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EFFICIENT AND INDUSTRIALLY VIABLE SYNTHESIS OF MECLOFENOXATE HYDROCHLORIDE

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ABSTRACT:

An efficient, industrially viable process has been developed for large-scale preparation of Meclofenoxate HCl (1), a cholinergic nootropic. The process involves the chlorination of 4-chlorophenoxy acetic acid in the presence of Thionyl chloride at room temperature to yield 4-Chlorophenoxy acetyl chloride, which is condensed with Dimethyl amino ethanol in Methylene di chloride at 0^{o}C to give Meclofenoxate.

Keywords: cholinergic nootropic, Chlorination, condensation, Meclofenoxate, Industrially Viable

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1. INTRODUCTION

For chemists working in the lab at the milligram stage, developing new processes and scaling them up through kilo Laboratory runs to commercial scales are always difficult tasks. Every step of The process and mechanism must be understood by the chemist. From the laboratory to the pilot plant, then from the factory to the point of commercialization. In this case, the research chemist must recognize the value of active pharmaceutical ingredients (APIs) and comprehend the methods and strategies used by the producer under management.

Many unprecedented impurities are encountered by chemists during the commercialization and synthesis of APIs, raising serious concerns for the medicine's approval during the last phases of drug manufacture. New and inventive methods have emerged to address these issues, bringing in high yields with low impurities through route evolution, impurity profiling, analysis, and technological development

Active Pharmaceutical Ingredient (API)

"A substance used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have a direct effect in the diagnosis cure, mitigation, treatment, or prevention of disease, or to have a direct effect in restoring, correcting or modifying physiological functions in human beings." API – active pharmaceutical ingredient is an active part of the pharmaceutical dosage form. In most drugs, there are usually two different kinds of chemical ingredients, one is an inert part of a drug called an Excipient and another is an active ingredient called API. For any disease, the remedy is chosen based on the type of active ingredient used in it. Always API is mixed with excipients to reach the site of action and achieve the desired pharmacological effect. In herbal medicines, Active pharmaceutical ingredients and made up by combining several different substances that function as an API when mixed at the desired concentration together. These are several different and standard methods for calculating the relative strength of various APIs inside the dosage form. The methods vary from manufacturer to manufacturer. Unless and until the proper amount of active pharmaceutical ingredients is mixed up within the medicine. It won't be as efficient as it was supposed to be ideally. Active pharmaceutical ingredients are generally manufactured through the below-mentioned process. A generic drug is a drug that is manufactured and marketed without any patent protection. The generic drug may still have a patent on the formulation but not on the active ingredient. As per USFDA regulations, generic drugs should contain the same drug substance with a satisfactory bioequivalent range compared to innovator drugs with respect to the properties in the monographs of pharmacopeia. Since innovator Drugs are expensive, generic drugs have become popular in the US market. Generic drugs are available at moderately low prices due to the low production cost in competition between the generic companies. The demand for drugs effectively at low cost is a growing trend across the pharma sector The complete life cycle for process development of an API flow diagram in the generic pharmaceutical company is shown in Figure. The process development follows seven phases, as given below.

Product selection by market scenario

1. **Literature search**
2. **Process optimization, identification and synthesis**
3. **Process validation**
4. **Commercialization**
5. **Stability study**
6. **DMF filling**

Brief Review of Process Development on few Active Pharmaceutical Ingredients Keeping the above parameters in to consideration, we have identified some key areas and we believe that the research work presented would be imperative in the direction to ensure availability of affordable medicines with highest quality in the most economical, robust, safe, rapid, and environment friendly way to the patient population.

2. DRUG PROFILE

Meclofenoxate [CAS number 51-68-3] (Figure 1) is one of the older nootropic drugs used to treat the symptoms of senile dementia and Alzheimer's disease. It is a white powder, soluble in cold water and methanol, sparingly soluble in cold isopropanol and acetone and practically insoluble in benzene, ether and chloroform However, meclofenoxate containing ester is easy to produce hydrolysis reaction, resulting in that its medicinal property becomes poor. Several different methods have been used for the determination of meclofenoxate including electrochemical method proton magnetic resonance spectroscopy, capillary electrophoresis resonance Rayleigh scattering method, and high-performance liquid chromatography.

