

Section I

Chapter 4: Results and Discussion

4. Results and Discussion

The work carried out towards achieving the proposed plan has been discussed under the following two main headings:

1. Chemical Studies
2. Biological Studies

4.1 Chemical Studies

To synthesize the envisaged compounds research schemes were planned and discussed under the following headings:

4.1.1 Synthesis of 3-Methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one derivatives

- 4.1.1.1 Synthesis of 3-methyl-4,5-dihydro-3*H*-benzo[*d*]azepine-1,2-dione (**4**)
- 4.1.1.2 Synthesis of 1-hydroxy-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**5**)
- 4.1.1.3 Synthesis of 3-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-1-yl methanesulfonate (**6**)
- 4.1.1.4 Synthesis of 1-amino substituted 3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one derivatives (**7-24**)
- 4.1.1.5 Synthesis of 1-oxy substituted 3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one derivatives (**25-27**)

4.1.2 Synthesis of 3-Ethyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one derivatives

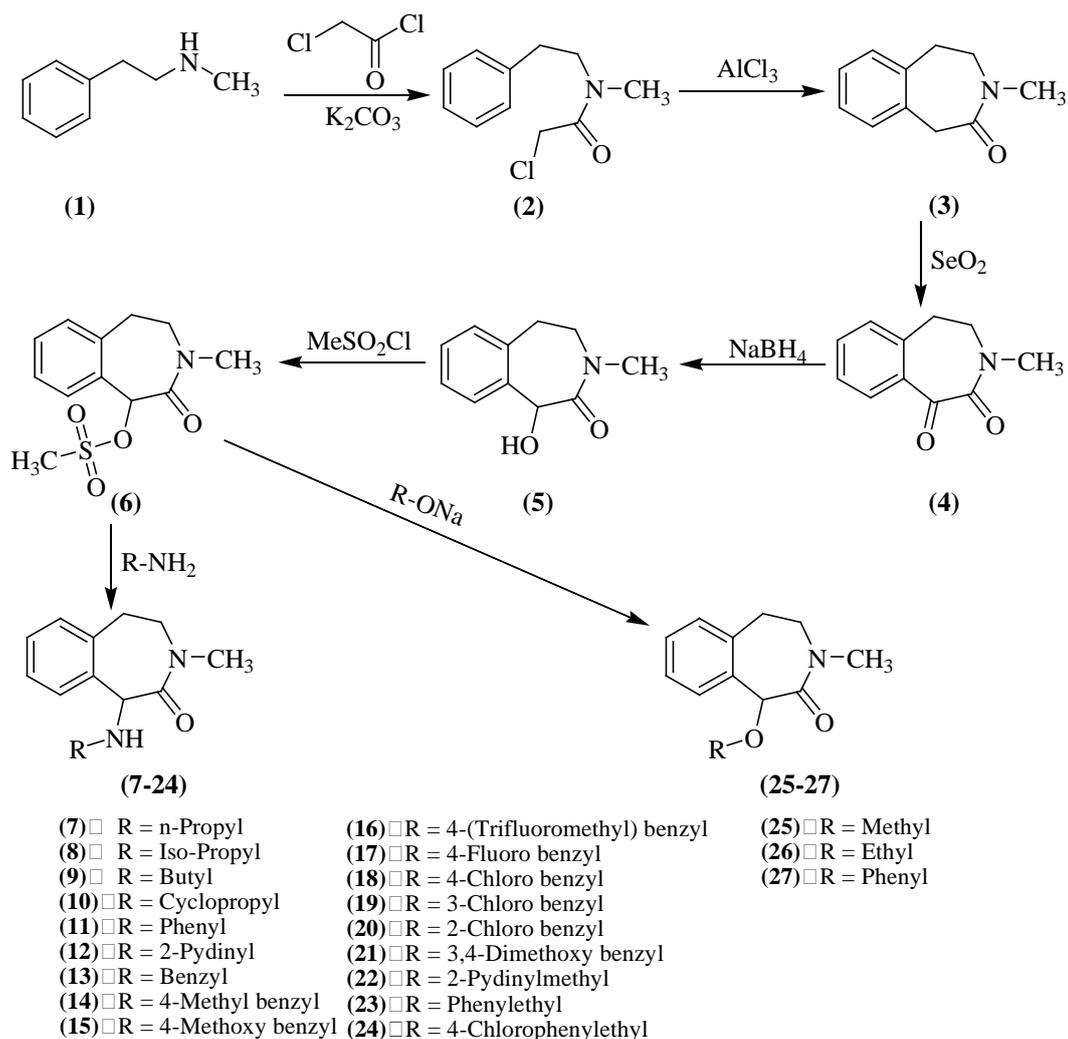
- 4.1.2.1 Synthesis of 3-ethyl-4,5-dihydro-3*H*-benzo[*d*]azepine-1,2-dione (**31**)
- 4.1.2.2 Synthesis of 3-ethyl-1-hydroxy-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**32**)
- 4.1.2.3 Synthesis of 3-ethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-1-yl methanesulfonate (**33**)
- 4.1.2.4 Synthesis of 1-amino substituted 3-ethyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one derivatives (**34-48**)

4.1.3 Synthesis of 1-imino derivatives of 3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**49-63**)

4.1.1 Synthesis of 3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one derivatives

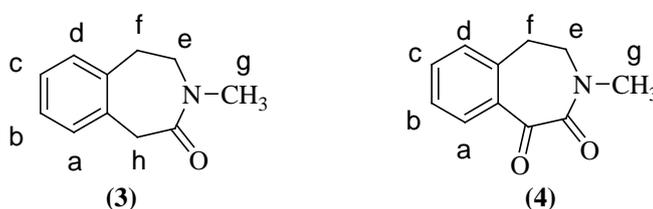
4.1.1.1 Synthesis of 3-methyl-4,5-dihydro-3*H*-benzo[*d*]azepine-1,2-dione (4)

Synthesis of 3-methyl-4,5-dihydro-3*H*-benzo[*d*]azepine-1,2-dione (4) was carried out by the method reported by Nair *et al.*²¹¹ for the synthesis of 3-methylbenzazepine. Commercially available 40% aqueous solution of methylamine was taken for the nucleophilic substitution with 2-phenylethyl bromide for the synthesis of secondary amine *N*-methyl-2-phenylethylamine (1). The secondary amine (1) on reaction with chloroacetyl chloride gave 2-chloro-*N*-methyl-*N*-phenethylacetamide (2) in the biphasic chloroform:water solvent system. The biphasic solvent system not only improves the total yield of the product but it also helps in the easy workup as the entire product goes into organic layer which on separation gave the intermediate (2) with enough purity for the next reaction. The compound (2) was confirmed by the absence of secondary amine peak and presence of intense peak of carbonyl stretching at 1652 cm⁻¹.



Scheme 4.1: Synthesis of 3-Methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one derivatives

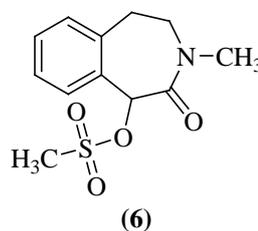
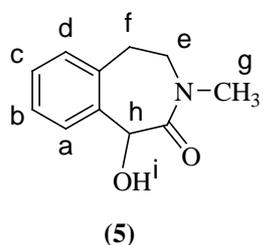
A solution of 2-chloro-*N*-methyl-*N*-phenethylacetamide in 1,2-DCB was used in Friedel-Crafts alkylation using anhydrous AlCl₃ for the synthesis of 3-methyltetrahydro-3*H*-benzazepin-2-one (**3**) as shown in the scheme 4.1. The reaction can also be carried out by fusion of 2-chloro-*N*-methyl-*N*-phenethylacetamide and anhydrous AlCl₃ without using any solvent for nearly one hour at 165 °C. The cyclized product benzazepine (**3**) showed characteristic intense peak of C=O stretching at 1645 cm⁻¹ in its IR spectrum. ¹H-NMR spectrum showed peaks at δ 7.26 (d, 1H, ArH_a), 7.19-7.12 (m, 2H, ArH_{b,c}), 7.10 (d, 1H, ArH_d), 3.90 (s, 2H, CH_{2h}), 3.72-3.69 (m, 2H, CH_{2e}), 3.15-3.12 (m, 2H, CH_{2f}) and 3.02 (s, 3H, CH_{3g}). Its mass spectrum showed molecular ion peak at 175.



Substitution at C-1 position on 3-benzazepine structure requires strong basic conditions with 3-benzazepin-2-one and this can afford limited number of functional groups on the ring.^{56,57} Therefore, inspired by the work of Saintruf and Bourgead,⁵⁸ we thought of oxidizing the α -carbon of the cyclic amide of the benzazepine ring. They have used SeO₂ to convert homophthalimides a six membered ring structure into phthalonimides. The same method using SeO₂ as the oxidizing agent was adopted for the seven membered ring, 3-methyltetrahydro-3*H*-benzazepin-2-one (**3**) to obtain 3-methyl-4,5-dihydro-3*H*-benzo[*d*]azepine-1,2-dione (**4**) using dioxane as a solvent. Compound (**4**) was characterized as it showed characteristic carbonyl stretching at 1690 cm⁻¹ and 1657 cm⁻¹ for two C=O groups along with other IR peaks. Its PMR spectrum showed similar peaks as compound (**3**) but the 2 protons near to the α -carbon of the cyclic amide were absent confirming the formation of the dione (**4**). ¹H-NMR spectrum showed peaks at δ 7.76 (d, 1H, ArH_a), 7.52-7.48 (m, 1H, ArH_b), 7.36-7.33 (m, 1H, ArH_c), 7.27 (d, 1H, ArH_d), 3.74-3.72 (m, 2H, CH_{2e}), 3.26-3.24 (m, 2H, CH_{2f}) and 3.13 (s, 3H, CH_{3g}). Its mass spectrum showed molecular ion peak at 189.44.

4.1.1.2 Synthesis of 1-hydroxy-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**5**)

1-Hydroxy-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**5**) was prepared by the reduction of the 3-methyl-4,5-dihydro-3*H*-benzo[*d*]azepine-1,2-dione (**4**) using a mild reducing agent NaBH₄ (sodium borohydride). Compound (**5**) showed characteristic broad peak for hydroxyl group at 3424 cm⁻¹ and C=O stretching at 1664 cm⁻¹ along with other IR peaks. Its PMR spectrum showed doublets at δ 5.71 with the *J* value 5.1 Hz along with δ 4.55 with *J* value 5.1 Hz indicating the hydroxy proton and C-1 proton respectively. ¹H-NMR spectrum showed peaks at δ 7.77 (d, 1H, ArH_a), 7.28-7.18 (m, 2H, ArH_{b,c}), 7.10 (d, 1H, ArH_d), 5.71 (d, 1H, OH_i), 4.55 (d, 1H, CH_h), 4.05-3.99 (m, 1H, CH_{2e}), 3.33-3.06 (m, 3H, CH_{2e}, CH_{2f}) and 3.04 (s, 3H, CH_{3g}). Its mass spectrum showed molecular ion peak at 191.31.



4.1.1.3 Synthesis of 3-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-1-yl methanesulfonate (**6**)

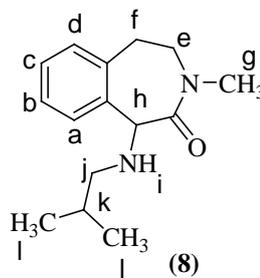
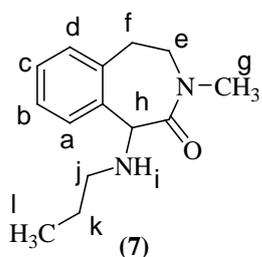
Mesylation of 1-hydroxy-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**5**) was carried out for the conversion of the poor leaving group -OH to a better leaving group mesylate ester using methansulfonyl chloride to afford 3-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-1-yl methanesulfonate (**6**). Compound (**6**) showed characteristic IR peaks at 1657 (C=O str), 1397 (C-N str) and 752 cm⁻¹ (*o*-disubstituted benzene ring) with absence of hydroxyl group peak. Its mass spectrum showed molecular ion peak at 269.31.

4.1.1.4 Synthesis of 1-amino substituted 3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one derivatives (**7-24**)

For the synthesis of 1-amino substituted 3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one derivatives, 3-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-1-yl methanesulfonate (**6**) was taken under nitrogen environment with anhydrous K₂CO₃ and different amines. Reaction completes with the substitution at C-1 position with different amines offering C-1 substituted compounds. It was observed that all of the synthesized compounds were racemic mixtures showing no optical rotation. In order to get better

structure activity correlation, different aliphatic and aromatic amines were used. All the synthesized compounds so obtained were purified by column chromatography on silica gel using hexane/ether solvent system and characterized before their biological evaluation.

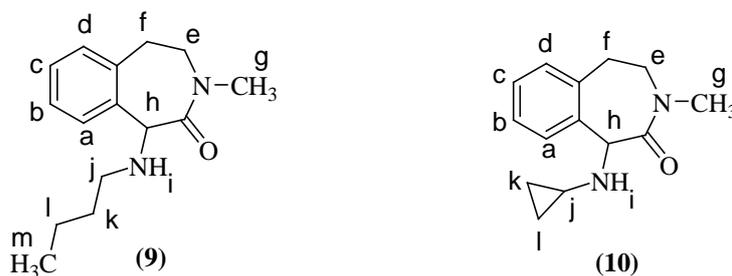
3-Methyl-1-propylamino-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**7**) was synthesized by reacting compound (**6**) with *n*-propylamine. It showed characteristic IR peaks at 3129 (N-H str), 1657 (C=O str), 1399 (C-N str) and 748 cm⁻¹ (*o*-disubstituted benzene ring). ¹H-NMR spectrum showed peaks at δ 7.68 (d, 1H, ArH_a), 7.23-7.15 (m, 2H, ArH_{b,c}), 7.09 (d, 1H, ArH_d), 4.88 (s, 1H, CH_h), 4.09-4.02 (m, 1H, CH_{2e}), 3.59-3.53 (m, 1H, CH_{2e}), 3.28-3.06 (m, 2H, CH_{2f}), 3.01 (s, 3H, NCH_{3g}), 2.73-2.67 (m, 1H, CH_{2j}), 2.56-2.50 (m, 1H, CH_{2j}), 1.97 (bs, 1H, NH_i), 1.64-1.55 (m, 2H, CH_{2k}) and 0.97 (t, 3H, CH_{3l}) Its mass spectrum showed M-1 peak at 231.22.



