COST EFFECTIVE ONE POT SYNTHESIS OF 6-CHLORO-5-(2-CHLOROETHYL) OXINDOLE

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ABSTRACT
The current process for ziprasidone involves preparation and isolation of the key intermediate 6-chloro-5-(2-chloroethyl) oxindole (**III**). An improved process for the synthesis of this intermediate is reported here. The new process involves use of a sodium borohydride in presence of triethylsilyl hydride. The new method affords the desired compound in a one-pot process obviating the need for isolation of the potentially hazardous precursor ketone.

KEY WORDS: Ziprasidone, $NaBH_4$, One-pot synthesis, TES.

1.   INTRODUCTION

Ziprasidone hydrochloride is a selective Tourette's syndrome, serotonin and dopamine antagonist that is marketed as Geodon by Pfizer as the brand name GEODON as a capsule containing ziprasidone hydrochloride monohydrate and in a lyophilized form of ziprasidone mesylate trihydrate for reconstitution and injection. The Tourette's syndrome is chronic neuropsychiatric disorder of childhood causes that is characterized by multiple motor and vocal ties, somatosensory urges, and behavior problems such as attention deficit hyperactivity disorder, learning disabilities, obsessive compulsive disorder, anxiety and depression[I]. It is a typical antipsychotic that has good efficacy and safety profile. Ziprasidone hydrochloride is well tolerated and is not associated with any clinically significant weight gain or adverse effects on glycemic control. The existing process for the preparation of ziprasidone involves preparation of a key intermediate (**III**). Here we report an improved process for the preparation of this intermediate. The US Patent number 4,831,031 describe ziprasidone, its related compounds and their synthesis. Referring to the reactions in following scheme, the reduction of 5-(2-chloroacetyl)-6-chloro-2-oxindole (**II**) using triethylsilane (TES) and strong acid (trifluoroacetic acid) forming the mixture of 5-(2chloroethyl)-6-chloro-2-oxindole along with its alcoholic (**A**) and keto (**II**) impurities which will be condensed with 3-(1-piperazinyl)-1,2-benzisothiazole forming ziprasidone along with keto and hydroxyl impurity[II]. The 5-(2-chloroacetyl)-6-chloro-2-oxindole (II) was synthesized from 6-chloro-2-oxindole (I) and monochloroacetyl chloride in dichloromethane in presence of anhydrous aluminum chloride as shown in **scheme I**.
The reduction of α-chloroketone (**II**) to chloride (**III**) is carried out by reaction with trifluoroacetic acid and triethyl silane[II] which are very expensive and thus remarkably affecting

the product cost. The α-chloroketone (**II**) is an eye irritant and its presence, even in traces as an impurity in reduced product (**III**) is problem for the operator.

The compound (**III**) can be synthesized in two steps from α-chloroketone (**II**). The α-chloroketone (**II**) can be partially reduced by giving the treatment of alkali metal borohydride in particular sodium or lithium, generally $NaBH_4$ is used[III] The reaction is carried out in various solvents such as water, C_1-C_4 alcohols, ethers, glycols, acetic acid, etc at the temperature between $20 – 60^0C$. The intermediate partially reduced alcohol (**A**) is subsequently can be reduced by the treatment with trifluororacetic acid and triethylsilane by the known methods[IV]. The compound (**III**) [6-chloro-5-(2-chloroethyl)-2-oxindole] is the key intermediate for the synthesis of ziprasidone was synthesized by using novel Lewis acid-mediated selective deoxygenation of the ketone (**II**) with tetramethyldisiloxane [TMDS]. It is one pot synthesis of (**III**) along with various impurities including (**A**)[V]. Again this methods is costly because of high cost of tetramethyldisiloxane reagent.

2.   RESULTS AND DISCUSSION

The existing process for the preparation of ziprasidone hydrochloride is shown in Scheme I. This process involves the preparation of a key intermediate chloride (**III**) which is then coupled to 3-benzisothiazolylpiperazine, resulting in the formation of ziprasidone free base. The intermediate chloride (**III**) is prepared from 6-chlorooxindole by a two-step process involving Friedel-Crafts acylation reaction followed by reductive deoxygenation (single or two steps) of the chloroketone (**II**). In this process the precursor α-chloroketone (**II**) is first isolated, dried, and then carried forward to the next reduction step. This chloroketone is known to be a strong skin sensitizer. The manufacture and handling of this intermediate on large scale is potentially hazardous. Due to the hazardous nature of the intermediate and reagents that are used in the process, the manufacture of the first two steps of the process can only be performed in the commercial-scale manufacturing facility with high level of containment. In order to provide operational flexibility and enhance safety it is desirable to avoid either formation of the chloroketone intermediate or to have a process that would not involve isolation of this intermediate. Several attempts have been made to design synthetic routes that did not require formation of the hazardous intermediate (**II**)[V] however, the route reported below is the first commercially viable process.

