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Synthesis of *N*-Heterocycles *via* Palladium-Catalyzed Reductive Cyclization Reactions of Nitroarenes and Nitroalkenes Using Formic Acid Derivatives as CO Surrogates

PhD Thesis of:

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"When I was a child, I thought of my Delta town as the center of the universe, but now I know how little I know about the universe. As a child I thought I was immortal, but now I recognize how limited a time we all have. As a child success meant scoring (A) on every exam, but now I take it to mean good health, close family and friends, achievements in my work and helping others."

Ahmed H. Zewail

Egyptian Chemist, the Nobel Prize in Chemistry 1999

To my family and friends …

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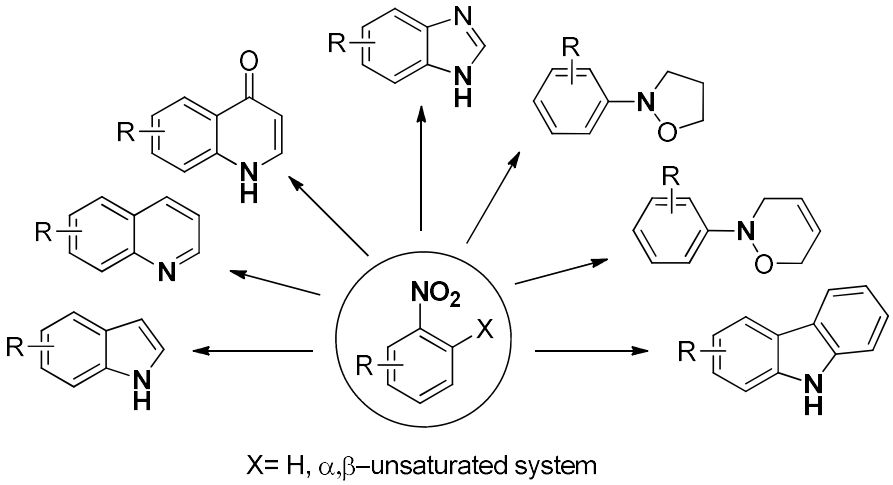
Introduction

Nitrogen-heterocycles are the core frameworks of numerous naturally occurring products, alkaloids, drugs, and other biologically active compounds.[1-3] They also exist as key units in many functional materials [4] and, for example, have been intensively studied as basic materials in high-performance organic field-effect transistors (OFETs), organic light-emitting diodes (OLED), and organic photovoltaics (OPVs).[5,6] Due to the important utility of *N*-heterocycles, their synthesis has received great attention. Traditional methods for the synthesis of *N*-heterocycles are largely based on anilines because anilines are central building blocks in C–N bond formation.[7-10] One of the most efficient ways to obtain anilines is through the reduction of nitroarenes, including hydrogenation, electrochemical reduction, and hydride-transfer.[11-13] In comparison with anilines, one or more synthetic steps can be saved by directly converting the corresponding nitroaromatics into *N*-heterocycles (**Scheme 1**).[14,15] Therefore, the one-pot synthesis of *N*-heterocycles from nitroarenes has attracted considerable interest.



Scheme 1. Representative examples of reductive transformations of nitroarenes.

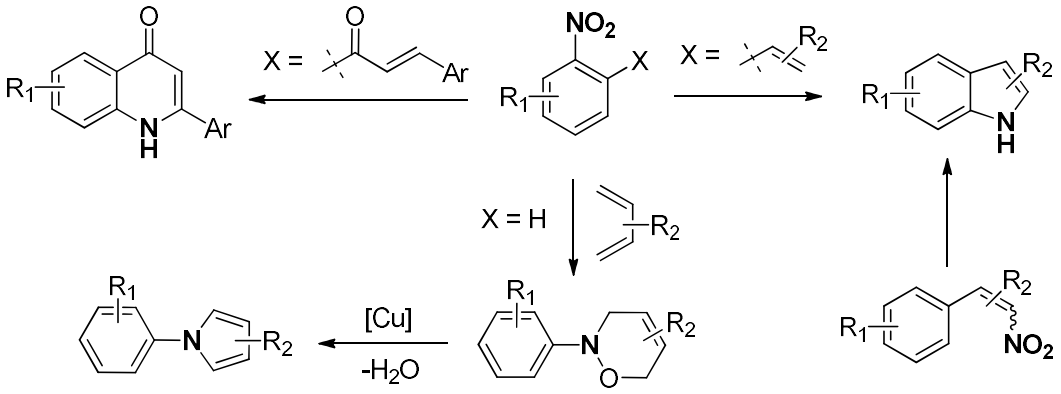
Nitroarenes as substrates have attracted more attention due to their ready availability in organic synthesis. They are feedstocks and can be easily constructed by electrophilic aromatic nitration of arenes,[16] many of which are commercially available and inexpensive. Reductive cyclization of nitroarenes to generate nitrogen-containing compounds by using (super)stoichiometric amount of phosphines [17,18] or carbon monoxide (CO) [19,20] has previously been developed. However, it has a conspicuous limitation in the production of a large amount of phosphorus oxide waste or the pressurization required using CO. Thus, it is of great significance to find alternative effective synthetic methods of *N*-heterocycles.

Despite that the use of CO as a reductant in the transition metals catalyzed reductive cyclization reactions of nitroarenes is accompanied by several drawbacks such as the need for strict safety measures and the use of autoclaves, it remains one of the most effective strategies to synthesize *N*-heterocycles for the following reasons:

1. Reduction of nitroarenes is a fundamental and widely used transformation for the construction of complex and functionalized heterocyclic architectures.
2. CO is cheap compared to other reducing agents except for dihydrogen, which however affords anilines and not heterocyclic compounds in most cases.
3. The only stoichiometric byproduct is CO_2, which spontaneously separates from the reaction products at the end of the reaction, thus simplifying the workup.
4. Remarkable functional group tolerance in addition to the very high yields in the desired heterocycles, with the possibility of employing low catalyst loading.[21]

To remove the need for autoclaves and pressurized CO lines, different solid or liquid substances able to liberate CO under the reaction conditions (known as CO surrogates) have been used in carbonylation reactions. Recently, we introduced the use of formate esters as a cheap, non-, or little-toxic CO source in the reductive cyclization of different nitroarenes to give *N*-heterocycles.[22-26]

Consequently, this thesis focuses on the use of phenyl formate and formic acid as efficient CO sources in the palladium-catalyzed *intra*-molecular reductive cyclization reactions of *o*-nitrostyrenes and *β*-nitrostyrenes into indoles and 2'-nitrochalcones into 4-quinolones, and the palladium-catalyzed *inter*-molecular cyclization reactions of nitroarenes in the presence of diene into 1,2-oxazines, which in turn could be catalytically transformed into *N*-arylpyrroles (**Scheme 2**).



Scheme 2. Palladium catalyzed reductive cyclization reactions investigated in this thesis.

To turn this kind of reaction into a "general tool" for all the synthetic chemists, all the reactions were carried out in a pressure tube, a cheap glass equipment easily accessible for all laboratories.

Chapter I:

Reductive Cyclization of Nitrostyrenes to Indoles Using Formic Acid Derivatives as CO-surrogates.

1. Introduction

Heterocycles containing nitrogen are essential frameworks that widely exist in many pharmaceuticals and agrochemicals. Therefore, in recent years, the advance of new approaches for the production of *N*-heterocycles has become an important consideration for chemists.[27-29] Among various *N*-heterocycles, 5-membered nitrogen containing heterocycles like indoles broadly exist in agrochemicals,[30] pharmaceuticals,[31,32] functional materials,[33] bioactive compounds [34] and natural products, [35] which puts the indoles among the top 10 of the most important organic chemistry scaffolds (**Fig.1**).[32] Thus, the functionalization and the production of the indole moiety have attracted significant consideration from scientists.

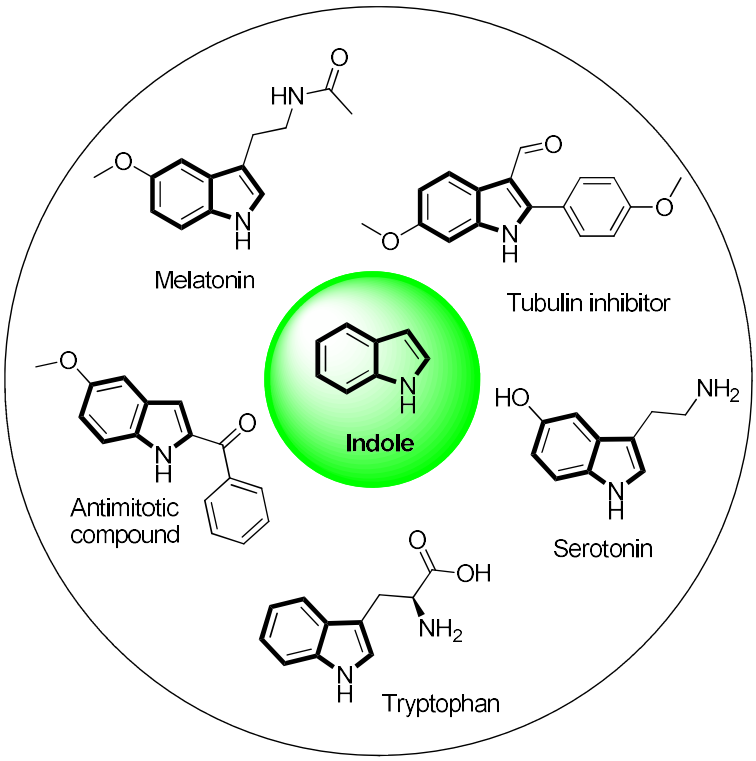
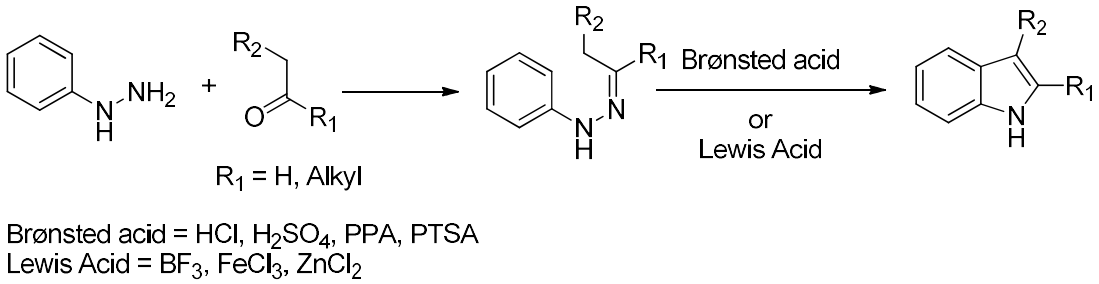


Fig. 1. Biologically potent molecules containing indole as a moiety.

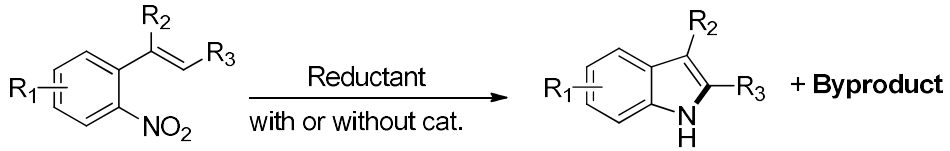
Not surprisingly, myriads of synthetic methods were described to access the indole core. However, many of the well-established indole synthetic methods suffer from harsh reaction conditions,

limited substrate scope, use of (halogenated) hydrocarbons as solvents or other sustainability issues.[36,37] For example, the classical Fischer indole synthesis (FIS) is often performed under highly acidic refluxing conditions of the pre-condensed phenylhydrazone (**Scheme 3**).[38] The synthesis of the hazardous phenylhydrazine precursor involves the diazotization of aniline, the reduction of the resulting diazonium salt with an excess amount of sodium sulfite, and the hydrolysis of phenylhydrazine sulfonic acid salt with hydrochloric acid, also known as the Fischer phenylhydrazine synthesis.[39]



Scheme 3. Fischer indole synthesis (FIS).

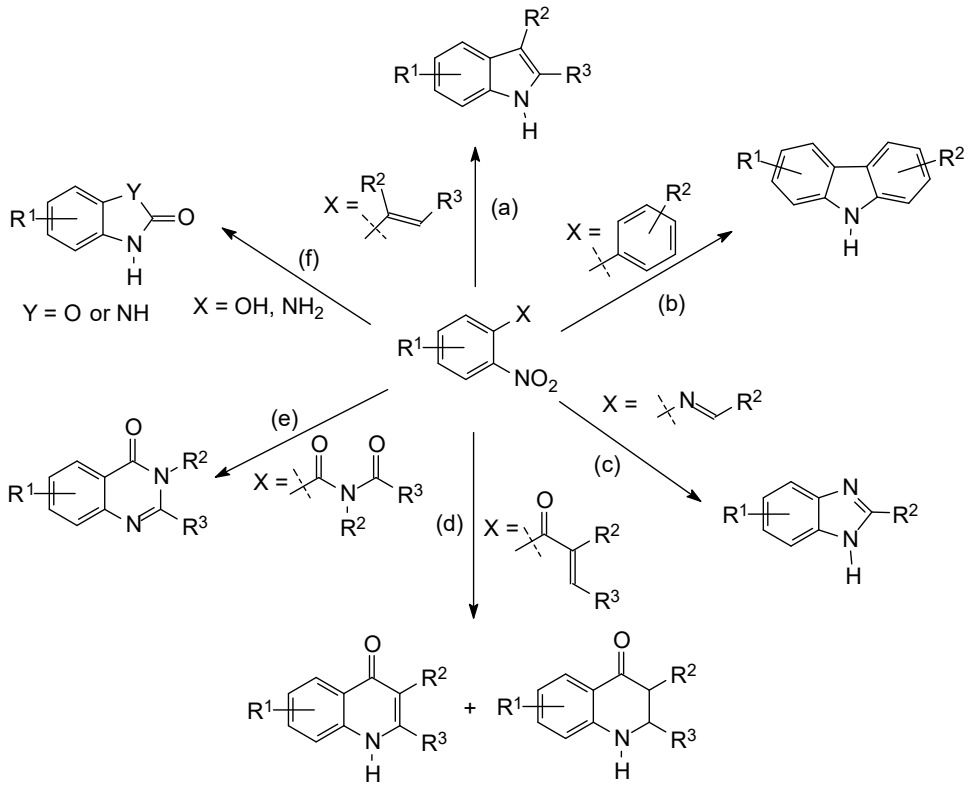
The production of indoles by *intra*-molecular reductive cyclization of *o*-nitrostyrenes was first reported by Cadogan[40,41] and Sundberg[17] using triethyl phosphite both as the solvent and the reductant. These methodologies are widely used in laboratories despite the harsh reaction conditions (>156 °C). Moreover, these methodologies generate an equal quantity of phosphorus waste and sometimes lead to decreased product yields because of the formation of *N*-ethoxyindoles as byproducts (**Scheme 4a**).[42,43] Various approaches have been developed for the synthesis of indoles. The use of phosphines in metal-catalyzed,[44,45] metal-free,[31,46] or photochemical reactions[47] generates either oxidized phosphines or *N*-ethoxyindoles, in the case of employing $P(OEt)_3$ (classical Cadogan reaction), as byproducts. Yet, because of the prominence of this protocol, chemists have developed approaches using environmentally benign reactants as compared to phosphorous (III) reagents. Methods employing stoichiometric metal-containing compounds,[48-52] organocatalyzed and transition metal catalyzed reactions using diborane [53] or silanes [54,55] as terminal reductants (**Scheme 4b**) have been developed. Among the several alternatives to phosphorous (III) reagents, use of pressurized CO has been considered by numerous groups in chalcogen [56,57] or metal [20,58-64] catalyzed reactions (**Scheme 4c**). In this context, Cenini *et al.* [20] first described a procedure for the production of indoles through *intra*-molecular cyclization of *o*-nitrostyrenes under forcing reaction conditions (80 bar of CO and 220 °C), and employing metal carbonyl clusters as catalysts.



	Reductant	Byproducts
a) **Cadogan-Sundberg and related methods**	$P(OR)_3$ or PR_3	$O=P(OR)_3$ or $O=PR_3$
b) **Alternative reductants**	stoichiometric metal-containing species	stoichiometric oxidized metal-containing species
	B_2pin_2	$(pinB)_2O$
	silanes	siloxanes
c) **Pressurized reductant**	CO	CO_2
d) **CO surrogates**	$M_x(CO)_n$ (M= Mo, Co)	CO_2 + [M]
	TFBen	CO_2 + Phloroglucinol

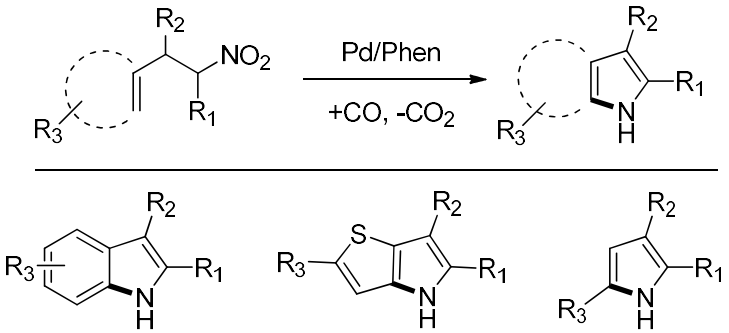
Scheme 4. Different routes of reductive cyclization of o-nitrostyrenes and their byproducts.

Among all the previously mentioned classes of reactions that can be employed to produce indoles, the reductive cyclization of nitrostyrenes by carbon monoxide is one of the most appealing from this point of view because only CO_2 is formed as a stoichiometric byproduct and the excess of reducing agent is easily removed with the produced CO_2 simply upon venting the autoclave.[21,65-67] As a matter of fact, a large variety of bulk [19,68] and fine [65,69,70] chemicals have been prepared with high efficiency with these systems. A plethora of nitrogen-containing heterocycles have been prepared by *intra*-molecular cyclization of suitably *ortho*-substituted nitroarenes using CO as a stoichiometric reductant (**Scheme 5**).



Scheme 5. *Intra*-molecular cyclization reactions of nitroarenes.

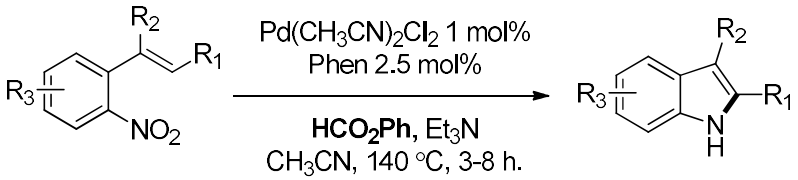
It is worth noting that most of the reported reactions for the synthesis of *N*-heterocycles starting from organic nitro compounds and CO as the reductant employ suitably substituted *o*-nitroarenes as substrates [59,61,64,71-75], although examples of *inter*-molecular reactions of nitroarenes have also been reported [76-78] (see examples reported in chapter III). much less attention has been paid to the use of nitroalkenes as substrates. Dong was the first to report the use of *α*-aryl-*β*-nitrostyrenes as substrates for the synthesis of indoles by reductive cyclization using CO as the reductant and employing Pd(II)/Phen as a catalyst.[79] Our group later extended the range of suitable substrates for the same reaction [80] and also applied as substrates *β*-nitrothiophenes, to give thienopyrroles,[81] and nitrodienes, to give pyrroles [82] (**Scheme 6**).



Scheme 6. Reductive cyclization of nitroalkenes.

Despite the high efficiency of several of these reactions, their use has not spread outside the limited number of groups that reported them. This is because they generally involve the use of pressurized CO, requiring safety measures that are not available in most synthetic organic laboratories. This problem is common even to other carbonylation reactions and in recent years many reagents have been developed that are able to release CO *in-situ*, thus avoiding the need for autoclaves and CO lines.[83,84] However, some of these reagents have been employed to deoxygenate nitroarenes, for example, $Mo(CO)_6$ [85] $Co_2(CO)_8$,[86,87] triformate ester [88,89] or CO_2/silanes [90] (**Scheme 4d**). The drawbacks accompanied to the use of surrogates are in some cases the relatively high cost, the toxicity of some compounds or the formation of undesired coproduct because of their decomposition. Moreover, in several cases the decomposition of the CO-releasing molecule and the actual catalytic reaction need to be performed in two separate reactors connected to each other. Since the reactors should be able to withstand a moderate pressure (a few bars), this fact limits the scale of the reaction to the available reactors.

Our group has reported that formate esters can be employed as suitable CO releasing substances in the synthesis of indoles from *o*-nitrostyrenes,[26] for the synthesis of oxazines from nitroarenes and conjugated dienes,[25] and even for the synthesis of carbazoles form *o*-nitrobiphenyl.[24] Formate esters are convenient because of their commercial availability, low cost and low toxicity. It has been demonstrated that alkyl formate could be a successful CO surrogate in the reductive cyclization of *o*-nitroarenes. Phenyl formate was found to be more effective than alkyl formates, allowing lower temperatures to be employed and higher selectivities to be achieved. Moreover, phenyl formate can be activated by weak organic bases, whereas alkyl formates require the use of strong bases or the addition of a ruthenium catalyst, which makes the catalytic system more complex. The reactions could be performed in a single glass pressure tube. This equipment is cheap and available in different sizes. A steel autoclave can also be used, but without the need for pressurized CO. The optimized reaction conditions for the synthesis of indoles include the use of $Pd(CH_3CN)_2Cl_2$ as catalyst, with 1.10-phenanthroline as ligand, phenyl formate as the CO releasing agent and triethylamine as the base to activate it in acetonitrile at 140 °C. (**Scheme 7**).[23,26]



Scheme 7. Optimized catalytic system for the indole synthesis using phenyl formate as CO source.

However, the temperature remains moderately high and leads to low selectivity in the cyclization of certain substrates especially in the presence of sensitive groups such as an aldehyde or a pyrrole ring. Consequently, this chapter will concentrate on:

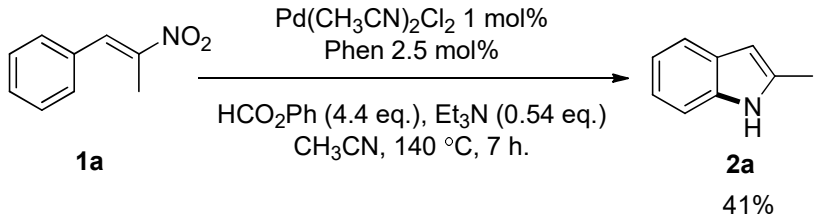
1. Optimizing the reaction conditions to enable the synthesis of indoles *via* the reductive cyclization reaction of *β*-nitrostyrenes using phenyl formate as a CO surrogate.

2. Making further optimization to get indoles from *o*-nitrostyrenes with a new set of experimental conditions in the hope that this feature will allow to deal also with very reactive functional groups on the molecule.
3. Development of suitable experimental conditions to employ formic acid as a CO surrogate in the reductive cyclization reaction of *o*-nitrostyrenes. Thus eliminating the problem of the formation of phenol as a coproduct of phenyl formate decomposition, whose complete separation was problematic in some cases.[91]

2. Results and Discussion

2.1. Pd-catalyzed reductive cyclization of *β*-nitrostyrenes using phenyl formate

The only previously reported data on the use of formate esters as CO surrogates for the reductive cyclization of a nitroalkene refers to a single preliminary test on the cyclization of *β*-methyl-*β*-nitrostyrene **1a** (**Scheme 8**) employing $Pd(CH_3CN)_2Cl_2$/Phen as catalyst, CH_3CN as solvent and phenyl formate as the CO surrogate [23,26]. Et_3N was employed as the base necessary to catalyze the decomposition of phenyl formate into CO and phenol.



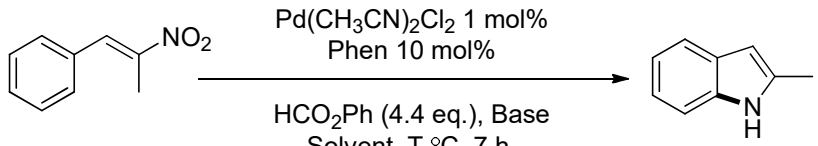
Scheme 8. Reductive cyclization of *β*-methyl-*β*-nitrostyrene.[23]

For our preliminary investigations, we took the reductive cyclization reaction of **1a** as the model reaction. The tests were performed in screw-cap thick-walled glass tubes (pressure tubes).

2.1.1. Optimization of the reaction conditions

We first reproduced only the previous experiment (**Table 1**, entry 1), obtaining similar results (39% selectivity and 80% conversion vs. 41% selectivity and 100% conversion). The small difference is attributable to the different experimental apparatus employed in the two cases (see experimental section for more details). Starting from this test, we changed a series of parameters. By a few explorative tests, we have found that a larger amount of phenanthroline and base afforded a more active and stable catalytic system, even though the selectivity in indole was not improved (**Table 1**, entry 2). The only other tested solvent (**Table 1**, entries 2–6) that gave results comparable to CH_3CN was DMF. However, DMF is more toxic and less easy to separate from the reaction products than CH_3CN and we decided not to use it.

Table 1. Optimization of the reaction conditions for the reductive cyclization of *β*-methyl-*β*-nitrostyrene **1a** to 2-methylindole **2a**.[a]



1a **2a**

Entry	Base	Base amount (mmol)	T (°C)	Solvent	Conv.(%)[b]	Sel. (%)[b]	Yield (%)[b]
1[c]	Et_3N	0.29	140	CH_3CN	80	39	31
2	Et_3N	2.30	140	CH_3CN	>99	40	40
3	Et_3N	2.30	140	THF	85	30	26
4	Et_3N	2.30	140	DMF	>99	41	41
5	Et_3N	2.30	140	$C_6H_5CH_3$	52	12	6
6	Et_3N	2.30	140	CH_3OH	85	9	8
7[d]	-	-	140	CH_3CN	~0	0	0
8[e]	Et_3N	2.30	140	CH_3CN	61	0	0
9	Et_3N	0.29	120	CH_3CN	32	31	10
10	Pyridine	0.29	120	CH_3CN	<1	<1	~0
11	Pyridine	0.29	150	CH_3CN	17	18	3
12	NaOAc	0.29	120	CH_3CN	62	17	11
13	Na_3PO_4	0.29	120	CH_3CN	78	7	5
14[f]	Et_3N	2.30	140	CH_3CN	>99	26	26
15[f]	Et_3N	0.29	140	CH_3CN	95	28	27
16[g]	Et_3N	2.30	140	CH_3CN	>99	47	47

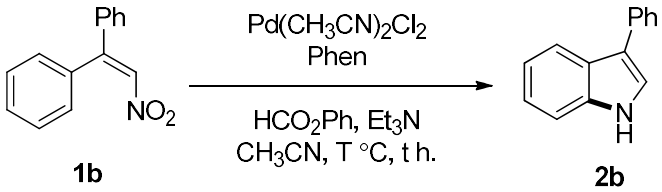
a: Experimental conditions: 0.54 mmol **1a**, 1 mol% $Pd(CH_3CN)_2Cl_2$, 10 mol% Phen, 260 μL HCO_2Ph, in 10 mL of the indicated solvent, for 7 h; other amounts and conditions as in the table. 0.29 mmol Et_3N corresponds to 40 μL. ***b***: Determined by GC using naphthalene as the internal standard. **c**: 2.5 mol% of Phen. ***d***: No phenyl formate and no base were added. ***e***: No phenyl formate was added. ***f***: 5 mol% $Pd(CH_3CN)_2Cl_2$. ***g***: 350 μL HCO_2Ph.

In order to understand the reasons for the failure in reaching selectivities comparable with those previously obtained for the same reaction by the use of gaseous CO,[92] we investigated the stability of the starting *β*-nitrostyrene under the reaction conditions and in the presence of only some of the reagents. No reaction was observed under typical reaction conditions in the absence of phenyl formate when only the palladium catalyst and phenanthroline were added (**Table 1**, entry 7). On the other hand, when the base was also added in the absence of any formate, a significant 61% conversion of *β*-nitrostyrene was observed. A very small amount of benzaldehyde, the product of a retro-Henry hydrolysis of the reagent, was observed by GC and ^{1}H-NMR. No other decomposition product was observed by GC analysis, suggesting that they are oligomeric or polymeric species. *β*-Nitrostyrenes are known to be prone to polymerization by a base-catalyzed process.[93] Clearly, a competition is occurring between the cyclization and the decomposition reaction, with the base accelerating both. Bases different from Et_3N could promote the reaction to different extent, but they apparently also promoted the alternative decomposition pathways and the selectivities in indole were always lower (**Table 1**, entries 9–13). Unfortunately, increasing the catalyst amount to 5 mol% did not solve the problem (**Table 1**, entries 14, 15).

At this point, it is worth recalling that when gaseous CO was employed as the reductant for the reductive cyclization of *β*-substituted-*β*-nitrostyrenes, high selectivities were only observed at CO pressures higher than 20 bar (measured at RT).[92] Retrospectively, these relatively high pressures are likely needed to speed-up the reduction reaction with respect to the polymerization, which is likely insensitive to the CO pressure. Indeed, the only attempt in which the selectivity in indole could be improved was that performed employing a larger amount of formate (**Table 1**, entry 16). However, working with such a large amount of formate is unsafe because in the worst-case scenario, complete decomposition of the formate and no CO consumption, the total pressure inside the reaction vessel at the reaction temperature would exceed 10 bar, which is considered as the safety pressure limit of glass pressure tubes. Thus, we decided not to pursue this strategy anymore. Although the problem may be solved by performing the reaction in a steel autoclave, this was not the aim of the present work. The key role of a high CO pressure is also evidenced by the failure to increase the selectivity of the reaction by increasing the catalyst amount at a fixed formate concentration.

Since the reductive cyclization of *α*-aryl-*β*-nitrostyrenes is faster than that of *β*-substituted-*β*-nitrostyrenes [79,92] we then moved to optimizing the reaction conditions for *α*-phenyl-*β*-nitrostyrene **1b**, keeping in mind the results we obtained in case of **1a** (**Table 2**).

Table 2. Optimization of the reaction conditions for the reductive cyclization of *α*-phenyl-*β*-nitrostyrene **1b** to 3-phenylindole **2b**.[a]



1b **2b**

Entry	Pd (mol%)	Phen (mol%)	T (°C)	t (h)	Et_3N (µL)	HCO_2Ph (µL)	Conv. (%)[b]	Sel. (%)[b]	Yield (%)[b]
1	1	5	110	3	120	260	>99	84	84
2	1	5	120	3	120	260	>99	87	87
3	1	5	130	3	120	260	>99	90	90
4	1	5	140	3	120	260	>99	92	92
5	1	5	150	3	120	260	>99	77	77
6	1	5	140	3	20	260	>99	84	84
7	1	5	140	3	40	260	>99	85	85
8	1	5	140	3	60	260	>99	87	87
9	1	5	140	3	80	260	>99	88	88
10	1	5	140	3	120	200	97	81	79
11	1	5	140	3	120	350	>99	91	91
12	1	5	140	3	200	350	>99	90	90
13	1	2.5	140	3	120	260	94	85	80
14	1	2.5	140	3	80	260	>99	83	83
15	1	2.5	140	7	40	260	>99	87	87

16	1	2.5	140	16	40	260	>99	87	87
17	1	10	140	3	120	260	>99	90	90
18	0.5	5	140	3	120	260	>99	78	78
19	0.5	5	140	6	120	260	>99	79	79
20[c]	2	5	140	3	120	260	>99	90	90
21[c]	2	5	140	1.5	120	260	>99	90	90
22[d]	1	5	140	3	120	260	>99	88	88
23[e]	1	5	140	3	120	260	>99	85	85

a: Experimental conditions: 0.54 mmol **1b**, in 10 mL CH_3CN; other amounts and conditions as in the table. ***b***: Determined by GC using naphthalene as the internal standard. ***c***: Pd-black precipitation was observed after 1 h reaction. ***d***: In DMF (10 mL) as solvent. ***e***: In CH_3CN + DMF (9 + 1 mL) as solvent.

The reaction temperature was first optimized (**Table 2**, entries 1–5 and **Fig. 2A**). As expected, based on the reactivity observed under CO pressure, the reaction can be performed even at 110 °C. However, the selectivity in the formation of the desired indole increases up to 140 °C, after which a drop is observed. The effect of the amount of base is moderate, but an almost linear increase in the selectivity is observed at 140 °C on passing from 20 to 120 µL of Et_3N (**Table 2**, entries 4, 6–9 and **Fig. 2B**).

Decreasing the phenyl formate amount (**Table 2**, entry 10 vs. entry 4) led to an incomplete conversion of the reagent and a lower selectivity in indole, which is not surprising. However, contrary to what was observed in the case of **1a**, even increasing the formate amount (**Table 2**, entry 11) did not improve the selectivity. The difference between the two substrates is likely because whereas the reductive carbonylation of **1a** requires pressures in excess of 20 bar to selectively afford **2a**, the corresponding reaction of **1b** can be successfully performed at much lower pressures.[79] Thus, a larger excess of formate is not needed. By working at the larger formate amount, the effect of a larger amount of base was also tested (**Table 2**, entry 12), but no improvement was observed, indicating that 120 µL of Et_3N is the best base amount to be added.

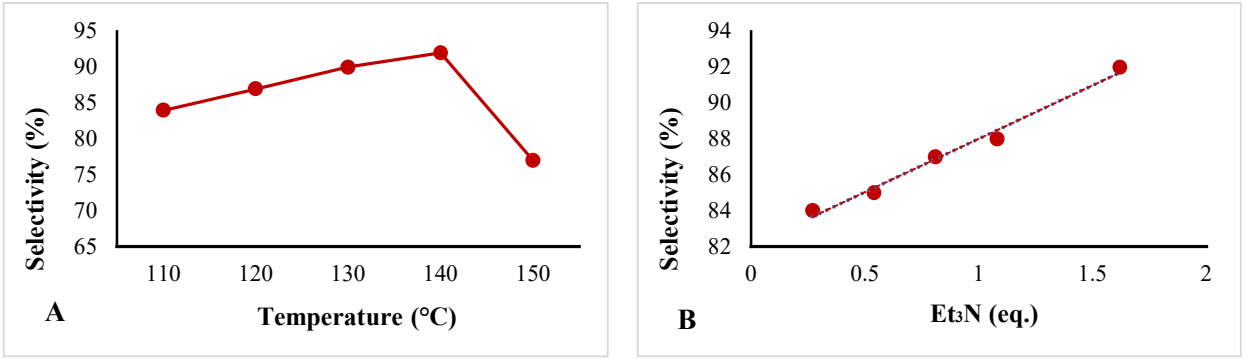


Fig. 2. Effect of temperature and amount of the base on the reductive cyclization of **1b.**

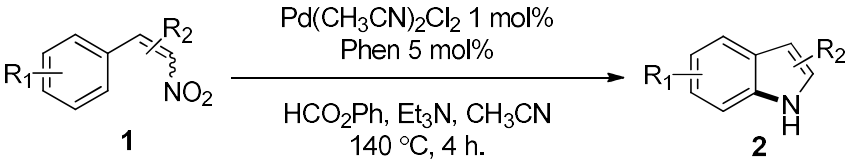
When we reduced the amount of phenanthroline to half (**Table 2**, entry 13) it led to a less stable catalytic system, but doubling it (**Table 2**, entry 17) did not lead to any improvement. At the lowest ligand amount, the effect of a different base concentration and reaction time was also investigated. Elongation of the reaction time does not alter the selectivity of the reaction (**Table 2**, entries 15,

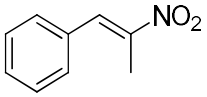
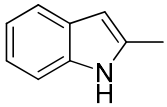
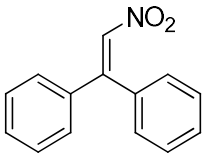
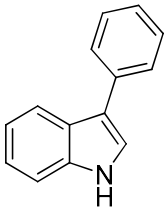
16). This on one side means that **2b** is stable under the reaction conditions; on the other hand, the lower selectivity with respect to the ideal conditions is not due to the accumulation of a long-lived intermediate, for example the *N*-hydroxyindole, which only more slowly converts to the final product. Halving the amount of catalyst decreases the selectivity, an effect which cannot be compensated for by increasing reaction time (**Table 2**, entries 18, 19). On the other hand, when the amount of catalyst was doubled, the reaction accelerated and was complete in less than one hour (**Table 2**, entries 20, 21) as evidenced by the formation of palladium black on the walls of the reaction tube, but the selectivity was even decreased with respect to that achievable by working at a 1 mol% catalyst amount. Though the decrease in selectivity is not easily explained, the early formation of palladium black is a consequence of the reaction ending in a short time. Moreover, we tested the use of the CH_3CN/DMF (9:1) solvent mixture which afforded a positive effect in the reductive cyclization of *o*-nitrostyrenes [23] (see later for details), but in the case of reductive cyclization of **1b** both the use of neat DMF and that of the CH_3CN/DMF mixture led to a lower indole selectivity (**Table 2**, entries 22, 23).

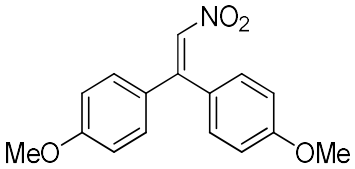
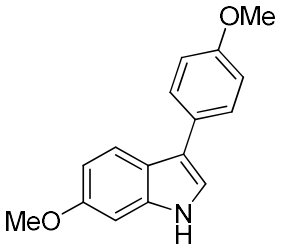
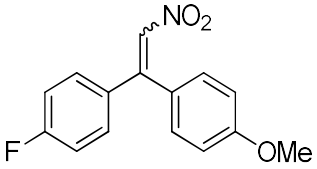
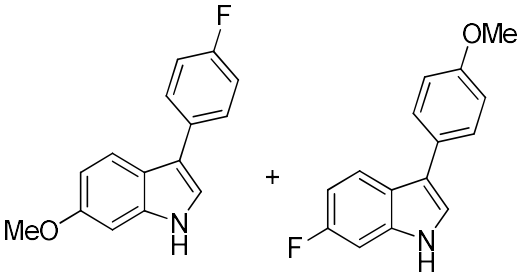
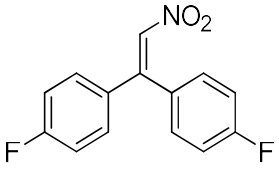
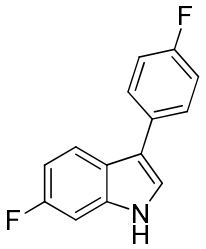
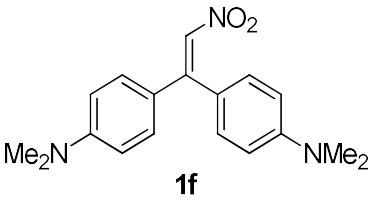
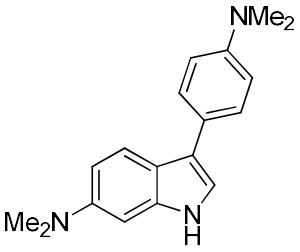
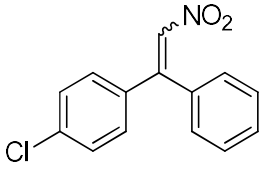
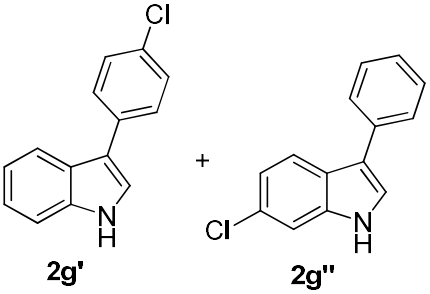
2.1.2. Substrate scope

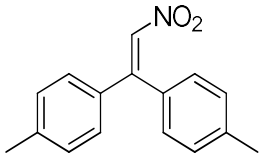
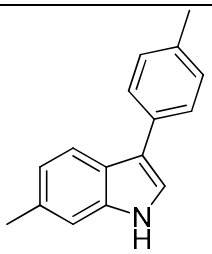
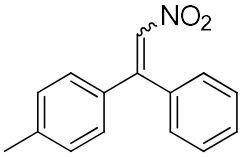
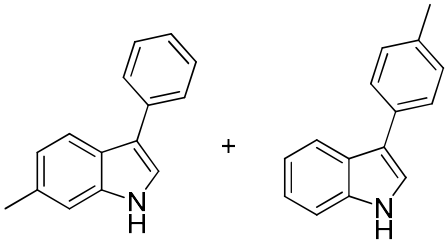
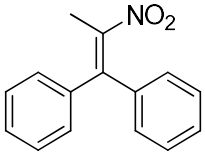
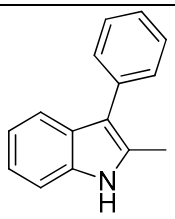
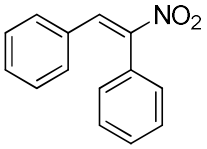
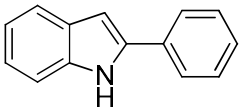
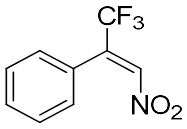
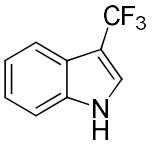
With the optimized conditions in our hands, we investigated the reaction scope of the cyclization (**Table 3**). The only difference with respect to the optimized conditions was that the reaction time was increased from three to four hours. To ensure that even less reactive substrates would give complete conversion under the same set of experimental conditions.

Table 3. Substrate scope of the Pd-catalyzed reductive cyclization reaction of *β*-nitrostyrens **1** using phenyl formate as CO source.[a]



Entry	Substrate	Product	Yield (%)[b]
1[c]	 **1a**	 **2a**	43 (47)[d]
2	 **1b**	 **2b**	89 (92)[d]

3	 **1c**	 **2c**	66
4	 **1d**	 **2d'** + **2d''**	21 (**2d'**) + 38 (**2d''**)
5	 **1e**	 **2e**	49
6	 **1f**	 **2f**	-[e]
7	 **1g**	 **2g'** + **2g''**	67 (1:2.5)

8	 **1h**	 **2h**	70
9	 **1i**	 **2i'** + **2i''**	71 (1.3:1)
10	 **1j**	 **2j**	47
11	 **1k**	 **2k**	(34)[d]
12	 **1l**	 **2l**	-[e]

a: Experimental conditions: 0.54 mmol **1**, 1 mol% $Pd(CH_3CN)_2Cl_2$, 5 mol% Phen, 260 µL HCO_2Ph, 120 µL Et_3N, 140 °C for 4 h, in 10 mL CH_3CN. ***b***: Isolated yields. ***c***: Experimental conditions: 0.54 mmol **1a**, 1 mol% $Pd(CH_3CN)_2Cl_2$, 10 mol% Phen, 350 µL HCO_2Ph, 320 µL Et_3N, 140 °C for 7 h, in 10 mL CH_3CN. ***d***: GC yield in parenthesis. ***e***: No product could be isolated.

With respect to the substituent on the aryl rings of *α*-aryl-*β*-nitrostyrenes, both electron withdrawing groups (F, Cl. **Table 3**, entries 5, 7) and donating (Me, MeO, entries 3, 8) are well tolerated. The only exception is represented by the very strongly electron donating group dimethylamino (**Table 3**, entry 6). This group is often incompatible with this kind of reactions and had also failed to give the desired product when $Mo(CO)_6$ had been used as a CO surrogate [85]. The

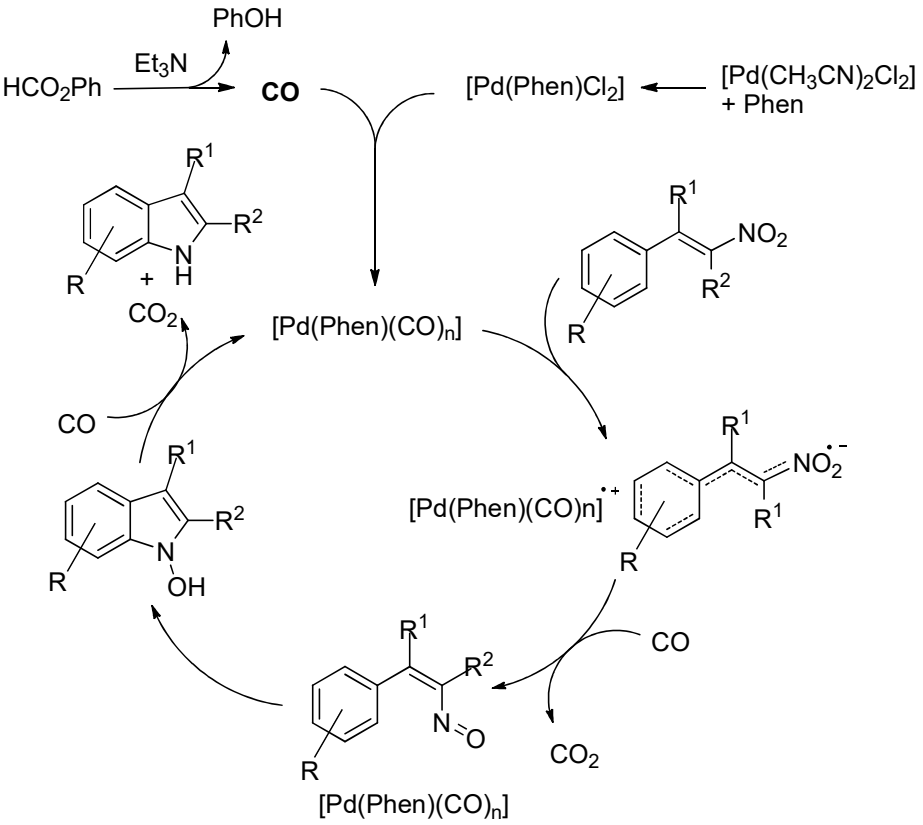
result was expected anyway since it has been shown before that the initial reduction of the nitro compound is an electron transfer from the metal complex to the nitro compound in all of the cases in which this step has been investigated in detail.[94-105] As a result, the presence of electron withdrawing groups close to the nitro group accelerates the reaction while that of electron donating groups slows it down. In our case, it should also be considered that alkenes with electron withdrawing groups can coordinate to zerovalent palladium complexes and, specifically, the coordination of nitrostyrenes to the Pd^0(2,9-Me_2-4,7-Ph_2-Phen) moiety has been experimentally prooven.[106] However, this coordination may have led to catalyst stabilization or catalyst deactivation and these are difficult to analyze without an extensive series of kinetic data. Thus, we will only discuss the former type of contribution. The potential for a regioselective reaction when two different aryl rings are present in the substrate is intriguing from a synthetic perspective. Recall that under the reaction conditions, rotation around the central C=C bond is clearly simple (the explanation is given later). Despite the fact that they are prepared by a Henry condensation that selectively affords the compound with the nitro and aryl groups *trans* with respect to the double bond, *β*-alkyl-*β*-nitrostyrenes was cyclized successfully, both when the reaction is carried out under a CO pressure [80,81] and when $Mo(CO)_6$ was employed.[85] Despite the lower efficiency of the procedure used in this work for this kind of substrates, the same conclusion clearly applies to the experimental conditions here employed. From a general point of view, the cyclization step involves an aromatic electrophilic substitution reaction and is easier on an electron rich ring. For instance, despite the nitro group in the reagent being specifically oriented towards the phenyl ring, the cyclization of (*E*)-3-(2-nitropropenyl)thiophene, in which a phenyl and a thiophene ring are in competition, produced a mixture of products with a 55/40 prevalence of those derived from the functionalization of the electron-rich thiophene ring.[81] In this work, the possible selectivity of the reaction with respect to the preferentially reacting ring was tested by putting in competition the couples 4-fluorophenyl-4-methoxyphenyl, chlorophenyl-phenyl, methyl-phenyl (**Table 3**, entries 4, 7, 9). However, only moderate regioselectivity was observed and a preferential functionalization of the most electron rich ring was observed only in one out of three cases. The obtained regioselectivity does neither match the initial *cis-trans* ratio in the starting nitroalkenes. This indicates a more sophisticated reaction mechanism, possibly involving an active role by the metal. However, data are now insufficient to draw any general conclusion and a dedicated mechanistic study should be performed to give a final answer to this point.

The reaction is tolerating the presence of both a phenyl ring in the *alpha* position and methyl group in the *beta* position of the styrene (**Table 3**, entry 10). The better result with respect to that achievable in the absence of the *α*-phenyl substituent (**Table 3**, entry 1) is further evidence that electronic delocalization effects on both aryl rings of the substrate are the reason for the better results obtainable when an *α*-aryl ring is present. The position of the aryl ring is important and moving it from the *alpha* to the *beta* position led to much worse results (**Table 3**, entries 2, 11).

Given the importance of trifluoromethyl groups in pharmaceutical chemistry, we also cyclized *α*-trifluoromethyl-*β*-nitrostyrene **1l**. However, no indole could be isolated from the corresponding cyclization reaction (**Table 3**, entry 12).

2.1.3. Reaction mechanism

Although no specific mechanistic study was made during this work, the obtained results are fully consistent with a scenario analogous to those identified for other related reactions (**Scheme 9**).



Scheme 9. Proposed reaction mechanism of the *β*-nitrostyrenes reductive cyclization.

Initially, the active catalyst is generated by coordination of phenanthroline to palladium, followed by reduction of Pd(II) to Pd(0) by the CO evolved by the decomposition of phenyl formate. The so-formed complex has the ability to activate nitrostyrene by electron transfer. At this point, rotation around the weakened C=C double bond can occur. We have previously suggested such possibility based on general orbital considerations,[81,82,92] however, we recently became aware that *trans-cis* isomerization of *β*-nitrostyrenes has indeed been experimentally observed upon generation of the corresponding radical anion.[107] Collapse of the radical couple results in the reduction of the nitro group to nitroso. Electrophilic attack of the nitroso group on the arene then affords a hydroxyindole. It is not certain if this step occurs outside the coordination sphere of the metal or if palladium accelerates it. Hydroxyindoles have been observed or even isolated in related reactions [21]. Reduction of the latter by the palladium-carbonyl complex eventually affords the final indole with regeneration of the active catalyst.

2.2. Pd-catalyzed reductive cyclization of *o*-nitrostyrenes

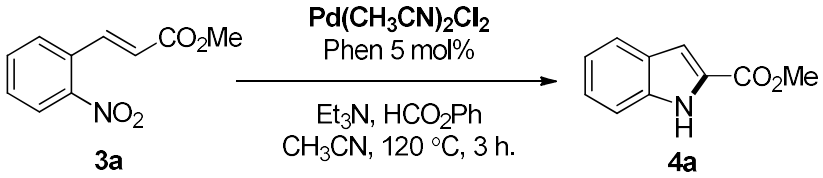
2.2.1. Phenyl formate as CO source

As mentioned before, our group pioneered the use of formate esters as *in situ* CO sources in the catalytic reductive cyclization of *o*-nitrostyrenes. However, it has been shown that replacing alkyl formate with phenyl formate gives better selectivities and yields of the desired products, except for those substrates bearing sensitive functional groups or those with stability issues.[23,26] In light of the previously published results, we decided to make an extra effort to optimize a new set of experimental conditions using phenyl formate-based catalytic procedure and apply several modifications that could allow the reaction to be performed at a lower temperature. Another objective was to reduce the amount of catalyst to make the process more engaging even from an industrial point of view. For our preliminary investigations, we took the reductive cyclization reaction of methyl-2-nitrocinnamate **3a** as the model reaction. The tests were performed in screw-cap thick-walled glass tubes (pressure tubes).

2.2.1.1. Re-optimization of the catalytic system

We initially tested the effect of lowering the catalyst amount when working at 120 °C (**Table 4**). Fortunately, the catalyst amount can be decreased to 0.2 mol% essentially without affecting the results (**Table 4**, entry 3) and the catalyst is still active even at lower loadings, although with a decreased performance (**Table 4**, entries 4-5).

Table 4. Effect of catalyst loading in the Pd-catalyzed reductive cyclization of **3a** using phenyl formate as a CO source.[a]



3a **4a**

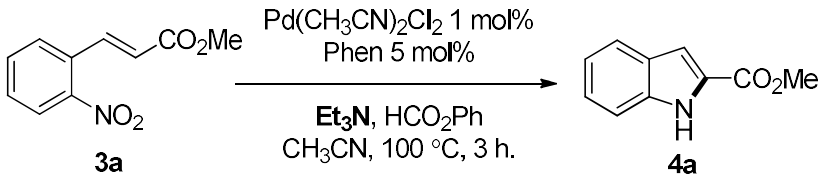
Entry	Catalyst loading (mol%)	Conv. (%)[b]	Sel. (%)[b]	Yield (%)[b]
1	1	98	>99	97
2	0.33	99	>99	98
3	0.2	99	98	97
4	0.1	97	87	84
5	0.02	27	21	6
6	0.01	3	48[c]	1

a: Experimental conditions: 0.27 mmol **3a**, 5 mol% Phen, 200 µL HCO_2Ph, 40 µL Et_3N, CH_3CN 10 mL, at 120 °C for 3 h. ***b***: Determined by GC analysis using biphenyl as the internal standard. ***c****:* Value affected by a large experimental error because of the low conversion value.

When we tried to further lower the temperature to 100 °C we faced a problem with the reproducibility of the reaction. We hypothesize that this may have been due to an insufficient rate of CO generation. Based on the fact that in our previous study on phenyl formate decomposition we had demonstrated through kinetic studies that the rate of the decomposition is directly proportional to the amount of the base,[26] we tested the effect of increasing the amount of base

(**Table 5**) and found that the use of ~2.5 eq. of Et_3N with respect to the substrate (100 µL absolute amount) not only improved conversion and selectivity but also solved the reproducibility problem.

Table 5. Et_3N amount optimization for reactions run at 100 °C. [a]



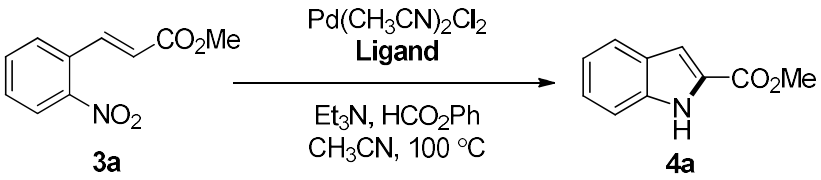
3a 4a

Entry	Et_3N (eq.)[b]	Conv. (%)[c]	Sel. (%)[c]	Yield (%)[c]
1a	1	77	93	72
1b	1	53	89	47
2a	1.5	87	96	84
2b	1.5	57	92	52
3a	2.5	95	97	92
3b	2.5	93	97	90

a: Reactions labelled as "a" and "b" were run in duplicate to test reproducibility. Experimental conditions: 0.27 mmol of **1**, 1 mol% $Pd(CH_3CN)_2Cl_2$, 5 mol% Phen, 200 µL HCO_2Ph, CH_3CN 10 mL, at 100 °C for 3 h. ***b***: With respect to **3a**. 1 eq. corresponds to 40 µL Et_3N. ***c***: Determined by GC using biphenyl as the internal standard.

The ligand identity plays a very important role in most catalytic systems and phenanthrolines substituted with electron-donating substituents afford better results than unsubstituted phenanthroline in several cases in the field of nitro compounds reduction by CO.[59,81,82,108,109] Moreover, the ligand-to-metal ratio is also very important and may vary between differently substituted phenanthrolines.[110,111] Thus, several experiments were run employing four different phenanthrolines. High selectivities and conversions were observed with all of the tested ligands when 1 mol% of $Pd(CH_3CN)_2Cl_2$ was used and the reaction was allowed to proceed for three hours (**Table 6**, entries 1-4). Nevertheless, shortening the reaction time to two hours revealed a variation in the obtained results. The conversion of the nitroarene and thus the yield of the reaction increased in the order 3,4,7,8-tetramethylphenanthroline < 4,7-dimethylphenanthroline < 4,7-dimethoxyphenanthroline < Phen (**Table 6**, entries 5-8) although more donor ligands should increase the reduction rate of the nitro group. Different ligand ratios of the Phen and 4,7-dimethoxyphenanthroline were tested employing lower catalyst loading (0.2 mol%) in order to further elucidate the differences and confirm that Phen is the optimal ligand. However, using at least 2.5 mol% of Phen was enough to reach a high selectivity but 5 mol% was recommended to guarantee the stability of the catalytic system (**Table 6**, entries 9-11). The low conversion (30-39%) was the only obstacle, despite the high selectivity we observed when 4,7-dimethoxyphenanthroline was used as the ligand (**Table 6**, entries 12,13).

Table 6. Effect of ligand identity and ligand amount in the $Pd(CH_3CN)_2Cl_2$ catalyzed reductive cyclization of **3a** using phenyl formate as CO source.[a]



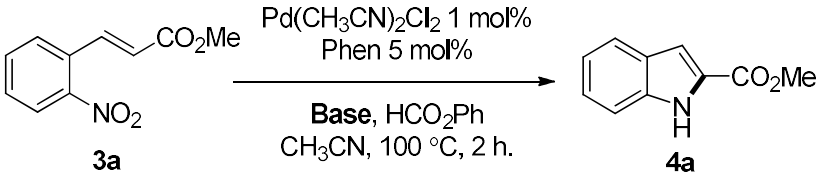
3a 4a

Entry	Pd (mol%)	Ligand	Ligand (mol%)	t (h)	Conv. (%)[b]	Sel. (%)[b]	Yield (%)[b]
1	1	Phenanthroline	2.5	3	91	97	88
2	1	4,7-Dimethoxyphenanthroline	2.5	3	91	97	88
3	1	3,4,7,8-Tetramethylphenanthroline	2.5	3	87	97	84
4	1	4,7-Dimethylphenanthroline	2.5	3	87	97	84
5	1	Phenanthroline	2.5	2	84	97	82
6	1	4,7-Dimethoxyphenanthroline	2.5	2	76	97	74
7	1	3,4,7,8-Tetramethylphenanthroline	2.5	2	67	93	62
8	1	4,7-Dimethylphenanthroline	2.5	2	74	93	69
9	0.2	Phenanthroline	1	2	37	88	33
10	0.2	Phenanthroline	2.5	2	62	94	58
11	0.2	Phenanthroline	5	2	60	94	56
12	0.2	4,7-Dimethoxyphenanthroline	2.5	2	30	99	30
13	0.2	4,7-Dimethoxyphenanthroline	5	2	39	97	38

a**:* Experimental conditions: 0.27 mmol of **3a**, 200 µL HCO_2Ph, CH_3CN 10 mL, 2.5 eq of Et_3N, at 100 °C, other amounts, and conditions as in the table. ***b: Determined by GC using biphenyl as the internal standard.

In the aim of further improving the selectivity of the whole process, we looked at the possibility of changing the base and possibly reducing its amount. During our previous work on the reductive cyclization of *o*-nitrobiphenyl we have found that inorganic phosphates improve the yields of the observed carbazole reducing the amount of substituted aniline and other products formed.[24] Thus, we have used different phosphates with inorganic (K_3PO_4, Na_3PO_4) or organic ($[Me_4N]_3[PO_4]$) counterions in place of Et_3N but they all gave worse results in our case (**Table 7**).

Table 7. Basic promoter screening with 1,10-phenanthroline.[a]



3a 4a

Entry	Ligand	Basic Promoter	Conv. (%)[b]	Sel. (%)[b]	Yield (%)[b]
1	Phenanthroline	Et_3N	63	94	59
2	Phenanthroline	K_3PO_4	17	68	12
3	Phenanthroline	Na_3PO_4	24	91	22
4	4,7-Dimethoxyphenanthroline	Et_3N	45	97	44
5	4,7-Dimethoxyphenanthroline	K_3PO_4	19	43	8
6	4,7-Dimethoxyphenanthroline	Na_3PO_4	21	99	21

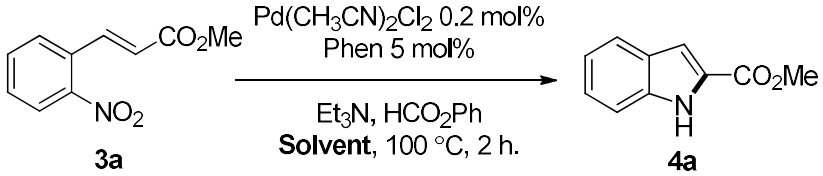
7[c]	Phenanthroline	$[Me_4N]_3[PO_4]$	10	99	10
8[c]	4,7-Dimethoxyphenanthroline	$[Me_4N]_3[PO_4]$	17	45	8

a: Experimental conditions: 0.27 mmol of **3a**, 1 mol% $Pd(CH_3CN)_2Cl_2$, 5 mol% Phen, 200 µL HCO_2Ph, CH_3CN 10 mL, 2.5 eq of basic promoter, reaction time 2 hours, temperature 100 °C. ***b***: Determined by GC using biphenyl as the internal standard. ***c***: Reaction run at 120 °C for 3 h.

Employing both Phen and 4,7-dimethoxyphenanthroline with all the tested phosphates does not change the fact that Phen is the best ligand for our reaction since it gave selectivities higher than the ones obtained using 4,7-dimethoxyphenanthroline in all cases. Overall, it has been observed that among the phosphates used, Na_3PO_4 seemed to give the best selectivities despite the lower conversions, especially in the case of 4,7-dimethoxyphenanthroline (**Table 7**, entries 1-6). This may be due to the poor solubility of the inorganic bases in CH_3CN at 100 °C. In order to address this issue, we investigated the possibility of changing the counterion to $(NMe_4)^+$ instead of alkali metal, accompanied by increasing both temperature and reaction time. However, no tangible positive effect was observed (**Table 7**, entries 7, 8).

On the other hand, during our attempts to better solubilize the used inorganic basic promoters in the reaction mixture using DMF as a solvent or co-solvent we found an unexpected solvent effect (**Table 8**). DMF as the solvent is clearly inferior to neat CH_3CN as a reaction medium (**Table 8,** entries 1 and 6). However, lower amounts of DMF in CH_3CN can be highly beneficial on the reaction rate, with 1 mL DMF allowing an increase in conversion from 60% in neat CH_3CN to 92% in the 9:1 CH_3CN/DMF mixture. The selectivity in indole was less sensitive to the reaction medium, but the best result was again obtained at the 9:1 ratio. It may be noted that DMF was the ideal solvent under the reaction conditions reported by Davies for the same cyclization, but with gaseous CO.[62]

Table 8. Effect of DMF addition in the $Pd(CH_3CN)_2Cl_2$ catalyzed reductive cyclization of **3a** using phenyl formate as CO source.[a]



3a **4a**

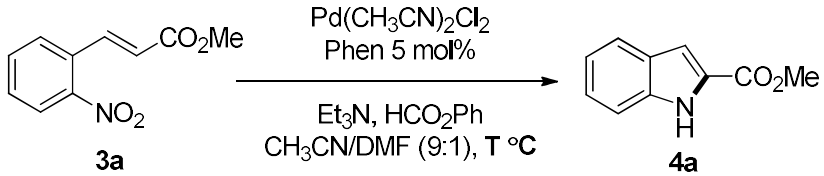
Entry	DMF Vol (mL)	Conv. (%)[b]	Sel. (%)[b]	Yield (%)[b]
1	10	25	86	22
2	2	48	93	45
3	1	92	97	89
4	0.5	86	97	83
5	0.1	60	95	57
6	0	60	94	56
7[c]	1	15	92	14

a: Experimental conditions: 0.27 mmol of **3a**, 0.2 mol% $Pd(CH_3CN)_2Cl_2$, 5 mol% Phen, 200 µL HCO_2Ph, 2.5 eq. of Et_3N, at 100 °C in CH_3CN + DMF (total volume

10 mL), for 2 h. ***b***: Determined by GC using biphenyl as the internal standard. ***c***: Na_3PO_4 was employed as a base in place of Et_3N.

Additional experiments were also performed at lower temperatures (80 °C and 60 °C). Full conversion and virtually quantitative selectivity could still be obtained at 80 °C, but the catalyst loading had to be increased to 1 mol% and 5 eq. of Et_3N were necessary to decompose phenyl formate at an acceptable rate (**Table 9**). Thus, we decided not to develop these reaction conditions any further. However, working at less than 100 °C is clearly possible if the stability of the substrate or product requires it.

Table 9. Explorative experiments at lower temperatures. ***a***



3a 4a

Entry	Pd (mol%)	Et_3N (eq.)	T (°C)	t (h)	Conv. (%)[b]	Sel. (%)[b]	Yield (%)[b]
1[c]	1	2.5	80	2	20	91	18
2[c]	0.2	2.5	80	2	6	90[d]	5
3[c]	1	2.5	80	6	79	94	74
4	1	5	80	6	98	99	97
5	1	2.5	80	6	85	91	77
6	0.2	5	80	6	58	93	54
7	0.2	5	80	3	29	91	26
8	1	2.5	60	6	12	98	12
9	1	5	60	6	32	92	29

a: Experimental conditions: 0.27 mmol **3a**, $Pd(CH_3CN)_2Cl_2$, 5 mol% Phen, 200 µL HCO_2Ph, Et_3N in CH_3CN/DMF (9:1, total volume 10 mL), other amounts and conditions as in the table. ***b***: Determined by GC using biphenyl as the internal standard. **c**: CH_3CN was used as the solvent (10 mL). ***d***: Value affected by a large experimental error because of the low conversion value.

The effect of the level of filling of the tube or flask used to perform the reaction, which influences the headspace volume, is almost never studied in the literature on CO surrogates. As a matter of fact, neither traditional reactions nor autoclave reactions, where the gaseous reagent is usually present in a large molar excess or is continuously refilled, are affected by this parameter. However, in the case of reactions in which CO is produced, the headspace volume can play an important role. In fact, one must take into account that in this reaction, CO is generated directly in the liquid phase, but can later escape into the gas phase and then reenter the liquid phase from the latter. As demonstrated by our group before,[23,26] the reaction proceeds much more slowly and stops long before the initial nitro compound is completely consumed when it is run in a conventional Schlenk flask connected to a dinitrogen line. This observation shows that some of the released CO may be captured by the palladium catalyst while it is still in the liquid phase, but under these

circumstances, most of it escapes into the gas phase and is only marginally, if at all, recaptured. Likely, performing the same reaction in a closed vessel of large volume would produce a similar outcome.

Overall, one must consider that different and competing effects arise when decreasing the solvent amount keeping other reaction parameters constant:

1. The concentration of the solution will increase as the solvent is reduced, and this should improve at least the reaction rate. This eventually might have, in some cases, also a negative effect increasing the formation of byproducts or the rate of catalyst deactivation (*i.e.* Pd-black formation).
2. The corresponding increase of the headspace volume will result in a lower average CO pressure during the reaction and a less effective CO utilization. This may slow down the reaction and possibly also cause the deactivation of the catalyst or the onset of competing reactions that do not use CO (e.g. the Heck reaction in the current scenario when substrates with aryl bromide moieties are used).
3. Increasing the solvent amount should have the opposite effect, but much caution should be exerted in not leaving a too small headspace volume because this may cause the onset of a too high pressure and the explosion of the glass vessel. The maximum amount of phenyl formate we employed was chosen so that even in the worst scenario, *i.e.* complete decomposition of the formate with no consumption of the produced CO, the pressure inside the tube would not exceed 10 bar even at the highest temperature.

Obviously, a strong dependency of the reaction outcome on the solvent and vessel volumes would detract from the general applicability of our protocol. Therefore, we tested the effect of decreasing the solvent amount (**Fig. 3**).

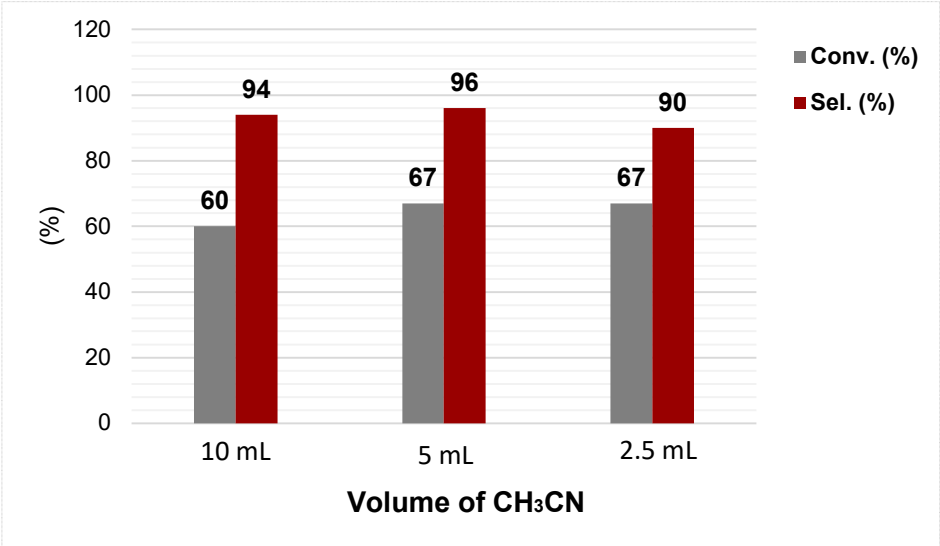


Fig. 3. Effect of decreasing the solvent amount. Reaction conditions: 0.27 mmol **3a**, 0.2 mol% $Pd(CH_3CN)_2Cl_2$, 5 mol% Phen, 200 µL HCO_2Ph, 2.5 eq. of Et_3N, at 100 °C for 2 h. Reactions were performed into heavy-wall glass tubes. Conversion and selectivity were determined by GC using biphenyl as the internal standard.

The optimized protocol tolerates quite large variations in the solvent and headspace volumes without impairing the outcome of the reaction, as evidenced by the small, if not negligible, effects of reducing the solvent from 10 to 5 and even 2.5 mL (resulting in an increase of the headspace from 13 to 18 and 20.5 mL respectively).
During the work using phenyl formate, we found that in a few cases the co-produced phenol might be annoying to separate by column chromatography from the product. Aiming to overcome the aforementioned problems, we decided to develop a protocol based on the use of reagents that are typically available in all synthetic laboratories.

2.2.2. Formic Acid as CO source

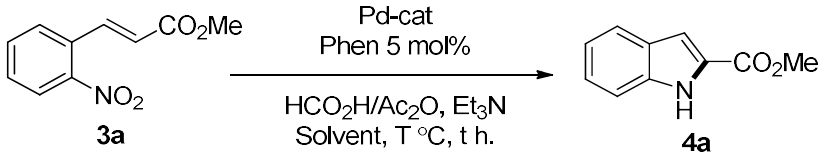
In terms of cost, availability and atom-economy, formic acid,[112-116] is one of the most convenient molecules. In our continued efforts to explore the use of efficient CO surrogates, in this section we describe a modified method for the synthesis of indoles by reductive cyclization of *o*-nitrostyrenes that makes use of formic acid (FA) as the source of the reductant that can be performed in cheap reactors. However, for our reaction, the use of FA must be accompanied with acetic anhydride to be able to liberate the CO *in situ.* The use of this mixture, from which the mixed anhydride is generated *in situ*, not only avoids the coproduction of phenol but also saves a synthetic step and improves the atom economy of the full process because phenyl formate is itself prepared by the reaction of phenol with an excess of HCO_2H/Ac_2O (see experimental section).

2.2.2.1. Optimization of the reaction conditions

The preliminary tests were performed using HCO_2H as the CO source in the presence of 1 mol% of $Pd(CH_3CN)_2Cl_2$ and 5 mol% of phenanthroline as the catalyst system under conditions previously discussed for the same reaction using phenyl formates as the CO surrogate. Despite the fact that HCO_2H can decompose under acidic conditions to CO and H_2O without the need of an activator under relatively mild conditions,[113,117-119] an activator is needed in most cases.[114] Acetic anhydride is particularly convenient because it reacts with HCO_2H even at room temperatures to generate the mixed acetic formic anhydride and release CO affording acetic acid as the only byproduct.[120] Attracted by the possibility of using a solid source of the formate fragment, some preliminary tests were performed using formate salts (**Table 10**, entries 1-4) in combination with acetic anhydride. All tests led to low indole yields regardless of the temperature, reaction time and presence of further base. Using a 1:1 ratio of FA and Ac_2O in a 4.4-fold excess with respect to **3a** under the experimental conditions previously employed with phenyl formate led to a fair yield of indole **4a** (**Table 10**, entry 5). In all successful reactions, the presence of a base was necessary to ensure a fast release of CO, which in fact starts even at room temperature. Et_3N was the base of choice due to its low cost, low toxicity, and easy separation (b.p. 89°C). The amount of base could be decreased with respect to those of FA and Ac_2O, but a less selective reaction was observed when it was lowered under 2 equivalents with respect to the substrate (**Table 10**, entries 6-9). Even if in a few previous literature reports Ac_2O has been used as a catalytic activator,[120,121] in our case halving its amount led to lower yields (<50%). The cyclization reaction is fast and affords high

yields between 140 °C and 110 °C, whereas it becomes less selective when the temperature is further lowered. Fortunately, the amount of FA/Ac_2O/Et_3N, and thus of released CO, needed for an effective cyclization is only in slight excess with respect to the 2 equivalents required by the stoichiometry of the reaction (**Table 10**, entry 16).

Table 10. Optimization of the reaction conditions for the reductive cyclization of methyl 2-nitrocinnamate **3a** to methyl 2-indolecarboxylate **4a** using FA as the CO source.[a]



Entry	FA/Ac_2O/Et_3N to **3a** mol ratio	Solvent	t (h)	T (°C)	Conv. (%)[b]	Sel. (%)[b]	Yield (%)[b]
1[c]	4.4/4.4/0	CH_3CN	20	100	4	13	<1
2[c]	4.4/4.4/0	CH_3CN	6	140	<1	>0	<1
3[d]	4.4/4.4/0	CH_3CN	6	120	8	38	3
4[d]	3/3/0.2	CH_3CN	6	120	3	94	3
5	4.4/4.4/4.4	CH_3CN	4	100	86	74	64
6	4/4/4	CH_3CN	6	120	100	87	87
7	4/4/2	CH_3CN	6	120	100	88	88
8	4/4/1	CH_3CN	6	120	100	69	69
9	3/3/3	CH_3CN	6	120	100	92	92
10	2.1/2.1/2.1	CH_3CN	6	120	90	81	73
11	3/3/3	CH_3CN	4	140	100	89	89
12	3/3/3	CH_3CN	8	100	84	85	71
13	3/3/3	CH_3CN/DMF[e]	8	100	95	83	79
14	3/3/3	CH_3CN	10	100	91	85	77
15	3/3/3	CH_3CN	8	110	100	91	91
16	2.5/2.5/2.5	CH_3CN	8	110	100	91	91
17[f]	2.5/2.5/2.5	CH_3CN	8	110	82	93	76
18[f]	2.5/2.5/2.5	Acetone	8	110	100	94	94
19[f]	2.5/2.5/2.5	MEK[g]	8	110	100	89	89
20[f]	2.5/2.5/2.5	EtOAc	8	110	54	61	33
21[f,h]	2.5/2.5/2.5	Acetone	8	110	100	94	94
22[i]	2.5/2.5/2.5	Acetone	8	110	100	93	93
23[i,j]	2.5/2.5/2.5	Acetone	10	110	100	93	93
24[i,k]	2.5/2.5/2.5	Acetone	10	110	100	94	94
25[i,l]	2.5/2.5/0	Acetone	10	110	55	24	13

a**:* Experimental conditions: 0.5 mmol **3a**, 1 mol% $Pd(CH_3CN)_2Cl_2$, 5 mol% Phen, FA,Ac_2O, Et_3N, solvent 10 mL. ***b: Determined by GC using biphenyl as the internal standard. ***c***: HCO_2NH_4 was used in place of FA. ***d***: HCO_2Na was used in place of FA. ***e**:* CH_3CN/DMF ratio 9:1. ***f**:* 0.5 mol% of $Pd(CH_3CN)_2Cl_2$. ***g**:* MEK = methyl ethyl ketone. ***h**:* Deoxygenated, but undried, solvent was used. ***i***: 0.5 mol% of $Pd(acac)_2$ instead of

$Pd(CH_3CN)_2Cl_2$. ***j***: Aqueous FA (85 wt%) was used. ***k***: The reaction was assembled in the air. ***l***: Aqueous ammonia (25 wt%, 25 μL) was used.

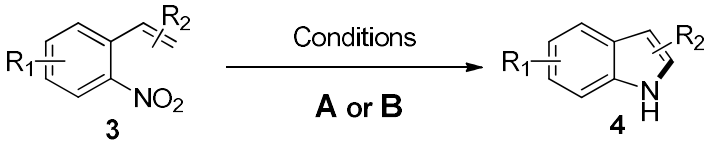
Further optimization of the catalytic system concerned the solvent. Although reductive cyclization of nitro compounds to heterocycles is known to perform better in DMF or CH_3CN, both solvents are expensive and toxic,[122] and DMF has a high boiling point that makes its evaporation difficult. Looking for an alternative, using a 0.5 mol% Pd loading to better evidence the different performances, we found that employing acetone as the solvent ensures a higher yield by both accelerating the reaction rate and increasing the selectivity towards indole, even if it is not dried before use (**Table 10**, entries 18, 21). Triggered by this unexpected water tolerance, we tested 85 wt% aqueous FA instead of the one with 99% purity, obtaining virtually the same yield (**Table 10**, entry 23).

Having an optimized set of reaction conditions to perform the reductive cyclization of the substrates in our hands, we started to explore the reactivity of different *o*-nitrostyrenes. Disappointingly, when those conditions were employed in the cyclization of methyl 4-bromo-2-nitrocinnamate **3b** precipitation of palladium black, which typically only happens as complete conversion of the nitro compound approaches, occurred before full conversion (77% after 10h). Indeed, deactivation of the catalyst could be visually detected after a few hours from the start of the reaction indicating a low stability of the catalytic system. The use of a pre-catalyst containing a chelating anionic ligand such as $Pd(acac)_2$ instead of $Pd(CH_3CN)_2Cl_2$ was sufficient to stabilize the catalytic system and avoid early palladium black formation (**Table 10**, entry 22 and **Table 11**, entry 2). Moreover, the system was also stable to dioxygen, which allow us to set up the reaction in the air (**Table 10**, entry 24). On the contrary, a strict exclusion of dioxygen was necessary when phenyl formate was used as the CO source.

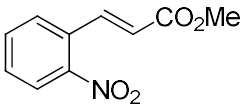
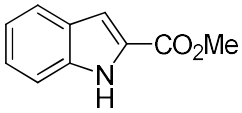
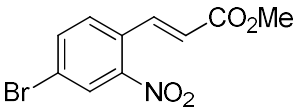
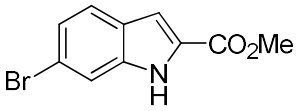
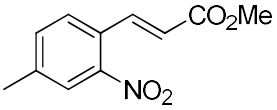
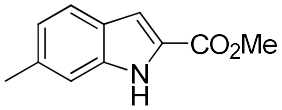
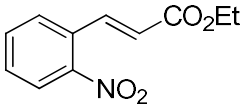
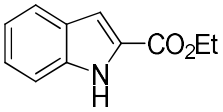
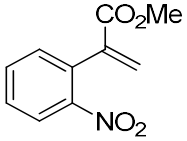
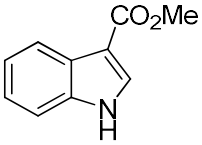
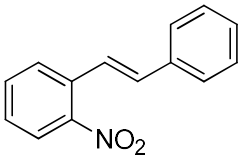
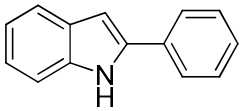
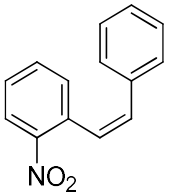
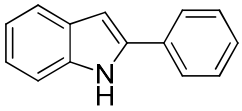
2.2.3. Substrate scope

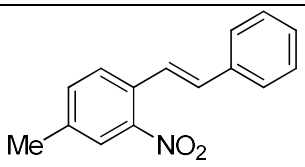
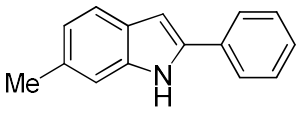
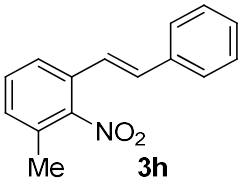
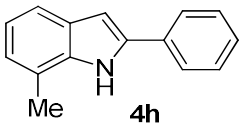
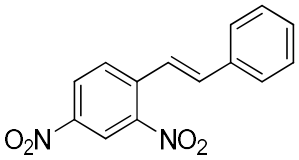
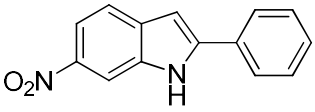
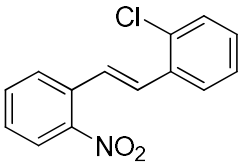
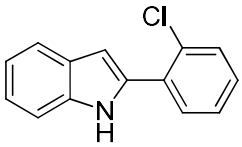
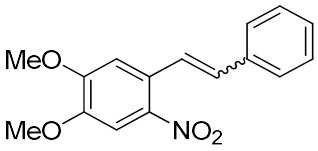
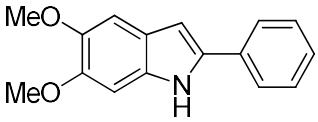
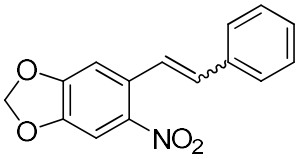
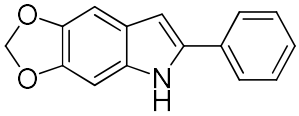
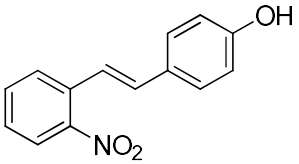
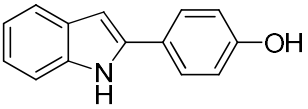
With the optimized conditions in our hands, we started to investigate the reactivity of different *o*-nitrostyrenes in the presence of phenyl formate (Conditions A) or formic acid (Conditions B) (**Table 11**). The reductive cyclization of *o*-nitrostyrenes using gaseous CO as the reductant was already reported to be tolerant of a large number of substituents,[62,64] however, the use of phenyl formate as the CO source allows to perform the reaction under milder reaction conditions and yields that, in most cases, are higher than those obtained using gaseous CO. However, the presence of the highly reactive Ac_2O and FA does not allow to take for granted the extension of the tolerance of the reaction to the present method. Fortunately, in most cases, the cyclization of the substrates into indoles took place in yields comparable to or better than those obtained using HCO_2Ph as the CO source. It is worth mentioning that we have been focusing on those substrates that either had not given high yields or had failed at all to give an isolable product under previously reported conditions using phenyl formate and the same catalytic system (**Scheme 7**).[26] Furthermore several new substrates were also explored. In the case of phenyl formate, to ensure that even less reactive substrates would give complete conversion under the same set of experimental conditions, a 1 mol% of Pd-catalyst loading was employed and the reaction time increased to 6 h.

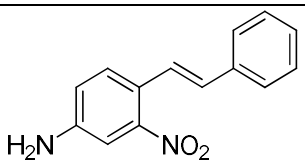
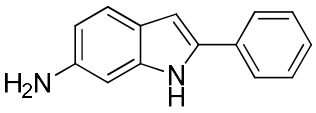
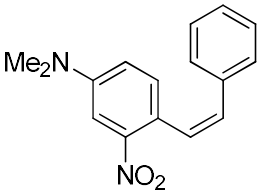
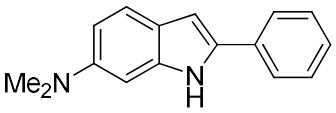
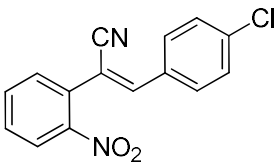
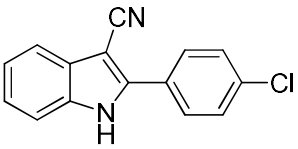
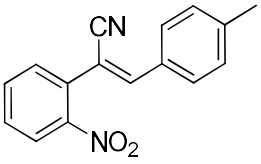
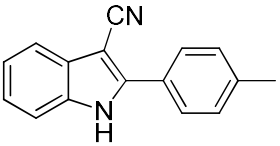
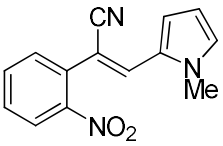
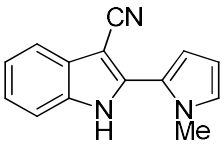
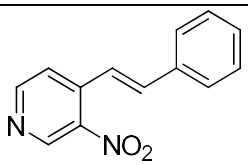
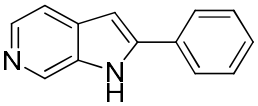
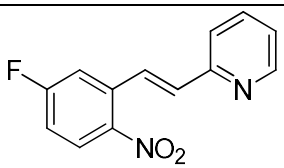
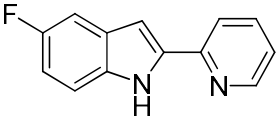
Table 11. Substrate scope of the Pd-catalyzed reductive cyclization reaction of *o*-nitrostyrens using phenyl formate or formic acid as CO source.[a]

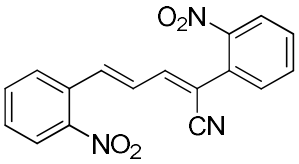
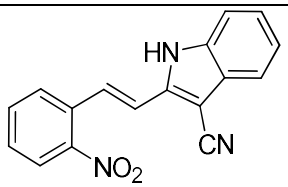
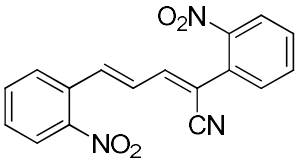
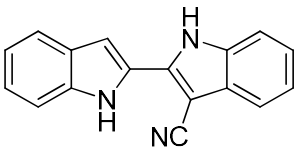
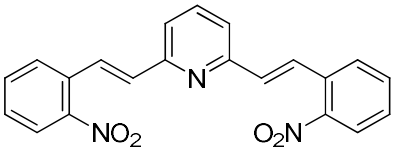
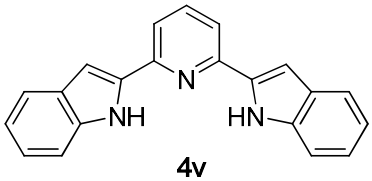
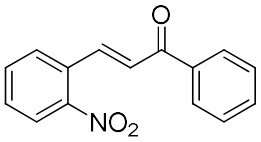
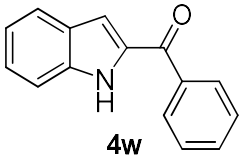
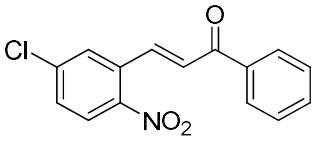
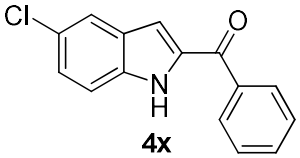
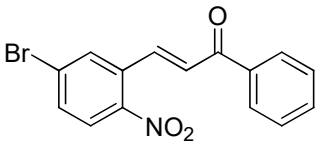
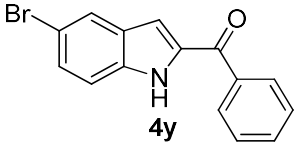
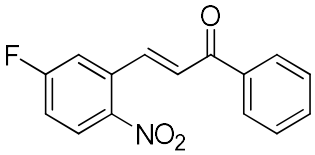
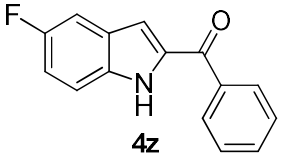
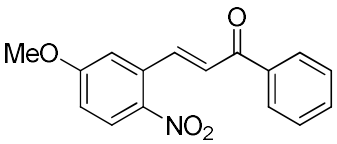
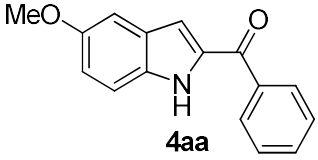


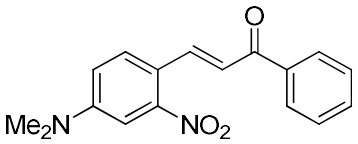
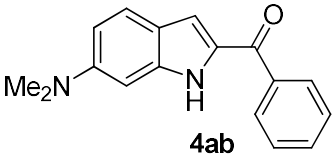
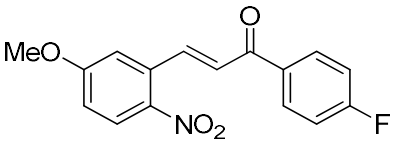
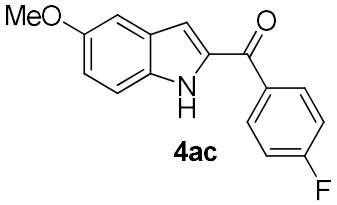
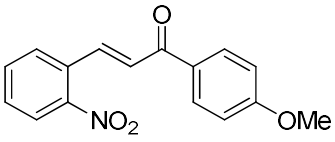
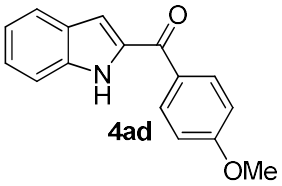
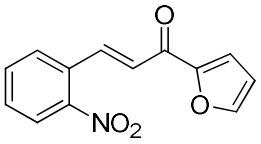
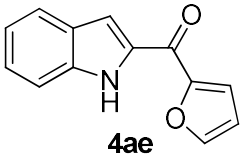
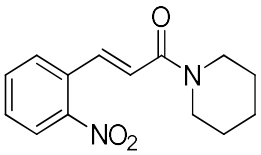
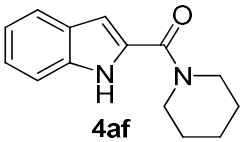
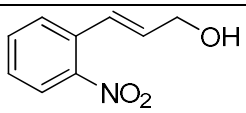
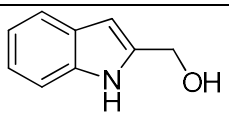
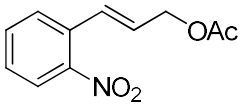
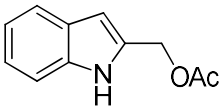
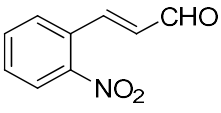
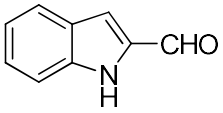
3 4

Entry	Substrate	Product	Yield (%)		
			Ref (26)[b]	A	B
1	 **3a**	 **4a**	95	97 (99)[c]	93
2	 **3b**	 **4b**	90		95 (80)[d]
3	 **3c**	 **4c**	96		83
4	 **3d**	 **4d**	92		95
5	 **3e**	 **4e**	45	64	
6	 ***E*-3f**	 **4f**		95	92
7	 ***Z*-3f**	 **4f**		96	

8	 **3g**	 **4g**		96	84
9	 **3h**	 **4h**		-[e]	
10	 **3i**	 **4i**		78	54
11	 **3j**	 **4j**	69	94	
12	 **3k**	 **4k**	-[e]	71	
13	 **3l**	 **4l**		72	84[f]
14	 **3m**	 **4m**		-[e]	47 (86)[g]

15	 **3n**	 **4n**	-[e]	-[e]	
16	 **3o**	 **4o**	45	60	
17	 **3p**	 **4p**	94		99
18	 **3q**	 **4q**	95		98
19	 **3r**	 **4r**	51	77	61
20	 **3s**	 **4s**	91		86
21	 **3t**	 **4t**			91

22	 **3u**	 **4u'**		61	
23[h]	 **3u**	 **4u''**		90[f]	
24[h]	 **3v**	 **4v**	78		70
25	 **3w**	 **4w**	79		82
26	 **3x**	 **4x**			72
27	 **3y**	 **4y**			81
28	 **3z**	 **4z**			84
29	 **3aa**	 **4aa**			91[f]

30	 **3ab**	 **4ab**			89
31	 **3ac**	 **4ac**			76
32	 **3ad**	 **4ad**			79
33	 **3ae**	 **4ae**			85
34	 **3af**	 **4af**	73	91	95
35	 **3ag**	 **4ag**	-[e]	-[e]	74 (83)[g]
36	 **3ah**	 **4ah**	-[e]	-[e]	70[i]
37	 **3ai**	 **4ai**	50	65	20

a: Isolated yields unless otherwise noted, Experimental conditions: Conditions A: 0.54 mmol of **3**, 1 mol% $Pd(CH_3CN)_2Cl_2$, 5 mol% Phen, 260 µL (2.38 mmol) HCO_2Ph, 100 µL (0.72 mmol) Et_3N, in CH_3CN + DMF (9+1 mL), at 100 °C for 6 h. Conditions B: 0.5 mmol of **3**, 0.5 mol% $Pd(acac)_2$, 5 mol% Phen, FA (1.25 mmol), Ac_2O (1.25 mmol), Et_3N (1.25 mmol) in 10 mL of acetone, for 10 h. Reactions were performed into heavy-wall glass tubes ***b***: Previously reported reaction conditions: 0.54 mmol of **3**, 1 mol% $Pd(CH_3CN)_2Cl_2$, 2.5 mol% Phen, 240

μL (2.2 mmol) HCO_2Ph, 40 μL (0.29 mmol) Et_3N, in CH_3CN (10 mL), 140 °C for 3 h (see Scheme 5). ***c***: GC yield in parentheses (using biphenyl as the internal standard). ***d:*** $Pd(CH_3CN)_2Cl_2$ (1 mol%) was used as the pre-catalyst. ***e*****:** Complex mixture of products was observed ***f***: Reaction time = 16 h. ***g***: Acetylation of the -OH group was detected. Value in parentheses refers to the overall yield of cyclized products. ***h***: half of the mmol of **3u** or **3v** was used to keep constant the concentration of the nitro groups. ***i***: 1 mol% of $Pd(acac)_2$ was used.

We have tested the reactivity of a wide range of nitrostyrenes as 2-nitrocinnamates (**Table 11**, entries 1-4), 2-nitrostilbenes (**Table 11**, entries 6-24) and 2-nitrochalcones (**Table 11**, entries 25-33). In most cases the substrates were cyclized to the corresponding indoles in good to excellent yields, regardless of the presence of electron donating group (**Table 11**, entries 3, 8, 12, 16, 29, 30 and 31), electron withdrawing group (**Table 11**, entries 2, 10, 11, 21, 26-28) or electron poor heterocycle (**Table 11**, entry 20) on the ring bearing the nitro group. The new re-optimized reaction conditions (A) and formic acid conditions (B) finally constitute a marked improvement and allowed us to get higher yields of the desired indoles in all cases in which a comparison with first conditions was made. Starting with indoles **4a-d**, which we get it in an excellent yield. Moving to the ester group to the alpha position of the starting nitrostyrene **3e** leads to a less satisfactory yield. This is the only substrate among those tested for which markedly better results have been previously obtained by using gaseous CO, albeit with much higher catalyst loadings (10-12 mol%).[64,123] The fact that the yield did not increase when the reaction time was prolonged shows that the catalyst deactivates before the reaction is finished.

On the other hand, the cyclization of different nitrostilbenes to get 2-phenyl indole derivatives was of great interest. A mixture of ***E/Z*-3f** (*Z:E* = 2:1) was previously cyclized successfully using phenyl formate as a CO source to give **4f** in 90%,[26] however, better yields and complete conversions were observed in our case employing the separate isomers. Interestingly, under conditions A, if the reactions in entries 6 and 7 were run for just 3 h instead of 6, a 64 % conversion of ***E*-3f** was observed, but the conversion of ***Z*-3f** was just 29%. This parallels the lower reactivity of *Z* isomer with respect to the *E* one already observed and discussed before in the literature for the $[Pd(Phen)_2][BF_4]_2/Ru_3(CO)_{12}$/Phen catalytic system with *n*-butyl formate.[23,26] However, at variance with the results obtained at 180 °C (when butyl formate used in place of phenyl formate), no isomerized nitrostilbene was detected in the unreacted substrate, confirming that the previously observed nitrostilbene isomerization was due to the high temperature only. This observation also has a mechanistic implication. If any isomerization of nitrostilbene had been observed even at a temperature low enough that a thermal process can be excluded, this would have implied that the initial nitroarene activation was reversible. That no isomerization of the starting material is observed whereas isomerization clearly occurs during the cyclization is a clear proof that the initial substrate activation by the catalyst is irreversible. Despite the fact that electron-donating groups on the aryl ring are known to deactivate the nitro group in these reactions, good to excellent results could be obtained not only in the presence of the mildly electron-donating methyl group **3g**, but even in the presence of two methoxy groups **3k** or dimethylamino **3o**. Additionally, the presence of a substituent in the second position *ortho* to the nitro group also blocked the reaction (**Table 11**, entry 9). The sensitivity of this kind of cyclization to steric hindrance in this position is a known

problem [64] and unfortunately our strategy did not solve it. Nitrostilbenes substituted with electron-withdrawing groups **3i** and **3j** gave excellent results, but the case of **3i** is especially captivating. Two nitro groups are present on the substrate and the one in the *para* position with respect to the vinyl substituent should be the most reactive for steric reasons. Indeed, when 2,4-dinitrotoluene is carbonylated to the corresponding methyl dicarbamate by Pd/Phen catalysts and the reaction is stopped before completion, the nitro group in the position 4 is carbonylated to a quite larger extent than that in the position 2 over a range of experimental conditions.[124] The fact that in the present case the reactions proceeds selectively on the *ortho* nitro group supports the previous proposal that the olefin groups may coordinate to palladium before the reduction occurs, facilitating and addressing the reaction.[21,63] However, when formic acid was employed as the CO source, the cyclization of **3i** became less selective, though still favored over the reduction of the nitro group in the *para* position, and the reaction is not sensitive to air, although it is also slower. These observations point to a different resting state of the catalytic system and to a lower importance of the olefin-coordinated complex as an intermediate. Whether the latter is formed anyway or not will require a more detailed mechanistic study, which is in progress in our laboratories. Worth noting, the dioxolo substituted stilbene afforded the corresponding indole **4l** in higher yield when formic acid was used compared to phenyl formate conditions.

