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Highlights:

- Triazole derivatives of rupestonic acid (RA) prepared using click chemistry;
- Some of them more active against Influenza A (H1N1) and B viruses than RA;
- Best compounds 4 times more efficient than Ribavirin against Influenza B virus.

1,2,3-Triazole-containing derivatives of rupestonic acid: Click-chemical synthesis and antiviral activities against influenza viruses

Yao-Wu He[1, 2], Chang-Zhi Dong[2,3,*], Jiang-Yu Zhao[1], Lin-Lin MA[4], LI Yu-Huan[4], Haji Akber Aisa[1,*]

[1] Key Laboratory of Plant Resources and Chemistry in Arid Regions, Xinjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing South Road 40–1, Urumqi, Xinjiang, 830011, P. R. China

[2] Université Paris Diderot, Sorbonne Paris Cité, ITODYS, UMR 7086 CNRS, 15 rue J-A de Baïf, 75205 Paris Cedex 13, France.

[3] School of Light Industry and Chemical Engineering, Guangdong University of Technology, Guangzhou, 510006, P. R. China.

[4] Institute of Medicinal Biotechnology, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, 100050, P. R. China

Corresponding authors. Tel. : +33 1 57 27 88 81, fax : +33 1 57 27 72 63, E-mail address: *dong@univ-paris-diderot.fr* (C. Z. Dong); Tel. : +86 991 368 06 35, fax : +86 *991 383 89 57*, *haji@ms.xjb.ac.cn* (H. A. Aisa)

Abstract: Two series of rupestonic acid derivatives, (1-substituted-1*H*-1,2,3-triazol-4-yl)methyl 2-((5*R*,8*S*,8a*S*)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate and *N*-(1-substituted-1*H*-1,2,3-triazol-4-yl)methyl 2-((5*R*,8*S*,8a*S*)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide were easily and efficiently synthesized via click chemistry. These compounds were tested for their *in vitro* activities against various strains of influenza A virus (H1N1, oseltamivir resistant H1N1, H3N2) and influenza B virus. The results showed that nine compounds were active against the H1N1 strain of influenza A virus and among them the best one **14a**, was as active as the reference drugs, Oseltamivir and Ribavirin. Some of them were also active on the Oseltamivir resistant H1N1 strain. In regards to influenza B virus, twenty-one compounds over thirty were active and seven of them **7b**, **8b**, **9b**, **10a**, **11b**, **12b**, **13b** showed better activity than Ribavirin. The structure-activity relationship of these compounds is discussed on the basis of each type of the viruses studied. Furthermore, four best representative compounds **7b**, **10a**, **12b** and **14a** were evaluated in a plaque assay experiment using MDCK cells and RBV as control compound and the results showed that **7b**, **10a** and **12b** were better than RBV in inhibiting plaque formation, in good accordance with their anti-influenza B activities.

Keywords: Rupestonic acid; 1,2,3-triazole; click chemistry; influenza virus.

1. Introduction

Influenza is a serious public health problem that causes severe illnesses and deaths for higher risk populations [1]. It is an acute viral infection that spreads easily from person to person and anybody in any age group. An epidemic can take an economic toll through reduction of workforce productivity, and strain health services. Annual epidemics of influenza result in about 3 to 5 million cases of severe illness, and up to 500 000 deaths worldwide [2]. The influenza is caused by influenza viruses which can be classified into three types, A, B and C [3]. Type A influenza viruses are further divided into subtypes according to different combinations of virus surface proteins. Among many subtypes of influenza A viruses, currently H1N1 and H3N2 subtypes are circulating in human beings. The subtype H7N9 has been reported since a few weeks to have infected humans in China, but no evidence has been found for its capacity to be vehiculated from man to man. Influenza B viruses are normally found only in humans. Although influenza type B viruses can cause human epidemics, they have not caused pandemics. Type C influenza viruses are much less frequent than A and B [1].

To date, two types of small molecular drugs are available for the treatment of influenza. Adamantine (amantadine and remantadine) are effective against the type A viruses and the inhibitors of influenza neuraminidase, such as oseltamivir and zanamivir, are used for the treatment of both types A and B viruses [4]. However, the amantidine is strictly limited actually because of rapid emergence of the drug resistance and its CNS side effects [5]. Meanwhile, the oseltamivir resistant viruses have been reported as well [6]. Therefore, it is necessary to develop novel and effective drugs to overcome the limitations of the existing antiviral agents.

Natural products represented and will represent an important source of lead compounds for drug discovery [7]. *Artemisia rupestris* L is a well-known medicinal plant in Xinjiang, China and has been traditionally used for detoxification, anti-hypersusceptibility and protecting liver, also as antitumor, antibacterial and antiviral agents [8]. It is the main ingredient in Compound Yizhihao Granule (Fufang Yizhihao Keli, No. Z20026711), which is prescribed to treat colds in China since more than 10 years. 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylic acid (rupestonic acid, R.A.), isolated from *Artemisia rupestris* L [9], is a guaiane type sesquiterpene with multifunctional groups. It shows anti-influenza virus activities and low toxicity (IC_{50} = 25.8 μM and TC_{50} = 4653 μM against influenza H3N2 virus) [10]. In order to improve its efficacy, our research group has long been

involved in synthesizing and testing rupestonic acid derivatives against influenza A and B viruses. The rupestonic acid derivatives, bearing a 1,3,4-triazoles [10] or isoxazole moiety [11] we developed recently, exhibit a good *in vitro* inhibitory activity against influenza A and B viruses. Unfortunately, the high toxicity associated has limited their further development. Hence, it remains a challenge for us to design and synthesize new derivatives with higher efficiency and less toxicity against influenza virus.

1,2,3-Triazole has been frequently used in drugs with a large spectrum of therapeutic properties, such as anti-allergic, antifungal, antibacterial and antiviral (against HIV or influenza virus) activities [12-17]. Recent innovations in click chemistry have made 1,4-disubstituted-1,2,3-triazoles easily accessible from alkynes and azides, through Huisgen 1,3-dipolar cycloaddition [18]. This copper (I) catalyzed reaction is mild and very efficient, requiring no protecting groups and no purification in many cases with the reaction rate accelerated up to 10^7 times. This has put it in a class of its own and enabled many novel applications [19], in particular in the synthesis of drug-like molecules to accelerate drug discovery process [20].

Starting from rupestonic acid, we report in this work the synthesis of its 1,2,3-triazole-containing derivatives and their *in vitro* biological activities against influenza viruses. The structure-activity relationship of these compounds is discussed on the basis of each type of the viruses studied. Furthermore, in a plaque assay experiment three representative compounds were shown to be better inhibitors than RBV, in good accordance with their anti-influenza B activities.

2. Results and discussion

2.1. Chemistry

The synthetic route for the title compounds is shown in Scheme 1. Rupestonic acid was isolated from raw roots of A. *rupestris* L. in a global yield of about 0.1%. It reacted with 3-bromoprop-1-yne or prop-2-yn-1-amine to afford the compounds **a** or **b** containing a terminal alkyne function. In parallel, substituted benzyl and alkyl azides (**1**-**15**) were prepared according to the experimental procedures described in the literature [21] and characterized by the absorption at 2100 cm^{-1} in the IR spectra, corresponding to the azide function. They were used without further purification. The compounds **a** and **b** were then submitted to the copper-catalyzed [3+2] cycloaddition with the azides (**1**-**15**) in the presence of $CuSO_4$ and sodium ascorbate in a non-homogeneous mixture of solvents (CH_2Cl_2/H_2O, 1:1,

v/v) to give the rupestonic acid derivatives **1-15a** and **1-15b** in moderate to good yields (35% to 74%).

One aromatic singlet was observed in the corresponding ^{1}H NMR spectra (δ about 7.50 ppm) and can be attributed to the proton H-5' of the triazole ring of all the final products. Besides of the NMR data, the identity of all the rupestonic acid derivatives was further confirmed by elemental analysis, as well as HRMS for the majority of the compounds.

Scheme 1. Synthesis of 1,2,3-triazole-containing derivatives of rupestonic acid. Reagents and conditions: i) NaN_3, DMSO; ii) K_2CO_3, DMF; iii) EDCI, HOBt, DCM; iv) $CuSO_4$/Na-Ascorbate, DCM/H_2O

2.2. Antiviral activities against influenza viruses

The antiviral activities of the synthesized compounds against influenza A virus of the subtypes FM/1/47/H1N1, oseltamivir resistant tianjinjinnan/15/2009/H1N1, hanfang/359/95/H3N2, as well as influenza B virus of the subtype jifang/13/97 were evaluated by cytopathic effects (CPE) using MDCK cells with oseltamivir and Ribavirin (RBV) as control drugs. The results are summarized in **Table 1**. The cytotoxicity of each compound was determined and is reported in **Table 1** as well. Since one substituent to the triazole ring had not the same influence on the toxicity in the ester series as in the amide series, the highest concentrations tested were not the same in both series for a given substituent.

When tested against influenza A virus, there were nine compounds (**2a**, **6a**, **14a**, **15a**, **3b**, **4b**, **5b**, **6b** and **14b**) active against the strain A/FM/1/47/H1N1. The most active compound, **14a** (IC_{50} = 2.82 μg/mL) is as active as the control drugs, Oseltamivir (IC_{50} = 2.81 μg/mL) and RBV (IC_{50} = 1.92 μg/mL). Unfortunately, its selectivity index is less interesting, due to its higher cytotoxicity than the control drugs. Curiously, all compounds containing a triazole ring substituted by a halogenated (F or Cl) benzyl group are inactive, no matter what is the nature or the number of the halogens. As for the others, one substituent seems not to influence the antiviral activity in the same manner in the ester series as in the amide one. The compound **2a** in the ester series containing a 3-methylbenzyl substituent is active, while the compound **2b** in the amide series containing the same substituent is not. This is also the case for the couples **3a**/**3b**-**5a**/**5b**.

Interestingly, when tested against Oseltamivir-resistant influenza A virus (the strain of

Tianjinjinnan/15/2009/H1N1), seven of the new rupestonic acid derivatives (**2a**, **6a**, **7a**, **15a**, **13b**, **14b** and **15b**) were revealed active and the compounds **2a** and **14b** demonstrated the best activity (IC_{50} = 19.7 μg/mL), only about three times less active than RBV, the unique reference drug**.** But their selectivity index is much worse than that of RBV, due to their relatively high cytotoxicity.

On the contrary to rupestonic acid, the new derivatives seem quite inefficient against the H3N2 subtype of influenza A virus, since only two of them (**7a**, **13b**) display moderate potency against the H3N2 strain, hanfang/359/95/H3N2, compared to the control compounds.

In brief, these new compounds are much more efficient against the H1N1 subtypes of influenza A virus (H1N1, Oseltamivir resistant H1N1) than the H3N2 subtype. Their selectivity index is in general moderate compared to the reference drugs, due to their high cytotoxicity and modest activity.

However, the results were much more encouraging when the new compounds were tested against influenza B virus. More than two thirds of them are active (**Table 1**) and seven of them (**10a**, **7b**, **8b**, **9b**, **11b**, **12b**, **13b**) possess a higher potency than RBV, more than four times better for the best ones. In contrary to the results observed with influenza A viruses, the majority of the compounds bearing a halogen atom or two showed interesting activity against influenza B virus. In addition, it seems that the position of the halogen on the phenyl group has an influence on the antiviral activity. Introduction of a chlorine atom to the position 2 (**7a**, **7b**) or position 4 (**9a**, **9b**) of the phenyl ring confers a better potency than to the position 3 (**8a**, **8b**). Note that the amide derivatives are generally more active against the type B virus than the ester ones. On the other hand, the presence of a deactivating group on the phenyl ring as F and Cl induces a beneficial effect to the activity, while an activating group as methyl or methoxyl, no matter where it is attached to the phenyl ring, is detrimental to the activity. Nevertheless, there are some exceptions to these general trends: 1) the compound **11a**, **13a** and **10b** were observed inactive although they possess one or more halogens on the phenyl ring, and 2) **2a** in which is found a methyl group at the position 2 of the phenyl ring is as active as **7a** in which is found a chlorine atom at the same position.

In brief, this SAR study seems indicating that an electron-withdrawing group on the phenyl ring in particular at the positions 3 or 4 would increase the antiviral activity against influenza B virus.

Four representative compounds **10a**, **14a**, **7b** and **12b** were evaluated in a plaque assay experiment using MDCK cells and Ribavirin (RBV) as control drug. The results (Table 2) demonstrated that the

compounds **10a**, **7b** and **12b** with good anti-influenza B activities were better inhibitors than RBV and the compound **14a** with good anti-influenza A activities, but lower anti-influenza B activities was as good as the control drug. This result is consistent with the anti-viral activities of these compounds.

Insert Table 1 here

Insert Table 2 here

3. Conclusion

In this work, we have synthesized two series of rupestonic acid derivatives, (1-substituted-1*H*-1,2,3-triazol-4-yl)methyl esters and *N*-(1-substituted-1*H*-1,2,3-triazol-4-yl)methyl amides. Their antiviral activity has been evaluated against the influenza A and B viruses. Certain compounds display interesting potencies against influenza A viruses and the best one is as active as the reference drugs to kill the H1N1 subtype virus. Unfortunately, the selectivity index of these compounds is in general moderate compared to that of the controls. When tested against influenza B virus, the results are really exciting, as seven of the new compounds are more active than RBV, the only reference drug in this study. Although the selectivity index of these compounds remains to be a little worse than RBV, it may be acceptable taking into account their better performance than the control (more than four times better). The SAR study did not give any clear correlation between the substituent and the activity when they were evaluated against influenza A viruses. However, a deactivating group on the phenyl ring seems beneficial to the antiviral activity against the type B virus. The results obtained in this work will help us to adjust our research focus in this field and the best compounds in this work are actually under investigation for their pharmacological properties.

4. Experimental Procedures and Characterization

4.1. General Information

All chemicals and solvents were purchased from Aldrich, Sodipro and VMR. IR spectra were recorded on Perkin Elmer Spectrum 100 FT-IR. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE III 400 NMR. Results are presented as, chemical shift δ in ppm, multiplicity, *J* values in Hertz (Hz), number of protons, proton's position. Multiplicities are shown as the

abbreviations: s (singlet), brs (broad singlet), d (doublet), t (triplet), m (multiplet). Elemental analyses were performed for C, H and N by the Service de Microanalyse, ICSN-CNRS and were within ± 0.4% of theoretical values. Mass spectrometry was performed using a QSTAR Elite LC/MS/MS system from Applied Biosystems/MDS Sciex (Concord, ON, Canada) equipped with an electrospray ionization (ESI) ion source. The reactions were monitored by TLC on Merck silica gel 60 F254 plates with UV and iodine vapor detection. Commercial solvents in reagent grade were used without any treatment.

4.2. Preparation of 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylic acid (Rupestonic acid)

Raw roots of A. *rupestris* L. (2 kg) were extracted three times with 95% ethanol. The extracts were combined and evaporated to dryness under reduced pressure. The residue was dissolved in water, then the solution was extracted three times with ethyl acetate, and the combined ethyl acetate layers were extracted three times with 5% $NaHCO_3$. The $NaHCO_3$ fractions were combined and neutralized to pH 2 with conc. HCl, then extracted with ethyl acetate. After evaporation of the solvent to dryness, the crude sample (400 g) was purified by silica gel chromatography (petroleum ether /EtOAc, 5:1 to 2:1, v/v) to furnish the title compound (2.3 g) as colorless crystals; m.p. 131-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (s, 1H, CH_2=C), 5.73 (s, 1H, CH_2=C), 3.18 (m, 1H, C<u>H</u>CH_2CO), 2.89 (m, 2H, C<u>H</u>CCO_2H, CH_2C=C), 2.61 (dd, *J* = 18.0, 6.0 Hz, 1H, CH_2CO), 2.46 (dd, *J* = 19.2, 12.0 Hz, 1H, CH_2C=C), 2.13 (m, 1H, C<u>H</u>CH_3), 2.06 (d, *J* = 18.9 Hz, 1H, CH_2CO), 1.87 – 1.80 (m, 2H, C<u>H$_2$</u>$CHCH_3$), 1.80 – 1.66 (m, 2H, C<u>H$_2$</u>CH_2CHCH_3), 1.64 (s, 3H, CH_3C=C), 0.66 (d, *J* = 7.1 Hz, 3H, C<u>H$_3$</u>CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.73, 174.93, 171.56, 145.86, 138.01, 125.55, 46.10, 41.44, 38.49, 37.85, 36.70, 35.42, 31.72, 12.23, 8.11 [10]; IR (ν/cm^{-1}): 2952, 2923, 2897, 1712, 1660, 1617.

*4.3. General procedure for the synthesis of alkyl and aryl azides (**1-15**)*

The title compounds were prepared according to the method previously reported [21]. Briefly, alkyl or benzyl bromides or chlorides (5 mmol) and sodium azide (6 mmol) in DMSO (10 mL) were stirred overnight. The reaction mixture was diluted with cold water (10 mL) and extracted with diethyl ether. The combined organic layers were washed successively with water, brine and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporator to produce liquid azides. The azides (50-85% yields) were used in the following reaction without further purification.

*4.4. Synthesis of prop-2-ynyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (**a**)*

To a solution of rupestonic acid (1.24 g, 5.0 mmol) in dry DMF (10 mL) were added successively anhydrous potassium carbonate (1.04 g, 7.5 mmol) and 3-bromoprop-1-yne (0.88 g, 7.5 mmol). The resultant mixture was stirred at room temperature overnight and the reaction was stopped by addition of water (20 mL). It was then extracted with diethyl ether and the organic layer was washed successively with water, brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the crude product was purified by silica gel (60–120 mesh) column chromatography using hexane–EtOAc, (1:1, v/v) as eluent to give the title compound as white oil (1.28 g, 90% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (s, 1H, CH_2=C), 5.70 (s, 1H, CH_2=C), 4.78 (d, *J* = 2.5 Hz, 2H, CH_2O), 3.20 – 3.17 (m, 1H, C<u>H</u>CH_2CO), 2.96 – 2.90 (m, 1H, C<u>H</u>CCO_2), 2.86 – 2.80 (m, 1H, CH_2C=C), 2.59 (ddd, *J* = 18.8, 6.6, 1.2Hz, 1H, CH_2CO), 2.49 (t, *J* = 2.4 Hz, 1H, CH), 2.46 (ddd, *J* = 19.4, 12.4, 1.2 Hz, 1H, CH_2C=C), 2.17-2.10 (m, 1H, C<u>H</u>CH_3), 2.04 (dt, *J* = 18.8, 1.6 Hz, 1H, CH_2CO), 1.89 – 1.74 (m, 3H, C<u>H$_2$</u>$CHCH_3$, C<u>H$_2$</u>CH_2CHCH_3), 1.68 – 1.60 (m, 4H, CH_3C=C, C<u>H$_2$</u>CH_2CHCH_3), 0.66 (d, *J* = 7.1 Hz, 3H, C<u>H$_3$</u>CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.21, 174.10, 166.09, 145.76, 138.01, 124.45, 75.10, 52.49, 45.99, 41.50, 38.35, 38.21, 36.70, 35.46, 31.78, 12.25, 8.13; IR (*v*/cm^{-1}): 3267, 2957, 2920, 2875, 1717, 1688, 1627; HRMS (ESI) calcd for $C_{18}H_{23}O_3(M+H)^+$: 287.1647, found: 287.1655; Anal. Calcd. for $C_{18}H_{22}O_3 \cdot 0.22\ CHCl_3$: C, 70.00; H, 7.16; Found: C, 69.66; H, 7.17.

*4.5. Synthesis of N-(prop-2-ynyl) 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide (**b**)*

To a stirred solution of rupestonic acid (1.24 g, 5.0 mmol) in dry DCM (10 mL) at 0°C were added successively EDCI (1.15 g, 6.0 mmol), HOBt▪H_2O (0.92 g, 6.0 mmol), *N*,*N*-diisopropylethylamine (1.0 mL, 6.0 mmol) and prop-2-yn-1-amine (0.41g, 7.5 mmol). After stirred at room temperature overnight, the reaction mixture was diluted with DCM (10 mL), washed successively with saturated $NaHCO_3$ solution and water (three times). The organic layer was then dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The crude product was purified by silica gel (60–120 mesh) column chromatography using hexane–EtOAc (1:1, v/v) as eluent to give the title compound as yellow oil (1.16 g, 81% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (s, 1H, NH), 5.55 (s, 1H, CH_2=C), 5.37 (s, 1H, CH_2=C), 4.11 (dd, *J* = 5.3, 2.6 Hz, 2H, <u>CH_2</u>NH), 3.21 –

3.14 (m, 1H, C<u>H</u>CH_2CO), 2.96-2.90 (m, 1H, C<u>H</u>CCONH), 2.89-2.83 (m, 1H, CH_2C=C), 2.58 (ddd, *J* = 18.8, 6.6, 1.2 Hz, 1H, CH_2CO), 2.56 (t, *J* = 2.6 Hz, CH), 2.46 (ddd, *J* = 19.5, 12.2, 1.3 Hz, 1H, CH_2C=C), 2.18 – 2.06 (m, 1H, C<u>H</u>CH_3), 2.03 (dt, *J* = 18.8, 1.4 Hz, 1H, CH_2CO), 1.84-1.74 (m, 3H, C<u>H$_2$</u>$CHCH_3$, C<u>H$_2$</u>CH_2CHCH_3), 1.66-1.55 (m, 4H, CH_3C=C, C<u>H$_2$</u>CH_2CHCH_3), 0.64 (d, *J* = 7.1 Hz, 3H, C<u>H$_3$</u>CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.14, 174.18, 168.55, 151.21, 137.81, 115.55, 79.32, 71.84, 45.85, 41.38, 38.65, 38.12, 36.56, 35.33, 31.26, 29.47, 12.08, 7.99; IR (*v*/cm^{-1}): 3298, 2958, 2920, 1734, 1683, 1659, 1619, 1519; HRMS (ESI) calcd for $C_{18}H_{24}NO_2(M+H)^+$: 286.1807, found: 286.1807; Anal. Calcd. for $C_{18}H_{22}NO_3 \cdot 0.25H_2O$: C, 74.58; H, 8.17; N, 4.83; Found: C, 74.42; H, 8.18; N, 4.60.

*4.6. General procedure for the synthesis of (1-substituted-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (**1-15a**) and N-(1-substituted-1H-1,2,3-triazol-4-yl)methyl 2-(5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide (**1-15b**)*

Prop-2-ynyl 2-((5*R*,8*S*,8a*S*)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate or *N*-(prop-2-ynyl) 2-((5*R*,8*S*,8a*S*)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide (1.0 eq.) and alkyl or aryl azide (2.0 eq.) was dissolved in DCM/H_2O (1:1). To this solution, CuSO4 (1 eq.) and sodium ascorbate (2 eq.) were added. The reaction mixture was stirred at room temperature overnight. After completion of the reaction, the product was extracted with DCM. The organic extract was washed with water and brine. The solvent was removed under reduced pressure to afford crude product, which was purified by column chromatography on silica gel using either cyclohexane/ ethyl acetate (3:1 to 2:1, v/v) as eluent to furnish the compounds (**1-15a**), or MeOH/DCM (100:1 to 50:1, v/v) as eluent to provide the compounds (**1-15b**).

4.6.1. *(1-(2-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (**1a**)*: yellow oil (70 % yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H, H-het), 7.31 – 7.14 (m, 4H, H-Ph), 6.22 (s, 1H, CH_2=C), 5.63 (s, 1H, CH_2=C), 5.53 (s, 2H, NCH_2Ph), 5.28 (s, 2H, CH_2O), 3.22–3.07 (m, 1H, C<u>H</u>CH_2CO), 2.88 (t, J = 11.0 Hz, 1H, C<u>H</u>CCO_2), 2.78 (d, J = 19.6 Hz, 1H, CH_2C=C), 2.58 (dd, J = 18.8, 6.5 Hz, 1H, CH_2CO), 2.47 – 2.33 (m, 1H, CH_2C=C), 2.27 (s, 3H, CH_3-Ph), 2.12 (m, 1H, C<u>H</u>CH_3), 2.03 (d, J = 18.8 Hz, 1H, CH_2CO), 1.82 – 1.73 (m, 3H, C<u>H$_2$</u>$CHCH_3$, C<u>H$_2$</u>CH_2CHCH_3), 1.71 – 1.54 (m, 4H, CH_3C=C, C<u>H$_2$</u>CH_2CHCH_3), 0.64 (d, J = 7.1 Hz, 3H, C<u>H$_3$</u>CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ

208.22, 174.20, 166.71, 145.94, 143.05, 137.97, 137.06, 132.35, 131.24, 129.62, 129.43, 126.85, 124.17, 123.62, 58.09, 52.59, 45.80, 41.33, 38.22, 36.68, 35.45, 31.77, 19.10, 12.23, 8.12; IR (v/cm^{-1}): 2954, 2922, 2853, 1689, 1626, 1457; HRMS (ESI) calcd for $C_{26}H_{32}N_3O_3(M+H)^+$: 434.2444, found: 434.2440; Anal. Calcd. for $C_{26}H_{31}N_3O_3 \cdot 1.5H_2O \cdot 0.45\ C_6H_{12}$: C, 69.16; H,7.97; N, 8.43; Found: C, 69.35; H, 7.72; N, 8.04.

*4.6.2. (1-(3-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (**2a**)*: yellow oil (72.6% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H, H-het), 7.27 – 7.06 (m, 4H, H-Ph), 6.22 (s, 1H, CH_2=C), 5.63 (s, 1H, CH_2=C), 5.47 (s, 2H, NCH_2Ph), 5.28 (s, 2H, CH_2O), 3.18 – 3.13 (m, 1H, C<u>H</u>CH_2CO), 2.88 (t, J = 11.2 Hz, 1H, C<u>H</u>CCO_2), 2.78 (d, J = 19.0 Hz, 1H, CH_2C=C), 2.57 (ddd, J = 18.8, 6.6, 1.1 Hz, 1H, CH_2CO), 2.46 – 2.36 (m, 1H, CH_2C=C), 2.33 (s, 3H, CH_3-Ph), 2.14 – 2.08 (m, 1H, C<u>H</u>CH_3), 2.03 (dt, J = 18.8, 1.4 Hz, 1H, CH_2CO), 1.80-1.71(m, 3H, C<u>H$_2$</u>$CHCH_3$, C<u>H$_2$</u>CH_2CHCH_3), 1.64-1.56 (m, 4H, CH_3C=C, C<u>H$_2$</u>CH_2CHCH_3), 0.64 (d, J = 7.1 Hz, 3H, C<u>H$_3$</u>CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.38, 174.43, 166.72, 145.91, 143.18, 139.16, 137.94, 134.35, 129.75, 129.16, 128.98, 125.31, 124.19, 123.80, 58.08, 54.40, 45.98, 41.45, 38.20, 36.64, 35.41, 31.76, 21.43, 12.22, 8.10; IR (v/cm^{-1}): 3142, 2922, 1690, 1627, 1440; Anal. Calcd. for $C_{26}H_{31}N_3O_3 \cdot 0.42\ CHCl_3$: C, 65.61; H, 6.55; N, 8.69; Found: C, 65.21; H, 6.62; N, 8.46

*4.6.3. (1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (**3a**)*: yellow oil

(74.2% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H, H-het), 7.17 (s, 4H, H-Ph), 6.22 (s, 1H, CH_2=C), 5.62 (s, 1H, CH_2=C), 5.47 (s, 2H, NCH_2Ph), 5.28 (s, 2H, CH_2O), 3.21 – 3.10 (m, 1H, C<u>H</u>CH_2CO), 2.88 (m, 1H, C<u>H</u>CCO_2), 2.78 (d, *J* = 19.5 Hz, 1H, CH_2C=C), 2.57 (ddd, *J* = 18.7, 6.6, 1.0 Hz, 1H, CH_2CO), 2.41 (dd, *J* = 19.0, 12.0 Hz, 1H, CH_2C=C), 2.34 (s, 3H, CH_3-Ph), 2.11 (m, 1H, C<u>H</u>CH_3), 2.03 (d, *J* = 18.8 Hz, 1H, CH_2CO), 1.80 – 1.76 (m, 3H, C<u>H$_2$</u>$CHCH_3$, C<u>H$_2$</u>CH_2CHCH_3), 1.64-1.76 (m, 4H, CH_3C=C, C<u>H$_2$</u>CH_2CHCH_3), 0.64 (d, *J* = 7.1 Hz, 3H, C<u>H$_3$</u>CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.19, 174.19, 166.58, 145.86, 143.17, 138.97, 137.94, 131.44, 129.93, 128.30, 124.14, 123.67, 58.09, 54.19, 45.95, 41.47, 38.21, 36.66, 35.43, 31.75, 21.27, 12.22, 8.09; IR (*v*/cm^{-1}):2953, 2923, 2853, 1691, 1627, 1458; HRMS (ESI) calcd for $C_{26}H_{32}N_3O_3\ (M+H)^+$: 434.2444, found: 434.2445;

Anal. Calcd. for $C_{26}H_{31}N_3O_3 \cdot 0.5\ H_2O \cdot 0.5C_6H_{12}$: C, 71.87; H, 7.90; N, 8.67; Found: C, 72.12; H, 7.76; N, 8.42

*4.6.4 (1-benzyl-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate(**4a**)*: yellow oil (73.4% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H, H-het), 7.42 – 7.25 (m, 5H, H-Ph), 6.22 (s, 1H, CH_2=C), 5.63 (s, 1H, CH_2=C), 5.52 (s, 2H, NCH_2Ph), 5.28 (s, 2H, CH_2O), 3.22 – 3.08 (m, 1H, C<u>H</u>CH_2CO), 2.97 – 2.83 (m, 1H, C<u>H</u>CCO_2), 2.78 (dd, *J* = 19.5, 1.0 Hz, 1H, CH_2C=C), 2.57 (ddd, *J* = 18.7, 6.6, 1.1 Hz, 1H, CH_2CO), 2.48 – 2.33 (m, 1H, CH_2C=C), 2.21–2.07 (m, 1H, C<u>H</u>CH_3), 2.01 (d, *J* = 18.9 Hz, 1H, CH_2CO), 1.81 – 1.69 (m, 3H, C<u>H$_2$</u>$CHCH_3$, C<u>H$_2$</u>CH_2CHCH_3), 1.65 – 1.54 (m, 4H, CH_3C=C, C<u>H$_2$</u>CH_2CHCH_3), 0.64 (d, *J* = 7.1 Hz, 3H, C<u>H$_3$</u>CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.22, 174.23, 166.73, 145.99, 138.03, 134.48, 129.36, 129.09, 128.23, 124.13, 123.78, 58.13, 54.43, 45.99, 41.50, 38.39, 38.10, 36.70, 35.46, 31.79, 12.25, 8.14; IR (*v*/cm^{-1}): 2955, 2923, 2854, 1687, 1627, 1497, 1455; HRMS (ESI) calcd for $C_{25}H_{30}N_3O_3$ $(M+H)^+$: 420.2287, found: 420.2281; Anal. Calcd. for $C_{25}H_{29}N_3O_3 \cdot 0.3CHCl_3 \cdot 0.35C_6H_{12}$: C, 67.88; H, 6.97; N, 8.67; Found: C, 67.74; H, 7.23; N, 8.38.

