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 and
2. Biological studies

4.1 Chemical studies

To synthesize the envisaged compounds, general Scheme-1 was adopted, wherein phenylethylamine (**A**) and 4-chlorophenylethylamine **(B)** were independently reacted with 2-chloropropionyl chloride **(C)** to obtain *N*-phenylethyl-2-chloropropanamide **(D)** and *N*-(4-chlorophenylethyl)-2-chloropropanamide **(E)** respectively which were cyclized under acidic conditions to obtain 1-methyl-3-benzazepin-2-one **(F)** and 8-chloro-1-methyl-3-benzazepin-2-one (**G)**. 1-Methyl-3-benzazepin-2-ones (**F, G**) were reacted with one mole of alkyl halide under basic conditions to obtain 3-substituted 1-methyl-3-benzazepin-2-ones **(H, I).** 1-Methyl-3-benzazepin-2-one **(F)** was reacted with 2.5 mole of sodium hydride and two moles of alkyl halide to obtain 1,3-disubsituted3-benzazepin-2-ones **(L).** 1-Methyl-3-benzazepin-2-one **(F)** was reacted with methyl 4-(bromoethyl)benzoate and sodium hydride to offer the ester **(J),** which was further reacted with 10% potassium hydroxide in methanol to obtain the acid derivative **(K)**. 2-Bromoacetamide **(M)** was reacted with triphenylmethanol in acidic conditions to give *N*-trityl derivative **(N)** which was further reacted with 1-methyl-3-benzazepin-2-one **(F)** and sodium hydride to afford the *N*- protected amide **(O)**. Deprotection of the amide under acidic conditions yielded 3-(2-acatamido)-1-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one **(P)**.

In order to execute Scheme-1, various amines and 2-bromoacetamide available commercially were used as such. The work related to the synthesis of *N*-phenylethyl-2-chloropropanamide **(D)** and *N*-(4-chlorophenylethyl)-2-chloropropanamide **(E),** 1-methyl-3-benzazepin-2-one **(F)** and 8-chloro-1-methyl-3-benzazepin-2-one (**G),** the intermediates **(M, N** and **O)** and the targeted products **(F, G, H, I, J, K, L** and **P)** has been described under the following major heads:

4.1.1 Synthesis of *N*-(arylethylamine)-2-chloropropanamides **(4, 5)**

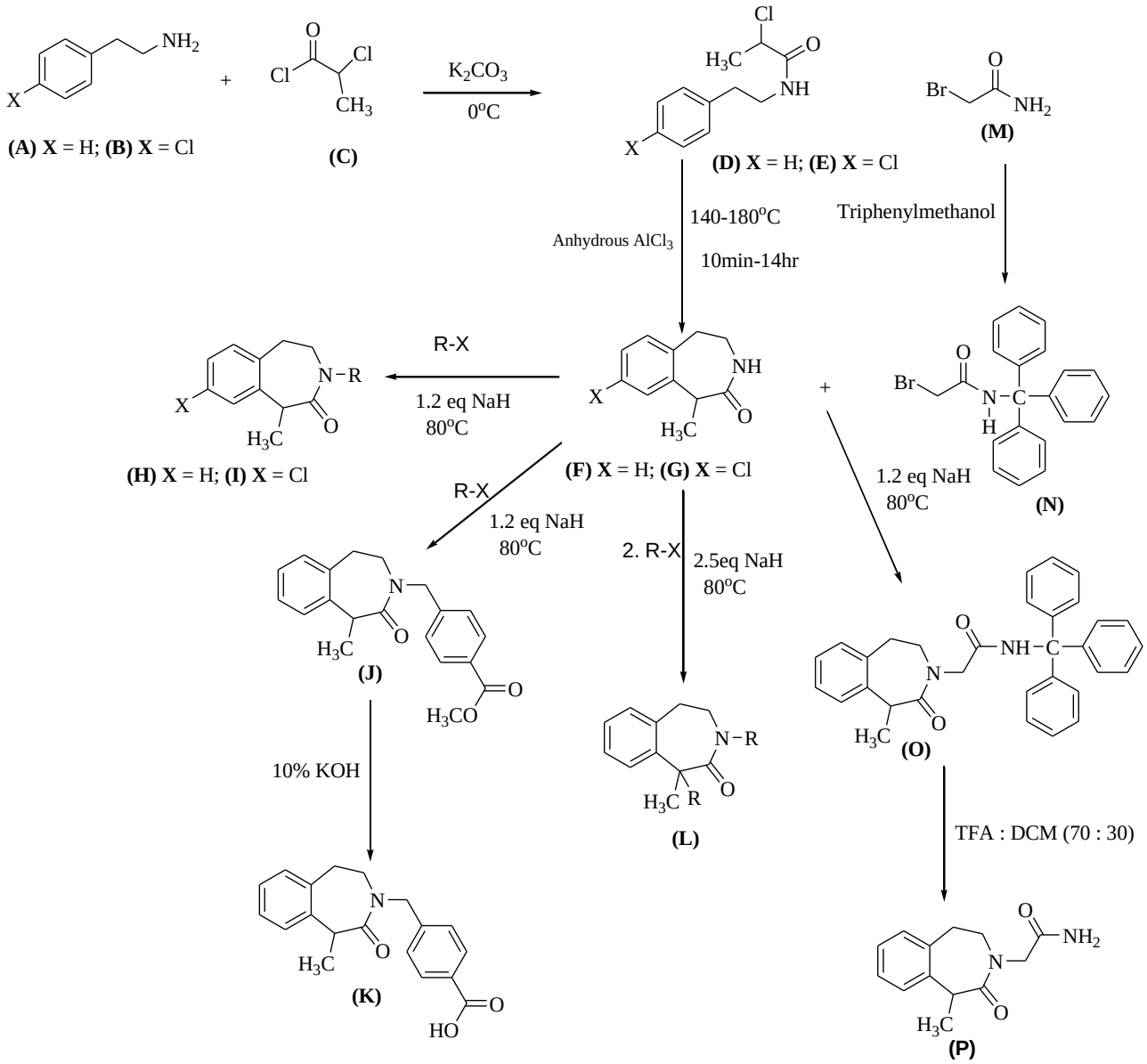
4.1.2 Synthesis of 1-methyl-3-benzazepin-2-ones **(6, 7)**

4.1.3 Synthesis of 3-substitued 1-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-ones **(8-43)**

4.1.4 Synthesis of 3-(4-carboxybenzyl)-1-methyl-2-oxo-1,3,4,5-tetrahydrobenzo [*d*]azepin-2-(3*H*)-one **(44, 45)**

4.1.5 Synthesis of 1,3-disubstitued 1-methyl-4,5-dihydro-1H-benzo[*d*]azepin-2(3*H*)-one **(46, 47)**

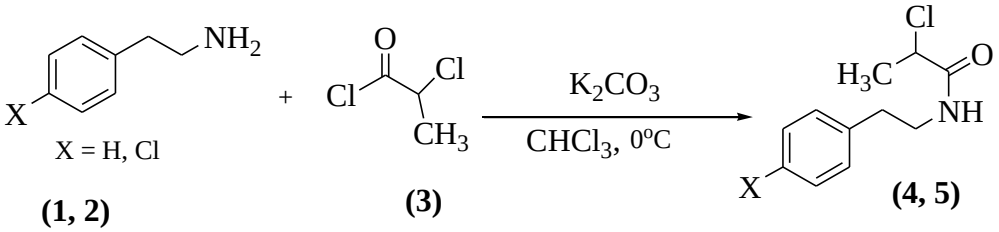
4.1.6 Synthesis of 2-(1-methyl-4,5-dihydro-2(3*H*)-oxo-1*H*-benzo[*d*]azepin-3-yl) acetamide **(51)**



General Scheme-1

4.1.1 Synthesis of *N*-(arylethyl)-2-chloropropanamides (4, 5)

In Scheme-2, 2-arylethylamine **(1, 2)** was reacted at 0 ^{o}C with 2-chloropropionyl chloride **(3)** to form substituted *N*-(arylethyl)-2-chloropropanamide intermediates **(4, 5)**. The yield of the products was around 95 %. In the IR spectrum of compound **(4)**, the stretching vibrations of N-H were observed at 3285 cm^{-1}. The C=O stretching of amide was seen at 1655 cm^{-1}. The mass spectrum showed molecular ion peak at 211.93 $(M)^{+}$. In the IR spectrum of compound **(5)**, the stretching vibrations of N-H were observed at 3277 cm^{-1}. The C=O stretching of the amide was seen at 1652 cm^{-1}. The mass spectrum showed molecular ion peak at 247.74 $(M)^{+}$.



(1, 2) **(3)** **(4, 5)**

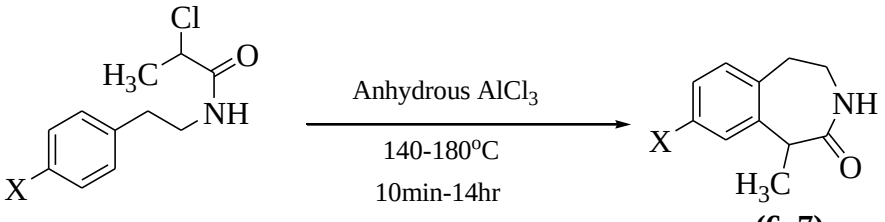
(1, 4) X = H

(2, 5) X = Cl

Scheme-2

4.1.2 Synthesis of 1-methyl-3-benzazepin-2-ones (6, 7)

In Scheme-3, *N*-(arylethyl)-2-chloropropanamides **(4, 5)** were reacted individually with Lewis acid like anhydrous aluminium chloride to form intermediates **(6, 7)** as white solids. The reaction was carried at higher temperature like above 180 ^{o}C and the reaction was completed within 10 min. The yield of the products was around 55 %. In the IR spectrum of



(4, 5) **(6, 7)**

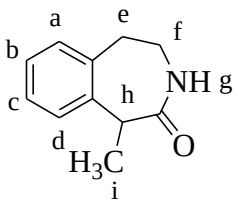
(4, 6) X = H

(5, 7) X = Cl

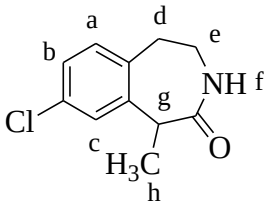
Scheme-3

compound **(6)**, the stretching vibration of *N*-H was observed at 3321 cm^{-1}. The C=O stretching of cyclic amide was seen at 1645 cm^{-1}. Its PMR spectrum showed aromatic protons

at δ 7.20-7.16 (m, $4H_{a-d}$). It also gave a broad singlet at δ 7.14 (bs, *N*-H_g) due to the proton attached to the amidic nitrogen. Among the aliphatic protons, the proton (CH_h) was observed at δ 4.24-4.22 as a quartet which coupled with protons (CH_{3i}) which were observed at δ 1.50-1.48 as a doublet with coupling constant of 6.9 Hz. Other signals were at δ 3.74 (CH_e) for one proton, δ 3.35 (CH_e) for one proton, δ 3.32 (CH_f) for one proton and δ 2.95 (CH_f) for one



(6)

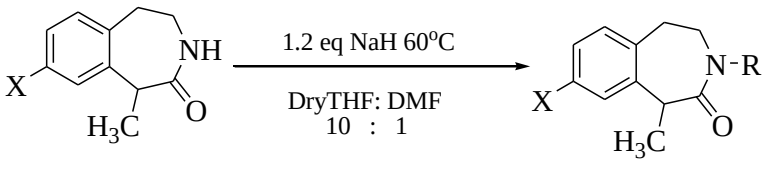


(7)

proton. Its mass spectrum showed molecular ion peak at 175.38 $(M)^+$. In IR spectrum of compound **(7)**, the stretching vibration of *N*-H was observed at 3321cm^{-1}. The C=O stretching of cyclic amide was seen at 1645 cm^{-1}. Its PMR spectrum showed a broad singlet at δ 7.44 (bs, $1H_f$) due to the proton attached to the amidic nitrogen. The aromatic protons gave a multiplet at δ7.19-7.15 (m, $2H_{a,b}$) for two protons. It gave a broad singlet at δ 7.12 (s, $1H_c$) for the other aromatic proton. Among the aliphatic protons, the proton (CH_g) was observed at δ 4.30-4.24 as a quartet which coupled to proton (CH_{3h}) observed at δ 1.38-1.36 as a doublet with coupling constant of 6.8 Hz. Other signals were at δ 3.78-3.72 (CH_d) for one proton, δ 3.25-3.12 (CH_e) for two protons, and δ 3.10-2.94 (CH_d) for one proton. Its mass spectrum showed molecular ion peak at 209.41 $(M)^+$.

4.1.3 Synthesis of 3-substitued 1-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-ones (8-43)

In Scheme-4, 1-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-ones **(6, 7)** were reacted independently with equimolar quantities of NaH and different alkyl/alkynyl/cyclo-

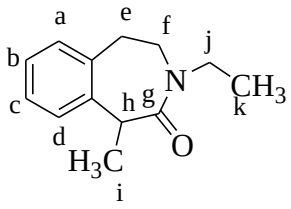


(6), X = H
(7), X = Cl
(8-36), X = H
(37-43), X = Cl

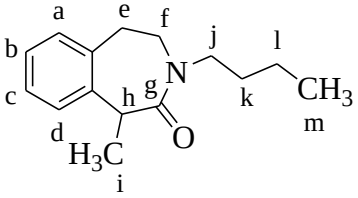
Scheme-4

hexylmethyl/arylmethyl halides resulting into the formation of 3-substituted derivatives **(8-43).** The reaction was carried out at 60 °C for 2-3 hrs.

