Green Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/greenchem

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

An Aza-Michael Addition Protocol to Fluoroalkylated β-Amino Acids Derivatives and Enantiopure Trifluoromethylated N-Hetereocycles

Xing Yang,[a] Zhuo Chen,[a] Yuan Cai,[a] Yi-Yong Huang*[a] and Norio Shibata*[b]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

The aza-Michael reaction with β-fluoroalkylated acylates provided the corresponding fluoroalkylated β-amino acids derivatives in up to 99% yield under catalyst- and solvent-free conditions. An enantioriched β-trifluoromethylated β-amino acid was obtained in good yield through a scale-up diasteroselective aza-Michael addition, which facilitated the installation of enantiopure trifluoromethylated analogues of β-lactam and dihydroquinolin-4-one.

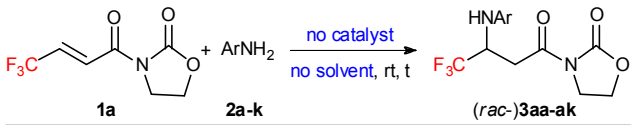
It has been well demonstrated that the incorporation of fluoroalkylated group can effectively enhance the lipophilicity, electronic interactions, binding selectivity and stability to metabolic degradation of the parent compounds.[1] β-amino acids are present in naturally occurring biologically active peptides,[2] and have found wide spectrum of applications in organic synthesis and medicinal chemistry.[3] In view of the synthetic application of fluorinated β-amino acids to fluorinated β-lactams,[4] or key motifs in peptides,[5] peptidomimetics[6] and other molecules[7] with various important biological activities (Figure 1), the development of reliable methodologies for their preparation has been a topic of great interest during the last decade.[8] Especially, the asymmetric synthesis of optically pure β-trifluomethylated (CF_3) β-amino acids (TFAAs) displays a challenge for organic chemists. The enantioselective approach remains relatively rare and difficult to reach high enantioselectivity.[9] An alternative strategy is based on diastereoselective transformation. All diastereoselective protocols explored so far to generate TFAAs involved reactions with trifluoromethylated ketones or imines exclusively.[10] For instance, the Fustero group described a diastereoselective addition of chiral 2-(*p*-tolylsulfinyl)-benzylic carbanions to trifluoromethylated imines followed by a desulfuration/oxidation sequence to get optically pure TFAAs derivatives in good yields.[10b] In the mean time, Saigo et al. disclosed a highly practical asymmetric hydride reduction of a seven-membered cyclic enamino-ester derived from 4,4,4-trifluoro-3-oxobutanoate to form chiral TFAA.[10c] In 2013, Grellepois applied the asymmetric Reformatsky reaction with chiral α-CF_3 N-*tert*-butanesulfinyl hemiaminals into the preparation of TFAAs derivatives and further incorporation into peptides.[10f] Recently, Shibata, Soloshonok and co-workers demonstrated a practical approach to enantiomerically pure TFAAs after hydrolysis and decarboxylation of the corresponding β-aminomalonates obtained from diastereoselective Mannich additions.[10g]

One of the most simple and powerful tools to construct β-amino acid skeleton is the 1,4-addition of amines to unsaturated esters (aza-Michael reaction). Over the past decades, tremendous efforts have been devoted in the development of highly efficient and selective aza-Michael reactions.[11] These reactions are usually accomplished in an organic solvent with the assistance of an organo- or organometallic catalyst. The philosophy of green chemistry requires that all atoms are converted into the desired products by minimizing or avoiding the use of solvents, most ideally, in the absence of any catalyst. The aza-Michael addition in both catalyst- and solvent-free conditions remains a challenge, but highly desirable for the economic and environmentally benign advantage. To the best of our knowledge, there is no literature that describes the synthesis of TFAAs and their derivatives via aza-Michael addition without any catalyst and solvent. In this context, as continuing efforts on synthetic fluorine chemistry,[12] we report herein the research results on a simple and novel aza-Michael reaction between fluorinated acrylic acids derivatives **1** and amines **2** without any solvent and catalyst. Under the same conditions, the scale-up synthesis via diastereoselective aza-Michael addition allows for an efficient access to enantiopure TFAA **6**, and thus to two enantioriched trifluoromethylated heterocyclic compounds as well (see Scheme 2).

Previously, we have shown the versatility of β-trifluoromethylated acrylate **1a** in the asymmetric Friedel–Crafts alkylation to install optically pure trifluoromethylated heliotridane.[12b] In order to explore more function of **1a**, we initially envisioned a catalytic asymmetric aza-Michael addition between **1a** and aniline **2a** to get a chiral analogue of **3aa** with β-CF_3 amino acid skeleton. However, even after a thorough screening of several parameters of the model reaction, including the 3,3'-substituents of chiral BINOL-derived phosphoric acids catalysts, organic solvents and temperature, the efficient and highly enantioselective transformation to **3aa** was hardly established. A control experiment revealed that the mixture of **1a** and **2a** in the absence of any catalyst in CH_2Cl_2 at room temperature gave **3aa** in 45% yield. But the yield is difficult to be improved by prolonging the reaction time. To our delight, neat condition enabled us to establish a novel reaction system, which afforded the desired compound **3aa** in quantitative yield after 22 h (entry 1, Table 1). Most importantly, after evaporating the very small excess of aniline, **3aa** was obtained with a satisfactory purity. **3aa** could be further purified by preparative thin layer chromatography (PTLC). It should be noted that this is the first

case of aza-Michael addition reaction with trifluoromethylated electrophile under catalyst- and solvent-free conditions. Because all acrylate substrates used herein are in solid state, all amines selected in the aza-Michael protocol are limited to be liquid at room temperature for guaranteeing a homogeneous reaction process.

Table 1 Scope of different aromatic amine nucleophiles[a]



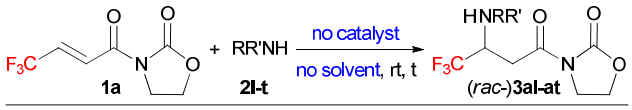
entry	Ar	product	time (h)	yield (%)[b]
1	Ph (**2a**)	**3aa**	22	97
2	*o*-OMe-Ph (**2b**)	**3ab**	32	95
3	*o*,*p*-(OMe)$_2$-Ph (**2c**)	**3ac**	3	99
4	*m*-Me-Ph (**2d**)	**3ad**	12	94
5[c]	*m*-F-Ph (**2e**)	**3ae**	60	92
6[c]	*m*-Cl-Ph (**2f**)	**3af**	56	88
7[c]	*m*-Br-Ph (**2g**)	**3ag**	36	92
8[c]	*m*-CF$_3$-Ph (**2h**)	**3ah**	60	52
9	*p*-Et-Ph (**2i**)	**3ai**	3	99
10	*p*-^{t}Bu-Ph (**2j**)	**3aj**	1	97
11	*p*-F-Ph (**2k**)	**3ak**	3	96

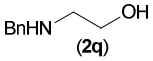
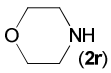
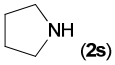
[a] All reactions were carried out by using **1a** (0.2 mmol) and **2a-k** (0.22 mmol) at room temperature for the time given. [b] Isolated yield after preparative thin layer chromatography. [c] 0.30 mmol amine was used.

In the established reaction system, a variety of primary aromatic amines reacted efficiently with **1a** to form racemic TFAAs derivatives **3** (Table 1). Methoxyl-substituted sterically hindered amine **2b** resulted in a slight drop in conversion efficiency to furnish **3ab** in 95% yield after 32 h (entry 2). To our surprise, when one more electron-donating methoxyl group was introduced at the 4-position of **2b**, compound **1a** was consumed completely within 3 h (entry 3). The examination of meta-substituents showed that electronic effect played a key role in the reaction outcomes. Amine **2d** featuring an electron-donating group (-Me) worked well (entry 4), whereas electron-withdrawing groups (-F, -Cl, -Br) yielded the adducts **3ae**–**3ag** with diminished levels of efficiency (entries 5−7). Notably, the presence of a strong electron-withdrawing group like a CF_3 group was also tolerated with moderate isolated yield (entry 8). Substituting the para- position of aniline, regardless of the electronic and steric nature, generated the target compounds **3ai**–**3ak** in excellent yields within 3 h (entries 9−11).

Encouraged by these results, the scope of aliphatic amine nucleophiles was next examined. From the point of view of nucleophilicity and steric hindrance, benzylamine should have a higher activity than aniline in aza-Michael reaction. Treatment of **1a** with 1.1 equivalent of benzylamine led to **3al** in 91% yield and a small amount of an amidolysis product **3al'** (Eq. 1, Scheme 1). Increasing the amount of benzylamine to 2.2 equivalent mainly gave rise to **3al'** in 93% yield after 1.5 h (Eq. 2, Scheme 1). Inspired by this result, we focused on the cascade aza-Michael/amidolysis reaction between **1a** and a bis-nucleophile benzylhydrazine **2m**.[13] As expected, small-ring heterocycles pyrazolidinones **3am** and **3am'**, as core structure in many pharmacological and biological active molecules,[14] were obtained in 66% and 25% yield, respectively. The less hindered amine part of the hydrazine privileged the 1,4-addition to afford the major product **3am**. In addition, a variety of N-substituents (-Me, -Et, -Bn and -$(CH_2)_2$OH) of secondary benzylamine were also tested and the corresponding products **3an**–**3aq** were obtained uniformly in excellent yields within a short time (entries 2−5, Table 2). In the case of two cyclic secondary amines of morpholine **2r** and pyrrolidine **2s**, comparable results were obtained (entries 6−7). Cyclohexylamine **2t** also proved to be a perfect nucleophile in this protocol (99% yield, entry 8). It should be mentioned that no cleavage of oxazolidin-2-one auxiliary through amidolysis reaction occurred under the present condition except with benzylamine **2l** and benzylhydrazine **2m**.

Table 2 Scope of different aliphatic amine nucleophiles[a]



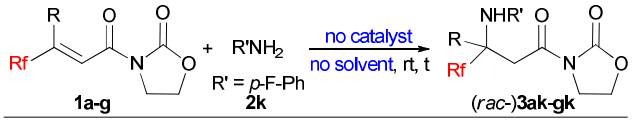
entry	RR'NH	product	time (h)	yield (%)[b]
1	$BnNH_2$ (**2l**)	**3al**	1.5	91
2	Bn(Me)NH (**2n**)	**3an**	6	95
3	Bn(Et)NH (**2o**)	**3ao**	4	95
4	Bn_2NH (**2p**)	**3ap**	1.5	99
5	 (**2q**)	**3aq**	1	92
6	 (**2r**)	**3ar**	2	94
7	 (**2s**)	**3as**	2	91
8	$CyNH_2$ (**2t**)	**3at**	1.5	99

[a] All reactions were carried out by using **1a** (0.2 mmol) and **2k-s** (0.22 mmol) at room temperature for the time given. [b] Isolated yield after preparative thin layer chromatography.

As evident in Table 3, we turned our attention to the scope of fluoroalkylated acrylates **1**. The electrophiles **1b-h** bearing various fluoroalkylated groups at the β-position were synthesized by using the same route as for **1a**. Modification of β-substituent may result in different types of β-fluoromethylated β-amino acids derivatives. The replacement of fluorine atom(s) with one or two proton(s) reduces the reaction rate (entries 2-3, Table 3). For comparison, methyl oxazolidinone **1d** was also engaged in this reaction with a markedly lower reactivity (entry 4). Other variation on the β-carbon of **1**, such as -C_2F_5, -$CClF_2$, and -$CBrF_2$, slightly influences the reaction speed comparing with **1a** (entries 5-7). These results indicate that strong electron-withdrawing action of fluorinated groups, in particular a CF_3 group, plays a crucial role in the transformation. However, such

protocol could not be extended to β-CF_3-β-phenyl disubstituted acrylate **1h**, and no desired adduct **3hk** was delivered even after long reaction time.

Table 3 Scope of various acrylate electrophiles[a]



1a-g 2k (*rac*-)3ak-gk

entry	Rf	R	product	time (h)	yield (%)[b]
1	CF_3 (**1a**)	H	**3ak**	3	96
2	CF_2H (**1b**)	H	**3bk**	18	93
3	CFH_2 (**1c**)	H	**3ck**	24	92
4	CH_3 (**1d**)	H	**3dk**	44	72
5	C_2F_5 (**1e**)	H	**3ek**	18	87
6	$CClF_2$ (**1f**)	H	**3fk**	6	92
7	$CBrF_2$ (**1g**)	H	**3gk**	10	87
8	CF_3 (**1h**)	Ph	**3hk**	48	0

[a] All reactions were carried out by using **1** (0.2 mmol) and **2k** (0.22 mmol) at room temperature for the time given. [b] Isolated yield after preparative thin layer chromatography.

The plausible mechanism of this aza-Michael reaction is illustrated in Figure 2. Two components of the reaction are organized through hydrogen bonding interaction between carbonyl oxygen atom and amine NH proton. Sequentially, the formed intermediate **I** undergoes intramolecular-like amine conjugate addition to provide enolized intermediate **II**. The strong electron-withdrawing nature of the CF_3 group in acrylate **1** plays a vital role in this smooth direct addition step. Finally, a rapid tautomerization occurs to generate the aza-Michael adduct **3**.

The development of novel synthetic methodologies for optically pure fluorinated β-amino acids is of particular interest in synthetic organic fluorine chemistry. The present protocol is difficult to be performed in a highly catalytic enantioselective manner due to the fast background reaction mentioned above. The issue of stereo-outcome of this aza-Michael addition could be effectively addressed by use of a chiral oxazolidinone auxiliary. In a scale-up reaction between the chiral acrylate **4** (4 mmol) and amine **2k** (Scheme 2), the major diastereomer (*S*,*R*)-**5** was obtained pure in a 68% yield, based on the recovered starting material (brsm), after chromatographic separation of the diastereomeric mixture (dr = 2.8). An important advantage of the present chemistry is that the aza-Michael adduct **5** could be easily hydrolyzed into enantioriched TFAA **6** with LiOH-H_2O_2. With **6** in hand, the access to two enantiomerically pure heterocycles with a CF_3 group at the chiral tertiary carbon center was elaborated. Chiral 2-CF_3-2,3-dihydro-1H-quinolin-4-one **7**, serving as a building block for creating trifluoromethlyated analogues of dihydroquinolinone or tetrahydroquinoline type drugs,[15] was successfully installed via a polyphosphoric acid (PPA)-promoted intramolecular Friedel-Crafts reaction.[16] Furthermore, the β-CF_3 β-amino ester **8** derived from **6** was cyclized in the presence of CH_3MgBr to construct enantioriched trifluoromethylated β-lactam **9** in 69% yield, which represents the key part of Ezetimibe analogue as a potent inhibitor of cholesterol absorption. The absolute stereochemistry of **9** was determined as *S* by comparison of the optical rotation with that found in the literature,[4b] so the configurations of compound **6** and **7** were both assigned as *S*.

The features of the present aza-Michael addition are summarized as follows: (1) This study represents the first example of building TFAAs derivatives via aza-Michael addition in a highly enviromentally benign and atom-economic fashion; (2) Fluorinated groups at the β-position of electrophiles are critical for the efficient transformation; (3) Benzylhydrazine as a bis-nucleophile generated a trifluoromethylated pyrazolidinone (5- membered ring) via a novel cascade aza-Michael/amidolysis cyclization reaction; (4) The reported green process is a potentially practical and generalized approach. It has been easily and successfully scaled-up to synthesize enantioriched TFAAs and, thereby, giving a rapid access to two structurally diverse chiral trifluoromethylated N-heterocycles (4- and 6-membered ring) in good yields. We will extend this green strategy to other research involving the expeditious construction of enantiomerically pure trifluoromethylated heterocycles. This investigation is underway in our laboratory.

Acknowledgements

We gratefully thank the financial support of this investigation by the National Natural Science Foundation of China (21303128), Scientific Research Foundation for Returned Scholars, Ministry of Education of China ([2013]1792), and the Fundamental Research Funds for the Central Universities (WUT: 2014-Ia-002).

Notes and references

[a] *Department of Chemistry, School of Chemistry, Chemical Engineering and Life Science, Wuhan University of Technology, Wuhan 430070, P.R. China; E-mail: huangyy@whut.edu.cn*
[b] *Department of Frontier Materials, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya, 466-8555, Japan. E-mail: nozshiba@nitech.ac.jp*

† Electronic Supplementary Information (ESI) available: General experimental procedures, NMR and HRMS data of all new compounds are included. See DOI: 10.1039/b000000x/

1 (a) J. T. Welch and S. Eswarakrishnan, Fluorine in Bioorganic Chemistry, John Wiley & Sons, New York, 1990; (b) P. Kirsch, Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications, Wiley-VCH, Weinheim, 2004. (c) J. Nie, H.-C. Guo, D. Cahard and J.-A. Ma, *Chem. Rev.*, 2011, **111**, 455.
2 (a) D. C. Cole, *Tetrahedron*, 1994, **50**, 9517; (b) S. H. Gelman, *Acc. Chem. Res.*, 1998, 31, 173; (b) F. Von Nussbaum and P. Spiteller, In Highlights in Bioorganic Chemistry: Methods and Applications, C. Schmuck and H. Wennemers, Eds., Wiley-VCH: Weinheim, 2004, 63; (c) B. E. Sleebs, T. T. Van Nguyen and A. B. Hughes, *Org. Prep. Proced. Int.*, 2009, **41**, 429.
3 (a) L. Kiss and F. Fülöp, *Chem. Rev.*, 2014, **114**, 1116; (b) E. Juaristi, D. Quintana and J. Escalante, *Aldrichim. Acta*, 1994, **27**, 3; (c) Enantioselective Synthesis of β-Amino Acids, ed. E. Juaristi and V. Soloshnok, John Wiley & Sons, Inc., Hoboken, 2005; (d) P. S. Bhadury, S. Yang and B.-A. Song, *Curr. Org. Syn.*, 2012, **9**, 695.

4 (a) J. Jiang, H. Shah and R. J. DeVita, *Org. Lett*., 2003, **5**, 4101; (b) Y.-L. Liu, J.-L. Chen, G.-H. Wang, P. Sun, H.-Y. Huang and F.-L. Qing, *Tetrahedron Lett*., 2013, **54**, 5541.

5 (a) P. Bravo, L. Bruche, C. Pasenti, F. Viani, A. Volonterio and M. Zanda, *J. Fluorine Chem*., 2001, **112**, 153; (b) M. Zanda, *New J. Chem*., 2004, **28**, 1401; (c) K. Nakayama, H. C. Kawato, H. Inagaki, R. Nakajima, A. Kitamura, K. Someya and T. Ohta, *Org. Lett*., 2000, **2**, 977.

6 M. Molteni, C. Pesenti, M. Sani, A. Volonterio and M. Zanda, *J. Fluorine Chem*., 2004, **125**, 1735.

7 (a) L. Kuznetsova, I. M. Ungureanu, A. Pepe, I. Zanardi, X.-Y. Wu and I. Ojima, *J. Fluorine Chem*., 2004, **115**, 487; (b) O. M. Saavedra, S. W. Claridge, L.-J. Zhang, F. Raeppel, A. Vaiburg, S. Raeppel, R. Deziel, M. Mannion, N. Z. Zhou, F. Gaudette, L. Isakovic, A. Wahhab, M.-C. Granger and N. Bernstein, *US Pat*., 20070004675, 2007.

8 X.-L. Qiu, W.-D. Meng and F.-L. Qing, *Tetrahedron*, 2004, **60**, 6711; (b) X. L. Qiu and F.-L. Qing, *Eur. J. Org. Chem*., 2011, **2011**, 3261; (c) K. Mikami, S. Fustero, M. Sánchez-Rosello, J. L. Aceña, V. Soloshonok and A. Sorochinsky, *Synthesis*, 2011, 3045.

9 (a) Q. Dai, W.-R. Yang and X.-M. Zhang, *Org. Lett*., 2005, **7**, 5343; (b) V. A. Soloshonok, H. Ohkura and M. Yasumoto, *J. Fluorine Chem*., 2006, **127**, 924; (c) V. A. Soloshonok, H. Ohkura and M. Yasumoto, *J. Fluorine Chem*., 2006, **127**, 930; (d) V. Michaut, F. Metz, J. M. Paris and J. C. Plaquevent, *J. Fluorine Chem*., 2007, **128**, 500; (e) M. Weiß and H. Gröger, *Synlett*, 2009, 1251.

10 For a review see: D.-Z. Lin, J. Wang and H. Liu, *Chin. J. Org. Chem*., 2013, **33**, 2098. Selected recent examples: (a) M. Dos Santos, B. Crousse and D. Bonnet-Delpon, *Synlett*, 2008, 399; (b) S. Fustero, C. del Pozo, S. Catalán, J. Alemán, A. Parra, V. Marcos and J. L. Garcia Ruano, *Org. Lett*., 2009, **11**, 641; (c) Y. Ishida, N. Iwahashi, N. Nishizono and K. Saigo, *Tetrahedron Lett*., 2009, **50**, 1889; (d) H. Mimura, K. Kawada, T. Yamashita, T. Sakamoto and Y. Kikugawa, *J. Fluorine Chem*., 2010, **131**, 477; (e) N. Shibata, T. Nishimine, N. Shibata, E. Tokunaga, K. Kawada, T. Kagawa, A. E. Sorochinsky and V. A. Soloshonok, *Chem. Commun*., 2012, **48**, 4124; (f) F. Grellepois, *J. Org. Chem*., 2013, **78**, 1127; (g) N. Shibata, T. Nishimine, N. Shibata, E. Tokunaga, K. Kawada, T. Kagawa, J. L. Aceña, A. E. Sorochinsky and V. A. Soloshonok, *Org. Biomol. Chem*., 2014, **12**, 1454.

11 For reviews see: (a) L.-W. Xu, C.-G. Xia, *Eur. J. Org. Chem*., 2005, **2005**, 633; (b) J. Wang, P.-F. Li, P.-Y. Choy, A. S. C. Chan and F.-Y. Kwong, *ChemCatChem*., 2012, **4**, 917; (c) D. Enders, C. Wang and J. X. Liebich, *Chem. Eur. J*., 2009, **15**, 11058.

12 S. Noritake, N. Shibata, Y. Nomura, Y.-Y. Huang, A. Matsnev, S. Nakamura, T. Toru and D. Cahard, *Org. Biomol. Chem*., 2009, **7**, 3599; (b) Y.-Y. Huang, E. Tokunaga, S. Suzuki, M. Shiro and N. Shibata, *Org. Lett*., 2010, **12**, 1136; (c) Y.-Y. Huang, S. Satoru, G.-K. Liu, E. Tokunaga, S. Suzuki, M. Shiro and N. Shibata, *New J. Chem*., 2011, **35**, 2614.

13 For selected cascade reactions to construct chiral trifluoromethylated heterocycles, see: (a) K. Matoba, H. Kawai, T. Furukawa, A. Kusuda, E. Tokunaga, S. Nakamura, M. Shiro and Norio Shibata, *Angew. Chem. Int. Ed*., 2010, **49**, 5762; (b) J. Mo, X. Chen and Y. R. Chi, *J. Am. Chem. Soc*., 2012, **134**, 8810; (d) Y. Su, J.-B. Ling, S. Zhang and P.-F. Xu, *J. Org. Chem*., 2013, **78**, 11053; (c) P. Li, Z. Chai, S.-L. Zhao, Y.-Q. Yang, H.-F. Wang, C.-W. Zheng, Y.-P. Cai, G. Zhao and S.-Z. Zhu, *Chem. Common*., 2009, 7369; (d) L. C. Morrill, J. Douglas, T. Lebl, A. M. Z. Slawin, D. J. Fox and A. D. Smith, *Chem. Sci*., 2013, **4**, 4146.

14 (a) H. L. White, J. L. Howard, B. R. Cooper, F. E. Soroko, J. D. McDermed, K. J. Ingold and R. A. Maxwell, *J. Neurochem*., 1982, **39**, 271; (b) K. J. Ingold, J. L. Howard and J. D. Mcdermed, *EP Pat*., 19810101497, 1981.

15 (a) Y. Kohno, K. Awano, M. Miyashita, T. Ishizaki, K. Kuriyama, Y. Sakoe, S. Kudoh, K. Saito and E. Kojima, *Bioorg. Med. Chem. Lett*., 1997, **7**, 1519; (b) R. I. Higuchi, J. P. Edwards, T. R. Caferro, J. D. Ringgenberg, J. W. Kong, L. G. Hamann, L. Arienti, K. B. Marschke, R. L. Davis, L. J. Farmer and T. K. Jones, *Bioorg. Med. Chem. Lett*., 1999, **9**, 1335; (c) Z. Lin, C. M. Tegley, K. B. Marschke and T. K. Jones, *Bioorg. Med. Chem. Lett*., 1999, **9**, 1009; (d) Y. Xia, Z.-Y. Yang, P. Xia, K. F. Bastow, Y. Tachobana, S.-C. Kuo, E. Hamel, T. Hackl and K. H. Lee, *J. Med. Chem*., 1998, **41**, 1155.

16 Y.-F. Gong and K. Kato, *J. Fluorine Chem*., 2004, **125**, 767.

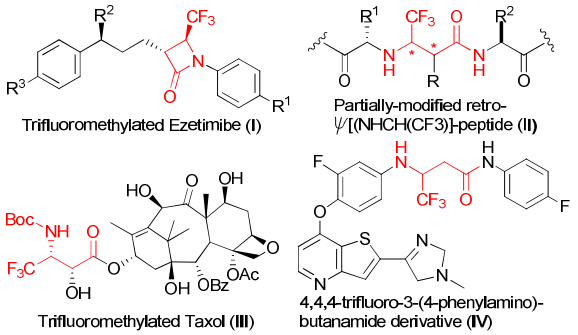
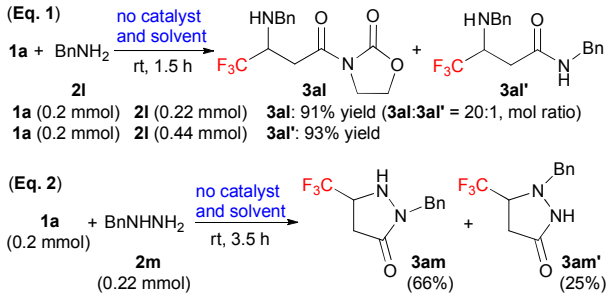


Figure 1 Selected bioactive compounds containing fluorinated β-amino acid scaffolds.



Scheme 1 Aza-Michael reaction between **1a** and **2l** or **2m**.

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

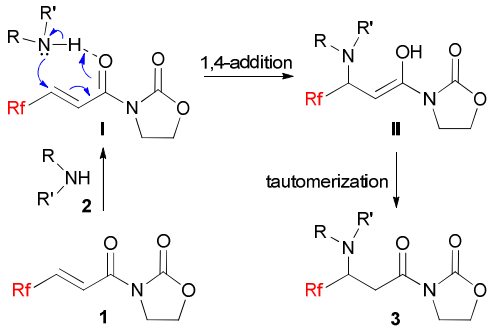
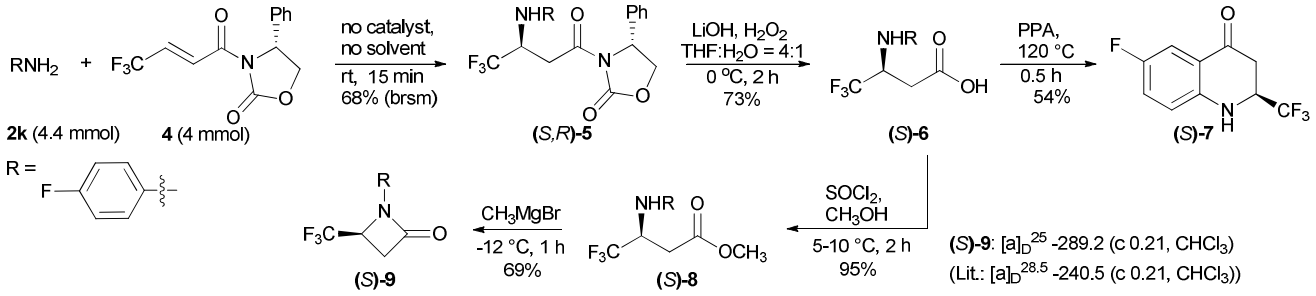


Figure 2 Plausible mechanism of the aza-Michael reaction.



Scheme 2 Synthetic utility of chiral β-CF_3 β-amino acid **6**.

Supporting Information

An Aza-Michael Addition Protocol to Fluoroalkylated β-Amino Acids Derivatives and Enantiopure Trifluoromethylated N-Hetereocycles

Xing Yang,[a] Zhuo Chen,[a] Yuan Cai,[a] Yi-Yong Huang*[a] and Norio Shibata*[b]

[a] Department of Chemistry, School of Chemistry, Chemical Engineering and Life Science, Wuhan University of Technology, Wuhan 430070, P. R. China

[b] Department of Frontier Materials, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan

Contents

General methods……S1

General procedure for the aza-Michael reactions……...S2

Characterization data of the aza-Michael adducts (3aa-3at and 3bk-3gk)……..S3

Synthesis of enantiopure trifluoromethylated *N*-hetereocycles (7 and 9)……S23

^{1}H, ^{13}C and ^{19}F NMR spectra (3aa-3at, 3bk-3gk, 7 and 9)...…….S26

General methods

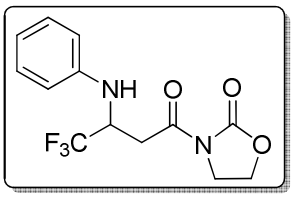
All reactions and manipulations involving air-sensitive compounds were performed using standard Schlenk techniques. All reactions were monitored by TLC. TLC analysis was performed by illumination with a UV lamp (254 nm). All flash chromatography was packed with silica-gel as the stationary phase. Melting points were measured on a SGW X-4 apparatus. ^{1}H NMR (500 MHz) spectra were recorded on a Bruker

Avance 500 instrument, and chemical shifts were reported in ppm downfield from internal TMS with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26 ppm). ^{13}C NMR (126 MHz) spectra were recorded on a Bruker Avance 500 instrument, and chemical shifts were reported in ppm downfield from TMS with the solvent resonance as the internal standard ($CDCl_3$, δ = 77.2 ppm). ^{19}F NMR (471 MHz) spectra were recorded on a Bruker Avance 500 instrument. Optical rotations were measured on a Roudolph Autopl VI. Infrared spectra were recorded on a NICOLET FT/IR-200 spectrometer. High resolution mass spectra (HRMS) (EI+) were recorded on an AB SCIEX TripleTOF 5600 instrument.

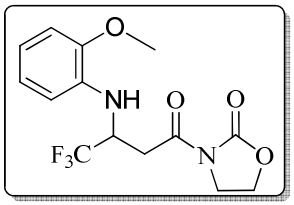
General procedure for the aza-Michael reactions

Amine (1.1 or 1.5 equiv) and β-fluoroalkylated acrylate (1.0 equiv) were added to a 1 mL test tube, followed by stirring at r.t.. The reaction process was monitored by TLC. While some aza-Michael adducts have the same polarity as the starting material on TLC, the reaction would be monitored by ^{19}F NMR. After the starting material disappeared, the residue was directly subjected to the preparative thin layer chromatography to afford the title product.

Characterization data of the aza-Michael reaction products

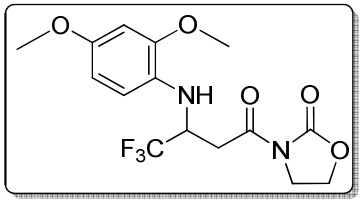


3-(4,4,4-trifluoro-3-(phenylamino)butanoyl)oxazolidin-2-one (3aa): Aniline (20.5 mg, 0.22 mmol) and acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 22 h, then passed through a plug of silica gel (PE:EA = 3:1) to afford the title compound (58.5 mg, 97%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16-7.08 (m, 2H), 6.73 (t, 7.4 Hz, 1H), 6.65 (d, 7.7 Hz, 2H), 4.64-4.59 (m, 1H), 4.27 (t, 8.1 Hz, 2H), 3.86-3.82 (m, 3H), 3.47 (dd, 15.8 Hz, 9.5 Hz, 1H), 3.20 (dd, 15.8 Hz, 4.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 152.6, 144.6, 128.4, 124.5 (q, 284.5 Hz), 118.4, 112.9, 61.2, 51.9 (q, 30.2 Hz), 41.5, 34.3; ^{19}F NMR (471 MHz, $CDCl_3$) δ -76.0 (d, 6.9 Hz, 3F); IR (KBr): 3419.3, 3371.5, 2926.2, 1772.6, 1700.8, 1603.2, 1414.1, 1192.3, 1038.6, 752.4, 692.2 cm^{-1}; mp = 133-134 ^{o}C; HRMS calcd. for $[M+H]^+$: 303.0957, found: 303.0953.



3-(4,4,4-trifluoro-3-((2-methoxyphenyl)amino)butanoyl)oxazolidin-2-one (3ab): 2-methoxyaniline (27.1 mg, 0.22 mmol) and acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 32 h, then passed through a plug of silica gel (PE:EA = 3:1) to afford the title compound (63.2 mg, 95%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84-6.61 (m, 4H), 4.74-4.56 (m,

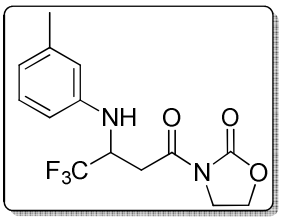
1H), 4.47 (d, 10.7 Hz, 1H), 4.31-4.27 (m, 2H), 3.87-3.86 (m, 2H), 3.76 (s, 3H), 3.47 (dd, 16.3 Hz, 9.2 Hz, 1H), 3.23 (dd, 16.3 Hz, 4.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 152.5, 146.0, 134.6, 124.6 (q, 283.5 Hz), 120.2, 117.5, 110.3, 109.1, 61.2, 54.6, 51.2 (q, 30.2 Hz), 41.5, 34.6; ^{19}F NMR (471 MHz, $CDCl_3$) δ -76.1 (d, 6.8 Hz, 3F); IR (KBr): 3373.4, 2925.8, 1773.1, 1705.3, 1597.2, 1396.6, 1303.8, 1174.6, 1128.0, 1034.1, 746.9, 640.7 cm^{-1}; mp = 64-65 ^{o}C; HRMS calcd. for $[M+H]^+$: 333.1062, found: 333.1060.



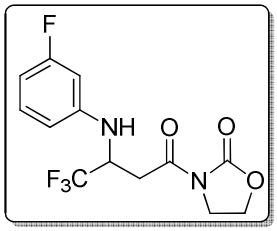
3-(3-((2,4-dimethoxyphenyl)amino)-4,4,4-trifluorobutanoyl)oxazolidin-2-one (3ac):

2,4-dimethoxyaniline (33.7 mg, 0.22 mmol) and acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 3 h, then passed through a plug of silica gel (PE:EA = 1:1) to afford the title compound (72.0 mg, 99%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67 (d, 8.6 Hz, 1H), 6.37 (d, 2.6 Hz, 1H), 6.33 (dd, 8.6 Hz, 2.7 Hz, 1H), 4.51 (dd, 9.8 Hz, 6.0 Hz, 1H), 4.35-4.24 (m, 2H), 4.12 (d, 10.7 Hz, 1H), 3.93-3.82 (m, 2H), 3.74 (s, 3H), 3.68 (s, 3H), 3.46 (dd, 16.3 Hz, 9.2 Hz, 1H), 3.19 (dd, 16.3 Hz, 4.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 152.5, 152.2, 147.4, 128.7, 124.8 (q, 283.5 Hz), 111.6, 103.0, 98.3, 61.2, 54.7, 54.5, 52.4 (q, 30.2 Hz), 41.5, 34.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ -76.0 (d, 6.9 Hz, 3F); IR (KBr): 3398.4, 2950.1, 1775.2, 1681.5, 1525.0, 1441.9, 1292.3, 1214.8, 1157.2,

1126.4, 1041.3, 842.5, 788.1, 755.6 cm^{-1}; mp = 116-117 ^{o}C; HRMS calcd. for $[M+H]^{+}$: 363.1168, found: 363.1147.

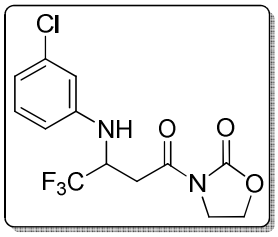


3-(4,4,4-trifluoro-3-(m-tolylamino)butanoyl)oxazolidin-2-one (3ad): 3-methylaniline (23.6 mg, 0.22 mmol) and acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 12 h, then passed through a plug of silica gel (PE:EA = 3:1) to afford the title compound (59.6 mg, 94%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (t, 7.7 Hz, 1H), 6.55 (d, 7.5 Hz, 1H), 6.46 (d, 7.8 Hz, 2H), 4.76-4.46 (m, 1H), 4.27 (t, 8.1 Hz, 2H), 3.90-3.75 (m, 3H), 3.46 (dd, 15.8 Hz, 9.5 Hz, 1H), 3.19 (dd, 15.8 Hz, 4.1 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 152.6, 144.6, 138.3, 128.2, 124.5 (q, 283.5 Hz), 119.3, 113.7, 110.0, 61.2, 51.8 (q, 31.5 Hz), 41.5, 34.2, 20.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ -76.0 (d, 6.9 Hz, 3F); IR (KBr): 3378.4, 2925.5, 1762.6, 1712.6, 1610.5, 1451.2, 1362.6, 1326.5, 1253.0, 1111.7, 959.1, 765.4, 634.3 cm^{-1}; mp = 107-108 ^{o}C; HRMS calcd. for $[M+H]^{+}$: 317.1113, found: 317.1108.



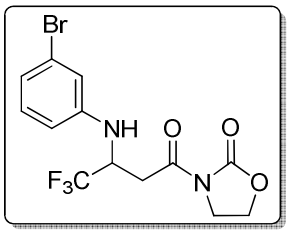
3-(4,4,4-trifluoro-3-((3-fluorophenyl)amino)butanoyl)oxazolidin-2-one (3ae): 3-fluoroaniline (33.3 mg, 0.3 mmol) and acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 60 h, then passed through a plug of silica gel (PE:EA =

3:1) to afford the title compound (59.0 mg, 92%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07-7.03 (m, 1H), 6.51-6.21 (m, 3H), 4.74 – 4.47 (m, 1H), 4.32 (t, 8.2 Hz, 2H), 4.04 (d, 10.4 Hz, 1H), 3.91-3.88 (m, 2H), 3.47 (dd, 16.3 Hz, 9.4 Hz, 1H), 3.19 (dd, 16.3 Hz, 3.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 162.9 (d, 244.4 Hz), 152.6, 146.5 (d, 10.5 Hz), 129.6 (d, 10.1 Hz), 124.4 (q, 283.5 Hz), 108.5 (d, 2.2 Hz), 105.0 (d, 21.4 Hz), 99.9 (d, 26.5 Hz), 61.3, 51.6 (q, 31.5 Hz), 41.5, 34.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ -76.0 (d, 6.8 Hz, 3F), -112.2-112.3 (m, 1F); IR (KBr): 3366.2, 2926.1, 1770.1, 1703.5, 1619.5, 1411.8, 1258.2, 1148.3, 1039.4, 949.1, 764.9, 682.0 cm^{-1}; mp = 103-104 ^{o}C; HRMS calcd. for $[M+H]^{+}$: 321.0862, found: 321.0843.

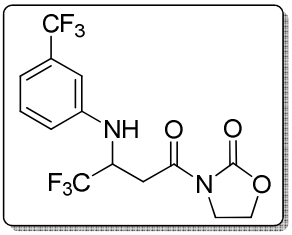


3-(3-((3-chlorophenyl)amino)-4,4,4-trifluorobutanoyl)oxazolidin-2-one (3af): 3-chloroaniline (38.3 mg, 0.3 mmol) and acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 56 h, then passed through a plug of silica gel (PE:EA = 3:1) to afford the title compound (58.9 mg, 88%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (t, 8.0 Hz, 1H), 6.69 (d, 7.9 Hz, 1H), 6.64 (s, 1H), 6.52 (d, 8.1 Hz, 1H), 4.57-4.52 (m, 1H), 4.30 (t, 8.0 Hz, 2H), 3.97 (d, 10.3 Hz, 1H), 3.87 (t, 8.1 Hz, 2H), 3.47 (dd, 16.1 Hz, 9.3 Hz, 1H), 3.19 (dd, 16.1 Hz, 3.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 152.6, 145.9, 134.1, 129.4, 124.3 (q, 283.5 Hz), 118.4, 112.8, 111.0, 61.3,

51.6 (q, 31.5 Hz), 41.5, 34.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ -75.9 (d, 6.8 Hz, 3F); IR (KBr): 3365.6, 2989.5, 1767.4, 1725.4, 1696.5, 1603.3, 1533.5, 1411.3, 1324.9, 1254.1, 1133.6, 1044.8, 939.7, 763.9, 635.8 cm^{-1}; mp = 108-109 °C; HRMS calcd. for $[M+H]^+$: 337.0567, found: 337.0544.

