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Rational design and synthesis of novel dibenzo[*b,d*]furan-1,2,3-triazole conjugates as potent inhibitors of *Mycobacterium tuberculosis*

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Research Highlights

- A series of novel dibenzofuran-1,2,3-triazole conjugates were synthesized *via* click chemistry.
- All the new analogues were evaluated for their *in vitro* antimycobacterial activity.
- Three derivatives **5a**, **5d** and **5f** were resulted as best active antitubercular agents with selectivity index >25.
- Dibenzofuran- triazole conjugates were emerged as lead antitubercular agents for optimization.

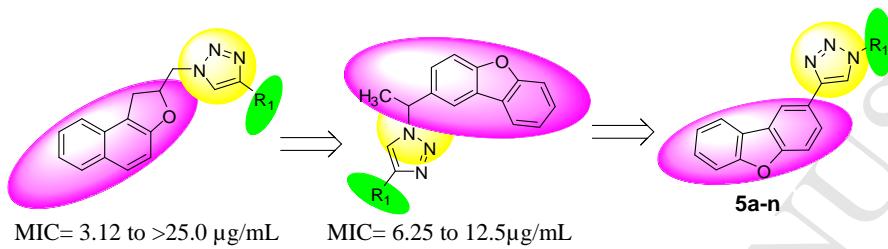
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Rational design and synthesis of novel dibenzo[*b,d*]furan-1,2,3-triazole conjugates as potent inhibitors of *Mycobacterium tuberculosis*

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Thirumal Yempala, Jonnalagadda Padma Sridevi , Perumal Yogeeshwari, Dharmarajan Sriram and Srinivas Kantevari*



| Triazole | MIC ($\mu\text{g}/\text{mL}$) | Selectivity Index |
|-----------|---------------------------------|-------------------|
| 5a | 1.56 | >25 |
| 5d | 0.78 | ~25 |
| 5f | 0.78 | >>25 |

Rational design and synthesis of novel dibenzo[*b,d*]furan-1,2,3-triazole conjugates as potent inhibitors of *Mycobacterium tuberculosis*

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Abstract: A series of novel dibenzo[*b,d*]furan-1,2,3-triazole conjugates, rationally designed by reorientation of dibenzo[*b,d*]furan pharmacophore and alkyl/aryl groups appended on 1,2,3-triazole core, were synthesized using click chemistry. The required key intermediate, 2-ethynyl dibenzo[*b,d*]furan **3** was prepared from dibenzofuran-2-carboxaldehyde using Corey-Fuchs reaction. Further reaction of **3** with various alkyl/aryl azides in the presence of copper catalyst produced 1,2,3-triazole conjugates in excellent yields. Evaluation of all the new compounds for *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv (ATCC27294), resulted **5a** (MIC: 1.56 μ g/mL), **5d** (MIC: 0.78 μ g/mL) and **5f** (MIC: 0.78 μ g/mL) as promising lead analogues. Among these three compounds, 1-(4-bromobenzyl)-4-(dibenzo[*b,d*]furan-2-yl)-1*H*-1,2,3-triazole (**5f**) emerged as the most promising antitubercular agent with lowest cytotoxicity (selectivity index: >>25) against the HEK-293T cell line.

Keywords: Dibenzofuran; *Mycobacterium tuberculosis*; Click Chemistry; Corey-Fuchs reaction; Cytotoxicity.

1.0 Introduction:

Tuberculosis (TB) is an ancient, contagious disease caused by pathogen *Mycobacterium tuberculosis* (MTB) and is characterized by tubercle lesions in the lungs [1]. It is the second-leading cause in mortalities and is responsible for infecting one-third of the world's population [2-4]. The World Health Organization (WHO) estimated 1.4 million deaths in 2011 are due to TB, which included 350,000 TB associated HIV infected deaths [5-7]. Additionally, the resurgence of its new virulent forms like multi drug resistant (MDR-TB) and extremely drug resistant (XDR-TB) has become a major threat to human kind [8-11]. The worsening situation necessitated an urgent need for discovery of modern curative drugs active in all the forms of TB [12, 13]. All these facts prompted re-engineering and repositioning of old natural and synthetic bioactives for the development of fast acting new antitubercular drugs with novel mechanism of action to achieve effective TB control [14-16].

Natural products derived from plants or microbes play a major role in drug discovery as a source of original bioactive structures and offer models for rational drug design [17-19]. In antitubercular agents, the lichen secondary metabolite Usnic acid (**I**) derived from dibenzofuran has shown to display an interesting antimycobacterial activity [20], but its weak potency did not permit its further development as an antitubercular drug. Synthetic analogues, for example, benzofuro-benzopyran **IV** (Fig.1) derived from dibenzofuran have shown good inhibitory activity against *M. tuberculosis* H37Rv but were found to be more cytotoxic [21-23]. On the other hand, 1,2,3-triazoles have gained enormous interest in recent years due to their broad spectrum pharmaceutical and therapeutic applications like antimicrobial activity against gram-positive bacteria, therapeutic fungicides of second generation, anti-inflammatory agents, inhibitors of tumor proliferation, invasion, metastasis and anti-HIV activity, etc. [24,25]. Triazole based antitubercular agents (for example, example **V-VIII**) may be regarded as a new class providing truly effective lead candidates [26-28] which are reported to inhibit bacteria and among them **VII** is presently in pre-clinical trials [29-31].

(Figure 1)

Additionally, these 1,2,3-triazoles possess remarkable metabolic stability and prove to be amide surrogates in various bioactive compounds [32, 33]. In our efforts to fight against tuberculosis, a series of dibenzofuran derived new molecules **II** and **III** (Fig. 1) designed and synthesized in our laboratory [34-37], exhibited promising antimycobacterial activity and are undergoing detailed investigations. Further, 1,2,3-triazole clubbed dibenzo[*b,d*]furans exhibited moderate activity with MICs ranging from 6.25-25.0 $\mu\text{g}/\text{mL}$ [38]. Continuing our work to attain potent antitubercular agents by integrating dibenzo[*b,d*]furan and triazole units, we herein report an efficient synthesis and antitubercular evaluation of new variants of dibenzo[*b,d*]furan-1,2,3-triazole conjugates in excellent yields *via* copper catalyzed click chemistry. Screening all ‘14’ new compounds for *in vitro* activity against *Mycobacterium tuberculosis* H37Rv (MTB) resulted three compounds **5a**, **5d** and **5f** as promising lead analogues with MIC ranging from 1.56 to 0.78 $\mu\text{g}/\text{mL}$ and has shown lower cytotoxicity with good selectivity index (SI).

2.0 Results and Discussion:

2.1 Chemistry:

The design strategy adopted here is based on the structural modification of our recently reported hybrids **IX** (Fig. 2) [38] through re-alignment and positioning of pharmacophore dibenzo[*b,d*]furan and alkyl/aryl fragments of the 1,2,3-triazole nucleus to result newer analogues for biological evaluation.

(Figure 2)

To begin with, dibenzo[*b,d*]furan-2-caraboxaldehyde (**1**), required was prepared by formylation of dibenzofuran following the literature procedure [39]. Aldehyde **1** was then reacted with CBr_4 in the presence of triphenyl phosphine under standard reaction conditions [40-43] resulted 2-(2,2-dibromovinyl)dibenzo[*b,d*]furan **2** in excellent yield (Scheme 1). Compound **2** was used as such without any further purification. Initial attempts to convert 2-(2,2-dibromovinyl)dibenzo[*b,d*]furan **2** to 2-ethynylbenzo[*b,d*]furan in the presence of a base under standard Corey-Fuchs reaction conditions [44-46] were unsuccessful. After series experiments by varying reaction parameters, 2-ethynylbenzo[*b,d*]furan **3** (Scheme 1) was successfully achieved in very good yields through the addition of *n*-butyl lithium (1.6 M) to a solution of **2** in THF at 0°C followed by stirring the reaction mixture at room temperature for 3h. The alkyne **3** thus obtained was fully characterized by IR, ^1H and ^{13}C NMR, and mass spectral data. Further the required azides **4a-n**

depicted in Figure 3 was prepared by following the reported procedures and were fully characterized by correlating their spectral data with literature [38, 47].

(Scheme 1) (Figure 3)

Having both alkyne **3** and azides **4a-n** in hand, we employed Huisgen's (3+2) cycloaddition in the presence of CuSO₄ catalyst, sodium ascorbate in *t*-butanol and water (1:1, v/v)[48,49]. All the azides **4a-n** reacted well with 2-ethynylbenzo[*b,d*]furan **3** to give triazole hybrids **5a-n** in excellent yields (Scheme 2). Here we notice that coupling of alkyne **3** with azides bearing electron withdrawing functional groups produced triazoles in slightly lower yields (for example, example **5h**) compared with the coupling of alkyne **3** with azides bearing electron donating functional groups (for example, example **5e**). All the triazoles **5a-n** obtained was fully characterized by ¹H, ¹³C NMR and mass (ESI and HR-MS) spectroscopic data. The purity of all the compounds (>95%) was determined by HPLC analysis.

(Scheme 2)

2.2. Pharmacology

A total of “14” newly synthesized dibenzo[*b,d*]furan-1,2,3-triazole conjugates **5a-n** were screened for *in vitro* antimycobacterial activity against *M. tuberculosis* H37Rv (ATCC27294) by agar dilution method. The MIC is defined as the minimum concentration of compound required to completely inhibit the bacterial growth. The MIC values ($\mu\text{g/mL}$) of all the compounds, **5a-n** and three standard antitubercular drugs determined in triplicate at pH 7.40 are presented in Figure 4. All the new compounds **5a-n** screened to have shown *in vitro* activity against MTB with MICs ranging from 0.78–50.0 $\mu\text{g/mL}$. Among them seven triazole analogues **5a**, **5d-g** and **5j-k** displayed MIC values below 6.25 $\mu\text{g/mL}$, a value postulated by the global program on the discovery of new antitubercular drugs as an upper threshold for the evaluation of new *M. tuberculosis* therapies. Out of these seven triazole analogues, two compounds **5d** and **5f** inhibited MTB with MIC 0.78 $\mu\text{g/mL}$, g/mL; one compound **5a** inhibited MTB with MIC 1.56 $\mu\text{g/mL}$ and three compounds **5e**, **5j** and **5k** inhibited MTB with MIC of 3.12 $\mu\text{g/mL}$. When compared to first-line TB drug Ethambutol (MIC 3.13 $\mu\text{g/mL}$), six compounds **5a**, **5d-f**, **5j** and **5k** were found to be more potent, though all the compounds were less potent than other anti-TB drug's isoniazid (0.1 $\mu\text{g/mL}$) and Rifampicine (0.2 $\mu\text{g/mL}$).

(Figure 4)

Structure-activity correlation of new compounds with respect to their antitubercular activity revealed that dibenzo[*b,d*]furan-1,2,3-triazole derivatives **5d-e** bearing electron donating methoxy group on phenyl ring are found to be more potent than **5h-i** have electron withdrawing group (-NO₂,COOMe-COOMe) on phenyl ring. It was also observed that triazole **5f** bearing 4-bromo phenyl is most active (MIC 0.78 µg/mL) than triazole **5g** bearing 3-bromophenylgroup. Conversely, in **5d** & **5e**, 3-methoxy analogue **5d** is comparatively more active than respective 4-methoxy analogue **5e**. Compared with our previous work [38] on antitubercular dibenzo[*b,d*]furan clubbed triazoles, dibenzofuran unit linked through C-C bond to the 1,2,3-triazole core may be pharmacologically better positioned to exhibit improved antitubercular activity.

(Table 1)

The *in vitro* cytotoxicity of all compounds evaluated for anti-TB activity were also assessed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay (MTT) assay against HEK-293Tcells at 50µg/ mL concentration. Percentage growth of cells was reported in table 1. Compounds that exhibited selectivity Index (SI) values greater than 10 in HEK-293Tcells were considered nontoxic. The most promising anti-TB compound **5d** and **5f** exhibited 62.1% and 27.8% inhibition at 50µg/mL with selectivity index of >25. Compounds **5b**, **5g** and **5k** were also found to be less cytotoxic at 50 µg/mL with favorable selectivity index. The results obtained here demonstrated that the compound **5f** with high inhibitory activity against *M. tuberculosis* (0.78 µg/mL) also exhibited lowest toxicity, i.e., high SI (>>25) against HEK-293Tcells.

3.0 Conclusion:

In conclusion, we have designed and synthesized a novel series of dibenzo[*b,d*]furan-1,2,3-triazoles **5a-n** through click chemistry. These new analogues were prepared by Huisgen's (3+2) cycloaddition reaction of 2-ethynylbenzo[*b,d*]furan **3** and different azides **4a-n** in presence of copper sulphate and sodium ascorbate. All these products were obtained in excellent yields and were fully characterized by spectral data. Screening all these new derivatives against *M. tuberculosis* H37Rv (MTB) and cytotoxicity revealed that **5a**, **5d** and **5f** are best active antitubercular agents with therapeutic index >25 compared to the other evaluated compounds. Among these three antitubercular agents, **5f** is the most active (MIC 0.78 µg/mL) and least

cytotoxic ($SI >> 25$) compound. The results described here demonstrate the potential utility of dibenzo[*b,d*]furan-1,2,3-triazoles as antitubercular agents for further optimization.

4.0 Experimental Section:

Melting points were measured with a Fischer-Johns melting point apparatus and are uncorrected. IR spectra was recorded as neat liquids or KBr pellets and absorptions are reported in cm^{-1} . NMR spectra was recorded on 300 (Bruker) and 500 MHz (Varian) spectrometers in appropriate solvents using TMS as internal standard or the solvent signals as secondary standards and the chemical shifts are shown in δ scales. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), etc. ^{13}C NMR spectra was recorded on 75 and 125 MHz spectrometers. High-resolution mass spectra was obtained by using ESI-QTOF mass spectrometry. All the experiments were monitored by analytical thin layer chromatography (TLC) performed on silica gel GF254 pre-coated plates. After elution, plate was visualized under UV illumination at 254 nm for UV active materials. Further visualization was achieved by staining with PMA and charring on a hot plate. Solvents were removed under vacuum and heated in a water bath at 35 °C. Silica gel finer than 200 mesh was used for column chromatography. Columns were packed as the slurry of silica gel in hexane and equilibrated with the appropriate solvent/solvent mixture prior to use. The compounds were loaded neat or as a concentrated solution using the appropriate solvent system. The elution was assisted by applying pressure with an air pump. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. Appropriate names (if possible) for all the new compounds were given with the help of ChemBioOffice 12.0; 2010.

4.1. 2-(2,2-Dibromovinyl)dibenzo[*b,d*]furan 2:

A solution of dibenzo[*b,d*]furan-2-carbaldehyde **1** (1.96 g, 10 mmol), triphenyl phosphine (10.48 g, 40 mmol) and carbon tetrabromide (6.62 g, 20 mmol) in dry dichloromethane at 0°C was stirred for 1h at RT. Precipitation of triphenyl phosphine oxide using pentane(50 mL) and filtration through a short column of silica gel, evaporation of dichloromethane resulted 2-(2,2-dibromovinyl)dibenzo[*b,d*]furan **2** (3.4 g, 95%) as yellow solid. It was directly used in the next step without any further purification.

4.2 Preparation of 2-Ethynylbenzo[*b,d*]furan 3:

To a solution of dibromide **2** (3.52 g, 10 mmol) in dry THF (30 mL), n-BuLi (1. 6M, 25 mmol) was added with stirring at 0°C. After completion (TLC), the reaction mixture was quenched with saturated NH₄Cl at 0°C, extracted with ether (3 x 20 mL), dried over anhydrous sodium sulphate and concentrated at reduced pressure. The crude reaction mixture was purified over silica gel column chromatography (n-pentane) to give 2-ethynylbibenzo [b,d]furan **3** (1.72 g, 90%) as white solid.

4.2.1 Analytical data of compound 3: m.p. 86-88 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.07(d, J=0.9Hz, 1H, Ar-H), 7.89(d, J=7.5Hz, 1H, Ar-H), 7.59-7.39 (m, 4H, Ar-H), 7.32(dd, J=0.7&8.1Hz, 1H, Ar-H), 3.00(s, 1H, ≡C-H). ¹³C NMR (100 MHz, CDCl₃) δ 156.5, 155.9, 131.1, 127.6, 124.6, 124.4, 123.4, 123.0, 120.7, 116.6, 111.7, 111.7, 83.7 (-C≡C-), 76.2 (≡C-H). IR (KBr) 3268 (≡C-H), 3046, 2925, 1775, 1445, 1279, 1197, 888, 821, 745, 722cm⁻¹. MS-EI Calcd. for C₁₄H₈O: 192, found: [M]⁺=192 (100%).

4.3 General procedure for the synthesis of 1,2,3-Triazoles **5a-5n**:

Compound **3** (1.0 mmol), Azide **4a-4n** (1.0 mmol), copper sulphate pentahydrate (20 mol %) and sodium ascorbate (20 mol %) in *tert*-butanol &water (1:1, v/v, 4mL) was stirred at RT for appropriate time. After completion (TLC), the reaction mixture was treated with ethyl acetate (2x10 mL) and water (5 mL), the organic layer was separated, washed with brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel using ethyl acetate/ hexane (1:2) to obtain corresponding 1,2,3-triazoles **5a-n**.

4.3.1 Ethyl 2-(4-(dibenzob[b,d]furan-2-yl)-1*H*-1,2,3-triazol-1-yl)acetate **5a**:

White solid. M.p. 131-133 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.50 (d, J=1.5Hz, 1H, Ar-H), 8.02-7.85(m, 3H, Ar-H), 7.59(t, J=7.5Hz, 2H, Ar-H), 7.48(t, J=7.5Hz, 1H, Ar-H), 7.36(t, J=7.5Hz, 1H, Ar-H), 5.24(s, 2H, Ar-CH₂-), 4.31(q, J=6.7Hz, 2H, -OCH₂-), 1.33(t, J=6.7Hz, 3H, -CH₃). ¹³C NMR(75 MHz, CDCl₃) δ 166.2 (C=O), 156.5, 155.9, 148.2, 127.3, 125.2, 125.0, 124.7, 123.9, 122.8, 120.7, 117.9, 111.8, 111.6, 62.4 (Ar-CH₂), 50.9 (-OCH₂), 14.0 (-CH₃). IR (KBr) 3132, 3103, 2924, 2852, 1885, 1755 (C=O), 1459, 1373, 1203, 841, 751cm⁻¹. MS (ESI) m/z 322[M+H]⁺; HRMS (ESI) Calcd for C₁₈H₁₆N₃O₃: 322.1186, found: 322.1186.

4.3.2 4-(4-(Dibenzob[b,d]furan-2-yl)-1*H*-1,2,3-triazol-1-yl)butan-1-ol **5b**:

White solid. m.p. 127-129 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.45 (s, 1H, Ar-H), 7.96(d, $J=6.8\text{Hz}$, 1H, Ar-H), 7.89-7.73(m, 2H, Ar-H), 7.57(t, $J=8.3\text{Hz}$, 2H, Ar-H), 7.45(t, $J=7.5\text{Hz}$, 1H, Ar-H), 7.34(t, $J=7.5\text{Hz}$, 1H, Ar-H), 4.47(t, $J=6.0\text{Hz}$, 2H, Ar- CH_2 -), 3.72(t, $J=5.3\text{Hz}$, 2H, -OCH₂-), 2.18-2.00(m, 2H, -CH₂-), 1.74-1.55(m, 2H, -CH₂-). ^{13}C NMR(75 MHz, CDCl_3) δ 156.5, 155.9, 147.7, 127.3, 125.4, 124.9, 123.9, 122.8, 120.7, 119.3, 117.8, 111.8, 111.6, 61.7 (Ar-CH₂-), 50.1(-OCH₂-), 29.2 (-CH₂-), 26.9 (-CH₂-). IR (KBr) 3381(-OH), 3143, 2926, 2860, 1586, 1473, 1447, 1200, 1061, 842, 745cm⁻¹. MS (ESI) m/z 308 [M+H]⁺; HRMS (ESI) Calcd for C₁₈H₁₈N₃O₂: 308.1393, found: 308.1394.

4.3.3 1-Benzyl-4-(dibenzo[b,d]furan-2-yl)-1H-1,2,3-triazole **5c**:

White solid. m.p. 184-186 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.45 (d, $J=1.5\text{Hz}$, 1H, Ar-H), 7.96(d, $J=7.7\text{Hz}$, 1H, Ar-H), 7.84(dd, $J=1.6\&8.3\text{Hz}$, 1H, Ar-H), 7.72(s, 1H, Ar-H), 7.57(dd, $J=2.2\&8.5\text{Hz}$, 2H, Ar-H), 7.47 (t, $J=7.3\text{Hz}$, 2H, Ar-H), 7.43-7.31(m, 5H, Ar-H), 5.57(s, 2H, Ar-CH₂-). ^{13}C NMR (75 MHz, CDCl_3) δ 156.5, 155.9, 148.2, 134.6, 129.1, 128.7, 128.0, 127.4, 125.4, 125.0, 124.7, 123.9, 122.8, 120.8, 119.2, 117.9, 111.8, 111.7, 54.2 (Ar-CH₂-). IR (KBr) 3142, 2881, 1682, 1538, 1462, 1344, 1239, 1098, 1027, 856, 794cm⁻¹. MS (ESI) m/z 326 [M+H]⁺; HRMS (ESI) Calcd for C₂₁H₁₆N₃O: 326.1287, found: 326.1291.

4.3.4 4-(Dibenzo[b,d]furan-2-yl)-1-(3-methoxybenzyl)-1H-1,2,3-triazole **5d** :

White solid. m.p. 91-93 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.45 (s, 1H, Ar-H), 7.97(d, $J=7.9\text{Hz}$, 1H, Ar-H), 7.84(d, $J=7.9\text{Hz}$, 1H, Ar-H), 7.73(s, 1H, Ar-H), 7.57(d, $J=8.9\text{Hz}$, 2H, Ar-H), 7.46 (t, $J=7.9\text{Hz}$, 1H, Ar-H), 7.38-7.28(m, 2H, Ar-H), 6.95-6.82(m, 3H, Ar-H), 5.57(s, 2H, Ar-CH₂-), 3.80(s, 3H, -OCH₃). ^{13}C NMR (75 MHz, CDCl_3) δ 160.1, 156.5, 155.9, 148.2, 136.0, 130.1, 127.3, 125.5, 125.0, 124.7, 123.9, 122.8, 120.7, 120.2, 117.9, 114.1, 113.6, 111.8, 111.6, 55.2 (Ar-CH₂-), 54.1(-OCH₃). IR (KBr) 3418, 2927, 2095, 1583, 1437, 1259, 1194, 1047, 846, 751cm⁻¹. MS (ESI) m/z 356[M+H]⁺; HRMS (ESI) Calcd for C₂₂H₁₈N₃O₂: 356.1393, found: 356.1397.

4.3.5 4-(Dibenzo[b,d]furan-2-yl)-1-(4-methoxybenzyl)-1H-1,2,3-triazole **5e**:

Pale white solid. m.p. 121-123 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.45 (d, $J=1.5\text{Hz}$, 1H, Ar-H), 8.04-7.91(m, 1H, Ar-H), 7.84(dd, $J=1.7\&8.4\text{Hz}$, 1H, Ar-H), 7.68(s, 1H, Ar-H), 7.57(d, $J=8.3\text{Hz}$, 2H, Ar-H), 7.40-7.24(m, 4H, Ar-H), 6.93(d, $J=8.4\text{ Hz}$, 2H, Ar-H), 5.54(s, 2H, Ar-CH₂-), 3.82(s, 3H, -OCH₃). ^{13}C NMR (75 MHz, CDCl_3) δ 159.8, 156.5, 155.9, 148.1, 129.6, 127.3, 126.5, 125.5,

124.9, 124.6, 123.7, 122.8, 120.7, 119.0, 117.8, 114.4, 111.8, 111.6, 55.2 (Ar-CH₂-), 53.7 (-OCH₃). IR (KBr) 3053, 2923, 2940, 1896, 1611, 1535, 1446, 1201, 1181, 803, 741cm⁻¹. MS (ESI) m/z 356 [M+H]⁺; HRMS (ESI) Calcd for C₂₂H₁₈N₃O₂: 356.1393, found: 356.1398.

4.3.6 1-(4-Bromobenzyl)-4-(dibenzo[b,d]furan-2-yl)-1H-1,2,3-triazole **5f**:

White solid. m.p. 125-127 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.45 (s, 1H, Ar-H), 7.96(d, J=8.3Hz, 1H, Ar-H), 7.84(dd, J=1.5&8.3Hz, 1H, Ar-H), 7.72(s, 1H, Ar-H), 7.62-7.43(m, 5H, Ar-H), 7.40-7.32(m, 1H, Ar-H), 7.20(d, J=8.3Hz, 2H, Ar-H), 5.50(s, 2H, Ar-CH₂-). ¹³C NMR (75 MHz, CDCl₃) δ 156.5, 156.0, 148.5, 133.6, 132.3, 129.6, 127.4, 125.3, 124.9, 124.7, 123.9, 122.9, 122.8, 120.8, 119.1, 117.9, 111.9, 111.7, 53.5(Ar-CH₂-). IR (KBr) 3082, 2925, 1916, 1589, 1443, 1339, 1201, 1070, 1013, 843, 746cm⁻¹. MS (ESI) m/z 404 [M+H]⁺; HRMS (ESI) Calcd for C₂₁H₁₅Br N₃O: 404.0393, found: 404.0398.

4.3.7 1-(3-Bromobenzyl)-4-(dibenzo[b,d]furan-2-yl)-1H-1,2,3-triazole **5g**:

White solid. m.p. 143-145 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.45 (d, J=1.5Hz, 1H, Ar-H), 8.00-7.92(m, 1H, Ar-H), 7.85(dd, J=1.5&8.3Hz, 1H, Ar-H), 7.75(s, 1H, Ar-H), 7.57(dd, J=3.0&8.3Hz, 2H, Ar-H), 7.53-7.42(m, 3H, Ar-H), 7.39-7.30(m, 1H, Ar-H), 7.29-7.23(m, 2H, Ar-H), 5.57(s, 2H, Ar-CH₂-). ¹³C NMR (75 MHz, CDCl₃) δ 156.5, 156.0, 148.4, 136.8, 131.9, 130.9, 130.6, 127.4, 126.5, 125.0, 124.7, 123.9, 123.0, 122.8, 120.7, 119.2, 117.9, 111.8, 111.6, 53.4(Ar-CH₂-). IR (KBr) 3056, 2923, 1775, 1594, 1474, 1440, 1200, 1069, 841, 749cm⁻¹. MS (ESI) m/z 404 [M+H]⁺; HRMS (ESI) Calcd for C₂₁H₁₅Br N₃O: 404.0393, found: 404.0398.