*4.6.5 (1-(3-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (**5a**)*: yellow oil

(65% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H, H-het), 7.31 – 7.27, 6.98 - 6.79 (m, 4H, H-Ph), 6.23 (s, 1H, CH_2=C), 5.64 (s, 1H, CH_2=Cb), 5.49 (s, 2H, NCH_2Ph), 5.29 (s, 2H, CH_2O), 3.78 (s, 3H, OCH_3), 3.16 – 3.18 (m, 1H, C<u>H</u>CH_2CO), 2.89 (t, *J* = 11.6 Hz, 1H, C<u>H</u>CCO_2), 2.79 (d, *J* = 20.3 Hz, 1H, CH_2C=C), 2.58 (dd, *J* = 18.8, 6.6 Hz, 1H, CH_2CO), 2.42 (dd, *J* = 17.8, 9.3 Hz, 1H, CH_2C=C), 2.12 (m, 1H, C<u>H</u>CH_3), 2.04 (d, *J* = 20.2 Hz, 1H, CH_2CO), 1.89 – 1.67 (m, 3H, C<u>H$_2$</u>$CHCH_3$, C<u>H$_2$</u>CH_2CHCH_3), 1.63 (m, 4H, CH_3C=C, C<u>H$_2$</u>CH_2CHCH_3), 0.65 (d, *J* = 7.1 Hz, 3H, C<u>H$_3$</u>CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.34, 174.37, 166.72, 160.28, 145.92, 143.26, 137.95, 135.89, 130.38, 124.20, 123.83, 120.42, 114.35, 113.98, 58.09, 55.44, 54.33, 45.99, 41.47, 38.37, 38.06, 36.66, 35.43, 31.77, 12.23, 8.11; IR (*v*/cm^{-1}): 2958, 2923, 1689, 1627; HRMS (ESI) calcd for $C_{26}H_{32}N_3O_4$ $(M+H)^+$: 450.2393, found: 450.2338; Anal. Calcd. for $C_{26}H_{31}N_3O_4 \cdot 0.25\ CHCl_3$: C, 65.74; H, 6.57; N, 8.77; Found: C, 65.85; H, 6.75; N, 8.54

*4.6.6. (1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (**6a**)*: yellow oil (67.2% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H, H-het), 7.23 (d, *J* = 8.8 Hz, 2H, H-Ph), 6.89 (d, *J* = 8.7 Hz, 2H, H-Ph), 6.22 (s, 1H, CH_2=C), 5.63 (s, 1H, CH_2=C), 5.45 (s, 2H, NCH_2Ph), 5.28 (s, 2H, CH_2O), 3.80 (s, 3H, OCH_3), 3.23 – 3.12 (m, 1H, C<u>H</u>CH_2CO), 2.91-2.86 (m, 1H, C<u>H</u>CCO_2), 2.79 (dd, *J* = 19.5, 1.0 Hz, 1H, CH_2C=C), 2.58 (ddd, *J* = 18.7, 6.6, 1.1 Hz, 1H, CH_2CO), 2.49 – 2.35 (m, 1H, CH_2C=C), 2.17 – 2.08 (m, 1H, C<u>H</u>CH_3), 2.08 – 1.99 (dt, *J* = 18.8, 1.2 Hz , 1H, CH_2CO), 1.81 – 1.70 (m, 3H, C<u>H$_2$</u>$CHCH_3$, C<u>H$_2$</u>CH_2CHCH_3), 1.67 – 1.58 (m, 4H, CH_3C=C, C<u>H$_2$</u>CH_2CHCH_3), 0.64 (d, *J* = 7.1 Hz, 3H, C<u>H$_3$</u>CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.28, 174.27, 166.76, 160.20, 145.98, 143.18, 137.99, 129.89, 126.44, 124.17, 123.56, 114.69, 58.14, 55.50, 53.98, 46.01, 41.50, 38.24, 36.70, 35.46, 31.80, 29.85, 12.25, 8.13; IR (*v*/cm^{-1}): 2921, 1698, 1611, 1513; Anal. Calcd. for $C_{26}H_{31}N_3O_4$·0.55 $CHCl_3$·0.40 C_6H_{12}: C, 63.32; H, 6.68; N, 7.66; Found: C, 63.14; H, 6.88; N, 7.36.

*4.6.7. (1-(2-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (**7a**)*: yellow oil (66% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H, H-het), 7.43 (dd, *J* = 7.9, 1.3 Hz, 1H, H-Ph), 7.34 – 7.21 (m, 3H, H-Ph), 6.23 (s, 1H, CH_2=C), 5.66 (s, 2H, NCH_2Ph), 5.63 (s, 1H, CH_2=C), 5.30 (s, 2H, CH_2O), 3.17 – 3.15 (m, 1H, C<u>H</u>CH_2CO), 2.90 – 2.88 (m, 1H, C<u>H</u>CCO_2), 2.79 (dd, *J* = 19.5, 0.9 Hz, 1H, CH_2C=C), 2.58 (ddd, *J* = 18.7, 6.6, 1.1 Hz, 1H, CH_2CO), 2.42 (ddd, *J* = 19.8, 12.4, 1 Hz, 1H, CH_2C=C), 2.16 – 2.10 (m, 1H, C<u>H</u>CH_3), 2.03 (dt, *J* = 18.8, 1.4 Hz , 1H, CH_2CO), 1.81 – 1.66 (m, 3H, C<u>H$_2$</u>$CHCH_3$, C<u>H$_2$</u>CH_2CHCH_3), 1.65 – 1.57 (m, 4H, CH_3C=C, C<u>H$_2$</u>CH_2CHCH_3), 0.64 (d, *J* = 7.1 Hz, 3H, C<u>H$_3$</u>CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.31, 174.30, 166.74, 145.97, 143.17, 137.99, 133.76, 132.33, 130.69, 130.57, 130.16, 127.79, 124.20, 124.15, 58.10, 51.66, 46.01, 41.50, 38.38, 38.14, 36.70, 35.46, 31.80, 12.25, 8.13; IR (*v*/cm^{-1}): 2922, 2852, 1699, 1624, 1447; HRMS (ESI) calcd for $C_{25}H_{29}N_3O_3Cl$ $(M+H)^+$: 454.1897, found: 454.1851; Anal. Calcd. for $C_{25}H_{28}ClN_3O_3$·0.25 $CHCl_3$·0.35 C_6H_{12}: C, 63.97; H, 6.38; N, 8.19; Found: C, 64.16; H, 6.60; N, 7.96.

*4.6.8. (1-(3-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (**8a**)*: yellow oil (47% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H, H-het), 7.36 – 7.28 (m, 2H, H-Ph), 7.25 (dd, *J* = 2.3, 1.8 Hz, 1H, H-Ph), 7.15 (dt, *J* = 6.9, 1.7 Hz, 1H, H-Ph), 6.24 (s, 1H, CH_2=C), 5.64 (s, 1H,

CH_2=C), 5.50 (s, 2H, NCH_2Ph), 5.30 (s, 2H, CH_2O), 3.17 – 3.15 (m, 1H, C<u>H</u>CH_2CO), 2.92 – 2.86 (m, 1H, C<u>H</u>CCO_2), 2.79 (dd, *J* = 19.5, 1.0 Hz, 1H, CH_2C=C), 2.58 (ddd, *J* = 18.7, 6.6, 1.1 Hz, 1H, CH_2CO), 2.42 (ddd, *J* = 19.3, 12.3, 1.2 Hz, 1H, CH_2C=C), 2.14 – 2.10 (m, 1H, C<u>H</u>CH_3), 2.03 (dt, *J* = 18.8, 1.4 Hz, 1H, CH_2CO), 1.81 – 1.70 (m, 3H, C<u>H</u>$_2$$CHCH_3$, C<u>H</u>$_2$$CH_2CHCH_3$), 1.65 – 1.58 (m, 4H, CH_3C=C, C<u>H</u>$_2$$CH_2CHCH_3$), 0.64 (d, *J* = 7.1 Hz, 3H, C<u>H</u>$_3$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.28, 174.24, 166.76, 145.93, 143.53, 137.99, 136.44, 135.26, 130.61, 129.27, 128.28, 126.27, 124.26, 123.91, 58.06, 53.68, 46.00, 41.49, 38.24, 36.69, 35.45, 31.81, 27.04, 12.24, 8.13; IR (*v*/cm^{-1}): 2922, 2852, 1693, 1626, 1435; Anal. Calcd. for $C_{25}H_{28}ClN_3O_3$·0.25 $CHCl_3$·0.35 C_6H_{12}: C, 63.97; H, 6.38; N, 8.19; Found: C, 64.18; H, 6.61; N, 8.09.

*4.6.9. (1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (**9a**)*: yellow oil (53.5% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H, H-het), 7.35 (d, *J* = 11.0 Hz, 2H, H-Ph), 7.21 (d, *J* = 8.6 Hz, 2H, H-Ph), 6.23 (s, 1H, CH_2=C), 5.62 (s, 1H, CH_2=C), 5.49 (s, 2H, NCH_2Ph), 5.29 (s, 2H, CH_2O), 3.17-3.16 (m, 1H, C<u>H</u>CH_2CO), 2.89 (dd, *J* = 16.2, 5.6 Hz, 1H, C<u>H</u>CCO_2), 2.81 – 2.76 (m, 1H, CH_2C=C), 2.58 (ddd, *J* = 18.7, 6.6, 1.1 Hz, 1H, CH_2CO), 2.46 – 2.37 (m, 1H, CH_2C=C), 2.18 – 2.08 (m, 1H, C<u>H</u>CH_3), 2.04 (m, *J* = 18.9 Hz, 1H, CH_2CO), 1.80 – 1.69 (m, 3H, C<u>H</u>$_2$$CHCH_3$, C<u>H</u>$_2$$CH_2CHCH_3$), 1.65 – 1.55 (m, 4H, CH_3C=C, C<u>H</u>$_2$$CH_2CHCH_3$), 0.65 (d, *J* = 7.1 Hz, 3H, C<u>H</u>$_3$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.19, 174.17, 166.70, 161.95, 159.48, 145.94, 137.96, 131.22, 130.82, 125.01, 124.08, 121.80, 116.13, 115.92, 58.07, 47.93, 45.96, 41.48, 38.36, 38.10, 36.59, 35.44, 31.76, 12.23, 8.10; IR (*v*/cm^{-1}): 2953, 2923, 2853, 1690, 1628, 1607, 1511; HRMS (ESI) calcd for $C_{25}H_{29}ClN_3O_3$ $(M+H)^+$: 454.1897, found: 454.1893; Anal. Calcd. for $C_{25}H_{28}ClN_3O_3$·0.20 $CHCl_3$·0.60 C_6H_{12}: C, 65.44; H, 6.75; N, 7.95; Found: C, 65.50; H, 6.82; N, 7.86.

*4.6.10. (1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (**10a**)*: yellow oil (45.7% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H, H-het), 7.43 – 7.05 (m, 4H, H-Ph), , 6.23 (s, 1H, CH_2=C), 5.63 (s, 1H, CH_2=C), 5.58 (s, 2H, NCH_2Ph), 5.29 (d, *J* = 1.7 Hz, 2H, CH_2O), 3.17 – 3.16 (m, 1H, C<u>H</u>CH_2CO), 2.89 (t, *J* = 11.1 Hz, 1H, C<u>H</u>CCO_2), 2.79 (d, *J* = 19.5 Hz, 1H, CH_2C=C), 2.58 (dd, *J* = 18.2, 7.2 Hz, 1H, CH_2CO), 2.42 (dd, *J* = 19.5, 12.2 Hz, 1H, CH_2C=C), 2.12 (m, 1H, C<u>H</u>CH_3), 2.03 (d, *J* = 18.8 Hz, 1H, CH_2CO), 1.82 – 1.68 (m, 3H, C<u>H</u>$_2$$CHCH_3$, C<u>H</u>$_2$$CH_2CHCH_3$), 1.65 – 1.55 (m, 4H,

$CH_3C=C$, $C\underline{H}_2CH_2CHCH_3$), 0.64 (dd, *J* = 7.1, 2.0 Hz, 3H, $C\underline{H}_3CH$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.19, 174.17, 166.70, 161.95, 159.48, 145.94, 137.96, 131.21, 130.83, 125.01, 124.18, 123.97, 121.80, 116.02, 58.07, 47.93, 45.96, 41.48, 38.36, 38.10, 36.59, 35.44, 31.76, 12.23, 8.10; IR (*v*/cm^{-1}): 3143, 2957, 2922, 2854, 1711, 1688, 1628, 1589, 1493; HRMS (ESI) calcd for $C_{25}H_{29}N_3O_3F$ $(M+H)^+$: 438.2193, found: 438.2187; Anal. Calcd. for $C_{25}H_{28}FN_3O_3 \cdot 0.6\ H_2O \cdot 0.25\ C_6H_{12}$: C, 67.81; H, 6.91; N, 8.95; Found: C, 68.04; H, 7.13; N, 8.57.

*4.6.11. (1-(3-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (**11a**)*: yellow oil (60.1% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H, H-het), 7.35 (m, 1H, H-Ph), 7.08 – 6.93 (m, 3H, H-Ph), 6.24 (s, 1H, CH_2=C), 5.64 (s, 1H, CH_2=C), 5.52 (s, 2H, NCH_2Ph), 5.30 (s, 2H, CH_2O), 3.19 – 3.13 (m, 1H, $C\underline{H}CH_2CO$), 2.92 – 2.86 (m, 1H, $C\underline{H}CCO_2$), 2.77 (d, *J* = 19.5 Hz, 1H, $CH_2C=C$), 2.58 (ddd, *J* = 18.7, 6.6, 1.0 Hz, 1H, CH_2CO), 2.49 – 2.32 (m, 1H, $CH_2C=C$), 2.15 – 2.09 (m, 1H, $C\underline{H}CH_3$), 2.02 (dt, *J* = 18.8, 1.2 Hz , 1H, CH_2CO), 1.81 – 1.69 (m, 3H, $C\underline{H}_2CHCH_3$, $C\underline{H}_2CH_2CHCH_3$), 1.66 – 1.55 (m, 4H, $CH_3C=C$, $C\underline{H}_2CH_2CHCH_3$), 0.64 (d, *J* = 7.1 Hz, 3H, $C\underline{H}_3CH5$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.15, 174.12, 166.62, 164.27, 161.80, 145.76, 143.37, 137.85, 130.84, 124.11, 123.69, 115.94, 115.03, 57.91, 53.50, 45.86, 41.34, 38.23, 37.97, 36.54, 35.30, 31.66, 12.09, 7.97; IR (*v*/cm^{-1}): 3142, 2959, 2922, 1712, 1687, 1628, 1592, 1489, 1452; HRMS (ESI) calcd for $C_{25}H_{29}N_3O_3F$ $(M+H)^+$: 438.2193, found: 438.2179; Anal. Calcd. for $C_{25}H_{28}FN_3O_3 \cdot H_2O$: C, 65.92; H, 6.64; N, 9.22; Found: C, 65.88; H, 6.34; N, 9.25..

*4.6.12. (1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (**12a**)*: yellow oil (57.2% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H, H-het), 7.28 – 7.06 (m, 4H, H-Ph), 6.23 (s, 1H, CH_2=C), 5.64 (s, 1H, CH_2=C), 5.49 (s, 2H, NCH_2Ph), 5.29 (s, 2H, CH_2O), 3.17 – 3.16 (m, 1H, $C\underline{H}CH_2CO$), 2.89 (dd, *J* = 15.8, 5.5 Hz, 1H, $C\underline{H}CCO_2$), 2.83 – 2.73 (m, 1H, $CH_2C=C$), 2.58 (ddd, *J* = 18.7, 6.6, 1.1 Hz, 1H, CH_2CO)., 2.49 – 2.35 (m, 1H, $CH_2C=C$), 2.15 – 2.10 (m, 1H, $C\underline{H}CH_3$), 2.04 (d, *J* = 18.9 Hz, 1H, CH_2CO), 1.83-1.76 (m, 3H, $C\underline{H}_2CHCH_3$, $C\underline{H}_2CH_2CHCH_3$), 1.65 – 1.57 (m, 4H, $CH_3C=C$, $C\underline{H}_2CH_2CHCH_3$), 0.64 (d, *J* = 7.1 Hz, 3H, $C\underline{H}_3CH$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.19, 174.12, 166.74, 164.30, 161.83, 130.39, 130.36, 130.20, 130.12, 124.21, 123.71, 116.44, 116.22, 58.07, 53.64, 45.98, 41.47, 38.36, 38.09, 36.68, 35.44, 31.78, 12.23, 8.12; IR (*v*/cm^{-1}): 3140, 2923, 2853, 1690,

1628, 1607, 1511; HRMS (ESI) calcd for $C_{25}H_{29}N_3O_3F$ $(M+H)^+$: 438.2193, found: 438.2194; Anal. Calcd. for $C_{25}H_{28}FN_3O_3 \cdot 0.30\ CHCl_3 \cdot 0.60\ C_6H_{12}$: C, 66.24; H, 6.84; N, 8.02; Found: C, 66.06; H,6.86; N, 7.90.

*4.6.13. (1-(3,4-dichlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (**13a**)*: yellow oil (76.6% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H, H-het), 7.45 (d, *J* = 8.2 Hz, 1H, H-Ph), 7.36 (d, *J* = 2.1 Hz, 1H, H-Ph), 7.11 (dd, *J* = 8.3, 2.1 Hz, 1H, H-Ph), 6.24 (s, 1H, CH_2=C), 5.65 (s, 1H, CH_2=C), 5.48 (s, 2H, NCH_2Ph), 5.30 (s, 2H, CH_2O), 3.21 – 3.11 (m, 1H, C<u>H</u>CH_2CO), 2.97-2.86 (m, 1H, C<u>H</u>CCO_2), 2.79 (dd, *J* = 19.4, 0.9 Hz, 1H, CH_2C=C), 2.58 (ddd, *J* = 18.7, 6.6, 1.1 Hz, 1H, CH_2CO), 2.42 (ddd, *J* = 19.5, 12.4, 0.9 Hz, 1H, CH_2C=C), 2.22 – 2.07 (m, 1H, C<u>H</u>CH_30), 2.04 (d, *J* = 18.8 Hz , 1H, CH_2CO), 1.83 – 1.72 (m, 3H, C<u>H$_2$</u>$CHCH_3$, C<u>H$_2$</u>CH_2CHCH_3), 1.66 – 1.55 (m, 4H, CH_3C=C, C<u>H$_2$</u>CH_2CHCH_3), 0.64 (d, *J* = 7.1 Hz, 3H, C<u>H$_3$</u>CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.19, 174.10, 166.75, 145.90, 143.67, 138.00, 134.63, 133.56, 133.48, 131.32, 130.09, 127.38, 124.29, 123.91, 58.02, 53.07, 45.98, 41.48, 38.35, 38.08, 36.68, 35.44, 31.82, 12.24, 8.13; IR (ν/cm^{-1}): 2954, 2923, 2853, 1688, 1627, 1462; Anal. Calcd. for $C_{25}H_{27}Cl_2N_3O_3 \cdot 0.25\ CHCl_3 \cdot 0.30\ C_6H_{12}$: C, 59.74; H, 5.72; N, 7.73; Found: C, 59.82; H, 5.90; N, 7.53.

*4.6.14. (1-(cyclohex-2-enyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (**14a**)*: yellow oil (39% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H, H-het), 6.25 (s, 1H, CH_2=C), 6.15 (m, 1H, CH=CH), 5.77 (m, 1H, CH=CH), 5.64 (s, 1H, CH_2=C), 5.28 (m, 3H, CH_2O, CHN), 3.18 – 3.17 (m, 1H, C<u>H</u>CH_2CO), 2.91 (m, 1H, C<u>H</u>CCO_2), 2.81 (m, *J* = 19.3 Hz, 1H, 1H, CH_2C=C), 2.58 (ddd, *J* = 18.4, 6.2, 0.8 Hz, 1H, CH_2CO), 2.45-2.37 (m, 1H, CH_2C=C), 2.22 -2.10 (m, 1H, C<u>H</u>CH_3), 2.03 (d, *J* = 18.8 Hz, 1H, CH_2CO), 1.99 – 1.57 (m, 13H, C<u>H$_2$</u>$CHCH_3$, C<u>H$_2$</u>CH_2CHCH_3, CH_3C=C, $CH_2CH_2CH_2$), 0.65 (d, *J* = 7.1 Hz, 3H, C<u>H$_3$</u>CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.24, 174.28, 166.79, 146.00, 137.95, 134.26, 124.14, 123.95, 58.23, 56.18, 46.00, 41.48, 38.42, 38.10, 36.68, 35.45, 31.75, 24.70, 19.13, 12.24, 8.11; IR (ν/cm^{-1}): 2954, 2921, 2852, 1690, 1627, 1456; HRMS (ESI) calcd for $C_{24}H_{32}N_3O_3$ $(M+H)^+$: 410.2443, found: 410.2431; Anal. Calcd. for $C_{24}H_{31}N_3O_3 \cdot 0.6\ H_2O \cdot 0.33C_6H_{12}$: C, 69.65; H, 8.14; N, 9.37; Found: C, 69.54; H, 7.92; N, 9.30.

*4.6.15. (1-cyclohexyl-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (**15a**)*: yellow oil (64.8% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H, H-het), 6.25 (s, 1H, CH_2=C), 5.64 (s, 1H, CH_2=C), 5.30 (s, *J* = 2H, CH_2O), 4.43 (m, 1H, CHN), 3.24 – 3.11 (m, 1H, C<u>H</u>CH_2CO), 2.93 – 2.88 (m, 1H, C<u>H</u>CCO_2), 2.81 – 2.78 (m, CH_2C=C), 2.58 (ddd, *J* = 18.7, 6.6, 1.0 Hz, 1H, CH_2CO), 2.42 (ddd, *J* = 20.0, 12.4 0.8 Hz, 1H, CH_2C=C), 2.23 –2.17 (m, 2H, NCHC<u>H_2</u>), 2.15 – 2.07 (m, 1H, C<u>H</u>CH_3), 2.05 – 2.01 (m, *J* = 18.8, 1.2 Hz, 1H, CH_2CO), 1.95 – 1.88 (m, 2H, NCHC<u>H_2</u>), 1.81 – 1.59 (m, 13H, C<u>H_2</u>$CHCH_3$, C<u>H_2</u>CH_2CHCH_3, CH_3C=C, CH_2C<u>H_2</u>C<u>H_2</u>C<u>H_2</u>CH_2), 0.64 (d, *J* = 7.1 Hz, 3H, C<u>H_3</u>CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.24, 174.28, 166.80, 146.00, 137.94, 124.12, 60.37, 58.25, 45.99, 41.47, 38.42, 38.07, 36.67, 35.44, 33.66, 31.75, 25.25, 25.21, 12.23, 8.11; IR (*v*/cm^{-1}): 3142, 2924, 2855, 1691, 1628, 1450; HRMS (ESI) calcd for $C_{24}H_{34}N_3O_3$ $(M+H)^+$: 412.2600, found: 412.2599; Anal. Calcd. for $C_{24}H_{33}N_3O_3 \cdot 0.3\ CHCl_3 \cdot 0.30\ C_6H_{12}$: C, 66.30; H, 7.87; N, 8.89; Found: C, 66.08; H,7.92; N, 8.61.

*4.6.16. N-(1-(2-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide (**1b**)*: yellow oil (52% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H, H-het), 7.32 – 7.13 (m, 4H, H-Ph), 6.67 (br, 1H, NH), 5.55 (s, 1H, CH_2=C), 5.51 (s, 2H, NCH_2Ph), 5.34 (d, J = 0.8 Hz, 1H, CH_2=C), 4.54 (s, 2H, C<u>H_2</u>NHCO), 3.19-3.13 (m, 1H, C<u>H</u>CH_2CO), 2.93 – 2.85 (m, 1H, C<u>H</u>CCO_2), 2.82 (d, J = 19.6 Hz, 1H, CH_2C=C), 2.57 (ddd, J = 18.7, 6.6, 1.0 Hz, 1H, CH_2CO), 2.43 (dd, J = 19.3, 12.3 Hz, 1H, CH_2C=C), 2.28 (s, 3H, CH_3-Ph), 2.15 – 2.07 (m, 1H, C<u>H</u>CH_3), 2.07 – 1.98 (dt, J = 18, 1 Hz, 1H, CH_2CO), 1.83 – 1.70 (m, 3H, C<u>H_2</u>$CHCH_3$, C<u>H_2</u>CH_2CHCH_3), 1.67 – 1.51 (m, 4H, CH_3C=C, C<u>H_2</u>CH_2CHCH_3), 0.65 (d, J = 7.2 Hz, 3H, C<u>H_3</u>CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.29, 174.41, 169.08, 151.34, 137.92, 137.04, 132.32, 131.25, 129.65, 129.45, 126.87, 115.71, 60.53, 52.67, 45.99, 41.52, 38.71, 38.29, 36.71, 35.48, 31.38, 19.12, 12.22, 8.13; IR (v/cm^{-1}): 3330, 2923, 1687, 1622; HRMS (ESI) calcd for $C_{26}H_{33}N_4O_2$ $(M+H)^+$: 433.2603, found: 433.2603; Anal. Calcd. for $C_{26}H_{32}N_4O_2 \cdot 0.9\ CH_2Cl_2 \cdot 0.2\ CH_3OH$: C, 63.13; H, 6.77; N, 10.87; Found: C, 63.26; H,6.67; N, 10.72.

*4.6.17. N-(1-(3-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide (**2b**)*: yellow oil (59.4% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H, H-het), 7.2 (t, J = 7.4 Hz, 1H, H-Ph), 7.16 (d,

J = 7.6 Hz, 1H, H-Ph), 7.08 – 7.04 (m, 2H, H-Ph), 6.72 (t, J = 4.8 Hz, 1H, NH), 5.55 (s, 1H, CH_2=C), 5.45 (s, 2H, NCH_2Ph), 5.33 (d, 1H, CH_2=C), 4.53 (d, J = 5.6 Hz, 2H, $C\underline{H}_2NHCO$), 3.17 – 3.13 (m, 1H, $C\underline{H}CH_2CO$), 2.94 – 2.86 (m, 1H, $C\underline{H}CCO_2$), 2.83 (d, J = 19.6 Hz, 1H, CH_2C=C), 2.56 (ddd, J = 18.7, 6.6, 0.9 Hz, 1H, CH_2CO), 2.43 (ddd, J = 19.8, 12.2, 0.8 Hz, 1H, CH_2C=C), 2.33 (s, 3H, CH_3-Ph), 2.14 – 2.07 (m, 1H, $C\underline{H}CH_3$), 2.02 (d, J = 19.0 Hz, 1H, CH_2CO), 1.82 – 1.69 (m, 3H, $C\underline{H}_2CHCH_3$, $C\underline{H}_2CH_2CHCH_3$), 1.65 – 1.53 (m, 4H, CH_3C=C, $C\underline{H}_2CH_2CHCH_3$), 0.63 (d, J = 7.1 Hz, 3H, $C\underline{H}_3CH$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.27, 174.40, 169.09, 151.32, 144.77, 139.17, 137.90, 134.35, 129.77, 129.17, 129.00, 125.33, 122.19, 115.71, 54.45, 45.97, 41.50, 38.67, 38.30, 36.69, 35.46, 35.22, 31.39, 21.45, 12.20, 8.11; IR (v/cm^{-1}): 3330, 3142, 2956, 2921, 2873, 1684, 1658, 1618; Anal. Calcd. for $C_{26}H_{32}N_4O_2 \cdot 0.5\ CH_2Cl_2 \cdot 0.3\ CH_3OH$: C, 66.40; H, 7.11; N, 11.56; Found: C, 66.13; H,7.12; N, 11.46.

*4.6.18. N-(1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide (**3b**)*: yellow oil (34.8% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H, H-het), 7.16 (s, 4H, H-Ph), 6.69 (br, 1H, NH), 5.55 (s, 1H, CH_2=C), 5.45 (s, 2H, NCH_2Ph), 5.33 (d, J = 0.6 Hz, 1H, CH_2=C), 4.52 (d, J = 5.5 Hz, 2H, $C\underline{H}_2NHCO$), 3.18 – 3.13 (m, 1H, $C\underline{H}CH_2CO$), 2.94 – 2.85 (m, 1H, $C\underline{H}CCO_2$), 2.82 (d, J = 19.9 Hz, 1H, CH_2C=C), 2.57 (ddd, J = 18.7, 6.6, 0.9 Hz, 1H, CH_2CO), 2.42 (ddd, J = 19.5, 11.7, 0.8 Hz, 1H, CH_2C=C), 2.34 (s, 3H, CH_3-Ph), 2.16 – 2.07 (m, 1H, $C\underline{H}CH_3$), 2.06 – 1.98 (m, 1H, CH_2CO), 1.82-1.71 (m, 3H, $C\underline{H}_2CHCH_3$, $C\underline{H}_2CH_2CHCH_3$), 1.69 – 1.50 (m, 3H, CH_3C=C, $C\underline{H}_2CH_2CHCH_3$), 0.64 (t, J = 7.3 Hz, 3H, $C\underline{H}_3CH$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.28, 174.42, 169.09, 151.32, 139.02, 137.90, 131.41, 129.96, 128.33, 122.11, 115.71, 60.52, 54.27, 45.97, 41.51, 38.49, 36.69, 35.47, 35.19, 31.38, 21.29, 12.20, 8.11; IR (v/cm^{-1}): 3331, 2956, 2923, 2855, 1683, 1658, 1617, 1516; HRMS (ESI) calcd for $C_{26}H_{33}N_4O_2$ $(M+H)^+$: 433.2604, found: 433.2584; Anal. Calcd. for $C_{26}H_{32}N_4O_2 \cdot 0.2\ CH_2Cl_2 \cdot 0.4\ CH_3OH$: C, 69.08; H, 7.41; N, 12.12; Found: C, 69.41; H,7.49; N, 11.97.

