

Synthesis of Macrocyclic Peptide–Diterpenoid Conjugates by a sequential Arylation/Peptide Coupling/Click Macrocyclization Procedure

Mariia A. Gromova,^a Yurii V. Kharitonov,^b Tatyana C. Golubeva,^c Elvira E. Shults^b

^aNovosibirsk State Pedagogical University (NSPU), 630126, Novosibirsk, Russia.

^bNovosibirsk Institute of Organic Chemistry SB RAS (NIOCH SB RAS), 630090, Novosibirsk, Russia

^cThe Federal Research Center Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, 630090, Novosibirsk, Russia

@E-mail: schultz@nioch.nsc.ru

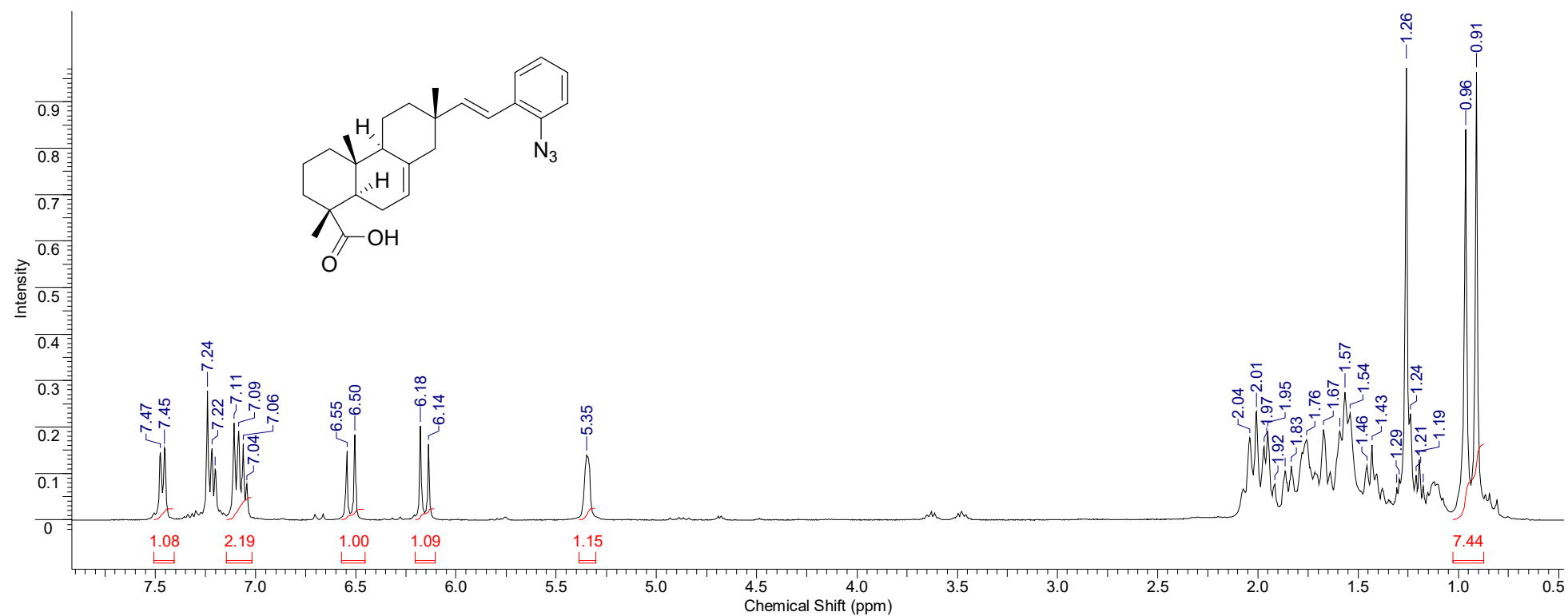
NMR spectra of compounds 3, 8c, 9b,c, 10a-d, 11a-d

(1R,4aR,4bS,7S,10aR)-7-((E)-2-Azidostyryl)-1,4a,7-trimethyl-1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydrophenanthrene-1-carboxylic acid (3)	3
<i>tert</i> -Butyl (2-(((S)-3-methyl-1-oxo-1-(prop-2-yn-1-ylamino)butan-2-yl)amino)-2-oxoethyl)carbamate (8c)	5.
2-(((S)-3-Methyl-1-oxo-1-(prop-2-yn-1-ylamino)butan-2-yl)amino)-2-oxoethan-1-aminium 2,2,2-trifluoroacetate (9c)	7
(S)-3-Methyl-1-(((S)-3-methyl-1-oxo-1-(prop-2-yn-1-ylamino)butan-2-yl)amino)-1-oxobutan-2-aminium 2,2,2-trifluoroacetate (9b)	9
(1R,4aR,4bS,7S,10aR)-7-((E)-2-azidostyryl)-1,4a,7-trimethyl-N-(2-oxo-2-((2-oxo-2-(prop-2-yn-1-ylamino)ethyl)amino)ethyl)-1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydrophenanthrene-1-carboxamide (10a)	11
(1R,4aR,4bS,7S,10aR)-7-((E)-2-azidostyryl)-1,4a,7-trimethyl-N-((S)-3-methyl-1-(((S)-3-methyl-1-oxo-1-(prop-2-yn-1-ylamino)butan-2-yl)amino)-1-oxobutan-2-yl)-1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydrophenanthrene-1-carboxamide (10b)	13
(1R,4aR,4bS,7S,10aR)-7-((E)-2-azidostyryl)-1,4a,7-trimethyl-N-(2-(((S)-3-methyl-1-oxo-1-(prop-2-yn-1-ylamino)butan-2-yl)amino)-2-oxoethyl)-1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydrophenanthrene-1-carboxamide (10c)	15
(1R,4aR,4bS,7S,10aR)-7-((E)-2-azidostyryl)-1,4a,7-trimethyl-N-((S)-3-methyl-1-oxo-1-((2-oxo-2-(prop-2-yn-1-ylamino)ethyl)amino)butan-2-yl)-1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydrophenanthrene-1-carboxamide (10d)	17
(14Z,52S,54aS,54bR,58R,58aR,510Z,3E)-52,54b,58-trimethyl-51,52,53,54,54a,54b,55,56,57,58,58a,59-dodecahydro-11H-7,10,13-triaza-1(1,4)-triazola-5(2,8)-phenanthrena-2(1,2)-benzenacyclotetradecaphan-3-ene-6,9,12-trione (11a)	19

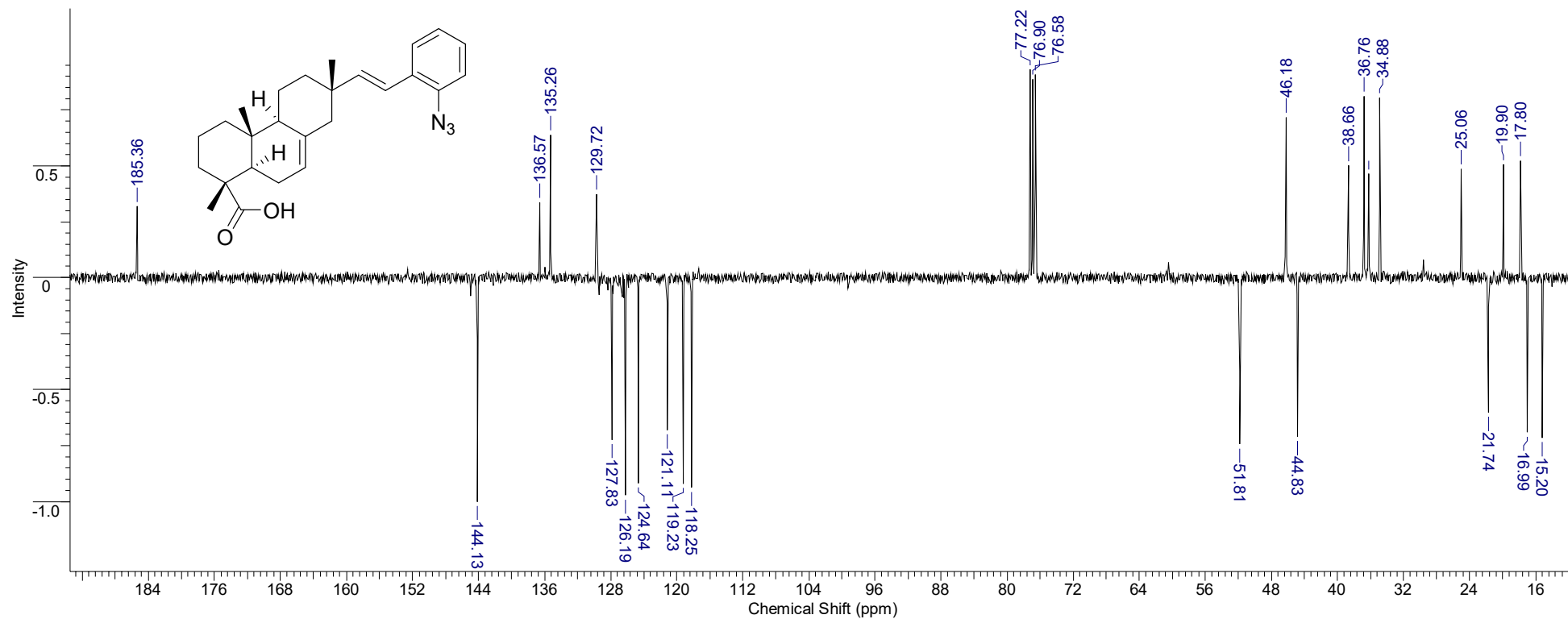
(14Z,52S,54aS,54bR,58R,58aR,510Z,3E,8S,11S)-8,11-diisopropyl-52,54b,58-trimethyl-51,52,53,54,54a,54b,55,56,57,58,58a,59-dodecahydro-11H-7,10,13-triaza-1(1,4)-triazola-5(2,8)-phenanthrena-2(1,2)-benzenacyclotetradecaphan-3-ene-6,9,12-trione (11b)	21
(14Z,52S,54aS,54bR,58R,58aR,510Z,3E,11S)-11-isopropyl-52,54b,58-trimethyl-51,52,53,54,54a,54b,55,56,57,58,58a,59-dodecahydro-11H-7,10,13-triaza-1(1,4)-triazola-5(2,8)-phenanthrena-2(1,2)-benzenacyclotetradecaphan-3-ene-6,9,12-trione (111c).....	23
(1 ⁴ Z,5 ² S,5 ^{4a} S,5 ^{4b} R,5 ⁸ R,5 ^{8a} R,5 ¹⁰ Z,3E,8S)-8-isopropyl-5 ² ,5 ^{4b} ,5 ⁸ -trimethyl-5 ¹ ,5 ² ,5 ³ ,5 ⁴ ,5 ^{4a} ,5 ^{4b} ,5 ⁵ ,5 ⁶ ,5 ⁷ ,5 ⁸ ,5 ^{8a} ,5 ⁹ -dodecahydro-11H-7,10,13-triaza-1(1,4)-triazola-5(2,8)-phenanthrena-2(1,2)-benzenacyclotetradecaphan-3-ene-6,9,12-trione (11d).....	25

(1R,4aR,4bS,7S,10aR)-7-((E)-2-Azidostyryl)-1,4a,7-trimethyl-1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydrophenanthrene-1-carboxylic acid (3)