4.3.8 4-(Dibenzo[b,d]furan-2-yl)-1-(4-nitrobenzyl)-1H-1,2,3-triazole **5h**:

Light yellow solid. m.p. 156-158 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.47 (d, J=1.7Hz, 1H, Ar-H), 8.26(d, J=8.6Hz, 2H, Ar-H), 7.98(d, J=7.5Hz, 1H, Ar-H), 7.86(dd, J=1.7&8.4Hz, 1H, Ar-H), 7.81(s, 1H, Ar-H), 7.63-7.56(m, 2H, Ar-H), 7.53-7.44(m, 3H, Ar-H), 7.37(td, J=1.1&7.5Hz, 1H, Ar-H), 5.73(s, 2H, Ar-CH₂-). ¹³C NMR (75 MHz, CDCl₃) δ 155.7, 155.0, 147.1, 146.8, 143.3, 128.9, 127.7, 125.8, 124.9, 124.0, 123.8, 123.3, 123.1, 121.6, 121.2, 117.7, 112.0, 111.6, 52.1(Ar-CH₂-). IR (KBr) 3130, 3088, 2924, 1603, 1515 (N-O), 1451, 1346 (N-O), 1195, 840, 750cm⁻¹. MS (ESI) m/z 371 [M+H]⁺; HRMS (ESI) Calcd for C₂₁H₁₅N₄O₃: 371.1138, found: 371.1149.

4.3.9 Methyl 4-((4-(dibenzo[b,d]furan-2-yl)-1H-1,2,3-triazol-1-yl)methyl)benzoate **5i**:

White solid. m.p. 177-179 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.47 (s, 1H, Ar-H), 8.08(d, $J=7.5\text{Hz}$, 2H, Ar-H), 7.99(d, $J=7.5\text{Hz}$, 1H, Ar-H), 7.86(d, $J=8.3\text{Hz}$, 1H, Ar-H), 7.76(s, 1H, Ar-H), 7.66-7.55(m, 2H, Ar-H), 7.53-7.32(m, 4H, Ar-H), 5.68(s, 2H, Ar- CH_2 -), 3.93(s, 3H, -OCH₃). ^{13}C NMR (75 MHz, CDCl_3) δ 166.3 (C=O), 156.5, 156.0, 148.5, 139.4, 130.5, 130.3, 127.7, 127.4, 125.3, 125.0, 124.7, 123.9, 122.8, 120.8, 119.3, 117.9, 111.9, 111.7, 53.7 (Ar-CH₂-), 52.2 (-OCH₃). IR (KBr) 3077, 2923, 2852, 1716 (C=O), 1459, 1277, 1191, 840, 725cm⁻¹. MS (ESI) m/z 384 [M+H]⁺; HRMS (ESI) Calcd for C₂₃H₁₈N₃O₃: 384.1342, found: 384.1351.

4.3.10 4-(Dibenzo[b,d]furan-2-yl)-1-(1-p-tolylethyl)-1H-1,2,3-triazole **5j**:

White solid. m.p. 91-93 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.44(s, 1H, Ar-H), 7.97(d, $J=7.3\text{Hz}$, 1H, Ar-H), 7.84(dd, $J=1.5\&8.4\text{Hz}$, 1H, Ar-H), 7.68(s, 1H, Ar-H), 7.56(d, $J=8.3\text{Hz}$, 2H, Ar-H), 7.47(t, $J=7.1\text{Hz}$, 1H, Ar-H), 7.36 (t, $J=7.5\text{Hz}$, 1H, Ar-H), 7.30-7.16(m, 4H, Ar-H), 5.87(q, $J=6.9\text{Hz}$, 1H, Ar-CH-), 2.36(s, 3H, Ar-CH₃), 2.04(d, $J=7.1\text{Hz}$, 3H, -CH₃). ^{13}C NMR (75 MHz, CDCl_3) δ 156.4, 155.8, 147.6, 138.3, 136.7, 129.6, 127.2, 126.4, 125.6, 124.9, 124.6, 123.9, 122.7, 120.7, 120.4, 118.0, 117.8, 111.7, 111.6, 60.0 (Ar-CH-), 21.2 (Ar-CH₃), 21.0 (-CH₃). IR (KBr) 3125, 2923, 2854, 1892, 1589, 1514, 1447, 1359, 1202, 1125, 1019, 822, 745cm⁻¹. MS (ESI) m/z 354[M+H]⁺; HRMS (ESI) Calcd for C₂₃H₂₀N₃O: 354.1600, found: 354.1603.

4.3.11 4-(Dibenzo[b,d]furan-2-yl)-1-(1-(4-methoxyphenyl)ethyl)-1H-1,2,3-triazole **5k**:

White solid. m.p. 89-91 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.44(d, $J=1.3\text{Hz}$, 1H, Ar-H), 8.05-7.91(m, 1H, Ar-H), 7.84(dd, $J=1.8\&8.6\text{Hz}$, 1H, Ar-H), 7.66(s, 1H, Ar-H), 7.57(d, $J=8.3\text{Hz}$, 2H, Ar-H), 7.51-7.42 (m, 1H, Ar-H), 7.40-7.28(m, 3H, Ar-H), 6.92(d, $J=8.6\text{Hz}$, 2H, Ar-H), 5.86(q, $J=6.9\text{Hz}$, 1H, Ar-CH-), 3.81(s, 3H, -OCH₃), 2.03 (d, $J=6.9\text{Hz}$, 3H, -CH₃). ^{13}C NMR (75 MHz, CDCl_3) δ 156.4, 155.8, 147.5, 131.5, 127.8, 127.3, 125.3, 124.4, 124.6, 123.8, 122.7, 120.7, 118.0, 117.8, 114.2, 111.7, 111.5, 59.7 (-OCH₃), 21.1(-CH₃). IR(KBr) 3382, 3090, 2935, 2258, 1751, 1610, 1513, 1442, 1214, 1030, 839, 727cm⁻¹. MS (ESI) m/z 370[M+H]⁺; HRMS (ESI) Calcd for C₂₃H₂₀N₃O₂: 370.1550, found: 370.1557.

4.3.12 4-(Dibenzo[b,d]furan-2-yl)-1-(1-(4-nitrophenyl)ethyl)-1H-1,2,3-triazole **5l**:

Light yellow syrup; ^1H NMR (300 MHz, CDCl_3) δ 8.47(s, 1H, Ar-H), 8.25(d, $J=8.3\text{Hz}$, 2H, Ar-H), 7.98(d, $J=7.5\text{Hz}$, 1H, Ar-H), 7.91-7.76(m, 2H, Ar-H), 7.64-7.55(m, 2H, Ar-H), 7.53-7.43(m, 3H, Ar-H), 7.36(t, $J=7.5\text{Hz}$, 1H, Ar-H), 5.99(q, $J=6.7\text{Hz}$, 1H, Ar-CH-), 2.11(d, $J=7.5\text{Hz}$, 3H, -CH₃). ^{13}C

NMR (75 MHz, CDCl₃) δ 156.4, 155.9, 148.1, 147.6, 146.9, 127.4, 127.2, 126.0, 125.1, 124.9, 124.7, 124.1, 122.8, 120.7, 118.7, 118.2, 117.8, 111.8, 111.6, 59.4(Ar-CH-), 21.1(-CH₃).IR (Neat) 2924, 2853, 1605, 1519 (N-O), 1446, 1346 (N-O), 1159, 1105, 856, 748, 716cm⁻¹. MS (ESI) m/z 385[M+H]⁺; HRMS (ESI) Calcd for C₂₂H₁₇N₄O₃: 385.1295, found: 385.1308.

4.3.13 4-(Dibenzo[b,d]furan-2-yl)-1-(1-(dibenzo[b,d]furan-2-yl)ethyl)-1H-1,2,3-triazole **5m**:

White solid. m.p. 125-127 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.44(d, J=1.5Hz, 1H, Ar-H), 8.01-7.91(m, 3H, Ar-H), 7.85(dd, J=1.5&8.3Hz, 1H, Ar-H), 7.72(s, 1H, Ar-H), 7.63-7.54(m, 4H, Ar-H), 7.52-7.41 (m, 3H, Ar-H), 7.39-7.29(m, 2H, Ar-H), 6.07(q, J=7.5Hz, 1H, Ar-CH-), 2.17(d, J=6.7 Hz, 3H, -CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 156.5, 156.4, 155.8, 147.7, 134.3, 127.5, 127.2, 125.6, 124.9, 124.7, 124.5, 123.8, 123.5, 122.8, 122.7, 121.2, 121.0, 120.6, 118.8, 118.1, 117.7, 112.0, 111.7, 111.6, 111.5, 60.2 (Ar-CH-), 21.5 (-CH₃). IR (KBr) 3435, 2924, 1876, 1586, 1447, 1242, 1195, 1119, 1021, 811, 743cm⁻¹. MS (ESI) m/z 430 [M+H]⁺; HRMS (ESI) Calcd for C₂₈H₂₀N₃O₂: 430.15500, found: 430.15573.

4.3.14 4-(Dibenzo[b,d]furan-2-yl)-1-(1-(dibenzo[b,d]thiophen-2-yl)ethyl)-1H-1,2,3-triazole **5n**:

White solid. m.p. 95-97 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.44 (s, 1H, Ar-H), 8.23-8.09(m, 2H, Ar-H), 8.00-7.82(m, 4H, Ar-H), 7.73(s, 1H, Ar-H), 7.62-7.40(m, 6H, Ar-H), 7.33 (t, J=7.5Hz, 1H, Ar-H), 6.06(q, J=6.7Hz, 1H, Ar-CH-), 2.18(d, J=6.7 Hz, 3H, -CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 156.5, 155.9, 147.8, 139.8, 139.6, 136.2, 134.8, 127.3, 125.6, 125.0, 125.0, 124.5, 123.9, 122.8, 122.8, 121.6, 120.7, 119.6, 118.2, 117.8, 111.7, 111.6, 60.3(Ar-CH-), 21.4(-CH₃). IR(KBr) 3119, 2923, 1639, 1468, 1440, 1323, 1192, 1021, 841, 813, 758cm⁻¹. MS (ESI) m/z 446[M+H]⁺; HRMS (ESI) Calcd for C₂₈H₂₀N₃OS: 446.1321, found: 446.1322.

4.4. Antitubercular evaluation:

Two-fold serial dilutions (50.0, 25.0, 12.5, 6.25, 3.13, 1.56, 0.78 and 0.4 µg/mL) of each test compounds **5a-n** and drugs were prepared and incorporated into Middlebrook 7H11 agar medium with OADC Growth Supplement. Inoculum of *M. tuberculosis* H₃₇Rv ATCC 27294 was prepared from fresh Middlebrook 7H11 agar slants with OADC (oleic acid, albumin, dextrose and catalase; Difco) Growth Supplement adjusted to 1 mg/mL (wet weight) in Tween 80 (0.05%) saline diluted to 10⁻² to give a concentration of ~ 10⁷ cfu/mL. A 5 µL amount of bacterial suspension was spotted into 7H11 agar tubes containing 10-fold serial dilutions of drugs per mL. The tubes were incubated

at 37 °C, and final readings were recorded after 28 days. This method is similar to that recommended by the National Committee for Clinical Laboratory Standards for the determination of MIC in triplicate.

4.5. Cytotoxicity:

All the new compounds synthesized were further examined for cytotoxicity against Human Embryonic Kidney Cell-line 293T (HEK-293T) cells at the concentration of 50 µg/mL (Table 1).

After 72 h of exposure, viability was assessed on the basis of cellular conversion of MTT into a formazan product using the Promega Cell Titer 96 non-radioactive cell proliferation assay. The selectivity index (SI) values were determined based on the approximation of IC₅₀ values.

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Appendix. Supplementary data:

Supplementary data associated with this article can be found in online version. Copies of ¹H, ¹³C NMR and mass (ESI-MS and HRMS) spectra of all the new compounds were incorporated in that.

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Captions to illustrations

Table 1: Percentage Inhibition and selectivity index (SI) values of dibenzofuran analogues **5a-n** against HEK-293T cell line.

Figure 1: Representative antitubercular agents of dibenzofurans (**I-IV**), triazoles (**V-VII**) and their hybrid **VIII**.

Figure 2: Design strategy for new dibenzofuran-triazole hybrids

Figure 3: Azides **4a-n** used in the study.

Figure 4: Antitubercular evaluation of new analogues **5a-n** against *M. tuberculosis* H₃₇RV

Scheme 1: Synthesis of 2-ethynylidibenzod[b,d]furan **3**

Scheme 2: Synthesis of dibenzod[b,d]furan-1,2,3-triazoles **5a-n**.

Table 1.

| Entry | Product | % cell inhibition at 50µg/mL | IC ₅₀ approximation (µg/ mL) | SI index (IC ₅₀ /MIC) |
|-------|---------|------------------------------|---|----------------------------------|
| 1 | 5a | 38.8 | >50 | >25 |
| 2 | 5b | 21.9 | >>50 | ~1-2 |
| 3 | 5c | 36.1 | >50 | ~1-2 |
| 4 | 5d | 62.1 | <50 | ~25 |
| 5 | 5e | 52.7 | ~50 | ~16 |
| 6 | 5f | 27.8 | >50 | >>25 |
| 7 | 5g | 12.0 | >>50 | >10 |
| 8 | 5h | 46.3 | ~50 | ~1-2 |
| 9 | 5i | 58.1 | <50 | ~1-2 |
| 10 | 5j | 43.1 | ~50 | ~16 |
| 11 | 5k | 18.9 | >>50 | >>16 |
| 12 | 5l | 38.9 | >50 | ~2 |
| 13 | 5m | 52.6 | ~50 | ~1-2 |
| 14 | 5n | 61.1 | <50 | ~1-2 |

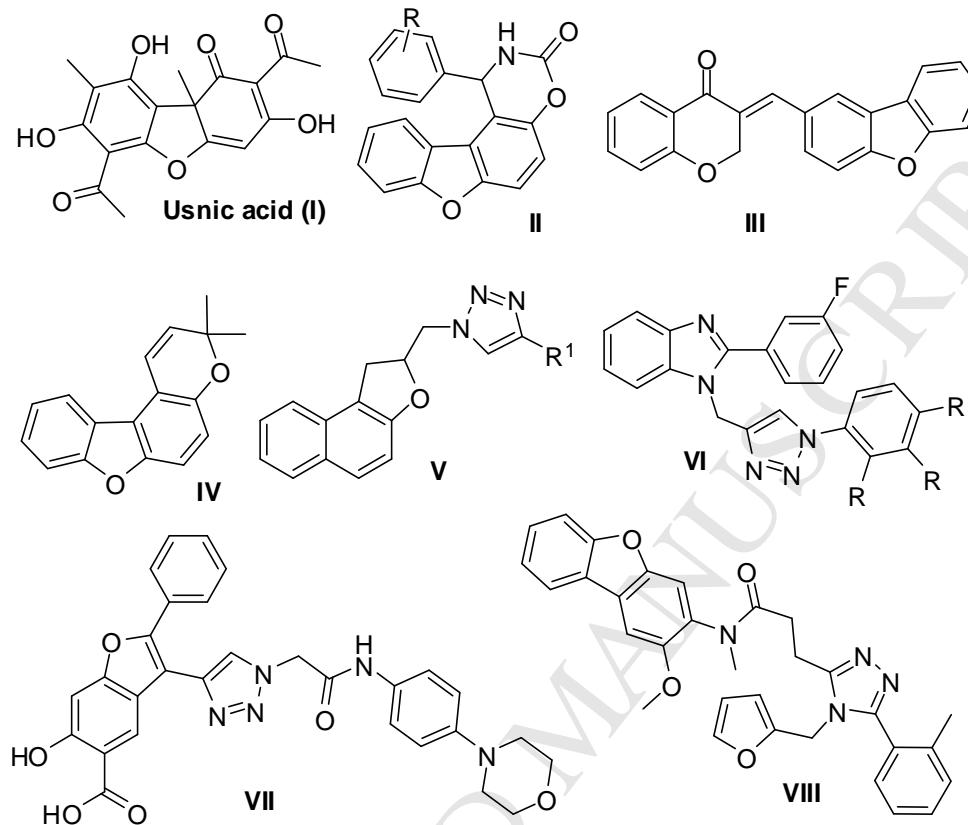
Figure 1.

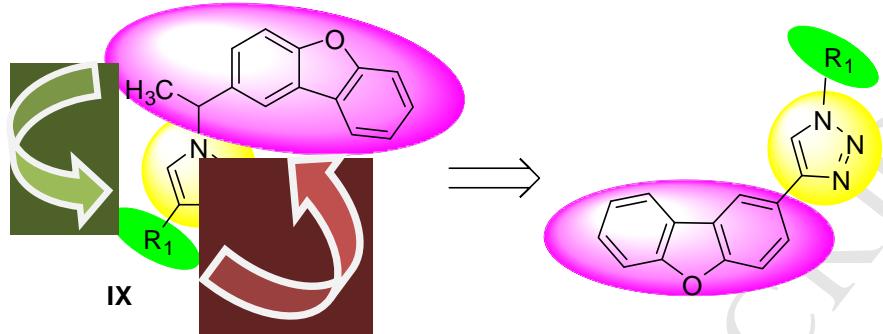
Figure 2.

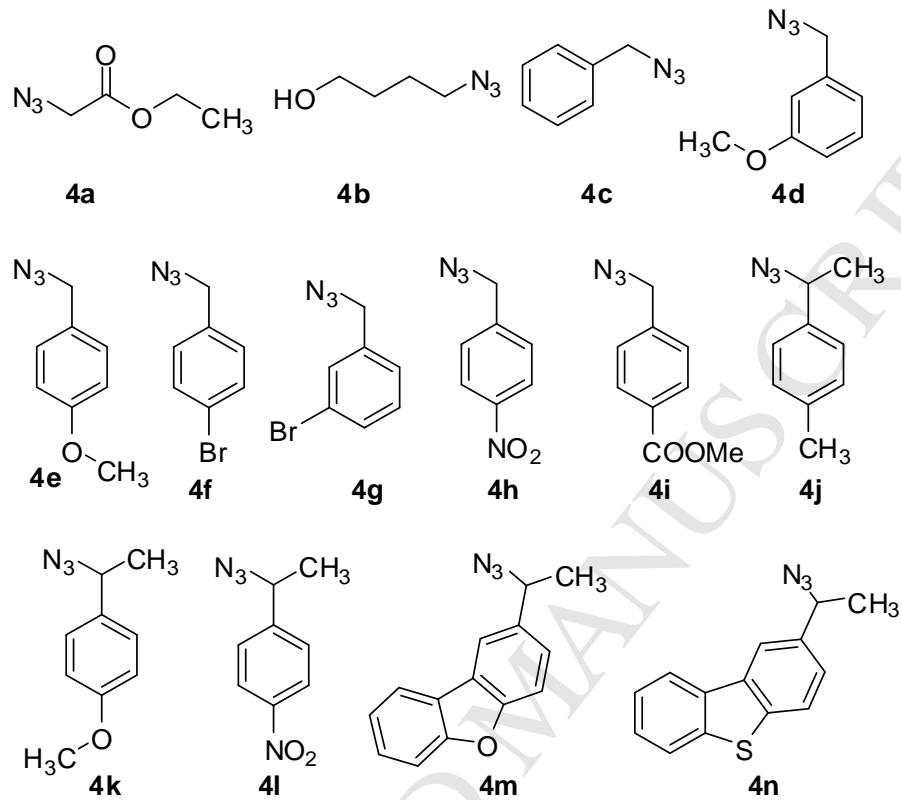
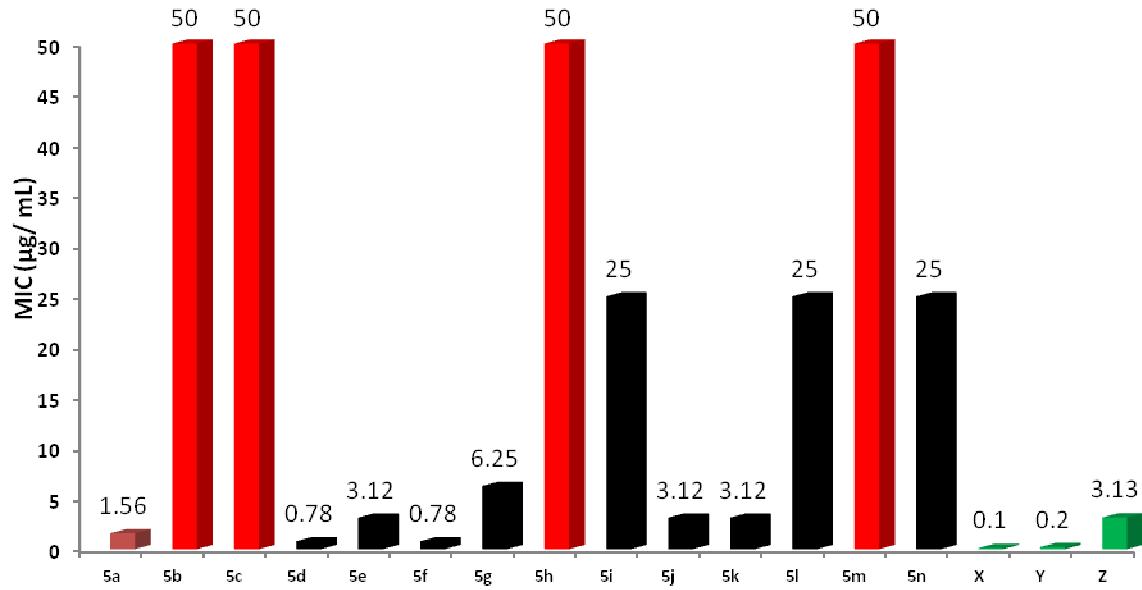
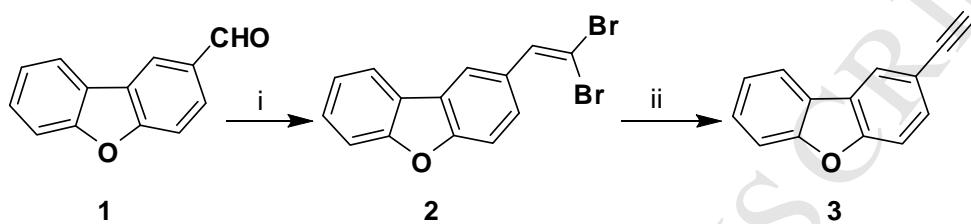
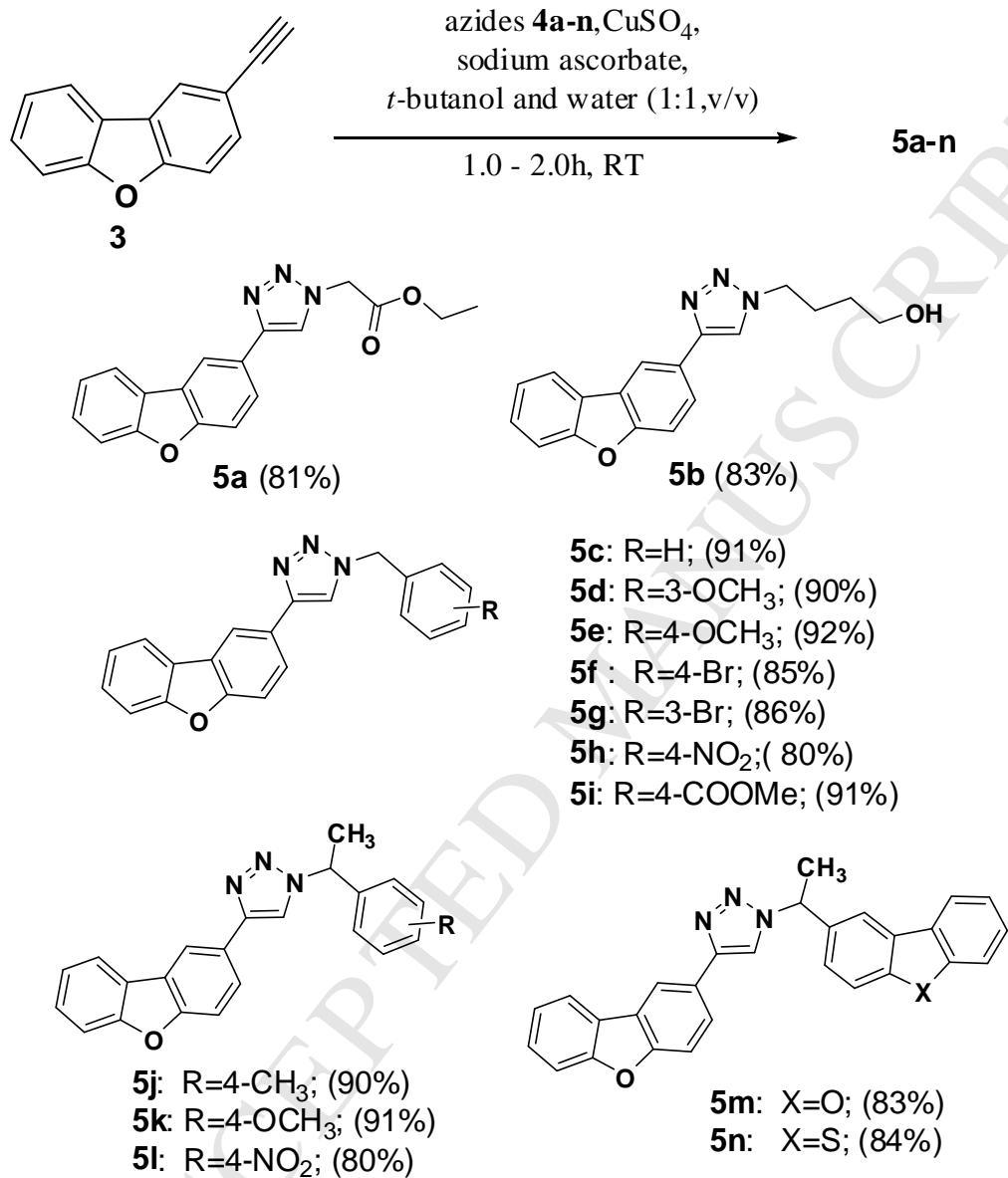
Figure 3.

Figure 4.

X: Isoniazide, Y: Rifampicine, Z: Ethambutol

Scheme 1:

Reaction conditions: (i).CBr₄, PPh₃, DCM, 1h, 95 % (ii). nBu-Li, THF, 0°C to RT, 3h, 90%.

Scheme 2.

Rational design and synthesis of novel dibenzo[*b,d*]furan-1,2,3-triazole conjugates as potent inhibitors of *Mycobacterium tuberculosis*

Thirumal Yempala,^a Jonnalagadda Padma Sridevi,^b Perumal Yogeeshwari,^b Darmarajan Sriram,^b and Srinivas Kantevari^{*a}

^aOrganic Chemistry Division-II (C P C Division), CSIR-Indian Institute of Chemical Technology, Hyderabad-500007, INDIA.