*4.6.19. N-(1-benzyl-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide (**4b**)*: yellow oil (63.4% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H, H-het), 7.36 – 7.23 (m, 5H, H-Ph), 6.82 (br, 1H, NH), 5.56 (s, 1H, CH_2=C), 5.48 (s, 2H, NCH_2Ph), 5.33 (s, 1H, CH_2=C), 4.52 (d, J = 4.9 Hz, 2H, $C\underline{H}_2NHCO$), 3.18 – 3.12 (m, 1H, $C\underline{H}CH_2CO$), 2.93 – 2.76 (m, 2H, $C\underline{H}CCO_2$, CH_2C=C), 2.56 (dd, J = 18.8, 6.6 Hz, 1H, CH_2CO), 2.42 (dd, J = 19.3, 12.0 Hz, 1H, CH_2C=C), 2.17 – 2.05 (1H, $C\underline{H}CH_3$), 2.01

(d, J = 18.8 Hz, 1H, CH_2CO), 1.82 – 1.71 (m, 3H, C<u>H</u>$_2$CHCH$_3$, C<u>H</u>$_2$CH$_2$CHCH$_3$), 1.65 – 1.47 (m, 4H, CH_3C=C, C<u>H</u>$_2$CH$_2$CHCH$_3$), 0.62 (d, J = 7.1 Hz, 3H, C<u>H</u>$_3$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.34, 174.53, 169.11, 151.24, 137.87, 134.47, 129.28, 129.00, 128.95, 128.38, 128.33, 128.24, 122.31, 115.75, 54.41, 45.97, 41.49, 38.63, 38.29, 36.67, 35.44, 35.17, 31.36, 12.19, 8.10; IR (v/cm^{-1}): 3330, 2957, 2922, 1683, 1658, 1621; HRMS (ESI) calcd for $C_{25}H_{31}N_4O_2(M+H)^+$: 419.2447, found: 419.2448; Anal. Calcd. for $C_{25}H_{30}N_4O_2 \cdot 0.4\ CDCl_3 \cdot 0.2\ CH_3Ph$: C, 66.33; H, 6.57; N, 11.55; Found: C, 66.45; H,6.32; N, 11.42.

*4.6.20. N-(1-(3-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide (**5b**)*: yellow oil (54.9% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H, H-het), 7.28 – 6.79 (m, 4H, H-Ph), 6.63 (t, J = 4.3 Hz, 1H, NH), 5.55 (s, 1H, CH_2=C), 5.47 (s, 2H, NCH_2Ph), 5.34 (d, J = 0.9 Hz, 1H, CH_2=C), 4.55 (d, J = 5.6 Hz, 2H, C<u>H</u>$_2$NHCO), 3.78 (s, 3H, OCH_3), 3.19 – 3.13 (m, 1H, C<u>H</u>CH$_2$CO), 2.94-2.87 (m, 1H, C<u>H</u>CCO$_2$), 2.83 (d, J = 19.9 Hz, 1H, CH_2C=C), 2.57 (ddd, J = 18.7, 6.6, 1.1 Hz, 1H, CH_2CO), 2.43 (dd, J = 19.0, 12.8 Hz, 1H, CH_2C=C), 2.14 – 2.08 (m, 1H, C<u>H</u>CH$_3$), 2.07 – 1.99 (m, 1H, CH_2CO), 1.82 – 1.72 (m, 3H, , C<u>H</u>$_2$CHCH$_3$, C<u>H</u>$_2$CH$_2$CHCH$_3$), 1.64 – 1.57 (m, 4H, CH_3C=C, C<u>H</u>$_2$CH$_2$CHCH$_3$), 0.64 (d, J = 7.1 Hz, 3H, C<u>H</u>$_3$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.34, 174.45, 169.11, 160.28, 151.35, 137.93, 135.90, 130.41, 120.44, 115.73, 114.33, 114.06, 55.46, 54.39, 46.00, 41.52, 38.69, 38.31, 36.70, 35.48, 35.22, 31.41, 12.22, 8.13; IR (v/cm^{-1}): 3331, 2957, 2922, 2854, 1683, 1659, 1614; HRMS (ESI) calcd for $C_{26}H_{33}N_4O_3$ $(M+H)^+$: 449.2553, found: 449.2555; Anal. Calcd. for $C_{26}H_{32}N_4O_3 \cdot 0.1\ CH_2Cl_2 \cdot 0.4\ CH_3OH$: C, 67.72; H, 7.26; N, 11.93; Found: C, 68.02; H,7.33; N, 11.60.

*4.6.21 N-(1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide (**6b**)*: yellow oil (62.1% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H, H-het), 7.21 (dt, J = 8.8, 2.6 Hz, 2H, H-Ph), 6.88 (dt, J = 8.8, 2.6 Hz, 2H, H-Ph), 6.76 (t, J = 5.2 Hz, 1H, NH), 5.55 (s, 1H, CH_2=C), 5.42 (s, 2H, NCH_2Ph), 5.32 (d, J = 0.8 Hz, 1H, CH_2=C), 4.51 (d, J = 5.6 Hz, 2H, C<u>H</u>$_2$NHCO), 3.79 (s, 3H, OCH_3), 3.27 – 3.13 (m, 1H, C<u>H</u>CH$_2$CO), 2.93 – 2.86 (m, 1H, C<u>H</u>CCO$_2$), 2.82 (d, J = 20.2 Hz, 1H, CH_2C=C), 2.56 (ddd, J = 18.8, 6.6, 1.2 Hz, 1H, CH_2CO), 2.46 (ddd, J = 19.5, 12.2, 1.3 Hz, 1H, CH_2C=C), 2.14 – 2.06 (m, 1H, C<u>H</u>CH$_3$), 2.02 (dt, J = 18.8, 1.4 Hz, 1H, CH_2CO), 1.82 – 1.70 (m, 3H, C<u>H</u>$_2$CHCH$_3$, C<u>H</u>$_2$CH$_2$CHCH$_3$), 1.63 – 1.51 (m, 4H, CH_3C=C, C<u>H</u>$_2$CH$_2$CHCH$_3$), 0.63 (d, J = 7.1 Hz, 3H, C<u>H</u>$_3$CH);

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.26, 174.42, 169.08, 160.14, 151.29, 144.74, 137.87, 129.83, 126.44, 121.96, 115.69, 114.64, 55.46, 53.96, 45.96, 41.49, 38.65, 38.28, 36.67, 35.45, 35.21, 31.36, 12.19, 8.10; IR (v/cm^{-1}): 3323, 3136, 2956, 2922, 1683, 1657, 1613; Anal. Calcd. for $C_{26}H_{32}N_4O_3 \cdot 0.35\ CH_2Cl_2$: C, 66.15; H, 6.90; N, 11.71; Found: C, 66.02; H,7.02; N, 11.98.

*4.6.22. N-(1-(2-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide (**7b**)*: yellow oil (66% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H, H-het), 7.44 – 7.20 (m, 4H, H-Ph), 6.75 (br, 1H, NH), 5.66 (s, 2H, NCH_2Ph), 5.56 (s, 1H, CH_2=C), 5.34 (s, 1H, CH_2=C), 4.62 (br, 2H, C$\underline{H_2}$NHCO), 3.19 – 3.13 (m, 1H, C$\underline{H}CH_2CO$), 2.91 (t, J = 11.0 Hz, 1H, C$\underline{H}CCO_2$), 2.83 (d, J = 19.5 Hz, 1H, CH_2C=C), 2.57 (dd, J = 18.8, 6.4 Hz, 1H, CH_2CO), 2.43 (dd, J = 19.3, 11.8 Hz, 1H, CH_2C=C), 2.15 – 2.07 (m, 1H, C$\underline{H}CH_3$), 2.02 (d, J = 19.4 Hz, 1H, CH_2CO), 1.82 – 1.71 (m, 3H, C$\underline{H_2}CHCH_3$, C$\underline{H_2}CH_2CHCH_3$), 1.65 – 1.53 (m, 4H, CH_3C=C, C$\underline{H_2}CH_2CHCH_3$), 0.63 (d, J = 7.1 Hz, 3H, C$\underline{H_3}$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.26, 174.38, 169.07, 151.34, 137.93, 133.85, 132.22, 130.69, 130.60, 130.13, 127.72, 115.87, 53.53, 52.36, 46.03, 41.51, 38.75, 38.30, 36.74, 35.47, 31.38, 12.22, 8.13; IR (v/cm^{-1}): 3328, 3142, 2962, 2921, 2874, 1682, 1658, 1619; HRMS (ESI) calcd for $C_{25}H_{30}ClN_4O_2$ $(M+H)^+$: 453.2057, found: 453.2036; Anal. Calcd. for $C_{25}H_{29}ClN_4O_2 \cdot 0.35\ CH_2Cl_2$: C, 63.05; H, 6.20; N, 11.61; Found: C, 62.86; H,6.25; N, 11.56.

*4.6.23. N-(1-(3-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide (**8b**)*: yellow oil (57.8% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H, H-het), 7.36 – 7.12 (m, 4H, H-Ph), 6.68 (br, 1H, NH), 5.56 (s, 1H, CH_2=C), 5.47 (s, 2H, NCH_2Ph), 5.34 (s, 1H, CH_2=C), 4.56 (d, J = 5.2 Hz, 2H, C$\underline{H_2}$NHCO), 3.18 – 3.13 (m, 1H, C$\underline{H}CH_2CO$), 2.96 – 2.77 (m, 2H, C$\underline{H}CCO_2$, CH_2C=C), 2.57 (ddd, J = 18.7, 6.6, 1.0 Hz, 1H, CH_2CO), 2.43 (dd, J = 18.7, 12.1 Hz, 1H, CH_2C=C), 2.15 – 2.07 (m, 1H, C$\underline{H}CH_3$), 2.02 (d, J = 19.2 Hz, 1H, CH_2CO), 1.82 – 1.71 (m, 3H, C$\underline{H_2}CHCH_3$, C$\underline{H_2}CH_2CHCH_3$), 1.64 – 1.52 (m, 4H, CH_3C=C, C$\underline{H_2}CH_2CHCH_3$), 0.63 (d, J = 7.1 Hz, 3H, C$\underline{H_3}$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.26, 174.34, 169.15, 151.30, 137.93, 136.40, 135.24, 130.60, 129.27, 128.29, 126.28, 115.80, 53.76, 45.98, 41.51, 38.69, 38.30, 36.70, 35.47, 35.19, 31.41, 12.21, 8.13; IR (v/cm^{-1}): 3320, 3137, 3054, 2957, 2922, 1683, 1657, 1619; Anal. Calcd. for $C_{25}H_{29}ClN_4O_2 \cdot 0.45\ CH_2Cl_2 \cdot 0.2\ CH_3OH$: C, 61.88; H, 6.22; N, 11.26; Found: C, 61.72; H,6.18; N, 11.23.

4.6.24. *N-(1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide (**9b**)*: yellow oil (54.5% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H, H-het), 7.37 – 7.32 (m, 2H, H-Ph), 7.23 – 7.18 (m, 2H, H-Ph), 6.63 (br, 1H, NH), 5.55 (s, 1H, CH_2=C), 5.47 (s, 2H, NCH_2Ph), 5.34 (d, J = 0.9 Hz, 1H, CH_2=C), 4.54 (d, J = 5.6 Hz, 2H, $C\underline{H}_2NHCO$), 3.19 – 3.13 (m, 1H, $C\underline{H}CH_2CO$), 2.94 – 2.86 (m, 1H, $C\underline{H}CCO_2$), 2.83 (d, J = 19.6 Hz, 1H, CH_2C=C), 2.57 (ddd, J = 18.8, 6.6, 1.1 Hz, 1H, CH_2CO), 2.43 (ddd, J = 18.5, 12.3, 0.8 Hz, 1H, CH_2C=C), 2.16 – 2.09 (m, 1H, $C\underline{H}CH_3$), 2.05 (dt, J =18.8, 2.4Hz, 1H, CH_2CO), 1.82 – 1.70 (m, 3H, $C\underline{H}_2CHCH_3$, $C\underline{H}_2CH_2CHCH_3$), 1.66 – 1.55 (m, 4H, CH_3C=C, $C\underline{H}_2CH_2CHCH_3$), 0.64 (d, J = 7.1 Hz, 3H, $C\underline{H}_3CH$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.28, 174.33, 169.15, 151.32, 137.94, 135.17, 132.97, 129.59, 129.55, 122.24, 115.76, 53.71, 45.99, 41.52, 38.70, 38.29, 36.71, 35.48, 35.19, 31.41, 12.22, 8.14; IR (v/cm^{-1}): 3330, 2961, 2922, 1682, 1657, 1618; Anal. Calcd. for $C_{25}H_{29}ClN_4O_2 \cdot 0.2\ CH_2Cl_2$: C, 64.38; H, 6.31; N, 11.92; Found: C, 64.39; H,6.41; N, 11.80.

4.6.25. *N-(1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide (**10b**)*: yellow oil (59.8% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H, H-het), 7.41 – 7.08 (m, 4H, H-Ph), 6.65 (br, 1H, NH), 5.56 (s, 2H, NCH_2Ph), 5.55 (s, H, CH_2=C), 5.34 (d, J = 0.9 Hz, 1H, CH_2=C), 4.53 (d, J = 5.6 Hz, 2H, $C\underline{H}_2NHCO$), 3.19 – 3.13 (m, 1H, $C\underline{H}CH_2CO$), 2.94 – 2.87 (m, 1H, $C\underline{H}CCO_2$), 2.83 (d, J = 19.6 Hz, 1H, CH_2C=C), 2.57 (ddd, J = 18.7, 6.6, 1.1 Hz, 1H, CH_2CO), 2.43 (dd, J = 19.0, 11.8 Hz, 1H, CH_2C=C), 2.15 – 2.07 (m, 1H, $C\underline{H}CH_3$), 2.03 (dt, J = 19.2, 1.2 Hz, 1H, CH_2CO), 1.83 – 1.72 (m, 3H , $C\underline{H}_2CHCH_3$, $C\underline{H}_2CH_2CHCH_3$), 1.67 – 1.53 (m, 4H, CH_3C=C, $C\underline{H}_2CH_2CHCH_3$), 0.64 (t, J = 7.1 Hz, 3H, $C\underline{H}_3CH$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.31, 174.40, 169.11, 161.98, 151.37, 137.94, 131.26, 130.83, 125.02, 116.19, 115.98, 115.71, 48.02, 45.99, 41.53, 38.72, 38.30, 36.71, 35.49, 35.18, 31.39, 12.22, 8.13; IR (v/cm^{-1}): 3315, 2921, 1682, 1618; HRMS (ESI) calcd for $C_{25}H_{30}N_4O_2F$ $(M+H)^+$: 437.2354, found: 437.2351; Anal. Calcd. for $C_{25}H_{29}FN_4O_2 \cdot 0.9\ CH_2Cl_2 \cdot 0.5\ CH_3OH$: C, 59.92; H, 6.25; N, 10.59; Found: C, 59.84; H,6.03; N, 10.55.

4.6.26. *N-(1-(3-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide (**11b**)*: yellow oil (58.8% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H, H-het), 7.34 (m, 1H, H-Ph), 7.09 – 6.87 (m, 3H, H-Ph), 6.70 (br, 1H, NH), 5.55 (s, 1H, CH_2=C), 5.49 (s, 2H, NCH_2Ph), 5.34 (d, J = 0.9 Hz, 1H,

CH_2=C), 4.55 (d, J = 5.5 Hz, 2H, C$\underline{H_2}$NHCO), 3.18 – 3.13 (m, 1H, C$\underline{H}CH_2CO$), 2.94 – 2.78 (m, 2H, C$\underline{H}CCO_2$, CH_2C=C), 2.58 (ddd, J = 18.8, 6.6, 1.2 Hz, 1H, CH_2CO), 2.46 (ddd, J = 19.5, 12.2, 1.3 Hz, 1H, CH_2C=C), 2.15 – 2.07 (m, 1H, C$\underline{H}CH_3$), 2.02 (dt, J = 19.2, 1.4 Hz, 1H, CH_2CO), 1.82 – 1.71 (m, 3H, C$\underline{H_2}CHCH_3$, C$\underline{H_2}CH_2CHCH_3$), 1.64 – 1.50 (m, 4H, CH_3C=C, C$\underline{H_2}CH_2CHCH_3$), 0.63 (d, J = 7.1 Hz, 3H, C$\underline{H_3}CH$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.27, 174.23, 166.75, 164.40, 161.93, 145.92, 143.50, 137.98, 136.86, 131.98, 124.26, 123.71, 116.08, 115.17, 58.06, 53.71, 45.99, 41.48, 38.37, 38.09, 36.68, 35.44, 31.79, 12.23, 8.12; IR (v/cm^{-1}): 3315, 3138, 3056, 2958, 2922, 1683, 1658, 1618; Anal. Calcd. for $C_{25}H_{29}FN_4O_2 \cdot 0.55\ CH_2Cl_2 \cdot 0.3\ CH_3OH$: C, 62.97; H, 6.41; N, 11.37; Found: C, 62.82; H, 6.39; N, 11.20.

*4.6.27. N-(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide (**12b**)*: yellow oil (61.7% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H, H-het), 7.26 – 7.20 (m, 2H, H-Ph), 7.03 (m, 2H, H-Ph), 6.89 (br, 1H, NH), 5.55 (s, 1H, CH_2=C), 5.45 (s, 2H, NCH_2Ph), 5.32 (s, 1H, CH_2=C), 4.51 (d, J = 5.5 Hz, 2H, C$\underline{H_2}$NHCO), 3.19 – 3.08 (m, 1H, C$\underline{H}CH_2CO$), 2.92 – 2.85 (m, 1H, C$\underline{H}CCO_2$), 2.81 (d, J = 19.6 Hz, 1H, CH_2C=C), 2.54 (ddd, J = 18.7, 6.6, 1.0 Hz, 1H, CH_2CO), 2.41 (ddd, J = 19.6, 12.2, 0.6 Hz, 1H, CH_2C=C), 2.16 – 2.04 (m, 1H, C$\underline{H}CH_3$), 2.00 (dt, J = 19.2, 1.2 Hz, 1H, CH_2CO), 1.79 – 1.70 (m, 3H, C$\underline{H_2}CHCH_3$, C$\underline{H_2}CH_2CHCH_3$), 1.64 – 1.47 (m, 4H, CH_3C=C, C$\underline{H_2}CH_2CHCH_3$), 0.62 (t, J = 7.3 Hz, 3H, C$\underline{H_3}CH$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.28, 174.34, 169.14, 164.31, 161.84, 151.35, 137.94, 130.21, 130.13, 116.45, 116.23, 115.73, 53.71, 46.00, 41.51, 38.71, 38.29, 36.71, 35.47, 35.22, 31.40, 12.21, 8.13; IR (v/cm^{-1}): 3321, 2957, 2922, 1683, 1657, 1618; Anal. Calcd. for $C_{25}H_{29}FN_4O_2 \cdot 0.85\ CH_2Cl_2 \cdot 0.3\ CH_3OH$: C, 60.57; H, 6.21; N, 10.81; Found: C, 60.78; H, 6.05; N, 10.65.

4.6.28. *N-(1-(3,4-dichlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide (**13b**)*: yellow oil (66.7% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H, H-het), 7.43 (d, J = 8.2 Hz, 1H, H-Ph), 7.34 (d, J = 2.1 Hz, 1H, H-Ph, 7.10 (dd, J = 8.3, 2.1 Hz, 1H, H-Ph), 6.82 (t, J = 5.3 Hz, 1H, NH), 5.56 (s, 1H, CH_2=C), 5.44 (s, 2H, NCH_2Ph), 5.34 (d, J = 0.8 Hz, 1H, CH_2=C), 4.54 (d, J = 5.7 Hz, 2H, C$\underline{H_2}$NHCO), 3.17 – 3.12 (m, 1H, C$\underline{H}CH_2CO$), 2.93 – 2.86 (m, 1H, C$\underline{H}CCO_2$), 2.82 (d, J = 19.6 Hz, 1H, CH_2C=C), 2.55 (ddd, J = 18.7, 6.6, 1.0 Hz, 1H, CH_2CO), 2.42 (ddd, J = 19.8, 12.5, 0.8 Hz, 1H, CH_2C=C), 2.14 – 2.06 (m, 1H, C$\underline{H}CH_3$), 2.01 (dt, J =18.8, 1.2 Hz, 1H, CH_2CO), 1.84 – 1.67 (m, 3H, C$\underline{H_2}CHCH_3$,

$C\underline{H_2}CH_2CHCH_3$), 1.64 – 1.51 (m, 4H, CH_3C=C, $C\underline{H_2}CH_2CHCH_3$), 0.62 (d, J = 7.1 Hz, 3H, $C\underline{H_3}CH$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.25, 174.37, 169.16, 151.20, 145.34, 137.88, 134.65, 133.49, 133.40, 131.25, 130.07, 127.36, 122.46, 115.82, 60.50, 53.05, 45.96, 41.48, 38.63, 38.27, 36.66, 35.30, 31.39, 12.18, 8.10; IR (v/cm^{-1}): 3317, 2957, 2922, 1683, 1658, 1618; Anal. Calcd. for $C_{25}H_{28}Cl_2N_4O_2\cdot 1.1\ CH_2Cl_2\cdot 0.3\ CH_3OH$: C, 53.67; H, 5.36; N, 9.49; Found: C, 53.76; H, 5.15; N, 9.37.

4.6.29. *N-(1-(cyclohex-2-enyl)-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide (**14b**)*: yellow oil (63.1% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H, H-het), 6.72 (brs, 1H, NH), 6.14 (m, 1H, CH=CH), 5.76 (m, 1H, CH=CH), 5.56 (s, 1H, , CH_2=C), 5.34 (s, 1H, CH_2=C), 5.23 (m, 1H, CHN), 4.56 (d, *J* = 5.6 Hz, 2H, $C\underline{H_2}NHCO$), 3.23 – 3.14 (m, 1H, $C\underline{H}CH_2CO$), 2.92 (t, *J* = 11.7 Hz, 1H, $C\underline{H}CCO_2$), 2.84 (d, *J* = 19.0 Hz, 1H, CH_2C=C), 2.57 (dd, *J* = 19.2, 6.0 Hz, 1H, CH_2CO), 2.44 (dd, *J* = 19.6, 12.2 Hz, 1H, CH_2C=C), 2.18 – 2.15 (m, 1H, $C\underline{H}CH_3$), 2.06 – 1.89 (m, 1H, CH_2CO), 1.86 – 1.53 (m, 13H, $C\underline{H_2}CHCH_3$, $C\underline{H_2}CH_2CHCH_3$, CH_3C=C, $CH_2CH_2CH_2$), 0.64 (d, *J* = 7.1 Hz, 3H, $C\underline{H_3}CH$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.36, 174.52, 169.11, 151.37, 137.91, 134.20, 123.96, 120.97, 115.65, 56.21, 46.00, 41.52, 38.72, 38.30, 36.71, 35.48, 35.26, 31.40, 30.69, 24.70, 19.18, 12.22, 8.13; IR (*v*/cm^{-1}): 3335, 2924, 2872, 1683, 1658, 1620; Anal. Calcd. for $C_{24}H_{32}N_4O_2\cdot 0.7\ CH_2Cl_2\cdot 0.7\ CH_3OH$: C, 62.18; H, 7.44; N, 11.42; Found: C, 62.16; H,7.18; N, 11.12

4.6.30. *N-(1-cyclohexyl-1H-1,2,3-triazol-4-yl)methyl 2-((5R,8S,8aS)-3,8-dimethyl-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylamide (**15b**)*: yellow oil (53.0% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H, H-het), 6.75 (brs, 1H, NH), 5.57 (s, 1H, CH_2=C), 5.34 (s, 1H, CH_2=C), 4.56 (d, *J* = 5.6 Hz, 2H, $C\underline{H_2}NHCO$), 4.41 (m, 1H, CHN), 3.20 – 3.15 (m, 1H, $C\underline{H}CH_2CO$), 2.92 (t, *J* = 11.7 Hz, 1H, $C\underline{H}CCO_2$), 2.88 – 2.78 (m, 1H, CH_2C=C), 2.57 (ddd, *J* = 18.7, 6.6, 1.1 Hz, 1H, CH_2CO), 2.49 – 2.37 (m, 1H, CH_2C=C), 2.18-2.15 (m, 2H, $NCHC\underline{H_2}$), 2.14 – 2.09 (m, 1H, $C\underline{H}CH_3$), 2.07 – 1.98 (m, 1H, CH_2CO), 1.96 – 1.88 (m, 2H, $NCHC\underline{H_2}$), 1.84 – 1.21 (m, 13H, $C\underline{H_2}CHCH_3$, $C\underline{H_2}CH_2CHCH_3$, CH_3C=C, $CH_2C\underline{H_2}C\underline{H_2}C\underline{H_2}CH_2$), 0.64 (t, *J* = 6.0 Hz, 3H, CH_3CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.26, 174.43, 169.11, 151.36, 137.89, 115.68, 60.45, 53.55, 45.99, 41.51, 38.69, 38.31, 36.71, 35.48, 35.27, 33.65, 31.39, 25.27, 25.22, 12.20, 8.12; IR (*v*/cm^{-1}): 3336, 3137, 2929, 2858, 1688, 1659, 1620; Anal. Calcd. for $C_{24}H_{34}N_4O_2\cdot 0.35\ CH_2Cl_2\cdot 0.1\ CH_3OH$: C, 66.20; H, 7.98; N, 12.63; Found: C, 66.04; H,8.02; N, 12.62

4.7. Activity screening

4.7.1. The procedure for the anti-influenza virus assay

Each compound was dissolved in DMSO at an initial concentration of 20 mg/mL and then diluted three fold successively to obtain 8 different concentrations as stock solutions for the following experiments. Madin-Darby canine kidney (MDCK) cells were seeded in 96-well trays and cultured at 37 °C in a humidified CO_2 incubator (95% air, 5%CO_2) for 24 h. Then, the cells were infected with influenza A virus. All of infected tissue culture plates (96 wells) were incubated at 37 °C for 2 h, and then the medium was removed. Subsequently, different concentrations of drug maintain solutions were added to the wells (one per well), and the plates were incubated again for 40 h at 37 °C. Then, the inhibition of the virus-induced cytopathic effect (CPE) for each sample was recorded relative to the cell control and the virus control. The 50% cell-inhibitory concentration (IC_{50}) values of active compounds were calculated accordingly. The commercial drugs ribavirin (RBV) and oseltamivir as Positive contrast

4.7.2. The procedure for cytotoxicity assay

MDCK cells were seeded in 96-well trays, each well 25000 cells and cultured at 37 °C in a humidified CO_2 incubator (95% air, 5% CO_2) for 24 h. 3 times dilution compound was added cell monolayer, and continue to cultivate 48 hours, then observe the cytopathic record results. The 50% cytotoxic concentration (TC_{50}) values of active compounds were calculated by the methods of Reed & Muench

4.7.3. The procedure for the anti-influenza B virus plaque inhibition assay

Monolayers of MDCK cells in twelve well plate were washed with PBS and infected with 1mL/well of certain dilution of the virus in the maintenance medium without trypsin. After 2 h incubation at 37 °C in 5% CO_2, the virus was removed and washed plate with PBS for 3 times ,then added 1mL/well of 1.5% agarose overlay (1 ml) containing Eagle minimal essential medium, trypsin (2 μg/ml), and different concentration drug or compounds. Plates were incubated at 37°C in 5% CO_2 for future 3-4 days to allow plaque formation. Whereafter, agar was removed and plaques were stained with crystal violet (0.5%) and counted. The percentage of plaque inhibition relative to the infected control (no drug) plates was determined for each drug concentration, and the 50% inhibitory concentration (IC_{50}) was calculated by the Reed & Muench methods.

Acknowledgments

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Scheme 1. Synthesis of 1,2,3-triazole-containing derivatives of rupestonic acid. Reagents and conditions: i) NaN_3, DMSO; ii) K_2CO_3, DMF; iii) EDCI, HOBt, DCM; iv) $CuSO_4$/Na-Ascorbate, DCM/H_2O.

Table 1. Structure and inhibitory activity of compounds against influenza A and B viruses

Table 2. Inhibition of the plaque formation by four best representative compounds using MDCK cells and RBV as control drug.

