CHAPTER-6

CDI mediated synthesis of Novel N-Methyl Thiadiazine Amides
6.1 LITERATURE REVIEW

The general introduction part for Amide and N-alkylation is already mentioned in the chapter-3 and chapter-4 respectively. No much work has been published for these kind of molecules having benzamide derivatives specifically at the 4th position of the thiadiazine ring system.

A variety of biological activities have been reported for different heterocycles containing the sulfamide moiety. The following biological effects have been mentioned for 2,6-disubstituted 3,5-dioxothiadiazines: antiinflammatory, antipyretic, and analgetic, fungicide, insecticides and micticide and antibacterial. The antiinflammatory, analgetic, and antipyretic activities of thiadiazinones related to phenylbutazone and antipyrine have been tested and compared to those of the pyrazolones. 4 substituted derivatives have been reported to cause the lowering of blood sugar levels. A pyrazolothiadiazinone and an aminothiazolothiadiazine, prepared as potential transition-state analogs, were found to be inhibitors of guanase. Many of the thiadiazine nucleoside were prepared as potential antimetabolites, but only 3-(2,3,5-tri-O-benzoylribofuranosyl)-7-aminofurazano derivative showed cytostatic activity against HeLa cells. The antiparasitic activity of 3,5-diaminothiadiazine derivatives has been tested, the most active compound being the parent one. Some 4-nitro derivatives of 1,2,6-thiadiazine have shown antimalarial and trichomonicidal activity. Benzothiadiazine dioxides have been claimed to act as sedatives and mild tranquilizers. Basagrana, the biologically active form of bentazone, as already mentioned, a wide variety of thiadiazines fused to heterocyclic systems have been synthesized in the search for herbicides and success is frequently claimed in the patent literature.

Nevertheless, since the discovery of their potential as “urea equivalent moiety” in the development of new histamine H1-receptor antagonists, the interest in them has greatly increased. Some of the most active compounds of this class are, in fact, aminothiadiazole 1-oxide and 1,1-dioxide derivatives. Numerous patents covering the preparation of these compounds have been published every year since 1981. Antihypertensive and vasodilating properties have also been claimed for some
aminothiadiazole 1,1-dioxides, o-Lactam antibiotics, quinazoline cardiac stimulants, and antiparasitic nitroimidazoles carrying a thia- diazolidine 1,1-dioxide-derived side chain have been reported. Central nervous system depressant, muscle relaxant, tranquilizer\textsuperscript{12}, and, more specifically, antihypertensive\textsuperscript{13} activities have been claimed for some benzothiadiazolines and benzothiadiazoline-substituted alanines, respectively. Benzothiadiazoline analogs of epinephrine\textsuperscript{14} and dopamine have been reported to be inactive, probably owing to the enhanced acidity of this ring. Furthermore, according to the publication, pesticide activity can be inferred for some thia- diazoline 1,1-dioxides prepared by authors in the Soviet Union. Finally, thia- diazole 1,1-dioxides have found other uses, such as auxiliary agents in textile treatments\textsuperscript{15}, electrodeposition processes, and color photography. A wide variety of 1,2,4,6-thiatriazine 1,1-dioxide derivatives have been claimed as herbicidal in numerous patents. In other reports, fungicidal and bactericidal activities have been claimed for these heterocycles. Resins produced by treating thia- diazines with aldehydes are acid resistant, and provide shrink and crease resistance to textiles\textsuperscript{16}.

With consideration of the above biologically important facts now we wish to report the synthesis of novel 2-alkylated 1,2,6-thiadiazine 1,1-dioxide having different benzamides at 4\textsuperscript{th} position of the thia- diazine ring. The biological importance of Amide and their preparation is already mentioned in the introduction part of Chapter-3.
6.2 REACTION SCHEME

A) Reaction Scheme for Preparation of N-Methyl Thiadiazine Amides

![Reaction Scheme]

6.3 Physical Data Table

<table>
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<tr>
<th>Code</th>
<th>R</th>
<th>Mol.Formula</th>
<th>Mol.Wt</th>
<th>M.P °C</th>
<th>Rxn.Time (Hrs)</th>
<th>Yield (%)</th>
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TLC Mobile Phase: Water: Acetic acid: Chloroform: Methanol :: 14:06:80:20
6.4 EXPERIMENTAL

6.4.1 MATERIALS AND METHODS:

All the chemicals used for preparation of novel compounds were purified by means of chemical purifications. Melting points were measured by capillaries. IR spectra were analysed on Perkin elmer SP-100 spectrophotometer. III ¹H-NMR of compounds were analysed by Bruker Ac-80 spectrometer instrument (300MHz in DMSO-d6) using Tetramethyl silane as internal standard and chemical shifts are presented in δ (ppm). The completion of the reaction was checked by TLC. Elemental analyses performed on Perkin-Elmer C, H, and N analyzer. IV