In order to avoid isolation of hazardous (**II**), we decided to evaluate $AlCl_3$-mediated in situ reduction of this ketone with silane. Although several methods exist for the deoxygenation of carbonyl oxygen to methylene, all of them have some limitations[VI].

The existing process for the preparation of ziprasidone hydrochloride is shown in Scheme II. This process involves the preparation of a key intermediate (**III**) which is then coupled to 3-benzisothiazolylpiperazine, resulting in the formation of ziprasidone free base. The intermediate (**III**) is prepared from 6-chlorooxindole (**I**) by a two-step process involving Friedel-Crafts acylation reaction followed by reductive deoxygenation of the chloroketone (**II**). In this process the precursor R-chloroketone (**II**) is first isolated, dried, and then carried forward to the next reduction step. This chloroketone is known to be a strong skin sensitizer. The manufacture and handling of this intermediate on large scale is potentially hazardous. Due to the hazardous nature of the intermediate and reagents that are used in the process, the manufacture of the first two steps of the process can only be performed in the commercial-scale manufacturing facility with high level of containment. In order to provide operational flexibility and enhance safety it is desirable to avoid either formation of the chloroketone intermediate or to have a process that would not involve isolation of this intermediate. Several attempts have been made to design

synthetic routes that did not require formation of the hazardous intermediate **(II)**; however, the route reported below is the first commercially viable process.

A new one-pot process for preparation of the key intermediate **(III)** was developed shown in scheme II. This process does not require isolation of the hazardous intermediate chloroketone **(II)**. The new process was scaled up on multikilo scale to afford desired product **(III)** in high yield and good quality.

3.   Development of the New Process:

In order to avoidisolation of hazardous **1**, we decided to evaluate $AlCl_3$-mediatedin situ reduction of this ketone with silane. Although several methods exist for the deoxygenation of carbonyl oxygen to methylene, all of them have some limitations. Lewis acidmediated reductive deoxygenation of carbonyl compounds with silanes has previously been reported. Depending on the substrate, these reductions are often accompanied by minor side products of the corresponding alcohols and ethers. After Friedel-Crafts acylation (step 1) was complete, triethyl silane (TES) (2 equiv) was added slowly to the reaction mixture at 0-5 ^{0}C. After ~2 h a mixture of products was obtained containing primarily desired **2** and starting material **1** along with a minor amount of intermediate alcohol **6** (Scheme 2). Addition of excess (4 equiv) triethyl silane resulted in the complete reduction of chloroketone side chain, affording mainly **5** as the major product. We found it difficult to minimize formation of this side product to an acceptable level under a variety of reaction conditions. Aluminum chloride-catalyzed reduction of activated and unactivated alkyl halides with triethyl silane occurs under mild conditions. Under similar conditions polymeric siloxane (PMHS) was reported to be unreactive for this transformation. There are very few literature reports of Lewis acid catalyzed reductive deoxygenation of carbonyl compounds with siloxanes. In order to improve chemoselectivity of our transformation we decided to attempt this reduction with tetramethyl disiloxane (TMDS). In our experience the silyl byproducts originating from this reagent after aqueous workup are easier to purge in organic solvents compared to byproduct from the longer-chain siloxanes.

