

Asymmetric Organocatalytic Synthesis of β -Hydroxyynones with a Quaternary Carbon Center under Aqueous Conditions

Guowei Kang, Jun Jiang,* Hongxin Liu and Huayue Wu*

College of Chemistry and Materials Engineering, Wenzhou University, Chashan University Town,
Wenzhou, Zhejiang Province 325035, People's Republic of China

A reação aldólica direta de metil inonas não-modificadas sob condições aquosas catalisada pela amina terciária quiral de tiouréia é descrita. Este procedimento evitou a reação retroaldólica dos produtos β -hidroxinonas, e admite as isatinas (1H-indol-2,3-diona) e os menos ativos ésteres α -ceto acíclicos como aceptores, oferecendo um arranjo estruturalmente diverso de β -hidroxinonas tendo um centro de carbono quaternário, com rendimentos de moderado a bom e enantioselectividade.

The chiral tertiary amine thiourea catalyzed direct aldol reaction of unmodified methyl ynones under aqueous conditions is described. This procedure avoided the retro-aldol reaction of the β -hydroxyynone products, and tolerated both the isatin (1H-indole-2,3-dione) and the less active acyclic α -keto esters as acceptors, affording a structurally diverse array of β -hydroxyynones bearing a quaternary carbon center with moderate to good yields and enantioselectivities.

Keywords: β -hydroxyynones, chiral thiourea, aldol reaction, aqueous condition

Introduction

Enantioriched β -hydroxyynones are highly functionalized building blocks for the synthesis of biologically active compounds and natural products, such as fostriecin¹ and maitotoxin.² Although the aldol reaction is the most efficient way to construct β -hydroxy carbonyl structures, the β -hydroxyynone products are usually synthesized via the addition of alkynyllithium or alkynylmagnesium halide to the corresponding β -hydroxylated Weinreb amides.³⁻¹² This is due to the fact that ynones are good Michael acceptors and the ynone-derived β -hydroxy ketones tend to undergo retro-aldol reactions.^{13,14} Thus, direct catalytic asymmetric aldol reactions involving ynones are highly desirable. In 2004, Trost *et al.*¹³ reported the first enantioselective aldol additions of methyl ynones to α -ketal aldehydes using a chiral dinuclear zinc catalyst. Subsequently, Silva *et al.*¹⁴ found that proline derived sulfonamide could efficiently catalyze the aldol reaction of the methoxymethyl ether (MOM)-protected ynones and aldehyde with good yields and enantioselectivities.¹⁴ However, the unmodified simple methyl ynones are not good substrates under proline-sulfonamide catalysis conditions with low yields because of several

side products.¹⁴ More importantly, no example of the asymmetric catalytic synthesis of β -hydroxyynones resulting in a quaternary carbon center has been reported. Since List *et al.*¹⁵ reported the proline catalyzed cross-aldol reaction between ketones and aldehydes,¹⁵ many amine derivatives such as proline-amide type catalysts¹⁶⁻¹⁸ have been developed for such transformations,¹⁹⁻²² being most of which based on the enamine-activation mechanism.¹⁹⁻²² However, in comparison with simple ketones, the formation of enamine intermediates with primary or secondary amine catalysts and inactive unmodified ynones remains a great challenge. Based on the fact that DABCO can efficiently catalyze the direct aldol reaction between simple methyl ynone and isatin (1H-indole-2,3-dione) in our pilot experiment, it was envisioned the developing of the chiral tertiary amine catalysts in order to realize this asymmetric transformation. During the preparation of this study, Guo *et al.*²³ and Allu *et al.*²⁴ reported chiral tertiary amine thiourea and urea catalyzed enantioselective aldol reactions of ketones with excellent results. Herein, we report our preliminary results with chiral tertiary amine thiourea²⁵ catalyzed direct aldol reactions of methyl ynones, affording β -hydroxyynones with a quaternary carbon center under aqueous conditions²⁶ with moderate to good yields and enantioselectivities (Figure 1).

*e-mail: junjiang@wzu.edu.cn; huayuewu@wzu.edu.cn

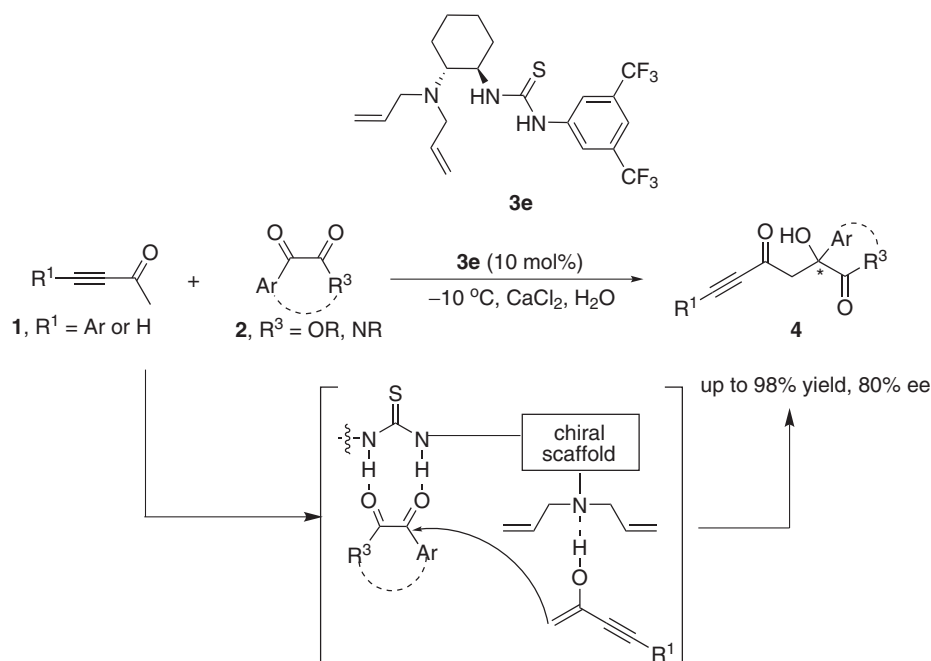


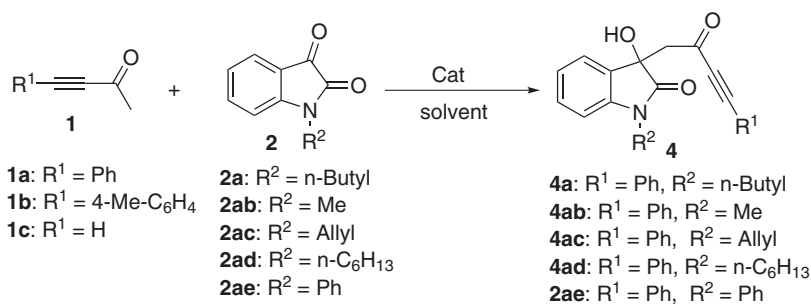
Figure 1. Thiourea catalyzed direct aldol reaction of methyl ynone and active ketones.

Results and Discussion

The organocatalyzed asymmetric aldol reactions between simple ketones or aldehydes and isatins have been intensely studied,²⁷⁻³⁷ as these chiral 3-alkyl-3-hydroxyindolin-2-one products are important building blocks in both natural products and medicinal compound syntheses.^{38,39} However, the asymmetric aldol reactions between ynones and isatins remain a synthetic challenge since the products tend to undergo retro-aldol reaction in organic solvents. For example, 42% of product **4a** converted to starting materials after stirring with 20 mol% DABCO in CH_2Cl_2 for 24 h, and a similar result was obtained when CHCl_3 was used as solvent. Moreover, ynones have the ability to act as both electrophile and nucleophile under certain conditions, such as base catalysis. Initially, our investigation began with the reaction of ynone **1a** with *N*-butyl substituted isatin **2a** by using 20 mol% of DABCO as the catalyst. To our delight, the reaction catalyzed by DABCO gave the desired product with 80% yield in 3 days at room temperature in CHCl_3 . Several solvents were then tested (Table 1, entries 1-6), and water was found to dramatically enhance the reaction rate with 88% yield in 1 h (Table 1, entry 6). Because this β -hydroxyynone product was stable in water, it was supposed that using water as the solvent may not only increase the reaction concentration but also avoid the retro-aldol reaction.

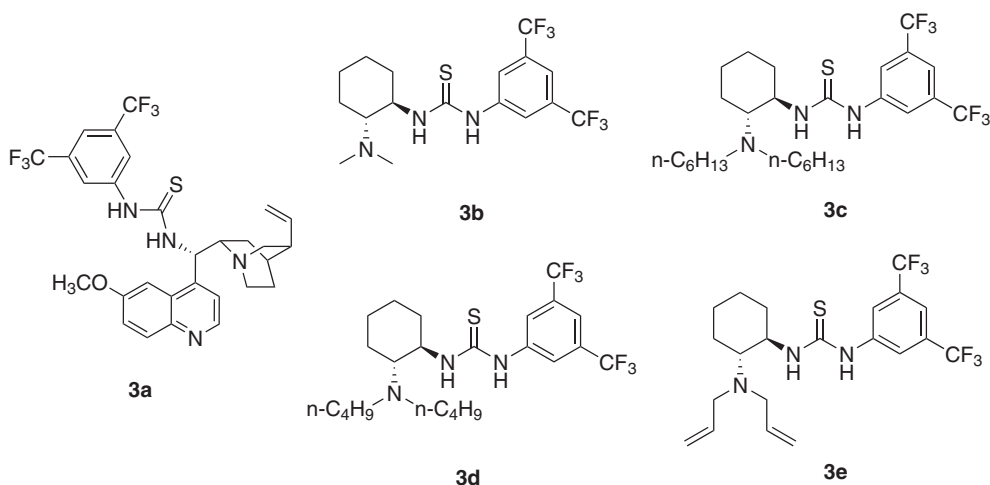
In the sequence, it was examined the asymmetric catalytic ability of chiral thiourea catalysts (Figure 2) at 0°C with 5 equivalents of ynone **1a**, using brine as solvent

instead of water to avoid freezing (Table 1, entries 7-13). The reactions catalyzed by quinine and cinchonidine proceeded smoothly but with very low enantioselectivities (ee) (Table 1, entries 7-8). Better results were obtained when tertiary amine thioureas were used as catalysts (Table 1, entries 9-13). The screening studies revealed that catalyst **3e** was the best choice in terms of enantioselectivity, which gave the desired product with 82% yield and 71% ee after 10 h. The variation of the group bonded to nitrogen of the isatin heterocycle did not increase the enantioselectivity (Table 1, entries 13-17). For example, *N*-hexyl isatin or *N*-phenyl isatin led to slightly lower enantioselectivities (Table 1, entries 16-17), while the use of *N*-methyl isatin afforded the corresponding product **4ab** in relatively low ee (Table 1, entry 14), and *N*-Boc isatin was found inactive when used in this reaction under aqueous condition. Next, several solvents were screened at 0°C with 5 equivalents of ynone **1a** to improve the enantioselectivity (Table 2). The reactions in these screened organic solvents either led to long reaction time and low yield or decreased the enantiocontrol (Table 2, entries 1-5). Further experiments investigated the influence of additives. It was shown that salts affect the enantioselectivity. The best result was obtained when CaCl_2 was used as the additive, giving the desired product with 93% yield and 73% ee at 0°C . Finally, the enantioselectivity was improved to 80% ee by cooling the reaction to -10°C . Further cooling (-20°C) was tried, but did not improve the enantioselectivity. The reaction was then performed on a 1 mmol scale of **2a** and 5 mmol of **1a** in 5 mL of solvent under the optimal conditions (Table 2, entry 13).

Table 1. Catalyst screening on the direct aldol reaction between ynone and isatin^a

entry	Catalyst	2	Solvent	4	Yield / % ^d	ee / % ^e
1 ^b	DABCO	2a	dioxane	4a	24	—
2 ^b	DABCO	2a	CH ₂ Cl ₂	4a	18	—
3 ^b	DABCO	2a	CHCl ₃	4a	10	—
4 ^b	DABCO	2a	THF	4a	19	—
5 ^b	DABCO	2a	toluene	4a	21	—
6 ^b	DABCO	2a	H ₂ O	4a	88	—
7 ^c	quinine	2a	brine	4a	91	6
8 ^c	cinchonidine	2a	brine	4a	87	12
9	3a	2a	brine	4a	89	38
10	3b	2a	brine	4a	92	56
11	3c	2a	brine	4a	95	50
12	3d	2a	brine	4a	96	45
13	3e	2a	brine	4a	82	71
14	3e	2ab	brine	4ab	98	56
15	3e	2ac	brine	4ac	95	65
16	3e	2ad	brine	4ad	91	69
17	3e	2ae	brine	4ae	97	68

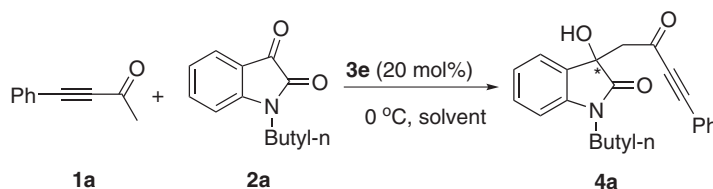
^aUnless otherwise noted, reactions were carried out with 0.5 mmol **1a**, 0.1 mmol of **2** and 10 mol% of catalyst in 0.5 mL solvent at 0 °C for 10 h; ^breactions were carried out with 0.2 mmol **1a**, 0.1 mmol of **2** at room temperature for 1 h; ^creactions were carried out for 3 h; ^disolated yield; ^eee: enantioselectivity determined by chiral HPLC.

**Figure 2.** Chemical structure of screened catalysts.

However, decreased enantioselectivity was observed (85% yield, 53% ee).

With the optimal reaction conditions in hand, it was then examined the scope of the direct aldol reactions

between ynones and active ketones. The reactions were generally conducted in saturated CaCl₂ solution at –10 to 20 °C for 9–72 h. The results are summarized in Table 3. All of the isatins showed high reactivities and

Table 2. Effects of reaction condition on the direct aldol reaction between ynone and isatin^a

entry	Solvent	time / h	Temperature / °C	Yield / % ^b	ee / % ^c
1	CHCl ₃	48	0	77	59
2	Toluene	48	0	90	57
3	THF	48	0	25	66
4	CH ₃ CN	48	0	66	64
5	MeOH	48	0	80	24
6	AcONa/H ₂ O	9	0	96	68
7	KF/H ₂ O	9	0	62	58
8	NH ₄ Cl/H ₂ O	9	0	97	65
9	LiF/H ₂ O	9	0	97	66
10	KBr/H ₂ O	9	0	97	67
11	CaCl ₂ /H ₂ O	9	0	93	73
12	CaCl ₂ /H ₂ O	14	−10	95	80
13 ^d	CaCl ₂ /H ₂ O	12	−10	85	53

^aUnless otherwise noted, reactions were carried out with 0.5 mmol of **1a**, 0.1 mmol of **2a** and 10 mol% of catalyst **3e** in 0.5 mL solvent; ^bisolated yield; ^cee: enantioselectivity determined by chiral HPLC; ^dreaction was performed on a 1 mmol scale of **2a** and 5 mmol of **1a** in 5 mL solvent.

afforded the β -hydroxyynones containing a quaternary carbon center with excellent yields and moderate to good ees. The position of the substituent on the isatin had an obvious influence on the enantioselectivity. For example, 4-substituted isatins afforded products with low ees (Table 3, entries 2-3, 46-54% ee), while substituents at other positions on the isatin heterocycle led to higher enantioselectivities (Table 3, entries 4-11, 57-78% ee). The electronic nature of the substituents also plays an important role on the enantiocontrol. Isatins with an electron-donating group on the aromatic ring gave similar results to **2a** (Table 3, entries 1, 4 and 9), whilst the presence of an electron-withdrawing group resulted in reduced enantioselectivity (such as Table 3, entry 8). Next, other ynones were also tested. Because both of the reactants are solid, the reaction involving **1b** was carried out in CH₃CN instead of CaCl₂ solution, and led to the product **4ba** with 53% yield and 78% ee (Table 3, entry 12). When but-3-yn-2-one **1c** was used as the donor in this reaction, the racemic product was obtained (Table 3, entry 13). Notably, besides isatins, less active acyclic α -keto esters **2l-2o** can also be applied in this reaction, but only under aqueous conditions. The reaction of α -keto esters with ynone **1a** led to the desired products with moderate yields and enantioselectivities (Table 3, entries 14-17, 34-44% yield, 47-63% ee). The ester group

will affect the yield and ee as the result of steric hindrance. For example, more sterically congested **2m** and **2n** afforded the β -hydroxyynones with relatively low yields and moderate ees (Table 3, entries 15-16).

Conclusion

In conclusion, we have developed the chiral tertiary amine thiourea catalyzed direct aldol reactions of unactivated methyl ynones, efficiently resulting in β -hydroxyynones containing a quaternary carbon center as the only product with moderate to good yields and enantioselectivities (34-98% yield, 46-80% ee). Importantly, aqueous conditions were found to not only dramatically enhancing the reaction rate, but also increase the enantioselectivity. Notably, besides isatins, less active acyclic α -keto esters can also be used as substrates in this reaction under standard conditions, albeit in lower yields.

Experimental

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker-500 MHz spectrometer. High-resolution mass spectrometry (HRMS, Micromass GCT-MS) spectra were recorded on a P-SIMS-Gly from

Table 3. Direct aldol reaction of ynones and active ketones^a

entry	R ¹	2		time / h	Yield of 4 / % ^e	ee / % ^f
1	1a		2a	14	4a , 90	80
2	1a	R = 4-Cl	2b	12	4b , 86	46
3	1a	R = 4-Br	2c	10	4c , 97	54
4	1a	R = 5-Me	2d	22	4d , 90	77
5	1a	R = 5-F	2e	12	4e , 98	70
6	1a	R = 5-Cl	2f	18	4f , 90	66
7	1a	R = 5-Br	2g	16	4g , 90	66
8	1a	R = 5-NO ₂	2h	9	4h , 89	57
9	1a	R = 5-MeO	2i	13	4i , 94	78
10	1a	R = 6-Br	2j	10	4j , 97	70
11	1a	R = 7-F	2k	11	4k , 95	65
12 ^b	1b		2a	50	4ba , 53	78
13 ^c	1c		2a	46	4ca , 70	2
14 ^d	1a		2l	72	4l , 42	47
15 ^d	1a		2m	72	4m , 36	63
16 ^d	1a		2n	72	4n , 34	62
17 ^d	1a		2o	72	4o , 44	60

^aUnless otherwise noted, reactions were carried out with 0.5 mmol of **1**, 0.1 mmol of **2** and 10 mol% of catalyst **3e** at -10 °C in 0.5 mL saturated CaCl₂ solution; ^breaction was carried out in CH₃CN at -5 °C; ^creaction was carried out at 10 °C; ^dreaction was carried out at 20 °C; ^eisolated yield; ^fee: enantioselectivity determined by chiral HPLC.