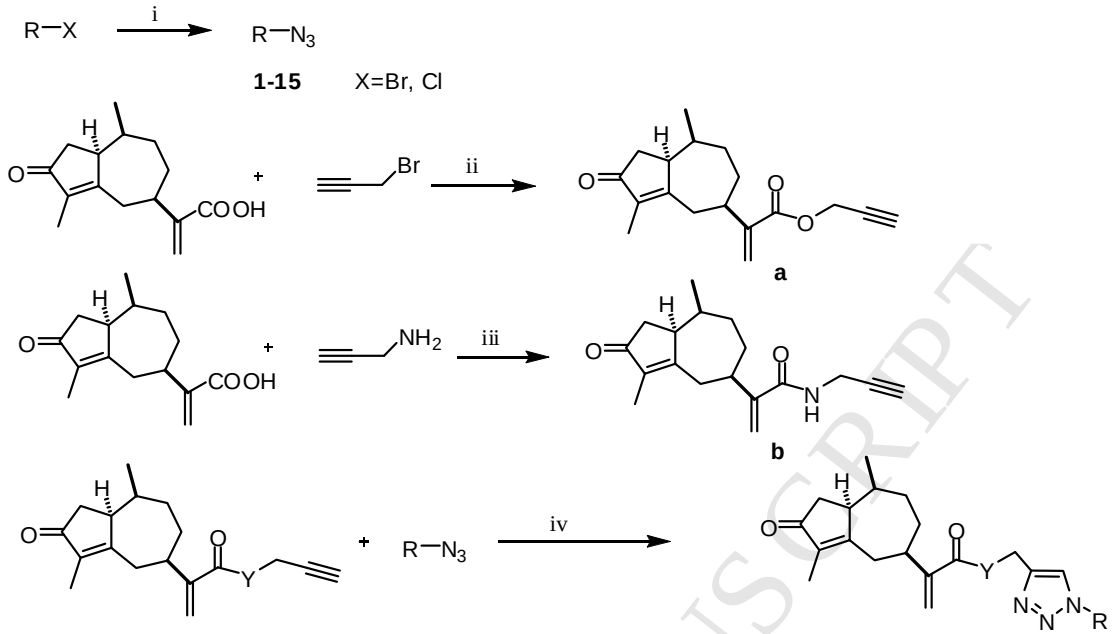

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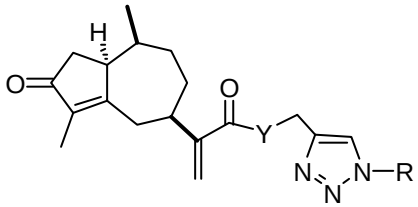
Table 1 Structure and inhibitory activity of compounds against influenza A and B viruses



1a-15a: Y=O

1b-15b: Y=NH

Compound	R	TC_{50}[a](μg/ml)	Anti-influenza A (strain A/FM/1/47/H1N1) virus		Oseltamivir resistant influenza A (strainA/tianjinjinnan/15/2009/H1N1)		Anti-influenza A (strain A/hanfang/359/95/H3N2)		Anti-influenza B(strain/jifang/13/97)	
			IC_{50}[b](μg/mL)	SI[c]	IC50(μg/mL)	SI	IC_{50}(μg/mL)	SI	IC_{50}(μg/mL)	SI
1a	2-methylbenzyl	46.22	>22.22	nd[d]	>22.22	nd	>22.22	nd	18.82±3.4	2.55±0.45
2a	3-methylbenzyl	38.49	12.32±4.92	3.76±1.43	19.73±2.49	1.98±0.25	>22.22	nd	≥9.54	≥4.0
3a	4-methylbenzyl	96.15	>22.22	nd	>22.22	nd	>22.22	nd	≥22.22	≥4.32
4a	benzyl	28.63	>7.41	nd	>7.41	nd	>7.41	nd	≥7.41	≥3.9
5a	3-methoxybenzyl	96.15	>22.22	nd	>22.22	nd	>22.22	nd	>22.22	nd
6a	4-methoxylbenzyl	46.22	19.73±2.49	2.68	22.22	2.08	>22.22	nd	≥22.22	≥2.1
7a	2-chlorobenzyl	115.47	>66.67	nd	59.20±7.46	1.98±0.25	40.19±11.55	3.31±0.9	14.82±7.2	10.4±5.2
8a	3-chlorobenzyl	138.67	≥66.67	≥2.08	>66.67	nd	>66.67	nd	66.67	2.1
9a	4-chlorobenzyl	66.67	>22.22	nd	>22.22	nd	>22.22	nd	12.83	5.2
10a	2-fluorobenzyl	66.67	>22.22	nd	>22.22	nd	>22.22	nd	2.26±0.2	29.7±2.7
11a	3-fluorobenzyl	96.15	>22.22	nd	>22.22	nd	>22.22	nd	≥22.22	≥4.3
12a	4-fluorobenzyl	66.67	>22.22	nd	>22.22	nd	>22.22	nd	8.98±3.84	9.1±3.9
13a	3,4-dichlorobenzyl	22.22	>7.41	nd	>7.41	nd	>7.41	nd	>7.41	nd
14a	cyclohex-2-enyl	22.22	2.82±0.36	8.0±1.00	>7.41	nd	>7.41	nd	≥5.14	≥4.3

15a	cyclohexyl	115.47	66.67	1.73	59.20±7.46	1.98±0.25	≥66.67	≥1.73	18.52≥3.7	6.5±1.3
1b	2-methylbenzyl	66.67	>22.22	nd	>22.22	nd	>22.22	nd	15.04±2.2	4.55±0.65
2b	3-methylbenzyl	66.67	>22.22	nd	>22.22	nd	>22.22	nd	11.76±1.08	5.7±0.5
3b	4-methylbenzyl	96.15	17.52±4.70	5.91±1.58	>22.22	nd	>22.22	nd	11.76±1.08	8.25±0.75
4b	benzyl	96.15	17.24	5.58	>22.22	nd	>22.22	nd	11.32±6.05	12.15±6.55
5b	3-methoxybenzyl	66.67	12.83	5.2	>22.22	nd	>22.22	nd	19.73±2.49	3.45±0.45
6b	4-methoxylbenzyl	96.15	14.01±8.21	10.46±6.12	>22.22	nd	>22.22	nd	11.76±1.08	8.25±0.75
7b	2-chlorobenzyl	38.49	>7.41	nd	>7.41	nd	>7.41	nd	1.71	22.5
8b	3-chlorobenzyl	28.63	>7.41	nd	>7.41	nd	>7.41	nd	7.41	3.9
9b	4-chlorobenzyl	17.25	>2.47	nd	>2.47	nd	>2.47	nd	2.09±0.38	8.55±1.55
10b	2-fluorobenzyl	115.47	>66.67	nd	>66.67	nd	>66.67	nd	>66.67	nd
11b	3-fluorobenzyl	66.67	>22.22	nd	>22.22	nd	>22.22	nd	4.71±0.43	14.3±1.3
12b	4-fluorobenzyl	115.47	≥66.67	≥1.73	>66.67	nd	>66.67	nd	3.92±0.36	43.75±16.75
13b	3,4-dichlorobenzyl	66.67	≥17.24	≥3.87	22.22	3	17.52±4.70	4.1±1.1	6.79±0.62	9.9±0.9
14b	cyclohex-2-enyl	96.15	9.75	9.86	19.73±2.49	4.96±0.62	>22.22	nd	13.39±3.85	7.85±2.25
15b	cyclohexyl	38.49	>7.41	nd	22.22	1.73	>7.41	nd	19.73±2.49	1.95±0.25
R.A.		248	4653	>111.11	_	>1344	_	25.8	180.6	>4032
oseltamivir		1260	2.81	448.4	>500.0	nd	1.02±0.1	1235±12.	-	-
RBV		1164	1.92±0.98	819.8±418.	6.52±1.2	184.6±33	5.59±0.82	212.8±31	7.84±4.41	205.6±108.

[a] 50% cytotoxic concentration. Results are expressed as mean values (± SEM) derived from two replicates.

[b] 50% virus-inhibitory concentration, determined by the CPE inhibition assay.

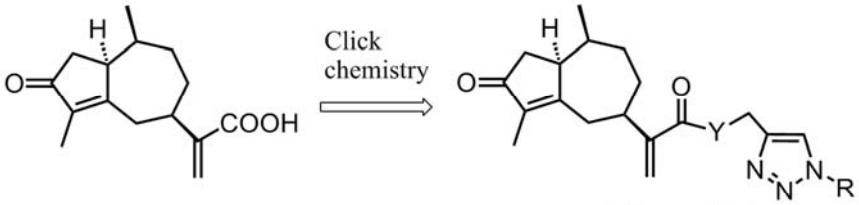
[c] Selectivity Index (TC_{50}/IC_{50})

[d] nd: not determined.

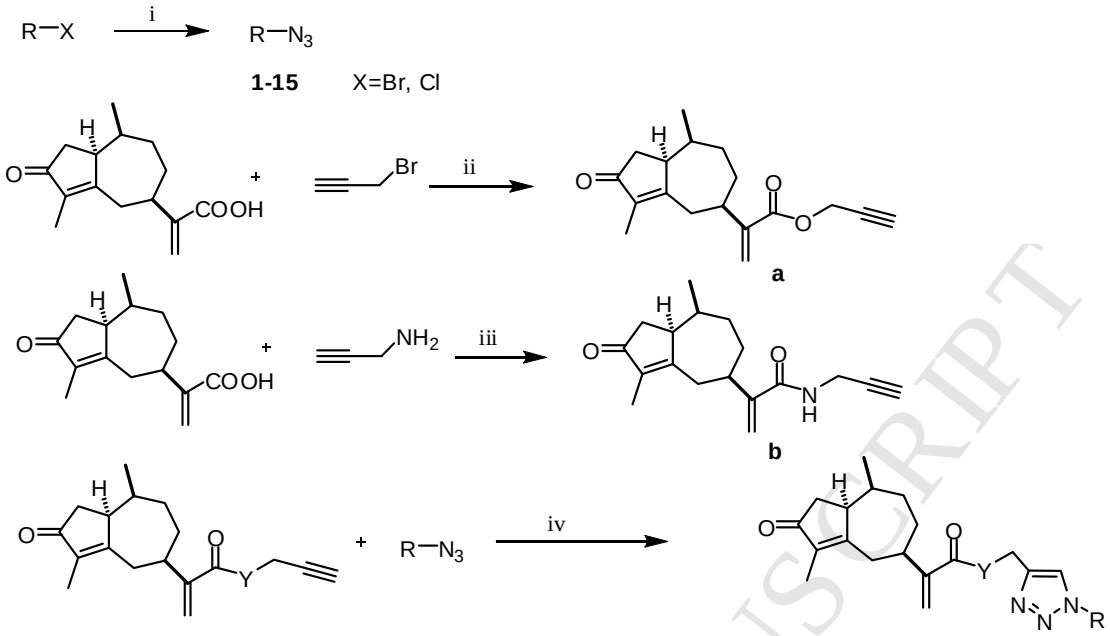
Table 2. Inhibition of the plaque formation by four best representative compounds using MDCK cells and RBV as control drug.

Compound	IC_{50} [a](μg/mL)
10a	0.91
14a	3.28
7b	0.21
12b	0.73
RBV	3.27

[a] 50% virus-inhibitory concentration



Y	R	Influenza B virus IC_{50} (μg/mL)	SI
O	2-FBn	2.26	30
NH	2-ClBn	1.71	22.5
Ribavirin		7.84	206



1, **1a**, **1b**: R = 2-methylbenzyl
2, **2a**, **2b**: R = 3-methylbenzyl
3, **3a**, **3b**: R = 4-methylbenzyl
4, **4a**, **4b**: R = benzyl
5, **5a**, **5b**: R = 3-methoxybenzyl
6, **6a**, **6b**: R = 4-methoxylbenzyl
7, **7a**, **7b**: R = 2-chlorobenzyl
8, **8a**, **8b**: R = 3-chlorobenzyl
9, **9a**, **9b**: R = 4-chlorobenzyl
10, **10a**, **10b**: R = 2-fluorobenzyl
11, **11a**, **11b**: R = 3-fluorobenzyl
12, **12a**, **12b**: R = 4-fluorobenzyl
13, **13a**, **13b**: R = 3,4-dichlorobenzyl
14, **14a**, **14b**: R = cyclohex-2-enyl
15, **15a**, **15b**: R = cyclohexyl

Scheme1 Synthesis of 1,2,3-triazole-containing derivatives of rupestonic acid. Reagents and conditions: i) NaN_3, DMSO; ii) K_2CO_3, DMF; iii) EDCI, HOBt, DCM; iv) $CuSO_4$/Na-Ascorbate, DCM/H_2O.

Supplementary data

1,2,3-Triazole-containing derivatives of rupestonic acid: Click-chemical synthesis and antiviral activities against influenza viruses

Yao-Wu He[1, 2], Chang-Zhi Dong[2,3,*], Jiang-Yu Zhao[1], Lin-Lin MA[4], LI Yu-Huan[4], Haji Akber Aisa[1,*]

[1] Key Laboratory of Plant Resources and Chemistry in Arid Regions, Xinjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing South Road 40–1, Urumqi, Xinjiang, 830011, P. R. China

[2] Université Paris Diderot, Sorbonne Paris Cité, ITODYS, UMR 7086 CNRS, 15 rue J-A de Baïf, 75205 Paris Cedex 13, France.

[3] School of Light Industry and Chemical Engineering, Guangdong University of Technology, Guangzhou, 510006, P. R. China.

[4] Institute of Medicinal Biotechnology, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, 100050, P. R. China

