Synthesis, characterization and potential anticonvulsants activity of various 3-(substituted)-benzylidene-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

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A number of new 3-(substituted)-benzaldehyde derivatives of 7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one have been synthesized and their anticonvulsant activity tested through Maximal Electroshock (M.E.S.) model and PTZ animal model by using Phenytoin and Diazepam as reference drugs respectively. The five compounds, namely 3-(4-chlorobenzylidene)-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 4a, 3-(2-chloro-benzylidene)-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 4b, 3-(3-hydroxybenzylidene)-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 4d, 3-(4-N, N-dimethyl-benzylidene)-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 4h and 3-(4-florobenzylidene)-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one 4j have shown significant anticonvulsant activity as compared to reference drugs.

Keywords: 1,4-Benzodiazepin-2-one, benzaldehyde derivatives, anticonvulsant activity, benzodiazepine receptors

Benzodiazepines are bicyclic heterocyclic compounds possessing a benzene nucleus fused to a seven membered ring containing two nitrogen atoms. Depending upon the two nitrogen positions, there are six types of benzodiazepines: 1,2-benzodiazepine, 1,3-benzodiazepine, 2,3-benzodiazepine, 1,4-benzodiazepine and 1,5-benzodiazepine. However, only the members of 1,4-benzodiazepine group have shown significant pharmacological and clinical activity. Among seven membered heterocyclic nuclei the main interest of work was on 1,4-benzodiazepine-2-one which provides a versatile pharmacophore exhibiting anticonvulsant, antianxiety, antidepressant, anticancer, anti-inflammatory activities, etc.

Therefore, some novel substituted benzaldehyde derivatives of 7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one were prepared and evaluated for anticonvulsant activity. They were synthesized by reacting 7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one with different types of benzaldehyde derivatives in the presences of absolute ethanol (Scheme I). Elemental analysis, IR, 1H NMR and mass spectra characterized the structures of newly synthesized compounds. The structure activity relationship studies have revealed that electron withdrawing substituents such as chloro, bromo and fluoro at C-7 conferred high activity. Replacement of phenyl group at C-2 by other substituents decrease the pharmacological activity but substituents at C-3 have not been studied widely. Therefore, the focus was on synthesizing novel 7-chloro-3-benzaldehyde derivative-1,3-dihydro-1H,3H-1,4-benzodiazepine-2-one-5-phenyl and study of their anticonvulsant activity.

Experimental Section

The chemicals were supplied by E. Merck (Germany) and S.D. Fine Chemicals (India). Melting points were determined by open tube capillary method and are uncorrected. The homogeneity of the compounds was checked on thin layer chromatography (TLC) plates (silica gel G) using the solvent system: Toluene: Ethyl acetate: Formic acid (5:4:1) and benzene: methanol (8:2).

The spots were evaluated by exposure to iodine vapors and UV light. IR spectra were obtained on a Perkin-Elmer 1720 FT-IR spectrometer (KBr pellets). 1H NMR spectra were recorded on a Bruker AC300 MHz spectrometer using TMS as internal standard in DMSO-d_6/CDCl_3 and mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing voltage with a VG Prospec instrument and are presented as m/z. Microanalysis of the compounds was performed on a Perkin Elmer model 240 analyzer.

Synthesis of 2-chloro-N-(4-halophenyl) acetamide, 1

p-Chloroaniline (25.5 g, 0.2 mol) was suspended in 250 mL toluene and chloro acetyl chloride (90.4 g, 0.8 mol) was gradually added with stirring. The mixture was then allowed to reflux for 12 hr. The completion of reaction was indicated by TLC using silica gel as stationary phase and Toluene : Ethyl acetate : Formic acid (5:4:1) as the mobile phase. It was then cooled to RT. After the completion of the
reaction, the mixture was poured into crushed ice. The solid product so obtained was separated and dried.$^{14,15}$

**N-(2-Benzoyl-4-chlorophenyl)-2-chloroacetamide, 2**

2-Chloro-N-(4-chlorophenyl) acetamide was dissolved completely in carbon tetrachloride, and then mixed with benzoyl chloride in equimolar quantity. Finely powdered anhydrous aluminium chloride was added with frequent shaking, during 10 min to the contents of the flask. A reflux condenser was fitted and the mixture refluxed for 9 hr. The completion of reaction was indicated by TLC using silica gel as stationary phase and Toluene : Ethyl acetate : Formic acid (5:4:1) as the mobile phase. The mixture was then poured into crushed ice. The solid product so obtained was washed with aq. NaOH followed by water.$^{16,17}$