Bruker Daltonics Inc. Infrared (IR) spectra were recorded on a Nicolet MX-1E FT-IR spectrometer. High performance liquid chromatography (HPLC) analysis was performed on a Shimadzu LC-20AT series HPLC. Chiralpak AS, AD, OD and IA were purchased from Daicel Chemical Industries, Ltd. Optical rotation data were acquired on a PolAAr 3005 automatic polarimeter. Solvents for the column chromatography were distilled before use.

General procedure for the asymmetric organocatalytic synthesis of β-hydroxyynones with a quaternary carbon center under aqueous conditions

Active ketone (0.1 mmol) and catalyst **3e** (10 mol%) were added to the saturated CaCl₂ solution (0.5 mL) in a tube and the mixture was stirred at the corresponding temperature for 15 min, then the ynone (0.5 mmol) was

added and the resulting mixture was stirred for 9-72 h at the determined temperature (monitored by thin layer chromatography (TLC)). The reaction mixture was extracted with CH_2Cl_2 (3×0.5 mL) and the organic phase was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 5/1-3/1) to yield pure products.

Supplementary Information

Supplementary data are available free of charge at <http://jbcs.sbq.org.br> as a PDF file.

Acknowledgements

We are grateful for the financial support from NSFC (21002071 and 21072153), Department of Education of Zhejiang Province (Y201017083) and Science and Technology Department of Zhejiang Province (2009R50002).

References

1. Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B. T.; *J. Am. Chem. Soc.* **2005**, *127*, 3666.
2. Nicolaou, K. C.; Aversa, R. J.; Jin, J.; Rivas F.; *J. Am. Chem. Soc.* **2010**, *132*, 6855.
3. Chavez, D. E.; Jacobsen, E. N.; *Angew. Chem., Int. Ed.* **2001**, *40*, 3667.
4. Marshall, J. A.; Ellis, K.; *Tetrahedron Lett.* **2004**, *45*, 1351.
5. Evans, D. A.; Starr, J. T.; *J. Am. Chem. Soc.* **2003**, *125*, 13531.
6. Fujii, K.; Maki, K.; Kanai, M.; Shibasaki, M.; *Org. Lett.* **2003**, *5*, 733.
7. Funel, J.-A.; Prunet, J.; *J. Org. Chem.* **2004**, *69*, 4555.
8. Shin, Y.; Fournier, J.-H.; Balachandran, R.; Madiraju, C.; Raccor, B. S.; Zhu, G.; Edler, M. C.; Harnel, E.; Day, B. W.; Curran, D. P.; *Org. Lett.* **2005**, *7*, 2873.
9. Handa, M.; Scheidt, K. A.; Bossart, M.; Zheng, N.; Roush, W. R.; *J. Org. Chem.* **2008**, *73*, 1031.
10. O'Neil, G. W.; Fürstner, A.; *Chem. Commun.* **2008**, 4294.
11. Shimp, H.; Micalizio, G. C.; *Tetrahedron* **2009**, *65*, 5908.
12. Cook, C.; Guinchard, X.; Liron, F.; Roulland, E.; *Org. Lett.* **2010**, *12*, 744.
13. Trost, B. M.; Fettes, A.; Shireman, B. T.; *J. Am. Chem. Soc.* **2004**, *126*, 2660.
14. Silva, F.; Sawicki, M.; Gouverneur, V.; *Org. Lett.* **2006**, *8*, 5417.
15. List, B.; Lerner, R. A.; Barbas III, C. F.; *J. Am. Chem. Soc.* **2000**, *122*, 2395.
16. Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D.; *J. Am. Chem. Soc.* **2003**, *125*, 5262.
17. Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D.; *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5755.
18. Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z.; *J. Am. Chem. Soc.* **2005**, *127*, 9285.
19. List, B.; *Acc. Chem. Res.* **2004**, *37*, 548.
20. Notz, W.; Tanaka, F.; Barbas III, C. F.; *Acc. Chem. Res.* **2004**, *37*, 580.
21. List, B.; *Tetrahedron* **2002**, *58*, 5573.
22. Pellissier, H.; *Tetrahedron* **2007**, *63*, 9267.
23. Guo, Q.; Bhanushali, M.; Zhao, C.-G.; *Angew. Chem., Int. Ed.* **2010**, *49*, 9460.
24. Allu, S.; Molleti, N.; Panem, R.; Singh, V. K.; *Tetrahedron Lett.* **2011**, *52*, 4080.
25. Doyle, A. G.; Jacobsen, E. N.; *Chem. Rev.* **2007**, *107*, 5713.
26. Paradowska, J.; Stodulski, M.; Mlynarski, J.; *Angew. Chem., Int. Ed.* **2009**, *48*, 4288.
27. For a review see: Zhou, F.; Liu, Y.-L.; and Zhou, J.; *Adv. Synth. Catal.* **2010**, *352*, 1381.
28. Chen, J.-R.; Liu, X.-P.; Zhu, X.-Y.; Li, L.; Qiao, Y.-F.; Zhang, J.-M.; Xiao, W.-J.; *Tetrahedron* **2007**, *63*, 10437.
29. Malkov, A. V.; Kabeshov, M. A.; Bella, M.; Kysilka, O.; Malyshev, D. A.; Pluhackova, K.; Kocovsky, P.; *Org. Lett.* **2007**, *9*, 5473.
30. Nakamura, S.; Hara, N.; Nakashima, H.; Kubo, K.; Shibata, N.; Toru, T.; *Chem. Eur. J.* **2008**, *14*, 8079.
31. Itoh, T.; Ishikawa, H.; Hayashi, Y.; *Org. Lett.* **2009**, *11*, 3854.
32. Angelici, G.; Corrêa, R. J.; Garden, S. J.; Tomasini, C.; *Tetrahedron Lett.* **2009**, *50*, 814.
33. Raj, M.; Veerasamy, N.; Singh, V. K.; *Tetrahedron Lett.* **2010**, *51*, 2157.
34. Chen, W.-B.; Du, X.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C.; *Tetrahedron* **2010**, *66*, 1441.
35. Hara, N.; Nakamura, S.; Shibata, N.; Toru, T.; *Adv. Synth. Catal.* **2010**, *352*, 1621.
36. Luppi, G.; Monari, M.; Corrêa, R. J.; Violante, F. D.; Pinto, A. C.; Kaptein, B.; Broxterman, Q. B.; Garden, S. J.; Tomasini, C.; *Tetrahedron* **2006**, *62*, 12017.
37. Corrêa, R. J.; Garden, S. J.; Angelici, G.; Tomasini, C.; *Eur. J. Org. Chem.* **2008**, *4*, 736.
38. Goehring, R. R.; Sachdeva, Y. P.; Pisipati, J. S.; Sleevi, M. C.; Wolfe, J. F.; *J. Am. Chem. Soc.* **1985**, *107*, 435.
39. Tokunaga, T.; Hume, W. E.; Nagamine, J.; Kawamura, T.; Taiji, M.; Nagata, R.; *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1789.

Submitted: September 15, 2011

Published online: November 17, 2011

Supplementary Information

Asymmetric Organocatalytic Synthesis of β -Hydroxyynones with a Quaternary Carbon Center under Aqueous Conditions

Guowei Kang, Jun Jiang,* Hongxin Liu and Huayue Wu*

College of Chemistry and Materials Engineering, Wenzhou University, Chashan University Town,
Wenzhou, Zhejiang Province 325035, People's Republic of China

Experimental

General

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker-500 MHz spectrometer. High-resolution mass spectrometry (HRMS, Micromass GCT-MS) spectra were recorded on a P-SIMS-Gly from Bruker Daltonics Inc. Infrared (IR) spectra were recorded on a Nicolet MX-1E FT-IR spectrometer. High performance liquid chromatography (HPLC) analysis was performed on a Shimadzu LC-20AT series HPLC. Chiralpak AS, AD, OD and IA were purchased from Daicel Chemical Industries, Ltd. Optical rotation data were acquired on a PolAAR 3005 automatic polarimeter. Solvents for the column chromatography were distilled before use.

Commercial reagents were used as received, unless otherwise stated. α -Keto ester **2l-2o** were prepared as reported.¹ Thiourea **3a** was prepared according to the procedure of Vakulya *et al.*² Catalyst **3b-3e** were prepared according to the literature of Arjan *et al.*³ and Okino *et al.*⁴

General procedure for the asymmetric organocatalytic synthesis of β -hydroxyynones with quaternary carbon center under aqueous condition

Active ketone (0.1 mmol) and catalyst **3e** (10 mol%) were added to the saturated CaCl_2 solution (0.5 mL) in a tube and the mixture was stirred at corresponding temperature for 15 min, then the ynone (0.5 mmol) was added and the resulting mixture was stirred for 9-72 h at determined temperature (monitored by thin layer chromatography (TLC)). The reaction mixture was extracted by CH_2Cl_2 (3 \times 0.5 mL) and the organic phase was purified through flash column chromatography on a silica gel (eluent: petroleum ether/ethyl acetate = 5/1-3/1) to yield pure products.

1-Butyl-3-hydroxy-3-(2-oxo-4-phenylbut-3-ynyl)indolin-2-one (**4a**)

Yield: 90%; $[\alpha]_{\text{D}}^{15} = +5.56^\circ$ ($c = 0.232$, CHCl_3 , $ee = 80\%$), determined by HPLC (Daicel Chiralpak IA, hexane/isopropanol = 90/10, flow rate 1.0 mL min⁻¹) t_{R} /min 17.34 (minor), 18.58 (major); IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 2955, 2927, 2193, 1698, 1667, 1614, 1362, 1064, 753, 689; ^1H NMR (500 MHz, CDCl_3) δ 0.94 (t, 3H, J 7.4 Hz), 1.44-1.36 (m, 2H), 1.71-1.65 (m, 2H), 3.32 (d, 1H, J 16.7 Hz), 3.51 (d, 1H, J 16.7 Hz), 3.66-3.60 (m, 1H), 3.76-3.71 (m, 1H), 4.10 (s, 1H), 6.86 (m, 1H), 7.07 (m, 1H), 7.33-7.30 (m, 1H), 7.38-7.35 (m, 2H), 7.47-7.44 (m, 2H), 7.53-7.51 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 13.70, 20.10, 29.15, 39.95, 51.72, 73.99, 87.84, 92.53, 108.91, 119.42, 122.93, 124.24, 128.59, 129.22, 130.04, 131.03, 133.16, 143.11, 176.02, 183.76; HRMS (ESI) exact mass calcd. for $(\text{C}_{22}\text{H}_{21}\text{NNaO}_3)^+$ requires m/z 370.1419, found m/z 370.1412.

1-Butyl-4-chloro-3-hydroxy-3-(2-oxo-4-phenylbut-3-ynyl)indolin-2-one (**4b**)

Yield: 86%; $[\alpha]_{\text{D}}^{15} = +3.51^\circ$ ($c = 0.265$, CHCl_3 , $ee = 46\%$), determined by HPLC (Daicel Chiralpak IA, hexane/isopropanol = 90/10, flow rate 1.0 mL min⁻¹) t_{R} /min 17.65 (major), 20.67 (minor); IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 2959, 2200, 1705, 1668, 1607, 1362, 1131, 1067, 774, 759, 689; ^1H NMR (500 MHz, CDCl_3) δ 0.95 (t, 3H, J 7.4 Hz), 1.45-1.37 (m, 2H), 1.71-1.65 (m, 2H), 3.58 (s, 1H), 3.64-3.60 (m, 2H), 3.77-3.72 (m, 1H), 4.02 (d, 1H, J 16.6 Hz), 6.77-6.76 (m, 1H), 6.99-6.97 (m, 1H), 7.26-7.23 (m, 1H), 7.38-7.35 (m, 2H), 7.47-7.44 (m, 1H), 7.54-7.52 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 13.70, 20.09, 28.98, 40.24, 50.17, 74.39, 87.50, 92.01, 107.45, 119.50, 123.79, 125.15, 128.58, 130.96, 131.21, 131.50, 133.16, 145.48, 175.57, 182.73; HRMS (ESI) exact mass calcd. for $(\text{C}_{22}\text{H}_{20}\text{ClNNaO}_3)^+$ requires m/z 404.1029, found m/z 404.1031.

*e-mail: junjiang@wzu.edu.cn; huayuewu@wzu.edu.cn

4-Bromo-1-butyl-3-hydroxy-3-(2-oxo-4-phenylbut-3-ynyl)indolin-2-one (**4c**)

Yield: 97%; $[\alpha]_D^{15} = +1.96^\circ$ ($c = 0.271$, CHCl_3 , $ee = 54\%$), determined by HPLC (Daicel Chiralpak AS-H, hexane/isopropanol = 70/30, flow rate 1.0 mL min^{-1}) t_R/min 15.18 (major), 27.97 (minor); IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 2952, 2198, 1705, 1666, 1603, 1362, 1126, 1067, 760, 688; ^1H NMR (500 MHz, CDCl_3) δ 0.95 (t, 3H, J 7.0 Hz), 1.41-1.38 (m, 2H), 1.69-1.66 (m, 2H), 3.46 (m, 1H), 3.62-3.58 (m, 2H), 3.76-3.72 (m, 1H), 4.09 (d, 1H, J 16.6 Hz), 6.81-6.80 (m, 1H), 7.18-7.15 (m, 2H), 7.38-7.35 (m, 2H), 7.45-7.44 (m, 1H), 7.54-7.52 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 13.70, 20.10, 28.95, 40.16, 50.02, 74.99, 87.54, 92.00, 107.97, 119.45, 119.52, 126.81, 126.85, 128.58, 130.95, 131.39, 133.16, 145.71, 175.52, 182.68; HRMS (ESI) exact mass calcd. for $(\text{C}_{22}\text{H}_{20}\text{BrNNaO}_3)^+$ requires m/z 448.0524, found m/z 448.0525.

1-Butyl-3-hydroxy-5-methyl-3-(2-oxo-4-phenylbut-3-ynyl)indolin-2-one (**4d**)

Yield: 90%; $[\alpha]_D^{15} = +1.65^\circ$ ($c = 0.315$, CHCl_3 , $ee = 77\%$), determined by HPLC (Daicel Chiralpak OD-H, hexane/isopropanol = 90/10, flow rate 1.0 mL min^{-1}) t_R/min 13.92 (major), 16.34 (minor); IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 2595, 2923, 2198, 1698, 1669, 1496, 1361, 1124, 809, 759, 689; ^1H NMR (500 MHz, CDCl_3) δ 0.94 (t, 3H, J 7.4 Hz), 1.43-1.35 (m, 2H), 1.70-1.64 (m, 2H), 2.31 (s, 3H), 3.27 (d, 1H, J 16.7 Hz), 3.47 (d, 1H, J 16.7 Hz), 3.65-3.59 (m, 1H), 3.74-3.68 (m, 1H), 3.83 (s, 1H), 6.75-6.74 (m, 1H), 7.12-7.10 (m, 1H), 7.27 (s, 1H), 7.39-7.36 (m, 2H), 7.48-7.45 (m, 1H), 7.54-7.52 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 13.71, 20.10, 21.00, 29.18, 39.96, 51.70, 74.13, 87.88, 92.55, 108.69, 119.44, 125.06, 128.60, 129.20, 130.26, 131.04, 132.56, 133.16, 140.64, 175.84, 183.94; HRMS (ESI) exact mass calcd. for $(\text{C}_{23}\text{H}_{23}\text{NNaO}_3)^+$ requires m/z 384.1576, found m/z 384.1573.

1-Butyl-5-fluoro-3-hydroxy-3-(2-oxo-4-phenylbut-3-ynyl)indolin-2-one (**4e**)

Yield: 98%; $[\alpha]_D^{15} = +1.70^\circ$ ($c = 0.259$, CHCl_3 , $ee = 70\%$), determined by HPLC (Daicel Chiralpak AS-H, hexane/isopropanol = 80/20, flow rate 1.0 mL min^{-1}) t_R/min 15.24 (major), 1.53 (minor); IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 2959, 2200, 1704, 1669, 1489, 1362, 1065, 760, 689; ^1H NMR (500 MHz, CDCl_3) δ 0.94 (t, 3H, J 7.4 Hz), 1.43-1.35 (m, 2H), 1.69-1.63 (m, 2H), 3.33 (d, 1H, J 16.9 Hz), 3.51 (d, 1H, J 16.9 Hz), 3.64-3.58 (m, 1H), 3.75-3.70 (m, 1H), 4.25-4.20 (m, 1H), 6.79-6.77 (m, 1H), 7.03-6.99 (m,

1H), 7.22-7.20 (m, 1H), 7.38-7.35 (m, 2H), 7.47-7.44 (m, 1H), 7.54-7.52 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 13.69, 20.09, 29.06, 40.12, 51.66, 74.04, 87.71, 92.90, 109.49, 109.55, 112.51, 112.71, 116.12, 116.31, 119.29, 128.64, 130.76, 130.82, 131.15, 133.19, 139.01, 158.31, 160.23, 175.79, 183.53; HRMS (ESI) exact mass calcd. for $(\text{C}_{22}\text{H}_{20}\text{FNNaO}_3)^+$ requires m/z 388.1325, found m/z 388.1321.

