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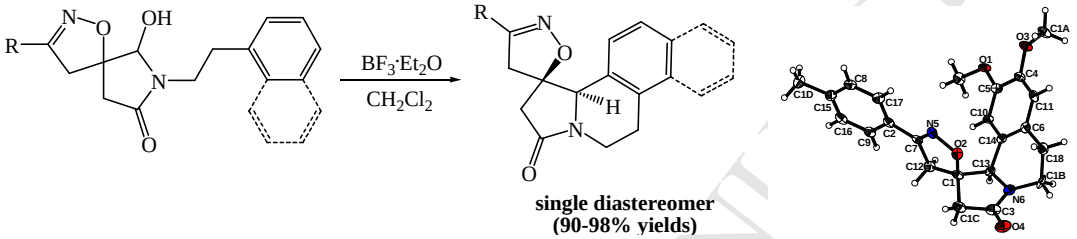

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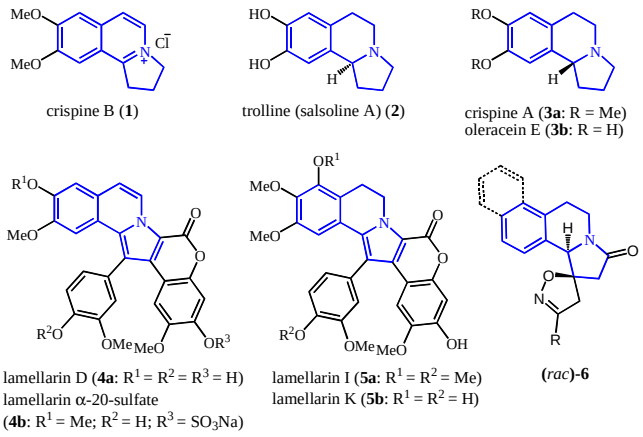
ABSTRACT

A simple and efficient strategy is reported for the synthesis of spiro-fused pyrrolo[2,1-*a*]isoquinoline ring systems. The spiro[isoxazolopyrroloisoquinolines] are readily prepared via diastereoselective *N*-acyliminium ion cyclization of 6-hydroxy-7-(2-arylethyl)-1-oxa-2,7-diazaspiro[4.4]non-2-en-8-ones derived from the corresponding spirocyclic dihydroisoxazoles.

1. Introduction

The pyrrolo[2,1-*a*]isoquinoline ring system is a major structural fragment of *Erythrina* and *lamellarin alkaloids*.[1] Natural products that contains pyrroloisoquinoline framework (Scheme 1) display a variety of pharmacological effects including cytotoxic [crispine B (**1**) and lamellarin D (**4a**)],[2] antitumor [crispine B (**1**), crispine A (**3a**), lamellarin I (**5a**) and lamellarin K (**5b**)],[2,3] antibacterial and antiviral activities [trolline (salsoline A) (**2**)],[4] DPPH free radical scavenging activity and inhibitory activity [oleracein E (**3b**) and lamellarin α-20-sulfate (**4b**)].[5] Various biological activities have been found for synthetic pyrroloisoquinolines, e.g., antineoplastic,[6] antitumor activity,[7] antidepressant,[8] antileukemic,[6a] antiviral[9] and activity as α2-adrenoreceptor antagonists[10] and calcium channel blockers.[11] In addition, compounds with a pyrroloisoquinoline fragment have been described as having hypotensive, sympatholytic and psychotropic activity,[12a] as well as being useful in the treatment of diseases such as psoriasis.[12b]



Scheme 1. Representative natural active pyrrolo[2,1-*a*]isoquinolines **1**–**5** and the spiro[isoxazolopyrroloisoquinolines] **6** from this work.

Thereby development of simple, effective and efficient synthetic methods for compounds containing such a structural fragment is still an important and actual challenge of organic chemistry and many approaches have been reported in the last years.[13] In particular, the intramolecular trapping of cyclic *N*-acyliminium ions has been successfully used for the preparation of pyrrolo[2,1-*a*]isoquinoline ring systems.[14]

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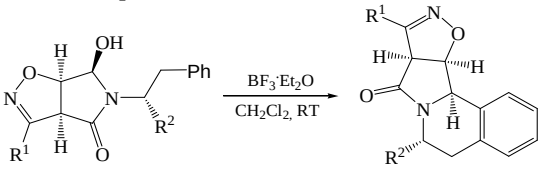
Previously, we described the first synthesis of isoxazolopyrroloisoquinolines **8** (Scheme 2) *via* diastereoselective intramolecular cyclization of 5-(2-arylethyl)-6-hydroxytetrahydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-ones **7** in the presence of boron trifluoride diethyl etherate.[15] In the present work we report a simple and efficient approach for the synthesis of the spiro[isoxazolopyrroloisoquinolines] **6** (Scheme 1) via the intramolecular trapping of an *N*-acyliminium ion as the key synthetic step.[16]



(rac)-**7** *(rac)*-**8**

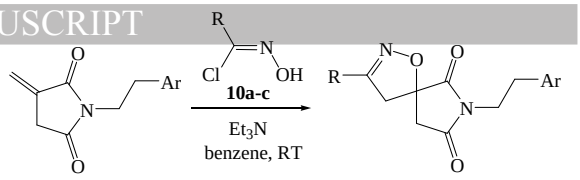
Scheme 2. Previous work: synthesis of pyrroloisoquinolines **8** by cyclization of hydroxylactams **7**.

2. Results and discussion

Our approach to spiro[isoxazolopyrroloisoquinolines] began with the synthesis of dihydroisoxazoles **11a–g** prepared by 1,3-dipolar cycloaddition of *N*-(2-arylethyl)itaconimides **9a–c** to nitrile oxides, generated from the corresponding hydroximoyl chlorides **10a–c** in the presence of triethylamine (Table 1). Benzonitrile oxide (generated *in situ* from the hydroximoyl chloride **10a** in the presence of Et_3N) was treated with **9a** in benzene at 20 °C to give a isoxazole **11a** in 86% yield (Table 1, entry 1). A similar reactions occurred between itaconimide **9a** and nitrile oxides generated from **10b**,**c**, giving spiro-isoxazoles **11b** and **11c** in yields of 42% and 25% respectively (Table 1, entries 2 and 3). The reactions of itaconimides **9b,c** with nitrile oxides generated from hydroximoyl chlorides **10a,b** lead to spiro-isoxazoles **11d–g** in yields ranging from 24% to 85% (Table 1, entries 4-7). The structural assignment of the isolated spiro-isoxazoles **11a–g** was made on the basis of their spectroscopic data: ^1H and ^{13}C NMR spectra indicate the regiochemistry of the [3+2] cycloadducts **11a–g** which are formed by the attack of the nitrile oxide's carbon at the CH_2 terminus of the α,β-unsaturated moiety (see Supplementary data).

For the next step in our study, we examined the reduction of the imide function of substrates **11a–g** with $NaBH_4$. The reduction was carried out in methylene chloride–ethanol at –80 to –20 °C to provide the corresponding hydroxylactams **12a–g** in yields ranging from 92% to 98% (Table 2). In all cases, only the carbonyl group at the β-position with respect to the oxygen atom in the dihydroisoxazole ring was reduced. Presumably, this is related to the inductive effect of the oxygen atom of the isoxazole ring.[17] The signals of the other possible regioisomers were not found in ^1H NMR spectra of crude reaction mixtures. A ^1H NMR analysis of crude reaction mixtures showed that the spiro-hydroxylactams **12a–e** are formed as the inseparable mixture of diastereomers, while products **12f,g** formed as a single diasteremers; and the stereochemistry of these products **12f,g** is not yet determined (Table 2). It should be noted that hydroxylactam **12g** in $CDCl_3$ for two weeks at room temperature is completely converted into other diastereomer.

Table 1
1,3-Dipolar cycloaddition of benzonitrile oxides to itaconimides (**9a–c**)[a]

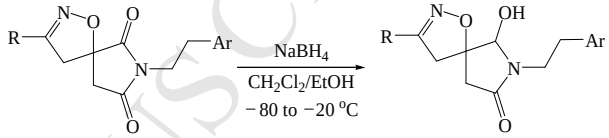


9a-c **11a-g**

Entry	Ar	R	Product	Yield (%)[b]
1	Ph (**9a**)	4-MeC_6H_4 (**10a**)	**11a**	86
2	Ph (**9a**)	4-ClC_6H_4 (**10b**)	**11b**	42
3	Ph (**9a**)	CO_2Et (**10c**)	**11c**	25
4	3,4-$(MeO)_2C_6H_3$ (**9b**)	4-MeC_6H_4 (**10a**)	**11d**	63
5	3,4-$(MeO)_2C_6H_3$ (**9b**)	4-ClC_6H_4 (**10b**)	**11e**	24
6	1-naphthyl (**9c**)	4-MeC_6H_4 (**10a**)	**11f**	85
7	1-naphthyl (**9c**)	4-ClC_6H_4 (**10b**)	**11g**	68

[a] Reaction conditions: **9** (1 equiv), **10** (1.5 equiv), Et_3N (1.5 equiv), benzene, RT. [b] Isolated yield.

Table 2
Reduction of compounds **11a–g** with $NaBH_4$[a]



11a-g **12a-g**

Entry	Substrate	Ar	R	Yield of **12** (%)[b]	dr of **12**[c]
1	**11a**	Ph	4-MeC_6H_4	**12a** (96)	2:1
2	**11b**	Ph	4-ClC_6H_4	**12b** (92)	5:1
3	**11c**	Ph	CO_2Et	**12c** (95)	11:1
4	**11d**	3,4-$(MeO)_2C_6H_3$	4-MeC_6H_4	**12d** (95)	5:1
5	**11e**	3,4-$(MeO)_2C_6H_3$	4-ClC_6H_4	**12e** (95)	9:1
6	**11f**	1-naphthyl	4-MeC_6H_4	**12f** (96)	1:0
7	**11g**	1-naphthyl	4-ClC_6H_4	**12g** (98)	1:0

[a] Reaction conditions: **11** (1 equiv), $NaBH_4$ (1.5 equiv), CH_2Cl_2/EtOH, –80 to –20 °C. [b] Isolated yield. [c] Determined by ^1H NMR of the crude mixture.

Next, the intramolecular Friedel-Crafts–type reactions of hydroxylactams **12a–g** were investigated (Table 3). Treatment of *N*-acyliminium precursors **12a** and **12b** with an excess of $BF_3{\cdot}OEt_2$ (5 equiv) in CH_2Cl_2 at room temperature gave the spiro-cyclic racemic products **13a** and **13b** as a single diastereomers in 98 and 90% yield, respectively (Table 3, entries 1 and 2). Similarly, cyclization of hydroxylactam **12c** afforded exclusively to **13c** in 96% yield (Table 3, entry 3). The signals of the other possible diastereomers were not found in ^1H NMR spectra of crude reaction mixtures. The *N*-acyliminium ion cyclization of methoxy-substituted aromatic ring containing hydroxylactams **12d,e** with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at room temperature proceeded cleanly to provide spiro[isoxazolopyrroloisoquinolines] **13d,e** in 98 and 92 % yields, respectively (Table 3, entries 4 and 5). Furthermore, in the case of the 1-naphthyl substituted *N*-acyliminium ion precursors **12f,g** formed the pentacyclic spiro-systems **13f,g** in 91 and 98% yields (Table 3, entries 6 and 7). From the analysis of ^1H NMR spectrum of the crude reaction mixtures it was concluded that the cyclization of hydroxylactams **12f,g** produced only a single diastereomers. The relative stereochemistry of the formed stereocenters of spiro[isoxazolopyrroloisoquinolines] **13** was determined by single-crystal X-ray diffraction (for compound **13d**) (Fig. 1) and supported the relative configuration deduced from NMR spectroscopy. The ^1H NMR spectrum of compound **13f** displayed a singlet at 5.19 ppm for *H*-C(10a), which showed a H,H-NOESY correlation with a doublet at 3.97 ppm (CH_2 group of the isoxazole ring), this fact indi-

cated that *H*-C(10a) and methylene group of isoxazole ring are *cis*-located relative to each other.

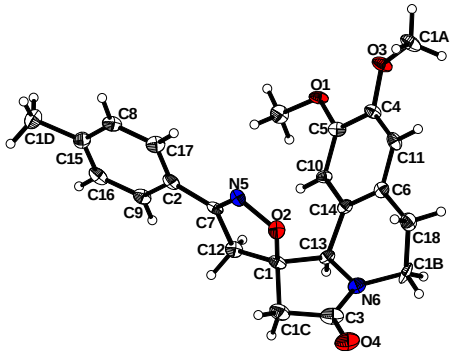
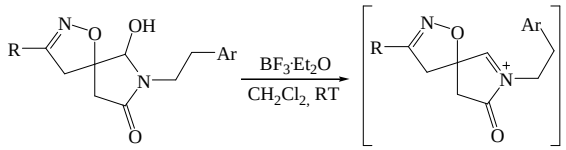
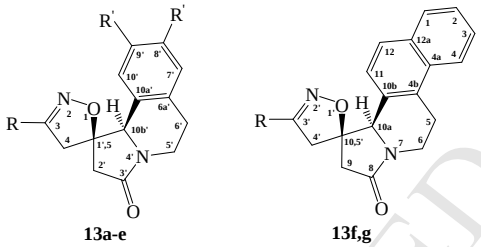


Fig. 1. ORTEP representation of compound **13d**.

Table 3.
$BF_3{\cdot}OEt_2$-catalyzed intramolecular diastereoselective Friedel-Crafts–type cyclization of hydroxylactams **12a–g**[a]



12a-g **14**

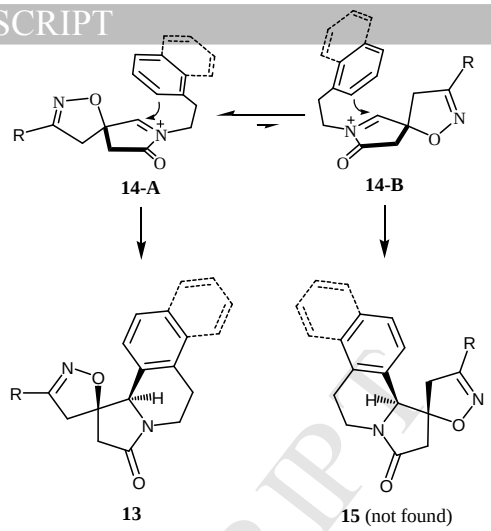


13a-e **13f,g**

Entry	Substrate	Ar	R	R′	Yield of **13** (%)[b]
1	**12a**	Ph	4-MeC_6H_4	H	**13a** (98)
2	**12b**	Ph	4-ClC_6H_4	H	**13b** (90)
3	**12c**	Ph	CO_2Et	H	**13c** (96)
4	**12d**	3,4-$(MeO)_2C_6H_3$	4-MeC_6H_4	MeO	**13d** (98)
5	**12e**	3,4-$(MeO)_2C_6H_3$	4-ClC_6H_4	MeO	**13e** (92)
6	**12f**	1-naphthyl	4-MeC_6H_4	–	**13f** (91)
7	**12g**	1-naphthyl	4-ClC_6H_4	–	**13g** (98)

[a] Reaction conditions: **12** (1 equiv.), $BF_3{\cdot}OEt_2$ (5 equiv.), CH_2Cl_2, RT.
[b] Isolated yield.

From the obtained results we can conclude that the reaction occurs by direct attack on the *N*-acyliminium ion intermediate **14** by the π-aromatic system linked to the nitrogen atom of the pyrrolidinone ring to produce the spiro[isoxazolopyrroloisoquinolines] **13**. Formation of diastereomers **13** occurs by π-nucleophile attack on the *N*-acyliminium ion from the less hindered isoxazole side, that is, in our case, the oxygen one (transition state **14-A,** Scheme 2). The transition state **14-A** should be lower in energy than the **14-B** due to repulsion between the CH2-C(R)-fragment of dihydroisoxazole ring and aromatic ring in transition state **14-B** (Scheme 3).



Scheme 3. Stereoselective outcome of the intramolecular *N*-acyliminium cyclization into the spiro-cyclic systems **13**.

3. Conclusion

In summary, we have developed a simple and efficient route to spiro[isoxazolopyrroloisoquinolines] *via* diastereoselective *N*-acyliminium ion cyclization of 6-hydroxy-7-(2-arylethyl)-1-oxa-2,7-diazaspiro[4.4]non-2-en-8-ones derived from the corresponding spirocyclic dihydroisoxazoles.

4. Experimental section

4.1. General remarks

IR spectra were obtained on an Bruker Tensor 27 spectrometer. Melting points were determined on a Boetius instrument and are uncorrected. NMR spectra were recorded on a Bruker Avance III spectrometer (^{1}H, 400 MHz; ^{13}C, 100 MHz). Chemical shifts δ are reported in ppm relative to residual $CHCl_3$ (^{1}H, δ = 7.26) and $CDCl_3$ (^{13}C, δ = 77.16) as internal standard. High-resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF 10223 spectrometer using electrospray ionization (ESI). The X-ray diffraction data were performed by means of an Bruker APEX-II CCD diffractometer with Mo-K X-ray radiation. Reactions were monitored by TLC analysis using Silufol UV-254 plates. Thin layer chromatography was performed on silica gel 5–40 mesh eluted with dichloromethane/methanol. Preparation and characterization of compounds **13a–g** are disclosed below, while compounds **9a–c**, **11a–g** and **12a–g** described in the Supplementary data.

4.2. General procedure for the synthesis of spiro[isoxazolopyrroloisoquinolines] 13a-g

Boron trifluoride diethyl etherate (5 equiv) was added to vigorously stirred solution of corresponding hydroxylactams (**12**) in anhyd. dichloromethane (3 mL) under argon. The reaction mixture was stirred in a capped vial at room temperature (TLC-control). After completion of the reaction, water was added carefully to the reaction mixture (6 mL). The aqueous layer was ex-

tracted with CH_2Cl_2 (3 x 5 mL), the organic layers were combined, dried over MgSO4 and evaporated to dryness. The product was recrystallized with Et_2O (for **13a,b,d-g**).

4.2.1. (5SR,10b'SR)-3-(4-methylphenyl)-6',10b'-dihydro-4H,5'H-spiro[isoxazole-5,1'-pyrrolo[2,1-a]isoquinolin]-3'(2'H)-one ***(13a)***, (98%) was obtained using general procedure from hydroxylactam **12a** and $BF_3{\cdot}OEt_2$. Colorless solid, m.p. 219–222 ºC. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.50 (d, *J*=8.0 Hz, 2H), 7.24 (d, *J*=8.0 Hz, 2H), 7.20-7.17 (m, 2H), 7.07-7.03 (m, 1H), 6.97 (d, *J*=7.8 Hz, 1H), 5.04 (s, 1H, CH), 4.49-4.45 (m, 1H, CH from CH_2), 3.87 (d, *J*=17.5 Hz, 1H from CH_2,), 3.64 (d, *J*=17.5 Hz, 1H from CH_2), 3.08-2.91 (m, 4H, isoxazoline CH_2 + 2CH from CH_2), 2.75 (d, *J*=15.1 Hz, 1H from CH_2), 2.41 (s, 3H, CH_3 from *Tol*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.4 (CO), 155.5 (C=N), 140.7 (C_{Ar}), 135.8 (C_{Ar}), 130.8 (C_{Ar}), 129.7 (CH_{Ar}), 129.6 ($2CH_{Ar}$), 127.5 (CH_{Ar}), 126.6 ($2CH_{Ar}$), 126.3 (CH_{Ar}), 126.2 (C_{Ar}), 125.0 (CH_{Ar}), 89.2 (C_{spiro}), 66.3 (CH), 45.1 (CH_2), 42.6 (CH_2), 37.4 (CH_2), 29.7 (CH_2), 21.5 (CH_3 from *Tol*). HRMS (ESI): calcd for $C_{21}H_{21}N_2O_3$ $[M+H]^+$ 333.1598, found 333.1603; calcd for $C_{21}H_{20}N_2NaO_3$ $[M+Na]^+$ 355.1422, found 355.1417.

4.2.2. (5SR,10b'SR)-3-(4-chlorophenyl)-6',10b'-dihydro-4H,5'H-spiro[isoxazole-5,1'-pyrrolo[2,1-a]isoquinolin]-3'(2'H)-one ***(13b)***, (90%) was obtained using general procedure from hydroxylactam **12b** and $BF_3{\cdot}OEt_2$. White solid, m.p. 188–190 ºC (decomposition). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.54 (d, *J*=8.5 Hz, 2H), 7.41 (d, *J*=8.5 Hz, 2H), 7.21-7.19 (m, 2H), 7.07-7.03 (m, 1H), 6.94 (d, 1H, 7.8 Hz), 5.05 (s, 1H, CH), 4.51-4.46 (m, 1H, CH from CH_2), 3.85 (d, 1H from CH_2, 17.5 Hz), 3.64 (d, 1H from CH_2, 17.5 Hz), 3.09-3.01 (m, 1H, CH from CH_2), 2.98 (s, 2H, isoxazoline CH_2), 2.93 (dd, 1H from CH_2, 2.9 Hz, 12.1 Hz), 2.76 (d, 1H from CH_2, 15.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.2 (CO), 154.6 (C=N), 136.4 (C_{Ar}), 135.9 (C_{Ar}), 130.6 (C_{Ar}), 129.8 (CH_{Ar}), 129.2 ($2CH_{Ar}$), 127.8 ($2CH_{Ar}$), 127.6 (CH_{Ar}), 127.5 (C_{Ar}), 126.3 (CH_{Ar}), 124.8 (CH_{Ar}), 89.9 (C_{spiro}), 66.3 (CH), 44.9 (CH_2), 42.2 (CH_2), 37.4 (CH_2), 29.7 (CH_2). HRMS (ESI): calcd for $C_{20}H_{18}N_2O_2$ $[M+H]^+$ 353.1057, found 353.1062; calcd for $C_{20}H_{17}N_2NaO_2$ $[M+Na]^+$ 375.0876, found 375.0879.

4.2.3. ethyl (5SR,10b'SR)-3'-oxo-2',3',6',10b'-tetrahydro-4H,5'H-spiro[isoxazole-5,1'-pyrrolo[2,1-a]isoquinoline]-3-carboxylate ***(13c)***, (96%) was obtained using general procedure from hydroxylactam **12c** and $BF_3{\cdot}OEt_2$. Yellow oil. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.26-7.16 (m, 3H), 7.02 (d, *J*=7.6 Hz, 1H), 5.03 (s, 1H, CH), 4.48-4.44 (m, 1H, CH from CH_2), 4.40-4.33 (m, 2H, CH_2), 3.80 (d, *J*=18.6 Hz, 1H from CH_2), 3.46 (d, *J*=18.6 Hz, 1H from CH_2), 3.05-2.88 (m, 4H, CH_2+CH_2), 2.74 (d, *J*=14.8 Hz, 1H from CH_2,), 1.40 (t, *J*=7.1 Hz, 3H, CH_3 from CO_2Et,). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.6 (CO), 160.2 ($\underline{CO_2}Et$), 150.4 (C=N), 136.0 (C_{Ar}), 130.1 (C_{Ar}), 129.9 (CH_{Ar}), 127.8 (CH_{Ar}), 126.6 (CH_{Ar}), 124.6 (CH_{Ar}), 92.3 (C_{spiro}), 65.7 (CH), 62.3 (CH_2), 45.1 (CH_2), 40.6 (CH_2), 37.4 (CH_2), 29.7 (CH_2), 14.1 (CH_3 from CO_2Et). HRMS (ESI): calcd for $C_{17}H_{20}N_2O_4$ $[M+H]^+$ 315.1339, found 315.1344; calcd for $C_{17}H_{18}N_2NaO_4$ $[M+Na]^+$ 337.1164, found 337.1169.

4.2.4. (5SR,10b'SR)-8',9'-dimethoxy-3-(4-methylphenyl)-6',10b'-dihydro-4H,5'H-spiro[isoxazole-5,1'-pyrrolo[2,1-a]isoquinolin]-3'(2'H)-one ***(13d)*** (98%) was obtained using general procedure from hydroxylactam **12d** and $BF_3{\cdot}OEt_2$. White solid, decomposition at 220 ºC. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.51 (d, *J*=8.0 Hz, 2H), 7.23 (d, *J*=8.0 Hz, 2H), 6.65 (s, 1H), 6.35 (s, 1H), 4.92 (s, 1H, CH), 4.50-4.46 (m, 1H, CH from CH_2), 3.86 (s, 3H, OMe), 3.83 (d, *J*=17.5 Hz, 1H from CH_2), 3.69 (d, *J*=17.5 Hz, 1H from CH_2,), 3.26 (s, 3H, OMe), 3.05-2.94 (m, 3H, isoxazoline CH_2 + CH from CH_2), 2.92 (dd, J_1=12.2 Hz, J_2=2.6 Hz, 1H from CH_2), 2.66 (d, *J*=15.1 Hz, 1H from CH_2), 2.40 (s, 3H, CH_3 from *Tol*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.2 (CO), 155.3 (C=N), 148.3 (C_{Ar}), 147.4 (C_{Ar}), 140.9 (C_{Ar}), 129.7 ($2CH_{Ar}$), 128.2 (C_{Ar}), 126.4 ($2CH_{Ar}$), 126.2 (C_{Ar}), 122.2 (C_{Ar}), 112.1 (CH_{Ar}), 107.9 (CH_{Ar}), 89.2 (C_{spiro}), 67.0 (CH), 55.7 (OMe), 55.3 (OMe), 44.4 (CH_2), 42.6 (CH_2), 37.4 (CH_2), 29.1 (CH_2), 21.5 (CH_3 from *Tol*). IR (KBr) ν_{max} 3591, 3431, 2922, 2846, 2249, 1686, 1609, 1519, 1441, 1422, 1358, 1267, 1229, 1117, 1025, 911. HRMS (ESI): calcd for $C_{23}H_{25}N_2O_4$ $[M+H]^+$ 393.1814, found 393.1812; calcd for $C_{23}H_{24}N_2NaO_4$ $[M+Na]^+$ 415.1634, found 415.1631.

4.2.5. (5SR,10b'SR)-3-(4-chlorophenyl)-8',9'-dimethoxy-6',10b'-dihydro-4H,5'H-spiro[isoxazole-5,1'-pyrrolo[2,1-a]isoquinolin]-3'(2'H)-one ***(13e)*** (92%) was obtained using general procedure from hydroxylactam **12e** and $BF_3{\cdot}OEt_2$. Light yellow solid, decomposition at 180 ºC. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.55 (d, *J*=8.5 Hz, 2H), 7.40 (d, *J*=8.5 Hz, 2H), 6.65 (s, 1H), 6.33 (s, 1H), 4.92 (s, 1H, CH), 4.49-4.45 (m, 1H, CH from CH_2), 3.85 (s, 3H, OMe), 3.81 (d, *J*=17.4 Hz, 1H from CH_2,), 3.67 (d, *J*=17.4 Hz, 1H from CH_2), 3.29 (s, 3H, OMe), 3.05-2.94 (m, 3H, isoxazoline CH_2 + CH from CH_2), 2.89 (dd, J_1=12.2 Hz, J_2=2.2 Hz, 1H from CH_2), 2.65 (d, *J*=14.5 Hz, 1H from CH_2,). IR (KBr) ν_{max} 3367, 3079, 2921, 2851, 2254, 1695, 1603, 1516, 1463, 1432, 1360, 1272, 1234, 1164, 1092, 1038, 913. HRMS (ESI): calcd for $C_{22}H_{22}{}^{35}ClN_2O_4$ $[M+H]^+$ 413.1268, found 413.1263; calcd for $C_{22}H_{21}{}^{35}ClN_2NaO_4$ $[M+Na]^+$ 435.1088, found 435.1086.

4.2.6. (10SR,10aSR)-3'-(4-methylphenyl)-5,10a-dihydro-4'H,6H-spiro[benzo[f]pyrrolo[2,1-a]isoquinoline-10,5'-isoxazol]-8(9H)-one ***(13f)*** (91%) was obtained using general procedure from hydroxylactam **12f** and $BF_3{\cdot}OEt_2$. Light yellow solid, m.p. 185–189 ºC. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.98 (d, *J*=8.5 Hz, 1H), 7.78 (d, *J*=7.9 Hz, 1H), 7.58-7.47 (m, 5H), 7.25 (d, *J*=8.0 Hz, 2H), 7.05 (d, *J*=8.5 Hz, 1H), 5.19 (s, 1H, CH), 4.68 (dd, J_1=12.7 Hz, J_2=5.2 Hz, 1H, CH from CH_2), 3.97 (d, *J*=17.5 Hz, 1H from CH_2), 3.68 (d, *J*=17.5 Hz, 1H from CH_2,), 3.38 (dd, 1H from CH_2, J_1=15.5 Hz, J_2=2.0 Hz), 3.23-3.15 (m, 1H from CH_2), 3.05-3.00 (m, 3H, isoxazoline CH_2 + CH from CH_2), 2.43 (s, 3H, CH_3 from *Tol*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.9 (CO), 155.4 (C=N), 140.7 (C_{Ar}), 132.6 (C_{Ar}), 132.2 (C_{Ar}), 131.4 (C_{Ar}), 129.6 ($2CH_{Ar}$), 128.5 (CH_{Ar}), 128.0 (C_{Ar}), 126.7 (CH_{Ar}), 126.6 ($3CH_{Ar}$), 126.2 (C_{Ar}), 125.9 (CH_{Ar}), 123.3 (CH_{Ar}), 122.5 (CH_{Ar}), 89.0 (C_{spiro}), 66.7 (CH), 45.4 (CH_2), 43.4 (CH_2), 36.8 (CH_2), 25.2 (CH_2), 21.5 (CH_3 from *Tol*). IR (KBr) ν_{max} 3055, 2921, 2851, 1696, 1612, 1513, 1439, 1389, 1360, 1313, 1231, 1146, 1032, 914. HRMS (ESI): calcd for $C_{25}H_{23}N_2O_2$ $[M+H]^+$ 383.1760, found 383.1762; calcd for $C_{25}H_{22}N_2NaO_2$ $[M+Na]^+$ 405.1579, found 405.1582.

4.2.7. (10SR,10aSR)-3'-(4-chlorophenyl)-5,10a-dihydro-4'H,6H-spiro[benzo[f]pyrrolo[2,1-a]isoquinoline-10,5'-isoxazol]-8(9H)-one ***(13g)*** (98%) was obtained using general procedure from hydroxylactam **12g** and $BF_3{\cdot}OEt_2$. Light yellow solid, m.p. 207–211 ºC (decomposition). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.97 (d, *J*=8.4 Hz, 1H), 7.78 (d, *J*=7.8 Hz, 1H), 7.57-7.49 (m, 5H), 7.41 (d, *J*=8.5 Hz, 2H), 7.00 (d, *J*=8.5 Hz, 1H), 5.16 (s, 1H, CH), 4.66 (dd, J_1=12.8 Hz, J_2=5.4 Hz, 1H, CH from CH_2), 3.93 (d, *J*=17.5 Hz, 1H from CH_2), 3.64 (d, *J*=17.5 Hz, 1H from CH_2), 3.36 (dd, J_1=16.0 Hz, J_2=2.1 Hz, 1H from CH_2), 3.20-3.12 (m, 1H from CH_2), 3.03-2.96 (m, 3H, isoxazoline CH_2 + CH from CH_2). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.8 (CO), 154.7 (C=N), 136.4 (C_{Ar}), 132.6 (C_{Ar}), 132.1 (C_{Ar}), 131.5 (C_{Ar}), 129.2 ($2CH_{Ar}$), 128.5 (CH_{Ar}), 127.9 ($2CH_{Ar}$), 127.8 (C_{Ar}), 127.5 (C_{Ar}), 126.7 (CH_{Ar}), 126.7 (CH_{Ar}), 126.0 (CH_{Ar}), 123.3 (CH_{Ar}), 122.4 (CH_{Ar}), 89.6 (C_{spiro}), 66.6 (CH), 45.3 (CH_2), 42.9 (CH_2), 36.8 (CH_2), 25.3

(CH_2). IR (KBr) ν_{max} 3056, 2920, 2851, 1689, 1597, 1440, 1358, 1313, 1271, 1093, 1013, 922. HRMS (ESI): calcd for $C_{24}H_{20}ClN_2O_2$ $[M+H]^+$ 403.1213, found 403.1219; calcd for $C_{24}H_{19}ClN_2NaO_2$ $[M+Na]^+$ 425.1033, found 425.1039.

Acknowledgments

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Supplementary Material

Crystallographic data for compound **13d** (CCDC-1402706) have been deposited at the Cambridge Crystallographic Data Centre and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data (experimental procedures, characterization data, and copies of NMR spectra) associated with this article can be found in the online version, at doi:

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An efficient synthesis of substituted spiro[isoxazolopyrroloisoquinolines] via diastereoselective *N*-acyliminium ion cyclization

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Supporting information

Preparative details, physical properties and spectroscopic data for compounds **9a–c**, **11a–g**, **12a–g** and **13a–g**.

General. IR spectra were obtained on an Bruker Tensor 27 spectrometer. Melting points were determined on a Boetius instrument and are uncorrected. NMR spectra were recorded on a Bruker Avance III spectrometer (^{1}H, 400 MHz; ^{13}C, 100 MHz). Chemical shifts δ are reported in ppm relative to residual $CHCl_3$ (^{1}H, δ = 7.26) and $CDCl_3$ (^{13}C, δ = 77.16) as internal standard. High-resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF 10223 spectrometer using electrospray ionization (ESI). The X-ray diffraction data were performed by means of an Bruker APEX-II CCD diffractometer with Mo-K X-ray radiation. Reactions were monitored by TLC analysis using Silufol UV-254 plates. Thin layer chromatography was performed on silica gel 5–40 mesh eluted with dichloromethane/methanol.