The only substrates for which our reaction failed to give clean isolable products under conditions A are those containing a phenolic **3m** or free amino **3n** groups and those in which the double bond is part of an allylic alcohol **3ag** or allylic acetate **3ah** moiety. The formation of a mixture of compounds in the case of **3n** may be due to the easy reaction of anilines with nitroarenes in the presence of Pd/Phen catalysts and CO to give diarylureas.[125] Indole **4n** may however be easily obtained by reduction of **4i** [126] and this indirect route is preferable anyway. In fact, preparation of the starting **3n** following the only published procedure [127] proceeded in our hands in poor yields, whereas synthesis of **3i** can be easily performed by reacting dinitrotoluene with benzaldehyde in the presence of a base and the reagents are very cheap and readily available (see experimental section of details). Allylic acetates are typical substrates for the generation of π-allyl complexes, and this is the probable entry to different reactions for **3ah**. Activation of allylic alcohols is usually more difficult, but, on the other hand, alcohols can enter a carbonylation reaction of nitroarene to give carbamates, a reaction that is again very efficiently catalyzed by Pd/Phen complexes.[128-130] It is worth noting that these compounds are very difficult substrates for this kind of reaction. However, cyclization of **3m** to **4m** or **3n** to **4n** has never been reported by any means, whereas that of **3ag** to **4ag** and **3ah** to **4ah** has been reported in just one case to occur with CO and a rhodium catalyst in low yields (11 and 26% respectively) despite the use of a high rhodium loading (10 mol%).[64] Swimmingly, **3m**, **3ag** and **3ah** were cyclized to the corresponding indoles when conditions B were applied, resulting in the formation of the acetylated indole as an extra product in the cases of **3m** and **3ag**. Indoles having a cyano group in position 2 and an aryl group in position 3, **4p**-**q**, were obtained in excellent yield independently of the presence of electron-withdrawing or donating groups on the aryl ring. When a sensitive pyrrole ring was present in place of the aryl

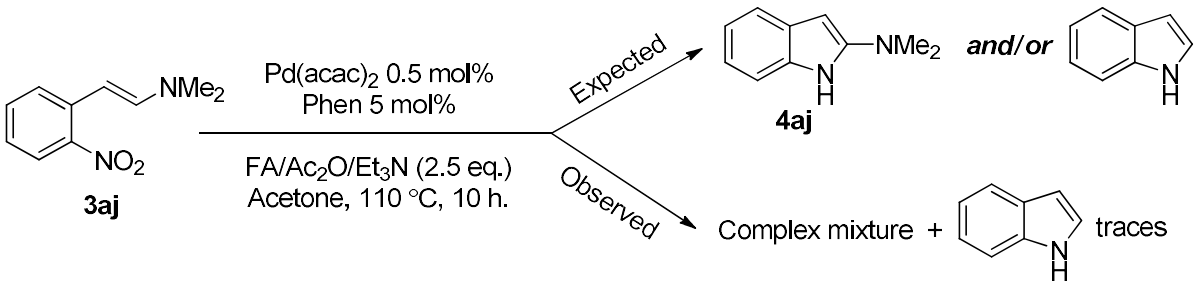
ring, **4r**, the yield markedly improved under both conditions A and B compared to the previous one.[26]

The presence of the nitro group attached to the electron-poor heterocyclic pyridine ring, **3s,** or the presence of the pyridine ring in position β of the double bond, **3t,** afforded the corresponding indoles, **4s,** and **4t,** in high yields, even when a double cyclization was involved (**Table 11**, entry 24). When the double cyclization of a non-symmetrically substituted conjugated diene was attempted under conditions A (**Table 11**, entries 22 and 23), after the standard 6 h reaction time, the main product, **4u'**, was isolated in a 61 % yield with a selective cyclization on the cyano-substituted side. The recovered unreacted diene accounted for the rest of the mass balance. The doubly cyclized bis-indole, **4u'',** could be obtained in high yield by increasing the reaction time to 16 h. It is worth mentioning that the product was isolated by simple precipitation from the reaction mixture. A few double cyclizations of non-symmetrically substituted *bis*-(2-nitrophenyl)dienes to give 2-2' indoles have been reported in the literature,[73] but the reactions were always run to complete conversion of the starting dinitro compound. That the reaction is easier on the side of the cyano-substituted olefin is not surprising, recalling the results we obtained when **3p** and **3q** were cyclized and the observation that the reactivity difference is large enough to allow for a selective mono-cyclization is, to the best of our knowledge, an unprecedented observation. This scenario opens the door for subsequent reactions in which the unreacted nitro group is converted into different functionalities, such as an amino or imino group.

Since 2-aroyl indoles are ubiquitously found in numerous natural products and biologically anticancer active compounds,[131,132] the cyclization of 2-nitrochalcones caught our interest. Cyclization of 2-nitrochalcones (**3w-ae**) afforded selectively 2-aroyl indoles in high yields. We did not detect any formation of the corresponding quinoline that was a major side product in several cases in which either CO [60,133-135] or triethyl phosphite [136] as the reductants were employed for effecting the cyclization.

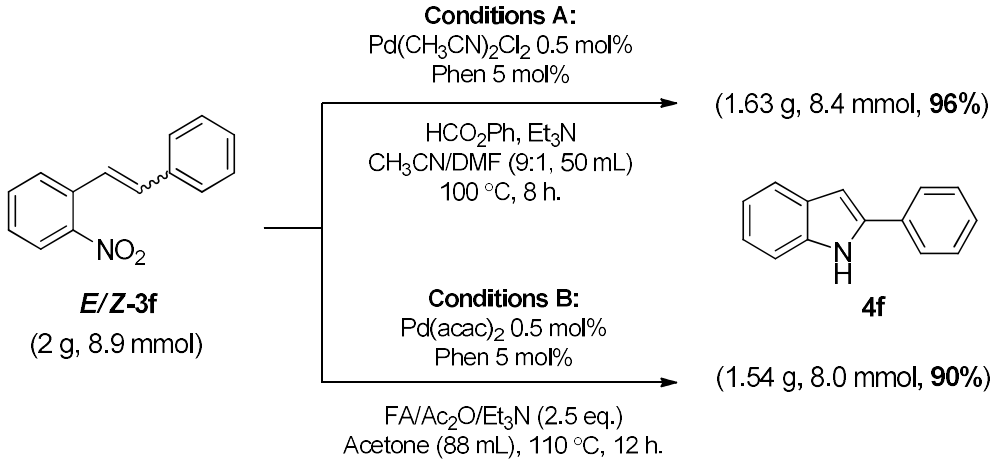
Gratefully, higher yields could be reached under the current conditions A or B compared to the previous conditions in the case of amide **3af**. Although the formic acid strategy is quite general and leads to high yields in most cases, a poor yield was obtained in the cyclization of 2-nitrocinnamaldehyde, **3ai**. The use of phenyl formate was indeed more effective in this case, allowing the isolation of indole **4ai** in 65% yield. Unfortunately, increasing the catalyst loading to 1 mol% did not improve the yield (26%).

In order to get an 2,3-unsubstituted indole, we have cyclized *trans*-β-dimethylamino-2-nitrostyrene **3aj** under conditions B, which was expected to yield either 2-dimethylaminoindole **4aj** or, more likely, unsubstituted indole.[137] A complex mixture of products was observed in which the unsubstituted indole was present only in traces (**Scheme 10**).



Scheme 10. Catalytic reductive cyclization of **3aj** using formic acid as a CO source.

More interestingly, a gram-scale reaction was conducted using a *Z*/*E* mixture (2:1 ratio) of 2-nitrostilbene **3f** (2.0 g, 8.9 mmol) employing phenyl formate or formic acid conditions (**Scheme 11**). Modifications consisted of the use of less amount of the required solvent (Conditions A: 45+5 mL CH_3CN/DMF, 5-fold increase. Conditions B: 88 mL acetone, 8.8-fold increase) and the elongation of the reaction time to ensure the complete conversion. However, since the chromatographic isolation of a multi-gram amount of product is expensive and time-consuming, the mixture was filtered over celite to remove the metallic palladium precipitated at full conversion and the indole was isolated by precipitation with water and filtration (see experimental section for details). The product was isolated in almost the same yield as that obtained by the 0.5 mmol scale reaction. It is worth noting that decreasing the catalyst loading (0.5 mol% of $Pd(CH_3CN)_2Cl_2$ was used instead of 1 mol% under conditions A) or even the workup at the end of the reaction did not affect the yield of the observed indole, which indeed strongly supports the utility of our protocol.



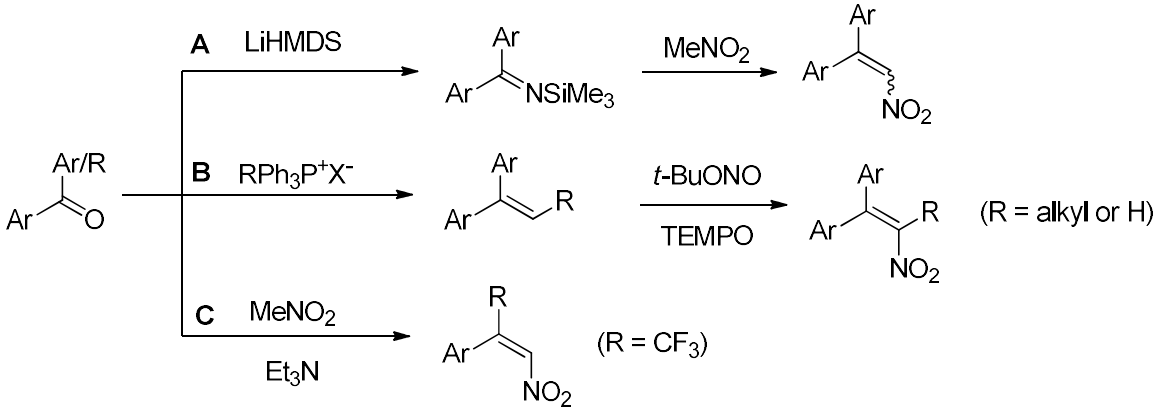
Scheme 11. Large-scale synthesis of 2-phenylindole **4f**.

3. Synthesis of the starting nitrostyrenes

3.1. Synthesis of *β*-nitrostyrenes

Since one of our lofty goals is to make the catalytic reductive cyclization reaction using CO as a reductant a general tool for all synthetic chemists, we have used different synthetic procedures for our starting *β*-nitrostyrenes.

Diaryl nitroalkenes **1d-j** were generated from their corresponding benzophenone derivatives via a straightforward two-step sequence, following a previously reported procedure [79] (**Scheme 12**, paths A) or through the Wittig-Olefination reaction followed by nitration[138,139] (**Scheme 12**, path B). Nitroalkene **1l** synthesis was effected from a simple single-step Henry reaction[140] (**Scheme 12**, path C).

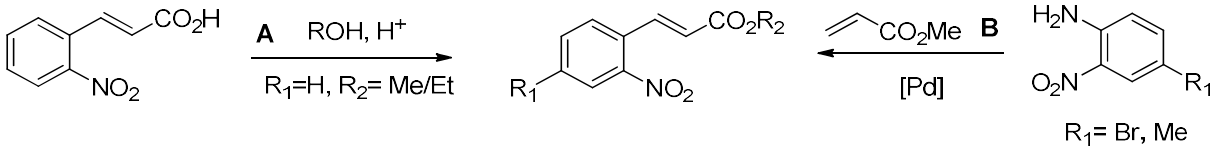


Scheme 12. Synthesis of *β*-nitrostyrenes starting from the corresponding ketones.

3.2. Synthesis of *o*-nitrostyrenes

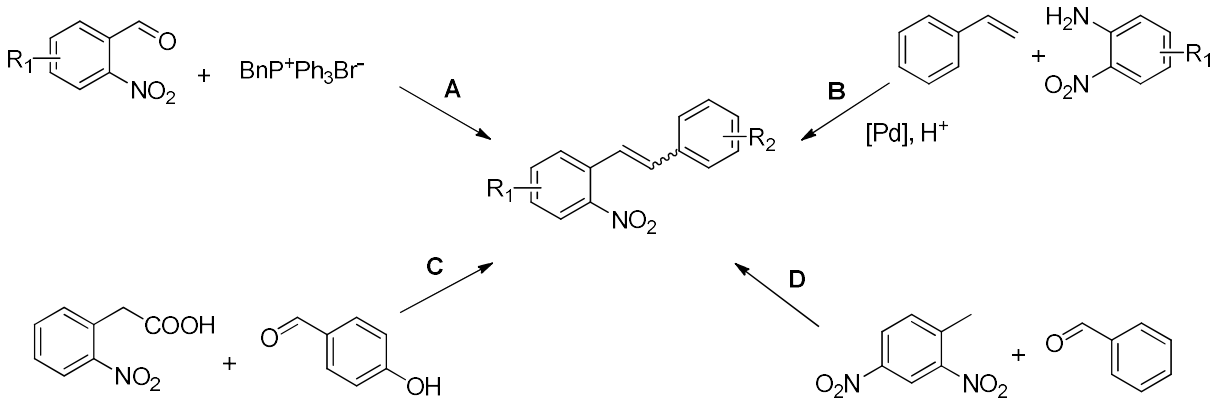
Most of *o*-nitrostyrenes are commercially unavailable, however, we used different protocols to get the desired *o*-nitrostyrenes starting from commercially available compounds that already bear the nitro group.

To prepare the *o*-nitrocinnmate esters, it is always easy to perform a classical esterification of commercially available (*E*)-2-nitrocinnamic acid using the alcohol and a suitable acid (**Scheme 13**, path A).[141] Additionally, Heck-Matsuda cross-coupling reaction also affords the cinnamate esters successfully (**Scheme 13**, path B), a reaction very convenient when the aryl ring bears some substituents, since the corresponding acids are not commercially available in these cases.[142]



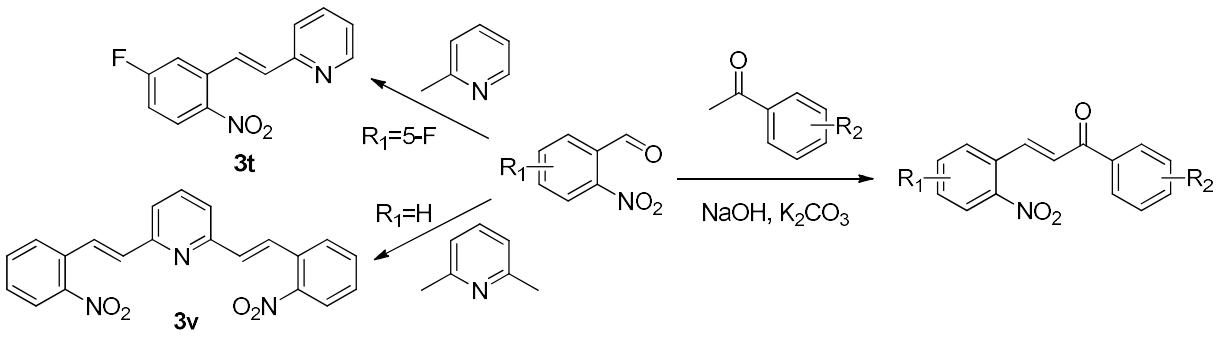
Scheme 13. Preparation of *o*-nitrocinnamates.

Moving to the nitrostilbenes, they have been prepared by several routes as the classical Wittig reaction (**Scheme 14**, path A),[143-145] modified Heck-Matsuda reaction (**Scheme 14**, path B),[146] or other simple classical condensation reactions (**Scheme 14**, paths C and D).[147,148]



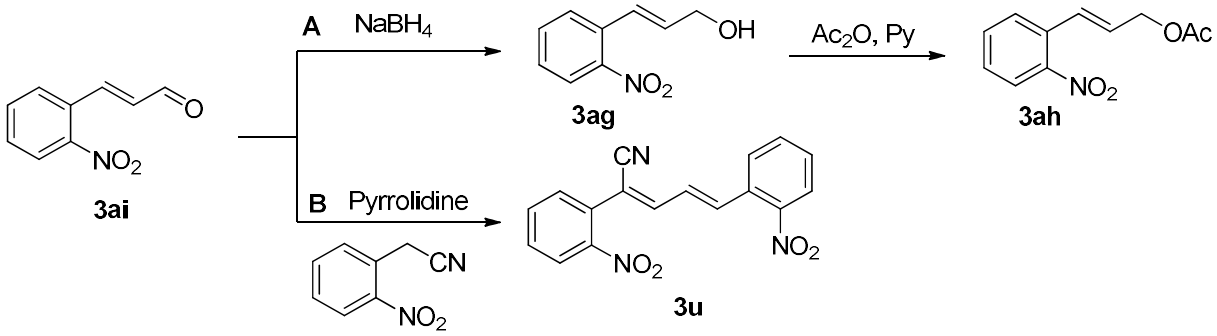
Scheme 14. Different routes for *o*-nitrostilbenes preparation.

A solvent-free Claisen-Schmidt condensation have been used to synthesize 2-nitrochalcone derivatives in good yields,[149] while a Knoevenagel-type condensation was employed to synthesize nitrostyrenes that bearing pyridine ring [150] (**Scheme 15**).



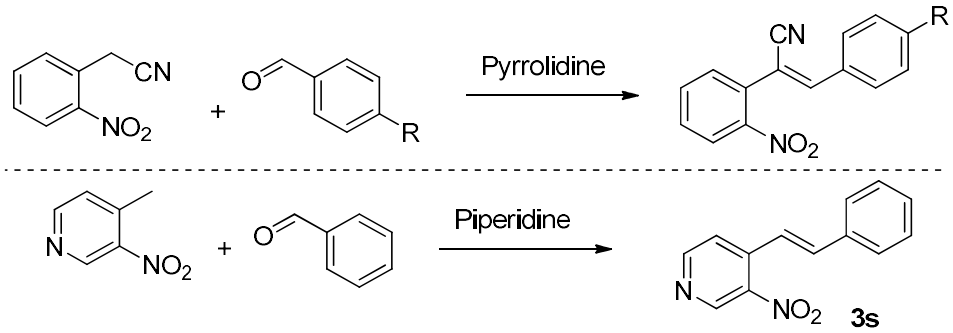
Scheme 15. Use of *o*-nitrobenzaldehyde for the synthesis of different *o*-nitrostyrenes.

Besides being employed as a substrate for the catalytic reaction, *o*-nitrocinnamaldehyde **3ai** was also used to get other substrates. A simple reduction of the aldehyde group followed by an acetylation of the formed alcohol afford **3ag** and **3ah** respectively (**Scheme 16**, path A).[64] Knoevenagel-type condensation was used to get **3u** successfully (**Scheme 16**, path B).[23,26]



Scheme 16. Preparation of **3ag**, **3ah** and **3u** starting from **3ai**.

In addition, Knoevenagel-type condensations were further used for the preparation of nitrostyrilpyridine **3s** and of other *o*-nitrostyrenes substituted in position α with a cyano group. Notably, in the latter cases the products precipitate from the reaction media allowing for a ready recovering (**Scheme 17**).[23,26]



Scheme 17. Other Knoevenagel-type condensations for the preparation of *o*-nitrostyrenes.

In conclusion, following previously mentioned protocols, we were able to synthesize various nitrostyrenes starting from cheap and commercially available nitro compounds in very good yields.

4. Conclusion

The use of CO as a reductant for nitrostyrenes presents many advantages from a synthetic point of view but is operationally complex for most research groups. In this chapter, we have presented our results on the use of phenyl formate and formic acid as convenient CO surrogates in the Pd-catalyzed reductive cyclization reactions of both β-nitrostyrenes and *o*-nitrostyrenes. The protocol's strength is the exclusion of pressurized CO lines or autoclave, allowing the synthetic chemist to perform the reaction in a pressure tube, a tool cheap and commonly available in any laboratory. In the case of β-nitrostyrenes, phenyl formate was employed as the CO source. Good results could be reached when a second aryl ring is present in the α-position of the styrene. Depending on the substrate, yields are comparable to or a little lower than those achieved using pressurized gaseous CO. However, the reaction was not satisfactory when no aryl substituent was present in the α-position of the nitrostyrene, at least when the results previously achieved using pressurized CO are taken as a reference. That the latter substrates required harsher reaction conditions had already been noted, but this fact had only been imputed to a lower reactivity of starting nitroalkene. Moreover, we have found that lower reactivity is only one aspect of the problem. The other is that bases, necessary for the decomposition of phenyl formate, promote unwelcome side reactions, mainly oligo- and polymerization reactions. Thus, a competition exists between cyclization and the side reactions and the only efficient way of favoring the former is to increase the CO pressure. Even if the problem may in theory be solved by increasing the phenyl formate amount, this cannot be safely done in a glass pressure tube. For these substrates, the use of pressurized CO seems to us to still be the best choice. On the other hand, we have re-optimized the previously published catalytic reaction conditions to get indoles from *o*-nitrostyrenes using

phenyl formate to beat problems related to the stability of some substrates. The reaction can be performed with low catalyst loading (just 1 mol% or even less), and in the presence of 1,10-phenanthroline, a cheap commercially available ligand. Although the reaction tolerates a wide range of substrate, in some cases we faced a problem in isolating the final product due to the formation of phenol (decomposition product of HCO_2Ph). As a result, we explored the possibility of using formic acid as the CO source in the catalytic reaction. The use of formic acid accompanied with Ac_2O allows for the isolation of the desired indoles in most cases with yields comparable to those previously obtained using HCO_2Ph. It has been found that the use of HCO_2Ph and HCO_2H is complementary for the cyclization of some *o*-nitrostyrenes. The undeniable benefits of using HCO_2H/Ac_2O over other CO surrogates include their accessibility in all synthetic organic labs, their affordability, and the easier isolation of the final product. Unlike the reaction using HCO_2Ph, when HCO_2H was used, the reaction tolerated water and air, thus did not require a strictly oxygen-free environment. As a bonus to the robustness and stability of our strategy, the reaction is also readily scaled up, providing 2-phenyl indole in a high yield (90–96%) even under harsher conditions and using a work-up avoiding the use of column chromatography. This makes our reaction even more accessible, useful for preparation purposes, and economically advantageous.

5. Experimental section

5.1. General information

Unless otherwise stated, all the reactions were carried out under dinitrogen atmosphere using standard Schlenk apparatus. All glassware and magnetic stirring bars were kept in an oven at 120 °C for at least two hours and let to cool under vacuum before use. CH_3CN was dried by distillation from CaH_2. DMF was dried by distillation from CaH_2, at 60 °C under reduced pressure. Acetone was degassed and dried over molecular sieves (4 Å) and stored under dinitrogen atmosphere. Formic acid (≥ 99% purity) and acetic anhydride (≥ 99% purity) were purchased from Sigma-Aldrich, formic acid (85% purity) was purchased from Carlo Erba Reagents. All were degassed by freeze-pump-thaw cycles and stored under dinitrogen atmosphere. Triethylamine was distilled from CaH_2 and kept under dinitrogen atmosphere. 1,10-Phenanthroline (Phen) was purchased as hydrate (TCI Europe NV). It was dissolved in CH_2Cl_2, dried over Na_2SO_4 followed by filtration under a dinitrogen atmosphere and evaporation of the solvent in vacuo. Phen was weighed in the air but stored under dinitrogen to avoid water absorbance. Deuterated solvents were purchased from Sigma-Aldrich: DMSO-d_6 (commercially available in 0.75 mL vials under dinitrogen atmosphere) was used as purchased, while $CDCl_3$ was filtered on basic alumina and stored under dinitrogen over 4 Å molecular sieves. All the other reagents were purchased from Merck (Sigma-Aldrich), TCI Europe NV or Fluorochem and used without further purification. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance DRX 300, Avance DRX 400 or Avance NEO 400. Chemical shifts are reported in ppm relative to tetramethylsilane. Elemental analyses were performed on a Perkin Elmer 2400 CHN elemental analyser. Thin-layer chromatography (TLC) was performed using precoated silica gel 60 F254 MACHEREY-NAGEL plates. TLC plates were visualized by exposing UV light. Flash column chromatography was performed on MACHEREY-

NAGEL flash silica gel 0.04-0.063 mm size. Gas-chromatographic analyses were performed using a *Shimadzu* 2010Pro gas chromatograph equipped with a Supelco SLB^{TM}-5 ms capillary column (L × I.D. 10 m × 0.10 mm, df 0.10 μm). A standard analysis involves the preparation of a sample solution in ethyl acetate (conc. 0.3 mg/mL calculated with respect to naphthalene or biphenyl as the internal standard).

5.2. General procedure for the catalytic reactions

To avoid weighing errors, stock solutions of Pd catalyst and Phen were separately prepared under dinitrogen in the reaction solvent. For a typical catalytic reaction, a pressure tube (**Fig. 4**) equipped with a magnetic stirring bar was charged with nitrostyrene (1 eq.). The tube was placed in a large mouth Schlenk tube and evacuated and filled with dinitrogen three times. The appropriate volume of stock solutions of the catalysts and Phen were added, and the mixture stirred for 10 min, to allow the formation of Pd/Phen complex. Precipitation of $Pd(Phen)Cl_2$ may be observed depending on the catalyst concentration. The solvent (total solvent amount was 10 mL), HCO_2Ph and the base were added in this order and the pressure tube sealed under nitrogen.

For the reactions using HCO_2H/Ac_2O, after the formation of Pd/Phen complex, the proper amounts of Et_3N and acetic anhydride were added without stirring and then the solvent (10 mL total volume) was carefully layered. Finally, formic acid was added, and the pressure tube sealed under dinitrogen.

The tube was then placed in a custom-made aluminum block preheated at the desired temperature and heated while stirring for the required time. Detailed experimental conditions are reported in the captions to the tables.

At the end of the reaction, the pressure tube was lifted from the heating block, let to cool to room temperature and opened (Caution: residual CO pressure is present in the pressure tube, perform the operation slowly under a hood). When quantitative GC analysis of the reaction was needed, the internal standard was then added to the reaction mixture, the reaction stirred until its complete solubilization and then the reaction mixture immediately analyzed. Otherwise, the solvent was evaporated, and the residue subjected to column chromatography (silica gel) using hexane/AcOEt as the eluent with the addition of 1 to 2% of Et_3N to partially deactivate acidic sites of silica gel. In our experience, absence of Et_3N causes extensive decomposition of the indoles over silica-gel.

The same reaction protocol was employed for running the catalytic tests in standard Schlenk glassware.

5.3. Procedure for the large-scale synthesis of indole (4f) under conditions A

The large-scale reaction was performed in a 250 mL Fisher-Porter pressure bottle. The reaction for the synthesis of **4f** under Conditions A was scaled up 16.5-fold with respect to the standard conditions.

The pressure bottle was charged with solid reagents, substrate **3f** (2.0 g, 8.9 mmol), catalyst (0.5 mol%, half the amount used in the catalytic reaction) and phenanthroline (5 mol%), and then placed in a Schlenk tube with a large mouth. The tube was evacuated and filled three times with

dinitrogen. Solvent (45+5 mL CH_3CN/DMF, 5-fold increase) was added. and the mixture stirred for 15 min. Phenyl formate (3.3 mL, 30.3 mmol, less amount used compared to the catalytic reaction 3.4 eq instead of 4.4) and Et_3N (1.6 mL, 11.5 mmol) were added, then the pressure bottle sealed under dinitrogen. To ensure completion of the reaction, the reaction time was increased from 6 to 8 h, although the reaction may have reached completion before. At the end of the reaction, metallic palladium had precipitated on the walls of the bottle. The solution was then filtered through a pad of Celite in a Pasteur pipette by cannula technique to remove even colloidal palladium particles possibly present. The product was then precipitated with water, dissolved in CH_2Cl_2 (50 mL) and washed with a saturated $NaHCO_3$ aqueous solution (3 × 30 mL), brine (1 × 50 mL) and water (1 × 50 mL). The organic phase was then dried over Na_2SO_4, filtered and the solvent was evaporated under vacuum to yield the final product as a white, analytically, and spectroscopically pure crystalline solid (1.63 g, 96 % yield), without the need for any chromatographic purification. Phenanthroline and any other by-product present in small amounts remained in solution by this procedure.

5.4. Procedure for the large-scale synthesis of indole (4f) under conditions B

The large-scale reaction was performed in a 250 mL heavy-walled glass pressure bottle (**Fig.4**) to prepare **4f** under the optimal conditions. The reaction for the synthesis of **4f** under Conditions B was scaled up 17.6-fold with respect to the standard conditions.

The pressure bottle was charged with solid reagents, substrate 1e (2.00 g, 8.8 mmol), $Pd(acac)_2$ (0.5 mol%) and phenanthroline (5 mol%), and then placed in a Schlenk tube with a large mouth. The tube was evacuated and filled three times with dinitrogen. Acetone (30 mL), triethylamine (3.1 mL, 22 mmol) and acetic anhydride (2.1 mL, 22 mmol) were added, and the mixture stirred for 10 minutes. The stirring was stopped, and the remaining solvent amount (acetone, 68 mL) was layered. Finally, formic acid (0.84 mL, 22 mmol) was added, and the bottle sealed with the screwcap under dinitrogen. The total amount of solvent was only 8.8 times increased instead of 17.6 to facilitate the subsequent workup. The pressure bottle was placed in a pre-heated (110 °C) oil bath. Despite the possibility that the reaction had already reached full conversion of the substrate, the reaction time was extended from 10 to 12 hours to ensure completion. Metallic palladium precipitated on the bottle walls at the end of the reaction. At the end of the reaction, the pressure bottle was raised from the oil bath, let to cool to room temperature and slowly opened under a fume hood. ATTENTION: Scale-up of the reaction should be performed carefully considering the maximum CO pressure developed by HCO_2H decomposition and scaling-up the reactor volume accordingly. Subsequently, the solution was filtered on a short pad of Celite in a Pasteur pipette using cannula technique to get rid of any potential colloidal palladium particles. The product was precipitated with water, collected by filtration on a Buchner funnel, dissolved in ethyl acetate (50 mL) and washed with saturated $NaHCO_3$ aqueous solution (3 × 30 mL), brine (50 mL) and water (50 mL). The organic layer was then dried over Na_2SO_4, filtered and the solvent was evaporated under vacuum to yield the final product as a white, analytically, and spectroscopically pure crystalline solid (1.54 g, 90% yield), without the need for any

chromatographic purification. Phenanthroline and any other by-products present in small amounts remained in solution after the first precipitation by this procedure.

Fig.4. Left: Pressure bottle used in the large-scale reaction under conditions B. Right: Pressure tube used during our study.

5.5. Preparation of palladium catalysts

5.5.1. Preparation of $Pd(CH_3CN)_2Cl_2$

The synthesis was performed following the procedure reported in the literature.[151]

$PdCl_2$ (1.01 g, 5.70 mmol) was suspended into 70 mL of CH_3CN and refluxed for 2 h. To remove undissolved material, the hot solution was filtered through filtering paper by using a Teflon cannula. The solution was cooled to 0 °C to promote the precipitation of the desired complex. The so-formed orange solid was filtered through a Buchner funnel. (1.47 g, 99% yield).

Elemental analysis calcd for $C_4H_6Cl_2N_2Pd$: C, 18.52; H, 2.33; N, 10.80, found: C, 18.80; H, 2.28; N, 10.80.

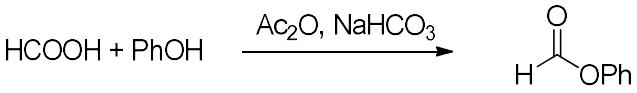
5.5.2. Preparation of $Pd(acac)_2$

The synthesis was performed following the procedure reported in the literature.[152]

$PdCl_2$ (1 g, 5.6 mmol) and NaCl (0.66 g, 11.2 mmol) were dissolved in methanol (25 mL) and stirred at room temperature overnight until the mixture became clear. The solution was diluted with methanol (25 mL), and then acetylacetone (1.23 g, 12.3 mmol) and Na_2CO_3 (0.59 g, 5.6 mmol) were added to the solution, followed by stirring at room temperature overnight. After the reaction, the precipitate was filtered and washed with distilled water. The yellow powder was dried under vacuum overnight. (1.6 g, 94% yield).

Elemental analysis calcd for $C_{10}H_{16}O_4Pd$: C, 39.17; H, 5.26; N, 0.00, found: C, 39.24; H, 5.17; N, 0.06.

5.6. Preparation of phenyl formate



The synthesis was performed following the procedure reported in the literature.[153]
In a dry 250 mL round bottom Schlenk flask, formic acid (35 mL, 0.93 mol) and acetic anhydride (70 mL, 0.74 mol) were stirred at 60 ºC for 1 hour. The mixture was then allowed to cool to room temperature and transferred using a cannula into an ice-cooled 500 mL Schlenk containing phenol (17.4 g, 0.19 mol) and sodium bicarbonate (15.5 g, 0.19 mol). After the addition, the reaction temperature let to reach to room temperature and stirred overnight under a dinitrogen atmosphere. A mixture of CH_2Cl_2 (80 mL) and water (100 mL) was then added, and the biphasic system was stirred vigorously. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with water (7×50 mL) and brine (3×25 mL), to get rid of residual acid, dried over Na_2SO_4 and filtered. The solvent was evaporated to give the final product as pale-yellow liquid (16.5 mL, 0.15 mol, 82%). The obtained formate is analytically (NMR) pure and can be used without further purification.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.43 (t, J = 7.8 Hz, 2H), 7.30 (t, J = 7.4 Hz, 1H, overlapped with $CDCl_3$ signal), 7.17 (d, J = 7.7 Hz, 2H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 149.9, 129.6, 126.3, 121.1 ppm.

5.7. Preparation of *β*-nitrostyrenes

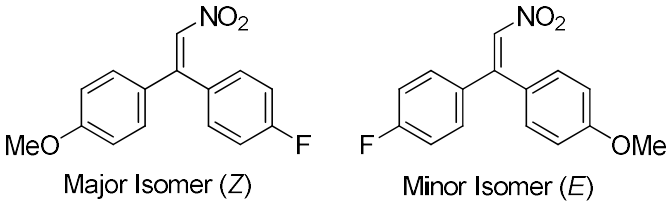
Nitroolefins **1a**,[154] **1b**,[80,155] **1c**,[156] **1e** [157] and **1k** [80] were prepared as previously reported in the literature. Analytical data were in agreement to previous reports.[158] The other substrates were synthesized following the modified procedure herein reported.

5.7.1. General synthetic procedure for the synthesis of *α*-aryl-*β*-nitrostyrenes – Method A

The synthesis was performed following the procedure reported in the literature.[156]
In an oven dried Schlenk flask, the substituted benzophenone (4 mmol.) was dissolved in dry THF (20 mL) and the flask cooled in an ice-bath. Lithium hexamethyldisilazane (LiHMDS) (9 mL, 1 M solution in THF) was added dropwise and then the mixture stirred for 24 h at room temperature. THF was then evaporated under vacuum and ethyl acetate (20 mL) was added in the air. The organic layer was washed with brine (3×15 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated, and nitromethane (15 mL) was added to the residue. The mixture was refluxed under a dinitrogen atmosphere for 48 h. Nitromethane was then evaporated to give the

residue, which was purified by either crystallization or column chromatography. Nitroalkenes **1d**, **1e** and **1g** were prepared using this method.

1-fluoro-4-(1-(4-methoxyphenyl)-2-nitrovinyl)benzene (1d).



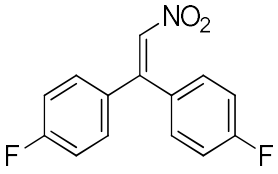
Obtained as a yellow solid (361 mg, 1.32 mmol, isomeric mixture *Z:E* = 1.7:1) after column chromatography (CH_2Cl_2/hexane 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H, *Z*-isomer), 7.32 (s, 1H, *E*-isomer), 7.29 (dd, *J* = 8.8, 5.3 Hz, 2H, *E*-isomer), 7.23 – 7.20 (m, 4H, *Z*-isomer), 7.18 – 7.06 (m, 2H, *Z*-isomer and 4H, *E*-isomer), 6.94 (d, *J* = 8.8 Hz, 2H *Z*-isomer), 6.90 (d, *J* = 8.9 Hz, 2H, *E*-isomer), 3.86 (s, 3H), 3.84 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4 (d, $^1J_{C\text{-}F}$ = 252.6 Hz), 163.2 (d, $^1J_{C\text{-}F}$ = 249.8 Hz), 162.2, 160.9, 149.7, 149.52, 133.8 (d, $^4J_{C\text{-}F}$ = 3.2 Hz), 133.5, 133.05, 131.6 (d, $^4J_{C\text{-}F}$ = 3.4 Hz), 131.3 (d, $^3J_{C\text{-}F}$ = 8.6 Hz) 131.0 overlapped with 130.9, 130.7, 116.0 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 115.7 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 114.4, 114.0, 55.5, 55.4 ppm.

Elemental Analysis calcd for $C_{15}H_{12}FNO_3$: C, 65.93; H, 4.43; N, 5.13, found: C, 65.53; H, 4.63; N, 5.14.

4,4'-(2-nitroethene-1,1-diyl)bis(fluorobenzene) (1e).



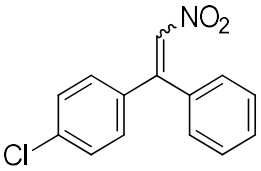
Obtained as a yellow solid (439 mg, 1.7 mmol, 42% yield) after recrystallization from hexane:isopropanol = 8:2.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.30 - 7.25 (m, 2H), 7.24 – 7.18 (m, 2H), 7.18 – 7.05 (m, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6 (d, $^1J_{C\text{-}F}$ = 253.2 Hz), 163.5 (d, $^1J_{C\text{-}F}$ = 250.2 Hz, *C*F), 148.5, 133.2 (d, $^4J_{C\text{-}F}$ = 3.1 Hz) 131.3 (d, $^4J_{C\text{-}F}$ = 3.4 Hz), 131.2, 131.1 (d, $^4J_{C\text{-}F}$ = 1.4 Hz), 116.4 (d, $^2J_{C\text{-}F}$ = 21.9 Hz, *C*H), 116.0 (d, $^2J_{C\text{-}F}$ = 21.9 Hz, *C*H) ppm.

Elemental Analysis calcd for $C_{14}H_9F_2NO_2$: C, 64.37; H, 3.47; N, 5.36, found: C, 64.84; H, 4.08; N, 5.46.

1-chloro-4-(2-nitro-1-phenylvinyl)benzene (1g).



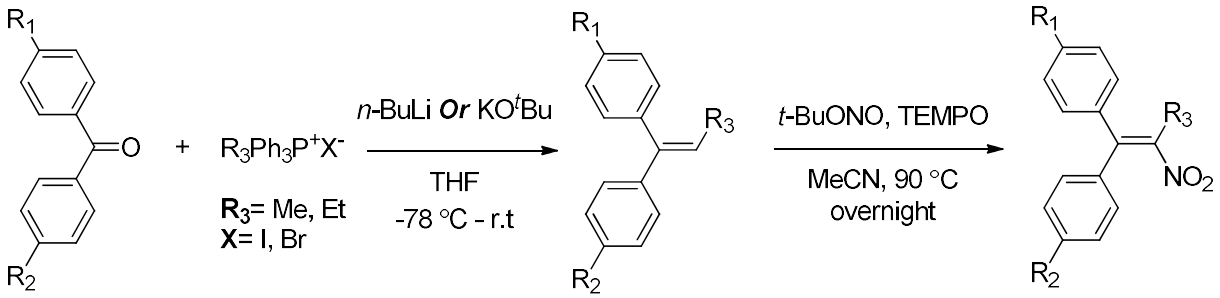
Obtained as a yellow solid (582 mg, 2.2 mmol, 56% yield, mixture of two isomers) after recrystallization from (hexane:isopropanol = 8:2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.33 (m, 6H), 7.28-7.16 (m, 4H, overlapped with $CDCl_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 149.3, 137.4, 136.8, 135.71, 135.68, 135.2, 134.8, 134.6, 134.0, 131.3, 130.4, 130.3, 129.7, 129.4, 129.2, 129.02, 129.00, 128.9, 128.8 ppm.

Elemental Analysis calcd for $C_{14}H_{10}ClNO_2$: C, 64.75; H, 3.88; N, 5.39, found: C, 64.84; H, 4.08; N, 5.46.

5.7.2. General synthetic procedure for the synthesis of *α*-aryl-*β*-nitrostyrenes – Method B



General procedure for the synthesis of the olefins by Wittig reaction

The synthesis was performed following the procedure reported in the literature.[138] In an oven dried Schlenk flask, the phosphonium salt (2 eq.) was added and dissolved in dry THF then cooled to -78 °C. *n*-BuLi (2 eq., 2.5 M solution in hexane) or KO^{t}Bu was slowly added (dark yellow color was immediately observed) then the mixture allowed to warm up to room temperature and stirred for 1 h. After that, the mixture was cooled again to -78 °C and a solution of benzophenone (1 eq.) in THF was added gradually. After stirring for another 0.5 h, the resulting solution was allowed to warm up to room temperature and left with stirring under nitrogen atmosphere overnight. The reaction was quenched by addition of a saturated aqueous ammonium chloride solution and was extracted with hexane several times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated. The residue was purified by column chromatography on silica-gel using hexane as the eluent to give the olefin.

General procedure for the synthesis of the nitroalkenes by nitration of the corresponding olefins

The synthesis was performed following the procedure reported in the literature.[139]

In an oven dried pressure tube equipped with a stirring bar, the olefin (1 eq.), TEMPO (1 eq.), *tert*-butyl nitrite (2 eq.) and acetonitrile were added. The reaction was closed under an oxygen atmosphere and left at 90 °C overnight. After reaction completion the solvent was evaporated and the reaction mixture was purified by column chromatography on silica-gel using hexane:AcOEt (95:5) as the eluent to give the nitroalkene.

Synthesis of 4,4'-(2-nitroethene-1,1-diyl)bis(methylbenzene) (1h)

4,4'-(ethene-1,1-diyl)bis(methylbenzene).

Prepared by Wittig reaction performed under inert atmosphere. Methyl triphenylphosphonium iodide (2.20 g, 5.4 mmol) was suspended in dry THF (30 mL) and KO^{t}Bu (640 mg, 5.7 mmol) was added. The mixture was stirred at room temperature for 1h and then 4,4'-dimethylbenzophenone (954 mg, 4.5 mmol) in dry THF (10 mL) was added gradually. The reaction was stirred overnight and then quenched with saturated aqueous ammonium chloride solution (25 mL) then extracted with hexane (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated. The residue was purified by column chromatography on silica-gel using hexane as the eluent to give the olefin as white solid (510 mg, 2.4 mmol, 53% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.1 Hz, 4H), 7.17 (d, J = 8.1 Hz, 4H), 5.41 (s, 2H), 2.40 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 138.9, 137.6, 129.0, 128.3, 113.1, 21.3 ppm.

Elemental Analysis calcd for $C_{16}H_{16}$: C, 92.26; H, 7.74, found: C, 92.25; H, 7.75.

4,4'-(2-nitroethene-1,1-diyl)bis(methylbenzene) (1h).

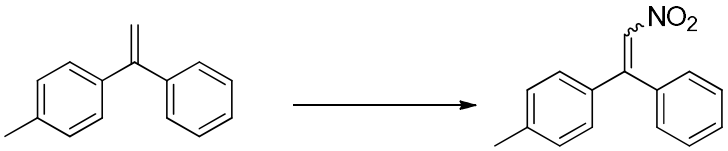
Prepared according to the general synthetic procedure for the nitration of olefins from 4,4'-(ethene-1,1-diyl)bis(methylbenzene) (312 mg, 1.5 mmol), TEMPO (234 mg, 1.5 mmol), *tert*-butyl nitrite (360 μL, 3.0 mmol) and acetonitrile (6 mL). The product was obtained as yellow crystals (220 mg, 0.87 mmol, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.23 (d, J = 7.9 Hz, 2H), 7.18 (s, 4H), 7.11 (d, J = 7.9 Hz, 2H), 2.42 (s, 3H), 2.39 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 141.6, 139.6, 134.7, 133.6, 132.8, 129.7, 129.3, 129.15, 129.10, 21.6, 21.5 ppm.

Elemental Analysis calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53, found: C, 75.75; H, 6.07; N, 5.49.

Synthesis of 1-methyl-4-(2-nitro-1-phenylvinyl)benzene (1i).



1-methyl-4-(1-phenylvinyl)benzene.

Prepared by Wittig reaction performed under inert atmosphere from methyl triphenylphosphonium iodide (1.62 g, 4.0 mmol) dissolved in dry THF (25 mL), *n*-BuLi (1.6 mL, 4.0 mmol, 2.5 M solution in hexane) and 4-methylbenzophenone (392 mg, 2 mmol) dissolved in dry THF (5 mL). The reaction was quenched with 30 mL of saturated aqueous ammonium chloride solution then extracted with hexane (3 × 15 mL). Column chromatography purification was performed using hexane as the eluent. The product was isolated as colorless oil (300 mg, 1.5 mmol, 77% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.43 (m, 5H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 5.57 (d, *J* = 1.0 Hz, 1H), 5.55 (d, *J* = 1.0 Hz, 1H), 2.50 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 141.8, 138.7, 137.6, 129.0, 128.4, 128.3, 128.2, 127.8, 113.7, 21.3 ppm.

Elemental Analysis calcd for $C_{15}H_{14}$: C, 92.74; H, 7.26, found: C, 92.62; H, 7.19.

1-methyl-4-(2-nitro-1-phenylvinyl)benzene (1i).

Prepared according to the general synthetic procedure for the nitration of olefins from 1-methyl-4-(1-phenylvinyl)benzene (220 mg, 1.1 mmol), TEMPO (177 mg, 1.1 mmol), *tert*-butyl nitrite (270 mL, 2.3 mmol) and acetonitrile (4.5 mL). The product was obtained as yellow crystals (172 mg, 0.72 mmol, 63% yield, mixture of two isomers ca. 1:1 ratio).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.34 (m, 8H), 7.32 – 7.26 (m, 2H), 7.26 – 7.15 (m, 6H, overlapped with the olefinic CH signal), 7.18 (s, 2H, olefinic CH), 7.12 (d, *J* = 8.1 Hz, 2H), 2.42 (s, 3H), 2.39 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 141.7, 139.7, 137.6, 135.9,134.3, 134.3, 133.9, 132.7, 130.9, 129.8, 129.3, 129.2, 129.1, 129.0, 128.95, 128.93, 128.6, 21.6, 21.5 ppm.

Elemental Analysis calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. found: C, 75.42; H, 5.50; N, 5.70.

Synthesis of 1-methyl-4-(2-nitro-1-phenylvinyl)benzene (1j).

Prop-1-ene-1,1-diyldibenzene.

Prepared by Wittig reaction performed under inert atmosphere from ethyl triphenylphosphonium bromide (6.00 g, 16.4 mmol) dissolved in dry THF (50 mL), *n*-BuLi (6.4 mL, 16.4 mmol, 2.5 M solution in hexane) and benzophenone (1.50 g, 8.2 mmol) in dry THF (10 mL). Reaction was quenched with saturated aqueous ammonium chloride solution (30 mL) then extracted with hexane (3 × 20 mL). The solvent was evaporated, and the residue was purified by column chromatography on silica-gel using hexane as the eluent to give the product as white solid (1.47 g, 7.6 mmol, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, *J* = 7.2 Hz, 2H), 7.39 – 7.21 (m, 8H), 6.24 (q, *J* = 7.0 Hz, 1H), 1.83 (d, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 142.6, 140.2, 130.2, 128.3, 128.2, 127.3, 127.0, 126.9, 124.3, 15.8 ppm.

Elemental Analysis calcd for $C_{16}H_{16:}$ C, 92.74; H, 7.26. found: C, 92.49; H, 7.25.

(2-nitroprop-1-ene-1,1-diyl)dibenzene (1j).

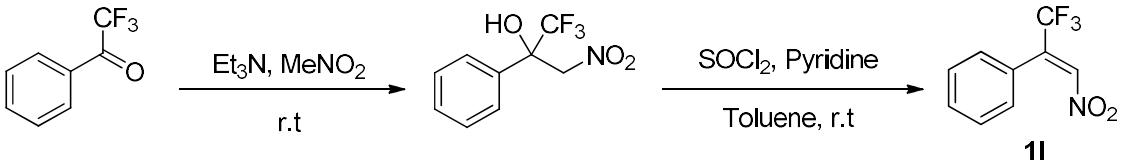
Prepared according to the general synthetic procedure for the nitration of olefins from prop-1-ene-1,1-diyldibenzene (291 mg, 1.5 mmol), TEMPO (234 mg, 1.5 mmol), *tert*-butyl nitrite (360 mL, 3 mmol) and acetonitrile (6 mL). The product was obtained as pale-yellow crystals (200 mg, 0.84 mmol, 55% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 3H), 7.33 – 7.28 (m, 3H), 7.21 (dd, *J* = 7.7, 1.8 Hz, 2H), 7.17-7.15 (m, 2H), 2.35 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 140.0, 138.4, 138.3, 129.5, 128.9, 128.7, 128.69, 128.67, 128.3, 18.3 ppm.

Elemental Analysis calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85, found: C, 75.38; H, 5.65; N, 5.79.

Synthesis of (*E*)-(3,3,3-trifluoro-1-nitroprop-1-en-2-yl)benzene (1l)



1l

The synthesis was performed following the procedure reported in the literature.[140]

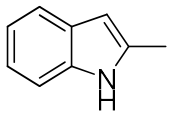
In a two neck round bottomed flask, Et_3N (1.2 mL, 8.6 mmol) was added, under N_2, to a solution of 2,2,2-trifluoroacetophenone (900 mg, 6.1 mmol) in nitromethane (8 mL). The mixture was stirred overnight at room temperature and then ethyl acetate (20 mL) was added. The mixture was washed with 1M HCl (10 mL), water (10 mL), and brine (10 mL) and then dried over Na_2SO_4. Filtration and evaporation of the solvent afforded the crude nitro alcohol that was used in the subsequent step without further purification. The crude was dissolved in toluene (8 mL) and $SOCl_2$ (0.70 mL, 9.6 mmol) and pyridine (1.5 mL, 18.6 mmol) were slowly added at 0 °C while stirring. The mixture was stirred at room temperature for 4h and then ethyl acetate (20 mL) was added. The organic phase was washed with water (3×10 mL) and brine (10 mL), dried over Na_2SO_4 and filtered. The solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel using hexane: CH_2Cl_2 (95:5). The product was obtained as yellow oil (638 mg, 2.9 mmol, 48% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 1.1 Hz, 1H), 7.51 – 7.43 (m, 3H), 7.32 (d, J = 7.0 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 136.1 (q, $^2J_{C\text{-}F}$ = 31.9 Hz), 130.7, 129.0, 128.3, 127.0, 122.0 (q, $^1J_{C\text{-}F}$ = 274 Hz) ppm.

5.8. Characterization data for indoles (2a-e) and (2g-j)

2-Methyl-1*H*-indole (2a).



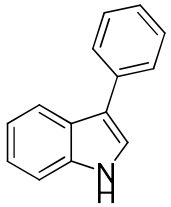
Obtained as a white solid (31 mg, 0.23 mmol, 43% yield) after column chromatography (hexane:AcOEt = 90:10 + 1% Et_3N).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (s, 1H), 7.51 (d, J = 7.3 Hz, 1H), 7.26 (d, J = 7.7 Hz, 1H), 7.15–6.99 (m, 2H), 6.22 (s, 1H), 2.43 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 135.7, 129.1, 120.9, 119. 7, 110.4, 100.3, 13.5 ppm.

Elemental Analysis calcd for C_9H_9N: C, 82.41; H, 6.92; N, 10.48, found: C, 82.12; H, 6.98; N, 10.30.

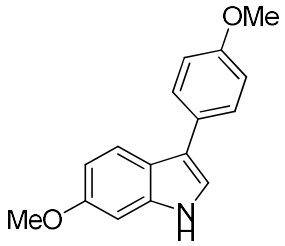
3-Phenyl-1*H*-indole (2b).



Obtained as a white solid (93 mg, 0.48 mmol, 89% yield) after column chromatography (hexane:AcOEt = 90:10 + 1% Et_3N).

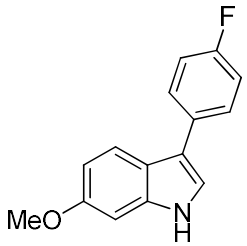
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.3 Hz, 2H), 7.52–7.44 (m, 3H), 7.40 (d, *J* = 2.1 Hz, 1H), 7.35–7.26 (m, 2H), 7.23 (t, *J* = 7.4 Hz, 1H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 135.7, 128.9, 127.7, 126.1, 125.9, 122.6, 121.9, 120.5, 120.0, 118.5, 111.5 ppm.
Elemental Analysis calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25, found: C, 86.90; H, 5.84; N, 7.01.

6-methoxy-3-(4-methoxyphenyl)-1*H*-indole (2c).



Obtained as a white solid (92 mg, 0.36 mmol, 66% yield) after column chromatography (hexane:AcOEt = 80:20 to 60:40 + 1% Et_3N).
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 2.2 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 1.8 Hz, 1H), 6.85 (dd, *J* = 8.7, 2.1 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 156.8, 137.5, 128.6, 128.3, 120.6, 120.5, 119.9, 118.1, 114.4, 110.2, 94.8, 55.8, 55.5 ppm.
Elemental Analysis calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53, found: C, 75.90; H, 6.14; N, 5.81.

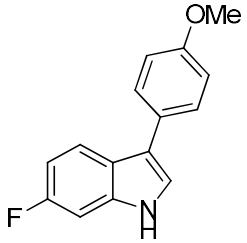
3-(4-fluorophenyl)-6-methoxy-1*H*-indole (2d').



Obtained as a white solid (27 mg, 0.21 mmol, 21% yield) after column chromatography (hexane:AcOEt = 85:15 + 1% Et_3N); 21% yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.65–7.54 (m, 2H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.16–7.09 (m, 2H), 6.92 (d, *J* = 2.2 Hz, 1H), 6.86 (dd, *J* = 8.7, 2.2 Hz, 1H), 3.87 (s, 1H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5 (d, $^1J_{C\text{-}F}$ = 244.4 Hz), 156.8, 137.6, 131.8 (d, $^4J_{C\text{-}F}$ = 3.1 Hz), 128.8 (d,$^3J_{C\text{-}F}$ = 7.7 Hz), 120.5, 120.3, 120.2, 117.4, 115.7 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 110.5, 94.9, 55.8 ppm.
^{19}F NMR (282 MHz, $CDCl_3$) δ -117.37 (s) ppm.

Elemental Analysis calcd for $C_{15}H_{12}FNO$: C, 74.67; H, 5.01; N, 5.81, found: C, 74.57; H, 5.21; N, 5.61.

6-fluoro-3-(4-methoxyphenyl)-1*H*-indole (2d'').



Obtained as a white solid (50 mg, 0.21 mmol, 38% yield) after column chromatography (hexane:AcOEt = 85:15 + 1% Et_3N).

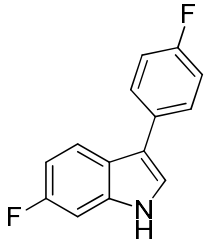
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.78 (dd, *J* = 8.8, 5.4 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 2.4 Hz, 1H), 7.06 (dd, *J* = 9.5, 2.3 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 6.94 (ddd, *J* = 9.4, 8.9, 2.3 Hz, 1H), 3.85 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5 (d, $^1J_{C\text{-}F}$ = 238.2 Hz), 158.7, 136.9 (d, $^3J_{C\text{-}F}$ = 12.4 Hz), 129.0, 128.1, 123.0, 121.7 (d, $^3J_{C\text{-}F}$ = 3.3 Hz), 121.0 (d, $^3J_{C\text{-}F}$ = 10.1 Hz), 118.5, 114.7, 109.3 (d, $^2J_{C\text{-}F}$ = 24.4 Hz), 98.0 (d, $^2J_{C\text{-}F}$ = 26.0 Hz), 55.8 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -121.17 (s) ppm.

Elemental Analysis calcd for $C_{15}H_{12}FNO$: C, 74.67; H, 5.01; N, 5.81, found: C, 74.78; H, 5.31; N, 5.49.

6-fluoro-3-(4-fluorophenyl)-1*H*-indole (2e).



Obtained as an off-white solid (61 mg, 0.27 mmol, 49% yield) after column chromatography (hexane:AcOEt = 90:10 + 1% Et_3N).

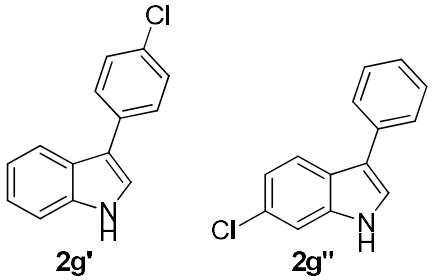
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.77 (dd, *J* = 8.7, 5.3 Hz, 1H), 7.63–7.54 (m, 3H), 7.28 (d, *J* = 2.3 Hz, 1H), 7.20–7.08 (m, 4H), 6.97 (td, *J* = 9.3, 2.2 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7 (d, $^1J_{C\text{-}F}$ = 244.9 Hz), 160.2 (d, $^1J_{C\text{-}F}$ = 238.6 Hz), 136.7 (d, $^3J_{C\text{-}F}$ = 12.4 Hz), 131.3 (d, $^4J_{C\text{-}F}$ = 3.3 Hz), 129.0 (d, $^3J_{C\text{-}F}$ = 7.8 Hz), 122.5, 121.9 (d, $^3J_{C\text{-}F}$ = 3.3 Hz), 120.5 (d, $^3J_{C\text{-}F}$ = 10.1 Hz), 117.7, 115.8 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 109.28 (d, $^2J_{C\text{-}F}$ = 24.4 Hz), 97.82 (d, $^2J_{C\text{-}F}$ = 26.0 Hz) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ -116.89 (s), -120.81 (s) ppm.

Elemental Analysis calcd for $C_{14}H_9F_2N$: C, 73.36; H, 3.96; N, 6.11, found: C, 72.95; H, 4.27; N, 5.84.

3-(4-chlorophenyl)-1*H*-indole (2g') and **6-chloro-3-phenyl-1*H*-indole (2g'').**



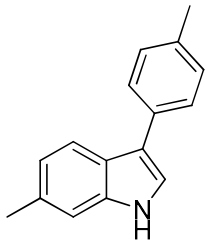
Obtained as an off-white solid (82 mg, 0.36 mmol, 67% yield) after column chromatography (hexane:AcOEt = 90:10 + 1% Et_3N).

^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H, N*H*, **2g'** isomer), 8.20 (s, 1H, N*H*, **2g''** isomer), 7.90 (d, *J* = 7.9 Hz, 1H, **2g'** isomer), 7.84 (d, *J* = 8.5 Hz, 1H, **2g''** isomer), 7.64 (d, *J* = 7.8 Hz, 2H, **2g''** isomer), 7.60 (d, *J* = 8.4 Hz, 2H, **2g'** isomer), 7.46 (t, *J* = 7.7 Hz, 2H, **2g''** isomer), 7.45–7.39 (m, 3H, **2g'** isomer and 1H, **2g''** isomer), 7.35–7.20 (m, 3H, **2g'** isomer and 2H, **2g''** isomer), 7.17 (dd, *J* = 8.6, 1.8 Hz, 1H, **2g''** isomer) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1, 135.1, 129.03, 128.99, 128.7, 128.4, 127.6, 126.4, 124.6, 122.7,122.4, 122.0, 121.2, 120.7, 120.6, 119.7, 118.7, 117.3, 111.6, 111.4 ppm.

Elemental Analysis calcd for $C_{14}H_{10}ClN$: C, 73.85; H, 4.43; N, 6.15, found: C, 74.15; H, 4.53; N, 5.84.

6-methyl-3-(4-methylphenyl)-1*H*-indole (2h).



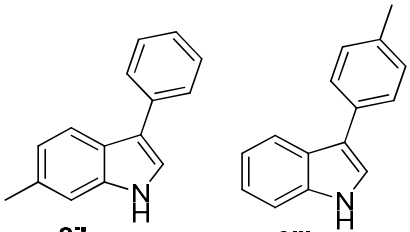
Obtained as a white solid (83 mg, 0.38 mmol, 70% yield) after column chromatography (hexane:AcOEt = 90:10 + 1% Et_3N).

^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.27–7.25 (m, 3H, overlapped with $CDCl_3$), 7.21 (s, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 2.49 (s, 3H), 2.41 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 135.6, 132.9, 132.3, 129.6, 127.4, 123.9, 122.1, 120.9, 119.7, 118.3, 111.4, 21.8, 21.3 ppm.

Elemental Analysis calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33, found: C, 87.10; H, 6.98; N, 6.02.

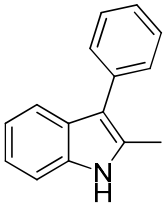
6-methyl-3-phenyl-1*H*-indole (2i') and **3-(4-methylphenyl)-1*H*-indole (2i'').**



2i' **2i''**

Obtained as a pale-yellow solid (78 mg, 0.38 mmol, 71% yield, mixture of the two isomers **2i'** and **2i''**, ratio **2i'**:**2i''** = 1.3:1) after column chromatography (hexane:AcOEt = 90:10 + 1% Et_3N).
^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (br, 1H, **2i''** isomer), 8.08 (br, 1H, **2i'** isomer), 7.95 (d, *J* = 7.9 Hz, 1H, **2i''** isomer), 7.85 (d, *J* = 8.2 Hz, 1H, **2i'** isomer), 7.69 (d, *J* = 7.2 Hz, 2H, **2i'** isomer), 7.59 (d, *J* = 8.0 Hz, 2H, **2i''** isomer), 7.50–7.40 (m, 2H, **2i'** isomer and 1H, **2i''** isomer), 7.36–7.17 (m, 3H, **2i'** isomer and 5H, **2i''** isomer, overlapped with $CDCl_3$), 7.05 (d, *J* = 8.2 Hz, 1H, **2i'** isomer), 2.51 (s, 3H, **2i'** isomer), 2.43 (s, 3H, **2i''** isomer) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.8, 135.9, 135.7, 132.7, 132.4, 129.6, 128.9, 127.6, 127.5, 126.0, 123.7, 122.5, 122.2, 121.6, 121.2, 120.3, 120.0, 119.6, 118.5, 118.3, 111.5, 111.4, 21.8, 21.3 ppm.
Elemental Analysis calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76, found: C, 87.22; H, 6.57; N, 6.44.

2-methyl-3-phenyl-1*H*-indole (2j).



Obtained as a yellow gum (53 mg, 0.26 mmol, 47% yield) after column chromatography (hexane:AcOEt = 95:5 + 1% Et_3N).
^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.53 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.37–7.29 (m, 2H), 7.18 (td, *J* = 7.6, 1.1 Hz, 1H), 7.12 (td, *J* = 7.6, 1.1 Hz, 1H), 2.52 (s, 3H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 135.4, 131.5, 129.6, 128.6, 128.0, 125.9, 121.7, 120.1, 118.9, 114.7, 110.4, 12.7 ppm.
Elemental Analysis calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76, found: C, 87.18; H, 6.52; N, 6.55.

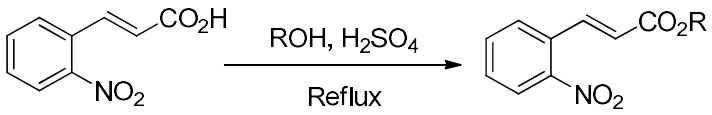
5.9. Preparation of *o*-nitrostyrenes

o-Nitrostyrenes **3e**,[23,26] **3j** [62] and **3af**,[141] were prepared as previously reported in the literature. Analytical data agreed to previous reports. The other substrates were synthesized following the modified procedure herein reported.

5.9.1. Synthesis of *o*-nitrocinnamates (3a-d)

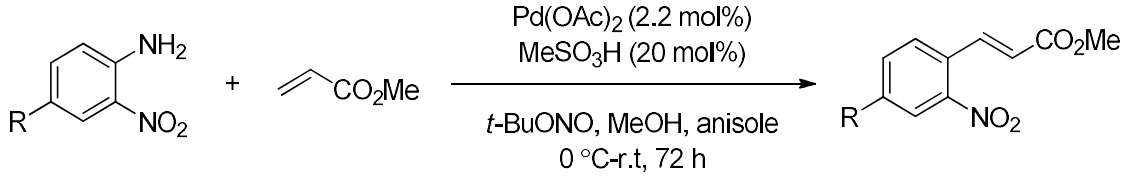
o-nitrocinnamates **3a-d** were prepared according to the following methods.

General procedure A



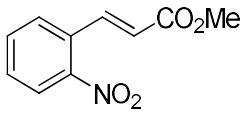
The synthesis was performed following the procedure reported in the literature.[141] In an oven dried 100 mL round bottom Schlenk flask, *(E)*-2-nitrocinnamic acid (2.02 g, 10.5 mmol) was dissolved in 60 mL of dehydrated alcohol and 200 µL of concentrated sulphuric acid (95 %) was added. The solution was refluxed under nitrogen atmosphere for 18 hours until the complete conversion of the reagent (monitored by TLC). The resulting mixture was allowed to cool to room temperature and the alcohol was evaporated. 30 mL of a saturated aqueous solution of $NaHCO_3$ were added to the crude. The mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with saturated solution of $NaHCO_3$ (3×30 mL) and with water (2×30 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated to give the product as a solid.

General procedure B



The synthesis was performed following the procedure reported in the literature.[142] To a solution of *o*-nitroaniline derivative (2 mmol) in MeOH (10 mL) at 0 °C was added *t*-BuONO (0.3 mL, 2.5 mmol). The resulting mixture was stirred for 30 minutes at 0 °C. To the reaction mixture, kept at 0 °C through an ice cooling bath, were sequentially added a solution of methyl acrylate (0.4 mL, 4.4 mmol) in MeOH (8 mL), $Pd(OAc)_2$ (10 mg, 2.2 mol%), and a solution of $MeSO_3H$ (26 µL, 20 mol%) in MeOH (4 mL). Eventually, anisole (1 mmol) was added dropwise. The reaction mixture was allowed to reach 25 °C and stirred for 72 hours. The reaction mixture was poured into 30 mL of saturated solution of $NaHCO_3$. The mixture was then extracted with CH_2Cl_2 (3×30 mL). Organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent was evaporated. The crude was purified by flash chromatography using (hexane/AcOEt) as the eluent to give the corresponding cross-coupled product.

(*E*)-methyl 3-(2-nitrophenyl)acrylate (3a)

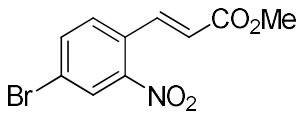


The synthesis was performed according to general procedure A, starting from *(E)*-2-nitrocinnamic acid and methanol.

The product was obtained as a pale-yellow solid (2.12 g, 10.2 mmol, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 15.8 Hz, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.72 – 7.60 (m, 2H), 7.59 – 7.49 (m, 1H), 6.37 (d, *J* = 15.8 Hz, 1H), 3.83 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 148.7, 140.5, 133.9, 130.9, 130.7, 129.5, 125.3, 123.2, 97.0, 52.4 ppm.

Elemental analysis calcd for $C_{10}H_9NO_4$: C, 57.47; H, 4.38; N, 6.76, found: C, 57.67; H, 4.50; N, 6.75.

(*E*)-methyl 3-(4-bromo-2-nitrophenyl)acrylate (3b)

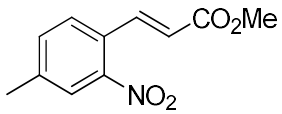


The synthesis was performed according to general procedure B, starting from 4-bromo-2-nitroaniline.

The product was obtained as a yellow solid after column chromatography using (hexane:AcOEt = 80:20) as the eluent (413 mg, 1.4 mmol, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 1.9 Hz, 1H), 8.03 (d, *J* = 15.8 Hz, 1H), 7.77 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 6.37 (d, *J* = 15.8 Hz, 1H), 3.83 (s, 3H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 148.6, 138.9, 136.5, 130.2, 129.4, 128.0, 123.8, 123.4, 52.1 ppm.
Elemental analysis calcd for $C_{10}H_8BrNO_4$: C, 41.98; H, 2.82; N, 4.90, found: C, 41.83; H, 2.88; N, 4.86.

(*E*)-methyl 3-(4-methyl-2-nitrophenyl)acrylate (3c)



The synthesis was performed according to general procedure B, starting from 4-methyl-2-nitroaniline.

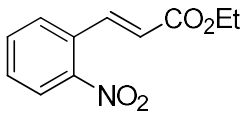
The product was obtained as a white solid after column chromatography using (hexane:AcOEt = 75:25) as the eluent (375 mg, 1.7 mmol, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 15.8 Hz, 1H), 7.82 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 6.33 (d, *J* = 15.8 Hz, 1H), 3.81 (s, 3H), 2.46 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 148.3, 141.4, 139.9, 134.2, 128.8, 127.6, 125.2, 122.1, 51.9, 21.1 ppm.

Elemental analysis calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33, found: C, 59.78; H, 5.23; N, 6.33.

(*E*)-ethyl 3-(2-nitrophenyl)acrylate (3d)



The synthesis was performed according to general procedure A, starting from *(E)*-2-nitrocinnamic acid and ethanol.

The product was obtained as a pale-yellow solid (2.0 g, 9.0 mmol, 87% yield).

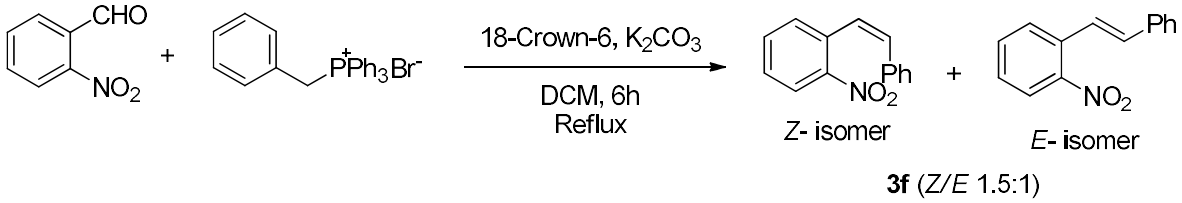
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 15.8 Hz, 1H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.68 – 7.51 (m, 2H), 7.47 (m, 1H), 6.28 (d, *J* = 15.8 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 148.2, 139.6, 133.5, 130.3, 129.0, 124.7, 123.2, 60.7, 14.1 ppm.

Elemental analysis calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33, found: C, 59.85; H, 5.09; N, 6.40.

5.9.2. Synthesis of *o*-nitrostilbenes (3f-i and 3k-v)

Synthesis of (*E*)- and (*Z*)-2-nitrostilbene (3f)



3f (*Z*/*E* 1.5:1)

The synthesis was performed following the procedure reported in the literature.[143,144]

In a dry 50 mL round bottomed flask, a solution of 2-nitrobenzaldehyde (604 mg, 4 mmol) in a freshly distilled dichloromethane (24 mL) was added in addition to benzyltriphenylphosphonium bromide (1.7 g, 4 mmol), potassium carbonate (608 mg, 4.4 mmol) and 18-crown-6 (190 mg, 0.72 mmol). The mixture was stirred under reflux for 6 hours then filtered and the filtrate was concentrated. The residue was purified by silica gel column chromatography using Hexane:Ethyl acetate (95:5) as eluent in order to separate the two isomers.

Both the target compounds were yellow solids (775 mg, 3.44 mmol, 86% yield)

Characterization data for *Z*- isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.05 (m, 1H), 7.45 – 7.34 (m, 2H), 7.28 (dd, *J* = 6.6, 3.1 Hz, 1H), 7.16 (dd, *J* = 6.5, 3.6 Hz, 3H), 7.11 – 7.02 (m, 2H), 6.90 (d, *J* = 12.1 Hz, 1H), 6.77 (d, *J* = 12.1 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 133.8, 133.2, 132.5, 132.0, 129.3, 128.4, 128.3, 127.7, 126.6, 124.8 ppm. Only one quaternary carbon was not detected.

Elemental Analysis calcd for $C_{14}H_{11}NO_2$ Calc.: C, 74.65; H, 4.92; N, 6.22, found: C, 74.85; H, 5.03; N, 6.41.

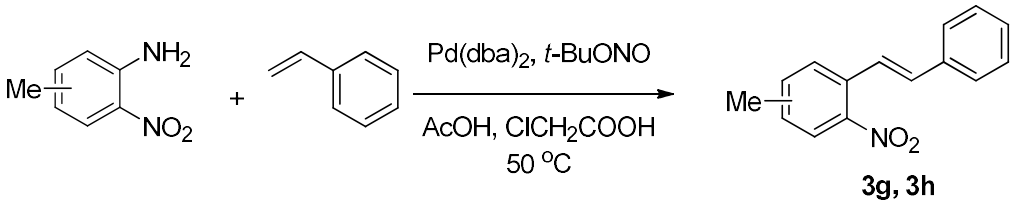
Characterization data for *E*- isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.66 – 7.51 (m, 4H), 7.40 (dd, *J* = 14.0, 7.1 Hz, 3H), 7.36 – 7.28 (m, 1H), 7.09 (d, *J* = 16.1 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 136.6, 134.0, 133.2, 129.0, 128.8, 128.3, 128.1, 127.2, 124.9, 123.7 ppm. Only one quaternary carbon was not detected.

Elemental Analysis calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22, found: C, 75.05; H, 5.09; N, 6.02.

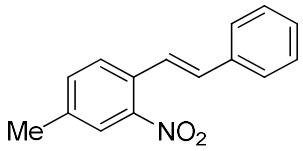
Synthesis of (*E*)-4-methyl-2-nitro-1-styrylbenzene (3g) and (*E*)-1-methyl-2-nitro-3-styrylbenzene (3h)



3g, 3h

The synthesis was performed following the procedure reported in the literature.[159]
In a 250 mL dry Schlenk flask methyl-2-nitroaniline (760 mg, 5.0 mmol), styrene (1.15 mL, 10.0 mmol) and monochloroacetic acid (10.0 g, 106 mmol) were dissolved in acetic acid (10 mL) under N_2. The mixture was stirred until complete solubilization of the solids. $Pd(dba)_2$ (144 mg, 0.25 mmol) was added, and the resulting mixture was heated at 50 °C for 45 min. A solution of *tert*-butyl nitrite (0.65 mL, 5.5 mmol) in acetic acid (5 mL) was added dropwise for 20 min and the reaction mixture was stirred for an additional 2 hours. The reaction was then neutralized with saturated aqueous solution of sodium carbonate and extracted with dichloromethane (5×50 mL). The combined organic layers were washed with water (3×50 mL) and brine (3×50 mL) then dried over Na_2SO_4, filtered and the solvent evaporated under vacuum. The resulting crude was purified by column chromatography (hexane:AcOEt) to give the product.

(*E*)-4-methyl-2-nitro-1-styrylbenzene (3g)



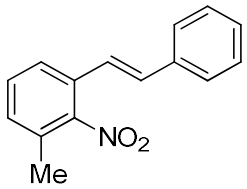
The product was obtained as a yellow solid after column chromatography (hexane:AcOEt = 95:5) (715 mg, 3 mmol, 60% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.59 (m, 3H), 7.44 – 7.27 (m, 4H), 7.05 (d, *J* = 16.1 Hz, 1H), 2.44 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 139.0, 137.1, 134.3, 133.4, 130.6, 129.2, 128.8, 128.3, 127.4, 125.4, 123.8, 21.3 ppm.

Elemental analysis calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85, found: C, 75.41; H, 5.62; N, 5.86.

(*E*)-1-methyl-2-nitro-3-styrylbenzene (3h)



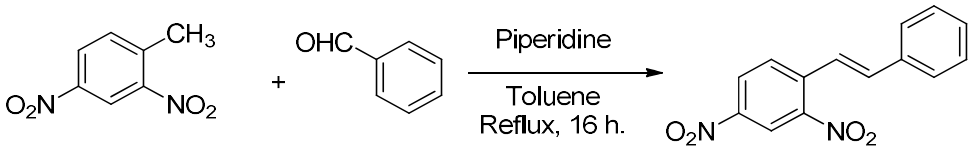
The product was obtained as a yellow solid after column chromatography (hexane:AcOEt = 90:10) (395 mg, 1.7 mmol, 33% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.41 – 7.34 (m, 3H), 7.33 – 7.28 (m, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 16.1 Hz, 1H), 6.97 (d, *J* = 16.1 Hz, 1H), 2.34 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 136.4, 133.9, 130.26, 130.22, 129.9, 129.8, 128.9, 128.7, 127.1, 124.2, 121.1, 17.5 ppm.

Elemental analysis calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85, found: C, 74.84; H, 5.52; N, 5.99.

Synthesis of (*E*)-2,4-dinitro-1-styrylbenzene (3i)



The synthesis was performed following the procedure reported in the literature.[160]

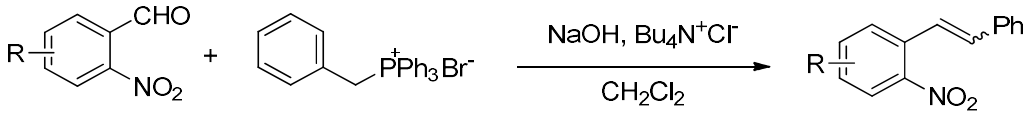
In a dry 100 mL round bottom flask, 2,4-dinitrotoluene (5.4 g, 29.6 mmol), benzaldehyde (2.9 mL, 28 mmol) and 30 mL toluene were added. After complete solubilization of reactants, piperidine (60 μL) was added and the reaction mixture was refluxed for 16 h. Toluene was then evaporated and the observed brown residue washed with a mixture of toluene: petroleum ether (1:1), separated by filtration and dried. The residue was then crystallized from methanol to give the product as yellow solid (5.50 g, 20.4 mmol, 72%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 2.3 Hz, 1H), 8.42 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.98 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 16.2 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.48 – 7.35 (m, 3H), 7.28 (d, *J* = 16.2 Hz, 1H overlapped with $CDCl_3$ signal) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 146.4, 138.9, 138.2, 135.6, 130.0, 129.2, 129.1, 127.7, 127.2, 121.4, 120.8 ppm.

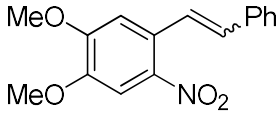
Elemental analysis calcd for $C_{14}H_{10}N_2O_4$: C, 62.22; H, 3.73; N, 10.37, found: C, 62.26; H, 3.90; N, 10.17.

General Wittig procedure for the synthesis of (3k, 3l and 3o)



The synthesis was performed following the procedure reported in the literature.[145]
In a dry 100 mL Schlenk flask, 2-nitrobenzaldehyde derivative (3.5 mmol) was dissolved in 50 mL of anhydrous CH_2Cl_2. Then, benzyltriphenylphosphonium bromide (2.1 g, 4.85 mmol) was added. After its solubilization, NaOH solution (170 mg in 1 mL of water) and tetrabutylammonium bromide (5.0 g, 15.5 mmol) were added. The mixture was stirred at room temperature monitoring the conversion of the starting aldehyde by TLC. At the end of the reaction 30 mL of water were added and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The product was isolated as a yellow oil by column chromatography (hexane:AcOEt) which crystallize upon standing to give the product as *Z/E* mixture.

***(Z/E)*- 1,2-dimethoxy-4-nitro-5-styrylbenzene (3k)**



The synthesis was performed according to the general procedure, starting from 4,5-dimethoxy-2-nitrobenzaldehyde.
The product was obtained as a yellow solid after column chromatography (hexane:AcOEt = 85:15) (983 mg, 3.4 mmol, 98% yield of both isomers).

Characterization data for *Z*- isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.21 – 7.13 (m, 3H), 7.11 – 7.05 (m, 2H), 6.95 (d, *J* = 12.0 Hz, 1H), 6.75 (d, *J* = 12.0 Hz, 1H), 6.59 (s, 1H), 3.95 (s, 3H), 3.51 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 148.1, 140.4, 136.3, 131.1, 129.2, 128.5, 128.3, 127.6, 127.5, 113.5, 107.8, 56.4, 56.1 ppm.

Elemental analysis calcd for $C_{16}H_{15}NO_4$: C, C, 67.36; H, 5.30; N, 4.91, found: C, 67.26; H, 5.33; N, 4.87.

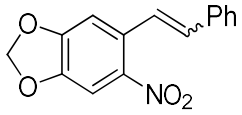
Characterization data for *E*- isomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 16.1, 11.0 Hz, 1H), 7.63 (s, 1H), 7.55 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 3H), 7.10 (s, 1H), 6.98 (d, *J* = 16.1 Hz, 1H), 4.04 (s, 3H), 3.97 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 148.4, 136.8, 132.7, 128.9, 128.6, 128.5, 127.1, 125.0, 109.5, 107.9, 56.59, 56.55 ppm. One quaternary carbon was not detected.

Elemental analysis calcd for $C_{16}H_{15}NO_4$: C, C, 67.36; H, 5.30; N, 4.91, found: C, 67.36; H, 5.41; N, 4.86.

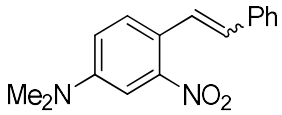
***(Z/E)*- 5-nitro-6-styrylbenzo[*d*][1,3]dioxole (3l)**



The synthesis was performed according to the general procedure, starting from 6-nitropiperonal. The product was obtained as a yellow solid after column chromatography (hexane:AcOEt = 90:10) (765 mg, 2.8 mmol, 80% yield of both isomers).

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.73 (s, 1H), 7.64 – 7.53 (m, 2H), 7.53 – 7.36 (m, 4H), 7.35 – 7.15 (m, 6H), 7.13 – 7.03 (m, 2H), 6.81 (d, *J* = 12.0 Hz, 1H), 6.72 (d, *J* = 12.1 Hz, 1H), 6.65 (s, 1H), 6.26 (s, 2H), 6.20 (s, 2H) ppm.
^{13}C NMR (75 MHz, DMSO-d_6) δ 151.8, 151.7, 147.3, 147.2, 142.0, 141.7, 136.5, 135.6, 132.5, 130.4, 129.9, 129.1, 128.8, 128.7, 128.4, 128.4, 127.5, 127.2, 126.8, 123.4, 109.7, 106.2, 105.04, 104.9, 103.4, 103.4 ppm.
Elemental analysis calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20, found: C, 66.81; H, 4.27; N, 5.30.

***(Z/E)*- *N,N*-dimethyl-3-nitro-4-styrylaniline (3o)**



The synthesis was performed according to the general procedure, starting from 4-(dimethylamino)-2-nitrobenzaldehyde.
The product was obtained as a red solid after column chromatography (hexane:AcOEt = 90:10) (857 mg, 3.2 mmol, 91% yield of both isomers). Only *Z*-isomer was used for the catalytic reaction.

Characterization data for *Z*- isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 2.7 Hz, 1H), 7.24 – 7.13 (m, 5H), 7.11 (d, *J* = 8.7 Hz, 1H), 6.81 (d, *J* = 12.0 Hz, 1H), 6.68 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.62 (d, *J* = 12.0 Hz, 1H), 3.00 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 149.0, 136.7, 132.6, 129.9, 129.1, 128.2, 127.1, 126.80, 120.1, 116.4, 106.6, 40.1 ppm.

Elemental analysis calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44, found: C, 71.21; H, 5.92; N, 10.25.

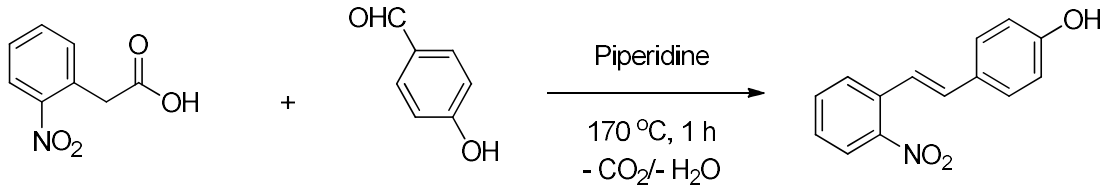
Characterization data for *E*- isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.8 Hz, 1H), 7.53 – 7.45 (m, 3H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.29 – 7.23 (m, 1H), 7.19 (d, *J* = 2.7 Hz, 1H), 6.99 – 6.91 (m, 2H), 3.05 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 149.2, 137.4, 130.1, 128.8, 128.7, 127.9, 126.8, 123.6, 120.5, 116.9, 107.2, 40.6 ppm.

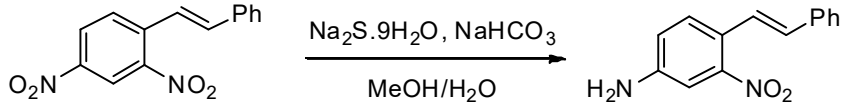
Elemental analysis calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44, found: C, 71.53; H, 6.08; N, 10.64.

Synthesis of (*E*)-4-(2-nitrostyryl)phenol (3m)



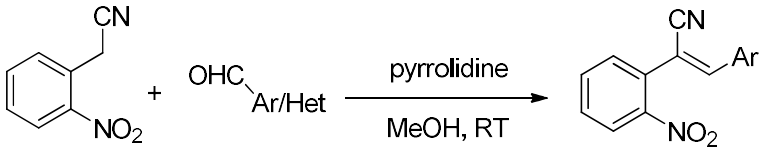
The synthesis was performed following the procedure reported in the literature.[147]
In a dry round bottomed flask add 2-nitrophenylacetic acid (1.00 g, 5.50 mmol), 4-hydroxybenzaldehyde (755 mg, 6.10 mmol) and 10 drops of piperidine. The mixture was heated to 170 °C while stirring. At this temperature, CO_2 bubbles start to form. Heating was maintained until the end of CO_2 evolution from the reaction mixture (about 1 hour). After letting cool to room temperature, a brown oily product was obtained. Hexane (10 mL) was added, and the crude filtered on filter paper. The filtrate was collected, and the solvent was evaporated. The dark sticky solid obtained was recrystallized from water : ethanol : hexane (5:2:1) to afford the product **3m** as yellow crystals (490 mg, 2.03 mmol, 37 % yield).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.50 – 7.41 (m, 3H), 7.40 – 7.33 (m, 1H), 7.04 (d, *J* = 16.1 Hz, 1H), 6.89 – 6.81 (m, 2H), 4.97 (br, 1H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 148.1, 133. 6, 133.4, 133.2, 129.7, 128.8, 128.0, 127.7, 124.9, 121.4, 115.9 ppm.
Elemental analysis calcd for $C_{14}H_{11}NO_3$ Calc.: C, 69.70; H, 4.60; N, 5.81, found: C, 69.55; H, 4.63; N, 5.77.

Synthesis of (*E*)-3-nitro-4-styrylaniline (3n)



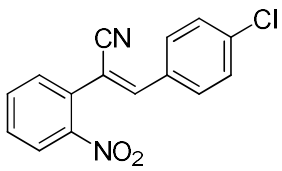
The synthesis was performed following the procedure reported in the literature.[127]
In a dry 10 mL two neck round bottomed flask 2,4-dinitrostilbene, **3i** (300 mg, 1.1 mmol) was refluxed with methanol (5 mL) for 1 h. A solution of sodium sulfide nonahydrate (533 mg, 2.2 mmol) and sodium bicarbonate (149 mg, 1.8 mmol) in water (1.3 mL) was heated and added gradually during 20 min to the reaction. After 2 hours, a red precipitate was obtained and collected by Büchner filtration and washed with methanol. The precipitate was purified by silica gel column chromatography using (hexane:AcOEt = 70:30 + 1% Et_3N) as the eluent to give the product **3n** as red crystalline solid (71 mg, 0.3 mmol, 27% yield)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.5 Hz, 1H), 7.53 – 7.46 (m, 3H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H, overlapped with $CDCl_3$ signal), 7.21 (d, *J* = 2.5 Hz, 1H), 6.94 (d, *J* = 16.1 Hz, 1H), 6.88 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.99 (s, 2H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 146.5, 137.2, 130.8, 129.2, 128.9, 128.1, 126.9, 123.7, 122.9, 119.7, 109.9 ppm.
Elemental analysis calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66, found: C, 69.81; H, 5.15; N, 11.47.

General Knoevenagel procedure for the synthesis of (3p-r and 3u)



The synthesis was performed following the procedure reported in the literature.[23,161]
2-Nitrophenylacetonitrile (750 mg, 4.63 mmol) and the desired benzaldehyde (4.63 mmol) were dissolved in methanol (8 mL). Then, 760 μL of pyrrolidine was added and the reaction mixture maintained under stirring at room temperature. Complete conversion of the starting materials was checked by TLC. After a reaction completion, the product precipitated and was collected by filtration through a Büchner funnel.

(*Z*)-3-(4-chlorophenyl)-2-(2-nitrophenyl)acrylonitrile (3p)

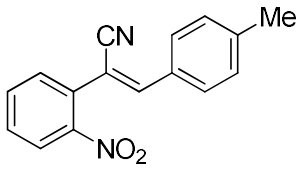


The synthesis was performed according to the general procedure, starting from 4-chlorobenzaldehyde.
The product was obtained as a white solid after the filtration (1.0 g, 3.5 mmol, 79% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 2H), 7.73 (td, *J* = 7.6, 1.2 Hz, 1H), 7.62 (td, *J* = 7.5, 1.4 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.13 (s, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 144.8, 137.4, 134.1, 131.9, 131.5, 130.9, 130.68, 130.63, 129.5, 125.5, 116.4, 109.3 ppm.

Elemental analysis calcd for $C_{15}H_9ClN_2O_2$: C, 63.28; H, 3.19; N, 9.84, found: C, 63.06; H, 3.20; N, 9.85.

(*Z*)-2-(2-nitrophenyl)-3-(*p*-tolyl)acrylonitrile (3q)

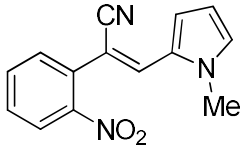


The synthesis was performed according to the general procedure, starting from 4-methylbenzaldehyde.
The product was obtained as a white solid after the filtration (1.1 g, 4 mmol, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.1 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 2H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.58 (dd, *J* = 16.3, 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.14 (s, 1H), 2.42 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 146.7, 142.4, 134.1, 132.2, 131.6, 130.7, 130.5, 130.2, 129.8, 125.7, 117.1, 107.5, 22.0 ppm.

Elemental analysis calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60, found: C, 72.48; H, 4.68; N, 10.63.

(*Z*)-3-(1-methyl-1H-pyrrol-2-yl)-2-(2-nitrophenyl)acrylonitrile (3r)

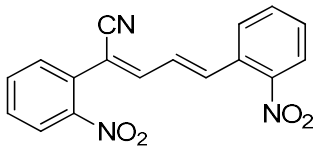


The synthesis was performed according to the general procedure, starting from 1-methyl-1*H*-pyrrole-2-carbaldehyde.
The product was obtained as a yellow solid after the filtration (702 mg, 2.8 mmol, 60% yield). ^{1}H NMR (300 MHz, CDCl3) δ 7.97 (d, *J* = 7.7 Hz, 1H), 7.66 (t, *J* = 8.1 Hz, 1H), 7.53 (t, *J* = 6.9 Hz, 3H), 7.02 (s, 1H), 6.84 (s, 1H), 6.32 (q, 1H), 3.68 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 133.6, 133.2, 131.9, 131.3, 129.8, 128.3, 128.2, 125.4, 117.9, 115.5, 110.8, 99.9, 34.4 ppm.

Elemental analysis calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 15.59, found: C, 66.72; H, 4.18; N, 15.44.

(2*Z*,4*E*)-2,5-bis(2-nitrophenyl)penta-2,4-dienenitrile (3u)

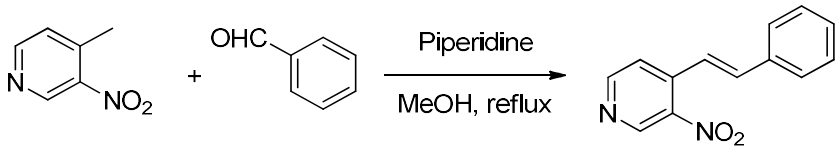


The synthesis was performed according to the general procedure, starting from 2-nitrocinnamaldehyde.
The product was obtained as a yellow solid after the filtration (707 mg, 2.2 mmol, 48% yield). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.16 (d, *J* = 8.1 Hz, 1H), 8.10 – 8.02 (m, 2H), 7.88 (t, *J* = 7.6 Hz, 1H), 7.84 – 7.72 (m, 4H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 15.0 Hz, 1H), 7.28 (dd, *J* = 15.0, 11.1 Hz, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 148.2, 147.2, 146.9, 137.4, 134.5, 133.8, 131.9, 131.1, 130.5, 129.84, 128.8, 128.4, 128.1, 125.3, 124.7, 115.1, 110.6 ppm.

Elemental analysis calcd for $C_{17}H_{11}N_3O_4$: C, 63.55; H, 3.45; N, 13.08, found: C, 63.40; H, 3.33; N, 12.97.

Synthesis of (*E*)-3-nitro-4-styrylpyridine (3s)



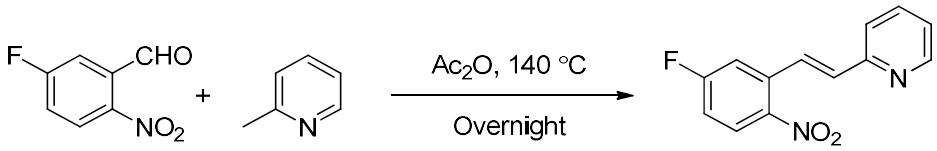
The synthesis was performed following the procedure reported in the literature.[23] 4-Methyl-2-nitropyridine (590 mg, 6.22 mmol), benzaldehyde (634 µL, 6.22 mmol) and piperidine (307 µL, 3.11 mmol) were added to 10 mL of distilled methanol. After 10 h of reflux a yellow solid precipitated. The precipitate was filtered through a Büchner funnel and washed with cold methanol. The product was obtained as a yellow solid (753 mg, 3.3 mmol, 54 % yield).

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 9.15 (s, 1H), 8.82 (d, *J* = 5.2 Hz, 1H), 8.02 (d, *J* = 5.2 Hz, 1H), 7.72 – 7.62 (m, 3H), 7.53 (d, *J* = 16.3 Hz, 1H), 7.49 – 7.36 (m, 3H) ppm.

^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 154.0, 146.7, 144.6, 140.2, 138.3, 136.5, 130.4, 129.8, 128.5, 122.1, 121.3 ppm.

Elemental analysis calcd for $C_{11}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38, found: C, 68.76; H, 4.49; N, 12.34.

Synthesis of (*E*)-2-(5-fluoro-2-nitrostyryl)pyridine (3t).



The synthesis was performed following the procedure reported in the literature.[150]

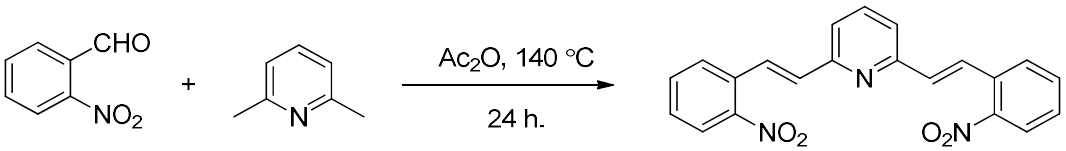
A Schlenk flask was charged with 5-fluoro-2-nitrobenzaldehyde (1 g, 6 mmol), 2-picoline (782 mg, 8.4 mmol) and acetic anhydride (2 mL) at room temperature. The resulting mixture was refluxed overnight under nitrogen atmosphere. After reaction completion, the mixture was distilled at 50 °C under reduced pressure to remove acetic anhydride and unreacted 2-picoline. The resulting crude was filtered on silica gel using (hexane:AcOEt 70:30 to 60:40) as the eluent to give the final product as yellow solid (1 g, 4.1 mmol, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 4.1 Hz, 1H), 8.10 – 7.99 (m, 2H), 7.69 (td, J = 7.7, 1.7 Hz, 1H), 7.50 – 7.40 (m, 2H), 7.21 (ddd, J = 7.5, 4.8, 0.8 Hz, 1H), 7.16 – 7.06 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9 (d, $^{1}J_{C-F}$ = 256.3 Hz), 154.5, 150.1, 144.4, 136.8, 136.0 (d, $^{3}J_{C-F}$ = 9.3 Hz), 134.4, 127.9 (d, $^{3}J_{C-F}$ = 10 Hz), 127.1, 123.3, 122.6, 115.71 (d, $^{2}J_{C-F}$ = 23.6 Hz), 115.17 (d, $^{2}J_{C-F}$ = 24.2 Hz) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -103.78 (s) ppm.