1-Isobutylamino-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**8**) was synthesized by reacting compound (**6**) with isobutylamine. It showed characteristic IR peaks at 3130 (N-H str), 1658 (C=O str), 1399 (C-N str) and 746 cm⁻¹ (*o*-disubstituted benzene ring). ¹H-NMR spectrum of the compound (**8**) showed peaks at δ 7.71 (d, 1H, ArH_a), 7.23-7.15 (m, 2H, ArH_{b,c}), 7.09 (d, 1H, ArH_d), 4.84 (s, 1H, CH_h), 4.06-3.99 (m, 1H, CH_{2e}), 3.61-3.58 (m, 1H, CH_{2e}), 3.23-3.06 (m, 2H, CH_{2f}), 3.01 (s, 3H, CH_{3g}), 2.58-2.54 (m, 1H, CH_{2j}), 2.38-2.28 (m, 1H, CH_{2j}), 2.17 (bs, 1H, NH_i), 1.85-1.79 (m, 1H, CH_k) and 0.98 (d, 6H, CH_{3l}). Its mass spectrum showed molecular ion peak at 246.4.

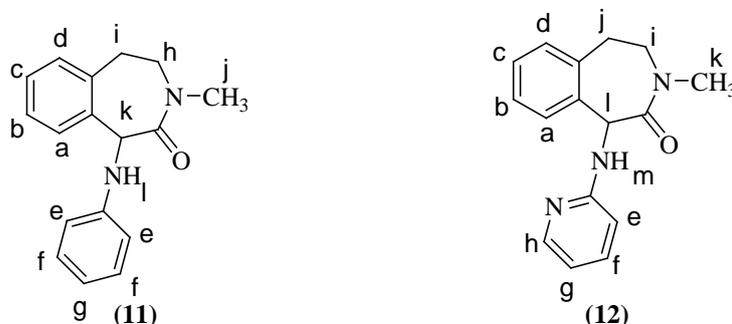
1-Butylamino-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**9**) was synthesized by reacting compound (**6**) with *n*-butylamine. It showed characteristic IR peaks at 3416 (N-H str), 1658 (C=O str), 1399 (C-N str) and 746 cm⁻¹ (*o*-disubstituted benzene ring). ¹H-NMR spectrum of the compound (**9**) showed peaks at δ 7.67 (d, 1H, ArH_a), 7.26-7.15 (m, 2H, ArH_{b,c}), 7.09 (d, 1H, ArH_d), 4.87 (s, 1H, CH_h), 4.09-4.01 (m, 1H, CH_{2e}), 3.60-3.53 (m, 1H, CH_{2e}), 3.28-3.06 (m, 2H, CH_{2f}), 3.01 (s, 3H, CH_{3g}), 2.75-2.69 (m, 1H, CH_{2j}), 2.57-2.53 (m, 1H, CH_{2j}), 2.03 (bs, 1H, NH_i), 1.60-1.55 (m, 2H, CH_{2k}),

1.46-1.39 (m, 2H, CH_{2l}) and 0.93 (t, 3H, CH_{3m}). Its mass spectrum showed molecular ion peak at 246.55.



1-Cyclopropylamino-3-methyl-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (**10**) was synthesized by reacting compound (**6**) with cyclopropylamine. It showed characteristic IR peaks at 3298 (N-H str), 1648 (C=O str), 1397 (C-N str) and 754 cm^{-1} (*o*-disubstituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**10**) showed peaks at δ 7.59 (dd, 1H, ArH_a), 7.19-7.13 (m, 2H, $ArH_{b,c}$), 7.09 (d, 1H, ArH_d), 5.05 (s, 1H, CH_h), 4.20-4.12 (m, 1H, CH_{2e}), 3.51-3.45 (m, 1H, CH_{2e}), 3.22-3.15 (m, 2H, CH_{2f}), 3.03 (s, 3H, CH_{3g}), 2.86 (bs, 1H, NH_i), 2.31-2.27 (m, 1H, CH_j) 0.57-0.47 (m, 2H, CH_{2k}) and 0.45-0.30 (m, 2H, CH_{2l}). Its mass spectrum showed molecular ion peak at 230.7.

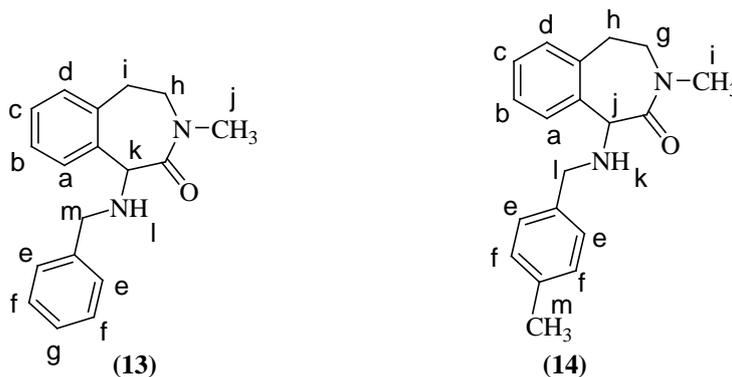
3-Methyl-1-phenylamino-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (**11**) was synthesized by reacting compound (**6**) with aniline. It showed characteristic IR peaks at 3362 (N-H str), 1660 (C=O str), 1400 (C-N str) and 751 & 693 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**11**) showed peaks at δ 7.51 (d, 1H, ArH_a), 7.25-7.11 (m, 5H, $ArH_{b,c,d,e}$), 6.69 (t, 1H, ArH_g), 6.53 (d, 2H, ArH_f), 5.67 (bs, 1H, NH_l), 5.55 (d, 1H, CH_k), 4.24-4.18 (m, 1H, CH_{2h}), 3.43-3.36 (m, 2H, CH_{2h} , CH_{2i}), 3.23-3.17 (m, 1H, CH_{2i}) and 3.05 (s, 3H, CH_{3j}). Its mass spectrum showed molecular ion peak at 266.41.



3-Methyl-1-(pyridin-2-ylamino)-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (**12**) was synthesized by reacting compound (**6**) with 2-aminopyridine. It showed characteristic

IR peaks at 3486 (N-H str), 1640 (C=O str), 1400 (C-N str) and 747 & 693 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**12**) showed peaks at δ 8.55-8.53 (d, 1H, NH_m), 7.78-7.09 (m, 8H, $\text{ArH}_{a,b,c,d,e,f,g,h}$), 5.29 (d, 1H, CH_l), 4.18-4.14 (m, 1H, CH_{2i}), 4.01-3.92 (m, 1H, CH_{2i}), 3.19-3.18 (m, 2H, CH_{2j}) and 3.01 (s, 3H, CH_{3k}). Its mass spectrum showed molecular ion peak at 267.3.

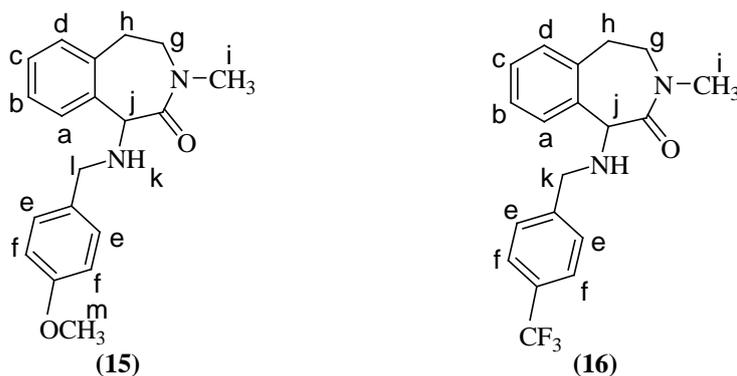
1-Benzylamino-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**13**) was synthesized by reacting compound (**6**) with benzylamine. It showed characteristic IR peaks at 3305 (N-H str), 1666 (C=O str), 1399 (C-N str) and 749 & 700 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**13**) showed peaks at δ 7.80 (d, 1H, ArH_a), 7.41 (d, 2H, ArH_e), 7.33-7.15 (m, 5H, $\text{ArH}_{b,c,f,g}$), 7.08 (d, 1H, ArH_d), 4.93 (s, 1H, CH_k), 4.04-3.96 (m, 2H, CH_{2h} , CH_{2m}), 3.77 (d, 1H, CH_{2m}), 3.51-3.48 (m, 1H, CH_{2h}), 3.17-3.12 (m, 2H, CH_{2i}), 3.03 (s, 3H, CH_{3j}) and 2.65 (bs, 1H, NH_l). Its mass spectrum showed M-1 ion peak at 278.81.



The compound 3-methyl-1-(4-methylbenzyl)amino-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**14**) was synthesized by reacting compound (**6**) with 4-methylbenzylamine. It showed characteristic IR peaks at 3305 (N-H str), 1657 (C=O str), 1396 (C-N str) and 755 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**14**) showed peaks at δ 7.68 (d, 1H, ArH_a), 7.22 (d, 2H, ArH_e , $J = 7.8$ Hz), 7.18-7.06 (m, 2H, $\text{ArH}_{b,c}$), 7.05 (d, 2H, ArH_f , $J = 7.8$ Hz), 7.00 (d, 1H, ArH_d), 4.88 (s, 1H, CH_j), 3.95-3.89 (m, 1H, CH_{2g}), 3.86 (d, 1H, CH_{2i} , $J = 13.0$ Hz), 3.67 (d, 1H, CH_{2i} , $J = 13.0$ Hz), 3.46-3.39 (m, 1H, CH_{2g}), 3.24 (bs, 1H, NH_k), 3.13-3.04 (m, 2H, CH_{2h}), 2.94 (s, 3H, CH_{3i}) and 2.25 (s, 3H, CH_{3m}). Its mass spectrum showed M-1 ion peak at 293.42.

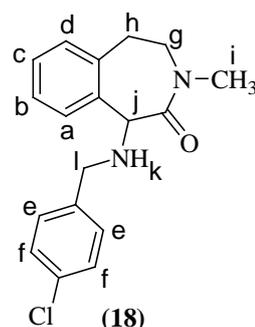
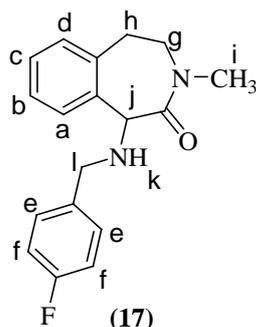
The compound 1-(4-methoxybenzyl)amino-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**15**) was synthesized by reacting compound (**6**) with 4-

methoxybenzylamine. It showed characteristic IR peaks at 3415 (N-H str), 1655 (C=O str), 1400 (C-N str) and 753 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound **(15)** showed peaks at δ 7.77 (d, 1H, ArH_a), 7.33 (d, 2H, ArH_e , $J = 8.6\text{ Hz}$), 7.25-7.15 (m, 2H, $\text{ArH}_{b,c}$), 7.08 (d, 1H, ArH_d), 6.86 (d, 2H, ArH_f , $J = 8.6\text{ Hz}$), 4.92 (s, 1H, CH_j), 4.04-3.96 (m, 1H, CH_{2g}), 3.90 (d, 1H, CH_{2i} , $J = 12.8\text{ Hz}$), 3.79 (s, 3H, CH_{3m}), 3.70 (d, 1H, CH_{2l} , $J = 12.8\text{ Hz}$), 3.52-3.48 (m, 1H, CH_{2g}), 3.17-3.12 (m, 2H, CH_{2h}), 3.02 (s, 3H, CH_{3i}) and 2.20 (bs, 1H, NH_k). Its mass spectrum showed M-2 ion peak at 307.65.



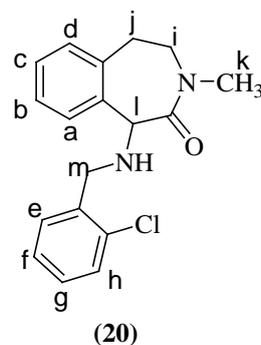
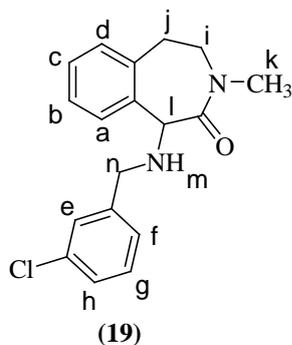
The compound 3-methyl-1-(4-trifluoromethylbenzyl)amino-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (**(16)**) was synthesized by reacting compound **(6)** with 4-trifluoromethylbenzylamine. It showed characteristic IR peaks at 3197 (N-H str), 1653 (C=O str), 1401 (C-N str) and 748 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound **(16)** showed peaks at δ 7.51 (d, 1H, ArH_a), 7.43-7.39 (m, 3H, $\text{ArH}_{b,e}$), 7.27-7.18 (m, 3H, $\text{ArH}_{c,f}$), 7.14 (d, 1H, ArH_d), 5.04 (s, 1H, CH_j), 4.37-3.30 (m, 1H, CH_{2g}), 3.53-3.47 (m, 1H, CH_{2d}), 3.50 (s, 2H, CH_{2k}), 3.17-3.12 (m, 2H, CH_{2h}) and 3.05 (s, 3H, CH_{3i}). Its mass spectrum showed M+1 ion peak at 349.64.

The compound 1-(4-Fluorobenzyl)amino-3-methyl-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (**(17)**) was synthesized by reacting compound **(6)** with 4-fluorobenzylamine. It showed characteristic IR peaks at 3302 (N-H str), 1658 (C=O str), 1399 (C-N str) and 748 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound **(17)** showed peaks at δ 7.78 (d, 1H, ArH_a), 7.39-7.36 (m, 2H, $\text{ArH}_{b,c}$), 7.24-7.16 (m, 2H, ArH_e), 7.09 (d, 1H, ArH_d), 7.02-6.97 (m, 2H, ArH_f), 4.91 (s, 1H, CH_j), 4.05-3.98 (m, 1H, CH_{2g}), 3.94 (d, 1H, CH_{2i} , $J = 13.1\text{ Hz}$), 3.72 (d, 1H, CH_{2l} , $J = 13.1\text{ Hz}$), 3.50-3.46 (m, 1H, CH_{2g}), 3.18-3.13 (m, 2H, CH_{2h}), 3.03 (s, 3H, CH_{3i}) and 2.61 (bs, 1H, NH_k). Its mass spectrum showed M-2 ion peak at 299.83.



