

# Synthesis and Evaluation of 1-Aryl-4-N-aryl-amino-2-phenyl-4-thiomethyl-1,3-diazabuta-1,3-dienes: A Novel Class of Antibacterial Agents<sup>1</sup>

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Several N-aryl-amino-1,3-diazabuta-1,3-dienes were prepared by the reaction of N-arylbenzimidoyl isothiocyanates with primary aromatic amines followed by S-methylation of the resultant thioureas. All these compounds were characterised by analytical and spectral data. Antibacterial activity was determined using agar diffusion technique against *Escherichia coli* MTCC 42, *Pseudomonas aeruginosa* MTCC 1034, *Bacillus subtilis* MTCC 121, *Bacillus cerus* MTCC 1272 and *Staphylococcus aureus* MTCC 1430. Some of the compounds showed significant antibacterial activity.

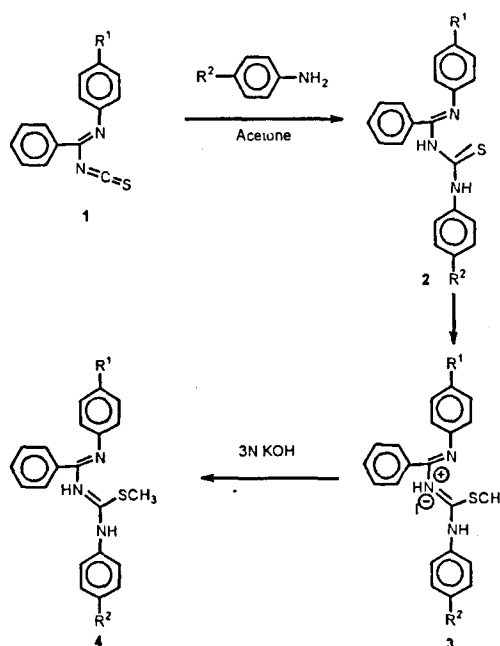
Amidine derivatives possess a broad spectrum of pharmacological action which are reflected by their use as antivirals<sup>2</sup>, antibacterial<sup>3-6</sup>, antiprotozoal<sup>7</sup>, anthelmintic<sup>8</sup>, antihypertensive<sup>9</sup>, antipyretic<sup>10</sup> and antiinflammatory<sup>11</sup>. In the light of these interesting biological activities, it was decided to synthesize some new amidine derived 1,3-diazabuta-1,3-dienes and assess antibacterial potential. The compounds were conveniently prepared by the reactions of N-aryl benzimidoyl isothiocyanates 1 with primary aromatic amines. Treatment of thioureas 2 with methyl iodide in dry acetone afforded the hydroiodides 3, which were converted into desired free compounds 4 in good yields by treatment with aqueous potassium hydroxide (Scheme 1). These were isolated as crystalline solids. The identities of products 4 were established by analytical and spectral data. All the compounds synthesized were screened for their antibacterial activity.

All melting points were determined in open capillaries and are uncorrected. IR absorption spectra ( $\nu_{\max}$  in  $\text{cm}^{-1}$ ) were recorded on a Fourier Transform Infrared 8101, Shimadzu spectrophotometer using KBr pellets. Mass spectra were obtained on a Shimadzu GCMS-QP-2000 mass spectrophotometer. Nuclear Magnetic Resonance spectra were recorded on AC 300F, 300 MHz and BZH 200/52, 200

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MHz Bruker spectrometers, respectively. Thin layer chromatography was performed using silica gel (G) and spots visualized by exposure to iodine vapours.



4 (a) R<sup>1</sup> = H; R<sup>2</sup> = H, 4(b), R<sup>1</sup> = H, R<sup>2</sup> = Cl, 4(c) R<sup>1</sup> = H; R<sup>2</sup> = CH<sub>3</sub>, 4(d) R<sup>1</sup> = H, R<sup>2</sup> = OCH<sub>3</sub>, 4(e) R<sup>1</sup> = CH<sub>3</sub>; R<sup>2</sup> = Cl, 4(f) R<sup>1</sup> = CH<sub>3</sub>, R<sup>2</sup> = OCH<sub>3</sub>, 4(g), R<sup>1</sup> = CH<sub>3</sub>; R<sup>2</sup> = CH<sub>3</sub>

Scheme 1:

N-arylbenzamidines<sup>12</sup>, N-arylimidoyl chlorides<sup>13</sup> and N-aryl-benzimidoyl isothiocyanates<sup>14</sup> were prepared by following the reported methods.

