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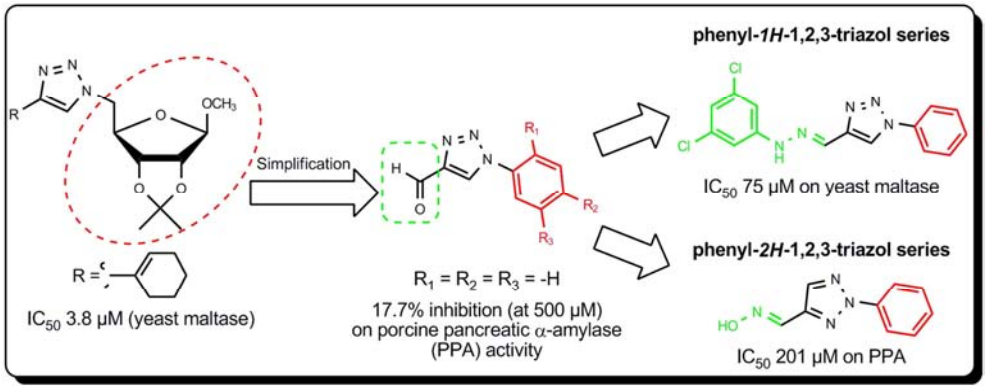

Highlights

- 60 non-glycoside triazoles divided into two regioisomers series were obtained.
- Series B (2-phenyl-2H-1,2,3-triazoles) contained potent yeast maltase inhibitors.
- Most of the active inhibitors are carboxaldehyde derivatives.
- Phenylhydrazones, N-methyleneisonicotinamides and oximes also provide active inhibitors.
- The new triazoles are promising leads for development as drugs for type 2 Diabetes.

1-phenyl-1*H*- and 2-phenyl-2*H*-1,2,3-triazol derivatives: Design, Synthesis and Inhibitory Effect on alpha-glycosidases

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Abstract

Due to aging and increasingly overweight in human population, the incidence of non-insulin dependent diabetes mellitus (NIDDM or Type 2 DM) is increasing considerably. Therefore, searching for new α-glycosidase inhibitors (GIs) capable of slowing down carbohydrate assimilation by humans is an important strategy towards control of NIDDM. In this report, we disclose the search for new easily accessible synthetic triazoles as anti-diabetic compounds. Two series of non-glycosid triazoles were synthesized (series A and B) and screened against baker's yeast α-glucosidase (MAL12) and porcine pancreatic α-amylase activity (PPA). Of the 60 compounds tested at 500 μM, were considered hits (≥ 60% inhibition) six triazoles against MAL12 and three against PPA, with the inhibition reaching up to 99.4% on MAL12 and 88.6% on PPA. The IC_{50} values were calculated for both enzymes and ranged from 54-482 μM for MAL12 and 145 to 282 μM for PPA. These results demonstrated the potential activity of simple and non-glycosidic triazoles as an important novel class of GIs for the development of drugs to treat Type 2 DM.

Keywords: Triazole, Diabetes, Amylase, Maltase, Glycosidase Inhibitors, Drug Design.

1. Introduction

The interest in 1,2,3-triazoles by the medicinal chemistry community began to increase after the improvement of Huisgen 1,3-dipolar cycloaddition [1-3] which made easy the preparation of these heterocycles. Several 1,2,3-triazoles were then screened for important biological activities, including anti-HIV [4], β-lactamase inhibition [5,6], anti-tubercular [7], α-glycosidase inhibition [8,9], anti-HSV [10], antiepileptic [11,12], antiplatelet [13], dopamine D2 receptor ligands (related to Schizophrenia) [14], anti-inflammatory [15,16], antimicrobial [17,18] and antifungal [19,20]. Currently, a few 1,2,3-triazoles are already in the final stages of clinical trials, the most promising compounds being the anticancer carboxyamidotriazole (CAI, **1**) and the reverse transcriptase inhibitor *tert*-butyldimethylsilylspiroaminooxathioledioxide (TSAO, **2**), in addition to two antibiotics, tazobactam (**3**) and cefatrizine (**4**) [21] (Figure 1).

Due to aging and increasingly overweight in human population, the incidence of non-insulin dependent diabetes mellitus (NIDDM) is increasing considerably. Therefore, searching for new α-glycosidase inhibitors (α-GIs) capable of slowing down or halting carbohydrate metabolism is an important goal in pharmacotherapeutic control of NIDDM. Inhibition of starch cleavage by α-amylase is the first step towards controlling the enzymatic degradation of polysaccharides, which is a process essential for carbohydrate assimilation.

Five-membered azaheterocycles, such as imidazole [23,24], 1,2,3-triazole [25,26] and tetrazole [27] derivatives, exhibit potent GI activity and are thought to achieve this by mimicking the sugar moieties. The latter can be rationalized by the fact that triazoles can actively participate in hydrogen bonding and dipole-dipole interactions due to their strong dipole moment, while still showing excellent stability toward hydrolysis and oxidative/reductive conditions. The triazole ring can be considered a bioisostere of the amide group because these moieties have a similar H-bond acceptor capacity, a similar distance between substituents (3.8-3.9 Å in amides and 5.0-5.1 Å in triazoles), and a similar dipolar character (amide 4.0 Debye; triazole 5.0 Debye).

Recently, a series of triazoles were synthesized and had their ability to inhibit α-glucosidase from *bacillus stearothermophilus* evaluated, with compound **5** (IC_{50} 1.15 μM) shown in Figure 2, being the most active inhibitor [28]. Also, the compounds **6** (n = 1) and **7** (n = 4) were moderate inhibitors toward glycosidase of *A. niger* [29]. Our group has synthesized several glycoconjugated triazoles that were subsequently assayed against the baker's yeast maltase (MAL12) and porcine pancreatic alpha-amylase (PPA) in the search for new α-GIs [8,9]. The results revealed that most of them presented a superior inhibitory profile than acarbose (IC_{50} 109 ± 12 μM), notably the derivatives **8** (IC_{50} 3.8 ± 0.5 μM), **9** (IC_{50} 5.7 ± 0.3 μM) and **10** (IC_{50} 5.2 ± 0.9 μM). The pharmacological potential of this triazole series was demonstrated by the reduction of post-prandial blood glucose levels in normal rats treated with a 50 mg/kg oral dose of compounds **8** or **9**. This result indicates that this triazole series could represent new candidates for the development of novel drugs for the treatment of metabolic diseases, such as diabetes (Figure 2). At that time, we found a modest but interesting inhibitory activity for compound **11** (Figure 2), in which the glycoside moiety in ribofuranosyl 1*H*-1,2,3-triazoles was replaced by an aryl ring. Since the triazoles reported as having highest activity against α-glycosidases have a carbohydrate moiety it was surprising to find this slight activity of **11**.

Triazoles with α-GI inhibitory ability are natural or synthetic glycosides. Since carbohydrate groups are known to be more synthetically challenging [30] we decided to synthesize other small molecules based on the non-glycosidic compound **11** (Scheme 1) by producing several classical and non-classical bioisoteres through simple interconvertion of

functional groups (bioisosteres with similar physical or chemical properties) and keeping the phenyl-1*H*-1,2,3-triazol framework (**12-17**) or making simple bioisosteres on ring equivalent 2*H*-1,2,3-triazol (**18-23**). With this strategy we also tried to circumvent the potential problems arising from the fact that compound **11** also has an aldehyde group that could form potential covalent adducts (Schiff base) with many other enzymes. The new triazoles were evaluated against two α-glycosidases: MAL12 and PPA.

2. Results

All 1,2,3-triazoles (series A and B) were prepared by known synthetic routes. The methodology for obtaining the 1*H*-1,2,3-triazoles (series A) was based on the Huisgen 1,3-dipolar cycloaddition reaction between propargylic alcohol and aromatic azides, which were catalyzed by Cu(I) and provided only the 1,4-regioisomers [31]. The aromatic azides were obtained by a diazotization/substitution sequence with the corresponding anilines [32] The derivatization reactions were performed using well-established methodologies. The esterified (**13**) and etherified (**14**) derivatives were made from the nucleophilic substitution reaction between the alcohol (**12**) and acid chlorides or alkyl bromides in basic medium, respectively. The partial oxidation of the alcohol (**12**) in the presence of IBX/DMSO led to formation of 4-carboxaldehyde-1,2,3-triazoles (**15**), which served as a synthetic intermediate for 4-vinyl-1*H*-1,2,3-triazoles (**16**). The 4-vinyl-1*H*-1,2,3-triazoles (**16**) were obtained from the Wittig reaction with methyltriphenylphosphonium bromide in THF/NaH. The hydrazones and oximes (**17**) were generated by reaction with aromatic hydrazines or $NH_2OH.HCl$.

Concurrently, the preparation of the derivatives 2*H*-1,2,3-triazoles followed the synthetic sequence for obtaining the Fisher osazone (D-Glucose adduct with substituted phenylhydrazines) followed by oxidative cyclization by Hudson's method (refluxed in aqueous solution of $CuSO_4$), generating the derivative phenyl-D-glucosotriazole [33-38]. Then, the oxidative cleavage of the glycotriazole in aqueous $NaIO_4$ afforded the 3-carboxaldehyde-2*H*-1,2,3-triazoles (**18**). The alditolyl-triazoles (**21**) were produced by reduction using $NaBH_4$. Next, several methods of derivatization were used as previously described to form 4-vinyl-1*H*-1,2,3-triazoles (**19**), hydrazones or oximes (**20**), esters **22** and ethers **23**. All of the compounds were obtained in good yields and were fully characterized by ^{1}H nuclear magnetic resonance (^{1}H NMR), ^{13}C NMR, infrared spectroscopy (FTIR), mass spectroscopy, and elemental analysis (CHN) (see **Experimental Section**).

As planned, the triazole moiety has been incorporated into 60 newly synthetized 1*H*- and 2*H*-1,2,3-triazoles and tested on two carbohydrate-active enzymes. It is worthy to note that the physicochemical properties of the triazole group are favorable for studies involving the discovery of new bioactive compounds since it acts as a rigid link, in which the substituents attached to the triazole at positions 1 and 4 are held at a fixed distance of 5.0 Å.

Table 1 summarizes the inhibitory screening of the compounds, which were tested at a concentration of 500 μM, against yeast MAL12 enzyme. Our results demonstrated that seven compounds inhibit enzymatic activity more effectively than acarbose, a commercial anti-diabetic drug. From those, the six compounds exhibiting ≥ 60% inhibition were selected for IC_{50} determination. Table 2 shows the IC_{50} and binding efficiency index (BEI) values for these compounds. BEI is a useful metric for the initial stages of drug development where it is necessary to optimize hits from initial screening into lead compounds [39,40]. This index reflects

the necessity to improve binding (as measured by pIC_{50}) without increasing excessively compound size or MW (which can bring solubility issues, for instance).

Table 3 summarizes the inhibitory screening against PPA activity; the samples were also tested at 500 μM. Acarbose was the most active inhibitor reaching 99.6% inhibition. Six compounds presenting ≥ 60% inhibition were considered active and selected for IC_{50} determination. Table 4 shows the IC_{50} and BEI values for these compounds.

3. Discussion

The triazoles are important compounds in medicinal chemistry and promising therapeutic agents for a variety of diseases, including type 2 Diabetes Mellitus. Previously, our group performed the synthesis and screening for the inhibitory activity of glycoconjugated triazoles (GCTs) on α-glucosidases, which confirmed them as promising prototype compounds [8,9,41]. Specifically, it was demonstrated that β-D-ribofuranosyl 1*H*-1,2,3-triazoles (ribofuranosyl GCTs) inhibiting MAL12 were also able to reduce post-prandial glucose levels in normal rats [8]. We hypothesized that this hypoglycemiant activity was due to inhibition of mammalian α-glucosidases involved in sugar metabolism, such as PPA. To test this hypothesis, we characterized the inhibitory mechanism of GCTs on porcine PA (PPA) [9]. Ribofuranosyl GCTs significantly inhibited PPA with IC_{50} in the middle to high micromolar range. We also demonstrated that ribofuranosyl GCTs are reversible noncompetitive inhibitors when we used 2-chloro-4-nitrophenyl-α-D-maltotrioside as the substrate. Finally, we have assayed the ability of 1,2,3-triazole glycoconjugates synthesized from D-glucose to inhibit yeast maltase but found that the latter are far less active than ribofuranosyl GCTs [41].

Following up with the discovery of novel α-GIs bearing a triazole ring, in this paper we report the design, synthesis and inhibitory activity of non-glycosidic *N*-phenyl-1*H*- and *N*-phenyl-2*H*-1,2,3-triazol derivatives on two α-glucosidases: MAL12 and PPA. The sugar moiety attached to the triazole ring was replaced by several substituted and non-substituted phenyl moieties, which is a departure from the GCTs previously characterized by our group. The compounds were divided into two series, depending on the attachment position of the phenyl ring: the 'A' series, where the phenyl ring is bonded to the N1 atom; and the 'B' series, where the phenyl ring is linked to the N2 atom. Further variation in each series was obtained by the conversion of the starting 4-methylalcohol (series A) or 4-carboxaldehyde (series B) derivatives into the respective aldehyde, alcohol, ester, ether, vinyl, oxime and phenylhydrazone derivatives by a series of known synthetic reactions.

Screening for α-GI activity against MAL12 and PPA showed a clear trend regarding the substitution pattern of the triazole core. Regardless of the enzyme tested in the experiment, only ring bioisosteres 2-phenyl-2*H*-1,2,3-triazoles showed inhibition above 50% when screened at a fixed concentration of 500 μM. As expected from previous results with prototype compound **11**, several carboxaldehydes (**11, 15a-b** and **18a-d**) were among the most active α-GIs. Noteworthy, some *N*-addition derivatives, such as those containing a phenylhydrazone (**20b**), oxime (**20i**) or *N*-methyleneisonicotinamide (**20h**) group also had interesting inhibition profiles.

Among the six compounds for which IC_{50} values against MAL12 were determined, four (**18a**, **18b**, **18d** and **20b**) presented IC_{50} values smaller (more potent) than acarbose (IC_{50}=109 μM).[8] Compound **18b** was the most potent with 54 μM (BEI = 20.6). It is interesting to note that addition of a chlorine to the 4-position in the 2-phenyl group (**18b**) results in slight improvement in IC_{50} in relation to **18a** but attachment of a fluorine atom to the same position (**18e**) has a

drastic negative effect on inhibitory potency (almost 10-fold increase in IC_{50} when compared to **18b**). Despite the lower BEI for the 3,5-dichlorophenylhydrazone **20b** (BEI is only 12.4), this compound is interesting for further consideration because it preserves strong maltase inhibition (IC_{50} = 75 µM) while preventing potential issues associated with analogs bearing the aldehyde group.

When comparing these values for yeast maltase inhibition with the data previously characterized by our group [8] concerning the GCT series, it was determined that the carbohydrate moiety attached to N1 in this series can be substituted with a 2-phenyl group, when the C5 substituent in the 2*H*-1,2,3-triazoles is either a carboxaldehyde or =N-R group. Among GCTs, the most potent maltase inhibitors (IC_{50} 3-5 µM) utilized bulky aromatic or hydrophobic groups, such as cyclohexenyl or phenoxymethyl, as C4 substituents and 1-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribofuranose as the carbohydrate moiety [8].

According to our previous modelling work with MAL12 [8], when binding to the free enzyme, the triazole ring may interact with the catalytic carboxylate Glu268 while the C4 substituent in 1H-1,2,3-triazole derivatives are involved in hydrophobic contacts at the -1 subsite of the enzyme. With the 2-phenyl-2*H*-1,2,3-triazoles synthesized in this work, preliminary modelling results indicate that the aromatic group may bind in similar fashion as the glycoside moiety in GCTs (data not shown). Further work is necessary to characterized the inhibition mode of these compounds thus allowing more accurate molecular modelling studies.

When compared with MAL12 results, fewer compounds showed significant activity on the PPA enzyme; this trend has been previously observed for other triazoles [9]. Two carboxaldehyde-substituted compounds (**18c** and **18d**) and the oxime **20i** presented the highest activity against PPA with IC_{50} values ranging from 145 to 282 µM. Compound **18d** presented the most similar activities against both α-glycosidases; this compound was also only 50% more potent on inhibition of MAL12 than on the inhibition of PPA. It can be hypothesized that compound **18d** binds to a homologous site shared by the enzymes; both enzymes belong to the GH13 family of glycoside hydrolases [42].

4. Conclusion

We have reported syntheses of 60 non-glycoside triazoles divided into two regioisomers series (ring bioisoteres). Series B, i.e. 2-phenyl-2*H*-1,2,3-triazoles, contained a number of potent yeast maltase inhibitors, which presented inhibition efficacy greater than the classical α-glucosidase inhibitor acarbose. Most of the active inhibitors are carboxaldehyde derivatives and these act upon both yeast maltase and PPA; aldehyde groups may react with amine groups in the enzyme polypeptide chain to form Schiff bases. This covalent attachment is usually reversible, and further work is being conducted by our group to determine the kinetics of the inhibition mechanism followed by these compounds. We also identified new active α-GI analogs where the carboxaldehyde group was substituted by phenylhydrazone, *N*-methyleneisonicotinamide and oxime groups, which are promising leads for further development of these triazoles as drugs to treat type 2 Diabetes.

5. Experimental Section

5.1. Chemistry

Reagents were purchased from Sigma-Aldrich and were used without further purification. Column chromatography was performed with silica gel 60 (Merck 70-230 mesh). Analytical thin-layer chromatography was performed with silica gel plates (Merck, TLC silica gel 60 F254), and the plots were visualized using UV light or aqueous solutions of ammonium sulfate. Yields refer to chromatographically and spectroscopically homogeneous materials. Melting points were obtained on a Fischer-Johns apparatus and were uncorrected. Infrared spectra were measured using KBr pellets on a Perkin-Elmer model 1420 FT-IR Spectrophotometer, calibrated relative to the 1601.8 cm^{-1} absorbance of polystyrene. NMR spectra were recorded on a Varian Unity Plus VXR (500 MHz) instrument in DMSO-d_6 or $CDCl_3$ solutions. The chemical shift data were reported in units of δ (ppm) downfield from tetramethylsilane or the solvent, either of which were used as an internal standard; coupling constants (*J*) are reported in Hertz and refer to apparent peak multiplicities. The high-resolution mass spectra (electrospray ionization) were obtained using a QTOF Micro (Waters, Manchester, UK) mass spectrometer (HRESIMS).

α-Glucosidase from *S. cerevisiae* (CAS number: 9001-42-7), *p*-nitrophenyl-α-D-glucopyranoside (PNP-G; CAS number: 3767-28-0), α-Amylase type I-A suspension in 2.9 M NaCl with 3 mM $CaCl_2$ from porcine pancreas (CAS number: 9000-90-2), 2-chloro-4-nitrophenyl-α-D-maltotrioside (CNPG3; CAS number: 118291-90), acarbose (CAS number: 56180-94-0), phosphate buffer, Hepes buffer, sodium chloride and calcium chloride, which were purchased from Sigma (USA).

Representative 1H and 13C NMR spectra for the compounds obtained in this work are provided as supplementary material online.

4.1.1 General procedure for preparation of 12a-d

In a round-bottom flask equipped with a magnetic stirring bar, the substituted aniline (10 mmols) was dissolved in HCl 6M (10 mL) cooled in an ice bath and the temperature was maintained between 0-5 ºC. Subsequently, $NaNO_2$ (15 mmols in 25 mL of water) was added dropwise. The reaction mixture was then stirred for 30 minutes at 0-5ºC. Next, sodium azide solution (40 mmols with 50 mL of water) was added drop-wise. After the addition, the system was stirred for another hour. Finally, the mixture was extracted with ethyl acetate and the combined organic extracts were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The aromatic azides obtained were used directly without further purification.

To a round-bottom flask equipped with a magnetic stirring bar were added an aromatic azide (0.83 mmol), propargyl alcohol (0.75 mmol), *tert*-butanol (0.7 mL), copper sulfate pentahydrate (0.04 mmol), sodium ascorbate (0.11 mmol) and water (0.7 mL). The reaction mixture was stirred for 48-72 hours at room temperature. Next, the mixture was extracted with ethyl acetate and the combined organic extracts were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The product was purified via silica-gel column chromatography, using gradient mixture of hexane-ethyl acetate, to afford the pure derivatives **12a-d**.

4.1.1.1 (1-phenyl-1*H*-1,2,3-triazole-4-yl)methanol (**12a**). White solid, m.p. 110-111°C (m.p lit. 109-110°C [7]); IR ν_{max} (cm^{-1}): 3202, 1595, 1499, 1240, 1007, 756, 686; ^{1}H NMR (DMSO-d_6, 300.00 MHz) δ: 4.74 (2H, d, *J* 5.5 Hz, H-6), 5.33 (1H, t, J 5.5, OH), 7.60 (2H, t, *J* 7.3 Hz, H-4'), 7.71 (2H, t, *J* 7.3 Hz, H-3' and H-5'), 8.02 (2H, d, J 7.3 Hz, H-3' and H-5') 8.78 (1H, s, H-5); ^{13}C NMR(DMSO-d_6, 75.0 MHz APT) δ: 55.0 (C-6), 120.0 (C-4'), 120.9 (C-5), 128.4 (C-3' and C-5'), 129.8 (C-2'and C-6'), 136.8 (C-1'), 149.1 (C-4).

4.1.1.2 (1-(4-methoxyphenyl)-1*H*-1,2,3-triazole-4-yl)methanol (**12b**). Brown solid, m.p. 128-129°C (m.p. lit. 127-129 °C [7]); IR ν_{max} (cm^{-1}): 3184, 3116, 3074, 2970, 1608, 1519, 1262, 1048, 1016, 838; ^{1}H NMR (DMSO-d_6, 300.00 MHz) δ: 3.94 (OCH_3), 4.72 (2H, d, *J* 5.5 Hz, H-6), 7.22-7.25 (2H, m, H-3'and H-5'), 7.88-7.92 (2H, m, H-2' and H-6'), 8.64 (1H, s, H-5); ^{13}C NMR(DMSO-d_6, 75.0 MHz APT) δ: 55.1 (C-6), 55.6 (OCH_3), 115.0 (C-3' and C-5'), 121.0 (C-5), 121.8 (C-2' and C-6'), 130.3 (C-4'), 148.9 (C-1'), 159.3 (C-4).

4.1.1.3 (1-(4-chlorophenyl)-1*H*-1,2,3-triazole-4-yl)methanol (**12c**). White solid, m.p. 143-144°C (m.p. lit. 144-145°C [7]); IR ν_{max} (cm^{-1}):3216, 1502, 1242, 1186, 1092, 1062, 1040, 1012, 835, 776, 701, 676; ^{1}H NMR (DMSO-d_6, 300.00 MHz) δ: 4.63 (2H, d, *J* 3.3 Hz, H-6), 5.33 (1H, t, *J* 3.3, OH), 7.62 (2H, d, *J* 9.1 Hz, H-3' and H-5'), 7.92 (2H, d, *J* 9.1 Hz, H-2' and H-6'); 8.66 (1H, s, H-5); ^{13}C NMR(DMSO-d_6, 75.0 MHz APT) δ: 55.0 (C-6), 121.1 (C-5), 121.6 (C-2' and C-6'), 129.9 (C-3' and C-5'), 132.8 (C-4'), 135.6 (C-1'), 149.4 (C-4).

4.1.1.4 (1-(2,5-dichlorophenyl)-1*H*-1,2,3-triazole-4-yl)methanol (**12d**). White solid, m.p. 117-118°C (m.p. lit. 114-116 °C [7]); IR ν_{max} (cm^{-1}):3338, 2361, 1585, 1485, 1445, 1238, 1099, 1037, 871, 819, 644; ^{1}H NMR (DMSO-d_6, 300.00 MHz) δ: 4.75 (2H, d, *J* 3.3 Hz, H-6), 5.47 (1H, t, *J* 3.3 Hz, OH), 7.84 (1H, dd, *J* 1.6 and 5.2 Hz), 7.93 (1H, d, *J* 5.2 Hz, H-3'), 7.99 (1H, d, *J* 1.6 Hz, H-6'), 8.55 (1H, s, H-5); ^{13}C NMR(DMSO-d_6, 75.0 MHz APT) δ: 54.9 (C-6), 124.9 (C-5), 127.5 (C-2'), 128.1 (C-6'), 131.3 (C-4'), 132.0 (C-3'), 132.5 (C-5'), 135.6 (C-1'), 148.2 (C-4).

4.1.2 General procedure for preparation of 13a-k and 22a-d

Into a round-bottom flask were added 5.71 mmols of alditolyl-triazole **12** or **21a** in 50 ml dichloromethane, 0.9 mL of pyridine (2 eq.), 5.71 mmols of acyl chloride and catalytic amount of DMAP. The mixture was stirred vigorously at room temperature, and the reaction progress was monitored by thin layer chromatography. Next, the mixture was washed with distilled water (3 x 100 mL), saturated sodium bicarbonate solution (5 x 100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The product was purified via silica-gel column chromatography using gradient mixture of hexane-ethyl acetate, to afford the pure derivatives **13a-k** and **22a-d**.

4.1.2.1 (1-phenyl-1*H*-1,2,3-triazole-4-yl)methylbenzoate (**13a**). White solid, m.p. 110-111 °C; IR ν_{max} (cm^{-1}): 3135, 3093, 2965, 2363, 2338, 1722, 1600, 1505, 1451, 1274, 1241, 1106, 1099; ^{1}H NMR ($CDCl_3$, 500.00 MHz)δ:5.66 (2H, s, H-6), 7.53-7.59 (1H, m, H-4'), 7.63-7.73 (4H, m, H-3', H-5', H-3" and H-5"), 7.77-7.83 (1H, m, H-4"), 8.11-8.16 (4H, m, H-2', H-6', H-2" and H-6"), 8.34 (1H, s, H-5); ^{13}C NMR($CDCl_3$, 125.0 MHz APT) δ: 57.9 (C-6), 120.2 (C-4'), 123.0 (C-5), 128.5 (C-3' and C-5'), 128.8 (C-2' and C-6'), 129.3, 129.9, 132.8, 133.5 (C-2", C-3", C-4",

C-5" and C-6"), 129.4 (C-1"), 136.6 (C-1'), 143.1 (C-4), 165.5 (C-8). Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.23; H, 4.96; N, 14.68.

4.1.2.2 (1-(2,5-dichlorophenyl)-1*H*-1,2,3-triazole-4-yl)methylbenzoate (**13b**). White solid, m.p. 85-86 ºC; IR ν_{max} (cm^{-1}): 3053, 1731, 1588, 1486, 1449, 1264, 1098, 1038, 733; ^{1}H NMR ($CDCl_3$, 500.00 MHz) δ: 5.65 (2H, s, H-6); 7.60-7.68 (3H, m, H-3", H-4" and H-5"), 7.72-7.81 (1H, m, H-6'), 7.85 (1H, dd, *J*1.8 and 5.4 Hz, H-4'), 7.93 (1H, d, *J*5.4 Hz, H-3'), 8.05-8.13 (2H, m, H-2" and H-6"); 8.86 (1H, s, H-5); ^{13}C NMR($CDCl_3$, 125.0 MHz APT) δ: 57.6 (C-6), 126.8 (C-5), 127.5 (C-2' and C-6'), 128.5 (C-3' and C-5'), 128.8, 129.3, 129.8, 133.1 and 133.5 (C-2", C-3", C-4", C-5"and C-6"), 130.8 (C-1'), 132.1 (C-4'), 135.4 (C-1"), 143.3 (C-4), 165.5 (C-8). Anal. Calcd for $C_{16}H_{11}Cl_2N_3O_2$: C, 55.19; H, 3.18; N, 12.07. Found: C, 55.63; H, 3.21; N, 11.92.

4.1.2.3 (1-(2,5-dichlorophenyl)-1*H*-1,2,3-triazole-4-yl)methyl hexanoate (**13c**). Yellow oil; IR ν_{max} (cm^{-1}): 3153, 3098, 2932, 2958, 1738, 1589, 1489, 1451, 1240, 1166, 1099, 1042, 1003, 809; ^{1}H NMR ($CDCl_3$, 500.00 MHz) δ: 0.97 (3H, t, *J* 6.8 Hz,C-13), 1.36-1.41 (4H, m, H-11 and H-12), 1.67 (2H, p, *J* 7.3 Hz, H-10), 2.46 (2H, t, *J* 7.3 Hz, H-9), 5.37 (2H, s, H-6), 7.85 (1H, dd, *J* 2.5 and 8.5 Hz, H-4'); 7.93 (1H, d, *J* 8.5 Hz, H-3'), 8.01 (1H, d, *J* 2.5 Hz, H-6'), 8.72 (1H, s, H-5); ^{13}C NMR($CDCl_3$, 125.0 MHz APT) δ: 13.6 (C-13), 21.7 (C-12), 24.0 (C-10), 30.5 (C-11), 33.3 (C-9), 56.7 (C-6), 126.6 (C-5), 127.4 (C-2'), 128.1 (C-6'), 131.4 (C-4'), 131.9 (C-3'), 132.5 (C-5'), 135.3 (C-1'), 142.3 (C-4), 172.6 (C-8); Anal. Calcd for $C_{15}H_{17}Cl_2N_3O_2$: C, 52.64; H, 5.01; N, 12.28. Found: C, 52.77; H, 5.11; N, 12.16.

4.1.2.4 (1-(4-chlorophenyl)-1*H*-1,2,3-triazole-4-yl)methylacetate (**13d**). Brown solid, m.p. 74-75 ºC; IR ν_{max} (cm^{-1}): 3180, 3074, 2964, 1741, 1581, 1487, 1232, 1097, 1047, 1028, 993, 834, 805; ^{1}H NMR ($CDCl_3$, 500.00 MHz) δ: 2.19 (3H, s, H-8), 5.35 (2H, s, H-6), 7.85 (1H, dd, *J* 1.5 and 4.8 Hz, H-4'), 7.93(1H, d, *J* 4.8 Hz, H-3'), 8.03 (1H, d, *J* 1.5 Hz, H-6'), 8.74 (1H, s, H-5); ^{13}C NMR($CDCl_3$, 125.0 MHz APT) δ:20.6 (C-9), 56.8 (C-6), 126.9 (C-5), 127.6 (C-2'), 128.3 (C-6'), 131.6 (C-4'), 132.0 (C-3'), 132.6 (C-5'), 135.3 (C-1'), 142.3 (C-4), 170.1 (C-8); Anal. Calcd for $C_{11}H_{10}ClN_3O_2$: C, 52.50; H, 4.01; N, 16.70. Found: C, 52.59; H, 4.01; N, 16.58.

4.1.2.5 (1-(4-chlorophenyl)-1*H*-1,2,3-triazole-4-yl)methylbenzoate (**13e**).White solid, m.p. 55-56 ºC; IR ν_{max} (cm^{-1}): 3150, 2926, 2869, 1739, 1645, 1554, 1503, 1444, 1381, 1232, 1157, 1093, 1047, 988, 820, 773, 741, 696, 651; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 5.62 (2H, s, H-6), 7.59-7.82 (5H, m, H-1", H-2", H-3", H-4", H-5", H-6"), 8.05-8.14 (4H, m, H-2', H-3', H-5', H-6'), 9.08 (1H, s, H-5); ^{13}C NMR(DMSO-d_6, 125.0 MHz APT) δ: 57.8 (C-6), 121.9 (C-5), 123.1 (C-3' and C-5'), 128.5 (C-2'and C-6'), 128.8, 129.3, 129.8, 133.1 and 133,5 (C-2", C-3", C-4", C-5"and C-6"), 130.8 (C-1'), 132.1 (C-4'), 135.4 (C-1"), 143.3 (C-4), 165.5 (C-8); Anal. Calcd for $C_{16}H_{12}ClN_3O_2$: C, 61.25; H, 3.86; N, 13.39. Found: C, 61.28; H, 3.91; N, 13.14.

4.1.2.6 (1-phenyl-1*H*-1,2,3-triazole-4-yl)methyl hexanoate (**13f**). Yellow oil; IR ν_{max} (cm^{-1}): 3147, 2957, 2872, 1736, 1597, 1503, 1466, 1239, 1167, 1045, 759, 690; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 0.84 (3H, t, *J* 7,0 Hz, H-13), 1.21-1.31 (4H, m, H-11 and H-12), 1.55 (2H, p, *J* 7.5 Hz, H-10), 2.33 (2H, t, *J* 7.5 Hz, H-9), 5.23 (2H, s, H-6), 7.50 (1H, t, *J* 8.0 Hz, H-4'), 7.60 (2H, t, *J* 8.0 Hz, H-3' and H-5'), 7.90 (2H, d, *J* 8.0 Hz, H-2' and H-6'), 8.82 (1H, s, H-5);^{13}C NMR(DMSO-d_6, 125.0 MHz APT) δ: 13.7 (C-13), 21.7 (C-12), 24.1 (C-11), 30.6 (C-10), 33.3 (C-9), 56.8 (C-6), 120.1 (C-4'), 122.8 (C-5), 128.8 (C-3' and C-5'), 129.9 (C-2' and C-6'), 136.6

(C-1'), 143.2 (C-4), 172.6 (C-8); Anal. Calcd for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.61; H, 7.03; N, 15.52.

4.1.2.7 (1-(2,5-dichlorophenyl)-1*H*-1,2,3-triazole-4-yl)methylacetate (**13g**). Brown solid, m.p. 112-113 ºC; IR ν_{max} (cm^{-1}): 3149, 3110,1738, 1503, 1367, 1254, 1233, 1098, 1056, 1035, 823; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 2.18 (3H, s, H-8), 5.33 (2H, s, H-6), 7.78-7.81 (2H, m, H-3' and H-5'), 8.05-8.07 (2H, m, H-4' and H-6'), 8.98 (1H, s, H-5); ^{13}C NMR(DMSO-d_6, 125.0 MHz APT) δ: 20.6 (C-9), 56.9 (C-6), 121.9 (C-5), 123.0 (C-2' and C-6'), 129.8 (C-3' and C-5'), 133.1 (C-1'), 135.3 (C-4'), 143.3 (C-4), 170.0 (C-8). Anal. Calcd for $C_{11}H_9Cl_2N_3O_2$: C, 46.18; H, 3.17; N, 14.69. Found: C, 46.36; H, 3.13; N, 14.45.

4.1.2.8 (1-(4-chlorophenyl)-1*H*-1,2,3-triazole-4-yl)methyl hexanoate (**13h**). White solid, m.p. 55-56 ºC; IR ν_{max} (cm^{-1}):3150, 2927, 2869, 1739, 1645, 1603, 1554, 1503, 1444, 1382, 1317, 1232, 1157, 1093, 1047, 988, 820, 773, 741, 696, 651; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 0.96 (t, 3H, *J* 6.6 Hz, H-13), 1.35-1.41 (m, 4H, H-11 and H-12), 1.62-1.72 (m, 2H), 2.46 (t, 2H, *J* 7.2 Hz, H-9), 5.35 (s, 2H, H-6), 7.78 (d, 2H, *J* 9.0 Hz, H-2' and H-6'),8.05 (d, 2H, *J* 9.0 Hz, H-3' and H-5'), 8.92 (s, 1H, H-5); ^{13}C NMR(DMSO-d_6, 125.0 MHz APT) δ: 13.7 (C-13), 21.7 (C-12), 24.1 (C-11), 30.6 (C-10), 33.3 (C-9), 56.8 (C-6), 121.8 (C-5), 123.0 (C-3' and C-5'), 129.9 (C-2' and C-6'), 133.1 (C-4'), 135.3 (C-1'), 143.4 (C-4), 172.6 (C-8); Anal. Calcd for $C_{15}H_{18}ClN_3O_2$: C, 58.54; H, 5.89; N, 13.65. Found: C, 59.21; H, 6.05; N, 13.37.

4.1.2.9 (1-phenyl-1*H*-1,2,3-triazole-4-yl)methyl decanoate (**13i**). Yellow solid, m.p. 45-46 ºC; IR ν_{max} (cm^{-1}): 3141, 2919, 2849, 1742, 1506, 1466, 1253, 1223, 1212, 1158, 1052, 757; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 0.83 (t, 3H, *J* 7.0 Hz, H-17), 1.21-1.24 (m, 12H, H-11, H-12, H-13, H-14, H-15 and H-16), 1.51-1.58 (m, 2H, H-10), 2.34 (t, 2H, *J* 7.0 Hz, H-9), 5.23 (s, 2H, H-6), 7.50 (t, 1H, *J* 8.5 Hz, H-4'), 7.61 (t, 2H, *J* 8.5 Hz, H-2' and H-6'), 7.90 (d, 2H, *J* 8.5 Hz, H-3' and H-5'), 8.81 (s, 1H, H-5); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 14.0 (C-17), 22.1 (C-16), 24.5 (C-10), 28.5 (C-11), 28.7 (C-12), 28.7 (C-14), 28.9 (C-13), 31.3 (C-14), 30.6 (C-9), 56.9 (C-6), 120.1 (C-4'), 122.9 (C-5), 128.8 (C-3' and C-5'), 129.9 (C-2' and C-6'), 136.6 (C-1'), 143.3 (C-4), 172.7 (C-8); Anal. Calcd for $C_{19}H_{27}N_3O_2$: C, 69.27; H, 8.26; N, 12.76. Found: C, 69.19; H, 8.17; N, 12.45.

4.1.2.10 (1-(4-chlorophenyl)-1*H*-1,2,3-triazole-4-yl)methyl decanoate (**13j**). Yellow solid, m.p. 46-48 ºC; IR ν_{max} (cm^{-1}): 3143, 2916, 2851, 1738, 1503, 1470, 1415, 1384, 1350, 1291, 1250, 1229, 1157, 1095, 1048, 991, 930, 827, 785, 743, 715, 678; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 0.83 (3H, t, *J* 7.0 Hz, H-15), 1.20-1.24 (12H, m, H-9, H-10, H-11, H-12, H-13, and H-14), 1.50-1.60 (2H, m, H-9), 2.33 (2H, t, *J* 7.0 Hz, H-8), 5.20 (2H, s, H-6), 7.67 (2H, d, *J* 8.5 Hz H-3' and H-5'), 7.95 (2H, d, *J* 8.5 Hz, H-2' and H-6'), 8.86 (1H, s, H-5); ^{13}C NMR(DMSO-d_6, 125.0 MHz APT) δ: 11.2 (C-16), 19.3 (C-15), 21.7 (C-9), 25.7 (C-10), 25.9 (C-11), 25.9 (C-13), 26.1 (C-12), 28.5 (C-14), 30.6 (C-8), 54.0 (C-6), 119.1 (C-5), 120.2 (C-3' and C-5'), 127.1 (C-2' and C-6'), 130.4 (C-1'), 132.6 (C-4'), 140.7 (C-4), 169.9 (C-8). Anal. Calcd for $C_{19}H_{26}ClN_3O_2$: C, 62.71; H, 7.20; N, 11.55. Found: C, 63.12; H, 7.34; N, 11.25.

4.1.2.11 (1-phenyl-1*H*-1,2,3-triazole-4-yl)methylacetate (**13k**).White solid, m.p. 54-55 ºC; IR ν_{max} (cm^{-1}): 3146, 3100, 2997, 2965, 1950, 1727, 1599, 1509, 1448, 1238, 1051, 756; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 2.19 (3H, s, CH_3), 5.34 (2H, s, H-6), 7.59-7.65 (1H, m, H-4'),

7.69-7.76 (2H, m, H-3' and H-5'); 7.99-8.04 (2H, m, H-2' and H-6'), 8.42 (1H, s, H-5); ^{13}C NMR(DMSO-d_6, 125.0 MHz APT) δ: 20.7 (C-9), 57.0 (C-6), 120.2 (C-4'), 122.9 (C-5), 128.8 (C-3' and C-5'), 129.9 (C-2' and C-6'), 136.6 (C-1'), 143.2 (C-4), 170.1 (C-8). Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.84; H, 5.21; N, 19.29.

4.1.2.12 (2-phenyl-2*H*-1,2,3-triazole-4-yl)methyl decanoate (**22a**). Yellow oil; IR ν_{max} (cm^{-1}): 2953, 2952, 2852, 1740, 1600, 1500, 1464, 1418, 1352, 1322, 1156, 1112, 1046, 967, 1022, 756; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 0.83 (3H, t, *J* 6.9 Hz), 1.21-1.27 (12H, m, H-10, H-11, H-12, H-13, H-14 and H-15), 1.50-1.57 (2H, m, H-9), 2.35 (2H, t, *J* 6.9 Hz, H-8), 5.72 (2H, s, H-6), 7.40-7.46 (1H, m, H-4'), 7.54-7.60 (2H, m, H-2' and H-6'), 7.97-8.00 (2H, m, H-3' and H-5'), 8.07 (1H, s, H-4); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 13.9 (C-16), 22.1 (C-15), 24.4 (C-9), 28.4 (C-10), 28.6 (C-11), 28.7 (C-13), 28.8 (C-12), 31.2 (C-14), 33.3 (C-8), 56.7 (C-6), 118.4 (C-4'), 127.9 (C-3' and C-5'), 129.7 (C-2' and C-6'), 135.9 (C-4), 139.1 (C-1'), 145.2 (C-4), 172.6 (C-7); Anal. Calcd for $C_{19}H_{27}N_3O_2$: C, 69.27; H, 8.26; N, 12.76. Found: C, 69.31; H, 8.36; N, 12.51.