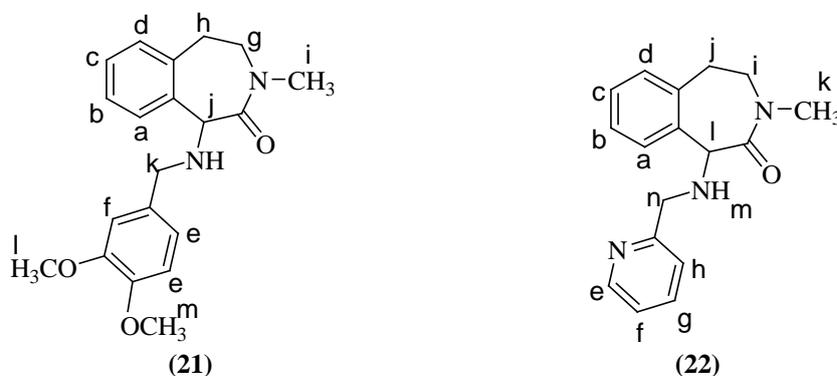
The compound 1-(4-chlorobenzyl)amino-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**18**) was synthesized by reacting compound (**6**) with 4-chlorobenzylamine. It showed characteristic IR peaks at 3302 (N-H str), 1659 (C=O str), 1399 (C-N str) and 746 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**18**) showed peaks at δ 7.78 (d, 1H, ArH_a), 7.35 (d, 2H, ArH_e , $J = 8.4$ Hz), 7.28 (d, 2H, ArH_f , $J = 8.4$ Hz), 7.23-7.16 (m, 2H, $\text{ArH}_{b,c}$), 7.09 (d, 2H, ArH_d), 4.89 (s, 1H, CH_j), 4.04-3.88 (m, 1H, CH_{2g}), 3.96 (d, 1H, CH_{2i} , $J = 13.5$ Hz), 3.72 (d, 1H, CH_{2l} , $J = 13.5$ Hz), 3.49-3.45 (m, 1H, CH_{2g}), 3.18-3.13 (m, 2H, CH_{2h}), 3.03 (s, 3H, CH_{3i}) and 1.59 (bs, 1H, NH_k). Its mass spectrum showed molecular ion peak at 314.28.

The compound 1-(3-chlorobenzyl)amino-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**19**) was synthesized by reacting compound (**6**) with 3-chlorobenzylamine. It showed characteristic IR peaks at 3129 (N-H str), 1659 (C=O str), 1400 (C-N str) and 747 & 684 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**19**) showed peaks at δ 7.79 (d, 1H, ArH_a), 7.42 (s, 1H, ArH_e), 7.31-7.17 (m, 5H, $\text{ArH}_{b,c,f,g,h}$), 7.09 (d, 1H, ArH_d), 4.91 (s, 1H, CH_j), 4.06-4.00 (m, 1H, CH_{2i}), 3.98 (d, 1H, CH_{2n} , $J = 13.5$ Hz), 3.74 (d, 1H, CH_{2n} , $J = 13.5$ Hz), 3.51-3.44 (m, 1H, CH_{2i}), 3.19-3.11 (m, 2H, CH_{2j}) and 3.06 (s, 3H, CH_{3k}). Its mass spectrum showed molecular ion peak at 315.67 ($\text{M}^+ + 1$).



The compound 1-(2-chlorobenzyl)amino-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**20**) was synthesized by reacting compound (**6**) with 2-chlorobenzylamine. It showed characteristic IR peaks at 3129 (N-H str), 1657 (C=O str), 1400 (C-N str) and 746 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**20**) showed peaks at δ 7.79 (d, 1H, ArH_a), 7.42-7.17 (m, 6H, $\text{ArH}_{b,c,e,f,g,h}$), 7.09 (d, 1H, ArH_d), 4.91 (s, 1H, CH_l), 4.06-4.00 (m, 1H, CH_{2i}), 3.97 (d, 1H, CH_{2m} , $J = 13.5$ Hz), 3.73 (d, 1H, CH_{2m} , $J = 13.5$ Hz), 3.50-3.44 (m, 1H, CH_{2i}), 3.18-3.11 (m, 2H, CH_{2j}) and 3.06 (s, 3H, CH_{3k}). Its mass spectrum showed molecular ion peak at 314.89.

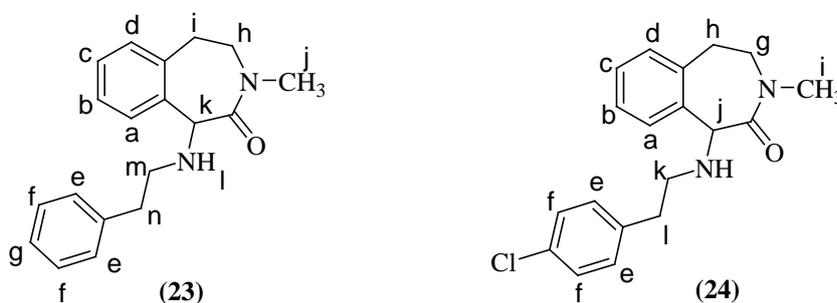
The compound 1-(3,4-dimethoxybenzyl)amino-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**21**) was synthesized by reacting compound (**6**) with 3,4-dimethoxybenzylamine. It showed characteristic IR peaks at 3128 (N-H str), 1657 (C=O str), 1399 (C-N str) and 761 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**21**) showed peaks at δ 7.80 (d, 1H, ArH_a), 7.25-7.16 (m, 2H, $\text{ArH}_{b,c}$), 7.09 (d, 1H, ArH_d), 7.20 (s, 1H, ArH_f), 6.92 (d, 1H, ArH_e , $J = 8.1$ Hz), 6.81 (d, 1H, ArH_e , $J = 8.1$ Hz), 4.94 (s, 1H, CH_j), 4.04-3.98 (m, 1H, CH_{2g}), 3.95 (d, 1H, CH_{2k} , $J = 13.0$ Hz), 3.86 (s, 6H, $\text{CH}_{3l,m}$), 3.76 (d, 1H, CH_{2k} , $J = 13.0$ Hz), 3.48-3.44 (m, 1H, CH_{2g}), 3.17-3.12 (m, 2H, CH_{2h}) and 3.02 (s, 3H, CH_{3i}). Its mass spectrum showed molecular ion peak at 340.18.



The compound 3-methyl-1-((pyridin-2-yl)-methylamino)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**22**) was synthesized by reacting compound (**6**) with 2-amino methyl pyridine. It showed characteristic IR peaks at 3309 (N-H str), 1654 (C=O str), 1399 (C-N str) and 750 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**22**) showed peaks at δ 8.46-8.45 (m, 1H, ArH_b), 7.69 (d, 1H, ArH_a), 7.58-7.54 (m, 1H, ArH_c), 7.42 (d, 1H, ArH_d), 7.19-6.99 (m, 4H, $\text{ArH}_{e,f,g,h}$), 4.89 (s, 1H, CH_l), 4.04 (d, 1H, CH_{2n} , $J = 13.0$ Hz), 3.93-3.87 (m, 1H, CH_{2i}), 3.84 (d, 1H, CH_{2n} , $J = 13.0$ Hz), 3.70 (bs,

1H, NH_m), 3.52-3.46 (m, 1H, CH_{2i}), 3.14-2.98 (m, 2H, CH_{2j}) and 2.93 (s, 3H, CH_{3k}). Its mass spectrum showed molecular ion peak at 281.8.

The compound 3-methyl-1-phenethylamino-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**23**) was synthesized by reacting compound (**6**) with 2-phenethylamine. It showed characteristic IR peaks at 3416 (N-H str), 1656 (C=O str), 1393 (C-N str) and 754 & 699 cm^{-1} (substituted benzene ring). 1H -NMR spectrum of the compound (**23**) showed peak at δ 7.63-7.61 (d, 1H, ArH_a), 7.30-7.13 (m, 7H, $ArH_{b,c,e,f,g}$), 7.09-7.07 (m, 1H, ArH_d), 4.86 (s, 1H, CH_k), 3.24-3.05 (m, 4H, $CH_{2h,i}$), 3.02 (s, 3H, CH_{3j}), 2.99-2.79 (m, 4H, $CH_{2m,n}$) and 1.85 (bs, 1H, NH_l). Its mass spectrum showed M-2 ion peak at 290.61.



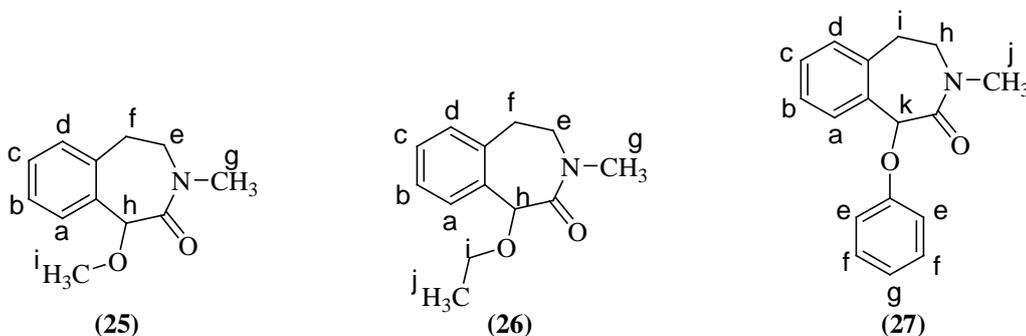
The compound 1-(4-chlorophenethyl)amino-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**24**) was synthesized by reacting compound (**6**) with 2-(4-chlorophenyl)ethylamine. It showed characteristic IR peaks at 3302 (N-H str), 1661 (C=O str), 1398 (C-N str) and 759 cm^{-1} (substituted benzene ring). 1H -NMR spectrum of the compound (**24**) showed peaks at δ 7.61 (d, 1H, ArH_a), 7.25-7.15 (m, 6H, $ArH_{b,c,e,f}$), 7.08 (d, 1H, ArH_d), 4.88 (s, 1H, CH_j), 4.00-3.94 (m, 1H, CH_{2g}), 3.51-3.47 (m, 1H, CH_{2g}), 3.21-3.10 (m, 2H, CH_{2h}), 2.99 (s, 3H, CH_{3j}) and 2.91-2.80 (m, 4H, $CH_{2k,l}$). Its mass spectrum showed M+2 ion peak at 330.87.

4.1.1.5 Synthesis of 1-oxy substituted 3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one derivatives (**25-27**)

Alkyl and phenylether substitution at the C-1 position of the 3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one was carried out by substitution of mesyl group of 3-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-1-yl methanesulfonate (**6**) with sodium salt of alcohols/phenol under nitrogen environment.

The compound 1-methoxy-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**25**) was synthesized by reacting compound (**6**) with sodium methoxide. It showed

characteristic IR peaks at 1654 (C=O str), 1489 (C-N str) 1083 (C-O str) and 749 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**25**) showed peaks at δ 7.42 (d, 1H, ArH_a), 7.27-7.18 (m, 2H, $\text{ArH}_{b,c}$), 7.14 (d, 1H, ArH_d), 5.01 (s, 1H, CH_h), 4.37-4.30 (m, 1H, CH_{2e}), 3.53-3.47 (m, 1H, CH_{2e}), 3.50 (s, 3H, CH_{3g}), 3.17-3.12 (m, 2H, CH_{2f}) and 3.05 (s, 3H, CH_{3i}). Its mass spectrum showed molecular ion peak at 205.9.



The compound 1-ethoxy-3-methyl-4,5-dihydro-1H-benzo[*d*]azepin-2(3H)-one (**26**) was synthesized by reacting compound (**6**) with sodium ethoxide. It showed characteristic IR peaks at 1657 (C=O str), 1398 (C-N str) 1076 (C-O str) and 749 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**26**) showed peak at δ 7.75 (d, 1H, ArH_a), 7.40 (d, 1H, ArH_d), 7.20-7.08 (m, 2H, $\text{ArH}_{b,c}$), 5.07 (s, 1H, CH_h), 4.56-4.44 (m, 1H, CH_{2e}), 4.05-3.57 (m, 2H, CH_{2i}), 3.46-3.40 (m, 1H, CH_{2e}), 3.33-3.07 (m, 2H, CH_{2f}), 3.04 (s, 3H, CH_{3g}) and 1.26 (t, 3H, CH_{3j}). Its mass spectrum showed molecular ion peak combined with sodium ion at 241.8.

