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PII: S0223-5234(17)30663-3

DOI: 10.1016/j.ejmech.2017.08.052

Reference: EJMECH 9696

To appear in: *European Journal of Medicinal Chemistry*

Received Date: 31 March 2017

Revised Date: 22 August 2017

Accepted Date: 23 August 2017

Please cite this article as: B. Bano, Arshia, K.M. Khan, Kanwal, B. Fatima, M. Taha, N.H. Ismail, A. Wadood, MehreenGhufran, S. Perveen, Synthesis, *in vitro* β-glucuronidase inhibitory potential and molecular docking studies of quinolines, *European Journal of Medicinal Chemistry* (2017), doi: 10.1016/j.ejmech.2017.08.052.

**Synthesis, *in vitro* β–glucuronidase inhibitory potential and molecular docking studies of quinolines**

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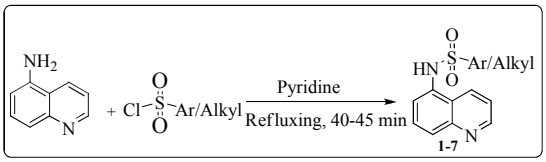
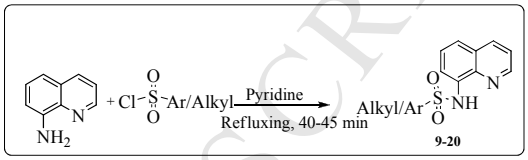
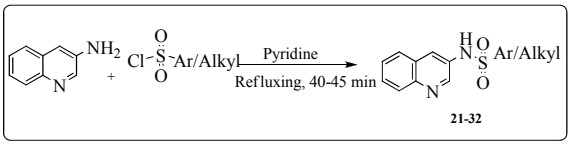
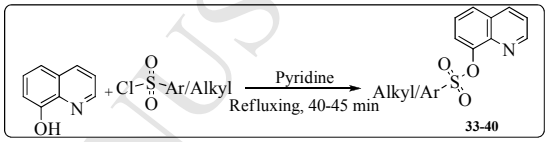
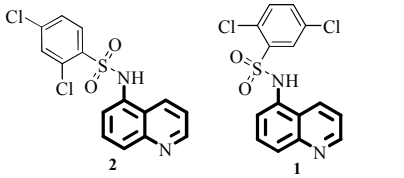
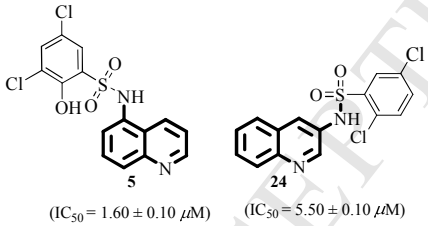


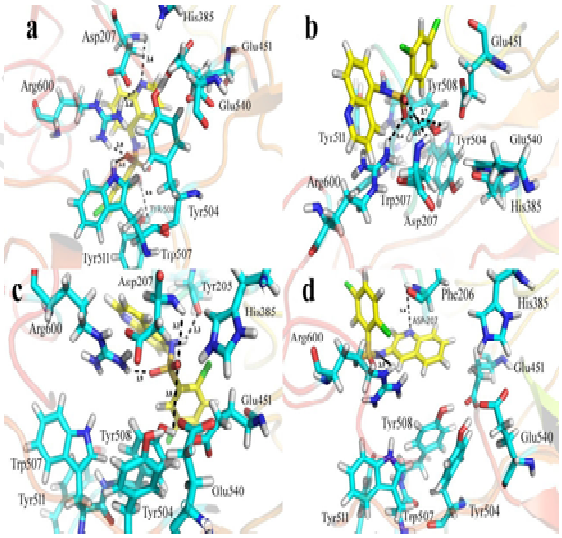




**Synthetic compounds**




**Docking conformation of (a) compound 5, (b) compound 2, (c) compound 1 and (d) compound 24 in the active site of β-glucuronidase.**

# Synthesis, *in vitro* $\beta$-glucuronidase inhibitory potential and molecular docking studies of quinolines

Bilquees Bano,[a] Arshia,[a] Khalid Mohammed Khan,[a*] Kanwal,[a] Bibi Fatima,[a] Muhammad Taha,[b,c] Nor Hadiani Ismail,[b] Abdul Wadood,[d] MehreenGhufran,[d] Shahnaz Perveen[e]

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[c]*Department of Clinical Pharmacy, Institute for Research and Medical Consultations (IRMC), University of Dammam, Dammam 31441, Saudi Arabia*
[d]*Department of Biochemistry, Computational Medicinal Chemistry Laboratory, UCSS, Abdul Wali Khan University, Mardan, Pakistan*
[e]*PCSIR Laboratories Complex, Karachi, Shahrah-e-Dr. Salimuzzaman Siddiqui, Karachi-75280, Pakistan*

**Abstract:** In this study synthesis and $\beta$-glucuronidase inhibitory potential of 3/5/8 sulfonamide and 8-sulfonate derivatives of quinoline (**1-40**) are discussed. Studies reveal that all the synthetic compounds were found to have good inhibitory activity against $\beta$-glucuronidase. Nonetheless, compounds **1**, **2**, **5**, **13**, and **22-24** having $IC_{50}$ values in the range of 1.60 – 8.40 $\mu$M showed superior activity than the standard saccharic acid 1,4-lactone ($IC_{50}$ = 48.4 ± 1.25 $\mu$M). Moreover, molecular docking studies of selected compounds were also performed to see interactions between active compounds and binding sites. Structures of all the synthetic compounds were confirmed through $^1$H-NMR, EI-MS and HREI-MS spectroscopic techniques.

**Keywords:** $\beta$-Glucuronidase; quinoline; sulfonamide; sulfonate; molecular docking studies.

## 1. Introduction:

Quinoline is a aza heterocyclic compound and consists of a structurally fused benzene and pyridine nucleus [1]. It is found in many natural products and there are many methods reported for its synthesis [2]. Many drugs are based on a quinoline scaffold such as captothecine anticancer [3] and cryptolepine antimalarial [4] drugs. Moreover, this skeleton also showed a broad spectrum of biological activities including antidiabetic [5], antiasthmatic [6], antitoxoplasma [7], antibacterial [8], anti-HIV [9] and antifungal [10] activities. The quonoline

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nitrogen atom can act as a chelating agent as well as a weak base [11]. The quinoline moiety can undergo both nucleophilic and electrophilic substitution reactions.

*β*-Glucuronidase (EC 3.2.1.31) found in unicellular microorganisms including *Escherichia coli* and *Pepto streptococcus* genera to multicellular organisms including plants and humans [12,15]. Moreover, this enzyme is found in many parts of human body including kidney, lung, liver serum, spleen, and urine blood cells [16]. *β*-Glucuronidase is a glycosidase that catalyses the hydrolysis of *β*-linked glucuronides to yield derivatives and free glucuronic acid. It is involved in degradation of glucuronic acid containing glycosaminoglycans such as heparin, haparan, dermatan, and chondroitin sulfates [17]. *β*-Glucuronidase has enhanced activity in a variety of pathological conditions such as urinary tract infection [18-21], epilepsy [22], neoplasm of bladder [23], renal diseases [24], breast, larynx testes, and alimentary tract cancer [25]. In addition, *β*-glucuronidase has been reported to be released in the synovial fluid in inflammatory joint diseases, for instance, rheumatoid arthritis [26,27]. The involvement of *β*-glucuronidase in colon cancer and the higher intestinal levels of the enzyme can be correlated to the higher incidence of colon carcinoma [28]. Liver damage results in increased *β*-glucuronidase levels in blood which can cause liver cancer [29,30]. Therefore, *β*-glucuronidase inhibitors can function to minimize this carcinogenic potential [31]. Consequently, inhibition of *β*-glucuronidase enzyme is effective in preventing various diseases. Our research group is working for many years in this field to discover new lead molecules as *β*-glucuronidase inhibitors [32-34]. Recently, our research group published work on the quinazoline nucleus which has structural similarity to quionline and showed good *β*-glucuronidase inhibition. Therefore, to extend our research, we synthesized several quinoline derivatives and screened them against *β*-glucuronidase enzyme activity and got encouraging results (Figure-1) [35]. To the best of our knowledge compounds **4**, **16**-**20**, **26**, **27** [36-40] **10**, **11**, and **13** [41] are previously known, while the remaining compounds are being reported for the first time.

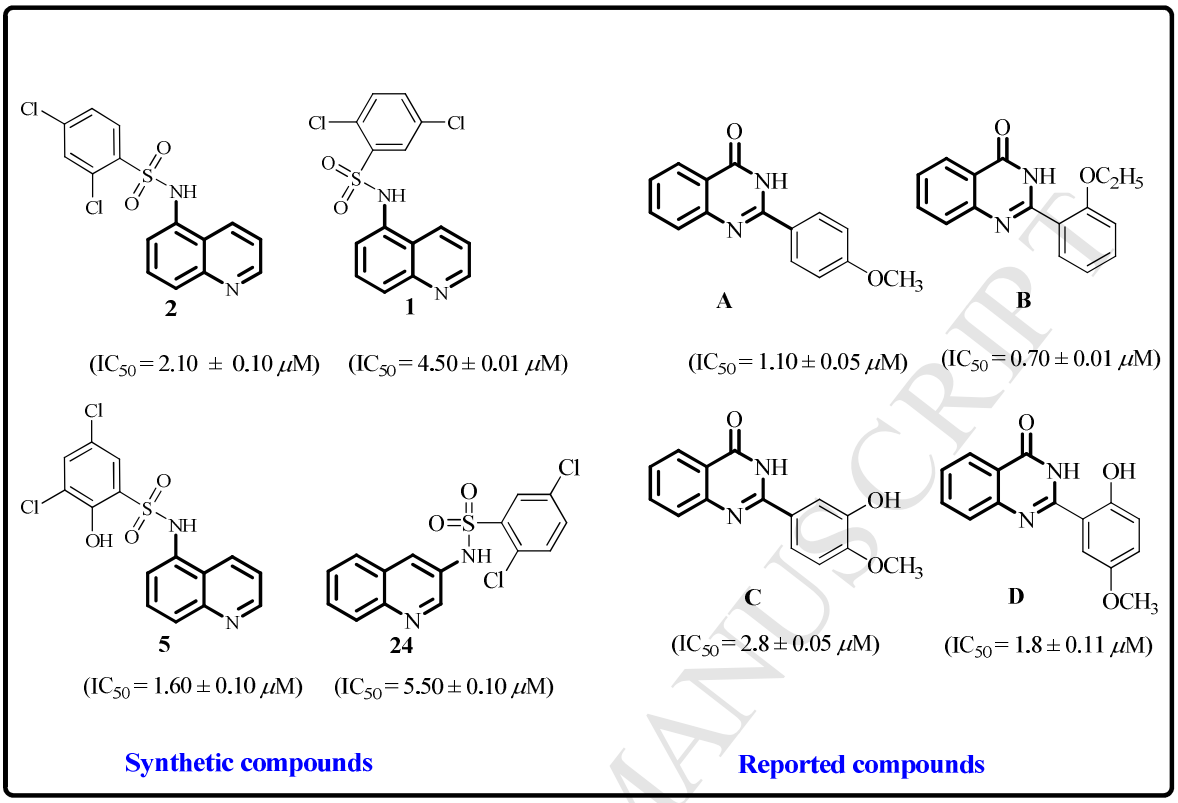
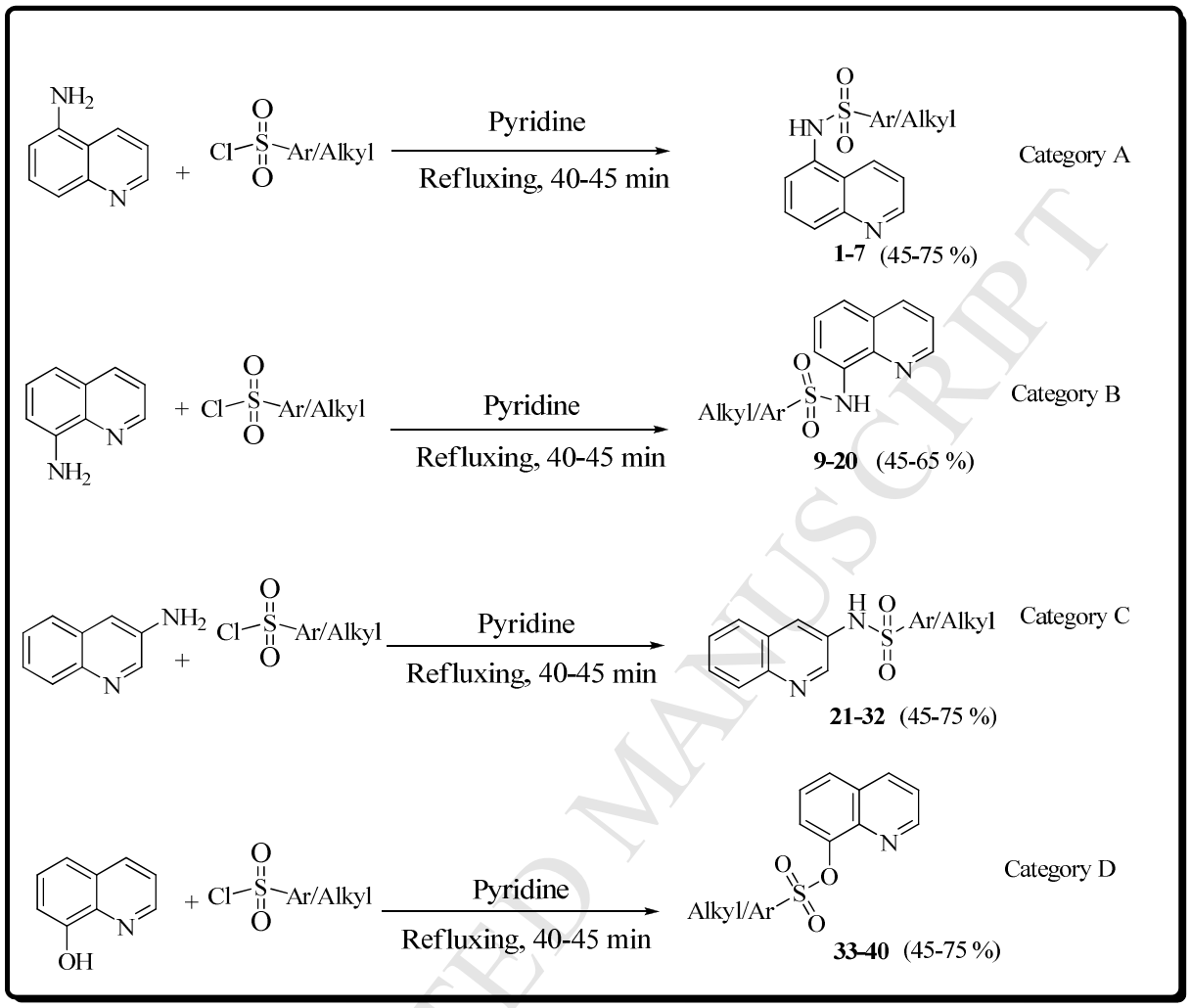



**Figure-1:** Rationale of present study

## 2. Results and discussions:

### 2.1. Chemistry:

Sulfonamides of 5/3/8 aminoquinoline and sulphonyl ester of 8-hydroxyquinoline were synthesized **1-40** in the presence of pyridine. The reaction was performed using 5-amino, 3-amino, 8-amino and 8-hydroxy quinoline and benzene sulphonyl chloride. Pyridine acts as a base where it abstracts the proton from respective quinolines and converts into anions which then attack the benzene sulphonyl chloride by replacing the chloride ion to afford the desired product.




**Schemes-1: Synthesis of quinoline derivatives**

## 2.2. Spectroscopic studies of new and most active compound 3,5-dichloro-2-hydroxy-*N*-(quinolin-5-yl)benzene sulfonamide (5):

Structure of 3,5-dichloro-2-hydroxy-*N*-(quinolin-5-yl) benzene sulfonamide (**5**) was elucidated by $^{1}$H- and $^{13}$C-NMR in deuterated methanol and DMSO and recorded on Bruker AM 400 MHz and 300 MHz instruments, respectively. In $^{1}$H-NMR spectrum the most downfield signal appeared at $\delta_H$ 8.83 for H-2 due to the presence of electronegative nitrogen adjacent to C-2. H-6 also appeared in downfield region at $\delta_H$ 8.71 ($J_{(6,7)}$ = 8.8 Hz) as doublet, due to attachment of a sulfonamide nitrogen at the adjacent carbon-5. H-3 resonated as triplet at $\delta_H$ 7.68 ($J_{3(4,2)}$= 8.0 Hz). However, two singlets resonate at $\delta_H$ 7.41 and 7.43 for H-4′ and H-6′, respectively.

However, others aromatic protons resonate at their resonace frequency along with their respective *J* values (Figure-2).

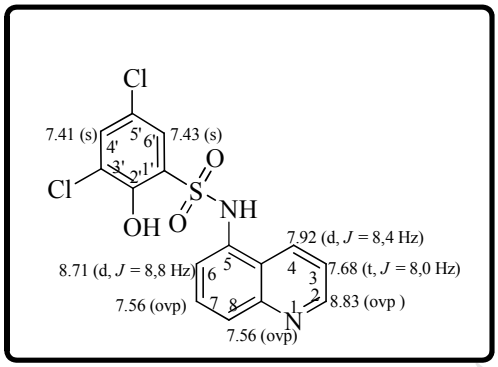



**Figure-2:** $^{1}$H-NMR Chemical shift values for compound **5**

In broad band decoupled $^{13}$C-NMR spectra, total 15 signals resonated, out of which 8 signals were for methines, and 7 signals for quarternary carbons. The most deshielded signal resonated at $\delta_C$ 151.6 and was due to phenolic carbon-2′. Signal at $\delta_C$ 149.3 which in turn was due to aromatic carbon-2 directly attached to a cyclic nitrogen C-4′. Adjacent to sulfonamide two carbon C-1′ and C-5 resonated at $\delta_C$ 132.9, and 139.8, respectively. Rest of carbons in the compound resonated in the normal aromatic range (Figure-3).

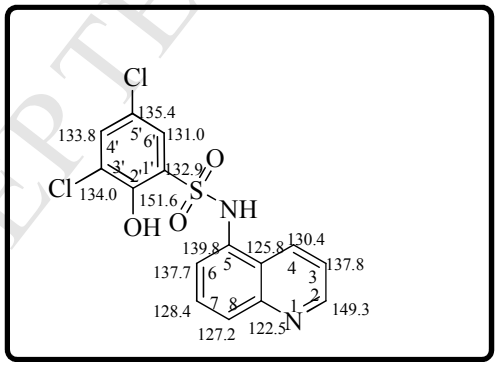



**Figure-3:** $^{13}$C-NMR Chemical shift values for compound **5**

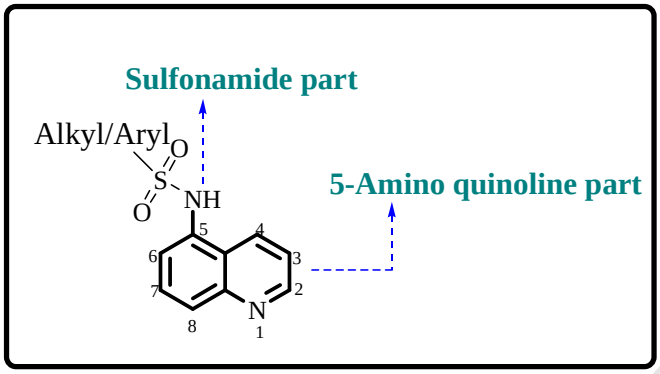
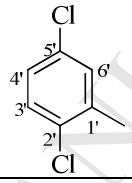
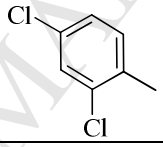
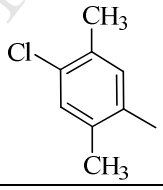
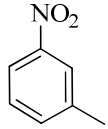
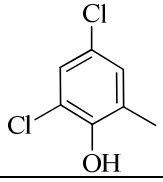
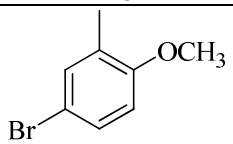
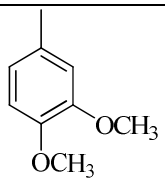



**Figure-4: General structure of 5-amino quinoline sulfonamide**

**Table-1:** *β*-Glucuronidsase inhibitory activity of 5-amino quinoline derivatives **1-8**

| Compound No. | Category | Ar/Alkyl | $IC_{50}$ ± SEM[a] [$\mu$M] |
|---|---|---|---|
| **1** | A |  | 4.50 ± 0.01 |
| **2** | A |  | 2.10 ± 0.10 |
| **3** | A |  | 23.50 ± 0.20 |
| **4** | A |  | 12.20 ± 0.20 |
| **5** | A |  | 1.60 ± 0.10 |
| **6** | A |  | 50.20 ± 1.30 |
| **7** | A |  | 43.20 ± 0.85 |

| | | | |
|---|---|---|---|
| **8** | A | *n*-Propyl | 75.10 ± 1.60 |

[a]SEM is the standard error of mean

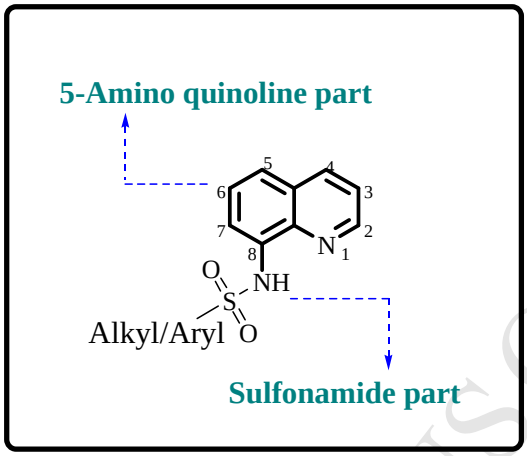
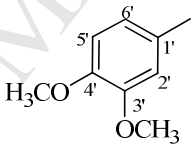
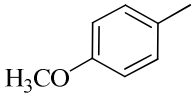
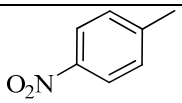
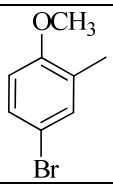
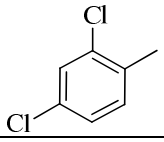
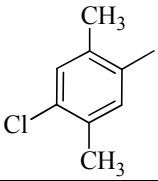
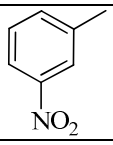
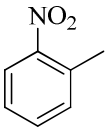
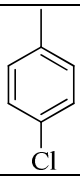
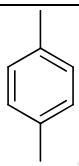
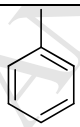



**Figure-5: General structure of 5-amino quinoline sulfonamide**

**Table-2:** *β*-Glucuronidase inhibitory activity of 8-amino quinoline derivatives **9-20**

| Compound No. | Category | Ar/Alkyl | $IC_{50}$ ± SEM[a] [$\mu$M] |
|---|---|---|---|
| **9** | B |  | 42.60 ± 0.85 |
| **10** | B |  | 49.20 ± 1.10 |
| **11** | B |  | 31.30 ± 0.40 |
| **12** | B |  | 68.50 ± 1.25 |
| **13** | B |  | 6.10 ± 0.10 |
| **14** | B |  | 24.50 ± 0.25 |

| | | | |
|---|---|---|---|
| **15** | B |  | 16.10 ± 0.30 |
| **16** | B |  | 18.20 ± 0.20 |
| **17** | B | –Methyl | 48.60 ± 1.10 |
| **18** | B |  | 33.40 ± 0.60 |
| **19** | B |  | 70.50 ± 1.40 |
| **20** | B |  | 66.40 ± 1.40 |

[a]SEM is the standard error of mean

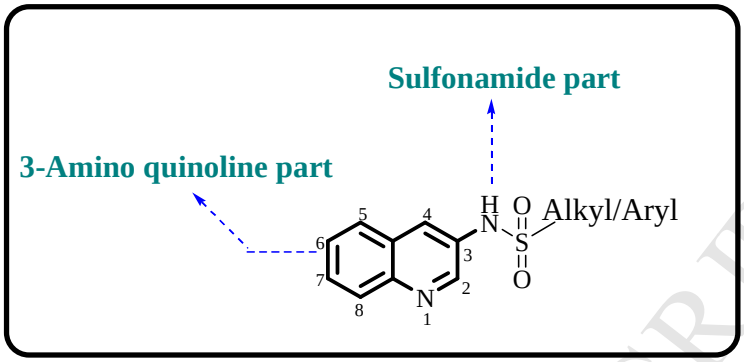
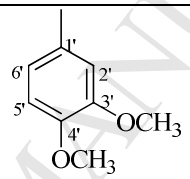
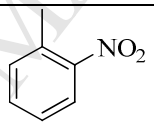
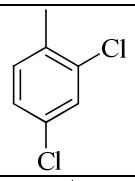
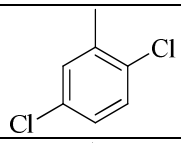
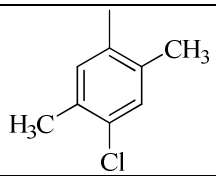
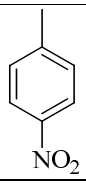
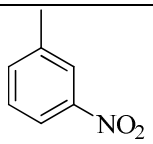
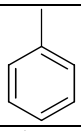
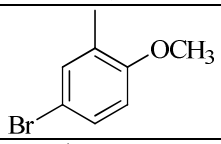
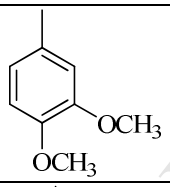
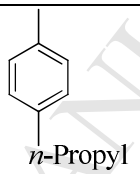



**Figure-6:General structure of 3-amino quinoline sulfonamide**

**Table-3:** *β*-Glucuronidase inhibitory activity of 3-amino quinoline derivatives **21-32**

| Compound No | Category | Ar/Alkyl | $IC_{50}$ ± SEM[a] [$\mu$M] |
|---|---|---|---|
| **21** | C |  | 33.50 ± 0.60 |
| **22** | C |  | 8.10 ± 0.20 |
| **23** | C |  | 8.40 ± 0.1 |
| **24** | C |  | 5.50 ± 0.10 |
| **25** | C |  | 34.40 ± 0.60 |
| **26** | C |  | 31.60 ± 0.45 |

| | | | |
|---|---|---|---|
| **27** | C |  | 46.20 ± 0.90 |
| **28** | C |  | 53.40 ± 1.20 |
| **29** | C |  | 66.50 ± 1.40 |
| **30** | C |  | 53.60 ± 1.30 |
| **31** | C |  | 27.20 ± 0.35 |
| **32** | C | –*n*-Octyl | 75.10 ± 1.60 |

[a]SEM is the standard error of mean

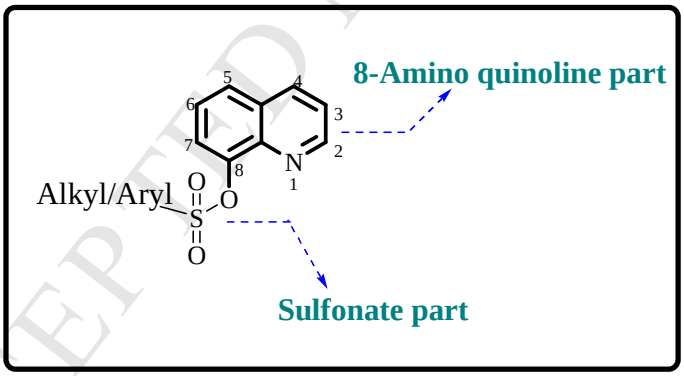
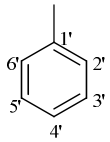
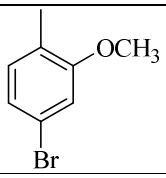
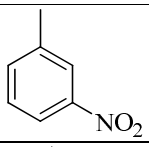
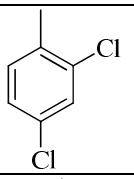
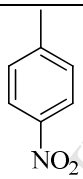
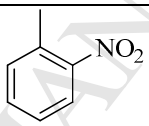
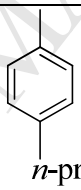
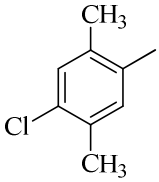



**Figure-7: General structure of 8-amino quinoline sulfonate**

**Table-4:** *β*-Glucuronidase inhibitory activity of 8-sulfonatequinoline derivatives **21-32**

| Compound No. | Category | Ar/Alkyl | $IC_{50}$ ± SEM[a] [$\mu$M] |
|---|---|---|---|
| **33** | D |  | 49.50 ± 1.20 |

| | | | |
|---|---|---|---|
| **34** | D |  | 49.50 ± 1.20 |
| **35** | D |  | 30.10 ± 0.50 |
| **36** | D |  | 9.70 ± 0.10 |
| **37** | D |  | 15.40 ± 0.30 |
| **38** | D |  | 6.40 ± 0.10 |
| **39** | D |  | 84.40 ± 1.50 |
| **40** | D |  | 41.60 ± 0.85 |
| | **Standard** | Saccharic acid 1,4-lactone | 48.4 ± 1.25 |

[a]SEM is the standard error of mean

## 2.2 Enzyme inhibitory study

Structure-activity relationship (SAR) studies suggested that the *β*-glucuronidase inhibitory activities of these class of compounds depend mainly on the substitutions on the phenyl ring and different quinoline substituents. In order to understand SAR, all synthetic compounds were divided into four categories *i.e.* A, B, C, and D. Categories A, B, and C correspond to compounds in which the quinoline ring is substituted with an amino moiety at position 5, 8, and 3, respectively, while in category D, the quinoline ring is substituted with a hydroxyl moiety at

position 8. Several synthetic analogs showed better activity than the standard saccharic acid 1,4-lactone.($IC_{50}$ = 48.4 ± 1.25 $\mu$M).

**Category A:**

It is worth noting that in category A, seven compounds **1**-**7** are more active than the standard saccharic acid 1,4-lactone ($IC_{50}$ = 48.4 ± 1.25 $\mu$M). 2-Hydroxy-3,5-dichloro substituted compound **5** ($IC_{50}$ = 1.60 ± 0.10) was found to be thirty-fold more active than the standard in category A. Comparison of **5** with compound **2** ($IC_{50}$ = 2.10 ± 0.10 $\mu$M) suggested that the hydroxyl substitution in compound **5** plays an important role in $\beta$-glucuronidase inhibition and absence of hydroxyl group in compound **2** showed decreased activity as compared to **5** but was still twenty-four time more active than the standard. Similarly, when the chloro group was shifted from position *ortho*, and *para* to *ortho* and *meta* as in compound **1** ($IC_{50}$ = 4.50 ± 0.01 $\mu$M), decreased activity was observed as compared to compound **2**. Replacement of hydroxyl and chloro group with methyl as in compound **3** ($IC_{50}$ = 23.50 ± 0.20 $\mu$M), also decreases its activity. Replacement of chloro group with a nitro group as in compound **4** ($IC_{50}$ = 12.20 ± 0.20 $\mu$M) results in increased activity. Compounds **7**, **8** showed $IC_{50}$ values of 43.20 ± 0.85 and 75.1 ± 1.60 $\mu$M, respectively (Figure-8) (Table-1).

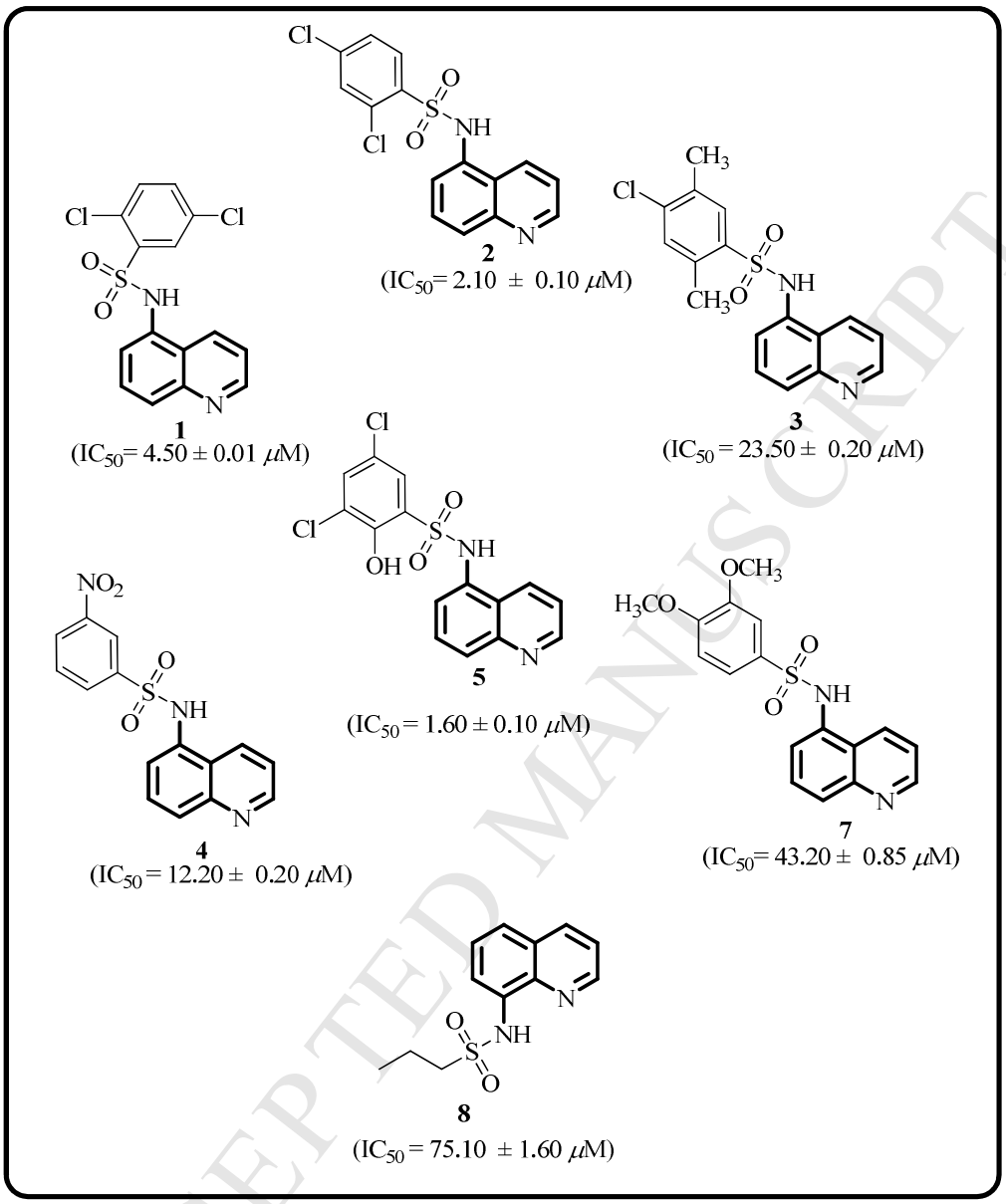



**Figure-8:** SAR studies of category A

**Category B:**

This category consists of eleven compounds of 8-substituted sulfonamide analogs of quinoline. Compound **13** ($IC_{50}$ = 6.10 ± 0.10 $\mu$M) was found to be the most active compound in this category having an eight-fold better inhibitory activity than the standard saccharic acid 1,4-lactone ($IC_{50}$ = 48.4 ± 1.25$\mu$M). If we compare it's activity with the closely related compound **5**

($IC_{50}$ = 1.60 ± 0.10 $\mu$M), it was observed that the 5-amino substitution is more effective for its activity than its 8-amino counterpart.

The single *meta*-nitro group containing compound **15** ($IC_{50}$ = 16.10 ± 0.30 $\mu$M) showed a decreased activity as compared to compound **5** which is the most active analog of the seires. When the nitro group was shifted from *meta* to *ortho*, a comparable activity was observed as in **16** ($IC_{50}$ = 18.20 ± 0.20 $\mu$M). Surprisingly, when it was switched to *para* then compound **11** ($IC_{50}$ = 31.30 ± 0.40 $\mu$M) lost half of its activity as compared to compounds **15** and **16**. Nevertheless, still these compounds were about three-fold more active than the standard saccharic acid 1,4-lactone.($IC_{50}$ = 48.4 ± 1.25 $\mu$M). The non-substituted benzene containing compound **20** ($IC_{50}$ = 66.40 ±1.40 $\mu$M) and methoxy and bromo substituted **12** ($IC_{50}$ = 68.50 ± 1.25 $\mu$M) were found to be weakly active. Whilst, mono-chloro substituted compound **18** ($IC_{50}$ = 33.40 ± 0.60 $\mu$M) and chloro and methyl substituted compound **14** ($IC_{50}$ = 24.50 ± 0.25 $\mu$M) showed good inhibitory potential. Mono-methoxy and dimethoxy compounds **10** ($IC_{50}$ = 49.20 ± 1.10 $\mu$M) and **9** ($IC_{50}$ = 42.60 ± 0.85 $\mu$M) displayed weak activity, respectively.When aryl was replaced by alkyl groups as in compound **17** (48.60 ± 1.10 $\mu$M) and **19** (70.50 ± 1.40 $\mu$M), a decreased activity was observed (Figure-9) (Table-2).

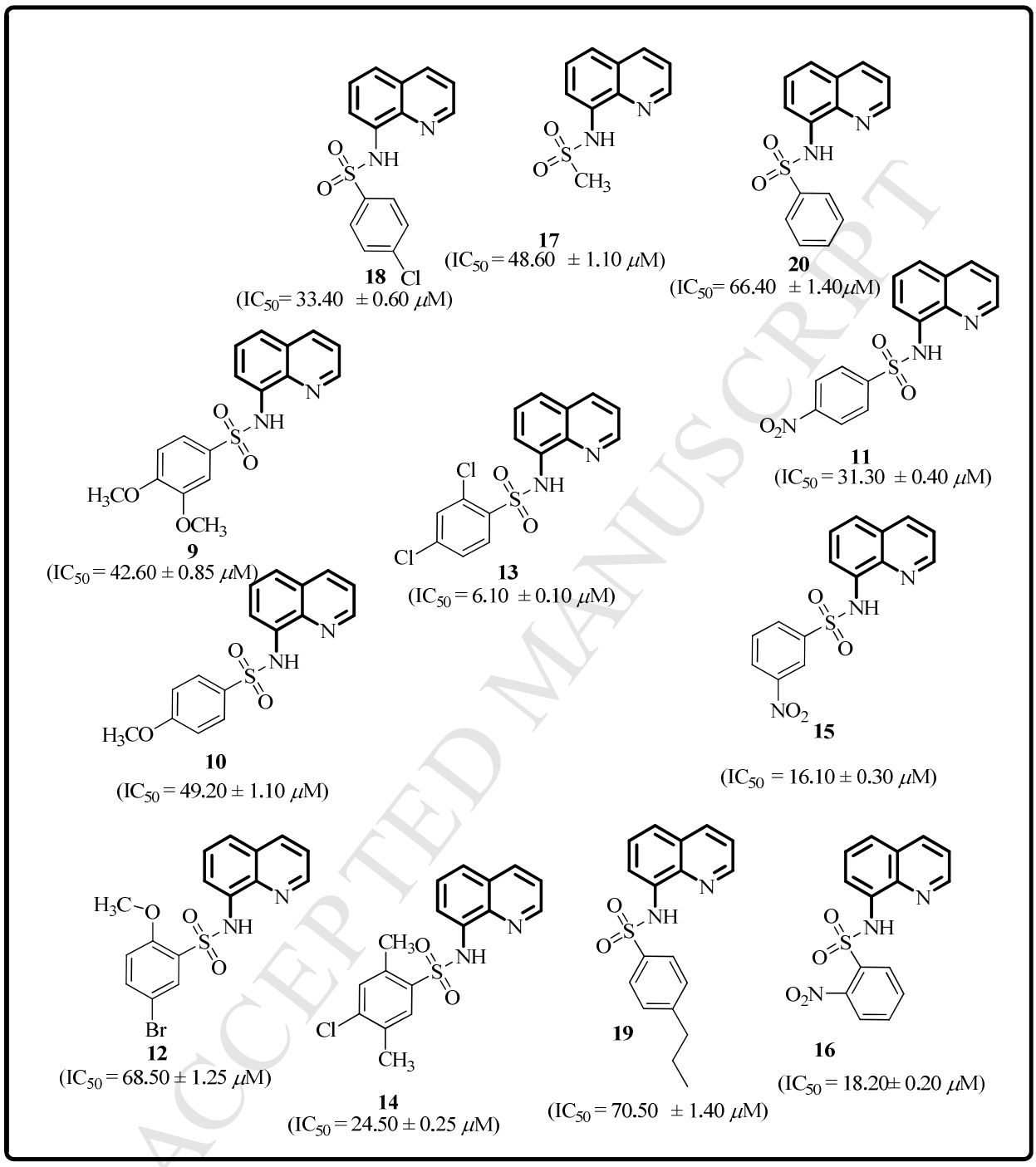



**Figure-9:** SAR studies of category B

**Category C:**

This category consists of twelve compounds of 3-substituted sulfonamide analogs of quinoline. In category C, compound **24** ($IC_{50}$ = 5.5 ± 0.10 $\mu$M) having *ortho* and *meta* dichloro substituents

showed superior activity than the standard saccharic acid 1,4-lactone ($IC_{50}$ = 48.4 ± 1.25 $\mu$M). It also confirmed the pronounced effect of 5-amino over 8- and 3-amino quinoline with reference to $\beta$-glucuronidase inhibitory activity of this series. Compound **23** ($IC_{50}$ = 8.4 ± 0.10 $\mu$M) having *ortho* and *para* dichloro substituent displayed a six-fold more activity than the standard. The compound **25** ($IC_{50}$ = 34.40 ± 0.60 $\mu$M) having *para* chloro along with two methyls at *ortho* and *meta*, displayed a decreased activity as compared to compounds **23** and **24**. Compound **29** ($IC_{50}$ = 66.50 ± 1.40 $\mu$M) having *ortho* methoxy and *meta* bromo substituents demonstrated a weak activity.

In nitro substituted derivatives, *ortho* substituted compound **22** ($IC_{50}$ = 8.10 ± 0.20 $\mu$M), *para* substituted **26** ($IC_{50}$ = 31.60 ± 0.45 $\mu$M), and *meta* substituted **27** ($IC_{50}$ = 46.20 ± 0.90 $\mu$M) showed different activities due to the different positions of the substituents. Alkyl substituted compounds **31** ($IC_{50}$ = 27.20 ± 0.35 $\mu$M) and **32** ($IC_{50}$ = 43.20 ± 0.85 $\mu$M) showed less activity. However, methoxy containing compound **30** ($IC_{50}$ = 53.60 ± 1.30 $\mu$M), showed sharp decrease in activity. Compound **29** having methoxy and bromo substituent at aryl part and non-substituted aryl part containing compound **28** exhibited weak activities with $IC_{50}$ values of 66.50 ± 1.40 and 53.40 ± 1.20 $\mu$M, respectively (Figure-10) (Table-3).

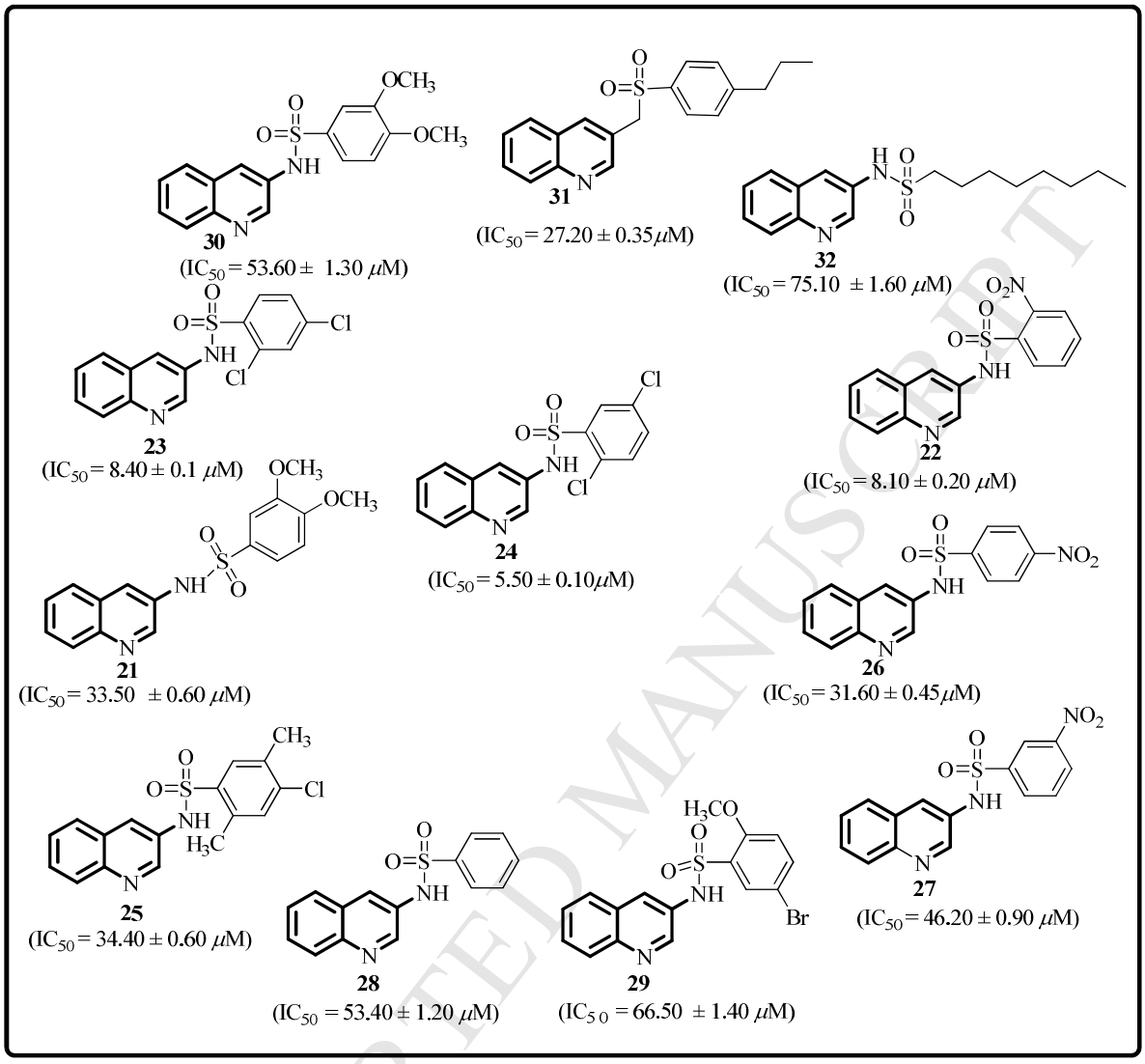



**Figure-10:** SAR studies of category C

**Category D:**

This category has eight compounds of 8-substituted sulfonates of quinoline and compound **38** was found to be the most active with an $IC_{50}$ value of 6.4 ± 0.10 $\mu$M and superior than the standard, whilst, its positional isomers **35** ($IC_{50}$ = 30.10 ± 0.50 $\mu$M) and **37** ($IC_{50}$ = 15.54 ± 0.45 $\mu$M) displayed less activity than **38**. However, dichloro compound **36** ($IC_{50}$ = 9.70 ±0.10 $\mu$M) was found to be more active than the standard. Placement of bromo group at the aryl part, as in **34** ($IC_{50}$= 49.50 ± 1.20 $\mu$M) resulted in decreased activity. Non-substituted and methyl substituted aryl part compounds **40** and **33** exhibited $IC_{50}$values of 41.60 ± 0.85 and 49.50 ± 1.20 $\mu$M, respectively (Figure-11) (Table-4).