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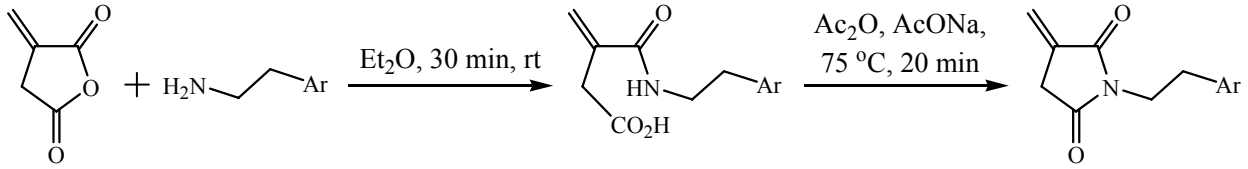
General procedure for the synthesis of itaconic acid imides

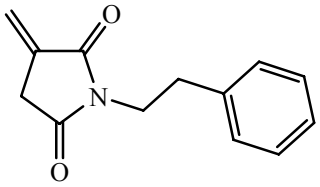


Ar = Ph, 3,4-$(MeO)_2C_6H_3$, 1-naphthyl

To the round bottom flask were placed 4.48 g of itaconic acid anhydride and 35 ml of diethyl ether, then 0.04 mol of corresponding amine in 15 ml of Et_2O was added dropwise under water bath cooling (approx. 5-10 ºC). After this the resulting mixture was stirred at room temperature for 30 minutes and quenched with 50 ml of hexane. Formed precipitate was filtered and twice washed with hexane. Imidoacid yield 80-95 %.

Previously synthesized imidoacid and acetic acid anhydride were placed into the round bottom flask, then sodium acetate was added and the resulting mixture was heated at 75 ºC for 20 minutes. Attention please, the temperature must not be overheated! After this reaction mixture was poured into ice water and leaved until oil was formed. The latter was carefully decanted from water and imides (itaconic and citraconic imides are formed in the mixture) were extracted by heating of organics in isooctane and chromatographically separated. Yield of desired imide 15-30 %.

3-Methylene-1-(phenethyl)pyrrolidine-2,5-dione (9a)



Isolated by column chromatography with hexane/ethyl acetate, yield 6 %;

M.p. 53-60 ºC; light yellow solid;

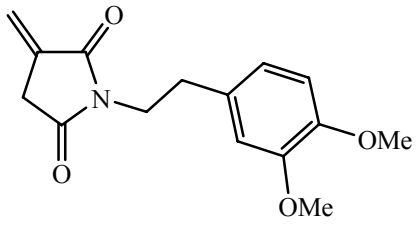
^1H (400.1 MHz, $CDCl_3$) δ_H: 7.34-7.24 (m, 5H), 6.36 (t, 1H, CH_2(double bond), 2.4 Hz), 5.63 (t, 1H, CH_2(double bond), 2.0 Hz), 3.85 (t, 2H, CH_2, 7.8 Hz), 3.29 (t, 2H, CH_2 in the ring, 2.2 Hz), 2.94 (t, 2H, CH_2, 7.8 Hz);

^{13}C (100.6 MHz, $CDCl_3$) δ_C: 173.55 (CO), 169.26 (CO), 137.80 (C_{Ar}), 133.25 (C_{quat}), 128.82 ($2CH_{Ar}$), 128.57 ($2CH_{Ar}$), 126.71 (CH_{Ar}), 120.44 (CH_2 at double bond), 39.98 (CH_2), 33.67 (CH_2), 33.62 (CH_2);

IR (KBr, cm^{-1}): 3457, 3430, 3075, 3029, 2960, 2940, 2867, 1888, 1771, 1704, 1666, 1433, 1406, 1341, 1270, 1130, 1021, 956;

HRMS (ESI): calcd for $C_{13}H_{14}NO_2$ $[M+H]^+$ 216.1025, found 216.1025; calcd for $C_{13}H_{13}NNaO_2$ $[M+Na]^+$ 238.0844, found 238.0850.

3-Methylene-1-(2-(3,4-dimethoxyphenyl)ethyl)pyrrolidine-2,5-dione (9b)



Isolated by column chromatography with hexane/ethyl acetate, yield 10 %;

M.p. 123-126 ºC; yellow solid;

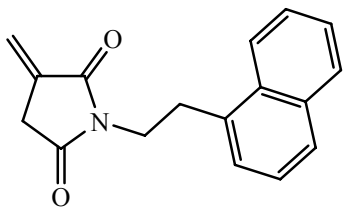
^1H (400.1 MHz, $CDCl_3$) δ_H: 6.80-6.76 (m, 3H), 6.35 (t, 1H, CH_2(double bond), 2.4 Hz), 5.63 (t, 1H, CH_2(double bond), 1.9 Hz), 3.89 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.83 (dd, 2H, CH_2, 7.6 Hz, 8.7 Hz), 3.29 (t, 2H, CH_2 in the ring, 2.1 Hz), 2.89 (t, 2H, CH_2, 7.6 Hz);

^{13}C (100.6 MHz, $CDCl_3$) δ_C: 173.61 (CO), 169.34 (CO), 148.92 (C_{Ar}), 147.78 (C_{Ar}), 133.17 (C_{Ar}), 130.21 (C_{quat}), 120.85 (CH_{Ar}), 120.54 (CH_2 at double bond), 111.94 (CH_{Ar}), 111.27 (CH_{Ar}), 55.88 (2*OMe), 40.07 (CH_2), 33.71 (CH_2), 33.15 (CH_2);

IR (KBr, cm^{-1}): 3459, 3130, 3085, 2995, 2940, 2923, 2836, 1773, 1708, 1662, 1590, 1516, 1434, 1402, 1343, 1274, 1232, 1145, 1026, 973;

HRMS (ESI): calcd for $C_{15}H_{18}NO_4$ $[M+H]^+$ 276.1236, found 276.1239; calcd for $C_{15}H_{17}NNaO_4$ $[M+Na]^+$ 298.1055, found 298.1061.

3-Methylene-1-(2-(naphth-1-yl)ethyl)pyrrolidine-2,5-dione (9c)



Isolated by column chromatography with hexane/ethyl acetate, yield 10 %;

M.p. 75-81 ºC; light yellow solid;

^1H (400.1 MHz, $CDCl_3$) δ_H: 8.28 (d, $1H_{Ar}$, 8.4 Hz), 7.87 (d, $1H_{Ar}$, 8.2 Hz), 7.79 (dd, $1H_{Ar}$, 6.3 Hz, 3.0 Hz), 7.63-7.59 (m, $1H_{Ar}$), 7.52 (t, $1H_{Ar}$, 7.2 Hz), 7.44-7.41 (m, $2H_{Ar}$), 6.39 (t, 1H,

CH_2(double bond), 2.4 Hz), 5.65 (t, 1H, CH_2(double bond), 1.9 Hz), 3.98-3.94 (m, 2H, CH_2), 3.41-3.37 (m, 2H, CH_2), 3.32 (t, 2H, CH_2, 2.1 Hz);

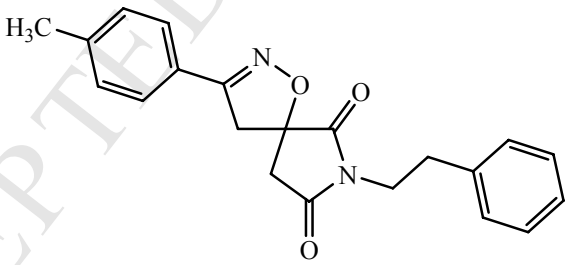
^{13}C (100.6 MHz, $CDCl_3$) δ_C: 173.62 (CO), 169.41 (CO), 134.00 (C_{Ar}), 133.88 (C_{Ar}), 133.27 (C_{Ar}), 131.99 (C_{quat}), 128.81 (CH_{Ar}), 127.65 (CH_{Ar}), 127.06 (CH_{Ar}), 126.43 (CH_{Ar}), 125.75 (CH_{Ar}), 125.52 (CH_{Ar}), 123.64 (CH_{Ar}), 120.60 (CH_2 at double bond), 39.60 (CH_2), 33.80 (CH_2), 31.20 (CH_2);

HRMS (ESI): calcd for $C_{17}H_{15}NNaO_2$ $[M+Na]^+$ 288.1000, found 288.0996.

General procedure for the synthesis of 7-(2-arylethyl)-1-oxa-2,7-diazaspiro[4.4]non-2-ene-6,8-diones

To vigorously stirring solution of 1.5 equiv of corresponding chloroxime and 1 equiv of 3-methylene-1-(2-arylethyl)pyrrolidine-2,5-dione (**9**) in dry benzene was slowly added 1.5 equiv of triethylamine in benzene. Formed mixture then stirred at room temperature until the reaction was completed (TLC-control). After the reaction was completed, the water was added and the product was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$. After this, the solvent was evaporated and the residue was recrystallized with ethanol.

7-Phenethyl-3-p-tolyl-1-oxa-2,7-diazaspiro[4.4]non-2-ene-6,8-dione (11a)



M.p. 193-196 ºC; white solid, yield 86 %;

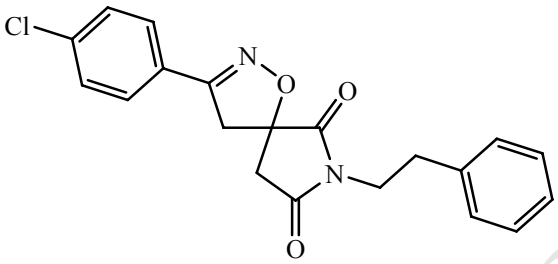
^1H (400.1 MHz, $CDCl_3$) δ_H: 7.55 (d, 2H, 8.1 Hz), 7.33 (d, 2H, 7.5 Hz), 7.27-7. 24 (m, 5H), 3.91-3.80 (m, 3H, CH_2 + CH from CH_2), 3.32 (d, 1H from CH_2, 16.8 Hz), 3.16 (d, 1H from CH_2, 18.5 Hz), 2.98 (t, 2H, CH_2, 7.5 Hz), 2.85 (d, 1H from CH_2, 18.5 Hz), 2.42 (s, 3H, CH_3);

^{13}C (100.6 MHz, $CDCl_3$) δ_C: 174.91 (CO), 172.78 (CO), 155.64 (C=N), 141.19 (C_{Ar}), 137.37 (C_{Ar}), 129.60 ($2CH_{Ar}$), 128.95 ($2CH_{Ar}$), 128.63 ($2CH_{Ar}$), 126.89 ($2CH_{Ar}$), 126.87 (CH_{Ar}), 125.35 (C_{Ar}), 83.75 (C_{quat}), 43.72 (CH_2), 42.58 (CH_2), 40.37 (CH_2), 33.31 (CH_2), 21.51 (CH_3 from *Tol*);

IR (KBr, cm^{-1}): 3483, 3063, 3026, 2995, 2949, 2868, 1787, 1708, 1610, 1455, 1406, 1356, 1253, 1139, 995;

HRMS (ESI): calcd for $C_{21}H_{21}N_2O_3$ $[M+H]^+$ 349.1552, found 349.1548, calcd for $C_{21}H_{20}N_2NaO_3$ $[M+Na]^+$ 371.1372, found 371.1366.

3-(4-Chlorophenyl)-7-phenethyl-1-oxa-2,7-diazaspiro[4.4]non-2-ene-6,8-dione (11b)



M.p. 189-192 ºC; white solid, yield 42 %;

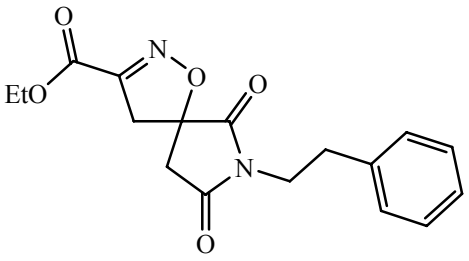
^{1}H (400.1 MHz, $CDCl_3$) δ_H: 7.60 (d, 2H, 8.6 Hz), 7.43 (d, 2H, 8.6 Hz), 7.42-7.23 (m, 5H), 3.93-3.74 (m, 3H, CH_2 + CH from CH_2), 3.31 (d, 1H from CH_2, 17.0 Hz), 3.17 (d, 1H from CH_2, 18.5 Hz), 2.98 (t, 2H, CH_2, 7.5 Hz), 2.86 (d, 1H from CH_2, 18.5 Hz);

^{13}C (100.6 MHz, $CDCl_3$) δ_C: 174.65 (CO), 172.55 (CO), 154.78 (C=N), 137.31 (C_{Ar}), 136.88 (C_{Ar}), 129.23 ($2CH_{Ar}$), 128.94 ($2CH_{Ar}$), 128.64 ($2CH_{Ar}$), 128.15 ($2CH_{Ar}$), 126.89 (CH_{Ar}), 126.71 (C_{Ar}), 84.15 (C_{quat}), 43.29 (CH_2), 42.40 (CH_2), 40.41 (CH_2), 33.28 (CH_2);

IR (KBr, cm^{-1}): 3474, 3084, 3054, 3026, 2988, 2947, 1782, 1712, 1598, 1492, 1406, 1364, 1251, 1142, 1094, 994;

HRMS (ESI): calcd for $C_{20}H_{17}ClN_2NaO_3$ $[M+Na]^+$ 391.0825, found 391.0831.

6,8-Dioxo-7-phenethyl-1-oxa-2,7-diazaspiro[4.4]non-2-ene-3-carboxylic acid ethyl ester (11c)



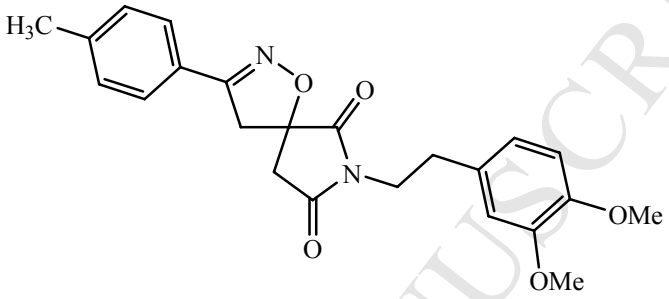
M.p. 83-85 ºC; colorless solid, yield 25 %;

^{1}H (400.1 MHz, $CDCl_3$) δ_H: 7.34-7.20 (m, 5H), 4.40 (q, 2H, CH_2 from CO_2Et, 7.2 Hz), 3.87-3.82 (m, 2H, CH_2), 3.68 (d, 1H from CH_2, 18.0 Hz), 3.22 (d, 1H from CH_2, 18.0 Hz), 3.12 (d, 1H from CH_2, 18.6 Hz), 2.96 (t, 2H, CH_2, 7.5 Hz), 2.82 (d, 1H from CH_2, 18.6 Hz), 1.40 (t, 3H, CH_3 from CO_2Et, 7.2 Hz);

^{13}C (100.6 MHz, $CDCl_3$) δ_C: 173.60 (CO), 172.04 (CO), 159.46 ($\underline{CO_2}$Et), 150.62 (C=N), 137.13 (C_{Ar}), 128.89 ($2CH_{Ar}$), 128.65 ($2CH_{Ar}$), 126.96 (CH_{Ar}), 85.90 (C_{quat}), 62.62 (CH_2), 42.09 (CH_2), 42.02 (CH_2), 40.51 (CH_2), 33.20 (CH_2), 14.09 (CH_3 from CO_2Et);

HRMS (ESI): calcd for $C_{17}H_{18}N_2NaO_5$ $[M+Na]^+$ 353.1113, found 353.1107.

7-[2-(3,4-Dimethoxyphenyl)ethyl]-3-p-tolyl-1-oxa-2,7-diazaspiro[4.4]non-2-ene-6,8-dione (11d)



M.p. 168-169 ºC; white solid, yield 63 %;

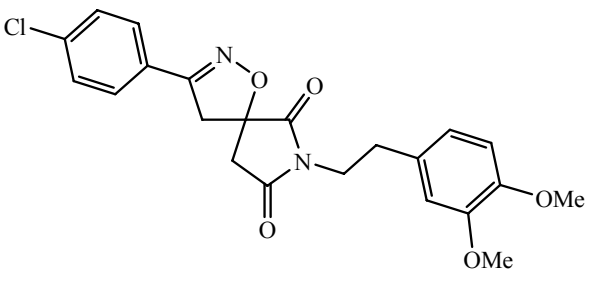
^{1}H (400.1 MHz, $CDCl_3$) δ_H: 7.55 (d, 2H, 7.9 Hz), 7.25 (d, 2H, 7.9 Hz), 6.85-6.76 (m, 3H), 3.92 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.86-3.82 (m, 3H, CH_2 + CH from CH_2), 3.32 (d, 1H from CH_2, 16.8 Hz), 3.16 (d, 1H from CH_2, 18.5 Hz), 2.93 (t, 2H, CH_2, 7.4 Hz), 2.86 (d, 1H from CH_2, 18.5 Hz), 2.42 (s, 3H, CH_3 from *Tol*);

^{13}C (100.6 MHz, $CDCl_3$) δ_C: 174.98 (CO), 172.79 (CO), 155.67 (C=N), 149.02 (C_{Ar}), 147.96 (C_{Ar}), 141.20 (C_{Ar}), 129.84 (C_{Ar}), 129.60 ($2CH_{Ar}$), 126.89 ($2CH_{Ar}$), 125.34 (C_{Ar}), 120.98 (CH_{Ar}), 112.12 (CH_{Ar}), 111.34 (CH_{Ar}), 83.75 (C_{quat}), 55.96 (OMe), 55.91 (OMe), 43.67 (CH_2), 42.57 (CH_2), 40.45 (CH_2), 32.87 (CH_2), 21.50 (CH_3 from *Tol*);

IR (KBr, cm^{-1}): 3482, 3064, 3033, 3001, 2962, 2941, 2923, 2843, 1789, 1715, 1590, 1519, 1408, 1339, 1272, 1236, 1141, 1029, 921;

HRMS (ESI): calcd for $C_{23}H_{24}N_2NaO_5$ $[M+Na]^+$ 431.1583, found 431.1587.

3-(4-Chlorophenyl)-7-[2-(3,4-dimethoxyphenyl)ethyl]-1-oxa-2,7-diaza-spiro[4.4]non-2-ene-6,8-dione (11e)



M.p. 155-158 ºC; white solid, yield 24 %;

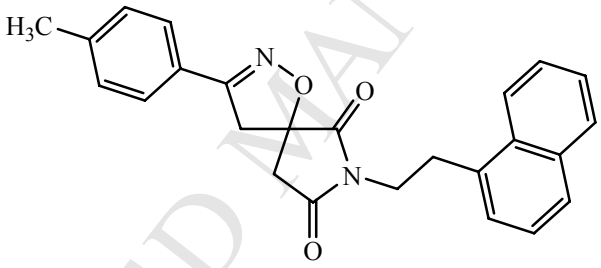
^{1}H (400.1 MHz, $CDCl_3$) δ_H: 7.60 (d, 2H, 8.6 Hz), 7.43 (d, 2H, 8.6 Hz), 6.84-6.75 (m, 3H), 3.91 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.90-3.79 (m, 3H, CH_2 + CH from CH_2), 3.31 (d, 1H from CH_2, 16.8 Hz), 3.17 (d, 1H from CH_2, 18.5 Hz), 2.93 (t, 2H, CH_2, 7.6 Hz), 2.86 (d, 1H from CH_2, 18.5 Hz);

^{13}C (100.6 MHz, $CDCl_3$) δ_C: 174.73 (CO), 172.55 (CO), 154.80 (C=N), 149.02 (C_{Ar}), 147.98 (C_{Ar}), 136.90 (C_{Ar}), 129.76 (C_{Ar}), 129.24 ($2CH_{Ar}$), 128.15 ($2CH_{Ar}$), 126.68 (C_{Ar}), 121.00 (CH_{Ar}), 112.14 (CH_{Ar}), 111.35 (CH_{Ar}), 84.15 (C_{quat}), 55.97 (OMe), 55.92 (OMe), 43.26 (CH_2), 42.40 (CH_2), 40.48 (CH_2), 32.84 (CH_2);

IR (KBr, cm^{-1}): 3482, 3062, 2994, 2958, 2922, 2850, 1789, 1715, 1596, 1519, 1406, 1339, 1272, 1237, 1141, 1029, 923.

HRMS (ESI): calcd for $C_{22}H_{21}ClN_2NaO_5$ $[M+Na]^+$ 451.1037, found 451.1042.

7-(2-Naphthalen-1-yl-ethyl)-3-p-tolyl-1-oxa-2,7-diazaspiro[4.4]non-2-ene-6,8-dione (11f)



M.p. 183-185 ºC (CH_2Cl_2/MeOH); white solid, yield 85 %;

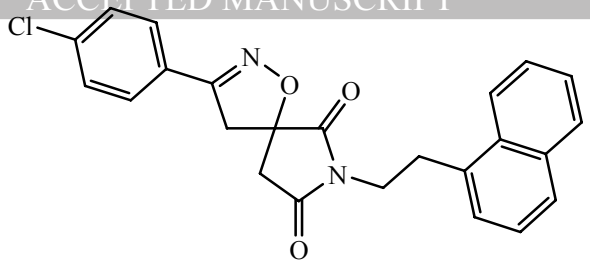
^{1}H (400.1 MHz, $CDCl_3$) δ_H: 8.20 (d, 1H, 8.0 Hz), 7.90 (d, 1H, 8.0 Hz), 7.80 (d, 1H, 8.0 Hz), 7.62-7.42 (m, 6H), 7.26 (d, 2H, 6.0 Hz), 3.98 (t, 2H, CH_2, 8.0 Hz), 3.70 (d, 1H from CH_2, 17.0 Hz), 3.46-3.40 (m, 2H, CH_2), 3.22 (d, 1H from CH_2, 17.0 Hz), 3.17 (dd, 1H from CH_2, 18.5 Hz), 2.83 (d, 1H from CH_2, 18.5 Hz), 2.42 (s, 3H, CH_3);

^{13}C (100.6 MHz, $CDCl_3$) δ_C: 175.00 (CO), 172.91 (CO), 155.63 (C=N), 141.19 (C_{Ar}), 133.86 (C_{Ar}), 133.66 (C_{Ar}), 132.03 (C_{Ar}), 129.60 ($2CH_{Ar}$), 128.90 (CH_{Ar}), 127.76 (CH_{Ar}), 127.35 (CH_{Ar}), 126.88 ($2CH_{Ar}$), 126.45 (CH_{Ar}), 125.76 (CH_{Ar}), 125.61 (CH_{Ar}), 125.32 (C_{Ar}), 123.49 (CH_{Ar}), 83.72 (C_{quat}), 43.72 (CH_2), 42.67 (CH_2), 40.12 (CH_2), 30.69 (CH_2), 21.51 (CH_3 from *Tol*);

IR (KBr, cm^{-1}): 3473, 3056, 2985, 2948, 2922, 2851, 1783, 1707, 1597, 1509, 1437, 1398, 1354, 1247, 1166, 1137, 1051, 990;

HRMS (ESI): calcd for $C_{25}H_{23}N_2O_3$ $[M+H]^+$ 399.1709, found 399.1710.

3-(4-Chlorophenyl)-7-(2-naphthalen-1-yl-ethyl)-1-oxa-2,7-diaza-spiro[4.4]non-2-ene-6,8-dione (11g)



M.p. 173-176 ºC (EtOH); white solid, yield 68 %;

^{1}H (400.1 MHz, $CDCl_3$) δ_H: 8.19 (d, 1H, 8.4 Hz), 7.90 (d, 1H, 7.9 Hz), 7.80 (d, 1H, 7.8 Hz), 7.62-7.41 (m, 8H), 3.98 (t, 2H, CH_2, 7.7 Hz), 3.65 (d, 1H from CH_2, 16.9 Hz), 3.46-3.38 (m, 2H, CH_2), 3.19 (d, 1H from CH_2, 16.9 Hz), 3.17 (dd, 1H from CH_2, 18.5 Hz), 2.84 (d, 1H from CH_2, 18.5 Hz);

^{13}C (100.6 MHz, $CDCl_3$) δ_C: 174.75 (CO), 172.71 (CO), 154.78 (C=N), 136.88 (C_{Ar}), 133.86 (C_{Ar}), 133.61 (C_{Ar}), 132.03 (C_{Ar}), 129.23 ($2CH_{Ar}$), 128.92 (CH_{Ar}), 128.14 ($2CH_{Ar}$), 127.78 (CH_{Ar}), 127.38 (CH_{Ar}), 126.67 (C_{Ar}), 126.45 (CH_{Ar}), 125.77 (CH_{Ar}), 125.63 (CH_{Ar}), 123.45 (CH_{Ar}), 84.12 (C_{quat}), 43.29 (CH_2), 42.48 (CH_2), 40.17 (CH_2), 30.64 (CH_2);

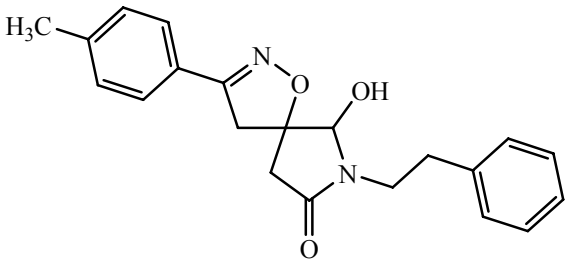
IR (KBr, cm^{-1}): 3479, 3057, 2987, 2950, 2922, 2851, 1786, 1709, 1596, 1493, 1402, 1351, 1247, 1138, 1095, 991;

HRMS (ESI): calcd for $C_{24}H_{19}ClN_2NaO_3$ $[M+Na]^+$ 441.0982, found 441.0987.

General procedure for the reduction of 7-(2-arylethyl)-1-oxa-2,7-diaza-spiro[4.4]non-2-ene-6,8-diones

To vigorously stirred solution of dihydroisoxazoles **11** in CH_2Cl_2/EtOH 3:1 at -78 ºC was added 1.5 equiv of sodium borohydride in ethanol (final ratio CH_2Cl_2/EtOH must be 1:1). Then the reaction flask was left in refrigerator at −20 ºC until the end of reaction (monitored by TLC). After completion of the reduction, the reaction mixture was treated with saturated NH_4Cl solution, extracted with CH_2Cl_2, dried over anhyd. Na_2SO_4, solvent was removed by concentration.

6-Hydroxy-7-phenethyl-3-p-tolyl-1-oxa-2,7-diazaspiro[4.4]non-2-en-8-one (12a)



Was obtained as 5:3 mixture of two diastereomers (unseparable by chromatography), 1H and 13C NMR signals are given for major one.

M.p. 177-182 ºC; white solid, yield 96 %;

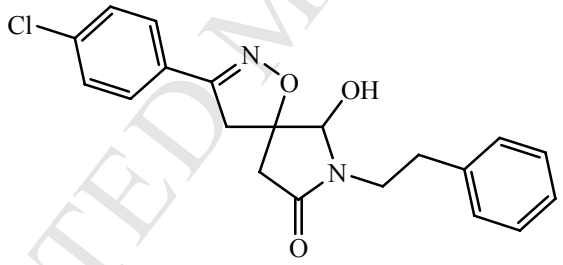
^{1}H (400.1 MHz, $CDCl_3$) δ_H: 7.49 (d, 2H, 8.1 Hz), 7.35-7. 21 (m, 7H), 4.68 (s, 1H, CH at OH), 3.87-3.50 (m, 2H, CH_2), 3.30 (d, 1H from CH_2, 17.1 Hz), 3.19 (d, 1H from CH_2, 17.1 Hz), 3.02-2.91 (m, 3H, CH_2+CH from CH_2), 2.80 (s, 1H, OH), 2.56 (d, 1H from CH_2, 18.5 Hz), 2.41 (s, 3H, CH_3);

^{13}C (100.6 MHz, $CDCl_3$) δ_C: 170.27 (CO), 157.46 (C=N), 141.22 (C_{Ar}), 138.78 (C_{Ar}), 129.52 ($2CH_{Ar}$), 129.45 ($2CH_{Ar}$), 128.54 ($2CH_{Ar}$), 126.70 ($2CH_{Ar}$), 126.65 (CH_{Ar}), 125.61 (C_{Ar}), 87.80 (CH at OH), 85.21 (C_{quat}), 43.46 (CH_2), 41.43 (CH_2), 41.34 (CH_2), 33.78 (CH_2), 21.35 (CH_3 from *Tol*);

IR (KBr, cm^{-1}): 3136, 3051, 2923, 2852, 1710, 1653, 1468, 1403, 1339, 1158, 1090, 990;

HRMS (ESI): calcd for $C_{21}H_{23}N_2O_3$ $[M+H]^+$ 351.1709, found 351.1712, calcd for $C_{21}H_{22}N_2NaO_3$ $[M+Na]^+$ 373.1528, found 373.1531.

3-(4-Chlorophenyl)-6-hydroxy-7-phenethyl-1-oxa-2,7-diazaspiro[4.4]non-2-en-8-one (12b)



M.p. 155-160 ºC (darkens after 144 ºC); light yellow solid, yield 92 %;

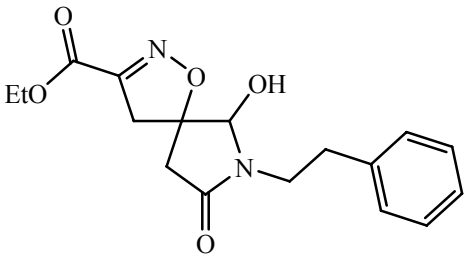
^{1}H (400.1 MHz, $CDCl_3$) δ_H: 7.53 (d, 2H, 8.6 Hz), 7.41 (d, 2H, 8.6 Hz), 7.33-7. 25 (m, 5H), 4.67 (s, 1H, CH at OH), 3.84-3.77 (m, 1H, from CH_2), 3.57-3.50 (m, 1H, from CH_2), 3.28 (d, 1H from CH_2, 17.1 Hz), 3.16 (d, 1H from CH_2, 17.2 Hz), 3.11-2.89 (m, 3H, CH_2+CH from CH_2), 2.81 (s, 1H, OH), 2.57 (d, 1H from CH_2, 17.2 Hz);

^{13}C (100.6 MHz, $CDCl_3$) δ_C: 170.13 (CO), 156.53 (C=N), 138.75 (C_{Ar}), 136.98 (C_{Ar}), 129.16 ($2CH_{Ar}$), 128.87 ($2CH_{Ar}$), 128.56 ($2CH_{Ar}$), 127.95 ($2CH_{Ar}$), 126.95 (C_{Ar}), 126.56 (CH_{Ar}), 87.82 (CH at OH), 85.79 (C_{quat}), 43.09 (CH_2), 41.40 (CH_2), 41.30 (CH_2), 33.74 (CH_2);

IR (KBr, cm^{-1}): 3207, 3063, 3026, 2926, 2853, 1680, 1596, 1454, 1405, 1363, 1281, 1136, 1092, 1014, 926;

HRMS (ESI): calcd for $C_{20}H_{20}ClN_2O_3$ $[M+H]^+$ 371.1162, found 371.1166, calcd for $C_{20}H_{19}ClN_2NaO_3$ $[M+Na]^+$ 393.0982, found 393.0987.

6-Hydroxy-8-oxo-7-phenethyl-1-oxa-2,7-diaza-spiro[4.4]non-2-ene-3-carboxylic acid ethyl ester (12c)



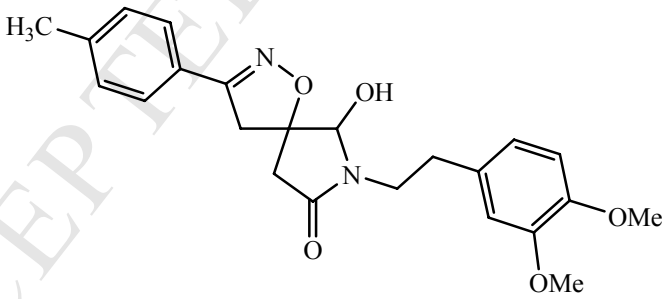
M.p. 100-104 ºC; white solid, yield 100 %;

^{1}H (400.1 MHz, $CDCl_3$) δ_H: 7.33-7.22 (m, 5H), 4.63 (s, 1H, CH), 4.35 (q, 2H, CH_2 from CO_2Et, 7.2 Hz), 3.53-3.45 (m, 2H, CH_2), 3.20 (d, 1H from CH_2, 18.5 Hz), 3.13 (d, 1H from CH_2, 18.5 Hz), 2.97-2.89 (m, 3H, 1H from CH_2 + CH_2), 2.54 (d, 1H from CH_2, 17.5 Hz), 1.87 (br s, 1H, OH), 1.37 (t, 3H, CH_3 from CO_2Et, 7.2 Hz);

^{13}C (100.6 MHz, $CDCl_3$) δ_C: 169.64 (CO), 159.60 ($\underline{CO_2}Et$), 152.33 (C=N), 138.60 (C_{Ar}), 128.88 ($2CH_{Ar}$), 128.65 ($2CH_{Ar}$), 126.71 (CH_{Ar}), 88.33 (C_{quat}), 87.85 (CH at OH), 62.54 (CH_2), 41.51 (2*CH_2), 41.58 (CH_2), 33.73 (CH_2), 14.06 (CH_3 from CO_2Et);

HRMS (ESI): calcd for $C_{17}H_{20}N_2NaO_5$ $[M+Na]^+$ 355.1270, found 355.1265.

