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PII: S0040-4020(13)00962-9

DOI: 10.1016/j.tet.2013.06.032

Reference: TET 24508

To appear in: *Tetrahedron*

Received Date: 16 April 2013

Revised Date: 29 May 2013

Accepted Date: 10 June 2013

Please cite this article as: Kothandaraman P, Lauw SJL, Chan PWH, Metal-free synthesis of 1*H*-indole-2-carbaldehydes by *N*-iodosuccinimide-mediated cyclization of 1-(2'-anilinyl)prop-2-yn-1-ols in water. A formal synthesis of (*R*)-calindol, *Tetrahedron* (2013), doi: 10.1016/j.tet.2013.06.032.

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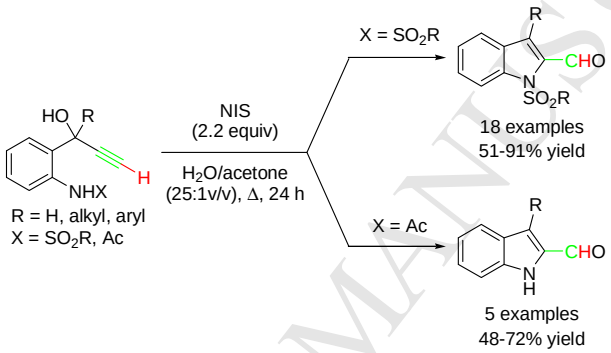

Tetrahedron
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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Cycloisomerization
N-Iodosuccinimide
1*H*-Indole-2-carbaldehydes
Propargylic alcohols
Water

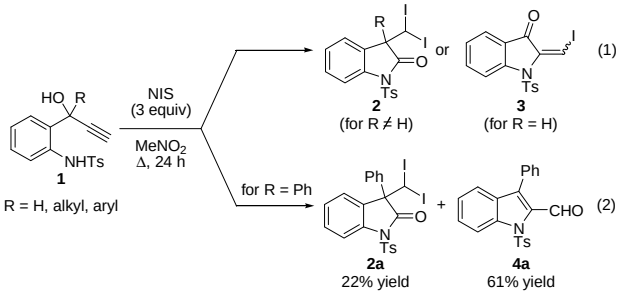
ABSTRACT

A *N*-iodosuccinimide (NIS)-mediated method to prepare 1*H*-indole-2-carbaldehydes efficiently from cycloisomerization of 1-(2-aminophenyl)prop-2-yn-1-ols is described. The reaction is operationally straightforward and accomplished in good to excellent yields (48-91%) from a wide range of alcohol substrates that are low cost, easily accessible and ecologically benign. The utility of the approach as a potential scale-up strategy for the synthesis of the indole was exemplified by the large-scale synthesis of one example in an excellent yield. The synthetic utility of this chemistry was also demonstrated in a formal synthesis of (*R*)-calindol.

1. Introduction

Over the years, indoles have been shown to be immensely valuable building blocks in a variety of synthetic strategies to many natural products and bioactive compounds as well as in optoelectronic functional materials.[1] For this reason, there has been widespread interest in accessing this structural motif and this has led to a myriad of impressive methods being developed.[1-6] This has included synthetic routes to 1*H*-indole-2-carbaldehydes that have typically relied on formylation of an indole substrate under strongly acidic or basic conditions.[1,3] However, the main drawback of these synthetic approaches has been the incompatibility of indole substrates containing functional groups that cannot tolerate such harsh reaction conditions. The use of stoichiometric or excess and often environmentally unfriendly amounts of various reagents, such as $POCl_3$ in the Vilsmeier-Haack reaction, is also typically required, which can lead to the production of equimolar quantities of waste products. Added to this is the need to introduce structural elements to direct the formylation process to occur regioselectively at the C2 position of the indole ring. In this regard, it would be desirable to establish synthetic methods that can sequentially construct the indole ring and aldehyde moiety efficiently in a single operation from a wide variety of readily accessible, low cost and simple acyclic substrates. This is all the more so given synthetic approaches that simultaneously address the preparation and derivatization of indoles are still far from common.[1-6]

Recently, we delineated a synthetic method which allowed for the conversion of propargylic alcohols **1** to 2-oxindoles **2** and 3-oxindoles **3** when treated with NIS in $MeNO_2$ (Scheme 1, eq 1).[4-7] In the course of this study, we noticed that when 1-phenyl-1-(2-(tosylamino)phenyl)prop-2-yn-1-ol (**1a**, R = Ph) was treated with NIS in non-distilled $MeNO_2$, 3-phenyl-1-tosyl-1*H*-indole-2-carbaldehyde **4a** was obtained as the major adduct instead of the anticipated 2-oxindole **2a** (Scheme 1, eq 2). It also contrasted to an earlier work by us on the gold(I)-catalyzed conversion of **1** to 1*H*-indole-2-carbaldehydes that showed the analogous reaction of **1a** with NIS in non-distilled acetone and in the absence of the metal catalyst gave only the recovery of the substrate.[2e] This intriguing solvent effect on the reactivity of the alcohol toward



Scheme 1. NIS-mediated cyclization of 1-(2-(tosylamino) phenyl)prop-2-yn-1-ols 1 in $MeNO_2$.

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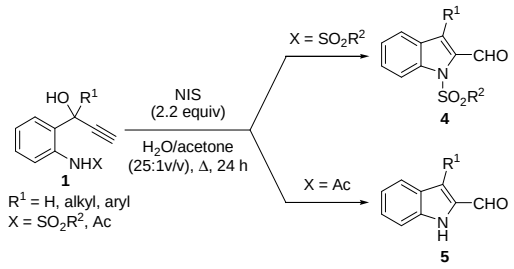
the iodinating reagent prompted us to anticipate that NIS-mediated cycloisomerization of **1** to **4** could be achieved by identifying the appropriate solvent medium and reaction conditions, which would be attractive from a scale-up applications stand point.

As part of our efforts to develop this type of reaction,[2d-2f] we disclose herein our discovery that NIS can mediate the aminocyclization of propargylic alcohols of the type **1** with an appropriately placed aniline moiety (Scheme 2)[8]. Accomplished in an aqueous reaction medium under mild conditions, this provides an expedient and low cost route to 1*H*-indole-2-carbaldehydes that constructs both the nitrogen ring and aldehyde moiety sequentially for a broad range of readily available substrates.[9,10] The approach also avoids the need for structural elements to direct aldehyde formation to occur regioselectively at the C-2 position of the indole ring. The application of this 1*H*-indole-2-carbaldehyde formation process to the large-scale synthesis of one example and formal synthesis of (*R*)-calindol in a single step is also presented.[11]

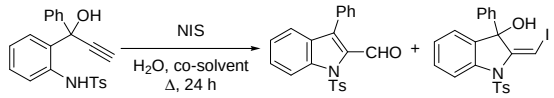


Scheme 2. NIS-mediated cycloisomerizations of *N*-substituted 1-(2-aminophenyl)prop-2-yn-1-ols in water and acetone (25:1 v/v).

2. Results and discussion

We began by first examining the reaction of 1-phenyl-1-(2-(tosylamino)phenyl)prop-2-yn-1-ol **1a** with 3 equiv of NIS in water at reflux for 24 h and found **4a** could be furnished in 58% yield (Table 1, entry 1). Our studies subsequently showed that when the reaction was repeated in water and acetone (25:1 v/v) as a co-solvent, a further increase of 35% in product yield was obtained (Table 1, entry 2). A similar product yield was afforded on decreasing the amount of NIS from 3 to 2.2 equiv (Table 1, entry 3). However, lower product yields were afforded when the amount of NIS was further decreased to 2, 1.5 or 1.2 equiv (Table 1, entries 4-6). A similar outcome was observed for the analogous reactions of **1a** with 1.5, 2 or 2.2 equiv of NIS at room temperature (Table 1, entries 7-9). The only exception was the control experiment of **1a** with 1.2 equiv of NIS, which was found to give the indolin-3-ol **6a** in 85% yield (Table 1, entry 10). A survey of other organic co-solvents was found to provide no improvements in product yields (Table 1, entries 11-19). In these latter reactions with 2 equiv of NIS, changing the co-solvent from acetone to $MeNO_2$, THF, DMSO, MeCN, DMF, CH_2Cl_2, $CHCl_3$, EtOAc or EtOH gave **4a** in yields of 44-82%. Likewise, control experiments with 2 equiv of I_2 in place of NIS at room temperature or reflux provided product yields of 60 and 67%, respectively (Table 1, entries 20 and 21). In our hands, changing the halogenating source from NIS to either 2 equiv of NBS (*N*-bromosuccinimide) or NCS (*N*-chlorosuccinimide) were the only instances that led to the recovery of **1a** in 75% yield along with a mixture of decomposition products that could not be identified by ^{1}H NMR spectroscopy (Table 1, entries 22 and 23). On the basis of the above results, reaction of **1a** with 2.2 equiv of NIS in H_2O and acetone (25:1 v/v) at reflux for 24 h provided the optimum conditions. Using these optimized conditions, we were pleased to find that a product yield of 87% (0.86 g) could be reproduced when the reaction was repeated on a large scale with 1 g of **1a**.

Table 1. Optimization of the reaction conditions[a]



Entry	NIS (equiv)	Co-solvent[b]	Yield (%)
1	3	-	58
2	3	acetone	93
3	2.2	acetone	91
4	2	acetone	82
5	1.5	acetone	71
6	1.2	acetone	65
7[c]	2.2	acetone	76
8[c]	2	acetone	70
9[c]	1.5	acetone	63
10[c]	1.2	acetone	-[d]
11	2	$MeNO_2$	67
12	2	THF	81
13	2	DMSO	75
14	2	MeCN	61
15	2	DMF	56
16	2	CH_2Cl_2	81
17	2	$CHCl_3$	82
18	2	EtOAc	81
19	2	EtOH	44
20[c,e]	-	acetone	60
21[e]	-	acetone	67
22[f]	-	acetone	-[g]
23[h]	-	acetone	-[g]

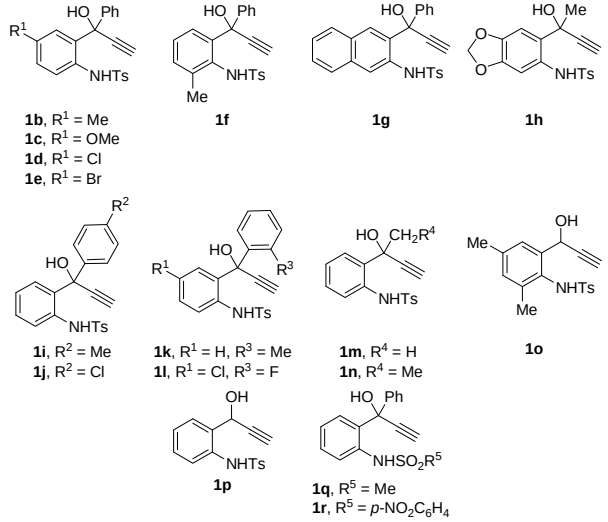
[a] Unless otherwise stated, all reactions were performed with NIS at reflux for 24 h with 0.132 mmol of **1a**.
[b] Reaction performed with H_2O:solvent ratio of 25:1 v/v. [c]Reaction performed at room temperature for 24 h.
[d] Compound **6a** was obtained in 85% yield.
[e] Reaction performed with 2 equiv of I_2.
[f] Reaction performed with 2 equiv of NBS.
[g] Recovery of **1a** in 75% yield along with mixture of side products that could not be identified based on ^{1}H NMR analysis of the crude reaction mixture.
[h] Reaction performed with 2 equiv of NCS.

We next turned our attention to the reactions of a variety of propargylic alcohols to determine the scope of the present procedure and the results are summarized in Table 2. We were pleased to find that these experiments showed the reaction conditions to be broad, providing a variety of substituted indole-2-carbaldehydes in good to excellent yields. Substrates containing an electron-donating group or electron-withdrawing group or benzofused ring on the aniline moiety were found to be well tolerated and afforded the corresponding products **4b-h** in 54-85% yield. Notably, this included access to **4d** and **4e**, which we had previously found could not be prepared in the analogous reactions of the same substrates using gold catalysis.[2e] Likewise, *N*-tosyl-indole-2-carbaldehydes **4i-l**, in which the carbinol carbon position is occupied by an aryl substituent with an electron-donating or electron-withdrawing group at the ortho or para position, were obtained in excellent yields of 75-91% from the corresponding propargylic alcohols **1i-l**. Changing the pendant group at this position from an aryl to alkyl moiety was found to have no influence on the course of the reaction with **4m** and **4n** afforded in 89 and 91% yield, respectively. Similarly, the secondary alcohols **1o** and **1p** provided the corresponding *N*-tosyl-1*H*-indole-2-carbaldehydes **4o** and **4p** in 90 and 51% yield, respectively, at room temperature or with 1.1 equiv NIS. As

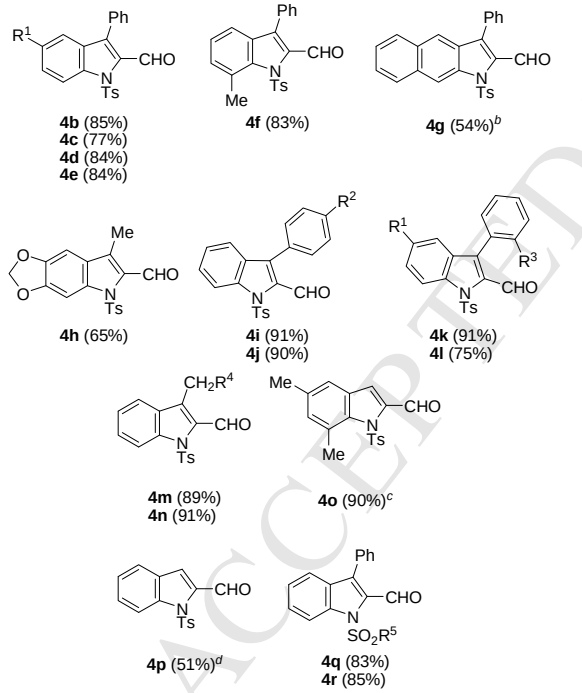
expected, starting alcohols **1q** and **1r**, with a pendant Ms or Ns protecting group on the nitrogen center, were also found to proceed well under the reaction conditions, giving the corresponding *N*-sulfonyl-1*H*-indole-2-carbaldehydes in respective yields of 83 and 85%.

Table 2. NIS-mediated cycloisomerization of 2-tosylamino phenylprop-2-yn-1-ols **1b-r** in H_2O[a]

Substrate



Product



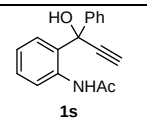
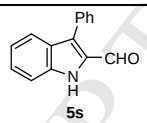
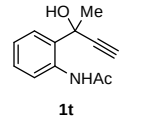
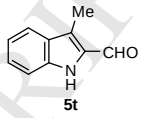
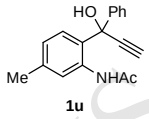
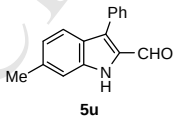
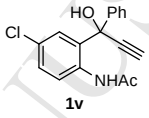
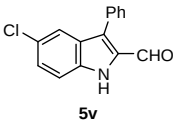
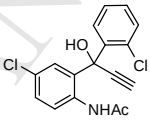
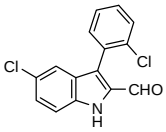
[a] Unless otherwise stated all reactions were performed at reflux for 24 h with 0.13 mmol of **1** and 0.29 mmol of NIS in H_2O/acetone (25:1 v/v) Values in parentheses denote product yields.

[b] Starting material recovered in 32% yield.

[c] Reaction performed at room temperature. [d]Reaction performed with 1.1 equiv of NIS.

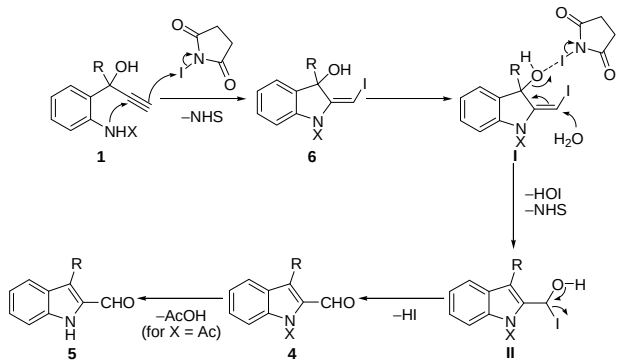
Interestingly, the NIS reactions with substrates in which an acyl substituent was employed as the nitrogen protecting group, as in **1s-1w** shown in Table 3, did not give the expected *N*-acetyl-1*H*-indole-2-carbaldehydes. We found subjecting **1s** to 2.2 equiv of NIS in the water/acetone solvent system, at a ratio of 6:1 v/v due to the poorer solubility of the substrate, at reflux for 24 h gave the deprotected indole product **5s** in 70% yield. A similar outcome was obtained on applying these slightly modified conditions to **1t-w**, with the corresponding 1*H*-indole-2-carbaldehyde adducts **5t-w** furnished in 52-72% yield.

Table 3. NIS-mediated cycloisomerization of 2-acylamino phenylprop-2-yn-1-ols **1s-w** in H_2O[a]

Entry	Substrate	Product	Yield (%)
1	 **1s**	 **5s**	70
2	 **1t**	 **5t**	72
3	 **1u**	 **5u**	62
4	 **1v**	 **5v**	57
5	 **1w**	 **5w**	52

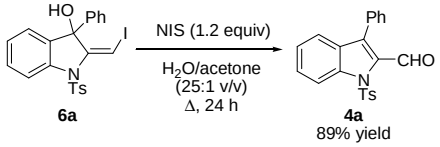
[a] All reactions were performed at reflux for 24 h with 0.19 mmol of **1** and 0.41 mmol of NIS in H_2O/acetone (6:1 v/v)

A tentative mechanism for the present NIS-mediated reaction to form 1*H*-indole-2-carbaldehydes is put forward in Scheme 3. This could involve nucleophilic addition of the aniline group to the alkyne moiety of the substrate and concomitant quenching of the resultant cycloadduct to give **6**. Activation of the hydroxyl group of the resultant indolin-3-ol intermediate by another molecule of NIS would then give the coordinated species **I**. Nucleophilic substitution of this newly formed activated adduct by H_2O would result in the formation of iodomethanol adduct **II**, which subsequently eliminates HI to deliver **4**. Presumably, in cycloadducts containing an Ac protecting group at the nitrogen center, the aqueous acidic conditions promote a facile deacylation process to produce **5**. While it remains unclear whether the substitution step proceeds in an S_N1' or S_N2' manner, the added



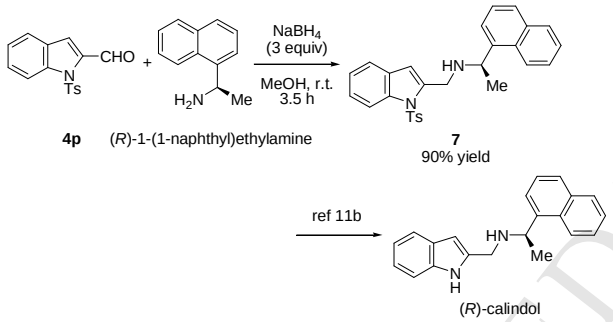
Scheme 3. Proposed mechanism.

role of NIS in making **6** susceptible to nucleophilic attack by H_2O would be consistent with our earlier findings showing formation of only this adduct when 1.2 equiv of the iodinating reagent was used under the conditions described in Table 1, entry 6. This is further supported by the conversion of **6a** to **4a** in 89% yield when it was re-subjected to 1.2 equiv of NIS under the conditions depicted in Scheme 4.



Scheme 4. Nucleophilic substitution of **6a** by water mediated by NIS.

Having established an efficient route to 1*H*-indole-2-carbaldehydes, we applied this new strategy to the formal synthesis of the bioactive indole alkaloid (*R*)-calindol (Scheme 5). At room temperature, reductive amination of **4p** with (*R*)-1-(1-naphthyl)ethylamine in the presence of 3 equiv of $NaBH_4$ in MeOH gave (*R*)-*N*-tosylcalindol **7** in 90% yield and as a single enantiomer.[11d] As (*R*)-*N*-tosylcalindol **7** has been previously converted into (*R*)-calindol by removal of the *N*-tosyl protecting group,[11b] this route constitutes a formal synthesis of the enantiopure indole alkaloid.



Scheme 5. A formal synthesis (*R*)-calindol.

3. Conclusion

In summary, we have described an efficient synthetic method for the preparation of 1*H*-indole-2-carbaldehydes from NIS-mediated cycloisomerization of *N*-substituted 1-(2-aminophenyl) prop-2-yn-1-ols in water. The attractiveness of the synthetic approach lies in the fact that both the indole ring and aldehyde functional group are sequentially formed from the cyclization process. Previous synthetic methods to this immensely important member of the indole family of compounds have mainly relied on formylation of the nitrogen heterocycle and structural elements to direct the functional group transformation to occur regioselectively at the C2 position of the substrate. Our approach also offers a potential scale-up strategy for the synthesis of the indole, which was demonstrated by the large-scale synthesis of one example in an excellent yield. This is notable as the present method makes use of a wide range of inexpensive and easily accessible alcohol substrates in combination with the low cost and green credentials often associated with such metal-free mediated systems. The synthetic utility of this chemistry was also demonstrated in a formal synthesis of (*R*)-calindol.

4. Experimental section

4.1. General remarks

Unless specified, all reagents and starting materials were purchased from commercial sources and used as received. Solvents were purified following standard literature procedures. Analytical thin layer chromatography (TLC) was performed using pre-coated silica gel plate. Visualization was achieved by UV light (254 nm) Flash chromatography was performed using silica gel (230-400 mesh) and gradient solvent system (EtOAc:*n*-hexane as eluent). ^{1}H and ^{13}C NMR spectra were measured on a 300, 400, and 500 MHz spectrometer. Chemical shifts (ppm) were recorded with tetramethylsilane (TMS) as the internal reference standard. Multiplicities are given as: s (singlet), brs (broad singlet), d (doublet), t (triplet), dd (doublet of doublets) or m (multiplet). The number of protons (*n*) for a given resonance is indicated by *n*H and coupling constants are reported as a *J* value in Hz. Infrared spectra were recorded on a FTIR spectrometer. Solid samples were examined as a thin film between NaCl salt plates. Low resolution mass spectra were determined on a mass spectrometer and reported in units of mass to charge (*m/z*) High resolution mass spectra (HRMS) were obtained on a LC/HRMS TOF spectrometer using simultaneous electrospray (ESI) Optical rotations were measured in $CHCl_3$ on a polarimeter with a sodium vapor lamp at 589 nm and 10 cm cell (*c* given in g/100 mL)

4.2. General experimental procedure for the preparation of *N*-protected aniline substituted propargylic alcohols (1a, d, h, i, j, m, o and p)[2e,f] To a solution of the appropriate 1-(2-aminophenyl)-ketone or -aldehyde (1.1 mmol) in pyridine (0.4 mL) was added p-toluenesulfonyl chloride (1.6 mmol) at room temperature under a nitrogen atmosphere. The resulting solution was stirred for 4 h at room temperature. On completion, the reaction mixture was quenched by adding H_2O (5 mL) and filtered. The resulting solid was dried and then used directly for the next step. The solid (0.51 mmol) was dissolved in anhydrous THF (8 mL) and a solution of ethynylmagnesium bromide (0.5 M THF solution; 1.5 mmol) was added at room temperature. The resulting mixture was allowed to reflux for 3 h. On completion, the reaction mixture was cooled to room temperature and treated with saturated NH_4Cl (7 mL). After additional stirring at room temperature for 10 min, EtOAc (15 mL) was added and phases were separated. The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (10% EtOAc/*n*-hexane as eluent) gave the title compound.

4.3. General experimental procedure for the preparation of propargylic alcohols (1b, c, e, f, g, k, l and n)[13a,b] To a solution of the appropriate 2-aminobenzoic acid (1.0 mmol) in H_2O/THF (2:1 v/v, 9 mL) was added triethylamine (0.30 g, 0.42 mL, 3.0 mmol) at room temperature followed by p-toluenesulfonyl chloride (0.23 g, 1.2 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 3 h. On completion, THF was removed and the aqueous solution was washed with diethyl ether (5 mL). The diethyl ether layer was discarded while the aqueous layer was acidified with hydrochloric acid (2 M, pH 2) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting solid was dried under vacuum for 16 h and used directly for the next step. The solid (0.8 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C under a nitrogen atmosphere. The solution was then treated with N,O-dimethylhydroxylamine.HCl (DMHA) (0.9 mmol) followed by N-methylmorpholine (NMM, 0.26 mL, 2.4

mmol). The hydrochloride salt of 1-ethyl-3-(3-dimethylamino propyl)carbodiimide (EDCI·HCl, 0.17 g, 0.9 mmol) was then added portion-wise over a 15 min period. The reaction mixture was allowed to stir for further 3 h at 0 °C and an additional 15 h at room temperature. On completion, the reaction mixture was treated with saturated sodium bicarbonate solution (7 mL). The organic and aqueous phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with 10% citric acid solution (5 mL) followed by brine solution (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The solid product was washed with a mixture of 5% EtOAc/n-hexane solution and the resulting Weinreb amide solid was dried under vacuum for 16 h. After drying, the solid (0.6 mmol) was dissolved in anhydrous THF (5 mL) followed by the addition of the respective bromide of the Grignard reagent (0.5, 1 M or 2 M THF solution, 2.1 mmol) at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for another 18 h at room temperature. On completion, the reaction mixture was treated with saturated NH_4Cl or 2 M aqueous HCl solution (7 mL) and the resulting mixture was stirred at room temperature for 15 min before EtOAc (15 mL) was added. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine solution (15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the 1-(2-tosylaminophenyl)ketone adduct that was then dried under reduced pressure for 5 h. The ketone (0.51 mmol) was dissolved in anhydrous THF (8 mL) and a solution of ethynylmagnesium bromide (0.5 M THF solution; 1.5 mmol) was added at room temperature. The resulting mixture was allowed to reflux for 3 h. On completion, the reaction mixture was cooled to room temperature and treated with saturated NH_4Cl (7 mL). After additional stirring at room temperature for 10 min, EtOAc (15 mL) was added and the phases were separated. The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (10% EtOAc/*n*-hexane as eluent) gave the title compound.

4.4. General experimental procedure for the preparation of propargylic alcohols (1s-w)[2e,f,13b] To a solution of the appropriate 1-(2-aminophenyl)ketone (1.0 mmol) and pyridine (0.48 mL, 6.0 mmol) in dichloromethane (5 mL) was added acetyl chloride (1.2 mmol) in dichloromethane (2 mL) in a dropwise manner at 0 °C under a nitrogen atmosphere. The resulting solution was stirred for 0.25 h at 0 °C and then brought up to room temperature slowly and monitored to completion by TLC analysis. After 3 h, the reaction mixture was quenched with 10% aqueous HCl solution and the aqueous solution was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afforded the 1-(2-acetylaminophenyl)ketone adduct which was dried under reduced pressure for 5 h. The ketone (0.51 mmol) was dissolved in anhydrous THF (8 mL) and a solution of ethynylmagnesium bromide (0.5 M THF solution; 1.5 mmol) was added at room temperature. The resulting mixture was allowed to reflux for 3 h. On completion, the reaction mixture was cooled to room temperature and treated with saturated NH_4Cl (7 mL). After additional stirring at room temperature for 10 min, EtOAc (15 mL) was added and the phases were separated. The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (10% EtOAc/*n*-hexane as eluent) gave the title compound.

4.5. General procedure for the NIS-Mediated cycloisomerization of 1-(2-(sulfonylamino)phenyl)prop-2-yn-1-ols to 1*H*-indole-2-carbaldehydes (4) To a solution of NIS (66 mg, 0.29 mmol) in water (2.5 mL) was added dropwise a solution of 1 (0.13 mmol) in acetone (0.1 mL) at room temperature. The addition was performed under an ambient atmosphere. The resulting mixture was stirred at reflux for 24 h. On completion, the reaction mixture was cooled to room temperature, quenched with 10% $Na_2S_2O_3.5H_2O$ solution (5 mL) and extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (9% EtOAc/*n*-hexane as eluent) gave the title compound.

4.6. General procedure for the NIS-mediated cycloiso merization of 1-(2-(acetylamino)phenyl)prop-2-yn-1-ols to 1*H*-indole-2-carbaldehydes (5) To a solution of NIS (93 mg, 0.41 mmol) in water (2.5 mL) was added dropwise a solution of 1 (0.19 mmol) in acetone (0.4 mL). The addition was performed at room temperature under an ambient atmosphere. The resulting mixture was stirred at reflux for 24 h. On completion, the reaction mixture was cooled to room temperature, quenched with 10% $Na_2S_2O_3.5H_2O$ solution (5 mL) and extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (10% EtOAc/*n*-hexane as eluent) gave the title compound.

4.7. Experimental procedure for the synthesis of (*R*)-*N*-tosyl calindol (7)[11d] To a solution of N-tosylindole-2-carbaldehyde (0.017 g, 0.056 mmol) in MeOH (2 mL) was added (R)-1-(1-naphthyl)ethylamine (0.010 g, 0.061 mmol) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 3 h until the aldimine formation was completed based on TLC analysis. Upon confirmation, $NaBH_4$ (6.4 mg, 0.17 mmol) was added to the reaction mixture and stirred for another 0.5 h before quenching with 1 M NaOH (1 mL). The product was extracted with diethyl ether (2 x 5 mL). The diethyl ether extract was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The solvent was evaporated to give the crude product. Purification by flash column chromatography on silica gel (20% EtOAc/*n*-hexane as eluent) gave the title compound (0.023g, 90% yield).

4.8. Characterization of compounds

4.8.1. 1-Phenyl-1-(2-(tosylamino)phenyl)prop-2-yn-1-ol ***(1a)***[2e,f] Yield 87%; 0.166 g; colorless solid; R_f (10% EtOAc/n-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.47 (1H, brs), 7.54 (1H, dd, *J* = 8.32Hz, 12.4 Hz), 7.38 (2H, d, *J* = 6.6 Hz), 7.29-7.36 (5H, m), 7.21 (1H, d, J = 7.48 Hz), 7.05 (2H, d, *J* = 8.0 Hz), 6.98 (1H, t, *J* = 7.64 Hz) 3.22 (1H, brs), 2.90 (1H, s), 2.33 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.4, 142.2, 136.3, 135.8, 130.1, 129.6, 129.4, 128.8, 128.7, 128.3, 127.3, 125.8, 122.8, 119.0, 84.4, 77.8, 74.9, 21.5; MS (ESI) *m/z* 400 $[M+Na]^+$.

4.8.2. 1-(5-Methyl-2-(tosylamino)phenyl)-1-phenylprop-2-yn-1-ol ***(1b)***[2e,f] Yield 80%; 0.190 g; colorless solid; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 8.46 (1H, brs), 7.43 (1H, d, *J* = 8.2 Hz), 7.24-7.36 (8H, m), 7.00 (3H, dd, *J* = 6.9 Hz, 7.6 Hz), 3.77 (1H, s), 2.87 (1H, s), 2.31 (3H, s), 2.24 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 143.3, 142.4, 136.4, 133.2, 132.6, 130.2, 130.1, 129.5, 129.4, 128.6, 128.2, 127.4, 125.9, 119.3, 84.7, 77.6, 74.9, 21.5, 20.9; IR (NaCl, neat) ν: 3419, 3305, 3021, 2113, 1647, 1635, 1497, 1392, 1330, 1157, 1091, 844, 813 cm^{-1}; MS (ESI) *m/z* 414 $[M+Na]^+$.

*4.8.3. 1-(5-Methoxy-2-(tosylamino)phenyl)-1-phenylprop-2-yn-1-ol (**1c**)*[2e,f] Yield 75%; 0.185 g; beige solid; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (1H, brs), 7.49 (1H, d, *J* = 8.8 Hz), 7.26-7.40 (7H, m), 7.13 (1H, d, *J* = 2.8 Hz), 7.06 (2H, d, *J* = 8.8 Hz), 6.76 (1H, dd, *J* = 2.8 Hz, 8.9 Hz), 3.72 (3H, s), 3.30 (1H, s), 2.87 (1H, s), 2.35 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.4, 143.3, 142.2, 136.5, 132.7, 129.4, 128.7, 128.6, 128.3, 127.3, 125.8, 121.6, 115.4, 113.7, 84.6, 77.5, 74.7, 55.4, 21.5; IR (NaCl, neat) ν: 3392, 3292, 3020, 2113, 1153, 1089, 1035, 844, 812 cm^{-1}; MS (ESI) *m/z* 430 $[M+Na]^+$; HRMS (ESI) calcd. for $C_{23}H_{21}NO_4SNa$ (M^++Na) 430.1089, found: 430.1082.

*4.8.4. 1-(5-Chloro-2-(tosylamino)phenyl)-1-phenylprop-2-yn-1-ol (**1d**)*[2e,f] Yield 84%; 0.175 g; pale-yellow solid; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.52 (1H, brs), 7.55 (1H, s), 7.49 (1H, d, *J* = 8.6 Hz), 7.16-7.37 (8H, m), 7.03 (2H, d, *J* = 7.3 Hz), 3.81 (1H, s), 2.91 (1H, s), 2.33 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.6, 141.6, 135.8, 134.4, 131.9, 129.5, 129.4, 128.8, 128.7, 128.6, 128.3, 127.3, 125.8, 120.2, 83.8, 78.3, 74.4, 21.5; IR (NaCl, neat) ν: 3406, 3302, 3018, 2113, 1637, 1485, 1332, 1157, 1089, 813 cm^{-1}; MS (ESI) *m/z* 434 $[M+Na]^+$; HRMS (ESI) calcd. for $C_{22}H_{18}ClNO_3SNa$ (M^++Na) 434.0594, found: 434.0598.