^1H NMR (CDCl_3 , 400.13 MHz) δ ppm

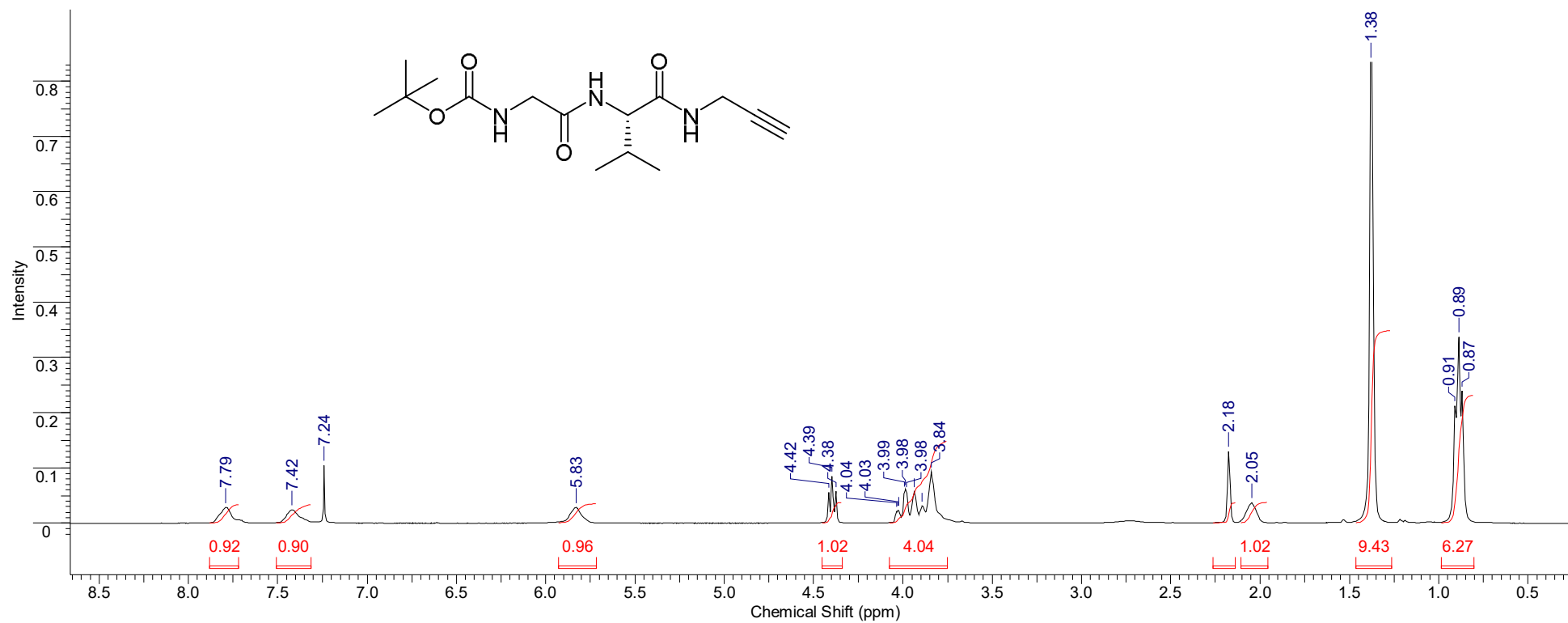


¹³C NMR (100.61 MHz, CDCl₃) δ (ppm)

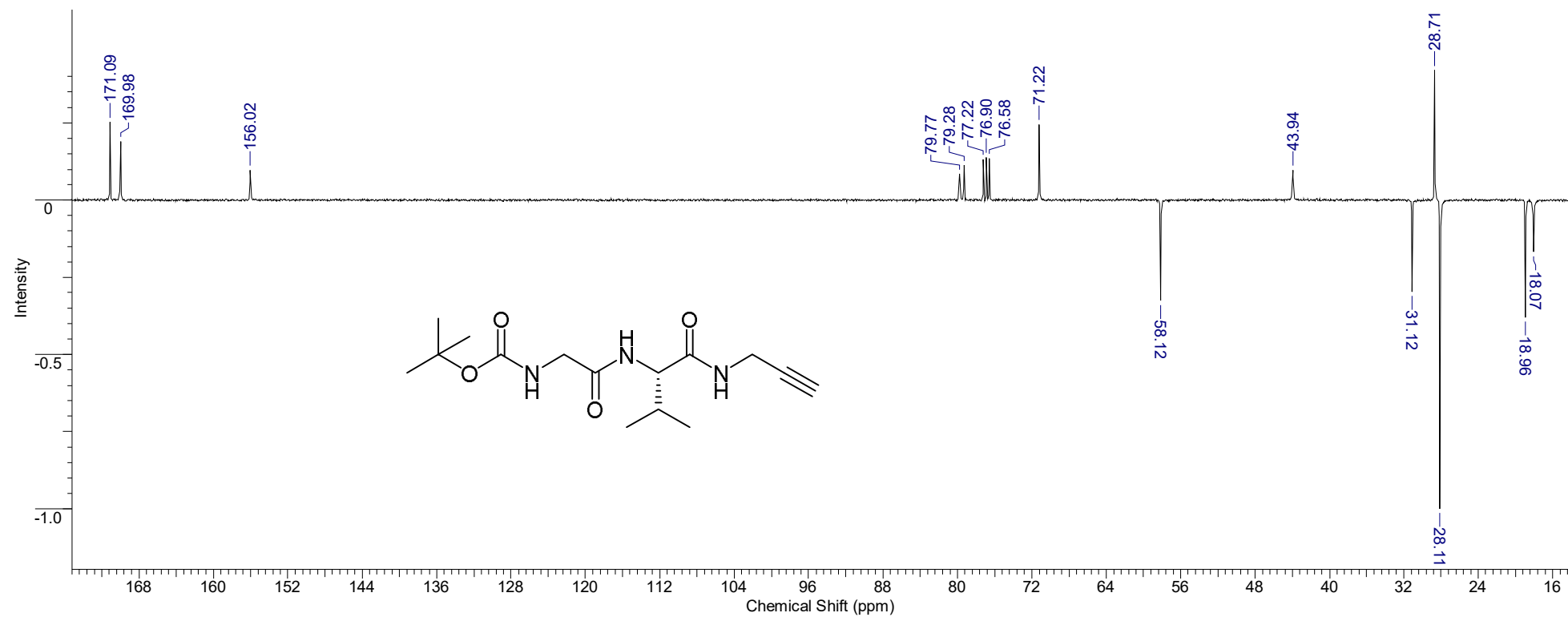


***tert*-Butyl (2-(((*S*)-3-methyl-1-oxo-1-(prop-2-yn-1-ylamino)butan-2-yl)amino)-2-oxoethyl)carbamate (8c)**

^1H NMR (CDCl_3 , 400.13 MHz) δ ppm

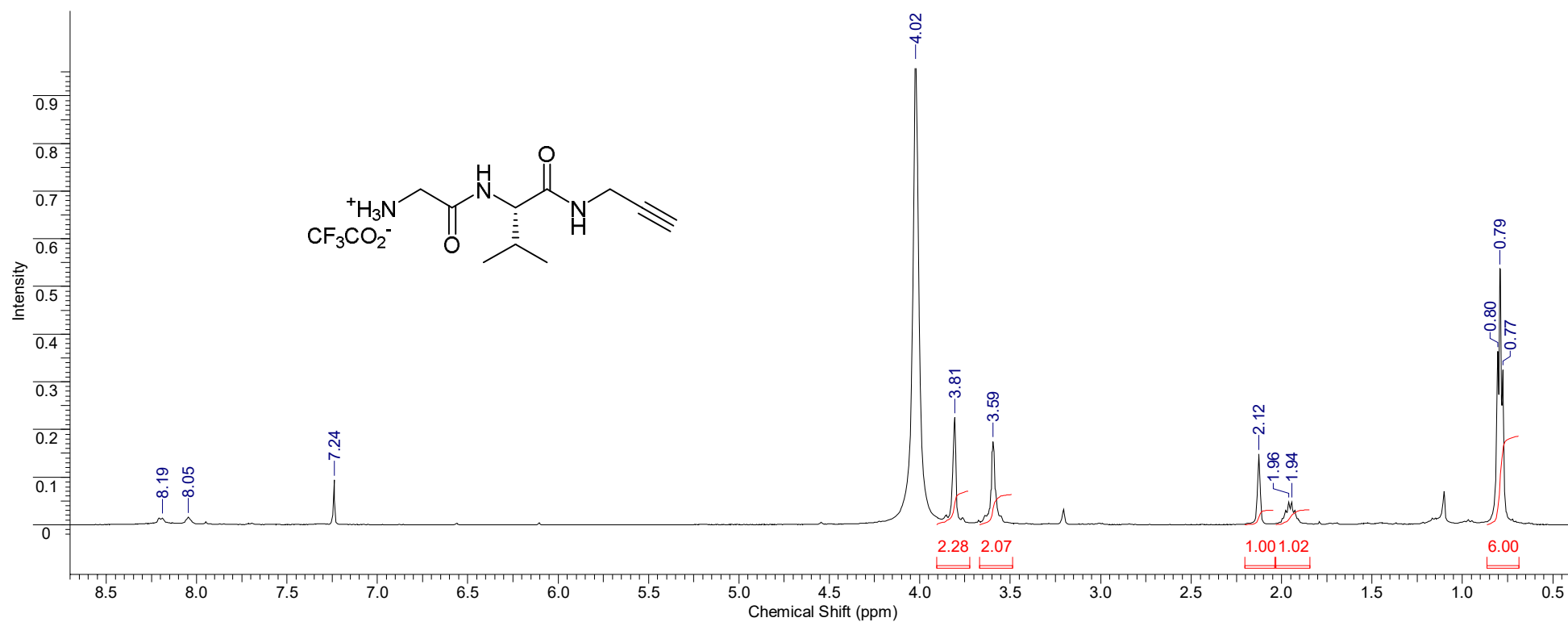


^{13}C NMR of compound **8c** (100.61 MHz, CDCl_3) δ (ppm)