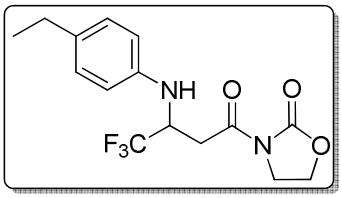


3-(3-((3-bromophenyl)amino)-4,4,4-trifluorobutanoyl)oxazolidin-2-one (3ag): 3-bromoaniline (51.6 mg, 0.3 mmol) and acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 36 h, then passed through a plug of silica gel (PE:EA = 3:1) to afford the title compound (69.7 mg, 92%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (t, 8.0 Hz, 1H), 6.84 (d, 7.9 Hz, 1H), 6.80 (s, 1H), 6.58-6.56 (m, 1H), 4.58-4.53 (m, 1H), 4.31 (t, 8.0 Hz, 2H), 4.02 (d, 10.4 Hz, 1H), 3.89 (t, 8.0 Hz, 2H), 3.47 (dd, 16.2 Hz, 9.5 Hz, 1H), 3.18 (dd, 16.2 Hz, 3.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 152.7, 146.1, 129.7, 124.3 (q, 283.5 Hz), 122.2, 121.2, 115.7, 111.4, 61.3, 51.5 (q, 31.5 Hz), 41.5, 34.1; ^{19}F NMR (471 MHz, $CDCl_3$) δ -75.9 (d, 6.8 Hz, 3F); IR (KBr): 3365.3, 2949.1, 1767.3, 1694.8, 1602.1, 1530.6, 1412.4, 1282.1, 1253.5, 1132.8, 762.8, 715.8, 635.5 cm^{-1}; mp = 123-124 °C; HRMS calcd. for $[M+H]^+$: 381.0062, found: 381.0047.



3-(4,4,4-trifluoro-3-((3-(trifluoromethyl)phenyl)amino)butanoyl)oxazolidin-2-one (3ah): 3-(trifluoromethyl)aniline (48.3 mg, 0.3 mmol) and

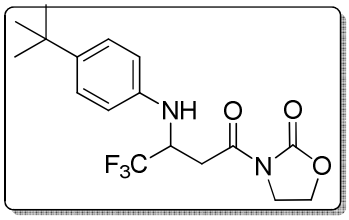
acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 60 h, then passed through a plug of silica gel (PE:DCM = 1:2) to afford the title compound (38.8 mg, 52%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (t, 7.9 Hz, 1H), 6.96 (d, 7.7 Hz, 1H), 6.86 (s, 1H), 6.82 (d, 8.2 Hz, 1H), 4.66 - 4.60 (m, 1H), 4.32 (t, 8.2 Hz, 2H), 4.13 (d, 10.4 Hz, 1H), 3.99 - 3.79 (m, 2H), 3.51 (dd, 16.4 Hz, 9.5 Hz, 1H), 3.20 (dd, 16.4 Hz, 3.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 152.7, 145.1, 130.8 (q, 29.0 Hz), 128.9, 124.4 (q, 284.8 Hz), 123.0 (q, 273.4 Hz), 115.6, 114.9 (q, 3.9 Hz), 109.4 (d, 3.9 Hz), 61.3, 51.5 (q, 30.2 Hz), 41.5, 34.1. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.9 (s, 3F), -75.9 (s, 3F).



3-(3-((4-ethylphenyl)amino)-4,4,4-trifluorobutanoyl)oxazolidin-2-one (3ai):

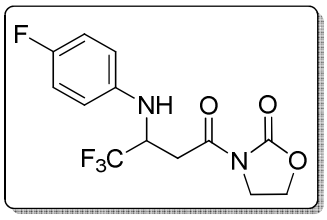
4-ethylaniline (26.7 mg, 0.22 mmol) and acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 3 h, then passed through a plug of silica gel (PE:EA = 2:1) to afford the title compound (65.2 mg, 99%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (d, 8.4 Hz, 2H), 6.59 (d, 8.4 Hz, 2H), 4.57 (s, 1H), 4.26 (t, 8.1 Hz, 2H), 3.87-3.79 (m, 2H), 3.76 (s, 1H), 3.45 (dd, 15.8 Hz, 9.4 Hz, 1H), 3.18 (dd, 15.8 Hz, 4.1 Hz, 1H), 2.47 (q, 7.6 Hz, 2H), 1.11 (t, 7.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 152.6, 142.5, 134.3, 127.7, 124.6 (q, 284.5 Hz), 113.1, 61.2, 52.2 (q, 30.2

Hz), 41.5, 34.2, 26.9, 14.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ -76.0 (d, 6.9 Hz, 3F); IR (KBr): 3362.8, 2965.2, 1773.6, 1689.2, 1638.5, 1389.4, 1348.6, 1222.1, 1044.9, 973.9, 758.7, 707.9 cm^{-1}; mp = 84-85 °C; HRMS calcd. for $[M+H]^+$: 331.1270, found: 331.1261.



3-(3-((4-(tert-butyl)phenyl)amino)-4,4,4-trifluorobutanoyl)oxazolidin-2-one (3aj):

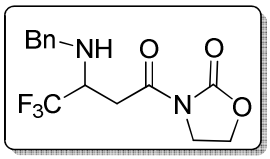
4-(*tert*-butyl)aniline (32.8 mg, 0.22 mmol) and acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 1 h, then passed through a plug of silica gel (PE:EA = 2:1) to afford the title compound (69.2 mg, 97%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17-7.11 (m, 2H), 6.67-6.47 (m, 2H), 4.59 (s, 1H), 4.26 (t, 8.1 Hz, 2H), 3.85-3.80 (m, 2H), 3.78 (s, 1H), 3.46 (dd, 15.7 Hz, 9.4 Hz, 1H), 3.19 (dd, 15.7 Hz, 4.2 Hz, 1H), 1.20 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 152.6, 142.1, 141.2, 125.2, 124.6 (q, 283.5 Hz), 112.6, 61.2, 52.0 (q, 30.2 Hz), 41.5, 34.2, 32.9, 30.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ -76.0 (d, 6.9 Hz, 3F); IR (KBr): 3388.9, 2963.5, 1774.7, 1679.3, 1527.9, 1401.2, 1298.2, 1161.7, 1076.1, 820.7, 755.5 cm^{-1}; mp = 143-144 °C; HRMS calcd. for $[M+H]^+$: 359.1583, found: 359.1567.



3-(4,4,4-trifluoro-3-((4-fluorophenyl)amino)butanoyl)oxazolidin-2-one (3ak):

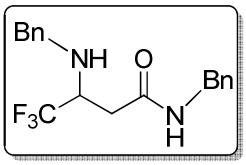
4-fluoroaniline (24.4 mg, 0.22 mmol) and

acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 3 h, then passed through a plug of silica gel (PE:EA = 3:1) to afford the title compound (61.4 mg, 96%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (t, 8.7 Hz, 2H), 6.69-6.54 (m, 2H), 4.54-4.47 (m, 1H), 4.32 (t, 8.1 Hz, 2H), 3.91-3.88 (m, 2H), 3.72 (d, 10.6 Hz, 1H), 3.47 (dd, 16.2 Hz, 9.5 Hz, 1H), 3.17 (dd, 16.2 Hz, 3.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 155.8 (d, 238.1 Hz), 152.6, 141.0 (d, 2.1 Hz), 124.5 (q, 284.8 Hz), 114.9 (d, 22.7 Hz), 114.3 (d, 7.6 Hz), 61.2, 52.8 (q, 30.2 Hz), 41.5, 34.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ -75.9 (d, 6.9 Hz, 3F), -125.2--125.3 (m, 1F); IR (KBr): 3363.8, 2932.2, 1770.3, 1704.5, 1513.5, 1356.9, 1221.3, 1124.2, 1103.9, 822.8, 665.6 cm^{-1}; mp = 144-145 °C; HRMS calcd. for $[M+H]^+$: 321.0862, found: 321.0851.

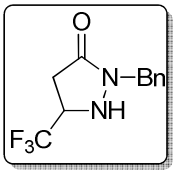


3-(3-(benzylamino)-4,4,4-trifluorobutanoyl)oxazolidin-2-one (3al): Phenylmethanamine (23.6 mg, 0.22 mmol) and acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 1.5 h, then passed through a plug of silica gel (PE:EA = 2:1) to afford the title compound (57.3 mg, 91%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.25 (m, 5H), 4.38-4.34 (m, 2H), 4.01 (d, 10.0 Hz, 1H), 3.99-3.90 (m, 2H), 3.86 (d, 10.0 Hz, 1H), 3.83-3.81 (m, 1H), 3.28 (dd, 16.1 Hz, 9.7 Hz, 1H), 3.17 (dd, 16.1 Hz, 4.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ

169.6, 153.4, 139.6, 128.4, 128.3, 127.3, 126.5 (q, 284.8 Hz), 62.1, 55.5 (q, 27.7 Hz), 51.9, 42.5, 35.5 (d, 1.9 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ -74.5 (d, 9.4 Hz, 3F); IR (neat): 3360.7, 2921.7, 1779.8, 1701.3, 1390.6, 1266.8, 1131.7, 1038.2, 755.1, 701.2 cm^{-1}; HRMS calcd. for $[M+H]^+$: 317.1113, found: 317.1107.

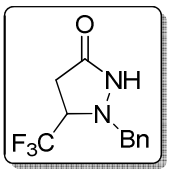


N-benzyl-3-(benzylamino)-4,4,4-trifluorobutanamide (3al'): Phenylmethanamine (47.2 mg, 0.44 mmol) and acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 1.5 h, then passed through a plug of silica gel (PE:EA = 2:1) to afford the title compound (62.5 mg, 93%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.14 (m, 8H), 7.12-7.07 (m, 2H), 6.89 (s, 1H), 4.34 (d, 5.6 Hz, 2H), 3.93 (d, 12.7 Hz, 1H), 3.74 (d, 12.7 Hz, 1H), 3.61-3.50 (m, 1H), 2.69-2.40 (m, 1H), 2.28 (dd, 15.4 Hz, 10.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 137.9, 136.9, 127.8, 127.6, 127.3, 126.9, 126.6, 126.5, 125.3 (q, 284.8 Hz), 55.4 (q, 29.0 Hz), 50.7, 42.7, 34.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ -74.3 (d, 7.1 Hz, 3F); IR (KBr): 3304.2, 2927.5, 1630.4, 1542.3, 1455.5, 1268.9, 1123.0, 1028.9, 750.4, 698.2, 506.7 cm^{-1}; mp = 78-79 ^oC; HRMS calcd. for $[M+H]^+$: 337.1528, found: 337.1529.

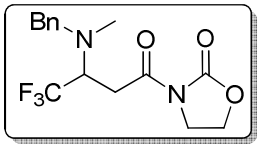


2-benzyl-5-(trifluoromethyl)pyrazolidin-3-one (3am): Benzylhydrazine dihydrochloride (42.9 mg, 0.22 mmol) was neutralized by triethylamine (44.5 mg, 0.44 mmol) in a

1 mL test tube, then acrylate **1a** (41.8 mg, 0.2 mmol) was added. The mixture was stirred at r.t. for 3.5 h, then passed through a plug of silica gel (PE:EA = 3:1) to afford the compound **3al** (31.9 mg, 66%) and **3al'** respectively. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.28 (m, 5H), 4.96 (d, 14.6 Hz, 1H), 4.62 (d, 7.8 Hz, 1H), 4.27 (d, 14.6 Hz, 1H), 3.97-3.92 (m, 1H), 3.00 (dd, 17.5 Hz, 10.0 Hz, 1H), 2.71 (dd, 17.4 Hz, 3.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 135.0, 128.9, 128.5, 128.2, 124.6 (q, 279.7 Hz), 53.9 (q, 32.8 Hz), 48.4, 31.8.



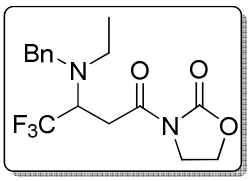
1-benzyl-5-(trifluoromethyl)pyrazolidin-3-one (3am'): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.31 (m, 5H), 4.04 (d, 12.6 Hz, 1H), 3.94 (d, 12.6 Hz, 1H), 3.79-3.75 (m, 1H), 2.84 (dd, 17.7 Hz, 9.9 Hz, 1H), 2.46 (dd, 17.7 Hz, 2.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 134.3, 129.6, 128.9, 128.6, 124.6 (q, 279.7 Hz), 64.6, 61.6 (q, 31.5 Hz), 29.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ -78.1 (d, 7.3 Hz, 3F); IR (KBr): 3196.1, 3071.6, 1708.1, 1397.0, 1347.9, 1273.6, 1188.5, 1166.3, 1118.1, 1058.2, 1029.6, 963.2, 699.8 cm^{-1}; mp = 78-79 ^{o}C; HRMS calcd. for $[M+H]^+$: 245.0902, found: 245.0894.



3-(3-(benzyl(methyl)amino)-4,4,4-trifluorobutanoyl)oxazolidin-2-one (3an):

N-methyl-1-phenylmethanamine (26.7 mg, 0.22 mmol) and acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 6 h, then passed through a plug of silica gel (PE:EA = 3:1)

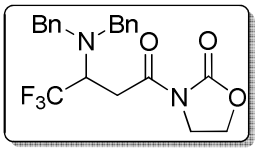
to afford the title compound (62.8 mg, 95%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.09 (m, 5H), 4.30 (t, 8.1 Hz, 2H), 4.06-3.86 (m, 3H), 3.75 (q, 13.7 Hz, 2H), 3.48 (dd, 16.3 Hz, 9.7 Hz, 1H), 3.03 (dd, 16.3 Hz, 4.3 Hz, 1H), 2.30 (d, 1.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 152.3, 138.0, 127.4, 127.2, 126.2, 126.0 (q, 291.1 Hz), 61.1, 59.5 (q, 26.5 Hz), 58.5, 41.6, 35.9, 31.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ -68.9 (d, 8.2 Hz, 3F); IR (neat): 3544.5, 2923.9, 1776.0, 1701.2, 1479.0, 1454.1, 1388.6, 1313.8, 1222.5, 1104.7, 962.1, 741.6, 683.7 cm^{-1}. HRMS calcd. for $[M+H]^+$: 331.1270, found: 331.1259.



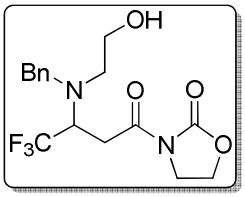
3-(3-(benzyl(ethyl)amino)-4,4,4-trifluorobutanoyl) oxazolidin-2-one (3ao):

N-ethyl-1-phenylmethanamine (29.8 mg, 0.22 mmol) and acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 4 h, then passed through a plug of silica gel (PE:EA = 2:1) to afford the title compound (65.7 mg, 95%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.11 (m, 5H), 4.33-4.20 (m, 2H), 4.05-3.85 (m, 3H), 3.83 (d, 13.8 Hz, 1H), 3.68 (d, 14.3 Hz, 1H), 3.32 (dd, 15.8 Hz, 9.3 Hz, 1H), 3.12 (dd, 15.8 Hz, 4.9 Hz, 1H), 2.73-2.63 (m, 2H), 0.99 (t, 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 152.1, 138.6, 127.4, 127.2, 126.0, 125.9 (q, 291.1 Hz), 60.9, 55.8 (q, 26.5 Hz), 53.3, 43.5, 41.5, 31.9, 12.9; ^{19}F NMR (471 MHz, $CDCl_3$) δ -69.4 (d, 8.3 Hz, 3F); IR (KBr): 2979.7, 2845.5, 1776.5, 1700.8, 1392.3, 1279.1,

1155.5, 1107.9, 968.4, 758.9, 636.2 cm^{-1}; mp = 33-34 ^{o}C; HRMS calcd. for $[M+H]^{+}$: 345.1426, found: 345.1417.

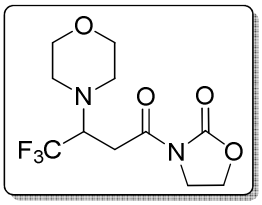


3-(3-(dibenzylamino)-4,4,4-trifluorobutanoyl)oxazolidin-2-one (3ap): Dibenzylamine (43.4 mg, o.22 mmol) and acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 1.5 h, then passed through a plug of silica gel (PE:EA = 2:1) to afford the title compound (80.9 mg, 99%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.08 (m, 10H), 4.22-4.10 (m, 2H), 4.02-3.90 (m, 1H), 3.90-3.84 (m, 1H), 3.81 (d, 13.6 Hz, 2H), 3.77-3.68 (m, 1H), 3.64 (d, 14.0 Hz, 2H), 3.24 (dd, 15.0 Hz, 4.8 Hz, 1H), 3.15 (dd, 15.0 Hz, 9.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 151.9, 137.7, 128.2, 127.2, 126.3, 126.0 (q, 291.1 Hz), 60.8, 54.7 (q, 26.5 Hz), 53.2, 41.4, 32.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ -68.6 (d, 8.1 Hz, 3F); IR (neat): 3537.3, 3029.2, 2855.4, 1780.2, 1703.4, 1430.4, 1390.7, 1265.5, 1210.1, 1109.4, 1036.6, 982.8, 751.5 cm^{-1}; HRMS calcd. for $[M+H]^{+}$: 407.1583, found: 407.1568.

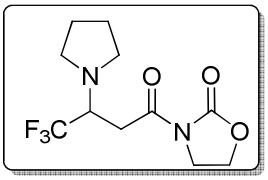


3-(3-(benzyl(2-hydroxyethyl)amino)-4,4,4-trifluorobutanoyl)oxazolidin-2-one (3aq): 2-(benzylamino)ethanol (33.3 mg, 0.22 mmol) and acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 1 h, then passed through a plug of silica gel (PE:EA = 1:1) to afford the title compound (66.1 mg, 92%) as a white

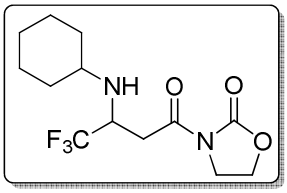
solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, 7.2 Hz, 2H), 7.22-7.15 (m, 3H), 4.26-4.15 (m, 2H), 3.96-3.78 (m, 3H), 3.74-3.71 (m, 1H), 3.69-3.58 (m, 2H), 3.46 (d, 8.6 Hz, 1H), 3.15 (d, 7.2 Hz, 3H), 3.06-2.96 (m, 1H), 2.85 (d, 14.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 151.8, 137.9, 128.0, 127.4, 126.3, 125.9 (q, 291.1 Hz), 61.0, 58.8, 56.1 (q, 26.5 Hz), 53.8, 52.3, 41.4, 32.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ -68.5 (d, 8.0 Hz, 3F); IR (KBr): 3471.3, 2977.5, 2974.6, 1781.8, 1681.7, 1483.1, 1390.3, 1364.9, 1246.5, 1078.4, 920.8, 761.4, 637.2 cm^{-1}; mp = 84-85 ^{o}C; HRMS calcd. for $[M+H]^+$: 361.1375, found: 361.1359.



3-(4,4,4-trifluoro-3-morpholinobutanoyl)oxazolidin-2-one (3ar): Morpholine (19.2 mg, 0.22 mmol) and acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 2 h, then passed through a plug of silica gel (PE:EA = 3:1) to afford the title compound (56.0 mg, 94%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.39 (t, 8.3 Hz, 2H), 4.08-3.93 (m, 2H), 3.84-3.69 (m, 1H), 3.55-3.50 (m, 5H), 2.95 (dd, 16.6 Hz, 4.3 Hz, 1H), 2.84-2.81 (m, 2H), 2.68-2.53 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7, 152.4, 125.4 (q, 290.0 Hz), 66.7, 61.2, 60.7 (q, 27.7 Hz), 49.0, 41.7, 31.1 (d, 1.2 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ -69.2 (d, 8.5 Hz, 3F); IR (neat): 3542.4, 2961.4, 2853.6, 1779.6, 1702.5, 1392.1, 1316.0, 1266.0, 1156.6, 1114.7, 1036.8, 855.2, 802.5, 760.0, 684.0 cm^{-1}; HRMS calcd. for $[M+H]^+$: 297.1062, found: 297.1048.

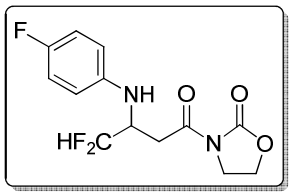


3-(4,4,4-trifluoro-3-(pyrrolidin-1-yl)butanoyl)oxazolidin-2-one (3as): Pyrrolidine (15.7 mg, 0.22 mmol) and acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 2 h, then passed through a plug of silica gel (PE:EA = 2:1) to afford the title compound (51.2 mg, 91%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.37 (t, 8.1 Hz, 2H), 4.12-4.02 (m, 1H), 4.01-3.94 (m, 2H), 3.37 (dd, 17.2 Hz, 7.9 Hz, 1H), 3.09 (dd, 17.2 Hz, 5.0 Hz, 1H), 2.78 (dd, 7.5 Hz, 5.4 Hz, 2H), 2.70 (d, 6.8 Hz, 2H), 1.73-1.59 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 152.4, 125.6 (q, 288.5 Hz), 61.1, 56.1 (q, 27.7 Hz), 47.9, 41.6, 30.9 (d, 1.2 Hz), 22.9; ^{19}F NMR (471 MHz, $CDCl_3$) δ -70.8 (d, 8.5 Hz, 3F); IR (KBr): 3380.0, 2923.9, 2851.7, 1780.8, 1699.2, 1479.7, 1312.2, 1261.0, 1166.3, 1069.8, 944.5, 802.8, 760.6 cm^{-1}; mp = 30-31 ^{o}C; HRMS calcd. for $[M+H]^{+}$: 281.1113, found: 281.1107.



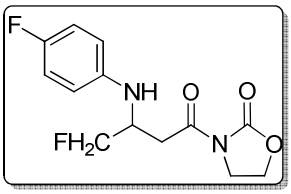
3-(3-(cyclohexylamino)-4,4,4-trifluorobutanoyl) oxazolidin-2-one (3at): Cyclohexanamine (21.9 mg, 0.22 mmol) and acrylate **1a** (41.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 1.5 h, then passed through a plug of silica gel (PE:EA = 2:1) to afford the title compound (61.3 mg, 99%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.37 (t, 8.2 Hz, 2H), 4.03-3.91 (m, 2H), 3.86-3.70 (m,

1H), 3.22 (dd, 16.2 Hz, 9.0 Hz, 1H), 3.07 (dd, 16.2 Hz, 4.4 Hz, 1H), 2.60 (t, 10.1 Hz, 1H), 1.86-1.46 (m, 5H), 1.45-1.25 (m, 1H), 1.24-0.86 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 152.5, 125.5 (q, 284,8 Hz), 61.1, 53.4, 52.1 (q, 29.0 Hz), 41.6, 35.0 (d, 1.9 Hz), 33.1, 32.0, 24.9, 23.6, 23.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ -75.2 (d, 7.0 Hz, 3F); IR (KBr): 3358.5, 2929.8, 2857.2, 1787.0, 1700.3, 1391.6, 1269.0, 1222.9, 1125.9, 1040.3, 760.2, 631.1 cm^{-1}; mp = 36-37 ^{o}C; HRMS calcd. for $[M+H]^+$: 309.1426, found: 309.1408.

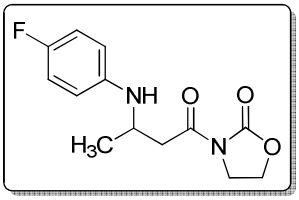


3-(4,4-difluoro-3-((4-fluorophenyl)amino)butanoyl)oxazolidin-2-one (3bk): 4-fluoroaniline (24.5 mg, 0.22 mmol) and acrylate **1b** (38.2 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 18 h, then passed through a plug of silica gel (PE:EA = 2:1) to afford the title compound (56.3 mg, 93%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (t, 8.6 Hz, 2H), 6.69-6.42 (m, 2H), 5.86 (td, 56.0 Hz, 2.5 Hz, 1H), 4.34-4.27 (m, 2H), 4.25-4.21 (m, 1H), 3.87 (t, 8.1 Hz, 2H), 3.78 (d, 10.5 Hz, 1H), 3.36 (dd, 16.4 Hz, 7.9 Hz, 1H), 3.15 (dd, 16.4 Hz, 4.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 155.6 (d, 236.9 Hz), 152.5, 141.2 (d, 2.1 Hz), 114.7 (d, 22.7 Hz), 114.1 (d, 7.5 Hz), 114.0 (t, 246.3 Hz), 61.2, 52.3 (t, 22.7 Hz), 41.5, 32.8 (d, 4.0 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ -125.2--125.9 (m, 1F), -125.7--125.9 (m, 1F), -128.9--129.6 (m, 1F); IR (KBr): 3350.7, 2981.8, 1772.6, 1695.9,

1527.7, 1512.3, 1405.5, 1312.6, 1208.9, 1121.5, 1045.1, 824.0, 761.9, 680.6 cm^{-1}; mp = 127-128 ^{o}C; HRMS calcd. for $[M+H]^{+}$: 303.0957, found: 303.0950.

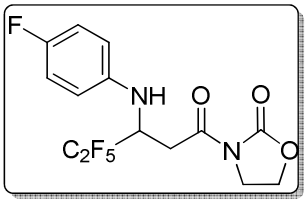


3-(4-fluoro-3-((4-fluorophenyl)amino)butanoyl) oxazolidin-2-one (3ck): 4-fluoroaniline (24.5 mg, 0.22 mmol) and acrylate **1c** (34.6 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 24 h, then passed through a plug of silica gel (PE:EA = 2:1) to afford the title compound (52.1 mg, 92%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (t, 8.7 Hz, 2H), 6.64-6.43 (m, 2H), 4.51 (dd, 3.9 Hz, 1.3 Hz, 1H), 4.42 (dd, 3.8 Hz, 1.8 Hz, 1H), 4.36-4.26 (m, 2H), 4.17-4.02 (m, 1H), 3.93-3.87 (m, 2H), 3.85 (s, 1H), 3.33 (dd, 16.4 Hz, 6.8 Hz, 1H), 3.12 (dd, 16.4 Hz, 6.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 155.3 (d, 238.1 Hz), 152.6, 141.5 (d, 1.9 Hz), 114.9 (d, 22.7 Hz), 114.0 (d, 7.5 Hz), 83.0 (d, 172.6 Hz), 61.1, 50.0 (d, 19.8 Hz), 41.4, 35.0 (d, 4.2 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ -126.4--126.5 (m, 1F), -230.4--230.6 (m, 1F); IR (KBr): 3350.0, 2926.7, 1778.7, 1680.4, 1510.9, 1394.5, 1209.1, 1036.8, 928.9, 826.2, 758.5, 700.5 cm^{-1}; mp = 112-113 ^{o}C; HRMS calcd. for $[M+H]^{+}$: 285.1051, found: 285.1047.



3-(3-((4-fluorophenyl)amino)butanoyl)oxazolidi n-2-one (3dk): 4-fluoroaniline (24.5 mg, 0.22 mmol) and acrylate **1d** (31.0 mg, 0.2 mmol) were

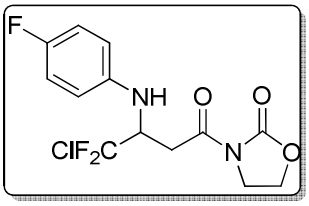
added to a 1 mL test tube. The mixture was stirred at r.t. for 44 h, then passed through a plug of silica gel (PE:EA = 2:1) to afford the title compound (38.6 mg, 72%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (t, 8.6 Hz, 2H), 6.51-6.48 (m, 2H), 4.28 (dd, 16.0 Hz, 7.7 Hz, 2H), 3.97-3.95 (m, 1H), 3.86 (dd, 11.7 Hz, 5.0 Hz, 2H), 3.60 (s, 1H), 3.26 (dd, 15.4 Hz, 7.1 Hz, 1H), 2.91 (dd, 15.4 Hz, 5.6 Hz, 1H), 1.21 (d, 6.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 155.0 (d, 236.9 Hz), 152.7, 142.3, 114.7 (d, 22.7 Hz), 113.7 (d, 7.4 Hz), 61.0, 46.2, 41.5, 40.3, 20.1; ^{19}F NMR (471 MHz, $CDCl_3$) δ -127.5--127.6 (m, 1F); IR (KBr): 3356.0, 2972.6, 2925.4, 1774.9, 1681.2, 1510.9, 1393.2, 1315.6, 1210.3, 1146.4, 1036.9, 1020.5, 825.9, 702.0 cm^{-1}; mp = 106-107 °C; HRMS calcd. for $[M+H]^+$: 267.1145, found: 267.1132.



3-(4,4,5,5,5-pentafluoro-3-((4-fluorophenyl)amino)pentanoyl)oxazolidin-2-one (3ek):

4-fluoroaniline (24.5 mg, 0.22 mmol) and acrylate **1e** (51.8 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 18 h, then passed through a plug of silica gel (PE:DCM = 1:2) to afford the title compound (64.2 mg, 87%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (t, 8.7 Hz, 2H), 6.67-6.50 (m, 2H), 4.77-4.59 (m, 1H), 4.26 (t, 8.1 Hz, 2H), 3.87-3.74 (m, 2H), 3.67 (d, 11.2 Hz, 1H), 3.47 (dd, 15.8 Hz, 9.1 Hz, 1H), 3.24 (dd, 15.8 Hz, 3.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 155.7 (d, 238.1 Hz), 152.6,

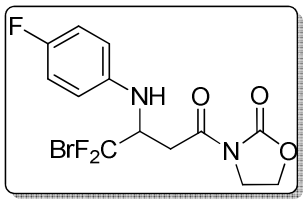
140.5 (d, 2.1 Hz), 117.9 (qt, 287.3 Hz, 35.3 Hz), 114.9 (d, 22.7 Hz), 114.0 (d, 7.6 Hz), 113.2 (tq, 259.6 Hz, 36.5 Hz), 61.2, 51.2 (dd, 26.5 Hz, 21.4 Hz), 41.5, 33.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ -81.4 (S, 3F), -118.5 (dd, 274.7 Hz, 6.8 Hz, 1F), -125.2--125.3 (m, 1F), -126.7 (dd, 274.7 Hz, 18.2 Hz, 1F); IR (KBr): 3362.1, 2935.2, 1774.3, 1702.4, 1510.2, 1347.9, 1221.6, 1120.4, 1113.2, 832.3, 664.6 cm^{-1}; mp = 110-111 ^{o}C; HRMS calcd. for $[M+H]^+$: 371.0830, found: 371.0814.



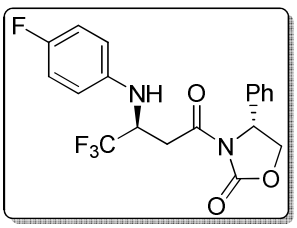
3-(4-chloro-4,4-difluoro-3-((4-fluorophenyl)amino)butanoyl)oxazolidin-2-one (3fk):

4-fluoroaniline (24.5 mg, 0.22 mmol) and acrylate **1f** (45.1 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 6 h, then passed through a plug of silica gel (PE:DCM = 1:2) to afford the title compound (61.8 mg, 92%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (t, 8.6 Hz, 2H), 6.72-6.47 (m, 2H), 4.73-4.50 (m, 1H), 4.31 (t, 8.1 Hz, 2H), 3.90-3.87 (m, 2H), 3.78 (d, 10.6 Hz, 1H), 3.50 (dd, 16.0 Hz, 9.8 Hz, 1H), 3.22 (dd, 16.0 Hz, 3.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 155.8 (d, 238.1 Hz), 152.6, 141.1 (d, 2.1 Hz), 129.1 (t, 300.0 Hz), 114.8 (d, 22.7 Hz), 114.4 (d, 7.6 Hz), 61.2, 58.1 (t, 23.9 Hz), 41.5, 35.3; ^{19}F NMR (471 MHz, $CDCl_3$) δ -59.8--60.6 (m, 2F), -125.3--125.4 (m, 1F); IR (KBr): 3358.0, 3028.9, 1775.8, 1689.1, 1512.5, 1399.0, 1312.8, 1228.8, 1067.2, 958.7, 819.8,

758.4, 602.4 cm^{-1}; mp = 105-106 °C; HRMS calcd. for $[M+H]^+$: 337.0567, found: 337.0543.

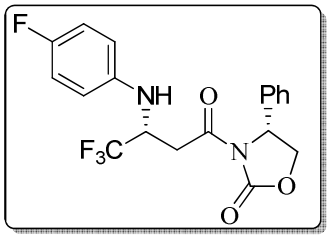


3-(4-bromo-4,4-difluoro-3-((4-fluorophenyl)amino)butanoyl)oxazolidin-2-one (3gk): 4-fluoroaniline (24.5 mg, 0.22 mmol) and acrylate **1g** (54.0 mg, 0.2 mmol) were added to a 1 mL test tube. The mixture was stirred at r.t. for 10 h, then passed through a plug of silica gel (PE:DCM = 1:2) to afford the title compound (66.4 mg, 87%) as a yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 6.83 (t, 8.7 Hz, 2H), 6.68-6.59 (m, 2H), 4.61-4.46 (m, 1H), 4.31 (t, 8.1 Hz, 2H), 3.90-3.86 (m, 2H), 3.79 (d, 10.5 Hz, 1H), 3.50 (dd, 16.0 Hz, 9.8 Hz, 1H), 3.23 (dd, 16.0 Hz, 3.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 155.8 (d, 238.1 Hz), 152.6, 141.0 (d, 2.1 Hz), 124.0 (t, 313.7 Hz), 114.9 (d, 22.7 Hz), 114.5 (d, 7.6 Hz), 61.2, 59.5 (t, 23.9 Hz), 41.5, 35.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ -53.0--53.8 (m, 2F), -125.2--125.3 (m, 1F); IR (KBr): 3358.1, 3023.3, 1777.2, 1689.5, 1512.2, 1401.7, 1311.3, 1230.0, 1130.0, 940.8, 819.9, 760.3 cm^{-1}; mp = 116-117 °C; HRMS calcd. for $[M+H]^+$: 381.0062, found: 381.0043.



(R)-4-phenyl-3-((S)-4,4,4-trifluoro-3-((4-fluorophenyl)amino)butanoyl)oxazolidin-2-one (*R*,*S*)-5: 4-fluoroaniline (0.49 g, 4.4 mmol) and compound **4** (1.14 g, 4 mmol) were added to a 10 mL test tube. After

stirring at r.t. for 15 min, the reaction was stopped. The diastereoselective ratio was determined as 2.8:1 by the ^{1}H NMR of the crude mixture of diastereomers (page S66). The major isomer (*R*,*S*)-**5** was purified by column chromatography (PE:DCM = 1:1) as a yellow solid (0.56 g, 68% (brsm)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21-7.15 (m, 1H), 7.11 (t, 7.6 Hz, 2H), 7.09-7.04 (m, 2H), 6.78 (t, 8.7 Hz, 2H), 6.53-6.42 (m, 2H), 5.37-5.33 (m, 1H), 4.58 (t, 8.8 Hz, 1H), 4.38-4.27 (m, 1H), 4.18 (dd, 8.9 Hz, 3.5 Hz, 1H), 3.90 (d, 10.5 Hz, 1H), 3.60 (dd, 15.1 Hz, 9.6 Hz, 1H), 3.10 (dd, 15.1 Hz, 4.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 155.8 (d, 238.1 Hz), 152.9, 140.8, 137.0, 128.1, 127.7, 124.5, 124.4 (q, 284.8 Hz), 114.8 (d, 22.7 Hz), 114.3 (d, 7.6 Hz), 69.2, 56.8, 53.4 (q, 30.2 Hz), 34.0. ^{19}F NMR (471 MHz, $CDCl_3$) δ -76.1 (d, 6.6 Hz, 3F), -125.4--125.5 (m, 1F).

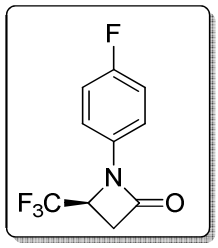


(R)-4-phenyl-3-((R)-4,4,4-trifluoro-3-((4-fluoro phenyl)amino)butanoyl)oxazolidin-2-one

(*R*,*R*)-5: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.20 (m, 3H), 7.17-7.10 (m, 2H), 6.81 (t, 8.6 Hz, 2H), 6.62-6.47 (m, 2H), 5.32 (dd, 8.7 Hz, 3.9 Hz, 1H), 4.59 (t, 8.9 Hz, 1H), 4.49-4.47 (m, 1H), 4.21 (dd, 9.0 Hz, 3.9 Hz, 1H), 3.65 (d, 10.2 Hz, 1H), 3.43 (dd, 16.1 Hz, 9.8 Hz, 1H), 3.21 (dd, 16.1 Hz, 3.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 155.8 (d, 238.1 Hz), 152.8, 140.9, 137.2, 128.2, 127.9, 124.8, 124.5 (q, 284.8 Hz), 114.9 (d, 22.7 Hz), 114.2 (d, 7.5 Hz), 69.2, 56.7, 52.5 (q, 30.2

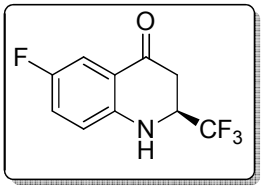
Hz), 34.8. ^{19}F NMR (471 MHz, $CDCl_3$) δ -75.9 (d, 6.7 Hz, 3F), -125.4--125.5 (m, 1F).

Synthesis of enantiopure trifluoromethylated *N*-hetereocycles



(*S*)-1-(4-fluorophenyl)-4-(trifluoromethyl)azetidin-2-one (9)[1]: To the solution of compound **(*R*,*S*)-5** (0.56 g, 1.42 mmol) in THF/H_2O (4:1, 8 mL), H_2O_2 (30%, 1 mL) and aqueous solution of LiOH•H_2O (0.10 g, 2.38 mmol) were slowly added at 0 ^oC. After stirring at 0 ^oC for 2 h, Na_2SO_3 was added to consume the remained H_2O_2. The solution was adjusted to pH 12, then extracted with ethyl acetate (3×5 mL). The aqueous phase was acidified by dilute HCl to pH 2, then extracted with ethyl acetate (3×10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the residue was purified by column chromatography (PE:EA = 2:1) to afford compound **(*S*)-6** (0.26 g, 73%) as a yellow solid. Under N_2 atmosphere, compound **(*S*)-6** (0.16 g, 0.64 mmol) and anhydrous CH_3OH (1.44 mL) were added to a 10 mL oven-dried Schlenk tube. $SOCl_2$ (0.07 mL, 1 mmol) was slowly added to the mixture at 5 ^oC, then warmed to 60 ^oC. After 1.5 h stirring at the temperature, the solution was cooled to r.t. and toluene (1.3 mL) was added. $NaHCO_3$ (0.13 g, 1.5 mmol) was added to the above solution at 0 ^oC, then stirred for 1h. The resulting solution was extracted with ethyl acetate and dried over anhydrous

Na_2SO_4. Evaporating the solvent under vacuum gave compound **(*S*)-8** (0.16 g, 95%) as a yellow solid without purification. To a solution of compound **(*S*)-8** (0.16 g, 0.60 mmol) in anhydrous Et_2O (1.5 mL) was slowly added a solution of MeMgBr (0.4 mL, 3M in Et_2O) at -12 ^oC under nitrogen atmosphere. After stirring at -12 ^oC for 1h, the reaction was quenched by adding an excess amount of saturated aqueous NH_4Cl solution, followed by extracting with Et_2O (3×10 mL). The organic phase was washed with brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the residue was purified by column chromatography (PE:EA = 10:1) to afford the title compound **9** (96.5 mg, 69%) as a yellow solid. $[\alpha]_D^{25}$ = -289.2 (*c* 0.21, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.53-7.31 (m, 2H), 7.06 (t, 8.6 Hz, 2H), 4.64-4.39 (m, 1H), 3.37 (dd, 15.5 Hz, 5.8 Hz, 1H), 3.21 (dd, 15.5 Hz, 2.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.6, 159.7 (d, 245.7 Hz), 132.9 (d, 2.8 Hz), 124.2 (q, 180 Hz), 119.1 (d, 8.1 Hz), 116.0 (d, 22.7 Hz), 50.8 (q, 35.3 Hz), 38.6 (d, 1.7 Hz).