4.1.2.13 (2-phenyl-2*H*-1,2,3-triazole-4-yl)methylhexanoate (**22b**). Yellow oil; IR ν_{max} (cm^{-1}): 2957, 2931, 2872, 2861, 1741, 1599, 1499, 1464, 1353, 1316, 1241, 1161, 1110, 1099, 1046, 967, 756, 690, 669; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 0.84 (3H, t, *J* 5.7 Hz, H-13), 1.23-1.28 (4H, m, H-11 and H-12), 1.51-1.61 (2H, m, H-10), 2.36 (2H, t, *J* 7.8 Hz, H-9), 5.30 (2H, s, H-6), 7.41-7.46 (1H, m, H-4'), 7.55-7.60 (2H, m, H-3' and H-5'), 8.00-8.03 (m, 2H, H-2' and H-6'), 8.10 (s, 1H, H-4); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ:13.6 (C-13), 21.7 (C-12), 24.1 (C-11), 30.6 (C-10), 33.3 (C-9), 56.7 (C-6), 118.3 (C-4'), 127.8 (C-3' and C-5'), 129.6 (C-2' and C-6'), 135.8 (C-4), 139.1 (C-1'), 145.2 (C-5), 172.6 (C-8); Anal. Calcd for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 64.93; H, 6.84; N, 14.86.

4.1.2.14 (2-phenyl-2*H*-1,2,3-triazole-4-yl)methylbenzoate (**22c**). Brown solid, mp 55-56 ºC; IR ν_{max} (cm^{-1}): 3465, 3127, 3067, 3025, 2950, 2472, 2159, 1977, 1745, 1597, 1500, 1238, 1062; ^{1}H NMR ($CDCl_3$, 500.00 MHz) δ: 5.63 (2H, s, H-6), 7.53-7.59 (1H, m, H-4'), 7.63-7.73 (4H,m, H-3', H-5', H-3" and H-5"), 7.77-7.83 (1H, m, H-4"), 8.11-8.16 (4H, m, H-2', H-6', H-2" and H-6"), 8.34 (1H, s, H-4); ^{13}C NMR ($CDCl_3$, 125.0 MHz APT) δ: 57.8 (C-6), 118.5 (C-4'), 128.0 (C-3' and C-5'), 128.9 (C-1"), 129.2 (C-3" and C-5"), 129.4 (C-4"), 129.8 (C-2' and C-6'), 133.6 (C-2" and C-6"), 136.2 (C-4), 139;1 (C-1'), 145.1 (C-5), 165.5 (C-8); Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.88; H, 4.92; N, 14.93.

4.1.2.15 (2-phenyl-2*H*-1,2,3-triazole-4-yl)methylacetate (**22d**). Brown oil; IR ν_{max} (cm^{-1}): 3464, 3126, 3067, 2025, 2950, 2473, 2159, 1958, 1745, 1597, 1499, 1458, 1412, 1323, 1305, 1237, 1174, 1062; ^{1}H NMR ($CDCl_3$, 500.00 MHz) δ: 2.12 (3H, s, CH_3), 5.27 (2H, s, H-6), 7.32-7.38 (1H, m, H-4), 7.44-7.51 (2H, m, H-3' and H-5'), 7,81 (1H, s, H-1), 8.03-8.07 (2H, m, H-2' and H-6'); ^{13}C NMR ($CDCl_3$, 125.0 MHz APT) δ: 20.8 (CH_3), 57.4 (C-6), 118.8 (C-4'), 127.7 (C-3' and C-5'), 129.2 (C-2' and C-6'), 135.4 (C-4), 139.6 (C-1'), 144.6 (C-5), 170.6 (C-8); Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34 Found: C, 60.84; H, 5.21; N, 19.29.

4.1.3 General procedure for preparation of 14a-g and 23a-b

Into a round bottom flask was added 5.71 mmols of triazole type **12** or **21a** in 50 mL of dry THF, 17.13 mmols of sodium hydride and 57.1 mmols of alkyl bromide. The mixture was heated to reflux, and reaction progress was monitored by TLC. Subsequently, the solvent was evaporated and the mixture was extracted with ethyl acetate, washed with distilled water (3 x 100 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the product was purified via silica-gel column chromatography using a gradient mixture of hexane-ethyl acetate, to afford the pure derivatives **14a-g** and **23a-b**.

4.1.3.1 4-(ethoxymethyl)-1-phenyl-1*H*-1,2,3-triazole (**14a**). Yellow oil; IR ν_{max} (cm^{-1}): 3140, 3065, 2963, 2929, 2859, 2359, 1653, 1599, 1503, 1465, 1388, 1231, 1099, 1044, 758, 690; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 1.28 (3H, t, *J* 7.0 Hz,CH_3), 3.67 (2H, q, *J* 7.0 Hz,H-8), 4.71 (2H, s, H-6), 7.61 (1H, t, *J*7.5 Hz, H-4'), 7.72 (2H, t, *J*7.5 Hz H-3' and H-5'), 7.61 (2H, d, *J*7.0 Hz, H-2' and H-6'), 8.90 (1H, s, H-3); ^{13}C NMR ($CDCl_3$, 125.0 MHz APT) δ: 15.0 (C-9), 63.0 (C-6), 65.0 (C-8), 120.0 (C-4'), 122.0 (C-5), 128.5 (C-3' and C-5'), 129.8 (C-2' and C-6'), 136.7 (C-1'), 145.4 (C-4); Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.68. Found: C, 65.21; H, 6.41; N, 20.04.

4.1.3.2 4-(butoxymethyl)-1-phenyl-1*H*-1,2,3-triazole (**14b**). Yellow oil; IR ν_{max} (cm^{-1}): 3105, 3073, 2957, 2926, 2859, 2365, 1599, 1504, 1466, 1340, 1296, 1231, 1191, 1098, 1042, 759, 699; ^{1}H NMR ($CDCl_3$, 500.00 MHz) δ: 0.98 (3H, t, *J* 7,5 Hz, CH_3), 1.38-1.50 (2H, m, H-10), 1.58-1.68 (2H, m, H-10), 3.60 (2H, t, *J* 6,3 Hz, H-8), 4.70 (2H, s, H-6), 7.57-7.63 (1H, m, H-4'), 7.68-7.74 (2H, m, H-3' and H-5'), 7.99-8.03 (2H, m, H-2' and H-6'), 8.87 (1H, s, H-3); ^{13}C NMR ($CDCl_3$, 125.0 MHz APT) δ: 13.8 (C-11), 18.9 (C-10), 31.3 (C-9), 63.3 (C-6), 69.5 (C-8), 120.0 (C-4'), 122.0 (C-5), 128.6 (C-3' and C-5'), 129.9 (C-2' and C-6'), 136.8 (C-1'); 145.5 (C-4); Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.41; N, 18.17. Found: C, 68.34; H, 7.73; N, 16.45.

4.1.3.3 1-(4-chlorophenyl)-4-(ethoxymethyl)-1*H*-1,2,3-triazole (**14c**). Brown solid, m.p. 90-91 ºC; IR ν_{max} (cm^{-1}): 3141, 3101, 2925, 2855, 2359, 1563, 1504, 1461, 1438, 1376, 1343, 1232, 1096, 1052, 1029, 1011, 824; ^{1}H NMR ($CDCl_3$, 500.00 MHz) δ: 1.27 (3H, t, *J* 7.0 Hz, CH_3), 3.67 (2H, q, *J* 7.0 Hz, H-8), 4.70 (2H, s, H-6), 7.78-7.80 (2H, m, H-3' and H-5'), 8.06-8.09 (2H, m, H-2' and H-6'), 8.93 (1H, s, H-3);^{13}C NMR ($CDCl_3$, 125.0 MHz APT) δ: 13.8 (C-9),62.9 (C-6),65.1 (C-8),121.7 (C-5),122,1 (C-3' and C-5'), 129.8 (C-2' and C-6'), 132.8(C-4'), 135.5 (C-1'), 145.5 (C-4); Anal. Calcd for $C_{11}H_{12}ClN_3O$: C, 55.59; H, 5.09; N, 17.68. Found: C, 56.01; H, 5.00; N, 20.45.

4.1.3.4 1-(4-chlorophenyl)-4-(butoxymethyl)-1*H*-1,2,3-triazole (**14d**). Brown solid, m.p. 63-64 ºC; IR ν_{max} (cm^{-1}): 2157, 2960, 2931, 2867, 1504, 1350, 1230, 1096, 1048, 992, 838, 814; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 0.87 (3H, t, *J* 6.9 Hz, H-11), 1.27-1.39 (2H, m, H-10), 1.47-1.56 (2H, m, H-9), 3.49 (2H, t, *J* 6.6 Hz, H-8), 4.58 (2H, s, H-6), 7.65-7.69 (2H, m, H-3' and H-5'), 7.93-7.98 (2H, m, H-2' and H-6'), 8.80 (1H, s, H-3); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 13.7 (C-11), 18.8 (C-10), 31.2 (C-9), 63.2 (C-6), 69.4 (C-8), 121.7 (C-5), 122.0 (C-3' and C-5'), 129.8 (C-2' and C-6'), 132.9 (C-4'), 135.5 (C-1'), 145.5 (C-4). Anal. Calcd for $C_{13}H_{16}ClN_3O$: C, 58.76; H, 6.07; N, 15.81. Found: C, 60.08; H, 6.41; N, 15.04.

4.1.3.5 1-(4-methoxyphenyl)-4-(ethoxymethyl)-1*H*-1,2,3-triazole (**14e**).Yellow oil; IR ν_{max} (cm^{-1}): 3139, 2973, 2865, 1611, 1518, 1461, 1379, 1303, 1253, 1191, 1096, 1042, 893, 832, 765, 695,

660 ;^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 1.27 (3H, t, *J* 7.0 Hz, H-8), 3.66 (q, 2H, *J* 7.0 Hz, H-7), 3.96 (s, 1H, CH_3), 4.68 (s, 2H, H-6), 7.25 (d, 2H, *J* 9.0 Hz), 7.92 (d, J 9.0 Hz, 1H), 8.78 (d, 1H, *J* 2.5 Hz, H-6'), 8.63 (s, 1H, H-5); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ:15.0 (C-9), 55.6 (CH_3), 63.0 (C-6), 65.0 (C-8), 114.9 (C-5), 116.1 (C-2' and C-6'),121.8 (C-3' and C-5'), 130.2 (C-1'), 145.1 (C-4'), 159.3 (C-4). Anal. Calcd for $C_{11}H_{11}ClN_3O$: C, 48.55; H, 4.07; N, 15.44. Found: C, 48.65; H, 4.01; N, 15.04.

4.1.3.6 1-(2,5-dichlorophenyl)-4-(butoxymethyl)-1*H*-1,2,3-triazole (**14f**). Yellow oil; IR ν_{max} (cm^{-1}): 3139, 2932, 2863, 1719, 1586, 1475, 1443, 1371, 1229, 1091, 1040, 1003, 852, 810, 666; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 0.99 (3H, t, *J* 6.9 Hz, H-11), 1.40-1.48 (2H, m, H-10), 1.60-1.66 (2H, m, H-9), 3.61 (2H, t, *J* 6.9 Hz, H-8), 4.71 (2H, s, H-6), 7.84 (1H, dd, *J* 3.0 and 9.0 Hz, H-4'), 7.92 (1H, d, *J* 9.0 Hz, H-3'), 8.01 (1H, d, *J* 3.0 Hz, H-6'), 8.66 (1H, s, H-5); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 13.6 (C-11), 18.8 (C-10), 31.2 (C-9), 63.0 (C-6), 69.4 (C-8), 125.8 (C-5), 127.4 (C-2'), 128.1 (C-6'), 131.3 (C-4'), 131.9(C-3'), 132.4 (C-5'), 135.5 (C-1'), 144.4 (C-4). Anal. Calcd for $C_{13}H_{15}Cl_2N_3O$: C, 52.01; H, 5.04; N, 14.00. Found: C, 51.52; H, 4.47; N, 13.63.

4.1.3.7 1-(2,5-dichlorophenyl)-4-(ethoxymethyl)-1*H*-1,2,3-triazole (**14g**). Yellow oil; IR ν_{max} (cm^{-1}): 3141, 2975, 2868, 1732, 1588, 1487, 1448, 1376, 1231, 1097, 1038, 874, 809, 698, 671, 651; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 1.27 (3H, t, *J* 3.9 Hz, H-9), 3.67 (2H, q, *J*3.9 Hz, H-8), 4.70 (s, 2H, H-6), 7.84 (1H, dd, *J* 1.5 and 5.4Hz), 7.92 (1H, d, *J* 5.4 Hz), 8.02 (1H, d, *J* 1.5 Hz, H-6'), 8.63 (1H, s, H-5); ^{13}C NMR ($CDCl_3$, 125.0 MHz APT) δ: 14.9 (C-9), 62.8 (C-6), 65.0 (C-8), 125.8 (C-5), 127.4 (C-2'), 128.0 (C-6'), 131.2 (C-4'), 131.8(C-3'), 132.4 (C-5'), 135.5 (C-1'), 144,4 (C-4). Anal. Calcd for $C_{11}H_{11}Cl_2N_3O$: C, 48.55; H, 4.07; N, 15.41. Found: C, 48.46; H, 4.24; N, 13.74.

4.1.3.8 4-(ethoxymethyl)-2-phenyl-2*H*-1,2,3-triazole (**23a**). Yellow oil; IR ν_{max} (cm^{-1}): 3142, 3066, 3052, 2976, 2930, 2870, 2455, 1949, 1878, 1741, 1599, 1499, 1463, 1415, 1370, 1352, 1312, 1261, 1230, 1170, 1102, 1040, 966, 911, 850, 756; ^{1}H NMR ($CDCl_3$, 500.00 MHz) δ: 1.19 (3H, t, *J* 7.0 Hz, CH_3), 3.55 (2H, q, *J* 7.0 Hz, H-8), 4.61 (2H, s, H-6), 7.24-7.29 (1H, m, H-4'), 7.36-7.43 (2H, m, H-3' and H-5'), 7.73 (1H, s, H-4), 7.96-8.00 (2H, m, H-2' and H-6'); ^{13}C NMR ($CDCl_3$, 125.0 MHz APT) δ: 15.0 (C-9), 63.7 (C-6), 66.1 (C-8), 118.7 (C-4'), 127.3 (C-3' and C-5'), 129.1 (C-2' and C-6'), 134.8 (C-4), 139.7 (C-1'), 146.8 (C-4). Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.68. Found: C, 63.81; H, 6.25; N, 20.12.

4.1.3.9 4-(butoxymethyl)-2-phenyl-2*H*-1,2,3-triazole (**23b**); Yellow oil; IR ν_{max} (cm-^{1}): 3125, 3078, 3066, 3053, 2959, 2933, 2871, 2454, 1949, 1876, 1742, 1599, 1500, 1464, 1415, 1355, 1313, 1261, 1231, 1168, 1155, 1102, 1038, 966, 849, 756, 703, 691, 666; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 0.93 (3H, t, *J* 7.3 Hz,CH_3), 1.34-1.36 (2H, m, H-10), 1.57-1.67 (2H, m, H-9), 3.55 (2H, t, *J* 6.6 Hz, H-8), 4.68 (2H, s, H-6), 7.30-7.36 (1H, m, H-4'), 7.43-7.50 (2H, m, H-3' and H-5'), 7.79 (1H, s, H-4), 8.03-8.07 (2H, m, H-2' and H-6'); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 13.8 (C-11), 19.2 (C-10), 31.6 (C-9), 63.9 (C-6), 70.6 (C-8), 118.7 (C-4'), 127.3 (C-3' and C-5'), 129.1 (C-2' and C-6'), 134.7 (C-4), 139.7 (C-1'), 147.0 (C-5). Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.41; N, 18.17 Found: C, 66.98; H, 7.61; N, 17.65.

4.1.4 General procedure for preparation of 15a-b

Into a round-bottom flask equipped with a magnetic stirring bar already containing a solution of 10 mmols of 1,2,3-triazoles type **12** in 27.5 mL of DMSO was added 11 mmols of IBX. This mixture was stirred at room temperature for 4 h. Next, distilled water (20 mL) was added, and stirring was continued for 15 minutes at room temperature. Subsequently, the mixture was filtered, extracted with ethyl acetate and dried over with $MgSO_4$. The product was purified via silica-gel column chromatography using gradient mixture of hexane-ethyl acetate to afford the pure derivatives **11** and **15a-b**.

4.1.4.1 1-Phenyl-1*H*-1,2,3-triazole-4-carbaldehyde (**11**). White solid, m.p. 96-98^{o}C (m.p. lit. 95-96 ºC [7]); IR ν_{max} (cm^{-1}): 3431, 3131, 1691, 1529, 1209, 1168, 990, 853, 782, 761, 683; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 7.65-7.70 (1H, m, H-4'), 7.73-7.79 (2H, m, H-3' and H-5'), 8.02-8.12 (2H, m, H-2' and H-6'), 9.66 (1H, s, H-5), 10.24 (1H, s, H-6); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 120.7 (C-2' and C-6'), 126.1 (C-5), 129.5 (C-3' and C-5'), 129.9 (C-4'), 136.0 (C-1'), 147.6 (C-4), 184.8 (C-6).

4.1.4.2 1-(4-Chlorophenyl)-1*H*-1,2,3-triazole-4-carbaldehyde (**15a**). Yellow solid, m.p. 159-160^{o}C (m.p. lit. 159-160 ºC [7]); IR ν_{max} (cm-^{1}): 3096, 3041, 2844, 2360, 1905, 1705, 1531, 1499, 1355, 1254, 1216, 1099, 1053, 989, 877, 828, 773; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 7.71 (2H, d, *J* 5.4 Hz, H-3' and H-5'), 8.02 (2H, d, *J* 5.4 Hz, H-2" and H-6"), 9.56 (1H, s, H-5), 10.12 (1H, s, H-6); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 122.5 (C-2' and C-6'), 126.3 (C-5), 129.9 (C-3' and C-5'), 133.9 (C-4), 134.8 (C-4'), 147.6 (C-4), 184.9 (C-6).

4.1.4.3 1-(2,5-Dichlorophenyl)-1*H*-1,2,3-triazole-4-carbaldehyde (**15b**). White solid, m.p. 160-161^{o}C (m.p. lit. 163-164 ºC [7]); IR ν_{max} (cm^{-1}): 3138, 3092, 2860, 1704, 1573, 1529, 1487, 1456, 1402, 1371, 1261, 1199, 1170, 1142, 1100,1075, 1042, 982, 857, 816, 765, 698, 649; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 8.03-8.05 (1H, m, H-4'), 8.10-8.11 (1H, m, H-3'), 8.28 (1H, s, H-6'), 9.62 (1H, s, H-5), 10.38 (1H, s, H-6); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 127.8 (C-2'), 128.4 (C-6'), 130.6 (C-5), 132.0 (C-4'), 132.1 (C-3'), 132.6 (C-5'), 134.7 (C-1'), 146.7 (C-4), 184.7 (C-6).

4.1.5 General Procedure for preparation of 16a and 19a

In a round-bottom flask equipped with a magnetic stirring bar already containing a suspension of anhydrous THF (50 mL) and NaH (2.0 equiv.) was added methyltriphenylphosphonium bromide (2.90 mmols) under argon atmosphere. The mixture was stirred during 15 minutes in ultrasound bath and acquired an intense yellow color. The agitation was maintained for 2 hours at room temperature before the triazole-substituted aldehyde (1.45 mmols) was added. After 1-2 hours, the reaction mixture was poured into distilled water at 0 °C. This mixture was extracted with ethyl acetate (3 x 50 mL). The organic phases were combined and washed with distilled water (2 x 50 mL) and dried over with anhydrous sodium sulfate. The product was purified via flash column chromatography using gradient mixture of hexane-ethyl acetate.

4.1.5.1 1-phenyl-4-vinyl-1*H*-1,2,3-triazole (**16a**). White solid, m.p. 83-85^{o}C (m.p. lit 85-87 ºC [7]); IR ν_{max} (cm^{-1}):3134, 1597, 1500, 1465, 1236, 1043, 996, 926, 827, 757, 687; ^{1}H NMR ($CDCl_3$, 300.00 MHz) δ: 5.42 (1H, dd, *J* 1.2and 11.0 Hz, H-6), 6.02 (1H, dd, *J* 1.2 and 17.8Hz, H-7a), 6.80 (1H, dd, *J* 11.0 and 17.6 Hz, H-7), 7.41-7.75 (5H, m,H-2', H-3', H-4', H-5' and H-

6'), 7.95 (1H, s, H-5); ^{13}C NMR ($CDCl_3$, 75.0 MHz APT) δ: 116.4 (C-7), 120.1 (C-5), 125.7 (C-2'and C-6'), 128.7 (C-3'and C-5' or C-4'), 129.9 (C-3'and C-5' or C-4'), 136.6 (C-6), 146.3 (C-4).

4.1.5.2 2-phenyl-4-vinyl-2*H*-1,2,3-triazole (**19a**). Yellow oil; IR ν_{max} (cm^{-1}): 2923, 2857, 2359, 1599, 1502, 1461, 1375, 1313, 955, 915, 753; ^{1}H NMR ($CDCl_3$, 300.00 MHz)δ:5.49 (1H, dd, *J*1.2 and 11.3 Hz, H-6), 5.96 (1H, dd, *J* 1.2 and 17.7Hz, H-7a), 6.82 (1H, dd, *J* 11.3 and 17.7 Hz, H-7b), 7.31-7.37 (1H,m, H-4'), 7.45-7.51 (2H, m, H-3' and H-5'), 7.85 (1H, s, H-4), 8.05-8.08 (1H, m, H-2' and H-3'); ^{13}C NMR ($CDCl_3$, 75.0 MHz APT) δ: 117.9 (C-1' and C-7), 118.6 (C-6), 125.4 (C-3' and C-5'), 127.2 (C-2' and C-6'), 129.1 (C-4'), 132.7 (C-4), 147.6 (C-5); Anal. Calcd for $C_{10}H_9N_3$: C, 70.16; H, 5.30; N, 24.54. Found: C, 70.26; H, 5.25; N, 24.12.

4.1.6 General Procedure for preparation of 17a-l and 20a-i

Into a round-bottom flask equipped with a magnetic stirring bar already containing a solution of 2.89 mmols of aldehyde triazole **11**, **15a-b** or **18a-e** in 50 mL of ethanol were added phenylhydrazine hydrochloride (2.89 mmols) or hydroxylamine hydrochloride (20 mmols) and a few drops of sulfuric acid. After 24 hours of stirring at room temperature, water was added, and the product was collected via vacuum filtration.

4.1.6.2 (*E*)-1-phenyl-4-((2-phenylhydrazono)methyl)-1*H*-1,2,3-triazole (**17a**). Brown solid, m.p. 124-125 ºC; IR ν_{max} (cm^{-1}): 3276, 3144, 3042, 1599, 1531, 1496, 1370, 1270, 1173, 1107, 1067, 1046, 907, 888, 867, 737, 693; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 7.16-7.19 (3H, m, H-3', H-5' and H-6), 7.24-7.29 (2H, m, H-2" and H-6"), 7.32-7.38 (1H, m, H-4'), 7.46-7.52 (2H, m, H-3' and H-5'), 7.80 (1H, s, H-4), 8.01-8.05 (2H, m, H-2' and H-6'), 11.06 (1H, s, H-8); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 112.7 (C-5), 120.1, 120.7, 121.8, 122.9, 129.2, 129.4 (C-2', C-3', C-4', C-5', C-6', C-2", C-3", C-4", C-5" and C-6"), 130.0 (C-7), 136.2 (C-1'), 143.0 (C-1"), 144.7 (C-4); Anal. Calcd for $C_{13}H_{13}N_5$: C, 68.42; H, 4.98; N, 25.55. Found: C, 68.04; H, 5.21; N, 26.27.

4.1.6.2 (*E*)-4-((2-(2,5-dichlorophenyl)hydrazono)methyl)-1-phenyl-1*H*-1,2,3-triazole (**17b**). Brown solid, m.p. 164-165 ºC; IR ν_{max} (cm^{-1}): 3412, 3238, 2361, 1596, 1533, 1494, 1453, 1403, 1367, 1262, 1197, 1137, 1097, 1082, 1042, 847, 823, 753, 684, 626; ^{1}H NMR (DMSO-d_6, 300.00 MHz) δ: 7.03-7.06 (1H, m, H-4"), 7.59 (2H, d, *J* 5.4 Hz, H-4" and H-6"), 7.67-7.71 (2H, m, H-3" and H-4"), 7.74-7.80 (2H, m, H-3' and H-5'), 8.09-8.13 (2H, m, H-2' and H-6'), 8,40 (1H, s, H-5), 9.30 (1H, s, H-6), 12.12 (1H, s, H-7); ^{13}C NMR (DMSO-d_6, 75.0 MHz APT) δ: 117.0 (C-5), 118.6 (C-6"), 122.8 (C-4"), 128.2 (C-3"), 129.7 (C-2' and C-6'), 129.8 (C-2"), 130.0 (C-3' and C-5'), 134.7 (C-4'), 137.7 (C-5"), 138.8 (C-1'), 139.5 (C-6), 144.3 (C-1"), 145.4 (C-4); Anal. Calcd for $C_{17}H_{15}Cl_2N_5$: C, 54.23; H, 3.34; N, 21.08. Found: C, 54.21; H, 2.92; N, 20.76

4.1.6.3 (*E*)-4-((2-(4-fluorophenyl)hydrazono)methyl)-1-phenyl-1*H*-1,2,3-triazole (**17c**). Yellow solid, m.p. 206-207 ºC; IR ν_{max} (cm^{-1}): 3275, 3149, 1605, 1592, 1502, 1369, 1209, 1210, 1110, 1047,829, 759, 691; ^{1}H NMR (DMSO-d_6, 300.00 MHz) δ: 7.18-7.27 (2H, m, H-3" and H-5"),

7.32-7.37 (2H, m, H-2" and H-6"), 7.32-7.38 (1H, m, H-4'), 7.45 (1H, s, H-5), 7.46-7.52 (2H, m, H-3' and H-5'), 8.01-8.05 (2H, m, H-2' and H-6'), 9.26 (1H, s, H-6), 11.06 (1H, s, H-8); ^{13}C NMR (DMSO-d_6, 75.0 MHz APT) δ: 113.9 (d, *J* 7,74 Hz, C-3" and C-5"), 115.6, 115.9, 120.1, 122.1, 122.9, 128.8, 129.4 (C-2', C-3', C-4', C-5', C-6', C-2", C-6"), 120.8 (C-5), 130.1 (C-6), 136.2 (C-1'), 141.4 (C-1"), 141.7 (C-4), 144.4 (d, *J* 213.4 Hz, C-4"); Anal. Calcd for $C_{15}H_{12}FN_5$: C, 64.05; H, 4.30; N, 24.90. Found: C, 64.11; H, 4.25; N, 24.85.

4.1.6.4 (*E*)-4-((2-(4-Chlorophenyl)hydrazono)methyl)-1-phenyl-1*H*-1,2,3-triazole (**17d**). Yellow solid, m.p. 143-145 ºC; IR ν_{max} (cm^{-1}): 3266, 1598, 1527, 1490, 1367, 1263, 1172, 1075, 1045, 906, 865, 822, 758, 688; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 7.20 (1H, d, *J* 5.4 Hz, H-2" or H-6"), 7.34-7.39 (2H, m, H-3" and H-5"), 7.43 (1H, d,*J* 5.4 Hz, H-2" or H-6"), 7.49 (1H, s, H-5), 7.61-7.80 (3H, m, H-3', H-4' and H-5'), 8.07-8.14 (2H, m, H-2', H-3' and H-6'), 8.40 (H-6), 10.70 (H-8); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 113.5, 114.3, 120.1, 120.7, 122.8, 128.8, 129.0, 129.9 (C-2', C-3', C-4', C-5', C-6', C-2", C-3", C-5" and C-6"), 123.5 (C-5), 130.1 (C-6), 136.2 (C-1'), 142.8 (C-1"), 145.6 (C-4); Anal. Calcd for $C_{15}H_{12}ClN5$: C, 60.51; H, 4.06; N, 23.52. Found: C, 60.48; H, 4.02; N, 22.91.

4.1.6.5 (*E*)-4-((2-(4-bromophenyl)hydrazono)methyl)-1-phenyl-1*H*-1,2,3-triazole (**17e**). Yellow solid, m.p. 228-229 ºC; IR ν_{max} (cm^{-1}): 3267, 3145, 1593, 1529, 1489, 1368, 1264, 1068, 1047, 822, 760; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 7.28-7.33 (2H, m, H-3" and H-5"), 7.50 (1H, s, H-5), 7.52-7.58 (2H, m, H-2" and H-6"), 7.68-7.88 (3H, m, H-3', H-4' and H-5'), 8.07-8.10 (2H, m, H-2' and H-6'), 9.30 (1H, s, H-6), 11.28 (1H, s, H-8); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 111.0 (C-4"), 114.8 (C-5), 123.1 (C-2" and C-6"), 129.4 (C-3', C-4' and C-5'), 130.0 (C-2' and C-6'), 131.9 (C-6), 136.2 (C-1'), 142.7 (C-1"), 144.1 (C-4); Anal. Calcd for $C_{15}H_{12}BrN_5$: C, 52.65; H, 3.53; N, 20.47. Found: C, 52.31; H, 3.68; N, 20.13.

4.1.6.6 (*E*)-4-((2-(2,5-dimethylphenyl)hydrazono)methyl)-1-phenyl-1*H*-1,2,3-triazole (**17f**). Yellow solid, m.p. 109-111 ºC; IR ν_{max} (cm^{-1}): 3268, 1597, 1489, 1293, 1264, 1068, 1047, 821, 757, 689; ^{1}H NMR ($CDCl_3$, 500.00 MHz)δ: 2.20 (2 x CH_3), 6.72 (1H, d, *J* 8.5 Hz, H-4"), 7.14 (1H, d, H-3"), 7.44 (s, 1H, H-6"), 7.47 (1H, s, H-5), 7.63-7.69 (m, 3H, H-3', H-4' and H-5'), 8.08-8.13 (m, 2H, H-2' and H-6'), 9.25 (s, 1H, H-5), 11.56 (1H, s, H-7); ^{13}C NMR ($CDCl_3$, 125.0 MHz APT) δ: 16.6 (CH_3), 21.1 (CH_3), 112.0 (C-6"), 117.4 (C-2"), 120.3 (C-5), 120.6 (C-4"), 121.5 (C-2' and C-6'), 122.7 (C-2"), 129.3 (C-3' and C-5' and C-4'), 130.2 (C-6), 135.9 (C-5"), 136.2 (C-1'), 142.3 (C-1"), 143.5 (C-4); Anal. Calcd for $C_{17}H_{17}N_5$: C, 70.08; H, 5.88; N, 24.04. Found: C, 69.66; H, 5.89; N, 23.34

4.1.6.7 (*E*)-4-((2-(2,4-dinitrophenyl)hydrazono)methyl)-1-phenyl-1*H*-1,2,3-triazole (**17g**). Orange solid, m.p. 190-192 ºC; IR ν_{max} (cm^{-1}): 3282, 3147, 3112, 2973, 1619, 1586, 1513, 1500, 1418, 1334, 1311, 1220, 1136, 1087, 1045, 830, 768; ^{1}H NMR ($CDCl_3$, 500.00 MHz) δ: 7.67 (1H, t, *J* 7.8 Hz, H-4'), 7.77 (2H, t, *J* 7.8 Hz, H-3' and H-5'), 8.12 (2H, d, *J*7.8 Hz, H-2" and H-6"), 8.23 (1H, d, *J* 9.8 Hz, H-2"), 8.50 (1H, dd, *J* 2.7 and 9.8 Hz, H-3"), 8.71 (1H, s, H-4), 8.98 (1H, d, *J* 2.7 Hz, H-5"), 9.03 (1H, s, H-8);^{13}C NMR ($CDCl_3$, 125.0 MHz APT) δ: 116.8 (C-2"), 120.3 (C-5), 121.9 (C-2' and C-6'), 123.0 (C-3"), 129.1 (C-3' and C-5'), 129.5(C-4'), 129.8 (C-2"), 130.0 (C-5"), 136.3 (C-1'), 137.6 (C-4"), 140.8 (C-6), 144.1 (C-1"), 144.6 (C-4); Anal. Calcd for $C_{15}H_{11}N_7O_4$: C, 50.99; H, 3.14; N, 27.75. Found: C, 50.79; H, 3.11; N, 27.36

4.1.6.8 (*E*)-*N*'-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methylene)isonicotinohydrazide [7] (**17h**). White solid, m.p. 212-213 ºC (m.p. lit. 212-213 ºC); IR ν_{max} (cm^{-1}): 3436, 2980, 2861, 1672, 1585, 1552, 1499, 1300, 1056, 763, 753, 681; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 7.64 (t, 1H, *J* 7.5 Hz, H-4'), 7.74 (t, 2H, *J* 7.5 Hz, H-3' and H-5'), 7.96 (d, 2H, *J* 6.0 Hz, H-2" and H-5"), 8.13 (d, 2H, *J* 7.5 Hz, H-2' and H-6'), 8.77 (s, 1H, H-5), 8.92 (d, 2H, *J* 6.0 Hz, H-3" and H-4"), 9.43 (s, 1H, H-6), 12.2 (s, 1H, H-7); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 120.4 (C-4), 121.7 (C-2' and C-6'), 129.2 (C-2" and C-6"), 130.0 (C-3', C-4' and C-5'), 136.4 (C-1'), 140.4 (C-1"), 141.0 (C-3" and C-4"), 144.1 (C-4), 150.5 (C-6), 161,8 (C-8).

4.1.6.9 (*E*)-1-(4-chlorophenyl)-4-((2-phenylhydrazono)methyl)-1*H*-1,2,3-triazole (**17i**). White solid, m.p. 211-213 ºC; IR ν_{max} (cm^{-1}): 3272, 1596, 1526, 1487, 1368, 1265, 1170, 1092, 1042, 1014, 986, 864, 834, 803, 754, 683; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 6.98 (1H, t, *J* 4.5 Hz, H-4"), 7.32 (2H, d, *J* 4.5 Hz, H-3" and H-5"), 7.40 (2H, t, *J* 4.5 Hz, H-2" and H-6"), 7.45 (1H, s, H-5), 7.85-7.87 (2H, m, H-2" and H-6"), 8.12-8.15 (2H, m, H-3" and H-5"), 9.29 (1H, s, H-6), 11.30 (1H, s, H-7); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 118.4 (C-5), 125.8, 127.4, 128.1, 128.2, 128.6, 134,9 (C-2', C-3', C-5', C-6', C-2", C-3", C-4", C-5" and C-6"), 135.7 (C-6), 139.4 (C-4'), 140.7 (C-1'), 148.7 (C-1"), 150,3 (C-4); Anal. Calcd for $C_{15}H_{12}ClN_5$: C, 60.51; H, 4.07; N, 23.52. Found: C, 60.58; H, 4.02; N, 22.35.

4.1.6.10 (*E*)-4-((2-(4-bromophenyl)hydrazono)methyl)-1-(4-chlorophenyl)-1*H*-1,2,3-triazole (**17j**). White solid, m.p. 205-206 ºC; IR ν_{max} (cm^{-1}): 3429, 3267, 3144, 1593, 1527, 1486, 1291, 1261, 1171, 1100, 1069, 1045, 987, 905, 863, 818, 703; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 7.30 (d, 2H, *J* 8,8 Hz, H-2" e H-6"), 7.49 (s, 1H, H-5), 7.54 (d, 2H, *J* 8.8 Hz, H-3"and H-5"), 7.84-7.86 (m, 2H, H-2' and H-6'), 8.12-8.14 (m, 2H, H-3'and H-5'), 9.31 (s, 1H, H-6), 11.32 (s, 1H, H-7); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 113.5 (C-5), 114.2, 121.7, 122.3, 122.6, 123.0, 128.9 (C-2', C-3', C-5', C-6', C-2", C-3", C-5", C-6"), 123.4 (C-4"), 129.9 (C-6), 133.7 (C-4'), 134.9 (C-1'), 142,7 (C-1"), 143.6 (C-4). Anal. Calcd for $C_{13}H_{11}BrClN_5$: C, 47.83; H, 2.94; N, 18.59. Found: C, 48.31; H, 3.11; N, 18.36.

4.1.6.11 (*E*)-1-phenyl-1*H*-1,2,3-triazole-4-carbaldehyde oxime (**17k**). White solid, m.p. 97-99 ºC; IR ν_{max} (cm^{-1}): 3411, 3214, 3187, 3156, 3091, 3021, 2989, 2929, 2882, 2801, 2361, 2348, 1661, 1599, 1501, 1466, 1250, 1236, 1121, 1161, 1051, 987; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 7.48-7.54 (1H, m, H-4'), 7.58-7.63 (2H, m, H-3' and H-5'), 7.92-7.96 (2H, m, H-2' and H-6'), 8.24 (1H, s, H-5), 9.04 (1H, s, H-6); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 120.5 (C-4'),120.8 (C-5), 129.1 (C-3' and C-5'), 130.1 (C-2' and C-6'), 136.6 (C-1'), 140.2 (C-6), 142.4 (C-4); Anal. Calcd for $C_9H_8N_4O$: C, 57.4; H, 4.3; N, 29.8. Found: C, 57.8; H, 4.7; N, 30.3

4.1.6.12 (*E*)-1-(4-chlorophenyl)-1*H*-1,2,3-triazole-4-carbaldehyde oxime (**17l**). White solid, m.p. 65-66 ºC; IR ν_{max} (cm^{-1}): 3101, 3028, 2930, 2821, 1503, 1345, 1269, 1235, 1098, 1039, 982, 924, 821, 699; ^{1}H NMR ($CDCl_3$, 500.00 MHz) δ: 7.77-7.83 (2H, m, H-3' and H-5'), 7.91 (1H, s, H-5), 8.09-8.17 (2H, m, H-2' and H-6'), 9.36 (1H, s, H-6), 12.20 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 125.0 MHz APT) δ: 122.3 (C-5), 129.8 (C-3' and C-5'), 133.3 (C-4'), 135.2 (C-1'), 137.3 (C-2' and C-6'), 138.5 (C-4), 142.5 (C-6); Anal. Calcd for $C_9H_7ClN_4O$: C, 48.55; H, 3.17; N, 25.17. Found: C, 47.83; H, 3.41; N, 24.45

4.1.6.13 (*E*)-2-phenyl-4-((2-phenylhydrazono)methyl)-2*H*-1,2,3-triazole (**20a**). Brown solid, m.p. 111-112 ºC; IR ν_{max} (cm^{-1}): 3271, 3114, 3028, 2963, 2924, 2854, 1599, 1575, 1497, 1399, 1340, 1309, 1262, 1122, 1066, 1036, 966, 909, 865, 792, 753, 687, 654; ^{1}H NMR ($CDCl_3$, 500.00 MHz) δ: 7.16-7.19 (3H, m, H-3', H-5' and H-6), 7.24-7.29 (2H, m, H-2" and H-6"), 7.32-7.38 (1H, m, H-4'), 7.46-7.52 (2H, m, H-3' and H-5'), 7.80 (1H, s, H-4), 8.01-8.05 (2H, m, H-2' and H-6'), 11.06 (1H, s, H-8); ^{13}C NMR ($CDCl_3$, 75.0 MHz APT) δ: 112.9 (C-4), 118.4, 119.4, 120.6, 127.6, 128.9, 129.1 (C-2', C-3', C-4', C-5', C-6', C-2", C-3", C-4", C-5" and C-6"), 134.8 (C-7), 138.8 (C-1'), 143.0 (C-5), 143.8 (C-1"); Anal. Calcd for $C_{13}H_{13}N_5$: C, 68.42; H, 4.98; N, 25.55. Found: C, 68.22; H, 4.88; N, 26.60.

4.1.6.14 (*E*)-4-((2-(2,5-dichlorophenyl)hydrazono)methyl)-2-phenyl-2*H*-1,2,3-triazole (**20b**). Brown solid, m.p. 164-165 ºC; IR ν_{max} (cm^{-1}): 3260, 2939, 1591, 1498, 1461, 1342, 1263, 1136, 1096, 1043, 973, 873, 836, 814, 754, 662; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 7.10 (dd, 1H, *J* 2.7 and 8.5 Hz, H-4"), 7.61-7.66 (m, H-6"), 7.73-7.81 (m, 3H, H-2", H-3" and H-4'), 7,80 (s, 1H, H-5), 8.24-8.27 (m, 2H, *J* H-3' and H-5'), 8.24-8.27 (m, 2H, H-2' and H-6'), 8.60 (s, 1H, H-6), 11.53 (s, 1H, H-7); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 113.0 (C-4), 115.2 (C-2"), 130.8, 129.9, 129.7, 128.5, 125.0, 120.6, 119.1 and 118.5 (C-2", C-4", C-6", C-2', C-3', C-4', C-5' and C-6'), 133.1 (C-5"), 137.3 (C-6), 138.5 (C-1'), 141.4 (C-1"), 142.4 (C-4); Anal. Calcd for $C_{15}H_{11}Cl_2N_5$: C, 54.23; H, 3.34; N, 21.08. Found: C, 54.14; H, 3.51; N, 21.12.