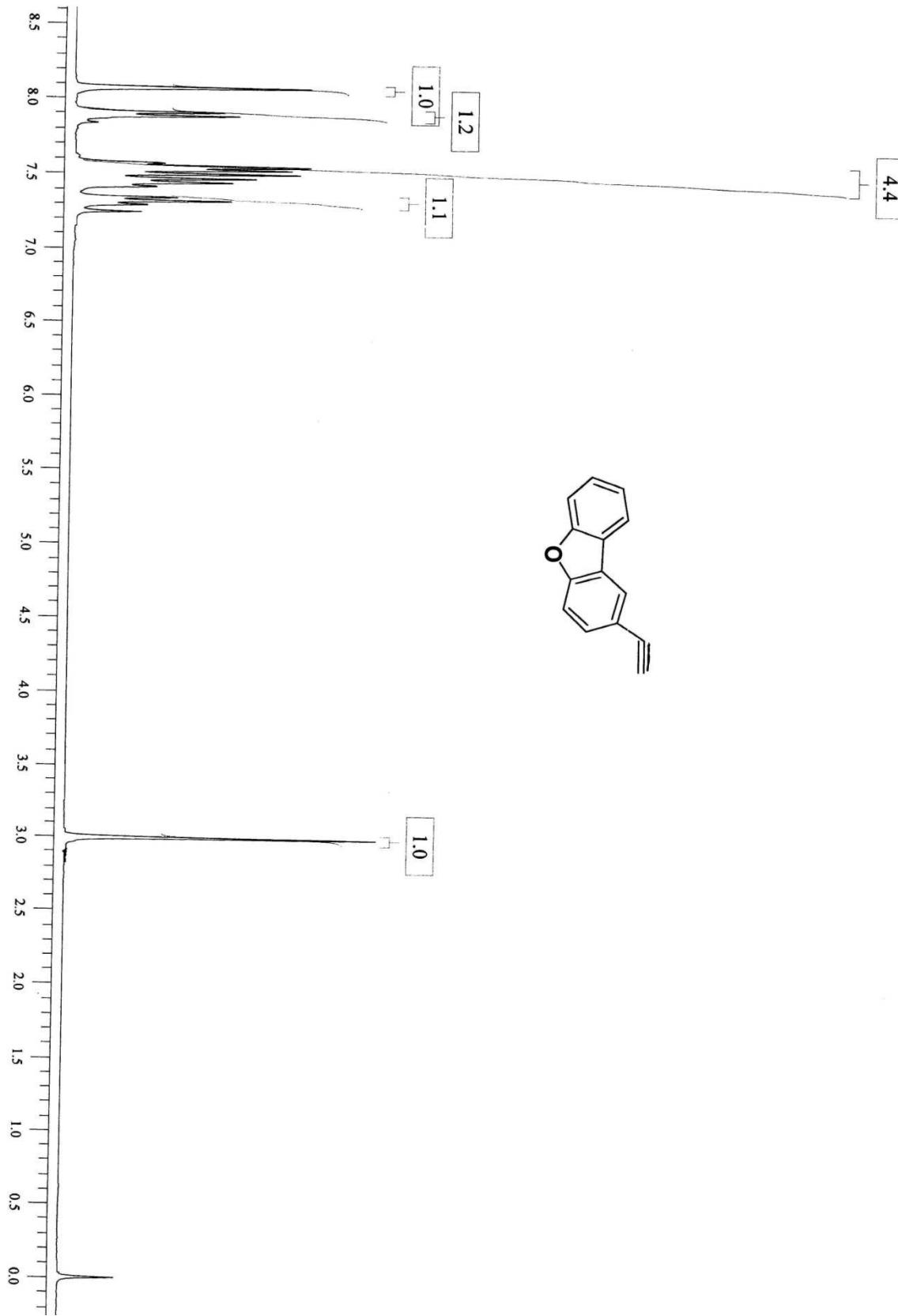
^bMedicinal Chemistry and Antimycobacterial Research Laboratory, Pharmacy Group, Birla Institute of Technology & Science-Pilani, Hyderabad Campus, Jawahar Nagar, Hyderabad-500078 INDIA.

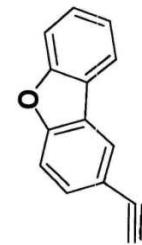
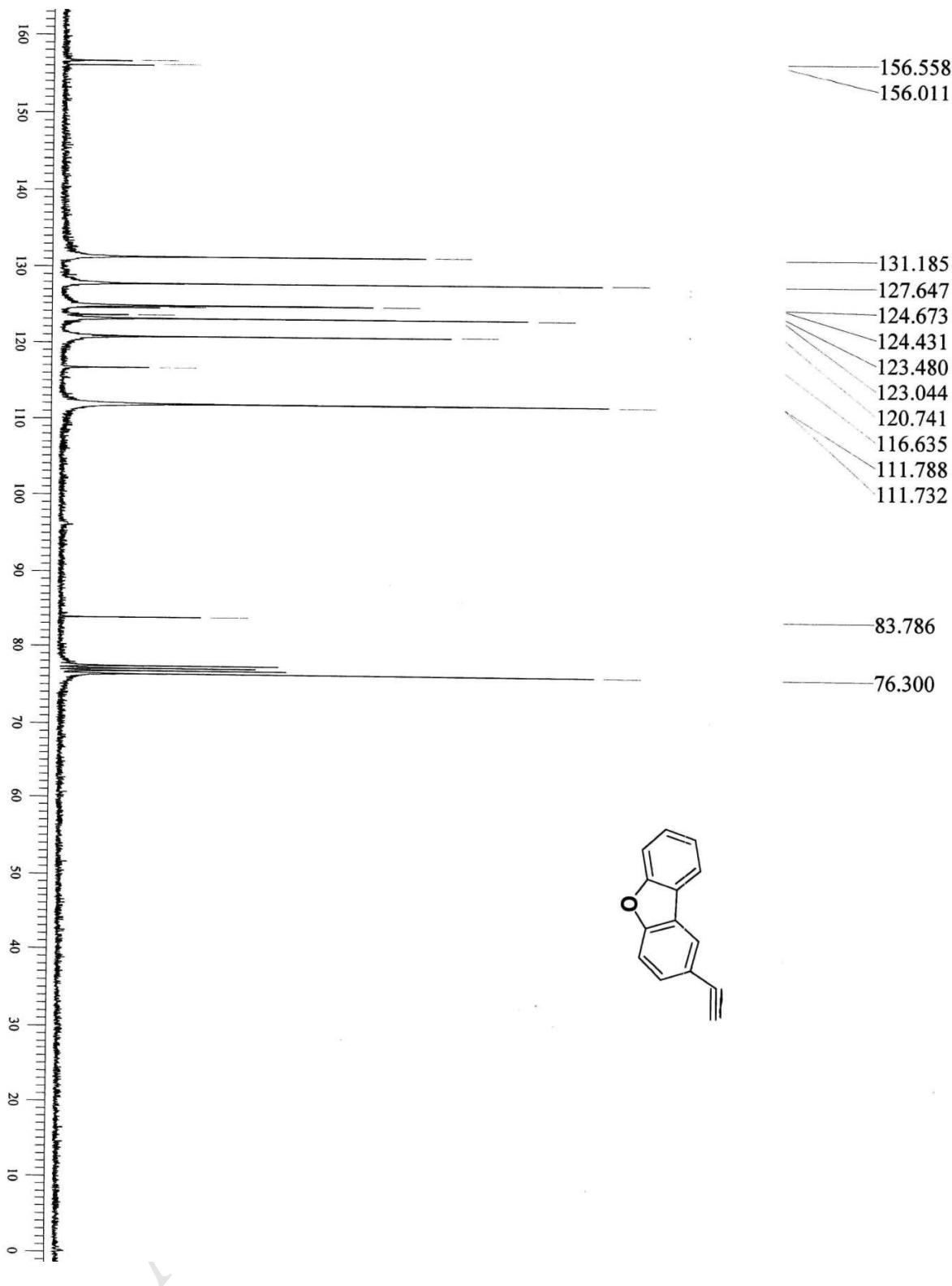
*Corresponding author. Tel.: +91-4027191438; fax: +91-4027198933;

e-mail: kantevari@yahoo.com, kantevari@gmail.com.

Supporting Information

| Table of Contents | ----- | Page |
|--|-------|----------|
| 1. Copies of ¹ H NMR, ¹³ C NMR spectra of 3 | | : S2-S4 |
| 2. Copies of ¹ H NMR, ¹³ C NMR, HRMS and EI-MS spectras of 5a-n | | : S5-S46 |





National Centre for Mass Spectrometry
 Indian Institute of Chemical Technology

Sample ID

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Data File

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Analyzed by

: Admin

Tuning File

: 7/5/2010 5:00:55 PM

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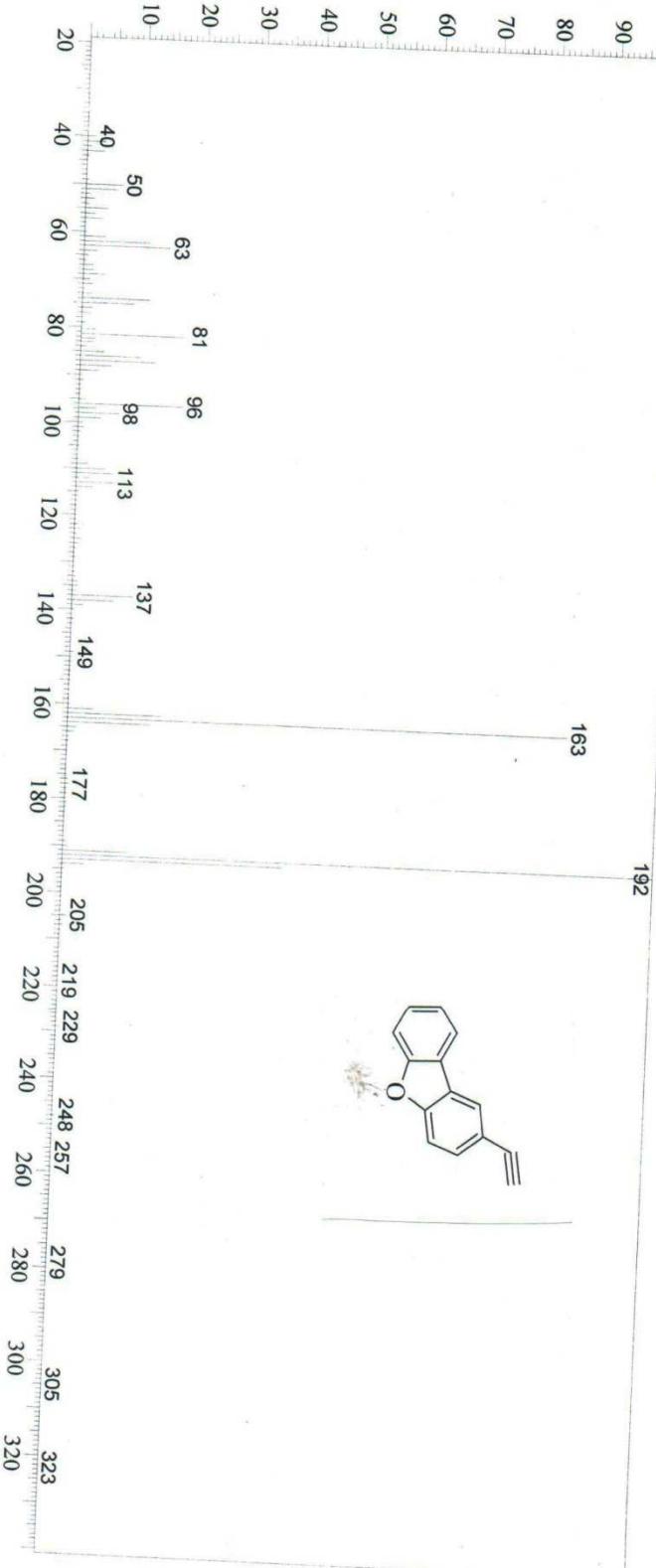
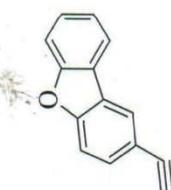
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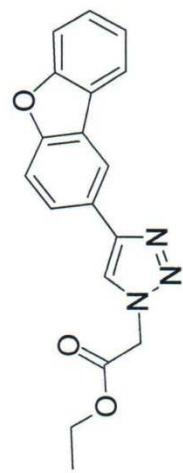
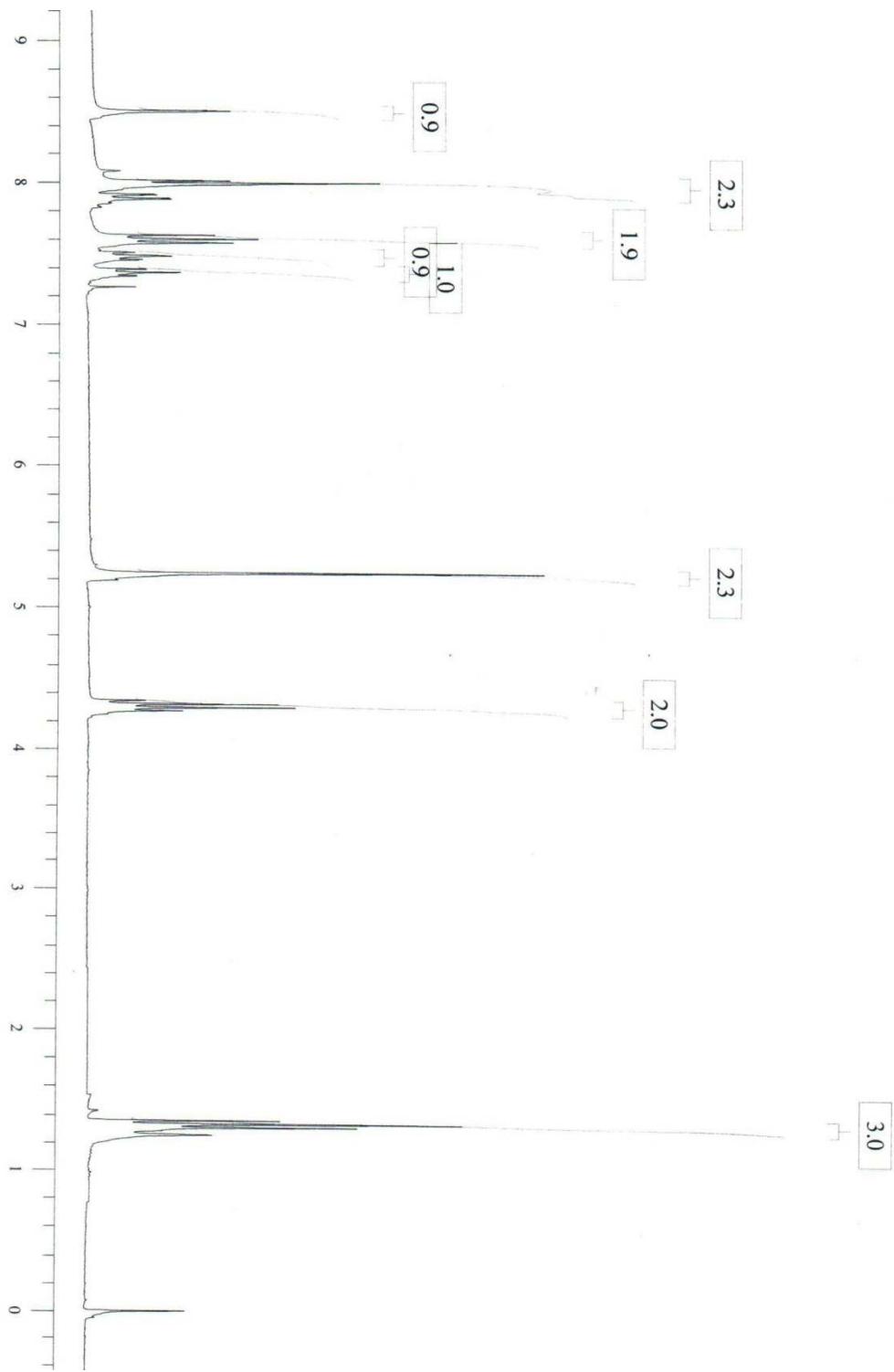
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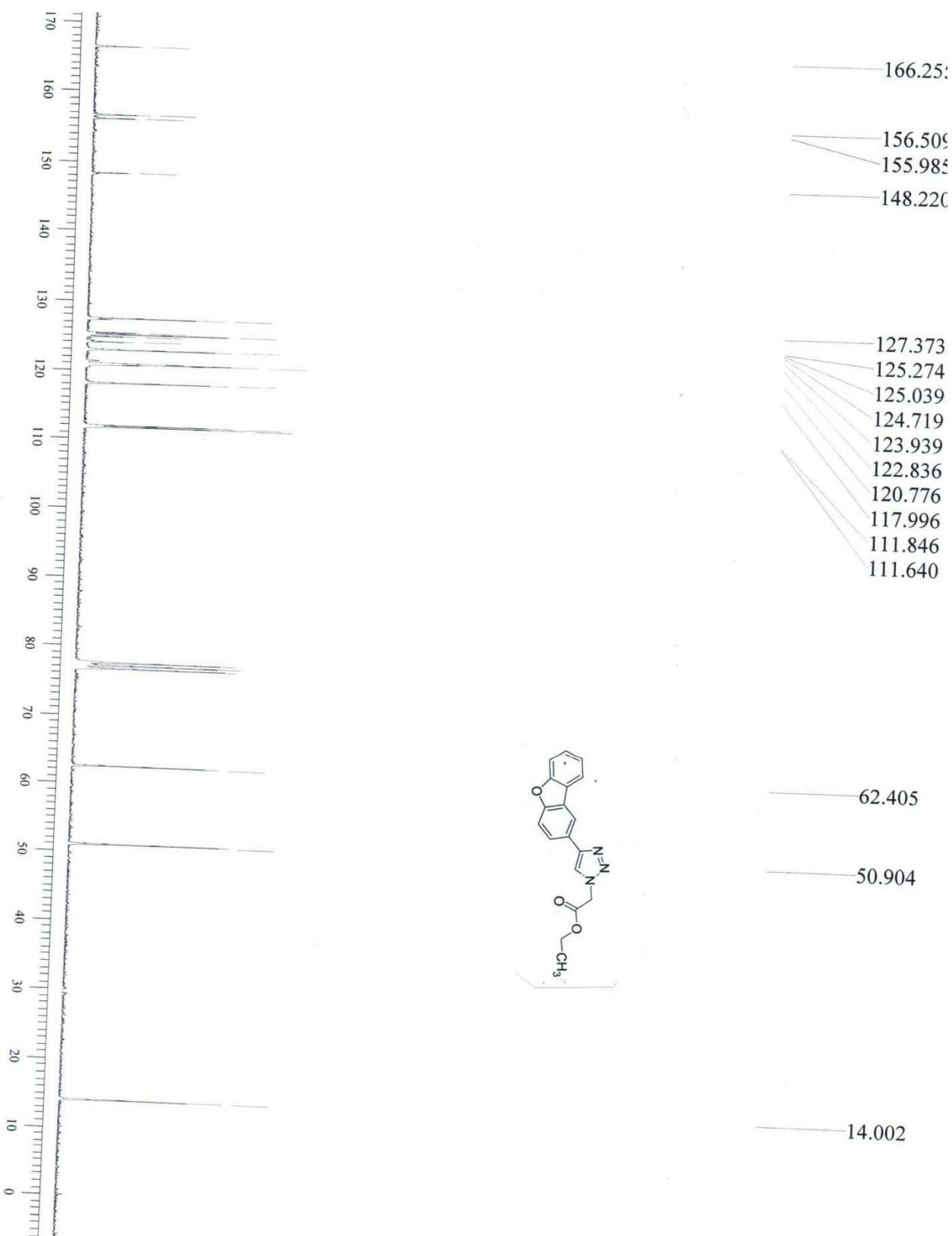
Spectrum

192

163



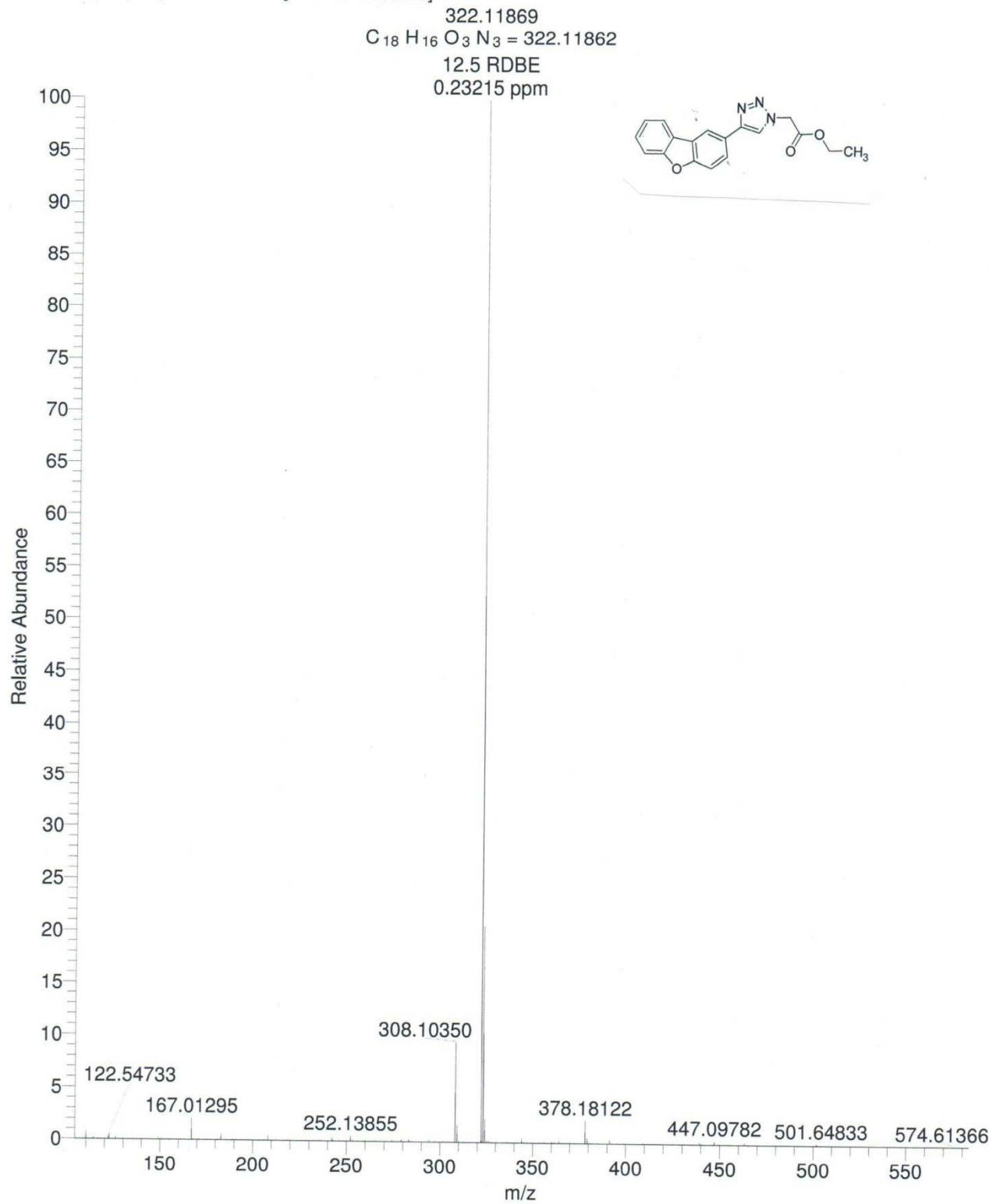


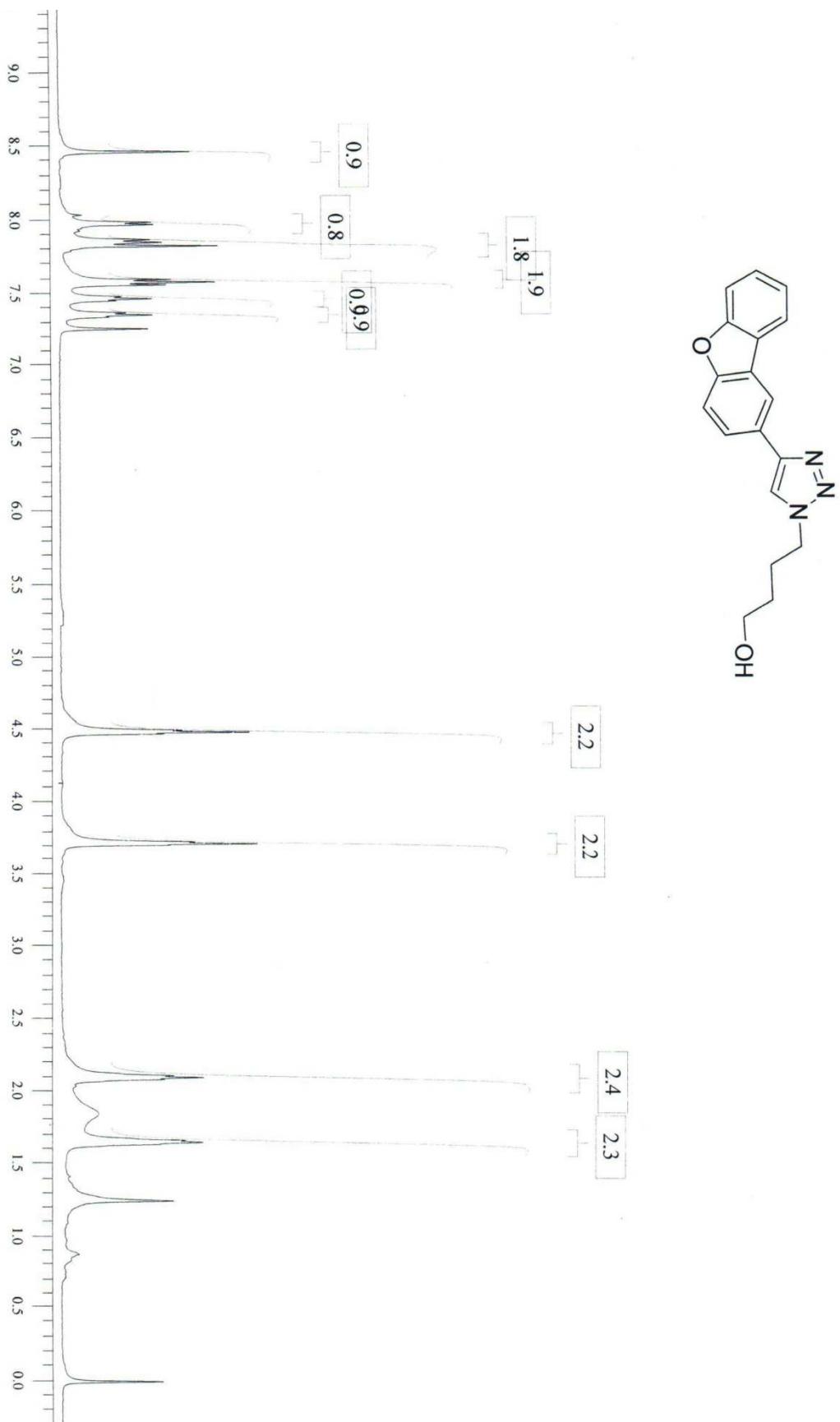


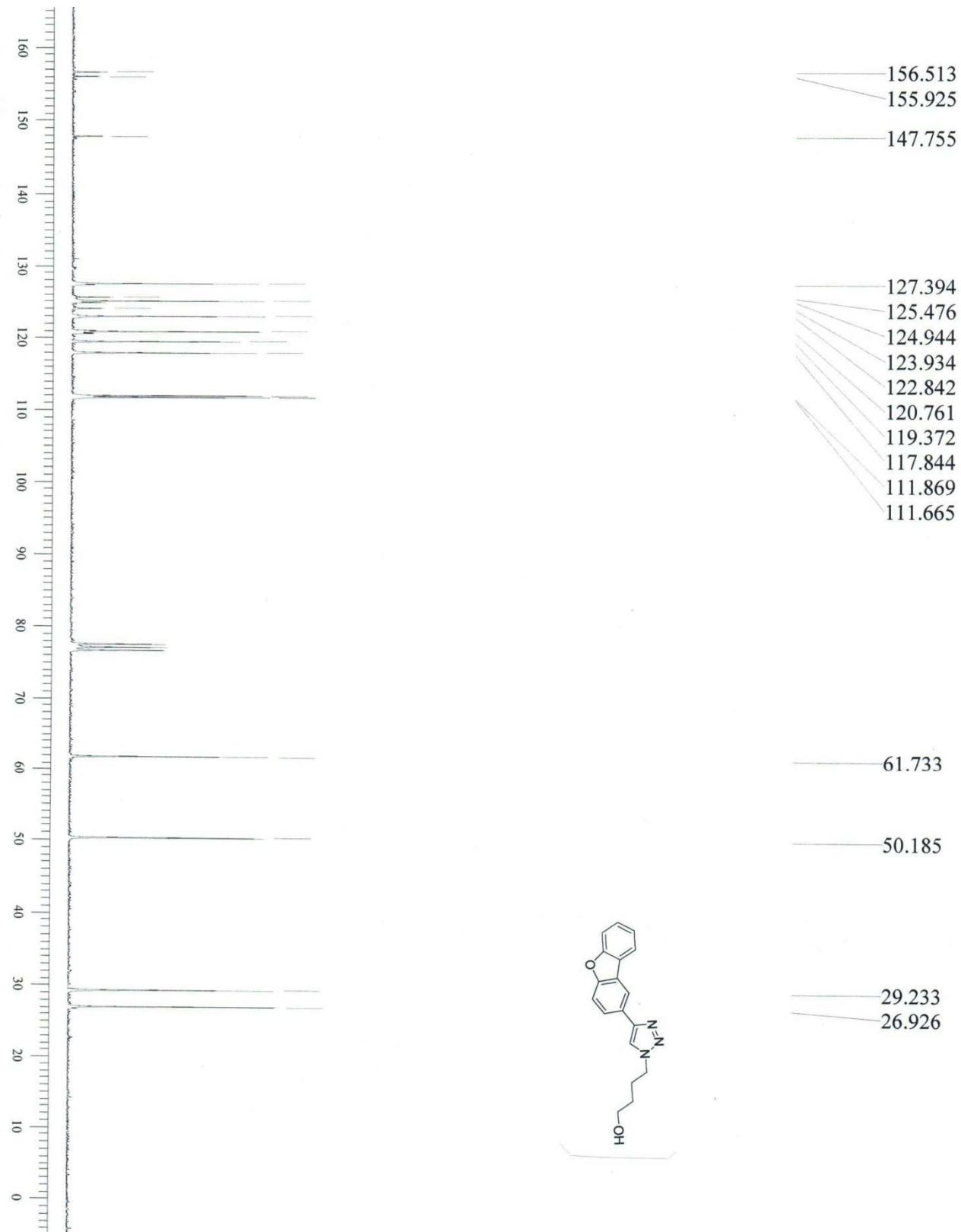
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INDIAN INSTITUTE OF CHEMICAL TECHNOLOGY
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T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]