(*S*)-6-fluoro-2-(trifluoromethyl)-2,3-dihydroquinolin-4(1*H*)-one (7): Compound **(*S*)-6** (0.1 g, 0.4 mmol) and polyphosphoric acids (1.0 g) were added to a 10 mL test tube. After stirring at 120-130 ^oC for 0.5 h, the viscous solution was cooled, and ice water (4 mL) was added, followed by extracting with ethyl acetate (3×10 mL). The organic phase was washed

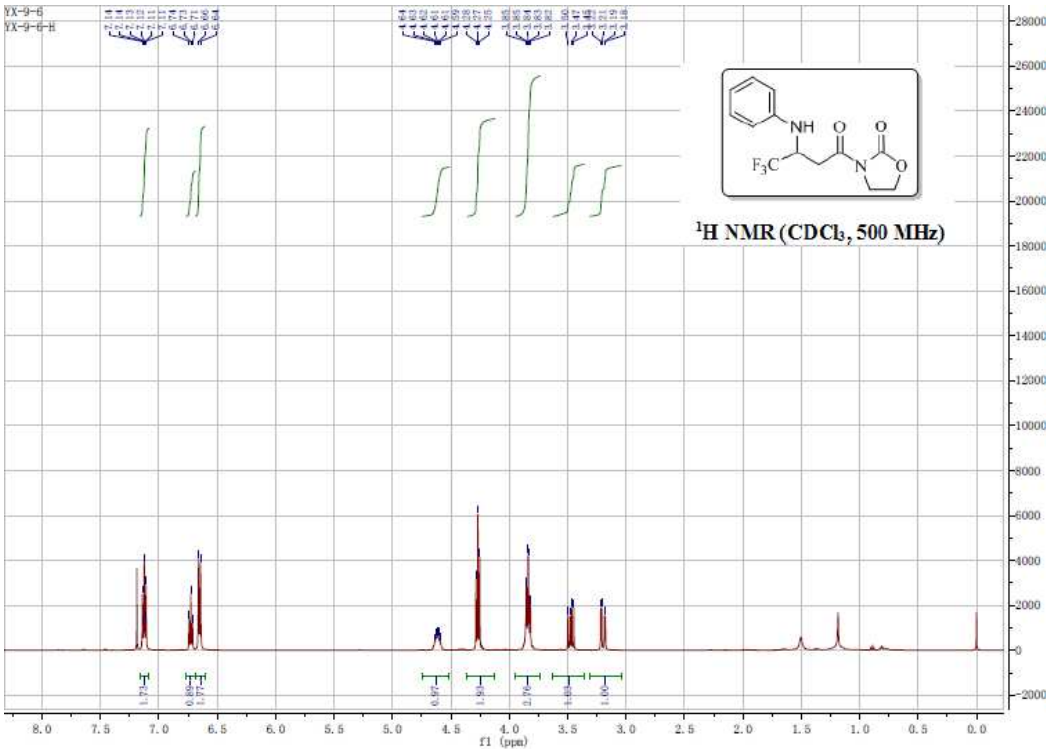
with brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the residue was purified by column chromatography (PE:EA = 4:1) to afford the title compound **7** (49.8 mg, 54%) as a yellow solid.[2] $[\alpha]_D^{25}$ = -159.0 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, 8.5 Hz, 2.9 Hz, 1H), 7.14 (td, 8.7 Hz, 3.0 Hz, 1H), 6.74 (dd, 8.9 Hz, 4.0 Hz, 1H), 4.50 (s, 1H), 4.15 (dd, 12.8 Hz, 6.8 Hz, 1H), 2.97 (dd, 16.7 Hz, 5.5 Hz, 1H), 2.88 (dd, 16.8 Hz, 8.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.2, 156.4 (d, 240.7 Hz), 145.3, 124.9 (q, 282.7 Hz), 123.8 (d, 23.9 Hz), 119.2 (d, 6.0 Hz), 117.5 (d, 6.9 Hz), 112.3 (d, 22.7 Hz), 54.5 (q, 31.5 Hz), 35.9; ^{19}F NMR (471 MHz, $CDCl_3$) δ -77.3 (d, 6.3 Hz, 3F), -124.1--124.2 (m, 1F); IR (KBr): 3698.5, 3350.0, 2998.3, 1659.3, 1507.1, 1424.6, 1269.5, 1183.1, 1169.2, 1122.2, 918.8, 826.3, 683.2 cm^{-1}; mp = 103-104 ^oC; HRMS calcd. for $[M+H]^+$: 234.0542, found: 234.0535.

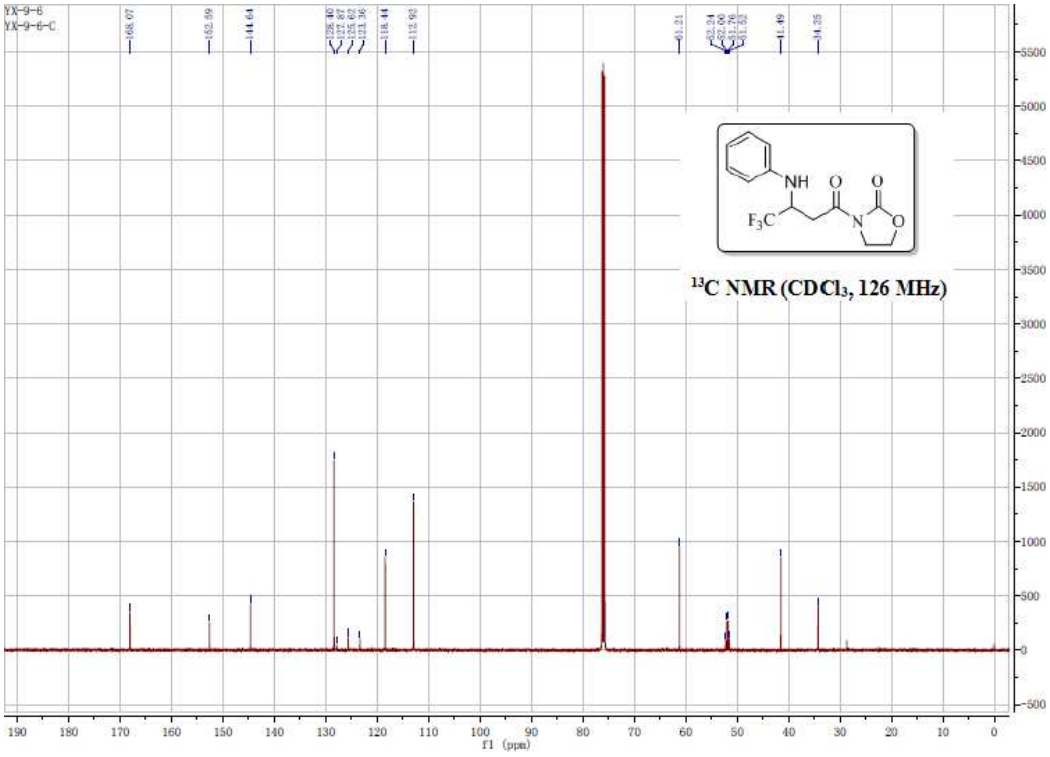
References

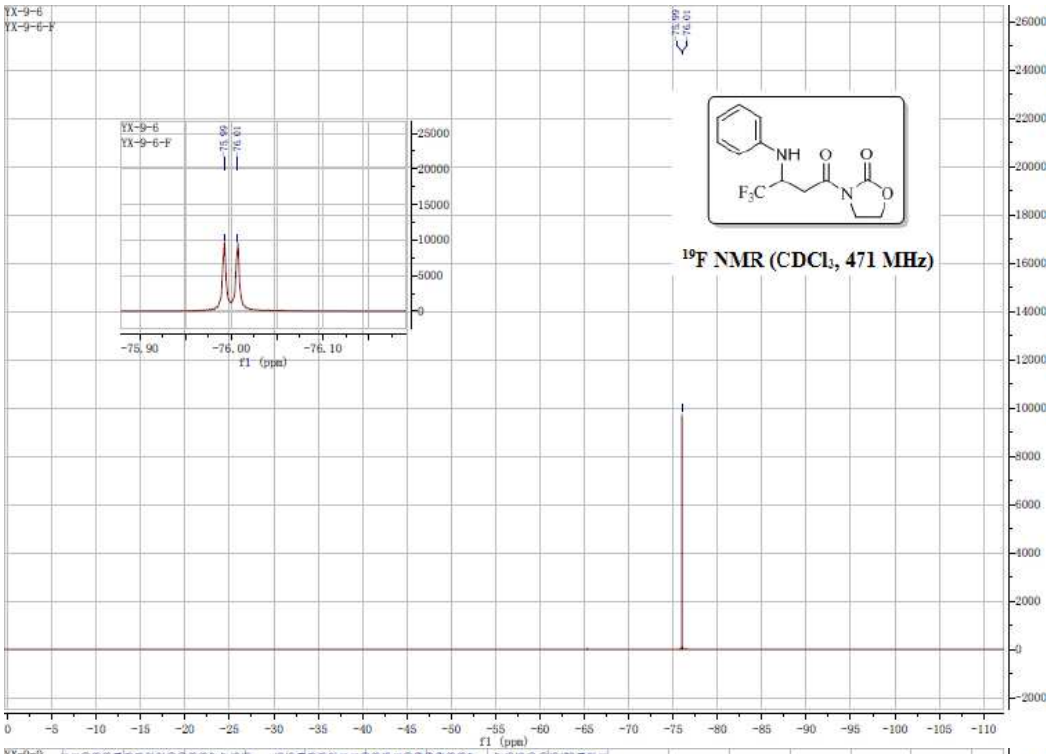
(1) K. Tamura, T. Yamazaki, T. Kitazume, T. Kubota, *J. Fluorine Chem.* 2005, **126**, 918-930.

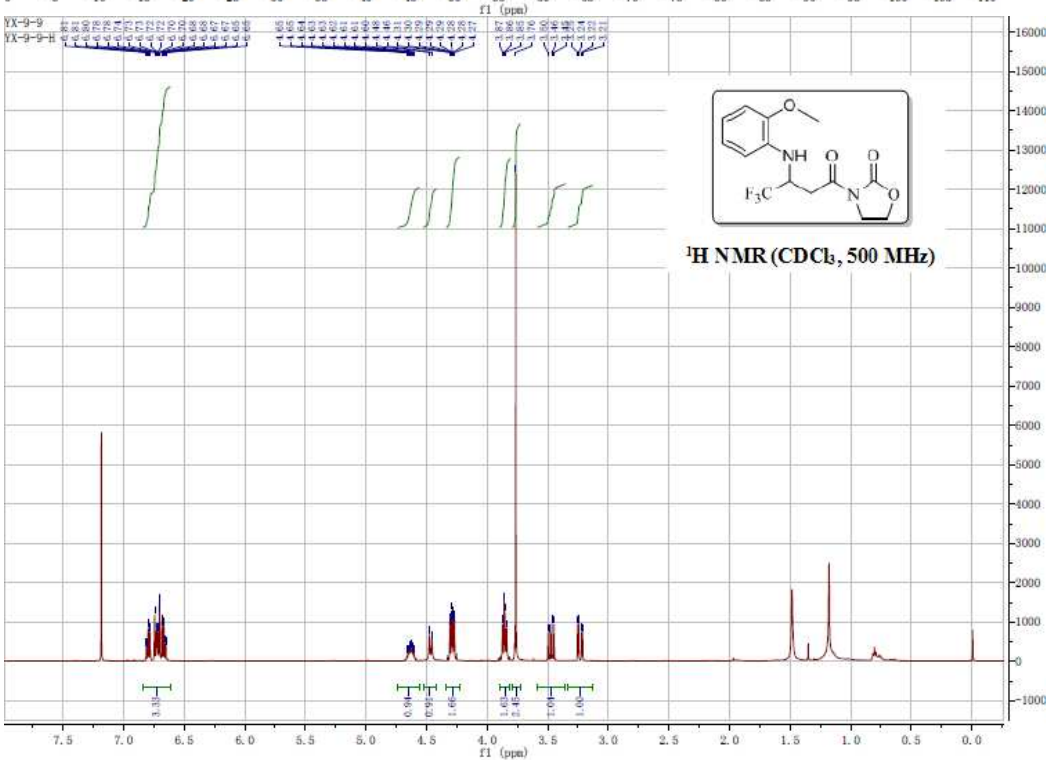
(2) Y.-F. Gong, K. Kato, *J. Fluorine Chem.* 2004, **125**, 767-773.