7-[2-(3,4-Dimethoxy-phenyl)ethyl]-6-hydroxy-3-p-tolyl-1-oxa-2,7-diaza-spiro[4.4]non-2-en-8-one (12d)



M.p. 205-208 ºC; white solid, yield 95 %;

^{1}H (400.1 MHz, acetone-d_6) δ_H: 7.42 (d, 2H, 7.7 Hz), 7.16 (d, 2H, 7.7 Hz), 6.77-6.71 (m, 3H), 4.70 (s, 1H, CH at OH), 3.81 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.83-3.72 (m, 1H from CH_2), 3.43-3.38 (m, 1H from CH_2), 3.26 (d, 1H from CH_2, 17.2 Hz), 3.13 (d, 1H from CH_2, 17.2 Hz), 2.94-2.76 (m, 3H, CH_2+CH from CH_2), 2.52 (d, 1H from CH_2, 16.9 Hz), 2.46 (br s, 1H, OH), 2.32 (s, 3H, CH_3);

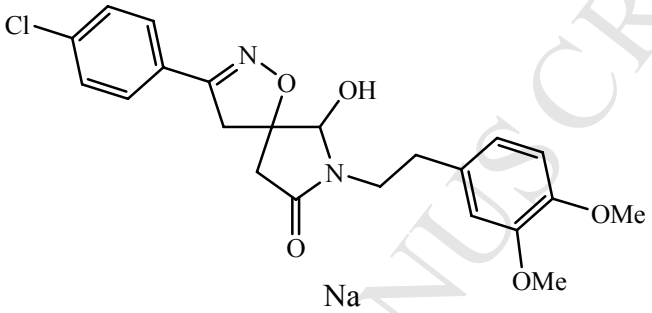
^{13}C (100.6 MHz, acetone-d_6) δ_C: 170.56 (CO), 157.18 (C=N), 148.95 (C_{Ar}), 147.64 (C_{Ar}), 140.86 (C_{Ar}), 131.28 (C_{Ar}), 129.42 ($2CH_{Ar}$), 126.57 ($2CH_{Ar}$), 125.79 (C_{Ar}), 120.74 (CH_{Ar}), 112.04

(CH_{Ar}), 111.28 (CH_{Ar}), 87.62 (CH at OH), 85.38 (C_{quat}), 55.78 (OMe), 55.75 (OMe), 43.36 (CH_2), 41.19 (CH_2), 41.13 (CH_2), 33.21 (CH_2), 21.28 (CH_3 from *Tol*);

IR (KBr, cm^{-1}): 3413, 3370, 3141, 3036, 3001, 2959, 2922, 2840, 1687, 1590, 1518, 1454, 1411, 1336, 1267, 1235, 1157, 1138, 1028, 924;

HRMS (ESI): calcd for $C_{23}H_{27}N_2O_5$ $[M+H]^+$ 411.1920, found 411.1923, calcd for $C_{23}H_{26}N_2NaO_5$ $[M+Na]^+$ 433.1739, found 433.1745.

3-(4-Chlorophenyl)-7-[2-(3,4-dimethoxy-phenyl)ethyl]-6-hydroxy-1-oxa-2,7-diaza-spiro[4.4]non-2-en-8-one (12e)



M.p. 181-184 ºC; light beige solid, yield 100 %;

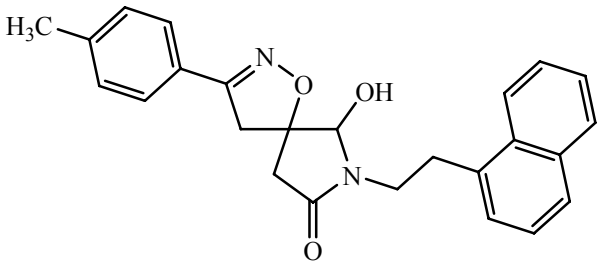
^1H (400.1 MHz, $CDCl_3$) δ_H: 7.54 (d, 2H, 8.5 Hz), 7.42 (d, 2H, 8.5 Hz), 6.84-6.78 (m, 3H), 4.69 (s, 1H, CH at OH), 3.90 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.82-3.75 (m, 1H from CH_2), 3.55-3.48 (m, 1H from CH_2), 3.31 (d, 1H from CH_2, 17.2 Hz), 3.19 (d, 1H from CH_2, 17.2 Hz), 3.02 (d, 1H from CH_2, 17.3 Hz), 2.99-2.82 (m, 2H, CH_2), 2.59 (d, 1H from CH_2, 17.3 Hz), 1.80 (br s, 1H, OH);

^{13}C (100.6 MHz, $CDCl_3$) δ_C: 170.10 (CO), 156.62 (C=N), 149.05 (C_{Ar}), 147.78 (C_{Ar}), 136.98 (C_{Ar}), 131.18 (C_{Ar}), 129.23 ($2CH_{Ar}$), 127.98 ($2CH_{Ar}$), 126.82 (C_{Ar}), 120.78 (CH_{Ar}), 112.13 (CH_{Ar}), 111.36 (CH_{Ar}), 87.73 (CH at OH), 85.84 (C_{quat}), 55.97 (OMe), 55.93 (OMe), 42.87 (CH_2), 41.39 (CH_2), 41.36 (CH_2), 33.28 (CH_2);

IR (KBr, cm^{-1}): 3416, 3065, 3006, 2922, 2850, 1690, 1672, 1592, 1519, 1454, 1410, 1335, 1269, 1239, 1158, 1138, 1029, 923;

HRMS (ESI): calcd for $C_{22}H_{24}ClN_2O_5$ $[M+H]^+$ 431.1374, found 431.1376, calcd for $C_{22}H_{23}ClN_2NaO_5$ $[M+Na]^+$ 453.1193, found 453.1199.

6-Hydroxy-7-[2-(naphthalen-1-yl)ethyl]-3-p-tolyl-1-oxa-2,7-diaza-spiro[4.4]non-2-en-8-one (12f)



M.p. 215-218 ºC; white solid, yield 96 %;

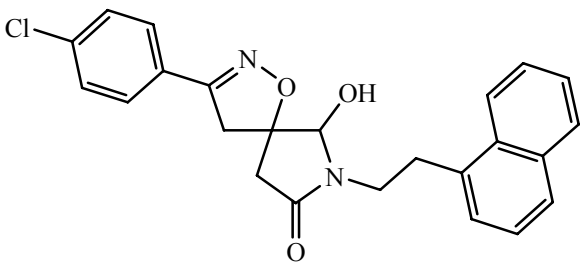
^{1}H (400.1 MHz, $CDCl_3$) δ_H: 8.20 (d, 1H, 8.4 Hz), 7.89 (d, 1H, 7.6 Hz), 7.78 (dd, 1H, 7.4 Hz, 1.7 Hz), 7.59-7.42 (m, 6H), 7.24 (d, 2H, 7.9 Hz), 4.52 (d, 1H, CH at OH, 9.0 Hz), 3.92-3.85 (m, 1H from CH_2), 3.69-3.53 (m, 2H, CH_2), 3.37-3.31 (m, 1H from CH_2), 3.26 (d, 1H, OH, 9.0 Hz), 3.21 (d, 1H from CH_2, 17.4 Hz), 3.01 (“t”, 2H, CH_2, 17.1 Hz), 2.59 (d, 1H from CH_2, 17.4 Hz), 2.41 (s, 3H, CH_3);

^{13}C (100.6 MHz, $CDCl_3$) δ_C: 170.48 (CO), 157.50 (C=N), 141.28 (C_{Ar}), 135.10 (C_{Ar}), 133.84 (C_{Ar}), 132.17 (C_{Ar}), 129.55 ($2CH_{Ar}$), 128.81 (CH_{Ar}), 127.38 (CH_{Ar}), 127.02 (CH_{Ar}), 126.71 ($2CH_{Ar}$), 126.35 (CH_{Ar}), 125.79 (CH_{Ar}), 125.59 (CH_{Ar}), 125.44 (C_{Ar}), 123.78 (CH_{Ar}), 88.22 (CH at OH), 85.09 (C_{quat}), 43.42 (CH_2), 41.64 (CH_2), 41.51 (CH_2), 31.07 (CH_2), 21.50 (CH_3 from *Tol*);

IR (KBr, cm^{-1}): 3219, 3060, 3008, 2937, 2872, 2738, 1705, 1653, 1510, 1460, 1433, 1332, 1283, 1166, 1122, 981;

HRMS (ESI): calcd for $C_{25}H_{25}N_2O_3$ $[M+H]^+$ 401.1865, found 401.1871, calcd for $C_{25}H_{25}N_2O_3$ $C_{25}H_{24}N_2NaO_3$ $[M+Na]^+$ 423.1685, found 423.1691.

3-(4-Chlorophenyl)-6-hydroxy-7-[2-(naphthalen-1-yl)ethyl]-1-oxa-2,7-diaza-spiro[4.4]non-2-en-8-one (12g)



After staying for two weeks in $CDCl_3$ at room temperature hydroxylactam was turned to other stereoisomer (by carbon at OH). All data that not referred specially must be assigned to firstly formed product.

M.p. 181-183 ºC; white solid, yield 98 %;

1st diastereomer: ^{1}H (400.1 MHz, $CDCl_3$) δ_H: 8.19 (d, 1H, 8.5 Hz), 7.88 (d, 1H, 7.5 Hz), 7.77 (dd, 1H, 7.5 Hz, 1.5 Hz), 7.57-7.40 (m, 8H), 4.49 (br s, 1H, CH at OH), 3.93-3.86 (m, 1H from CH_2), 3.70-3.53 (m, 2H, CH_2), 3.36-3.30 (m, 1H from CH_2), 3.18 (d, 1H from CH_2, 17.4 Hz), 3.16-3.13 (m, 1H, OH), 3.03 (d, 1H from CH_2, 17.2 Hz), 2.93 (d, 1H from CH_2, 17.4 Hz), 2.59 (d, 1H from CH_2, 17.2 Hz);

2nd diastereomer: ^{1}H (500.0 MHz, $CDCl_3$+acetone-d_6) δ_H: 8.11 (d, 1H, 8.4 Hz), 7.78 (d, 1H, 7.9 Hz), 7.66 (dd, 1H, 7.1 Hz, 2.0 Hz), 7.48-7.29 (m, 8H), 4.49 (s, 1H, CH at OH), 3.83-3.75 (m, 1H from CH_2+OH), 3.57-3.51 (m, 1H from CH_2), 3.47-3.41 (m, 1H from CH_2), 3.26-3.19 (m, 1H from CH_2), 3.10 (d, 1H from CH_2, 17.2 Hz), 2.91 (d, 1H from CH_2, 17.1 Hz), 2.86 (d, 1H from CH_2, 17.2 Hz), 2.51 (d, 1H from CH_2, 17.1 Hz);

2nd diastereomer: ^{13}C (125.7 MHz, $CDCl_3$+acetone-d_6) δ_C: 170.46 (CO), 156.29 (C=N), 136.52 (C_{Ar}), 135.06 (C_{Ar}), 133.74 (C_{Ar}), 132.09 (C_{Ar}), 128.96 ($2CH_{Ar}$), 128.68 (CH_{Ar}), 127.88 ($2CH_{Ar}$), 127.23 (CH_{Ar}), 127.03 (C_{Ar}), 126.89 (CH_{Ar}), 126.21 (CH_{Ar}), 125.67 (CH_{Ar}), 125.50 (CH_{Ar}), 123.73 (CH_{Ar}), 88.23 (CH at OH), 85.75 (C_{quat}), 43.04 (CH_2), 41.45 (CH_2), 41.31 (CH_2), 30.92 (CH_2);

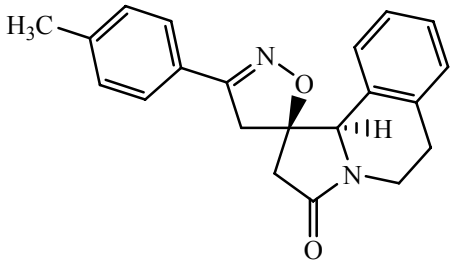
IR (KBr, cm^{-1}): 3316, 3268, 3060, 2980, 2921, 2850, 1681, 1596, 1494, 1422, 1361, 1328, 1278, 1136, 1092, 1013, 925;

HRMS (ESI): calcd for $C_{24}H_{22}ClN_2O_3$ $[M+H]^+$ 421.1319, found 421.1324, calcd for $C_{24}H_{21}ClN_2NaO_3$ $[M+Na]^+$ 443.1138, found 443.1144.

General procedure for the cyclization reactions

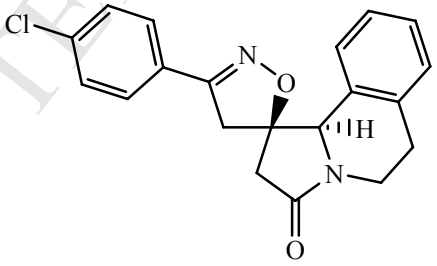
5 Equiv of boron trifluoride diethyl etherate was added to vigorously stirred solution of corresponding hydroxylactams (**12**) in anhyd. dichloromethane (3 ml) under argon. The reaction mixture was stirred in a capped vial at room temperature (TLC-control). After completion of the reaction, water was added carefully to the reaction mixture (6 mL). The aqueous layer was extracted with CH_2Cl_2 (3x5 mL), the organic layers were combined, dried over MgSO4 and evaporated to dryness. The product was recrystallized with Et_2O (for **13a,b,d-g**).

(5*SR*,10b'*SR*)-3-(4-methylphenyl)-6',10b'-dihydro-4*H*,5'*H*-spiro[isoxazole-5,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(2'*H*)-one (13a)



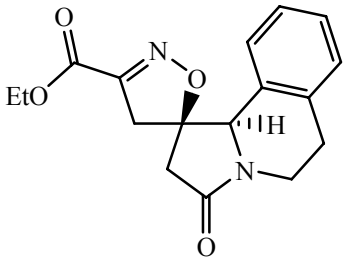
Colorless solid, m.p. 219–222 ºC. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.50 (d, J=8.0 Hz, 2H), 7.24 (d, J=8.0 Hz, 2H), 7.20-7.17 (m, 2H), 7.07-7.03 (m, 1H), 6.97 (d, J=7.8 Hz, 1H), 5.04 (s, 1H, CH), 4.49-4.45 (m, 1H, CH from CH_2), 3.87 (d, J=17.5 Hz, 1H from CH_2,), 3.64 (d, J=17.5 Hz, 1H from CH_2), 3.08-2.91 (m, 4H, isoxazoline CH_2 + 2CH from CH_2), 2.75 (d, J=15.1 Hz, 1H from CH_2), 2.41 (s, 3H, CH_3 from *Tol*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.37 (CO), 155.46 (C=N), 140.71 (C_{Ar}), 135.76 (C_{Ar}), 130.77 (C_{Ar}), 129.67 (CH_{Ar}), 129.56 ($2CH_{Ar}$), 127.49 (CH_{Ar}), 126.55 ($2CH_{Ar}$), 126.28 (CH_{Ar}), 126.22 (C_{Ar}), 124.96 (CH_{Ar}), 89.24 (C_{spiro}), 66.25 (CH), 45.07 (CH_2), 42.63 (CH_2), 37.40 (CH_2), 29.66 (CH_2), 21.49 (CH_3 from *Tol*). HRMS (ESI): calcd for $C_{21}H_{21}N_2O_3$ $[M+H]^+$ 333.1598, found 333.1603; calcd for $C_{21}H_{20}N_2NaO_3$ $[M+Na]^+$ 355.1422, found 355.1417.

(5*SR*,10b'*SR*)-3-(4-chlorophenyl)-6',10b'-dihydro-4*H*,5'*H*-spiro[isoxazole-5,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(2'*H*)-one (13b)



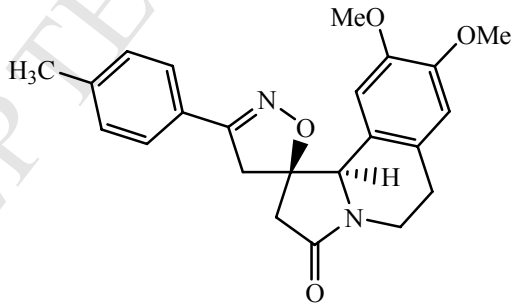
White solid, m.p. 188–190 ºC (decomposition). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.54 (d, J=8.5 Hz, 2H), 7.41 (d, J=8.5 Hz, 2H), 7.21-7.19 (m, 2H), 7.07-7.03 (m, 1H), 6.94 (d, 1H, 7.8 Hz), 5.05 (s, 1H, CH), 4.51-4.46 (m, 1H, CH from CH_2), 3.85 (d, 1H from CH_2, 17.5 Hz), 3.64 (d, 1H from CH_2, 17.5 Hz), 3.09-3.01 (m, 1H, CH from CH_2), 2.98 (s, 2H, isoxazoline CH_2), 2.93 (dd, 1H from CH_2, 2.9 Hz, 12.1 Hz), 2.76 (d, 1H from CH_2, 15.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.16 (CO), 154.57 (C=N), 136.43 (C_{Ar}), 135.89 (C_{Ar}), 130.56 (C_{Ar}), 129.78 (CH_{Ar}), 129.18 ($2CH_{Ar}$), 127.79 ($2CH_{Ar}$), 127.62 (CH_{Ar}), 127.53 (C_{Ar}), 126.28 (CH_{Ar}), 124.79 (CH_{Ar}), 89.85 (C_{spiro}), 66.27 (CH), 44.94 (CH_2), 42.20 (CH_2), 37.42 (CH_2), 29.67 (CH_2). HRMS (ESI): calcd for $C_{20}H_{18}N_2O_2$ $[M+H]^+$ 353.1057, found 353.1062; calcd for $C_{20}H_{17}N_2NaO_2$ $[M+Na]^+$ 375.0876, found 375.0879.

ethyl (5*SR*,10b'*SR*)-3'-oxo-2',3',6',10b'-tetrahydro-4*H*,5'*H*-spiro[isoxazole-5,1'-pyrrolo[2,1-*a*]isoquinoline]-3-carboxylate (13c)



Yellow oil. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.26-7.16 (m, 3H), 7.02 (d, J=7.6 Hz, 1H), 5.03 (s, 1H, CH), 4.48-4.44 (m, 1H, CH from CH_2), 4.40-4.33 (m, 2H, CH_2), 3.80 (d, J=18.6 Hz, 1H from CH_2), 3.46 (d, J=18.6 Hz, 1H from CH_2), 3.05-2.88 (m, 4H, CH_2+CH_2), 2.74 (d, J=14.8 Hz, 1H from CH_2,), 1.40 (t, J=7.1 Hz, 3H, CH_3 from CO_2Et,). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.63 (CO), 160.16 ($\underline{CO_2}$Et), 150.38 (C=N), 135.97 (C_{Ar}), 130.05 (C_{Ar}), 129.85 (CH_{Ar}), 127.77 (CH_{Ar}), 126.60 (CH_{Ar}), 124.58 (CH_{Ar}), 92.33 (C_{spiro}), 65.72 (CH), 62.29 (CH_2), 45.05 (CH_2), 40.60 (CH_2), 37.41 (CH_2), 29.69 (CH_2), 14.06 (CH_3 from CO_2Et). HRMS (ESI): calcd for $C_{17}H_{20}N_2O_4$ $[M+H]^+$ 315.1339, found 315.1344; calcd for $C_{17}H_{18}N_2NaO_4$ $[M+Na]^+$ 337.1164, found 337.1169.

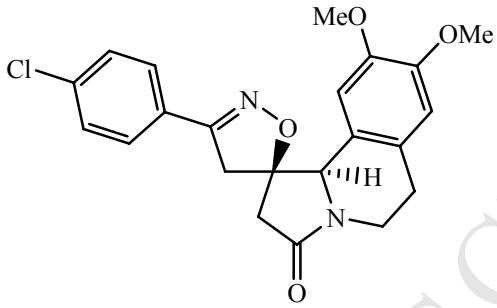
(5*SR*,10b'*SR*)-8',9'-dimethoxy-3-(4-methylphenyl)-6',10b'-dihydro-4*H*,5'*H*-spiro[isoxazole-5,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(2'*H*)-one (13d)



White solid, decomposition at 220 ºC. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.51 (d, J=8.0 Hz, 2H), 7.23 (d, J=8.0 Hz, 2H), 6.65 (s, 1H), 6.35 (s, 1H), 4.92 (s, 1H, CH), 4.50-4.46 (m, 1H, CH from CH_2), 3.86 (s, 3H, OMe), 3.83 (d, J=17.5 Hz, 1H from CH_2), 3.69 (d, J=17.5 Hz, 1H from CH_2,), 3.26 (s, 3H, OMe), 3.05-2.94 (m, 3H, isoxazoline CH_2 + CH from CH_2), 2.92 (dd, J_1=12.2 Hz, J_2=2.6 Hz, 1H from CH_2), 2.66 (d, J=15.1 Hz, 1H from CH_2), 2.40 (s, 3H, CH_3 from *Tol*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.15 (CO), 155.33 (C=N), 148.33 (C_{Ar}), 147.39 (C_{Ar}), 140.86 (C_{Ar}), 129.65 ($2CH_{Ar}$), 128.23 (C_{Ar}), 126.41 ($2CH_{Ar}$), 126.18 (C_{Ar}), 122.16 (C_{Ar}), 112.13 (CH_{Ar}), 107.88 (CH_{Ar}), 89.18 (C_{spiro}), 67.00 (CH), 55.74 (OMe), 55.31 (OMe), 44.37 (CH_2), 42.63 (CH_2), 37.44 (CH_2), 29.10 (CH_2), 21.46 (CH_3 from *Tol*). IR (KBr) ν_{max} 3591, 3431,

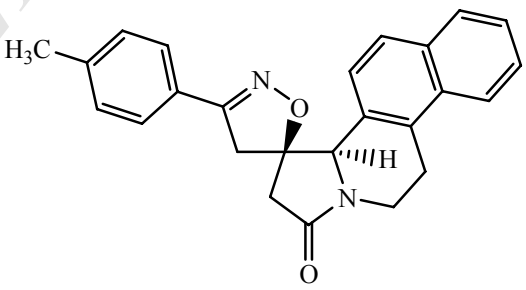
2922, 2846, 2249, 1686, 1609, 1519, 1441, 1422, 1358, 1267, 1229, 1117, 1025, 911. HRMS (ESI): calcd for $C_{23}H_{25}N_2O_4$ $[M+H]^+$ 393.1814, found 393.1812; calcd for $C_{23}H_{24}N_2NaO_4$ $[M+Na]^+$ 415.1634, found 415.1631.

(5*SR*,10b'*SR*)-3-(4-chlorophenyl)-8',9'-dimethoxy-6',10b'-dihydro-4*H*,5'*H*-spiro[isoxazole-5,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(2'*H*)-one (13e)



Light yellow solid, decomposition at 180 ºC. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.55 (d, J=8.5 Hz, 2H), 7.40 (d, J=8.5 Hz, 2H), 6.65 (s, 1H), 6.33 (s, 1H), 4.92 (s, 1H, CH), 4.49-4.45 (m, 1H, CH from CH_2), 3.85 (s, 3H, OMe), 3.81 (d, J=17.4 Hz, 1H from CH_2,), 3.67 (d, J=17.4 Hz, 1H from CH_2), 3.29 (s, 3H, OMe), 3.05-2.94 (m, 3H, isoxazoline CH_2 + CH from CH_2), 2.89 (dd, J_1=12.2 Hz, J_2=2.2 Hz, 1H from CH_2), 2.65 (d, J=14.5 Hz, 1H from CH_2,). IR (KBr) ν_{max} 3367, 3079, 2921, 2851, 2254, 1695, 1603, 1516, 1463, 1432, 1360, 1272, 1234, 1164, 1092, 1038, 913. HRMS (ESI): calcd for $C_{22}H_{22}ClN_2O_4$ $[M+H]^+$ 413.1268, found 413.1263; calcd for $C_{22}H_{21}ClN_2NaO_4$ $[M+Na]^+$ 435.1088, found 435.1086.

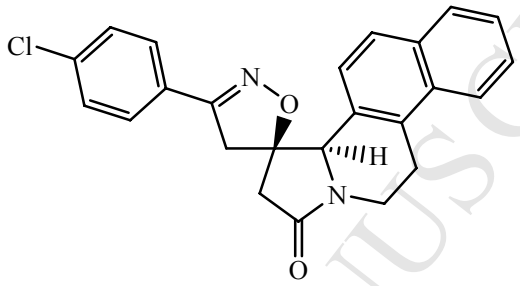
(10*SR*,10a*SR*)-3'-(4-methylphenyl)-5,10a-dihydro-4'*H*,6*H*-spiro[benzo[*f*]pyrrolo[2,1-*a*]isoquinoline-10,5'-isoxazol]-8(9*H*)-one (13f)



Light yellow solid, m.p. 185–189 ºC. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.98 (d, J=8.5 Hz, 1H), 7.78 (d, J=7.9 Hz, 1H), 7.58-7.47 (m, 5H), 7.25 (d, J=8.0 Hz, 2H), 7.05 (d, J=8.5 Hz, 1H), 5.19 (s, 1H, CH), 4.68 (dd, J_1=12.7 Hz, J_2=5.2 Hz, 1H, CH from CH_2), 3.97 (d, J=17.5 Hz, 1H from CH_2), 3.68 (d, J=17.5 Hz, 1H from CH_2,), 3.38 (dd, 1H from CH_2, J_1=15.5 Hz, J_2=2.0 Hz), 3.23-3.15 (m, 1H from CH_2), 3.05-3.00 (m, 3H, isoxazoline CH_2 + CH from CH_2), 2.43 (s, 3H, CH_3 from *Tol*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.91 (CO), 155.42 (C=N), 140.73 (C_{Ar}),

132.59 (C_{Ar}), 132.15 (C_{Ar}), 131.41 (C_{Ar}), 129.57 ($2CH_{Ar}$), 128.48 (CH_{Ar}), 128.00 (C_{Ar}), 126.65 (CH_{Ar}), 126.57 ($3CH_{Ar}$), 126.24 (C_{Ar}), 125.92 (CH_{Ar}), 123.34 (CH_{Ar}), 122.51 (CH_{Ar}), 88.95 (C_{spiro}), 66.67 (CH), 45.42 (CH_2), 43.43 (CH_2), 36.82 (CH_2), 25.23 (CH_2), 21.50 (CH_3 from *Tol*). IR (KBr) ν_{max} 3055, 2921, 2851, 1696, 1612, 1513, 1439, 1389, 1360, 1313, 1231, 1146, 1032, 914. HRMS (ESI): calcd for $C_{25}H_{23}N_2O_2$ $[M+H]^+$ 383.1760, found 383.1762; calcd for $C_{25}H_{22}N_2NaO_2$ $[M+Na]^+$ 405.1579, found 405.1582.

(10*SR*,10a*SR*)-3'-(4-chlorophenyl)-5,10a-dihydro-4'*H*,6*H*-spiro[benzo[*f*]pyrrolo[2,1-*a*]isoquinoline-10,5'-isoxazol]-8(9*H*)-one (13g)



Light yellow solid, m.p. 207–211 ºC (decomposition). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.97 (d, J=8.4 Hz, 1H), 7.78 (d, J=7.8 Hz, 1H), 7.57-7.49 (m, 5H), 7.41 (d, J=8.5 Hz, 2H), 7.00 (d, J=8.5 Hz, 1H), 5.16 (s, 1H, CH), 4.66 (dd, J_1=12.8 Hz, J_2=5.4 Hz, 1H, CH from CH_2), 3.93 (d, J=17.5 Hz, 1H from CH_2), 3.64 (d, J=17.5 Hz, 1H from CH_2), 3.36 (dd, J_1=16.0 Hz, J_2=2.1 Hz, 1H from CH_2), 3.20-3.12 (m, 1H from CH_2), 3.03-2.96 (m, 3H, isoxazoline CH_2 + CH from CH_2). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.77 (CO), 154.65 (C=N), 136.43 (C_{Ar}), 132.57 (C_{Ar}), 132.14 (C_{Ar}), 131.52 (C_{Ar}), 129.18 ($2CH_{Ar}$), 128.49 (CH_{Ar}), 127.85 ($2CH_{Ar}$), 127.81 (C_{Ar}), 127.53 (C_{Ar}), 126.68 (CH_{Ar}), 126.66 (CH_{Ar}), 126.04 (CH_{Ar}), 123.34 (CH_{Ar}), 122.37 (CH_{Ar}), 89.56 (C_{spiro}), 66.57 (CH), 45.26 (CH_2), 42.89 (CH_2), 36.80 (CH_2), 25.25 (CH_2). IR (KBr) ν_{max} 3056, 2920, 2851, 1689, 1597, 1440, 1358, 1313, 1271, 1093, 1013, 922. HRMS (ESI): calcd for $C_{24}H_{20}ClN_2O_2$ $[M+H]^+$ 403.1213, found 403.1219; calcd for $C_{24}H_{19}ClN_2NaO_2$ $[M+Na]^+$ 425.1033, found 425.1039.

Figure 1. ^{1}H NMR spectrum of **9a** ($CDCl_3$, 400MHz)

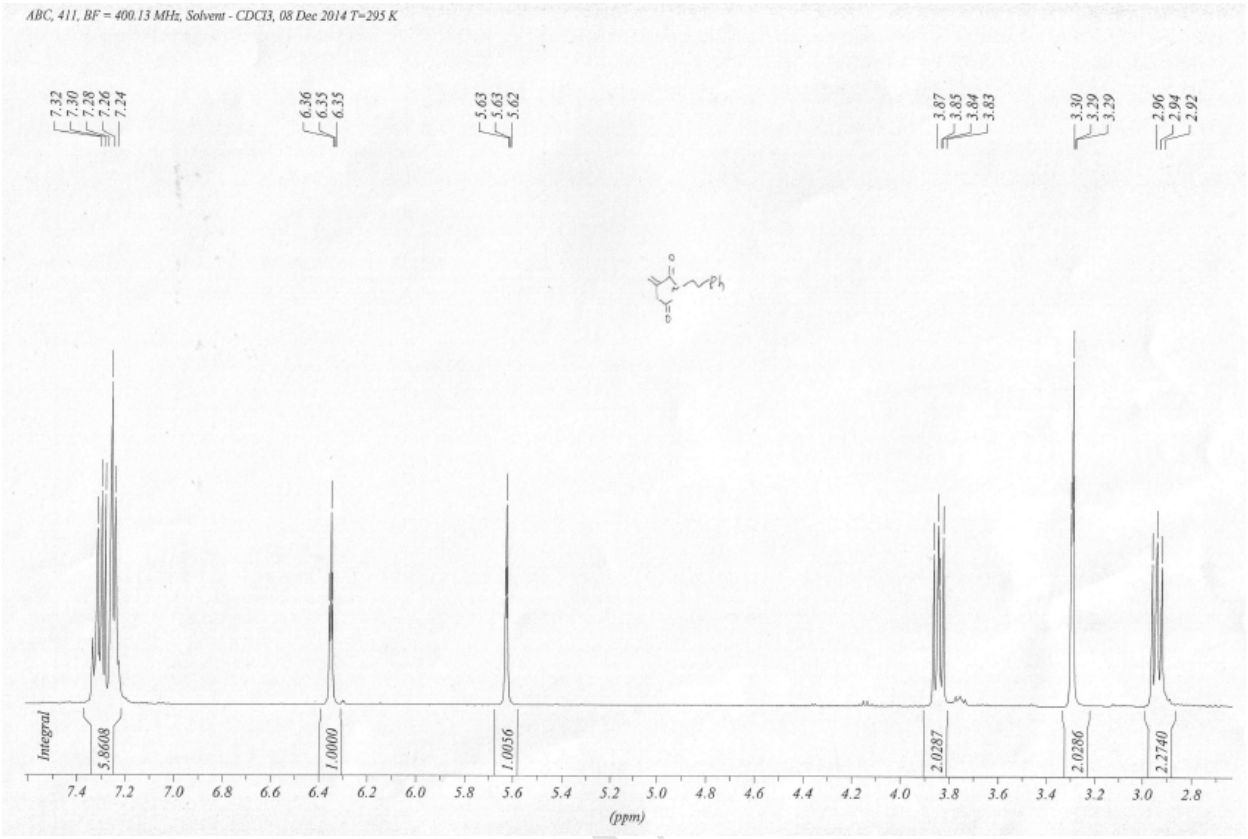


Figure 2. ^{13}C NMR spectrum of **9a** ($CDCl_3$, 100MHz)