Scheme I: Reduction of (II) with silyl hydride and NaBH₄/TES reducing agents:
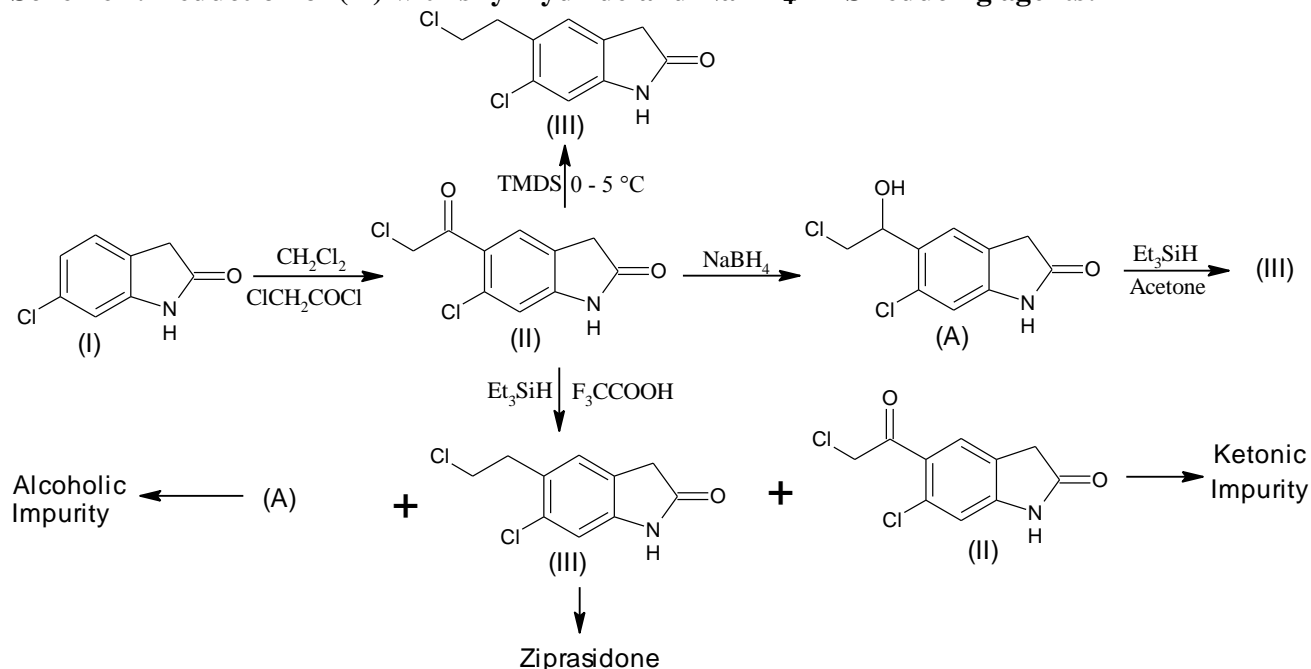
Scheme II: Improved process for preparation of 2:

6-chlorooxiindole   chloroacetyl chloride
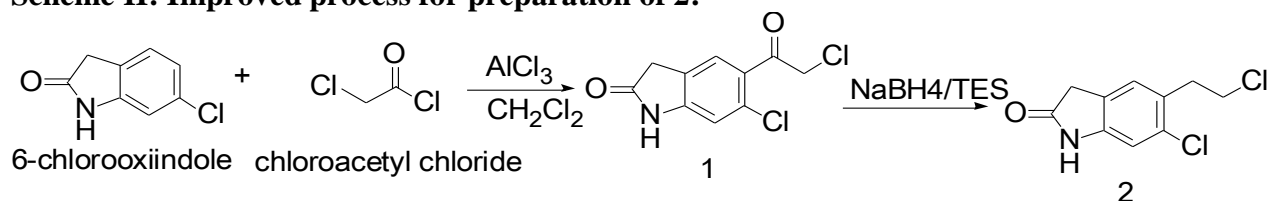
New Process for the Preparation of 6-Chloro-5-(2-chloroethyl)-1,3-dihydro-2H-indol-2-one (2).
A dry 50 L reactor was charged with methylene chloride (10 L) and anhydrous aluminum chloride (6.56 kg, 49.2 mol, 3.3 equiv) under nitrogen. The contents were cooled to 10-15 ^{0}C and stirred for 15 min. Chloroacetyl chloride (2.70 kg, 23.9 mol, 1.6 equivalents) was added over 2 h. To this reaction mixture was added 6-chlorooxindole (2.50 kg, 14.9 mol, 1 equivalent) as a solid. The reaction mixture was stirred and heated at 30-40 °C under nitrogen atmosphere until an in-process control sample indicated completion of reaction by HPLC assay. At the end of the reaction period, the mixture was cooled to 0-5 ^{0}C. To the reaction mixture was slowly added sodium borohydride (4.01 kg, 29.8 mol, 5.0 equiv). The reaction mixture was stirred at this temperature for 4-6 h. After completion of the reaction as acetyl intermediate **1** judged by the HPLC assay, then by adding 0.2 - 0.4 equivalent Triethyl silane to convert the hydroxyl impurity 6, stir the reaction mass for 4-5 h. After completion of reaction   the reaction mixture was quenched in water slowly (30 - 40 Lit) over 3 h. The HCl gas that evolved during this quench was scrubbed by a caustic scrubber. The reaction mixture was distilled at atmospheric pressure until the temperature reached 50 ^{0}C to remove most of the methylene chloride. The reaction mixture was cooled to 25 ^{0}C. Tetrahydrofuran (65.7 Lit) was charged, and the reaction mixture was agitated and heated to dissolve all solids. The reaction mixture was allowed to settle. The lower aqueous phase was separated and discarded. The organic layer was concentrated to a volume of 10 - 15 Lit by distillation under reduced pressure. The resulting product slurry was cooled to 25 ^{0}C, and isopropanol (5 Lit) was added to the slurry. The reactor contents were cooled to 0-5 ^{0}C and stirred for 2 h. The product slurry was filtered through a large (I.D. 457 mm) Buchner filter funnel. The product was washed with isopropanol (1 Lit). The isolated material was dried in a tray drier at 40-50 ^{0}C for 12 h to yield 2.98 kg (70% yield) of the desired product **2**.
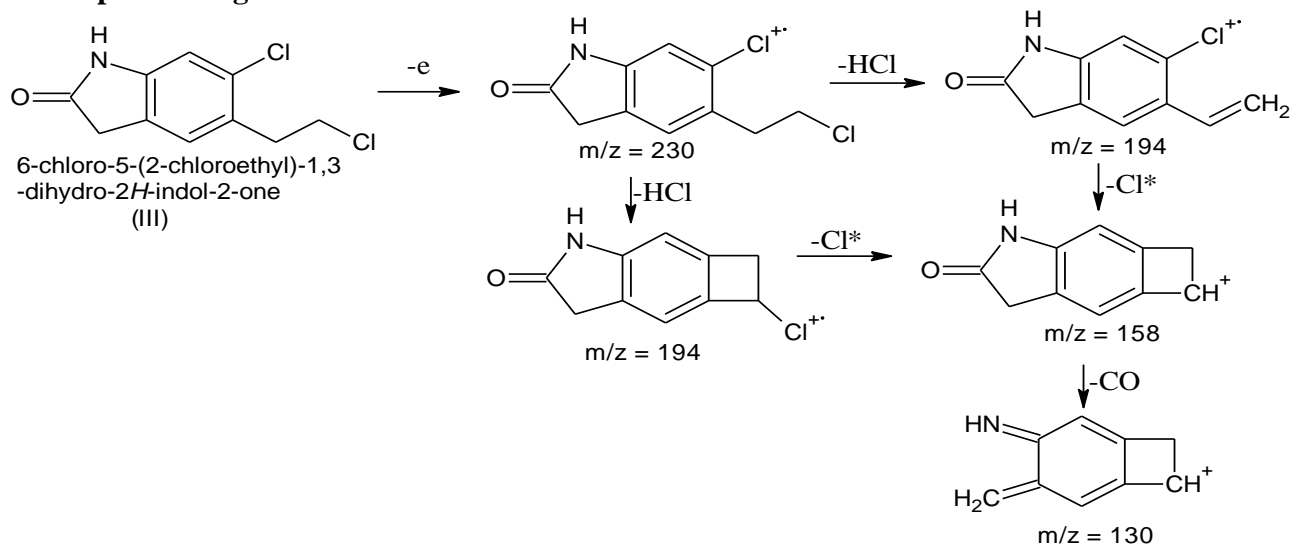**UV-spectra** (λ in nm): 253.5 nm
FT-IR spectra (in cm^{-1}): 3149 (m, NH stretching), 3100 – 3000 (s, CH stretching), 2920 – 2800 (m, CH$_2$ stretching), 1700 (s, -NH-C=O), 1627 (s, Ar-CH stretching), 1480 (s, Aromatic Ring C=C stretching), 788 – 850 (m, Ar-C-Cl).
1H NMR (D6-DMSO) (chemical shift, δ in ppm): 10.455 (s, 1H, NH); 7.247 (s, 1H, Ar-H); 6.814 (s, 1H, Ar-H); 3.97 – 3.74 (t, 2H, CH$_2$); 3.457 (s, 2H, CH$_2$); 3.095 – 3.050 (t, 2H, CH$_2$).
CMR spectra (chemical shift, δ in ppm): 176, 144, 131, 128, 127, 125, 109, 43, 39, 35.
Mass spectra: 230.05 (M$^+$), 194, 158, 130.