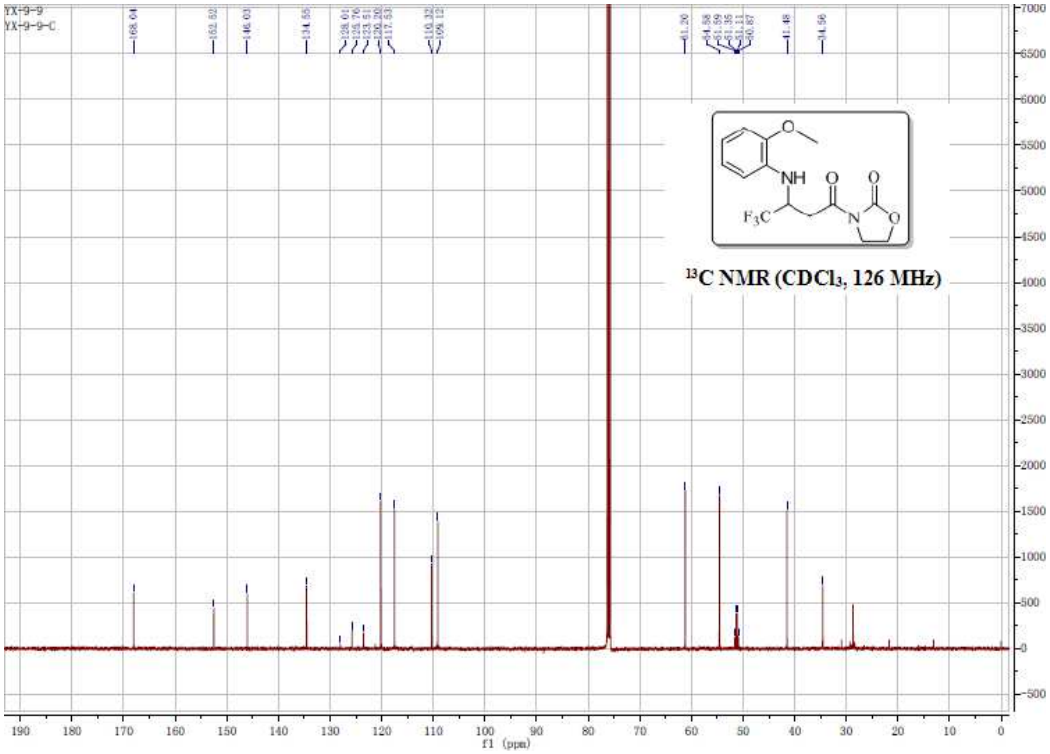
^{1}H, ^{13}C, and ^{19}F NMR spectra

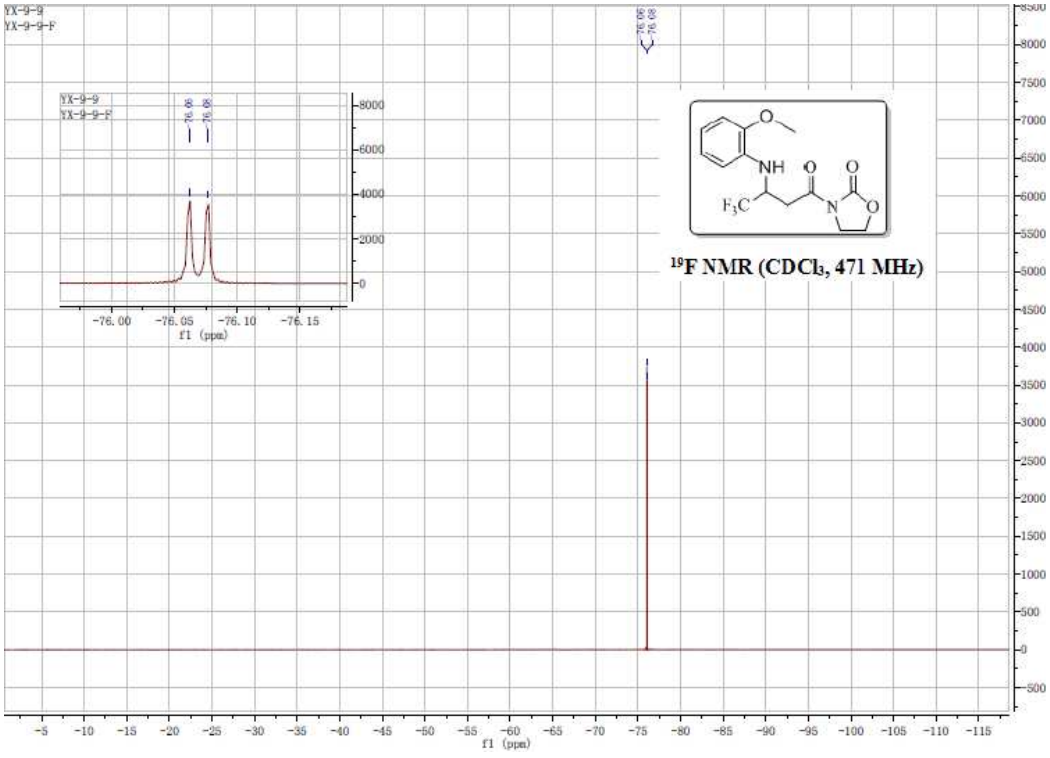


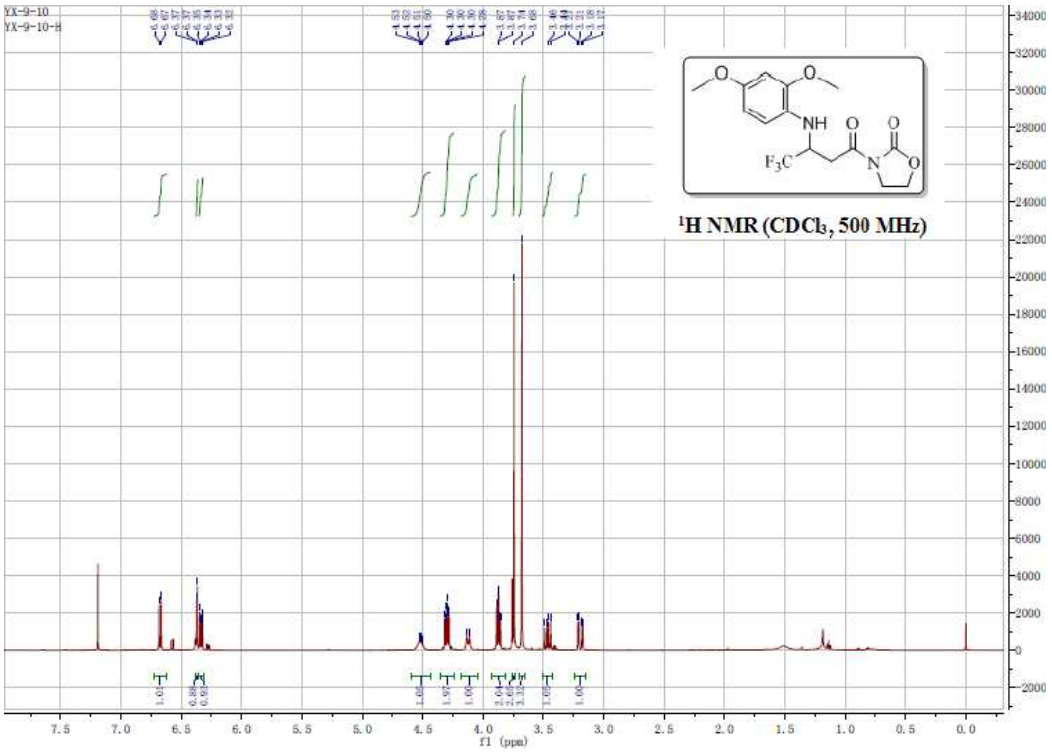


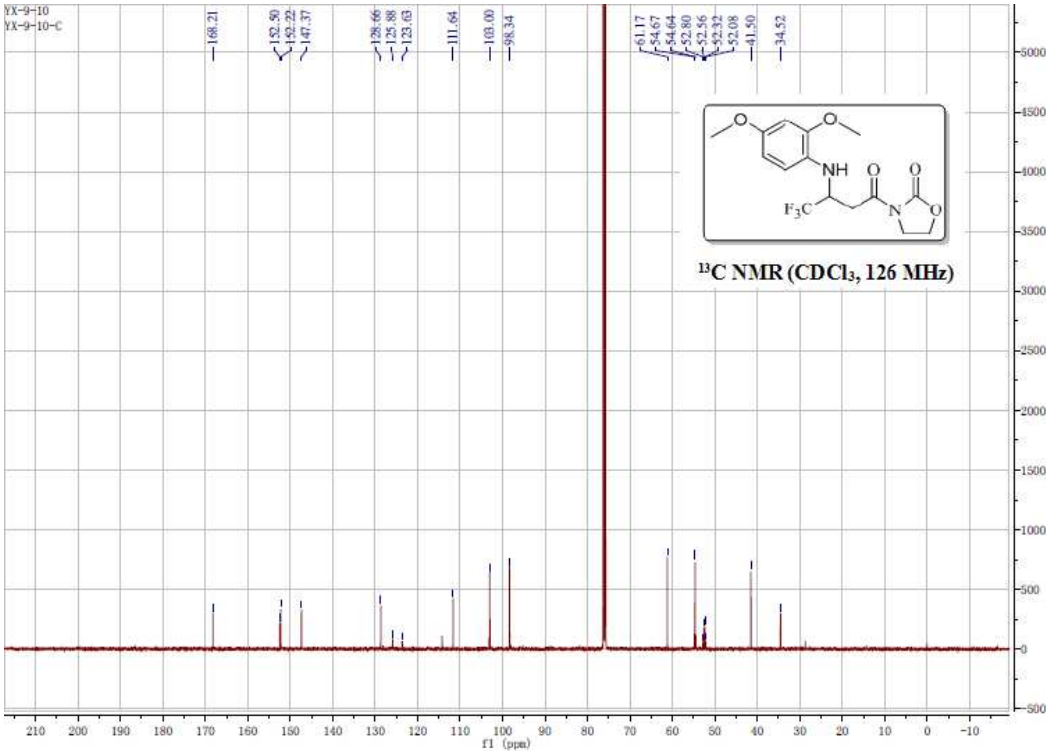


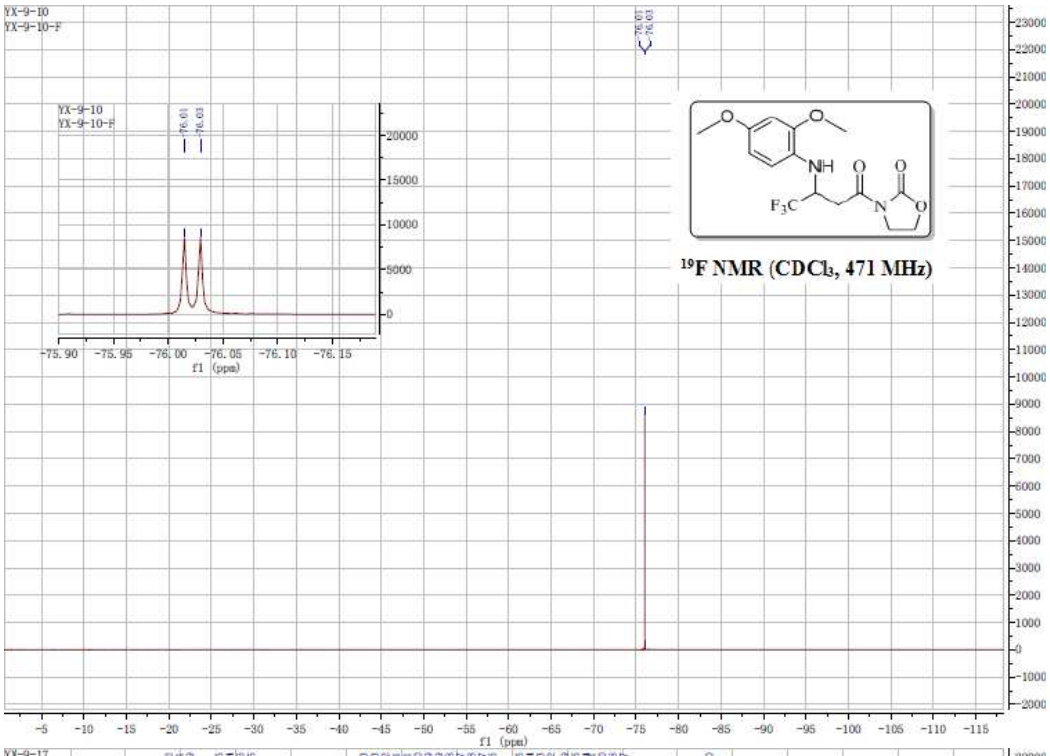


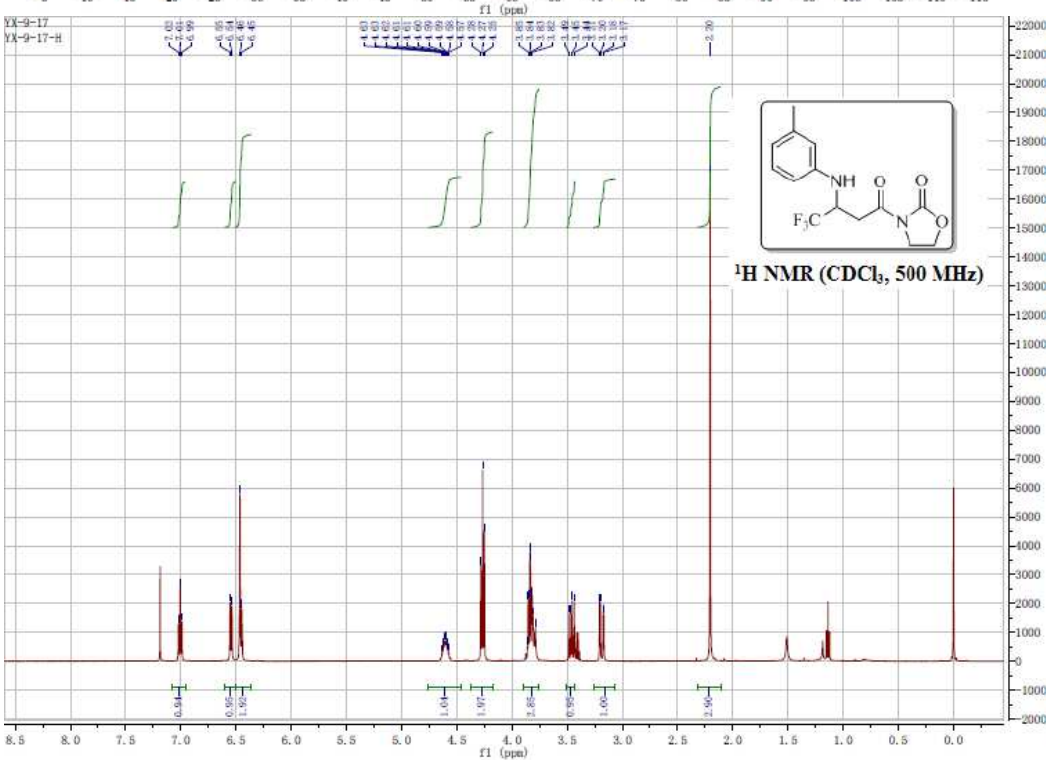


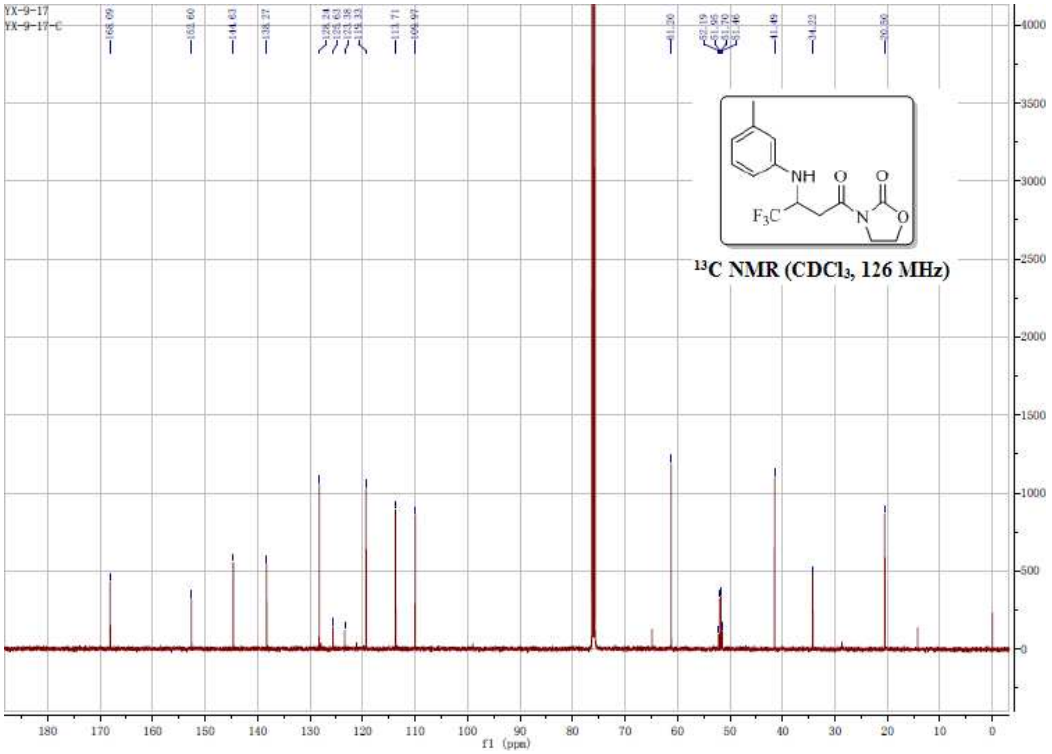


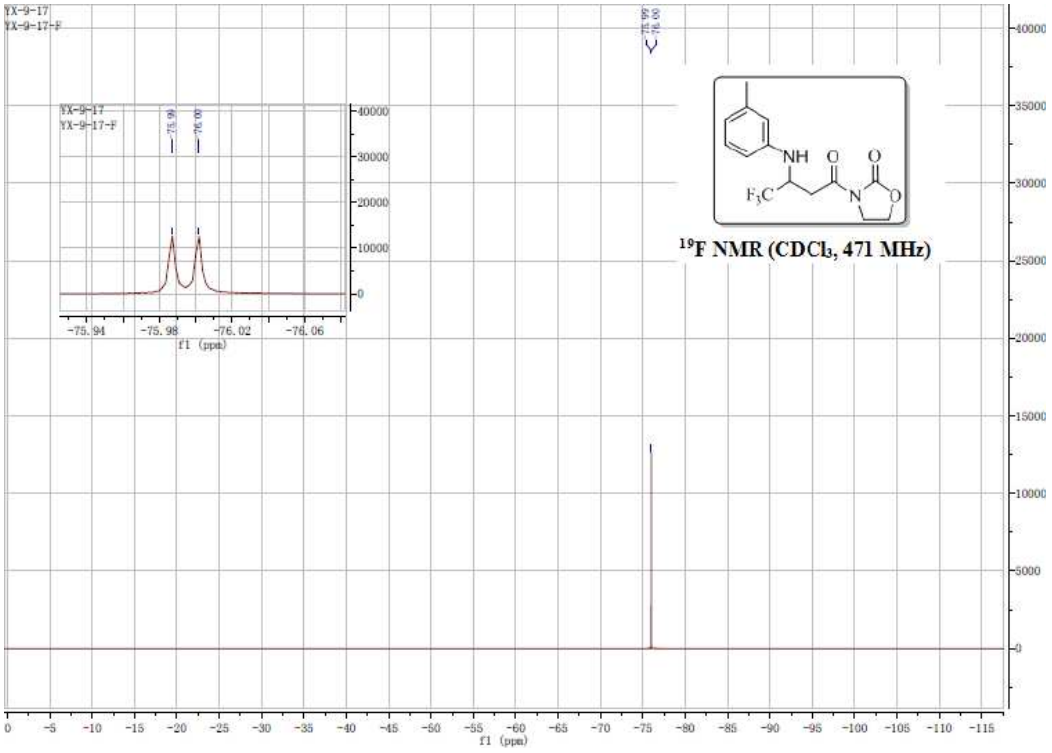


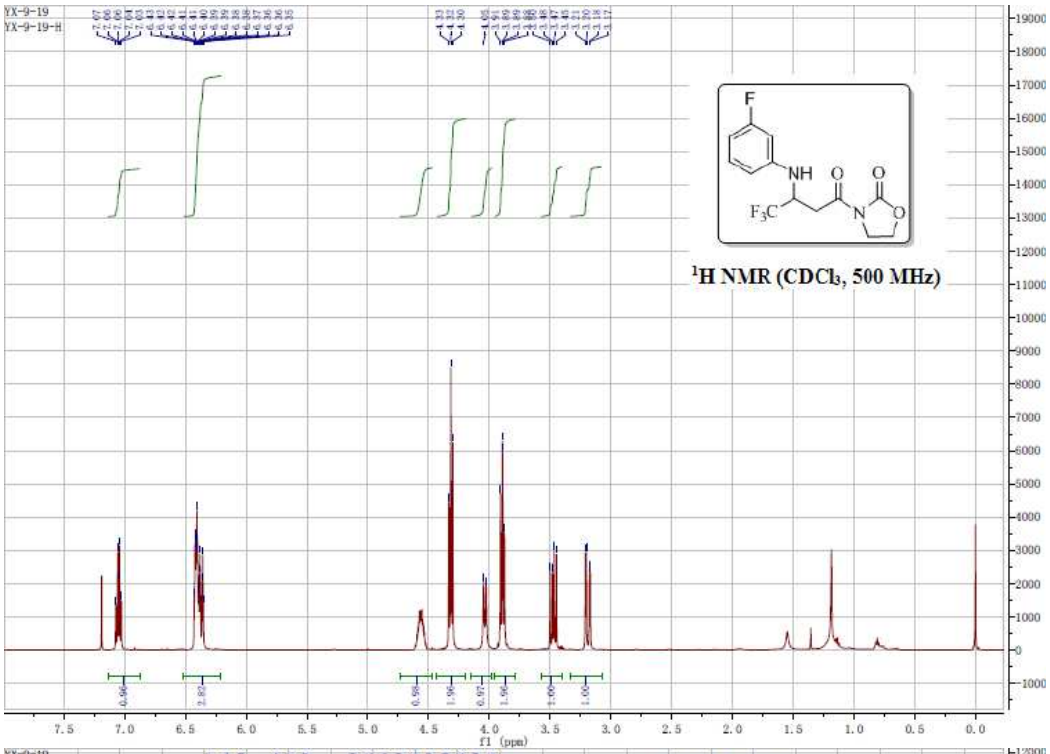


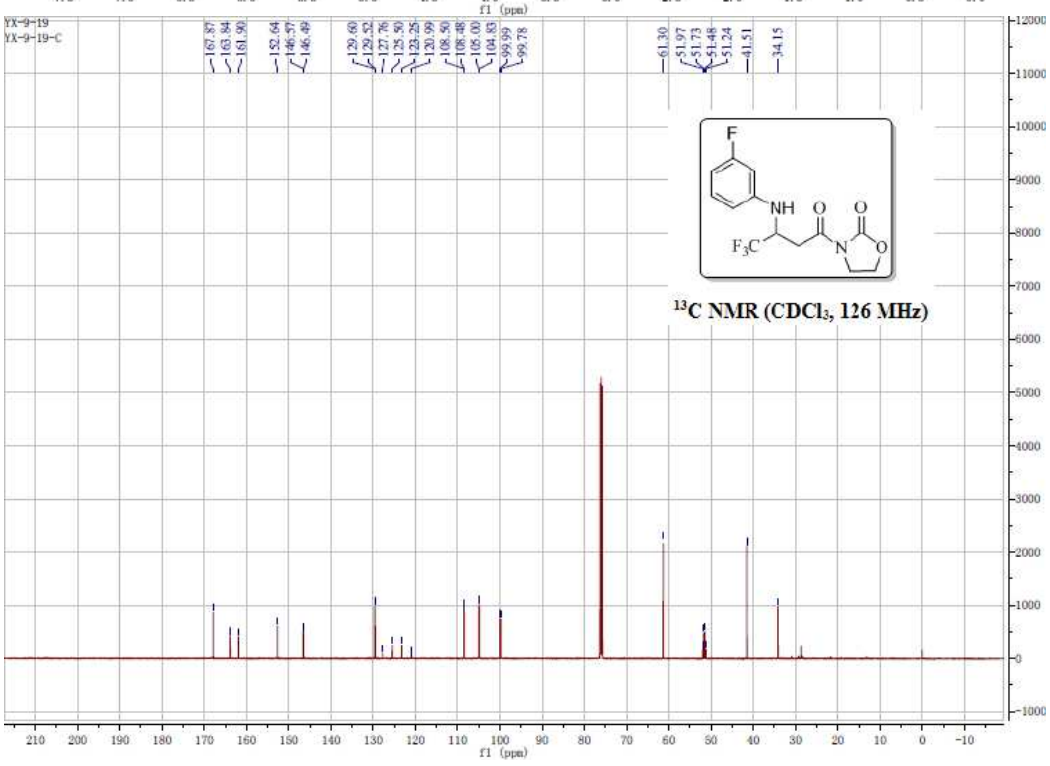


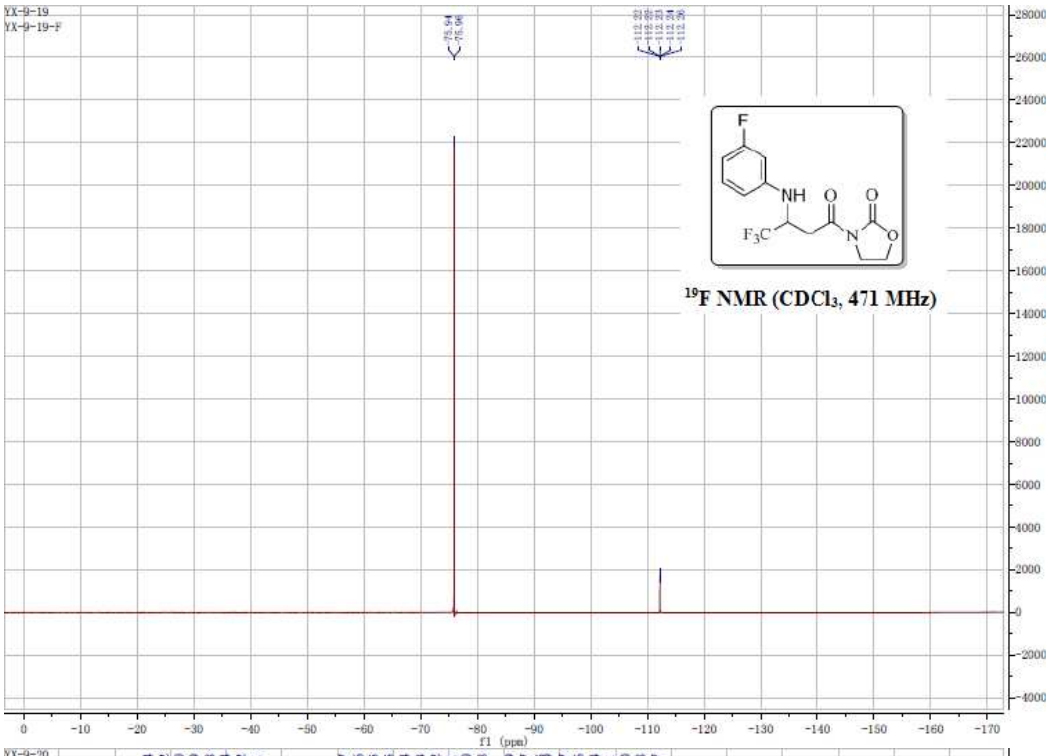


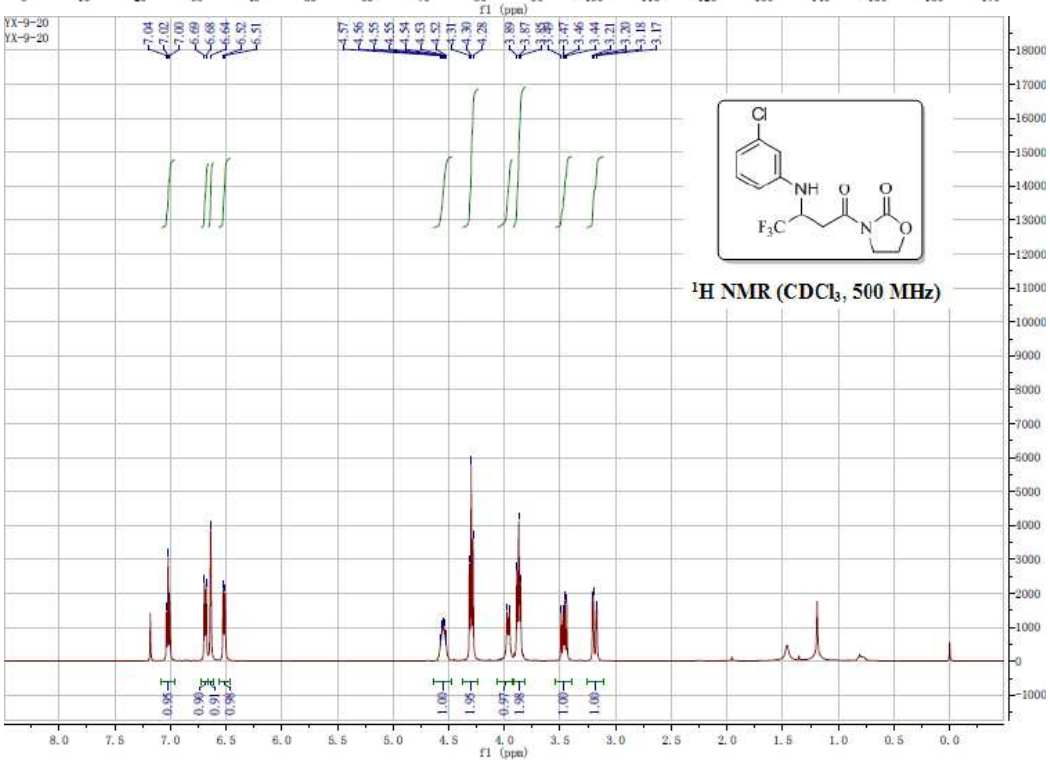


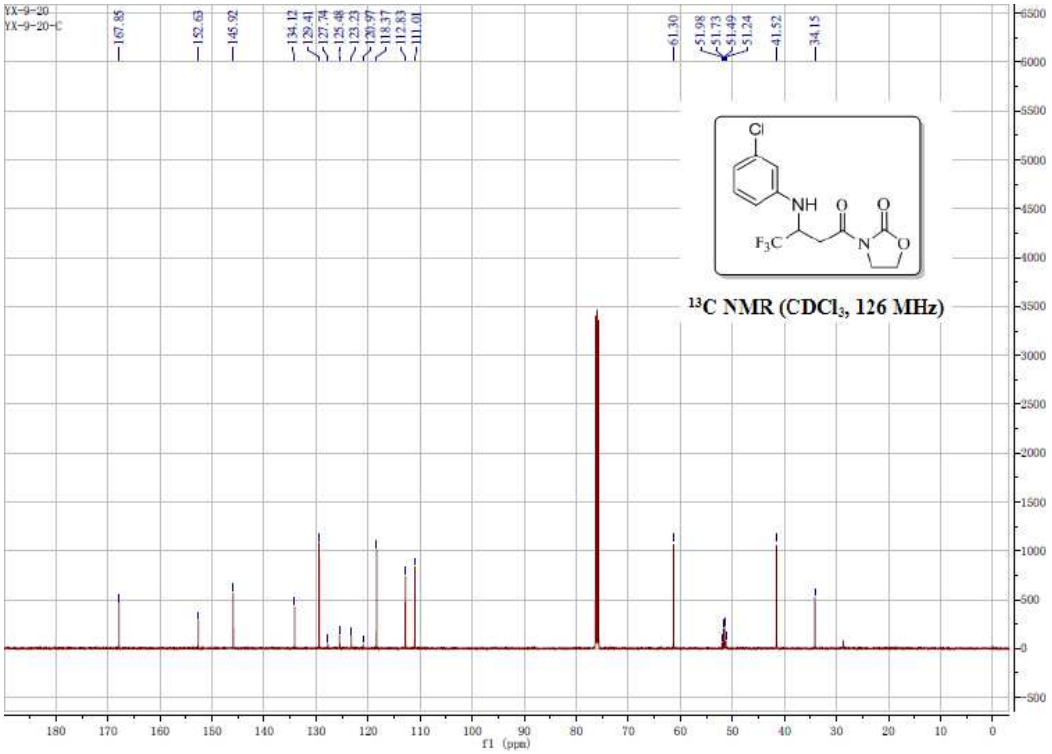


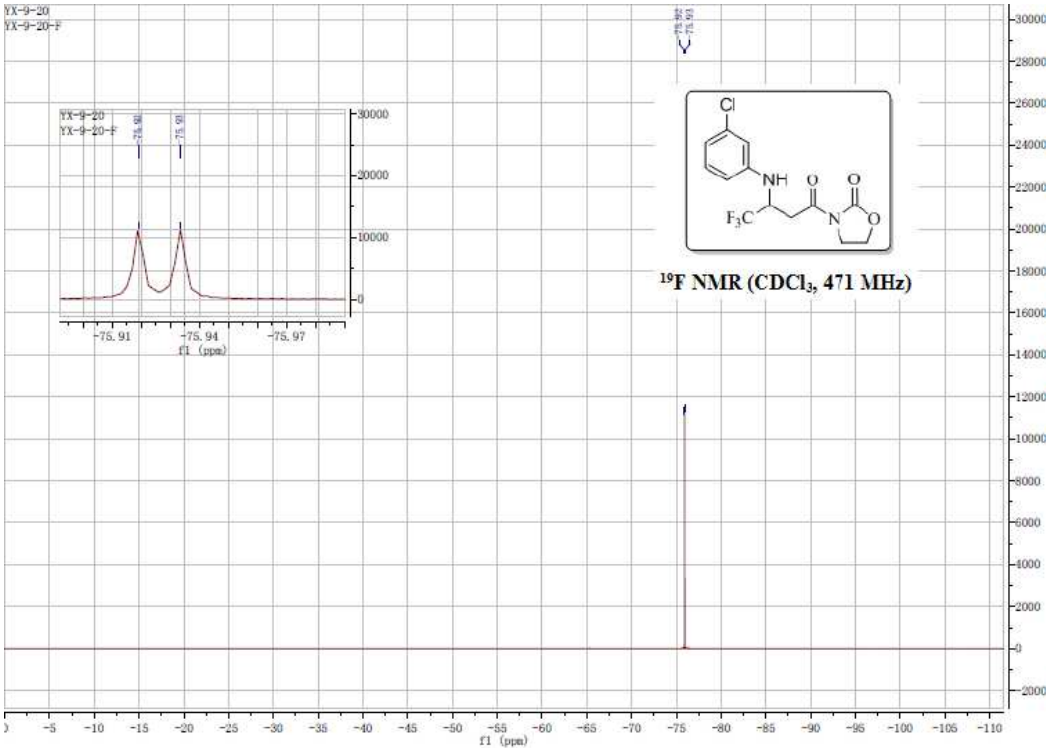


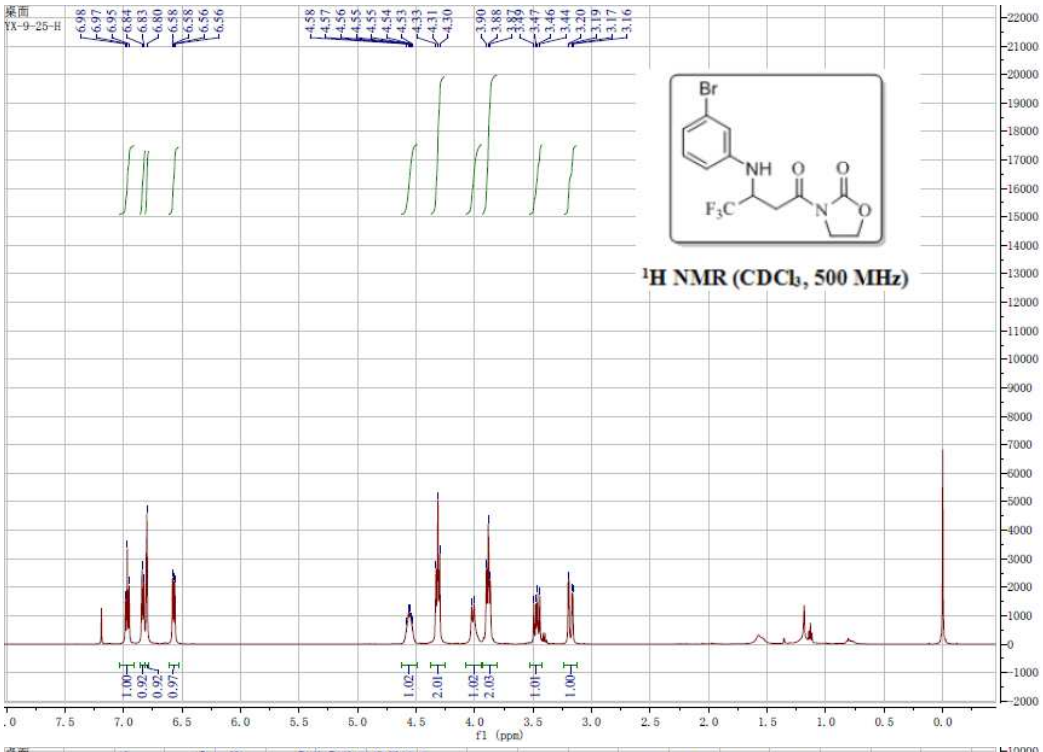


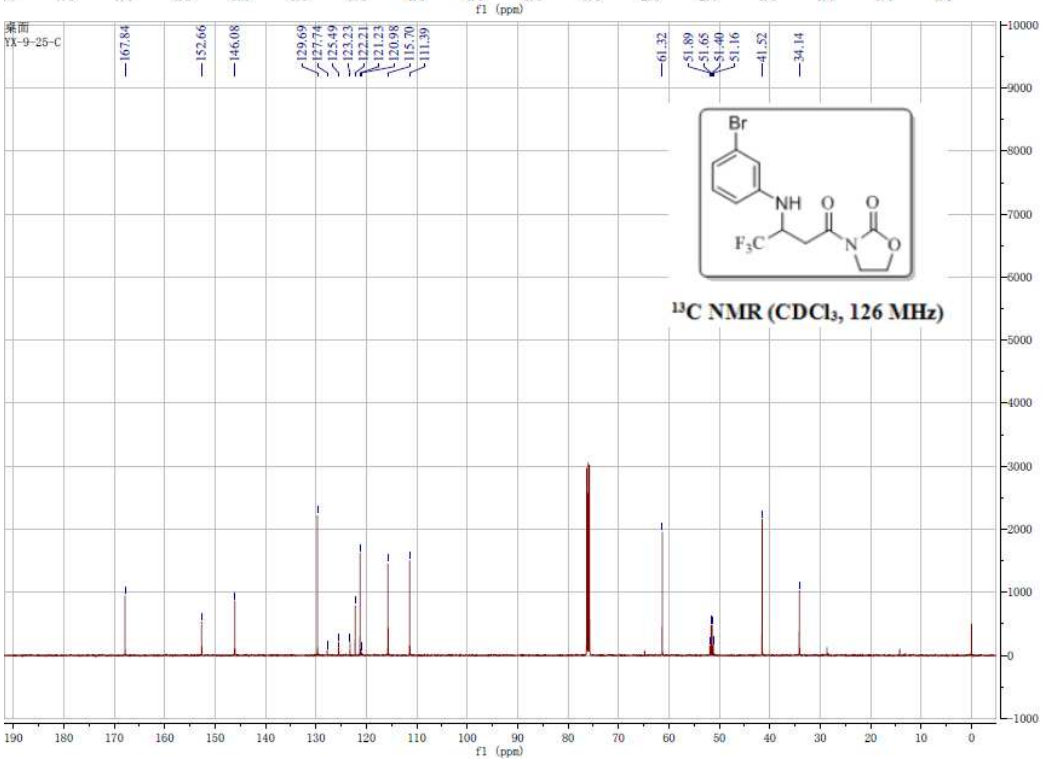


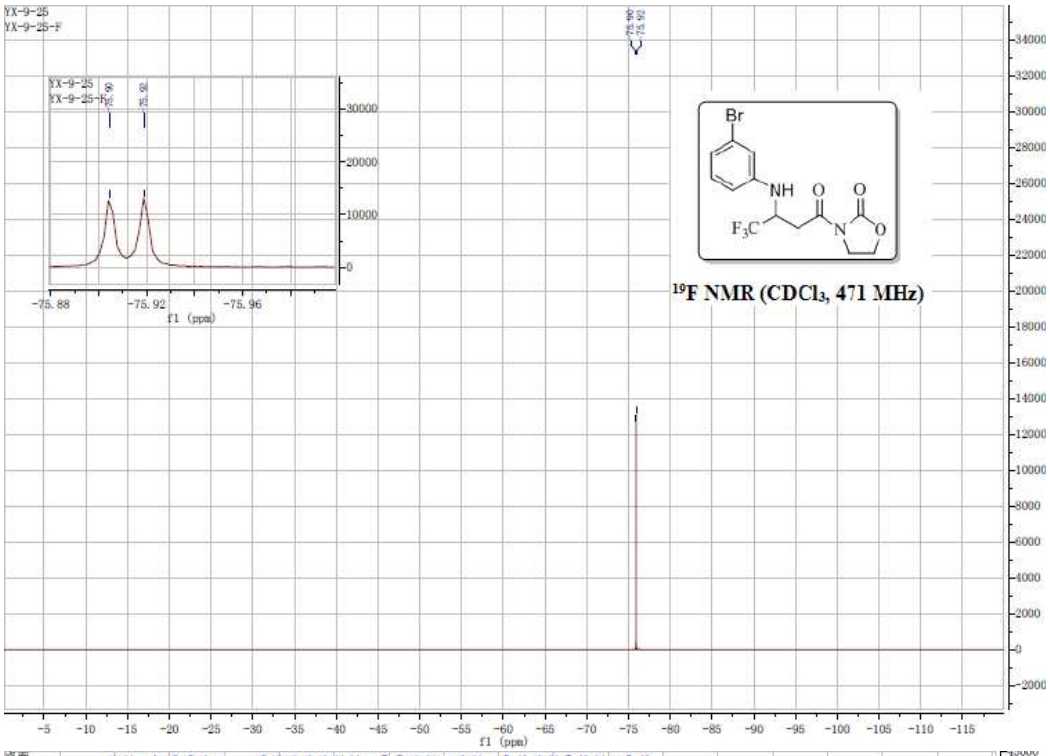


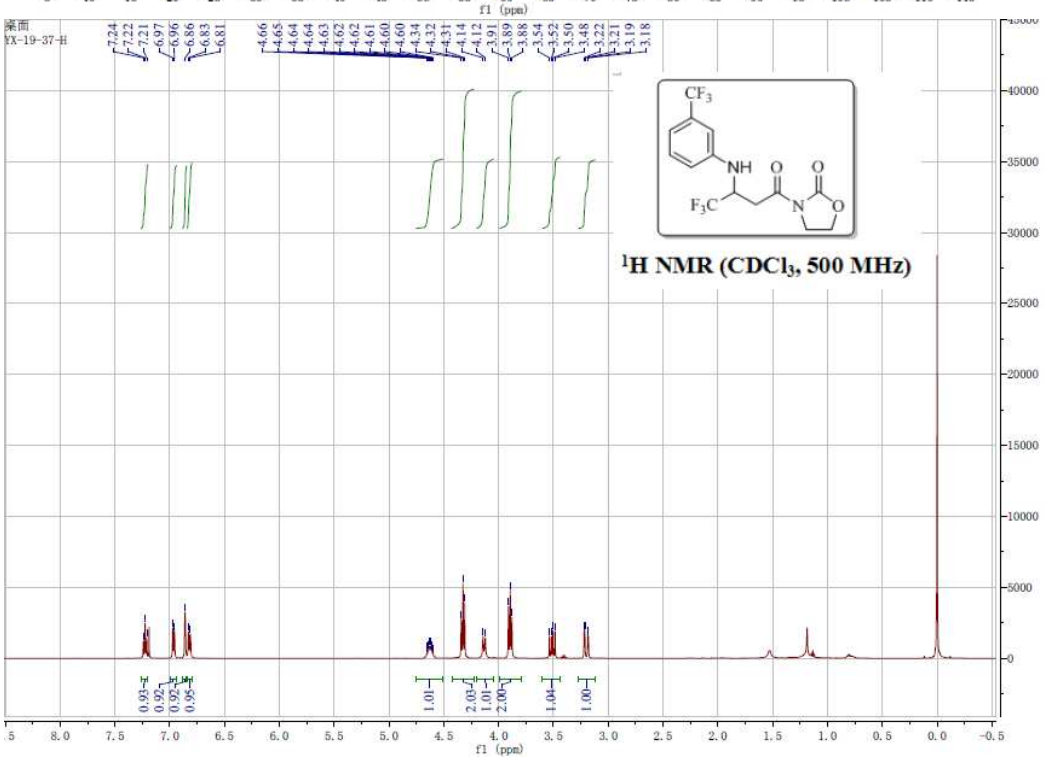


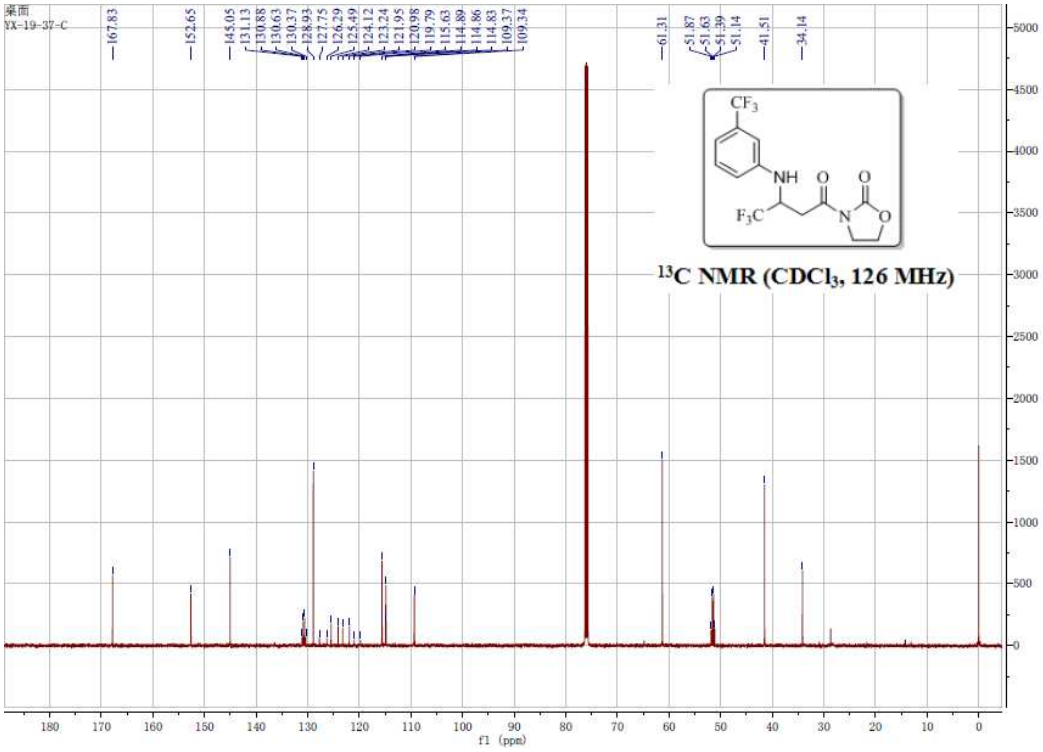