In the IR spectrum of compound **(8)**, the C=O stretching of cyclic amide was seen at 1639 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.17-7-09 (m, $4H_{a,b,c,d}$). Among the aliphatic protons, the proton (CH_h) was observed at δ 4.41-4.36 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.45-1.43 as a doublet with coupling constant of 6.9 Hz. Other signals were at δ 4.20-4.13 (CH_f) for one proton, δ 3.49-3.22 ($CH_{f,j,e}$) for four protons, and δ 3.15-3.08 (CH_e) for one proton. Other aliphatic protons were observed at δ 1.07-1.03 (CH_{3k}) as triplet with coupling constant of 7.1 Hz. Its ^{13}C-NMR spectrum showed peak at δ 175.58 due to C=O carbon of the amide. Aromatic carbons appeared at δ 137.67, 129.62, 128.95, 127.61, 126.96 and 125.85 whereas aliphatic carbons appeared at δ 41.85, 40.89, 32.92, 18.35 and 14.69. Its mass spectrum showed molecular ion peak at 203.88 $(M)^+$. The compound also showed high chromatographic purity (> 98 %) by HPLC.



(8)

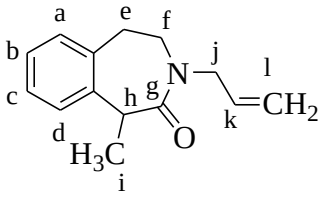


(9)

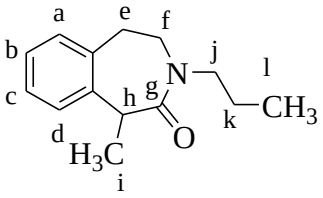
In the IR spectrum of compound **(9)**, the C=O stretching of cyclic amide was seen at 1658 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.18-7-08 (m, $4H_{a,b,c,d}$). Among the aliphatic protons, proton (CH_h) was observed at δ 4.43-4.38 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.44-1.43 as a doublet with coupling constant of 6.9 Hz. Other signals were at δ 4.22-4.16 (CH_f) for one proton, 3.43-3.41 ($CH_{f,j}$) for two protons, δ 3.38-3.36 (CH_j) for one proton, δ 3.32-3.28 (CH_e) for one proton, δ 3.27-3.25 (CH_e) for one protons, δ 1.41-1.40 (CH_k) for two protons, δ 1.26-1.16 (CH_l) for two protons and the other aliphatic protons were observed at δ 0.88-0.85 (CH_{3m}) as triplet with coupling constant of 7.3 Hz. Its ^{13}C-NMR spectrum showed peak at δ 175.63 due to C=O carbon of the amide. Aromatic carbons appeared at δ 137.65, 137.13, 129.99, 128.95 and 125.86 whereas the aliphatic carbons appeared at δ 47.60, 46.49, 41.47, 32.99, 30.33, 29.72, 20.10 and 14.70. Its mass spectrum showed molecular ion peak at 231.28 $(M)^+$.

In the IR spectrum of compound **(10)**, the C=O stretching of the cyclic amide was observed at 1657 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.20-7-09 (m, $4H_{a,b,c,d}$). The alkene proton was observed at δ 5.74-5.55 (CH_k) for one proton and the other doublet was observed at δ 5.07-5.06 (CH_l) for two protons. Among the aliphatic protons, proton (CH_h) was observed at δ 4.46-4.41 as a quartet which coupled with protons

(CH_{3i}) observed at δ 1.46-1.44 as a doublet with coupling constant of 6.8 Hz. Other signals were at δ 4.16-4.09 (CH_f) for one proton, δ 4.04-4.00 (CH_f) for one proton, δ 3.90-3.89 (CH_j) for one proton, δ 3.37-3.28 (CH_j) for one proton, δ 3.20-3.10 (CH_e) for one proton and δ 3.08-3.05 (CH_e) for one proton. Its mass spectrum showed molecular ion peak at 215.79 $(M)^+$.



(10)

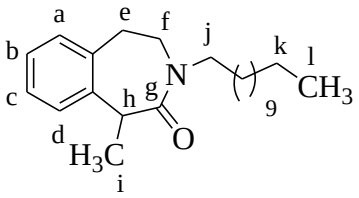


(11)

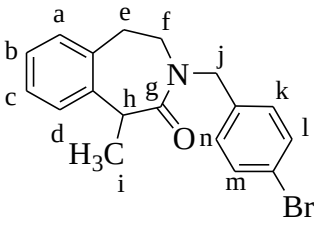
In the IR spectrum of compound **(11)**, the C=O stretching of the cyclic amide was observed at 1655 cm^{-1}. Its PMR spectrum showed the aromatic protons at δ 7.19-7-08 (m, $4H_{a,b,c,d}$). Among the aliphatic protons, proton (CH_h) was observed at δ 4.40-4.38 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.46-1.43 as a doublet with coupling constant of 6.8 Hz. Other signals were at δ 4.21-4.17 (CH_f) for one proton, δ 3.44-3.41 ($CH_{f,j}$) for two protons, δ 3.31-3.29 (CH_{je}) for two protons, δ 3.22-3.21 (CH_e) for one proton, δ 1.52-1.48 (CH_k) for two protons and the other aliphatic protons were observed at δ 0.82-0.78 (CH_{3l}) as triplet with coupling constant of 7.3 Hz. Its ^{13}C-NMR spectrum showed peak at δ 173.79 due to the C=O carbon of amide. Aromatic carbons appeared at δ 137.29, 136.13, 130.02, 126.70, 126.71 and 125.95 whereas the aliphatic carbons appeared at δ 49.48, 46.57, 40.49, 33.05, 21.47, 14.84 and 11.32. Its mass spectrum showed molecular ion peak at 217.66 $(M)^+$.

In the IR spectrum of compound **(12)**, the C=O stretching of the cyclic amide was observed at 1641 cm^{-1}. Its PMR spectrum showed aromatic protons, proton (Ar-H_a) was observed at δ 7.26-7-23 as a doublet which coupled with proton (d, $1H_b$) δ 7.09-7.06 with coupling constant of 8.7 Hz and the other aromatic protons appeared at δ 7.20-7.13 (m, $2H_{cd}$). Among the aliphatic protons, the proton (CH_h) was observed at δ 4.36-4.30 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.55-1.52 as a doublet with coupling constant of 6.9 Hz. Other signals were at δ 4.13-4.06 (CH_f) for one proton, δ 3.45-3.32 ($CH_{f,j}$) for three protons, δ 3.22-3.17 (CH_e) for one proton, δ 3.13-3.10 (CH_e) for one proton and also (CH_k) were observed at δ 1.50-1.47 as multiplet which coupled with protons ($CH3_l$) observed at δ 0.84-0.86 as triplet with coupling constant of 7.2 Hz. Other aliphatic protons were observed at δ 1.31-1.22 for eighteen protons. Its ^{13}C-NMR spectrum showed peak at δ 173.70 due to

C=O carbon of the amide. Aromatic carbons appeared at δ 137.30, 130.14, 129.99, 126.69 and 125.92 whereas the aliphatic carbons appeared at δ 47.94, 46.56, 40.49, 33.06, 31.97, 29.68, 29.61, 29.59, 29.46, 29.40, 28.27, 26.91, 22.74, 14.81, 14.17. Its mass spectrum showed molecular ion peak at 343.14 $(M)^+$.



(12)

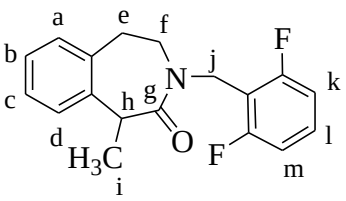


(13)

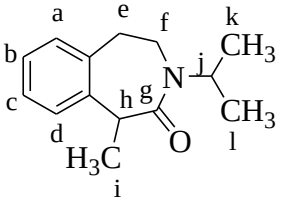
In the IR spectrum of compound **(13)**, the C=O stretching of the cyclic amide was observed at 1647 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.40-7-37 (d, $2H_{m,l}$) for two protons. Other aromatic protons were observed at δ 7.22 -7-13 (m, $3H_{a,b,d}$) for three protons and δ 7.07 -7.05 (m, $3H_{c,n,k}$) for three protons. Among the aliphatic protons, signals were observed at δ 4.58-4.43 (m, $3H_{f,j}$) for three protons, δ 4.18-4.10 (m, $1H_h$) for one proton, δ 3.33-3.31 (m, $1H_j$) for one proton, δ 3.20-3.15 (m, $1H_e$) for one proton and δ 2.99-2.93 (m, $1H_e$) for one proton. Other aliphatic protons were observed at δ 1.48-1.47 (d, $3H_i$) with a coupling constant of 6.8 Hz. Its ^{13}C-NMR spectrum showed peak at δ 174.01 due to C=O carbon of the amide. Aromatic carbons appeared at δ 137.12, 136.86, 136.12, 131.64, 129.87, 129.70, 126.90, 126.81, 125.67 and 121.22 whereas the aliphatic carbons appeared at δ 50.24, 46.39, 40.30, 32.45 and 14.59. Its mass spectrum showed molecular ion peak at 343.22 $(M)^+$. The compound also showed high chromatographic purity (> 98 %) by HPLC.

In the IR spectrum of compound **(14)**, the C=O stretching of the cyclic amide was observed at 1662 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.35-7.31 (m, $1H_l$) for one proton and δ 7.18-7.10 (m, $3H_{k,m,b}$) for three protons. Other aromatic proton signals were at δ 7.03-7.01 (d, $1H_a$) for one proton and δ 6.97-6.93 (m, $2H_{c,d}$) for two protons. Among the aliphatic protons, the proton (CH_j) was observed at δ 4.79-4.76 as a doublet which coupled geminaly with proton (CH_j) observed at δ 4.54-4.45 as a doublet with a coupling constant of 14.1 Hz. Other aliphatic proton (CH_h) was observed at δ 4.45-4.43 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.45-1.43 as doublet with a coupling constant of 6.8 Hz. Other signals were at δ 4.20-4.12 (CH_f) for one proton, δ 3.41-3.37 (CH_f) for one proton, δ 3.17-3.12 (CH_e) for one proton, δ 2.99-2.92 (CH_e) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 172.55 due to C=O carbon of the amide. Aromatic

carbons appeared at δ 162.16, 159.68, 135.74, 135.01, 128.88, 128.55, 125.66, 124.82, 112.34 and 110.46 whereas the aliphatic carbons appeared at δ 44.57, 39.29, 37.28, 31.43 and 13.67. Its mass spectrum showed molecular ion peak at 301.64 $(M)^+$. The compound also showed high chromatographic purity (> 98 %) by HPLC.



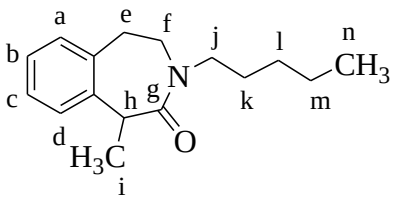
(14)



(15)

In the IR spectrum of compound **(15)**, the C=O stretching of the cyclic amide was observed at 1639 cm^{-1}. Its PMR spectrum showed signals for aromatic protons observed at δ 7.46-7.43 (m, $2H_{a,b}$) for two protons, δ 7.36-7.34 (m, $1H_c$) for one proton and δ 7.24-7.22 (m, $1H_d$) for one proton. Among the aliphatic protons, multiplets were observed at δ 7.18-7.16 (m, $1H_j$) for one proton, δ 7.13-7.09 (m, $1H_h$) for one proton, δ 5.65-5.60 (CH_f) for one proton, δ 5.32-5.29 ($CH_{f,}$) for one proton and δ 3.94-3.88 (CH_e) for two protons. Other signals were at δ 1.32-1.30 (d, $3H_i$) as doublet for three protons with coupling constant of 7.0 Hz. A signal was observed at δ 1.09-1.07 as doublet which coupled with protons (CH_k) observed at δ 1.02-1.01 (CH_l) as doublet with a coupling constant of 6.6 Hz. Its mass spectrum showed molecular ion peak at 216.46 $(M)^+$.

In the IR spectrum of compound **(16)**, the C=O stretching of the cyclic amide was observed at 1641 cm^{-1}. Its PMR spectrum showed signals for aromatic protons at δ 7.26-7.24 (d, $1H_a$) for one proton with coupling constant of 8.3 Hz, δ 7.20-7.13 (m, $2H_{b,c}$), for two protons and δ 7.09-7.07 (m, $1H_d$) for one proton. Among the aliphatic protons, proton (CH_h) was observed at δ 4.36-4.31 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.56-1.50 as a doublet with coupling constant of 6.8 Hz. Other signals were at δ 4.14-4.06 (CH_f) for one proton, δ 3.45-3.27 ($CH_{f,j,e}$) for four protons, δ 3.17-3.10 (CH_e) for one proton, δ 1.48-1.46 (CH_k) for two protons, δ 1.31-1.16 ($CH_{i,m}$) for four protons and δ 0.86-0.83 (CH_n) for three protons as triplet with coupling constant of 7.1 Hz. Its ^{13}C-NMR spectrum showed peak at δ 173.66 due to C=O carbon of the amide. Aromatic carbons appeared at 137.29, 136.12, 129.96, 126.66, 126.58 and 125.88 whereas the aliphatic carbons appeared at 47.85, 46.51, 40.43, 33.02, 29.02, 27.89, 22.14, 14.77 and 14.01. Its mass spectrum showed molecular ion peak at 245.79 $(M)^+$.