*4.8.5. 1-(5-Bromo-2-(tosylamino)phenyl)-1-phenylprop-2-yn-1-ol (**1e**)*[2e,f] Yield 77%; 0.213 g; pale-brown solid; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.46 (1H, brs), 7.72 (1H, d, *J* = 2.1 Hz), 7.44 (1H, d, *J* = 8.8 Hz), 7.26-7.38 (8H, m), 7.04 (2H, d, *J* = 8.1 Hz), 3.58 (1H, s), 2.93 (1H, s), 2.34 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.8, 141.5, 135.8, 135.0, 132.5, 132.1, 131.5, 129.5, 128.9, 128.6, 127.4, 125.8, 120.5, 115.8, 83.8, 78.4, 74.4, 21.5; MS (ESI) *m/z* 478 $[M+Na]^+$.

*4.8.6. 1-(3-Methyl-2-(tosylamino)phenyl)-1-phenylprop-2-yn-1-ol (**1f**)*[2e,f] Yield 78%; 0.185 g; light brown solid; m.p. 124-127 °C; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.65 (2H, d, *J* = 8.1 Hz), 7.55 (1H, s), 7.52-7.49 (2H, m), 7.34-7.28 (4H, m), 7.22 (2H, d, *J* = 8.1 Hz), 7.13-7.03 (2H, m), 4.58 (1H, s), 2.90 (1H, s), 2.38 (3H, s), 1.93 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.6, 143.6, 139.4, 138.3, 137.8, 133.4, 132.1, 129.2, 128.4, 128.2, 127.8, 127.2, 126.5, 126.5, 86.1, 77.2, 74.5, 21.62, 19.93; IR (NaCl, neat) ν: 3412, 3302, 3018, 1599, 1429, 1329, 1153, 1092, 908 cm^{-1}. MS (ESI) *m/z* 392 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{22}NO_3S$ (M^++H) 392.1320, found: 392.1320.

*4.8.7. 1-(Naphthalen-2-yl)-1-(2-(tosylamino)phenyl)prop-2-yn-1-ol (**1g**)*[2e,f] Yield 80%; 0.207 g; colorless solid; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.65 (1H, brs), 7.80 (2H, d, *J* = 6.4 Hz), 7.69 (4H, dd, *J* = 7.5 Hz, 8.7 Hz), 7.48 -7.67 (2H, m), 7.34 (1H, dd, *J* = 1.9 Hz, 8.7 Hz), 7.29 (1H, dd, *J* = 1.5 Hz, 7.5 Hz), 7.06 (2H, d, *J* = 8.3 Hz), 7.02 (1H, dd, *J* = 0.9 Hz, 7.6 Hz), 6.57 (2H, d, *J* = 8.1 Hz), 3.67 (1H, s), 2.93 (1H, s), 2.15 (3H, s); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ 143.3, 140.9, 136.5, 136.3, 133.1, 133.0, 130.6, 129.3, 129.1, 129.0, 128.4, 128.3, 127.6, 126.8, 126.5, 124.0, 123.9, 122.6, 118.1, 84.9, 78.4, 74.6, 20.5; MS (ESI) *m/z* 450 $[M+Na]^+$.

*4.8.8. 2-(5-(Tosylamino)benzo[d][1,3]dioxol-6-yl)but-3-yn-2-ol (**1h**)*[2e,f] Yield 88%; 0.160 g; yellow solid; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.97 (1H, brs), 7.72 (2H, d, *J* = 8.4 Hz), 7.24 (2H, d, *J* = 8.2 Hz), 7.12 (1H, s), 7.03 (1H, s), 5.90 (2H, s), 3.55 (1H, brs), 2.68 (1H, s), 2.36 (3H, s), 1.55 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.7, 143.8, 143.8, 136.9, 129.8, 129.6, 127.2, 125.0, 107.3, 102.6, 101.6, 85.8, 74.5, 71.2, 31.3, 21.5; MS (ESI) *m/z* 360 $[M+H]^+$.

*4.8.9. 1-p-Tolyl-1-(2-(tosylamino)phenyl)prop-2-yn-1-ol (**1i**)*[2e,f] Yield 82%; 0.163 g; colourless gum; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.49 (1H, brs), 7.50 (1H, d, *J* = 7.5 Hz), 7.47 (1H, dd, *J* = 1.35 Hz, 7.85 Hz), 7.28 (2H, d, *J* = 8.4 Hz), 7.18-7.12 (3H, m), 7.02 (2H, d, *J* = 8.1 Hz), 6.98 (2H, d, *J* = 8.15 Hz), 6.92-6.89 (1H, m), 2.78 (1H, s), 2.29 (3H, s), 2.25 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.3, 139.4, 138.1, 136.4, 135.8, 130.2, 129.5, 129.3, 128.8, 127.3, 125.7, 122.8, 119.0, 84.6, 77.5, 74.8, 21.5, 21.2; MS (ESI) *m/z* 414 $[M+Na]^+$.

*4.8.10. 1-(4-Chlorophenyl)-1-(2-(tosylamino)phenyl)prop-2-yn-1-ol (**1j**)*[2e,f] Yield 80%; 0.167 g; pale-yellow solid; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ 9.02 (1H, brs), 7.71 (1H, dd, *J* = 1.5 Hz, 3.8 Hz), 7.68 (1H, dd, *J* = 1.6 Hz, 4.3 Hz), 7.34 (2H, d, *J* = 8.3 Hz), 7.32 (1H, d, *J* = 1.8 Hz), 7.27 (4H, d, *J* = 5.9 Hz), 7.14 (2H, d, *J* = 8.0 Hz), 7.03 (1H, td, *J* = 1.2 Hz, 7.7 Hz), 3.52 (1H, s), 2.33 (3H, s); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ 143.7, 142.6, 136.7, 136.3, 133.4, 130.3, 129.5, 129.4, 128.9, 128.4, 127.3, 126.9, 122.7, 118.4, 84.6, 78.5, 74.1, 20.7; MS (ESI) *m/z* 434 $[M+Na]^+$.

*4.8.11. 1-o-Tolyl-1-(2-(tosylamino)phenyl)prop-2-yn-1-ol (**1k**)* Yield 82%; 0.195 g; colorless solid; m.p. 98-101 °C; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.60 (1H, s), 7.78 (1H, d, *J* = 7.2 Hz), 7.59 (1H, d, *J* = 8.1 Hz), 7.45 (1H, d, *J* = 8.4 Hz), 7.28-7.15 (4H, m), 7.09 (3H, d, *J* = 8.1 Hz), 6.91-6.85 (1H, m), 3.46 (1H, s), 2.83 (1H, s), 2.31 (3H, s), 1.96 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.6, 139.2, 137.0, 136.5, 136.0, 132.9, 129.9, 129.4, 129.4, 128.9, 128.9, 127.5, 126.7, 126.1, 123.2, 119.7, 83.8, 78.0, 75.5, 21.5, 21.2; IR (NaCl, neat) ν: 3421, 3304, 3019, 2120, 1653, 1480, 1339, 1159, 928 cm^{-1}; MS (ESI) *m/z* 392 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{22}NO_3S$ (M^++H) 392.1320, found: 392.1317.

*4.8.12. 1-(5-Chloro-2-(tosylamino)phenyl)-1-(2-fluorophenyl) prop-2-yn-1-ol (**1l**)* Yield 76%; 0.193 g; pale-brown solid; m.p. 116-118 °C; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.46 (1H, brs), 7.51 (1H, s), 7.41 (2H, d, *J* = 8.4 Hz), 7.31 (3H, d, *J* = 8.1 Hz), 7.05-7.12 (1H, m), 7.00 (3H, d, *J* = 8.1 Hz), 6.91 (1H, dd, *J* = 8.4 Hz, 11.4 Hz), 4.60 (1H, brs), 2.83 (1H, s), 2.25 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.6, 158.2, 143.9, 136.1, 134.5, 130.9, 130.8, 130.6, 129.6, 129.1, 129.0, 128.8, 128.7, 128.5, 127.3, 127.2, 127.1, 124.4, 124.3, 120.6, 116.8 (d, J_{C-F} = 22.5 Hz) 82.4, 77.9, 72.7, 21.5. IR (NaCl, neat) ν: 3682, 3576, 3302, 3019, 2122, 1599, 1487, 1389, 1335, 1262, 1161, 1091, 930, 910, 887 cm^{-1}; MS (ESI) *m/z* 430 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{18}ClFNO_3S$ (M^++H) 430.0680, found: 430.0690.

*4.8.13. 2-(2-(Tosylamino)phenyl)but-3-yn-2-ol (**1m**)*[2e,f] Yield 90%; 0.150 g; colorless solid; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.19 (1H, brs), 7.74 (2H, d, *J* = 8.3 Hz), 7.53 (2H, d, *J* = 8.0 Hz), 7.20 (3H, d, *J* = 8.3 Hz), 6.97 (1H, td, *J* = 1.0 Hz, 7.7 Hz), 3.62 (1H, s), 2.69 (1H, s), 2.35 (3H, s), 1.67 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.8, 137.0, 135.7, 130.9, 129.7, 129.1, 127.3, 127.2, 123.5, 119.9, 85.7, 74.7, 71.6, 31.2, 21.5; MS (ESI) *m/z* 338 $[M+Na]^+$.

*4.8.14. 2-(2-(Tosylamino)phenyl)pent-3-yn-2-ol (**1n**)*[2e,f] Yield 55%; 0.105 g; colorless solid; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.09 (1H, brs), 7.73 (2H, d, *J* = 6.8 Hz), 7.60 (1H, dd, *J* = 1.0 Hz, 8.25 Hz), 7.55 (1H, dd, *J* = 1.5 Hz, 7.9 Hz), 7.23-7.19 (3H, m), 7.01-6.98 (1H, td, *J* = 1.1 Hz, 7.75 Hz), 3.26 (1H, brs), 2.76 (1H, s), 2.35 (3H, s), 1.28-1.75 (1H, m), 1.69-1.61 (1H, m), 0.75 (3H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.7, 137.5, 135.6, 129.7, 129.6, 129.0, 128.6, 127.1, 123.3, 120.3, 84.3, 76.4, 76.1, 35.6, 21.4, 8.9; MS (ESI) m/z 352 $[M+Na]^+$.

*4.8.15. 1-(3,5-Dimethyl-2-(tosylamino)phenyl)prop-2-yn-1-ol (**1o**)* Yield 78%; 0.130 g; pale-brown solid; m.p. 160-162 °C; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58

(2H, d, *J* = 8.4 Hz), 7.49 (1H, s), 7.26 (2H, d, *J* = 8.1 Hz), 6.93 (1H, s), 6.35 (1H, s), 5.64 (1H, dd, *J* = 2.3 Hz, 5.3 Hz), 3.26 (1H, d, *J* = 5.4 Hz), 2.61 (1H, d, *J* = 2.4 Hz), 2.43 (3H, s), 2.33 (3H, s), 1.76 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.4, 138.6, 136.8, 132.3, 129.8, 128.6, 127.7, 127.3, 83.2, 74.8, 60.8, 21.6, 21.1, 18.0. IR (NaCl, neat) ν: 3688, 3304, 3018, 2135, 1599, 1521, 1474, 1419, 1379, 1325, 1161, 1091, 1018, 927 cm^{-1}; MS (ESI) *m/z* 330 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{20}NO_3S$ (M^++H) 330.1164, found: 330.1158.

4.8.16. 1-(2-(Tosylamino)phenyl)prop-2-yn-1-ol ***(1p)***[2e,f] Yield 90%; 0.137 g; yellow oil; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (1H, brs), 7.67 (2H, d, *J* = 8.0 Hz), 7.52 (1H, d, *J* = 7.6 Hz), 7.32 (2H, d, *J* = 8.1 Hz), 7.24 (2H, dd, *J* = 8.0 Hz, 13.2 Hz), 7.13 (1H, t, *J* = 7.6 Hz), 5.33 (1H, d, *J* = 2.4 Hz), 3.61 (1H, brs), 2.64 (1H, d, *J* = 2.1 Hz), 2.36 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.2, 136.5, 135.2, 131.4, 129.7, 129.6, 128.4, 127.3, 125.6, 123.4, 81.6, 76.4, 62.3, 21.6; MS (ESI) *m/z* 324 $[M+Na]^+$.

4.8.17. 1-Phenyl-1-(2-(mesylamino)phenyl)prop-2-yn-1-ol ***(1q)*** Yield 73%; 0.111 g; colorless solid; m.p. 148-151 ^{o}C; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.18 (1H, brs), 7.85 (1H, dd, *J* = 1.4, 7.84 Hz), 7.74 (1H, d, *J* = 8.16 Hz), 7.55 (2H, d, *J* = 1.4 Hz), 7.42-7.21 (4H, m), 7.19 (1H, t, *J* = 6.64 Hz), 3.61 (1H, s), 3.04 (1H, s), 2.16 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.1, 135.8, 132.3, 130.0, 128.8, 128.3, 125.8, 124.0, 120.9, 84.5, 78.0, 74.4, 38.0; IR (NaCl, neat) ν: 3414, 3281, 3019, 2120, 1584, 1489, 1323, 1267, 1148, 970, 926 cm^{-1}. MS (ESI) *m/z* 302 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{16}NO_3S$ (M^++H) 302.0851, found: 302.0857.

4.8.18. 1-Phenyl-1-(2-(nosylamino)phenyl)prop-2-yn-1-ol ***(1r)*** Yield 70%; 0.145 g; brown solid; m.p. 166-168 ^{o}C; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.84 (1H, brs), 7.92 (2H, d, *J* = 8.7 Hz), 7.60-7.53 (2H, m), 7.26 (2H, d, *J* = 8.7 Hz), 7.24-7.11 (6H, m), 7.02-6.97 (1H, m), 2.81 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.8, 144.8, 142.3, 135.0, 130.8, 129.9, 129.3, 128.7, 128.4, 128.3, 125.6, 124.0, 123.9, 119.4, 84.3, 78.1, 74.6; IR (NaCl, neat) ν: 3420, 3302, 3019, 2119, 1637, 1531, 1410, 1348, 1165, 1091, 930, 855 cm^{-1}; MS (ESI) *m/z* 409 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{17}N_2O_5S$ (M^++H) 409.0858, found: 409.0860.

4.8.19. 1-Phenyl-1-(2-(acetylamino)phenyl)prop-2-yn-1-ol ***(1s)*** Yield 75%; 0.10 g; light-brown solid; m.p. 136-139 ^{o}C; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.53 (1H, brs), 7.94 (1H, d *J* = 7.9), 7.73 (1H, d, *J* = 7.8 Hz), 7.46 - 7.43 (2H, m), 7.36-7.25 (4H, m), 7.14 (1H, t, *J* = 7.5 Hz), 4.31 (1H, s), 2.91 (1H, s), 1.75 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.3, 162.3, 142.8, 136.1, 132.1, 129.4, 128.5, 128.2, 127.9, 125.6, 124.3, 123.9, 84.8, 74.4, 24.2; IR (NaCl, neat) ν: 3397, 3302, 3019, 2119, 1682, 1587, 1520, 1447, 1304, 1163, 1040, 988, 928, 901 cm^{-1}; MS (ESI) *m/z* 288 $[M+Na]^+$; HRMS (ESI) calcd. for $C_{17}H_{15}NO_2Na$ (M^++Na) 288.1000, found: 288.1012.

4.8.20. 2-(2-(Acetylamino)phenyl)but-3-yn-2-ol ***(1t)*** Yield 78%; 0.080 g; light-brown solid; m.p. 158-160 ^{o}C; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.28 (1H, brs), 8.14 (1H, d, *J* = 8.1), 7.65 (1H, d, *J* = 7.8 Hz), 7.33 (1H, t, *J* = 7.2 Hz), 7.10 (1H, t, *J* = 7.5 Hz), 3.37 (1H, s), 2.77 (1H, s), 2.15 (3H, s), 1.89 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.4, 136.2, 131.3, 129.0, 126.3, 123.9, 123.5, 85.8, 74.4, 71.1, 30.4, 25.0; IR (NaCl, neat) ν: 3340, 3294, 3019, 2110, 1658, 1581, 1520, 1449, 1366, 1306, 1184, 1042, 955, 878 cm^{-1}; MS (ESI) *m/z* 226 $[M+Na]^+$; HRMS (ESI) calcd. for $C_{12}H_{13}NO_2Na$ (M^++Na) 226.0844, found: 226.0844.

4.8.21. 1-(4-Methyl-2-(acetylamino)phenyl)-1-phenylprop-2-yn-1-ol ***(1u)*** Yield 82%; 0.109 g; light-brown solid; m.p. 167-169 ^{o}C; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.34 (1H, brs), 7.79 (1H, s), 7.60 (1H, d, *J* = 8.1 Hz), 7.46 (2H, d, *J* = 6.6 Hz), 7.37-7.29 (3H, m), 6.95 (1H, d, *J* = 8.1 Hz), 3.56 (1H, s), 2.94 (1H, s), 2.34 (3H, s), 1.78 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.1, 162.3, 142.8, 139.6, 135.8, 128.6, 128.3, 127.9, 125.6, 125.1, 124.6, 84.9, 77.2, 74.3, 24.2, 21.3; IR (NaCl, neat) ν: 3420, 3275, 3019, 2102, 1668, 1531, 1472, 1418, 1335, 1300, 1121, 1059, 984, 826 cm^{-1}; MS (ESI) *m/z* 280 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{18}NO_2$ (M^++H) 280.1338, found: 280.1338.

4.8.22. 1-(4-Methyl-2-(acetylamino)phenyl)-1-phenylprop-2-yn-1-ol ***(1v)*** Yield 77%; 0.117 g; light-brown solid; m.p. 182-185 ^{o}C; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30 (1H, brs), 7.94 (1H, d, *J* = 8.7 Hz), 7.75 (1H, d, *J* = 2.4 Hz), 7.47-7.44 (2H, m), 7.40-7.32 (4H, m), 3.55 (1H, s), 3.00 (1H, s), 1.80 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.4, 141.9, 134.5, 133.7, 129.2, 129.1, 128.7, 128.6, 127.8, 125.5, 84.0, 77.9, 74.0, 24.1; IR (NaCl, neat) ν: 3358, 3227, 3019, 2112, 1665, 1533, 1396, 1317, 1169, 1047, 887, 829 cm^{-1}; MS (ESI) *m/z* 300 $[M+H]^+$; HRMS (ESI) calcd. for $C_{17}H_{15}ClNO_2$ (M^++H) 300.0791, found: 300.0788.

4.8.23. 1-(5-Chloro-2-(tosylamino)phenyl)-1-(2-chlorophenyl) prop-2-yn-1-ol ***(1w)*** Yield 80%; 0.157 g; light-brown solid; m.p. 179-182 ^{o}C; R_f (10% EtOAc/*n*-hexane) 0.25; ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ 8.64 (1H, brs), 8.19 (1H, d, *J* = 8.7), 7.84-8.0 (2H, m), 7.52-7.45 (1H, m), 7.41-7.32 (2H, m), 6.84 (1H, s), 3.56 (1H, s), 2.91 (1H, brs); 1.81 (3H, s); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ 167.6, 139.7, 134.9, 134.1, 131.6, 129.8, 129.2, 128.3, 128.0, 127.6, 126.8, 125.8, 82.9, 77.62, 72.6, 23.2; IR (NaCl, neat) ν: 3385, 3273, 3019, 2118, 1668, 1518, 1310, 1171, 991, 889, 833 cm^{-1}; MS (ESI) *m/z* 334 $[M+H]^+$; HRMS (ESI) calcd. for $C_{17}H_{14}Cl_2NO_2$ (M^++H) 334.0402, found: 334.0408.

4.8.24. 3-Phenyl-1-tosyl-1H-indole-2-carbaldehyde ***(4a)***[2e,f] Yield 91%; 0.045 g; yellow solid; R_f (8% EtOAc/*n*-hexane) 0.42; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.22 (1H, s), 8.30 (1H, d, *J* = 8.5 Hz), 7.83 (2H, d, *J* = 8.3 Hz), 7.52-7.58 (2H, m), 7.45 (5H, m), 7.26 (1H, m), 7.24 (2H, d, *J* = 6.5 Hz), 2.36 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.4, 145.3, 138.2, 135.8, 135.2, 132.5, 130.5, 130.4, 129.7, 129.3, 129.2, 129.0, 128.4, 127.2, 124.6, 122.6, 115.7, 21.7; MS (ESI) *m/z* 376 $[M+H]^+$.

4.8.25. 5-Methyl-3-phenyl-1-tosyl-1H-indole-2-carbaldehyde ***(4b)***[2e,f] Yield 85%; 0.042 g; yellow gum; R_f (8% EtOAc/*n*-hexane) 0.42; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.21 (1H, s), 8.17 (1H, d, *J* = 8.6 Hz), 7.79 (2H, d, *J* = 8.2 Hz), 7.45 (5H, m), 7.36 (1H, d, *J* = 7.0 Hz), 7.22-7.29 (3H, m), 2.38 (3H, s), 2.36 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.5, 145.2, 136.5, 135.6, 135.1, 134.6, 132.6, 130.6, 130.5, 129.7, 129.6, 129.5, 129.0, 128.4, 127.2, 122.1, 115.5, 21.7, 21.3; MS (ESI) *m/z* 390 $[M+H]^+$.

4.8.26. 5-Methoxy-3-phenyl-1-tosyl-1H-indole-2-carbaldehyde ***(4c)***[2e,f] Yield 77%; 0.038 g; yellow solid; R_f (8% EtOAc/*n*-hexane) 0.42; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.23 (1H, s), 8.19 (1H, d, *J* = 9.2 Hz), 7.76 (2H, d, *J* = 8.3 Hz), 7.43 (5H, m), 7.22 (2H, d, *J* = 8.0 Hz), 7.16 (1H, dd, *J* = 2.6 Hz, 9.2 Hz), 6.86 (1H, d, *J* = 2.4 Hz), 3.76 (3H, s), 2.36 (3H s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.6, 157.3, 145.2, 135.4, 134.9, 133.1, 132.8, 130.6, 130.4, 129.7, 128.9, 128.4, 127.1, 119.2, 116.9, 103.4, 55.7, 21.6; MS (ESI) *m/z* 406 $[M+H]^+$.

4.8.27. 5-Chloro-3-phenyl-1-tosyl-1H-indole-2-carbaldehyde ***(4d)*** Yield 84%; 0.041 g; yellow gum; R_f (8% EtOAc/*n*-hexane) 0.42; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.21 (1H, s), 8.25 (1H, d, *J* = 9.8 Hz), 7.81 (2H, d, *J* = 8.3 Hz), 7.51-7.41 (7H, m), 7.26 (2H, d, *J* = 8.1 Hz), 2.36 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.3, 162.3, 145.7, 136.3, 134.9, 134.4, 133.3, 130.6, 130.5, 129.9,

129.8, 129.4, 129.2, 128.8, 128.6, 127.2, 121.9, 116.9, 21.7; IR (NaCl, neat) ν: 3019, 2926, 1686, 1597, 1543, 1491, 1443, 1373, 1265, 1171, 1090, 1022, 928, 912, 812 cm^{-1}; MS (ESI) *m/z* 410 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{17}ClNO_3S$ (M^++H) 410.0618, found: 410.0615.

4.8.28. 5-Bromo-3-phenyl-1-tosyl-1H-indole-2-carbaldehyde ***(4e)*** Yield 84%; 0.041 g; yellow gum; R_f (8% EtOAc/*n*-hexane) 0.42; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.21 (1H, s), 8.19 (1H, d, *J* = 9.3 Hz), 7.81 (2H, d, *J* = 8.4 Hz), 7.66-7.62 (2H, m), 7.49-7.41 (5H, m), 7.27 (2H, d, *J* = 7.8 Hz), 2.38 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.3, 162.3, 145.6, 136.7, 134.9, 134.3, 133.1, 132.0, 131.0, 130.4, 129.9, 129.7, 129.2, 128.6, 127.2, 125.0, 118.2, 117.2, 21.7; IR (NaCl, neat) ν: 3019, 2920, 1686, 1600, 1541, 1491, 1439, 1375, 1265, 1171, 1090, 1022, 928, 910, 810 cm^{-1}; MS (ESI) *m/z* 454 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{17}NO_3SBr$ (M^++H) 454.0113, found: 454.0116.

4.8.29. 7-Methyl-3-phenyl-1-tosyl-1H-indole-2-carbaldehyde ***(4f)*** Yield 83%; 0.041 g; colorless solid; m.p. 173-175 ^{o}C; R_f (8% EtOAc/*n*-hexane) 0.42; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.04 (1H, s), 7.71 (2H, d, *J* = 8.4 Hz), 7.47-7.44 (3H, m), 7.38-7.25 (3H, m), 7.23-7.18 (4H, m), 2.66 (3H, s), 2.37 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.5, 162.3, 144.9, 140.5, 140.0, 136.1, 134.3, 132.8, 132.6, 132.5, 130.1, 129.2, 128.9, 127.5, 125.9, 120.6, 21.6, 21.5; IR (NaCl, neat) ν: 3019, 2920, 1682, 1597, 1558, 1494, 1445, 1362, 1283, 1171, 1088, 1007, 928, 910, 810 cm^{-1}; MS (ESI) *m/z* 390 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{20}NO_3S$ (M^++H) 390.1164, found: 390.1166.

4.8.30. 3-Phenyl-1-tosyl-1H-benzo[f]indole-2-carbaldehyde ***(4g)***[2e,f] Yield 54%; 0.026 g; yellow solid; R_f (8% EtOAc/*n*-hexane) 0.42; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.33 (1H, s), 8.71 (1H, s), 8.04 (1H, d, *J* = 8.4 Hz), 7.97 (1H, s), 7.83 (1H, d, *J* = 8.3 Hz), 7.74 (2H, d, *J* = 8.3 Hz), 7.44 (7H, m), 7.16 (2H, d, *J* = 8.2 Hz), 2.30 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.0, 145.2, 136.4, 135.7, 134.7, 134.3, 133.8, 131.0, 130.6, 130.2, 130.0, 129.7, 129.2, 128.5, 128.4, 127.2, 126.8, 125.5, 122.1, 113.3, 21.6; MS (ESI) *m/z* 426 $[M+H]^+$.

4.8.31. 7-Methyl-5-tosyl-5H-[1,3]dioxolo[4,5-f]indole-6-carbaldehyde ***(4h)***[2e,f] Yield 65%; 0.032 g; colorless gum; R_f (8% EtOAc/*n*-hexane) 0.42; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.50 (1H, s), 7.71 (1H, s), 7.58 (2H, d, *J* = 8.2 Hz), 7.19 (2H, d, *J* = 8.2 Hz), 6.87 (1H, s) 6.07 (2H, s), 2.45 (3H, s), 2.35 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.3, 150.3, 146.3, 145.2, 134.2, 133.5, 132.7, 129.8, 126.7, 125.2, 102.0, 99.1, 96.7, 21.6, 10.8; MS (ESI) *m/z* 358 $[M+H]^+$.

4.8.32. 3-p-Tolyl-1-tosyl-1H-indole-2-carbaldehyde ***(4i)***[2e,f] Yield 91%; 0.045 g; yellow solid; R_f (8% EtOAc/*n*-hexane) 0.42; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.2 (1H, s), 8.29 (1H, d, *J* = 8.4 Hz), 7.82 (2H, d, *J* = 8.4 Hz), 7.52 (2H, d, *J* = 7.8 Hz), 7.32 (2H, d, *J* = 8.1 Hz), 7.23 (5H, m), 2.42 (3H, s), 2.36 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.4, 145.2, 139.0, 138.3, 136.1, 135.2, 132.5, 130.4, 129.7, 129.3, 129.1, 127.2, 124.6, 122.7, 115.7, 79.5, 21.6, 21.4; MS (ESI) *m/z* 390 $[M+H]^+$.

4.8.33. 3-(4-Chlorophenyl)-1-tosyl-1H-indole-2-carbaldehyde ***(4j)***[2e,f] Yield 90%; 0.044 g; colorless solid; R_f (8% EtOAc/*n*-hexane) 0.42; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.31 (1H, s), 8.29 (1H, d, *J* = 8.6 Hz), 7.77 (2H, d, *J* = 8.4 Hz), 7.54 (1H, td, *J* = 1.2 Hz, 8.5 Hz), 7.38-7.49 (5H, m), 7.29-7.33 (2H, m), 7.23 (1H, d, *J* = 9.3 Hz), 2.36 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.6, 162.3, 145.5, 137.8, 135.0, 134.8, 133.6, 132.5, 131.8, 129.8, 129.3, 129.1, 128.9, 128.6, 127.1, 124.9, 122.3, 115.7, 21.7; MS (ESI) *m/z* 410 $[M+H]^+$.

4.8.34. 3-o-Tolyl-1-tosyl-1H-indole-2-carbaldehyde ***(4k)*** Yield 91%; 0.045 g; colorless solid; m.p. 98-101 ^{o}C; R_f (8% EtOAc/*n*-hexane) 0.42; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.24 (1H, s), 8.31 (1H, d, *J* = 8.4 Hz), 7.76 (2H, d, *J* = 8.1 Hz), 7.55 (1H, t, *J* = 7.5 Hz), 7.26-7.20 (6H, m), 7.10 (2H, d, *J* = 7.2 Hz), 2.35 (3H, s), 1.97 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.5, 145.4, 138.1, 137.3, 135.4, 134.9, 132.8, 130.4, 130.2, 130.0, 129.9, 129.7, 129.2, 128.8, 127.1, 125.6, 124.8, 122.7, 115.9, 21.6, 19.8; IR (NaCl, neat) ν: 3019, 2920, 1684, 1599, 1543, 1489, 1443, 1373, 1263, 1175, 1090, 922, 910, 805 cm^{-1}; MS (ESI) *m/z* 390 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{20}NO_3S$ (M^++H) 390.1164, found: 390.1163.

4.8.35. 5-Chloro-3-(2-fluorophenyl)-1-tosyl-1H-indole-2-carbaldehyde ***(4l)*** Yield 75%; 0.037 g; colorless solid; m.p. 110-111 ^{o}C; R_f (8% EtOAc/*n*-hexane) 0.42; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.39 (1H, s), 8.23 (1H, d, *J* = 8.9 Hz), 7.73 (2H, d, *J* = 8.4 Hz), 7.51-7.42 (2H, m), 7.36-7.31 (2H, m), 7.28-7.17 (4H, m), 2.37 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.6, 145.8, 135.9, 134.4, 134.0, 131.9, 131.1, 131.0, 130.8, 130.4, 130.0, 129.3, 127.0, 126.4, 124.2, 124.1, 121.8, 116.8, 116.1 (d, J_{C-F} = 22.5 Hz), 21.7; IR (NaCl, neat) ν: 3019, 2960, 1688, 1599, 1545, 1493, 1445, 1377, 1263, 1171, 1090, 926, 849 cm^{-1}; MS (ESI) *m/z* 428 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{16}ClFNO_3S$ (M^++H) 428.0523, found: 428.0521.

4.8.36. 3-Methyl-1-tosyl-1H-indole-2-carbaldehyde ***(4m)***[2e,f] Yield 89%; 0.044 g; colorless solid; R_f (8% EtOAc/*n*-hexane) 0.42; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.61 (1H, s), 8.20 (1H, d, *J* = 8.5 Hz), 7.55 (3H, d, *J* = 8.2 Hz), 7.50 (1H, dd, *J* = 1.1 Hz, 8.4 Hz), 7.29 (1H, dd, *J* = 0.7 Hz, 7.9 Hz), 7.12 (2H, d, *J* = 8.1 Hz), 2.51 (3H, s), 2.30 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 185.3, 145.3, 137.5, 134.2, 133.0, 132.1, 130.6, 129.8, 129.1, 126.7, 124.6, 121.6, 115.8, 21.6, 10.5; MS (ESI) *m/z* 314 $[M+H]^+$.

4.8.37. 3-Ethyl-1-tosyl-1H-indole-2-carbaldehyde ***(4n)***[2e,f] Yield 91%; 0.045 g; colorless gum; R_f (8% EtOAc/*n*-hexane) 0.42; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.58 (1H, s), 8.22 (1H, d, *J* = 8.5 Hz), 7.59-7.49 (4H, m), 7.33 (1H, t, *J* = 7.5 Hz), 7.14 (2H, d, *J* = 8.2 Hz), 2.99 (2H, q, *J* = 7.5 Hz), 2.30 (3H, s), 1.18 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.9, 145.2, 138.4, 137.8, 134.1, 132.3, 129.7, 129.6, 128.9, 126.7, 124.6, 121.4, 116.0, 21.5, 18.1, 14.4; MS (ESI) *m/z* 328 $[M+H]^+$.

4.8.38. 5,7-Methyl-1-tosyl-1H-indole-2-carbaldehyde ***(4o)*** Yield 90%; 0.044 g; pale-brown solid; m.p. 110-113 ^{o}C; R_f (8% EtOAc/*n*-hexane) 0.42; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.24 (1H, s), 7.38 (2H, d, *J* = 8.2 Hz), 7.27 (1H, s), 7.10 (4H, d, *J* = 7.1 Hz), 2.68 (3H, s), 2.33 (3H, s), 2.31 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.4, 145.0, 141.6, 138.5, 135.9, 134.0, 133.1, 131.9, 129.3, 127.0, 123.2, 121.4, 21.6, 21.5, 20.9; IR (NaCl, neat) ν: 3019, 2920, 1682, 1600, 1555, 1473, 1460, 1400, 1368, 1169, 1090, 999, 876, 810 cm^{-1}; MS (ESI) *m/z* 328 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{18}NO_3S$ (M^++H) 328.1007, found: 328.1002.