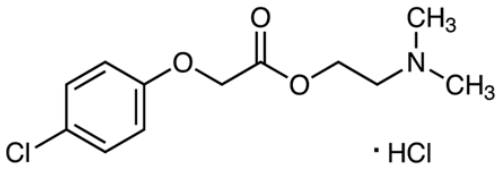


Figure 1

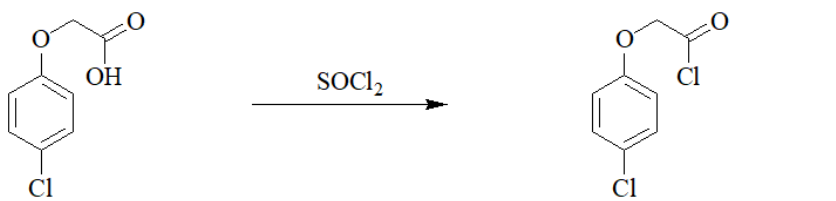
DESCRIPTION:

Meclofenoxate hydrochloride contain not less than 98% of $C_{12}H_{16}ClNO_3$.HCl calculated on the anhydrous basis. Meclofenoxate hydrochloride occurs as white crystalline powder, it has a faint characteristic order and bitter taste. It is freely soluble in water and ethanol sparingly soluble in diethyl ether, the pH of a sol is between 3.5 to 4.5

3. MATERIAL AND METHODS

Preparation of 4-Chlorophenoxyacetyl chloride

P-chlorophenoxyacetic acid 100g is put into methylene chloride and DMF, stirred for 10 min at room temperature and then 100 ml thionyl chloride is added dropwise and stirred for 40°C, then Methylene chloride is added to obtain a clear solution. Concentrate solvent at 60-70°C for completion of solvent distillation and maintain for half an hour at same temperature under vacuum. Obtain a white solid material obtain white solid 116g, yield 84.6%, purity 99.8%