T ANUSHA
5/21/2012 6:47:58 PM

INDIAN INSTITUTE OF CHEMICAL TECHNOLOGY
NATIONAL CENTRE FOR MASS SPECTROMETRY

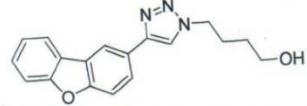
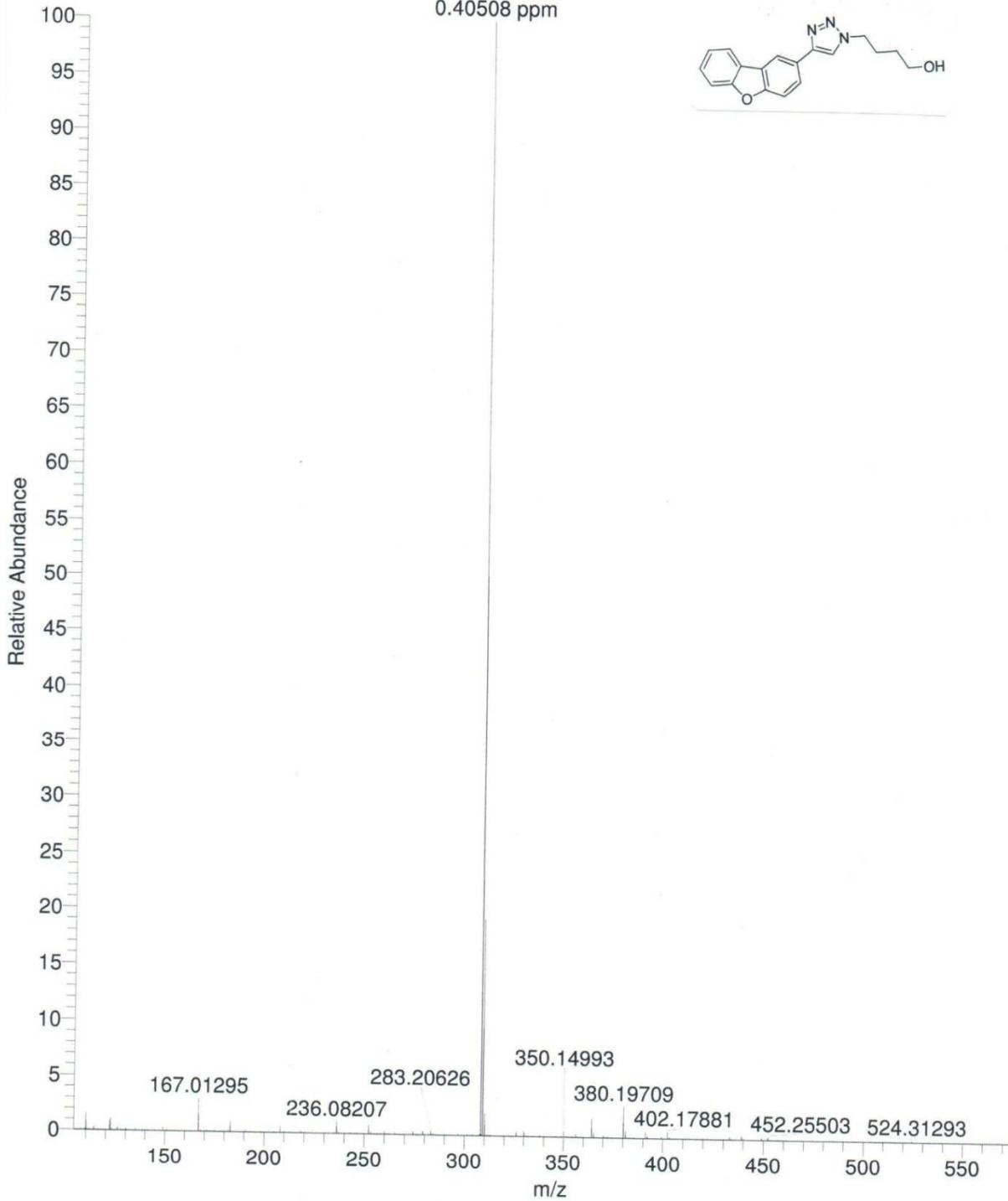
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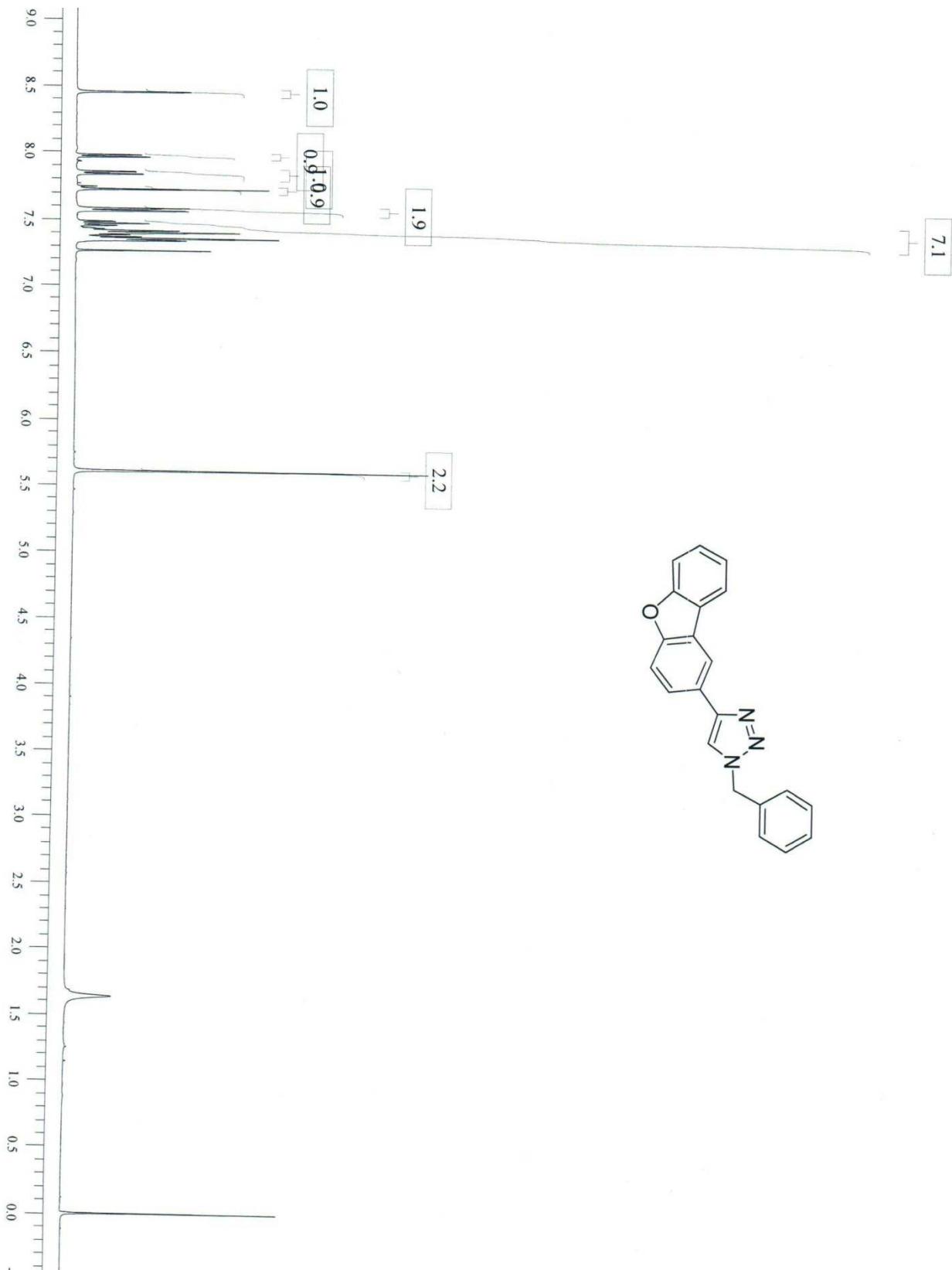
308.13948

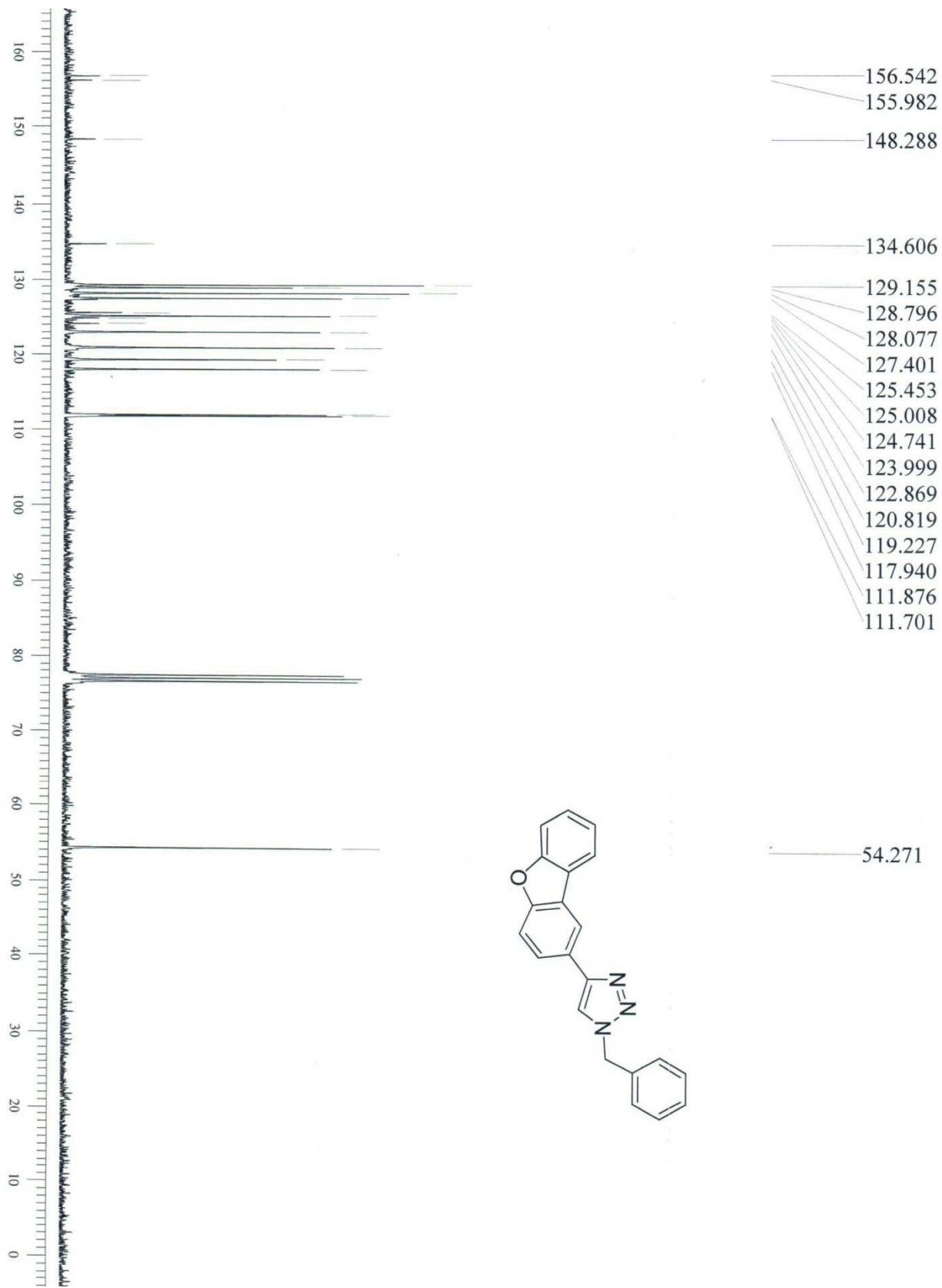
C₁₈H₁₈O₂N₃ = 308.13935

11.5 RDBE

0.40508 ppm







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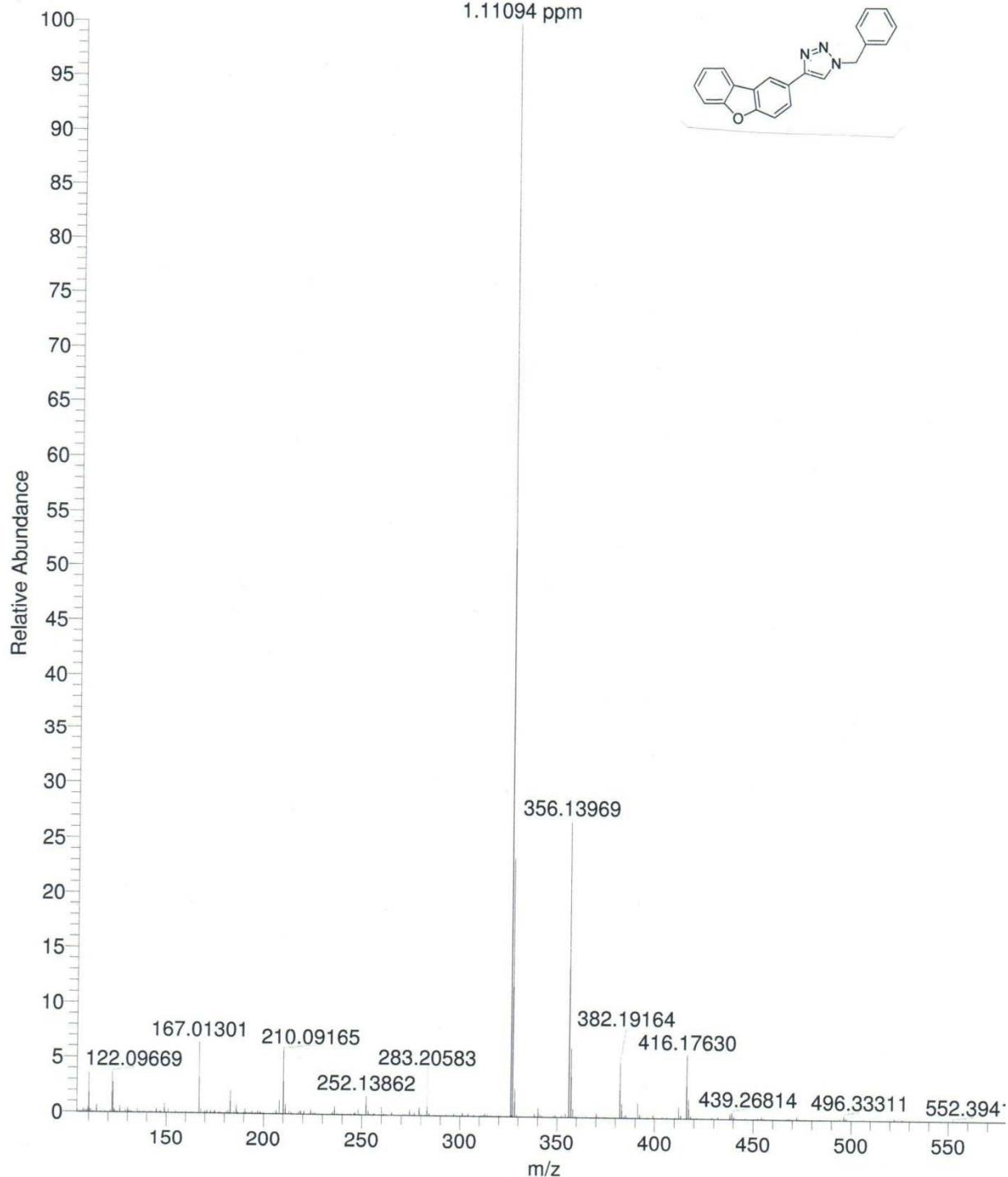
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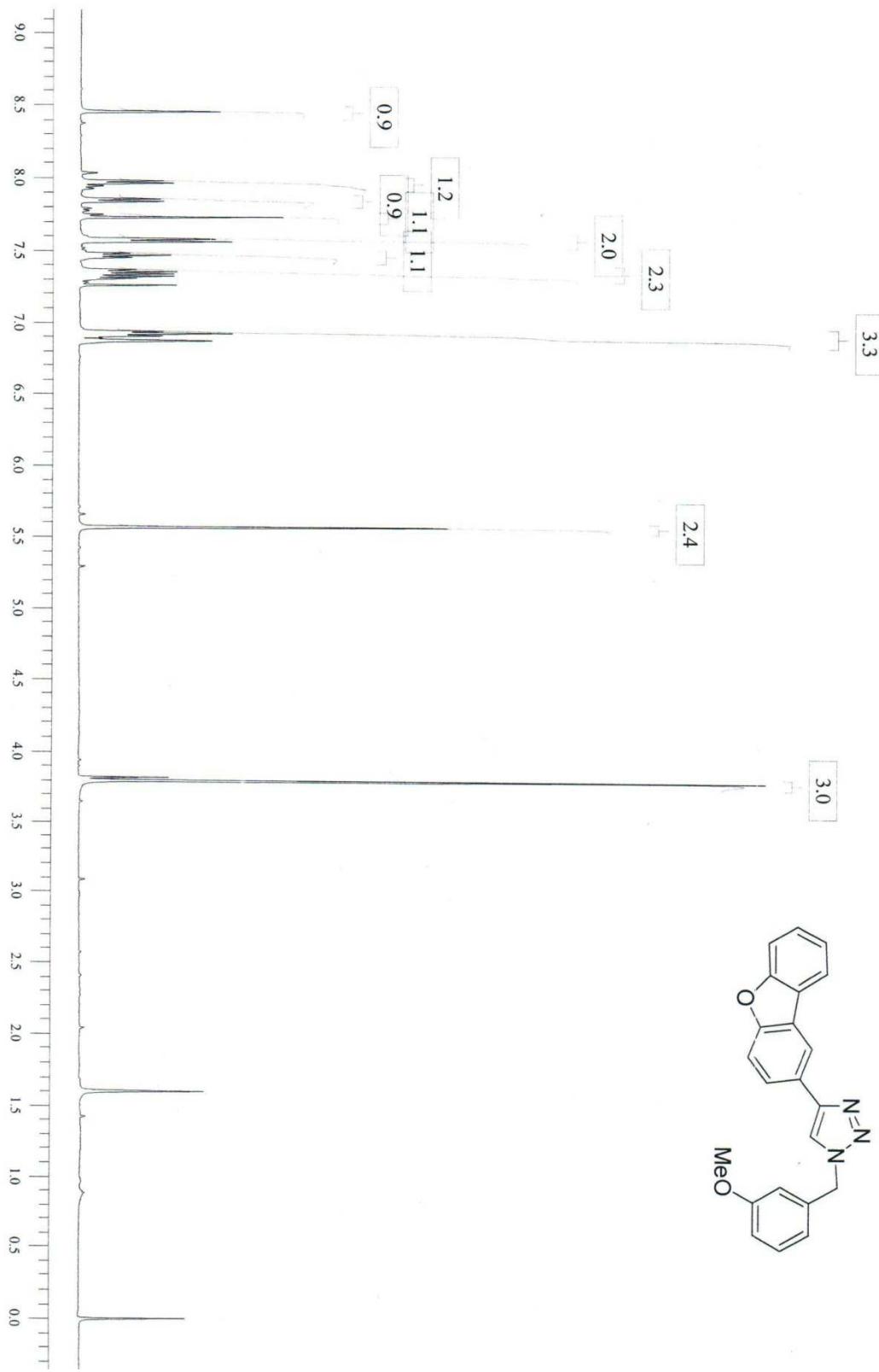
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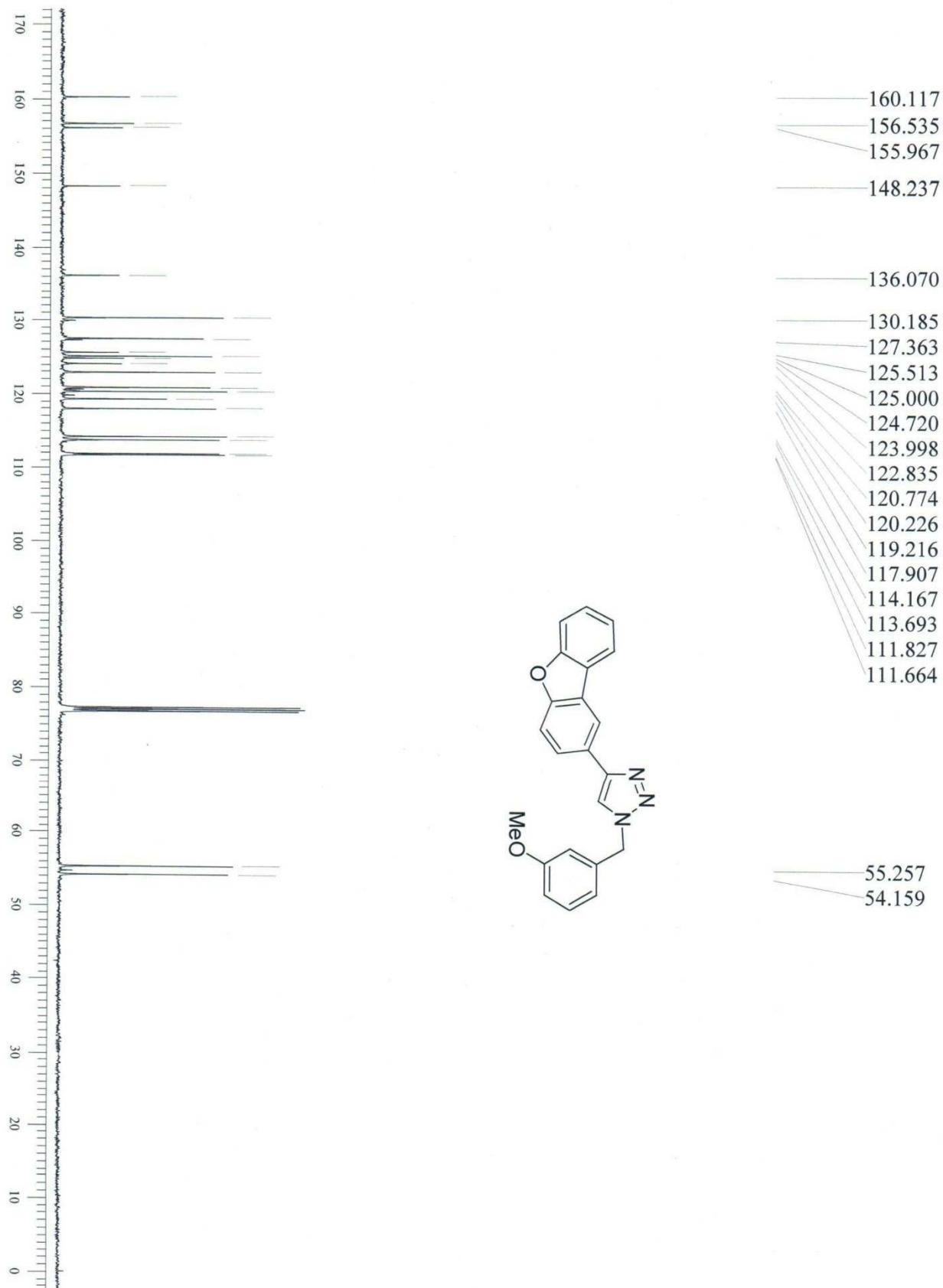
326.12915
 $C_{21}H_{16}ON_3 = 326.12879$