4.1.6.15 (*E*)-4-((2-(4-fluorophenyl)hydrazono)methyl)-2-phenyl-2*H*-1,2,3-triazole (**20c**). Brown solid, m.p. 113-115 ºC; IR ν_{max} (cm^{-1}): 3260, 1683, 1592, 1499, 1352, 1264, 1212, 1152, 969, 821, 755, 687, 656; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 7.20 (2H, d, *J* 2.0 Hz, H-2" and H-6"); 7.23 (1H, s, H-4), 7.51-7.57 (1H, m, H-3" or H-5"), 7.49-7.60 (3H, m, H-3" or H-5", H-2' and H-6'), 8.12-8.15 (3H, m, H-3', H-4' and H-5'), 8.49 (1H, s, H-6), 10.75 (H-8); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 113.3 (d, *J* 7.4 Hz, C-3" or C-5"), 115.5 (C-2" and C-6"), 115.6 (C-2' and C-6'), 118.2 (C-5), 126.7 (C-3' and C-5'), 127.6 (C-4'), 129.7 (C-6), 139.1 (C-1"), 141.3 (C-1'), 147.0 (C-5), 156.3 (d, *J* 234.4 Hz, C-4"); Anal. Calcd for $C_{15}H_{12}FN_5$: C, 64.05; H, 4.30; N, 24.90. Found: C, 63.72; H, 4.31; N, 23.24

4.1.6.16 (*E*)-4-((2-(4-chlorophenyl)hydrazono)methyl)-2-phenyl-2*H*-1,2,3-triazole (**20d**). Yellow solid, m.p. 143-145 ºC; IR ν_{max} (cm^{-1}): 3266, 1598, 1527, 1490, 1367, 1263, 1172, 1075, 1045, 906, 865, 822, 758, 688; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 7.21-7.25 (2H, m, H-2" and H-6"), 7.38-7.42 (2H, m, H-3" and H-5"), 7.46 (1H, s, H-4), 7.52-7.57 (1H, m, H-4), 7.67-7.73 (2H, m, H-3'and H-5'), 8.12-8.16 (2H, m, H-2' and H-6'), 8.50 (H-6), 10.88 (H-8); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ:113.7 (C-4), 114.9, 118.2, 118.9, 127.6, 129.0 (C-2', C-3', C-4', C-5', C-6', C-2", C-3", C-4", C-5" and C-6"), 129.7 (C-7), 122.8 (C-1'), 139.0 (C-1"), 144,7 (C-4); Anal. Calcd for $C_{15}H_{12}ClN5$: C, 60.51; H, 4.06; N, 23.52. Found: C, 60.58; H, 4.02; N, 23.35.

4.1.6.17 (*E*)-4-((2-(4-bromophenyl)hydrazono)methyl)-2-phenyl-2*H*-1,2,3-triazole (**20e**). Yellow solid, m.p. 117-118 ºC; IR ν_{max} (cm^{-1}): 3313, 2360, 2339, 1595, 1495, 1401, 1273, 1255, 1152, 1098, 1070, 962, 890, 825, 761, 658; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 7.16-7.20 (2H, m, H-2" and H-6"), 7.49-7.60 (3H, m, H-3", H-5" and H-4'), 7.66-7.73 (2H, m, H-3' and H-5'), 8.12-8.14 (2H, m, H-2' and H-6'), 8.16 (1H, s, H-4), 8.50 (H-6), 10.90 (H-8); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 110.4 (C-4"), 114.2 (C-2" and C-6"), 115.3 (C-2' and C-6'), 118.2 (C-4), 127.6 (C-3', C-4' and C-5'), 129.7 (C-3" and C-5"), 131.8 (C-6), 139.0 (C-1'), 144.0 (C-1"),

146.8 (C-5); Anal. Calcd for $C_{15}H_{12}BrN_5$: C, 60.51; H, 3.53; N, 20.47. Found: C, 52.52; H, 3.61; N, 19.63

4.1.6.18 (*E*)-4-((2-(2,4-dimethylphenyl)hydrazono)methyl)-2-phenyl-2*H*-1,2,3-triazole (**20f**). Yellow solid, m.p. 174-175 ºC; IR ν_{max} (cm^{-1}): 3299, 3129, 3039, 2965, 2915, 2853, 2359, 1865, 1598, 1582, 1534, 1501, 1486, 1403, 1373, 1287, 1272, 1143, 1039, 952, 866, 802, 757; ^{1}H NMR ($CDCl_3$, 500.00 MHz) δ: 2.41 (3H, s, CH_3), 2.49 (3H, s, CH_3), 6.78 (1H, dd, *J* 1.2 and 7.6 Hz, H-3"), 7.18 (1H, d, *J* 7.6, H-5"), 7.50 (1H, d, *J* 1.2 Hz, H-5"), 7.60 (1H,s, H-6), 7.73-7.80 (2H, m, H-3' and H-5'), 8.19-8.23 (2H, m, H-2" and H-6"), 8.60 (1H,s, H-4), 10.98 (1H, s, H-8); ^{13}C NMR ($CDCl_3$, 125.0 MHz APT) δ: 112.2 (C-4), 117.6 (C-6"), 118.6, 121.1, 121.2, 128.3, 129.9, 130.3, 136.2 (C-2', C-3', C-4', C-5', C-6', C-2", C-3" and C-5"), 136.8 (C-4"), 138.8 (C-1"), 141.8 (C-1'), 143.1 (C-5); Anal. Calcd for $C_{17}H_{17}N_5$: C, 70.08; H, 5.88; N, 24.04. Found: C, 69.53; H, 5.86; N, 23.46.

4.1.6.19 (*E*)-4-((2-(2,4-dinitrophenyl)hydrazono)methyl)-2-phenyl-2*H*-1,2,3-triazole [43] (**20g**). Orange solid, m.p. 189-190 ºC (m.p. lit. 198-200ºC); IR ν_{max} (cm^{-1}): 3286, 3131, 1620, 1587, 1517, 1497, 1425, 1366, 1335, 1312, 1294, 1270, 1220, 1145, 1075, 961, 757; ^{1}H NMR ($CDCl_3$, 500.00 MHz) δ: 7.56-7.61 (1H, m, H-4'), 7.69-7.78 (2H, m, H-3' and H-5'), 8.11-8.18 (2H, m, H-2" and H-6"), 8.25 (1H, d, *J* 9.8 Hz, H-2"), 8.50 (1H, dd, *J* 2.7 and 9.8 Hz, H-3"), 8.71 (1H, s, H-4), 8.98 (1H, d, *J* 2.7 Hz, H-5"), 9.03 (1H, s, H-8); ^{13}C NMR ($CDCl_3$, 125.0 MHz APT) δ: 117.0 (C-2"), 118.5 (C-5), 118.8 (C-2' and C-6'), 122.8 (C-3"), 128.2 (C-3' and C-5'), 128.7(C-4'), 130.0 (C-2"), 134.7 (C-5"), 137.6 (C-1'), 138.8 (C-4"), 139.5 (C-6), 144.2 (C-1"), 145.4 (C-4); Anal. Calcd for $C_{15}H_{11}N_7O_4$: C, 50.99; H, 3.14; N, 27.75. Found: C, 50.73; H, 3.11; N, 26.88.

4.1.6.20 (*E*)-*N*'-((2-phenyl-2*H*-1,2,3-triazol-4-yl)methylene)isonicotinohydrazide (**20h**). Brown solid, m.p. 210-211 ºC; IR ν_{max} (cm^{-1}): 3405, 3178, 3038, 3004, 2847, 1673, 1653, 1598, 1567, 1503, 1408, 1385, 1357, 1328, 1303, 1226, 1155, 1071, 968, 842, 797, 753, 688, 680, 665; ^{1}H NMR (DMSO-d_6, 300.00 MHz) δ: 7.60 (t, 1H, J=7.5 Hz, H-4'), 7.72 (t, 2H, *J* 7.5 Hz, H-3" and H-5"), 7.97 (s, 3H, H-2" and H-5"), 8.18 (d, 2H, *J* 7.5 Hz, H-2' and H-6'), 8.61 (s, 1H, H-4), 8.79 (s, 1H, H-6), 11.53 (s, 1H, H-7), 8.93-9.13 (m, 2H, H-3" and H-4"); ^{13}C NMR (DMSO-d_6, 75.0 MHz APT) δ: 118.7 (C-4), 128.4 (C-2' and C-6'), 130.0 (C-2" and C-6"), 134.7 (C-3', C-4' and C-5'), 139.0 (C-1'), 139.9 (C-3" and C-4"), 140.3 (C-1"), 145.4 (C-4), 150.5 (C-6), 162.0 (C-8); Anal. Calcd for $C_{15}H_{12}N_6O$: C, 61.64; H, 4.14; N, 28.75. Found: C, 60.35; H, 4.11; N, 27.87

4.1.6.21 (*E*)-2-phenyl-2*H*-1,2,3-triazole-4-carbaldehyde oxime (**20i**). White solid, m.p. 111-112 ºC; IR ν_{max} (cm^{-1}): 3253, 3042, 2937, 2823, 1596, 1496, 1445, 1330, 1032, 969, 930, 849, 823, 755, 671; ^{1}H NMR ($CDCl_3$, 500.00 MHz) δ: 7.35-7.46 (1H, m, H-4'), 7.47-7.54 (2H, m, H-3' and H-5'), 8.06-8.09 (2H, m, H-2' and H-6'), 8.14 (1H, s, H-4), 8.35 (1H, s, H-6); ^{13}C NMR ($CDCl_3$, 125.0 MHz APT) δ: 121.5 (C-4'), 121.8, 130.5, 130.8, 131.9 (C-2', C-3', C-4', C-5' and C-6'), 136.1 (C-4), 142.2 (C-1'), 145.3 (C-6); Anal. Calcd for $C_9H_8N_4O$: C, 57.4; H, 4.3; N, 29.8. Found: C, 57.4; H, 4.4; N, 31.2.

4.1.7 General Procedure for preparation of 18a-e

Into a round-bottom flask containing a suspension of 5 g of glucose (27.8 mmols) in 50 mL of water were added 83.3 mmols of the appropriate hydrazine, 14 g of sodium acetate, 150 mL of water and 2 drops of acetic acid. After reaction was complete, the osazone was collected by vacuum filtration.
Next, the osazone (24.7 mmols) was mixed with 8.8 g of copper sulfate pentahydrate in 185 mL of water. The reaction was heated to reflux for 2 hours. Next, the reaction was filtered hot to remove the copper salts and the product was crystallized at room temperature.
Finally, some of the D-arabino triazole-1,2-fenilosotriazole (56 mmols) was dissolved in 80 mL of water and 19 mmols of sodium metaperiodate was added. The reaction medium was vigorously stirred for 24 hours at room temperature. Upon completion of the reaction, the reaction medium was vacuum filtered.

4.1.7.1 2-phenyl-2*H*-1,2,3-triazole-4-carbaldehyde (**18a**). Brown solid, m.p. 67-68 ºC (m.p. lit. 68-69ºC [44]); IR ν_{max} (cm^{-1}): 3129, 2868, 1694, 1595, 1492, 1313, 1215, 1184, 1069, 1030, 964, 875, 760, 666; ^{1}H NMR (DMSO-d_6, 300.00 MHz) δ: 7.62-7.68 (1H, m, H-4'), 7.73-7.79 (2H, m, H-3' and H-5'), 8.20-8.24 (2H, m, H-2' and H-6'), 8.77 (1H, s, H-5), 10.29 (1H, s, H-6); ^{13}C NMR (DMSO-d_6, 75.0 MHz APT) δ: 119.4 (C-3' and C-5'), 129.3 (C-2' and C-6'), 129.8 (C-4'), 130.1 (C-4), 147.7 (C-5), 185.0 (C-6).

4.1.7.2 2-(4-chlorophenyl)-2*H*-1,2,3-triazole-4-carbaldehyde (**18b**). Brown solid, m.p. 86-87 ºC; IR ν_{max} (cm^{-1}): 1708, 1490, 1313, 1099, 967, 888, 831, 763,674; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 7.80 (d, 1H, *J* 8.7 Hz, H-2'and H-6'), 8.23 (d, 1H, *J* 8.7 Hz, H-3' and H-5'), 8.77 (s, 1H, H-5), 10.30 (s, 1H, H-6); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 120.7 (C-2' and C-6'), 129.8 (C-3' and C-5'),133.5 (C-1'), 136.8 (C-4), 137.3 (C-4'), 147.7 (C-5), 184.5 (C-6); Anal. Calcd for $C_9H_6ClN_3O$: C, 52.07; H, 2.91; N, 20.24. Found: C, 52.5; H, 2.72; N, 20.6

4.1.7.3 2-(2,5-dimethylphenyl)-2*H*-1,2,3-triazole-4-carbaldehyde (**18c**). Brown solid, m.p. 33-34 ºC; IR ν_{max} (cm^{-1}): 3133, 2852, 1707, 1513, 1494, 1447, 1312, 1032, 878, 803, 770; ^{1}H NMR (DMSO-d_6, 300.00 MHz) δ: 2.38 (3H, s, CH_3), 2.49 (3H, s, CH_3), 7.43 (1H, d, *J* 7.5 Hz, H-4'), 7.49 (1H, d, *J* 7.5 Hz, H-3'), 7.57 (1H, s, H-6'), 8.73 (1H, s, H-5), 10.29 (1H, s, H-6); ^{13}C NMR (DMSO-d_6, 75.0 MHz APT) δ: 17.6 (CH_3), 20.3 (CH_3), 125.6 (C-6'), 129.4 (C-5'), 130.7 (C-3'), 131.7 (C-4'), 136.0 (C-4), 136.8 (C-2'), 138.6 (C-1'), 147.5 (C-5), 185.0 (C-6). Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 62.69; H, 5.25; N, 18.85

4.1.7.4 2-(2,5-dichlorophenyl)-2*H*-1,2,3-triazole-4-carbaldehyde (**18d**). Brown solid, m.p. 114-115 ºC; IR ν_{max} (cm^{-1}): 3048, 2892, 2768, 1674, 1573, 1444, 1265, 1211, 1111, 1044, 805; ^{1}H NMR (DMSO-d_6, 300.00 MHz) δ: 7.45 (1H, d, *J* 7.5 Hz, H-4'), 7.50 (1H, d, *J* 7.5 Hz, H-3'), 7.58 (1H, s, H-6'), 8.74 (1H, s, H-5), 10.30 (1H, s, H-6); ^{13}C NMR (DMSO-d_6, 75.0 MHz APT) δ: 125.3 (C-6'), 129.1 (C-5'), 130.4 (C-3'), 131.4 (C-4'), 135.7 (C-4), 136.4 (C-2'), 138.3 (C-1'), 147.1 (C-5), 184.7 (C-6); Anal. Calcd for $C_{10}H_8Cl_2N_3O$: C, 44.66; H, 2.08; N, 17.36. Found: C, 44.81; H, 2.13; N, 17.45

4.1.7.5 2-(4-fluorophenyl)-2*H*-1,2,3-triazole-4-carbaldehyde (**18e**). Brown solid, m.p. 77-78 ºC; IR ν_{max} (cm^{-1}): 1699,1511, 1313, 1219, 1032, 967, 839, 758, 675,640; ^{1}H NMR (DMSO-d_6, 500.00 MHz) δ: 7.58-7.61 (m, 2H, H-2' and H-6'), 8.24-8.27 (m, 2H, H-3' and H-5'), 8.78 (s, 1H, H-5), 10.30 (s, 1H, H-6); ^{13}C NMR (DMSO-d_6, 125.0 MHz APT) δ: 117.0 (d, *J* 23.5 Hz, C-

3' and C-5'), 122.0 (d, *J* 8.8 Hz, C-2' and C-6'), 135.5 (C-1'), 137.1 (C-4), 147.9 (C-5), 162.3 (d, *J* 247.5 Hz, H-4'), 185.0 (C-6); Anal. Calcd for $C_9H_6FN_3O$: C, 56.55; H, 3.16; N, 21.98. Found: C, 56.50; H, 3.12; N, 21.6.

4.1.8 General Procedure for preparation of 21a

Into a round-bottom flask already containing a solution of 5.8 mmols of triazole-carbaldehyde **18a** in 50 mL of methanol was added 17 mmols of sodium borohydride in an ice bath. Next, the methanol was evaporated under reduced pressure, and the product was extracted with ethyl acetate, washed with water (3 x 100 mL), dried over with anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure to give **21a**.

4.1.8.1 2-(2-phenyl-2*H*-1,2,3-triazole-4-yl)methanol (**21a**). Brown solid, m.p. 64-65^{o}C (m.p. lit. 64-65 ºC [45]); IR ν_{max} (cm^{-1}): 3309, 3229, 2939, 2876, 1594, 1493, 1410, 1352, 1048, 1014, 962, 759; ^{1}H NMR ($CDCl_3$, 500.00 MHz) δ: 4.77 (2H, s, H-6), 7.49-7.55 (1H, m, H-4'), 7.64-7.71 (2H, m, H-3' and H-5'), 8.09-8.13 (2H, m, H-2'and H-6'), 8.14 (1H, s, H-4); ^{13}C NMR ($CDCl_3$, 125.0 MHz APT) δ: 54.9 (C-6), 118.2 (C-4'), 127.4 (C-3' and C-5'), 129.7 (C-2' and C-6'), 135.0 (C-4), 150.8 (C-5).

4.2. Biological assays

4.2.1 Enzyme activity assays

***S. cerevisiae* maltase assay (MAL12)**: α-Glucosidase activity was determined in a manner analogous to previous studies [8]. A reaction mixture with a final volume of 200 µL, containing 50 mM phosphate buffer, 100 mM NaCl and 1 mM PNP-G pH 7.0, was pre-incubated at 37 ^{o}C for 5 min. The reaction was then initiated by the addition of 25 µL [100 µg/mL] of α-glucosidase. The absorbance observed at 405 nm, corresponding to the liberated *p*-nitrophenol, was measured using a FlexStation 3 Benchtop Multi-Mode Microplate Reader (Molecular Devices, Sunnyvale, CA). All the experiments were repeated at least twice, each experiment using samples in triplicate.

4.2.2 Porcine pancreatic α-amylase (PPA) assay: α-amylase activity was determined in a manner analogous to previous reports [9]. A reaction mixture with a final volume of 200 µL, containing 50 mM Hepes buffer, 5 mM $CaCl_2$, 100 mM NaCl and 1 mM CNPG3 pH 7.0, was pre-incubated at 37 ^{o}C for 5 min before the reaction was initiated by the addition of 20 µL of PPA 1.5-2 units. The absorbance observed at 405 nm, which corresponds to the liberated 2-chloro-4-nitrophenol, was measured using a FlexStation 3 Benchtop Multi-Mode Microplate Reader (Molecular Devices, Sunnyvale, CA). All the experiments were repeated at least two times, each experiment using samples in triplicate.

4.2.3 Inhibitor Screening and IC_{50} determination: The triazoles were stored in 100% DMSO and diluted in Milli-Q water (Millipore Corporation) before the experiments. DMSO (1-5 %) was unable to significantly inhibit both enzymatic activities (data not shown), and a maximum of 1 % DMSO was utilized for further assays. All compounds were screened for glucosidase and amylase inhibition at 500 µM in the reaction medium described above. For the determination of the inhibitor concentration at which 50 % inhibition of enzyme activity occurs (IC_{50}), the assay was performed as above except that the compound concentrations were varied from 1-1000 µM.

IC_{50} values were calculated using Sigmaplot 12.0 software (Systat software Inc, USA) by fitting residual activity data and inhibitor concentration to the four-parameter logistic equation: Res. Activity = min + (max-min) / (1 + ([I]/EC50) ^ (-Hillslope)).

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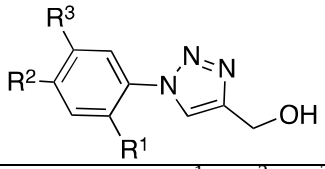
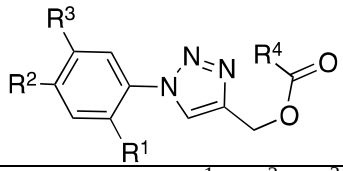
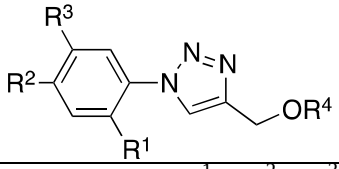
TABLES

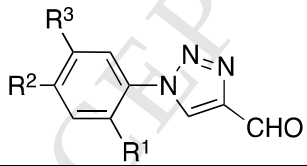
Table 1
Inhibitory screening of the compounds at 500 µM on yeast α-glucosidase activity.

Compounds	Substituents	$V_o \pm SD$ (mAU/min)	% inhibition
Control	-	388.3 ± 11.6	-
Acarbose	-	177.0 ± 11.9	52.8
A series			
			
12a	$R^1 = R^2 = R^3 = H$	380.3 ± 57.6	2.1
12b	$R^1 = R^3 = H$ $R^2 = OCH_3$	332.4 ± 33.2	14.4
12c	$R^1 = R^3 = H$ $R^2 = Cl$	322.8 ± 40.1	16.9
12d	$R^1 = R^3 = Cl$ $R^2 = H$	384.0 ± 34.5	1.1
			
13a	$R^1 = R^2 = R^3 = H$ $R^4 = C_6H_5$	355.9 ± 4.5	8.4
13b	$R^1 = R^3 = Cl$ $R^2 = H$ $R^4 = C_6H_5$	323.6 ± 11.7	16.7
13c	$R^1 = R^3 = Cl$ $R^2 = H$ $R^4 = (CH_2)_4CH_3$	337.2 ± 2.5	13.2
13d	$R^1 = R^3 = H$ $R^2 = Cl$ $R^4 = CH_3$	344.4 ± 1.0	11.3
13e	$R^1 = R^3 = H$ $R^2 = Cl$ $R^4 = C_6H_5$	352.3 ± 31.3	9.3
13f	$R^1 = R^2 = R^3 = H$ $R^4 = (CH_2)_4CH_3$	355.7 ± 5.7	8.4
13g	$R^1 = R^3 = Cl$ $R^2 = H$ $R^4 = CH_3$	363.5 ± 4.1	6.4
13h	$R^1 = R^3 = H$ $R^2 = Cl$ $R^4 = (CH_2)_4CH_3$	371.2 ± 29.2	4.4

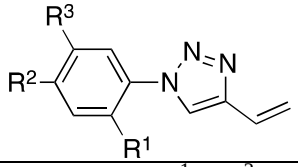
13i	$R^1 = R^2 = R^3 = H$ $R^4 = (CH_2)_8CH_3$	364.9 ± 12.8	6.0
13j	$R^1 = R^3 = H$ $R^2 = Cl$ $R^4 = (CH_2)_8CH_3$	381.9 ± 9.2	1.7
13k	$R^1 = R^2 = R^3 = H$ $R^4 = CH_3$	398.5 ± 30.3	-2.6



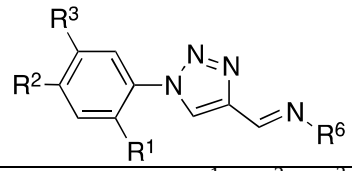
14a	$R^1 = R^2 = R^3 = H$ $R^4 = C_2H_5$	387.3 ± 2.0	0.3
14b	$R^1 = R^2 = R^3 = H$ $R^4 = (CH_2)_3CH_3$	389.0 ± 4.8	-0.2
14c	$R^1 = R^3 = H$ $R^2 = Cl$ $R^4 = C_2H_5$	387.7 ± 11.8	0.2
14d	$R^1 = R^3 = H$ $R^2 = Cl$ $R^4 = (CH_2)_3CH_3$	386.3 ± 23.1	0.5
14e	$R^1 = R^3 = H$ $R^2 = OCH_3$ $R^4 = C_2H_5$	342.5 ± 10.8	11.8
14f	$R^1 = R^3 = Cl$ $R^2 = H$ $R^4 = (CH_2)_3CH_3$	333.5 ± 17.9	14.1
14g	$R^1 = R^3 = Cl$ $R^2 = H$ $R^4 = C_2H_5$	350.1 ± 11.3	9.8



11	$R^1 = R^2 = R^3 = H$	346.9 ± 14.9	10.7
15a	$R^1 = R^3 = H$ $R^2 = Cl$	338.6 ± 3.2	12.8
15b	$R^1 = R^3 = Cl$ $R^2 = H$	345.2 ± 26.0	11.1

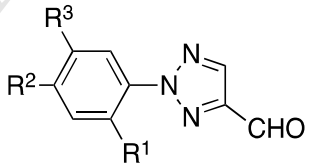


16a	$R^1 = R^2 = R^3 = H$	370.8 ± 31.4	4.5

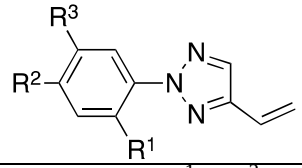
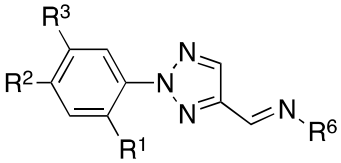
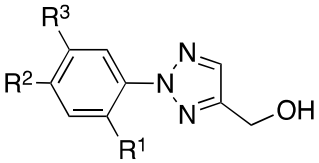


17a	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}C_6H_5$	385.5 ± 13.6	0.7
17b	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}2,5\text{-}Cl\text{-}C_6H_3$	362.2 ± 12.0	6.7
17c	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}4\text{-}F\text{-}C_6H_4$	272.5 ± 16.0	29.8
17d	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}4\text{-}Cl\text{-}C_6H_4$	230.8 ± 17.2	40.6
17e	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}4\text{-}Br\text{-}C_6H_4$	320.8 ± 8.8	17.4
17f	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}2,5\text{-}CH_3\text{-}C_6H_5$	243.0 ± 29.3	37.4
17g	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}2,4\text{-}NO_2\text{-}C_6H_3$	352.1 ± 9.2	9.3
17h	$R^1 = R^2 = R^3 = H$ $R^6 = CO\text{-}4\text{-}pyridyl$	357.3 ± 26.4	8.0
17i	$R^1 = R^3 = H$ $R^2 = Cl$ $R^6 = NH\text{-}C_6H_5$	352.6 ± 17.2	9.2
17j	$R^1 = R^3 = H$ $R^2 = Cl$ $R^6 = 4\text{-}Br\text{-}C_6H_4$	272.2 ± 16.2	29.9
17k	$R^1 = R^2 = R^3 = H$ $R^6 = OH$	341.7 ± 12.1	12.0
17l	$R^1 = R^3 = H$ $R^2 = Cl$ $R^6 = OH$	224.9 ± 4.7	42.1

B series



18a	$R^1 = R^2 = R^3 = H$	51.2 ± 20.0	86.8
18b	$R^1 = R^3 = H$	2.5 ± 0.4	99.4

18c	R^2 = Cl R^1 = R^3 = CH_3 R^2 = H	160.3 ± 9.8	58.7
18c	R^1 = R^3 = Cl R^2 = H	119.3 ± 10.8	69.3
18d	R^1 = R^3 = H R^2 = F	154.0 ± 14.9	60.3
		-	-
19a	R^1 = R^2 = R^3 = H	364.9 ± 12.2	6.0
		-	-
20a	R^1 = R^2 = R^3 = H R^6 = NH-C_6H_5	281.6 ± 5.5	27.5
20b	R^1 = R^2 = R^3 = H R^6 = NH-2,5-Cl-C_6H_3	3.5 ± 1.5	99.1
20c	R^1 = R^2 = R^3 = H R^6 = NH-4-F-C_6H_4	265.1 ± 22.0	31.7
20d	R^1 = R^2 = R^3 = H R^6 = NH-4-Cl-C_6H_4	309.4 ± 19.9	20.3
20e	R^1 = R^2 = R^3 = H R^6 = NH-4-Br-C_6H_4	355.4 ± 15.2	8.5
20f	R^1 = R^3 = R^2 = H R^6 = NH-2,4-CH_3-C_6H_3	283.2 ± 17.4	27.1
20g	R^1 = R^2 = R^3 = H R^6 = NH-2,4-NO_2-C_6H_3	211.4 ± 21.7	45.6
20h	R^1 = R^2 = R^3 = H R^6 = CO-4-pyridyl	123.5 ± 8.9	68.2
20i	R^1 = R^2 = R^3 = H R^6 = OH	359.8 ± 33.0	7.3
			

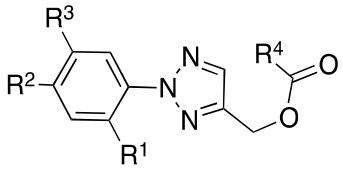
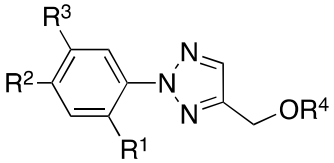
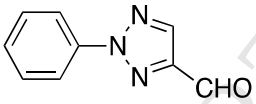
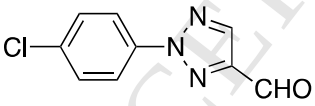
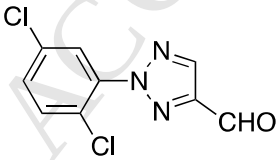
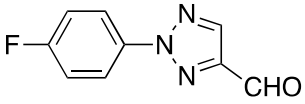
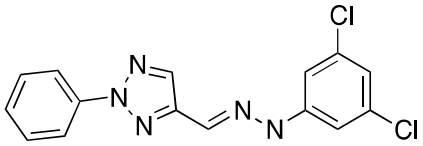
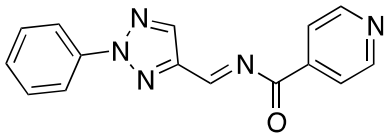
21a	$R^1 = R^2 = R^3 = H$	384.6 ± 15.5	0.9
			
22a	$R^1 = R^2 = R^3 = H$ $R^4 = (CH_2)_8CH_3$	354.7 ± 17.4	8.7
22b	$R^1 = R^2 = R^3 = H$ $R^4 = (CH_2)_4CH_3$	360.8 ± 22.6	7.1
22c	$R^1 = R^2 = R^3 = H$ $R^4 = C_6H_5$	368.0 ± 11.9	5.2
22d	$R^1 = R^2 = R^3 = H$ $R^4 = CH_3$	371.9 ± 19.8	4.2
			
23a	$R^1 = R^2 = R^3 = H$ $R^4 = C_2H_5$	391.7 ± 4.0	-0.9
23b	$R^1 = R^2 = R^3 = H$ $R^4 = (CH_2)_3CH_3$	381.4 ± 13.0	1.8

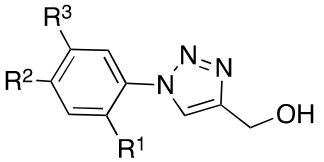
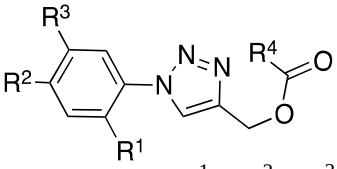
Table 2
IC_{50} and ligand binding efficiency indexes (BEI) of triazoles against yeast α-glucosidase activity.

Inhibitor	MW (Da)	IC50 (μM)[a]	BEI[b,a]
 **18a**	173.17	72 ± 12	23.9
 **18b**	207.62	54 ± 6	20.6
 **18c**	242.06	93 ± 12.0	16.6
 **18d**	191.16	482 ± 49	17.4

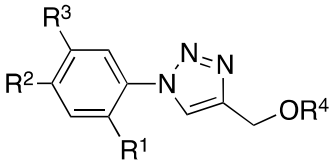
 **20b**	332.19	75 ± 5	12.4
 **20h**	292.30	369 ± 25	11.7

[a]Assay conditions were as described in experimental section. [b]BEI = pIC50/MW(kDa) [39,40].

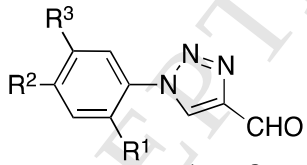
Table 3
Inhibitory activity of the compounds at 500 µM on porcine pancreatic α-amylase activity.

Compounds	Substituents	V_o ± SD (mAU/min)	% inhibition
Control	-	840.4±49.9	-
Acarbose	-	3.8 ± 0.4	99.6
A series			
			
12a	$R^1 = R^2 = R^3 = H$	700.2±33.7	16.7
12b	$R^1 = R^3 = H$ $R^2 = OCH_3$	836.0±36.1	0.5
12c	$R^1 = R^3 = H$ $R^2 = Cl$	713.3±49.9	15.1
12d	$R^1 = R^3 = Cl$ $R^2 = H$	715.4±71.2	14.9
			
13a	$R^1 = R^2 = R^3 = H$ $R^4 = C_6H_5$	686.2±87.0	18.4
13b	$R^1 = R^3 = Cl$ $R^2 = H$ $R^4 = C_6H_5$	691.2±6.7	17.8
13c	$R^1 = R^3 = Cl$ $R^2 = H$ $R^4 = (CH_2)_4CH_3$	651.6±24.6	22.5
13d	$R^1 = R^3 = H$ $R^2 = Cl$ $R^4 = CH_3$	739.4±46.8	12.0
13e	$R^1 = R^3 = H$ $R^2 = Cl$ $R^4 = C_6H_5$	653.4±31.3	22.3
13f	$R^1 = R^2 = R^3 = H$ $R^4 = (CH_2)_4CH_3$	825.9±90.7	1.7
13g	$R^1 = R^3 = Cl$ $R^2 = H$ $R^4 = CH_3$	776.2±48.4	7.6
13h	$R^1 = R^3 = H$ $R^2 = Cl$ $R^4 = (CH_2)_4CH_3$	612.9±7.0	27.1
13i	$R^1 = R^2 = R^3 = H$ $R^4 = (CH_2)_8CH_3$	713.5±33.2	15.1

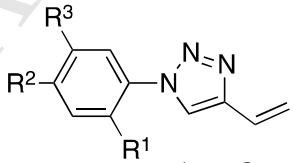
13j	$R^1 = R^3 = H$ $R^2 = Cl$ $R^4 = (CH_2)_8CH_3$	694.7±36.7	17.3
13k	$R^1 = R^2 = R^3 = H$ $R^4 = CH_3$	835.0±79.7	0.6



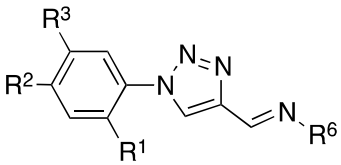
14a	$R^1 = R^2 = R^3 = H$ $R^4 = C_2H_5$	867.9±16.0	-3.3
14b	$R^1 = R^2 = R^3 = H$ $R^4 = (CH_2)_3CH_3$	823.1±20.3	2.1
14c	$R^1 = R^3 = H$ $R^2 = Cl$ $R^4 = C_2H_5$	832.0±12.6	1.0
14d	$R^1 = R^3 = H$ $R^2 = Cl$ $R^4 = (CH_2)_3CH_3$	816.7±13.6	2.8
14e	$R^1 = R^3 = H$ $R^2 = OCH_3$ $R^4 = C_2H_5$	866.4±33.3	-3.1
14f	$R^1 = R^3 = Cl$ $R^2 = H$ $R^4 = (CH_2)_3CH_3$	709.3±50.9	15.6
14g	$R^1 = R^3 = Cl$ $R^2 = H$ $R^4 = C_2H_5$	850.4±16.4	-1.2



11	$R^1 = R^2 = R^3 = H$	691.5±27.4	17.7
15a	$R^1 = R^3 = H$ $R^2 = Cl$	666.2±53.6	20.7
15b	$R^1 = R^3 = Cl$ $R^2 = H$	714.2±36.9	15.0

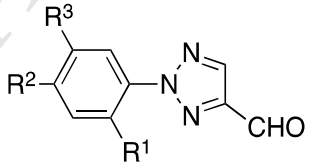


16a	$R^1 = R^2 = R^3 = H$	619.5±51.5	26.3

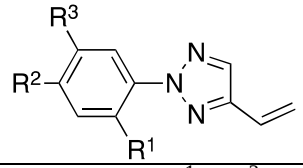
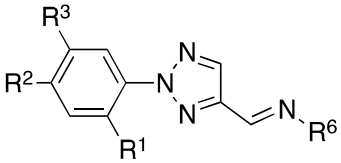


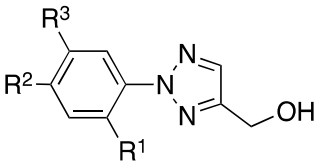
17a	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}C_6H_5$	790.3±44.2	6.0
17b	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}3,5\text{-}Cl\text{-}C_6H_3$	670.6±32.3	20.2
17c	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}4\text{-}F\text{-}C_6H_4$	592.1±57.9	29.5
17d	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}4\text{-}Cl\text{-}C_6H_4$	771.4±14.9	8.2
17e	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}4\text{-}Br\text{-}C_6H_4$	630.9±27.3	24.9
17f	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}3,5\ CH_3\text{-}C_6H_5$	603.9±38.0	28.1
17g	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}2,4\text{-}NO_2\text{-}C_6H_3$	820.7±48.0	2.3
17h	$R^1 = R^2 = R^3 = H$ $R^6 = CO\text{-}4\text{-}pyridyl$	587.9±35.0	30.0
17i	$R^1 = R^3 = H$ $R^2 = Cl$	709.4 ± 42.6	15.6
17j	$R^1 = R^3 = H$ $R^2 = Cl$ $R^6 = 4\text{-}Br\text{-}C_6H_4$	776.5±64.7	7.6
17k	$R^1 = R^2 = R^3 = H$ $R^6 = OH$	805.4±58.5	4.2
17l	$R^1 = R^3 = H$ $R^2 = Cl$ $R^6 = OH$	675.6±17.8	19.6

B series

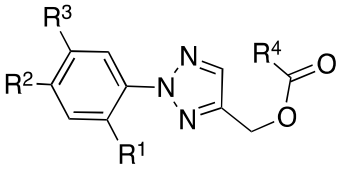


18a	$R^1 = R^2 = R^3 = H$	808.9±17.9	3.7
18b	$R^1 = R^3 = H$ $R^2 = Cl$	636.9 ± 15.5	24.2

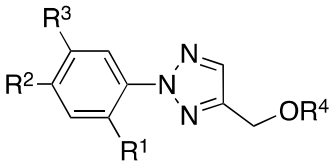
18c	$R^1 = R^3 = CH_3$ $R^2 = H$	199.7 ± 19.6	76.2
18d	$R^1 = R^3 = Cl$ $R^2 = H$	95.5 ± 3.6	88.6
18e	$R^1 = R^3 = H$ $R^2 = F$	729.9 ± 26.0	13.1
			
19a	$R^1 = R^2 = R^3 = H$	834.3±5.9	0.7
			
20a	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}C_6H_5$	742.9±23.2	11.6
20b	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}3,5\text{-}Cl\text{-}C_6H_3$	656.3±37.4	21.9
20c	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}4\text{-}F\text{-}C_6H_4$	739.7±39.4	12.0
20d	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}4\text{-}Cl\text{-}C_6H_4$	751.2±47.0	10.6
20e	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}4\text{-}Br\text{-}C_6H_4$	624.8±31.8	25.7
20f	$R^1 = R^3 = R^2 = H$ $R^6 = NH\text{-}3,5\text{-}CH_3\text{-}C_6H_3$	699.0±21.8	16.8
20g	$R^1 = R^2 = R^3 = H$ $R^6 = NH\text{-}2,4\text{-}NO_2\text{-}C_6H_3$	693.5±14.1	17.5
20h	$R^1 = R^2 = R^3 = H$ $R^6 = CO\text{-}4\text{-}pyridyl$	676.5±46.4	19.5
20i	$R^1 = R^2 = R^3 = H$ $R^6 = OH$	335.6 ± 7.3	60.1



21a	$R^1 = R^2 = R^3 = H$	830.4±15.0	1.2

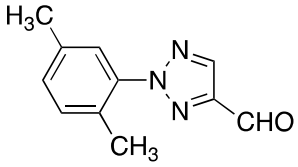
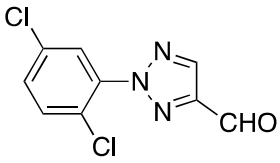
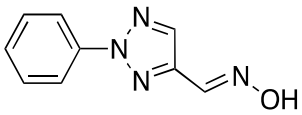


22a	$R^1 = R^2 = R^3 = H$ $R^4 = (CH_2)_8CH_3$	608.2±15.0	27.6
22b	$R^1 = R^2 = R^3 = H$ $R^4 = (CH_2)_4CH_3$	634.5±35.4	24.5
22c	$R^1 = R^2 = R^3 = H$ $R^4 = C_6H_5$	826.4±47.7	1.7
22d	$R^1 = R^2 = R^3 = H$ $R^4 = CH_3$	806.4±11.6	4.0



23a	$R^1 = R^2 = R^3 = H$ $R^4 = C_2H_5$	814.8±11.4	3.0
23b	$R^1 = R^2 = R^3 = H$ $R^4 = (CH_2)_3CH_3$	812.4±19.5	3.3

Table 4
IC_{50} and ligand binding efficiency indexes of triazoles against porcine pancreatic α-amylase.

Inhibitor	MW (Da)	IC_{50} (μM)[a]	BEI[b,a]
 **18c**	201.22	282 ± 7	17.6
 **18d**	242.06	145 ± 7.6	15.9
 **20i**	188.07	201 ± 23	19.7

[a]Assay conditions were as described in experimental section. [b] BEI = pIC_{50}/MW(kDa) [39,40].

LEGEND TO FIGURES AND SCHEMES

Figure 1: Some examples of 1,2,3-triazoles in clinical trials.

Figure 2. Some examples of 1*H*-1,2,3-triazoles as antidiabetic candidates.

Scheme 1: Synthetic routes to series A and B of the 1*H*-1,2,3- and 2*H*-1,2,3-triazoles. Reagents and conditions: i) R5Br, NaH, THF, reflux; ii) R4COCl, DCM, Py, DMAP cat., r.t.; iii) IBX, DMSO, r.t.; iv) R6NHNH$_2$.HCl, EtOH, H_2SO_4 cat., r.t.; v) $Ph_3(CH_3)PBr$, NaH, THF, r.t.; vi) $NaBH_4$, MeOH, 0 ºC.