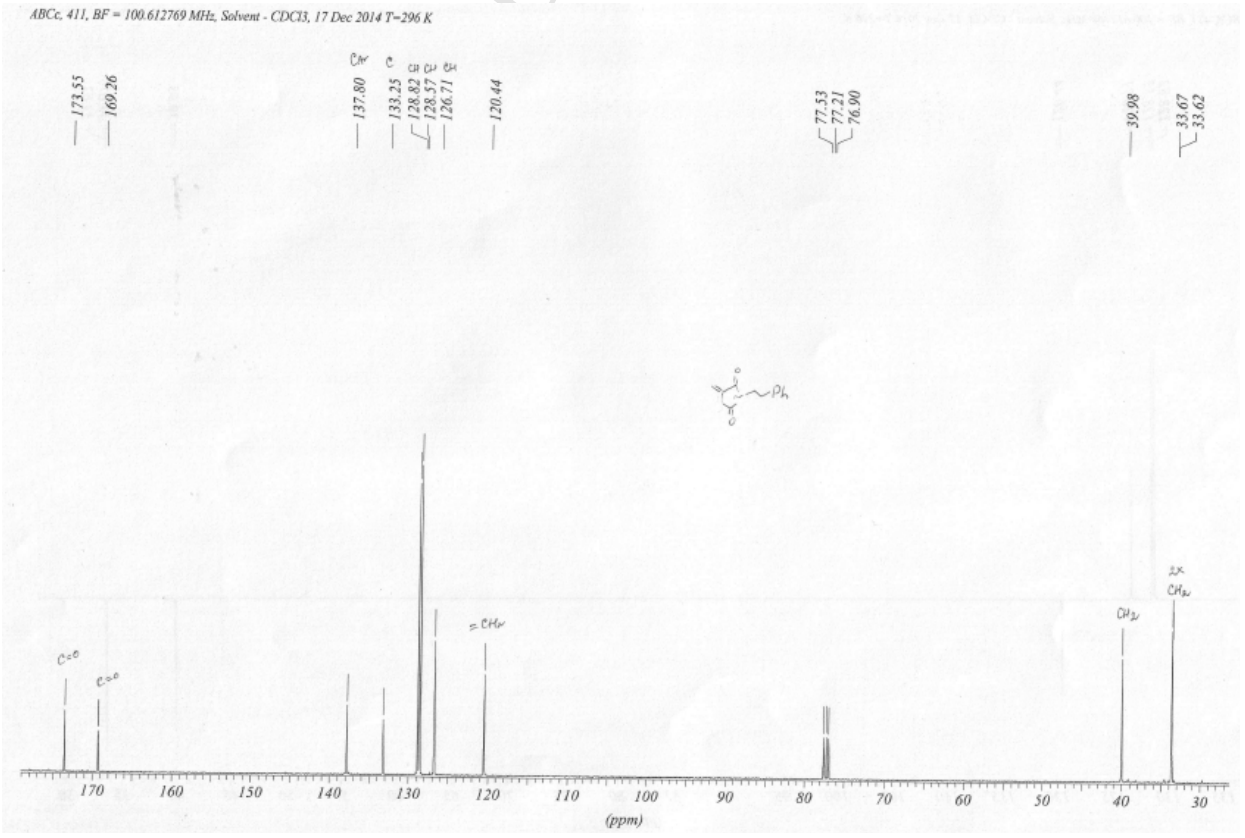


Figure 3. ^{1}H NMR spectrum of **9b** ($CDCl_3$, 400MHz)

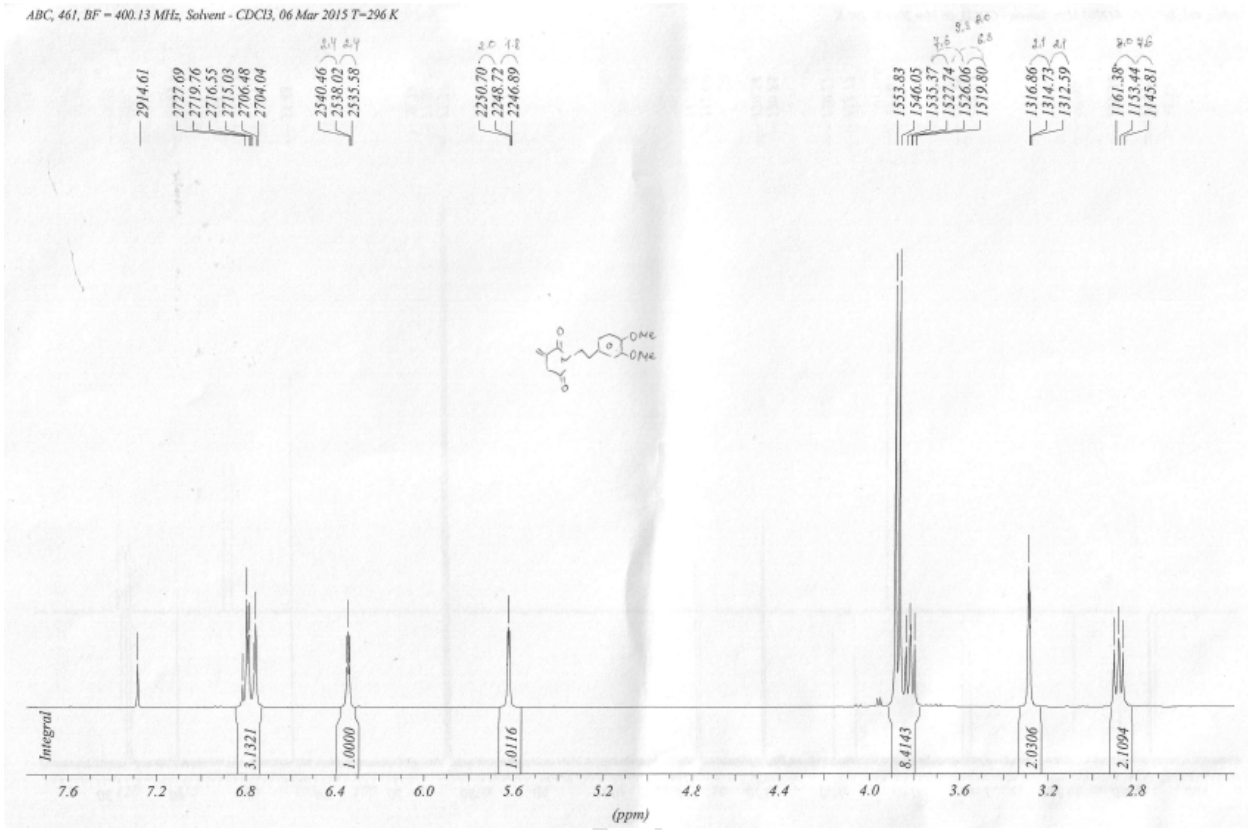


Figure 4. ^{13}C NMR spectrum of **9b** ($CDCl_3$, 100MHz)

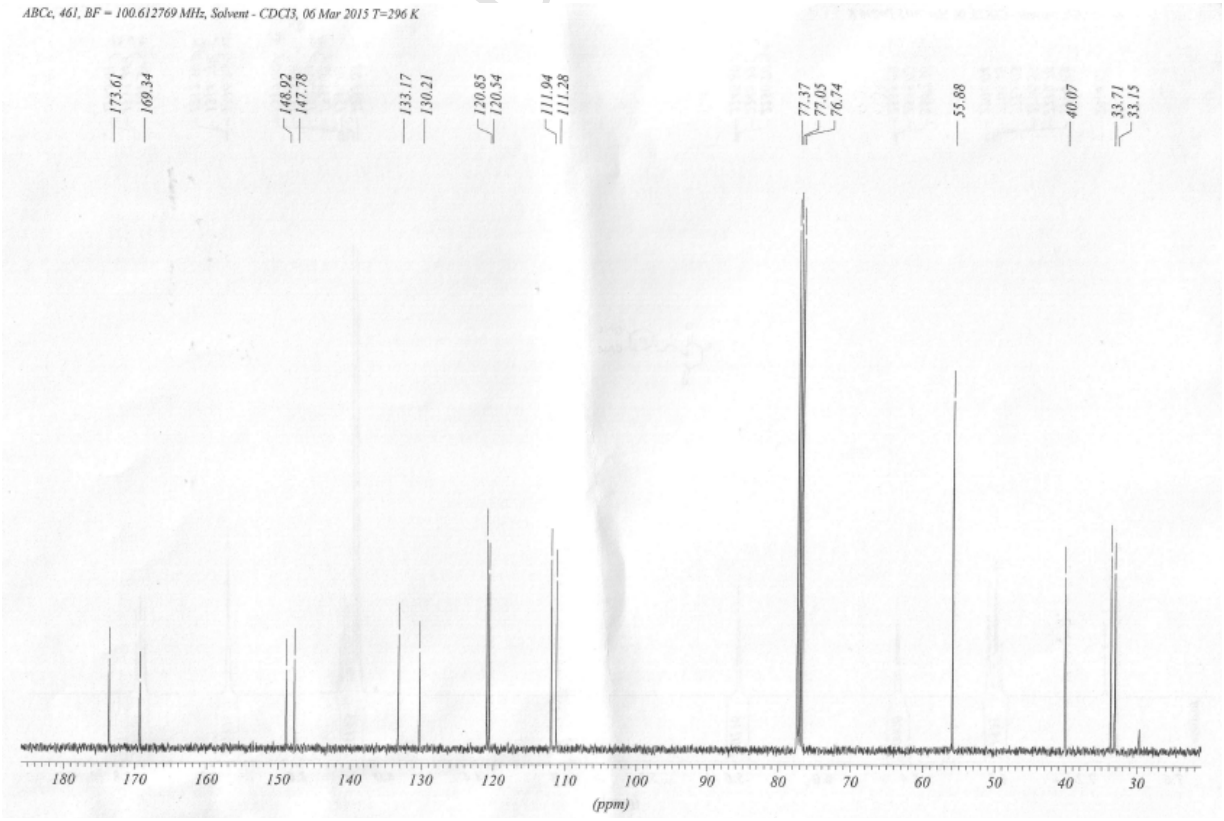


Figure 5. ^{1}H NMR spectrum of **9c** ($CDCl_3$, 400MHz)

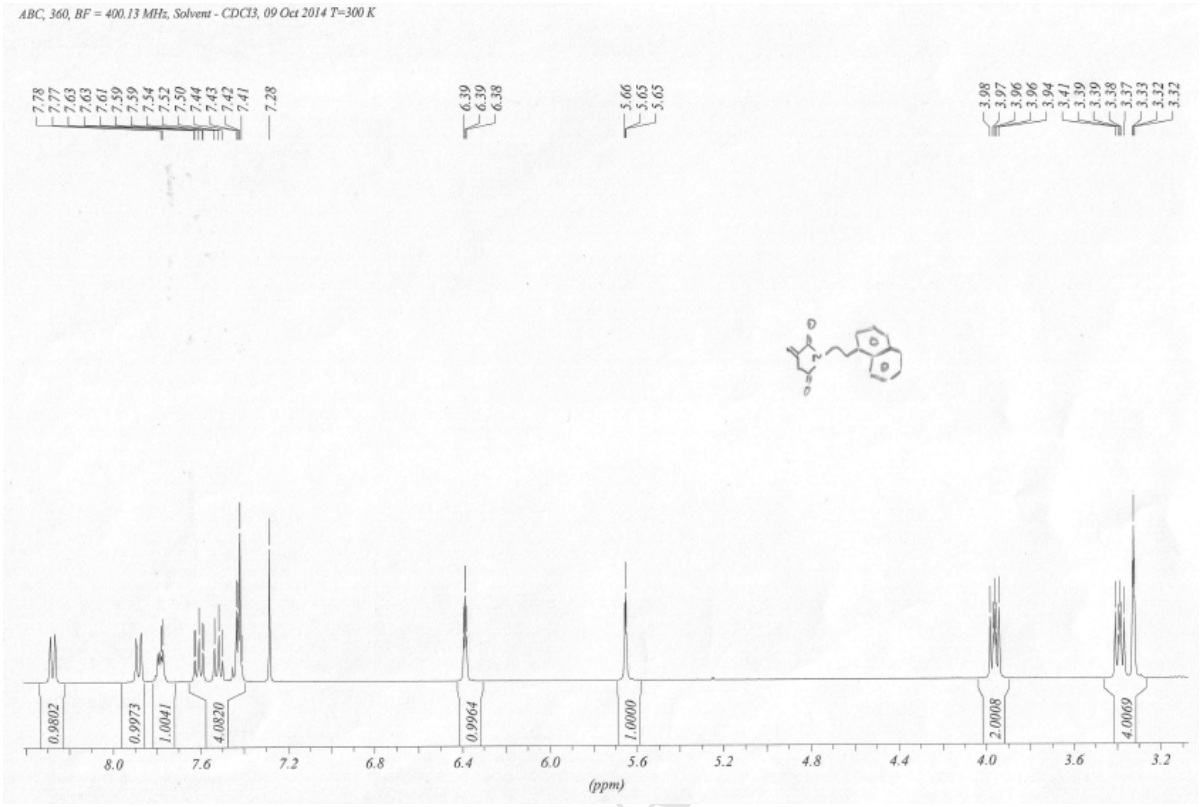


Figure 6. ^{13}C NMR spectrum of **9c** ($CDCl_3$, 100MHz)

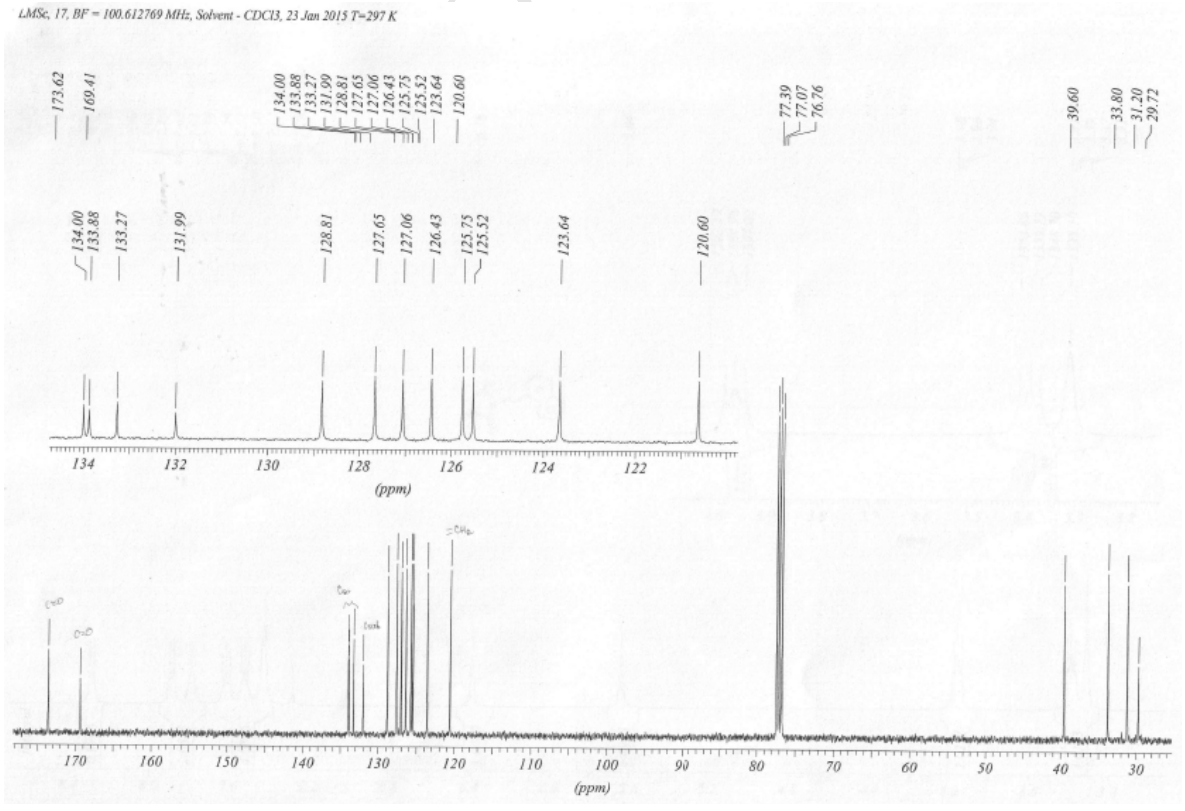


Figure 7. ^{1}H NMR spectrum of **11a** ($CDCl_3$, 400MHz)

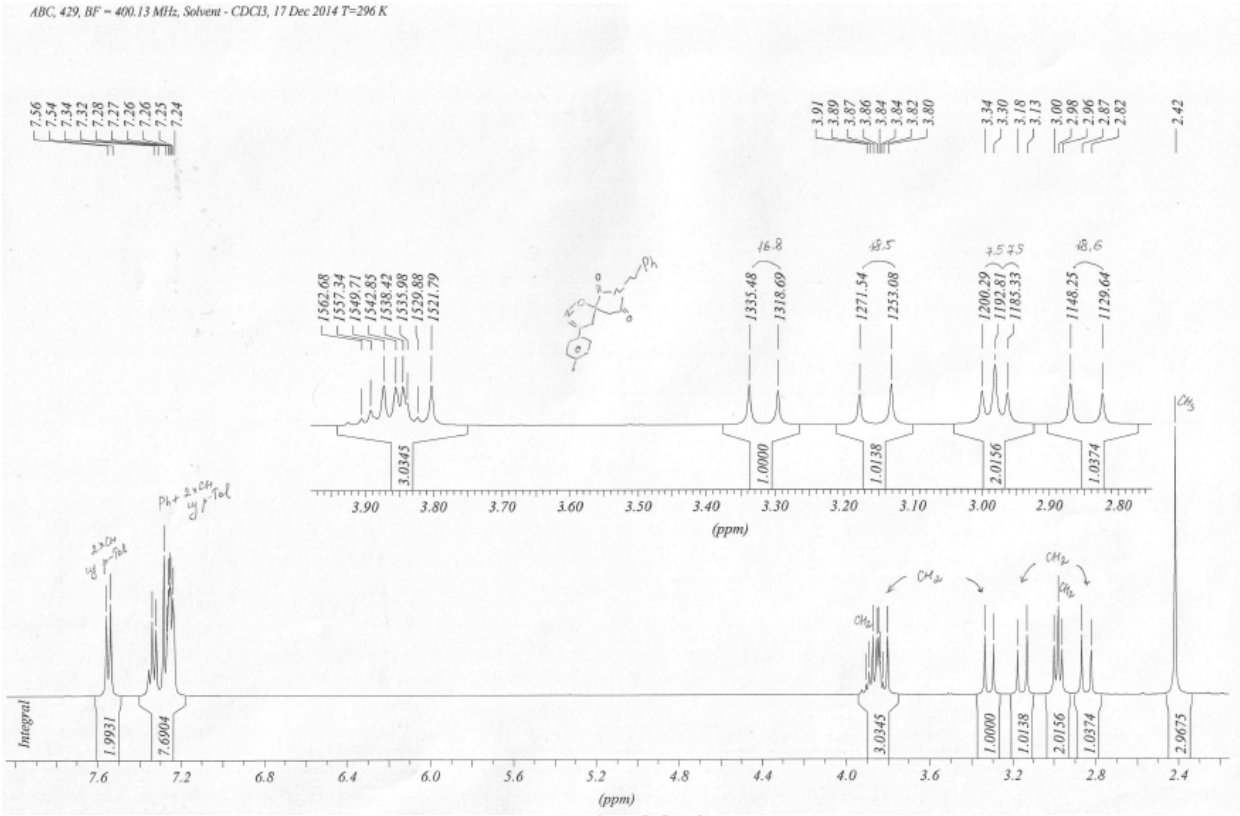


Figure 8. ^{13}C NMR spectrum of **11a** ($CDCl_3$, 100MHz)

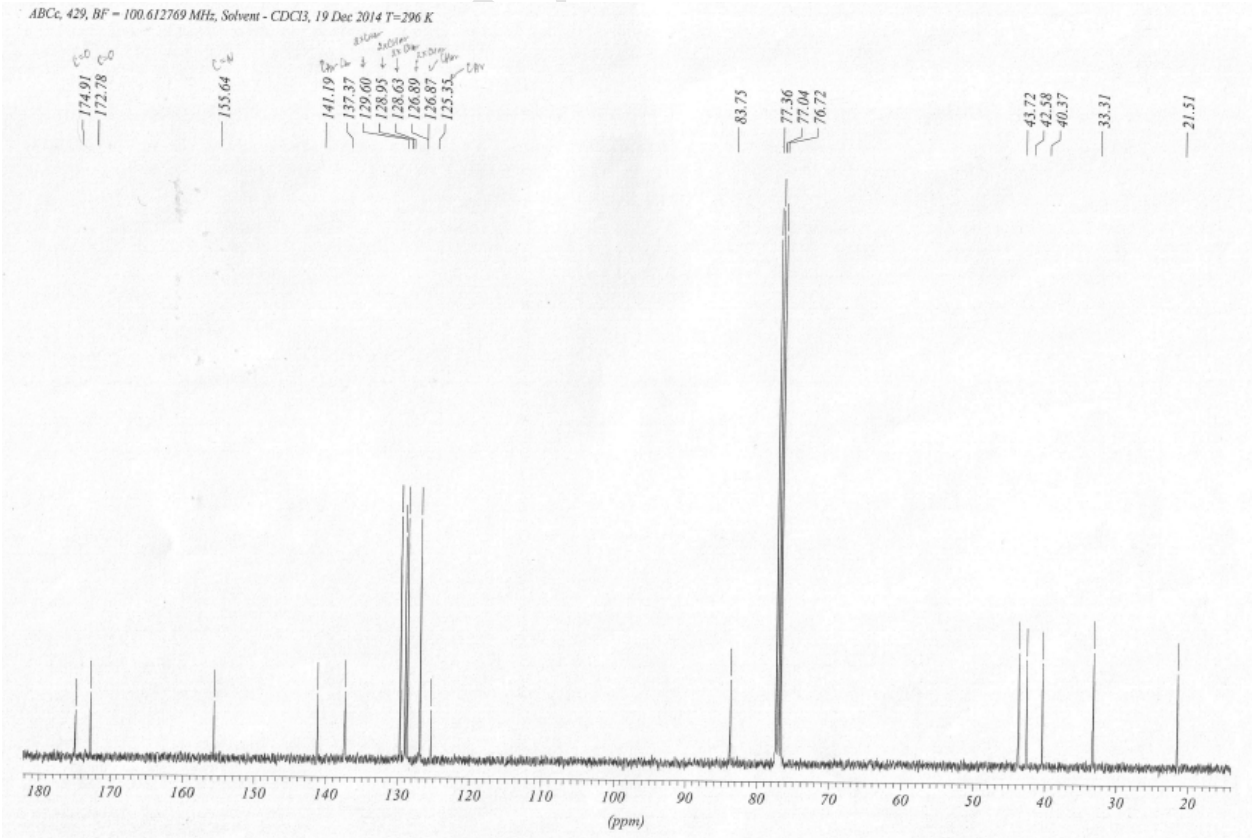


Figure 9. ^{1}H NMR spectrum of **11b** ($CDCl_3$, 400MHz)

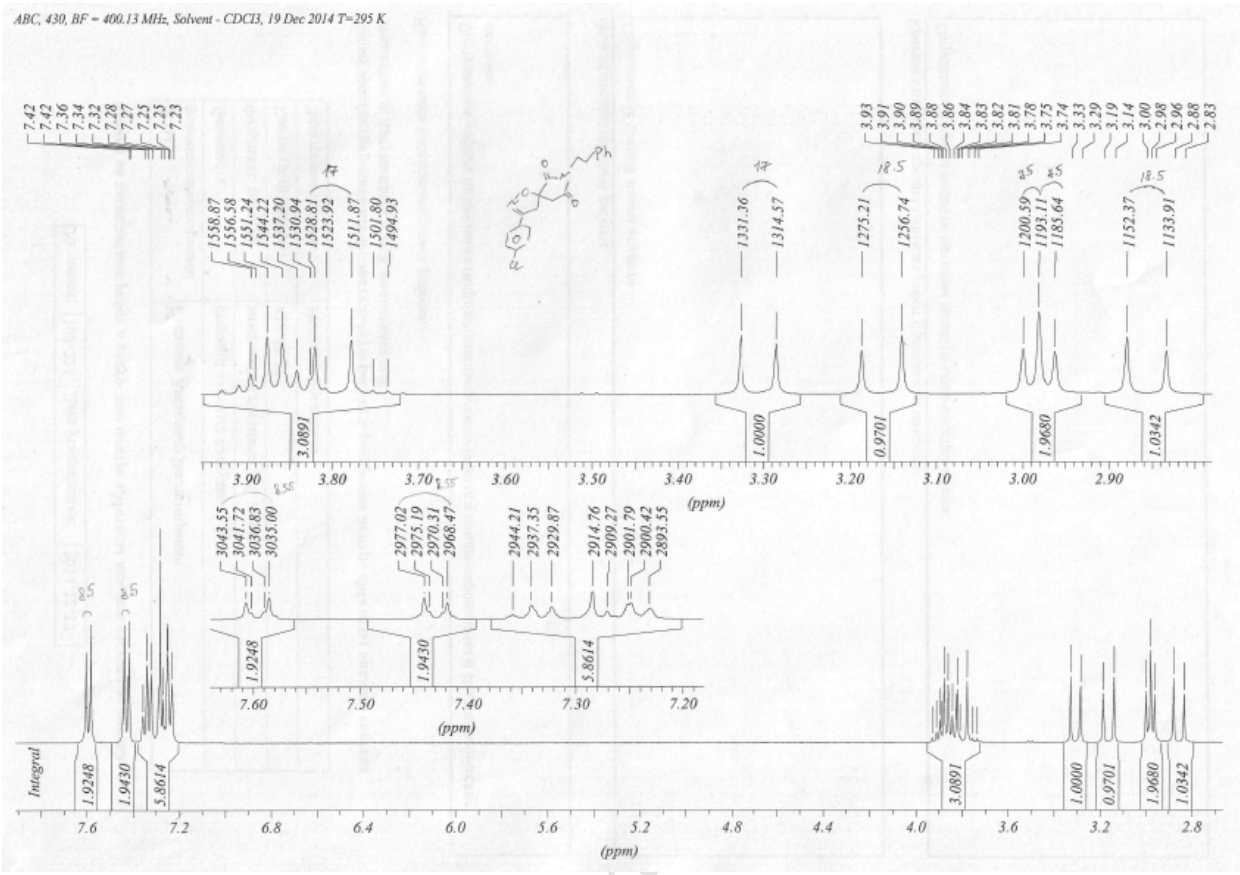


Figure 10. ^{13}C NMR spectrum of **11b** ($CDCl_3$, 100MHz)

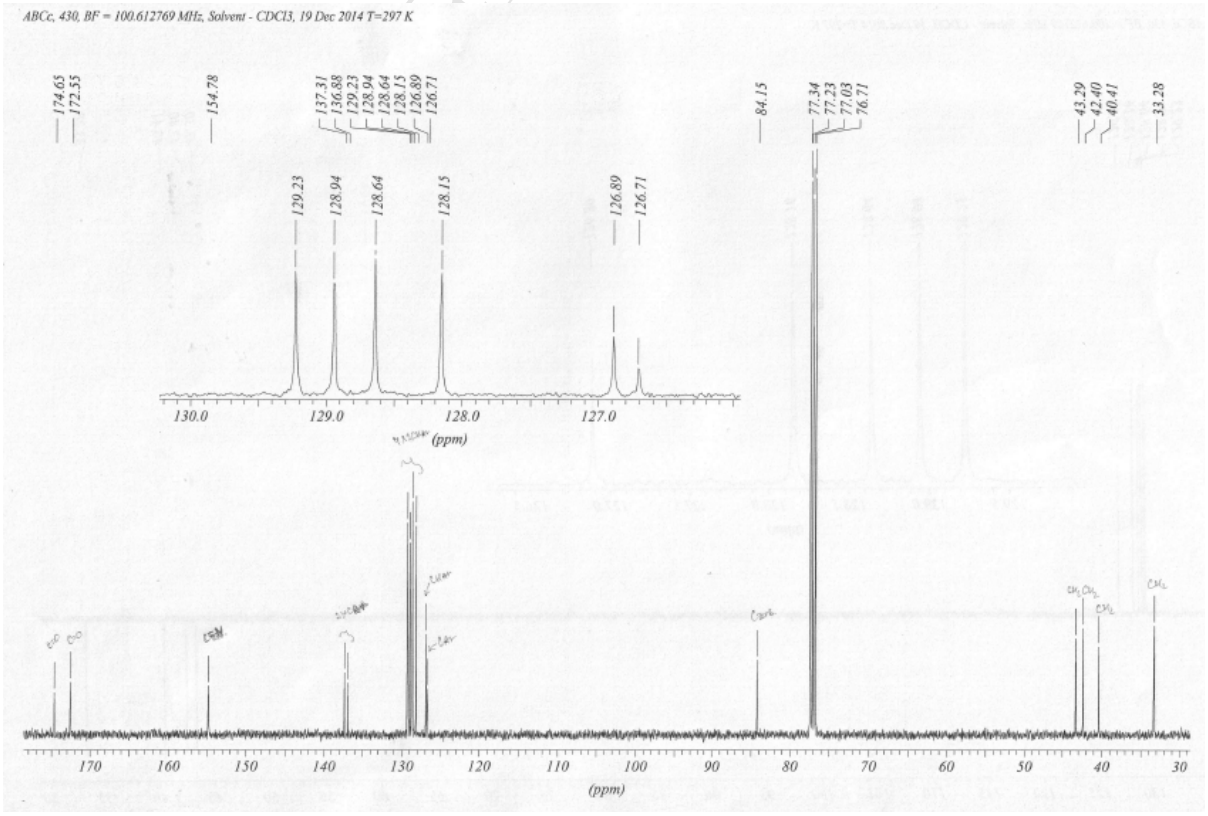


Figure 11. ^{1}H NMR spectrum of **11c** ($CDCl_3$, 400MHz)

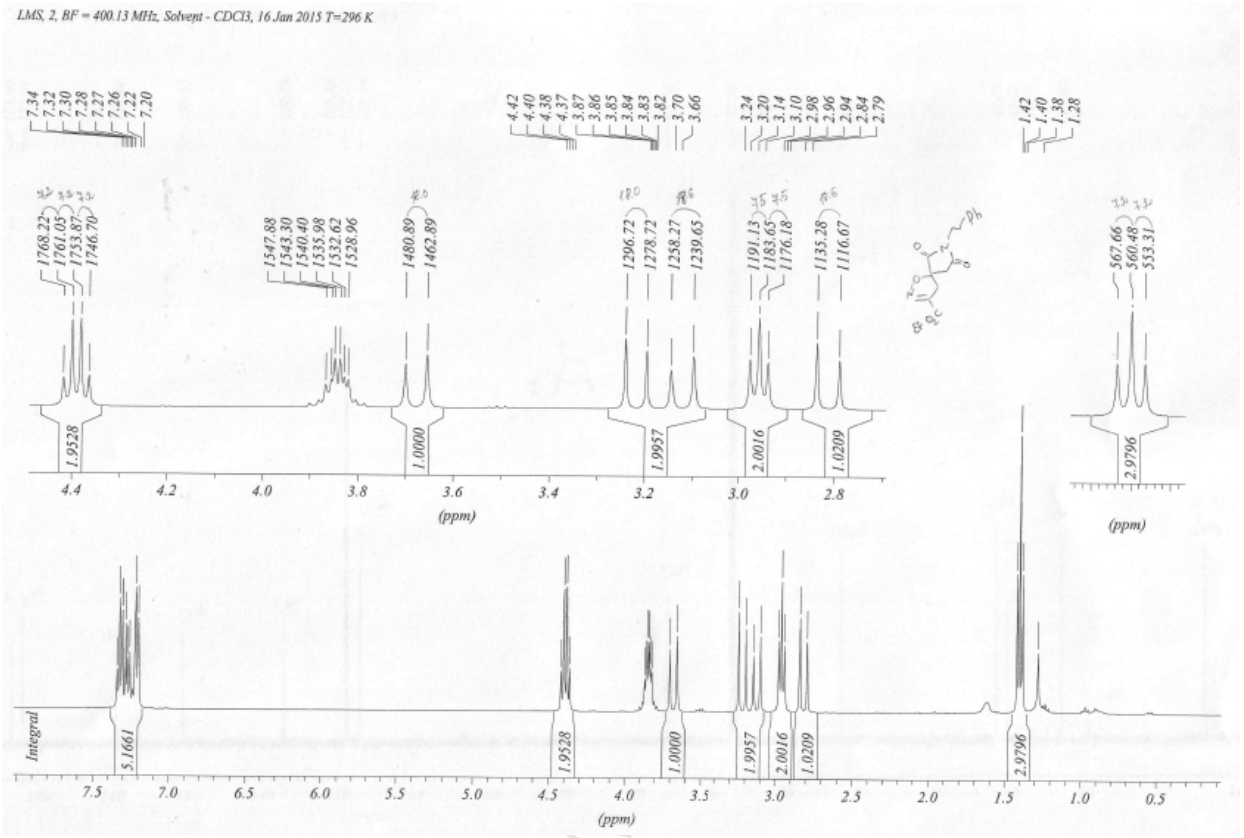


Figure 12. ^{13}C NMR spectrum of **11c** ($CDCl_3$, 100MHz)

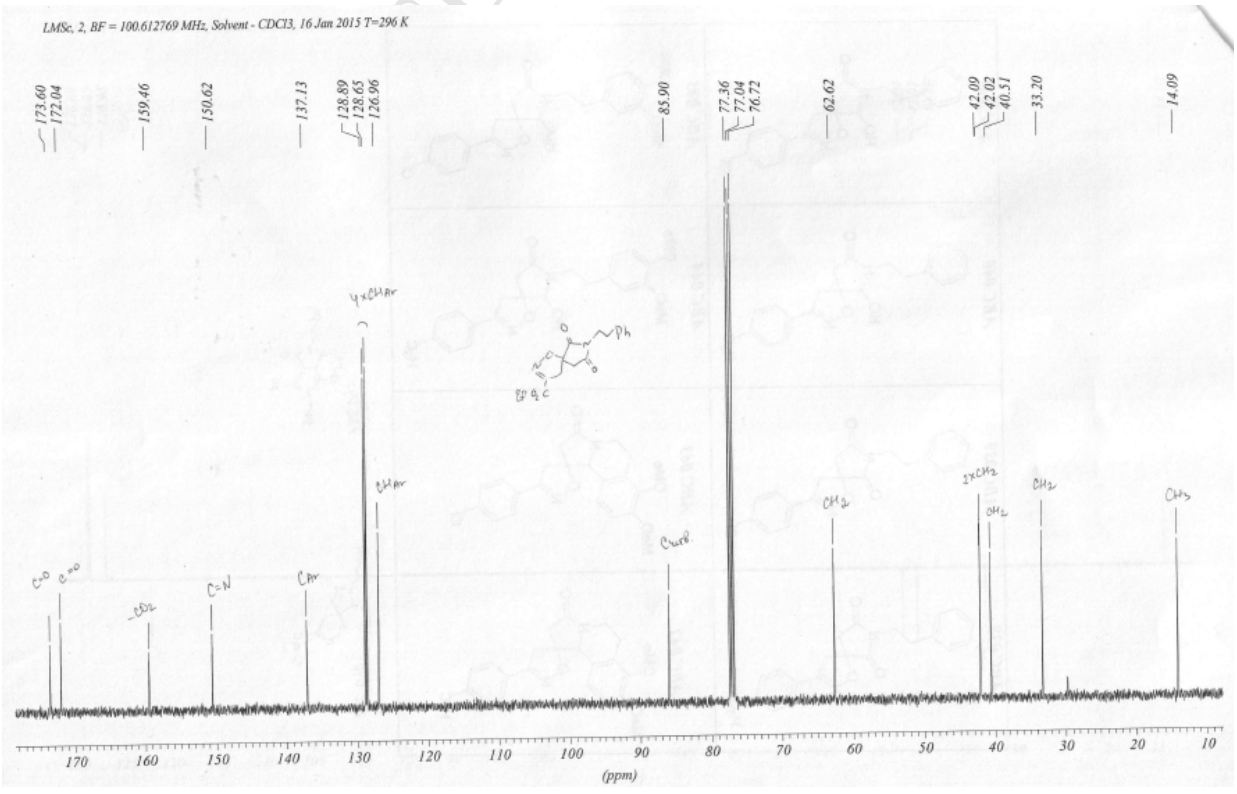


Figure 13. ^{1}H NMR spectrum of **11d** ($CDCl_3$, 400MHz)