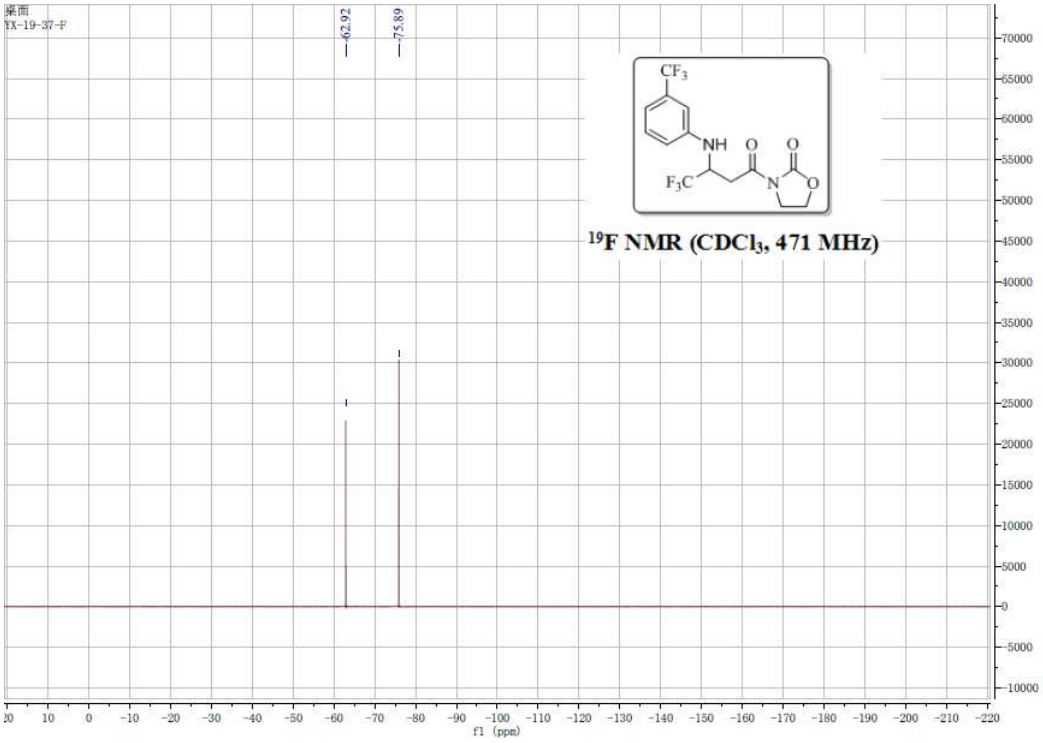


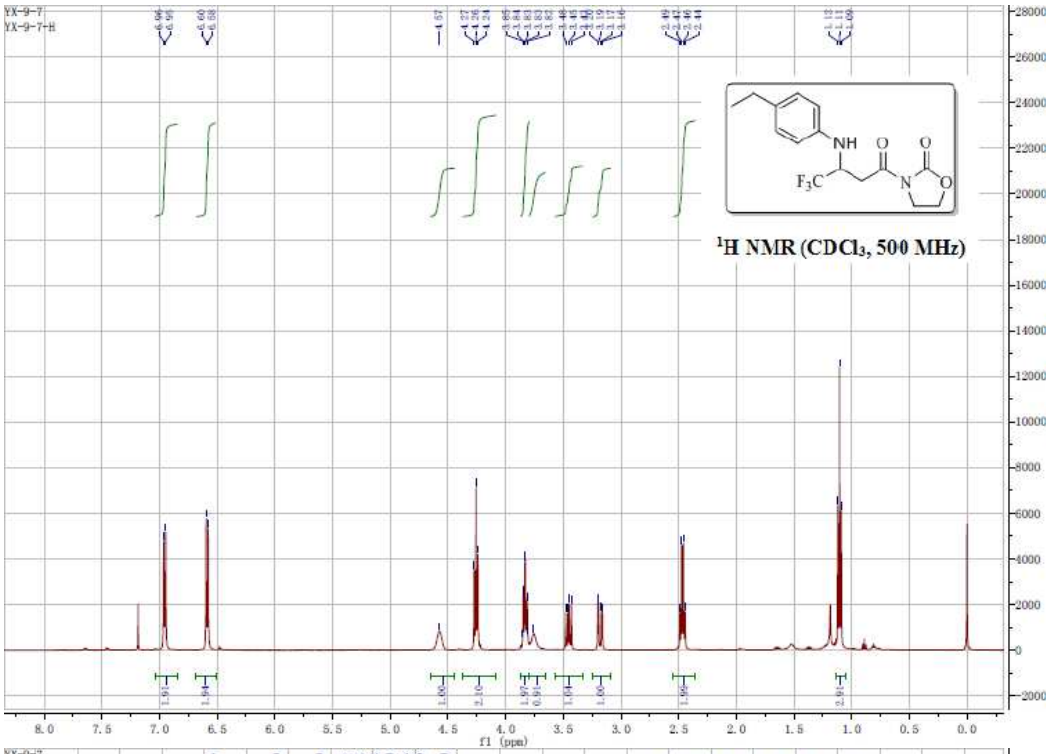


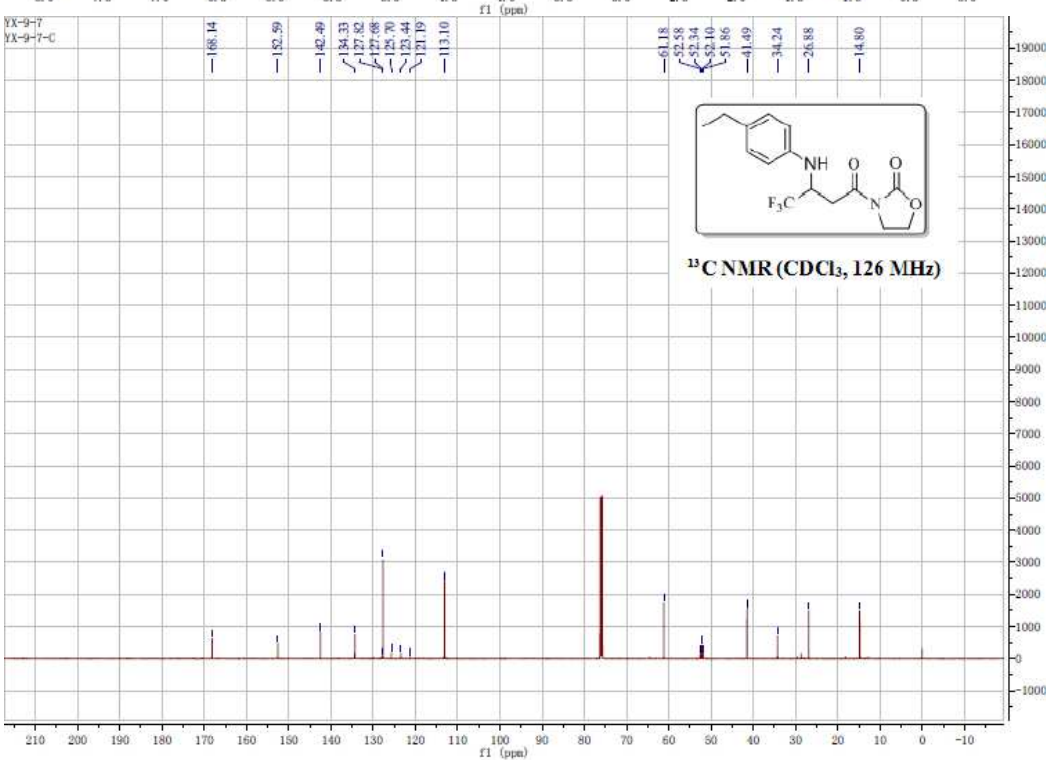


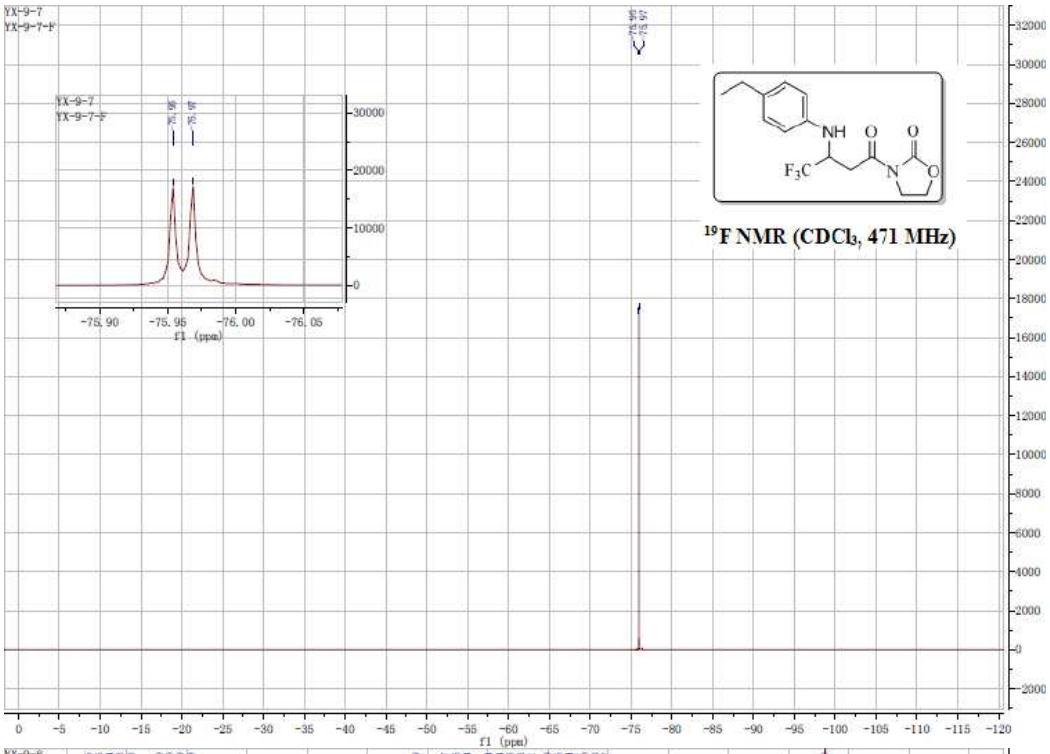


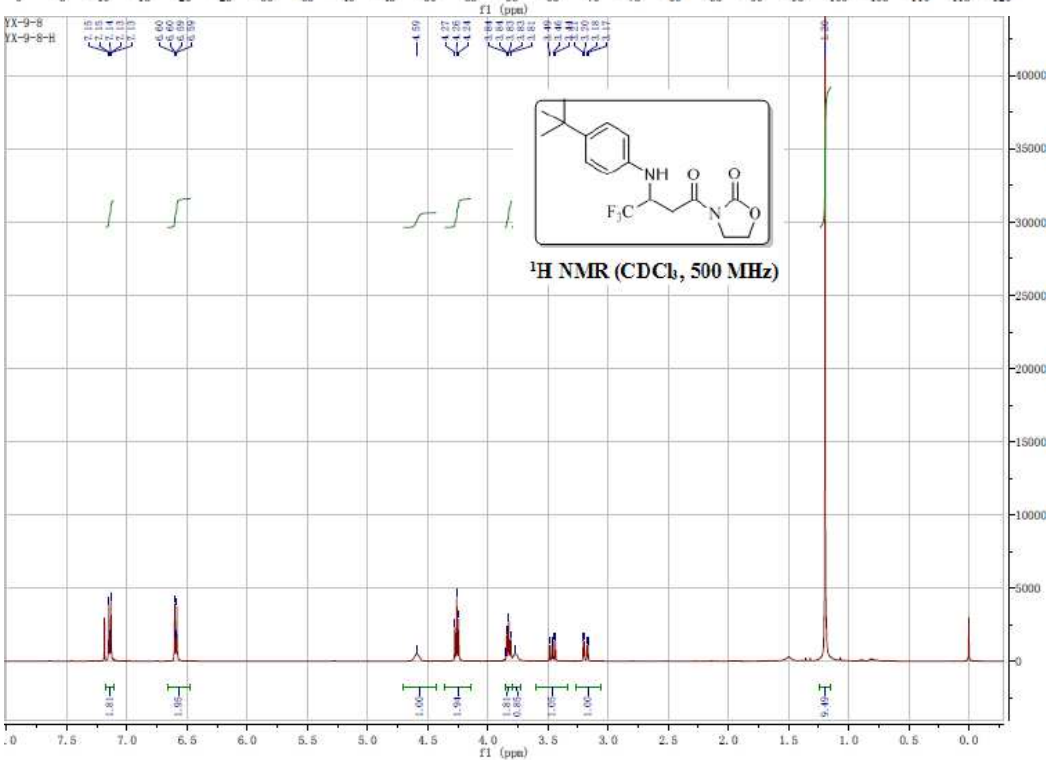


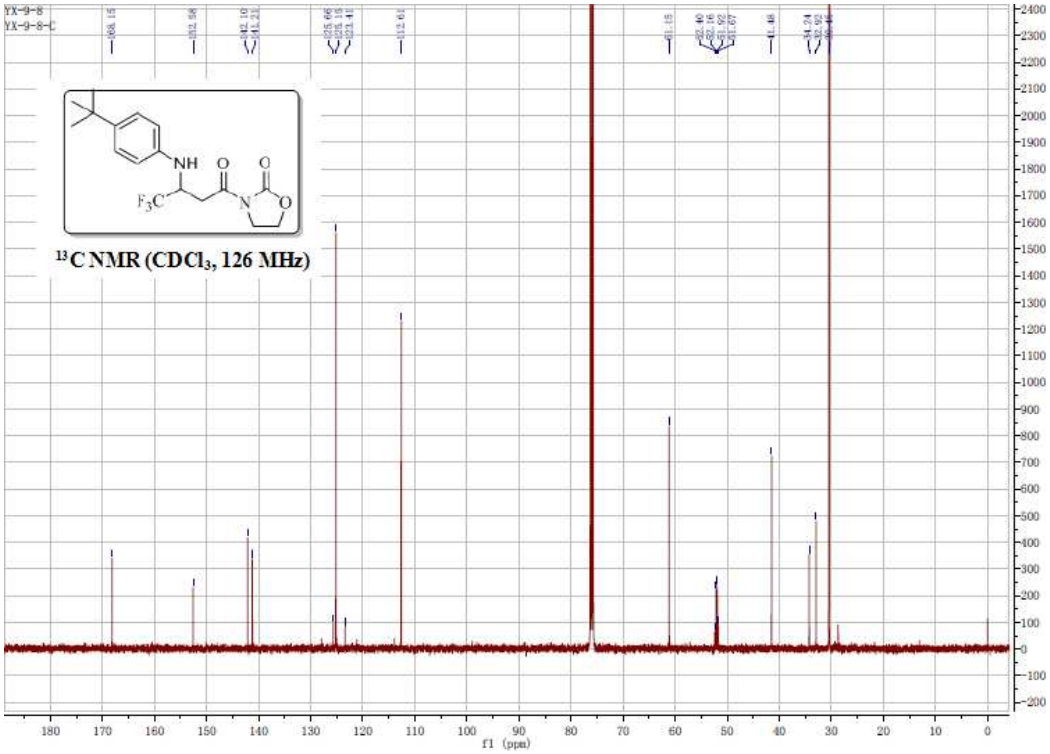


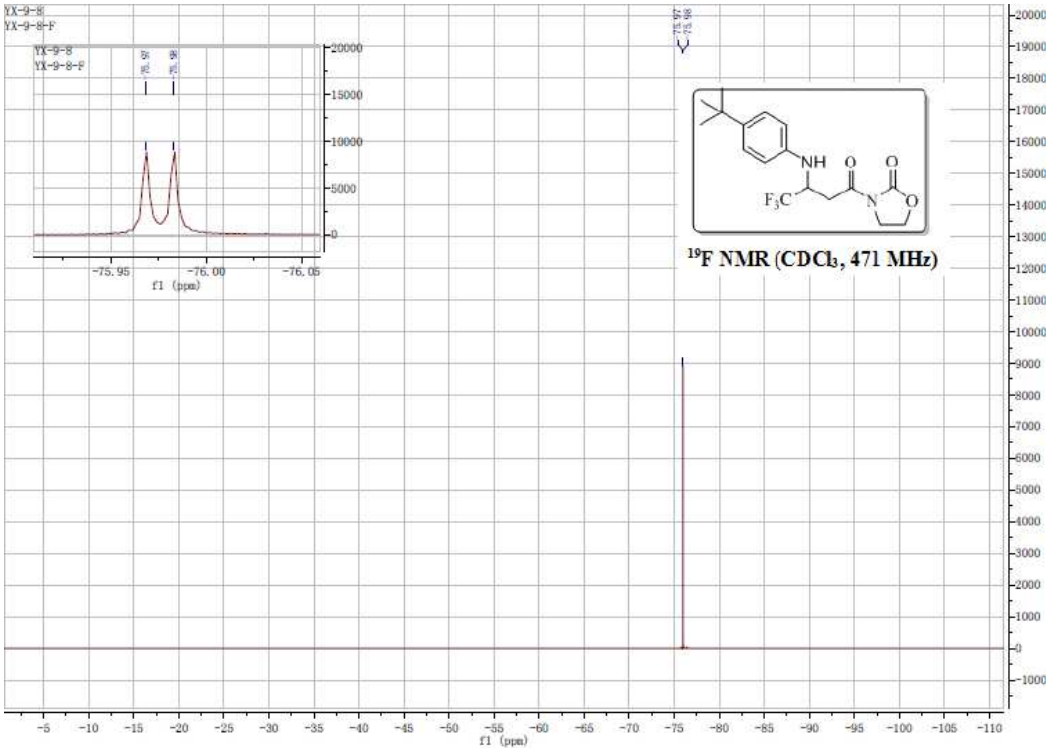


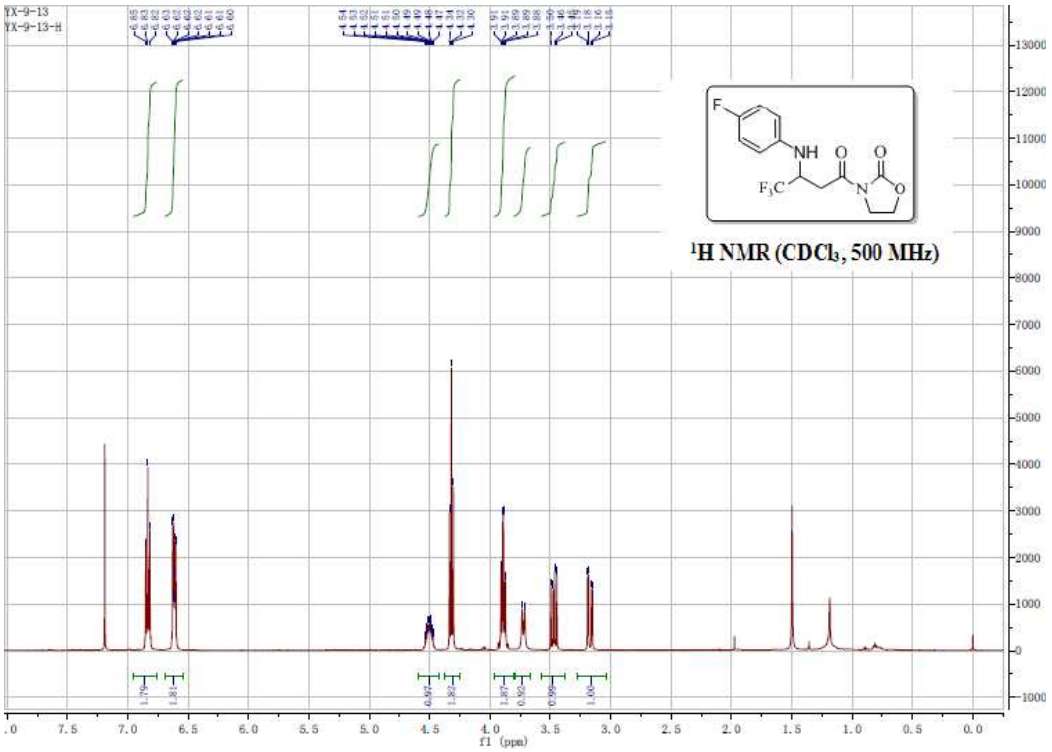


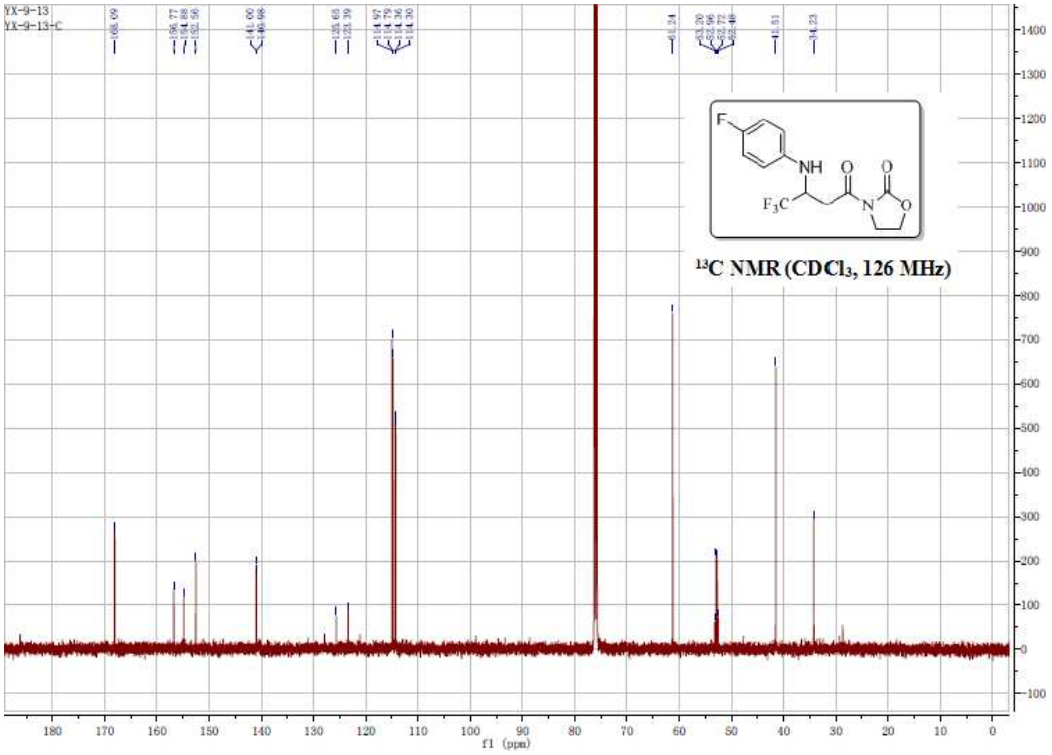


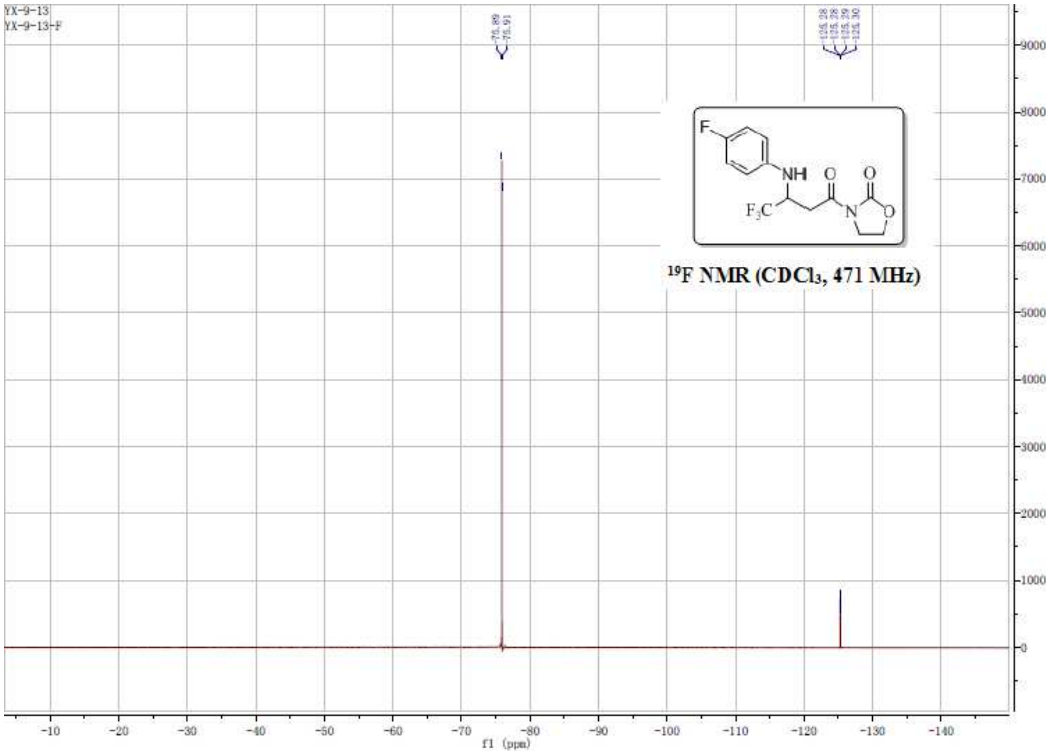


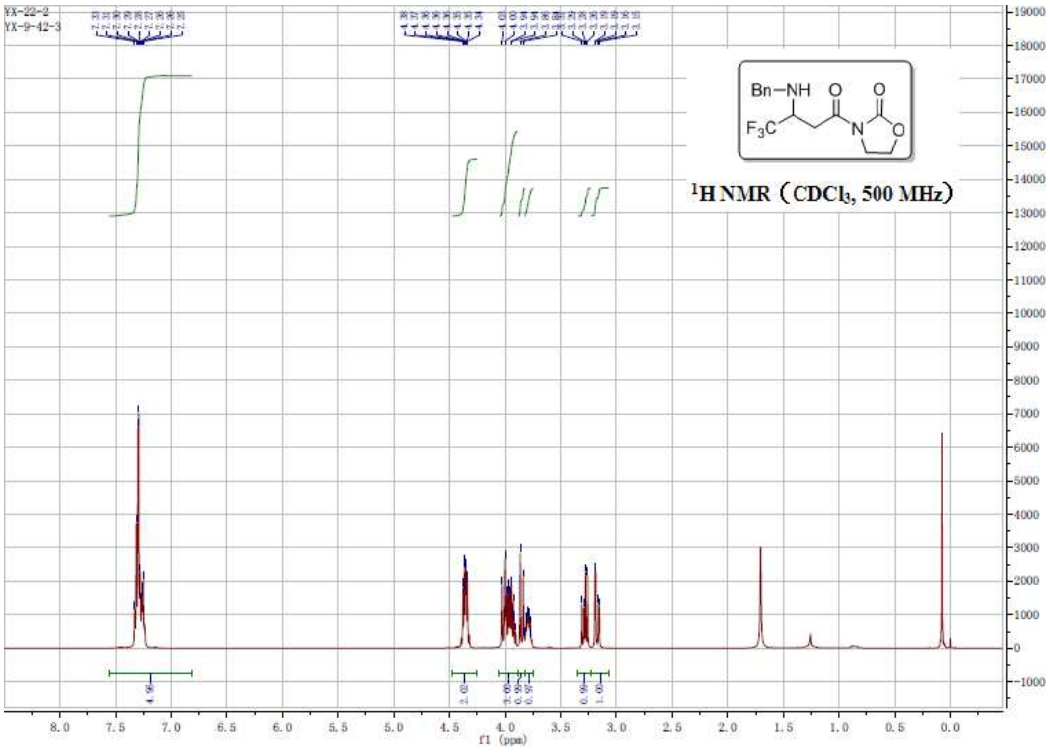


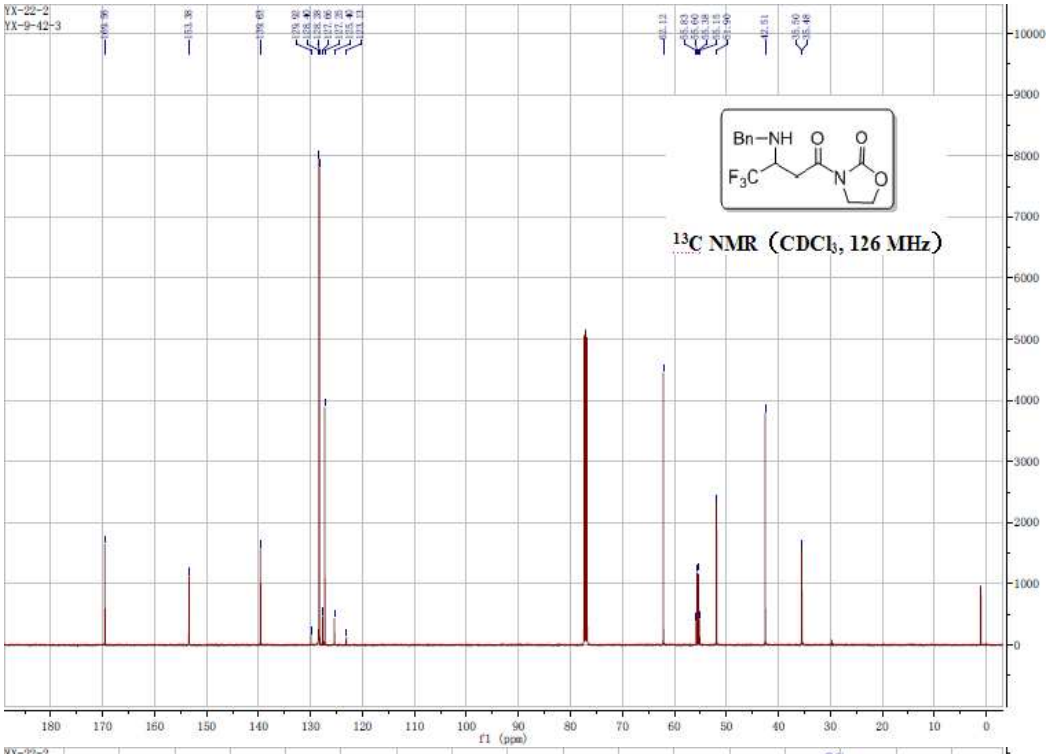


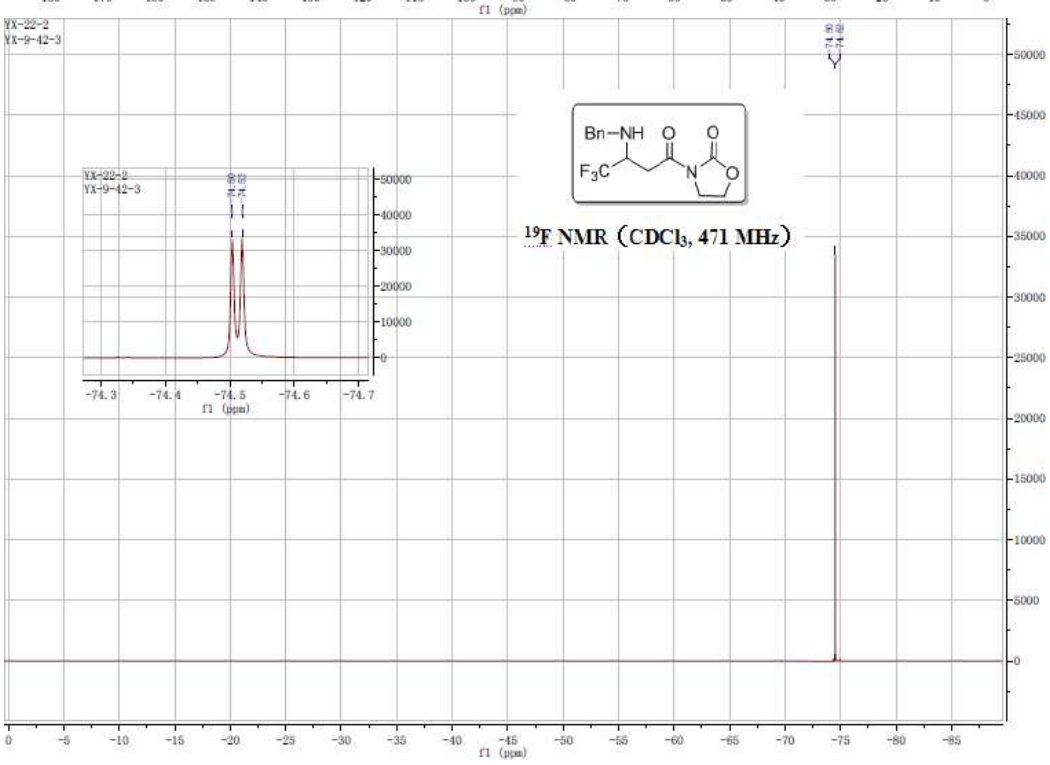


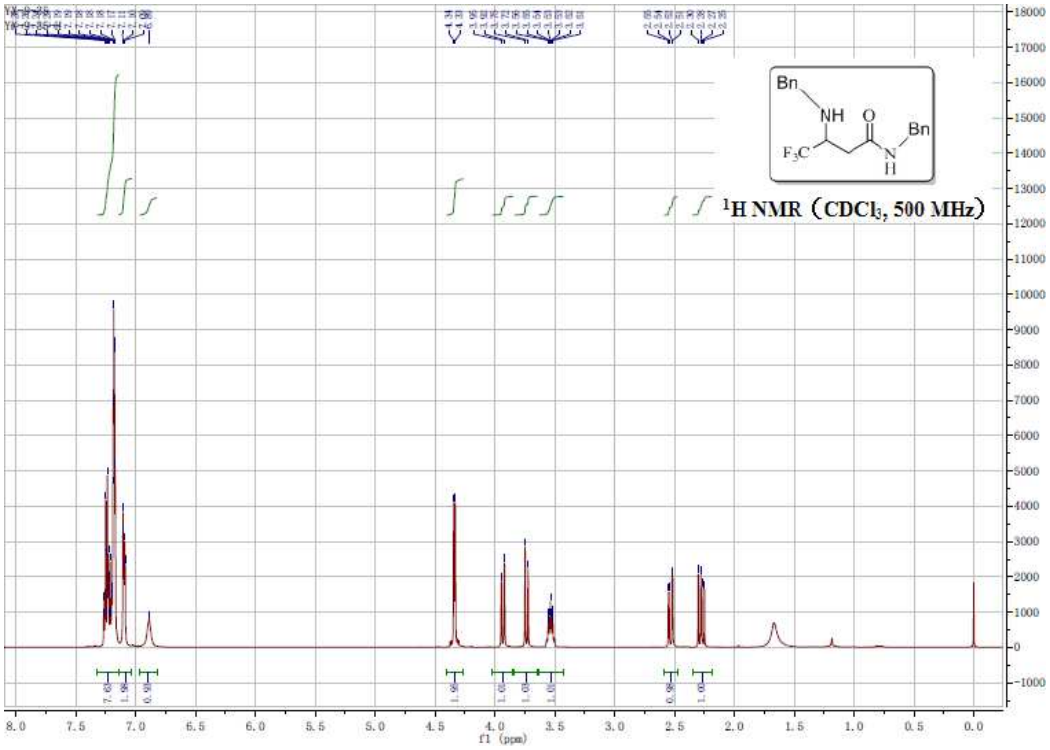


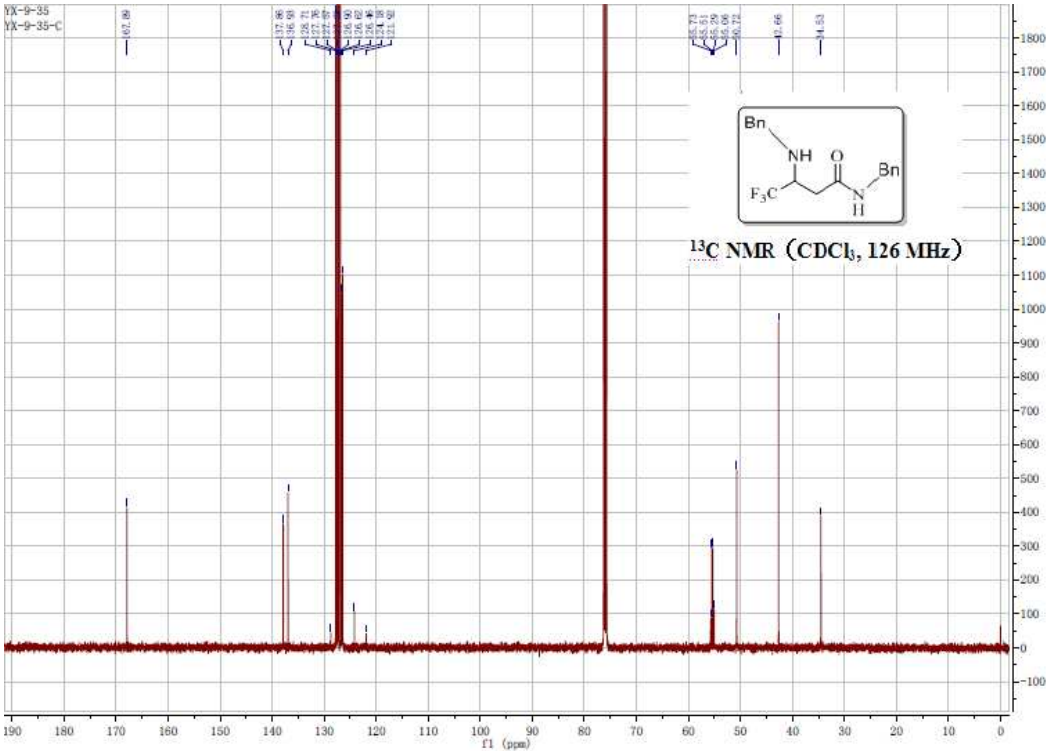


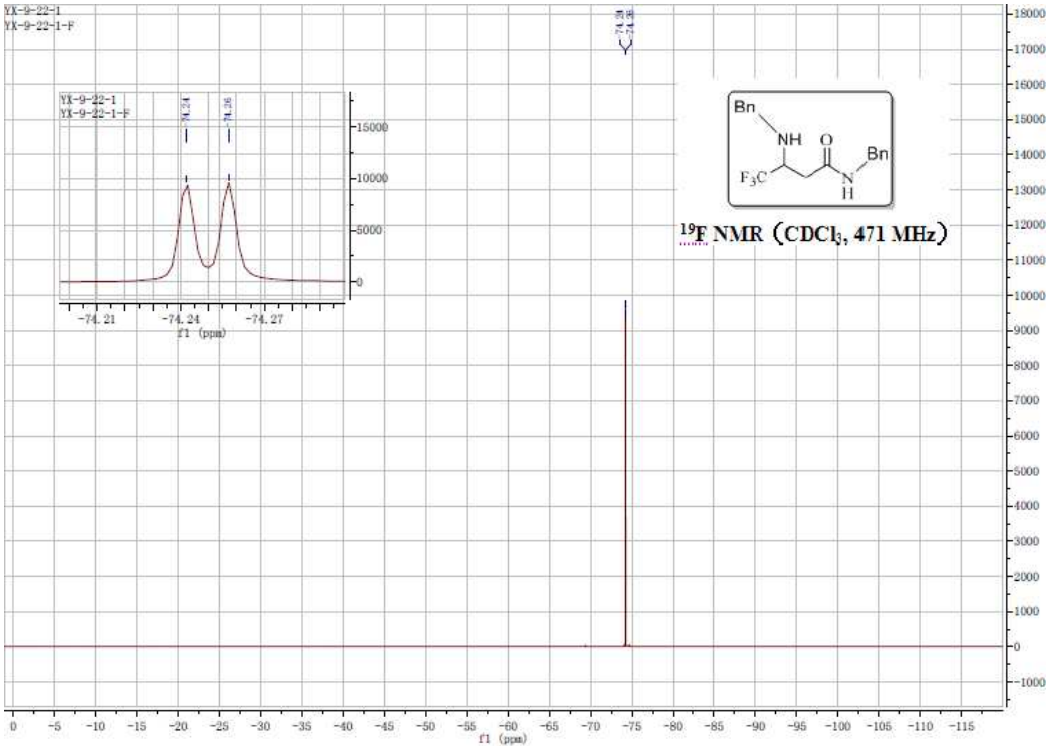


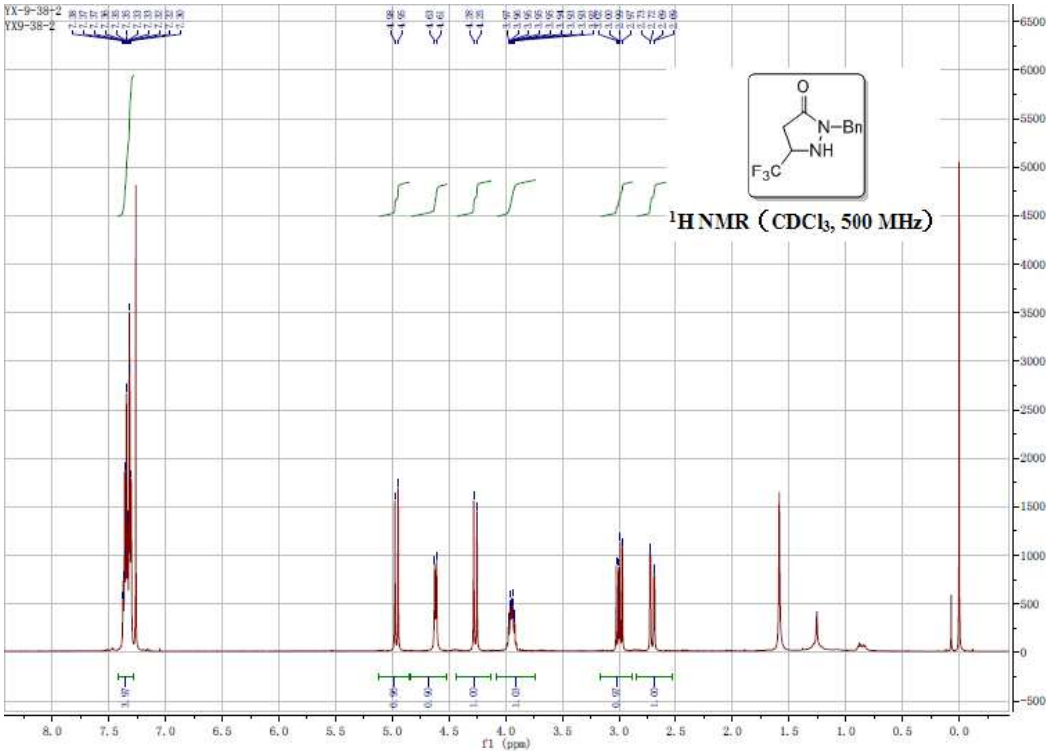


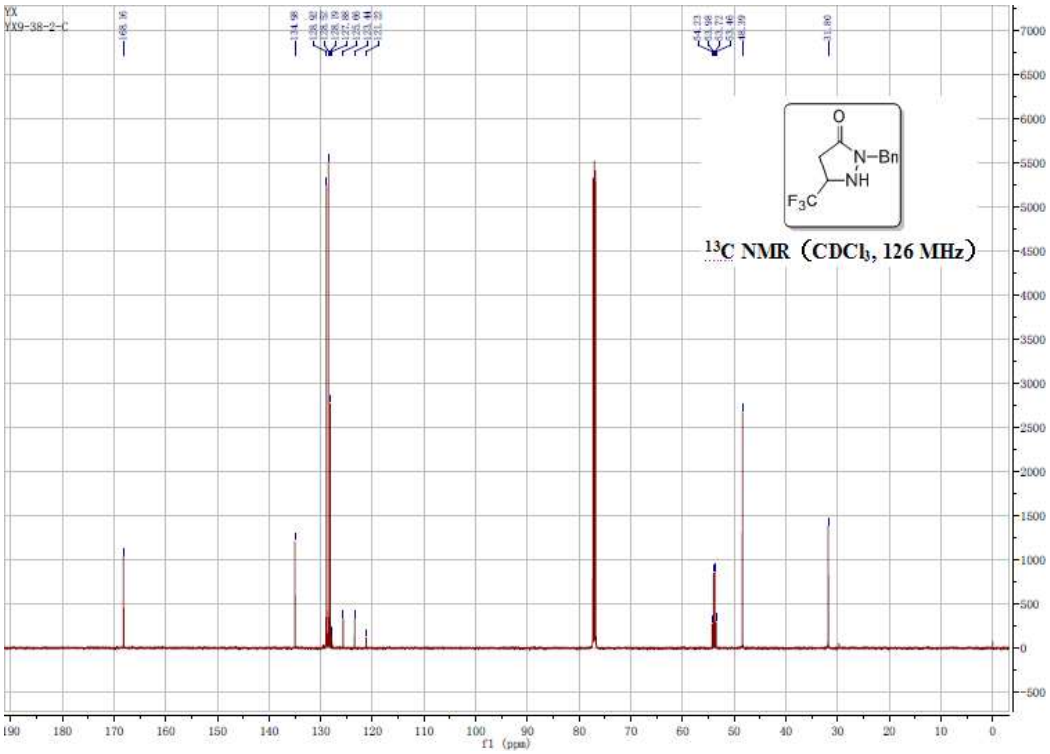


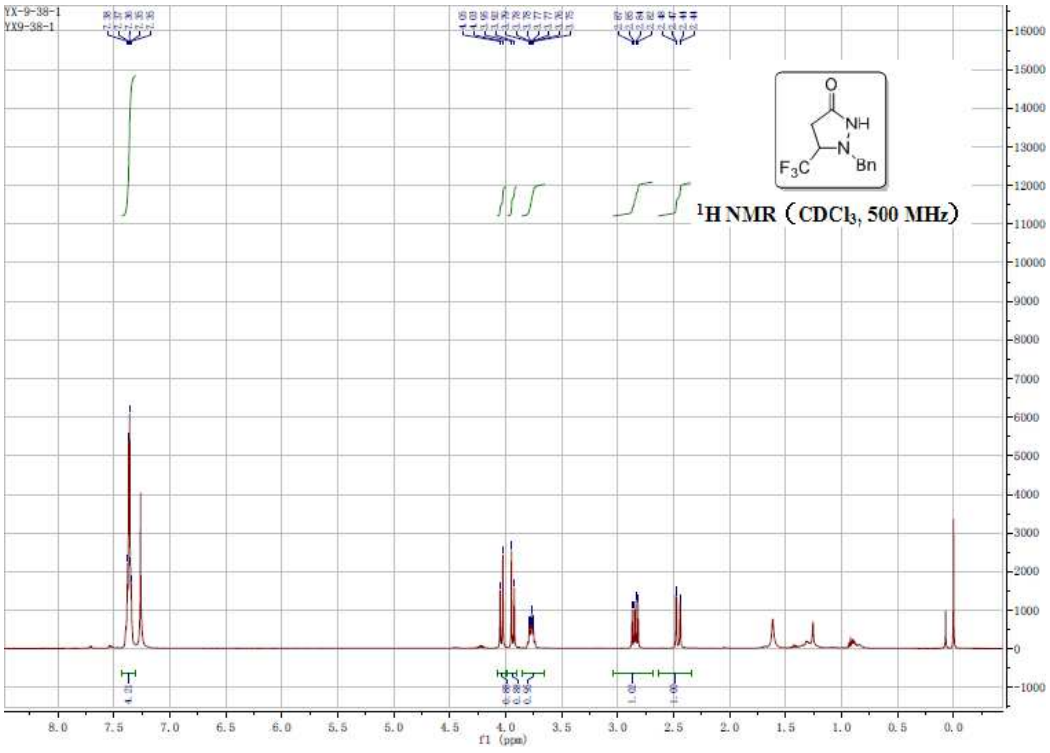


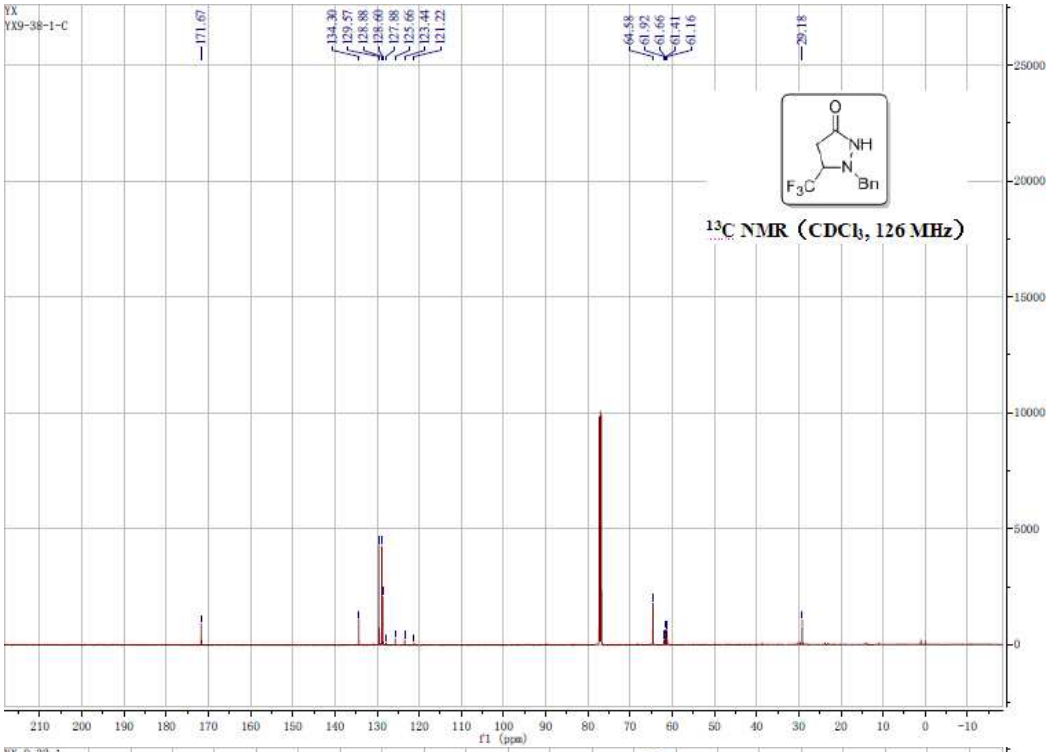


