

**Synthesis and Pharmacological Activities of S&N Mannich Bases of 5-Aryl-1,3,4-Thiadiazolin-2-Thiones**

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**ABSTRACT**

**T**welve different S&N-Mannich bases has prepared with 5-aryl-1,3,4-thiadiazolidin-2-thiones in different conditions. N-Mannich Bases were prepared by treating 5-aryl-1,3,4-thiadiazolidin-2-thiones with formaldehyde in ethanol. 5-aryl-1,3,4-thiadiazolidin-2-thiones treated with formaldehyde in potassium carbonate to get S-Mannich Bases. The prepared compounds obtained in each case were purified and characterized by IR and <sup>1</sup>HNMR and by their MASS spectral analysis. All the two types of new derivatives of 5-aryl-1,3,4-thiadiazolidin-2-thiones were assayed for their antibacterial, antifungal and anticholinergic activities by standard methods.

**Keywords:** 5-aryl-1,3,4-thiadiazolidin-2-thiones Derivatives, Anti-Bacterial, Anti-Fungal and Anti-Cholinergic Activities.

**INTRODUCTION**

1,3,4-thiadiazole system and its derivatives are known to possess various biological activities such as Anti-Bacterial activity [1-4], Anti-Fungal activity [5-9], Anti-Inflammatory [10, 11] and Anti-Hypertensive activities [12] based on the previous work we synthesized some S&N Mannich bases of 5-aryl-1,3,4-thiadiazolidin-2-thiones and characterized and screened for their possible Anti-Microbial, Anti-Cholinergic activities by standard methods.

**EXPERIMENTAL**

**a). Synthesis of N-Mannich bases of 5-aryl-1,3,4-thiadiazolidin-2-thione ( In neutral medium):**

An appropriate 5-aryl-1,3,4-thiadiazolidin-2-thione (0.01 mol) in ethanol (25ml) formaldehyde (40%,1.5ml), an appropriate secondary amine (0.01 mol) was added and stirred over with a magnetic stirrer for a 1 hr. The reaction mixture was heated under reflux on a water bath for about 4 hrs. The solvent was removed cooled and left overnight in a refrigerator. The product thus separated was filtered, washed with cold water, dried and purified. Adopting the above described general procedure the following compounds were prepared.

**1)5-Phenyl-3-(N,N-dicyclohexylaminomethyl)-1,3,4-thiadiazolin-2-thione (VII; Ar = C<sub>6</sub>H<sub>5</sub>; - NR<sup>1</sup>R<sup>2</sup> = dicyclohexyl amino):**

Purification was effected by recrystallization from ethanol to get a colourless crystalline solid (yield:90%), m.p: 140 [Found: C, 65.10; H, 7.40; N, 10.80; C<sub>21</sub>H<sub>29</sub>N<sub>3</sub>S<sub>2</sub> requires C, 65.11; H, 7.41; N, 10.85%]

**2)5-Phenyl-3-(4-morpholinomethyl)-1,3,4-thiadiazolin-2-thione VII; Ar=C<sub>6</sub>H<sub>5</sub>; - NR<sup>1</sup>R<sup>2</sup>=morphoino):**

Recrystallized from methanol to obtain a colourless crystalline solid (yield: 85%) m.p: 113 [found C, 53.20; H, 5.07; N, 14.30; C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>S<sub>2</sub>O requires C, 53.20; H, 5.07; N, 14.30%]

**3) 5-Phenyl-3-(1-piperidinomethyl)-1,3,4-thiadiazolin-2-thione VII;Ar=C<sub>6</sub>H<sub>5</sub>; -NR<sup>1</sup>R<sup>2</sup>=piperidiino):**

Recrystallized from methanol to obtain a colourless crystalline solid (yield: 85%) m.p: 154 [found C, 62.50; H, 5.80; N, 14.40; C<sub>14</sub>H<sub>17</sub>N<sub>3</sub>S<sub>2</sub> requires C, 62.54; H, 5.84; N, 14.43%].

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**4)5-Nitrophenyl-3-(N,N-dicyclohexylaminomethyl)-1,3,4-thiadiazolin-2-thione VII; Ar=C<sub>6</sub>H<sub>5</sub>; -NR<sup>1</sup>R<sup>2</sup>=dicyclohexyl amino):**

It was purified by recrystallization from methanol to get a light yellow solid (yield: 90%) m.p: 180 [found C, 58.10; H, 6.40; N, 12.90; C<sub>21</sub>H<sub>28</sub>N<sub>4</sub>S<sub>2</sub>O<sub>2</sub> requires C, 58.19; H, 6.46; N, 12.93%].

