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SYNTHESIS OF NEFOPAM ANALOGUES AND CHARACTERISATION

Katuroju Srinivasachary [*1,2], Shashikant Tiwari [1], Y. S. Somannavar [1] and Bhoomireddy Ramadevi [2]

APL Research Centre-II [1], Chemical Research and Development, Aurobindo Pharma Ltd., Sangareddy - 502329, Telangana, India.
Department of Chemistry [2], Jawaharlal Nehru Technological University, Hyderabad - 500072, Telangana, India.

Keywords:

Analgesic,
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Correspondence to Author:
Katuroju Srinivasachary

Scientist,
Chemical Research and Development,
APL Research Centre-II, Aurobindo Pharma Ltd., Survey No. 71 & 72,
Indrakaran, Sangareddy - 502329,
Telangana, India.

E-mail: kathrojusrinivasachary@gmail.com

ABSTRACT: Modified Benzoxazocine moiety of Nefopam with N-Protected-ethanolamine, fluorobenzene benzylbromide, 2,3-dimethyl-benzene, naphthalene, fluro-naphthalene. In these modification Friedel Craft alkylation plays vital role with using grignard reagent and aluminum chloride with the starting phthalic anhydride to form acid compound and was converted to amide compound with using of thionyl chloride, N-Protected ethanol amino and further converted to benzhydrol follows two synthetic routes, one routes is amide is converted to choro intermediate with thionyl chloride and then converted to benzhydrol, and another route is amide compound is directly converted into benzhydrol. Benzhydrol is the key intermediate for the preparation of all Nefopam analogs. These benzhydrol is undergone cyclization with p-Toluene sulfonic acid to forms benzoxazocine moiety of Nefopam analogs, by these ways disclosed nefopam analogs containing Benzoxazocine moiety as a novel analgesic therapeutic compounds, and these compounds were characterized by IR, ^{1}H NMR Mass analysis.

INTRODUCTION: Nefopam Hydrochloride is 1H-meth-2,5-Benzoxazocine,3,4,5,6-Tetrahydro-5-methyl-1-Phenyl, Hydrochloride. Nefopam is an analgesic drug which is used in post-operation for the patient it is not a narcotic drug; it is a non – opioid analgesic drug [6] in the treatment of acute pain for adults. In a search for new better analgesic drugs commonly found in literature compound designated as analogs or derivatives. Based on knowledge obtained from literature we attempted to prepare nefopam analogs by using different N-alkylated amines.

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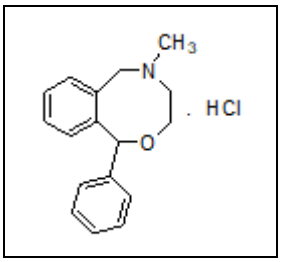


NEFOPAM HYDROCHLORIDE

For the preparation of nefopaman analogs, introduced fluorophenyl, ethyl, fluoronapthyl, naphthyl, benzyl groups A series of Nefopam analogs were synthesized and characterized and hopefully which are similar properties like a nefopam.

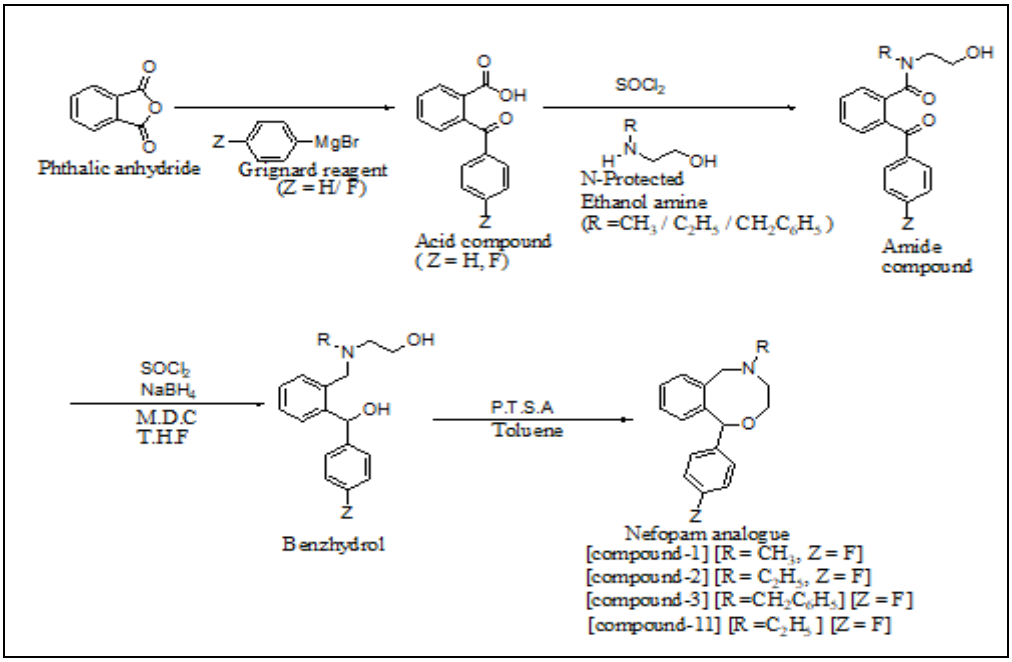
Scheme 1:

Compound 1: (1H-2, 5-Benzoxazocine-3, 4, 5, 6-tetrahydro- 5- methyl- 1- (4- fluoro)- phenyl hydrochloride.

Compound 2: (1H-2,5-Benzoxazocine-3,4,5,6-tetra-hydro-5-ethyl-1-(4-fluoro)- Phenyl hydrochloride.

Compound 3: (1H-2,5-Benzoxazocine-3,4,5,6-tetra-hydro-5-benzyl-1-(4-fluoro)- Phenyl hydrochloride.

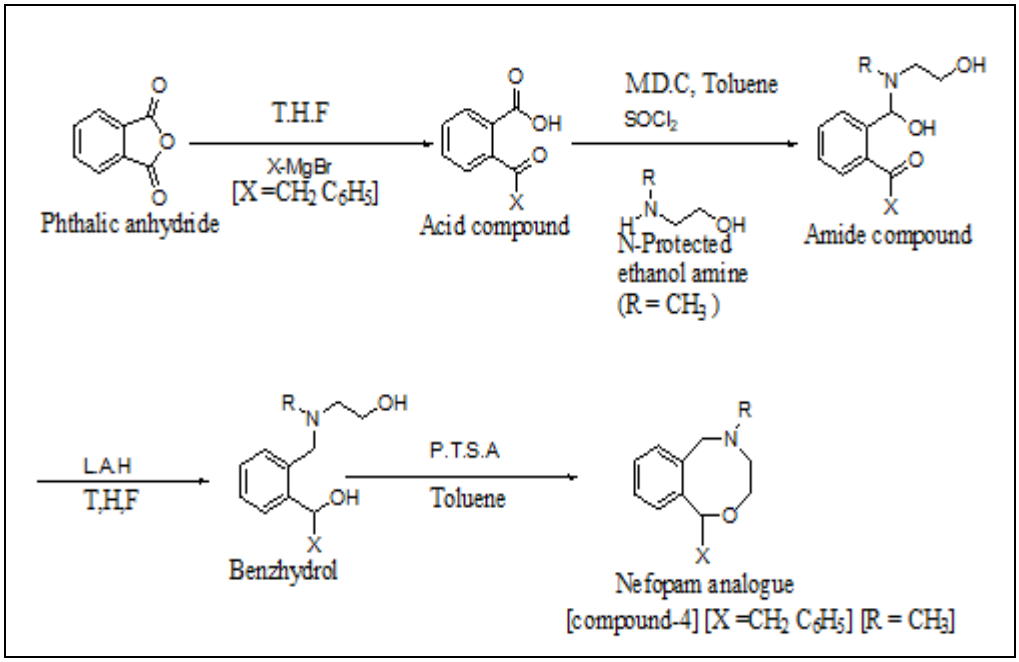
Compound 11: (1H-2,5-Benzoxazocine-3,4,5,6-tetrahydro-5-ethyl-Pheny Hydrochloride.



SCHEME 1

Scheme 2:

Compound 4: (1-Benzyl-5-methyl-3,4,5,6-Tetra hydro-1H-2,5-Benzoxazocine).

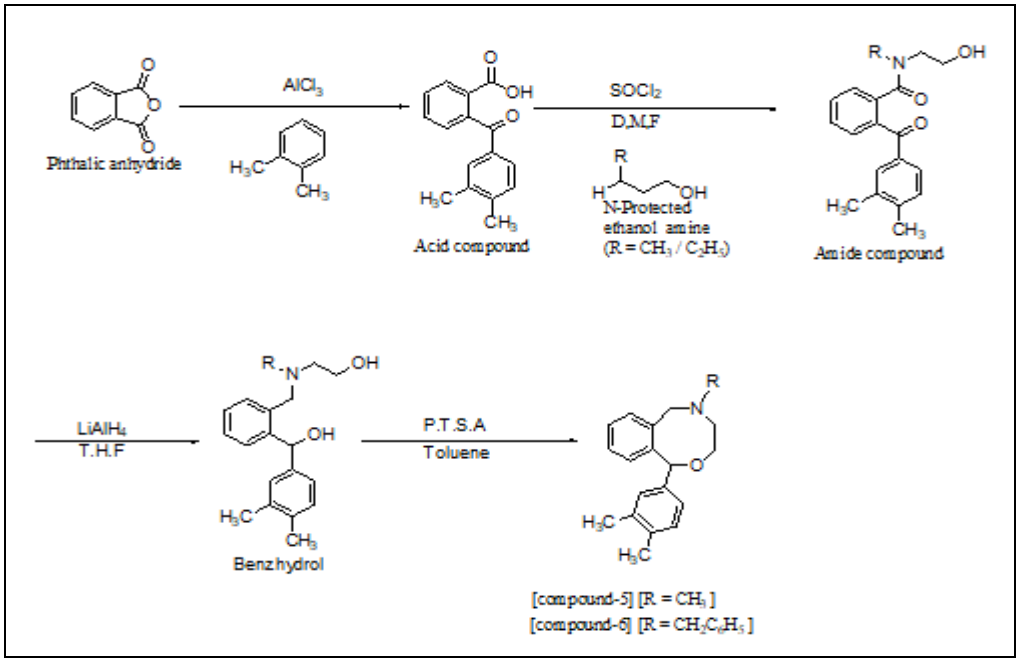


SCHEME 2

Scheme 3:

Compound 5: (3,4,5,6-Tetrahydro-5-methyl-1-(3,4-Dimethyl)-Phenyl-1H-2,5-Benzoxazocine).

Compound 6: (3,4,5,6-Tetrahydro-5-benzyl-1-(3,4-Dimethyl)-Phenyl-1H-2,5-Benzoxazocine).



SCHEME 3

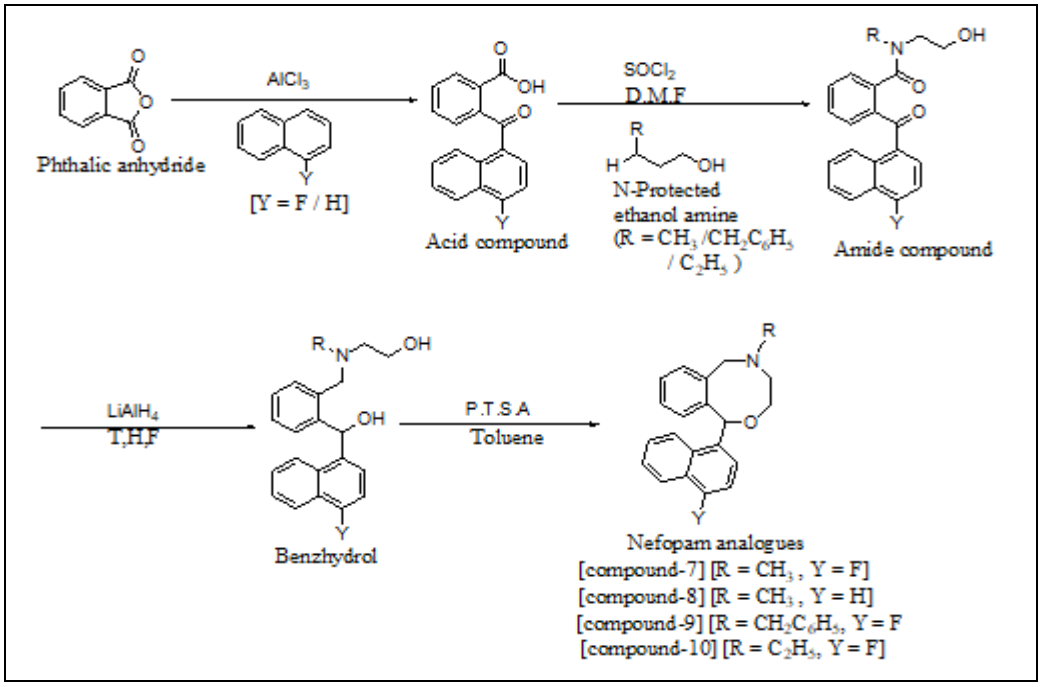
Scheme 4:

Compound 7: (1H-2,5-Benzoxazocine,3,4,5,6-Tetrahydro-5-methyl-1(4-Fluoro)-Napthalenyl Hydrochloride.

Compound 8: (1H-2,5-Benzoxazocine,3,4,5,6-Tetrahydro-5-methyl-1-Napthalenyl Hydrochloride.

Compound 9: (1H-2,5-Benzoxazocine,3,4,5,6-Tetrahydro-5-benzyl-1(4-Fluoro)-Napthalenyl Hydrochloride.

Compound 10: (1H-2,5-Benzoxazocine,3,4,5,6-Tetrahydro-5-ethyl-1(4-Fluoro)-Napthalenyl Hydrochloride.



SCHEME 4

EXPERIMENTAL SECTION: General experimental procedure: ^{1}H NMR were recorded on Bruker 300 spectrometer at 300 MHz, and the chemical shifts were reported as δvalues in parts per million relatives to TMS as an internal standard Infrared spectrum were recorded in the solid-state as KBr.