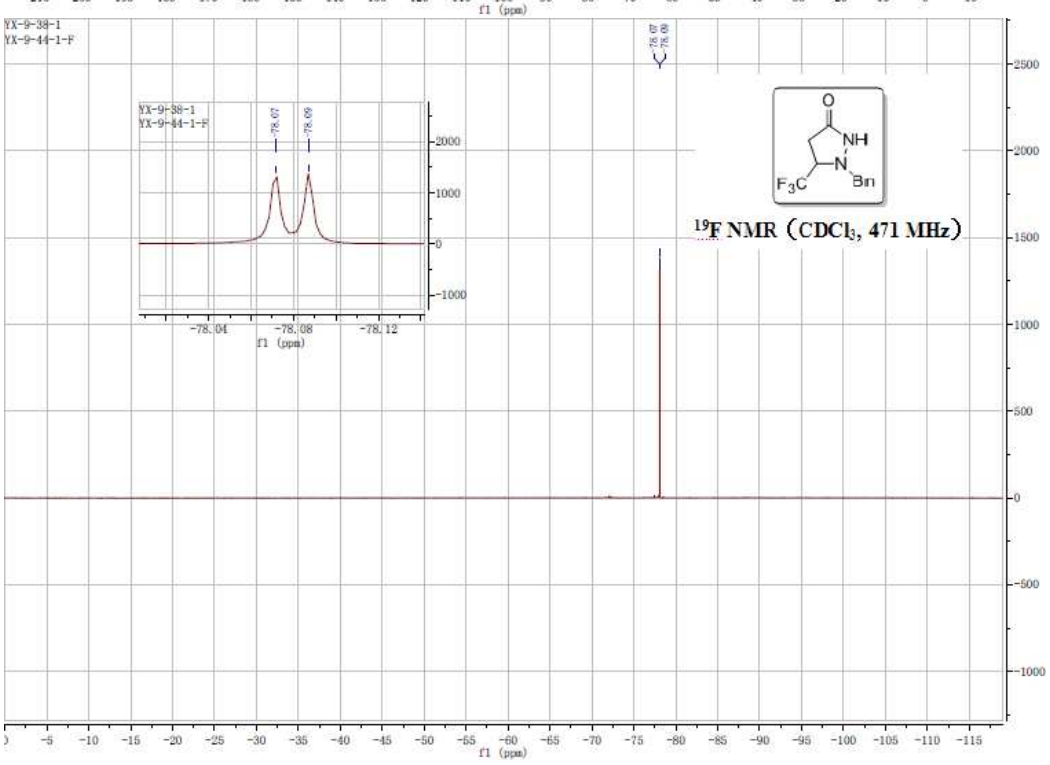


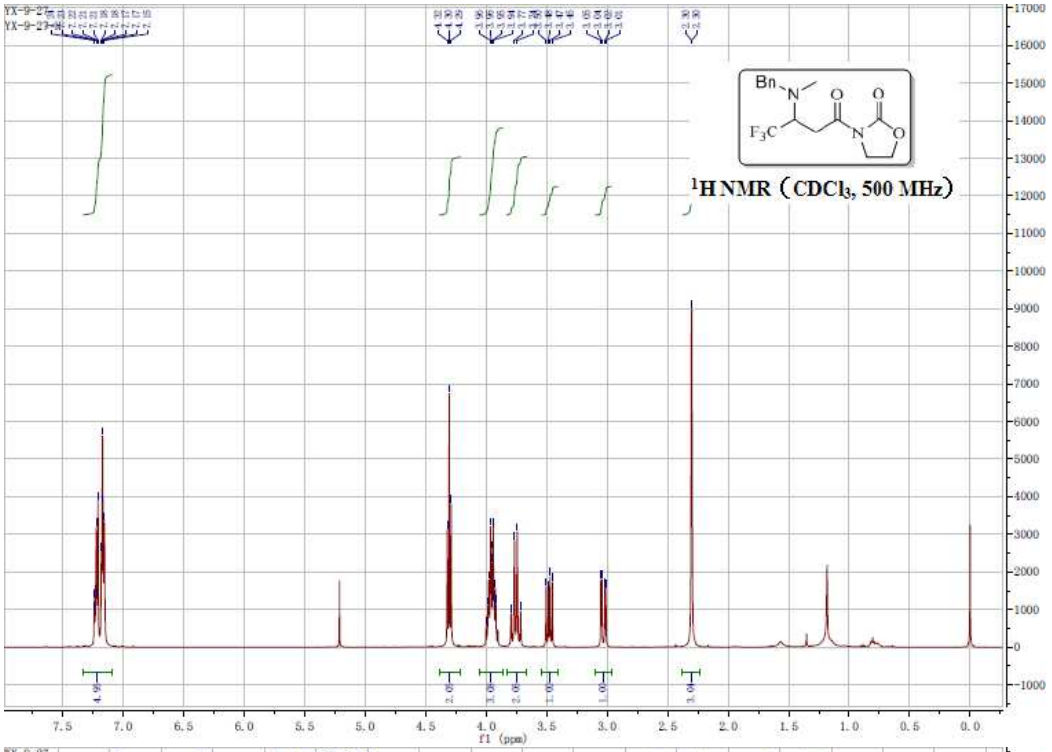


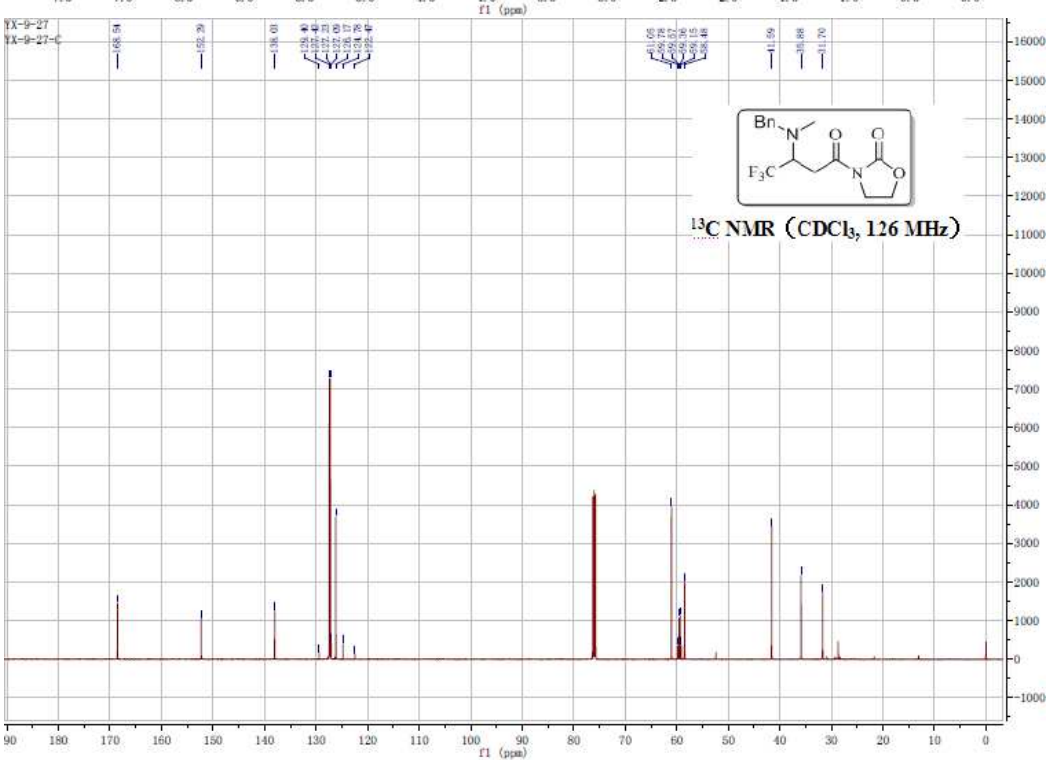


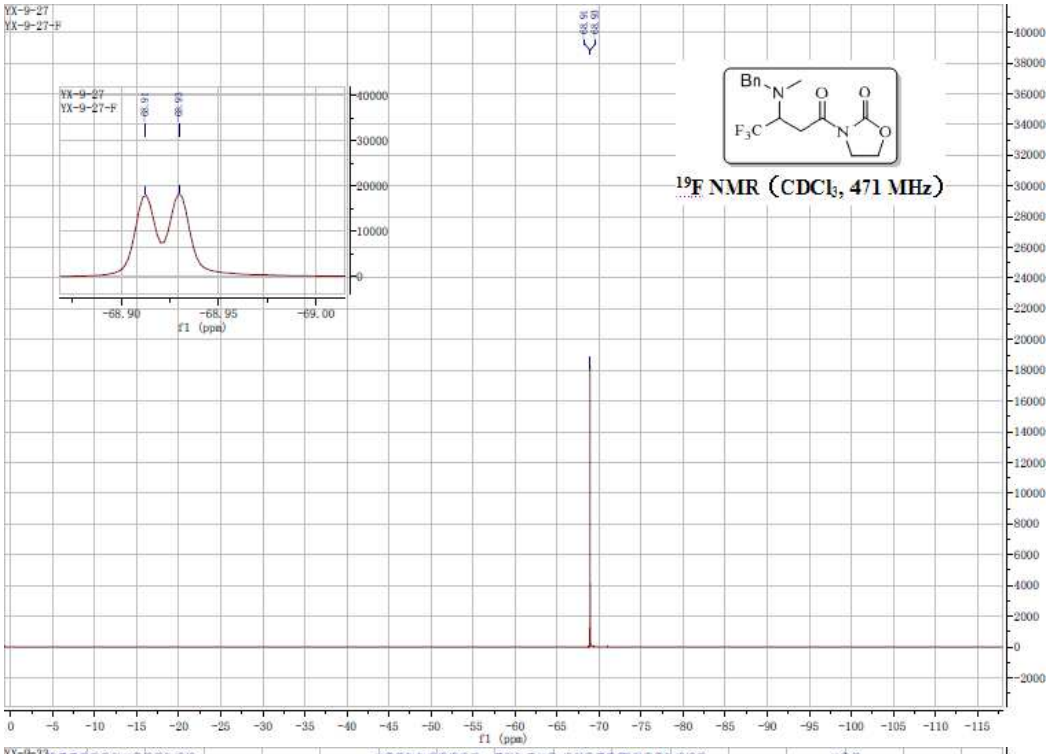


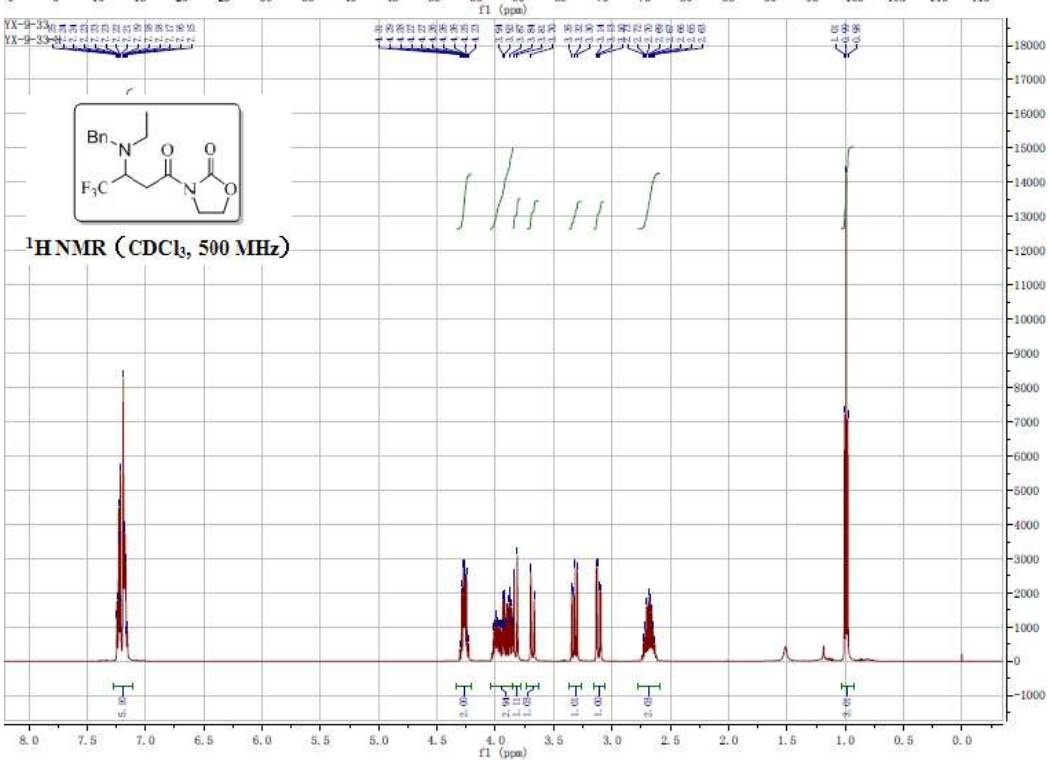


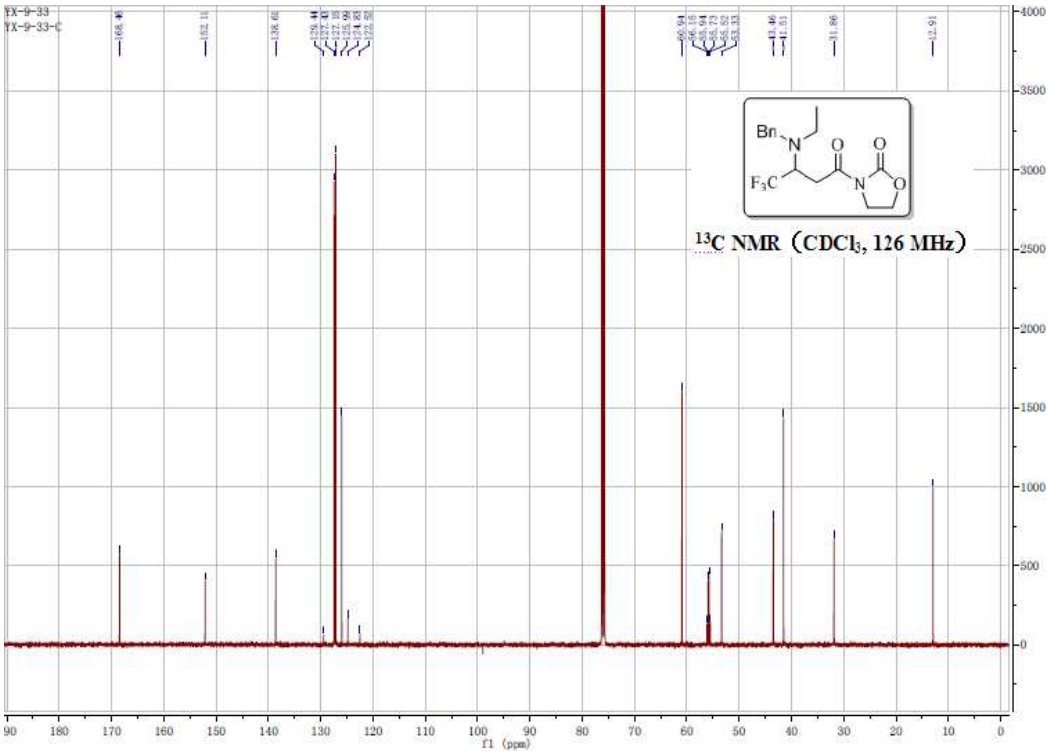


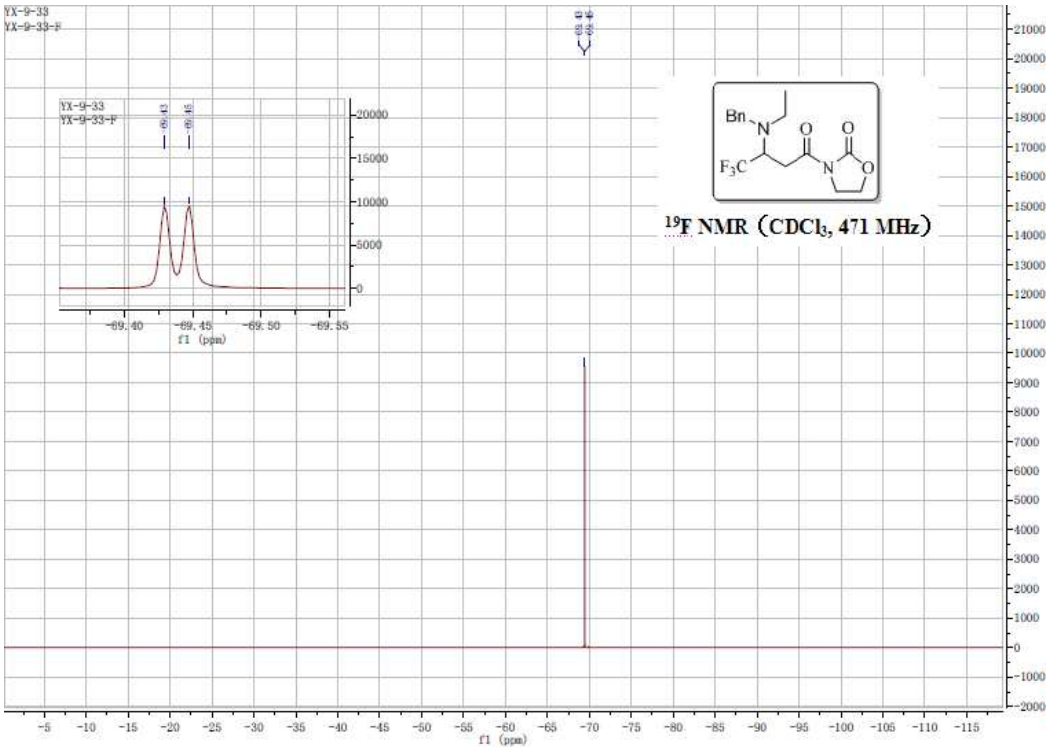


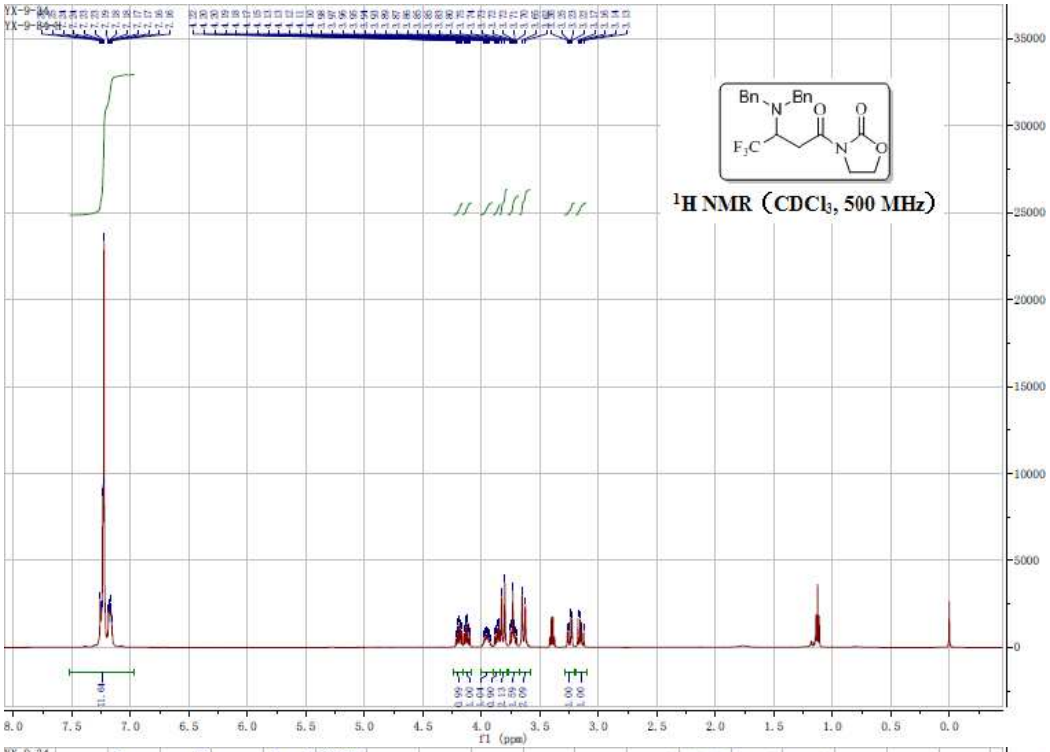


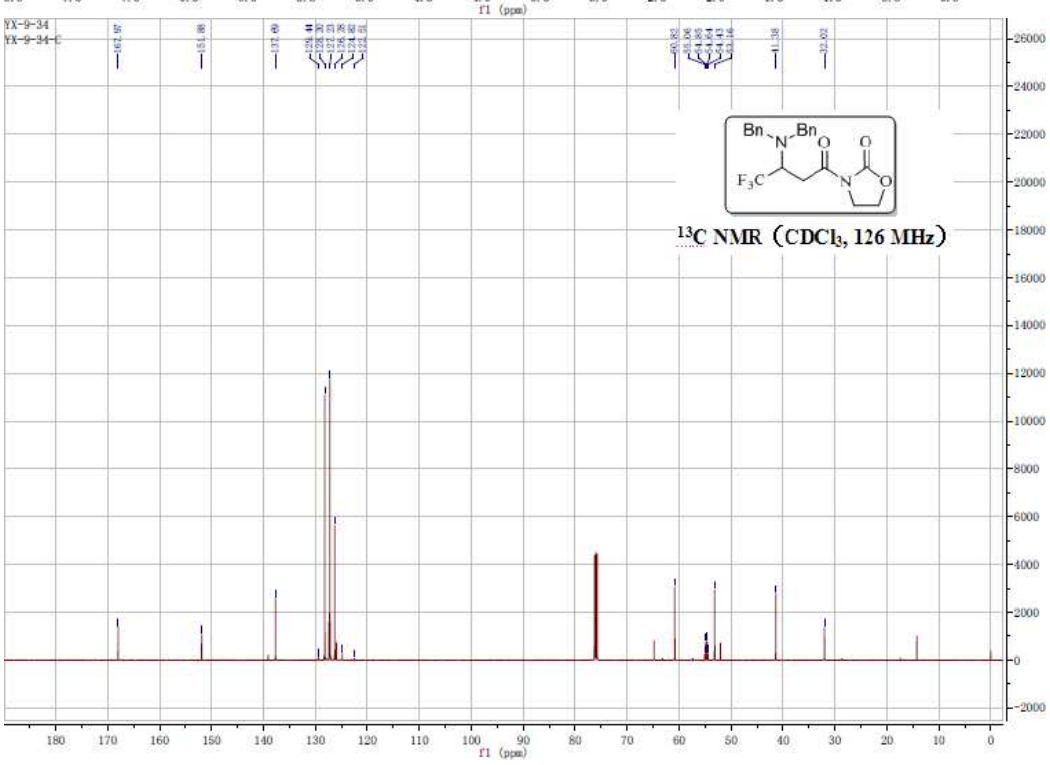


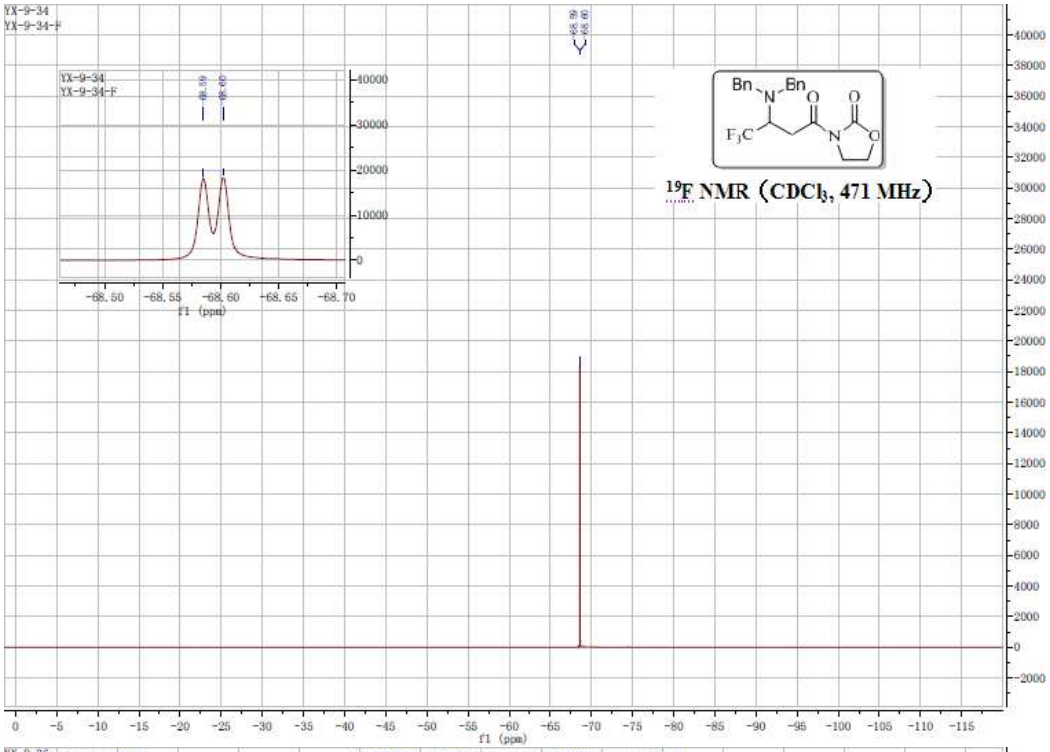


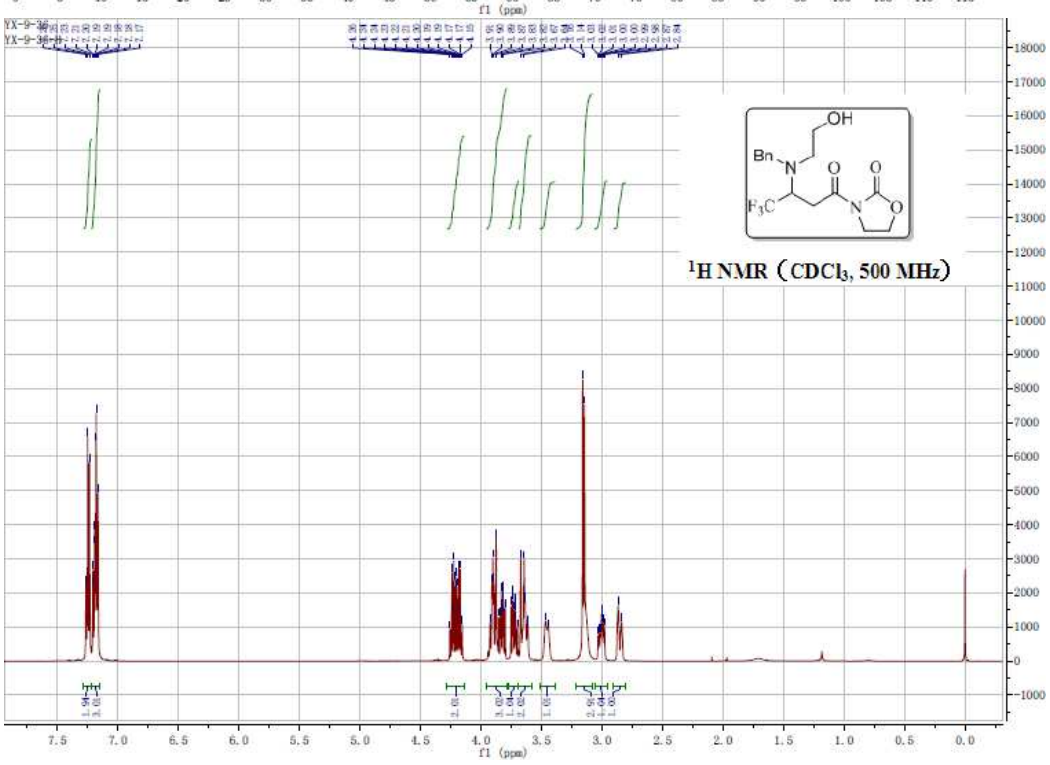


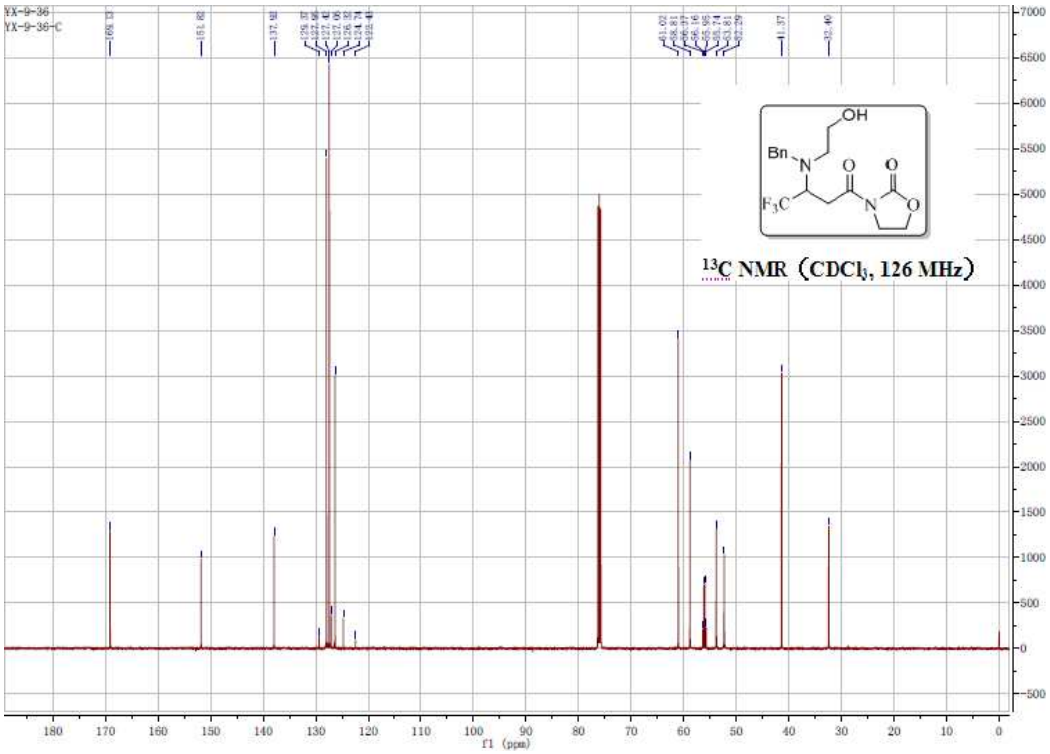


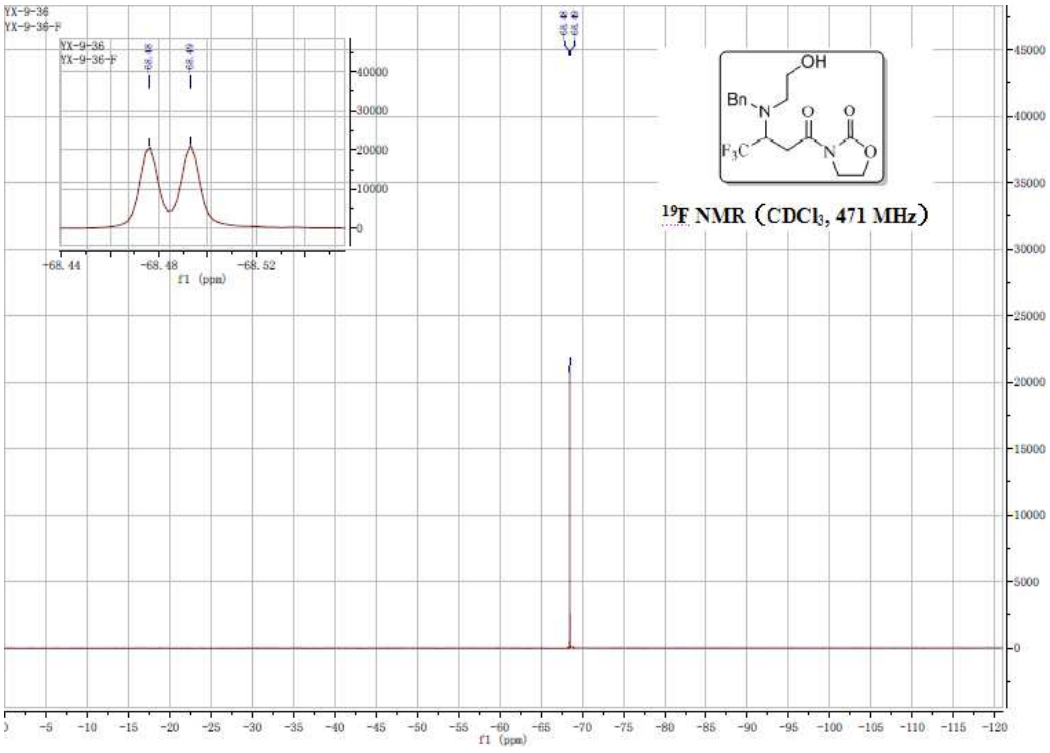


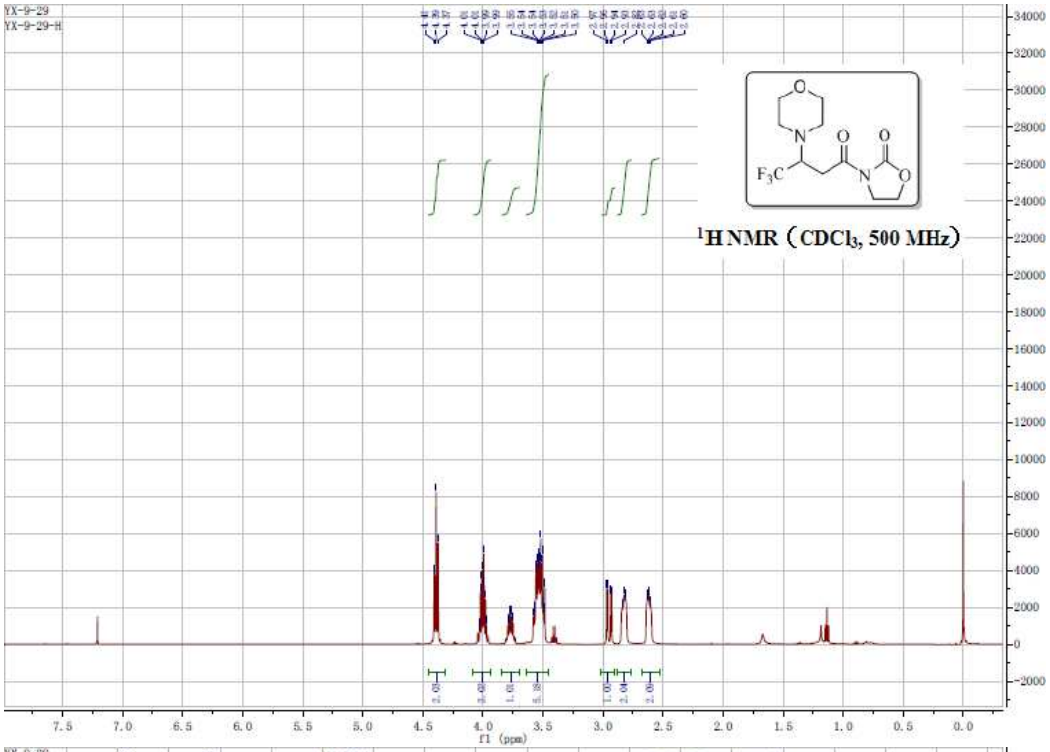


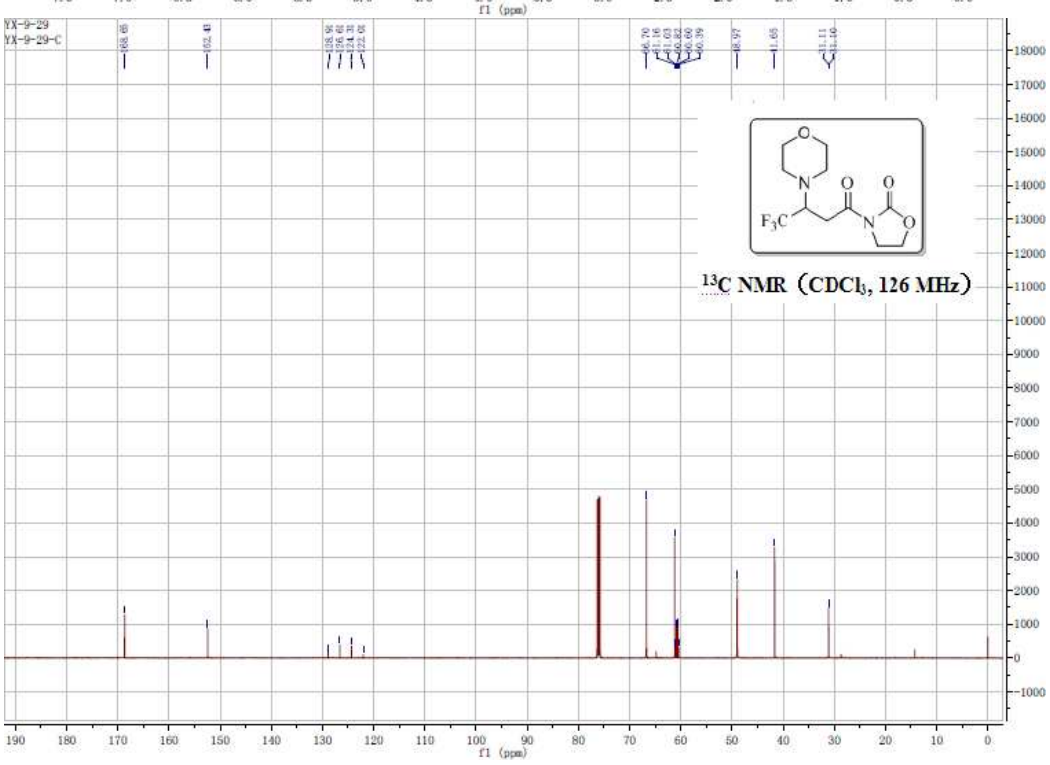


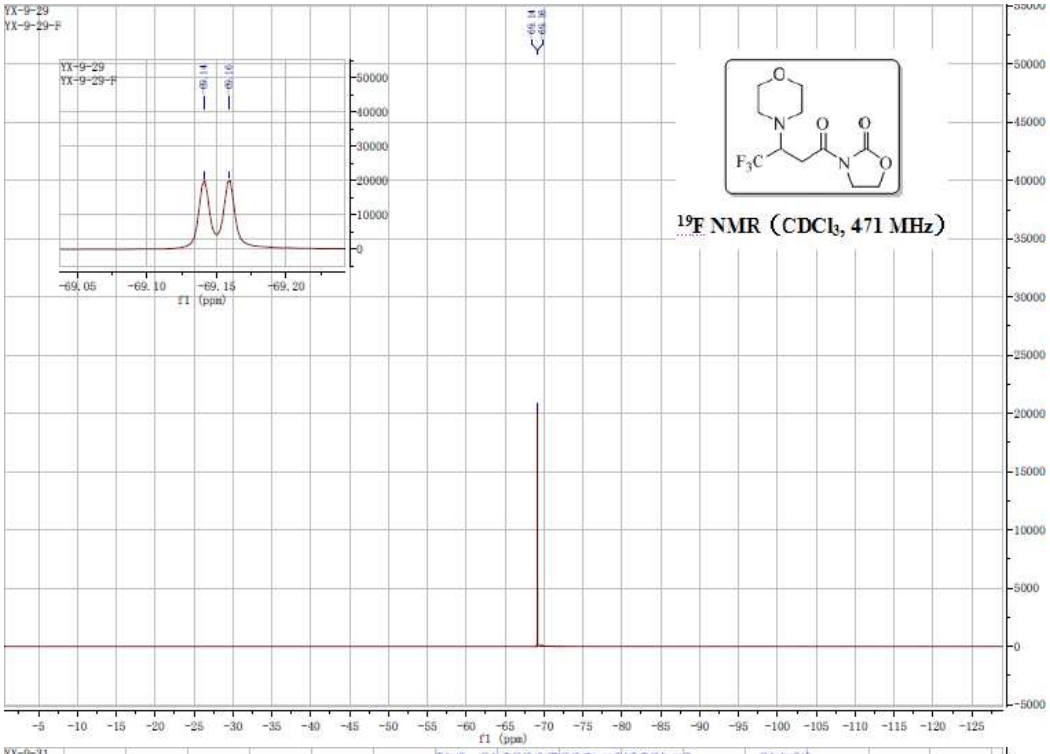


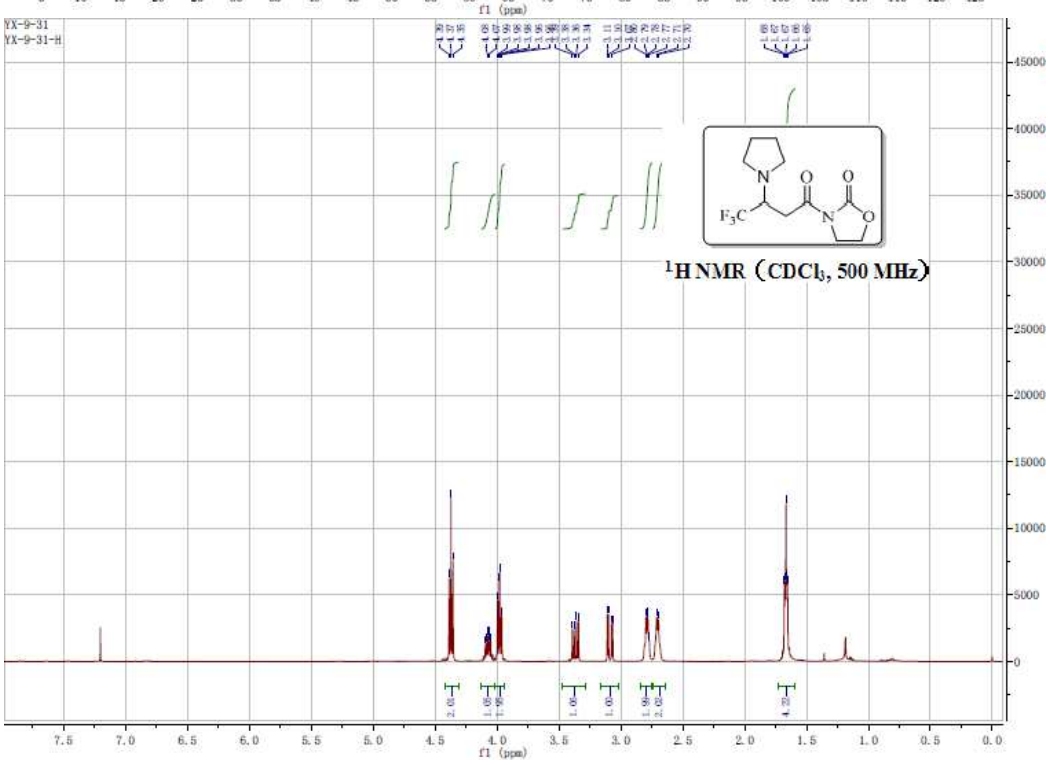


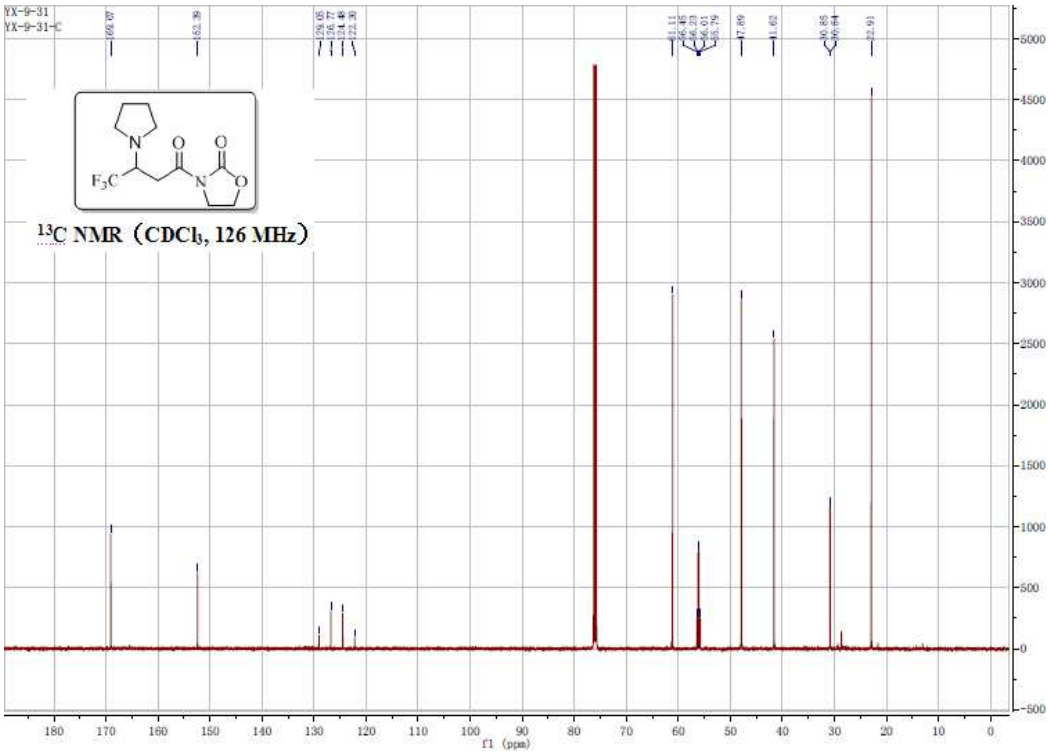


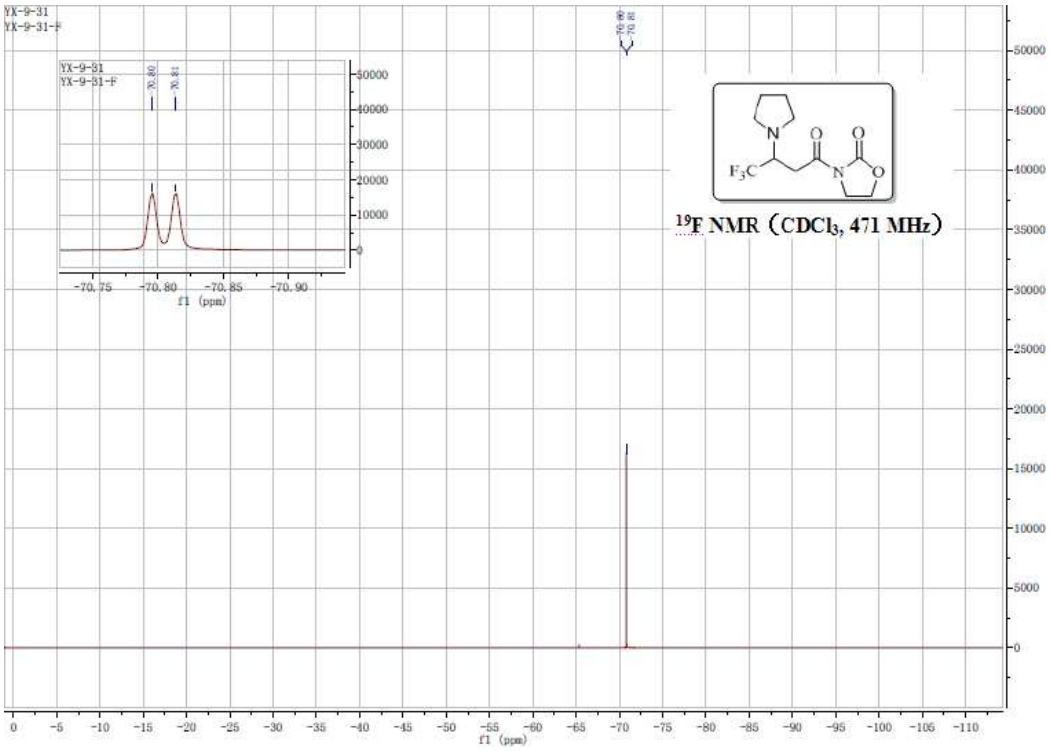