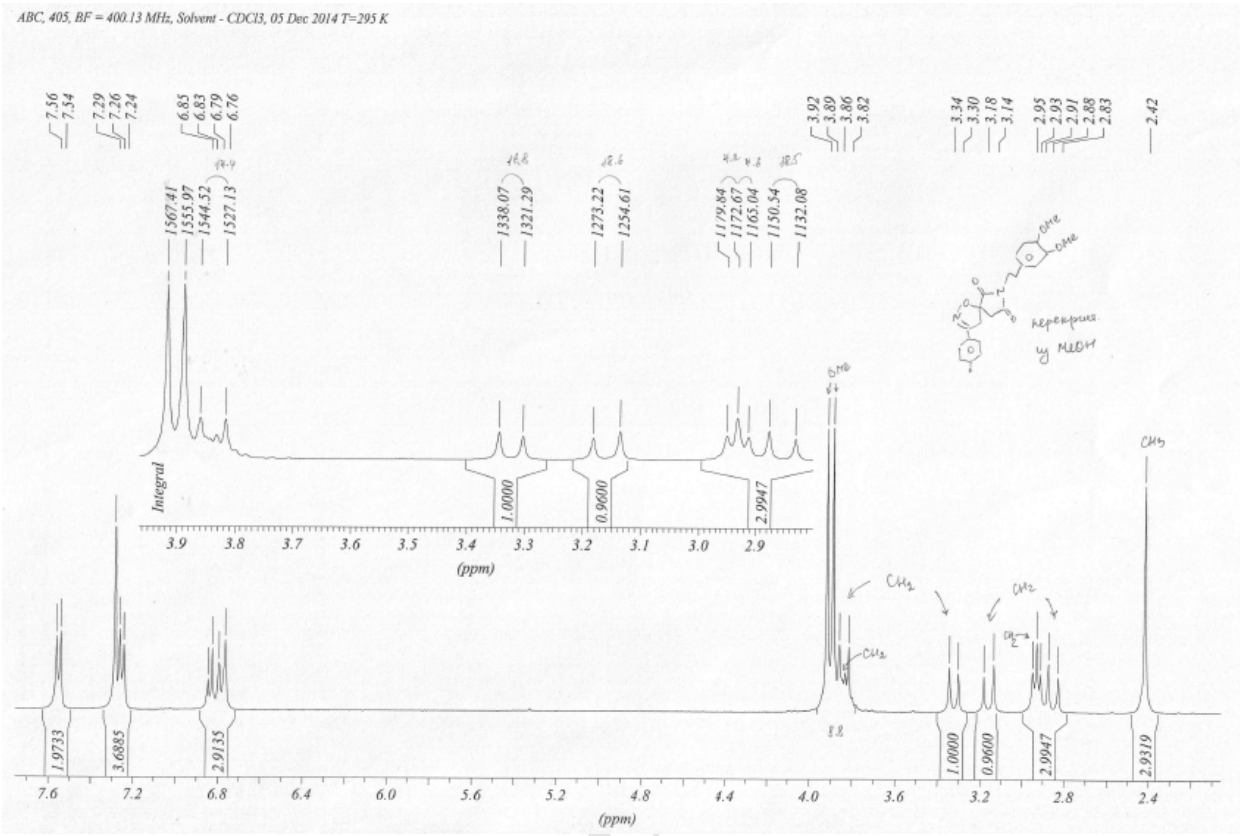


Figure 14. ^{13}C NMR spectrum of **11d** ($CDCl_3$, 100MHz)

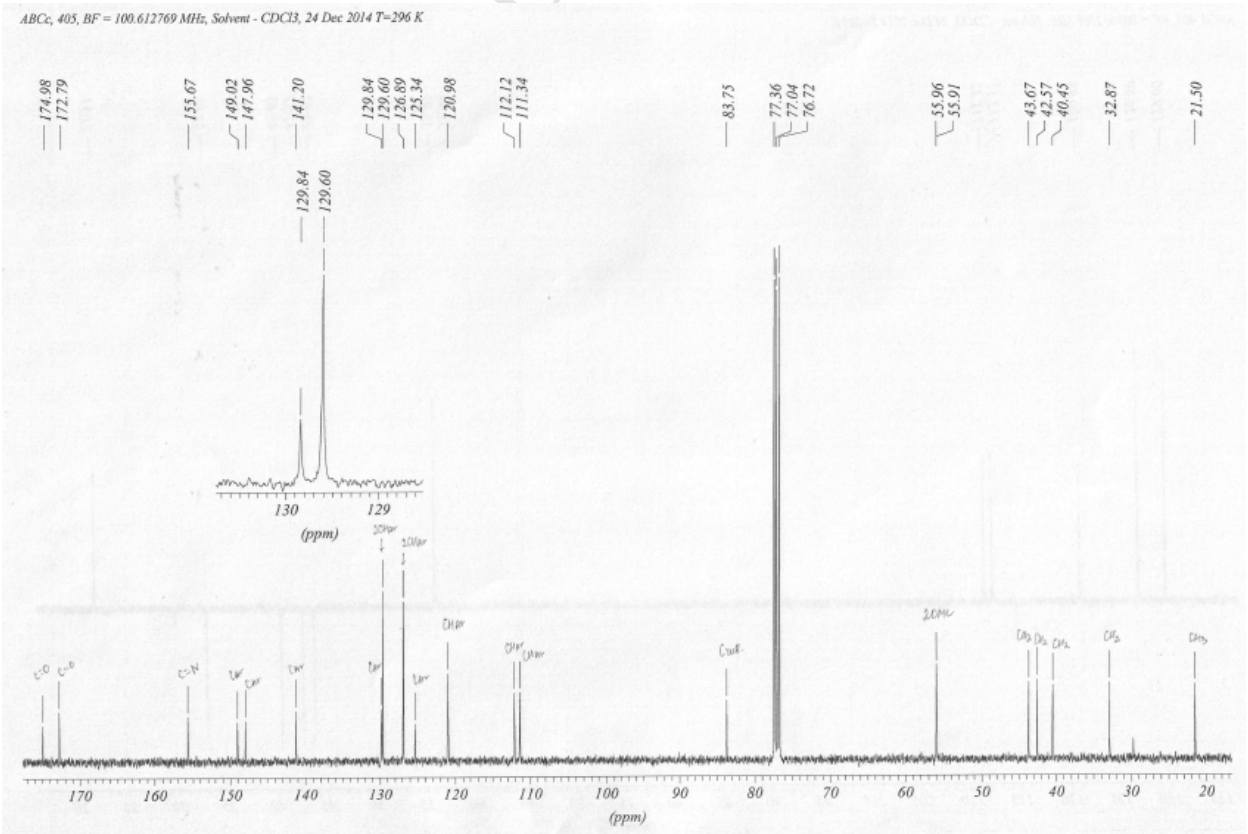


Figure 15. ^{1}H NMR spectrum of **11e** ($CDCl_3$, 400MHz)

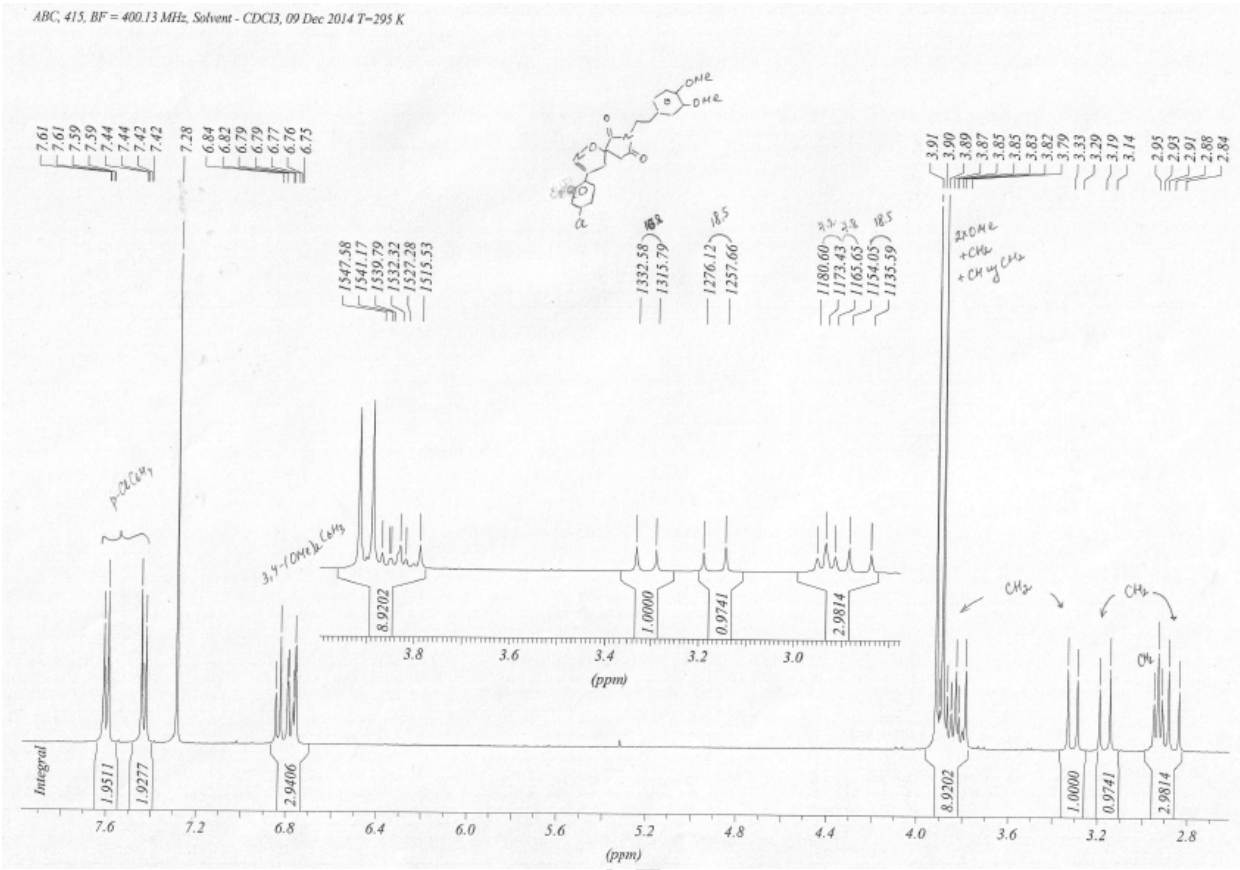


Figure 16. ^{13}C NMR spectrum of **11e** ($CDCl_3$, 100MHz)

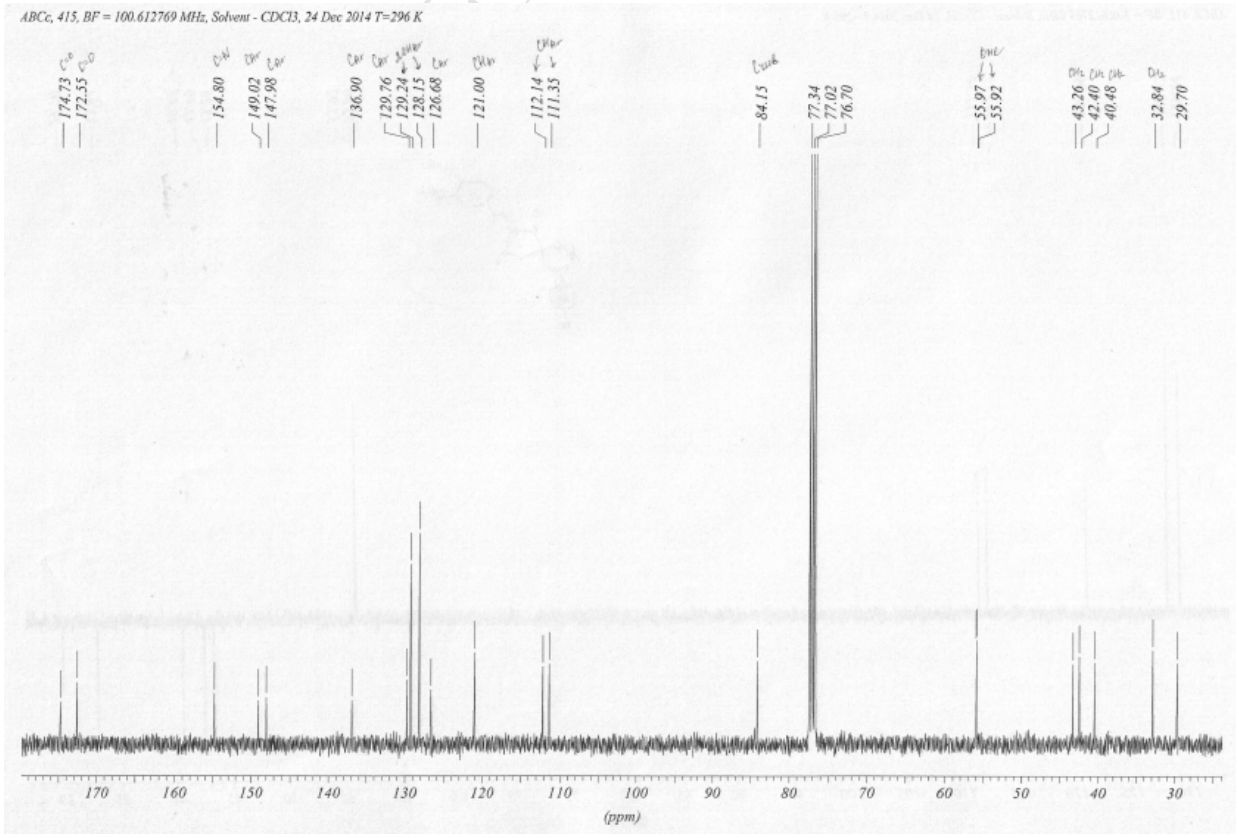


Figure 17. ^{1}H NMR spectrum of **11f** ($CDCl_3$, 400MHz)

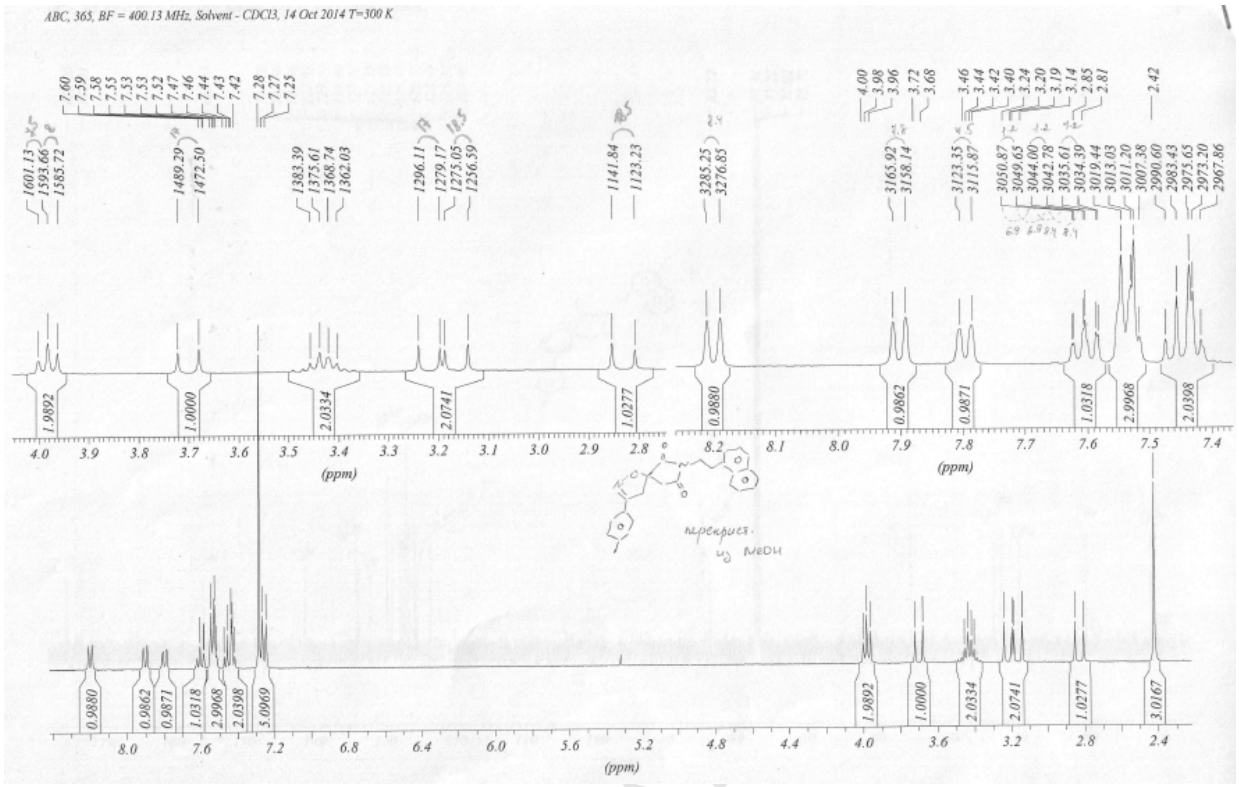


Figure 18. ^{13}C NMR spectrum of **11f** ($CDCl_3$, 100MHz)

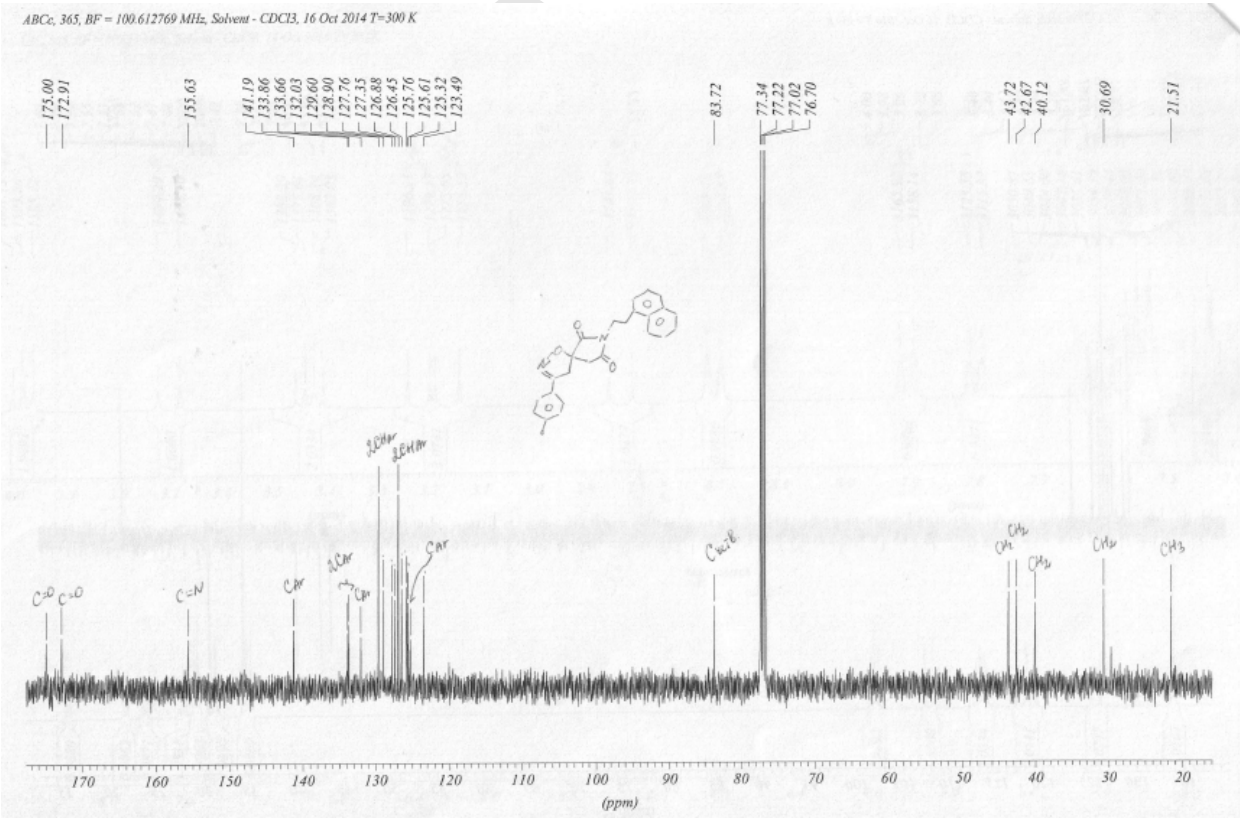


Figure 19. ^{1}H NMR spectrum of **11g** ($CDCl_3$, 400MHz)

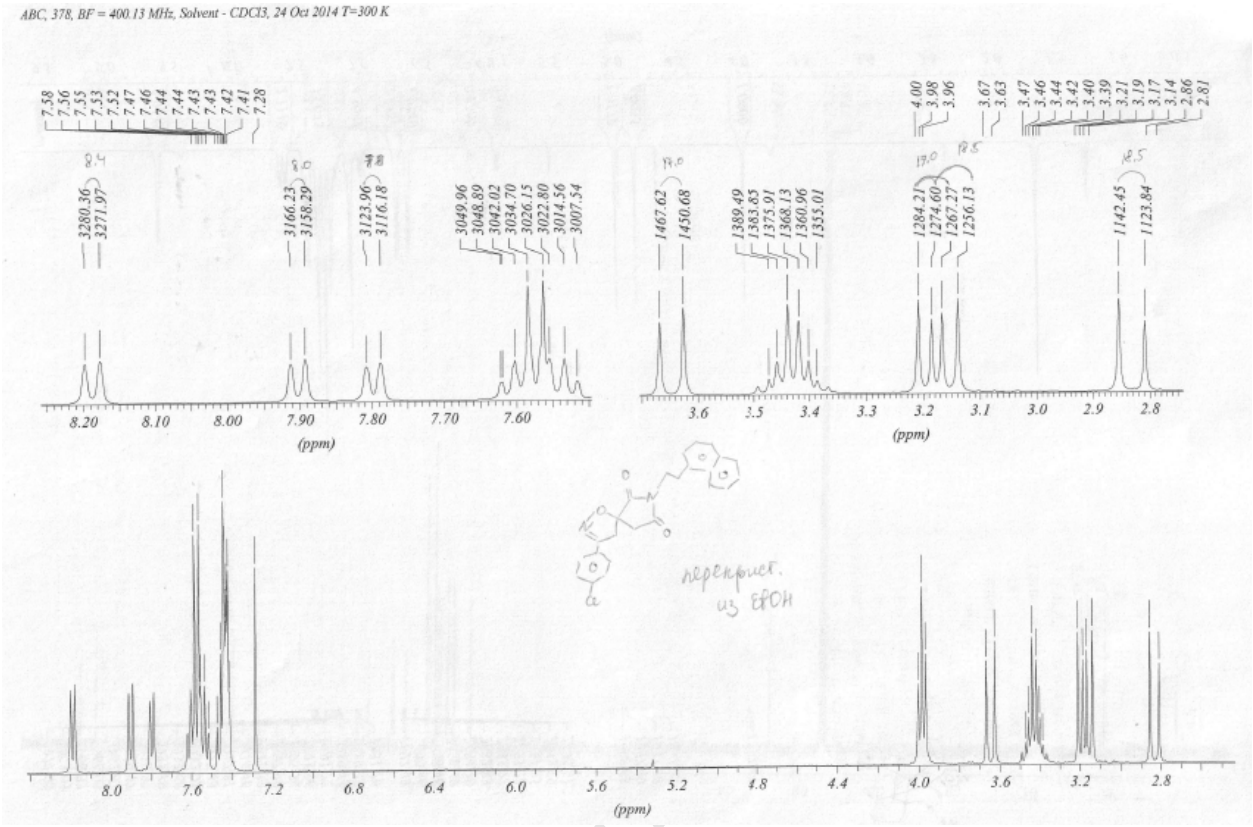


Figure 20. ^{13}C NMR spectrum of **11g** ($CDCl_3$, 100MHz)

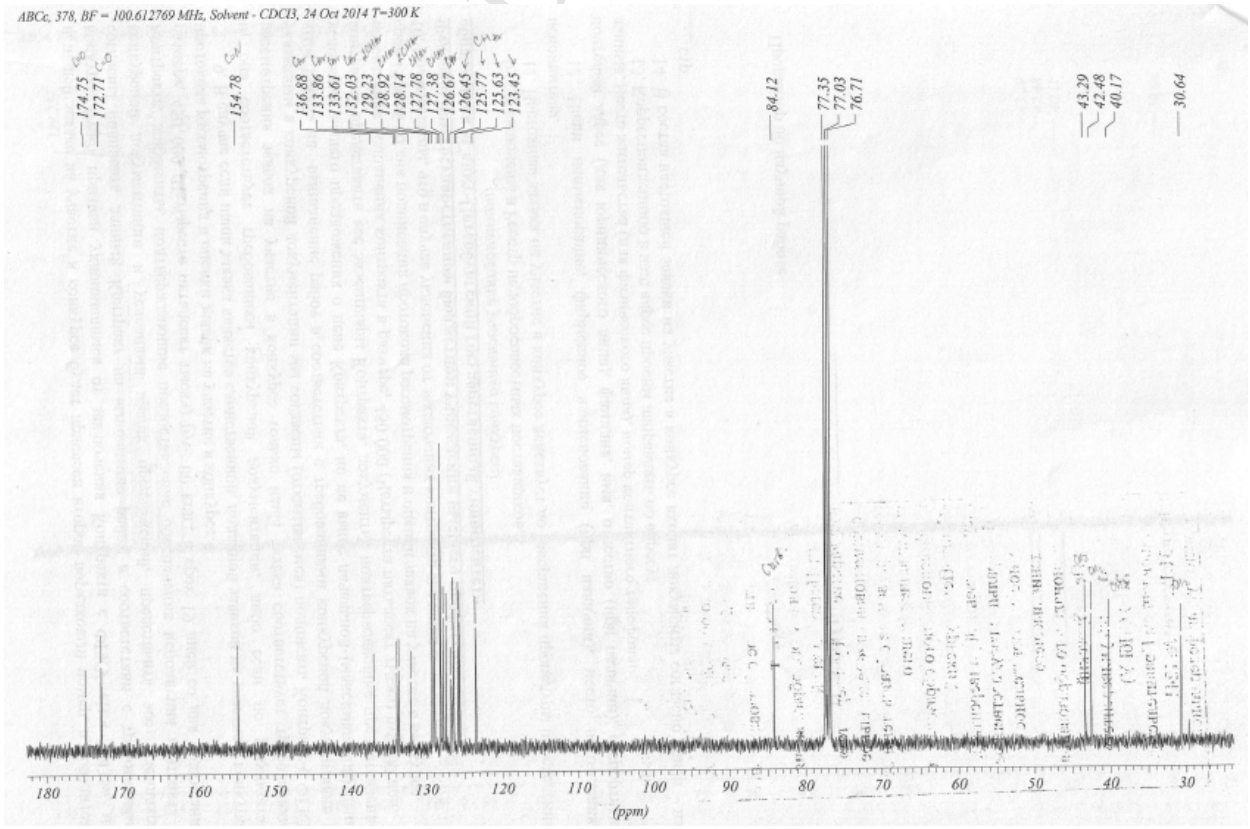


Figure 21. ^{1}H NMR spectrum of **12a** ($CDCl_3$, 400MHz)

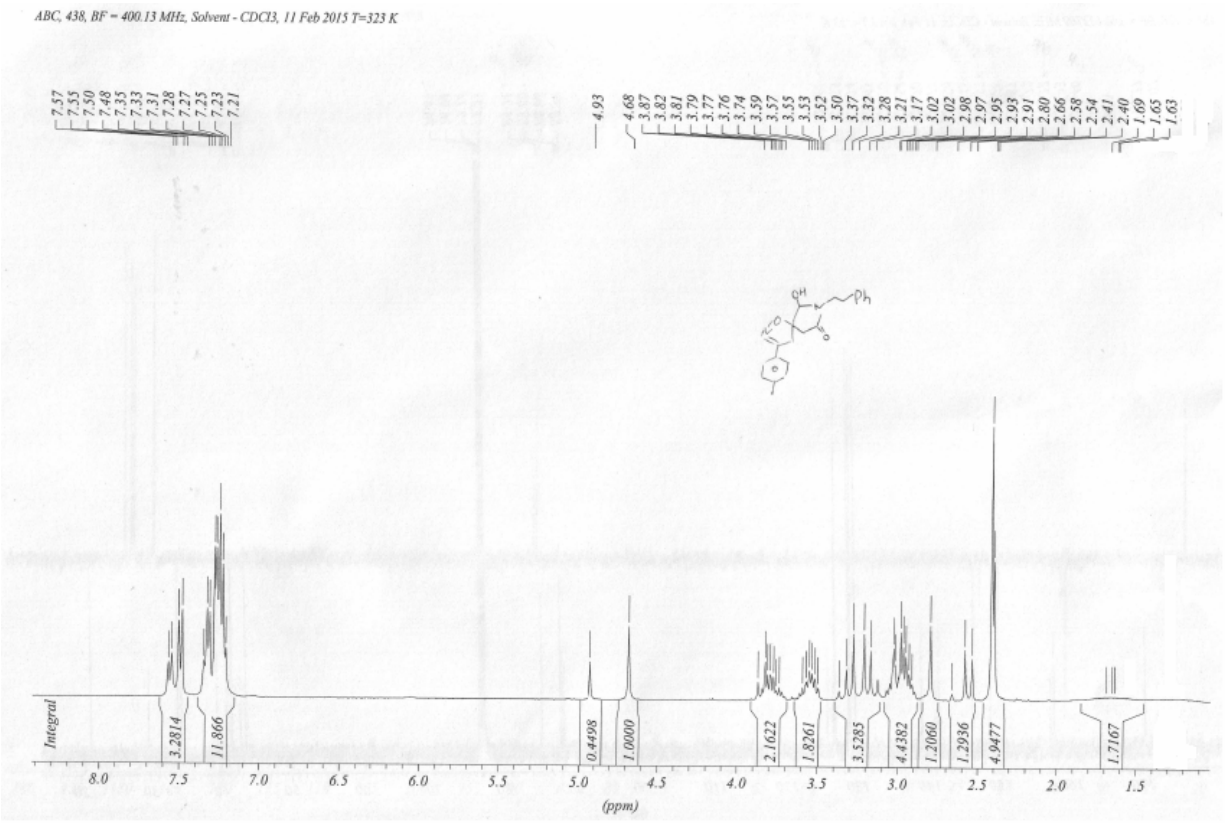


Figure 22. ^{13}C NMR spectrum of **12a** ($CDCl_3$, 100MHz)

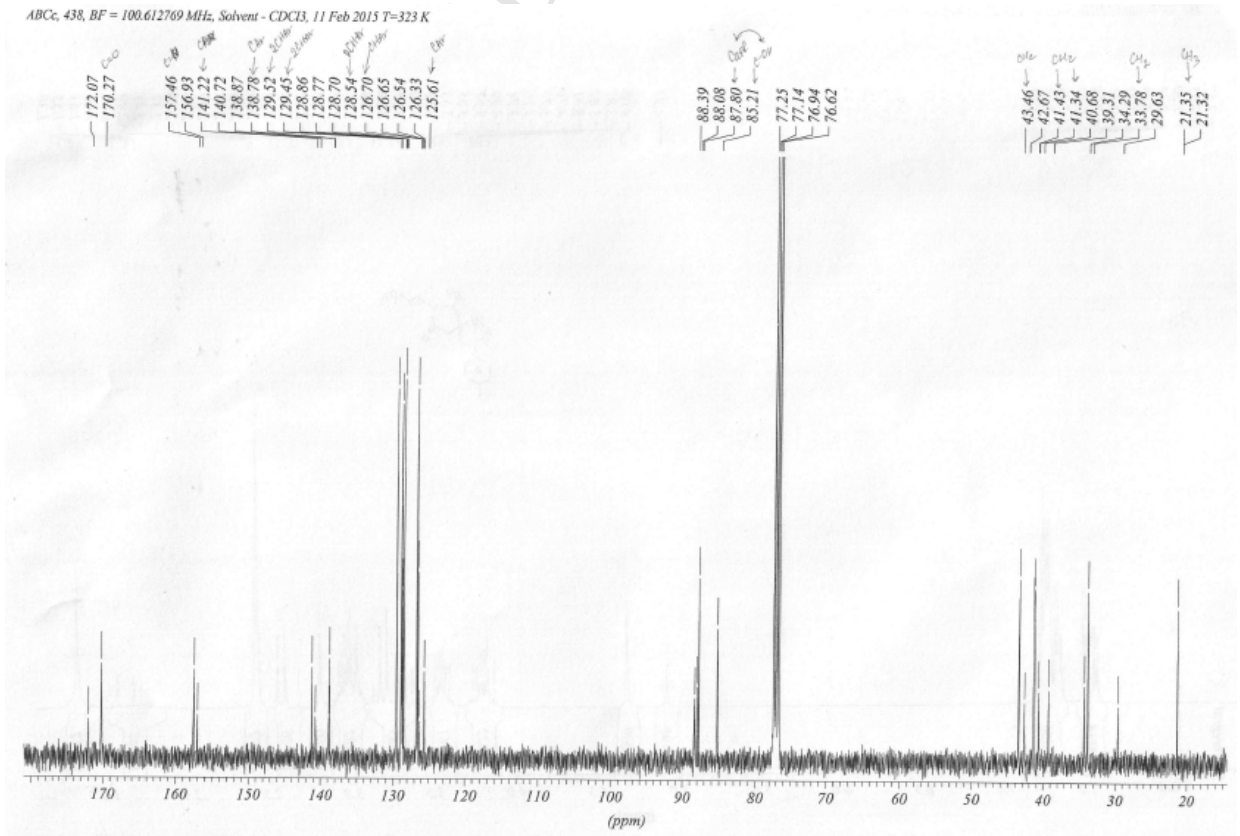


Figure 23. ^{1}H NMR spectrum of **12b** ($CDCl_3$, 400MHz)