Dispersion using a Perkin Elmer spectrometer. Mass spectra were recorded on API 2000 Perkin-Elmer PE-SCIEX mass spectrometer.

Synthesis of 1H-2, 5-Benzoxazocine 3, 4, 5, 6-tetrahydro- 5- methyl- 1- (4- fluoro)- Phenyl - hydrochloride: Suspended Magnesium turnings (2 g, 0.08 moles) in tetrahydrofuran (60 mL) under nitrogen atmosphere and heated to 50-55 °C added crystal of Iodine followed by 2.5 g of 4-Fluoro-Bromo-benzene (0.014 mole) for initiate Grignard reaction, and slowly added mixture of 11.7g of 4-Fluoro- Bromo-benzene (0.07 mole) and tetrahydrofuran (10 mL) at 45-65 °C In 1 h and agitated reaction mass at 60-65 °C for 1 h, then cooled the reaction mass to 25-30 °C and the above prepared Grignard reagent added to mixture of phthalic-anhydride (10g)-dichloromethane (80 mL) at 0-5 °C in 1 h, stirred the reaction mass for 1 h at 0-5 °C, and quenched the reaction mass with 5N aqueous hydrochloric acid solution (25 mL) at 0-5 °C and separated below organic layer these organic layers were mixed with DM water (100 mL) and adjusted the pH to 11-11.5 with 10% w/ aqueous sodium hydroxide solution (30 mL) at 25-30 °C and organic layer was separated, and adjusted the pH of aqueous layer (at pH- 11-11.5) to pH-2 with conc. hydrochloric acid (12 mL) result acid compound (4-fluoro-benzoyl -benzoic- acid) obtained (dried wt: 15g).

The above 4-fluoro-benzoyl benzoic acid (15g) was suspended in toluene (75mL) at 25-30 °C and added catalytic N,N-dimethyl formamide (16g) followed by the addition of thionyl chloride (9g, 0.073 mole) under nitrogen atmosphere at 25-30 °C and stirred the reaction mass for 2 h at 25-30 °C and reaction completed by checking of TLC and concentrated under reduced pressure at 45-50 °C and diluted the conc. mass in toluene (60 mL) at 25-30 °C and cooled to 10-15 °C and added mixture of N-methyl ethanolamine (10g, 0.135 mole) and toluene (15 mL) at 15-20 °C stirred the reaction mass at 25-30 °C for 3 h then observed that reaction was completed by checking of TLC, Then added DM water (120 mL) and stirred the reaction mass for 1 h at 25-30 °C, filtered the produc 4-fluoro-benzoyl-N-(2-Hydroxyethyl)-N-methyl benzamide, dried wt. 16g.

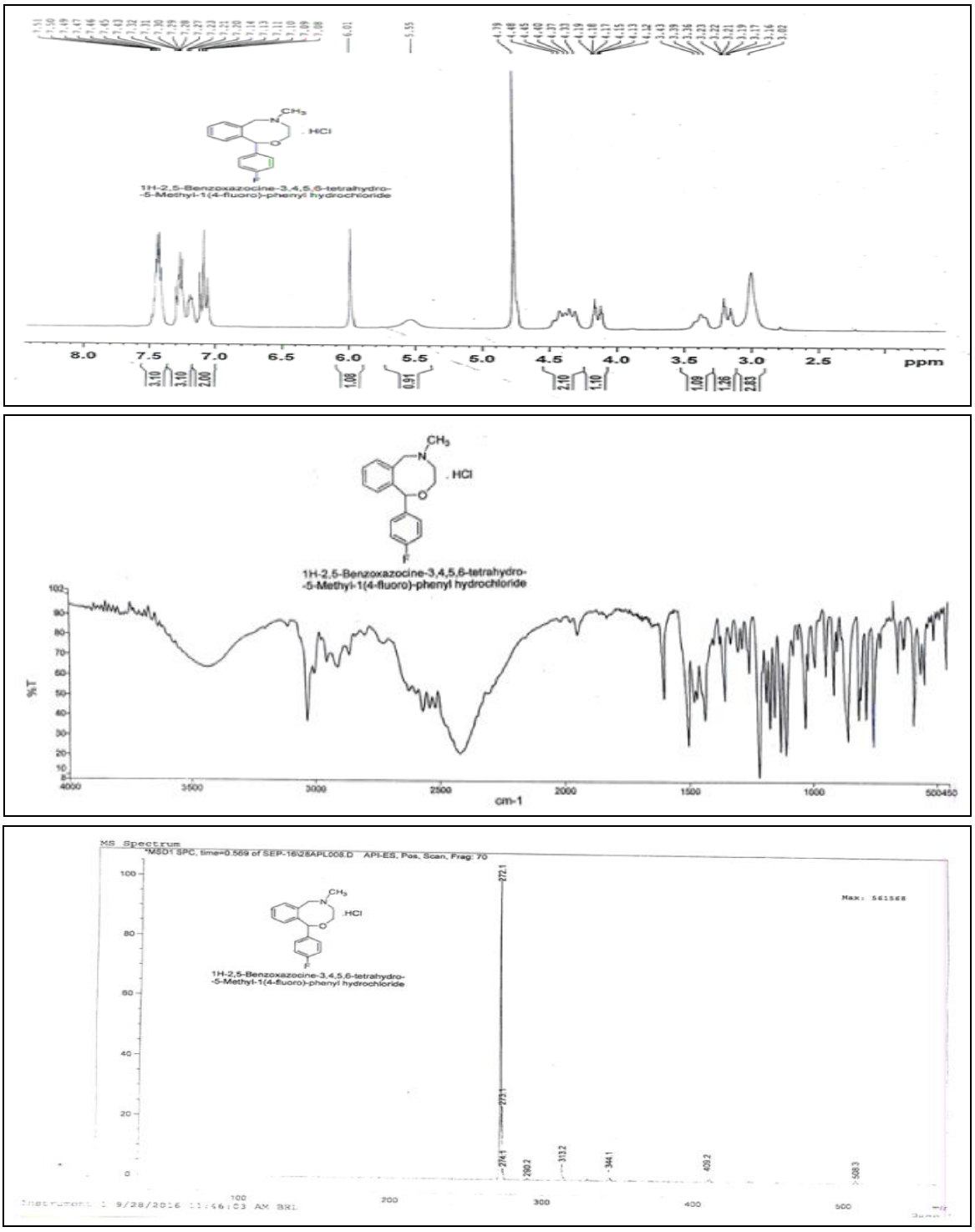
The above 4-fluoro-benzoyl-N-(2-Hydroxy ethyl)-N-methyl benzamide (16g) was dissolved in dichloromethane (80 mL) at 25-30 °C and catalytic amount of N,N-dimethyl formamide (0.2g), followed by addition of thionyl chloride (7g, 0.06 mole) and stirred the reaction mass for 2 h at 25-30 °C and observed that reaction was completed by checking of TLC. Cooled the reaction mass to 0-5°C, adjusted the pH to 6.5-7 with 5% w/v aqueous sodium hydroxide solution (137 mL) and raised the reaction mass temperature to 25-30 °C separated the organic layer it contains 4-fluoro-Benzoyl-N-(2-Chloro ethyl)-N-methyl Benzamide product.

The above 4-fluoro-Benzoyl-N-(2-Chloro ethyl)-N-methyl Benzamide product. Reaction mass was mixed with glacial acetic acid (2g, 0.033 mole) and was added to the suspension mass of sodium borohydride (4g, 0.106 mole) in dichloromethane (20 mL)[1] at 25-30 °C and subjected the above reaction mass to heated to 35-40 °C and maintained 35-40 °C for 20 h and observed that reaction completed by checking of TLC. Then cooled the reaction mass to 0-5 °C and added cold DM water (36mL) at 0-5°C, followed by the addition of 40% w/v aqueous sodium hydroxide solution (12 mL) at below 30°C. Thereafter heated to 65-70 °C by simultaneous removal of dichloromethane at atmospheric pressure continued stirring at 65-70 °C for 1 h to break the boron complexes and then cooled to 25-30 °C, then added dichloromethane (20 mL) and separated the organic layer, mixed the organic layer with DM water (16 mL) and adjusted the pH to 0.5-1 with conc. hydrochloric acid (9 mL, 35% w/w) at 25-30 °C and stirred for 1 h 25-30 °C. Then separated the aqueous layer and adjusted the aqueous layer pH from pH~1 to pH ~12 with 40% w/w aqueous sodium hydroxide solution (12mL) and then extracted in to dichloromethane (25mL) and concentrated the organic layer which contains 2-(N-(2-((4-Fluoro phenyl) (Hydroxy) methyl) benzyl)-N-methyl amino) ethanol product

The above 2-(N-(2-((4-Fluoro phenyl) (Hydroxy) methyl) benzyl)-N-methyl amino) ethanol concentrated mass was diluted with toluene (80 mL) and added p-toluene sulfonic acid monohydrate (15g) at 25-30 °C and stirred the reaction mass at 85-110 °C with azeotropic removal of water for 4 h and observed that reaction completed by checking of TLC and cooled the reaction mass to 25-30 °C and DM water (60 mL) was added, adjusted the pH to 10.5 to 11 with 24%

w/v aqueous sodium hydroxide solution (25 mL) and separated the organic layer and concentrated under reduced pressure then diluted the conc. mass in acetone (96 mL) and cooled to 0-5°C and slowly added conc. hydrochloric acid (5g,~35% w/w) then product (1H-2,5-Benzoxazocine 3,4,5,6-tetrahydro-5- methyl- 1- (4- fluoro)- phenyl-hydrochloride) precipitated out and filtered the product (dry weight 9g)

Analysis Calculated for $C_{17}H_{19}ClFNO$: C, 66.34; H, 6.22; Cl, 11.52; F, 6.17; N, 4.55; O, 5.20; IR (KBr cm^{-1}): 3876 (Alkyl-Ar-F), 3109 (Ar-F), 3018 (Aromatic C-H stretch), 2908 (CH_3 -CH_2-); ^1H NMR (300MHz, D_2O, δppm): δ 7.155-7.297 (m,8H), δ 5.78 (S, 1H), δ4.29 (dd, 1H), δ 2.487 (tt, 1H), δ 3.235 (S, 3H); MS: *m/z* 272.1 $[M+H]^+$.



1H-2,5-Benzoxazocine-3,4,5,6-tetrahydro-5-methyl-1-(4-fluoro)-Phenyl -hydrochloride

Synthesis of 1H-2,5-Benzoxazocine 3,4,5,6-tetra-hydro- 5- ethyl- 1- (4- fluoro)- Phenyl- hydro-chloride: Suspended Magnesium turnings (2g, 0.08 moles) in tetrahydrofuran (60mL) under nitrogen atmosphere and heated to 50-55 °C added crystal of Iodine followed by 2.5 g of 4-Fluoro-Bromo-benzene (0.014 mole) for initiate Grignard reaction, and slowly added mixture of 11.7g of 4-Fluoro- Bromo-benzene (0.07 mole) and tetra-hydrofuran (10mL) at 45-65 °C In 1 h and agitated reaction mass at 60-65 °C for 1 h , then cooled the reaction mass to 25-30 °C and the above prepared Grignard reagent added to mixture of Phthalic-anhydride (10g) -dichloromethane (80mL) at 0-5 °C in 1 h, stirred the reaction mass for 1 h at 0-5° C, and quenched the reaction mass with 5N aqueous hydrochloric acid solution (25 mL) at 0-5 °C and separated below organic layer these organic layer was mixed with DM water (100 mL) and adjusted the pH to 11-11.5 with 10% w/w aqueous sodium hydroxide solution (30mL) at 25-30 °C and organic layer was separated out, and adjusted the pH of aqueous layer (at pH- 11-11.5) to pH- 2 with conc. hydrochloric acid (12 mL) result from acid compound (4-fluoro-benzoyl -benzoic- acid) obtained (dried wt: 15g)

The above 4-fluoro-benzoyl benzoic acid (15g) was suspended in toluene (75 mL) at 25-30 °C and added catalytic N, N-dimethyl formamide (16 g) followed by the addition of thionyl chloride (9g, 0.073 mole) under nitrogen atmosphere at 25-30 °C and stirred the reaction mass for 2 h at 25-30 °C and reaction completed by checking of TLC and concentrated under reduced pressure at 45-50 °C and diluted the conc. mass in toluene (60 mL) at 25-30 °C and cooled to 10-15 °C and added mixture of N-ethyl ethanolamine (10g, 0.135 mole) and toluene (15 mL) at 15-20 °C stirred the reaction mass at 25-30 °C for 3 h then observed that reaction was completed by checking of TLC, Then added DM water (120 mL) and stirred the reaction mass for 1 h at 25-30 °C, filtered the product 4-fluoro-benzoyl-N-(2-Hydroxyethyl)-N-ethyl benzamide, dried wt 14g.

The above 4-fluoro-benzoyl-N-(2-Hydroxy ethyl)-N-ethyl benzamide (14g) was dissolved in dichloromethane (80mL) at 25-30 °C and catalytic amount of N,N-dimethyl formamide (0.2g), followed by addition of thionyl chloride (7g, 0.06 mole) and stirred the reaction mass for 2 h at 25-30 °C and observed that reaction was completed by checking of TLC. Cooled the reaction mass to 0-5 °C, adjusted the pH to 6.5-7 with 5% w/v aqueous sodium hydroxide solution (137 mL) and raised the reaction mass temperature to 25-30 °C, separated the organic layer, it contains 4-fluoro-Benzoyl-N-(2-Chloro ethyl)-N-ethyl Benzamide product.