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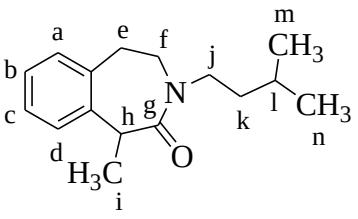
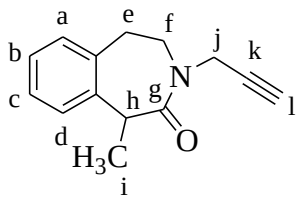


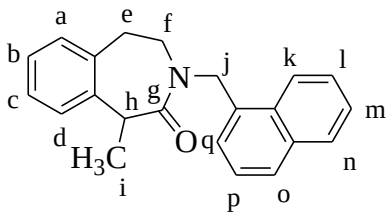
(17)

In the IR spectrum of compound **(17)**, the C=O stretching of the cyclic amide was observed at 1645 cm^{-1}. Its PMR spectrum showed signals for aromatic protons observed at δ 7.19-7.18 (d, $1H_{,a}$) for one proton with coupling constant of 8.4 Hz, δ 7.13-7.06 (m, $2H_{b,c}$), for two protons, δ 7.02-7.00 (m, $1H_d$) for one proton. Among the aliphatic protons, proton (CH_h) was observed at δ 4.28-4.23 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.48-1.44 as doublet with a coupling constant of 6.8 Hz. Other signals were at δ 4.06-3.99 (CH_f) for one proton, δ 3.45-3.27 ($CH_{f,j}$) for three protons, δ 3.22-3.15 (CH_e) for one proton, δ 3.07-3.01 (CH_e) for one proton, δ 1.40-1.36 (CH_k) for one proton, δ 1.32-1.27 ($CH_{k,l}$) for two protons, δ 0.82-0.80 ($CH_{m,n}$) for six protons as doublet with coupling constant of 6.6 Hz. Its ^{13}C-NMR spectrum showed peak at δ 172.52 due to C=O carbon of the amide. Aromatic carbons appeared at δ 136.15, 135.06, 128.90, 125.61, 125.53 and 124.78 whereas the aliphatic carbons appeared at δ 45.42, 45.28, 39.26, 35.92, 31.95, 25.01, 21.54 and 13.66. Its mass spectrum showed molecular ion peak at 245.39 $(M)^+$.

In the IR spectrum of compound **(18)**, the C=O stretching of cyclic amide was observed at 1664 cm^{-1}. Its PMR spectrum showed aromatic signals at δ 7.24-7.23 (m, $1H_{,a}$) for one proton, δ 7.22-7.15 (m, $2H_{c,d}$) for two protons, δ 7.13-7.10 (m, $1H_b$) for one proton. Among the aliphatic protons, proton (CH_f) was observed at δ 4.41-4.36 as double doublet with coupling constants of 2.5 Hz and 17.4 Hz. The other proton (CH_h) was observed at δ 4.34-4.30 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.58-1.56 as doublet with a coupling constant of 6.6 Hz. Other signals were at δ 4.16-4.11 (CH_j) for one proton, δ 3.65-3.58 ($CH_{,j}$) for one proton, δ 3.36-3.29 (CH_e) for one proton, δ 3.24-3.16 (CH_e) for one proton and δ 2.19-2.18 (CH_l) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 173.21 due to C=O carbon of the amide. Aromatic carbons appeared at δ 136.96, 136.42, 129.77, 126.91, 126.79, and 125.79 whereas the signals observed at 79.26 and 71.78 were due to alkynes and aliphatic carbons at δ 46.31, 40.50, 36.25, 32.49 and 14.05. Its mass spectrum showed molecular ion peak at 213.46 $(M)^+$.



(18)

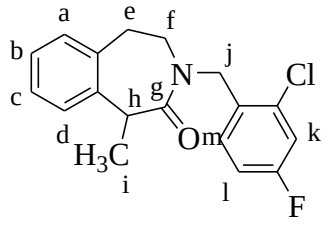


(19)

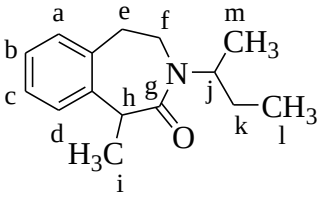
In the IR spectrum of compound **(19)**, the C=O stretching of cyclic amide was seen at 1662 cm^{-1}. Its PMR spectrum offered peaks for aromatic proton at δ 7.81-7.80 (d, $1H_a$) for one proton with coupling constant of 8.2 Hz, δ 7.22-7.15 (d, $2H_{c,d}$) for two protons with coupling constant of 8.2 Hz, δ 7.36-7.15 (m, $5H_{k,l,m,n,o}$) for five protons, δ 7.12-7-08 (m, $1H_p$) for one proton, δ 7.00-6.96 (m, $1H_q$) for one proton, δ 6.71-6.69 (d, $1H_b$) for one proton with coupling constant of 8.2 Hz. Among the aliphatic protons, proton (CH_f) was observed at δ 5.03-5.00 as doublet which coupled geminally with δ 4.98-4.94 as doublet with a coupling constant of 14.8 Hz , another proton (CH_h) was observed at δ 4.35-4.30 as a quartet coupled which protons (CH_{3i}) observed at δ 1.56-1.54 as doublet with coupling constant of 6.8 Hz. Other signals were at δ 3.88-3.81 (CH_j) for one proton, δ 3.30-3.24 (CH_j) for one proton, δ 2.94-2.88 (CH_e) for one proton and δ 2.61-2.53 (CH_e) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 173.88 due to C=O carbon of the amide. Aromatic carbons appeared at δ 136.75, 136.03, 133.73, 133.07, 131.80, 129.99, 128.52, 128.45, 127.10, 126.75, 126.55, 126.38, 125.97, 125.68, 125.12 and 123.87 whereas aliphatic carbons appeared at δ 48.07, 44.60, 40.38, 32.19 and 14.67. Its mass spectrum showed molecular ion peak at 315.67 $(M)^+$.

In the IR spectrum of compound **(20)**, the C=O stretching of cyclic amide was seen at 1658 cm^{-1}. Its PMR spectrum gave signals for aromatic protons. Signals were observed at δ 7.30-7.28 (d, $1H_a$) for one proton with coupling constant of 7.5 Hz, δ 7.24-7.19 (m, $2H_{b,c}$) for two protons, δ 7.11-6.99 (m, $3H_{k,l,m}$) for three proton, δ 6.85-6-83 (d, $1H_d$) for one proton with coupling constant of 8.2 Hz. Among the aliphatic protons, proton (CH_f) was observed at δ 4.74-4.64 as double doublet with coupling constants of 15.5 and 21.44 Hz. Another proton (CH_h) was observed at δ 4.43-4.38 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.61-1.59 as doublet with coupling constant of 6.8 Hz. Other signals were at δ 4.41-4.03 (CH_j) for one proton, δ 3.44-3.38 (CH_j) for one proton, δ 3.27-3.20 (CH_e) for one proton and δ 3.01-2.94 (CH_e) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 174.21 due to C=O carbon of the amide. Aromatic carbons appeared at δ 162.91, 137.18, 136.81, 134.05, 133.95, 131.21, 130.67, 129.92, 127.00, 125.76, 116.88 and 114.52 whereas the aliphatic

carbons appeared at δ 47.60, 46.93, 40.41, 32.55 and 14.59. Its mass spectrum showed molecular ion peak at 317.73 $(M)^+$.



(20)



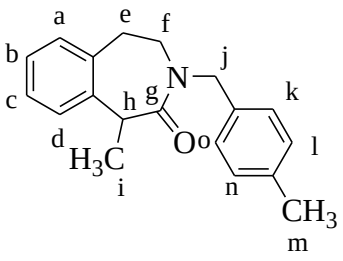
(21)

In the IR spectrum of compound **(21)**, the C=O stretching of cyclic amide was observed at 1637 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.44-7.41 (m, $1H_a$) for one proton, δ 7.26-7.17 (m, $3H_{b,c,d}$) for three protons, δ 6.94-6.86 (m, $1H_j$) for one proton. Among the aliphatic protons, proton δ 5.59-5.54 (m, $1H_f$) for one proton, δ 5.30-5.27 (m, $1H_f$) for one proton and 3.82-3.73 (m, $2H_{h,e}$) for two proton. Other signals were at δ 1.45-1.44 (d, 3Hi) for one proton as doublet with a coupling constant of 7.2 Hz, δ 1.34-1.10 (m, $3H_{e,k}$) for three protons, δ 0.99-0.88 (CH_m) for three protons as doublet with coupling constant of 6.6 Hz and δ 0.75-0.63 (t, $3H_l$) for three protons as triplet with coupling constant of 7.4 Hz.

The IR spectrum of compound **(22)** offered the C=O stretching of cyclic amide was at 1672 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.28-7.26 (d, $1H_a$) for one proton with coupling constant of 7.6 Hz, another aromatic protons appeared at δ 7.22-7.20 (d, 1H), δ 7.16-7.12 (d, 1H) and δ 7.07-7.00 (m, 5H). Among the aliphatic protons, proton (CH_f) was observed at δ 4.63-4.59 as a doublet which coupled geminally with the other signals appearing at δ 4.53-4.49 as doublet with coupling constant of 14.6 Hz. The other proton (CH_h) was observed at δ 4.40-4.35 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.69-1.59 as doublet with coupling constant of 6.8 Hz. Other signals were at δ 4.01-3.93 (CH_j) for one proton, δ 3.39-3.33 (CH_j) for one proton, δ 3.16-3.11 (CH_e) for one proton, δ 2.95-2.86 (CH_e) for one proton and δ 2.30 (s, 3H) for three protons due to methyl group. Its ^{13}C-NMR spectrum showed peak at δ 173.95 due to C=O carbon of the amide. Aromatic carbons appeared at δ 137.19, 136.99, 136.31, 134.71, 129.93, 129.23, 128.08, 126.75, 126.65 and 125.78 whereas the aliphatic carbons appeared at δ 50.33, 45.90, 40.41, 32.51, 21.13 and 14.78. Its mass spectrum showed molecular ion peak at 279.26 $(M)^+$.

In the IR spectrum of compound **(23)**, the C=O stretching of cyclic amide was seen at 1644 cm^{-1}. Its PMR spectrum showed signals for aromatic protons at δ 7.30-7.28 (d, $1H_a$) for

one proton with coupling constant of 7.6 Hz, δ 7.23-7.12 (m, $4H_{c,b,k,o}$) for four protons, δ 7.09-7.07 (d, $2H_{l,n}$) for two protons, δ 7.03-7.01 (d, $1H_d$) for one proton with coupling constant of 7.2 Hz. The aliphatic protons (CH_f) were observed at δ 4.69-4.65 as doublet whi-



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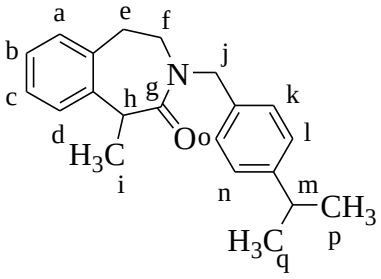
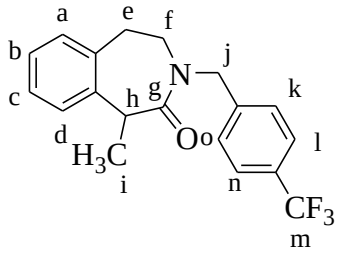


(23)

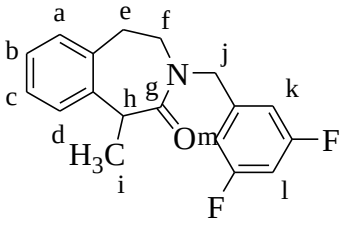
ch coupled geminally with δ 4.51-4.47 as doublet with coupling constant of 14.7 Hz. Peak for proton (CH_h) was observed at δ 4.40-4.39 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.62-1.61 as doublet with a coupling constant of 6.9 Hz. Other signals were observed at δ 4.00-3.96 (CH_j) for one proton, δ 3.41-3.35 ($CH_{,j}$) for one proton, δ 3.18-3.13 (CH_e) for one proton, δ 2.93-2.86 ($CH_{e,m}$) for two protons and δ 1.24-1.22 (d, 6H) for six protons with coupling constant of 6.9 Hz. Its ^{13}C-NMR spectrum showed peak at δ 172.86 due to C=O carbon of the amide. Aromatic carbons appeared at δ 146.94, 136.16, 135.26, 133.99, 128.86, 126.98, 125.69, 125.63, 125.53 and 124.71 whereas aliphatic carbons appeared at δ 49.29, 44.94, 39.34, 32.73, 31.41, 22.97 and 13.71. Its mass spectrum showed molecular ion peak at 307.65 $(M)^+$.

In the IR spectrum of compound **(24)**, the C=O stretching of cyclic amide was observed at 1658 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.51-7.49 (d, $2H_{l,m}$) for two protons with a coupling constant of 8.1 Hz, δ 7.31-7.29 (d, $1H_k$) for one proton with a coupling constant of 7.6 Hz, δ 7.25-7.16 (m, $4H_{a,b,c,d}$) for four protons and δ 7.05-7.03 (d, $1H_n$) for one proton with a coupling constant of 7.6 Hz. Among the aliphatic protons, proton (CH_f) was observed at δ 4.70-4.60 as double doublet with coupling constant of 15.2 and 13.1 Hz, whereas the other proton (CH_h) was observed at δ 4.42-4.37 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.63-1.61 as doublet with a coupling constant of 6.8 Hz. Other signals were at δ 4.07-4.00 (CH_j) for one proton, δ 3.40-3.33 (CH_j) for one proton, δ 3.25-3.18 (CH_e) for one proton and δ 2.98-2.90 (CH_e) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 174.08 due to C=O carbon of the amide. Aromatic carbons appeared at δ 141.96, 137.23, 136.12, 129.83, 129.48, 128.22, 126.92, 125.68, 125.58, 125.47

and 122.81 whereas aliphatic carbons appeared at δ 50.62, 46.83, 40.41, 32.44 and 14.56. Its mass spectrum showed a molecular ion peak at 333.78 $(M)^+$.