6.4.2 General method for the preparation of N-Methyl:

5.0g (0.017mole) of 2-(2,3,5-trimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl)benzoic acid and 2.89g (0.017mole) of Carbonyldiimidazole in 50ml of dry Tetrahydrofuran were stirred for 0.5hr at 50-55° C. Slowly charged (0.021mole) of aliphatic or aromatic amine and stirred for 12 hrs at RT. Solvent was completely removed and the residual mass was reacted with 25 ml, 5% HCl for 1hr. Filtered pale yellow to light brown solid and recrystallized using Ethanol: Water to get pure solid.
6.5 ANALYTICAL DATA

6.5.1 N-methyl Methyl Amide: (NB-41)

Mol. Wt: 307.36, M. P.: 164-65 °C; Yield 71 % Rf 0.80; IR (cm⁻¹): 1681 (C=O amide), 1151, 1367 (>S=O); 1573 (C=N); 3468 (NH-C=O); 1H NMR (δppm): 1.60 (s, 6H, Di-Methyl), 2.86 (d, 3H, -CH₃-N-), 3.21 (s, 3H, -CONH-CH₃), 6.90-7.32 (m, 4H, Ar-H); Elemental analysis for C₁₄H₁₇N₃O₃S; Calculated: C, 54.71; H, 5.57; N, 13.67; O, 15.62; S, 10.43 Found: C, 54.29; H, 5.32; N, 13.59 O, 15.45; S, 10.62

6.5.2 N-methyl N-tert-butyl Amide: (NB-42)

Mol. Wt: 349.44, M. P.: 154-55 °C; Yield 70 % Rf 0.80; IR (cm⁻¹): 1778 (C=O amide), 1163, 1347 (>S=O); 1531 (C=N); 3444 (NH-C=O); 1H NMR (δppm): 1.59 (s, 6H, Di-Methyl), 1.22 (s, 9H, -CH₃), 3.18 (s, -N-CH₃), 6.89-7.29 (m, 4H, Ar-H); Elemental analysis for C₁₇H₂₃N₃O₃S; Calculated: C, 58.43; H, 6.63; N, 12.02; O, 13.74; S, 9.18 Found: C, 58.30; H, 6.43; N, 12.18; O, 13.39; S, 9.33

6.5.3 N-methyl N-cyclopropyl Amide: (NB-43)

Mol. Wt: 333.40, M. P.: 181-82 °C; Yield 69 % Rf 0.80; IR (cm⁻¹): 1685 (C=O amide), 1136, 1331 (>S=O); 1517 (C=N); 3412 (NH-C=O); 1H NMR (δppm): 1.79 (s, 6H, Di-Methyl), 0.73-0.86 (m, 4H, -(CH₂)₂), 2.59 (m, 1H, -CH-), 3.08 (s, -N-CH₃), 7.29-7.78 (m, 4H, Ar-H); Elemental analysis for C₁₆H₁₉N₃O₃S; Calculated: C, 57.64; H, 5.74; N, 12.60; O, 14.40; S, 9.62 Found: C, 57.37; H, 5.51; N, 12.49; O, 14.53; S, 9.55
6.5.4 N-methyl N-propyl Amide: (NB-44)

Mol. Wt: 335.42, M.P.: 146-47 °C; Yield 72 % Rf 0.80 ;
IR (cm⁻¹): 1697 (C=O amide), 1145, 1327 (>S=O); 1519 (C=N); 3442 (NH-C=O), 1H NMR (δppm): 1.93 (s, 6H, Di-Methyl), 0.96 (t, 3H, -CH₂-CH₃), 1.62 (m, 2H, -CH₂-CH₃), 3.13 (s, -N-CH₃), 3.27 (m, 2H, -NH-CH₂-), 7.30-7.72 (m, 4H, Ar-H); Elemental analysis for C₁₆H₂¹N₃O₃S; Calculated: C, 57.29; H, 6.31; N, 12.53; O, 14.31; S, 9.56

6.5.5 N-methyl N-butyl Amide: (NB-45)

Mol. Wt: 349.44, M.P.: 173-74 °C; Yield 76 % Rf 0.80 ; IR (cm⁻¹): 1687 (C=O amide), 1158, 1319 (>S=O); 1527 (C=N); 3454 (NH-C=O), 1H NMR (δppm): 1.89 (s, 6H, Di-Methyl), 0.86 (t, 3H, -CH₂-CH₃), 1.32 (m, 2H, -CH₂-CH₃), 1.52 (m, 2H, -CH₂-CH₂-), 3.36 (m, 2H, -NH-CH₂-), 3.10 (s, -N-CH₃), 7.28-7.63 (m, 4H, Ar-H); Elemental analysis for C₁₇H₂₃N₃O₃S; Calculated: C, 58.43; H, 6.63; N, 12.02; O, 13.74; S, 9.18; Found: C, 58.31; H, 6.38; N, 12.19 O, 13.52; S, 9.42