1-Butyl-5-chloro-3-hydroxy-3-(2-oxo-4-phenylbut-3-ynyl)indolin-2-one (**4f**)

Yield: 90%; $[\alpha]_D^{15} = +1.08^\circ$ ($c = 0.358$, CHCl_3 , $ee = 66\%$), determined by HPLC (Daicel Chiralpak AS-H, hexane/isopropanol = 80/20, flow rate 1.0 mL min^{-1}) t_R/min 14.68 (major), 18.29 (minor); IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 2955, 2199, 1705, 1668, 1487, 1362, 1111, 1063, 758, 688; ^1H NMR (500 MHz, CDCl_3) δ 0.94 (t, 3H, J 7.4 Hz), 1.43-1.35 (m, 2H), 1.69-1.63 (m, 2H), 3.33 (d, 1H, J 17.0 Hz), 3.52 (d, 1H, J 17.0 Hz), 3.64-3.58 (m, 1H), 3.75-3.69 (m, 1H), 4.04 (s, 1H), 6.79-6.78 (m, 1H), 7.30-7.28 (m, 1H), 7.39-7.36 (m, 2H), 7.44-7.43 (m, 1H), 7.48-7.45 (m, 1H), 7.55-7.53 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 13.70, 20.09, 29.07, 40.12, 51.57, 73.86, 87.67, 93.03, 109.91, 119.27, 124.89, 128.35, 128.66, 129.94, 130.87, 131.18, 133.21, 141.75, 175.52, 183.54; HRMS (ESI) exact mass calcd. for $(\text{C}_{22}\text{H}_{20}\text{ClNNaO}_3)^+$ requires m/z 404.1029, found m/z 404.1024.

5-Bromo-1-butyl-3-hydroxy-3-(2-oxo-4-phenylbut-3-ynyl)indolin-2-one (**4g**)

Yield: 90%; $[\alpha]_D^{15} = -0.71^\circ$ ($c = 0.225$, CHCl_3 , $ee = 66\%$), determined by HPLC (Daicel Chiralpak AS-H, hexane/isopropanol = 80/20, flow rate 1.0 mL min^{-1}) t_R/min 15.29 (major), 18.28 (minor); IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 2952, 2199, 1705, 1668, 1361, 1222, 1123, 1059, 758, 688; ^1H NMR (500 MHz, CDCl_3) δ 0.93 (t, 3H, J 7.4 Hz), 1.42-1.34 (m, 2H), 1.68-1.62 (m, 2H), 3.36 (d, 1H, J 17.0 Hz), 3.52 (d, 1H, J 17.0 Hz), 3.62-3.56 (m, 1H), 3.74-3.69 (m, 1H), 4.19 (s, 1H), 6.74-6.72 (m, 1H), 7.38-7.35 (m, 2H), 7.47-7.42 (m, 2H), 7.56-7.52 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 13.69, 20.08, 29.04, 40.09, 51.65, 73.78, 87.65, 92.96, 110.40, 115.57, 119.27, 127.57, 128.64, 131.15, 131.24, 132.84, 133.20, 142.27, 175.52, 183.41; HRMS (ESI) exact mass calcd. for $(\text{C}_{22}\text{H}_{20}\text{BrNNaO}_3)^+$ requires m/z 448.0524, found m/z 448.0521.

1-Butyl-3-hydroxy-5-nitro-3-(2-oxo-4-phenylbut-3-ynyl)indolin-2-one (**4h**)

Yield: 89%; $[\alpha]_D^{15} = -0.64^\circ$ ($c = 0.326$, CHCl_3 , $ee = 57\%$), determined by HPLC (Daicel Chiralpak OD-H,

hexane/isopropanol = 90/10, flow rate 1.0 mL min⁻¹) t_R /min 28.49 (major), 36.37 (minor); IR (KBr) ν_{\max} /cm⁻¹ 2955, 2930, 2196, 1728, 1704, 1667, 1614, 1519, 1330, 1068, 756, 689; ¹H NMR (500 MHz, CDCl₃) δ 0.96 (t, 3H, J 7.3 Hz), 1.46-1.38 (m, 2H), 1.74-1.67 (m, 2H), 3.48 (d, 1H, J 17.5 Hz), 3.63 (d, 1H, J 17.5 Hz), 3.71-3.67 (m, 1H), 3.85-3.79 (m, 1H), 4.07-3.98 (m, 1H), 6.96-6.94 (m, 1H), 7.38-7.35 (m, 2H), 7.48-7.45 (m, 1H), 7.54-7.52 (m, 2H), 8.30-8.29 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 13.66, 20.08, 29.07, 40.51, 51.74, 73.08, 87.37, 93.43, 108.55, 119.09, 120.07, 127.17, 128.70, 130.05, 131.31, 133.21, 143.52, 149.24, 176.46, 182.87; HRMS (ESI) exact mass calcd. for (C₂₂H₂₀N₂NaO₅)⁺ requires m/z 415.1270, found m/z 415.1264.

1-Butyl-3-hydroxy-5-methoxy-3-(2-oxo-4-phenylbut-3-ynyl) indolin-2-one (4i)

Yield: 94%; $[\alpha]_D^{15} = +1.37^\circ$ ($c = 0.277$, CHCl₃, $ee = 78\%$), determined by HPLC (Daicel Chiralpak OD-H, hexane/isopropanol = 80/20, flow rate 1.0 mL min⁻¹) t_R /min 10.62 (major), 14.88 (minor); IR (KBr) ν_{\max} /cm⁻¹ 2933, 2193, 1694, 1667, 1489, 1352, 1284, 1036, 758, 689; ¹H NMR (500 MHz, CDCl₃) δ 0.93 (t, 3H, J 7.4 Hz), 1.43-1.35 (m, 2H), 1.69-1.63 (m, 2H), 3.29 (d, 1H, J 16.7 Hz), 3.49 (d, 1H, J 16.7 Hz), 3.64-3.57 (m, 1H), 3.74-3.68 (m, 1H), 3.77 (s, 3H), 4.09 (s, 1H), 6.77-6.75 (m, 1H), 6.85-6.82 (m, 1H), 7.09-7.08 (m, 1H), 7.38-7.35 (m, 2H), 7.47-7.44 (m, 1H), 7.54-7.52 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 13.73, 20.12, 29.19, 40.03, 51.68, 55.82, 74.39, 87.88, 92.67, 109.43, 111.49, 114.64, 119.42, 128.62, 130.39, 131.07, 133.18, 136.34, 156.18, 175.60, 183.89; HRMS (ESI) exact mass calcd. for (C₂₃H₂₃NNaO₄)⁺ requires m/z 400.1525, found m/z 400.1521.

6-Bromo-1-butyl-3-hydroxy-3-(2-oxo-4-phenylbut-3-ynyl) indolin-2-one (4j)

Yield: 97%; $[\alpha]_D^{15} = +4.14^\circ$ ($c = 0.406$, CHCl₃, $ee = 70\%$), determined by HPLC (Daicel Chiralpak IA, hexane/isopropanol = 90/10, flow rate 1.0 mL min⁻¹) t_R /min 14.83 (minor), 16.84 (major); IR (KBr) ν_{\max} /cm⁻¹ 2955, 2930, 2198, 1708, 1668, 1606, 1488, 1363, 1061, 758, 688; ¹H NMR (500 MHz, CDCl₃) δ 0.95 (t, 3H, J 7.4 Hz), 1.43-1.36 (m, 2H), 1.69-1.63 (m, 2H), 3.31 (d, 1H, J 16.9 Hz), 3.50 (d, 1H, J 16.9 Hz), 3.62-3.56 (m, 1H), 3.73-3.67 (m, 1H), 4.10-3.98 (m, 1H), 7.00-6.99 (m, 1H), 7.20-7.19 (m, 1H), 7.30-7.29 (m, 1H), 7.39-7.36 (m, 2H), 7.48-7.45 (m, 1H), 7.53-7.51 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 13.69, 20.10, 29.07, 40.15, 51.53, 73.62, 87.72, 93.00, 112.41, 119.29, 123.88, 125.59, 125.74, 128.15,

128.67, 131.19, 133.21, 144.57, 175.77, 183.60; HRMS (ESI) exact mass calcd. for (C₂₂H₂₀BrNNaO₃)⁺ requires m/z 448.0524, found m/z 448.0523.

1-Butyl-7-fluoro-3-hydroxy-3-(2-oxo-4-phenylbut-3-ynyl) indolin-2-one (4k)

Yield: 95%; $[\alpha]_D^{15} = +3.61^\circ$ ($c = 0.338$, CHCl₃, $ee = 65\%$), determined by HPLC (Daicel Chiralpak IA, hexane/isopropanol = 85/15, flow rate 1.0 mL min⁻¹) t_R /min 9.02 (minor), 10.33 (major); IR (KBr) ν_{\max} /cm⁻¹ 2959, 2200, 1705, 1669, 1362, 1126, 1058, 759, 732, 689; ¹H NMR (500 MHz, CDCl₃) δ 0.94 (t, 3H, J 7.4 Hz), 1.44-1.36 (m, 2H), 1.72-1.67 (m, 2H), 3.35 (d, 1H, J 16.9 Hz), 3.51 (d, 1H, J 16.9 Hz), 3.89-3.77 (m, 2H), 4.14 (s, 1H), 7.08-6.99 (m, 2H), 7.24-7.22 (m, 1H), 7.39-7.36 (m, 2H), 7.48-7.44 (m, 1H), 7.54-7.52 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 13.70, 19.88, 30.66, 30.68, 42.01, 42.05, 51.75, 74.01, 74.03, 87.74, 92.86, 118.21, 118.37, 119.34, 119.99, 120.02, 123.73, 123.79, 128.65, 129.77, 129.84, 131.15, 132.15, 132.17, 133.20, 146.55, 148.50, 175.66, 183.56; HRMS (ESI) exact mass calcd. for (C₂₂H₂₀FNNaO₃)⁺ requires m/z 388.1325, found m/z 388.1318.

1-Butyl-3-hydroxy-3-(2-oxo-4-*p*-tolylbut-3-ynyl)indolin-2-one (4ba)

Yield: 53%; $[\alpha]_D^{15} = +12.4^\circ$ ($c = 0.062$, CHCl₃, $ee = 78\%$), determined by HPLC (Daicel Chiralpak AS-H, hexane/isopropanol = 80/20, flow rate 1.0 mL min⁻¹) t_R /min 13.03 (major), 18.40 (minor); IR (KBr) ν_{\max} /cm⁻¹ 2955, 2199, 1704, 1669, 1362, 1062, 817, 753; ¹H NMR (500 MHz, CDCl₃) δ 0.94 (t, 3H, J 7.4 Hz), 1.44-1.36 (m, 2H), 1.70-1.65 (m, 2H), 2.38 (s, 3H), 3.28 (d, 1H, J 16.7 Hz), 3.49 (d, 1H, J 16.7 Hz), 3.68-3.60 (m, 1H), 3.76-3.70 (m, 1H), 4.05-4.01 (m, 1H), 6.86-6.84 (m, 1H), 7.07-7.04 (m, 1H), 7.18-7.16 (m, 2H), 7.33-7.30 (m, 1H), 7.45-7.42 (m, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 13.72, 20.13, 21.75, 29.20, 39.95, 51.47, 74.10, 87.85, 93.53, 108.90, 116.29, 122.92, 124.31, 129.30, 129.44, 130.05, 133.26, 141.94, 143.10, 175.81, 184.08; HRMS (ESI) exact mass calcd. for (C₂₃H₂₃NNaO₃)⁺ requires m/z 384.1576, found m/z 384.1574.

1-Butyl-3-hydroxy-3-(2-oxobut-3-ynyl)indolin-2-one (4ca)

Yield: 70%; IR (KBr) ν_{\max} /cm⁻¹ 3234, 2952, 2923, 2087, 1682, 1614, 1338, 1125, 1099, 752; ¹H NMR (500 MHz, CDCl₃) δ 0.96 (t, 3H, J 7.4 Hz), 1.44-1.40 (m, 2H), 1.69-1.65 (m, 2H), 3.24 (d, 1H, J 17.1 Hz), 3.27 (s, 1H), 3.43 (d, 1H, J 17.1 Hz), 3.66-3.60 (m, 1H), 3.76-3.70

(m, 1H), 3.76 (s, 1H), 6.86-6.85 (m, 1H), 7.08-7.05 (m, 1H), 7.34-7.31 (m, 1H), 7.40-7.38 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 13.72, 20.13, 29.17, 39.99, 51.67, 73.69, 79.99, 81.20, 108.98, 122.96, 124.13, 128.91, 130.21, 143.21, 175.77, 183.20; HRMS (ESI) exact mass calcd. for $(\text{C}_{16}\text{H}_{17}\text{NNaO}_3)^+$ requires m/z 294.1106, found m/z 294.1102.

Benzyl 2-hydroxy-4-oxo-2,6-diphenylhex-5-ynoate (**4l**)

Yield: 42%; $[\alpha]_{\text{D}}^{15} = +2.65^\circ$ ($c = 0.066$, CHCl_3 , ee = 47%), determined by HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 80/20, flow rate 1.0 mL min $^{-1}$) t_{R} /min 24.39 (major), 30.26 (minor); IR (KBr) ν_{max} /cm $^{-1}$ 2936, 2196, 1732, 1668, 1204, 1178, 1086, 757, 695; ^1H NMR (500 MHz, CDCl_3) δ 3.35 (d, 1H, J 17.8 Hz), 3.80 (d, 1H, J 17.8 Hz), 4.24 (s, 1H), 5.23-5.17 (m, 2H), 7.26-7.24 (m, 2H), 7.32-7.29 (m, 4H), 7.39-7.33 (m, 4H), 7.48-7.44 (m, 1H), 7.55-7.53 (m, 2H), 7.60-7.57 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 54.72, 68.14, 76.07, 87.61, 92.49, 119.52, 125.10, 128.20, 128.39, 128.49, 128.52, 128.63, 131.01, 133.13, 134.96, 140.02, 173.46, 184.73; HRMS (ESI) exact mass calcd. for $(\text{C}_{25}\text{H}_{20}\text{NaO}_4)^+$ requires m/z 407.1259, found m/z 407.1258.

Isopropyl 2-hydroxy-4-oxo-2,6-diphenylhex-5-ynoate (**4m**)

Yield: 36%; $[\alpha]_{\text{D}}^{15} = +2.69^\circ$ ($c = 0.078$, CHCl_3 , ee = 63%), determined by HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90/10, flow rate 1.0 mL min $^{-1}$) t_{R} /min 18.79 (major), 28.04 (minor); IR (KBr) ν_{max} /cm $^{-1}$ 2923, 2190, 1722, 1670, 1263, 1219, 1104, 1085, 758, 689; ^1H NMR (500 MHz, CDCl_3) δ 1.27-1.24 (m, 6H), 3.34 (d, 1H, J 17.8 Hz), 3.76 (d, 1H, J 17.8 Hz), 4.19 (s, 1H), 5.10 (hept, 1H, J 6.3 Hz), 7.33-7.29 (m, 1H), 7.40-7.35 (m, 4H), 7.48-7.44 (m, 1H), 7.57-7.54 (m, 2H), 7.64-7.61 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 21.49, 54.88, 70.50, 75.82, 87.66, 92.07, 119.61, 125.05, 128.07, 128.41, 128.63, 130.95, 133.12, 140.48, 173.05, 184.48; HRMS (ESI) exact mass calcd. for $(\text{C}_{21}\text{H}_{20}\text{NaO}_4)^+$ requires m/z 359.1259, found m/z 359.1256.

Isobutyl 2-hydroxy-4-oxo-2,6-diphenylhex-5-ynoate (**4n**)

Yield: 34%; $[\alpha]_{\text{D}}^{15} = +3.13^\circ$ ($c = 0.083$, CHCl_3 , ee = 62%), determined by HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 80/20, flow rate 1.0 mL min $^{-1}$) t_{R} /min 12.56 (major), 15.99 (minor); IR (KBr) ν_{max} /cm $^{-1}$ 2959, 2190, 1723, 1668, 1278, 1205, 1125, 1086, 758, 689; ^1H NMR (500 MHz, CDCl_3) δ 0.89 (d, 6H, J 6.7 Hz), 2.01-1.92 (m, 1H), 3.37 (d, 1H, J 17.8 Hz), 3.80 (d, 1H, J 17.8 Hz), 3.98 (d, 2H, J 6.6 Hz), 4.24 (s, 1H), 7.33-7.30 (m, 1H), 7.40-7.36 (m, 4H), 7.48-7.44 (m, 1H), 7.57-7.55 (m, 2H), 7.64-7.62 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 18.92, 18.96, 27.61, 54.71, 72.50, 75.94, 87.61, 92.28, 119.56, 125.10, 128.15, 128.45, 128.63, 130.98, 133.13, 140.35, 173.68, 184.61; HRMS (ESI) exact mass calcd. for $(\text{C}_{22}\text{H}_{22}\text{NaO}_4)^+$ requires m/z 373.1416, found m/z 373.1411.

Ethyl 2-hydroxy-4-oxo-2,6-diphenylhex-5-ynoate (**4o**)

Yield: 44%; $[\alpha]_{\text{D}}^{15} = +4.43^\circ$ ($c = 0.07$, CHCl_3 , ee = 60%), determined by HPLC (Daicel Chiralpak IA, hexane/isopropanol = 90/10, flow rate 1.0 mL min $^{-1}$) t_{R} /min 14.92 (major), 16.93 (minor); IR (KBr) ν_{max} /cm $^{-1}$ 2962, 2923, 2200, 1731, 1669, 1363, 1261, 1221, 1085, 759, 689; ^1H NMR (500 MHz, CDCl_3) δ 1.28 (t, 3H, J 7.1 Hz), 3.34 (d, 1H, J 17.8 Hz), 3.79 (d, 1H, J 17.8 Hz), 4.22 (s, 1H), 4.27 (q, 2H, J 7.1 Hz), 7.34-7.31 (m, 1H), 7.40-7.37 (m, 4H), 7.48-7.45 (m, 1H), 7.57-7.55 (m, 2H), 7.63-7.62 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 13.96, 54.90, 62.54, 75.94, 87.62, 92.29, 119.57, 125.05, 128.15, 128.48, 128.64, 130.99, 133.14, 140.31, 173.57, 184.69; HRMS (ESI) exact mass calcd. for $(\text{C}_{20}\text{H}_{18}\text{NaO}_4)^+$ requires m/z 345.1103, found m/z 345.1107.