(24)

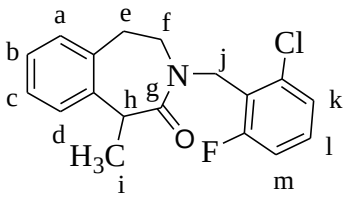


(25)

In the IR spectrum of compound **(25)**, the C=O stretching of cyclic amide was observed at 1657 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.31-7.29 (d, $1H_a$) for one proton with coupling constant of 7.3 Hz, δ 7.26-7.24 (d, $1H_d$) for one proton with coupling constant of 7.3 Hz, δ 7.19-7.17 (m, $1H_c$) for one proton, δ 7.08-7.06 (m, $1H_b$) for one proton and δ 6.69-6.60 (m, 3H). Among the aliphatic protons, proton (CH_f) was observed at δ 4.62-4.58 as a doublet which was coupled geminally with δ 4.54-4.50 as a doublet with coupling constant of 15.3 Hz, proton (CH_h) was observed at δ 4.42-4.37 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.62-1.61 as a doublet with coupling constant of 6.8 Hz. Other signals were at δ 4.07-4.00 (CH_j) for one proton, δ 3.39-3.33 ($CH_{,j}$) for one proton, δ 3.28-3.23 (CH_e) for one proton and δ 3.03-2.94 ($CH_{e,}$) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 174.06 due to C=O carbon of the amide. Aromatic carbons appeared at δ 164.41, 161.93, 141.96, 141.78, 137.15, 129.79, 127.04, 125.62, 110.57 and 103.01 whereas aliphatic carbons appeared at δ 50.30, 46.86, 40.30, 32.32 and 14.48. Its mass spectrum showed molecular ion peak at 301.23 $(M)^+$. The compound also showed high chromatographic purity (> 98 %) by HPLC.

In the IR spectrum of compound **(26)**, the C=O stretching of cyclic amide was seen at 1663 cm^{-1}. Its PMR spectrum showed aromatic proton at δ 7.27-7.12 (m, $5H_{a,b,c,d,k}$) for five protons and δ 7.00-6.96 (m, $2H_{m,l}$) for two protons. Among the aliphatic protons, proton (CH_f) was observed at δ 5.02-4.98 as a doublet coupled geminally with δ 4.73-4.69 as a doublet with a coupling constant of 14.3 Hz. Proton (CH_h) was observed at δ 4.40-4.35 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.59-1.57 as a doublet with a coupling constant of 6.8 Hz. Other signals were at δ 4.01-3.93 (CH_j) for one proton, δ 3.37-3.31 ($CH_{,j}$) for one proton, δ 3.15-3.09 (CH_e) for one proton and δ 2.96-2.88 ($CH_{e,}$) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 172.66 due to C=O carbon of the amide.

Aromatic carbons appeared at δ 162.47, 135.67, 135.17, 135.02, 128.96, 128.58, 125.65, 124.83, 124.52, 122.06, 121.89 and 113.29 whereas aliphatic carbons appeared at δ 43.61, 39.95, 39.33, 31.45 and 13.72. It showed molecular ion peak showed at 317.03 $(M)^+$ in its mass spectrum.



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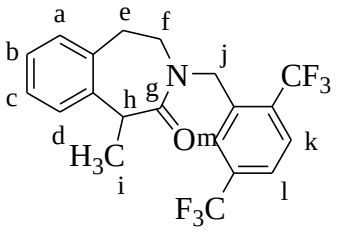
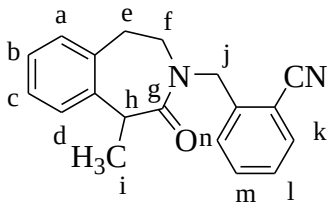


(27)

In the IR spectrum of compound **(27)**, the C=O stretching of cyclic amide was observed at 1657 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.73 (s, $1H_m$) for one proton, δ 7.48 (bs, $2H_{k,l}$) for two protons, δ 7.32-7.30 (d, $1H_a$) for one proton with coupling constant of 7.3 Hz, δ 7.26-7.24 (d, $1H_d$) for one proton with coupling constant of 7.4 Hz, δ 7.20-7.18 (m, $1H_b$) for one proton and δ 7.07-7.05 (m, $1H_d$) for one proton. Among the aliphatic protons, the proton (CH_f) was observed at δ 4.84-4.80 as a doublet which coupled geminaly with δ 4.60-4.56 as a doublet with a coupling constant of 15.5 Hz. Proton (CH_h) was observed at δ 4.43-4.38 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.63-1.55 as a doublet with coupling constant of 6.8 Hz. Other signals were at δ 4.12-4.06 (CH_j) for one proton, δ 3.40-3.35 ($CH_{j,e}$) for two protons and δ 3.00-2.92 (CH_e) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 174.25 due to C=O carbon of the amide. Aromatic carbons appeared at δ 140.67, 137.26, 135.77, 132.41, 131.75, 129.73, 127.65, 127.23, 125.40, 124.55, 121.43, 121.39, 121.35 and 121.31 whereas aliphatic carbons appeared at δ 50.42, 47.37, 40.24, 32.27 and 14.16.

In the IR spectrum of compound **(28)**, the C=O stretching of cyclic amide was observed at 1650 cm^{-1}. The peak at 2225 cm^{-1} was due to nitrile group. Its PMR spectrum showed signals for aromatic protons at δ 7.67-7.61 (m, $1H_k$) for one proton, δ 7.45-7.41 (m, $1H_l$) for one proton, δ 7.34-7.30 (m, $2H_{m,n}$) for two protons, δ 7.21-7.17 (m, $3H_{a,b,c}$) for three protons and δ 7.06-7.04 (d, $1H_d$) for one proton. Among the aliphatic protons, proton (CH_f) was observed at δ 4.87-4.77 as a double doublet with coupling constants of 15.6 and 19.08 Hz. Proton (CH_h) was observed at δ 4.45-4.39 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.65-1.60 as a doublet with coupling constant of 6.8 Hz. Other signals were at δ 4.14-4.08 (CH_j) for one proton, δ 3.52-3.42 (CH_j) for one proton, δ 3.30-3.23 (CH_e) for one

proton and δ 3.02-2.93 ($CH_{e,}$) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 174.16 due to C=O carbon of amide. Aromatic carbons appeared at δ 141.72, 137.02, 136.08, 133.19, 132.71, 129.82, 128.88, 127.79, 126.97, 125.62 and 117.64 whereas the signal at δ 111.67 was due to nitrile carbon. The aliphatic carbons appeared at δ 49.11, 47.37, 40.24, 32.41 and 14.45. Its mass spectrum showed molecular ion peak at 291.1 $(M+1)^+$.



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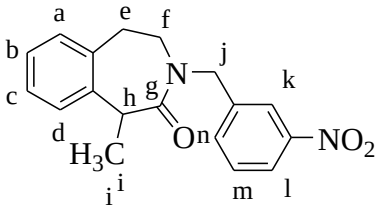
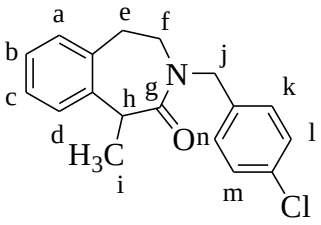


(29)

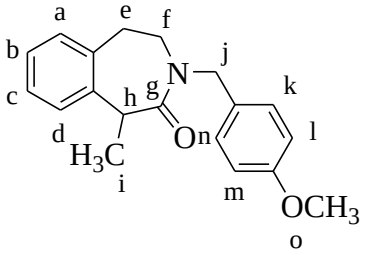
In the IR spectrum of compound **(29)**, the C=O stretching of cyclic amide was observed at 1655 cm^{-1}. The peaks observed at 1525 cm^{-1} and 1348 were due to nitro group asymmetric and symmetric stretching. Its PMR spectrum showed aromatic protons at δ 8.10-8.07 (d, $1H_l$) for one proton with coupling constant of 7.3 Hz, δ 7.96 (s, $1H_k$) for one proton, δ 7.43-7.41 (m, 2H), δ 7.31-7.29 (d, $1H_a$) for one proton with coupling constant of 7.2 Hz, δ 7.26-7.24 (m, $1H_b$) for one proton, δ 7.21-7.19 (m, $1H_c$) for one proton and δ 7.06-7.04 (d, $1H_d$) for one proton with a coupling constant of 7.2 Hz. Among the aliphatic protons, proton (CH_f) was observed at δ 4.68-4.66 as a doublet with a coupling constant of 14.9 Hz. Proton (CH_h) was observed at δ 4.42-4.40 as a quartet which coupled with proton (CH_{3i}) observed at δ 1.63-1.61 as a doublet with a coupling constant of 6.8 Hz. Other signals appeared at δ 4.09-4.07 (CH_j) for one proton, δ 3.42-3.38 (CH_j) for one proton, δ 3.24-3.20 (CH_e) for one proton and δ 2.97-2.87 ($CH_{e,}$) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 173.08 due to C=O carbon of the amide. Aromatic carbons appeared at δ 147.30, 139.00, 136.07, 134.88, 132.94, 128.75, 128.59, 126.03, 125.95, 124.55, 121.40 and 121.38. The aliphatic carbons appeared at δ 49.42, 46.08, 39.22, 31.30 and 13.36. Its mass spectrum showed molecular ion peak at 311.00 $(M+1)^+$.

In the IR spectrum of compound **(30)**, the C=O stretching of cyclic amide was observed at 1649 cm^{-1}. Its PMR spectrum showed peak for aromatic protons at δ 7.20-7.14 (m, $5H_{l,m,a,d,c}$), for five protons and δ 7.05-7.00 (m, $3H_{k,n,b}$) for three protons. Among the aliphatic protons, proton (CH_f) was observed at δ 4.62-4.50 as a double doublet with coupling constants of 14.9 and 21.26 Hz. Proton (CH_h) was observed at δ 4.40-4.38 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.60-1.59 as a doublet with coupling constant of

6.8 Hz. Other signals were at δ 4.00-3.96 (CH_j) for one proton, δ 3.37-3.30 ($CH_{,j}$) for one proton, δ 3.19-3.12 (CH_e) for one proton and δ 2.94-2.85 ($CH_{e,}$) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 173.98 due to C=O carbon of the amide. Aromatic carbons appeared at δ 137.16, 136.12, 133.14, 129.84, 128.68, 126.87 and 125.69 whereas the aliphatic carbons appeared at δ 50.21, 46.37, 40.40, 32.46 and 14.60. Its mass spectrum showed molecular ion peak at 300.01 $(M+1)^+$.



(30)

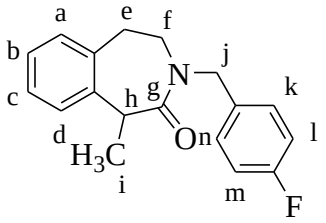


(31)

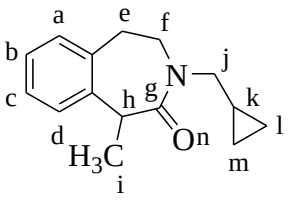
In the IR spectrum of compound **(31)**, the C=O stretching of the cyclic amide was observed at 1649 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.23-7.18 (m, $1H_c$), for one proton, δ 7.15-7.11 (d, $1H_a$) for one proton with coupling constant of 7.2 Hz, δ 7.09-7.06 (d, $1H_d$) for one proton with coupling constant of 7.2 Hz, δ 7.00-6.99 (m, $2H_{b,k}$) for two protons, δ 6.94-6.92 (d, $1H_l$) for one proton with coupling constant of 7.3 Hz, δ 6.74-6.71 (m, $2H_{m,n}$) for two protons. Among the aliphatic protons, proton (CH_f) was observed at δ 4.55-4.52 as a doublet which coupled geminally with δ 4.48-4.42 as a doublet with coupling constant of 14.6 Hz. Proton (CH_h) was observed at δ 4.32-4.30 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.65-1.60 as a doublet with a coupling constant of 6.8 Hz. Other signals were at δ 3.95-3.88 (CH_j) for one proton, δ 3.70 (s, $3H_o$) for three protons, δ 3.33-3.27 ($CH_{,j}$) for one proton, δ 3.20-3.08 (CH_e) for one proton and δ 2.86-2.82 ($CH_{e,}$) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 173.92 due to C=O carbon of the amide. Aromatic carbons appeared at δ 158.91, 137.14, 136.27, 129.93, 129.87, 129.41, 126.73, 126.64, 125.76 and 113.91 whereas the aliphatic carbons appeared at δ 55.28, 50.01, 45.78, 40.40, 32.52 and 14.74. Its mass spectrum offered molecular ion peak at 296.01 $(M+1)^+$. The compound also showed high chromatographic purity (> 98 %) by HPLC.

In the IR spectrum of compound **(32)**, the C=O stretching of cyclic amide was observed at 1653 cm^{-1}. Aromatic protons were observed at δ 7.29-7.14 (m, $3H_{a,b,c}$) for three protons, δ 7.12-7.08 (m, $2H_{d,k}$) for two protons, δ 7.03-7.02 (m, $1H_n$) for one proton and δ 6.96-6.91 (m, $2H_{l,m}$) for two protons in its PMR spectrum. Among the aliphatic protons, proton (CH_f) was observed at δ 4.60-4.52 as double doublet with coupling constants of 14.8

and 18.14 Hz. Proton (CH_h) was observed at δ 4.40-4.35 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.61-1.51 as a doublet with coupling constant of 6.8 Hz. Other signals were at δ 4.04-3.96 (CH_j) for one proton, δ 3.39-3.32 ($CH_{,j}$) for one proton, δ 3.19-3.12 (CH_e) for one proton and δ 2.89-2.85 ($CH_{e,}$) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 174.03 due to C=O carbon of the amide. Aromatic carbons appeared at δ 163.44, 137.22, 136.21, 133.65, 130.07, 129.93, 127.69, 126.82, 125.77 and 115.69 whereas the aliphatic carbons appeared at δ 50.16, 46.27, 40.48, 32.60 and 14.69. Its mass spectrum showed molecular ion peak at 284.01 $(M+1)^+$.