4.8.39. 1-Tosyl-1H-indole-2-carbaldehyde ***(4p)***[2e,f,12a] Yield 51%; 0.025 g; colorless solid; R_f (8% EtOAc/*n*-hexane) 0.42; ^{1}H NMR ($CDCl_3$, 400MHz) δ = 10.53 (1H, s), 8.23 (1H, dd, *J* = 0.4 Hz, 8.4 Hz), 7.65 (2H, d, *J* = 8.4 Hz), 7.62 (1H, dd, *J* = 1.2 Hz, 8.0 Hz), 7.52 (1H, ddd, *J* = 1.2 Hz, 7.2 Hz, 7.2 Hz,), 7.46 (1H, s), 7.31 (1H, ddd, *J* = 0.8 Hz, 7.2 Hz, 7.2 Hz), 7.18 (2H, d, *J* = 8.4 Hz), 2.32 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 183.3, 145.6, 138.4, 137.7, 134.6, 129.9, 128.8, 128.1, 126.6, 124.8, 123.6, 118.8, 115.3, 21.6; MS (ESI) *m/z* 300 $[M+H]^+$.

4.8.40. 3-Phenyl-1-mesyl-1H-indole-2-carbaldehyde ***(4q)*** Yield 83%; 0.041 g; colorless solid; m.p. 126-129 ^{o}C; R_f (8% EtOAc/*n*-hexane) 0.42; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.84 (1H, s), 8.19 (1H, d, *J* = 8.7 Hz), 7.65 (1H, d, *J* = 8.1 Hz), 7.58-7.54 (6H, m), 7.33 (1H, t, *J* = 7.8 Hz), 3.78 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 181.9, 162.3, 139.0, 138.6, 132.8, 130.6, 130.0, 129.7, 129.3, 129.9, 128.0, 124.3, 122.6, 115.6, 43.7; IR (NaCl, neat) ν: 3019,

2916, 1678, 1604, 1543, 1445, 1368, 1172, 1022, 968, 926 cm^{-1}; MS (ESI) *m/z* 300 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{14}NO_3S$ (M^++H) 300.0694, found: 300.0694.

*4.8.41. 3-Phenyl-1-nosyl-1H-indole-2-carbaldehyde (**4r**)* Yield 85%; 0.042 g; colorless solid; m.p. 151-153 °C; R_f (8% EtOAc/*n*-hexane) 0.42;^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.92 (1H, s), 8.34 (3H, d, *J* = 9.3 Hz), 8.24 (2H, d, *J* = 9.1 Hz), 7.65-7.60 (2H, m), 7.50 (5H, s), 7.38 (1H, t, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 181.3, 162.3, 150.6, 144.3, 138.7, 138.4, 132.5, 130.5, 130.0, 129.6, 128.9, 128.8, 128.7, 125.1, 124.2, 123.0, 115.6; IR (NaCl, neat) ν: 3019, 1684, 1603, 1533, 1420, 1350, 1261, 1182, 1090, 1022, 968, 928, 855 cm^{-1}; MS (ESI) *m/z* 407 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{15}N_2O_5S$ (M^++H) 407.0702, found: 407.0698.

*4.8.42. 3-Phenyl-1H-indole-2-carbaldehyde (**5s**)*[12c] Yield 70%; 0.029 g; colorless solid; R_f (10% EtOAc/*n*-hexane) 0.32; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.88 (1H, s), 9.33 (1H, brs), 7.82 (1H, d, *J* = 8.1 Hz), 7.62 (1H, d, *J* = 8.4 Hz), 7.56-7.41 (6H,m), 7.20 (1H, t, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 182.9, 137.3, 132.0, 131.8, 130.6, 129.6, 128.9, 128.1, 127.8, 126.8, 122.3, 121.5, 112.5; MS (ESI) *m/z* 222 $[M+H]^+$.

*4.8.43. 3-Methyl-1H-indole-2-carbaldehyde (**5t**)*[12b] Yield 71%; 0.028 g; colorless solid; R_f (10% EtOAc/*n*-hexane) 0.32; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.0 (1H, s), 9.56 (1H, brs), 7.67 (1H, d, *J* = 8.1 Hz), 7.42-7.33 (2H, m), 7.12 (1H, t, *J* = 7.8 Hz), 2.60 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.8, 137.9, 132.2, 128.1, 127.7, 125.3, 121.3, 120.4, 112.5, 8.4; MS (ESI) *m/z* 160 $[M+H]^+$.

*4.8.44. 6-Methyl-3-phenyl-1H-indole-2-carbaldehyde (**5u**)* Yield 62%; 0.026 g; colorless solid; m.p. 167-169 °C; R_f (10% EtOAc/*n*-hexane) 0.32; ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ 10.92 (1H, brs), 9.84 (1H, s), 7.67 (3H, d, *J* = 8.1 Hz), 7.57 (2H, t, *J* = 7.2 Hz), 7.49-7.44 (1H,m), 7.10 (1H, s), 7.05 (1H, d, *J* = 8.4 Hz), 2.47 (3H, s); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ 181.57, 138.29, 137.35, 132.51, 131.88, 130.43, 128.8, 128.19, 127.7, 124.6, 123.3, 121.3, 112.3, 21.2; IR (NaCl, neat) ν: 3447, 2850, 1643, 1522, 1435, 1375, 1339, 1009, 928 cm^{-1}; MS (ESI) *m/z* 236 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{14}NO$ (M^++H) 236.1075, found: 236.1078.

*4.8.45. 5-Chloro-3-phenyl-1H-indole-2-carbaldehyde (**5v**)*[12c] Yield 57%; 0.024 g; colorless solid; R_f (10% EtOAc/*n*-hexane) 0.32; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.87 (1H, s), 9.20 (1H, brs), 7.78 (1H, s), 7.74 (1H, d, *J* = 7.2 Hz), 7.59-7.54 (4H, m), 7.41-7.39 (2H, m); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ 182.0, 141.6, 131.7, 130.4, 129.0, 128.5, 128.0, 127.5, 127.2, 127.1, 126.4, 120.6, 114.6; MS (ESI) *m/z* 256 $[M+H]^+$.

*4.8.46. 5-Chloro-3-(2-chlorophenyl)-1H-indole-2-carbaldehyde (**5w**)* Yield 52%; 0.022 g; colorless solid; m.p. 164-169 °C; R_f (10% EtOAc/*n*-hexane) 0.32; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.71 (1H, s), 9.37 (1H, brs), 7.61-7.58 (1H, m), 7.51 (1H, s), 7.49-7.36 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.4, 135.2, 134.4, 133.1, 132.9, 130.3, 130.2, 130.0, 128.1, 127.3, 127.0, 124.9, 121.6, 113.7; IR (NaCl, neat) ν: 3445, 2860, 1653, 1551, 1494, 1475, 1419, 1430, 1373, 1339, 1294, 1072, 1055, 1003, 955, 930 cm^{-1}. MS (ESI) *m/z* 290 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{10}Cl_2NO$ (M^++H) 290.0139, found: 290.0137.

*4.8.47. (E)-2-(Iodomethylene)-3-phenyl-1-tosylindolin-3-ol (**6a**)*[2e,f] Yield 85%; 0.056 g; yellow solid; m.p. 84-86 °C; R_f (12% EtOAc/*n*-hexane) 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (1H, d, *J* = 8.3 Hz), 7.58 (2H, d, *J* = 8.2 Hz), 7.31 (2H, d, *J* = 8.2 Hz), 7.24 (2H, d, *J* = 8.1 Hz), 7.12 (3H m), 7.01 (3H, m), 6.95 (1H, d, *J* = 7.5 Hz), 2.65 (1H, s), 2.41 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.0, 145.3, 142.3, 139.7, 135.1, 133.6, 130.2, 129.8, 128.2, 127.6, 127.3, 126.0, 125.6, 125.3, 116.6, 82.9, 65.9, 21.7; MS (ESI) *m/z* 504 $[M+H]^+$.

*4.8.48. (R)-N-Tosylcalindol (**7**)* Yield 90%; 0.023 g; colorless solid: m.p. 102-105 °C; R_f (20% EtOAc/*n*-hexane) 0.17; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (1H, d, *J* = 8.3 Hz), 8.07 (1H, d, *J* = 8.0 Hz), 7.88 (1H, d, *J* = 7.76 Hz), 7.75-7.77 (2H, m), 7.56 (2H, d, *J* = 8.3 Hz), 7.37-7.51 (4H, m), 7.19-7.30 (2H, m), 7.04 (2H, d, *J* = 8.3 Hz), 6.35 (1H, s), 4.69 (1H, q, *J* = 6.4 Hz), 4.16 (1H, d, *J* = 15.4 Hz), 3.97 (1H, d, *J* = 15.4 Hz), 2.50 (1H, br s), 2.25 (3H, s), 1.49 (3H, d, *J* = 6.52 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.7, 140.5, 139.6, 137.4, 135.7, 134.0, 131.3, 129.7, 129.4, 128.9, 127.2, 126.2, 125.8, 125.7, 125.3, 124.4, 123.6, 123.2, 123.0, 120.6, 114.7, 111.3, 51.7, 44.9, 23.8, 21.5; MS (ESI) *m/z* 455 $[M+H]^+$; HRMS (ESI) calcd. for $C_{28}H_{27}N_2O_2S$ (M^++H) 455.1793, found: 455.1791; $[\alpha]_D^{22}$ –30.05° (*c* = 0.51, $CHCl_3$).

Acknowledgments

This work is supported by a College of Science Start-Up Grant from Nanyang Technological University and a Science and Engineering Research Council Grant (092 101 0053) from A*STAR, Singapore.

Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra for all starting materials and products. This material is available free of charge via the Internet at

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8. A provisional U.S. patent application of this work has been filed, application no. 61/684,344.

9. Approximate number of commercially available 2-aminoketone substrates ~1000 (source: Scifinder Scholar)

10. Approximate price of commercially available 1-tosyl-1*H*-indole-2-carbaldehyde (**4p**): US$ 300 for 500 mg (source: Matrix Scientific; Catalogue No: 064706; page no. 7151) Cost of **4p** by our method: S$ 11.05 for 500 mg.

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Supporting Information

Metal-free synthesis of 1*H*-indole-2-carbaldehydes by *N*-iodosuccinimide-mediated cyclization of 1-(2'-Anilinyl)prop-2-yn-1-ols in water. A formal synthesis of (*R*)-Calindol

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Figure S1. ^{1}H and ^{13}C NMR Spectra of 1-Phenyl-1-(2-(tosylamino)phenyl)prop-2-yn-1-ol **(1a)**

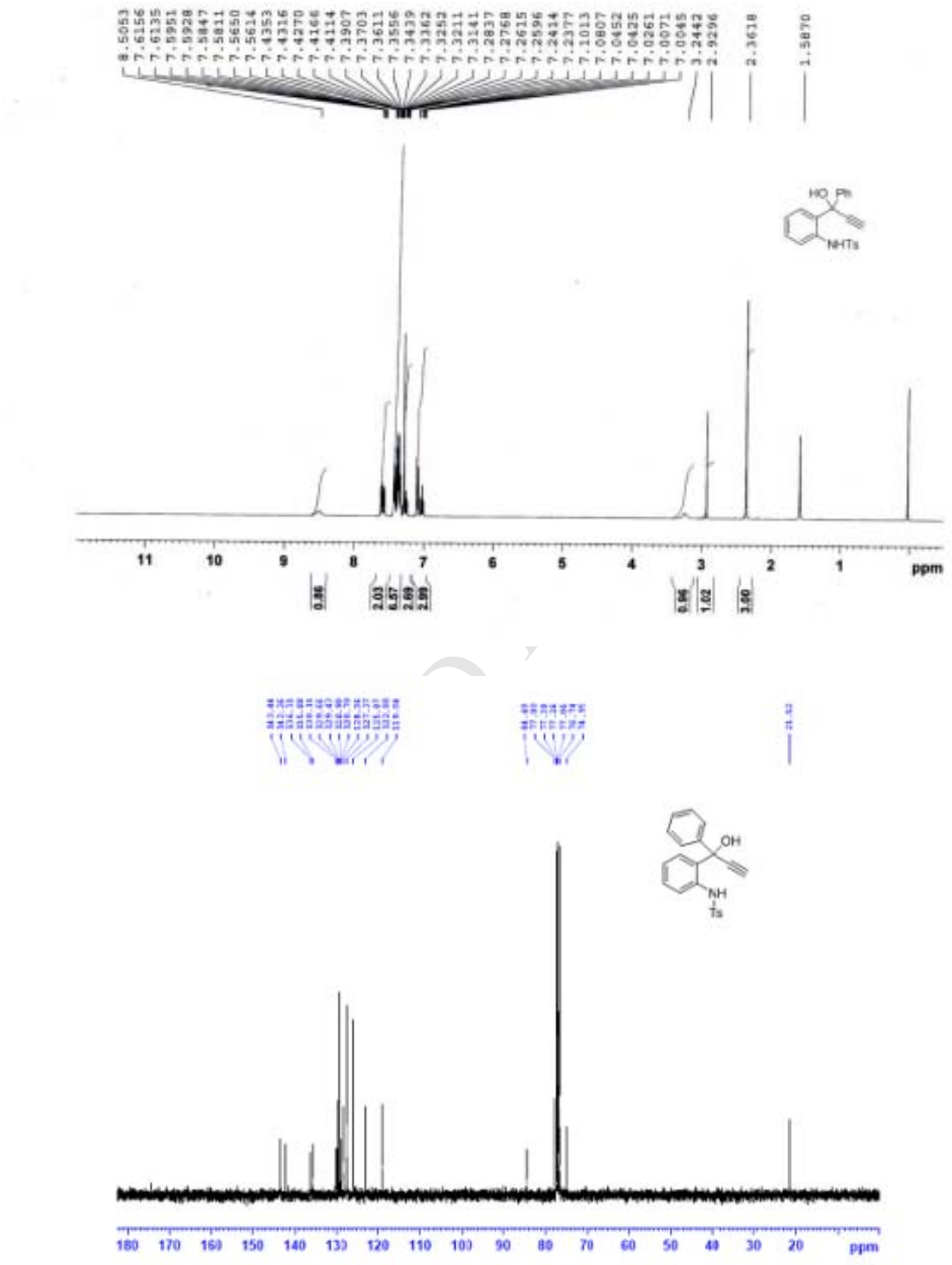


Figure S2. ^{1}H and ^{13}C NMR Spectra of *N*-(2-(1-Hydroxy-1-phenylprop-2-ynyl)-4-methylphenyl)-4-methylbenzene sulfonamide **(1b)**

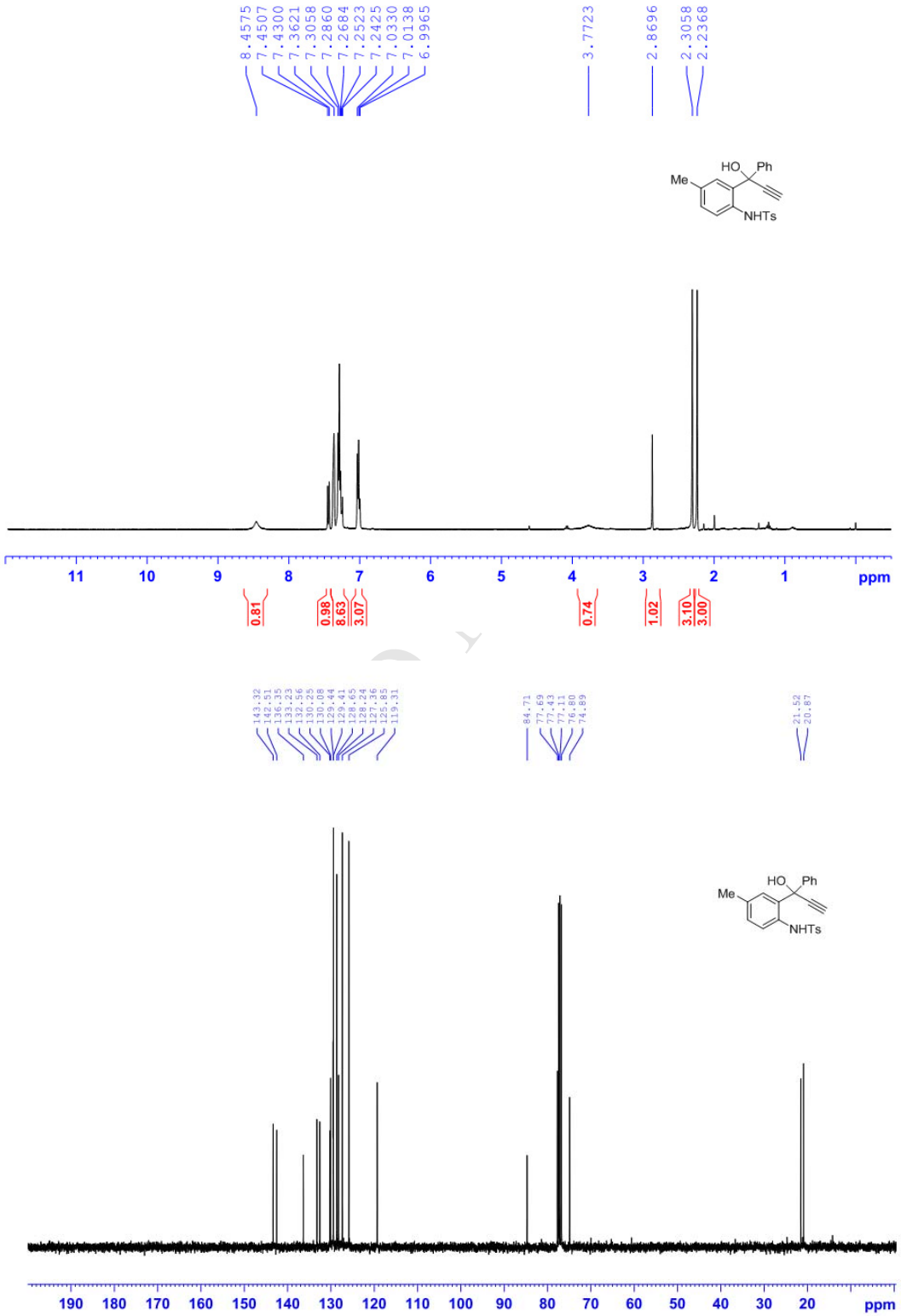


Figure S3. ^{1}H and ^{13}C NMR Spectra of *N*-(2-(1-Hydroxy-1-phenylprop-2-ynyl)-4-methoxyphenyl)-4-methylbenzene sulfonamide **(1c)**

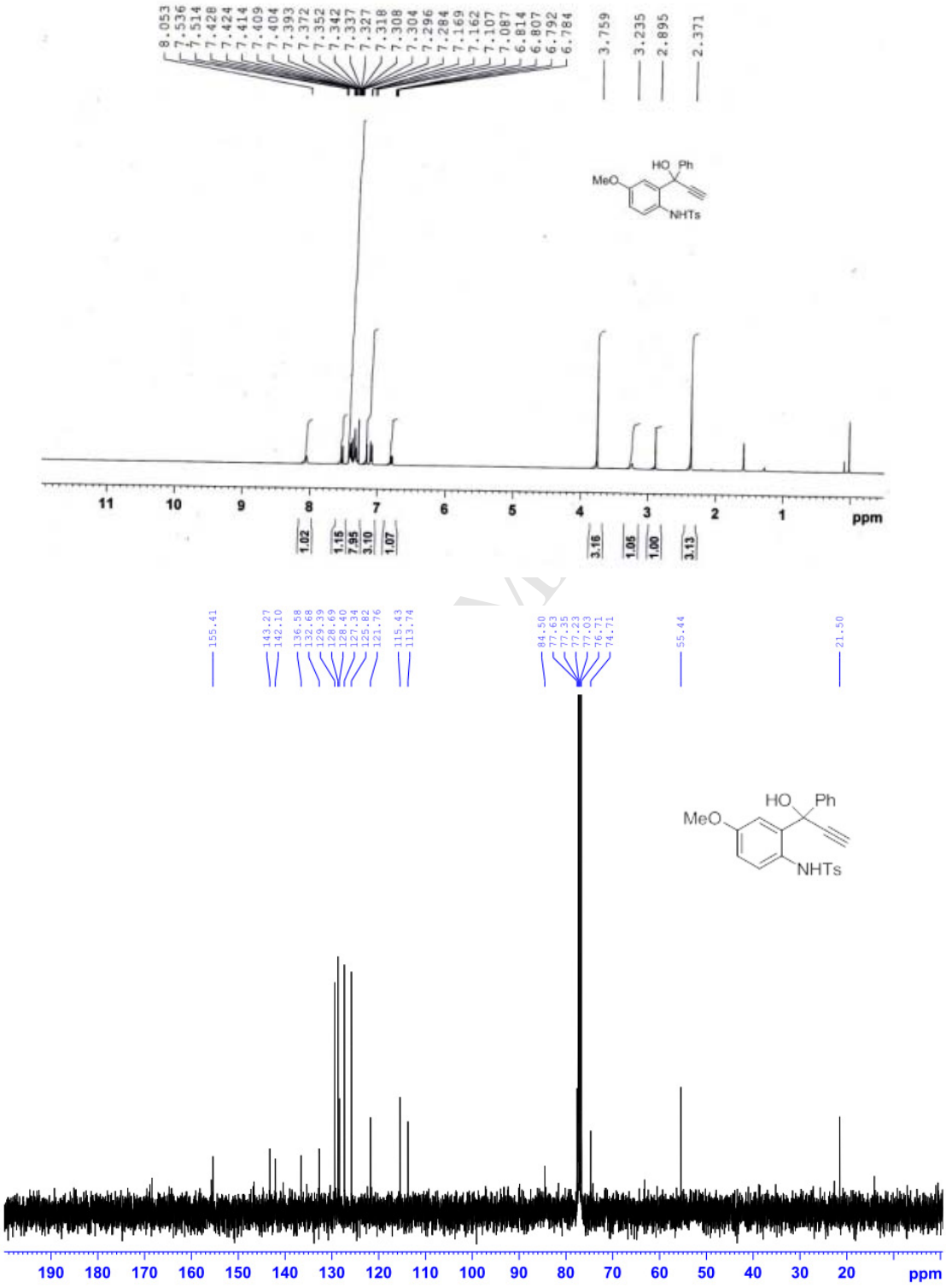


Figure S4. ^{1}H and ^{13}C NMR Spectra of *N*-(4-Chloro-2-(1-hydroxy-1-phenylprop-2-ynyl)phenyl)-4-methylbenzene sulfonamide **(1d)**

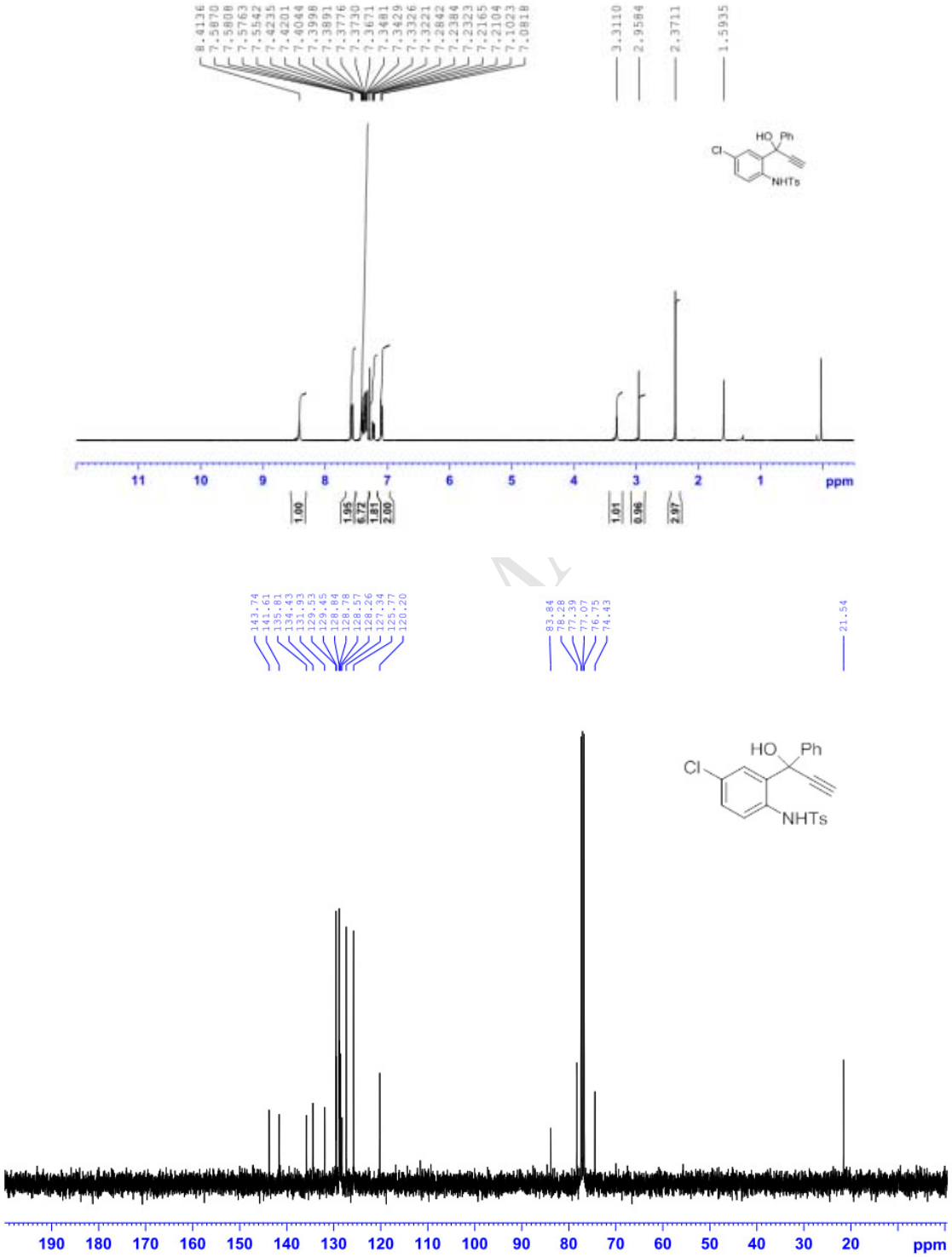


Figure S5. ^{1}H and ^{13}C NMR Spectra of *N*-(4-Bromo-2-(1-hydroxy-1-phenylprop-2-ynyl)phenyl)-4-methylbenzene sulfonamide **(1e)**

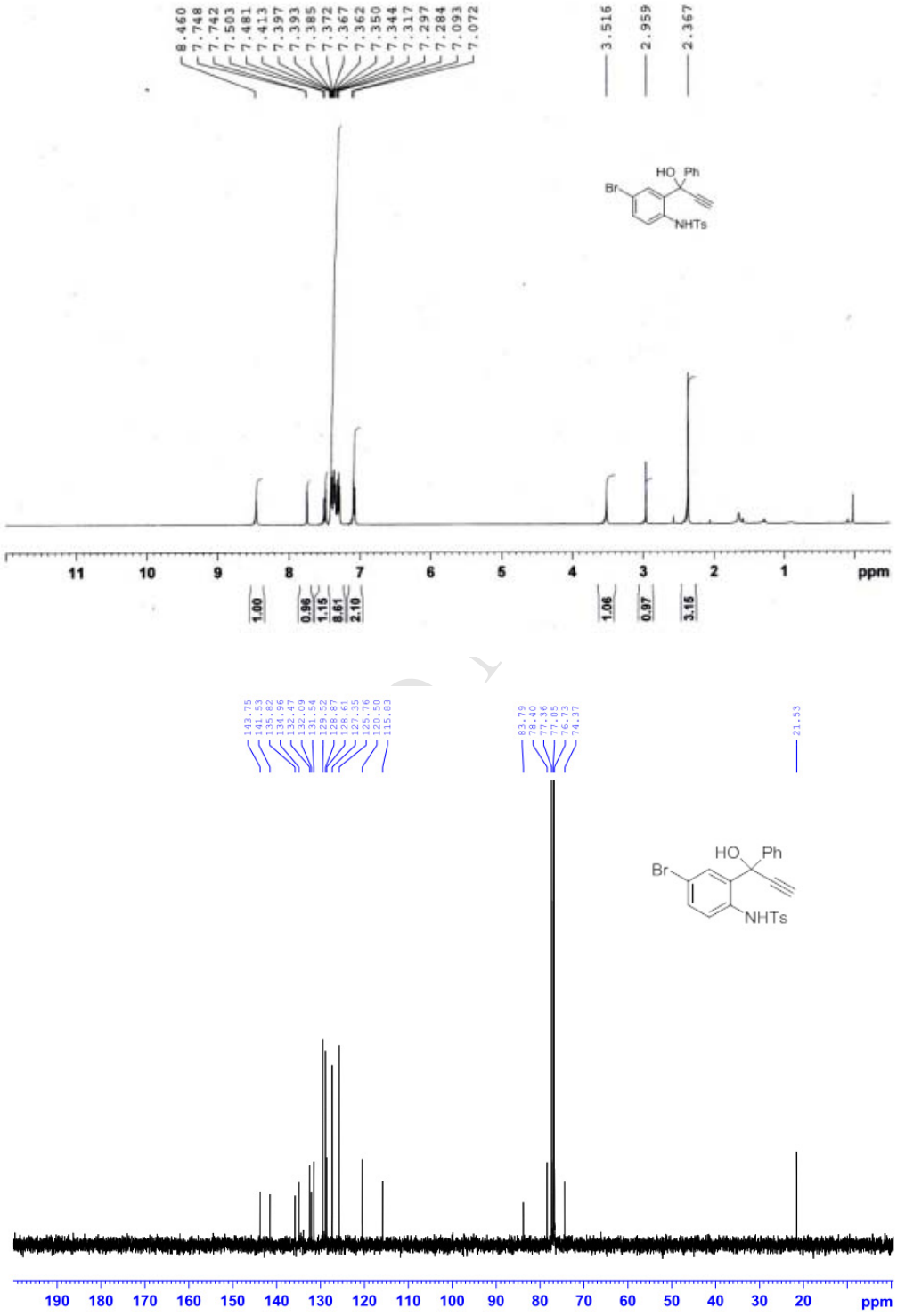


Figure S6. ^{1}H and ^{13}C NMR Spectra of 1-(3-Methyl-2-(tosylamino)phenyl)-1-phenylprop-2-yn-1-ol (**1f**)

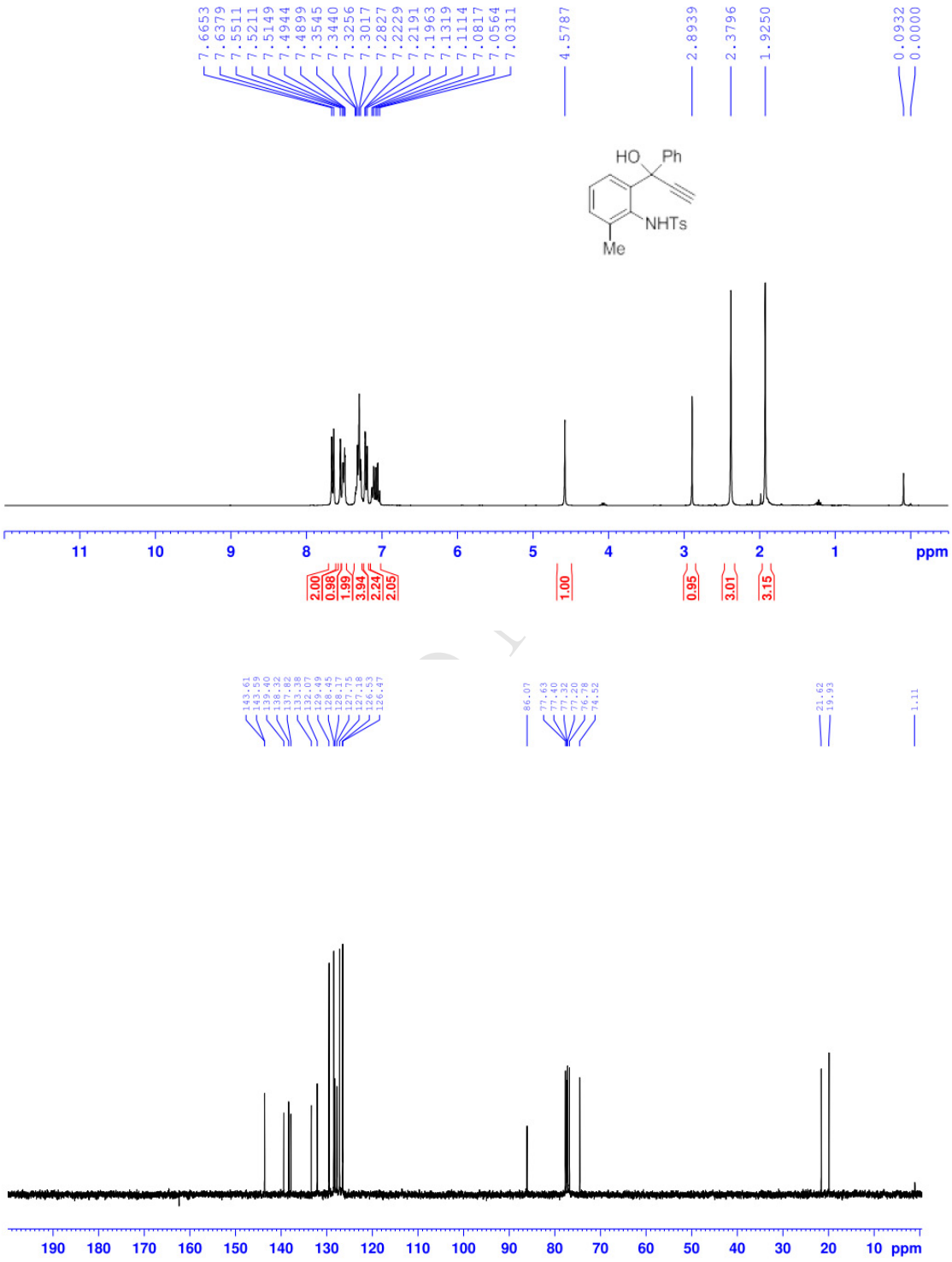


Figure S7. ^{1}H and ^{13}C NMR Spectra of *N*-(3-(1-Hydroxy-1-phenylprop-2-ynyl)naphthalen-2-yl)-4-methylbenzene sulfonamide **(1g)**