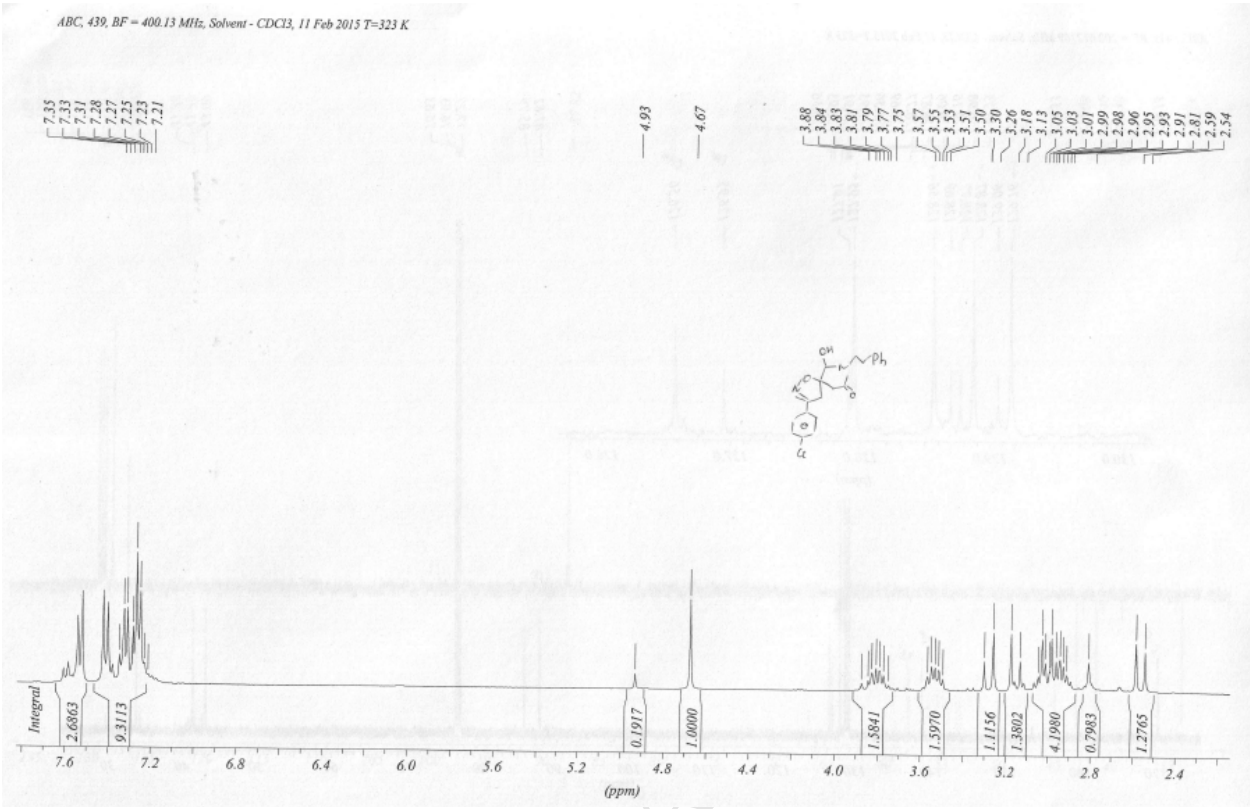


Figure 24. ^{13}C NMR spectrum of **12b** ($CDCl_3$, 100MHz)

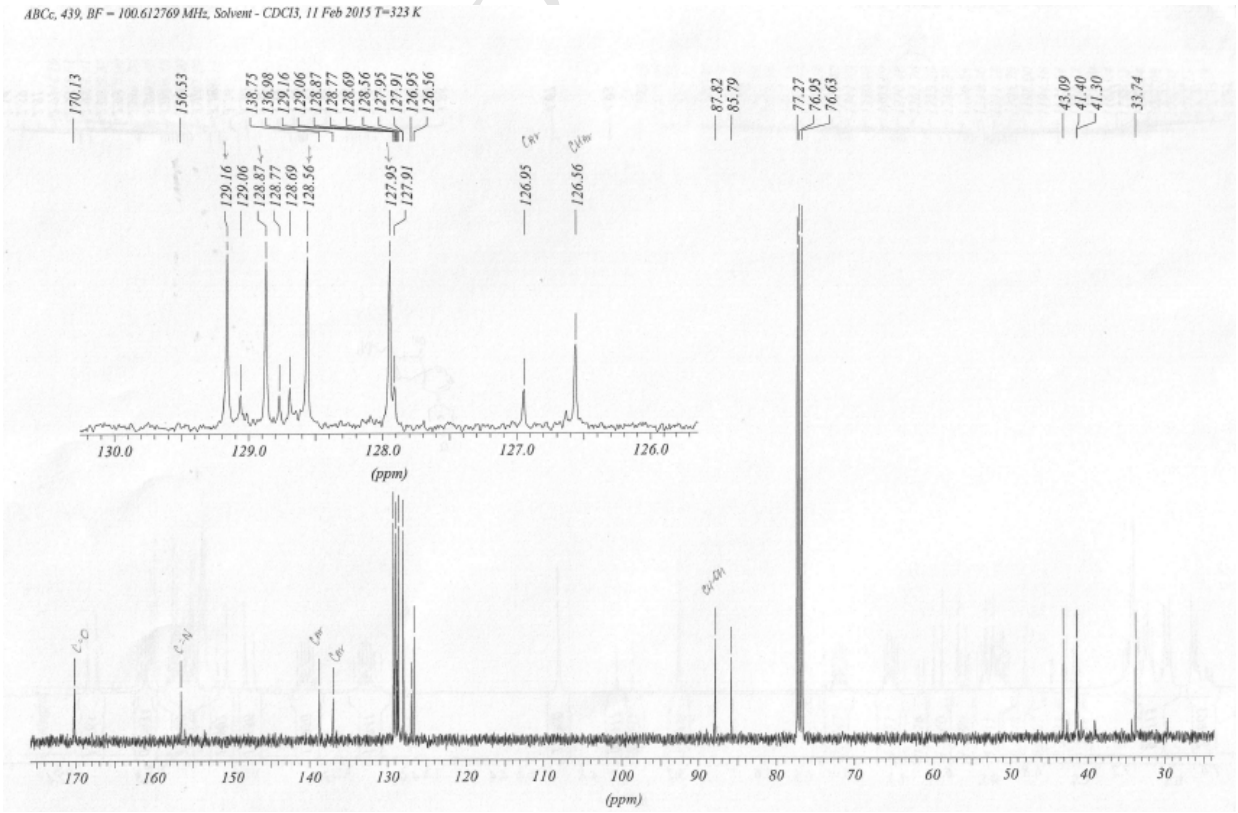


Figure 25. ^{1}H NMR spectrum of **12c** ($CDCl_3$, 400MHz)

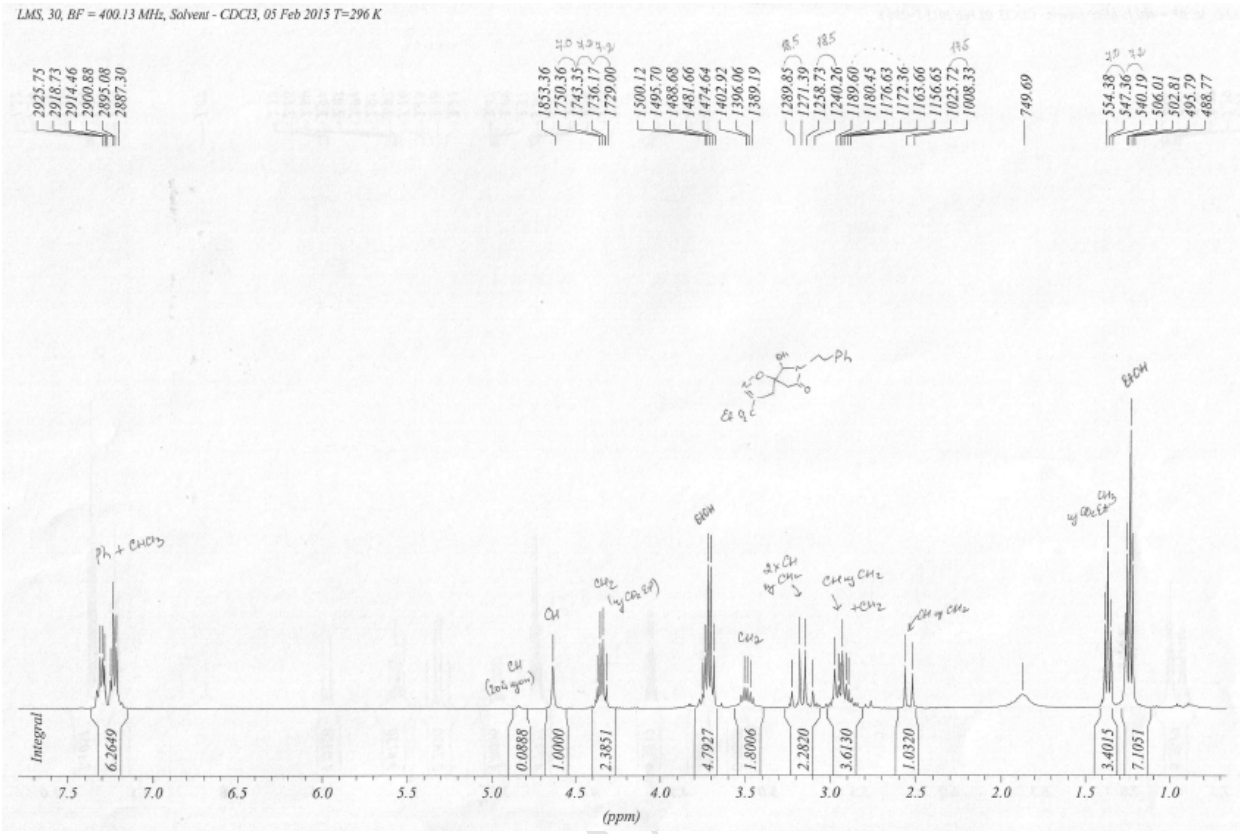


Figure 26. ^{13}C NMR spectrum of **12c** ($CDCl_3$, 100MHz)

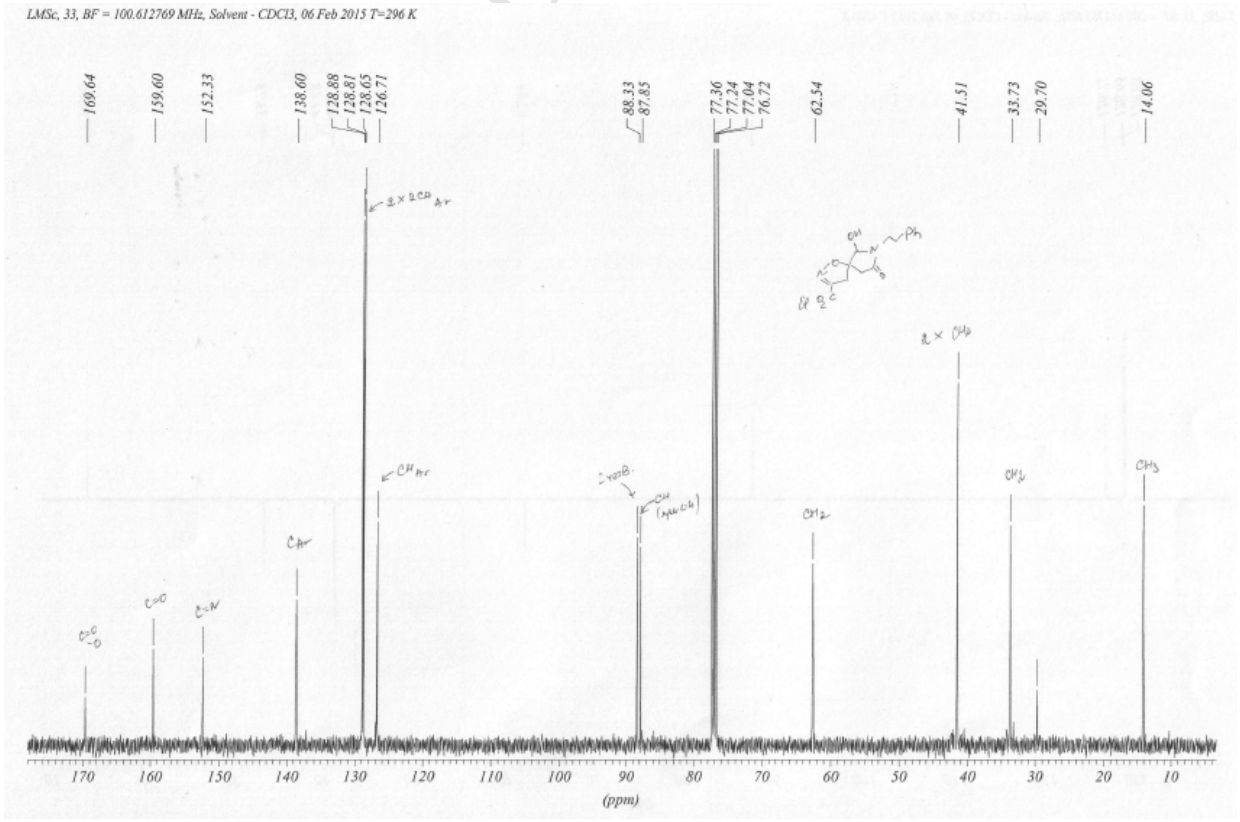


Figure 27. ^{1}H NMR spectrum of **12d** ($CDCl_3$, 400MHz)

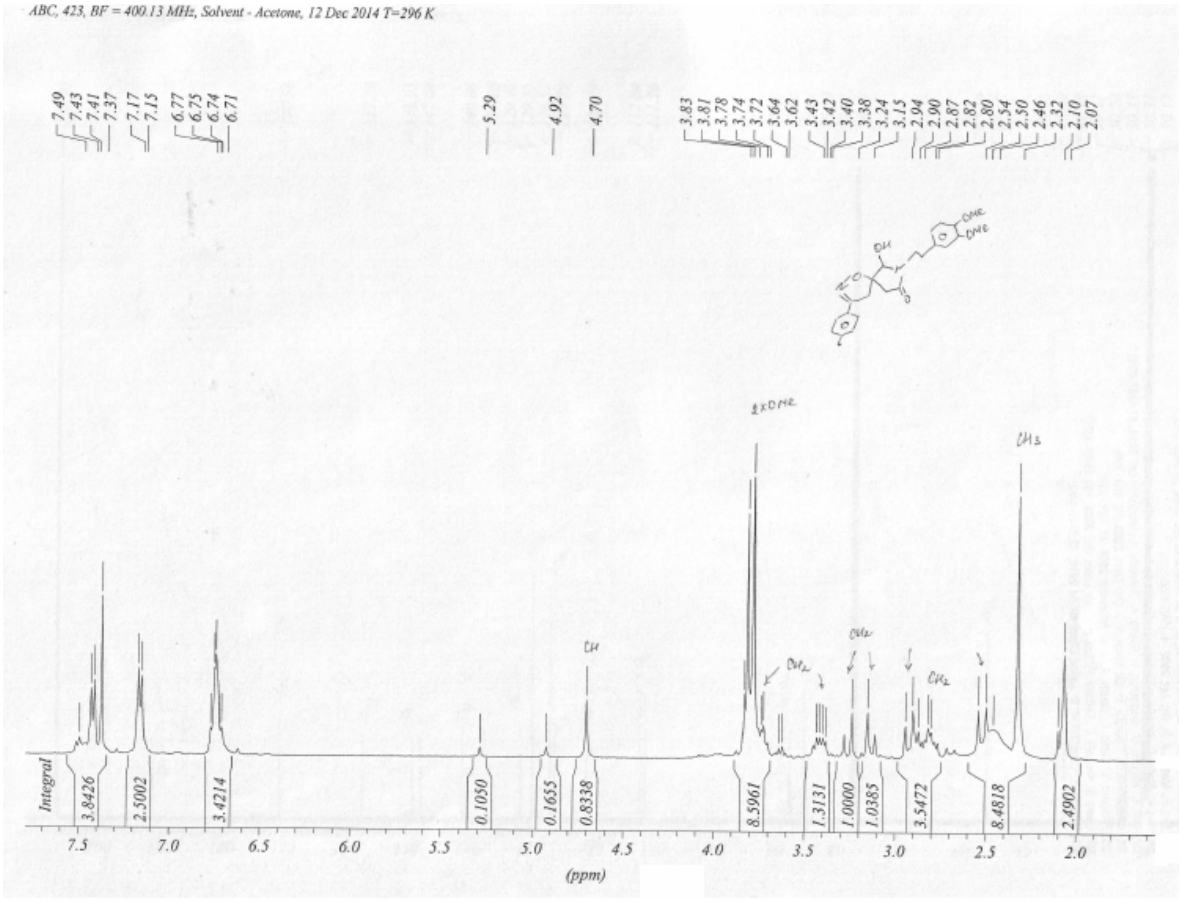


Figure 28. ^{13}C NMR spectrum of **12d** ($CDCl_3$, 100MHz)

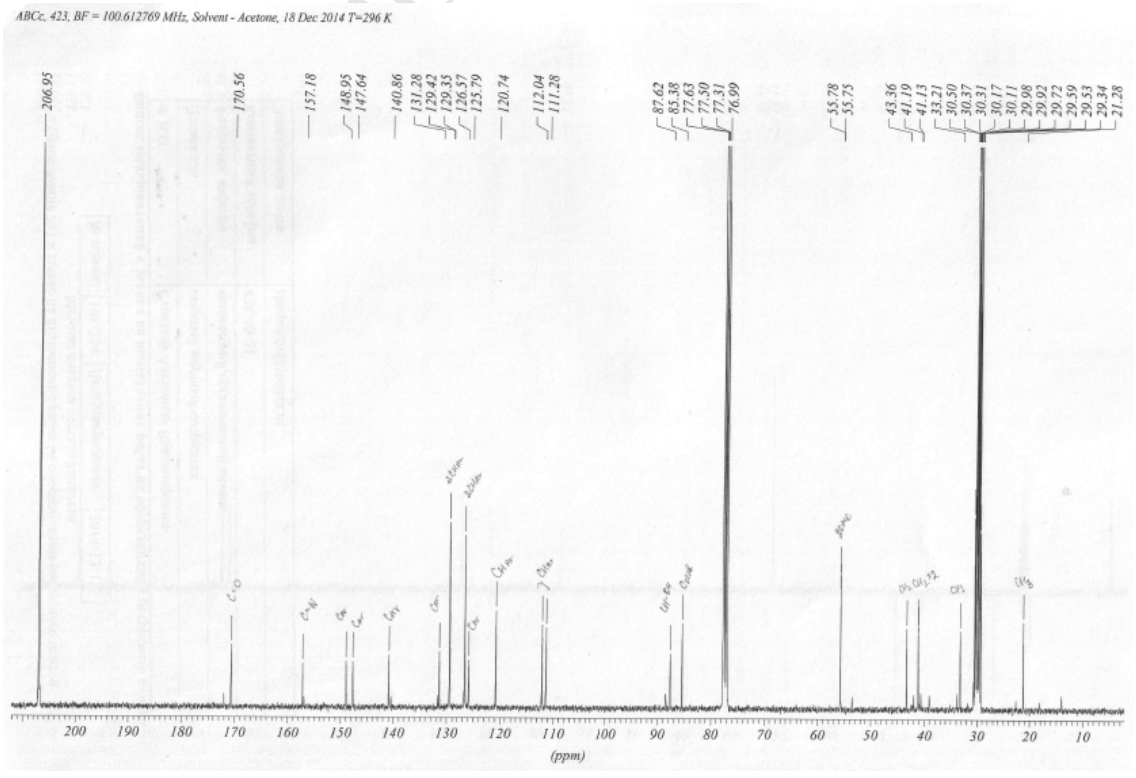


Figure 29. ^{1}H NMR spectrum of **12e** ($CDCl_3$, 400MHz)

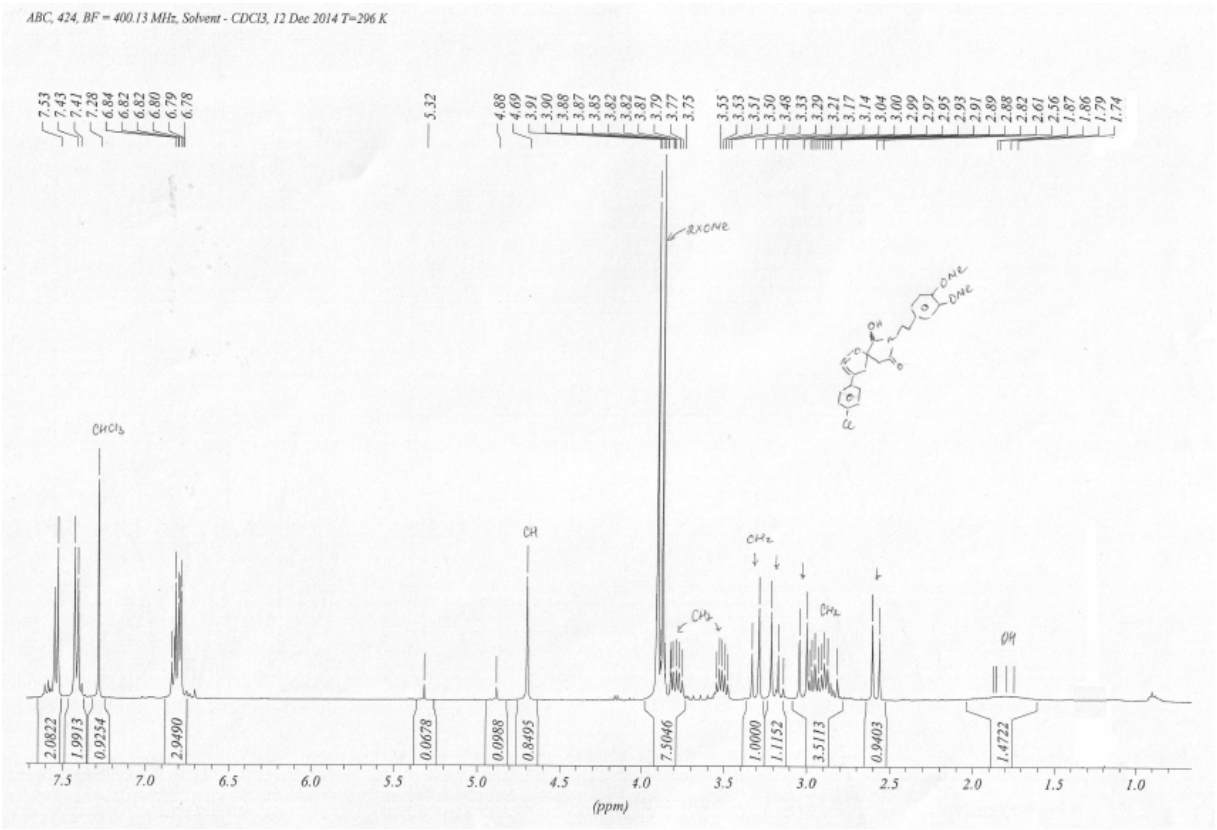


Figure 30. ^{13}C NMR spectrum of **12e** ($CDCl_3$, 100MHz)

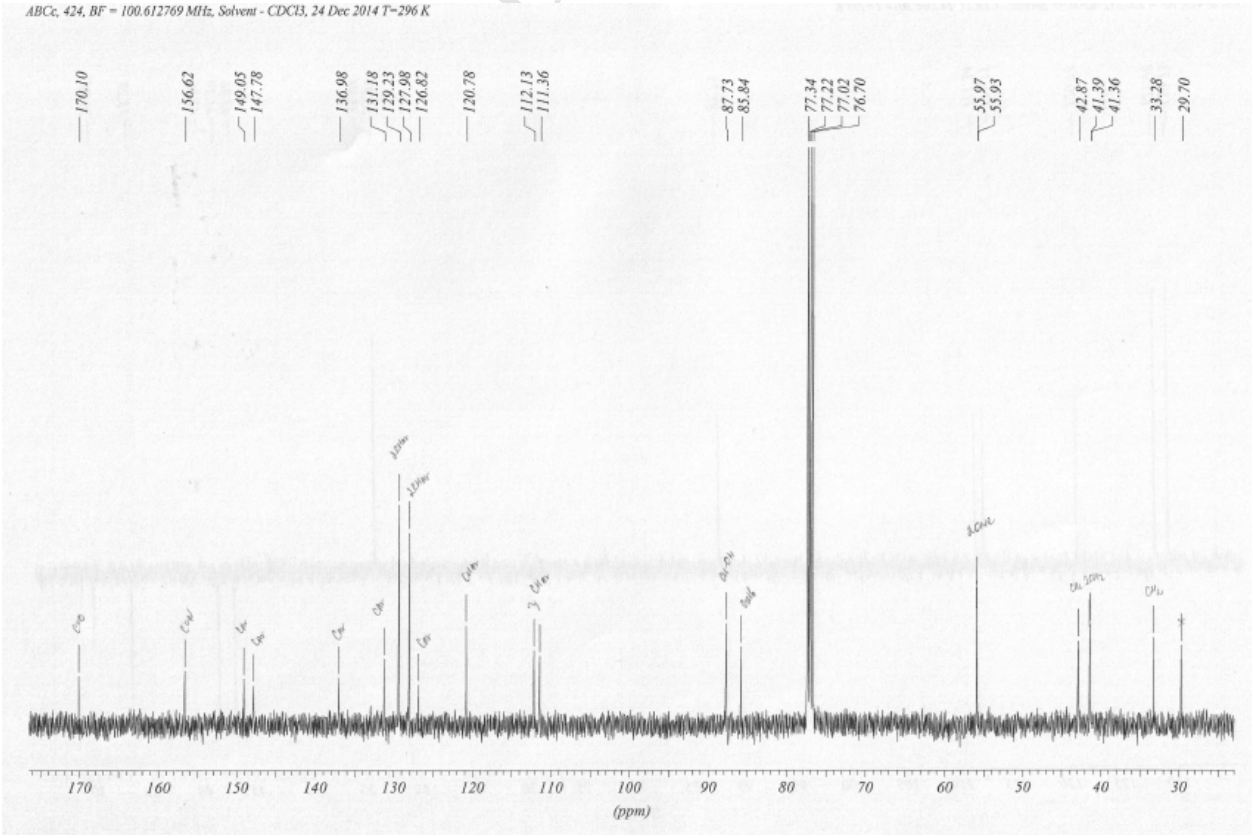


Figure 31. ^{1}H NMR spectrum of **12f** ($CDCl_3$, 400MHz)

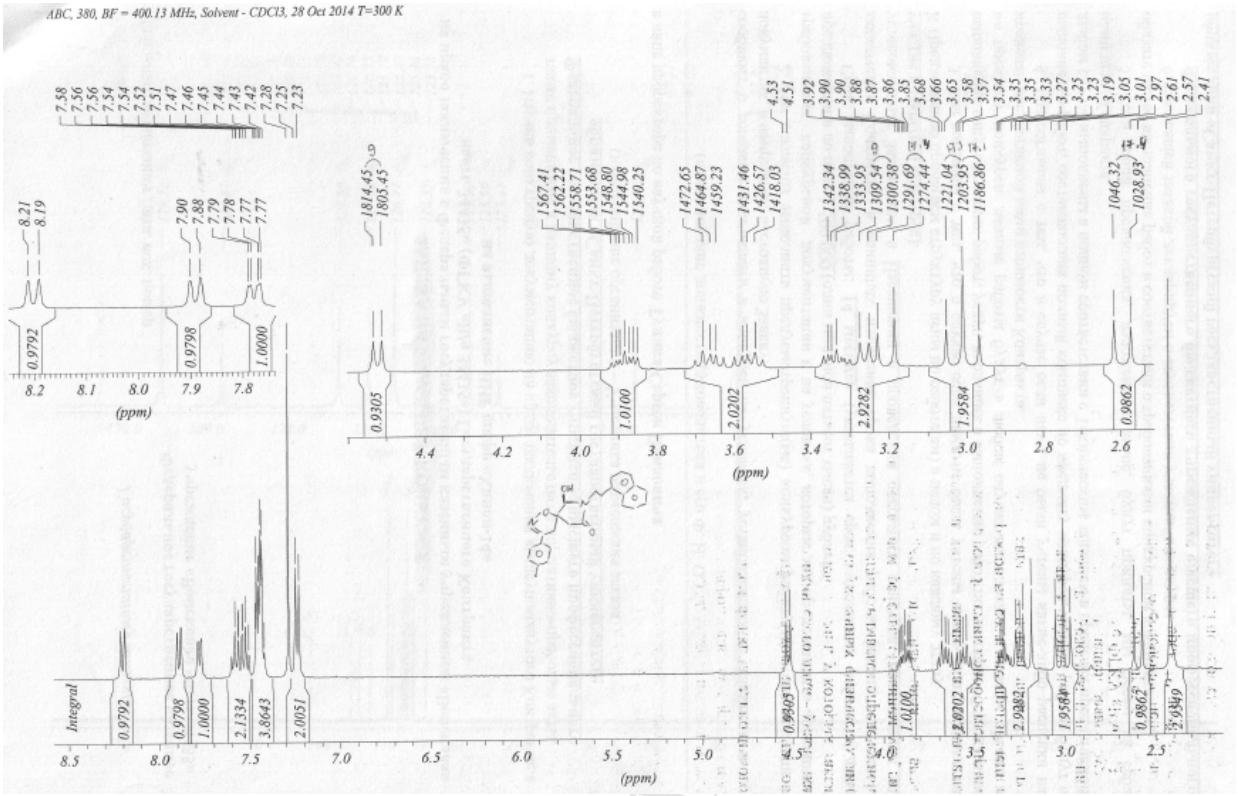


Figure 32. ^{13}C NMR spectrum of **12f** ($CDCl_3$, 100MHz)