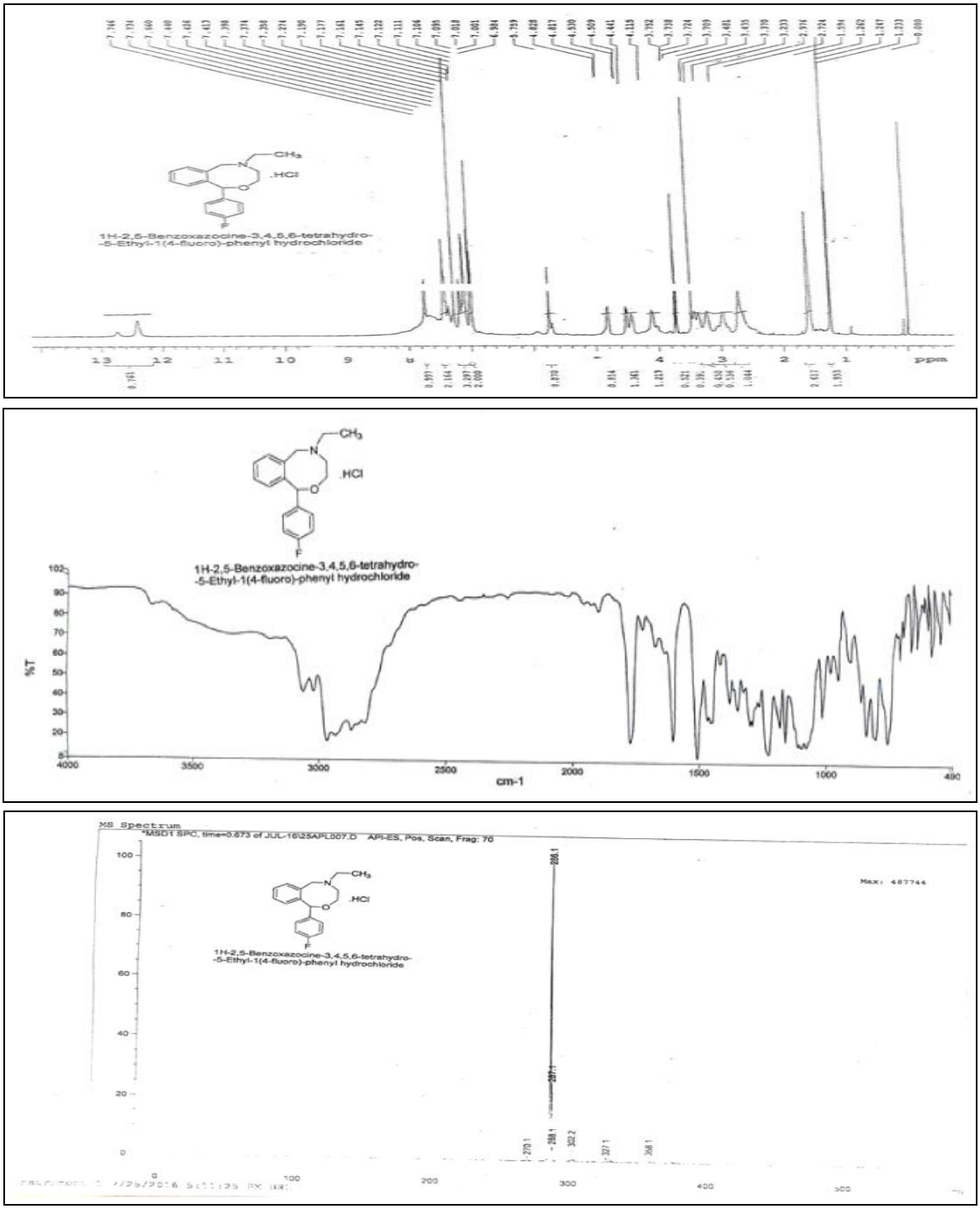
The above 4-fluoro-Benzoyl-N-(2-Chloro ethyl)-N-ethyl Benzamide product. Reaction mass was mixed with glacial acetic acid (2g, 0.033 mole) and was added to the suspension mass of sodium borohydride (4g, 0.106 mole) in dichloromethane (20 mL) at 25-30 °C and subjected the above reaction mass to heated to 35-40 °C and maintained 35-40 °C for 20 h and observed that reaction completed by checking of TLC. Then cooled the reaction mass to 0-5 °C and added cold DM water (36 mL) at 0-5°C, followed by the addition of 40% w/v aqueous sodium hydroxide solution (12 mL) at below 30 °C.

Thereafter heated to 65-70 °C by simultaneous removal of dichloromethane at atmospheric pressure continued stirring at 65-70 °C for 1 h to break the boron complexes and then cooled to 25-30 °C, then added dichloromethane (20 mL) and separated the organic layer, mixed the organic layer with DM water (16 mL) and adjusted the pH to 0.5-1 with conc. hydrochloric acid (9 mL, 35% w/w) at 25-30 °C and stirred for 1 h 25-30 °C.

Then separated the aqueous layer and adjusted the aqueous layer pH from pH~1 to pH ~12 with 40% w/w aqueous sodium hydroxide solution (12mL) and then extracted in to dichloromethane (25mL) and concentrated the organic layer which contains 2-(N-(2-((4-Fluoro phenyl) (Hydroxy) ethyl) benzyl)-N-ethyl amino)ethanol product.

The above 2-(N-(2-((4-Fluoro phenyl)(Hydroxy) methyl)benzyl)-N-ethylamino) ethanol conc. mass was diluted with toluene (80 mL) and added p-toluene sulfonic acid monohydrate (15 g) at 25-30 °C and stirred the reaction mass at 85-110 °C with azeotropic removal of water for 4 h and observed that reaction completed by checking of TLC and cooled the reaction mass to 25-30 °C and DM water (60 mL) was added, adjusted the pH to 10.5 to 11 with 24% w/v aqueous sodium hydroxide

solution (25 mL) and separated the organic layer and concentrated under reduced pressure then diluted the conc. mass in acetone (96 mL) and cooled to 0-5 ℃ and slowly added conc. hydrochloric acid (5g, ~35% w/w) then product (1H-2,5-Benzoxazocine 3,4,5,6-tetrahydro-5-ethyl-1-(4-fluoro)-phenyl-hydro-chloride) precipitated out and filtered the product (dry weight 9g).



1H-2,5-Benzoxazocine 3,4,5,6-tetrahydro-5-ethyl-1-(4-fluoro)-Phenyl -hydrochloride

Analysis Calculated for $C_{18}H_{21}ClFNO$: C, 67.18; H, 6.58; Cl, 11.02; F, 5.9; N, 4.35; O, 4.97; IR (NEAT BG, cm^{-1}): 3061 (Alkyl-Ar-F), 3109 (Ar-F), 2967 (Aromatic C-H stretch), 2934 (CH_3-CH_2), 1223(C-O); ^1H NMR (500MHz, $cdcl_3$, ppm): δ12.200-12.800 (brS, 1H), δ 6.984-7.746 (m, 8H), δ 5.759 (S, 1H), δ4.817-4.828 (S1H), δ 4.509-4.530 (dd,1H), δ 4.115 (dd, 1H), δ3.370-3.435 (dd, 1H), δ 3.233-3.476 (tt, 1H), δ 1.594 (t, 3H), δ 1.233(q, 2H), MS: *m/z* 286.1 $[M+H]^+$.

Synthesis of1H-2,5-Benzoxazocine 3,4,5,6-tetrahydro-5-benzyl-1-(4-fluoro)-Phenyl - hydrochloride: Suspended Magnesium turnings (2g, 0.08 moles) in tetrahydrofuran (60 mL) under nitrogen atmosphere and heated to 50-55 °C added crystal of Iodine followed by 2.5 g of 4-Fluoro-Bromo-benzene (0.014 mole) for initiate Grignard reaction, and slowly added mixture of 11.7g of 4-Fluoro- Bromo-benzene (0.07 mole) and tetrahydrofuran (10 mL) at 45-65 °C In 1 h and agitated reaction mass at 60-65 °C for 1 h, then cooled the reaction mass to 25-30 °C and the above prepared Grignard reagent added to mixture of Phthalic-anhydride(10g)-dichloromethane (80 mL) at 0-5 °C in 1h, stirred the reaction mass for 1h at 0-5 °C, and quenched the reaction mass with 5N aqueous hydrochloric acid solution (25 mL) at 0-5 °C and separated below organic layer these organic layers were mixed with DM water (100 mL) and adjusted the pH to 11-11.5 with 10% w/v aqueous sodium hydroxide solution (30 mL) at 25-30 °C and organic layer was separated out , and adjusted the pH of aqueous layer (at pH:11-11.5) to pH :2 with conc. hydrochloric acid (12 mL) result Acid compound (4-fluoro-benzoyl -benzoic- acid) obtained (dried wt: 15g).

The above 4-fluoro-benzoyl benzoic acid (15g) was suspended in toluene (75 mL) at 25-30 °C and added catalytic N,N-dimethyl formamide (16g) followed by the addition of thionyl chloride (9g, 0.073 mole) under nitrogen atmosphere at 25-30 °C. and stirred the reaction mass for 2 h at 25-30 °C and reaction completed by checking of TLC and concentrated under reduced pressure at 45-50 °C and diluted the conc. mass in toluene (60mL) at 25-30 °C and cooled to 10-15°C and added mixture of N-benzyl ethanolamine (10g, 0.135 mole) and toluene (15 mL) at 15-20 °C stirred the reaction mass at 25-30 °C for 3 h then observed that reaction was completed by checking of TLC, Then added DM water (120 mL) and stirred the reaction mass for 1 h at 25-30 °C, filtered the product 4-fluoro- benzoyl- N- (2- Hydroxyethyl)- N- benzyl benzamide, dried wt. 12g.

The above 4-fluoro-benzoyl-N-(2-Hydroxy ethyl)-N-benzyl benzamide (12g) was dissolved in dichloromethane (80 mL) at 25-30 °C and catalytic amount of N,N-dimethyl formamide (0.2g), followed by addition of thionyl chloride (7g, 0.06 mole) and stirred the reaction mass for 2 h at 25-30 °C and observed that reaction was completed by checking of TLC. Cooled the reaction mass to 0-5 °C, adjusted the pH to 6.5-7 with 5% w/v aqueous sodium hydroxide solution (137 mL) and raised the reaction mass temperature to 25-30 ° C, separated the organic layer, it contains 4-fluoro-Benzoyl-N-(2-Chloro ethyl)-N-benzyl Benzamide product.

The above 4-fluoro-Benzoyl-N-(2-Chloro ethyl)-N-benzyl Benzamide product. Reaction mass was mixed with glacial acetic acid (2g, 0.033 mole) and was added to the suspension mass of sodium borohydride (4g, 0.106 mole) in dichloromethane (20mL) at 25-30 °C and subjected the above reaction mass to heated to 35-40 °C and maintained 35-40 °C for 20 h and observed that reaction completed by checking of TLC. Then cooled the reaction mass to 0-5 °C and added cold DM water (36 mL) at 0-5° C, followed by the addition of 40% w/v aqueous sodium hydroxide solution (12 mL) at below 30 °C.

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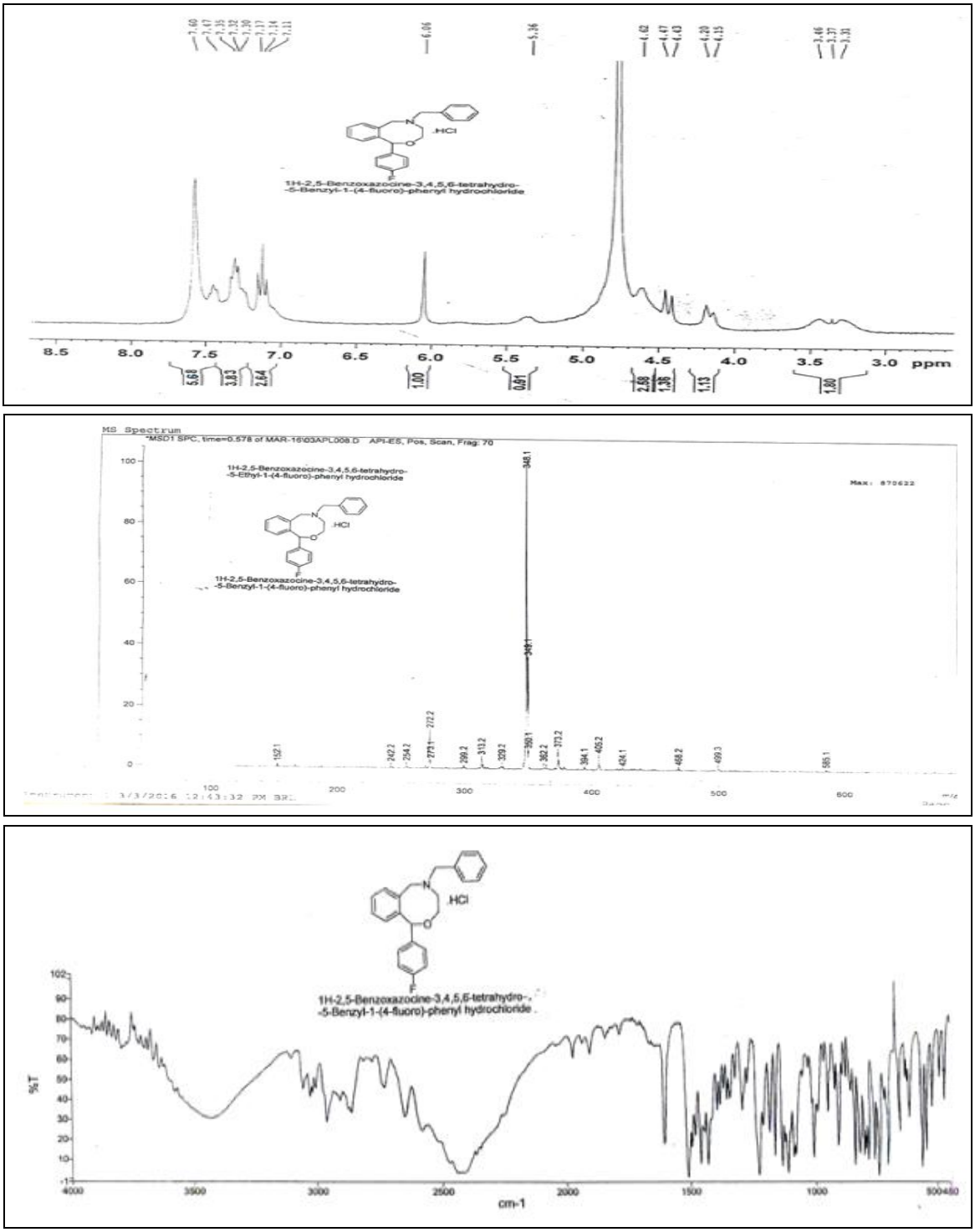
The above 2-(N-(2-((4-Fluoro phenyl)(Hydroxy) methyl)benzyl)-N-benzyl amino)ethanol concentrated mass was diluted with toluene (80 mL) and added p-toluene sulfonic acid monohydrate(15 g) at 25-30 °C and stirred the reaction mass at 85-110 °C with azeotropic removal of water for 4 h and observed that reaction completed by checking of TLC and cooled the reaction mass to 25-30 °C and DM water (60 mL) was added, adjusted the pH to 10.5 to 11 with 24% w/v aqueous sodium hydroxide solution (25mL)