FIGURES AND SCHEMES

Figure 1

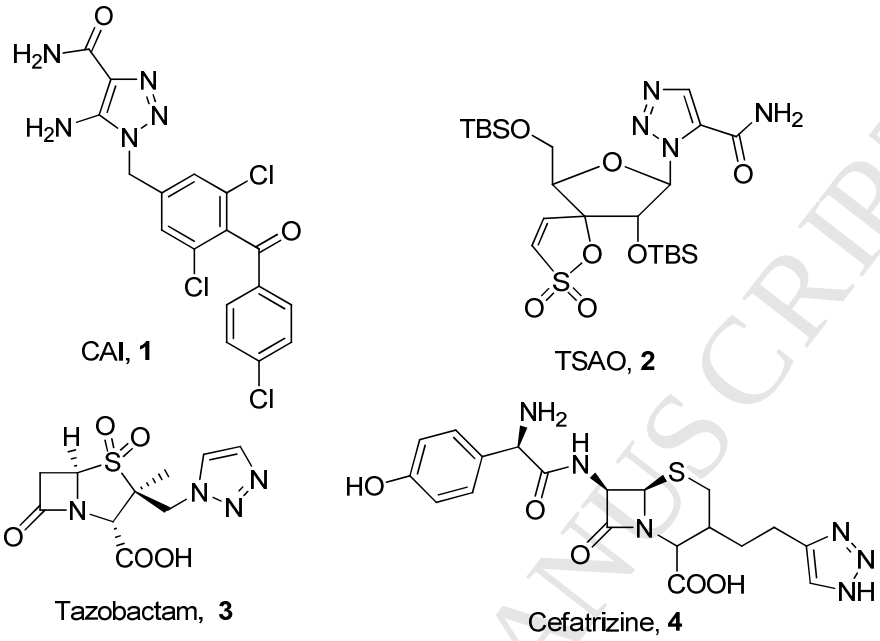
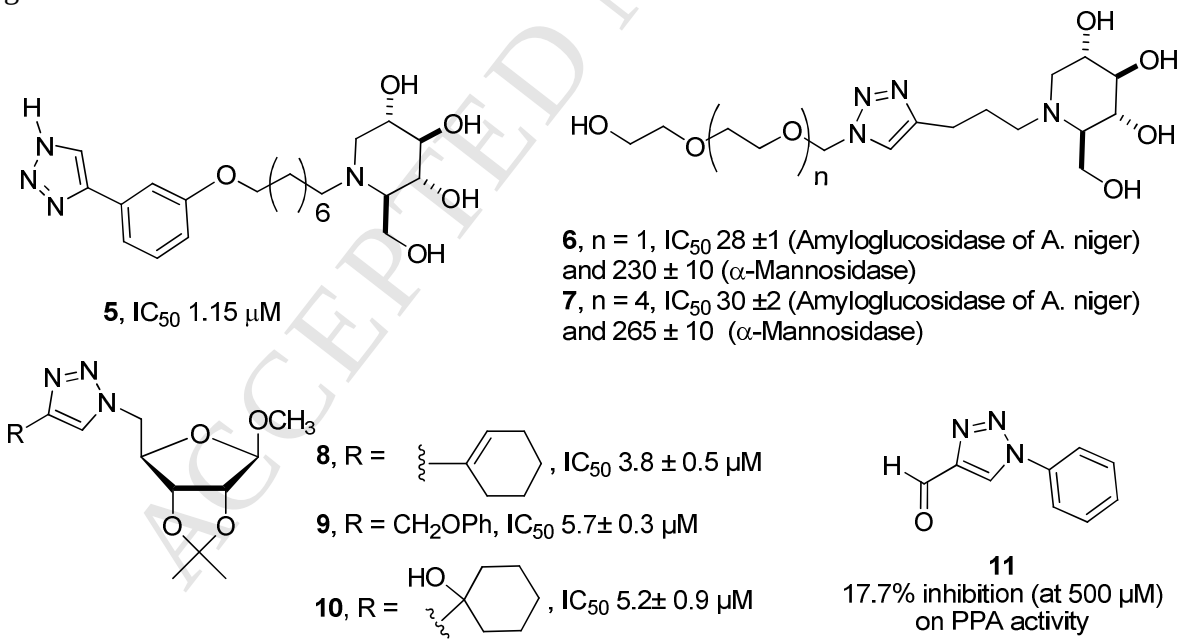
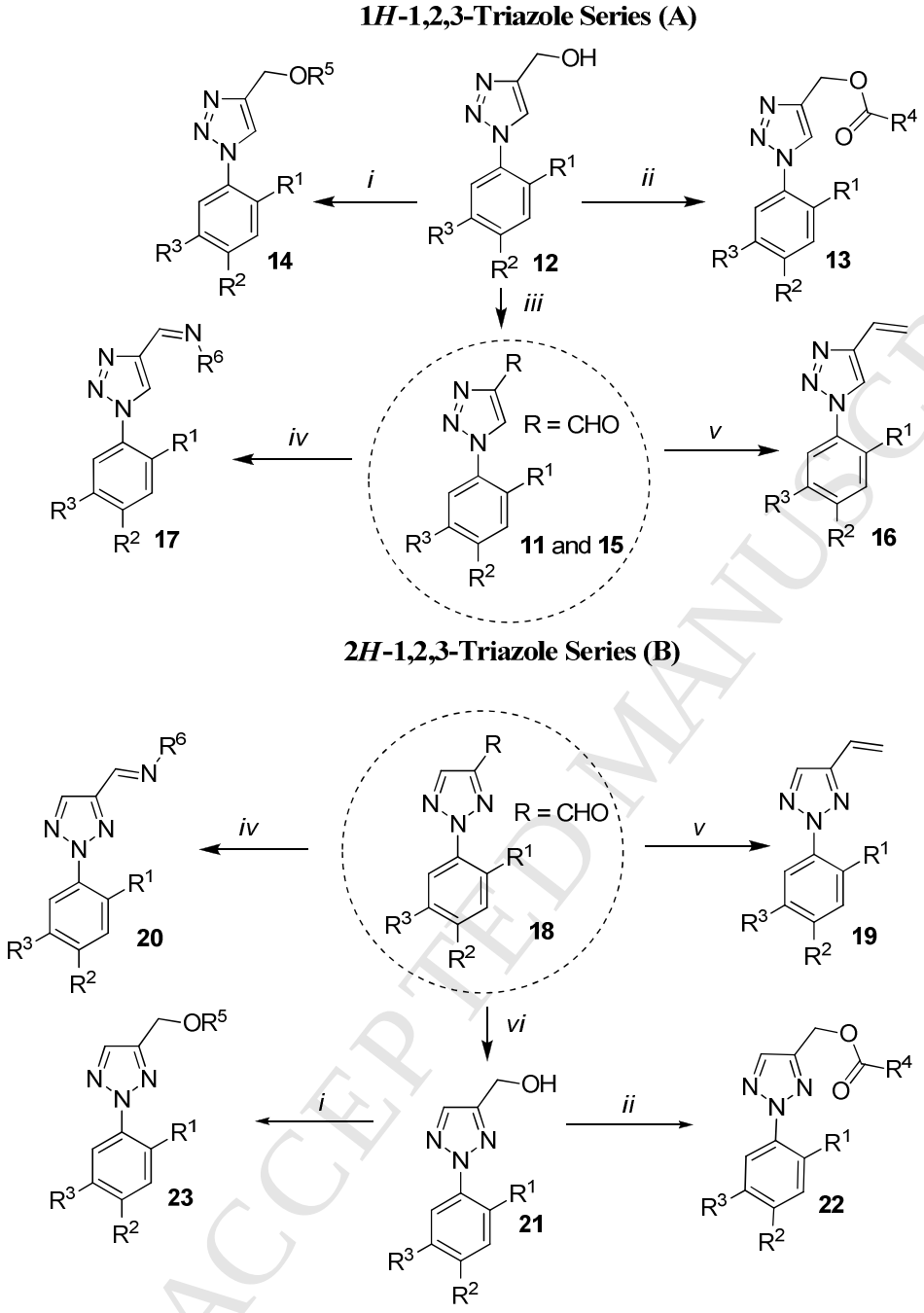
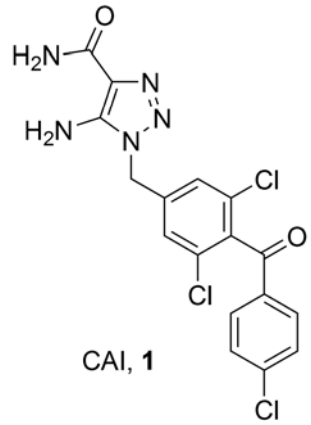


Figure 2:



Scheme 1





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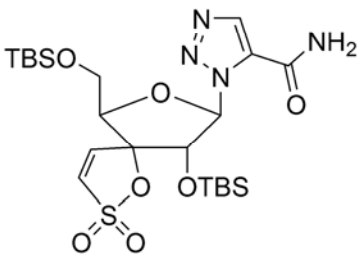

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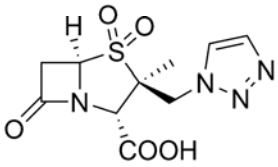
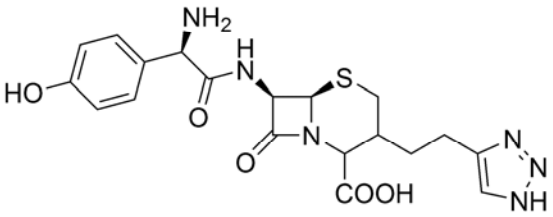
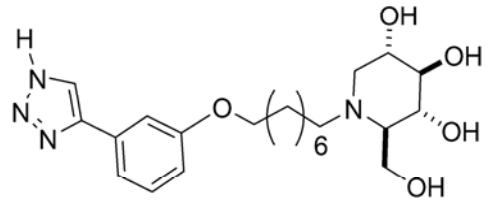


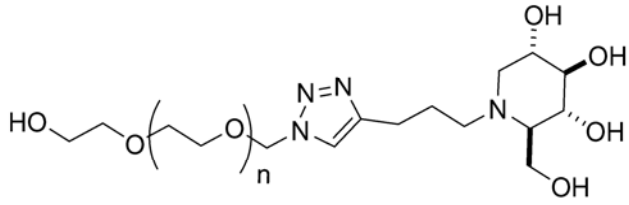
Tazobactam, **3**



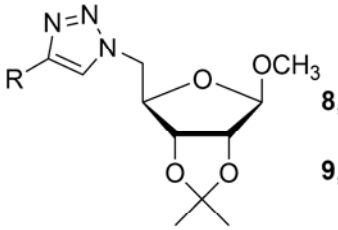
Cefatrizine, **4**

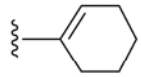


5, IC_{50} 1.15 μM

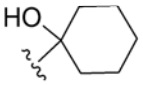


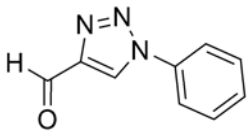
6, n = 1, IC_{50} 28 ±1 (Amyloglucosidase of A. niger) and 230 ± 10 (α-Mannosidase)
7, n = 4, IC_{50} 30 ±2 (Amyloglucosidase of A. niger) and 265 ± 10 (α-Mannosidase)



8, R =  , IC_{50} 3.8 ± 0.5 μM

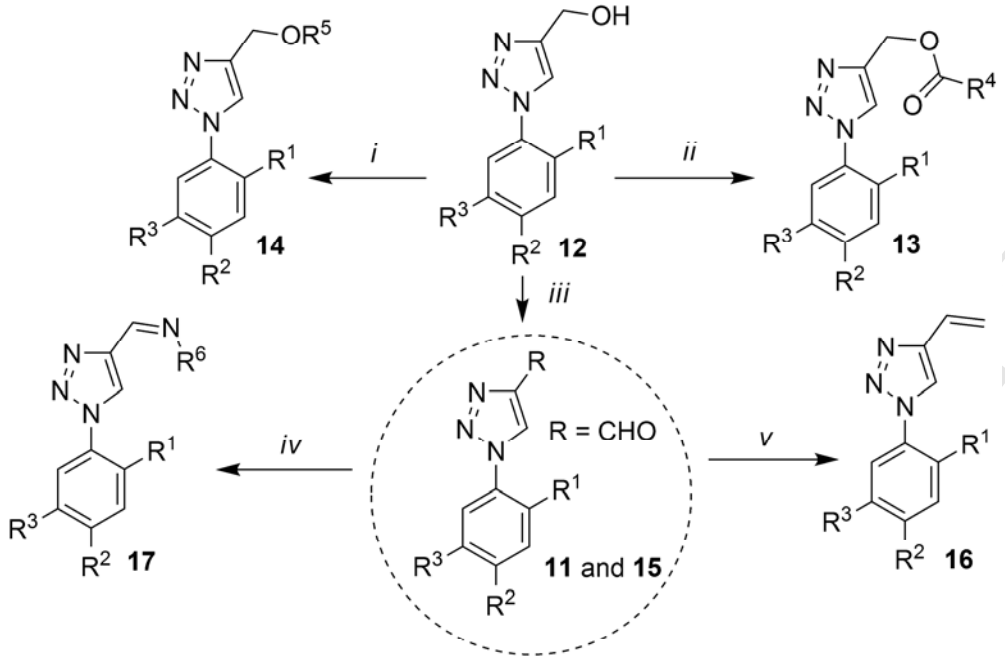
9, R = CH_2OPh, IC_{50} 5.7± 0.3 μM

10, R =  , IC_{50} 5.2± 0.9 μM

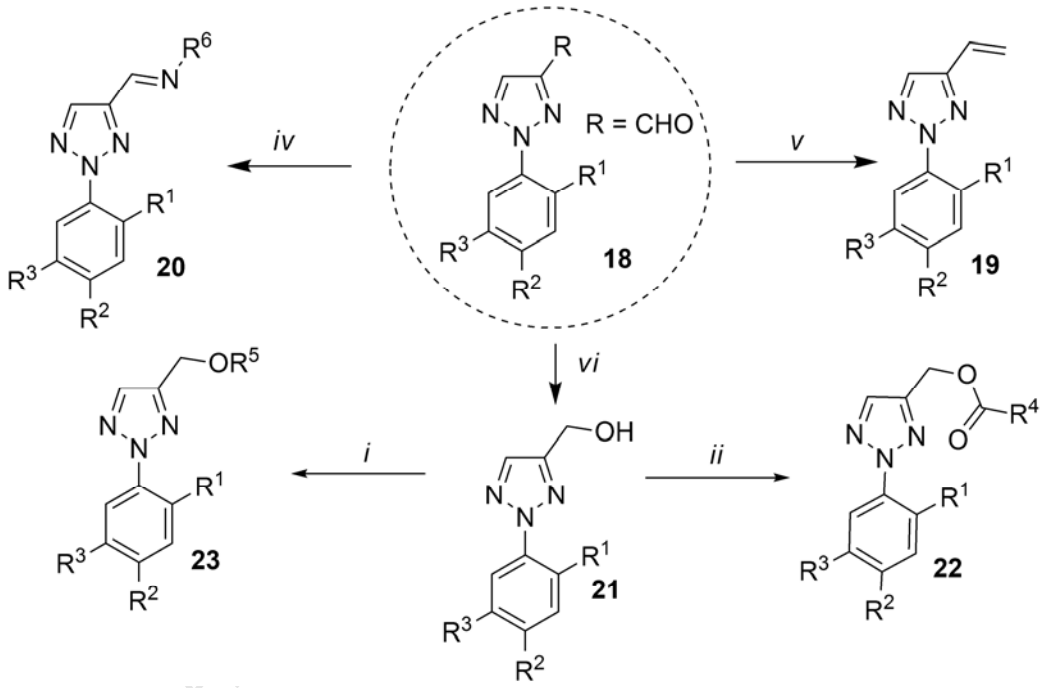


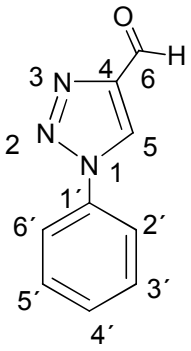
11
17.7% inhibition (at 500 μM) on PPA activity

1*H*-1,2,3-Triazole Series (A)



2*H*-1,2,3-Triazole Series (B)

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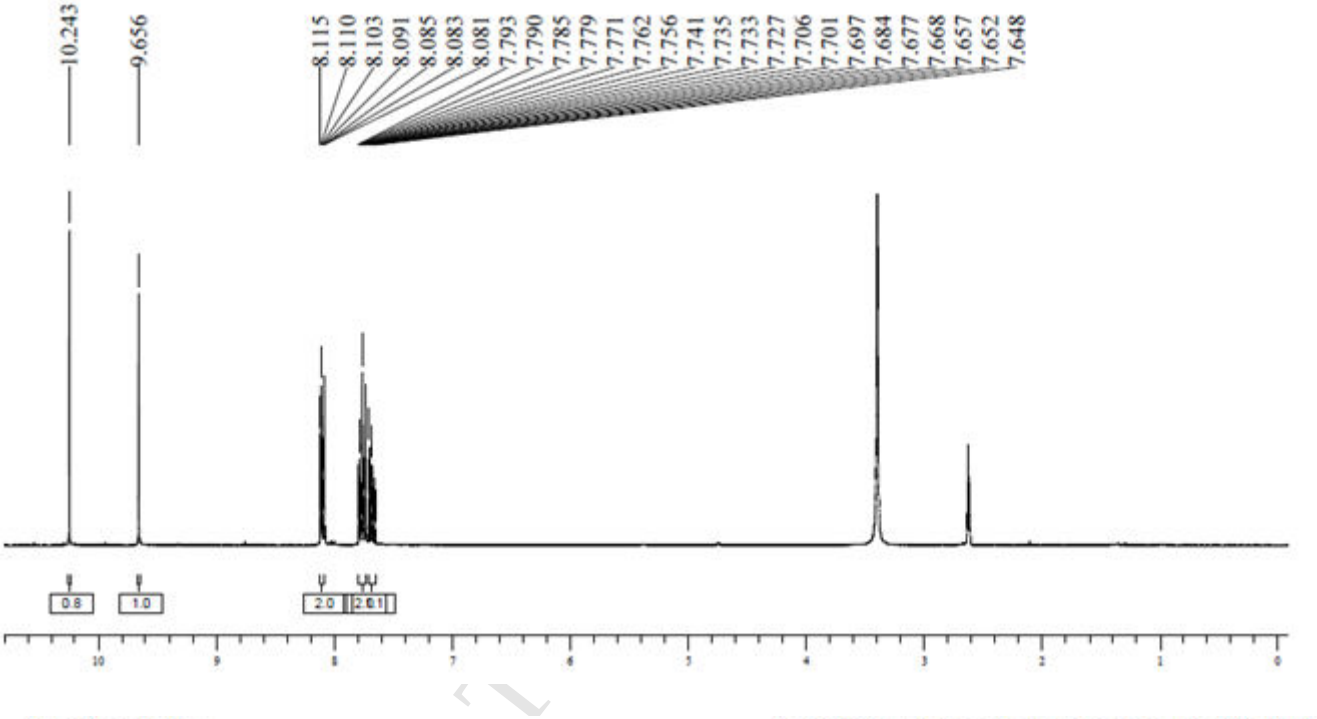
6
2
N
5
N
1
1′
6′
2′
5′
3′
4′

11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8.091
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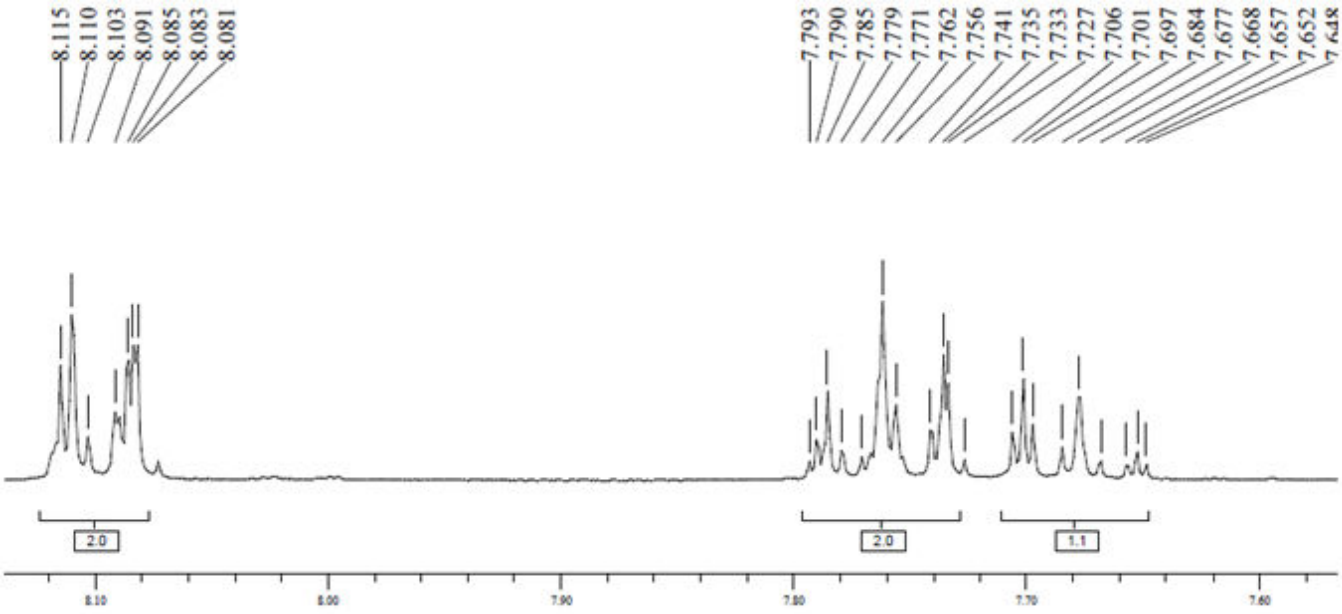
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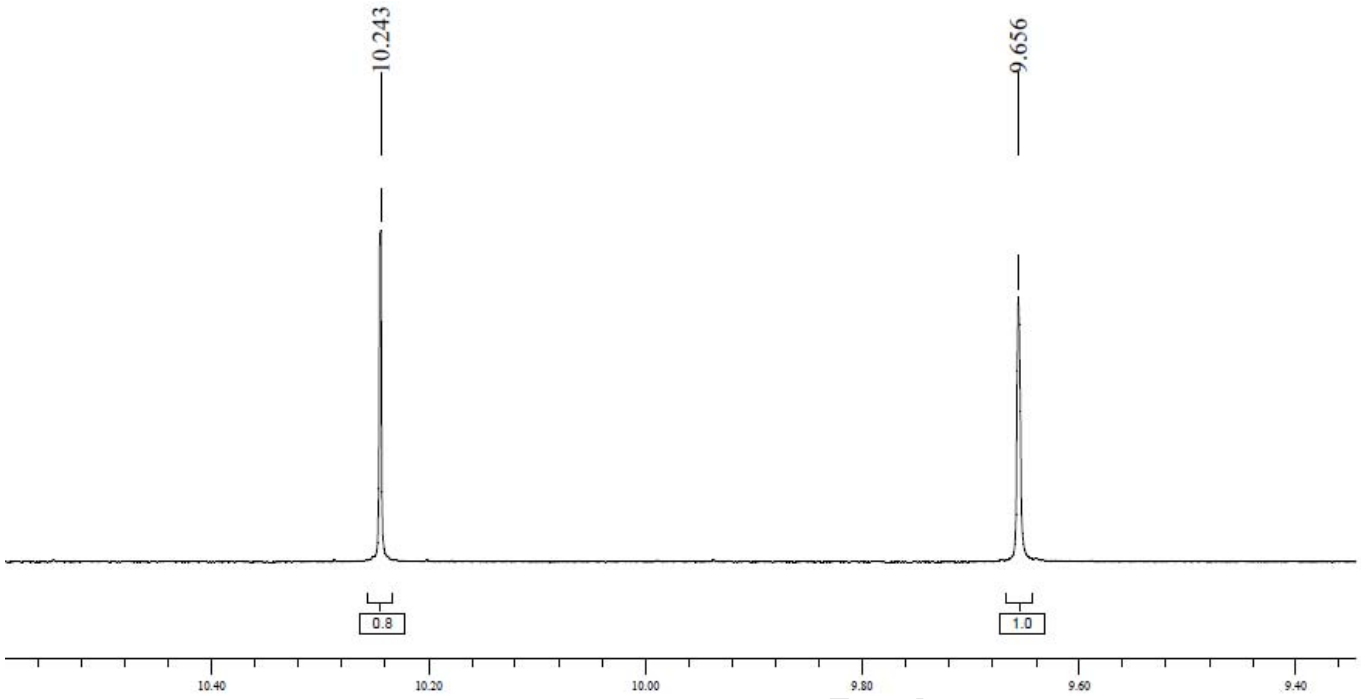
1.1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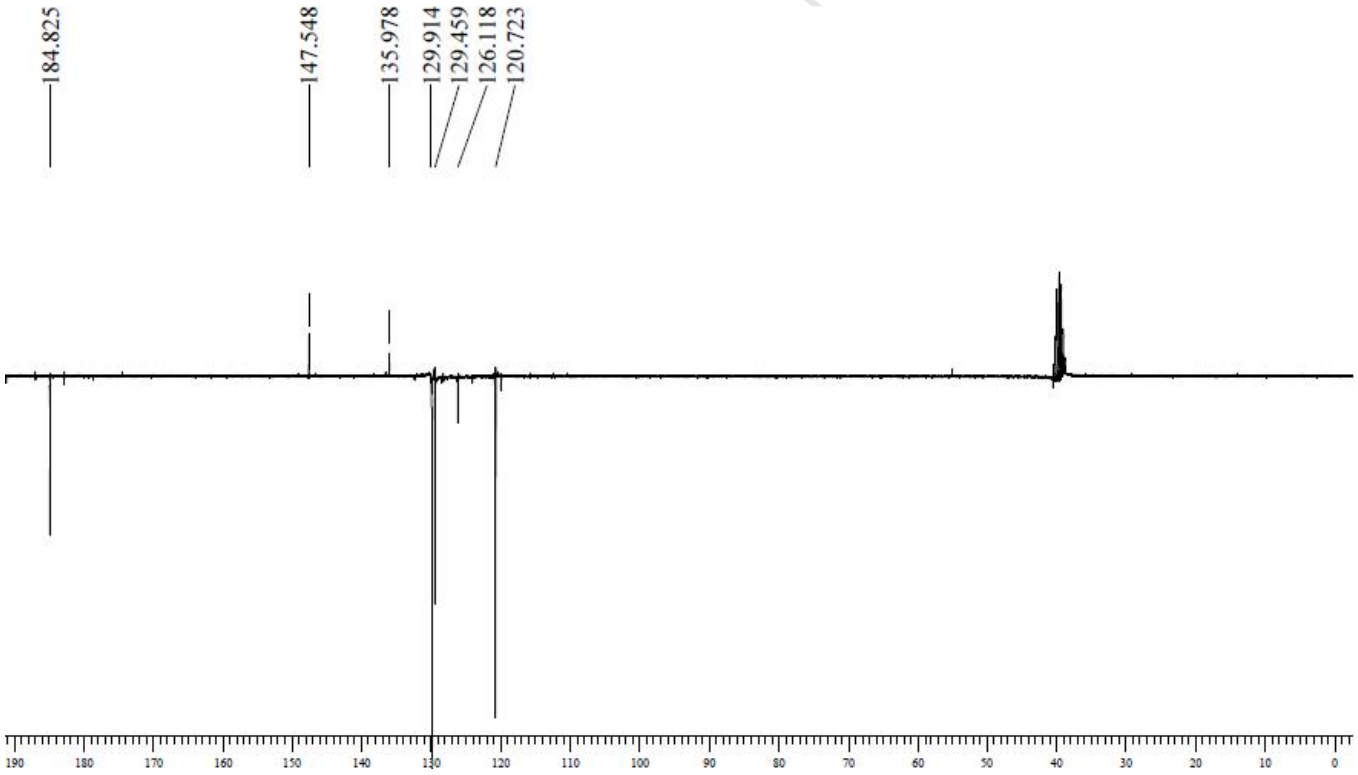
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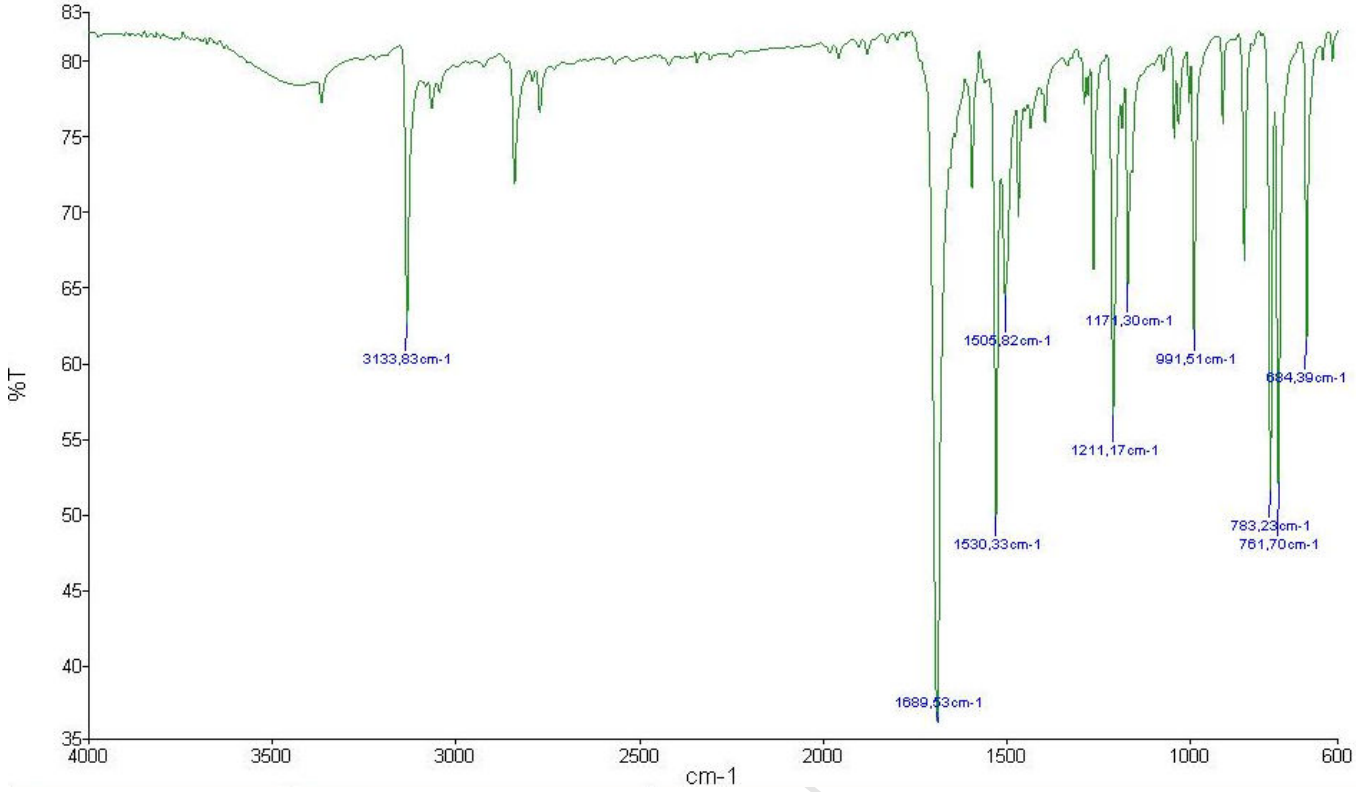

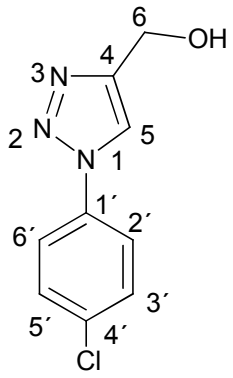
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OH
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N
2
N
5
N
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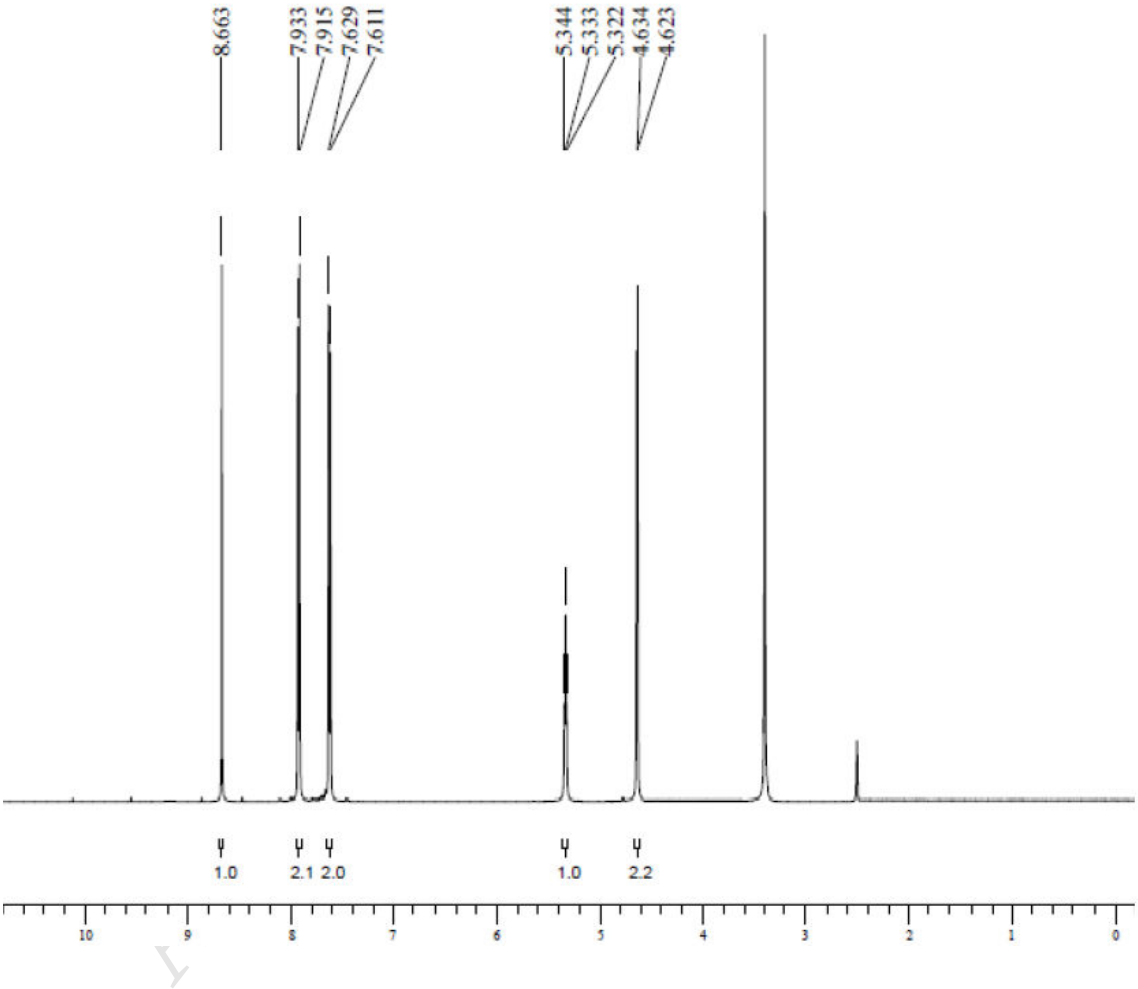
1´
2´
6´
3´
5´
4´
Cl

12c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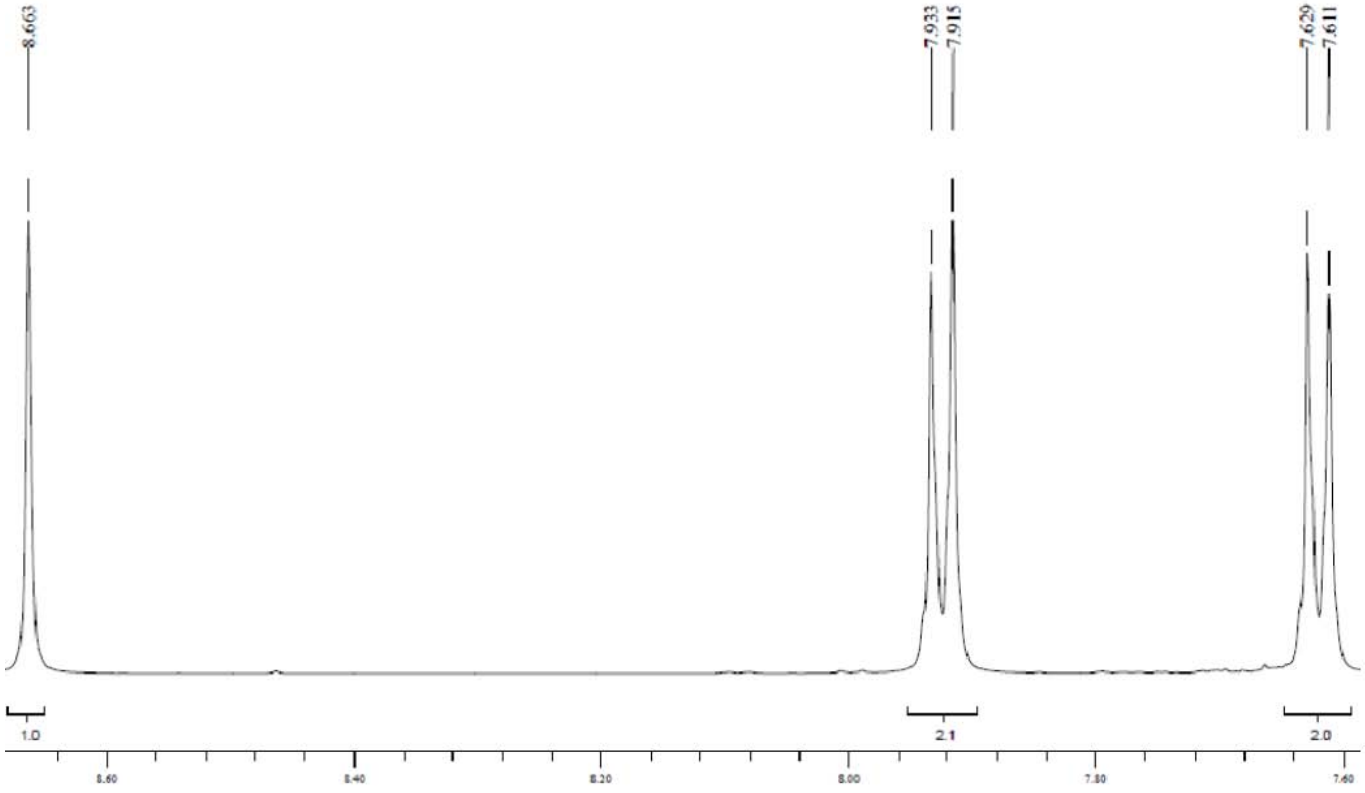

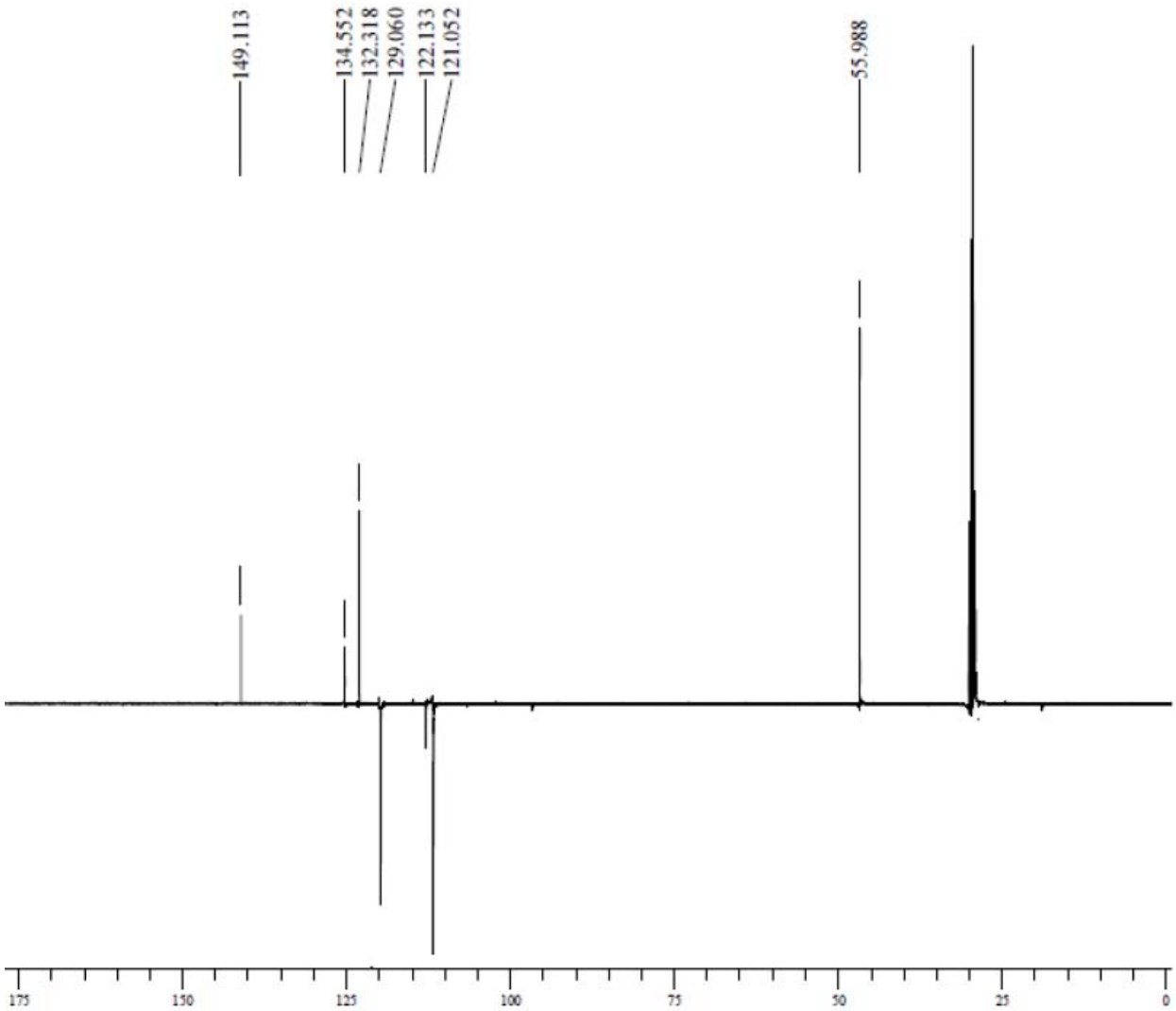
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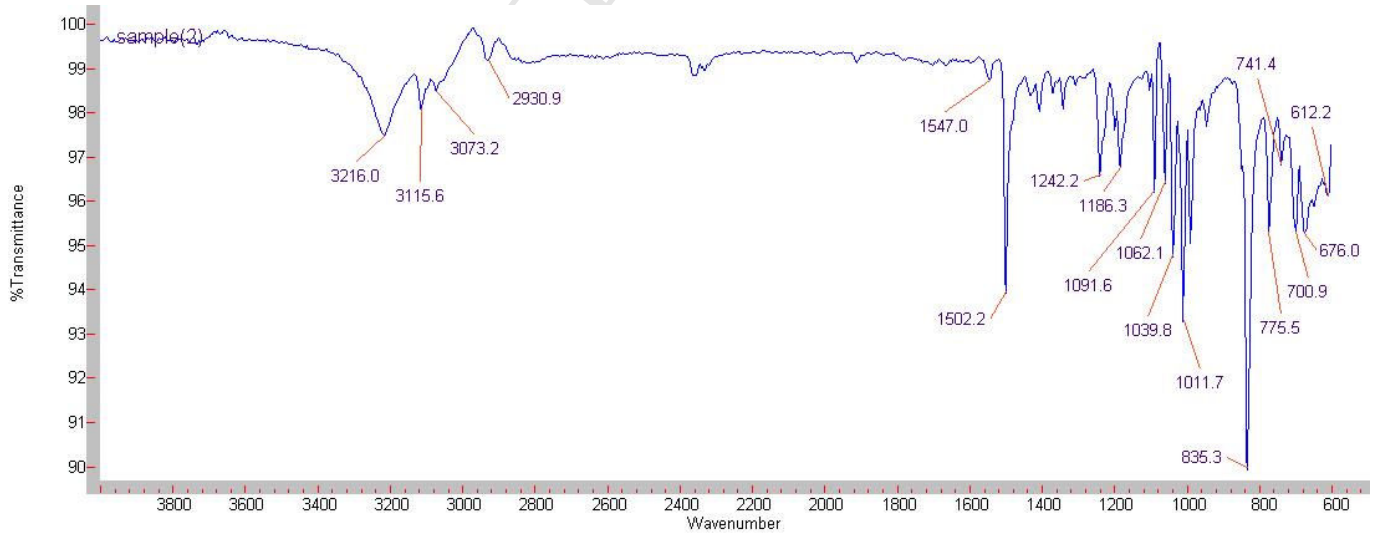
sample(2)
%Transmittance
Wavenumber
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3115.6
3073.2
2930.9
1547.0
1502.2
1242.2
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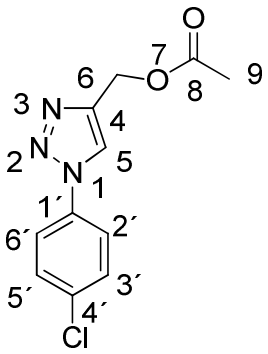
612.2


