. Finally the product was purified by column chromatography over silica gel using ethyl acetate: benzene (30:70) as an eluent. Yield was 48%. M.p.156-7<sup>0</sup>C uncorrected.

Analysis: C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>S<sub>2</sub> (285)

	C%	H%	N%	S%
Cal.	58.94	3.86	14.73	22.45
Fin.	58.8	3.75	14.6	22.3

IR : 3400-3200cm<sup>-1</sup> NH<sub>2</sub>, 3030, 1600, 1100 cm<sup>-1</sup> aromatic, 1550 cm<sup>-1</sup> C=N

NMR : δ = 7.2-8.9 ppm multiplate aromatic 8H, δ = 4.1ppm, S NH<sub>2</sub>

*Preparation of Schiff base (3a-h)***General procedure**

A mixture of equimolar amount (0.01) of 2-amino-6-naphthalenylthiazolo [3,2-d] thiadiazole (1), benzaldehyde derivative (2a-h) in ethanol : 1,4-dioxane (50 : 50) (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)***General Procedure**

A mixture of Schiff base (3a-h) (0.002 mol) and triethyl amine [TEA] (0.004 mol) 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 45-55% yield.

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

Compound	Molecular Formula	Mol. Wt	Yield (%)	M.P.* (°C)	% Analysis								PMR ( $\delta$ PPM)**
					C		H		N		S		
					Cald	Found	Cald	Found	Cald	Found	Cald	Found	
4a	C <sub>23</sub> H <sub>16</sub> ClN <sub>3</sub> OS <sub>2</sub>	449.5	55	193.4	61.4	61.3	3.56	3.5	9.34	9.2	14.23	14.1	9-2 1H d C <sub>3</sub> H 9-2-7-8 (13 H mtd aromatic, C <sub>4</sub> H and S of thiazole-CH 9.2 (H d C <sub>3</sub> H)
4b	C <sub>24</sub> H <sub>18</sub> ClN <sub>3</sub> OS <sub>2</sub>	463.5	55	181-2	62.13	62.0	3.88	3.8	9.06	9.00	13.8	13.7	9.2 (H d. C <sub>3</sub> H) 1.9 (3H <sub>2</sub> CH)
4c	C <sub>23</sub> H <sub>16</sub> ClN <sub>3</sub> O <sub>2</sub> S <sub>2</sub>	465.5	50	175-6	59.29	59.2	3.43	3.4	9.02	8.9	13.74	13.6	9.2 (H d. C <sub>3</sub> H) 3.9 (H S OH)
4d	C <sub>23</sub> H <sub>16</sub> ClN <sub>3</sub> O <sub>2</sub> S <sub>2</sub>	465.5	55	203-4	59.29	59.2	3.43	3.4	9.02	8.9	13.74	13.6	9.2 (H d. C <sub>3</sub> H) 3.9 (H S OH)
4e	C <sub>24</sub> H <sub>18</sub> ClN <sub>3</sub> O <sub>2</sub> S <sub>2</sub>	479.5	50	163-4	60.06	59.9	3.75	3.6	8.76	8.6	13.34	13.2	9.2 (H d. C <sub>3</sub> H) 2.1 (3 H <sub>3</sub> OCH <sub>3</sub> )
4f	C <sub>24</sub> H <sub>16</sub> ClN <sub>3</sub> O <sub>3</sub> S <sub>2</sub>	493.5	52	171-2	58.35	58.2	3.24	3.7	8.51	8.4	12.96	12.85	9.2 (H d. C <sub>3</sub> H) 3.9 (2H of CH <sub>3</sub> )
4g	C <sub>24</sub> H <sub>18</sub> ClN <sub>3</sub> O <sub>3</sub> S <sub>2</sub>	495.5	50	200-1	58.12	58	3.63	3.5	8.47	8.3	12.91	12.8	9.2 (H d. C <sub>3</sub> H) 2.1 (3 H <sub>3</sub> OCH)
4h	C <sub>25</sub> H <sub>20</sub> ClN <sub>3</sub> O <sub>3</sub> S <sub>2</sub>	509.5	45	180-1	58.8	58.7	3.92	3.8	8.24	8.1	12.56	12.4	9.2 (H d. C <sub>3</sub> H) 2.5 (q, 4H of CH <sub>2</sub> ) 2.0 (t, 6H of CH <sub>3</sub> )

\* Uncorrected \*\* All the NMR spectra containing multiplate between 7.8 to 8.2 which assigned aromatic ring + C<sub>4</sub>H and thiazole CH.