**Scheme 1** — Synthetic protocol for compounds 4a-j. Reagents and conditions: (a) Toluene; (b) CCl$_4$, AlCl$_3$, absolute ethanol; (c) NH$_4$Cl, hexamine, 5-7 hr

**General procedure for the synthesis of various benzaldehyde derivatives of 3-(substituted)-benzylidene-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one, 4a-j (Table I)**

7-Chloro-5-phenyl-1,3-dihydro-1H,3H-1,4-benzodiazepin-2-one (8.12 g, 0.03 mol) was mixed with 4-chloro benzaldehyde (4.2 g, 0.03 mol) in 25 mL of absolute ethanol. After that, a few drops of piperidine (3-4 drops) were added and refluxed for 7 hr. The completion of the reaction was indicated by TLC using silica gel as stationary phase and toluene : ethyl
Synthesis of 3(4-chlorobenzylidene)-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4] diazepin-2-one, 4a

FTIR (KBr): 3220-3070 (N-H str, amide), 3000-3100 (=C-H str), 1700 (C=O str), 1650 (C=N str, imine), 1610 (Ar C=C str, Bz), 830 (Ar-C=Cl str), 720 cm\(^{-1}\) (Ar C-H def(Bz)); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 8.92 (1H, s, ArCH=13), 8.19, 7.84, 7.58, 7.39, 7.28, 7.15, 7.06 (12H, 7brm, aromatic proton), 5.84 (1H, s, ArN-H-1); MS: \(m/z\) 356 (M\(^+\), C\(_{22}H_{13}N_{2}ClO_2\)), 281 (C\(_{16}H_{10}N_{2}ClO_1\)), 152 (C\(_7H_NCl_2\)), 138 (C\(_2H_NClI\)), 124 (C\(_2H_NClI\)). Anal. Calcd for C\(_{22}H_{13}N_{2}O_2Cl_2\): C, 72.05; H, 5.04; N, 12.05. Found: C, 72.02; H, 5.04; N, 12.02%.

Synthesis of 3(2-chlorobenzylidene)-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4] diazepin-2-one, 4b

FTIR (KBr): 3300-3070 (N-H str, amide), 3000-3100 (=C-H str), 1690 (C=O str), 1650 (C=N str, imine), 1610 (Ar C=C str, Bz), 850 (Ar-C=Cl str), 720 cm\(^{-1}\) (Ar C-H def(Bz)); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 9.92 (1H, s, ArCH=13), 8.19, 7.84, 7.58, 7.39, 7.28, 7.15, 7.06 (12H, 7brm, aromatic proton), 5.82 (1H, s, ArN-H-1). Anal. Calcd for C\(_{22}H_{14}N_{2}O_2Cl_2\): C, 72.05; H, 4.86; N, 13.05. Found: C, 72.12; H, 4.84; N, 13.02%.

Synthesis of 3(3, 4-dimethoxybenzylidene)-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4] diazepin-2-one, 4c

FTIR (KBr): 3220-3080 (N-H str, amide), 3030-3110 (=C-H str), 1618 (Ar C=C str, Bz), 1440 (C=N str, imine), 1710 (C=O str), 1375 (C=N str), 2850-2815(CH=O str), 812 cm\(^{-1}\) (Ar C-Cl str); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 9.88 (1H, s, Ar-CH= 13), 7.85, 7.27, 7.02, 7.01, 6.99, 6.88 (11H, 6brm, aromatic proton), 5.34 (1H, s,Ar-NH-1), 3.85 (3H, s, Ar-OCH\(_3\)-27); MS: \(m/z\) 417 (M\(^+\), C\(_{22}H_{18}N_{2}ClO_3\)), 281 (C\(_{14}H_{10}N_{2}ClO_1\)), 152 (C\(_8H_7NClI\)), 138 (C\(_2H_8NClI\)), 152 (C\(_8H_7O_2\)). Anal. Calcd for C\(_{22}H_{19}N_{2}O_2Cl_2\): C, 73.23; H, 5.04; N, 9.23. Found: C,73.20; H, 5.02; N, 9.17%.