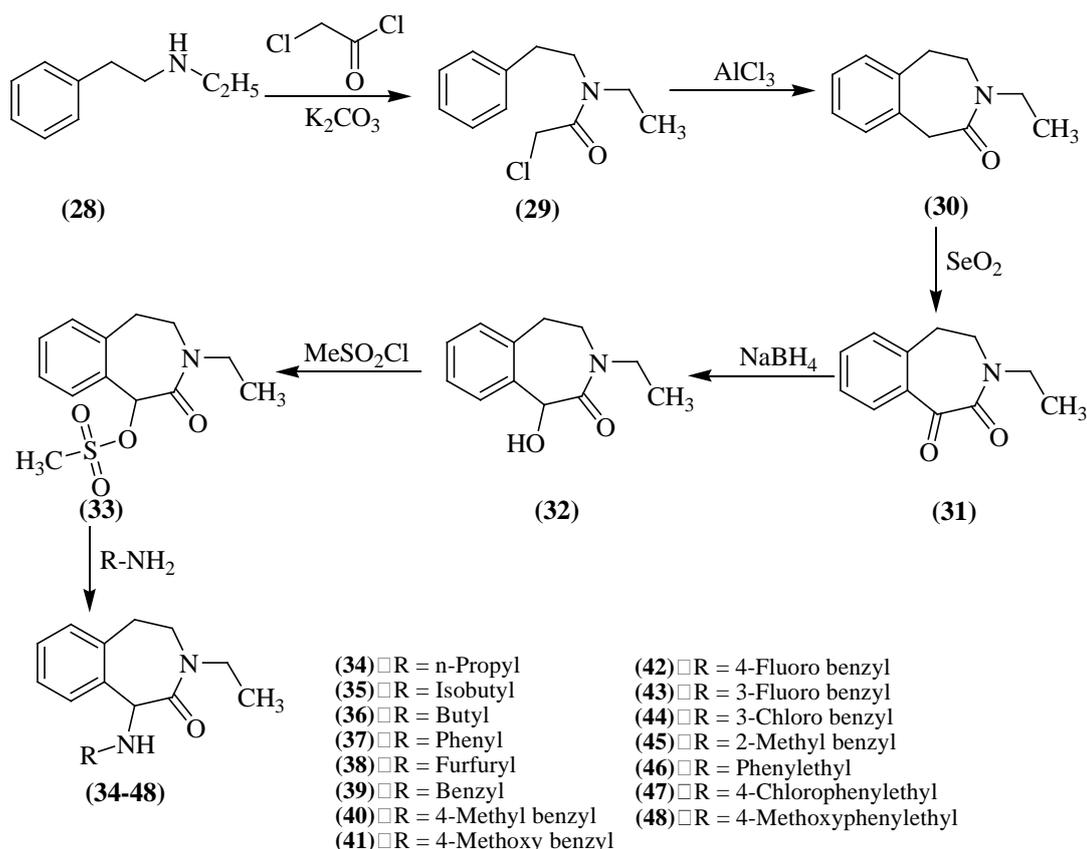
The compound 3-methyl-1-phenoxy-4,5-dihydro-1H-benzo[*d*]azepin-2(3H)-one (**27**) was synthesized by reacting compound (**6**) with sodium phenoxide. It showed characteristic IR peaks at 1655 (C=O str), 1400 (C-N str) 1239 (C-O str) and 753 & 691 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**27**) showed peaks at δ 7.38 (d, 1H, ArH_a), 7.22-6.88 (m, 8H, $\text{ArH}_{b,c,d,e,f,g}$), 5.16 (s, 1H, CH_k), 4.38-4.31 (m, 1H, CH_{2h}), 3.44-3.37 (m, 1H, CH_{2h}), 3.15-3.08 (m, 2H, CH_{2i}) and 2.90 (s, 3H, CH_{3j}). Its mass spectrum showed molecular ion peak at 267.8.

4.1.2 Synthesis of 3-ethyl-4,5-dihydro-1H-benzo[*d*]azepin-2(3H)-one derivatives

4.1.2.1 Synthesis of 3-ethyl-4,5-dihydro-3H-benzo[*d*]azepine-1,2-dione (**31**)

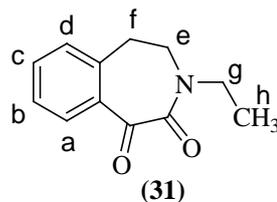
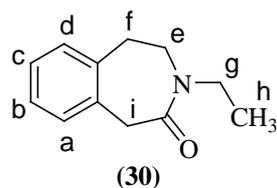
Synthesis of 3-ethyl-4,5-dihydro-3H-benzo[*d*]azepine-1,2-dione (**31**) was carried out by a method similar to that reported earlier for the synthesis of 3-methyl-4,5-dihydro-

3*H*-benzo[*d*]azepine-1,2-dione (**4**). Commercially available 70% aqueous solution of ethylamine was taken for the nucleophilic substitution with 2-Phenylethylbromide for the synthesis of secondary amine *N*-ethyl-2-phenylethylamine (**28**) which showed secondary amine peak at 3443 cm^{-1} . Secondary amine on reaction with chloroacetyl chloride gave 2-chloro-*N*-ethyl-*N*-phenethylacetamide (**29**) in the biphasic chloroform:water solvent system which confirmed by removal of secondary amine peak and showed intense peak of carbonyl stretching at 1650 cm^{-1} .



Scheme 4.2: Synthesis of 3-ethyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one derivatives

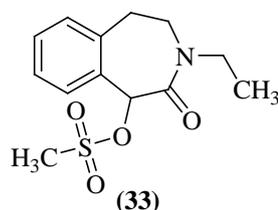
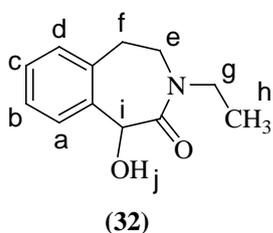
Solution of 2-chloro-*N*-ethyl-*N*-phenethylacetamide in 1,2-DCB was used in Friedel-Crafts alkylation using anhydrous AlCl_3 for the synthesis of 3-ethyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**30**) as shown in the scheme 4.2. The cyclized product was confirmed by melting point and spectral techniques. Its IR spectrum showed characteristic intense peak of $\text{C}=\text{O}$ stretching at 1639 cm^{-1} along with other peaks. $^1\text{H-NMR}$ spectrum of the compound (**30**) showed peaks at δ 7.77-7.75 (m, 1H, ArH_a), 7.52-7.35 (m, 2H, $\text{ArH}_{b,c}$), 7.27-7.25 (m, 1H, ArH_d), 3.89 (s, 2H, CH_{2i}), 3.72- 3.70 (m, 2H, CH_{2e}), 3.58 (q, 2H, CH_{2g}), 3.26-3.24 (m, 2H, CH_{2f}) and 1.26 (t, 3H, CH_{3h}).



The 3-ethyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**30**) was oxidized by selenium oxide, similar to the synthesis of compound (**4**) to afford a white solid compound 3-ethyl-4,5-dihydro-3*H*-benzo[*d*]azepine-1,2-dione (**31**). Compound (**31**) showed characteristic carbonyl stretching at 1729 cm^{-1} and 1658 cm^{-1} for two C=O groups along with other IR peaks. PMR spectrum showed similar peaks as compound (**30**) but the 2 protons near to the α -carbon of the cyclic amide were absent that conformed the formation of the dione. $^1\text{H-NMR}$ spectrum of the compound (**31**) showed peaks at δ 7.76 (d, 1H, ArH_a), 7.50-7.35 (m, 2H, $\text{ArH}_{b,c}$), 7.26 (d, 1H, ArH_d), 3.72-3.70 (m, 2H, CH_{2e}), 3.58 (q, 2H, CH_{2g} , $J = 7.2$ Hz), 3.26-3.24 (m, 2H, CH_{2f}) and 1.26 (t, 3H, CH_{3h} , $J = 7.2$ Hz). Its mass spectrum showed molecular ion peak at 204.1.

4.1.2.2 Synthesis of 3-ethyl-1-hydroxy-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**32**)

3-Ethyl-1-hydroxy-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**32**) was prepared by the reduction of 3-ethyl-4,5-dihydro-3*H*-benzo[*d*]azepine-1,2-dione (**31**) using mild reducing agent NaBH_4 . Compound (**32**) showed characteristic broad peak for hydroxyl group at 3419 cm^{-1} and C=O stretching at 1655 cm^{-1} along with other IR peaks. $^1\text{H-NMR}$ spectrum of the compound (**32**) showed peaks at δ 7.80 (d, 1H, ArH_a), 7.28-7.19 (m, 2H, $\text{ArH}_{b,c}$), 7.09 (d, 1H, ArH_d), 5.73 (d, 1H, OH_j , $J = 5.0$ Hz), 4.53 (d, 1H, CH_i , $J = 5.0$ Hz), 4.09-4.02 (m, 1H, CH_{2e}), 3.67-3.58 (m, 1H, CH_{2e}), 3.49-3.24 (m, 2H, CH_{2g}), 3.17-3.08 (m, 2H, CH_{2f}) and 1.17 (t, 3H, CH_{3h}). Its mass spectrum showed molecular ion peak at 206.1.



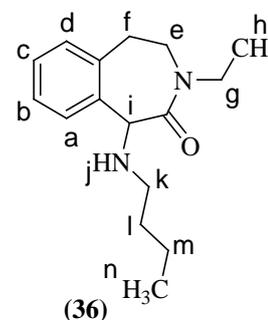
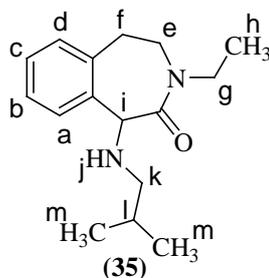
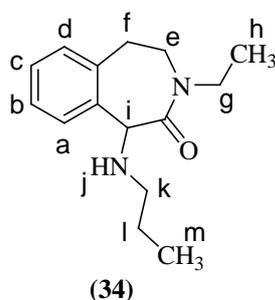
4.1.2.3 Synthesis of 3-ethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-1-yl methanesulfonate (**33**)

Mesylation of 3-ethyl-1-hydroxy-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**32**) was carried out using methansulfonyl chloride to afford 3-ethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-1-yl methanesulfonate (**33**). Compound (**33**) showed characteristic IR peaks at 1655 (C=O str), 1203 (C-N str), 762 cm⁻¹ (*o*-disubstituted benzene ring) with the absence of hydroxyl group peak.

4.1.2.4 Synthesis of 1-amino substituted 3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one derivatives (**34-48**)

For the synthesis of 1-amino substituted 3-ethyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one derivatives, 3-ethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-1-yl-methanesulfonate (**6**) was reacted under nitrogen environment with anhydrous K₂CO₃ and different amines. Reaction completes with the substitution at C-1 position with different amines offering C-1 substituted compounds. It was observed that all of the synthesized compounds were obtained as racemic mixtures showing no optical rotation. All of the synthesized compounds so obtained were purified by column chromatography on silica gel using hexane/ether solvent system and characterized before their biological evaluation.

3-Ethyl-1-propylamino-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**34**) was synthesized by reacting compound (**33**) with *n*-propylamine. It showed characteristic IR peaks at 3292 (N-H str), 1648 (C=O str), 1424 (C-N str) and 743 cm⁻¹ (*o*-disubstituted benzene ring). ¹H-NMR spectrum of the compound (**34**) showed peaks at δ 7.60 (d, 1H, ArH_a), 7.14-7.07 (m, 2H, ArH_{b,c}), 7.00 (d, 1H, ArH_d), 4.78 (s, 1H, CH_i), 4.00-3.92 (m, 1H, CH_{2e}), 3.59- 3.53 (m, 1H, CH_{2e}), 3.51-3.30 (m, 2H, CH_{2g}), 3.19-3.01 (m, 2H, CH_{2f}), 2.65-2.59 (m, 1H, CH_{2k}), 2.49-2.43 (m, 1H, CH_{2k}), 1.59-1.47 (m, 2H, CH_{2l}), 1.05 (t, 3H, CH_{3h}) and 0.90 (t, 3H, CH_{3m}). Its mass spectrum showed molecular ion peak at 246.04.

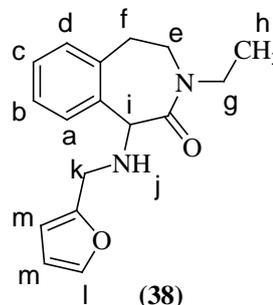
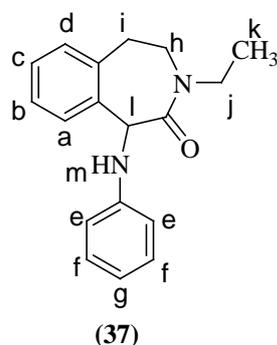


3-Ethyl-1-isobutylamino-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**35**) was synthesized by reacting compound (**33**) with isobutylamine. It showed characteristic IR

peaks at 3292 (N-H str), 1655 (C=O str), 1471 (C-N str) and 753 cm^{-1} (*o*-disubstituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**35**) showed peaks at δ 7.63 (d, 1H, ArH_a), 7.15-7.07 (m, 2H, $\text{ArH}_{b,c}$), 7.00 (d, 1H, ArH_d), 4.75 (s, 1H, CH_i), 3.97-3.90 (m, 1H, CH_{2e}), 3.64- 3.58 (m, 1H, CH_{2e}), 3.49-3.32 (m, 2H, CH_{2g}), 3.19-3.04 (m, 2H, CH_{2f}), 2.51-2.47 (m, 1H, CH_{2k}), 2.33-2.29 (m, 1H, CH_{2k}), 1.80-1.73 (m, 1H, CH_l), 1.06 (t, 3H, CH_{3h}) and 0.94-0.90 (m, 6H, CH_{3m}). Its mass spectrum showed molecular ion peak at 259.86.

1-Butylamino-3-ethyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**36**) was synthesized by reacting compound (**33**) with *n*-butylamine. It showed characteristic IR peaks at 3305 (N-H str), 1657 (C=O str), 1477 (C-N str) and 755 cm^{-1} (*o*-disubstituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**36**) showed peaks at δ 7.59 (d, 1H, ArH_a), 7.15-7.07 (m, 2H, $\text{ArH}_{b,c}$), 7.00 (d, 1H, ArH_d), 4.78 (s, 1H, CH_i), 4.00-3.92 (m, 1H, CH_{2e}), 3.60- 3.32 (m, 3H, $\text{CH}_{2e,g}$), 3.18-3.01 (m, 2H, CH_{2f}), 2.68-2.62 (m, 1H, CH_{2k}), 2.53-2.47 (m, 1H, CH_{2k}), 1.54-1.46 (m, 2H, CH_{2l}), 1.39-1.30 (m, 2H, CH_{2m}), 1.05 (t, 3H, CH_{3h}) and 0.86 (t, 3H, CH_{3n}). Its mass spectrum showed molecular ion peak at 260.11.