References

- Hu, S.; Neckers, D. C.; *J. Org. Chem.* **1996**, *61*, 6407; Di Mauro, E. F.; Kozlowshi, M. C.; *J. Am. Chem. Soc.* **2002**, *124*, 12668.
- Vakulya, B.; Varga, S.; Csampai, A.; Soos, T.; *Org. Lett.* **2005**, *7*, 1967.
- Arjan, H.; Boyd, E.; Coumbarides, G. S.; Eames, J.; Jones, R. V. H.; Stenson, R. A.; Suggate, M. J.; *Tetrahedron Lett.* **2005**, *46*, 1921.
- Okino, T.; Hoashi, Y.; Takemoto, Y.; *J. Am. Chem. Soc.* **2003**, *125*, 12672.

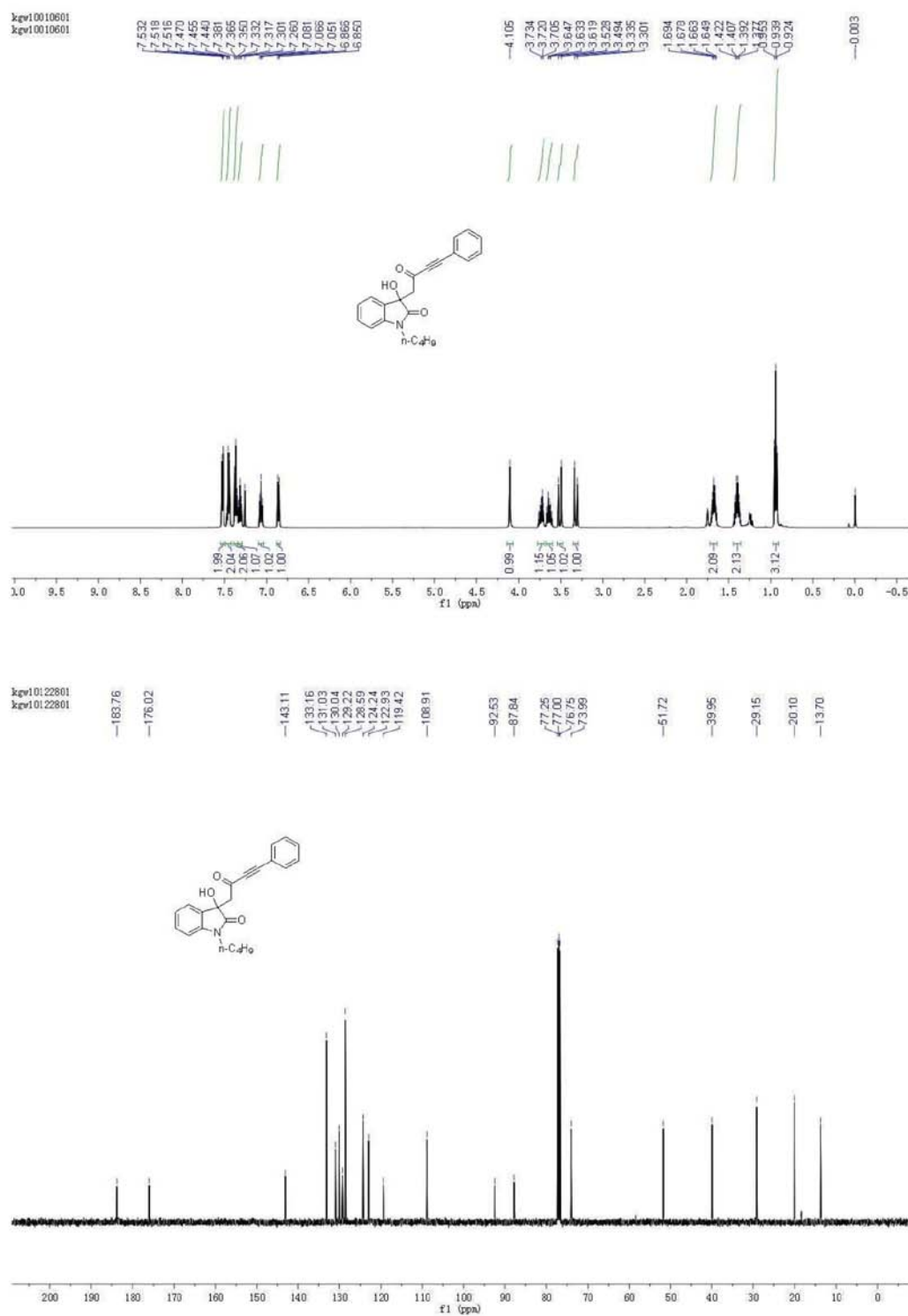


Figure S1. ^1H NMR spectrum (500 MHz, CDCl_3) and ^{13}C NMR spectrum (126 MHz, CDCl_3) of compound **4a**.

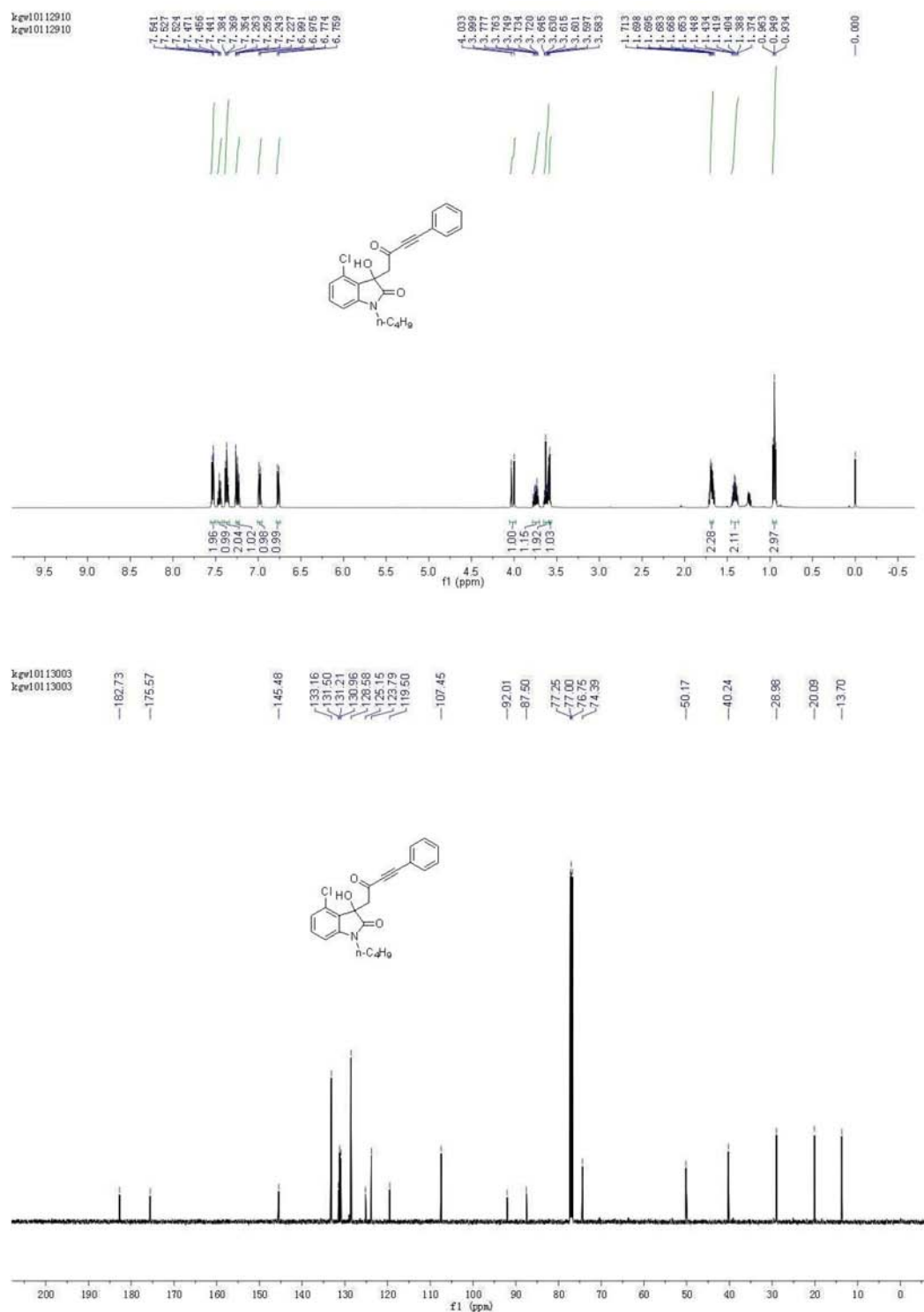


Figure S2. ^1H NMR spectrum (500 MHz, CDCl_3) and ^{13}C NMR spectrum (126 MHz, CDCl_3) of compound **4b**.

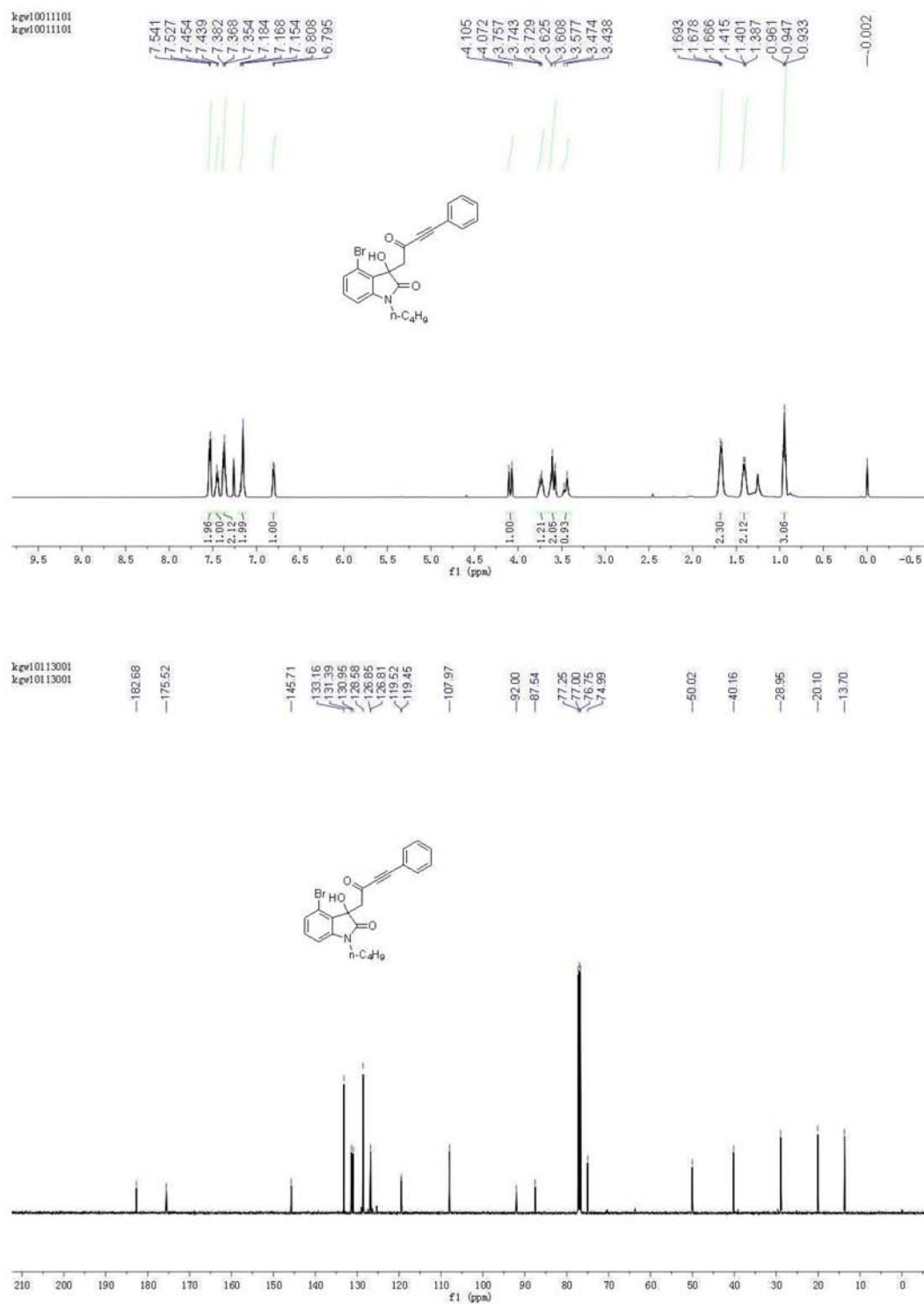


Figure S3. ¹H NMR spectrum (500 MHz, CDCl₃) and ¹³C NMR spectrum (126 MHz, CDCl₃) of compound **4c**.

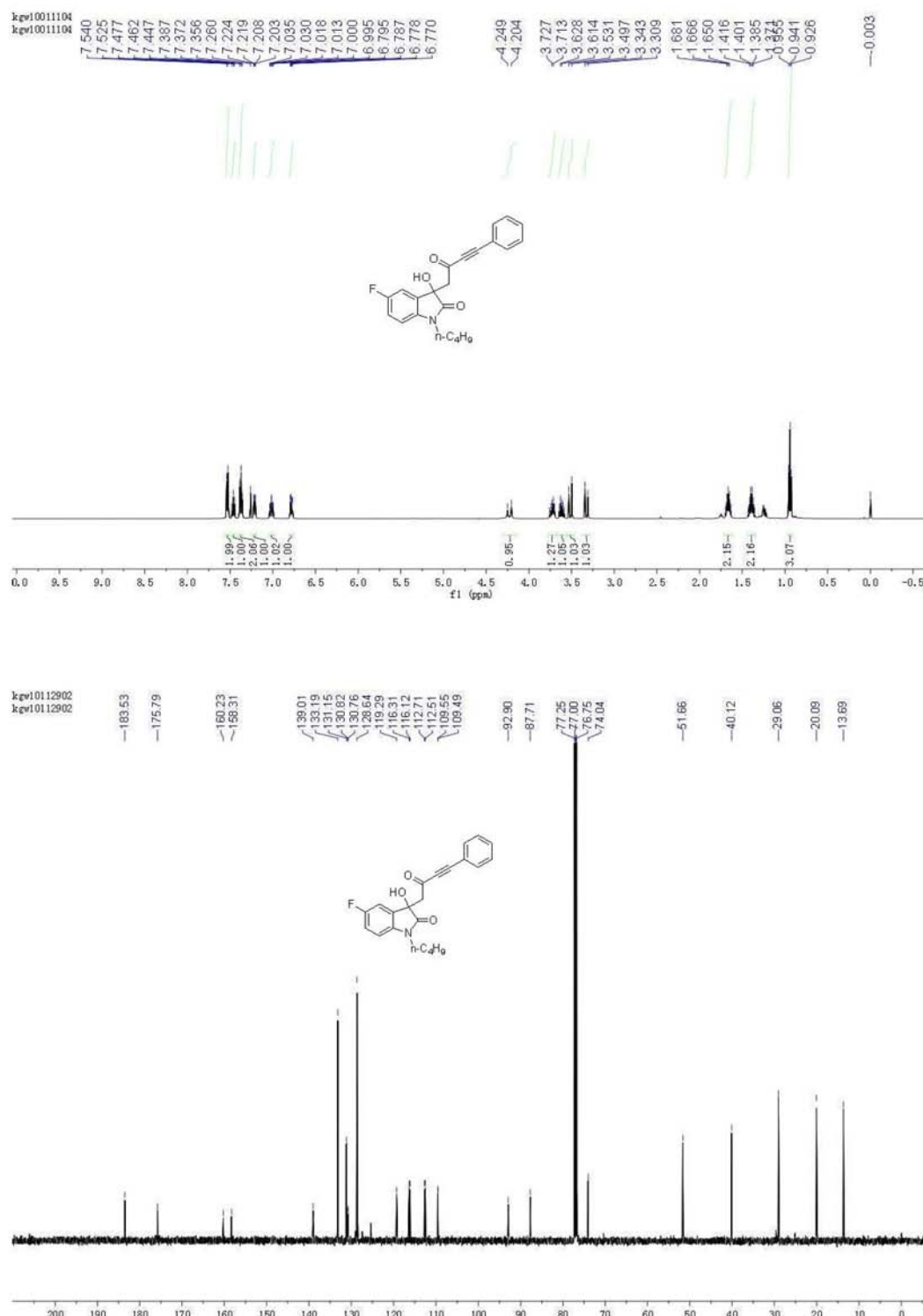


Figure S4. ^1H NMR spectrum (500 MHz, CDCl_3) and ^{13}C NMR spectrum (126 MHz, CDCl_3) of compound **4e**.