Elemental analysis calcd for $C_{13}H_9FN_2O_2$: C, 63.93; H, 3.71; N, 11.47, found: C, 64.27; H, 3.78; N, 11.39.

Synthesis of 2,6-bis((*E*)-2-nitrostyryl)pyridine (3v)



The synthesis was performed following the procedure reported in the literature.[150]
In a 25 mL Schlenk flask *o*-nitrobenzaldehyde (1.43 g, 9.46 mmol) and 2,6-lutidine (330 µL, 2.85 mmol) were dissolved in 2 mL of acetic anhydride. After 24 h of reflux a yellow solid precipitated. It was filtered through a Büchner funnel and washed with cold hexane. The product was obtained as a yellow solid (726 mg, 2 mmol, 68 % yield).

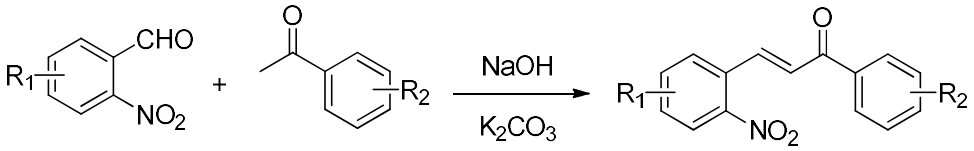
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.09 – 7.96 (m, 6H), 7.88 (t, J = 7.7 Hz, 1H), 7.78 (t, J = 7.6 Hz, 2H), 7.64 – 7.51 (m, 4H), 7.41 (d, J = 15.8 Hz, 2H) ppm.

^{13}C NMR (75 MHz, DMSO-d_6) δ 154.90, 149.14, 138.82, 134.35, 133.67, 131.88, 130.13, 129.26, 127.62, 125.37, 123.41 ppm.

Elemental analysis calcd for $C_{21}H_{15}N_3O_4$: C, 67.56; H, 4.05; N, 11.25, found: C, 67.82; H, 4.19; N, 10.90.

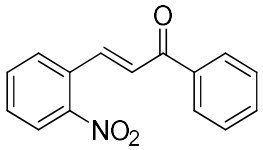
5.9.3. Synthesis of *o*-nitrochalcones (3w-ae)

General Claisen-Schmidt procedure for synthesis of (3w-ae)



The synthesis was performed following the procedure reported in the literature.[149] In a dry 10 mL round bottomed flask 2-nitrobenzaldehyde derivative (2.5 mmol) was stirred vigorously with potassium carbonate (0.2 mmol) and sodium hydroxide (0.2 mmol). At room temperature acetophenone derivative (2.5 mmol) was added dropwise. After 1 hour, 15 mL of water and 15 mL of ethyl acetate were added. The organic layer separated, and the aqueous phase extracted with ethyl acetate (3×15 mL). The combined organic layer was washed with water (3×50 mL) and brine (1×50 mL), dried over Na_2SO_4, filtered and the organic solvent removed under reduced pressure to afford the crude product. The crude was recrystallized from ethanol or purified by column chromatography to give the final product.

(*E*)-3-(2-nitrophenyl)-1-phenylprop-2-en-1-one (3w)



The synthesis was performed according to the general procedure, starting from 2-nitrobenzaldehyde and acetophenone.

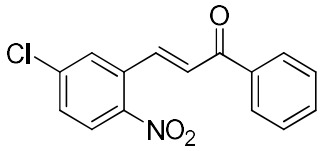
The product was obtained as a white solid after column chromatography using (hexane:AcOEt = 80:20) as the eluent (350 mg, 1.4 mmol, 56% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 15.7 Hz, 1H), 8.10 (d, *J* = 7.9 Hz, 1H), 8.04 (d, *J* = 7.1 Hz, 2H), 7.81 – 7.67 (m, 2H), 7.58 (m, 4H), 7.34 (d, *J* = 15.7 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9, 148.9, 140.5, 137.8, 133.9, 133.5, 131.7, 130.7, 129.6, 129.0, 128.4, 127.8, 125.4 ppm.

Elemental analysis calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53, found: C, 71.46; H, 4.19; N, 5.31.

***(E)*-3-(5-chloro-2-nitrophenyl)-1-phenylprop-2-en-1-one (3x).**



The synthesis was performed according to the general procedure, starting from 5-chloro-2-nitrobenzaldehyde and acetophenone.

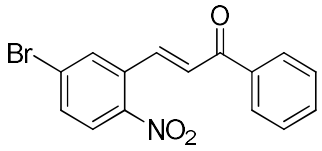
The product was obtained as a yellow solid after crystallization from ethanol (398 mg, 1.4 mmol, 55% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 15.7 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 8.04 – 8.00 (m, 2H), 7.70 (d, *J* = 2.2 Hz, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.57 – 7.49 (m, 3H), 7.33 (d, *J* = 15.6 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 146.8, 140.3, 139.1, 137.3, 133.5, 133.5, 130.3, 129.3, 129.0, 128.9, 128.3, 126.7 ppm.

Elemental analysis calcd for $C_{15}H_{10}ClNO_3$**:** C, 62.62; H, 3.50; N, 4.87, found: C, 62.46; H, 3.68; N, 4.72.

(*E*)-3-(5-bromo-2-nitrophenyl)-1-phenylprop-2-en-1-one (3y)



The synthesis was performed according to the general procedure, starting from 5-bromo-2-nitrobenzaldehyde and acetophenone.

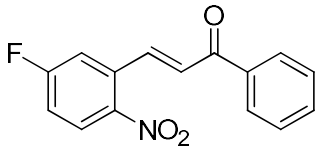
The product was obtained as a green solid after crystallization from ethanol (413 mg, 1.2 mmol, 50% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 15.6 Hz, 1H), 8.05 – 7.99 (m, 2H), 7.96 (d, *J* = 8.7 Hz, 1H), 7.86 (d, *J* = 2.0 Hz, 1H), 7.68 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 15.6 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 147.2, 138.9, 137.3, 133.5, 133.4, 133.3, 132.3, 128.9, 128.9, 128.6, 128.2, 126.6 ppm.

Elemental analysis calcd for $C_{15}H_{10}BrNO_3$: C, 54.24; H, 3.03; N, 4.22, found: C, 54.23; H, 3.18; N, 4.29.

(*E*)-3-(5-fluoro-2-nitrophenyl)-1-phenylprop-2-en-1-one (3z)



The synthesis was performed according to the general procedure, starting from 5-fluoro-2-nitrobenzaldehyde and acetophenone.

The product was obtained as a yellow solid after crystallization from ethanol (305 mg, 1.1 mmol, 45% yield).

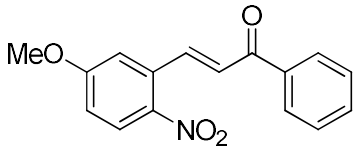
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.09 (m, 2H), 8.05 – 7.98 (m, 2H), 7.64 – 7.59 (m, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.41 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.31 (d, *J* = 15.7 Hz, 1H), 7.26 – 7.19 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2, 166.3, 163.7, 139.4, 137.3, 134.9 (d, $^{3}J_{C\text{-}F}$= 9.1 Hz), 133.5, 128.9, 128.3, 128.2, 128.1, 117.4, 117.2, 116.4, 116.1 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -102.93 (s) ppm.

Elemental analysis calcd for $C_{15}H_{10}FNO_3$: C, 66.42; H, 3.72; N, 5.16, found: C, 66.36; H, 3.87; N, 5.36.

(*E*)-3-(5-methoxy-2-nitrophenyl)-1-phenylprop-2-en-1-one (3aa)



The synthesis was performed according to the general procedure, starting from 5-methoxy-2-nitrobenzaldehyde and acetophenone.

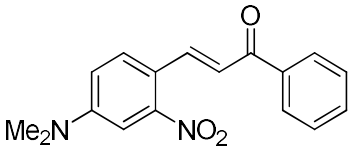
The product was obtained as a yellow solid after crystallization from ethanol (413 mg, 1.5 mmol, 50% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 15.7 Hz, 1H), 8.13 (d, *J* = 9.1 Hz, 1H), 8.04 – 7.97 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.21 (d, *J* = 15.6 Hz, 1H), 7.08 (d, *J* = 2.7 Hz, 1H), 6.98 (dd, *J* = 9.1, 2.7 Hz, 1H), 3.93 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 163.6, 141.6, 141.3, 137.5, 134.6, 133.2, 128.9, 128.8, 127.9, 127.4, 114.8, 114.5, 56.2 ppm.

Elemental analysis calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.72; H, 4.77; N, 4.89.

(*E*)-3-(4-(dimethylamino)-2-nitrophenyl)-1-phenylprop-2-en-1-one (3ab)



The synthesis was performed according to the general procedure, starting from 4-dimethylamino-2-nitrobenzaldehyde and acetophenone.

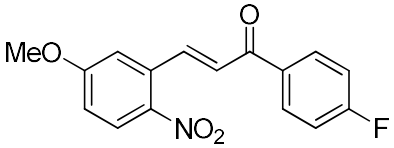
The product was obtained as a red solid after crystallization from ethanol (482 mg, 1.6 mmol, 65% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 15.6 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 2H), 7.66 (d, *J* = 8.9 Hz, 1H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.25 (d, *J* = 15.6 Hz, 1H, overlapped with $CDCl_3$ signal), 7.14 (d, *J* = 2.6 Hz, 1H), 6.86 (dd, *J* = 8.9, 2.6 Hz, 1H), 3.08 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 151.5, 150.9, 140.1, 138.3, 132.7, 129.6, 128.7, 128.7, 122.8, 116.6, 115.6, 106.9, 40.3 ppm.

Elemental analysis calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.58; H, 5.40; N, 9.68.

(*E*)-1-(4-fluorophenyl)-3-(5-methoxy-2-nitrophenyl)prop-2-en-1-one (3ac)



The synthesis was performed according to the general procedure, starting from 5-methoxy-2-nitrobenzaldehyde and 4-fluoro-acetophenone.

The product was obtained as a yellow solid after crystallization from ethanol (300 mg, 1.0 mmol, 40% yield).

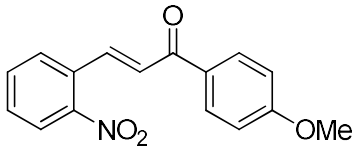
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 6.8 Hz, 1H), 8.17 (s, 1H), 8.10 – 8.02 (m, 2H), 7.23 – 7.11 (m, 3H), 7.08 (d, *J* = 2.7 Hz, 1H), 7.01 (dd, *J* = 9.1, 2.8 Hz, 1H), 3.95 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6, 165.9 (d, $^{1}J_{C-F}$ = 255.3 Hz), 163.7, 141.9, 134.6, 133.9 (d, $^{4}J_{C-F}$ = 3 Hz), 131.7 (d, $^{3}J_{C-F}$ = 9.3 Hz), 128.0, 127.3, 116.0 (d, $^{2}J_{C-F}$ = 21.9 Hz), 114.9, 114.6, 56.3 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.89 (dq, *J* = 8.4, 5.5 Hz) ppm.

Elemental analysis calcd for $C_{16}H_{12}FNO_4$: C, 63.79; H, 4.01; N, 4.65. Found: C,64.03; H,4.26; N,4.84.

(*E*)-1-(4-methoxyphenyl)-3-(2-nitrophenyl)prop-2-en-1-one (3ad)



The synthesis was performed according to the general procedure, starting from 2-nitrobenzaldehyde and 4-methoxy-acetophenone.

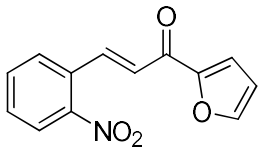
The product was obtained as a yellow solid after crystallization from ethanol (415 mg, 1.5 mmol, 50% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 15.6 Hz, 1H), 8.04 (t, *J* = 8.6 Hz, 3H), 7.74 (d, *J* = 7.7 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.55 (td, *J* = 8.0, 1.3 Hz, 1H), 7.32 (d, *J* = 15.6 Hz, 1H), 6.99 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 188.8, 163.9, 148.7, 139.3, 133.6, 131.7, 131.3, 130.5, 130.3, 129.4, 127.5, 125.1, 114.1, 55.7 ppm.

Elemental analysis calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.74; H,4.71; N,4.90.

(*E*)-1-(furan-2-yl)-3-(2-nitrophenyl)prop-2-en-1-one (3ae)



The synthesis was performed according to the general procedure, starting from 2-nitrobenzaldehyde and 1-(furan-2-yl)ethanone.

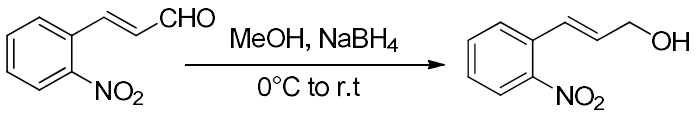
The product was obtained as a white solid after column chromatography using (hexane:AcOEt = 80:20) as the eluent (261 mg, 1.1 mmol, 43% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 15.7 Hz, 1H), 8.05 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.75 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.61 – 7.52 (m, 1H), 7.37 (dd, *J* = 3.6, 0.5 Hz, 1H), 7.29 (d, *J* = 15.7 Hz, 1H), 6.61 (dd, *J* = 3.6, 1.7 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 153.3, 148.8, 147.1, 139.3, 133.6, 131.3, 130.5, 129.4, 126.5, 125.1, 118.5, 112.9 ppm.

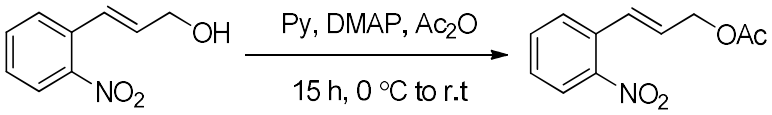
Elemental analysis calcd for $C_{13}H_9NO_4$: C, 64.20; H, 3.73; N, 5.76. Found: C,64.31; H,3.75; N,5.81.

5.9.4. Synthesis of (*E*)-3-(2-nitrophenyl)prop-2-en-1-ol (3ag)



The synthesis was performed following the procedure reported in the literature.[162]
In a dry 250 mL round bottom Schlenk flask, a solution of 2-nitrocinnamaldehyde (4.00 g, 22.6 mmol) in 50 mL of freshly distilled methanol was added in an ice bath. $NaBH_4$ (940 mg, 24.8 mmol) was added in portions under dinitrogen atmosphere. The reaction mixture was stirred for 15 min at 0 °C, then for 30 min at room temperature. After the completion of reaction, monitored by TLC analysis, distilled water was added (20 mL) and the reaction mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to remove MeOH. The resulting aqueous layer was extracted with CH_2Cl_2 (5×20 mL). The combined organic layers were washed with brine (3 × 30 mL), dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give the product as a pale-yellow solid (4.00 g, 22.3 mmol, 99 % yield).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.64 – 7.46 (m, 2H), 7.36 (ddd, *J* = 8.5, 7.2, 1.7 Hz, 1H), 7.05 (dt, *J* = 15.7, 1.6 Hz, 1H), 6.32 (dt, *J* = 15.7, 5.3 Hz, 1H), 4.35 (t, *J* = 4.1 Hz, 2H), 2.50 (t, *J* = 4.8 Hz, 1H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 134.3, 133.2, 132.6, 128.8, 128.2, 125.7, 124.5, 63.2 ppm.
Elemental analysis calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82, found: C, 60.70; H, 5.01; N, 7.44.

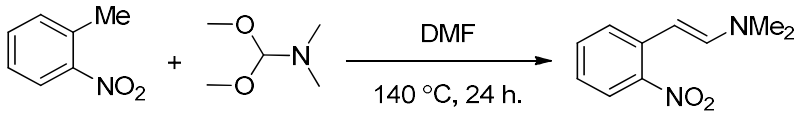
5.9.5. Synthesis of (*E*)-3-(2-nitrophenyl)allyl acetate (3ah)



The synthesis was performed following the procedure reported in the literature.[64]
In a dry 50 mL round bottom Schlenk flask, a solution of **3ag** (2.0 g, 11.0 mmol) and dimethylaminopyridine (11 mg) in 7 mL of pyridine was added Ac_2O (1.45 g, 14.3 mmol) at 0 °C then the mixture was stirred at room temperature for 15 h. The resulting mixture was poured into water, then extracted with diethyl ether (3×20 mL). The combined organic layers were washed with 10% HCl (3×20 mL), water (3×20 mL) and dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to give the product as a yellow solid (2.38 g, 10.76 mmol, 96% yield).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.1 Hz, 1H), 7.60 – 7.49 (m, 2H), 7.43 – 7.33 (m, 1H), 7.09 (d, *J* = 15.8 Hz, 1H), 6.23 (dt, *J* = 15.8, 5.9 Hz, 1H), 4.73 (d, *J* = 5.9 Hz, 2H), 2.08 (s, 3H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 147.8, 133.2, 132.0, 128.79, 128.75, 128.6 (the signals of two *C*H overlap), 124.6, 110.0, 64.3, 20.9 ppm.

Elemental analysis calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33, found: C, 59.94; H, 5.11; N, 5.96.

5.9.6. Synthesis of (*E*)-*N,N*-dimethyl-2-(2-nitrophenyl)ethenamine (3aj)

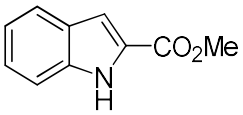


The synthesis was performed following the procedure reported in the literature.[163,164] In a dry Schlenk flask, a solution of 2-nitrotoluene (1.4 g, 10.0 mmol) and *N,N*-dimethyl-formamide dimethyl acetal (1.8 g, 15.0 mmol) in 10 mL of DMF was prepared under dinitrogen and heated at 140 °C for 24 hours. The dark reaction mixture was concentrated by first removing the lower boiling point components and then distilling the unreacted 2-nitrotoluene at 70 ºC under reduced pressure to give the product as a dark red liquid (1.78 g, 9.3 mmol, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 6.98 – 6.94 (m, 1H), 6.91 (d, *J* = 13.5 Hz, 1H), 5.83 (d, *J* = 13.4 Hz, 1H), 2.94 – 2.79 (m, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 144.7, 135.9, 132.5, 125.4, 124.4, 122.4, 91.2, 40.7 ppm.

5.10. Characterization data for indoles (4a-g), (4i-m) and (4o-ai)

methyl 1*H*-indole-2-carboxylate (4a)



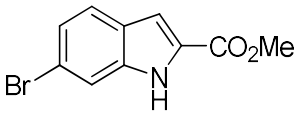
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 90:10 + 1% Et_3N), (92 mg, 0.52 mmol, 97% yield, conditions A), (81 mg, 0.46 mmol, 93% yield, conditions B).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.70 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.44 (dd, *J* = 8.3, 0.8 Hz, 1H), 7.33 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H), 7.24 (dd, *J* = 2.0, 0.8 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 3.96 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 137.0, 127.6, 127.3, 125.6, 122.8, 121.0, 112.0, 109.0, 52.2 ppm.

Elemental analysis calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25, found: C, 86.85; H, 5.80; N, 7.30.

methyl 6-bromo-1*H*-indole-2-carboxylate (4b)



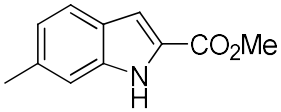
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 95:5 to 90:10 + 1% Et_3N), (121 mg, 0.48 mmol, 95% yield, conditions B).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.60 (s, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.26 (dd, *J* = 8.5, 1.7 Hz, 1H, overlapped with $CDCl_3$ signal), 7.19 (dd, *J* = 2.1, 0.9 Hz, 1H), 3.96 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 137.6, 127.9, 126.4, 124.6, 124.0, 119.4, 114.9, 109.0, 52.3 ppm.

Elemental analysis calcd for $C_{10}H_8BrNO_2$: C, 47.27; H, 3.17; N, 5.51, found: C, 47.64; H, 3.32; N, 5.44.

methyl 6-methyl-1*H*-indole-2-carboxylate (4c)



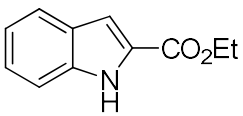
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 90:10 + 1% Et_3N), (79 mg, 0.42 mmol, 83% yield, conditions B).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.20 (d, *J* = 3.4 Hz, 2H), 7.00 (d, *J* = 8.2 Hz, 1H), 3.96 (d, *J* = 0.8 Hz, 3H), 2.48 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 137.6, 135.8, 126.7, 125.5, 123.1, 122.3, 111.7, 109.0, 52.0, 22.1 ppm.

Elemental analysis calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40, found: C, 69.67; H, 5.80; N, 7.40.

ethyl 1*H*-indole-2-carboxylate (4d)



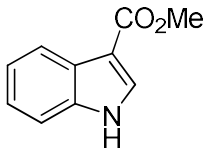
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 90:10 + 1% Et_3N), (89 mg, 0.47 mmol, 95% yield, conditions B).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.70 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.43 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.33 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.24 (dd, *J* = 2.0, 0.9 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.0, 0.9 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 136.9, 127.8, 127.7, 125.5, 122.8, 120.9, 112.0, 108.8, 61.2, 14.5 ppm.

Elemental analysis calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40, found: C, 69.67; H, 5.80; N, 7.40.

methyl 1*H*-indole-3-carboxylate (4e)



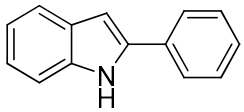
Obtained as a white solid after purification by flash column chromatography (hexane:CH_2Cl_2 = 80:20+1 % Et_3N), (62 mg, 0.35 mmol, 64 % yield, conditions A).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.26–8.10 (m, 1H), 7.92 (d, *J*=3.0 Hz, 1H), 7.46–7.36 (m, 1H), 7.35–7.21 (m, 2H), 3.93 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 136.1, 131.0, 125.8, 123.2, 122.1, 121.5, 111.5, 108.8, 51.1 ppm.

Elemental analysis calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00, found: C, 68.48; H, 5.26; N, 7.76.

2-phenyl-1*H*-indole (4f)



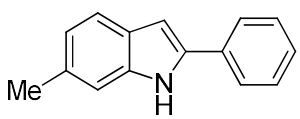
Obtained as a shiny colorless solid after purification by flash column chromatography (hexane:AcOEt = 90:10 + 1% Et_3N), (99 mg, 0.51 mmol, 95% yield, conditions A), (89 mg, 0.46 mmol, 92% yield, conditions B).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.70–7.62 (m, 3H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.41 (dd, *J* = 8.1, 0.7 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 1.4 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 137.0, 132.5, 129.4, 129.2, 127.9, 125.3, 122.5, 120.8, 120.4, 111.0, 100.2 ppm.

Elemental analysis calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25, found: C, 86.85; H, 5.80; N, 7.30.

6-methyl-2-phenyl-1*H*-indole (4g)



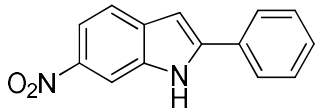
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 95:5 + 1% Et_3N), (107 mg, 0.52 mmol, 96 % yield, conditions A), (87 mg, 0.42 mmol, 84% yield, conditions B).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.65 (d, *J* = 7.7 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.19 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 1.3 Hz, 1H), 2.49 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 137.4, 132.7, 132.4, 129.1, 127.6, 127.2, 125.1, 122.2, 120.4, 111.0, 100.0, 21.9 ppm.

Elemental analysis calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76, found: C, 86.85; H, 6.40; N, 6.51.

6-nitro-2-phenyl-1*H*-indole (4i)



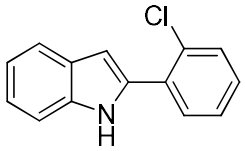
Obtained as an orange solid after purification by flash column chromatography (hexane:AcOEt = 70:30 + 1% Et_3N), (100 mg, 0.42 mmol, 78 % yield, conditions A), (62 mg, 0.26 mmol, 54% yield, conditions B).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H), 8.29 (d, *J* = 1.3 Hz, 1H), 7.98–7.86 (m, 3H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.13 (s, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 144.2, 141.9, 135.4, 133.7, 130.8, 129.1, 128.9, 125.7, 120.1, 114.8, 107.8, 99.8 ppm.

Elemental analysis calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76, found: C, 70.78; H, 4.27; N, 11.46.

2-(2-chlorophenyl)-1*H*-indole (4j)



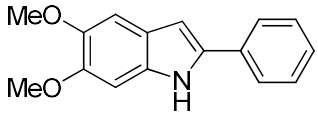
Obtained as a white solid after purification by flash column chromatography (hexane:CH_2Cl_2 = 70:30 +1 % Et_3N), (116 mg, 0.51 mmol, 94 % yield, conditions A).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.78–7.66 (m, 1H), 7.56–7.51 (m, 1H), 7.46 (d, *J*=8.1 Hz, 1H), 7.39 (dd, *J*=7.5, 1.4 Hz, 1H), 7.34 (dd, *J*=5.3, 1.7 Hz, 1H), 7.32–7.27 (m, 1H), 7.24–7.15 (m, 1H), 6.92 (d, *J*=1.3 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 135.5, 131.8, 131.6, 131.2, 131.1, 129.2, 128.6, 127.7, 123.1, 121.2, 120.6, 111.5, 104.0 ppm.

Elemental analysis calcd for $C_{14}H_{10}ClN$: C, 73.85; H, 4.43; N, 6.15, found: C, 73.50; H, 4.66; N, 6.01.

5,6-dimethoxy-2-phenyl-1*H*-indole (4k)



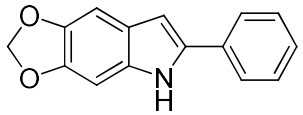
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt= 75:25+1 % Et_3N), (97 mg, 0.38 mmol, 71 % yield, conditions A).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.64–7.58 (m, 2H), 7.44–7.38 (m, 2H), 7.29 (m, 1H overlapped with residual solvent signal), 7.08 (s, 1H), 6.91 (s, 1H), 6.73 (dd, *J*=2.2, 0.8 Hz, 1H), 3.93 (d, *J*=5.6 Hz, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 145.6, 136.7, 132.8, 131.5, 129.1, 127.2, 124.7, 122.3, 102.4, 100.0, 94.6, 56.5, 56.3 ppm.

Elemental analysis calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53, found: C, 75.49; H, 6.09; N, 5.19.

6-phenyl-5*H*-[1,3]dioxolo[4,5-f]indole (4l)



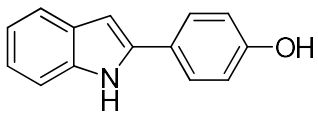
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 70:30 + 1% Et_3N), (92 mg, 0.39 mmol, 72 % yield, conditions A), (101 mg, 0.43 mmol, 84% yield, conditions B).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.06 (s, 1H), 6.92 (s, 1H), 6.76 (d, *J* = 2.0 Hz, 1H), 6.00 (s, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 143.5, 136.8, 132.7, 132.0, 129.2, 127.3, 124.7, 123.4, 100.8, 100.4, 99.3, 92.0 ppm.

Elemental analysis calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90, found: C, 75.69; H, 4.71; N, 5.55.

4-(1*H*-indol-2-yl)phenol (4m)



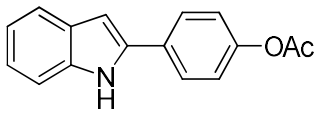
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 85:15 to 70:30 + 1% Et_3N), (53 mg, 0.25 mmol, 47% yield, conditions B).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.29 (s, 1H), 9.59 (s, 1H), 7.67 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 7.7 Hz, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.03 (t, J = 7.3 Hz, 1H), 6.95 (t, J = 7.4 Hz, 1H), 6.84 (d, J = 8.6 Hz, 2H), 6.67 (d, J = 1.2 Hz, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 157.1, 138.3, 136.8, 128.9, 126.4, 123.3, 120.7, 119.5, 119.1, 115.6, 110.9, 96.7 ppm.

Elemental analysis calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69, found: C, 80.54; H, 5.71; N, 6.21.

4-(1*H*-indol-2-yl)phenyl acetate (4m')



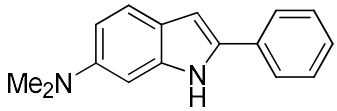
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 85:15 to 70:30 + 1% Et_3N), (44 mg, 0.18 mmol, 39% yield, conditions B).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.52 (s, 1H), 7.89 (d, J = 8.6 Hz, 2H), 7.53 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.6 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 7.00 (t, J = 7.3 Hz, 1H), 6.88 (d, J = 1.5 Hz, 1H), 2.29 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 169.2, 149.7, 137.1, 136.9, 129.9, 128.6, 126.0, 122.3, 121.6, 120.0, 119.4, 111.3, 98.8, 20.9 ppm.

Elemental analysis calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57, found: C, 76.59; H, 5.56; N, 5.58.

***N*,*N*-dimethyl-2-phenyl-1*H*-indol-6-amine (4o)**



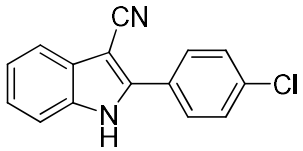
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 80:20 +1 % Et_3N), (77 mg, 0.33 mmol, 60 % yield, conditions A).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.61 (d, J=7.9 Hz, 2H), 7.49 (d, J=8.6 Hz, 1H), 7.41 (t, J=7.7 Hz, 2H), 7.27 (t, J=7.3 Hz, 1H, overlapped with $CDCl_3$), 6.82–6.70 (m, 3H), 2.98 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 138.6, 136.0, 132.9, 129.1, 127.0, 124.6, 121.8, 121.1, 110.1, 99.9, 94.9, 42.1 ppm.

Elemental analysis calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85, found: C, 81.23; H, 7.06; N, 11.49.

2-(4-chlorophenyl)-1*H*-indole-3-carbonitrile (4p)



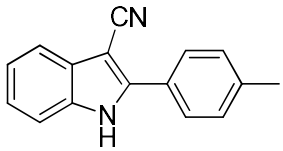
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 70:30 + 1% Et_3N), (125 mg, 0.49 mmol, 99% yield, conditions B).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.65 (s, 1H), 8.03–7.96 (m, 2H), 7.75–7.68 (m, 2H), 7.65 (d, J = 7.9 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.27 (t, J = 7.5 Hz, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 143.3, 135.6, 134.6, 129.4, 128.6, 128.20, 128.18, 124.1, 122.2, 118.4, 116.7, 112.7, 81.7 ppm.

Elemental analysis calcd for $C_{15}H_9ClN_2$: C, 71.29; H, 3.59; N, 11.09, found: C, 71.29; H, 3.62; N, 10.97.

2-(*p*-tolyl)-1*H*-indole-3-carbonitrile (4q)



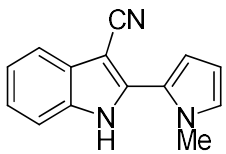
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 80:20 to 70:30 + 1% Et_3N), (114 mg, 0.49 mmol, 98% yield, conditions B).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.51 (s, 1H), 7.89 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.2 Hz, 2H), 7.30 (td, J = 8, 1.2 Hz, 1H), 7.25 (td, J = 7.7, 1.0 Hz, 1H), 2.40 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 144.9, 139.8, 135.4, 129.8, 128.3, 126.8, 126.6, 123.7, 121.9, 118.2, 117.1, 112.5, 80.9, 20.9 ppm.

Elemental analysis calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06, found: C, 82.38; H, 5.23; N, 11.72.

2-(1-methyl-1*H*-pyrrol-2-yl)-1*H*-indole-3-carbonitrile (4r)



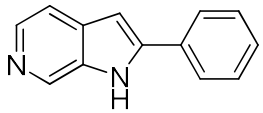
Obtained as a yellow solid after purification by flash column chromatography (hexane:AcOEt = 75:25 to 70:30 + 1% Et_3N), (92 mg, 0.42 mmol, 77 % yield, conditions A), (67 mg, 0.30 mmol, 61% yield, conditions B).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.17 (s, 1H), 7.61 (d, J = 7.4 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.30 (td, J = 7.5, 1.2 Hz, 1H), 7.25 (td, J = 7.5, 0.9 Hz, 1H), 7.11–7.03 (m, 1H), 6.59 (dd, J = 3.7, 1.7 Hz, 1H), 6.23 (dd, J = 3.5, 2.8 Hz, 1H), 3.80 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 138.4, 135.4, 127.6, 126.7, 123.5, 122.1, 121.8, 118.1, 116.8, 112.8, 112.5, 108.3, 82.8, 35.1 ppm.

Elemental analysis calcd for $C_{14}H_{11}N_3$: C, 76.00; H, 5.01; N, 18.99, found: C, 76.38; H, 5.24; N, 18.69.

2-phenyl-1*H*-pyrrolo[2,3-*c*]pyridine (4s)



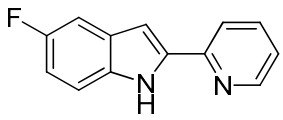
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 20:80 to 10:90 + 2% Et_3N), (83 mg, 0.43 mmol, 86% yield, conditions B).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 8.75 (s, 1H), 8.10 (d, J = 5.4 Hz, 1H), 7.93 (d, J = 7.6 Hz, 2H), 7.51 (t, J = 7.3 Hz, 3H), 7.40 (t, J = 7.0 Hz, 1H), 6.97 (s, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 141.3, 138.2, 134.22, 134.19, 132.7, 131.3, 129.0, 128.5, 125.8, 114.4, 97.9 ppm.

Elemental analysis calcd for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42, found: C, 80.29; H, 4.98; N, 14.23.

5-fluoro-2-(pyridin-2-yl)-1*H*-indole (4t)



Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 80:20 + 1% Et_3N), (97 mg, 0.46 mmol, 91% yield, conditions B).

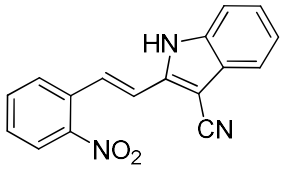
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (s, 1H), 8.63 (d, J = 4.2 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.84 (t, J = 7.7 Hz, 1H), 7.48 (dd, J = 8.5, 4.3 Hz, 1H), 7.39–7.24 (m, 2H), 7.12 (d, J = 1.0 Hz, 1H), 7.06–6.90 (m, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 157.2 (d, $^1J_{C–F}$ = 231.9 Hz), 150.0, 149.2, 138.9, 137.0, 133.9, 128.5 (d, $^3J_{C–F}$ = 10.5 Hz), 122.5, 120.0, 113.0 (d, $^3J_{C–F}$ = 9.8 Hz), 110.6 (d, $^2J_{C–F}$ = 26.3 Hz), 104.9 (d, $^2J_{C–F}$ = 23.1 Hz), 100.6 (d, $^4J_{C–F}$ = 4.9 Hz) ppm.

^{19}F NMR (376 MHz, DMSO-d_6) δ −124.4 (s) ppm.

Elemental analysis calcd for $C_{13}H_9FN_2$: C, 73.57; H, 4.27; N, 13.20, found: C, 73.77; H, 4.09; N, 13.58.

(*E*)-2-(2-nitrostyryl)-1*H*-indole-3-carbonitrile (4u')



Obtained as a yellow solid after purification by flash column chromatography (hexane:CH_2Cl_2= 40:60+ 1% Et_3N). (48 mg, 0.17 mmol, 61 % yield, conditions A), The yield reported in **Table 8** was calculated considering the molecular weight of the hemihydrate molecule.

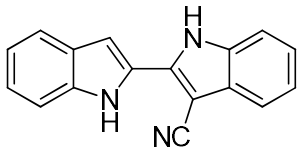
^{1}H NMR (300 MHz, DMSO-d_6) δ 12.62 (s, 1H), 8.11 (d, *J*=7.6 Hz, 1H), 8.05 (dd, *J*=8.1, 0.9 Hz, 1H), 7.83 (d, *J*=16.3 Hz, 1H, olefinic CH overlapped with multiplet at 7.84–7.76), 7.84–7.76 (m, 1H), 7.67–7.58 (m, 2H), 7.54 (d, *J*=8.1 Hz, 1H), 7.32 (d, *J*=16.3 Hz, 1H, olefinic CH overlapped with multiplet at 7.39–7.31), 7.39–7.31 (m, 1H), 7.28–7.21 (m, 1H) ppm.

^{13}C NMR (75 MHz, DMSO-d_6) δ 148.1, 142.4, 136.1, 133.7, 130.2, 129.8, 128.3, 127.4, 127.1, 124.9, 124.6, 122.1, 119.8, 118.6, 115.7, 112.51, 85.25 ppm.

MS (ESI+), *m/z* $[M+Na]^+$ calcd for $C_{17}H_{11}N_3NaO_2^+$: 312.07, found 312.32. MS (ESI$^-$), *m/z* $[M-H]^-$ calcd for $C_{17}H_{10}N_3O_2^-$: 289.08, found 288.57.

Elemental analysis calcd for $C_{17}H_{11}N_3O_2 \cdot ½\ H_2O$: C 68.45; H 4.05; N 14.09, found: C 68.58; H 4.61; N 14.09.

1*H*,1′*H*-[2,2'-biindole]-3-carbonitrile (4u'')



Obtained as a white solid and recovered without flash column chromatography. The product was precipitated from the reaction mixture by addition of water (15 mL), collected by filtration on a Buchner funnel, let it to dry on the filter paper and then washed several times with mixture of hexane and CH_2Cl_2 (3:1), (62 mg, 0.24 mmol, 90 % yield, conditions A).

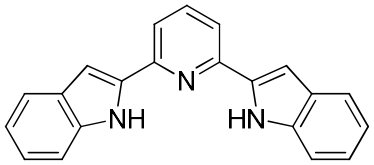
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (s, 1H), 11.54 (s, 1H), 7.69 (d, *J*=7.9 Hz, 1H), 7.65 (d, *J*=7.7 Hz, 1H), 7.59 (d, *J*=7.9 Hz, 1H), 7.55 (d, *J*=8.0 Hz, 1H), 7.33 (dd, 7.2, 1.2 Hz, 1H), 7.30–7.21 (m, 2H, partially overlapped with singlet at 7.21), 7.21 (s, 1H), 7.11 (t, *J*=7.9 Hz, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 138.2, 137.1, 135.3, 128.0, 127.9, 127.3, 123.9, 123.3, 122.2, 120. 9, 120.3, 118.2, 116.6, 112.6, 112.0, 103.3, 81.1 ppm.

MS (ESI-), *m/z* $[M-H]^-$ calcd for $C_{17}H_{10}N_3^-$: 256.09, found 256.43.

Elemental analysis calcd for $C_{17}H_{11}N_3$: C 79.36; H 4.31; N 16.33, found: C 78.98; H 4.65; N 15.97.

2,6-di(1*H*-indol-2-yl)pyridine (4v)



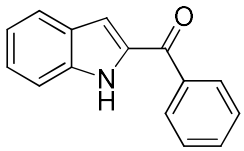
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 80:20 + 1% Et_3N), (54 mg, 0.17 mmol, 70% yield conditions B).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 2H), 7.92–7.85 (m, 3H), 7.63 (d, *J* = 7.9 Hz, 2H), 7.58 (dd, *J* = 8.0, 0.7 Hz, 2H), 7.28 (dd, *J* = 2.0, 0.7 Hz, 2H), 7.22 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 2H), 7.07 (ddd, *J* = 7.9, 7.0, 0.8 Hz, 2H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 149.4, 137.8, 137.0, 136.7, 128.6, 122.7, 120.9, 119.6, 117.8, 111.5, 100.8 ppm.

Elemental analysis calcd for $C_{21}H_{15}N_3$: C, 81.53; H, 4.89; N, 13.58, found: C, 81.75; H, 4.83; N, 13.34.

(1*H*-indol-2-yl)(phenyl)methanone (4w)



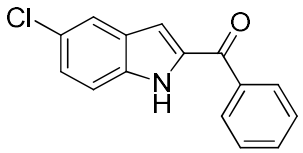
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 90:10 + 1% Et_3N), (90 mg, 0.41 mmol, 82% yield, conditions B).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.01 (d, *J* = 7.3 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.21–7.15 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 187.3, 138.2, 137.7, 134.5, 132.5, 129.4, 128.6, 127.9, 126.7, 123.4, 121.2, 112.9, 112.3 ppm.

Elemental analysis calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33, found: C, 81.60; H, 5.11; N, 6.30.

(5-chloro-1*H*-indol-2-yl)(phenyl)methanone (4x)



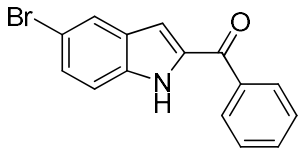
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 85:15 + 1% Et_3N), (92 mg, 0.36 mmol, 72% yield, conditions B).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1H), 8.00 (d, *J* = 7.2 Hz, 2H), 7.69 (s, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.33 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.10 (d, *J* = 1.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 187.3, 137.8, 135.9, 135.5, 132.8, 129.4, 128.8, 128.7, 127.1, 126.8, 122.4, 113.5, 111.9 ppm.

Elemental analysis calcd for $C_{15}H_{10}ClNO$: C, 70.46; H, 3.94; N, 5.48, found: C, 70.35; H, 4.12; N, 5.65.

(5-bromo-1*H*-indol-2-yl)(phenyl)methanone (4y)



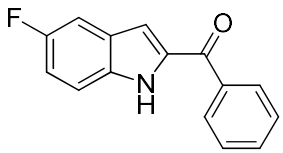
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 85:15 + 1% Et_3N), (122 mg, 0.41 mmol, 81% yield, conditions B).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.16 (s, 1H), 7.96–7.88 (m, 3H), 7.69 (t, *J* = 7.4 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.41 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.10 (s, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 186.5, 137.7, 136.5, 135.2, 132.5, 128.9, 128.7, 128.6, 128.2, 125.0, 114.8, 112.7, 111.2 ppm.

Elemental analysis calcd for $C_{15}H_{10}BrNO$: C, 60.02; H, 3.36; N, 4.67, found: C, 59.94; H, 3.67; N, 4.73.

(5-fluoro-1*H*-indol-2-yl)(phenyl)methanone (4z)



Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 95:5 + 1% Et_3N), (100 mg, 0.42 mmol, 84% yield, conditions B).

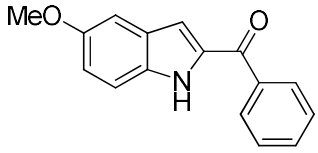
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 8.02 (d, J = 7.1 Hz, 2H), 7.65 (t, J = 7.4 Hz, 1H), 7.56 (t, J = 7.5 Hz, 2H), 7.47 (dd, J = 9.0, 4.3 Hz, 1H), 7.35 (dd, J = 9.1, 2.3 Hz, 1H), 7.16 (dd, J = 9.1, 2.5 Hz, 1H), 7.13–7.12 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 158.4 (d, $^{1}J_{C-F}$ = 237.4 Hz), 138.0, 135.8, 134.5, 132.7, 129.4, 128.7, 127.9 (d, $^{3}J_{C-F}$ = 10.3 Hz), 115.9 (d, $^{2}J_{C-F}$ = 27.1 Hz), 113.5 (d, $^{3}J_{C-F}$ = 9.5 Hz), 112.7 (d, $^{3}J_{C-F}$ = 5.7 Hz), 107.3 (d, $^{2}J_{C-F}$ = 23.2 Hz) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ −122.33 (td, J = 9.1, 4.3 Hz) ppm.

Elemental analysis calcd for $C_{15}H_{10}FNO$: C, 75.30; H, 4.21; N, 5.85, found: C, 75.24; H, 4.39; N, 5.63.

(5-methoxy-1*H*-indol-2-yl)(phenyl)methanone (4aa)



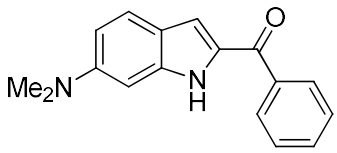
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 90:10 + 1% Et_3N), (114 mg, 0.45 mmol, 91% yield, conditions B).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 8.02 (d, J = 7.2 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.54 (t, J = 7.5 Hz, 2H), 7.42 (d, J = 8.8 Hz, 1H), 7.15–7.01 (m, 3H), 3.86 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 187.3, 155.0, 138.3, 134.9, 133.5, 132.4, 129.4, 128.6, 128.2, 118.6, 113.5, 112.6, 102.9, 55.8 ppm.

Elemental analysis calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57, found: C, 76.68; H, 4.95; N, 5.74.

(6-(dimethylamino)-1*H*-indol-2-yl)(phenyl)methanone (4ab)



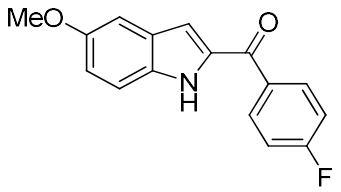
Obtained as an orange solid after purification by flash column chromatography (hexane:AcOEt = 80:20 + 1% Et_3N), (118 mg, 0.45 mmol, 89% yield, conditions B).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.46 (s, 1H), 7.87 (d, J = 7.0 Hz, 2H), 7.63 (t, J = 7.3 Hz, 1H), 7.55 (t, J = 7.4 Hz, 2H), 7.50 (d, J = 9.0 Hz, 1H), 6.98 (d, J = 1.3 Hz, 1H), 6.77 (dd, J = 9.0, 2.2 Hz, 1H), 6.60 (d, J = 1.4 Hz, 1H), 2.95 (s, 6H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 184.9, 149.9, 140.6, 138.7, 132.7, 131.6, 128.6, 128.4, 123.3, 119.3, 113.5, 110.7, 92.5, 40.5 ppm.

Elemental analysis calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60, found: C, 76.88; H, 6.18; N, 10.29.

(4-fluorophenyl)(5-methoxy-1*H*-indol-2-yl)methanone (4ac)



Obtained as a yellow solid after purification by flash column chromatography (hexane:AcOEt = 80:20 + 1% Et_3N), (102 mg, 0.38 mmol, 76% yield, conditions B).

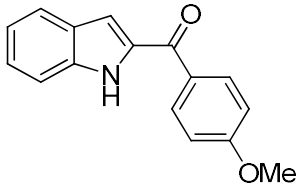
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 8.00 (dd, J = 8.1, 5.8 Hz, 2H), 7.40 (t, J = 8.7 Hz, 3H), 7.14 (d, J = 1.5 Hz, 1H), 7.03 (d, J = 0.8 Hz, 1H), 6.99 (dd, J = 9.0, 1.8 Hz, 1H), 3.76 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 184.8, 165.5 (d, $^1J_{C–F}$ = 250.3 Hz), 154.1, 134.5 (d, $^4J_{C–F}$ = 2.9 Hz), 134.4, 133.6, 131.5 (d, $^3J_{C–F}$ = 9.2 Hz), 127.3, 117.7, 115.6 (d, $^2J_{C–F}$ = 21.8 Hz), 113.7, 111.5, 102.4, 55.2 ppm.

^{19}F NMR (376 MHz, DMSO-d_6) δ −107.27 to −107.49 (m).

Elemental analysis calcd for $C_{16}H_{12}FNO_2$: C, 71.37; H, 4.49; N, 5.20, found: C, 71.25; H, 4.61; N, 5.39.

(1*H*-indol-2-yl)(4-methoxyphenyl)methanone (4ad)



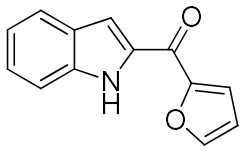
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 80:20 + 1% Et_3N), (99 mg, 0.39 mmol, 79% yield, conditions B).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 7.97 (d, J = 8.7 Hz, 2H), 7.71 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.2 Hz, 1H), 7.30 (t, J = 7.3 Hz, 1H), 7.15–7.05 (m, 4H), 3.87 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 185.1, 162.7, 137.7, 134.4, 131.3, 130.4, 127.0, 125.4, 122.7, 120.2, 113.9, 112.6, 111.0, 55.5 ppm.

Elemental analysis calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57, found: C, 76.33; H, 5.29; N, 5.70.

furan-2-yl(1*H*-indol-2-yl)methanone (4ae)



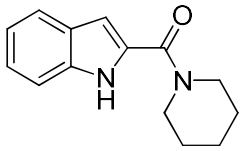
Obtained as a pale-yellow solid after purification by flash column chromatography (hexane:AcOEt = 85:15 + 1% Et_3N), (90 mg, 0.43 mmol, 85% yield, conditions B).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.96 (s, 1H), 8.11 (d, J = 0.8 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 1.3 Hz, 1H), 7.60 (d, J = 3.5 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.31 (t, J = 7.3 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 6.80 (dd, J = 3.5, 1.6 Hz, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 172.1, 151.9, 147.8, 137.8, 133.5, 127.2, 125.7, 122.9, 120.4, 118.9, 112.7, 110.3 ppm.

Elemental analysis calcd for $C_{13}H_9NO_2$: C, 73.92; H, 4.29; N, 6.63, found: C, 74.21; H, 4.72; N, 6.44.

(1*H*-indol-2-yl)(piperidin-1-yl)methanone (4af)



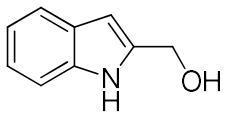
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 80:20 + 1% Et_3N), (112 mg, 0.49 mmol, 91 % yield, conditions A), (108 mg, 0.47 mmol, 95% yield, conditions B).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.26 (td, J = 7.2, 1.1 Hz, 1H), 7.12 (td, J = 7.2, 0.8 Hz, 1H), 6.77 (d, J = 1.4 Hz, 1H), 3.88 (s, 4H), 1.85–1.54 (m, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 135.9, 129.9, 127.6, 124.1, 121.8, 120.4, 112.0, 104.8, 26.3, 24.8 ppm.

Elemental analysis calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27, found C, 73.40; H, 7.04; N, 11.94.

(1*H*-indol-2-yl)methanol (4ag)



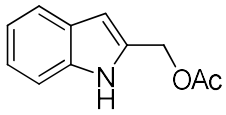
Obtained as a yellow solid after purification by flash column chromatography (hexane:AcOEt = 80:20 to 60:40 + 1%Et_3N), (56 mg, 0.38 mmol, 74% yield, conditions B).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.03 (td, J = 8, 0.8 Hz 1H), 6.94 (td, J = 8, 0.8 Hz 1H), 6.26 (d, J = 0.9 Hz, 1H), 5.21 (t, J = 5.6 Hz, 1H), 4.61 (d, J = 5.6 Hz, 2H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 140.1, 136.2, 127.9, 120.5, 119.6, 118.6, 111.0, 98.4, 56.9 ppm.

Elemental analysis calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52, found C, 73.63; H, 5.88; N, 9.23.

(1*H*-indol-2-yl)methyl acetate (4ah)



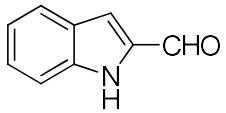
Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt:CH_2Cl_2 = 80:10:10 + 1%Et_3N), (66 mg, 0.35 mmol, 70% yield, conditions B).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.36 (dd, J = 8.1, 0.7 Hz, 1H), 7.09 (td, J = 8.2, 1.1 Hz, 1H), 6.98 (td, J = 7.9, 0.9 Hz, 1H), 6.44 (d, J = 1.3 Hz, 1H), 5.18 (s, 2H), 2.06 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 170.1, 136.4, 133.4, 127.4, 121.5, 120.1, 119.0, 111.3, 101.9, 59.0, 20.7 ppm.

Elemental analysis calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40, found C, 70.09; H, 5.78; N, 7.12.

1*H*-indole-2-carbaldehyde (4ai)



Obtained as a white solid after purification by flash column chromatography (hexane:AcOEt = 80:20 + 1%Et_3N), (51 mg, 0.35 mmol, 65 % yield conditions A), (15 mg, 0.1 mmol, 20% yield conditions B).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 9.24 (s, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.28 (s, 1H), 7.18 (t, J = 7.5 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 182.3, 138.2, 136.1, 127.50, 127.47, 123.6, 121.4, 115.0, 112.6 ppm.

Elemental analysis calcd for C_9H_7NO: C, 74.47; H, 4.86; N, 9.65, found C, 74.07; H, 4.85; N, 9.28.

Chapter II:

Synthesis of 4-Quinolones by Reductive Cyclization of 2'-Nitrochalcones Using Formic Acid as a CO-surrogate.

1. Introduction

In the early 20th century, infectious diseases were the most common cause of human illness leading to death, out of which bacterial infections accounted for about one-third of these infections.[165] In addition to bacterial infections, malaria also has an enormous impact on global human health, with over 200 million cases of malaria and over 600,000 deaths each year.[166] While different therapies were used for the treatment of these diseases, the introduction of antibiotic agents opened new avenues for the treatment of bacterial infections. The invention of antibiotics such as sulfonamide, and afterward penicillin by Alexander Fleming in 1928 and synthetic antibiotics such as quinolones were some of the great milestones of science.[167-169]

Here, we focus on an important class of synthetic antibiotics known as quinolones, which is the key scaffold of an important class of biologically active broad-spectrum antibacterial drugs.[170] The spectacular discovery of nalidixic acid (the first prototype 4-quinolone analogue to enter the market), which is chemically a naphthyridone and the prototype compound of the quinolones as a byproduct in chloroquine synthesis (**Fig. 5**) by Lesher and coworkers in 1962 initiated the improvement of quinolones.[171]

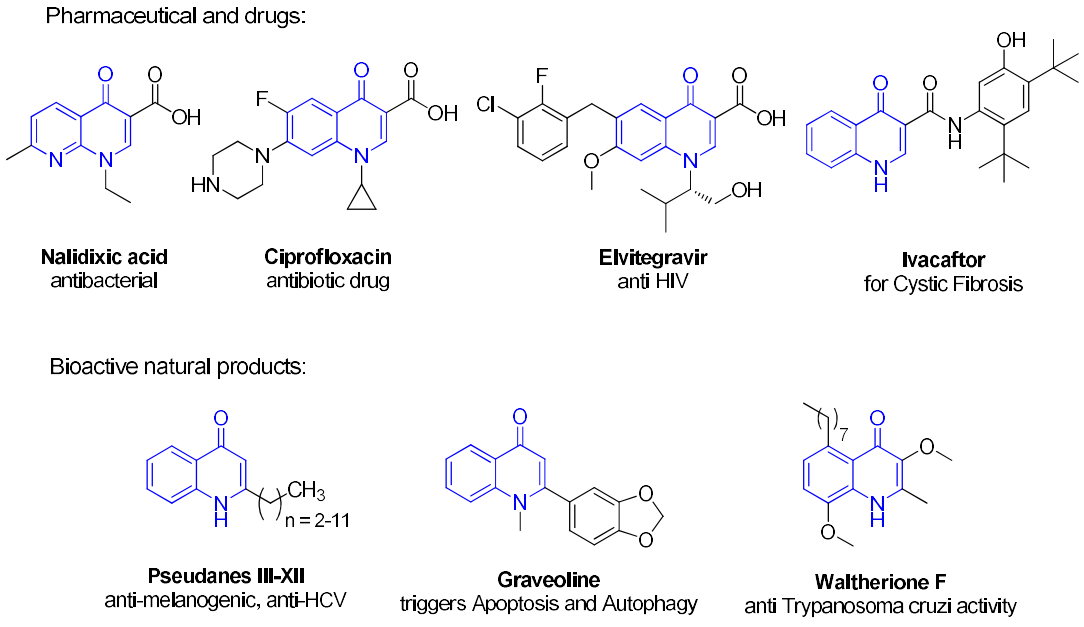
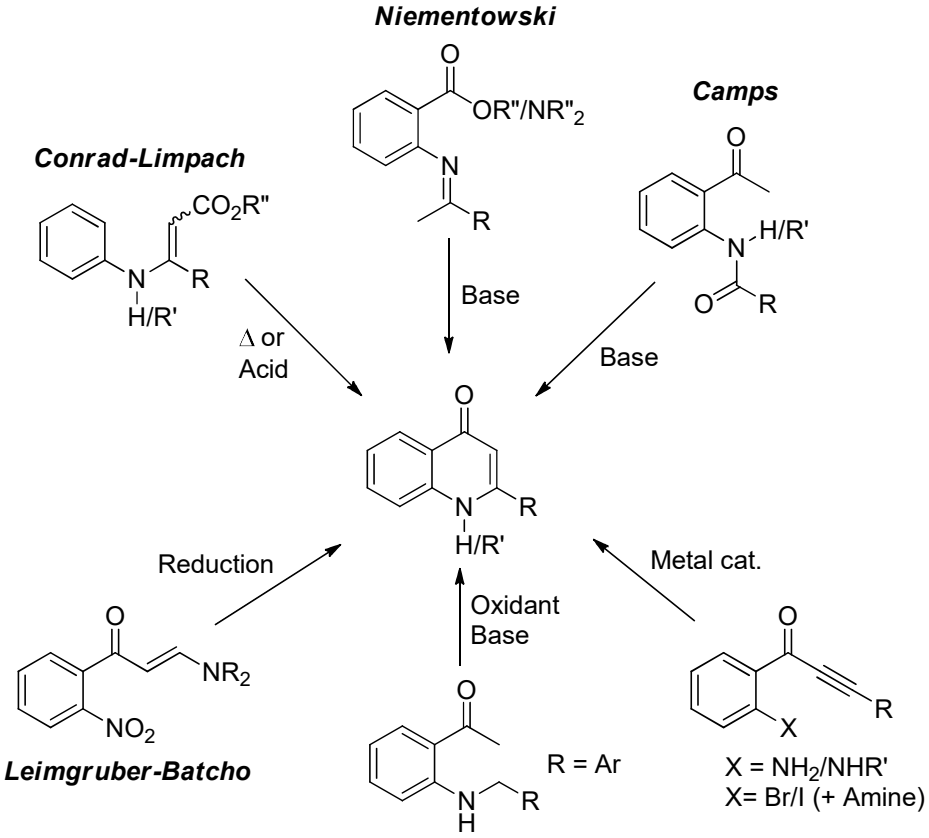


Fig. 5. 4-Quinolone pharmaceuticals and natural products.

Since then, the 4-quinolone scaffold with 6-fluoro and 3-carboxylic acid embellishments has evolved into several generations of antibacterial drugs with ciprofloxacin being the best known example.[172] Newer 3-substituted 4-quinolone derivatives like ivacaftor [173] and elvitegravir [174] are drugs used for cystic fibrosis, veternary medicine, and HIV infection. Apart from these synthetic quinolone drugs, a number of 2-alkyl/aryl-substituted quinolone natural products, harboring diverse bioactivities, have been reported over the years.[175] Among these quinolone alkaloids, 4-(1*H*)-quinolones are less abundant, with pseudanes (III−XII),[176] graveoline (*N*-Me),[175] and waltherione F [177] being very recent additions that have attracted the attention of the synthetic chemistry community mainly owing to their promising bioactivity profile (**Fig. 5**).

Various effective methods have been developed to produce quinolones.[178,179] The synthesis of quinolin-4-ones bearing alkyl or aryl residues at C-2 (and/or C-3) following established strategies like Conrad-Limpach synthesis (from anilines and *β*-ketoesters), Camps reaction (cyclization of *ortho*-acylaminoacetophenones), Niementowski and related reactions (from anthranilic acid-derived imines) has been extensively reviewed (**Scheme 18**).[178,180]

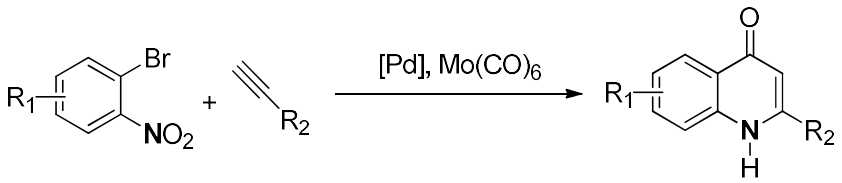


Scheme 18. Established methods for the construction of the 4-quinolone ring system.

Among the other methods, those involving enamino ketone intermediates have attracted considerable interest.[181] Whereas the modified Leimgruber-Batcho synthesis [182] and other protocols involving chelation-controlled C-H amidation reactions prior to cyclization with the

enamino ketone [183,184] are rather suited for the preparation of 2-unsubstituted quinolin-4-ones, several approaches starting from acetylenic ketones, and partly going through enamino ketones (arising from addition of amines to the alkyne) have been worked out in the recent years.[185,186] In 2015, Hu and coworkers designed a straightforward method for the synthesis of numerous 2-aryl-4-quinolone derivatives from *N*-aryl methyl-2-aminophenyl ketones through a metal-free oxidative intramolecular oxidative Mannich reaction, followed by $C(sp^3)$–H/$C(sp^3)$–H coupling and aromatization using an oxidant and a base (**Scheme 18**).[170]

Often the substrate scope of these reactions is limited by the necessity to employ harsh cyclization conditions, including temperatures of 250 °C or strong acids such as polyphosphoric acid or Eaton's reagent in some cases,[169,187] hence milder reactions have been explored. A recent example of the synthesis of 4-quinolones in which the source of nitrogen is the nitro group have been introduced starting from *o*-bromonitroarenes and alkynes and employing $Mo(CO)_6$ as a CO surrogate and a reductant (**Scheme 19**).[186]



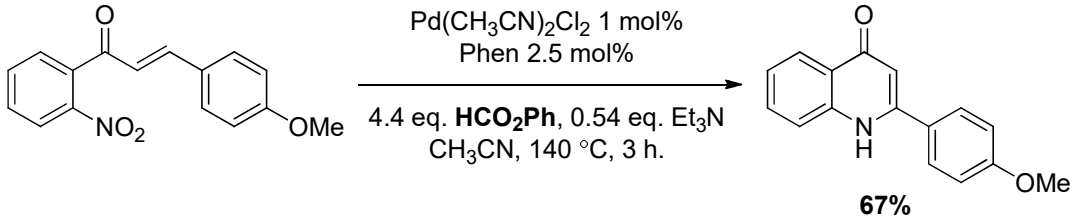
Scheme 19. Synthesis of 4-quinolones via *inter*-molecular cyclization of nitroarenes and alkynes.

As discussed in the first chapter, all methods have positive aspects and limitations, but most of them produce stoichiometric amounts of coproducts that may cause problems in the purification step. Considering that the nitrogen atom in most aromatic compounds is initially introduced in the form of a nitro group and only at a later stage converted into other groups, using a nitroarene as a reagent has the obvious advantage of saving at least one synthetic step. In this context, reactions employing nitroarenes or nitroalkenes as substrates and CO as the reductant are particularly appealing because CO permits the selective reduction of the nitro group in the presence of other reducible groups, such as olefinic, aldehyde and keto ones,[188,189] and only produces CO_2 as an easily separable stoichiometric byproduct.[21,65,66,70,190-192] Several years ago, the synthesis of 4-quinolones by reduction of 2'-nitrochalcones by CO, catalyzed by a Ru or Pd complexes was reported.[71,193-195] The method is particularly effective for the synthesis of 2-aryl-4-quinolones, whose synthesis, on the other hand, is difficult with most of the traditional quinolone synthesis.[196]

As the use of gaseous CO is always accompanied by many drawbacks, several research groups explored the possibility of employing solid or liquid CO surrogates which can liberate CO under the reaction conditions. During our previous studies on the synthesis of indoles using phenyl formate as the CO source (see chapter I), a single example of the cyclization of 2'-nitro-4-methoxychalcone to the corresponding 4-quinolone in 67% yield was reported, but this specific reaction was not investigated any further (**Scheme 20**).[23,26]

Since then, we were able to employ also the HCO_2H/Ac_2O mixture to this aim, thus eliminating the problem of the formation of phenol as a coproduct, whose complete separation was problematic

in some cases.[91] The use of this mixture also improves the atom efficiency of the reaction, since phenyl formate is itself synthesized by the reaction of phenol with the HCO_2H/Ac_2O mixture, but still the superiority of the use of gaseous CO is clearly undeniable from this point of view.



Scheme 20. Synthesis of 2-(4-methoxyphenyl)quinolin-4(1*H*)-one using HCO_2Ph.

Thus, in this chapter we will describe the use of the HCO_2H/Ac_2O mixture as a cheap, safe, and available CO surrogate in the Pd-catalyzed reductive cyclization of 2'-nitrochalcones, which allows to perform the reaction in a cheap and commercially available thick-walled glass tube and without adding any gaseous reagent.

2. Results and Discussion

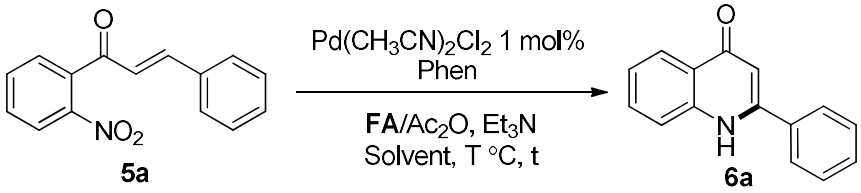
Since palladium complexes were shown to be the most active and robust catalysts for reactions involving the reduction of nitroarenes,[22,59,62,80,109,197-199] we employed a complex of palladium with 1,10-phenanthroline (Phen) as a ligand to form the active catalyst *in situ*. By employing this catalytic system together with the HCO_2H/Ac_2O mixture, we were able to convert a series of 2'-nitrochalcones **5** into the corresponding 4-quinolones **6** in high yields, with acetic acid and CO_2 as the only stoichiometric byproducts.

For our preliminary investigations, we took the reductive cyclization reaction of **5a** as the model reaction. The tests were performed in screw-cap thick-walled glass tubes (pressure tubes).

2.1. Optimization of the reaction conditions

As a first attempt, the reaction conditions previously optimized for the reductive cyclization of *o*-nitrostyrenes using HCO_2H were employed. The result was encouraging though not good (**Table 12**, entry 1); almost full conversion was reached but with a low **6a** yield (50%). This may be due to the poor solubility of **5a** in acetone.

Table 12. Optimization of the reaction conditions for the reductive cyclization of 2'-nitrochalcone **5a** to 2-phenylquinolin-4(1*H*)-one **6a** using FA as the CO source.[a]



Entry	FA/Ac_2O/Et_3N to **5a** mol ratio	Phen (mol%)	Solvent	t (h)	T (°C)	Conv. (%)[b]	Sel. (%)[b]	Yield (%)[b]

1[c]	2.5/2.5/2.5	5	Acetone	10	110	98	51	50
2	4.4/4.4/4.4	5	CH_3CN	10	140	>99	69	69
3	3/3/3	5	CH_3CN	10	140	96	76	73
4	2.5/2.5/2.5	5	CH_3CN	10	140	84	62	52
5[d]	3/3/3	5	CH_3CN	10	140	37	24	9
6[e]	3/3/3	5	CH_3CN	10	140	>99	47	47
7[f]	3/3/3	2.5	CH_3CN	10	140	98	58	57
8	3/3/3	5	CH_3CN	10	150	100	74	74
9	3/3/3	5	CH_3CN	10	130	84	80	67
10	3/3/3	5	CH_3CN	16	120	>99	55	55
11	3/3/3	2.5	CH_3CN	10	130	57	85	48
12	3/3/3	2.5	CH_3CN	16	130	96	76	73
13	3/3/3	2.5	CH_3CN/DMF[g]	16	130	>99	75	75
14	3/3/3	2.5	MEK	16	130	64	72	46
15	3/3/3	2.5	DMF	16	130	>99	>99	99
16	3/3/3	2.5	DMF	10	130	99	>99	99
17	3/3/3	2.5	DMF	6	130	88	93	82
18	3/3/3	2.5	DMF	4	130	59	93	55

a: Experimental conditions: 0.5 mmol **5a**, 1 mol% $Pd(CH_3CN)_2Cl_2$, Phen, FA, Ac_2O, Et_3N, solvent 10 mL, other amounts as in the table. ***b***: Determined by HPLC using benzophenone as the internal standard. ***c***: $Pd(acac)_2$ (1 mol%). ***d***: The reaction was assembled in the air. ***e***: TMPhen was used. ***f***: $(OMe)_2$Phen was used. ***g***: CH_3CN/DMF = 9:1.

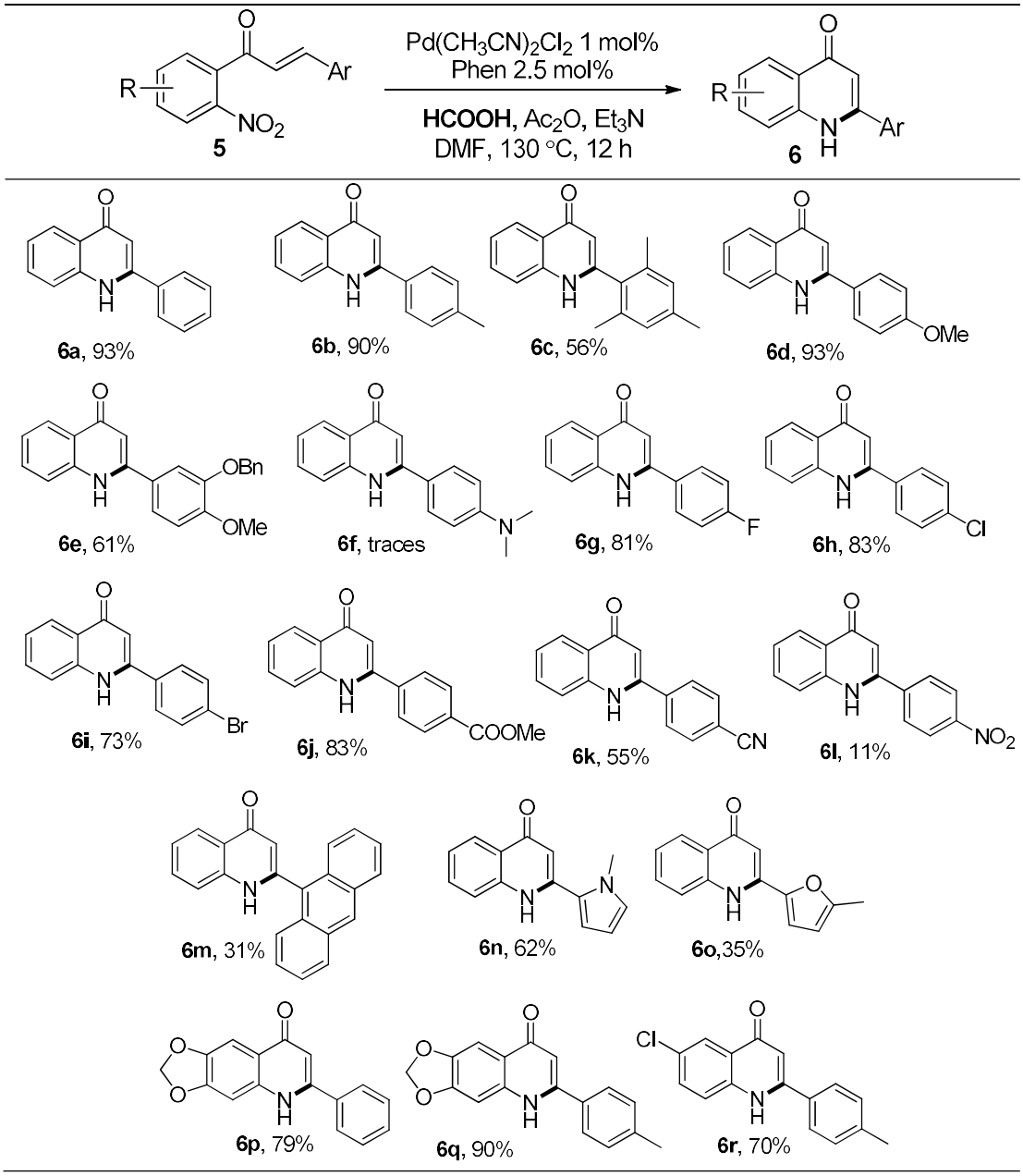
A higher selectivity was obtained using acetonitrile as the solvent at the temperature (140 °C) and CO-source to **5a** ratio (4.4) previously employed in the above-mentioned reaction (**Scheme 18**) in which HCO_2Ph had been employed as the CO surrogate (**Table 12**, entry 2). A decrease in the HCO_2H/Ac_2O amount, from 2.2-fold the stoichiometric amount (i.e., two CO for each nitro group) to 1.5-fold, causes a marginal decrease in the reaction rate concurrently with a selectivity increase, while below this threshold the selectivity decreased again (**Table 12**, entries 2-4), differently to what we noticed for *o*-nitrostyrenes cyclization (**Table 10**, chapter I). Assembling the reaction tube in the air led to a much-lower yield which implies a high sensitivity to the air (**Table 12**, entry 5). Contrary to what was shown for some comparable synthesis,[81] the use of 3,4,7,8-tetramethylphenathroline (TMPhen) or 4,7-dimethoxyphenanthroline ($(MeO)_2$Phen) as the ligands afforded lower selectivities (**Table 12**, entries 6 and 7). A screening of temperatures revealed that temperatures above 130 °C are needed to ensure high selectivities and complete solubility of **5a**, with a maximum at 130 °C (**Table 12**, entries 8-10). Despite a high selectivity towards **6a** being maintained, the reaction slowed down as the amount of ligand decreased (**Table 12,** entries 11 and 12). Eventually, a variation in the polar non-protic reaction solvents, led us to identify DMF as the best solvent to perform the reaction (**Table 12**, entries 12-15). It is worth noting that the use of the CH_3CN/DMF mixture (**Table 12**, entry 13) was tested because in the case of the reductive cyclization of *o*-nitrostyrenes to indoles (**Table 8**, entry 3, chapter I)[23] this mixed solvent had provided better results than either solvent alone. However, that positive effect was not observed in the present system. DMF permits the reactions to be finished in 10 hours as opposed to the 16

hours needed when acetonitrile was used, yielding a roughly quantitative HPLC yield (**Table 12**, entry 16).

2.2. Substrate scope

Having identified the best experimental conditions, the substrate scope was investigated (**Table 13**). The reaction time was elongated from 10 h to 12 h for these experiments to ensure complete conversion even for the less reactive substrates.

Table 13. Substrate scope of the Pd-catalyzed reductive cyclization reaction of 2'-nitrochalcones **5** using formic acid as CO source.[a]



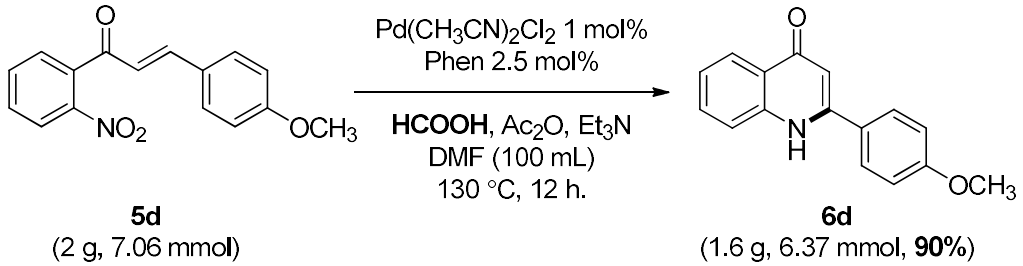
a: Experimental conditions: 0.5 mmol of **5**, $Pd(CH_3CN)_2Cl_2$ (1 mol%), Phen (2.5 mol%), FA/Ac_2O/Et_3N (3 eq.) DMF (10 mL) at 130 °C for 12h. Isolated yields are reported.

Quinolone **6a** was isolated in 93% yield. The loss in isolation with respect to the virtually quantitative yield measured by HPLC under the same experimental conditions is largely due to its poor solubility, which results in a longer chromatographic purification. Note that the same problem was encountered even with most of the products shown in **Table 13**.

Concerning substituents on the dangling aryl ring, alkyl and alkoxy substituents were well tolerated (**6b**-**6e**), although a lower yield was observed when they imposed significant steric shielding (**6c**). Interestingly, when the dimethylamino group was present, only trace amounts of quinolone (**6f**) could be detected by NMR spectroscopy and significant amounts of 4-dimethylaminobenzaldehyde, derived from a retro-Claisen-Schmidt condensation, were formed. High yields were also obtained in the presence of the electron-withdrawing halides (**6g-i**) and carbomethoxy (**6j**) groups, although the presence of a cyano group (**6k**) gave slightly less desirable results. Lower yields are anyhow often obtained in this kind of cyclization reaction when a cyano group is present. The yield was low in the presence of a second nitro group (**6l**), but the quinolone could anyway be isolated (see later for the explanation). Despite the steric hindrance that a fused polyaromatic ring causes (**6m**), it was nevertheless possible to get the corresponding quinolone. Most significantly, both the highly oxidizable pyrrole and furan rings (**6n-o**) were tolerated. It should be noted that this would not be the case for several of the reported quinolone synthesis, which require the presence of an oxidant.[170,178,187] Finally, both electron-donating (**6p-q**) and electron-withdrawing (**6r**) substituents on the aryl ring bearing the nitro group can be present.

Generally, yields compared very favorably with those previously obtained by the use of $Ru_3(CO)_{12}$/Ar-BIAN [71] or by the use of a palladium salt without any ligand.[200] However, in our case, there is no need to employ a pressurized CO line and an autoclave. It should be emphasized that in the case of the Ru-catalyst, the main byproduct was the corresponding dihydroquinolone, derived from the Michael addition of an intermediately formed aniline to the conjugated C=C double bond. In fact, the $Ru_3(CO)_{12}$/Ar-BIAN couple is known to be an excellent catalytic system for the reduction of nitroarenes to anilines by CO/H_2O [188] and water is present in trace amounts in CO by necessity as an impurity. Fortunately, Pd-catalysts are less prone to this secondary reaction.

To fully exploit the potentialities of our synthetic protocol, a large-scale synthesis of **6d** (~14-fold increase and only ~10-fold increase in the solvent amount) was also performed to give the product in 90% yield (only 3% loss compared to the standard conditions yield). Gratifyingly, we were able to isolate the product by simple evaporation of the solvent and crystallization without the need of any chromatographic purification (**Scheme 21**).

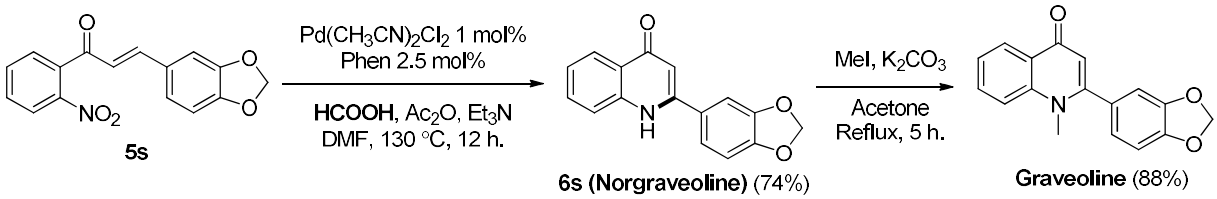


Scheme 21. Large-scale synthesis of 2-(4-methoxyphenyl)quinolin-4(1*H*)-one **6d**.

2.3. Graveoline synthesis

The alkaloid known as graveoline can be isolated from the *Ruta graveolens L*. plant, however the purification process is difficult and only small amounts of the pure substance can be recovered.[201,202] As illustrated earlier graveoline has been shown to display different pharmacological properties,[203] being an apoptosis and autophagy inducer in skin melanoma cancer cells.[204] Furthermore, it could be employed as a platform molecule for the synthesis of more elaborate compounds.[205]

Our synthetic approach could be successfully applied to the synthesis of Graveoline, through methylation of the initially formed Norgraveoline (**6s**). Both the cyclization and the methylation steps occur in high yields (**Scheme 22**) compared to the classical isolation method from ethanolic extract of *Ruta graveolens* (3-5%).[204,206]



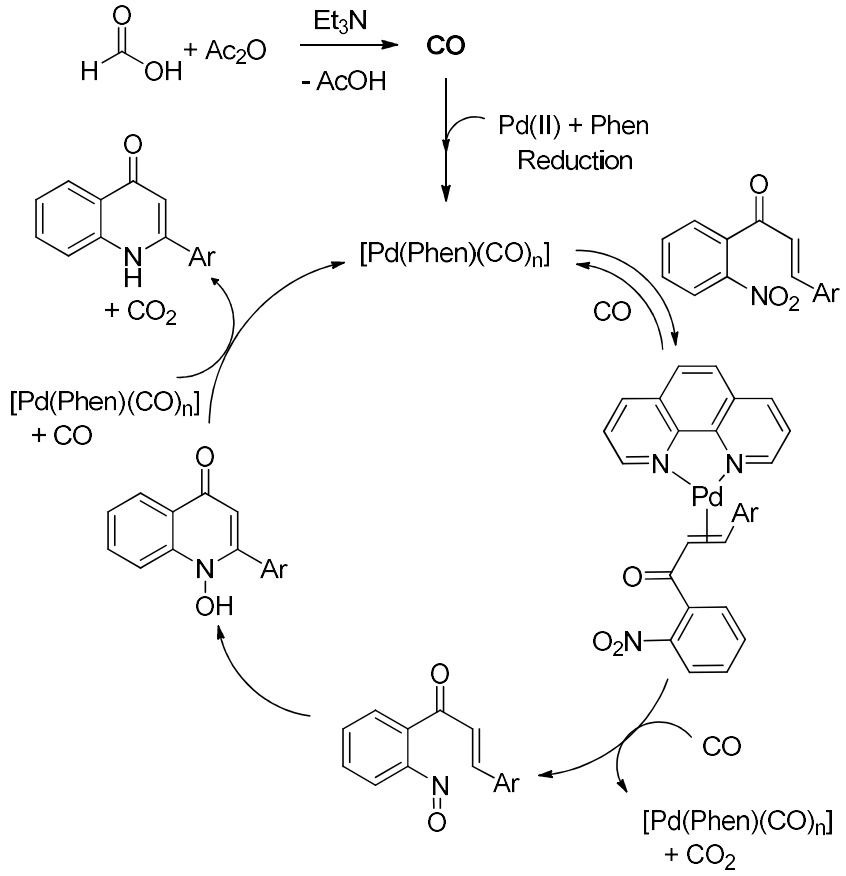
Scheme 22. Synthesis of graveoline alkaloid.

2.4. Reaction mechanism

Based on some information that comes from a few observations and previous data, we were able to propose the reaction mechanism shown in **Scheme 23**.

It is well assessed that the activation of nitroarenes by transition metal complexes occurs by an electron transfer from the metal complex to the nitroarene and this step requires the metal to be in a low oxidation state.[94-98,100,101,103] Due to the air sensitivity of zerovalent Pd-complexes, Pd(II) pre-catalysts are typically employed, but their reduction in the presence of CO is fast. The identity of the obtained zerovalent complex may depend on the reagents of the reaction. In the case of the reductive cyclization of *o*-nitrostyrenes to indoles, we proposed that in the formed complex the C=C double bond of the nitrostyrene coordinates to palladium. The rationale for this proposal was that the reaction of 2,4-dinitrostilbene afforded 2-phenyl-6-nitroindole in high yield even though the nitro group in the *para* position should be more easily accessible than that in the *ortho* one. Coordination of the C=C double bond would place the latter in a closer position to the metal and

justify the observed selectivity. In the present case, an analogous situation occurs in substrate **5l**, where the second and more accessible nitro group is on the dangling aryl ring. The observed selectivity in nitro quinolone is not as high as in the case of the indole synthesis, but still the product was obtained, suggesting that even in this case the C=C double bond is coordinated to the metal. The lower selectivity observed may be owing to the fact that the carbonyl group in **5l** increases the distance between palladium and the nitro group in the complex with respect to what occurs with *o*-nitrostyrenes, decreasing the tendency for the *ortho*-nitro group to react.
Nitrosoarene is produced by deoxygenating the nitro group. Such kind of compound is known to react quickly with olefinic groups present in the same molecule and the previously reported isolation of *N*-hydroxy-quinolones when a Pd-catalyst is employed in the absence of any ligand [200] strongly supports the idea that cyclization occurs at this stage.



Scheme 23. Proposed reaction mechanism of 2'-nitrochalcones reductive cyclization.

Another possibility is that the reduction of the nitro group proceeds up to the stage of the amino group. The so formed aminochalcone would afford a dihydroquinolone by Michael addition and the latter would be oxidized to a quinolone by a second molecule of nitrochalcone. However, this possibility has been tested several years ago by running a competition experiment in which a 2'-nitrochalcone and a 2'-aminochalcone bearing different substituents on the aryl ring were reacted

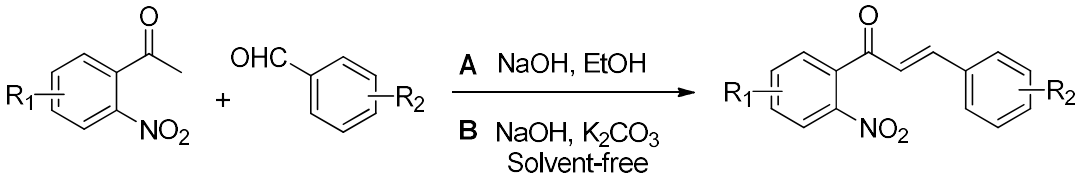
at the same time in the presence of a Pd-catalyst and under pressurized CO. Only the quinolone derived from the nitrochalcone was observed at the end of the reaction, with the aminochalcone being recovered unreacted.[134] It is improbable that a wholly distinct mechanism is occurring in the two situations, despite the fact that the experimental conditions of that experiment were different from those used in the current work, and the intermediate creation of anilines can thus be discounted.

In the final reaction stage, the *N*-hydroxyquinolone is deoxygenated by CO. Such a reaction has been shown to be catalyzed by the same complexes able to reduce nitroarenes in several cases [21,207] and should proceed easily in the present system.

It is also important to note that although imido complexes are still frequently hypothesized as intermediates in nitroarenes cyclization reactions, no sound experimental evidence has ever been gained for their involvement and that they are claimed as such is questionable.[21] Therefore, we did not take this into account in this case.

3. Synthesis of the starting 2'-nitrochalcones

The most general method of obtaining 2'-nitrochalcones is by Claisen−Schmidt condensation between substituted 2-nitroacetophenones and substituted benzaldehydes in the presence of conventional homogeneous bases, such as aqueous or alcoholic alkali metal hydroxide solutions.[208-210] However, we were able to use this strategy to synthesize 2'-nitrochalcones **5** either employing ethanol as the solvent [209] or using a solvent-free Claisen−Schmidt technique [23,149] (**Scheme 24**).



Scheme 24. Synthesis of 2'-nitrochalcones **5** using Claisen−Schmidt condensation.

4. Conclusion

Despite the fact that there are numerous methods for synthesizing 4-quinolones, the majority of them have difficulties when an aryl ring is introduced at position 2. In the present work, we have introduced a new protocol for the synthesis of 2-aryl-4-quinolones that, despite employing CO as a reducing agent, can be performed without employing any gaseous reagent. Considering what was discussed in the synthesis of indoles, cheap formic acid activated by acetic anhydride is employed as a CO surrogate and the reaction can be performed in an economical pressure tube, easily available in different dimensions from a few milliliters to about 1 liter. The only stoichiometric byproducts are CO_2 and acetic acid, both of which are easily separable from the other products of the reaction. The reaction tolerated different types of substituents and the isolated yields are higher than those previously obtained using pressurized CO, demonstrating the efficiency of formic acid as a CO surrogate in this kind of reaction.

5. Experimental Section

5.1. General information

Unless otherwise stated, all the reactions were carried out under dinitrogen atmosphere using standard Schlenk apparatus. All glassware and magnetic stirring bars were kept in an oven at 120 °C for at least two hours and let to cool under vacuum before use. All the solvents (either for catalytic reactions or for NMR) in this work have been treated, dried and/or distilled according to what was described in (Chapter I). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance DRX 400 or Avance NEO 400. Chemical shifts are reported in ppm relative to tetramethylsilane. Elemental analyses were performed on a Perkin Elmer 2400 CHN elemental analyzer. Thin-layer chromatography (TLC) was performed using precoated silica gel 60 F254 MACHEREY-NAGEL plates. TLC plates were visualized by exposing UV light. Flash column chromatography was performed on MACHEREY-NAGEL flash silica gel 0.04-0.063 mm size. HPLC analyses were performed using a HP 1050 chromatograph with a variable wavelength UV-VIS detector equipped with a LiChroCART 125-4 Purospher RP-18 end-capped (5 µm) column using isocratic elution (MeOH:H_2O 6:4 + 0.1 % formic acid). For a standard analysis, benzophenone was added to the reaction mixture in the pressure tube, after the reaction, and MeOH (5 mL) was added to ensure complete solubilization. After sonicating the mixture for 5 minutes, the opportune amount of the sample was taken and added to a 10 mL measuring flask containing the eluent used for the analysis (conc. 0.02 mg/mL calculated with respect to benzophenone used as the internal standard). Palladium precursors used in the present work have been prepared as the procedures reported in the literature [151,152] and as described in (Chapter I).

5.2. General procedure for the catalytic reactions

To avoid weighing errors, stock solutions of Pd catalyst and Phen were separately prepared under dinitrogen in the reaction solvent. For a typical catalytic reaction, a pressure tube equipped with a magnetic stirring bar (**Fig. 4**, chapter I) was charged with 2'-nitrochalcone derivative (0.5 mmol). The tube was placed in a large mouth Schlenk tube and evacuated and filled with dinitrogen three times. The appropriate volumes of stock solutions of the catalysts and Phen were added, and the mixture stirred for 10 minutes to allow the formation of the Pd/Phen complex. Subsequently, Et_3N (1.5 mmol) and acetic anhydride (1.5 mmol) were added with stirring by means of a micropipette. The stirring was then stopped, and the remaining amount of solvent (10 mL total volume) was layered carefully. Finally, formic acid (1.5 mmol) was added, and the pressure tube was sealed under dinitrogen. It is important to note that the order of addition of the reagents and solvent layering are critical to avoid loss of the formed CO. Indeed, as soon as HCO_2H, Ac_2O and the base are mixed, CO starts to evolve even at room temperature. The pressure tube was then placed and heated while stirring in an aluminum block preheated at 130 °C. At the end of the reaction, the pressure tube was removed from the aluminum block, let to cool to room temperature and slowly opened under a fume hood. For the optimization study, the internal standard was added, and the reaction mixture analyzed by HPLC. For the substrate scope study, the reaction mixture was transferred to a one-neck round bottom flask in the air, the possibly formed solid was taken up from the pressure tube with CH_2Cl_2 and the volatiles were evaporated under reduced pressure at

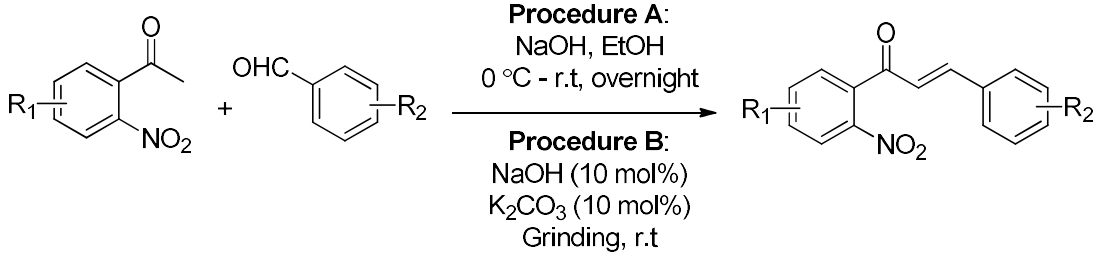
ca. 50 °C. The crude was subjected to silica-gel column chromatography using gradient elution from CH_2Cl_2 to CH_2Cl_2 + 4% MeOH, unless otherwise stated.

5.3. Procedure for the large-scale synthesis of 4-quinolone (6d)

A large-scale reaction was carried out in a 250 mL heavy-walled glass pressure bottle (**Fig. 4**, chapter I) to prepare **6d** under the optimal conditions. The reaction was scaled up increasing the substrate amount 14-fold with respect to the standard conditions. The pressure bottle was charged with solid reagents, substrate **5d** (2.00 g, 7.06 mmol), $Pd(CH_3CN)_2Cl_2$ (1 mol%) and phenanthroline (5 mol%), and then placed in a Schlenk tube with a large mouth. The tube was evacuated and filled three times with dinitrogen. DMF (30 mL), triethylamine (3.0 mL, 21 mmol) and acetic anhydride (2.0 mL, 21 mmol) were added, and the mixture was stirred for 10 minutes. The stirring was stopped, and the remaining solvent amount (DMF, 70 mL) was layered. Finally, formic acid (0.80 mL, 21 mmol) was added, and the bottle was sealed with the screw-cap. The total amount of solvent was increased only 10-fold instead of 14-fold to facilitate the subsequent workup. Metallic palladium precipitated on the bottle walls at the end of the reaction. Subsequently, the solution was filtered on a short pad of Celite in a Pasteur pipette using the cannula technique to get rid of any potential colloidal palladium particles. The solvent was evaporated, and the crude recrystallized from methanol/CH_2Cl_2 75:15 (80 mL). The product was collected by suction filtration on a Buchner funnel and dried under vacuum for several hours to give **6d** as an analytically pure white solid.

5.4. Preparation of 2'-nitrochalcones

2'-Nitrochalcones were synthesized following the modified procedures herein reported.



General Procedure A

The synthesis was performed following the procedure reported in the literature.[209]

Under nitrogen atmosphere, a 2-nitroacetophenone derivative (3 mmol) was dissolved in ethanol (5 mL), then a solution of sodium hydroxide (3 mmol) in ethanol (5 mL) was added dropwise at 0 °C. Subsequently a solution of the benzaldehyde derivative (3 mmol) in ethanol (5 mL) was added to the reaction mixture over 30 minutes at 0 °C. The reaction was stirred at room temperature overnight to allow the precipitation of the desired product. The product was recovered by filtration and washed with cold ethanol and hexane.

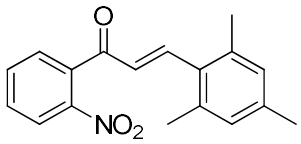
General Procedure B

The synthesis was performed following the procedure reported in the literature.[23,149]

In a dry mortar, benzaldehyde derivative (3 mmol) was grinded with potassium carbonate (0.3 mmol) and sodium hydroxide (0.3 mmol). 2-Nitroacetophenone derivative (3 mmol) was added dropwise at room temperature. After reaction completion (followed by TLC), water (15 mL) and ethyl acetate (15 mL) were added, and the mixture transferred to a separating funnel. The organic layer was separated, and the aqueous phase extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with water (3×50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and the organic solvent removed under reduced pressure to afford the crude product. The crude was recrystallized from methanol or purified by column chromatography to give the final product.

2'-Nitrochalcones **5a**, **b**, **d**, **f-i**, **s** were prepared according to general procedure **A** and their NMR analysis were in accordance to those previously reported in the literature.[211] **5k** was prepared following the general procedure **B** and its analytical data are in accordance to those previously reported in the literature.[208] The analysis for the other starting compounds are reported below.

(*E*)-3-mesityl-1-(2-nitrophenyl)prop-2-en-1-one (5c)



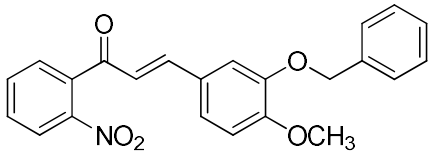
Prepared according to general procedure **A**. Obtained as a yellow solid (354 mg, 1.2 mmol, 40% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.77 (td, *J* = 7.5, 1.1 Hz, 1H), 7.65 (td, *J* = 8.2, 1.4 Hz, 1H), 7.54 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.38 (d, *J* = 16.6 Hz, 1H), 6.88 (s, 2H), 6.62 (d, *J* = 16.6 Hz, 1H), 2.27 (d, *J* = 4.0 Hz, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 146.9, 145.2, 139.2, 137.0, 136.4, 134.2, 131.6, 130.7, 130.5, 129.4, 128.9, 124.6, 21.2, 21.1 ppm.

Elemental Analysis calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74, found: C, 72.97; H, 5.96; N, 4.68.

(*E*)-3-(3-(benzyloxy)-4-methoxyphenyl)-1-(2-nitrophenyl)prop-2-en-1-one (5e)



Prepared according to general procedure **A**. Obtained as a yellow solid (1.1 g, 2.7 mmol, 91% yield).