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Mass spectra fragmentation:

6-chloro-5-(2-chloroethyl)-1,3
-dihydro-2*H*-indol-2-one
(III)

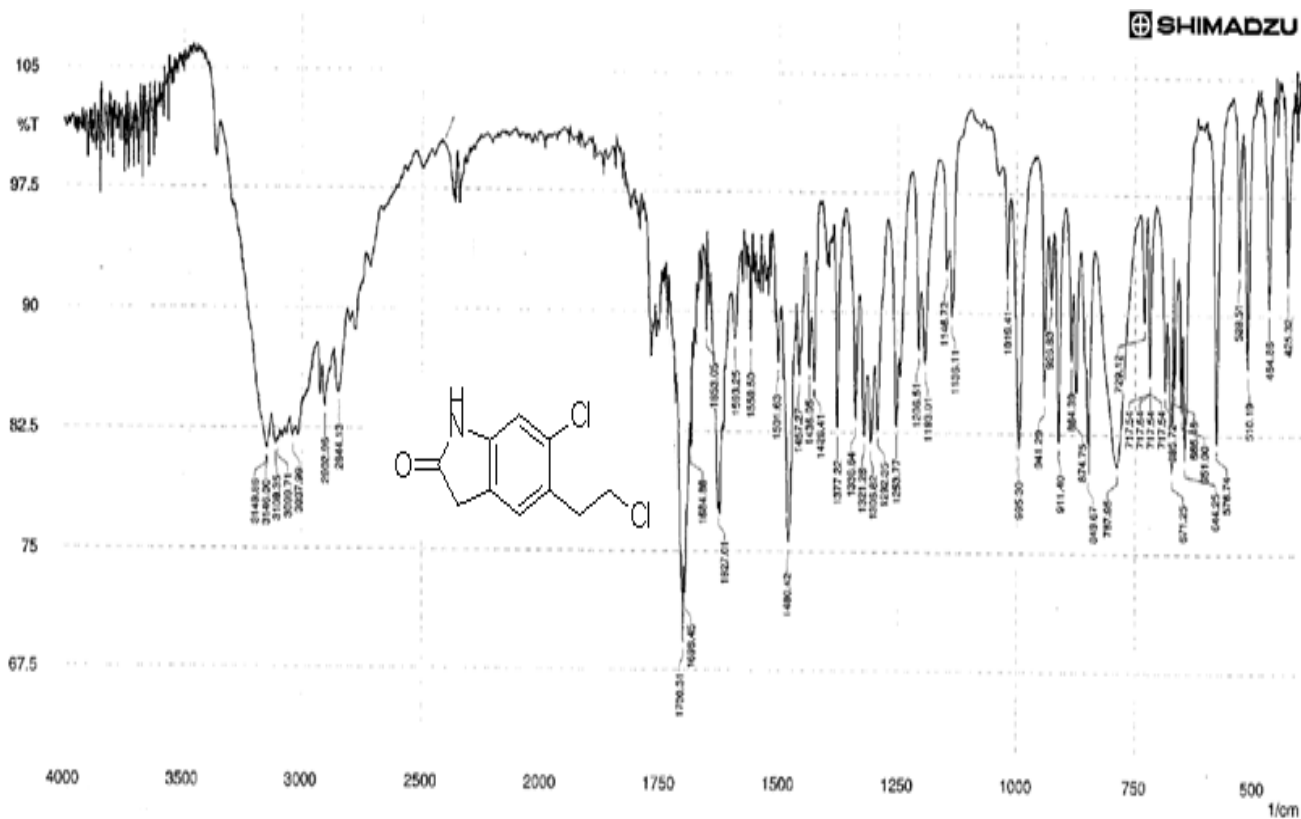m/z = 230

m/z = 194

m/z = 194

m/z = 158

m/z = 130