O
7
6
O
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N
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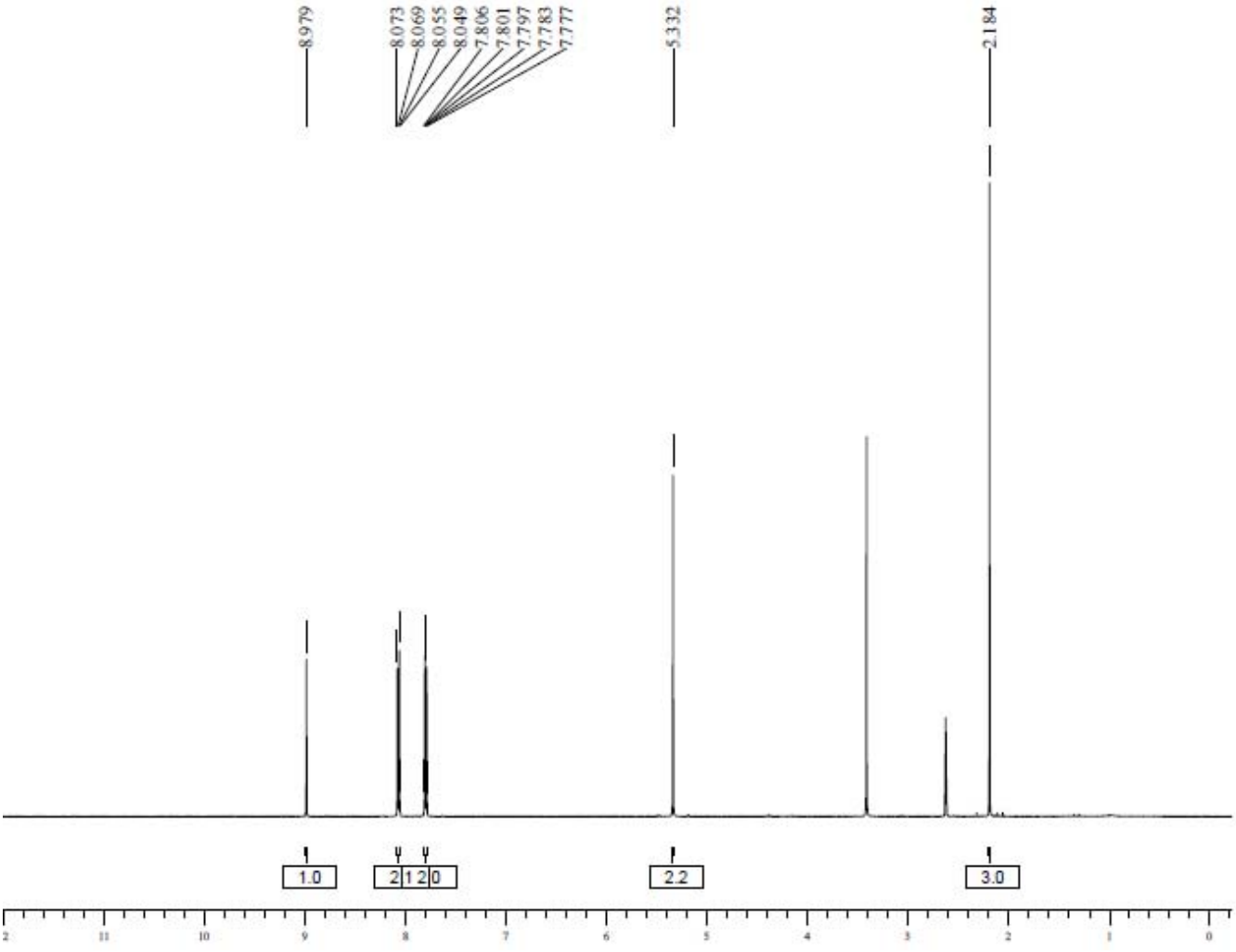
5´
4´
Cl

13d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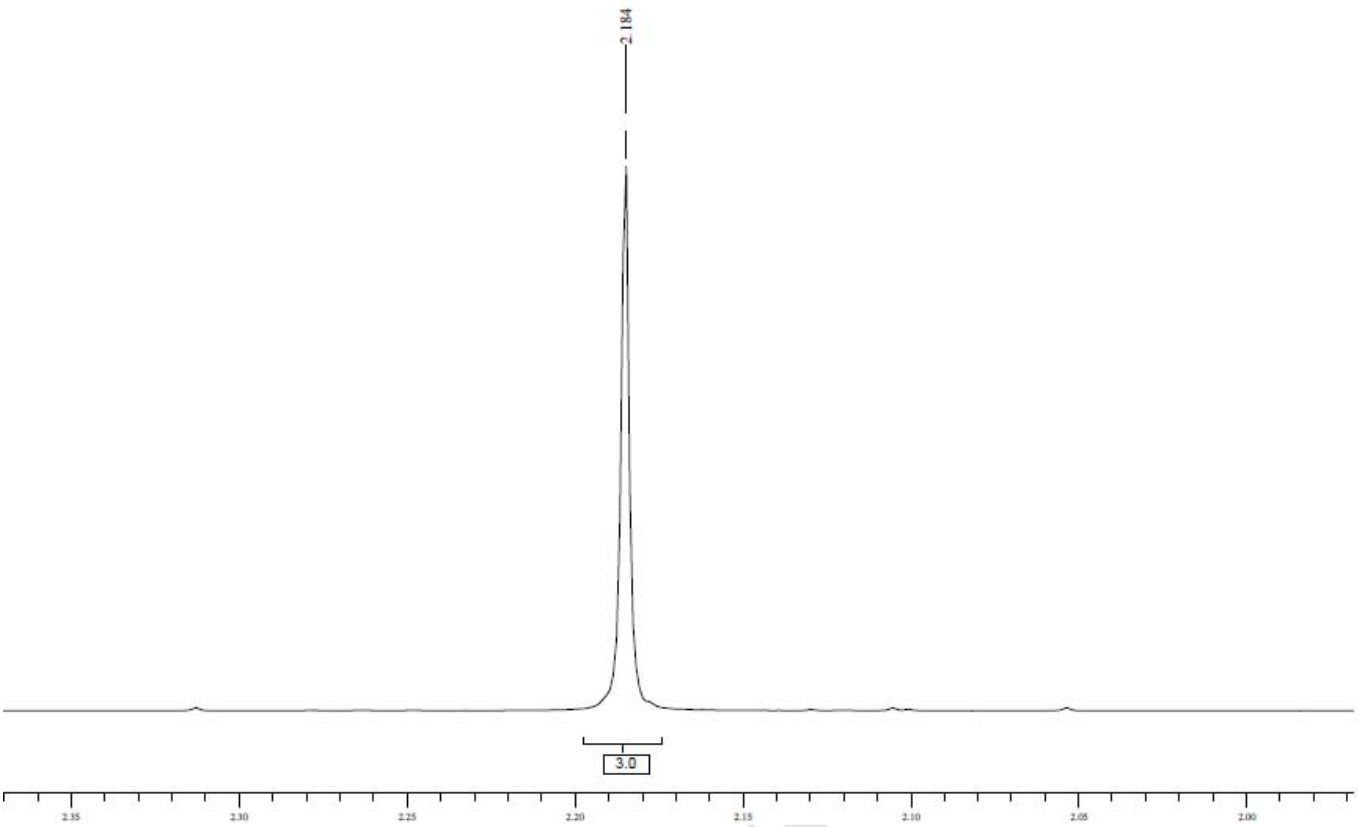
2.2
3.0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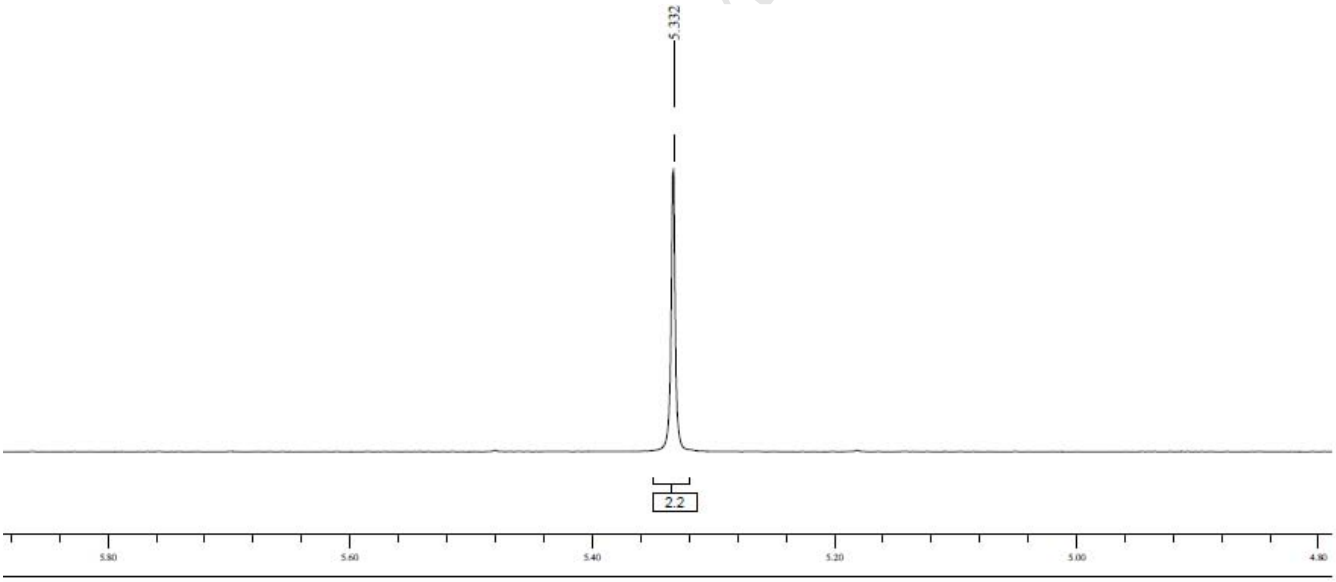
2.00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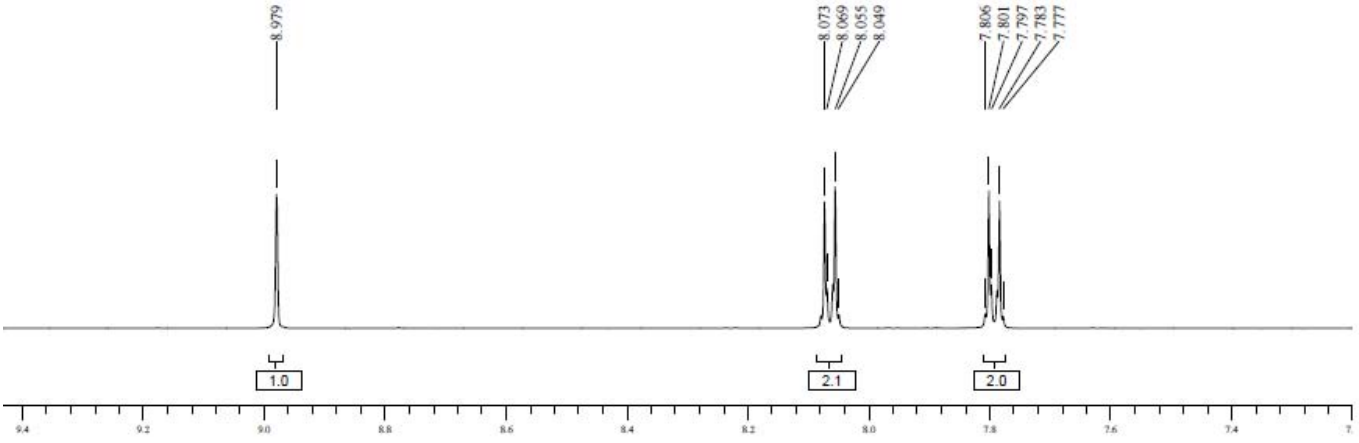
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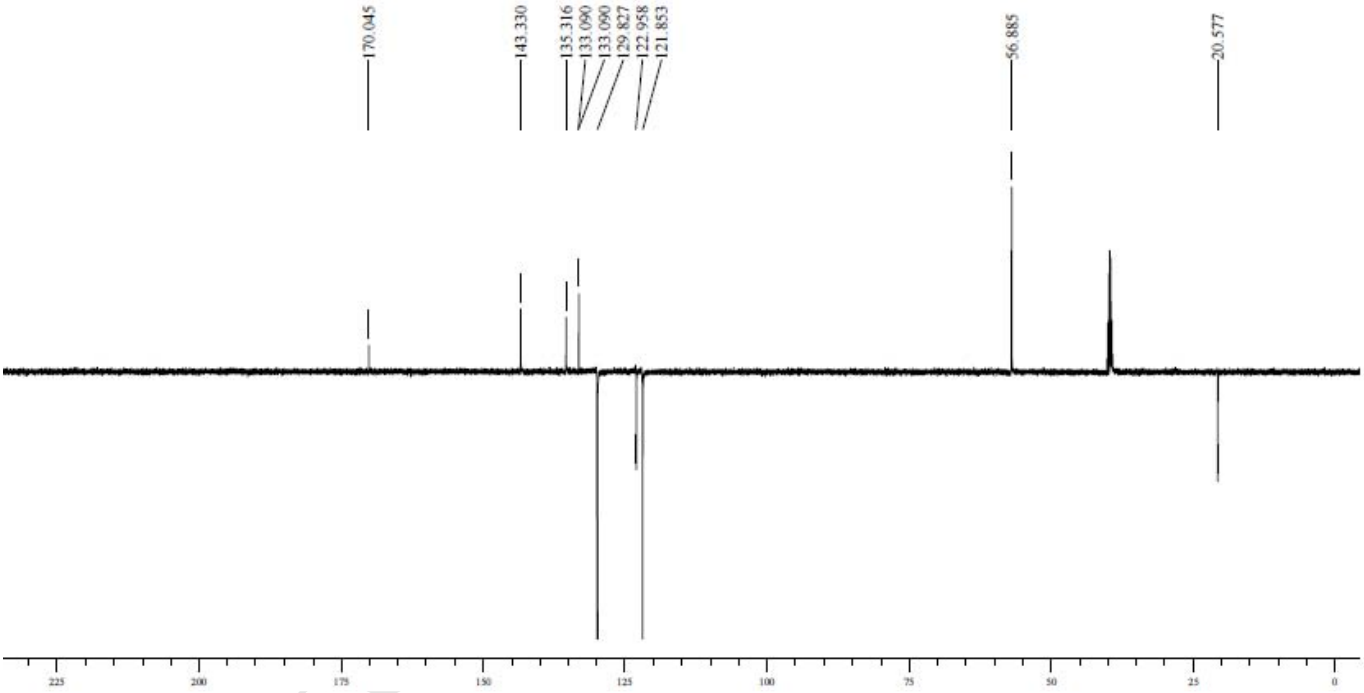
8.4
8.2
8.0
7.8
7.6
7.4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50
25
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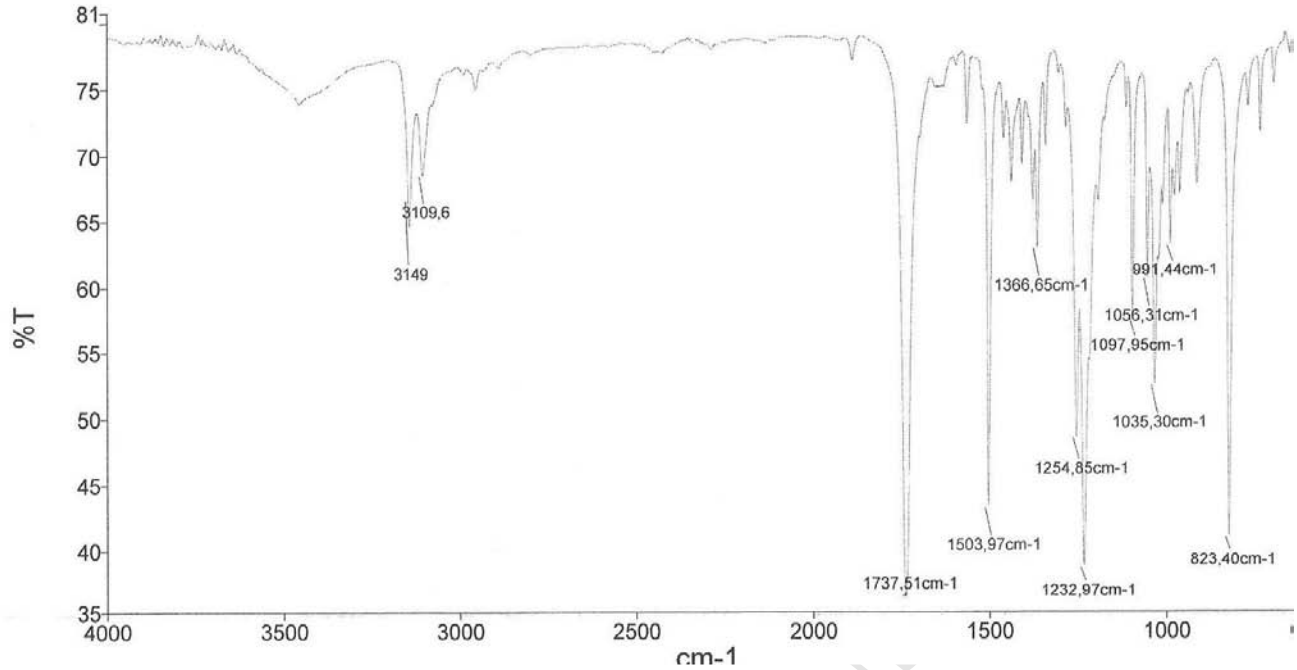

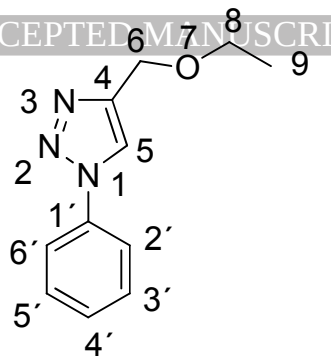

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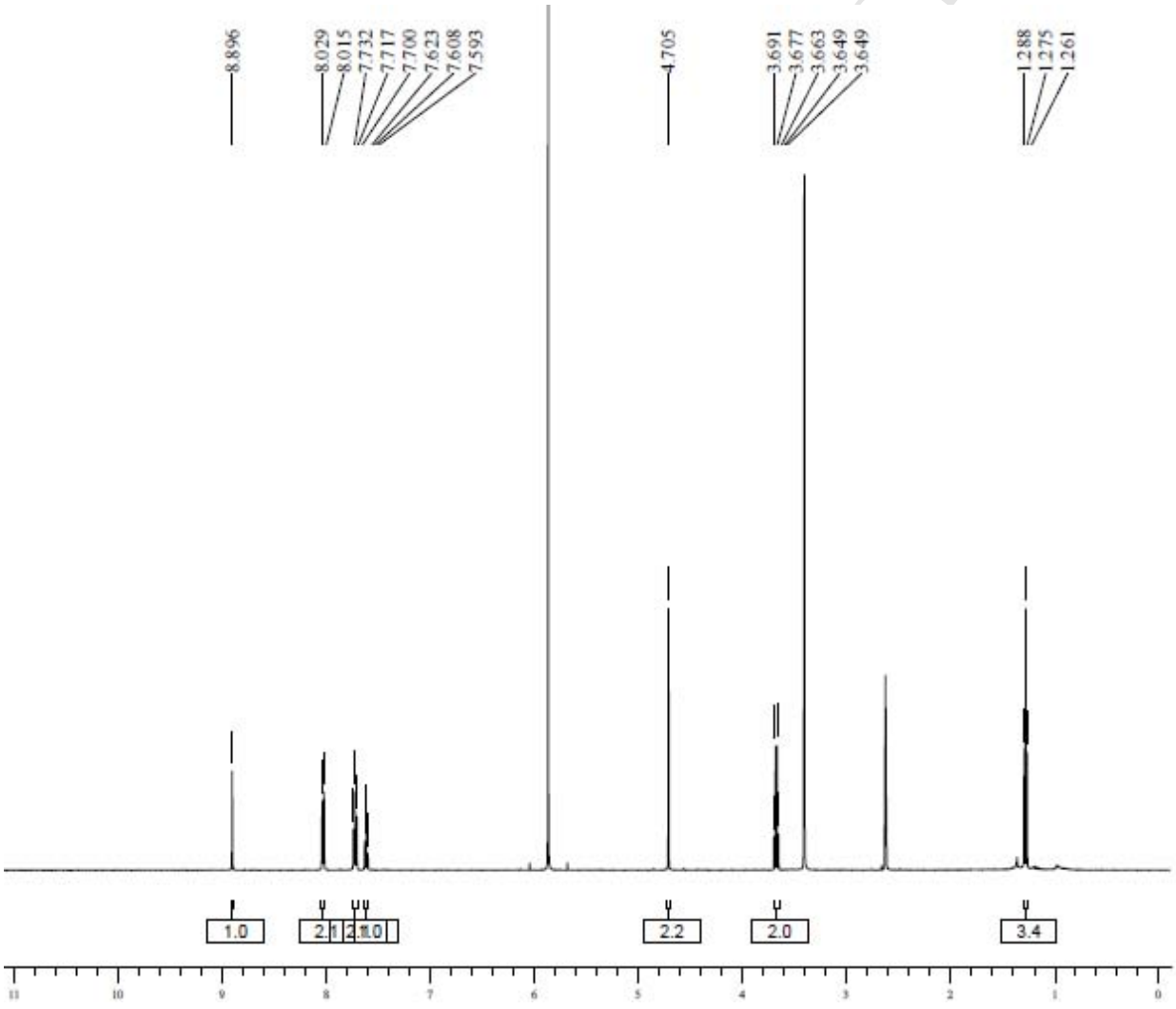

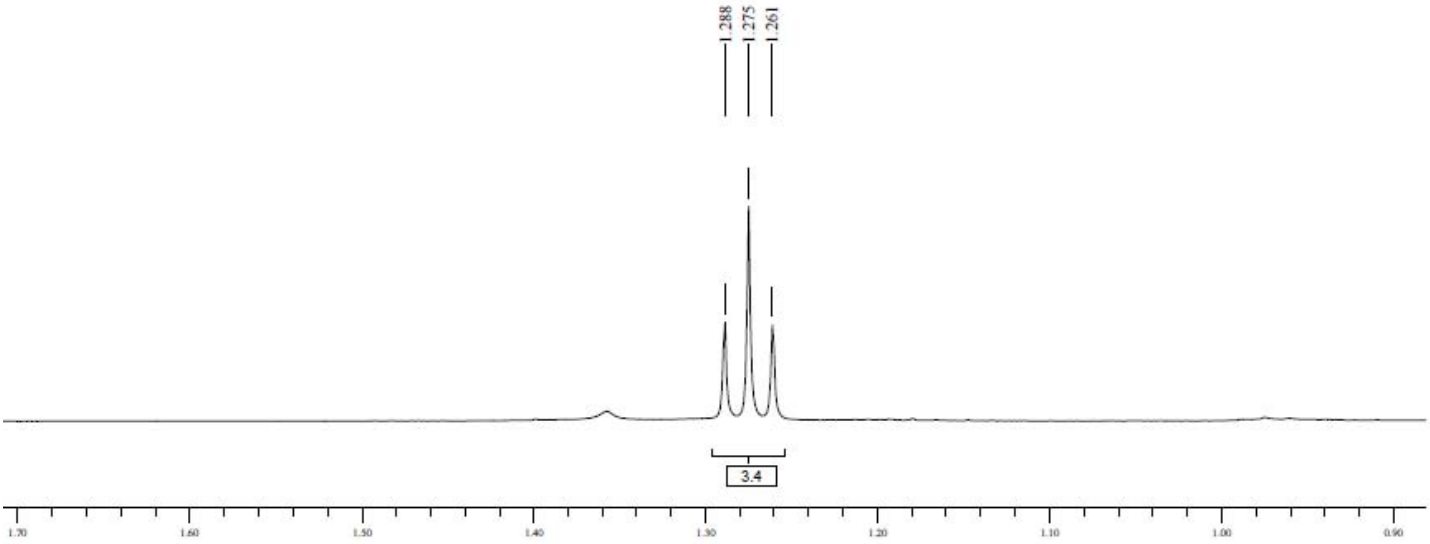
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1.40
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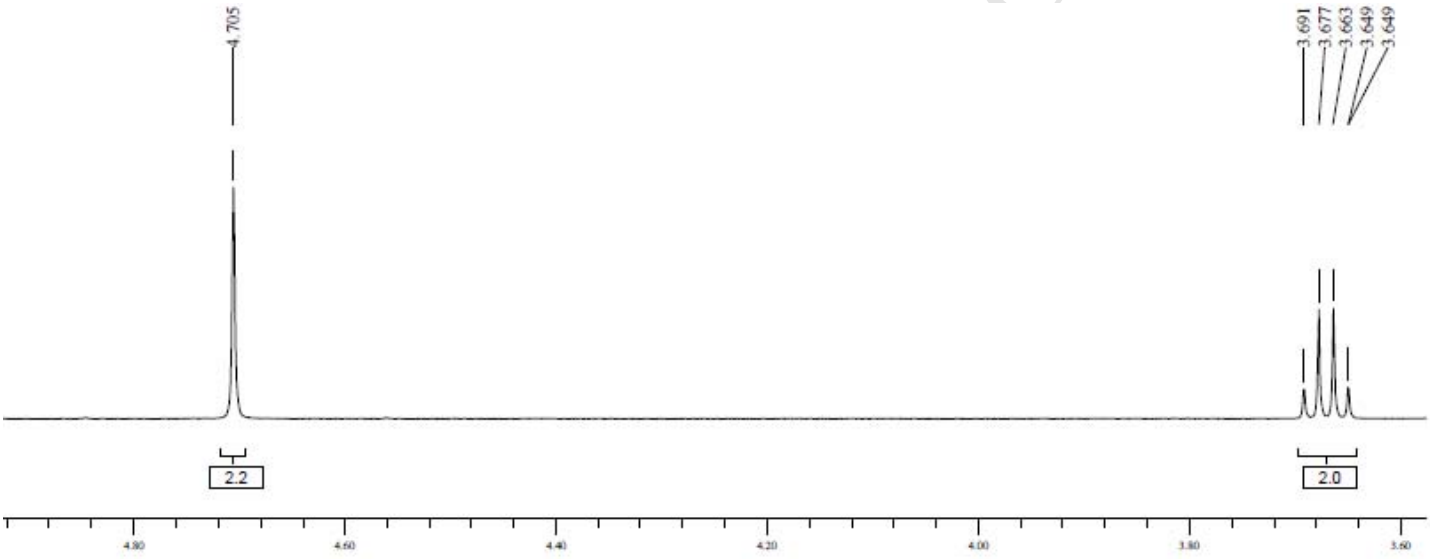
1.20
1.10
1.00
0.90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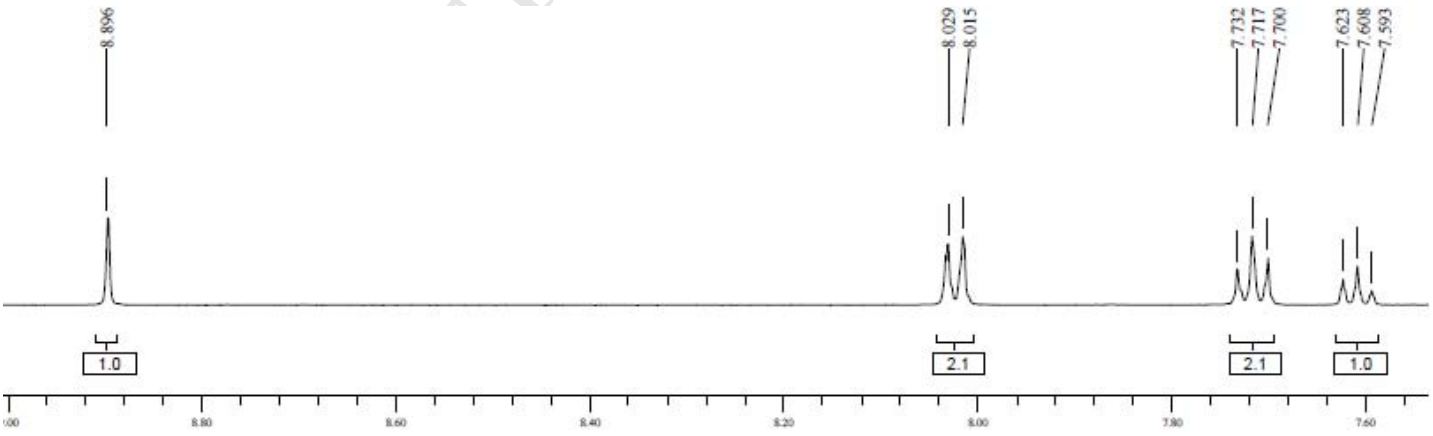
3.60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7.608
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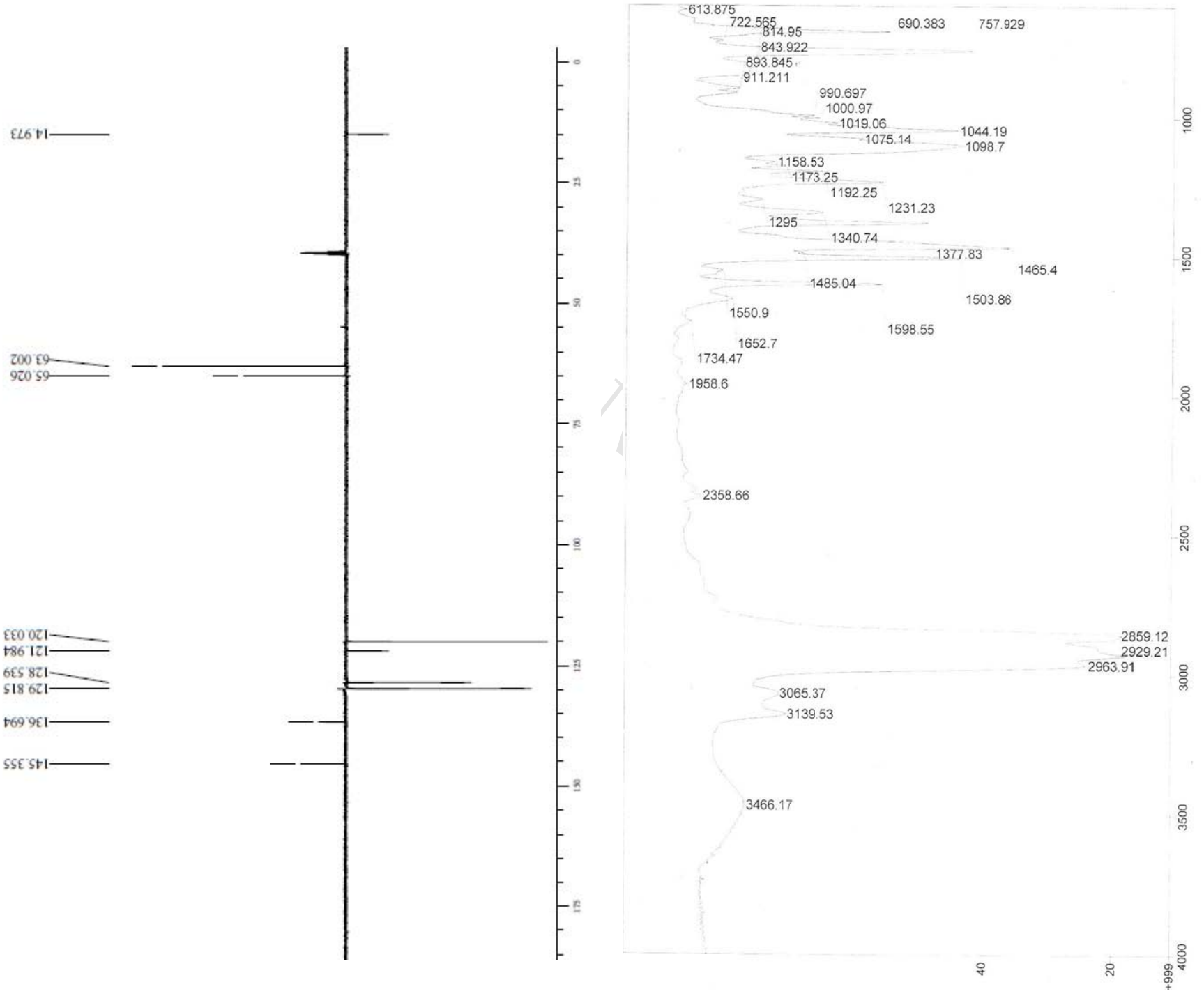
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1000.97
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1044.19
1075.14
1098.7
1158.53
1173.25
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1231.23
1295
1340.74
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1465.4
1485.04
1503.86
1550.9
1598.55
1652.7
1734.47
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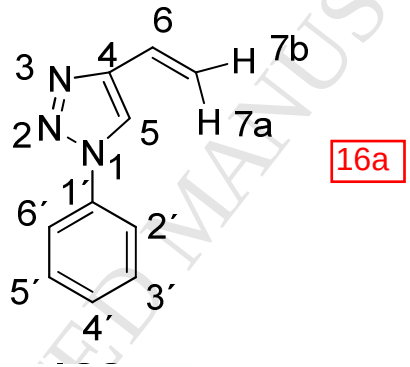