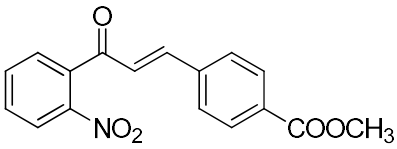
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.2 Hz, 1H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.33 (d, *J* =

7.2 Hz, 1H), 7.15 (d, *J* = 16.2 Hz, 1H), 7.11 – 7.03 (m, 2H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.80 (d, *J* = 16.1 Hz, 1H), 5.15 (s, 2H), 3.91 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 152.7, 148.6, 146.9, 146.6, 136.7, 134.1, 130.5, 129.0, 128.8, 128.2, 127.5, 127.0, 124.7, 124.3, 124.1, 112.9, 111.7, 71.3, 56.2 ppm.

Elemental Analysis calcd for $C_{23}H_{19}NO_5$: C, 70.94; H, 4.92; N, 3.60, found: C, 71.07; H, 4.94; N, 3.65.

(*E*)-methyl 4-(3-(2-nitrophenyl)-3-oxoprop-1-en-1-yl)benzoate (5j)



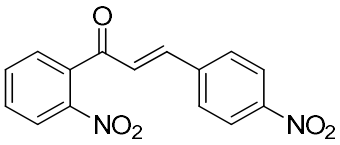
Prepared according to general procedure **B**. Obtained as a white solid (635 mg, 2 mmol, 68% yield) after purification by column chromatography (hexane:AcOEt = 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 7.1 Hz, 2H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.67 (t, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 7.4 Hz, 1H), 7.27 (d, *J* = 16.3 Hz, 1H, overlapped with $CDCl_3$), 7.05 (d, *J* = 16.3 Hz, 1H), 3.92 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 166.4, 146.8, 144.4, 138.3, 136.3, 134.3, 132.1, 130.9, 130.3, 128.9, 128.5, 128.3, 124.7, 52.5 ppm.

Elemental Analysis calcd for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.21; N, 4.50, found: C, 65.58; H, 4.35; N, 4.51.

(*E*)-1-(2-nitrophenyl)-3-(4-nitrophenyl)prop-2-en-1-one (5l)



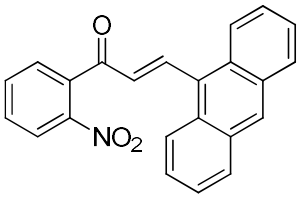
Prepared according to general procedure **B**. Obtained as a yellow solid (376 mg, 1.3 mmol, 42% yield) after purification by column chromatography (hexane:AcOEt = 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 - 8.12 (m, 3H), 7.80 (td, *J* = 7.5, 1.0 Hz, 1H), 7.70 (td, *J* = 8.0, 1.4 Hz 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.52 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.31 (d, *J* = 16.3 Hz, 1H), 7.08 (d, *J* = 16.3 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 148.9, 146.8, 142.3, 140.2, 136.0, 134.5, 131.2, 129.7, 129.2, 128.9, 124.8, 124.3 ppm.

Elemental Analysis calcd for $C_{15}H_{10}N_2O_5$: C, 60.41; H, 3.38; N, 9.39, found: C, 60.32; H, 3.53; N, 9.66.

(*E*)-3-(anthracen-9-yl)-1-(2-nitrophenyl)prop-2-en-1-one (5m)



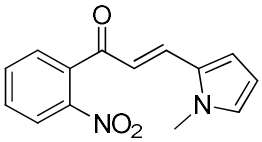
Prepared according to general procedure **B**. Obtained as a yellow solid (954 mg, 2.7 mmol, 90% yield) after recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 6.5 Hz, 1H), 8.26 (s, 1H), 8.23 (d, *J* = 8.8 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 2H), 8.00 (d, *J* = 8.1 Hz, 2H), 7.85 (t, *J* = 7.5 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 2H), 7.58 – 7.43 (m, 4H), 6.99 (d, *J* = 16.5 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 147.0, 143.4, 136.6, 135.3, 134.5, 131.0, 129.5, 129.1, 129.06, 129.0, 128.7, 126.9, 125.6, 125.0, 124.8 ppm.

Elemental Analysis calcd for $C_{23}H_{15}NO_3$: C, 78.17; H, 4.28; N, 3.96, found: C, 78.56; H, 4.19; N, 4.09.

(*E*)-3-(1-methyl-1*H*-pyrrol-2-yl)-1-(2-nitrophenyl)prop-2-en-1-one (5n)



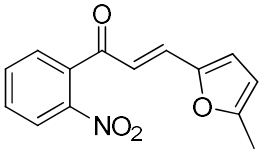
Prepared according to general procedure **A**. Obtained as a yellow solid (338 mg, 1.3 mmol, 44% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.72 (td, *J* = 7.5, 1.1 Hz, 1H), 7.60 (td, *J* = 8.0, 1.4 Hz, 1H), 7.51 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.36 (d, *J* = 15.7 Hz, 1H), 6.84 – 6.78 (m, 1H), 6.75 – 6.72 (m, 1H), 6.71 (d, *J* = 15.6 Hz, 1H), 6.19 (dd, *J* = 3.8, 2.7 Hz, 1H), 3.65 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 147.2, 137.1, 133.8, 133.7, 130.5, 129.4, 129.0, 128.9, 124.5, 119.9, 114.4, 110.3, 34.6 ppm.

Elemental Analysis calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93, found: C, 65.58; H, 4.83; N, 11.12.

(*E*)-3-(5-methylfuran-2-yl)-1-(2-nitrophenyl)prop-2-en-1-one (5o)



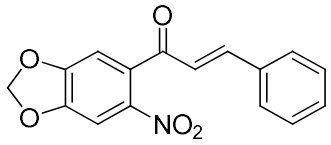
Prepared according to general procedure **A**. Obtained as a white solid (509 mg, 2 mmol, 66% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.07 (m, 1H), 7.72 (tdd, *J* = 7.5, 2.2, 1.2 Hz, 1H), 7.63 – 7.60 (m, 1H), 7.54 – 7.44 (m, 1H), 7.01 (dd, *J* = 15.8, 3.0 Hz, 1H), 6.79 (dd, *J* = 15.8, 2.7 Hz, 1H), 6.60 – 6.54 (m, 1H), 6.11 – 6.10 (m, 1H), 2.34 (d, *J* = 3.0 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 157.0, 149.3, 146.9, 136.8, 134.0, 132.2, 130.5, 128.9, 124.6, 121.6, 119.2, 109.7, 14.1 ppm.

Elemental Analysis calcd for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44, found: C, 65.25; H, 4.70; N, 5.09.

(*E*)-1-(6-nitrobenzo[d][1,3]dioxol-5-yl)-3-phenylprop-2-en-1-one (5p)



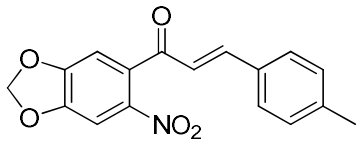
Prepared according to general procedure **A**. Obtained as a white solid (803 mg, 2.7 mmol, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 2.1 Hz, 1H), 7.54 – 7.44 (m, 2H), 7.40-7.36 (m, 3H), 7.24 (d, *J* = 17.2 Hz, 1H, overlapped with $CDCl_3$), 6.93 (d, *J* = 16.2 Hz, 1H), 6.83 (s, 1H), 6.21 (s, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 152.7, 149.1, 145.8, 141.4, 134.1, 133.2, 131.1, 129.1, 128.6, 126.5, 107.8, 105.2, 103.8 ppm.

Elemental Analysis calcd for $C_{16}H_{11}NO_5$: C, 64.65; H, 3.73; N, 4.71, found: C, 64.88; H, 3.95; N, 4.52.

(*E*)-1-(6-nitrobenzo[d][1,3]dioxol-5-yl)-3-(p-tolyl)prop-2-en-1-one (5q)



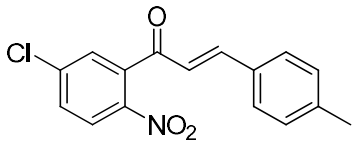
Prepared according to general procedure **A**. Obtained as a yellow solid (672 mg, 2.2 mmol, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.38 (d, *J* = 7.6 Hz, 2H), 7.25-7.17 (m, 3H), 6.89 (d, *J* = 16.2 Hz, 1H), 6.82 (s, 1H), 6.20 (s, 2H), 2.37 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 152.6, 149.0, 146.0, 141.8, 141.3, 133.4, 131.4, 129.9, 128.7, 125.5, 107.8, 105.2, 103.7, 21.7 ppm.

Elemental Analysis calcd for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.21; N, 4.50, found: C, 65.83; H, 4.56; N, 4.39.

(*E*)-1-(5-chloro-2-nitrophenyl)-3-(*p*-tolyl)prop-2-en-1-one (5r)



Prepared according to general procedure **A**. Obtained as a white solid (498 mg, 1.7 mmol, 55% yield).

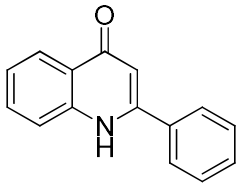
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.8 Hz, 1H), 7.59 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.45 (d, *J* = 2.2 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.24 – 7.17 (m, 3H), 6.94 (d, *J* = 16.2 Hz, 1H), 2.37 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 147.2, 145.0, 142.2, 141.0, 138.2, 131.2, 130.6, 129.9, 129.0, 128.8, 126.2, 124.9, 21.7 ppm.

Elemental Analysis calcd for $C_{16}H_{12}ClNO_3$: C, 63.69; H, 4.01; N, 4.64, found: C, 63.92; H, 3.91; N, 4.78.

5.5. Characterization data for 4-quinolones (6a-e) and (6g-r)

2-Phenylquinolin-4(1*H*)-one (6a).[212]

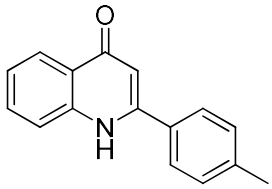


Obtained as a white solid (103 mg, 0.47 mmol, 93 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.87 – 7.80 (m, 2H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.61 – 7.57 (m, 3H), 7.34 (t, *J* = 7.5 Hz, 1H), 6.33 (s, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 176.9, 150.0, 140.5, 134.2, 131.8, 130.4, 129.0, 127.4, 124.9, 124.7, 123.2, 118.7, 107.3 ppm.

2-(4-Methylphenyl)quinolin-4(1*H*)-one (6b).[213]

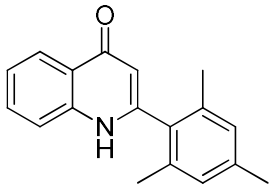


Obtained as a pale orange solid (106 mg, 0.45 mmol, 90% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.63 (s, 1H), 8.10 (dd, J = 8.1, 1.2 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.66 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 6.32 (s, 1H), 2.40 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 176.9, 149.9, 140.5, 140.3, 131.7, 131.3, 129.5, 127.2, 124.8, 124.7, 123.1, 118.7, 106.9, 20.9 ppm.

2-(2,4,6-trimethylphenyl)quinolin-4(1*H*)-one (6c).



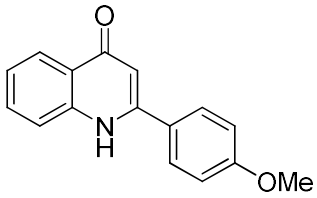
Obtained as a white solid (74 mg, 0.30 mmol, 56%yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.74 (s, 1H), 8.23 – 8.04 (m, 1H), 7.64 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.38 – 7.29 (m, 1H), 7.02 (s, 2H), 2.30 (s, 3H), 2.13 (s, 6H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 176.7, 149.8, 140.4, 138.4, 135.6, 132.1, 131.6, 128.1, 124.85, 124.81, 123.1, 118.3, 109.6, 20.6, 19.3 ppm.

Elemental Analysis calcd for $C_{18}H_{17}NO$: C, 81.10; H, 6.51; N, 5.32, found: C, 80.75; H, 6.73; N, 5.10.

2-(4-Methoxyphenyl)quinolin-4(1*H*)-one (6d).[213]

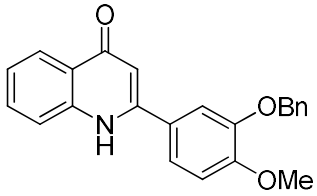


Obtained as an off-white solid (117 mg, 0.47 mmol, 93% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.62 (s, 1H), 8.10 (d, J = 7.7 Hz, 1H), 7.87 – 7.75 (m, 3H), 7.65 (t, J = 7.2 Hz, 1H), 7.32 (t, J = 7.0 Hz, 1H), 7.12 (d, J = 8.1 Hz, 2H), 6.32 (s, 1H), 3.84 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 176.8, 161.0, 149.7, 140.5, 131.6, 128.8, 126.2, 124.8, 124.7, 123.1, 118.6, 114.4, 106.5, 55.4 ppm.

2-(3-Benzyloxy-4-methoxy-phenyl)quinolin-4(1*H*)-one (6e).



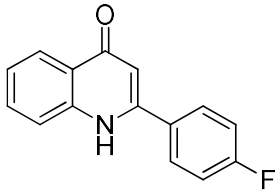
Obtained as a pale pink solid (109 mg, 0.30 mmol, 61% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.59 (s, 1H), 8.10 (dd, J = 8.0, 1.1 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.55 – 7.39 (m, 6H), 7.37 – 7.29 (m, 2H), 7.18 (d, J = 8.5 Hz, 1H), 6.38 (s, 1H), 5.23 (s, 2H), 3.86 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 176.8, 151.1, 149.8, 147.9, 140.5, 136.9, 131.7, 128.5, 127.94, 127.88, 126.4, 124.73, 124.67, 123.2, 120.5, 118.7, 112.6, 112.1, 106.6, 70.2, 55.8 ppm.

Elemental Analysis calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.36, found: C, 77.02; H, 5.08; N, 2.97.

2-(4-Fluorophenyl)quinolin-4(1*H*)-one (6g).[213]

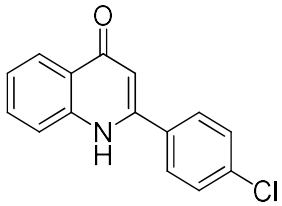


Obtained as a golden-yellow solid (97 mg, 0.41 mmol, 81% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.10 (ddd, J = 8.1, 1.5, 0.5 Hz, 1H), 7.91 (dd, J = 8.7, 5.6 Hz, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.67 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.34 (ddd, J = 8.1, 7.0, 1.3 Hz, 1H), 6.33 (br, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 176.9, 163.4 (d $^{1}J_{C\text{-}F}$, 248.0 Hz), 149.0, 140.5, 131.8, 129.9 (d $^{3}J_{C\text{-}F}$, 8.7 Hz), 124.7, 123.3, 118.7, 116.0 (d $^{2}J_{C\text{-}F}$, 21.8 Hz), 107.4 ppm.

2-(4-Chlorophenyl)quinolin-4(1*H*)-one (6h).[214]

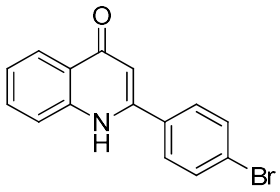


Obtained as an off-white solid (106 mg, 0.41 mmol, 83% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.72 (s, 1H), 8.10 (d, J = 7.9 Hz, 1H), 7.87 (d, J = 8.2 Hz, 2H), 7.80 – 7.62 (m, 4H), 7.34 (t, J = 7.3 Hz, 1H), 6.35 (s, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 176.9, 148.8, 140.5, 135.2, 131.9, 129.3, 129.0, 124.7, 123.4, 118.8, 107.5 ppm.

2-(4-Bromophenyl)quinolin-4(1*H*)-one (6i).[215]

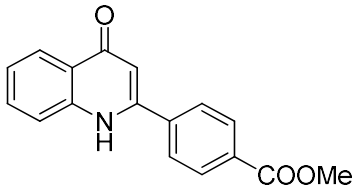


Obtained as a pink solid (109 mg, 0.36 mmol, 73% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.72 (s, 1H), 8.10 (d, J = 7.5 Hz, 1H), 7.80 (s, 4H), 7.75 (d, J = 8.3 Hz, 1H), 7.69 (dd, J = 11.0, 4.1 Hz, 1H), 7.35 (t, J = 7.4 Hz, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 177.0, 148.9, 140.5, 133.3, 131.9, 129.5, 124.9, 124.7, 124.0, 123.4, 118.7, 107.5 ppm.

2-(4-Carbomethoxyphenyl)quinolin-4(1*H*)-one (6j).[216]

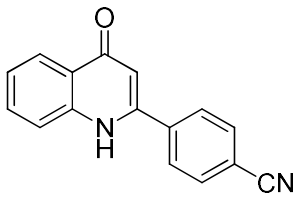


Obtained as a pink solid (116 mg, 0.42 mmol, 83% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.85 (s, 1H), 8.18 – 8.08 (m, 2H), 8.00 (d, J = 7.8 Hz, 2H), 7.79 (d, J = 8.3 Hz, 1H), 7.70 (t, J = 7.1 Hz, 1H), 7.36 (t, J = 7.4 Hz, 1H), 6.41 (s, 1H), 3.92 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 176.9, 165.7, 148.7, 140.5, 138.5, 132.0, 131.1, 129.6, 127.9, 124.9, 124.7, 123.4, 118.8, 108.0, 52.4 ppm.

2-(4-Cyanophenyl)quinolin-4(1*H*)-one (6k).[217]

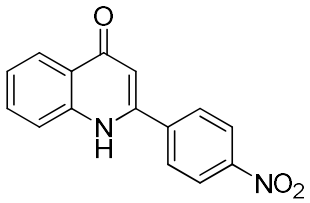


Obtained as a light orange solid (68 mg, 0.28 mmol, 55% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 8.12 (d, J = 7.9 Hz, 1H), 8.09 – 8.02 (m, 4H), 7.77 (d, J = 8.3 Hz, 1H), 7.70 (t, J = 7.2 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H), 6.45 (s, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 132.8, 132.0, 128.4, 124.6, 123.6, 118.4, 112.8 ppm. Due to the low solubility of the compound in DMSO-d_6, no quaternary carbon was detected.

2-(4-Nitrophenyl)quinolin-4(1*H*)-one (6l).[218]

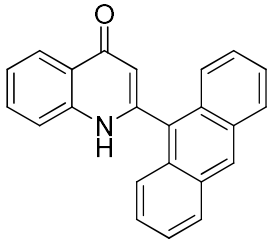


Obtained as a red solid (14 mg, 0.05 mmol, 11% yield) after purification by column chromatography using hexane:AcOEt (70:30).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.27 (d, J = 8.7 Hz, 2H), 8.01 (dd, J = 49.0, 8.6 Hz, 2H), 7.62 (d, J = 7.6 Hz, 1H), 7.54 (dt, J = 14.2, 6.8 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 6.98 (t, J = 7.4 Hz, 1H), 6.67 (s, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 186.6, 154.3, 146.0, 141.3, 137.0, 136.3, 130.4, 124.5, 123.9, 120.5, 119.7, 112.7, 106.1 ppm.

2-(Anthracen-9-yl)quinolin-4(1*H*)-one (6m).[217]

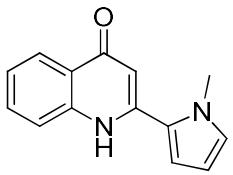


Obtained as a tan solid (50 mg, 0.16 mmol, 31%yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (s, 1H), 8.84 (s, 1H), 8.28 (dd, J = 8.1, 1.2 Hz, 1H), 8.24 – 8.19 (m, 2H), 7.80 (d, J = 8.3 Hz, 2H), 7.72 (ddd, J = 8.4, 7.1, 1.5 Hz, 1H), 7.64 – 7.52 (m, 5H), 7.47 – 7.41 (m, 1H), 6.20 (s, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 176.7, 147.9, 140.7, 132.0, 130.6, 129.1, 128.73, 128.74 128.64, 128.57, 127.2, 125.7, 125.3, 125.0, 123.5, 118.5, 112.1 ppm.

2-(1-Methyl-1*H*-pyrrol-2-yl)quinolin-4(1*H*)-one (6n).



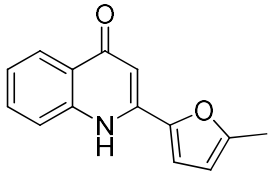
Obtained as a dark solid (70 mg, 0.31 mmol, 62% yield) after purification by column chromatography using hexane:AcOEt (60:40).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.31 (s, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.47 (ddd, *J* = 8.3, 7.3, 1.3 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 7.06 (dd, *J* = 2.3, 1.6 Hz, 1H), 6.96 (ddd, *J* = 3.9, 1.6, 0.6 Hz, 1H), 6.88 (ddd, *J* = 7.6, 7.1, 0.7 Hz, 1H), 6.66 (s, 1H), 6.26 (ddd, *J* = 3.9, 2.6, 0.6 Hz, 1H), 3.74 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 184.8, 152.7, 135.3, 130.9, 127.6, 127.3, 123.6, 120.6, 119.2, 113.7, 112.5, 109.5, 99.8, 33.7 ppm.

Elemental Analysis calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49, found: C, 75.34; H, 5.06; N, 12.67.

2-(5-Methylfuran-2-yl)quinolin-4(1*H*)-one (6o).



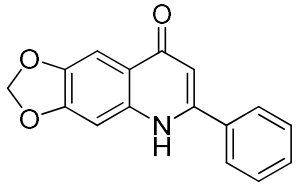
Obtained as an orange solid (40 mg, 0.18 mmol, 35% yield) after purification by column chromatography using hexane:AcOEt (80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.7 Hz, 1H), 7.62 (br, 1H), 7.47 – 7.33 (m, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.94 – 6.84 (m, 1H), 6.60 (s, 1H), 6.53 (d, *J* = 3.3 Hz, 1H), 6.16 – 6.10 (m, 1H), 2.43 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 185.8, 155.1, 152.0, 150.6, 135.8, 132.4, 124.8, 121.5, 120.0, 116.5, 111.5, 109.6, 99.0, 14.4 ppm.

Elemental Analysis calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22, found: C, 74.27; H, 5.11; N, 5.97.

6-Phenyl-[1,3]dioxolo[4,5-*g*]quinolin-8(5*H*)-one (6p).[170]

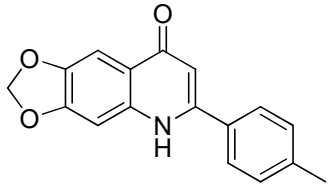


Obtained as a pink solid (105 mg, 0.40 mmol, 79% yield).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.58 (s, 1H), 7.80 (s, 3H), 7.57 (m, 3H), 7.40 (s, 1H), 7.20 (s, 1H), 6.27 (s, 1H), 6.15 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 175.8, 151.1, 148.5, 145.20, 137.4, 134.2, 130.2, 129.0, 127.2, 120.4, 106.5, 101.9, 101.2, 97.2 ppm.

6-(4-Methylphenyl)-[1,3]dioxolo[4,5-*g*]quinolin-8(5*H*)-one (6q).[219]

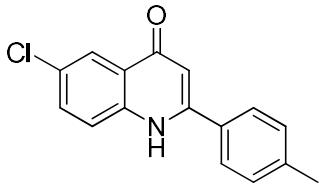


Obtained as a pink solid (126 mg, 0.45 mmol, 90% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (s, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.38 (m, 3H), 7.21 (s, 1H), 6.24 (d, J = 1.8 Hz, 1H), 6.15 (s, 2H), 2.40 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 175.7, 151.0, 148.5, 145.0, 140.1, 137.4, 131.2, 129.5, 127.0, 120.4, 106.2, 101.9, 101.2, 97.2, 20.9 ppm.

6-Chloro-2-(4-methylphenyl)quinolin-4(1*H*)-one (6r).



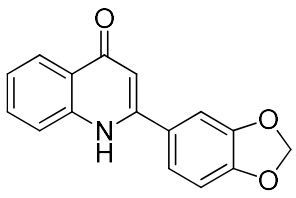
Obtained as a pink solid (95 mg, 0.35 mmol, 70% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.81 (s, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.81 (d, J = 8.9 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.71 (dd, J = 8.9, 2.4 Hz, 1H), 7.40 (d, J = 8.0 Hz, 2H), 6.38 (s, 1H), 2.41 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 150.3, 140.5, 131.8, 131.0, 129.57, 127.8, 127.25, 123.58, 107.00, 20.89 ppm. Due to the low solubility of the compound in DMSO, four quaternary carbons were not detected.

Elemental Analysis calcd for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.48; N, 5.19, found: C, 71.04; H, 4.66; N, 4.93.

2-(Benzo[*d*][1,3]dioxol-5-yl)quinolin-4(1*H*)-one (6s).[214]



Obtained as a white solid (98 mg, 0.37 mmol, 74% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.56 (s, 1H), 8.08 (dd, J = 8.0, 1.0 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.70 – 7.62 (m, 1H), 7.42 (d, J = 1.6 Hz, 1H), 7.37 (dd, J = 8.1, 1.7 Hz, 1H), 7.32 (t, J = 7.3 Hz, 1H), 7.11 (d, J = 8.1 Hz, 1H), 6.30 (s, 1H), 6.14 (s, 2H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 176.9, 149.5, 149.2, 147.9, 140.4, 131.7, 128.0, 124.8, 124.7, 123.1, 121.8, 118.6, 108.7, 107.6, 106.8, 101.8 ppm.

5.6. Synthesis of graveoline from (6s)

Norgraveoline **6s** was prepared and isolated according to the general catalytic procedure described above. In an oven dried Schlenk flask, **6s** (50 mg, 0.19 mmol), potassium carbonate (52 mg, 0.38) and methyl iodide (40 mg, 0.28 mmol) were dissolved in acetone (5 mL) and refluxed for 5 h. After reaction completion, acetone was removed by rotary evaporation and the crude was purified by filtration over silica-gel using hexane:AcOEt (1:9) as the eluent to afford the final product as yellow crystals (46.5 mg, 0.17 mmol, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, J = 8.3, 1.0 Hz, 1H), 8.06 (d, J = 8.2 Hz, 1H), 7.74 – 7.66 (m, 2H), 7.62 (dd, J = 8.1, 1.8 Hz, 1H), 7.46 (ddd, J = 8.2, 6.9, 1.1 Hz, 1H), 7.10 (s, 1H), 6.94 (d, J = 8.1 Hz, 1H), 6.04 (s, 2H), 4.11 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 158.38, 149.3, 148. 9, 148.4, 135.0, 130.1, 129.2, 125.3, 121.8, 121.8, 120.4, 108.5, 108.2, 101.5, 97.7, 55.8 ppm.

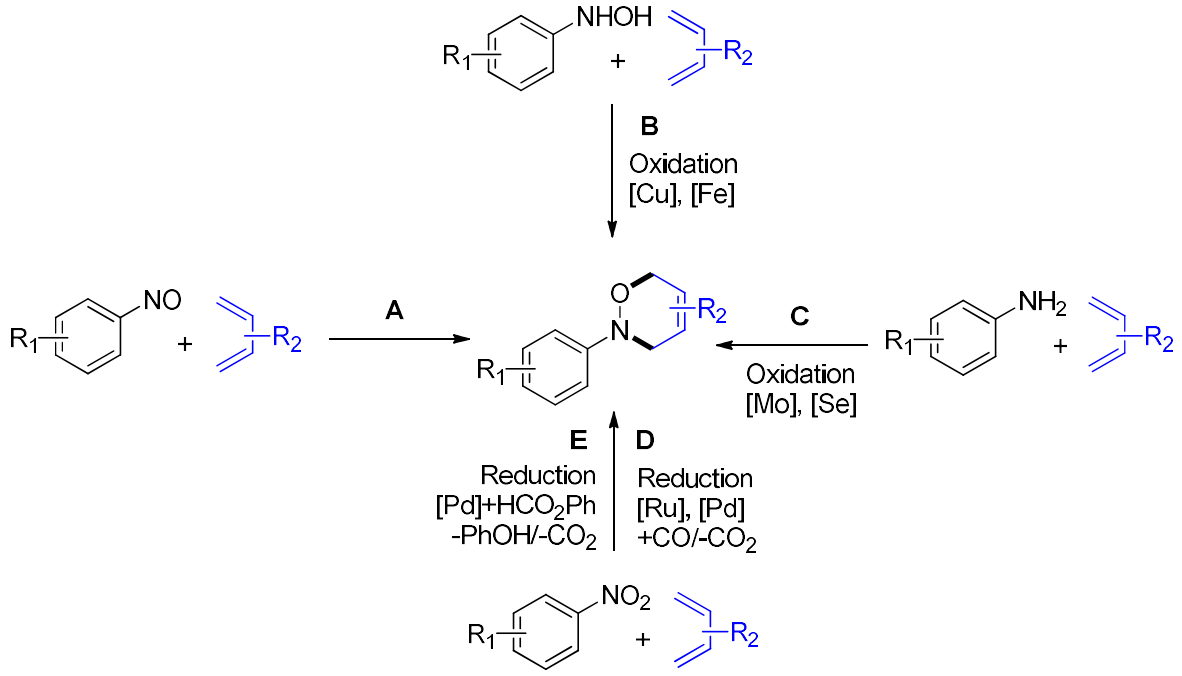
Elemental Analysis calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02, found: C, 73.16; H, 4.57; N, 5.14.

Chapter III:

Synthesis of 1,2-Oxazines and *N*-Arylpyrroles by Reductive Cyclization of Nitroarenes in Presence of Dienes Using Formic Acid as a CO-surrogate.

1. Introduction

Heterocyclic compounds belonging to the oxazines family are structural motifs present in a variety of natural products, life science molecules and, in general, biologically active compounds.[220] Within this family, 1,2-oxazines represent an intriguing class, for both their roles as bioactive molecules [221,222] and synthetic intermediates.[223-229] Among them, 1,2-oxazines bearing an aryl ring on the nitrogen atom are classically prepared by the hetero Diels-Alder [4+2] cycloaddition reaction between a nitrosoarene and a dienes and the field has extensively been reviewed (**Scheme 25**, path A).[220,223,224,230-237] However, this transformation is limited by the reduced availability and relatively low stability of nitroso compounds, which are also are suspected cancer promoters.[238]



Scheme 25. Synthetic approaches for the preparation of the 1,2-oxazine scaffold.

A more convenient alternative is represented by the domino reaction sequence in which a nitrosoarene intermediate is catalytically produced *in-situ* from more stable and easily available starting materials and subsequently trapped by the diene in the cycloaddition reaction. Oxidation

of hydroxylamines (**Scheme 25**, path B) is typically employed to this aim when acylnitroso compounds are desired, but the low stability of *N*-arylhydroxylamines makes this approach less convenient for the latter substrates.[239,240] A more interesting approach involves the use of arylamines and organic or inorganic peroxides (**Scheme 25**, path C).[241-243]

The preparation of 1,2-oxazines from nitroarenes can be a valuable approach because of the wide commercial availability and stability of the substrates (**Scheme 25**, path D). Several years ago, our group reported that both Ru/Ar-BIAN (Ar-BIAN=*bis*(aryl)acenaphthenequinonediimine)[76] and Pd/Phen[227] catalyze this reaction when CO is employed as a reductant for the nitro group. Even if Ru-complexes afforded only moderate yields due to the competitive formation of allylic amines, very good selectivities towards 1,2-oxazines could be obtained by using the Pd/Phen catalyst. However, in both cases, the use of pressurized CO is a drawback as indicated earlier. Recently we were able to obtain the desired 1,2-oxazines using Pd/Phen catalytic system and HCO_2Ph as a CO surrogate by reaction of nitroarenes with conjugated dienes (**Scheme 25**, path E).[25] We have demonstrated in the previous chapters that the stoichiometric byproducts formed as a result of using HCO_2Ph or even other surrogates [86-88,108] could complicate the work-up. To solve this problem, we decided to develop a new strategy based on using HCO_2H as the CO source to catalytically reduce nitroarenes in the presence of conjugated dienes to give oxazines. In addition to avoiding the coproduction of phenol that would have resulted from the use of HCO_2Ph, using HCO_2H activated by Ac_2O also saves a synthetic step and enhances the overall atom economy of the process (see Chapter I).

We have previously mentioned that 1,2-oxazines can be further transformed into other interesting compounds. Among these transformations, the dehydration reaction to give pyrroles has a high potential synthetic interest. Pyrrole is a 5-membered aromatic nitrogen-heterocycle that is ubiquitous in compounds of biological and material significance (**Fig. 6**).

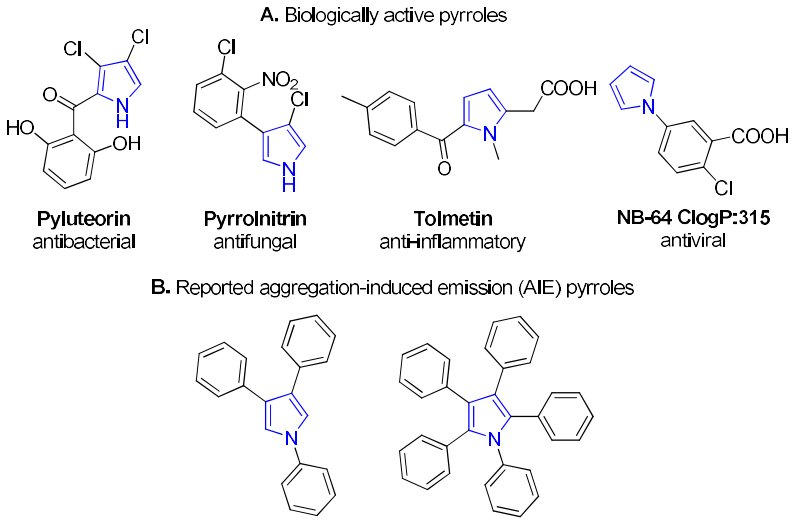
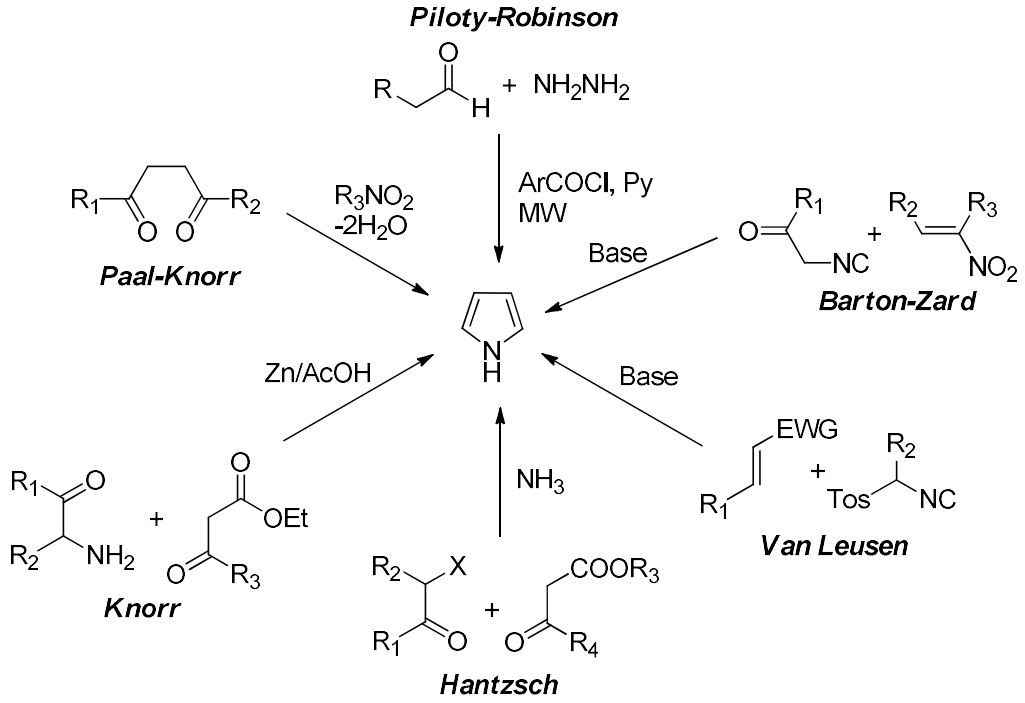


Fig. 6. Examples of useful pyrrole-containing molecules.

For instance, pyrrole is the key structural component in chlorophylls and hemes; both of which are molecules that play a crucial role for the existence of life. Some of the pyrroles have good bioactivity such as antibacterial,[244] antifungal,[245] anti-inflammatory,[246] antiviral,[247] antimalarial,[248] anticancer,[249] antiparasitic,[250] etc., and can also be used as enzyme inhibitor in the organism[251] (**Fig. 6A**). In addition, aryl-substituted pyrroles are important aggregation-induced emission materials (**Fig. 6B**) and have lots of potential applications in biological probes, organic light-emitting diodes and chemical sensors.[252]

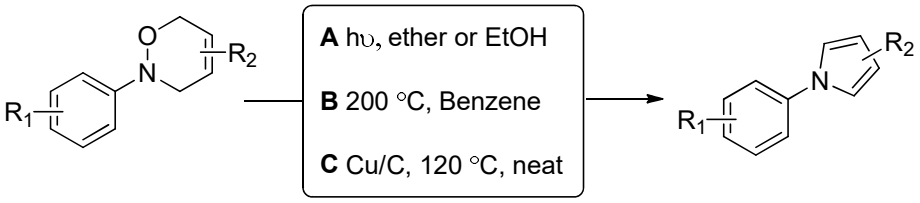
Since pyrroles play an important role in organic synthesis as well as in biology, the synthesis of five-membered heterocyclic pyrrole compounds has always been valued by synthetic chemists. Over the last decades, many methods for synthesizing pyrrole compounds in laboratory routes have been reported,[253,254] and the classical methods include Knorr pyrrole synthesis,[255] Paal-Knorr synthesis,[256] Hantzsch synthesis,[257] Barton-Zard reaction,[258] Van Leusen synthesis,[259] and Piloty–Robinson synthesis[260] (**Scheme 26**).



Scheme 26. Classical cycloaddition reactions for synthesis of pyrroles.

On the other hand, it has long been known that oxazines bearing electron-withdrawing groups on the oxazine ring easily evolve into pyrroles in the presence of bases or acids, but no reaction occurs in the absence of such substituents.[261-263] Photochemical activation of the oxazine apparently works even in the absence of electron-withdrawing groups (**Scheme 27**, path A),[264] but the best reported yield in pyrrole was 61%. Rhodium[228] and ruthenium[265] complexes have been also reported to catalyze the oxazine-pyrrole transformation, but in low yields. In 2003, we have reported that thermal decomposition of *in situ* generated 3,6-dihydro-2*H*-[1,2]-oxazines at 200 °C results in the

formation of *N*-arylpyrroles (**Scheme 27**, path B).[227] However, despite the simplicity of the two steps-one pot procedure, only a fair selectivity in the oxazine-pyrrole conversion was achieved. Moreover, a low-boiling point solvent for this reaction would not be compatible with the use of a glass pressure tube and high boiling point solvents may cause severe product losses due to the volatility of several pyrroles. More recently, Sajiki, Sawama, and co-workers reported that a heterogeneous Cu/C catalyst is effective in catalyzing the conversion of 3,6-dihydro-2*H*-[1,2]-oxazines into pyrroles, but despite the high yields obtained in several cases, the only pyrrole lacking any substituent in both the 2 and 5 positions was obtained in only 35% yield (**Scheme 27**, path C).[229]



Scheme 27. Synthetic pathways for the dehydration of 3,6-dihydro-2*H*-[1,2]-oxazines into *N*-arylpyrroles.

Use of CuCl in methanol afforded pyrroles in a specific system,[266] but only an amino alcohol was obtained in the absence of specific substituents.[267] Thus, it is clear that a general method for the conversion of 3,6-dihydro-2*H*-[1,2]-oxazines into pyrroles is still lacking.

Therefore, in this chapter we will focus on:

1. Describing the use of the HCO_2H/Ac_2O mixture as a cheap, safe, and available CO surrogate in the *inter*-molecular Pd-catalyzed reductive cyclization of nitroarenes in the presence of conjugated dienes, which allows us to get 3,6-dihydro-2*H*-[1,2]-oxazines.
2. Discussing the transformation of the obtained oxazines into the corresponding 2,5-unsubstituted-*N*-arylpyrroles which are difficult to produce employing most pyrrole synthesis.

2. Results and Discussion

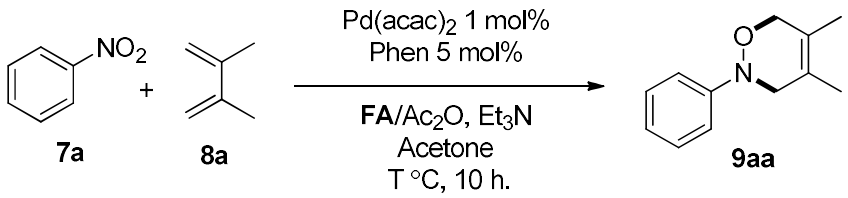
2.1. Optimization of the reaction conditions for the synthesis of 3,6-dihydro-2*H*-[1,2]-oxazines

The catalyst for the reduction of nitroarenes was once again chosen to be a palladium salt or complex with phenanthroline as a ligand forming the active species *in situ* since they are consistently effective in this kind of reactions and especially when CO is used as a reductant/carbonylating agent for nitroarenes and nitroalkenes as we demonstrated earlier.[62,63,78,80,81,109,198,199,268]

The synthesis of 4,5-dimethyl-2-phenyl-3,6-dihydro-2*H*-[1,2]–oxazine (**9aa**) by reaction of nitrobenzene (**7a**) with 2,3-dimethylbutadiene (**8a**) was chosen for the optimization of the reaction conditions.

We started our study employing the experimental conditions previously optimized for the synthesis of indoles using HCO_2H (FA)/Ac_2O mixture and employing $Pd(acac)_2$ as the pre-catalyst (**Table 14**). However, the results were not encouraging.

Table 14. Testing previously optimized conditions for the synthesis of 4,5-dimethyl-2-phenyl-3,6-dihydro-2*H*-[1,2]-oxazine using FA as the CO source.*a*

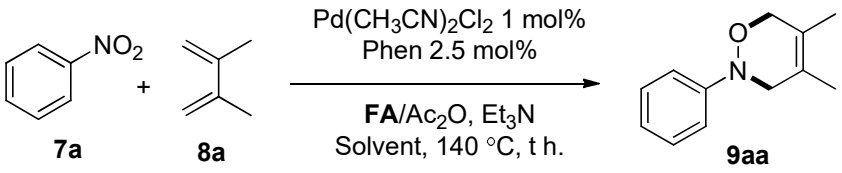


Entry	FA/Ac_2O/Et_3N to **7a** mol ratio	T (°C)	Conv. (%)*b*	Sel. (%)*b*	Yield (%)*b*
1	2.5/2.5/2.5	110	100	48	48
2	2.5/2.5/2.5	100	42	37	16
3	3/3/3	110	69	50	34

a: Experimental conditions: 0.5 mmol of **7a**, $Pd(acac)_2$ (1 mol%), Phen (5 mol%), **8a**/**7a** (mol ratio) = 4, FA/Ac_2O/Et_3N, acetone = 10 mL, t = 10 h. ***b***: Determined by GC using biphenyl as the internal standard.

Subsequently, we decided to test the experimental conditions previously optimized for the corresponding reaction employing HCO_2Ph as the CO surrogate,[25] simply substituting the latter with an equimolar amount of HCO_2H and Ac_2O (**Table 15**, entry 1). However, despite the almost complete conversion observed, the selectivity in oxazine was much lower than that achieved with the use of HCO_2Ph and increasing the reaction time did not improve the yield because the increase in conversion was accompanied by a decrease in selectivity (**Table 15**, entry 2). In order to ensure the stability of the catalytic system, we increased the Phen mole ratio and even changed the Pd-source ($Pd(OAc)_2$ instead of $Pd(CH_3CN)_2Cl_2$) but the selectivity was not enhanced (**Table 15**, entries 3, 4). Although the conversion was incomplete, employing 3 equiv. of each HCO_2H, Ac_2O and Et_3N with respect to nitrobenzene did not affect the selectivity until we increased the diene/nitrobenzene mole ratio to 6 eq. (**Table 15**, entry 5, 6).

Table 15. Optimization of the reaction conditions for the synthesis of 4,5-dimethyl-2-phenyl-3,6-dihydro-2*H*-[1,2]-oxazine using FA as the CO source.*a*



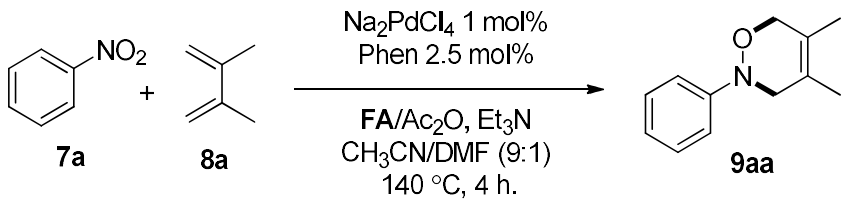
7a **8a** **9aa**

Entry	FA/Ac_2O/Et_3N to **7a** mol ratio	**8a**/**7a** mol ratio	Solvent	t (h)	Conv. (%)[b]	Sel. (%)[b]	Yield (%)[b]
1	4/4/4	4	CH_3CN	4	92	58	53
2	4/4/4	4	CH_3CN	8	100	47	47
3[c]	4/4/4	4	CH_3CN	4	99	47	46
4[d]	4/4/4	4	CH_3CN	4	99	55	54
5	3/3/3	4	CH_3CN	4	87	59	51
6	3/3/3	6	CH_3CN	5	99	67	66
7	3/3/3	6	Toluene	4	11	50	5
8[e]	4/4/4	4	CH_3CN	6	88	38	33
9[e]	3/3/3	6	CH_3CN	6	78	45	35
10	4/4/4	4	CH_3CN/DMF (9:1)	4	94	60	57
11[c]	4/4/4	4	CH_3CN/DMF (9:1)	4	100	50	50
12	3/3/3	4	CH_3CN/DMF (9:1)	4	96	64	62
13	3/3/3	6	CH_3CN/DMF (9:1)	4	97	71	69
14	3/3/3	8	CH_3CN/DMF (9:1)	4	98	71	70
15	3/3/2	6	CH_3CN/DMF (9:1)	4	97	68	66
16	3/3/4	6	CH_3CN/DMF (9:1)	4	98	73	72
17[e]	3/3/3	6	CH_3CN/DMF (9:1)	8	93	62	57
18	3/3/3	6	CH_3CN/DMF (8:2)	4	96	72	70
19[f]	3/3/3	6	CH_3CN/DMF (9:1)	4	>99	68	68

a: Experimental conditions: 0.5 mmol of **7a**, $Pd(CH_3CN)_2Cl_2$ (1 mol%), Phen (2.5 mol%), FA/Ac_2O/Et_3N, solvent = 10 mL, T = 140 °C. ***b***: Determined by GC using biphenyl as the internal standard. ***c***: Phen (5 mol%). ***d***: $Pd(OAc)_2$ (1 mol%) was used as the pre-catalyst. ***e***: T = 120 °C. ***f***: $Pd(acac)_2$ (1 mol%) was used as the pre-catalyst.

Running the reaction at lower temperature or using a low polarity solvent, toluene, was unsuitable (**Table 15**, entries 7-9). In the previous work on the synthesis of indoles (see Chapter I), we had found that the use of a CH_3CN/DMF 9:1 solvent mixture gave quite better results than the use of either solvent alone.[23] This effect was also found for the present system (**Table 15**, entry 10). Oxazine yield increased as the diene/nitrobenzene mole ratio was increased from 4 to 6, but a further increase to 8 gave no further improvement (**Table 15**, entries 12-14). The yield of oxazine was not further increased by altering the amount of Et_3N, lowering the temperature, or increasing the amount of DMF (**Table 15**, entries 15-18). Testing $Pd(acac)_2$ once again as the pre-catalyst under different conditions did not improve the results (**Table 15**, entry 19). In a recent study by our group on the synthesis of carbazoles,[24] we found that the addition of chlorides stabilizes the catalytic system. This led us to test Na_2PdCl_4 as the pre-catalyst, keeping the results in **Table 15** in mind.

Table 16. Optimization of the reaction conditions for the synthesis of 4,5-dimethyl-2-phenyl-3,6-dihydro-2*H*-[1,2]-oxazine using Na_2PdCl_4 as the catalyst and FA as the CO source.[a]



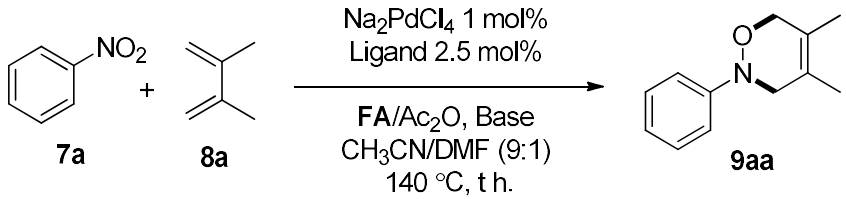
Entry	FA/Ac_2O/Et_3N to **7a** mol ratio	**8a**/**7a** mol ratio	Conv. (%)[b]	Sel. (%)[b]	Yield (%)[b]
1	3/3/3	4	94	68	64
2[c]	3/3/3	4	95	68	65
3	2.5/2.5/2.5	4	93	69	64
4[d]	3/3/3	4	98	65	63
5	**3/3/3**	**6**	**96**	**80**	**77**
6[e]	3/3/3	6	97	73	71
7[f]	3/3/3	6	85	68	58
8	3/3/3	8	97	80	77
9	3/3/4	6	90	67	60
10	3/3/3	2	78	51	39
11[g]	3/3/3	6	100	73	73

a: Experimental conditions: 0.5 mmol of **7a**, Na_2PdCl_4 (1 mol%), Phen (2.5 mol%), FA/Ac_2O/Et_3N, solvent = 10 mL, T = 140 °C, t = 4 h. ***b***: Determined by GC using biphenyl as the internal standard. ***c***: T = 150 °C. ***d***: Phen (5 mol%). ***e:*** Na_2PdCl_4 (1.5 mol%). ***f:*** Phen (1.5 mol%). ***g***: DMF used as the solvent.

Fortunately, the use of Na_2PdCl_4 in place of $Pd(CH_3CN)_2Cl_2$ afforded slightly better results (**Table 16**). Running the reaction at a temperature higher than 140 °C did not guarantee full conversion of **7a** (**Table 16**, entry 2). Although a slight decrease in the HCO_2H, Ac_2O and Et_3N ratio did not affect the oxazine yield, we decided to keep the ratio at 3 eq. to ensure enough CO pressure in the reaction (**Table 16**, entry 3). Increasing the molar ratio of Phen did not give any further improvement, while decreasing it determined a diminished stability of the catalytic system, which led to incomplete conversion (**Table 16,** entries 4, 7 respectively). Similar to what we observed in the case of using $Pd(CH_3CN)_2Cl_2$ as the pre-catalyst, the oxazine yield improved as the diene/nitrobenzene mole ratio was raised from 2 to 4 and then to 6; however, raising it to 8 did not afford a higher yield (**Table 16**, entries 1, 5, 8 and 10). Despite the complete conversion, employing DMF as the reaction solvent led only to a slight increase in conversion and a concomitant decrease of selectivity (**Table 16**, entry 11). Considering that DMF has a higher boiling point than acetonitrile and evaporation of large amount of it might lead to a partial loss of oxazine, we are pleased that the best result was obtained in the CH_3CN/DMF 9:1 solvent mixture. In the end, the best yield, 77%, was obtained by working under the conditions of (**Table 16**, entry 5).

Several other tests have been conducted to confirm that the conditions in (**Table 16**, entry 5) is indeed the optimal conditions. These tests include ligand and basic promoter screening (**Table 17**).

Table 17. Effect of ligand and base identities on the synthesis of 4,5-dimethyl-2-phenyl-3,6-dihydro-2*H*-[1,2]-oxazine using Na_2PdCl_4 as the pre-catalyst and FA as the CO source.[a]



Entry	FA/Ac_2O/Base to **7a** mol ratio	Base	Ligand	t (h)	Conv. (%)[b]	Sel. (%)[b]	Yield (%)[b]
1	3/3/3	Et_3N	Phenanthroline	4	96	80	77
2	3/3/3	Et_3N	3,4,6,7-Tetramethylphenanthroline	4	94	52	49
3	3/3/3	Et_3N	4,7-Dimethylphenanthroline	4	92	57	53
4	3/3/3	Et_3N	4,7-Dimethoxyphenanthroline	4	97	38	37
5	3/3/3	Et_3N	4,7-Dichlorophenanthroline	4	3	82	3
6	3/3/1	Na_3PO_4	Phenanthroline	4	16	70	25
7	3/3/1.5	Na_2CO_3	Phenanthroline	4	59	72	42
8	3/3/1.5	Na_2CO_3	Phenanthroline	10	37	70	26
9[c]	3/3/1.5	Na_2CO_3	Phenanthroline	5	49	70	35
10	4/4/2	Na_2CO_3	Phenanthroline	4	37	65	24

a: Experimental conditions: 0.5 mmol of **7a**, Na_2PdCl_4 (1 mol%), ligand (2.5 mol%), **8a**/**7a** (mol ratio) = 6, FA/Ac_2O/Base, solvent = 10 mL, T = 140 °C. ***b***: Determined by GC using biphenyl as the internal standard. ***c***: T = 150 °C.

The use of differently substituted phenanthrolines gave worse results (**Table 17**, entries 2-5). In general, the selectivity of the reaction decreased as the donating power of the phenanthroline ligand increased in the order 4,7-dichlorophenanthroline < Phen < 4,7-dimethylphenanthroline < 3,4,6,7-tetramethylphenanthroline < 4,7-dimethoxyphenanthroline, but the very low conversion obtained with 4,7-dichlorophenanthroline makes it unsuitable as a ligand even if it afforded high selectivity. On the other hand, different reagent ratios or the use of the inorganic bases Na_3PO_4 or Na_2CO_3 were less effective even when the reaction time elongated or the temperature increased (**Table 17**, entries 6-10). As a result, Phen and Et_3N have been confirmed to be the ligand and the base of choice.

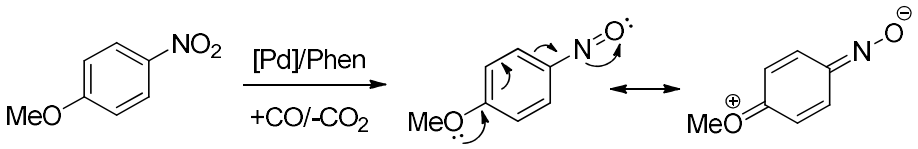
2.2. Substrate scope for 3,6-dihydro-2*H*-[1,2]-oxazines

Having the optimized reaction conditions, we investigated the reaction scope. Results are shown in **Table 18**.

First, we were pleased to find that oxazine **9aa** could be isolated from the reaction mixture with negligible losses (from 77% GC yield, to 76% isolated) (**Table 18**, entry 1). In terms of functional groups, fluoro, chloro and bromo substituents were well tolerated (**Table 18**, entries 2-4), as were

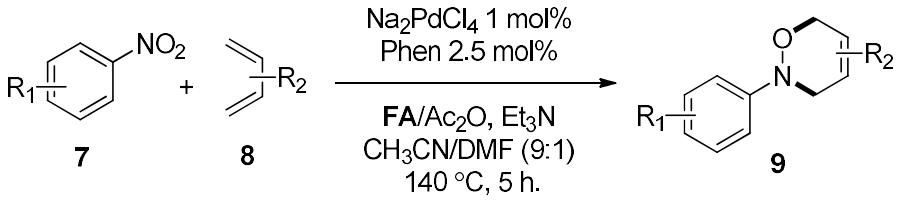
the electron-withdrawing groups cyano (CN) and trifluoro methyl (CF_3) (**Table 18**, entries 5, 12 respectively). The moderately electron-donating alkyl groups in the *para* position worked well (**Table 18**, entries 6, 7); nevertheless, in the case of the methyl group, it took 16 hours to completely convert 4-nitrotoluene. Very low yields were obtained in the case of *p*-methoxynitrobenzene (**7h**). In fact, this was expected since there are two known reasons why this kind of substrate is notoriously problematic for this kind of reaction:

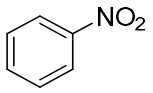
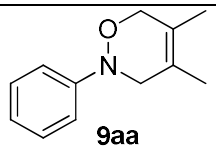
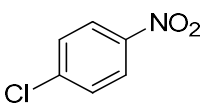
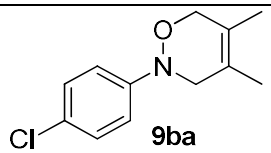
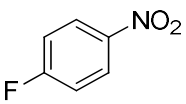
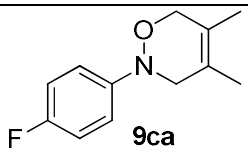
1. It has been shown in numerous cases that the activation of nitroarenes by low valent transition metal complexes involves an electron transfer from the metal to the nitroarene[94-103] and this step is retarded by strongly donating substituents on the nitroarene.
2. As the nitrosoarene is involved in a hetero Diels-Alder reaction and the latter is well known to proceed the better the lower is the level of the orbitals of the dienophile.[269] The presence of a *para* methoxy group on the aryl ring of nitrosobenzene allows a quinonoid resonance form for **7h**, where the nitroso group gains a negative charge and loses its double bond, making it unsuitable to undergo a Diels-Alder reaction (**Scheme 26**).[25,270]

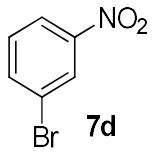
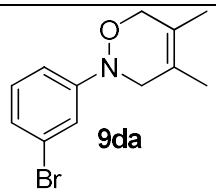
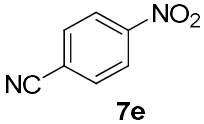
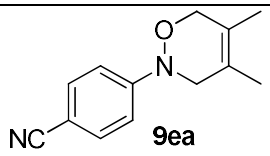
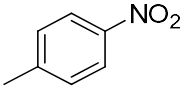
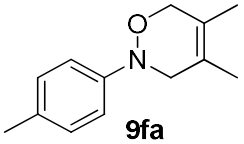
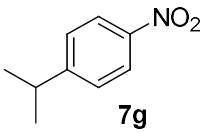
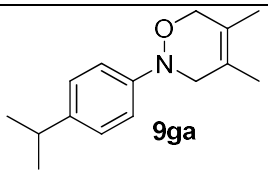
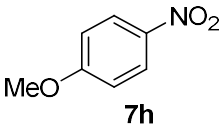
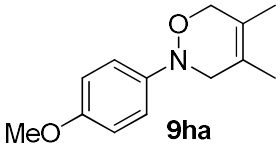
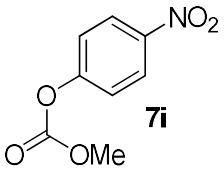
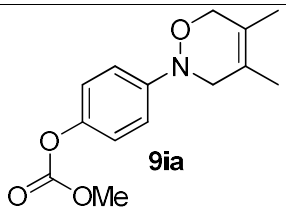
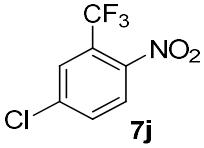
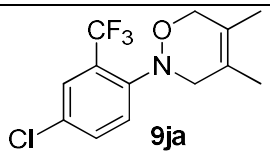
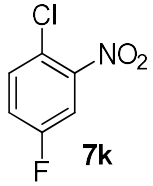
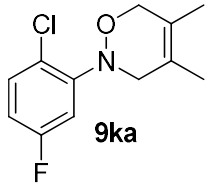
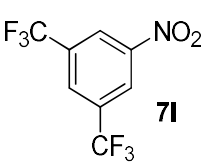
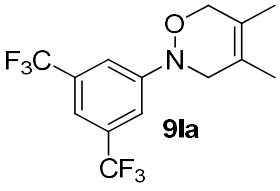


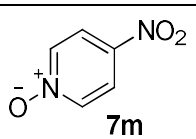
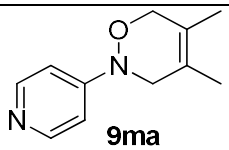
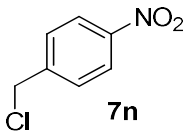
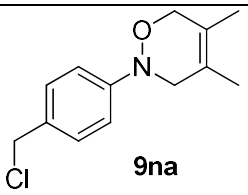
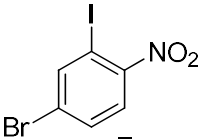
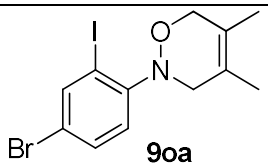
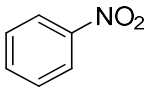
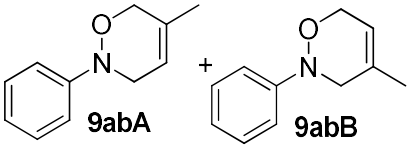
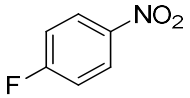
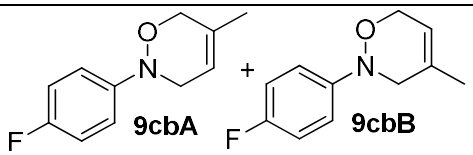
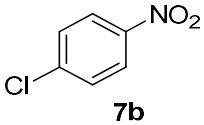
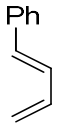
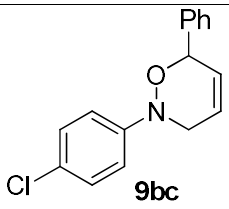
Scheme 26. Resonance forms of 4-nitrosoanisole (**7h**).

Table 18. Substrate scope for the synthesis of 3,6-dihydro-2*H*-[1,2]-oxazines.[a]



Entry	Nitroarene	Diene	Oxazine	Yield (%)[b]
1	 **7a**	 **8a**	 **9aa**	76
2	 **7b**	 **8a**	 **9ba**	77
3	 **7c**	 **8a**	 **9ca**	58

4	 **7d**	 **8a**	 **9da**	65
5	 **7e**	 **8a**	 **9ea**	43[c]
6	 **7f**	 **8a**	 **9fa**	26 (60)[d]
7	 **7g**	 **8a**	 **9ga**	70
8	 **7h**	 **8a**	 **9ha**	12[c]
9	 **7i**	 **8a**	 **9ia**	22[c]
10	 **7j**	 **8a**	 **9ja**	24
11	 **7k**	 **8a**	 **9ka**	50
12	 **7l**	 **8a**	 **9la**	70

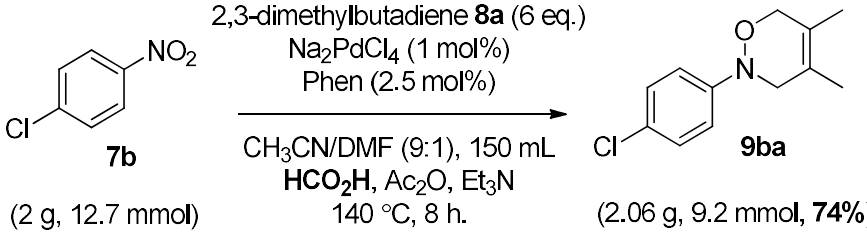
13	 **7m**	 **8a**	 **9ma**	32
14	 **7n**	 **8a**	 **9na**	N.D.
15	 **7o**	 **8a**	 **9oa**	N.D.
16	 **7a**	 **8b**	 **9abA** **9abB**	50 (A:B = 1:6)
17	 **7c**	 **8b**	 **9cbA** **9cbB**	57 (A:B = 1:6)
18	 **7b**	 **8c**	 **9bc**	59

a: Experimental conditions: 0.5 mmol of **7**, Na_2PdCl_4 (1 mol%), Phen (2.5 mol%), FA/Ac_2O/Et_3N/**7**/**8** (mol ratio) = 3:3:3:1:6, in 10 mL CH_3CN/DMF (9:1), T = 140 °C, for 5 h. ***b:*** Isolated yield, unless otherwise noted, N.D. = not detected. ***c:*** Yield determined by NMR using mesitylene as the internal standard. ***d:*** Reaction time 16 h.

That at least a measurable amount of **9ha** could be obtained under the present conditions (12% yield) represents anyway a positive result because only trace amounts of this oxazine could be detected in previous related works.[25,227] Results were somewhat better when the donating power of the oxygen atom in the para position was attenuated by the presence of an acyl group (**Table 18,** entry 9). Steric hindrance in the ortho position was tolerated, but at the expense of a diminished yield (**Table 18**, entries 10, 11). An interesting case is that in which the phenyl ring is substituted by a pyridine one (**9ma**). The corresponding nitropyridine is commercially available as the corresponding *N*-oxide (**7m**). Use of the latter without any pretreatment resulted not only in the reduction of the nitro group to nitroso but also in the deoxygenation of the *N*-oxide group. Note that this oxazine is very reactive and starts to decompose in the air after a few hours, even in solid state.

The only nitroarenes for which no oxazine at all could be observed are 4-nitrobenzyl chloride (**7n**) and 2-iodo-4-bromonitrobenzene (**7o**). This may be due to the presence of functional groups that give a fast oxidative addition to low valent metal complexes, likely competitive with the reduction of the nitro group. When the non-symmetric diene isoprene (**8b**) was employed, a mixture of the two expected regioisomers (proximal **A** and distal **B**) was obtained, with that whose formation is electronically favored in hetero-Diels-Alder reactions prevailing (**Table 18**, entries 16, 17). The two isomers were not separated because both would give the same pyrrole. The fact that the distal/proximal ratio is similar to that typically observed for the hetero-Diels-Alder reaction of free nitrosoarenes with isoprene suggests that the reaction is occurring off-metal and that free nitrosoarenes are formed. Employing 1-phenyl-1,3-butadiene (**8c**) as the diene, only the proximal isomer was obtained (**Table 18**, entry 18), again in accordance with the literature for the same [242] or related compounds.[229] It is worth noting that nitroarenes and dienes have been recently reported to afford amides when a different catalytic system ($Pd(PPh_3)_4$ with $Mo(CO)_6$ as a CO surrogate) was employed.[271] In this system, the formation of free nitrosoarenes as intermediates was excluded.

Finally, a large-scale (~ 25-fold) synthesis of **9ba** was performed under the optimized conditions, but with a decreased amount of solvent (15-fold) and a longer reaction time (8 h). The yield was only slightly lower (74% instead of 76%) than that obtained in the smaller scale reaction (**Scheme 27**).

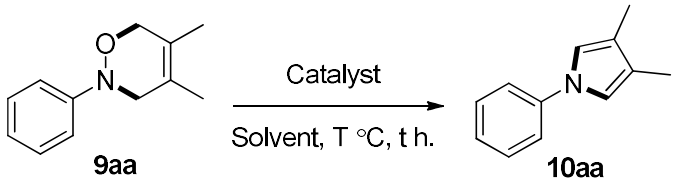


Scheme 27. Large-scale synthesis of 2-(4-chlorophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-oxazine (**9ba**).

2.3. Dehydration of 3,6-dihydro-2*H*-[1,2]-oxazines to *N*-arylpyrroles

In search of a general method to dehydrate oxazines into pyrroles, we investigated different reagents and conditions for the conversion of **9aa** into 2,3-dimethyl-*N*-phenylpyrrole (**10aa**) (**Table 19**). We first examined the effect of a high temperature treatment. However, in the absence of any other additive, the conversion to pyrrole proceeded only with a fair selectivity at 200 °C and no pyrrole was detectable by working at 140 °C (**Table 19**, entries 1-3). Bases, acids or even an acidic dehydrating agent (P_2O_5), showed some accelerating effect, but failed to give good yields of pyrroles (**Table 19**, entries 4-6). The use of triflic acid,[272] in particular, gave a complete conversion of the **9aa**, but afforded a mixture of products that does not include pyrrole (**Table 19**, entry 7). Since CuCl in methanol had been reported to be effective in promoting the desired transformation in one case,[266] we decided to test the effect of its addition or that of other Cu-salts on our substrate (**Table 20**).

Table 19. Effect of thermal, basic, and acidic treatment on the transformation of 4,5-dimethyl-2-phenyl-3,6-dihydro-2*H*-[1,2]-oxazine (**9aa**) into 3,4-dimethyl-*N*-phenylpyrrole (**10aa**).



9aa **10aa**

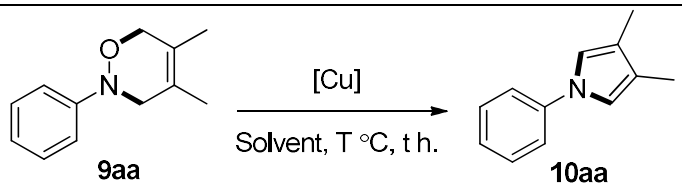
Entry	Cat. (mol%)	Solvent	T (°C)	t (h)	Conv. (%)[b]	Sel. (%)[b]	Yield (%)[b]
1[c]	-	CH_3CN	200	3	29	45	13
2[c]	-	Benzene	200	3	23	55	13
3	-	CH_3CN	140	72	13	0	0
4	DBU (25)	CH_3CN	140	16	5	79	4
5	NaOH (25)	CH_3CN	140	16	26	42	11
6	P_2O_5 (25)	CH_3CN	140	16	30	28	9
7	Triflic acid (25)	CH_3OH	140	16	>99	-	Traces

a: Experimental conditions: 50 mg (0.26 mmol) of **9aa**, in 2 mL of solvent. ***b***: Determined by GC using biphenyl as the internal standard. ***c:*** The reaction was performed in an autoclave under 20 bars of CO to avoid the boiling of the solvent.

The conversion was indeed complete, but only a fair 44% yield of pyrrole was obtained (**Table 20**, entry 1). Decreasing the temperature even decreased the selectivity of the reaction to 18% (**Table 20**, entry 2). An investigation of a range of solvents or solvents mixtures showed that acetonitrile was the one affording the best yield, despite the fact that the reaction is rather sluggish (**Table 20**, entries 3-14). Changing the solvent to acetone and lowering the temperature did not afford any improvements in the pyrrole yield (**Table 20**, entries 5-9). Although reasonably good selectivity was observed when toluene was utilized, incomplete conversion remained a problem that may be treated by increasing reaction time but at the expense of lower selectivity (**Table 20**, entries 10-12).

Lowering the temperature led to a decreased conversion, with little effect on the selectivity, so 140 °C was chosen as the temperature for further studies, even taking into account that this is the temperature at which the first stage of the reaction was performed.

Table 20. Optimization of the reaction conditions for the conversion of 4,5-dimethyl-2-phenyl-3,6-dihydro-2*H*-[1,2]-oxazine (**9aa**) into 3,4-dimethyl-*N*-phenylpyrrole (**10aa**).



9aa **10aa**

Entry	Cat. (mol%)	Solvent	T (°C)	t (h)	Conv. (%)[b]	Sel. (%)[b]	Yield (%)[b]

1	CuCl (20)	CH_3OH	140	16	100	44	44
2	CuCl (20)	CH_3OH	100	16	100	18	18
3	CuCl (20)	CH_3CN	140	60	96	77	74
4	CuCl (20)	Acetone	140	5	>99	48	47
5	CuCl (20)	Acetone	100	6	18	76	14
6	CuCl (20)	Acetone	100	10	24	43	10
7	CuCl (20)	Acetone	100	24	64	14	9
8	CuCl (20)	Acetone	120	6	66	26	17
9	CuCl (20)	Acetone	120	10	86	21	18
10	CuCl (20)	Toluene	140	5	44	77	34
11	CuCl (20)	Toluene	140	10	71	62	44
12	CuCl (20)	Toluene	140	15	90	57	51
13	CuCl (20)	CH_3CN:CH_3OH (1:1)	140	24	84	29	24
14	CuCl (20)	CH_3CN:H_2O (4:1)	140	24	99.7	22	22
15	CuCl/Phen (20/5)	CH_3CN	140	16	100	35	35
16	CuCl/Phen (20/5)	CH_3CN	100	20	35	81	28
17	CuCl/Phen (20/5)	CH_3CN	100	40	62	48	30
18	CuCl/Phen (20/20)	CH_3CN	100	20	52	54	28
19	CuCl/Phen (20/20)	CH_3CN	100	40	76	47	35
20	Phen (5)	CH_3CN	140	48	16	0	0
21	$Cu_2(OH)_3Cl$ (20)	CH_3CN	140	72	>99	11	11
22	$Cu_2(OH)_3Cl$/Phen (20/5)	CH_3CN	140	16	>99	35	35
23	$CuCl_2$ (20)	CH_3CN	140	3.5	100	5	5
24	$CuCl_2$/Phen (20/5)	CH_3CN	140	3.5	100	9	9
25	$CuSO_4 \cdot 5H_2O$ (20)	CH_3CN	140	72	96	17	16
26	$CuSO_4 \cdot 5H_2O$/Phen (20/5)	CH_3CN	140	72	100	18	18
27A	CuCl (10)	CH_3CN	140	30	69	50	34
27B[c]	CuCl (20)	CH_3CN	140	60	94	50	47
28	**CuCl (30)**	**CH_3CN**	**140**	**60**	**100**	**77**	**77**
29[d]	CuCl (30)	CH_3CN:DMF (9:1)	140	120	42	23	10

a: Experimental conditions: 50 mg (0.26 mmol) of **9aa**, in 2 mL of solvent. ***b***: Determined by GC using biphenyl as the internal standard. ***c:*** 10 mol% of CuCl was added after 30 h. of **27A**. ***d:*** CuCl was added directly on the catalytic reaction mixture after a reaction run under the conditions in (**Table 16**, entry 5).

The addition of Phen helped in solubilizing CuCl and accelerated the reaction, but at the expense of selectivity (**Table 20**, entry 15). On the other hand, lowering the temperature in the presence of Phen (5 or 20 mol%) had no significant impact on the obtained results (**Table 20**, entries 16-19). To make sure of the actual effect of Phen, we ran a test using only Phen as the additive; however, only 16% conversion was observed, and no pyrrole was detected, suggesting that CuCl is the active catalyst towards pyrroles (**Table 20**, entry 20). Since Cu(I) compounds can be easily contaminated by Cu(II) compounds if not stored strictly under an inert atmosphere, we also tested the effect of

several Cu(II) salts, both in the presence and absence of phenanthroline (**Table 20**, entries 21-26). At least chlorine-containing Cu(II) salts were indeed very active in decomposing the oxazine, but gave very poor yields of pyrrole. Thus, it is obvious that any Cu(II) contaminating the employed CuCl may cause the formation of byproducts but is not responsible for the formation of most of the pyrrole.

Adding the CuCl in two portions over the time led to worse results, indicating that the long reaction times are not due to a deactivation of the catalyst (**Table 20**, entries 27A, B), but increasing its amount to 30 mol% afforded a satisfying 77% yield (**Table 20**, entry 28), we considered this sufficient to proceed with investigating the substrate scope under these conditions.

Unfortunately, simply adding 30 mol% CuCl to the reaction mixture after the oxazine synthesis (see **Table 16**, entry 5) and performing the conversion to pyrrole under the optimized conditions (**Table 20**, entry 28) even for a prolonged time (120 h), did not give good results (**Table 20**, entry 29). Only 42% of the oxazine reacted and the pyrrole was obtained with poor selectivity in just 10% yield. Clearly, some of the components of the first catalytic system interfere with the second transformation. Therefore, isolating the oxazine before converting it into pyrrole was necessary under the conditions developed in this work.

2.4. Substrate scope for *N*-arylpyrroles

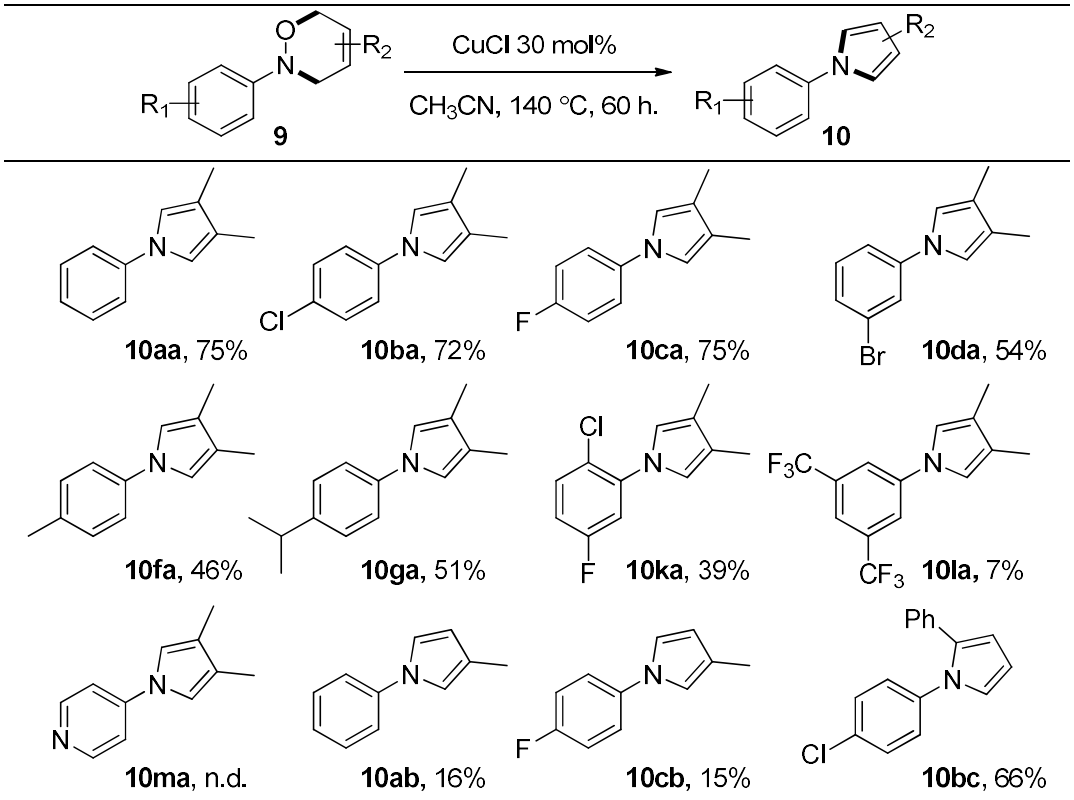
Having identified the best experimental conditions, the oxazines isolated in the first part of this work, except for those that had been isolated in a too low yield, were converted into pyrroles. Results are shown in (**Table 21**).

The reaction tolerates halogen and alkyl substituents on the aryl ring and affords good yields even when employing a 1-phenyl-1,4-butadiende-derived oxazine **9bc** as the substrate. Unfortunately, poor results were obtained when trifluoromethyl groups were present or when isoprene-derived oxazines were employed as substrates. In the first case, an immediate blue color developed upon mixing **9la** with CuCl at room temperature, indicating a different and specific reactivity. The low isolated yield of **10ab** and **10cb** is at least in part due to their high tendency to sublime and be evaporated with the solvent. In general, it should be stressed that we encountered this problem even with the other pyrroles, but the problem was more serious for these two products.

Although the yields obtained in several cases may appear to be only fair, it should be stressed that, to the best of our knowledge, apart from **10aa** (that had been previously isolated in a lower yield) and **10ab** (for which many synthetic strategies have been reported), most of the other pyrroles in **Table 21** have never been fully characterized previously, indicating that, despite the simplicity of their structure, they are not easily prepared even by other means.

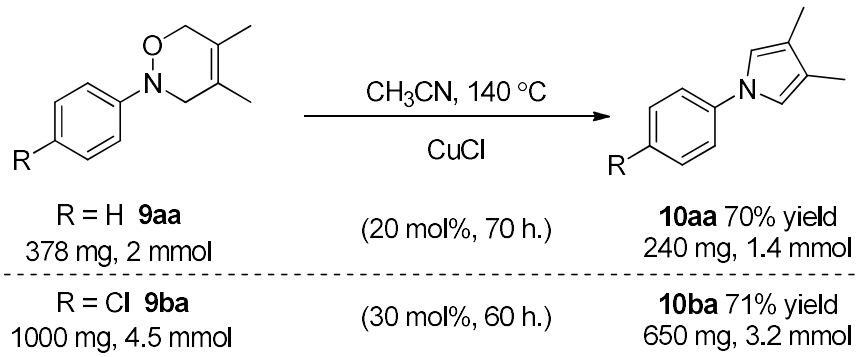
As an exception, a complete lack of reactivity was detected when a pyridine containing oxazine was employed as the substrate **9ma** which was recovered unconverted (90%) after the reaction. Coordination of the pyridine *N*-atom to copper is most likely deactivating the catalyst and preventing the oxazine conversion.

Table 21. Substrate scope for the conversion of oxazines **9** into pyrroles **10**.[a]



a: Experimental conditions: (0.25 mmol) of **9**, CuCl (30 mol%), in CH_3CN (2 mL) at 140 °C for 60 h. Isolated yields are shown.

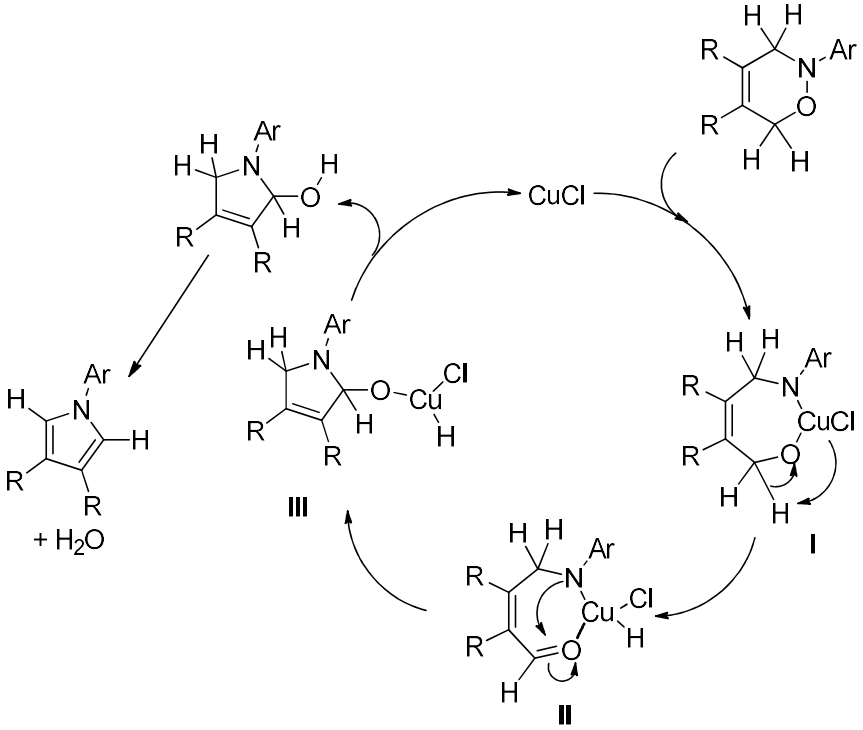
Finally, the synthesis of **10aa** and that of **10ba** were also tested on a larger scale (**Scheme 28**) and even in these cases the product could be isolated with only a small decrease in the yield with respect to the reaction run at the standard concentrations.



Scheme 28. Large-scale synthesis of pyrroles **10aa** and **10ba**.

2.5. Reaction mechanism of the transformation of 1,2-oxazines to pyrroles

A reaction mechanism for the oxazine ring contraction to pyrroles is proposed in (**Scheme 29**). Oxidative addition of the N–O bond to copper chloride is proposed to form intermediate **I**. Although the formation of Cu(III) species as intermediates in catalytic cycles is still debated,[273-275] they have been invoked in several N-O bond cleavage reactions.[276-281] *β*-Hydride elimination on the oxygen side of the formed metallacycle **I** leads to the formation of **II**, which in turn goes through an intramolecular ring closure to give the cyclic hemiaminal **III**. Reductive elimination from the copper center and subsequent dehydration/isomerization processes lead to pyrrole formation.



Scheme 29. Proposed mechanism for the CuCl mediated conversion of 1,2-oxazines to pyrroles.

3. Conclusion

In this project, we faced two problems. The first is the identification of a cheap, easily operated synthesis of 3,6-dihydro-2*H*-[1,2]-oxazines. In the literature, this type of compounds is frequently synthesized by reacting conjugated dienes with nitrosoarenes. However, the preparation of the latter, either as isolated molecules or as labile intermediates, is often performed under oxidative conditions, which do not permit a wide tolerance of various functional groups. Carbon monoxide, when in the presence of suitable transition metal catalysts, is extremely selective in reducing nitro- to nitroso-arenes without affecting other reducible groups and the procedure can be applied to the synthesis of oxazines, but using pressurized CO is typically not a viable option in most laboratories. The use of HCO_2Ph as a CO surrogate represents a solution, despite challenges in

separating co-produced phenol. The use of HCO_2H/Ac_2O mixture solves the problem, although yields were in several cases higher when HCO_2Ph was employed.

The second problem is the dehydration of the obtained oxazines into *N*-arylpyrroles. Even if scattered examples of this transformation have been known for decades, an in-depth review of the literature reveals that good yields have only been reported in specific cases, such as the presence of electron-withdrawing substituents on the oxazine ring or of an aryl group in position 2 of the finally obtained pyrrole. An efficient general procedure able to afford pyrroles lacking substituents in both the 2 and the 5 positions by this synthetic strategy was lacking. We found that cuprous chloride can play this role and optimized the reaction conditions to make its employment a synthetically effective tool.

The two reactions together represent a simple route into 2,5-unsubstituted-*N*-arylpyrroles, a class of interesting molecules difficult to access by other techniques.

4. Experimental section

4.1. General information

Unless otherwise stated, all the reactions were carried out under dinitrogen atmosphere using standard Schlenk apparatus. All glassware and magnetic stirring bars were kept in an oven at 120 °C for at least two hours and let to cool under vacuum before use. All the solvents (for catalytic reactions or for NMR) in this work have been treated, dried and/or distilled according to what was described in (Chapter I). Copper (I) chloride was purchased from TCI Europe NV and stored under dinitrogen to avoid air oxidation. 2,3-Dimethylbutadiene and isoprene were purchased from TCI Europe NV and used after filtration on basic alumina or distillation from CaH_2 under dinitrogen respectively. All the other reagents were purchased from Merck (Sigma-Aldrich), TCI Europe NV, or Fluorochem and used without further purifications.

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance DRX 400 or Avance NEO 400. Chemical shifts are reported in ppm relative to tetramethylsilane. Elemental analyses were performed on a Perkin Elmer 2400 CHN elemental analyzer. Thin-layer chromatography (TLC) was performed using precoated silica gel 60 F254 MACHEREY-NAGEL plates. TLC plates were visualized by exposing UV light. Flash column chromatography was performed on MACHEREY-NAGEL flash silica gel 0.04-0.063 mm size. Gas chromatographic analyses were performed using a Shimadzu 2010Pro gas chromatograph equipped with a Supelco SLB-5 ms capillary column (L × I.D. 10 m × 0.10 mm, df 0.10 μm). A standard analysis involves the preparation of a sample solution in ethyl acetate (conc. 0.1 mg/mL calculated with respect to biphenyl used as the internal standard). Palladium precursors used in the present work have been prepared as the procedures reported in the literature [151,152] and as described in (Chapter I).

4.2. General procedure for the synthesis of 3,6-dihydro-2*H*-[1,2]-oxazines

To avoid weighing errors, stock solutions of Na_2PdCl_4 in DMF and Phen in CH_3CN were prepared under a dinitrogen atmosphere. In a typical catalytic reaction, the nitrobenzene derivative (0.5 mmol) was weighed in the air and placed in a pressure tube equipped with a magnetic stirring bar (**Fig. 4**, chapter I). The tube was placed inside a Schlenk tube with a wide mouth, evacuated, and filled three times with dinitrogen. The appropriate volumes of stock solutions of Na_2PCl_4 and Phen were added, and the mixture was stirred for 15 min. to allow the formation of the Pd/Phen complex. Subsequently, diene (3 mmol), Et_3N (1.5 mmol) and Ac_2O (1.5 mmol) were added without stirring, then the remaining amount of solvent (CH_3CN:DMF (9:1) 10 mL total volume) was layered carefully. Finally, formic acid (1.5 mmol) was added, and the pressure tube was sealed under dinitrogen. The order of addition of the reagents and solvent layering is critical to avoid loss of CO which begins to evolve, even at room temperature, as soon as HCOOH, Ac_2O, and the base are mixed. The pressure tube was then placed and heated while stirring in a custom-made aluminum block preheated to 140 °C. At the end of the reaction, the pressure tube was removed from the aluminum block, allowed to cool to room temperature, and slowly opened under a fume hood. After the evaporation of CH_3CN, 10 mL of ethyl acetate were added. The reaction mixture was washed with $NaHCO_3$ (1×10 mL) and water (1×10 mL) to get rid of the acetic acid formed during the reaction. The organic layer was collected, dried over Na_2SO_4, filtered, and evaporated to get the crude, which was subjected to silica-gel column chromatography using hexane/AcOEt as the eluent with the addition of 1% of Et_3N to partly deactivate acidic sites in the silica gel.

4.3. Procedure for the large-scale synthesis of (9ba)

The reaction was carried out in an oven dried 250 mL heavy-walled glass pressure bottle (**Fig. 4**, chapter I) to prepare **9ba** under the optimal conditions. The reaction was scaled up by increasing the substrate amount ~ 25-fold with respect to the standard conditions. The pressure bottle was charged with Na_2PdCl_4 (37.4 mg, 0.127 mmol), Phen (57.2 mg, 0.318 mmol), and substrate **7b** (2 g, 12.7 mmol) and then placed in a Schlenk tube with a large mouth. The tube was evacuated and filled three times with dinitrogen. DMF (15 mL), CH_3CN (35 mL), 2,3-dimethylbutadiene (8.6 mL, 76.2 mmol), Et_3N (5.3 mL, 38.1 mmol), and Ac_2O (3.6 mL, 38.1 mmol) were added, and the mixture was stirred for 15 min. The stirring was stopped, and the remaining solvent amount (CH_3CN, 100 mL) was layered carefully. Finally, formic acid (1.4 mL, 38.1 mmol) was added, and the bottle was sealed with the screwcap under dinitrogen. The pressure bottle was placed in a preheated (140 °C) oil bath. The reaction time was increased from 5 to 8 hours to guarantee completion, despite the possibility that the substrate had already been fully converted at that point. At the end of the reaction, metallic palladium precipitated on the bottle walls. The pressure bottle was removed from the oil bath, allowed to cool to room temperature, and then slowly opened under a fume hood. ATTENTION: When scaling up the reaction, consider the maximum CO pressure that will be produced by the HCO_2H decomposition and scale up the reactor volume accordingly. Subsequently, most of the solvent was evaporated and 50 mL of ethyl acetate were added. The reaction mixture was washed with $NaHCO_3$ (1×50 mL), brine (1×50 mL), and water (1×50 mL) to get rid of the acetic acid formed during the reaction. The organic layer was collected, dried over

Na_2SO_4, filtered, and evaporated to get the crude, which was subjected to silica-gel column chromatography using (hexane:AcOEt 98:2 + 1% Et_3N) as the eluent to get the final product **9ba** as a white crystalline solid (2.06 g, 9.2 mmol, 74% yield).

4.4. General procedure for the synthesis of *N*-arylpyrroles

3,6-Dihydro-2*H*-[1,2]-oxazine derivative (0.25 mmol) and CuCl (0.08 mmol) were placed in a pressure tube of the same type used in the synthesis of oxazines. The tube was inserted into a wide-mouthed Schlenk tube, evacuated, and then filled three times with dinitrogen. 2 mL of dry CH_3CN were added, and the tube was sealed under dinitrogen and heated at 140 °C for 60 h. After reaction completion, the reaction was allowed to cool to room temperature and slowly opened inside a wide-mouthed Schlenk tube under dinitrogen. CH_3CN was evaporated, and the crude was subjected to silica-gel column chromatography using hexane as the eluent (the eluent was pushed using dinitrogen, and the fractions were collected under dinitrogen) to give the corresponding *N*-arylpyrrole.

4.5. Procedure for the large-scale synthesis of pyrroles (10aa) and (10ba)

3,6-Dihydro-2*H*-1,2-oxazine derivative (1 eq.) and CuCl were placed in a pressure tube or pressure bottle (depending on the volume of the solvent). The tube was inserted into a wide-mouthed Schlenk tube, evacuated, and then filled three times with dinitrogen then dry CH_3CN was added, and the tube was sealed under dinitrogen and heated at 140 °C. After reaction completion, the reaction was allowed to cool to room temperature and slowly opened inside a wide-mouthed Schlenk tube under dinitrogen. CH_3CN was evaporated, and the crude was subjected to silica-gel column chromatography using hexane as the eluent (the eluent was pushed using dinitrogen, and the fractions were collected under dinitrogen) to give the desired pyrroles.

10aa: 4,5-Dimethyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine **9aa** (379 mg, 2 mmol) and CuCl (39.6 mg, 0.4 mmol, 20 mol%) were placed in a pressure tube and 10 mL of dry CH_3CN were added. Isolated as a white crystalline solid (240 mg, 1.4 mmol, 70% yield).

10ba: 2-(4-chlorophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-oxazine **9ba** (1 g, 4.5 mmol), CuCl (132.7 mg, 1.34 mmol, 30 mol%) were placed in a pressure bottle and 35 mL of dry CH_3CN were added. Isolated as a white crystalline solid (650 mg, 3.2 mmol, 71% yield).

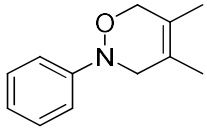
4.6. Preparation of Na_2PdCl_4

The synthesis was performed following the procedure reported in the literature.[24]

$PdCl_2$ (0.50 g, 2.8 mmol) was suspended in distilled water (3 mL) and NaCl (0.33 g, 5.6 mmol) was added. The reaction was heated at 70 °C until $PdCl_2$ is completely soluble. The obtained brown-red solution was allowed to cool to room temperature and filtered on filter paper by canula. Water was then evaporated under vacuum affording a brown solid that was smashed into powder and kept under vacuum at 80 °C for 12 h. (0.76 g, 93% yield).

4.7. Characterization data for 3,6-dihydro-2*H*-[1,2]-oxazines

4,5-dimethyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (9aa)



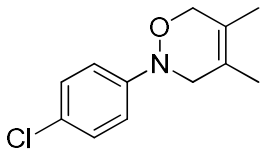
Obtained as a white solid (72 mg, 0.38 mmol, 76%) after purification by flash column chromatography (hexane:AcOEt 99:1+ 1% Et_3N).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H), 7.17 – 7.11 (m, 2H), 6.99 (tt, J = 7.5, 1.1 Hz, 1H), 4.33 (m, 2H), 3.67 (m, 2H), 1.74 (m, 3H), 1.65 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 128.9, 125.1, 122.5, 122.4, 116.0, 72.2, 56.5, 16.1, 13.8 ppm.

Elemental analysis calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40, found: C, 75.72; H, 7.96; N 7.38.

2-(4-chlorophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-oxazine (9ba)



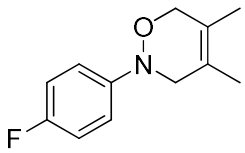
Obtained as a white solid (86 mg, 0.38 mmol, 77%) after purification by flash column chromatography (hexane:AcOEt 98:2 + 1% Et_3N).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.23 (m, 2H, overlapped with $CDCl_3$), 7.09 – 7.01 (m, 2H), 4.32 (m, 2H), 3.63 (m, 2H), 1.74 (m, 3H), 1.64 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 128.9, 127.3, 125.1, 122.2, 117.3, 72.2, 56.3, 16.0, 13.8 ppm.

Elemental analysis calcd for $C_{12}H_{14}ClNO$: C, 64.43; H, 6.31; N, 6.26, found: C, 64.29; H 6.92; N, 6.57.

2-(4-fluorophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-oxazine (9ca)



Obtained as a white solid (60 mg, 0.29 mmol, 58%) after purification by flash column chromatography (hexane:AcOEt 98:2 + 1% Et_3N).

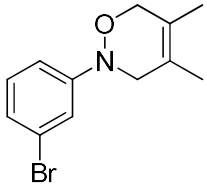
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.05 (m, 2H), 7.04 – 6.93 (m, 2H), 4.32 (s, 2H), 3.60 (s, 2H), 1.73 (m, 3H), 1.64 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9 (d, $^{1}J_{C-F}$ = 241.1 Hz), 146.9, 125.1, 122.5, 118.0 (d, $^{3}J_{C-F}$ = 7.9 Hz), 115.5 (d, $^{2}J_{C-F}$ = 22.4 Hz), 72.2, 57.2, 16.0, 13.8 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -121.45 ppm.

Elemental analysis calcd for $C_{12}H_{14}FNO$: C, 69.55; H, 6.81; N, 6.76, found: C, 69.52; H, 7.01; N, 6.70.

2-(3-bromophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-oxazine (9da)



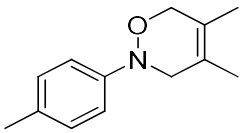
Obtained as a yellow solid (87 mg, 0.32 mmol, 65%) after purification by flash column chromatography (hexane:AcOEt 90:10 + 1% Et_3N).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 2.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.09 (ddd, J = 7.9, 1.7, 1.3 Hz, 1H), 6.99 (ddd, J = 8.1, 2.1, 1.2 Hz, 1H), 4.31 (s, 2H), 3.65 (s, 2H), 1.74 (m, 3H), 1.64 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 130.2, 125.1, 124.9, 123.0, 122.1, 118.7, 114.2, 72.2, 55.9, 16.0, 13.8 ppm.