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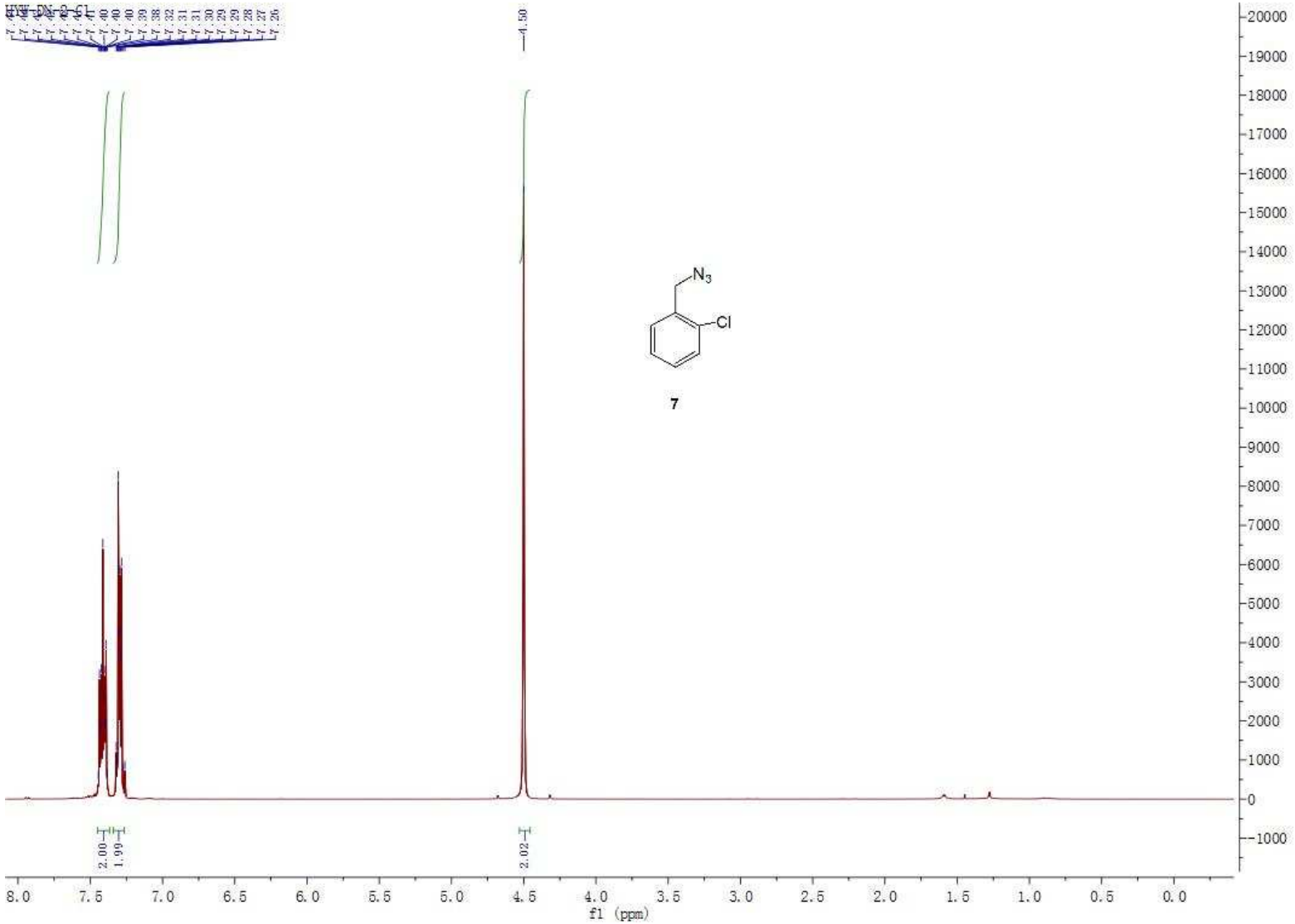
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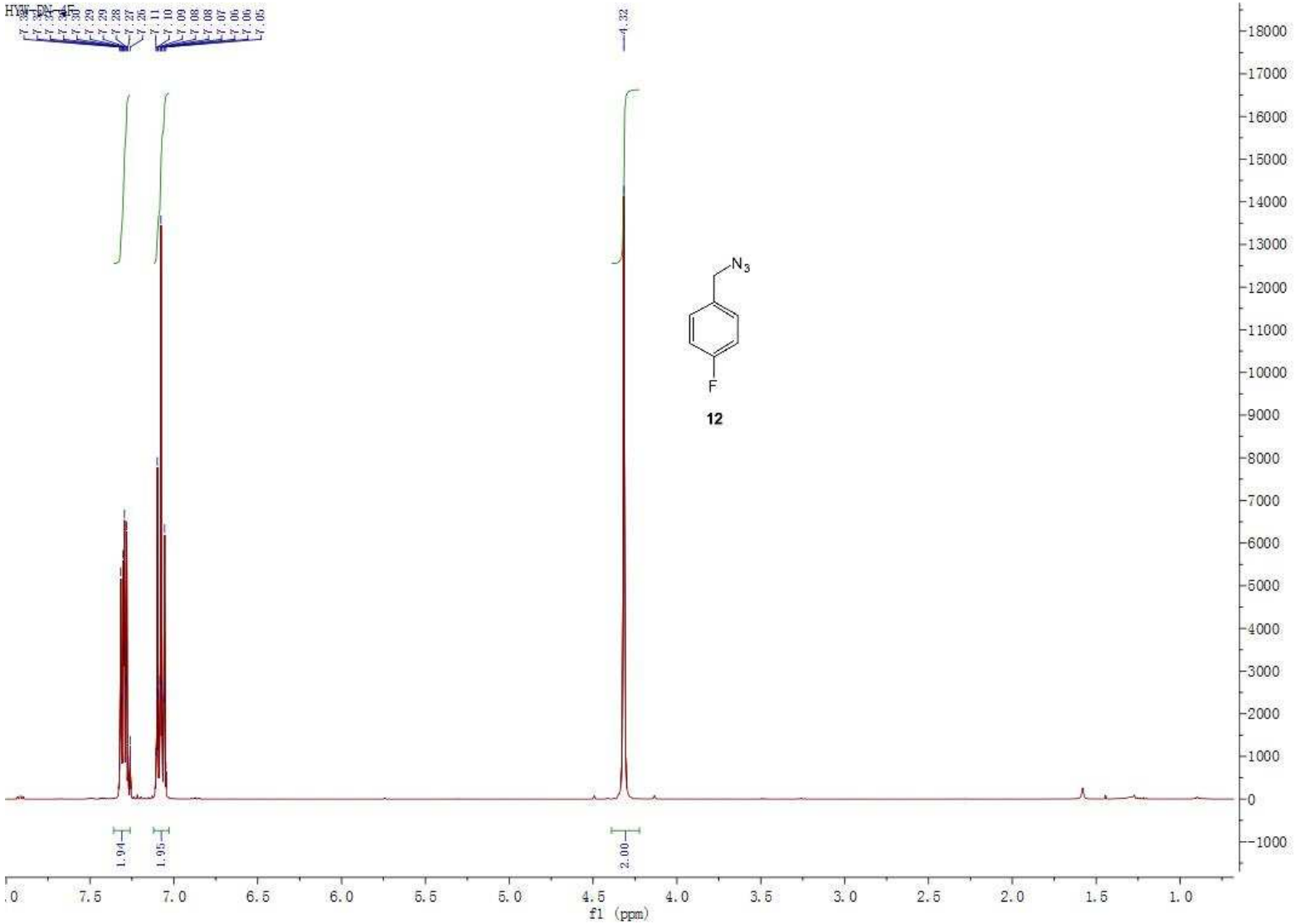
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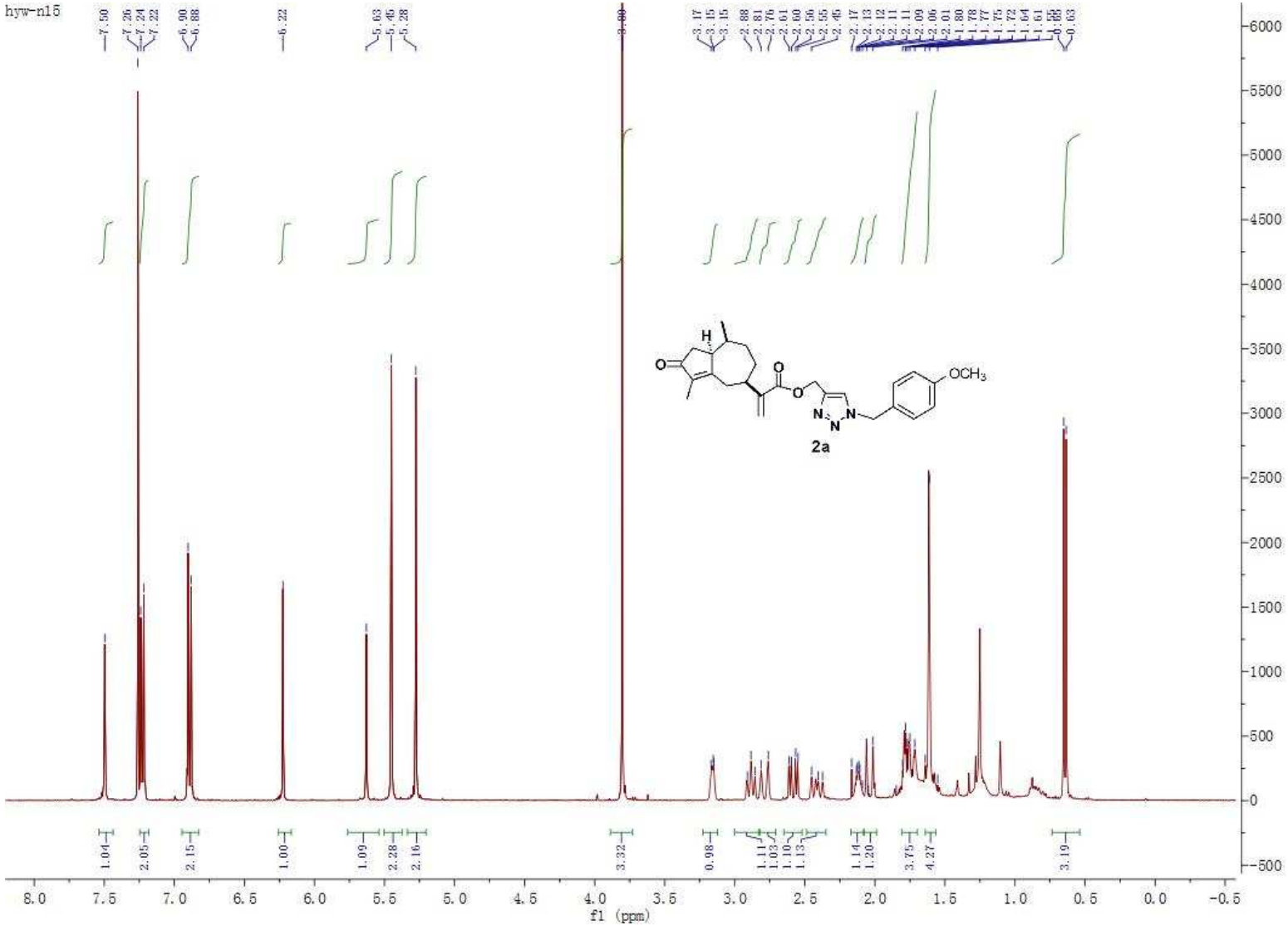
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N
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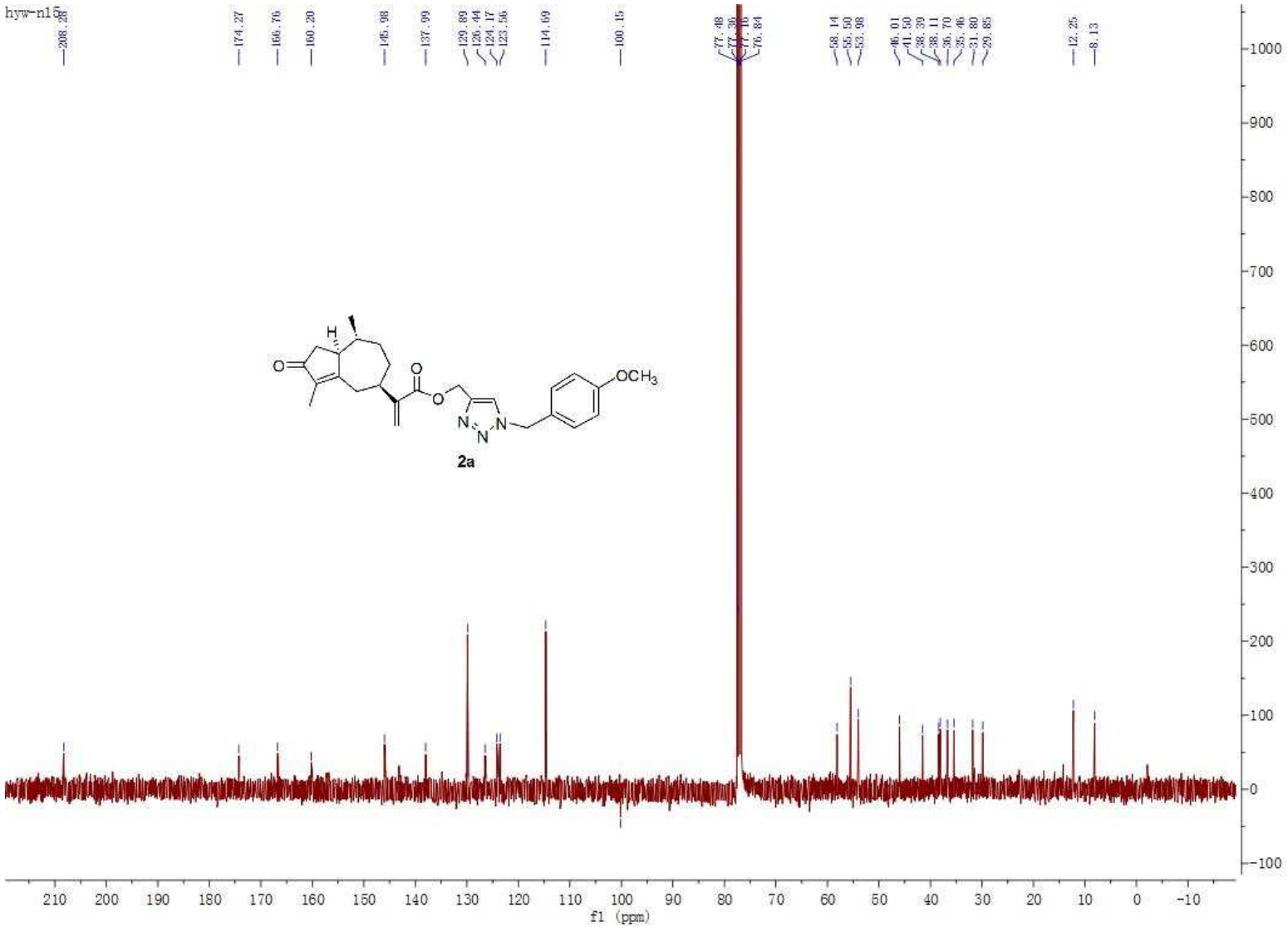
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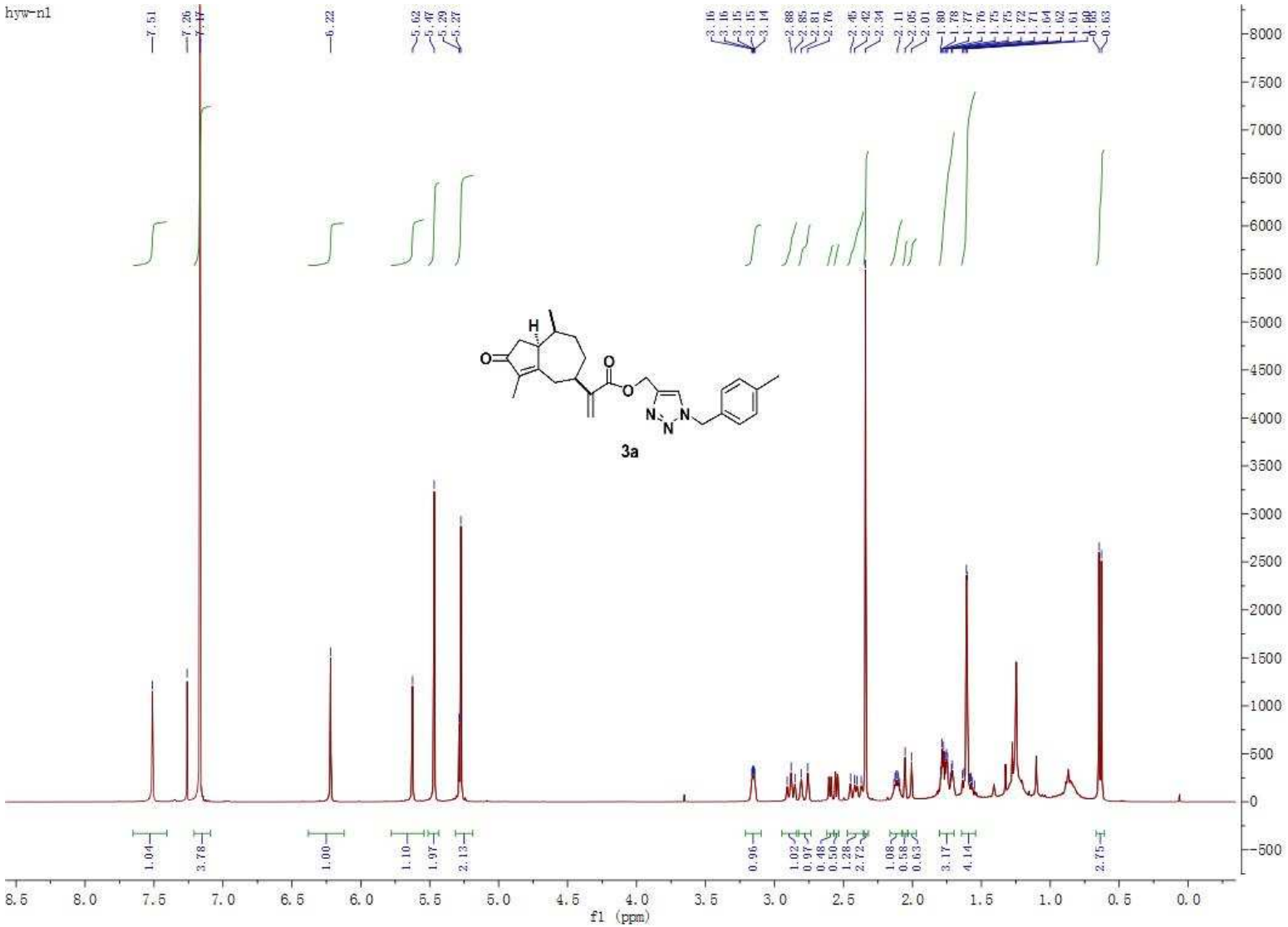
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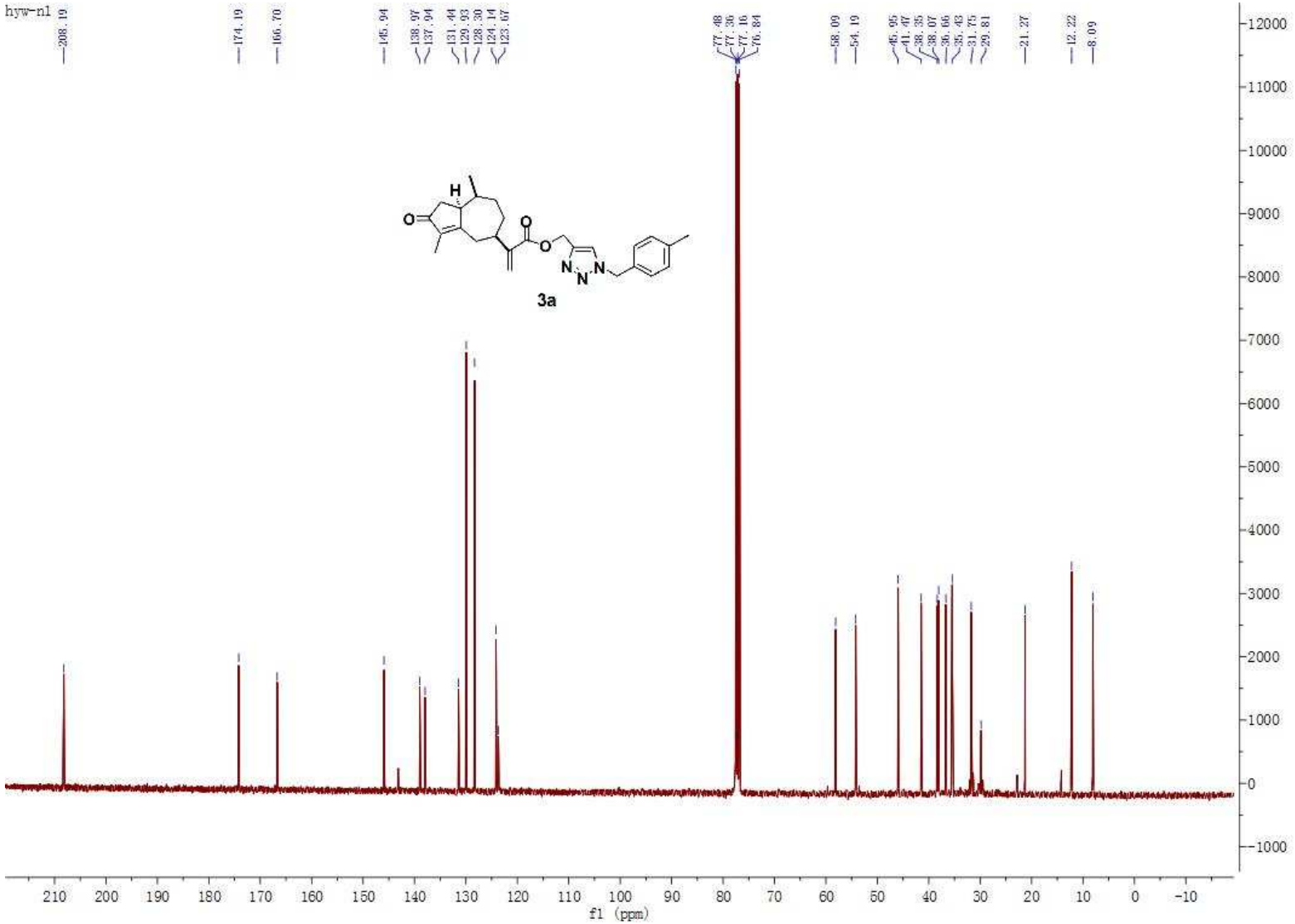
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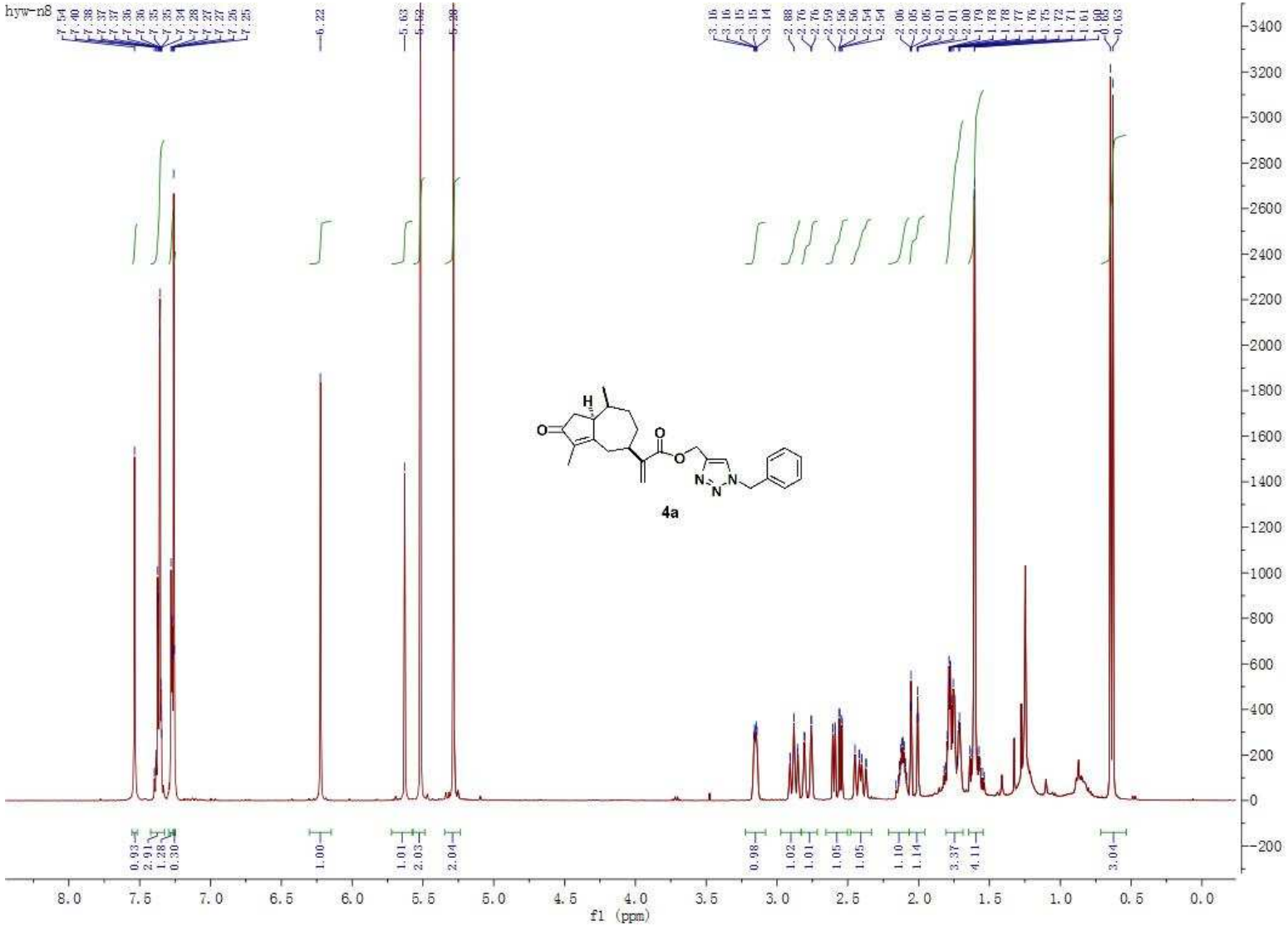
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O
O
O
N
N
N
4a
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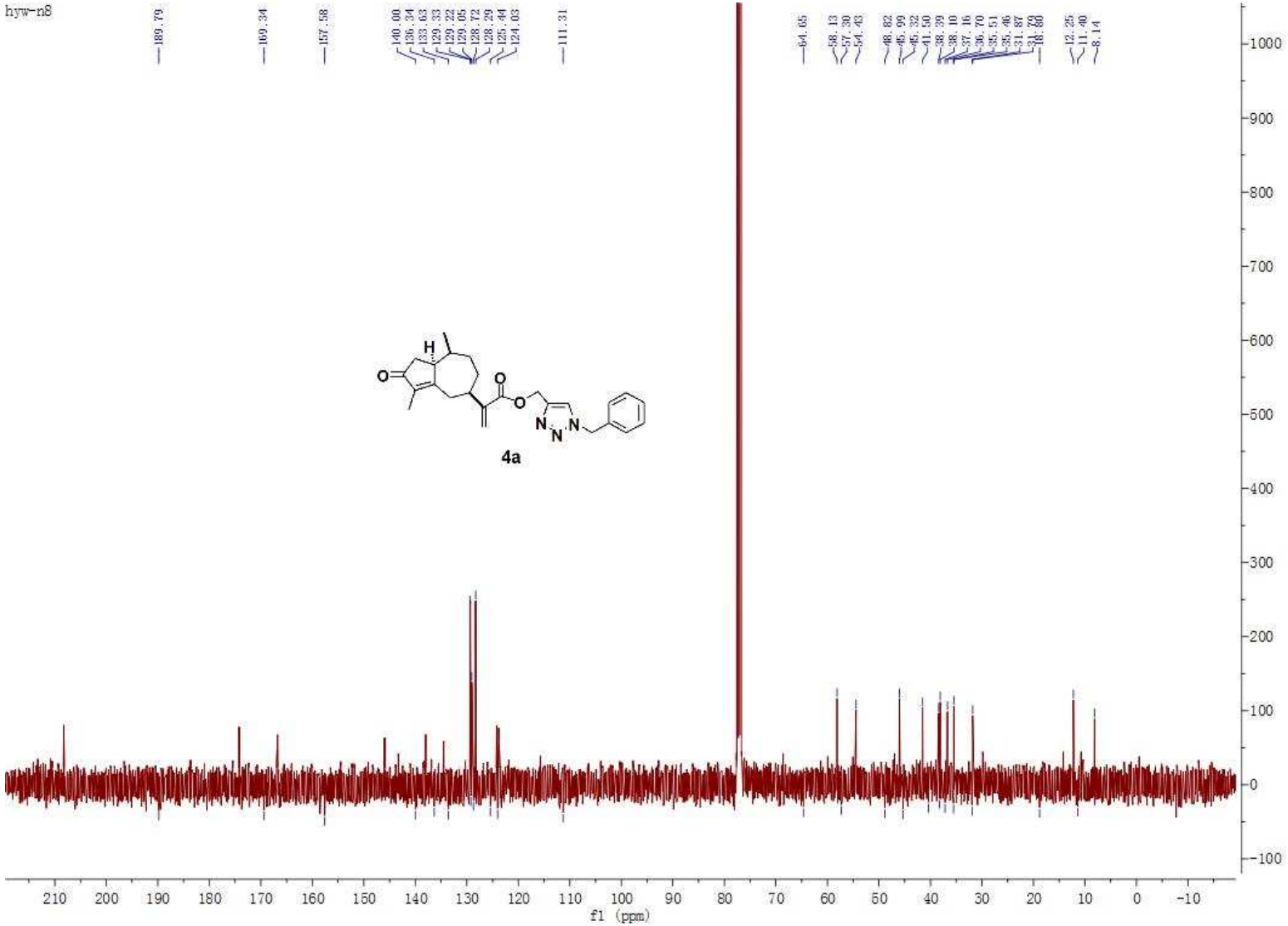
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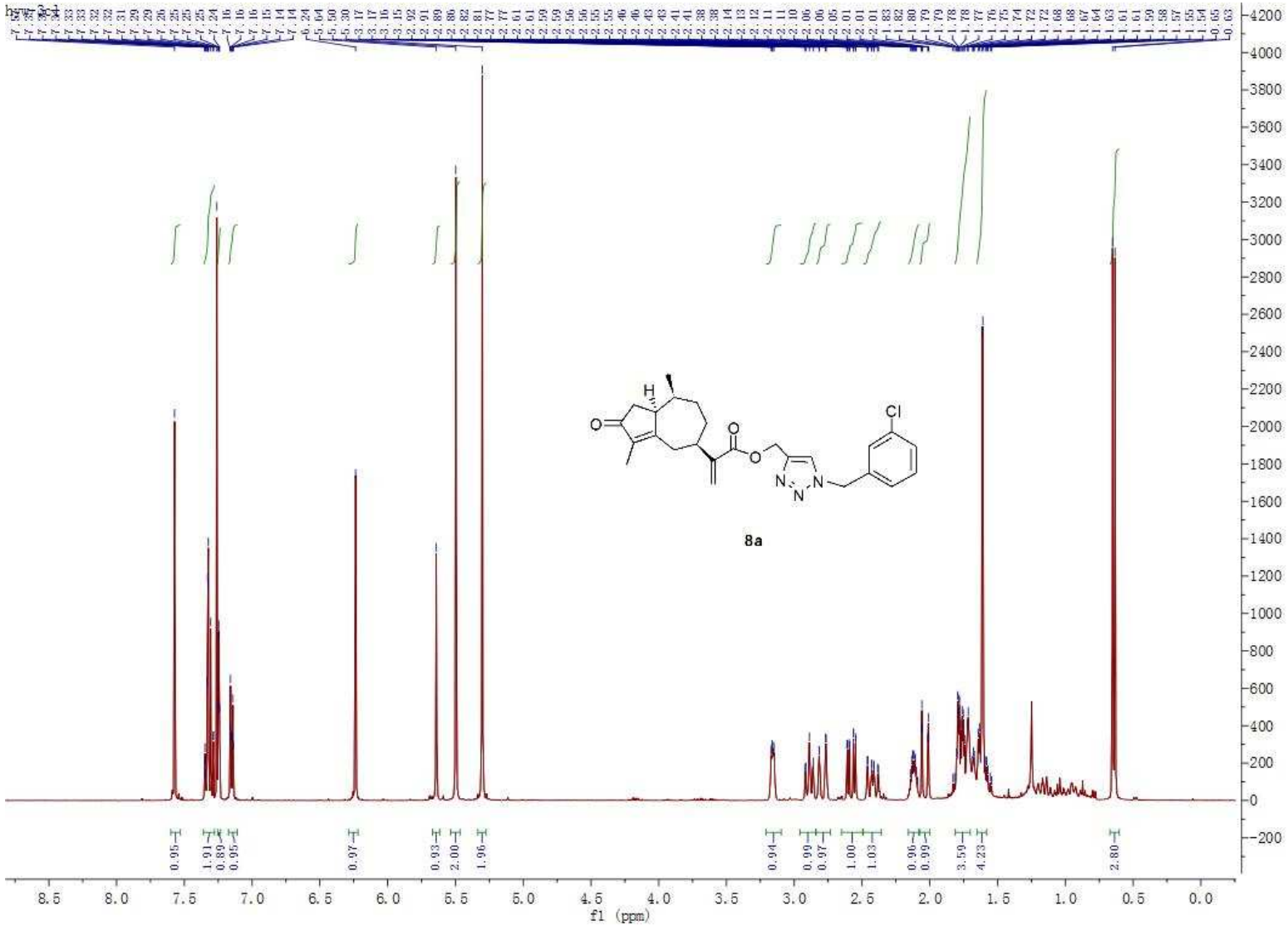
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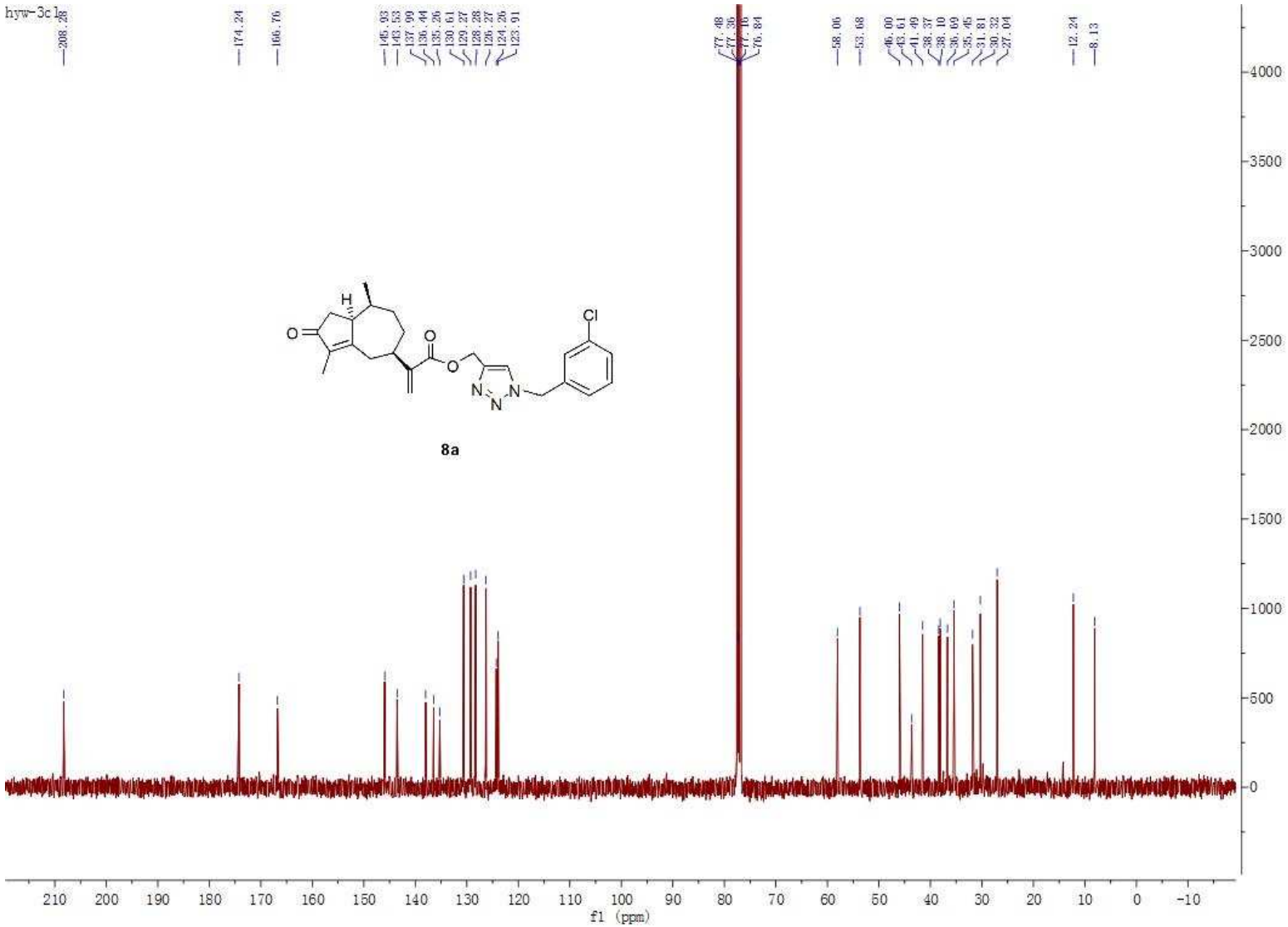
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H
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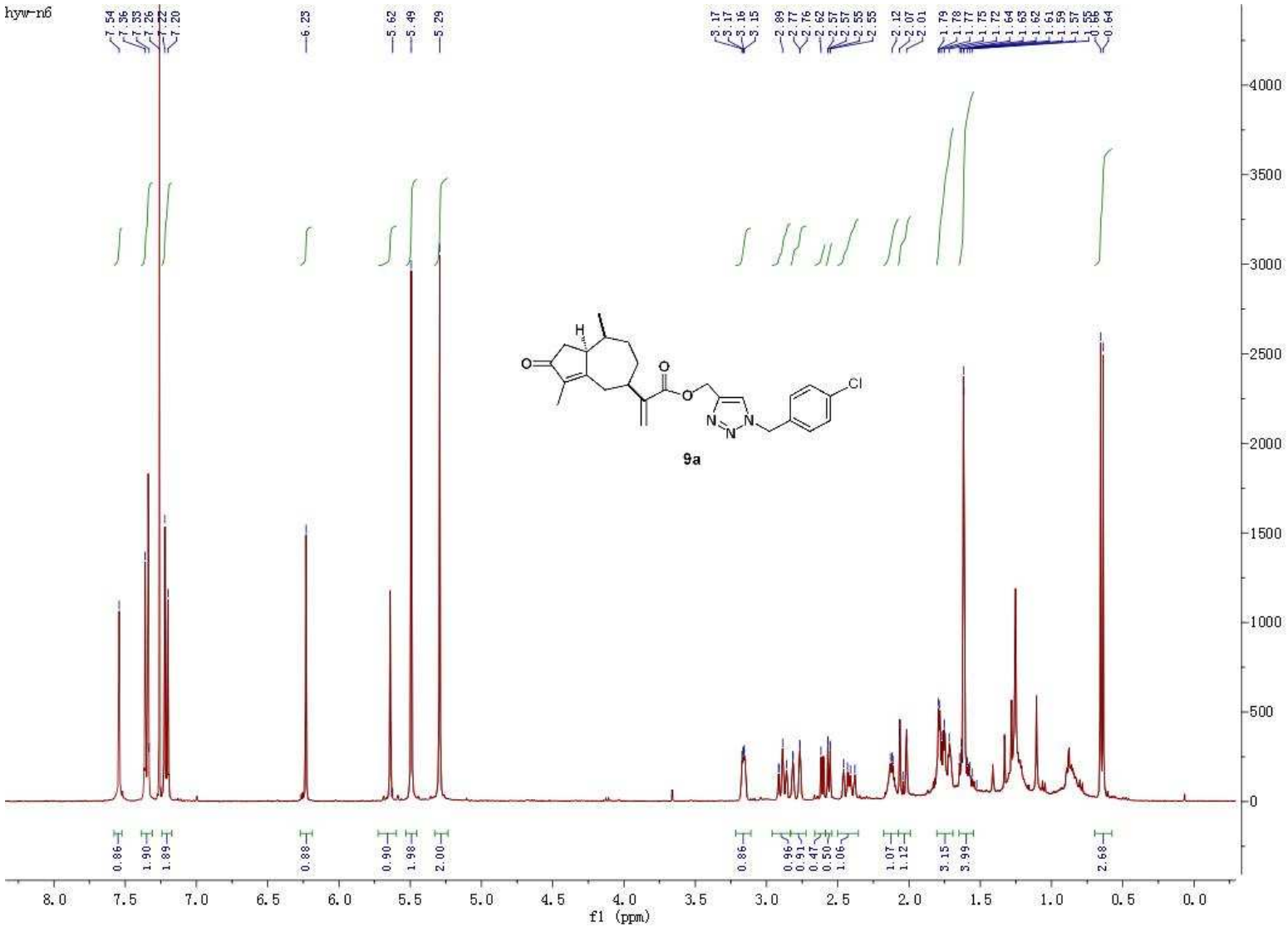
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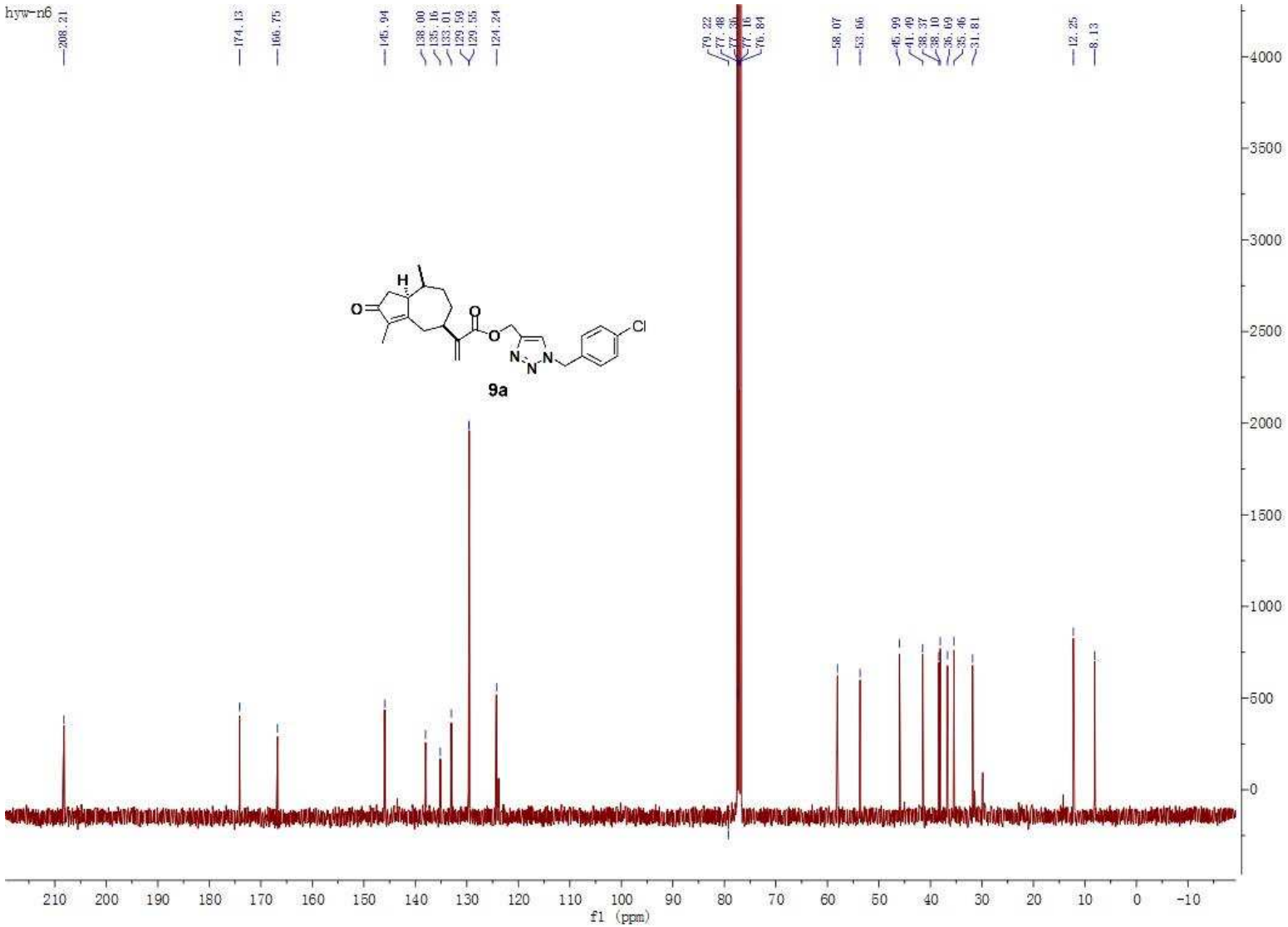
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O
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N
N
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9a
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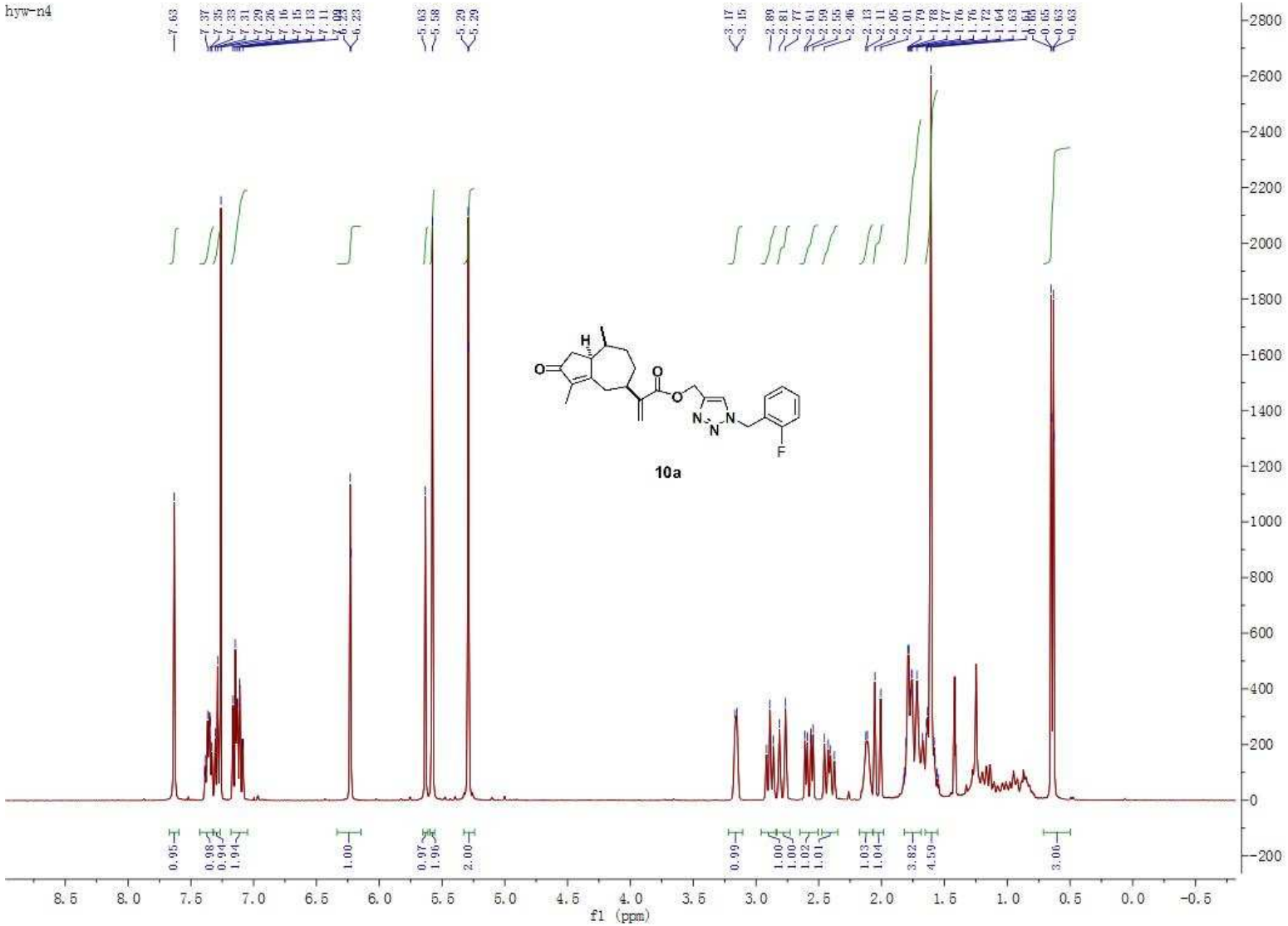
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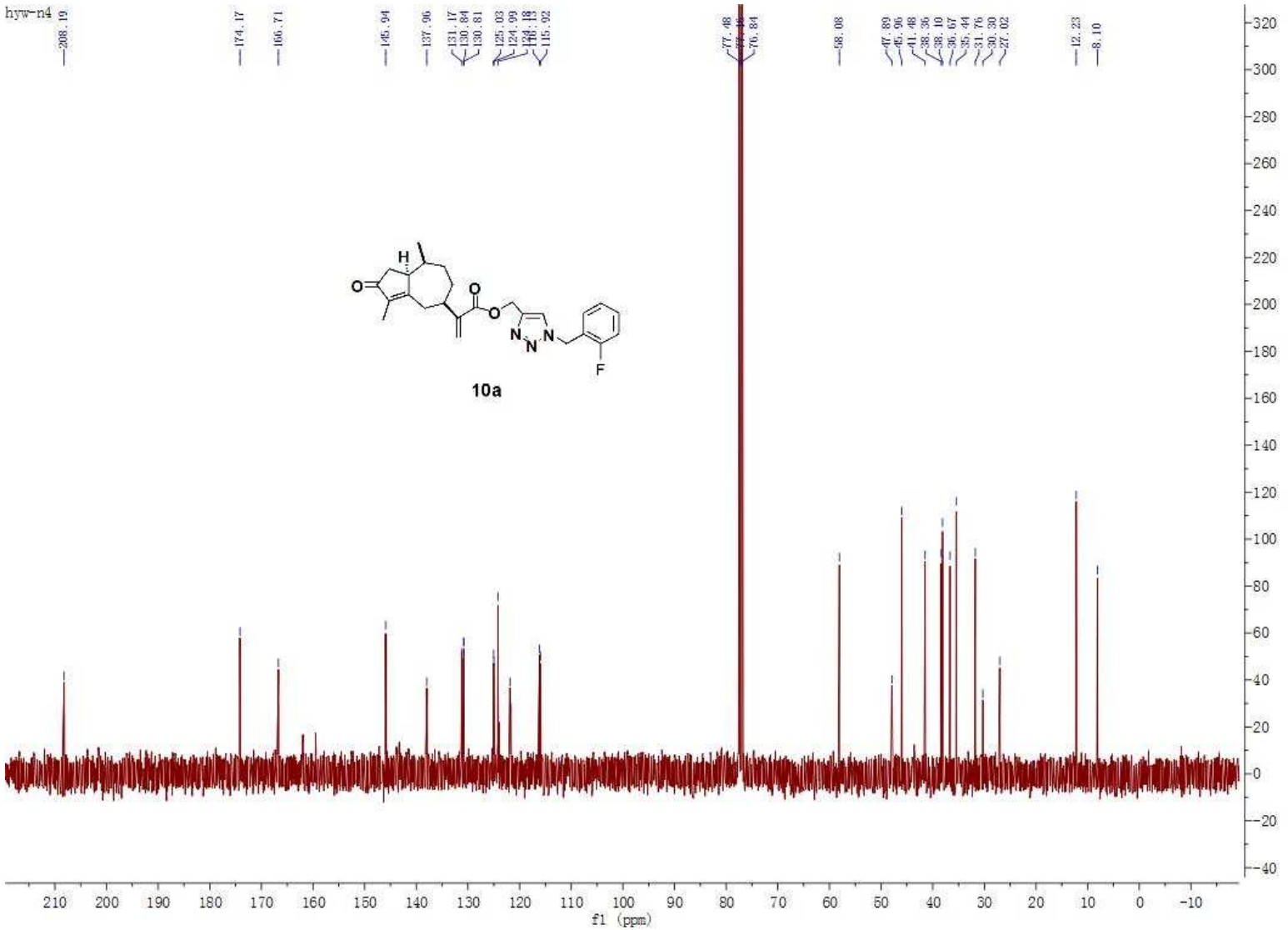
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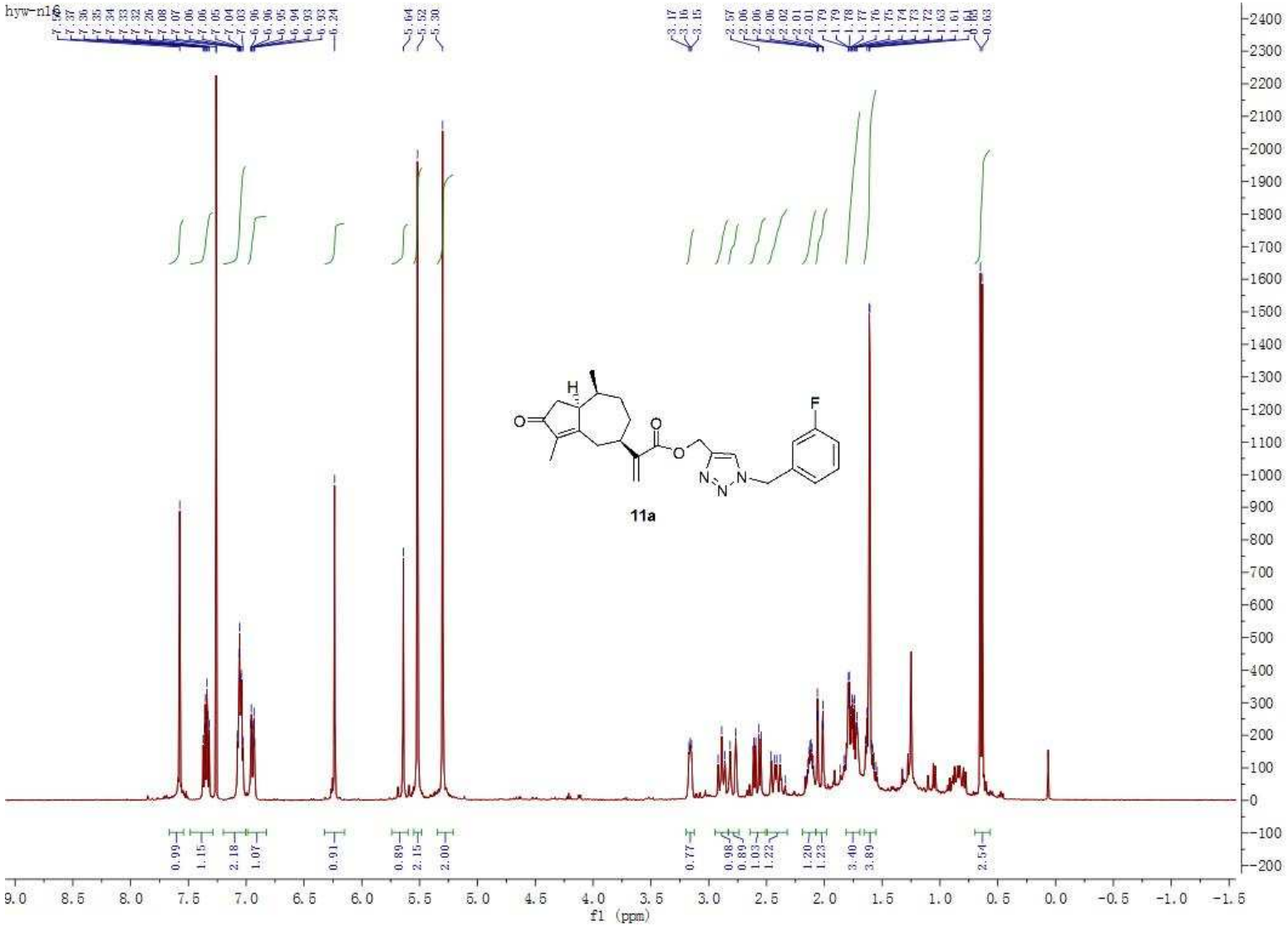
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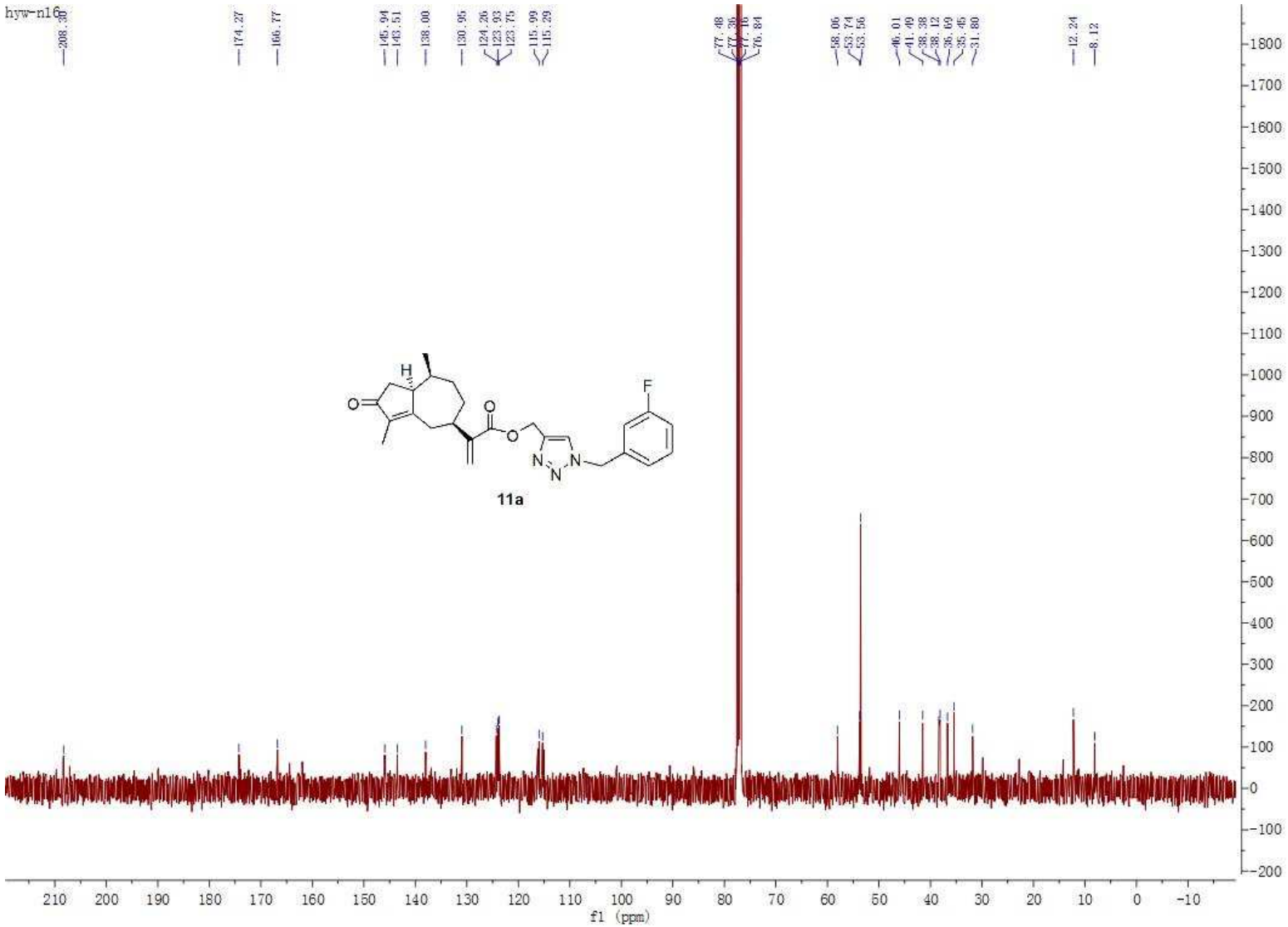
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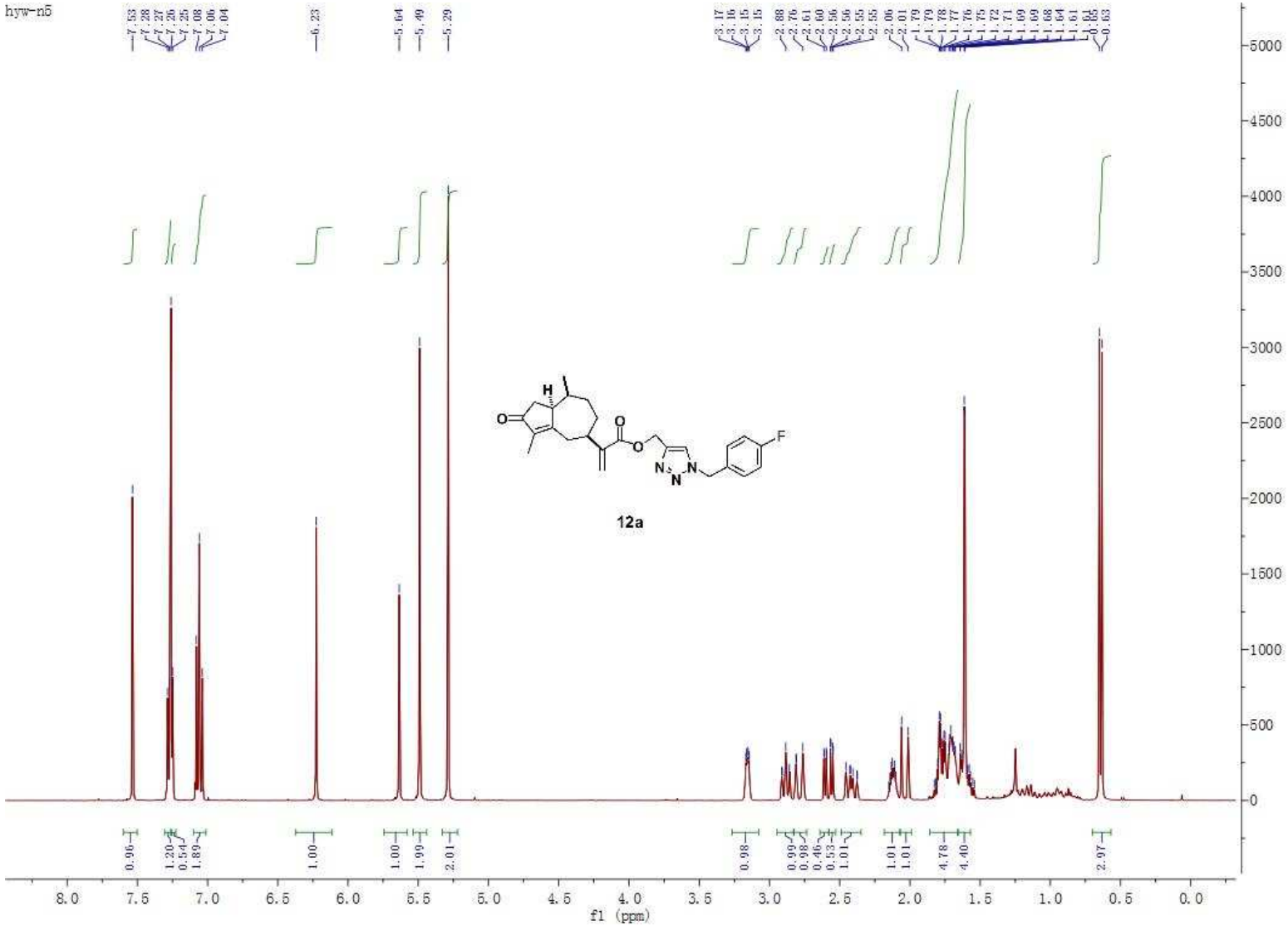
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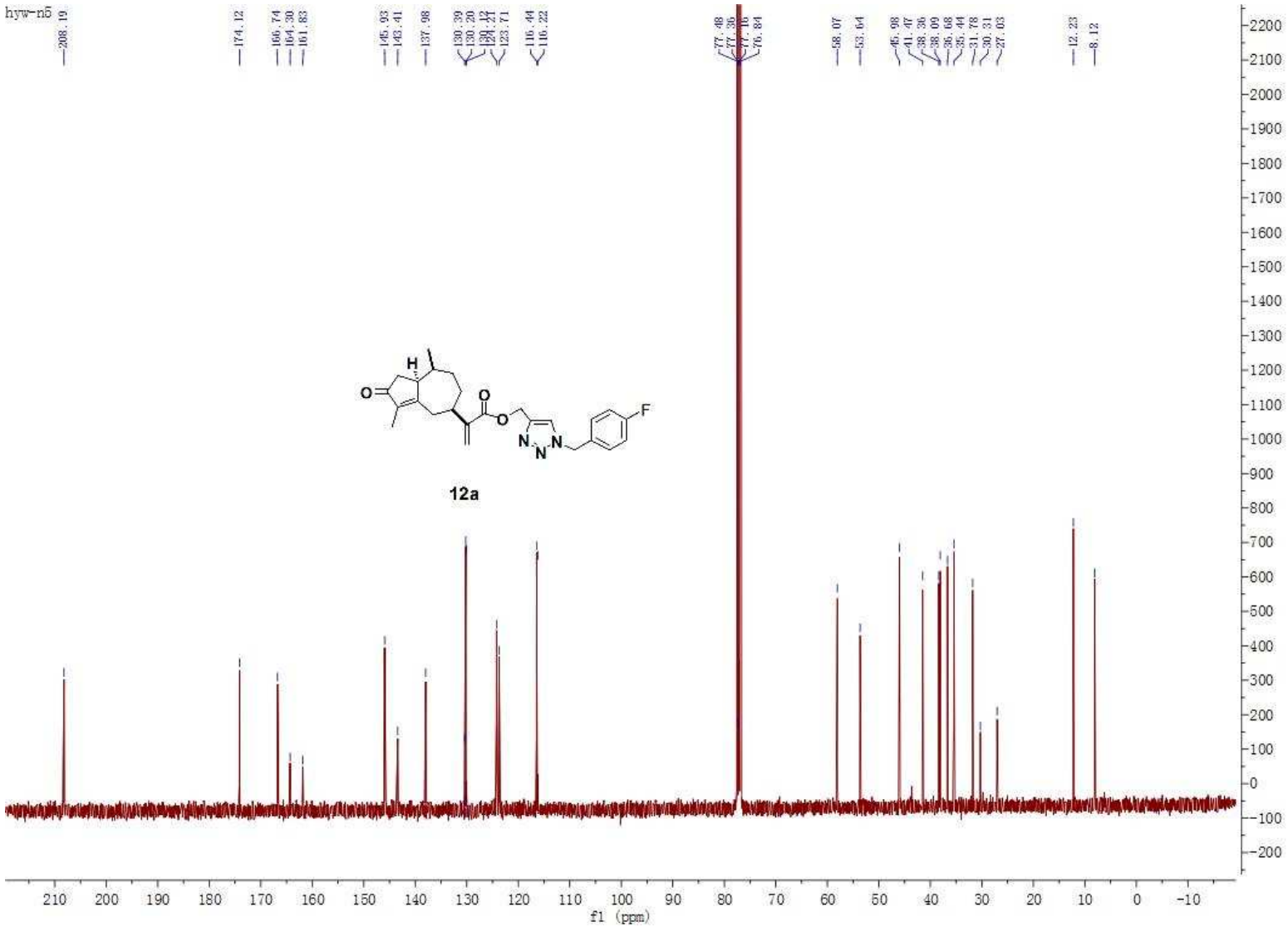
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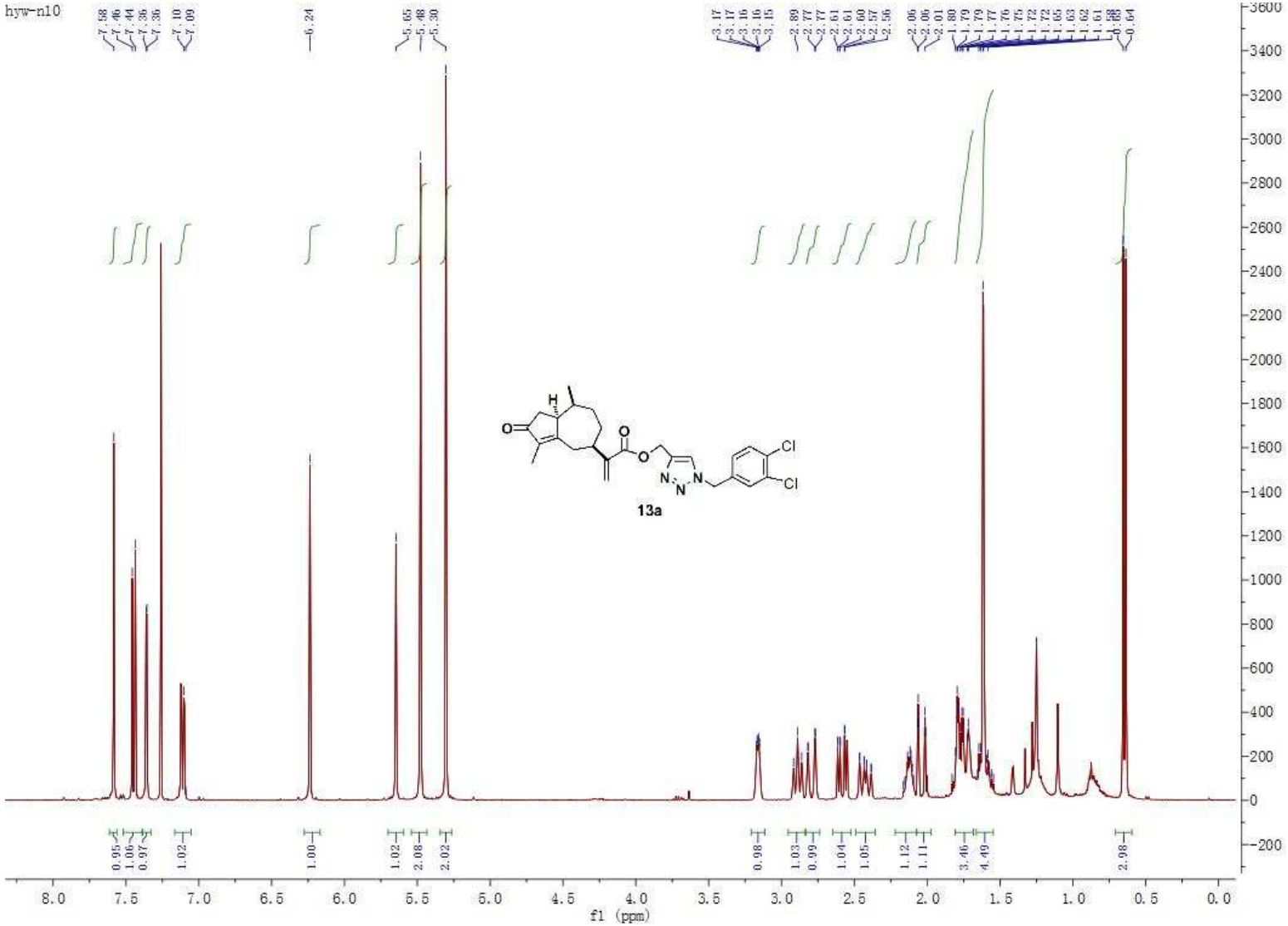
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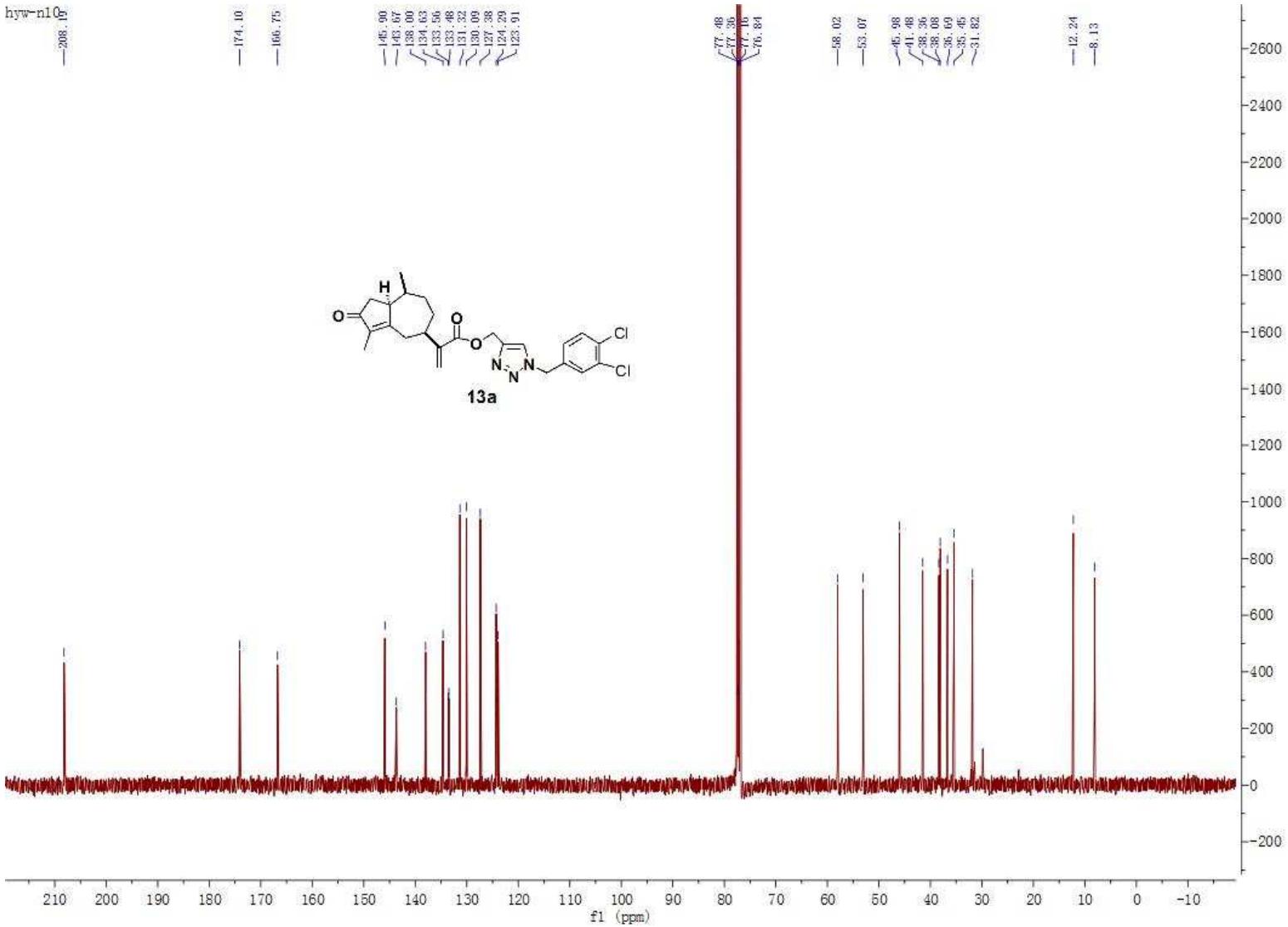
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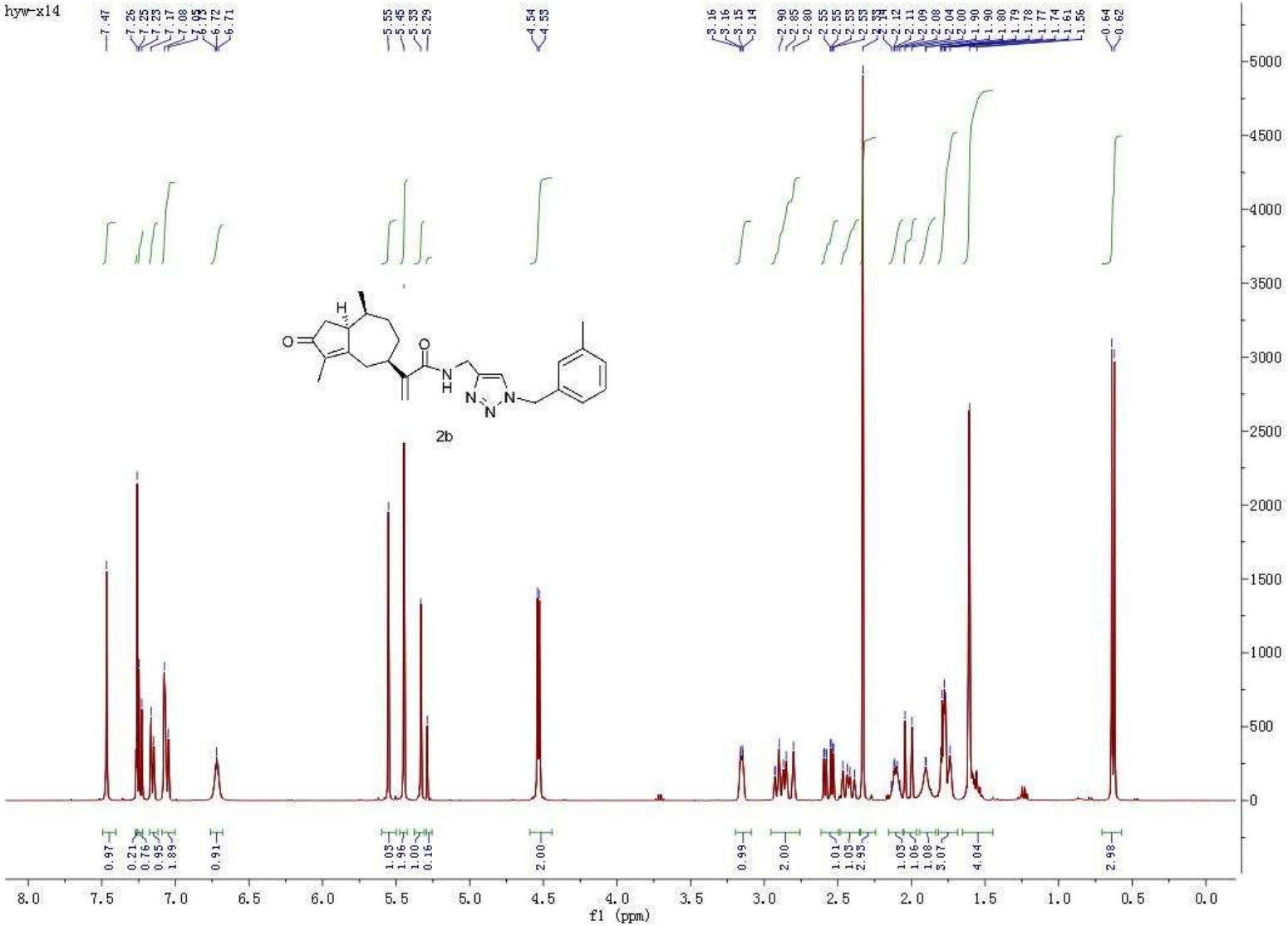
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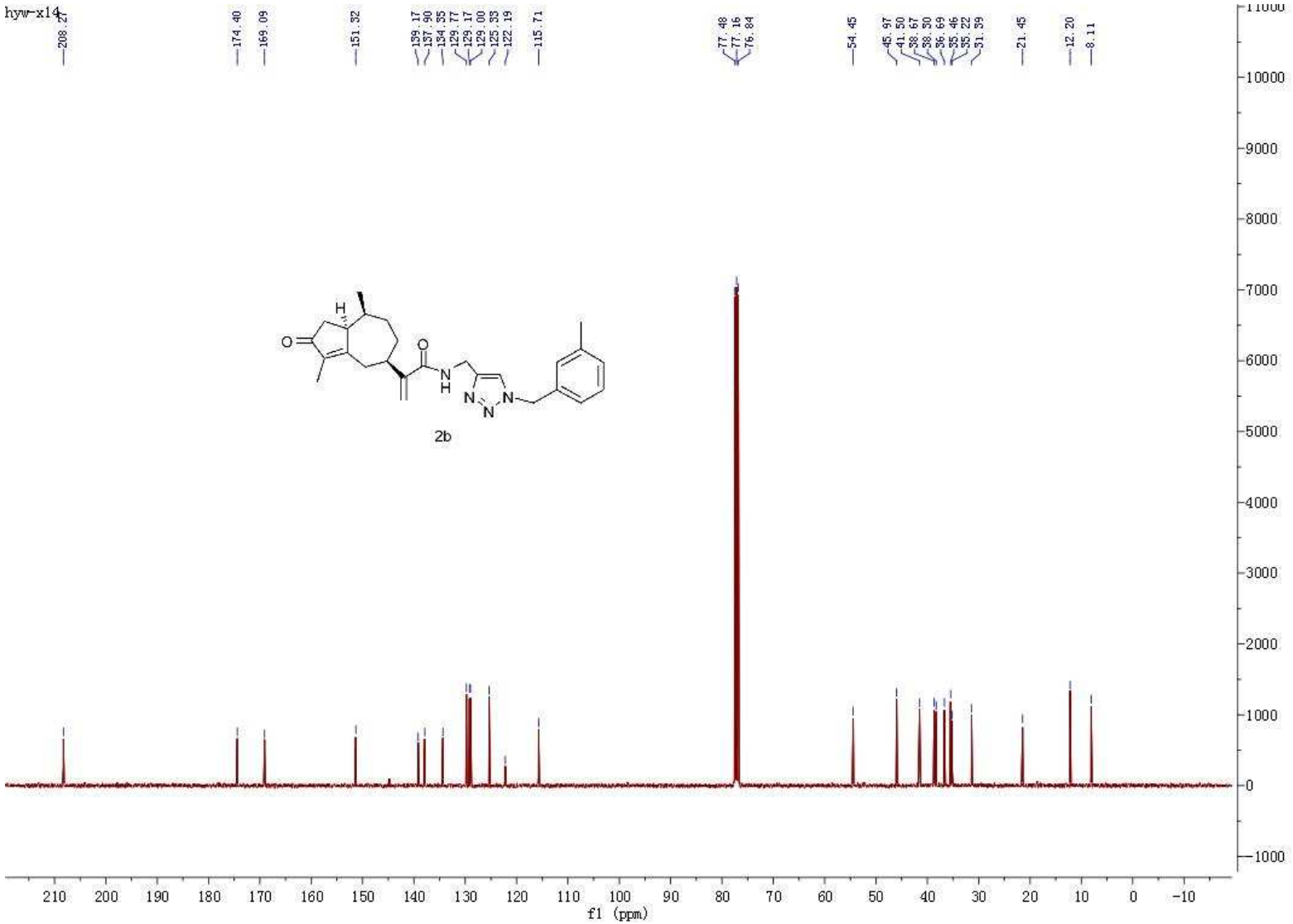
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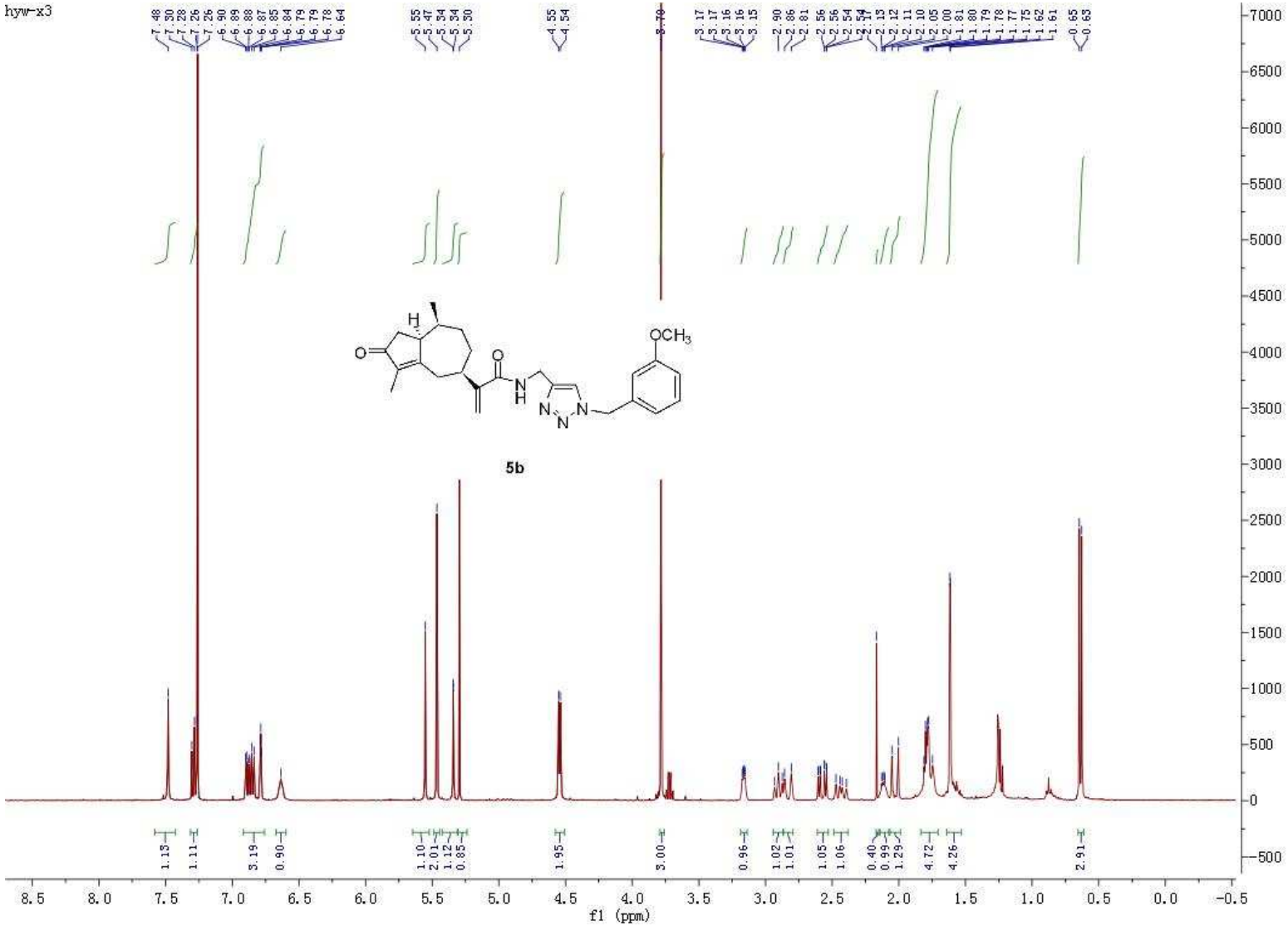
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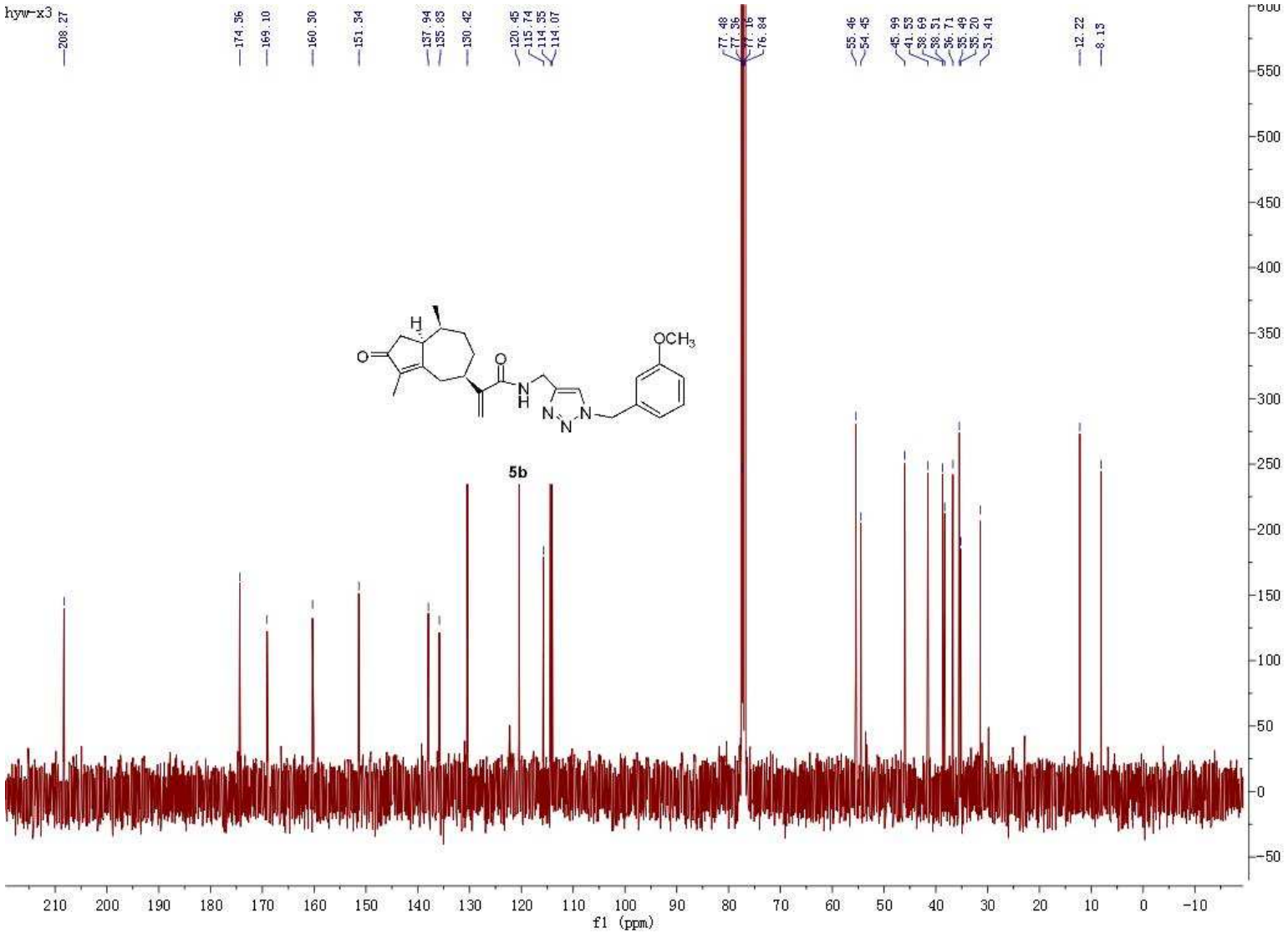
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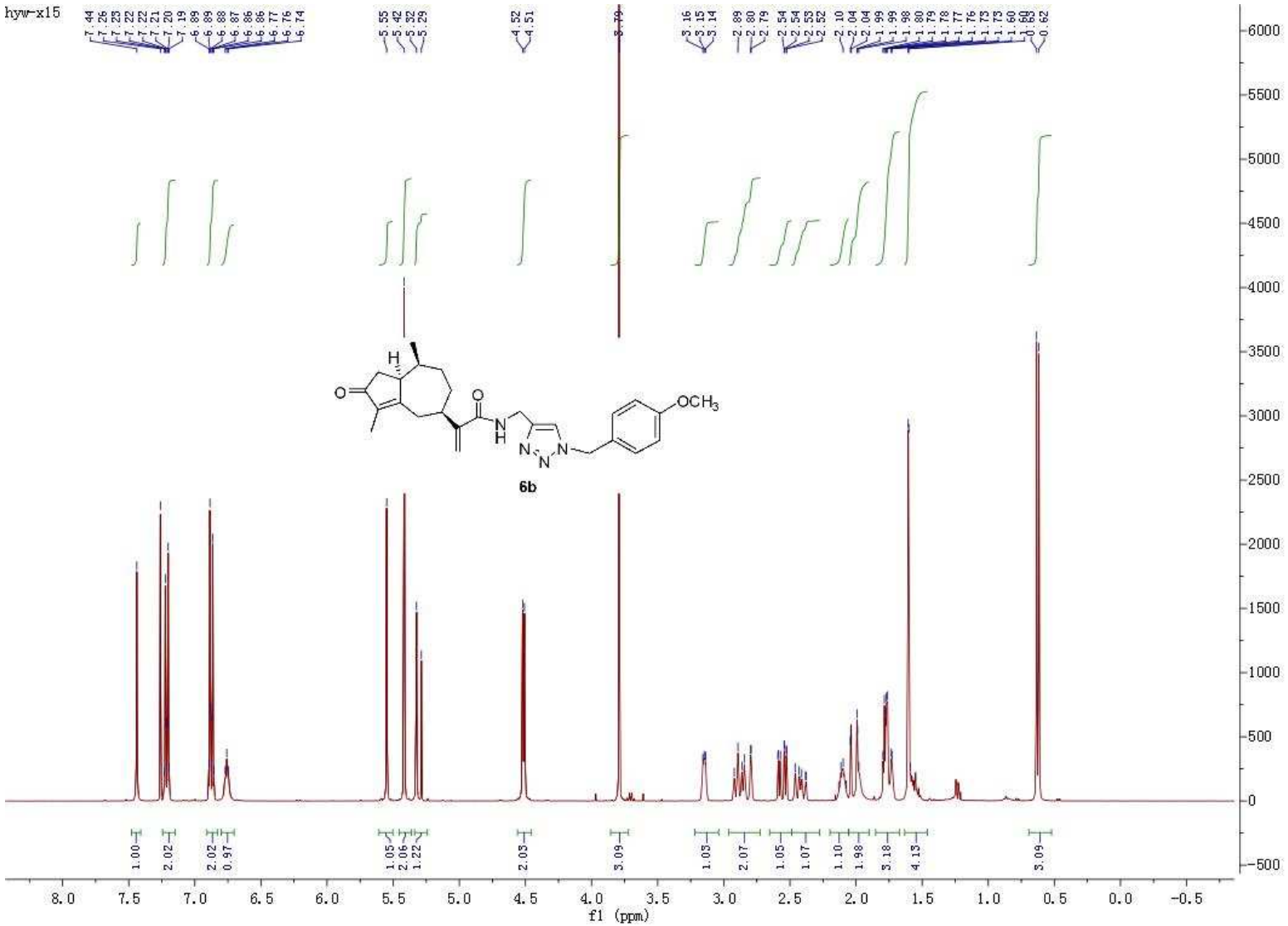
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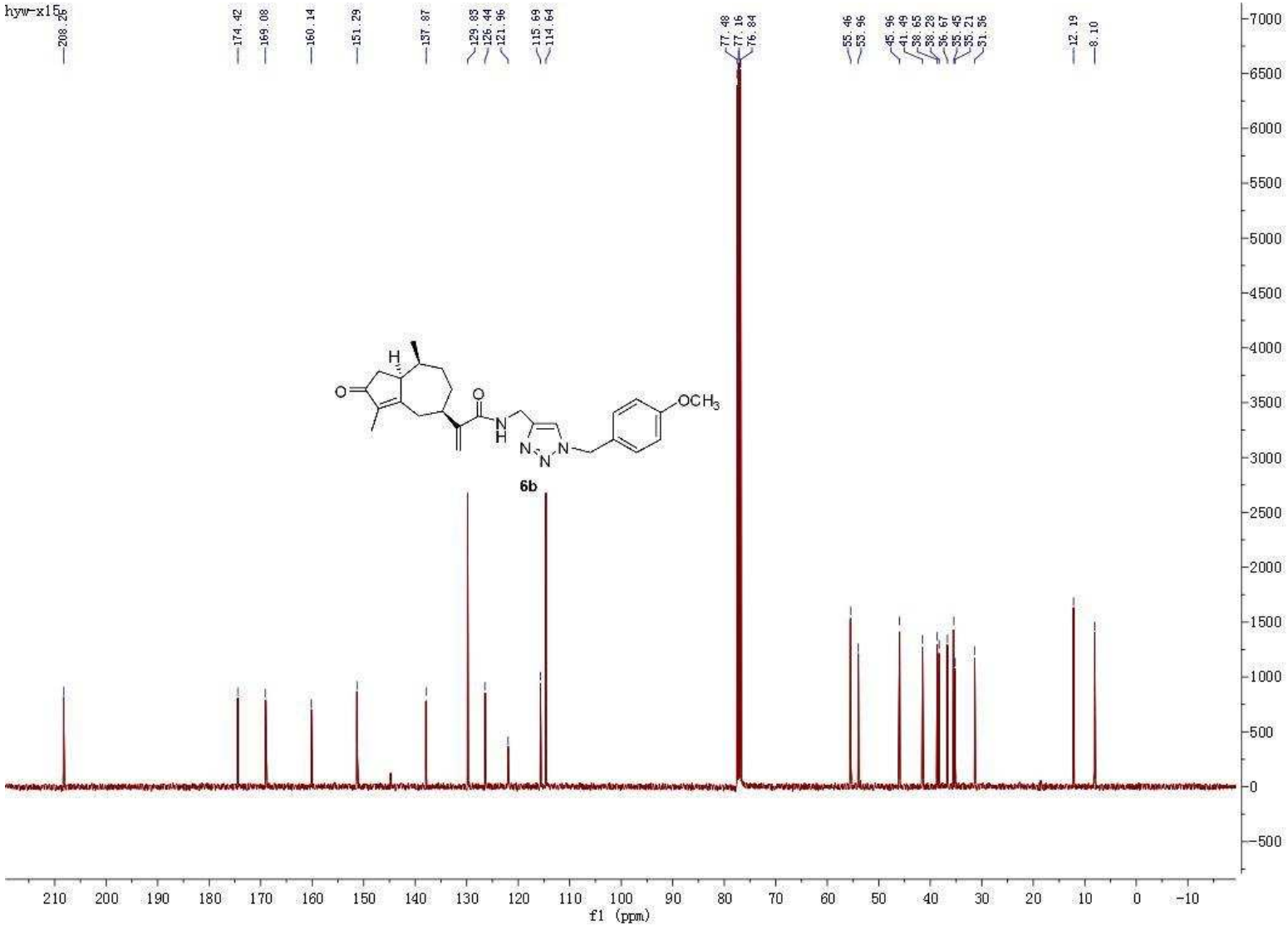
2.54
2.53
2.52
2.10
2.04
2.04
1.99
1.99
1.98
1.80
1.79
1.78
1.77
1.76
1.73
1.73
1.60
0.62
H
O
O
N
H
N
N
N
OCH3
6b
1.00
2.02
2.02
0.97
1.05
2.06
1.22
2.03
3.09
1.03
2.07
1.05
1.07
1.10
1.98
3.18
4.13
3.09
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500