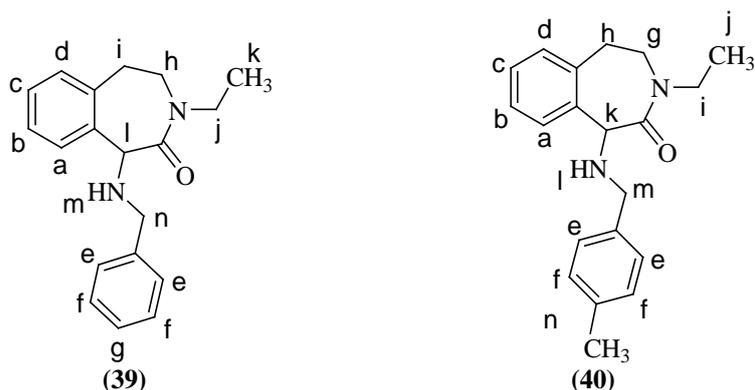
3-Ethyl-1-phenylamino-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**37**) was synthesized by reacting compound (**33**) with aniline. It showed characteristic IR peaks at 3361 (N-H str), 1656 (C=O str), 1499 (C-N str) and $759\text{ \& }692\text{ cm}^{-1}$ (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**37**) showed peaks at δ 7.55 (d, 1H, ArH_a), 7.28-7.15 (m, 5H, $\text{ArH}_{b,c,e,g}$), 6.72 (m, 2H, ArH_f), 6.58 (d, 1H, ArH_d), 5.70 (d, 1H, NH_m), 5.58 (d, 1H, CH_i), 4.28-4.20 (m, 1H, CH_{2h}), 3.70-3.62 (m, 1H, CH_{2h}), 3.51- 3.36 (m, 3H, $\text{CH}_{2j,i}$), 3.28-3.20 (m, 1H, CH_{2i}) and 1.17 (t, 3H, CH_{3k}). Its mass spectrum showed molecular ion peak at 279.11.



3-Ethyl-1-(2-furanylmethylamino)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**38**) was synthesized by reacting compound (**33**) with (furan-2-yl)-methylamine. It showed characteristic IR peaks at 3407 (N-H str), 1654 (C=O str), 1490 (C-N str) and 745 cm^{-1}

(substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**38**) showed peaks at δ 7.73 (d, 1H, ArH_a), 7.38 (m, 1H, ArH_l), 7.24-7.17 (m, 2H, $\text{ArH}_{b,c}$), 7.09 (d, 1H, ArH_d), 6.33-6.32 (m, 1H, ArH_m), 6.24-6.23 (m, 1H, ArH_n), 4.97 (s, 1H, CH_i), 4.06-3.98 (m, 1H, CH_{2e}), 3.95 (d, 1H, CH_{2k}), 3.84 (d, 1H, CH_{2k}), 3.63- 3.52 (m, 2H, CH_{2g}), 3.46-3.39 (m, 1H, CH_{2e}), 3.25-3.14 (m, 2H, CH_{2f}) and 1.14 (t, 3H, CH_{3h}). Its mass spectrum showed molecular ion peak at 284.73.

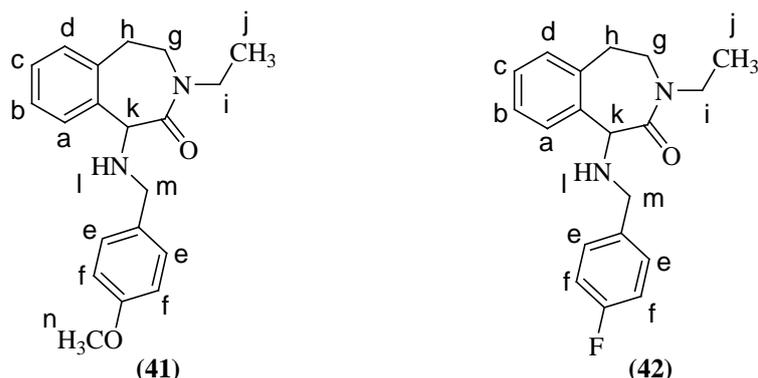
1-Benzylamino-3-ethyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**39**) was synthesized by reacting compound (**33**) with benzylamine. It showed characteristic IR peaks at 3439 (N-H str), 1653 (C=O str), 1425 (C-N str) and 769 & 698 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**39**) showed peaks at δ 7.79 (d, 1H, ArH_a), 7.43-7.41 (m, 2H, $\text{ArH}_{b,c}$), 7.33-7.30 (m, 2H, ArH_e), 7.29-7.27 (m, 1H, ArH_g), 7.25-7.15 (m, 2H, ArH_f), 7.06 (d, 1H, ArH_d), 4.92 (s, 1H, CH_l), 4.02-3.95 (m, 2H, $\text{CH}_{2h,n}$), 3.78 (d, 1H, CH_{2n}), 3.60-3.51 (m, 2H, CH_{2j}), 3.47-3.38 (m, 1H, CH_{2h}), 3.21-3.08 (m, 2H, CH_{2i}) and 1.13 (t, 3H, CH_{3k}). Its mass spectrum showed molecular ion peak at 293.74.



3-Ethyl-1-(4-methylbenzylamino)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**40**) was synthesized by reacting compound (**33**) with 4-methylbenzylamine. It showed characteristic IR peaks at 3283 (N-H str), 1654 (C=O str), 1441 (C-N str) and 744 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**40**) showed peaks at δ 7.77 (d, 1H, ArH_a), 7.30 (d, 2H, ArH_e), 7.25-7.11 (m, 4H, $\text{ArH}_{b,c,f}$), 7.06 (d, 1H, ArH_d), 4.91 (s, 1H, CH_k), 4.01-3.96 (m, 1H, CH_{2g}), 3.92 (d, 1H, CH_{2m}), 3.73 (d, 1H, CH_{2m}), 3.61-3.51 (m, 2H, CH_{2i}), 3.47-3.40 (m, 1H, CH_{2g}), 3.17-3.12 (m, 2H, CH_{2h}), 2.33 (s, 3H, CH_{3n}) and 1.13 (t, 3H, CH_{3j}). Its mass spectrum showed molecular ion peak at 307.44.

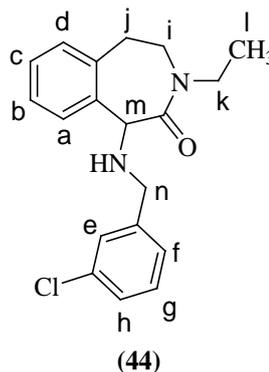
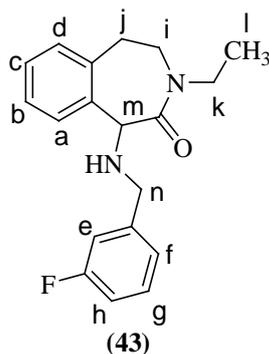
3-Ethyl-1-(4-methoxybenzylamino)- 4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**41**) was synthesized by reacting compound (**33**) with 4-methoxybenzylamine. It showed

characteristic IR peaks at 3283 (N-H str), 1647 (C=O str), 1442 (C-N str) and 744 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**41**) showed peaks at δ 7.76 (d, 1H, ArH_a), 7.34-7.32 (m, 2H, ArH_e), 7.20-7.14 (m, 2H, $\text{ArH}_{b,c}$), 7.07-7.05 (m, 1H, ArH_d), 6.87-6.85 (m, 2H, ArH_f), 4.91 (s, 1H, CH_k), 3.98-3.95 (m, 1H, CH_{2g}), 3.90 (d, 1H, CH_{2m}), 3.79 (s, 3H, CH_{3n}), 3.71 (d, 1H, CH_{2m}), 3.59-3.50 (m, 2H, CH_{2i}), 3.45-3.40 (m, 1H, CH_{2g}), 3.17-3.12 (m, 2H, CH_{2h}) and 1.13 (t, 3H, CH_{3j}). Its mass spectrum showed molecular ion peak at 323.70.



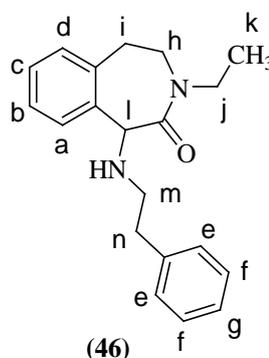
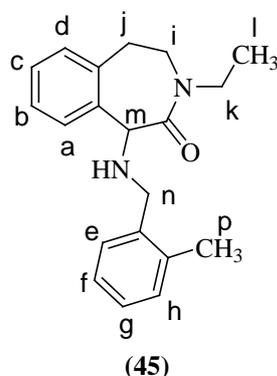
3-Ethyl-1-(4-fluorobenzylamino)-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (**42**) was synthesized by reacting compound (**33**) with 4-fluorobenzylamine. It showed characteristic IR peaks at 3307 (N-H str), 1654 (C=O str), 1508 (C-N str) and 750 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**42**) showed peaks at δ 7.69 (d, 1H, ArH_a), 7.32-7.29 (m, 2H, ArH_e), 7.15-7.07 (m, 2H, $\text{ArH}_{b,c}$), 6.99 (d, 1H, ArH_d), 6.95-6.89 (m, 2H, ArH_f), 4.82 (s, 1H, CH_k), 3.95-3.88 (m, 1H, CH_{2g}), 3.86 (d, 1H, CH_{2m}), 3.65 (d, 1H, CH_{2m}), 3.52-3.43 (m, 2H, CH_{2i}), 3.39-3.30 (m, 1H, CH_{2g}), 3.13-3.05 (m, 2H, CH_{2h}) and 1.05 (t, 3H, CH_{3j}). Its mass spectrum showed molecular ion peak at 311.82.

3-Ethyl-1-(3-fluorobenzylamino)-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (**43**) was synthesized by reacting compound (**33**) with 3-fluorobenzylamine. It showed characteristic IR peaks at 3437 (N-H str), 1652 (C=O str), 1482 (C-N str) and 771 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**43**) showed peaks at δ 7.71 (d, 1H, ArH_a), 7.21-7.07 (m, 5H, $\text{ArH}_{b,c,f,g,h}$), 6.98 (d, 1H, ArH_d), 6.87-6.82 (m, 1H, ArH_e), 4.81 (s, 1H, CH_m), 3.94-3.86 (m, 2H, $\text{CH}_{2i,n}$), 3.67 (d, 1H, CH_{2n}), 3.52-3.42 (m, 2H, CH_{2k}), 3.38-3.30 (m, 1H, CH_{2i}), 3.12-3.04 (m, 2H, CH_{2j}) and 1.05 (t, 3H, CH_{3i}). Its mass spectrum showed molecular ion peak at 311.27.



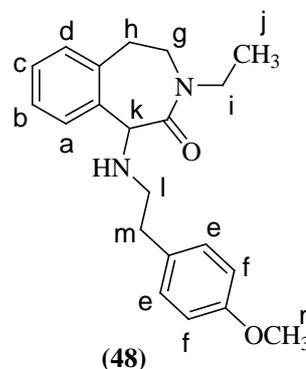
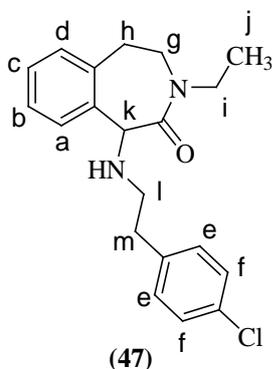
1-(3-Chlorobenzylamino)-3-ethyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**44**) was synthesized by reacting compound (**33**) with 3-chlorobenzylamine. It showed characteristic IR peaks at 3324 (N-H str), 1654 (C=O str), 1477 (C-N str) and 762 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**44**) showed peaks at δ 7.78 (d, 1H, ArH_a), 7.42 (s, 1H, ArH_e), 7.31-7.15 (m, 5H, $\text{ArH}_{b,c,f,g,h}$), 7.07 (d, 1H, ArH_d), 4.89 (s, 1H, CH_m), 4.03-3.94 (m, 2H, $\text{CH}_{2i,n}$), 3.73 (d, 1H, CH_{2n}), 3.60-3.51 (m, 2H, CH_{2k}), 3.46-3.37 (m, 1H, CH_{2i}), 3.21-3.12 (m, 2H, CH_{2j}) and 1.13 (t, 3H, CH_{3l}). Its mass spectrum showed molecular ion peak at 328.51.

3-Ethyl-1-(2-methylbenzylamino)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**45**) was synthesized by reacting compound (**33**) with 2-methylbenzylamine. It showed characteristic IR peaks at 3436 (N-H str), 1654 (C=O str), 1481 (C-N str) and 761 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**45**) showed peaks at δ 7.70 (d, 1H, ArH_a), 7.33-7.31 (m, 1H, ArH_b), 7.17-7.07 (m, 5H, $\text{ArH}_{c,e,f,g,h}$), 6.99 (d, 1H, ArH_d), 4.85 (s, 1H, CH_m), 3.95-3.86 (m, 2H, $\text{CH}_{2i,n}$), 3.67 (d, 1H, CH_{2n}), 3.55-3.44 (m, 2H, CH_{2k}), 3.41-3.34 (m, 1H, CH_{2i}), 3.10-3.05 (m, 2H, CH_{2j}), 2.31 (s, 3H, CH_{3p}) and 1.06 (t, 3H, CH_{3l}). Its mass spectrum showed molecular ion peak at 307.61.



3-Ethyl-1-phenethylamino-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**46**) was synthesized by reacting compound (**33**) with 2-phenethylamine. It showed characteristic IR peaks at 3302 (N-H str), 1650 (C=O str), 1484 (C-N str) and 747 & 702 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**46**) showed peaks at δ 7.62-7.59 (m, 1H, ArH_a), 7.29-7.23 (m, 4H, $\text{ArH}_{b,c,e}$), 7.21-7.13 (m, 3H, $\text{ArH}_{f,g}$), 7.06-7.04 (m, 1H, ArH_d), 4.85 (s, 1H, CH_l), 3.96-3.88 (m, 1H, CH_{2h}) 3.60- 3.45 (m, 3H, $\text{CH}_{2h,m}$), 3.20-2.80 (m, 6H, $\text{CH}_{2j,i,n}$) and 1.10 (t, 3H, CH_{3k}). Its mass spectrum showed molecular ion peak at 308.09.