15.5 RDBE

1.11094 ppm







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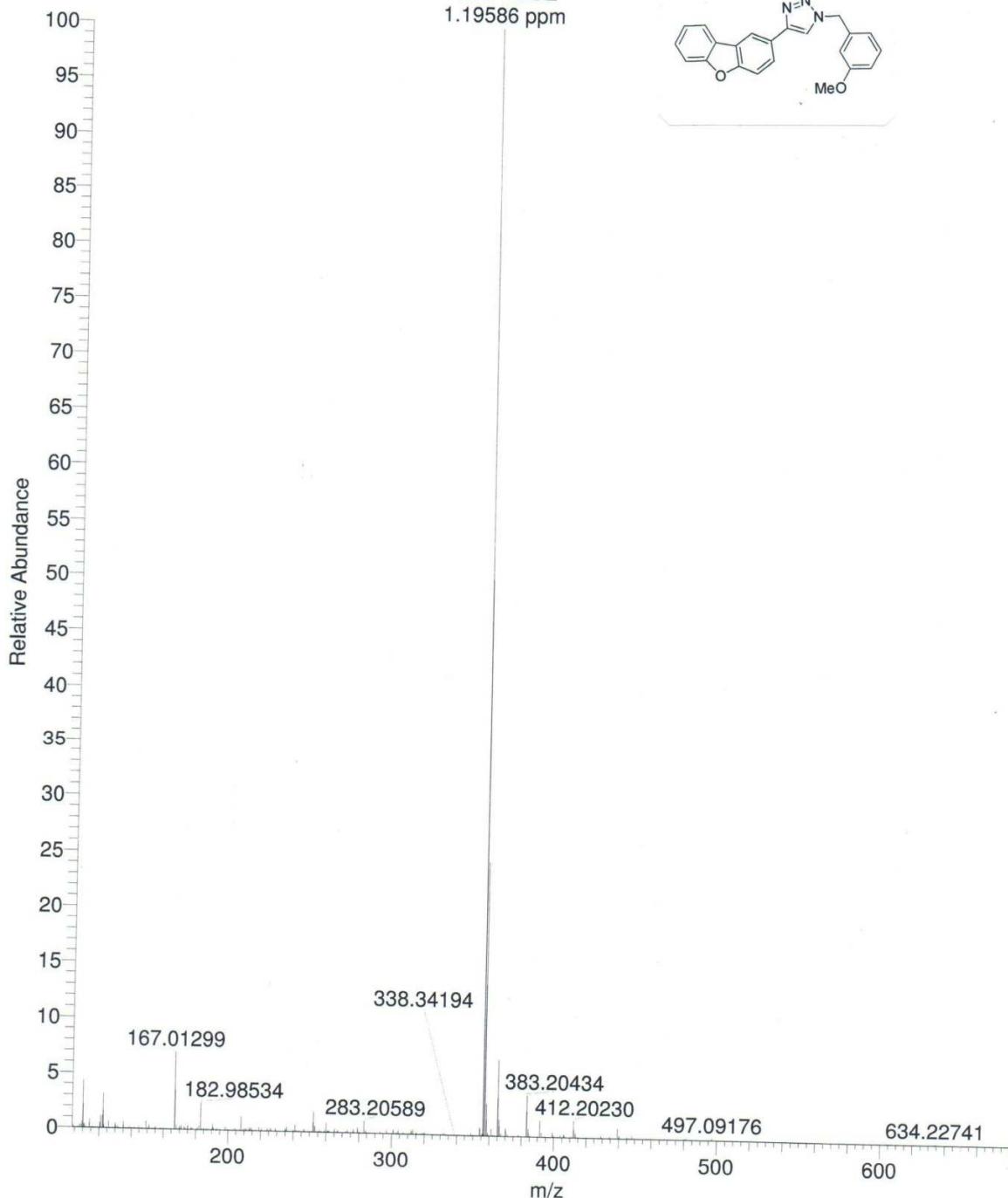
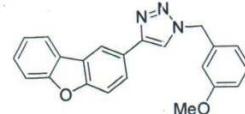
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356.13978

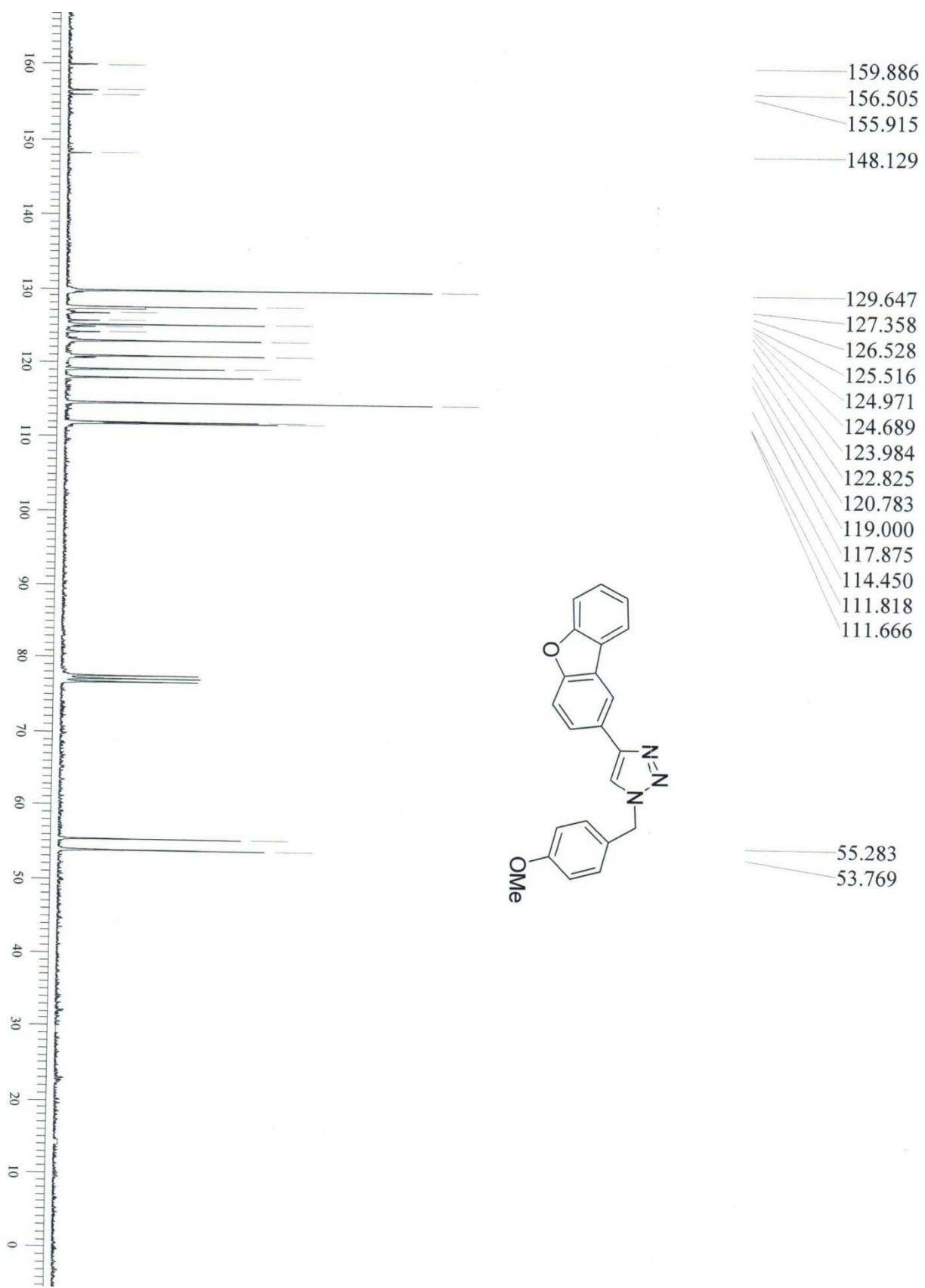
$C_{22} H_{18} O_2 N_3 = 356.13935$

15.5 RDBe

1.19586 ppm





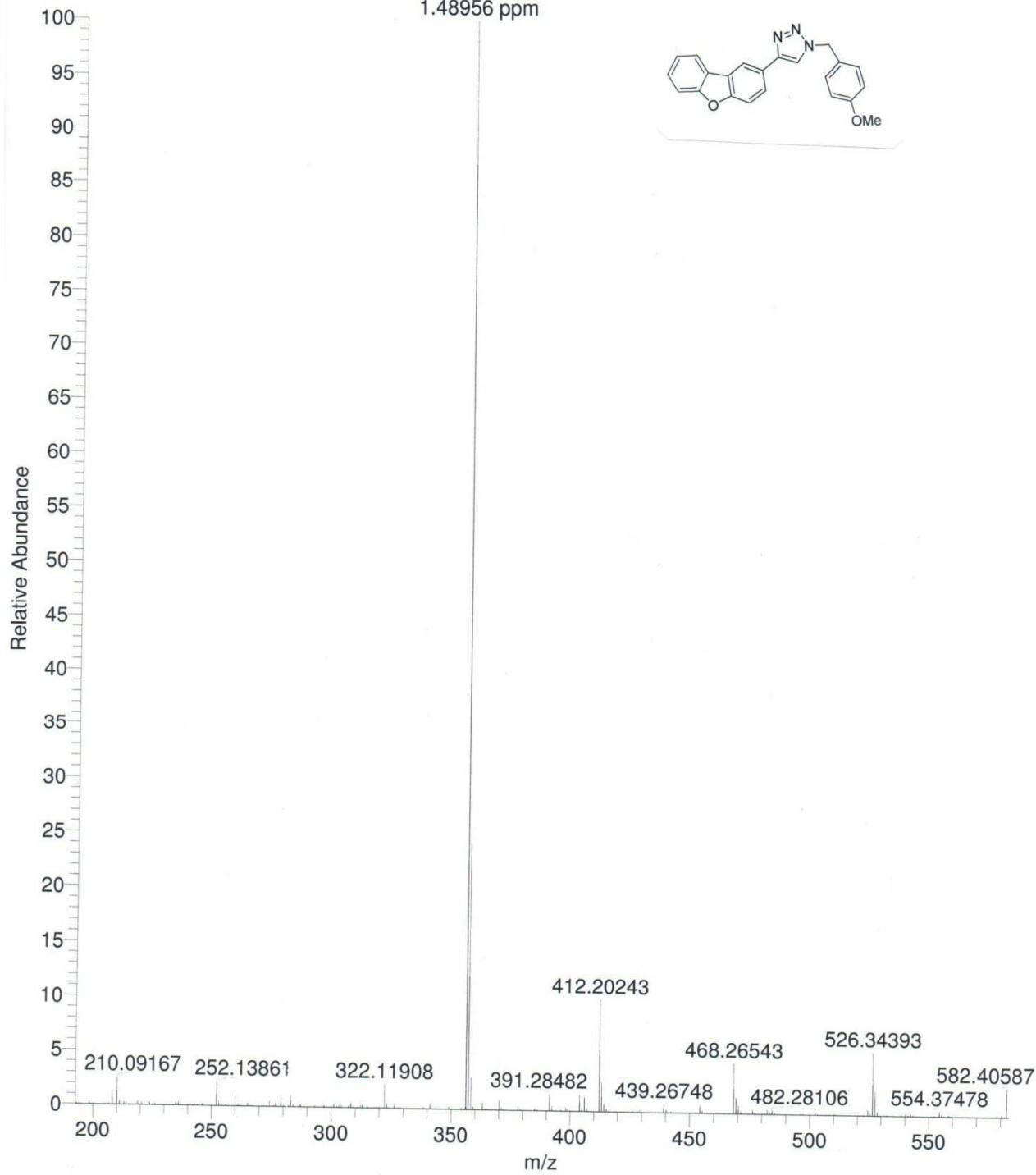


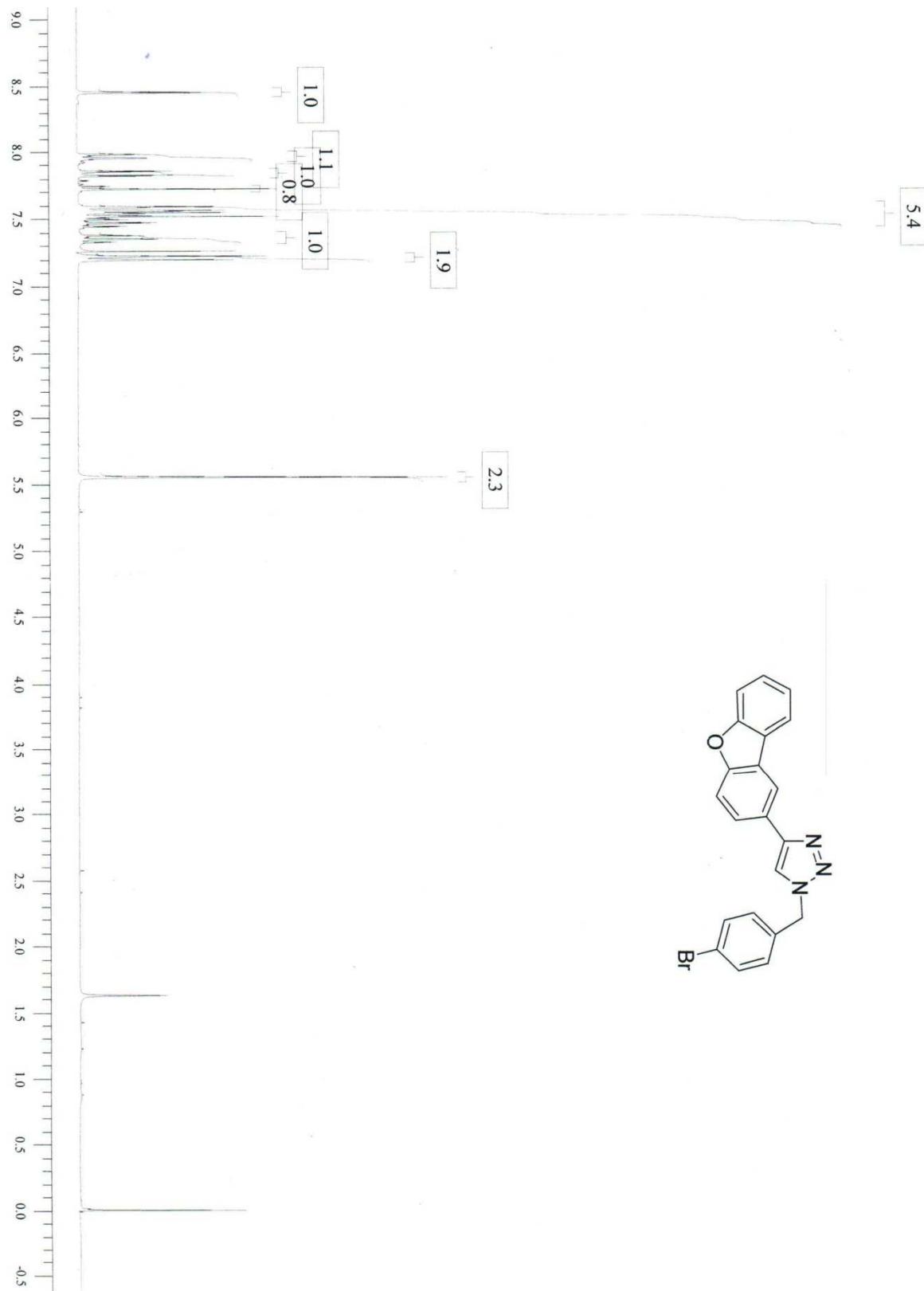
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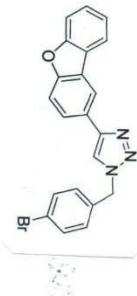
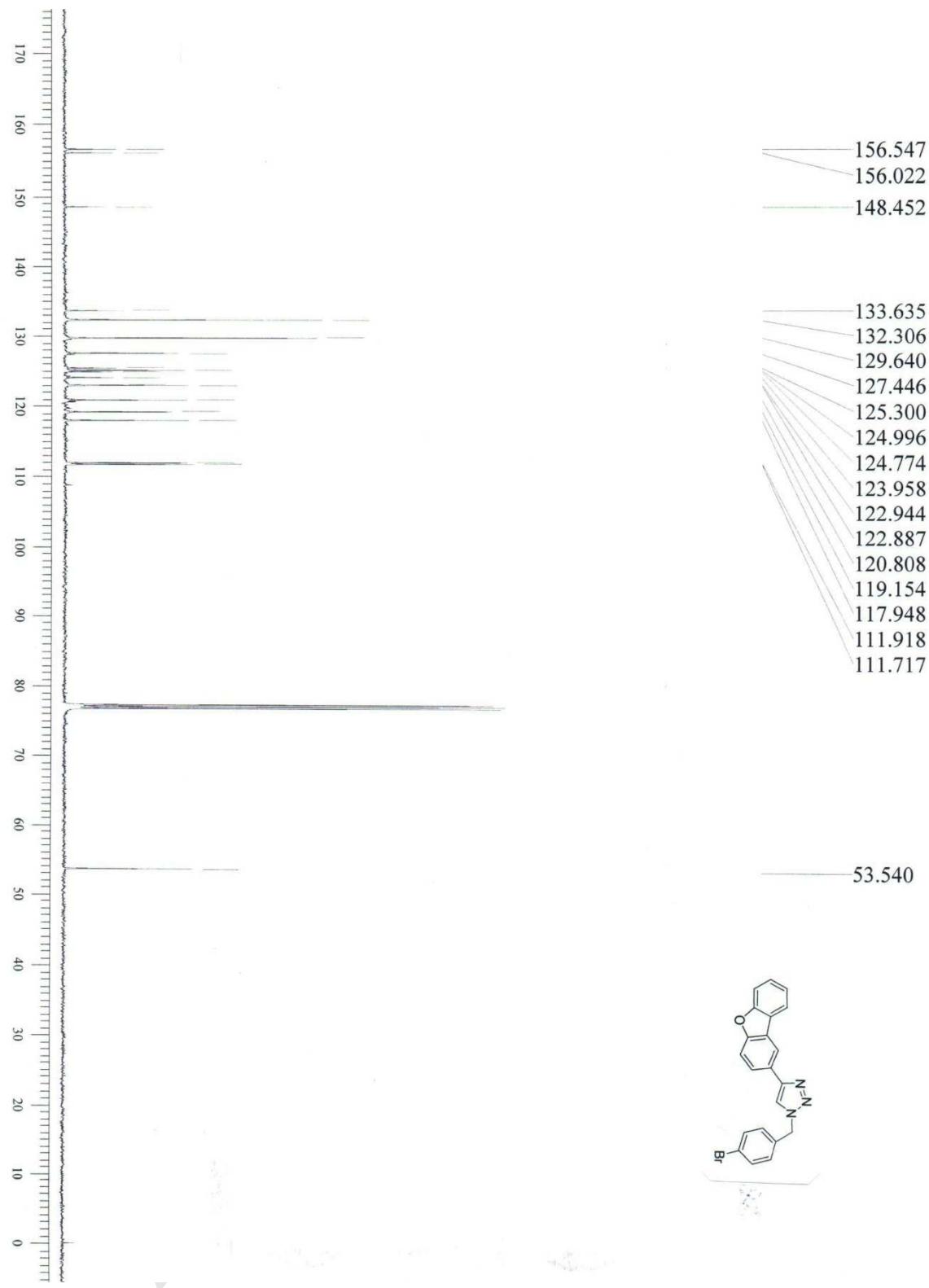
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356.13988
 $C_{22} H_{18} O_2 N_3 = 356.13935$
15.5 RDBE
1.48956 ppm





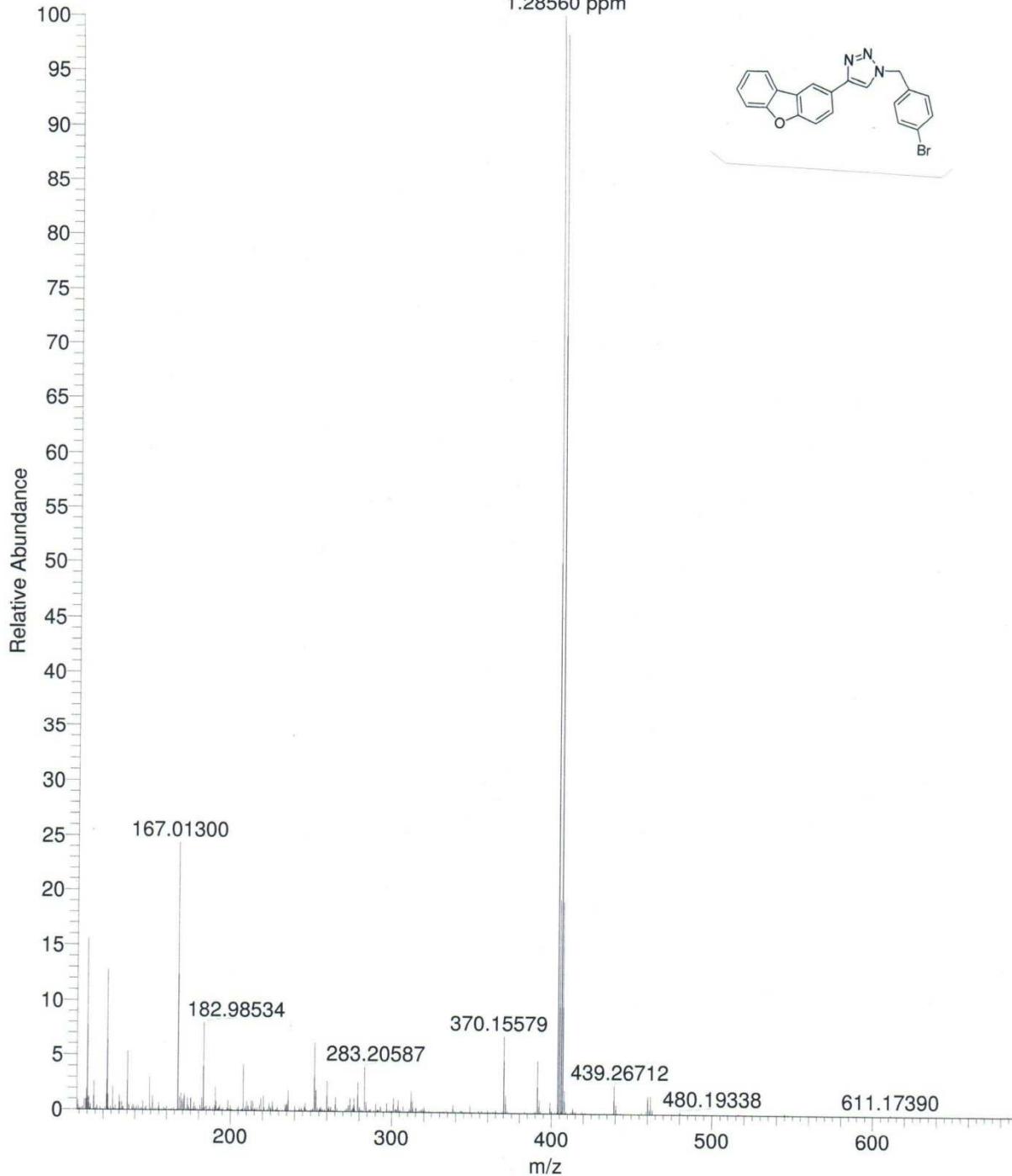


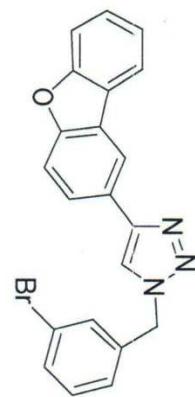
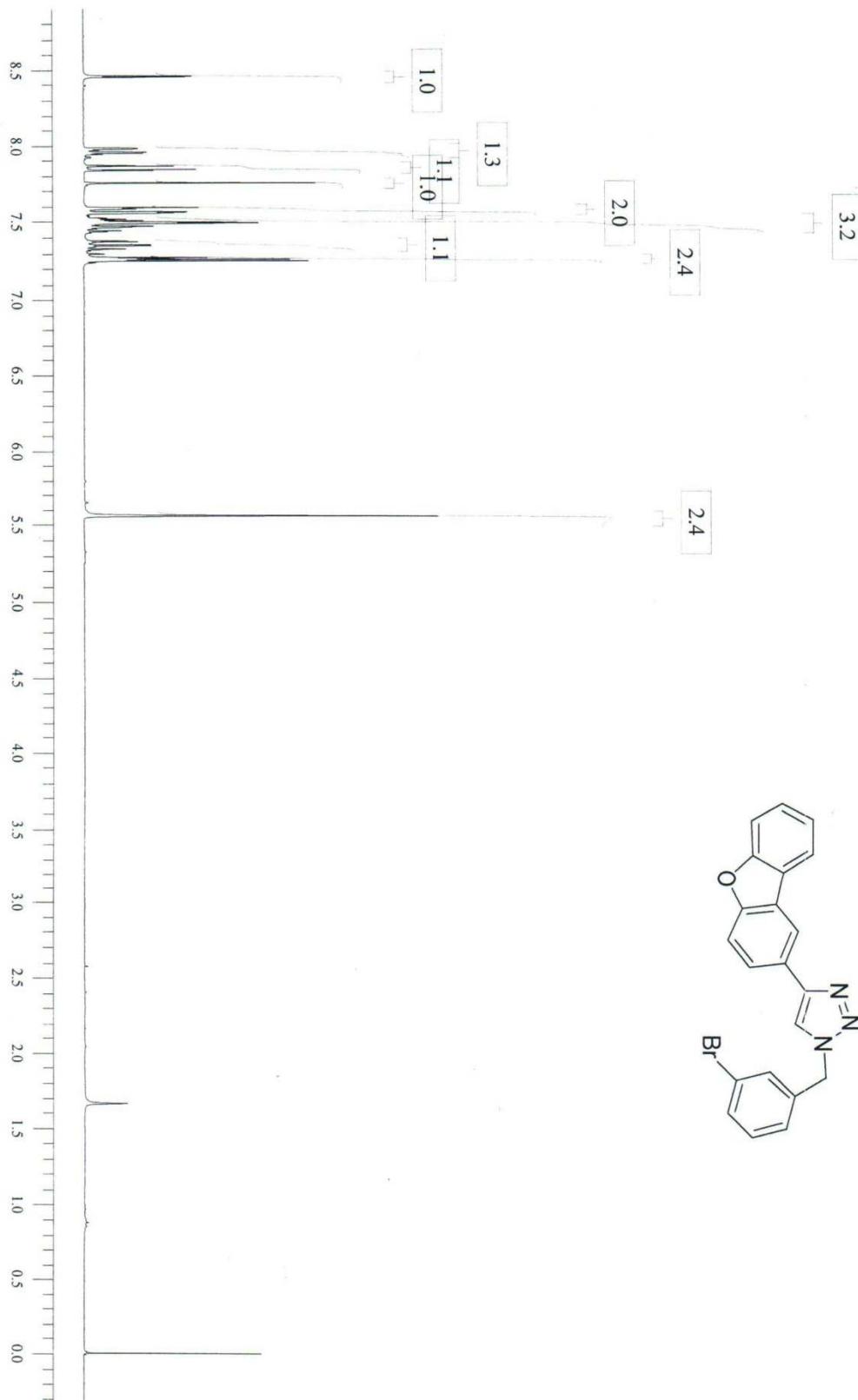
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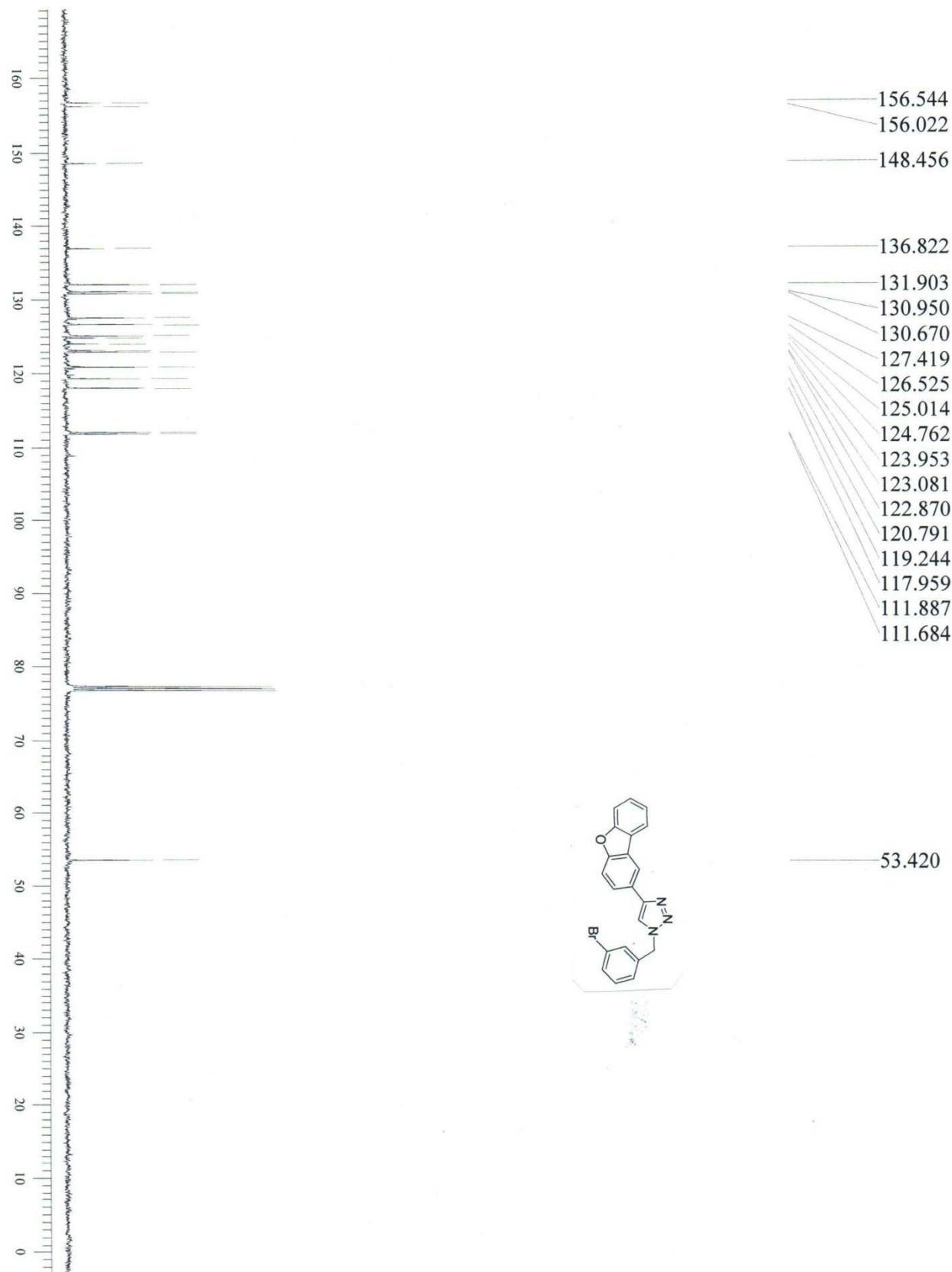
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T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