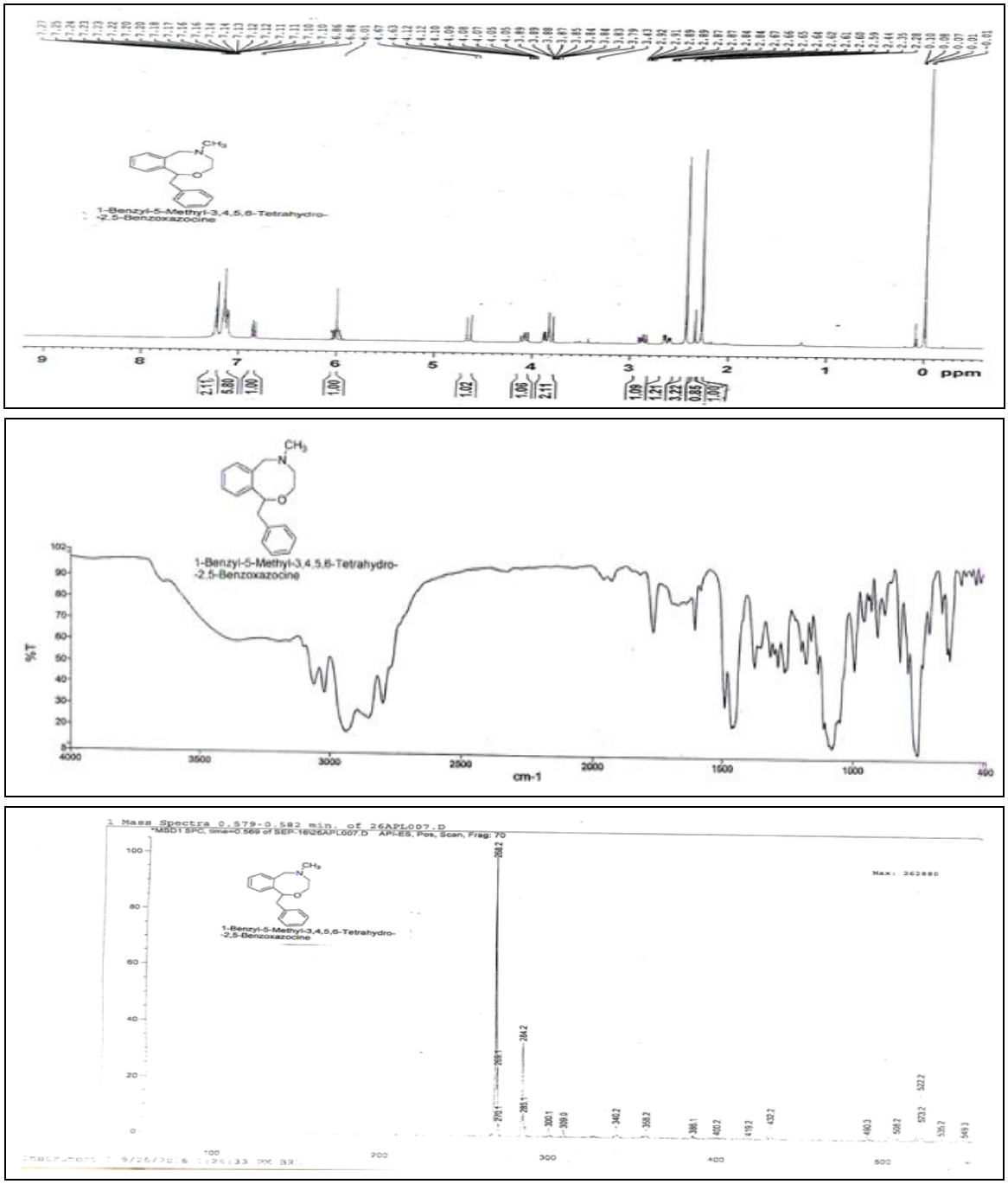
and separated the organic layer and concentrated under reduced pressure then diluted the conc. mass in acetone (96 mL) and cooled to 0-5°C and slowly added conc. hydrochloric acid (5g,~35% w/w) then product (1H- 2, 5- Benzoxazocine 3, 4, 5, 6- tetrahydro- 5- benzyl- 1- (4-fluoro)- phenyl –hydro-chloride) precipitated out and filtered the product (dry weight 9g)

Analysis Calculated for $C_{23}H_{23}ClFNO$: C, 71.96; H, 6.04; Cl, 9.24; F, 4.95; N, 3.65; O, 4.17; IR (KBr cm^{-1}): 3874 (Alkyl-Ar-F), 3109 (Ar-F), 3018 (Aromatic C-H stretch), 2934 (CH_3-CH_2-), 1223 (C-O); ^1H NMR (D_2O) δ 7.11-7.260 (m, 13H), δ 6.06 (S,1H), δ4.5-4.6, (d 2H), (S,2H) δ4.43-4.47 (tt,2H), δ 3.31-3.46 (SS, 2H); MS: *m/z* 348.1 $[M+H]^+$.



1H-2,5-Benzoxazocine 3,4,5,6-tetrahydro-5-benzyl-1-(4-fluoro)-Phenyl -hydrochloride

Synthesis of 1-Benzyl-5-methyl-3,4,5,6-Tetra hydro- 1H- 2, 5- Benzoxazocine: Suspended Magnesium turnings (2g, 0.08 moles) in tetrahydrofuran (60 mL) under nitrogen atmosphere and heated to 50-55 °C added crystal of Iodine followed by 1.374g of Benzyl bromide (0.00804 mole) for initiate Grignard reaction, and slowly added mixture of 12.36 g of Benzyl bromide (0.072 mole) and tetrahydrofuran (10mL) at 45-65 °C.



1-Benzyl-5-methyl-3,4,5,6-Tetra hydro-1H-2,5-Benzoxazocine

In 1 h and agitated reaction mass at 60-65 °C for 4 h, then cooled the reaction mass to 25-30 °C and the above prepared Grignard reagent added to mixture of Phthalic-anhydride (10g)-dichloro-methane (80 mL) at 0-5 °C in 1 h, stirred the reaction mass for 1 h at 0-5 °C, and quenched the reaction mass with 5N aqueous hydrochloric acid solution (25 mL) at 0-5 °C and separated below organic layer these organic layer was mixed with DM water (100mL) and adjusted the pH to 11-11.5 with 10% w/v aqueous sodium hydroxide solution (30 mL) at 25-30 °C and organic layer was

separated out, and adjusted the pH of aqueous layer (atpH:11-11.5) to pH- 2 with conc. hydrochloric acid (12 mL) result in acid compound (2-(2-phenyl acetyl)-benzoic acid) obtained (wt:12g).

2-(2-phenyl acetyl)-benzoic acid: (12 g) was taken in toluene (75 mL) at 25-30 ℃ and added catalytic N,N-dimethyl formamide (0.825g) followed by the addition of thionyl chloride (7.14g, 0.06 mole) under nitrogen atmosphere at 25-30 ℃ and stirred the reaction mass for 2 h at 25-30 ℃ and reaction completed by checking of TLC and concentrated under reduced pressure at 45-50 ℃ and diluted the conc. mass in toluene (60mL) at 25-30 ℃ and cooled to 10-15 ℃ and added mixture of N-methyl ethanolamine (8.25 g, 0.135 mole) and toluene (15 mL) at 15-20 ℃ stirred the reaction mass at 25-30 ℃ for 3 h then observed that reaction was completed by checking of TLC, Then added DM water (120mL) and stirred the reaction mass for 1h at 25-30 ℃, filtered the product 2-(2-phenyl acetyl)-N-methyl benzamide, wt 12g.

The above 2-(2-phenyl acetyl)-N-methyl benzamide (12g) was dissolved in tetrahydrofuran (60 mL) at 25-30 ℃ and added lithium aluminum hydride (4.23g, 0.111 mole)and reflux the reaction mass for 24 h and observed that reaction was completed by checking of TLC.

Cooled the reaction mass to 0-5 ℃, adjusted the pH to 6.5-7 with 5% w/v aqueous sodium hydroxide solution (137mL) and raised the reaction mass temperature to 25-30 ℃, separated the organic layer, it contains 2- (N- (2- ((benzyl) (Hydroxy) ethyl))-N-benzyl amino) ethanol product.

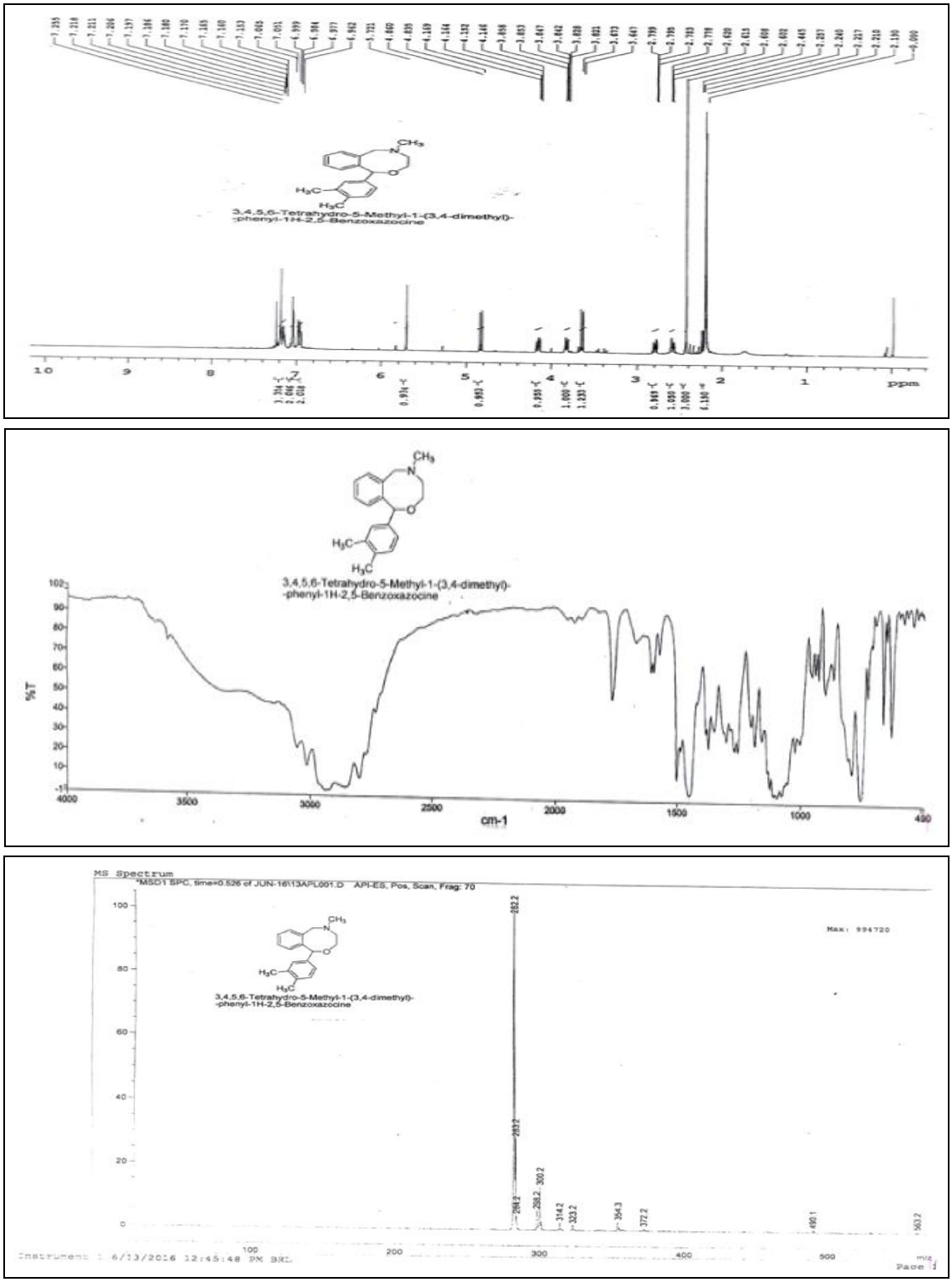
The above 2-(N-(2- ((benzyl) (Hydroxy) ethyl))-N-benzyl amino) ethanol concentrated mass was diluted with toluene (80 mL) and added p-toluene sulfonic acid monohydrate (10 g) at 25-30 ℃ and stirred the reaction mass at 85-110 ℃ with azeotropic removal of water for 4 h and observed that reaction completed by checking of TLC and cooled the reaction mass to 25-30 ℃ and DM water (60 mL) was added, adjusted the pH to 10.5 to 11 with 24% w/v aqueous sodium hydroxide solution (25 mL) and separated the organic layer and concentrated under reduced pressure then diluted the conc. mass in acetone (96 mL) and cooled to 0-5 ℃ and slowly added conc. hydrochloric acid (5g,~35% w/w) then product (1H-2, 5-Benzoxazocine, 3, 4, 5, 6 tetrahydro-5 methyl-1-benzyl hydrochloride) precipitated out and filtered the product (dry weight 5g).