Synthesis of 1-aryl-4-(N-aryl amino)-2-phenyl-4-thiomethyl-1,3-diazabuta-1,3-dienes (4a-4g) was achieved by stirring a stirred solution of N-arylbenzimidoyl isothiocyanate 1 (2 mmol) in dry acetone (250 ml) was adding dropwise a solution of primary amine (1mmol) in dry acetone (30 ml) and stirring continued for 1 h. To this solution, methyl iodide (1.2 mmol) was added dropwise and stirred for a further period of 3-4 h. The separated hydroiodide salt of 3 was filtered, basified with 3N aqueous KOH (50 ml) and extracted with chloroform (3x100 ml). The combined extract was washed with water (3x50 ml) and dried over anhydrous sodium sulphate. The removal of chloroform under reduced pressure afforded the products 4 which were recrystallised from a mixture (1:1) of ethylacetate and hexane.

1,2-Diphenyl-4-[N-phenylamino]-4-thiomethyl-1,3-diazabuta-1,3-diene(4a): 90%, m.p. 142-144°.  $\nu_{\max}$ : 1600  $\text{cm}^{-1}$  (C=N).  $\delta_{\text{H}}$ : 2.51 (s, 3H -SCH<sub>3</sub>); 7.08 - 7.80 (m, 15H, arom.) and 8.90-9.68 (bs, 1H, -NH). M<sup>+</sup>: 345. 1,2-Diphenyl-4-[N-(p-chlorophenylamino)]-4-thiomethyl-1,3-diazabuta-1,3-diene (4b): 92%, m.p. 140-142°.  $\nu_{\max}$ : 1592  $\text{cm}^{-1}$  (C=N).  $\delta_{\text{H}}$ : 2.53 (s, 3H, -SCH<sub>3</sub>); 6.82-7.48 (m, 12H, arom.); 7.54 - 7.70 (m, 2H, arom.); and 9.29 (bs, 1H, -NH). M<sup>+</sup>: 379. 1,2-Diphenyl-4-[N-(p-methyl phenyl amino)]-4-thiomethyl-1,3-diazabuta-1,3-diene (4c): 90%, m.p. 135-137°.  $\nu_{\max}$ : 1585  $\text{cm}^{-1}$  (C=N).  $\delta_{\text{H}}$ : 2.31 (s, 3H, -CH<sub>3</sub>); 2.51 (s, 3H, -SCH<sub>3</sub>); 6.80-7.43 (m, 12H, arom.); 7.54-7.70 (m, 2H, arom.) and 9.37 (bs, 1H, -NH).