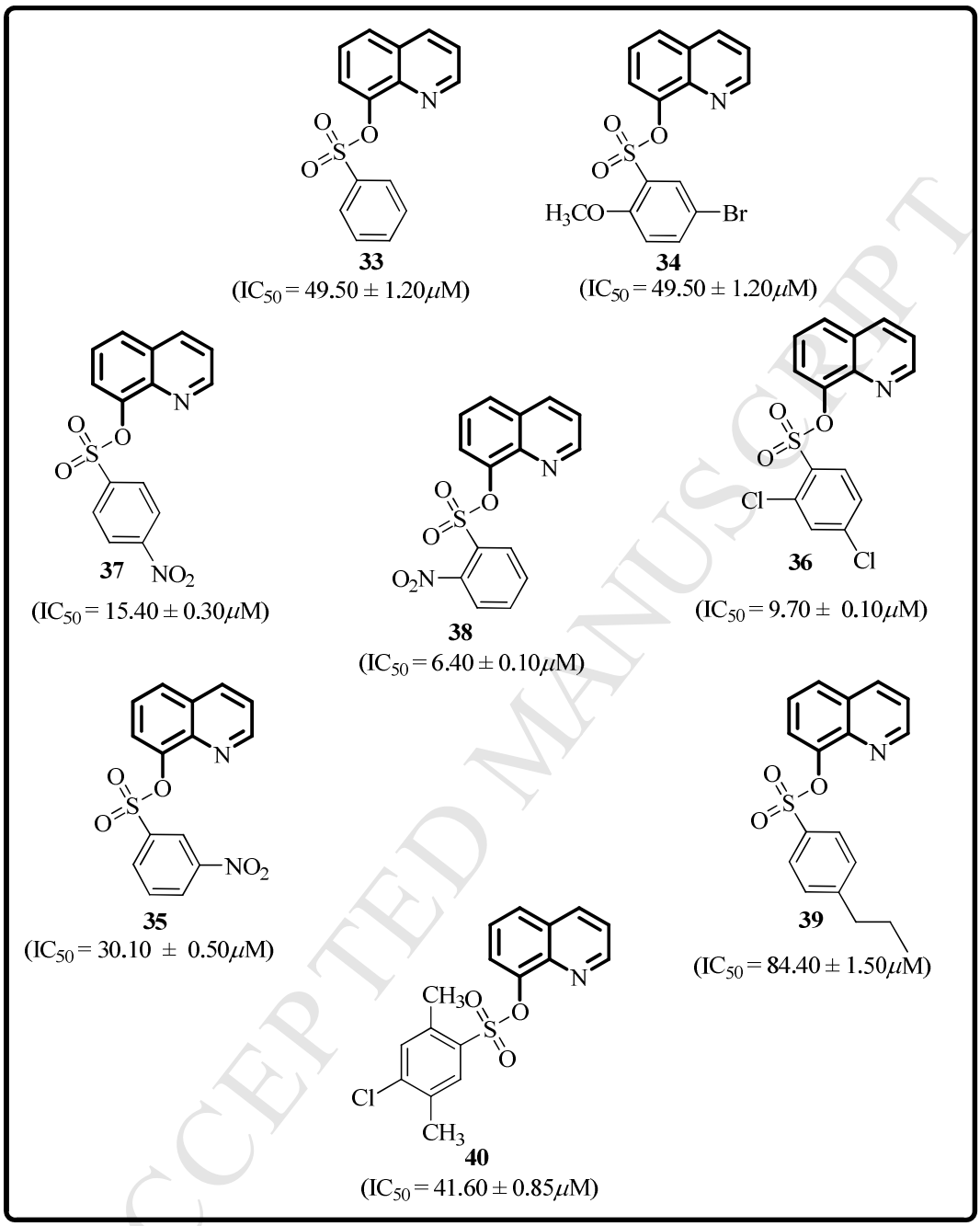



**Figure-11:** SAR studies of category D

## 2.4 Molecular docking studies:

To find the binding interactions of these synthetic compounds in the active site of *β*-D-glucuronidase, molecular docking was performed using MOE-Dock program (www.chemcomp.com). The x-ray crystallographic structure of human *β*-D-glucuronidase having 80% sequence similarity with bovine *β*-D-glucuronidase [42] was retrieved from the

protein data bank (PDB Code 1BHG) [43] as the 3D structure of bovine *β*-D-glucuronidase is not reported yet. The *β*-chain of protein and hetero-atoms including co-factors were removed from the original pdb file. The energy of the protein molecule was minimized after the 3D protonation using the default parameters of MOE (Molecular Operating Environment) software (www.chemcomp.com) energy minimization algorithm (gradient: 0.05, Force Field: Amber99). The three dimensional coordinates of the synthetic compounds were derived by using MOE (www.chemcomp.com). These molecules were than energy minimized using the default parameters of MOE energy minimization algorithm (gradient: 0.05, Force Field: Amber99). All the minimized molecules were saved in the mdb file format as an input file.

Prior to docking of the synthetic compounds, *p*-nitrophenyl *β*-D-glucuronide which is a known substrate molecule [46], was docked first into the active site of the enzyme by utilizing docking program MOE-Dock with default docking parameters. Similar to our previous results [44, 45], the docked conformation of the substrate displayed that the glycoside bond of *p*-nitrophenyl *β*-D-glucuronide was appropriately oriented towards the catalytic residues such as Glu540, Glu451, and Tyr504. Selected compounds were then docked into the binding pocket of *β*-glucuronidase enzyme using the same docking parameters. The catalytic site of *β*-D-glucuronidase [41] (PDB Code 1BHG) [42] is composed of Glu540, Glu451, and Tyr504 residues. The molecular docking studies have also disclosed some other important residues like Asp207, Arg600, Trp507, Tyr508, and Tyr511 in the *β*-D-glucuronidase inhibition in addition to the catalytic site residues of the enzyme. Thus the docking study of the sulfonamide and sulfonate derivatives of quinoline (**1-40**) and the esteemed variations of their binding site residues in addition to the catalytic site of the enzyme may lead to further investigation of these interesting interactions.

**2.5 Molecular docking interactions:**

From the docking studies, it was observed that selected compounds showed significant binding interactions with the catalytic site residues. In the case of the most active compound **5 ($IC_{50}$ = 1.60 ± 0.10, docking score = -15.9876)** form five hydrogen bonds and two arene-cation linkages with the active site residues of the enzyme. Asp207 and Arg600 made hydrogen bonds with the nitrogen atom of the quinoline ring, Trp507 and Arg600 formed hydrogen bond with the oxygen atom of the sulfonamide moiety, whereas the Tyr511 established hydrogen bond with hydroxyl moiety of the compound, respectively (Figure-14a). This compound also formed two arene-

cation interactions with the Tyr504 and Arg600 residues. The higher inhibitory potential of compound **5** might be due to the availability of the electron donating-OH group and the electron withdrawing group (-Cl) which creates an electron flow in the compound, making it more polarizable and a more potent inhibitor compared to the compounds having only electron withdrawing moiety (-Cl) *e.g.*, compound **2**, **13**, **1** *etc*. The docking conformation of the second most active compound **2** (**$IC_{50}$= 2.10 ± 0.10, docking score = -15.8651)** in the series, showed three hydrogen bonds and two arene-arene interactions where the active site residues of the enzyme.Asp207, Tyr508 and Arg600 were found to be involved in hydrogen bonding with the oxygen atoms of the sulfonamide moiety of the compound (Figure-12b). The arene-arene interaction was observed between the central phenyl ring of the compound and the hydrophobic residue Trp507 and Tyr511 of *β*-glucouronidase enzyme (Figure-12b). The slightly lower biological activity and poor binding interactions of compound **2** as compared to compound **5** might be due to the absence of the electron donating moiety. In case of compound **1** the third most active compound (**$IC_{50}$ = 4.50 ± 0.01**) of the series, the docking results showed that this compound formed four hydrogen bonding with the active site residues (Tyr205, Asp207, Tyr508 and Arg600) of the enzyme (Figure-13c). Tyr205 made hydrogen bonds with the nitrogen atom of the methanamine moiety while Asp207, Tyr508, and Arg600 formed hydrogen bonds with the oxygen atoms of the sulfonamide moiety of the compound. If, we compare the structures of compounds **1** and **2**, they have almost similar structures but the only difference is the positions of the -Cl moiety. The different attachment positions of chlorine might play a role in the activities as well as binding interaction of these compounds (Table-5 and Figure-13). The docking conformation of the forth most active compound, compound **24 ($IC_{50}$ = 5.50 ± 0.01)** showed two hydrogen bonds, one arene-cation and onearene-arene linkage with the Phe206, Tyr508, and Arg600 residues of the enzyme (Figure-12d). Phe206 showed hydrogen bond with the nitrogen atom of the quinoline ring and Arg600 established hydrogen bonding with the nitrogen atom of the sulfonamide moiety of the compound. Tyr508 and Arg600 showed arene-arene and arene-cation interactions with this compound, respectively. If, we compare the structures of compound **24** and **1**, both compounds have about similar structures the only difference is the attachment positions of the 2,5-dichloro-benzenesulfonamide substituent to the quinoline ring. This attachment position might play a role in the biological activities as well as binding modes of these compounds (Table-5, and Figure-12).

For the nitro phenyl containing compounds (**22**, **26**, **27**), it was observed that the position of the nitro moiety plays a role in the biological activity as well as binding modes of these compounds. For example, when the nitro group is at *ortho* position of the phenyl ring, then the compound (**22**) showed comparatively good inhibitory activity and interaction as compared to the compounds (**26** and **27**) in which the nitro group present at *meta* and *para* position of phenyl ring of the compounds (Figures 13a and 13b, compounds **25** and **26**). Comparable results were observed for compounds **39** and **38** (Table-5 and Figure-14c and-14d).

The methoxy benzene containing compounds (**9**, **10**, **21**) showed very low biological activities and poor interactions. The poor inhibitory activities and interactions of these compounds might be due to the presence of methoxy groups.

Overall the docking results showed that electron donating moiety is favorable for biological activities as compared to electron withdrawing moiety. Furthermore, the position of attachment at the aryl part as well as the quinoline ring played a role in the activities of these synthetic compounds.

Generally, a good correlation was observed between the docking stabilizing energies and biological activities of the active compounds showing a correlation coefficient of 0.114 as given in (Figure-14).

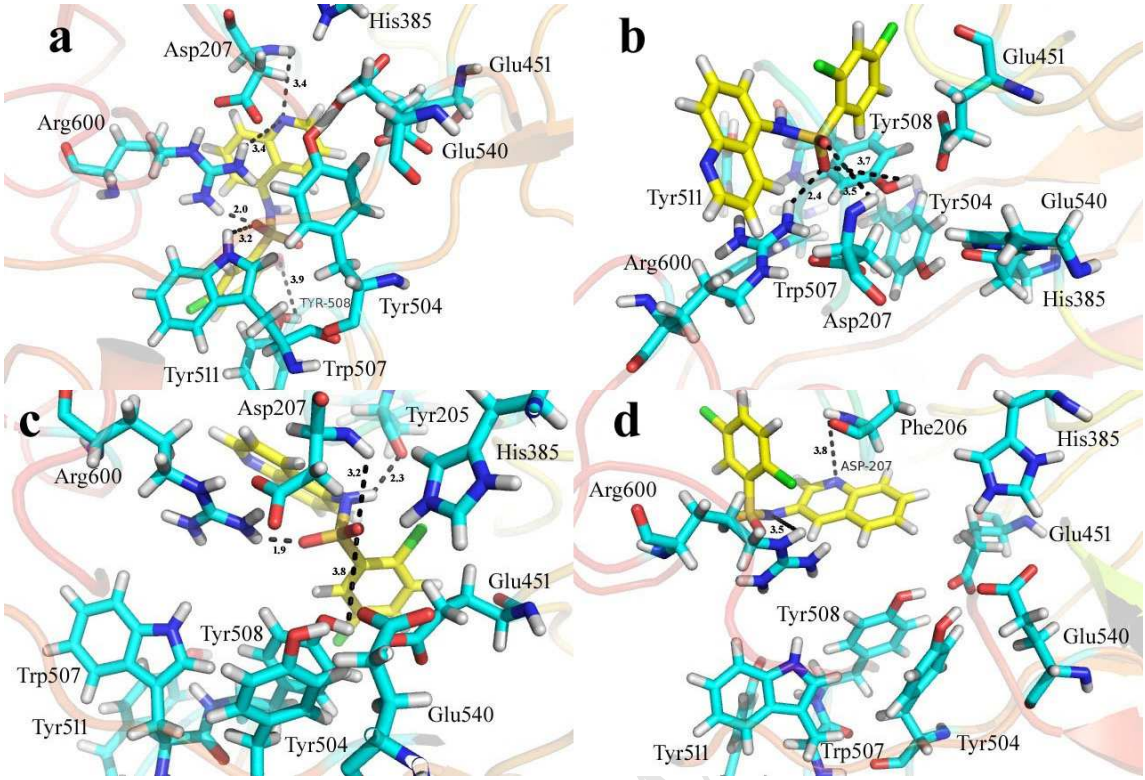



**Figure-12:** Docking conformation of (**a**)compound **5**, (**b**)compound **2**, (**c**) compound **1**and (**d**) compound **24** in the active site of *β*-glucuronidase

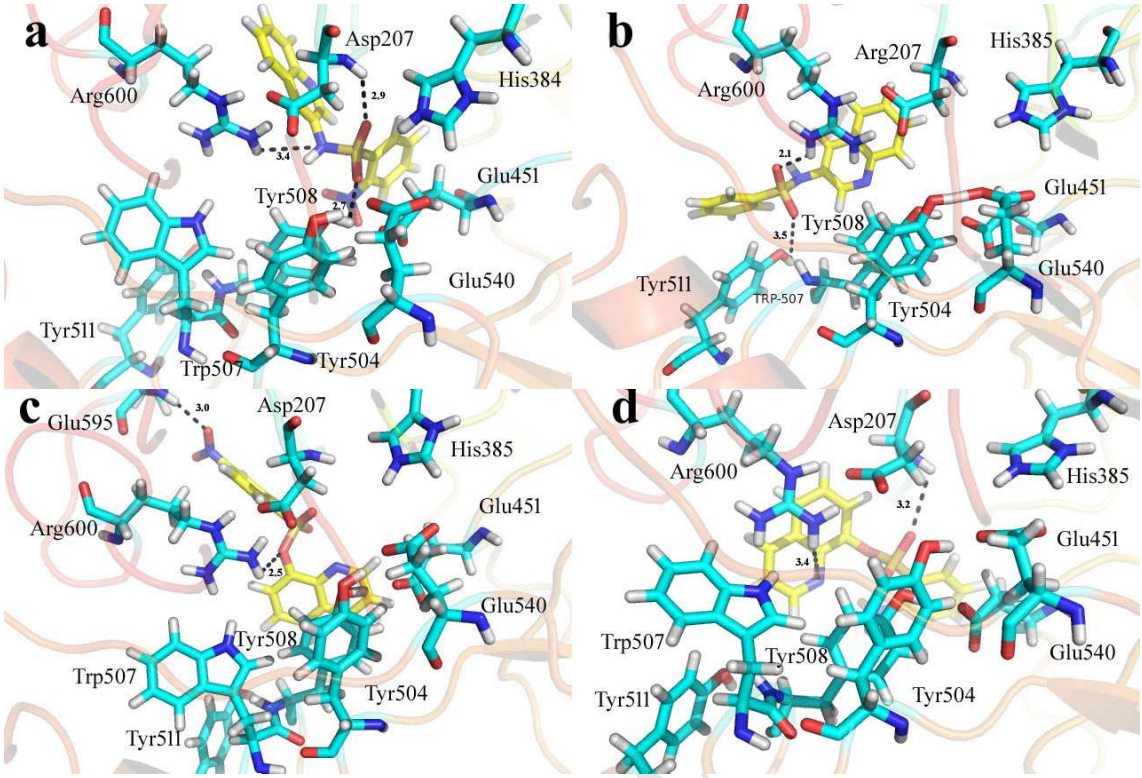



**Figure-13:** Docking conformation of (**a**)compound **22**, (**b**) compound**28**, (**c**) compound **38** and (**d**) compound **39** in the active site of *β*-glucuronidase

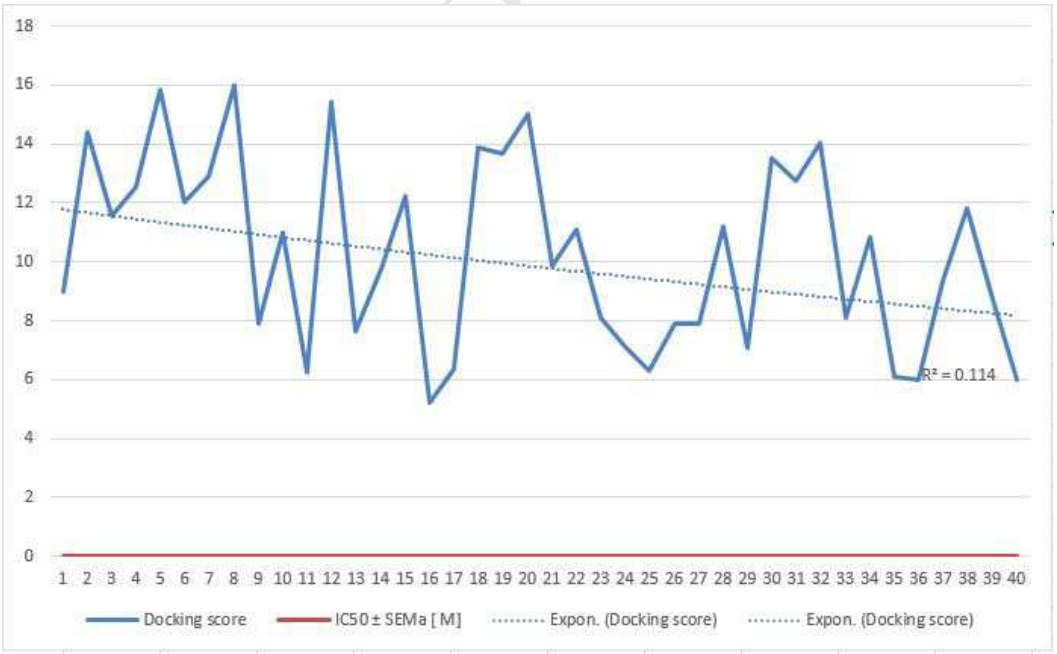



**Figure-14:** A correlation graph for docking predicted activity and $IC_{50}$ values

## 3. Conclusion:

This study deals with synthesis of quinoline analogs and their *β*-glucuronidase inhibitory potential. Amongst synthetic compounds most of the compounds that have electron donating substituents showed more inhibitory activity. However, some nitro substituted compounds also showed good inhibitory activity. These results were further supported by molecular docking studies which show efficient binding interaction between the active compound and *β*-glucuronidase enzyme proteins. Conclusively, some new lead molecules are identified as *β*-glucuronidase inhibitors and further studies on these molecules may direct to better inhibitors.

## 4. Experimental:

### 4.1. Material and methods:

Different sulfonyl chloride, 3-, 5-, 8-amino quinoline, 8-hydroxy quinoline and pyridine were purchased from TCI (Japan) and used as received without purification. UV light of wavelengths of 254 and 365 nm was used for visualization of chromatograms.

$^{1}$H- and $^{13}$C-NMR spectra were recorded on Bruker NMR 300, 400 and 500 MHz machines (Wissembourg, France). EI-MS, HREI-MS and FAB-MS spectroscopic analysis have been obtained on a Finnigan-MAT-311-A instrument (Bremen, Germany). Thin layer chromatography (TLC) was performed using pre-coated silica gel plates (Merck, Kieselgel 60 F-254, 0.20 mm).

### 4.2. *β*-Glucuronidase inhibition study:

*β*-Glucuronidase (E.C. 3.2.1.31, from bovine liver, G-0251) was purchased from Sigma Chemical Co. (USA). *β*-Glucuronidase activity was determined by measuring the absorbance at 405 nm of *p*-nitrophenol formed from the substrate by the spectrophotometric method. The total reaction volume was 250 $\mu$L. DMSO (100%) was used to dissolve the compound (5 $\mu$L) which become 2% in the final assay (250 $\mu$L) and the same conditions were used for standard (D-saccharic acid 1,4-lactone). The reaction mixture contained 185 $\mu$L of 0.1 M acetate buffer, 5 $\mu$L of test compound solution, 10 $\mu$L of enzyme solution was incubated at 37 $^{\circ}$C for 30 min. The plates were read on a multi-plate reader (SpectraMax plus 384) at 405 nm after the addition of 50 $\mu$L *p*-nitrophenyl-*β*-D-glucuronide. All assays were run in triplicate [47].

### 4.3 General procedure for synthesis of compounds 1-40

Quinoline analogs were synthesized by refluxing 1 mmol of sulfonyl chloride with 1 mmol of different quinoline in 10 mL of pyridine for 6 hours. Succession of reaction was studied by thin layer chromatography (TLC) analysis. On completion of reactions, the mixture was poured into cool water which resulted in precipitation. The precipitates were filtered, washed with hexane and dried to afford target compounds.

**2,5-Dichloro-*N*-(quinolin-5-yl)benzenesulfonamide (1)**

Yield: 55%; m.p. 176-180 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.84 (d, $J_{2,4}$ = 2.8 Hz, 1H, H-2), 8.26 (d, $J_{7,6}$ = 8.0Hz, 1H, H-7), 8.14 (d, $J_{4,2}$ = 2.4 Hz, 1H, H-4), 7.72 (d, $J_{3',4'}$ = 7.2 Hz, 1H, H-3'), 7.59 (d, $J_{4',3'}$ = 8.4 Hz, 1H, H-4'), 7.54 (overlapping multiplet, 4H, H-6'/H-3/H-6/ H-5); $^{13}$C-NMR (125 MHz, DMSO-$d_6$):$\delta$c 149.5, 138.8, 138.1, 136.6, 134.3, 133.6, 132.6, 132.0, 130.5, 129.5, 128.1, 126.7, 123.8, 122.5, 117.6; EI-MS: *m/z* (rel. abund. %) 354 $[M+2]^+$ (4.6), 352 $[M]^+$ (7.0), 253 (100), 143 (87.8), 116 (62.6); HREI-MS Calcd for $C_{15}H_{10}Cl_2N_2O_2S$ , 351.9840.Found, 351.9822.

**2,4-Dichloro-*N*-(quinolin-5-yl)benzenesulfonamide (2)**

Yield: 65%; m.p. 155-159 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.83 (overlapping multiplet, 1H, H-2), 8.71 (d, $J_{6,5}$ = 8.4 Hz, 1H, H-6), 7.90 (d, $J_{4,3}$ = 8.4 Hz, 1H, H-4), 7.79 (d, $J_{7,6}$ = 8.8 Hz, 1H, H-7), 7.69 (d, $J_{3',5'}$ = 1.6 Hz, 1H, H-3'), 7.64 (t, $J_{3,2}$ = $_{3,4}$ = 8.0 Hz, 1H, H-3) ,7.55 (overlapping multiplet, 1H, H-8), 7.37 (overlapping multiplet, 2H, H-5'/H-6'); $^{13}$C-NMR (125 MHz, DMSO-$d_6$): $\delta$c 150.7, 148.1, 137.5, 136.5, 136.1, 133.6, 132.4, 132.2, 131.4, 131.3, 129.0, 127.7, 124.7, 123. 2 , 121.3., 19.1, 18.8; EI-MS: *m/z* (rel. abund. %) [M+4] 356 (1.2), $[M+2]^+$ (3.7) (1.3), $[M]^+$ 352 (8.6), 253 (23.5), 209 (8.4), 143 (71.1), 116 (100), 109 (27.6), 89 (56.4); HREI-MS Calcd for $C_{15}H_{10}Cl_2N_2O_2S$ , 351.9840.Found, 351.9815.

**4-Chloro-2,5-dimethyl-*N*-(quinolin-5-yl)benzene sulfonamide (3)**

Yield: 75%; m.p. 197-200 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.83 (overlapping multiplet, 1H, H-4), 8.55 (d, $J_{5,6}$ =8.4 Hz, 1H, H-6), 7.92 (d, $J_{4,3}$ = 8.4 Hz, 1H, H-4), 7.64 (t, $J_{3,2}$ = $_{3,4}$ = $J_{6,'7'}$ = 8.0 Hz, 1H, H-3), 7.52 (s, 1H, H-6'), 7.52 (overlapping multiplet, 1H, H-8), 7.34 (s, 1H, H-3'), 7.21 (d, $J_{7,6}$ = 7.6 Hz, 1H, H-7), 2.45 (s, 3H, $CH_3$), 2.24 (s, 3H, $CH_3$); $^{13}$C-NMR (125 MHz, DMSO-

$d_6$): $\delta$c 150.7, 148.1, 137.5, 136.5, 136.1, 133.6, 132.4, 132.2, 131.4, 131.3, 129.0, 127.7, 124.7, 123. 2 , 121.3., 19.1, 18.8; EI-MS: *m/z* (rel. abund. %), 348 $[M+2]^+$ (18.2), $[M]^+$ 346 (45.5), 282 (31.1), 143.1 (100), 116.2 (93.2); HREI-MS Calcd for $C_{17}H_{15}ClN_2O_2S$, 346.0543, Found, 346.0562.

**3-Nitro-*N*-(quinolin-5-yl)benzenesulfonamide (4)**

Yield: 65%; m.p. 252-256 $^{\circ}$C; $^1$H-NMR (300 MHz, $CD_3OD$), $\delta_H$ 8.82 (overlapping multiplet, 1H, H-2), 8.47 (overlapping multiplet, 3H, H-6'/H-4'/H-6), 7.99 (overlapping multiplet, 1H, H-4), 7.93 (s, H, H-2'), 7.72 (overlapping multiplet, 2H, H-3/H-7), 7.49 (overlapping multiplet, 1H, H-8), 7.27 (dd, $J_{5,'6'}$ = 7.5 Hz, $J_{5',7'}$ = 0.9 Hz, 1H, H-5'); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta_C$ 150.8, 148.1, 147.8, 140.9, 132.6, 131.3, 129.0, 128.2, 127.5, 124.8, 124.0, 121.4; EI-MS: *m/z* (rel. abund. %), $[M]^+$ 329 (13.5), 218 (0.7), 143 (98.2), 116 (100), 89 (45.1). HREI-MS Calcd for 329.0470, Found 329.0472.

**3,5-Dichloro-2-hydroxy-*N*-(quinolin-5-yl)benzene sulfonamide (5)**

Yield: 45%; m.p. 174-178 $^{\circ}$C; $^1$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.83 (overlapping multiplet, 1H, H-2), 8.71 (d, $J_{6,5}$ = 8.8 Hz, 1H, H-6), 7.92 (d, $J_{4,3}$ = 8.4 Hz, 1H, H-4), 7.68 (t, $J_{3,2}$ = $J_{3,4}$ = 8.0 Hz, 1H, H-3), 7.56 (overlapping multiplet, 2H, H-7/H-8), 7.43 (s, 1H, H-6'), 7.41 (s, 1H, H-4'); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta_C$ 151.6, 149.3, 139.8, 137.8, 137.7, 135.4, 134.0, 133.8, 132.9, 131.0, 130.4, 128.4, 127.2, 125.8, 122.5; EI-MS: *m/z* (rel. abund. %), $[M+4]^+$ 372 (0.70), $[M+2]^+$ 370 (10), $[M]^+$ 368 (12), 304 (4.7), 162 (10.5), 144 (100), 11 6(45.4); HREI-MS Calcd for $C_{15}H_{10}Cl_2N_2O_3S$, 367.9789, .Found, 367.9794.

**5-Bromo-2-methoxy-*N*-(quinolin-5-yl)benzene sulfonamide (6)**

Yield: 45%; m.p. 203-208 $^{\circ}$C; $^1$H-NMR (300 MHz, $CD_3OD$), $\delta_H$ 8.82 (overlapping multiplet, 1H, H-2), 8.68 (d, $J_{6,5}$ = 8.7 Hz, 1H, H-6), 7.90 (d, $J_{4,5,}$ = 8.7 Hz, 1H, H-4), 7.69 (overlapping multiplet, 3H ,H-3'/H-4'/H-6'), 7.55 (overlapping multiplet, 1H, H-3), 7.39 (d, $J_{7,6,}$ = 7.2 Hz, 1H, H-7), 7.09 (d, $J_{8,7}$ = 9.0 Hz, 1H, H-8), 3.86 (s, 3H, $OCH_3$); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta_C$ 155.6, 150.6, 148.0, 137.4, 132.4, 131.5, 129.0, 128.7, 127.5, 124.5, 122.9, 121.2, 115.3, 110.8, 56.2; EI-MS: *m/z* (rel. abund. %), $[M+2]^+$ 394 (36.6) $[M]^+$, 392.0 (34.1), 327.9 (6.5), 312.8 (6.5),

298.9 (25.3), 218 (43.4), 157 (26.6), 143 (100); HREI-MS Calcd for $C_{16}H_{13}BrN_2O_3S$, 391.9830, Found 391.9818.

**3,4-Dimethoxy-N-(quinolin-5-yl)benzenesulfonamide (7)**

Yield: 55%; m.p.165-169 °C; (ethyl acetate/hexanes 3:7), $^1$H NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.80 (overlapping multiplet, 1H, H-2), 8.48 (d, $J_{6,7}$ = 8.4.Hz, 1H, H-6), 7.91(d, $J_{4,3}$ = 8.4 Hz, 1H, H-4), 7.66 (t, $J_{3(2,4)}$ = 8.0 Hz, 1H, H-3), 7.46 (overlapping multiplet, 1H, H-8), 7.27 (overlapping multiplet, 2H, H-7/H-6'), 7.09 (d, $J_{2',6'}$ = 2.0 Hz, 1H, H-2'), 6.95 (d, $J_{5',6'}$ = 8.4 Hz, 1H, H-5'), 3.82 (s, 3H, $OCH_3$), 3.66 (s, 3H, $OCH_3$); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$c 151.9, 150.3, 148.2, 132.6, 131.3, 130.5, 128.6, 127.2, 124.4, 123.0, 120.8, 120.3, 110.7, 109.1, 55.5, 55.3; EI-MS: *m/z* (rel. abund. %), $[M]^+$ 344 (100), 280 (90.2), 265 (11.0), 201 (35.5),143 (43.8) ,116 (72.7), 89 (24.3); HREI-MS Calcd for $C_{17}H_{16}N_2O_4S$ 344.0831, Found 344.0844

**4-Propyl-N-(quinolin-5-yl) sulfonamide (8)**

Yield: 55%; m.p 145-150 °C; $^1$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.78 (overlapping multiplet, 1H, H-2), 8.42 (d, $J_{4,2}$ = 8.4.Hz, 1H, H-4), 7.90 (d, $J_{8,7}$ = 8.8Hz, 1H, H-8), 7.64 (d, $J_{6,4}$ = 8.0 Hz, 1H, H-6), 7.54 (d, $J_{2.',3'}$ = $J_{6',5'}$ = 8.4Hz, 2H, H-2'/H-6'), 7.42 (overlapping multiplet, 1H, H-7), 7.27 (overlapping multiplet, 3H , H-3'/H-5'/H-3), 2.62 (t, 2H, $CH_2$), 1.62 (overlapping multiplet, 2H, $CH_2$), 0.89 (s, 3H, $CH_3$); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$c 151.9, 150.3, 148.2, 132.6, 131.3, 130.5, 128.6, 127.2, 124.4, 123.0, 120.8, 120.3, 110.7, 109.1, 55.5, 55.3; EI-MS *m/z* (rel. abund. %), 326 $[M]^+$, 262 (6.9), 233 (8.4), 219 (7.4). 183 (15.4), 143 (100.0), 116 (41.1); HREI-MS Calcd for $C_{18}H_{18}N_2O_2S$ 326.1089, Found 326.1085

**3,4-Dimethoxy-*N*-(quinolin-8-yl)benzene sulfonamide (9)**

Yield: 50%; m.p 180-184 °C; $^1$H-NMR (300 MHz, $CD_3OD$), $\delta_H$ 8.80 (overlapping multiplet, 1H, H-2), 8.23 (dd, $J_{7,6}$ = 8.4, $J_{7,5}$= 1.5 Hz, 1H, H-7), 7.84 (d, $J_{4,3}$ = 6.9 Hz, 1H, H-4), 7.58 (d, $J_{6,5}$ =7.2 Hz, 1H, H-6), 7.49 (overlapping multiplet, 3H, H-3/H-5/H-6'), 7.31 (d, $J_{2',4'}$ = 2.1 Hz, 1H, H-2'), 6.89 (d, $J_{5',6'}$ = 9.0 Hz, 1H, H-5'), 3.74 (s, 3H, $OCH_3$), 3.67 (s, 3H , $OCH_3$); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta_C$ 151.9,150.3, 148.2, 132.6, 131.3, 130.5, 128.6, 127.2, 124.4, 123.0, 120.8, 120.3, 110.7, 109.1, 55.5, 55.3; EI-MS: *m/z* (rel. abund. %), $[M]^+$ 344 (11.3), 280 (94.2), 265 (100), 143 (49.3), 116 (29); HREI-MS Calcd for $C_{17}H_{16}N_2O_4S$, 344.0831, Found 344.0846

**4-Methoxy-*N*-(quinolin-8-yl)benzenesulfonamide (10)**

Yield: 65%; m.p 162-167 °C; $^{1}$H-NMR (300 MHz, $CD_3OD$), $\delta_H$ 8.79 (overlapping multiplet, 1H, H-2), 8.22 (dd, $J_{7,5}$ = 1.5, $J_{7,6}$ = 8.4 Hz, 1H, H-7), 7.81 (overlapping multiplet, 3H, H-4/H-3/H-5), 7.57 (overlapping multiplet, 3H, H-2'/H-6'/H-6), 6.88 (overlapping multiplet, 2H, H-5'/H-3'), 3.72 (s, 3H, $OCH_3$); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$c 162.4, 150.3, 148.2, 132.6, 131.3, 128.6, 127.2, 124.4, 123.0, 121.1, 114.2, 55.5; EI-MS: *m/z* (rel. abund. %), $[M]^+$ 314 (11.0) 250 (100) 235 (76.1), 143 (91.9), 116(64.7); HREI-MS Calcd for$C_{16}H_{14}N_2O_3S$. 314.0725, Found 314.0728.

**4-Nitro-*N*-(quinolin-8-yl)benzenesulfonamide (11)**

Yield: 45%; m.p 168-172 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.76 (overlapping multiplet, 1H, H-2), 8.22 (overlapping multiplet, 3H, H-7/H-5'/H-3'), 8.09 (d, $J_{2',3'}$ = $J_{6',5'}$= 8.8 Hz, 2H, H-2'/H-6'), 7.89 (d, $J_{4,3,}$ = 7.6 Hz, 1H, H-4), 7.63 (d, $J_{5,6,}$ = 8.4 Hz, 1H, H-5), 7.52 (d, $J_{6,5,}$ = 8.0 Hz, 1H, H-6 ), 7.47 (overlapping multiplet, 1H, H-3); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$c 149.7, 149.4, 145.3, 139.5, 136.4, 133.0, 128.4, 128.2, 126.6, 124.2, 124.1, 122.2, 119.1, 40.3; EI-MS: *m/z* (rel. abund. %), $[M]^+$ 329 (19) 265 (65.6), 235 (8), 219 (14.7), 143 (100), 116(69.8); HREI-MS Calcd for $C_{15}H_{11}N_3O_4S$ 329.0470, Found 329.0485.

**5-Bromo-2-methoxy-*N*-(quinolin-8-yl)benzene sulfonamide (12)**

Yield: 65%; m.p 203-208 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.88 (overlapping multiplet, 1H, H-2), 8.24 (overlapping multiplet, 1H, H-7), 7.95 (overlapping multiplet, 1H, H-4), 7.76 (d, $J_{4',3'}$ = 7.6 Hz, 1H, H-4'), 7.56 (overlapping multiplet, 3H, H-5/H-3'/H-6'), 7.45 (t, $J_{3,2}$ = $J_{3,4}$ = 8.0 Hz, 1H, H-3), 6.90 (d, $J_{6,5}$ = 8.8 Hz, 1H, H-6), 3.78 (s, 3H, $OCH_3$); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$c 154.9, 148.9, 144.0, 137.6, 137.2, 136.0, 132.5, 132.3, 131.1, 126.2, 122.4, 121.9, 115.0, 114.8, 110.3, 56.1; EI-MS: *m/z* (rel. abund.%), $[M+2]^+$ 394 (2.4), 392 $[M]^+$ (1.8), 330 (7.5), 297 (100) 218.2 (10.6), 143 (72.2), 116 (75.5); HREI-MS Calcd for $C_{16}H_{13}BrN_2O_3S$, 391.9830, Found 391.9809.

**2,4-Dichloro-*N*-(quinolin-8-yl)benzenesulfonamide (13)**

Yield: 54%; m.p 165-169 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.84, (overlapping multiplet, 1H, H-2), 8.25 (overlapping multiplet, 1H, H-7), 8.14 (d, $J_{4,5}$ = 8.4 Hz, 1H, H-4), 7.69 (d, $J_{6,7}$ = 7.2

Hz, 1H, H-6), 7.57 (overlapping multiplet, 3H, H-6'/H-3'/H-5'), 7.45 (overlapping multiplet, 2H, H-5/H-3); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta_C$ 149.5, 138.8, 138.1, 136.6, 134.3, 132.5, 132.6, 132.0, 130.4, 129.5, 128.1, 126.7, 123.8, 122.5, 117.6; EI-MS: *m/z* (rel. abund. %), $[M+4]^+$ (356) (2.0), $[M+2]^+$ 354 (8.1), $[M]^+$ 352 (12.6), 316 (13.5), 253 (100), 238 (3.3). HREI-MS Calcd for $C_{15}H_{10}Cl_2N_2O_2S$, 351.9840. Found, 351.9818.

**4-Chloro-2,5-dimethyl-*N*-(quinolin-8-yl)benzene sulfonamide (14)**

Yield: 50%; m.p 200-206 °C; $^1$H-NMR (300 MHz, $CD_3OD$), $\delta_H$ 8.84, (overlapping multiplet, 1H, H-2), 8.25 (dd, $J_{7,6}$ = 8.4, $J_{5,7}$ = 1.5 Hz, 1H, H-7), 7.88 (s, 1H, H-3'), 7.71 (dd, $J_{4,3}$ = 7.5 Hz, $J_{4,2}$ = 0.9 Hz, 1H, H-4), 7.56 (overlapping multiplet, 2H, H-5/ H-6), 7.45 (t, $J_{3,2}$ = 7.5 Hz, $J_{3,4}$ = 8.4 Hz, 1H, H-3), 7.21 (s, 1H, H-6'), 2.62 (s, 3H, $CH_3$), 2.27 (s,3H,$CH_3$); $^{13}$C-NMR (125 MHz, DMSO-$d_6$): $\delta$c 149.4, 138.8, 137.8, 136.5, 136.1, 135.9, 133.4, 133.1, 132.4, 131.8, 128.1, 126.7, 123.2, 122.4, 117.0, 18.8, 18.8; EI-MS :*m/z*( rel. abund. %), $[M+2]^+$ 348 (5.1), $[M]^+$ 346 (11.1), 282 (72.6), 266 (35.0), 247 (10.4), 144 (100); HREI-MS Calcd for $C_{17}H_{15}ClN_2O_2S$, 346.0543, Found, 346.0534.

**3-Nitro-*N*-(quinolin-8-yl)benzenesulfonamide (15)**

Yield: 55%; m.p 252-256 °C; $^1$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.75 (overlapping multiplet, 1H, H-2), 8.65 (s, 1H, H-2'), 8.27 (d, $J_{7,6}$ = 8.0 Hz, 1H, H-7), 8.21 (overlapping multiplet, 2H, H-4/H-4'), 7.91 (d, $J_{6',5'}$ = 8.0 Hz, 1H, H-6'), 7.63 (overlapping multiplet, 2H, H-6/H-5'), 7.53 (t, $J_{3,2}$ = 8.0 Hz, $J_{3,4}$ =7.6 Hz, 1H, H-3), 7.45 (overlapping multiplet, 1H, H-5); $^{13}$C-NMR (125 MHz, DMSO-$d_6$): $\delta$ 149.4, 147.6, 141.5, 139.8, 136.4, 133.0, 132.7, 130.9, 128.2, 127.3, 126.6, 124.4, 122.1, 121.8, 120.0; EI-MS: *m/z* (rel. abund. %), $[M]^+$ 329 (16.3), 265 (44), 235 (6.5), 218 (16.5), 143 (100), 116 (62); HREI-MS Calcd for 329.0470, Found 329.0455.

**2-Nitro-*N*-(quinolin-8-yl)benzenesulfonamide (16)**

Yield: 55%, m.p 156-160 °C; $^1$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.80 (d, $J_{2,4}$ = 2.8 Hz, 1H, H-2), 8.25 (d, $J_{7,8,}$ = 8.4 Hz, 1H, H-7), 8.10 (d, $J_{3,4}$ = 7.6 Hz, 1H, H-4), 7.94 ($J_{2',3'}$ = 7.6 Hz, 1H, H-3'), 7.86 (d, $J_{4',3'}$ = 8.0 Hz, 1H, H-4'), 7.72 (t, $J_{5',6}$ = 7.6 Hz, $J_{5',4'}$ = 7.6 Hz, 1H, H-5'), 7.65 (overlapping multiplet, 2H, H-6/ H-5), 7.54 (overlapping multiplet, 2H, H-3/H-6 ); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta_C$ 154.1, 150.0, 137.3, 135.0, 131.7, 129.5, 127.3, 123.9, 122.9, 122.3, 117.9,

111.3, 110.8; EI-MS: *m/z* (rel abund %), $[M]^+$ 329 (27.4), 282.2 (5.8), 219 (89.5), 204 (18.2), 143 (100), 116 (71.4); EI-MS:*m/z* (rel. abund. %), $[M]^+$ 329 (27.4), 282.2 (5.8), 219 (89.5), 204 (18.2), 143 (100), 116 (71.4). HREI-MS Calcd for $C_{15}H_{11}N_3O_4S$ 329.0470, Found 329.0487.

**_N_-(Quinolin-8-yl)methanesulfonamide (17)**

Yield: 45%; m.p 186-190 °C; $^1$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.89 (overlapping multiplet, 1H, H-2), 8.33 (overlapping multiplet, 1H, H-4), 7.84 (d, $J_{3,4}$ = 7.2Hz, 1H, H-3), 7.68 (d, $J_{6,5}$ = 8.4 Hz, 1H, H-6), 7.58 (overlapping multiplet, 2H, H-5/H-7), 3.02 (s, 3H, $CH_3$); $^{13}$C-NMR (125 MHz, DMSO-$d_6$): $\delta$c 150.1, 131.1, 128.4, 127.0, 122.7, 120.6, 120.0, 110.4, 108.8, 55.2; EI-MS: *m/z* (rel. abund. %), $[M]^+$ 222 (64.5), 207 (9.8), 143 (100), 116 (51.9), 89 (10), 77 (0.9), 63(4.9), 44 (1.2); HREI-MS Calcd for $C_{10}H_{10}N_2O_2S$, 222.0463, Found, 222.0474.

**4-Chloro-_N_-(quinolin-8-yl)benzenesulfonamide (18)**

Yield: 65%; m.p 156-160 °C; $^1$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.78 (overlapping multiplet, 1H, H-2), 8.23 (overlapping multiplet, 1H, H-4), 7.83 (overlapping multiplet, 3H, H-5/H-6/H-3), 7.60 (d, $J_{7,6}$ = 8.0 Hz, H-1 ,H-7), 7.50 (overlapping multiplet, 2H, H-3'/H-5'), 7.38 (d, $J_{2',3'} = J_{6',5'}$ = 8.8 Hz, 2H, H-2'/H-6'); $^{13}$C-NMR (125 MHz, DMSO-$d_6$): $\delta$ 149.5, 138.8, 138.1, 136.6, 134.4, 133.5, 132.6, 132.0, 130.4, 129.5, 128.1, 126.7, 123.8, 122.5, 117.6; EI-MS: *m/z* (rel. abund. %), $[M+2]^+$ 320 (3.26) $[M]^+$ 318 (12.94), 254 (75.77), 218 (5.59), 175 (1.24), 144 (68.16), 116 (100), 89 (73.63); HREI-MS Calcd for $C_{15}H_{11}ClN_2O_2S$ 318.0230, Found, 318.0222.

**4-Propyl-_N_-(quinolin-8-yl)benzenesulfonamide (19)**

Yield: 65%; m.p 200-204 °C; $^1$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.77 (overlapping multiplet, H-1, H-2), 8.21 (d, $J_{4,5}$ = 8.0 Hz, H-1, H-4), 7.81 (d, $J_{5,6}$ = 7.6 Hz, H-1, H-5), 7.74 (d, $J_{5',6'} = J_{6',2,'}$ = 8.4 Hz, 2H, H-6'/H-2'), 7.56 (d, $J_{7,6}$ = 8.0 Hz, 1H, H-7), 7.47 (overlapping multiplet, 2H, H-3/H-6), 7.18 (d, $J_{2',3'} = J_{5,6,}$ = 8.0 Hz, 2H, H-3', H-5'), 2.53 (t, 2H, $CH_2$), 1.54 (overlapping multiplet, 2H, $CH_2$), 0.82 (overlapping multiplet, 3H, $CH_3$); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$c 149.2, 147.8, 138.6, 136.7, 136.4, 133.5, 128.9, 128.0, 126.9, 126.6, 122.8, 122.2, 116.3, 36.7, 23.4, 13.3; EI-MS: *m/z* (rel. abund.%), $[M]^+$ 326 (21), 262 (56), 233 (100), 218 (3.5), 143 (82.6), 116 (40.7), 89 (12.3); HREI-MS Calcd for $C_{18}H_{18}N_2O_2S$, 326.1089, Found, 326.1089.

**_N_-Quinolin-8-yl benzenesulfonate (20)**

Yield: 65%; m.p 186-190 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.79 (overlapping multiplet, 1H, H-2), 8.45 (d, $J_{4,3}$ ,= 8.4Hz, 1H, H-4), 7.88 (t, $J_{6,5} = J_{6,7} = J_{4',3'} = J_{4',5'}$ = 7.2 Hz, 2H, H-6/H-4') 7.91 (d, $J_{3,4,}$ = 8.4 Hz, 1H, H-3), 7.56 (t, $J_{4'(3',5')}$ = 7.6 Hz, H-4'), 7.66 (overlapping multiplet, 3H, H-7/H-6', H-2'), 7.48 (overlapping multiplet, 3H, H-3'/H-5'/H-5). $^{13}$C-NMR (75 MHz DMSO-$d_6$): $\delta_C$ 150.6, 148.1, 139.4, 132.8, 132.5, 131.5, 129.1, 127.7, 126.6, 124.6, 123.4, 121.1; EI-MS: *m/z* (rel. abund. %), $[M]^+$ 285 (20.4), 221 (100), 204 (8.6), 192 (5.0),1 67 (2.6), 149 (0.2), 145 (15.4) , 116 (69.5), 89 (22.1), 77(39.5); HREI-MS Calcd for $C_{15}H_{12}N_2O2S$, 285.0460, Found 285.0440

**3,4-Dimethoxy-*N*-(quinolin-3-yl)benzene sulfonamide(21)**

Yield: 75%; m.p 184-188 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.54 (d, $J_{2,4,}$ = 2.4 Hz, 1H, H-2), 8.02 (overlapping multiplet, 1H, H-4), 7.93 (d, $J_{5,6}$ = 8.4 Hz, 1H, H-5), 7.83 ($J_{7,8}$ = 8.4 Hz, 1H, H-7), 7.68 (overlapping multiplet, 1H, H-8), 7.65 (t, $J_{6,7}$ = 7.6 Hz, $J_{6,5}$ = 8.0 Hz, 1H, H-6), 7.37 (overlapping multiplet, 1H, H-5'), 7.26 (d, $J_{2,5'}$= 2.0 Hz, 1H, H-2'), 6.97 (d, $J_{6',7'}$ = 8.4 Hz, 1H, H-6'), 3.80 (s, 3H, $OCH_3$), 3.73 (s, 3H, $OCH_3$); $^{13}$C-NMR (75 MHz, DMSO-$d_6$):$\delta$c 154.1, 150.0, 137.3, 135.0, 131.7, 129.5, 127.3, 123.9, 122.9, 117.9, 111.3, 110.8, 56.2, 56.1; EI-MS: *m/z* (rel. abund. %), $[M]^+$ 343 (80.8), 280.3 (7.9), 201 (77.8), 157 (27.9), 143 (57.6), 137 (100),116 (67.7); HREI-MS Calcd for $C_{17}H_{16}N_2O_4S$ ,343.0753, Found 343.0768**.**

**2-Nitro-*N*-(quinolin-3-yl)benzenesulfonamide (22)**

Yield: 75; m.p 155-159 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.66 (d, $J_{2,4}$ = 2.4 Hz, 1H, H-2), 8.13 (d, $J_{4,2}$ = 2.4 Hz, 1H, H-4), 7.97 (overlapping multiplet, 2H, H-3'/H-5), 7.86 (t, $J_{6,5} = J_{6,7}$ = 7.6 Hz, $J_{7,6} = J_{7,8}$ = 7.6 Hz, 2H, H-6/H-7), 7.77 (overlapping multiplet, 3H, H-6'/H-5'/H-8), 7.60 (t, $J_{4',3'}$ = 7.2 Hz, $J_{4',5'}$ = 7.2 Hz, 1H, H-4'); $^{13}$C-NMR (125 MHz, DMSO-$d_6$):$\delta$c 154.2, 153.6, 152.0, 137.7, 136.9, 135.0, 133.3, 133.2, 129.0, 127.4, 126.0, 124.1, 123.5; EI-MS: *m/z* (rel. abund. %), $[M]^+$ 329 (56.32), 282 (0.9), 248 (3.7), 218 (7.8), 186 (5.9), 159 (5.7), 143 (100), 116 (97.8); HREI-MS Calcd for $C_{15}H_{11}N_3O_4S$ 329.0470, Found 329.0485.