Analysis Calculated for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24; O, 5.98; IR (NEAT BG cm^{-1}): 3360 (C_6H_5-CH_2-), 3109 (Ar-F), 3018 (Aromatic C-H stretch), 2940 (CH_3-CH_2-),1198 (C-O); ^{1}H NMR (300MHz, $CDCl_3$) δ 7.10-7.27 (m, 9H), δ 6.06 (s, 1H), δ4.63-4.67 (dd1H). δ 6.84-6.86 (dd, 1H), δ2.2-2.67 (t 1H), δ2.44 (S,1H), δ6.01 (S,1H), δ3.79-3.89 (t, 2H), δ2.42-2.89 (tt,1H) δ 4.05-4.12 (tt, 1H), δ 2.28 (S, 3H); MS: *m/z* 268.2 $[M+H]^+$.

Synthesis of 3,4,5,6-Tetrahydro-5-Methyl 1-(3,4-Dimethyl)-Phenyl-1H-2,5-Benzoxazocine:

Phthalic anhydride (10g, 0.0675 mole) was suspended in o-Xylene (44g) at 25-30 ℃. Aluminum chloride (22.4g, 0.1689 mole) at 25-40 ℃, stirred the reaction mass at 65-70 ℃ for 3 h, TLC indicates completion of reaction, conc. hydrochloric acid (100 mL) was added to the reaction mass at 25-30 ℃ ,and distilled the reaction mass under atmospheric pressure at 95-100 ℃ to remove the excess o-xylene and followed by addition of dichloromethane (80 mL) at 25-30 ℃ separated the organic layer, aqueous layer and organic layer with DM water (100 mL) pH was adjusted to pH 12 with 5% w/v aqueous sodium hydroxide solution (30 mL) separated the aqueous layer and product was precipitated at pH 1 of aqueous layer and filtered the product *i.e.* acid compound{o-(3,4-dimethyl)-benzoyl benzoic acid} and washed with DM water (15mL).

Above dried o-(3,4-dimethyl)-benzoyl benzoic acid (14g, 0.0551 mole) was suspended in toluene (70 mL) and dimethylformamide (0.2g, 0.00274 mole), Thionyl chloride (7.9g, 0.066 mole) and stirred for 2 h and evaporated the solvent under vacuum at 40 ℃ and diluted the conc. mass in dichloromethane (30mL) and triethylamine (8g, 0.0793 mole), N-methyl ethanolamine (5g, 0.066 mole), stirred the reaction mass for 2 h at 26-5-30 ℃, and followed by the addition of DM water (100 mL), concentrated the organic layer under reduced pressure oily residue (o-(3,4-dimethyl)-benzoyl-n-(2-hydroxy ethyl)-n-methyl benzamide, 13g) results.



3,4,5,6-Tetrahydro-5-Methyl 1-(3,4-Dimethyl)-Phenyl-1H-2,5-Benzoxazocine

Above o-(3,4-dimethyl)-Benzoyl-N-(2-Hydroxy ethyl)-N-methyl Benzamide (13g) was diluted in tetrahydrofuran (26mL) and added to suspension mass of Lithium aluminium -hydride(3.97g, 0.1045 mole) with tetrahydrofuran (65mL), at 25-30 °C and maintained the reaction mass at reflux temperature under nitrogen atmosphere for 40 h added pre-cooled DM water (26mL) followed by the addition of 20% w/w sodium hydroxide solution (15 mL) at 0-5 °C, concentrated the reaction mass under vacuum at 40°C added Water (50 mL), dichloromethane (100 mL) concentrated the organic layer under vacuum, oily mass results and these oily mass was diluted in toluene (80 mL),

and added p-toluene sulfonic acid mono-hydride (9.53g, 0.050 mole) and heated to 95-105 °C and maintained 95-105 °C for 4 h (during these period water was removed by azeotropically) and cooled the reaction mass to 25-30 °C and DM water (20 mL) and adjusted 11 pH with 20 w/w aqueous sodium hydroxide solution (15 mL) and concentrated organic layer under reduced pressure and diluted the conc. mass in methanol (50 mL) and added conc. hydrochloric acid (1.46g, 0.04 mole) and agitated for 24 h at 0-5 °C still product were not precipitated and concentrated reaction mass under reduced pressure at 45 °C, oily mass (3, 4,5,6-tetrahydro-5methyl 1-(3,4-dimethyl)-phenyl-1 h-2,5-benzoxazocine, 9.5g, yield: 76%) obtained.

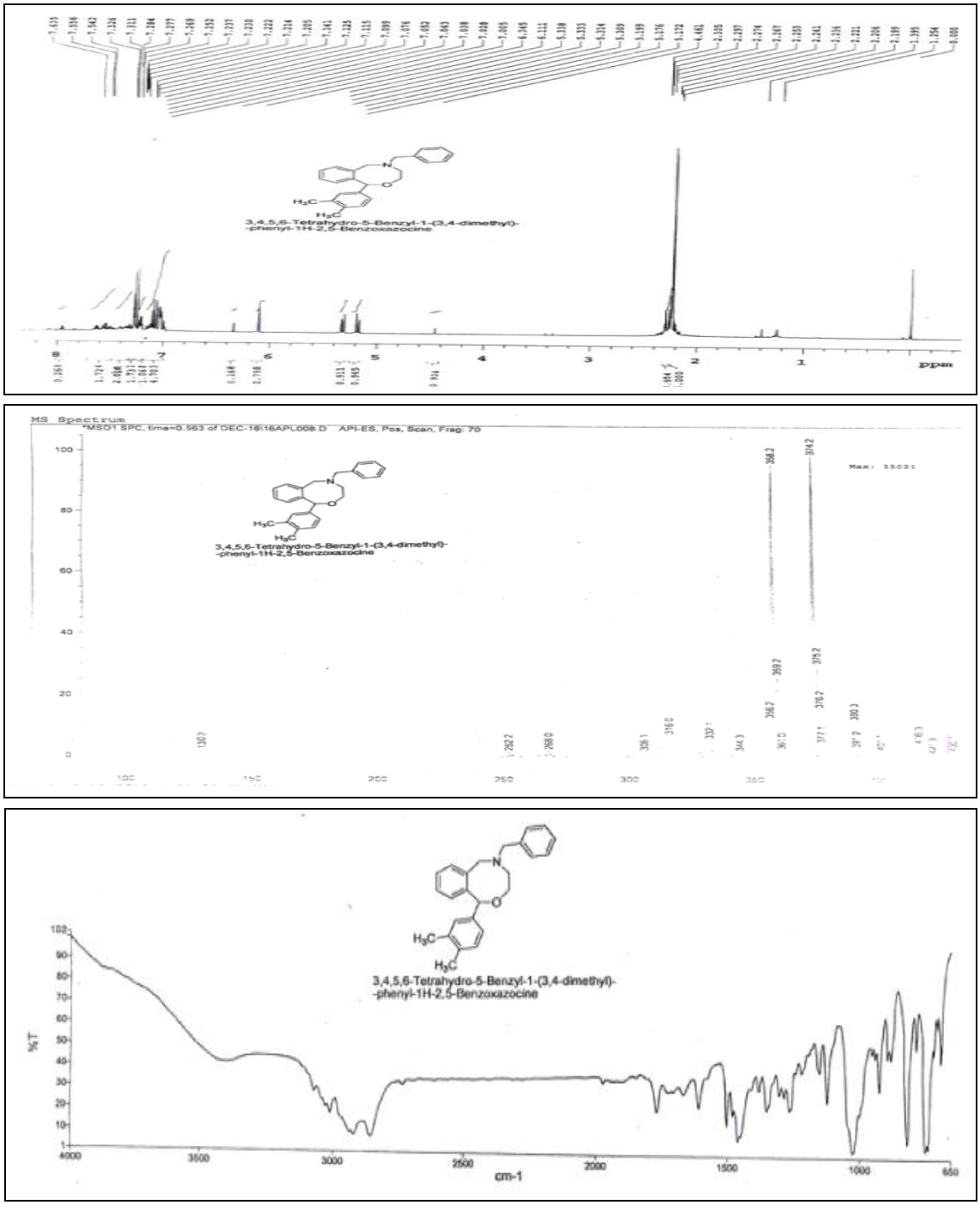
Analysis Calculated for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; Cl, 11.67; N, 4.98; O, 5.69; IR (NEAT BG cm^{-1}): 3910 ($(CH_3)_2(C_6H_3\text{-}CH_2)$, 3018 (Aromatic C-H stretch), 2937 ($CH_3\text{-}CH_2\text{-}$), 1198 (C-O);[1] H NMR (500MHz, $CDCl_3$) δ 6.962-7.255 (m,7H), δ5.721 (S,1H), δ4.169-4.835 (SS, 1H), δ4.146-4.164 (dd, 1H), δ3.829-3.853 (SS, 1H), δ2.795-2.799 (m,1H), δ2.602-2.620 (m, 1H), δ2.445 (S, 1H), δ 2.217-2.586 (S,6H), δ2.445 (S 3H), δ 2.190 ((S, 6H); MS*: m/z* 282.2 $[M+H]^+$.

Synthesis of 3,4,5,6-Tetrahydro-5-Benzyl- 1-(3,4-Dimethyl)-Phenyl-1H-2,5-Benzoxazocine: Phthalic anhydride (10 g, 0.0675 mole) was suspended in o-Xylene (44 g) at 25-30 °C. Aluminum chloride (22.4g, 0.1689 mole) at 25-40 °C, stirred the reaction mass at 65-70 °C for 3 h, TLC indicates completion of reaction, conc. hydrochloric acid (100 mL) was added to the reaction mass at 25-30 °C, and distilled the reaction mass under atmospheric pressure at 95-100 °C to remove the excess o-xylene and followed by addition of dichloromethane (80 mL) at 25-30 °C separated the organic layer, aqueous layer and organic layer with DM water (100 mL) pH was adjusted to pH 12 with 5% w/v aqueous sodium hydroxide solution (30mL) separated the aqueous layer and product was precipitated at pH 1 of aqueous layer and filtered the product *i.e.* acid compound{o-(3,4-dimethyl)-benzoyl benzoic acid} and washed with DM water (15mL).

Above dried o-(3,4-dimethyl)-benzoyl benzoic acid (14 g, 0.0551 mole) was suspended in toluene (70 mL) and dimethyl formamide (0.2g, 0.00274 mole), Thionyl chloride (7.9g, 0.066 mole) and stirred for 2 h and evaporated the solvent under vacuum at 40 °C and diluted the conc. mass in dichloromethane (30 mL) and triethylamine (8g, 0.0793 mole), N-benzyl ethanolamine (10g, 0.066 mole), stirred the reaction mass for 2 h at 26-5-30 °C, and followed by the addition of DM water (100 mL), conc. the organic layer under reduced pressure oily residue (o-(3,4-dimethyl)-Benzoyl-N-(2-Hydroxy ethyl)-N-benzyl Benzamide, 16.63g) results.

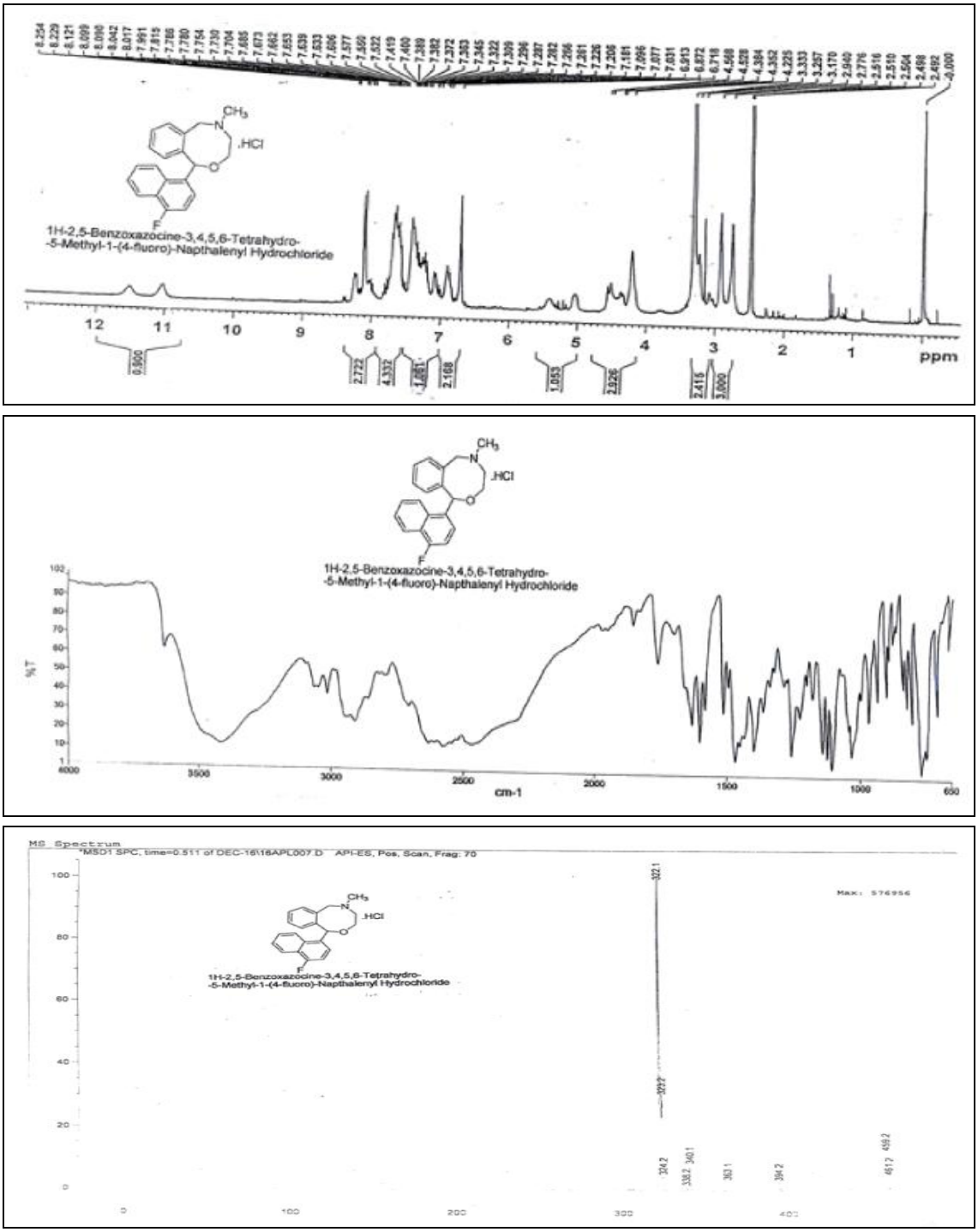
Above o-(3,4-dimethyl)-Benzoyl-N-(2-Hydroxy ethyl)-N-benzyl Benzamide (16.63g) was diluted in tetrahydrofuran (26 mL) and added to suspension mass of Lithium aluminium –hydride (3.6g, 0.094 mole) with tetrahydrofuran (65mL), at 25-30 °C and maintained the reaction mass at reflux temperature under nitrogen atmosphere for 42 h added pre-cooled DM water (26 mL) followed by the addition of 20% w/w sodium hydroxide solution (18 mL) at 0-5 °C, concentrated the reaction mass under vacuum at 40 °C added DM Water (50 mL), dichloromethane (100 mL) concentrated the organic layer under vacuum, oily mass results and these oily mass was diluted in toluene (80 mL), and added p-toluene sulfonic acid mono-hydride (10.6g, 0.056 mole) and heated to 95-105 °C and maintained 95-105 °C for 4 h (during these period water was removed by azeotropically) and cooled the reaction mass to 25-30 °C and DM water (20 mL) and adjusted 11 pH with 20 w/w aqueous sodium hydroxide solution (18 mL) and concentrated organic layer under reduced pressure and diluted the conc. mass in methanol (50 mL) and added conc. 35% hydrochloric acid (4.66g, 0.045 mole) and agitated for 24 h at 0-5 °C still product were not precipitated and then converted to free base, oily mass (3,4,5,6-Tetrahydro-5-Benzyl 1-(3,4-Dimethyl)-Phenyl-1H-2,5-Benzoxazocinehydrochloride) 11g, yield: 71%) obtained.

