Synthesis of 5H-dibenzo(b,f)azepine-5-carboxylic acid [3-chloro-2-(substitutedphenyl)-4-oxoazetidin-1-yl]amide from 5H-dibenzo(b,f) azepine-5-carbonyl chloride

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5H-Dibenzo(b,f)azepine-5-carbonyl chloride 1 has been prepared from 5H-dibenzo(b,f)azepine by phosgenation, which has been then treated with hydrazine hydrate to give 5H-dibenzo(b,f)azepine-5-acid hydrazide 2. It has been reacted with various aromatic aldehydes to afford 5H-dibenzo(b,f)azepine-5-carboxylic acid-(substitutedbenzylidene)hydrazide 3a-j. The synthesis of 5H-dibenzo(b,f)azepine-5-carboxylic acid [3-chloro-2-(substitutedphenyl)-4-oxoazetidin-1-yl]amide 4a-j has been achieved by the reaction of 3 with chloroacetyl chloride in presence of triethylamine. The products have been characterized by elemental analysis, IR, 1H NMR and mass spectral studies.

Key words: 5H-dibenzo(b,f)azepine-5-carbonyl chloride, 5H-dibenzo(b,f)azepine-5-acid hydrazide, 5H-dibenzo(b,f)azepine-5-carboxylic acid (4-methoxybenzylidene)-hydrazide, 5H-dibenzo(b,f)azepine-5-carboxylic acid [3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]amide.

IPC: Int.Cl. C 07 D

5H-Dibenzo(b,f)azepine-5-carbonyl chloride 1 is prepared from 5H-dibenzo(b,f) azepine and phosgene or triphosgene. Carbamazepine is prepared by the reaction of 5H-dibenzo(b,f)azepine-5-carbonyl chloride with liq. ammonia. Literature survey reveals that the active moiety carbamazepine [5H-dibenzo(b,f)azepine-5-carboxamide] and its derivative oxo-carbazepine are clinically widely used. Carbamazepine is a tricyclic (iminostilbene) compound with structural resemblance to the antidepressant drug imipramine. 5H-dibenzo(b,f)azepine-5-acid hydrazide 2 is found to be suitable for covalent attachment to a polymer particle reagent and for attachment to protein for the preparation of carbamazepine immunogens. Carbamazepine has been established as an effective agent in the management of epilepsy, trigeminal neuralgia and effective disorders. Various hydrazide-hydrazone derivatives have been reported to demonstrate biological activity.

The ketene-imine cycloaddition reaction is one of the most common methods for constructing the β-lactam skeleton present in different antibiotics. The Staudinger reaction is now widely employed in the preparation of β-lactams as it provides a direct access to such compounds from simple precursors.

Numerous β-lactams have been prepared by the reaction of acid chloride and imine in the presence of tertiary amine. Natural and synthetic azetidinone derivatives, especially those containing carbonyl group at C2 occupy a central place among medicinally important compounds due to their diverse and interesting antibiotic activity.

In the present paper is reported the synthesis and characterization of different 5H-dibenzo(b,f)azepine-5-carboxylic acids [3-chloro-2-(substitutedphenyl)-4-oxoazetidin-1-yl]amides 4a-j (Scheme 1) from 5H-dibenzo(b,f)azepine-5-carbonyl chloride 1, which was prepared from 5H-dibenzo(b,f)azepine and phosgene in toluene. Imines with substituted phenyl ring were prepared and used in the present work (Table I). All synthesized compounds were characterized by elemental analysis, IR, NMR and mass spectrometric (MS) techniques. The homogeneity of the compounds were checked by TLC [(methanol : toluene, 2:8 and ethyl acetate : carbon tetrachloride, 7:3)].

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. All the chemicals and
Scheme I — Synthesis of 5H-dibenzo(b,f)azepine-5-carboxylic acid [3-chloro-2-(substitutedphenyl)-4-oxoazetidin-1-yl]amide, 4a-j.