**2,4-Dichloro-*N*-(quinolin-3-yl)benzenesulfonamide (23)**

Yield: 55%; m.p 151-155 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$); $\delta_H$ 8.64 (d, $J_{2,4}$ = 2.4 Hz, 1H, H-2), 8.09 (d, $J_{5',6'}$ = 8.8 Hz, 1H, H-5'), 8.02 (d, $J_{4,6,}$ = 2.0 Hz, 1H, H-4), 7.92 (d, $J_{6,5}$ = 8.8 Hz, 1H, H-6), 7.81 (d, $J_{8,7}$ = 8.4 Hz, 1H, H-8), 7.67 (overlapping multiplet, 2H, H-5/H-3'), 7.57 (t, $J_{7,6}$ = $J_{7,8}$ = 7.6 Hz, 1H, H-7), 7.45 (overlapping multiplet, 1H, H-6); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta_C$ 149.5, 138.8, 138.1 ,136.6, 134.3, 133.5, 132.6, 132.0, 130.4, 129.5, 128.4, 126.7, 123.8, 122.5, 117.6; EI-MS: *m/z* (rel. abund. %), $[M+4]^+$ 356 (1.78), $[M+2]^+$ 354 (17.8), $[M]^+$ 352 (27.4), 253 (8.44), 143 (93.72), 116 (100), 89 (87.31); HREI-MS Calcd for $C_{15}H_{10}Cl_2N_2O_2S$, 351.9840. Found, 351.9822.

**2,5-Dichloro-*N*-(quinolin-3-yl)benzenesulfonamide (24)**

Yield: 75%; m.p 175-179 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.65 (d, $J_{2,4,}$ = 2.4 Hz, 1H, H-2), 8.08 (s, 1H, H-6'), 8.04 (d, $J_{4,2}$ = 2.4 Hz, 1H, H-4), 7.93 (d, $J_{3',4'}$ = 8.4 Hz, 1H, H-3'), 7.83 (d, $J_{4',5'}$ = 8.0 Hz, 1H, H-4'), 7.68 (overlapping multiplet, 1H, H-7), 7.58 (overlapping multiplet ,3H, H-5/H-6/H-8); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta_C$ 149.1, 139.7, 138.5, 137.8, 136.3, 134.0, 133.2, 131.7, 130.1, 129.2, 127.8, 126.4, 123.5, 122.1, 117.3; EI-MS: *m/z* (rel. abund. %), $[M+4]^+$ 356 (2.22), $[M+2]^+$, 355 (1.98), $[M]^+$, 352 (26.27), 253 (4.56), 218 (0.86), 143 (94.0), 116 (100), 89 (89.86); HREI-MS Calcd for $C_{15}H_{10}Cl_2N_2O_2S$, 351.9840. Found, 351.9855.

**4-Chloro-2,5-dimethyl-*N*-(quinolin-3-yl)benzene sulfonamide (25)**

Yield: 55%; m.p 201-206 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.57 (d, $J_{2,4}$ = 2.4 Hz, 1H, H-2), 7.96 (d, $J_{4,2}$ = 2.4 Hz, 1H, H-4), 7.92 (d, $J_{5,6}$ = 8.4 Hz, 1H, H-5), 7.86 (s, 1H, H-3') 7.80 (d, $J_{8,7}$ = 8.4 Hz, 1H, H-8), 7.67 (t, $J_{6,7}$ = 7.2 Hz, $J_{7,8}$ = 6.8 Hz, 1H, H-7), 7.57 (t, $J_{6,7}$ = 7.2 Hz, $J_{6,5}$ = 6.8 Hz ,1H, H-6), 7.35 (s, 1H, H-6'), 2.58 (s, 3H, $CH_3$), 2.30 (s, 3H, $CH_3$); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$c 150.7, 148.1, 137.5, 136.5, 133.6, 132.4, 132.2, 131.4, 129.0, 127.7, 124.7, 123.2, 121.3, 19.1, 18.8; EI-MS: *m/z* (rel. abund. %), $[M+2]^+$ 348 (10.09), $[M]^+$ 346 (30.49), 282 (2.95), 203 (6.0), 143 (98.89), 116 (100), 89 (86.89), 63 (54.33); HREI-MS Calcd for $C_{17}H_{15}ClN_2O_2S$, 346.0543, Found, 346.0548.

**4-Nitro-*N*-(quinolin-3-yl)benzenesulfonamide (26)**

Yield: 75%; m.p 138-142 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.56 (d, $J_{2,4,}$ = 2.4 Hz, 1H, H-2), 8.33 (d, $J_{3',2'}$ = $J_{5',6'}$ = 8.8 Hz, 2H, H-3'/H-5'), 8.07 (d, $J_{4,2}$ = 2.0 Hz, 1H, H-4), 8.03 (overlapping multiplet, 2H, H-2'/H-6'), 7.94 (d, $J_{8,7}$ = 8.4 Hz, 1H, H-8), 7.85 (d, $J_{5,4}$ = 8.0 Hz, 1H, H-5), 7.70 (t, $J_{7(6,8)}$ = 7.2 Hz, 1H, H-7), 7.59 (t, $J_{6,7}$ = 7.9 Hz, $J_{5,6}$ = 7.2 Hz, 1H, H-6); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$c 154.2, 153.6, 152.0, 137.7, 136.9, 135.0, 133.3, 133.2, 129.0, 127.4, 126.0, 124.1, 123.5; EI-MS: *m/z* (rel. abund.%), $[M]^+$ 329 (51.75), 299 (0.6), 219 (0.97), 186 (1.49), 143 (96.54), 116 (100), 89 (73.49), 63 (54.72); HREI-MS Calcd for $C_{15}H_{11}N_3O_4S$ 329.0470, Found 329.0481.

**3-Nitro-*N*-(quinolin-3-yl)benzenesulfonamide (27)**

Yield: 65%, m.p 181-185 °C; $^{1}$H-NMR (300 MHz $CD_3OD$) $\delta_H$ 8.63 (d, $J_{2,4}$ = 2.4 Hz, 1H, H-2), 8.57 (d, $J_{4,2}$ = 2.4 Hz, 1H, H-4), 8.43 (overlapping multiplet, 1H, H-2'), 8.13 (overlapping multiplet, 2H, H-4'/H-8), 7.95 (d, $J_{5,6}$ = 8.4 Hz, 1H, H-5), 7.85 (d, $J_{6',5'}$ = 7.8 Hz, 1H, H-6'), 7.76 (overlapping multiplet, 2H, H-6/H-7), 7.60 (overlapping multiplet, 1H ,H-5'); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$c 149.1, 139.7, 138.5, 137.8, 136.3, 134.0, 133.2, 131.7, 130.1, 129.2, 127.8, 126.4, 123.5, 122.1, 117.3; EI-MS:*m/z* (rel. abund.%), $[M]^+$ 328.9 (62.0), 299 (2.5), 142.9 (100), 116 (93.4), 89 (80.0), 63 (51.0); HREI-MS Calcd for $C_{15}H_{11}N_3O_4S$, 329.0470, Found 329.0461.

***N*-(Quinolin-3-yl)benzenesulfonamide (28)**

Yield: 55%; m.p 181-185 °C; $^{1}$H-NMR (300 MHz, $CD_3OD$), $\delta_H$ 8.54 (d, $J_{2,4,}$ = 3.0 Hz, 1H, H-2), 8.02 (d, $J_{4,2,}$ = 2.4 Hz, 1H, H-4), 7.93 (d, $J_{4',3'}$ = 8.4 Hz, 1H, H-4'), 7.80 (overlapping multiplet, 3H, H-5/H-6'/H-2'), 7.69 (overlapping multiplet, 1H, H-8), 7.58 (t, $J_{6(7,5)}$ = $J_{7(6,8)}$ = 7.2 Hz, 2H, H-7/H-6), 7.47 (overlapping multiplet, 2H, H-5'/H-3'); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$c 149.1, 139.7, 138.5, 137.8, 136.3, 134.0, 133.2, 131.7, 130.1, 129.2, 127.8, 126.4, 123.5, 122.1, 117.3; EI-MS, *m/z*.(rel. abund.%), $[M]^+$ 284 (48.5), 219 (2.1), 143 (100), 116 (66.1), 89 (18.4), 77 (13.5), 51 (5.2); HREI-MS Calcd for $C_{15}H_{12}N_2O_2S$, 284.0619, Found 284.0614.

**5-Bromo-2-methoxy-*N*-(quinolin-3-yl)benzene sulfonamide (29)**

Yield: 45%; m.p 195-199 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.62 (d, $J_{2,4}$ = 2.4 Hz, 1H, H-2), 8.01 (d, $J_{4,2}$ = 2.0 Hz, 1H, H-4), 7.93 (overlapping multiplet, 2H, H-4'/H-6'), 7.82 (d, $J_{8,7}$ = 8.0 Hz, 1H, H-8), 7.67 (overlapping multiplet, 2H, H-6/H-3'), 7.57 (t, $J_{7,6}$ = 7.6 Hz, $J_{7,8}$ = 7.2 Hz, 1H, H-7), 7.07 (d, $J_{5,4}$ = 8.8 Hz, 1H, H-5), 3.88 (s, 3H, $OCH_3$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$c 154.9, 148.9, 144.0, 137.2, 136.0, 132.5, 132.3, 131.1, 126.2, 122.4, 121.9, 115.0, 114.8, 110.3, 56.1; EI-MS: *m/z* (rel. abund. %) $[M+2]^+$ 396 (33.5), 394 $[M]^+$ (32.0), 328 (3.9), 251 (2.6), 143 (100), 116 (60.3), 89 (17.1), 63 (11.7); HREI-MS Calcd for $C_{16}H_{13}BrN_2O_3S$, 391.9830, Found 391.9825.

**3,4-Dimethoxy-*N*-(quinolin-3-yl)benzene sulfonamide(30)**

Yield: 75%; m.p 184-188 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.54 (d, $J_{2,4}$ = 2.4 Hz, 1H, H-2), 8.02 (d, $J_{4,2}$ = 2.0 Hz, 1H, H-4), 7.93 (d, $J_{5,6}$ = 8.4 Hz, 1H, H-5), 7.83 (d, $J_{8,7}$ = 8.0 Hz, 1H, H-8), 7.68 (t, $J_{7,6}$ = 7.2 Hz, $J_{7,8}$ =8.0 Hz, 1H, H-7), 7.58 (t, $J_{6,7}$ = $J_{6,5}$ = 7.6 Hz, 1H, H-6), 7.37 (overlapping multiplet, 1H , H-6'), 7.26 (d, $J_{2',4'}$ = 2.0 Hz, 1H, H-2'), 6.97 (d, $J_{5',6'}$ = 8.4 Hz, 1H, H-5'), 3.80 (s, 3H, $OCH_3$), 3.72 (s, 3H, $OCH_3$); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$c 162.6, 149.3, 149.2, 138.5, 136.5, 133.6, 130.8, 129.1, 128.0, 126.6, 122.6, 122.3, 115.9, 114.2, 55.6, 55.5; EI-MS: *m/z* (rel. abund.%), $[M]^+$ 344 (100), 329 (1.5), 298 (1.4), 280 (8.9), 201 (64.9), 185 (3.0), 170 (4.2), 153 (12.6), 143 (29.8), 137 (51.8), 116 (28.5); HREI-MS Calcd for $C_{17}H_{16}N_2O_4S$, 344.0831, Found 344.0820.

**4-Propyl-N-(quinolin-3-yl)benzenesulfonamide (31)**

Yield: 65%; m.p 165-169 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.54 (d, $J_{2,4}$ = 2.4 Hz, H-1, H-2), 8.00 (d, $J_{4,3}$ = 2.0 Hz, H-1, H-4), 7.92 (d, $J_{8,7}$ = 8.4 Hz, H-1, H-8), 7.81 (d, $J_{5,6}$ = 8.4 Hz, 1H, H-5), 7.69 (overlapping multiplet, 3H, H-2'/H-6'/H-7), 7.58 (t, $J_{6,5}$ = 7.6 Hz, $J_{6,7}$ = 7.2 Hz, 1H, H-6), 7.30 (d, $J_{4',3}$ = $J_{5'6'}$ = 8.0 Hz, 2H, H-3'/H-5') 2.61 (t, 2H, $CH_2$), 1.60 (overlapping multiplet, 2H, $CH_2$), 0.88 (s , 3H, $CH_3$); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$c 149.2, 147.8, 138.6, 136.7, 136.4, 133.5, 128.9, 128.0, 126.9, 126.6, 122.8, 122.2, 116.3, 36.7, 23.4, 13.3; EI-MS: *m/z* (rel. abund. %), $[M]^+$ 326 (79.9) 143 (100), 116 (60.2), 143 (100), 89 (16.5); HREI-MS Calcd for $C_{18}H_{18}N_2O_2S$, 326.1089, Found 326.1073.

***N*-(Quinolin-3-yl)octane-1-sulfonamide (32)**

Yield: 75%; m.p 180-184 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.71 (d, $J_{2,4}$ = 2.0 Hz, H-1, H-2), 8.16 (d, $J_{4,2}$ = 2.0 Hz, H-1, H-4), 7.98 (d, $J_{5,4}$ = 8.4 Hz, 1H, H-5), 7.89 (d, $J_{8,7}$ = 8.0 Hz, 1H, H-8), 7.70 (t, $J_{6,5}$ =7.6 Hz, $J_{6,7}$ = 7.2 Hz, 1H, H-6,), 7.61 (t, $J_{7,6}$ = 7.6 Hz, $J_{8,7}$ = 7.2 Hz, 1H, H-7), 3.20 (t, 2H, $CH_2$), 1.84 (overlapping multiplet, 2H, $CH_2$), 1.39 (overlapping multiplet, 10H, $CH_2$), 0.85 (s, 3H, $CH_3$); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$c 144.7, 144.3, 132.2, 128.5, 128.0, 127.7, 127.5, 127.2, 122.0, 50.8, 31.0, 28.2, 28.2, 27.1, 22.9, 21.9, 13.8; EI-MS: *m/z* (rel. abund. %), $[M]^+$ 320 (1.29), 263 (4.6), 235 (5), 208 (5), 144 (100), 116 (35), 89 (2.6); HREI-MS Calcd for $C_{17}H_{24}N_2O_2S$, 320.1558, Found 320.1563.

**Quinolin-8-yl benzenesulfonate (33)**

Yield: 65%; m.p 186-200 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.66 (d, $J_{2,4}$ = 3.2Hz, 1H, H-2), 8.31 (d, $J_{4,3,}$ = 8.4 Hz, 1H, H-4), 7.88 (t, $J_{3,2} = J_{3,4} = J_{6,5} = J_{6,7} = J_{4',3'} = J_{4',5'}$ = 7.2 Hz, 3H, H-3/H-6/H-4'), 7.65 (overlapping multiplet, 3H, H-7/H-6', H-2'), 7.48 (overlapping multiplet, 3H, H-3'/H-5'/H-5); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$c 149.1, 139.7, 138.5, 137.8, 136.3, 134.0, 133.2, 131.7, 130.1, 129.2, 127.8, 126.4, 123.5, 122.1, 117.3; EI-MS: *m/z* (rel. abund. %), $[M]^+$ 285 (20.4), 221 (100), 204 (8.6), 192 (5.0),1 67 (2.6), 149 (0.2), 145 (15.4) , 116 (69.5), 89 (22.1), 77(39.5); HREI-MS Calcd for $C_{15}H_{12}N_2O2S$ , 285.0460, Found 285.0440.

**5-Bromo-2-methoxy( quinolin-8-yl) benzene sulfonate (34)**

Yield: 65%; m.p 202-207 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.71 (overlapping multiplet, 1H, H-2), 8.35 (overlapping multiplet, 1H, H-4), 7.89 (overlapping multiplet, 2H, H-6'/H-4'), 7.75 (overlapping multiplet, 1H, H-5), 7.58 (overlapping multiplet, 2H, H-6 /H-3'), 7.52 (overlapping multiplet, 1H, H-3), 7.10 (d, $J_{7,8}$ = 8.8 Hz, 1H, H-7), 3.71 (s, 3H, $OCH_3$); $^{13}$C-NMR (75 MHz, DMSO-$d_6$):$\delta$c 154.9, 148.9, 144.0, 137.2, 136.0, 132.5, 132.3, 131.1, 126.2, 122.4, 121.9, 115.0, 114.8, 110.3, 56.1; EI-MS: *m/z* (rel. abund. %), $[M+2]^+$ 394 (0.9), $[M]^+$ 392 (0.9), 299.9 (100), 284 (2.4), 248.9 (7.2), 219 (9.3), 191(6.5), 170 (3.3), 157 (34.5), 116 (85.7); HREI-MS Calcd for $C_{16}H_{13}BrN_2O_3S$, 392.9670, Found 392.608.

**Quinolin-8-yl 3-nitrobenzenesulfonate (35)**

Yield: 45%; m.p 252-256 °C, $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.73 (s, 1H, H-2'), 8.62 (overlapping multiplet, 1H, H-4), 8.47 (d, $J_{4',3'}$ = 8.0 Hz, 1H, H-4'), 8.32 (overlapping multiplet, 1H, H-2'), 8.24 (d, $J_{6',5'}$ = 8.0 Hz, 1H, H-6'), 7.93 (d, $J_{3,2}$ = 8.4 Hz, 1H, H-3), 7.78 (overlapping multiplet, 2H, H-7/H-5'), 7.65 (t, $J_{7,6}$ = $J_{5,6}$ =8.0 Hz, 1H, H-6), 7.48 (overlapping multiplet, 1H, H-5); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$c 149.1, 139.7, 138.5, 137.8, 136.3, 134.0, 133.2, 131.7, 130.1, 129.2, 127.8, 126.4, 123.5, 122.1, 117.3; EI-MS: *m/z* (rel. abund.%), $[M]^+$ 330 (4.1) 284 (0.9), 266 (100), 249 (16.5), 235 (11.7), 219 (49.0), 191 (15), 144 (85.0), 116 (99.2), 89 (73. 5). HREI -MS Calcd for $C_{15}H_{10}N_2O_5S$, 330.0310, Found 330.0328.

**Quinolin-8-yl 2,4-dichlorobenzenesulfonate (36)**

Yield: 65%; m.p 165-170 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.67 (d, $J_{2,4}$ = 4.0 Hz, 1H, H-2), 8.34 (overlapping multiplet, 1H, H-4), 7.90 (overlapping multiplet, 3H, H-6'/H-5'), 7.80 (d, $J_{3',5'}$ = 2.0 Hz, 1H, H-3'), 7.57 (overlapping multiplet ,4H, H-6/H-3/H-7/H-5); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$c 149.1, 139.7, 138.5, 137.8, 136.3, 134.0, 133.2, 131.7, 130.1, 129.2, 127.8, 126.4, 123.5, 122.1, 117.3; EI-MS: *m/z* (rel. abund. %), $[M\text{-}Cl]^+$ 318 (1.9), 289 (13.3), 254 (100), 209 (3.4), 145 (12.7), 116 (31.3), 89 (7.8); HREI-MS Calcd for $C_{15}H_{10}Cl_2N_1O_3S$, 353.9758, Found 353.9771.

**Quinolin-8-yl 4-nitrobenzenesulfonate (37)**

Yield: 55%; m.p 168-172 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.64 (d, $J_{2,4}$ = 2.8 Hz, 1H, H-2), 8.33 (d, $J_{4',3'}$ = $J_{5',6'}$= $J_{3,4}$ = 8.8 Hz, 3H, H-4/H-5'/H-3'), 8.15 (d, $J_{2',3'}$ = $J_{6',5'}$ = 8.8 Hz, 2H, H-2'/H-6'), 7.92 (d, $J_{7,6}$ = 8.0 Hz, 1H, H-7), 7.73 (d, $J_{4,5}$ = 7.6 Hz, 1H, H-5),7.63 (t, $J_{3,2}$ = $J_{3,4}$ = 8.0 Hz, 1H, H-3), 7.49 (overlapping multiplet, 1H, H-6); $^{13}$C-NMR (100 MHz, DMSO-$d_6$):$\delta$c 154.2, 153.6, 152.0, 137.7, 136.9, 135.0, 133.3, 133.2, 129.0, 127.4, 126.0, 124.1, 123.5; EI-MS: *m/z* (rel. abund. %), $[M]^+$ 330 (0.9), 266 (100), 249 (8.0), 236 (6.7), 219 (8.6), 144 (60.5), 116 (95.1), 89 (50.8), 63 (19.7); HREI-MS Calcd for $C_{15}H_{10}N_2O_5S$, 330.0310, Found 330.0311.

**Quinolin-8-yl 2-nitrobenzenesulfonate (38)**

Yield: 75%; m.p 156-160 °C; $^{1}$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.68 (d, $J_{2,4}$ = 2.8 Hz, 1H, H-2), 8.36 (d, $J_{4,3}$ = 8.4 Hz, 1H, H-4), 8.15 (d, $J_{4,'3'}$ = 8.0 Hz, 1H, H-3'), 7.93 (overlapping multiplet,

3H, H-3/H-6/H-7), 7.80 (overlapping multiplet, 1H, H-5'), 7.58 (overlapping multiplet, 3H, H-4'/H-5'/H-6'); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$c 149.1, 139.7, 138.5, 137.8, 136.3, 134.0, 133.2, 131.7, 130.1, 129.2, 127.8, 126.4, 123.5, 122.1, 117.3; EI-MS: *m/z* (rel. abund. %), $[M]^+$ 330 (7.0), 266 (46.5), 220 (97.6), 186 (45.8), 160 (78.2), 145, (56.6), 132 (34.8), 116 (100), 89 (25.0); HREI -MS Calcd for $C_{15}H_{10}N_2O_5S$ , 330.0310, Found 330.0323.

**Quinolin-8-yl 4-propylbenzenesulfonate (39)**

Yield: 55%; m.p 150-152 $^{\circ}$C; $^1$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.64 (d, $J_{4,2}$ = 2.8 Hz, H-1 ,H-2), 8.30 (d, $J_{6,7}$ = 8.4 Hz, H-1, H-7), 7.87 (d, $J_{4,3}$ = 8.0 Hz, H-1, H-4), 7.72 (d, $J_{5',6'} = J_{2'3'}$ = 8.4 Hz, 2H, H-6'/H-2'), 7.66 ($J_{5,6}$ = 6.4Hz, 1H, H-5), 7.59 (t, $J_{3,2}$ = 7.6 Hz, $J_{4,3}$ = 8.0 Hz, 1H ,H-3), 7.47 (overlapping multiplet, 1H, H-7), 7.25 (d, $J_{2',3} = J_{5',6'}$ = 8.0 Hz, 2H, H-3'/H-5'), 2.61 (t, 2H, $CH_2$), 1.60 (overlapping multiplet, 2H, $CH_2$), 0.87 (s, 3H, $CH_3$); $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta$c 149.2, 147.8, 138.6, 136.7, 136.4, 133.5, 128.9, 128.0, 126.9, 126.6, 122.8, 122.2, 116.3, 36.7, 23.4, 13.3; FAB-MS *m/z* 327 $[M+H]^+$; HRFAB-MS Calcd for $C_{18}H_{17}NO_3S$, 326.0851, Found 326.0857.

**Quinolin-8-yl 4-chloro-2,5-dimethylbenzene sulfonate (40)**

Yield: 65%; m.p 202-204 $^{\circ}$C; $^1$H-NMR (400 MHz, $CD_3OD$), $\delta_H$ 8.71 (overlapping multiplet, 1H, H-2), 8.31 (d, $J_{4,2}$ = 1.2 Hz, $J_{4,3}$ = 8.4 Hz, 1H, H-4), 7.87 (overlapping multiplet, 1H, H-3), 7.64 (s, ,1H, H-3'), 7.56 (overlapping multiplet, 3H, H-5/H-7/H-6), 7.45 (s, 1H, H-6'), 2.76 (s, 3H, $CH_3$), 2.24 (s ,3H, $CH_3$); $^{13}$C-NMR (125 MHz, DMSO-$d_6$): $\delta$c 150.7, 148.1, 137.5, 136.5, 136.1, 133.6, 132.4, 132.2, 131.4, 131.3, 129.0, 127.7, 124.7, 123. 2 , 121.3., 19.1, 18.8; EI-MS : *m/z* (rel. abund. %), 283 (83.7), 266 (100), 248 (7.3), 204 (3.9), 172 (0.8), 139, (44.1), 116 (43.9), 103 (19.2), 89 (19.9), 77 (18.7); HREI-MS Calcd for $C_{17}H_{13}N_1O_3Cl_1S$, 346.0305, Found 346.0302.

**Acknowledgements:** This work was supported by the Higher Education Commission (HEC) Pakistan (Project No. 20-1910), under the National Research Program for Universities. Authors are thankful to Dr. Nessar Ahmed, Reader, Clinical Biochemistry at School of Healthcare Science, Manchester Metropolitan University, UK for proof reading and English editing of this manuscript.

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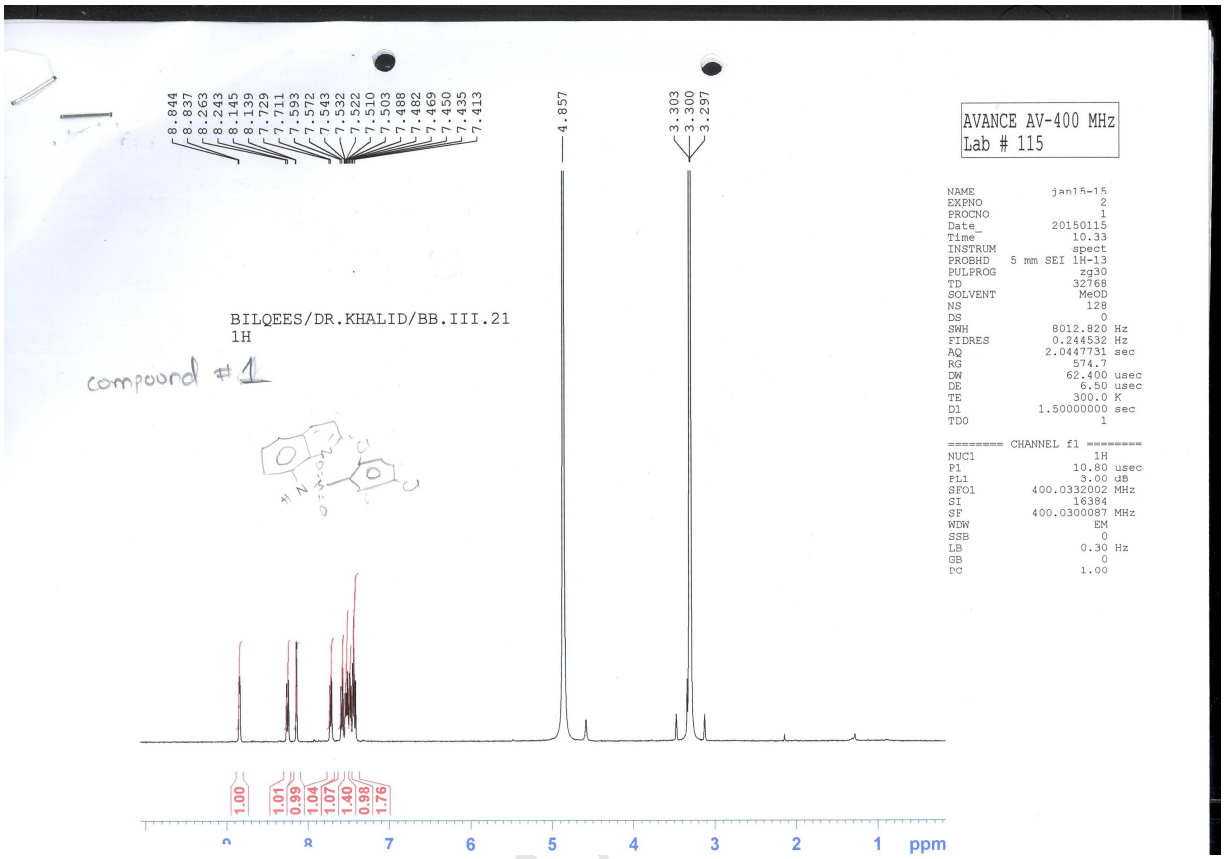
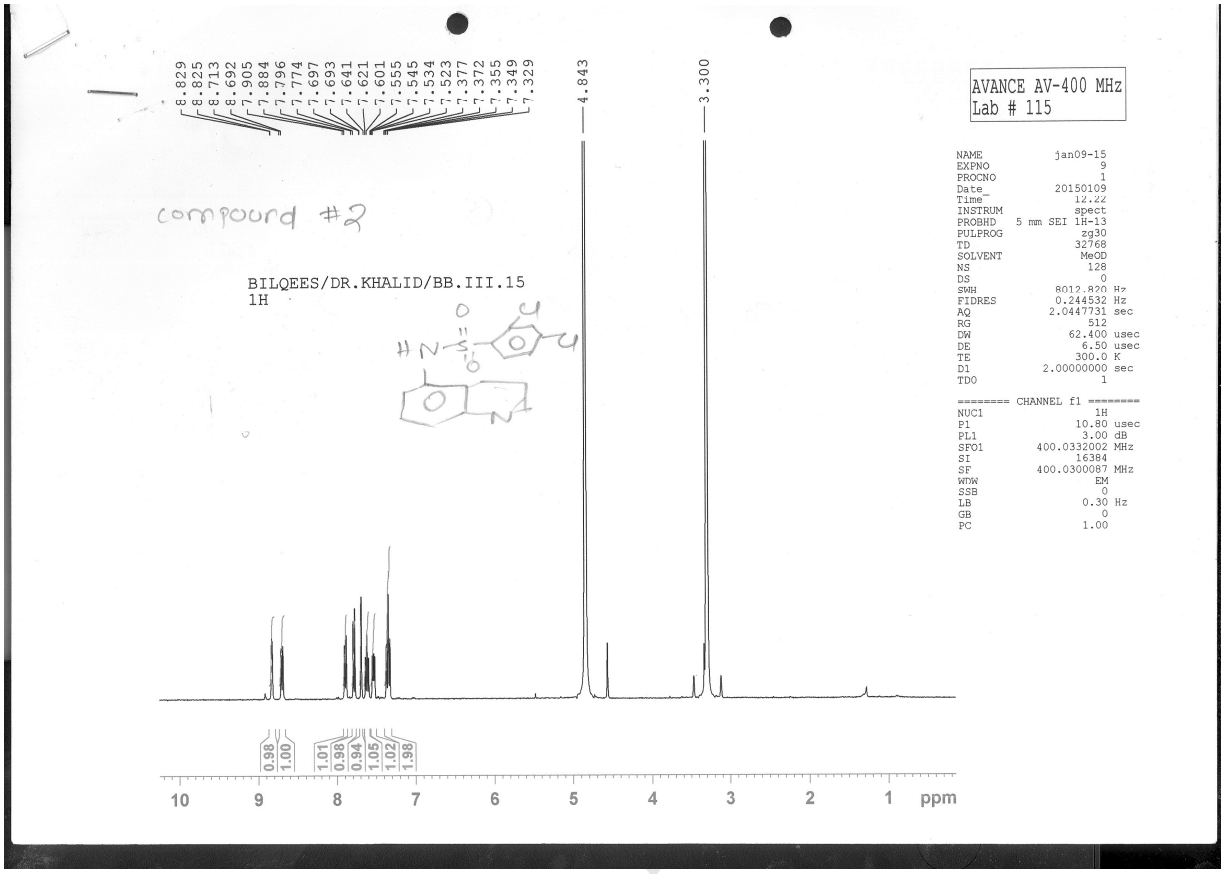
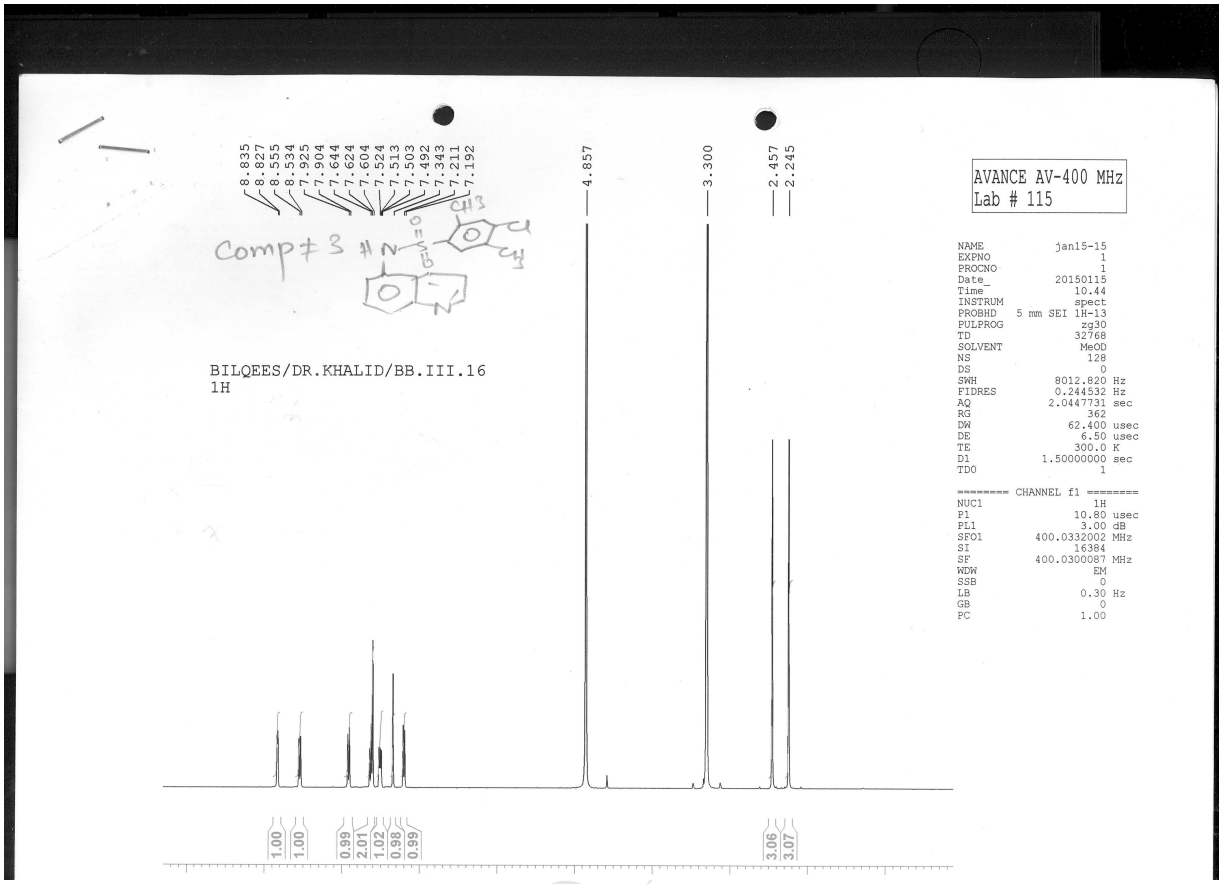
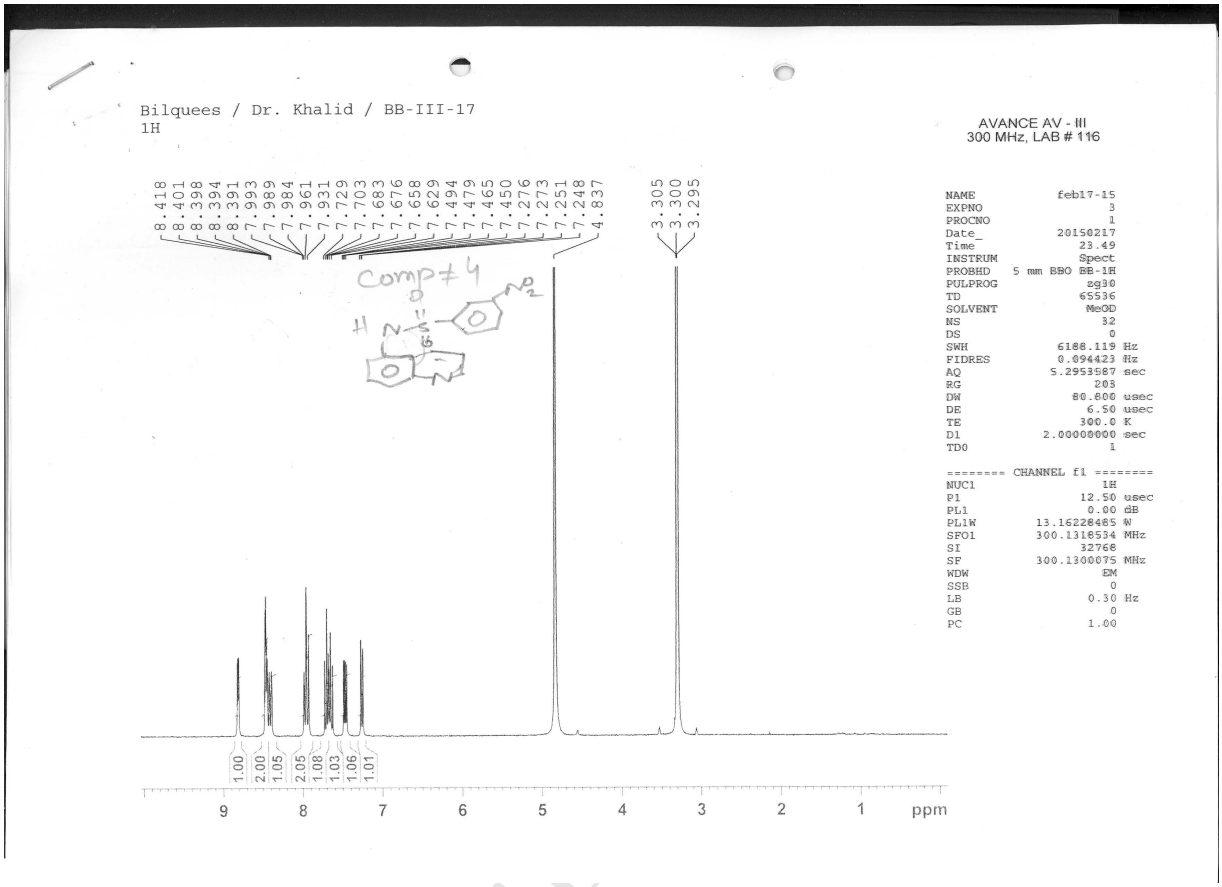
**Research Highlight**

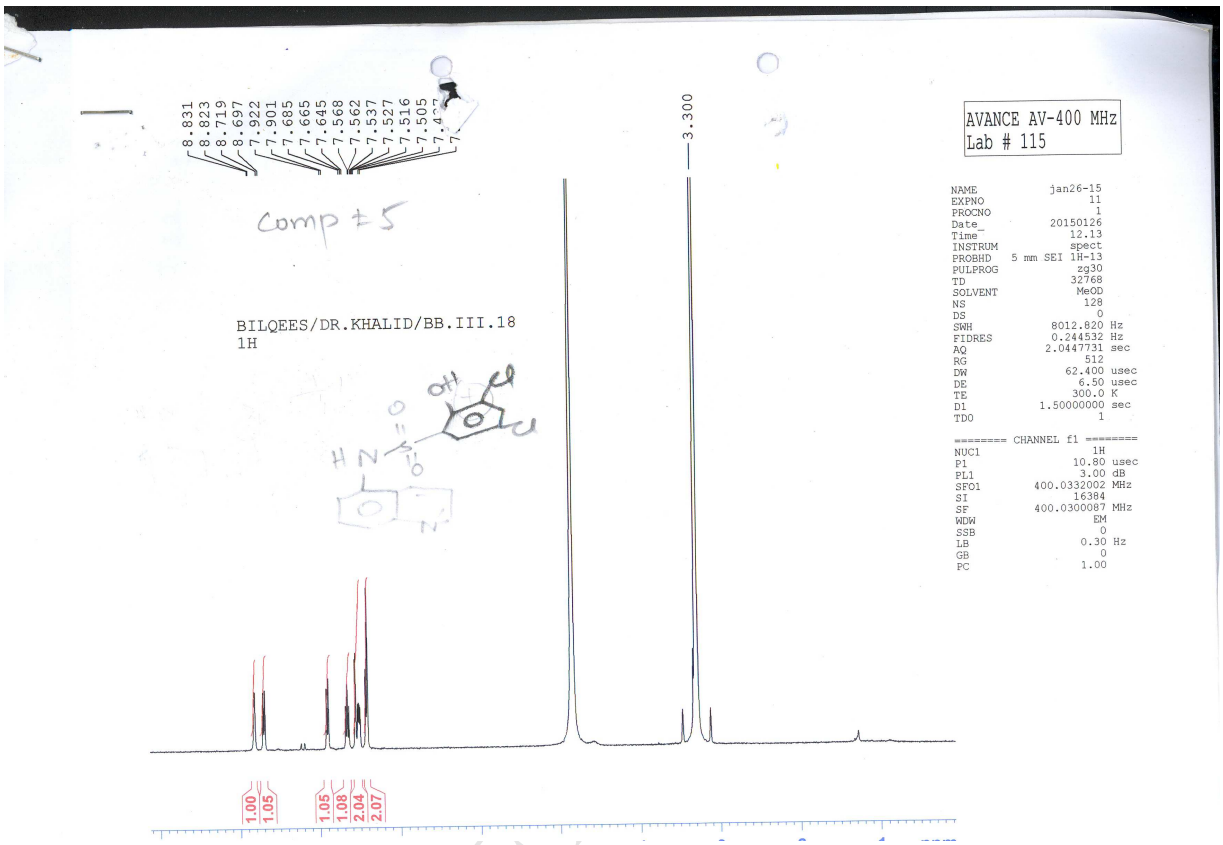
- Syntheses of sulfonamide and sulfonate derivatives of quinolines have been carried out.
- All synthetic compounds were characterized by spectroscopic techniques.
- *β*-Glucuronidase inhibitory of synthetic compounds has been carried out.
- Docking studies of active analogs have been performed.
- Structure-activity relationship has been evaluated.