Analysis Calculated for $C_{25}H_{27}NO$: C, 83.99; H, 7.61; Cl, 11.67; N, 3.92; O, 4.48; IR (KBr cm^{-1}): IR (KBr cm^{-1}): 3401 ($(CH_3)_2\text{-}C_6H_3\text{-}$), 3018 (Aromatic C-H stretch), 2937 ($CH_3\text{-}CH_2\text{-}$), 1216 (C-O); 1H NMR (500MHz, $CDCl_3$)), δ 7.125-7.635 (m, 12H); δ6.111 (S, 1H), δ 5.338 (dd, 1H), δ 5.176 (dd, 1H), δ5.172 (S, 1H); δ2.305 (m, 4H), δ2.26 (S, 6H); MS*: m/z* 358.2 $[M+H]^+$.



3,4,5,6-Tetrahydro-5-Benzyl- 1-(3,4-Dimethyl)-Phenyl-1H-2,5-Benzoxazocine

Synthesis of 1H-2,5-Benzoxazocine, 3,4,5,6-Tetrahydro-5-methyl-1(4-Fluoro)-Naphthalenyl Hydrochloride: Phthalic anhydride (10g, 0.0675 mole) was suspended in 1-fluoro-naphthalene (59.18g, 0.4054 mole) at 25-30 °C. Aluminum chloride (22.4 g, 0.1689 mole) at 25-40 °C, stirred the reaction mass at 65-70°C for 3h, TLC indicates completion of the reaction, conc. hydrochloric acid (100 mL) was added to the reaction mass at 25-30 °C, and distilled the reaction mass under atmospheric pressure at 95-100 °C to remove the excess 1-fluoro-napthalene and followed by addition of dichloromethane (80mL) at 25-30 °C separated the organic layer, aqueous layer and organic layer with DM water (100 mL) pH was adjusted to pH 12 with 5% w/v aqueous sodium hydroxide solution (30 mL) separated the aqueous layer and product was precipitated at pH 1 of aqueous layer and filtered the product *i.e.* acid compound{o- (1- fluoro-naphthalen- 4yl- carbonyl) benzoic acid} and washed with DM water (15 mL).



1H-2,5-Benzoxazocine,3,4,5,6-Tetrahydro-5-methyl-1(4-Fluoro)-Napthalenyl Hydrochloride

Above dried o-(1-fluoro-naphthalen-4yl-carbonyl) benzoic acid (16g, 0.0544 mole) was suspended in toluene (70 mL) and dimethylformamide (0.2g, 0.00274 mole), Thionyl chloride (7.76g, 0.065 mole) and stirred for 2 h and evaporated the solvent under vacuum at 40 °C and diluted the conc. mass in dichloromethane (30 mL) and triethylamine (8 g, 0.0793 mole), N-methyl ethanolamine (4.95g, 0.066 mole), stirred the reaction mass for 2 h at 26-5-30 °C, and followed by the addition of DM water (100 mL),concentrated the organic layer under reduced pressure oily residue (o-(1-fluoro-naphthalen-4yl-carbonyl) benzamide, 15g) results.

Above o- (1- fluoro- naphthalen- 4yl- carbonyl) benzamide, 15g was diluted in tetrahydrofuran (26 mL) and added to suspension mass of Lithium aluminium-hydride (3.6g, 0.094 mole) with tetrahydrofuran (65mL), at 25-30 °C and maintained the reaction mass at reflux temperature

under nitrogen atmosphere for 42 h added pre-cooled DM water (26 mL) followed by the addition of 20% w/w sodium hydroxide solution (18 mL) at 0-5°C, concentrated the reaction mass under vacuum at 40 °C added DM water (50mL), dichloromethane (100mL) concentrated the organic layer under vacuum, oily residue (10g, 2[[(2-hydroxy ethyl methyl amino-methyl naphthalene hydrol) obtained. Diluted the 2[[(2-hydroxy ethyl methyl amino-methyl naphthalene hydrol (10g, 0.0311 mole) in toluene (80 mL), and added p-toluene sulfonic acid mono-hydride (8.9g, 0.0467 mole) and heated to 95-105 °C and maintained 95-105 °C for 4 h (during these period water was removed by azeotropically) and cooled the reaction mass to 25-30 °C and DM water (20 mL) and adjusted 11 pH with 20 w/w aqueous sodium hydroxide solution (18mL) and concentrated organic layer under reduced pressure, diluted the conc. mass in methanol (50 mL) and added 35% hydrochloric acid (3.25g, 0.0317mole) and agitated for 2 h at 0-5 °C, product was precipitated out and filtered the product (1H-2,5-Benzoxazocine, 3, 4, 5, 6-Tetrahydro-5-Methyl--1(4-Fluoro)-naphthalenyl-Hydrochloride, 9.1g yield 70%.

Analysis Calculated for $C_{21}H_{21}$ ClFNO: C, 70.48; H, 5.91; Cl, 9.91; F, 5.31; N, 3.91; O, 4.47; IR (KBr cm^{-1}): 3855 (Alkyl-Ar-F), 3055 (Ar-F); 3020 (Aromatic C-H stretch), 2951 (CH_3-CH_2-), 1200 (C-O); ^{1}H NMR (DMSO) δ11-11.5 (brSS, 1H), δ 6.71-8.25 (m, 10H), δ 5.12-5.45 (S,1H), δ4.38-4.52 (m,3H), δ3.17-3.33 (m,3H), δ2.77-2.94 (SS, 3H; MS*: m/z* 322.1 $[M+H]^+$.

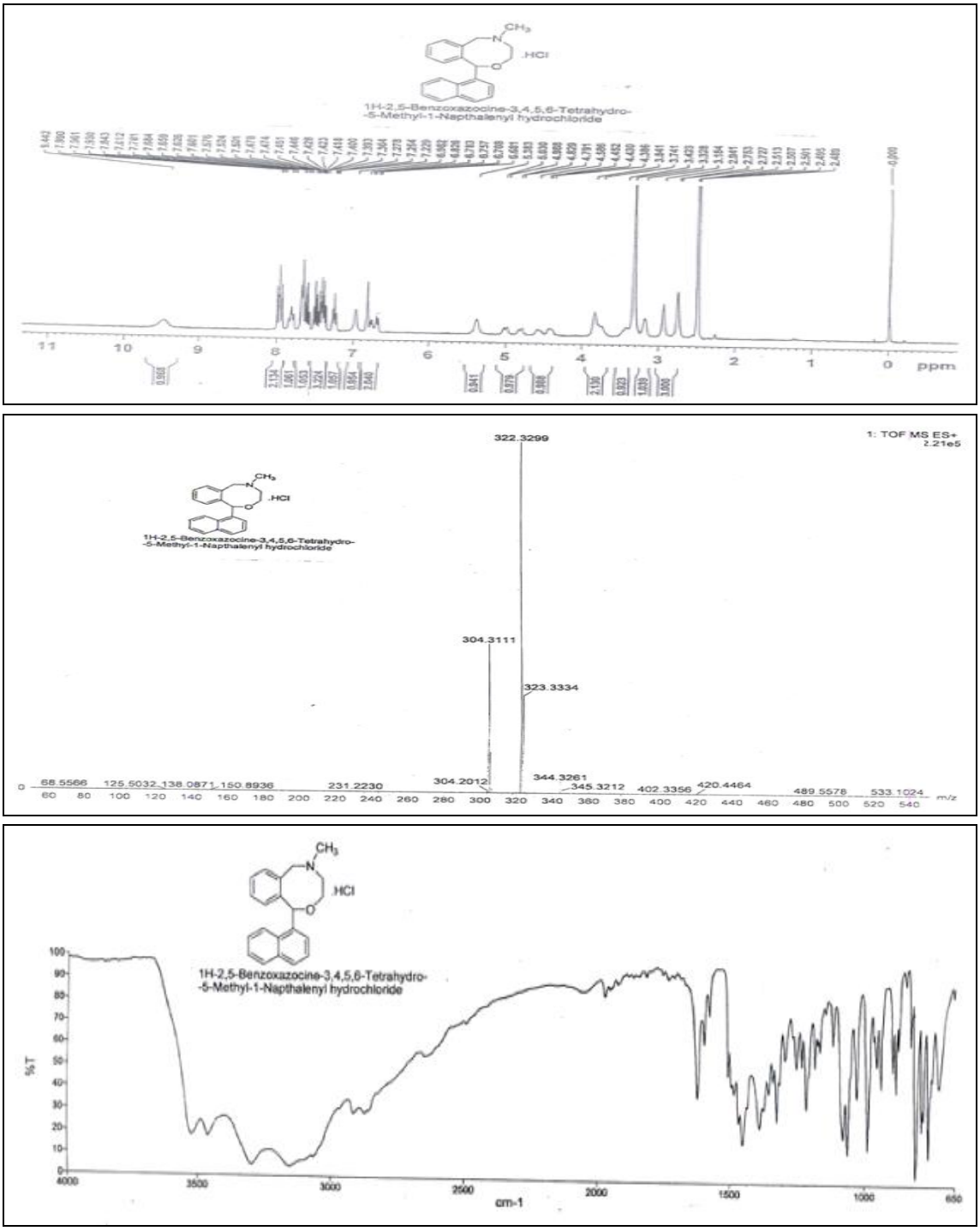
Synthesis of 1H-2,5-Benzoxazocine,3,4,5,6-Tetrahydro-5-Methyl-1-Naphthalenyl Hydrochloride: Phthalic anhydride (10g, 0.0675 mole), naphthalene (59.18g, 0.4054 mole) were suspended in dichloromethane (150 mL) at 25-30 °C. Aluminum chloride (22.4 g, 0.1689 mole) at 25-40 °C, stirred the reaction mass at 35-40 °C for 3 h, TLC indicates completion of reaction, conc. hydrochloric acid (100 mL) was added and followed by DM water (150mL to the reaction mass at 25-30 °C, and separated the organic layer and DM water (150 mL), and adjusted the pH to 11, by adding of 10% w/v aqueous sodium hydroxide solution (30 mL) and separated the aqueous layer which was washed with dichloromethane (2 × 20 mL) and cooled the aqueous layer to 0-5 °C and adjusted the pH to 1.0-1.2 by adding conc. hydrochloric acid (35% w/w, 8 mL) and the product starts precipitates out stirred the suspension mass for 1 h and filtered the product, *i.e.* acid compound (Naphthalen-1yl-carbonyl-benzoic acid).

Above dried Naphthalen-1yl-carbonyl-benzoic acid (15g) was suspended in toluene (70 mL) and dimethylformamide (0.2g, 0.00274 mole), Thionyl chloride (7.75g, 0.065 mole) and stirred for 2 h and evaporated the solvent under vacuum at 40 °C and diluted the conc. mass in toluene (30 mL) and N-methyl ethanolamine (9g, 0.1246 mole), stirred the reaction mass for 2 h at 25-30 °C, and followed by the addition of DM water (100 mL), product precipitates out and filtered the product (Naphthalen-1yl-carbonyl-benzamide) and washed with DM water (20 mL × 2).

Above dried Naphthalen-1yl-carbonyl-benzamide (13g, 0.04 mole) was diluted in tetrahydrofuran (26mL) and added to suspension mass of Lithium aluminium-hydride (3.2g, 0.086 mole) with tetrahydrofuran (65 mL), at 25-30 °C and maintained the reaction mass at reflux temperature under nitrogen atmosphere for 42 h added pre-cooled DM water (26mL) followed by the addition of 20% w/w sodium hydroxide solution (18 mL) at 0-5°C, concentrated the reaction mass under vacuum at 40 °C added DM water (50mL), dichloromethane (100 mL) concentrated the organic layer under vacuum, and these conc. mass was diluted in toluene (80mL), and added p-toluene sulfonic acid monohydrate (10.6g, 0.056 mole) and heated to 95-105 °C and maintained 95-105 °C for 4 h (during these period water was removed by azeotropically) and cooled the reaction mass to 25-30 °C and DM water (20 mL) and adjusted 11 pH with 20 w/w aqueous sodium hydroxide solution (18 mL) and concentrated organic layer under reduced pressure and diluted the conc. mass in methanol (50 mL) and added 35% hydrochloric acid (4.66g, 0.045 mole) and agitated for 24 h at 0-5 °C, product was precipitated out after 2 h maintenance and filtered the product (1H-2, 5-Benzoxazocine, 3, 4, 5, 6-Tetrahydro-5-Methyl-1-naphthalenyl-Hydrochloride, yield 76%.