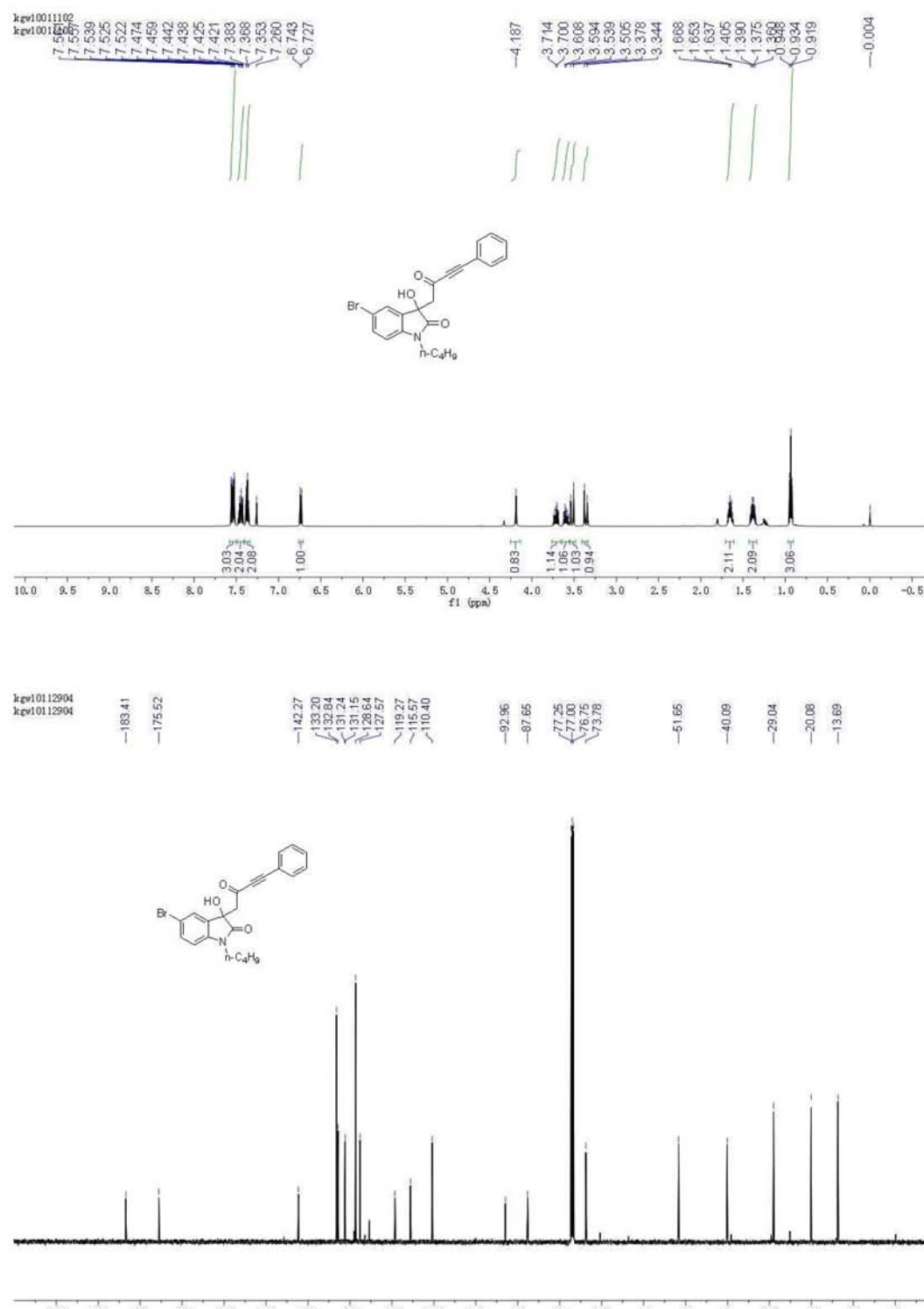


Figure S5. ¹H NMR spectrum (500 MHz, CDCl₃) and ¹³C NMR spectrum (126 MHz, CDCl₃) of compound **4g**.

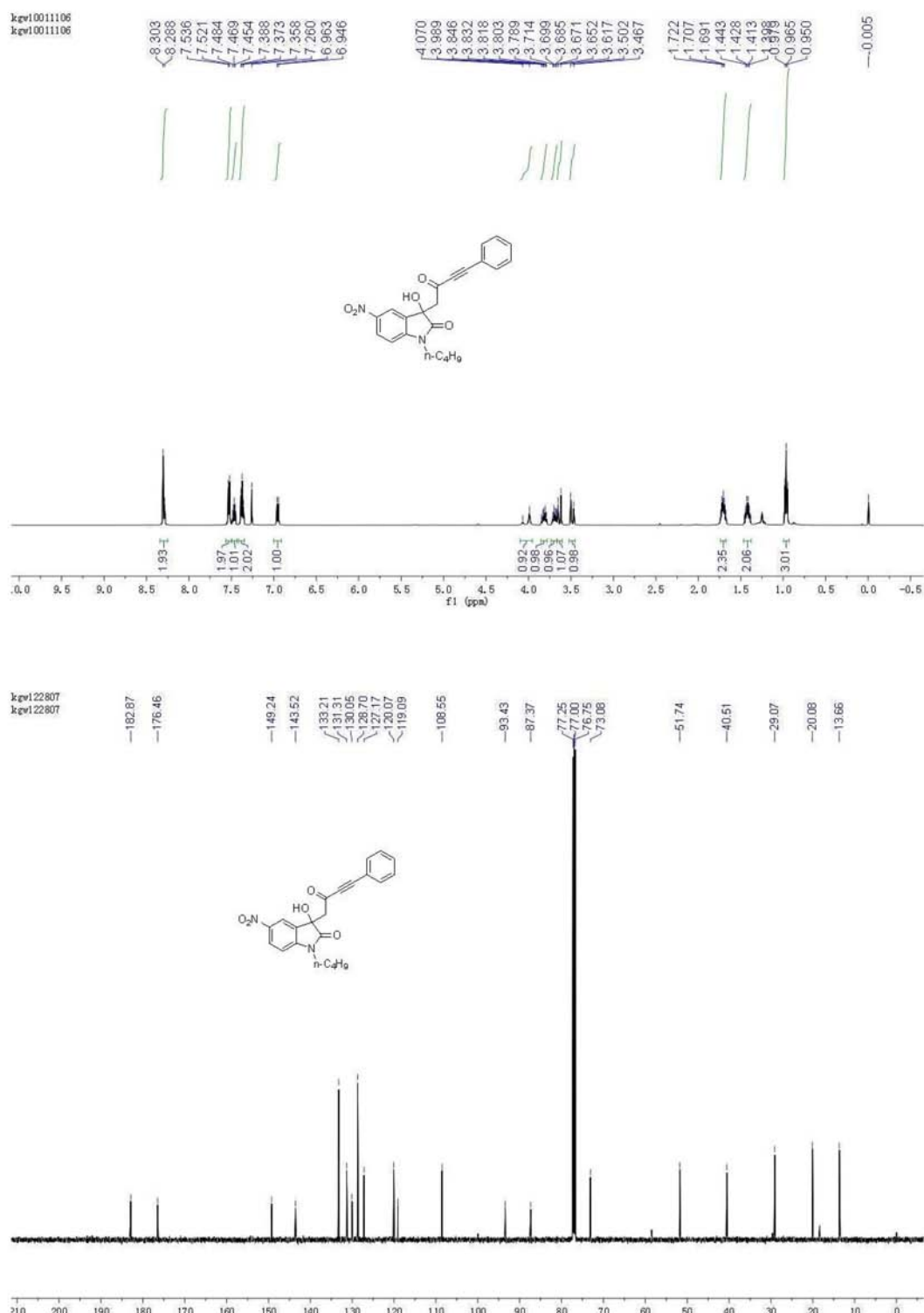


Figure S6. ^1H NMR spectrum (500 MHz, CDCl_3) and ^{13}C NMR spectrum (126 MHz, CDCl_3) of compound **4h**.

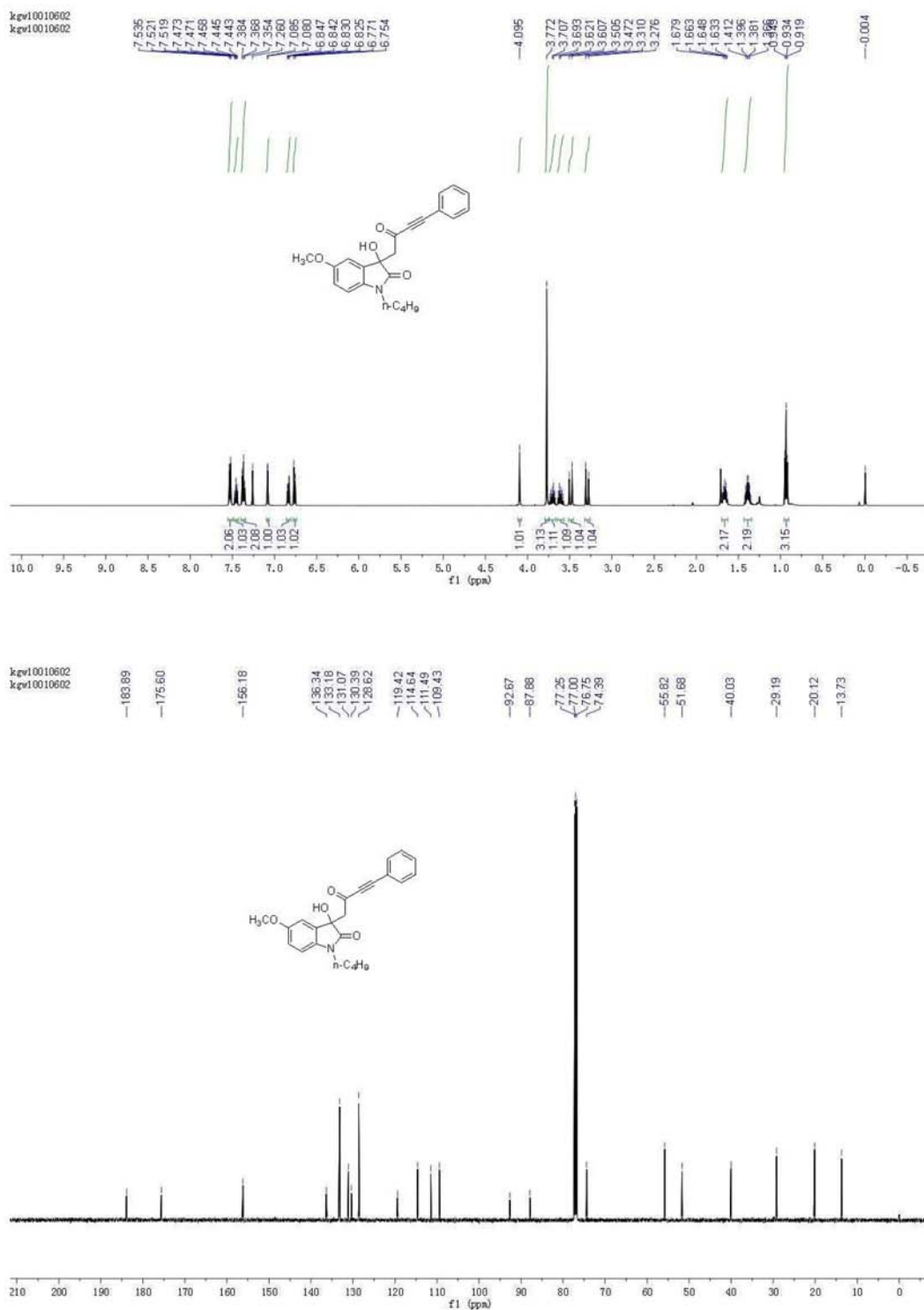


Figure S7. ¹H NMR spectrum (500 MHz, CDCl₃) and ¹³C NMR spectrum (126 MHz, CDCl₃) of compound **4i**.

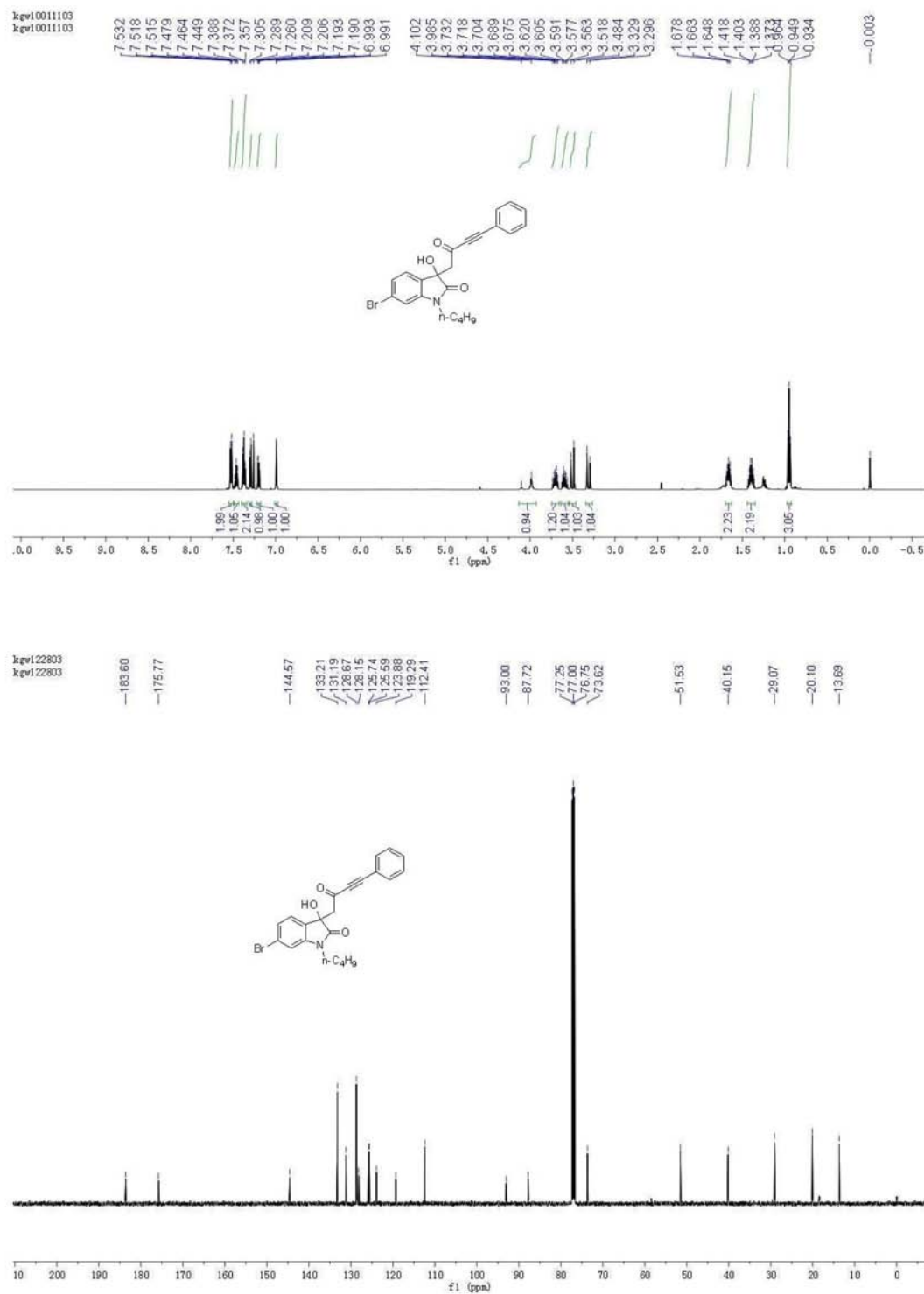
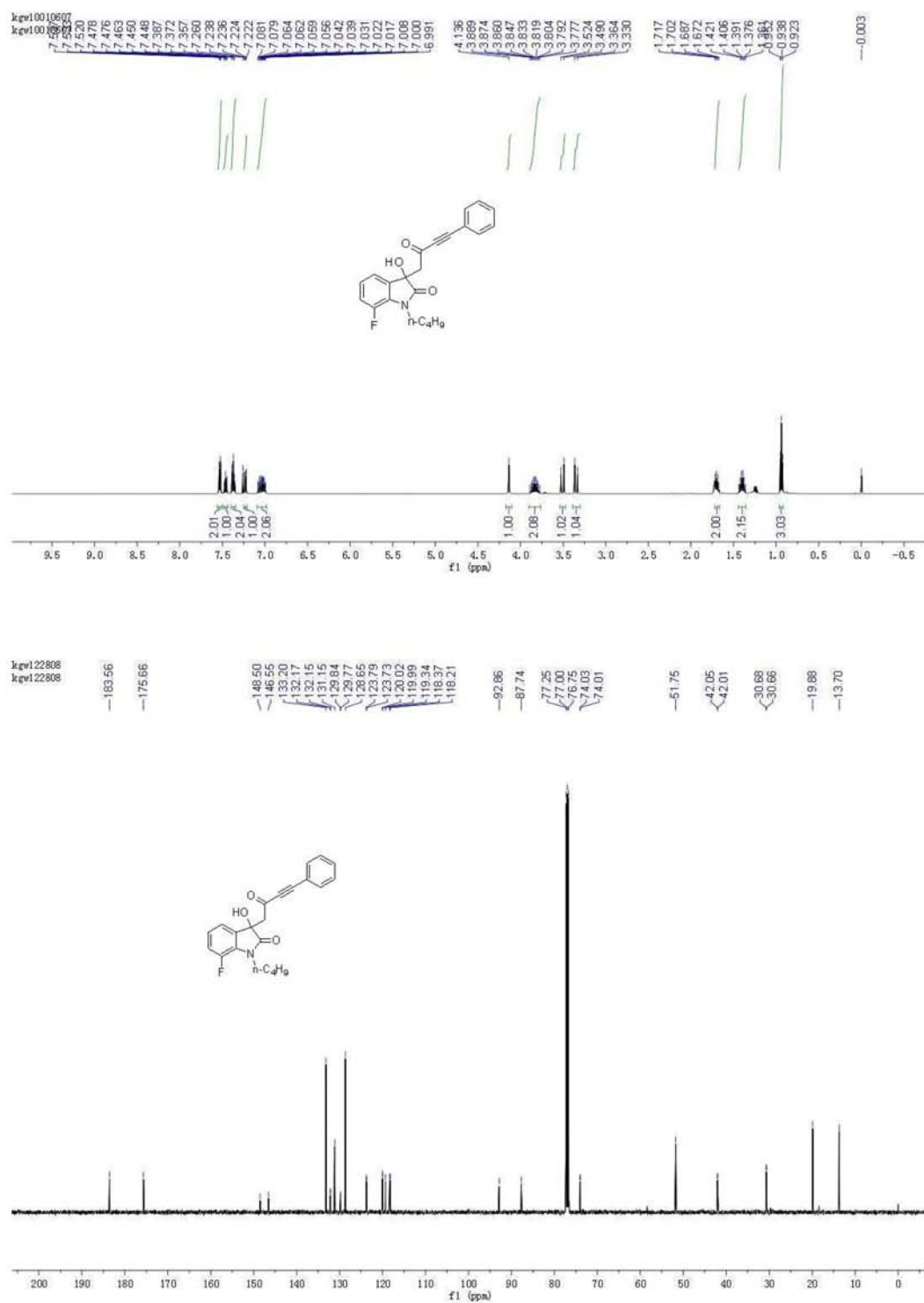


Figure S8. ^1H NMR spectrum (500 MHz, CDCl_3) and ^{13}C NMR spectrum (126 MHz, CDCl_3) compound of **4j**.