M<sup>+</sup>: 359. 1,2-Diphenyl-4-[N-(p-methoxy phenyl amino)]-4-thiomethyl-1,3-diazabuta-1,3-diene (4d): 96%, m.p. 104-106°.  $\nu_{\max}$ : 1600  $\text{cm}^{-1}$  (C=N).  $\delta_{\text{H}}$ : 2.51 (s, 3H, -SCH<sub>3</sub>); 3.80 (s, 3H, -OCH<sub>3</sub>); 6.80-7.46 (m, 12H, arom.); 7.51-7.74 (m, 2H, arom.) and 9.24 (bs, 1H, -NH). M<sup>+</sup>: 375. 4-[p-chloroanilino]-2-Phenyl-1-p-tolyl-4-thiomethyl-1,3-diazabuta-1,3-diene (4e): 91%, m.p., 127-129°.  $\nu_{\max}$ : 1599  $\text{cm}^{-1}$  (C=N).  $\delta_{\text{H}}$ : 2.30 (s, 3H, -CH<sub>3</sub>); 2.51 (s, 3H, -SCH<sub>3</sub>); 6.80-7.51 (m, 13H, arom.); and 9.39 (bs, 1H, -NH). M<sup>+</sup>: 375. 4-[p-methoxy anilino]-2-phenyl-1-p-tolyl-4-thiomethyl-1,3-diazabuta-1,3-diene (4f): 90%, m.p. 133-135°.  $\nu_{\max}$ : 1590  $\text{cm}^{-1}$  (C=N).  $\delta_{\text{H}}$ : 2.27 (s, 3H, -CH<sub>3</sub>); 2.53 (s, 3H, SCH<sub>3</sub>); 3.60 (s, 3H, -OCH<sub>3</sub>); 7.26 (m, 15H, arom.) and 9.39 (bs, 1H, -NH). M<sup>+</sup>: 389. 4-[p-methyl anilino]-2-Phenyl-1-p-tolyl-4-thiomethyl-1,3-diazabuta-1,3-diene (4g): 91%, m.p. 116-118°.  $\nu_{\max}$ : 1590  $\text{cm}^{-1}$  (C = N).  $\delta_{\text{H}}$ : 2.31 (s, 3H, -CH<sub>3</sub>); 2.40 (s, 3H, -CH<sub>3</sub>); 2.53 (s, 3H, -SCH<sub>3</sub>); 6.80-7.81 (m, 13H, arom.) and 9.46 (bs, 1H, -NH). M<sup>+</sup>: 373.

The antibacterial activity of the synthesized compounds was determined using agar well diffusion method<sup>15</sup>. The compounds were taken at a concentration of 1 mg/ml using dimethyl sulphoxide (DMSO) as solvent by agar well diffusion method against gram positive organisms that include, *Bacillus subtilis*, *Bacillus cerus* and *Staphylococcus aureus* and gram negative organisms such as *Escherichia coli* and *Pseudomonas aeruginosa*. Nutrient agar was melted in a water bath and cooled at 45° with gentle shaking to bring about uniform cooling. It was inoculated with 0.5 ml of 24 h. old culture aseptically and mixed well by gentle shaking before pouring onto the sterilized Petri dishes (20-25 ml each

TABLE 1: ANTIBACTERIAL ACTIVITY OF COMPOUNDS 4a-4g

Compound	<i>E. coli</i>	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>B. cerus</i>	<i>B. subtilis</i>
4a	+	-	-	+	+
4b	+	++	+	+	+
4c	++	+	-	++	-
4d	++	+	+	+	++
4e	+	+	+	-	-
4f	++	-	-	++	+
4g	-	+	++	-	+
Ciprofloxacin	+++	+++	++	++	+++
DMSO	-	-	-	-	-

\*Concentration in mg/ml (1 mg/ml): - inactive, +active, the diameter of zone of inhibition in mm is + (11-15 mm), ++ (16-20 mm) and +++ (21-25 mm).

Petri plate). The poured material was allowed to gel. After gelling the medium, pores were made using a sterile cork borer and scooping out the punched part of the agar. Into these wells were added 0.05 ml portions of the test compound in solvent. The drug solution was allowed to diffuse for about an hour into the medium. The plates were incubated at 37° for 48 h. DMSO was taken as control to know the activity of solvent. The standard drug ciprofloxacin was also screened under similar conditions for comparison. The results for the antibacterial screening are presented in Table 1.

It has been observed that some of these compounds exhibited interesting antibacterial activities. Results reveal that compound 4b and 4d were active against both gram positive and gram-negative bacteria where as compound 4c and 4f were active against *E. coli* and *B. cerus*. Antibacterial data indicated that compound 4a and 4e did not show any significant antibacterial activities. It has been observed that activity shown by compound 4g against *P. aeruginosa* was comparable to that of standard drug. The screening results indicated that compounds 4a-4f (except 4g) were mild to moderately active against *E. coli* at a concentration of 1 mg/ml.

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## Synthesis and Antiinflammatory Activity of Oleanolic Acid Hemiphthalate Disodium Salt

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**A simple method for synthesis of oleanolic acid hemiphthalate disodium salt has been successfully developed. The structures of the newly synthesized compounds were elucidated on the basis of analytical and spectral data. The antiinflammatory activity of oleanolic acid hemiphthalate disodium**

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