404.03982
 $C_{21} H_{15} O N_3 Br = 404.03930$
15.5 RDBE
1.28560 ppm





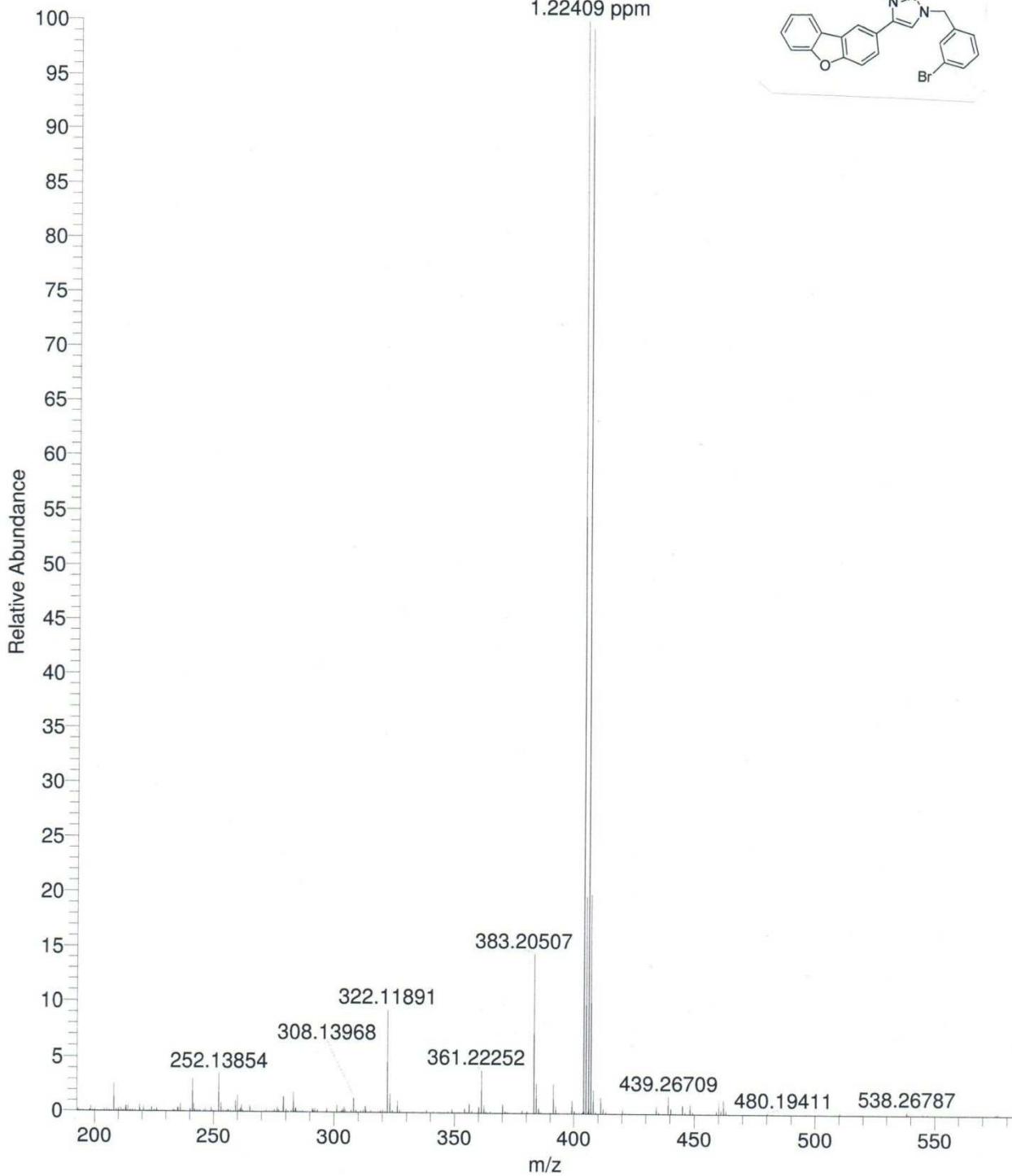
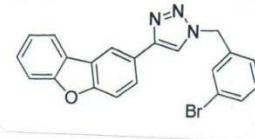


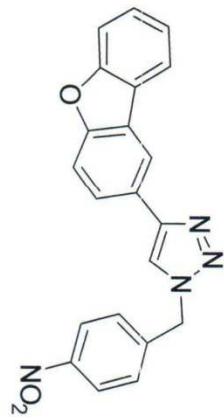
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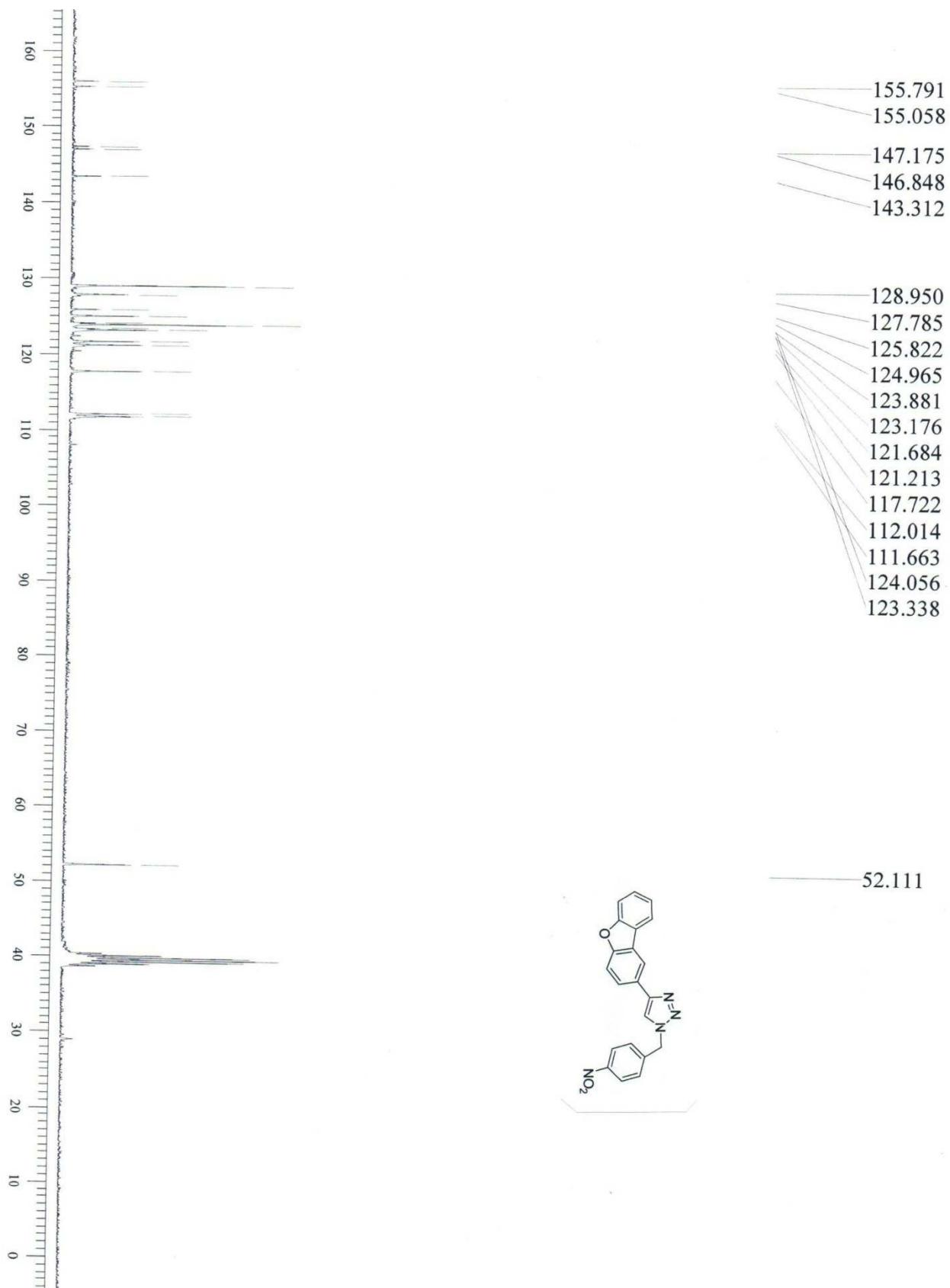
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KS-TRSBRRB #59-84 RT: 0.20-0.28 AV: 26 NL: 1.96E7
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

404.03980
C₂₁H₁₅O N₃ Br = 404.03930
15.5 RDBE
1.22409 ppm





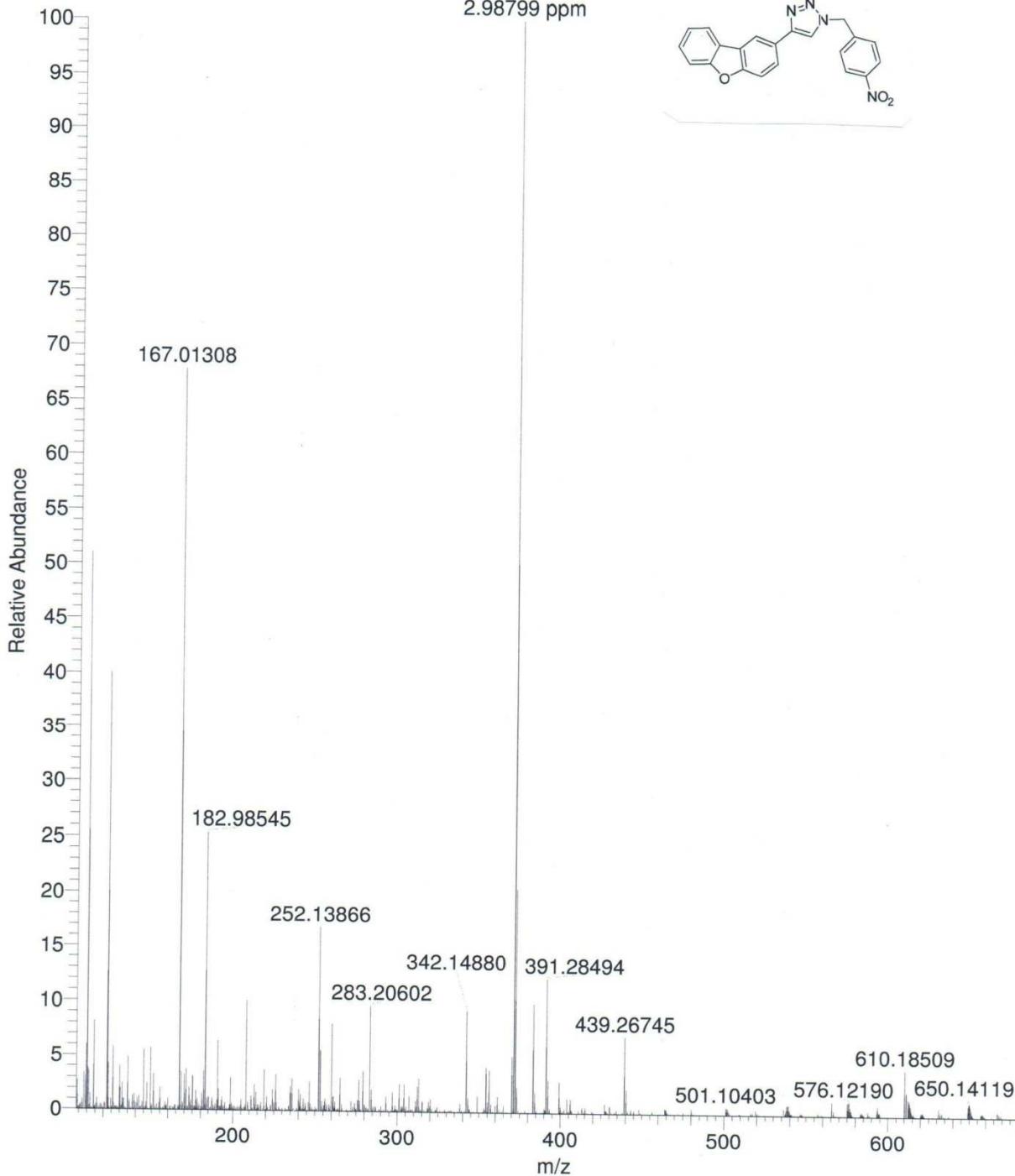
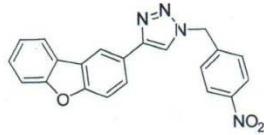


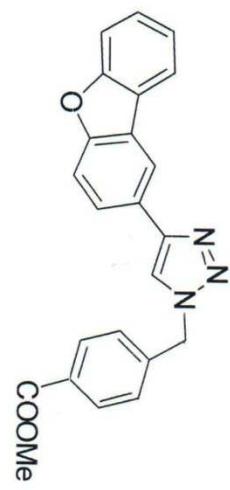
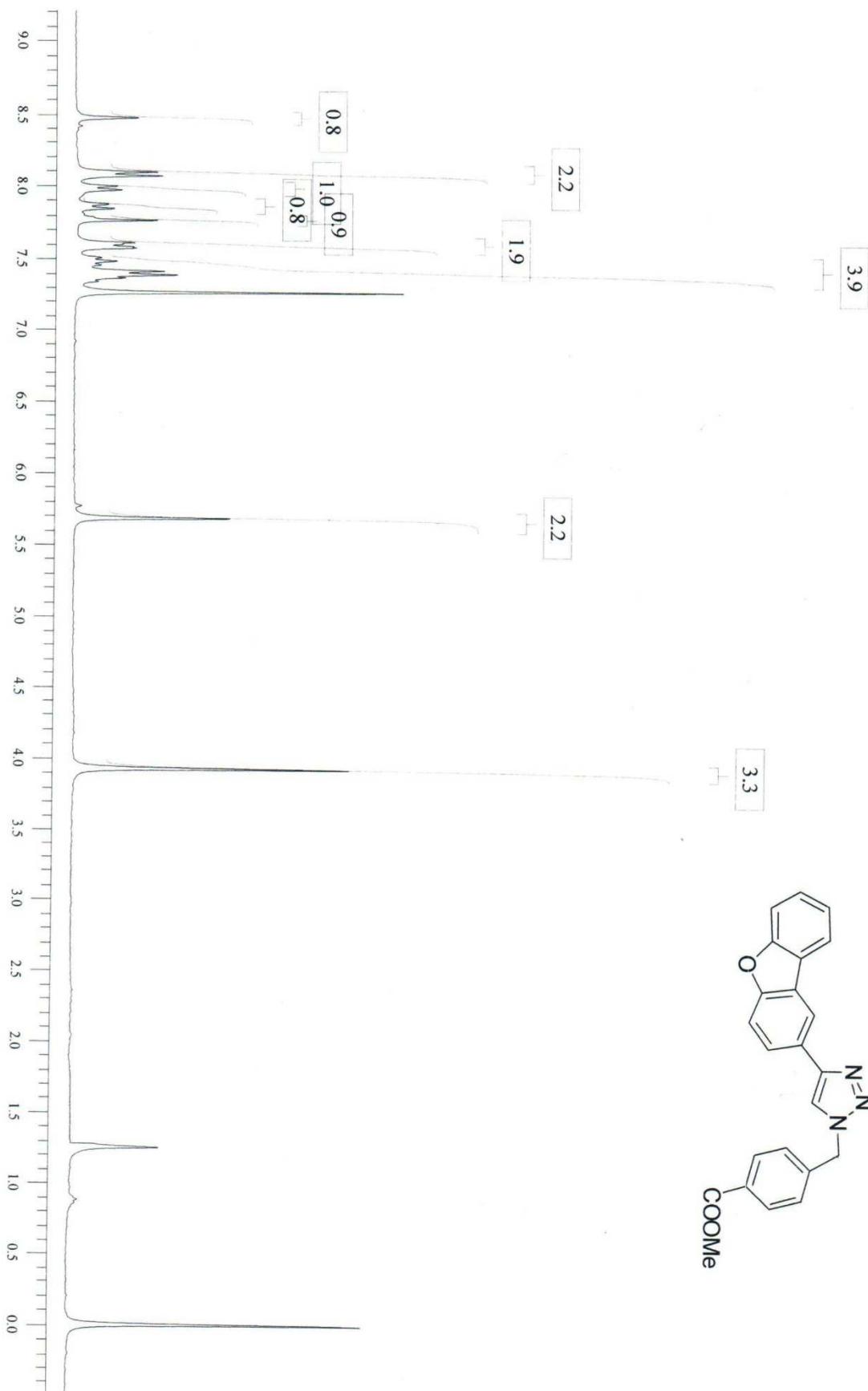
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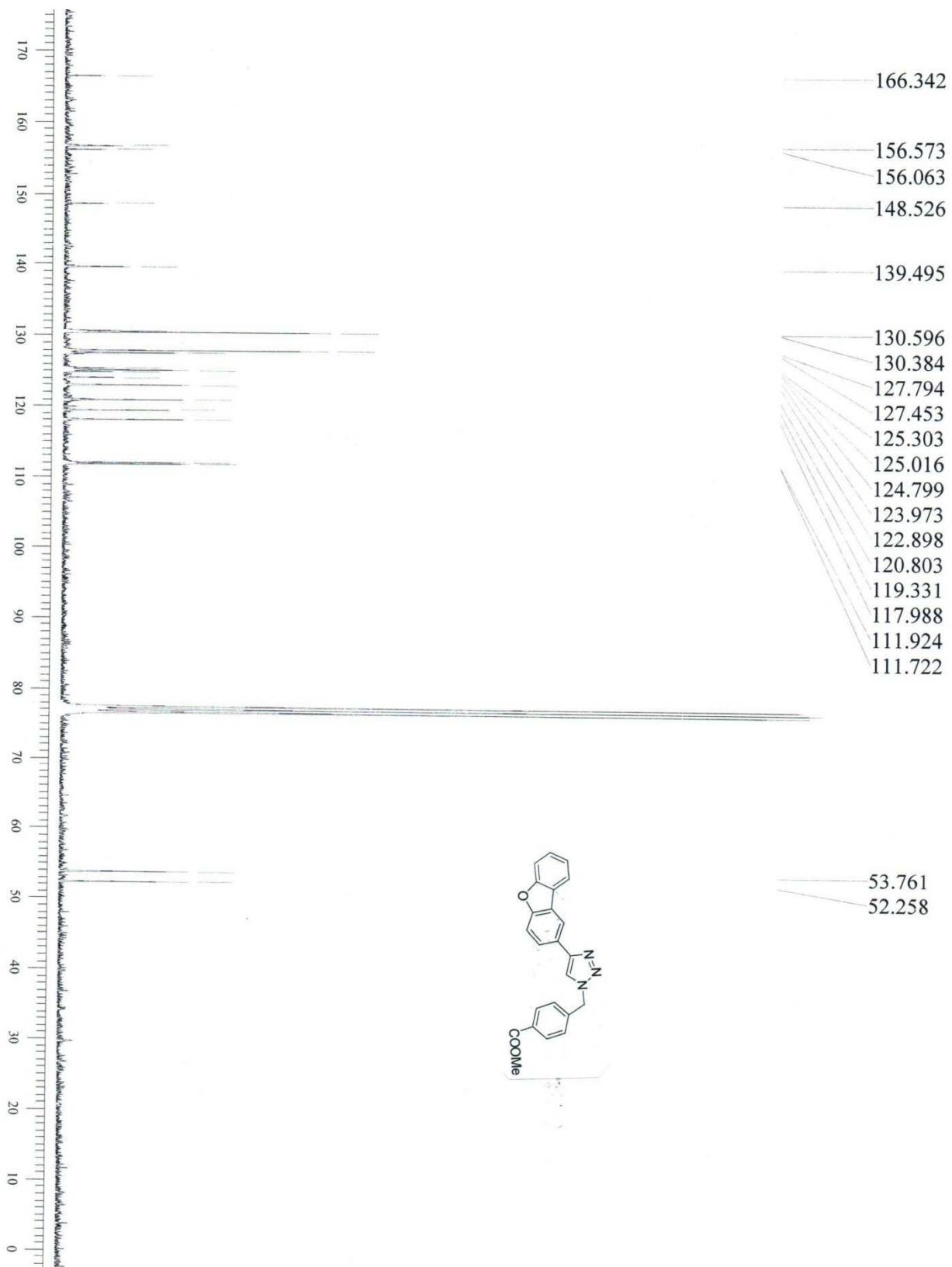
INDIAN INSTITUTE OF CHEMICAL TECHNOLOGY
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T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