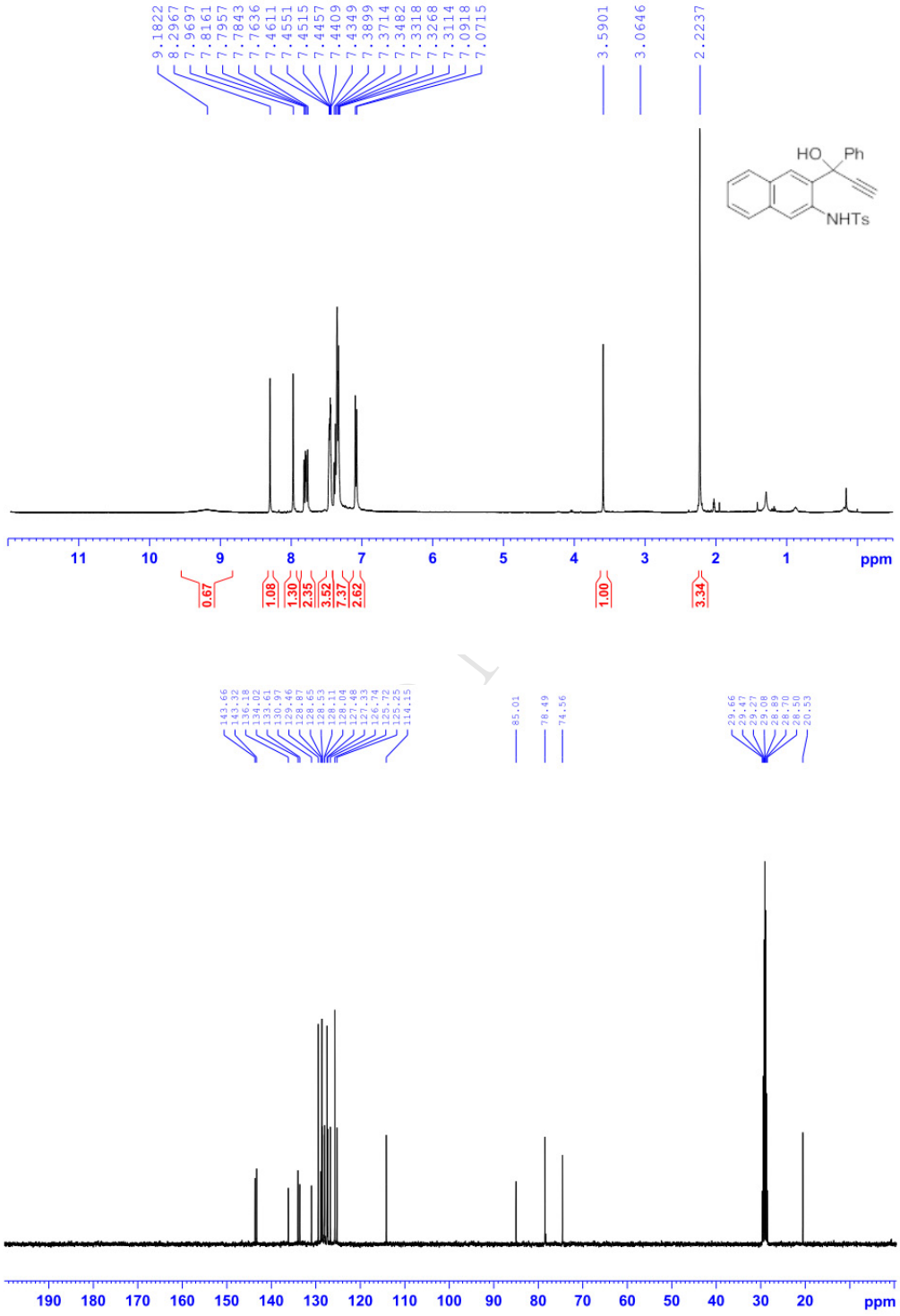


Figure S8. ^{1}H and ^{13}C NMR Spectra of 2-(5-(Tosylamino)benzo[*d*][1,3]dioxol-6-yl)but-3-yn-2-ol **(1h)**

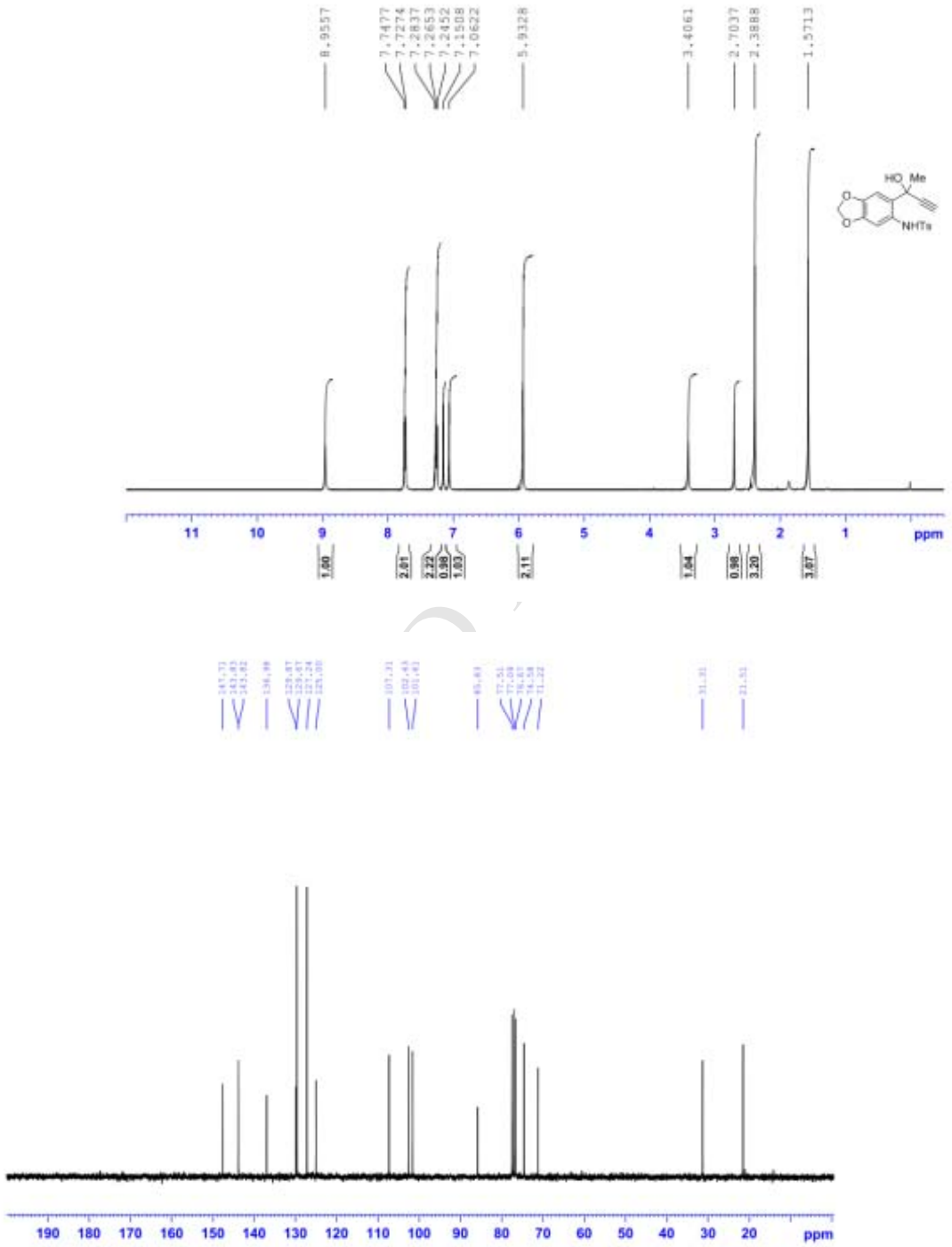


Figure S9. ^{1}H and ^{13}C NMR Spectra of 1-*p*-Tolyl-1-(2-(tosylamino)phenyl)prop-2-yn-1-ol **(1i)**

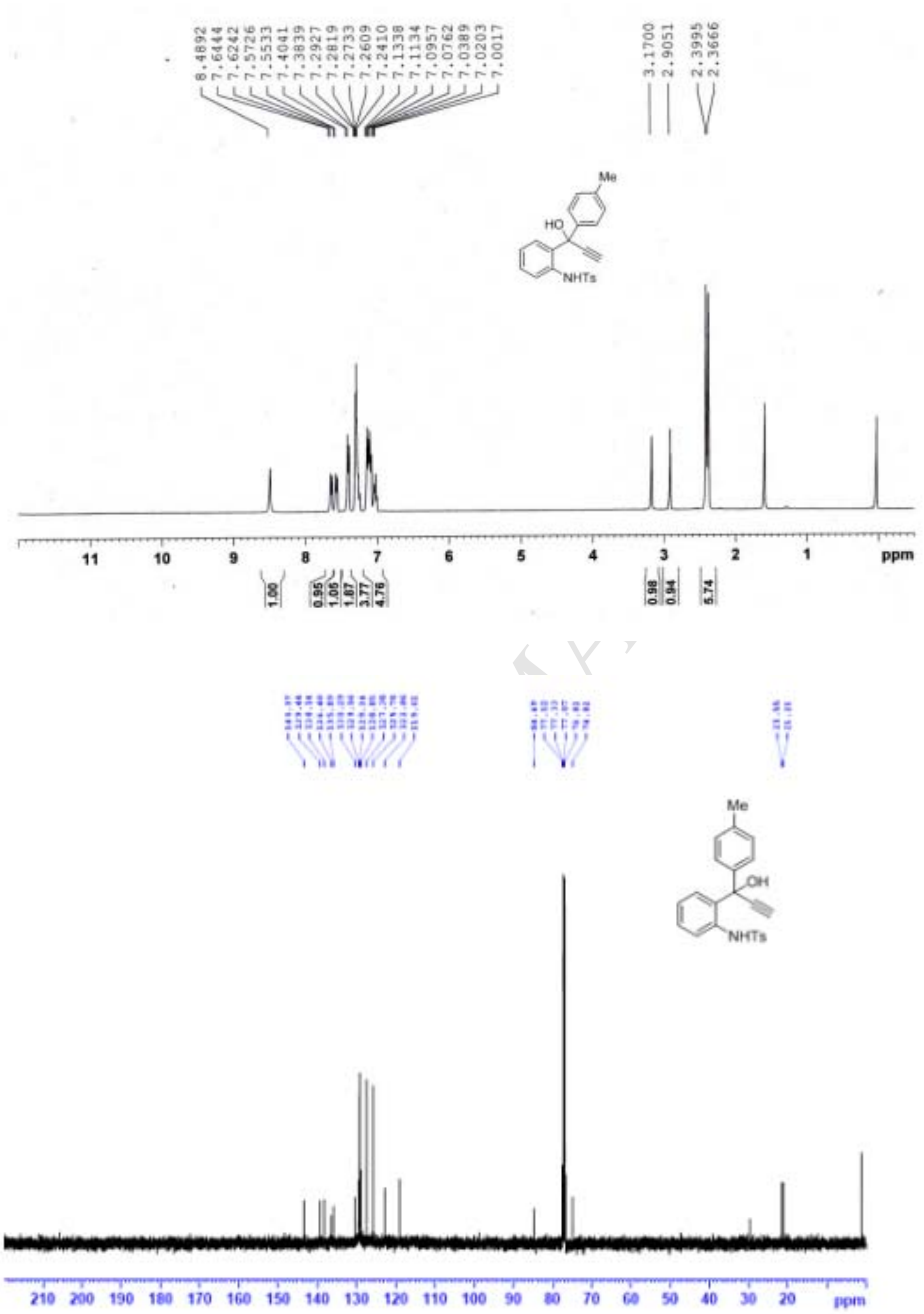


Figure S10. ^{1}H and ^{13}C NMR Spectra of 1-(4-Chlorophenyl)-1-(2-(tosylamino)phenyl) prop-2-yn-1-ol **(1j)**

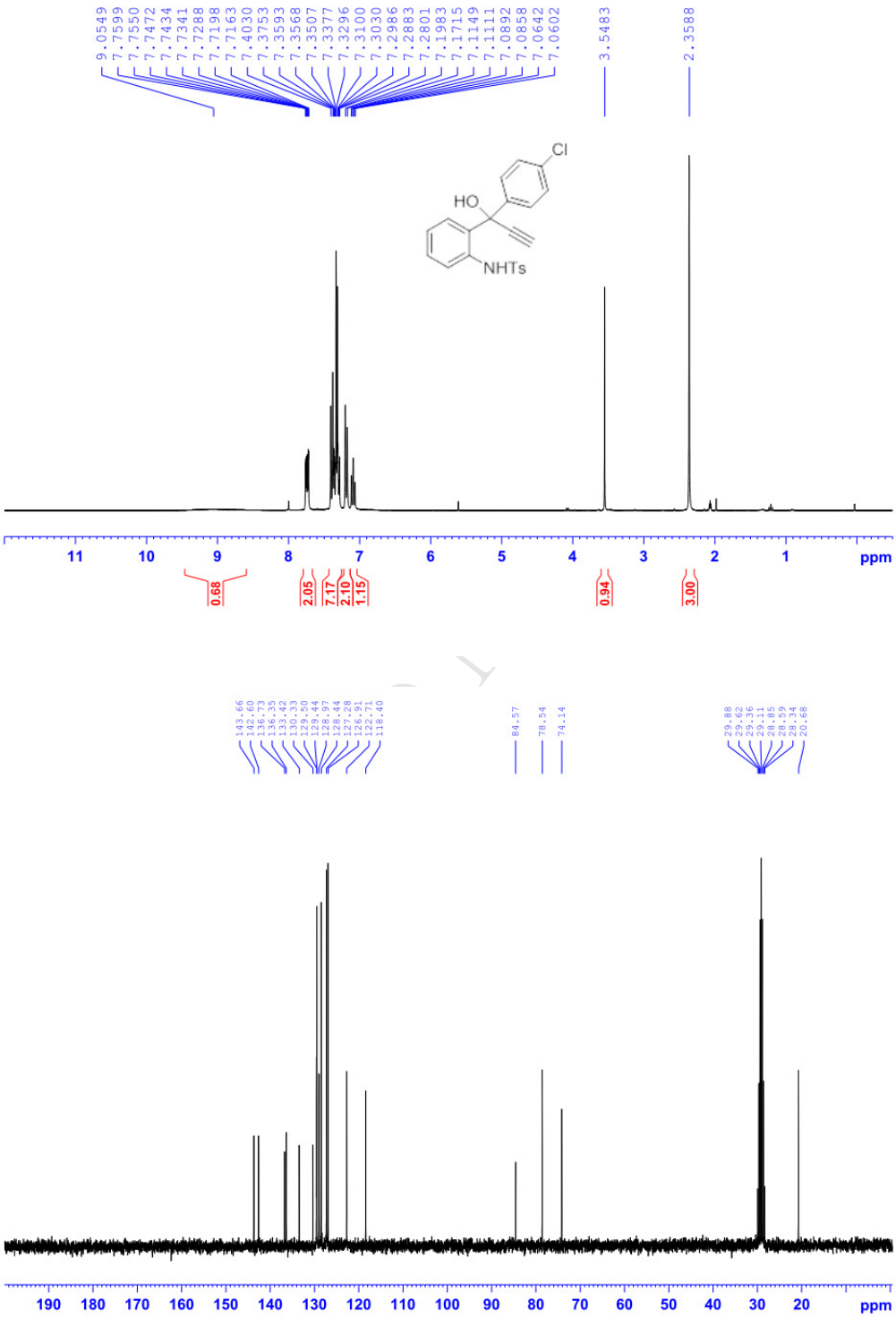


Figure S11. ^{1}H and ^{13}C NMR Spectra of 1-*o*-Tolyl-1-(2-(tosylamino)phenyl)prop-2-yn-1-ol **(1k)**

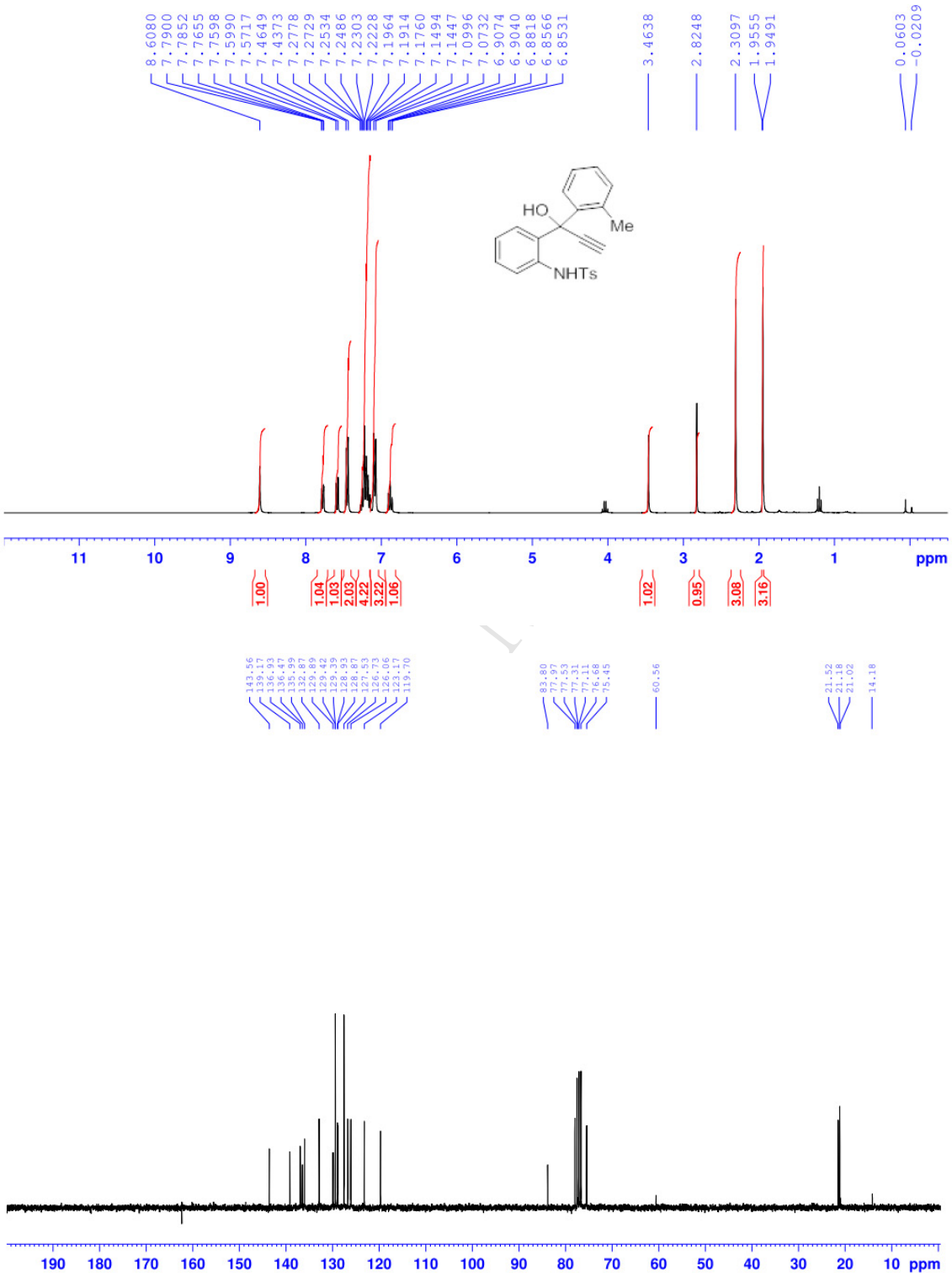


Figure S12. ^{1}H and ^{13}C NMR Spectra of 1-(5-Chloro-2-(tosylamino)phenyl)-1-(2-fluorophenyl)prop-2-yn-1-ol **(1l)**

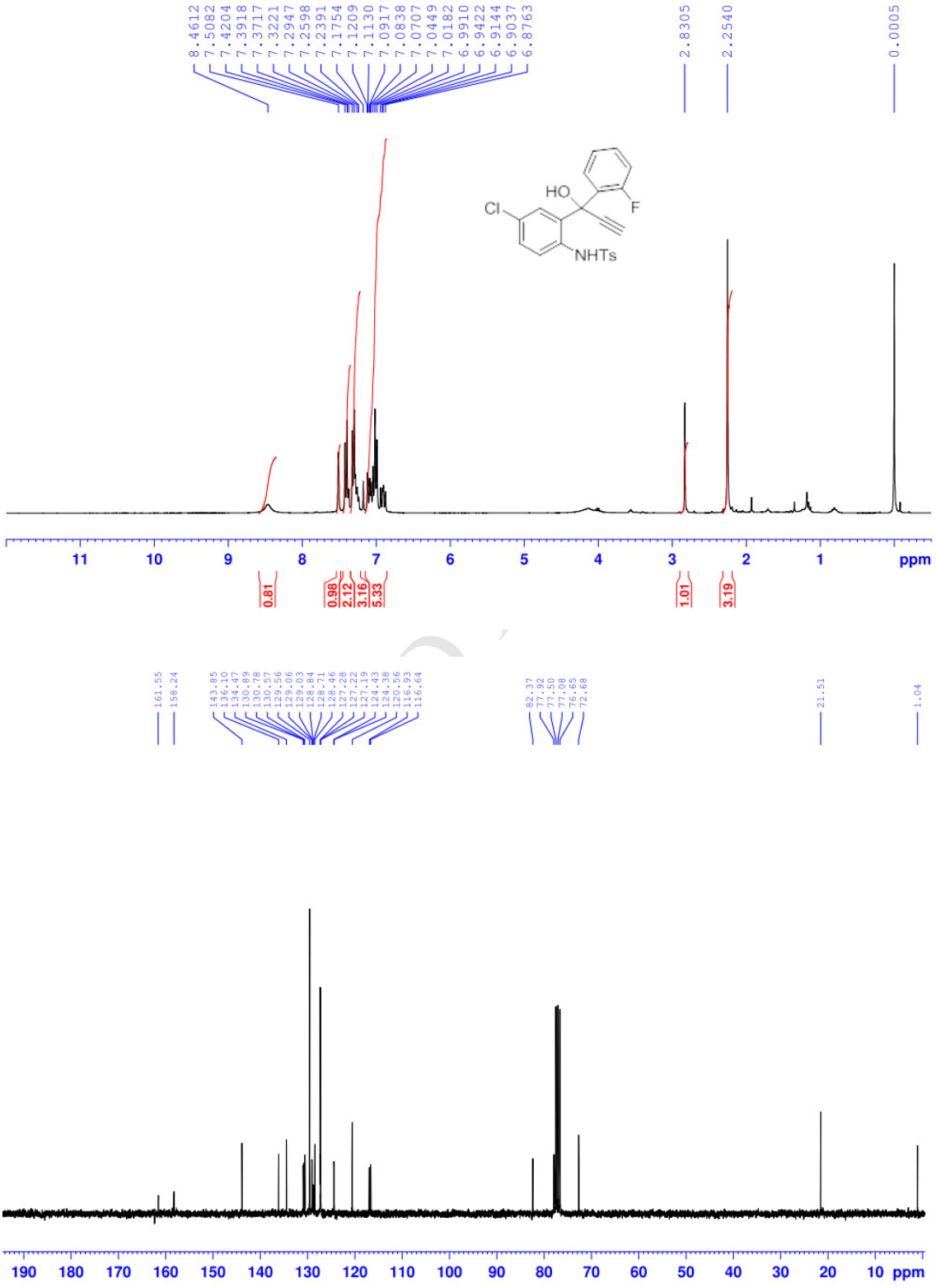


Figure S13. ^{1}H and ^{13}C NMR Spectra of 2-(2-(Tosylamino)phenyl)but-3-yn-2-ol **(1m)**

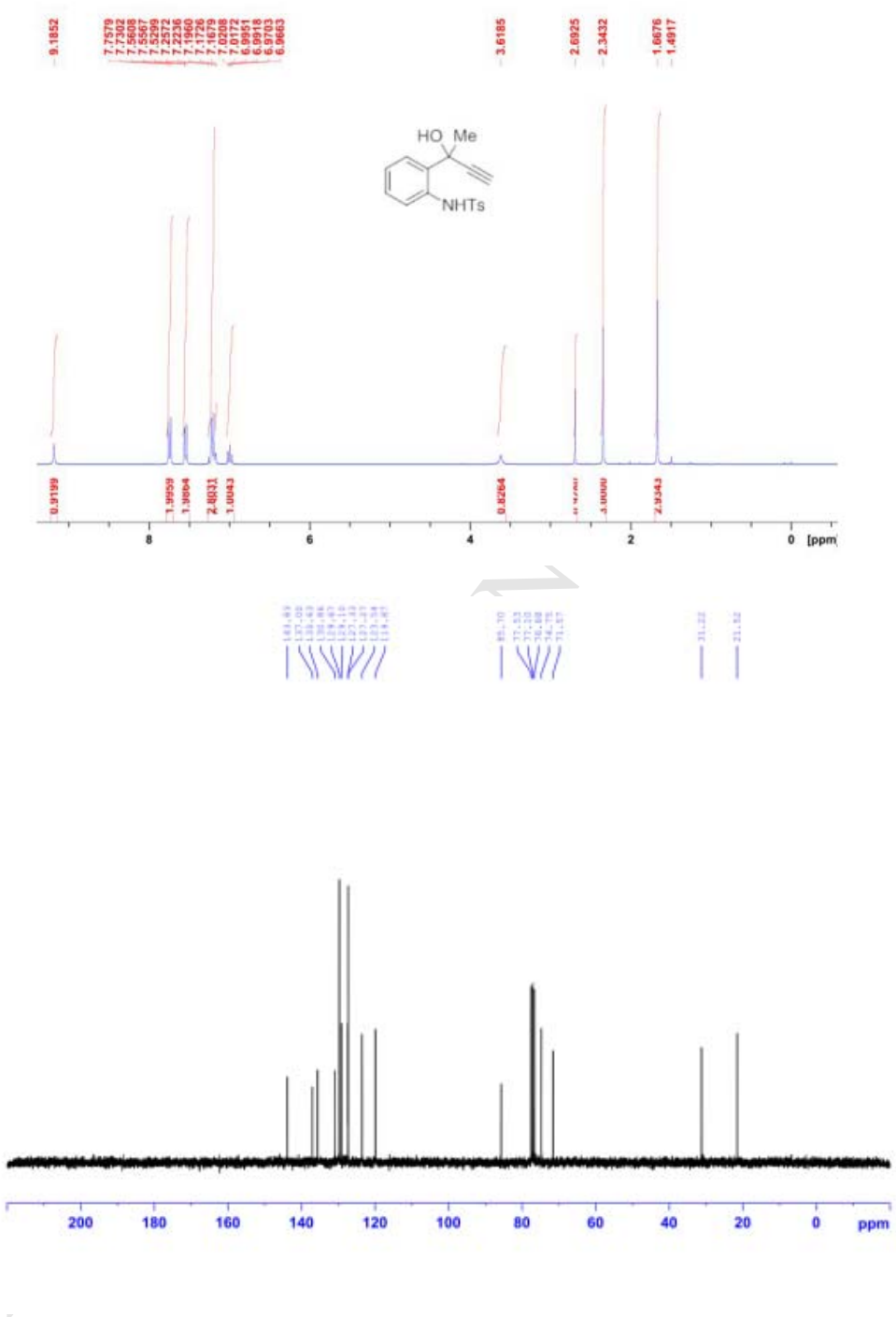


Figure S14. ^{1}H and ^{13}C NMR Spectra of 3-(2-(Tosylamino)phenyl)pent-1-yn-3-ol **(1n)**

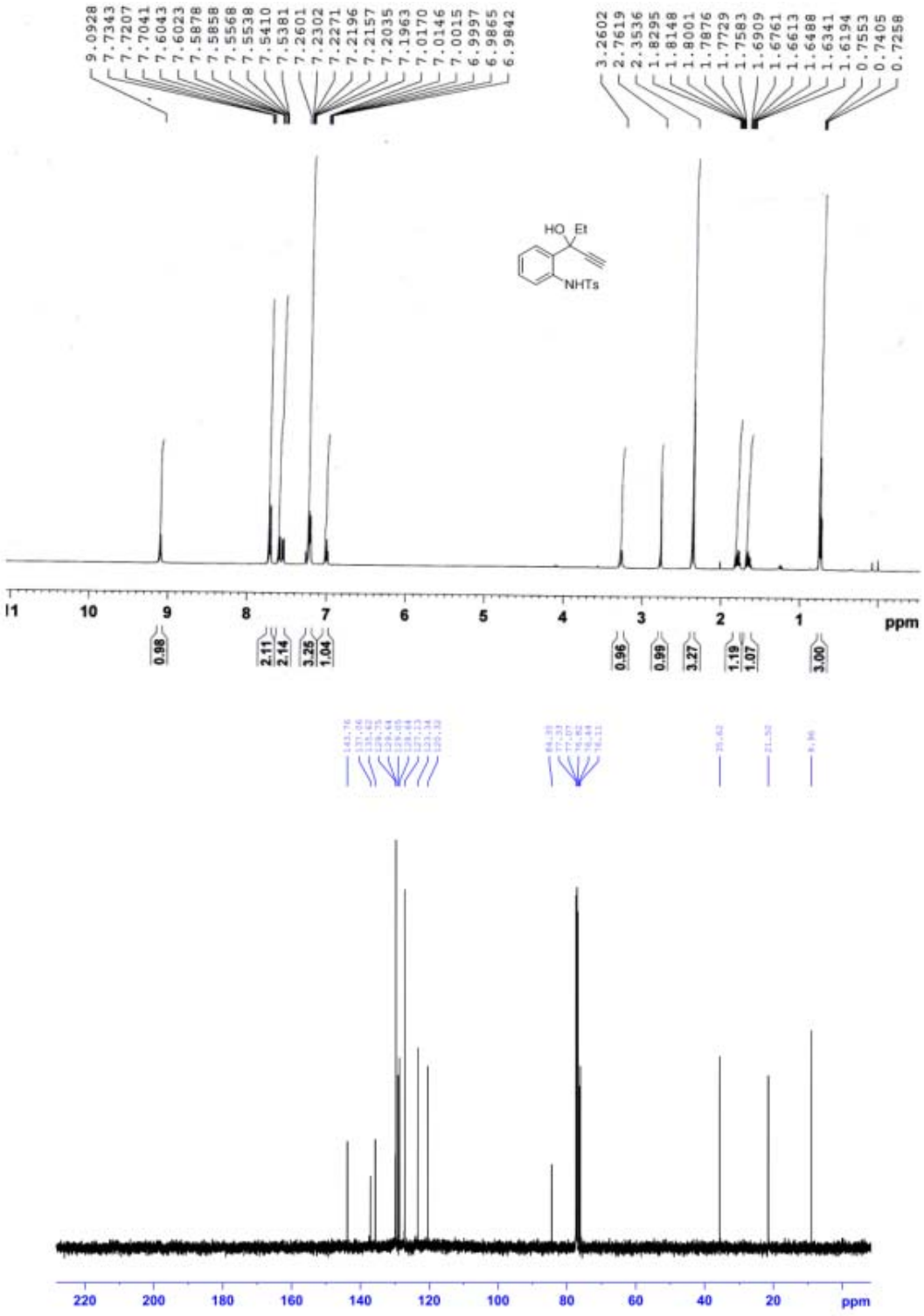


Figure S15. ^{1}H and ^{13}C NMR Spectra of 1-(3,5-Dimethyl-2-(tosylamino)phenyl)prop-2-yn-1-ol **(1o)**

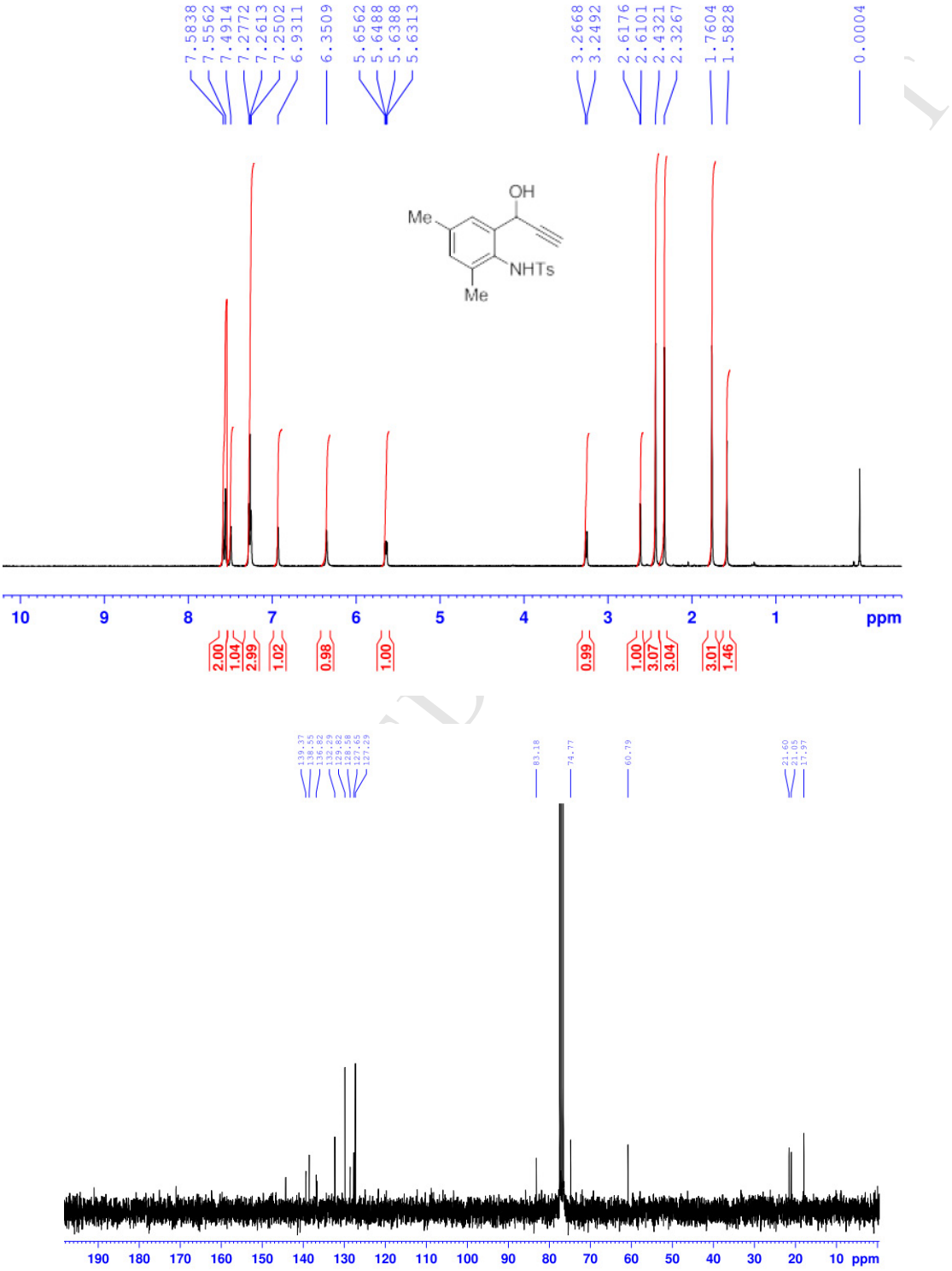


Figure S16. ^{1}H and ^{13}C NMR Spectra of 1-(2-(Tosylamino)phenyl)prop-2-yn-1-ol **(1p)**