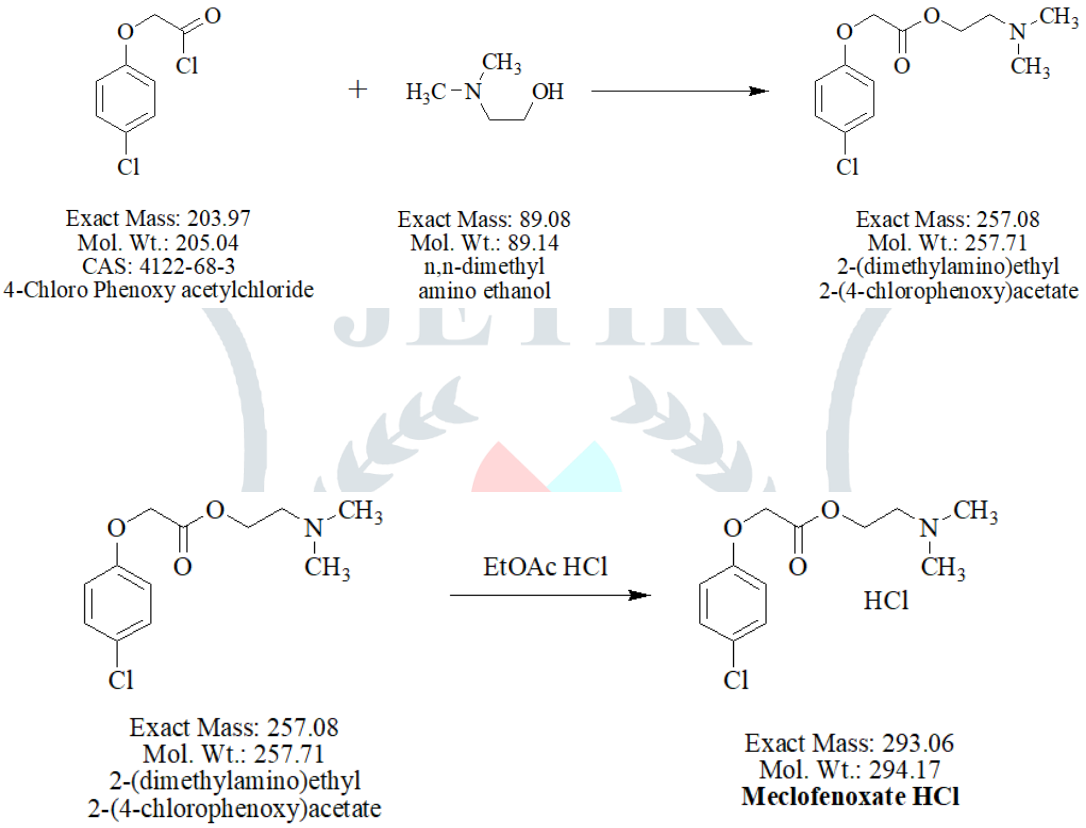


Exact Mass: 186.01
Mol. Wt.: 186.59
CAS: 122-88-3
4-Chloro Phenoxy Aceticacid

Exact Mass: 203.97
Mol. Wt.: 205.04
CAS: 4122-68-3
4-Chloro Phenoxy acetylchloride

Preparation of 2-(dimethylamino) ethyl-2-(4-chlorophenoxy) acetate Hydrochloride

Add the 4-Chlorophenoxyacetyl chloride in 250 ml of dichloromethane solution of 53 gm of N, N-dimethylaminoethanol being added in reaction flask. 100 ml Water is added to extract, obtained organic layer, the substrate is concentrated. In ethyl acetate, the hydrogen chloride gas is added to the substrate to hydrochloric acid salt, until solid is largely precipitated, is filtered after 25°C of heat preservations, obtain white solid 49g, yield 90.6%, purity 99.9%



4. RESULTS AND DISCUSSIONS

Spectral data

3a$_1$ 2-Dimethylaminoethyl (4-chlorophenoxy) acetate

Pale yellow crystals, **IR (KBr):** ν_{max} in cm^{-1}: 16012.5 (C=N), 3282.1 (N-H), 3056.2 (=C–H), 1292.4 (C-N),1541.6 (C=C), 1014.8 (C=S); **^{1}H NMR** (500 MHz, DMSO-d6) 1H NMR: δ 2.19 (3H, s), 7.48 (1H, dd, J = 8.2, 1.7 Hz), 7.60 (1H, dd, J = 8.2, 0.5 Hz), 7.66 (1H, dd, J = 1.7, 0.5 Hz), 7.75 (1H, s). **ESI-MS:** m/z Anal. Calcd. For $C_{11}H_{10}N_4O_2S$ ($[M + H]^+$): 262.29, found 263.25.

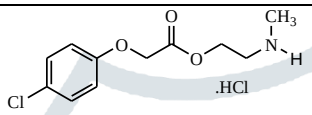
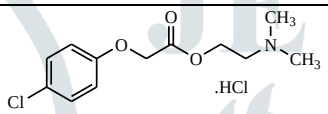
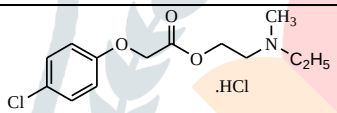
4a$_1$ 2-Dimethylamine ethyl-2-(4-chlorophenoxy) acetate

Pale yellow crystals, **IR (KBr):** ν_{max} in cm^{-1}: 1608 (C=N), 3282.5 (N-H), 3059.4 (=C–H), 1290.5 (C-N),1544.1 (C=C), 1013.5 (C=S); **^{1}H NMR** (500 MHz, DMSO-d6) δ 11.48 (s, 1H), 8.13 (q, J = 4.0 Hz, 1H), 7.92 – 7.87 (m, 1H), 7.56 (s, 1H), 7.48 (d, J = 1.2 Hz, 2H), 3.04 (s, 3H), 2.20 (s, 3H). **ESI-MS:** m/z Anal. Calcd. For $C_{12}H_{12}N_4O_2S$ ($[M + H]^+$): 276.30, found 277.25.