hyw-x15
208.26
174.42
169.08
160.14
151.29
137.87
129.83
126.44
121.96
115.69
114.64
77.48
77.16
76.84
55.46
53.96
45.96
41.49
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36.67
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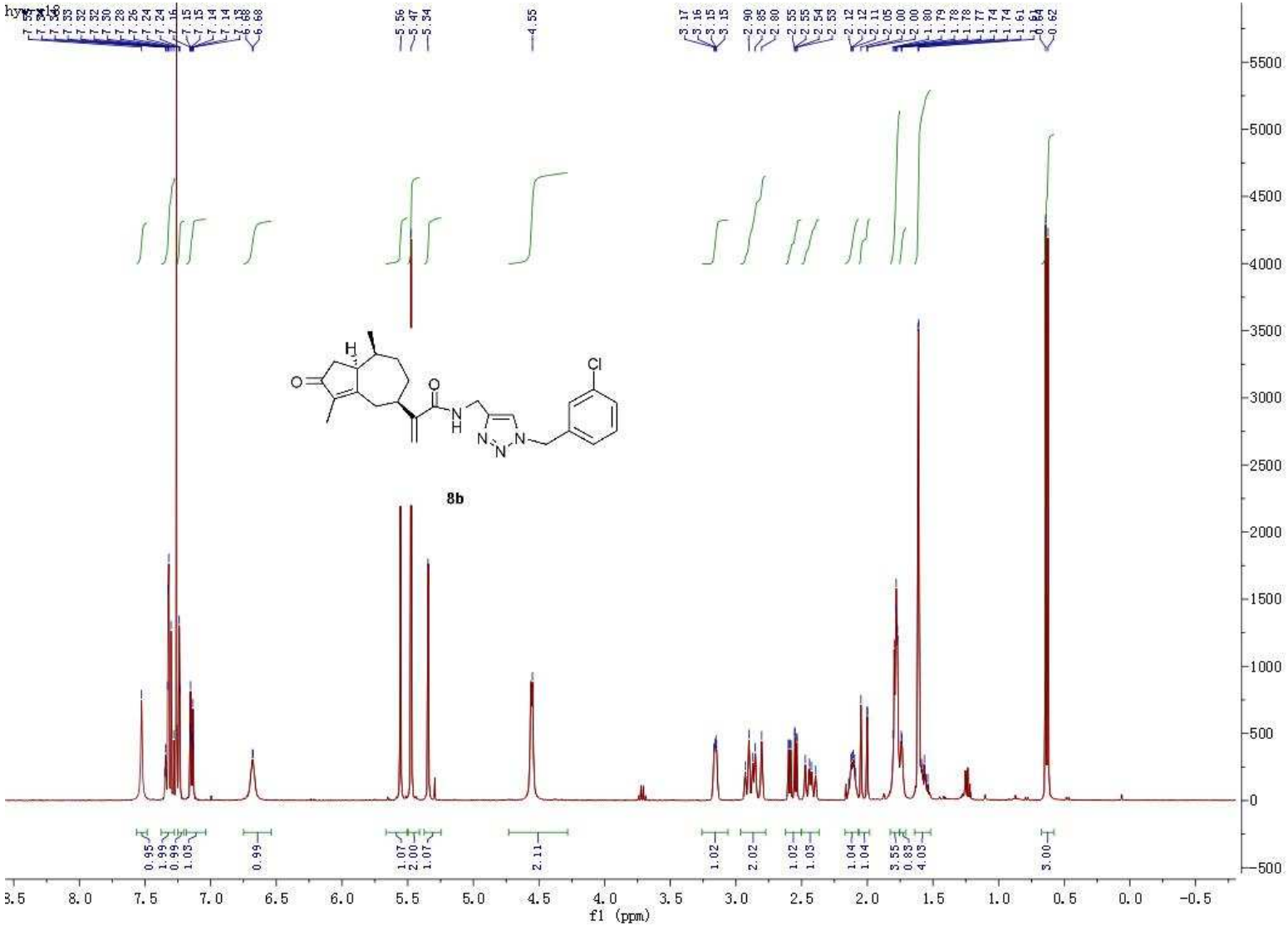
35.21
31.36
12.19
8.10
OCH3
6b
f1 (ppm)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7.34
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7.32
7.32
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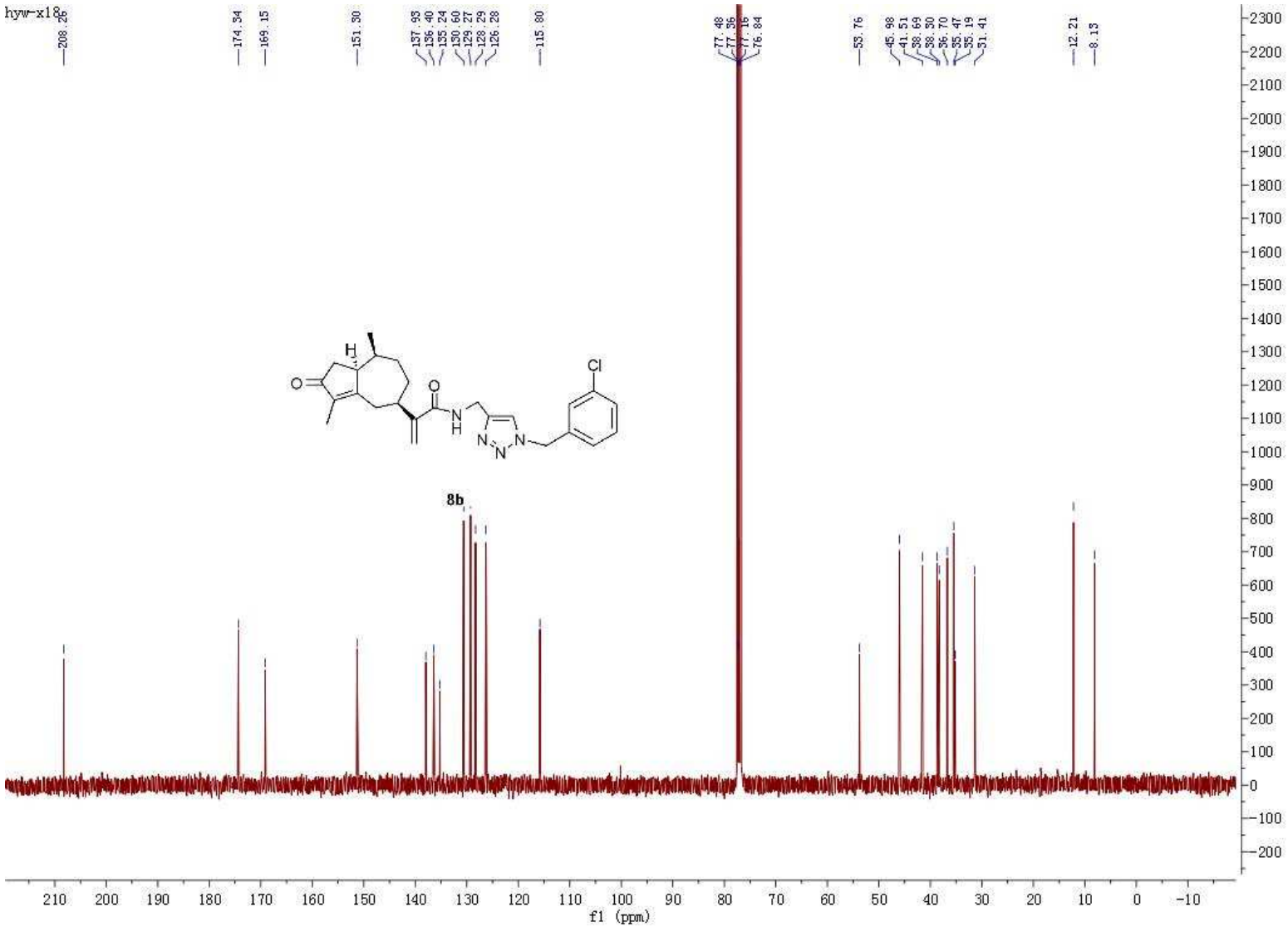
7.28
7.26
7.24
7.24
7.16
7.15
7.15
7.14
7.14
7.13
6.68
6.68
5.56
5.47
5.34
4.55
3.17
3.16
3.15
3.15
2.90
2.85
2.80
2.55
2.55
2.54
2.53
2.12
2.12
2.11
2.05
2.00
2.00
1.80
1.79
1.78
1.78
1.77
1.74
1.74
1.61
0.84
0.62
H
O
O
N
H
N
N
N
Cl
8b
0.95
1.99
0.99
1.03
0.99
1.07
2.00
1.07
2.11
1.02
2.02
1.02
1.03
1.04
1.04
3.55
0.83
4.03
3.00
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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169.15
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137.93
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135.24
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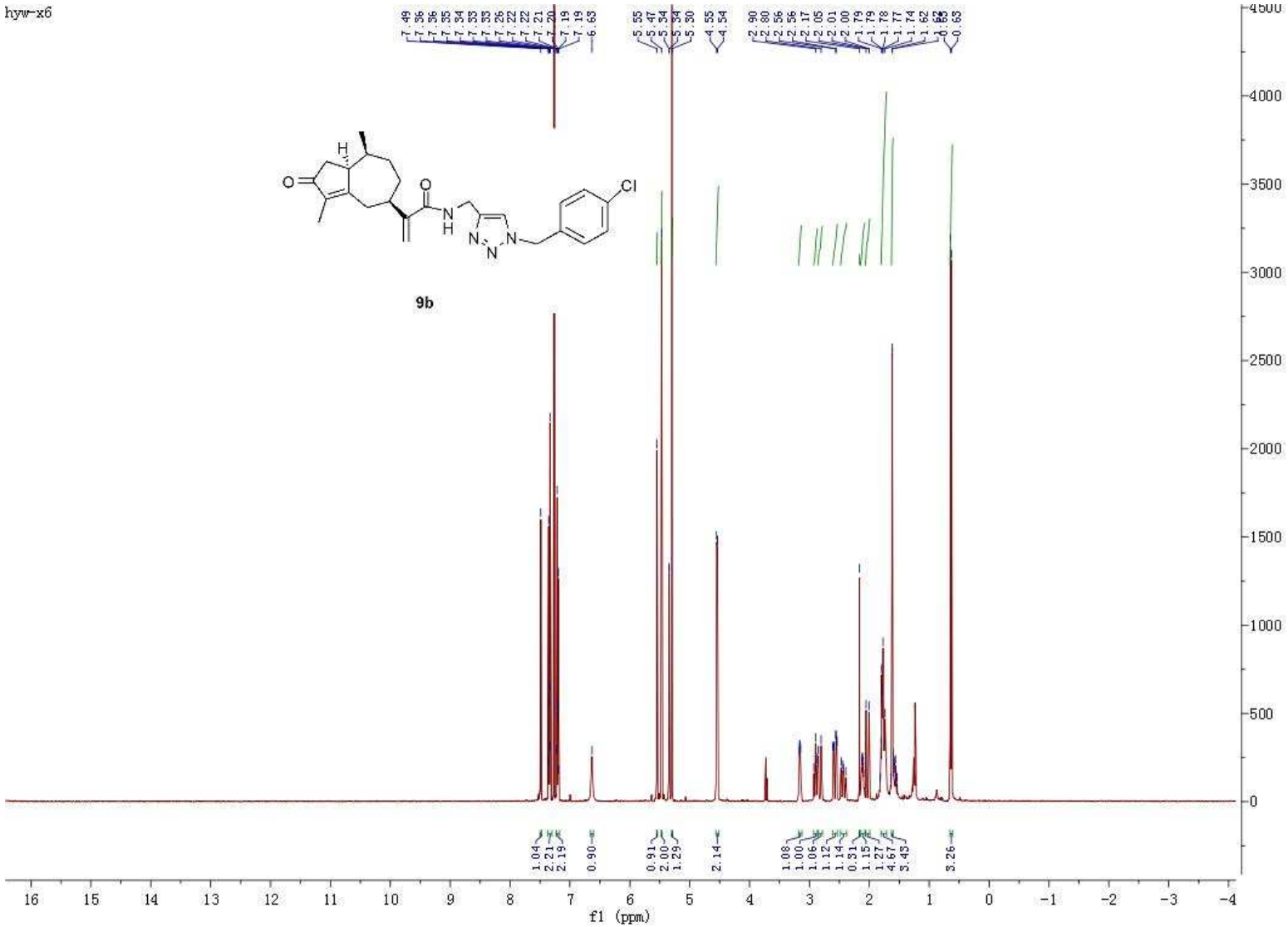
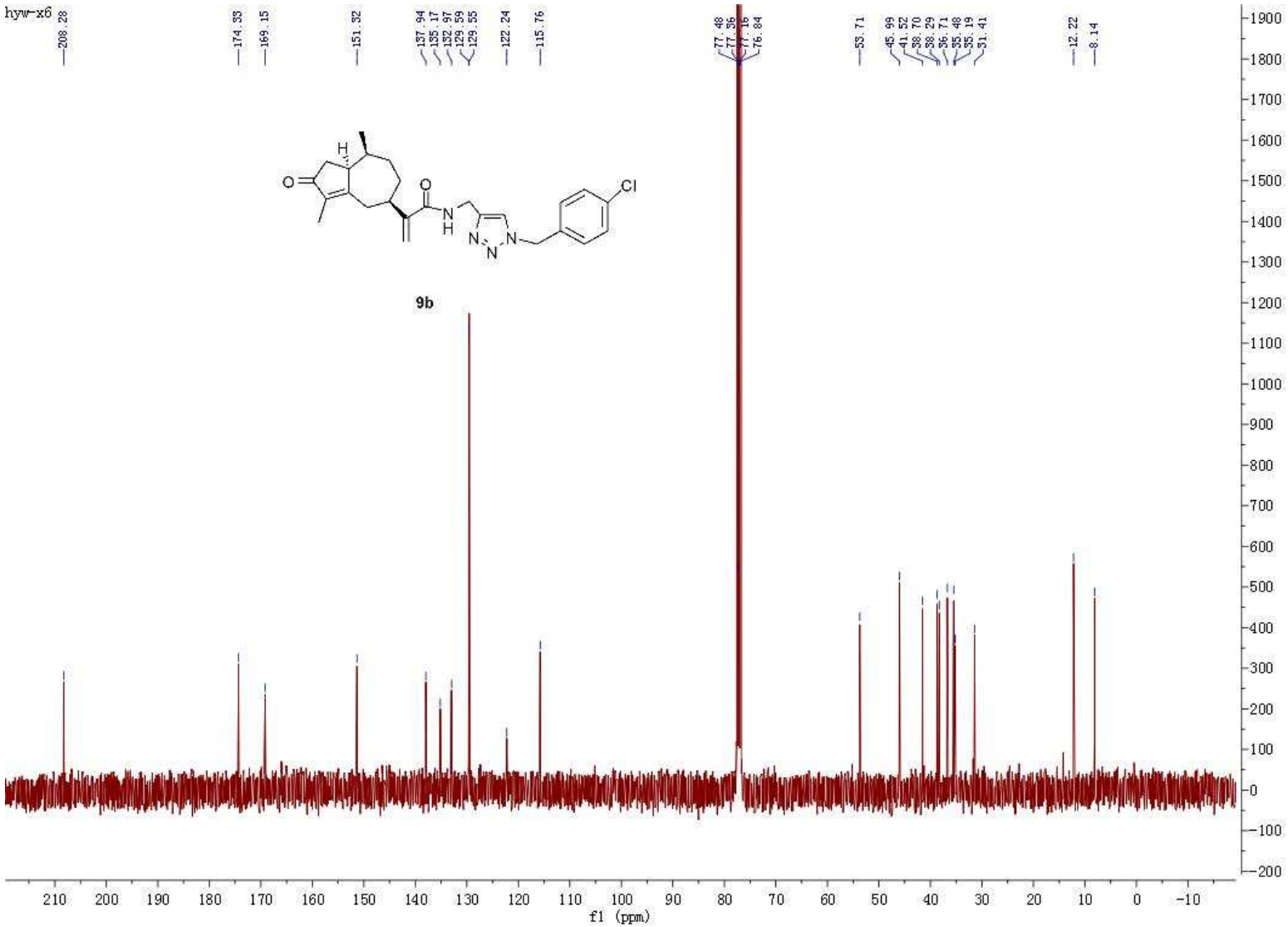
129.27
128.29
126.28
115.80
77.48
77.35
77.16
76.84
53.76
45.98
41.51
38.69
38.30
36.70
35.47
35.19
31.41
12.21
8.13
8b
Cl
f1 (ppm)