(32)

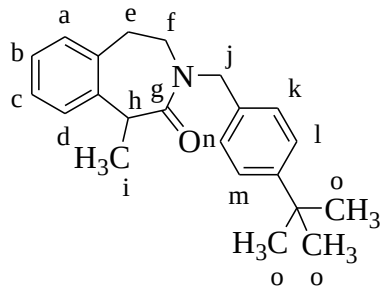


(33)

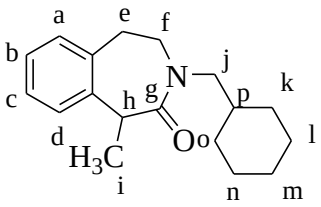
In the IR spectrum of compound **(33)**, the C=O stretching of cyclic amide was observed at 1650 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.26-7.24 (m, $1H_a$), for one proton, δ 7.19-7.15 (m, $2H_{b,c}$) for two protons and δ 7.08-7.07 (m, $1H_d$) for one proton. Among the aliphatic protons, proton (CH_h) was observed at δ 4.39-4.34 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.57-1.51 as a doublet with a coupling constant of 6.8 Hz. Other signals were at δ 4.21-4.13 (CH_f) for one proton, δ 3.57-3.50 ($CH_{,f}$) for one proton, δ 3.37-3.16 ($CH_{j,e}$) for four protons, δ 0.98-0.91 ($CH_{k,}$) for one proton. δ 0.49-0.41 ($CH_{l,}$) for two protons and δ 0.26-0.17 ($CH_{m,}$) for two protons. Its ^{13}C-NMR spectrum showed peak at δ 173.80 due to C=O carbon of the amide. Aromatic carbons appeared at δ 137.06, 136.20, 130.03, 126.64, 126.52 and 125.93 whereas the aliphatic carbons appeared at δ 51.72, 46.32, 40.33, 33.02, 14.81, 9.96 and 3.56. Its mass spectrum showed molecular ion peak at 230.00 $(M+1)^+$.

In the IR spectrum of compound **(34)**, the C=O stretching of cyclic amide was observed at 1645 cm^{-1}. Its PMR spectrum offered signals for aromatic protons at δ 7.20-7.18 (m, 3H), δ 7.13-7.04 (m, 2H), δ 7.00-6.98 (d, 2H) and δ 6.93-6.91 (d, 1H). Among the aliphatic protons, proton (CH_f) was observed at δ 4.59-4.53 as a doublet which coupled geminaly with δ 4.39-4.36 as a doublet with coupling constant of 14.7 Hz. Proton (CH_h) was observed at δ 4.31-4.26 as a quartet which coupled with protons (CH_{3i}) which were observed at δ 1.52-1.50 as a doublet with a coupling constant of 6.8 Hz. Other signals were at δ 3.98-

3.85 (CH_j) for one proton, δ 3.31-3.25 ($CH_{,j}$) for one proton, δ 3.08-3.01 (CH_e) for one proton, δ 2.97-2.87 ($CH_{e,}$) for one proton and δ 1.20 (s, $9H_{o,}$) for nine protons due to *t.*butyl group. Its ^{13}C-NMR spectrum showed peak at δ 172.85 due to C=O carbon of the amide. Aromatic carbons appeared at δ 149.19, 136.16, 135.27, 133.60, 128.86, 126.68, 125.69, 125.60, 124.71 and 124.39 whereas the aliphatic carbons appeared at δ 49.22, 44.99, 39.35, 33.44, 31.40, 30.32 and 13.72. Its mass spectrum showed molecular ion peak at 322.1 $(M+1)^+$.



(34)

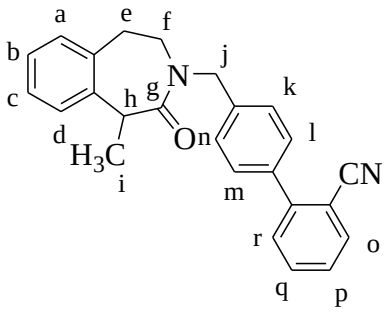


(35)

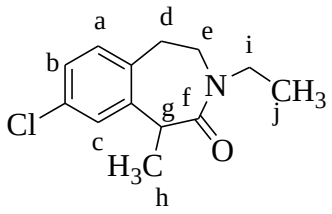
In the IR spectrum of compound **(35)**, the C=O stretching of cyclic amide was seen at 1637 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.92-7.85 (m, $1H_a$) for one proton, δ 7.23-7.08 (m, $2H_{b,c}$) for two protons and δ 6.99-6.94 (m, $1H_d$) for one proton. Among the aliphatic protons, proton (CH_h) was observed at δ 4.15-4.05 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.75-1.74 as a doublet with a coupling constant of 6.8 Hz. Other signals were at δ 5.67-5.62 (CH_f) for one proton, δ 3.74-3.65 ($CH_{,f}$) for one proton, δ 3.35-3.28 (CH_j) for one proton, δ 3.06-3.00 ($CH_{j,e}$) for three protons, δ 1.62-1.54 ($CH_{l,m,n}$) for six protons, δ 1.51-1.38 ($CH_{o.k}$) for four protons and δ 0.96-0.87 (CH_p) for one proton Its ^{13}C-NMR spectrum showed peak at δ 176.00 due to C=O carbon of the amide. Aromatic carbons appeared at δ 141.45, 134.39, 130.01, 128.11, 127.22 and 126.89 whereas the aliphatic carbons appeared at δ 56.53, 47.56, 36.73, 33.97, 32.74, 30.98, 30.96, 30.67, 26.36 and 25.88. Its mass spectrum showed molecular ion peak at 272.1 $(M+1)^+$.

In the IR spectrum of compound **(36)**, the C=O stretching of the cyclic amide was observed at 1647 cm^{-1}. The peak observed at 2220 cm^{-1} was due to the nitrile group. Its PMR spectrum showed aromatic protons at δ 7.77-7.74 (d, $1H_o$) for one proton with coupling constant of 7.9 Hz, δ 7.65-7.61 (m, $1H_p$) for one proton, δ 7.49-7.41 (m, $5H_{q,r,l,m,k}$) for five protons, δ 7.31-7.29 (d, $1H_a$) for one proton with coupling constant of 7.4 Hz, δ 7.24-7.20 (m, $2H_{b,c}$) for two protons, δ 7.17-7.15 (m, $1H_n$) for one protons, δ 7.07-7.05 (d, $1H_d$) for one proton with coupling constant of 7.4 Hz. Among the aliphatic protons, proton (CH_f) was

observed at δ 4.73-4.70 as a doublet which coupled geminally with δ 4.65-4.61 as a doublet with a coupling constant of 15.1 Hz. Proton for (CH_h) was observed at δ 4.45-4.40 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.64-1.62 as a doublet with a coupling constant of 6.8 Hz. Other signals were at δ 4.11-4.03 (CH_j) for one proton, δ 3.46-3.40 ($CH_{,j}$) for one proton, δ 3.24-3.18 (CH_e) for one proton and δ 2.99-2.94 ($CH_{e,}$) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 173.10 due to C=O carbon of the amide. Aromatic carbons appeared at δ 173.38, 136.15, 135.19, 132.72, 131.82, 129.01, 128.95, 127.93, 127.21, 126.53, 125.85, 125.70, 124.60 and 117.7. The signal observed at δ 110.12 was due to nitrile carbon and the aliphatic carbons appeared at 49.42, 45.41, 39.25, 31.36, 28.67 and 13.56. Its mass spectrum showed molecular ion peak at 367.01 $(M+1)^+$.



(36)

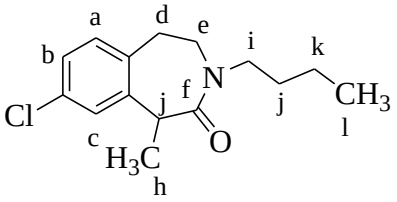


(37)

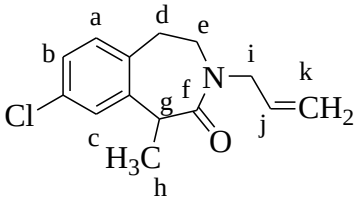
In the IR spectrum of compound **(37)**, the C=O stretching of cyclic amide was observed at 1643 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.26-7-21 (m, $1H_a$) for one proton, δ 7.16-7-11 (m, $1H_c$) for one proton and δ 7.08-7-00 (m, $1H_b$) for one proton. Among the aliphatic protons, proton (CH_g) was observed at δ 4.31-4.26 as a quartet which coupled with protons (CH_{3h}) observed at δ 1.54-1.52 as a doublet with coupling constant of 6.8 Hz. Other signals were at δ 4.12-4.04 (CH_e) for one proton, δ 3.53-3.36 ($CH_{e,i}$) for three protons, and δ 3.25-3.11 (CH_d) for one proton and δ 3.09-3.05 (CH_d) for one proton. It gave a triplet at δ 1.12-1.08 (t, $3H_j$) for the other aliphatic protons. Its ^{13}C-NMR spectrum showed peak at δ 172.94 due to C=O carbon of the amide. Aromatic carbons appeared at δ 139.19, 135.90, 132.49, 129.80, 127.48 and 126.60 whereas the aliphatic carbons appeared at 46.00, 42.66, 40.14, 33.02, 14.78 and 13.29. Its mass spectrum showed molecular ion peak at 238.10 $(M+1)^+$. The compound also showed high chromatographic purity (> 98 %) by HPLC.

In the IR spectrum of compound **(38)**, the C=O stretching of cyclic amide was observed at 1656 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.21-6.91 (m, $3H_{a,b,c}$) for three protons. Among the aliphatic protons, proton (CH_j) was observed at δ 4.31-4.25 as a quartet which coupled with protons (CH_{3h}) observed at δ 1.55-1.53 as a doublet with a

coupling constant of 6.9 Hz. Other signals were at δ 4.15-4.06 (CH_e) for one proton, δ 3.44-3.31 ($CH_{e,i}$) for three protons, δ 3.24-3.16 (CH_d) for one proton, δ 3.08-3.05 (CH_d) for one proton, δ 1.48-1.44 (CH_j) for two protons and δ 1.33-1.20 (CH_k) for two protons. It gave a triplet at δ 0.93-0.86 (t, $3H_l$) for the other aliphatic protons. Its ^{13}C-NMR spectrum showed peak at δ 173.26 due to C=O carbon of the amide. Aromatic carbons appeared at δ 139.08, 135.78, 132.40, 129.80, 127.43 and 126.75 whereas the aliphatic carbons appeared at δ 47.65, 46.25, 40.00, 32.92, 30.38, 20.12, 14.74 and 13.89. Its mass spectrum showed molecular ion peak at 266.1 $(M+1)^+$.



(38)

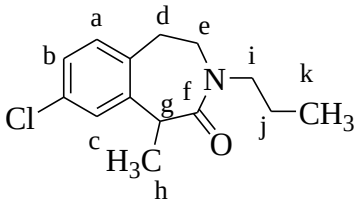


(39)

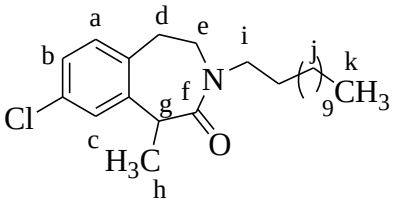
In the IR spectrum of compound **(39)**, the C=O stretching of cyclic amide was observed at 1658 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.19-6.92 (m, $3H_{a,b,c}$) for three protons. The alkene protons were observed at δ 5.74-5.55 (CH_k) for one proton, δ 5.70-5.60 (CH_j) for one proton and δ 5.07-5.00 (CH_k) for one proton, Among the aliphatic protons, proton (CH_g) was observed at δ 4.26-4.20 as a quartet which coupled with protons (CH_{3h}) observed at δ 1.48-1.45 as doublet with coupling constant of 6.8 Hz. Other signals were at δ 3.99-3.92 ($CH_{e,i}$) for three protons, δ 3.35-3.27 (CH_i) for one proton, δ 3.16-3.08 (CH_d) for one proton and δ 3.03-2.95 (CH_d) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 173.15 due to C=O carbon of the amide. Aromatic carbons appeared at δ 138.03, 135.07, 133.49, 132.41, 131.20, 129.70 and 127.33 whereas other signals at δ 126.81. 117.49 due to alkene and aliphatic carbons appeared at δ 50.01, 45.70, 39.81, 32.55 and 14.64. Its mass spectrum showed molecular ion peak at 250.1 $(M+1)^+$.

In the IR spectrum of compound **(40)**, the C=O stretching of cyclic amide was seen at 1646 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.26-6.99 (m, $3H_{a,b,c}$) for three protons. Among the aliphatic protons, proton (CH_g) was observed at δ 4.31-4.26 as a quartet which coupled with protons (CH_h) observed at δ 1.53-1.51 as a doublet with coupling constant 6.8 Hz. Other signals were at δ 4.15-4.07 (CH_e) for one proton, δ 3.44-3.28 ($CH_{e,i}$) for three protons, δ 3.25-3.05 (CH_d) for two protons, δ 3.22-3.21 (CH_e) for one proton and δ 1.50-1.48 (CH_j) for two protons. It gave a triplet at δ 0.94-0.81 (t, $3H_k$) for the other aliphatic protons. Its ^{13}C-NMR spectrum showed a peak at δ 173.42 due to C=O carbon of the

amide. Aromatic carbons appeared at δ 139.36, 135.78, 134.49, 132.34, 129.03, and 126.74 whereas the aliphatic carbons appeared at 50.63, 46.26, 39.89, 32.51, 21.06, 20.03, and 14.74. Its mass spectrum showed molecular ion peak at 252.10 $(M+1)^+$.