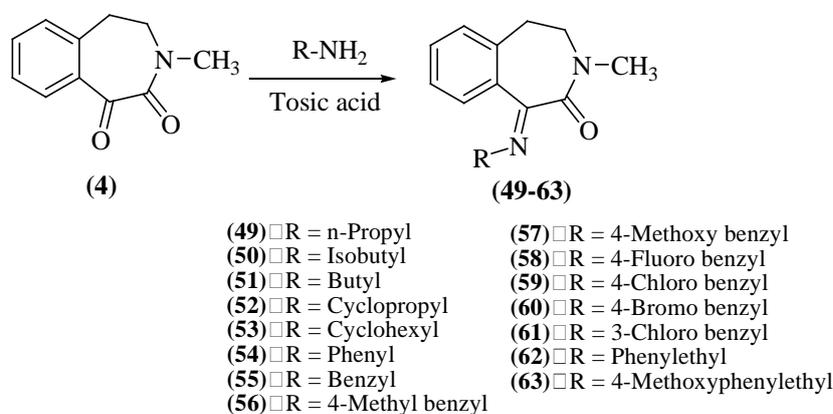
1-(4-Chlorophenethylamino)-3-ethyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**47**) was synthesized by reacting compound (**33**) with 2-(4-chloro)-phenylethylamine. It showed characteristic IR peaks at 3460 (N-H str), 1652 (C=O str), 1496 (C-N str) and 757 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**47**) showed peaks at δ 7.53-7.51 (m, 1H, ArH_a), 7.18-7.16 (m, 2H, ArH_e), 7.12-7.05 (m, 4H, $\text{ArH}_{b,c,f}$), 7.00-6.97 (m, 1H, ArH_d), 4.77 (s, 1H, CH_k), 3.90-3.84 (m, 1H, CH_{2g}), 3.52- 3.39 (m, 4H, $\text{CH}_{2l,m}$), 3.37-3.30 (m, 1H, CH_{2g}), 3.14-3.03 (m, 2H, CH_{2i}), 2.81-2.70 (m, 2H, CH_{2h}) and 1.03 (t, 3H, CH_{3j}). Its mass spectrum showed molecular ion peak at 342.75.



3-Ethyl-1-(4-methoxyphenethylamino)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**48**) was synthesized by reacting compound (**33**) with 2-(4-methoxy)phenylethylamine. It showed characteristic IR peaks at 3439 (N-H str), 1651 (C=O str), 1425 (C-N str) and 766 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**48**) showed peaks at δ 7.53-7.51 (m, 1H, ArH_a), 7.20-7.05 (m, 4H, $\text{ArH}_{b,c,f}$), 6.99-6.97 (m, 1H, ArH_d), 6.77-6.73 (m, 2H, ArH_e), 4.90 (s, 1H, CH_k), 4.33-4.26 (m, 1H, CH_{2g}), 3.70 (s, 3H, CH_{3n}), 3.53-3.29 (m, 4H, $\text{CH}_{2l,m}$), 3.14-3.02 (m, 2H, CH_{2i}), 2.93-2.89 (m, 1H, CH_{2g}), 2.80-2.71 (m, 2H, CH_{2h}) and 1.01 (t, 3H, CH_{3j}). Its mass spectrum showed molecular ion peak at 337.77.

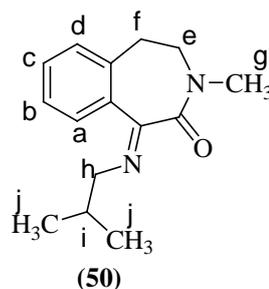
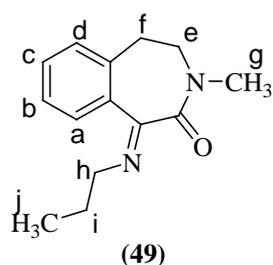
4.1.3 Synthesis of 1-imino derivatives of 3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (49-63)

Synthesis of 1-imino derivatives of 3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one was carried out by reaction of compound (4) with different amines to afford imines as a reaction of carbonyl group with amine. Reaction was explored to different polar and non-polar solvents and boric/tosic acids as proton source but better result was obtained with dry ethanol as solvent and tosic acid as proton source. As the reaction is reversible in nature, yield of the product obtained was less. All the synthesized product was purified by column chromatography using silica gel as stationary phase and hexane:ethylacetate as an eluent.



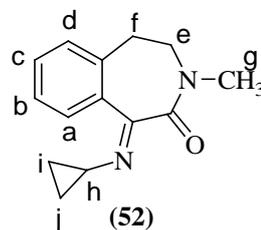
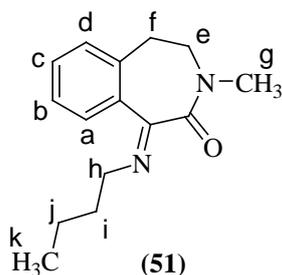
Scheme 4.3: Synthesis of 1-imino derivatives of 3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one

3-Methyl-1-propylimino-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**49**) was synthesized by reaction of compound (4) with *n*-propyl amine in presence of tosic acid. It showed characteristic IR peaks at 1651 (C=O str), 1483 (C=N str) and 745 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**49**) showed peaks at δ 7.56 (d, 1H, ArH_a), 7.34-7.23 (m, 2H, $\text{ArH}_{b,c}$), 7.13 (d, 1H, ArH_d), 3.70 (bs, 2H, CH_{2e}), 3.61 (t, 2H, CH_{2h}), 3.14-3.12 (m, 2H, CH_{2f}), 3.09 (s, 3H, CH_{3g}), 1.85-1.76 (m, 2H, CH_{2i}) and 1.00 (t, 3H, CH_{3j}). Its mass spectrum showed molecular ion peak at 231.3.



1-Isobutylimino-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**50**) was synthesized by reaction of compound (**4**) with isobutylamine in presence of tosic acid. It showed characteristic IR peaks at 1643 (C=O str), 1483 (C=N str) and 745 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**50**) showed peaks at δ 7.56 (d, 1H, ArH_a), 7.33-7.23 (m, 2H, $\text{ArH}_{b,c}$), 7.13 (d, 1H, ArH_d), 3.70 (bs, 2H, CH_{2e}), 3.45 (d, 2H, CH_{2h}), 3.14-3.12 (m, 2H, CH_{2f}), 3.08 (s, 3H, CH_3g), 2.17-2.10 (m, 1H, CH_i) and 1.00 (d, 6H, CH_3j). Its mass spectrum showed molecular ion peak at 245.3.

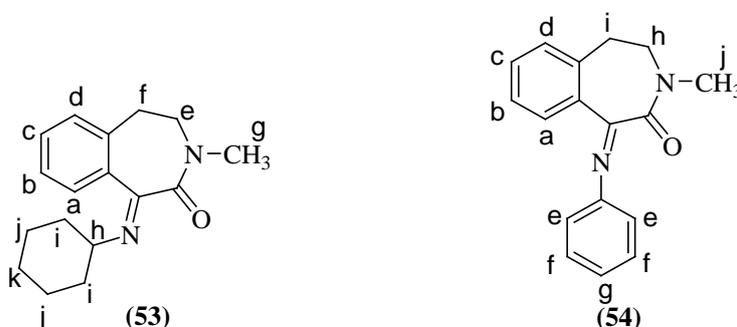
1-Butylimino-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**51**) was synthesized by reaction of compound (**4**) with *n*-butylamine in presence of tosic acid. It showed characteristic IR peaks at 1654 (C=O str), 1564 (C=N str) and 742 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**51**) showed peaks at δ 7.48 (d, 1H, ArH_a), 7.26-7.15 (m, 2H, $\text{ArH}_{b,c}$), 7.05 (d, 1H, ArH_d), 3.62-3.55 (m, 2H, CH_{2h}), 3.57 (t, 2H, CH_{2e}), 3.06 (t, 2H, CH_{2f}), 3.01 (s, 3H, CH_3g), 1.72-1.65 (m, 2H, CH_{2i}), 1.39-1.32 (m, 2H, CH_{2j}) and 0.88 (t, 3H, CH_3k). Its mass spectrum showed molecular ion peak at 245.2.



1-Cyclopropylimino-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**52**) was synthesized by reaction of compound (**4**) with cyclopropylamine in presence of tosic acid. It showed characteristic IR peaks at 1653 (C=O str), 1482 (C=N str) and 745 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**52**) showed peaks at δ 7.51 (d, 1H, ArH_a), 7.31-7.21 (m, 2H, $\text{ArH}_{b,c}$), 7.13 (d, 1H, ArH_d), 3.74 (m, 2H, CH_{2e}),

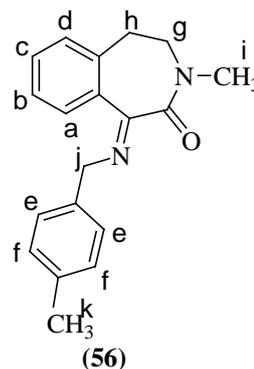
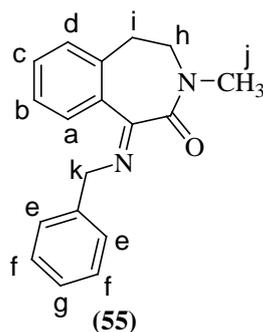
3.35-3.31 (m, 1H, CH_h), 3.15-3.11 (m, 5H, $CH_{2f}CH_{3g}$), 1.07-1.03 (m, 2H, CH_{2i}) and 1.00-0.98 (m, 2H, CH_{2j}). Its mass spectrum showed molecular ion peak at 229.3.

1-Cyclohexylimino-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**53**) was synthesized by reaction of compound (**4**) with cyclohexylamine in presence of tosic acid. It showed characteristic IR peaks at 1641 (C=O str), 1485 (C=N str) and 751 cm^{-1} (substituted benzene ring). 1H -NMR spectrum of the compound (**53**) showed peaks at δ 7.53 (d, 1H, ArH_a), 7.32-7.22 (m, 2H, $ArH_{b,c}$), 7.12 (d, 1H, ArH_d), 3.71 (bs, 2H, CH_{2e}), 3.62-3.5 (m, 1H, CH_h), 3.13 (bs, 2H, CH_{2f}), 3.08 (s, 3H, CH_{3g}), 1.81-1.78 (m, 4H, CH_{2i}), 1.68-1.55 (m, 4H, CH_{2j}) and 1.42-1.23 (m, 2H, CH_{2k}). Its mass spectrum showed molecular ion peak at 271.4.



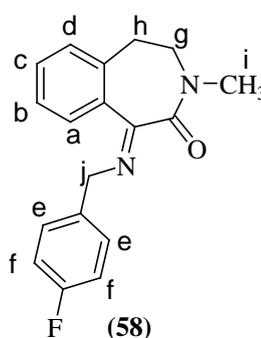
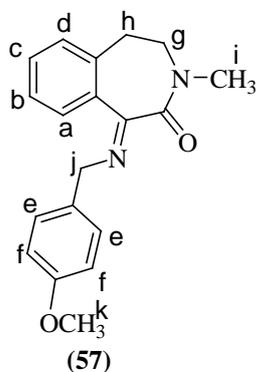
3-Methyl-1-phenylimino-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**54**) was synthesized by reaction of compound (**4**) with aniline in presence of tosic acid. It showed characteristic IR peaks at 1655 (C=O str), 1590 (C=N str) and 755 cm^{-1} (substituted benzene ring). 1H -NMR spectrum of the compound (**54**) showed peaks at δ 7.85 (d, 1H, ArH_a), 7.41-7.11 (m, 7H, $ArH_{b,c,e,f,g}$), 7.01 (d, 1H, ArH_d), 3.88-3.86 (m, 2H, CH_{2h}), 3.23-3.22 (m, 2H, CH_{2i}) and 3.08 (s, 3H, CH_{3j}). Its mass spectrum showed molecular ion peak at 265.2.

1-Benzylimino-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**55**) was synthesized by reaction of compound (**4**) with benzylamine in presence of tosic acid. It showed characteristic IR peaks at 1653 (C=O str), 1595 (C=N str) and 745 cm^{-1} (substituted benzene ring). 1H -NMR spectrum of the compound (**55**) showed peaks at δ 7.61 (d, 1H, ArH_a), 7.43-7.23 (m, 7H, $ArH_{b,c,e,f,g}$), 7.14 (d, 1H, ArH_d), 4.88 (s, 2H, CH_{2k}), 3.64-3.63 (m, 2H, CH_{2h}), 3.13-3.12 (m, 2H, CH_{2i}) and 3.10 (s, 3H, CH_{3j}). Its mass spectrum showed molecular ion peak at 265.2.



1-(4-Methylbenzylimino)-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**56**) was synthesized by reaction of compound (**4**) with 4-methylbenzylamine in presence of tosic acid. It showed characteristic IR peaks at 1656 (C=O str), 1598 (C=N str) and 743 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**56**) showed peaks at δ 7.53 (d, 1H, ArH_a), 7.29-7.05 (m, 7H, $\text{ArH}_{b,c}$), 4.76 (s, 2H, CH_{2g}), 3.56-3.58 (m, 2H, CH_{2d}), 3.07-3.05 (m, 2H, CH_{2e}), 3.03 (s, 3H, CH_{3f}) and 2.26 (s, 3H, CH_{3h}). Its mass spectrum showed molecular ion peak at 265.2.

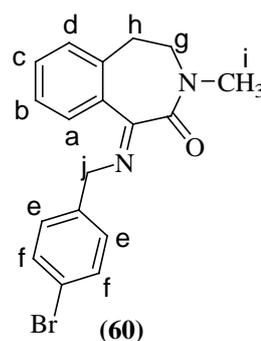
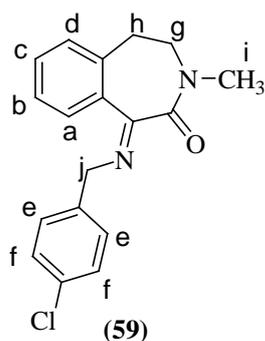
1-(4-Methoxybenzylimino)-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**57**) was synthesized by reaction of compound (**4**) with 4-methoxybenzylamine in presence of tosic acid. It showed characteristic IR peaks at 1659 (C=O str), 1608 (C=N str) and 743 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**57**) showed peaks at δ 7.51 (d, 1H, ArH_a), 7.28-7.14 (m, 4H, $\text{ArH}_{b,c,f}$), 7.05 (d, 1H, ArH_d), 6.82-6.79 (m, 2H, ArH_e), 4.74 (s, 2H, CH_{2j}), 3.71 (s, 3H, CH_{3k}), 3.58-3.55 (m, 2H, CH_{2g}), 3.06-3.03 (m, 2H, CH_{2h}) and 3.025 (s, 3H, CH_{3i}). Its mass spectrum showed molecular ion peak at 309.2.