hyw-x6
9b
f1 (ppm)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169.15
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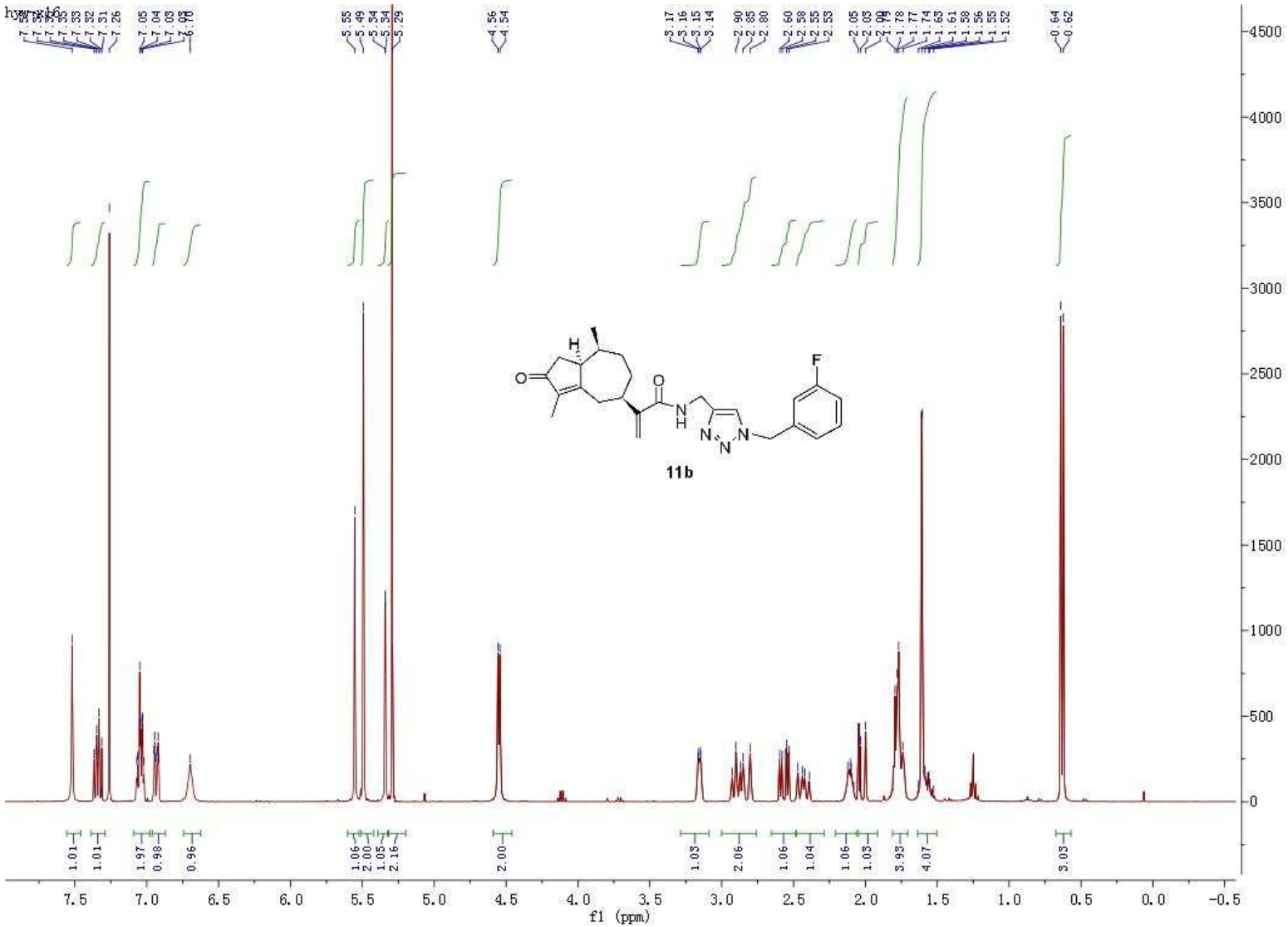
135.17
132.97
129.59
129.55
122.24
115.76
77.48
77.36
77.16
76.84
53.71
45.99
41.52
38.70
38.29
36.71
35.48
35.19
31.41
12.22
8.14
9b
Cl
f1 (ppm)