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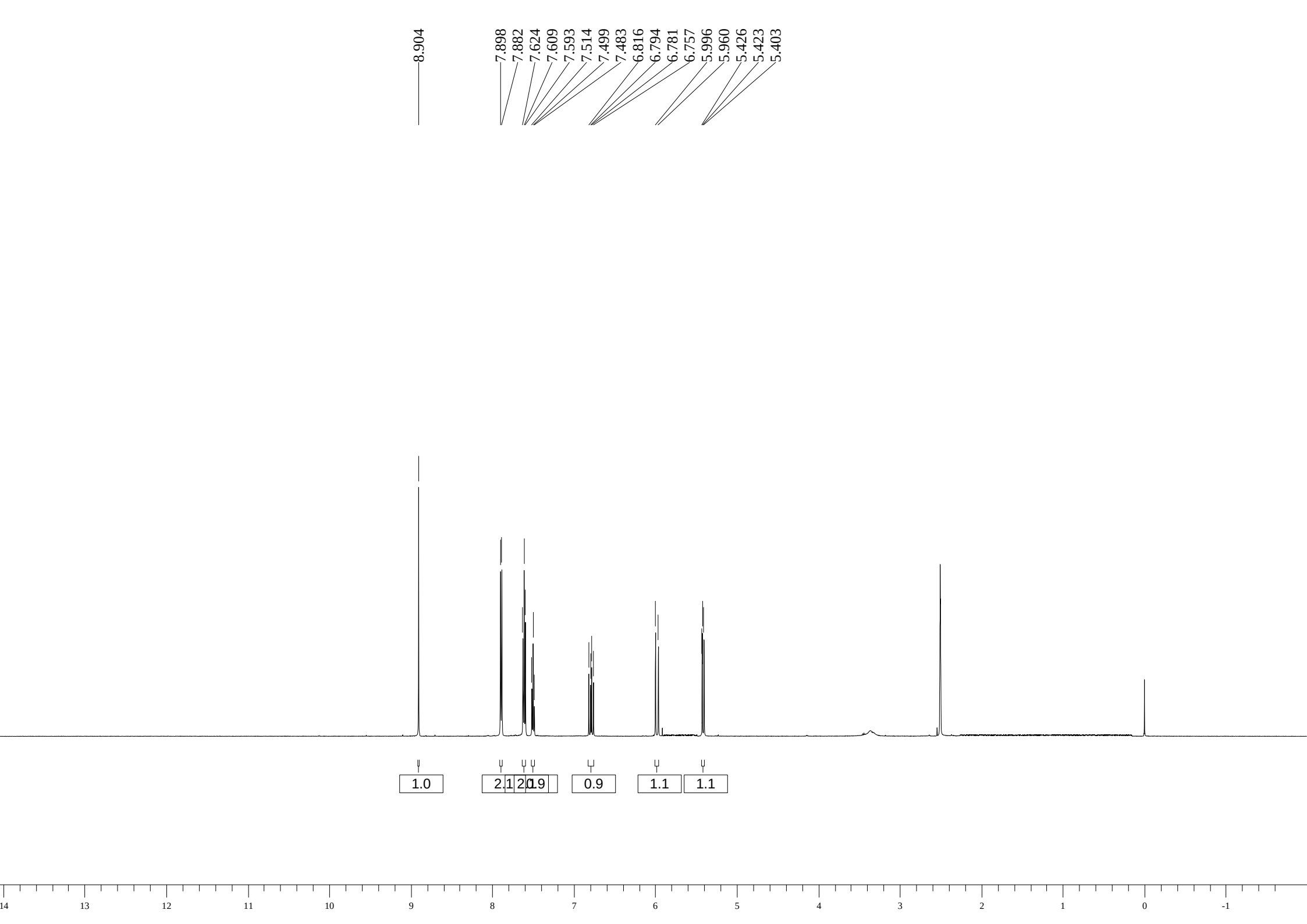
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7.624
7.609
7.593
7.514
7.499
7.483
6.816
6.794
6.781
6.757
5.996
5.960
5.426
5.423
5.403
1.0
2.1
2.0
1.9
0.9
1.1
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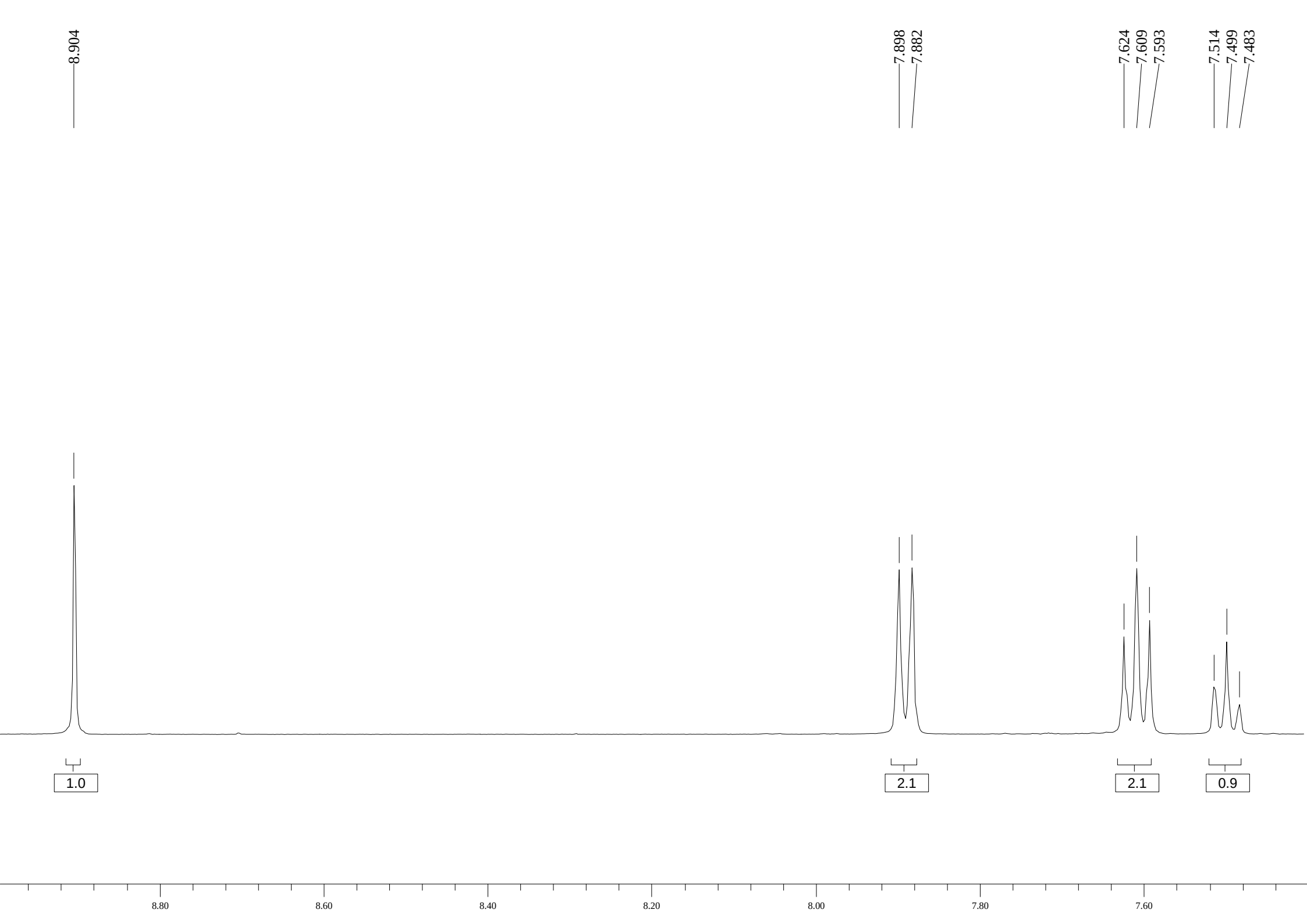
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7.898
7.882
7.624
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7.514
7.499
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8.40
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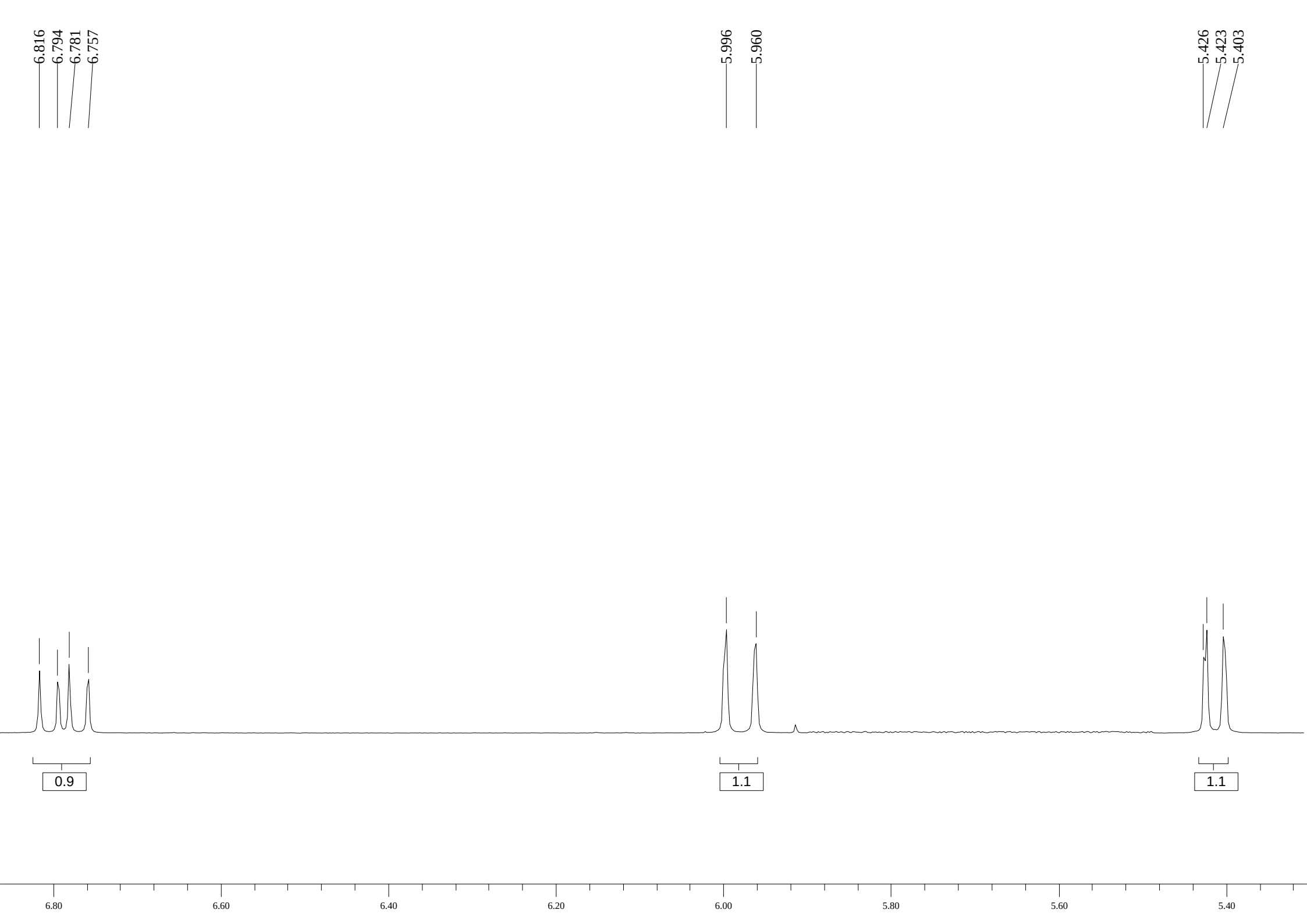
7.60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6.60
6.40
6.20
6.00
5.80
5.60
5.40


146.259
136.613
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125.732
120.059
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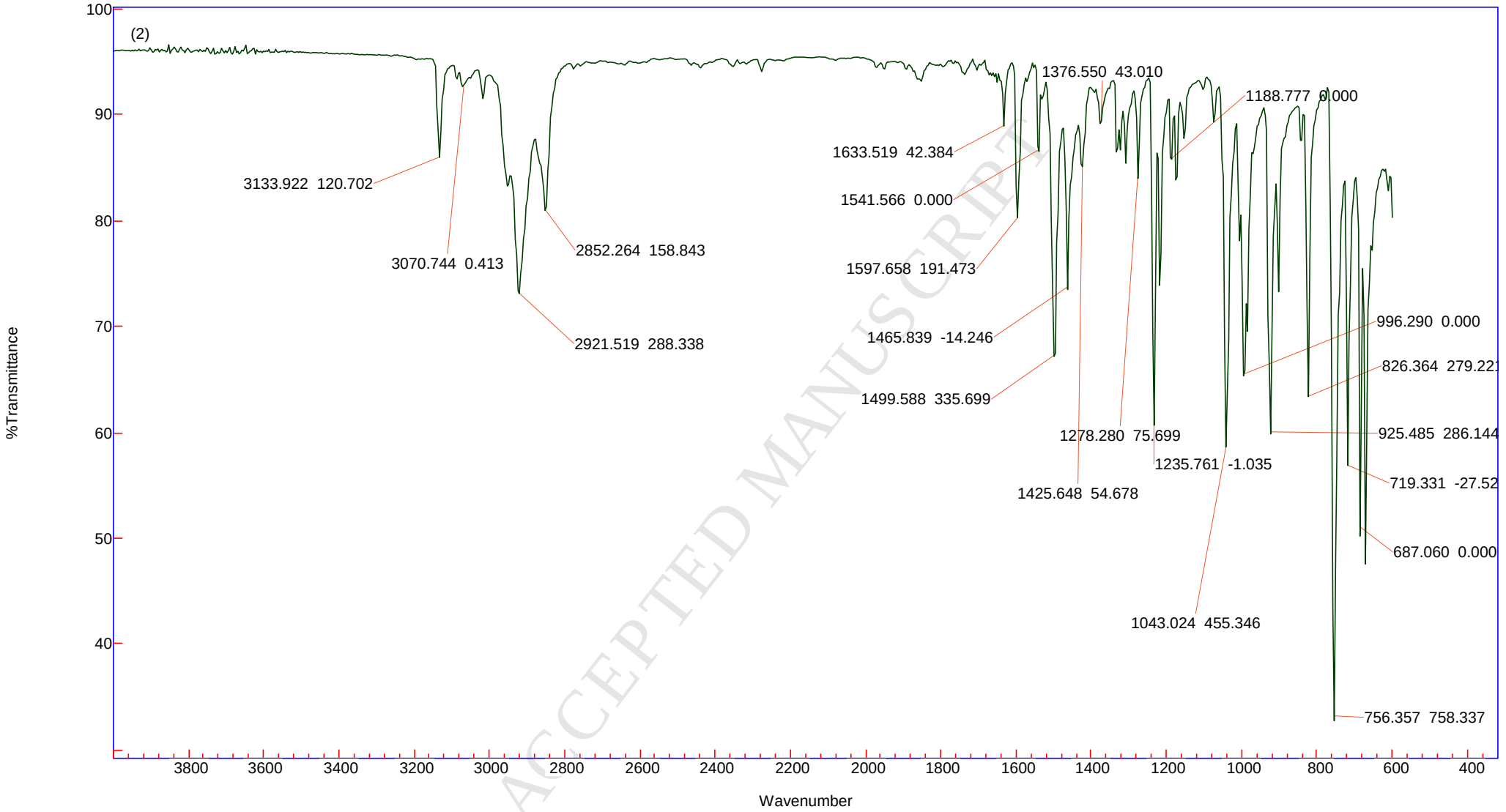
200
175
150
125
100
75
50
25
0

Agilent Resolutions Pro



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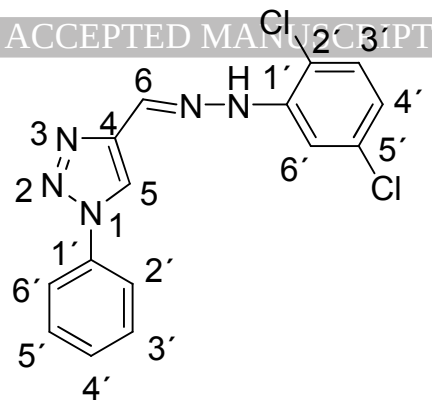

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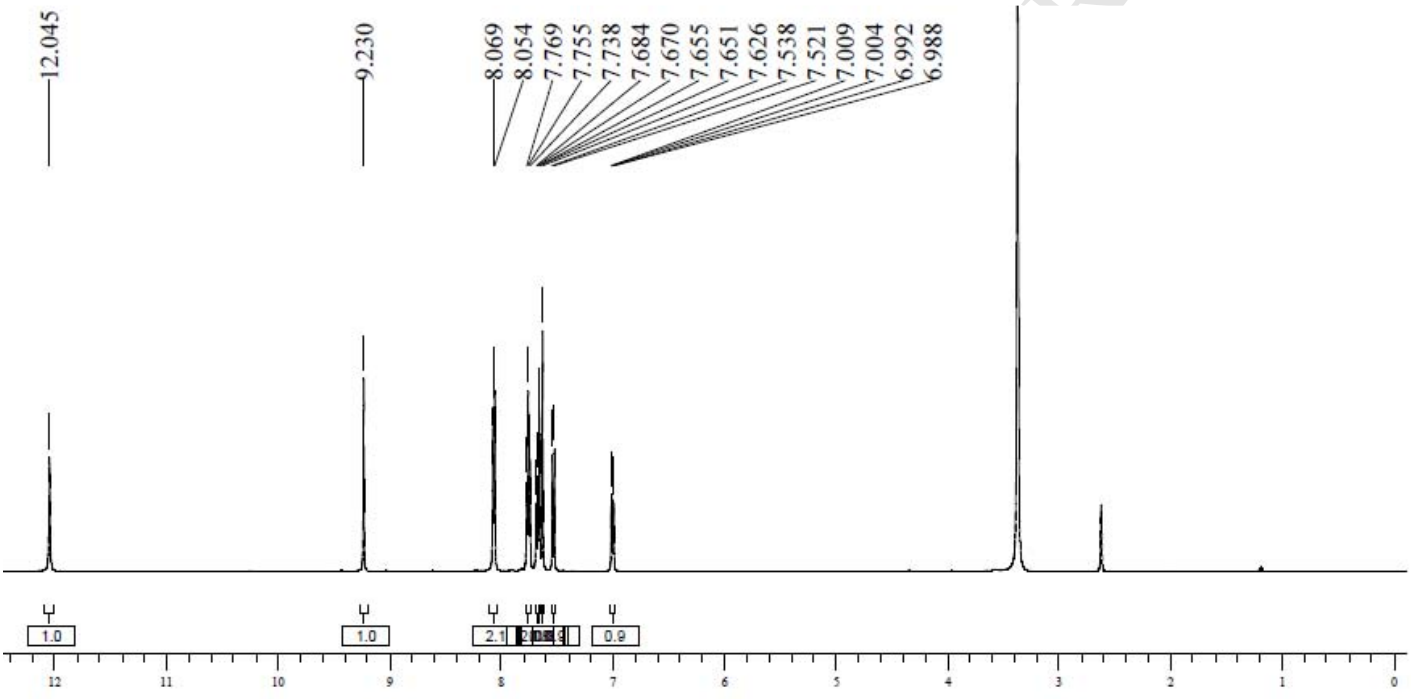

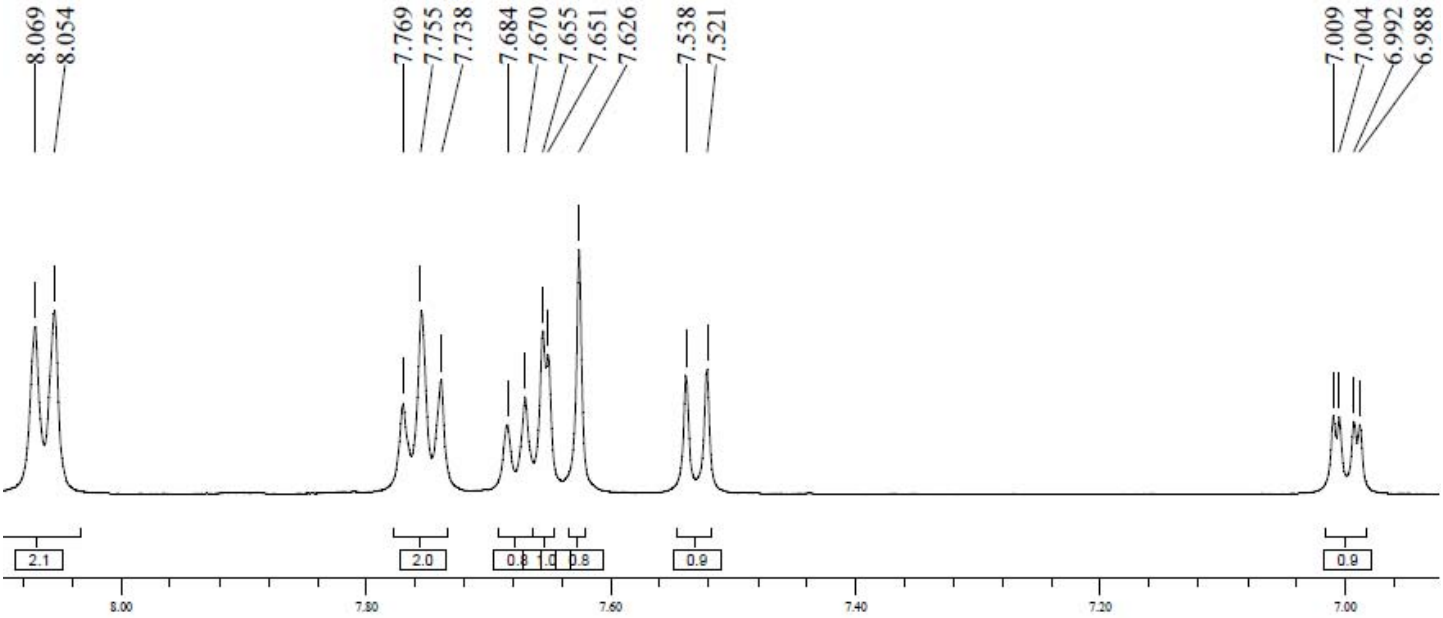

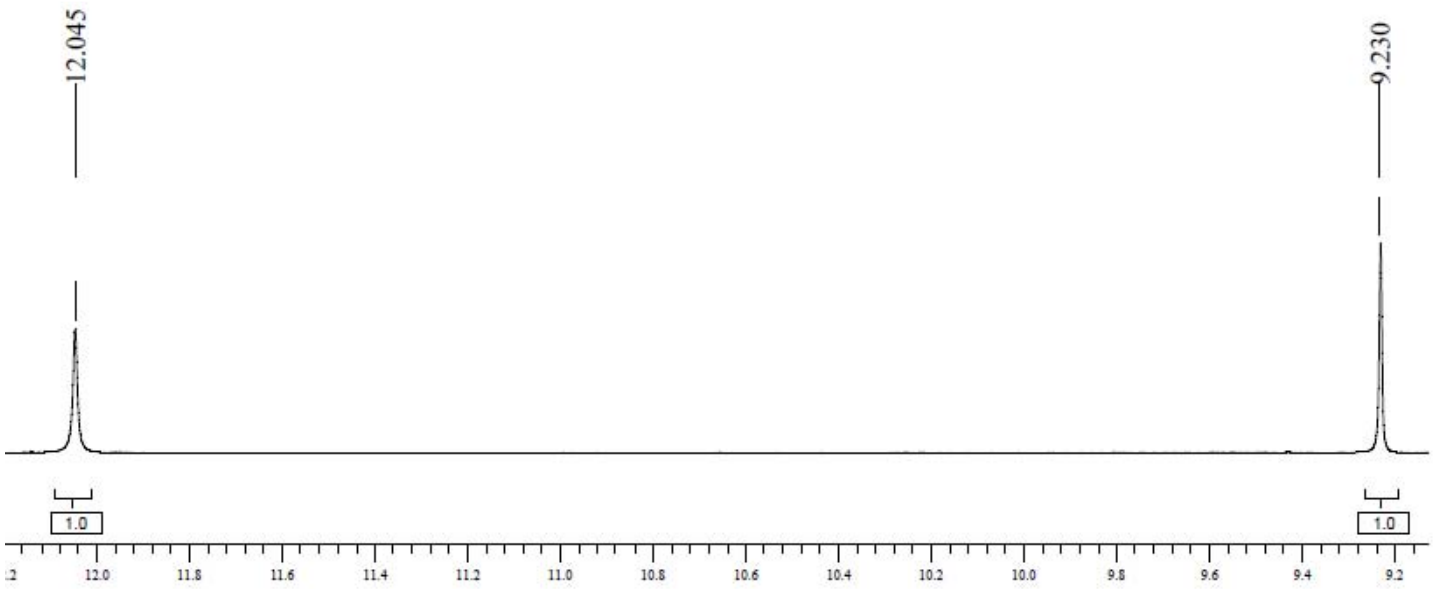
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11.0
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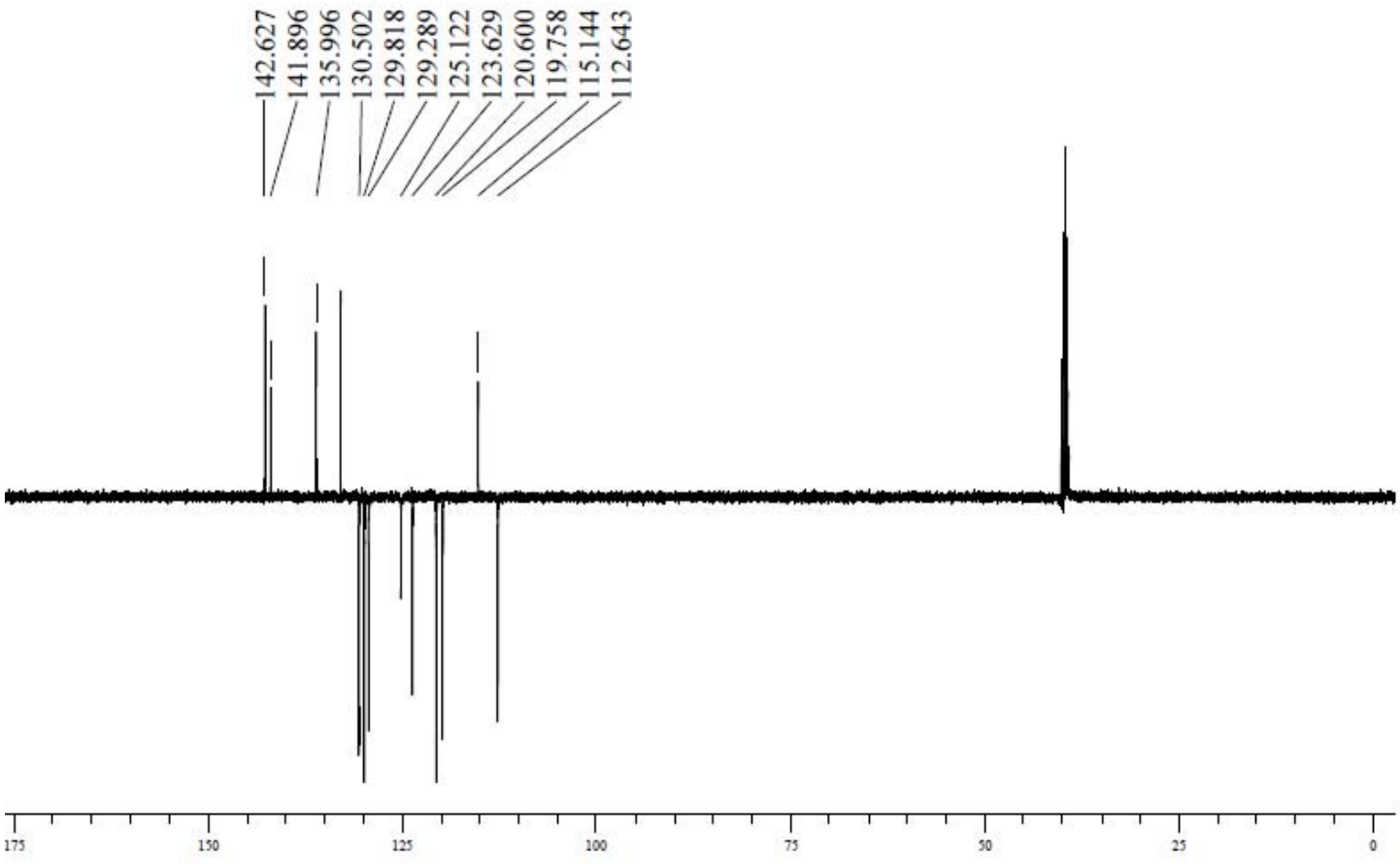
10.4
10.2
10.0
9.8
9.6
9.4
9.2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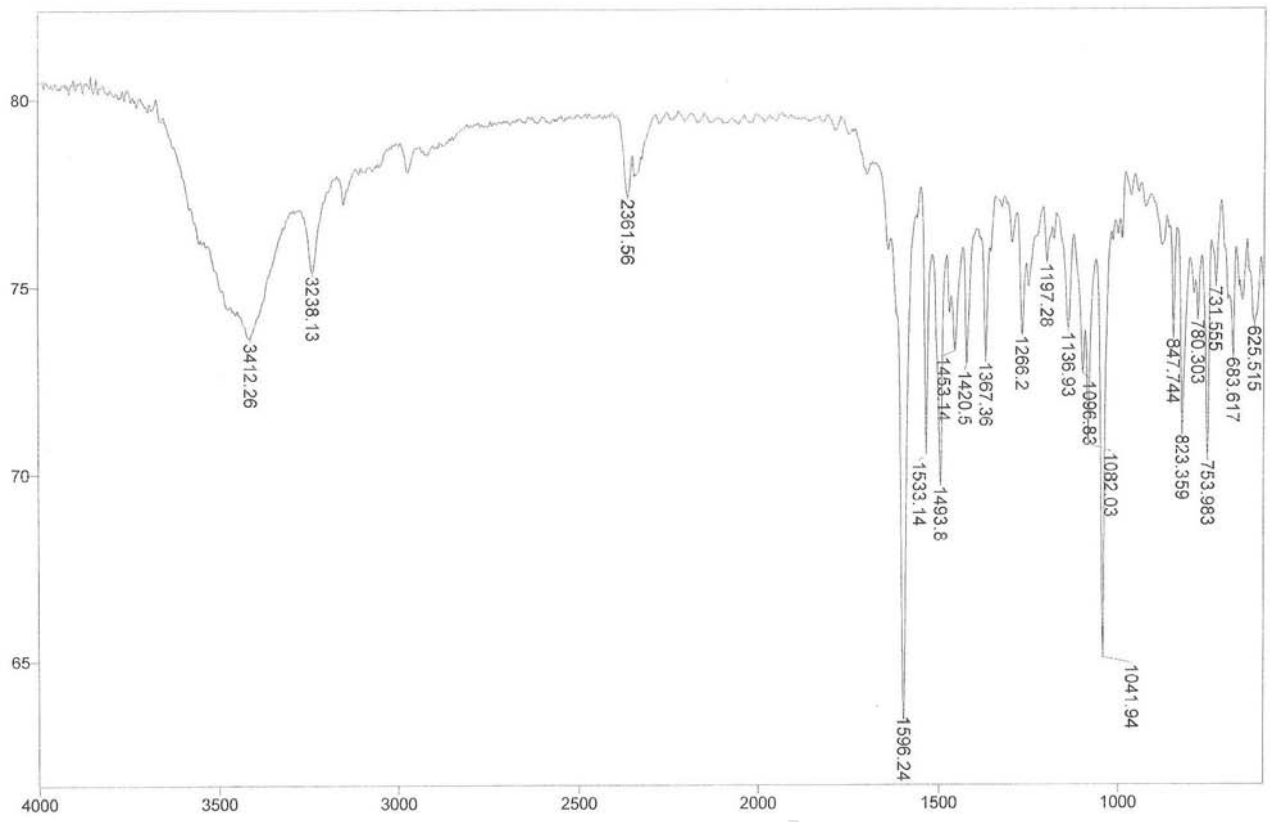

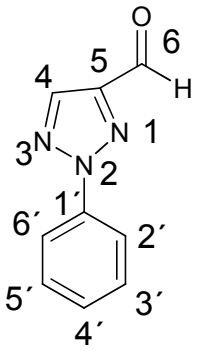
O
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5
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H
N
1
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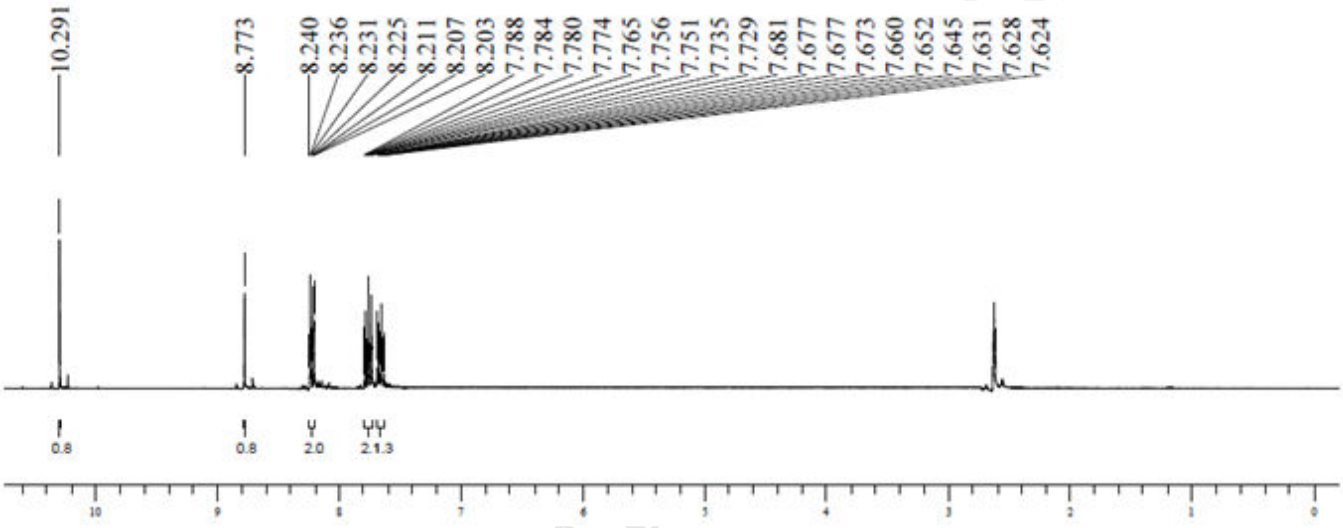
N
N
2
1′
6′
2′
5′
3′
4′

18a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2.0
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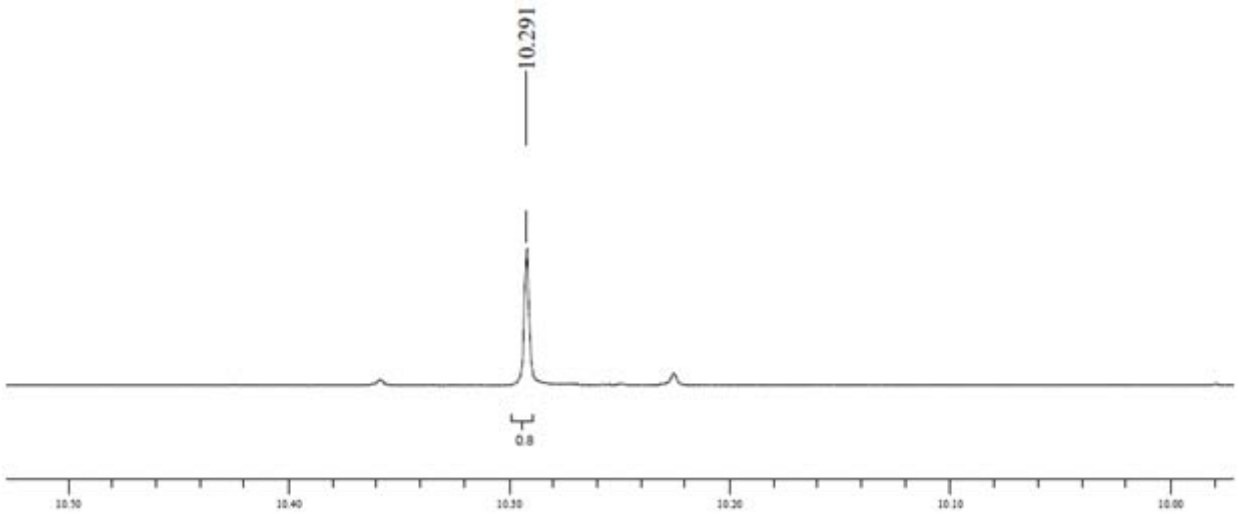
3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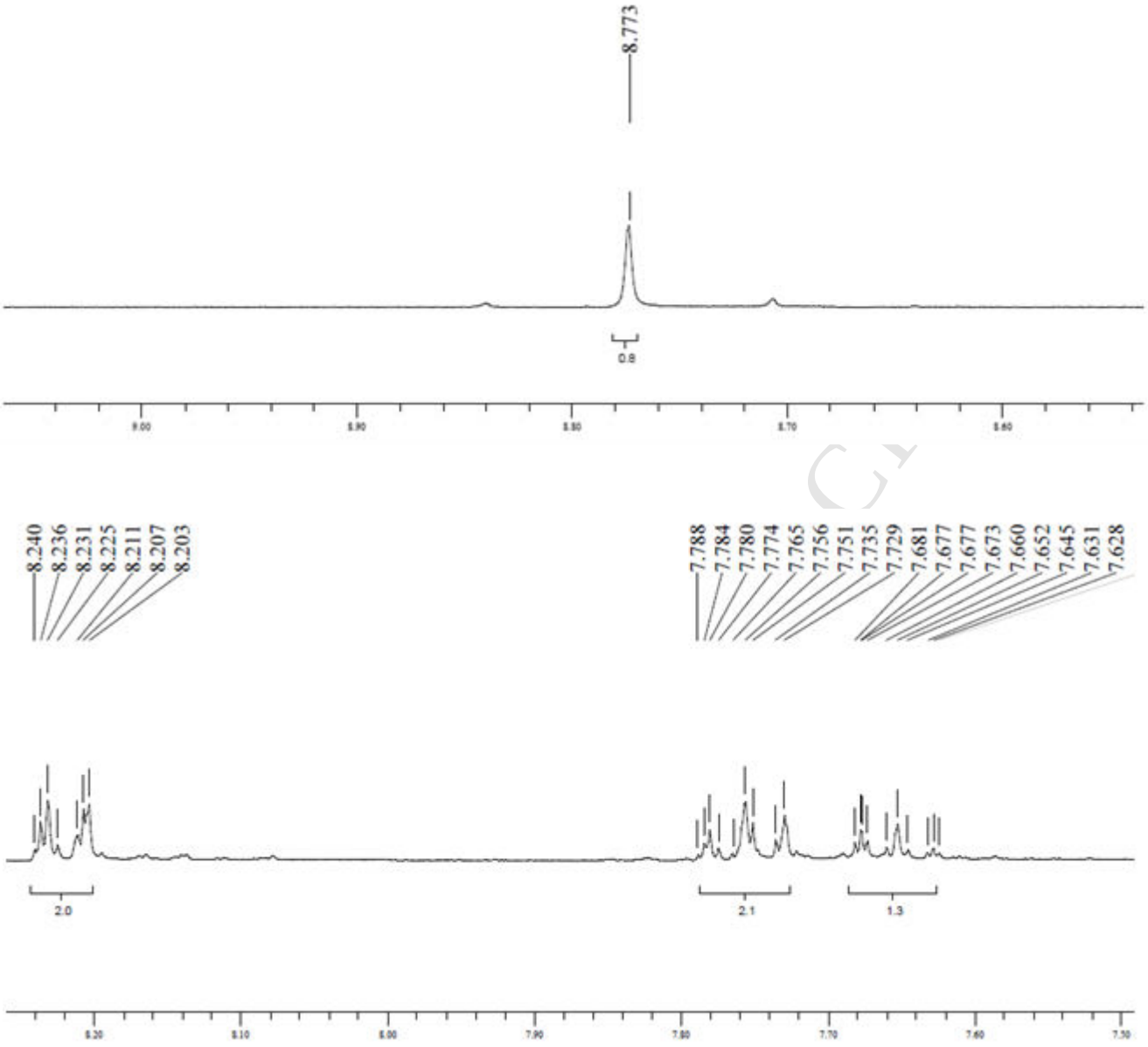

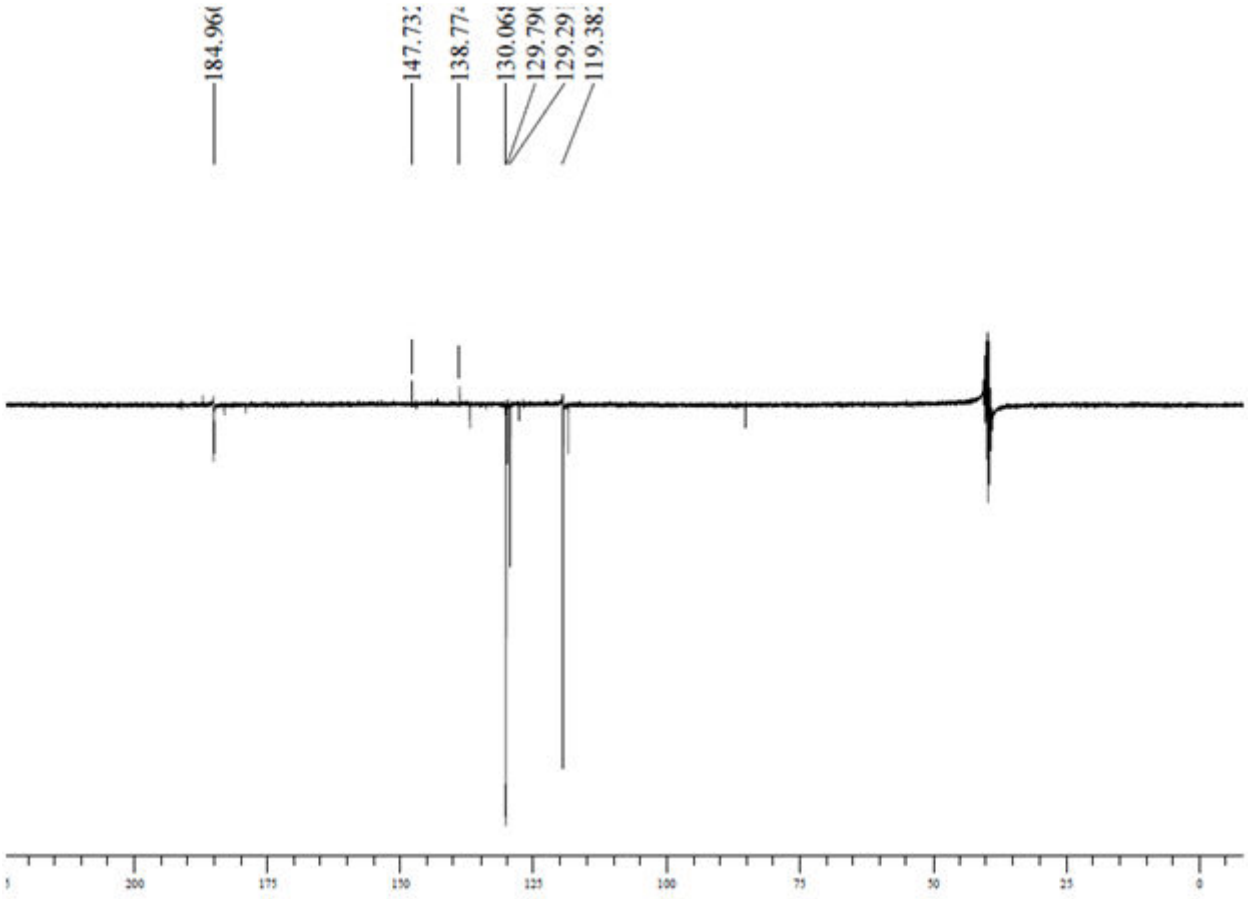
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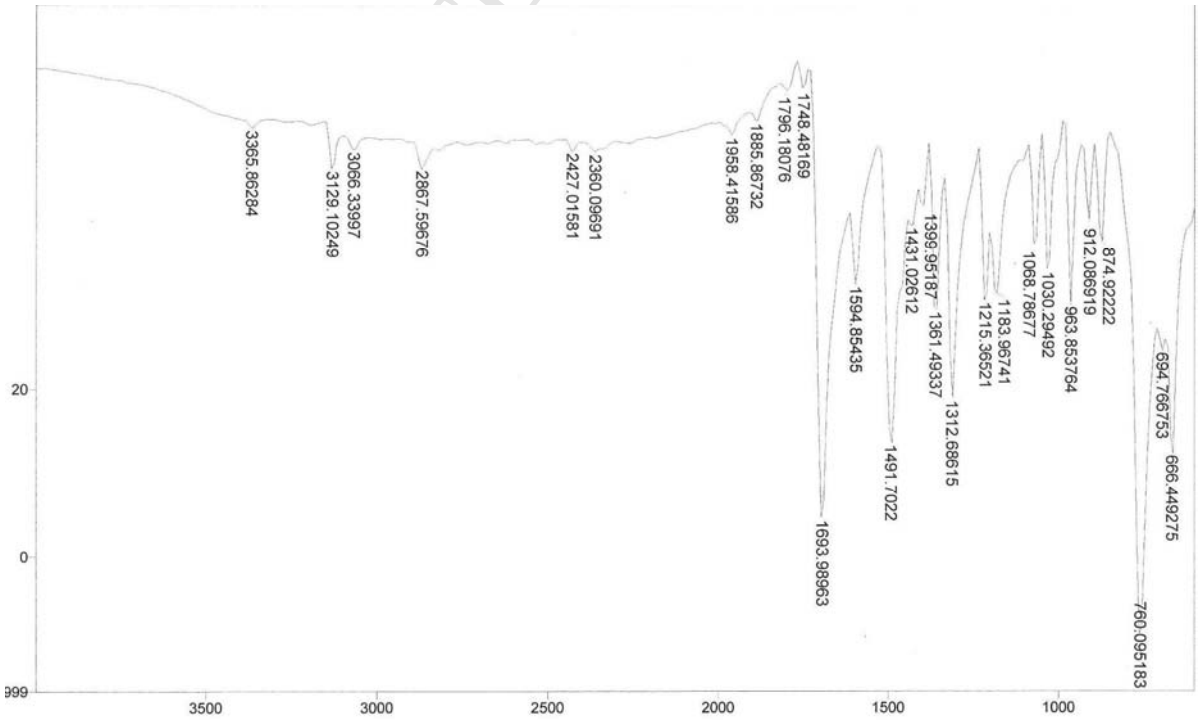
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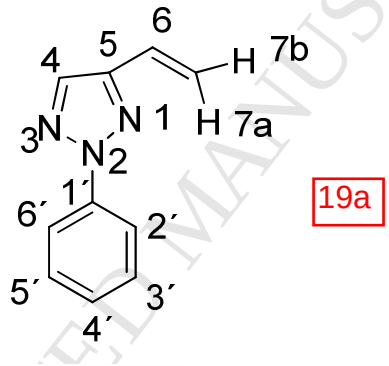