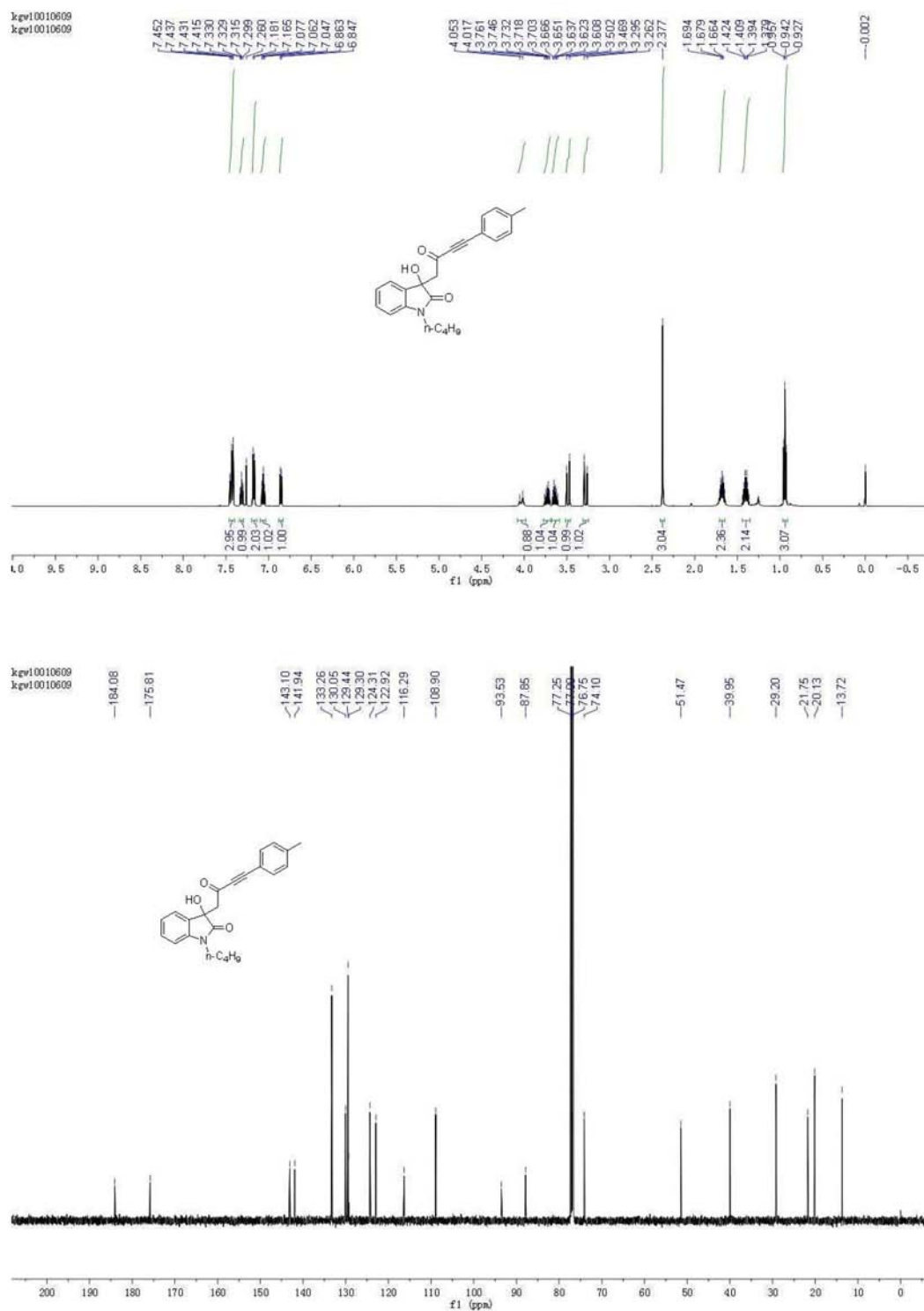


Figure S10. ^1H NMR spectrum (500 MHz, CDCl_3) and ^{13}C NMR spectrum (126 MHz, CDCl_3) of compound **4ba**.

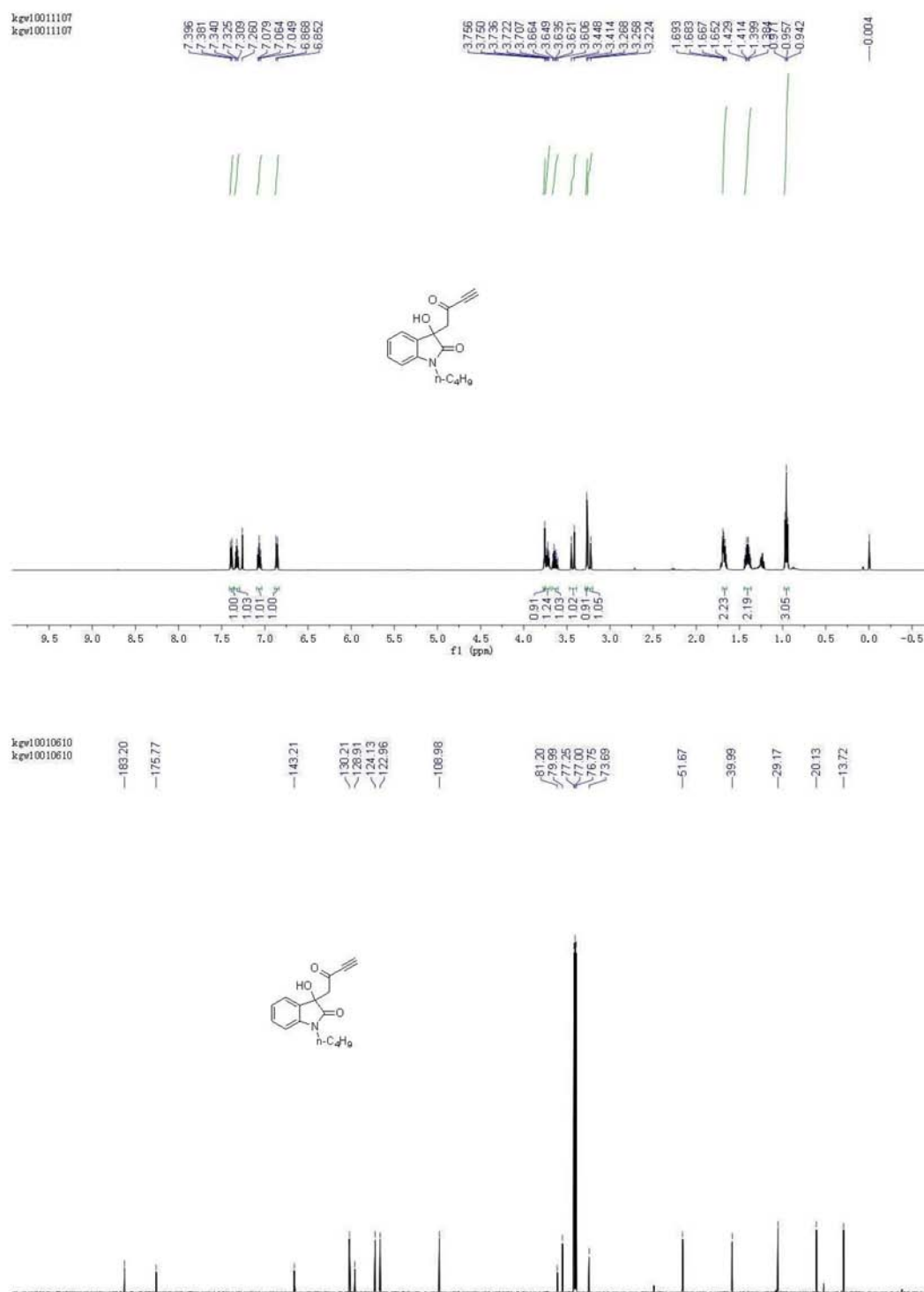
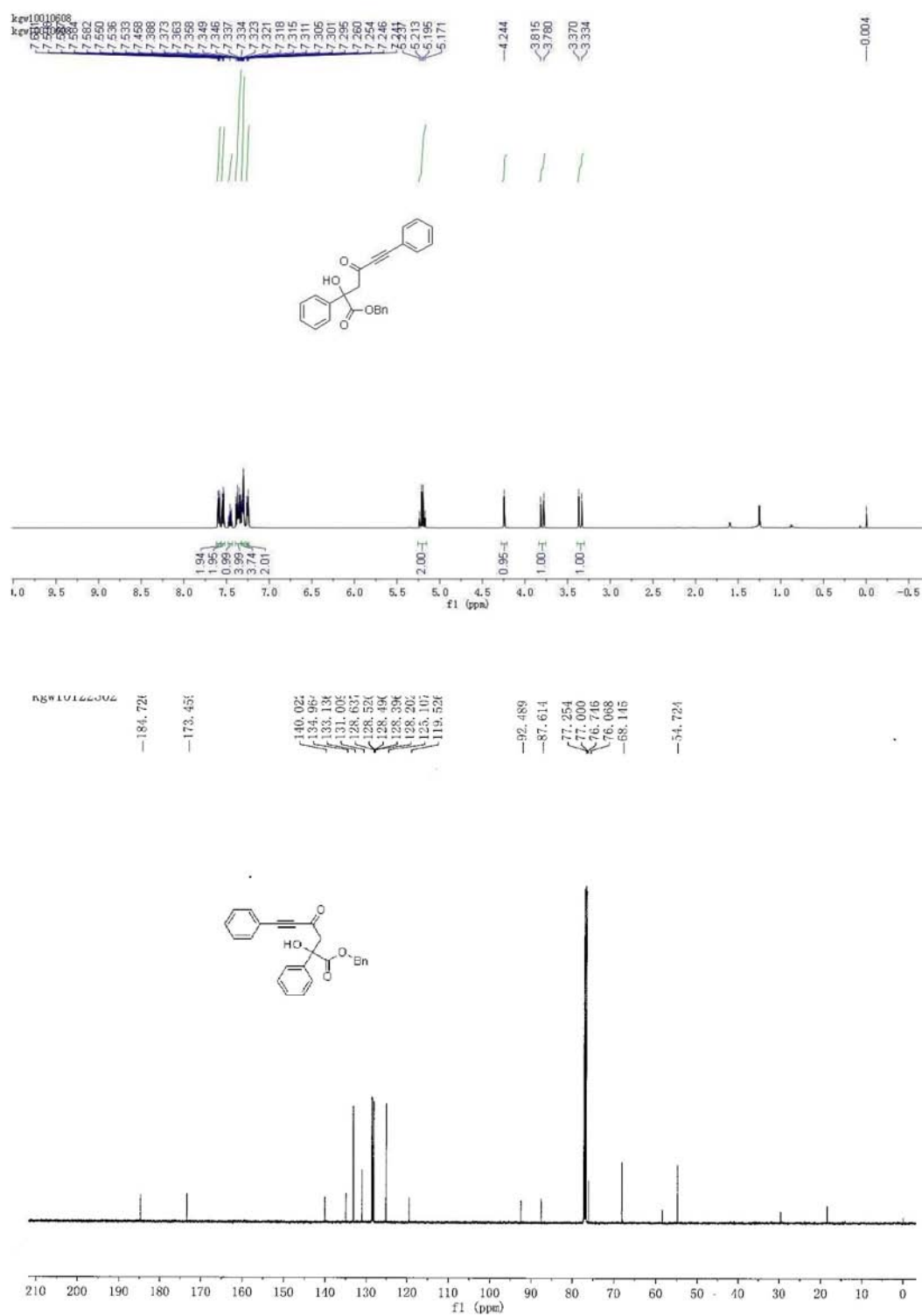
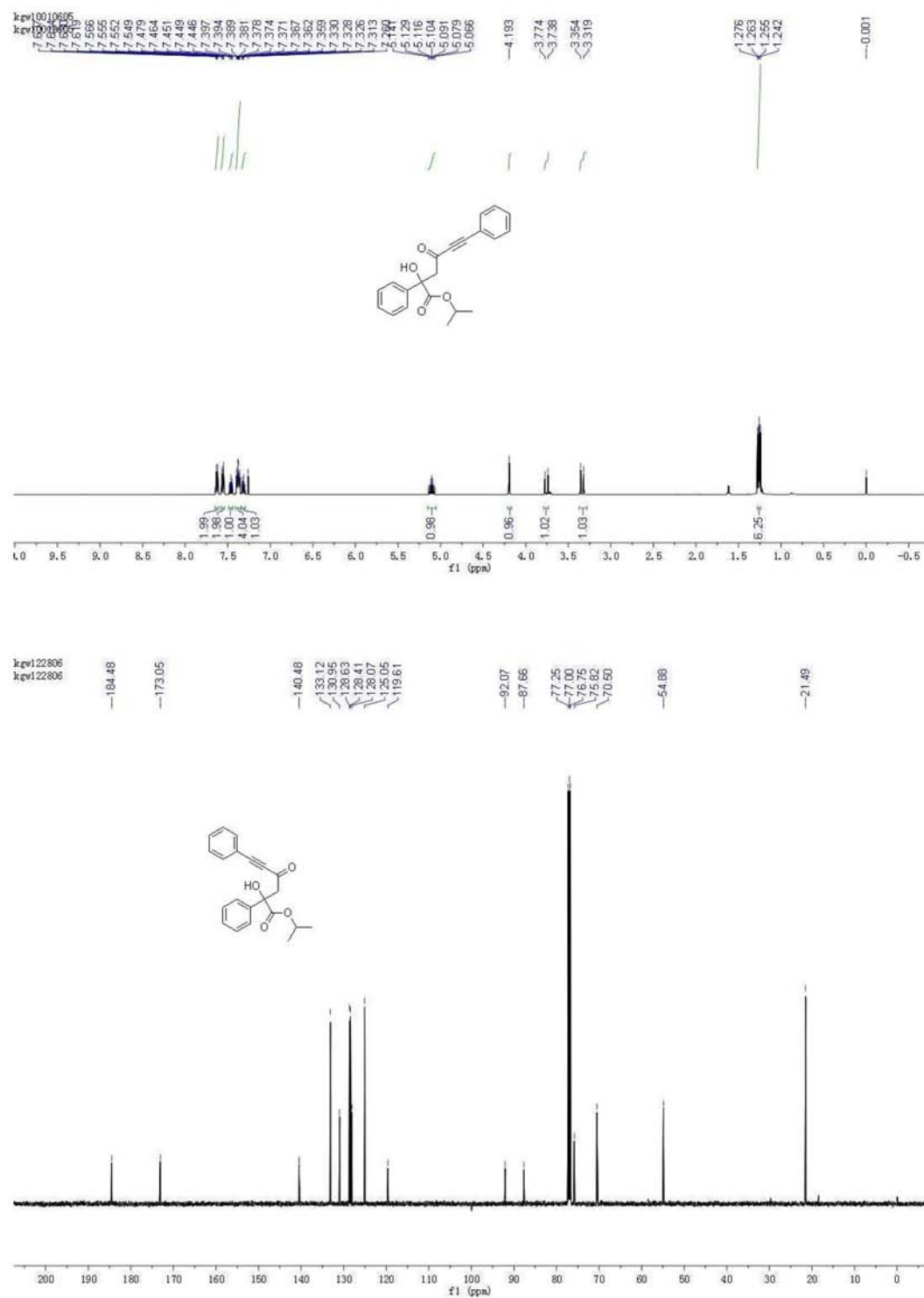


Figure S11. ¹H NMR spectrum (500 MHz, CDCl₃) and ¹³C NMR spectrum (126 MHz, CDCl₃) of compound **4ca**.





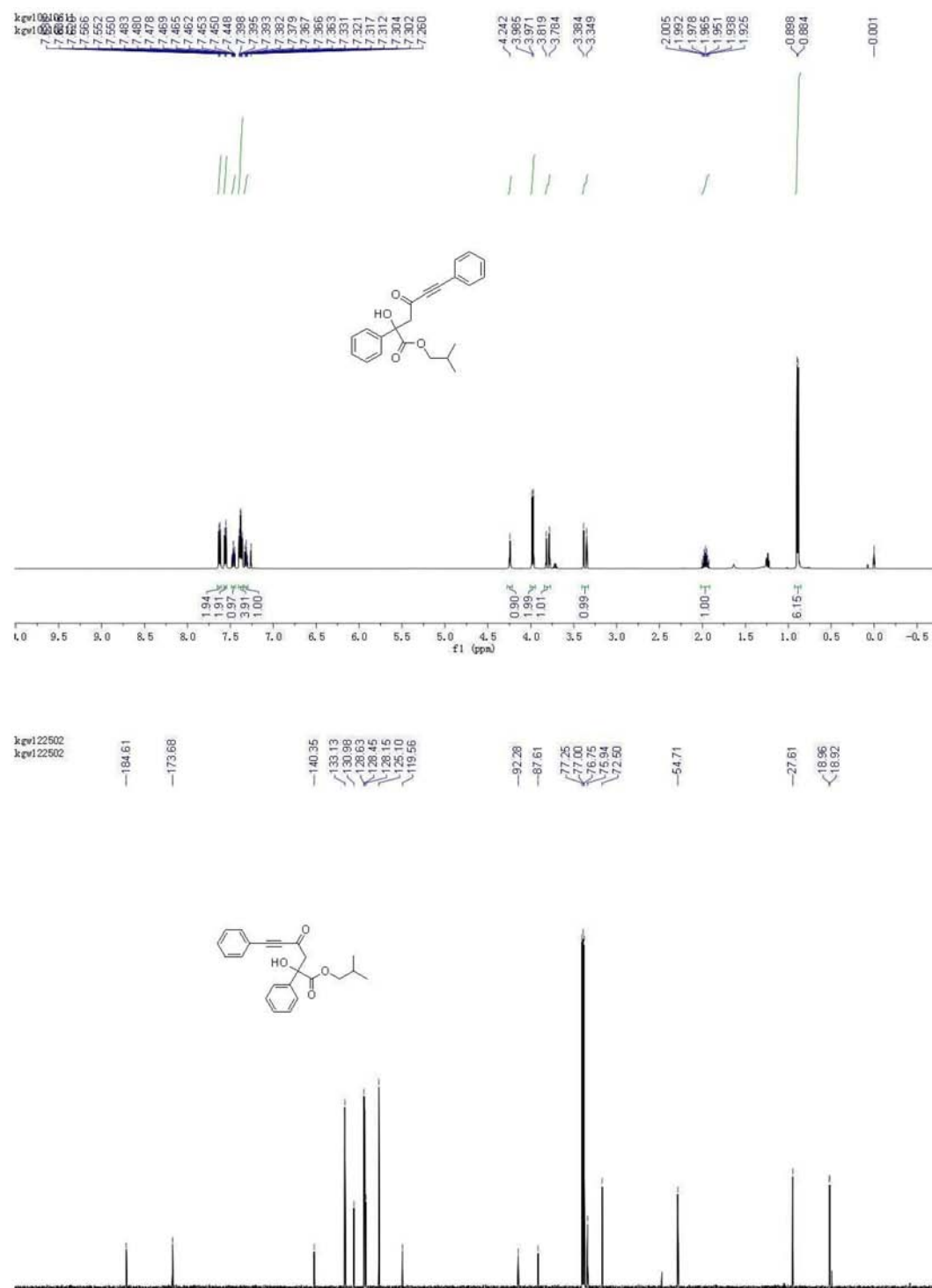


Figure S14. ^1H NMR spectrum (500 MHz, CDCl_3) and ^{13}C NMR spectrum (126 MHz, CDCl_3) of compound **4n**.