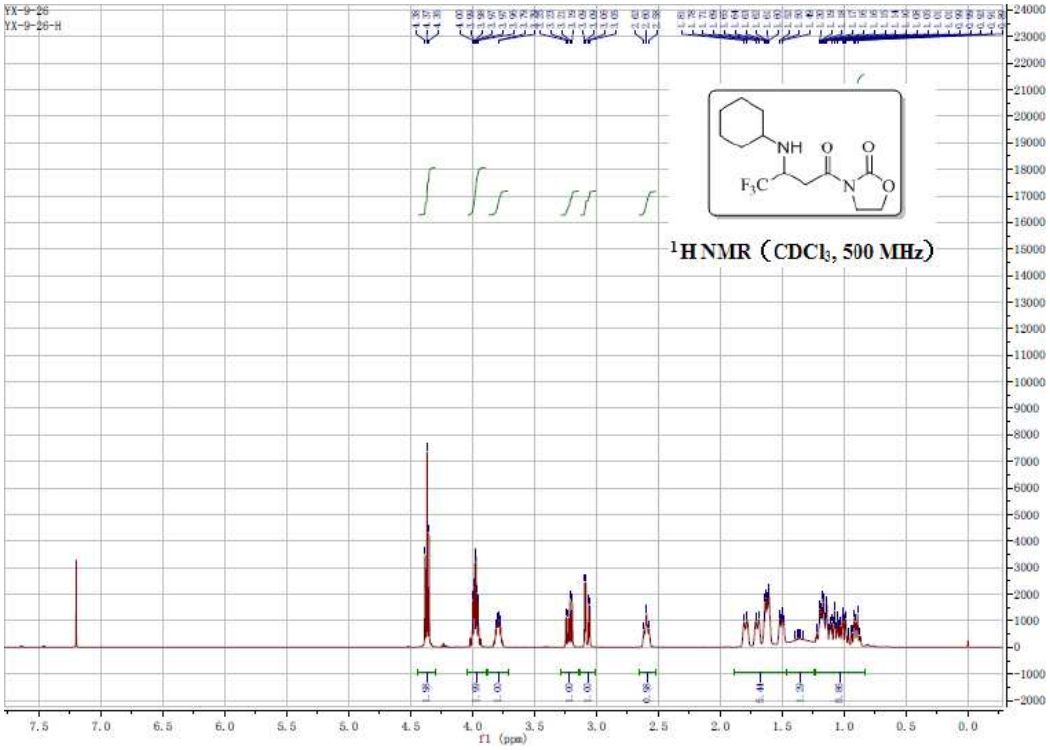


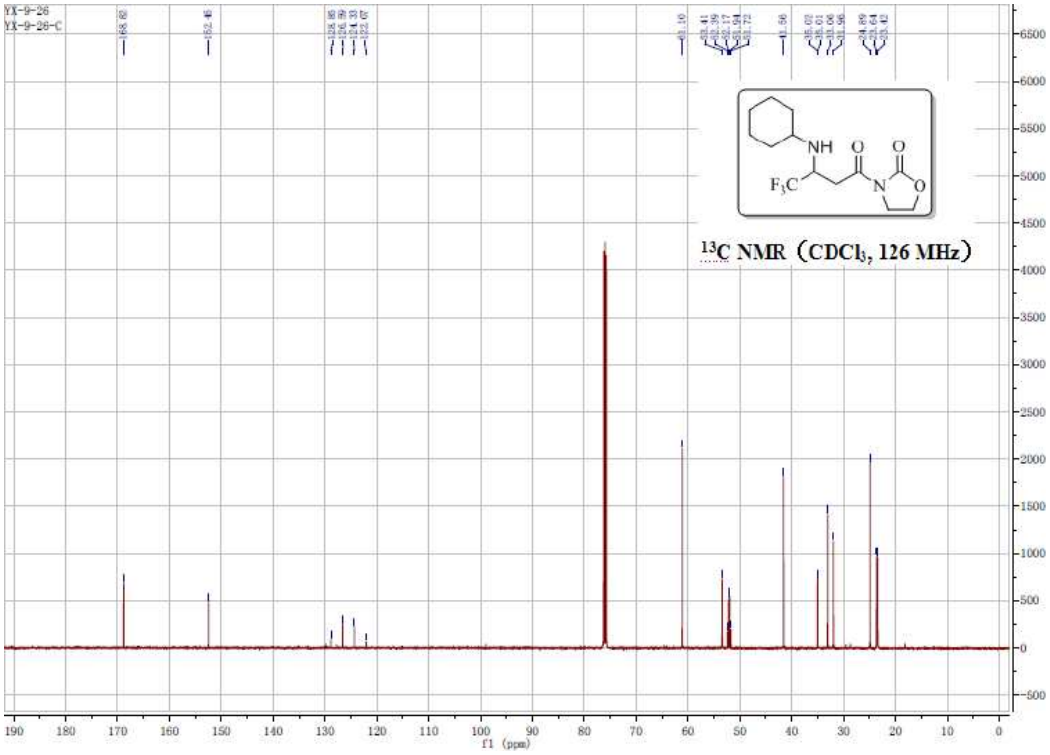


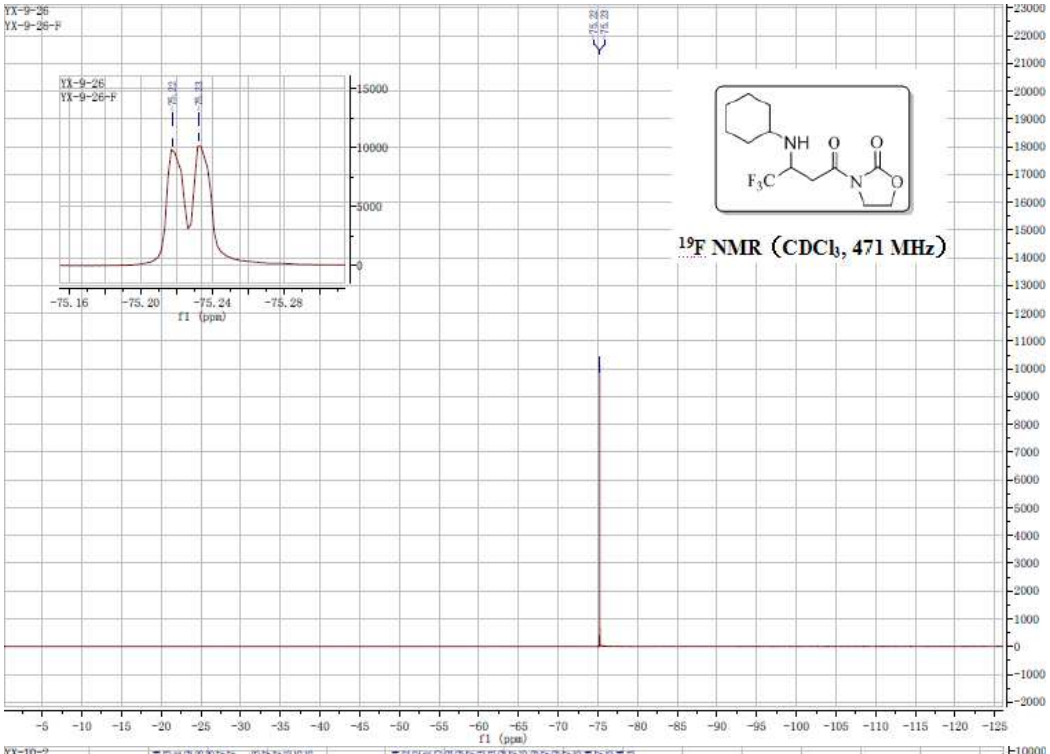


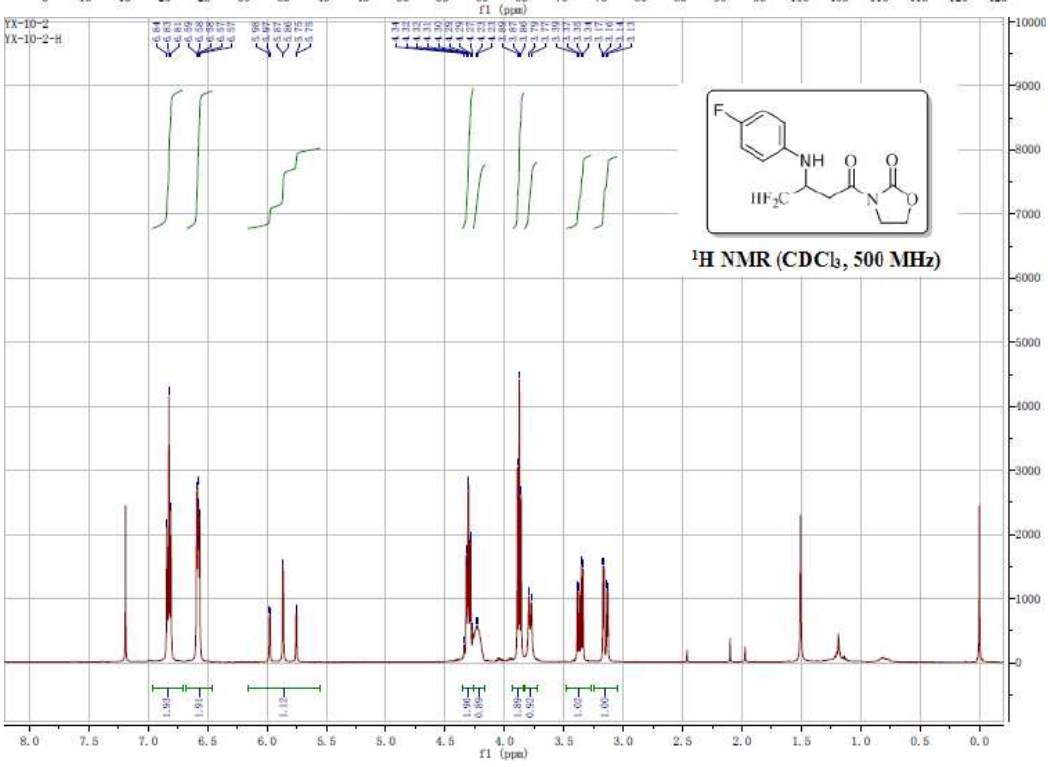


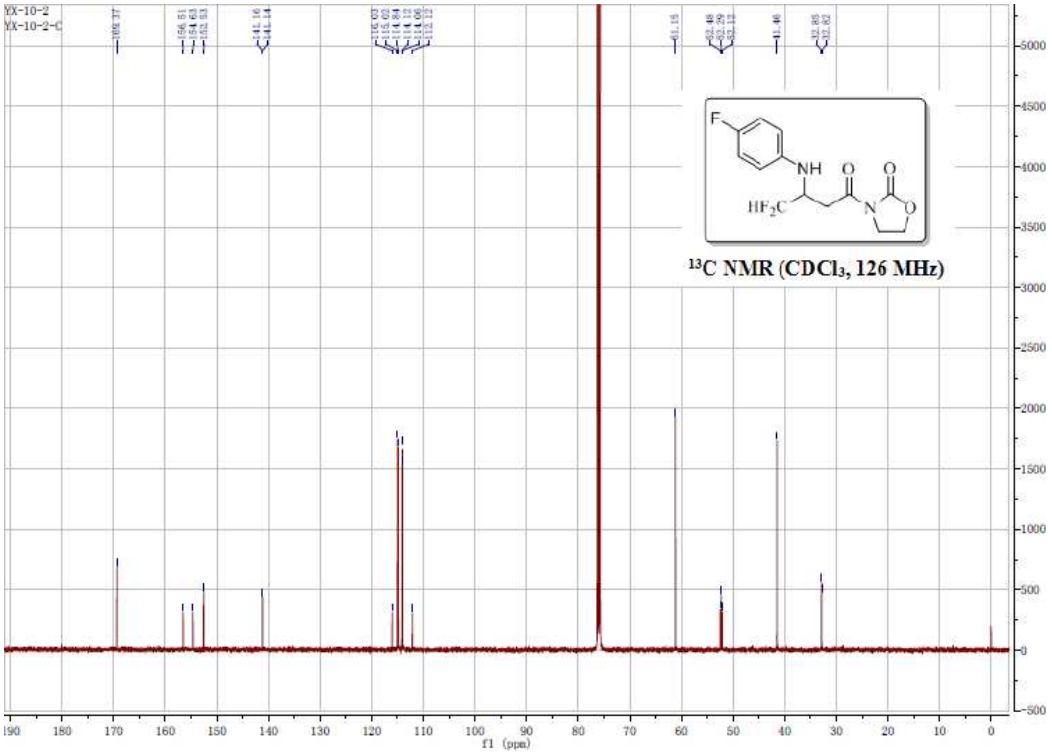


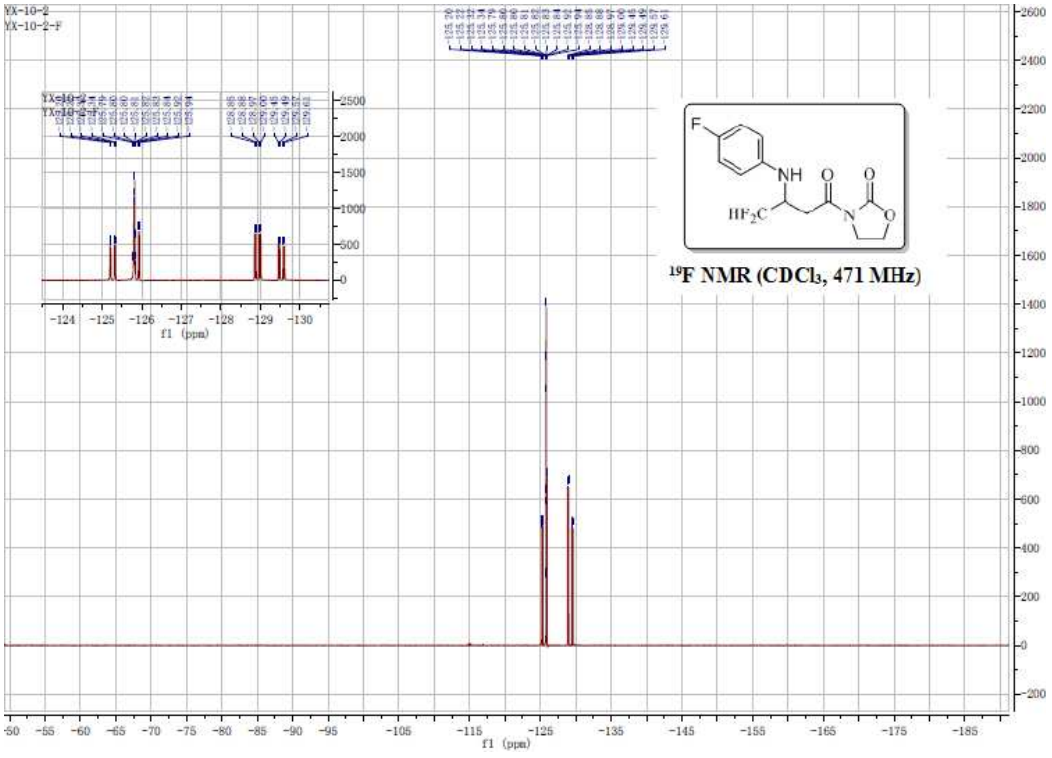


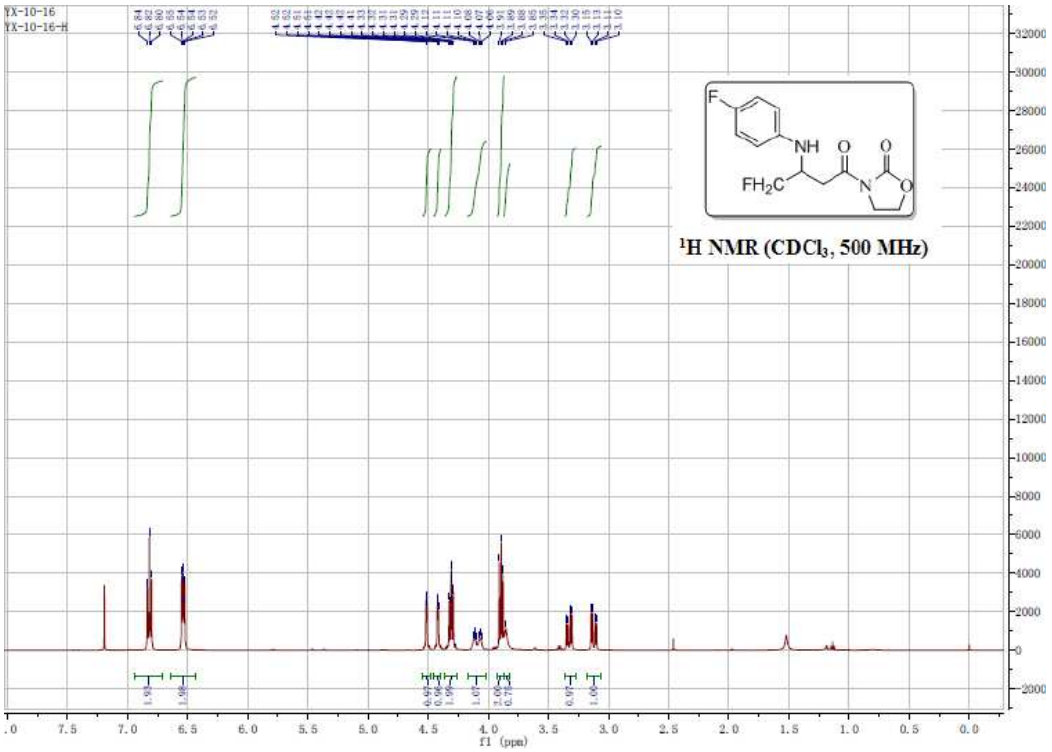


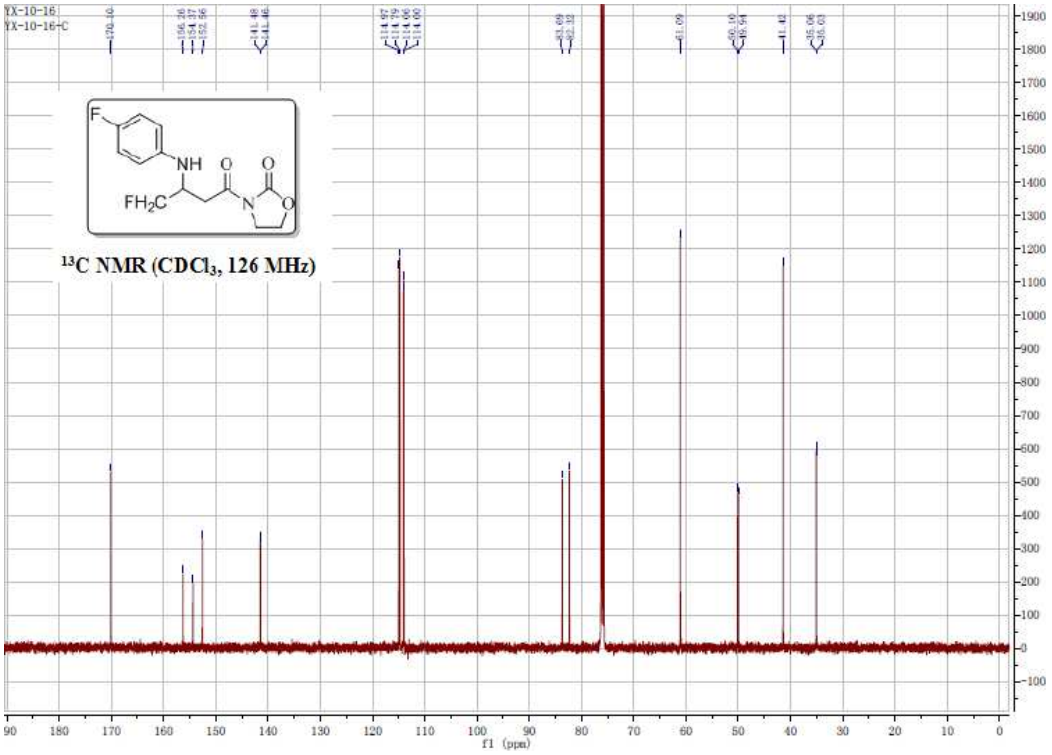


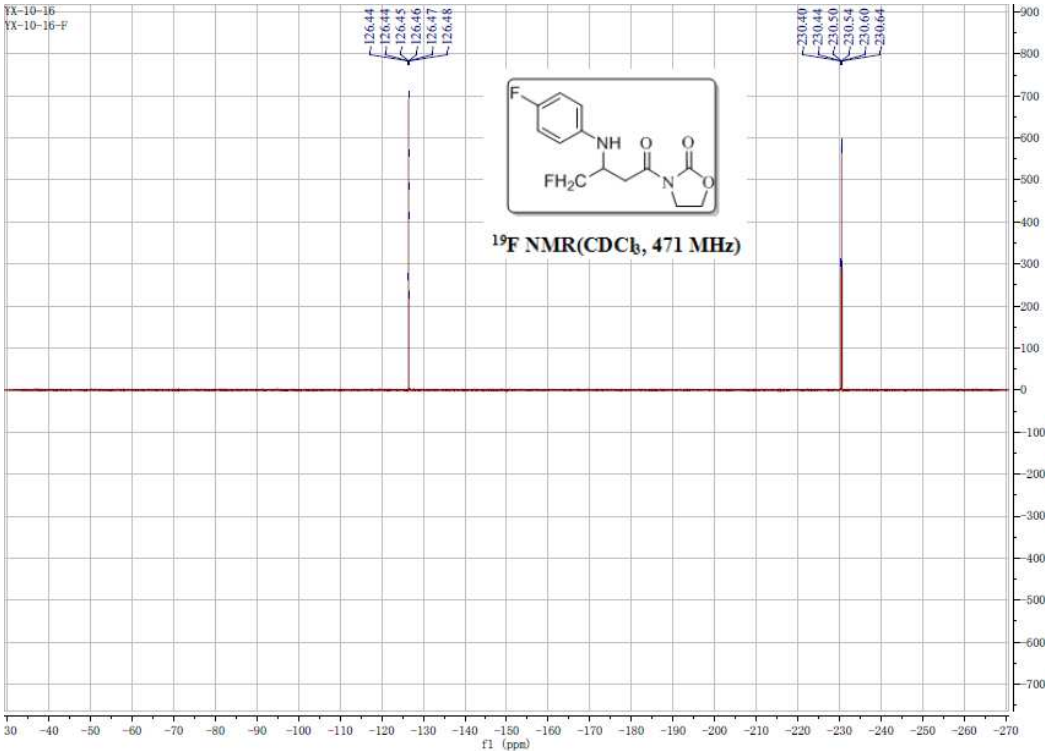


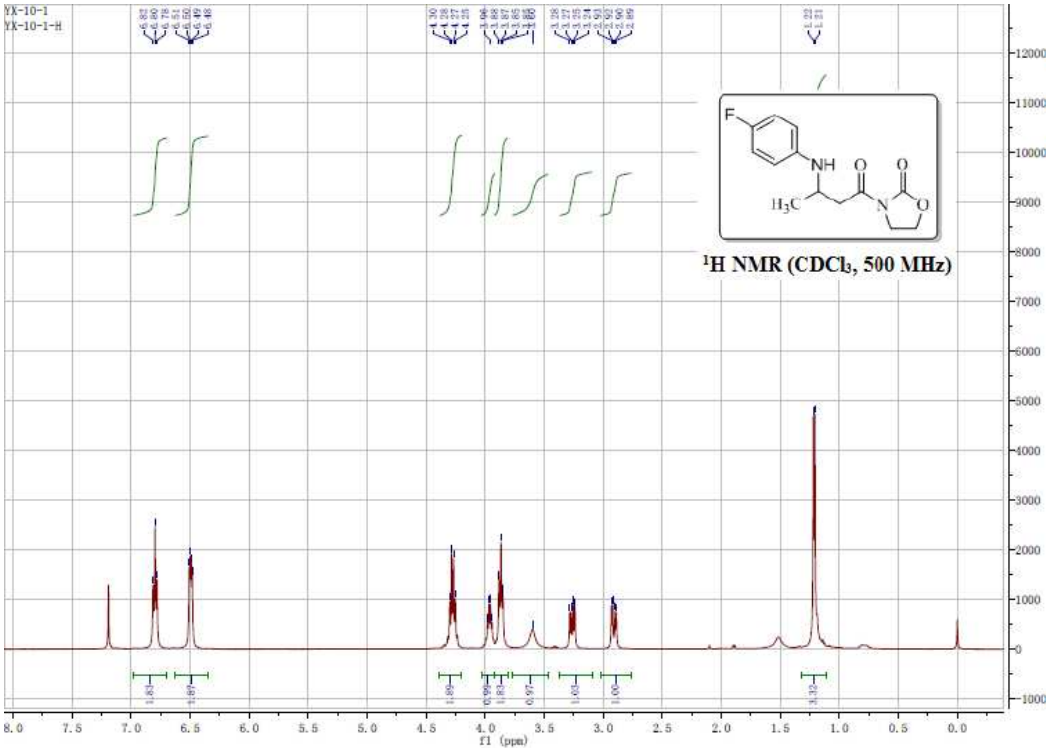


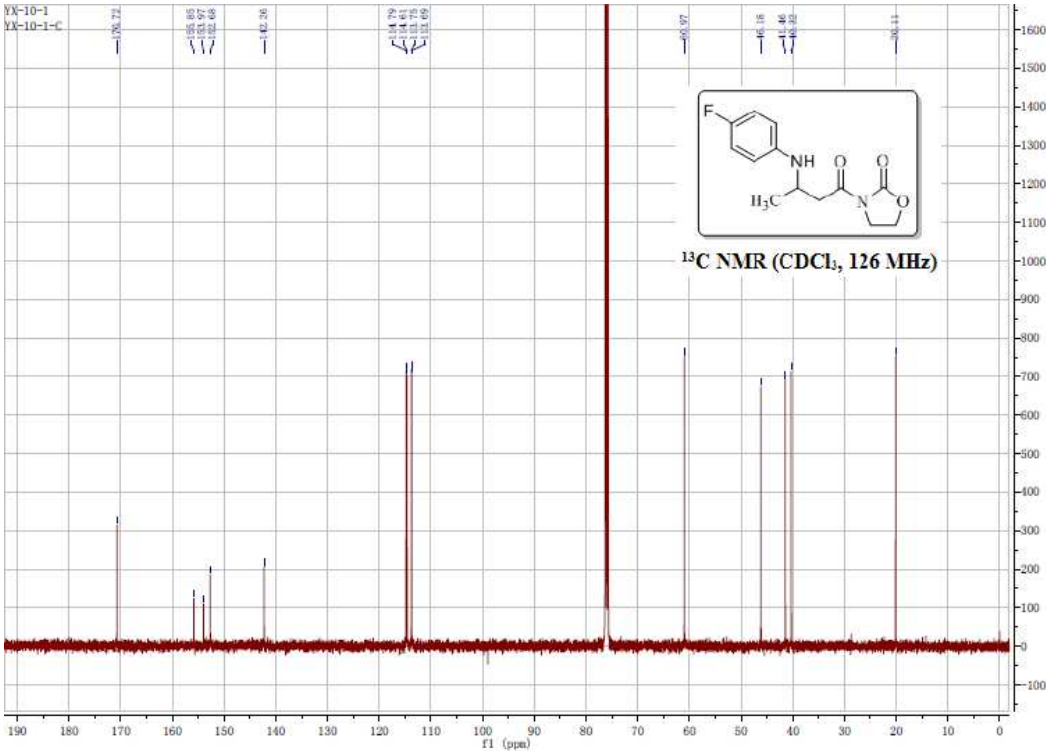


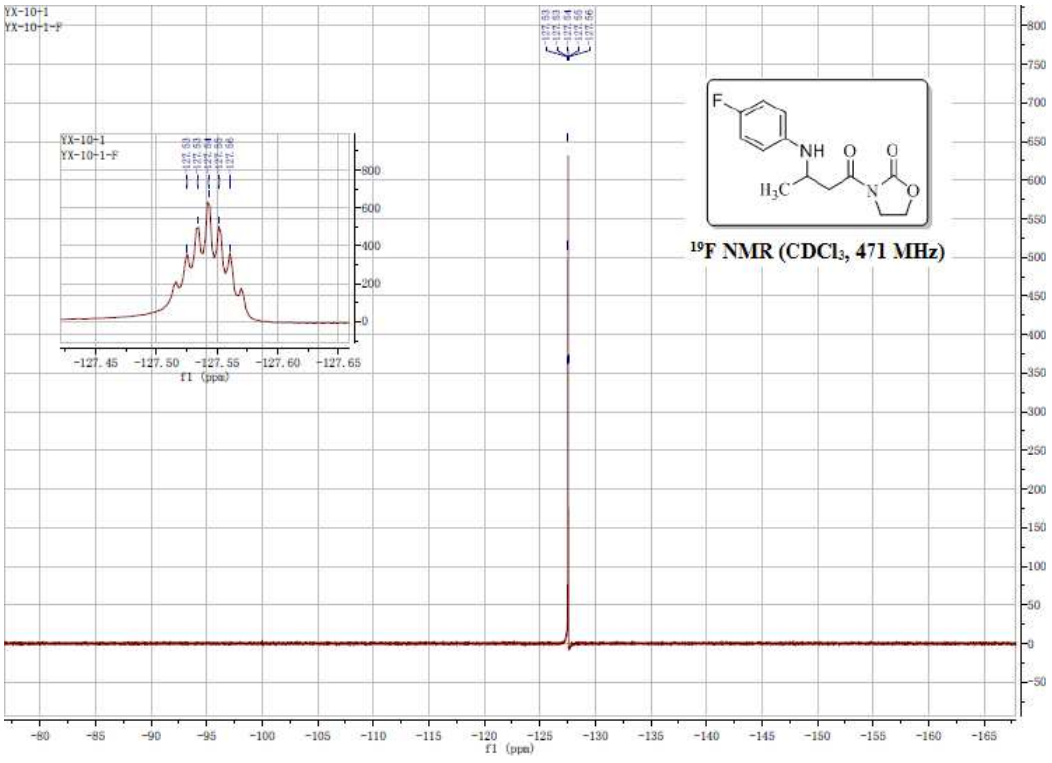


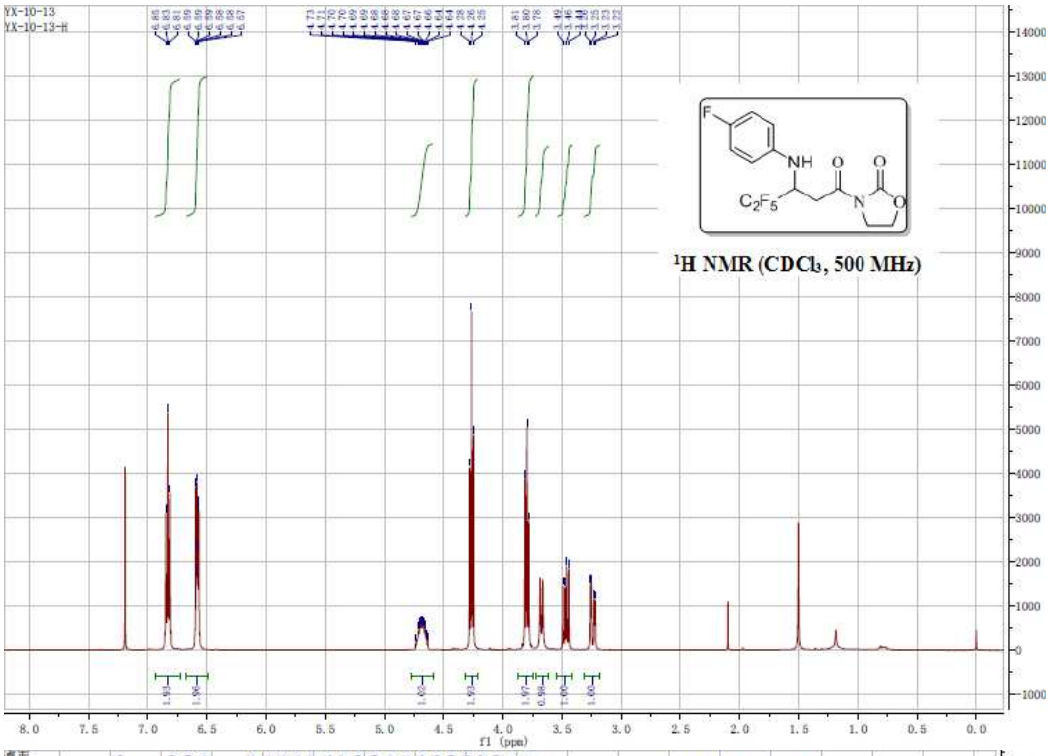


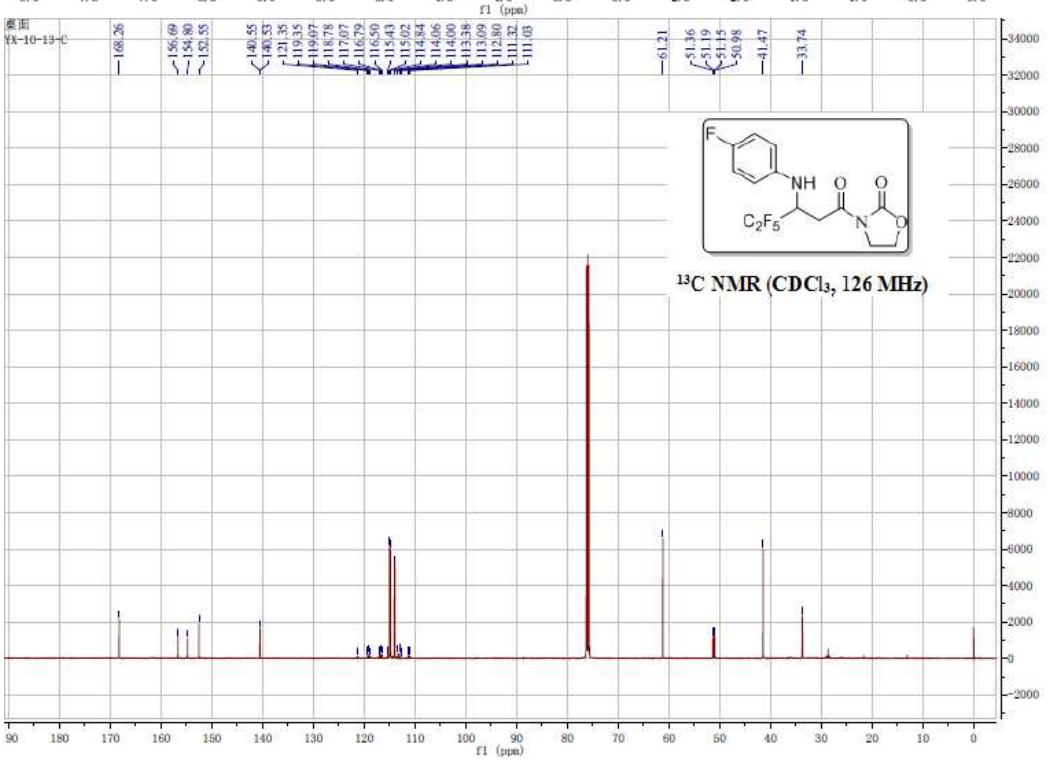


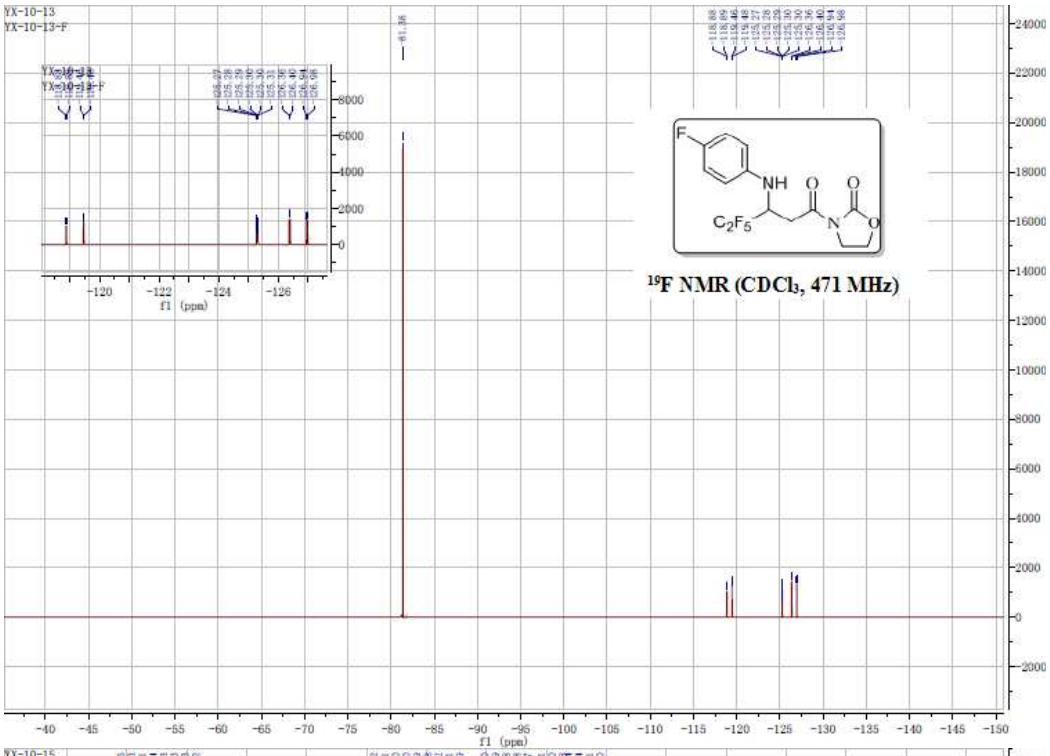


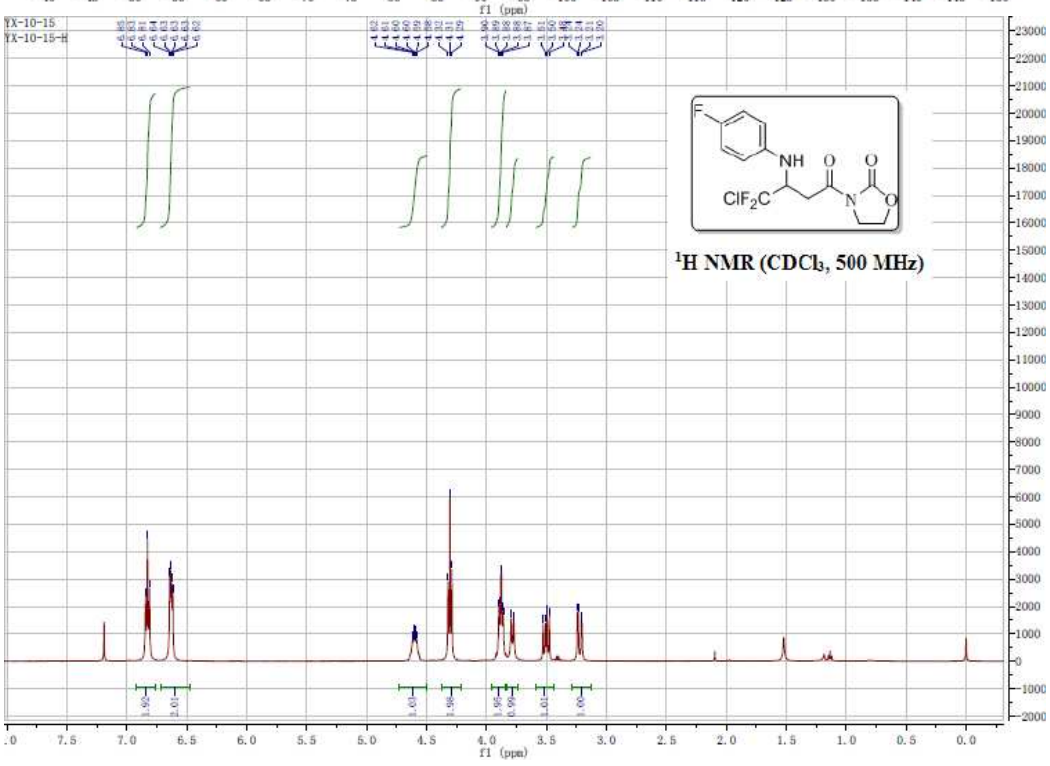


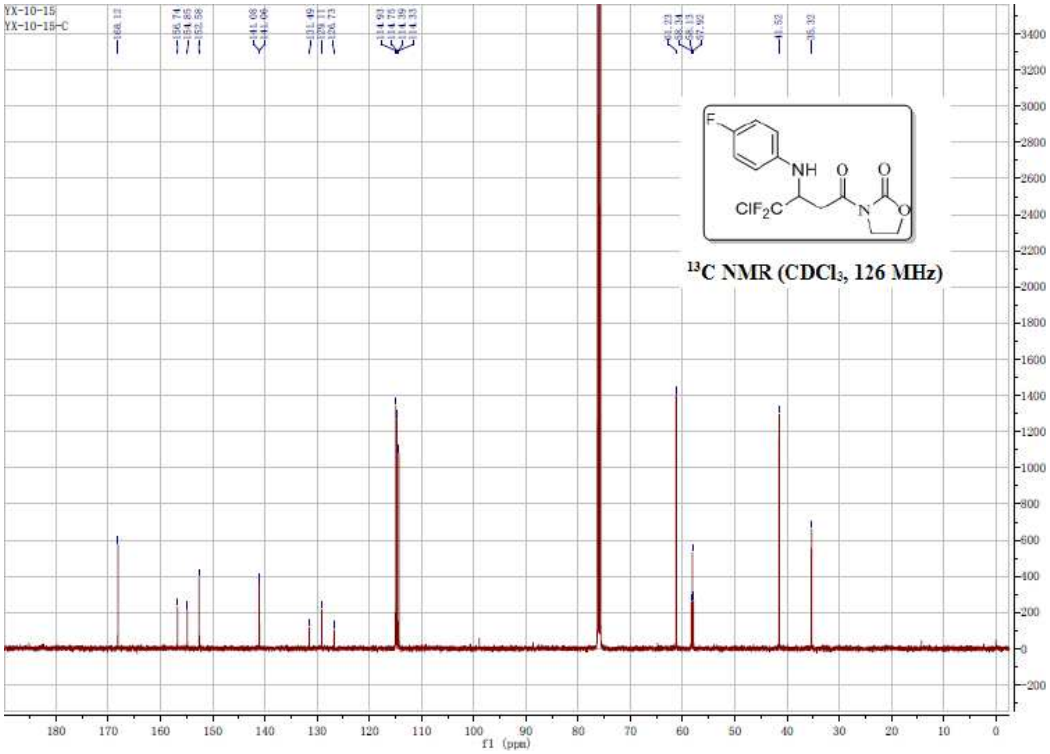


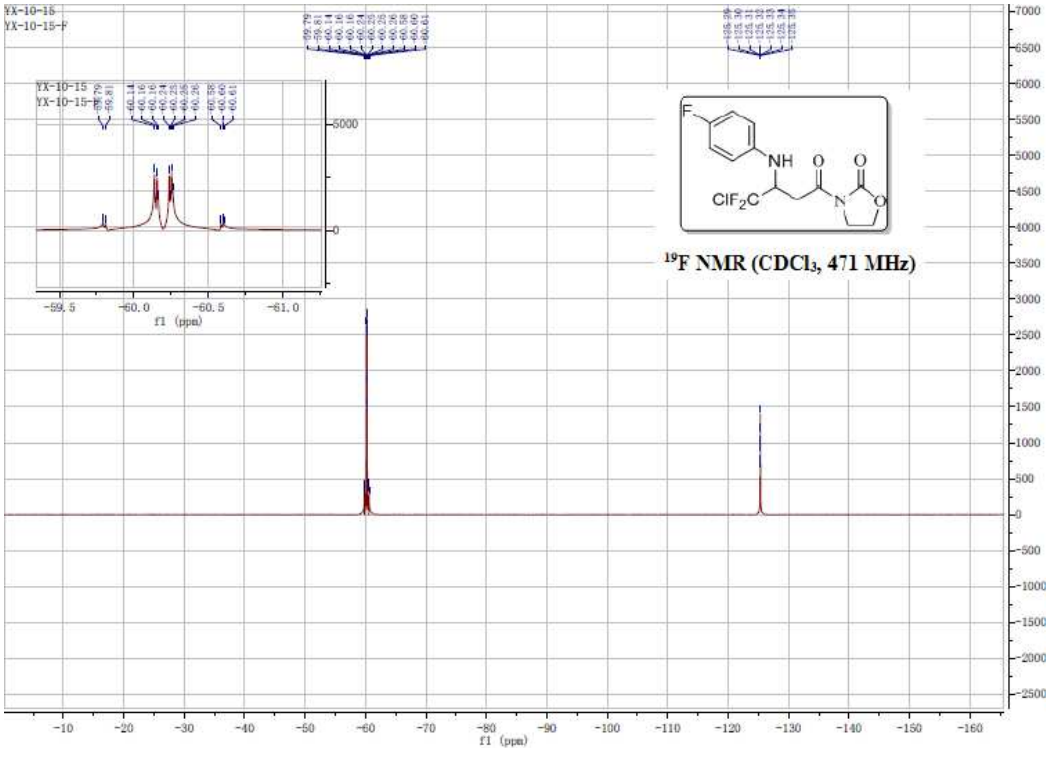


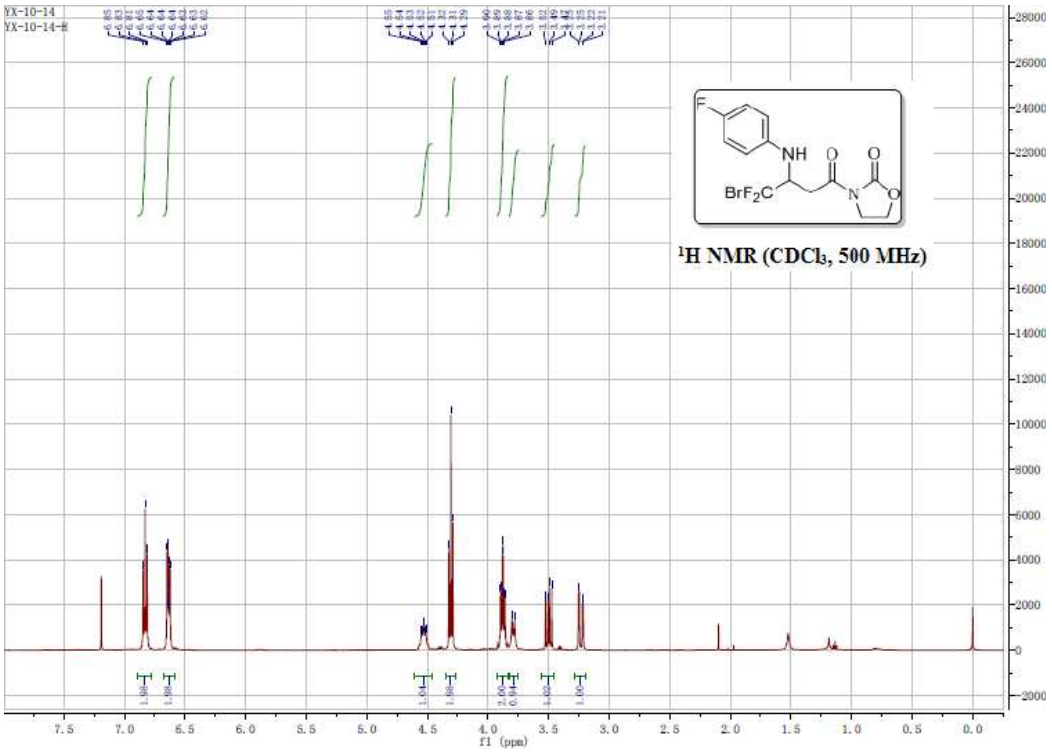


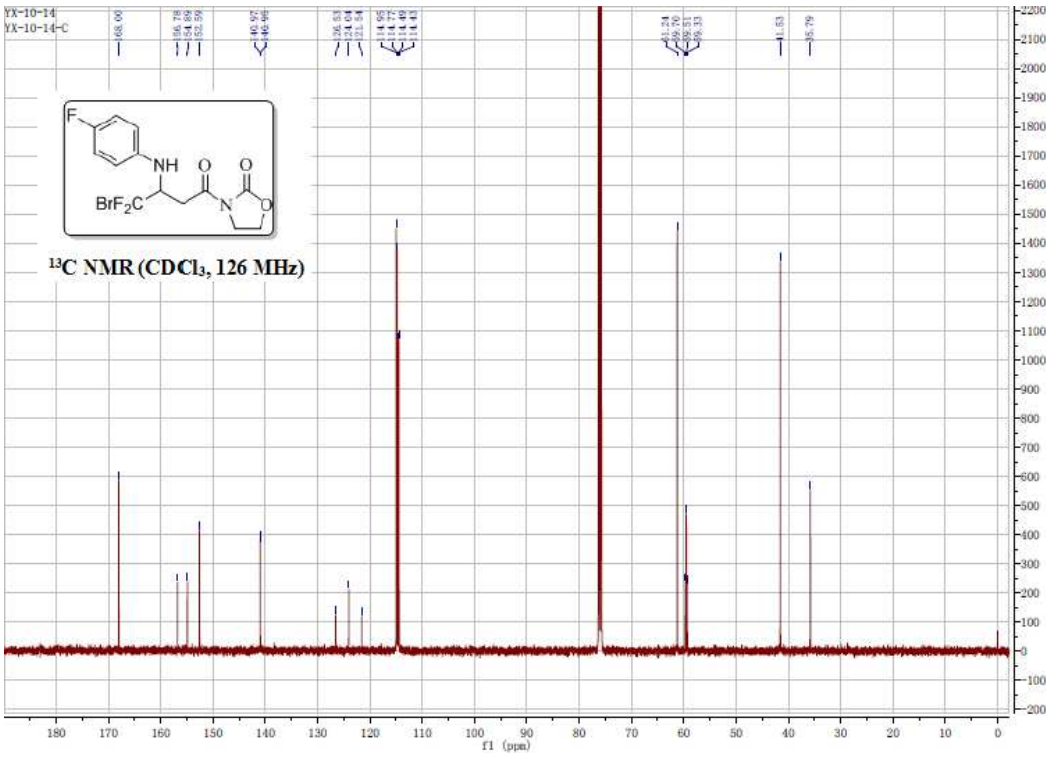