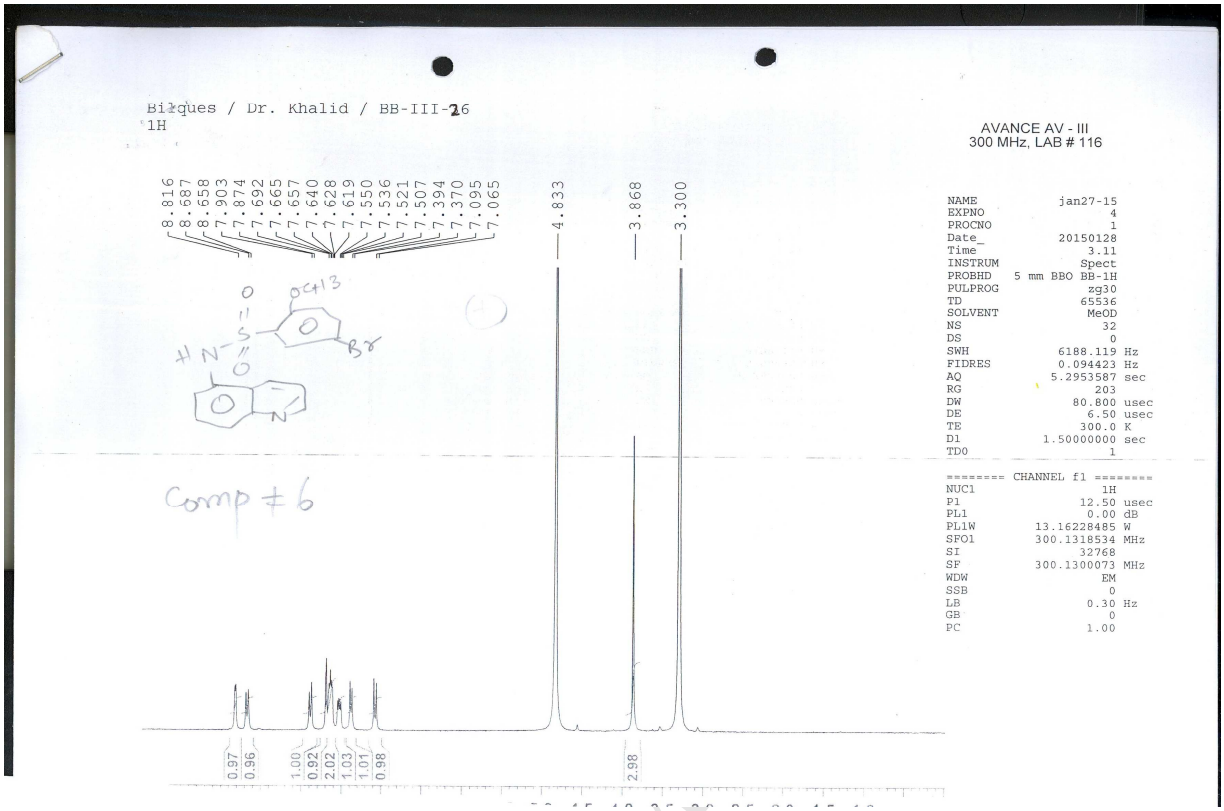


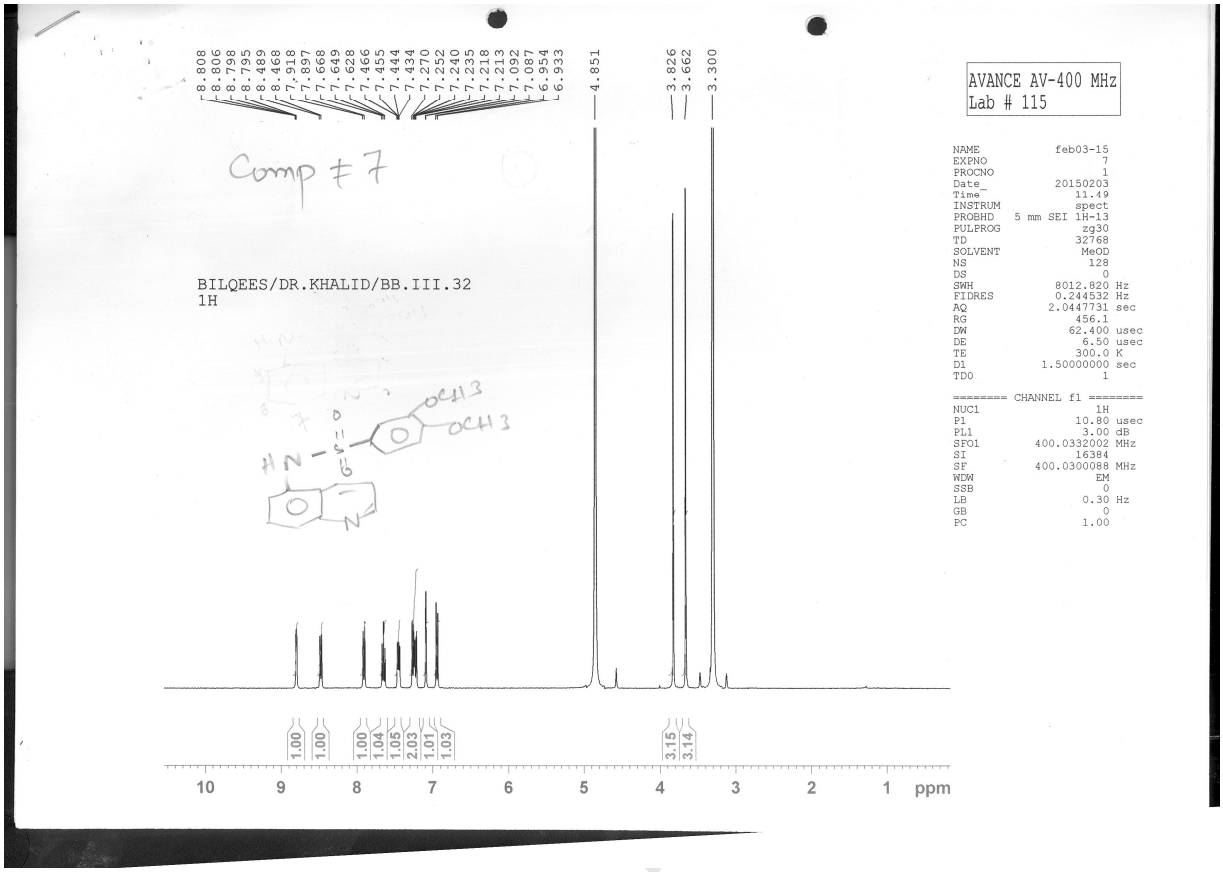


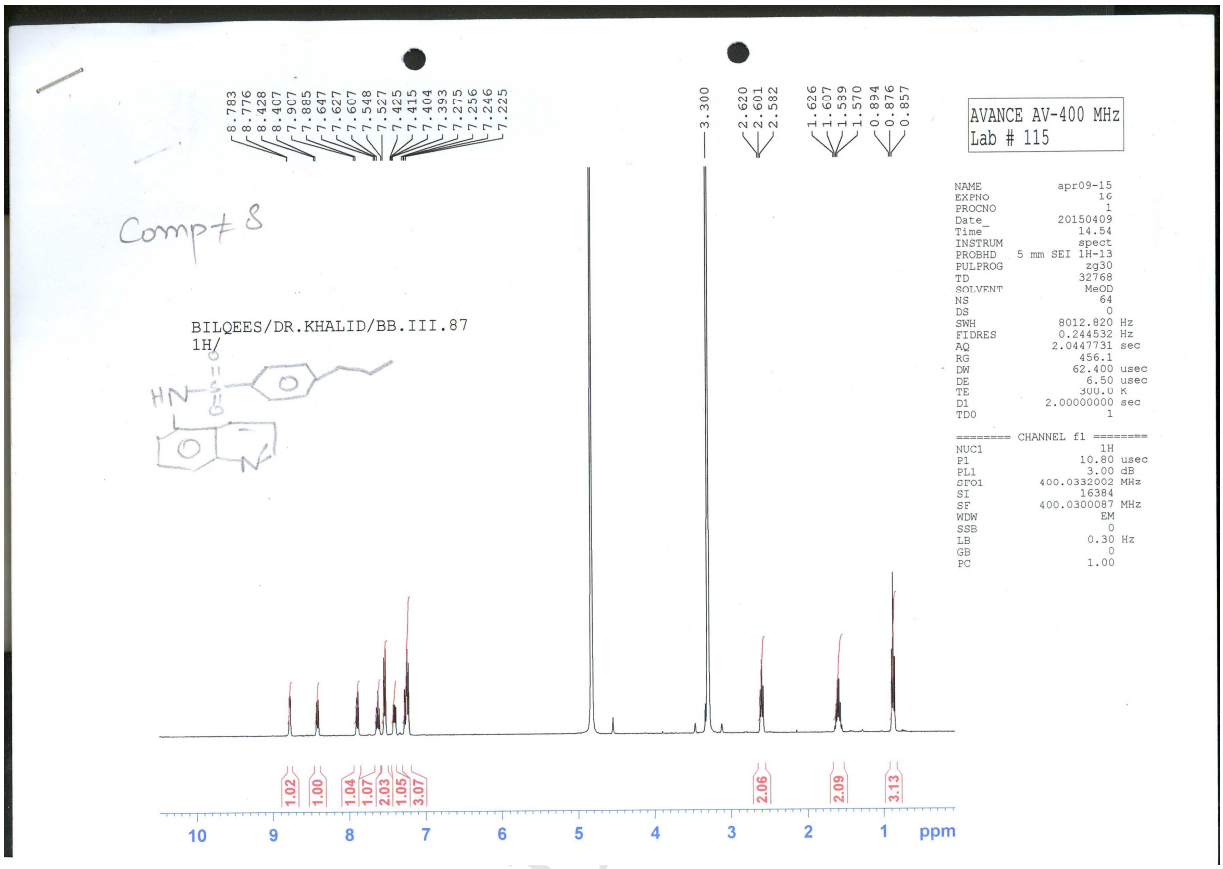


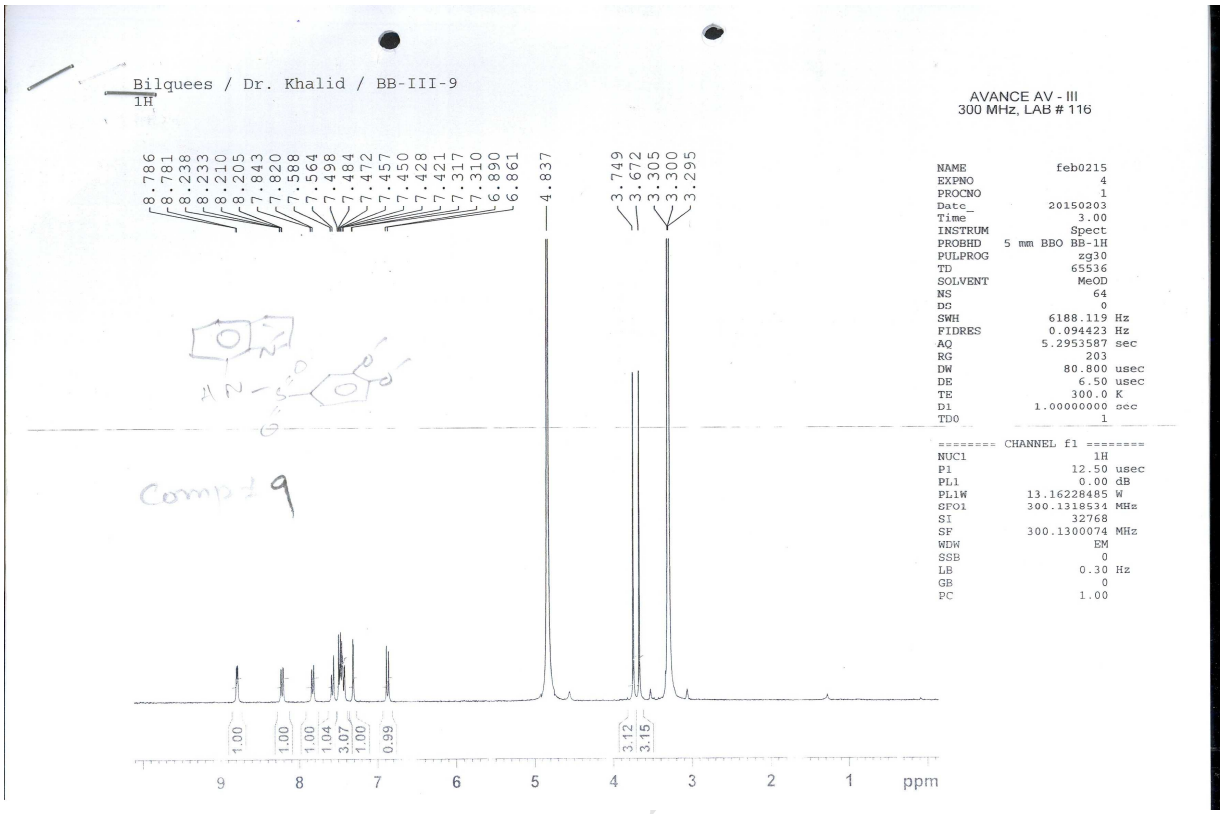


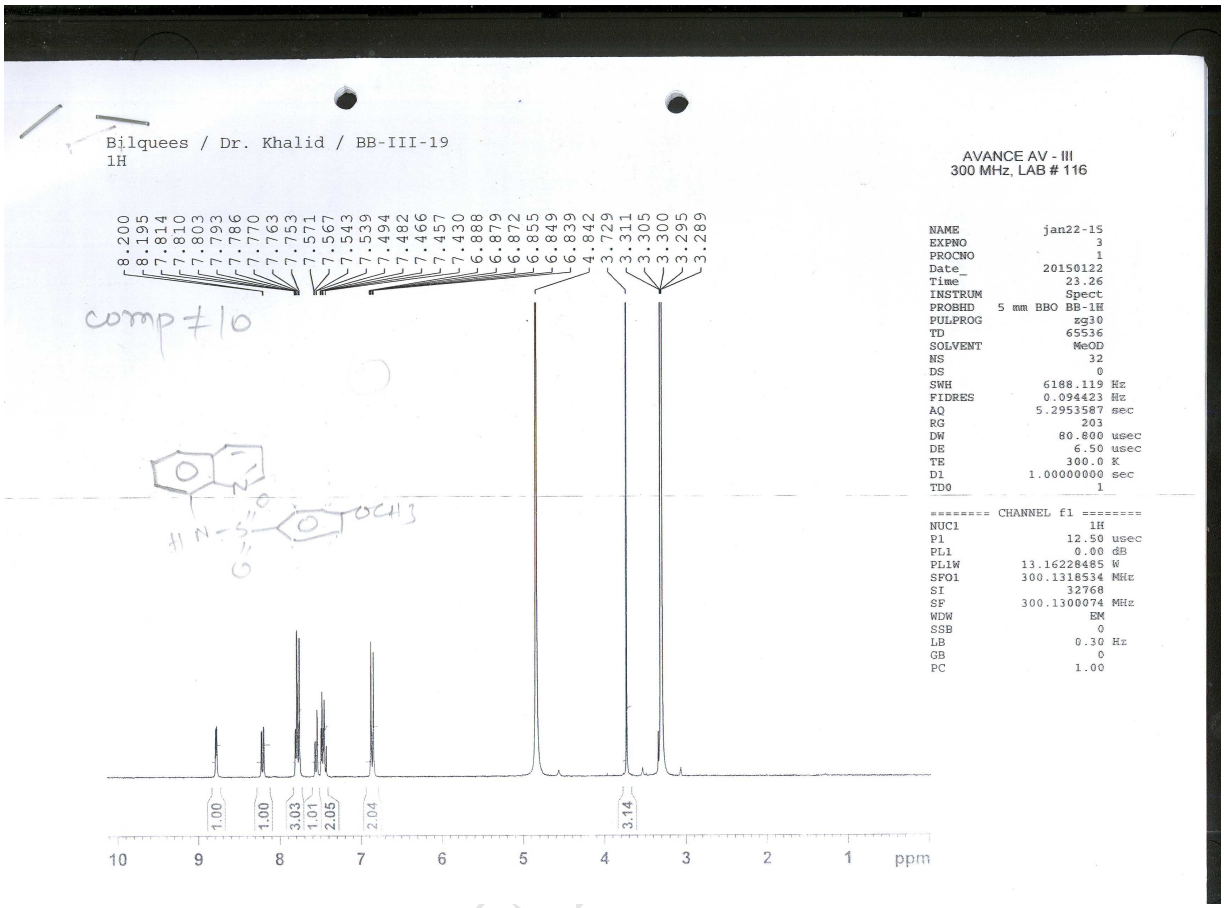


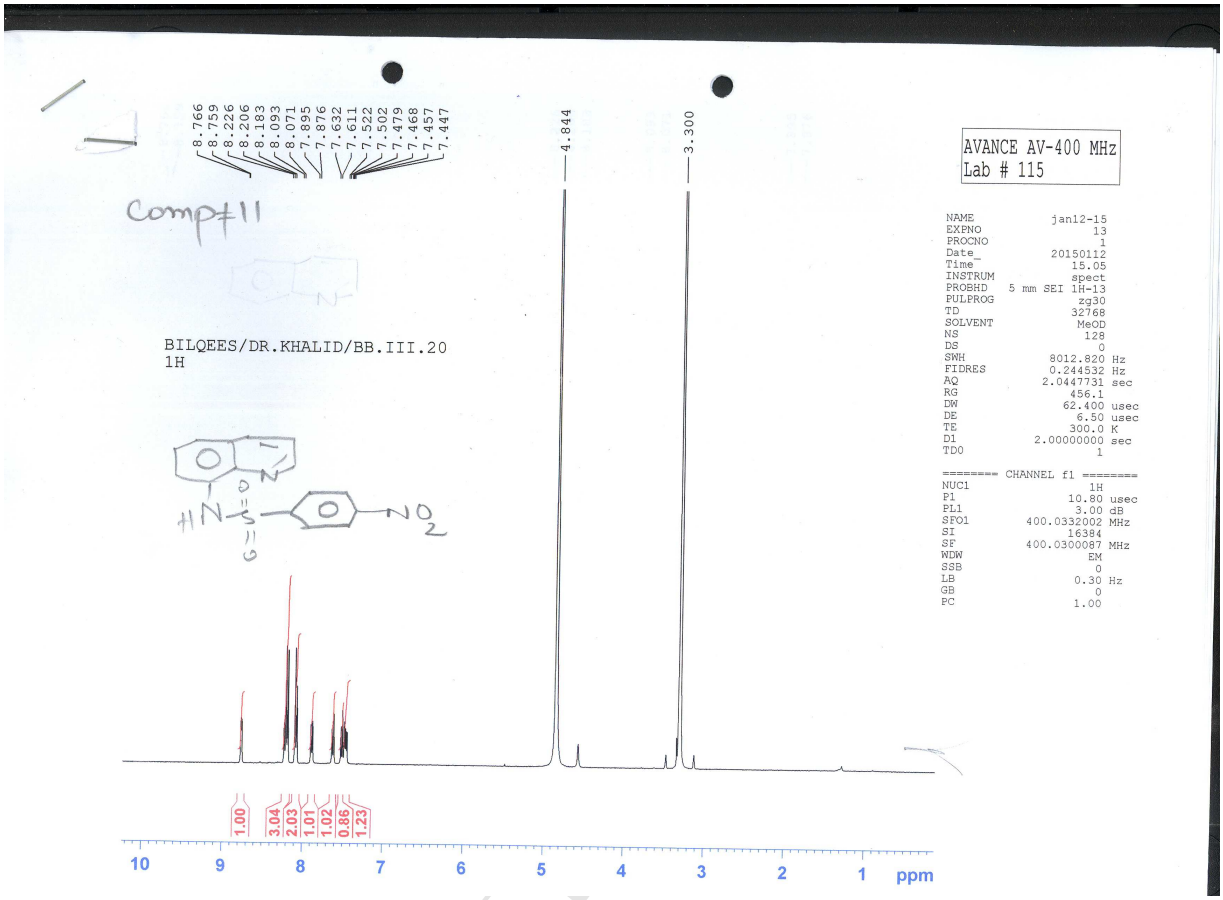


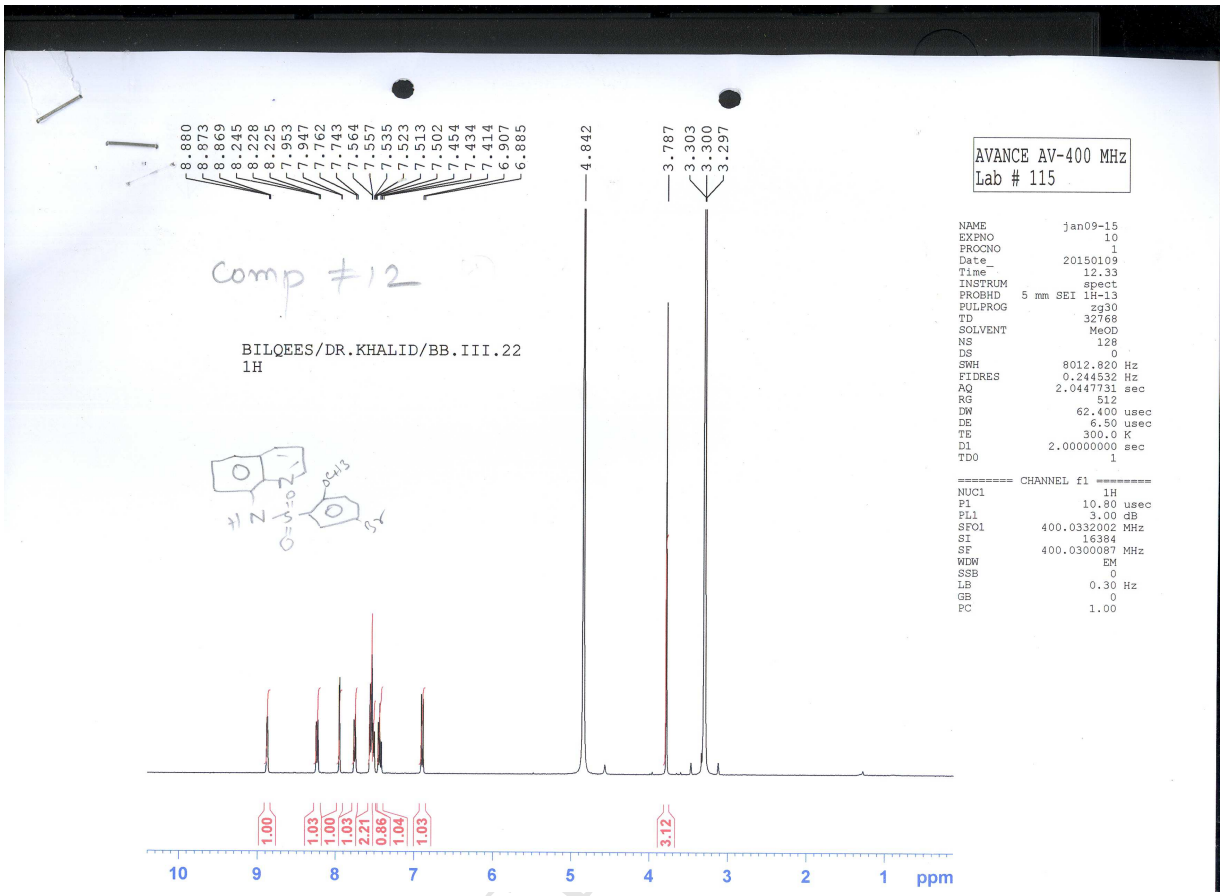


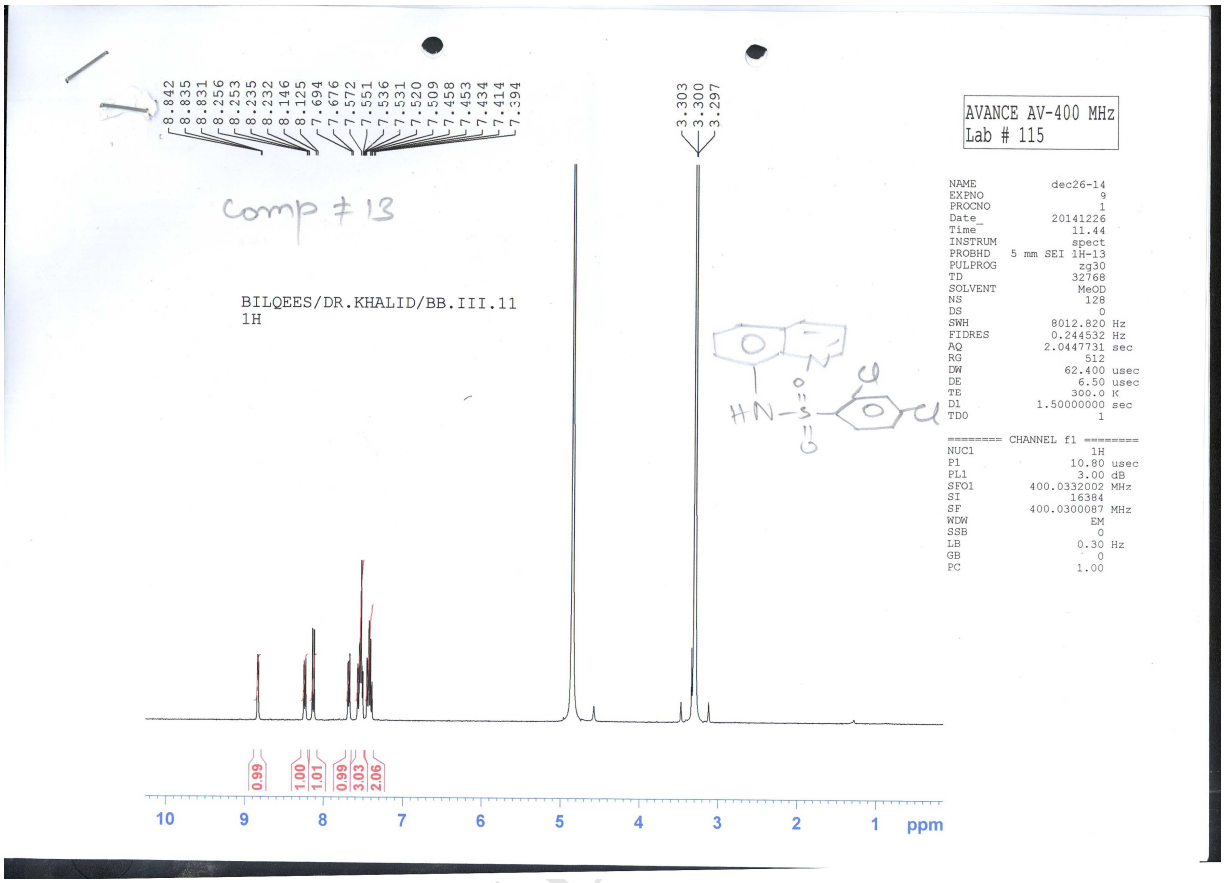


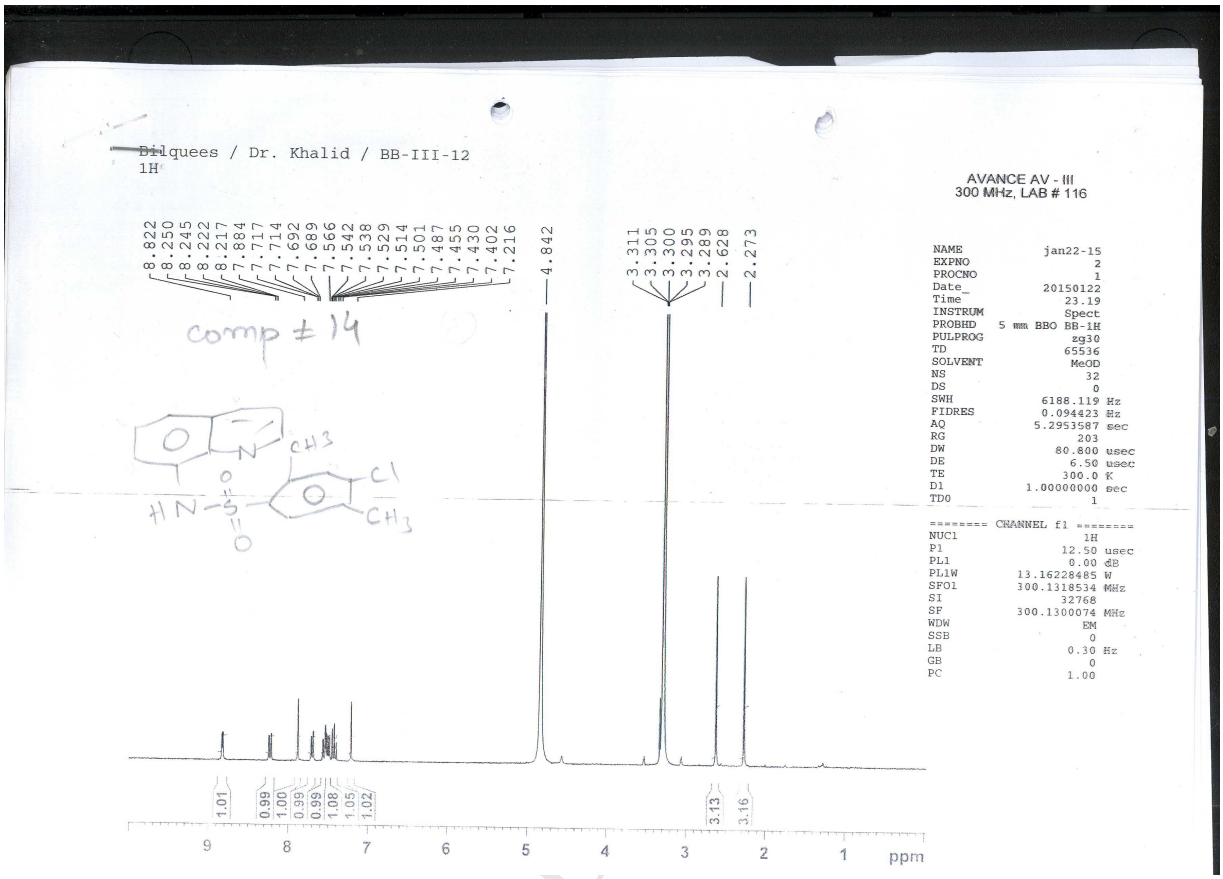


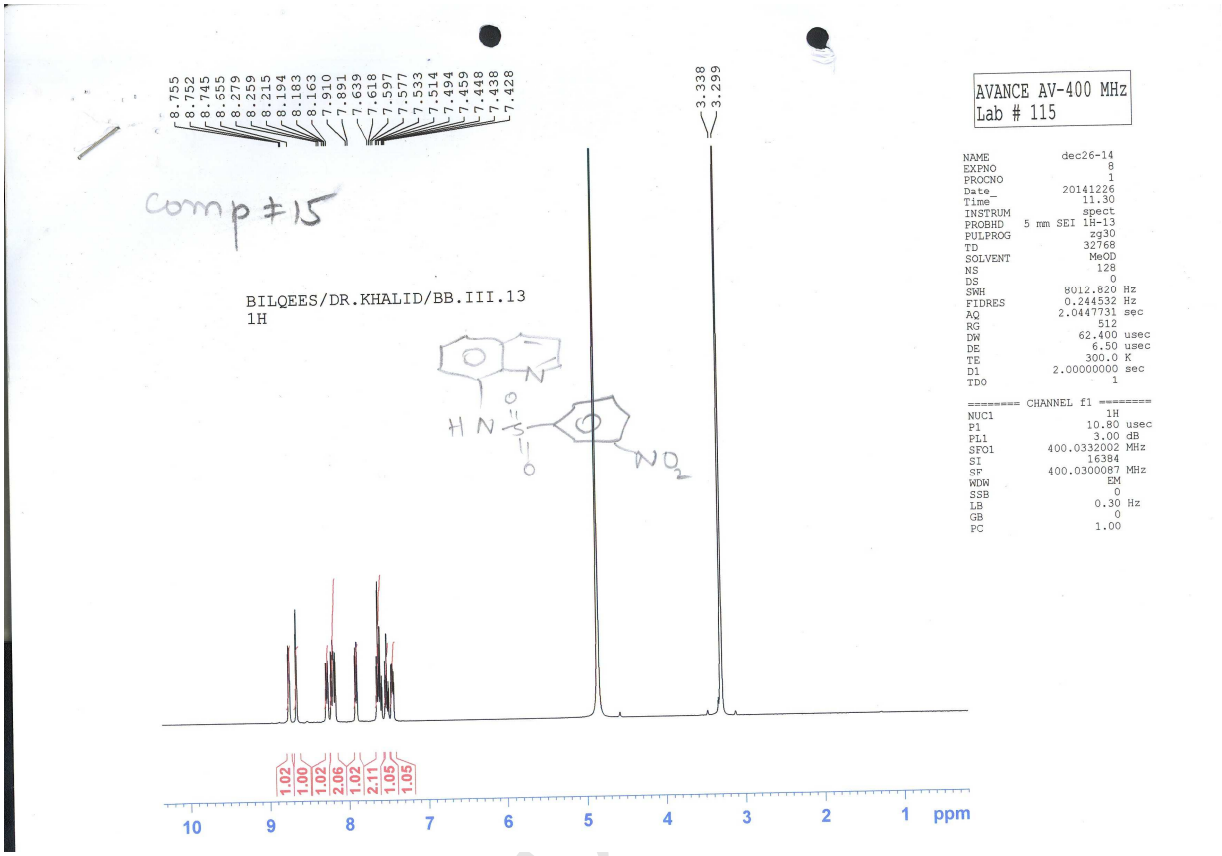


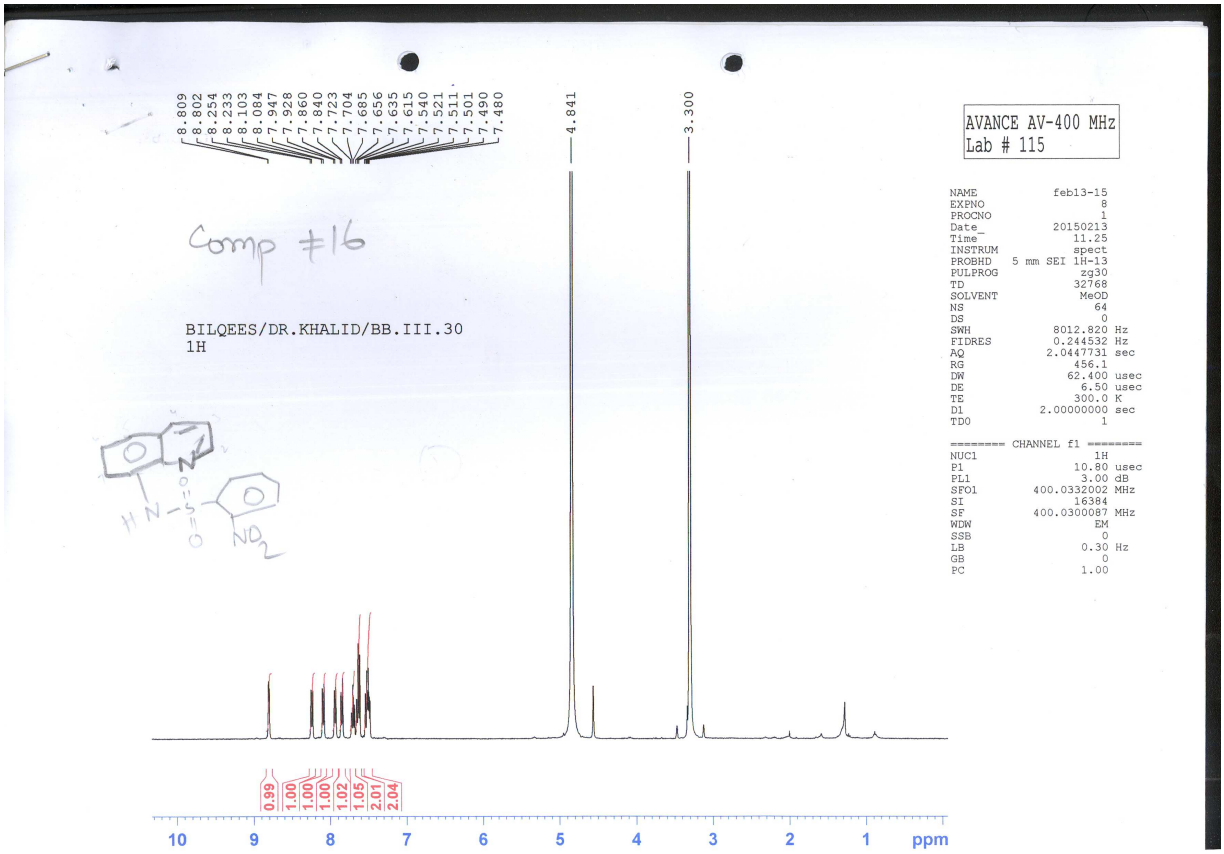


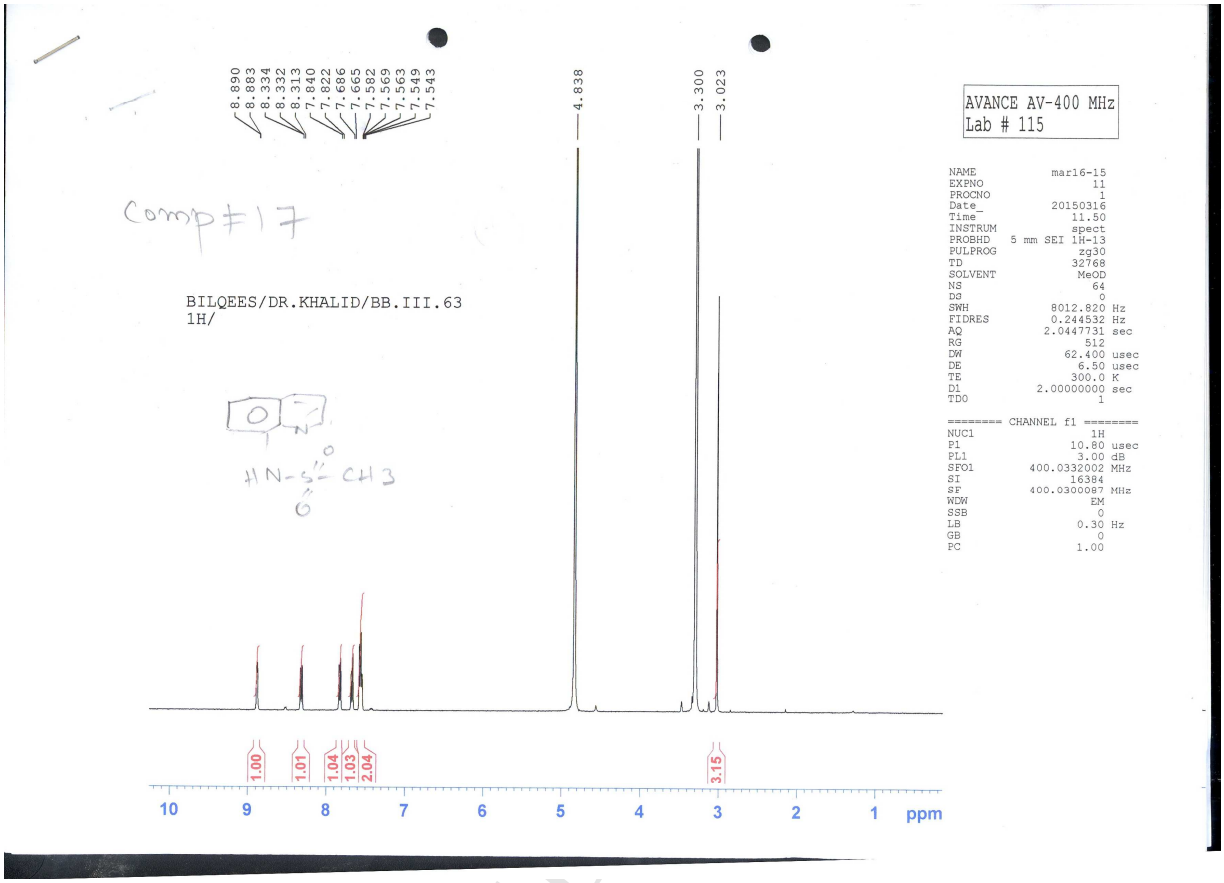


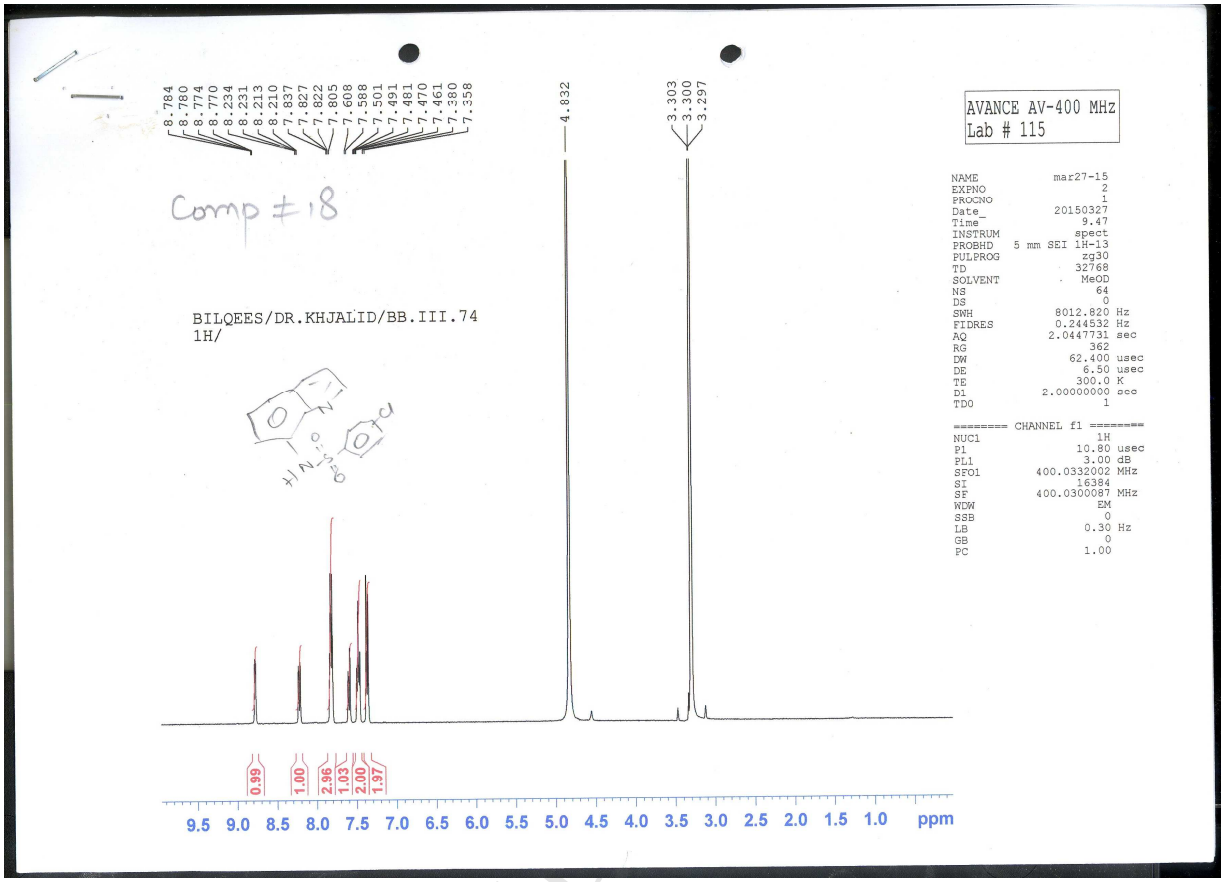


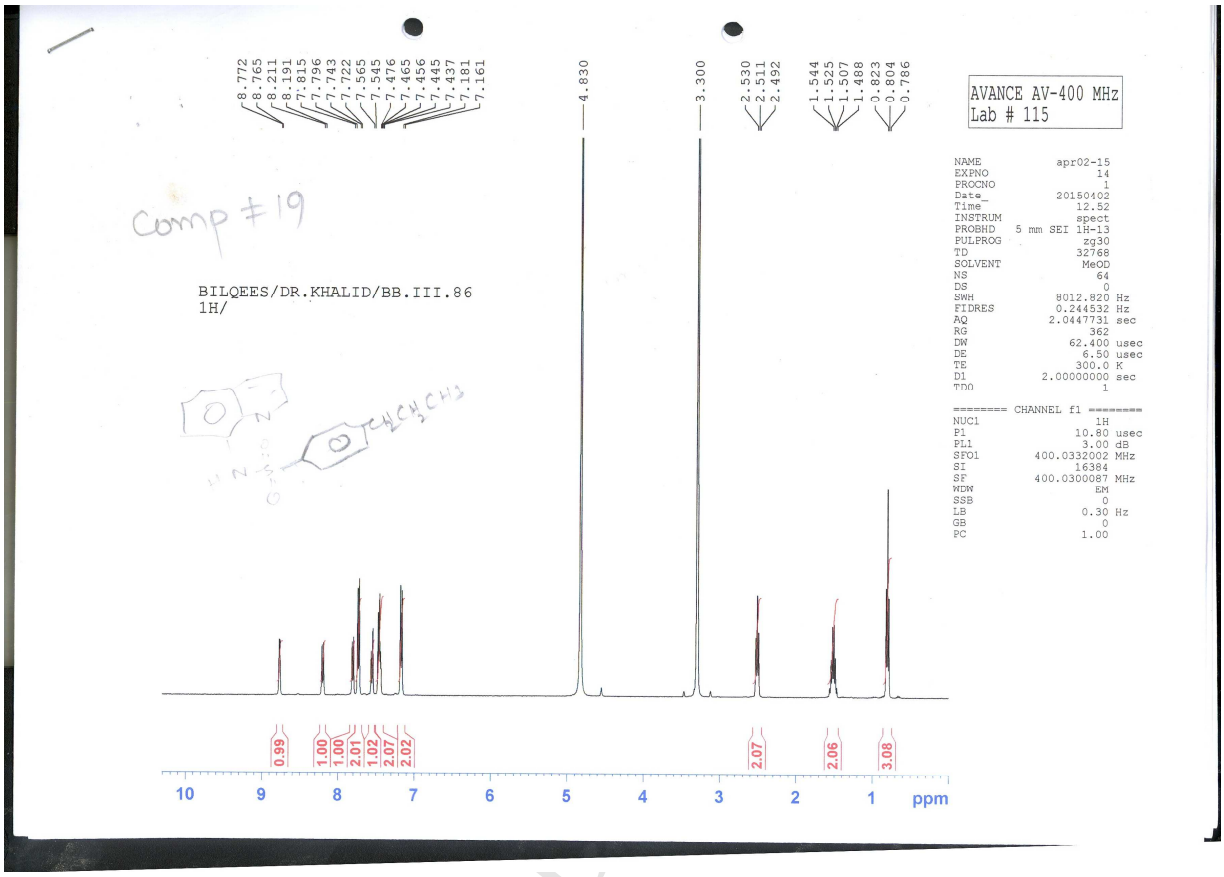


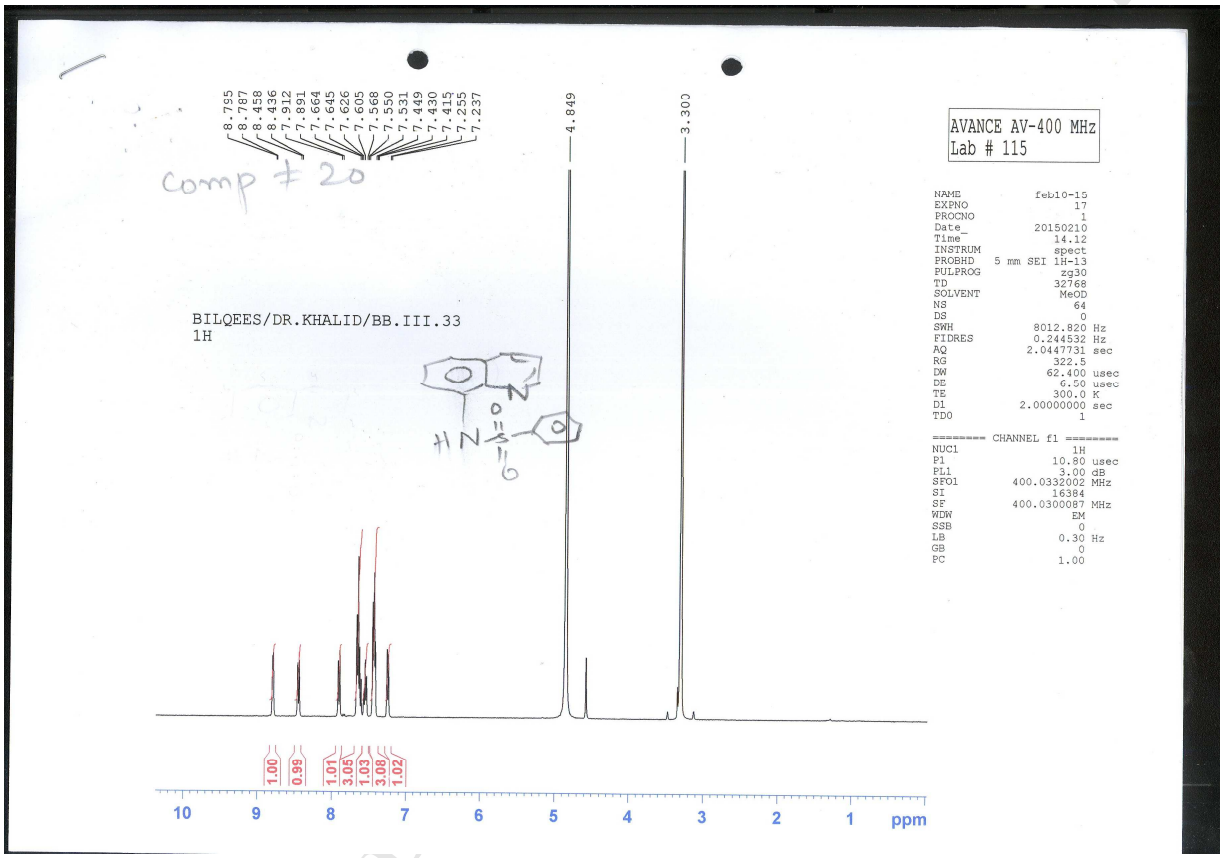








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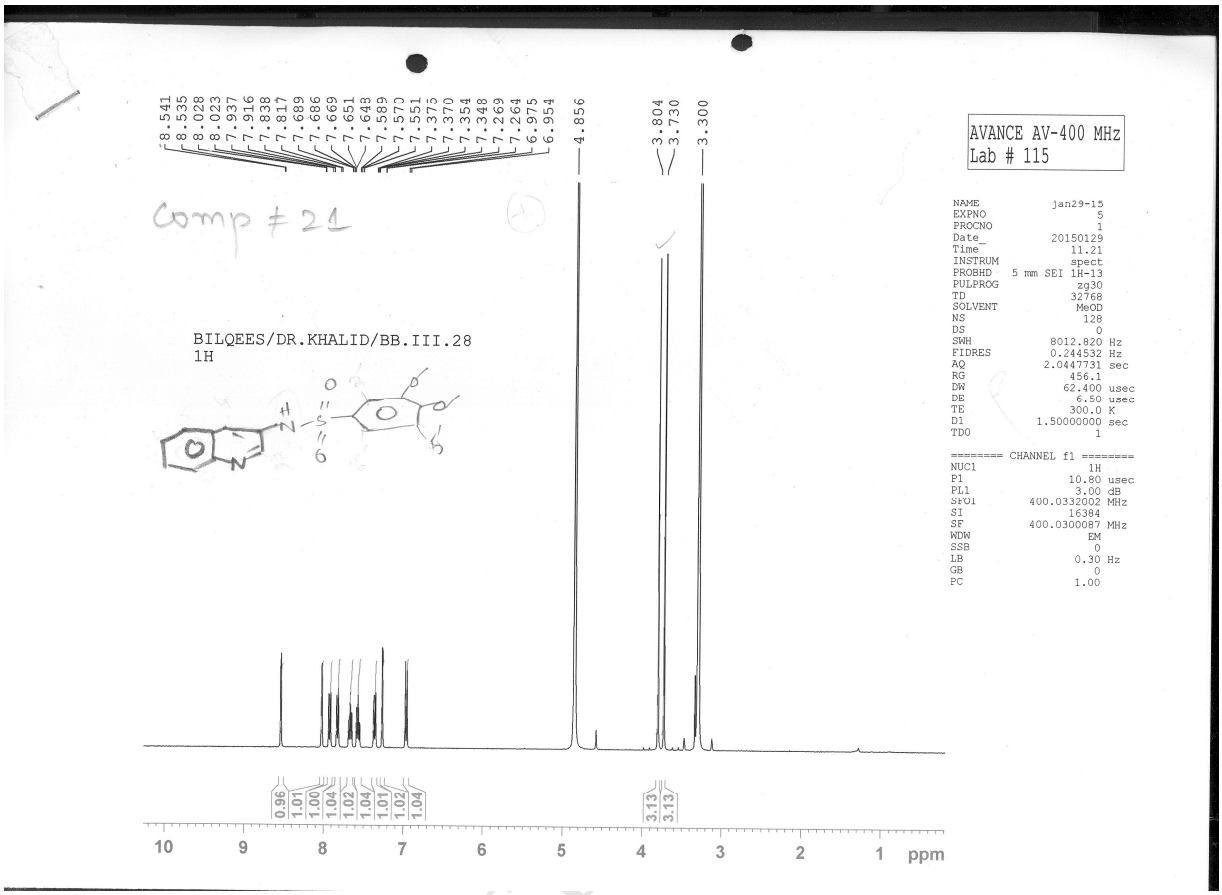
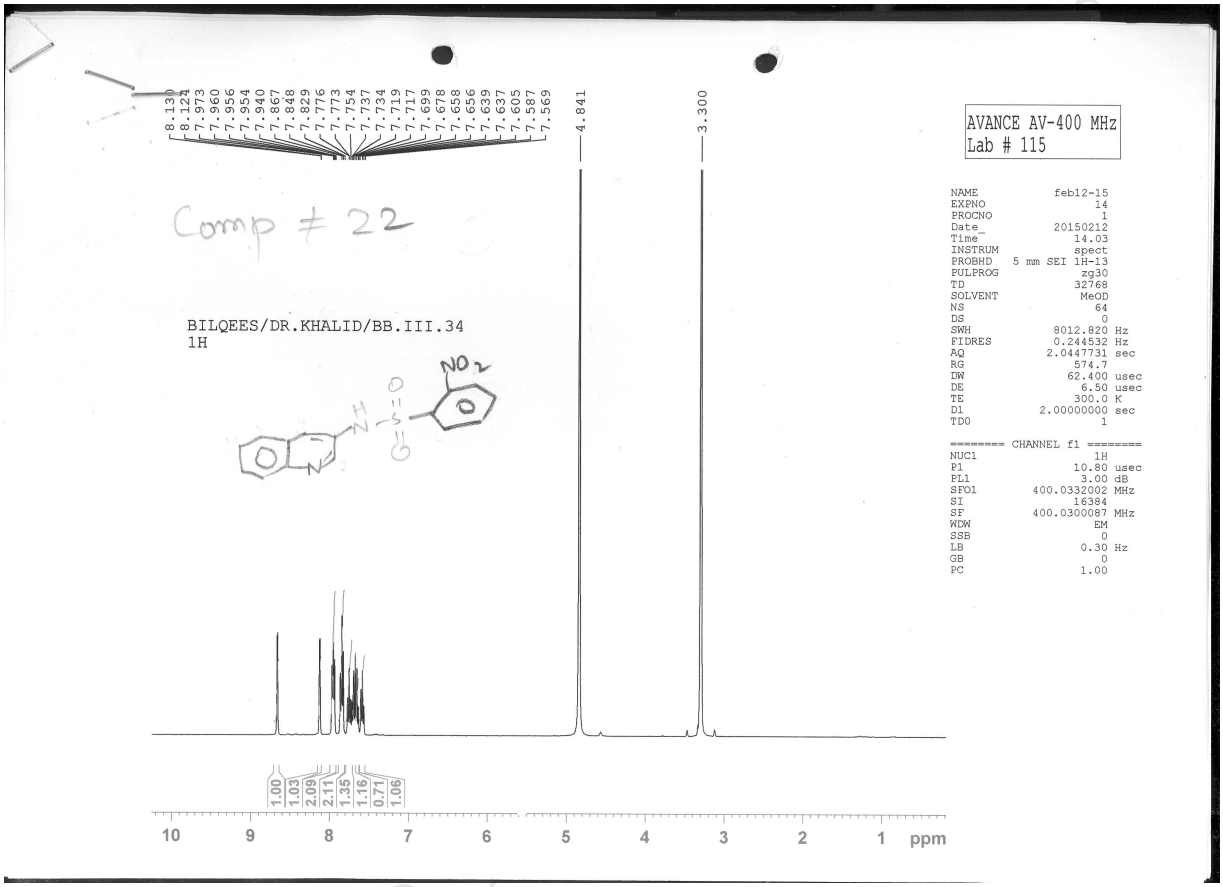
PULPROG zg30
TD 32768
SOLVENT MeOD
NS 64
DS 0
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 2.0447731 sec
RG 322.5
DW 62.400 usec
DE 6.50 usec
TE 300.0 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.80 usec
PL1 3.00 dB
SFO1 400.0332002 MHz
SI 16384
SF 400.0300087 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1.00
0.99
1.01
3.05
1.03
3.08
1.02
10
9
8
7
6
5
4
3
2
1
ppm