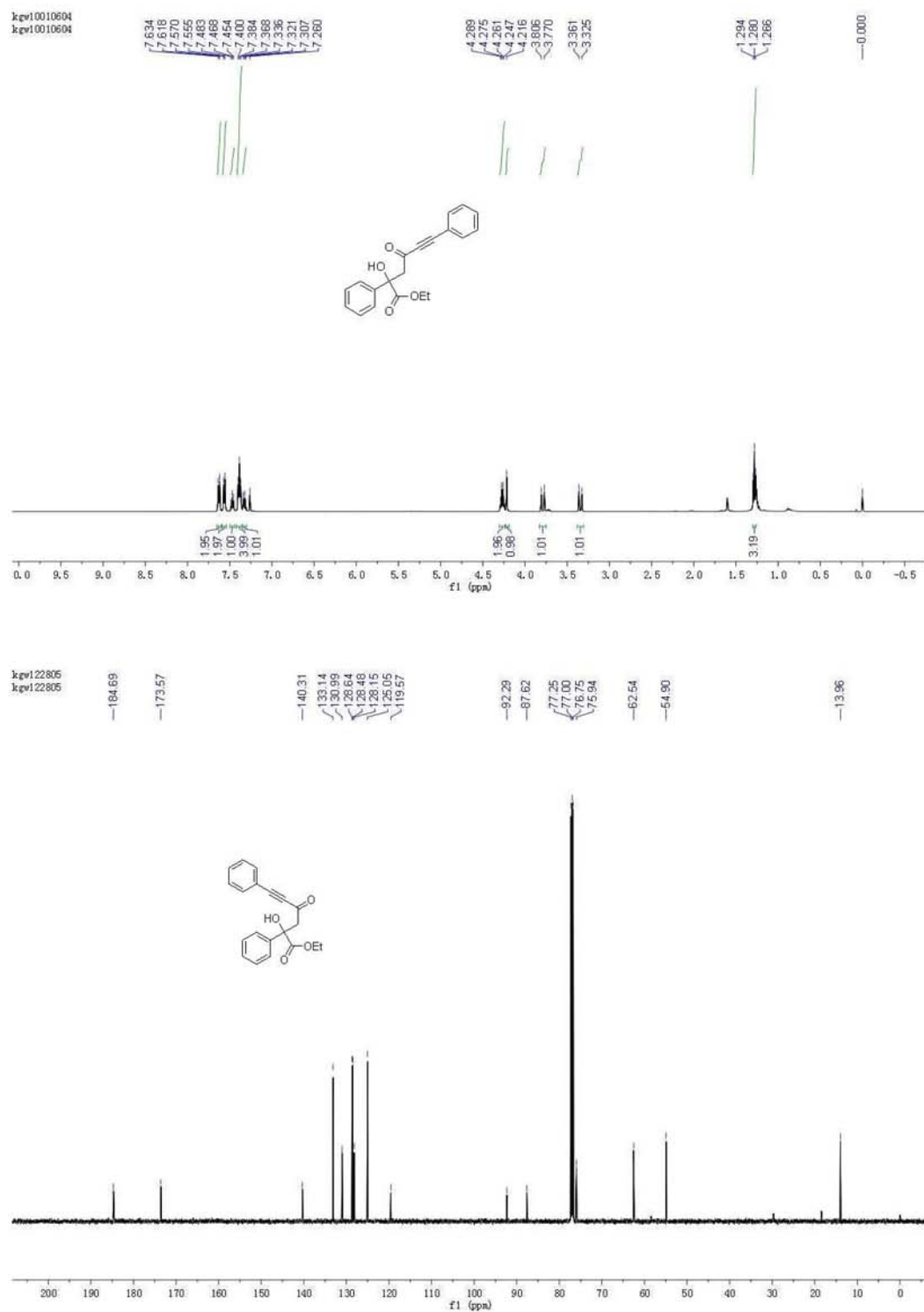


Figure S15. ^1H NMR spectrum (500 MHz, CDCl_3) and ^{13}C NMR spectrum (126 MHz, CDCl_3) of compound **4o**.

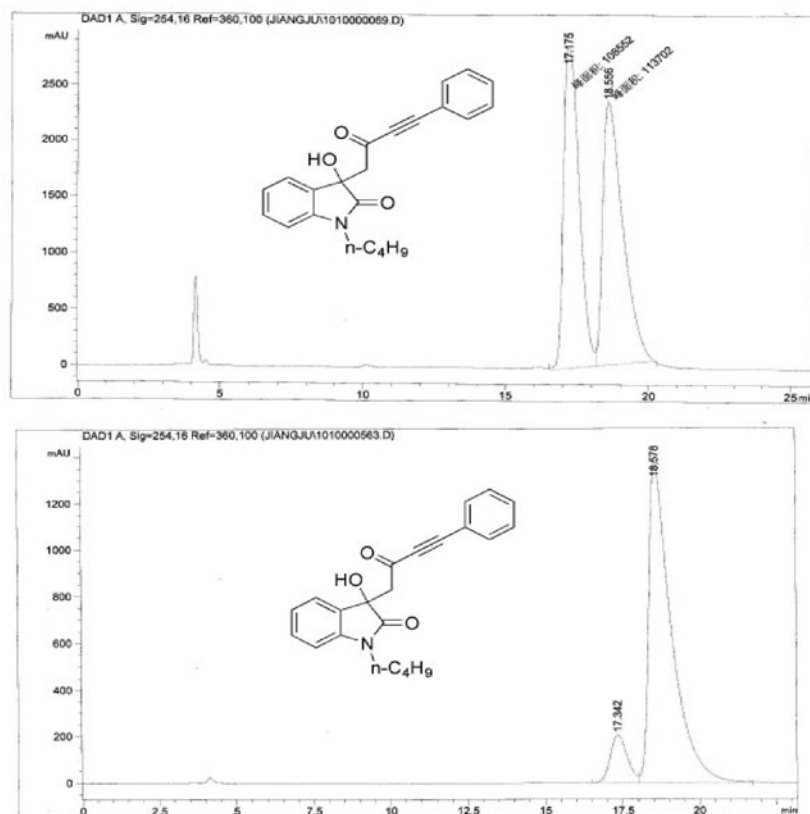


Figure S16. HPLC of compound 4a.

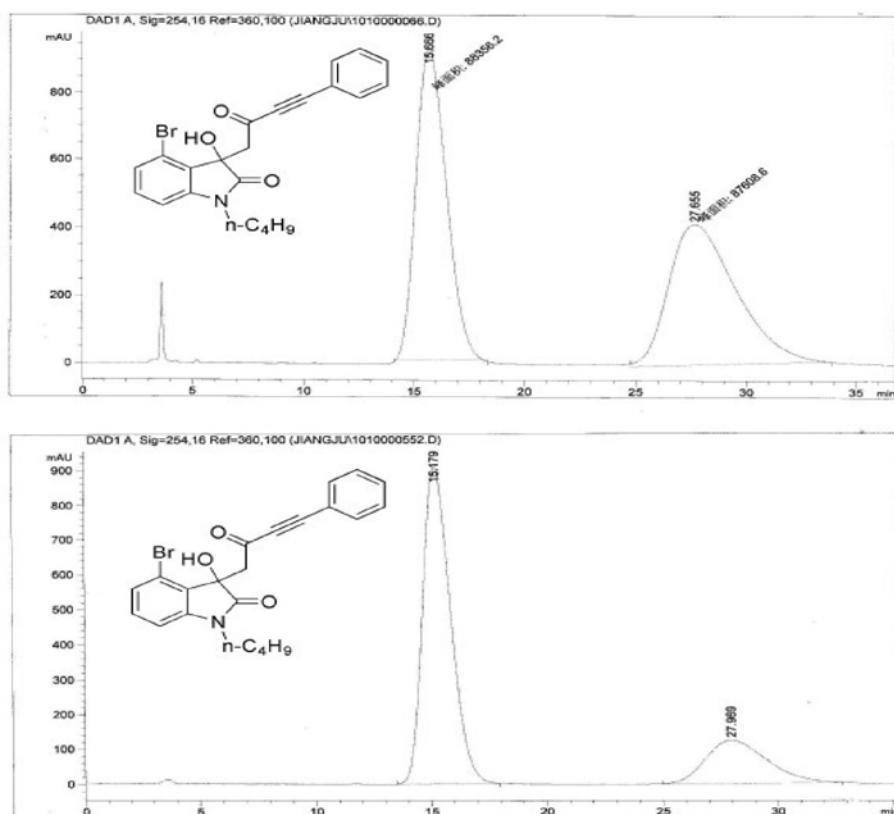


Figure S17. HPLC of compound 4c.

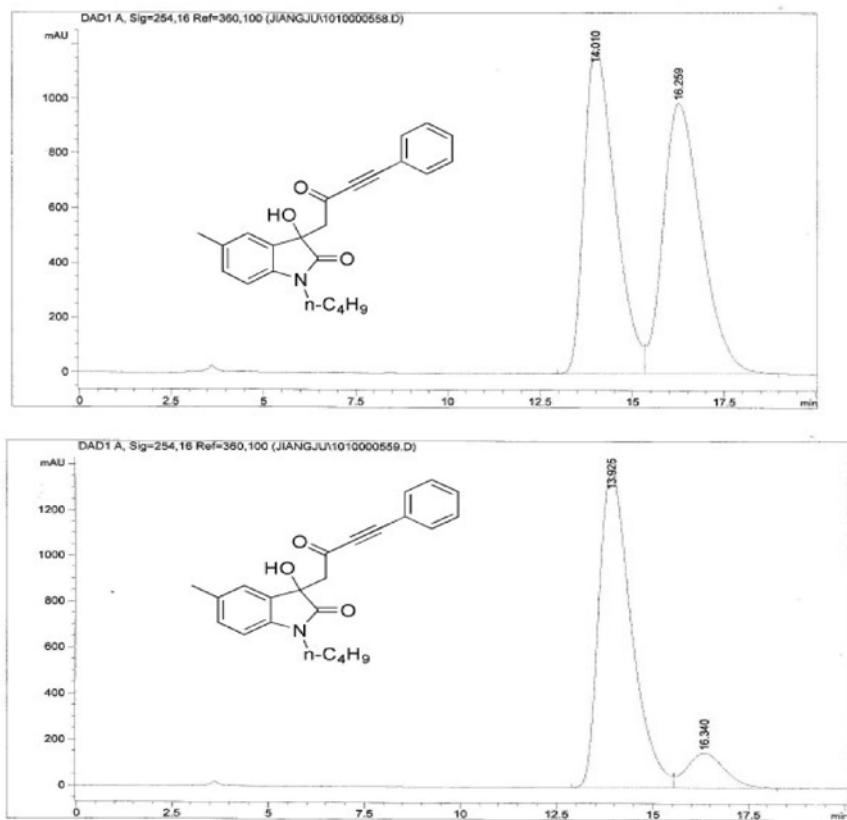


Figure S18. HPLC of compound 4d.

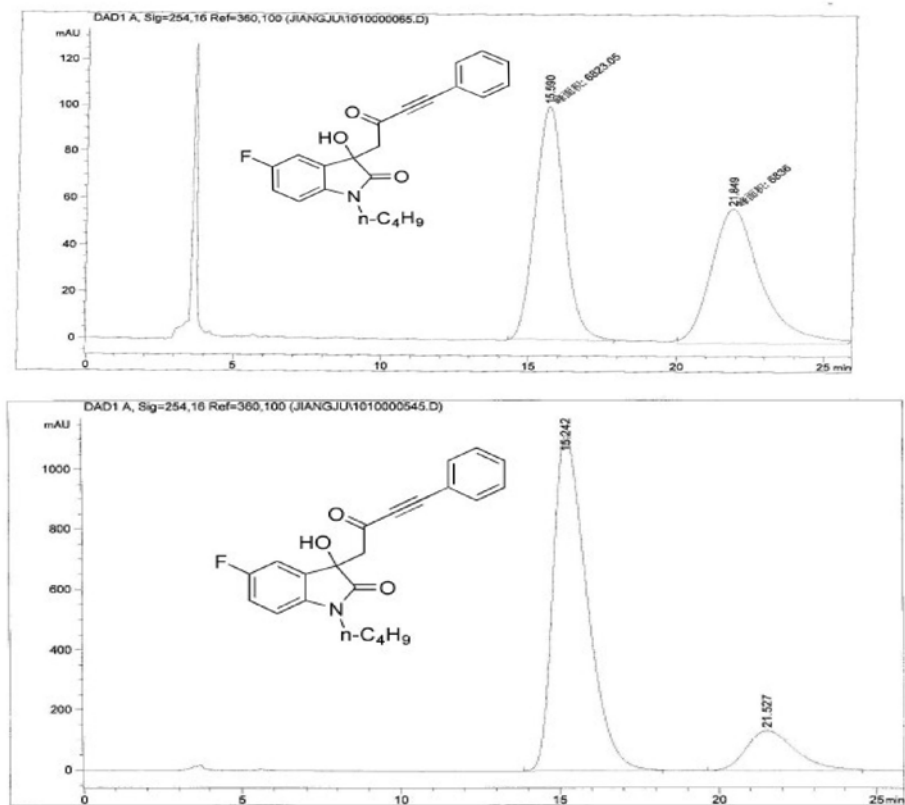


Figure S19. HPLC of compound 4e.

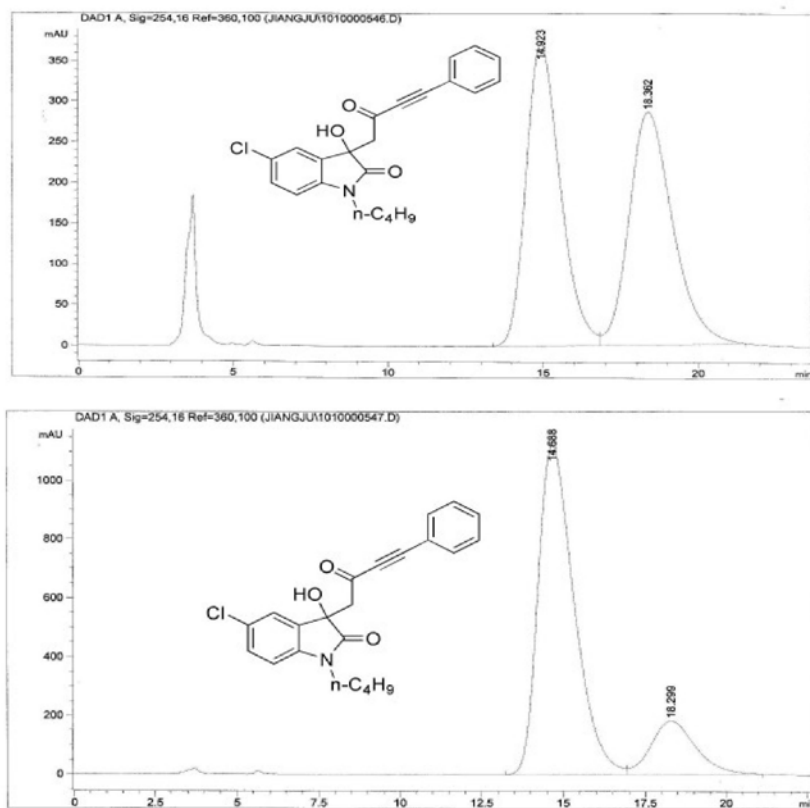


Figure S20. HPLC of compound 4f.

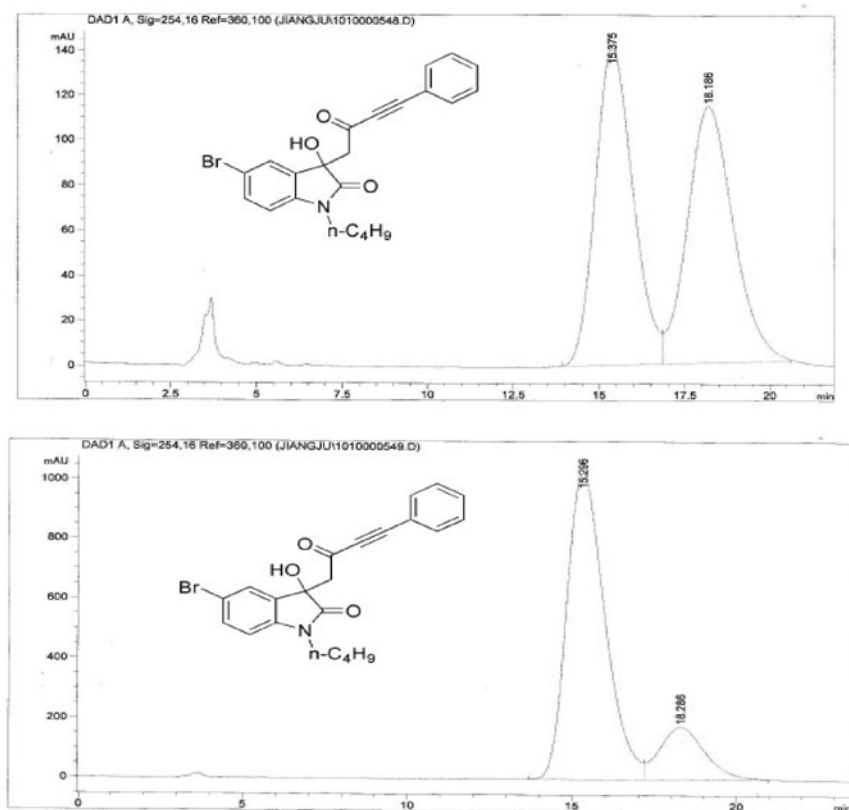


Figure S21. HPLC of compound 4g.