**5) 5-nitrophenyl-3-(4-morpholinomethyl)-1,3,4-thiadiazolin-2-thione VII; Ar = C<sub>6</sub>H<sub>5</sub>; - NR<sup>1</sup>R<sup>2</sup> = morphoino):**

Purification was effected by recrystallization from ethanol to obtain a yellow solid (yield: 90%) m.p: 99 [found C, 45.05; H, 4.09; N, 16.45; C<sub>14</sub>H<sub>16</sub>N<sub>4</sub>S<sub>2</sub>O<sub>2</sub> requires C, 46.01; H, 4.12; N, 16.51%].

**6) 5-Phenyl-3-(1-piperidinomethyl)-1,3,4-thiadiazolin-2-thione VII;Ar=C<sub>6</sub>H<sub>5</sub>; - NR<sup>1</sup>R<sup>2</sup>=piperidiino):**

m.p: 131 [found C, 49.80; H, 4.70; N, 16.55; C<sub>14</sub>H<sub>16</sub>N<sub>4</sub>S<sub>2</sub>O<sub>2</sub> requires C, 49.85; H, 4.74; N, 16.61%]

**b). Synthesis of S-Mannich bases of 5-aryl-1,3,4-thiadiazolidin-2-thione ( In basic medium ).**

To an alcoholic solution of 5-aryl-1,3,4-thiadiazolidin-2-thione (0.01), potassium carbonate (0.01mol) was added and stirred for 30 mints then added formaldehyde (40%, 1.5ml) and secondary amine (0.01). Stirring has continued for 1 hr. Then the reaction mixture has refluxed for 2hrs.It was concentrated, filtered dried and purified.

Adopting the above described general procedure the following compounds were prepared.

**7)5-Phenyl-3-(N,N-dicyclohexylaminomethyl)-1,3,4-thiadiazolin-2-thione VII; Ar = C<sub>6</sub>H<sub>5</sub>; - NR<sup>1</sup>R<sup>2</sup> = dicyclohexylamino):**

Purification was effected by recrystallization from ethanol to get a colourless crystalline solid (yield: 90%), m.p: 140 [Found: C, 65.10; H, 7.40; N, 10.80; C<sub>21</sub>H<sub>29</sub>N<sub>3</sub>S<sub>2</sub> requires C, 65.11; H, 7.41; N, 10.85%]

**8) 5-Phenyl-3-(4-morpholinomethyl)-1,3,4-thiadiazolin-2-thione VII;Ar=C<sub>6</sub>H<sub>5</sub>; - NR<sup>1</sup>R<sup>2</sup>=morphoino):**

Recrystallized from methanol to obtain a colourless crystalline solid (yield: 85%) m.p: 113 [found C, 53.20; H, 5.07; N, 14.30; C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>S<sub>2</sub>O requires C, 53.20; H, 5.07; N, 14.30%]

**9) 5-Phenyl-3-(1-piperidinomethyl)-1,3,4-thiadiazolin-2-thione VII;Ar=C<sub>6</sub>H<sub>5</sub>; - NR<sup>1</sup>R<sup>2</sup>=piperidiino):**

Recrystallized from methanol to obtain a colourless crystalline solid (yield: 85%) m.p: 154 [found C, 62.50; H, 5.80; N, 14.40; C<sub>14</sub>H<sub>17</sub>N<sub>3</sub>S<sub>2</sub> requires C, 62.54; H, 5.84; N, 14.43%]

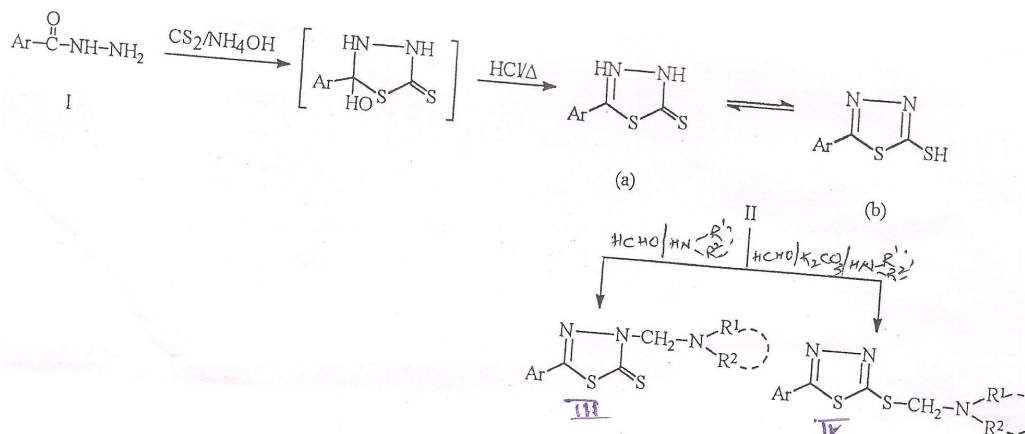
**10)5-Nitrophenyl-3-(N,N-dicyclohexylaminomethyl)-1,3,4-thiadiazolin-2-thione VII; Ar = C<sub>6</sub>H<sub>5</sub>; - NR<sup>1</sup>R<sup>2</sup> = dicyclohexyl amino):**

It was purified by recrystallization from methanol to get a light yellow solid (yield: 90%) m.p: 180 [found C, 58.10; H, 6.40; N, 12.90; C<sub>21</sub>H<sub>28</sub>N<sub>4</sub>S<sub>2</sub>O<sub>2</sub> requires C, 58.19; H, 6.46; N, 12.93%].