(40)

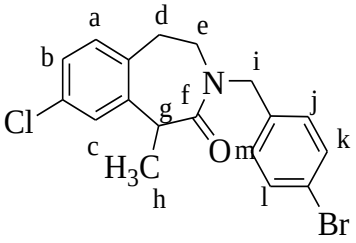


(41)

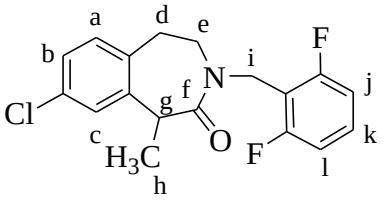
In the IR spectrum of compound **(41)**, the C=O stretching of cyclic amide was observed at 1655 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.18-7.15 (m, $2H_{a,b}$) for two protons and δ 7.07 (s, $1H_c$) for one proton. Among the aliphatic protons, proton (CH_g) was observed at δ 4.29-4.27 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.53-1.46 (CH_h) as doublet. Other signals were at δ 4.11-4.08 (CH_e) for one proton, δ 3.48-3.35 ($CH_{e,i}$) for three protons, δ 3.20-3.19 (CH_d) for one proton, δ 1.48-1.46 (CH_j) for two protons and δ 1.32-1.22 (CH_2) for at eighteen protons. It gave triplet at δ 0.89-0.83 (t, $3H_k$) for the other aliphatic protons. Its ^{13}C-NMR spectrum showed peak at δ 173.27 due to C=O carbon of the amide. Aromatic carbons appeared at δ 137.98, 135.85, 132.41, 129.83, 127.46 and 126.65 whereas the aliphatic carbons appeared at 47.97, 46.19, 39.95, 32.98, 32.00, 29.71, 29.63, 29.49, 29.43, 28.43, 26.93, 22.77, 14.75 and 14.19. Its mass spectrum showed molecular ion peak at 378.30 $(M+1)^+$.

In the IR spectrum of compound **(42)**, the C=O stretching of cyclic amide was observed at 1657 cm^{-1}. Its PMR spectrum showed the aromatic protons at δ 7.40-7.37 (m, $2H_{l,k}$) for two protons, δ 7.22-7.13 (m, $1H_a$) for one proton, δ 7.19-7.17 (m, $1H_b$) for one proton, δ 7.15-7.11 (m, $1H_c$) for one proton, δ 7.02-6.98 (m, $1H_j$) for one proton and δ 6.94-6.92 (d, $1H_m$) for one proton. Among the aliphatic protons, proton (CH_g) was observed at δ 4.37-4.30 as a quartet which coupled with protons (CH_{3h}) observed at δ 1.58-1.56 as a doublet with a coupling constant of 6.8 Hz. Other signals were at δ 4.58-4.43 (CH_e) for two protons, δ 4.06-3.97 (CH_i) for one proton, and δ 3.36-3.29 (CH_i) for one proton, δ 3.15-3.07 (CH_d) for one proton and δ 2.99-2.93 (CH_d) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 173.57 due to C=O carbon of the amide. Aromatic carbons appeared at δ 138.89, 137.95, 136.71, 135.59, 134.51, 132.59, 131.73, 129.74, 126.94 and 121.40 whereas the

aliphatic carbons appeared at 50.27, 46.05, 39.96, 32.36 and 14.62. Its mass spectrum showed molecular ion peak at 380.00 $(M+1)^+$.



(42)

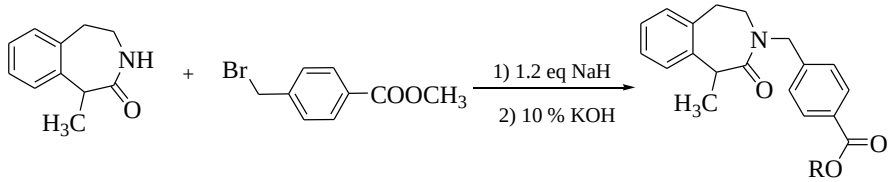


(43)

In the IR spectrum of compound **(43)**, the C=O stretching of cyclic amide was seen at 1643 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.28-7.20 (m, $2H_{a,b}$) for two protons, δ 7.16-7.09 (m, $1H_c$) for one proton, δ 6.98 (s, $1H_j$) for one proton, δ 6.91-6.83 (m, $2H_{k,l}$) for two proton. Among the aliphatic protons, proton (CH_g) was observed at δ 4.32-4.27 as a quartet which coupled with protons (CH_{3h}) observed at δ 1.45-1.43 as a doublet with coupling constant of 6.8 Hz. Other signals were at δ 4.94-4.82 (CH_e) for one proton, δ 4.63-4.56 (CH_e) for one proton, and δ 4.15-4.02 (CH_i) for one proton, δ 3.50-3.39 (CH_i) for one proton, δ 3.14-3.08 (CH_d) for one proton and δ 2.96-2.86 (CH_d) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 173.17 due to C=O carbon of amide. Aromatic carbons appeared at δ 163.18, 160.70, 138.74, 135.36, 132.39, 131.23, 129.70, 128.03, 127.35, 126.75, 113.21 and 111.53, whereas the aliphatic carbons appeared at 45.34, 39.98, 32.37, 30.53 and 14.81. Its mass spectrum showed molecular ion peak at 336.10 $(M+1)^+$.

4.1.4 Synthesis of 3-(4-carboxybenzyl)-1-methyl-2-oxo-1,3,4,5-tetrahyderobenzo [*d*]azepine-2-(3*H*)-one (44, 45)

In the Scheme-5, 1-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one **(6)** was reacted with equimolar quantities of NaH and methyl (4-bromomethyl)benzoate resulting in the formation of methyl 4-(1-methyl-2-oxo-1,3,4,5-tetrahydrobenzo[*d*]azepinyl)methylbenzoate **(44),** the ester **(44)** was reacted with potassium hydroxide (5%) in methanol to obtained the acid **(45)**.

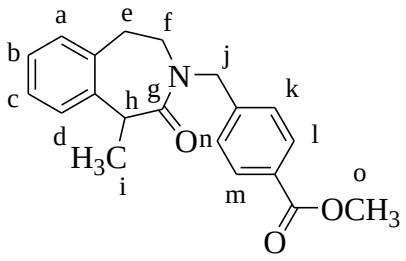


(6)

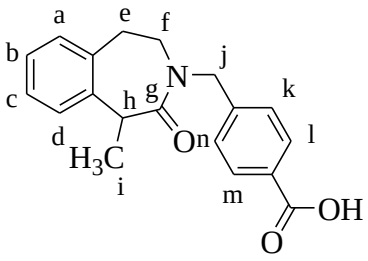
(44) R = CH3
(45) R = H

Scheme-5

In the IR spectrum of compound **(44)**, the C=O stretching of cyclic amide was observed at 1678 cm^{-1}. The peak at 1707 cm^{-1} was due to the C=O stretching of the ester. Its PMR spectrum showed aromatic protons at δ 7.85-7.83 (d, $2H_{l,m}$) for two protons with coupling constant of 7.9 Hz, δ 7.23-7.21 (d, $1H_k$) for one proton with coupling constant of 7.9 Hz, δ 7.18-7.14 (m, $1H_n$) for one proton, δ 7.12-7.09 (m, $3H_{b,c,d}$) for three protons and δ 6.96-6.94 (d, $1H_a$) for one proton with coupling constant of 7.4 Hz. Among the aliphatic protons, proton (CH_f) was observed at δ 4.64-4.60 as a doublet which coupled geminaly with δ 4.56-4.52 as a doublet with coupling constant of 15.2 Hz. Proton (CH_h) was observed at δ 4.36-4.30 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.55-1.53 as a doublet with a coupling constant of 6.8 Hz. Other signals were at δ 4.00-3.92 (CH_j) for one proton, δ 3.83 (s, $3H_o$) for three protons, δ 3.31-3.25 (CH_j) for one proton, δ 3.15-3.08 (CH_e) for one proton and δ 2.88-2.80 (CH_e) for one proton. Its ^{13}C-NMR spectrum showed peaks at δ 174.07 due to C=O carbon of the amide and another peak at δ166.89 due to C=O carbon of the ester. Aromatic carbons appeared at 143.10, 137.12, 136.09, 129.87, 129.85, 129.29, 127.76, 126.93, 126.83 and 125.65 whereas the aliphatic carbons appeared at 52.11, 50.01, 46.59, 40.28, 32.41 and 14.55. Its mass spectrum showed molecular ion peak at 337.7 $(M)^+$.



(44)



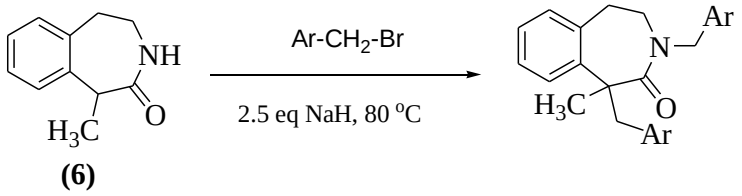
(45)

In the IR spectrum of compound **(45)**, the C=O stretching of cyclic amide was observed at 1652 cm^{-1}. The peak at 1700 cm^{-1} was due to C=O stretching of acid. Its PMR spectrum showed aromatic protons at δ 8.00-7.97 (d, $2H_{l,m}$) for two protons with coupling constant of 7.8 Hz, δ 7.31-7.21 (d, $1H_k$) for one proton with coupling constant of 7.8 Hz, δ 7.26-7.16 (m, $4H_{a,b,c,d}$) for four protons was δ 7.05-7.03 (d, $1H_n$) for one proton with coupling constant of 7.2 Hz. Among the aliphatic protons, proton (CH_f) was observed at δ 4.74-4.70 as a doublet which coupled geminaly with δ 4.67-4.63 as doublet with coupling constant of 15.3 Hz. Proton (CH_h) was observed at δ 4.44-4.39 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.64-1.62 as doublet with a coupling constant of 6.8 Hz. Other signals were at δ 4.09-4.01 (CH_j) for one proton, δ 3.41-3.34 (CH_j) for one proton, δ 3.25-3.18 (CH_e) for one proton and δ 2.98-2.90 (CH_e) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 174.19

due to C=O carbon of the amide and another peak at δ170.99 due to C=O carbon of the acid. The aromatic carbons appeared at δ 143.96, 137.14, 136.07, 130.50, 129.83, 128.43, 127.82, 126.97, 126.88 and 125.71 whereas the aliphatic carbons appear δ 50.77, 46.70, 40.43, 32.41 and 14.59. Its mass spectrum showed molecular ion peak at 310.00 $(M+1)^+$.

4.1.5 Synthesis of 1,3-disubstitued 1-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (46, 47)

In the Scheme-6, 1-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one **(6)** was reacted benzyl bromide or 3-flurobenzyl bromide using NaH (2.5 eq.) leading to the formation of trisubstituted derivatives **(46** and **47).** The reaction was carried out at 60 ^oC for 2-3 hrs.

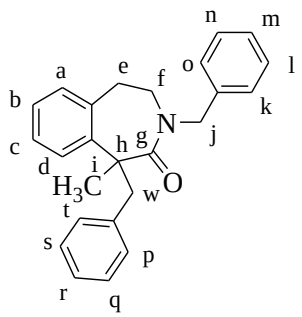


(6)

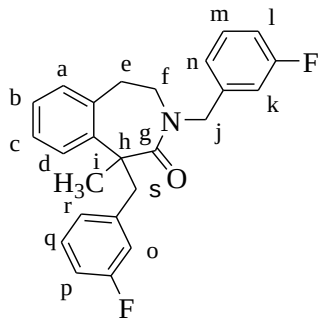
(46) Ar = C_6H_5
(47) Ar = $3FC_4H_4$

Scheme-6

In the IR spectrum of compound **(46)**, the C=O stretching of cyclic amide was observed at 1611 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.51-7.49 (d, $1H_a$) for one proton, δ 7.30-7.17 (m, $6H_{b,c.d,n,l,m}$) for six protons, δ 7.10-7.05 (m, $4H_{o,k,s,q}$) for four protons, δ 6.91-6.90 (m, $1H_r$) for one proton and δ 6.74-6.72 (m, $2H_{t,p}$) for two protons. Among the aliphatic protons, proton (CH_f) was observed at δ 4.68-4.64 as a doublet which coupled geminally with δ 4.54-4.51 as a doublet with coupling constant of 14.6 Hz. Other signals were at δ 3.68-3.64 (CH_j) for one proton, δ 3.37-3.30 ($CH_{j,e}$) for two protons, δ 3.13-3.10 (CH_e) for one proton, δ 2.70-2.60 (CH_w) for one proton and δ 2.56-2.48 (CH_w) for one proton. It gave a singlet at δ 1.78 (s, $3H_i$) for other three aliphatic protons. Its mass spectrum showed molecular ion peak at 355.09 $(M)^+$.