hywzx16
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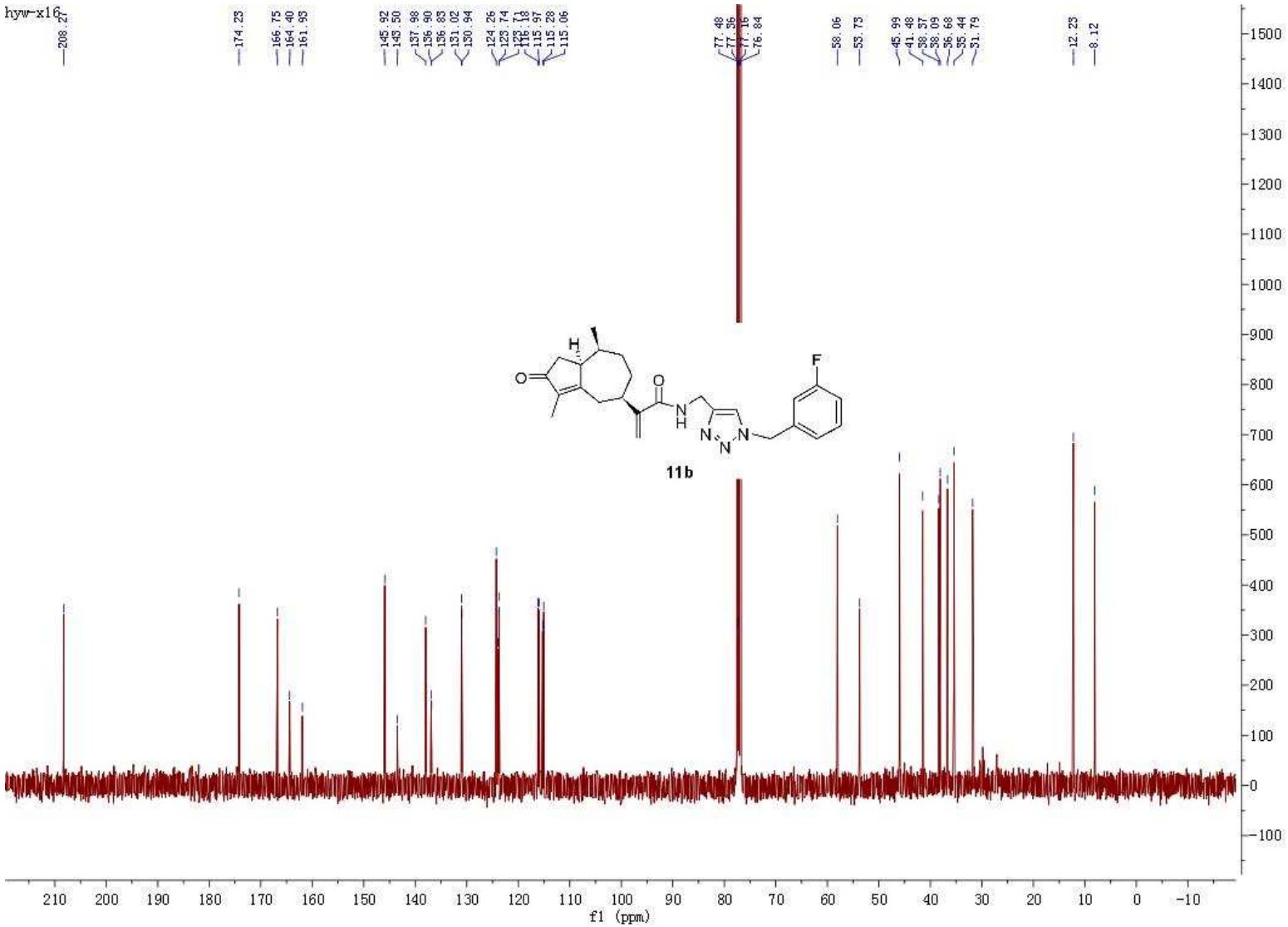
7.36
7.35
7.33
7.32
7.31
7.26
7.05
7.04
7.03
6.98
5.55
5.49
5.34
5.34
5.29
4.56
4.54
3.17
3.16
3.15
3.14
2.90
2.85
2.80
2.60
2.58
2.55
2.53
2.05
2.03
1.99
1.78
1.77
1.74
1.63
1.61
1.58
1.56
1.55
1.52
0.64
0.62
O
H
O
N
H
N
N
N
F
11b
1.01
1.01
1.97
0.98
0.96
1.06
2.00
1.05
2.16
2.00
1.03
2.06
1.06
1.04
1.06
1.03
3.93
4.07
3.03
f1 (ppm)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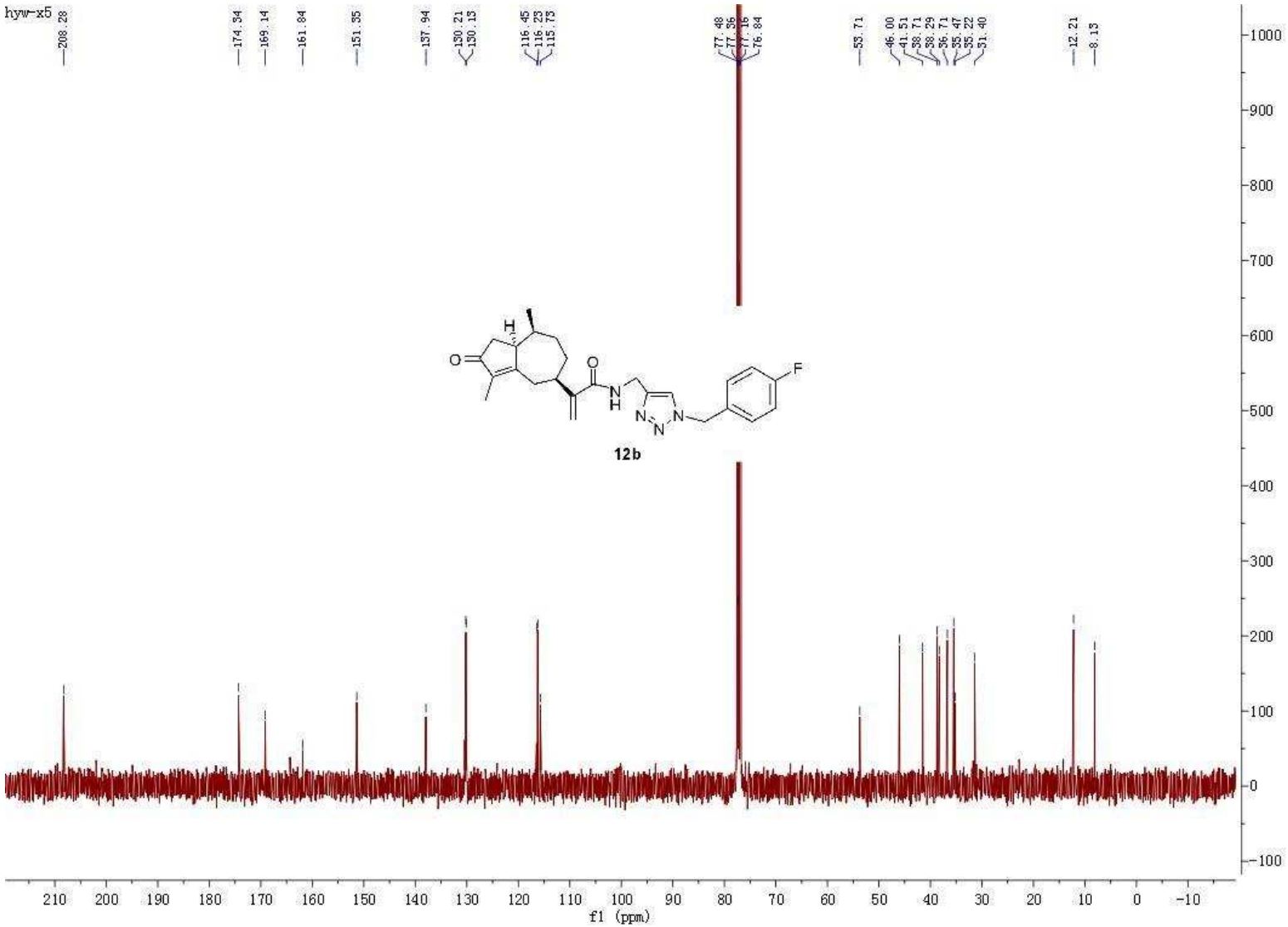
166.75
164.40
161.93
145.92
145.50
137.98
136.90
136.83
131.02
130.94
124.26
123.74
123.71
116.18
115.97
115.28
115.06
77.48
77.35
77.16
76.84
58.06
53.73
45.99
41.48
38.37
38.09
36.68
35.44
31.79
12.23
8.12
11b
f1 (ppm)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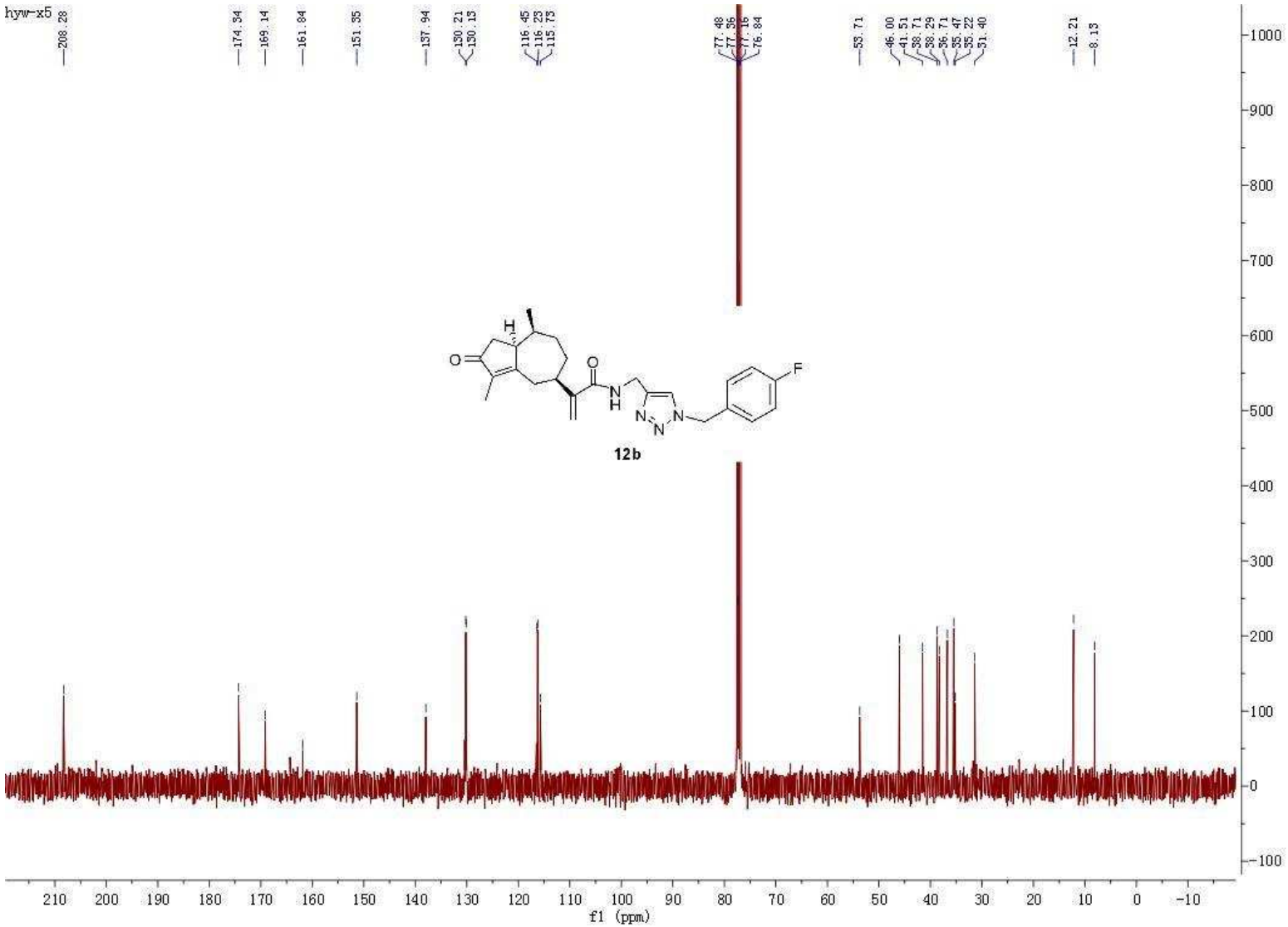
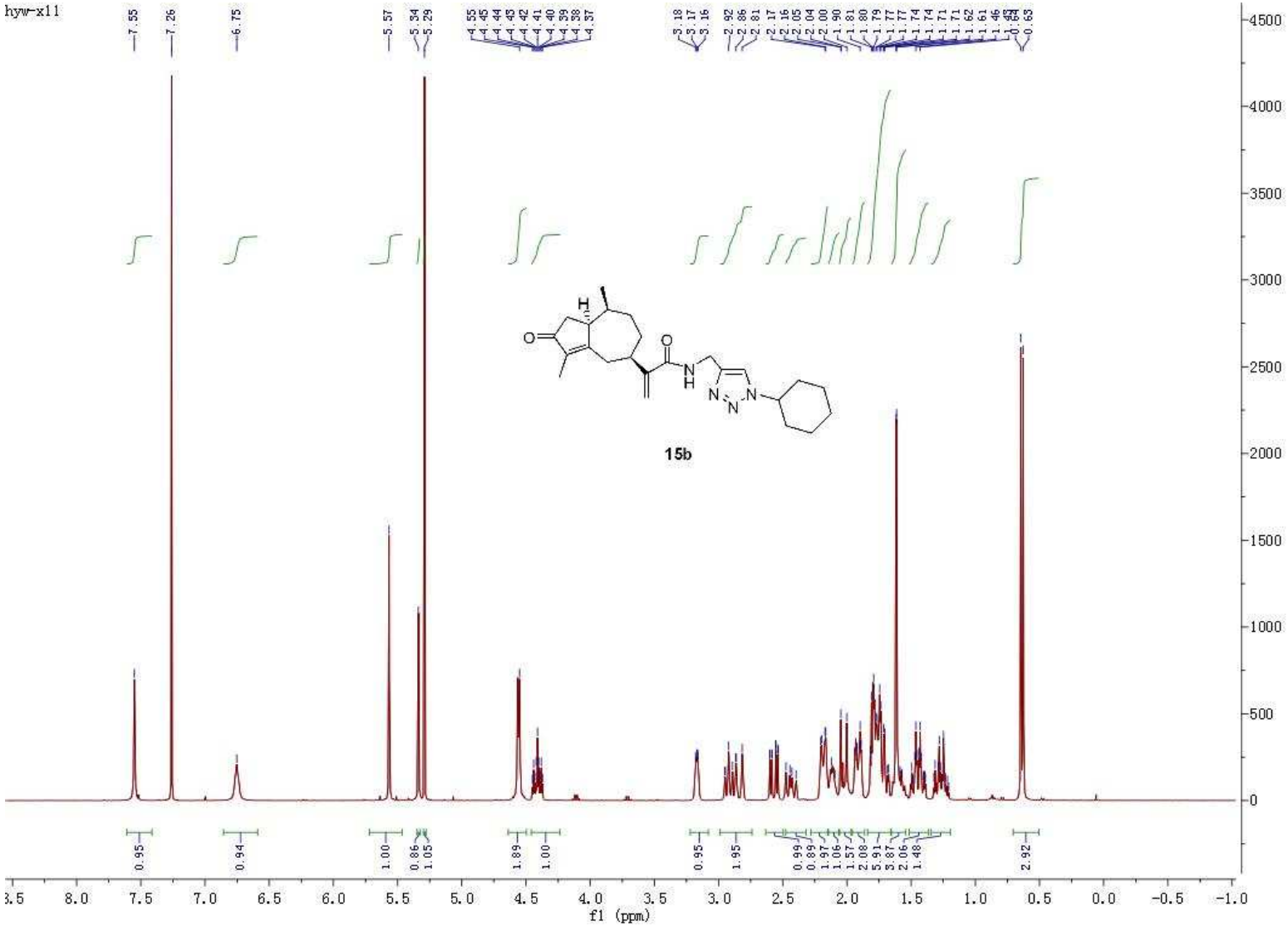
151.35
137.94
130.21
130.13
116.45
116.23
115.73
77.48
77.16
76.84
53.71
46.00
41.51
38.71
38.29
36.71
35.47
35.22
31.40
12.21
8.13
O
O
H
N
H
N
N
N
F
12b
f1 (ppm)


hyw-x5
208.28
174.34
169.14
161.84
151.35
137.94
130.21
130.13
116.45
116.23
115.73
77.48
77.16
76.84
53.71
46.00
41.51
38.71
38.29
36.71
35.47
35.22
31.40
12.21
8.13
O
O
H
N
H
N
N
N
F
12b
f1 (ppm)


hyw-x11
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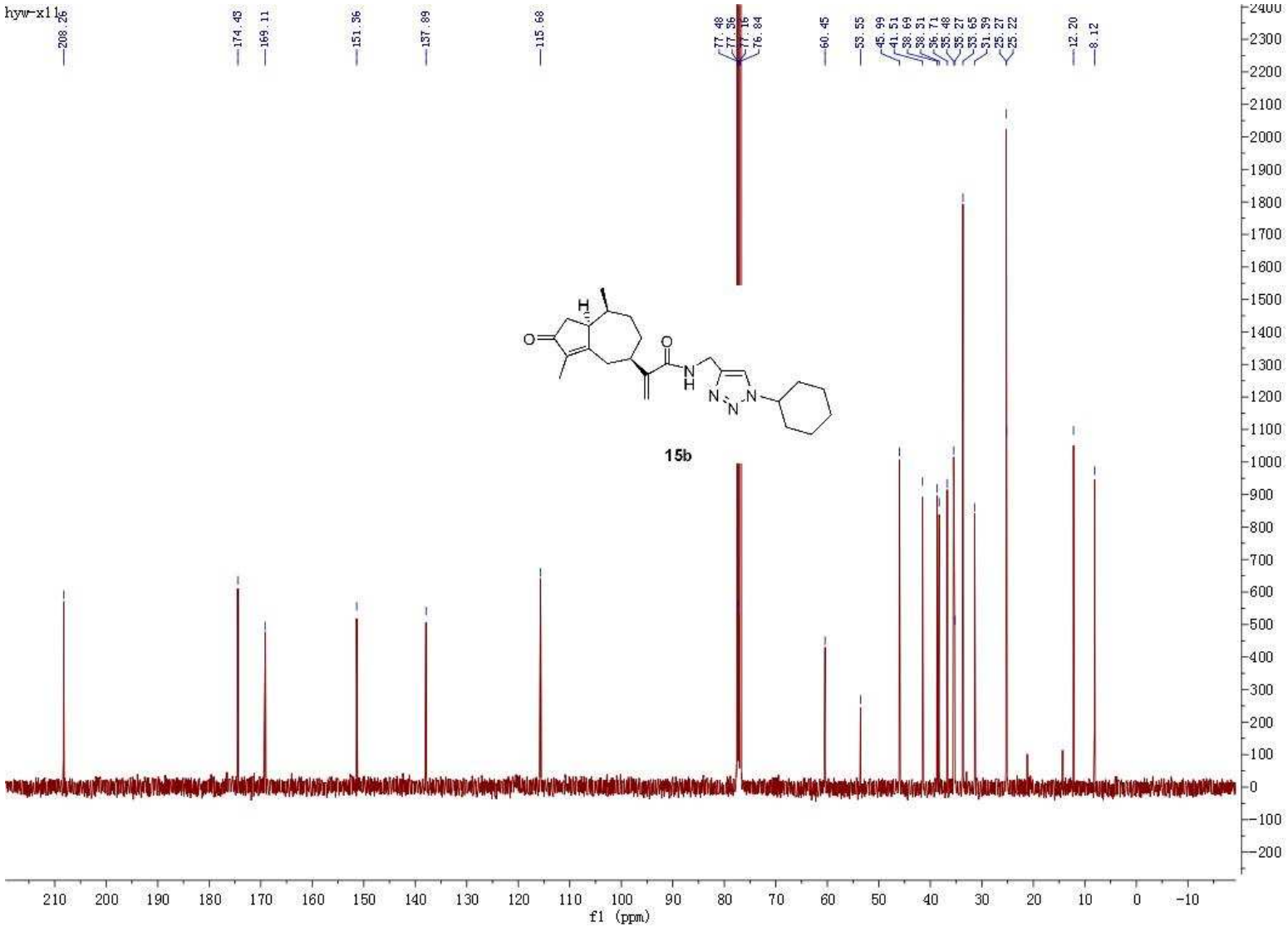
7.26
6.75
5.57
5.34
5.29
4.55
4.45
4.44
4.43
4.42
4.41
4.40
4.39
4.38
4.37
3.18
3.17
3.16
2.92
2.86
2.81
2.17
2.16
2.05
2.04
2.00
1.90
1.81
1.80
1.79
1.77
1.74
1.71
1.62
1.61
1.46
0.64
0.63
15b
0.95
0.94
1.00
0.86
1.05
1.89
1.00
0.95
1.95
0.99
0.89
1.97
1.06
1.57
2.08
5.91
3.87
2.06
1.48
2.92
f1 (ppm)


hyw-x11
208.26
174.43
169.11
151.36
137.89
115.68
77.48
77.36
77.16
76.84
60.45
53.55
45.99
41.51
38.69
38.51
36.71
35.48
35.27
33.65
31.39
25.27
25.22
12.20
8.12
15b
f1 (ppm)