6.5.6 N-methyl N-cyclohexyl Amide: (NB-46)

Mol. Wt: 375.48, M.P.: 158-59 °C; Yield 78 % Rf 0.80 ; IR (cm⁻¹): 1671 (C=O amide), 1154, 1313 (>S=O); 1519 (C=N); 3428 (NH-C=O), 1H NMR (δppm): 2.01 (s, 6H, Di-Methyl), 1.22-1.52 (m, 10H, -CH₂), 3.62 (m, NHCH-), 3.08 (s, -N-CH₃), 7.18-7.59 (m, 4H, Ar-H); Elemental analysis for C₁₉H₂₅N₃O₃S; Calculated: C, 60.78; H, 6.71; N, 11.19; O, 12.78; S, 8.54 Found: C, 60.54; H, 6.56; N, 11.39; O, 12.71; S, 8.66
6.5.7  N-methyl N,N-dimethyl Amide: (NB-47)

Mol. Wt: 321.39, M.P.: 138-39 °C; Yield 60 % Rf 0.80; IR (cm⁻¹): 1699 (C=O amide), 1137, 1333 (>S=O); 1499 (C=N); 3439 (NH-C=O), 1H NMR (δppm): 1.79 (s, 6H, Di-Methyl), 2.91 (m, 9H, -N-(CH₃)₂-N-CH₃), 7.28-7.62 (m, 4H, Ar-H); Elemental analysis for C₁₅H₁₉N₃O₃S; Calculated: C, 56.06; H, 5.96; N, 13.07; O, 14.93; S, 9.98; Found: C, 56.17; H, 5.85; N, 13.19; O, 14.88; S, 9.84

6.5.8  N-methyl pyrrolidin-1-yl Amide: (NB-48)

Mol. Wt: 347.43, M.P.: 143-45 °C; Yield 58 % Rf 0.80; IR (cm⁻¹): 1681 (C=O amide), 1149, 1337 (>S=O); 1516 (C=N), 3459 (NH-C=O), 1H NMR (δppm): 1.96 (s, 6H, Di-Methyl), 1.93-1.98 (m, 4H, -(CH₂)₂), 3.17-3.35 (m, 4H, N-(CH₂)₂), 3.11 (s, N-CH₃) 7.09-7.38 (m, 4H, Ar-H); Elemental analysis for C₁₇H₂₁N₃O₃S; Calculated: C, 58.77; H, 6.09; N, 12.09; O, 13.82; S, 9.23; Found: C, 58.62; H, 6.31; N, 12.22; O, 13.66; S, 9.37

6.5.9  N-methyl morpholin-4-yl Amide: (NB-49)

Mol. Wt: 363.43, M.P.: 141-42 °C; Yield 61 % Rf 0.80; IR (cm⁻¹): 1705 (C=O amide), 1177, 1337 (>S=O); 1526 (C=N); 3412 (NH-C=O), 1H NMR (δppm): 2.01 (s, 6H, Di-Methyl), 3.47-3.61 (m, 4H, -O-(CH₂)₂), 3.81-4.05 (m, 4H, N-(CH₂)₂), 3.23 (s, N-CH₃), 7.01-7.15 (m, 4H, Ar-H); Elemental analysis for C₁₇H₂₁N₃O₄S; Calculated: C, 56.18; H, 5.82; N, 11.56; O, 17.61; S, 8.82; Found: C, 56.33; H, 5.58; N, 11.29; O, 17.47; S, 8.49
6.5.10 N-methyl N,N-dicyclohexyl Amide: (NB-50)

Mol. Wt: 457.62, M.P.: 181-82 °C; Yield 86 % Rf 0.80;
IR (cm⁻¹): 1701(C=O ester), 1170, 1329(>S=O); 1522
(C=N); 3414 (NH-C=O), 1H NMR (δppm): 2.07 (s, 
6H, Di-Methyl), 1.23-1.71 (m, 20H-(CH₂)₁₀⁻), 3.41 (m,
NH-CH⁻), 3.19 (s, -N-CH₃), 7.19-7.42 (m, 4H, Ar-H);
Elemental analysis for C₂₅H₃₅N₃O₃S; Calculated:
C, 65.61; H, 7.71; N, 9.18; O, 10.49; S, 7.01 Found: C,
65.73; H, 7.55; N, 9.29; O, 10.64; S, 7.06
6.6 SPECTRAL DISCUSSION