(46)

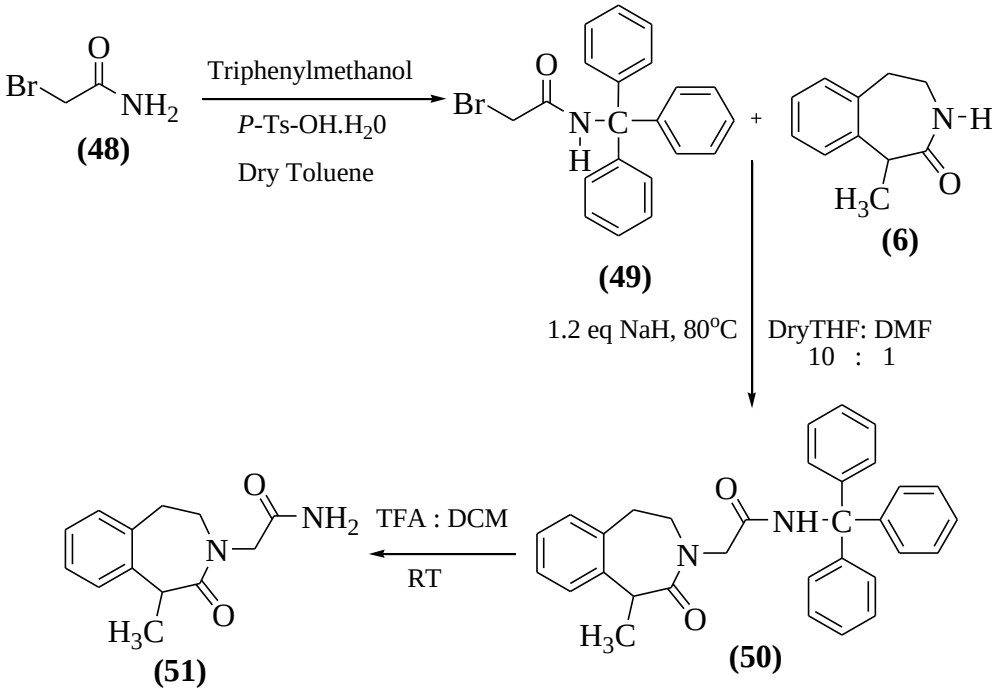


(47)

In the IR spectrum of compound **(47)**, the C=O stretching of cyclic amide was seen at 1616 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.44-7.42 (d, $1H_k$) for one proton with coupling constant of 8.08 Hz, δ 7.21-7.15 (m, $2H_{m,n}$) for two protons, δ 7.07-7.04 (m, $1H_l$) for one proton, δ 6.97-6.92 (m, $2H_{o,p}$) for two protons, δ 6.83-6.75 (m, $2H_{q,r}$) for two protons, δ 6.73-6.65 (m, $1H_a$) for one protons, δ 6.71-6.70 (m, $2H_b$) for two protons, δ 6.48-6.46 (d, $1H_d$) for one proton with coupling constant of 7.6 Hz and δ 6.33-6.29 (m, $1H_c$) for one proton. Among the aliphatic protons, signals were observed at δ 4.68-4.60 (CH_f) for one proton, δ 4.45-4.41 (CH_f) for one proton, δ 3.78-3.74 (CH_j) for one proton, δ 3.32-3.25 (CH_j) for one proton, δ 3.18-3.16 (CH_s) for one proton. δ 2.97-2.93 (CH_s) for one proton, δ 2.59-2.53 (CH_e) for one proton and δ 2.36-2.32 (CH_e) for one proton, it gave a singlet at δ 1.81 (s, $3H_i$) for other three aliphatic protons Its mass spectrum showed molecular ion peak at 391.00 $(M)^+$.

4.1.6 Synthesis of 2-(1-methyl-4,5-dihydro-2(3*H*)-oxo-1*H*-benzo[*d*]azepin-3-yl) acetamide (51)

Compound **(51)** having *N*-acetamide group was prepared from 2-bromoacetamide **(48)** and the benzazepine derivative (**6**). Direct reaction of 2-bromoacetamide **(48)** with 3-

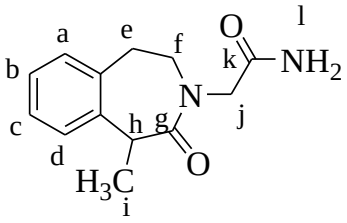


Scheme-7

benzazepin-2-one **(6)** failed to provide the desired product, so it was thought to protect the amide function in 2-bromoacetamide **(48)** using some suitable protecting group. 2-Bromoacetamide **(48)** was reacted with triphenylmethanol using tosic acid as a catalyst to

obtain *N*-trityl derivative **(49)** as white solid. The yield of the reaction was around above 88 %. In the IR spectrum of compound **(49)**, the stretching vibrations of N-H were observed at 3265 cm^{-1}. The C=O stretching of amide was seen at 1664 cm^{-1}. Compound **(49)** was treated with NaH and 3-benzazepin-2-one **(6)** to obtain the desired derivative **(50)**. Treatment of the derivative **(50)** with trifluroacetic acid: DCM (70:30) resulted in the formation of compound **(51)** as shown in Scheme 7.

In the IR spectrum of compound **(51)**, the C=O stretching of cyclic amide was seen at 1682 cm^{-1}. Its PMR spectrum showed aromatic protons at δ 7.28-7.13 (m, $4H_{a,b,c,d}$) for four protons. It gave a singlet at δ 6.08 (s, $1H_l$) and 5.24 (s, $1H_l$) for two protons due to amidic nitrogen. Among the aliphatic protons, proton (CH_h) was observed at δ 4.40-4.35 as a quartet which coupled with protons (CH_{3i}) observed at δ 1.59-1.57 as a doublet with coupling constant of 6.8 Hz. Other signals were at δ 4.23-4.17 (CH_j) for one proton, proton (CH_f) was observed at δ 4.09-4.03 as a doublet which coupled geminaly with δ 3.99-3.90 as doublet with coupling constant of 15.5 Hz, δ 3.55-3.49 (CH_j) for one proton, δ 3.37-3.30 (CH_e) for one proton and δ 3.29-3.13 (CH_e) for one proton. Its ^{13}C-NMR spectrum showed peak at δ 174.56 and 171.62 due to C=O carbon of the amide. Aromatic carbons appeared at δ 136.90, 129.88, 127.22, 127.04 and 125.52 whereas the aliphatic carbons appeared δ 52.51, 48.98, 40.11, 32.15 and 14.20. Its mass spectrum showed molecular ion peak showed at 255.1$(M+Na)^+$.



(51)

4.2 Biological studies

4.2.1 *In vitro* 5-HT_{2A} and 5-HT_{2B} receptors bioassays using rat thoracic aorta and rat fundus preparations: All of the synthesized compounds **(8-47** and **51)** were evaluated *in vitro* for 5-HT_{2A} and 5-HT_{2B} sensitivity by using rat thoracic aorta and rat fundus preparations to determine activity of the compounds on 5-HT_{2A} and 5-HT_{2B} receptors respectively (Table 1). Initially, the test compounds **(8-47** and **51)** were evaluated at 2×10^{-5} M concentration in both of the *in vitro* experiments to determine their 5-HT_{2A}/5-HT_{2B} agonist/antagonist activity. In case a compound showed agonist and/or antagonist activity on

either of the preparations, it was evidenced by their pD_2 and/or pA_2 values respectively. pD_2 value is the negative logarithm of the EC_{50} of an agonist which indicates its potency while pA_2 depicts the negative logarithm of the molar concentration of the antagonist that necessitates doubling of the concentration of the agonist needed to produce the original response. None of the compounds showed affinity for 5-HT_{2A} receptor on rat thoracic aorta preparation. However, compounds (**17, 19, 20-23, 26-28, 34-36, 40, 42** and **47**) were found to be 5-HT_{2B} receptor agonists, which was evident by their pD_2 values while compounds (**16, 39**

Table 1 *In vitro* assessment of the test compounds (**8-47** and **51**) for 5-HT_{2A} and 5-HT_{2B} receptors' actions using isolated rat thoracic aorta and rat fundus preparations respectively

Comp.	**5-HT_{2A}**		**5-HT_{2B}**		Comp.	**5-HT_{2A}**		**5-HT_{2B}**	
	Agonist	Antagonist	Agonist	Antagonist		Agonist	Antagonist	Agonist	Antagonist
	pD_2 value	pA_2 value	pD_2 value	pA_2 value		pD_2 value	pA_2 value	pD_2 value	pA_2 value
8	*	*	*	*	**29**	*	*	*	*
9	*	*	*	*	**30**	*	*	*	*
10	*	*	*	*	**31**	*	*	*	*
11	*	*	*	*	**32**	*	*	*	*
12	*	*	*	*	**33**	*	*	*	*
13	*	*	*	*	**34**	*	*	6.81±0.13	-
14	*	*	*	*	**35**	*	*	8.47±0.19	-
15	*	*	*	*	**36**	*	*	7.70±0.33	-
16	*	*	-	6.95±0.25	**37**	*	*	*	*
17	*	*	8.46±0.39	-	**38**	*	*	*	*
18	*	*	*	*	**39**	*	*	-	8.38±0.19
19	*	*	7.21±0.24	-	**40**	*	*	8.59±0.20	-
20	*	*	7.76±0.22	-	**41**	*	*	*	*
21	*	*	6.73±0.41	-	**42**	*	*	7.44±0.14	-
22	*	*	7.84±0.34	-	**43**	*	*	*	*
23	*	*	8.39±0.28	-	**44**	*	*	*	*
24	*	*	*	*	**45**	*	*	*	*
25	*	*	*	*	**46**	*	*	*	7.95
26	*	*	7.03±0.10	-	**47**	*	*	8.26	-
27	*	*	6.48±0.29	-	**51**	*	*	*	*
28	*	*	6.99±0.36	-					

Results are expressed as mean±SEM *Compounds were found inactive at 2×10^{-5} M concentration. Those compounds which showed activity at this concentration were later used for determining their pD_2 / pA_2 values.

and **46**) were shown to possess 5-HT_{2B} receptor antagonistic property offering pA_2 values greater than 6 (Table 1)**.** Only those compounds which did not show 5-HT_{2A} and 5-HT_{2B} affinities in the isolated tissue preparations were taken up further for *in vivo* study on 5-HT_{2C}

receptor. Thus, compounds (**8-15, 18, 24, 25, 29-33, 37, 38, 41, 43-45,** and **51**) were selected for 5-HT_{2C} receptor affinity studies since all these compounds were found to be inactive in the *in vitro* studies on both the tissues, suggesting their lack of affinity for the 5-HT_{2A} and 5-HT_{2B} receptors. These compounds could be active or inactive on 5-HT_{2C} receptor.

4.2.2 Despair swim test: There are evidences demonstrating that over-activation of 5-HT_{2C} receptor may develop depressive and anxiety symptoms in a certain population of patients. 5-HT mediated activation of 5-HT_{2C} receptor is responsible for the negative side effects associated with selective serotonin re-uptake inhibitor (SSRI) medication.[87] The despair swim test model was adopted for the assessment of depression.[88] Rajkumar *et al.* have demonstrated the ability of *m*-CPP **(XI)** to induce depressogenic behaviour in rodents due to its 5-HT_{2C} receptor agonist activity. Compounds (**8-15, 18, 24, 25, 29-33, 37, 38, 41, 43-45,** and **51**) were screened for the despair swim test. As expected for a positive control, *m*-CPP **(XI)** showed significant increase in the immobility time, indicative of the depressive effect (**Figure 4**, $p<0.001$). Compounds (**8, 13-15, 25, 31,** and **37**) showed significant increase in the immobility time as compared to the saline control (**Figure 4**, $p<0.001$) which was

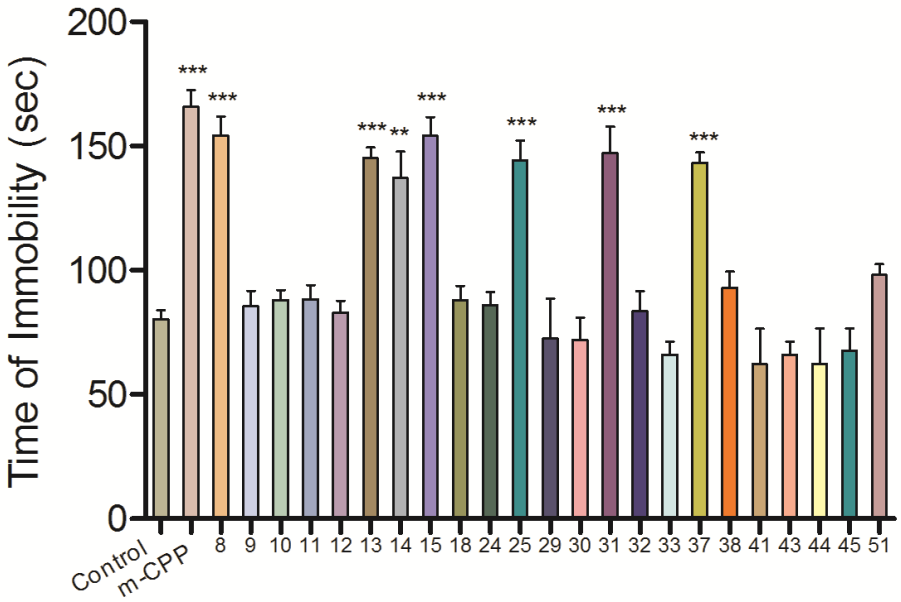


Figure 4. Effect of *m-CPP* **(XI)** (2 mg/kg, p.o.) and the test compounds (10 mg/kg, p.o.) in despair swim test. Values represent the immobility time. Data are expressed as mean ± SEM. $^{***}p<0.001$, $^{**}P<0.01$ indicate the level of significance *vs* vehicle-treated control group (N=6).

possibly due to their 5-HT_{2C} receptor agonist activity. These compounds showed 5-HT_{2C} agonist mediated depressogenic response similar to the standard *m*-CCP **(XI).** Rest of the

compounds **(9-12, 18, 24, 29, 30, 32, 33, 38, 41, 43-45,** and **51)** did not show significant effects in this test suggesting their inactivity for 5-HT_{2C} receptor. Compounds (**8, 13-15, 25, 31,** and **37**) demonstrating positive response in this test were proceeded for further evaluation.