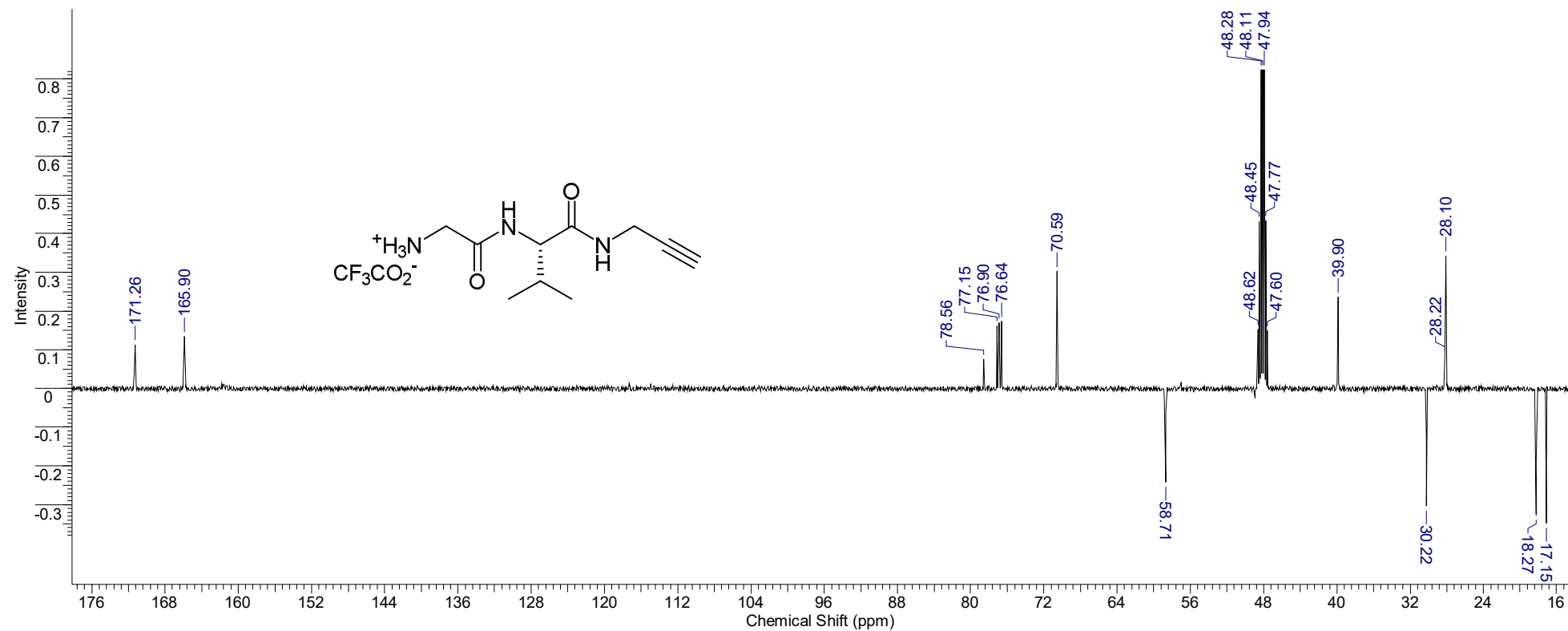


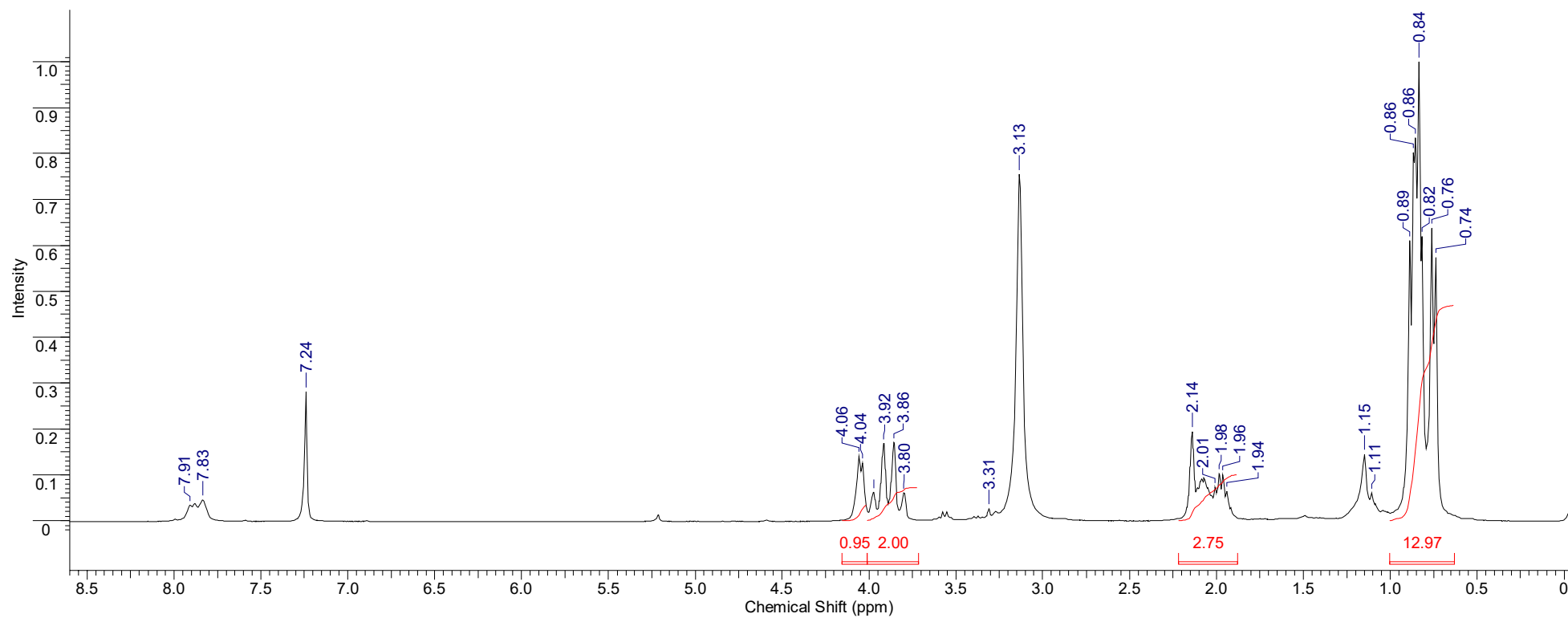
2-(((S)-3-Methyl-1-oxo-1-(prop-2-yn-1-ylamino)butan-2-yl)amino)-2-oxoethan-1-aminium 2,2,2-trifluoroacetate (9c)

^1H NMR ($\text{CDCl}_3\text{-CD}_3\text{OD}$, 400.13 MHz) δ ppm

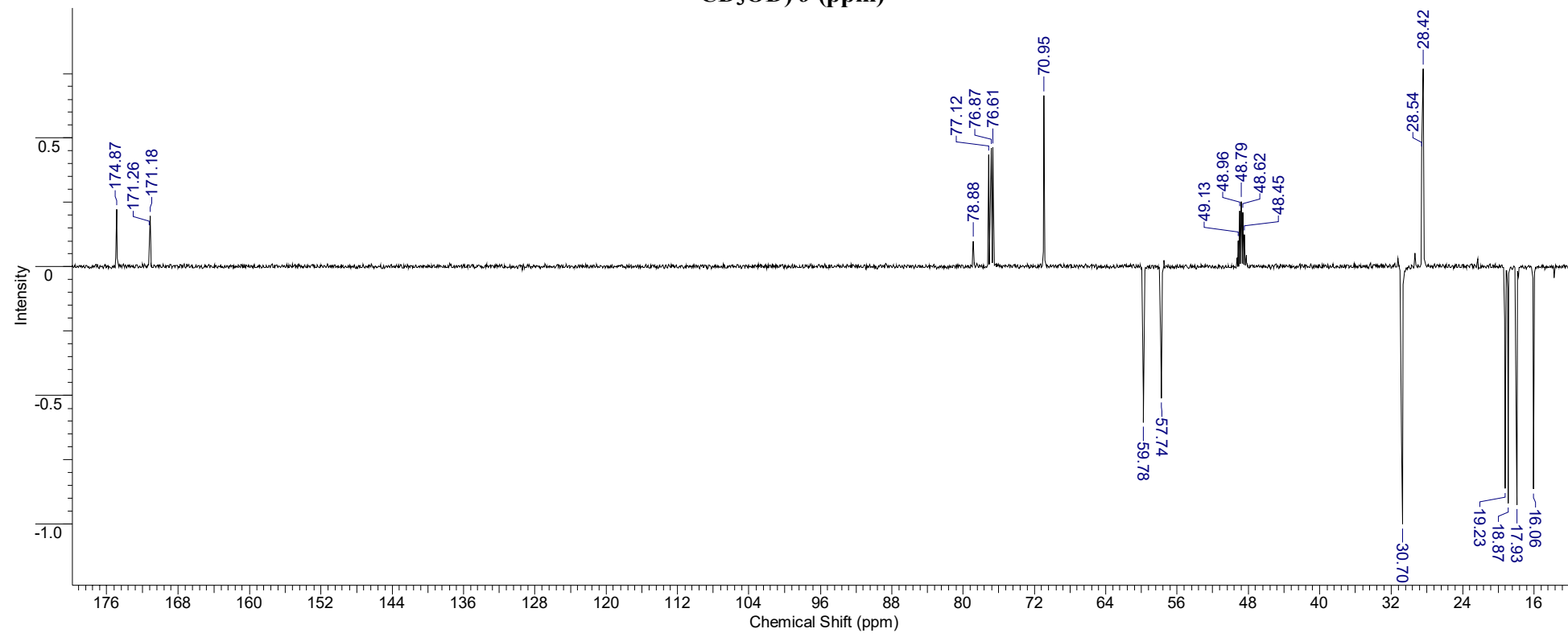


^{13}C NMR of compound **9c** (125.76 MHz, $\text{CDCl}_3\text{-CD}_3\text{OD}$) δ (ppm)



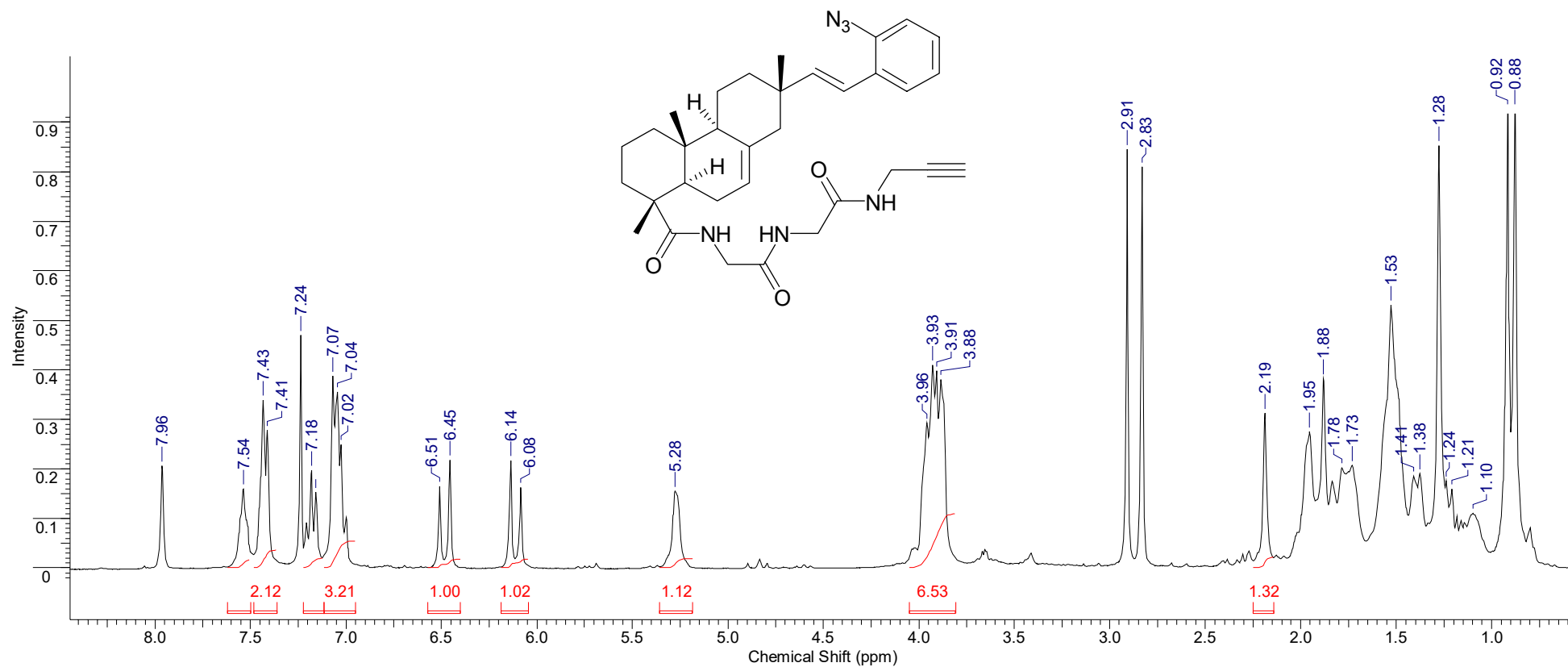
CC(C)[C@H](C(=O)N[C@@H](C)C(=O)NCC#C)[NH3+].[O-]C(F)(F)F¹H NMR (CDCl₃-CD₃OD, 300.13 MHz) δ ppm