Elemental analysis calcd for $C_{12}H_{14}BrNO$: C, 53.75; H, 5.26; N, 5.22, found: C, 53.71; H, 5.33; N, 5.16.

4,5-dimethyl-2-(*p*-tolyl)-3,6-dihydro-2*H*-1,2-oxazine (9fa)



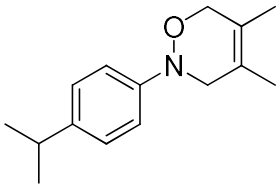
Obtained as a white solid (61 mg, 0.30 mmol, 60%) after purification by flash column chromatography (hexane:AcOEt 98:2 + 1% Et_3N).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 8.3 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 4.32 (s, 2H), 3.63 (s, 2H), 2.30 (s, 3H), 1.73 (s, 3H), 1.64 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 132.1, 129.5, 125.1, 122.6, 116.5, 72.2, 57.0, 20.8, 16.1, 13.8 ppm.

Elemental analysis calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89, found: C, 76.26; H, 8.25; N, 6.28.

2-(4-isopropylphenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-oxazine (9ga)



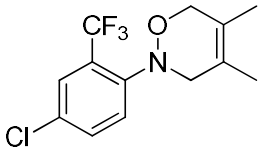
Obtained as a white solid (80 mg, 0.35 mmol, 70%) after purification by flash column chromatography (hexane:AcOEt 99:1 + 1% Et_3N).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.13 (m, 2H), 7.11 – 7.03 (m, 2H), 4.32 (s, 2H), 3.63 (s, 2H), 2.87 (hept, J = 6.7 Hz, 1H), 1.73 (m, 3H), 1.64 (m, 3H), 1.24 (s, 3H), 1.22 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 143.2, 126.8, 125.1, 122.7, 116.5, 72.2, 57.0, 33.6, 24.2, 16.1, 13.8 ppm.

Elemental analysis calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05, found: C, 77.67; H, 9.05; N, 5.77.

2-(4-chloro-2-(trifluoromethyl)phenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-oxazine (9ja)



Obtained as a white solid (36 mg, 0.12 mmol, 24%) after purification by flash column chromatography (hexane:CH_2Cl_2 99:1 + 1% Et_3N).

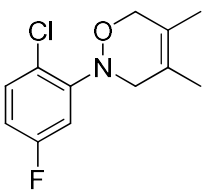
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 2.3 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.53 (dd, J = 8.7, 2.2 Hz, 1H), 4.29 (m, 2H), 3.45 (m, 2H), 1.69 (m3H), 1.64 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 133.0, 131.7, 126.9 (q, $^3J_{C-F}$ = 11.4 Hz), 126.4 (q, $^2J_{C-F}$ = 30.6 Hz, overlapped with CH signal at 126.9 ppm), 124.8, 122.7, 123.0 (q, $^1J_{C-F}$ = 273.7 Hz), 72.6, 59.5, 16.0, 13.8 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -60.16 ppm.

Elemental analysis calcd for $C_{13}H_{13}ClF_3NO$: C, 53.53; H, 4.49; N, 4.80, found: C, 53.68; H, 4.77; N, 5.14.

2-(2-chloro-5-fluorophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-oxazine (9ka)



Obtained as a white solid (61 mg, 0.25 mmol, 50%) after purification by flash column chromatography (hexane:AcOEt 97:3 + 1% Et_3N).

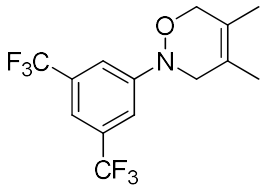
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, J = 8.7, 5.7 Hz, 1H), 7.20 (dd, J = 10.2, 2.8 Hz, 1H), 6.78 (td, J = 8.6, 2.9 Hz, 1H), 4.35 (s, 2H), 3.60 (s, 2H), 1.72 (s, 3H), 1.66 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, $^1J_{C-F}$ = 246.3 Hz), 131.0 (d, $^3J_{C-F}$ = 9 Hz), 124.7, 122.6, 113.8, 113.2, 112.2 (d, $^2J_{C-F}$ = 23.2 Hz), 107.6 (d, $^2J_{C-F}$ = 26.1 Hz), 72.6, 56.8, 16.0, 13.8 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -113.22 ppm.

Elemental analysis calcd for $C_{12}H_{13}ClFNO$: C, 59.63; H, 5.42; N, 5.80, found: C, 60.19; H, 5.67; N, 5.36.

2-(3,5-bis(trifluoromethyl)phenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-oxazine (9la)



Obtained as a white solid (112 mg, 0.34 mmol, 70%) after purification by flash column chromatography (hexane:AcOEt 99:1 + 1% Et_3N).

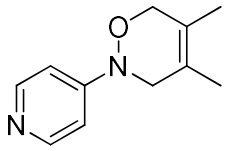
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 2H), 7.43 (s, 1H), 4.35 (s, 2H), 3.73 (s, 2H), 1.77 (s, 3H), 1.67 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 131.9 (q, $^2J_{C-F}$ = 33.2 Hz), 125.3, 123.6 (q, $^1J_{C-F}$ = 272.6 Hz), 121.6, 114.9, 72.4, 55.3, 16.0, 13.8 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.96 ppm.

Elemental analysis calcd for $C_{14}H_{13}F_6NO$: C, 51.70; H, 4.03; N, 4.31, found: C, 52.13; H, 4.51; N, 4.22.

4,5-dimethyl-2-(pyridin-4-yl)-3,6-dihydro-2*H*-1,2-oxazine (9ma)



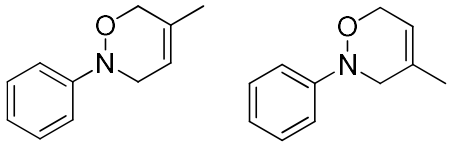
Obtained as a white solid (30 mg, 0.16 mmol, 32%) after purification by flash column chromatography (hexane:AcOEt 5:95 + 1% Et_3N).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, J = 5.0, 1.3 Hz, 2H), 6.87 (dd, J = 4.9, 1.5 Hz, 2H), 4.30 (s, 2H), 3.72 (s, 2H), 1.73 br, 3H), 1.63 (br, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 150.2, 125.0, 121.5, 108.7, 71.9, 53.1, 15.9, 13.8 ppm.

Elemental analysis calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73, found: C, 69.63; H, 7.27; N, 14.98.

5-methyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (9abA) and 4-methyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (9abB)



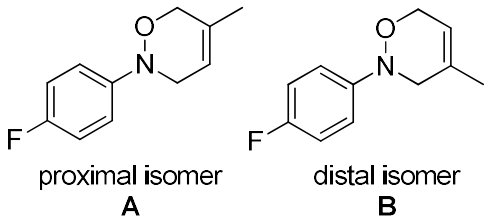
Obtained as a yellow oil (43 mg, 0.25 mmol, 50%) after purification by flash column chromatography (hexane:AcOEt 98:2 + 1% Et_3N).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H, both isomers), 7.19 – 7.09 (m, 2H, both isomers), 7.00 (tt, J = 7.6, 1.1 Hz, 1H, both isomers), 5.73 – 5.52 (m, 2H, both isomers), 4.51–4.47 (m, 2H, isomer B), 3.82 – 3.78 (m, 2H, isomer A), 3.72 – 3.68 (m, 2H, isomer B), 1.84 – 1.79 (m, 3H, isomer B)1.74 – 1.72 (m, 3H, isomer A) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6 (both isomers), 130.8 (both isomers), 128.9 (both isomers), 122.4 (both isomers), 119.9 (isomer B), 117.5 (isomer A), 116.1 (isomer A), 116.0 (isomer B), 114.1, 112.9, 72.2 (isomer A), 68.6 (isomer B), 56.2 (isomer B), 52.1 (isomer A), 20.3 (isomer B), 18.2 (isomer A) ppm.

Elemental analysis for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99; found: C, 75.81; H, 7.36; N, 8.26.

2-(4-fluorophenyl)-5-methyl-3,6-dihydro-2*H*-1,2-oxazine (9cbA) and 2-(4-fluorophenyl)-4-methyl-3,6-dihydro-2*H*-1,2-oxazine (9cbB)



Obtained as a yellow oil (55 mg, 0.28 mmol, 57%) after purification by flash column chromatography (hexane:AcOEt 100:0 + 1%Et_3N).

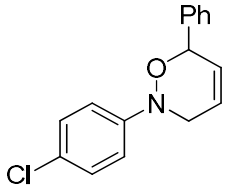
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.07 (m, 2H, both isomers), 7.04 – 6.96 (m, 2H, both isomers), 5.65 – 5.60 (m, 2H, both isomers), 4.49 – 4.45 (m, 2H, isomer B), 4.38 (br s, 2H, isomer A), 3.75 – 3.71 (m, 2H, isomerA), 3.65 – 3.60 (m, 2H, isomerB), 1.82 – 1.79 (m, 3H, isomer B) 1.74 – 1.71 (m, 3H, isomer A) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.9 (d, $^{1}J_{C-F}$ = 240.9 Hz, both isomers), 146.9 (d, $^{4}J_{C-F}$ = 2.3 Hz, both isomers),133.7 (isomer A), 130.8 (isomer B), 119.9 (both isomers), 118.05 (d, $^{3}J_{C-F}$ = 7.7 Hz, isomer A overlapped with signal at 118.01 ppm), 118.01 (d, $^{3}J_{C-F}$ = 7.9 Hz isomer B), 117.1 (d, $^{2}J_{C-F}$ = 29.0 Hz), 115.7 (d, $^{2}J_{C-F}$ = 22.4 Hz, isomer A, overlapped with signal at 115.5 ppm), 115.5 (d, $^{2}J_{C-F}$ = 22.0 Hz, isomer B), 72.3 (isomer A), 68.7, 56.9, 52.8 (isomer A), 20.3, 18.2 (isomer A) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -121.43 (isomer B), -128.19 (isomer A) ppm.

Elemental analysis calcd for $C_{11}H_{12}FNO$: C, 68.38; H, 6.26; N, 7.25, found: C, 68.24; H, 6.62; N, 7.55.

2-(4-chlorophenyl)-6-phenyl-3,6-dihydro-2*H*-1,2-oxazine (9bc)



Obtained as a white solid (80 mg, 0.29 mmol, 59%) after purification by flash column chromatography (hexane:AcOEt 100:0 to 90:10 + 1% Et_3N).

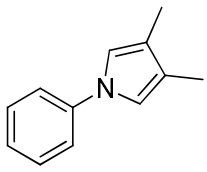
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, J = 7.9, 1.3 Hz, 2H), 7.42 – 7.31 (m, 3H), 7.22 (d, J = 8.9 Hz, 2H), 7.02 (d, J = 8.9 Hz, 2H), 6.20 – 5.99 (m, 2H), 5.60 (s, 1H), 4.02 – 3.78 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 138.8, 129.1, 128.8, 128.7, 128.6, 128.3, 127.3, 123.7, 117.2, 80.1, 51.7 ppm.

Elemental analysis calcd for $C_{16}H_{14}ClNO$: C, 70.72; H, 5.19; N, 5.15, found: C, 71.07; H, 5.23; N, 4.97.

4.8. Characterization data for *N*-arylpyrroles

3,4-dimethyl-1-phenyl-1*H*-pyrrole (10aa)



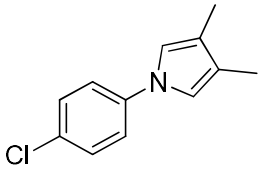
Obtained as a white solid (32 mg, 0.19 mmol, 75%) after purification by flash column chromatography using hexane.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 2H), 7.32 (dd, J = 8.6, 1.2 Hz, 2H), 7.16 (tt, J = 7.0, 1.3 Hz, 1H), 6.84 (s, 2H), 2.08 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 129.6, 124.7, 120.9, 119.6, 116.9, 10.3 ppm.

Elemental analysis calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18, found: C, 83.43; H, 7.77; N, 7.68.

1-(4-chlorophenyl)-3,4-dimethyl-1*H*-pyrrole (10ba)



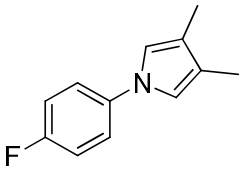
Obtained as a white solid (37 mg, 0.18 mmol, 72%) after purification by flash column chromatography using hexane.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 2H), 7.26 – 7.21 (m, 2H), 6.79 (s, 2H), 2.07 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 129.6, 124.3, 121.4, 120.6, 116.8, 10.3 ppm.

Elemental analysis calcd for $C_{12}H_{12}ClN$: C, 70.07; H, 5.88; N, 6.81, found; C, 70.25; H, 6.09; N, 7.14.

1-(4-fluorophenyl)-3,4-dimethyl-1*H*-pyrrole (10ca)



Obtained as a white solid (37 mg, 0.20 mmol, 75%) after purification by flash column chromatography using hexane.

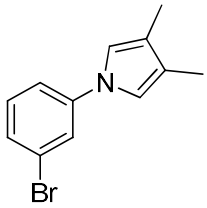
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 2H, overlapped with $CDCl_3$), 7.11 – 7.02 (m, 2H), 6.76 (s, 2H), 2.07 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (d, $^{1}J_{C-F}$ = 243.7 Hz), 137.4 (d, $^{4}J_{C-F}$ = 2.2 Hz), 121.3 (d, $^{3}J_{C-F}$ = 8.1 Hz), 121.0, 117.2, 116.3 (d, $^{2}J_{C-F}$ = 22.7 Hz), 116.2, 10.2 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -118.54 ppm.

Elemental analysis calcd for $C_{12}H_{12}FN$: C, 76.17; H, 6.39; N, 7.40, found: C, 75.04; H, 6.60; N, 6.84.

1-(3-bromophenyl)-3,4-dimethyl-1*H*-pyrrole (10da)



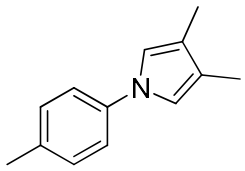
Obtained as a white solid (35 mg, 0.14 mmol, 54%) after purification by flash column chromatography using hexane.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.46 (m, 1H), 7.30 – 7.20 (m, 3H), 6.81 (s, 2H), 2.06 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 130.9, 127.5, 123.2, 122.5, 121.7, 117.8, 116.7, 10.3 ppm.

Elemental analysis calcd for $C_{12}H_{12}BrN$: C, 57.62; H, 4.84; N, 5.60, found: C, 58.00; H, 4.96; N, 5.54.

3,4-dimethyl-1-(*p*-tolyl)-1*H*-pyrrole (10fa)



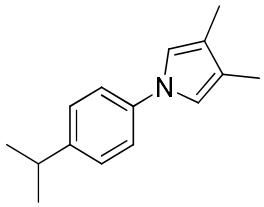
Obtained as a white solid (21 mg, 0.11 mmol, 46%) after purification by flash column chromatography using hexane.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.20 (m, 2H), 7.19 – 7.15 (m, 2H), 6.81 (s, 2H), 2.35 (s, 3H), 2.08 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 134.4, 130.1, 120.6, 119.7, 117.0, 20.9, 10.3 ppm.

Elemental analysis calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56, found: C, 84.35; H, 8.18; N, 7.70.

1-(4-isopropylphenyl)-3,4-dimethyl-1*H*-pyrrole (10ga)



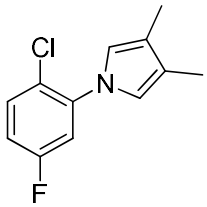
Obtained as a white solid (27 mg, 0.13 mmol, 51%) after purification by flash column chromatography using hexane.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 4H), 6.80 (s, 2H), 2.92 (p, J = 6.9 Hz, 1H), 2.08 (s, 6H), 1.27 (s, 3H), 1.26 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 138.9, 127.5, 120.5, 119.8, 117.0, 33.7, 24.2, 10.3 ppm.

Elemental analysis calcd for $C_{15}H_{19}N$: C, 84.46; H, 8.98; N, 6.57, found: C, 84.38; H, 9.12; N, 6.55.

1-(2-chloro-5-fluorophenyl)-3,4-dimethyl-1*H*-pyrrole (10ka)



Obtained as a colorless oil (22 mg, 0.10 mmol, 39%) after purification by flash column chromatography using hexane.

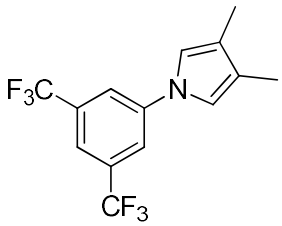
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, J = 8.9, 5.6 Hz, 1H), 7.01 (dd, J = 9.1, 3.0 Hz, 1H), 6.94 (ddd, J = 8.9, 7.5, 3.0 Hz, 1H), 6.68 (s, 2H), 2.07 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4 (d, $^{1}J_{C-F}$ = 249.0 Hz), 131.9 (d, $^{3}J_{C-F}$ = 8.8 Hz), 120.5, 119.6, 114.6 (d, $^{2}J_{C-F}$ = 23.4 Hz, overlapped with the *C*H at 114.4 ppm), 114.4 (d, $^{2}J_{C-F}$ = 22.6 Hz), 10.2 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -113.58 (dd, J = 14.0, 7.8 Hz) ppm.

Elemental analysis calcd for $C_{12}H_{11}ClFN$: C, 64.44; H, 4.96; N, 6.26, found: C, 64.73; H, 5.03; N, 5.88.

1-(3,5-bis(trifluoromethyl)phenyl)-3,4-dimethyl-1*H*-pyrrole (10la)



Obtained as a white solid (5 mg, 0.02 mmol, 7%) after purification by flash column chromatography using hexane.

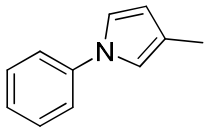
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 2H), 7.62 (s, 1H), 6.89 (s, 2H), 2.07 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 133.2 (q, $^{2}J_{C-F}$ = 33.4 Hz), 125.9 (q, $^{1}J_{C-F}$ = 273.1 Hz), 123.2, 118.7 (m, $^{4}J_{C-F}$ = 2.9 Hz), 117.6 (m, $^{4}J_{C-F}$ = 4 Hz), 116.5, 10.3 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.09 ppm.

Elemental analysis calcd for $C_{14}H_{11}F_6N$: C, 54.73; H, 3.61; N, 4.56, found: C, 54.75; H, 3.78; N, 4.40.

3-methyl-1-phenyl-1*H*-pyrrole (10ab)



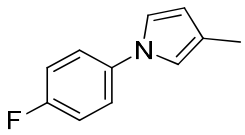
Obtained as a white solid (6 mg, 0.04 mmol, 16%) after purification by flash column chromatography using hexane.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.31 (m, 4H), 7.24 – 7.14 (m, 1H), 7.00 (t, J = 2.5 Hz, 1H), 6.88 (tt, J = 2.0, 1.1 Hz, 1H), 6.23 – 6.13 (m, 1H), 2.18 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 129.6, 125.3, 121.3, 120.1, 119.1, 117.3, 112.1, 12.1 ppm.

Elemental analysis calcd for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91, found: C, 83.84; H, 7.17; N, 8.95.

1-(4-fluorophenyl)-3-methyl-1*H*-pyrrole (10cb)



Obtained as a white solid (6 mg, 0.03 mmol, 15%) after purification by flash column chromatography using hexane.

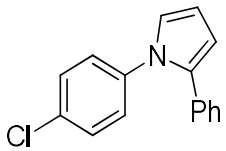
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H), 7.09 (t, J = 8.6 Hz, 2H), 6.91 (s, 1H), 6.79 (s, 1H), 6.17 (s, 1H), 2.16 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5 (d, $^{1}J_{C-F}$ = 244.1 Hz), 137.4 (d, $^{4}J_{C-F}$ = 2.2 Hz), 121.9 (d, $^{3}J_{C-F}$ = 8.1 Hz), 121.4, 119.4, 117.6, 116.4 (d, $^{2}J_{C-F}$ = 22.7 Hz), 112.2, 12.1 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -117.81 ppm.

Elemental analysis calcd for $C_{11}H_{10}FN$: C, 75.41; H, 5.75; N, 7.99, found: C, 75.35; H, 5.80; N, 8.22.

1-(4-chlorophenyl)-2-phenyl-1*H*-pyrrole (10bc)



Obtained as a white solid (42 mg, 0.17 mmol, 66%) after purification by flash column chromatography using hexane.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.25 – 7.16 (m, 3H), 7.16 – 7.07 (m, 4H), 6.91 (dd, J = 2.8, 1.8 Hz, 1H), 6.44 (dd, J = 3.5, 1.8 Hz, 1H), 6.39 – 6.34 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 134.0, 132.8, 132.4, 129.3, 128.5, 128.4, 127.0, 126.7, 124.3, 111.2, 109.8 ppm.

Elemental analysis calcd for $C_{16}H_{12}ClN$: C, 75.74; H, 4.77; N, 5.52, found: C, 75.55; H, 4.98; N, 5.34.

References

(1) Homer, J. A.; Sperry, J. *J. Nat. Prod.* **2017**, *80*, 2178.

(2) Nguyen, H. H.; Kim, M. B.; Wilson, R. J.; Butch, C. J.; Kuo, K. M.; Miller, E. J.; Tahirovic, Y. A.; Jecs, E.; Truax, V. M.; Wang, T.; Sum, C. S.; Cvijic, M. E.; Schroeder, G. M.; Wilson, L. J.; Liotta, D. C. *J. Med. Chem.* **2018**, *61*, 7168.

(3) Showalter, H. D. H. *J. Nat. Prod.* **2013**, *76*, 455.

(4) Stepek, I. A.; Itami, K. *ACS Mater. Lett.* **2020**, *2*, 951.

(5) McQuade, D. T.; Pullen, A. E.; Swager, T. M. *Chem. Rev.* **2000**, *100*, 2537.

(6) McCullough, R. D. *Adv. Mater.* **1998**, *10*, 93.

(7) Bhunia, S.; Pawar, G. G.; Kumar, S. V.; Jiang, Y.; Ma, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 16136.

(8) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564.

(9) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450.

(10) Wegener, G.; Brandt, M.; Duda, L.; Hofmann, J.; Klesczewski, B.; Koch, D.; Kumpf, R.-J.; Orzesek, H.; Pirkl, H.-G.; Six, C.; Steinlein, C.; Weisbeck, M. *Appl. Catal., A.* **2001**, *221*, 303.

(11) Tomkins, P.; Gebauer-Henke, E.; Leitner, W.; Müller, T. E. *ACS Catal.* **2015**, *5*, 203.

(12) Rai, R. K.; Mahata, A.; Mukhopadhyay, S.; Gupta, S.; Li, P.-Z.; Nguyen, K. T.; Zhao, Y.; Pathak, B.; Singh, S. K. *Inorg. Chem.* **2014**, *53*, 2904.

(13) Cantillo, D.; Moghaddam, M. M.; Kappe, C. O. *J. Org. Chem.* **2013**, *78*, 4530.

(14) Zou, D.; Wang, W.; Hu, Y.; Jia, T. *Org. Biomol. Chem.* **2023**, *21*, 2254.

(15) Khanal, H. D.; Perumal, M.; Lee, Y. R. *Org. Biomol. Chem.* **2022**, *20*, 7675.

(16) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 12898.

(17) Sundberg, R. J. *J. Org. Chem.* **1965**, *30*, 3604.

(18) Cadogan, J. I. G.; Todd, M. J. *J. Chem. Soc. C.* **1969**, 2808.

(19) Tafesh, A. M.; Weiguny, J. *Chem. Rev.* **1996**, *96*, 2035.

(20) Crotti, C.; Cenini, S.; Rindone, B.; Tollari, S.; Demartin, F. *J. Chem. Soc., Chem. Commun.* **1986**, 784.

(21) Ferretti, F.; Ramadan, D. R.; Ragaini, F. *ChemCatChem* **2019**, *11*, 4450.

(22) Ragaini, F.; Ferretti, F.; Fouad, M. A. *Catalysts* **2023**, *13*, 224.

(23) Fouad, M. A.; Ferretti, F.; Formenti, D.; Milani, F.; Ragaini, F. *Eur. J. Org. Chem.* **2021**, 4876.

(24) Ramadan, D. R.; Ferretti, F.; Ragaini, F. *J. Catal.* **2022**, *409*, 41.

(25) EL-Atawy, M. A.; Formenti, D.; Ferretti, F.; Ragaini, F. *ChemCatChem* **2018**, *10*, 4707.

(26) Formenti, D.; Ferretti, F.; Ragaini, F. *ChemCatChem* **2018**, *10*, 148.

(27) Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Wu, T. Y.-H.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2105.

(28) Kagata, T.; Saito, S.; Shigemori, H.; Ohsaki, A.; Ishiyama, H.; Kubota, T.; Kobayashi, J. i. *J. Nat. Prod.* **2006**, *69*, 1517.

(29) Rayabarapu, D. K.; Zhou, A.; Jeon, K. O.; Samarakoon, T.; Rolfe, A.; Siddiqui, H.; Hanson, P. R. *Tetrahedron* **2009**, *65*, 3180.

(30) Ninomiya, I. *J. Nat. Prod.* **1992**, *55*, 541.

(31) Kraikruan, P.; Rakchaya, I.; Sang-aroon, P.; Chuanopparat, N.; Ngernmeesri, P. *Synlett* **2022**, *33*, 1443.

(32) Lei, X.; Angeli, G. K.; Neochoritis, C. G.; Dömling, A. *Green Chem.* **2022**, *24*, 6168.

(33) Barden, T. C. In *Heterocyclic Scaffolds II: Reactions and Applications of Indoles*; Gribble, G. W., Ed.; Springer Berlin Heidelberg: Berlin, Heidelberg, 2010, p 31.

(34) Sravanthi, T. V.; Manju, S. L. *Eur. J. Pharm. Sci.* **2016**, *91*, 1.

(35) Chen, F.-E.; Huang, J. *Chem. Rev.* **2005**, *105*, 4671.
(36) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875.
(37) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29.
(38) Robinson, B. *Chem. Rev.* **1969**, *69*, 227.
(39) Fischer, E. In *Untersuchungen über Triphenylmethanfarbstoffe Hydrazine und Indole*; Fischer, E., Bergmann, M., Eds.; Springer Berlin Heidelberg: Berlin, Heidelberg, 1924, p 163.
(40) Cadogan, J. I. G.; Cameron-Wood, M. *Proc. Chem. Soc.* **1962**, 361.
(41) Cadogan, J. I. G.; Cameron-Wood, M.; Mackie, R. K.; Searle, R. J. G. *J. Chem. Soc.* **1965**, 4831.
(42) Sundberg, R. J.; Yamazaki, T. *J. Org. Chem.* **1967**, *32*, 290.
(43) Majgier-Baranowska, H.; Williams, J. D.; Li, B.; Peet, N. P. *Tetrahedron Lett.* **2012**, *53*, 4785.
(44) Sanz, R.; Escribano, J.; Pedrosa, M. R.; Aguado, R.; Arnaiz, F. J. *Adv. Synth. Catal.* **2007**, *349*, 713.
(45) Suárez-Pantiga, S.; Sanz, R. *Org. Biomol. Chem.* **2021**, *19*, 10472.
(46) Freeman, A. W.; Urvoy, M.; Criswell, M. E. *J. Org. Chem.* **2005**, *70*, 5014.
(47) Qu, Z.; Wang, P.; Chen, X.; Deng, G.-J.; Huang, H. *Chin. Chem. Lett.* **2021**, *32*, 2582.
(48) Tong, S.; Xu, Z.; Mamboury, M.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 11809.
(49) Ponticello, G. S.; Baldwin, J. J. *J. Org. Chem.* **1979**, *44*, 4003.
(50) Bujok, R.; Wróbel, Z.; Wojciechowski, K. *Synlett* **2012**, *23*, 1315.
(51) Wróbel, Z.; Wojciechowski, K. *Synlett* **2011**, 2567.
(52) Boyarskaya, D. V.; Ongaro, A.; Piemontesi, C.; Wang, Q.; Zhu, J. *Org. Lett.* **2022**, *24*, 7004.
(53) Yang, K.; Zhou, F.; Kuang, Z.; Gao, G.; Driver, T. G.; Song, Q. *Org. Lett.* **2016**, *18*, 4088.
(54) Shevlin, M.; Guan, X.; Driver, T. G. *ACS Catal.* **2017**, *7*, 5518.
(55) Nykaza, T. V.; Ramirez, A.; Harrison, T. S.; Luzung, M. R.; Radosevich, A. T. *J. Am. Chem. Soc.* **2018**, *140*, 3103.
(56) Umeda, R.; Nishimoto, Y.; Mashino, T.; Nishiyama, Y. *Heterocycles* **2013**, *87*, 1241.
(57) Nishiyama, Y.; Maema, R.; Ohno, K.; Hirose, M.; Sonoda, N. *Tetrahedron Lett.* **1999**, *40*, 5717.
(58) Ragaini, F.; Tollari, S.; Cenini, S.; Bettetini, E. *J. Mol. Catal. A: Chem.* **1996**, *111*, 91.
(59) Tollari, S.; Cenini, S.; Crotti, C.; Gianella, E. *J. Mol. Catal.* **1994**, *87*, 203.
(60) Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1994**, *59*, 3375.
(61) Söderberg, B. C.; Shriver, J. A. *J. Org. Chem.* **1997**, *62*, 5838.
(62) Davies, I. W.; Smitrovich, J. H.; Sidler, R.; Qu, C.; Gresham, V.; Bazaral, C. *Tetrahedron* **2005**, *61*, 6425.
(63) Glotz, G.; Gutmann, B.; Hanselmann, P.; Kulesza, A.; Roberge, D.; Kappe, C. O. *RSC Adv.* **2017**, *7*, 10469.
(64) Okuro, K.; Gurnham, J.; Alper, H. *J. Org. Chem.* **2011**, *76*, 4715.
(65) Soderberg, B. C. G. *Curr. Org. Chem.* **2000**, *4*, 727.
(66) Tsygankov, A. A.; Makarova, M.; Chusov, D. *Mendeleev Commun.* **2018**, *28*, 113.
(67) Afanasyev, O. I.; Chusov, D. *Ineos Open* **2020**, *3*, 133.
(68) Ragaini, F. In *Reference Module in Chemistry, Molecular Sciences and Chemical Engineering*; Elsevier: 2016.
(69) Ragaini, F.; Cenini, S.; Gallo, E.; Caselli, A.; Fantauzzi, S. *Curr. Org. Chem.* **2006**, *10*, 1479.
(70) Ferretti, F.; Formenti, D.; Ragaini, F. *Rend. Lincei* **2017**, *28*, 97.
(71) Tollari, S.; Cenini, S.; Ragaini, F.; Cassar, L. *J. Chem. Soc., Chem. Commun.* **1994**, 1741.
(72) Rahman, S. M. A.; Söderberg, B. C. G. *Tetrahedron* **2021**, *94*, 132331.

(73) Ansari, N. H.; Dacko, C. A.; Akhmedov, N. G.; Söderberg, B. C. G. *J. Org. Chem.* **2016**, *81*, 9337.
(74) Hubbard, J. W.; Piegols, A. M.; Soderberg, B. C. G. *Tetrahedron* **2007**, *63*, 7077.
(75) O'Dell, D. K.; Nicholas, K. M. *J. Org. Chem.* **2003**, *68*, 6427.
(76) Ragaini, F.; Cenini, S.; Borsani, E.; Dompe, M.; Gallo, E.; Moret, M. *Organometallics* **2001**, *20*, 3390.
(77) Penoni, A.; Nicholas, K. M. *Chem. Commun.* **2002**, 484.
(78) Ragaini, F.; Ventriglia, F.; Hagar, M.; Fantauzzi, S.; Cenini, S. *Eur. J. Org. Chem.* **2009**, *2009*, 2185.
(79) Hsieh, T. H. H.; Dong, V. M. *Tetrahedron* **2009**, *65*, 3062.
(80) Ferretti, F.; El-Atawy, M. A.; Muto, S.; Hagar, M.; Gallo, E.; Ragaini, F. *Eur. J. Org. Chem.* **2015**, 5712.
(81) El-Atawy, M. A.; Ferretti, F.; Ragaini, F. *Eur. J. Org. Chem.* **2017**, 1902.
(82) EL-Atawy, M. A.; Ferretti, F.; Ragaini, F. *Eur. J. Org. Chem.* **2018**, 4818.
(83) Wu, L.; Liu, Q.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 6310.
(84) Konishi, H.; Manabe, K. *Synlett* **2014**, *25*, 1971.
(85) Su, Z.; Liu, B.; Liao, H.; Lin, H.-W. *Eur. J. Org. Chem.* **2020**, 4059.
(86) Yao, L.; Wei, P.; Ying, J.; Wu, X.-F. *Org. Chem. Front.* **2022**, *9*, 2685.
(87) Yao, L.; Ying, J.; Wu, X.-F. *Org. Chem. Front.* **2021**, *8*, 6541.
(88) Qi, X.; Zhou, R.; Peng, J.-B.; Ying, J.; Wu, X.-F. *Eur. J. Org. Chem.* **2019**, *2019*, 5161.
(89) Zhou, R.; Qi, X.; Wu, X.-F. *ACS Comb. Sci.* **2019**, *21*, 573.
(90) Guan, X.; Zhu, H.; Zhao, Y.; Driver, T. G. *Eur. J. Org. Chem.* **2020**, *2020*, 57.
(91) Fouad, M. A.; Ferretti, F.; Ragaini, F. *J. Org. Chem.* **2023**, *88*, 5108.
(92) Ferretti, F.; El-Atawy, M. A.; Muto, S.; Hagar, M.; Gallo, E.; Ragaini, F. *Eur. J. Org. Chem.* **2015**, 5712.
(93) Carter, M. E.; Nash Jr, J. L.; Drueke Jr, J. W.; Schwietert, J. W.; Butler, G. B. *J Polym Sci Polym Chem Ed* **1978**, *16*, 937.
(94) Berman, R. S.; Kochi, J. K. *Inorg. Chem.* **1980**, *19*, 248.
(95) Skoog, S. J.; Gladfelter, W. L. *J. Am. Chem. Soc.* **1997**, *119*, 11049.
(96) Kunin, A. J.; Noirot, M. D.; Gladfelter, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 2739.
(97) Belousov, Y. A. *Russ. Chem. Rev.* **2007**, *76*, 41.
(98) Belousov, Y. A.; Kolosova, T. A. *Polyhedron* **1987**, *6*, 1959.
(99) Ragaini, F.; Song, J. S.; Ramage, D. L.; Geoffroy, G. L.; Yap, G. A. P.; Rheingold, A. L. *Organometallics* **1995**, *14*, 387.
(100) Ragaini, F. *Organometallics* **1996**, *15*, 3572.
(101) Liu, P. H.; Liao, H. Y.; Cheng, C. H. *J. Chem. Soc., Chem. Commun.* **1995**, 2441.
(102) Ragaini, F.; Cenini, S.; Demartin, F. *J. Chem. Soc., Chem. Commun.* **1992**, 1467.
(103) Ragaini, F.; Cenini, S.; Demartin, F. *Organometallics* **1994**, *13*, 1178.
(104) Gallo, E.; Ragaini, F.; Cenini, S.; Demartin, F. *J. Organomet. Chem.* **1999**, *586*, 190
(105) Tomson, N. C.; Labios, L. A.; Weyhermüller, T.; Figueroa, J. S.; Wieghardt, K. *Inorg. Chem.* **2011**, *50*, 5763.
(106) Popp, B. V.; Thorman, J. L.; Morales, C. M.; Landis, C. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2004**, *126*, 14832.
(107) Todres, Z. V. *J. Organomet. Chem.* **1992**, *441*, 349.
(108) Zhou, F.; Wang, D.-S.; Driver, T. G. *Adv. Synth. Catal.* **2015**, *357*, 3463.
(109) EL-Atawy, M. A.; Ferretti, F.; Ragaini, F. *Eur. J. Org. Chem.* **2019**, 4968.
(110) Ferretti, F.; Ragaini, F.; Lariccia, R.; Gallo, E.; Cenini, S. *Organometallics* **2010**, *29*, 1465.
(111) Ferretti, F.; Gallo, E.; Ragaini, F. *J. Organomet. Chem.* **2014**, *771*, 59.

(112) Peng, J.-B.; Chen, B.; Qi, X.; Ying, J.; Wu, X.-F. *Adv. Synth. Catal.* **2018**, *360*, 4153.
(113) Sang, R.; Kucmierczyk, P.; Dong, K.; Franke, R.; Neumann, H.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* **2018**, *140*, 5217.
(114) Hussain, N.; Chhalodia, A. K.; Ahmed, A.; Mukherjee, D. *ChemistrySelect* **2020**, *5*, 11272.
(115) Molaei, E.; Mohammadsaleh, F.; Niknam, K. *Catal. Lett.* **2020**, *150*, 1970.
(116) Qi, X.; Li, C.-L.; Jiang, L.-B.; Zhang, W.-Q.; Wu, X.-F. *Catal. Sci. Technol.* **2016**, *6*, 3099.
(117) Shibahara, F.; Kinoshita, S.; Nozaki, K. *Org. Lett.* **2004**, *6*, 2437.
(118) Ying, J.; Fu, L.-Y.; Zhou, C.; Qi, X.; Peng, J.-B.; Wu, X.-F. *Eur. J. Org. Chem.* **2018**, 2780.
(119) Shen, C.; Dong, K.; Wei, Z.; Tian, X. *Organometallics* **2022**, *41*, 246.
(120) Strazzolini, P.; G. Giumanini, A.; Cauci, S. *Tetrahedron* **1990**, *46*, 1081.
(121) Tien, C. H.; Trofimova, A.; Holownia, A.; Kwak, B. S.; Larson, R. T.; Yudin, A. K. *Angew. Chem. Int. Ed.* **2021**, *60*, 4342.
(122) Prat, D.; Pardigon, O.; Flemming, H.-W.; Letestu, S.; Ducandas, V.; Isnard, P.; Guntrum, E.; Senac, T.; Ruisseau, S.; Cruciani, P.; Hosek, P. *Org. Process Res. Dev.* **2013**, *17*, 1517.
(123) Soderberg, B. C. G.; Banini, S. R.; Turner, M. R.; Minter, A. R.; Arrington, A. K. *Synthesis* **2008**, 903.
(124) Gasperini, M.; Ragaini, F.; Cazzaniga, C.; Cenini, S. *Adv. Synth. Catal.* **2005**, *347*, 105.
(125) Gasperini, M.; Ragaini, F.; Remondini, C.; Caselli, A.; Cenini, S. *J. Organomet. Chem.* **2005**, *690*, 4517.
(126) Dai, W.-M.; Sun, L.-P.; Guo, D.-S. *Tetrahedron Lett.* **2002**, *43*, 7699.
(127) McGookin, A. *J. Soc. Chem. Ind., London* **1949**, *68*, 195.
(128) Alessio, E.; Mestroni, G. *J. Mol. Catal.* **1984**, *26*, 337.
(129) Wehman, P.; Kaasjager, V. E.; Delange, W. G. J.; Hartl, F.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Fraanje, J.; Goubitz, K. *Organometallics* **1995**, *14*, 3751.
(130) Ragaini, F.; Cognolato, C.; Gasperini, M.; Cenini, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 2886.
(131) Beckers, T.; Reissmann, T.; Schmidt, M.; Burger, A. M.; Fiebig, H. H.; Vanhoefer, U.; Pongratz, H.; Hufsky, H.; Hockemeyer, J.; Frieser, M.; Mahboobi, S. *Cancer Res.* **2002**, *62*, 3113.
(132) Manna, M. K.; Bairy, G.; Jana, R. *Org. Biomol. Chem.* **2017**, *15*, 5899.
(133) Umeda, R.; Kouno, H.; Kitagawa, T.; Okamoto, T.; Kawashima, K.; Mashino, T.; Nishiyama, Y. *Heteroat. Chem* **2014**, *25*, 698.
(134) Ragaini, F.; Sportiello, P.; Cenini, S. *J. Organomet. Chem.* **1999**, *577*, 283.
(135) Akazome, M.; Kondo, T.; Watanabe, Y. *Chem. Lett.* **1992**, *21*, 769.
(136) Gupta, A.; Khajuria, R.; Kapoor, K. K. *Synth. Commun.* **2016**, *46*, 31.
(137) Siu, J.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2004**, *2*, 160.
(138) Lu, B.-L.; Shi, M. *Chem. Eur. J.* **2011**, *17*, 9070.
(139) Maity, S.; Naveen, T.; Sharma, U.; Maiti, D. *Org. Lett.* **2013**, *15*, 3384.
(140) Martinelli, E.; Vicini, A. C.; Mancinelli, M.; Mazzanti, A.; Zani, P.; Bernardi, L.; Fochi, M. *Chem. Commun.* **2015**, *51*, 658.
(141) Lee, S. J.; Seo, H.-A.; Cheon, C.-H. *Adv. Synth. Catal.* **2016**, *358*, 1566.
(142) Callonnec, F. L.; Fouquet, E.; Felpin, F.-X. *Org. Lett.* **2011**, *13*, 2646.
(143) Motoshima, K.; Noguchi-Yachide, T.; Sugita, K.; Hashimoto, Y.; Ishikawa, M. *Bioorg. Med. Chem.* **2009**, *17*, 5001.
(144) Nomura, S.; Endo-Umeda, K.; Makishima, M.; Hashimoto, Y.; Ishikawa, M. *ChemMedChem* **2016**, *11*, 2347.
(145) Nepveu, F.; Kim, S.; Boyer, J.; Chatriant, O.; Ibrahim, H.; Reybier, K.; Monje, M.-C.; Chevalley, S.; Perio, P.; Lajoie, B. H.; Bouajila, J.; Deharo, E.; Sauvain, M.; Tahar, R.; Basco, L.; Pantaleo, A.; Turini, F.; Arese, P.; Valentin, A.; Thompson, E.; Vivas, L.; Petit, S.; Nallet, J.-P. *J. Med. Chem.* **2010**, *53*, 699.

(146) Kikukawa, K.; Maemura, K.; Kiseki, Y.; Wada, F.; Matsuda, T.; Giam, C. S. *J. Org. Chem.* **1981**, *46*, 4885.
(147) Cullinane, N. M. *J. Chem. Soc., Trans.* **1923**, *123*, 2053.
(148) Bishop, G.; Brady, O. L. *J. Chem. Soc., Trans.* **1922**, *121*, 2364.
(149) Zhang, G.; Yang, K.; Wang, S.; Feng, Q.; Song, Q. *Org. Lett.* **2021**, *23*, 595.
(150) Leung, D. H.; Ziller, J. W.; Guan, Z. *J. Am. Chem. Soc.* **2008**, *130*, 7538.
(151) Rimoldi, M.; Ragaini, F.; Gallo, E.; Ferretti, F.; Macchi, P.; Casati, N. *Dalton Trans.* **2012**, *41*, 3648.
(152) Lee, D. J.; Kim, M.; Kim, C. K.; Lee, I. M. *Bull. Korean Chem. Soc.* **2019**, *40*, 710.
(153) Álvarez-Calero, J. M.; Jorge, Z. D.; Massanet, G. M. *Org. Lett.* **2016**, *18*, 6344.
(154) Munoz, L.; Rodriguez, A. M.; Rosell, G.; Bosch, M. P.; Guerrero, A. *Org. Biomol. Chem.* **2011**, *9*, 8171.
(155) Charles, G. *Bull. Soc. Chim. Fr.* **1963**, 1573.
(156) Hsieh, T. H. H.; Dong, V. M. *Tetrahedron* **2009**, *65*, 3062.
(157) Dornow, A.; Lüpfert, S. *Chem. Ber.* **1957**, *90*, 1780.
(158) Isao, S.; Yoichi, T.; Tohru, T.; Akihiro, O.; Eisaku, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3048.
(159) Kikukawa, K.; Maemura, K.; Kiseki, Y.; Wada, F.; Matsuda, T.; Giam, C. S. *J. Org. Chem.* **1981**, *46*, 4885.
(160) Bishop, G.; Brady, O. L. *J. Chem. Soc., Trans.* **1922**, *121*, 2364.
(161) Lieber, S.; Scheer, F.; Meissner, W.; Naruhn, S.; Adhikary, T.; Müller-Brüsselbach, S.; Diederich, W. E.; Müller, R. *J. Med. Chem.* **2012**, *55*, 2858.
(162) Morrill, C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 2842.
(163) Garcia, E. E.; Fryer, R. I. *J. Heterocycl. Chem.* **1974**, *11*, 219.
(164) Vetelino, M. G.; Coe, J. W. *Tetrahedron Lett.* **1994**, *35*, 219.
(165) Armstrong, G. L.; Conn, L. A.; Pinner, R. W. *JAMA* **1999**, *281*, 61.
(166) Cross, R. M.; Flanigan, D. L.; Monastyrskyi, A.; LaCrue, A. N.; Sáenz, F. E.; Maignan, J. R.; Mutka, T. S.; White, K. L.; Shackleford, D. M.; Bathurst, I.; Fronczek, F. R.; Wojtas, L.; Guida, W. C.; Charman, S. A.; Burrows, J. N.; Kyle, D. E.; Manetsch, R. *J. Med. Chem.* **2014**, *57*, 8860.
(167) Baharoglu, Z.; Garriss, G.; Mazel, D. *Antibiotics* **2013**, *2*, 288.
(168) Walsh, C. *Nat. Rev. Microbiol.* **2003**, *1*, 65.
(169) Shen, C.; Wang, A.; Xu, J.; An, Z.; Loh, K. Y.; Zhang, P.; Liu, X. *Chem* **2019**, *5*, 1059.
(170) Hu, W.; Lin, J.-P.; Song, L.-R.; Long, Y.-Q. *Org. Lett.* **2015**, *17*, 1268.
(171) Lesher, G. Y.; Froelich, E. J.; Gruett, M. D.; Bailey, J. H.; Brundage, R. P. *J. Med. Chem.* **1962**, *5*, 1063.
(172) Pham, T. D. M.; Ziora, Z. M.; Blaskovich, M. A. T. *MedChemComm* **2019**, *10*, 1719.
(173) Barry, P. J.; Donaldson, A. L.; Jones, A. M. *BMJ* **2018**, *361*, k1783.
(174) Shimura, K.; Kodama, E.; Sakagami, Y.; Matsuzaki, Y.; Watanabe, W.; Yamataka, K.; Watanabe, Y.; Ohata, Y.; Doi, S.; Sato, M.; Kano, M.; Ikeda, S.; Matsuoka, M. *J. Virol.* **2008**, *82*, 764.
(175) Singh, S.; Nerella, S.; Pabbaraja, S.; Mehta, G. *Org. Lett.* **2020**, *22*, 1575.
(176) Kim, M. E.; Jung, I.; Lee, J. S.; Na, J. Y.; Kim, W. J.; Kim, Y.-O.; Park, Y.-D.; Lee, J. S. *Mar. Drugs* **2017**, *15*, 336.
(177) Cretton, S.; Breant, L.; Pourrez, L.; Ambuehl, C.; Marcourt, L.; Ebrahimi, S. N.; Hamburger, M.; Perozzo, R.; Karimou, S.; Kaiser, M.; Cuendet, M.; Christen, P. *J. Nat. Prod.* **2014**, *77*, 2304.
(178) Naeem, A.; Badshah, S. L.; Muska, M.; Ahmad, N.; Khan, K. *Molecules* **2016**, *21*, 268.
(179) Boteva, A. A.; Krasnykh, O. P. *Chem. Heterocycl. Comp.* **2009**, *45*, 757.
(180) Jones, C. P.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 7968.
(181) Dar'in, D. V.; Lobanov, P. S. *Russ. Chem. Rev.* **2015**, *84*, 601.

(182) Joussot, J.; Schoenfelder, A.; Larquetoux, L.; Nicolas, M.; Suffert, J.; Blond, G. *Synthesis* **2016**, *48*, 3364.
(183) Wang, F.; Jin, L.; Kong, L.; Li, X. *Org. Lett.* **2017**, *19*, 1812.
(184) Shi, P.; Wang, L.; Chen, K.; Wang, J.; Zhu, J. *Org. Lett.* **2017**, *19*, 2418.
(185) Ghosh, P.; Nandi, A. K.; Das, S. *Tetrahedron Lett.* **2018**, *59*, 2025.
(186) Wang, J.-S.; Li, C.; Ying, J.; Xu, T.; Lu, W.; Li, C.-Y.; Wu, X.-F. *J. Catal.* **2022**, *408*, 81.
(187) Dine, I.; Mulugeta, E.; Melaku, Y.; Belete, M. *RSC Adv.* **2023**, *13*, 8657.
(188) Ragaini, F.; Cenini, S.; Gasperini, M. *J Mol Catal a-Chem* **2001**, *174*, 51.
(189) Tafesh, A. M.; Beller, M. *Tetrahedron Lett.* **1995**, *36*, 9305.
(190) Söderberg, B. C. G.; Berkowitz, W. F. *Org. React.* **2023**, 417.
(191) Ragaini, F.; Cenini, S.; Gallo, E.; Caselli, A.; Fantauzzi, S. *Curr. Org. Chem.* **2006**, *10*, 1479.
(192) Cenini, S.; Ragaini, F. *Catalytic Reductive Carbonylation of Organic Nitro Compounds*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1996.
(193) Bernauer, J.; Pölker, J.; Jacobi von Wangelin, A. *ChemCatChem* **2022**, *14*, e202101182.
(194) Gasperini, M.; Ragaini, F.; Gazzola, E.; Caselli, A.; Macchi, P. *Dalton Trans.* **2004**, 3376.
(195) Annunziata, R.; Cenini, S.; Palmisano, G.; Tollari, S. *Synth. Commun.* **1996**, *26*, 495.
(196) Lin, J.-P.; Long, Y.-Q. *Chem. Commun.* **2013**, *49*, 5313.
(197) Ragaini, F.; Ventriglia, F.; Hagar, M.; Fantauzzi, S.; Cenini, S. *Eur. J. Org. Chem.* **2009**, 2185.
(198) Smitrovich, J. H.; Davies, I. W. *Org. Lett.* **2004**, *6*, 533.
(199) Clawson, R. W.; Dacko, C. A.; Deavers, R. E.; Akhmedov, N. G.; Soderberg, B. C. G. *Tetrahedron* **2009**, *65*, 8786.
(200) Tollari, S.; Penoni, A.; Cenini, S. *J. Mol. Catal. A: Chem.* **2000**, *152*, 47.
(201) Stashenko, E. E.; Acosta, R.; Martínez, J. R. *J. Biochem. Biophys. Methods* **2000**, *43*, 379.
(202) Wu, T.-S.; Shi, L.-S.; Wang, J.-J.; Iou, S.-C.; Chang, H.-C.; Chen, Y.-P.; Kuo, Y.-H.; Chang, Y.-L.; Tenge, C.-M. *J. Chin. Chem. Soc.* **2003**, *50*, 171.
(203) An, Z.-Y.; Yan, Y.-Y.; Peng, D.; Ou, T.-M.; Tan, J.-H.; Huang, S.-L.; An, L.-K.; Gu, L.-Q.; Huang, Z.-S. *Eur. J. Med. Chem.* **2010**, *45*, 3895.
(204) Ghosh, S.; Bishayee, K.; Khuda-Bukhsh, A. R. *Phytother. Res.* **2014**, *28*, 1153.
(205) Zhou, S.; Huang, G. *Biomed. Pharmacother.* **2022**, *146*, 112556.
(206) Kamal, L. Z. M.; Hassan, N. M.; Taib, N. M.; Soe, M. K. *Sains Malays* **2018**, *47*, 2429.
(207) Penoni, A.; Volkmann, J.; Nicholas, K. M. *Org. Lett.* **2002**, *4*, 699.
(208) Climent, M. J.; Corma, A.; Iborra, S.; Martí, L. *ACS Catal.* **2015**, *5*, 157.
(209) Lin, Z.; Hu, Z.; Zhang, X.; Dong, J.; Liu, J.-B.; Chen, D.-Z.; Xu, X. *Org. Lett.* **2017**, *19*, 5284.
(210) Yadav, G. D.; Wagh, D. P. *ChemistrySelect* **2020**, *5*, 9059.
(211) Aksenov, N. A.; Aksenov, D. A.; Arutiunov, N. A.; Aksenova, D. S.; Aksenov, A. V.; Rubin, M. *RSC Adv.* **2020**, *10*, 18440.
(212) Romek, A.; Opatz, T. *Eur. J. Org. Chem.* **2010**, *2010*, 5841.
(213) Haddad, N.; Tan, J.; Farina, V. *J. Org. Chem.* **2006**, *71*, 5031.
(214) Sun, F.; Zhao, X.; Shi, D. *Tetrahedron Lett.* **2011**, *52*, 5633.
(215) Åkerbladh, L.; Nordeman, P.; Wejdemar, M.; Odell, L. R.; Larhed, M. *J. Org. Chem.* **2015**, *80*, 1464.
(216) Lohrer, B.; Bracher, F. *Tetrahedron Lett.* **2019**, *60*, 151327.
(217) Singh, P.; Kumar Sahoo, S.; Sridhar Goud, N.; Swain, B.; Madhavi Yaddanapudi, V.; Arifuddin, M. *Asian J. Org. Chem.* **2022**, *11*, e202200181.
(218) Malbari, K.; Saha, P.; Chawla-Sarkar, M.; Dutta, S.; Rai, S.; Joshi, M.; Kanyalkar, M. *Bioorg. Chem.* **2021**, *114*, 105139.
(219) Li, L.; Wang, H.-K.; Kuo, S.-C.; Wu, T.-S.; Lednicer, D.; Lin, C. M.; Hamel, E.; Lee, K.-H. *J. Med. Chem.* **1994**, *37*, 1126.

(220) Balasubramanian, M. In *Comprehensive Heterocyclic Chemistry III*; Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; Vol. 8, p 333.
(221) Carosso, S.; Miller, M. J. *Org. Biomol. Chem.* **2014**, *12*, 7445.
(222) Wan, X.; Joullié, M. M. *Front. Chem. China* **2009**, *4*, 249.
(223) Yamamoto, H.; Momiyama, N. *Chem. Commun.* **2005**, 3514.
(224) Yamamoto, H.; Kawasaki, M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 595.
(225) Bodnar, B. S.; Miller, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 5630.
(226) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317.
(227) Ragaini, F.; Cenini, S.; Brignoli, D.; Gasperini, M.; Gallo, E. *J. Org. Chem.* **2003**, *68*, 460.
(228) Okuro, K.; Tuan, D.; Khumtaveeporn, K.; Alper, H. *Tetrahedron Lett.* **1996**, *37*, 2713.
(229) Yasukawa, N.; Kuwata, M.; Imai, T.; Monguchi, Y.; Sajiki, H.; Sawama, Y. *Green Chem.* **2018**, *20*, 4409.
(230) Needleman, S. B.; Chang Kuo, M. C. *Chem. Rev.* **1962**, *62*, 405.
(231) Hamer, J.; Ahmad, M. *1, 4 - Cycloaddition Reactions, the Diels-Alder Reaction in Heterocyclic Synthesis*; Academic Press: New York, 1967.
(232) Kresze, G.; Firl, J. *Fortschr. Chem. Forsch.* **1969**, *11*, 245.
(233) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.
(234) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press (New York), 1987.
(235) Streith, J.; Defoin, A. *Synthesis* **1994**, 1107.
(236) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668.
(237) Brulíková, L.; Harrison, A.; Miller, M. J.; Hlaváč, J. *Beilstein J. Org. Chem.* **2016**, *12*, 1949.
(238) Low, H. *Arch. Environ. Health.* **1974**, *29*, 256.
(239) Frazier, C. P.; Bugarin, A.; Engelking, J. R.; Read de Alaniz, J. *Org. Lett.* **2012**, *14*, 3620.
(240) Murru, S.; Srivastava, R. S. *Eur. J. Org. Chem.* **2014**, *2014*, 2174.
(241) Dongbo, Z.; Mikael, J.; Jan-E., B. *Eur. J. Org. Chem.* **2007**, *2007*, 4431.
(242) Moller, E. R.; Jorgensen, K. A. *J. Org. Chem.* **1996**, *61*, 5770.
(243) McClure, K. F.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 850.
(244) Idhayadhulla, A.; Kumar, R. S.; Nasser, A. J. A. *J. Mex. Chem. Soc.* **2011**, *55*, 218.
(245) Di Santo, R.; Tafi, A.; Costi, R.; Botta, M.; Artico, M.; Corelli, F.; Forte, M.; Caporuscio, F.; Angiolella, L.; Palamara, A. T. *J. Med. Chem.* **2005**, *48*, 5140.
(246) Wilkerson, W. W.; Copeland, R. A.; Covington, M.; Trzaskos, J. M. *J. Med. Chem.* **1995**, *38*, 3895.
(247) Jiang, S.; Lu, H.; Liu, S.; Zhao, Q.; He, Y.; Debnath, A. K. *Antimicrob. Agents Chemother.* **2004**, *48*, 4349.
(248) Okanya, P. W.; Mohr, K. I.; Gerth, K.; Jansen, R.; Müller, R. *J. Nat. Prod.* **2011**, *74*, 603.
(249) Paludetto, M.-N.; Bijani, C.; Puisset, F.; Bernardes-Genisson, V.; Arellano, C.; Robert, A. *J. Med. Chem.* **2018**, *61*, 7849.
(250) Scala, F.; Fattorusso, E.; Menna, M.; Taglialatela-Scafati, O.; Tierney, M.; Kaiser, M.; Tasdemir, D. *Mar. Drugs* **2010**, *8*, 2162.
(251) Ragno, R.; Simeoni, S.; Rotili, D.; Caroli, A.; Botta, G.; Brosch, G.; Massa, S.; Mai, A. *Eur. J. Med. Chem.* **2008**, *43*, 621.
(252) Gao, X.; Wang, P.; Wang, Q.; Chen, J.; Lei, A. *Green Chem.* **2019**, *21*, 4941.
(253) Philkhana, S. C.; Badmus, F. O.; Dos Reis, I. C.; Kartika, R. *Synthesis* **2021**, *53*, 1531.
(254) Xu, X. T.; Chen, J.; Ke, J. J.; Zhang, K.; Wu, P. P.; Wang, S. H. *Chin. J. Org. Chem.* **2021**, *41*, 206.
(255) Knorr, L. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1635.

(256) Paal, C. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2251.
(257) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474.
(258) Barton, D. H.; Kervagoret, J.; Zard, S. Z. *Tetrahedron* **1990**, *46*, 7587.
(259) Van Leusen, A.; Siderius, H.; Hoogenboom, B.; van Leusen, D. *Tetrahedron Lett.* **1972**, *13*, 5337.
(260) Milgram, B. C.; Eskildsen, K.; Richter, S. M.; Scheidt, W. R.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72*, 3941.
(261) Firl, J.; Kresze, G. *Chem. Ber.* **1966**, *99*, 3695.
(262) Defoin, A.; Fritz, H.; Geffroy, G.; Streith, J. *Tetrahedron Lett.* **1986**, *27*, 3135.
(263) Humenny, W. J.; Kyriacou, P.; Sapeta, K.; Karadeolian, A.; Kerr, M. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 11088.
(264) Givens, R. S.; Choo, D. J.; Merchant, S. N.; Stitt, R. P.; Matuszewski, B. *Tetrahedron Lett.* **1982**, *23*, 1327.
(265) Ragaini, F.; Cenini, S.; Borsani, E.; Dompe, M.; Gallo, E.; Moret, M. *Organometallics* **2001**, *20*, 3390.
(266) Berti, F.; Di Bussolo, V.; Pineschi, M. *J. Org. Chem.* **2013**, *78*, 7324.
(267) Yang, B.; Miller, M. J. *Org. Lett.* **2010**, *12*, 392.
(268) Cummings, M. M.; Clawson, R. W.; Sharma, S. B.; Byerly, R. A.; Akhmedov, N. G.; Soderberg, B. C. G. *Tetrahedron* **2011**, *67*, 4753.
(269) Yamamoto, Y.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, *2006*, 2031.
(270) Greci, L.; Tommasi, G.; Petrucci, R.; Marrosu, G.; Trazza, A.; Sgarabotto, P.; Righi, L.; Alberti, A. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2337.
(271) Lu, J.-L.; Kang, Y.; Zhang, Z.; Huang, Y.-A.; Tan, L.-Q.; Zhang, X.-Z.; Peng, J.-B. *Org. Chem. Front.* **2022**, *9*, 6505.
(272) Krchňák, V.; Waring, K. R.; Noll, B. C.; Moellmann, U.; Dahse, H.-M.; Miller, M. J. *J. Org. Chem.* **2008**, *73*, 4559.
(273) Leach, I. F.; Havenith, R. W. A.; Klein, J. E. M. N. *Eur. J. Inorg. Chem.* **2022**, *2022*, e202200247.
(274) Liu, H.; Shen, Q. *Coord. Chem. Rev.* **2021**, *442*, 213923.
(275) DiMucci, I. M.; Lukens, J. T.; Chatterjee, S.; Carsch, K. M.; Titus, C. J.; Lee, S. J.; Nordlund, D.; Betley, T. A.; MacMillan, S. N.; Lancaster, K. M. *J. Am. Chem. Soc.* **2019**, *141*, 18508.
(276) Todorović, U.; Martin Romero, R.; Anthore-Dalion, L. *Eur. J. Org. Chem.* **2023**, *26*, e202300391.
(277) Yang, Z.; Jiang, K.; Chen, Y.-C.; Wei, Y. *J. Org. Chem.* **2019**, *84*, 3725.
(278) Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521.
(279) Tobisch, S. *Chem. Eur. J.* **2016**, *22*, 8290.
(280) Zhu, H.; Shen, Y.; Deng, Q.; Tu, T. *Chem. Commun.* **2015**, *51*, 16573.
(281) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746.

Appendix

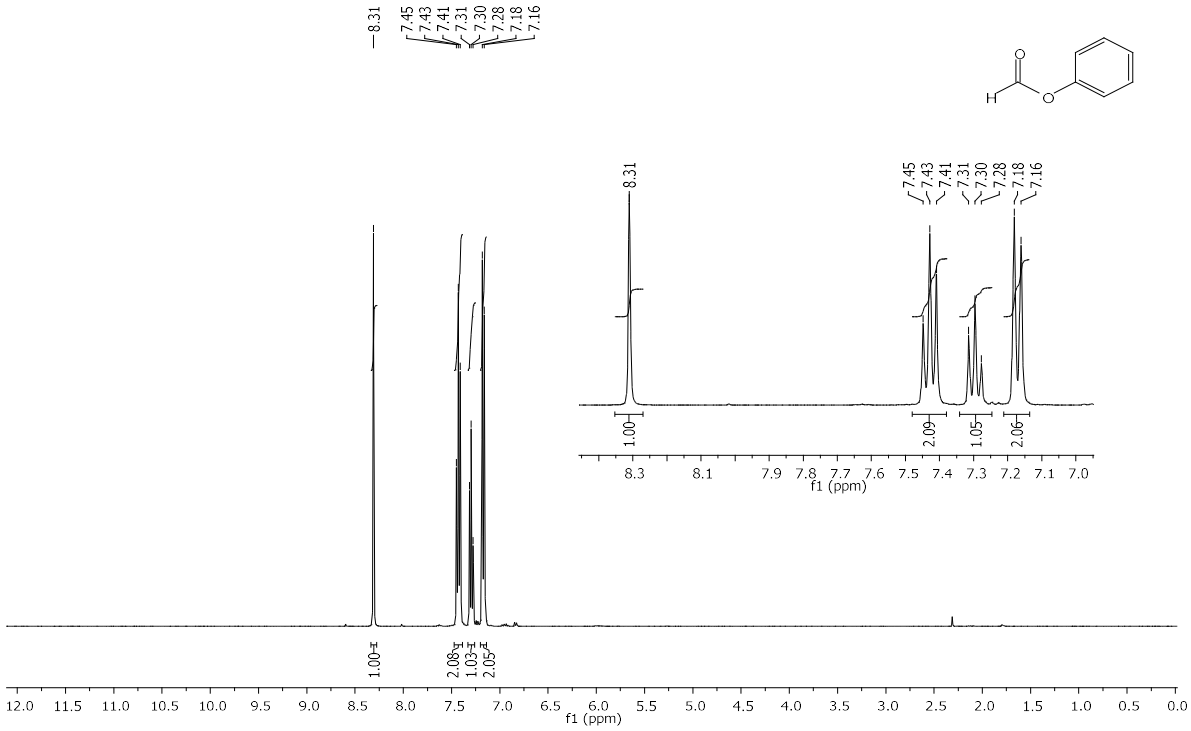


Fig. 7. ^{1}H NMR of phenyl formate in $CDCl_3$.

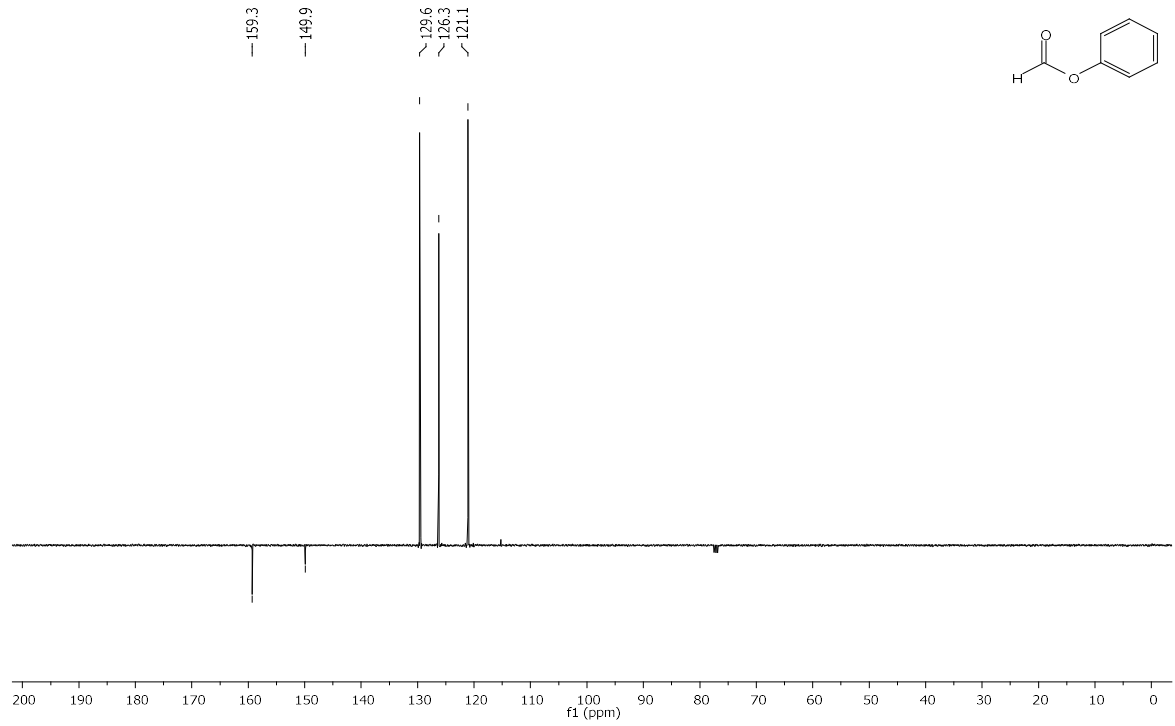


Fig. 8. ^{13}C NMR of phenyl formate in $CDCl_3$.

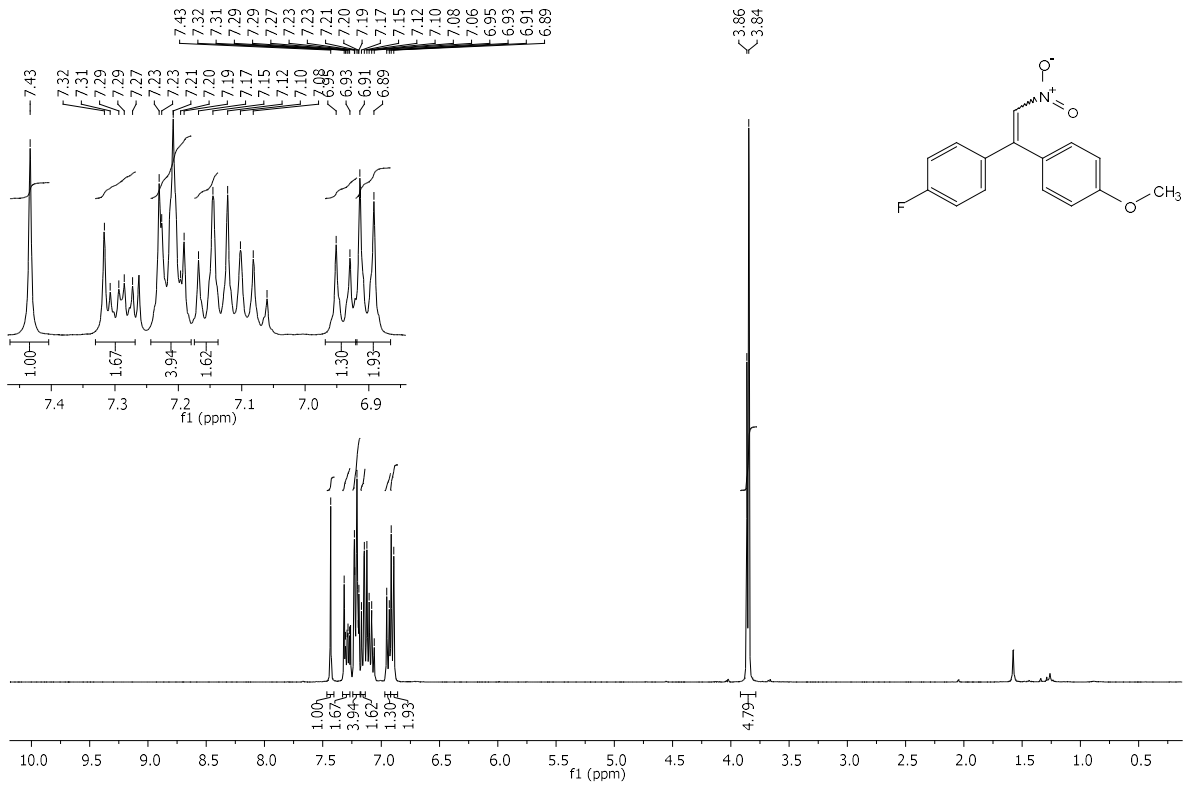


Fig. 9. ^{1}H NMR of **1d** in $CDCl_3$.

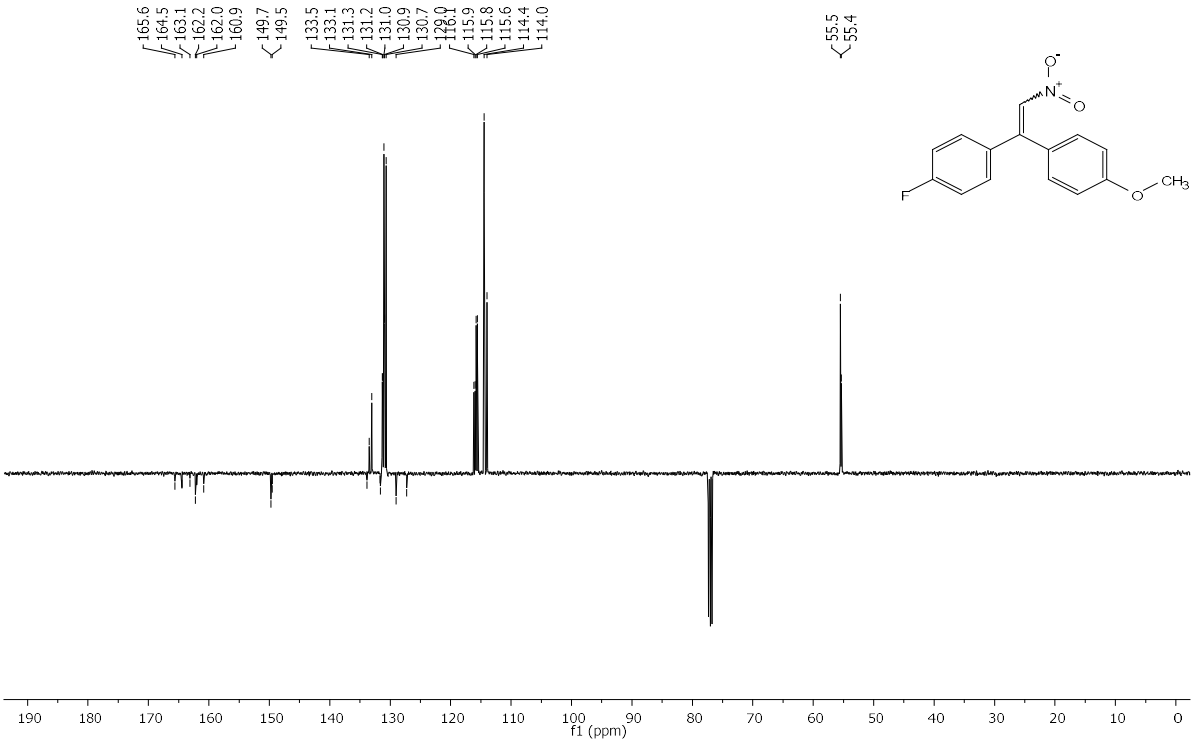


Fig. 10. ^{13}C NMR of **1d** in $CDCl_3$.

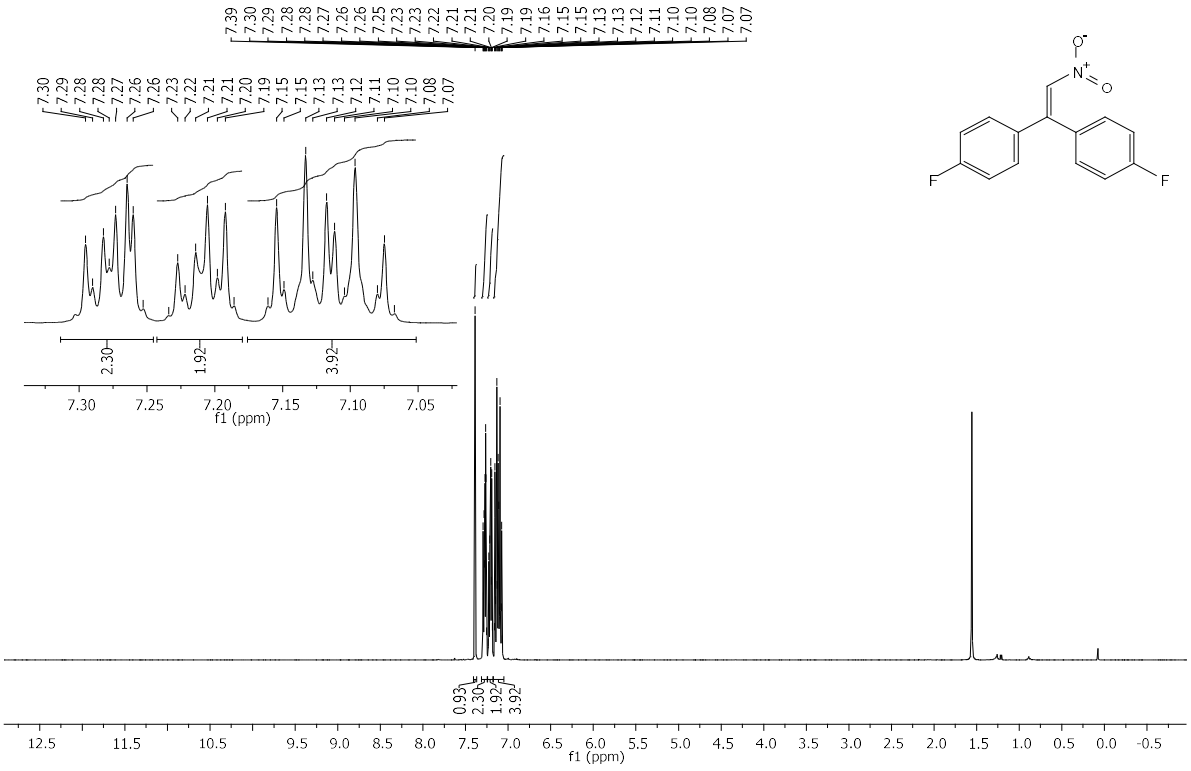


Fig. 11. ^{1}H NMR of **1e** in $CDCl_3$.

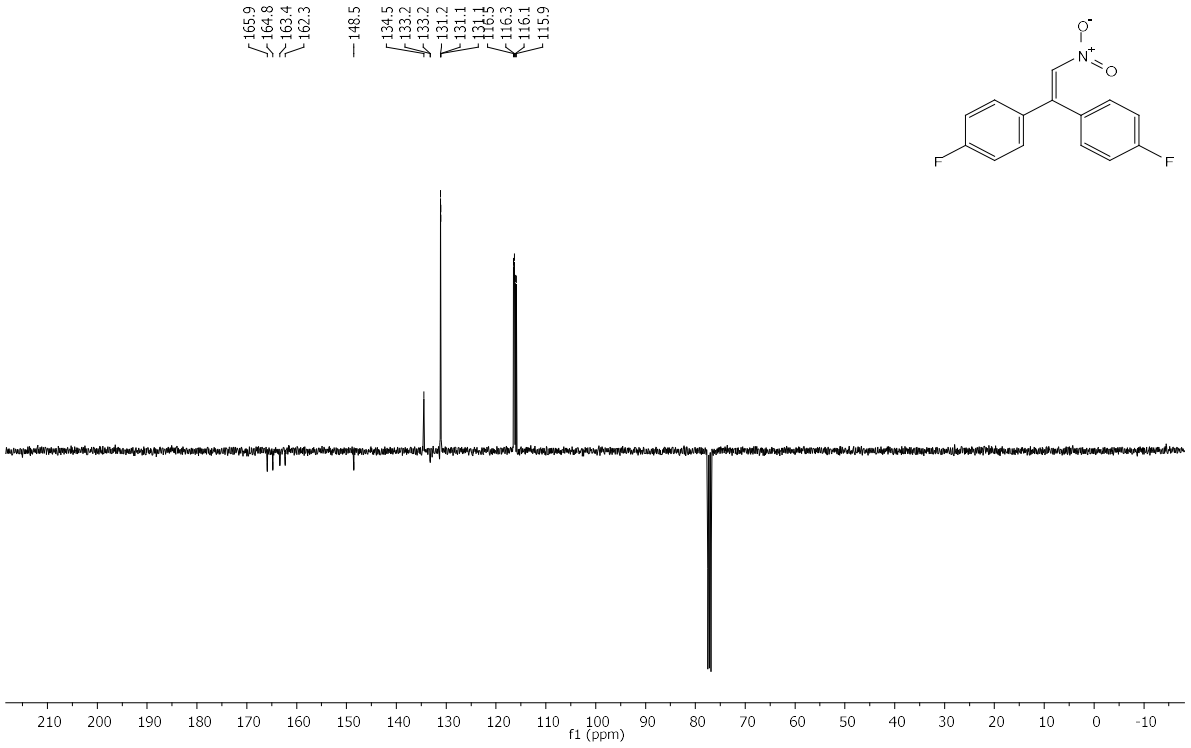


Fig. 12. ^{13}C NMR of **1e** in $CDCl_3$.

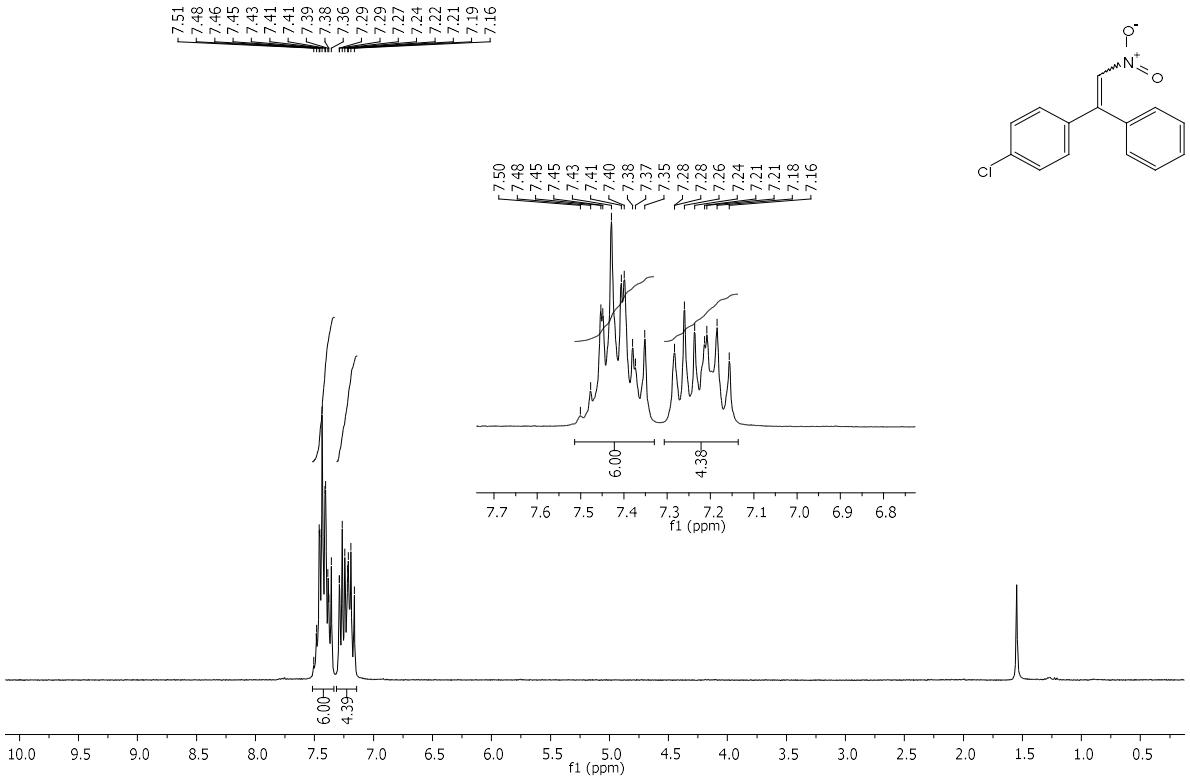


Fig. 13. ^{1}H NMR of **1g** in $CDCl_3$.

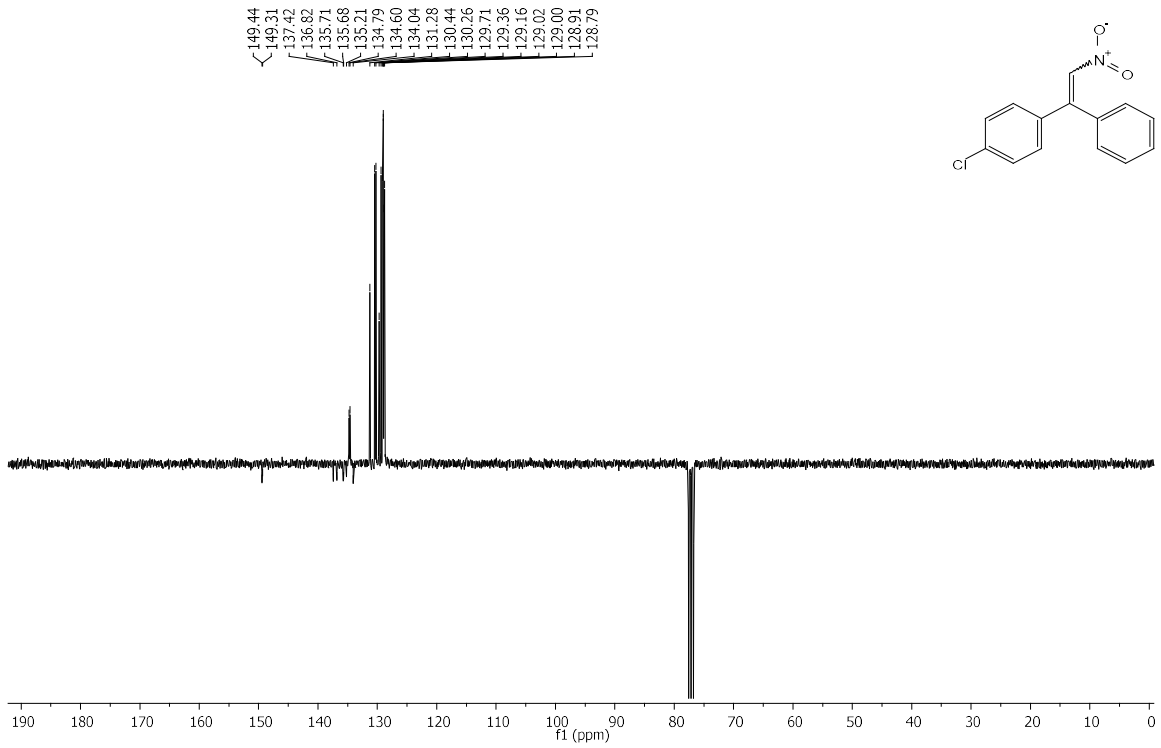


Fig. 14. ^{13}C NMR of **1g** in $CDCl_3$.

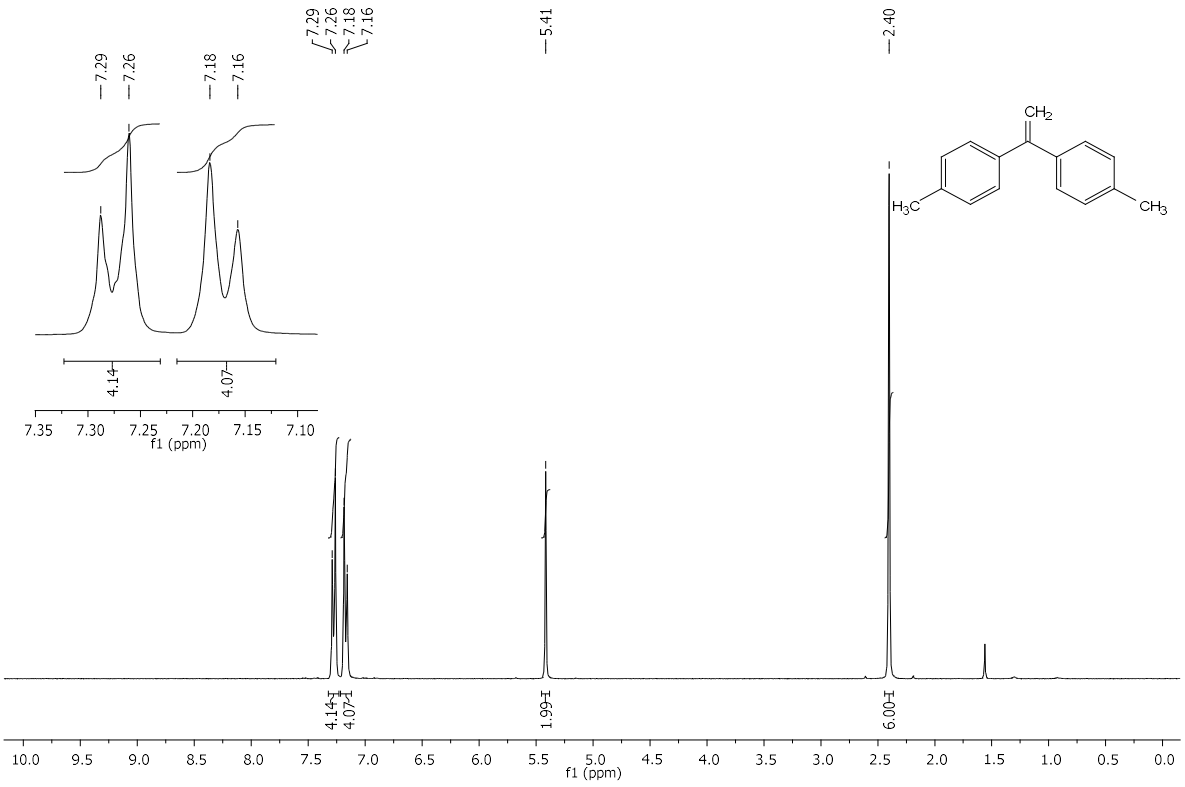


Fig. 15. ^{1}H NMR of 4,4'-(ethene-1,1-diyl)bis(methylbenzene) in $CDCl_3$.

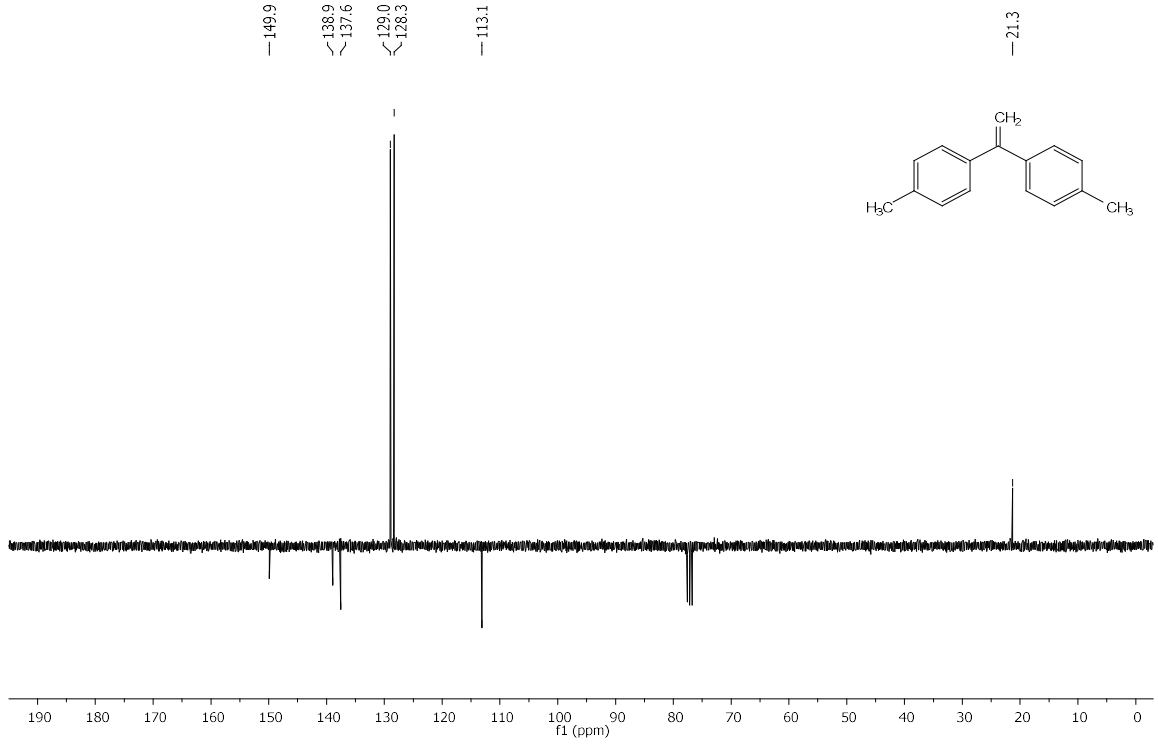


Fig. 16. ^{13}C NMR of 4,4'-(ethene-1,1-diyl)bis(methylbenzene) in $CDCl_3$.

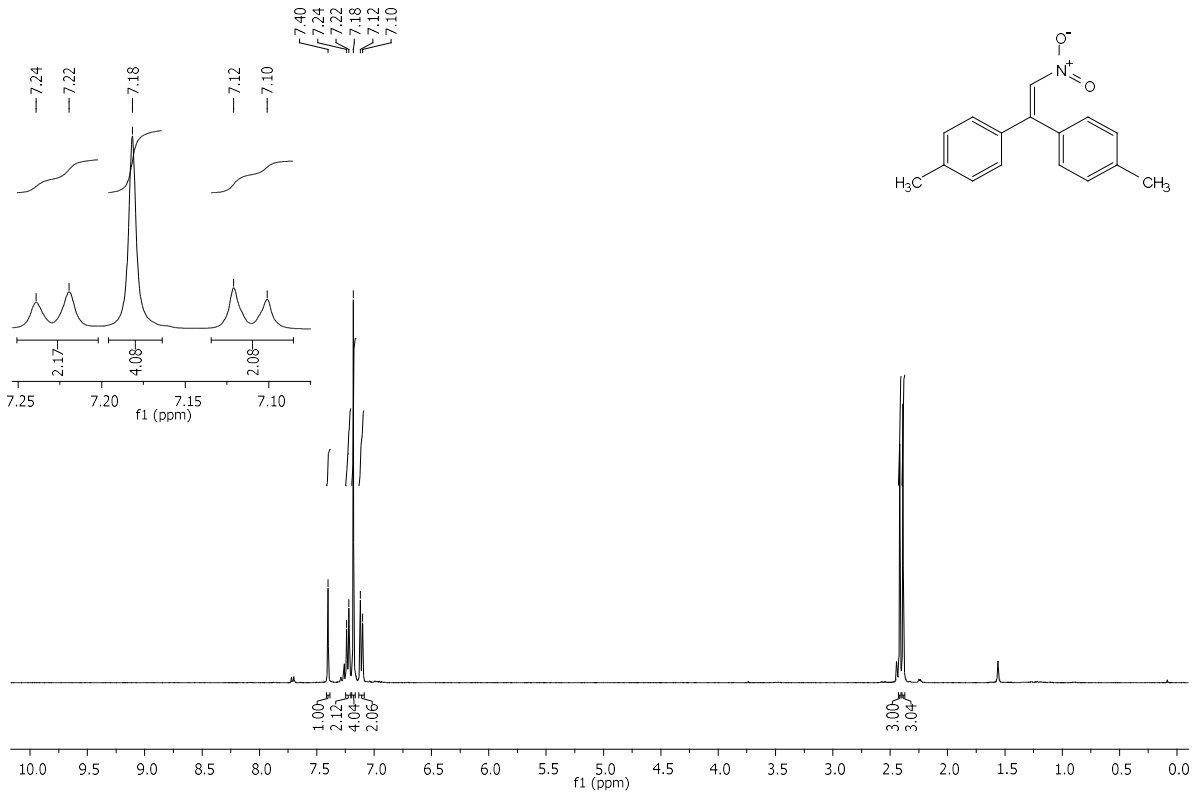


Fig. 17. ^{1}H NMR of **1h** in $CDCl_3$.

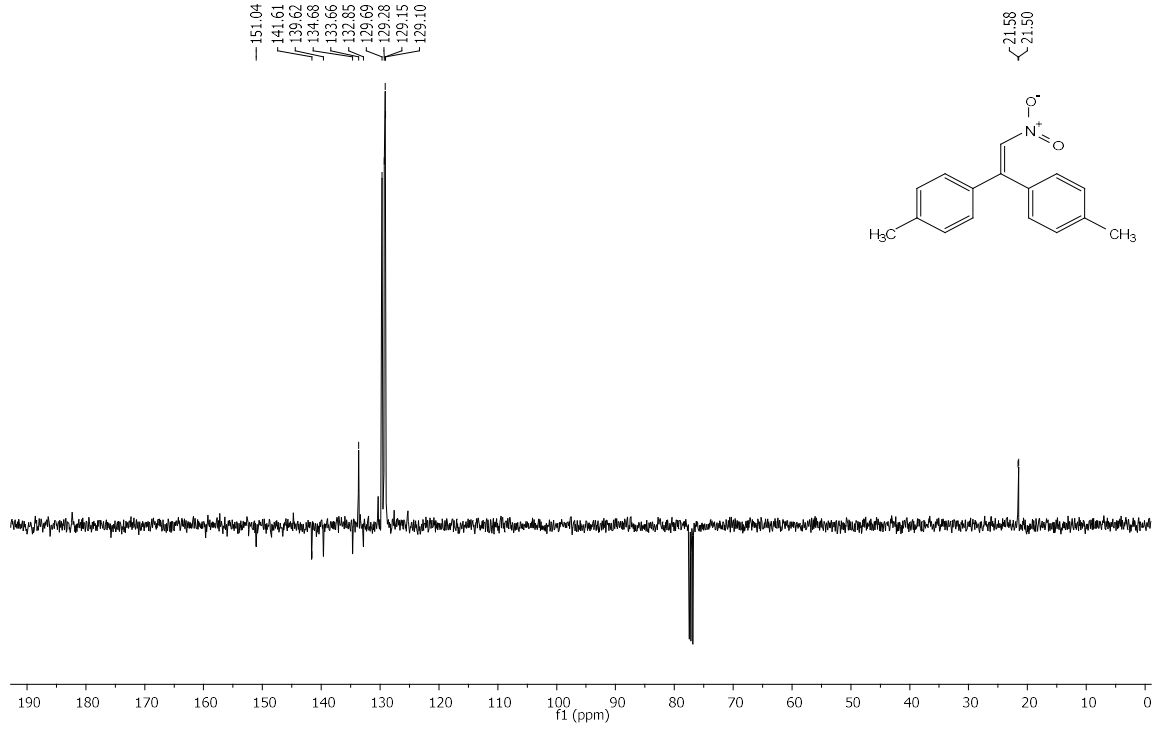


Fig. 18. ^{13}C NMR of **1h** in $CDCl_3$.