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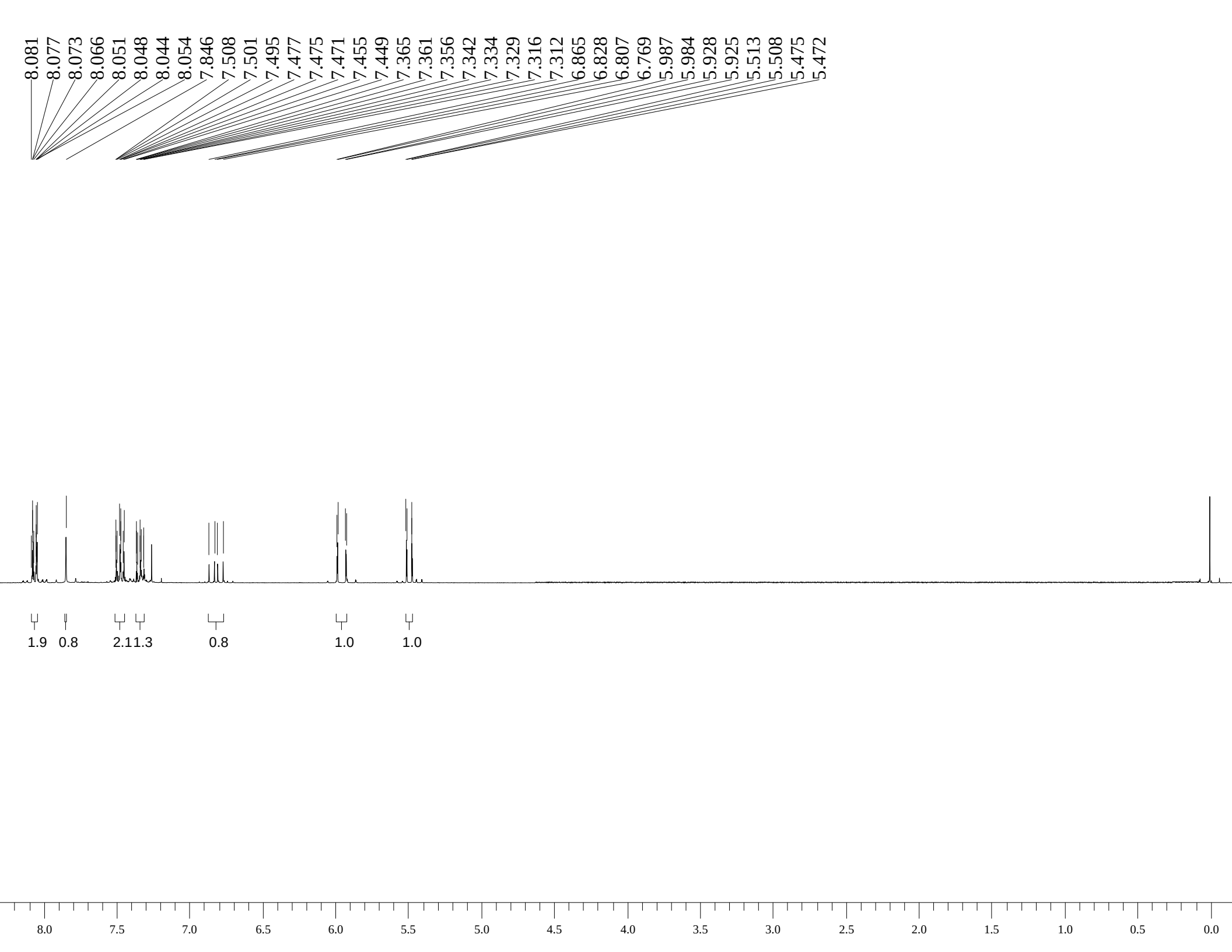
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7.477
7.475
7.471
7.455
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7.356
7.342
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7.329
7.316
7.312
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6.807
6.769
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5.984
5.928
5.925
5.513
5.508
5.475
5.472
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1.3
0.8
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1.0
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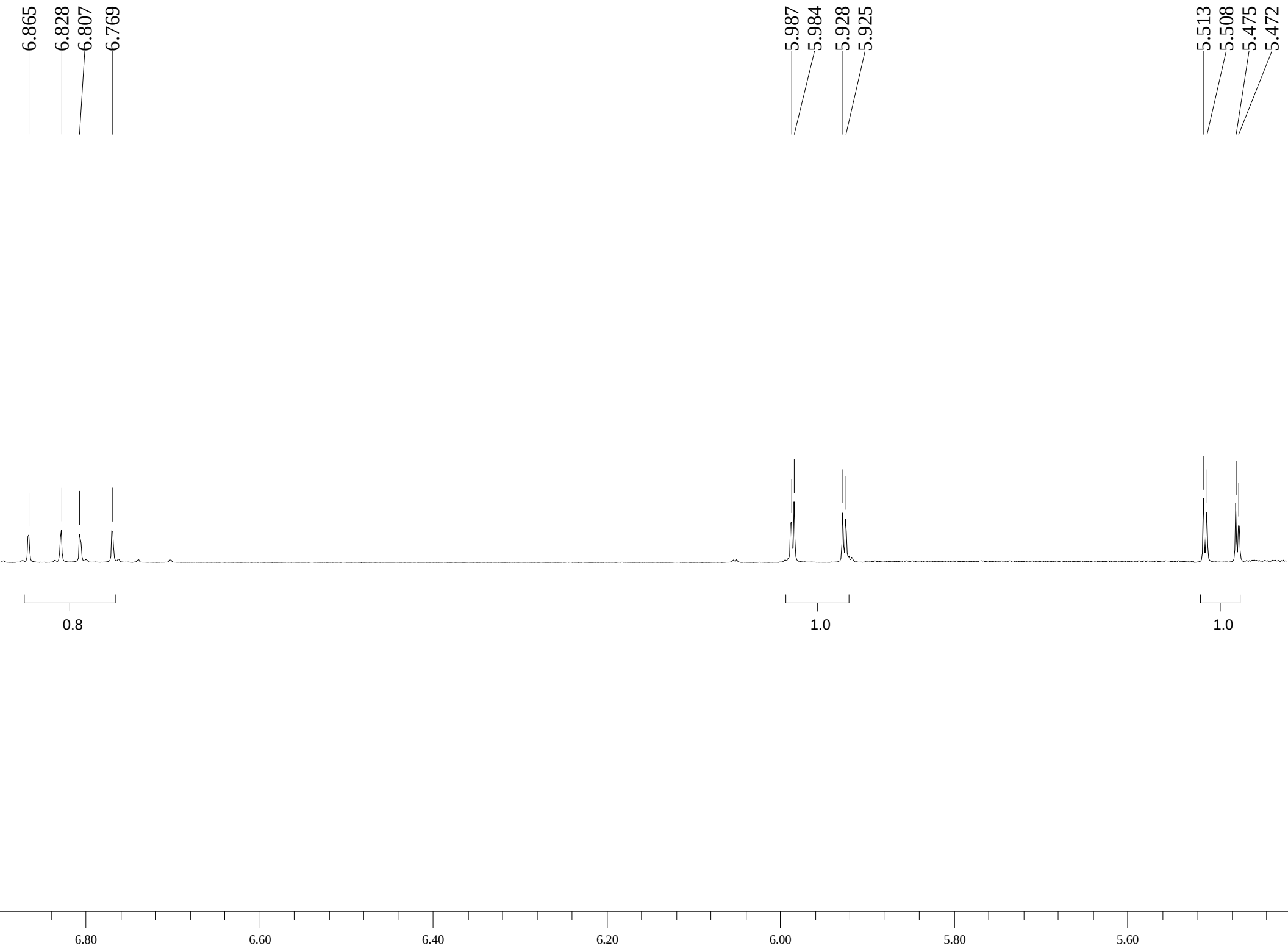
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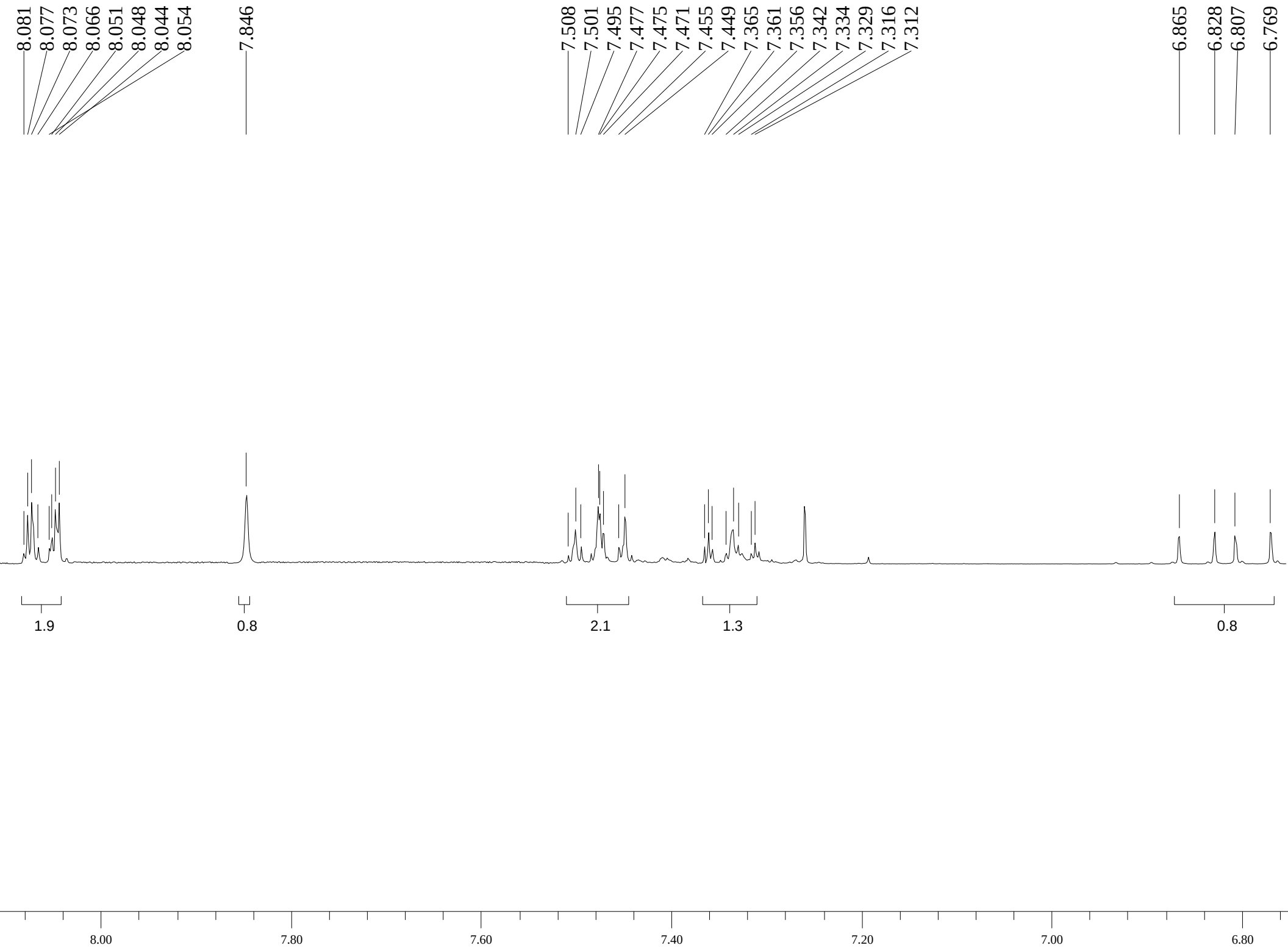
5.80
5.60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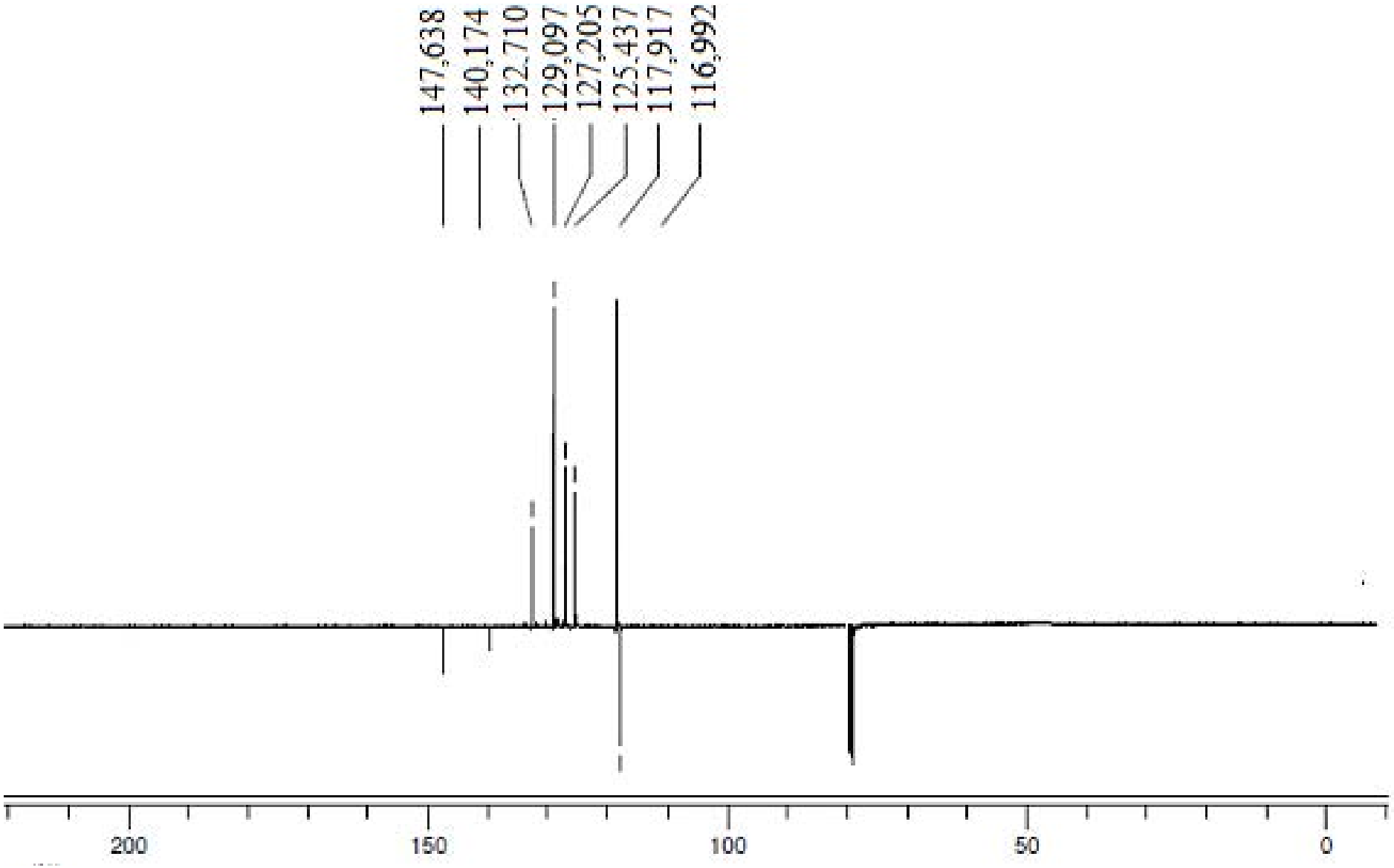
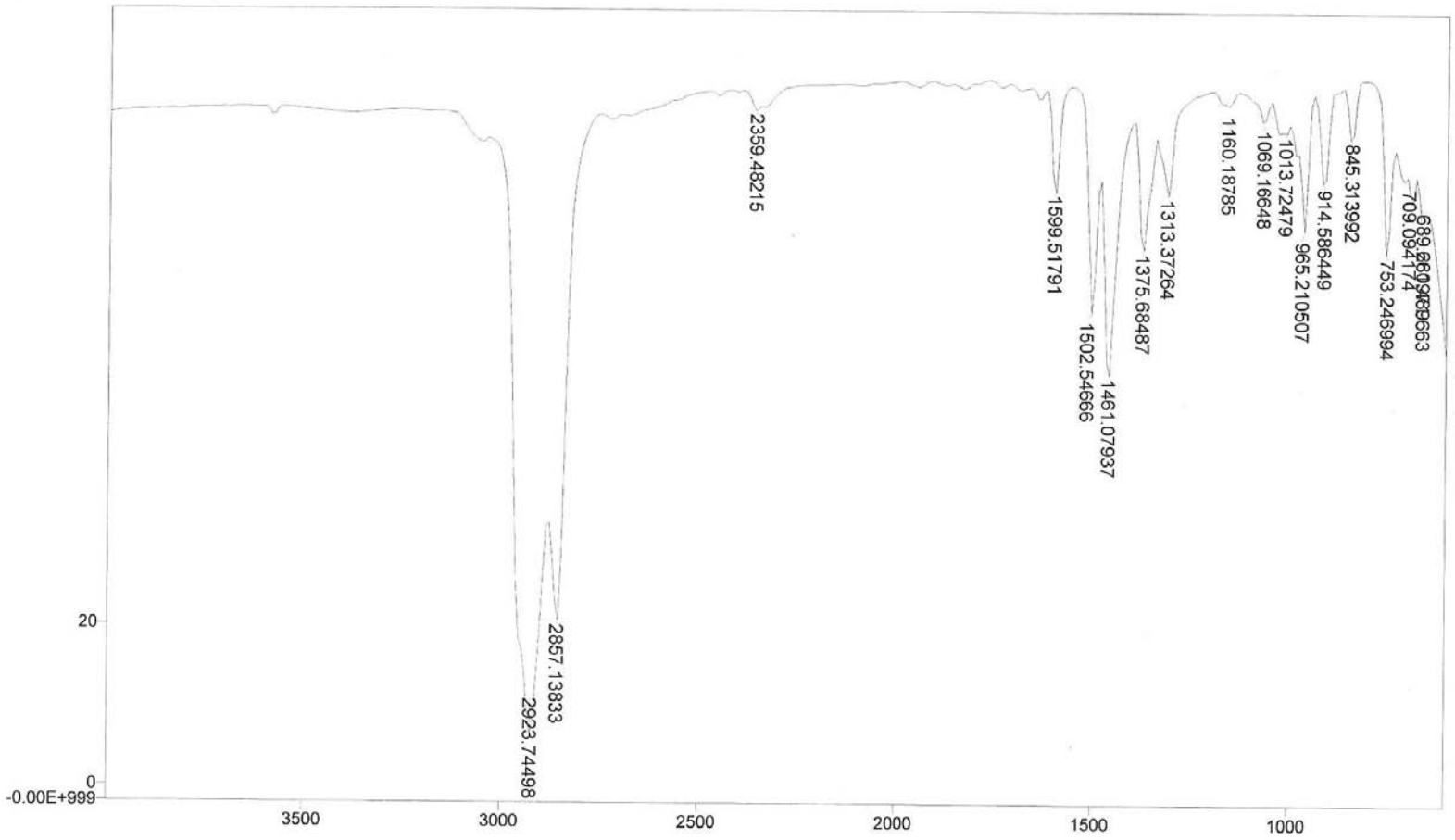
6.80

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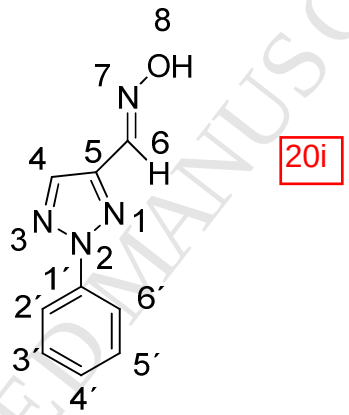
1000



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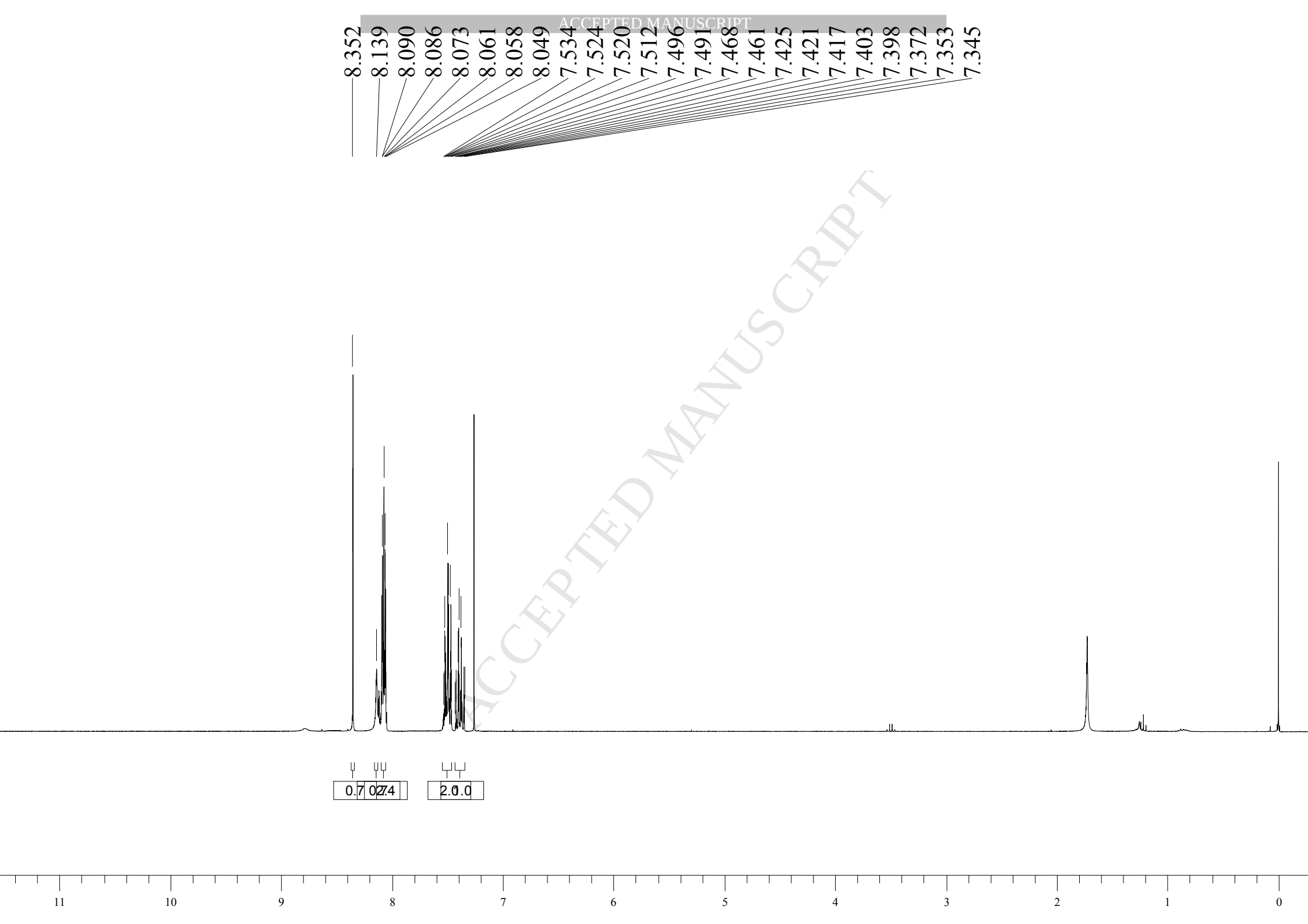

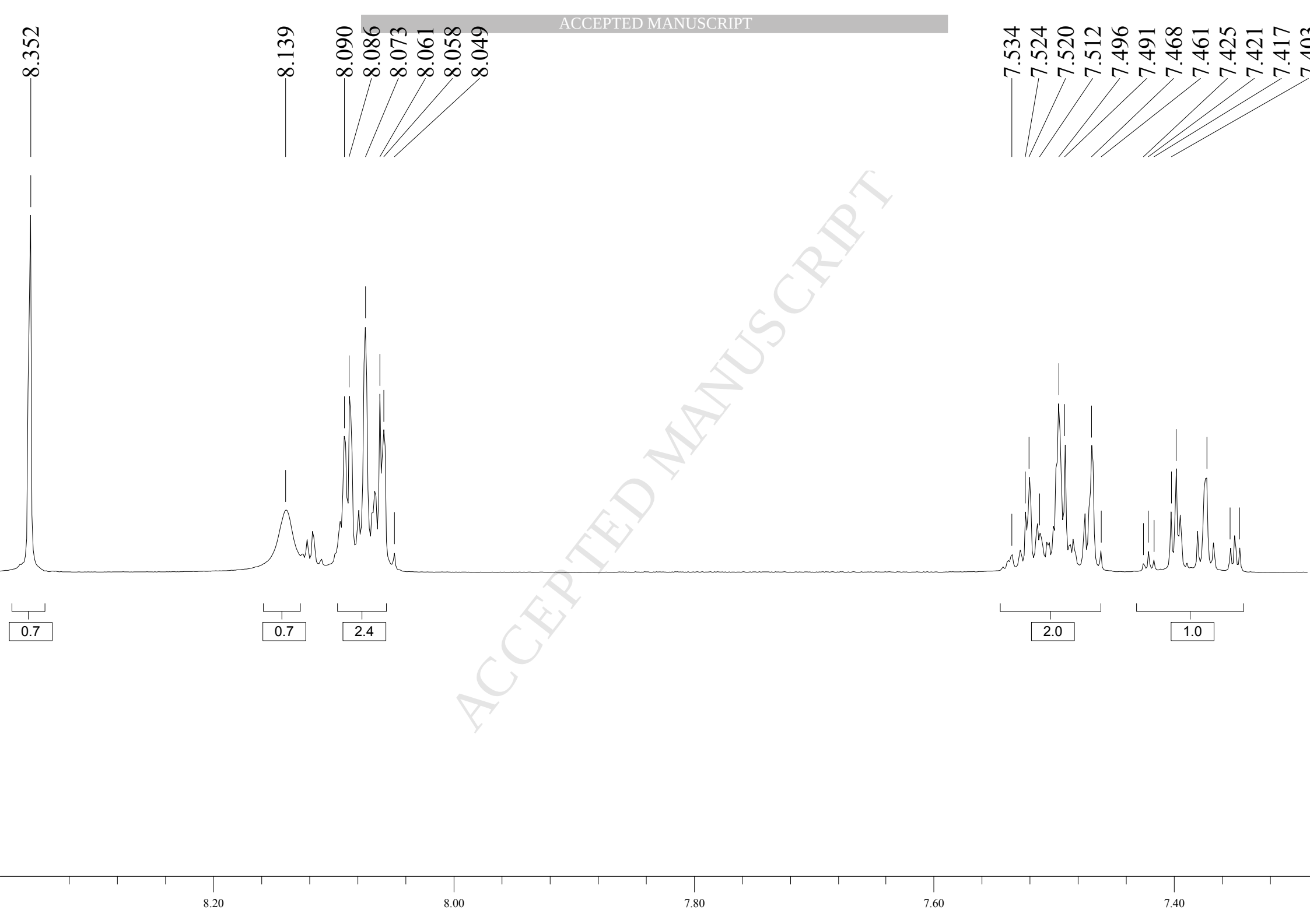

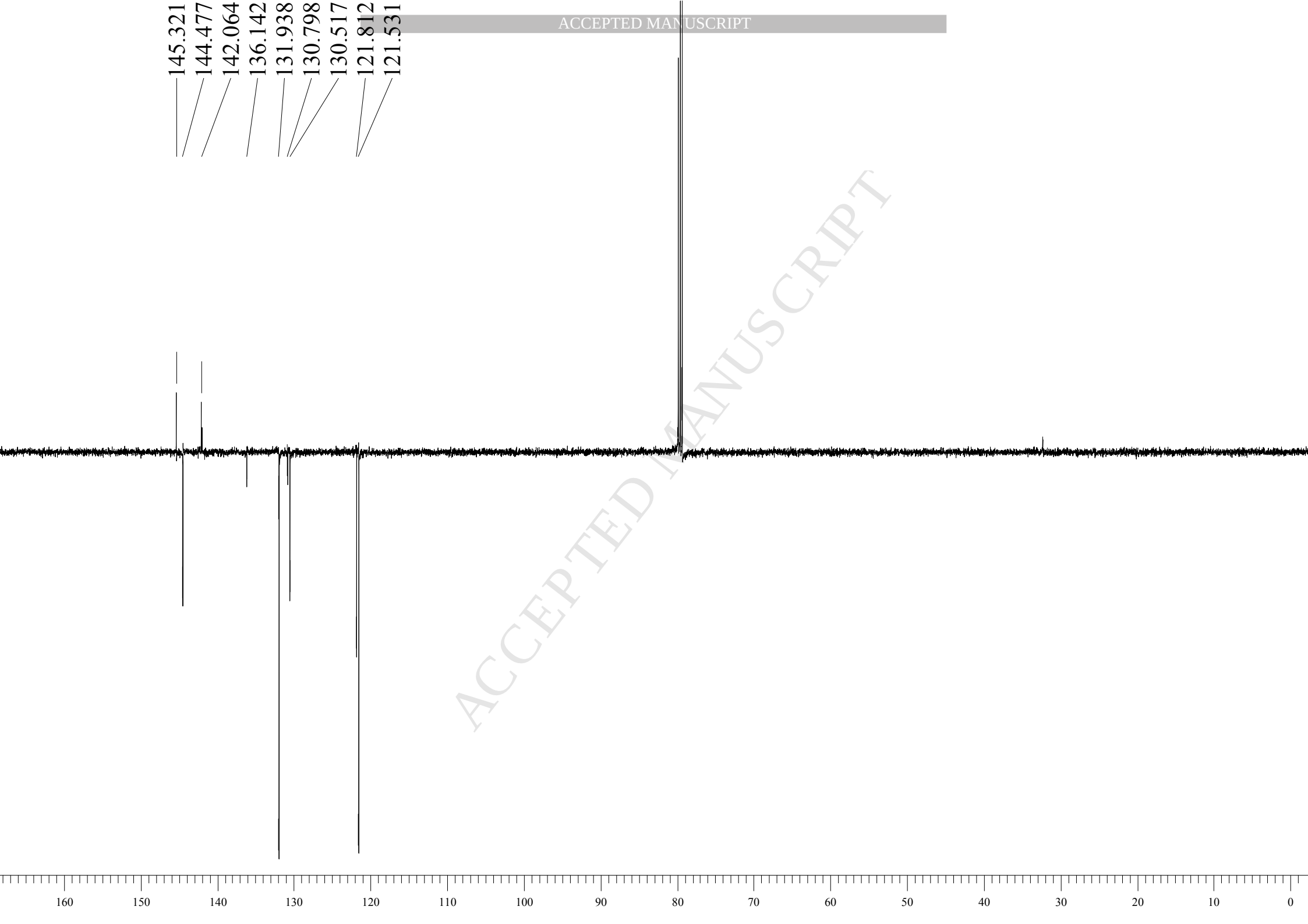

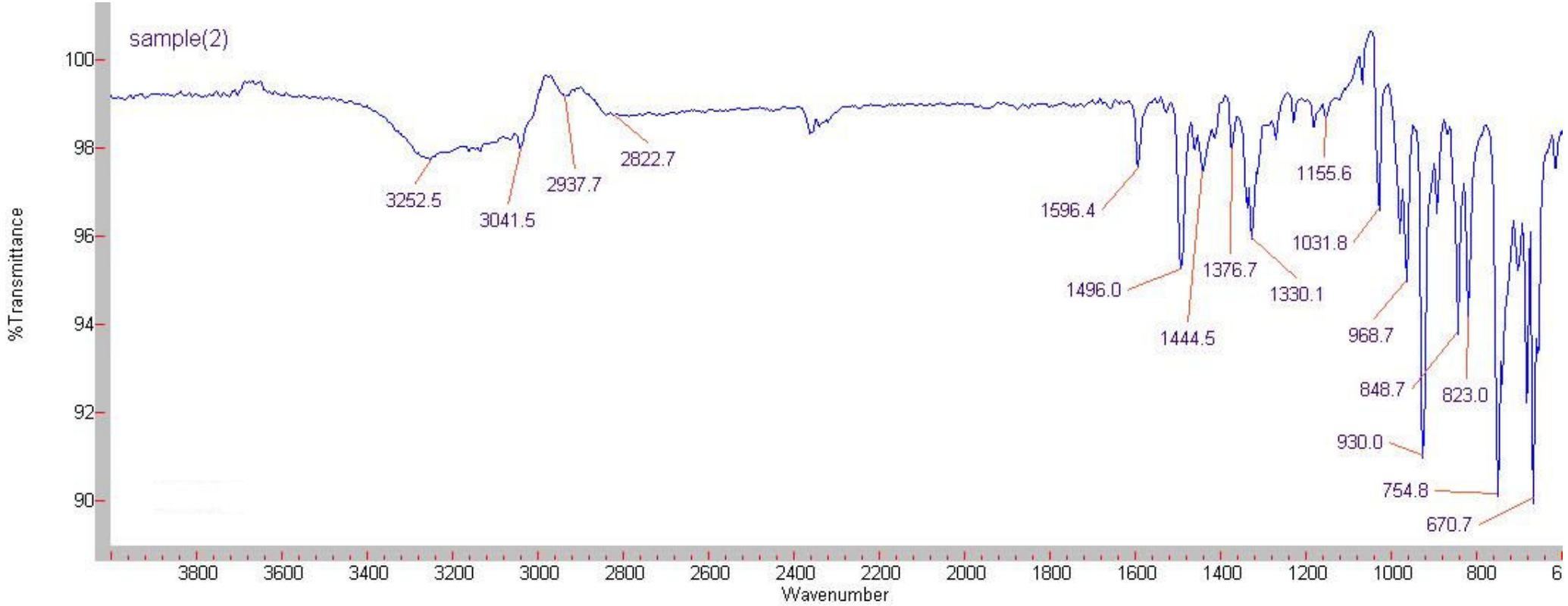

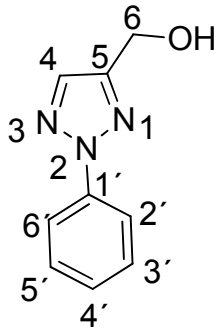
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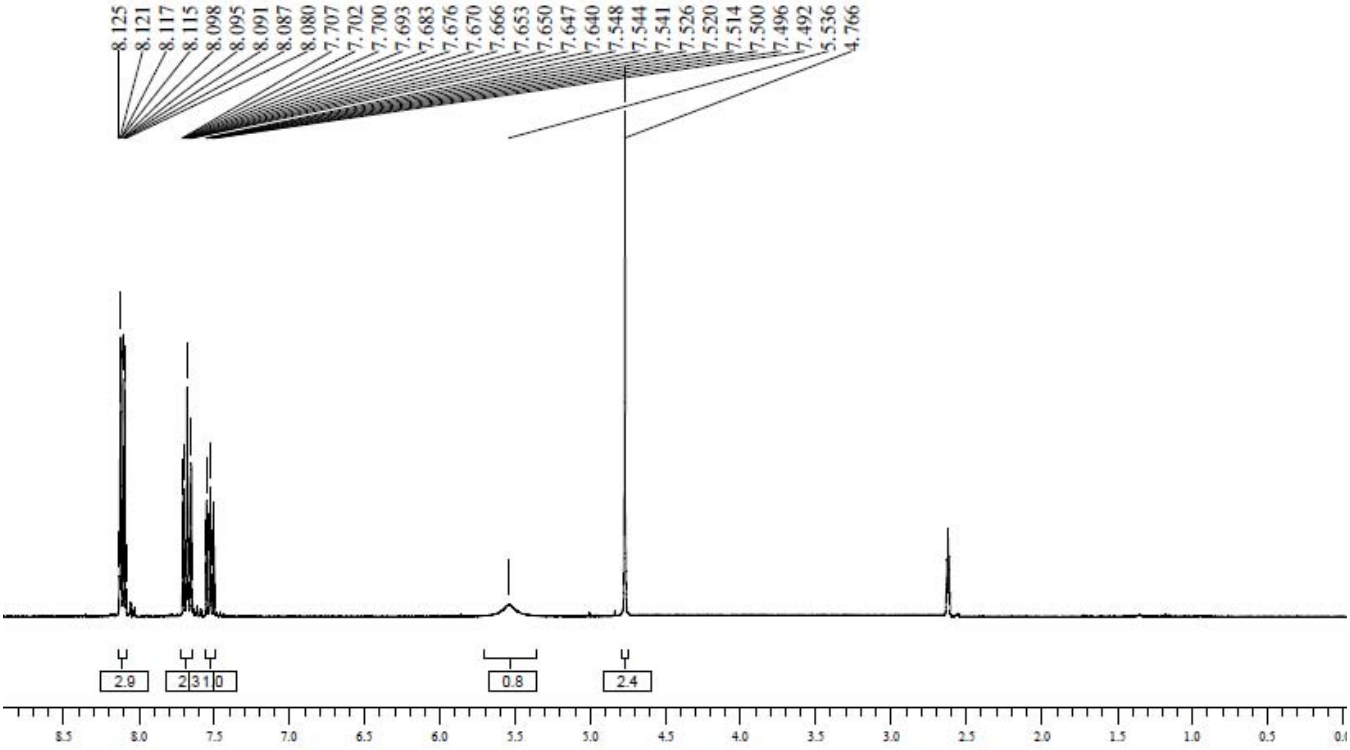
5´
4´

21a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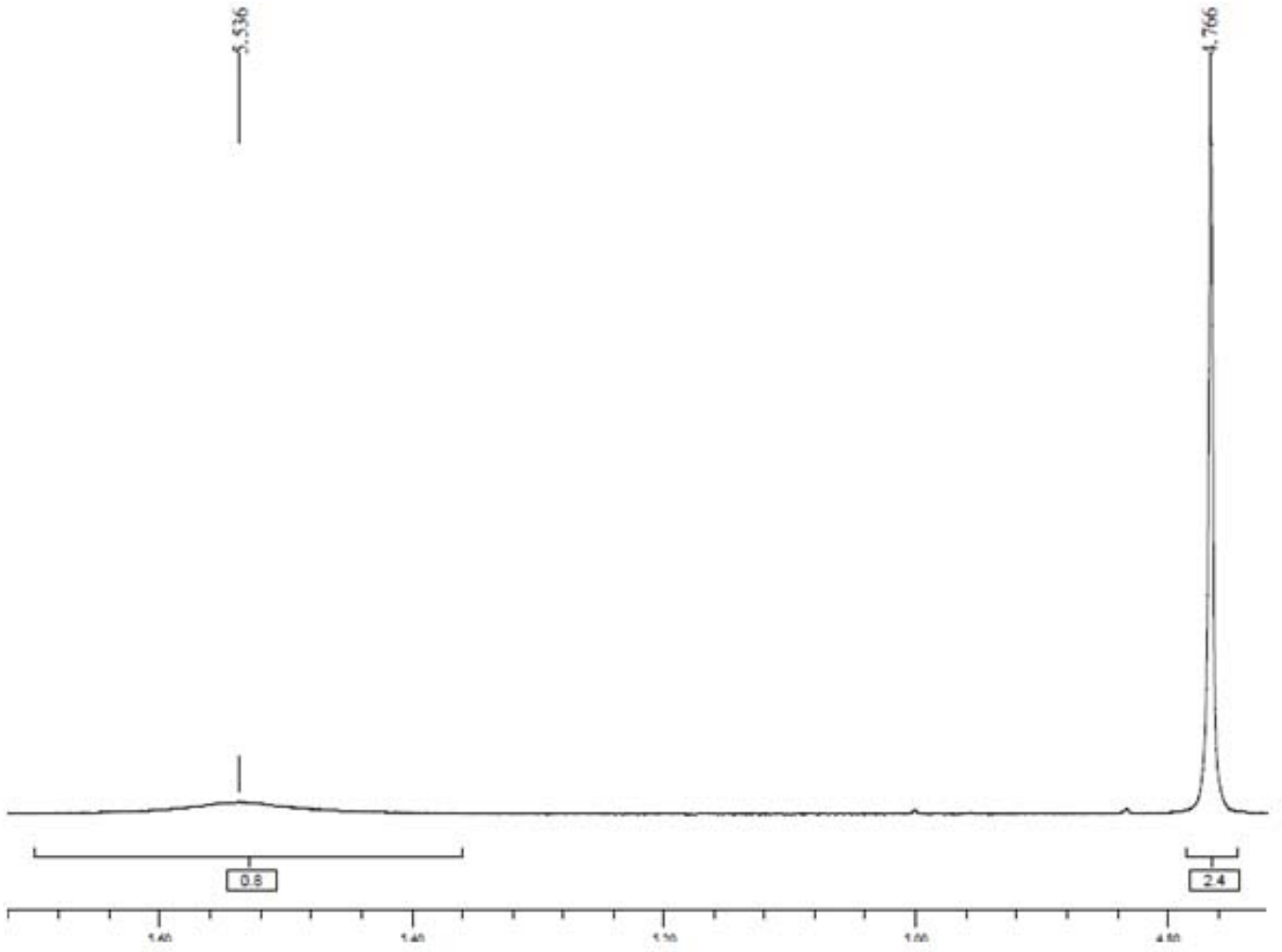
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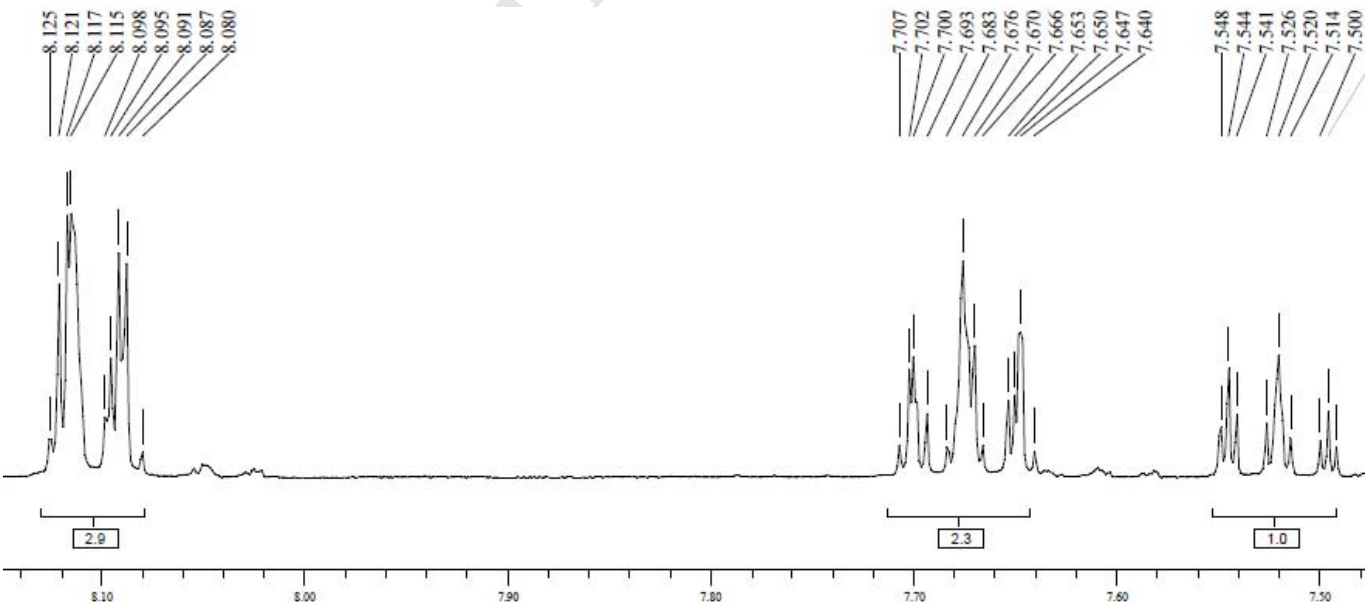
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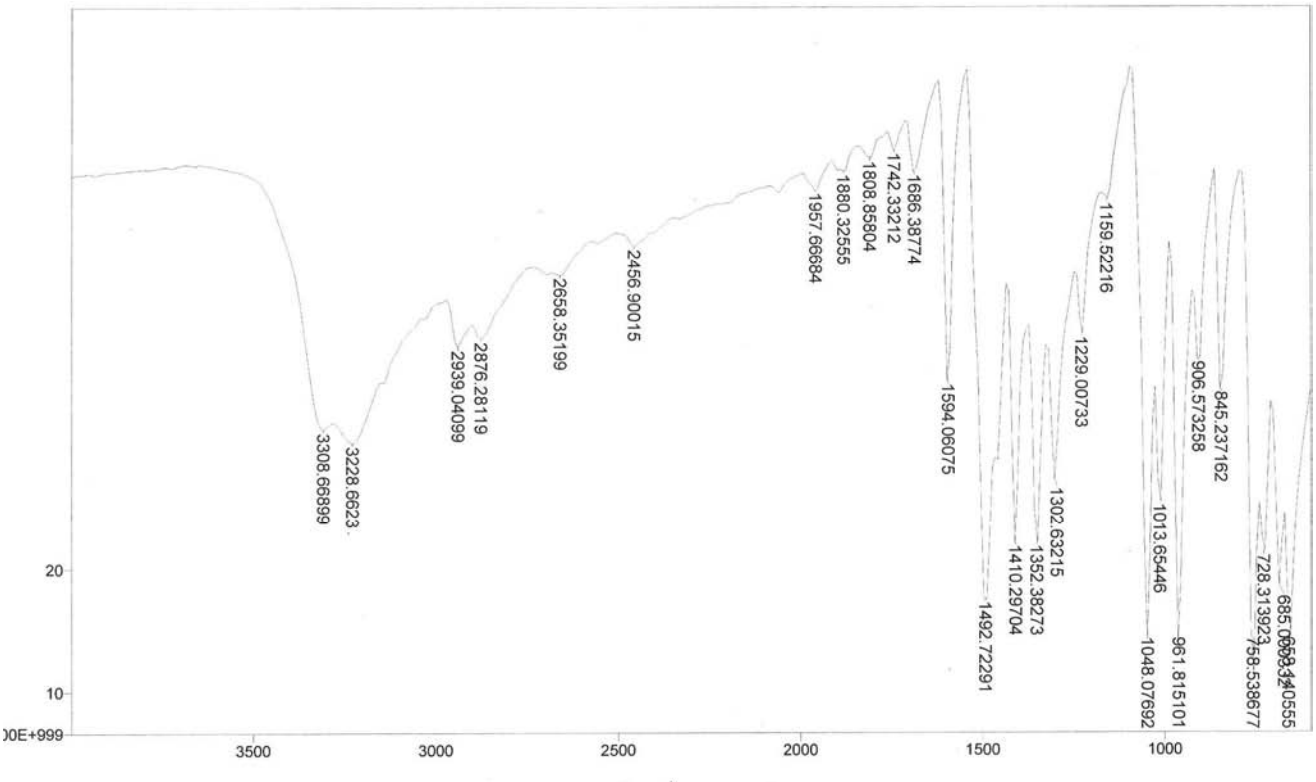