5a1 N-ethyl-2-((6-methyl-4-oxo-4H-benzo) methylene) hydrazine-1-carbothioamide

Pale yellow crystals, **IR (KBr):** ν_{max} in cm^{-1}: 1606.2 (C=N), 3284.3 (N-H), 3063.5 (=C–H), 1294.5 (C-N),1542.3 (C=C), 1016.4 (C=S); **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.10 (s, 1H), 7.99 (t, J = 3.0 Hz, 1H), 7.92 – 7.87 (m, 1H), 7.56 (s, 1H), 7.48 (d, J = 1.2 Hz, 2H), 3.62 (qd, J = 6.5, 2.9 Hz, 2H), 2.21 (s, 3H), 1.21 (t, J = 6.5 Hz, 3H). **ESI-MS:** m/z Anal. Calcd. For $C_{13}H_{14}N_4O_2S$ ($[M + H]^+$): 290.35, found 291.25.

Table 1. Molecular formula, melting point and yield of compounds

Comp. No	R_1	R_2	Structure	Mol. Form.	m.p in °C	% Yield
3a1	$-CH_3$	-H		$C_{11}H_{14}ClNO_3.HCl$	213-214	74
4a1	$-CH_3$	$-CH_3$		$C_{12}H_{16}NO_3.HCl$	221-222	78
5a1	$-CH_3$	$-C_2H_5$		$C_{13}H_{18}NO_3.HCl$	229-230	82