6.6.1 IR SPECTRAL STUDY

IR spectra were analysed by Perkin Elmer SP-100 model using KBr pellet method. Various functional groups present in molecule were identified by characteristic frequency obtained for them. The characteristic bands of C-H aromatic stretching frequencies were observed between 3100-3000 cm\(^{-1}\). The stretching frequency of carbonyl (\(>\text{C}=\text{O}\)) of amide were at 1760-1670 cm\(^{-1}\). NH-stretching of \(-\text{CONH}\)-group lies between 3400-3500. At 1130-1160, 1317-1325 cm\(^{-1}\) \(>\text{SO}\) symetric and asymetric stretching frequency and at 1500-1550 cm\(^{-1}\) \(>\text{C}=\text{N}\) vibrational frequency of thiadiazine ring has been observed. The above mentioned respective frequencies suggest the correct formation of the desired products.

6.6.2 MASS SPECTRAL STUDY

Mass spectra were recorded on Waters Q-TOF Premier model using Direct Injection Probe technique. Systematic fragmentation pattern was observed in mass spectral analysis. Molecular ion peak, [M+Na], [2M+Na] were observed in agreement with molecular weight of respective compound. The Mass spectrum for the representative compound of the series is discussed below.

N-methyl Methyl Amide (NB-41)
N-methyl N-tert-butyl Amide
(NB-42)

6.6.3 1H-NMR SPECTRAL STUDY

$^1$H-NMR spectra of the synthesized compounds were recorded on Bruker Ac-80 spectrometer (300MHz) spectrometer. Sample solutions were made in DMSO solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned. Numbers of protons identified from H-NMR spectrum and their chemical shift ($\delta$ ppm) were in the agreement of the structure of the molecule. In some cases, aromatic protons were obtained as multiplet. The spectral interpretation is discussed as under.
N-methyl Methyl amide (NB-41)

1. The proton no.1 is attached with one -NH- group which splits the three protons of the adjacent methyl group into doublet and gives a signal at 2.86 δ ppm.

2. The proton no. 2 and 3 are symmetrically placed. So collectively they give a singlet at 1.60 δ ppm for six protons of two Methyl groups attached to Thiadiazine ring.

3. The proton no. 4 is attached with electronegative nitrogen atom which gives a signal at 3.21 δ ppm.

4. In the region of 6.90-7.32 δ ppm the four distinct peaks due to four aromatic protons of phenyl ring attached to Thiadiazine ring can be seen in the NMR.

Thus, by assigning all the peaks as per the above given justifications and by calculating the shift value for the respective protons the proposed structure of NB-41 is confirmed.
1. The proton no.1,2 and 3 are equivalent protons having same environment and gives a collective peak at 1.22 δ ppm representing 9 protons.

2. The proton no. 4 is attached with electronegative nitrogen atom which gives a singlet at 3.18 δ ppm.

4. The proton no. 5 and 6 are symmetrically placed. So collectively they give a singlet at 1.59 δ ppm for six protons of two Methyl groups attached to Thiadiazine ring.

5. In the region of 6.89-7.29 δ ppm the four distinct peaks due to four aromatic protons of phenyl ring attached to Thiadiazine ring can be seen in the NMR.

Thus, by assigning all the peaks as per the above given justifications and by calculating the shift value for the respective protons the proposed structure of NB-42 is confirmed.
6.7 SPECTRAL PRESENTATION OF THE SYNTHESISED COMPOUNDS

6.7.1 IR Spectrum of NB-41

![IR Spectrum of NB-41](image)

6.7.2 Mass Spectrum of NB-41

![Mass Spectrum of NB-41](image)
6.7.3 $^1$H Spectrum of NB-41

6.7.4 IR Spectrum of NB-42
6.7.5 Mass Spectrum of NB-42

![Mass Spectrum of NB-42](image)

6.7.6 $^1$H Spectrum of NB-42

![$^1$H Spectrum of NB-42](image)
6.8 BIOLOGICAL SCREENING OF N-methyl Thiadiazine Amides

6.8.1 Biological Screening:

The biological screening of all newly synthesised compounds was carried out. Biological screening method part is described in Chapter-2 Page no 45.

All the compounds have been evaluated for their biological screening represented in Graphical Table no-B.

The biological screening was compared with standard drug viz Amoxycillin, Benzyl Penicillin Ampicillin, Norfloxacain, and antifungal activity was compared with viz Greseofulvin. The inhibition zones were measured in mm. The zones of inhibition that displayed by standard drugs are recorded in Table no-A.
### 6.8.2 ANTIMICROBIAL ACTIVITY ZONE OF INHIBITION OF STANDARD DRUGS AT 50MG/ML CONCENTRATION.

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<td>Greseofulvin</td>
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### 6.8.3 Biological Screening Data of N-methyl Thiadiazine Amides

#### Table-B

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