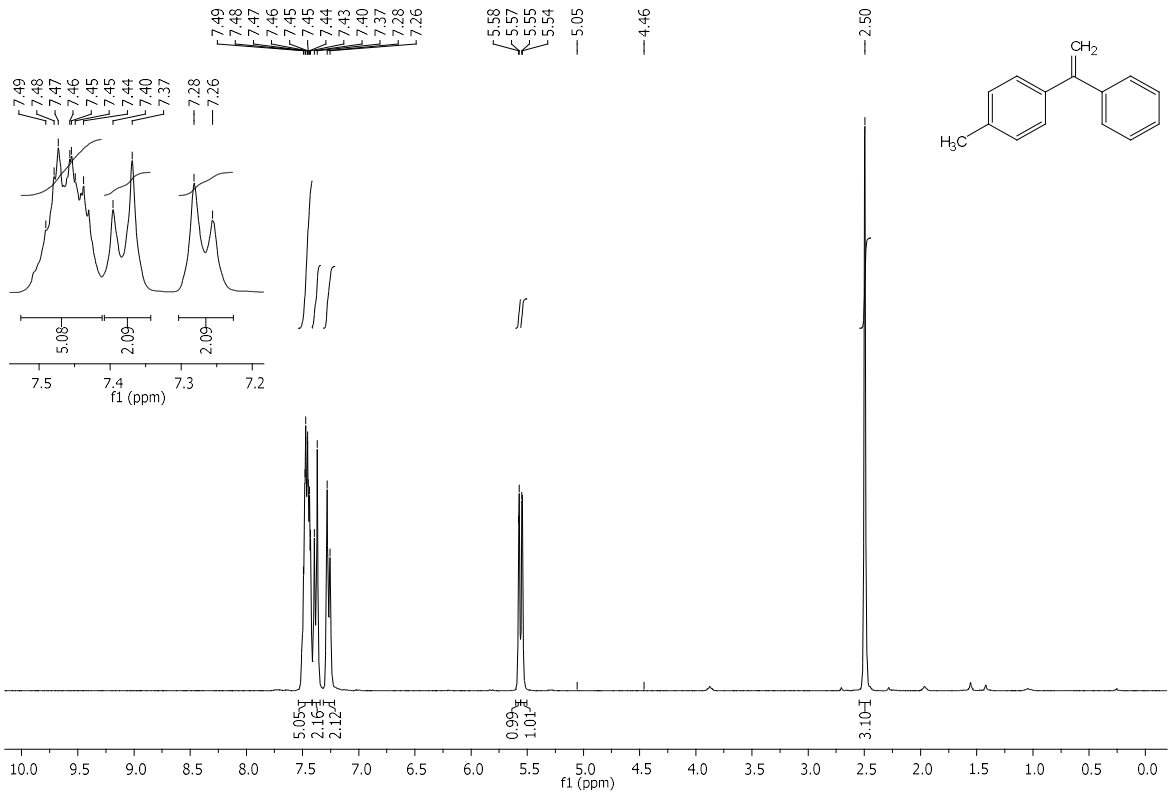


Fig. 19. ^{1}H NMR of 1-methyl-4-(1-phenylvinyl)benzene in $CDCl_3$.

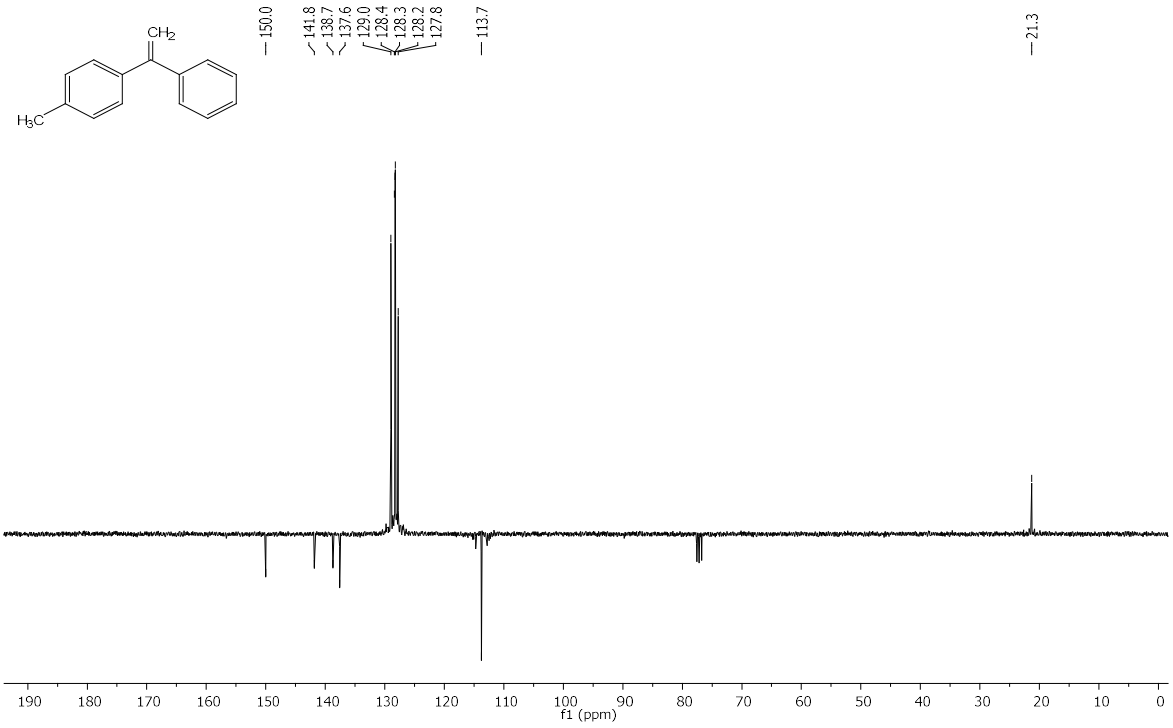


Fig. 20. ^{13}C NMR of 1-methyl-4-(1-phenylvinyl)benzene in $CDCl_3$.

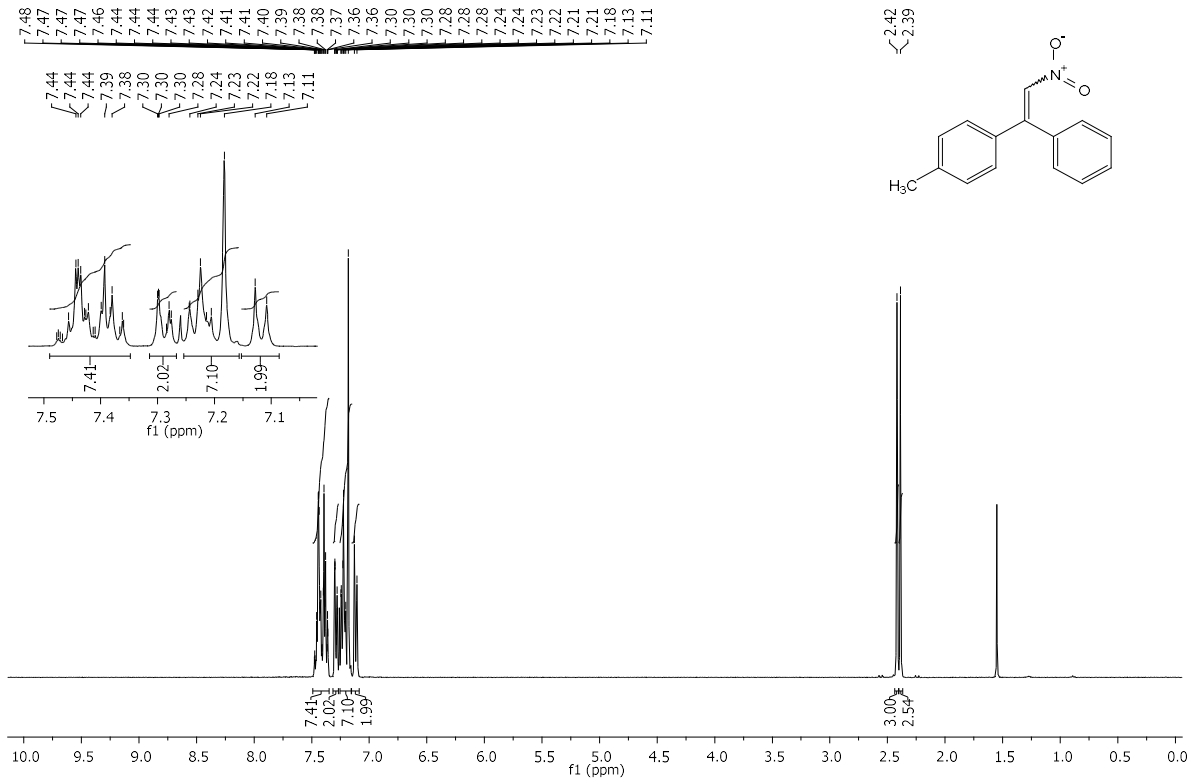


Fig. 21. ^{1}H NMR of **1i** in $CDCl_3$.

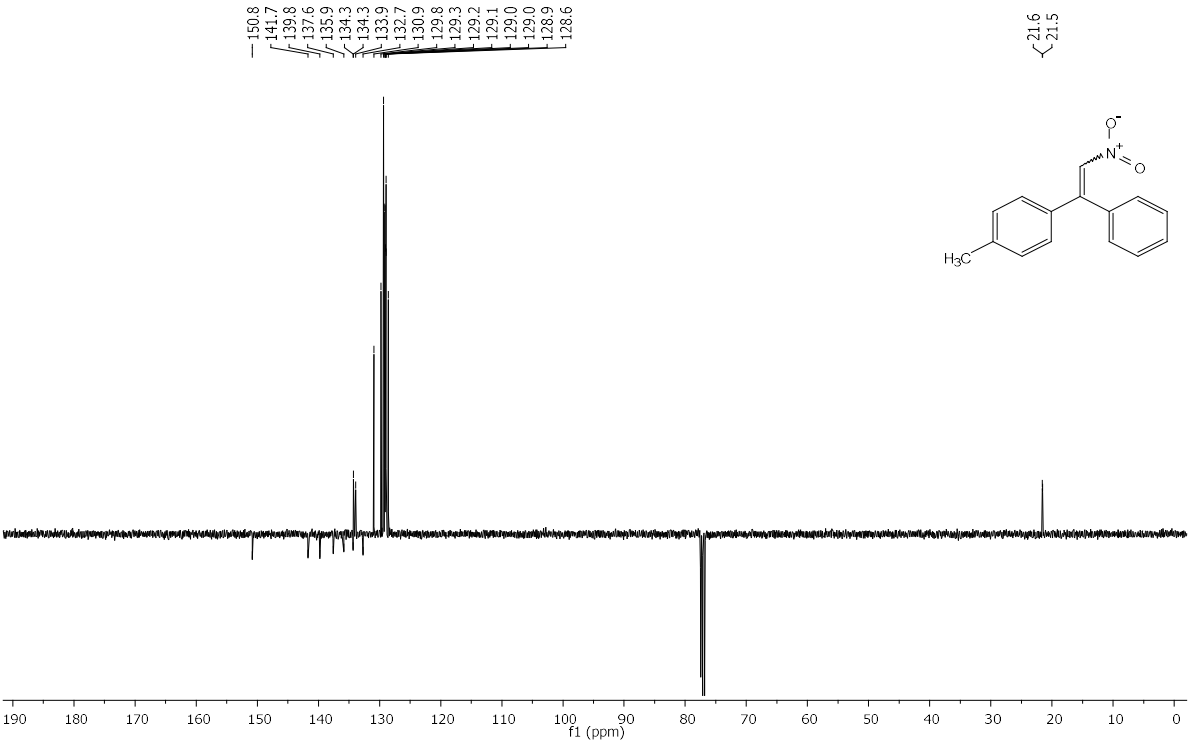


Fig. 22. ^{13}C NMR of **1i** in $CDCl_3$.

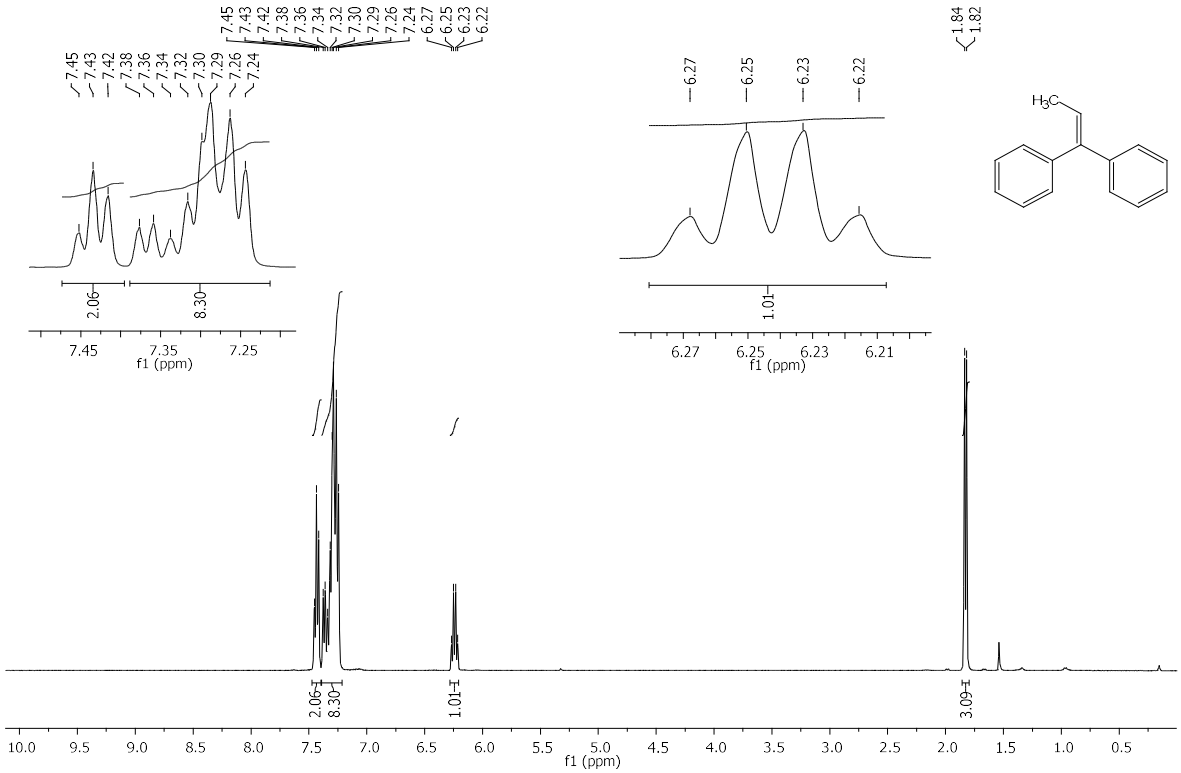


Fig. 23. ^{1}H NMR of prop-1-ene-1,1-diyldibenzene in $CDCl_3$.

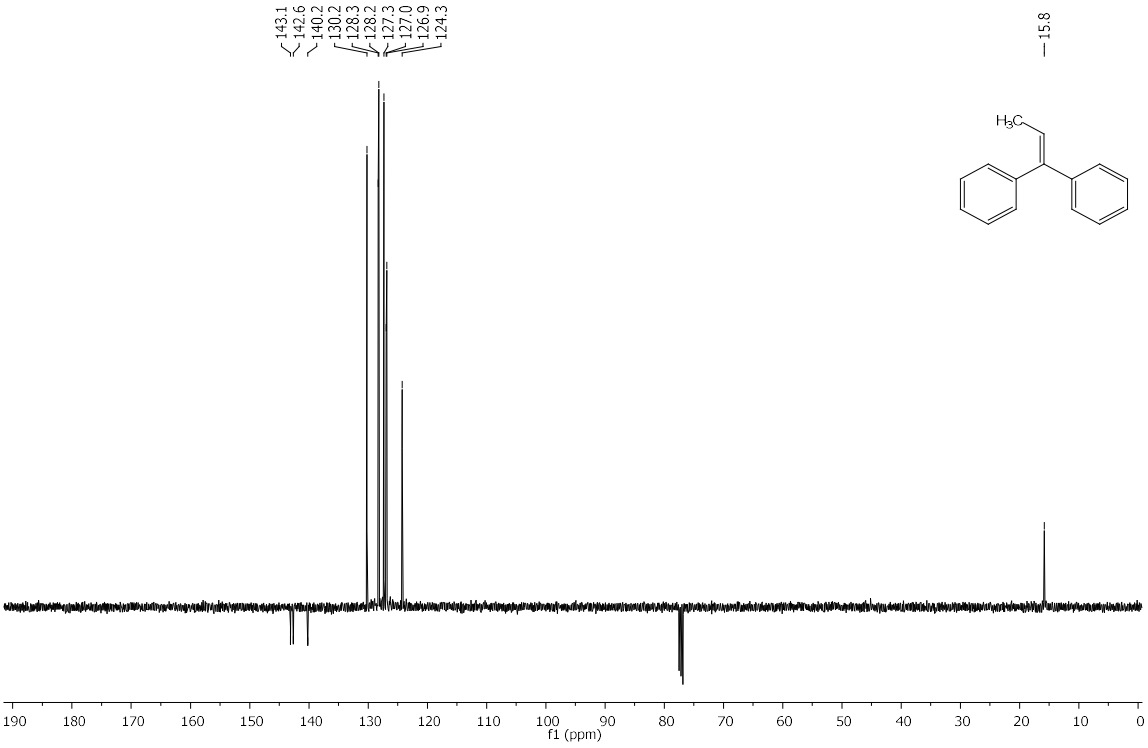


Fig. 24. ^{13}C NMR of prop-1-ene-1,1-diyldibenzene in $CDCl_3$.

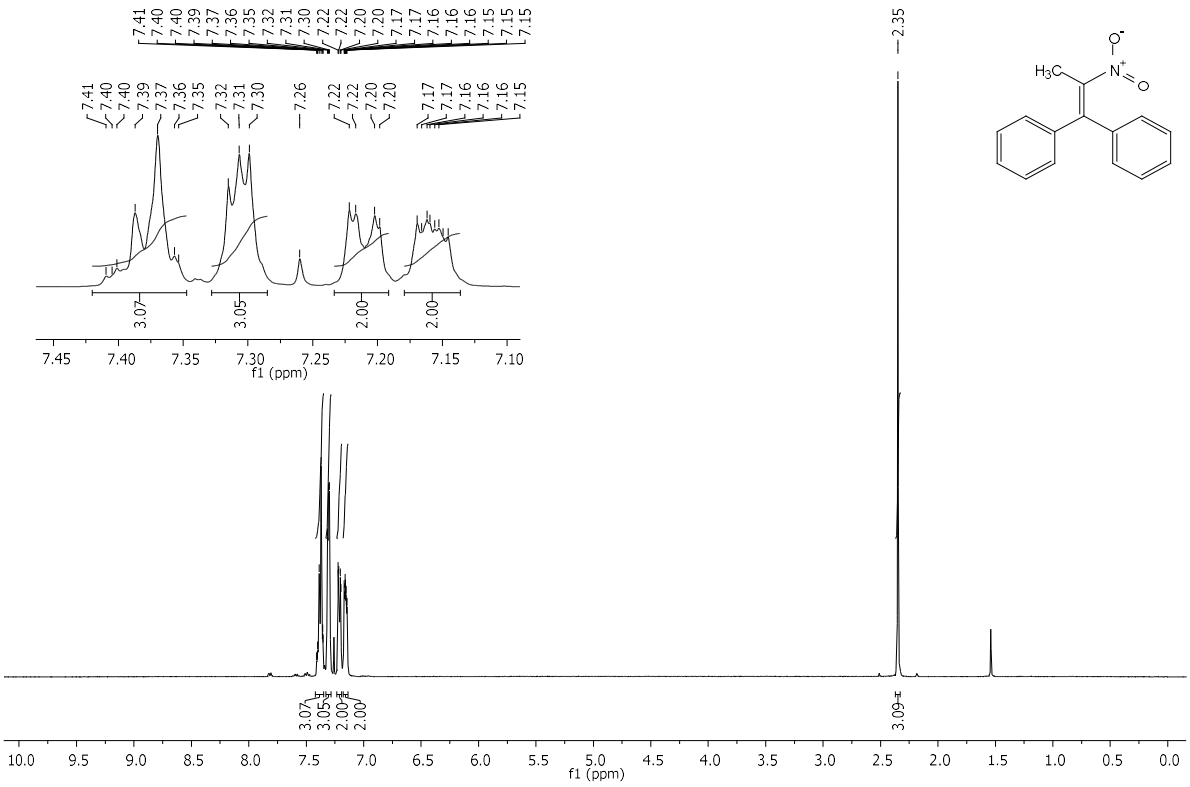


Fig. 25. ^{1}H NMR of **1j** in $CDCl_3$.

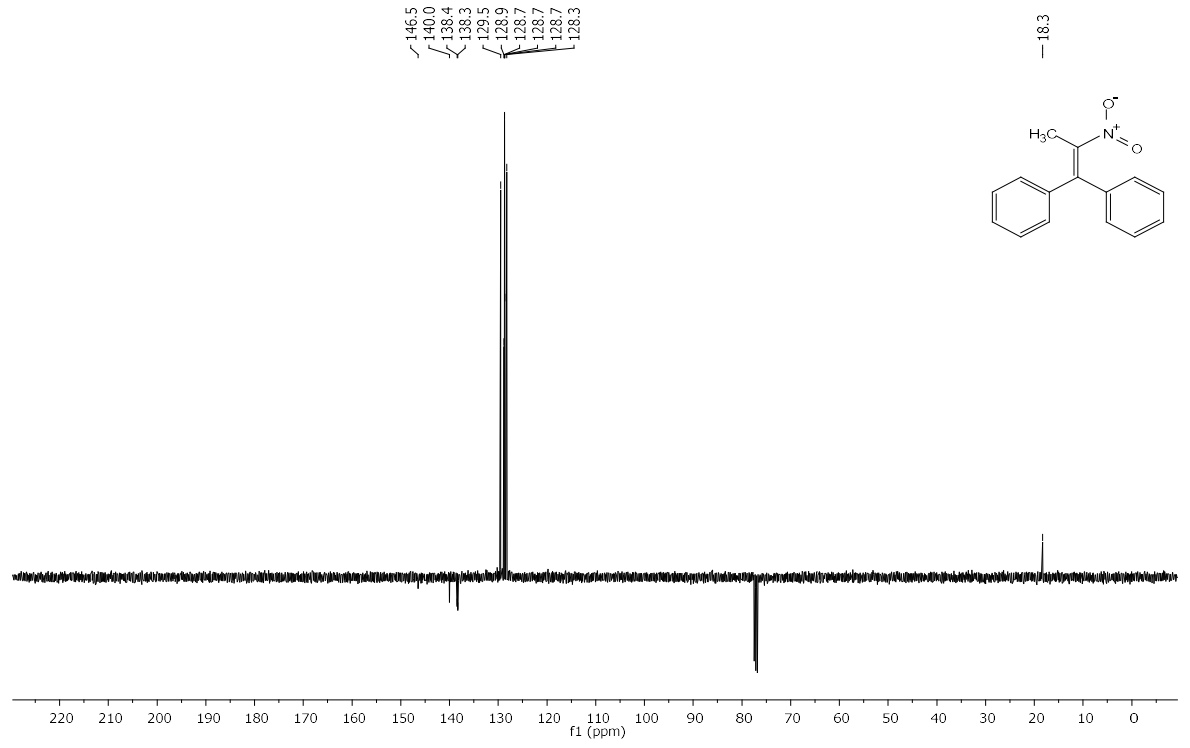


Fig. 26. ^{13}C NMR of **1j** in $CDCl_3$.

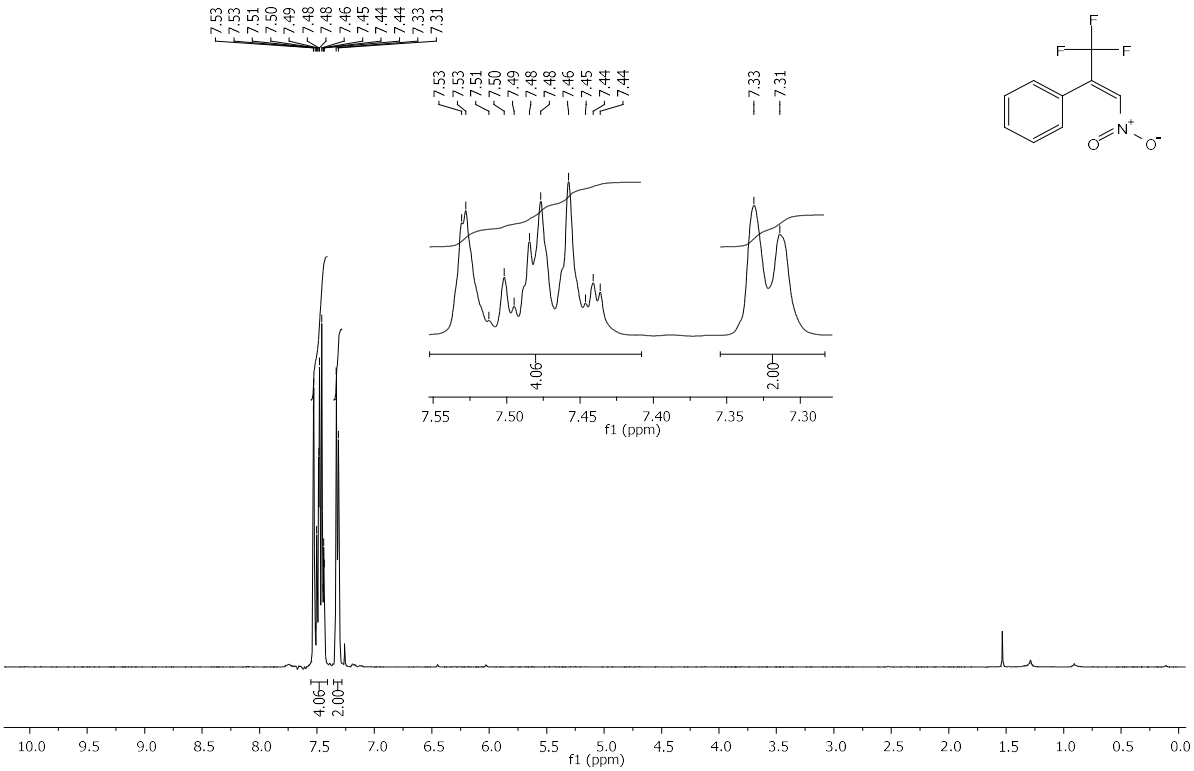


Fig. 27. ^{1}H NMR of **1l** in $CDCl_3$.

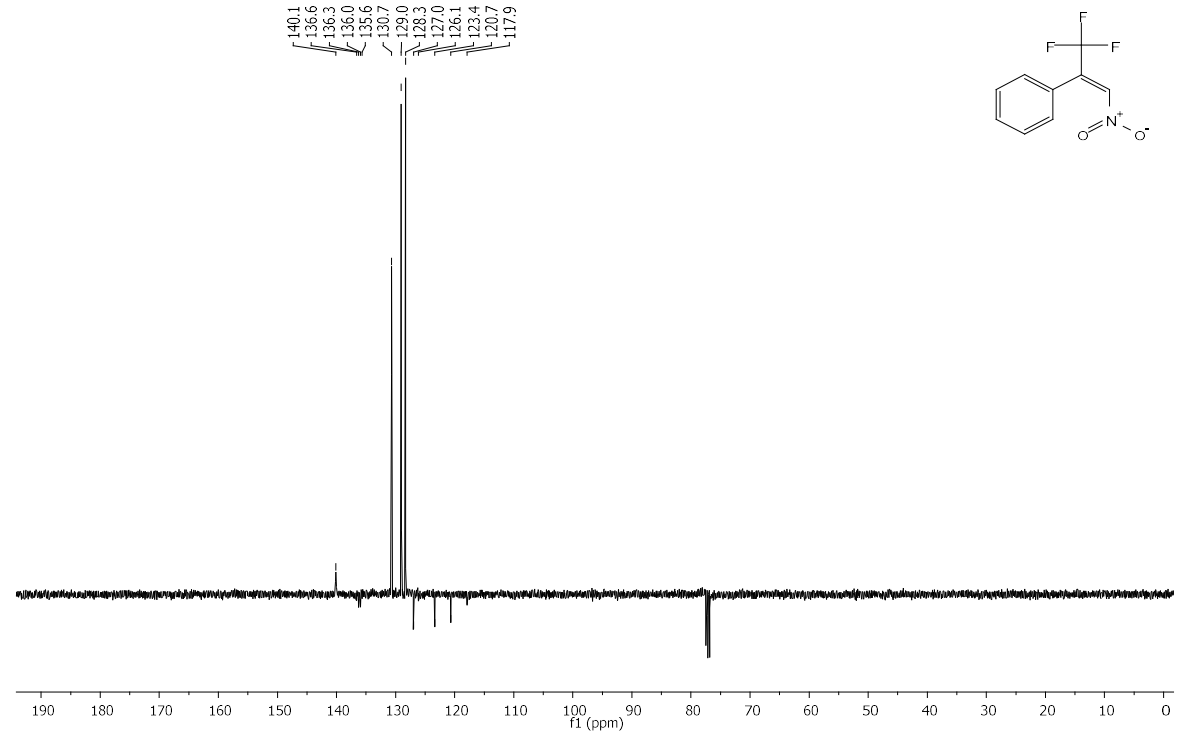


Fig. 28. ^{13}C NMR of **1l** in $CDCl_3$.

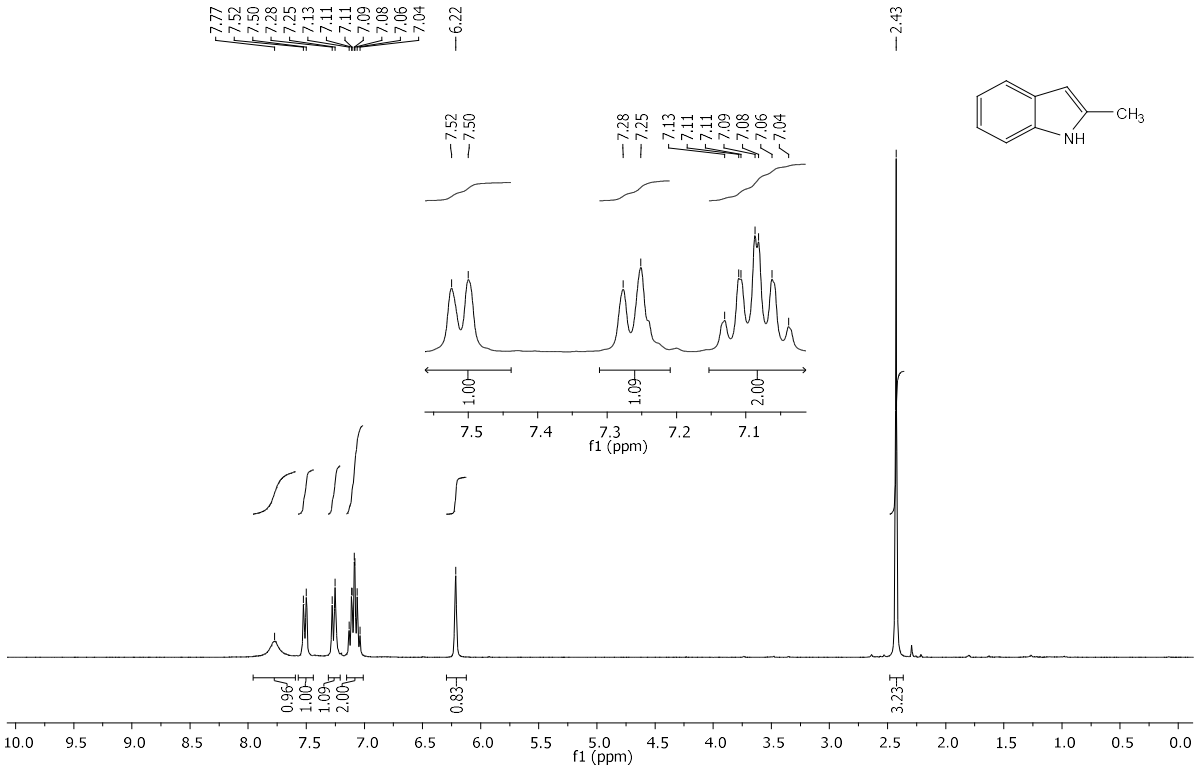


Fig. 29. ^{1}H NMR of **2a** in $CDCl_3$.

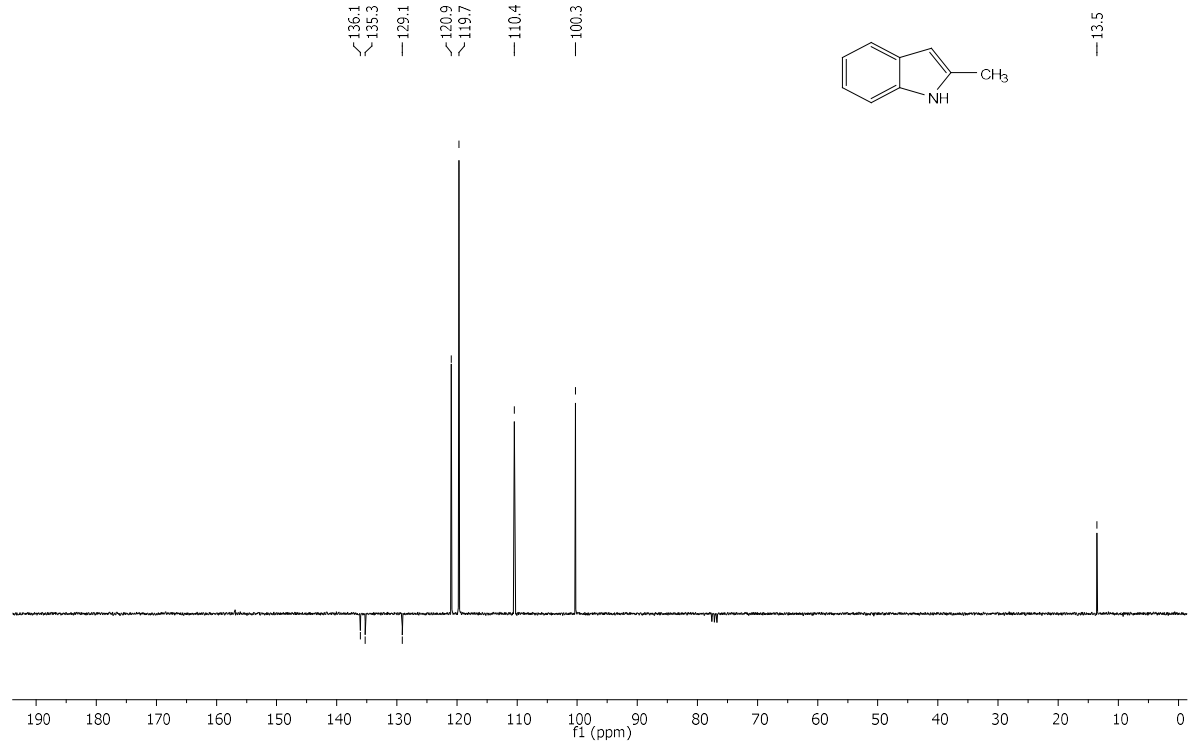


Fig. 30. ^{13}C NMR of **2a** in $CDCl_3$.

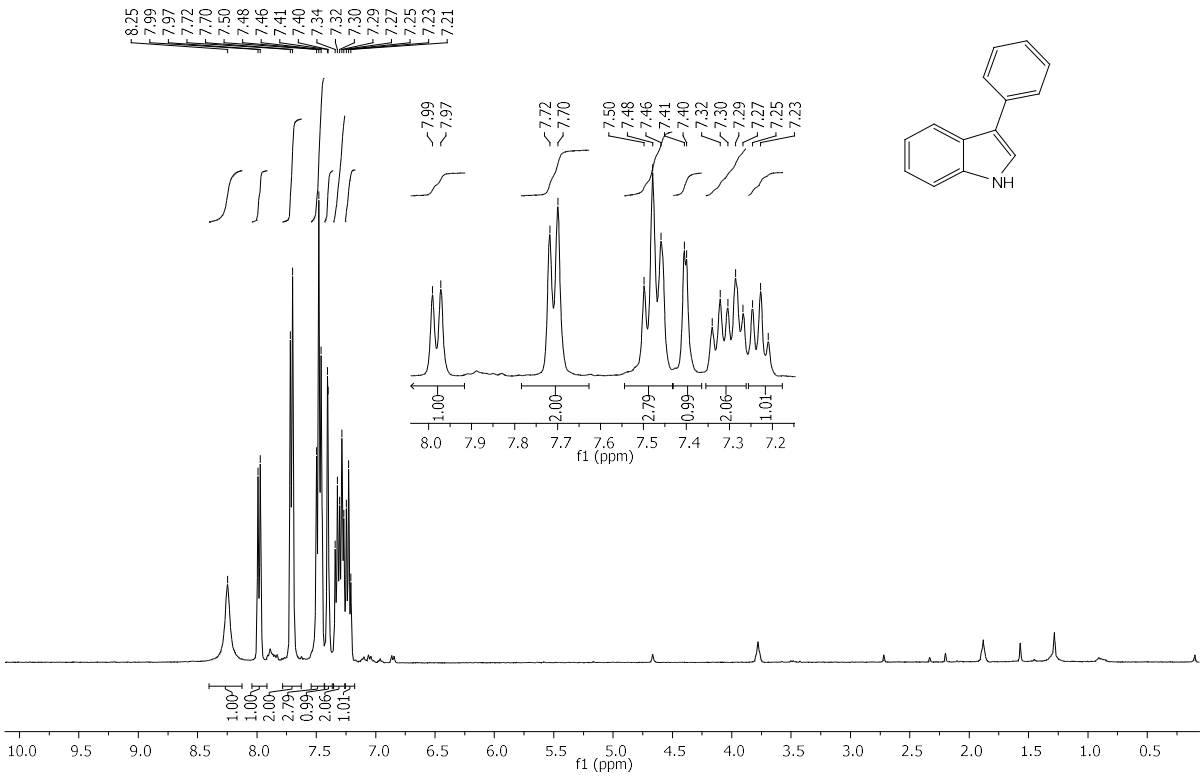


Fig. 31. ^{1}H NMR of **2b** in $CDCl_3$.

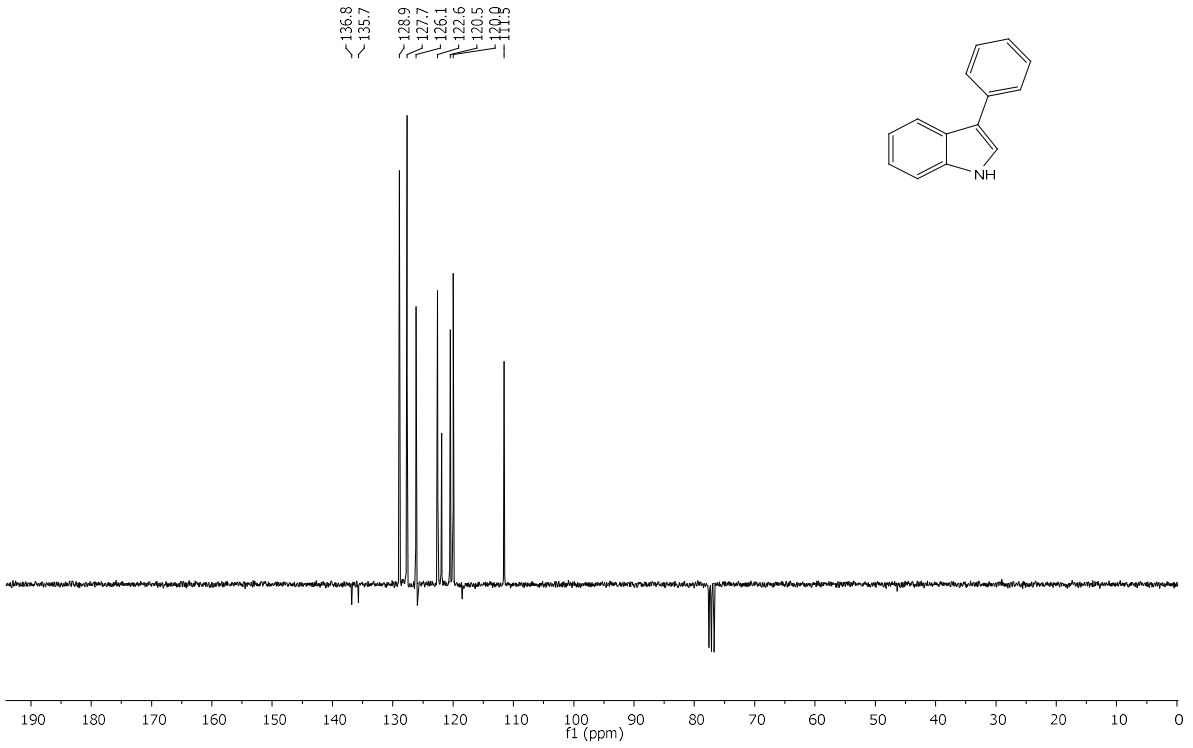


Fig. 32. ^{13}C NMR of **2b** in $CDCl_3$.

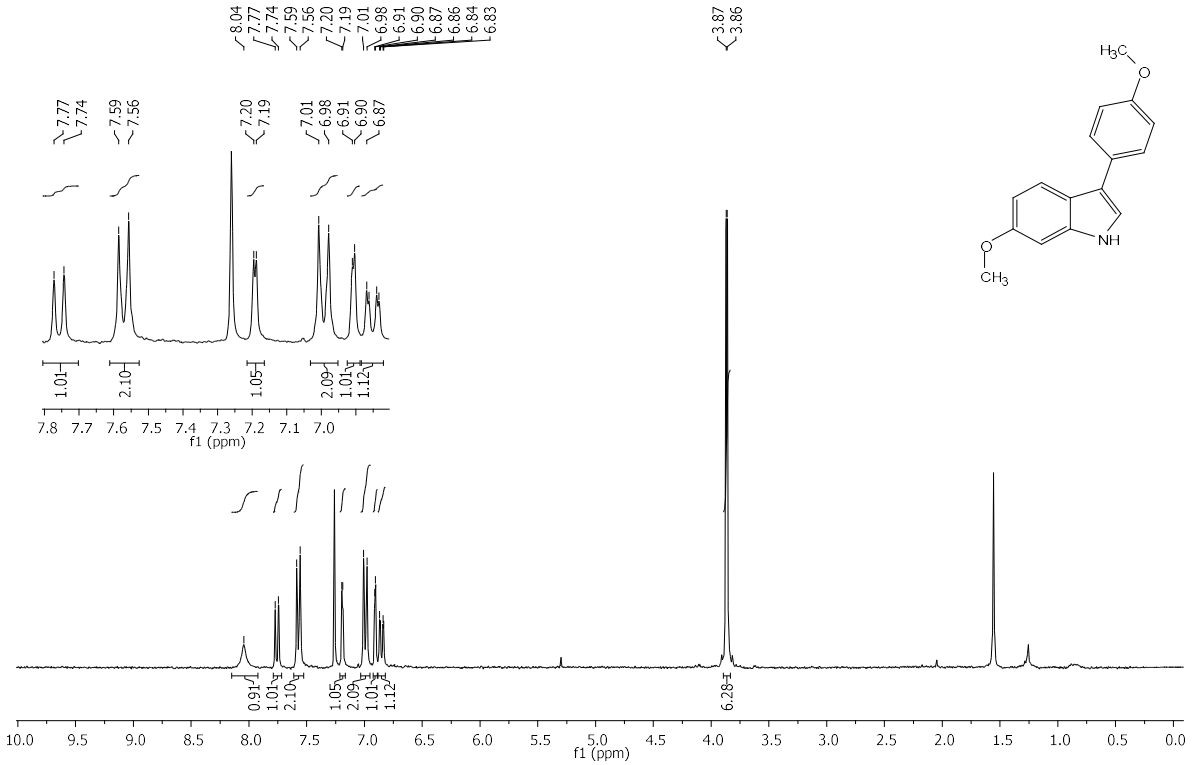


Fig. 33. ^{1}H NMR of **2c** in $CDCl_3$.

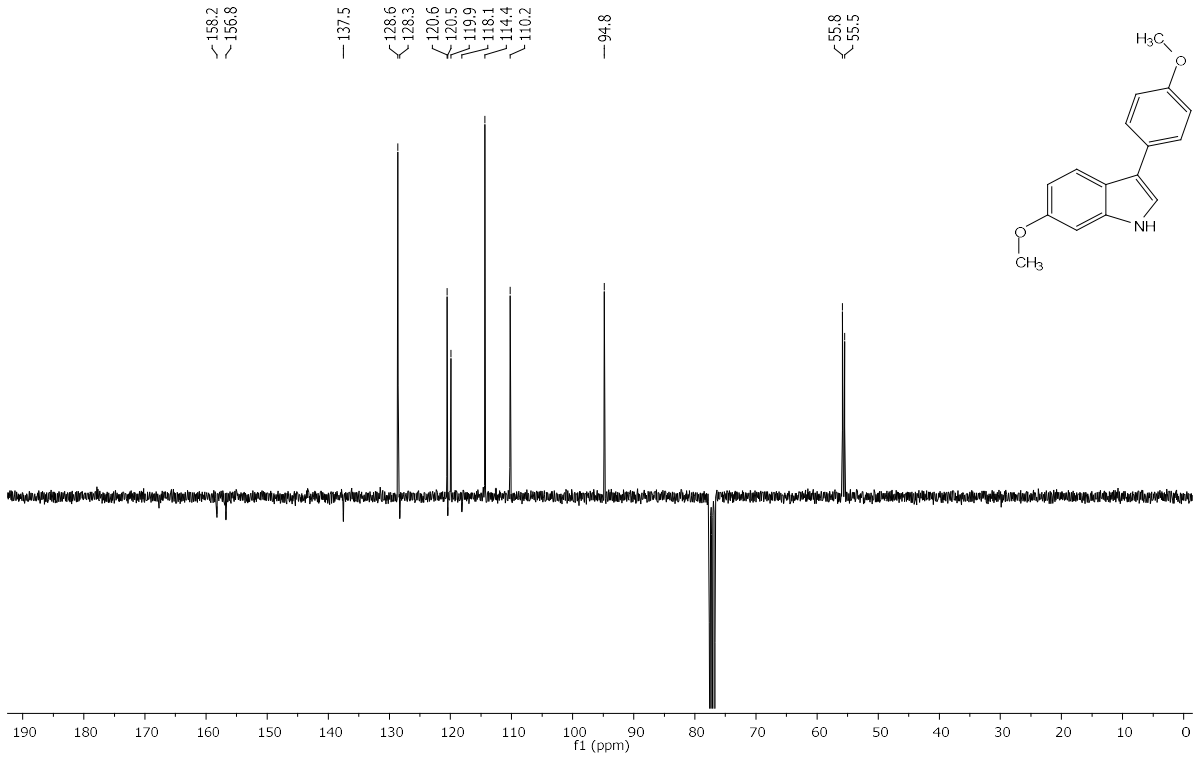


Fig. 34. ^{13}C NMR of **2c** in $CDCl_3$.

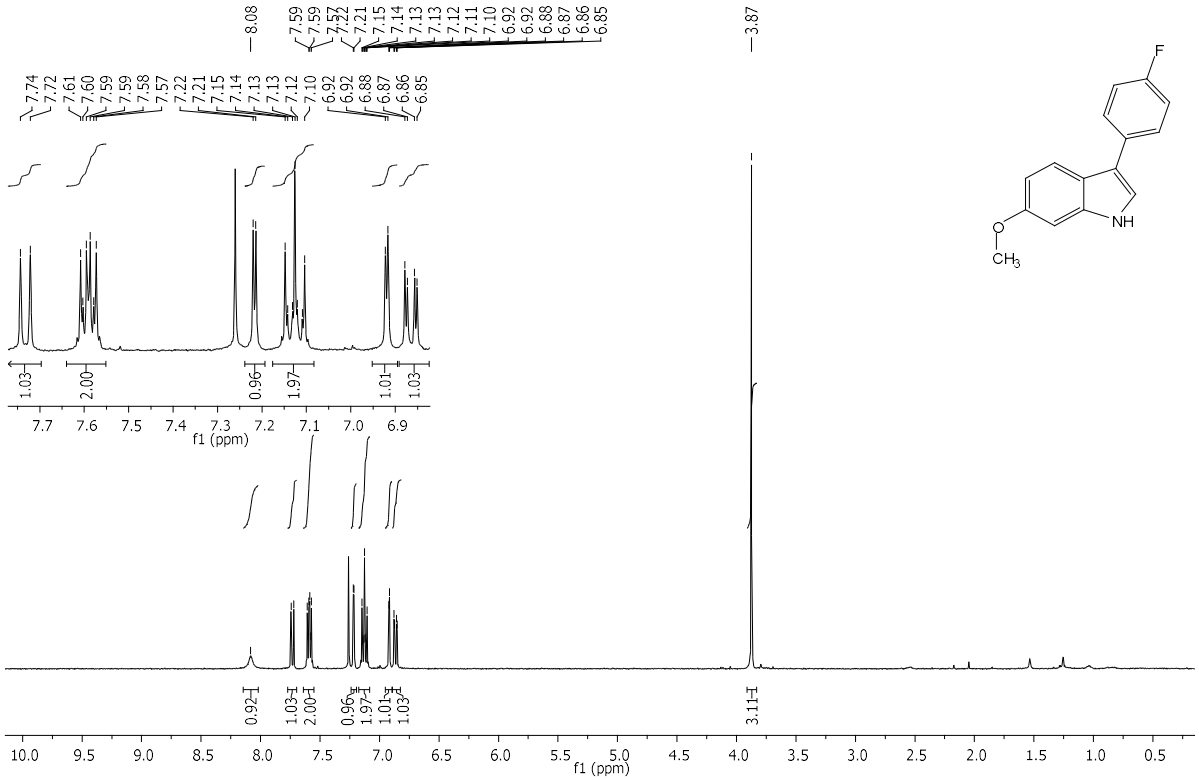


Fig. 35. ^{1}H NMR of **2d'** in $CDCl_3$.

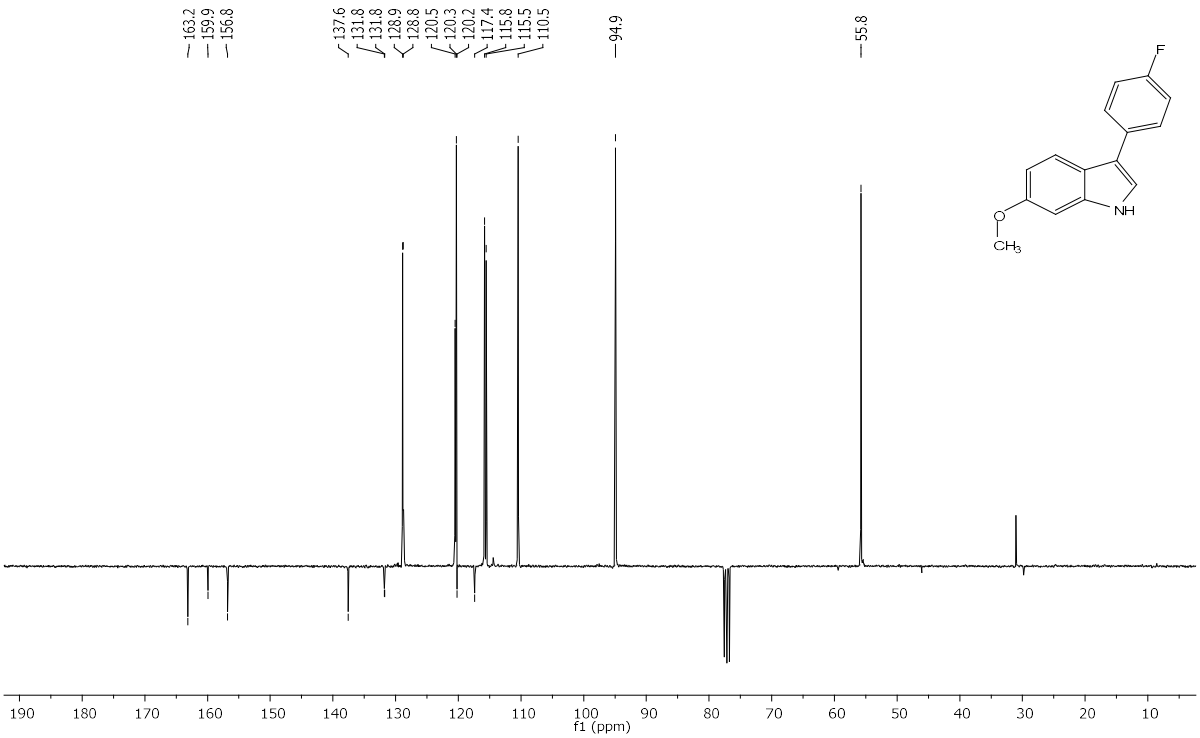


Fig. 36. ^{13}C NMR of **2d'** in $CDCl_3$.

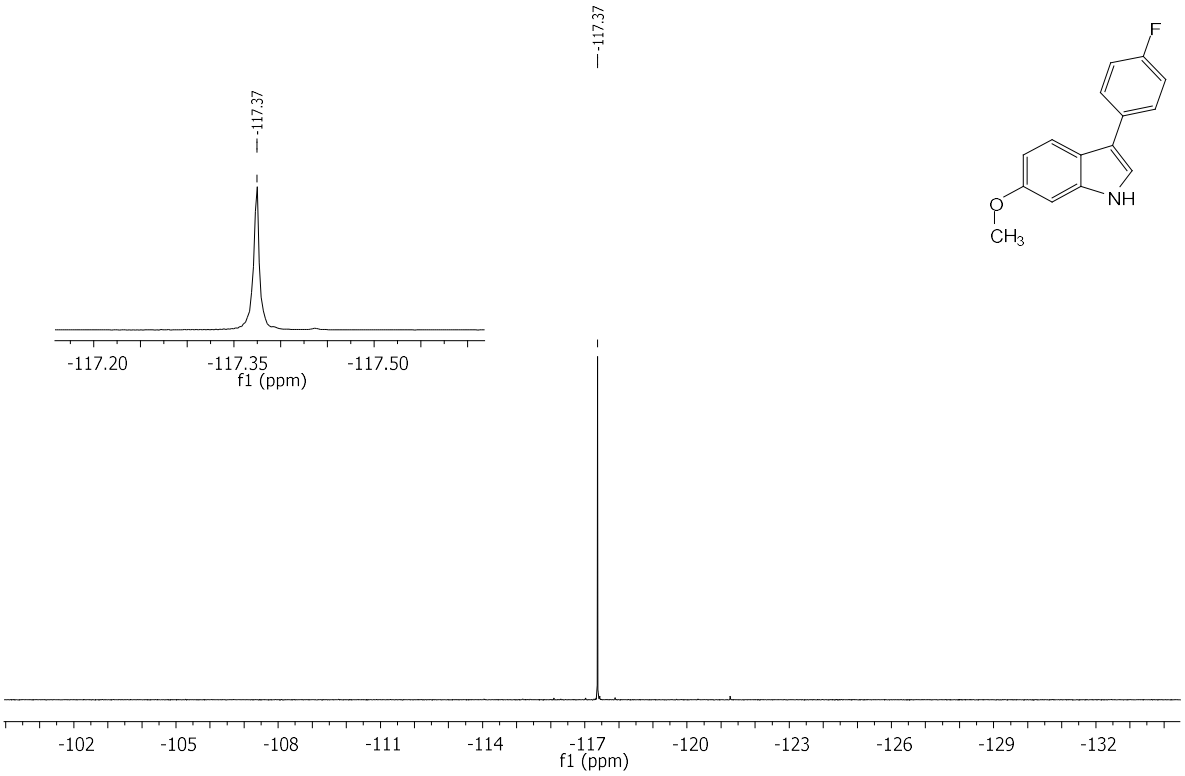


Fig. 37. ^{19}F NMR of **2d'** in $CDCl_3$.

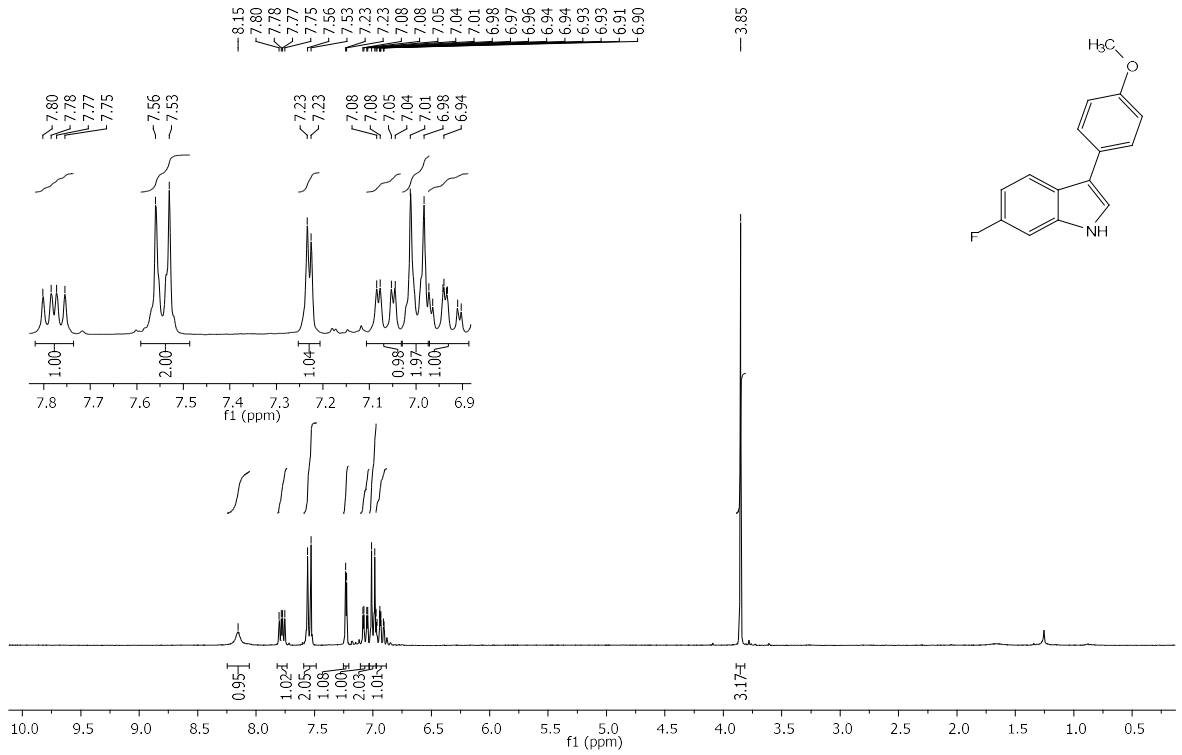


Fig. 38. ^{1}H NMR of **2d''** in $CDCl_3$.

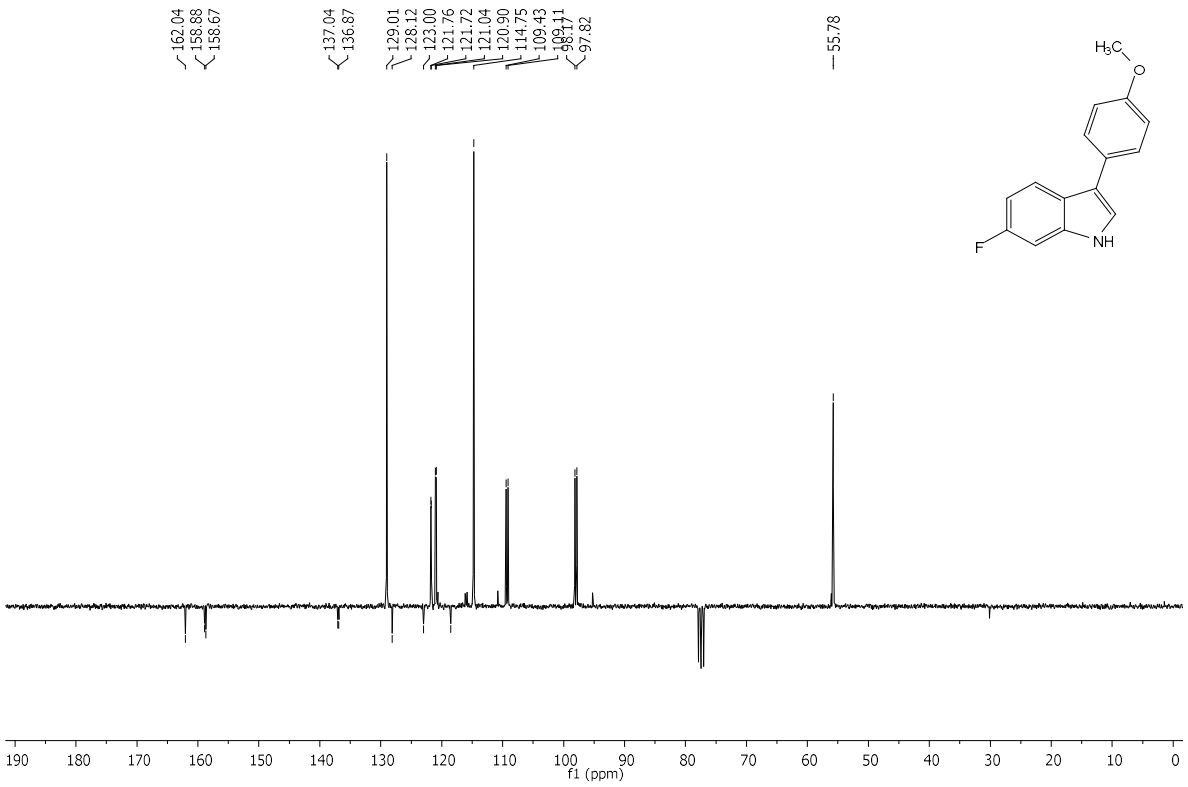


Fig. 39. ^{13}C NMR of **2d''** in $CDCl_3$.

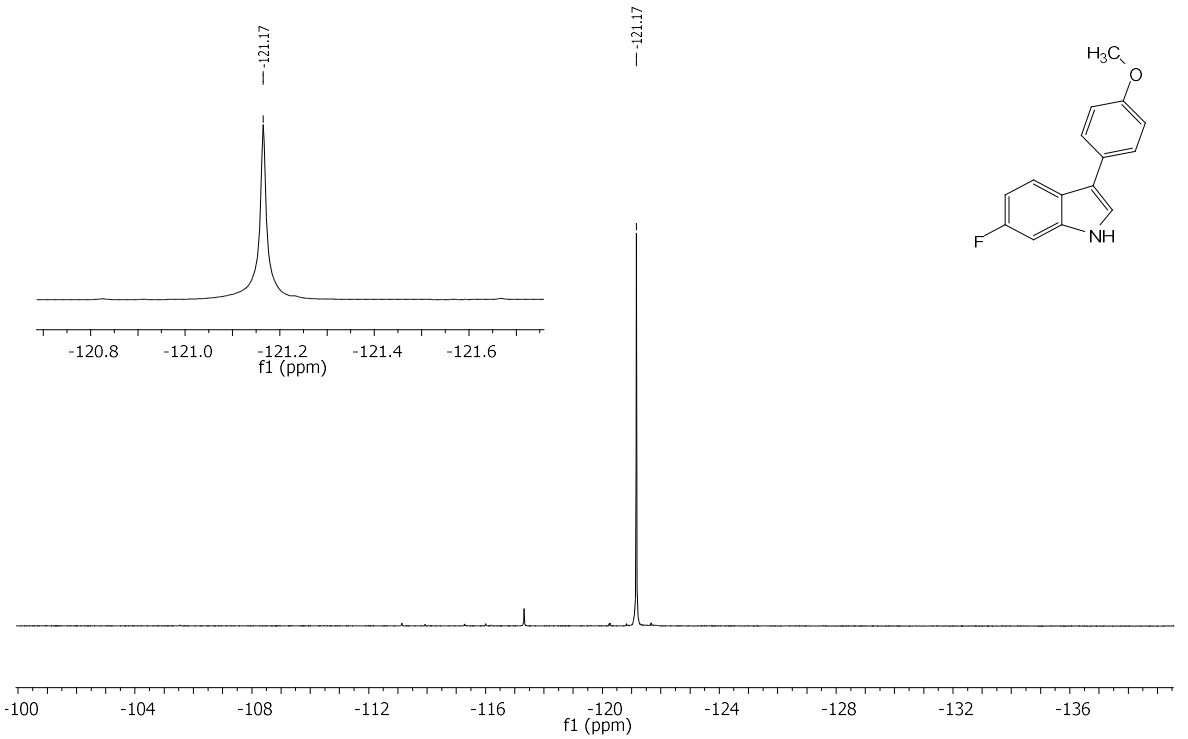


Fig. 40. ^{19}F NMR of **2d''** in $CDCl_3$.

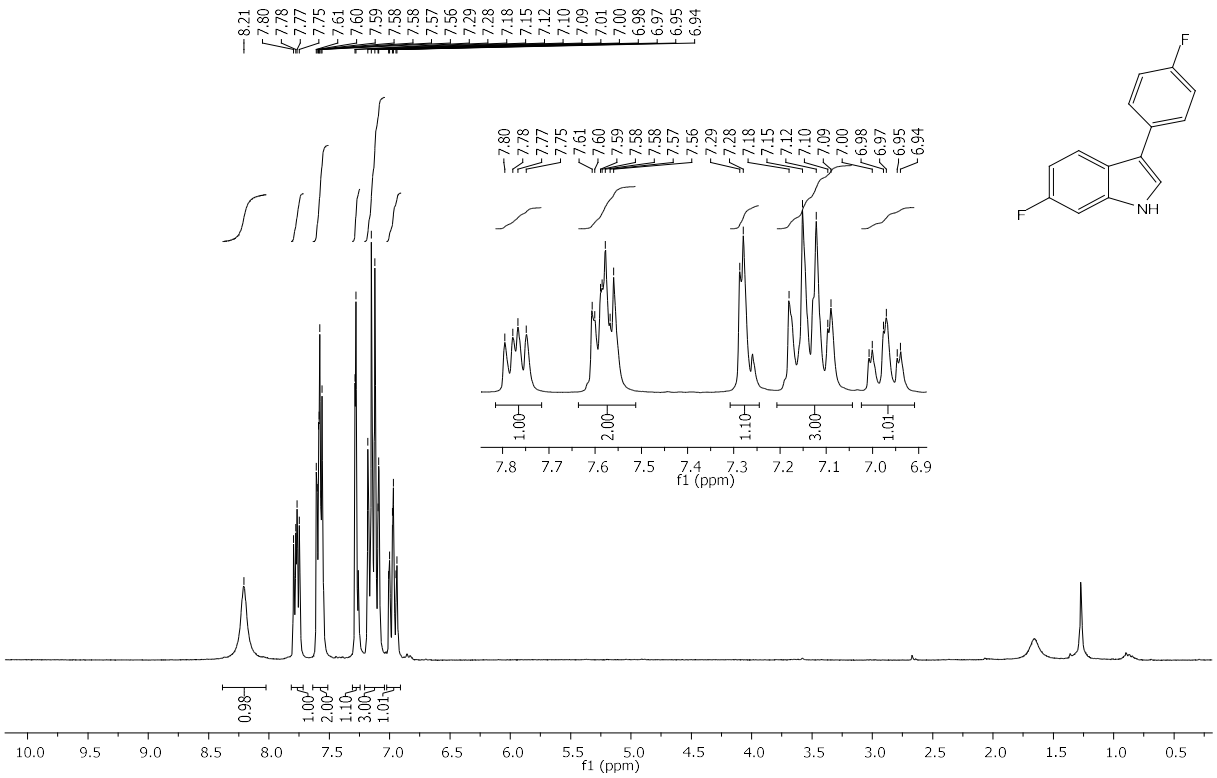


Fig. 41. ^{1}H NMR of **2e** in $CDCl_3$.

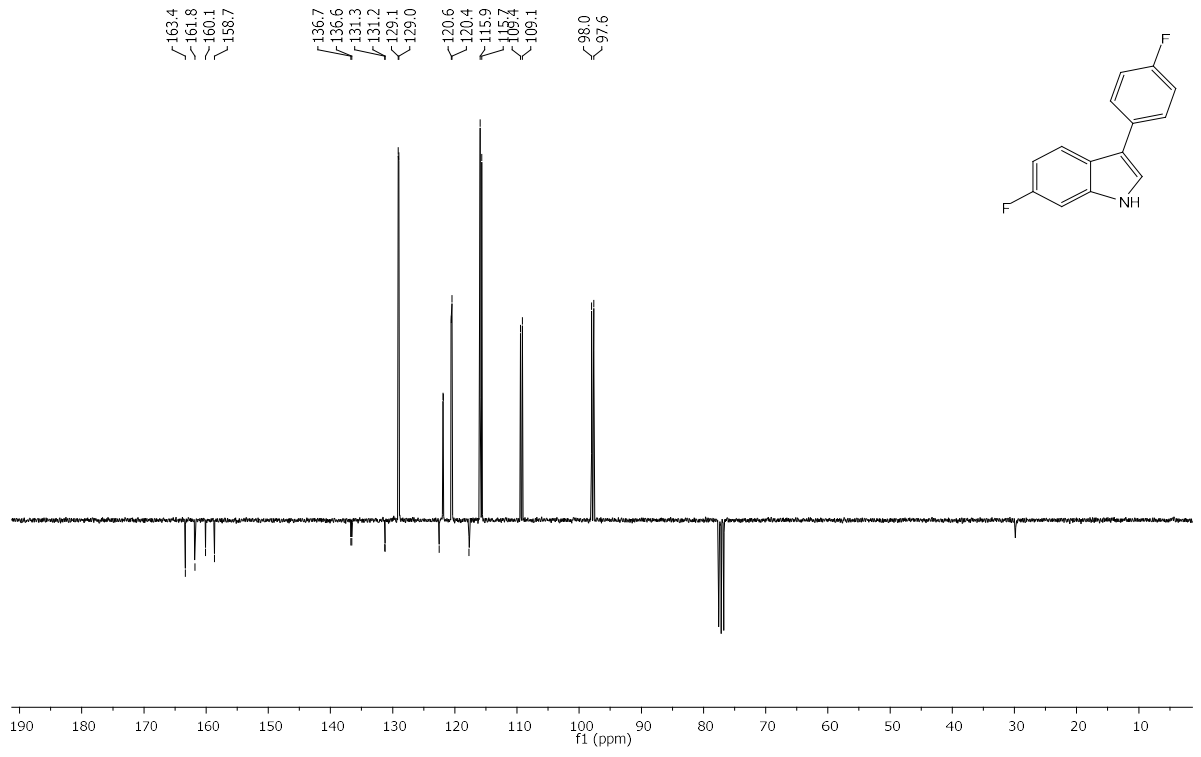


Fig. 42. ^{13}C NMR of **2e** in $CDCl_3$.

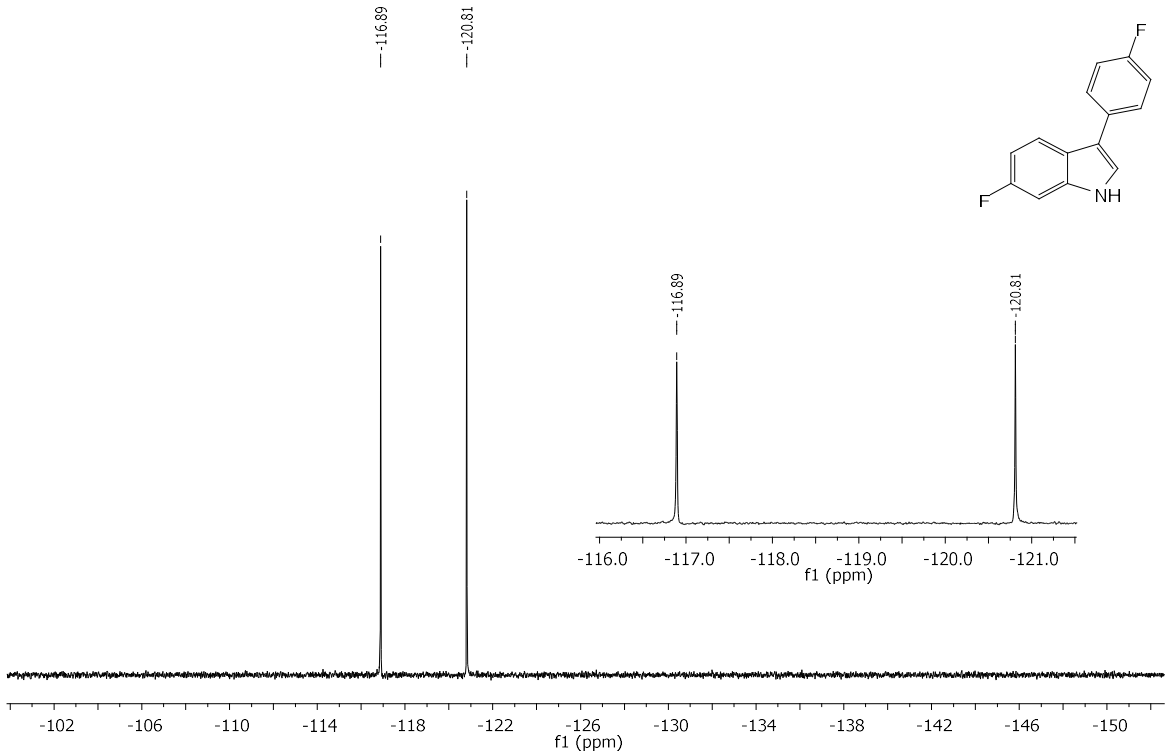


Fig. 43. ^{19}F NMR of **2e** in $CDCl_3$.

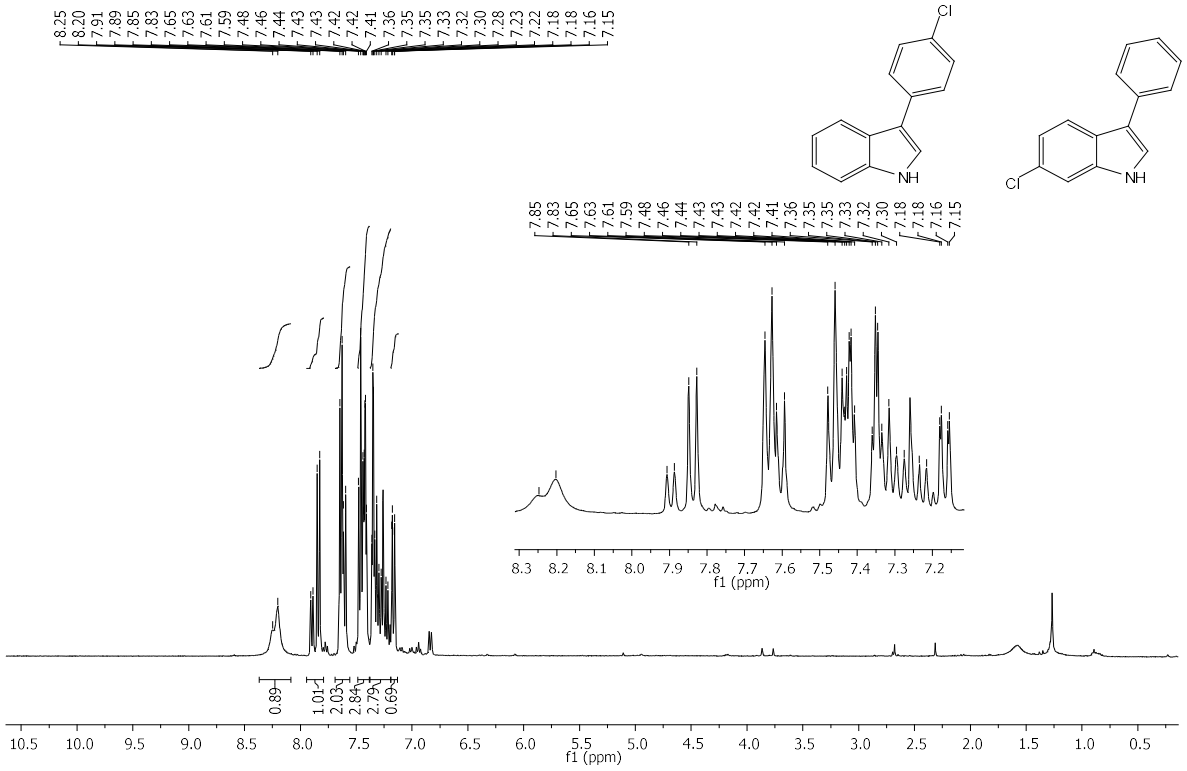


Fig. 44. ^{1}H NMR of **2g'** and **2g''** in $CDCl_3$.

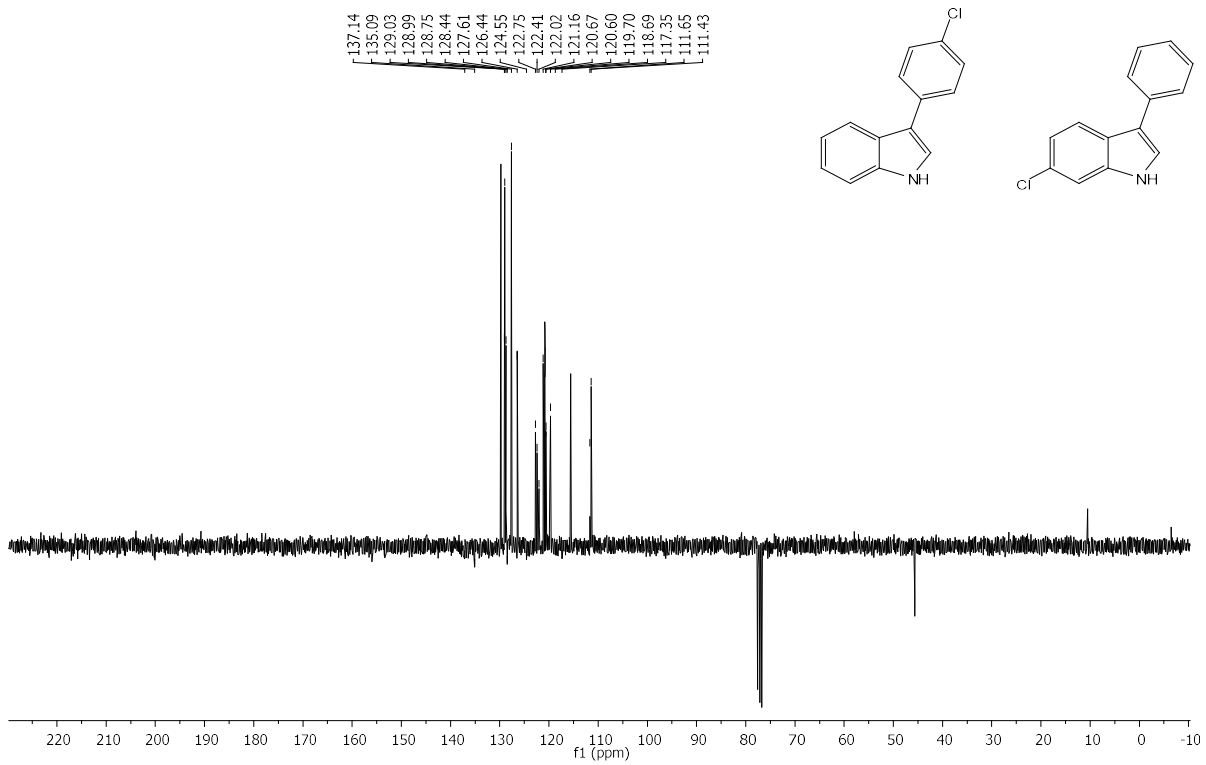


Fig. 45. ^{13}C NMR of **2g'** and **2g''** in $CDCl_3$.

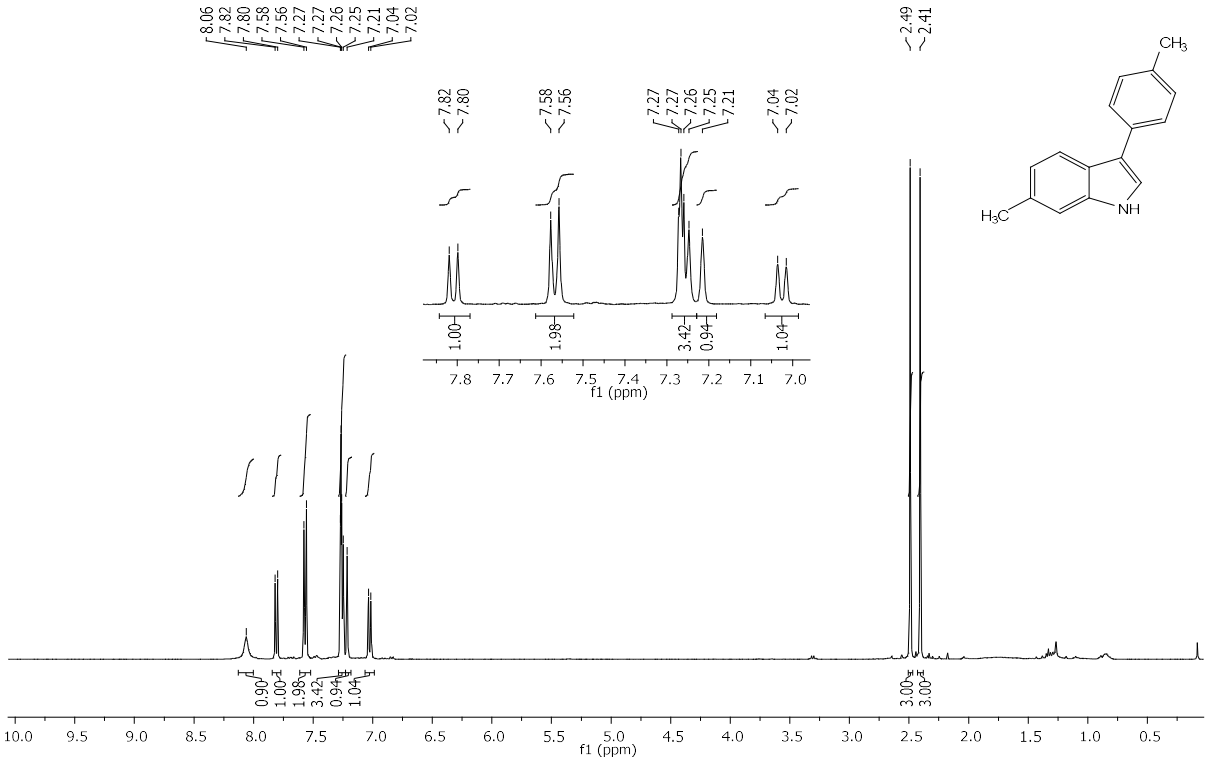


Fig. 46. ^{1}H NMR of **2h** in $CDCl_3$.

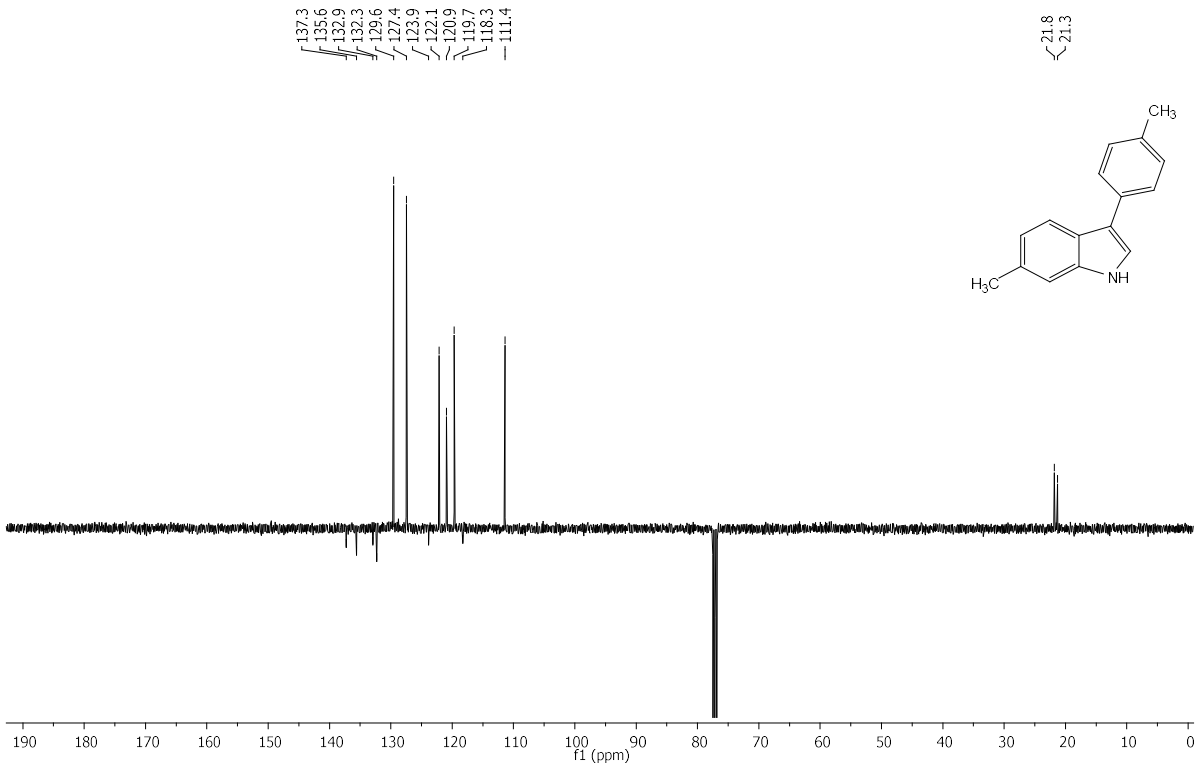


Fig. 47. ^{13}C NMR of **2h** in $CDCl_3$.

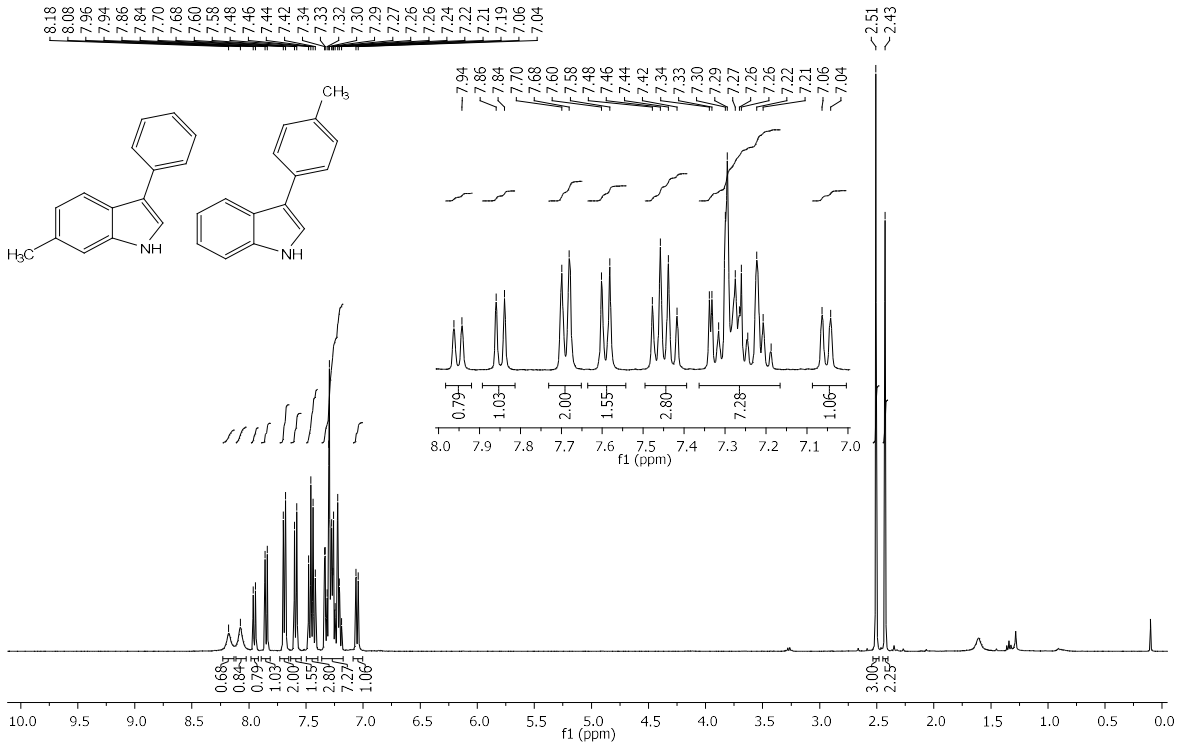


Fig. 48. ^{1}H NMR of **2i'** and **2i''** in $CDCl_3$.

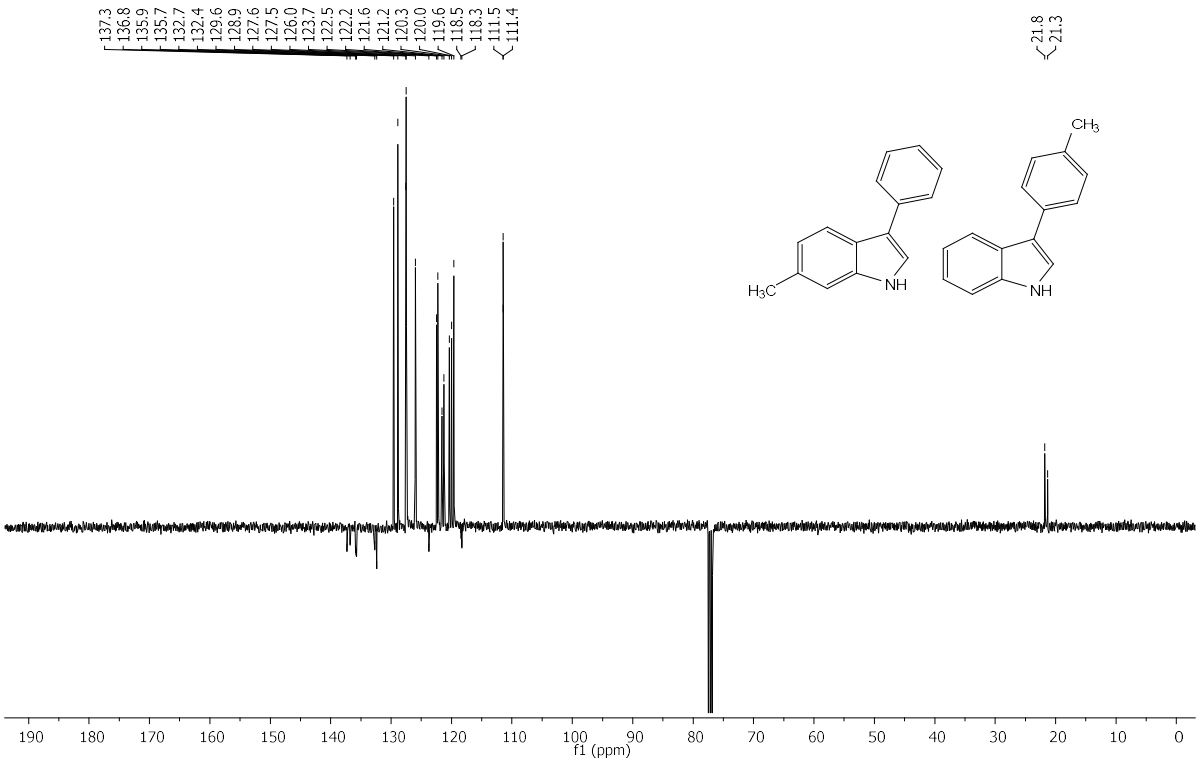


Fig. 49. ^{13}C NMR of **2i'** and **2i''** in $CDCl_3$.

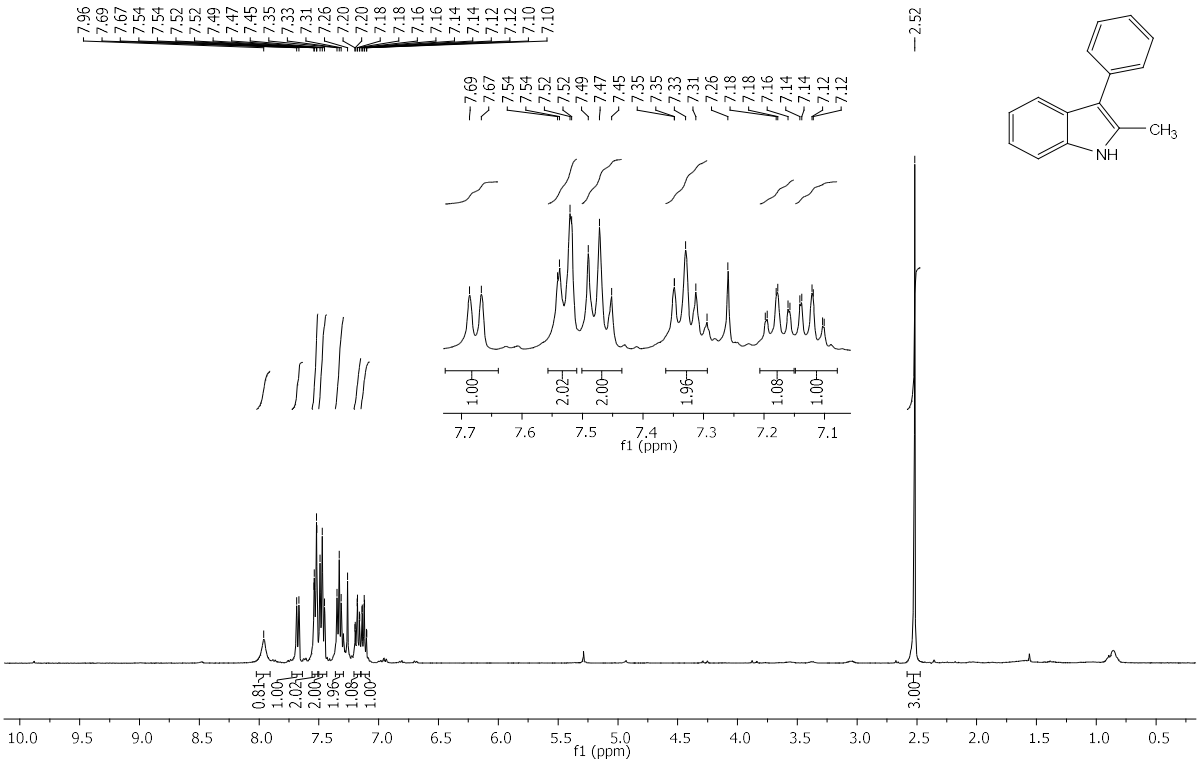


Fig. 50. ^{1}H NMR of **2j** in $CDCl_3$.

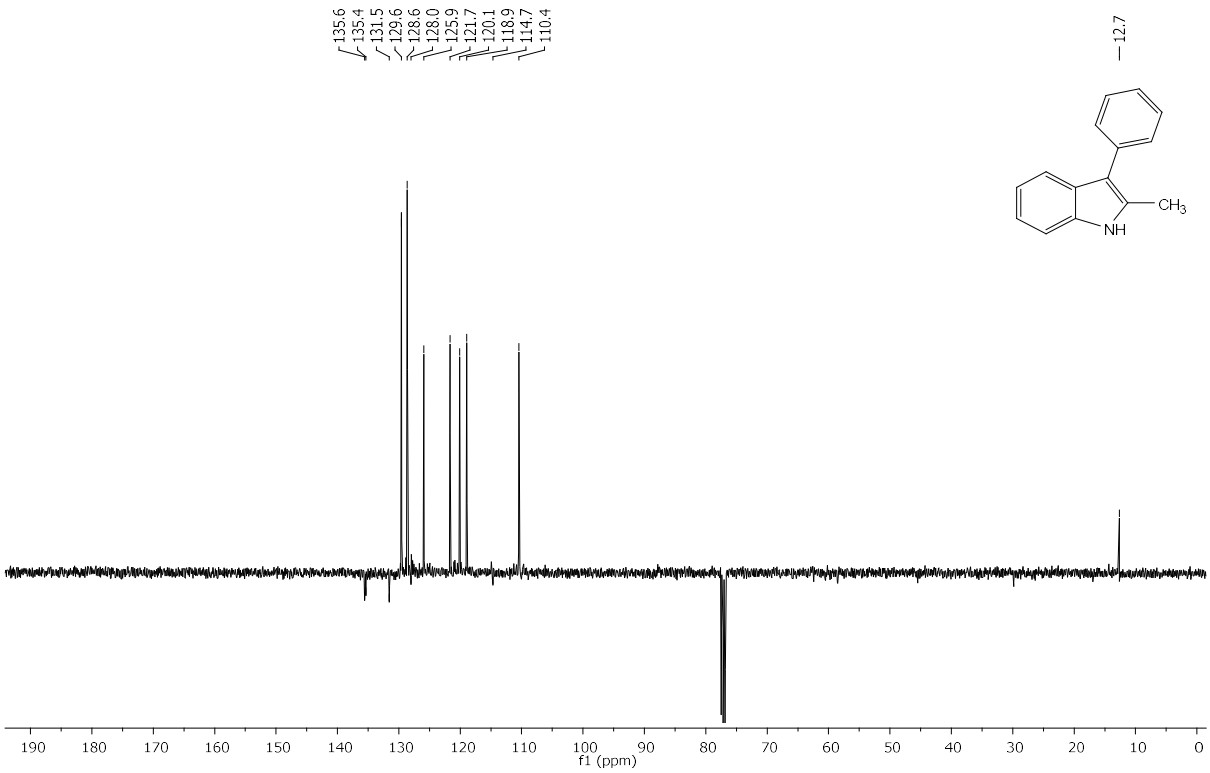


Fig. 51. ^{13}C NMR of **2j** in $CDCl_3$.