Table I — Physical data of synthesized compounds 3a-j and 4a-j

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<th>Compd</th>
<th>R</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
<th>Mol. formula</th>
<th>Recrystallization solvent</th>
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<td>3a</td>
<td>4-CH₃</td>
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<td>86</td>
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<td>88</td>
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<tr>
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<td>77</td>
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<td>91</td>
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<tr>
<td>3i</td>
<td>3,4,5-,OCH₃</td>
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<td>78</td>
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</tr>
<tr>
<td>4j</td>
<td>H</td>
<td>172</td>
<td>60</td>
<td>C₂₄H₁₉ClN₃O₂</td>
<td>2</td>
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</table>

solvents used were of Laboratory Grade and solvents were purified by suitable methods. IR spectra were recorded on a Shimadzu-8400 FT-IR spectrometer using KBr disc. 1H NMR spectra were recorded on a Brucker 300MHz spectrometer using TMS as an internal standard in CDCl3 and DMSO-d6 and mass spectra on a Hewlett-Packard 5989, Quadrupole Mass Spectrometer. The homogeneity of the products was checked using TLC (Silica Gel-G, Merck). Elemental analysis was performed on a Perkin-Elmer 2400 Series II instrument and found to be satisfactory.

5H-Dibenzo (b,f)azepine-5-acid hydrazone 2. A mixture of 5H-dibenzo(b,f)azepine-5-carboxyl chloride (0.01 mole) and hydrazine hydrate (0.01 mole, 80%) in absolute ethanol was stirred for 1 hr and then refluxed for 0.5 hr on a water bath. The contents were cooled and product obtained was filtered, washed with cold ethanol, dried and purified by recrystallisation from methanol to give 2. Yield 63%, m.p. 178°C; TLC (methanol : toluene, 2:8, Rf 0.35). Anal. Found: C, 74.56; H, 5.06; N, 9.24. C25H19N3O2 requires C, 74.79; H, 5.14; N, 9.1138%. IR(KBr): 3326 (NH amine), 3276 (-NH 2), 3021 (NH), 3015 (Ar C-H stretch), 1622 cm -1(N-C=O); 1H NMR (CDCl3): δ 8.67 (s, 1H, -NH), 7.75 (d, J=7.60 Hz, 2H, 4-OCH3 phenyl ring), 7.69-7.19 (m, 8H, Ar-H), 7.17 (s, 2H, CH=CH), 5.85 (bs, 1H, -NH), 3.47 (bs, 2H, -NH2); MS: m/z (%) 252 (53, M+), 192 (100), 192 (100), 165 (14.6).

General procedure for the preparation of 5H-dibenzo(b,f)azepine-5-carboxylic acid (substituted-benzylidene)hydrazone 3-a. A mixture of 2 (0.01 mole) and different aromatic aldehydes (0.01 mole) with a few drops of acetic acid in absolute ethanol was refluxed for 1 hr on a water bath. The contents were cooled and the product obtained was filtered, washed with a little petroleum ether, dried and purified by recrystallisation from suitable solvent.


General procedure for the preparation of 5H-dibenzo(b,f)azepine-5-carboxylic acid [3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]-amide 4a: Orange crystals, yield 68%, m.p. 182°C; TLC (ethyl acetate : carbon tetrachloride, 7:3, Rf 0.60). Anal. Found: C, 64.12; H, 3.75; N, 9.24. C25H17ClN3O2 requires C, 64.01; H, 3.81; N, 9.33%. IR(KBr): 3350 (NH), 3020 (NH-C=O), 1697 and 1681 (NH-C=O), 1506, 1361 (C-N), 1261, 1026 (C-O), 692 cm -1(C-Cl); 1H NMR (CDCl3): δ 8.67 (s, 1H, -NH), 7.75 (d, J=7.60 Hz, 2H, 4-OCH3 phenyl ring), 7.69-7.19 (m, 8H, Ar-Ch-N), 4.87 (d, J=10.19 Hz, 1H, N-Ch-Cl), 3.86 (s, 3H, -OCH3); MS: m/z (%) 446 (14.4, M+), 254 (46.8, M+), 220 (18.7, M+), 192 (100), 177 (10.9), 134 (20).

5H-Dibenzo(b,f)azepine-5-carboxylic acid [3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl]-amide 4b: Colourless compound, yield 67 %, m.p. 160°C; TLC (ethyl acetate : carbon tetrachloride, 7:3, Rf 0.58). Anal. Found: C, 64.12; H, 3.75; N, 9.24. C25H17Cl2N3O2 requires C, 64.01; H, 3.81; N, 9.33%. IR(KBr): 3350 (NH), 3025 (Ar C-H), 1743 and 1720 (C=O, β-lactam ring), 1692 and 1684 (NH-C=O), 1514, 1360 (C-N), 1254, 1025 (C-O), 695 cm -1(C-Cl); 1H NMR (CDCl3 + DMSO-d6): δ 8.52 (s, 1H, -NH), 7.88-6.80 (m, 8H, Ar-H + 4H, 4-Cl phenyl ring), 7.10 (s, 2H, CH=CH), 6.66 (d, J=10.50 Hz, 1H, Ar-Ch-N), 4.86 (d, J=10.20 Hz, 1H, N-Ch-Cl).