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

Compound	Molecular Formula	Mol. Wt	Yield (%)	M.P. (°C)*	% Analysis								PMR ( $\delta$ PPM)**
					C		H		N		S		
					Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	
5a	C <sub>23</sub> H <sub>17</sub> N <sub>3</sub> OS <sub>3</sub>	447	60	175-6	61.17	61.05	3.8	3.8	9.31	9.3	21.47	21.3	4.3 (s, 1H C <sub>2</sub> H, C <sub>3</sub> H) 1.25 (s, 2H, CH <sub>2</sub> )
5b	C <sub>24</sub> H <sub>19</sub> N <sub>3</sub> OS <sub>3</sub>	475	50	180-1	58.1	58.0	4.0	3.9	8.84	8.7	20.21	20.1	4.6 (1H d. C <sub>3</sub> H), 125 s, 1H, C <sub>2</sub> H 2.4 (3H s CH <sub>3</sub> )
5c	C <sub>23</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> S <sub>3</sub>	463	55	190-1	59.61	59.5	3.67	3.6	9.07	9.00	20.73	20.6	4.6 (1H d. C <sub>3</sub> H) 3.4 (3H s OH)
5d	C <sub>23</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> S <sub>3</sub>	463	70	173-4	59.61	59.5	3.67	3.6	9.07	9.00	20.73	20.6	4.6 (1H d. C <sub>3</sub> H) 3.4 (3H s OH)
5e	C <sub>24</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> S <sub>3</sub>	477	65	198-9	60.37	60.2	3.98	3.9	8.8	8.7	20.12	20.0	4.6 (1H d. C <sub>3</sub> H), 125 s, 1H, C <sub>2</sub> H 3.4 (3H s OCH <sub>3</sub> )
5f	C <sub>24</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub> S <sub>3</sub>	491	45	208-9	58.65	58.5	3.46	3.4	8.55	8.5	19.55	19.4	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>24</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub> S <sub>3</sub>	493	50	185-6	58.41	58.3	3.85	3.8	8.51	8.4	19.47	19.3	4.6 (1H d. C <sub>3</sub> H), 125 s, 1H, C <sub>2</sub> H 3.4 (3H s OCH <sub>3</sub> )
5h	C <sub>25</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub> S <sub>3</sub>	507	45	192-3	59.17	59.1	4.14	4.1	8.28	8.2	18.93	18.8	4.6 (1H d. C <sub>3</sub> H), 125 s, 1H, C <sub>2</sub> H 2.5 (4H q CH <sub>2</sub> ), 2.0 (6H t CH <sub>3</sub> )

\* Uncorrected

\*\* All the NMR spectra containing multiplet between 7.8 to 8.2 which assigned aromatic ring + C<sub>4</sub>H and thiazole CH.

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

Compound	Zone of inhibition at 1000 ppm (%)			
	<i>Penicillium Expansum</i>	<i>Botrydepladia Thiobromine</i>	<i>Nigrospora Sp.</i>	<i>Trichothesium Sp.</i>
4a	65	70	65	53
4b	77	85	75	74
4c	85	80	80	73
4d	81	81	79	83
4e	79	82	79	75
4f	78	80	72	71
4g	75	72	66	59
4h	74	70	61	66
Penicillin	85	65	75	75

**Table 4** Antifungal Activity of compounds 5a-h

Compound	Zone of inhibition at 1000 ppm (%)			
	<i>Penicillium Expansum</i>	<i>Botrydepladia Thiobromine</i>	<i>Nigrospora Sp.</i>	<i>Trichothesium Sp.</i>
5a	64	71	65	75
5b	83	87	86	88
5c	78	85	75	80
5d	77	80	89	87
5e	74	80	65	74
5f	71	79	60	74
5g	72	72	62	72
5h	70	73	80	71
Sulphanilamide	85	75	70	85