Synthesis of 3(3-hydroxybenzylidene)-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4] diazepin-2-one, 4d

FTIR (KBr): 3600 -3200 (Ar-OH str), 3220-3070 (N-H str), 3010-3090 (=C-H str), 720 (Ar C-H def Bz), 1688 (C=O str), 1654 (C=N str, imine), 1603-1561 (Ar C=C str, Bz), 1245(C=N str), 764 cm\(^{-1}\) (Ar C -Cl str); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 9.92 (H,Ar=CH=13), 7.42, 7.40, 7.37, 7.24, 7.11(12 H, 5brm, aromatic proton), 5.33 (1H, s, Ar-NH-1). Anal. Calcd for C\(_{22}H_{15}N_{2}O_2ClI\): C, 73.05; H, 6.61; N, 9.01. Found: C, 73.03; H, 6.60; N, 9.01%.

Synthesis of 3(4-hydroxybenzylidene)-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4] diazepin-2-one, 4e

FTIR (KBr): 3560-3200 (Ar-OH str), 3220-3070 (N-H str, amide), 3010-3100 (=C-H str), 1680 (C=O str), 1601 (C=N str, imine), 1514 (Ar C=C str, Bz), 1241(C=N str), 831 cm\(^{-1}\) (Ar-C=Cl str); \(^1\)H NMR (300 MHz, CDCl_3); \(\delta\) 9.87 (1H, s, ArCH=13), 7.81, 7.30, 7.26, 6.95 (12H, 4brm, aromatic proton), 5.34 (1H, s, Ar-NH-1). Anal. Calcd for C\(_{22}H_{15}N_{2}O_2ClI\): C, 73.01; H, 7.36; N, 12.05. Found: C, 73.02; H, 7.27; N, 12.01%.
Synthesis of 3(2-hydroxybenzylidene)-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4] diazepin-2-one, 4f

FTIR (KBr): 3580-3300(ArO-H str), 1610 (C=O str), 1540 (C=C str), 820-720 (ArC-Cl str), 720 cm⁻¹ (Ar C-Cl def Bz); ¹H NMR (300 MHz, DMSO-d₆): δ 11.02 (1H, s, Ar-CH=13), 7.85, 7.57, 7.53, 7.34, 7.23, 7.02, 6.98 (12H, 7brm, aromatic proton), 3.24 (1H, bs, N-H-1), 2.95 (6H, s, (1H, s, Ar-NH-1), 7.61, 7.58, 6.71, 6.68 (12H, 6brm, aromatic proton), 5.34 (1H, s, Ar-CH=13), 7.85, 7.27, 7.01, 6.99, 6.88 (12H, 6brm, aromatic proton), 5.34 (1H, s, Ar-NH-1), 3.85 (3H,s, Ar-OCH₃). Anal. Calcd for C₂₃H₁₇N₂O₂Cl₂: C, 73.33; H, 8.01; N, 13.05%. Found: C, 73.30; H, 8.01; N, 13.05%.

Synthesis of 3(4-methoxybenzylidene)-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4] diazepin-2-one, 4i

FTIR (KBr): 3220-3070 (N-H str, amide), 3010-3110 (=C-H str), 2950 (N-C≡N bnd str), 1610 (C=C str), 1540 (C≡N str), 1450 (C-N str), 1250 (C-N str), 780 cm⁻¹ (Ar C≡N str); ¹H NMR (300 MHz, CDCl₃): δ 9.58 (1H, s, Ar-CH=13), 7.61, 7.58, 6.71, 6.68 (12H, 4brm, aromatic proton), 3.24 (1H, bs, N-H-1), 2.95 (6H, s, Bz-N=2XCH₂, 28), 29; MS: m/z 399 (M⁺, C₂₂H₁₉ClN₂O₂); 152 (C₁₅H₁₀ClN₂O₂), 152 (C₁₅H₁₀ClN₂O₂), 134 (C₉H₇N₂). Anal. Calcd for C₂₂H₁₉N₂O₂Cl₂: C, 70.83; H, 14.36; N, 13.02%. Found: C, 70.80; H, 14.28; N, 13.03%.

Synthesis of 3(3(4-N, N-dimethyl benzylidene)-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4] diazepin-2-one, 4j

FTIR (KBr): 3220-3070 (N-H str, amide), 3000-3100 (=C-H str), 1610 (C=C str), 1540 (C≡N str), 1250 (C-N str), 780 cm⁻¹ (Ar C≡N str); ¹H NMR (300 MHz, DMSO-d₆): δ 9.58 (1H, s, Ar-CH=13), 7.61, 7.58, 6.71, 6.68 (12H, 4brm, aromatic proton), 3.24 (1H, bs, N-H-1), 2.95 (6H, s, Bz-N=2XCH₂, 28), 29; MS: m/z 399 (M⁺, C₂₂H₁₉ClN₂O₂); 152 (C₁₅H₁₀ClN₂O₂), 134 (C₉H₇N₂). Anal. Calcd for C₂₂H₁₉N₂O₂Cl₂: C, 70.83; H, 14.36; N, 13.02%. Found: C, 70.80; H, 14.28; N, 13.03%.