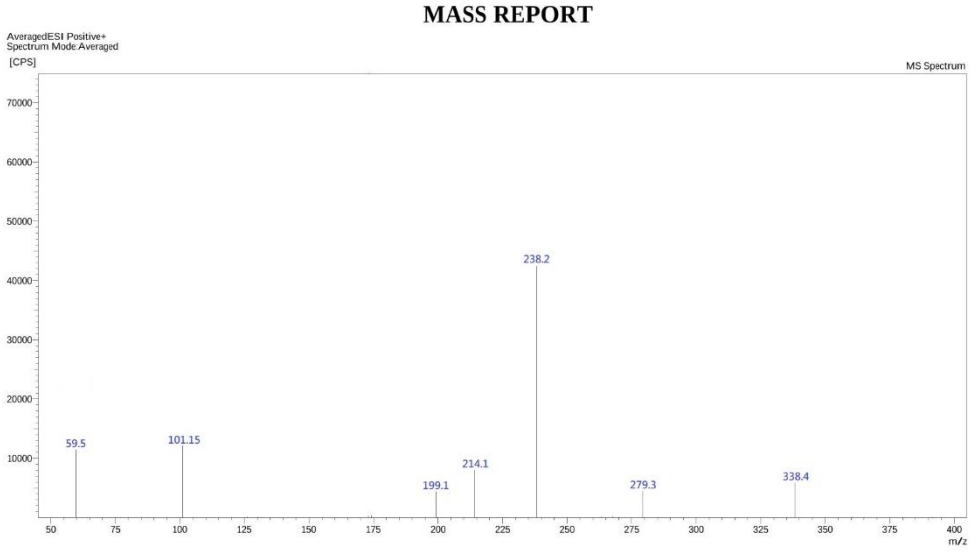
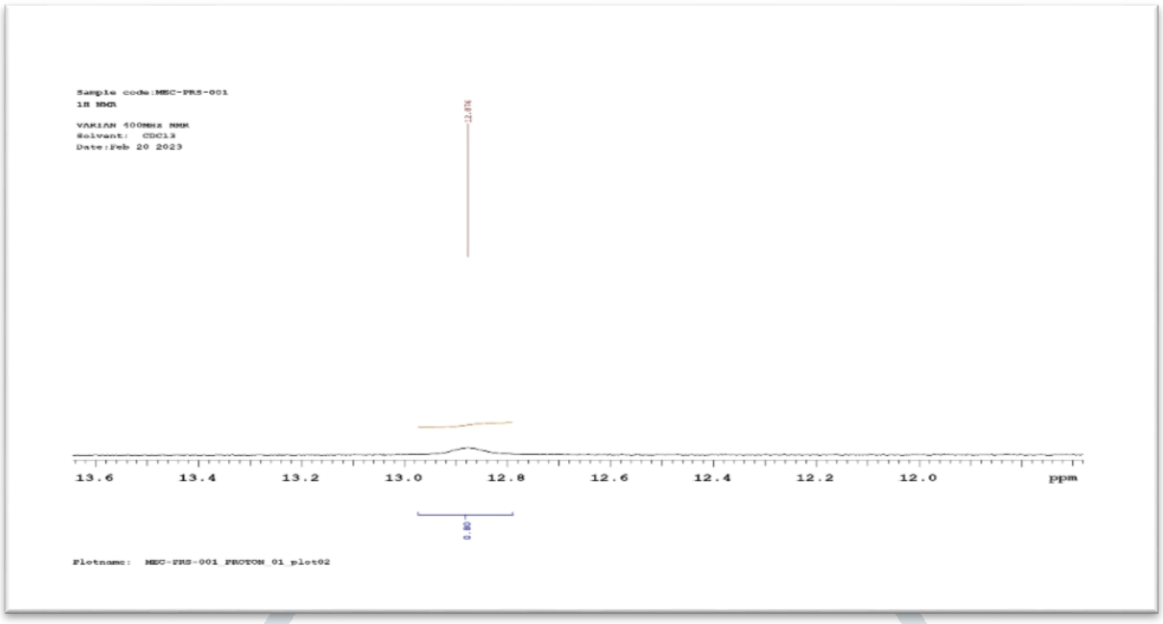
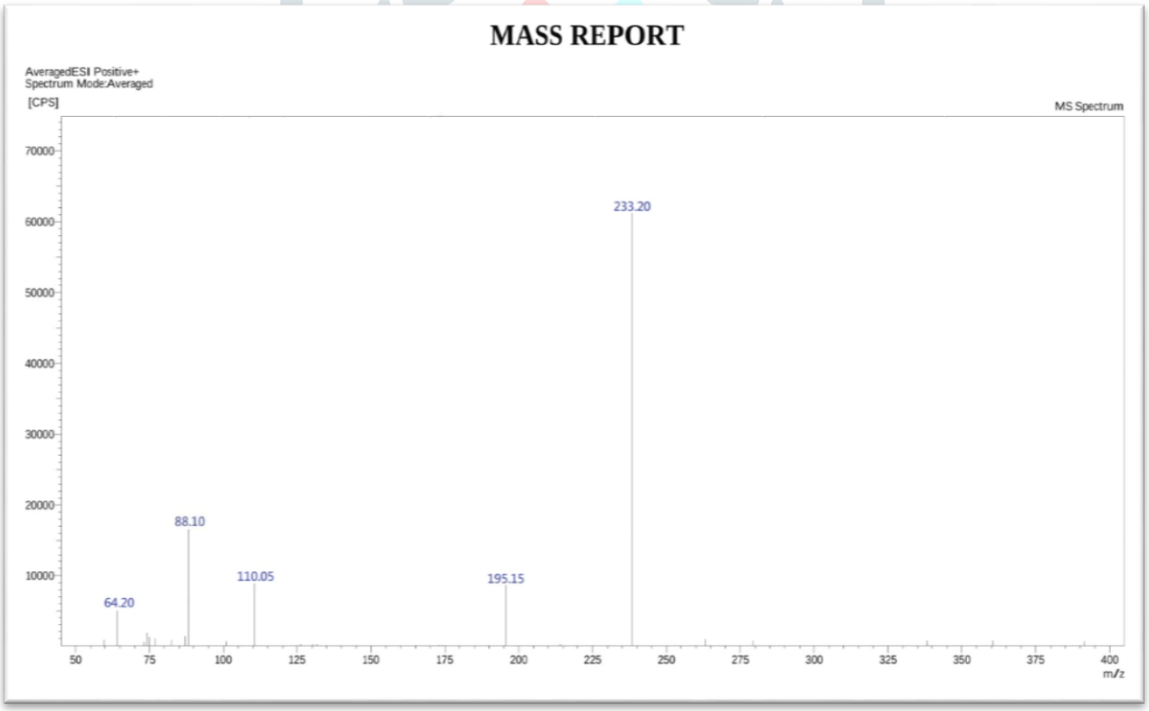