Fig 1: FT-IR spectra of 6-chloro-5-(2-chloroethyl) oxindole

Fig 2: NMR spectra of 6-chloro-5-(2-chloroethyl) oxindole

D2O exchange NMR

NH-CO
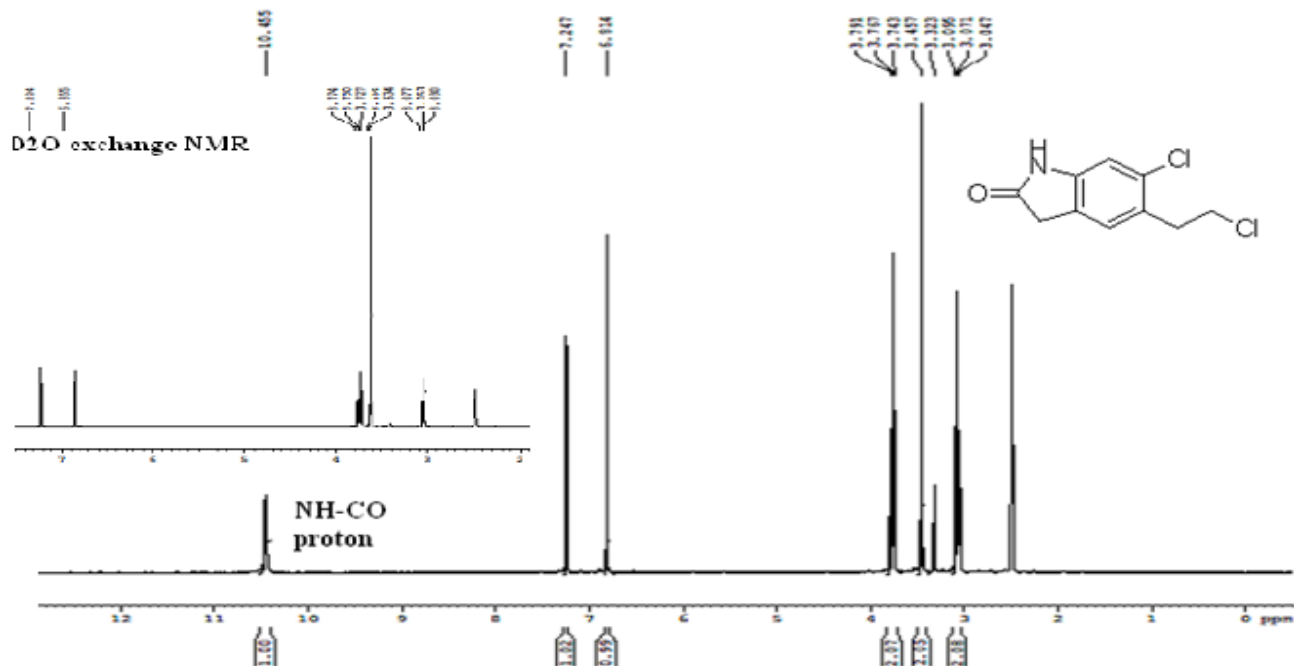proton

Fig 3: CMR spectra of 6-chloro-5-(2-chloroethyl) oxindole