Results and Discussion

The benzodiazepine receptor after primary recognition of the pharmacophore undergoes a shift in conformation either to an agonist or an inverse agonist state based on electronic, hydrophobic and steric characteristics of the incoming ligand (Figure 1). This conformational change allosterically modulates the binding of GABA to the receptor. An agonist facilitates the change for binding of GABA, which is observed as anticonvulsant in biological activity measures whereas the conformation that inhibits the binding of GABA to receptor behaves as proconvulsant. An antagonist binds to benzodiazepine receptor but does not undergo any conformational change.

The conformational changes are a key factor in defining the benzodiazepine activity. The minimal requirements for exhibiting anticonvulsant activity is the presence of an aromatic ring-A undergoing π/π stacking within the receptor with an aromatic amino acid residue and a proton accepting group existing in the plane of this aromatic ring interacting with histidine residue on the receptor. The unsubstituted C₃ phenyl contributes to the hydrophobic interaction and is necessary for minimal activity. An electron-rich substitution favors an increased activity.

The compounds synthesized are new in the 1,4-benzodiazepin-2-one skeletal series and could be recommended for further studies to find out the relationship with known anticonvulsant products in use today for developing newer templates for valuable drugs for CNS activity.

Anticonvulsant activity
There are different types of epilepsies: grandmal, petitmal or psychomotor type, which can be studied in
laboratory animals. The increasing current electroshock seizure induced convulsion on animals represents grandmal type of epilepsy\textsuperscript{20}.

Male albino mice (weighing between 20-30 g) used for the study were housed in groups of three or four mice per cage under standard laboratory condition for one week before experiments and the condition maintained at 25°C and humidity 45-50\%. The anticonvulsant activity was carried out by using both Maximal Electroshock (MES) and PTZ animal model. All the results obtained in both the method were statistically analyzed. The results have been expressed as the mean ± S.E.M.

**Maximal Electroshock (M.E.S.) Model**

In MES test the electroshock is applied through corneal electrodes. The MES induced convulsions were divided into five phases as: tonic flexion, tonic extension, clonic convulsion, stupor, recovery or death. A substance is known to possess anticonvulsant property if it reduces or abolishes the extensor phase. The investigations were conducted on albino mice of either sex (25-30 g). The albino mice were kept under standard conditions at an ambient temperature of 25±2°C. Food and water were withdrawn prior to the experiment. Standard drugs and test compounds: Phenytoin (20 mg/kg, i. p.), as standard drug and test compounds were used (20 mg/kg, i. p.). The solution of standard drug and test compound were prepared in propylene glycol and administered intraperitoneally 30 min before the test. The equipment used for this test is called as Electroconvulsometer\textsuperscript{21,22}.

The compounds screened for their anticonvulsant activity by electroshock seizure method were subjected to supra maximal electroshock of 50 mA, 60 Hz alternating current from a convulsometer for 0.2 sec through a pair of electrodes attached to each ear. The duration of the tonic hind limb extensor phase, clonic phase and the number of animals protected from convulsions were noted. The Results are given in Table II. All the tested compounds showed a reduction in the duration of tonic hind limb extensor phase. A complete abolition of hind limb tonic extensor was considered as 100\% protection. The abolition of the hind limb tonic extensor spasm was recorded as an increased anticonvulsant activity\textsuperscript{23}.

**PTZ animal model**

Pentylenetetrazole (PTZ) produces clonic convulsions in rats or mice. PTZ (Sigma Chemicals, USA) was used to produce convulsion and Diazepam (Ranbaxy Laboratories, India) was used as a standard drugs were dissolved in 2\% gum acacia suspension\textsuperscript{24,25}. The animals were divided into ten groups of six mice each. Group-1 served as control and received 0.1 mL of 2\% gum acacia. Group-2 received compound 4a, Group-3 received compound 4b, Group-4 received compound 4c, Group-5 received compound 4d, Group-6 received compound 4e, Group-7 compound received 4f, Group-8 received
compound 4g. Group-9 received compound 4h. Group-10 received compound 4i. Group-11 received compound 4j. Group-12 received standard drug. Convulsion was induced 1 hr after the administration of the standard drug or the test compounds by i.p. injection of (80 mg/kg) that was dissolved in saline to a volume of 0.1 mL/10g body weight. The results are given in Table III. The time needed for the development of unequivocal sustained clonic seizure activity involving the limbs (isolated myoclonic jerks or other preconvulsion chewing behavior were not counted) was carefully recorded. Duration of seizure was also noted. Seizure free duration for a period of 1 hr was taken as protection. The number of animals protected in each group was recorded and percent protection was calculated.