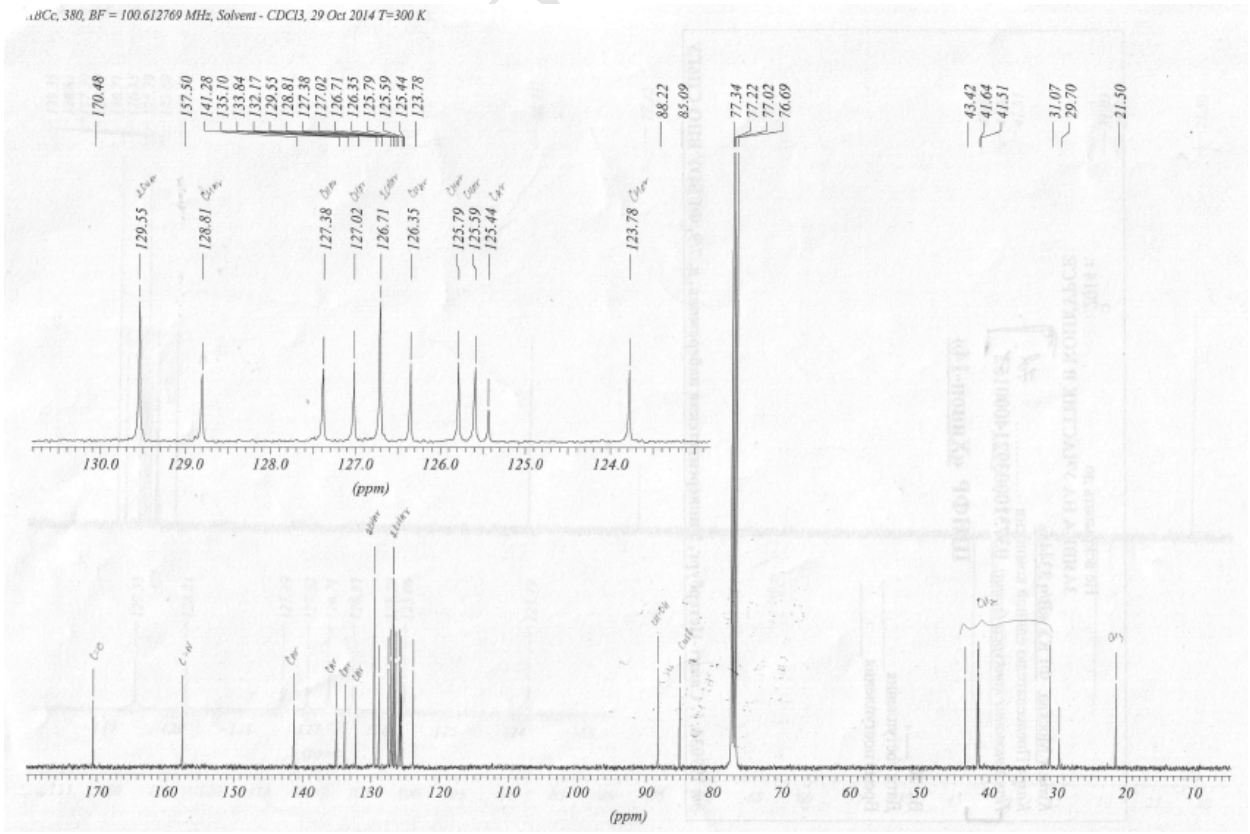


Figure 33. ^{1}H NMR spectrum of **12g** ($CDCl_3$, 400MHz), diastereomer 1

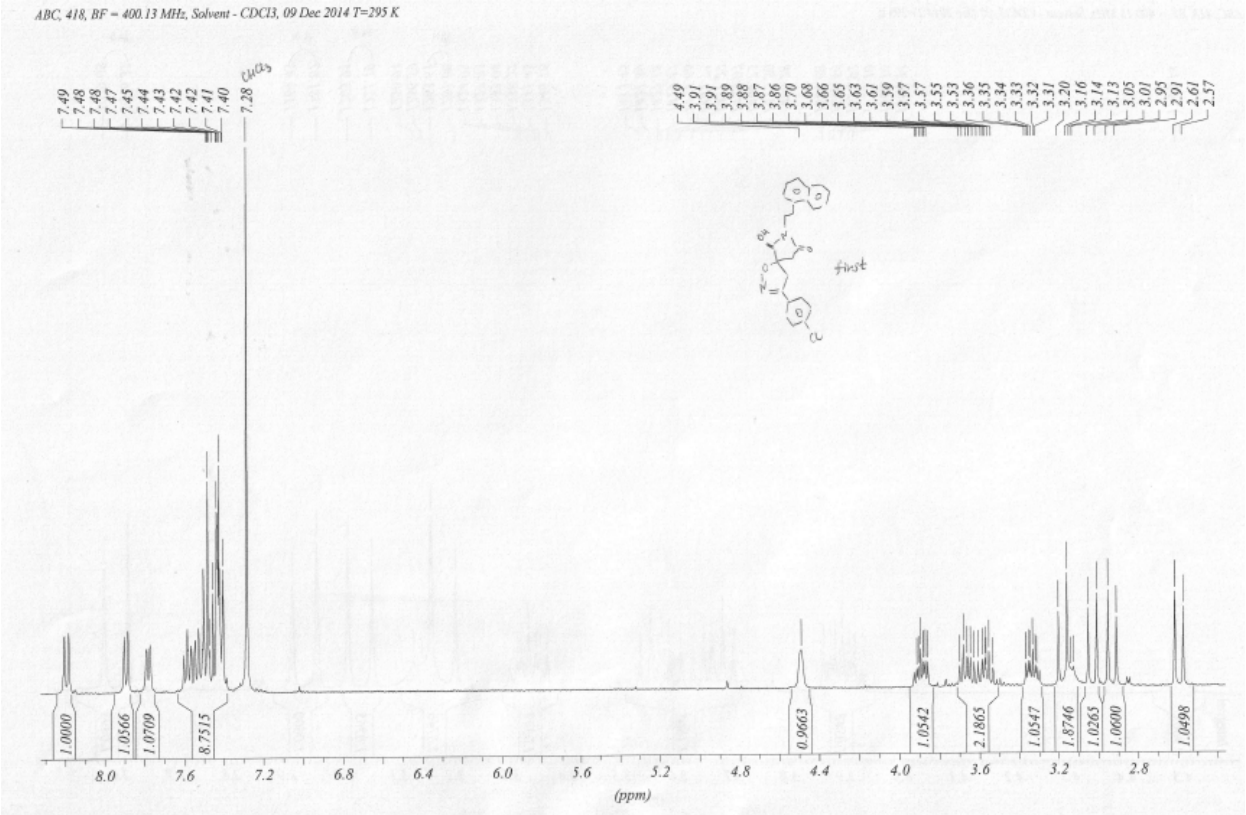


Figure 34. ^{1}H NMR spectrum of **12g** ($CDCl_3$, 400MHz), diastereomer 2

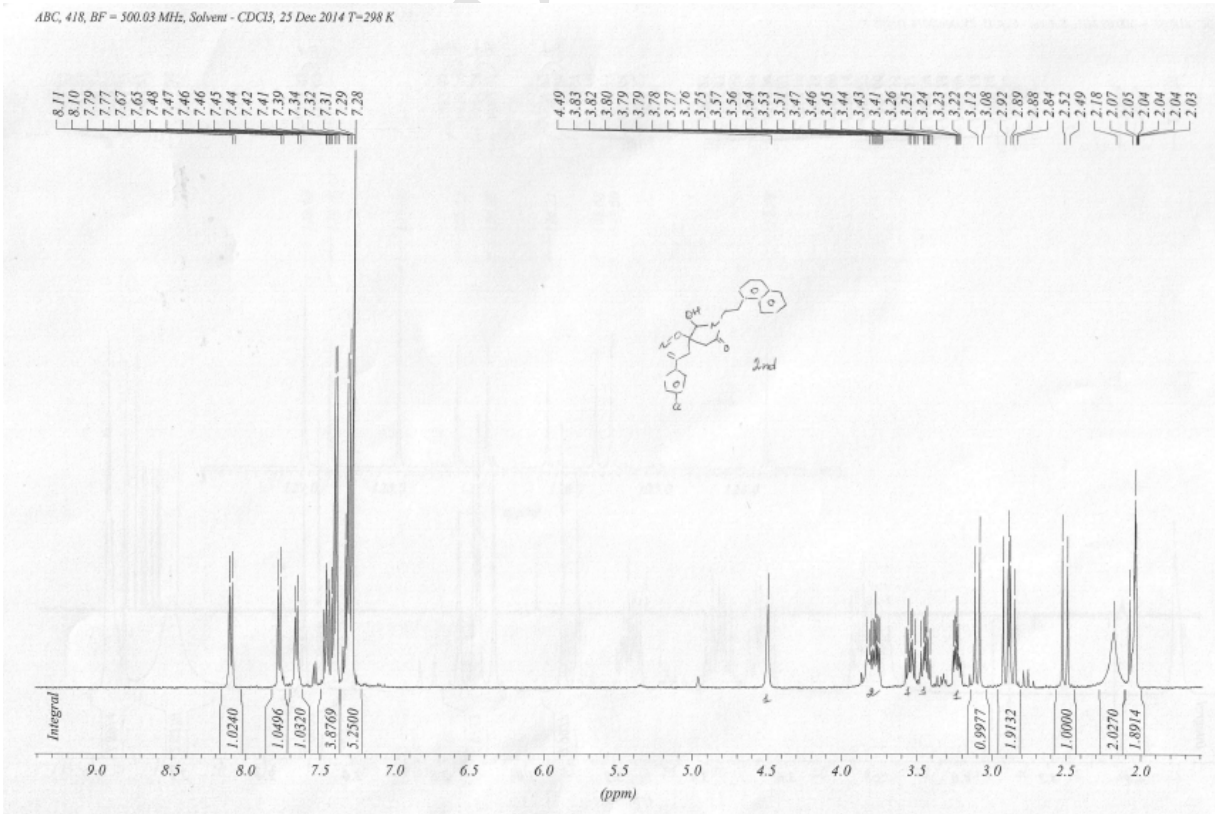


Figure 35. ^{13}C NMR spectrum of **12g** ($CDCl_3$, 100MHz), diastereomer 2

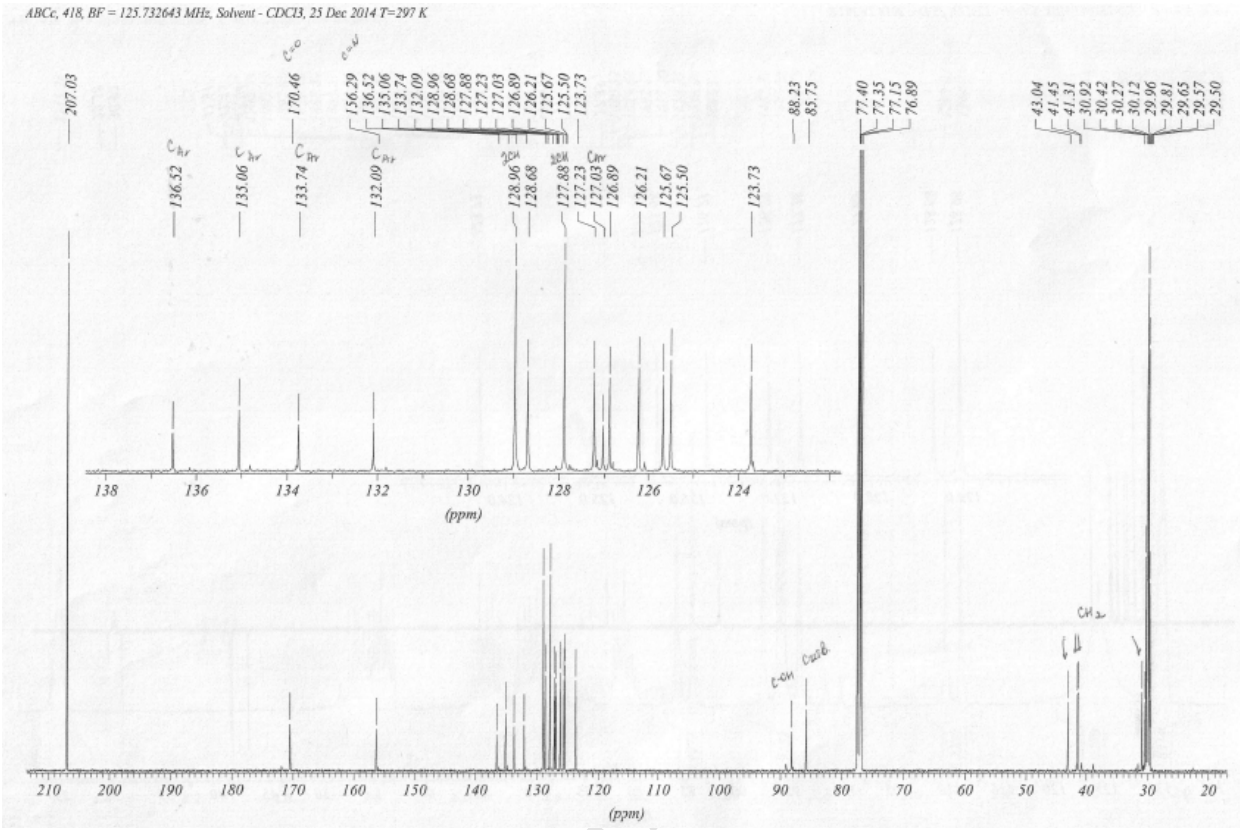


Figure 36. ^{1}H NMR spectrum of **13a** ($CDCl_3$, 400MHz)

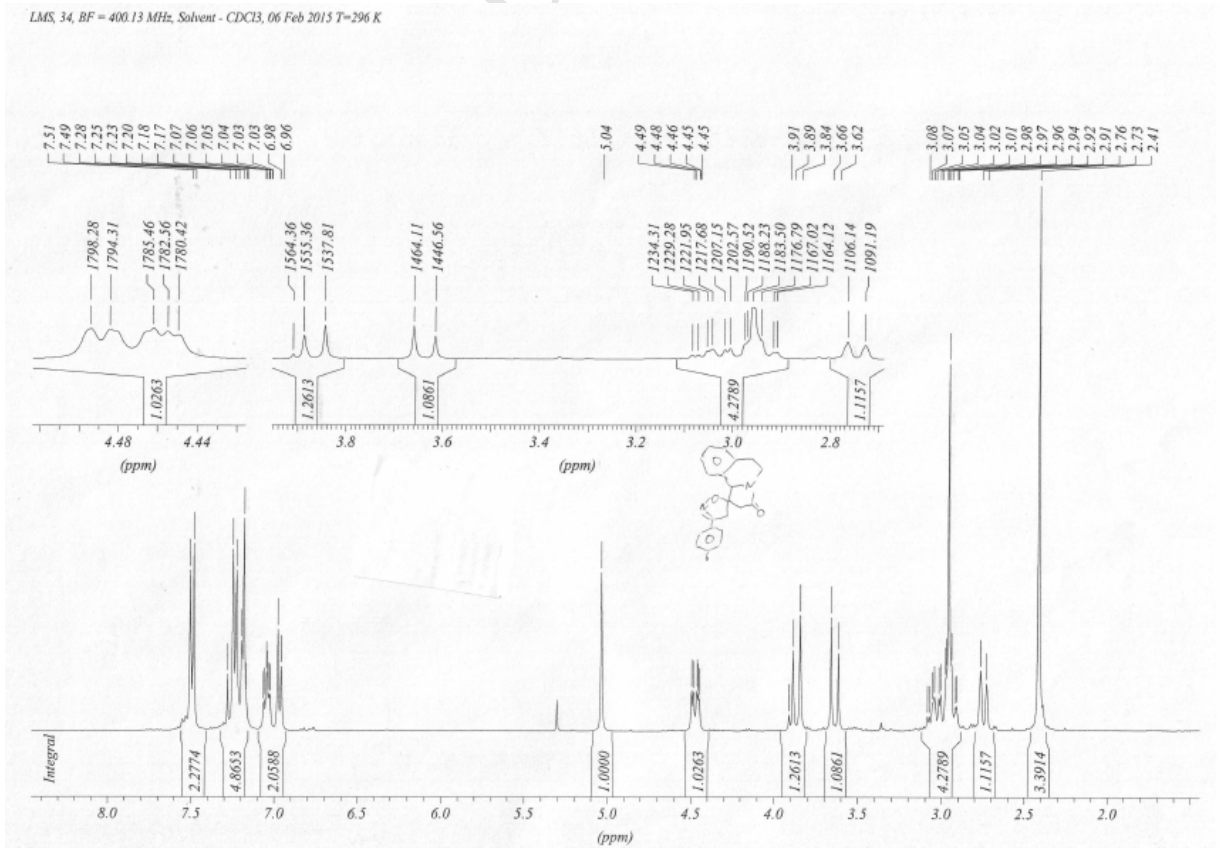


Figure 37. ^{13}C NMR spectrum of **13a** ($CDCl_3$, 100MHz)

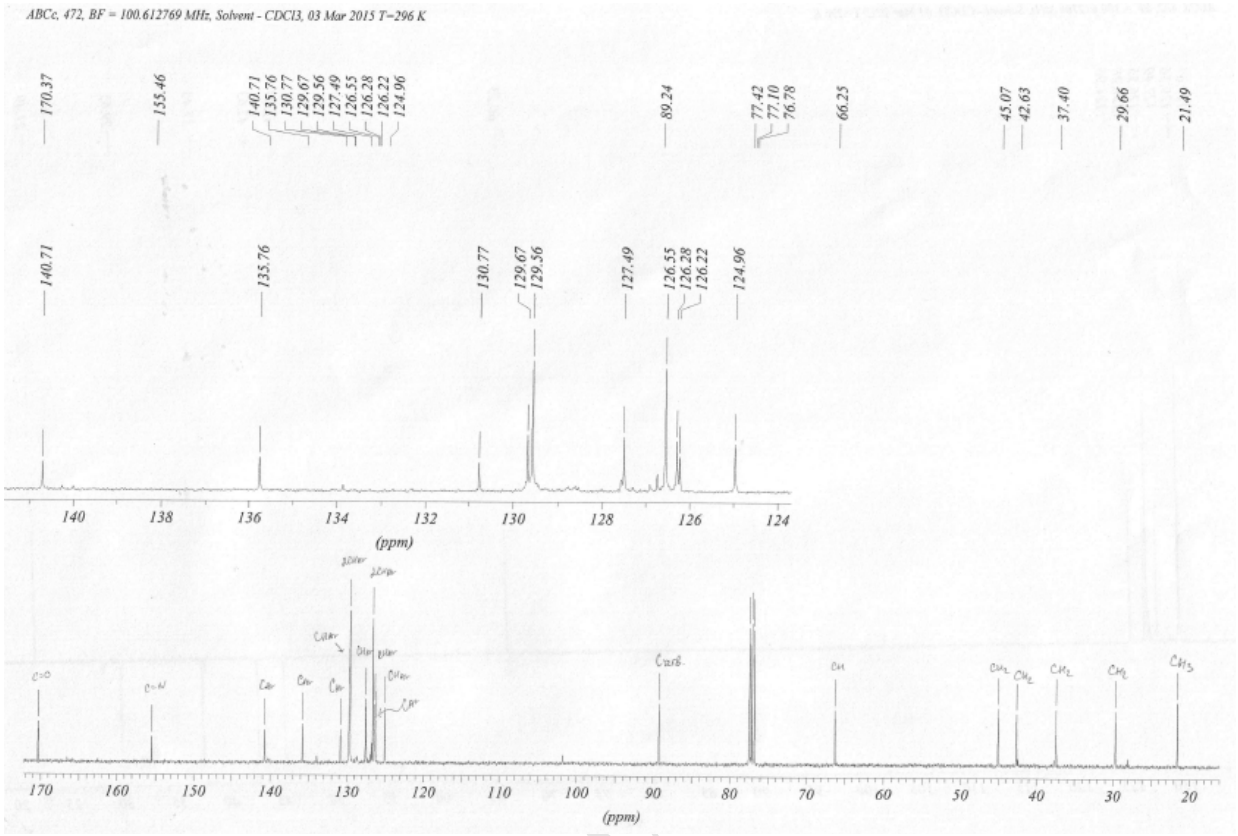


Figure 38. ^{1}H NMR spectrum of **13b** ($CDCl_3$, 400MHz)

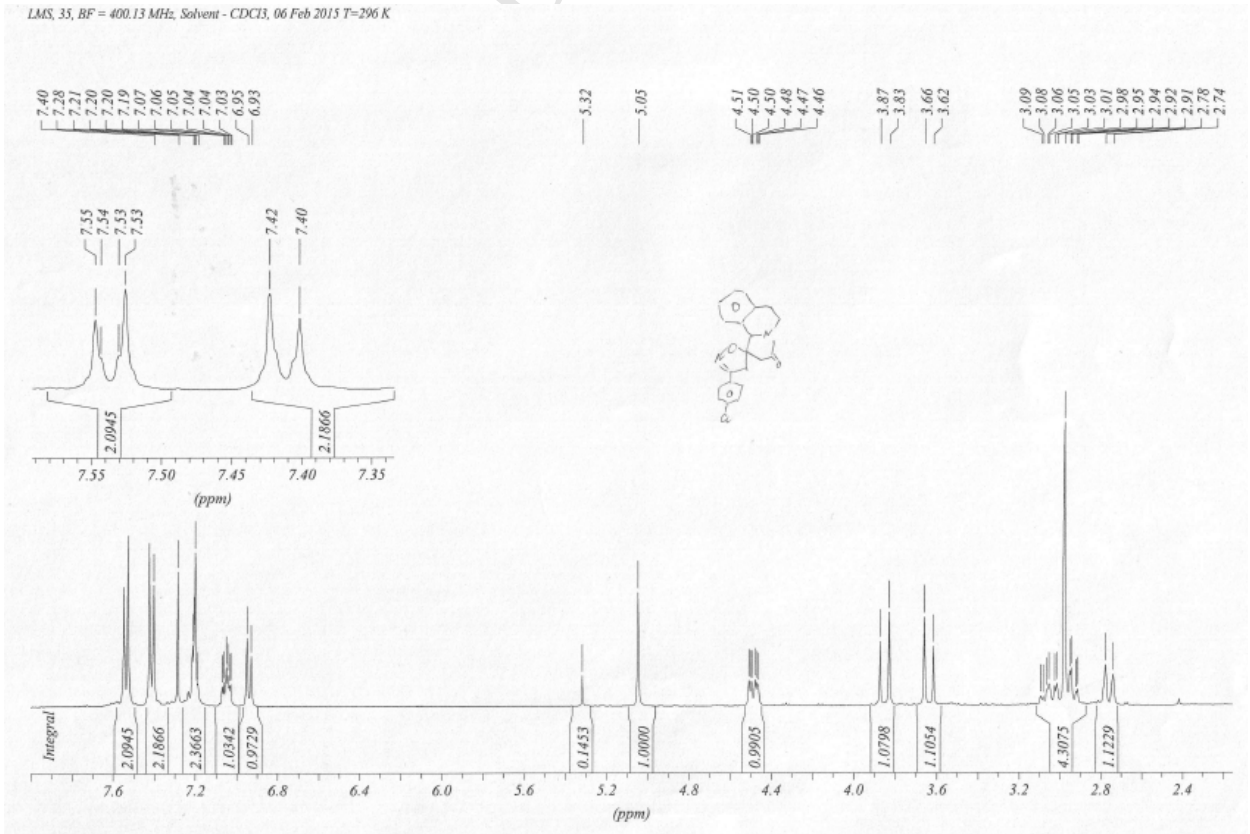


Figure 39. ^{13}C NMR spectrum of **13b** ($CDCl_3$, 100MHz)

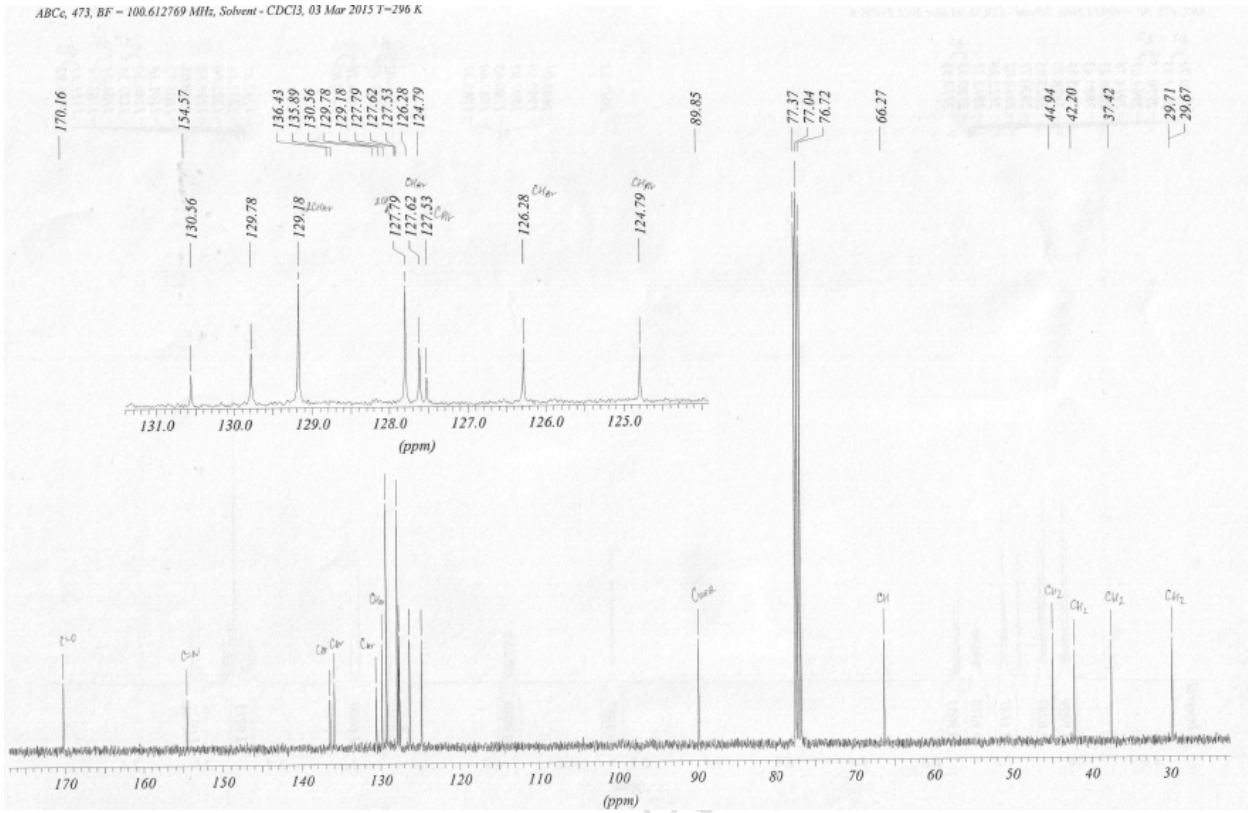


Figure 40. ^{1}H NMR spectrum of **13c** ($CDCl_3$, 400MHz)

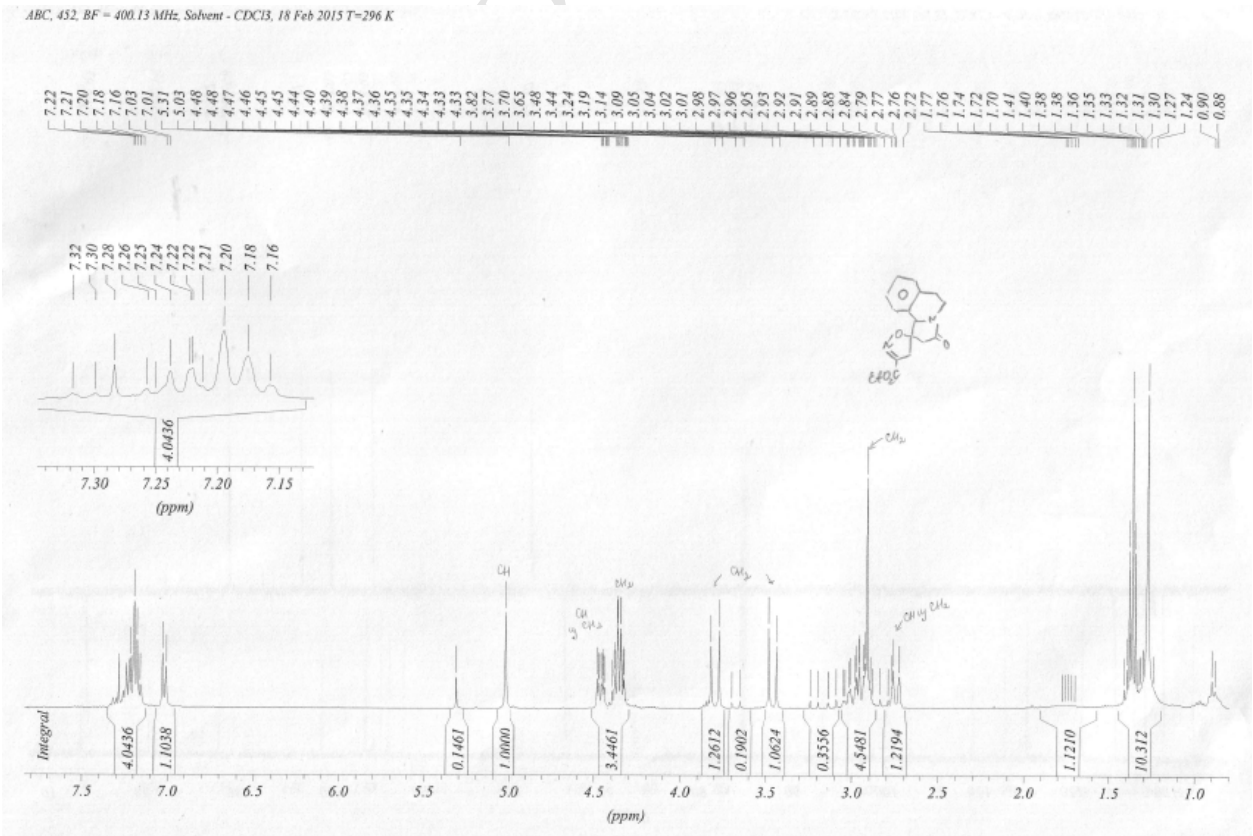


Figure 41. ^{13}C NMR spectrum of **13c** ($CDCl_3$, 100MHz)

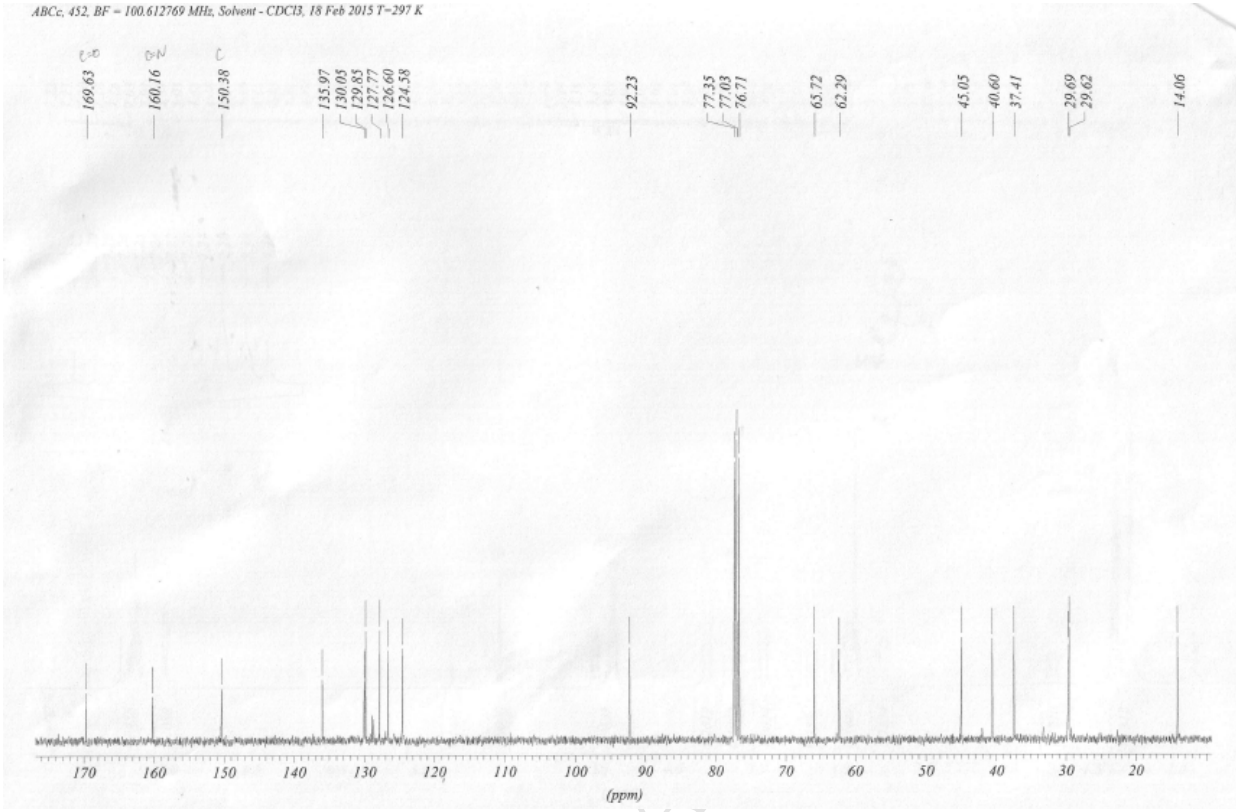


Figure 42. ^{1}H NMR spectrum of **13d** ($CDCl_3$, 400MHz)

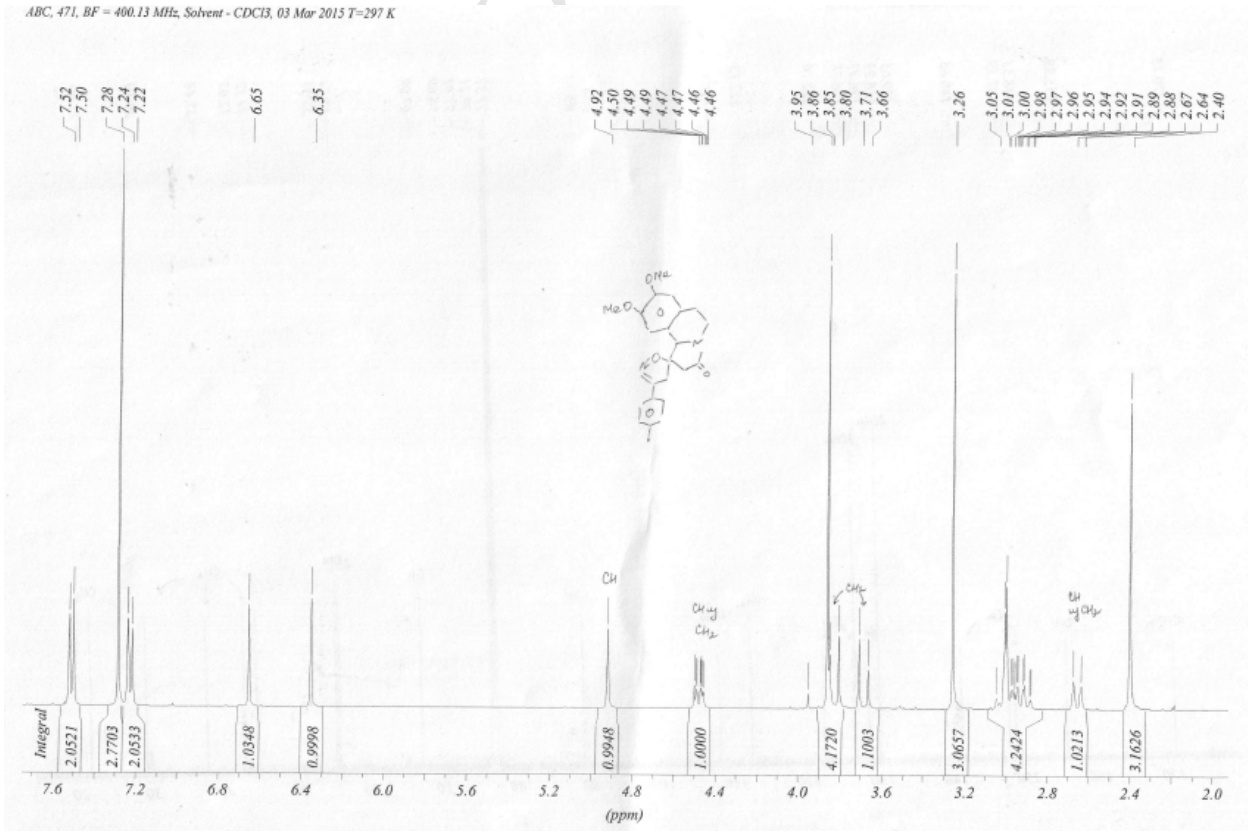


Figure 43. ^{13}C NMR spectrum of **13d** ($CDCl_3$, 100MHz)