**11) 5-nitrophenyl-3-(4-morpholinomethyl)-1,3,4-thiadiazolin-2-thione VII; Ar = C<sub>6</sub>H<sub>5</sub>; - NR<sup>1</sup>R<sup>2</sup> = morpholino):**

Purification was effected by recrystallization from ethanol to obtain a yellow solid (yield: 90%) m.p: 99 [found C, 45.05; H, 4.09; N, 16.45; C<sub>14</sub>H<sub>16</sub>N<sub>4</sub>S<sub>2</sub>O<sub>2</sub> requires C, 46.01; H, 4.12; N, 16.51%].

**12) 5-nitrophenyl-3-(1-piperidinomethyl)-1,3,4-thiadiazolin-2-thione VII; Ar = C<sub>6</sub>H<sub>5</sub>; - NR<sup>1</sup>R<sup>2</sup> = piperidino):**  
m.p: 131 [found C, 49.80; H, 4.70; N, 16.55; C<sub>14</sub>H<sub>16</sub>N<sub>4</sub>S<sub>2</sub>O<sub>2</sub> requires C, 49.85; H, 4.74; N, 16.61%]



SCHEME-1

**PHARMACOLOGICAL ACTIVITY**

**Biological /pharmacological activity:**

**Antibacterial activity:** [13]

The synthesized compounds were screened for their antibacterial activity against five different strains of bacteria: *B.subtilis*, *B.mycooides*, *E.coli*, *P.auroginosa* and *P.vulgaris* (two G+ve And three G-ve) by cup plate method in nutrient agar medium with an incubation of 24 hr at 37°. Benzyl penicillin and streptomycin as standard.

**Antifungal activity:** [13]

The synthesized compounds were screened for their antifungal activity by the cup-plate method against two fungal strains i.e. *F.oxysporum* and *c.lunata*. Clotrimazole employed as the standard.

**Anti cholinergic activity:**

The test compounds were screened for their anticholinergic activity.

Anticholinergic activity of the compounds was screened by using the rat intestine Atropine was used as an agonist for inducing the contractions. The test compounds and the agonist atropine were used in logarithmic doses.

**RESULTS AND DISCUSSION**

**Antibacterial activity:**

The preparation of 5-aryl -1,3,4-thiadiazolidin-2-thione derivatives is in depicted in **scheme-1**. All the compounds were evaluated for antibacterial activity. The N&S mannich bases of found to exhibit antibacterial activity against all the bacteria employed. All the compounds could be found to be less active against the microorganisms *B.mycooides* and more potent with 4-nitrophenyl substituent and morpholino substituent (recorded has potent against *P.auroginosa*). The results of anti-bacterial activity of new N-Mannich Bases (III) S-Mannich Bases (IV) 5-aryl-1,3,4-thiadiazolidin-2-thiones are presented in **Table. 1**, and Anti fungal Activity of new N-Mannich Bases (III) S-Mannich Bases (IV) 5-aryl-1,3,4-thiadiazolidin-2-thiones are presented in **Table. 2**.

**Table No. 1: Data on Antibacterial activity of new N-Mannich Bases (III) S-Mannich Bases (IV) 5-aryl-1,3,4-thiadiazolidin-2-thiones**