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8.124
7.973
7.960
7.956
7.954
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7.867
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7.754
7.737
7.734
7.719
7.717
7.699
7.678
7.658
7.656
7.639
7.637
7.605
7.587
7.569
4.841
3.300
AVANCE AV-400 MHz
Lab # 115
Comp # 22
BILQEES/DR.KHALID/BB.III.34
1H
NO2
NAME feb12-15
EXPNO 14
PROCNO 1
Date_ 20150212
Time 14.03
INSTRUM spect
PROBHD 5 mm SEI 1H-13
PULPROG zg30
TD 32768
SOLVENT MeOD
NS 64
DS 0
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 2.0447731 sec
RG 574.7
DW 62.400 usec
DE 6.50 usec
TE 300.0 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.80 usec
PL1 3.00 dB
SFO1 400.0332002 MHz
SI 16384
SF 400.0300087 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1.00
1.03
2.09
2.11
1.35
1.16
0.71
1.06
10
9
8
7
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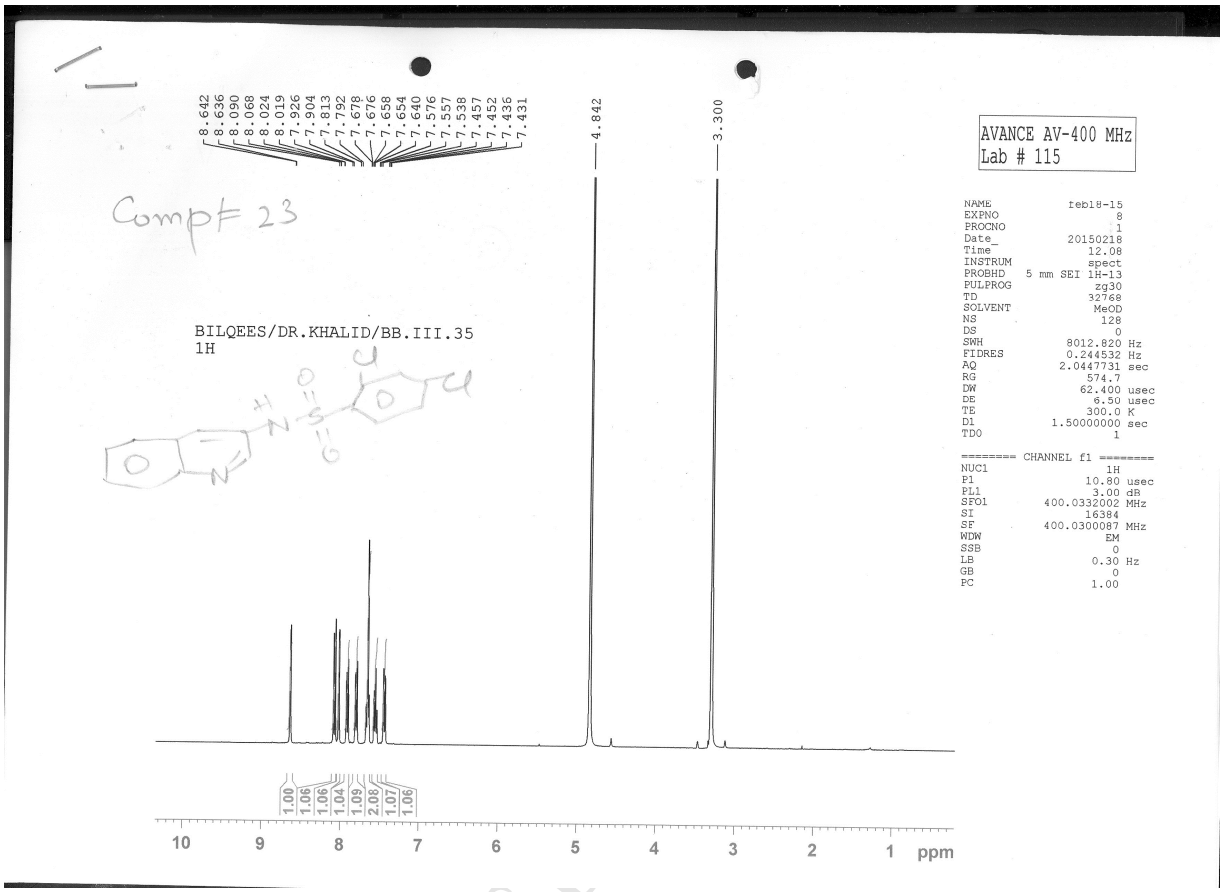
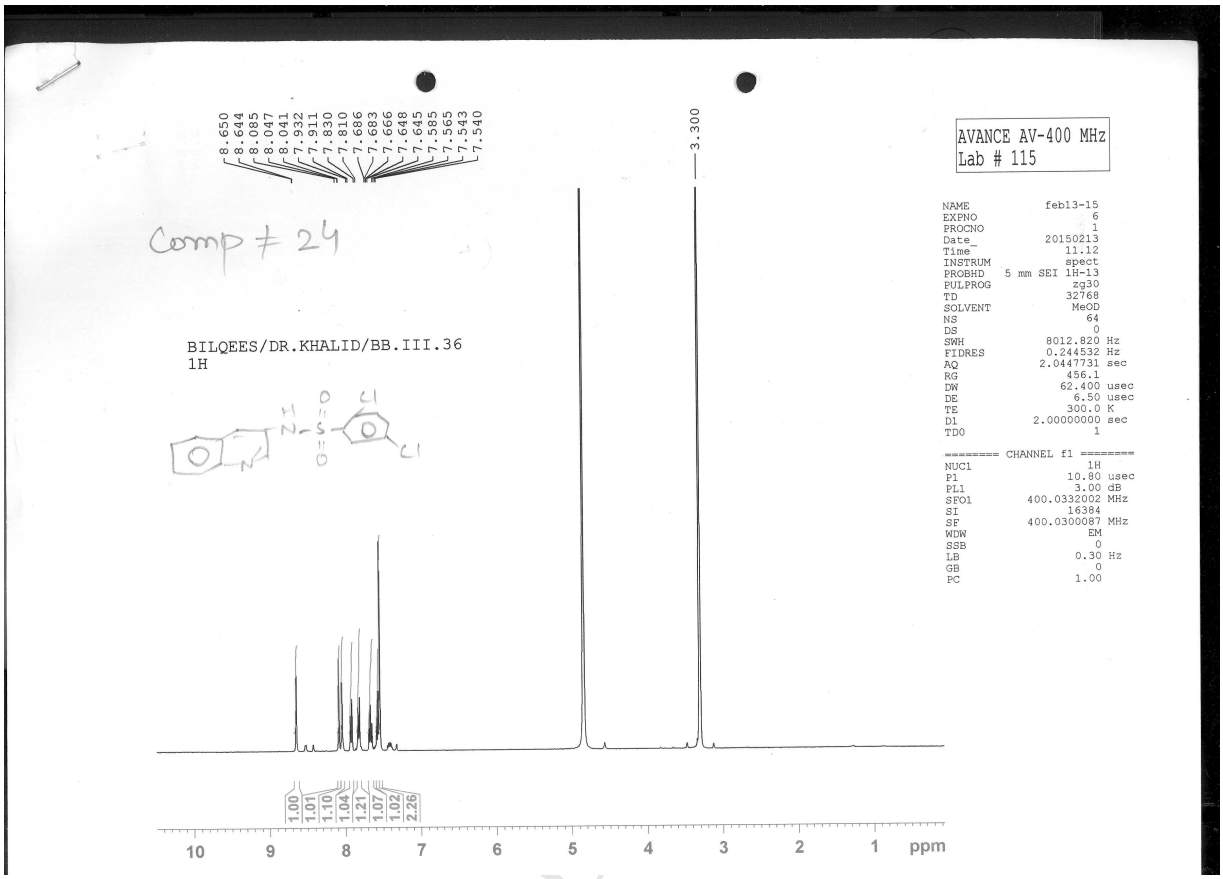
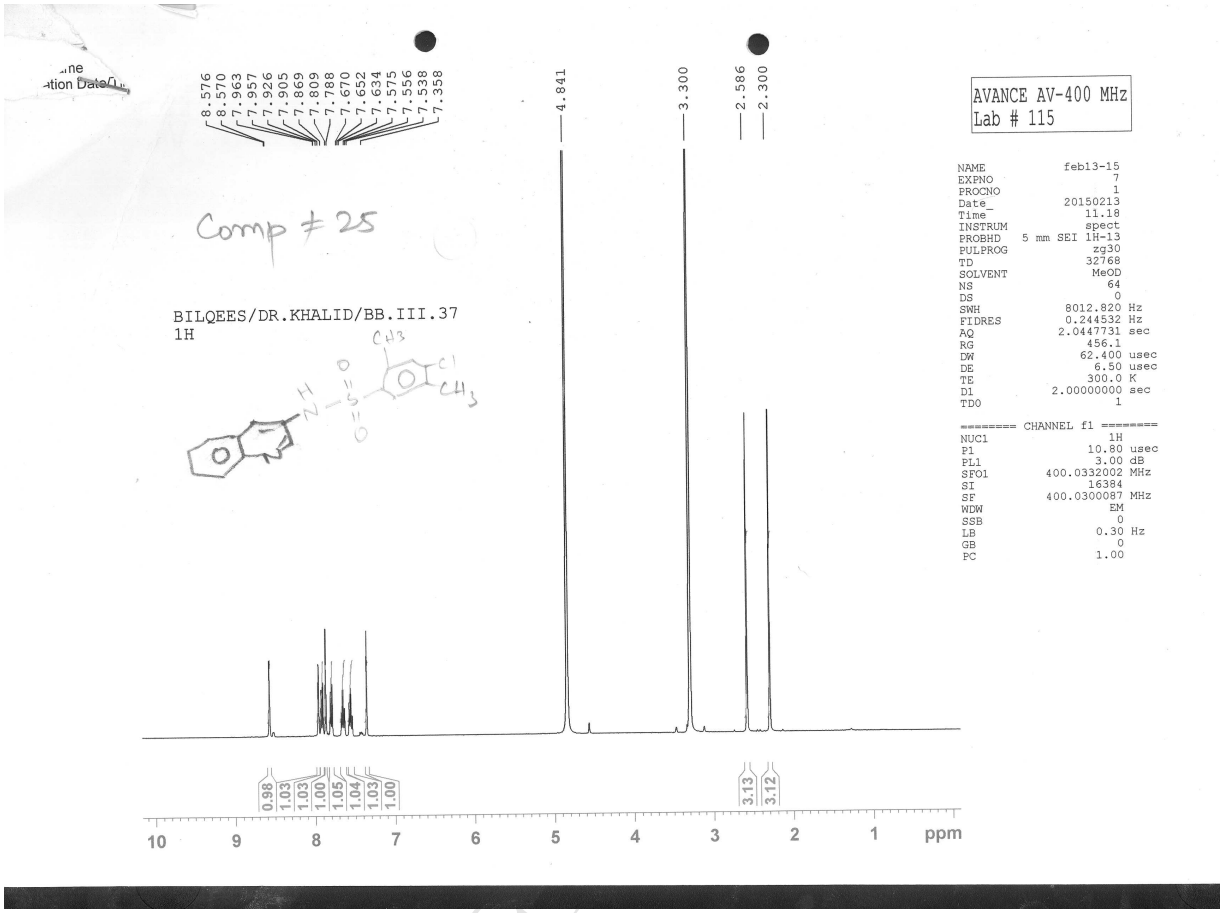
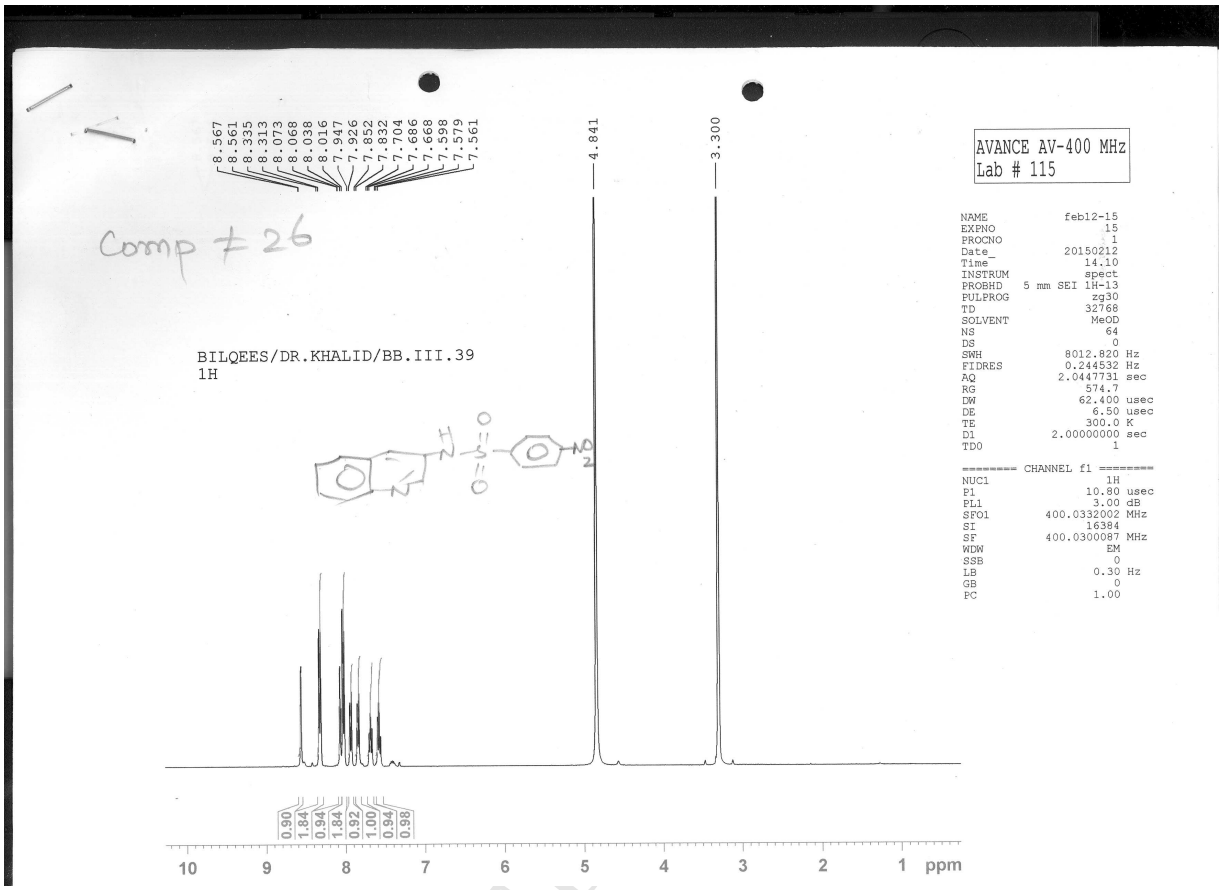
5
4
3
2
1
ppm





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8.313
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8.068
8.038
8.016
7.947
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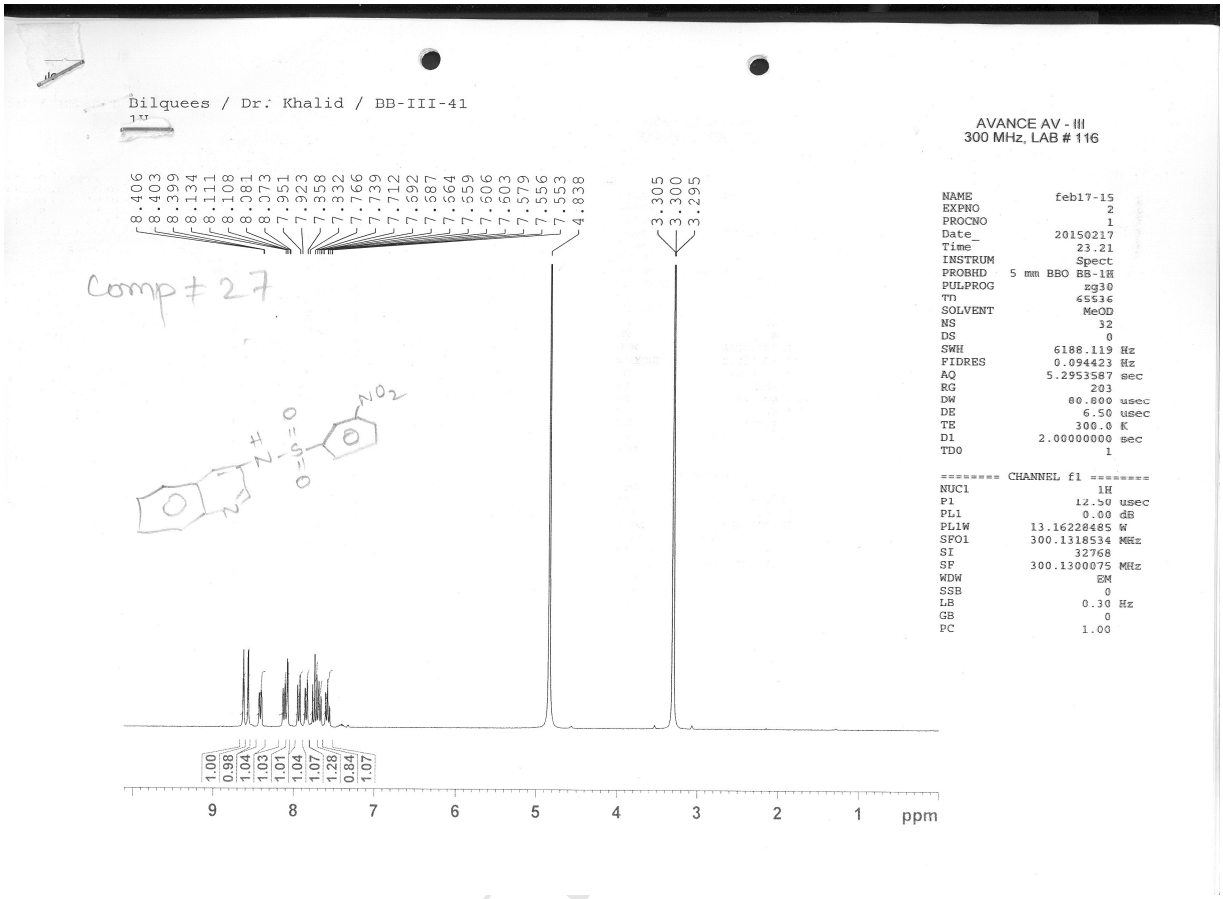
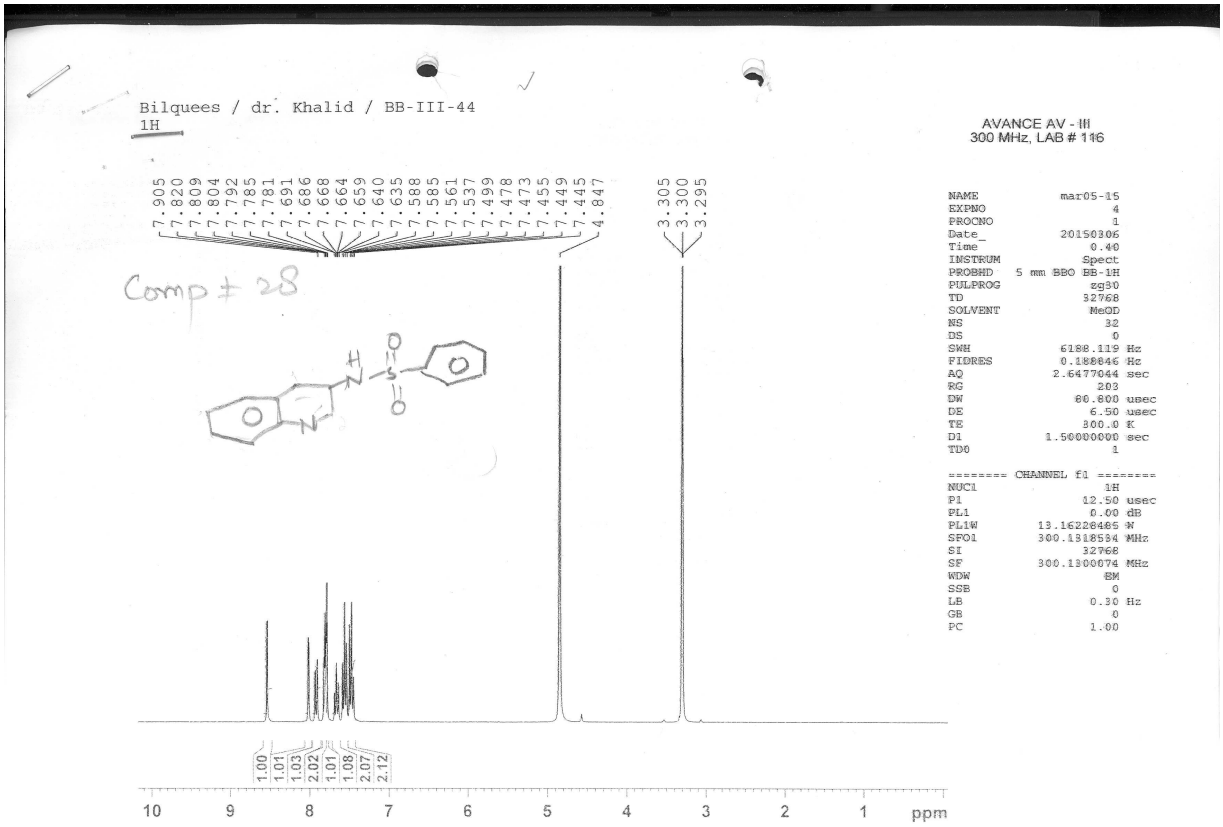
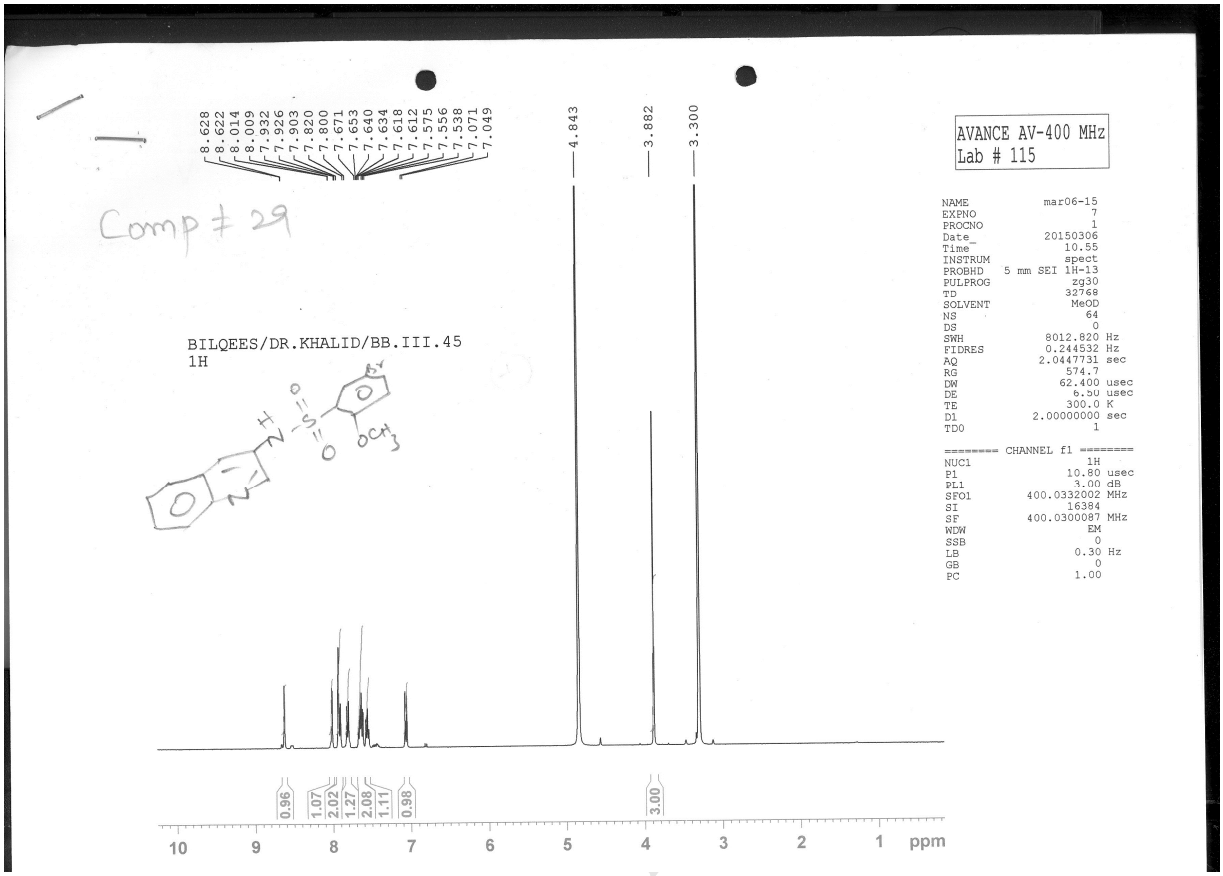
7.852
7.832
7.704
7.686
7.668
7.598
7.579
7.561
4.841
3.300
Comp # 26
BILQEES/DR.KHALID/BB.III.39
1H
AVANCE AV-400 MHz
Lab # 115
NAME feb12-15
EXPNO 15
PROCNO 1
Date_ 20150212
Time 14.10
INSTRUM spect
PROBHD 5 mm SEI 1H-13
PULPROG zg30
TD 32768
SOLVENT MeOD
NS 64
DS 0
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 2.0447731 sec
RG 574.7
DW 62.400 usec
DE 6.50 usec
TE 300.0 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.80 usec
PL1 3.00 dB
SFO1 400.0332002 MHz
SI 16384
SF 400.0300087 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
0.90
1.84
0.94
1.84
0.92
1.00
0.94
0.98
10
9
8
7
6
5
4
3
2
1
ppm



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8.622
8.014
8.009
7.932
7.926
7.903
7.820
7.800
7.671
7.653
7.640
7.634
7.618
7.612
7.575
7.556
7.538
7.071
7.049
4.843
3.882
3.300
Comp # 29
BILQEES/DR.KHALID/BB.III.45
1H
AVANCE AV-400 MHz
Lab # 115
NAME mar06-15
EXPNO 7
PROCNO 1
Date_ 20150306
Time 10.55
INSTRUM spect
PROBHD 5 mm SEI 1H-13
PULPROG zg30
TD 32768
SOLVENT MeOD
NS 64
DS 0
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 2.0447731 sec
RG 574.7
DW 62.400 usec
DE 6.50 usec
TE 300.0 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.80 usec
PL1 3.00 dB
SFO1 400.0332002 MHz
SI 16384
SF 400.0300087 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
0.96
1.07
2.02
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0.98
3.00
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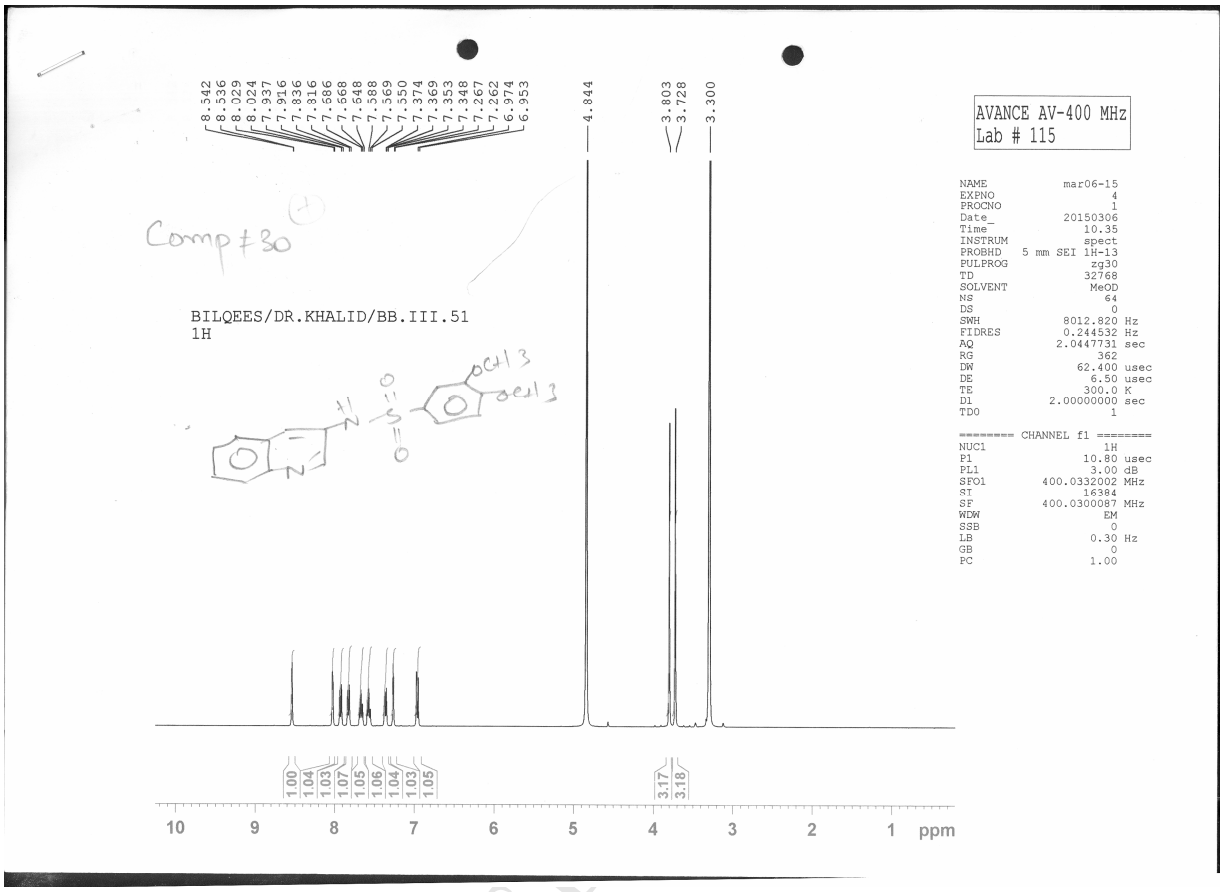
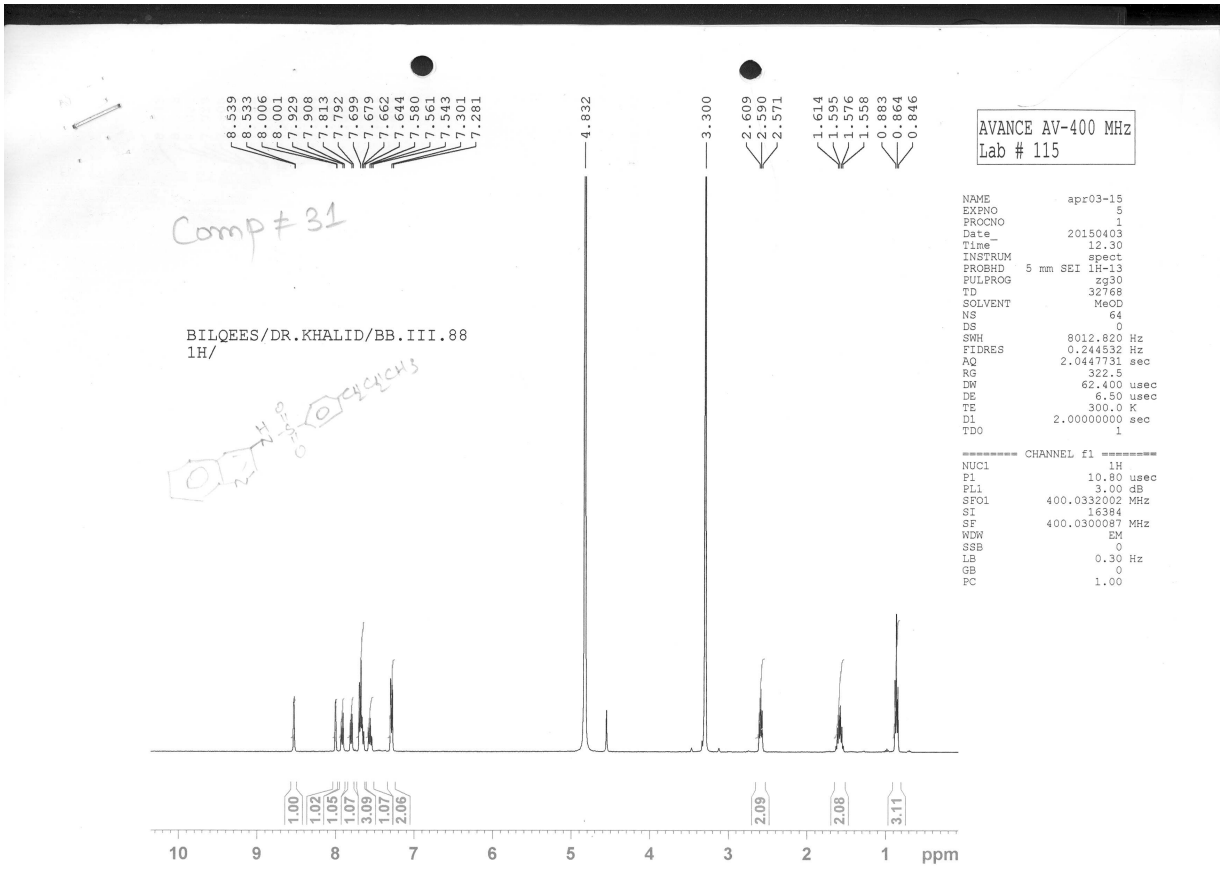
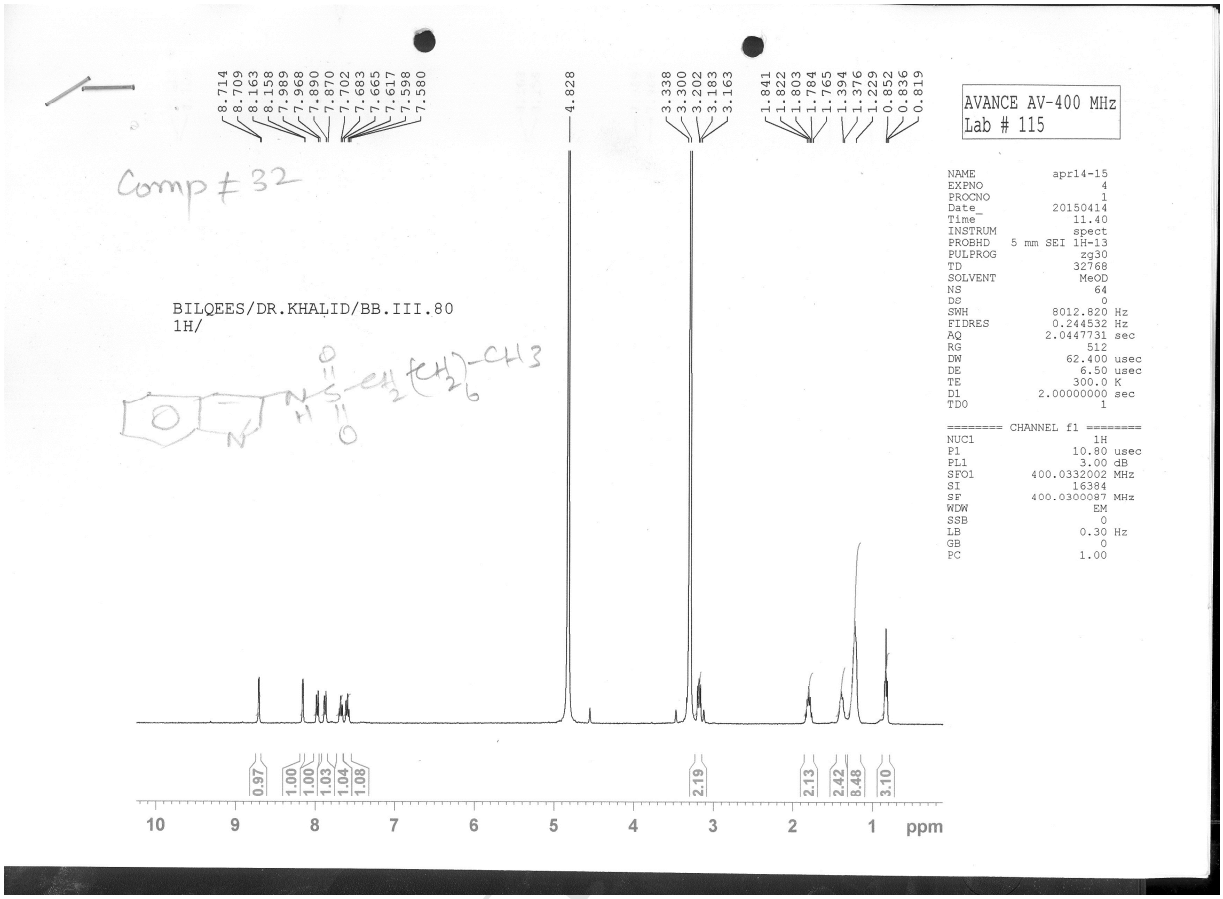
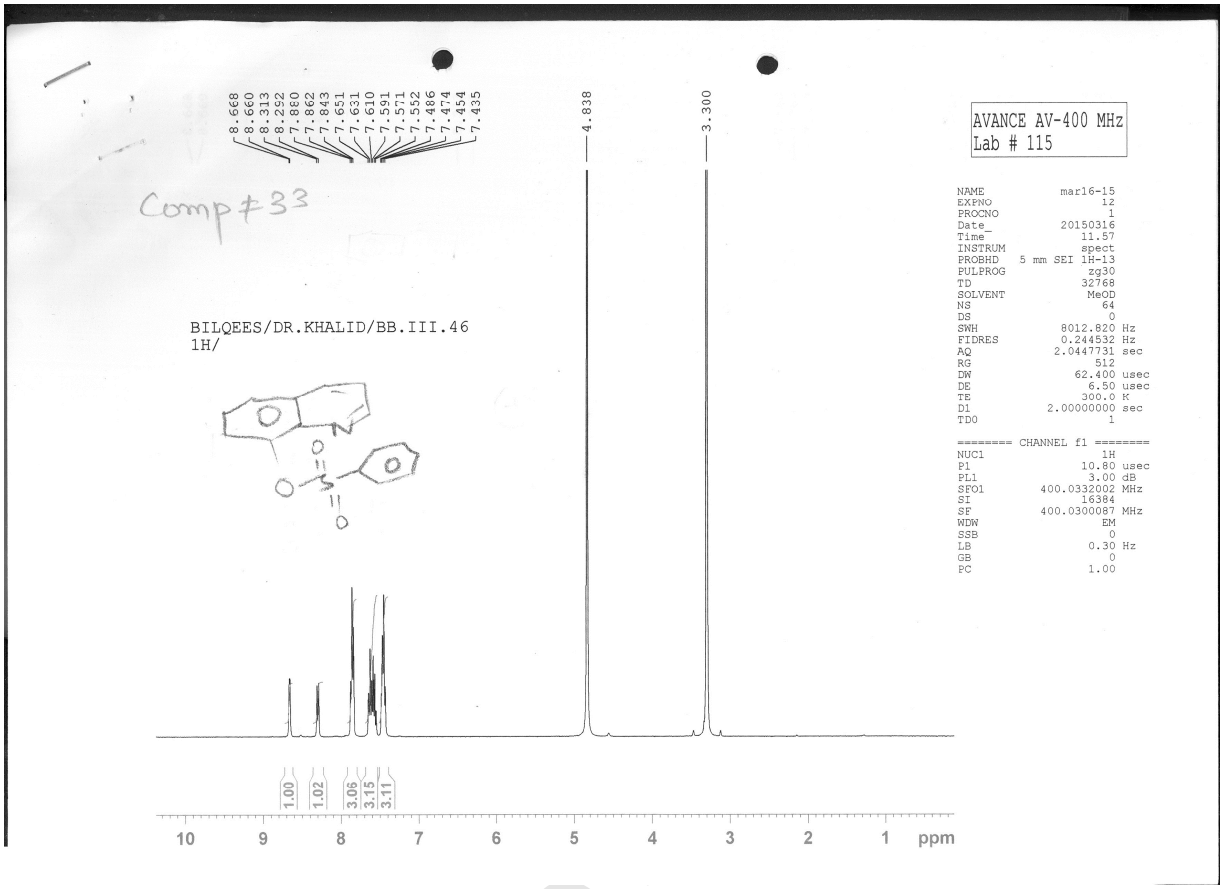
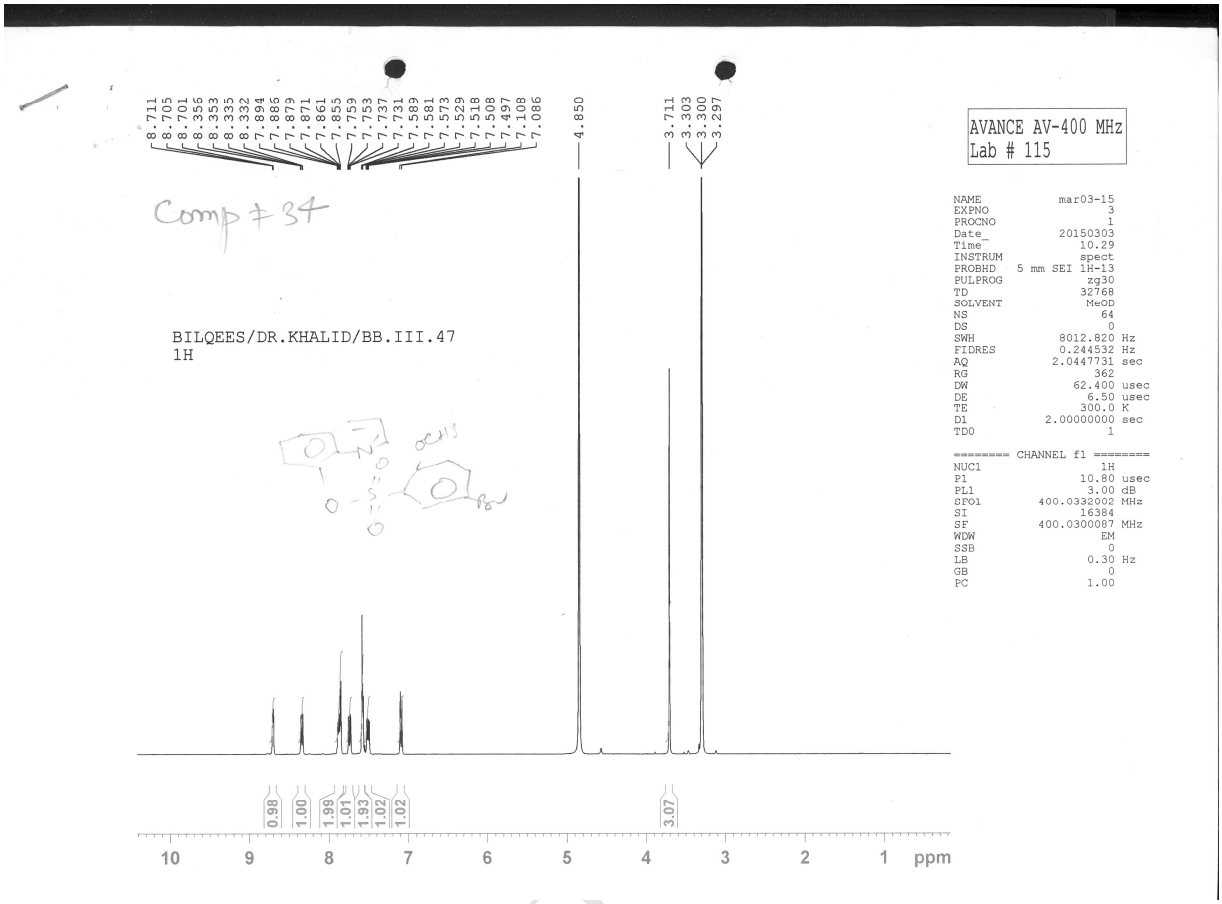
1
ppm