371.11498
 $C_{21} H_{15} O_3 N_4 = 371.11387$
16.5 RDBE
2.98799 ppm



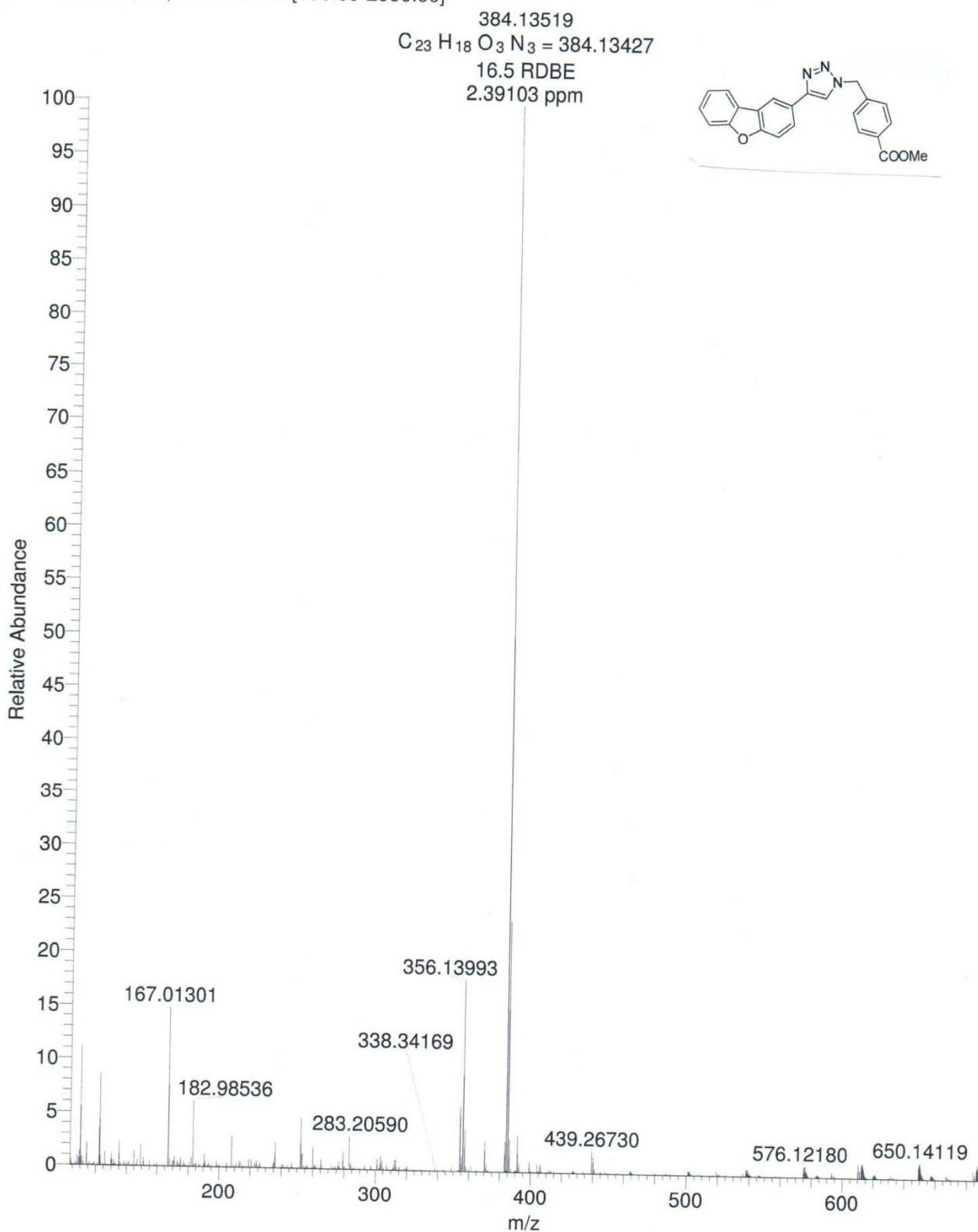


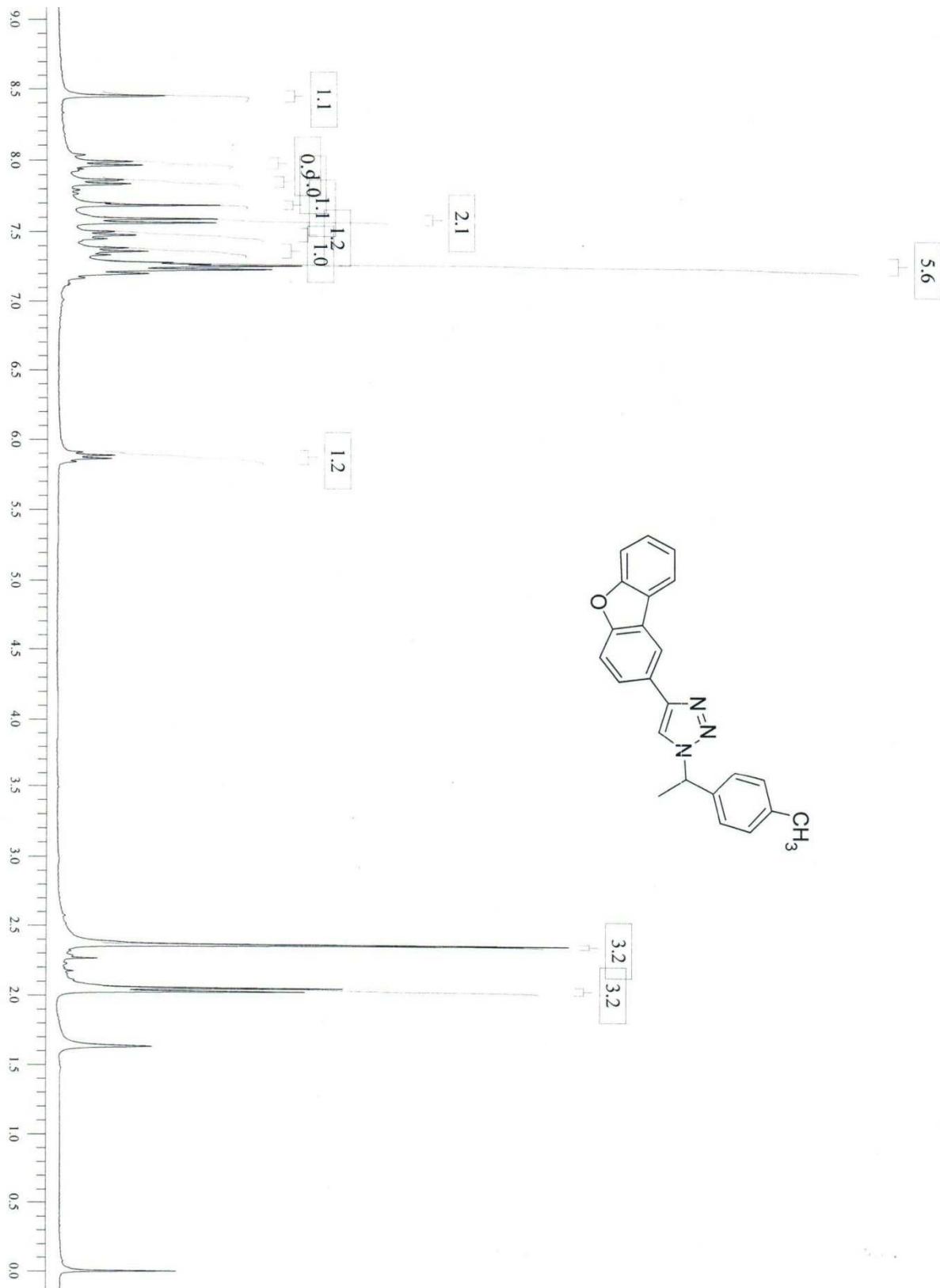


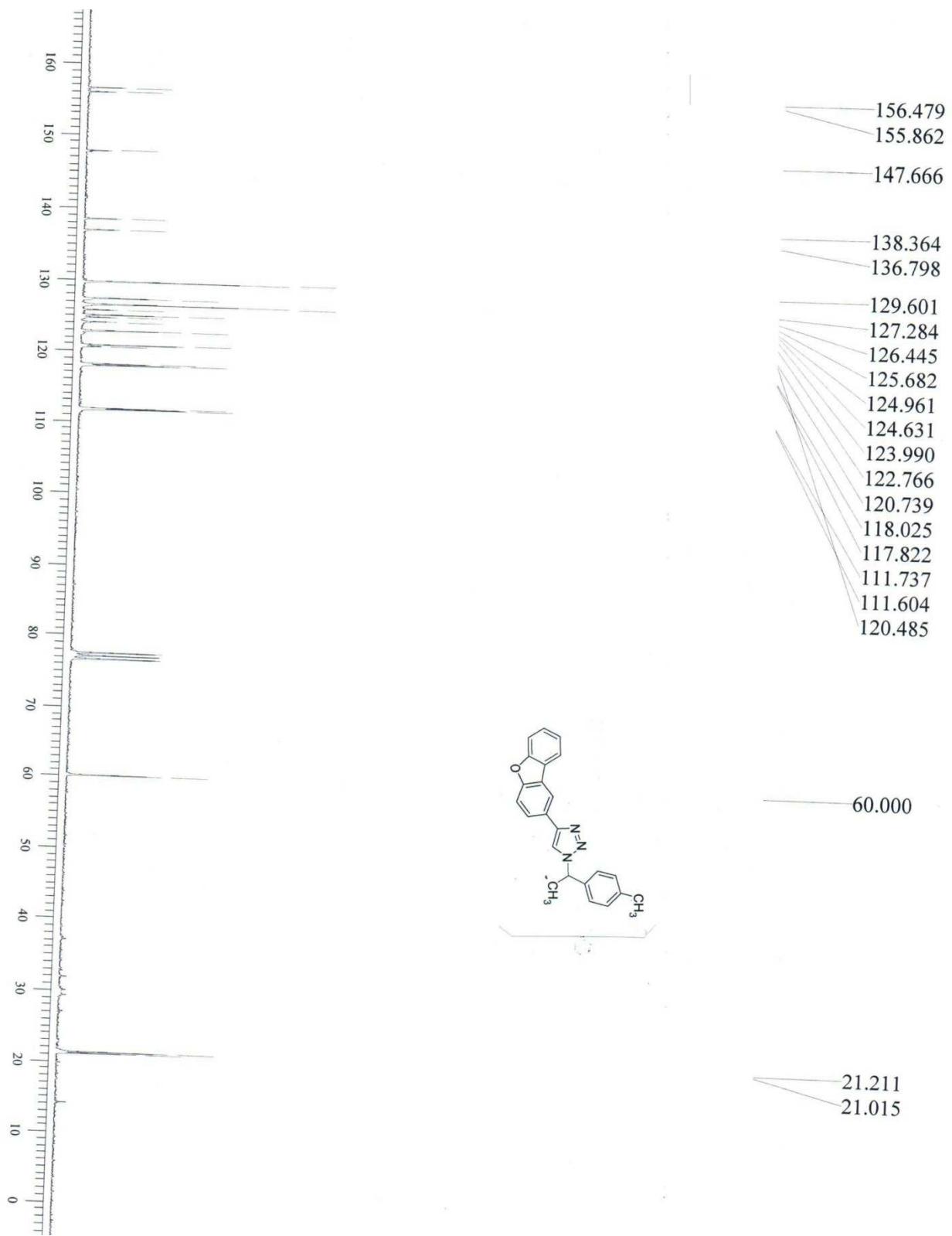
T ANUSHA
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KS-TR4COOME #59-84 RT: 0.20-0.28 AV: 26 NL: 1.85E7
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]







T ANUSHA
5/21/2012 6:29:30 PM

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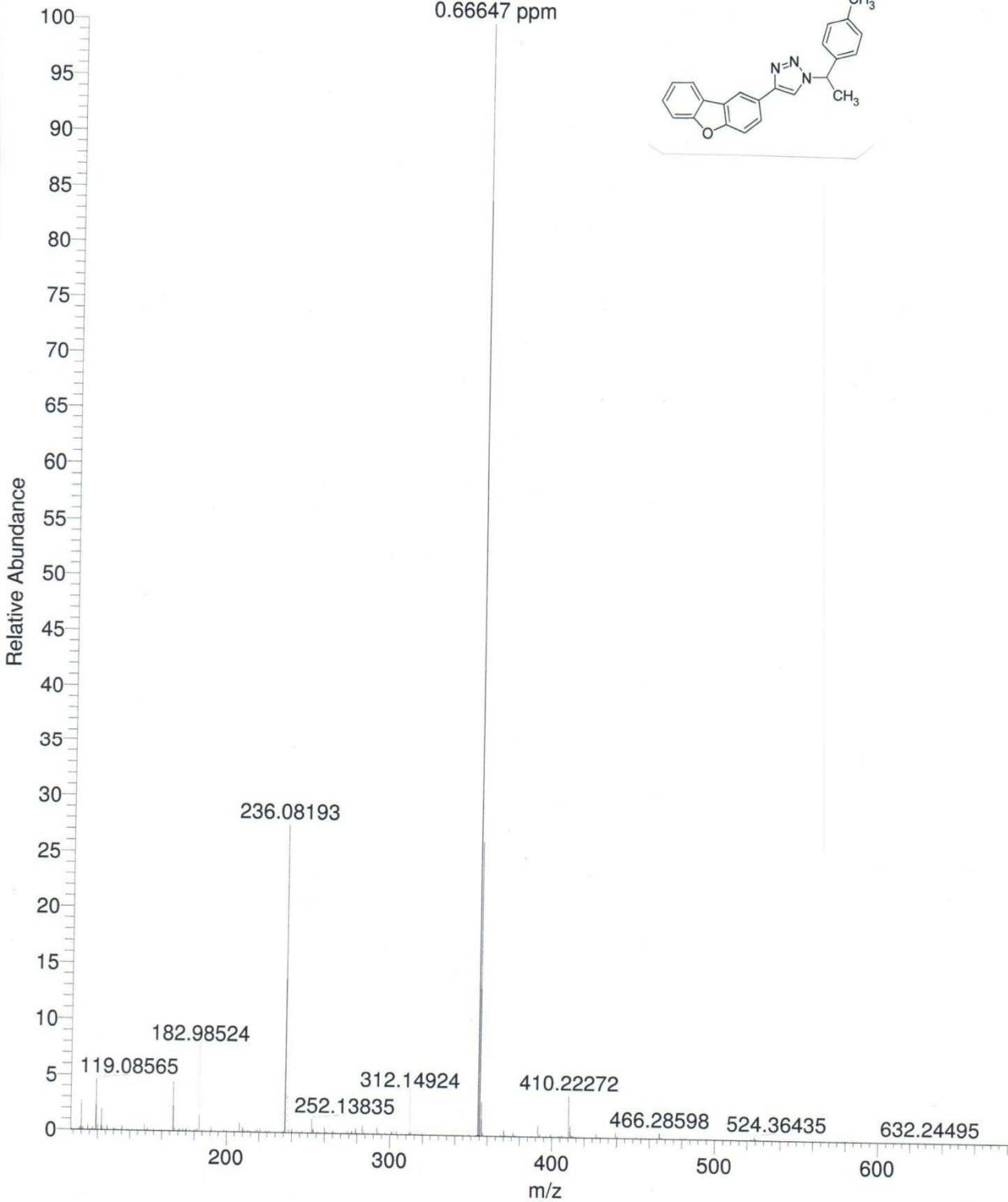
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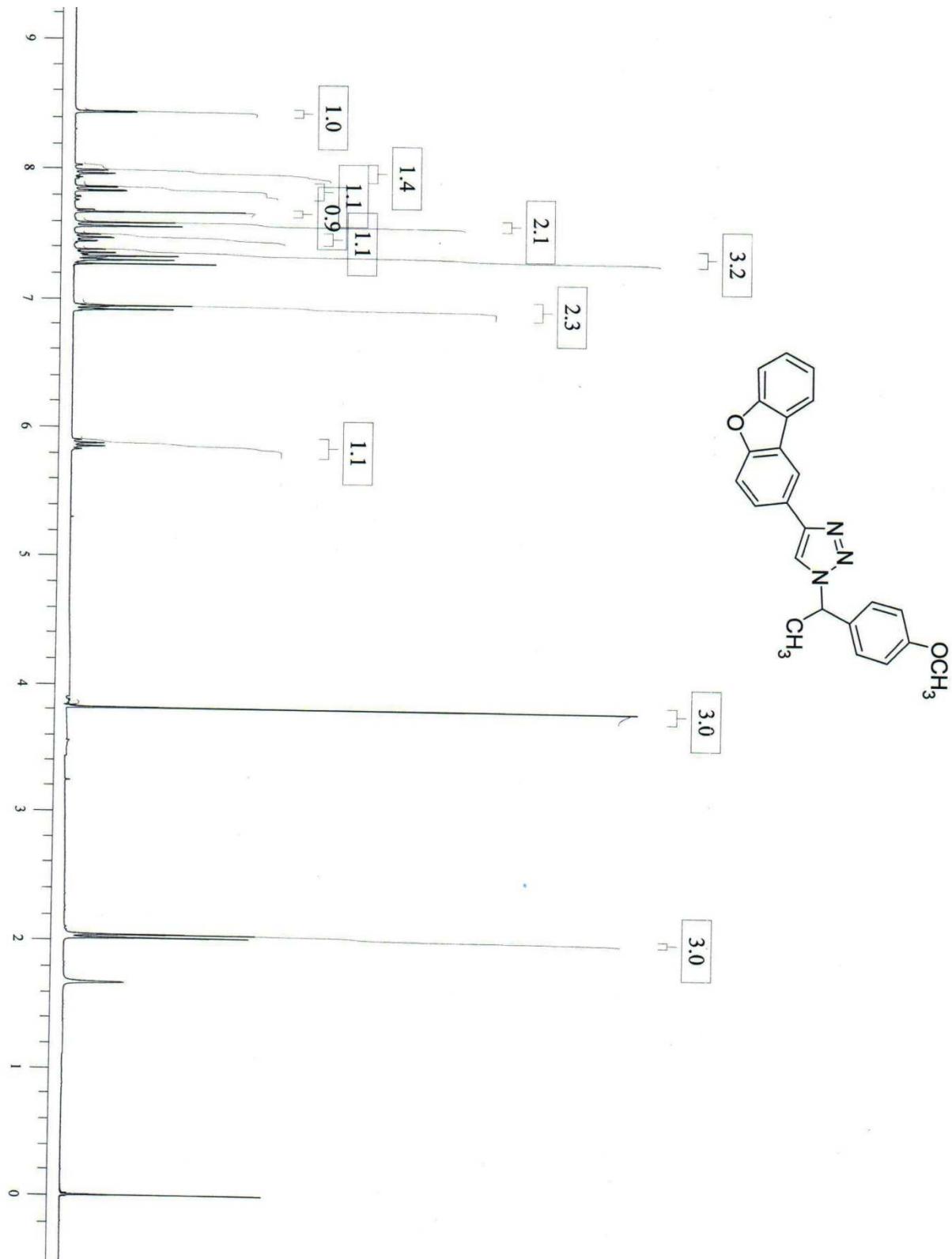
354.16032

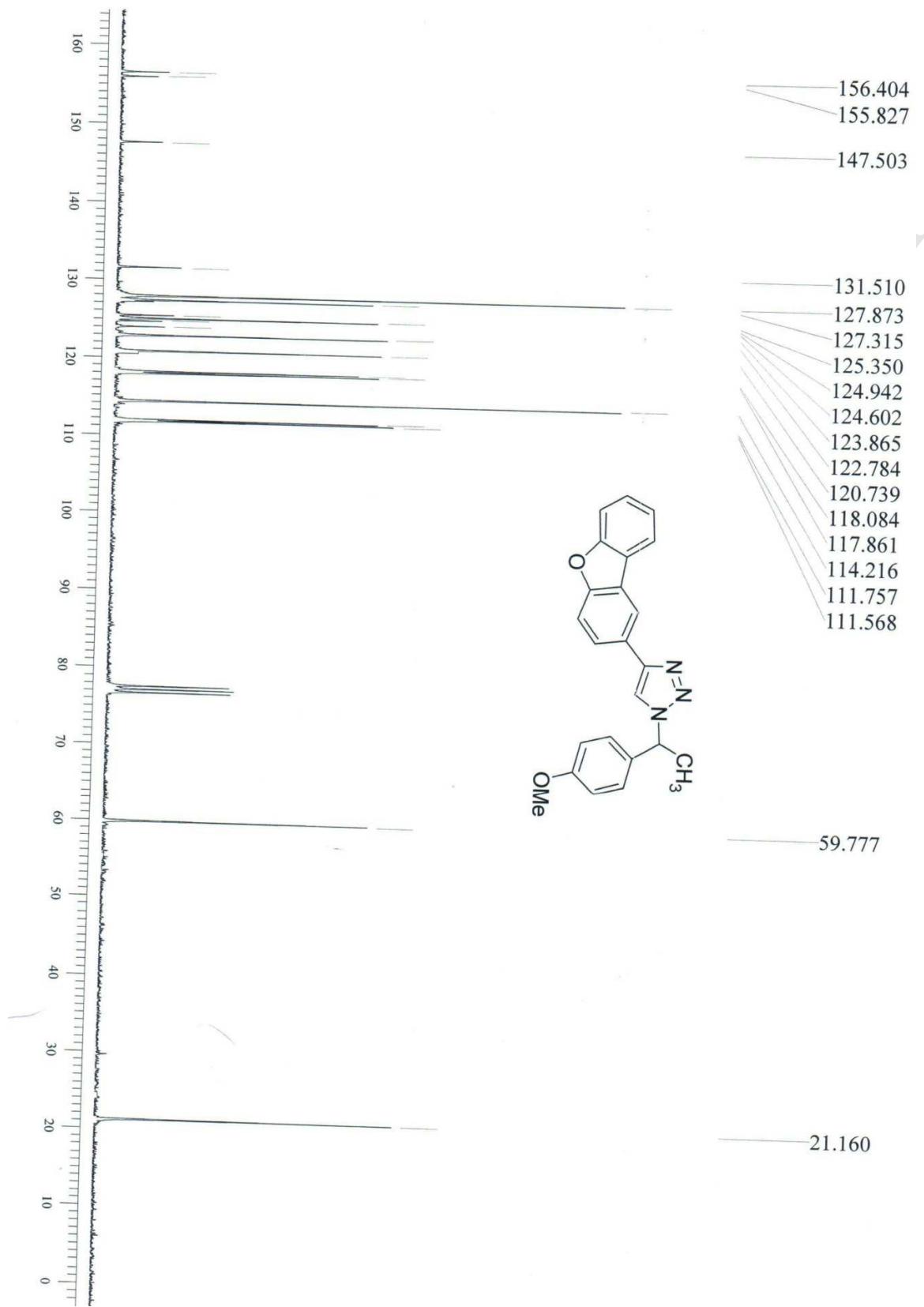
$C_{23} H_{20} O N_3 = 354.16009$

15.5 RDBE

0.66647 ppm







T ANUSH
5/21/2012 6:24:14 PM

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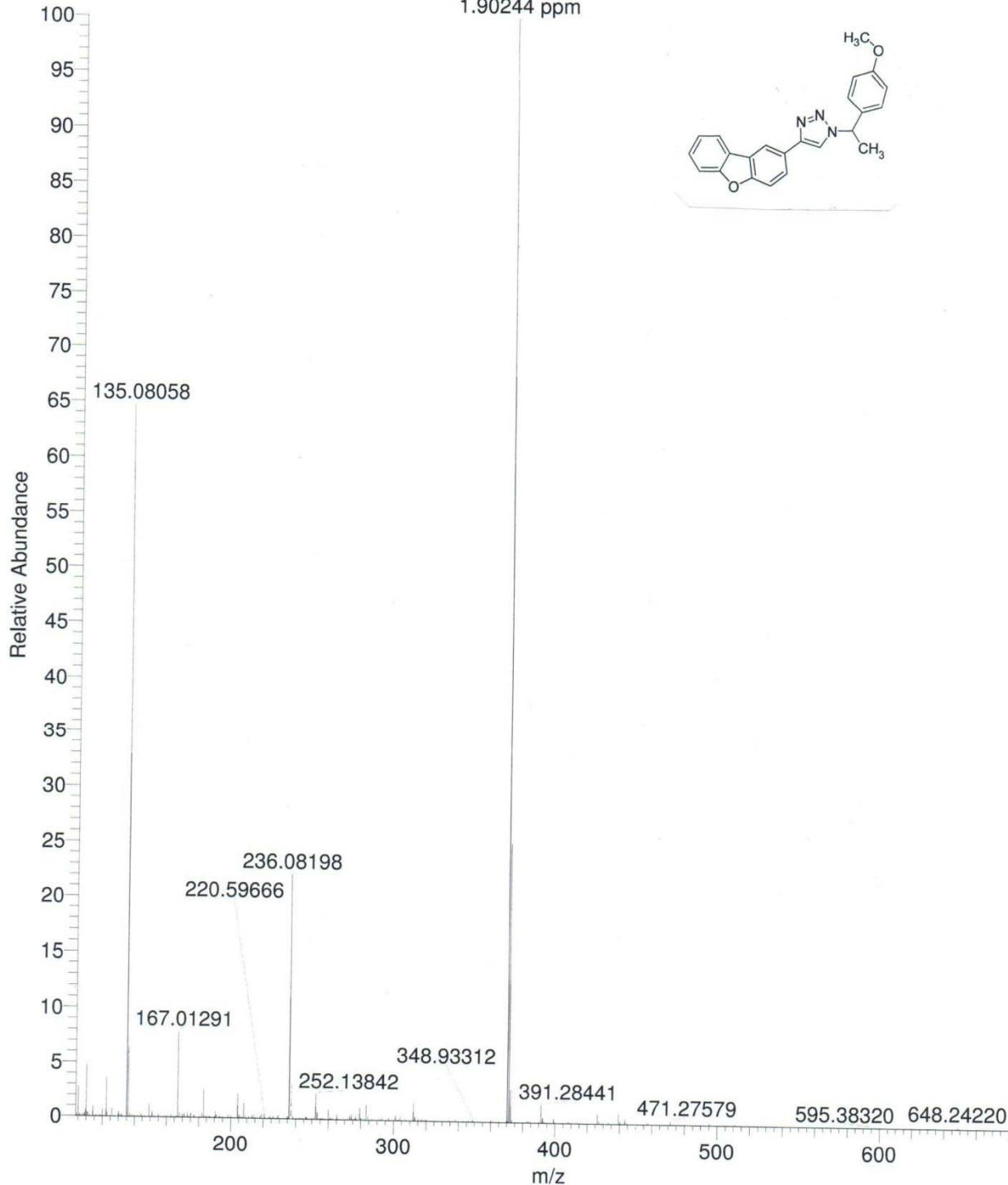
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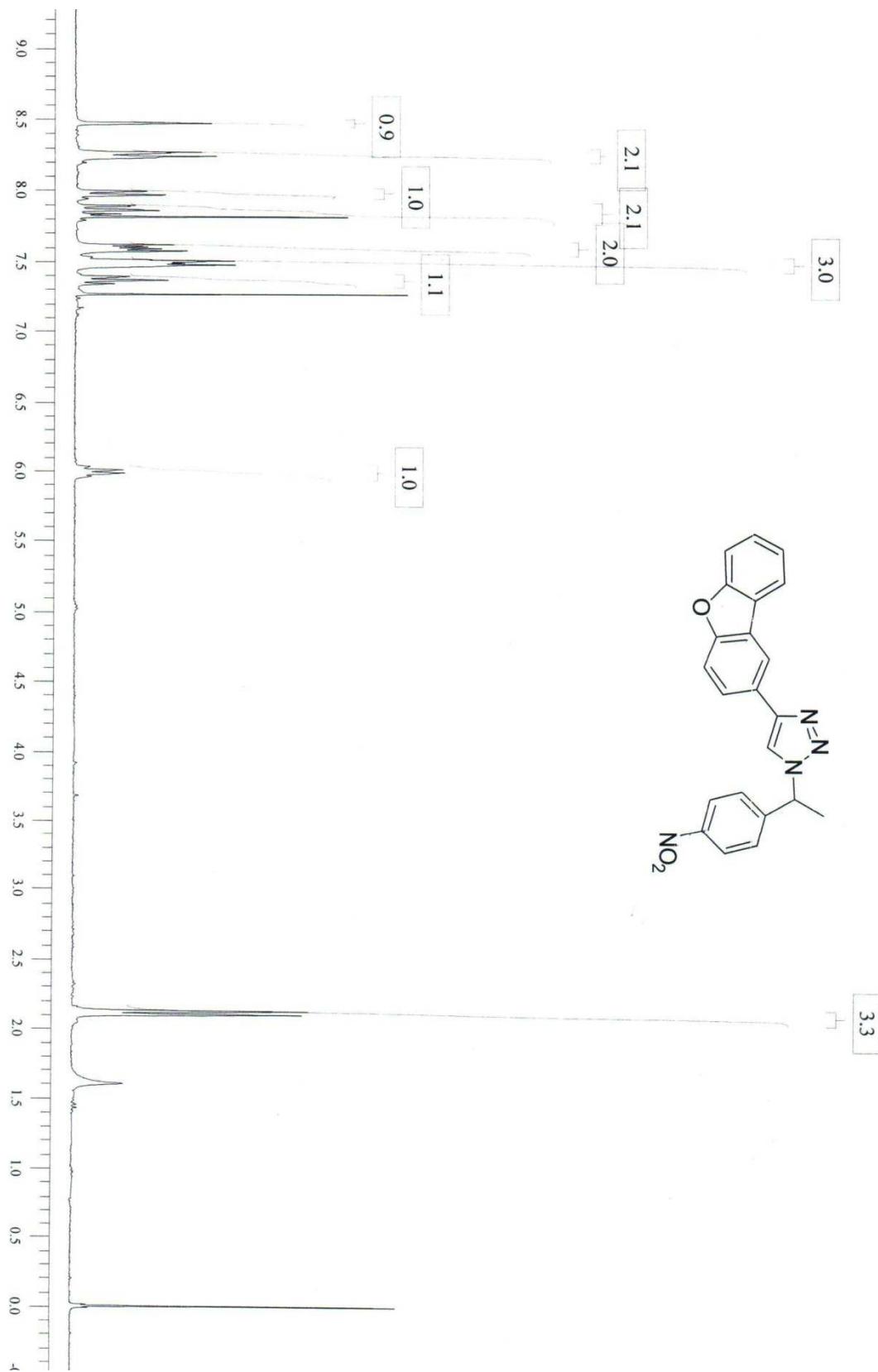
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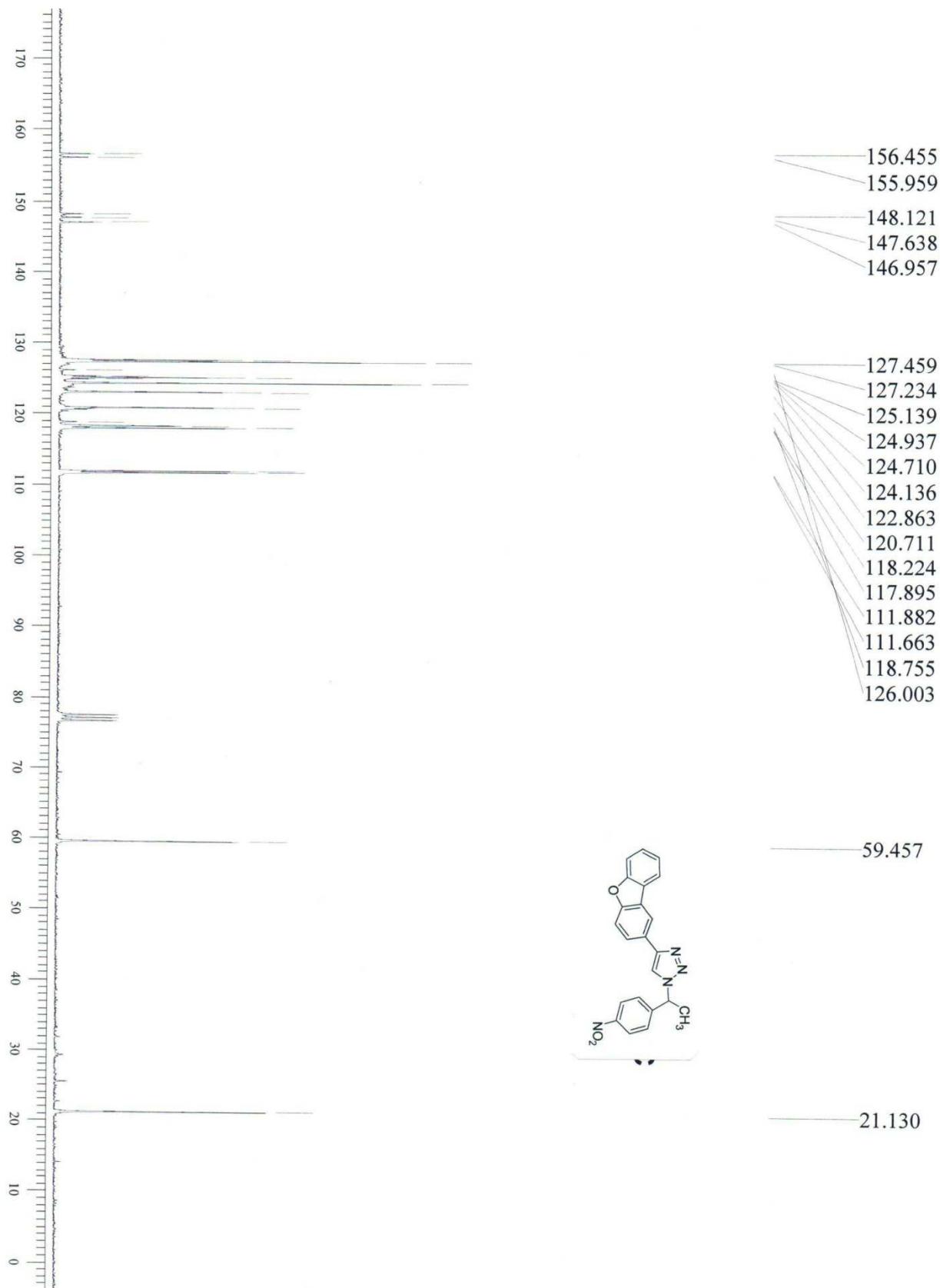
C₂₃H₂₀O₂N₃ = 370.15500