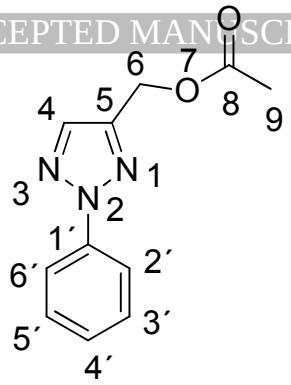

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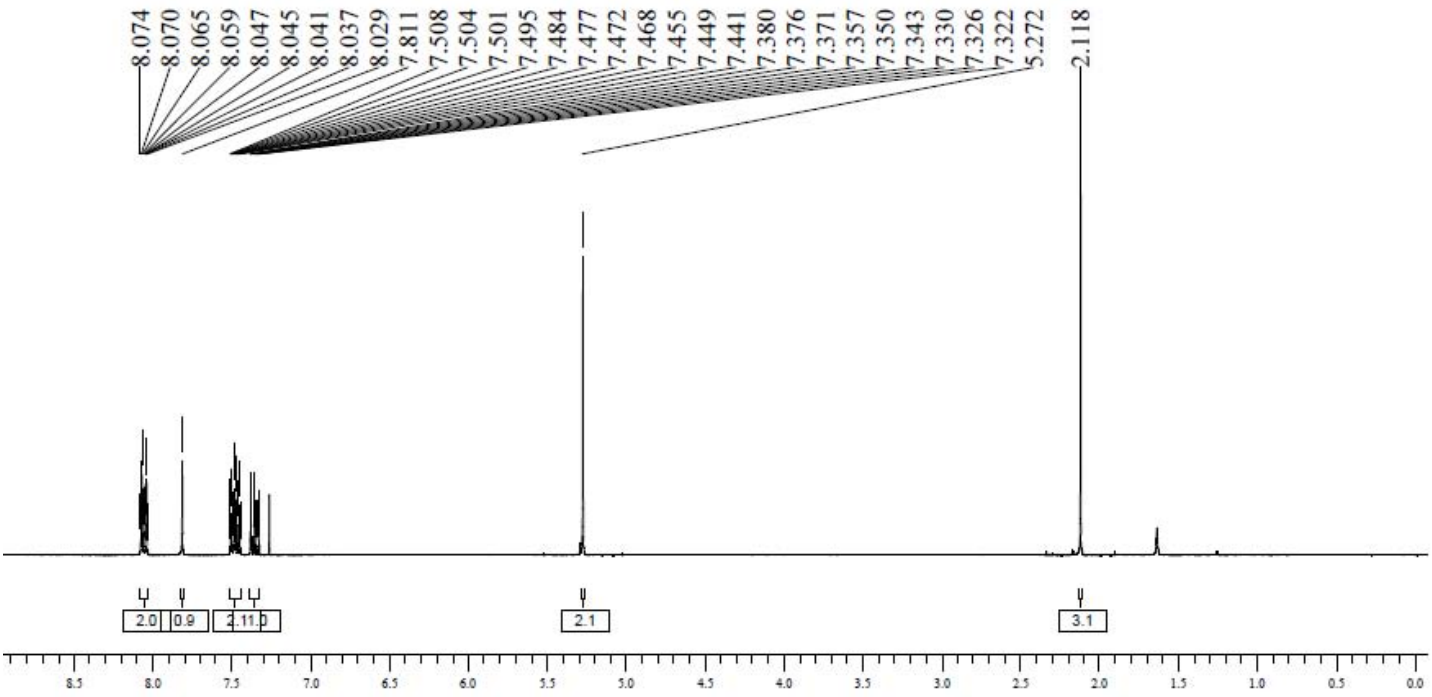

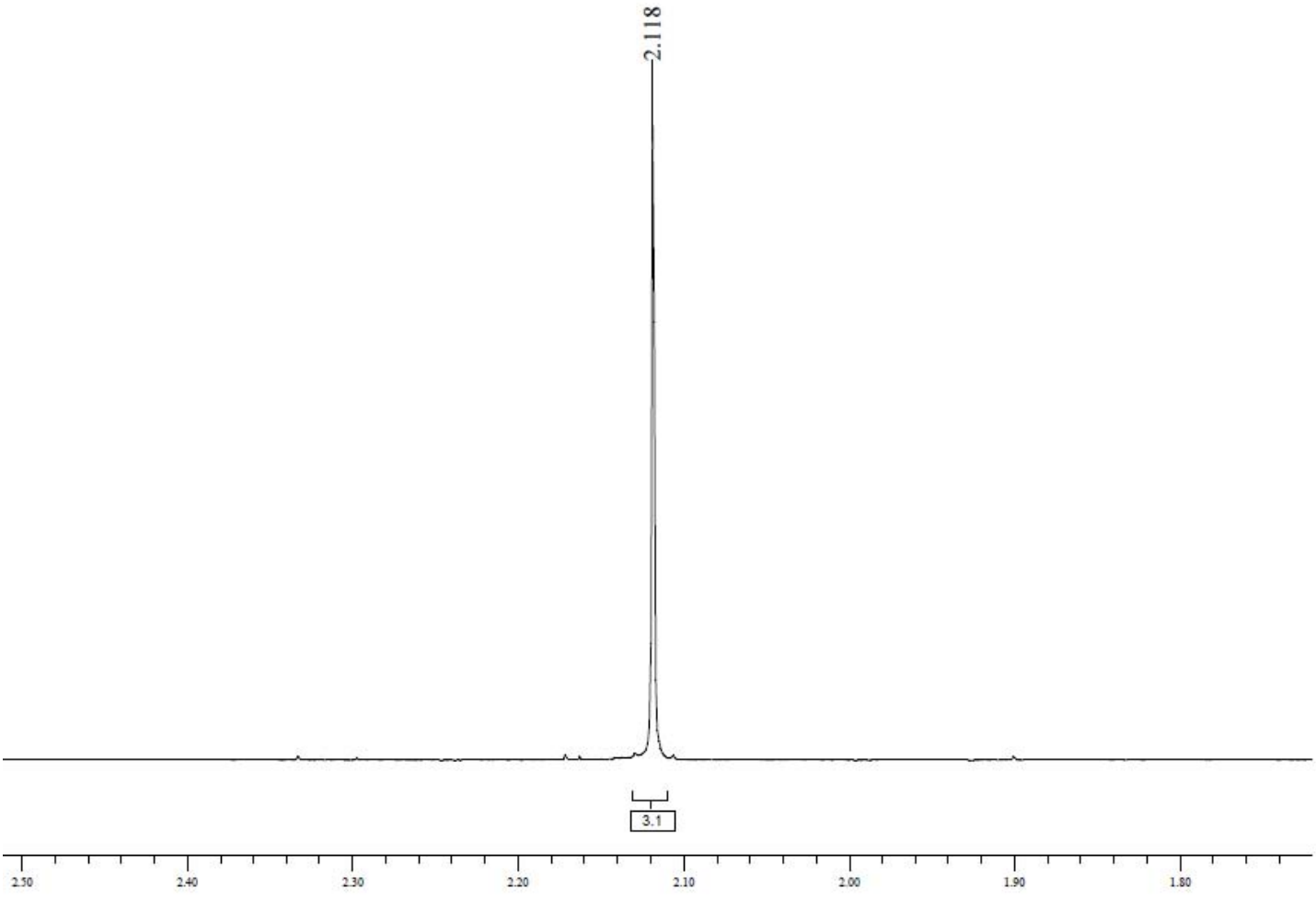
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2.00
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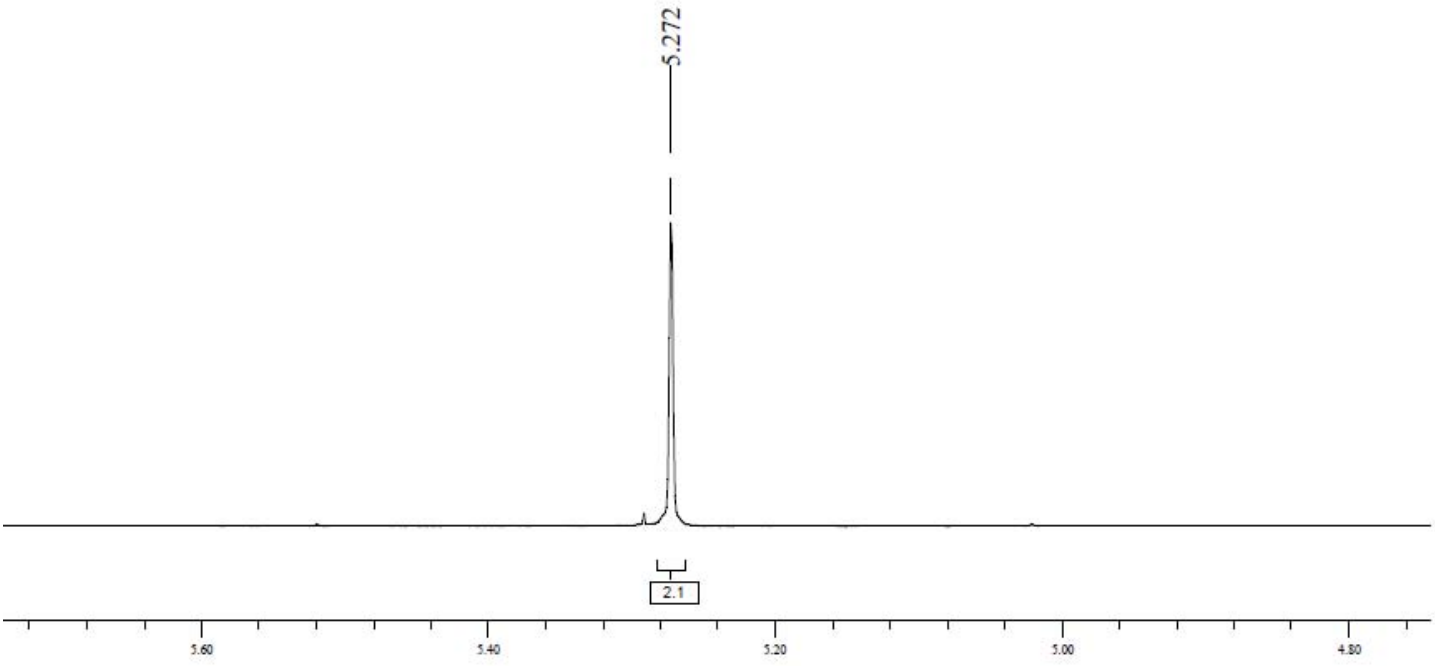
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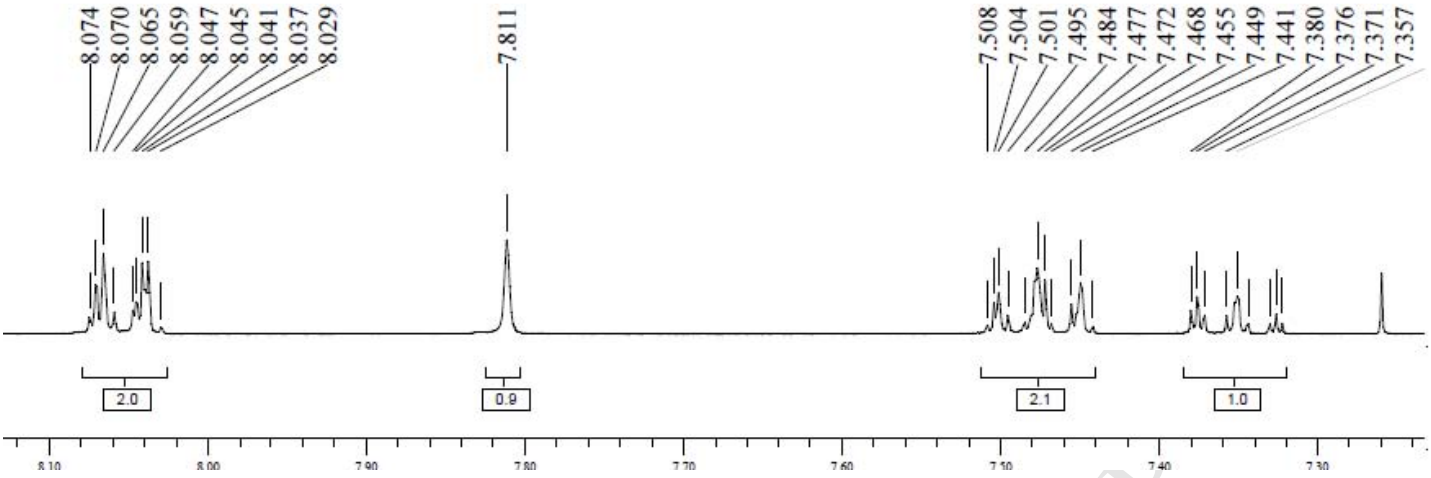
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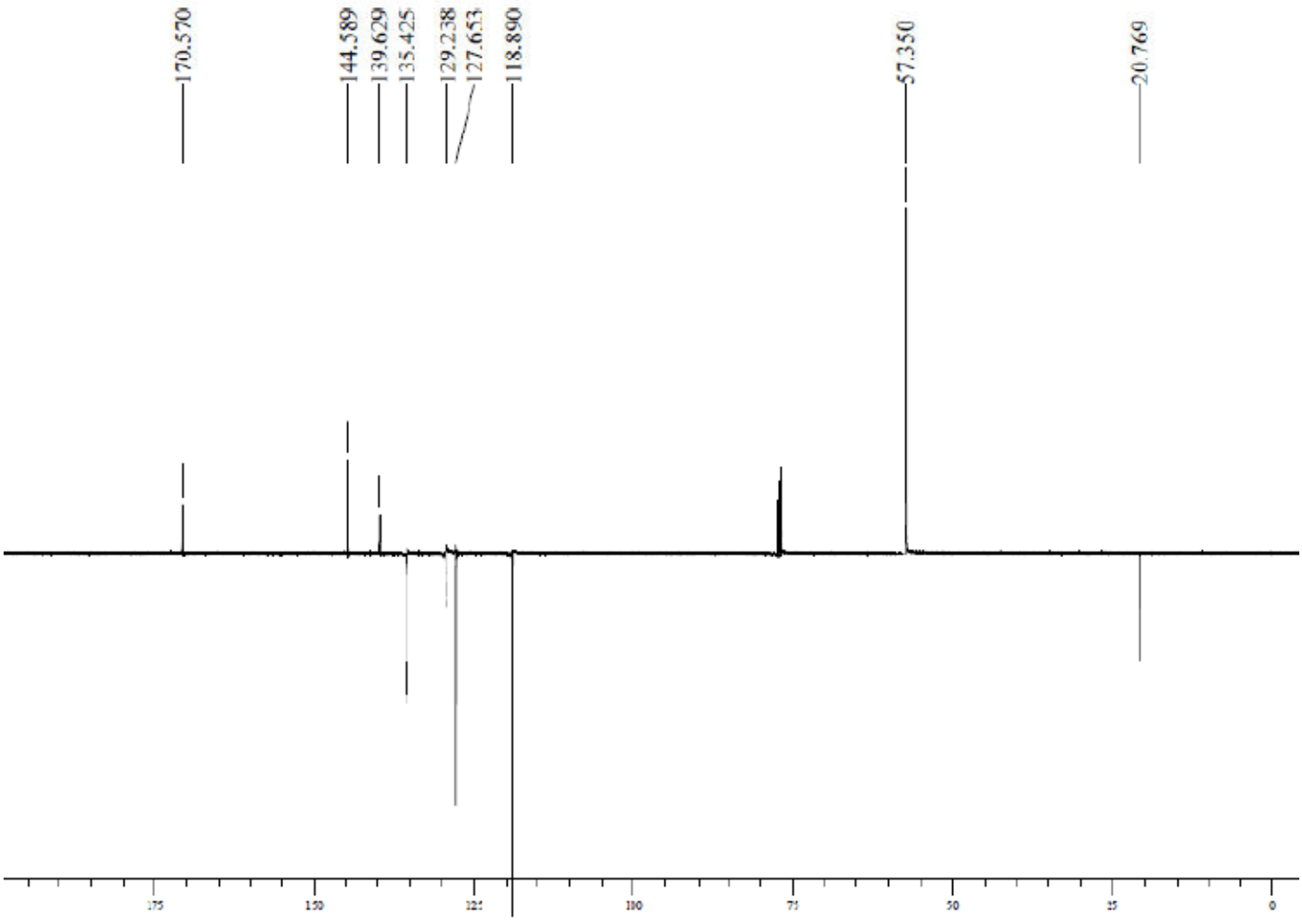
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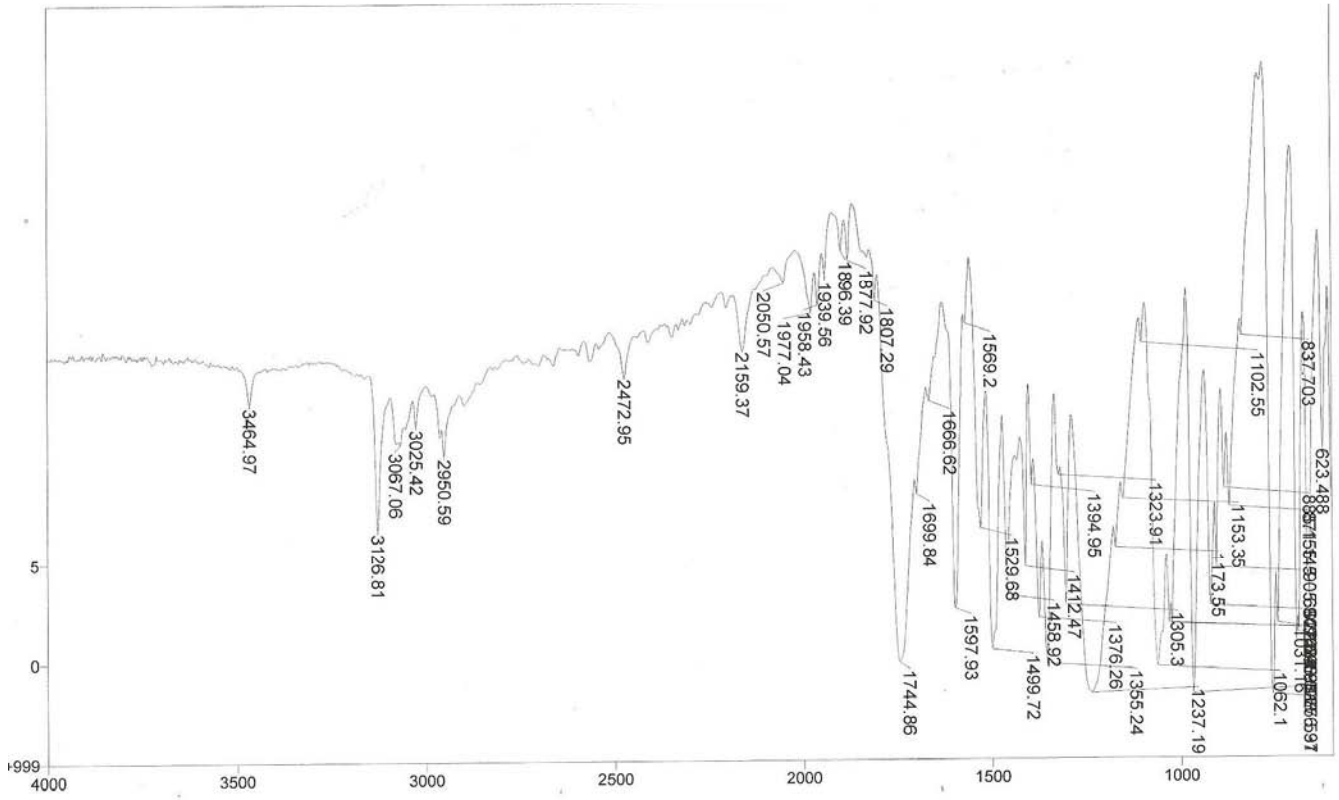

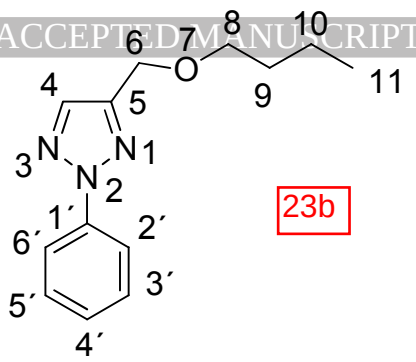

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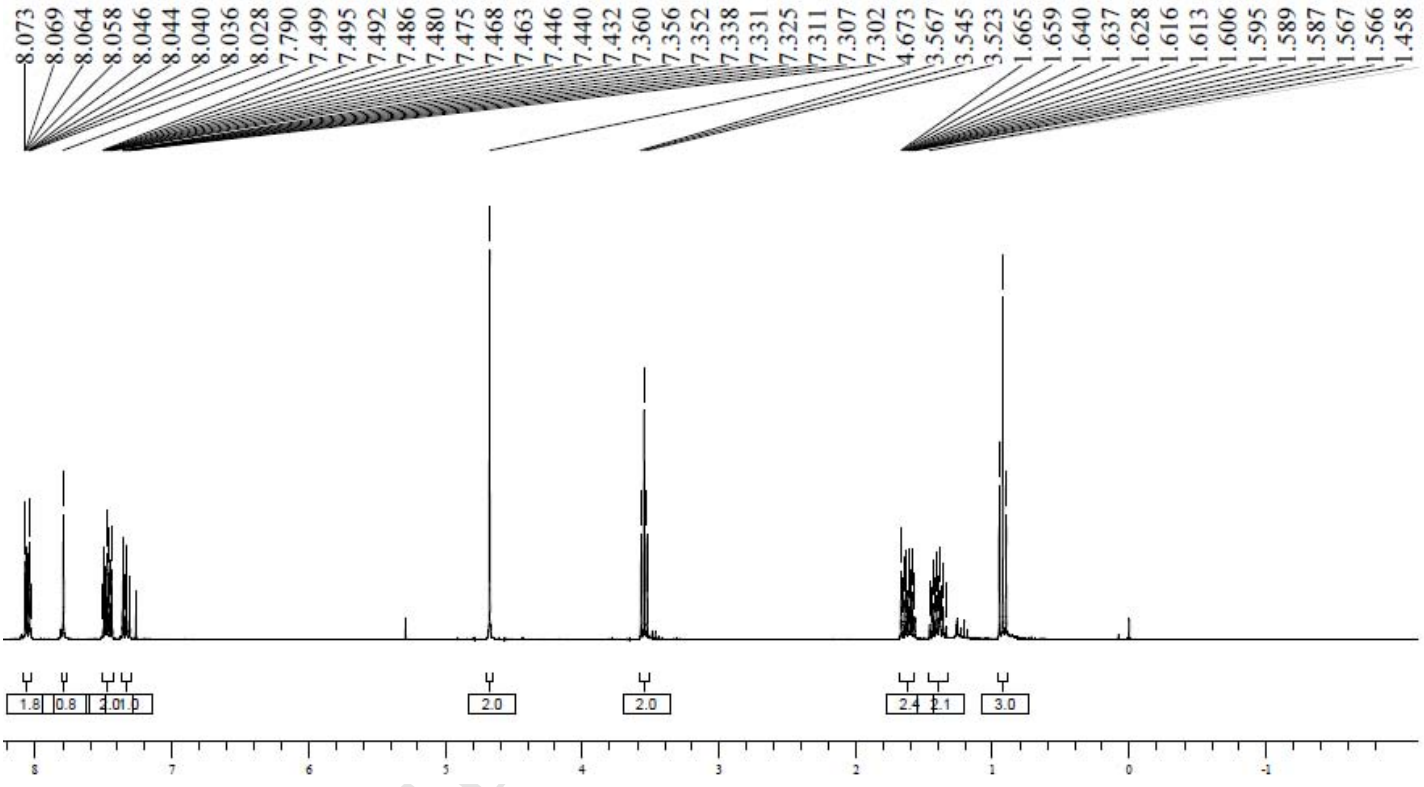

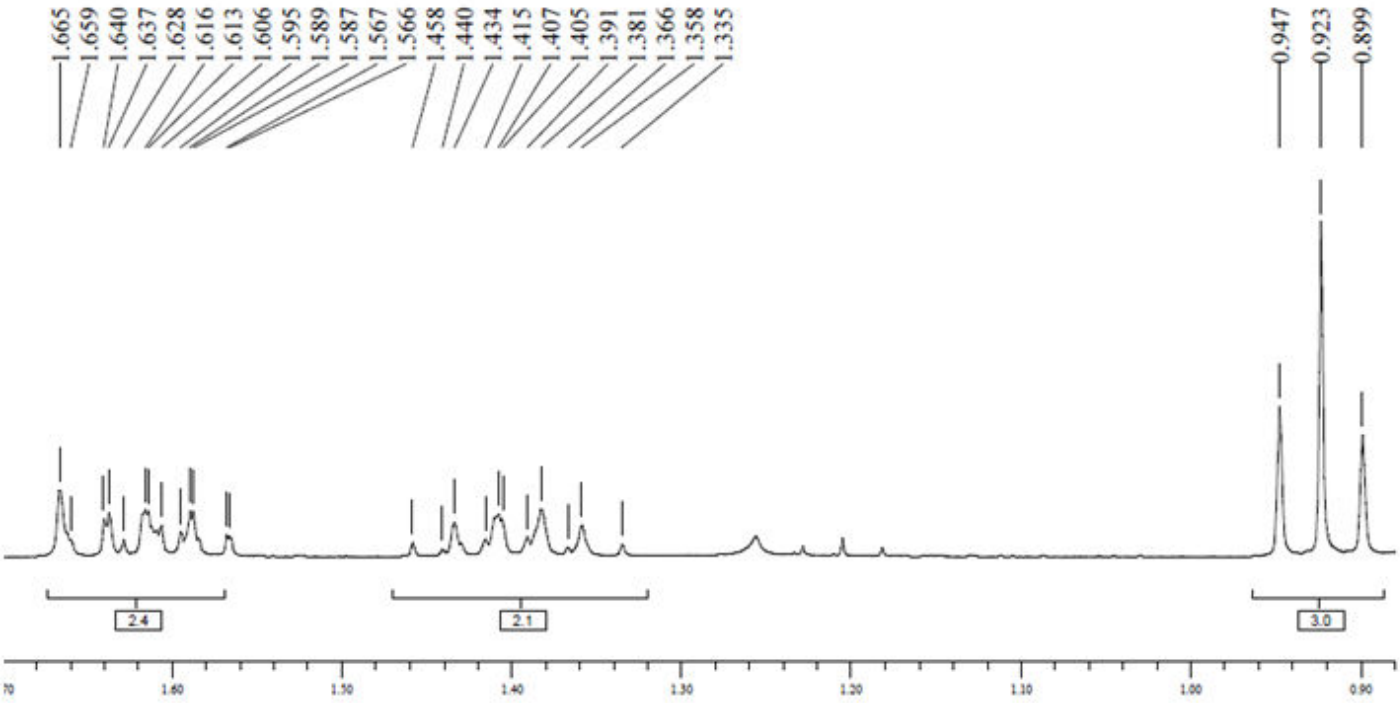
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1.391
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1.335
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0.923
0.899
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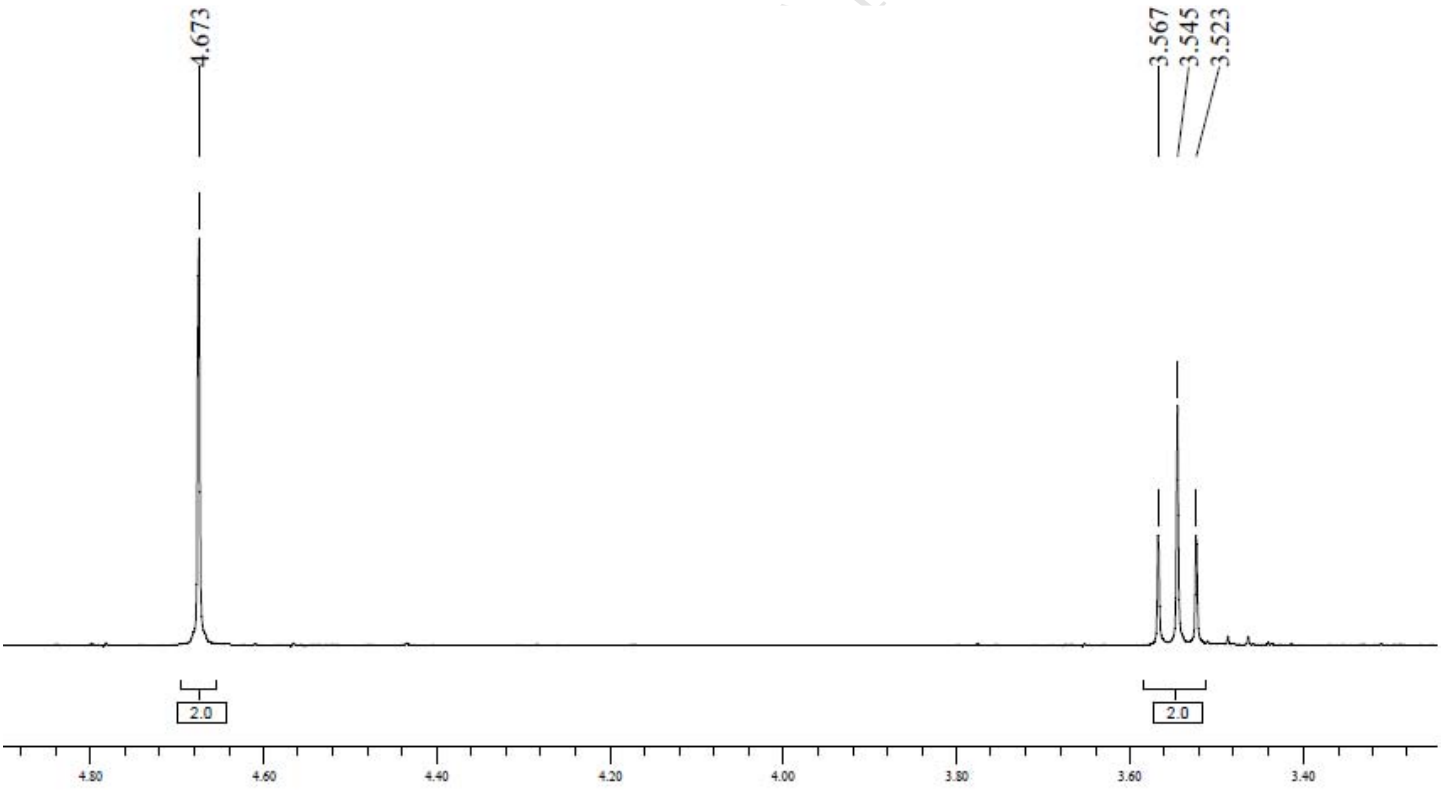
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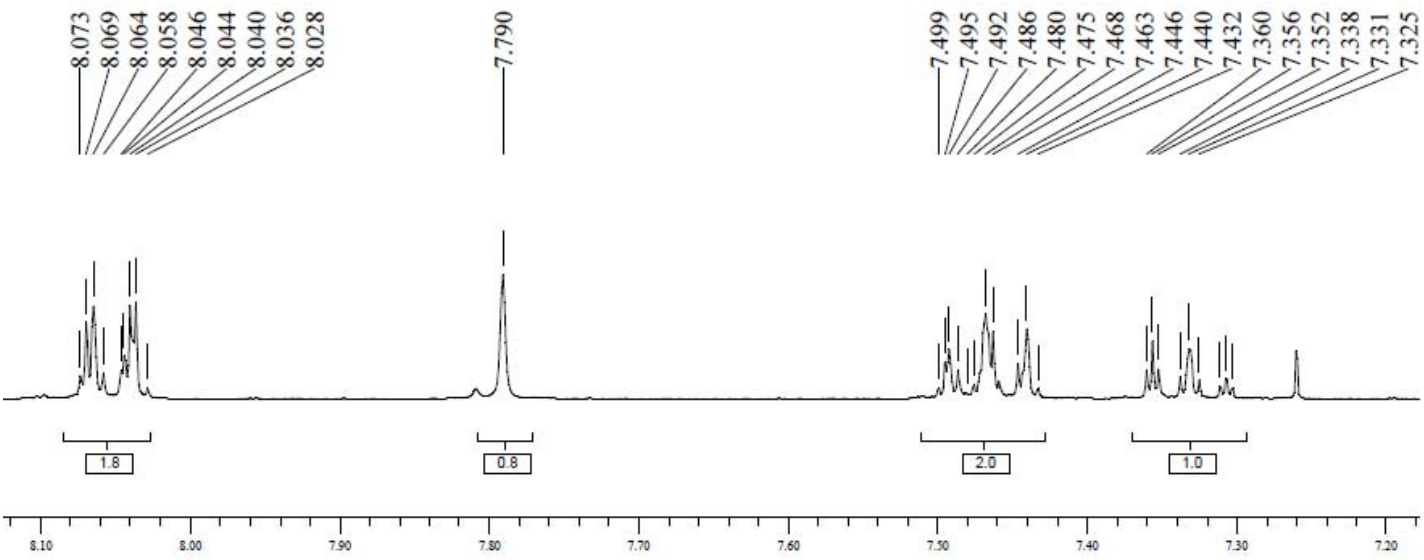
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7.492
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7.480
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7.468
7.463
7.446
7.440
7.432
7.360
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7.352
7.338
7.331
7.325
1.8
0.8
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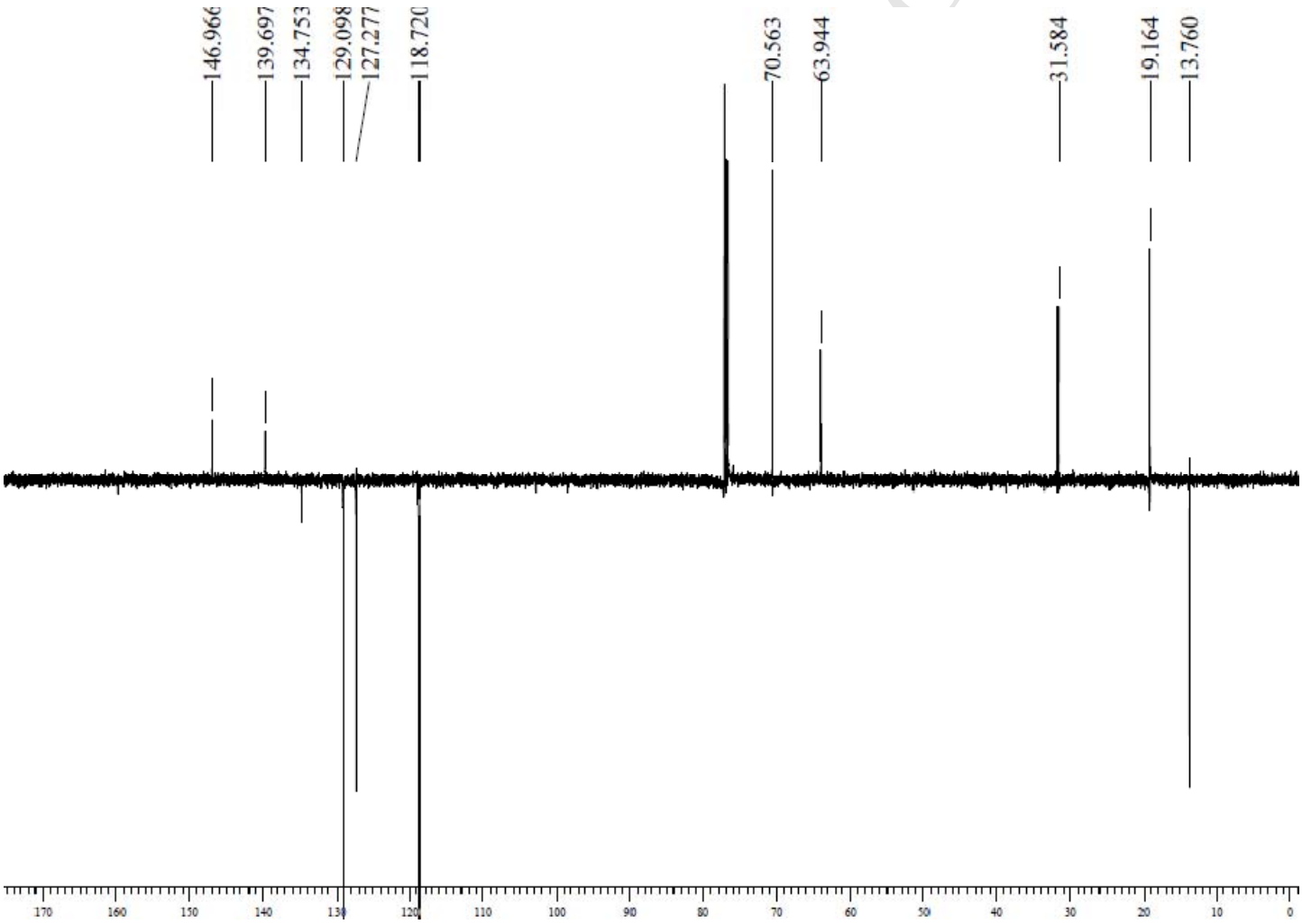
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0