S.No.	Compd.No.	Ar	NR <sup>1</sup> R <sup>2</sup> /R	B. subtilis	B. mycooides	E. Coli	P. auroginosa	P. vulgaris
1	IIIa	C <sub>6</sub> H <sub>5</sub>	Dicyclohexylamino	8	7	12	35	-
2	IIIb	C <sub>6</sub> H <sub>5</sub>	Morpholino	8	4	17	34	6
3	IIIc	C <sub>6</sub> H <sub>5</sub>	Piperidino	14	8	13	27	-
4	IIId	4-NO <sub>2</sub> .C <sub>6</sub> H <sub>4</sub>	Dicyclohexylamino	11	11	11	35	13
5	IIIe	4- NO <sub>2</sub> .C <sub>6</sub> H <sub>4</sub>	Morpholino	6	6	13	33	13
6	IIIf	4- NO <sub>2</sub> .C <sub>6</sub> H <sub>4</sub>	Piperidino	9	8	6	33	-
7	IVa	C <sub>6</sub> H <sub>5</sub>	Dicyclohexylamino	12	6	31	32	6
8	IVb	C <sub>6</sub> H <sub>5</sub>	Morpholino	16	7	31	34	7
9	IVc	C <sub>6</sub> H <sub>5</sub>	Piperidino	18	8	22	34	8
10	IVd	4-NO <sub>2</sub> .C <sub>6</sub> H <sub>4</sub>	Dicyclohexylamino	4	4	11	31	11
11	IVe	4-NO <sub>2</sub> .C <sub>6</sub> H <sub>4</sub>	Morpholino	-	7	31	36	16
12	IVf	4-NO <sub>2</sub> .C <sub>6</sub> H <sub>4</sub>	Piperidino	6	6	13	26	11
Benzyl penicillin and Streptomycin				38	36	-	-	-
				-	-	54	52	57

**Table No. 2: Data on Anti fungal Activity of N-Mannich Bases ((III) S-Mannich Bases (IV) 5-aryl-1,3,4-thiadiazolidin-2-thiones**

S. No.	Compd. No	Ar	NR <sup>1</sup> R <sup>2</sup> /R	F.Oxysporam	C.lunata
1	IIIa	C <sub>6</sub> H <sub>5</sub>	Dicyclohexylamino	17	25
2	IIIb	C <sub>6</sub> H <sub>5</sub>	Morpholino	15	34
3	IIIc	C <sub>6</sub> H <sub>5</sub>	Piperidino	7	34
4	IIId	4-NO <sub>2</sub> .C <sub>6</sub> H <sub>4</sub>	Dicyclohexylamino	18	21
5	IIIe	4-NO <sub>2</sub> .C <sub>6</sub> H <sub>4</sub>	Morpholino	18	21
6	IIIf	4-NO <sub>2</sub> .C <sub>6</sub> H <sub>4</sub>	Piperidino	17	27
7	IVa	C <sub>6</sub> H <sub>5</sub>	Dicyclohexylamino	-	21
8	IVb	C <sub>6</sub> H <sub>5</sub>	Morpholino	14	31

9	<b>IVc</b>	C <sub>6</sub> H <sub>5</sub>	Piperidino	17	21
10	<b>IVd</b>	4-NO <sub>2</sub> .C <sub>6</sub> H <sub>4</sub>	Dicyclohexylamino	11	27
11	<b>IVe</b>	4-NO <sub>2</sub> .C <sub>6</sub> H <sub>4</sub>	Morpholino	15	31
12	<b>IVf</b>	4-NO <sub>2</sub> .C <sub>6</sub> H <sub>4</sub>	Piperidino	15	34

The Anti-cholinergic values of this series of compounds also indicate that they are not comparable in potency with atropine employed as the standard. But at the same time it is interesting to note that a majority of these compounds exhibit relatively better activity. In N- mannich base 3-(4-morpholinomethyl)-5-phenyl-1,3,4-thiadiazolin-2-thione (IIIb) is more potent and in one S-mannich bases of, relatively better anti-cholinergic activity of the presentation, least effective compound as one with IC<sub>50</sub> 177.64.

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#### REFERENCES:

1. Anil Sen Gupta, Agarwal ND Mustaq. j. indian Chem. Soc., **1977**; 54: 1961.
2. R. P. Kapoor, Hitesh Batra, Pawan K. Sharma. Indian. J. Het. Chem., **1997**; 7: 1.

3. Rajiv Gupta, Sangeeta Sudan, Vandana Mengi and Kachroo. Indian J. Chem., **1996**; 35B: 718.
4. Arun kumar paddy. V, C. Nug and Panda. Indian J. Chem., **1999**; 38B: 998.
5. S. Giri and H. Singh, J. Indian. Chem. Soc., **1972**; 49: 175.
6. Bharati Misra, R. Ali and Nizamuddin. Indian J. Chem., **1988**; 27B: 576.
7. C. S. Andotra, T. C. Langer and Amrita Kotha. J. Indian Chem. soc., **1997**; 74: 125.
8. V. S. Pathak and V. Alagarsamy, Indian Drugs, **2000**; 37: 1.
9. Diane. H. Boschelli, David T. Conner, Dirik A. Borneme. Ir. J. Med. Chem., **1993**; 36: 1803.
10. Mohammad Amir and Shalini Shahani. Indian J. Chem., **1998**; 37B: 107.
11. M. I. Hussain and Mohammad Ragib Jamali. Indian j. Chem., **1988**; 27B: 43.
12. British Pharmacopoeia (Pharmaceutical press), London, **1953**; 796.
13. J. J. Reuse. Brit. J. Pharmacol., **1948**; 3: 174.

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