5H-Dibenzo(b,f)azepine-5-carboxylic acid [3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl]-amide 4c: Colourless compound, yield 60%, m.p. 184°C; TLC (ethyl acetate : carbon tetrachloride, 7:3, Rf 0.45). Anal. Found: C, 66.80; H, 4.12; N, 9.69. C23H18ClN3O3 requires C, 66.74; H, 4.17; N, 9.73%. IR(KBr): 3365 (NH), 3018 (Ar C-H), 1740 and 1718 (C=O, β-lactam ring), 1690 and 1680 (NH-C=O), 1510, 1365 (C-N), 1255, 1020 (C-O), 690 cm -1(C-Cl); 1H NMR (CDCl3): δ 8.62 (s, 1H, -NH), 7.80-6.90 (m, 8H, Ar-H + 4H, 4-OH phenyl ring), 6.95 (s, 2H,
5H-Dibenzo(b,f)azepine-5-carboxylic acid [3-chloro-2-(4-fluorophenyl)-4-oxoazetidin-1-yl]amide 4d: Colourless compound, yield 70%, m.p. 158°C; TLC (ethyl acetate : carbon tetrachloride, 7:3, Rf 0.59). Anal. Found: C, 66.80; H, 4.02; N, 9.65. \( \text{C}_{23}\text{H}_{17}\text{ClN}_{4}\text{O}_{4} \) requires C, 66.44; H, 3.95; N, 9.69%; IR(KBr): 3360 (NH), 3018 (Ar C-H), 2964 and 2852 (CH\(_3\), C-H), 1745 and 1714 (C=O, \( \beta \)-lactam ring), 1695 and 1678 (NH-C=O), 1506, 1355 (C-N), 1261, 1026 (C-O), 692 cm\(^{-1}\) (C-Cl); \(^1\)H NMR (CDCl\(_3\) + DMSO-\(d_6\)): \( \delta \) 8.49 (s, 1H, -NH), 7.82-6.93 (m, 8H, Ar-H + 4H, 4-N,N-dimethyl phenyl ring), 6.83 (s, 2H, CH=CH), 6.70 (d, \( J=10.45 \) Hz, 1H, N-CH-Cl), 4.36 (s, 9H, -OCH\(_3\)).

5H-Dibenzo(b,f)azepine-5-carboxylic acid [3-chloro-2-(4,N,N-dimethylphenyl)-4-oxoazetidin-1-yl]amide 4e: Red coloured compound, yield 70%, m.p. 158°C; TLC (ethyl acetate : carbon tetrachloride, 7:3, Rf 0.50). Anal. Found: C, 68.10; H, 4.98; N, 12.18. \( \text{C}_{25}\text{H}_{23}\text{ClN}_{5}\text{O}_{5} \) requires C, 67.12; H, 4.88; N, 10.12%; IR(KBr): 3344 (NH), 3008 (Ar C-H), 1735 and 1724 (C=O, \( \beta \)-lactam ring), 1692 and 1680 (NH-C=O), 1512, 1355 (C-N), 1250, 1023 (C-O), 690 cm\(^{-1}\) (C-Cl); \(^1\)H NMR (CDCl\(_3\) + DMSO-\(d_6\)): \( \delta \) 8.70 (s, 1H, -NH), 7.95-6.96 (m, 8H, Ar-H + 4H, 4-N,N-dimethyl phenyl ring), 6.83 (s, 2H, CH=CH), 6.70 (d, \( J=10.45 \) Hz, 1H, Ar-CH-N), 4.90 (d, \( J=10.15 \) Hz, 1H, N-CH-Cl), 3.65 (s, 6H, N(CH\(_3\))\(_2\)).