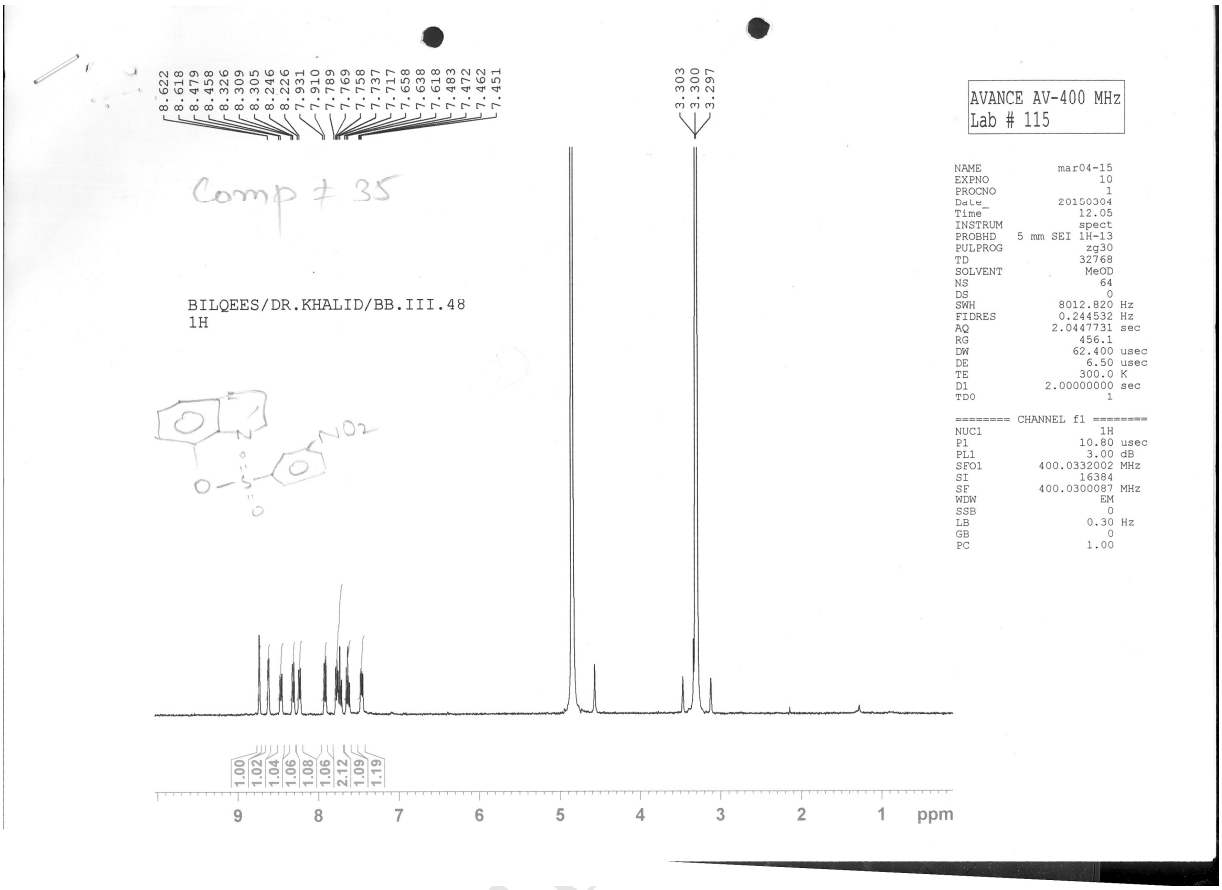


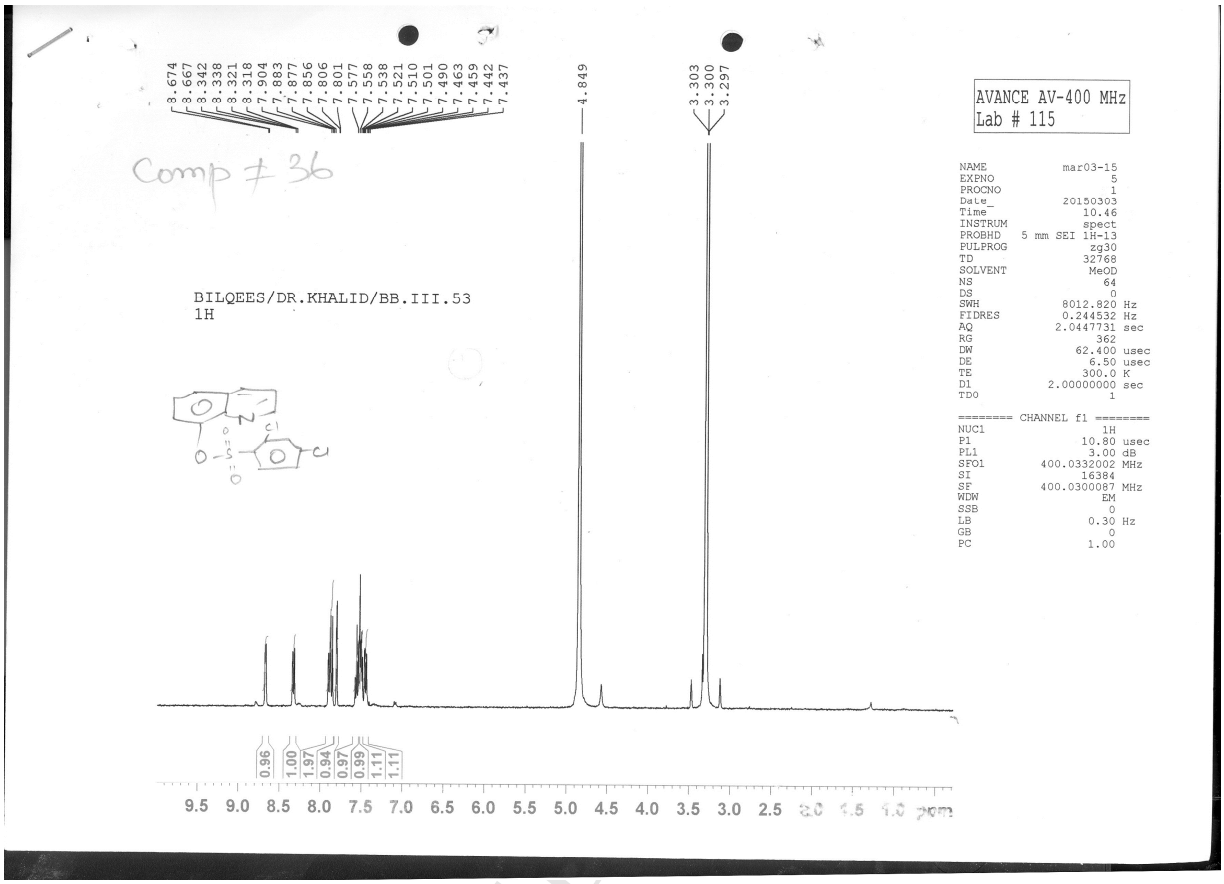


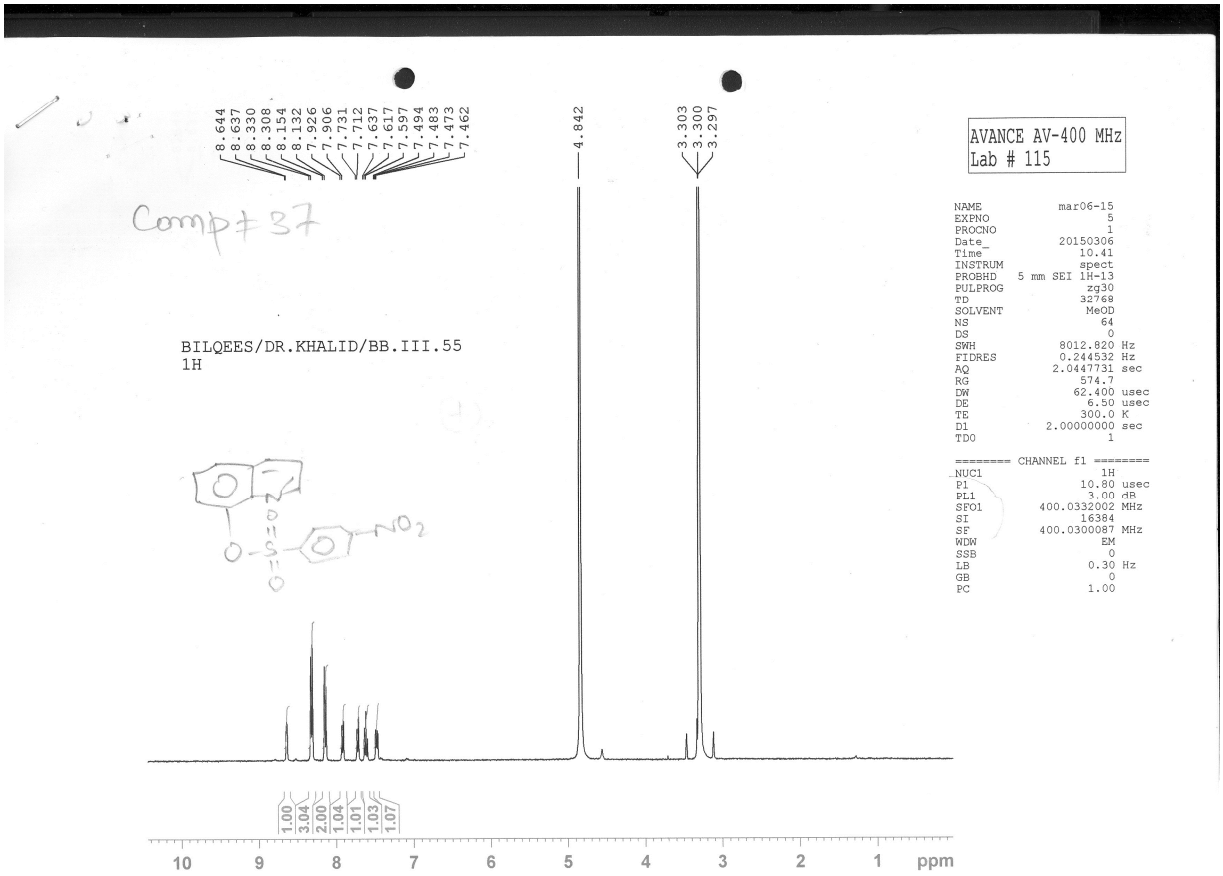


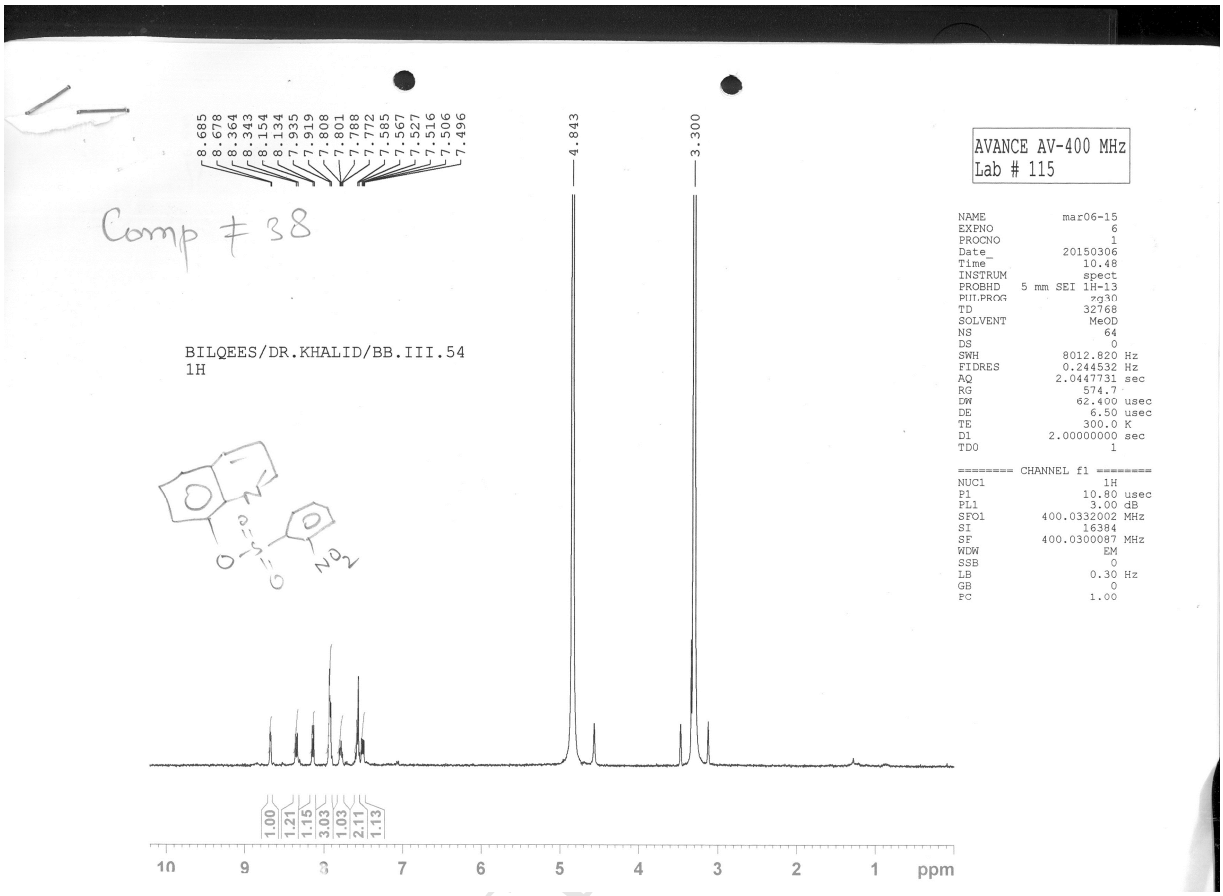


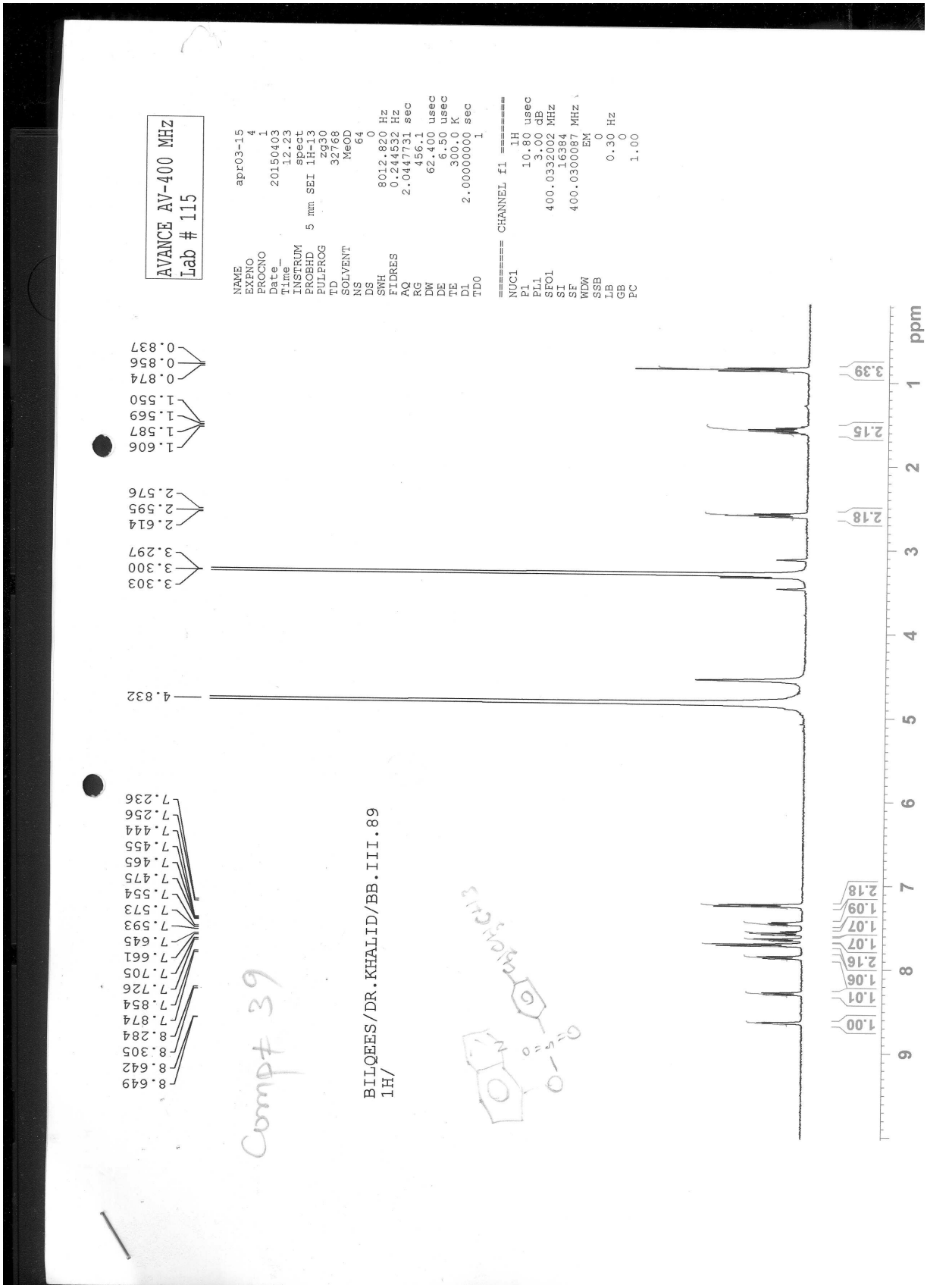


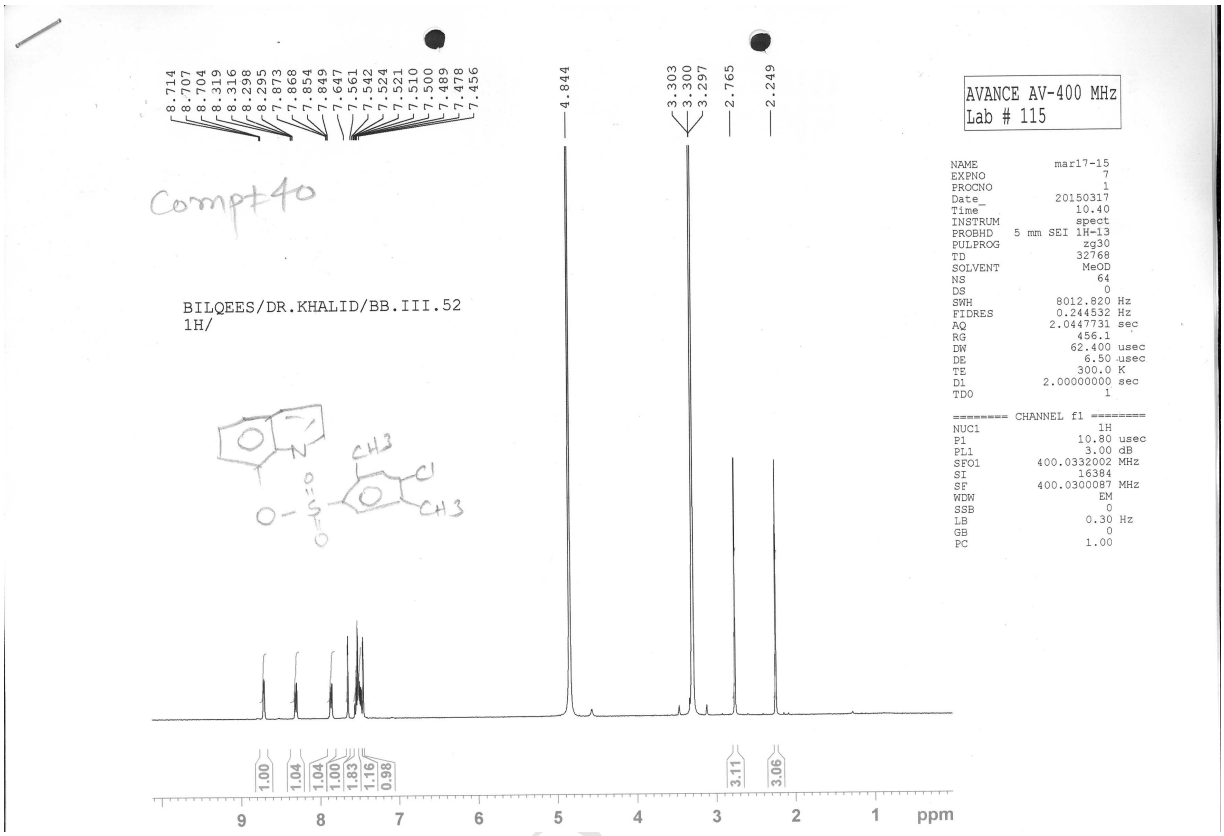












High resolution mass spectrum of compound **5** demonstrated the $M^+$ at *m/z* 367.9794 with a composition of $C_{15}H_{10}Cl_2N_2O_3S$ (Calcd 367.9789). The percent abundance of isotopic $[M]^+$ 12 % $[M+2]^+$ 10%, $[M+4]^+$ 0.7% at *m/z* 368, 370, and 372, respectively, confirmed the presence of two chlorine atoms in a molecule. Cleavage of sulfur nitrogen bond in sulphonamide resulted 5-quinoline fragment appeared at *m/z* 144 as base peak. This 5-quinoline fragment can be further cleaved into quinoline at *m/z* 129. However, removal of one chlorine atom from parent molecule resulted fragment at *m/z* 333 (Figure-4).

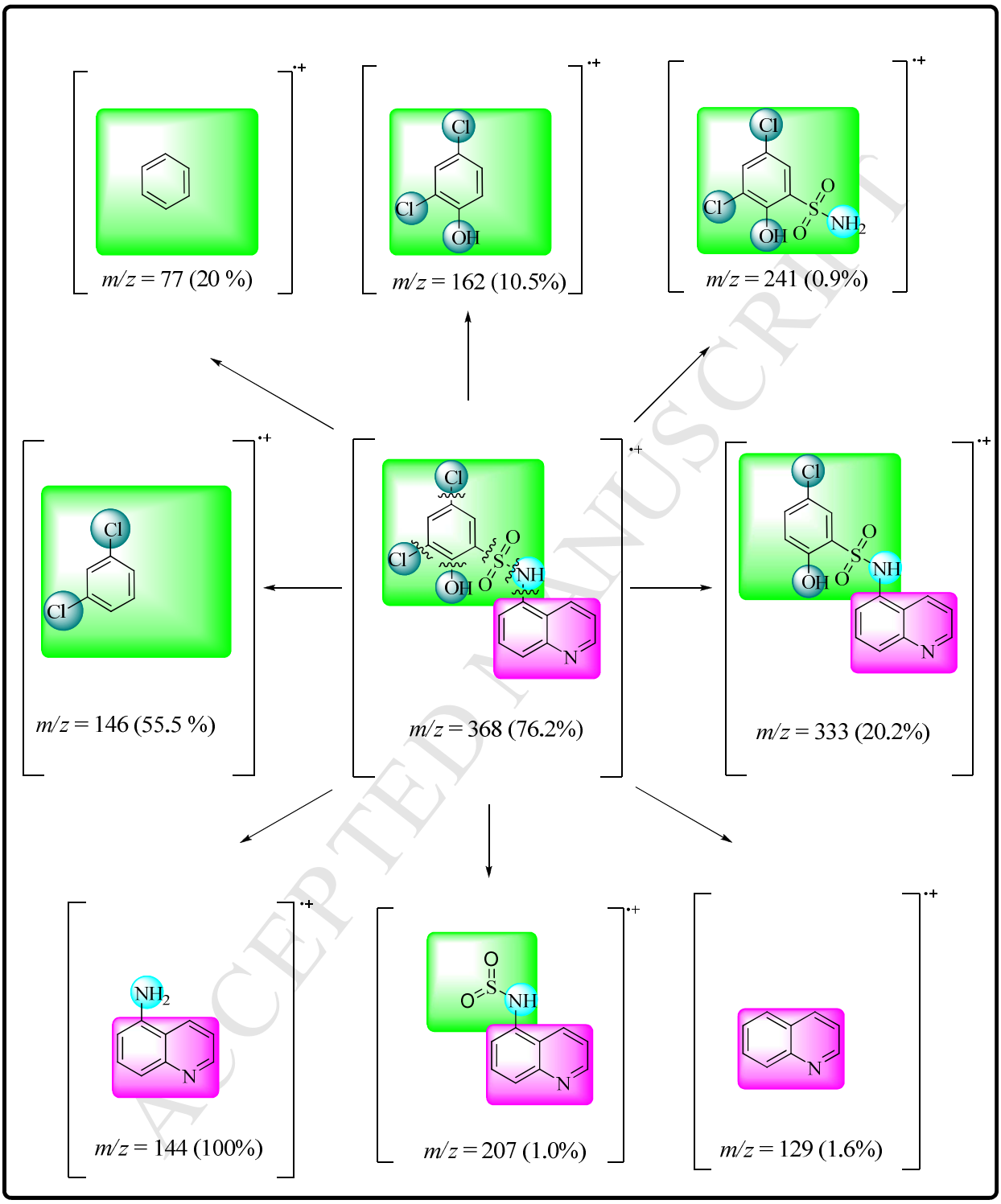
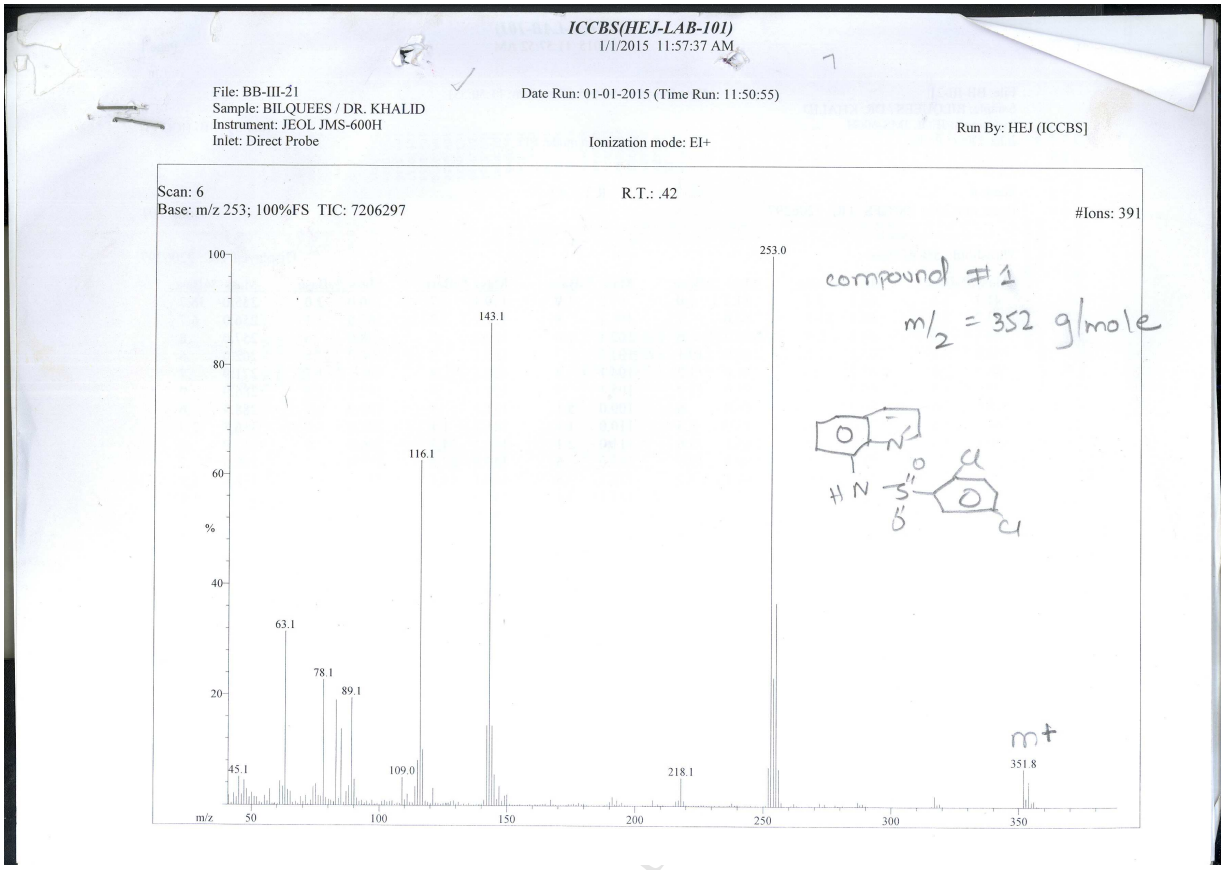
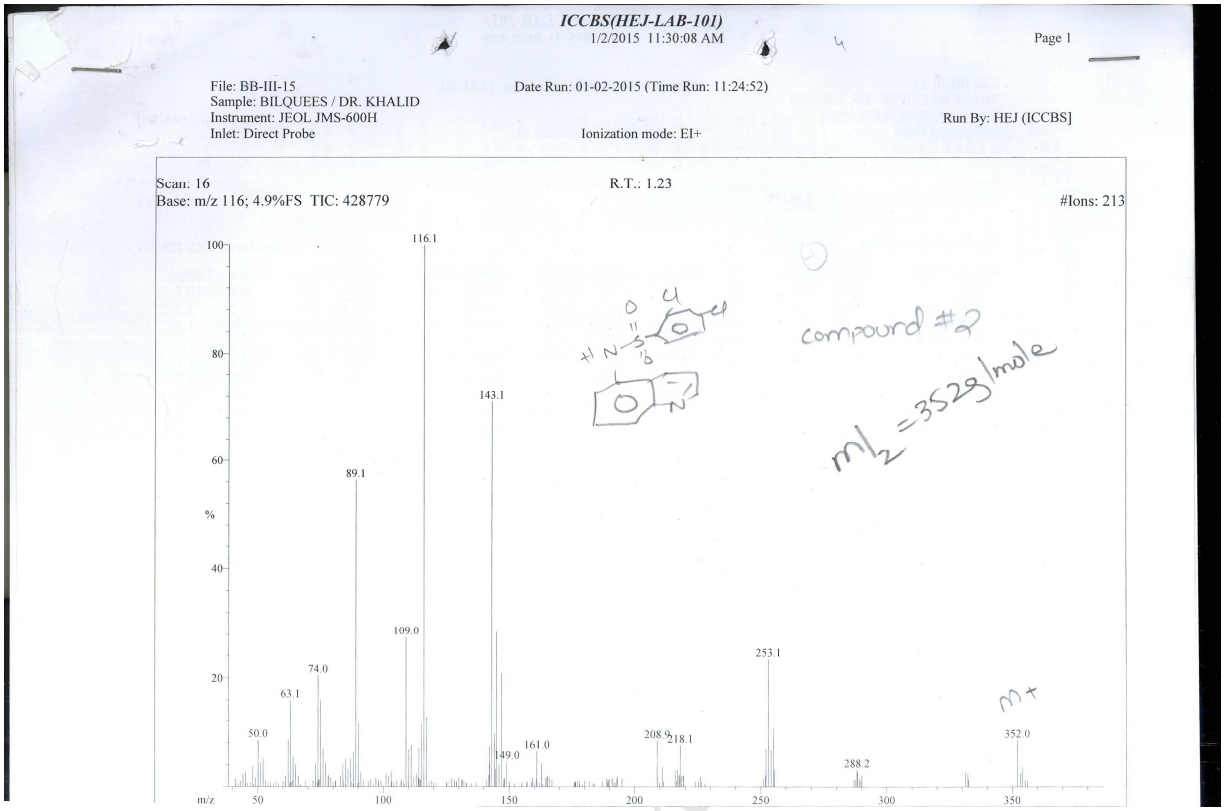
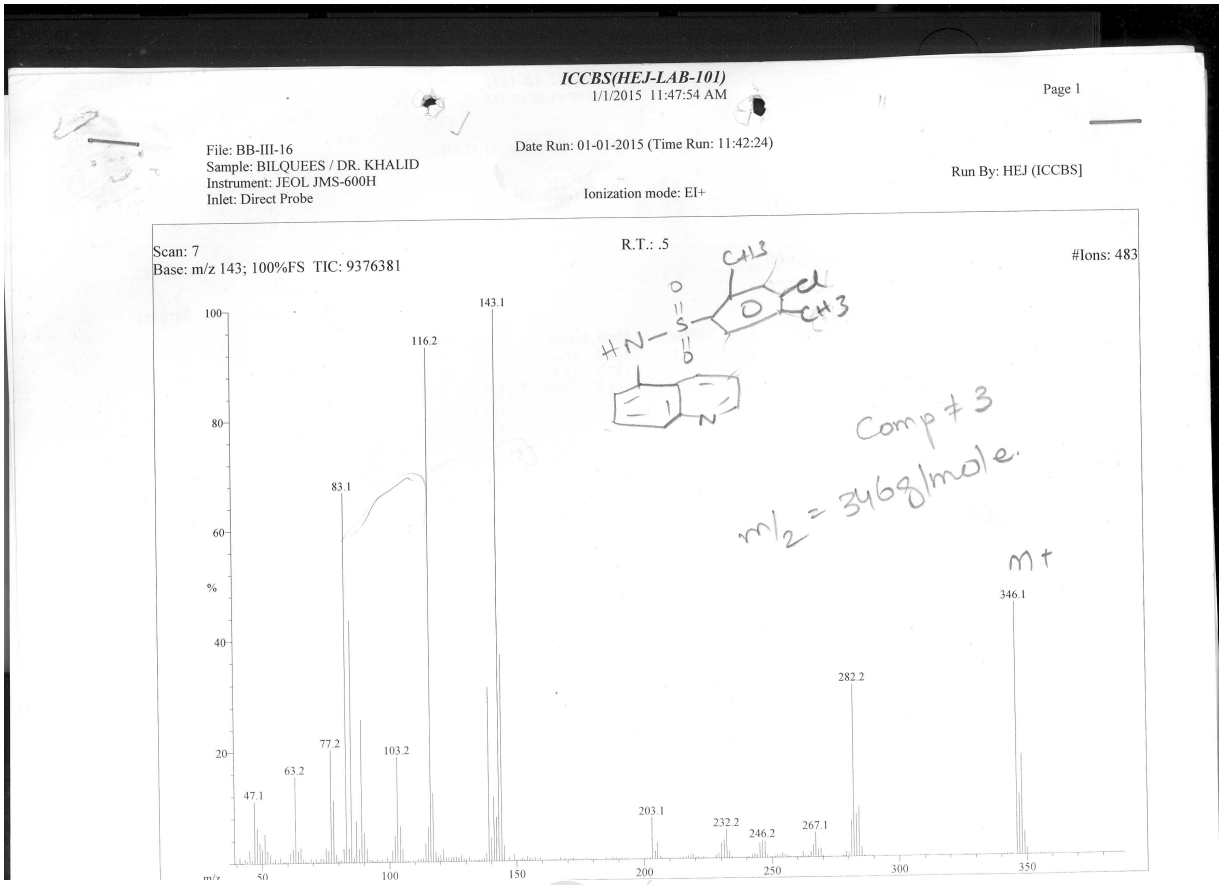
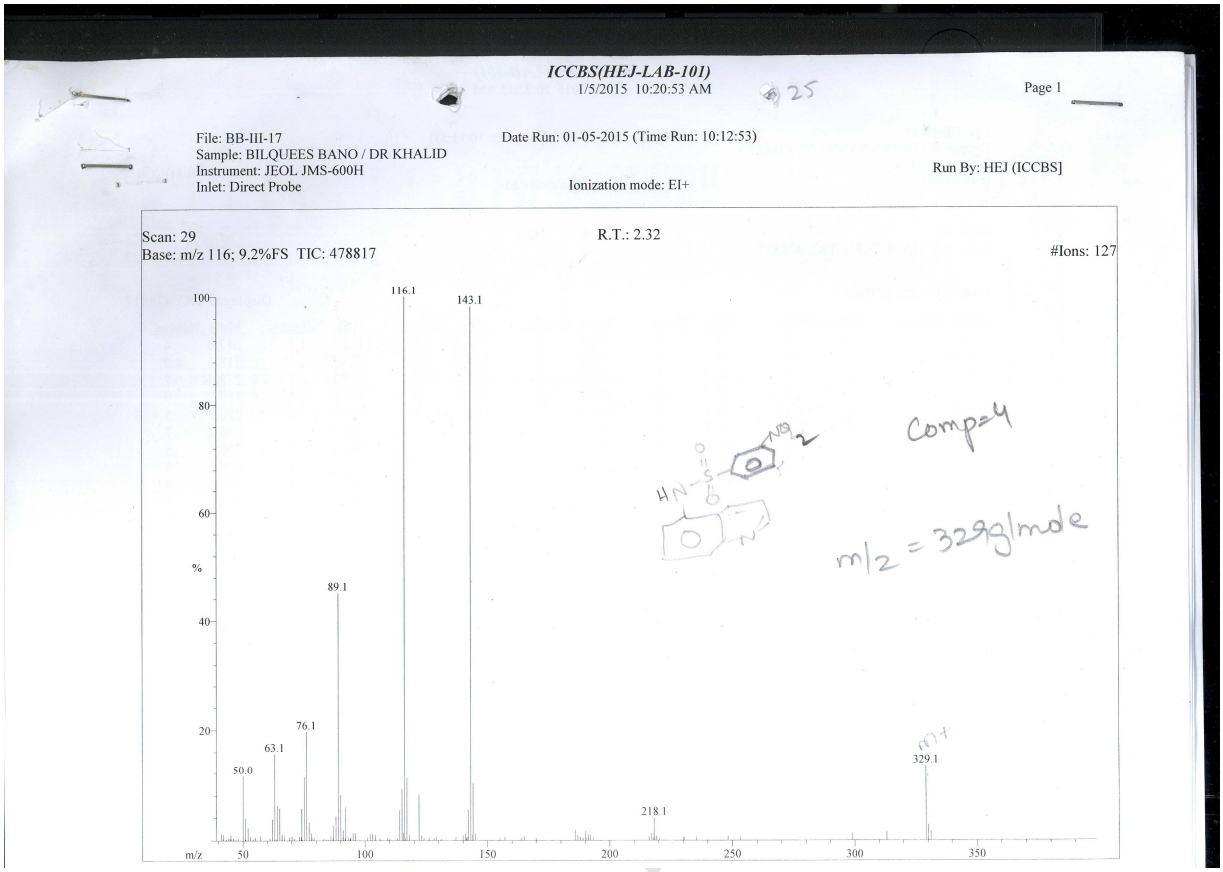