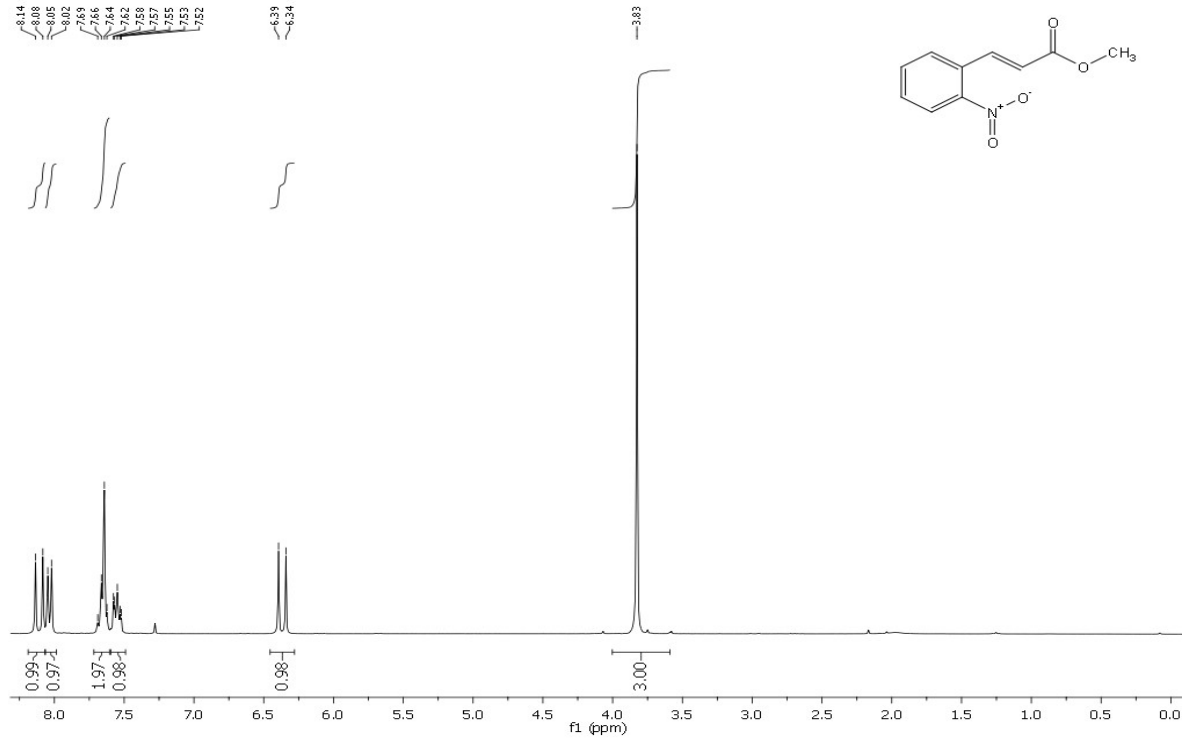


Fig. 52. ^{1}H NMR of **3a** in $CDCl_3$.

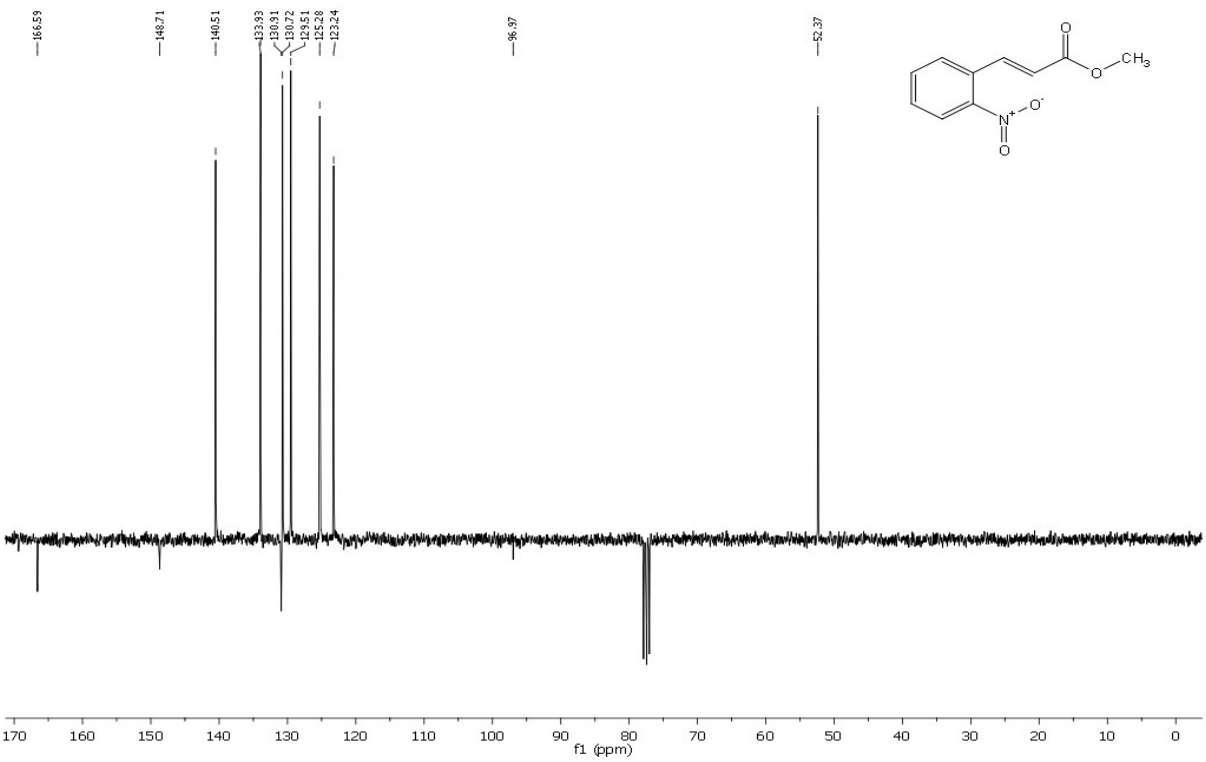


Fig. 53. ^{13}C NMR of **3a** in $CDCl_3$.

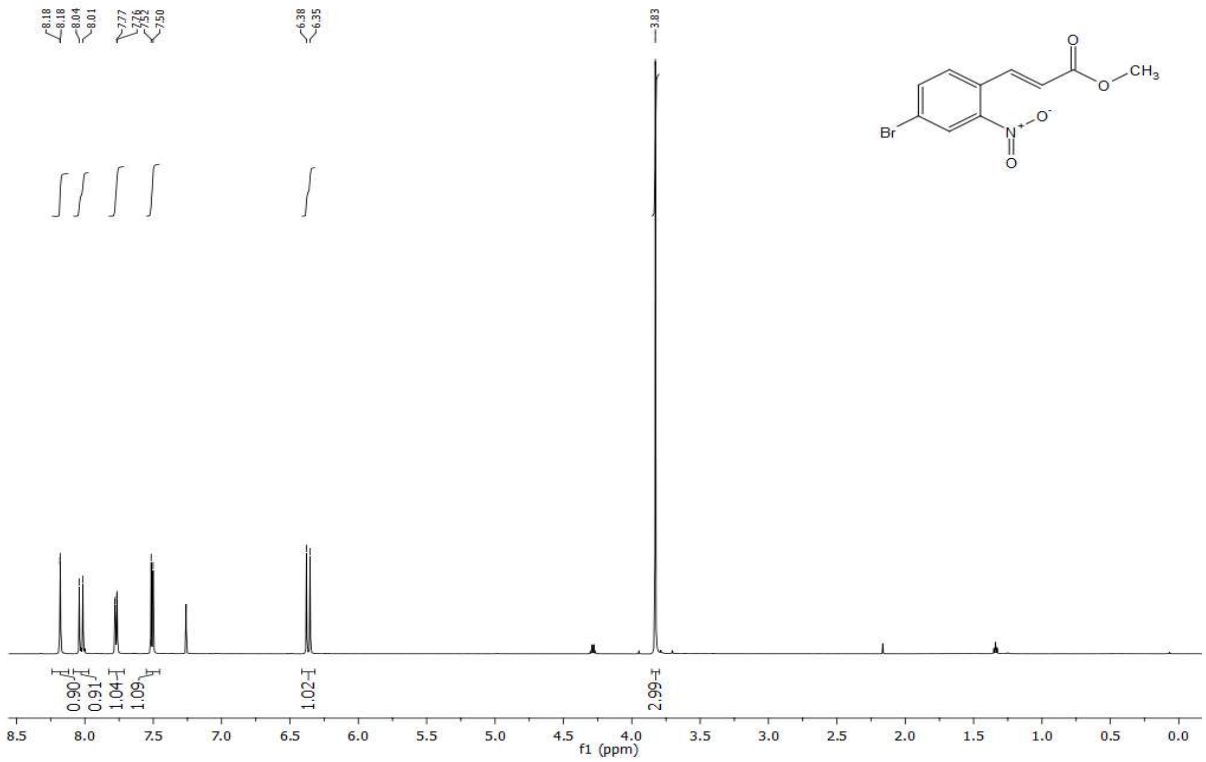


Fig. 54. ^{1}H NMR of **3b** in $CDCl_3$.

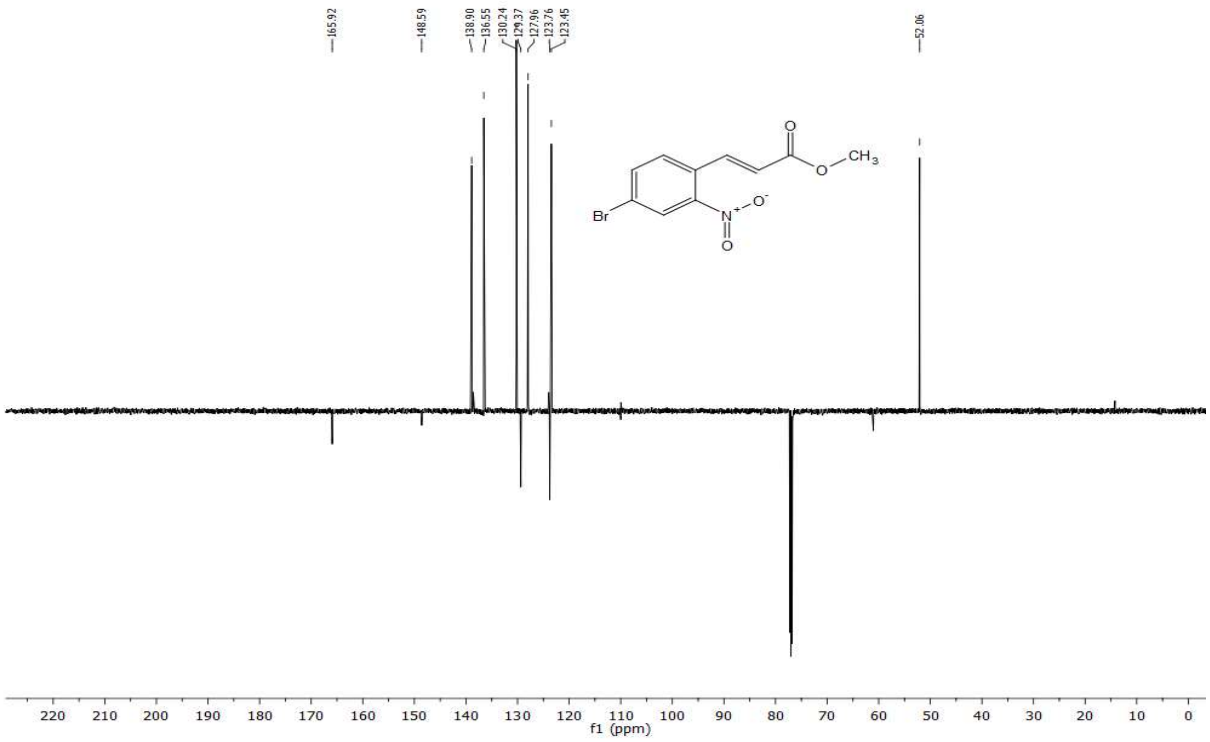


Fig. 55. ^{13}C NMR of **3b** in $CDCl_3$.

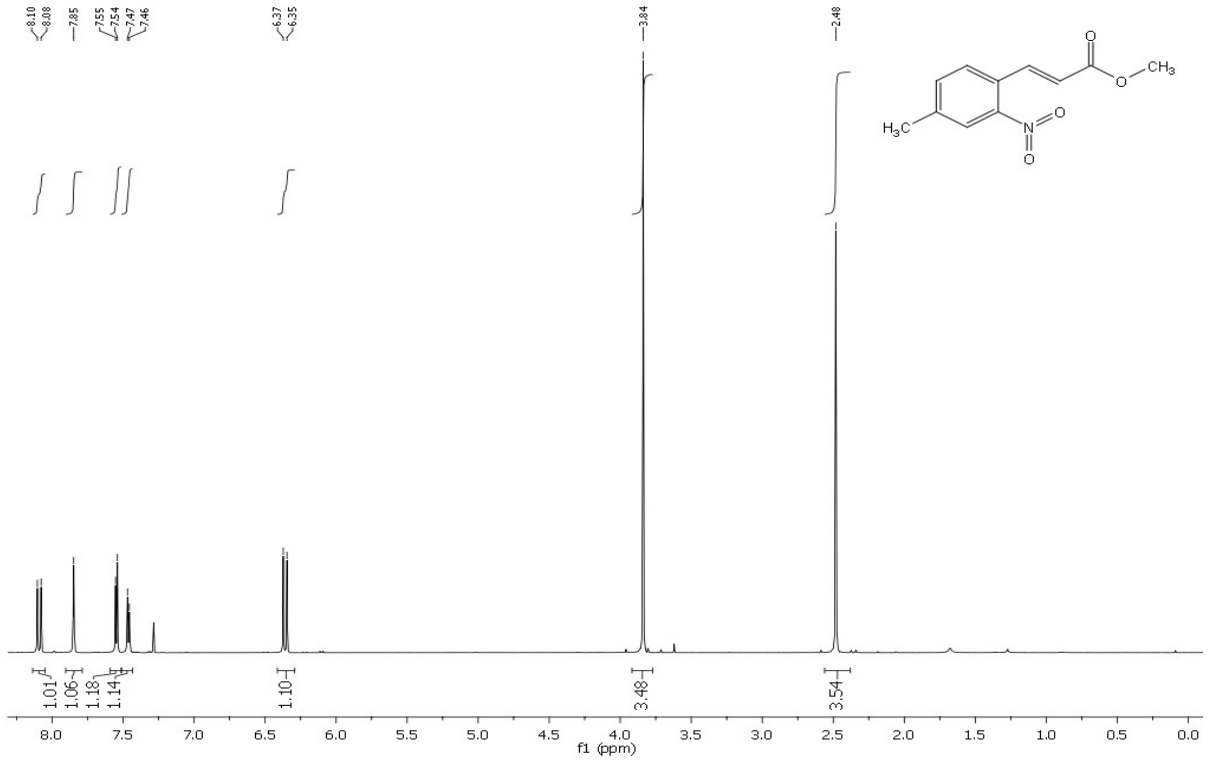


Fig. 56. ^{1}H NMR of **3c** in $CDCl_3$.

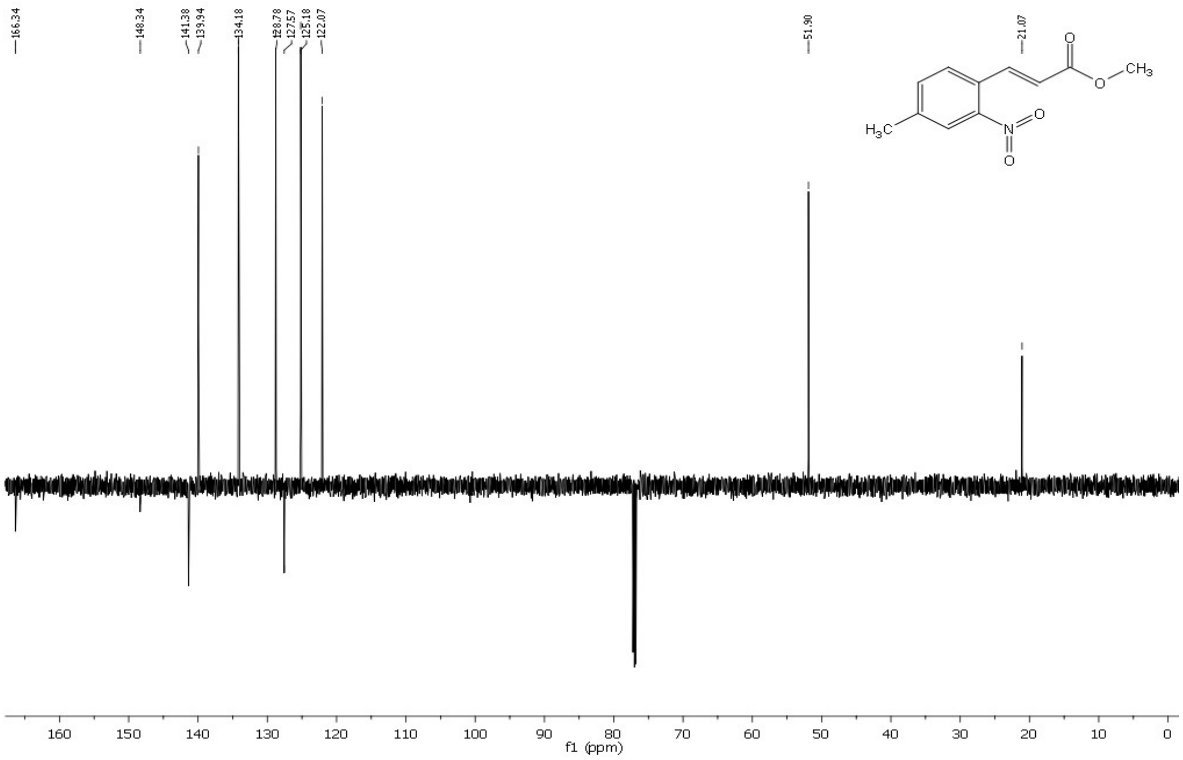


Fig. 57. ^{13}C NMR of **3c** in $CDCl_3$.

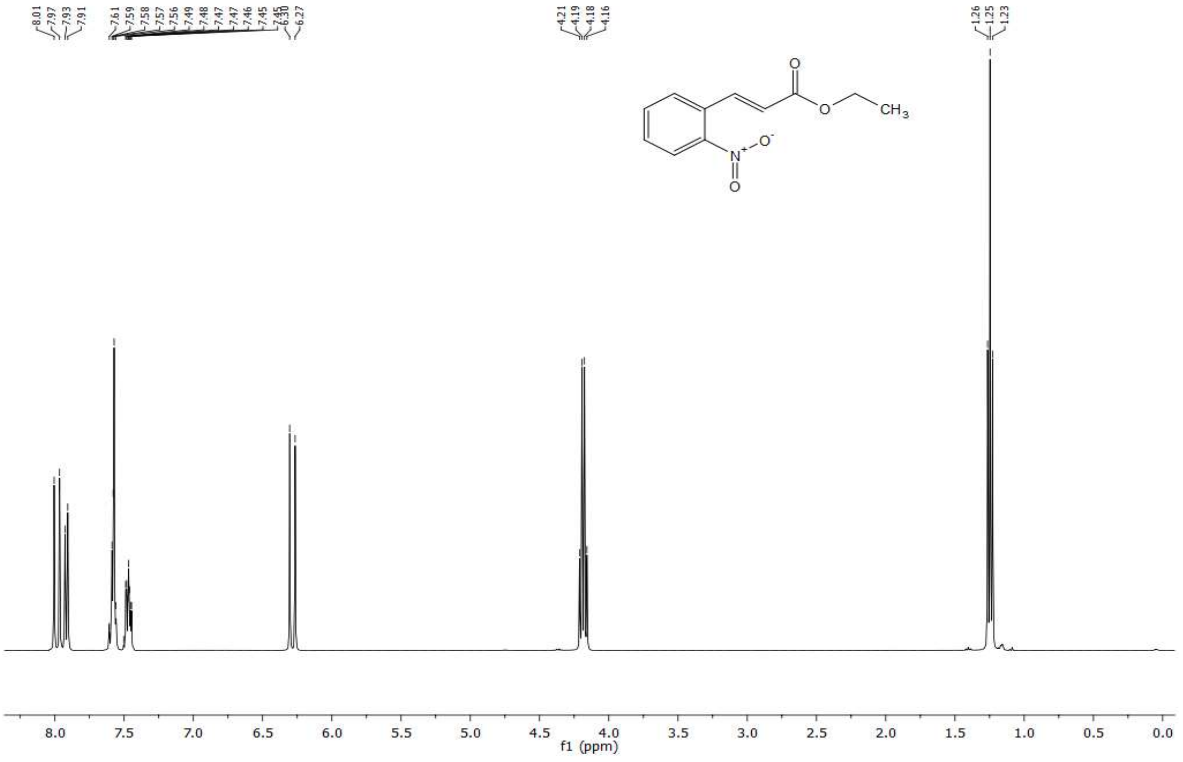


Fig. 58. ^{1}H NMR of **3d** in $CDCl_3$.

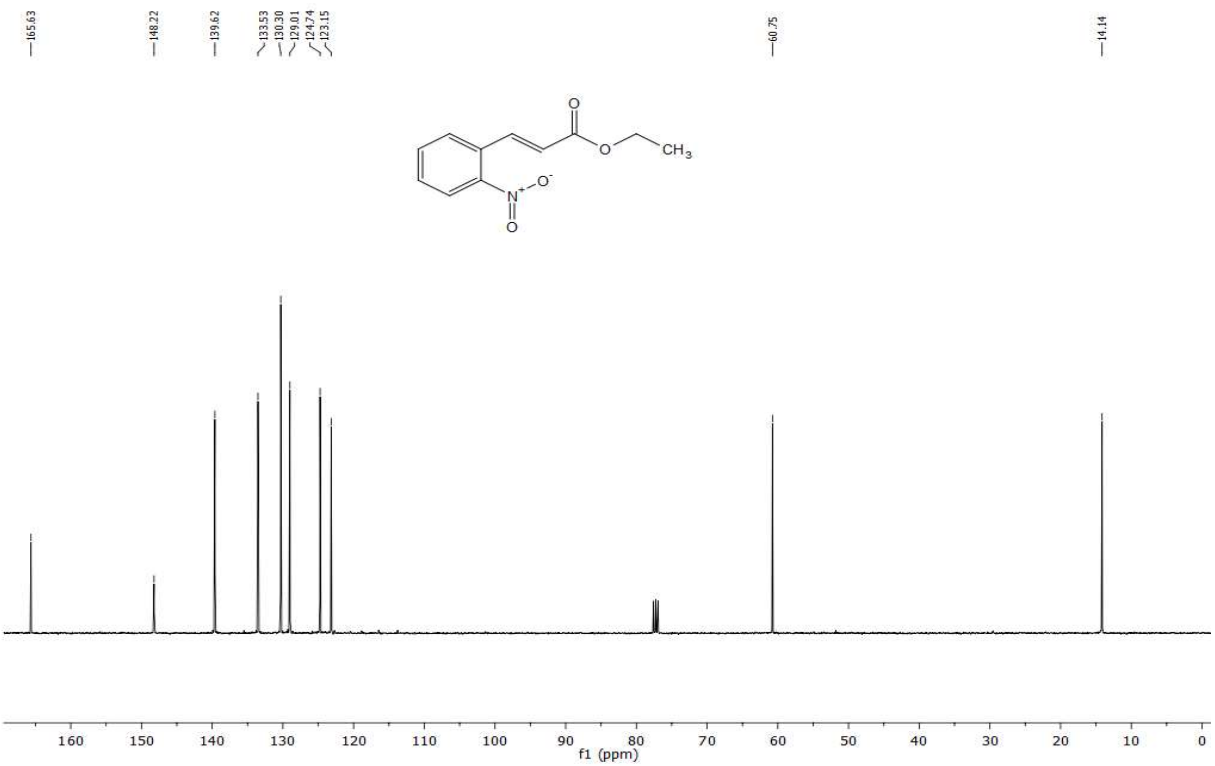


Fig. 59. ^{13}C NMR of **3d** in $CDCl_3$

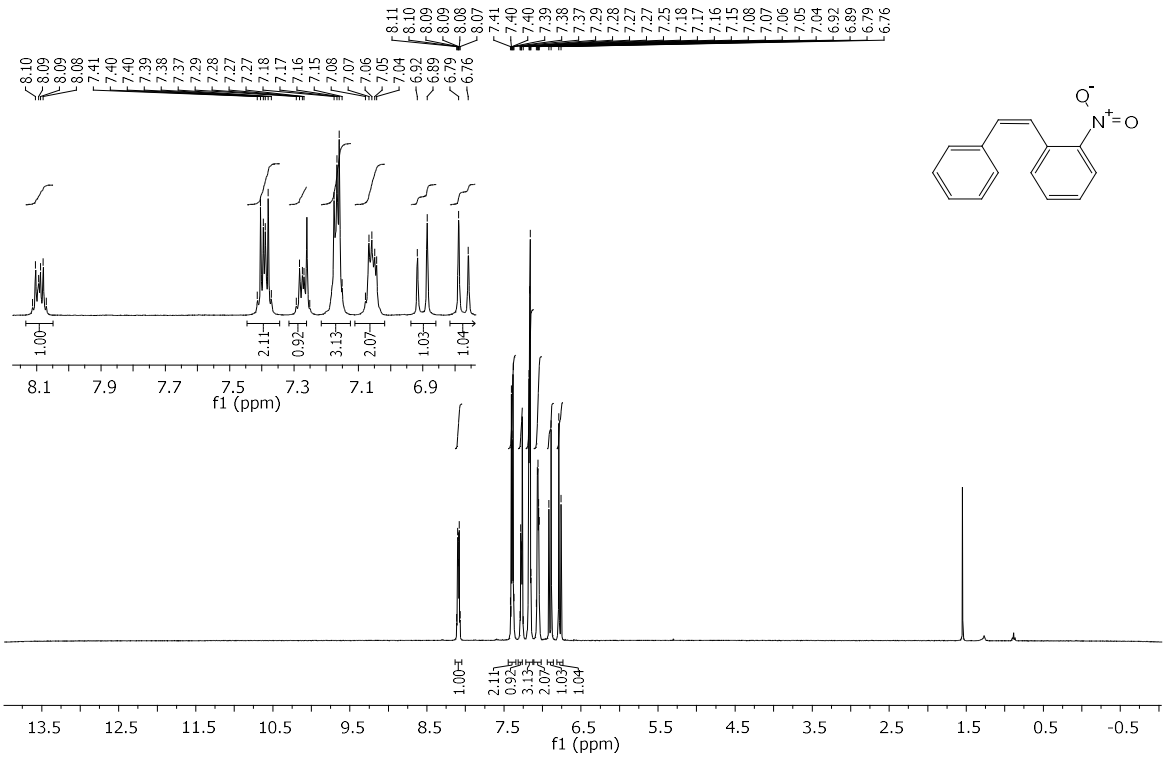


Fig. 60. ^{1}H NMR of ***Z*-3f** in $CDCl_3$.

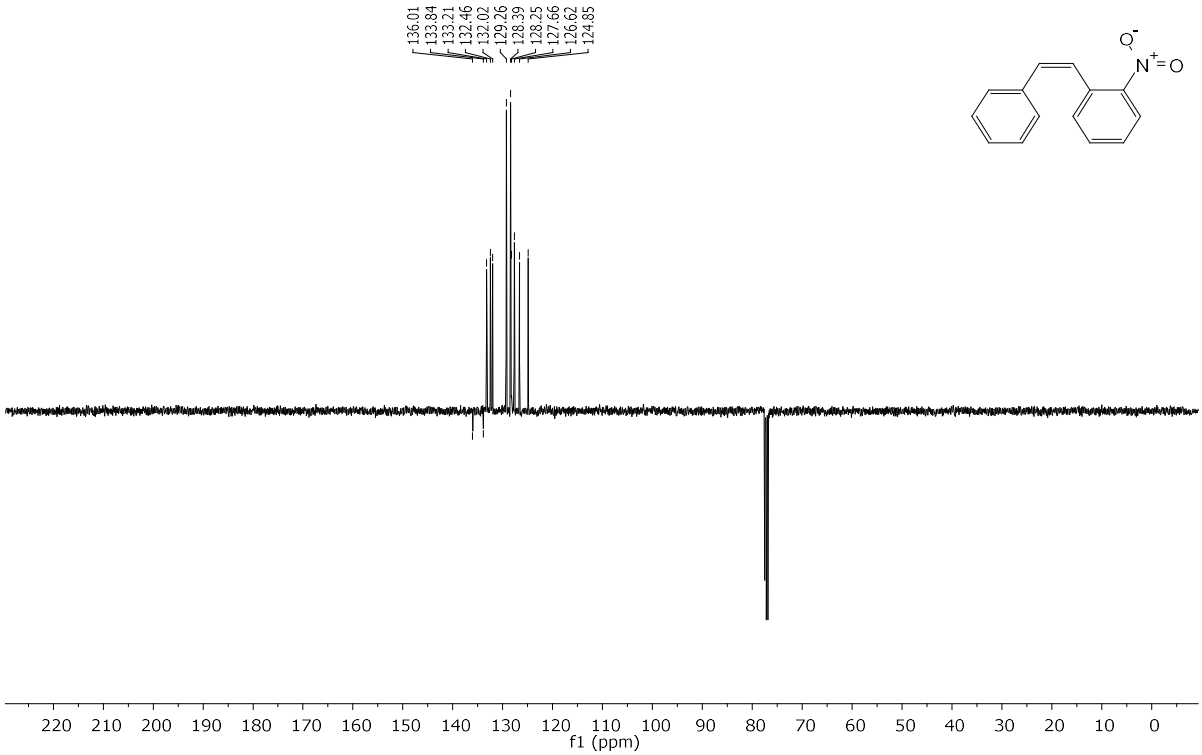


Fig. 61. ^{13}C NMR of ***Z*-3f** in $CDCl_3$

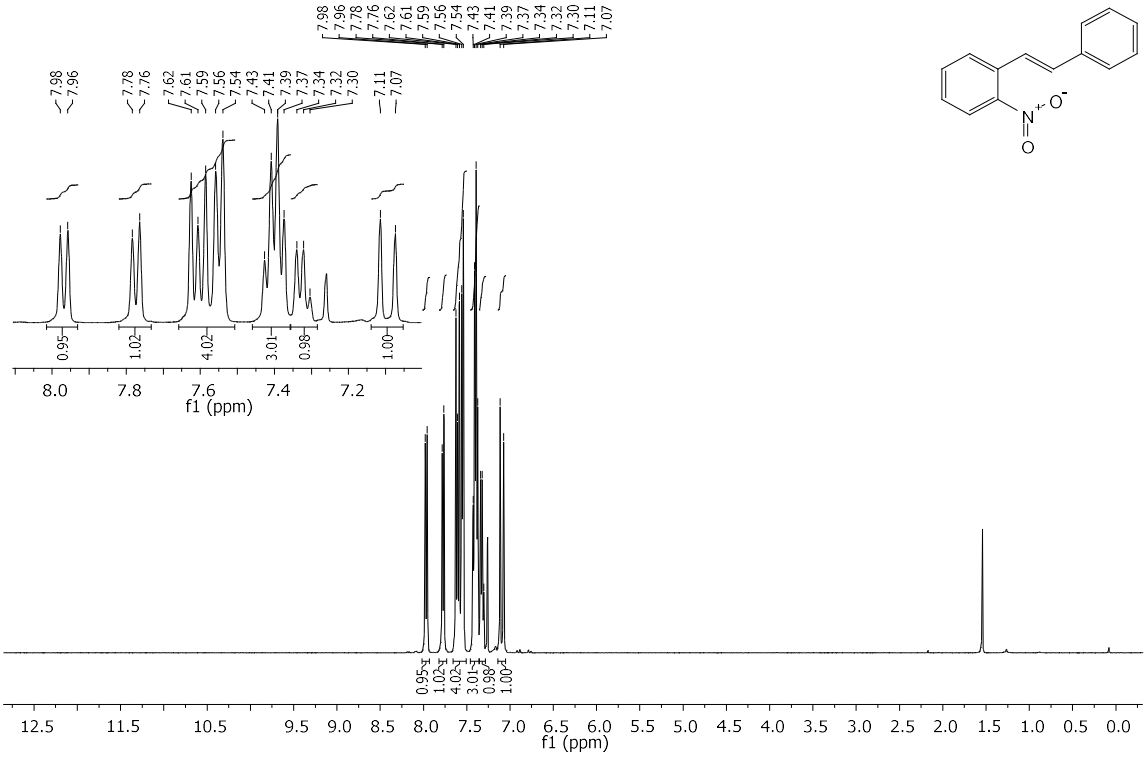


Fig. 62. ^{1}H NMR of ***E*-3f** in $CDCl_3$.

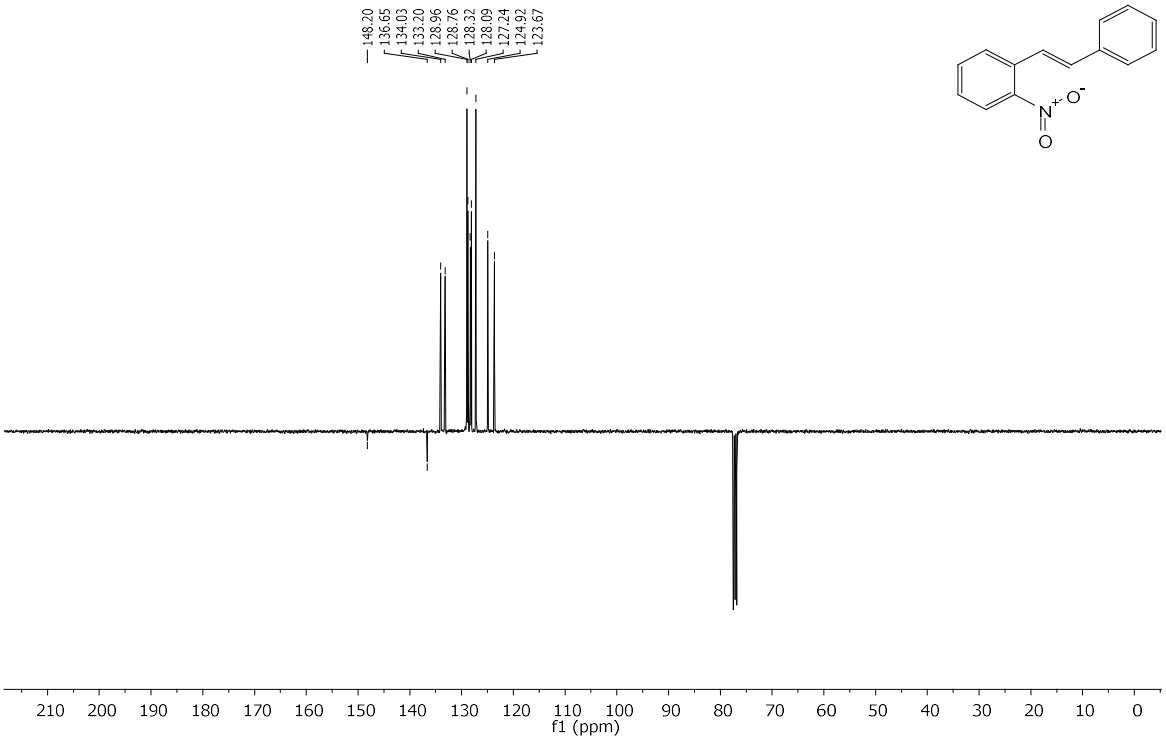


Fig. 63. ^{13}C NMR of ***E*-3f** in $CDCl_3$

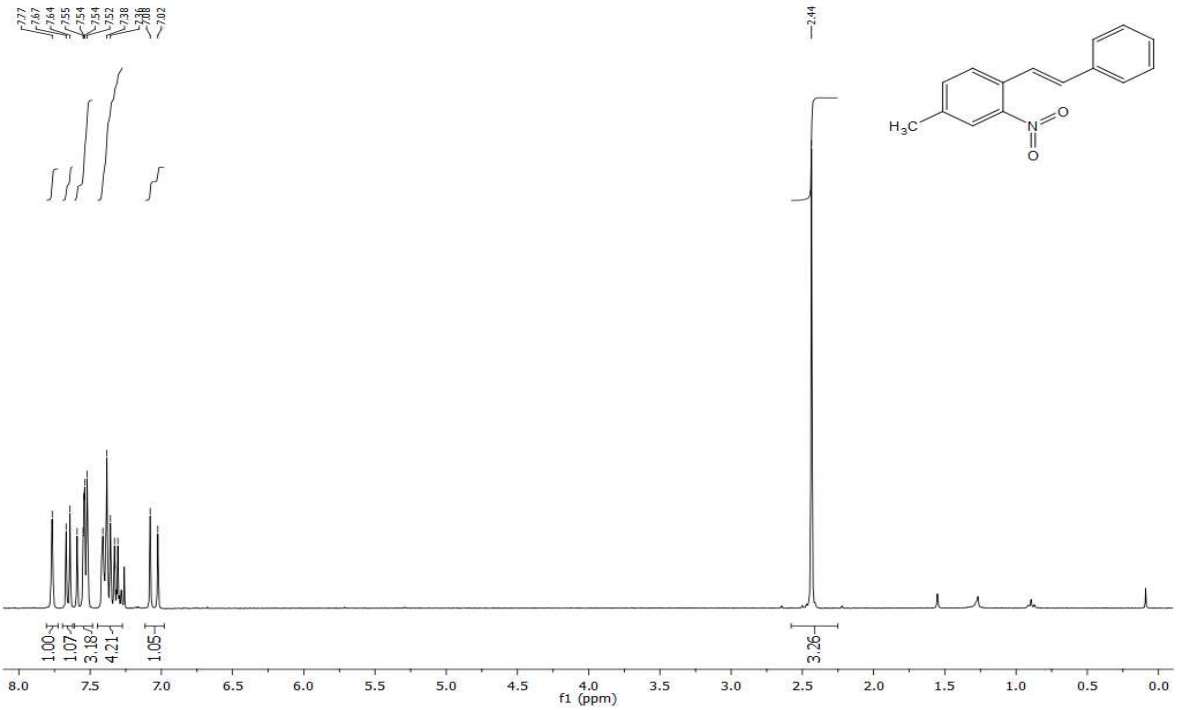


Fig. 64. ^{1}H NMR of **3g** in $CDCl_3$.

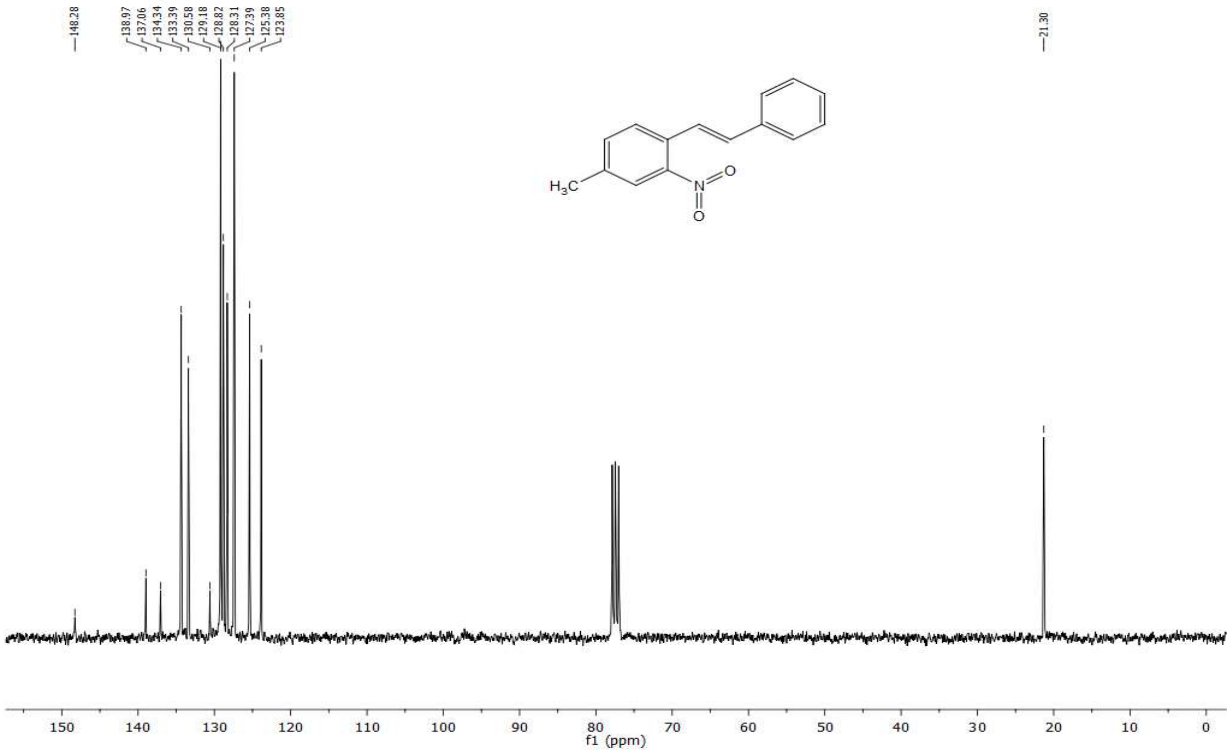


Fig. 65. ^{13}C NMR of **3g** in $CDCl_3$

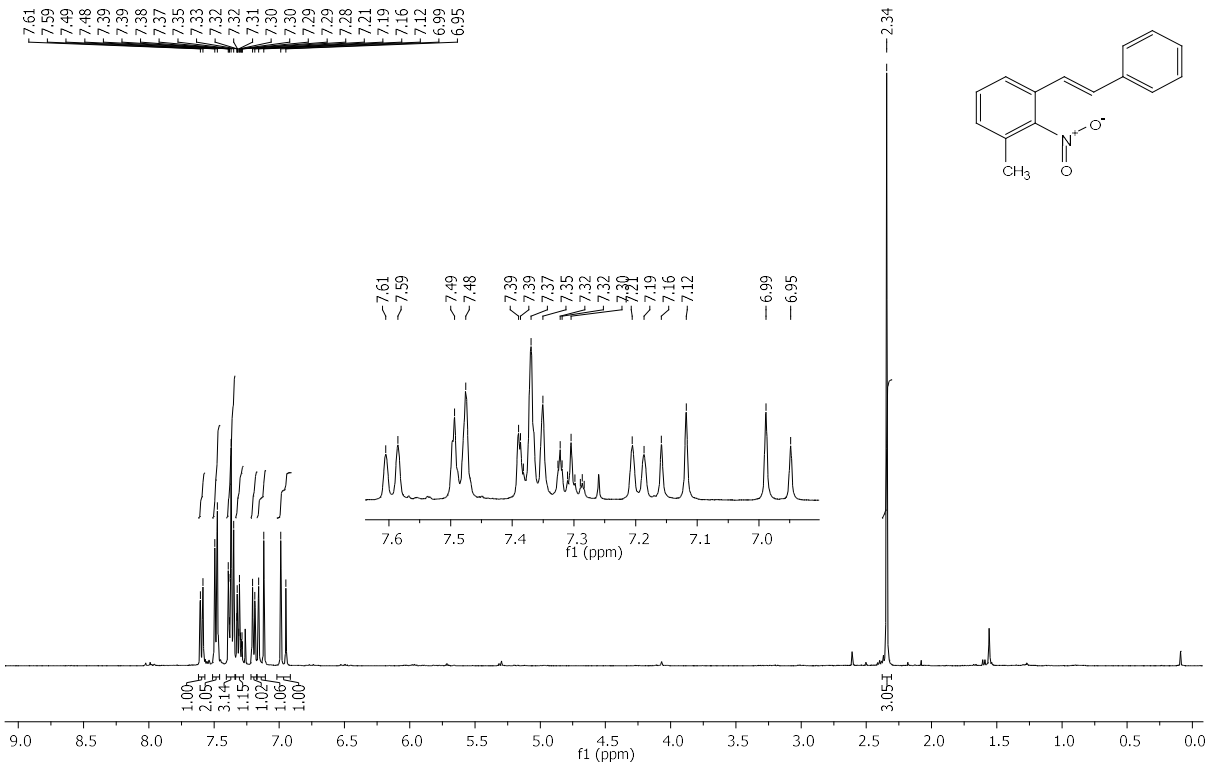


Fig. 66. ^{1}H NMR of **3h** in $CDCl_3$.

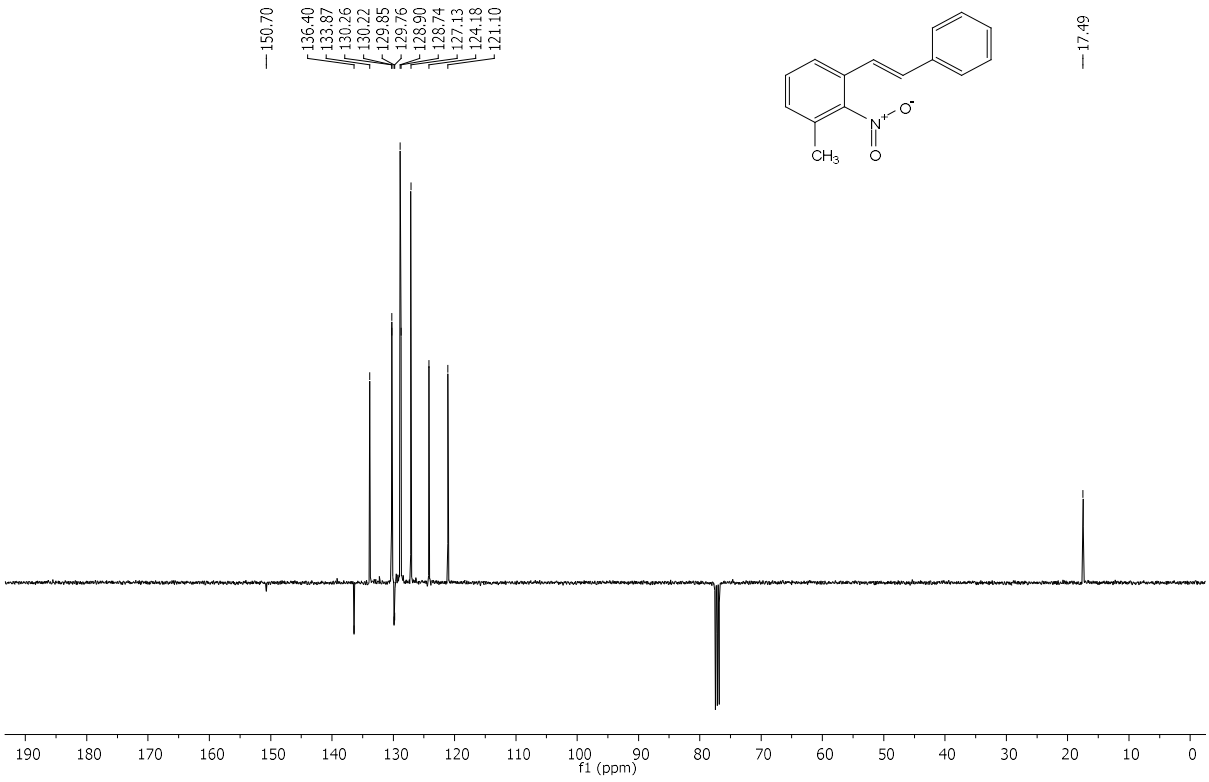


Fig. 67. ^{13}C NMR of **3h** in $CDCl_3$.

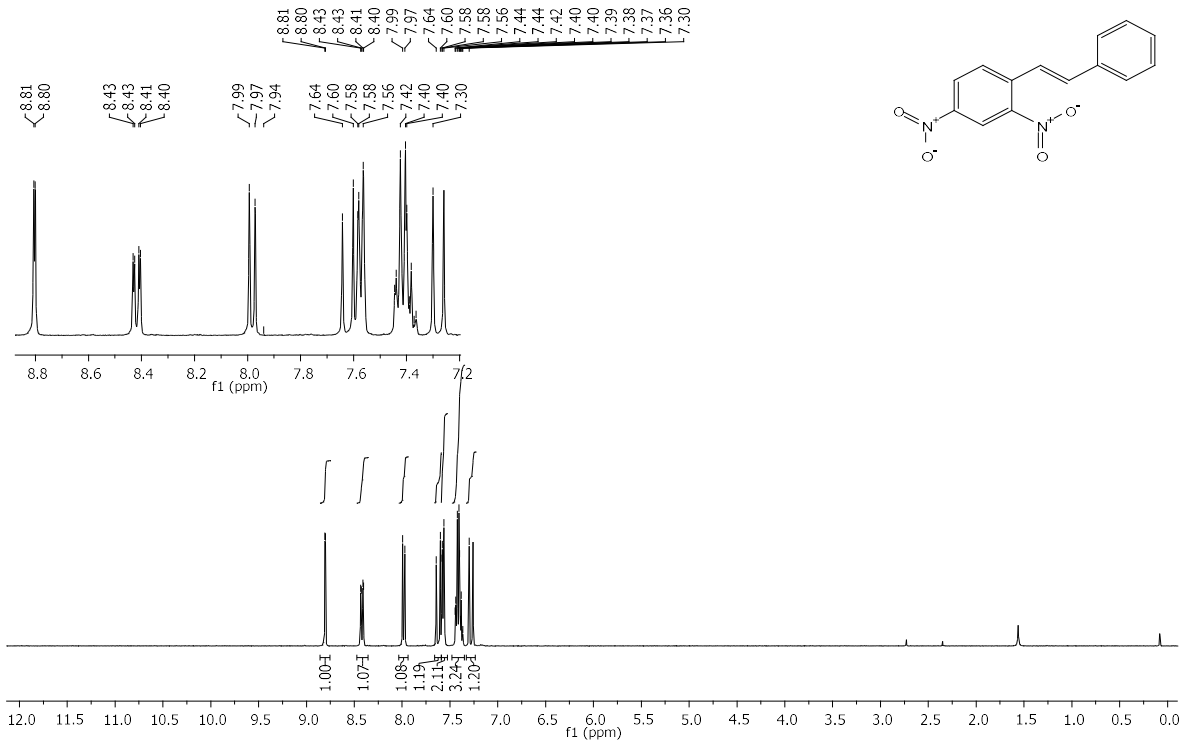


Fig. 68. ^{1}H NMR of **3i** in $CDCl_3$.

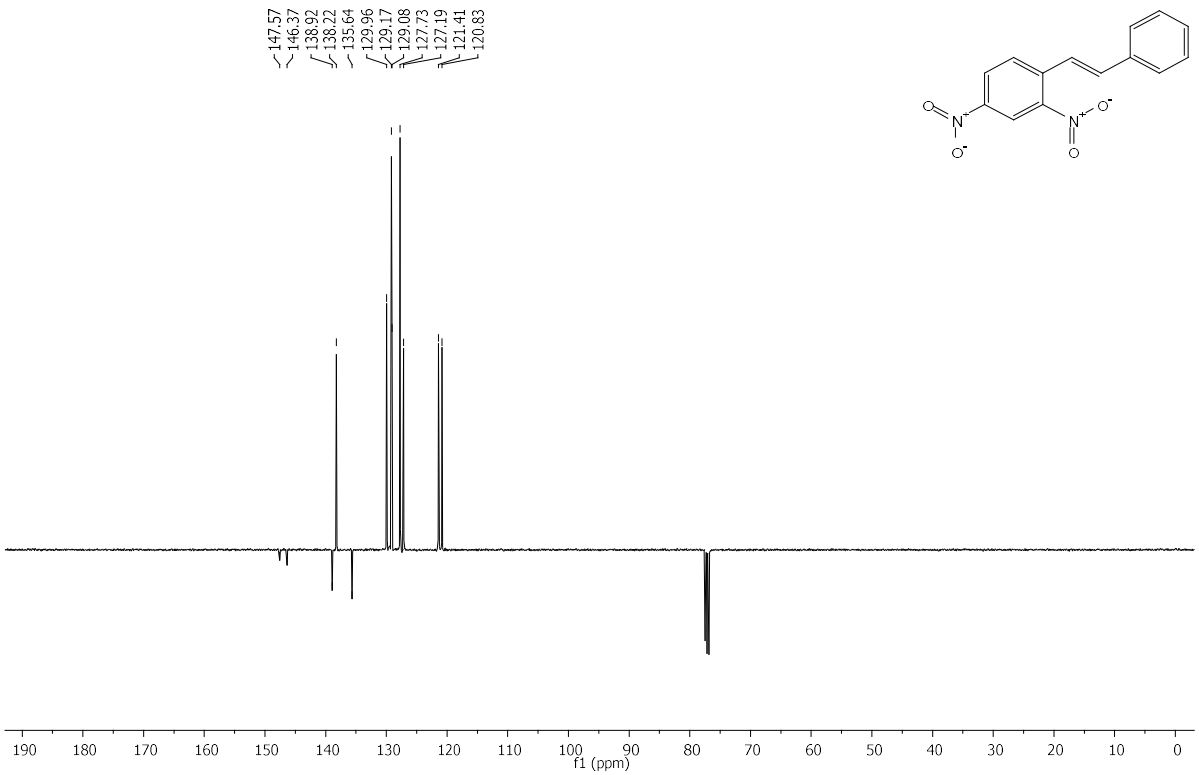


Fig. 69. ^{13}C NMR of **3i** in $CDCl_3$.

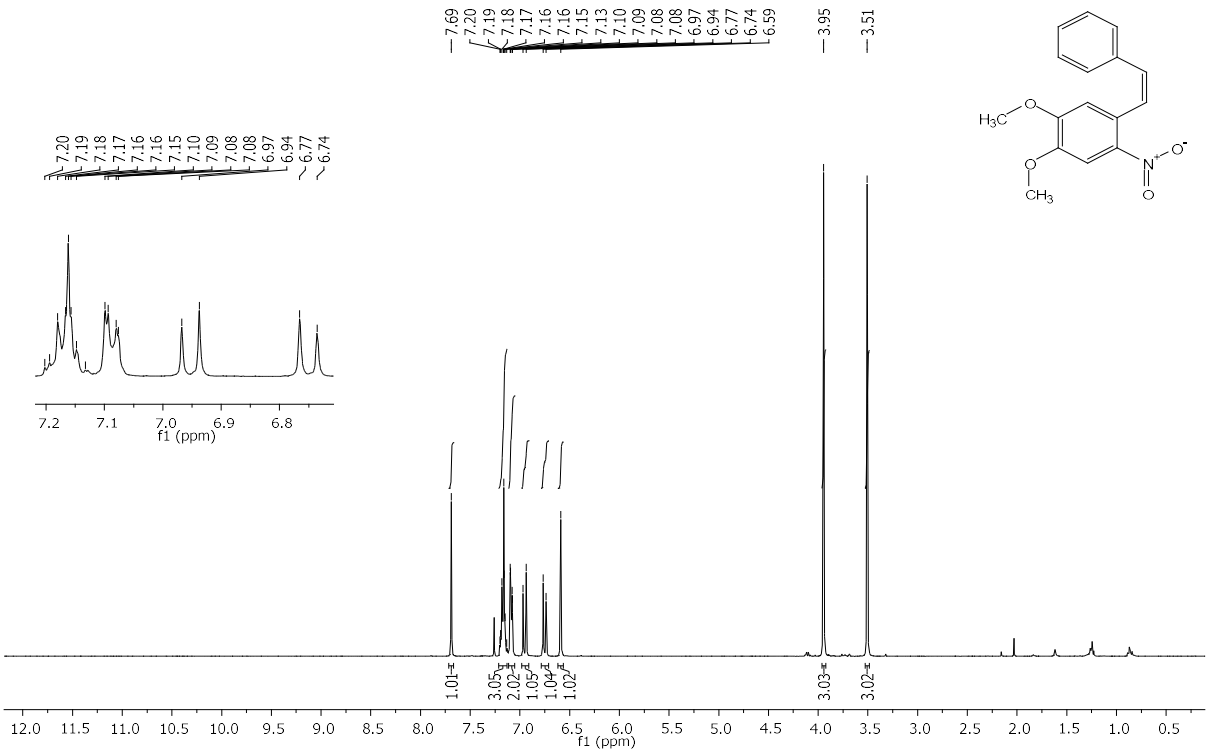


Fig. 70. ^{1}H NMR of ***Z*-3k** in $CDCl_3$.

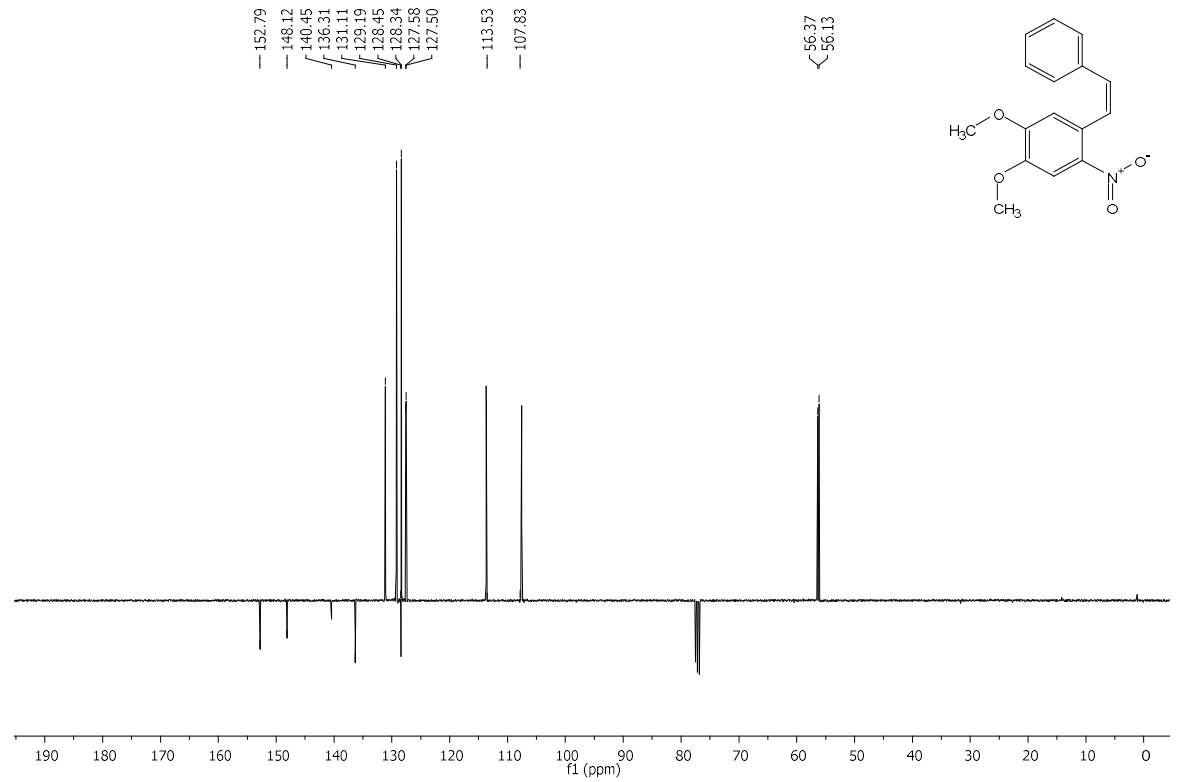


Fig. 71. ^{13}C NMR of ***Z*-3k** in $CDCl_3$.

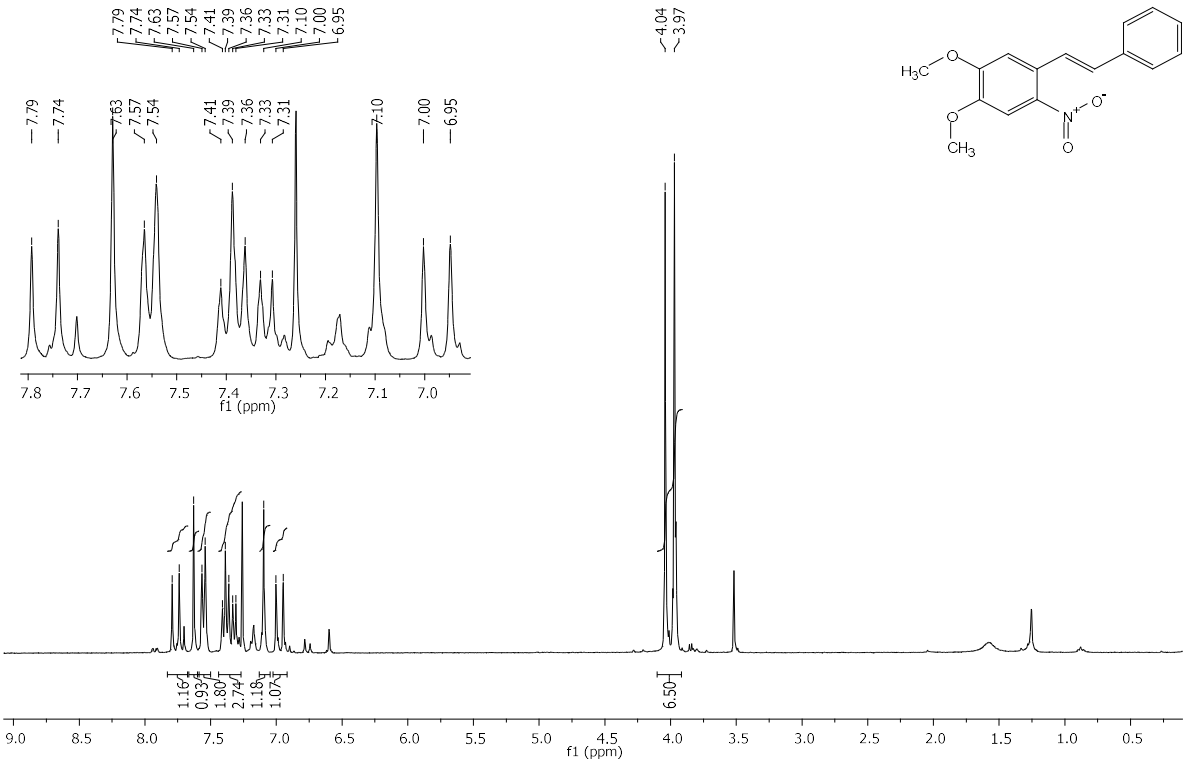


Fig. 72. ^{1}H NMR of ***E*-3k** in $CDCl_3$.

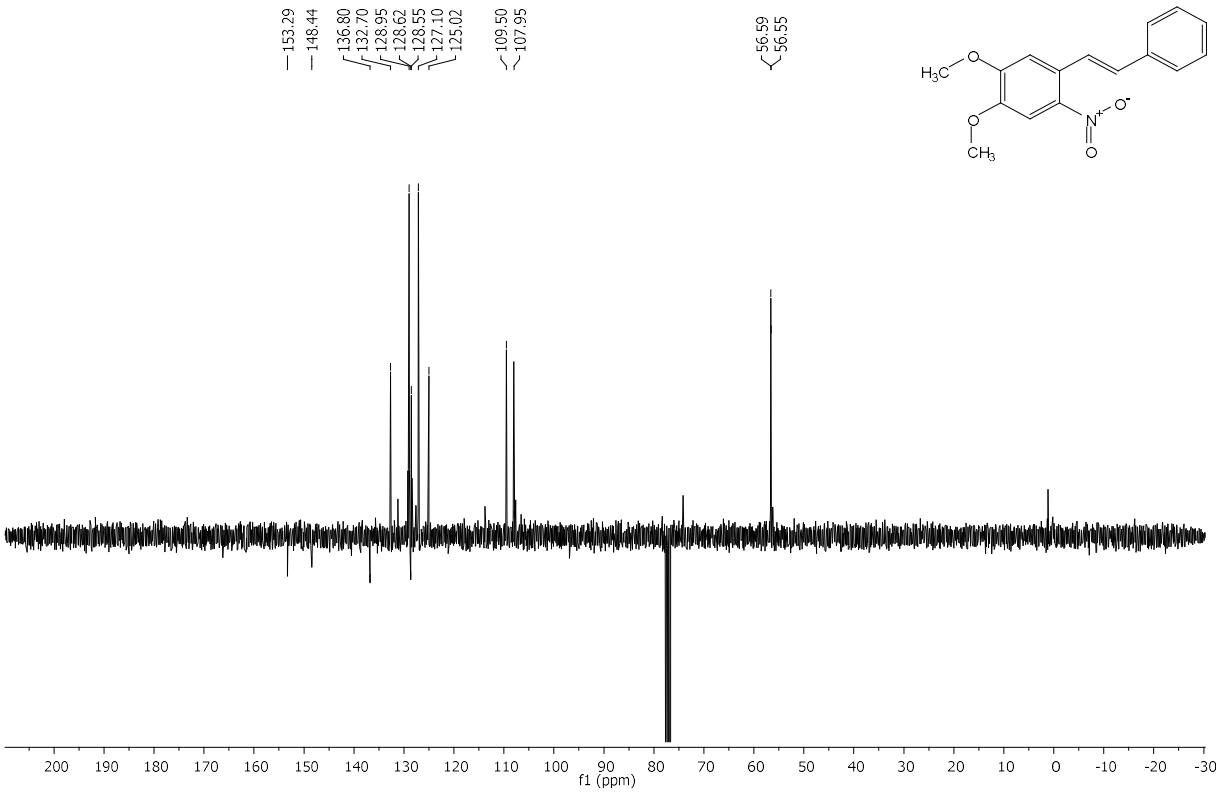


Fig. 73. ^{13}C NMR of ***E*-3k** in $CDCl_3$.

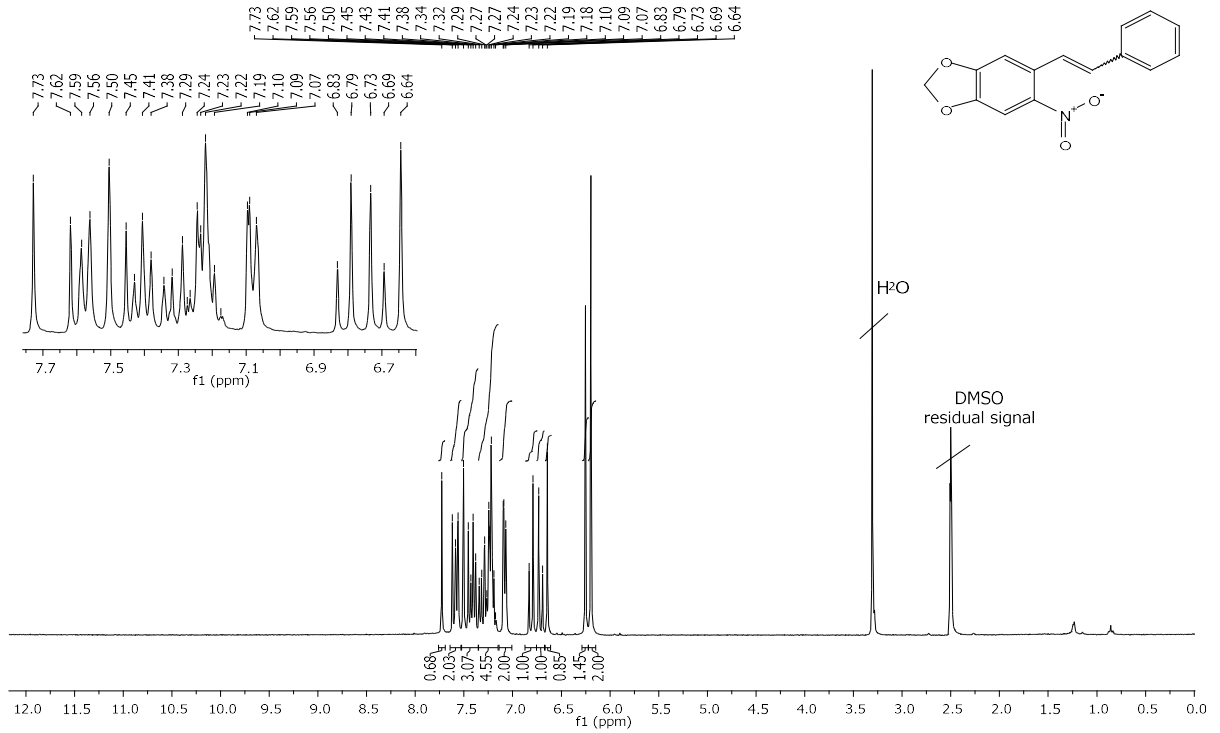


Fig. 74. ^{1}H NMR of **3l** in DMSO-*d*$_6$.

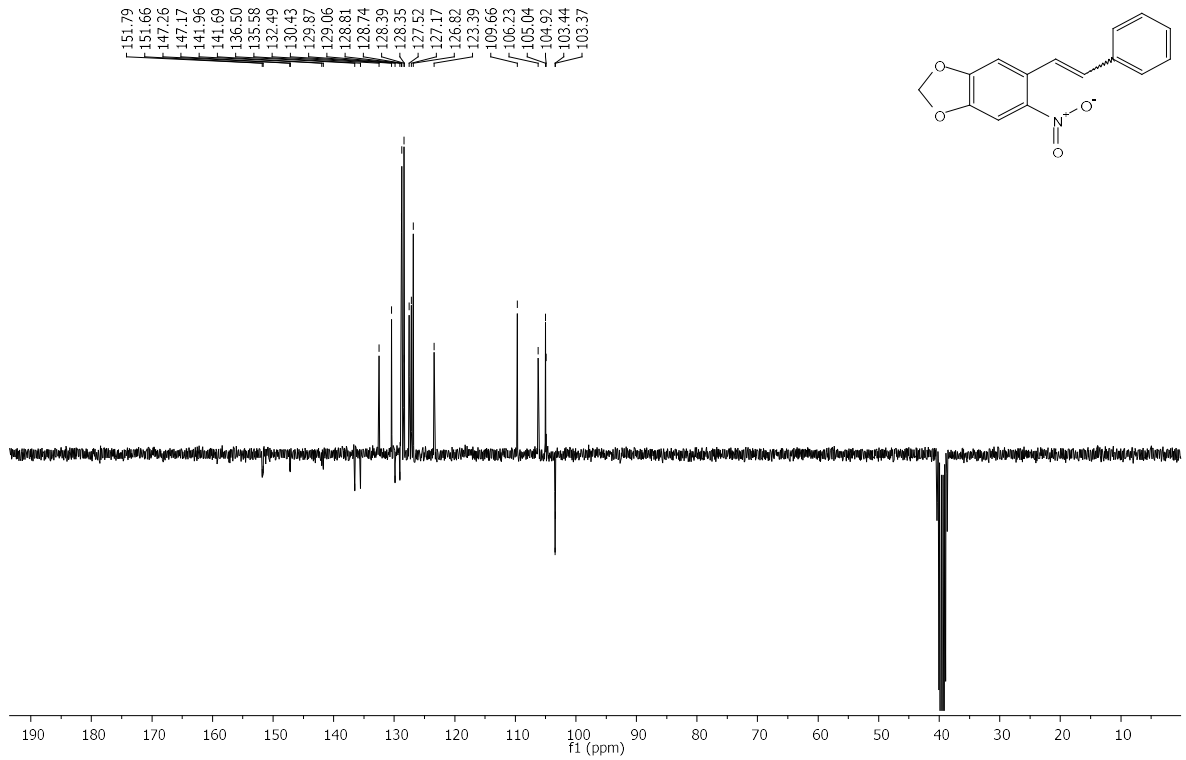


Fig. 75. ^{13}C NMR of **3l** in DMSO-d_6.

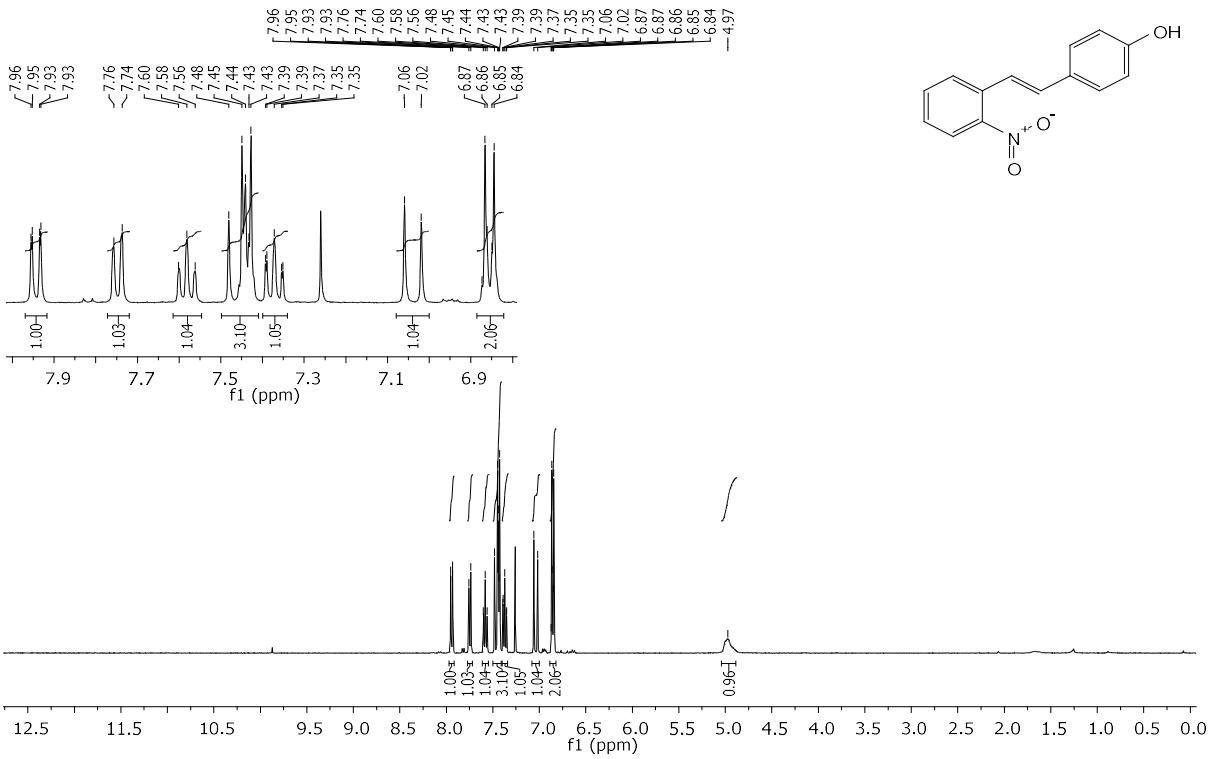


Fig. 76. ^{1}H NMR of **3m** in $CDCl_3$.

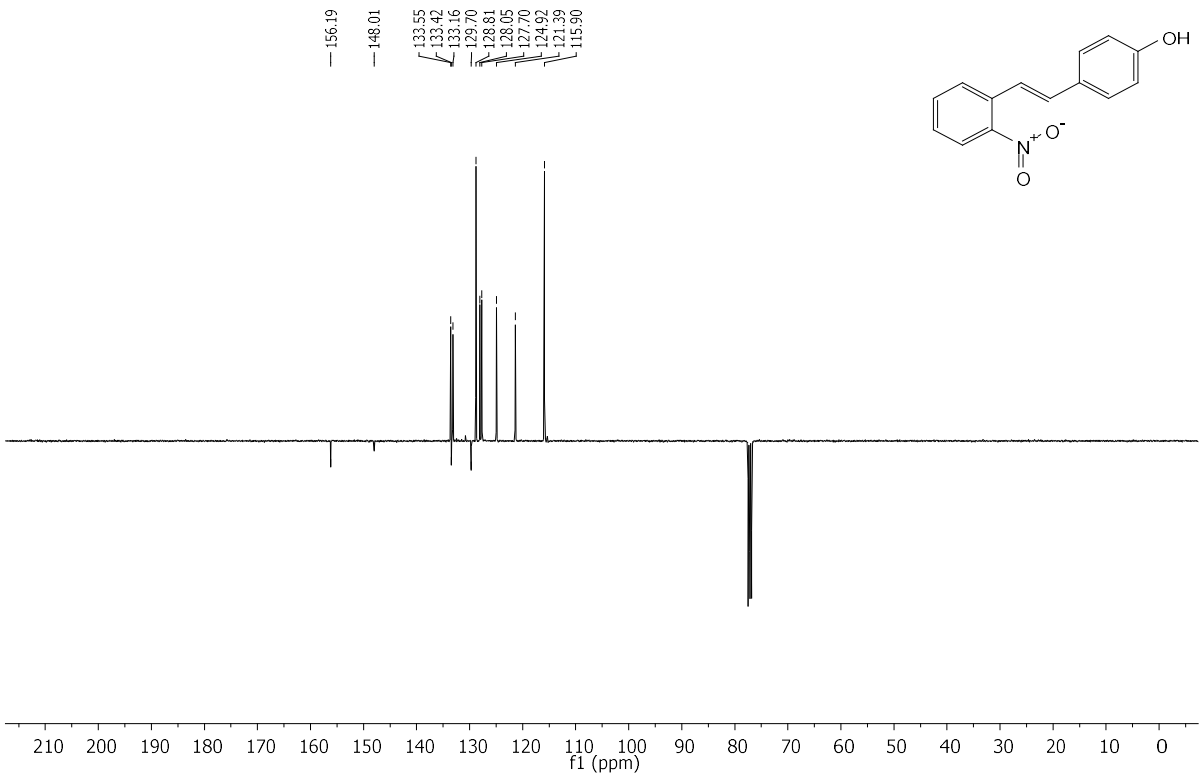


Fig. 77. ^{13}C NMR of **3m** in $CDCl_3$.

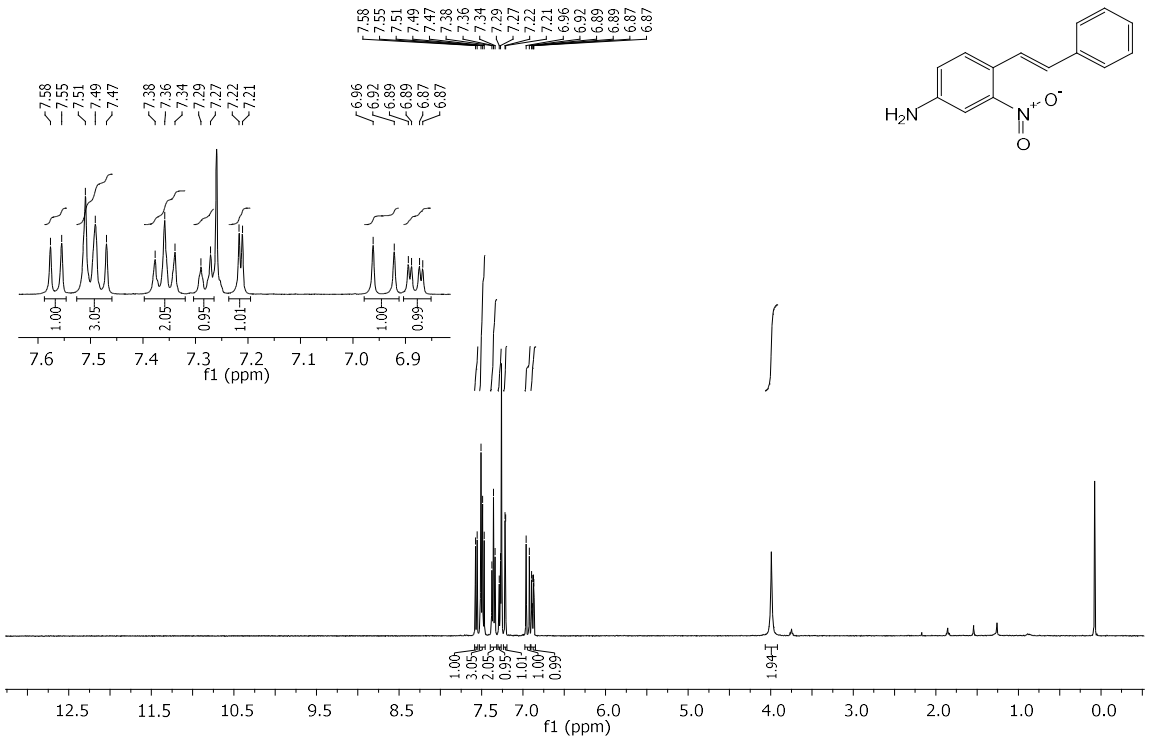


Fig. 78. ^{1}H NMR of **3n** in $CDCl_3$.

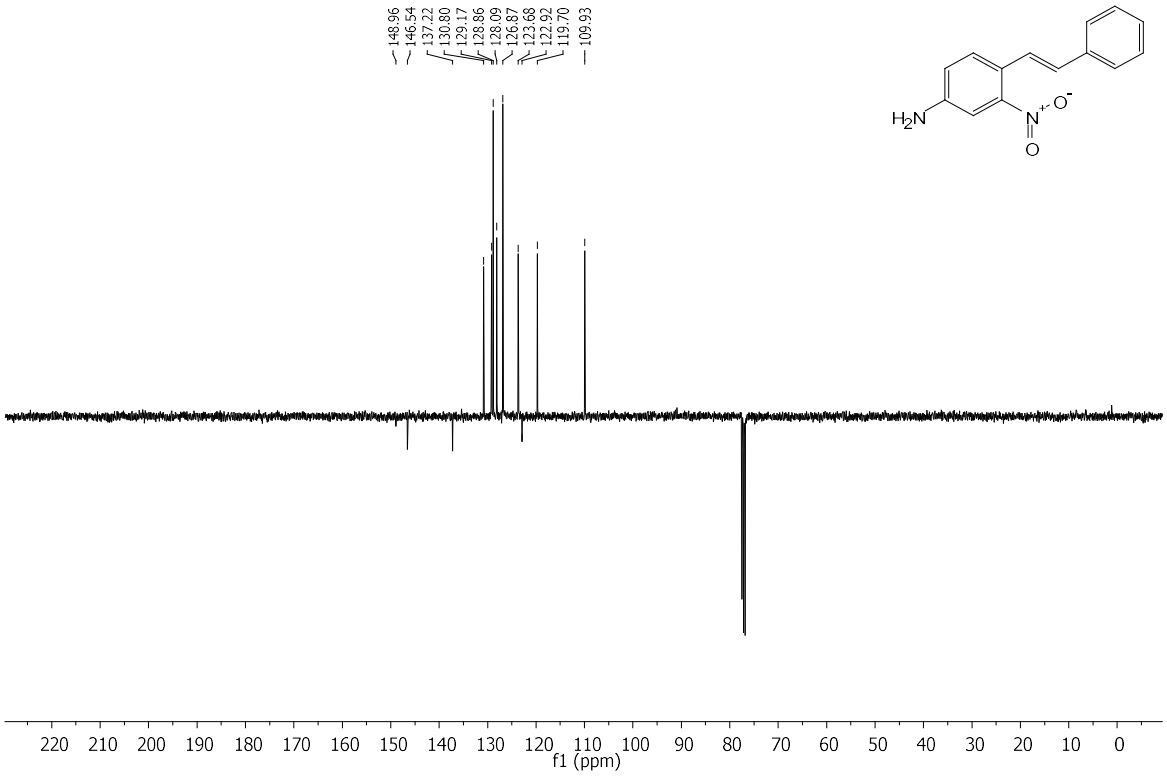


Fig. 79. ^{13}C NMR of **3n** in $CDCl_3$.

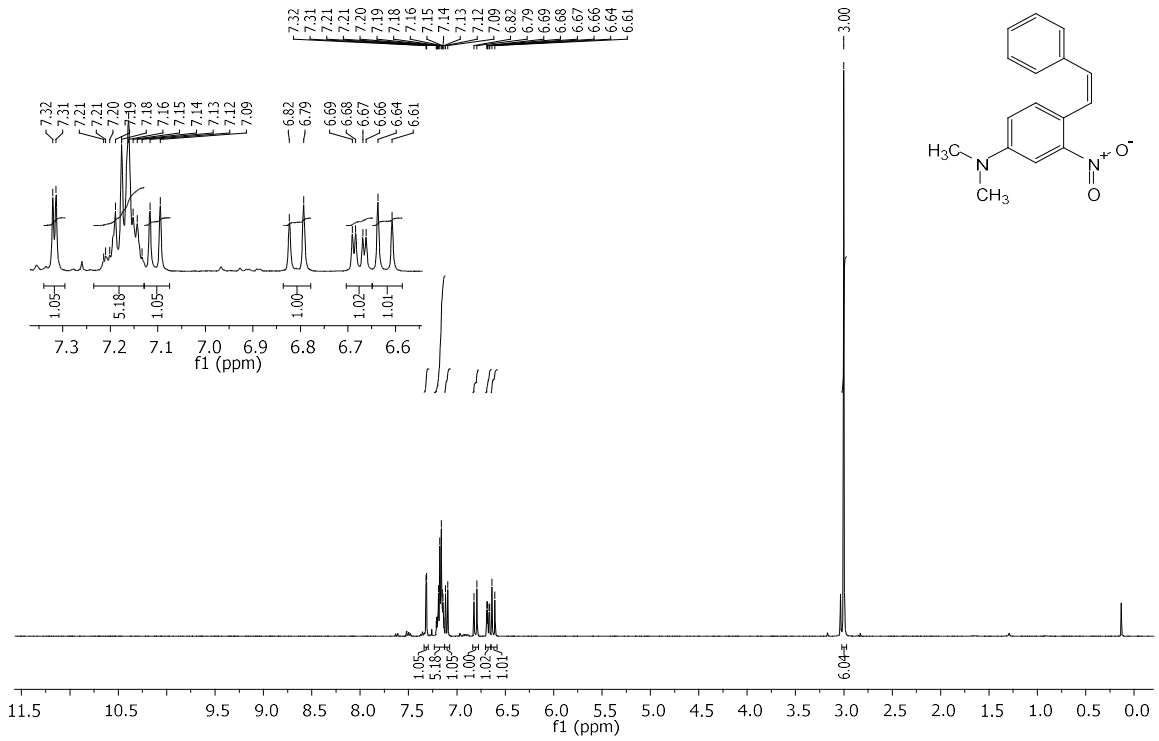


Fig. 80. ^{1}H NMR of ***Z*-3o** in $CDCl_3$.

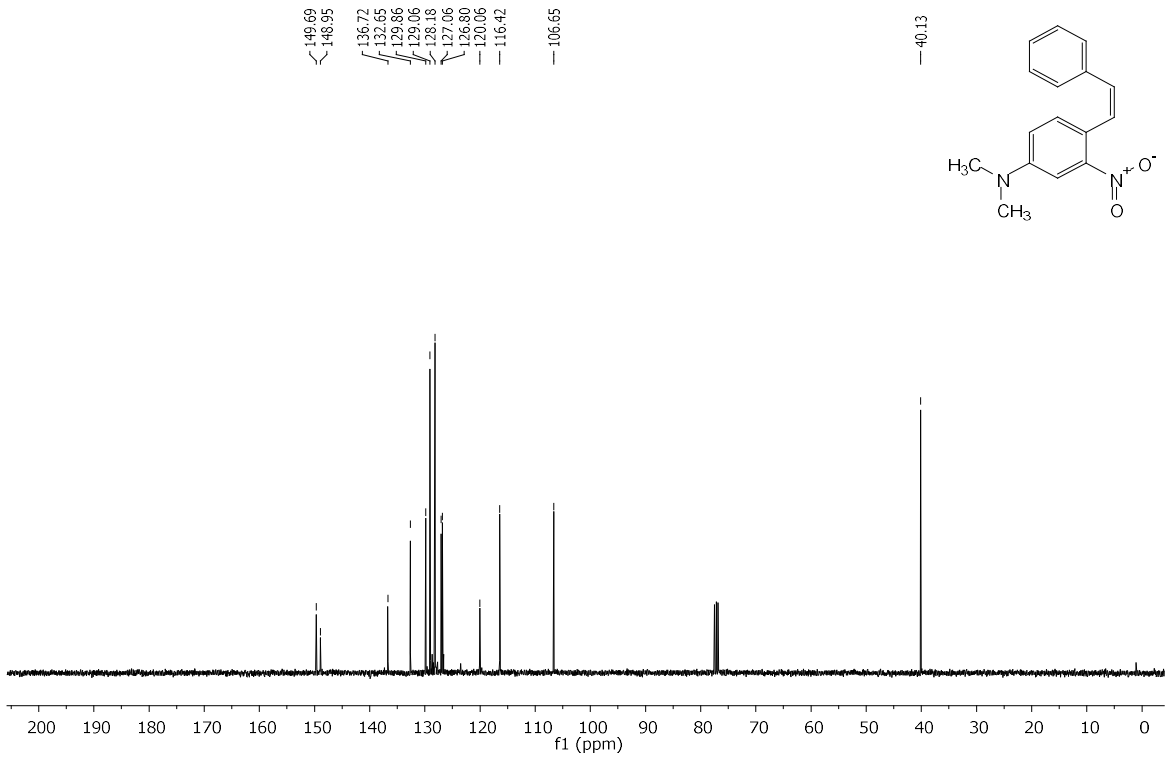


Fig. 81. ^{13}C NMR of ***Z*-3o** in $CDCl_3$.

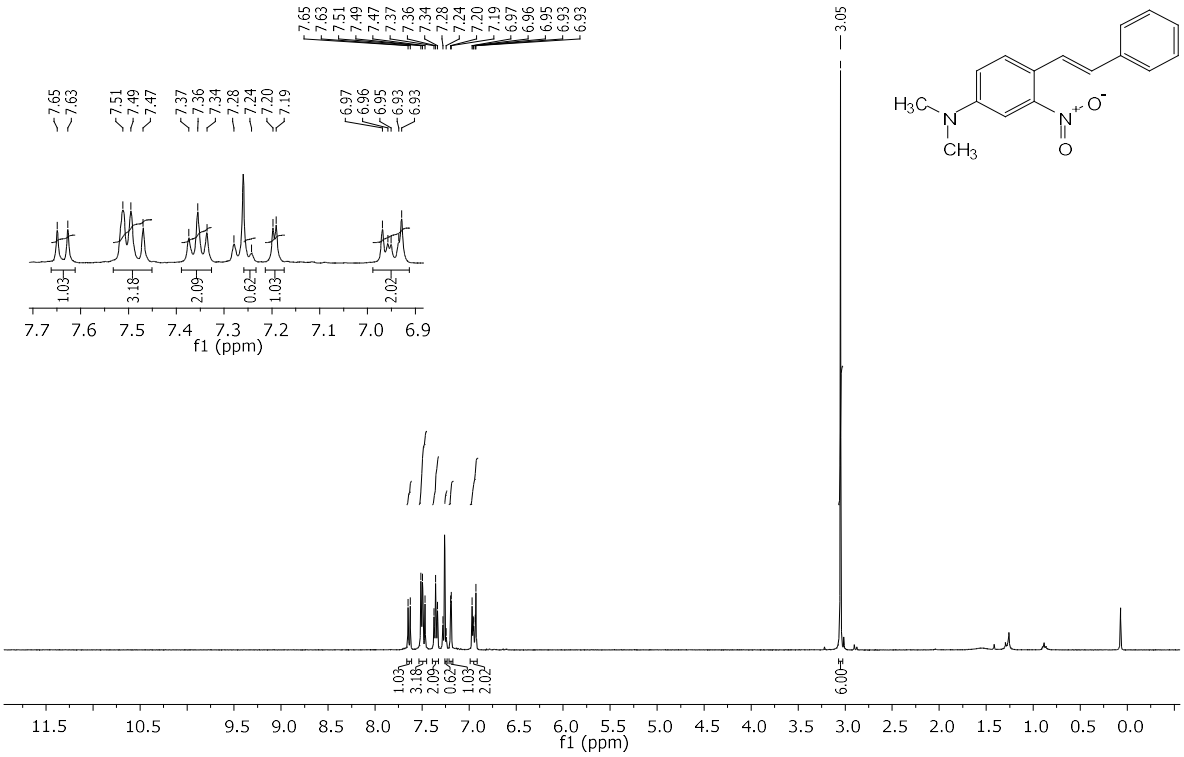


Fig. 82. ^{1}H NMR of ***E*-3o** in $CDCl_3$.

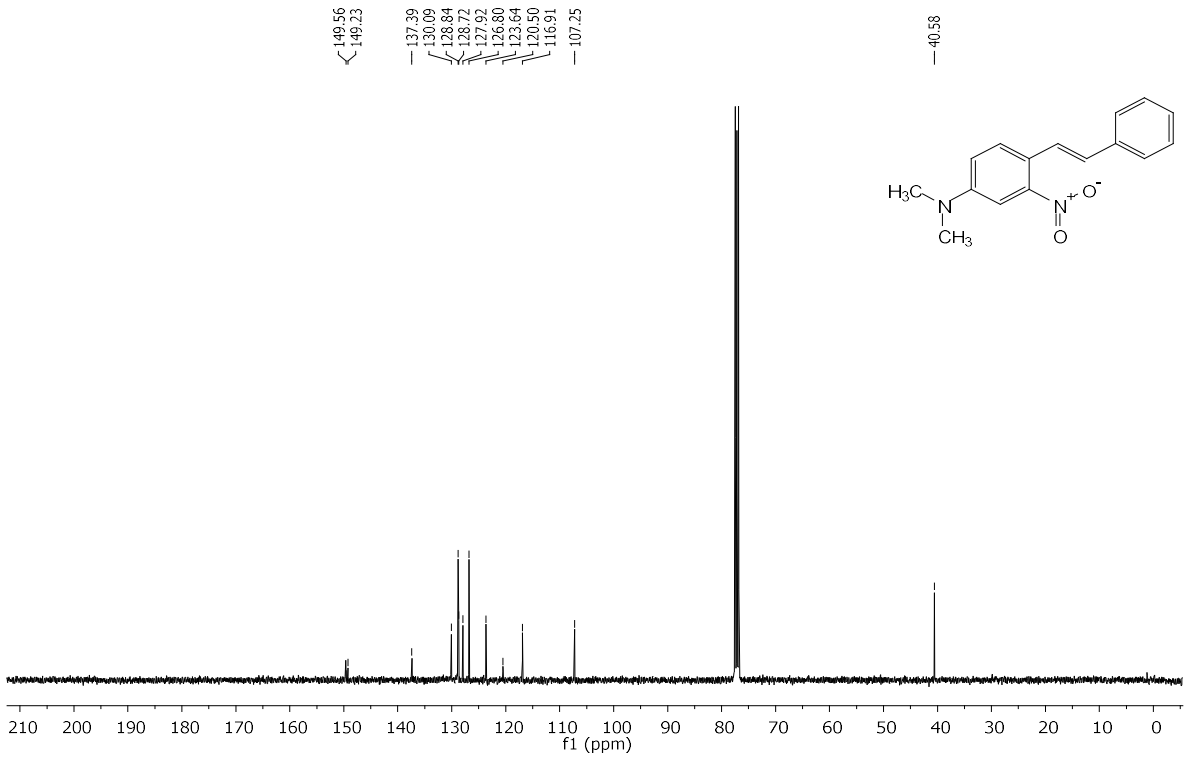


Fig. 83. ^{13}C NMR of ***E*-3o** in $CDCl_3$.