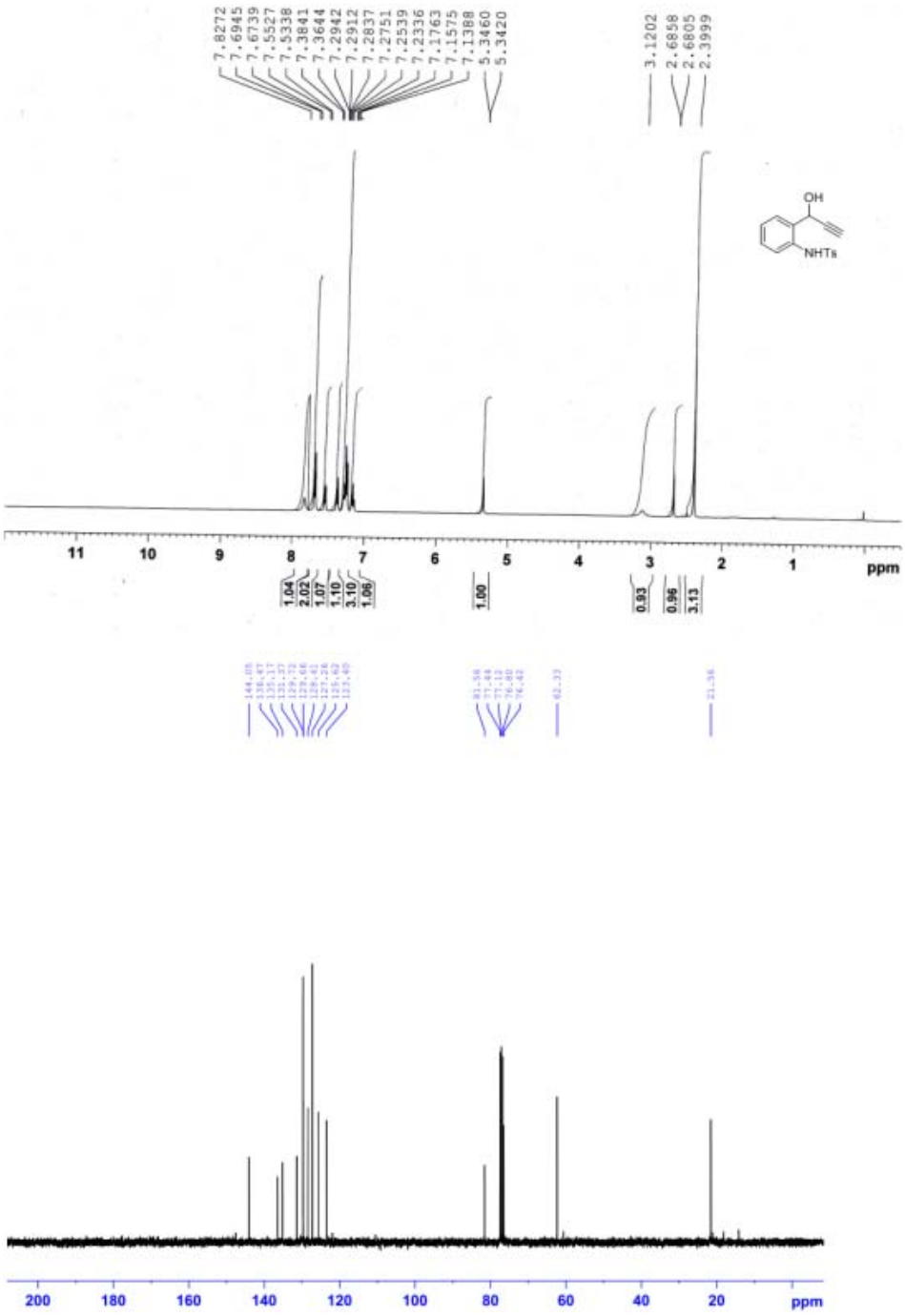


Figure S17. ^{1}H and ^{13}C NMR Spectra of 1-Phenyl-1-(2-(mesylamino)phenyl)prop-2-yn-1-ol **(1q)**

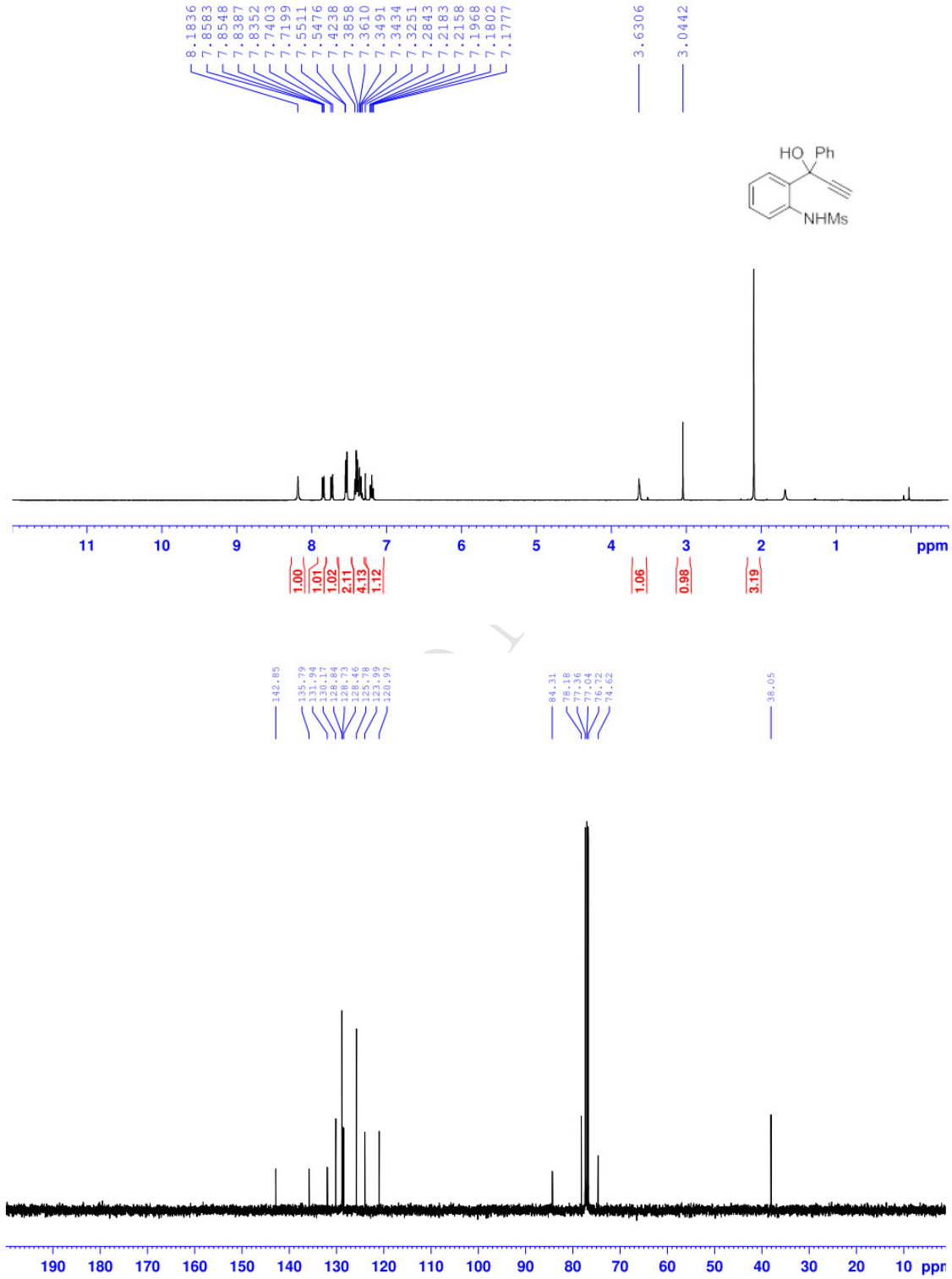


Figure S18. ^{1}H and ^{13}C NMR Spectra of 1-Phenyl-1-(2-(nosylamino)phenyl)prop-2-yn-1-ol **(1r)**

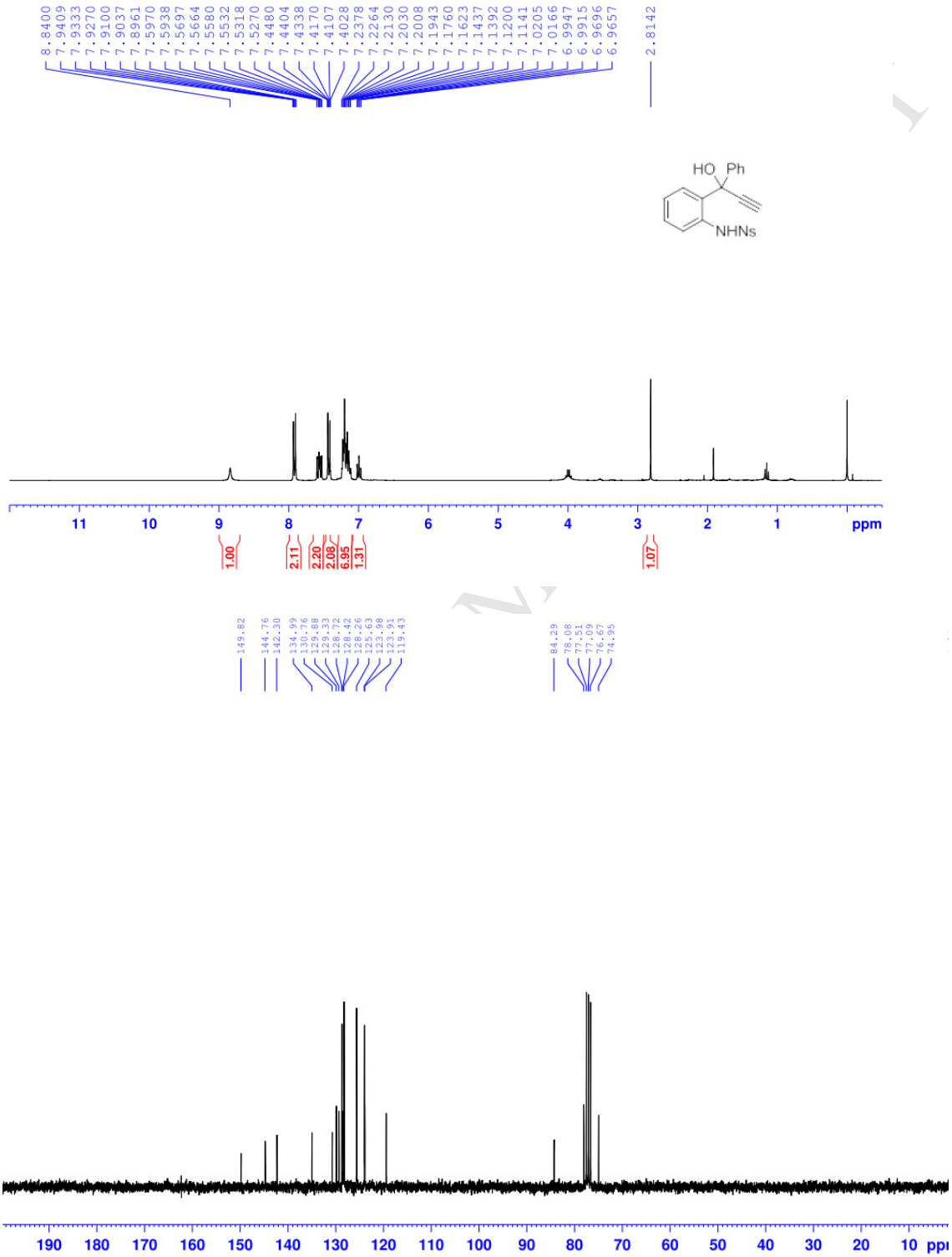


Figure S19. ^{1}H and ^{13}C NMR Spectra of 1-Phenyl-1-(2-(acetylamino)phenyl)prop-2-yn-1-ol **(1s)**

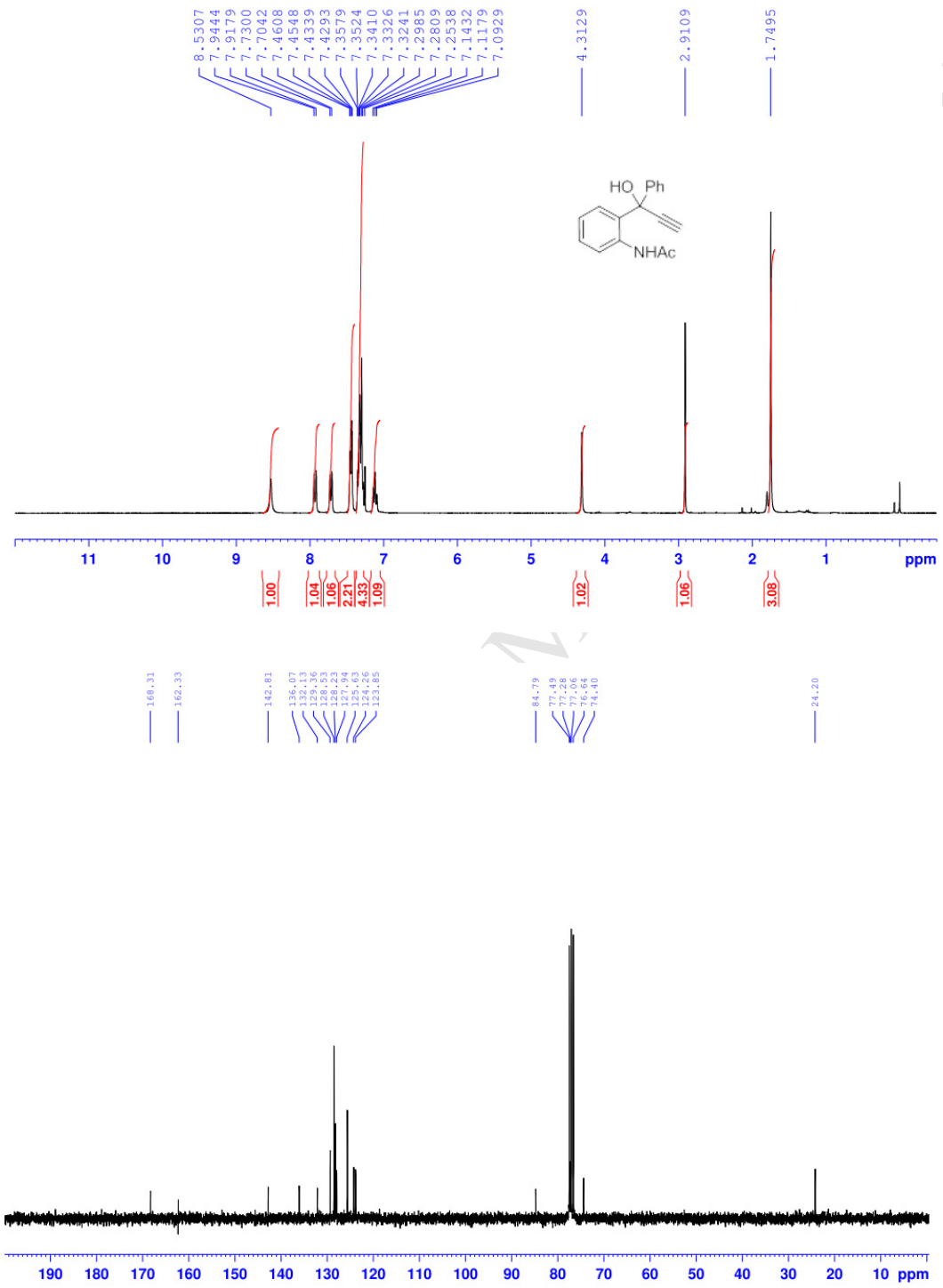


Figure S20. ^{1}H and ^{13}C NMR Spectra of 2-(2-(Acetylamino)phenyl)but-2-yn-1-ol (**1t**)

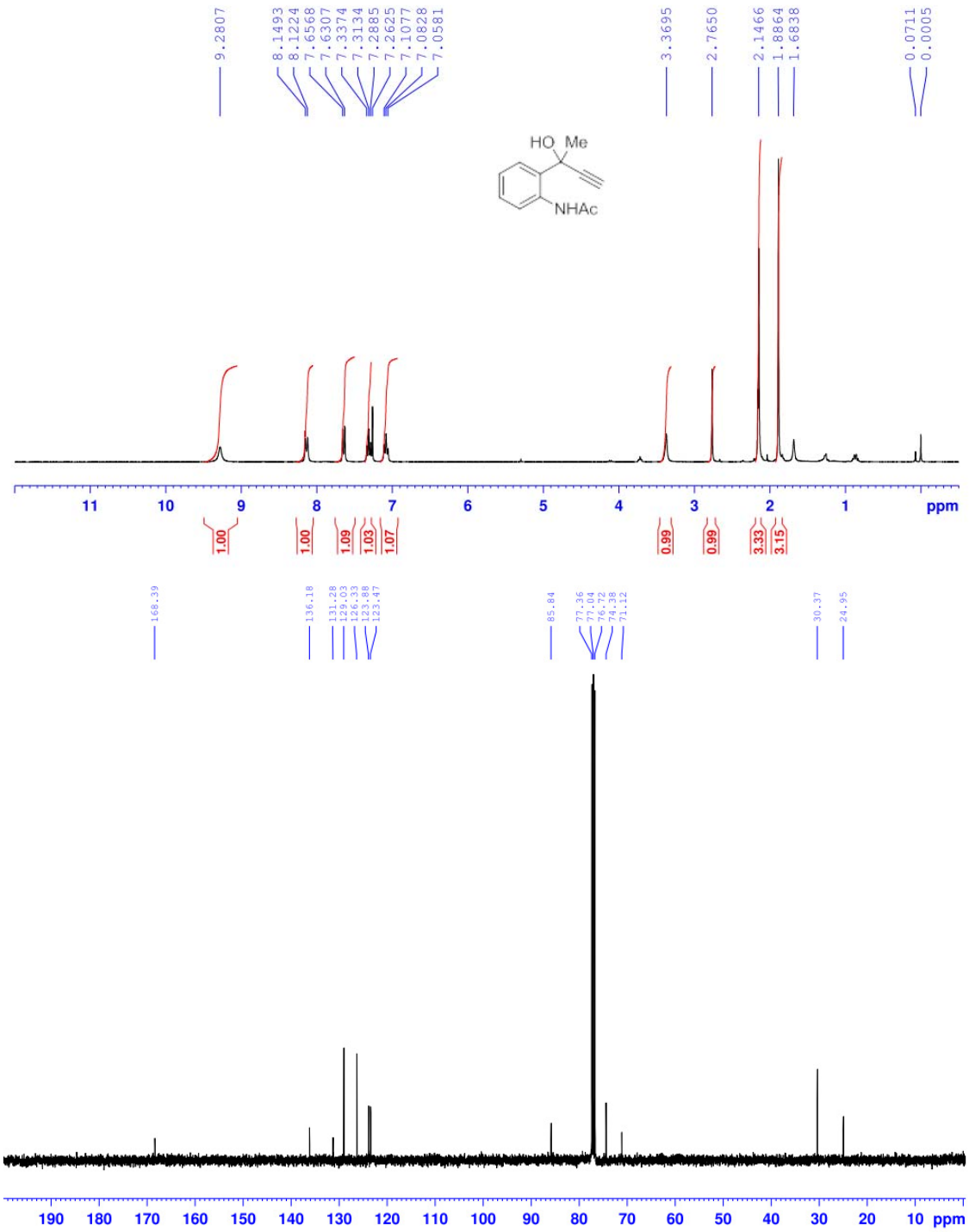


Figure S21. ^{1}H and ^{13}C NMR Spectra of 1-(4-Methyl-2-(acetylamino)phenyl)-1-phenylprop-2-yn-1-ol **(1u)**

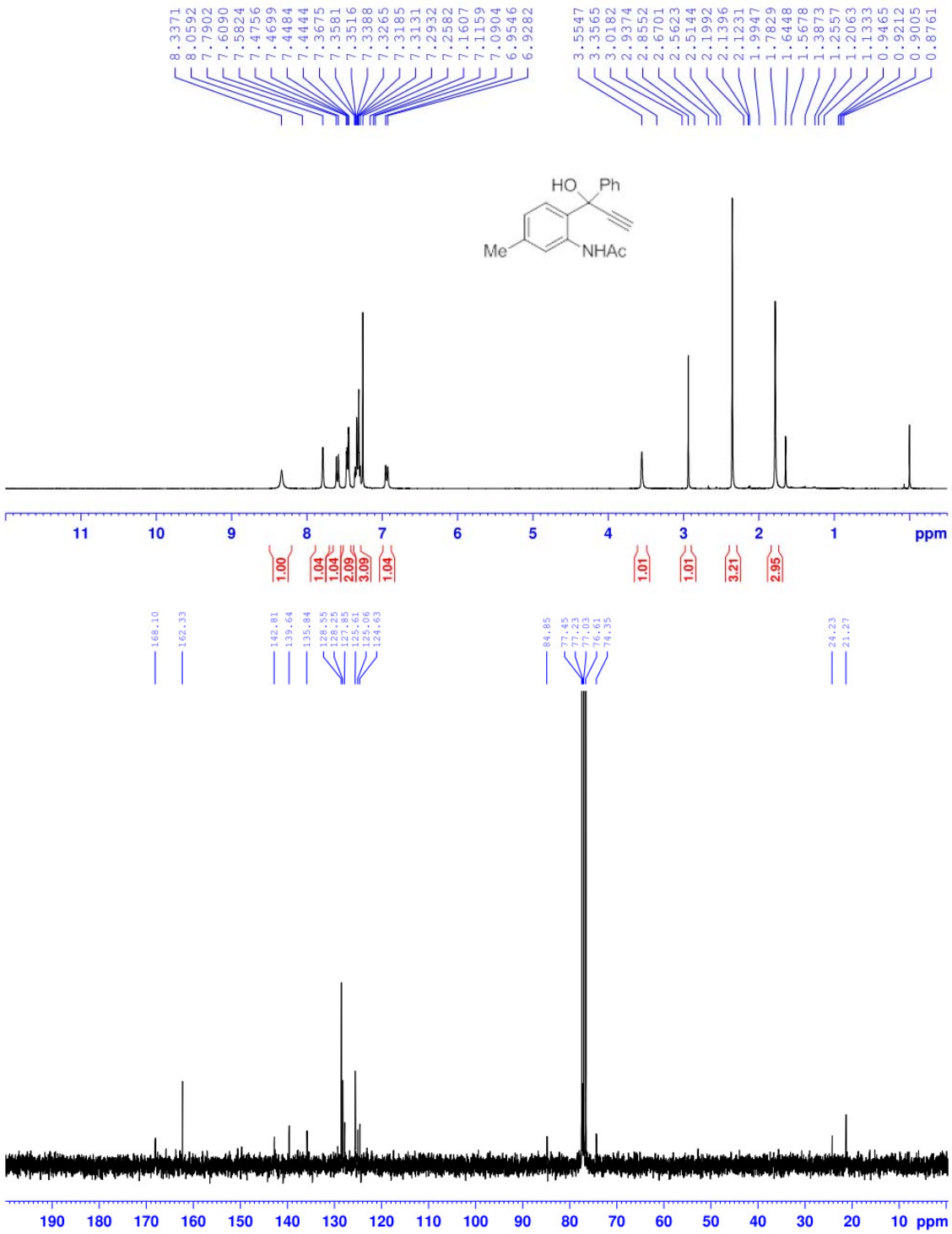


Figure S22. ^{1}H and ^{13}C NMR Spectra of 1-(4-Methyl-2-(acetylamino)phenyl)-1-phenylprop-2-yn-1-ol **(1v)**

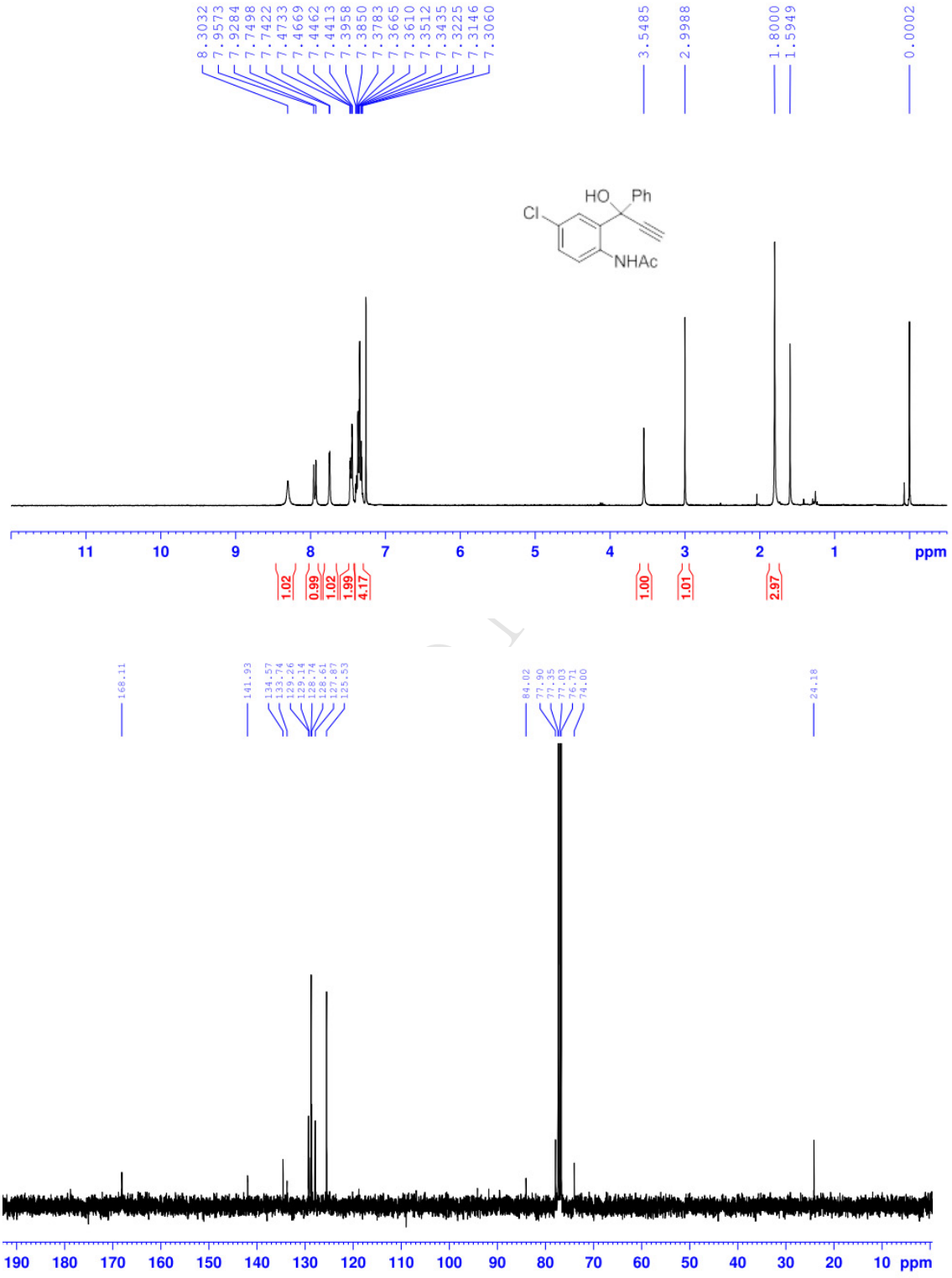


Figure S23. ^{1}H and ^{13}C NMR Spectra of 1-(5-Chloro-2-(tosylamino)phenyl)-1-(2-chlorophenyl)prop-2-yn-1-ol **(1w)**

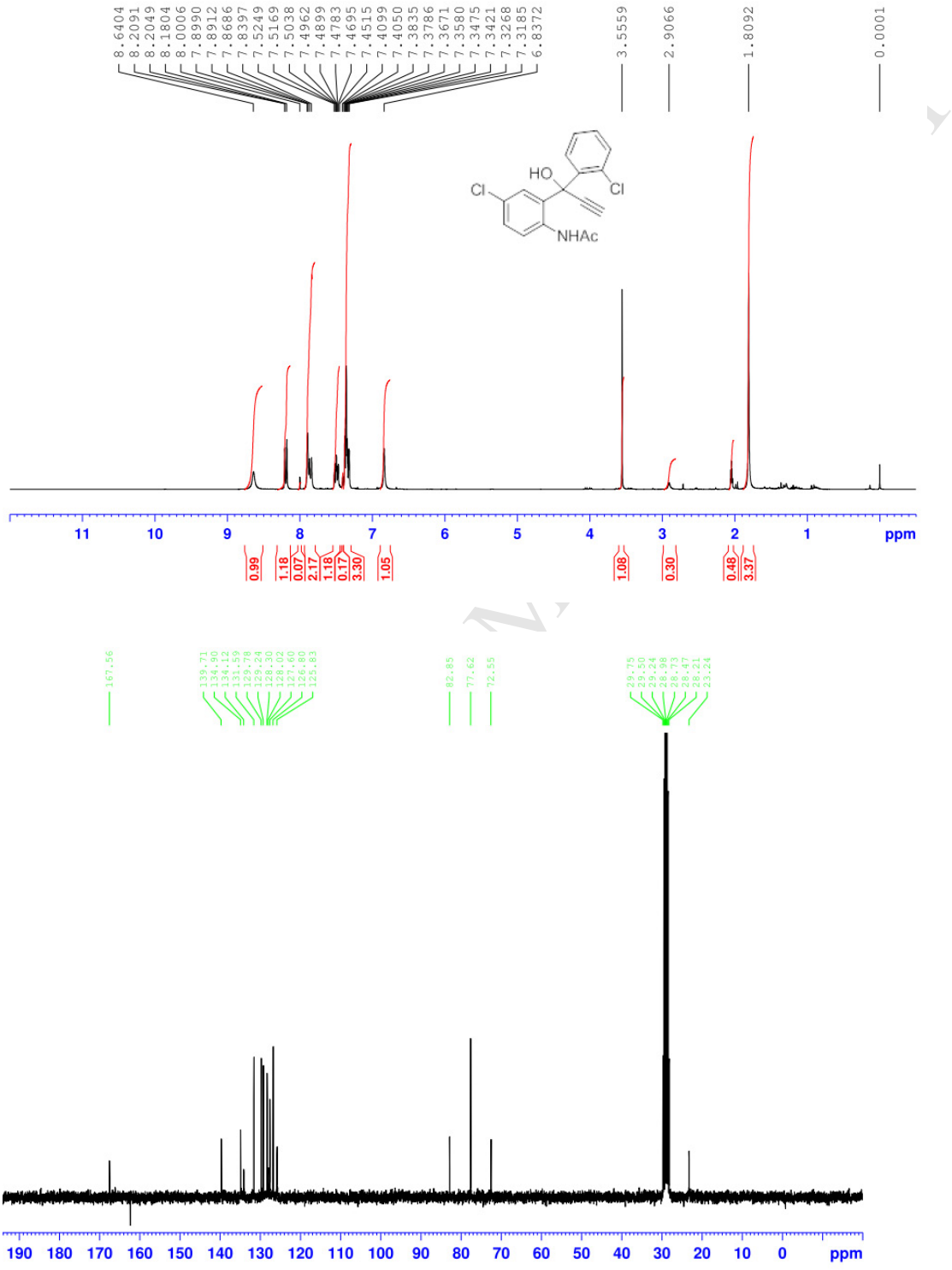


Figure S24. ^{1}H and ^{13}C NMR Spectra of 3-Phenyl-1-tosyl-1*H*-indole-2-carbaldehyde **(4a)**