^{13}C NMR of compound **9b** (125.76 MHz, CDCl_3 - CD_3OD) δ (ppm)

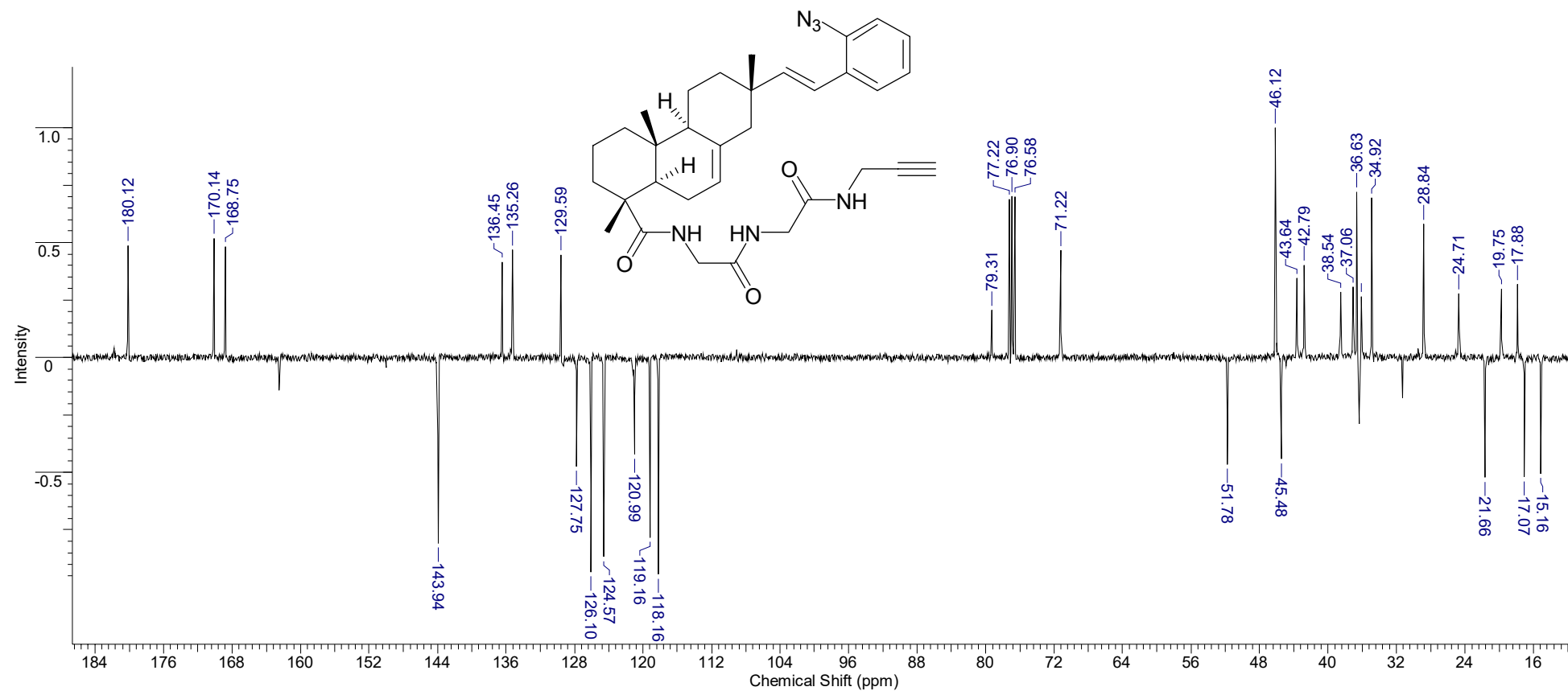


(1R,4aR,4bS,7S,10aR)-7-((E)-2-azidostyryl)-1,4a,7-trimethyl-N-(2-oxo-2-((2-oxo-2-(prop-2-yn-1-ylamino)ethyl)amino)ethyl)-1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydrophenanthrene-1-carboxamide (10a)

^1H NMR (CDCl_3 , 300.13 MHz) δ ppm

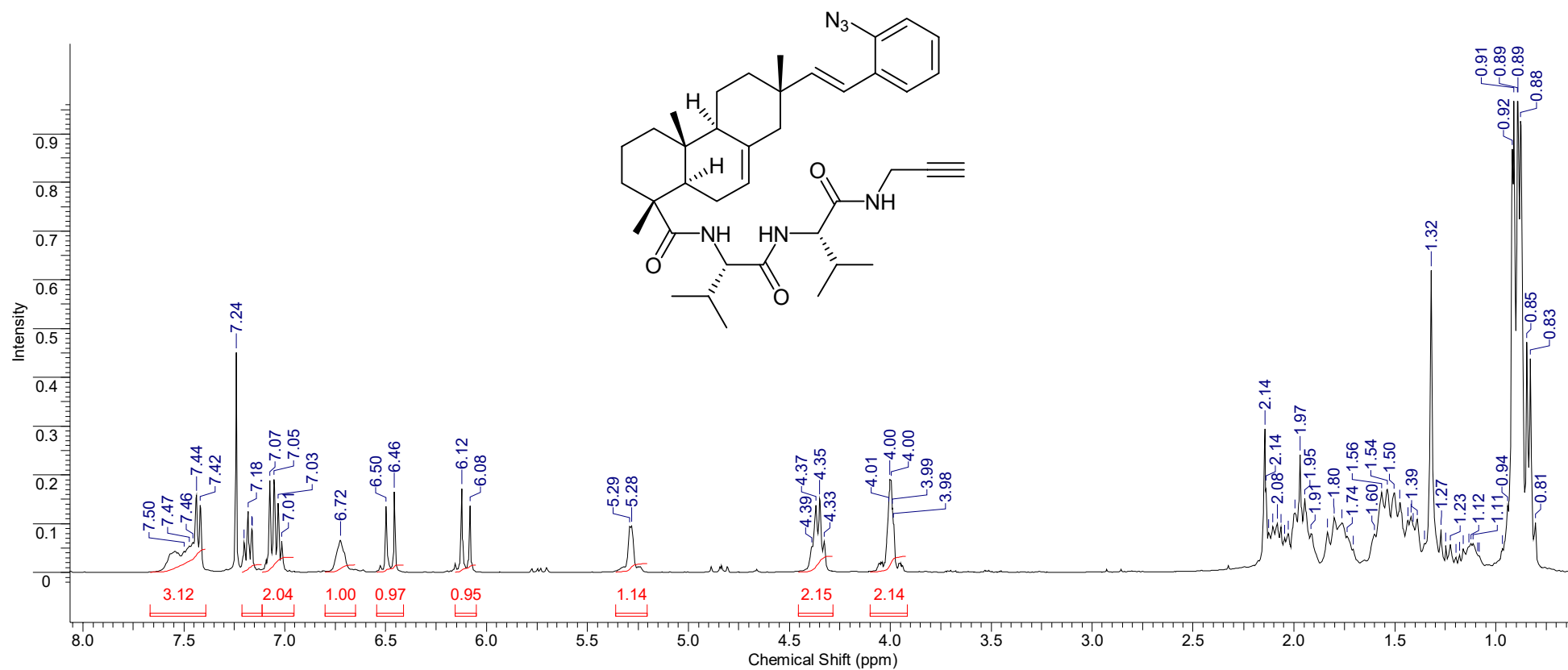


^{13}C NMR (100.61 MHz, CDCl_3) δ (ppm)

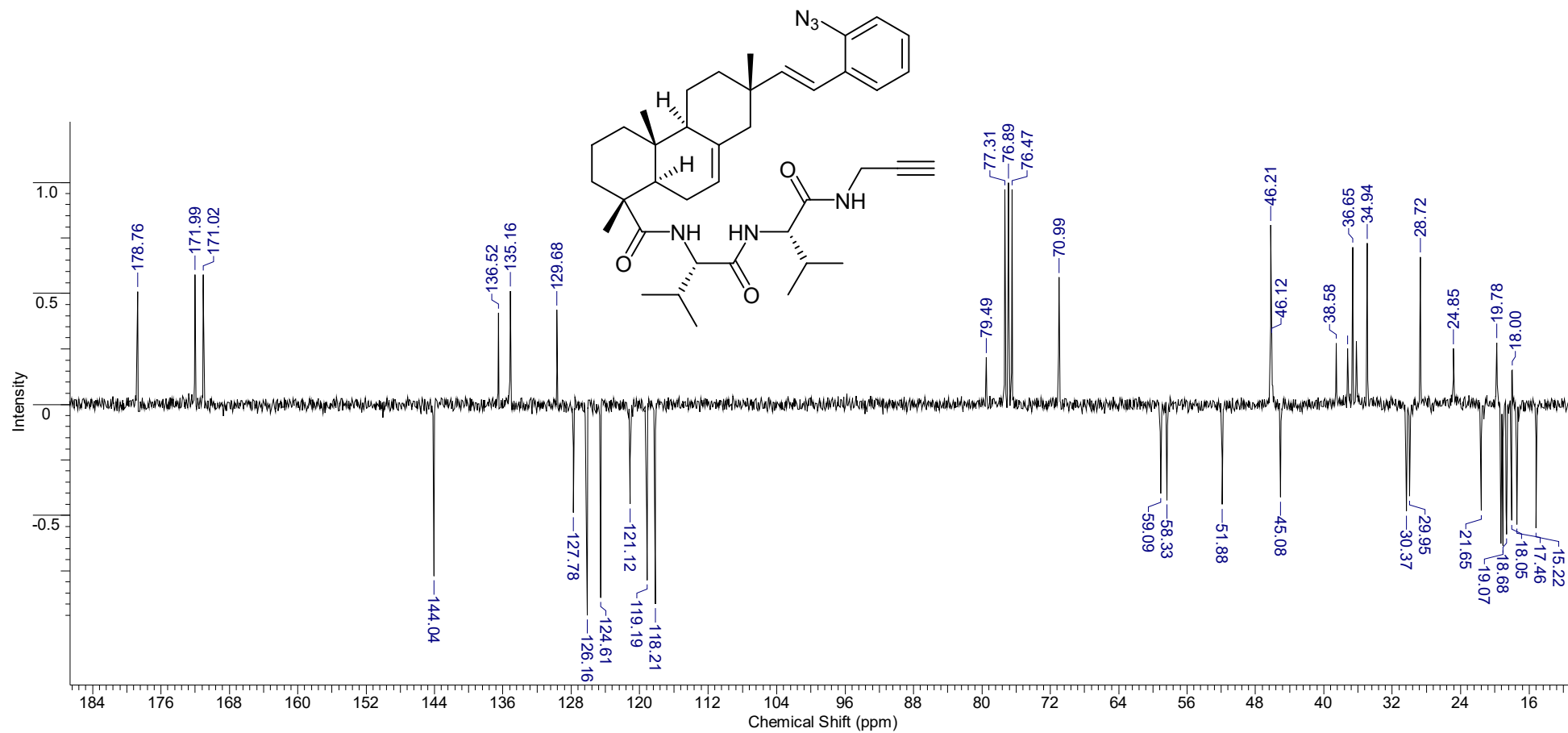


(1R,4aR,4bS,7S,10aR)-7-((E)-2-azidostyryl)-1,4a,7-trimethyl-N-((S)-3-methyl-1-(((S)-3-methyl-1-oxo-1-(prop-2-yn-1-ylamino)butan-2-yl)amino)-1-oxobutan-2-yl)-1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydrophenanthrene-1-carboxamide (10b)