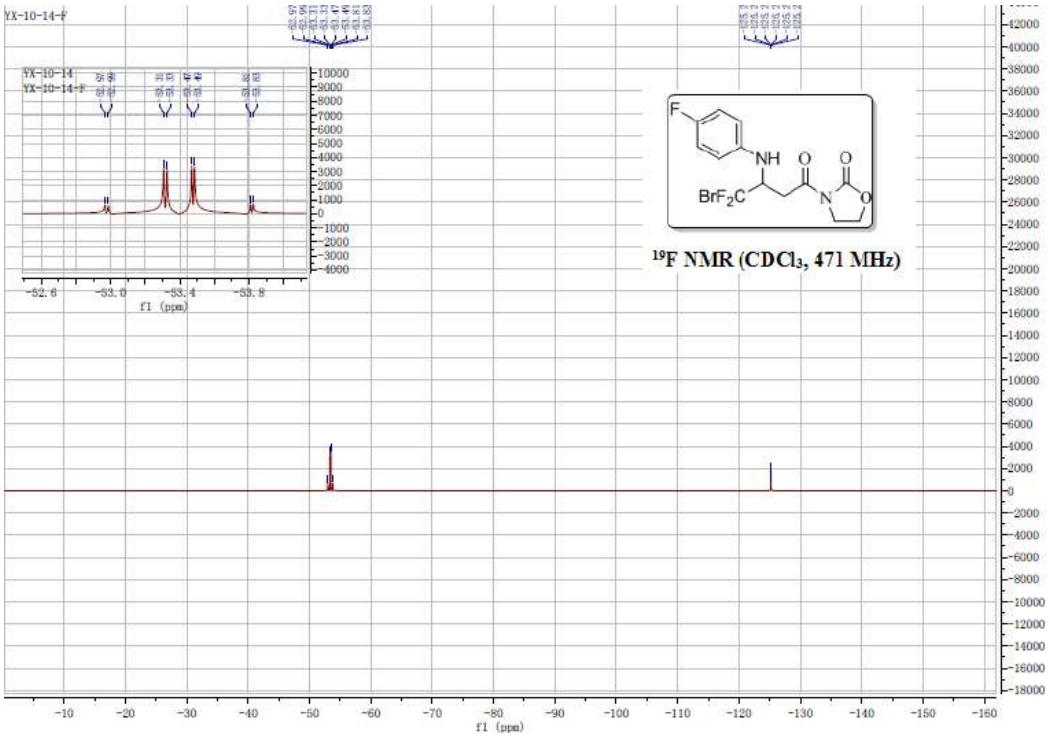




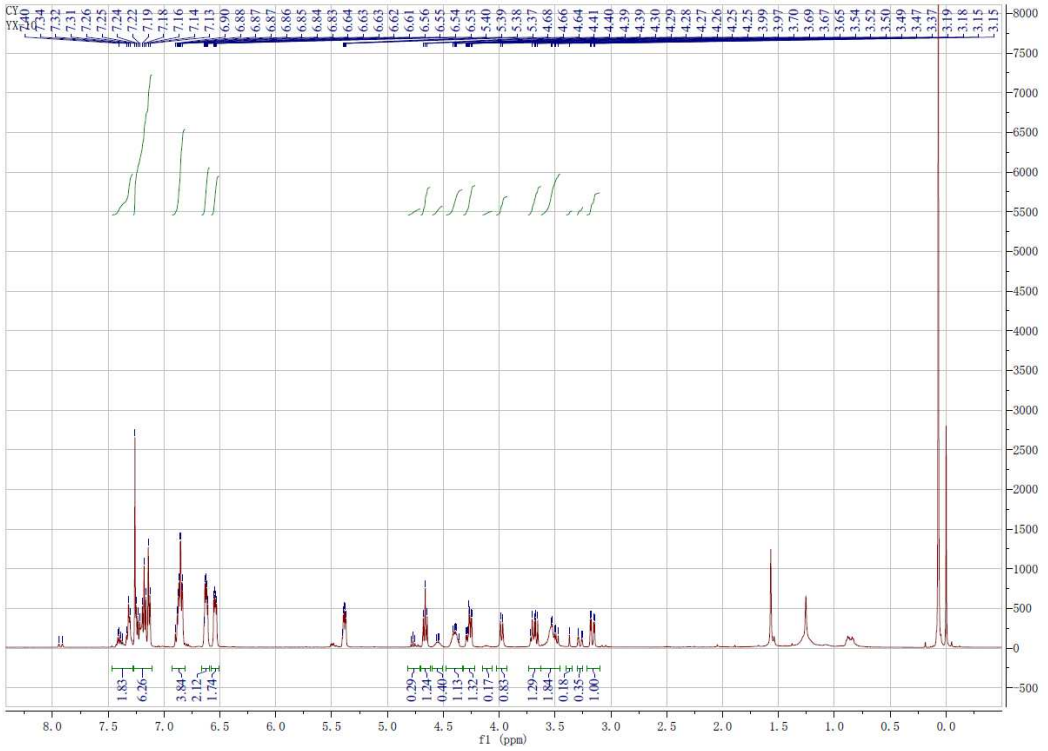


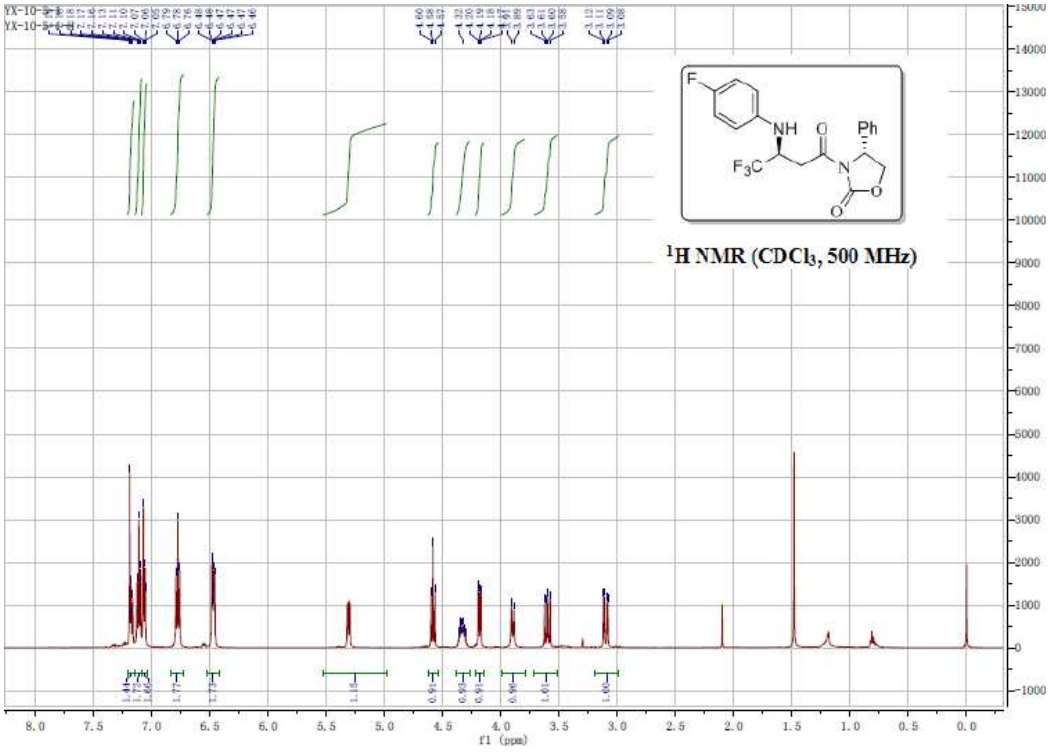


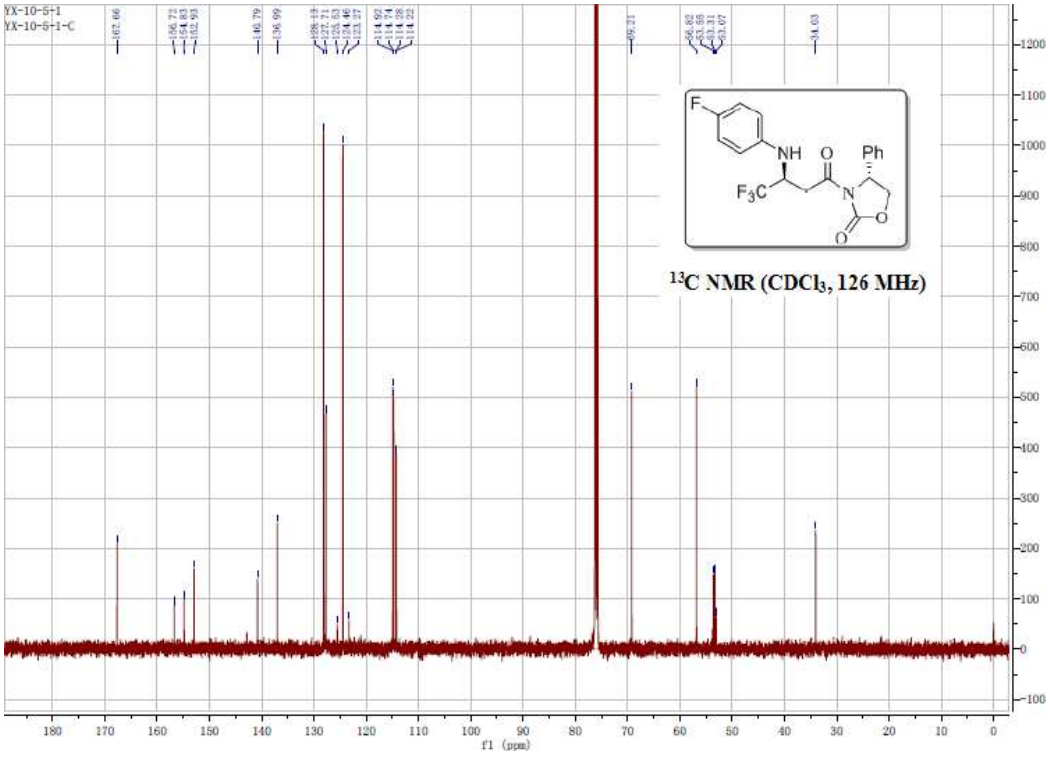


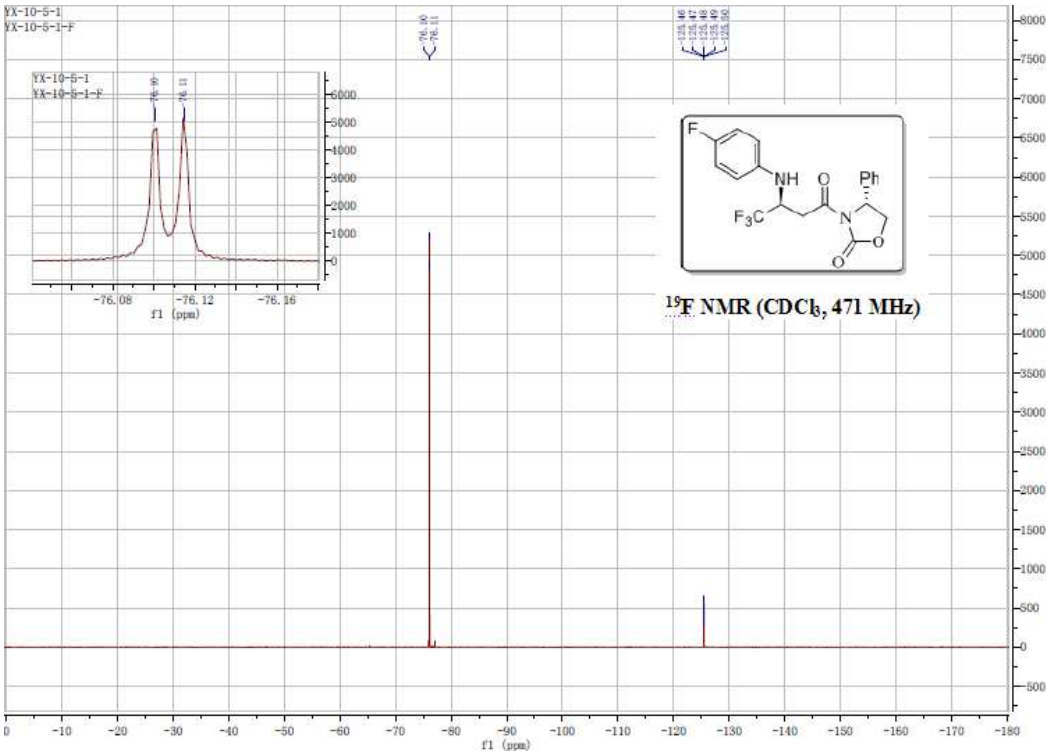


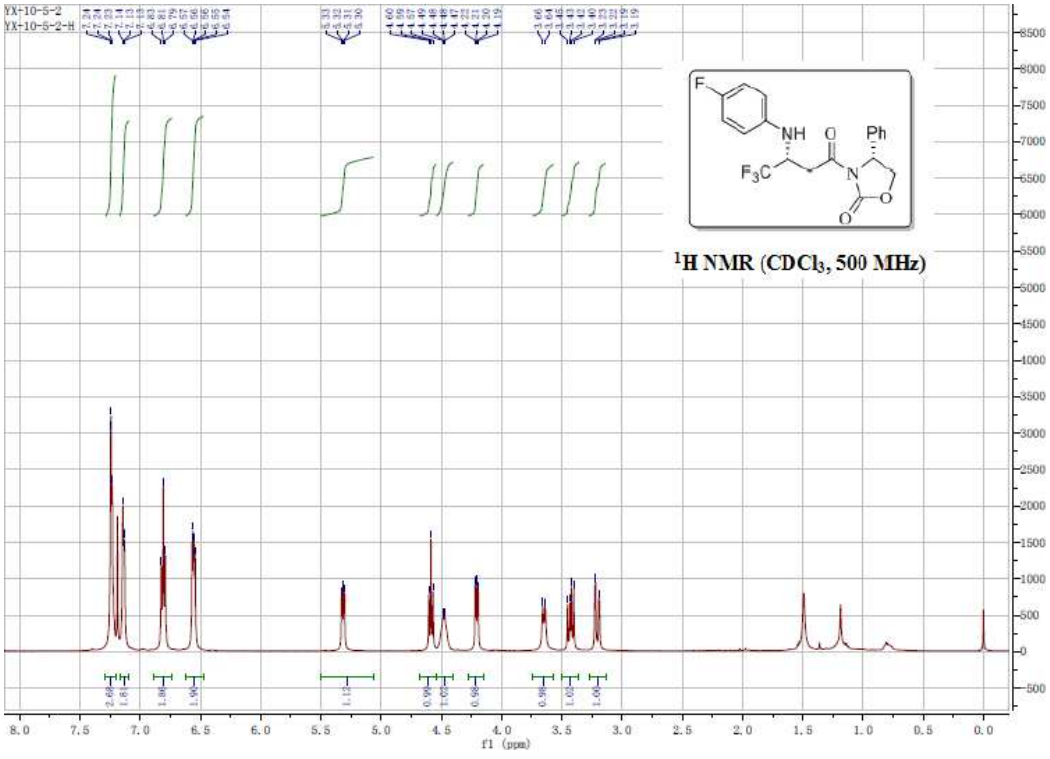
^{1}H NMR of the crude mixture of diastereomers (*S,R*)-**5** and (*R,R*)-**5**

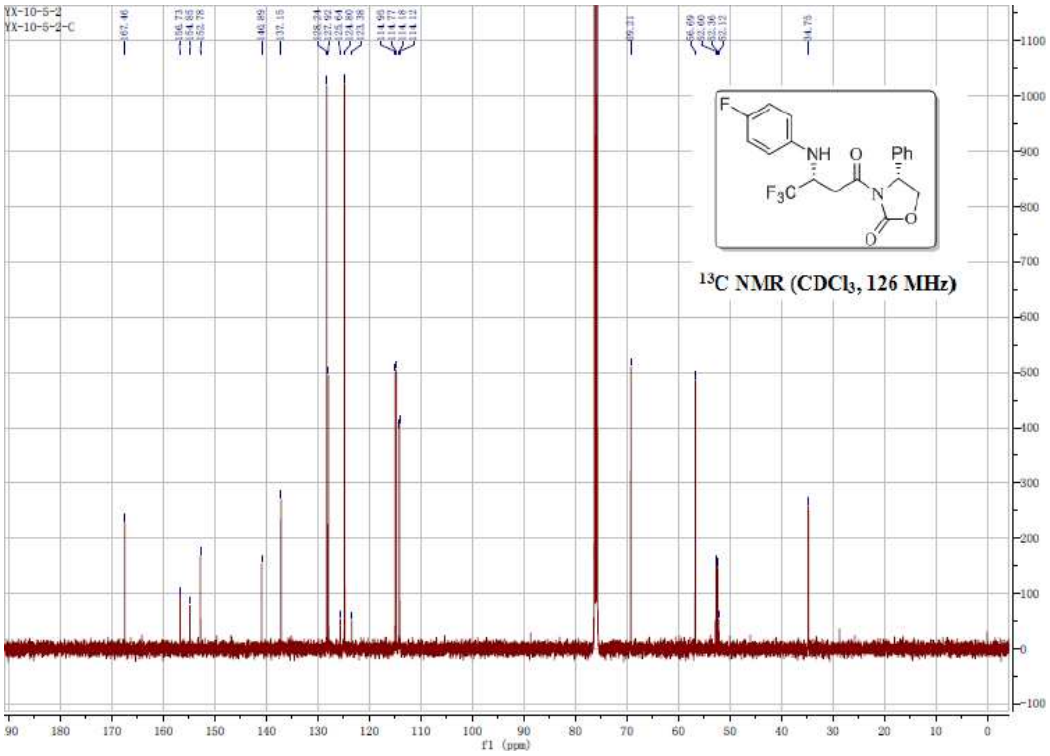


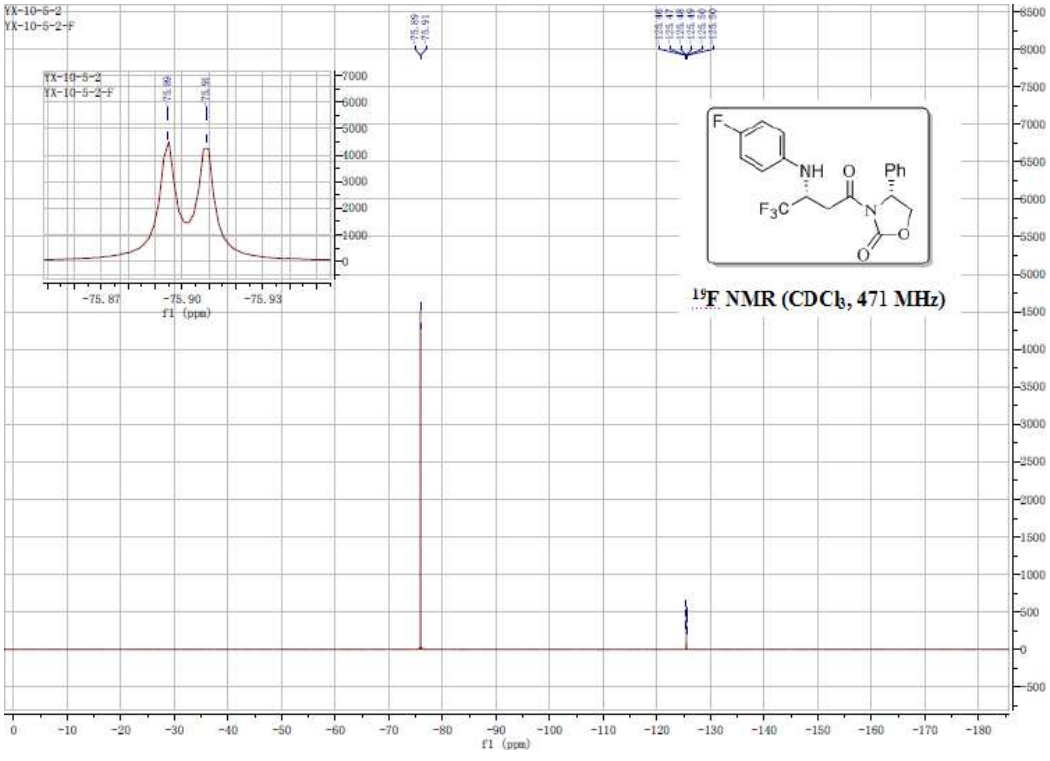


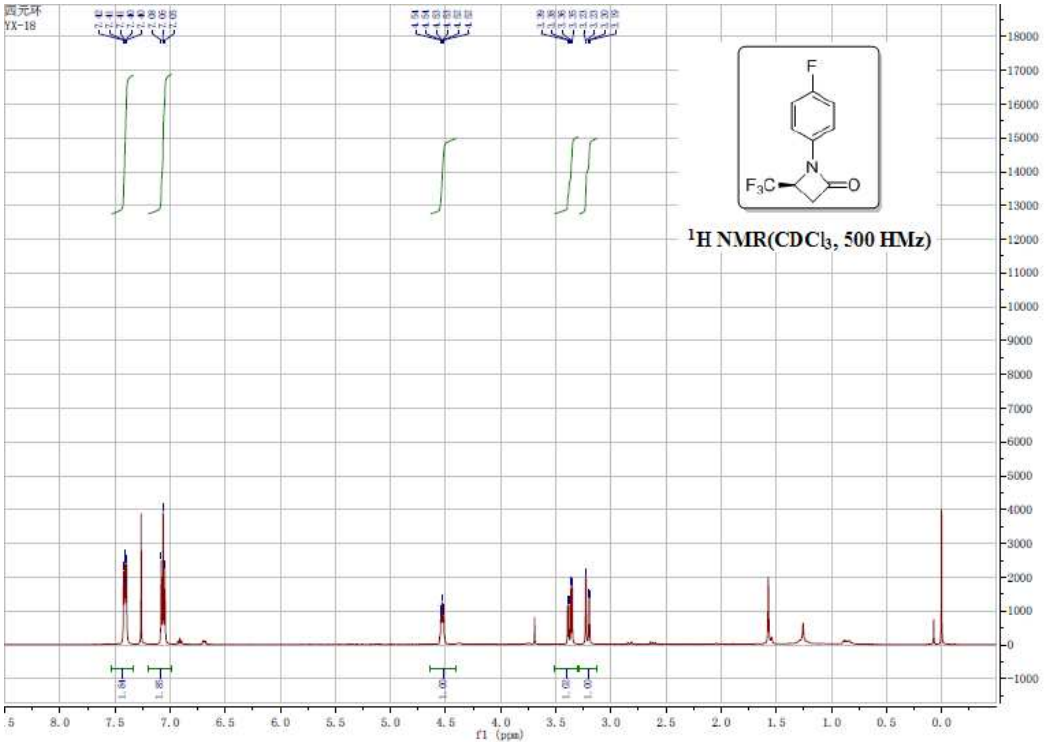


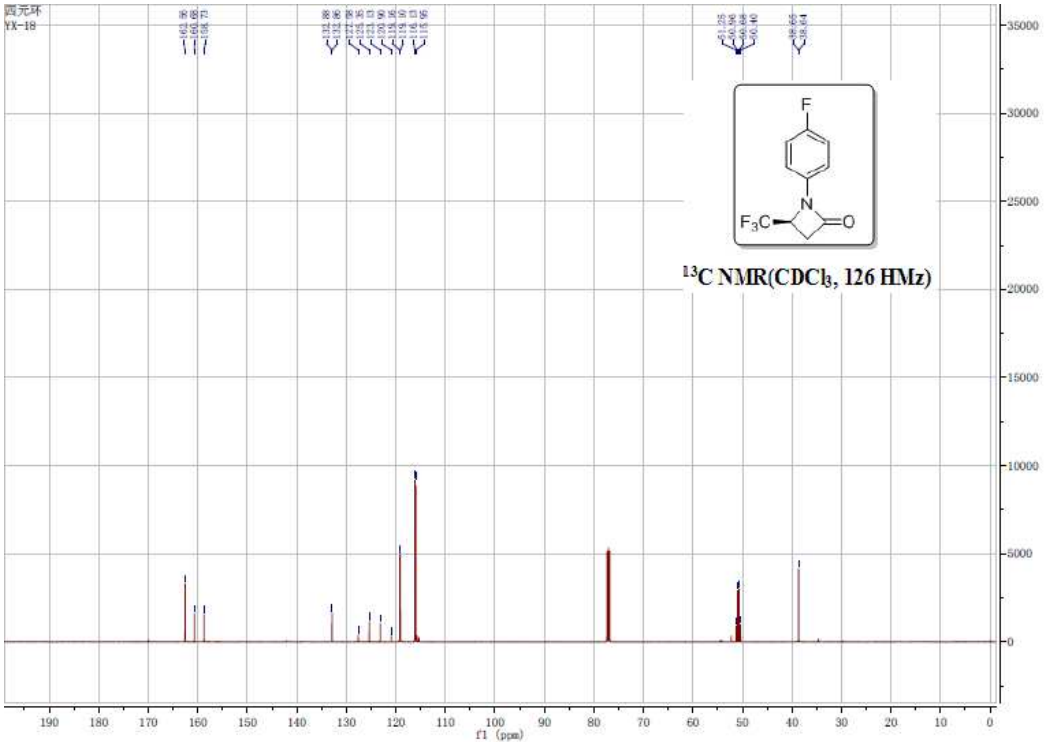


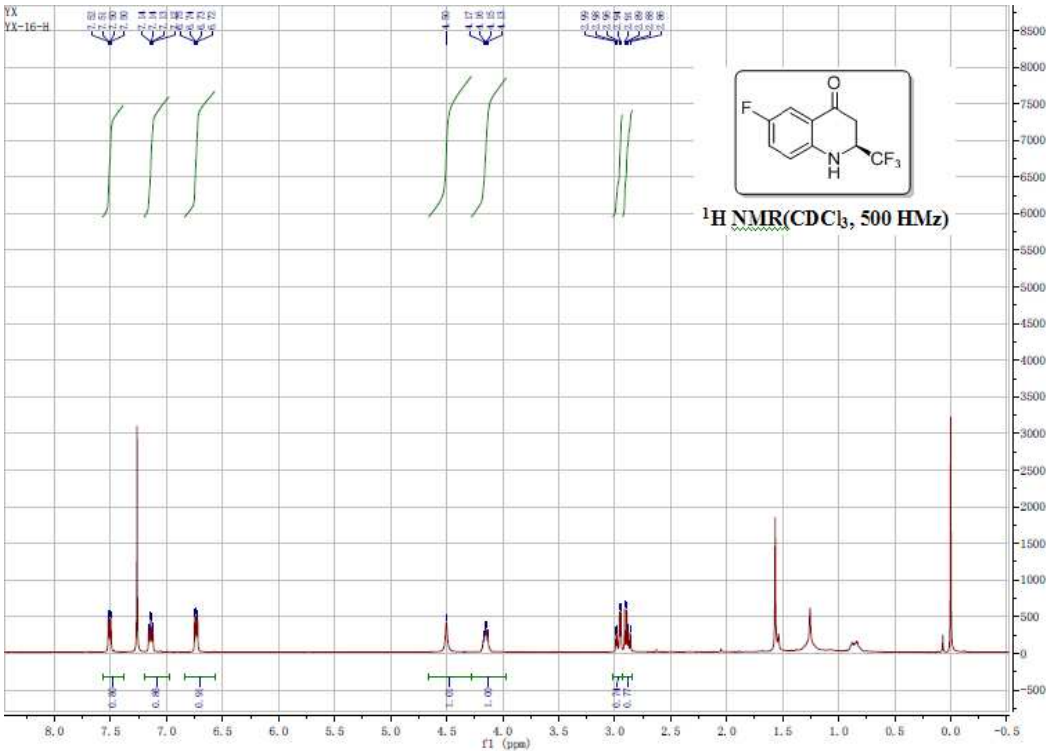


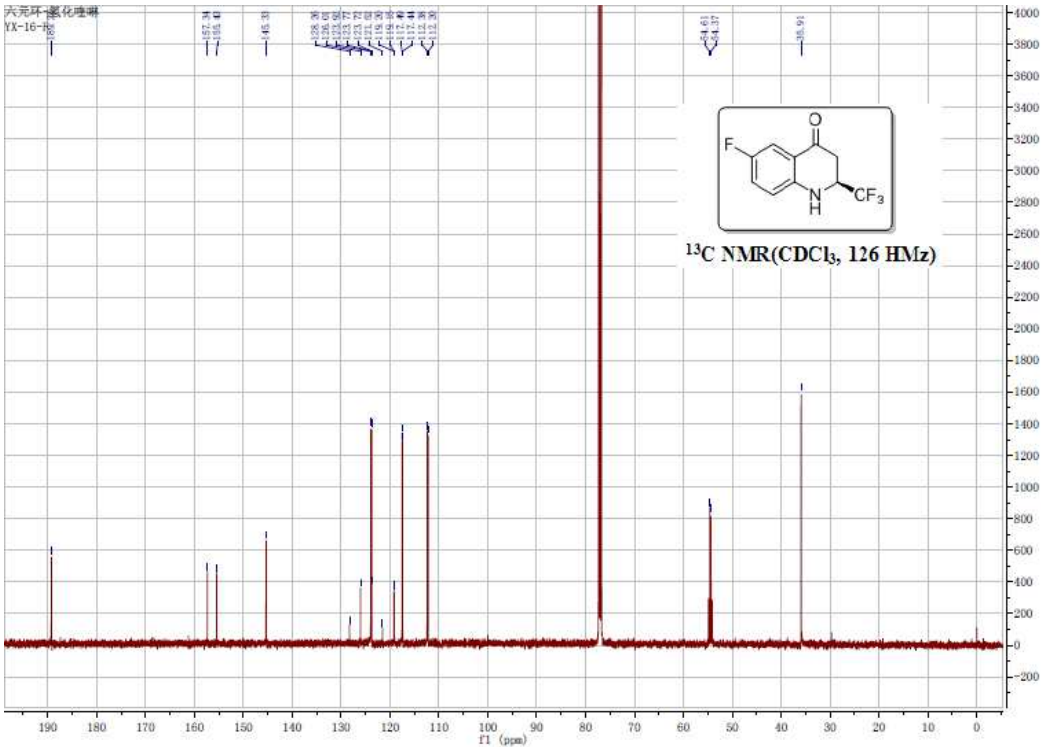


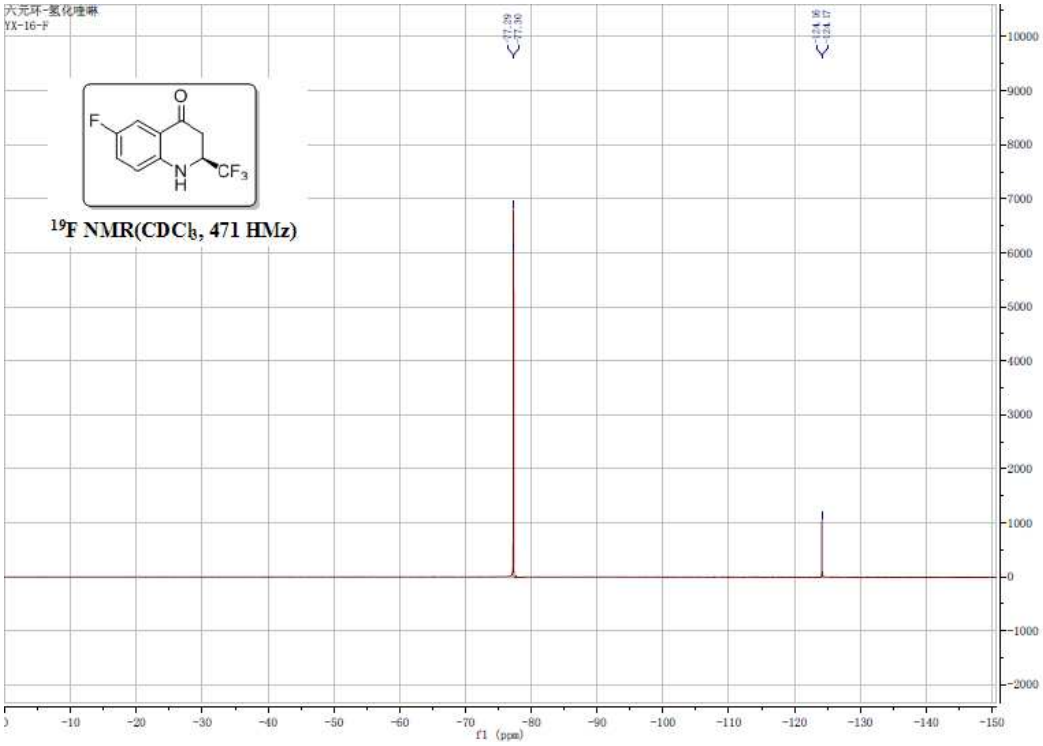












^{19}F NMR(CDCl$_3$, 471 HMz)

Aza-Michael addition under catalyst- and solvent-free conditions worked well to install various fluoroalkylated amino acids derivatives and three trifluoromethylated heterocycles.