1-(4-Fluorobenzylimino)-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**58**) was synthesized by reaction of compound (**4**) with 4-fluorobenzylamine in presence

of tosic acid. It showed characteristic IR peaks at 1676 (C=O str), 1597 (C=N str) and 747 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**58**) showed peaks at δ 7.52 (d, 1H, ArH_a), 7.34-7.17 (m, 6H, $\text{ArH}_{b,c,e,f}$), 7.08 (d, 1H, ArH_d), 4.76 (s, 2H, CH_{2j}), 3.59-3.58 (m, 2H, CH_{2g}), 3.09-3.07 (m, 2H, CH_{2h}) and 3.04 (s, 3H, CH_{3i}). Its mass spectrum showed molecular ion peak at 297.3.

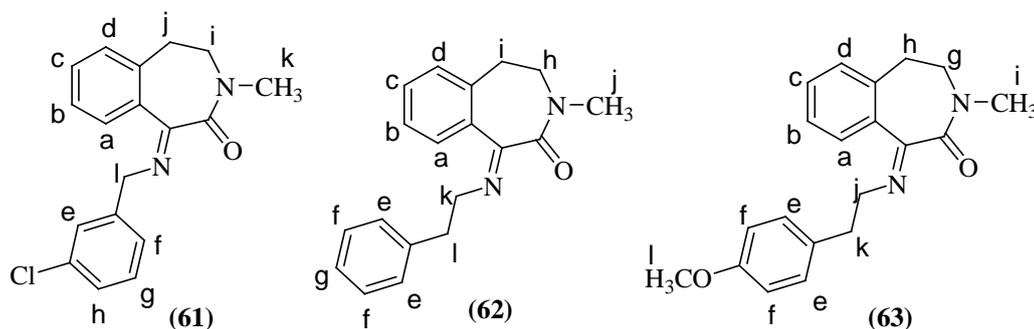
1-(4-Chlorobenzylimino)-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**59**) was synthesized by reaction of compound (**4**) with 4-chlorobenzylamine in presence of tosic acid. It showed characteristic IR peaks at 1651 (C=O str), 1549 (C=N str) and 751 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**59**) showed peaks at δ 7.59 (d, 1H, ArH_a), 7.38-7.24 (m, 6H, $\text{ArH}_{b,c,e,f}$), 7.15 (d, 1H, ArH_d), 4.83 (s, 2H, CH_{2j}), 3.66-3.65 (m, 2H, CH_{2g}), 3.16-3.15 (m, 2H, CH_{2h}) and 3.11 (s, 3H, CH_{3i}). Its mass spectrum showed molecular ion peak at 313.2.



1-(4-Bromobenzylimino)-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**60**) was synthesized by reaction of compound (**4**) with 4-bromobenzylamine in presence of tosic acid. It showed characteristic IR peaks at 1649 (C=O str), 1485 (C=N str) and 747 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**60**) showed peaks at δ 7.58 (d, 1H, ArH_a), 7.47-7.24 (m, 6H, $\text{ArH}_{b,c,e,f}$), 7.15 (d, 1H, ArH_d), 4.81 (s, 2H, CH_{2j}), 3.66-3.64 (m, 2H, CH_{2g}), 3.16-3.13 (m, 2H, CH_{2h}) and 3.10 (s, 3H, CH_{3i}). Its mass spectrum showed molecular ion peak at 357.1.

1-(3-Chlorobenzylimino)-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**61**) was synthesized by reaction of compound (**4**) with 3-chlorobenzylamine in presence of tosic acid. It showed characteristic IR peaks at 1654 (C=O str), 1573 (C=N str) and 742 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**61**) showed peaks at δ 7.61 (d, 1H, ArH_a), 7.43 (s, 1H, ArH_e), 7.37-7.21 (m, 5H, $\text{ArH}_{b,c,f,g,h}$), 7.16 (d, 1H,

ArH_d), 4.84 (s, 2H, CH_{2l}), 3.66-3.65 (m, 2H, CH_{2i}), 3.15-3.14 (m, 2H, CH_{2j}) and 3.11 (s, 3H, CH_{3k}). Its mass spectrum showed molecular ion peak at 313.3.



3-Methyl-1-(phenethylimino)-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (**62**) was synthesized by reaction of compound (**4**) with 2-phenethylamine in presence of tosic acid. It showed characteristic IR peaks at 1644 (C=O str), 1598 (C=N str) and 745 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**62**) showed peaks at δ 7.47 (d, 1H, ArH_a), 7.25-7.11 (m, 7H, $ArH_{b,c,e,f,g}$), 7.02 (d, 1H, ArH_d), 3.91 (t, 2H, CH_{2k}), 3.08-3.05 (m, 2H, CH_{2h}), 3.05 (t, 2H, CH_{2l}), 2.94-2.92 (m, 2H, CH_{2i}) and 2.91 (s, 1H, CH_{3j}). Its mass spectrum showed molecular ion peak at 293.2.

1-(4-Methoxyphenethylimino)-3-methyl-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (**63**) was synthesized by reaction of compound (**4**) with 4-methoxyphenethylamine in presence of tosic acid. It showed characteristic IR peaks at 1659 (C=O str), 1511 (C=N str) and 751 cm^{-1} (substituted benzene ring). $^1\text{H-NMR}$ spectrum of the compound (**63**) showed peaks at δ 7.54 (d, 1H, ArH_a), 7.33-7.29 (m, 1H, ArH_b), 7.26-7.23 (m, 1H, ArH_c), 7.18-7.14 (m, 2H, ArH_e), 7.10 (d, 1H, ArH_d), 6.83-6.79 (m, 2H, ArH_f), 3.94 (t, 2H, CH_{2j} , $J = 7.0\text{ Hz}$), 3.78 (s, 3H, CH_{3i}), 3.21-3.20 (m, 2H, CH_{2g}), 3.06 (t, 2H, CH_{2k} , $J = 7.0\text{ Hz}$), 3.02-3.00 (m, 2H, CH_{2h}) and 2.98 (s, 3H, CH_{3i}). Its mass spectrum showed molecular ion peak at 323.2.

4.2 Biological activity

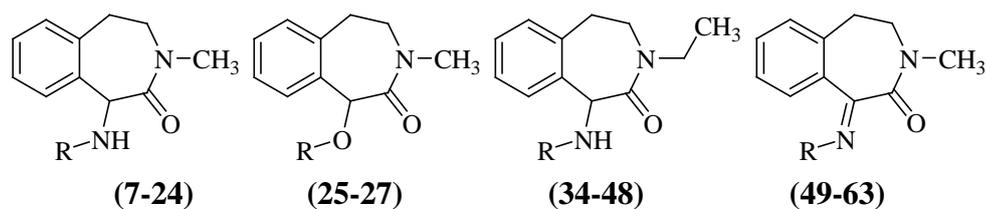
The newly synthesized benzazepine derivatives were assessed as potential NMDAR antagonists using cell-based assay. From the primary *in-vitro* screening some of the test compounds (**9**, **14**, **19**, **25**, **26**, **27**, **37**, **39** and **44**) were identified as potent NMDAR antagonists. These compounds were worthy of further evaluation for $A\beta_{1-42}$

aggregation inhibitory, neuroprotective, free radical scavenging, anti-oxidant and anti-apoptotic activities using different *in vitro* and *in vivo* experiments.

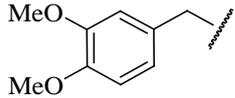
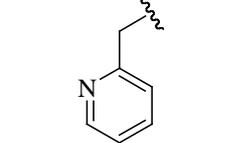
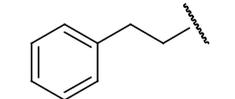
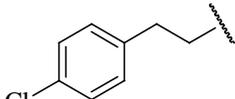
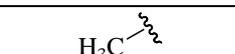
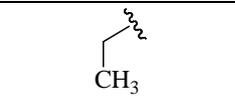
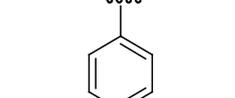
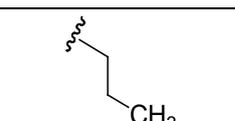
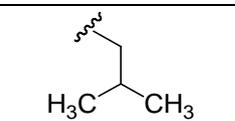
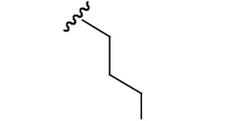
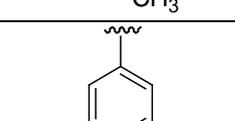
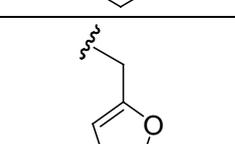
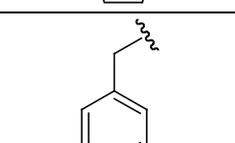
4.2.1 Test compounds protected SH-SY5Y cells against NMDA-induced excitotoxicity and A β ₁₋₄₂ aggregation inhibitory effects

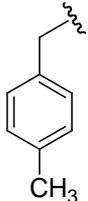
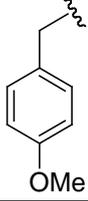
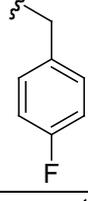
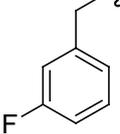
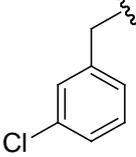
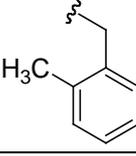
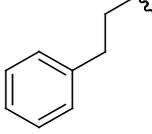
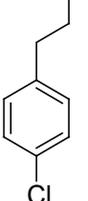
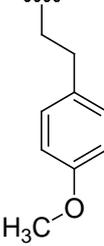
Neuroprotective potential of the synthesized benzazepine derivatives was assessed by MTT assay. SH-SY5Y cells were given NMDA (5 mM) treatment in absence and presence of the test compounds. NMDA-treated cells showed significant excitotoxic neuronal cell death (55-60 %). All the benzazepine derivatives were evaluated at 10 μ M concentration. As shown in Table 1, majority of the compounds demonstrated significant neuroprotection against NMDA-induced excitotoxicity in SH-SY5Y cells at 10 μ M concentration. Compounds (**9**, **14**, **19**, **25**, **26**, **27**, **37**, **39** and **44**) were found to be the most effective neuroprotective agents against NMDA receptor mediated excitotoxicity in SH-SY5Y human neuroblastoma cell lines. From the initially synthesized 15 compounds, the most effective compounds (**9** and **14**) were selected for further activities although rest of the compounds might also be potential NMDA receptor antagonist. To assess the multi-target-directed biological activity of the test compounds exhibiting potent NMDAR antagonist activity, they were evaluated for A β ₁₋₄₂ aggregation inhibitory activity using Thioflavin T (ThT) and Congo red (CR) binding assays. Compounds (**9** and **14**) demonstrated significant inhibition of A β ₁₋₄₂ aggregation at 10 μ M concentration in both the assays. The results revealed NMDAR antagonistic and A β ₁₋₄₂ aggregation inhibitory potentials of the test benzazepines (**9** and **14**) substantiating their beneficial role in excitotoxicity.

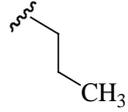
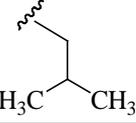
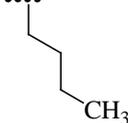
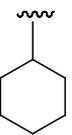
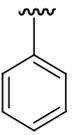
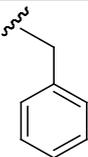
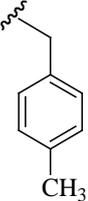
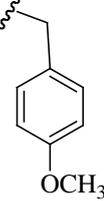
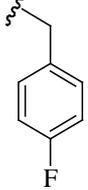
Table 4.1: Neuroprotective and A β ₁₋₄₂ aggregation inhibitory effects of the synthesized benzazepine derivatives.

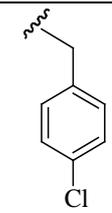
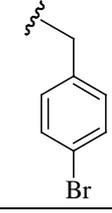
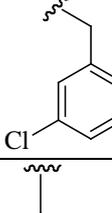
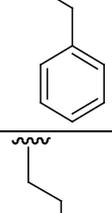
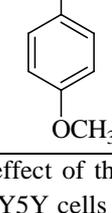


Compound	R	% Neuroprotection ^a (Assessed by MTT assay)	% Inhibition of Aβ ₁₋₄₂ aggregation ^b (at 10μM)	
			ThT assay	CR binding assay
Memantine	---	96.51 ± 2.55	nd	nd
7		30.36 ± 1.16	nd	nd
8		45.24 ± 4.29	nd	nd
9		83.55 ± 3.74	23.80 ± 2.74	28.79 ± 1.33
10		36.90 ± 3.90	nd	nd
11		51.79 ± 2.76	nd	nd
12		60.69 ± 3.51	nd	nd
13		55.23 ± 2.25	nd	nd
14		90.42 ± 3.51	34.86 ± 1.54	38.10 ± 1.54
15		47.65 ± 6.88	nd	nd
16		68.45 ± 1.68	nd	nd
17		53.43 ± 3.82	nd	nd
18		62.28 ± 1.58	nd	nd
19		80.86 ± 3.42	nd	nd
20		51.19 ± 4.87	nd	nd

21		70.62 ± 2.34	nd	nd
22		78.28 ± 2.59	nd	nd
23		57.76 ± 3.08	nd	nd
24		63.69 ± 4.87	nd	nd
25		80.53 ± 5.21	nd	nd
26		90.46 ± 1.69	nd	nd
27		87.02 ± 2.35	nd	nd
34		43.38 ± 1.59	nd	nd
35		60.05 ± 2.95	nd	nd
36		53.50 ± 3.06	nd	nd
37		82.87 ± 3.54	nd	nd
38		71.56 ± 2.64	nd	nd
39		80.34 ± 2.98	nd	nd

40		71.74 ± 4.47	nd	nd
41		66.83 ± 3.44	nd	nd
42		76.32 ± 3.85	nd	nd
43		71.70 ± 3.53	nd	nd
44		90.17 ± 2.99	nd	nd
45		75.92 ± 2.29	nd	nd
46		66.83 ± 3.47	nd	nd
47		54.54 ± 3.45	nd	nd
48		42.59 ± 2.65	nd	nd

49		27.89 ± 2.69	nd	nd
50		35.09 ± 3.81	nd	nd
51		57.88 ± 2.58	nd	nd
52		42.59 ± 2.04	nd	nd
53		31.79 ± 3.18	nd	nd
54		59.98 ± 2.86	nd	nd
55		44.09 ± 1.87	nd	nd
56		27.59 ± 1.59	nd	nd
57		37.79 ± 4.02	nd	nd
58		32.69 ± 2.57	nd	nd

59		36.59 ± 3.68	nd	nd
60		11.39 ± 2.68	nd	nd
61		36.89 ± 3.08	nd	nd
62		41.39 ± 2.49	nd	nd
63		34.79 ± 2.64	nd	nd

^aThe neuroprotective effect of the test derivatives (10 μ M) was assessed against NMDA-induced (5 mM) excitotoxicity in SH-SY5Y cells using MTT assay. ^bA β_{1-42} aggregation inhibitory effect of the most potent benzazepine derivatives (10 μ M) was assessed using thioflavin-T (ThT) and congo red (CR) binding assays. nd= Not determined.