^1H NMR (CDCl_3 , 400.13 MHz) δ ppm

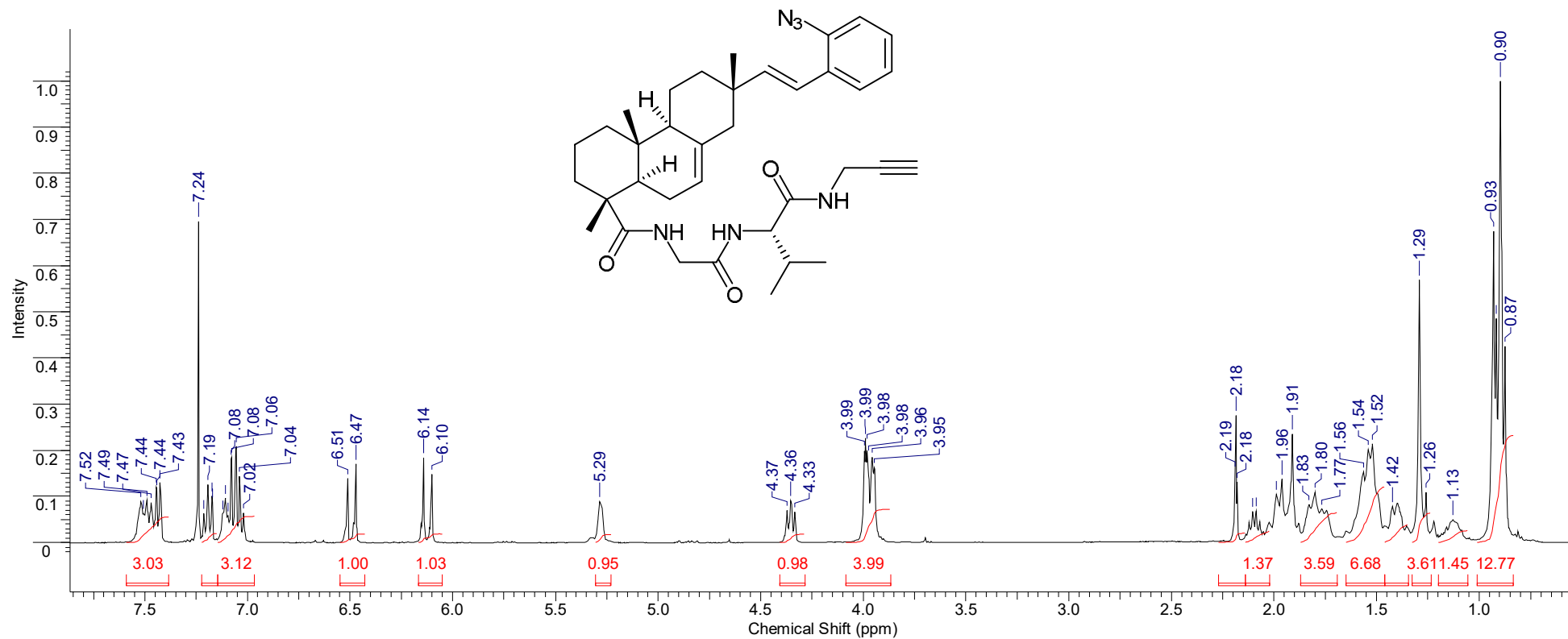


^{13}C NMR (75.47 MHz, CDCl_3) δ (ppm)

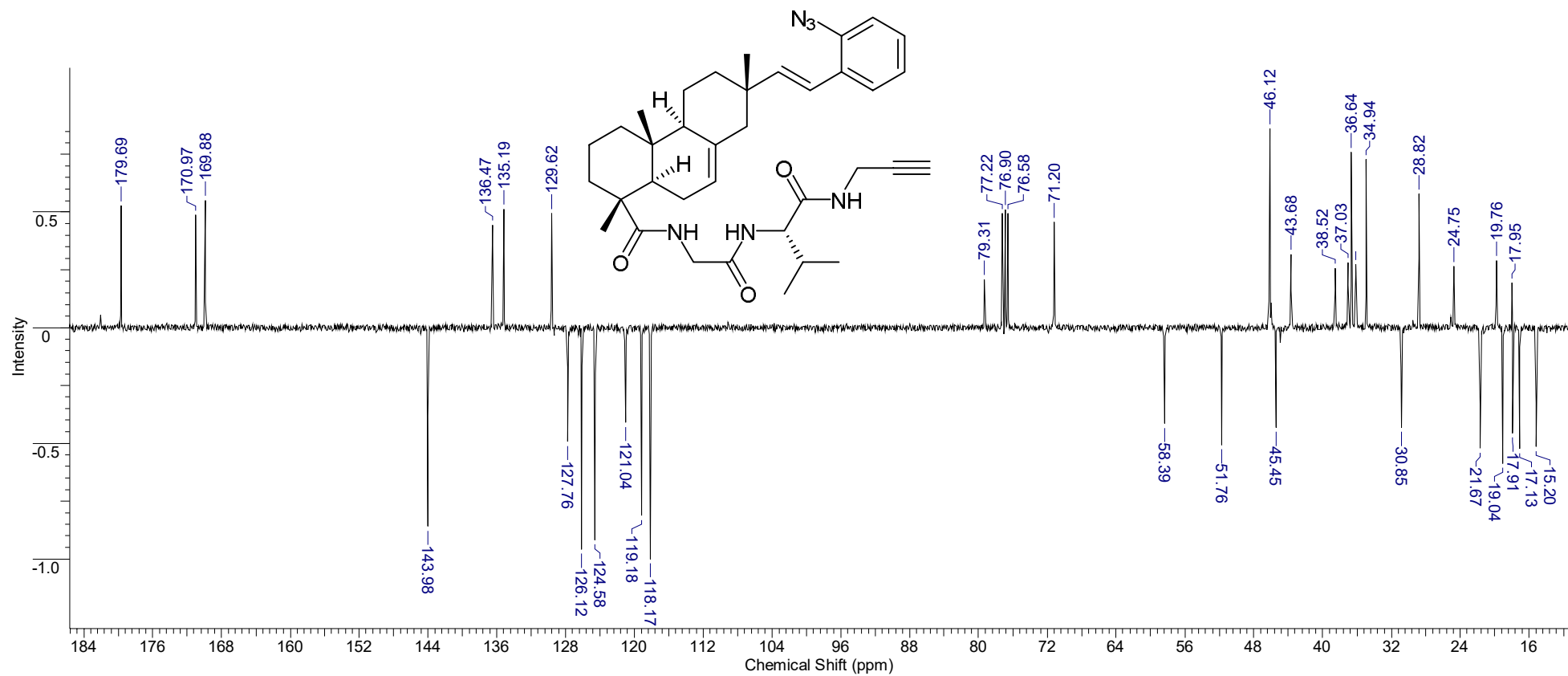


(1R,4aR,4bS,7S,10aR)-7-((E)-2-azidostyryl)-1,4a,7-trimethyl-N-(2-(((S)-3-methyl-1-oxo-1-(prop-2-yn-1-ylamino)butan-2-yl)amino)-2-oxoethyl)-1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydrophenanthrene-1-carboxamide (10c)

^1H NMR (CDCl_3 , 400.13 MHz) δ ppm

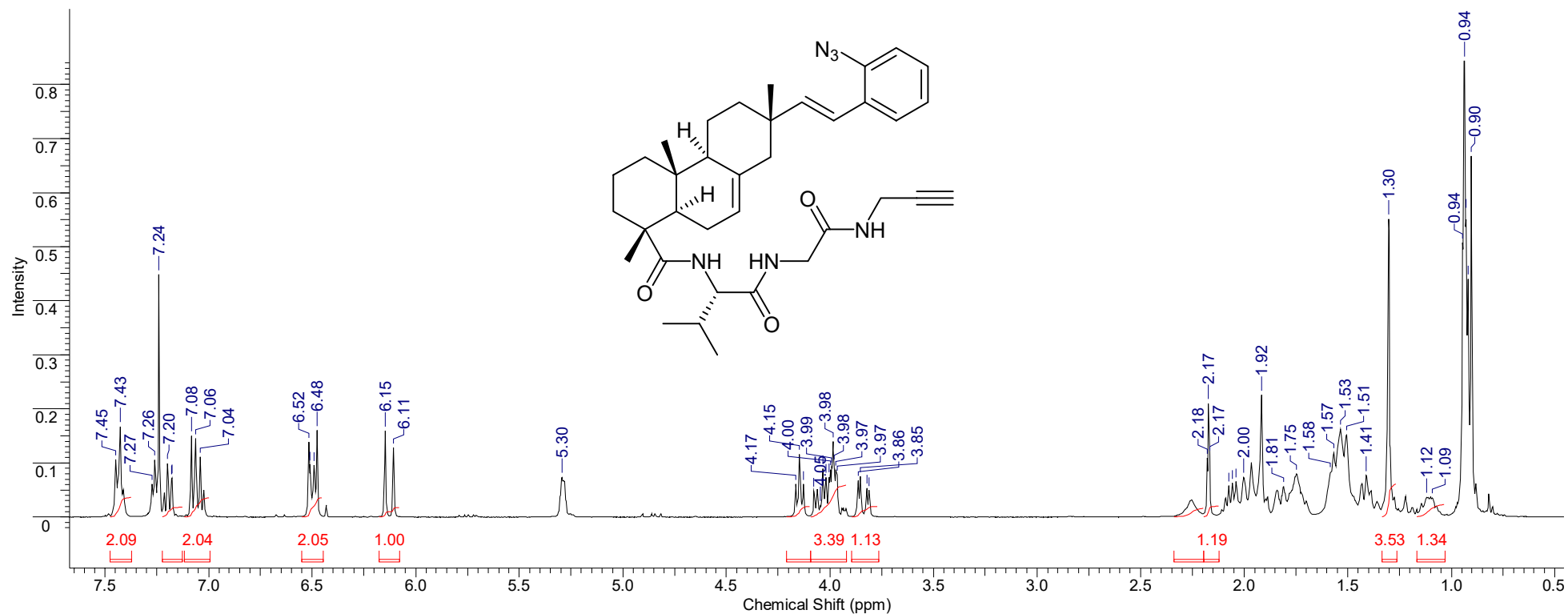


^{13}C NMR (100.61 MHz, CDCl_3) δ (ppm)