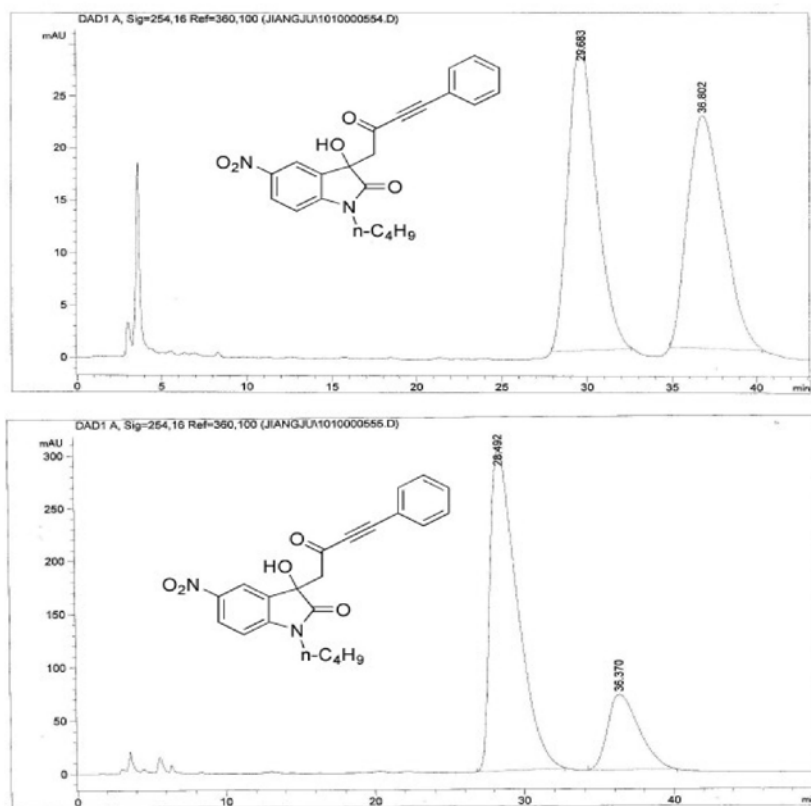


Figure S22. HPLC of compound 4h.

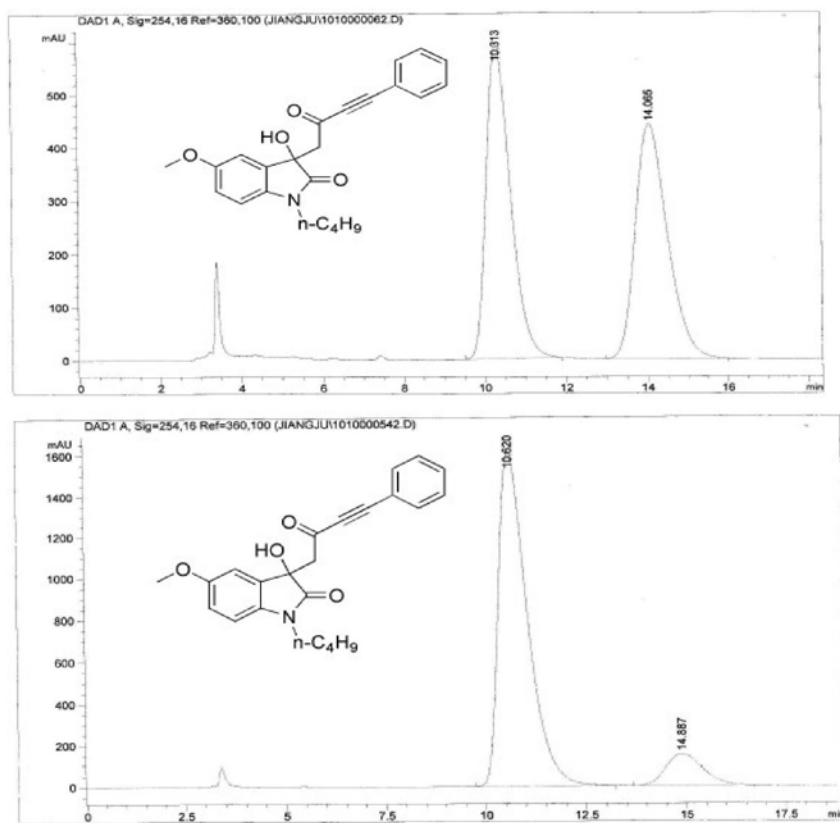


Figure S23. HPLC of compound 4i.

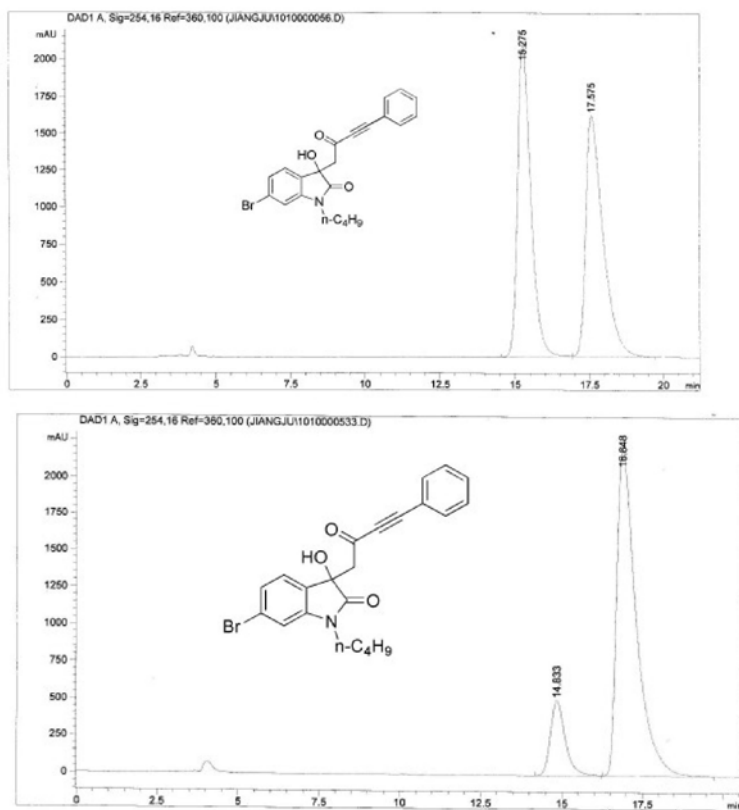


Figure S24. HPLC of compound 4j.

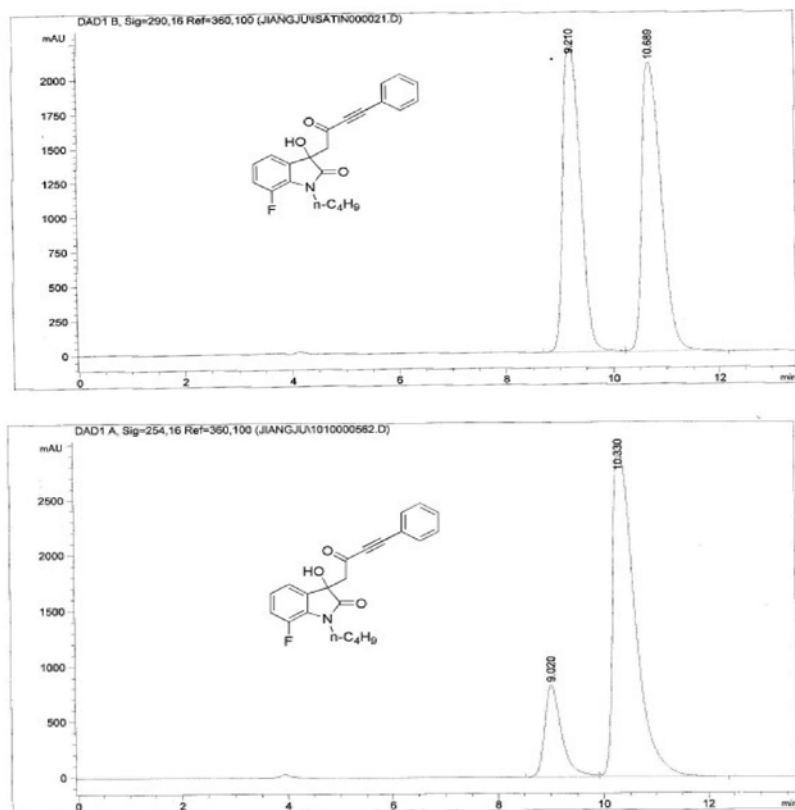


Figure S25. HPLC of compound 4k.

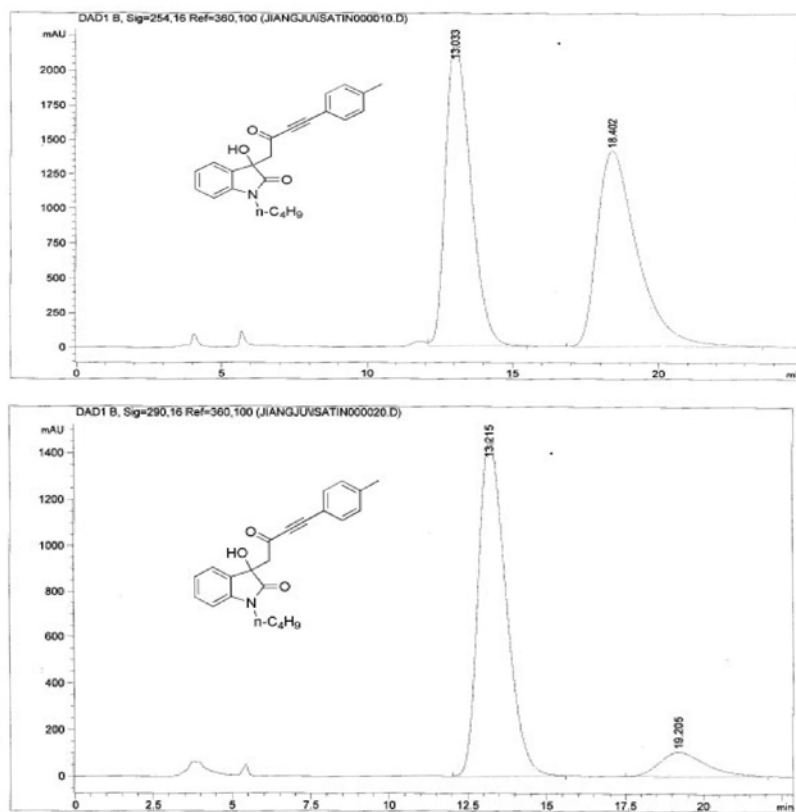


Figure S26. HPLC of compound 4ba.

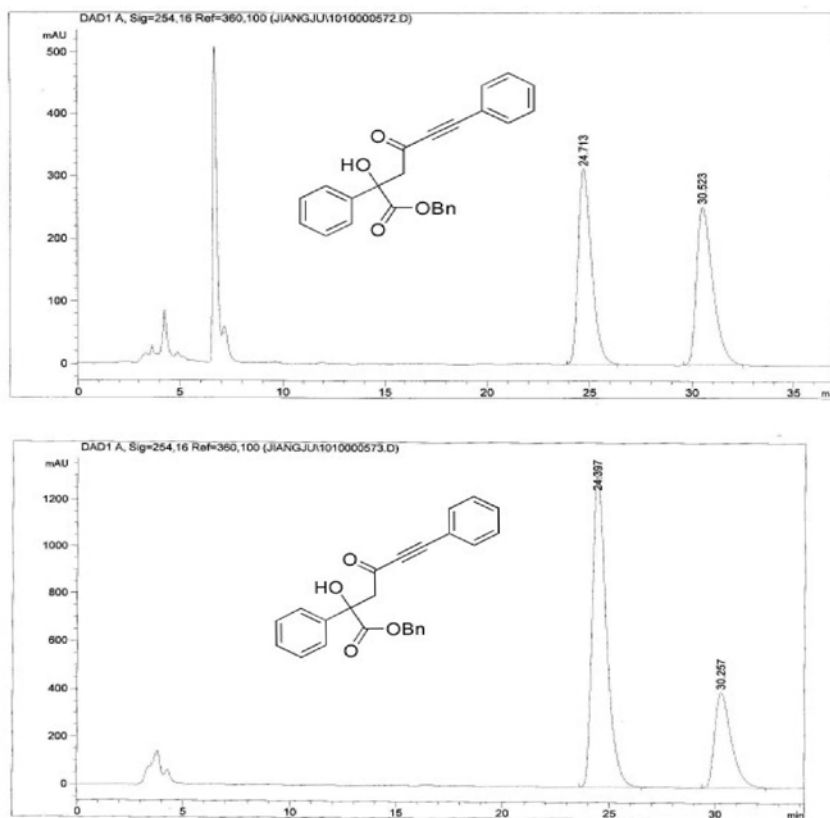


Figure S27. HPLC of compound 4l.

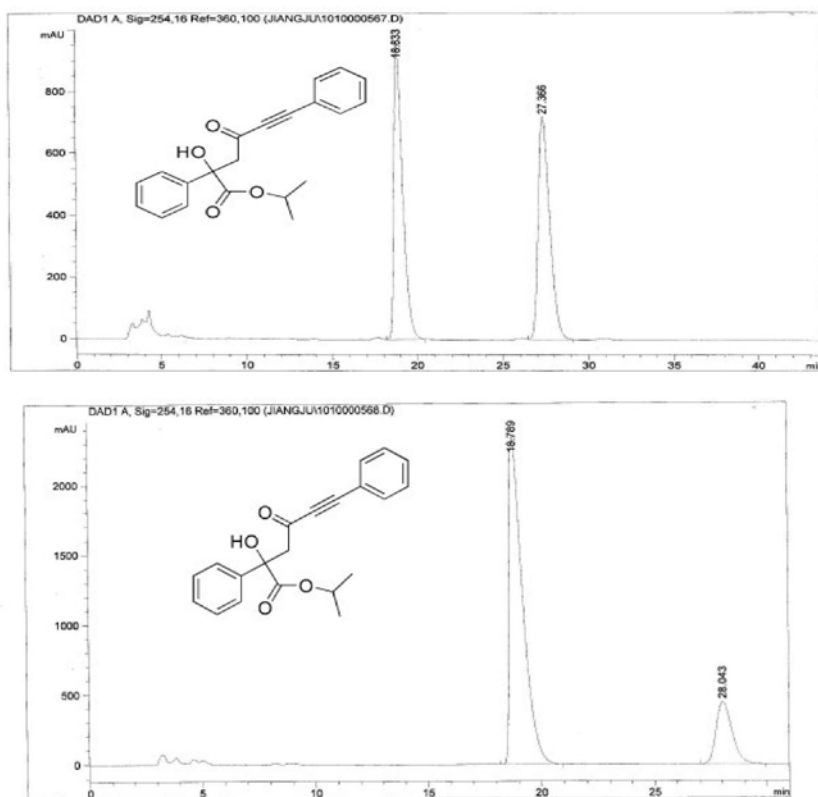


Figure S28. HPLC of compound 4m.

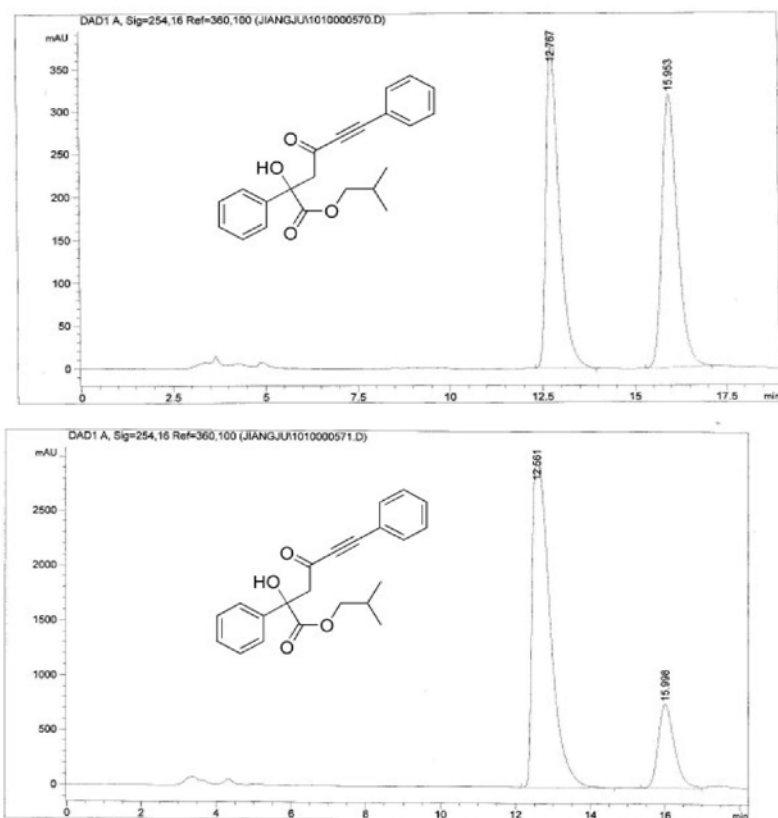


Figure S29. HPLC of compound 4n.