15.5 RDBE

1.90244 ppm



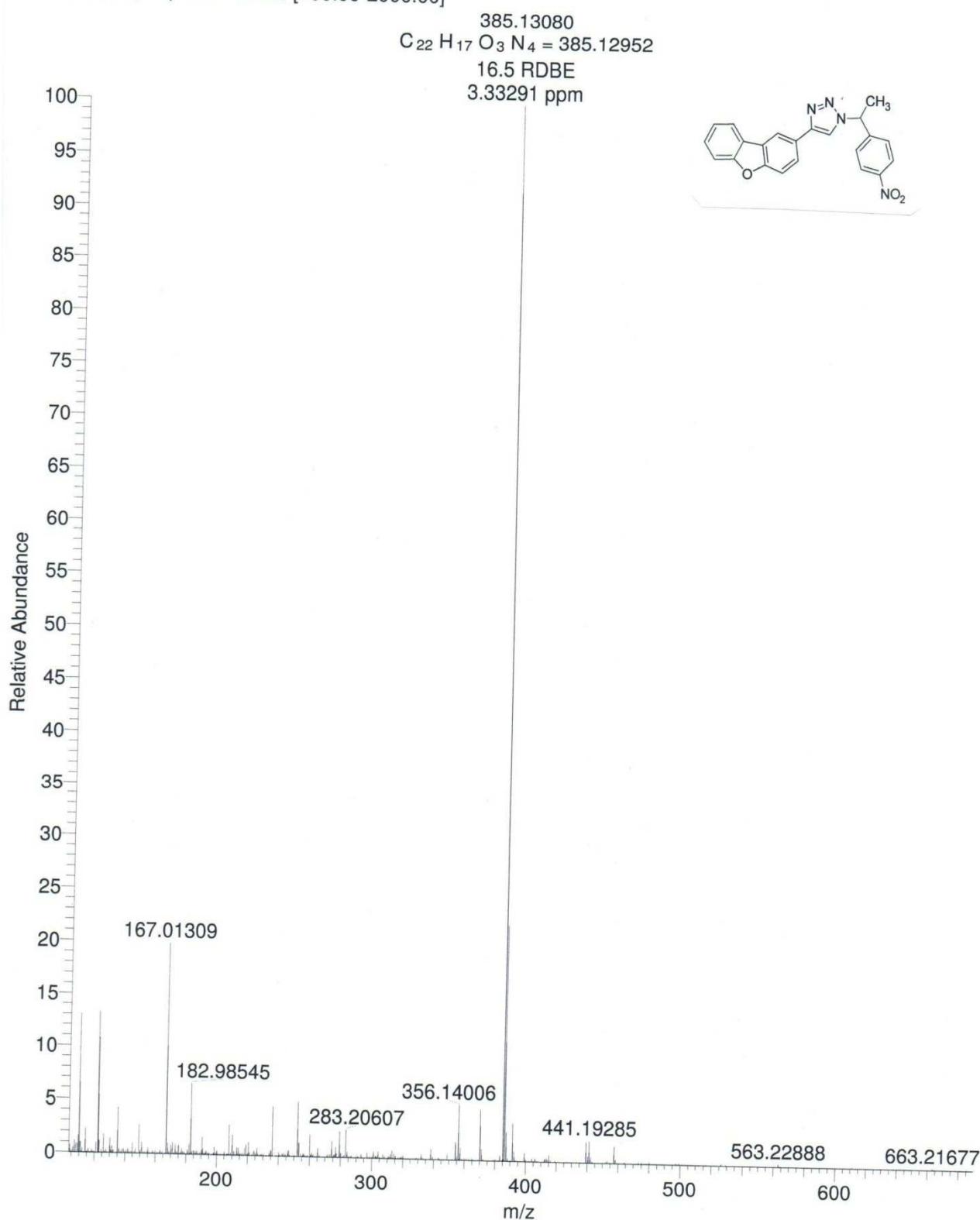


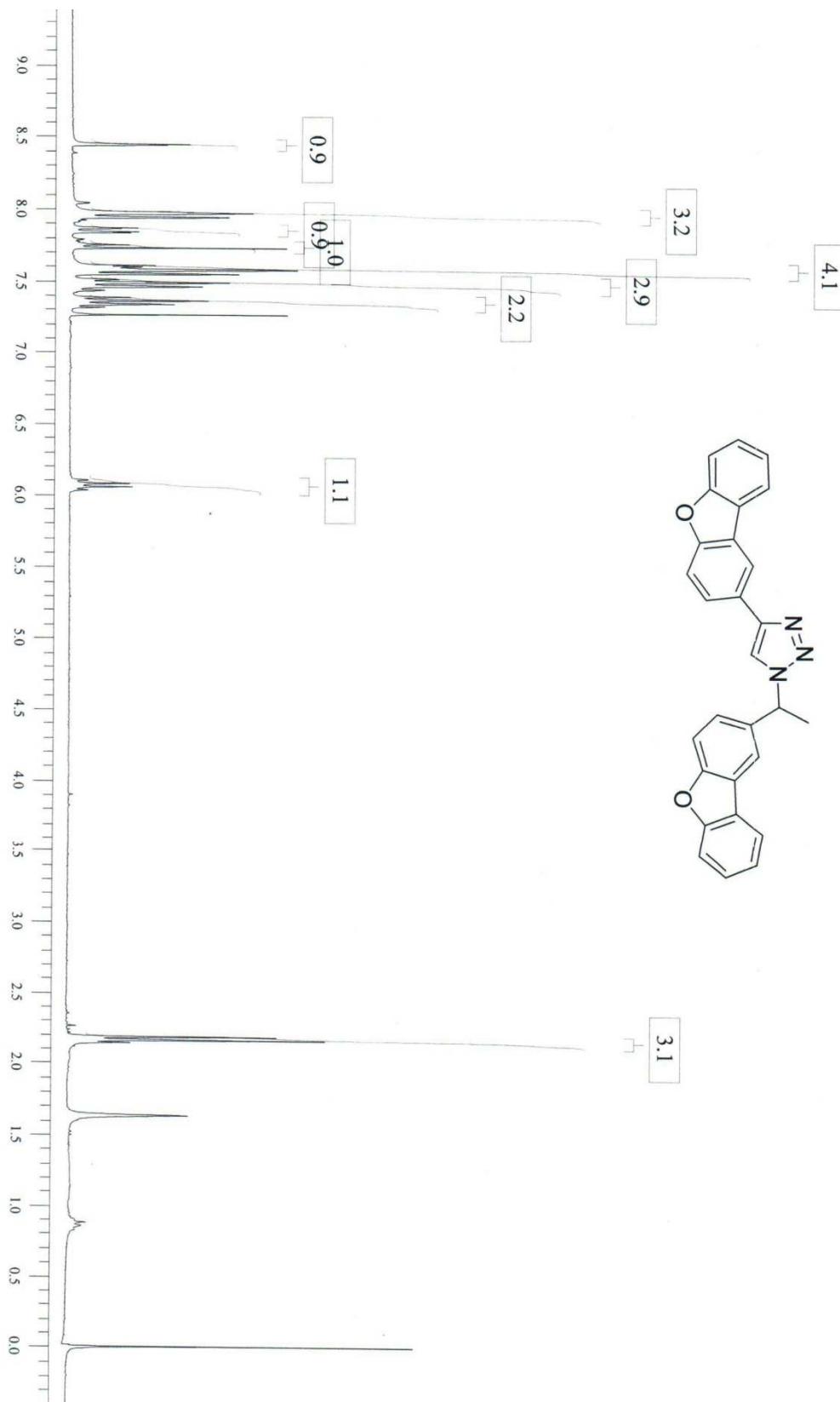


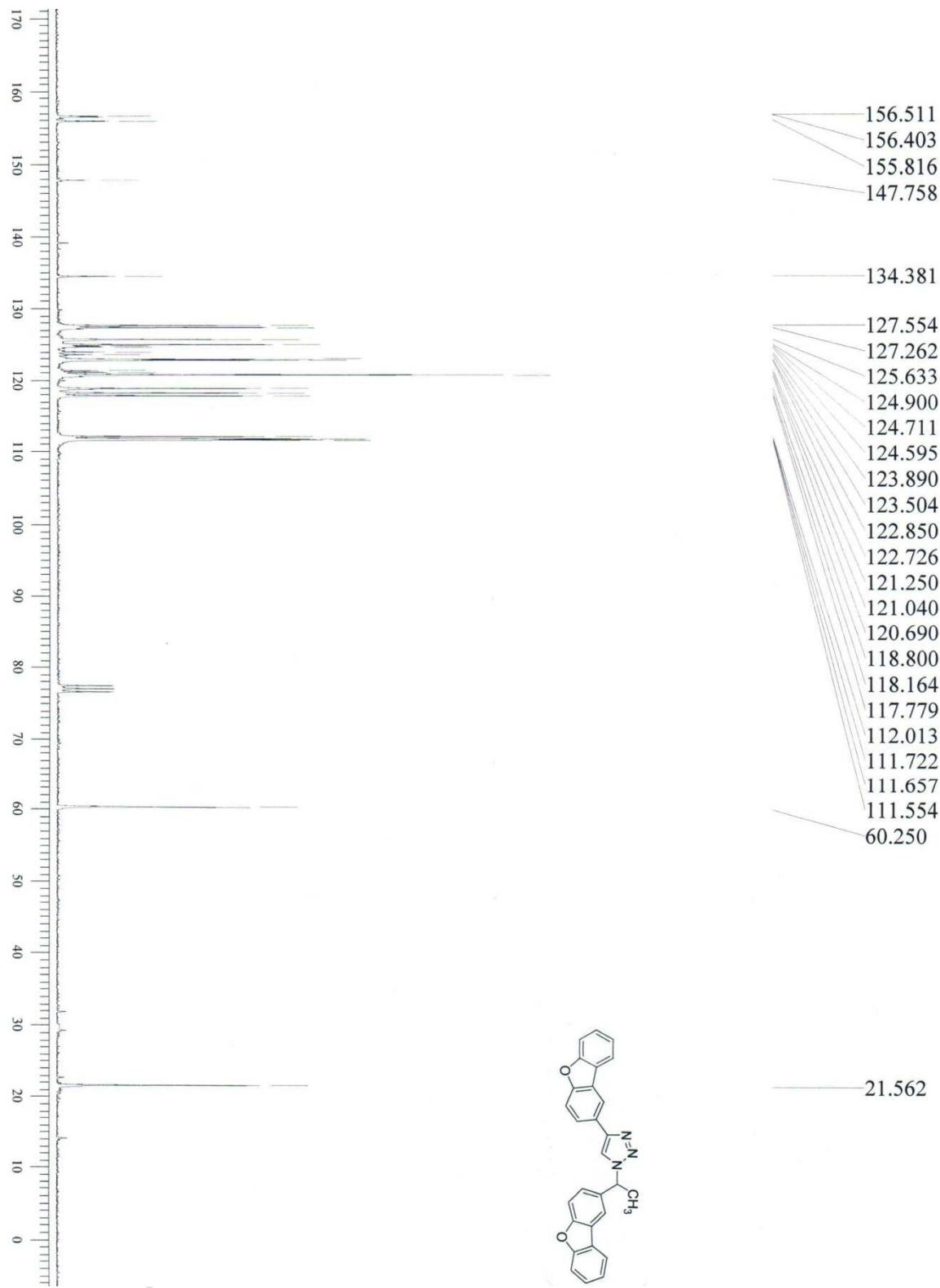
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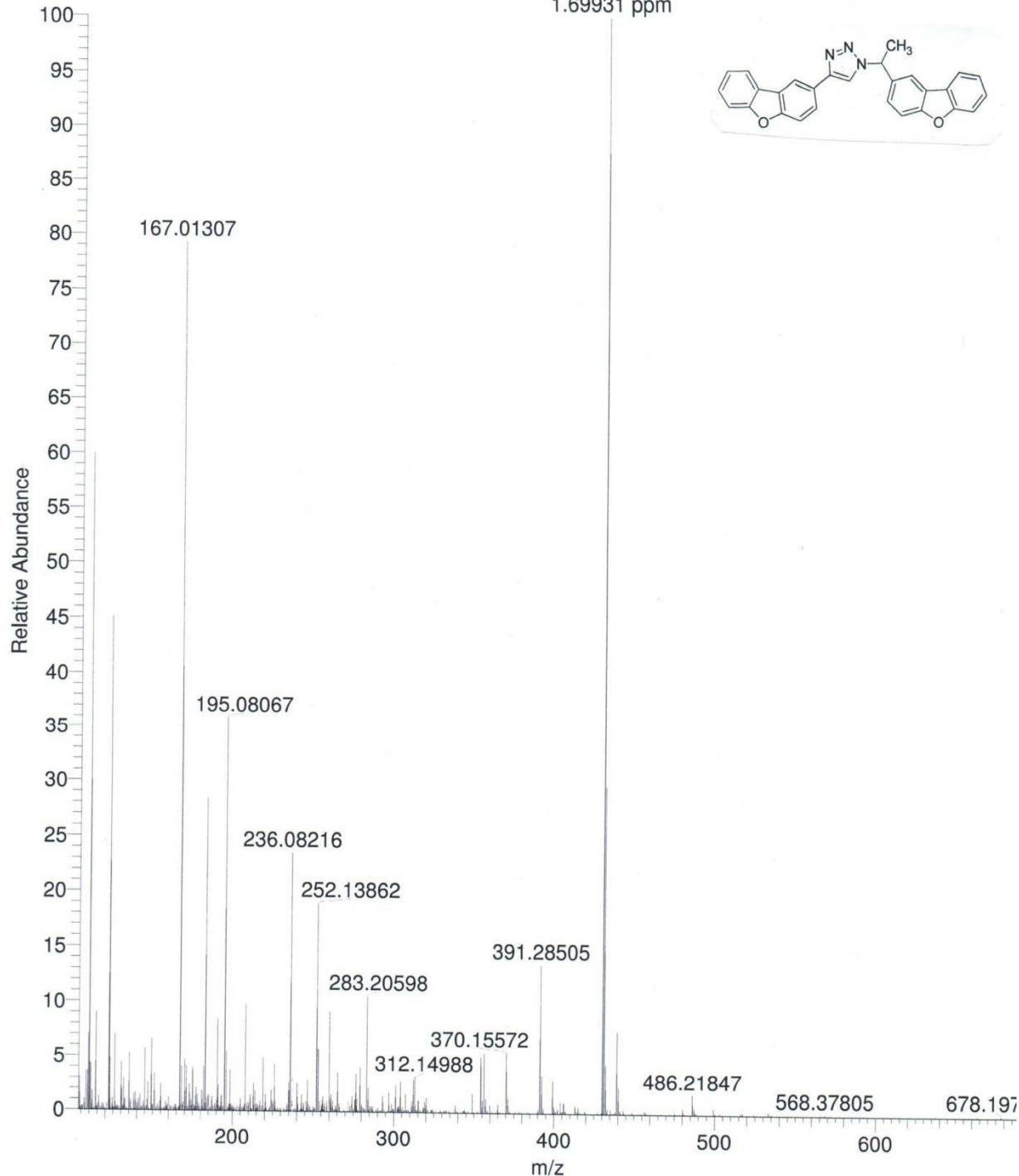


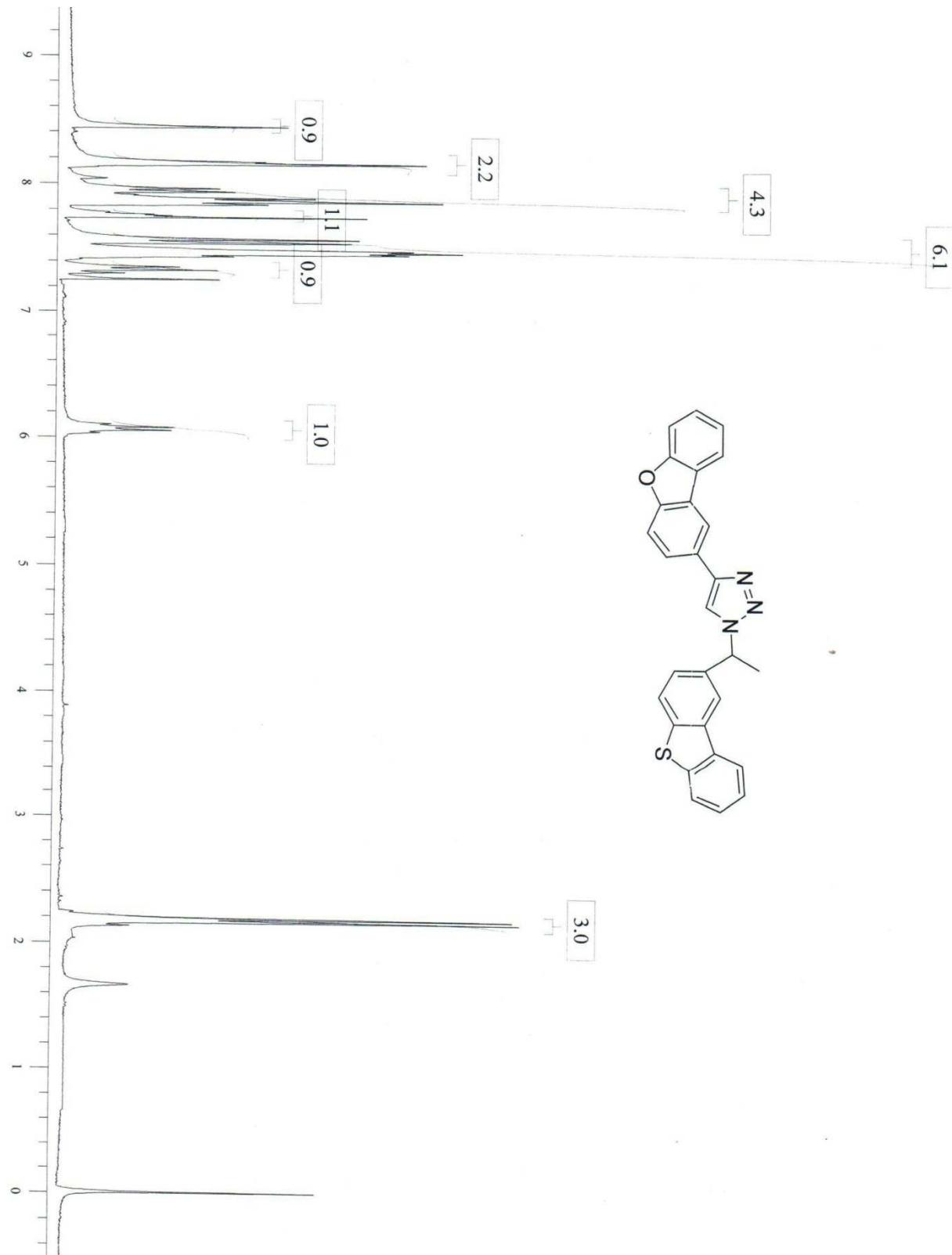
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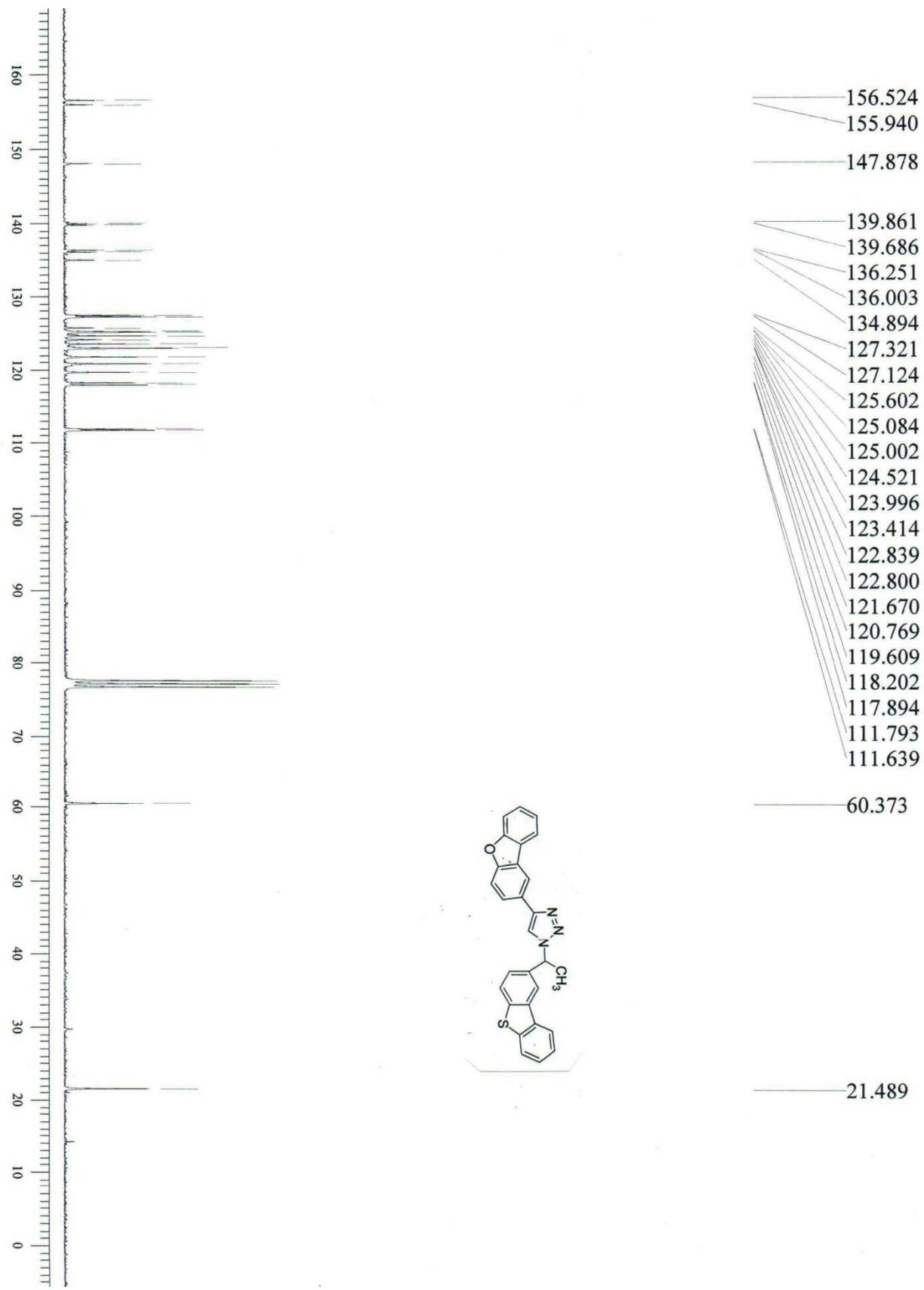
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T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

430.15573
 $C_{28} H_{20} O_2 N_3 = 430.15500$
20.5 RDBE
1.69931 ppm







T ANUSH
5/21/2012 6:58:30 PM

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KS-TRDBTAC #59-84 RT: 0.20-0.28 AV: 26 NL: 1.31E7
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

446.13226
 $C_{28} H_{20} O N_3 S = 446.13216$
20.5 RD BE
0.22629 ppm