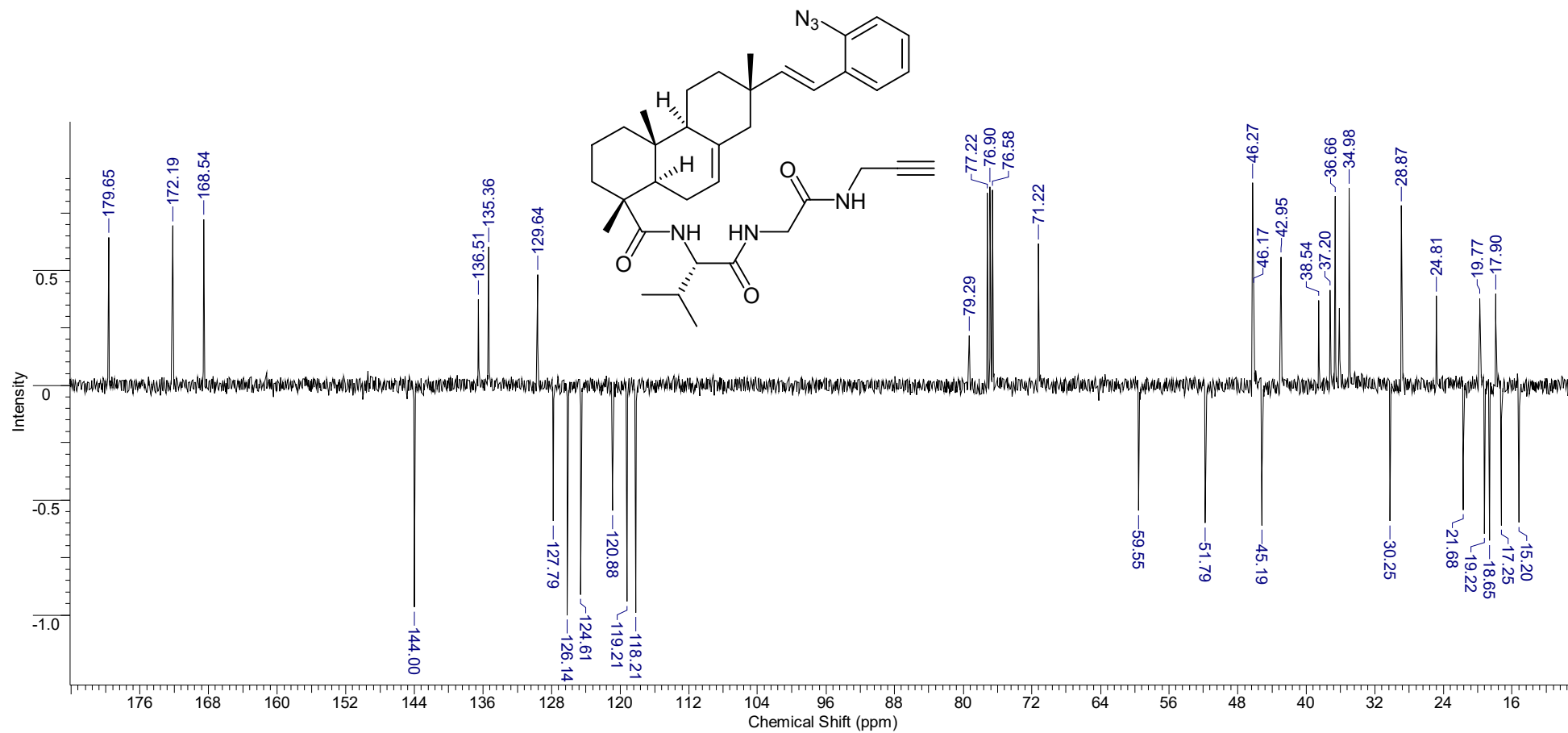


(1R,4aR,4bS,7S,10aR)-7-((E)-2-azidostyryl)-1,4a,7-trimethyl-N-((S)-3-methyl-1-oxo-1-((2-oxo-2-(prop-2-yn-1-ylamino)ethyl)amino)butan-2-yl)-1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydrophenanthrene-1-carboxamide (10d)

^1H NMR (CDCl_3 , 400.13 MHz) δ ppm

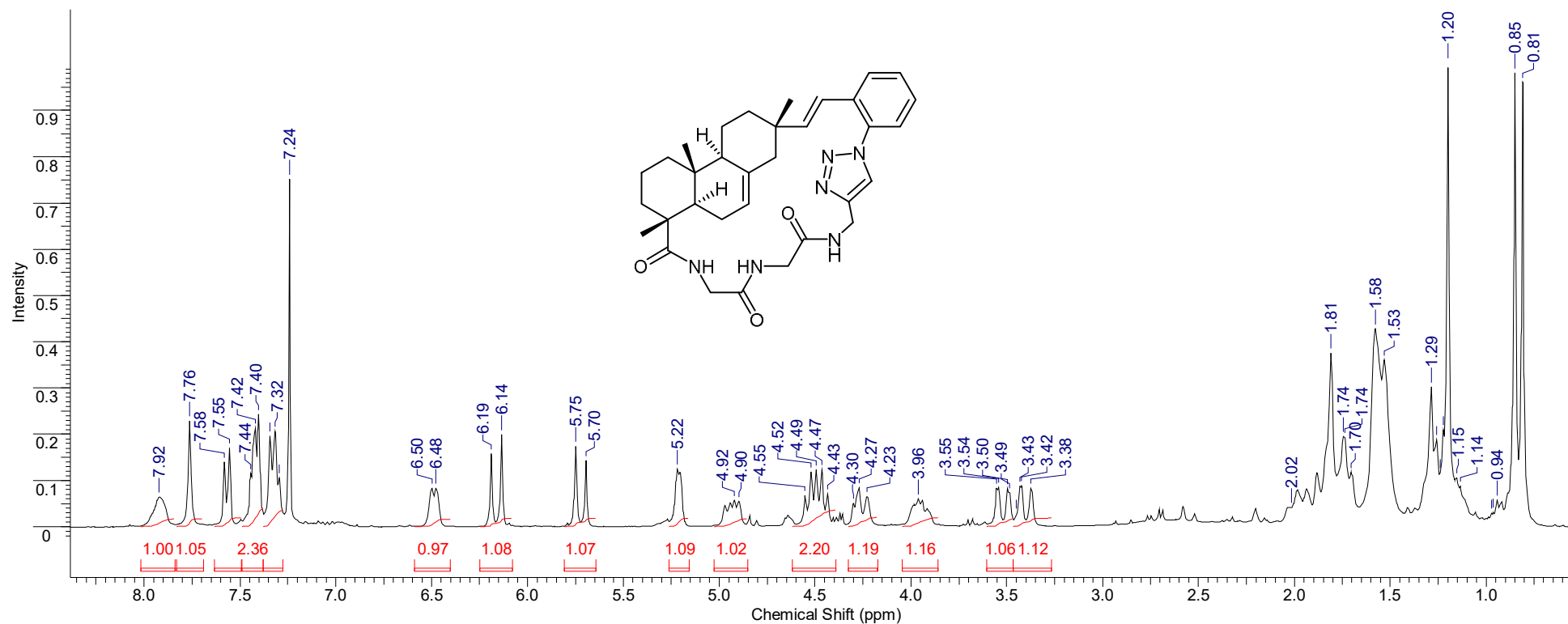


¹³C NMR (100.61 MHz, CDCl₃) δ (ppm)

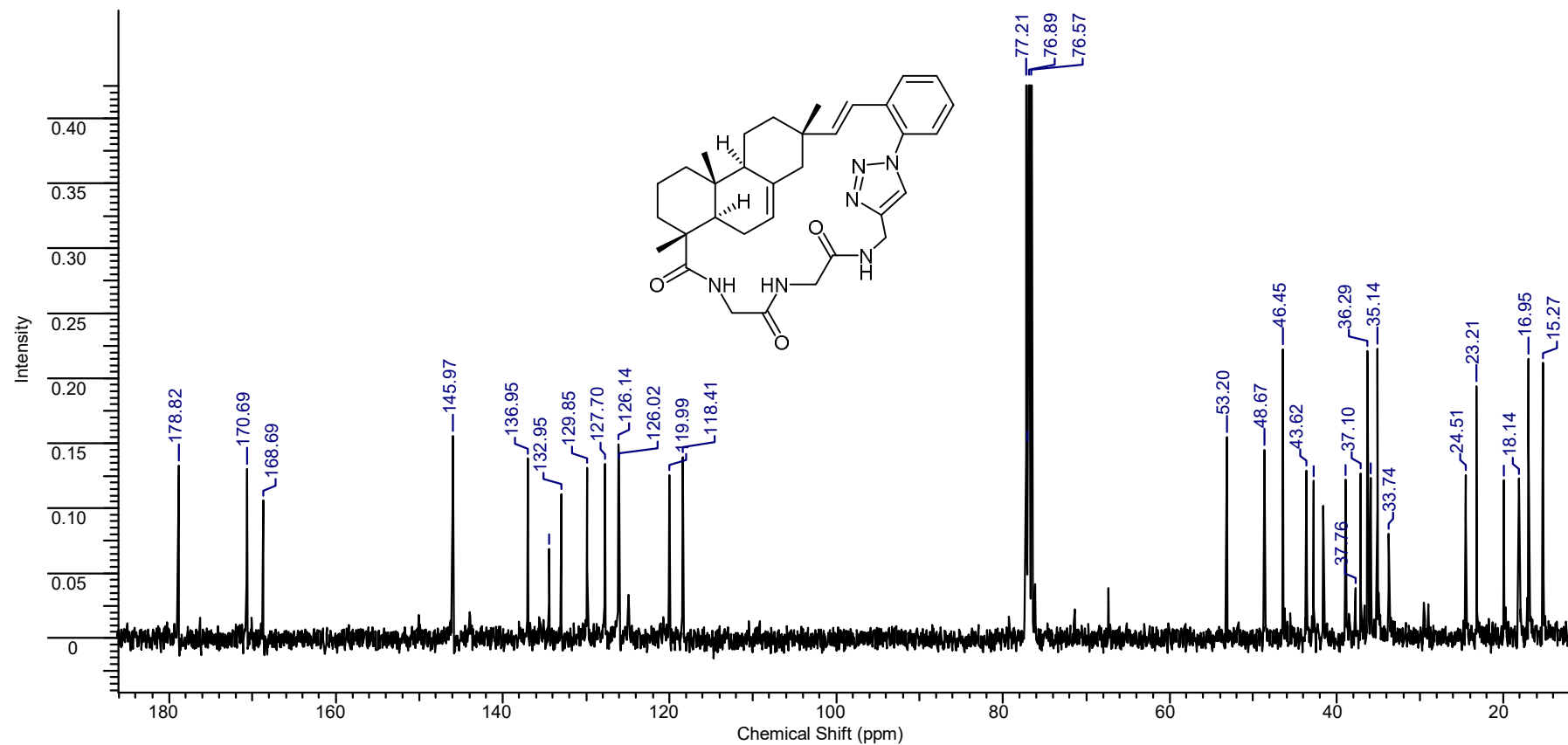


(14Z,52S,54aS,54bR,58R,58aR,510Z,3E)-52,54b,58-trimethyl-51,52,53,54,54a,54b,55,56,57,58,58a,59-dodecahydro-11H-7,10,13-triaza-1(1,4)-triazola-5(2,8)-phenanthrena-2(1,2)-benzenacyclotetradecaphan-3-ene-6,9,12-trione (11a)