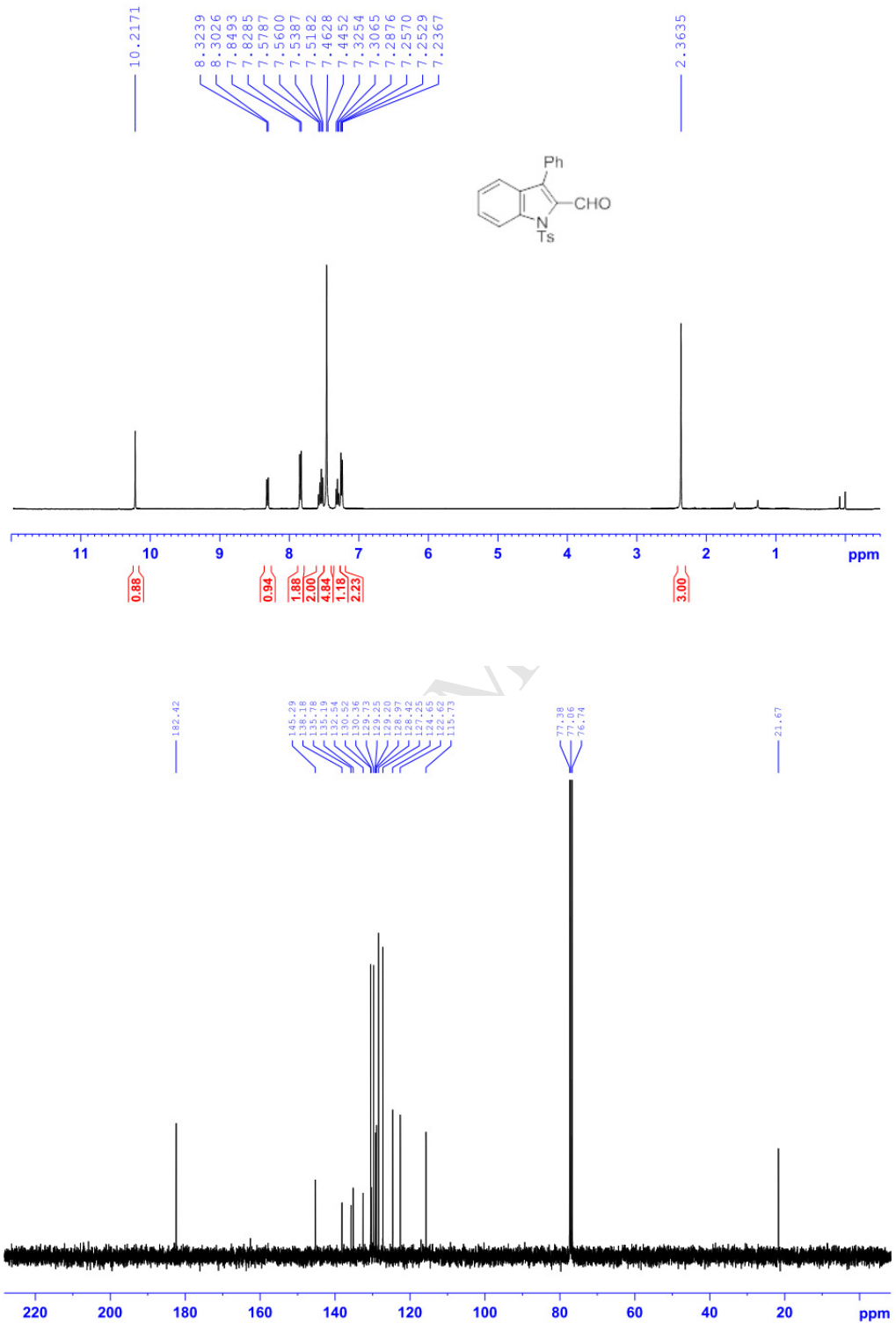


Figure S25. ^{1}H and ^{13}C NMR Spectra of 5-Methyl-3-phenyl-1-tosyl-1*H*-indole-2-carbaldehyde **(4b)**

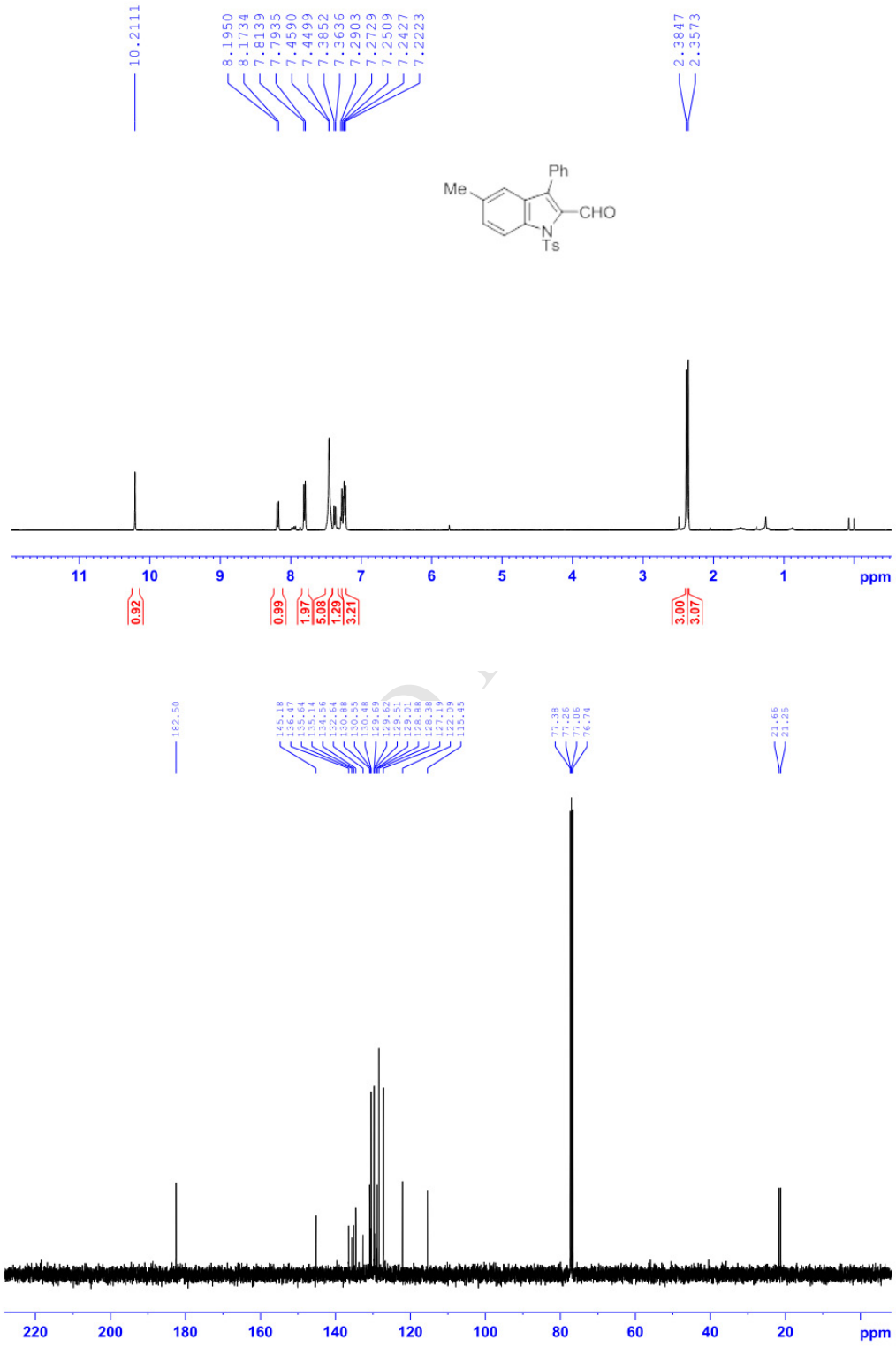


Figure S26. ^{1}H and ^{13}C NMR Spectra of 5-Methoxy-3-phenyl-1-tosyl-1*H*-indole-2-carbaldehyde **(4c)**

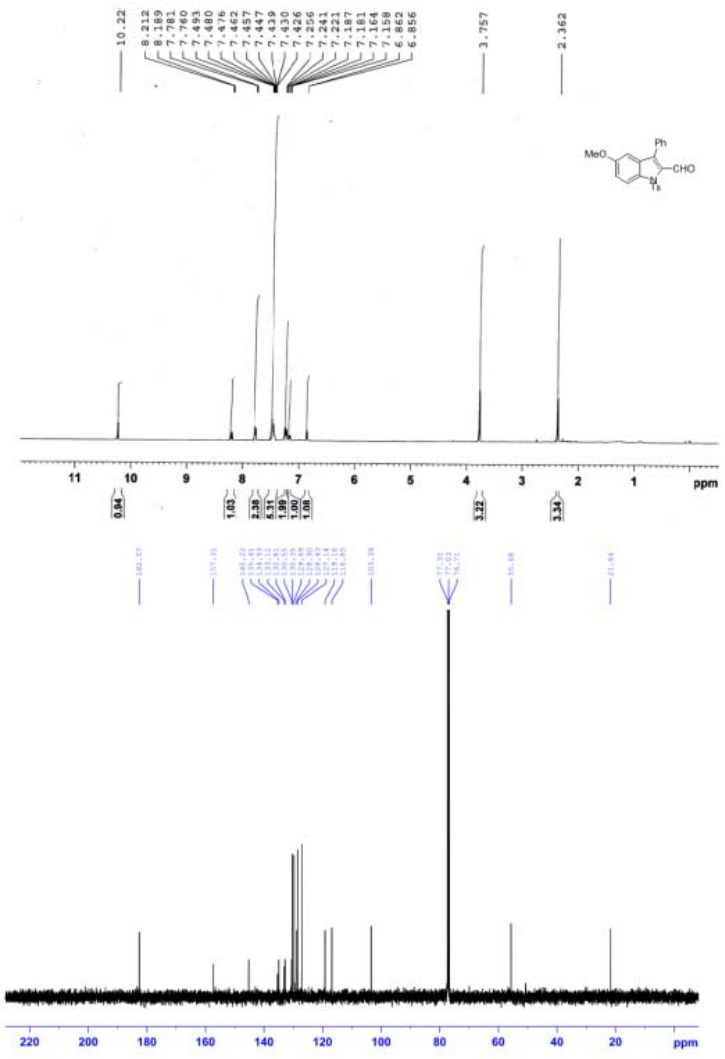
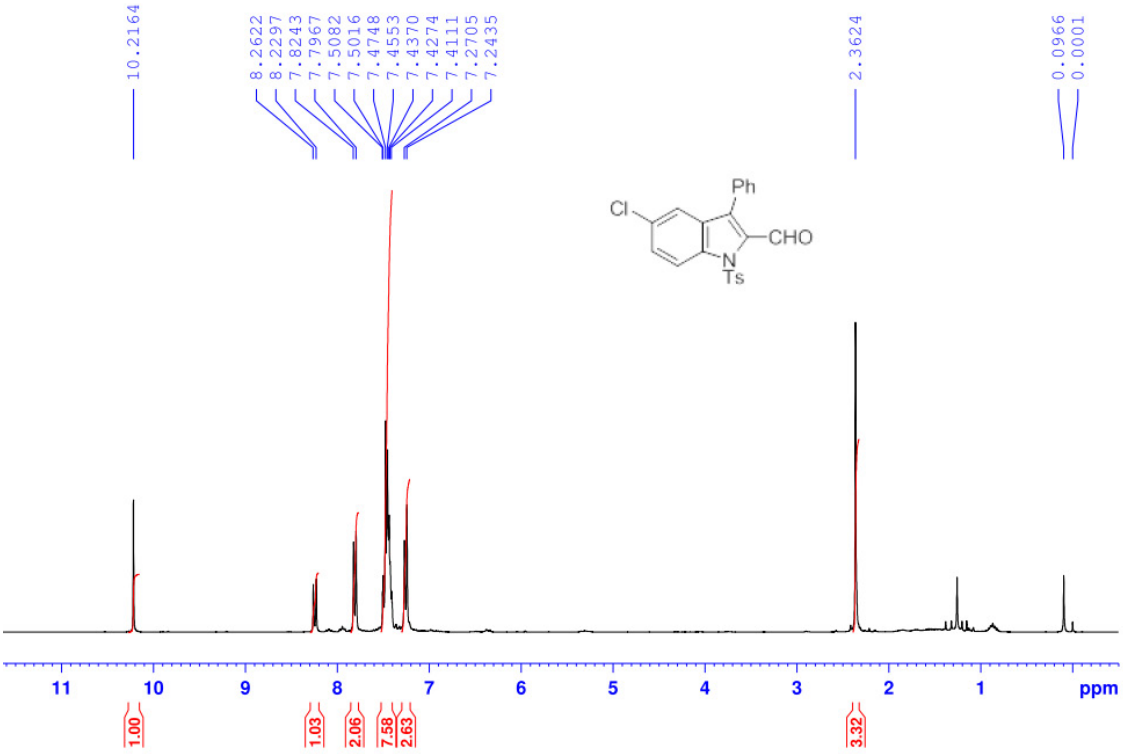


Figure S27. ^{1}H and ^{13}C NMR Spectra of 5-Chloro-3-phenyl-1-tosyl-1*H*-indole-2-carbaldehyde **(4d)**



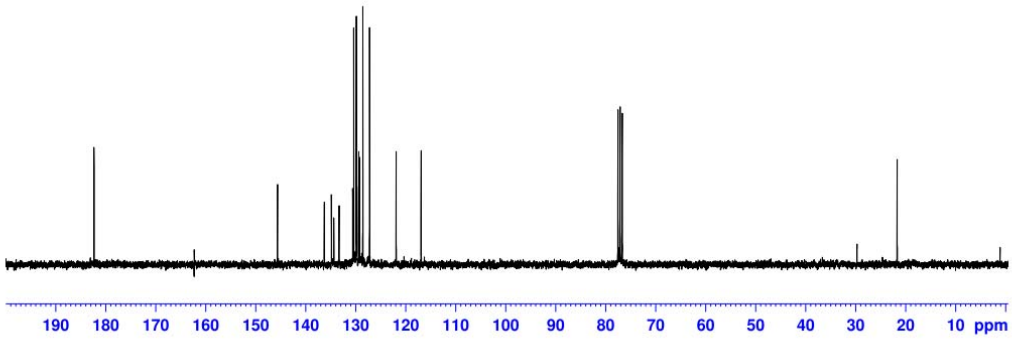


Figure S28. ^{1}H and ^{13}C NMR Spectra of 5-Bromo-3-phenyl-1-tosyl-1*H*-indole-2-carbaldehyde **(4e)**

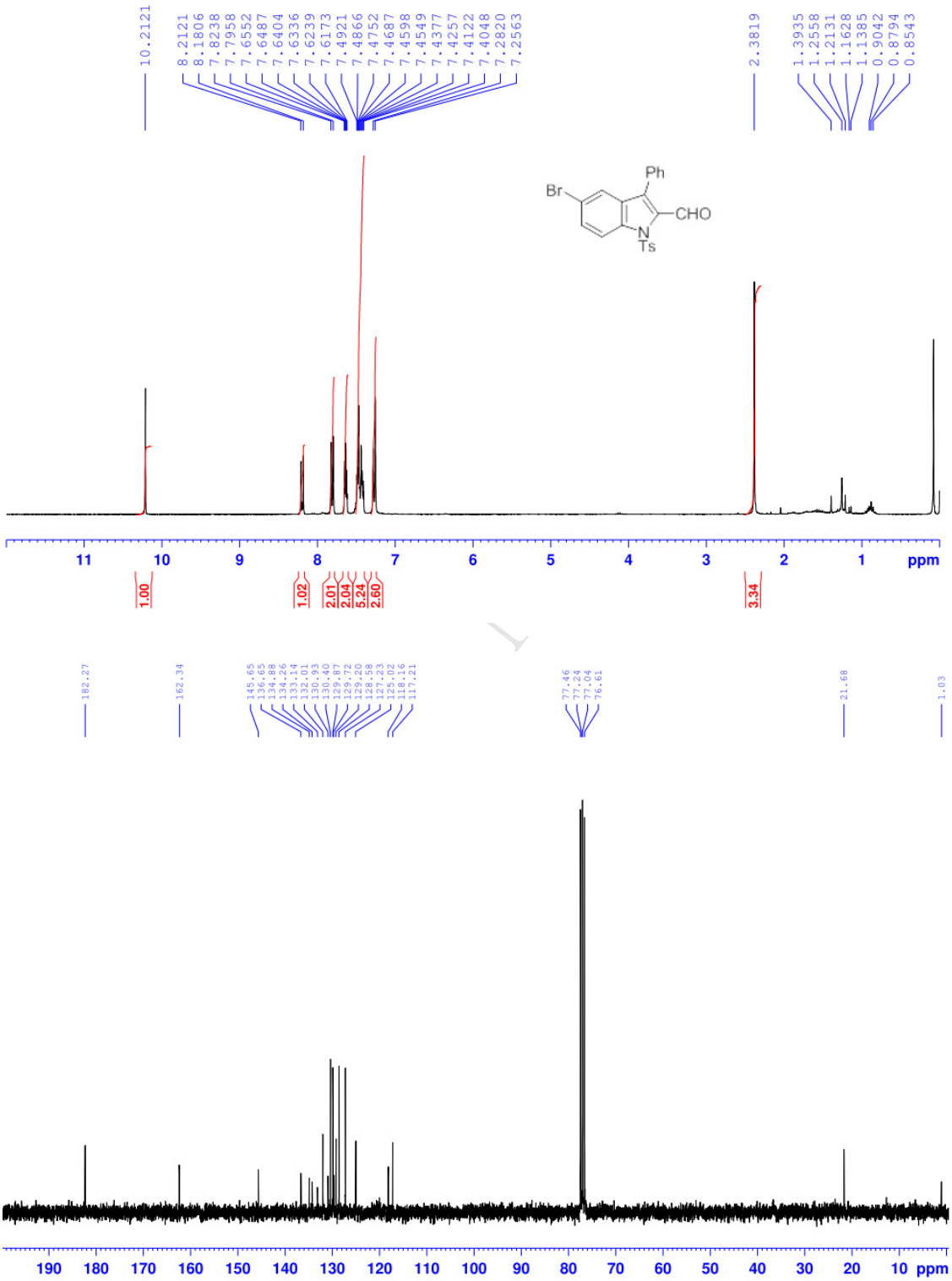


Figure S29. ^{1}H and ^{13}C NMR Spectra of 7-Methyl-3-phenyl-1-tosyl-1*H*-indole-2-carbaldehyde **(4f)**

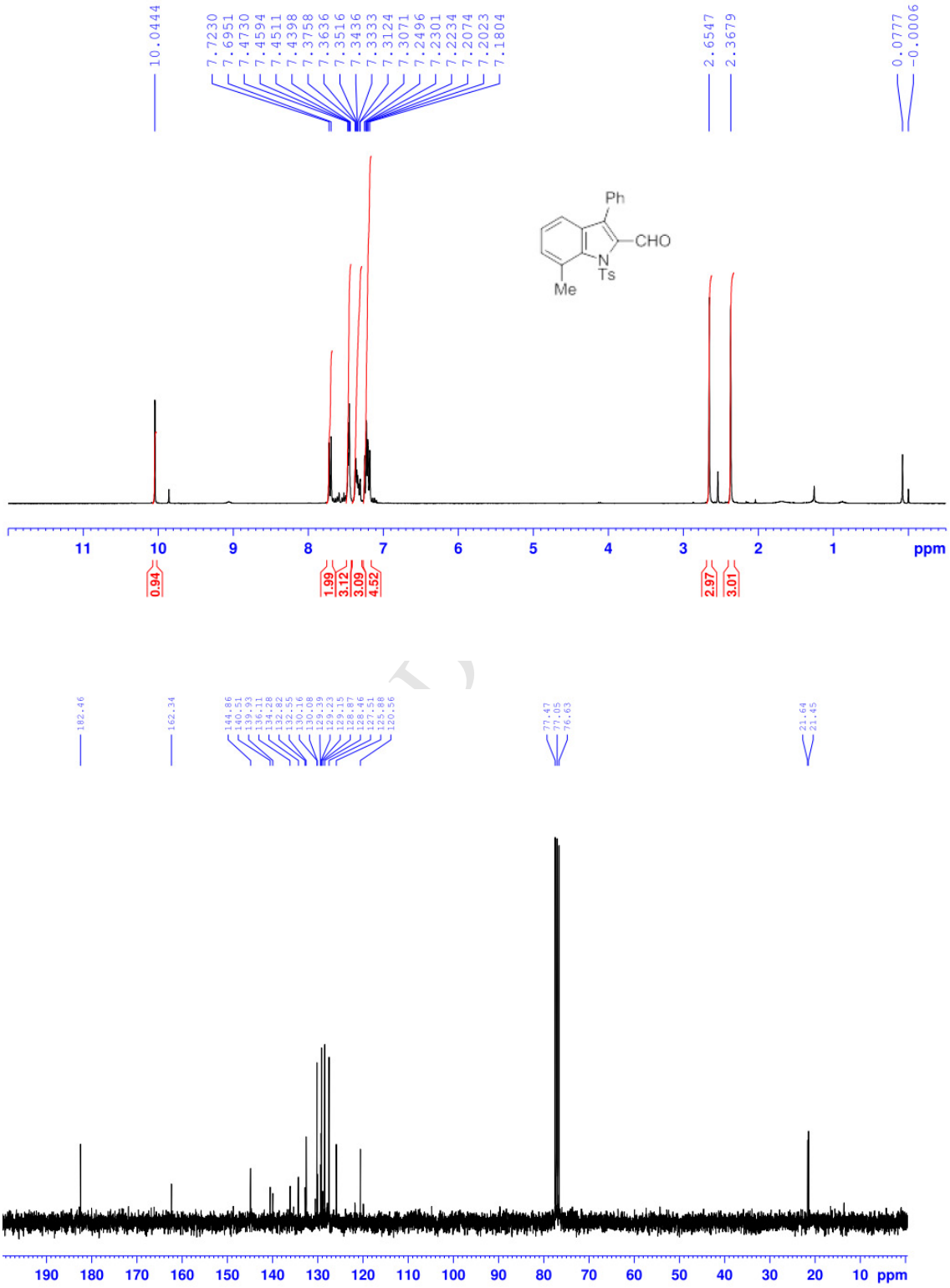


Figure S30. ^{1}H and ^{13}C NMR Spectra of 3-Phenyl-1-tosyl-1*H*-benzo[*f*]indole-2-carbaldehyde **(4g)**

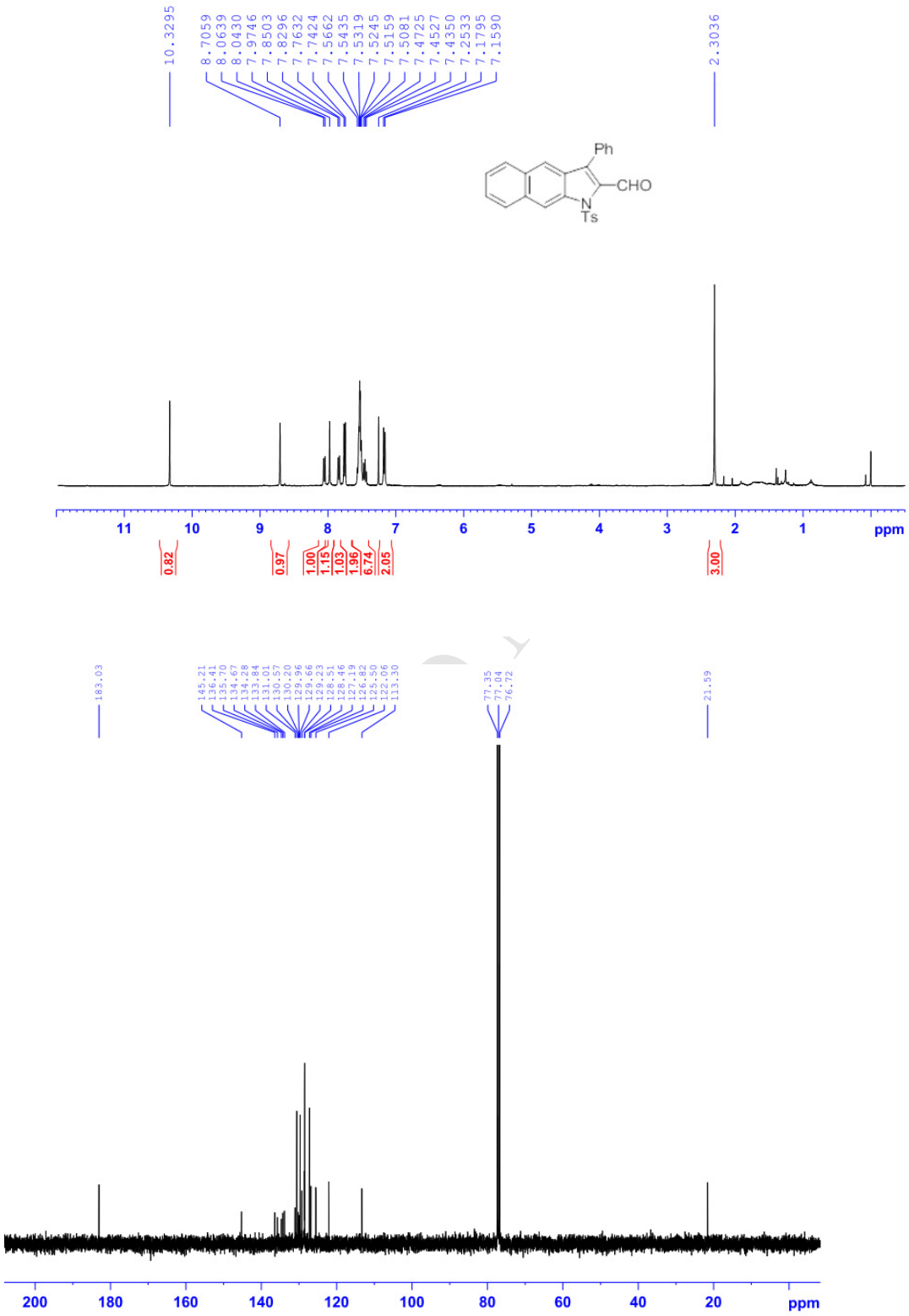


Figure S31. ^{1}H and ^{13}C NMR Spectra of 7-methyl-5-tosyl-5*H*-[1,3]dioxolo[4,5-*f*]indole-6-carbaldehyde **(4h)**

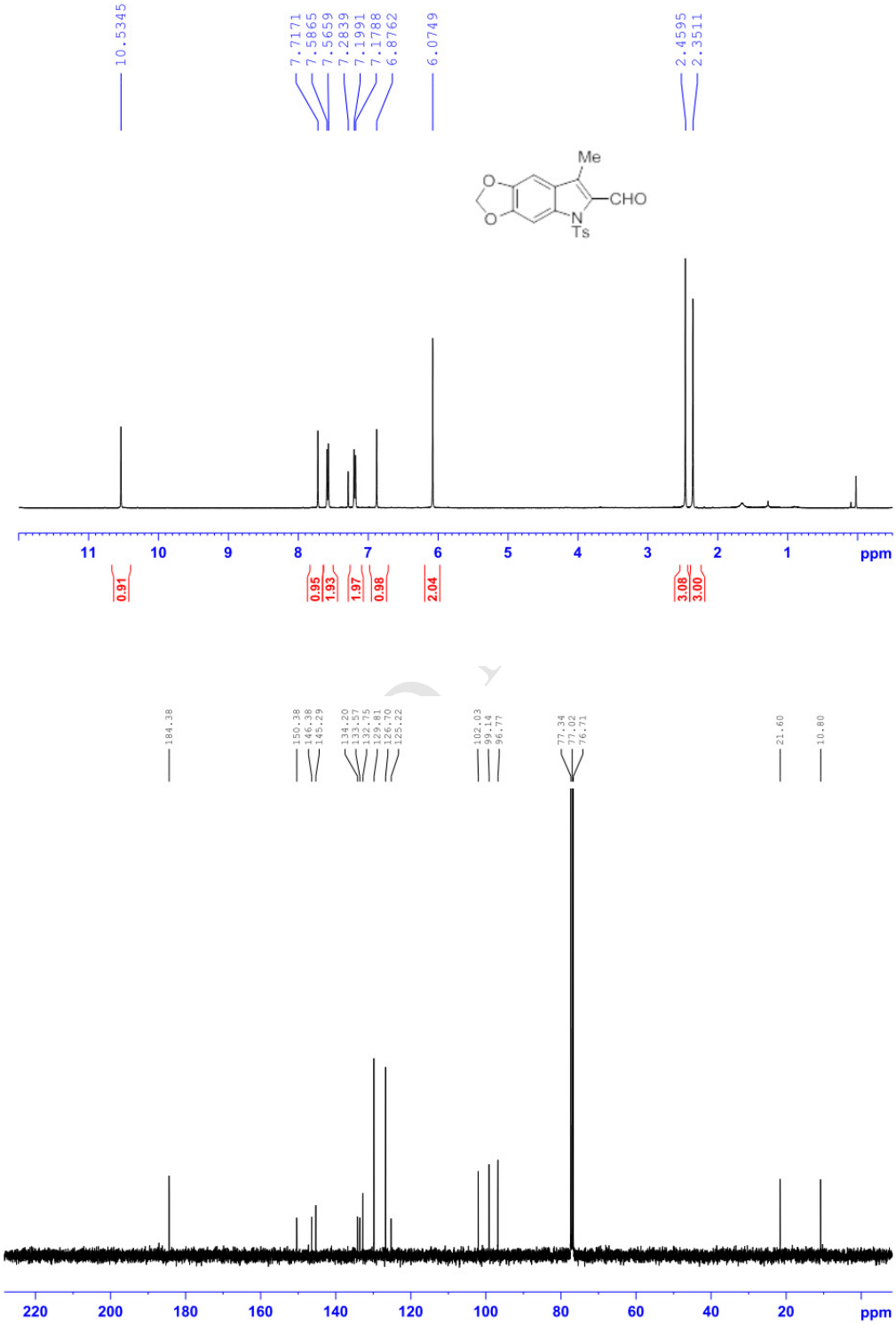


Figure S32. ^{1}H and ^{13}C NMR Spectra of 3-*p*-Tolyl-1-tosyl-1*H*-indole-2-carbaldehyde **(4i)**

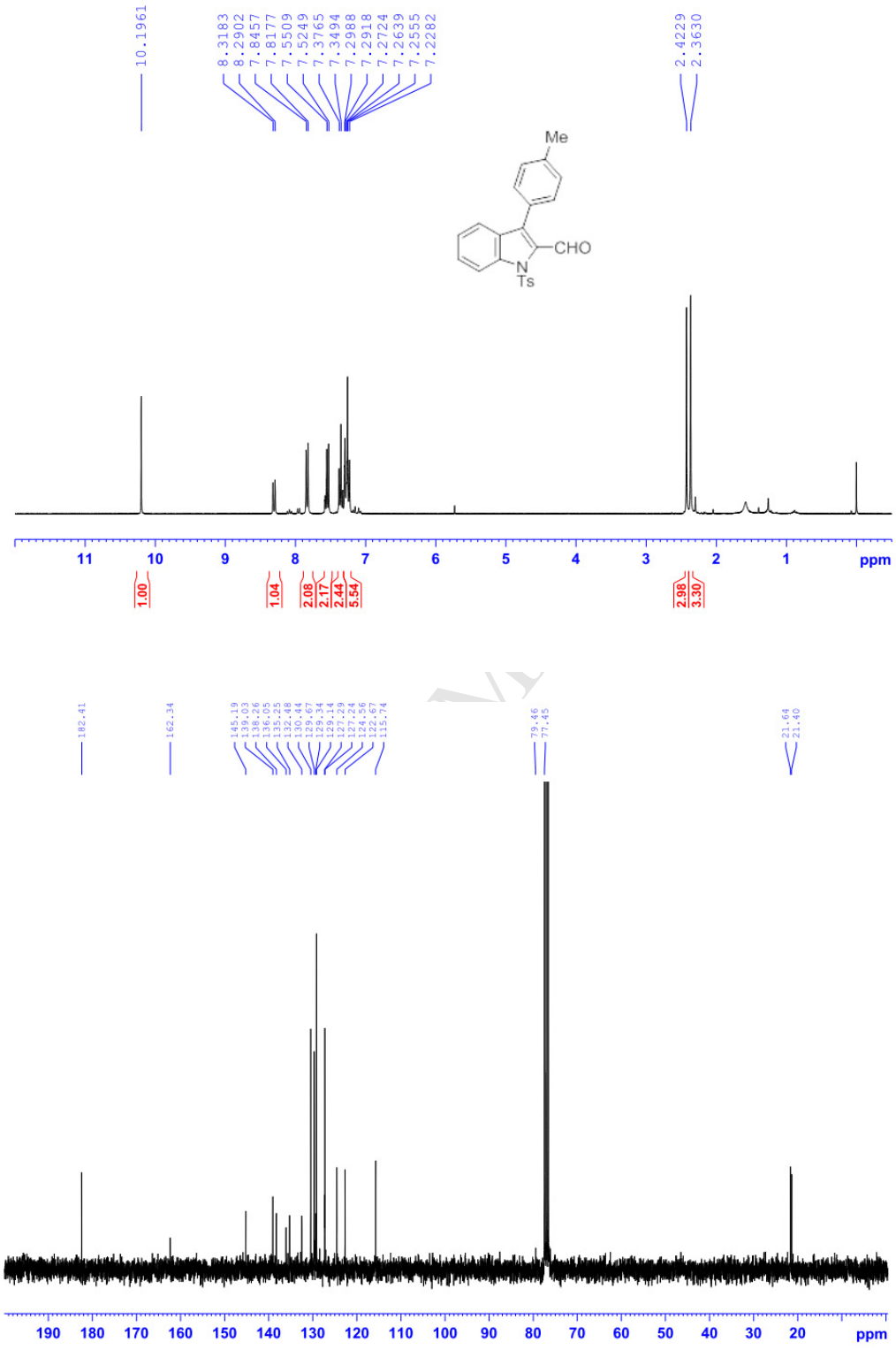


Figure S33. ^{1}H and ^{13}C NMR Spectra of 3-(4-Chlorophenyl)-1-tosyl-1*H*-indole-2-carbaldehyde **(4j)**