5H-Dibenzo(b,f)azepine-5-carboxylic acid [3-chloro-2-(2-nitrophenyl)-4-oxoazetidin-1-yl]amide 4f: Red coloured compound, yield 61%, m.p. 196°C; TLC (ethyl acetate : carbon tetrachloride, 7:3, Rf 0.55). Anal. Found: C, 62.58; H, 3.66; N, 12.14. \( \text{C}_{26}\text{H}_{19}\text{ClN}_{3}\text{O}_{2} \) requires C, 62.54; H, 3.69; N, 12.16%; IR(KBr): 3350 (NH), 3018 (Ar C-H), 2964 and 2852 (CH\(_3\), C-H), 1740 and 1714 (C=O, \( \beta \)-lactam ring), 1697 and 1681 (NH-C=O), 1506, 1361 (C-N), 1261, 1026 (C-O), 692 cm\(^{-1}\) (C-Cl); \(^1\)H NMR (CDCl\(_3\) + DMSO-\(d_6\)): \( \delta \) 8.66 (s, 1H, -NH), 7.82-7.19 (m, 8H, Ar-H + 2H, 3,4,5-tri OCH\(_3\) phenyl ring), 6.79 (s, 2H, CH=CH), 6.72 (d, \( J=10.51 \) Hz, 1H, Ar-CH-N), 4.87 (d, \( J=10.19 \) Hz, 1H, N-CH-Cl), 3.84 (s, 9H, -OCH\(_3\)).

5H-Dibenzo(b,f)azepine-5-carboxylic acid [3-chloro-2-oxo-4-(3,4,5-trimethoxy phenyl)azetidin-1-yl]amide 4i: Faint yellow coloured compound, yield 68%, m.p.155°C; TLC (ethyl acetate : carbon tetrachloride, 7:3, Rf 0.61). Anal. Found: C, 64.30; H, 4.70; N, 8.40. \( \text{C}_{27}\text{H}_{23}\text{ClN}_{3}\text{O}_{5} \) requires C, 64.10; H, 4.78; N, 8.31%; IR(KBr): 3359 (NH), 3008 (Ar C-H), 2964 and 2852 (CH\(_3\), C-H), 1745 and 1714 (C=O, \( \beta \)-lactam ring), 1697 and 1681 (NH-C=O), 1506, 1361 (C-N), 1261, 1026 (C-O), 692 cm\(^{-1}\) (C-Cl); \(^1\)H NMR (CDCl\(_3\) + DMSO-\(d_6\)): \( \delta \) 8.52 (s, 1H, -NH), 7.79-7.19 (m, 8H, Ar-H + 2H, 3,4,5-tri OCH\(_3\) phenyl ring), 7.17 (s, 2H, CH=CH), 6.74 (d, \( J=10.51 \) Hz, 1H, Ar-CH-N), 4.87 (d, \( J=10.19 \) Hz, 1H, N-CH-Cl), 3.84 (s, 9H, -OCH\(_3\)).

5H-Dibenzo(b,f)azepine-5-carboxylic acid [3-chloro-2-oxo-4-(3-methoxy-4-hydroxy phenyl)-4-oxoazetidin-1-yl]amide 4j: Light red coloured compound, yield 65%, m.p.126°C; TLC (ethyl acetate : carbon tetrachloride, 7:3, Rf 0.44). Anal. Found: C, 65.15; H, 4.27; N, 9.01. \( \text{C}_{25}\text{H}_{20}\text{ClN}_{4}\text{O}_{4} \) requires C, 65.11; H, 4.36; N, 9.10%; IR (KBr): 3360 (NH), 3018 (Ar C-H), 2964 and 2852 (CH\(_3\), C-H), 1740 and 1718 (C=O, \( \beta \)-lactam ring), 1690 and 1680 (NH-C=O), 1510, 1365 (C-N), 1261, 1026 (C-O), 690 cm\(^{-1}\) (C=O); \(^1\)H NMR (CDCl\(_3\) + DMSO-\(d_6\)): \( \delta \) 8.49 (s, 1H, -NH), 7.82-6.90 (m, 8H, Ar-H + 3H, 3-OCH\(_3\), 4-OH phenyl ring), 6.85 (s, 2H, CH=CH), 6.72 (d, \( J=10.51 \) Hz, 1H, Ar-CH-N), 4.81 (d, \( J=10.20 \) Hz, 1H, N-CH-Cl), 3.84 (s, 3H, -OCH\(_3\)).

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