4.2.2 Test compounds (**9** and **14**) protected primary rat hippocampal neurons against A β_{1-42} -induced excitotoxicity

Before determining the neuroprotective potential of the test compounds (**9** and **14**), their cytotoxicity was assessed on primary rat hippocampal neurons using MTT assay. They (**9** and **14**) did not show any sign of significant cytotoxicity up to a concentration of 40 μ M (Fig. 4.1). Similar results were observed for the standard drug memantine (Fig. 4.1A).

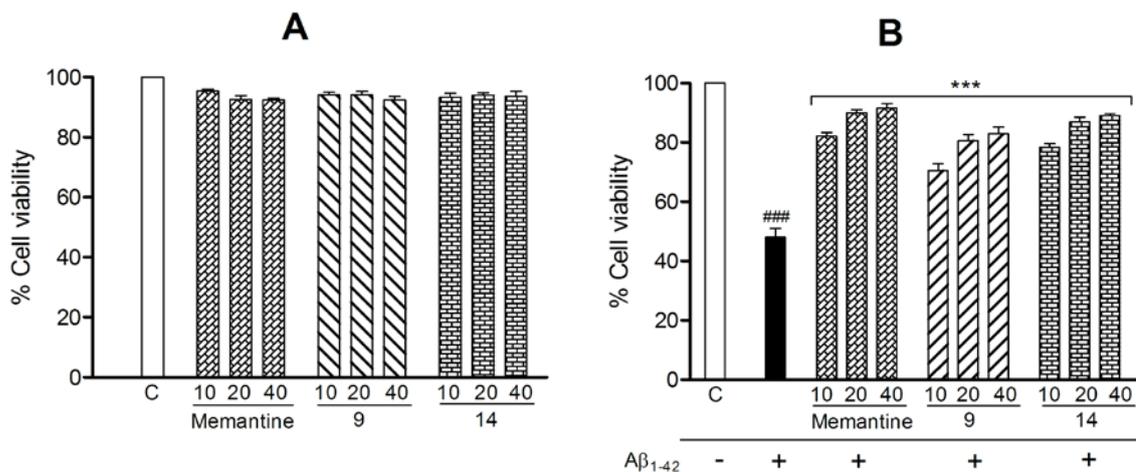


Fig. 4.1: *In vitro* neuroprotective potential of the test compounds (**9** and **14**) against A β ₁₋₄₂-induced toxicity. (A) Exposure of **9** or **14** (10-40 μ M) to the primary rat hippocampal neurons for 24 hr did not cause any significant toxicity. (B) Assessment of neuroprotective potential of **9** and **14** against A β ₁₋₄₂ insult. Data are expressed as mean \pm SEM (n=6). ### p <0.001 vs. control cells. *** p <0.001 vs. A β ₁₋₄₂-treated control cells. C=control cells.

The hippocampal neuronal cells exposed to A β ₁₋₄₂ (10 μ M) showed significant toxicity as compared to the control cells (Fig. 4.1B, p <0.001). However, pre-treatment of the cells with **9** or **14** significantly attenuated A β ₁₋₄₂-induced toxicity, which was evidenced by increased cell viability (Fig. 4.1B, p <0.001). These results revealed neuroprotective potential of the test compounds (**9** and **14**) against A β ₁₋₄₂-induced excitotoxic damage in the primary rat hippocampal neurons.

4.2.3 Morris water maze test and Y maze test for assessing learning ability and working memory

The spatial learning ability of the animals was assessed using Morris water maze (MWM) test and immediate working memory was evaluated using Y-maze test. The rats which underwent intrahippocampal injection of A β ₁₋₄₂ showed significantly increased ELT (Fig. 4.2A, p <0.001) and reduced the number of platform area crossings (Fig. 4.2B, p <0.001) as compared to the vehicle-treated control animals in all trial sessions. However, treatment with the test compounds (**9** and **14**) (5 mg/kg, p.o.) exhibited significantly reduced ELT (Fig. 4.2A, p <0.001) and increased the platform area crossings (Fig. 4.2B, p <0.01) as compared to the A β ₁₋₄₂-treated control group. Thus, the reduced ELT (Escape latency time) and increased platform area crossings by animals treated with **9** and **14**

revealed their potential to improve spatial learning and memory, impaired by direct A β ₁₋₄₂ toxicity.

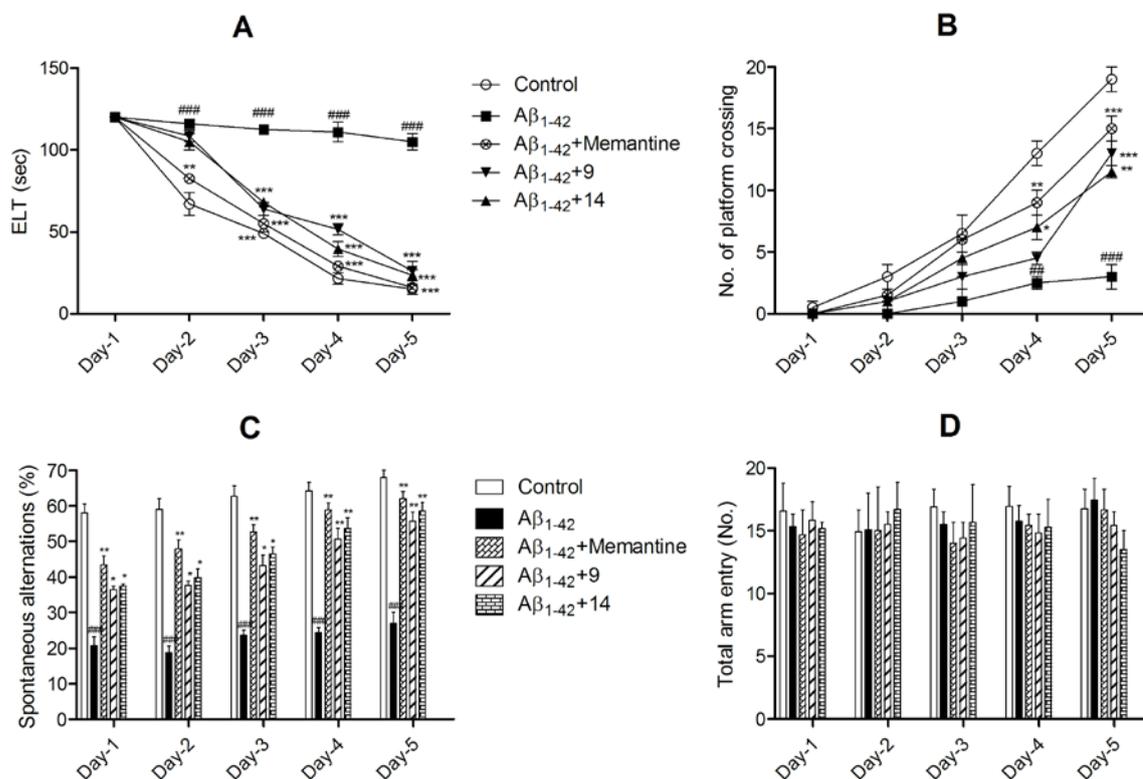


Fig. 4.2: In MWM test, (A) the ELT during probe trial sessions and (B) the number of platform area crossings In the Y maze test, (C) “spontaneous alteration” behaviour and (D) Mean number of the arm entries Data are expressed as mean \pm SEM (n=12). ### $p < 0.001$, ## $p < 0.01$ vs. vehicle-treated control group. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ vs. A β ₁₋₄₂-treated control group

In the Y maze test, A β ₁₋₄₂-treated rats exhibited significantly reduced “spontaneous alterations” which revealed impairment of immediate working memory in the animals. A significant rise in “spontaneous alterations” was observed after treatment of the animals with **9** and **14** (5 mg/kg, p.o.) (Fig. 4.2C, $p < 0.05$) which was attenuated by A β ₁₋₄₂ insult. However, the mean number of arm entries was found to remain unchanged in all experimental groups suggesting that general locomotor activity was not hampered by A β ₁₋₄₂-induced toxicity (Fig. 4.2D). The results revealed the potential of **9** and **14** to improve hippocampal dependant immediate working memory which was altered by A β ₁₋₄₂ treatment. Thus, treatment of the animals with **9** and **14** significantly improved learning and memory in both of the behavioural experimental models.

4.2.4 Test compounds (**9** and **14**) showed ROS scavenging activity

Oxidative stress also plays a major role in the pathogenesis of neurodegenerative conditions. Thus, a ligand exhibiting free radical scavenging, antioxidant and antiapoptotic properties could protect the cells efficiently against the $A\beta$ -induced excitotoxic damage. In the present study, the neuroprotective potential of the two promising benzazepines (**9** and **14**) was further assessed using primary rat hippocampal neuronal culture. The compounds (**9** and **14**) did not show any toxicity in hippocampal neurons even up to 40 μM concentrations while $A\beta_{1-42}$ imparted significant toxicity to the hippocampal neurons, which was significantly attenuated by pre-treatment of the cells with **9** and **14** in the MTT assay. Treatment with **9** and **14** significantly reduced $A\beta_{1-42}$ -induced ROS generation in DCFH-DA assay. Additionally, **9** and **14** significantly reduced the number of apoptotic nuclei in Hoechst staining assay and attenuated the rate of apoptosis in annexine V-FITC and PI staining assay performed using flow cytometry.

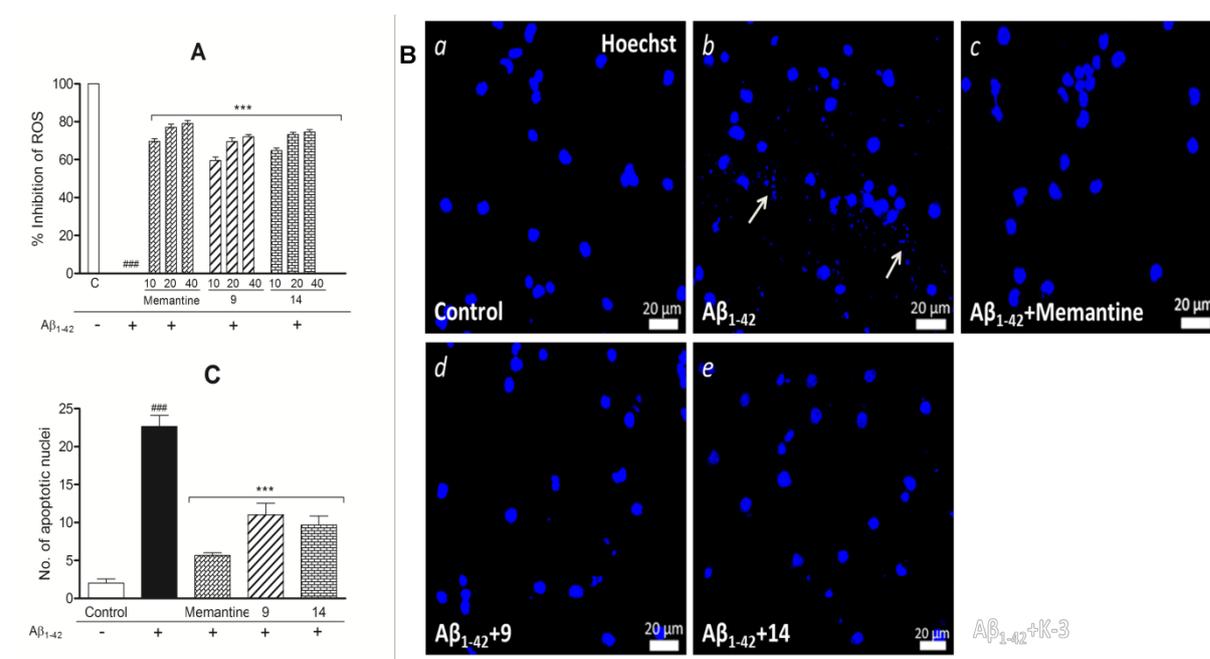


Fig. 4.3: *in vitro* ROS scavenging and antiapoptotic effects (A) $A\beta_{1-42}$ (10 μM)-induced elevated ROS level (B) Hoechst-stained hippocampal cell (C) Apoptotic nuclei. Data are expressed as mean \pm SEM. $###p < 0.001$ vs. control cells. $***p < 0.001$ vs. $A\beta_{1-42}$ -treated control cells. C=control cells.

In conclusion, the present study revealed the multi-target-directed potential of benzazepine derivatives against excitotoxicity as they have demonstrated efficient NMDAR antagonist, $A\beta_{1-42}$ aggregation inhibitory, neuroprotective, free radical scavenging, antioxidant and antiapoptotic activities in different *in vitro* and *in vivo*

experiments. Thus, the present study reveals that these benzazepine derivatives could be promising candidates for the treatment of a variety of neurodegenerative disorders.