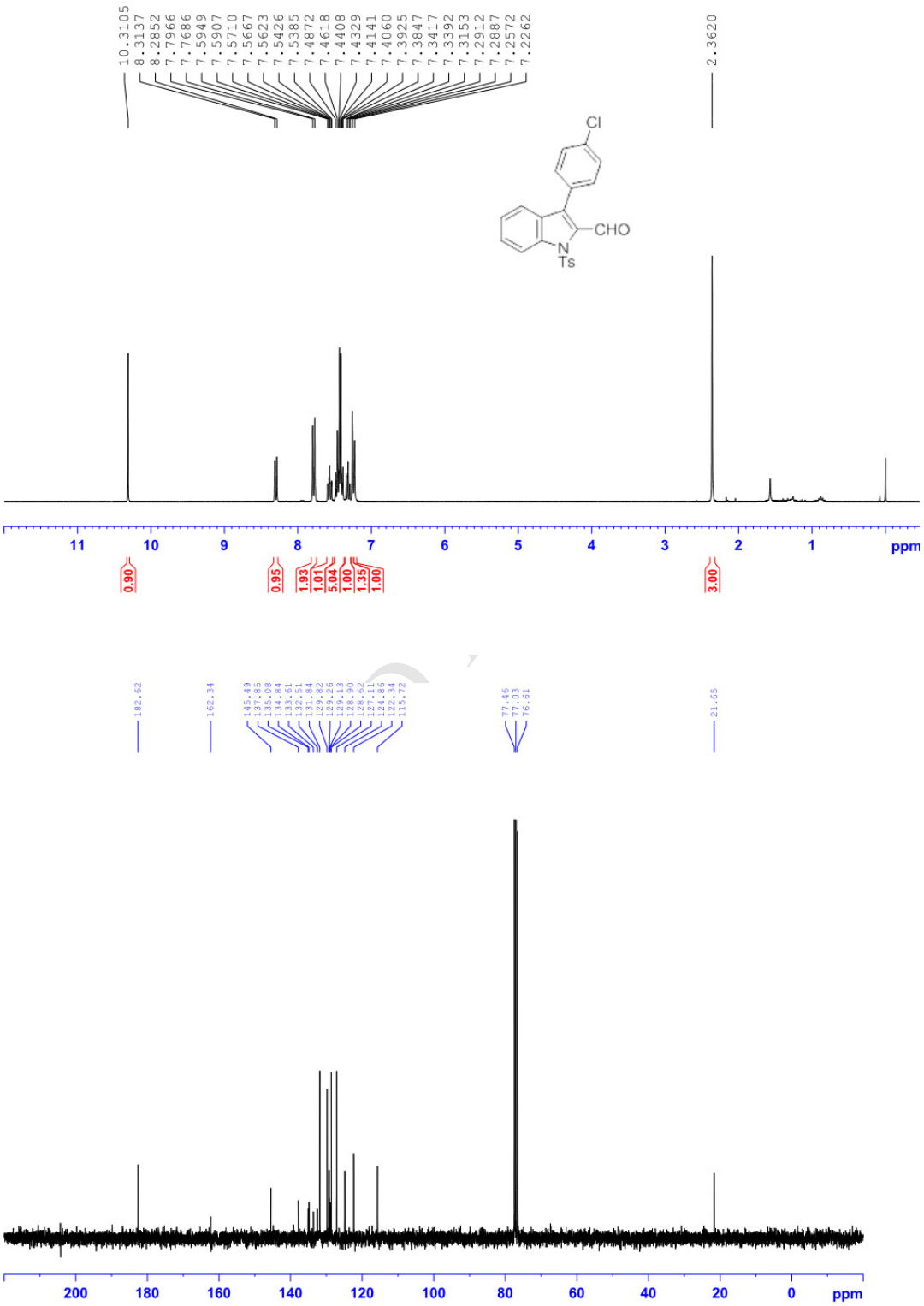


Figure S34. ^{1}H and ^{13}C NMR Spectra of 3-*o*-Tolyl-1-tosyl-1*H*-indole-2-carbaldehyde **(4k)**

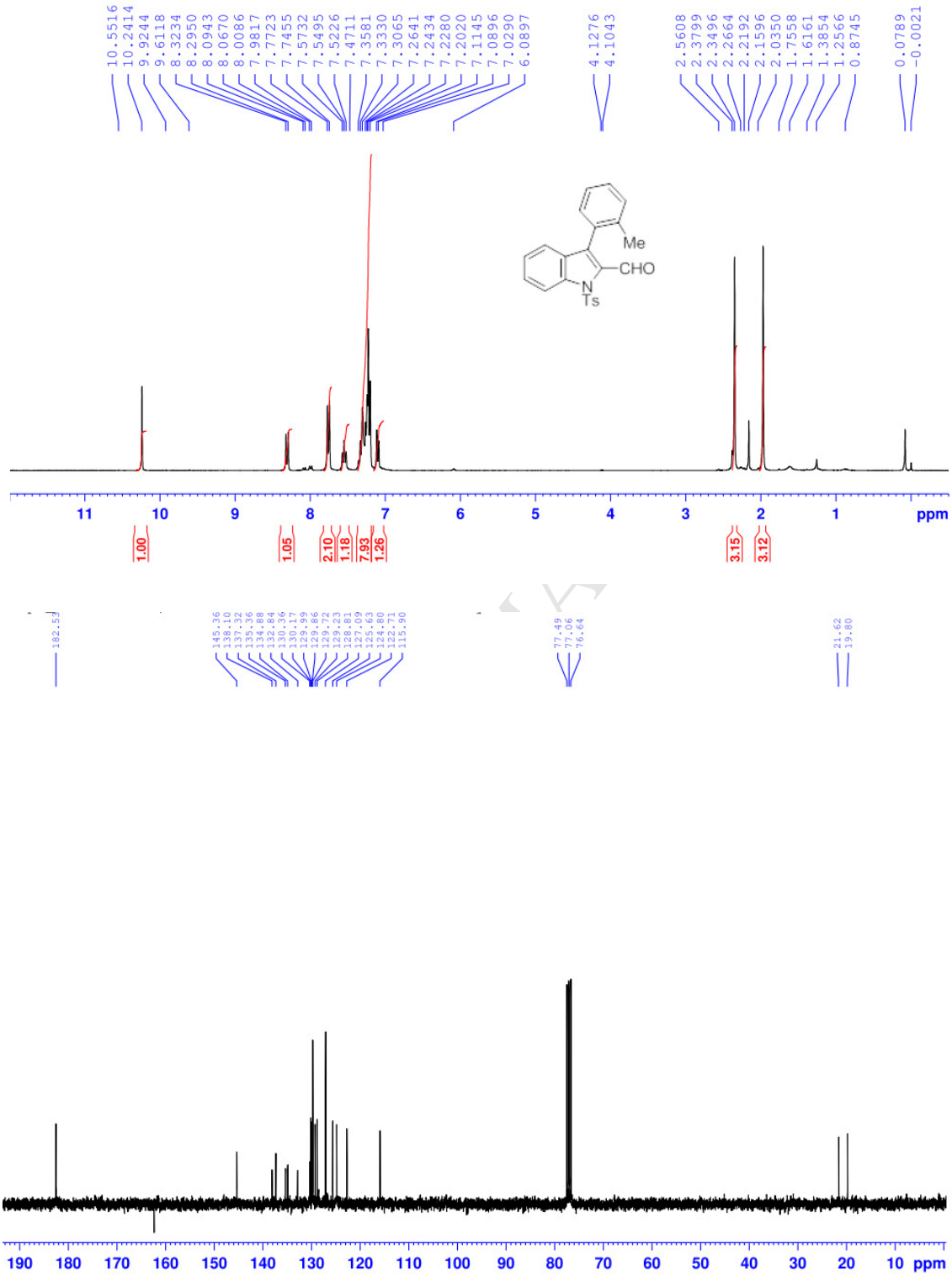


Figure S35. ^{1}H and ^{13}C NMR Spectra of 5-chloro-3-(2-fluorophenyl)-1-tosyl-1*H*-indole-2-carbaldehyde **(4l)**

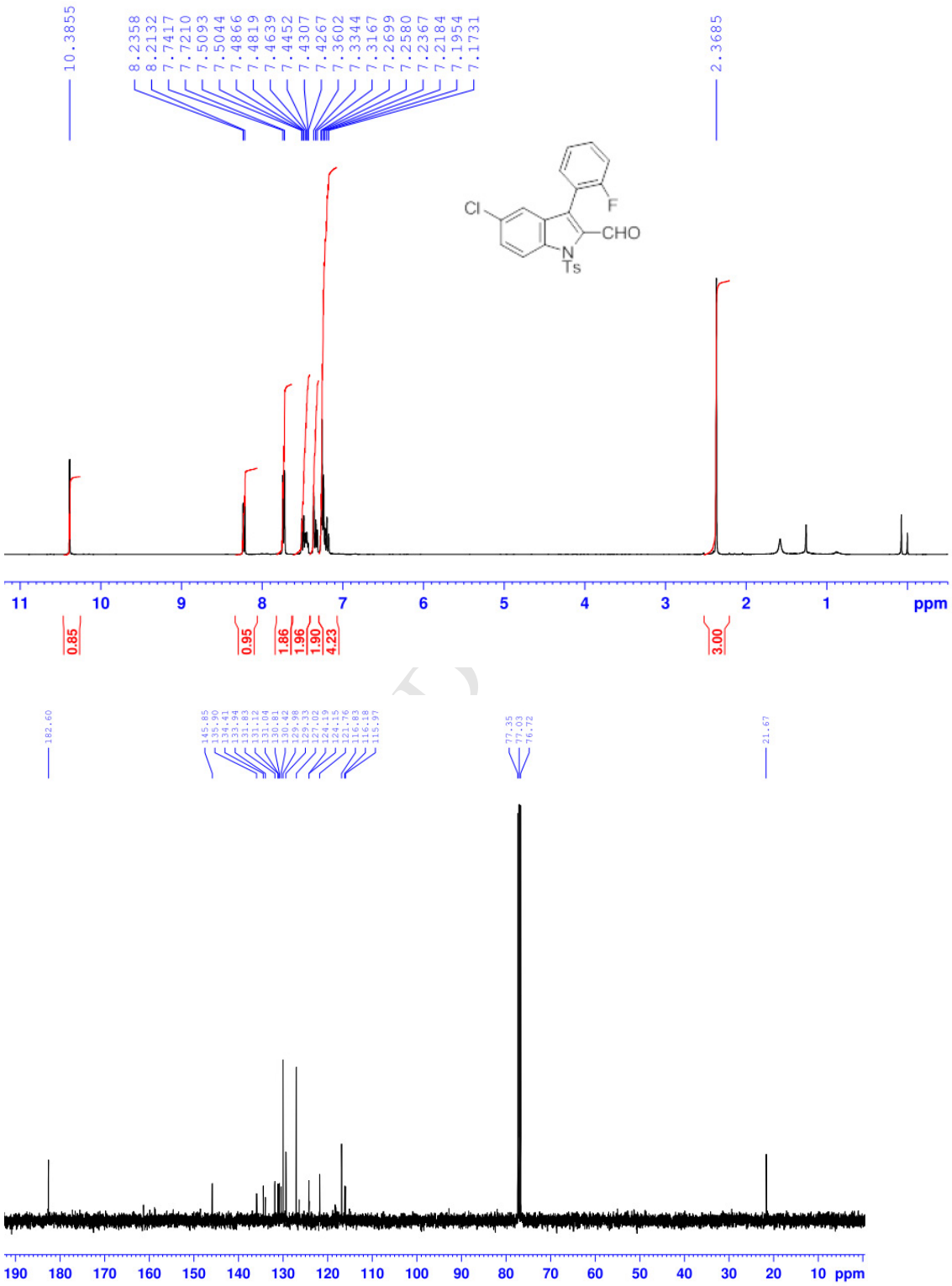


Figure S36. ^{1}H and ^{13}C NMR Spectra of 3-Methyl-1-tosyl-1*H*-indole-2-carbaldehyde **(4m)**

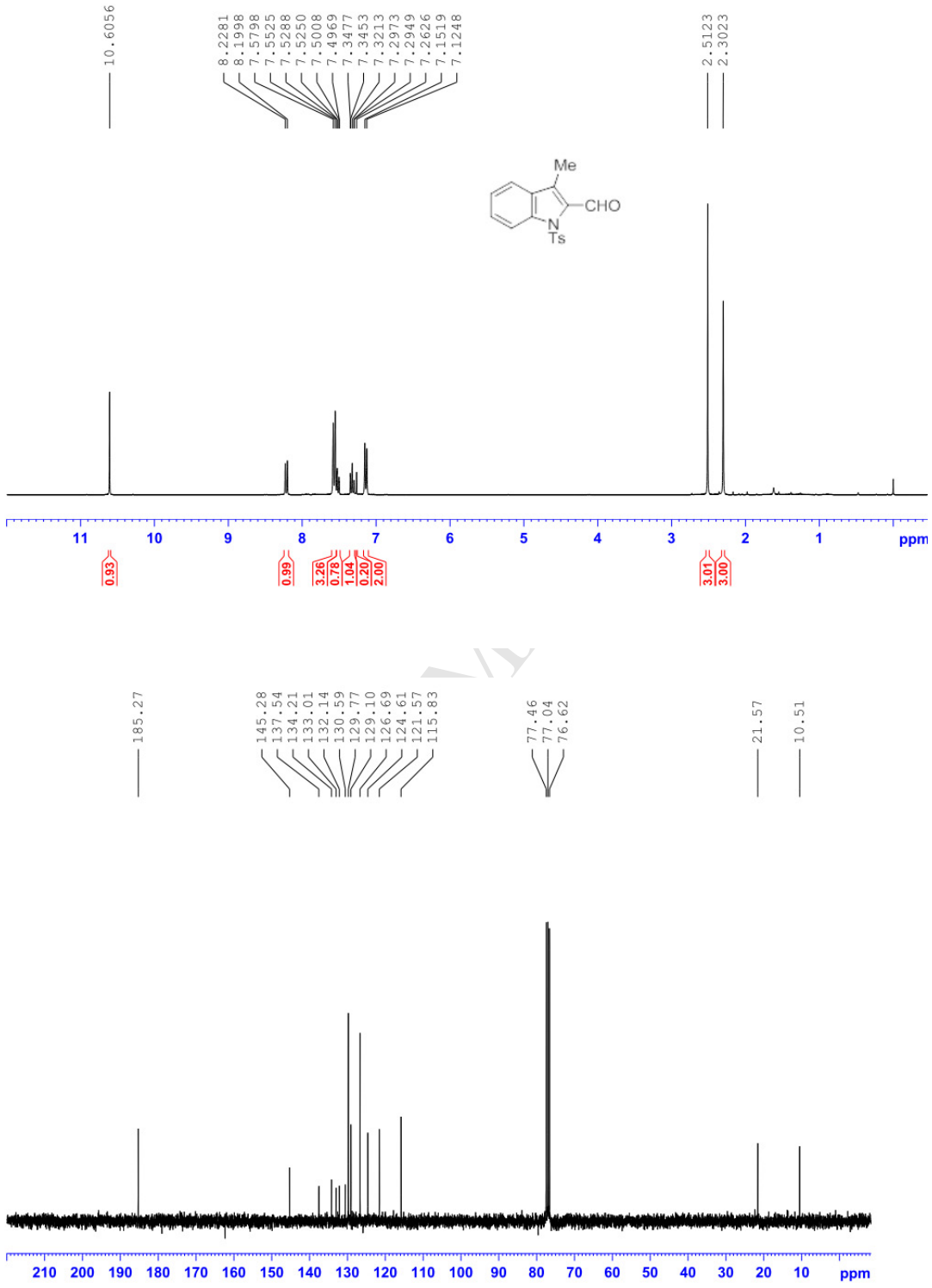


Figure S37. ^{1}H and ^{13}C NMR Spectra of 3-ethyl-1-tosyl-1H-indole-2-carbaldehyde **(4n)**

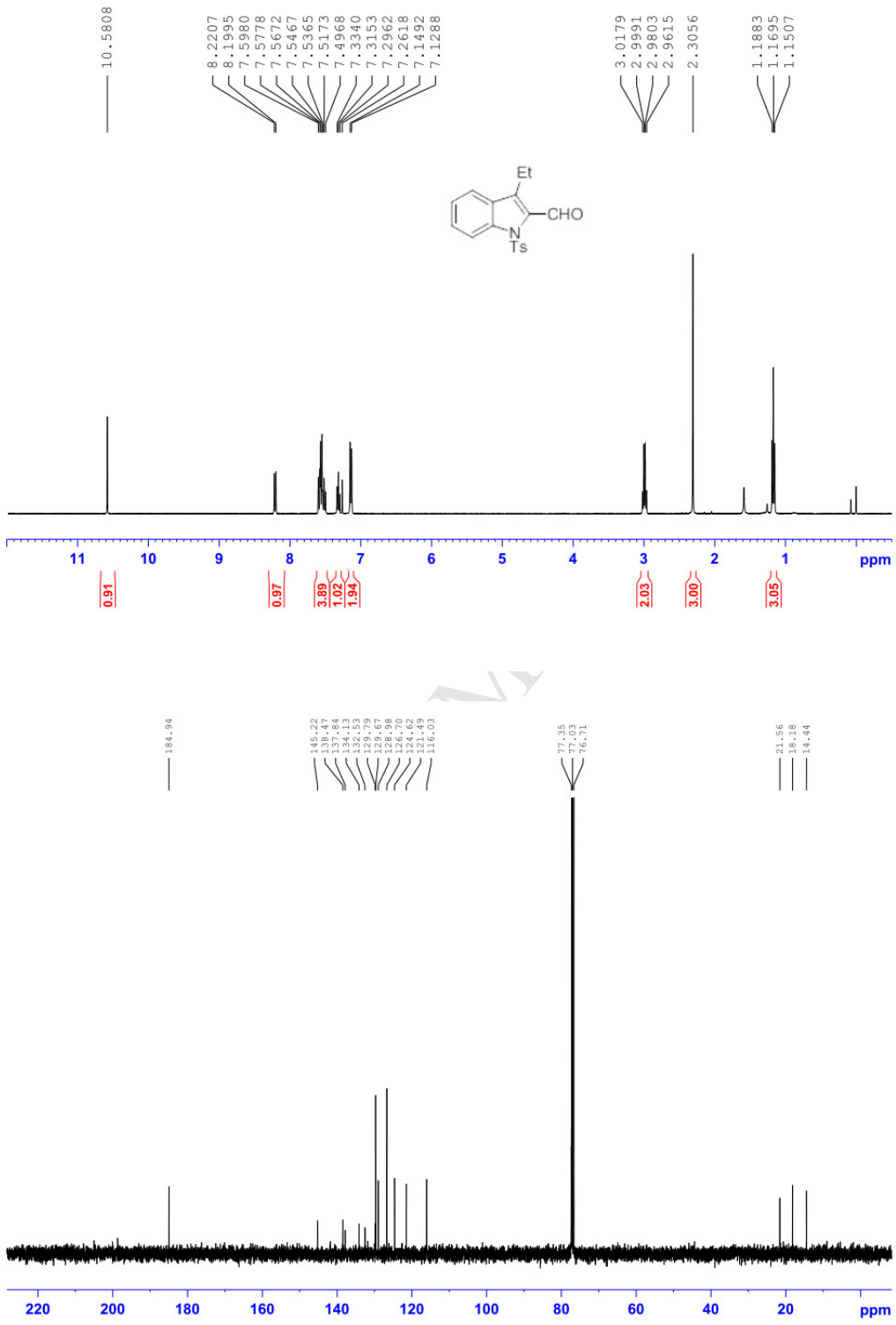


Figure S38. ^{1}H and ^{13}C NMR Spectra of 5,7-Methyl-1-tosyl-1*H*-indole-2-carbaldehyde **(4o)**

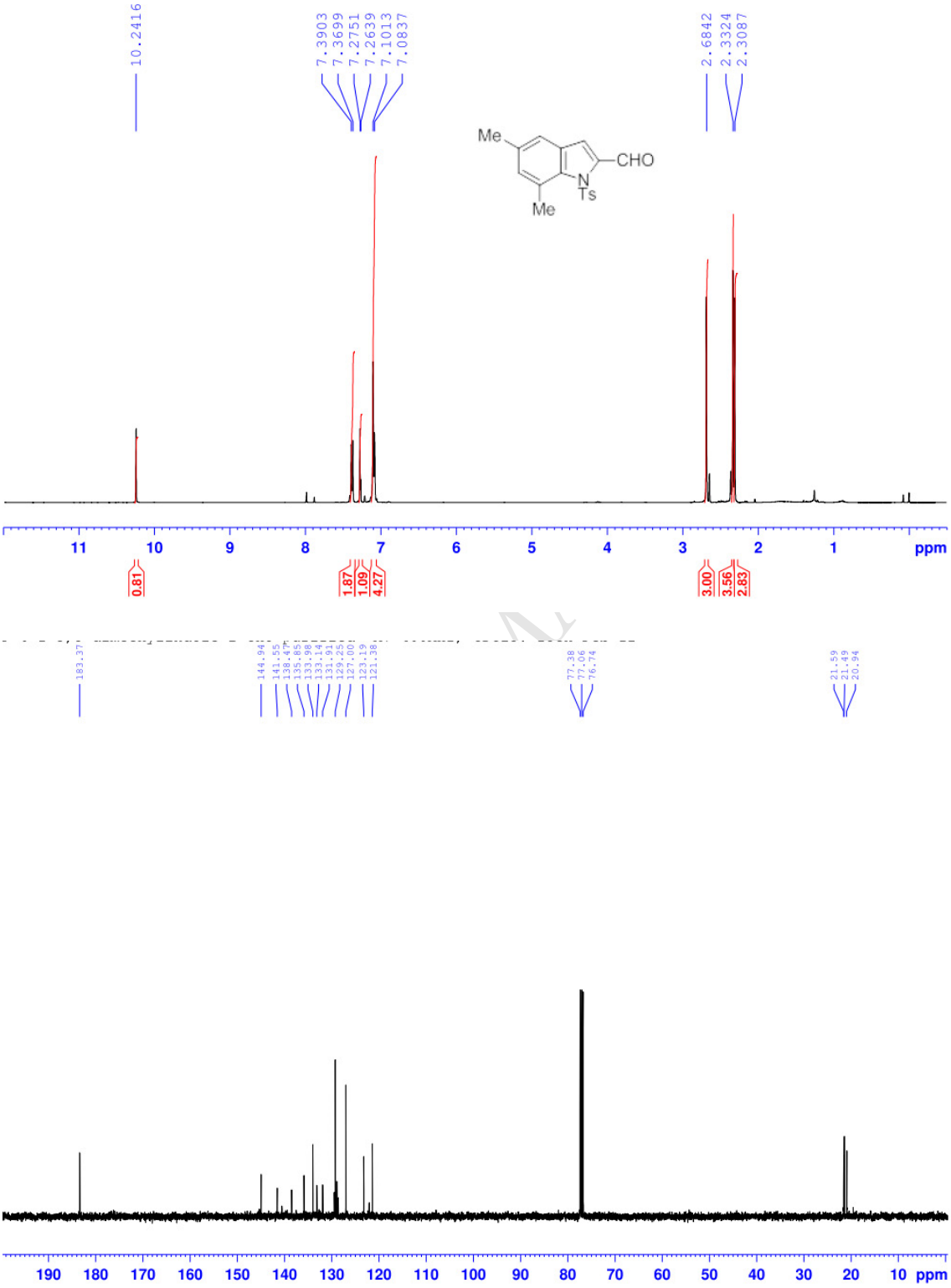


Figure S39. ^{1}H and ^{13}C NMR Spectra of 1-tosyl-1H-indole-2-carbaldehyde **(4p)**

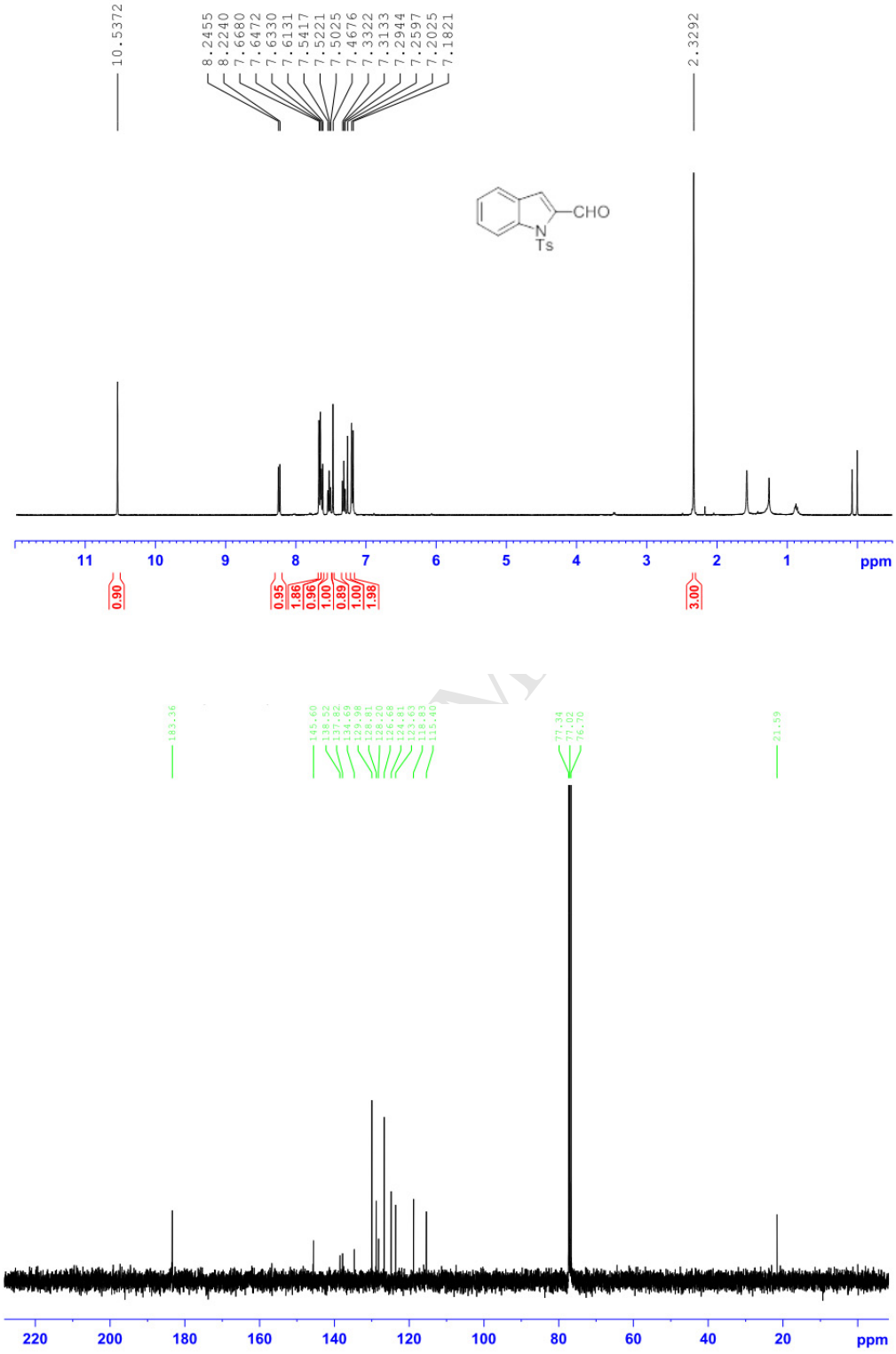


Figure S40. ^{1}H and ^{13}C NMR Spectra of 3-Phenyl-1-mesyl-1*H*-indole-2-carbaldehyde **(4q)**

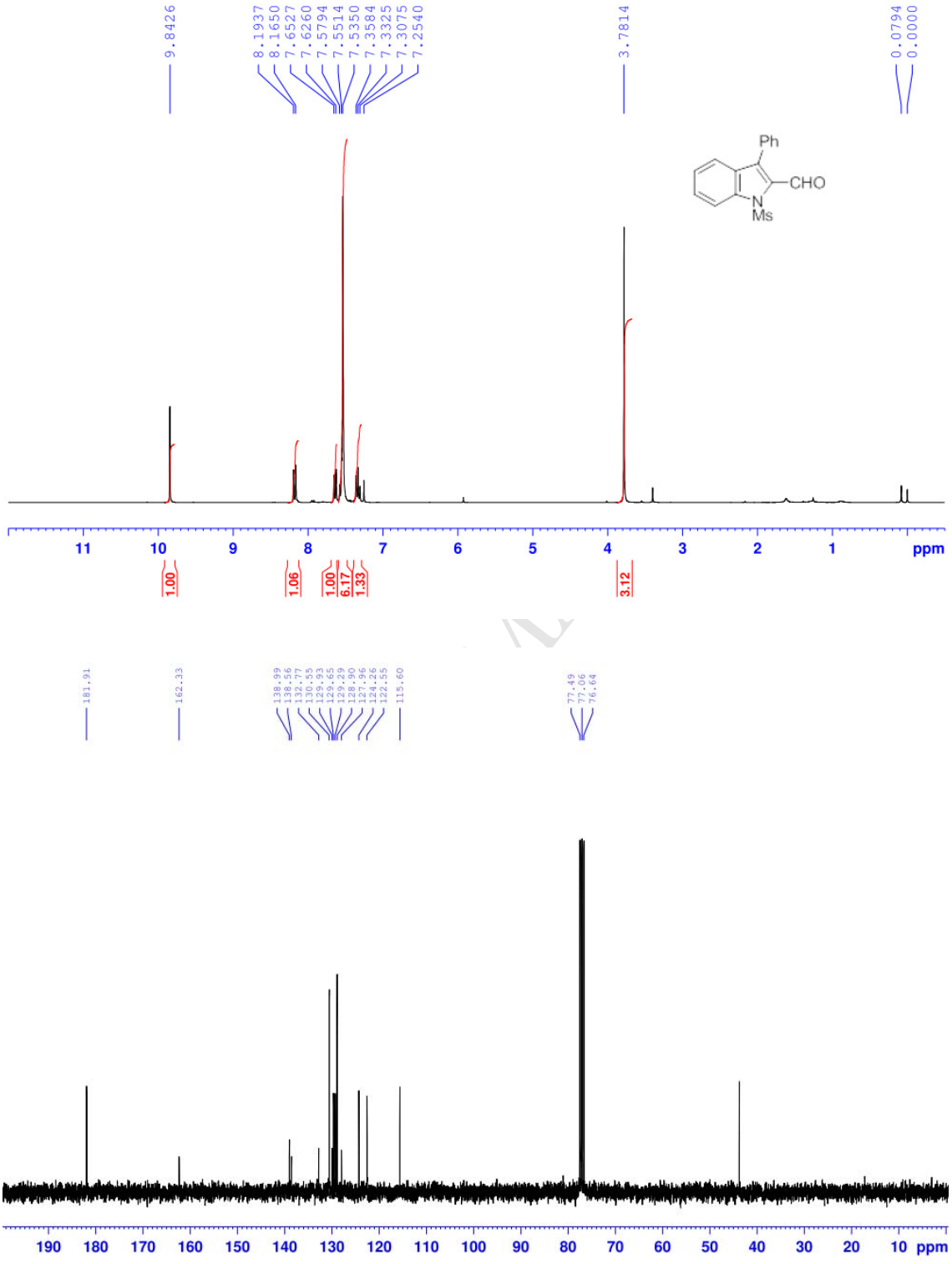


Figure S41. ^{1}H and ^{13}C NMR Spectra of 3-Phenyl-1-nosyl-1*H*-indole-2-carbaldehyde **(4r)**

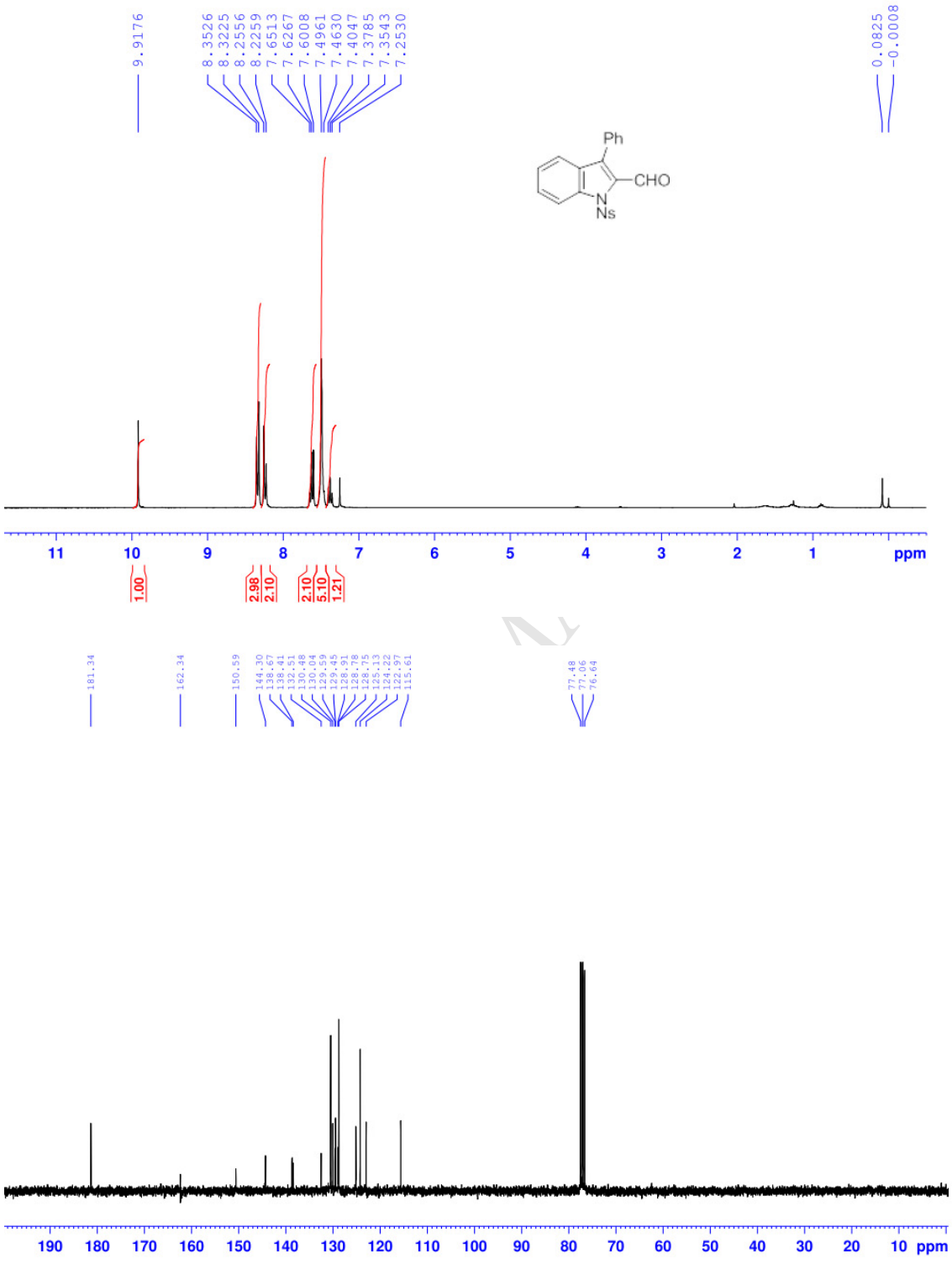


Figure S42. ^{1}H and ^{13}C NMR Spectra of (*E*)-2-(Iodomethylene)-3-phenyl-1-tosylindolin-3-ol **(6a)**