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### Table II — Anticonvulsant activity of the tested compound compared with standard drug (Phenytoin) (4a-j, M.E.S. model)

<table>
<thead>
<tr>
<th>Group</th>
<th>Test Compd</th>
<th>Dose (mg/kg)</th>
<th>N</th>
<th>Protection (%)</th>
<th>Recovery</th>
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<tbody>
<tr>
<td>1</td>
<td>control</td>
<td>0.1mL/10g</td>
<td>6</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>4a</td>
<td>20</td>
<td>6</td>
<td>100</td>
<td>Very soon</td>
</tr>
<tr>
<td>3</td>
<td>4b</td>
<td>20</td>
<td>6</td>
<td>100</td>
<td>Very soon</td>
</tr>
<tr>
<td>4</td>
<td>4c</td>
<td>20</td>
<td>6</td>
<td>67</td>
<td>Late</td>
</tr>
<tr>
<td>5</td>
<td>4d</td>
<td>20</td>
<td>6</td>
<td>100</td>
<td>Very soon</td>
</tr>
<tr>
<td>6</td>
<td>4e</td>
<td>20</td>
<td>6</td>
<td>60</td>
<td>Late</td>
</tr>
<tr>
<td>7</td>
<td>4f</td>
<td>20</td>
<td>6</td>
<td>100</td>
<td>Very soon</td>
</tr>
<tr>
<td>8</td>
<td>4g</td>
<td>20</td>
<td>6</td>
<td>83</td>
<td>Soon</td>
</tr>
<tr>
<td>9</td>
<td>4h</td>
<td>20</td>
<td>6</td>
<td>83</td>
<td>Soon</td>
</tr>
<tr>
<td>10</td>
<td>4i</td>
<td>20</td>
<td>6</td>
<td>62</td>
<td>Late</td>
</tr>
<tr>
<td>11</td>
<td>4j</td>
<td>20</td>
<td>6</td>
<td>100</td>
<td>Very soon</td>
</tr>
<tr>
<td>12</td>
<td>Phenytoin</td>
<td>20</td>
<td>6</td>
<td>100</td>
<td>Very soon</td>
</tr>
</tbody>
</table>

N = Number of animals

### Table III — Anticonvulsant activity of the tested compounds compared with standard drug (diazepam) (4a-j, PTZ animal model)

<table>
<thead>
<tr>
<th>Group</th>
<th>Test Compd</th>
<th>Dose (mg/kg)</th>
<th>N</th>
<th>Protection (%)</th>
<th>Duration of seizure (sec) (mean ± S.E.M.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control (2% Gum acacia)</td>
<td>0.1mL/10g</td>
<td>3</td>
<td>0</td>
<td>311±0.577</td>
</tr>
<tr>
<td>2</td>
<td>4a</td>
<td>20</td>
<td>3</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>4b</td>
<td>20</td>
<td>3</td>
<td>100</td>
<td>8±0.576</td>
</tr>
<tr>
<td>4</td>
<td>4c</td>
<td>20</td>
<td>3</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>4d</td>
<td>20</td>
<td>3</td>
<td>60</td>
<td>11±0.577</td>
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<tr>
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<td>4e</td>
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<td>100</td>
<td>0</td>
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<tr>
<td>7</td>
<td>4f</td>
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<td>50</td>
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</tr>
<tr>
<td>8</td>
<td>4g</td>
<td>20</td>
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<td>0</td>
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<tr>
<td>9</td>
<td>4h</td>
<td>20</td>
<td>3</td>
<td>80</td>
<td>9±0.577</td>
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<tr>
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<td>3</td>
<td>83</td>
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<tr>
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<td>4j</td>
<td>20</td>
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<td>100</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>Diazepam</td>
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<td>3</td>
<td>100</td>
<td>0</td>
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</table>

N = Number of animals (92% Gum acacia)
Institute) Lucknow for scanning the mass spectra of the compounds.

References