^1H NMR (CDCl_3 , 300.13 MHz) δ ppm

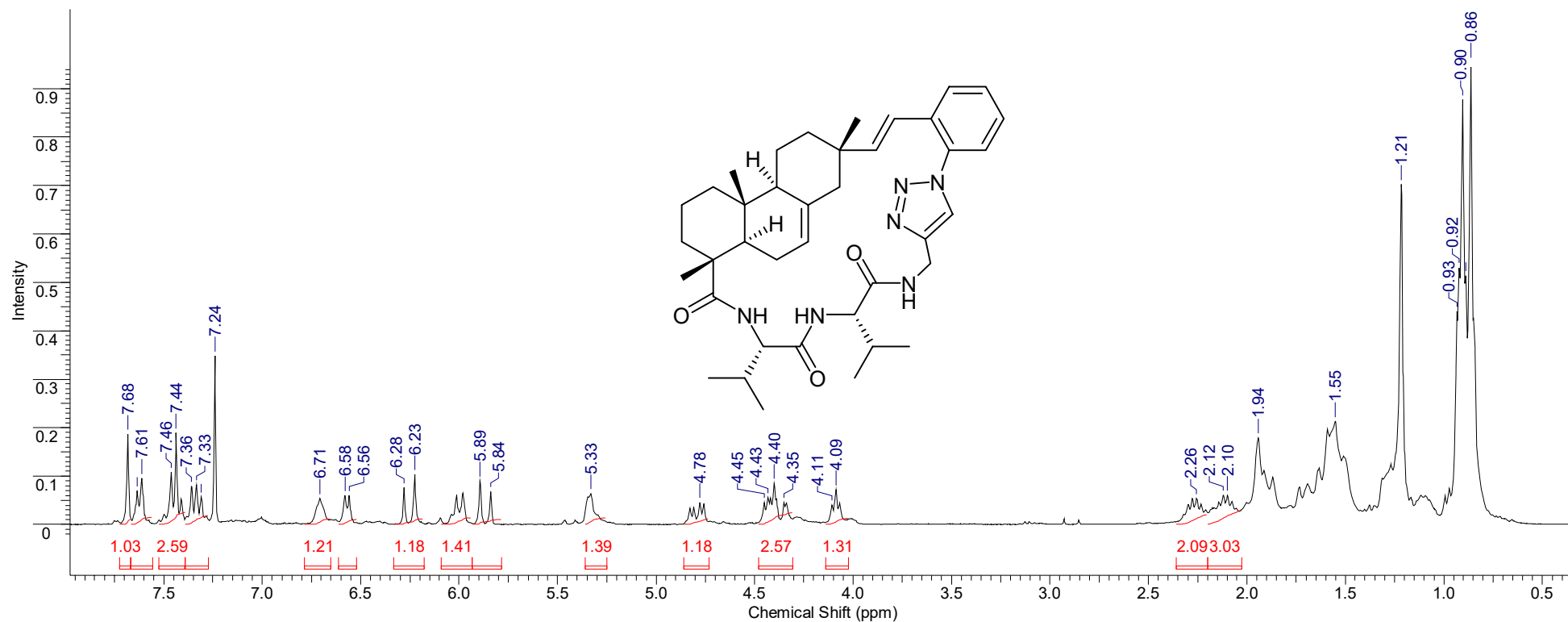


¹³C NMR (100.61 MHz, CDCl₃) δ (ppm)

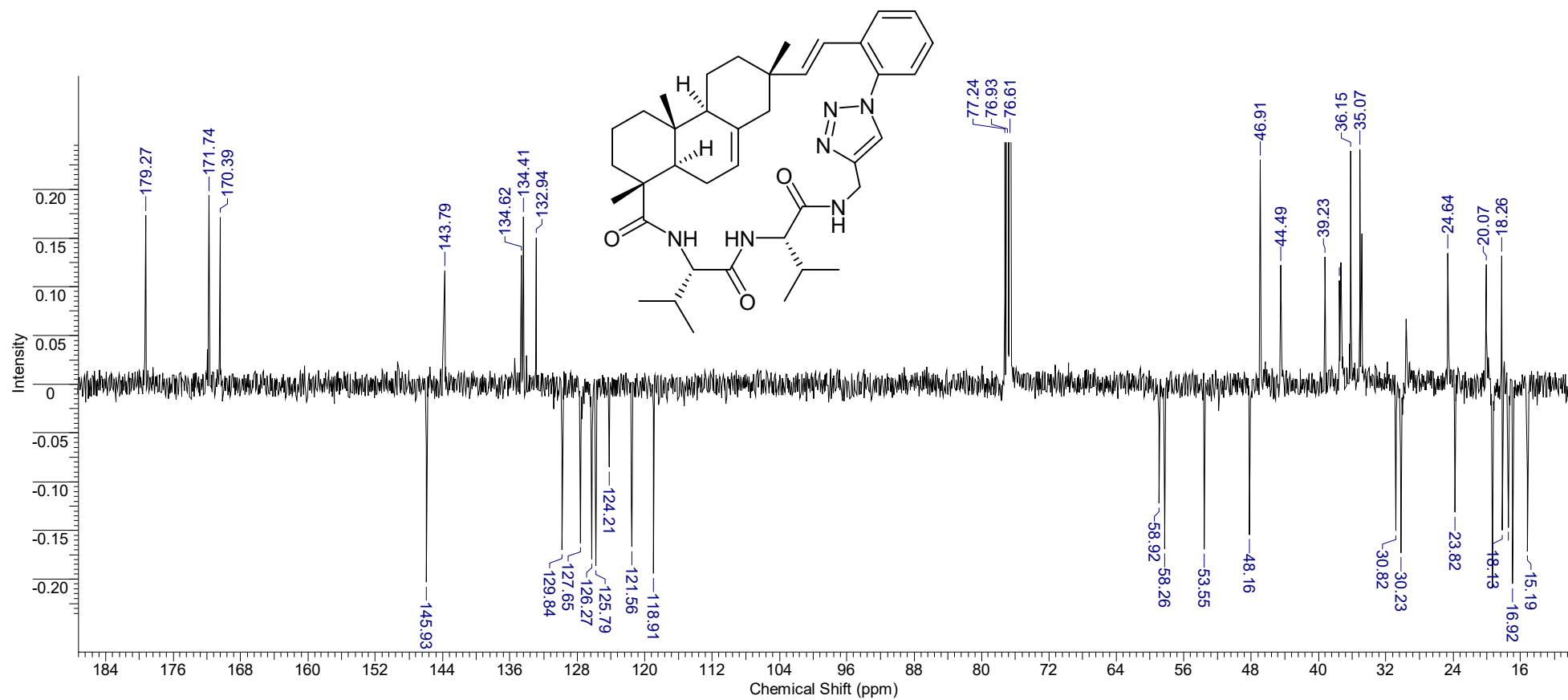


(14Z,52S,54aS,54bR,58R,58aR,510Z,3E,8S,11S)-8,11-diisopropyl-52,54b,58-trimethyl-51,52,53,54,54a,54b,55,56,57,58,58a,59-dodecahydro-11H-7,10,13-triaza-1(1,4)-triazola-5(2,8)-phenanthrena-2(1,2)-benzenacyclotetradecaphan-3-ene-6,9,12-trione (11b)

¹H NMR (CDCl₃, 300.13 MHz) δ ppm

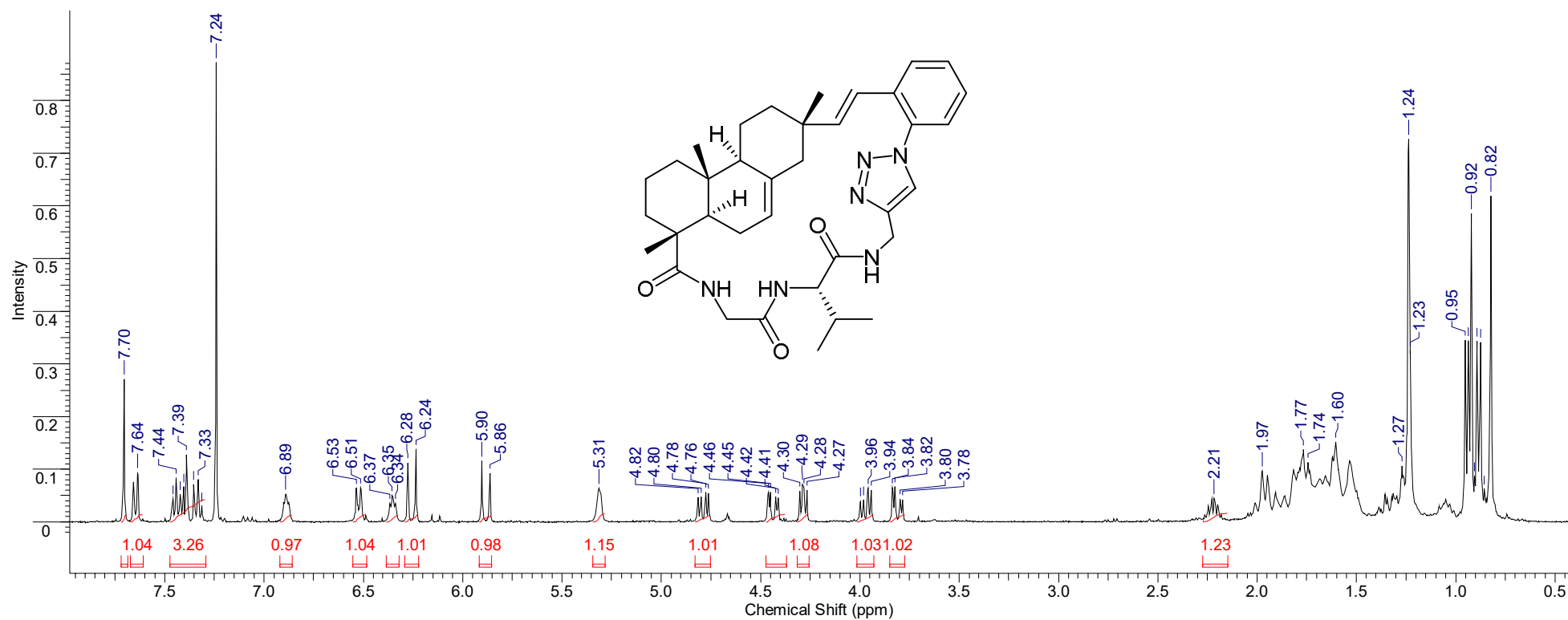


¹³C NMR (100.61 MHz, CDCl₃) δ (ppm)