*Preparation of 2-Thiazolidinones (5a-h)***General Procedure**

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-ethanol mixture 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-thiazolidinoines (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**

2-amino-6-naphthalenylthiazolo [3,2-d] thiadiazole was prepared according to method reported for benzthiazole from aniline<sup>17</sup>. The elemental contents and IR-NMR spectral

features shown in experimental section consistent with the predicted structure. The 2-amino-6-naphthalenylthiazolo [3,2-d] thiazazole (2) was dissolved in dioxane:ethanol (50:50) and was reacted with aromatic 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  $1630\text{ cm}^{-1}$  for the azomethine group<sup>18-20</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  $1690\text{ cm}^{-1}$  for cyclic  $>\text{C}=\text{O}$  group<sup>17,18</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 Tables 1 and 2. The values are consistent with their predicted structure (Scheme 1).

The antifungal activity of both the series (4a-h) and (5a-h), respectively, have been carried out against some strain of fungi. The results 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 fungi. The comparison of the antibacterial activity of these compounds with penicillin and sulphanilamide shows that these compounds have almost similar activity.

## References

1. Coppola K, PTC *Int.Appl.* wo, 2001, 01 10 8523.
2. Bian W, Jian Y N, Yang P, Xizng S H, Xuebzo S P and ZKexyeban, 2001,**23** ,231, C.A. 134, 237419.
3. Patil S and Bhagaval G, *J. Int. Char. Soc.* 1994, **71**, 205.
4. Manian A K, Khadse G G and Sengupta S R, *Indian drugs*, 1993, **30**, 324.
5. Joshi M M, Bhagavat V S and Parvati J A, *J. Ind. Chem. Soc.* 1995, **70**, 647.
6. Stepanor D E, Evanov E I and Evanov R Y, *Russ. J.Char.*, 2000, **70** (5), 784.
7. Sharma R C and Kumar D, *J. Ind. Chem. Soc.*, 2000, **77**,492.
8. Joshi H D, Sawale A R, Ingle R D, and Mane R A, *Ind. J. Chem.*, 2000, **39**, 967.
9. Ingle V S, Sawale A R, Ingle R D, and Mane R A, *Ind. J. Chem.*, 2001, **40**, 124.
10. Kagathara P, Upadhyay T, Doshi R and Parekh H H, *Indian J. Heterocycl. Chem.*, 2000, **10**,9.
11. Matsui N, *Jpn. Kokai Tokkyo JP*, ,2000, **07**, 652; *Chem. Abstr.*, 2000, **132**, 641094.
12. Desai K R, *Asian J. Chem. Abstr*, 2000, **132**,279145.
13. Thaker K M, *Ind. J. Chem.*, 2003, **42B**, 1544.
14. Patel K H and Mehta A G, *E- J.Chem.*, 2006, **11**, 109.
15. Tripathy H and Mahaputra G N, *J. Ind. Chem. Soc.*, 1975, **52**,168.
16. (a) Barry A L, *The antimicrobial susceptibility test: Principle and practices*, 4<sup>th</sup> ed. Philandelfphia , 1976 (b) *Bio. Abstr.* 1977, **64**, 25, 183.
17. Rangekar D W and Chaudhari M B, *Dyes and Pigment*, 1938, **10**,173.
18. Kemp W, *Organic Spectroscopy*, 2<sup>nd</sup> Edition. Basingtake, Macmillan, USA.
19. Furniss B, Hannaford A J, Smith P W G and Fatehell A R, *Vage's Psnelial organic chemistry*, Pearson Edition (Singapore) Pte.Ltd. Indian branch N.D 2004.
20. Panizzi J C, Davidovis G, Guglielmelti R, Mille G, Metzger J and Chateau J, *Can. J. Chem.*, 1971, **49**,956.