Analysis Calculated for $C_{21}H_{22}$ClNO: C, 74.21; H, 6.52; Cl, 10.43.; N, 4.12; O, 4.71; IR (KBr cm^{-1}):

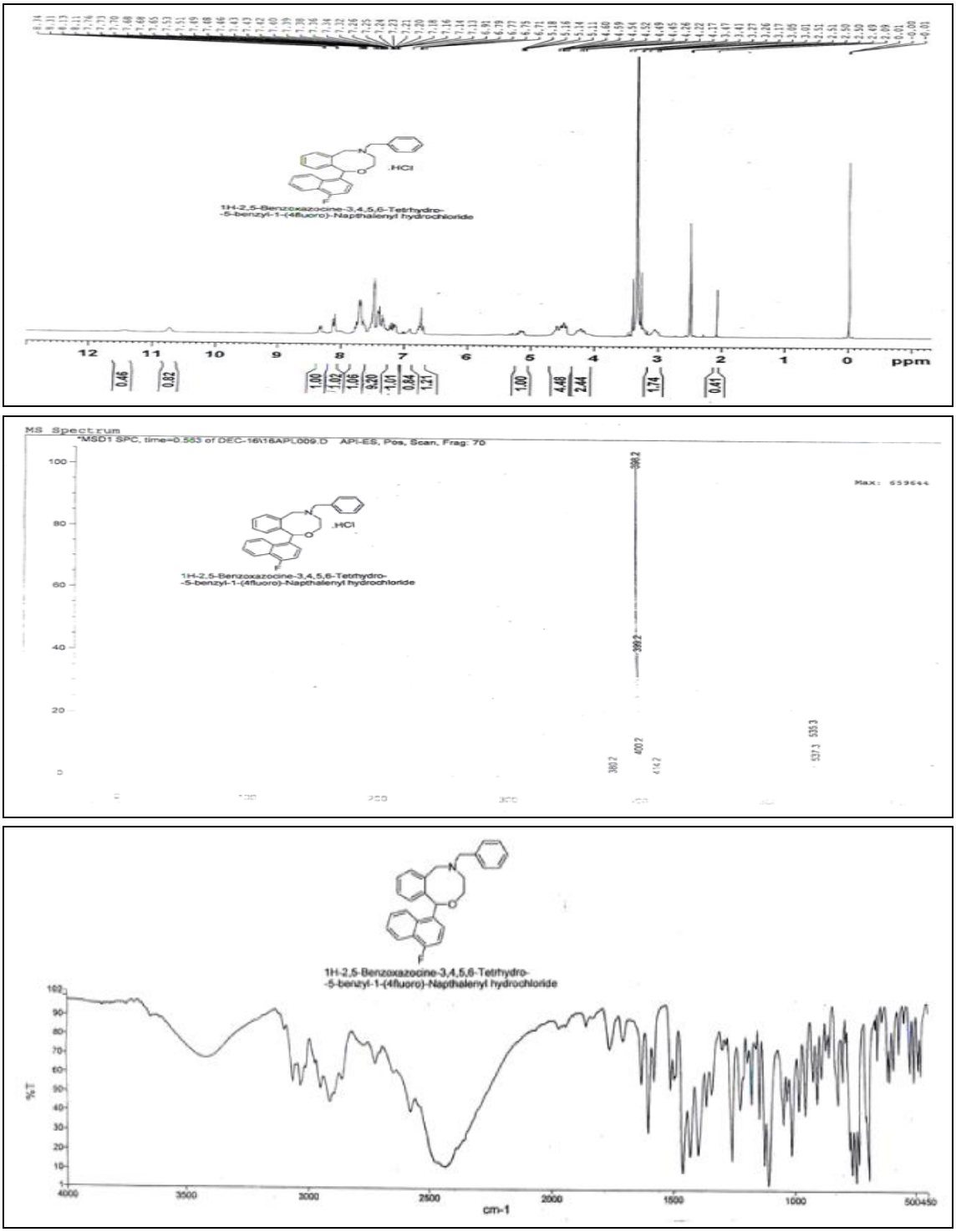
3858 (Ar-Alky), 3018 (Aromatic C-H stretch), 2914 (CH_3-CH_2-), 1180(C-O); ^{1}H NMR (DMSO-d6) δ 9.44 (brS 1H); δ6.68-7.99 (m, 11H); δ5.38 (S,1H), δ5.03 (dd1H)), δ 4.58 (dd, 1H); δ 3.84 (brd2H), δ 3.32 (brS, 1H) δ 3.18 (S, 1H), δ2.75-2.94 (SS, 3H); MS*: m/z* 304.3 $[M+H]^+$.



1H-2,5-Benzoxazocine,3,4,5,6-Tetrahydro-5-Methyl-1-Napthalenyl Hydrochloride

Synthesis of 1H-2,5-Benzoxazocine,3,4,5,6-Tetrahydro-5-benzyl-1(4-Fluoro)-Naphthalenyl Hydrochloride: Phthalic anhydride (10g, 0.0675 mole) was suspended in 1-fluoro-naphthalene (59.18g, 0.4054 mole) at 25-30 °C. Aluminum chloride (22.4 g, 0.1689 mole) at 25-40 °C, stirred the reaction mass at 65-70 °C for 3h, TLC indicates completion of reaction, conc. hydrochloric acid (100 mL) was added to the reaction mass at 25-30 °C, and distilled the reaction mass under atmospheric pressure at 95-100 °C to remove the excess 1-fluoro-napthalene and followed by

addition of dichloromethane (80 mL) at 25-30 °C separated the organic layer, aqueous layer and organic layer with DM water (100 mL) pH was adjusted to pH 12 with 5% w/v aqueous sodium hydroxide solution (30mL) separated the aqueous layer and product was precipitated at pH 1 of aqueous layer and filtered the product *i.e.* acid compound {o-(1-fluoro-naphthalen-4yl-carbonyl) benzoic acid} and washed with DM water (15 mL).



1H-2,5-Benzoxazocine,3,4,5,6-Tetrahydro-5-benzyl-1(4-Fluoro)-Napthalenyl Hydrochloride

Above dried o-(1-fluoro-naphthalen-4yl-carbonyl) benzoic acid (16g, 0.0544 mole) was suspended in toluene (70 mL) and dimethylformamide (0.2g, 0.00274 mole), Thionyl chloride (7.76g, 0.065 mole) and stirred for 2 h and evaporated the solvent under vacuum at 40 °C and diluted the conc. mass

in dichloromethane (30 mL) and triethylamine (8g, 0.0793 mole), N-benzyl ethanolamine (4.95g, 0.03 mole), stirred the reaction mass for 2 h at 26-5-30°C, and followed by the addition of DM water (100 mL), concentrated the organic layer under reduced pressure oily residue (o-(1-fluoro-naphthalen-4yl-carbonyl) benzamide, 15g) results.

Above o-(1-fluoro-naphthalen-4yl-carbonyl) benzamide, 15g was diluted in tetrahydrofuran (26 mL) and added to suspension mass of Lithium aluminium-hydride (3.6g, 0.094 mole) with tetrahydrofuran (65 mL), at 25-30 °C and maintained the reaction mass at reflux temperature under nitrogen atmosphere for 42 h added pre-cooled DM water (26mL) followed by the addition of 20% w/w sodium hydroxide solution (18 mL) at 0-5 °C, concentrated the reaction mass under vacuum at 40 °C added DM water (50 mL), dichloromethane (100 mL) concentrated the organic layer under vacuum, oily residue (10g, 2[[(2-hydroxyethyl) 5- Benzylamino- 1(4- fluoro naphthalene hydrol) obtained. Diluted the 2[[(2-hydroxy ethyl)5-Benzylamino-1(4-fluoro naphthalene hydrol) (10g, 0.0311 mole) in toluene (80 mL), and added p-toluene sulfonic acid mono-hydride (8.9g, 0.0467 mole) and heated to 95-105 °C and maintained 95-105 °C for 4 h (during these period water was removed by azeotropically) and cooled the reaction mass to 25-30 °C and DM water (20mL) and adjusted 11 pH with 20 w/w aqueous sodium hydroxide solution (18mL) and concentrated organic layer under reduced pressure, diluted the conc. mass in methanol (50mL) and added 35% hydrochloric acid (3.25g, 0.0317 mole) and agitated for 2 h at 0-5 °C, the product was precipitated out and filtered the product (1H-2,5-Benzoxazocine, 3, 4, 5, 6-Tetrahydro-5-Benzyl(4-naphthalen)-1yl-Hydrochloride, 9.1g yield 70%.

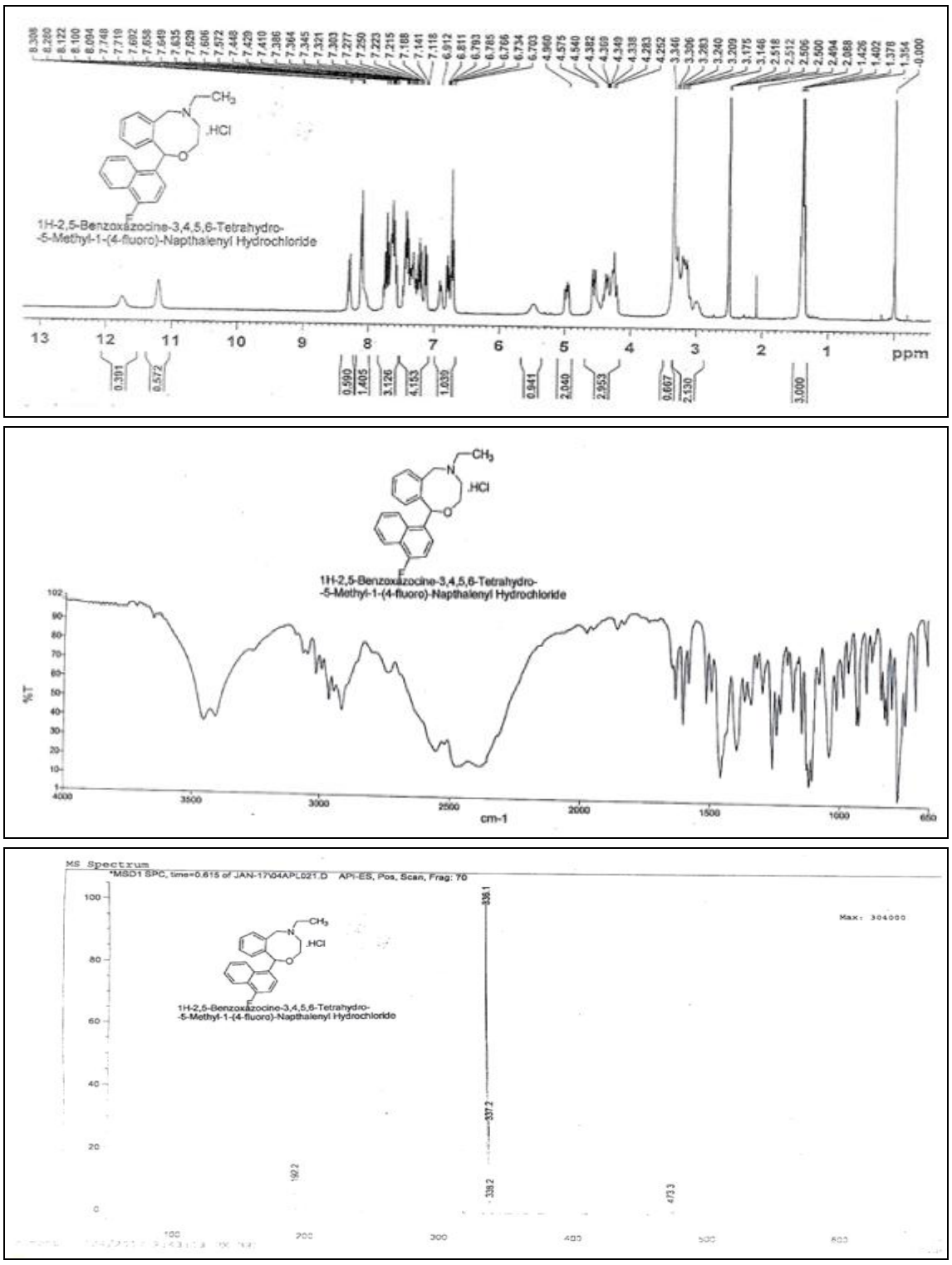
Analysis Calculated for $C_{27}H_{25}ClFNO$: C, 74.73; H, 5.81; Cl, 8.17; F, 4.38; N, 3.23; O, 3.69; IR (KBr cm^{-1}): 3850 (Alkyl-Ar-F, 3096 (Ar-F); 3011 (Aromatic C-H stretch), 2950 (CH_3-CH_2-), 1192 (C-O); ^{1}HNMR (DMSO) δ10.7-11.5 (SS,1H), δ6.71-8.34 (m,15H), δ 5.11-5.18 (S,1H), δ4.22-4.6, (m4H), δ4.17 (d,2H), δ3.01 (d,2H) MS*: m/z* 398.2 $[M+H]^+$.