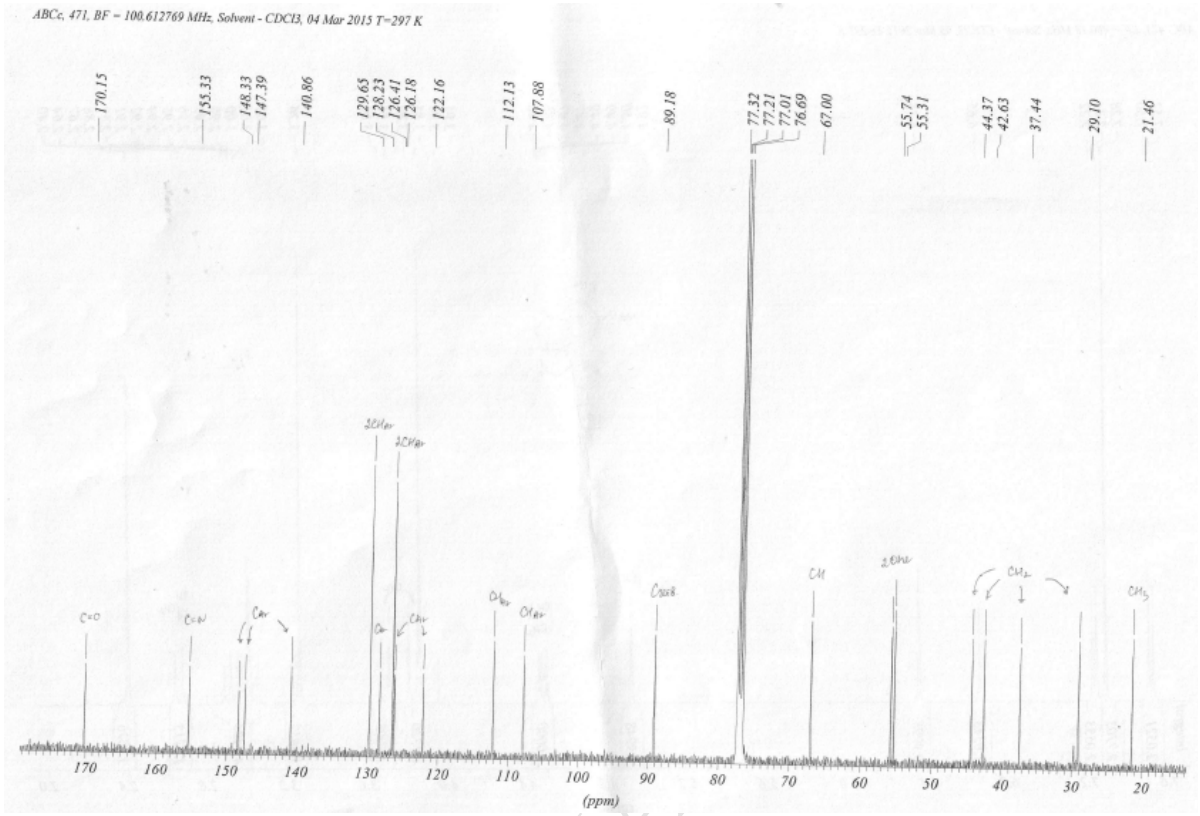


Figure 44. ^{1}H NMR spectrum of **13e** ($CDCl_3$, 400MHz)

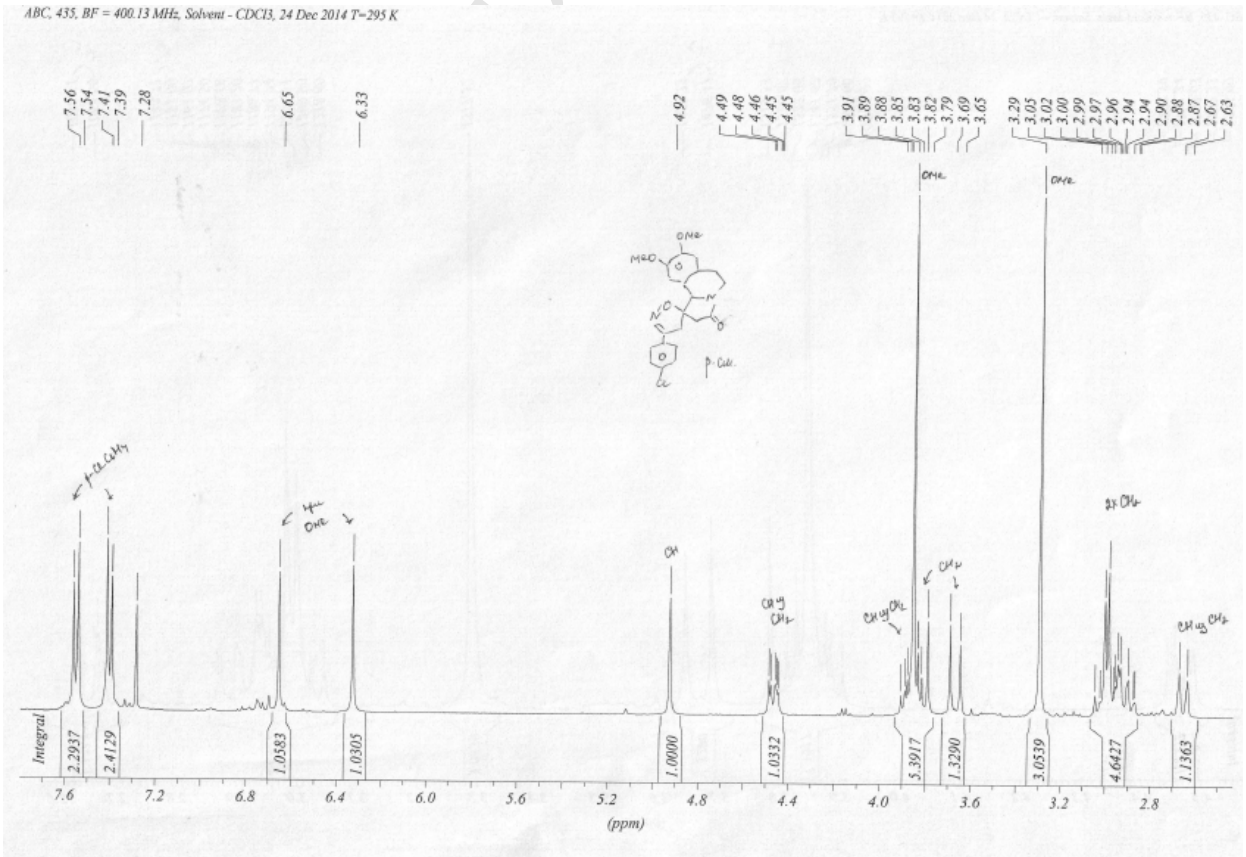


Figure 45. ^{1}H NMR spectrum of **13f** ($CDCl_3$, 400MHz)

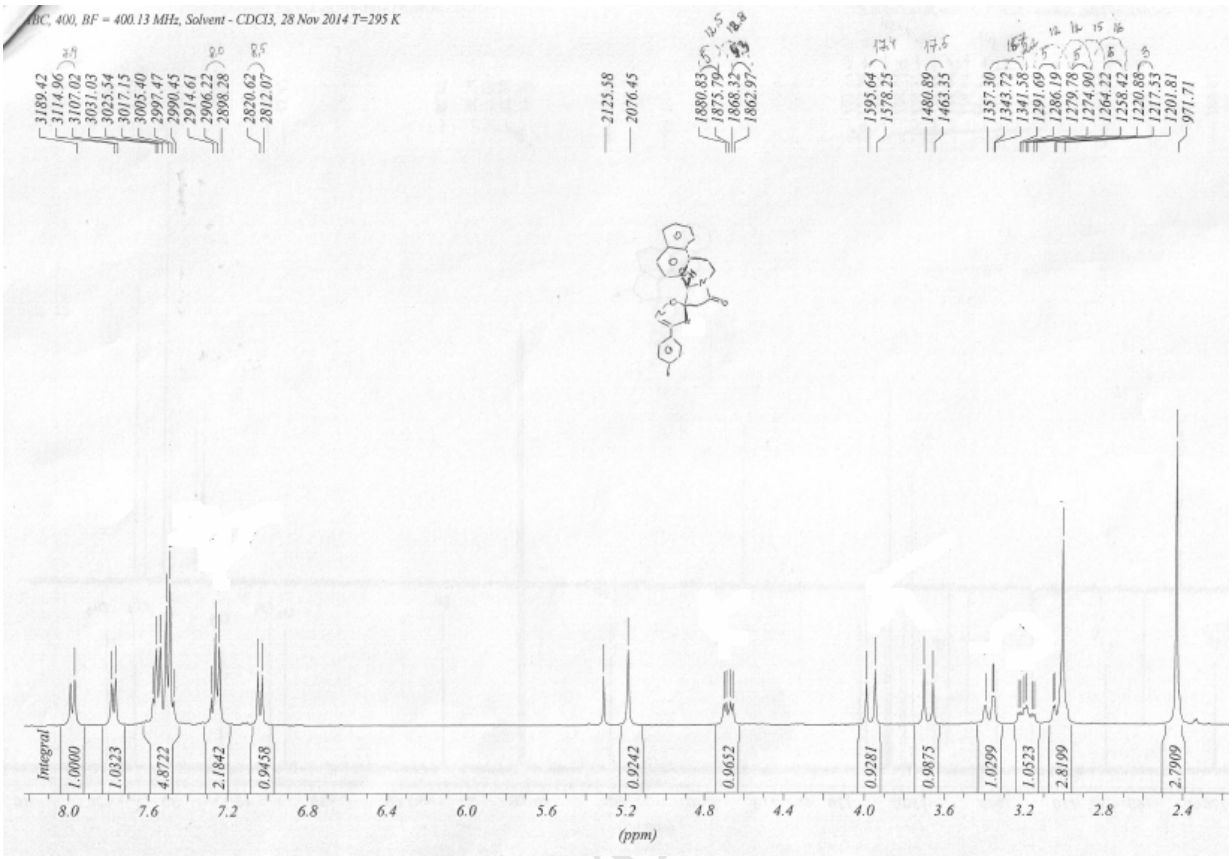


Figure 46. ^{13}C NMR spectrum of **13f** ($CDCl_3$, 100MHz)

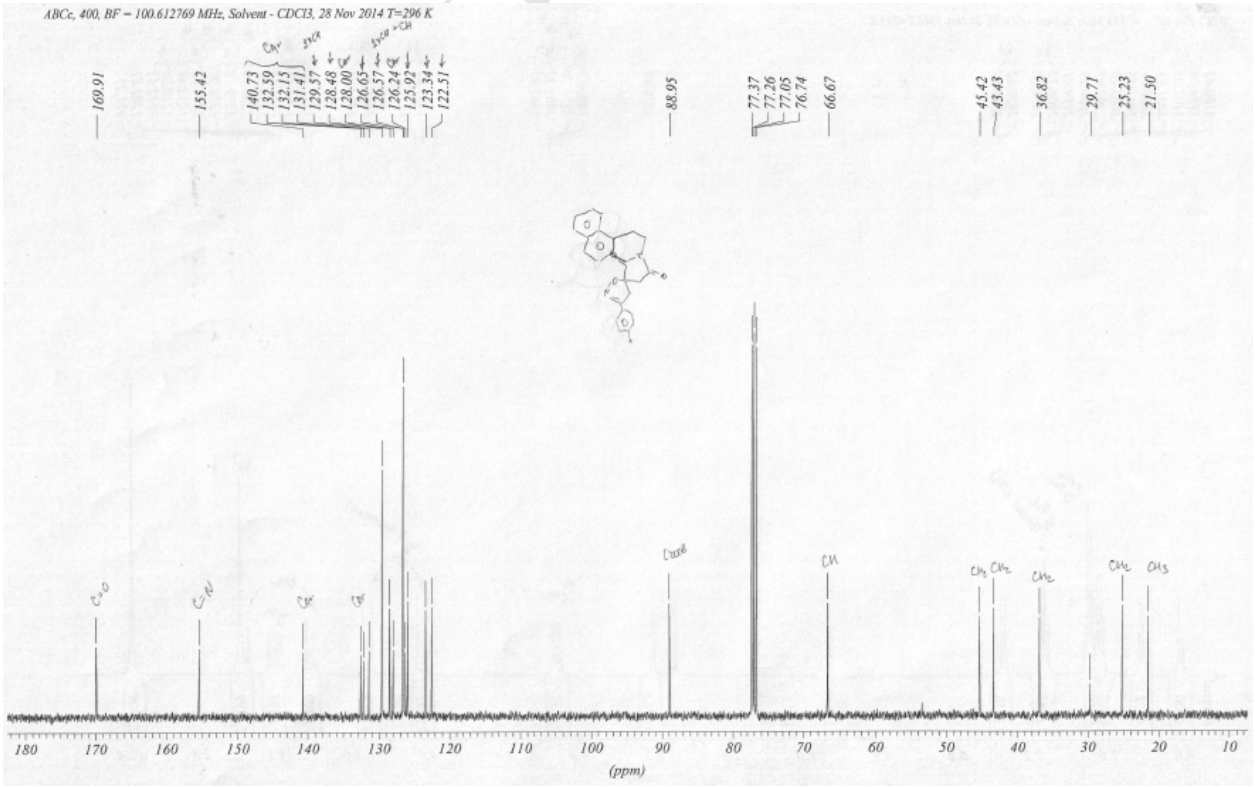


Figure 47. COSY spectrum of **13f** ($CDCl_3$, 400MHz)

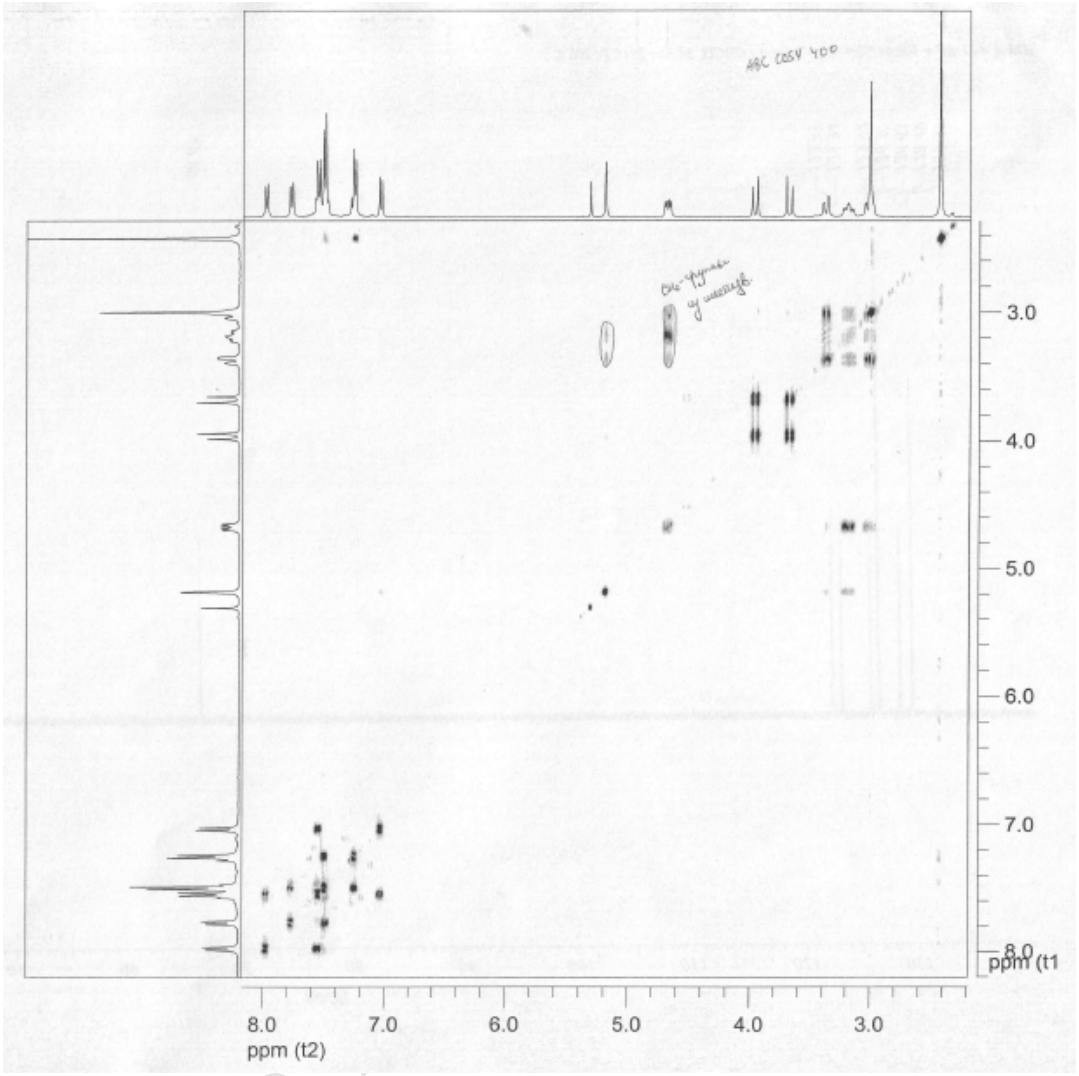
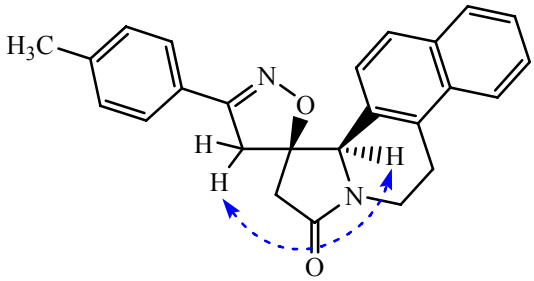


Figure 48. NOESY spectrum of **13f** ($CDCl_3$, 400MHz)



NOESY-correlations for (13f)

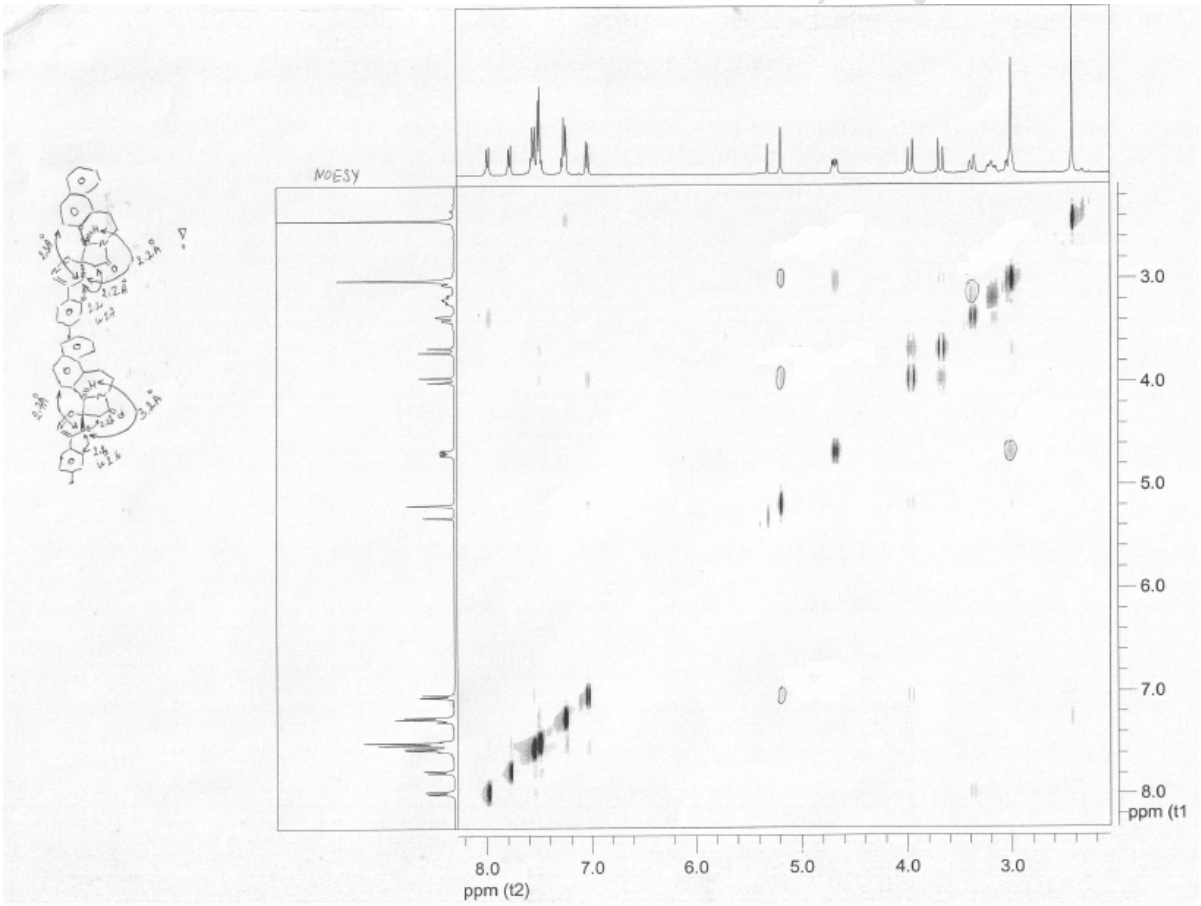


Figure 49. HSQC spectrum of **13f** ($CDCl_3$, 400MHz)

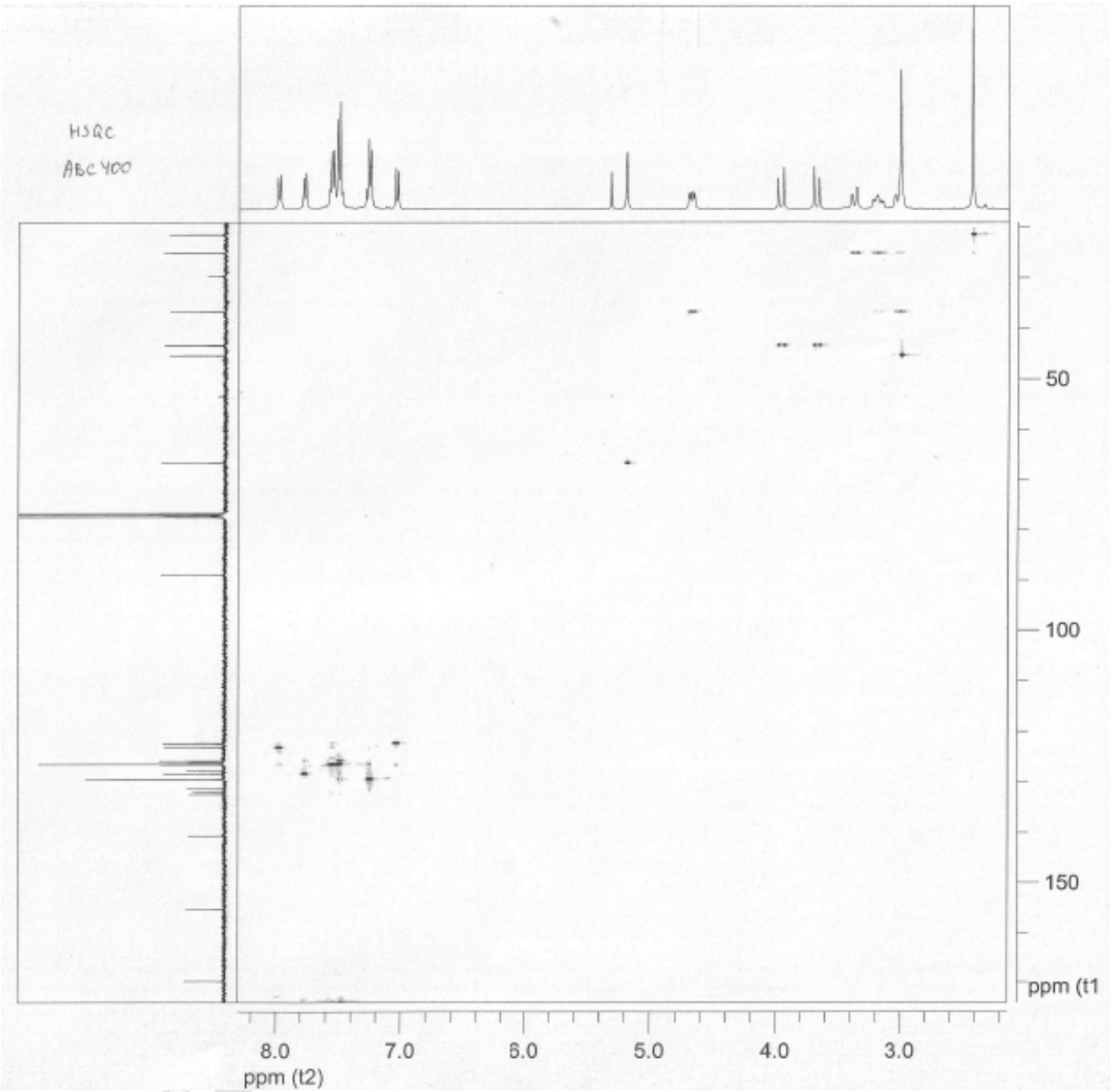


Figure 50. HMBC spectrum of **13f** ($CDCl_3$, 400MHz)

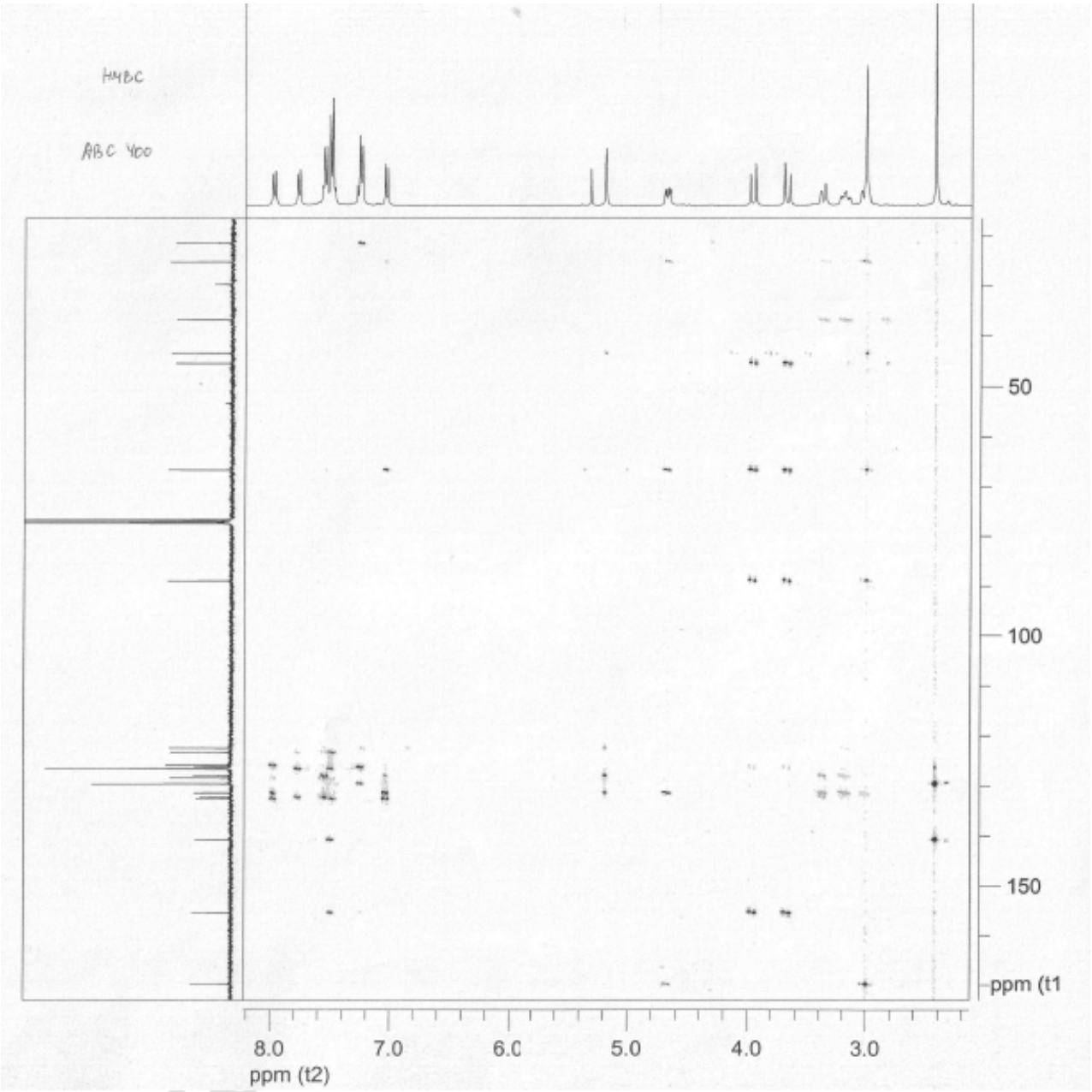


Figure 51. ^{1}H NMR spectrum of **13g** ($CDCl_3$, 400MHz)

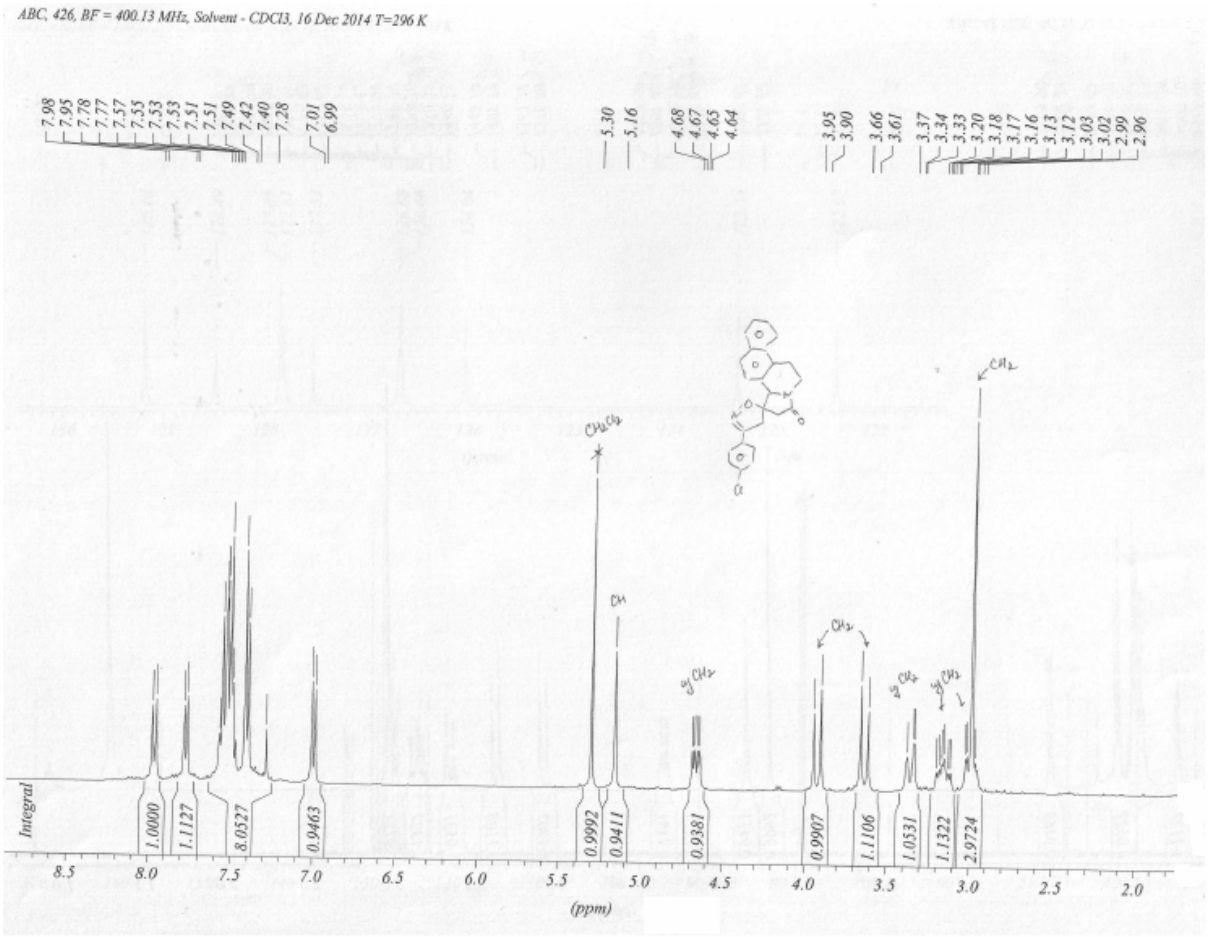


Figure 52. ^{13}C NMR spectrum of **13g** ($CDCl_3$, 100MHz)