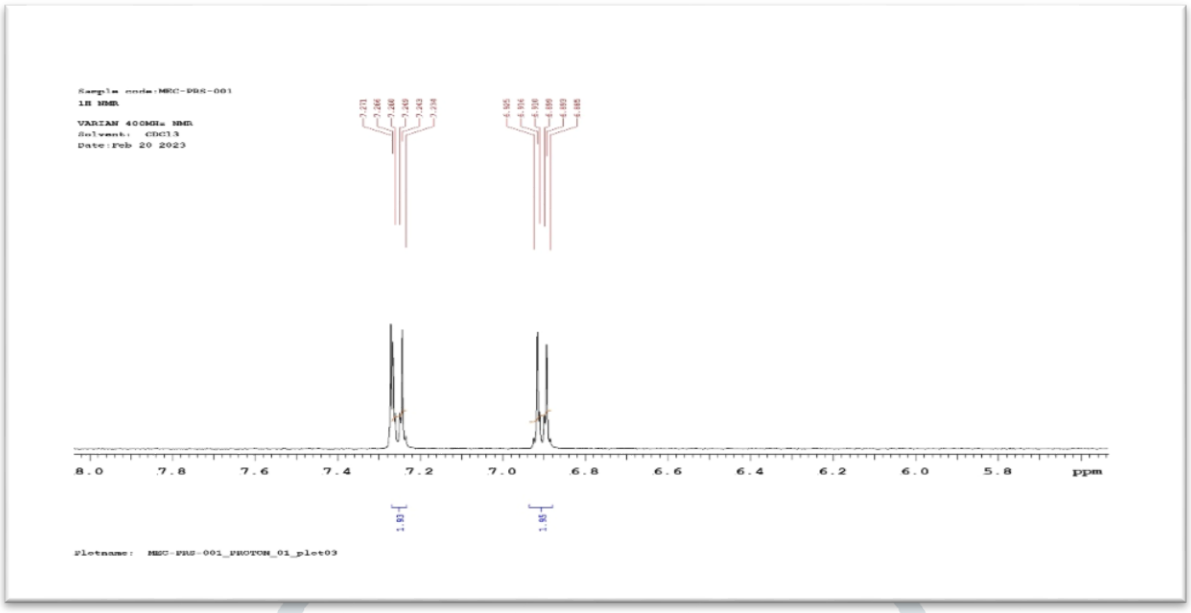
Figure 1. Mass Spectrum of compound 3a1



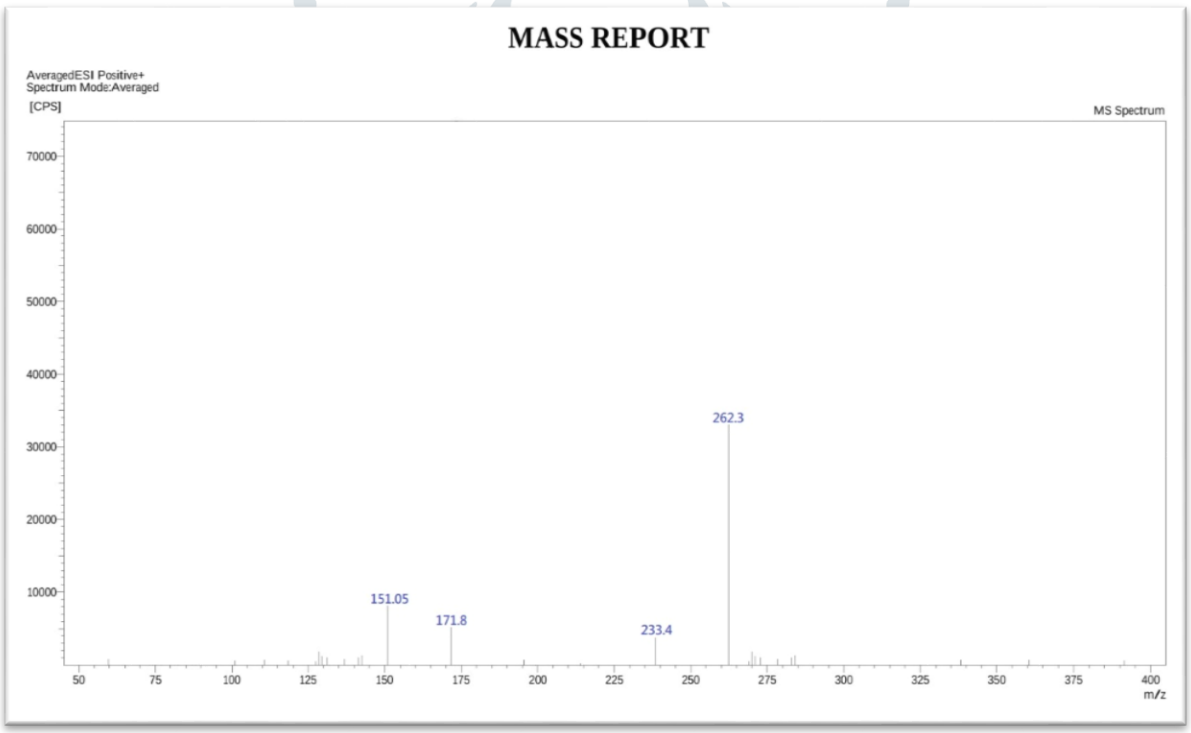
1H NMR Spectrum of compound 3a2



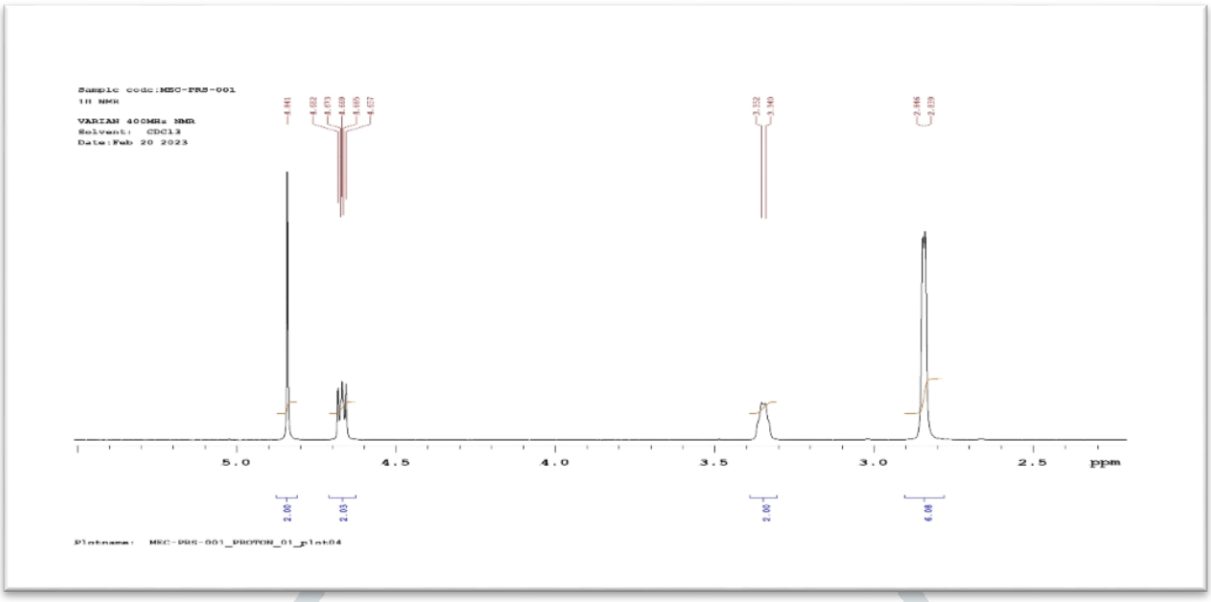
Mass Spectrum of compound 4a1



1H NMR Spectrum of compound $4a_2$



Mass Spectrum of compound $4a_1$



1H NMR Spectrum of compound 4a2

5. SUMMARY AND CONCLUSION

Synthesis of Meclofenoxate from the condensation of substituted methylene chloride and DMF with thionyl chloride that is oxidized using 4-Chlorophenoxyacetyl chloride to the corresponding aldehydes followed by the condensation.

Different novel derivatives of meclofenoxate was synthesized in adequate yields and characterization of the molecules was done by detailed spectral analysis using advanced analytical support. The titled compound was screened for antibacterial and antifungal activities.

Results proclaimed that all the synthesized compounds were exhibiting antimicrobial properties. Compound **5a1**was contended to bear potent nootropic effect. Further studies are needed to establish the possible MOA can helpful in the future development.

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