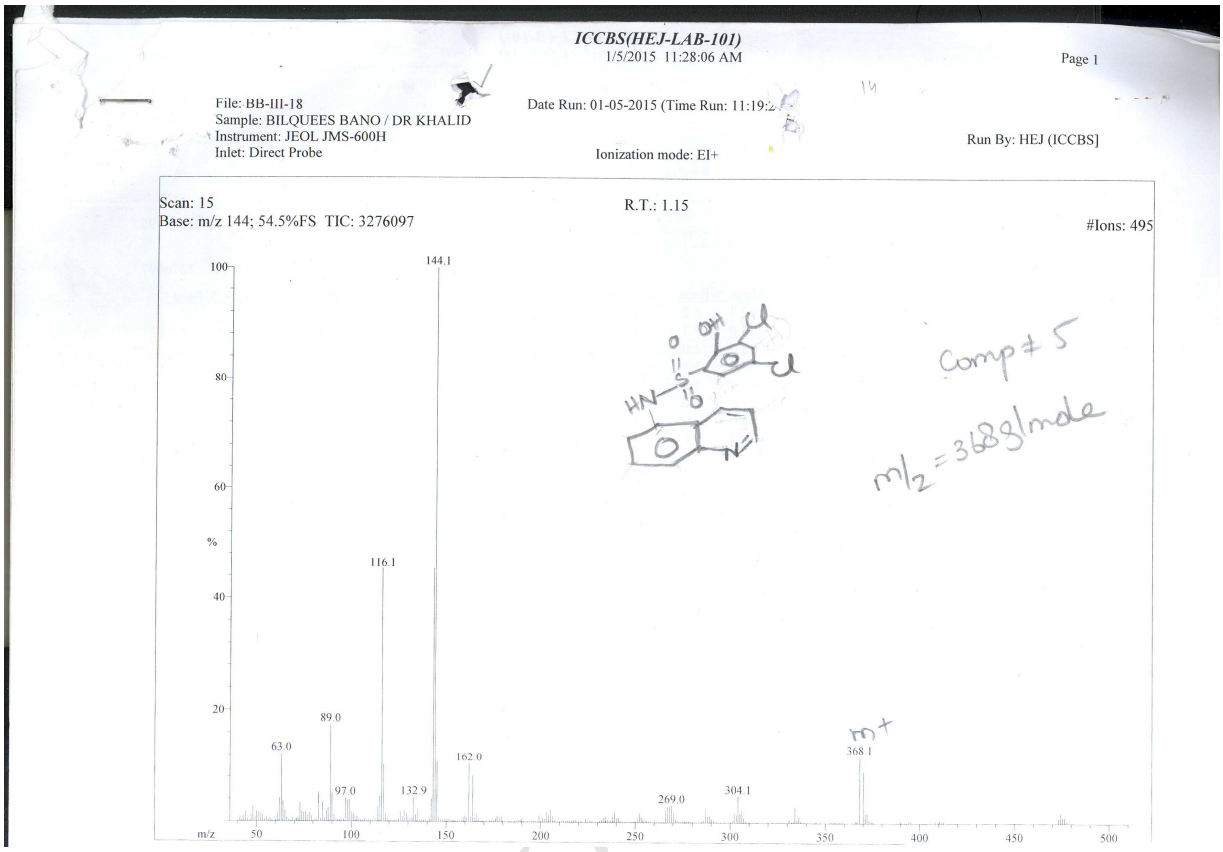

**Figure:** EI-MS fragmentation pattern of compound **5**.

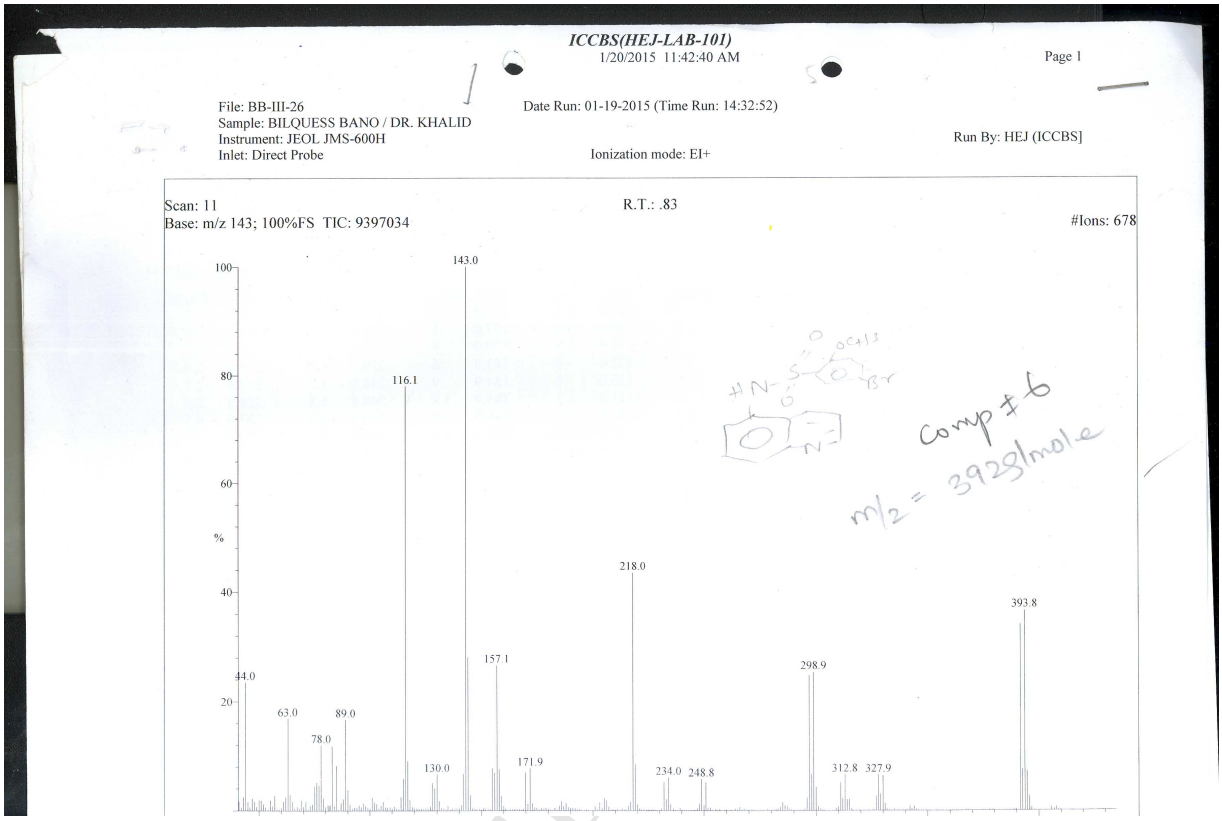


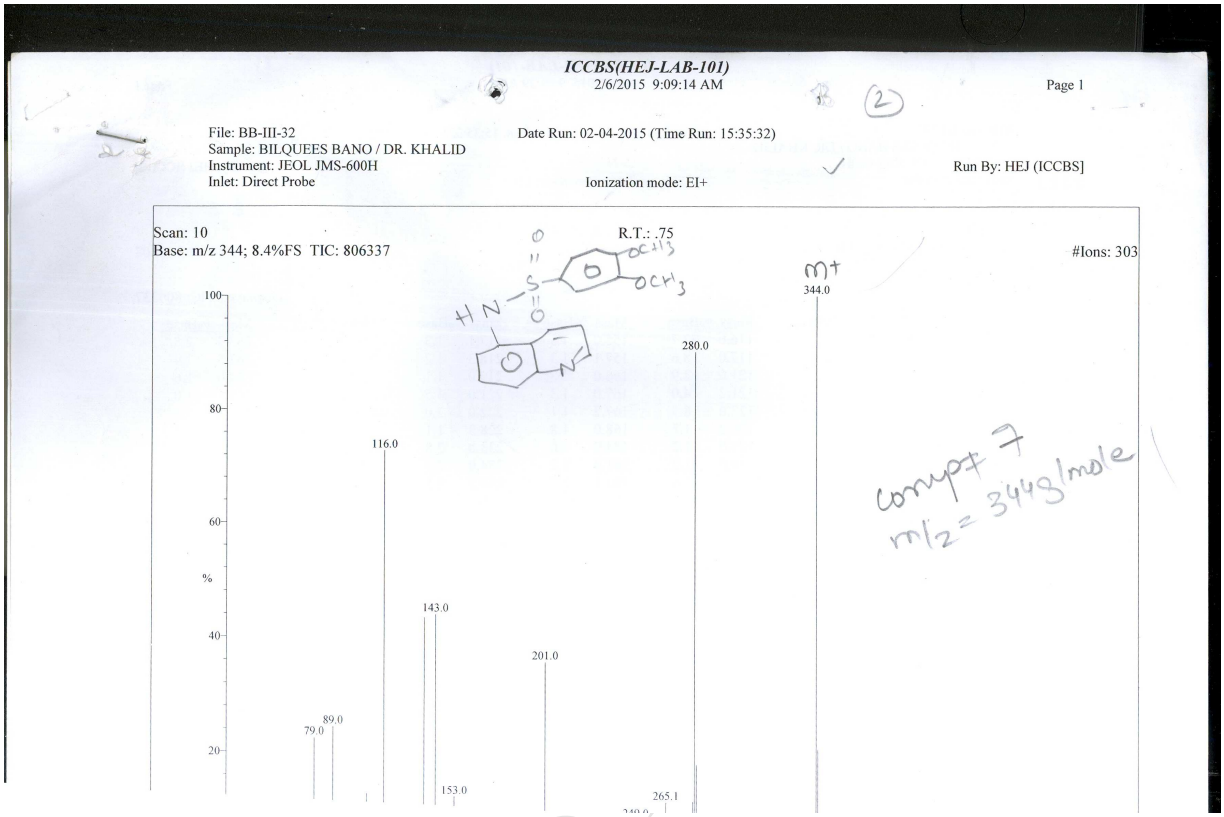


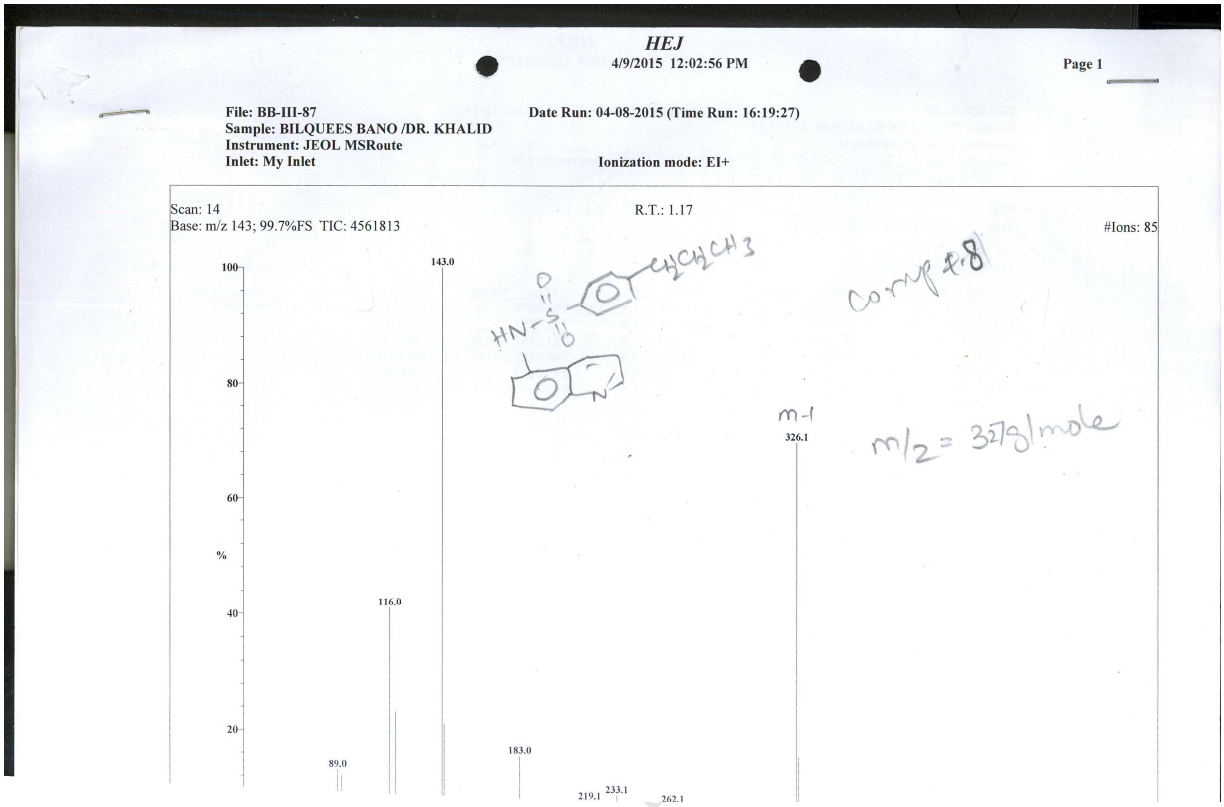


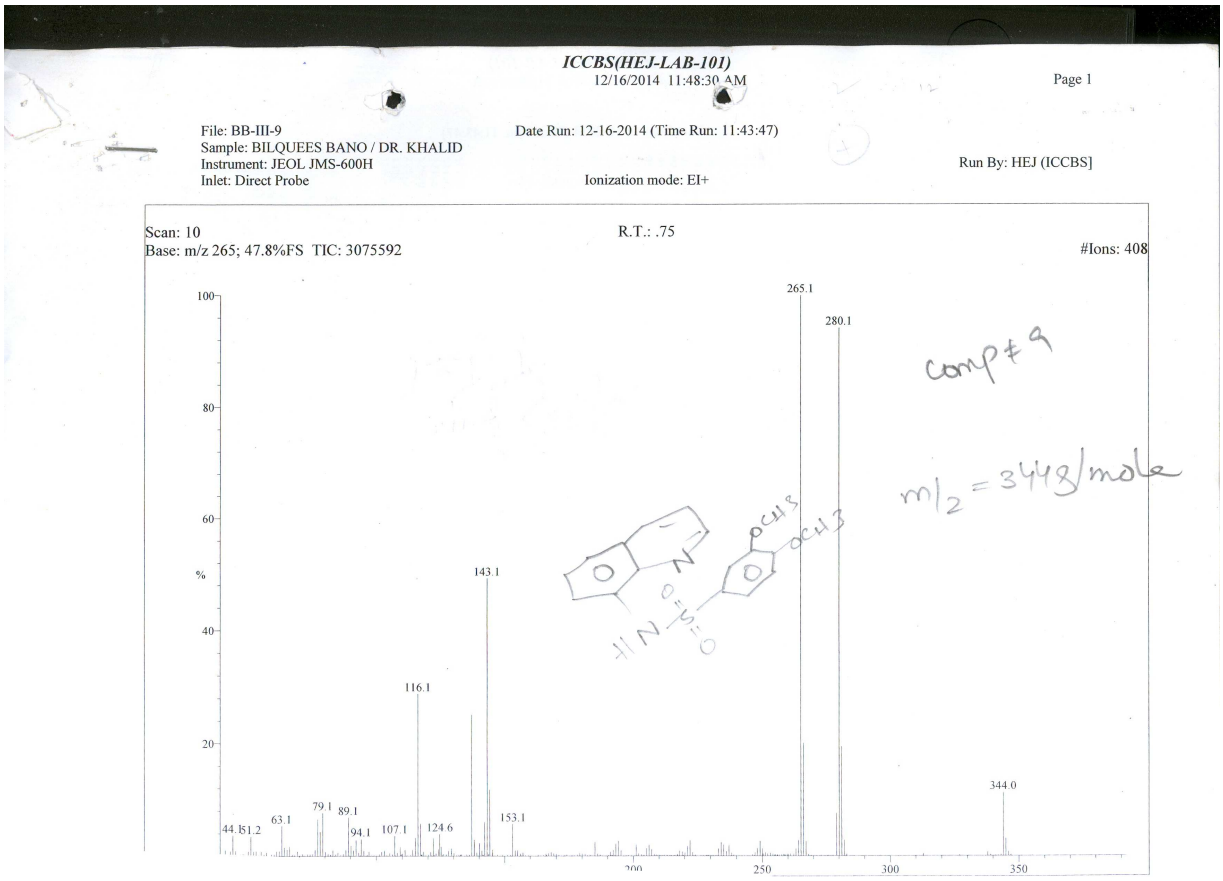


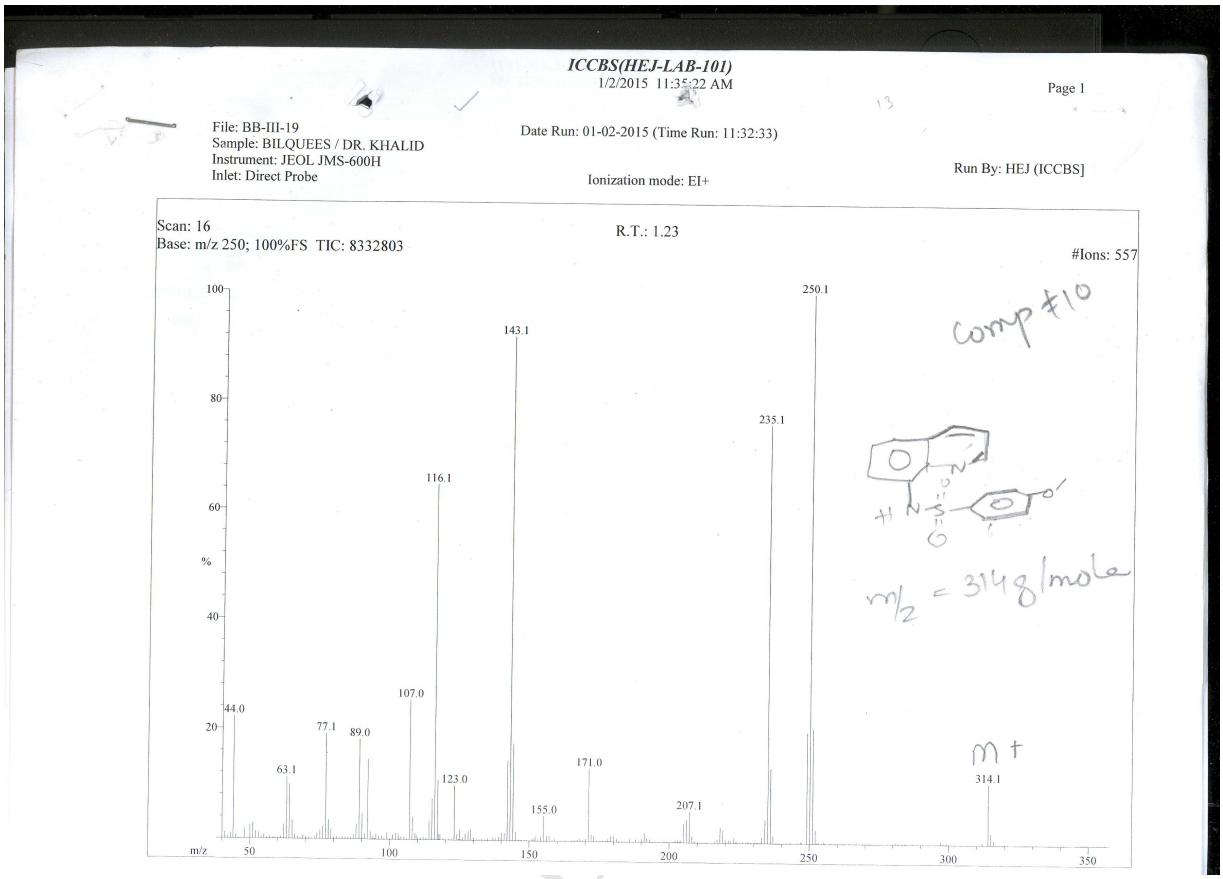


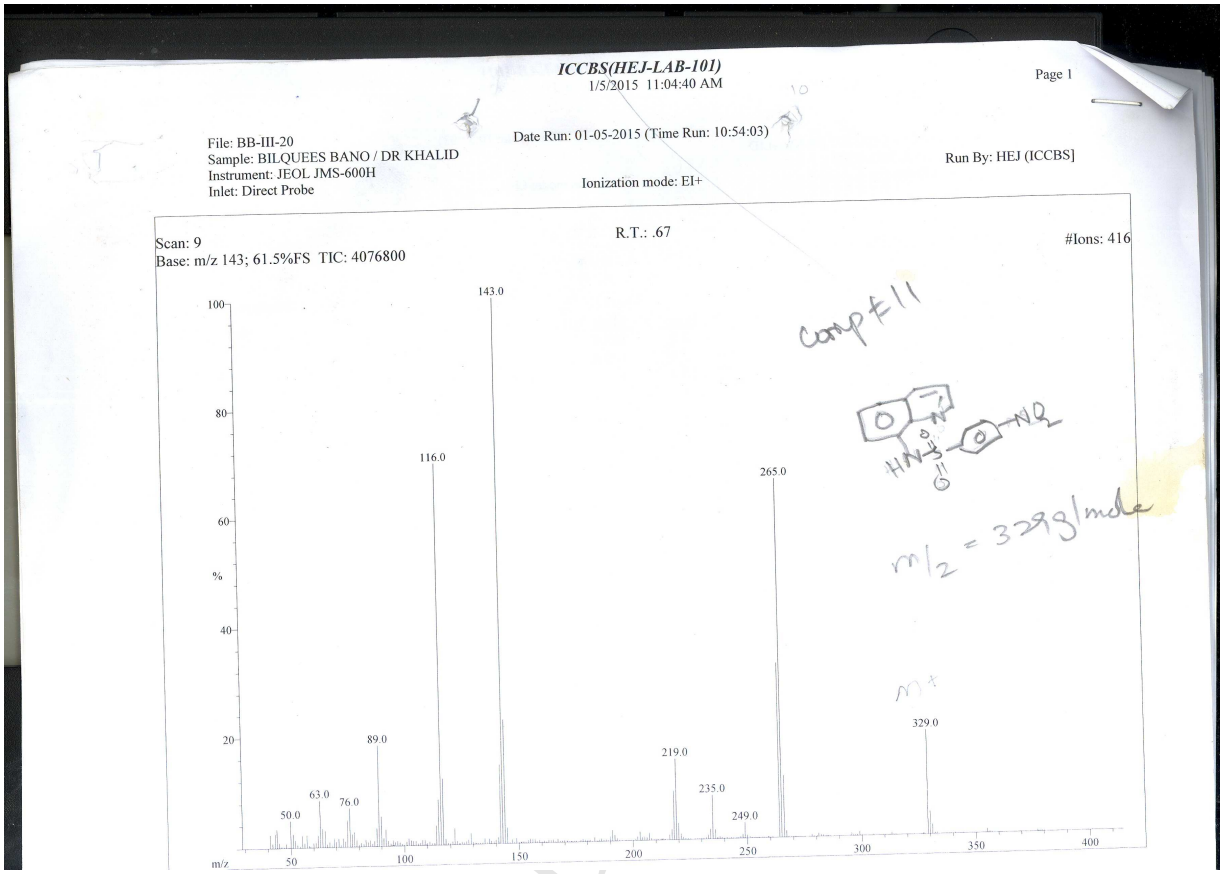


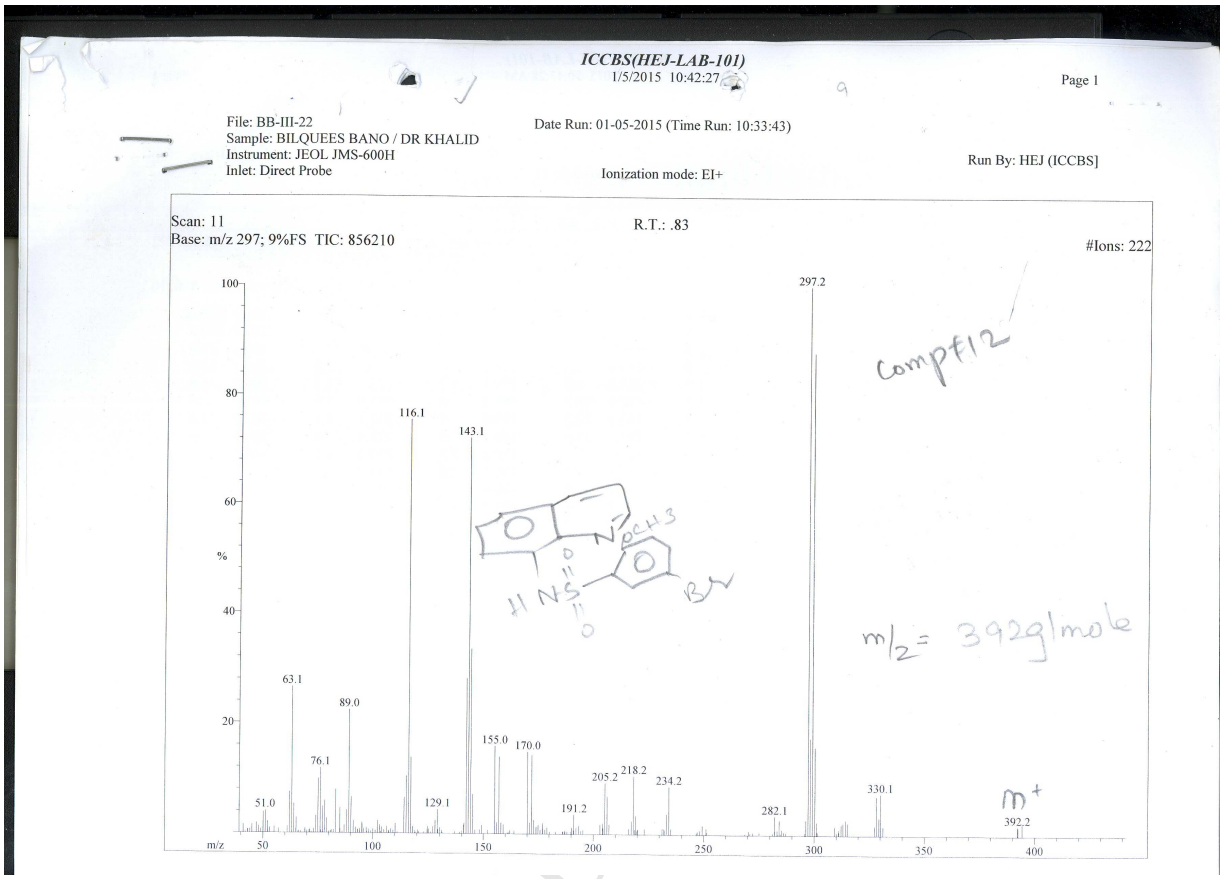


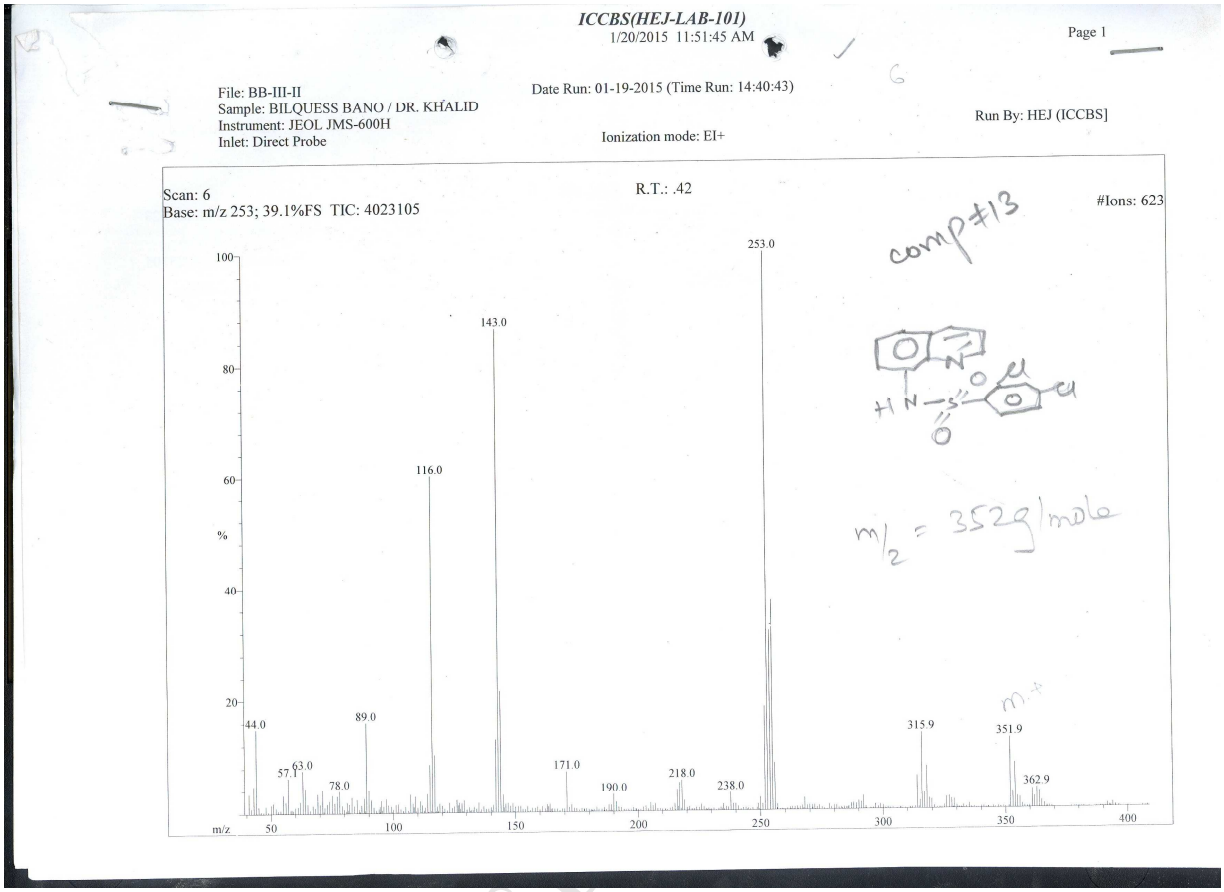


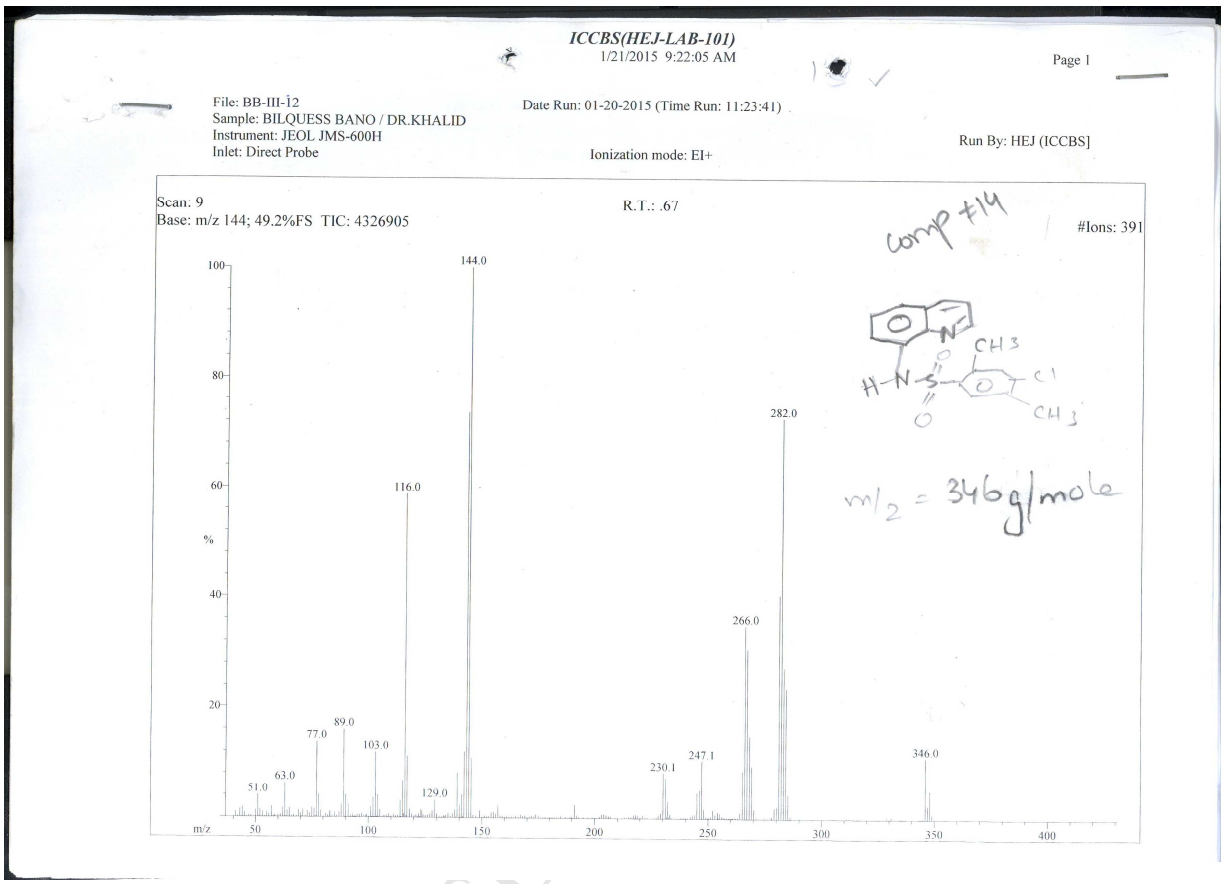


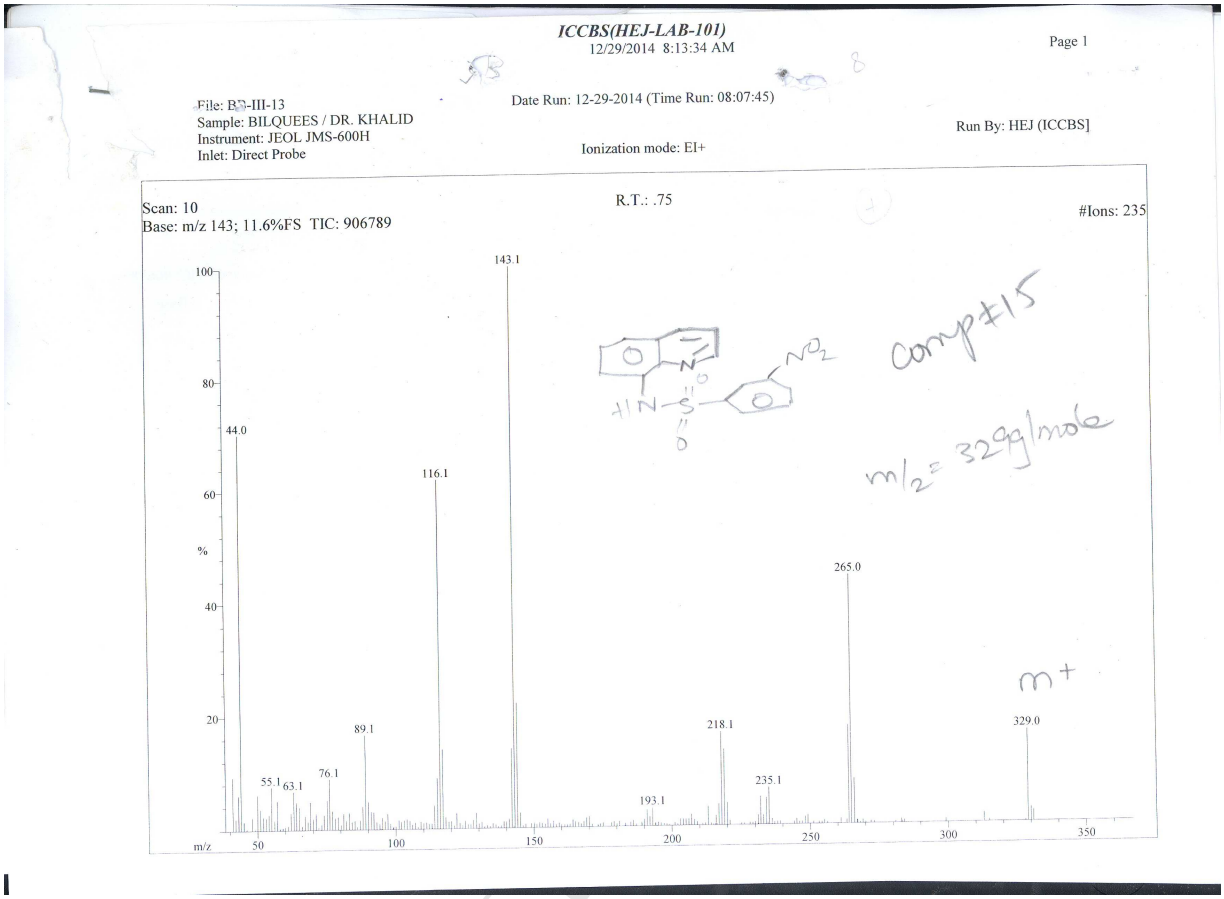


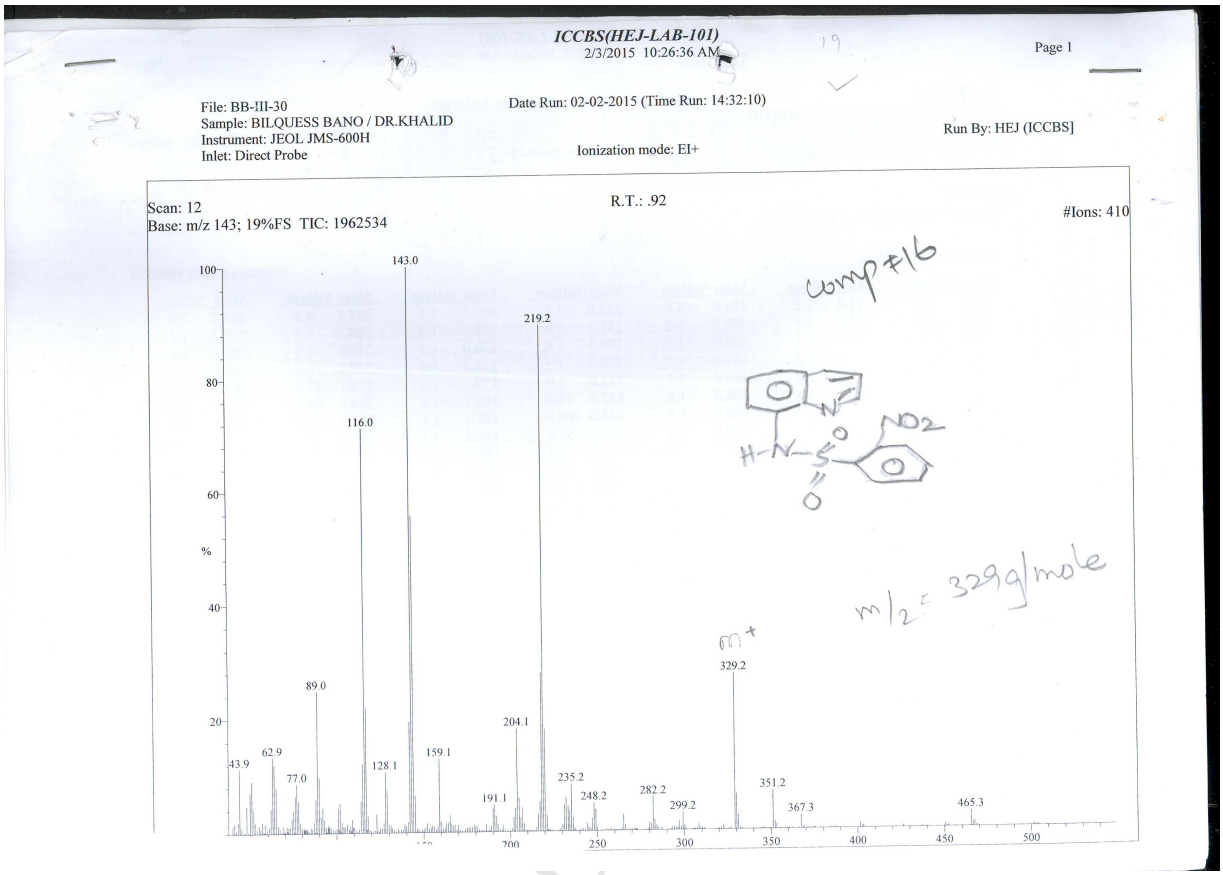


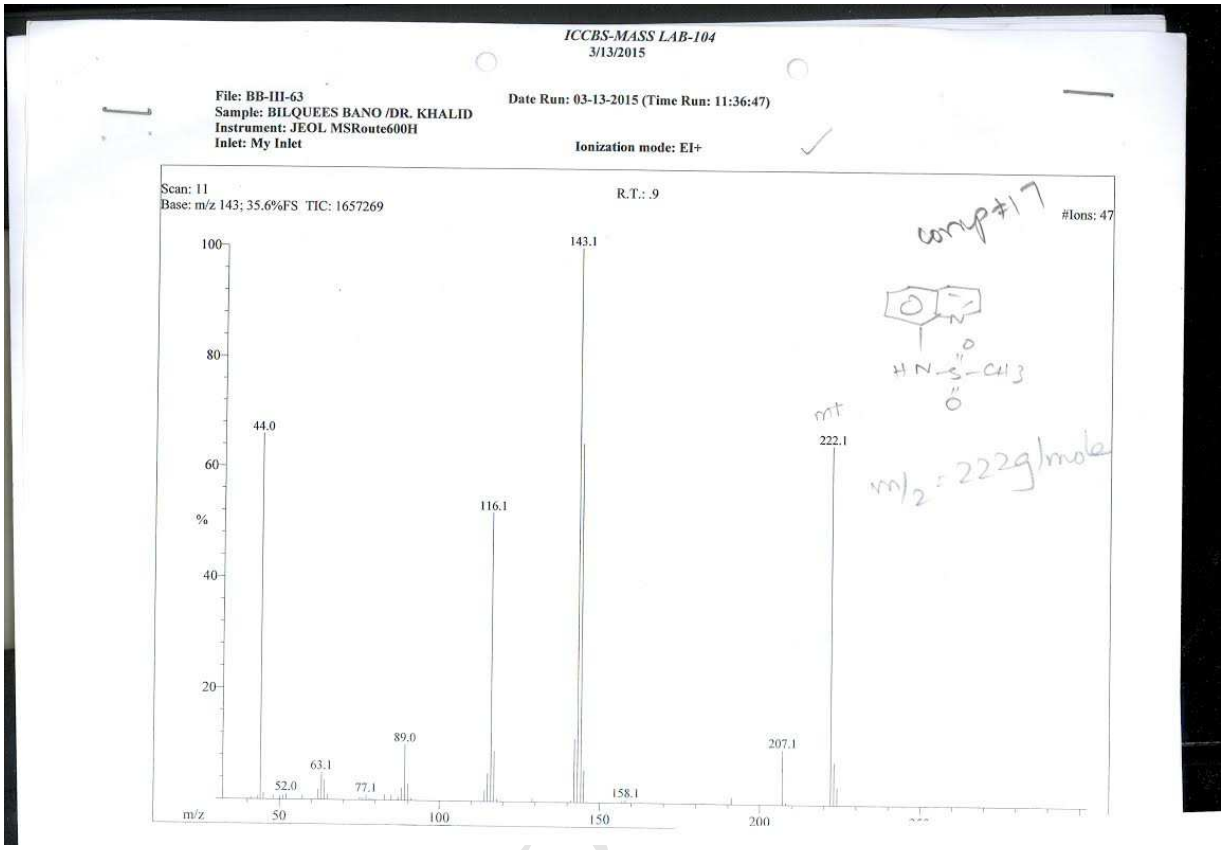


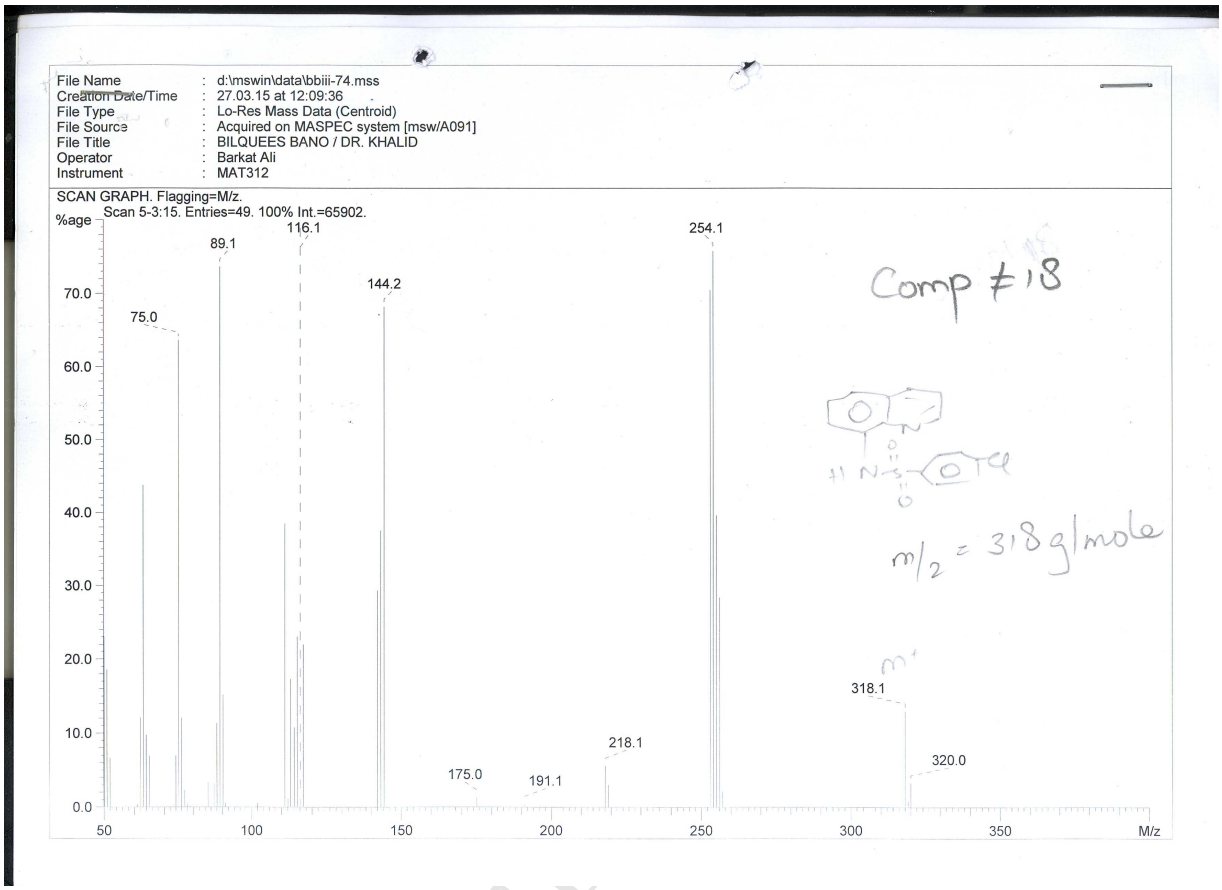


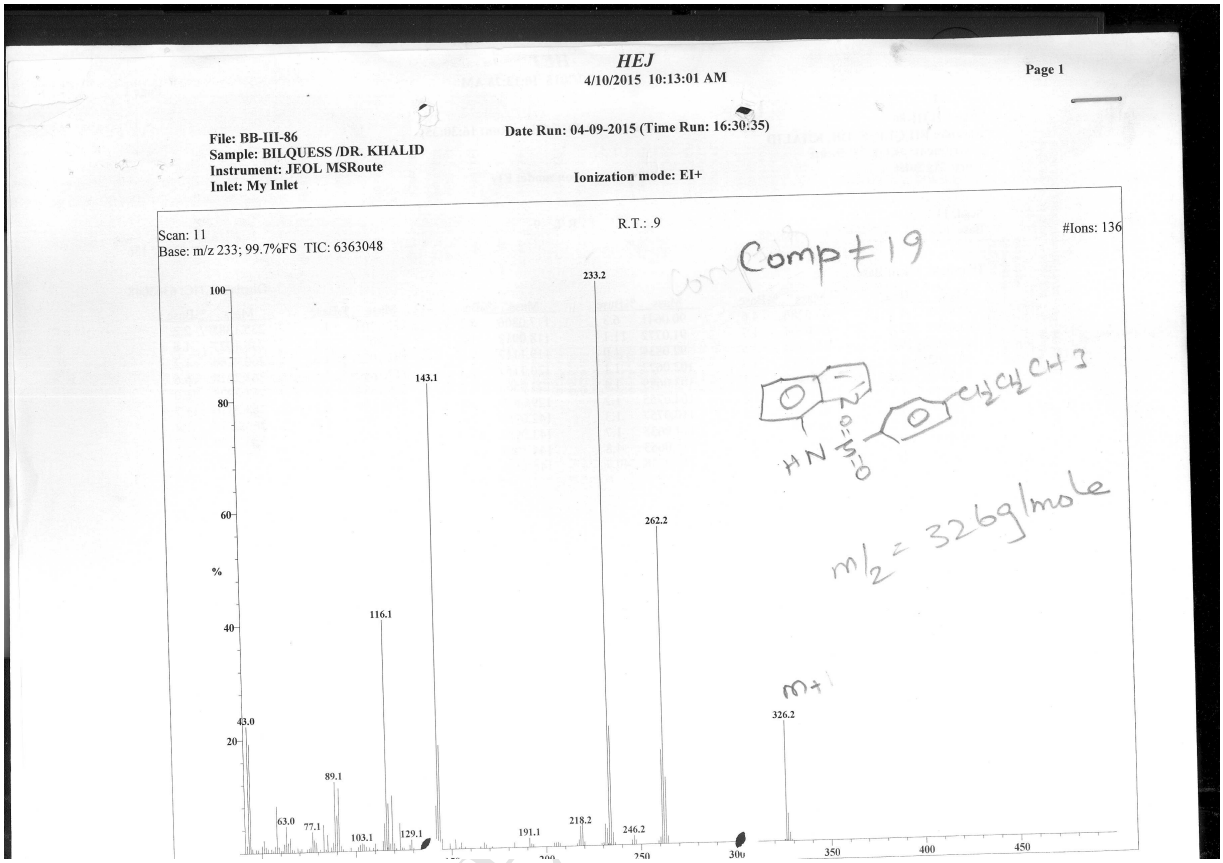


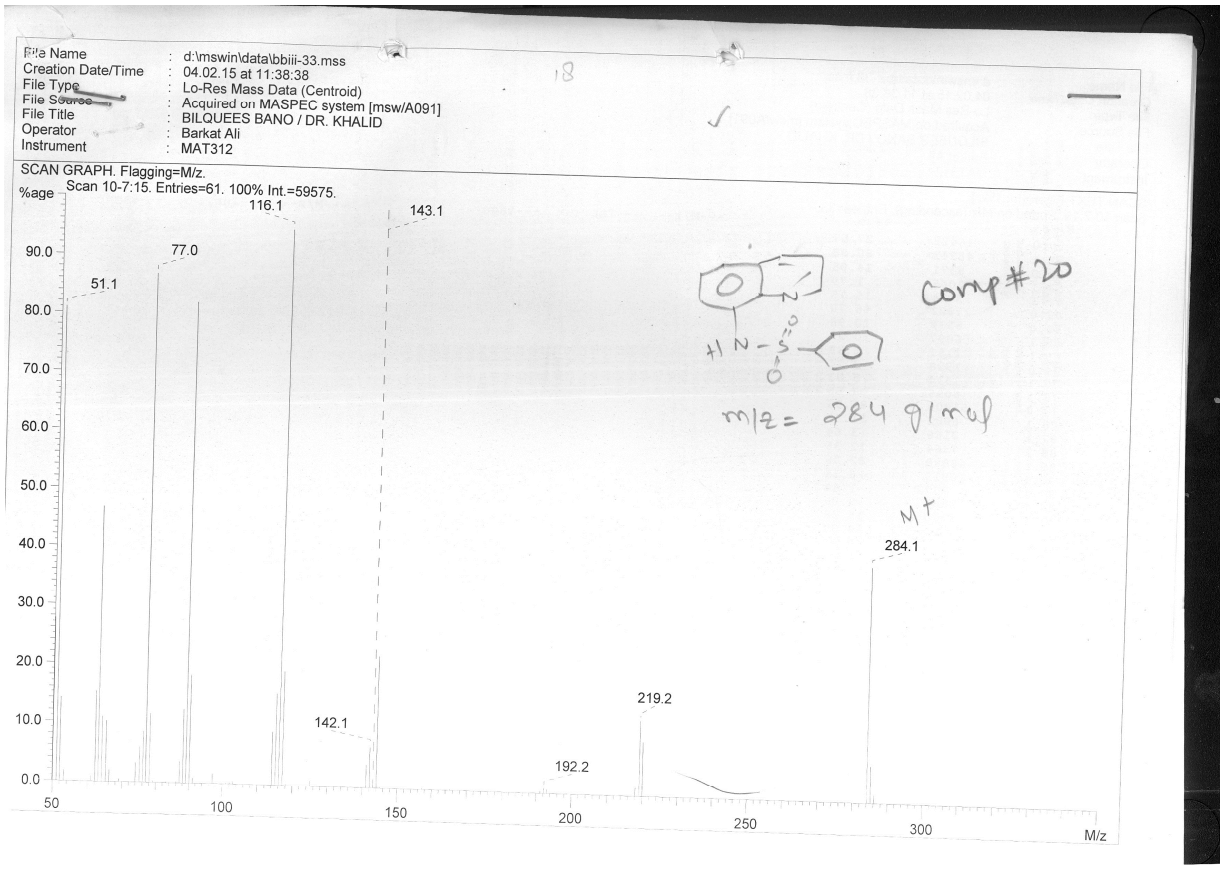


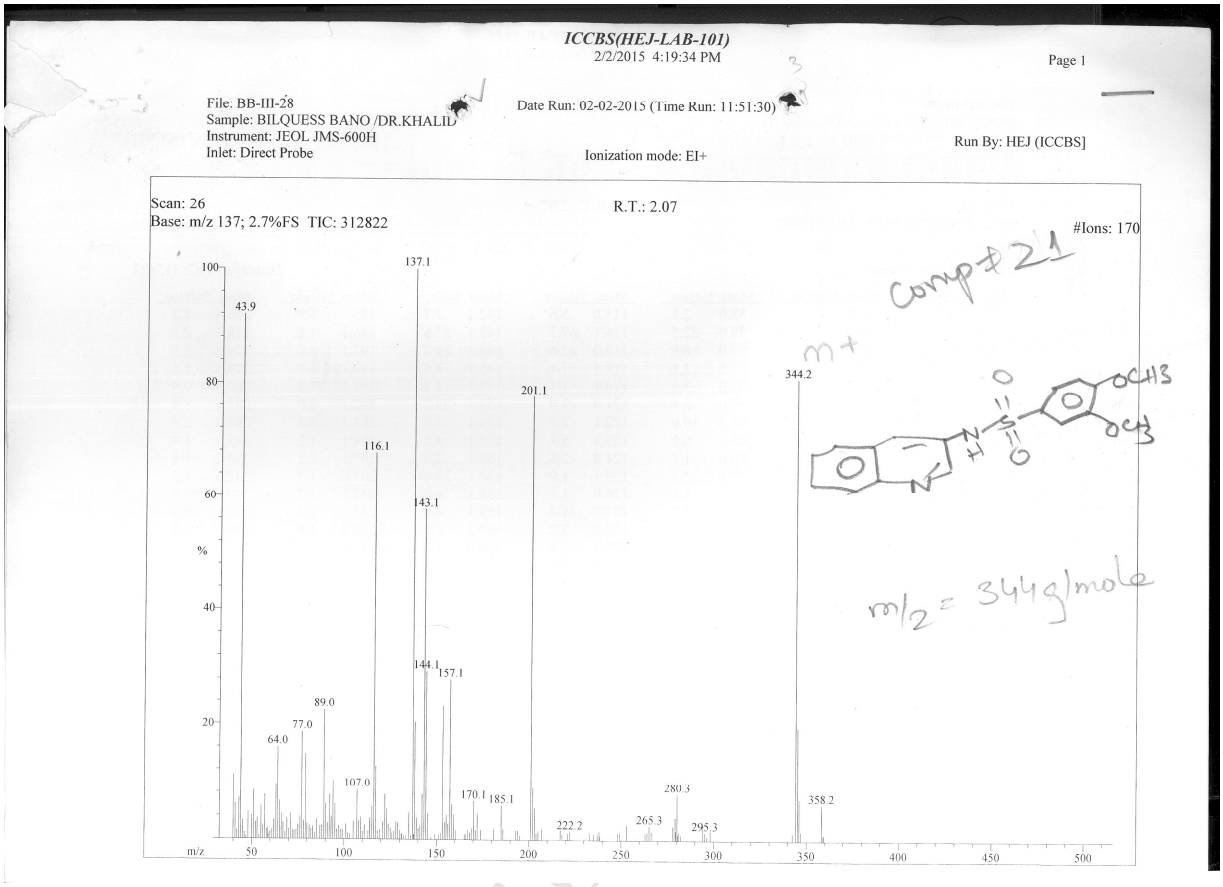


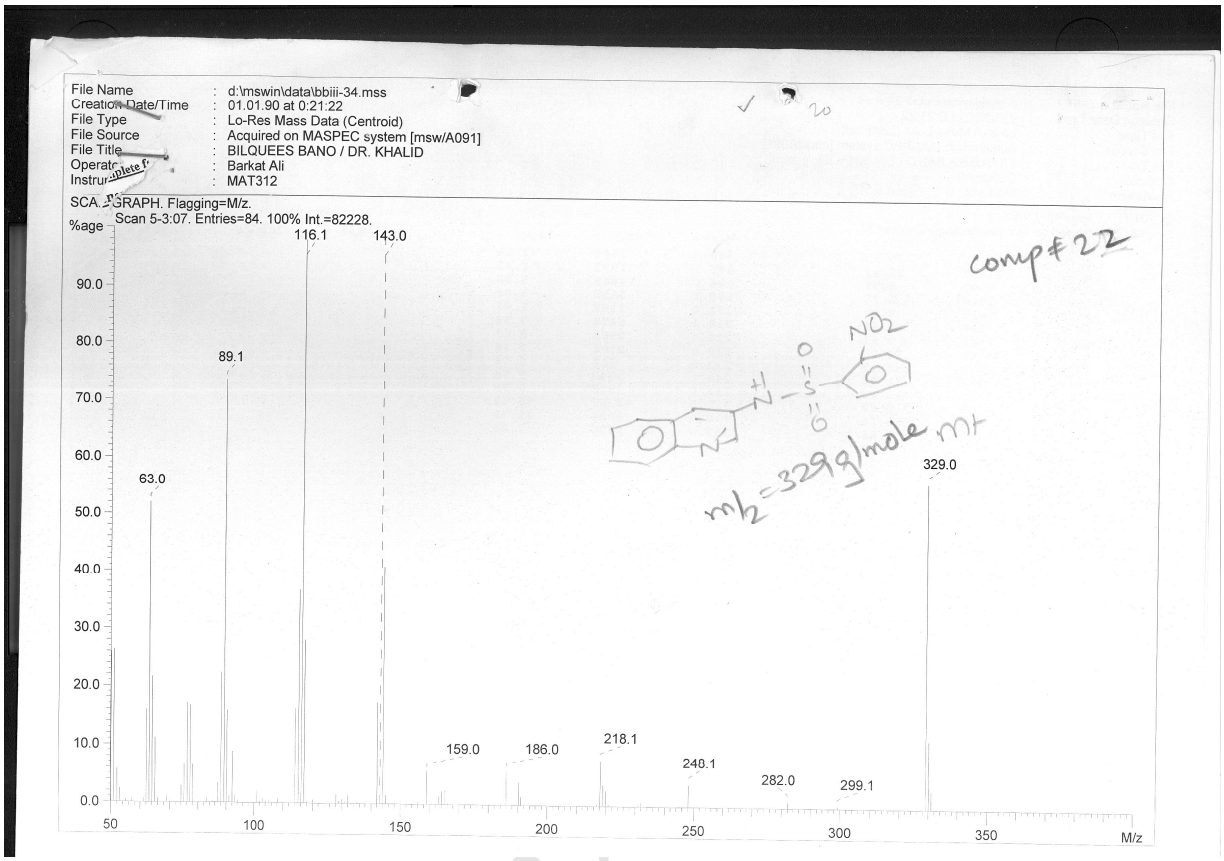


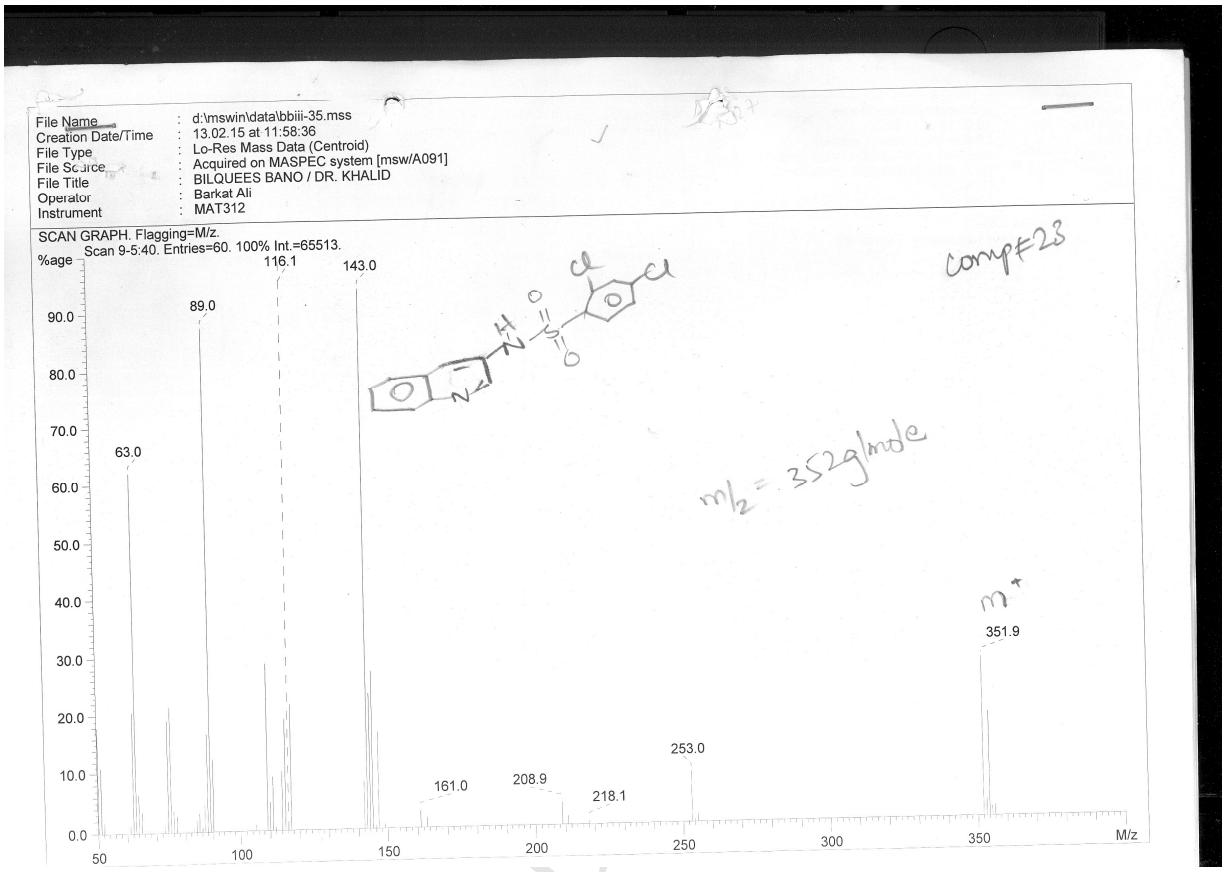


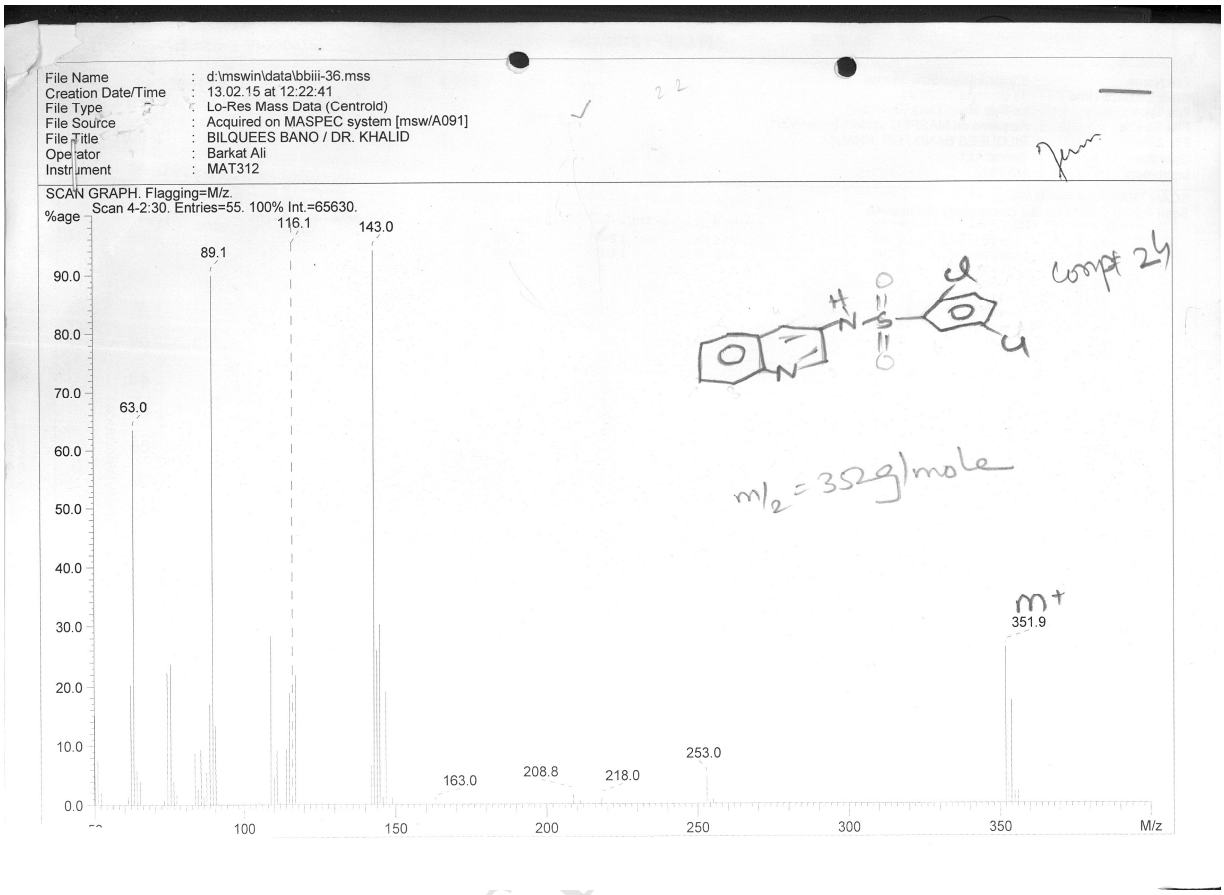


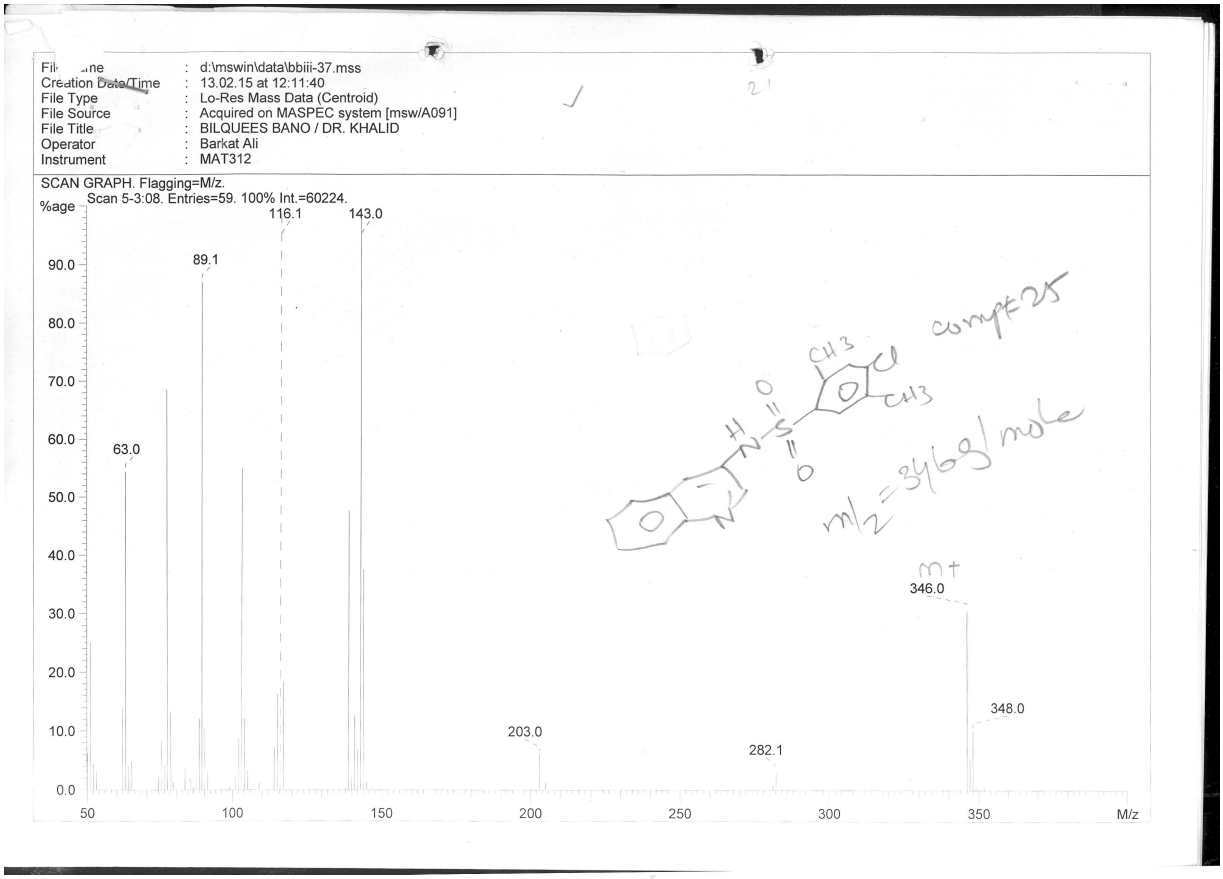








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Instrument : MAT312
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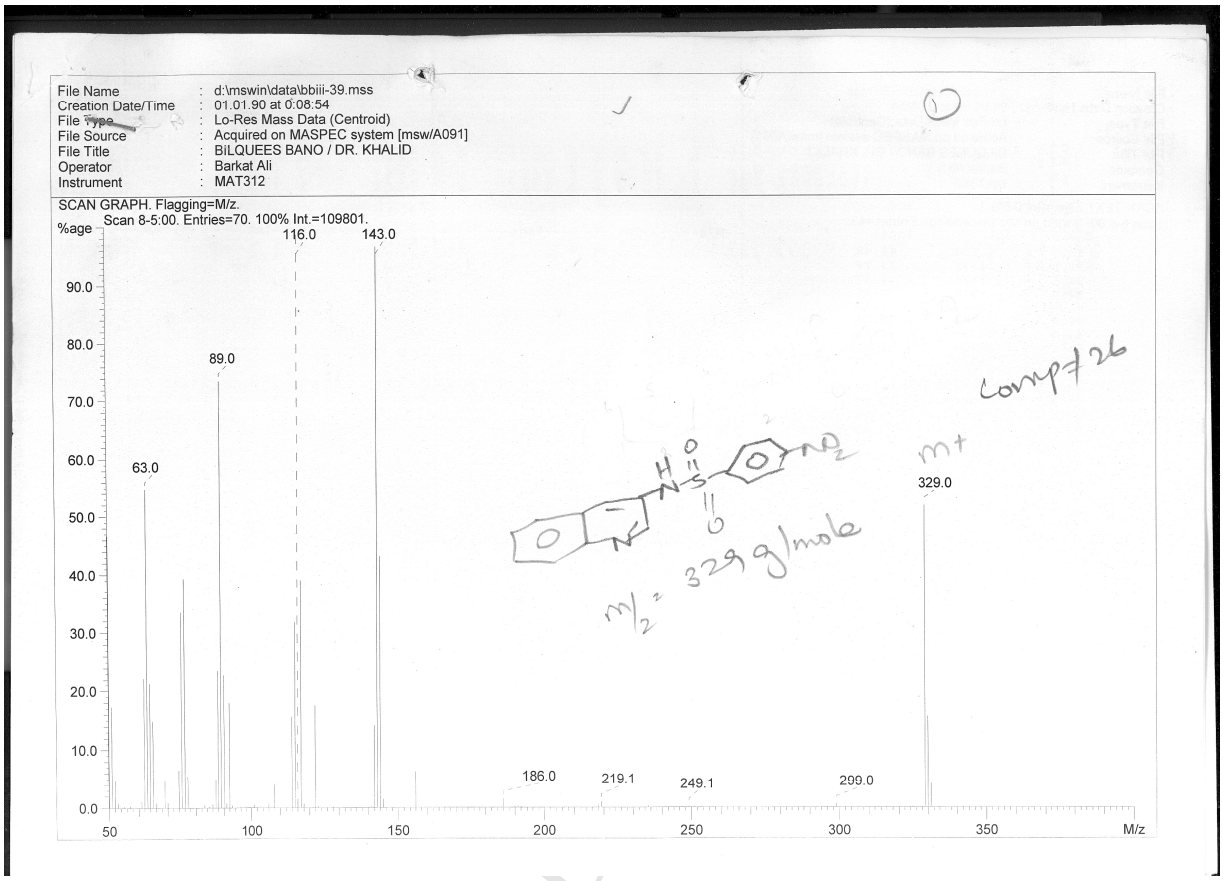
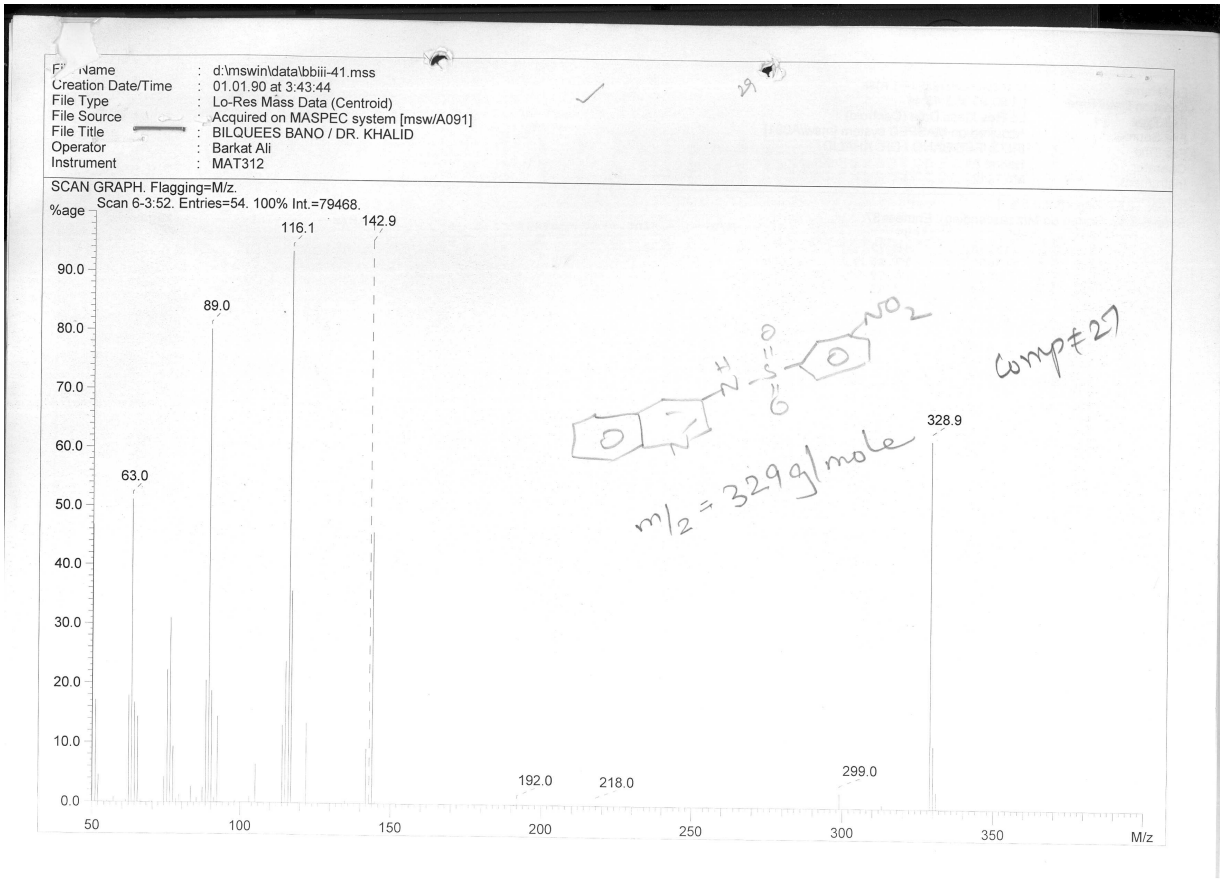
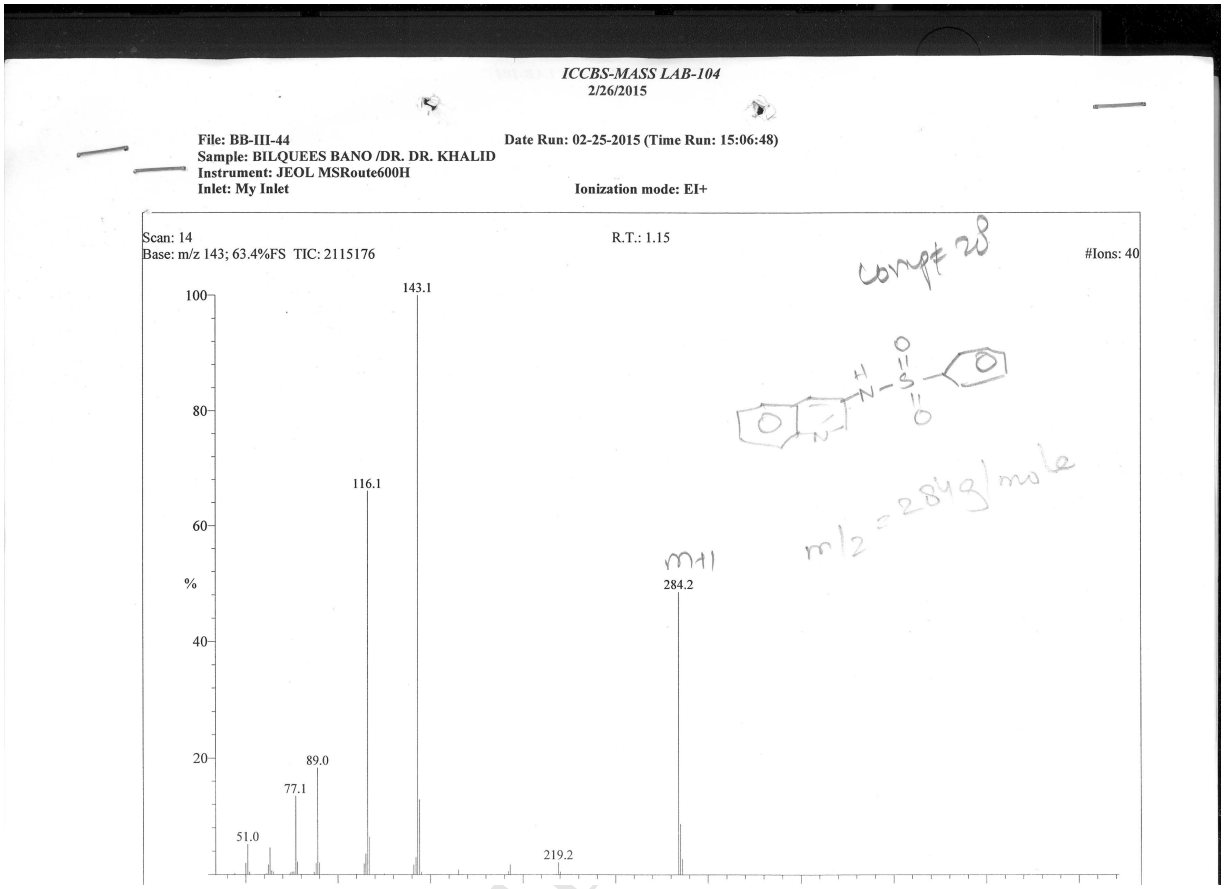
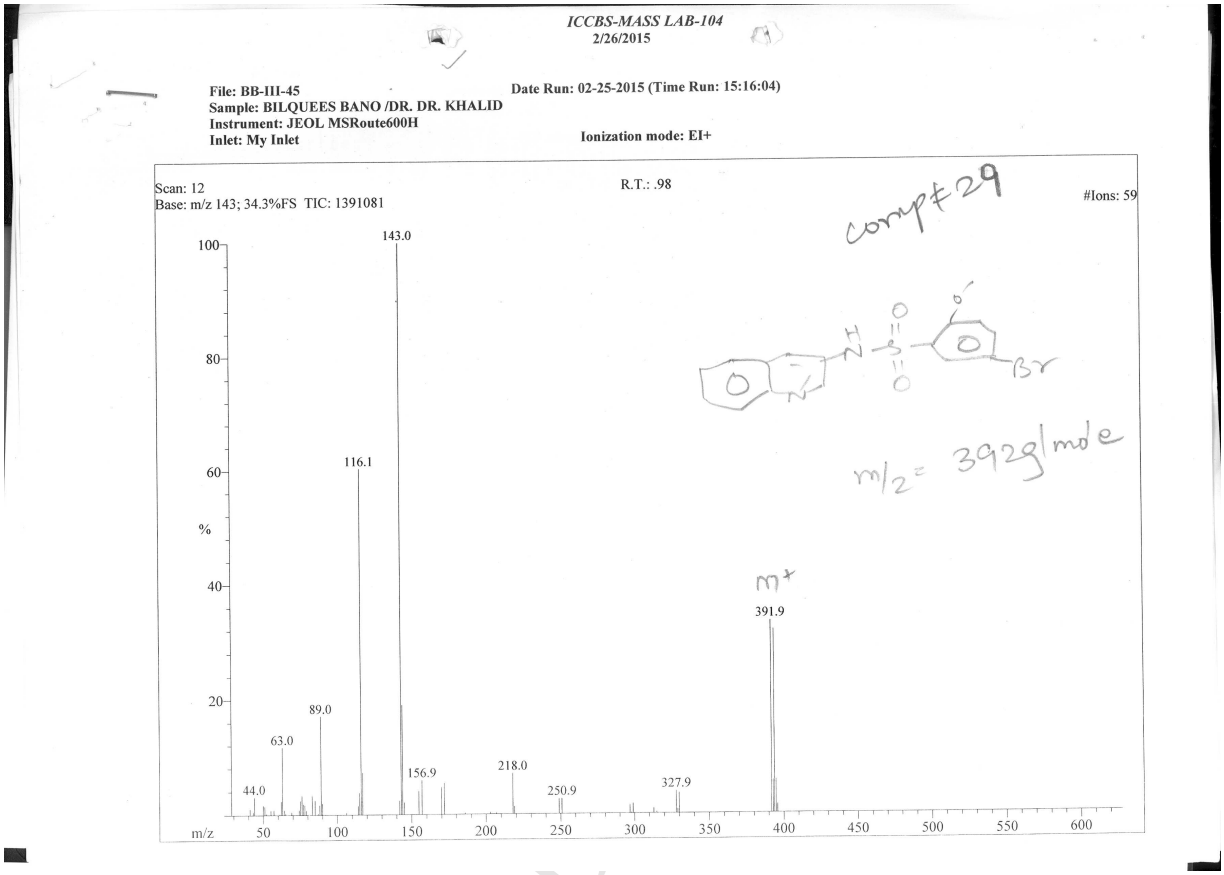
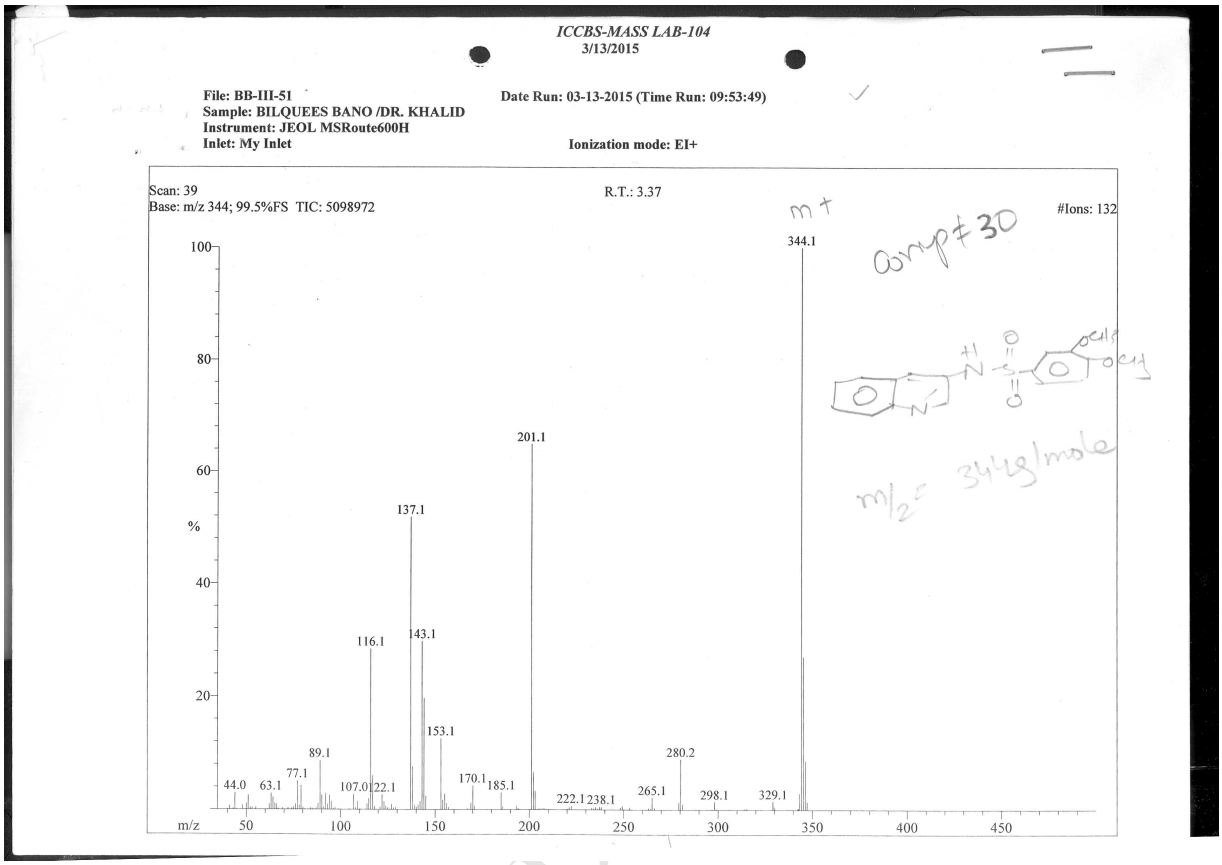
m/z = 346g/mole
M+

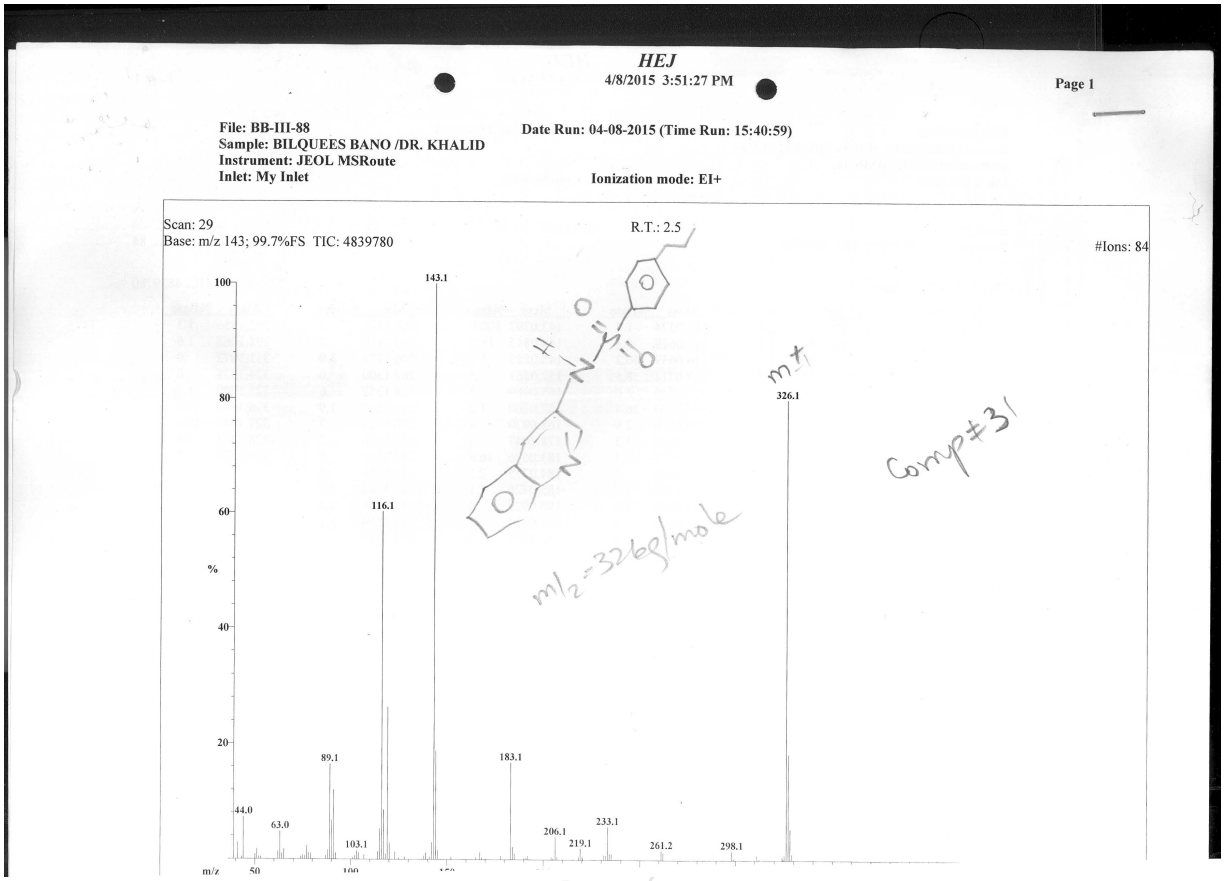