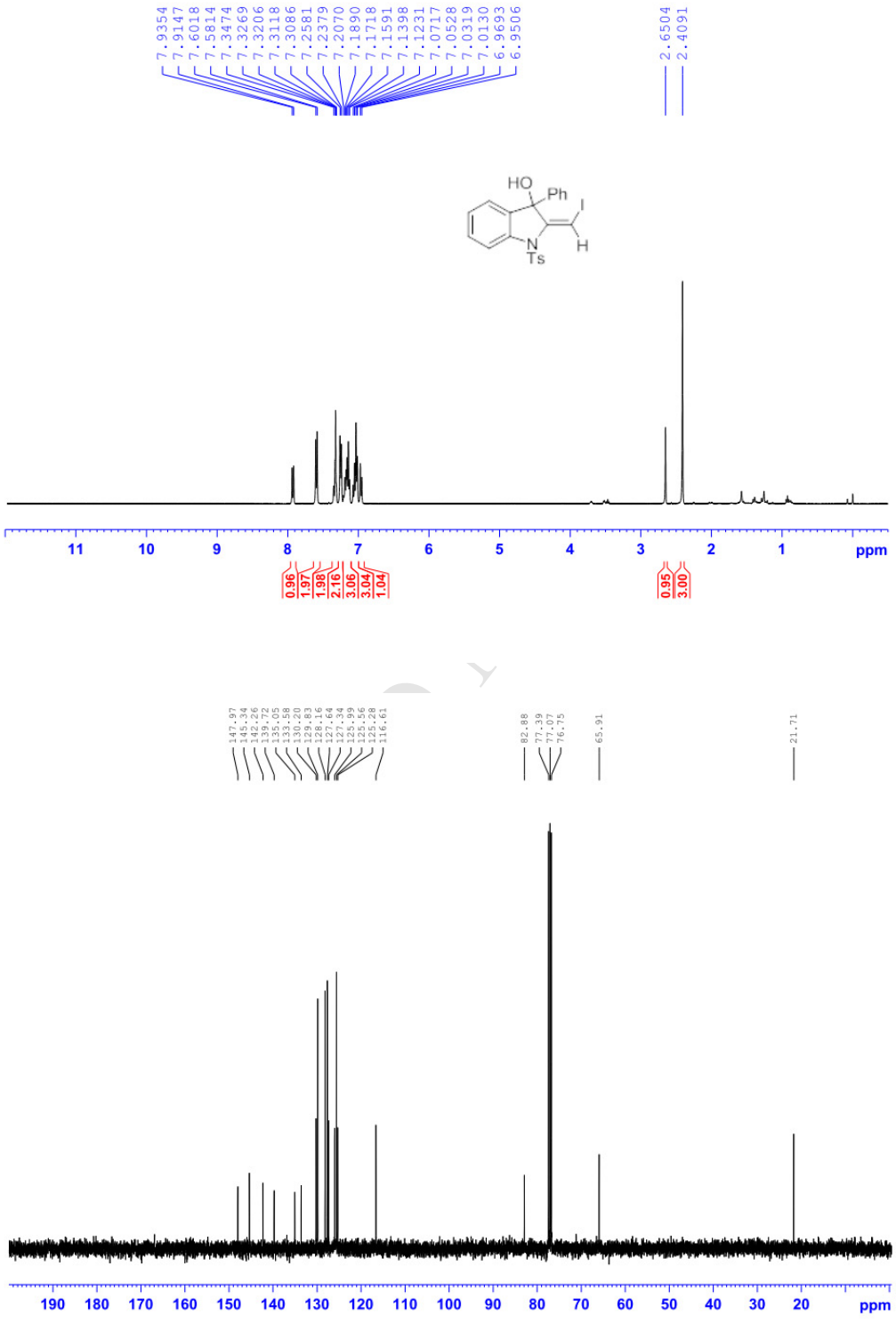


Figure S43. ^{1}H and ^{13}C NMR Spectra of 3-Phenyl-1*H*-indole-2-carbaldehyde **(5s)**

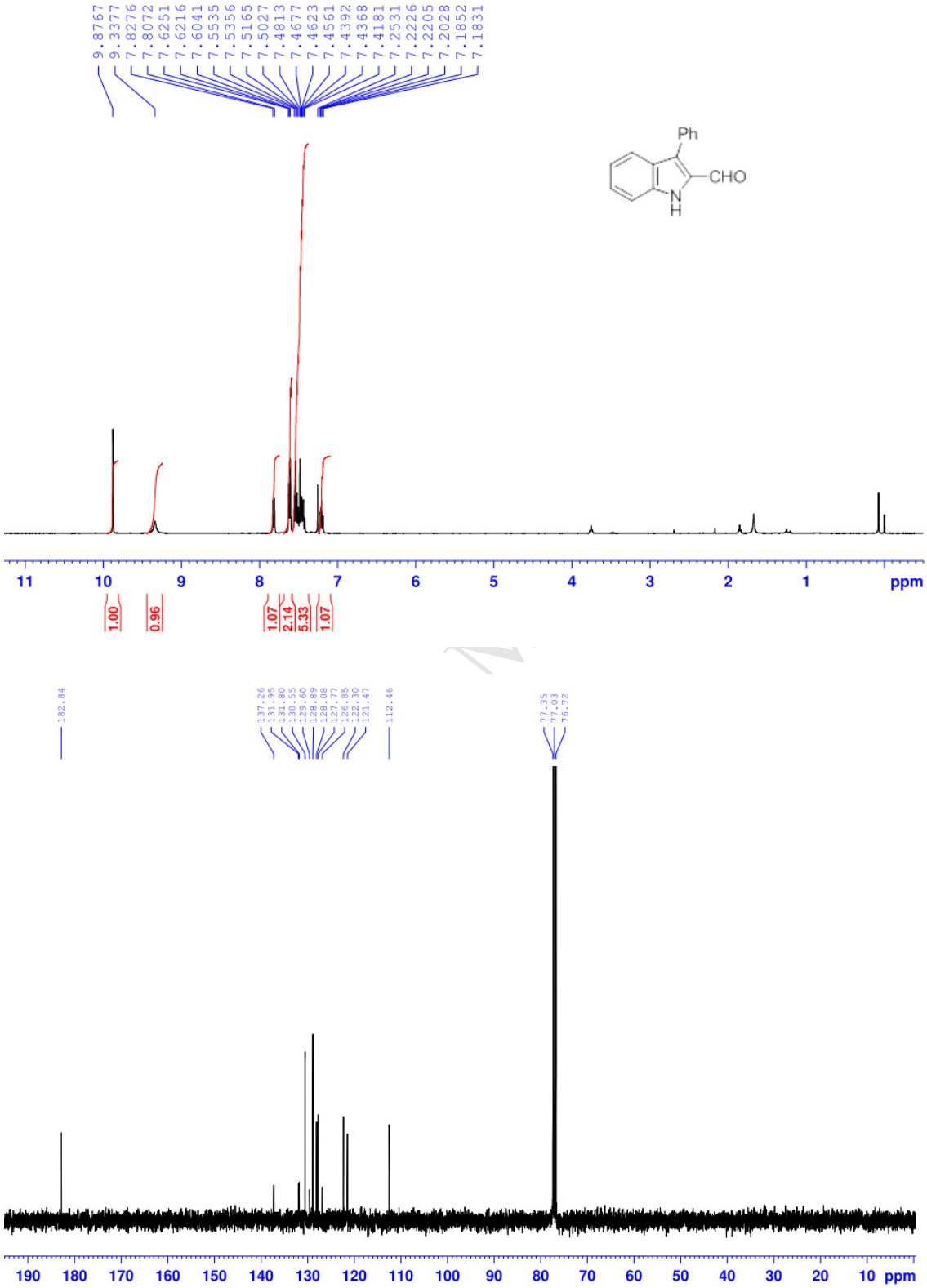


Figure S44. ^{1}H and ^{13}C NMR Spectra of 3-Methyl-1*H*-indole-2-carbaldehyde **(5t)**

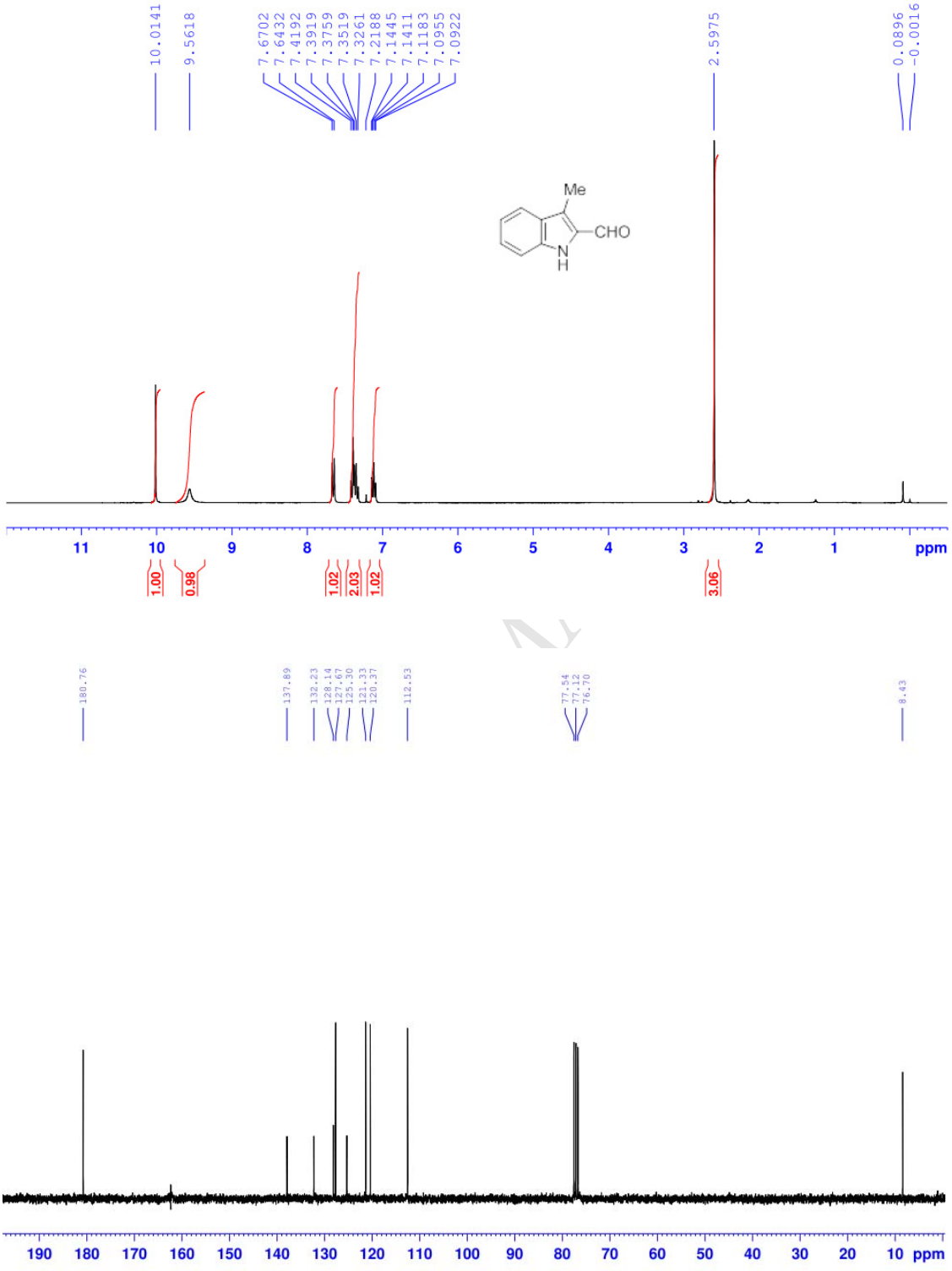


Figure S45. ^{1}H and ^{13}C NMR Spectra of 6-Methyl-3-Phenyl-1*H*-indole-2-carbaldehyde **(5u)**

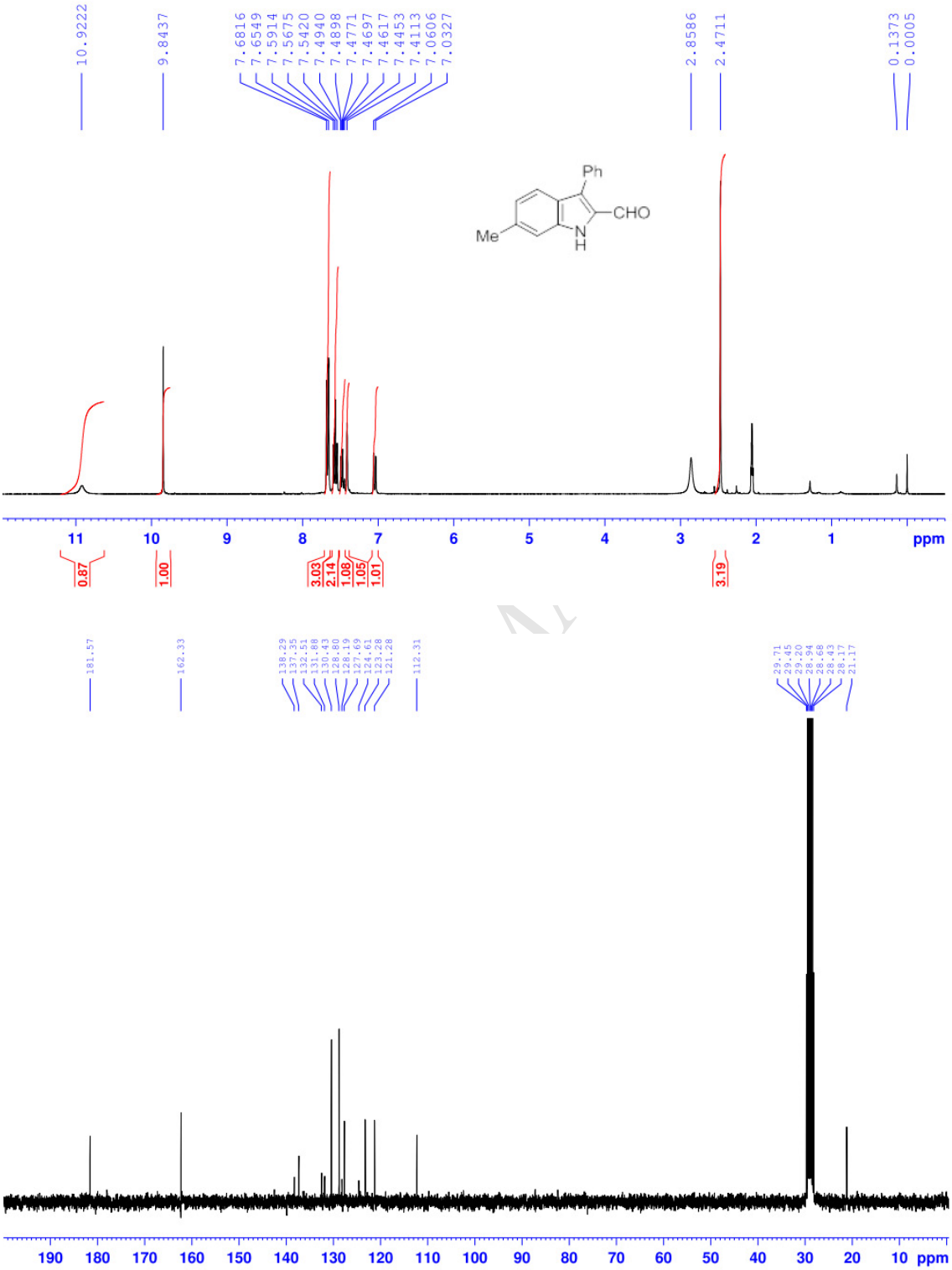


Figure S46. ^{1}H and ^{13}C NMR Spectra of 5-Methyl-3-Phenyl-1*H*-indole-2-carbaldehyde **(5v)**

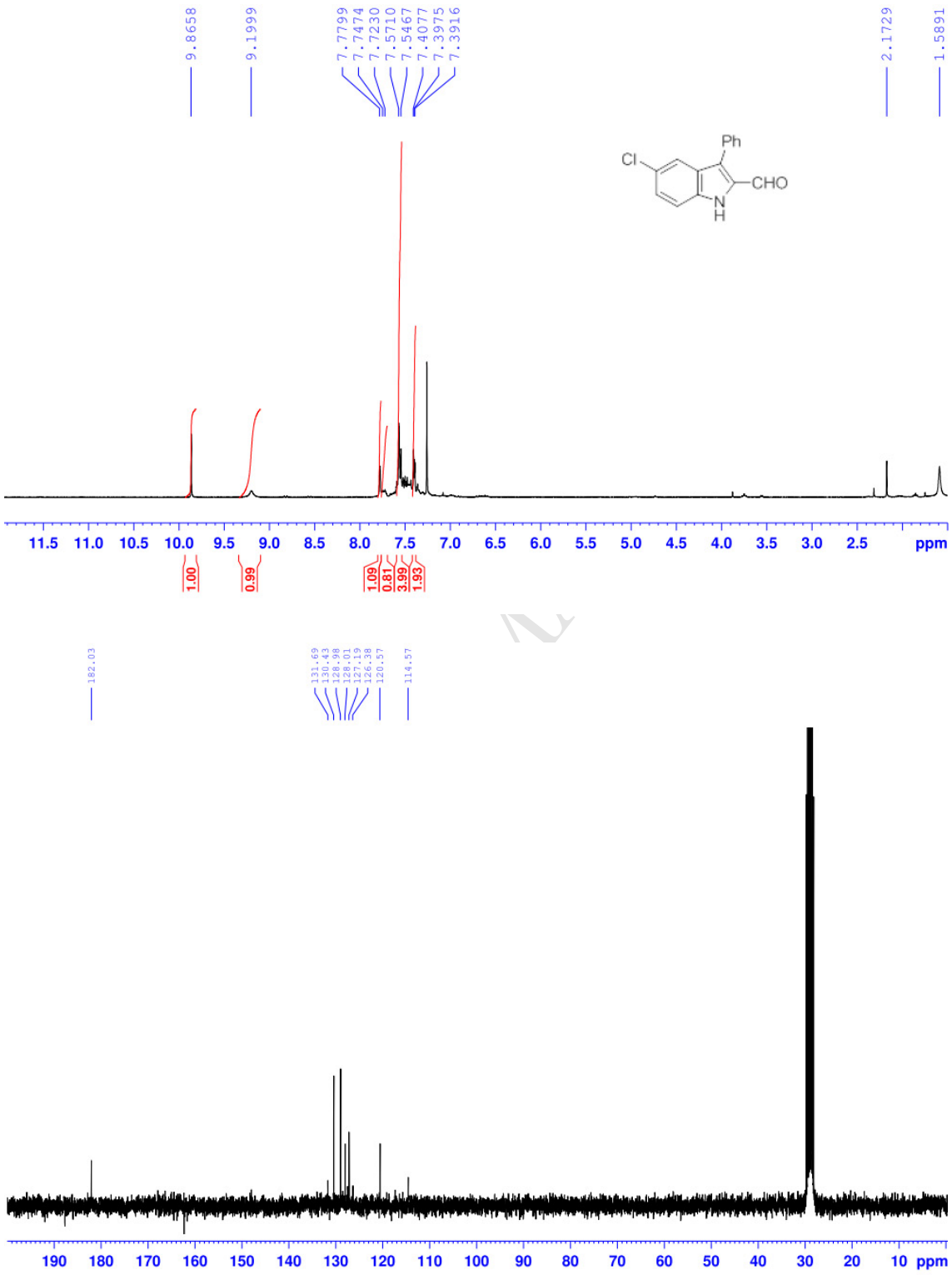


Figure S47. ^{1}H and ^{13}C NMR Spectra of 5-chloro-3-(2-chlorophenyl)-1*H*-indole-2-carbaldehyde **(5w)**

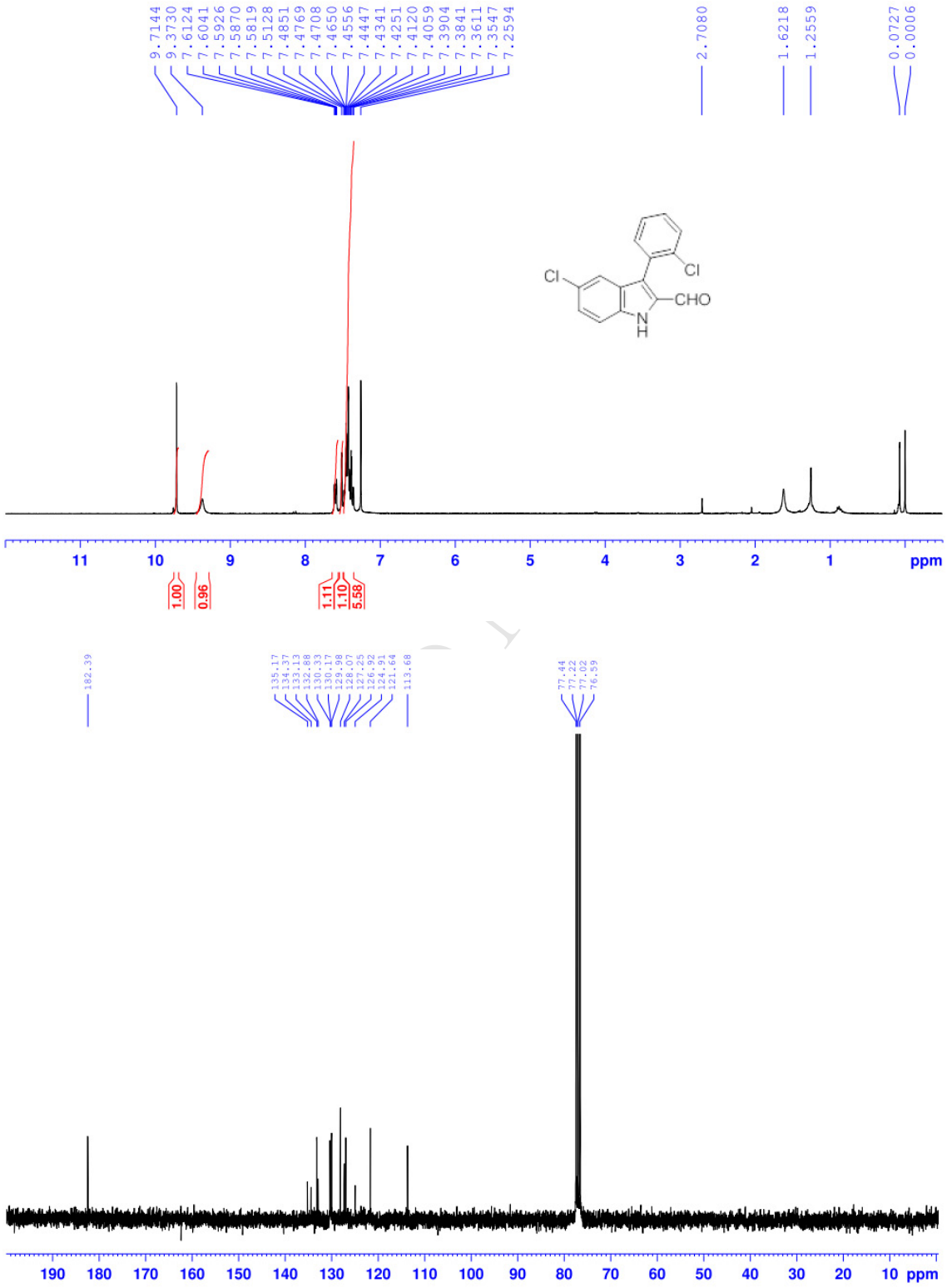


Figure S48. ^{1}H and ^{13}C NMR Spectra of (*R*)-*N*-Tosylcalindol **(7)**

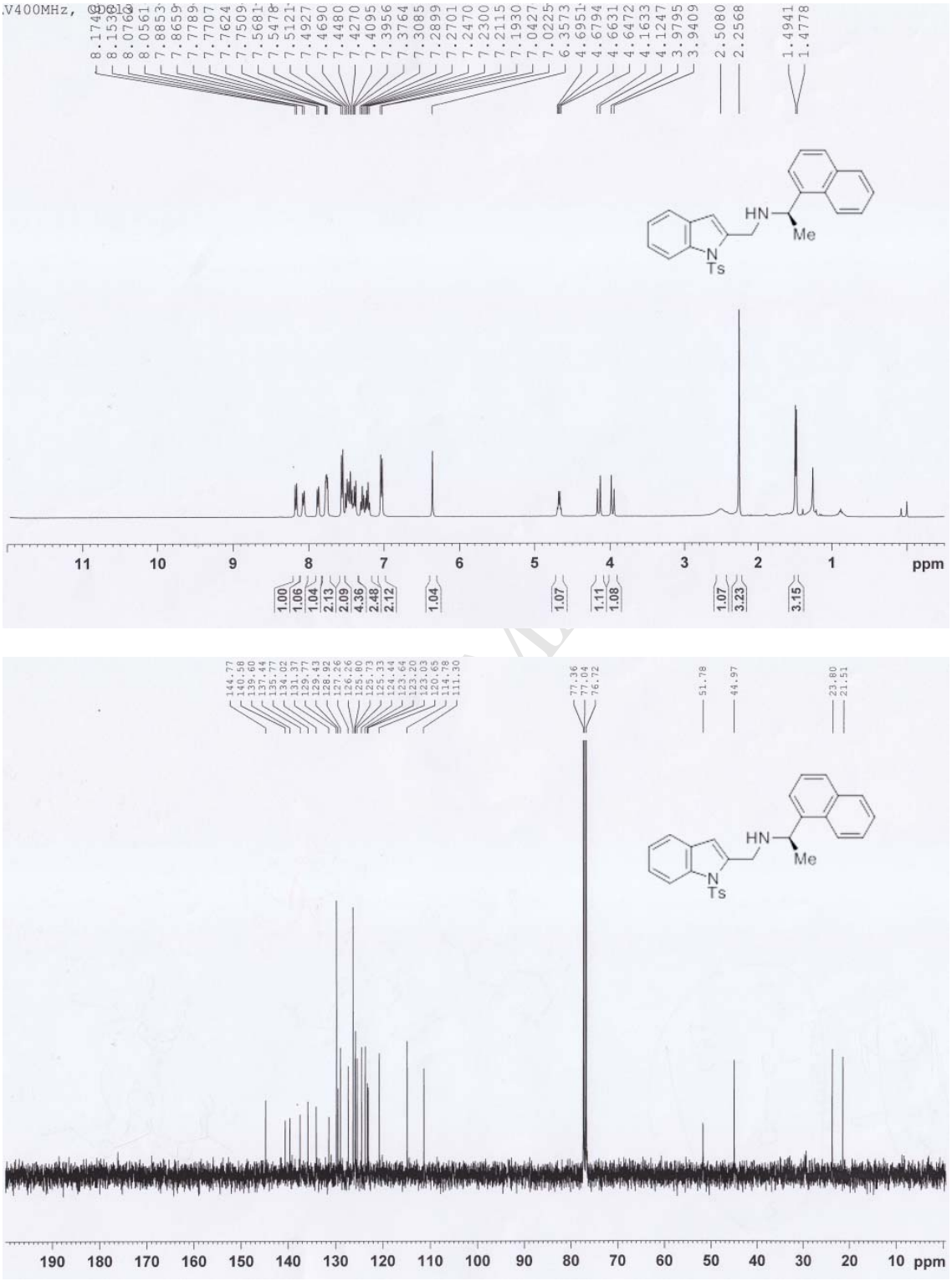
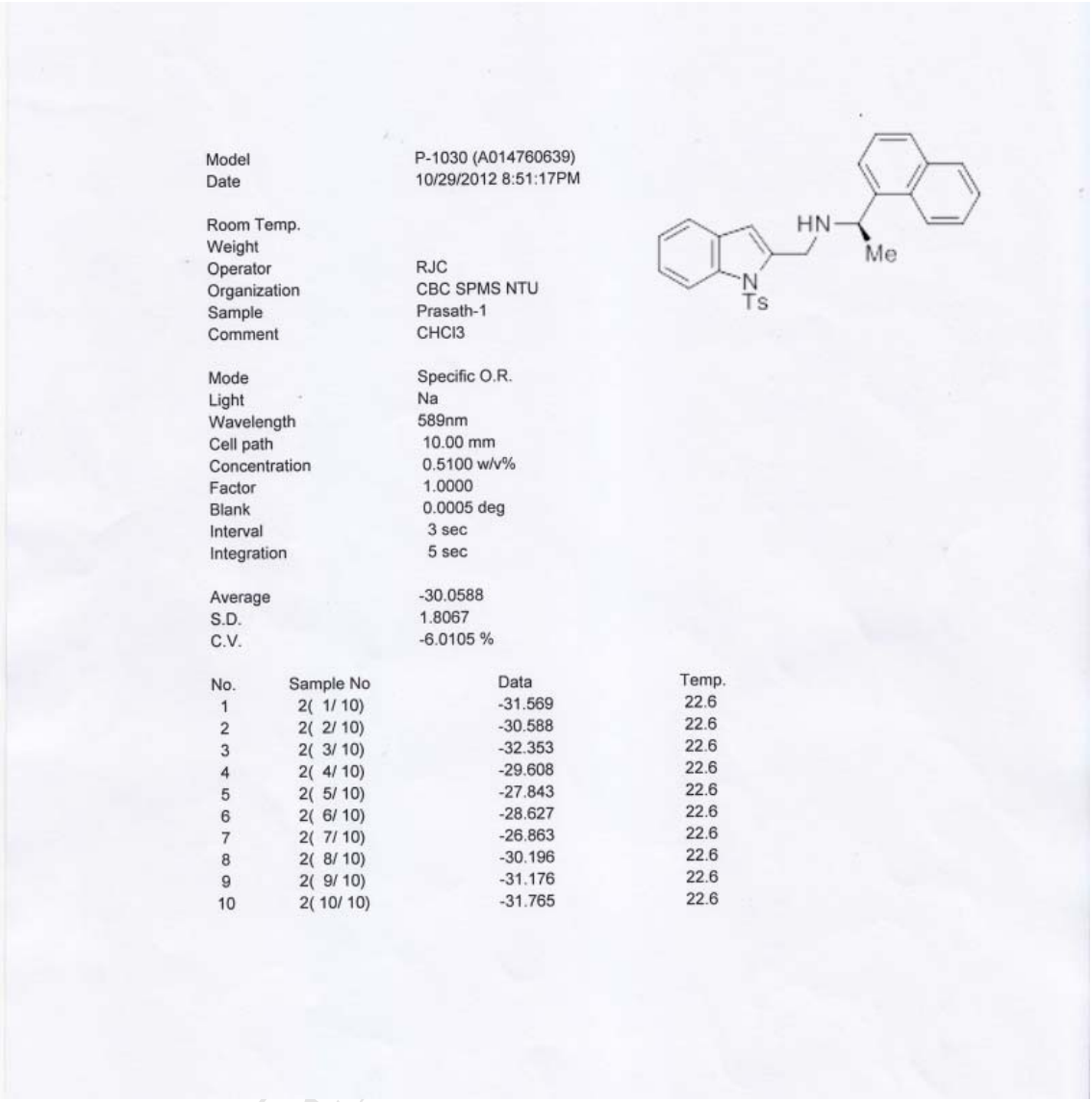


Figure S49. Specific Optical Rotation Value of (*R*)-*N*-Tosylcalindol **(7)**



Model	P-1030 (A014760639)
Date	10/29/2012 8:51:17PM
Room Temp.	
Weight	
Operator	RJC
Organization	CBC SPMS NTU
Sample	Prasath-1
Comment	CHCl3
Mode	Specific O.R.
Light	Na
Wavelength	589nm
Cell path	10.00 mm
Concentration	0.5100 w/v%
Factor	1.0000
Blank	0.0005 deg
Interval	3 sec
Integration	5 sec
Average	-30.0588
S.D.	1.8067
C.V.	-6.0105 %

No.	Sample No	Data	Temp.
1	2(1/ 10)	-31.569	22.6
2	2(2/ 10)	-30.588	22.6
3	2(3/ 10)	-32.353	22.6
4	2(4/ 10)	-29.608	22.6
5	2(5/ 10)	-27.843	22.6
6	2(6/ 10)	-28.627	22.6
7	2(7/ 10)	-26.863	22.6
8	2(8/ 10)	-30.196	22.6
9	2(9/ 10)	-31.176	22.6
10	2(10/ 10)	-31.765	22.6