Synthesis of 1H-2,5-Benzoxazocine,3,4,5,6-Tetrahydro-5-ethyl-1(4-Fluoro)-Napthalenyl Hydrochloride: Phthalic anhydride (10g, 0.0675 mole) was suspended in 1-fluoro-naphthalene (59.18g, 0.4054 mole) at 25-30 °C. Aluminum chloride (22.4 g, 0.1689 mole) at 25-40°C, stirred the reaction mass at 65-70 °C for 3 h, TLC indicates completion of reaction, conc. Hydro-chloric acid (100 mL) was added to the reaction mass at 25-30 °C, and distilled the reaction mass under atmospheric pressure at 95-100 °C to remove the excess 1-fluoro-naphthalene and followed by addition of dichloromethane (80 mL) at 25-30 °C separated the organic layer, aqueous layer and organic layer with DM water (100 mL) pH was adjusted to pH 12 with 5% w/v aqueous sodium hydroxide solution (30mL) separated the aqueous layer and product was precipitated at pH 1 of aqueous layer and filtered the product *i.e.* Acid compound {o-(1-fluoro-naphthalen-4yl-carbonyl) benzoic acid} and washed with DM water (15mL).

Above dried o-(1-fluoro-naphthalen-4yl-carbonyl) benzoic acid (16g, 0.0544 mole) was suspended in toluene (70 mL) and dimethylformamide (0.2g, 0.00274 mole), Thionyl chloride (7.76g, 0.065 mole) and stirred for 2 h and evaporated the solvent under vacuum at 40 °C and diluted the conc. mass in dichloromethane (30 mL) and triethylamine (8g, 0.0793 mole), N-methyl ethanolamine (4.95g, 0.066 mole), stirred the reaction mass for 2 h at 26-5-30 °C, and followed by the addition of DM water (100 mL), concentrated the organic layer under reduced pressure oily residue (o-(1-fluoro-naphthalen-4yl-carbonyl) benzamide, 15g) results.

Above o- (1- fluoro- naphthalen- 4yl- carbonyl) benzamide, 15g was diluted in tetrahydrofuran (26 mL) and added to suspension mass of Lithium aluminium –hydride (3.6g, 0.094 mole) with tetrahydrofuran (65mL), at 25-30°C and maintained the reaction mass at reflux temperature under nitrogen atmosphere for 42 h added pre-cooled DM water (26 mL) followed by the addition of 20% w/w sodium hydroxide solution (18 mL) at 0-5 °C, concentrated the reaction mass under vacuum at 40 °C added Dewater (50 mL), dichloromethane (100 mL) concentrated the organic layer under vacuum, oily residue (10g, 2[[(2-hydroxy ethyl methyl amino-methyl naphthalene hydrol) obtained. Diluted the 2[[(2-hydroxy ethyl methyl amino-methyl naphthalene hydro (10g, 0.0311 mole) in toluene (80 mL), and added p-toluene sulfonic acid

mono-hydride (8.9g, 0.0467 mole) and heated to 95-105 °C and maintained 95-105 °C for 4 h (during these period water was removed by azeotropically) and cooled the reaction mass to 25-30 °C and DM water (20 mL) and adjusted 11 pH with 20 w/w aqueous sodium hydroxide solution (18 mL) and concentrated organic layer under reduced pressure, diluted the conc. mass in methanol (50 mL) and added 35% hydrochloric acid (3.25g, 0.0317 mole) and agitated for 2 h at 0-5°C, the product was precipitated out and filtered the product (1H-2,5-Benzoxazocine, 3, 4, 5, 6-Tetrahydro- 5- Methyl-naphthalen- 1yl- Hydro-chloride, 9.1g yield 70%.



1H-2,5-Benzoxazocine,3,4,5,6-Tetrahydro-5-ethyl-1(4-Fluoro)-Napthalenyl Hydrochloride

Analysis Calculated for $C_{22}H_{23}ClFNO$: C, 71.05; H, 6.23; Cl, 9.53; F, 5.11; N, 3.77; O, 4.30; IR (KBr cm^{-1}): 3786 (Alkyl-Ar-F), 3053 (Ar-F), 3017 (Aromatic C-H stretch), 2966 (CH_3-CH_2-), 1197 (C-O); ^{1}HNMR (DMSO) δ11.2-11.8(SS,1H), δ6.7-8.31 (m, 10H), δ 4.9 (brs, 1H), δ4.25-4.57 (m, 3H), δ3.34 (m, 1H), δ3.14-3.34 (m, 4H), δ1.35-1.4 (S.1H); MS*: m/z* 336.1 $[M+H]^+$.

Synthesis of 1H-2,5-Benzoxazocine,3,4,5,6-Tetrahydro- 5- ethyl- phenyl hydrochloride: Suspended Magnesium turnings (2g, 0.08 moles) in tetrahydrofuran (60 mL) under nitrogen atmosphere and heated to 45-50 °C added crystal of Iodine followed by 2.5 g Bromo-benzene (0.016 mole) for initiate Grignard reaction, and slowly added mixture of 11.7g of Bromo-benzene (0.074 mole) and tetrahydrofuran (10 mL) at 45-65°C in 1 h and agitated reaction mass at 60-65 °C for 1 h, then cooled the reaction mass to 25-30 °C and the above prepared Grignard reagent added to mixture of Phthalic-anhydride (10g)- dichloromethane (80 mL) at 0-5 °C in 1 h, stirred the reaction mass for 1 h at 0-5 °C, and quenched the reaction mass with 5N aqueous hydrochloric acid solution (25 mL) at 0-5 °C and separated below organic layer these organic layers was mixed with DM water (100 mL) and adjusted the pH to 11-11.5 with 10% w/v aqueous sodium hydroxide solution (30 mL) at 25-30 °C and organic layer was separated out, and adjusted the pH of aqueous layer (at pH:11-11.5) to pH:2 with conc. hydrochloric acid (12 mL) result acid compound, *i.e.* o-benzoyl-benzoic acid obtained (dried wt: 15g).

The above o-benzoyl benzoic acid (15g) was suspended in toluene (75 mL) at 25-30 °C and added catalytic N,N-dimethyl formamide (16g) followed by the addition of thionyl chloride (9g, 0.073mole) under nitrogen atmosphere at 25-30 °C and stirred the reaction mass for 2 h at 25-30 °C and reaction completed by checking of TLC and concentrated under reduced pressure at 45-50 °C and diluted the conc. mass in toluene (60 mL) at 25-30 °C and cooled to 10-15 °C and added mixture of N-ethyl ethanolamine (10g, 0.11 mole) and toluene (15 mL) at 15-20 °C stirred the reaction mass at 25-30 °C for 3 h then observed that reaction was completed by checking of TLC, Then added DM water (120 mL) and stirred the reaction mass for 1 h at 25-30 °C, filtered the product o-benzoyl-N-(2-Hydroxy ethyl)-N-ethyl benzamide, dried wt 14g.

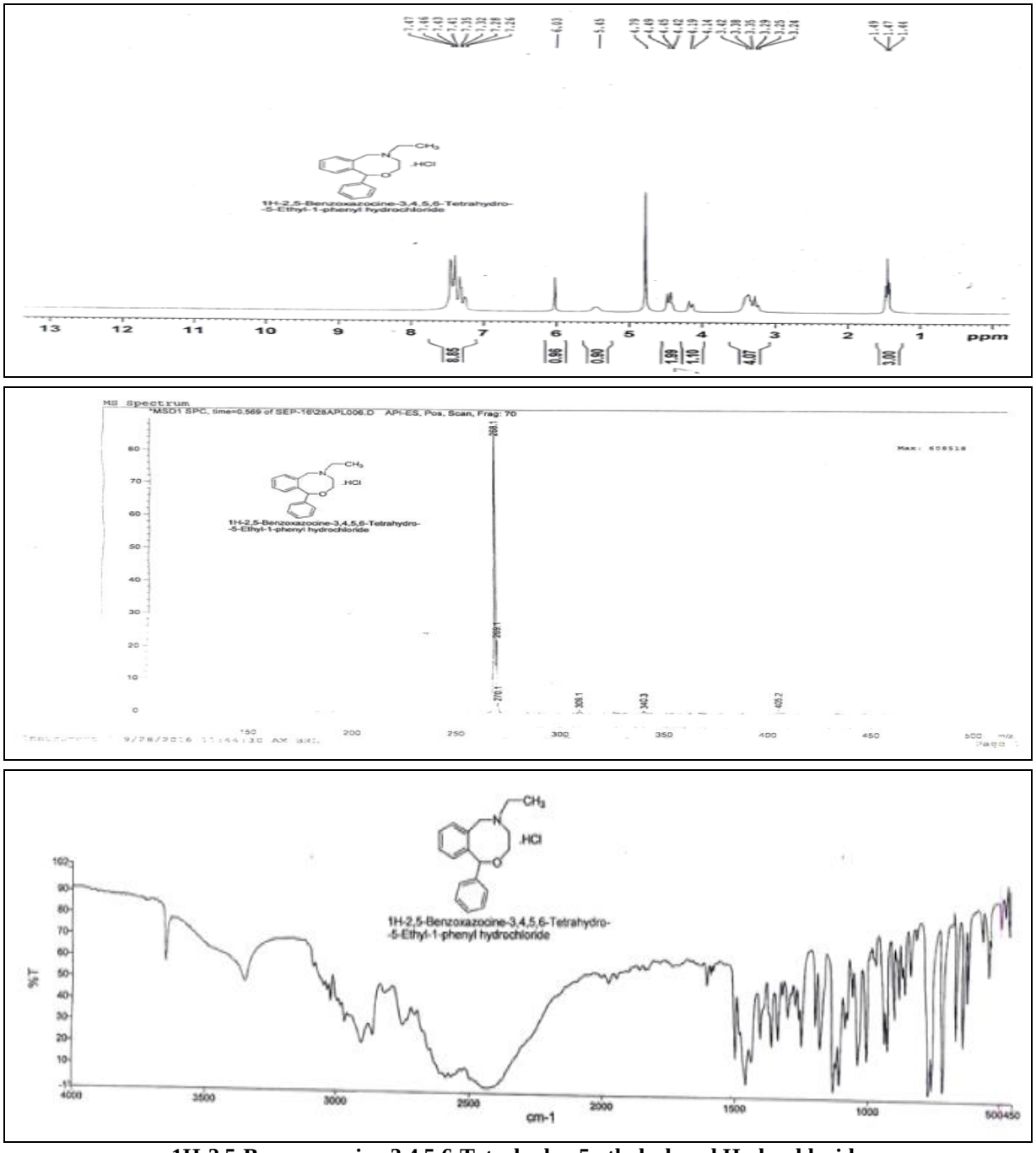
The above o-benzoyl-N-(2-Hydroxy ethyl)-N-ethyl benzamide (14g) was dissolved in dichloromethane (80 mL) at 25-30 °C and catalytic amount of N,N-dimethyl formamide (0.2g), followed by addition of thionyl chloride (7g, 0.06 mole) and stirred the reaction mass for 2 h at 25-30 °C and observed that reaction was completed by checking of TLC. Cooled the reaction mass to 0-5 °C, adjusted the pH to 6.5-7 with 5% w/v aqueous sodium hydroxide solution (137mL) and raised the reaction mass temperature to 25-30 °C, separated the organic layer, it contains o-Benzoyl-N-(2-Chloro ethyl)-N-ethyl Benzamide product.

The above o-Benzoyl-N-(2-Chloro ethyl)-N-ethyl Benzamide product. Reaction mass was mixed with glacial acetic acid (2g, 0.033 mole) and was added to the suspension mass of sodium borohydride (4g, 0.106 mole) in dichloromethane (20 mL) at 25-30 °C and subjected the above reaction mass to heated to 35-40 °C and maintained 35-40 °C for 20 h and observed that reaction completed by checking of TLC. Then cooled the reaction mass to 0-5 °C and added cold DM water (36 mL) at 0-5 °C, followed by the addition of 40% w/v aqueous sodium hydroxide solution (12 mL) at below 30 °C. There after heated to 65-70 °C by simultaneous removal of dichloromethane at atmospheric pressure continued stirring at 65-70 °C for 1 h to break the boron complexes and then cooled to 25-30 °C, then added dichloromethane (20 mL) and separated the organic layer, mixed the organic layer with DM water (16mL) and adjusted the pH to 0.5-1 with conc. hydrochloric acid (9mL, 35% w/w) at 25-30 °C and stirred for 1 h 25-30 °C. Then separated the aqueous layer and adjusted the aqueous layer pH from pH~1 to pH ~12 with 40% w/w aqueous sodium hydroxide solution (12mL) and then extracted in to dichloromethane (25mL) and concentrated the organic layer which contains product 2-(N-(2-hydroxy (phenyl) methyl) benzyl-n-ethyl amino) ethanol.

The above 2-(n-(2-hydroxy (phenyl)methyl)benzyl-n-ethylamino) ethanol concentrated mass was diluted with toluene (80 mL) and added p-toluene sulfonic acid monohydrate (15g) at 25-30 °C and stirred the reaction mass at 85-110 °C with

azeotropic removal of water for 4 h and observed that reaction completed by checking of TLC and cooled the reaction mass to 25-30 °C and DM water (60 mL) was added, adjusted the pH to 10.5 to 11 with 24% w/v aqueous sodium hydroxide solution (25mL) and separated the organic layer and concentrated under reduced pressure then diluted the conc. mass in acetone (96 mL) and cooled to 0-5 °C and slowly added conc. hydrochloric acid (5g,~35% w/w) then product (1H-2,5-Benzoxazocine 3,4,5,6-tetrahydro-5-ethyl-1-phenyl-hydrochloride) precipitated out and filtered the product (dry weight 9g).

Analysis Calculated for $C_{18}H_{22}ClNO$: C, 71.16; H, 7.30; Cl, 11.67; F, 5.31; N, 4.61; O, 5.27; IR (KBr cm^{-1}): 3644 (C_6H_5-CH(C)-), 3018 (Aromatic C-H stretch), 2968 (CH_3-CH_2-), 1196(C-O); NMR (D_2O) δ 7.26-7.47 (m, 9H), δ 6.03 (S,1H), δ5.45 (brS, 1H) 4.42-4.79 (d, 2H), δ4.14-4.19 (d, 2H), δ 3.24-3.42 (tt4H), δ1.44-1.49 (S, 3H); MS: *m/z* 268.1 $[M+H]^+$ as a free base.



1H-2,5-Benzoxazocine,3,4,5,6-Tetrahydro-5-ethyl-phenyl Hydrochloride

CONCLUSION: We have successfully modified the structure of nefopam analogs are new series of drugs.

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