CO-N carbon

Aromatic C
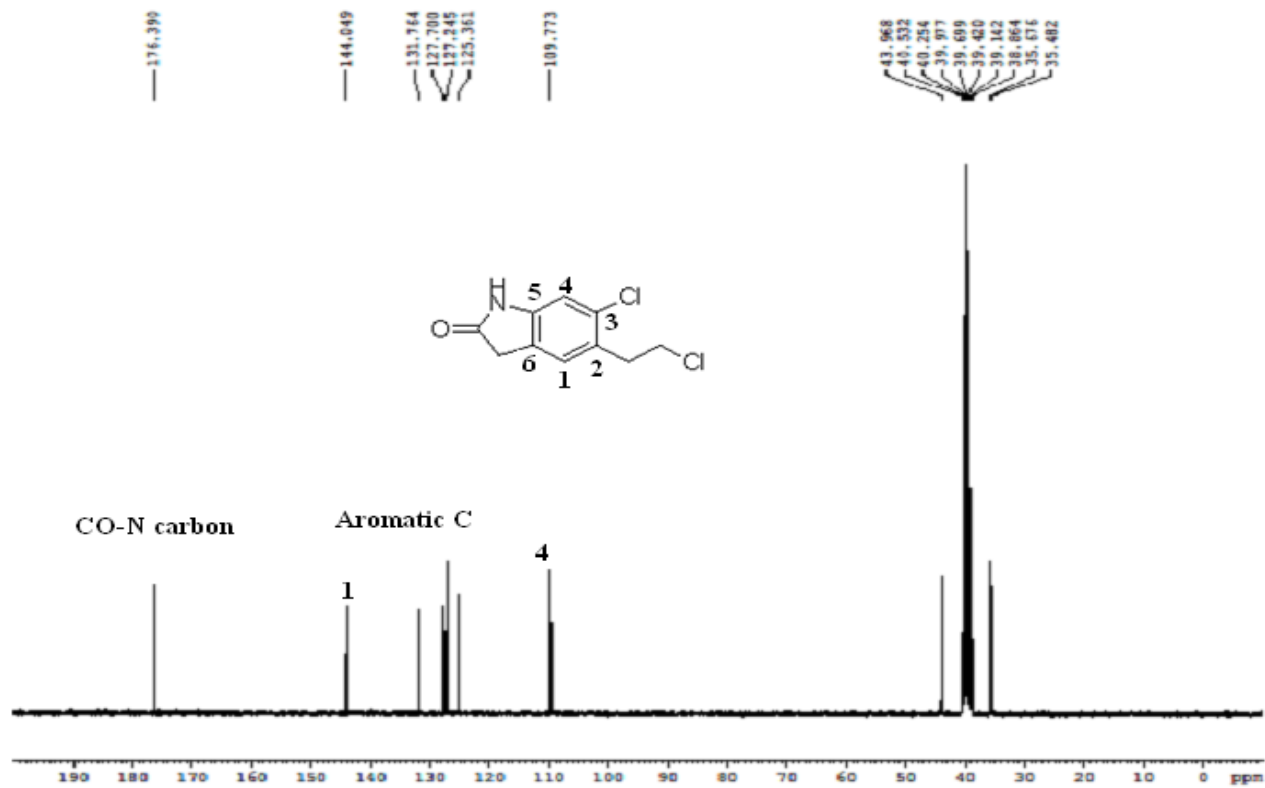
Fig 4: Mass spectra of 6-chloro-5-(2-chloroethyl) oxindole
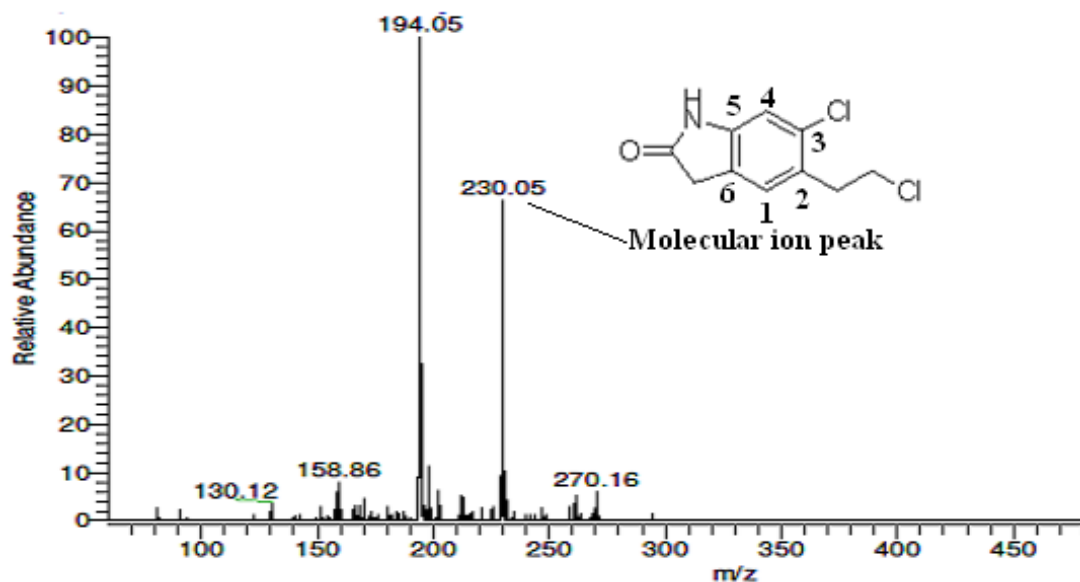
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