4.2.3 Elevated plus maze test: Anxiety is regulated mainly by the amygdala region of the brain with high levels of 5-HT_{2C} receptor expression. Previous report[89] demonstrated that activation of amygdala by a 5-HT_{2C} receptor agonist was strongly associated with the anxiety state. Thus antagonism of 5-HT_{2C} receptor might be beneficial for the treatment of anxiety.[90, 91] Thus, the chosen compounds (**8, 13-15, 25, 31,** and **37**) were evaluated on the anxiety model. The elevated plus maze test was adopted to assess the anxiety like condition. In the elevated plus maze test, *m*-CCP **(XI)** showed significant anxiogenic response in mice (**Figure 5A**, $p<0.001$). Compounds (**8, 13-15, 25, 31,** and **37**) showed significant decrease in the exploration (**Figure 5A**) as well as time spent (**Figure 5B**) in the open arm ($p<0.001$), demonstrating their anxiogenic effect like the one showed by *m*-CCP **(XI)**, substantiating their activity on 5-HT_{2C} receptor.

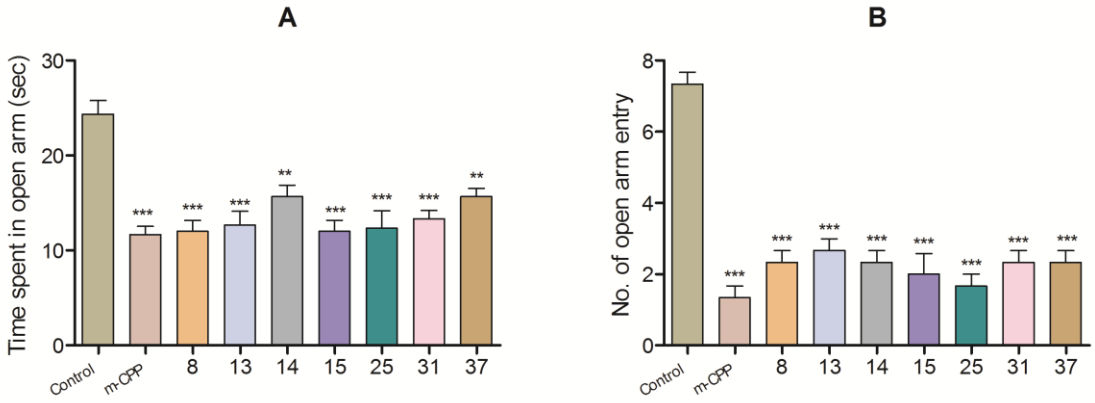


Figure 5. Effect of *m*-CPP **(XI)** (2 mg/kg, p.o.) and the test compounds (10 mg/kg, p.o.) on the elevated plus maze test. (A) represents time spent in open arm while (B) represents number of open arm entries. Data are expressed as mean ± SEM. $^{***}p<0.001$, $^{**}P<0.01$ indicate level of significance *vs* vehicle-treated control group (N=6).

4.2.4 Hypophagic response: Tecott *et al.* [92] demonstrated that 5-HT_{2C} receptor knockout mice developed obesity and remained hyperphagic throughout their life. Pro-opiomelanocortin (POMC) neurons express predominantly 5-HT_{2C} receptor mRNA wherein 5-HT_{2C} agonism leads to increased production of α-melanocyte stimulating hormone (MSH) which ultimately enhances MC4 receptor signalling[92-95] resulting in reduced food intake. 5-HT_{2C} receptor agonists also increase satiety resulting in reduced food intake. [94, 96] The test

compounds (**8, 13-15, 25, 31,** and **37**) were assessed for their 5-HT_{2C} receptor mediated hypophagic response. In accordance with the above cited findings, compounds (**8, 13-15, 25, 31,** and **37**) significantly decreased the amount of food intake (**Figure 6A**, p<0.001). Their hypophagic effects were significantly reversed by pre-treatment of the animals with RS-102221 **(3)** a selective 5-HT_{2C} receptor antagonist, (**Figure 6A**, p<0.001) confirming their 5-HT_{2C} receptor agonistic activity. *m*-CCP **(XI)** also showed a significant hypophagic effect (**Figure 6A**, p<0.001) in this model.

4.2.5 Penile erection: Compounds (**8, 13-15, 25, 31,** and **37**) were also evaluated for the 5-HT_{2C} receptor mediated penile erection in the absence and presence of RS-102221 **(VII)**, a 5-HT_{2C} antagonist. *m*-CCP **(XI)** induces penile erection, excessive grooming and increased levels of oxytocin, prolactin and corticosterone in rats. Paraventricular nucleus is believed to control sexual behaviour and neuroendocrine responses.[97] *m*-CCP **(XI)** significantly induced penile erection and engorged penis (**Figure 6B**, p<0.001) in the test. Compounds (**8, 13-15, 25, 31,** and **37**) also showed similar effects (**Figure 6B**, p<0.001) which were significantly suppressed by pre-treatment of the animals with RS-102221 **(VII)** (**Figure 6B**, p<0.001). These results substantiated selective antagonism of the test compounds towards 5-HT_{2C} receptor.

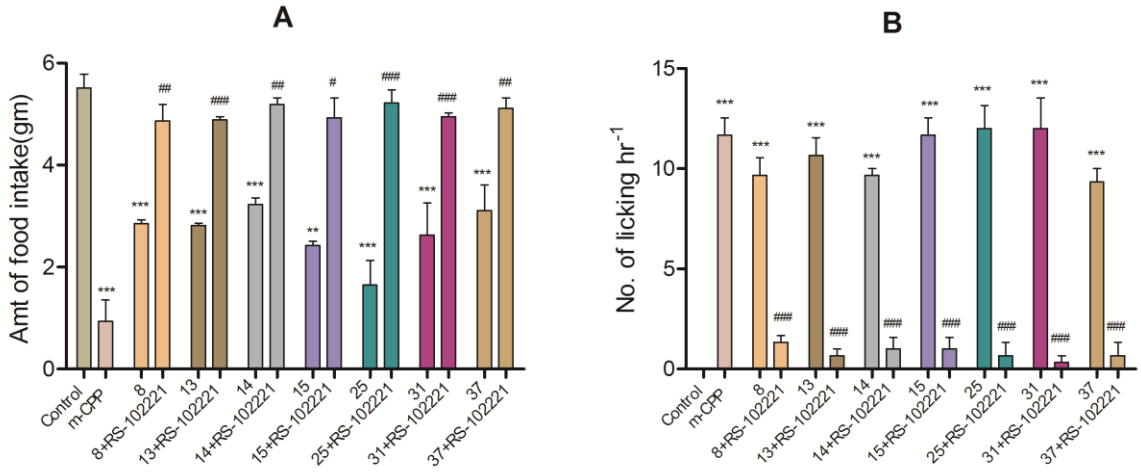


Figure 6. Effect of *m-CPP* **(XI)** (2 mg/kg, p.o.) and the test compounds (10 mg/kg, p.o.) on hypophagic and penile erection models. (A) represents amount of food intake upon test compound administration alone and with pretreatment of the animals with RS-102221 **(VII)** (2 mg/ kg, i.p.). (B) represents number of penile lickings upon test compound administration alone and with pretreatment of the animals with RS-102221 (2 mg/kg, i.p.). Data are expressed as mean ± SEM. $^{***}p$<0.001, $^{**}P$<0.01 indicate level of significance *vs* vehicle-treated control group (N=6). $^{###}p$<0.001, $^{##}p$<0.01, $^{##}p$<0.05 indicates significant difference from respective test compound treated group (compound alone) (N=6).

4.2.6 Estimation of monoamines: Previous studies [98-101] revealed that 5-HT_{2C} receptors have an influence on the firing of monoamine neurotransmitters. 5-HT_{2C} agonists negatively regulate the firing of dopamine (DA) and 5-HT neurons in the dorsal raphe nucleus (DRN) and ventral tegmental area (VTA), respectively. [102, 103] A significant decrease in the brain concentrations of DA (**Figure 7A**, $p<0.001$) and 5-HT (**Figure 7B**, $p<0.001$) was observed in the animals exposed to the test compounds (**8, 13-15, 25, 31,** and **37**) Pre-treatment of the animals with RS-102221 **(**Selective 5-HT_{2c} antagonist**)** at a dose of 2 mg/kg, p.o. significantly reversed the decreased levels of DA (**Figure 7A**, $p<0.001$) and 5-HT (**Figure 7B**, $p<0.001$) which further supported our above described observations. This study reaffirmed that the test compounds, which were found to be 5-HT_{2C} agonists in earlier described *in vivo* models, significantly decreased the DA and 5-HT levels in the brain similar to those caused by *m*-CCP **(11)**. Thus, these results have demonstrated that the evaluated compounds (**8, 13-15, 25, 31,** and **37**) are selective 5-HT_{2C} receptor agonists.

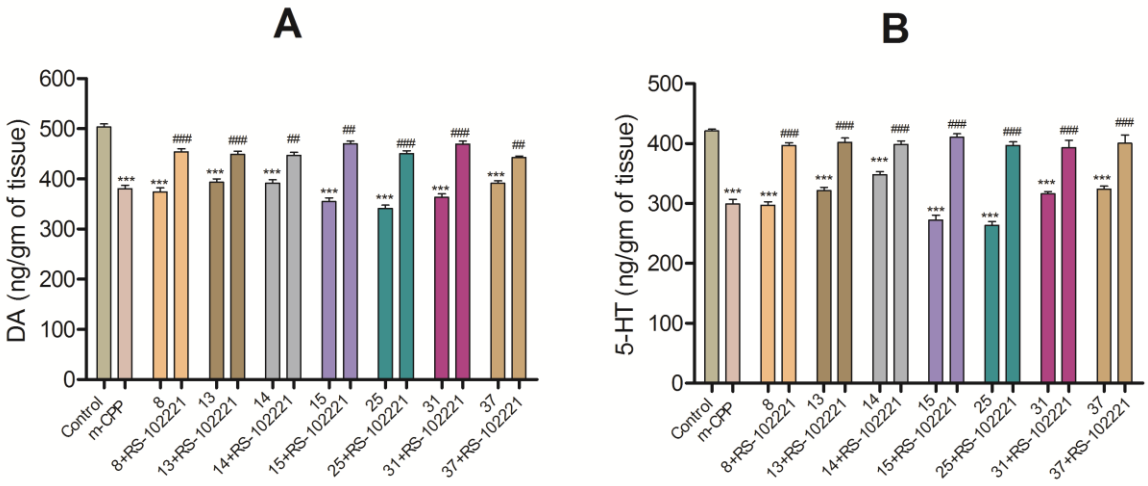


Figure 7: Effect of *m-CPP* **(XI)** (2 mg/kg, p.o.) and the test compounds (10 mg/kg, p.o.) on DA and 5-HT levels in the rat brain. Values represent the % fold change of in (A) DA and (B) 5-HT levels in the rat brain after treatment of compounds alone and in presence of RS-102221 (**VII**). Data are expressed as mean ± SEM. $^{***}p<0.001$ indicates level of significance *vs* vehicle-treated control group (N=6). $^{###}p<0.001$, $^{##}p<0.01$ indicates significant difference from respective test compound treated group (compound alone) (N=6).

4.2.7 Structure activity relationship (SAR): Different 3-substituted benzazepin-2-ones were synthesized maintaining 1-methyl group as a constant structural feature in all of the compounds like lorcaserine **(V)**. But unlike lorcaserin **(V)**, the synthesized compounds were racemic mixtures. It was not tried to resolve the racemic mixtures or to synthesize optically pure isomers because the primary aim of the study was to identify compounds with some

degree of selective agonist activity for 5-HT_{2C} receptors. It was observed that variations in groups at position 3 altered the activity and selectivity on 5-HT_2 receptors. Interestingly, none of these derivatives were found to be active on 5-HT_{2A} receptors as seen from the Table 1, as no compound gave an adequate response on isolated rat thoracic aorta preparation. Many of these derivatives showed agonist (**17, 19, 20-23, 26-28, 34-36, 44, 42** and **47**) or antagonist (**16, 39** and **46**) activity on 5-HT_{2B} receptors. Among the alkyl substituents, when the chain length or branching was increased, the resulting compounds either became inactive (**9-12**) towards all the receptors or became 5-HT_{2B} responsive [agonists (**17** and **21**) or antagonists (**16** and **39**)]. Substitution with cycloalkylmethyl also did not cause enhancement in activity as these compounds were either inactive (**33**) on 5-HT_2 receptors or proved agonist (**35**) for 5-HT_{2B} receptors. Ethyl (**8**) and *iso*propyl (**15**) were the only alkyl groups which offered good selectivity as seen from all of the *in vivo* experiments.

Substituted benzyl derivatives showed much more responsiveness towards the 5-HT_2 receptors. Majority of them were found to be 5-HT_{2B} agonists (**19, 20, 22, 23, 26-28, 34, 36** and **42**), some totally inactive (**24, 29, 30, 32,** and **43-45**) while some others showed a good level of selectivity (**13, 14, 25** and **31**) for 5-HT_{2C} receptors. It seems that 2- and 4-positions of the benzene ring are more suited for a compound to show 5-HT_{2C} receptor affinity. It could not become very clear whether electron withdrawing or donating groups favor binding of the compounds to 5-HT_{2C} receptors, but electronegative atoms in these positions (**13, 14** and **31**) favour binding to the 5-HT_{2C} receptors while alkyl groups (**22, 23** and **34**) at 2- or 4- positions and electron withdrawing groups at position 3 or 2 and/or 5 in the benzyl moiety (**27-29**) make the compounds 5-HT_{2B} agonists although, there are certain exceptions (**20, 26, 30, 32** and **36**) to the above observations.

Substitution of the chloro group at position 8 in the 3-substitued 3-benzazepin-2-one ring system with simple ethyl group (**37**) at position-3 offered 5-HT_{2C} selectivity, but other groups at 3-position make the compounds (**39, 40** and **42**) more responsive towards 5-HT_{2B} receptors. It seems 8-chloro substitution does not favour 5-HT_{2C} selectivity. Polar groups are also not desired at position 3 as both the compounds (**45** and **51**) were found to be inactive on 5-HTreceptors.