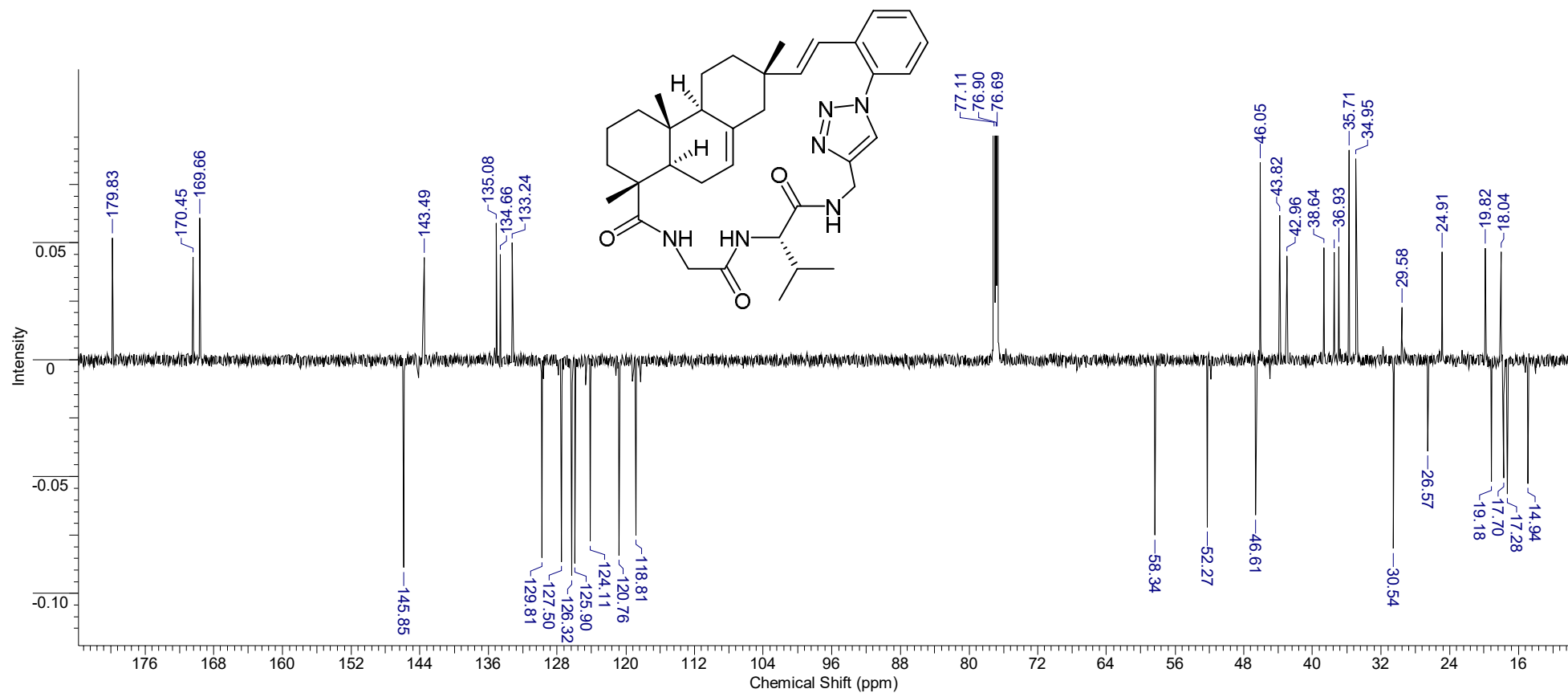


(14Z,52S,54aS,54bR,58R,58aR,510Z,3E,11S)-11-isopropyl-52,54b,58-trimethyl-51,52,53,54,54a,54b,55,56,57,58,58a,59-dodecahydro-11H-7,10,13-triaza-1(1,4)-triazola-5(2,8)-phenanthrena-2(1,2)-benzenacyclotetradecaphan-3-ene-6,9,12-trione (11c)

¹H NMR (CDCl₃, 400.13 MHz) δ ppm

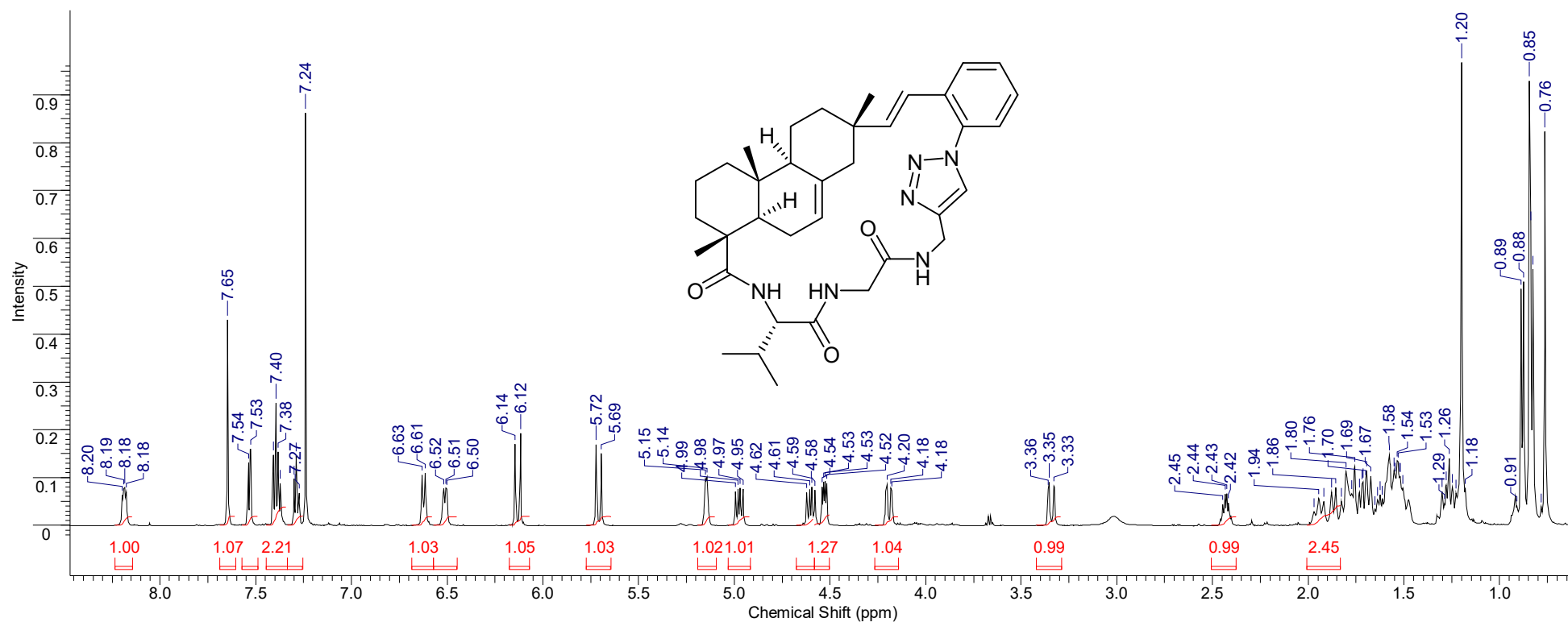


¹³C NMR (100.61 MHz, CDCl₃) δ (ppm)

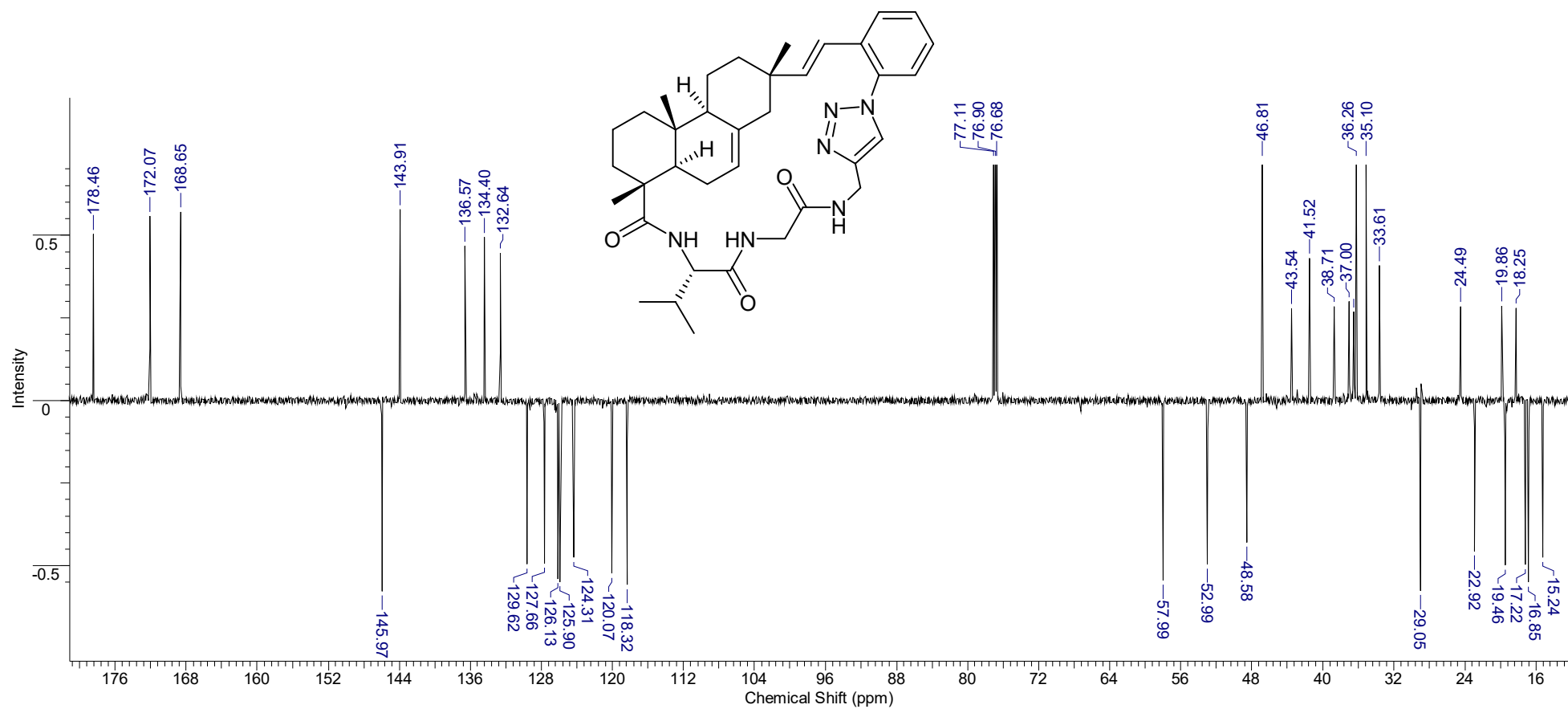


(1⁴Z,5²S,5^{4a}S,5^{4b}R,5⁸R,5^{8a}R,5¹⁰Z,3E,8S)-8-isopropyl-5²,5^{4b},5⁸-trimethyl-5¹,5²,5³,5⁴,5^{4a},5^{4b},5⁵,5⁶,5⁷,5⁸,5^{8a},5⁹-dodecahydro-11H-7,10,13-triaza-1(1,4)-triazola-5(2,8)-phenanthrena-2(1,2)-benzenacyclotetradecaphan-3-ene-6,9,12-trione (11d)

¹H NMR (CDCl₃, 600.30 MHz) δ ppm



^{13}C NMR (150.95 MHz, CDCl_3) δ (ppm)



11d