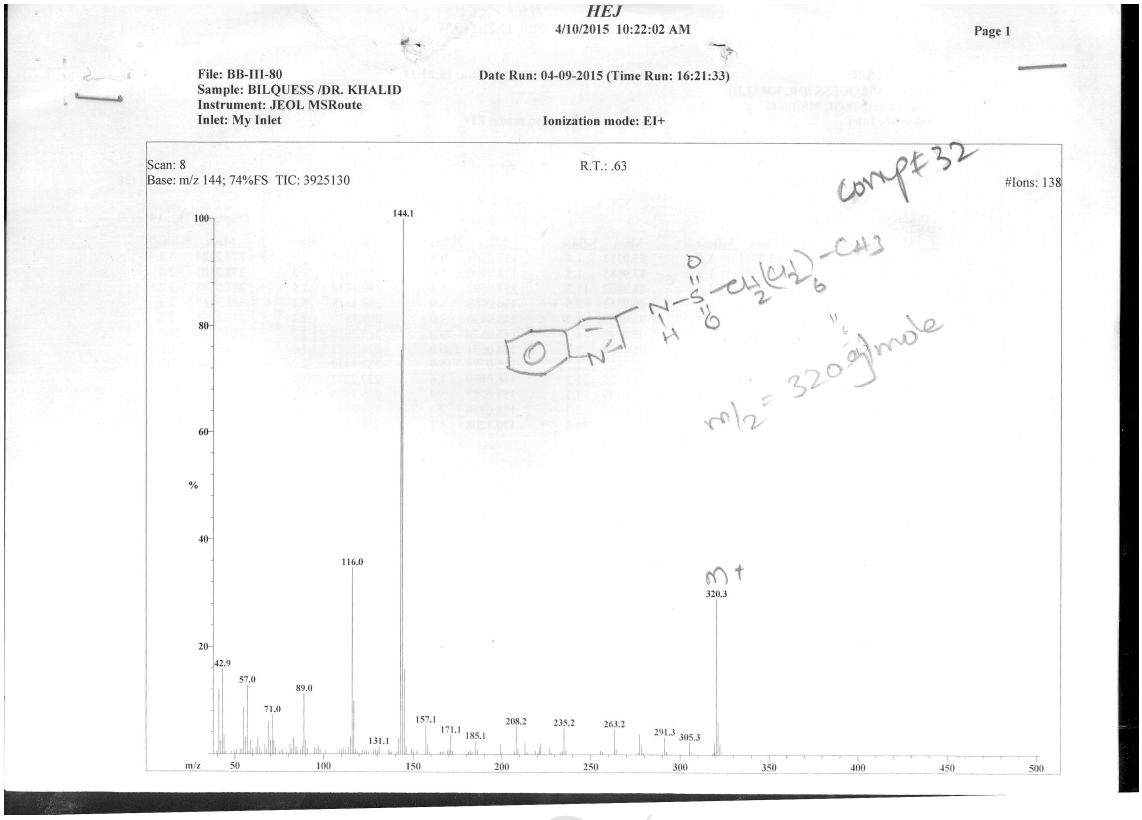












3/13/2015

File: BB-III-46
Sample: BILQUEES BANO /DR. KHALID
Instrument: JEOL MSRoute600H
Inlet: My Inlet

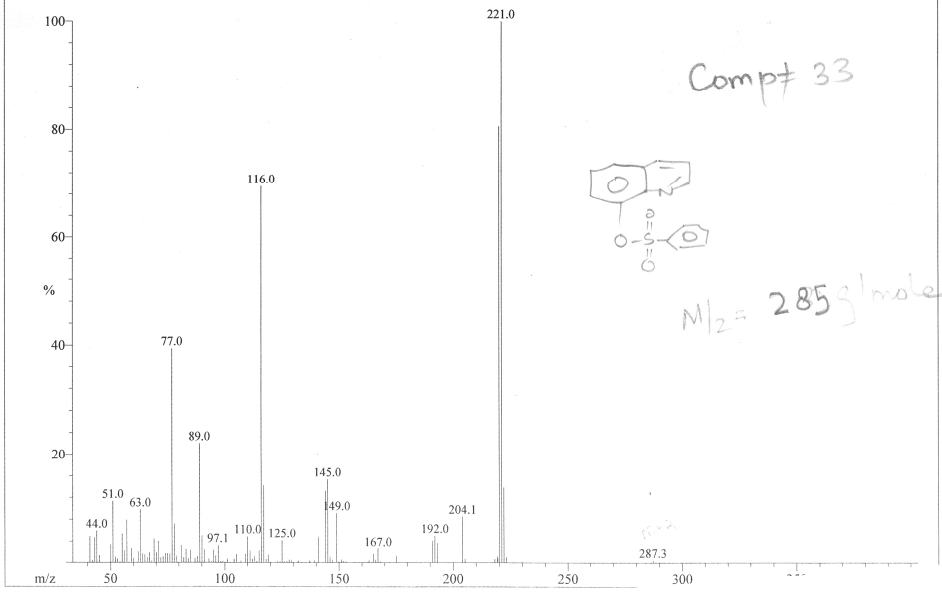
Date Run: 03-13-2015 (Time Run: 09:18:31)

Ionization mode: EI+

Scan: 4
Base: m/z 221; 33.7%FS TIC: 2006371

R.T.: .27

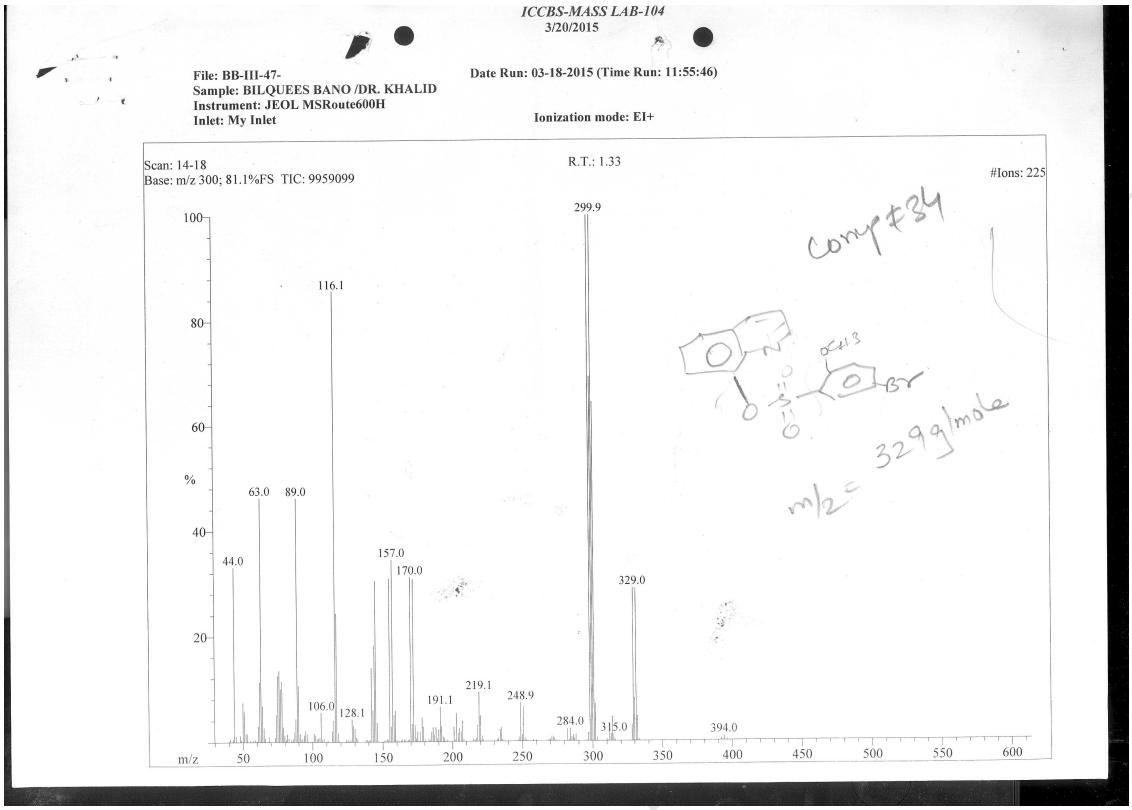
#Ions: 105

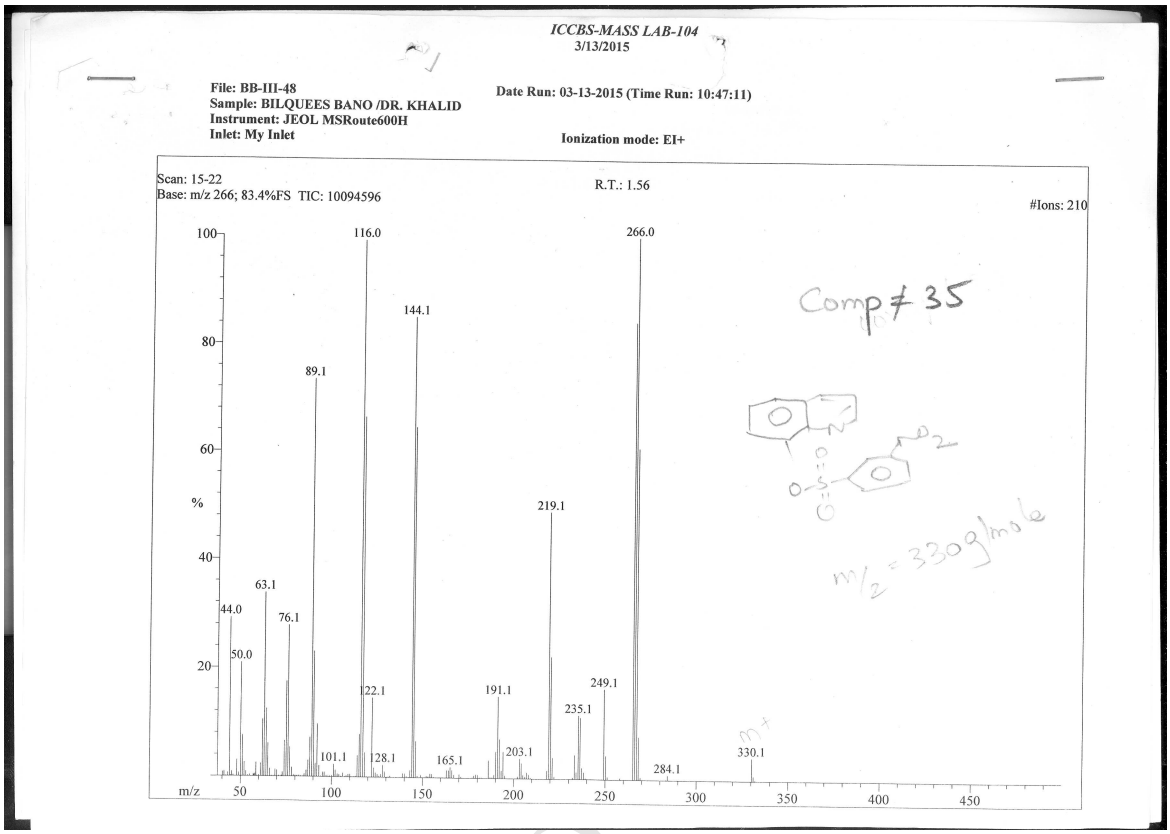


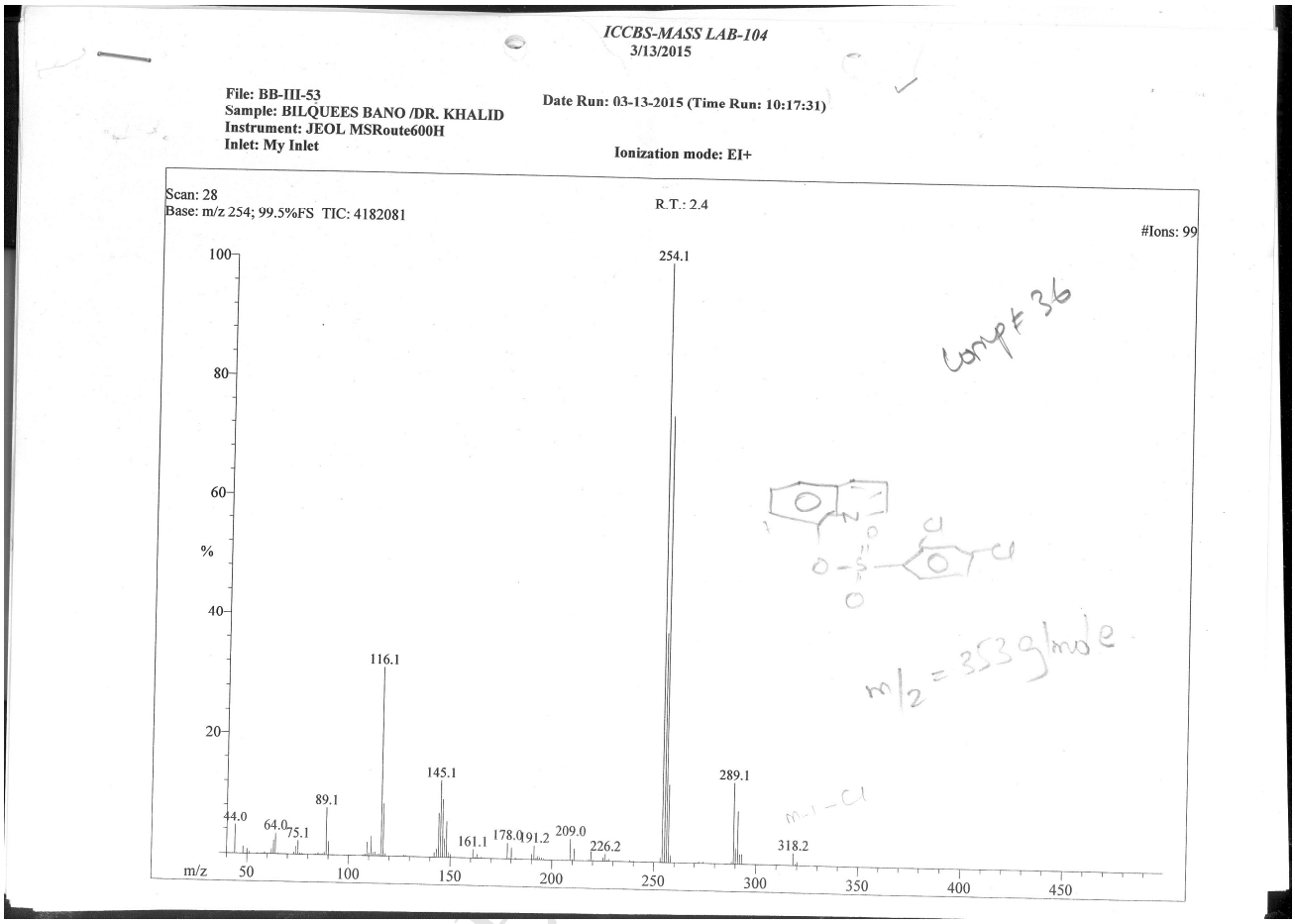

Compt 33



M/z = 285 g/mole







*ICCBS-MASS LAB-104*
3/13/2015

**File: BB-III-55**
**Sample: BILQUEES BANO /DR. KHALID**
**Instrument: JEOL MSRoute600H**
**Inlet: My Inlet**

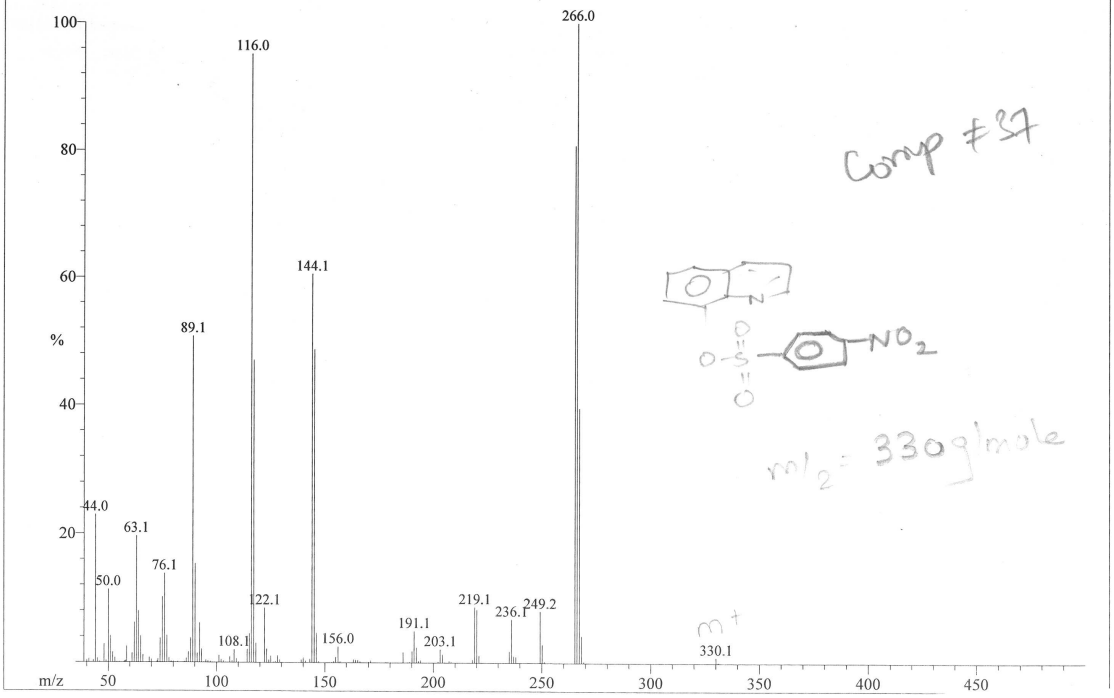
**Date Run: 03-13-2015 (Time Run: 10:05:31)**

**Ionization mode: EI+**

Scan: 21-25
Base: m/z 266; 74.4%FS TIC: 6118935

R.T.: 1.96

#Ions: 146



*ICCBS-MASS LAB-104*
**3/13/2015**

**File: BB-III-54**
**Sample: BILQUEES BANO /DR. KHALID**
**Instrument: JEOL MSRoute600H**
**Inlet: My Inlet**

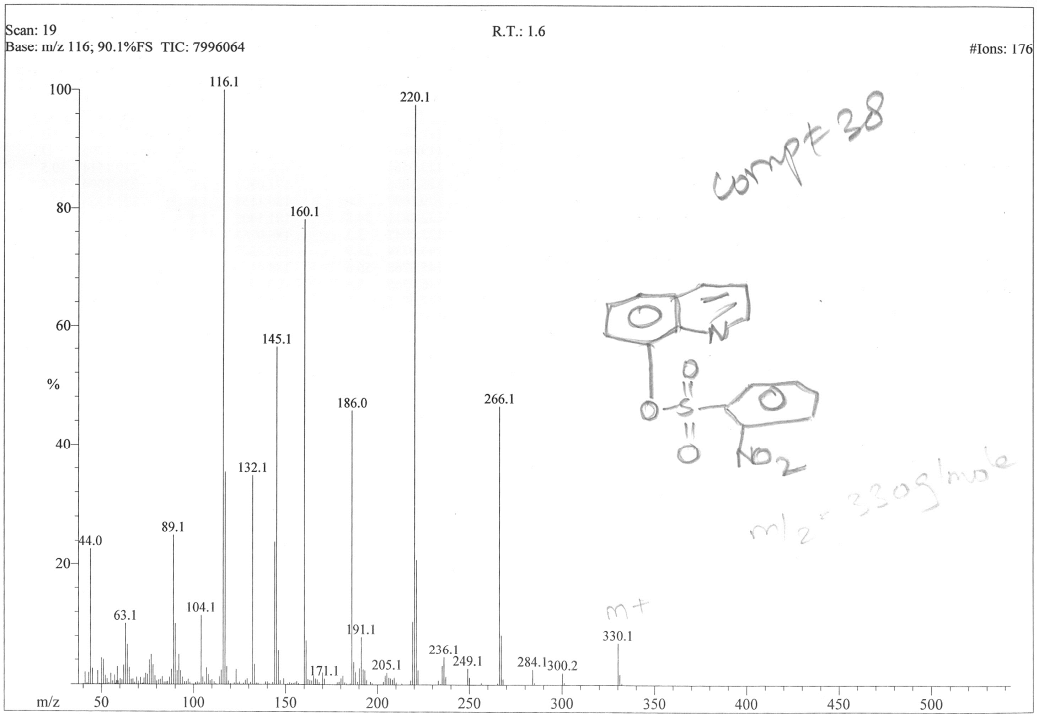
**Date Run: 03-13-2015 (Time Run: 09:28:44)**

**Ionization mode: EI+**

Scan: 19
Base: m/z 116; 90.1%FS TIC: 7996064

R.T.: 1.6

#Ions: 176



File: BB-III-89-FABP-
Sample: BILQUEES/DR.KHALID
Instrument: JEOL JMS-600H
Inlet: Direct Probe

Date Run: 04-10-2015 (Time Run: 16:57:05)

Ionization mode: FAB+

Run By: HEJ (ICCBS]

Scan: 21
Base: m/z 328; 24.3%FS TIC: 1487912

R.T.: 1.83

#Ions: 248