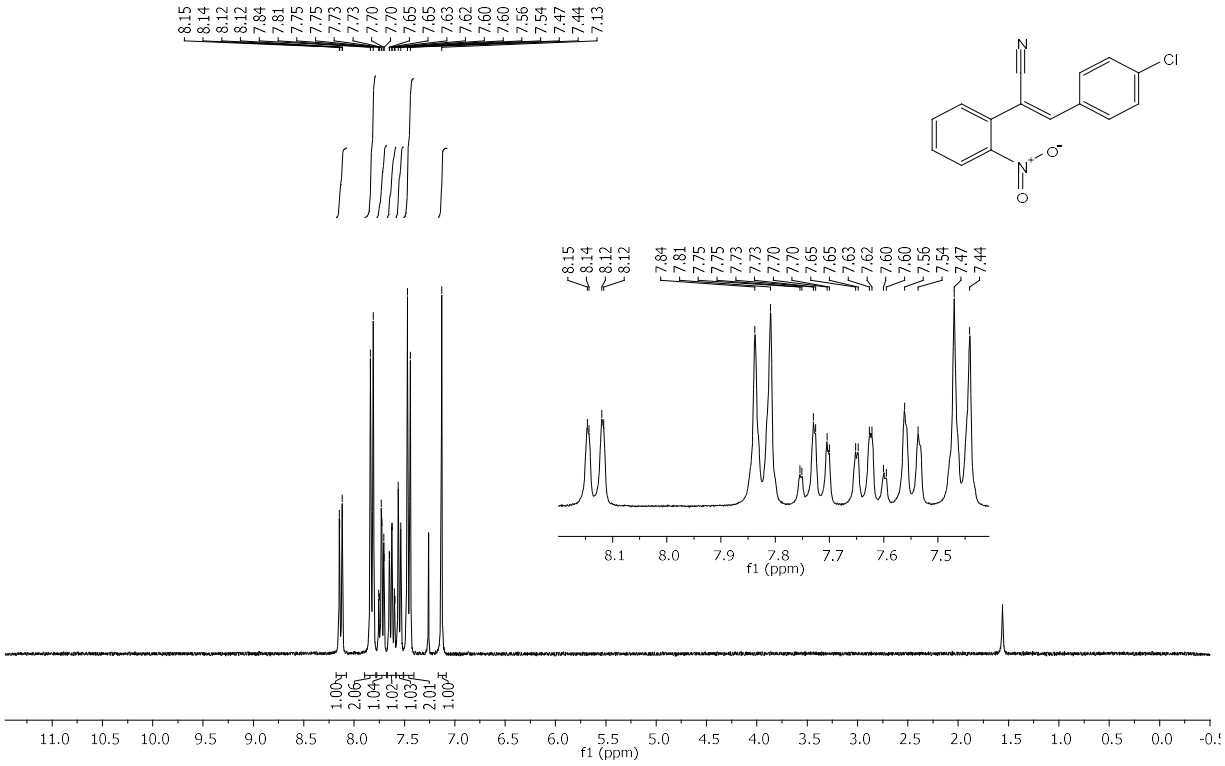


Fig. 84. ^{1}H NMR of **3p** in $CDCl_3$.

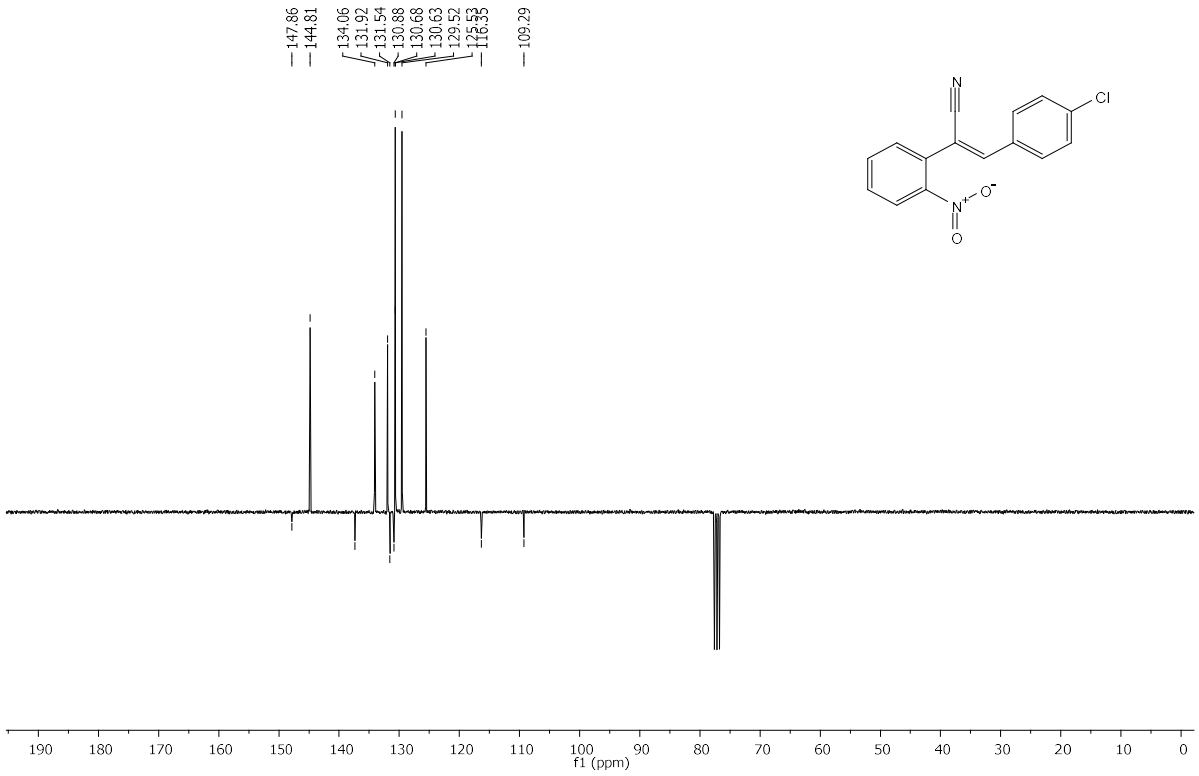


Fig. 85. ^{13}C NMR of **3p** in $CDCl_3$.

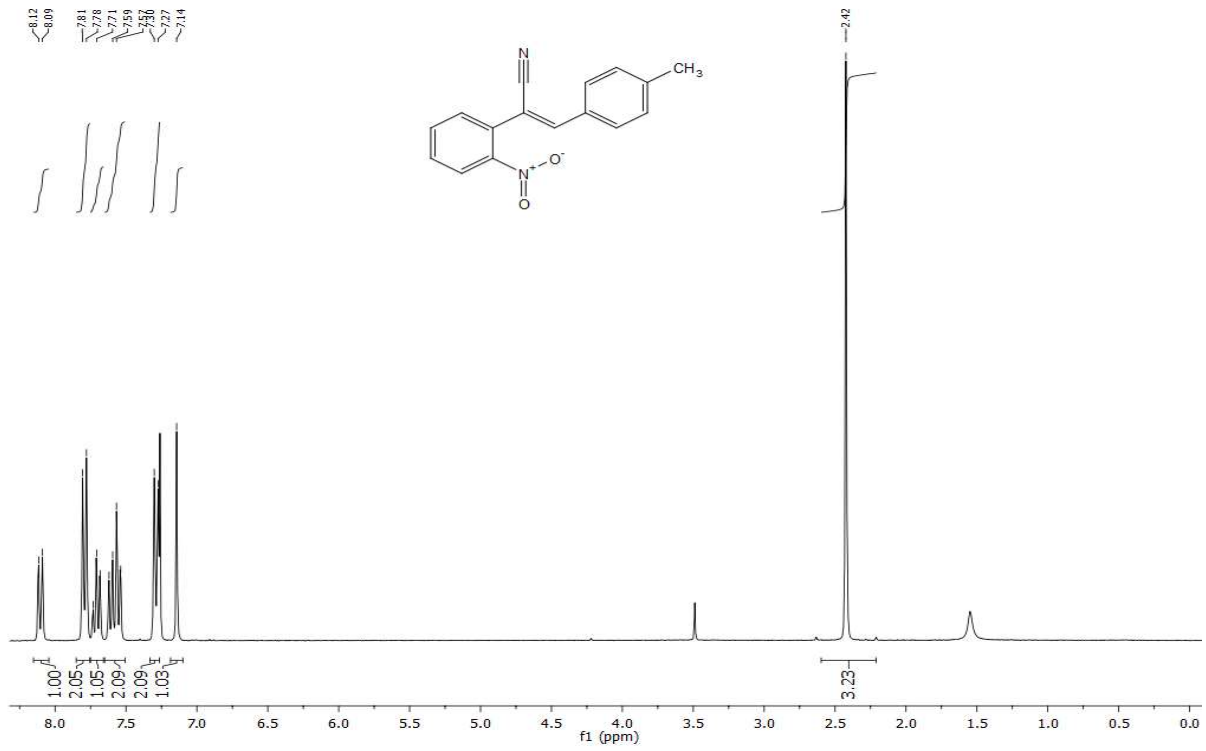


Fig. 86. ^{1}H NMR of **3q** in $CDCl_3$.

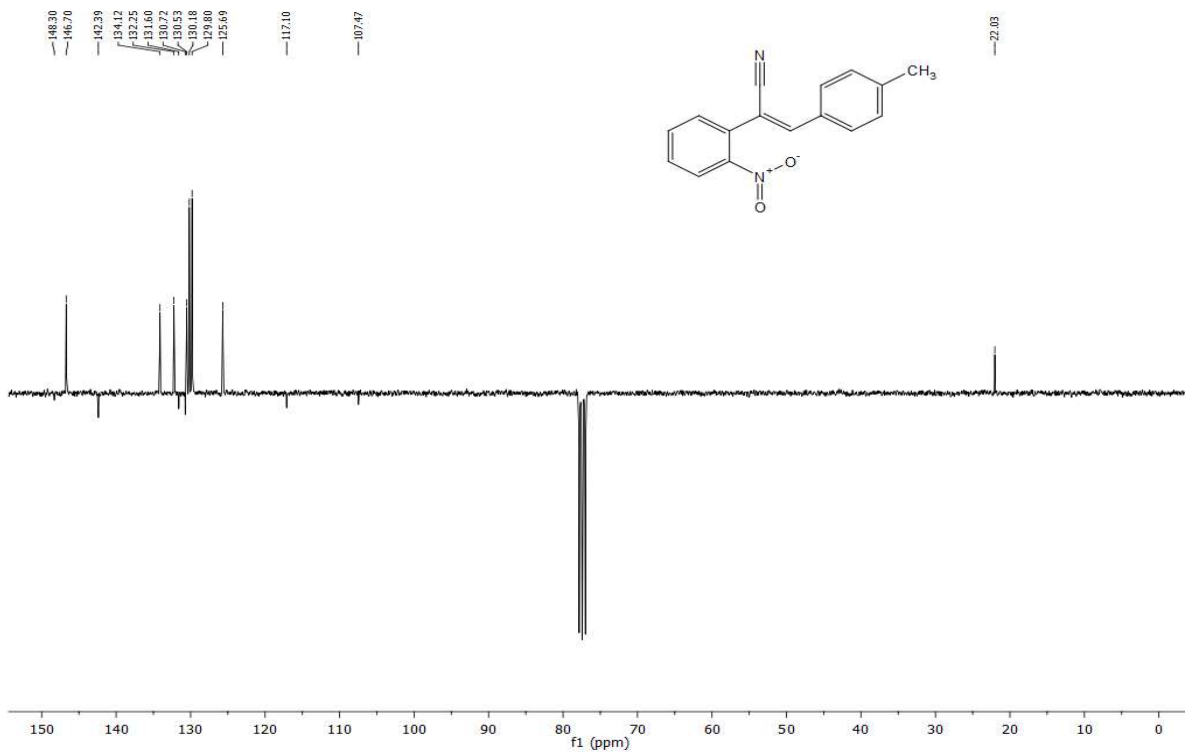


Fig. 87. ^{13}C NMR of **3q** in $CDCl_3$.

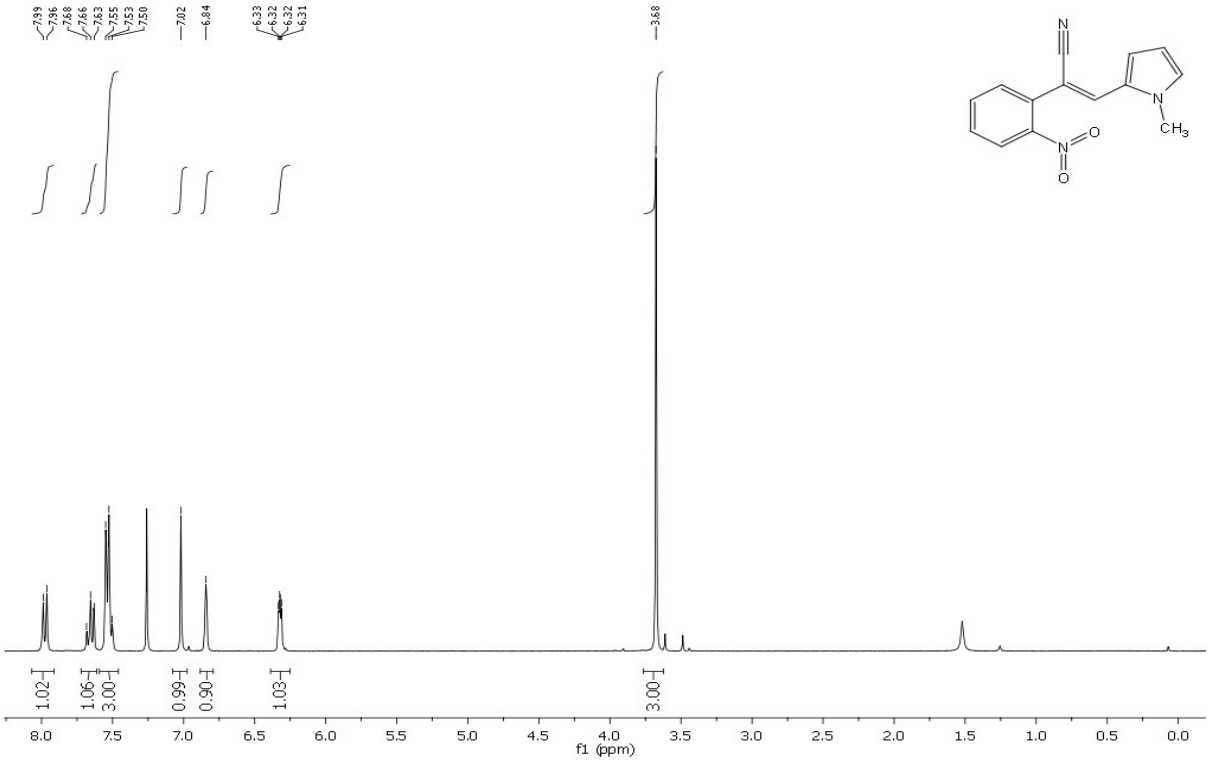


Fig. 88. ^{1}H NMR of **3r** in $CDCl_3$.

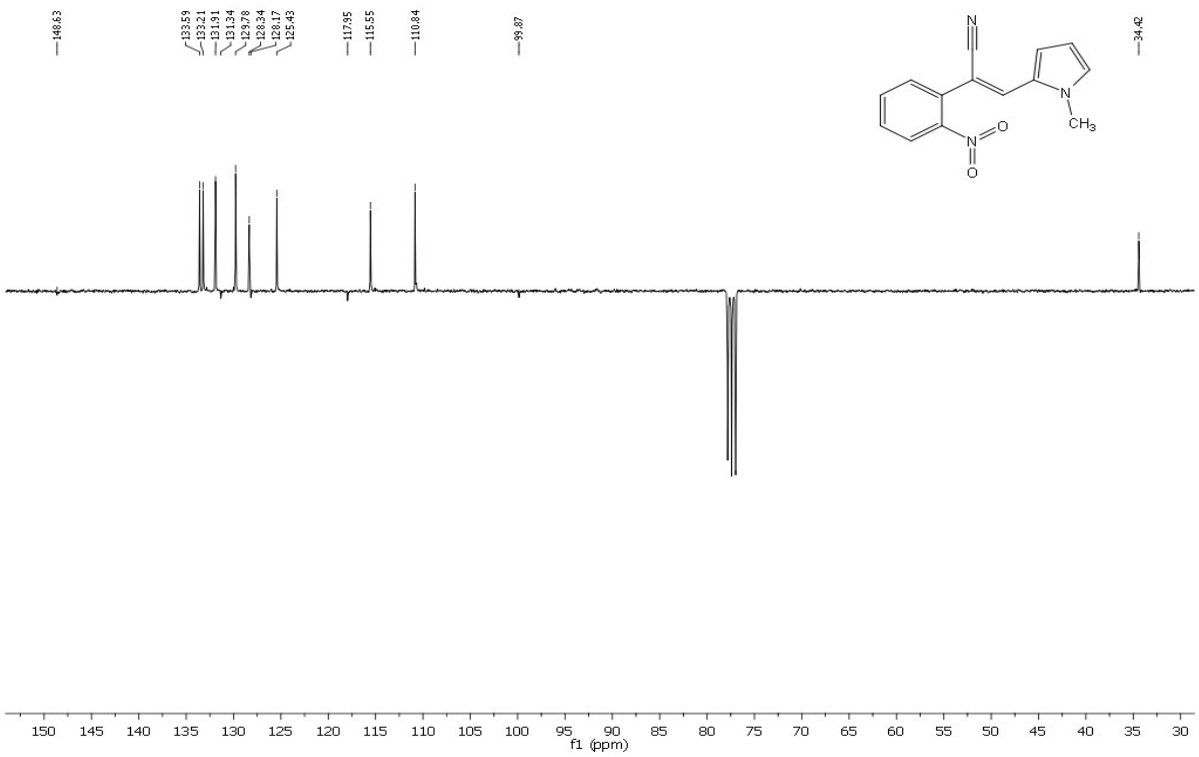


Fig. 89. ^{13}C NMR of **3r** in $CDCl_3$.

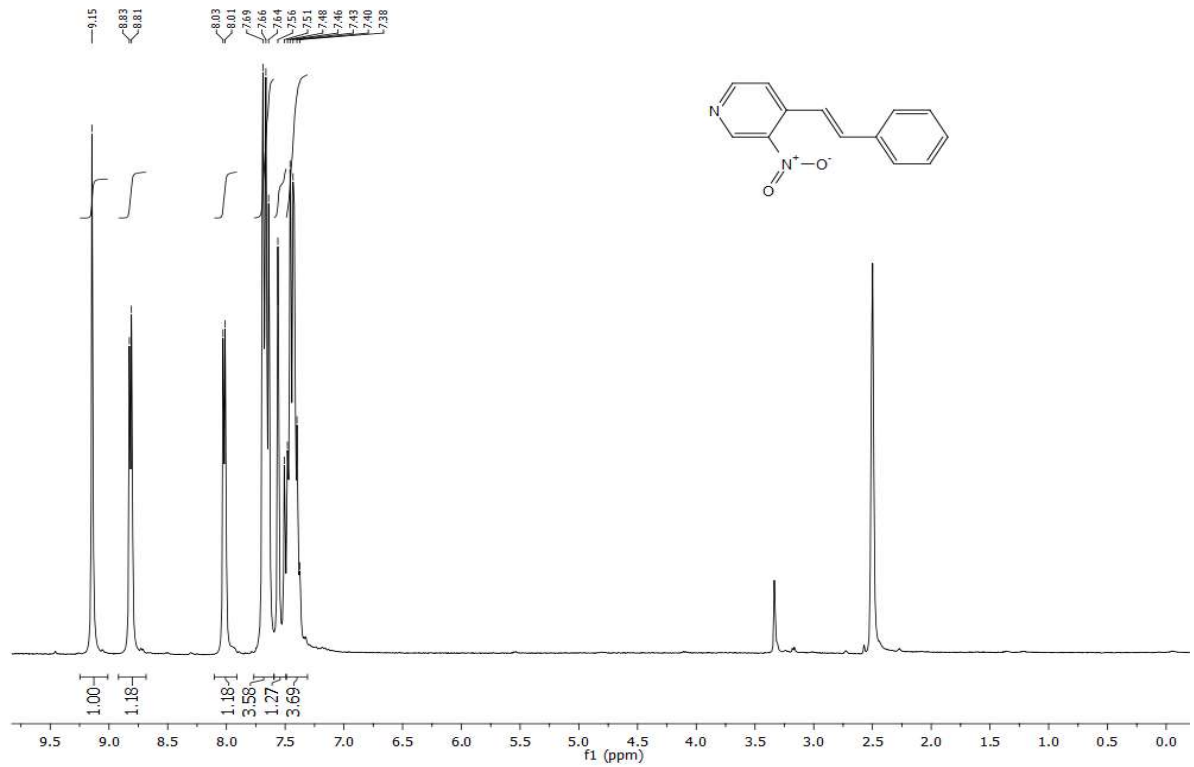


Fig. 90. ^{1}H NMR of **3s** in DMSO-d_6.

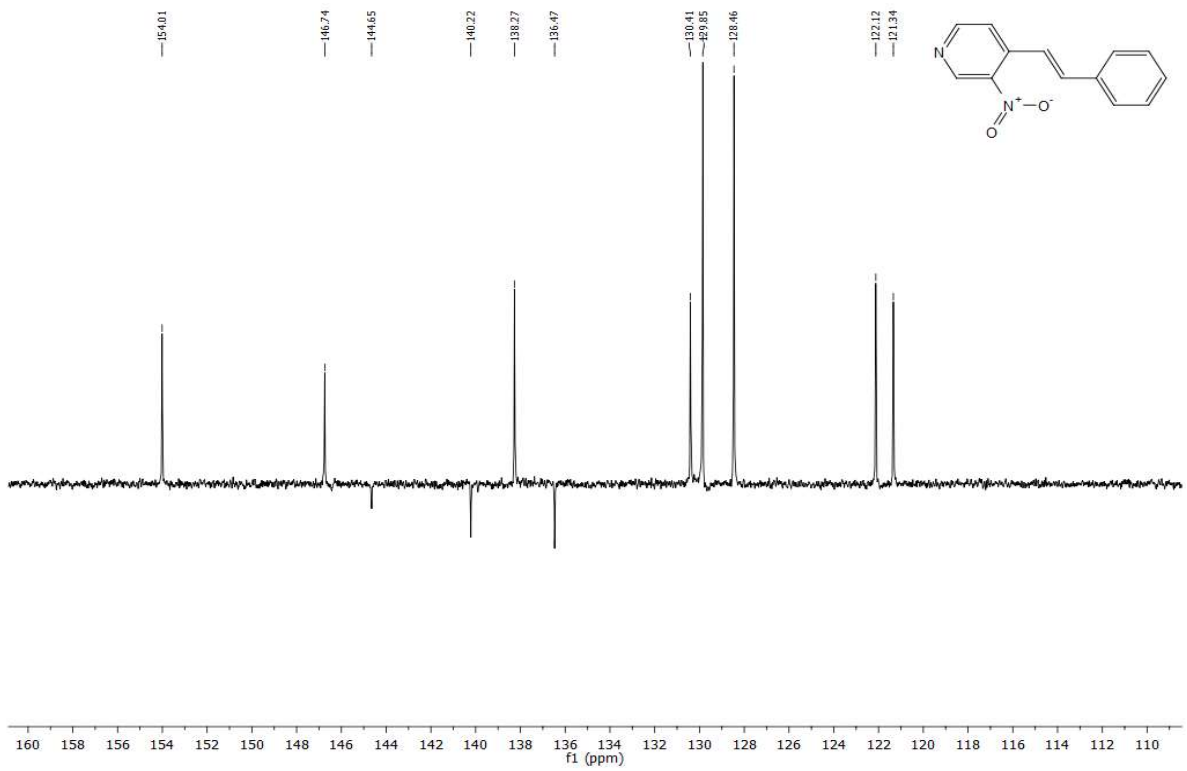


Fig. 91. ^{13}C NMR of **3s** in DMSO-d_6.

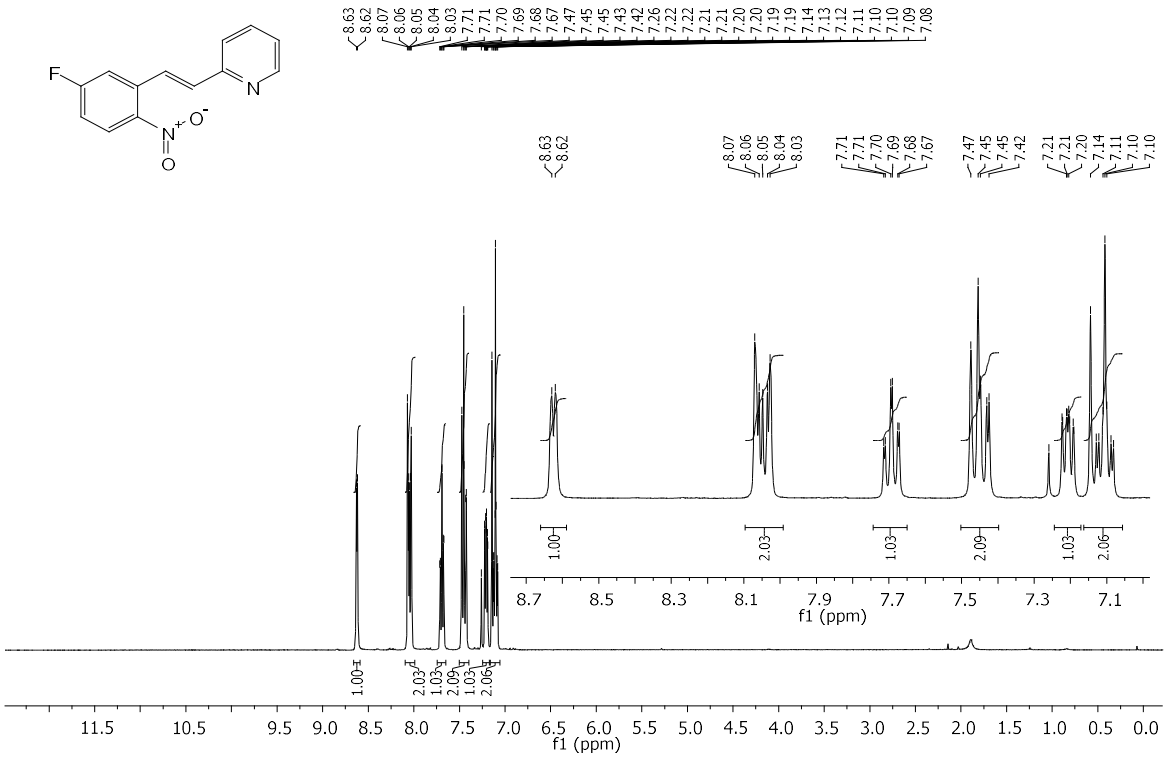


Fig. 92. ^{1}H NMR of **3t** in $CDCl_3$.

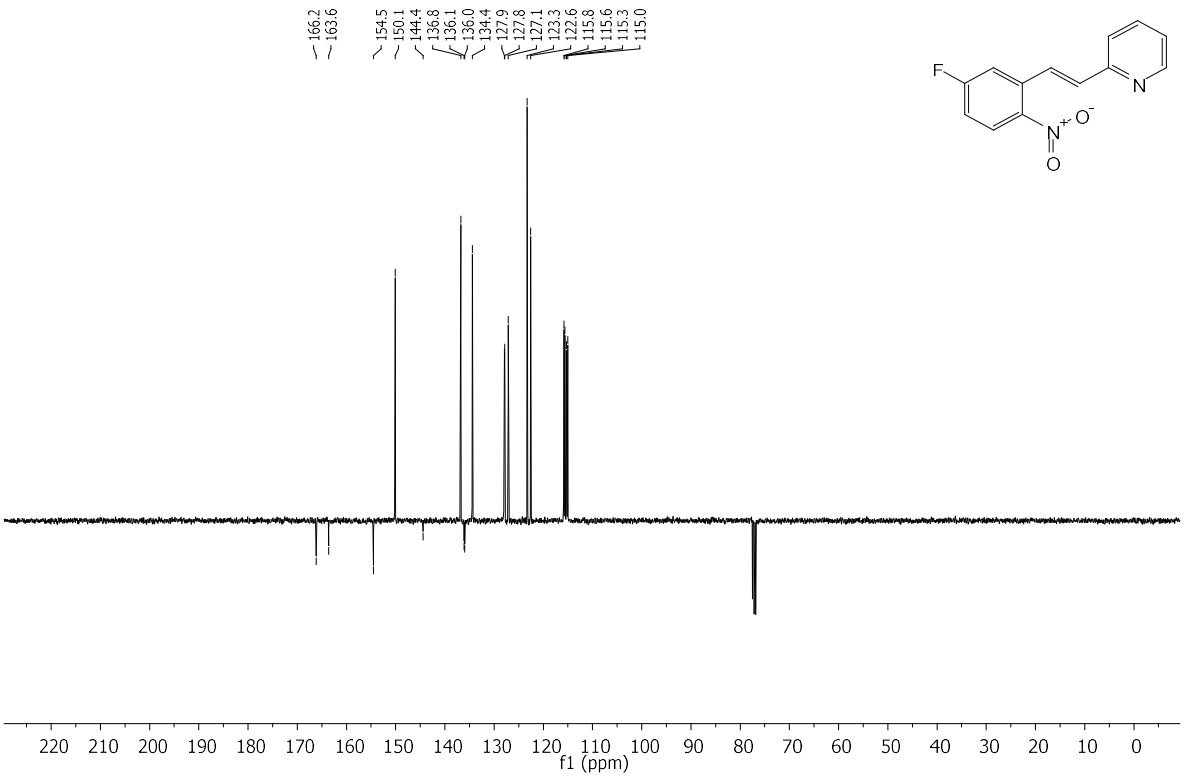


Fig. 93. ^{13}C NMR of **3t** in $CDCl_3$.

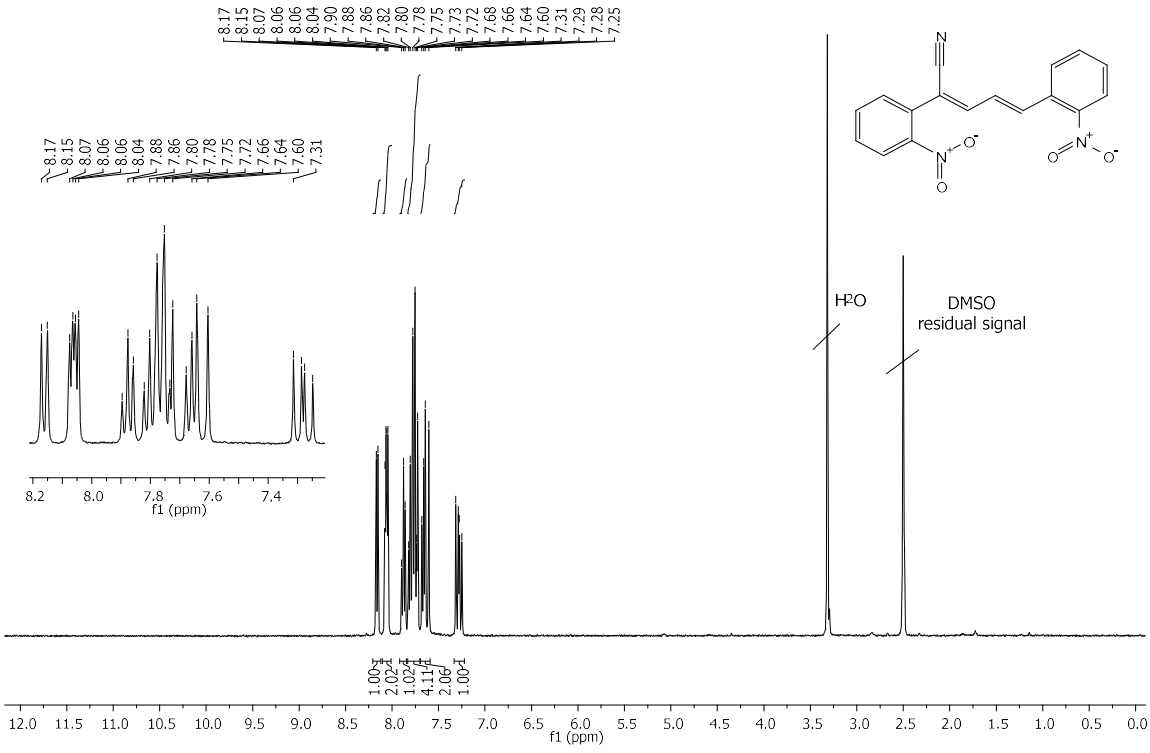


Fig. 94. ^{1}H NMR of **3u** in DMSO-d_6.

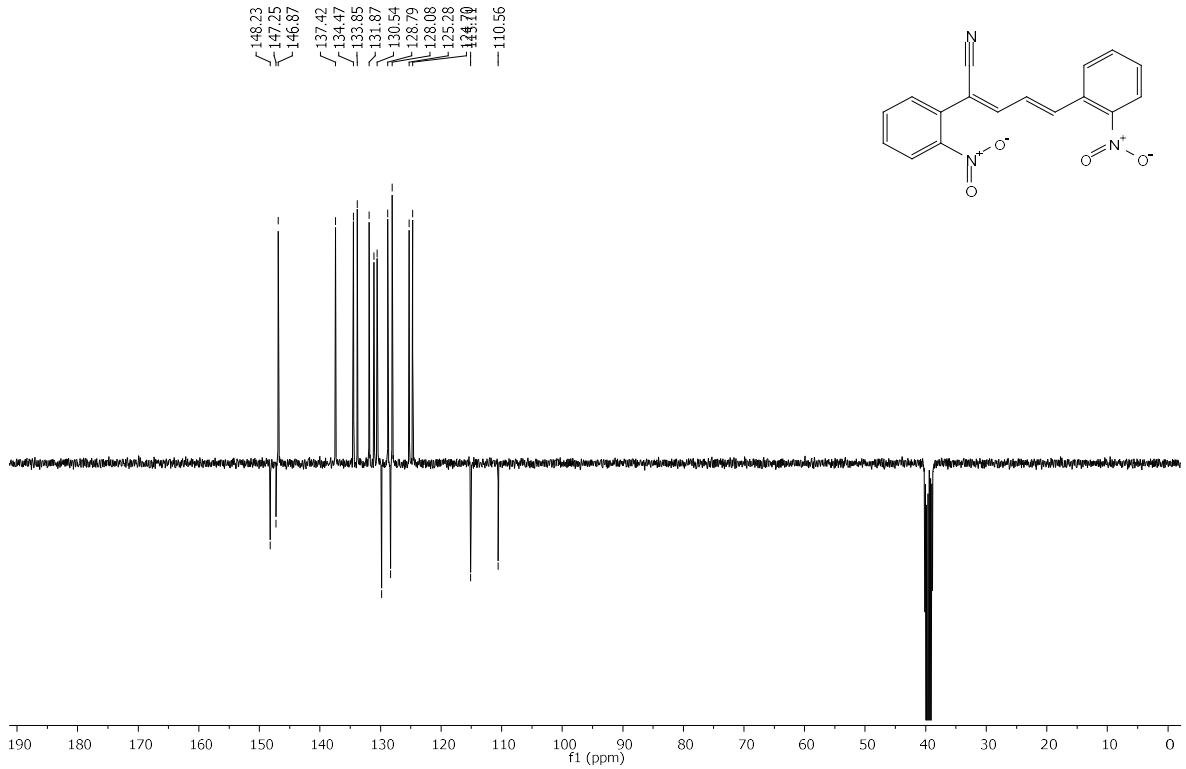


Fig. 95. ^{13}C NMR of **3u** in DMSO-d_6.

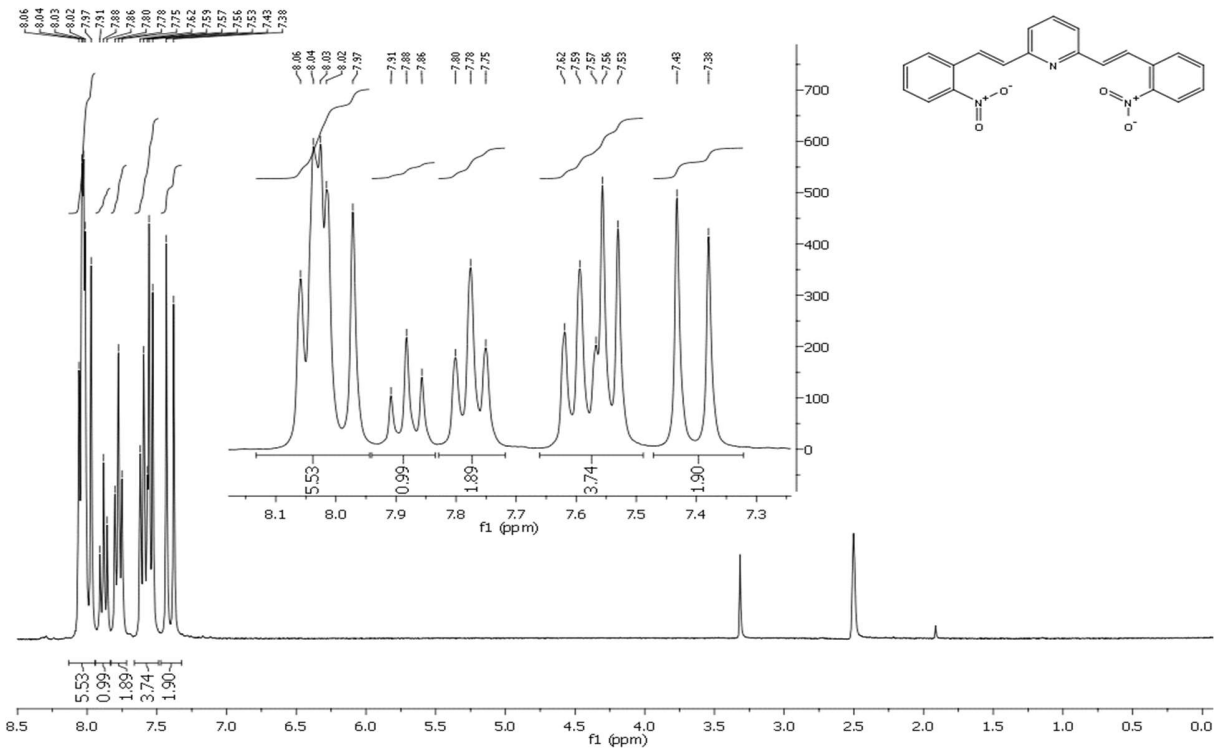


Fig. 96. ^{1}H NMR of **3v** in DMSO-d_6.

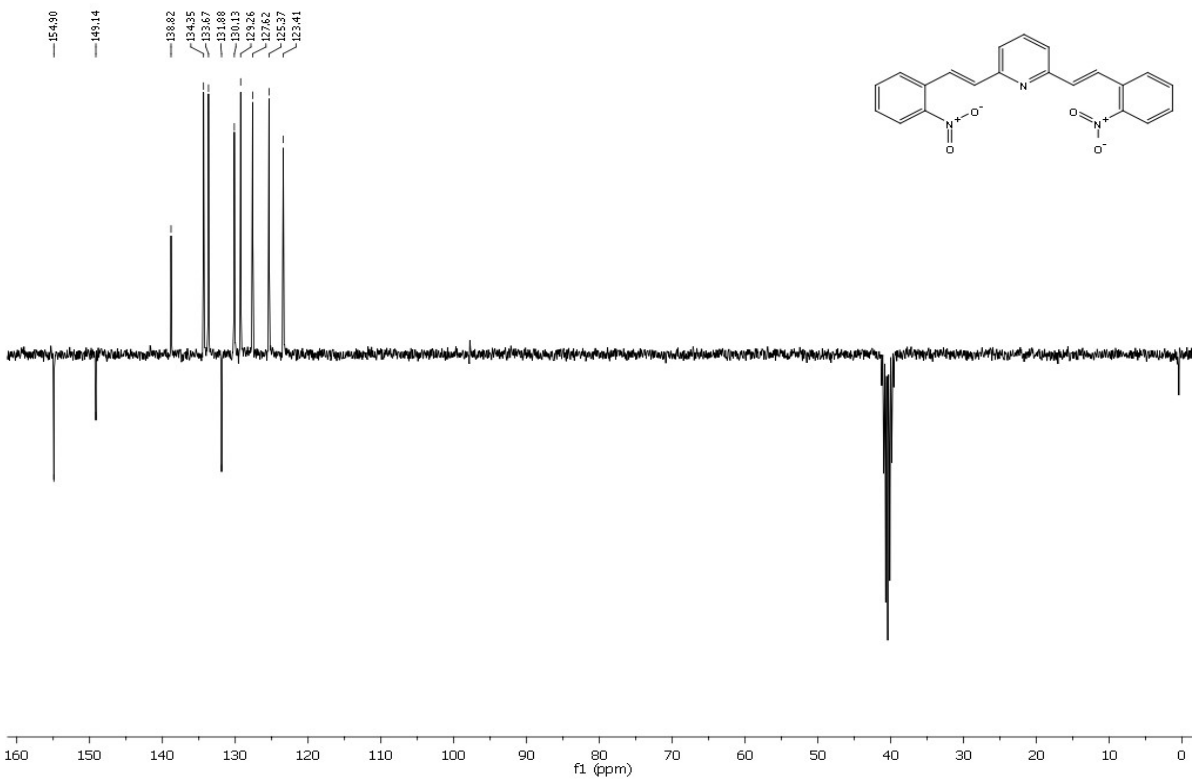


Fig. 97. ^{13}C NMR of **3v** in DMSO-d_6.

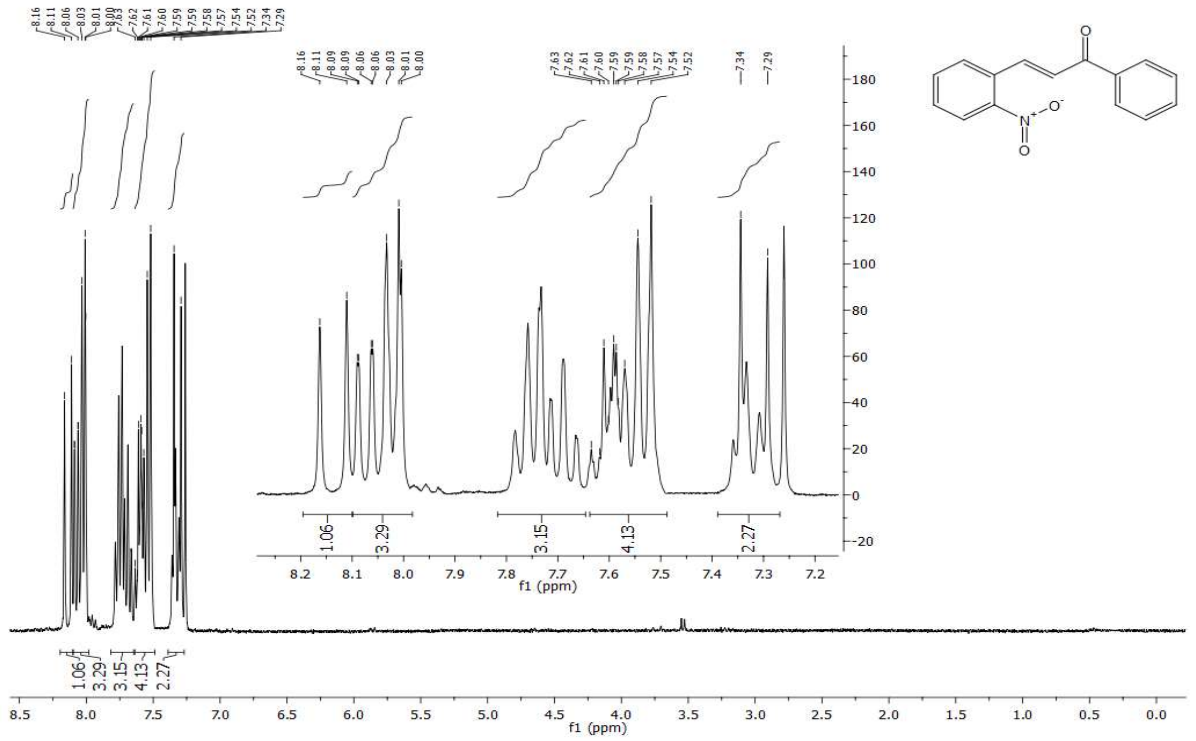


Fig. 98. ^{1}H NMR of **3w** in $CDCl_3$.

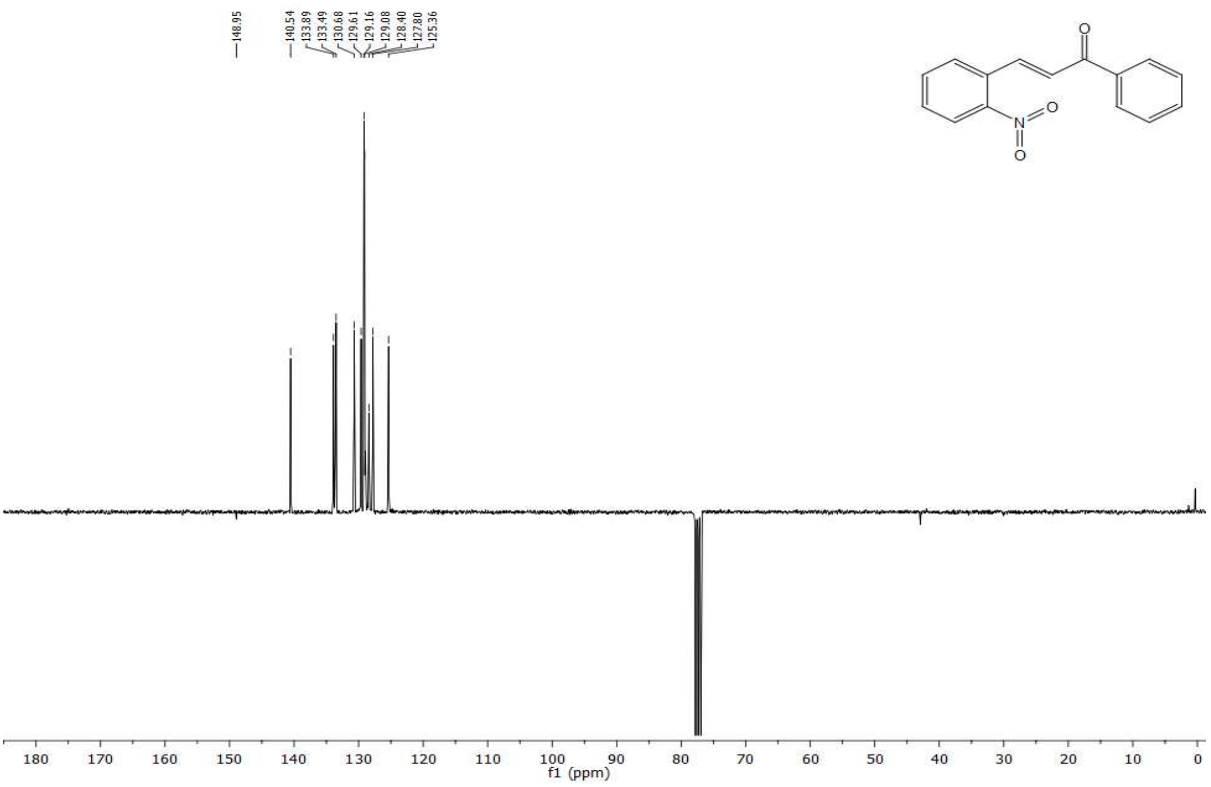


Fig. 99. ^{13}C NMR of **3w** in $CDCl_3$.

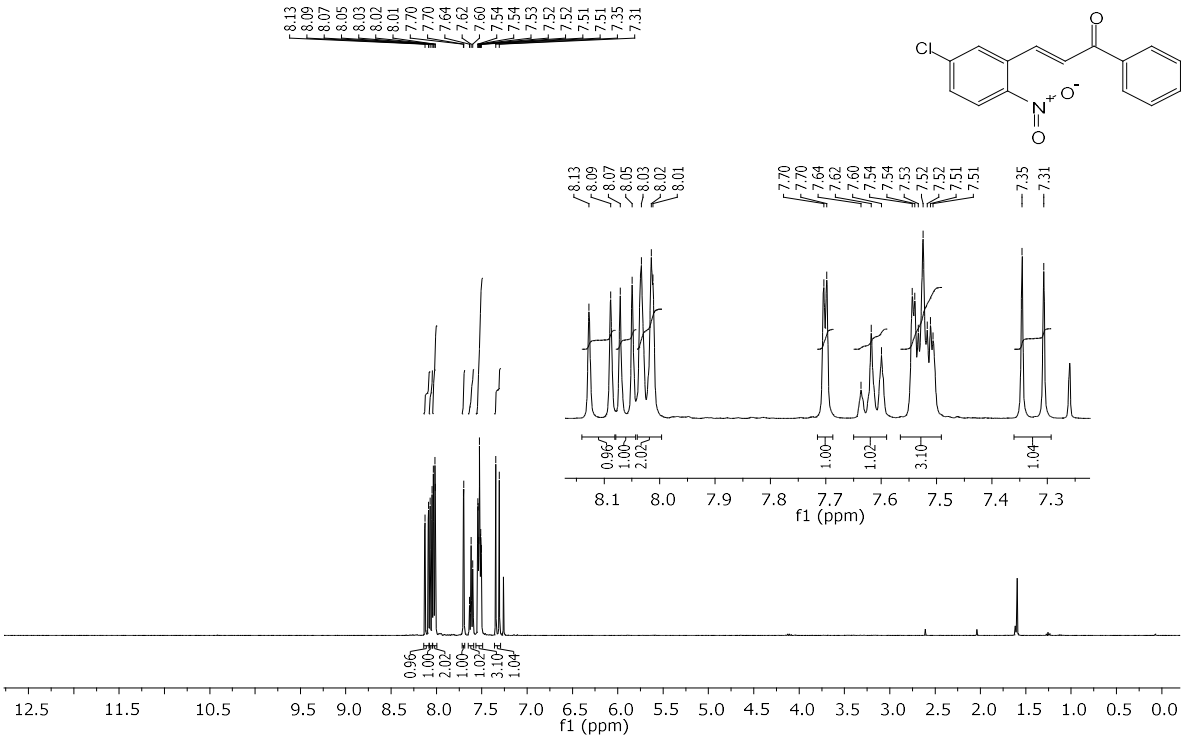


Fig. 100. ^{1}H NMR of **3x** in $CDCl_3$.

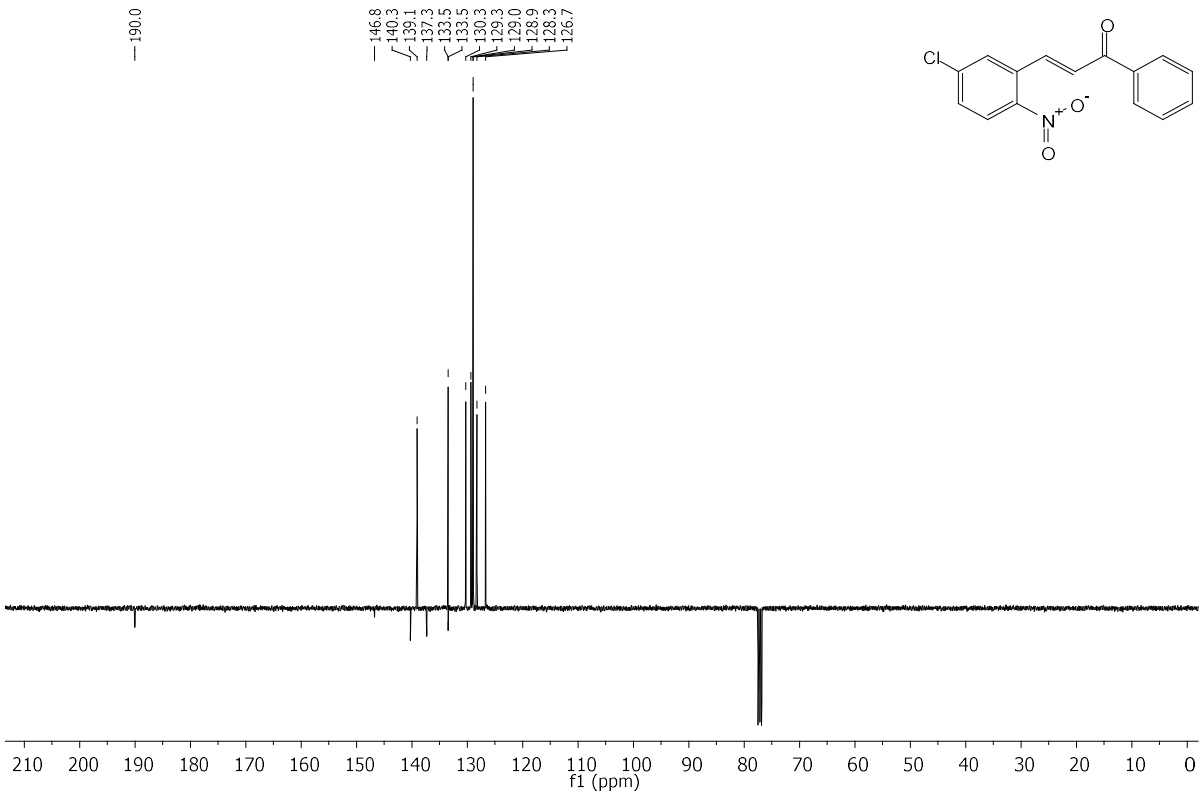


Fig. 101. ^{13}C NMR of **3x** in $CDCl_3$.

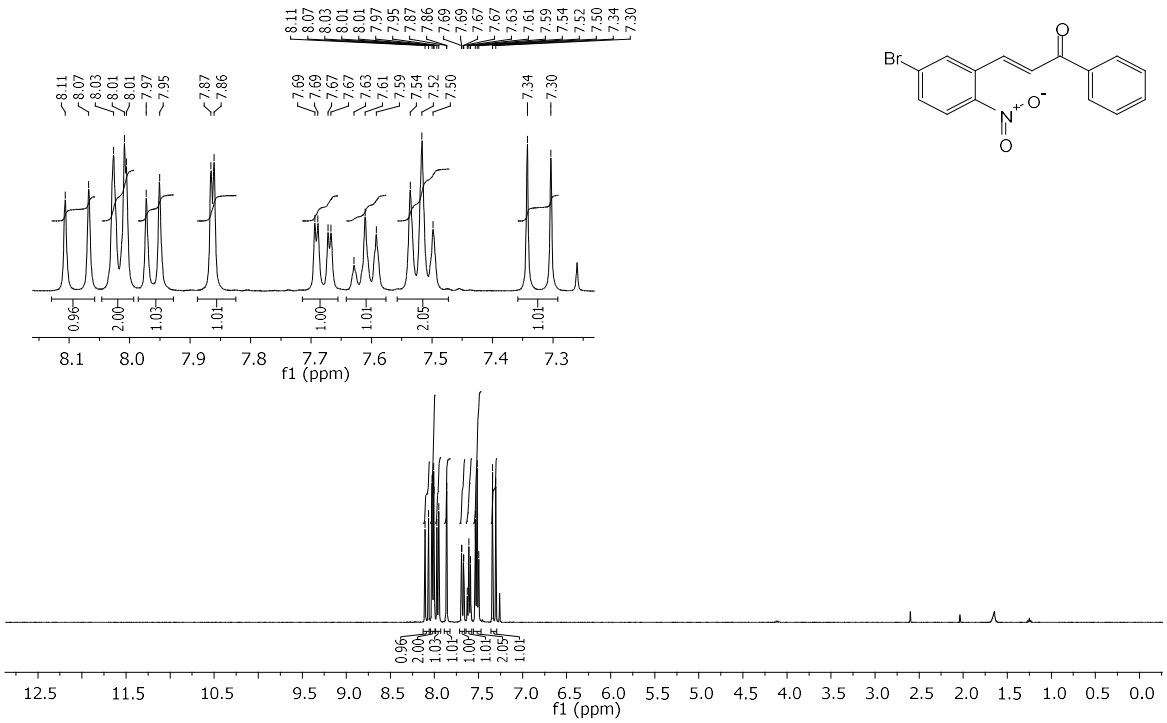


Fig. 102. ^{1}H NMR of **3y** in $CDCl_3$.

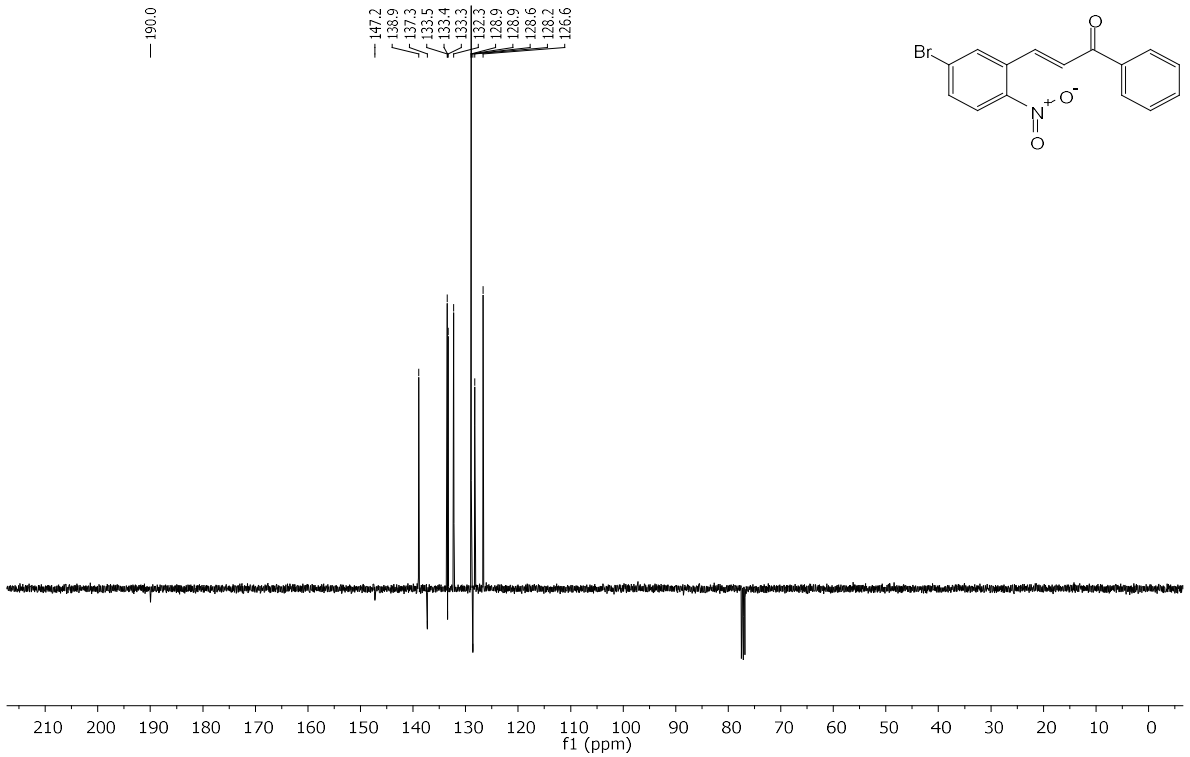


Fig. 103. ^{13}C NMR of **3y** in $CDCl_3$.

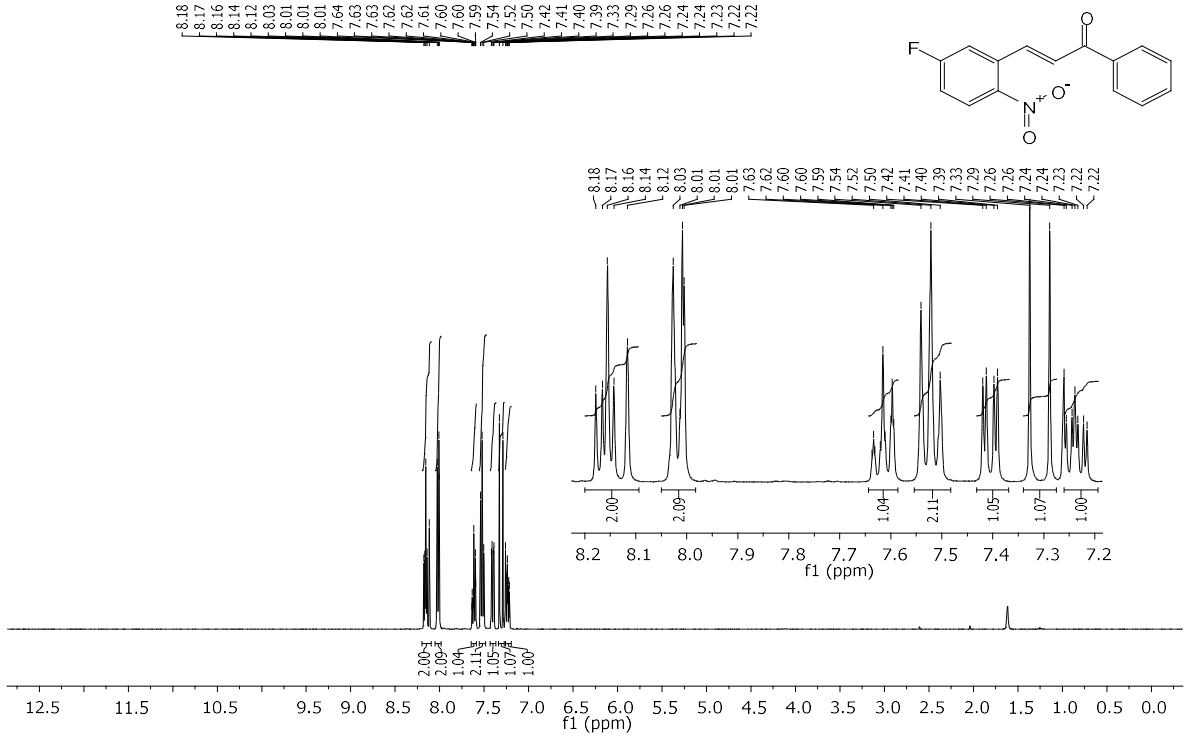


Fig. 104. ^{1}H NMR of **3z** in $CDCl_3$.

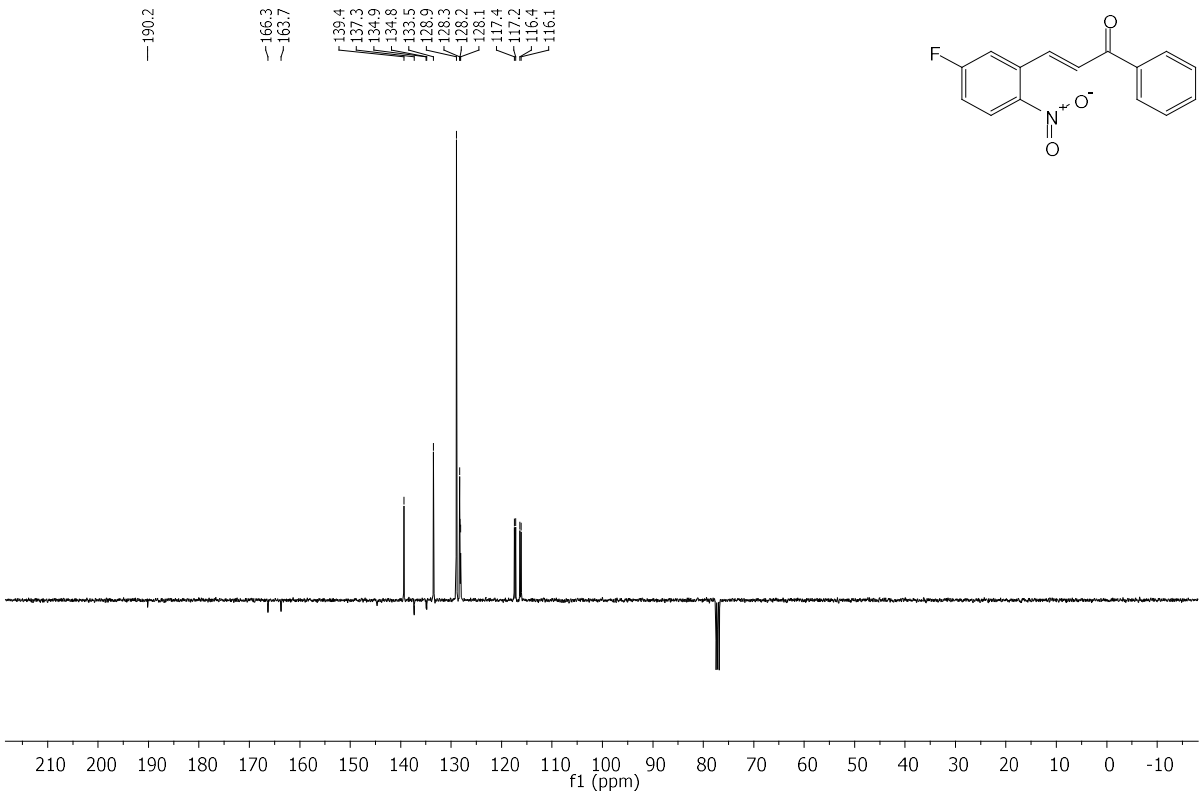


Fig. 105. ^{13}C NMR of **3z** in $CDCl_3$.

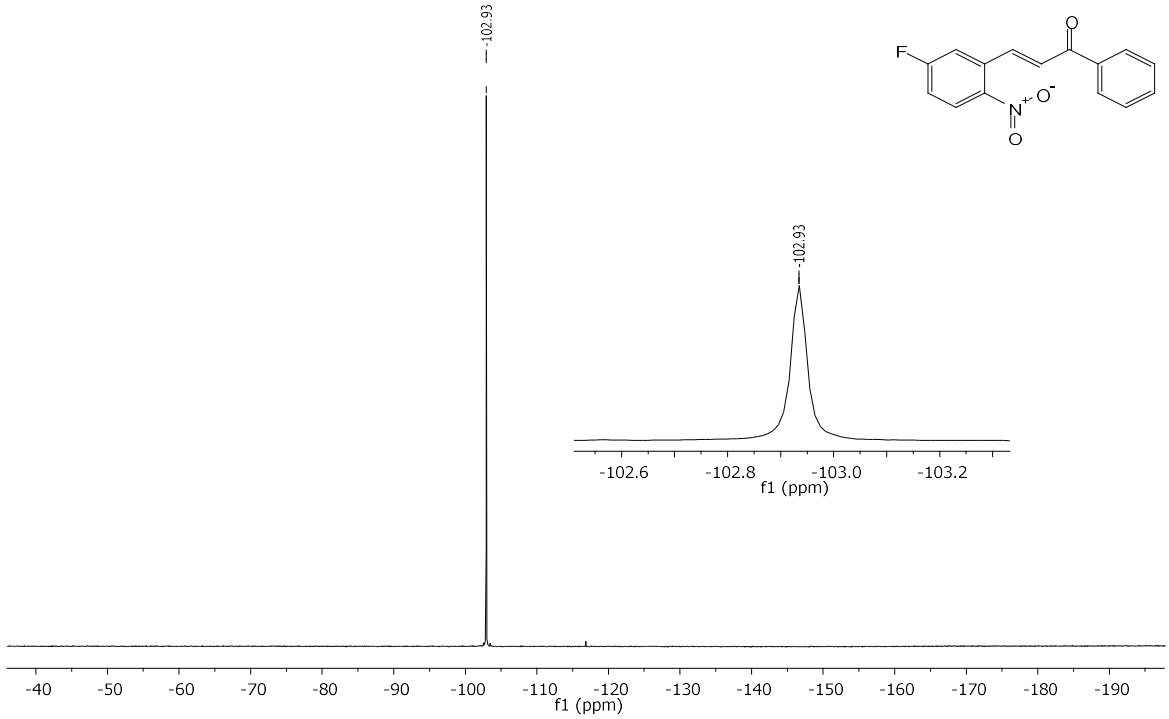


Fig. 106. ^{19}F NMR of **3z** in $CDCl_3$.

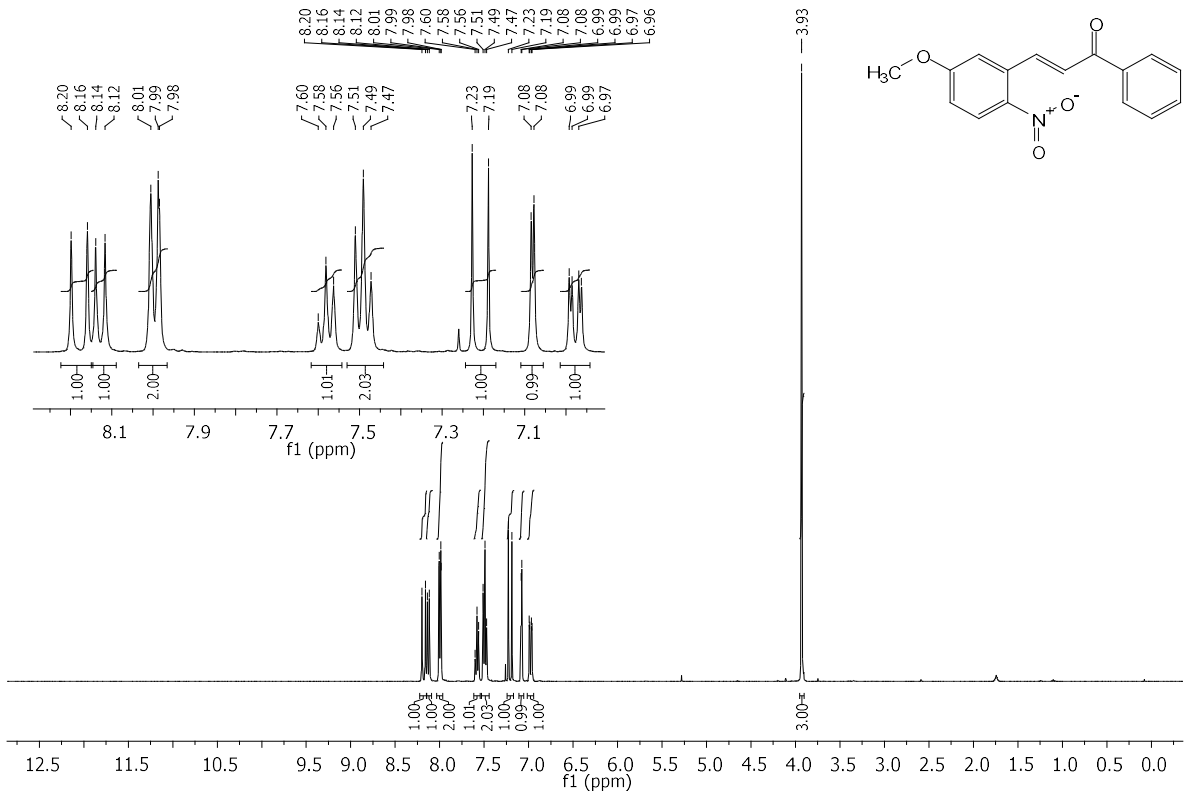


Fig. 107. ^{1}H NMR of **3aa** in $CDCl_3$.

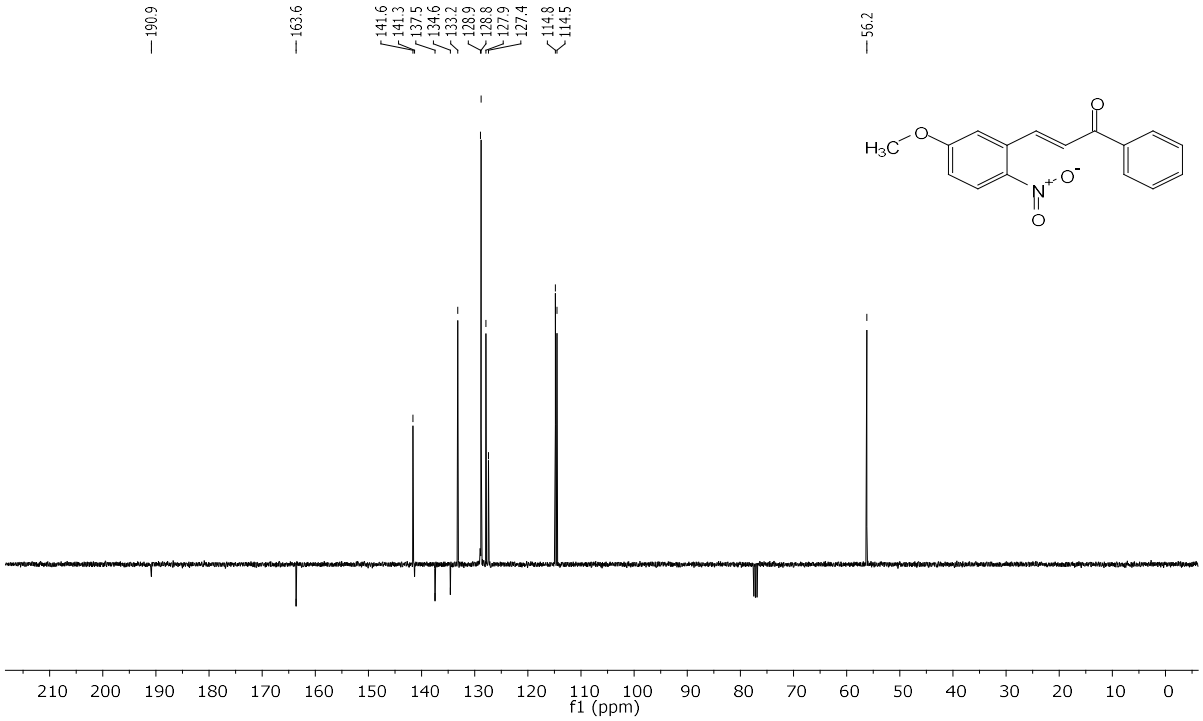


Fig. 108. ^{13}C NMR of **3aa** in $CDCl_3$.

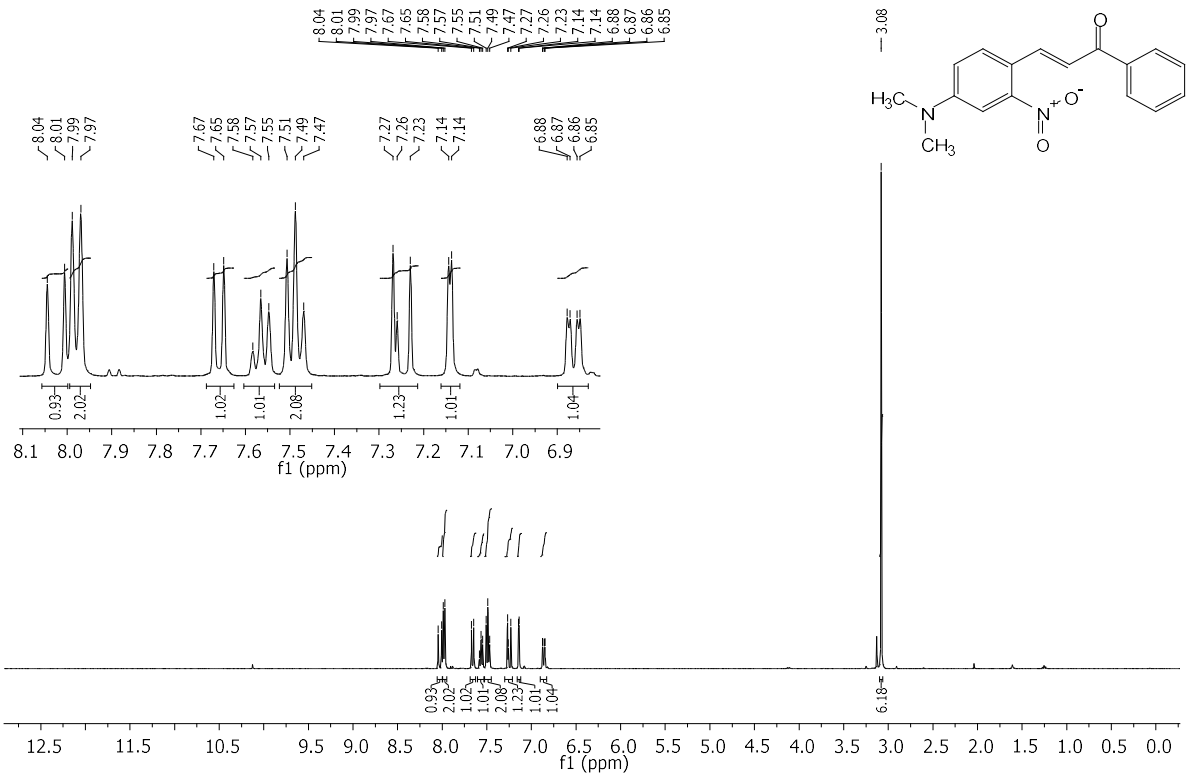


Fig. 109. ^{1}H NMR of **3ab** in $CDCl_3$.

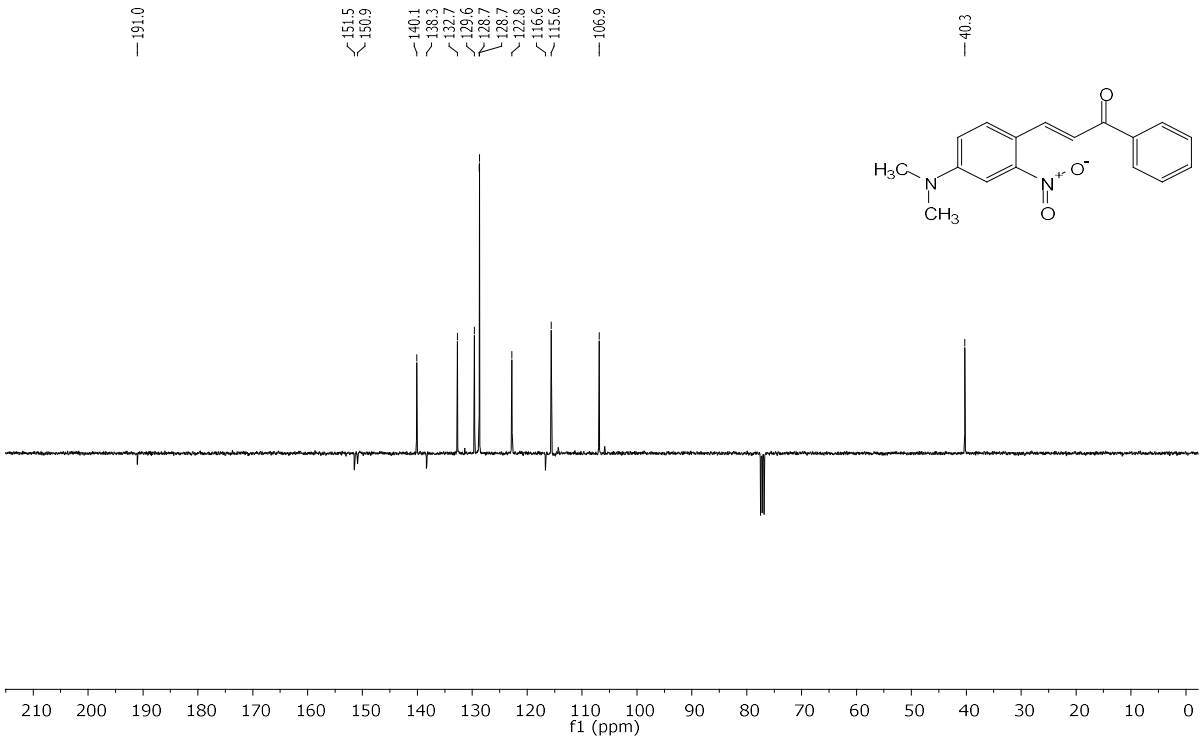


Fig. 110. ^{13}C NMR of **3ab** in $CDCl_3$.

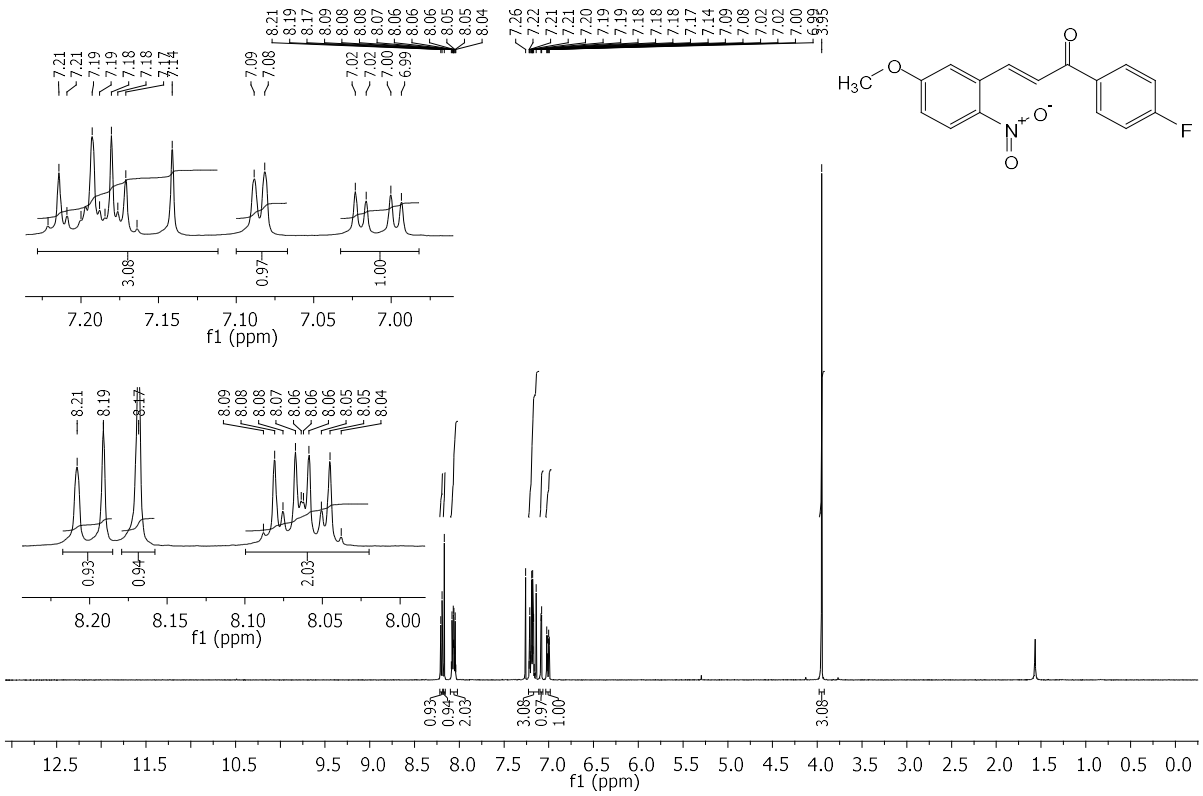


Fig. 111. ^{1}H NMR of **3ac** in $CDCl_3$.

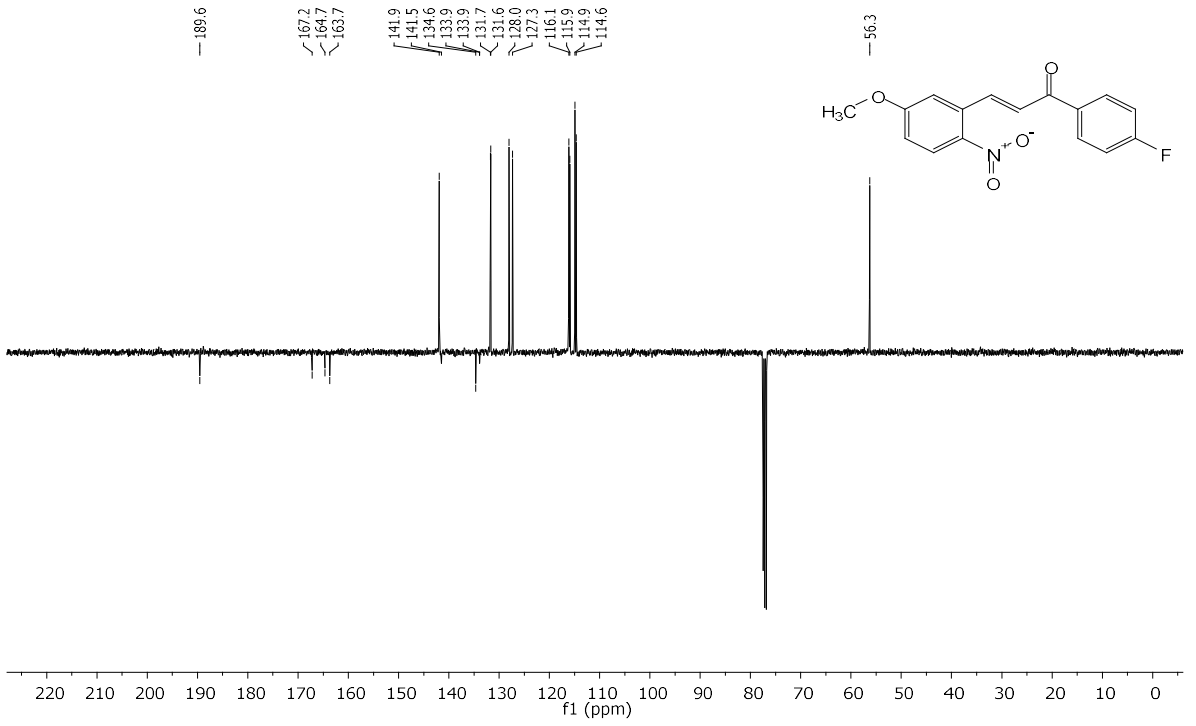


Fig. 112. ^{13}C NMR of **3ac** in $CDCl_3$.

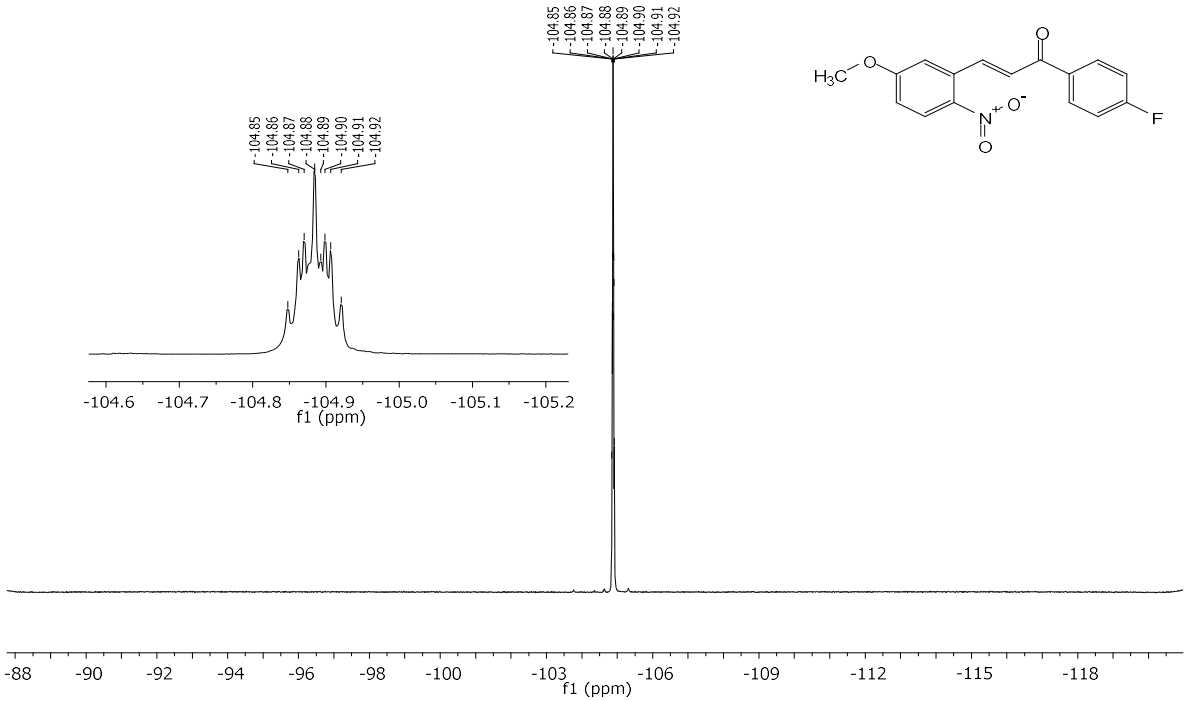


Fig. 113. ^{19}F NMR of **3ac** in $CDCl_3$.

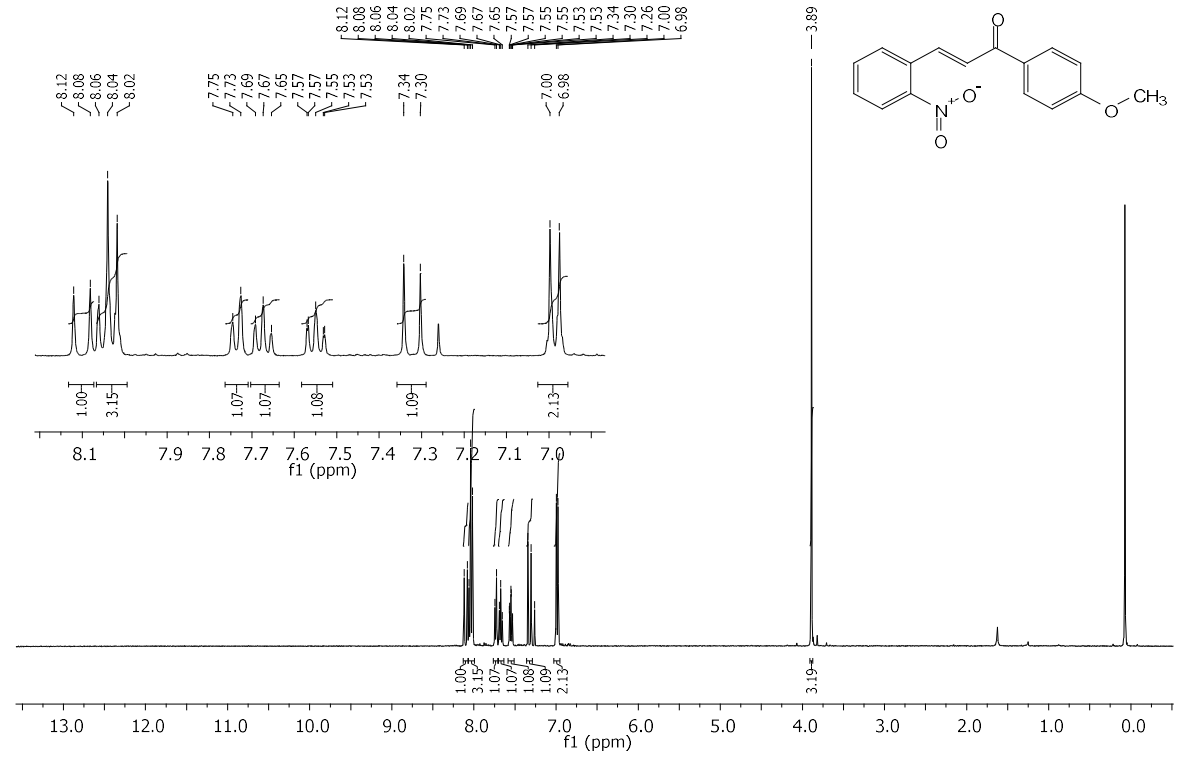


Fig. 114. ^{1}H NMR of **3ad** in $CDCl_3$.

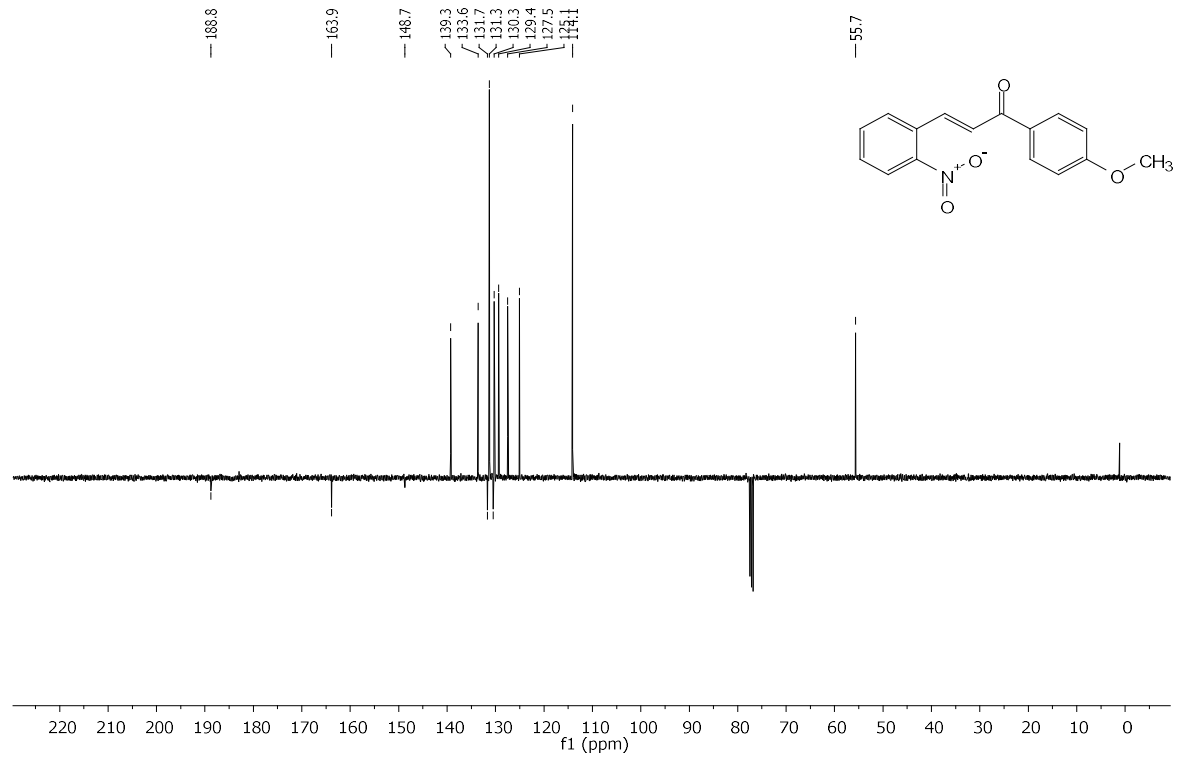


Fig. 115. ^{13}C NMR of **3ad** in $CDCl_3$.

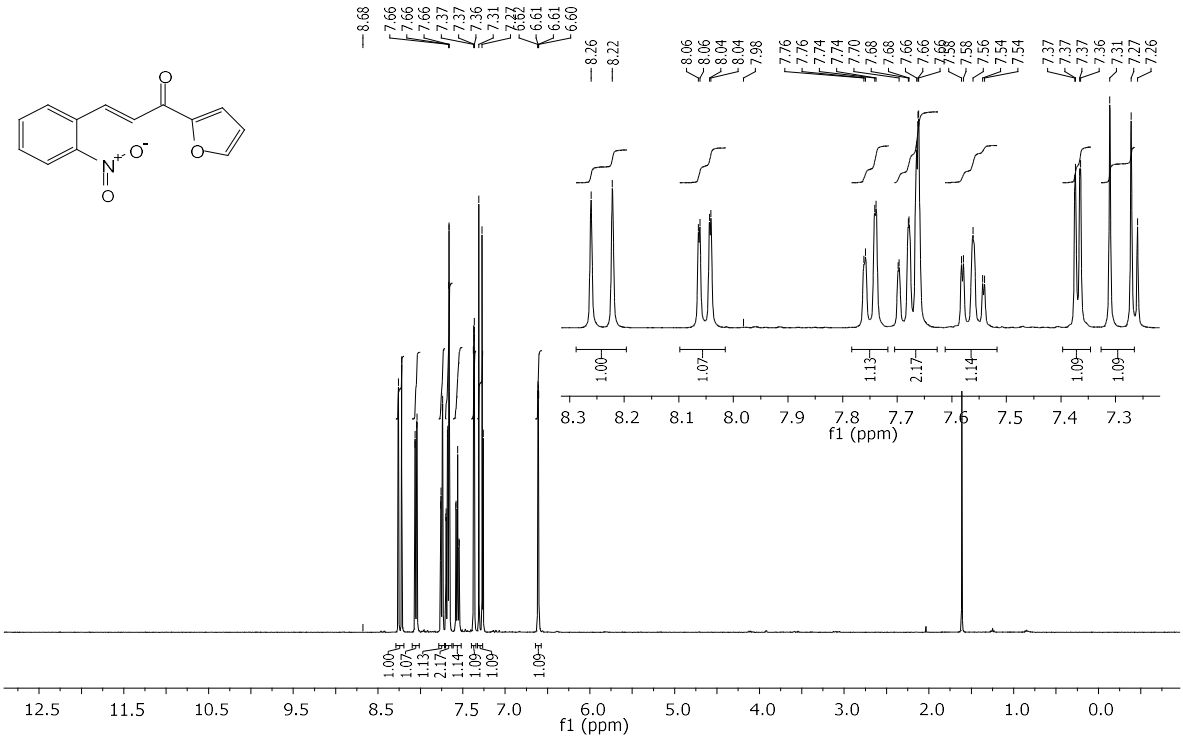


Fig. 116. ^{1}H NMR of **3ae** in $CDCl_3$.

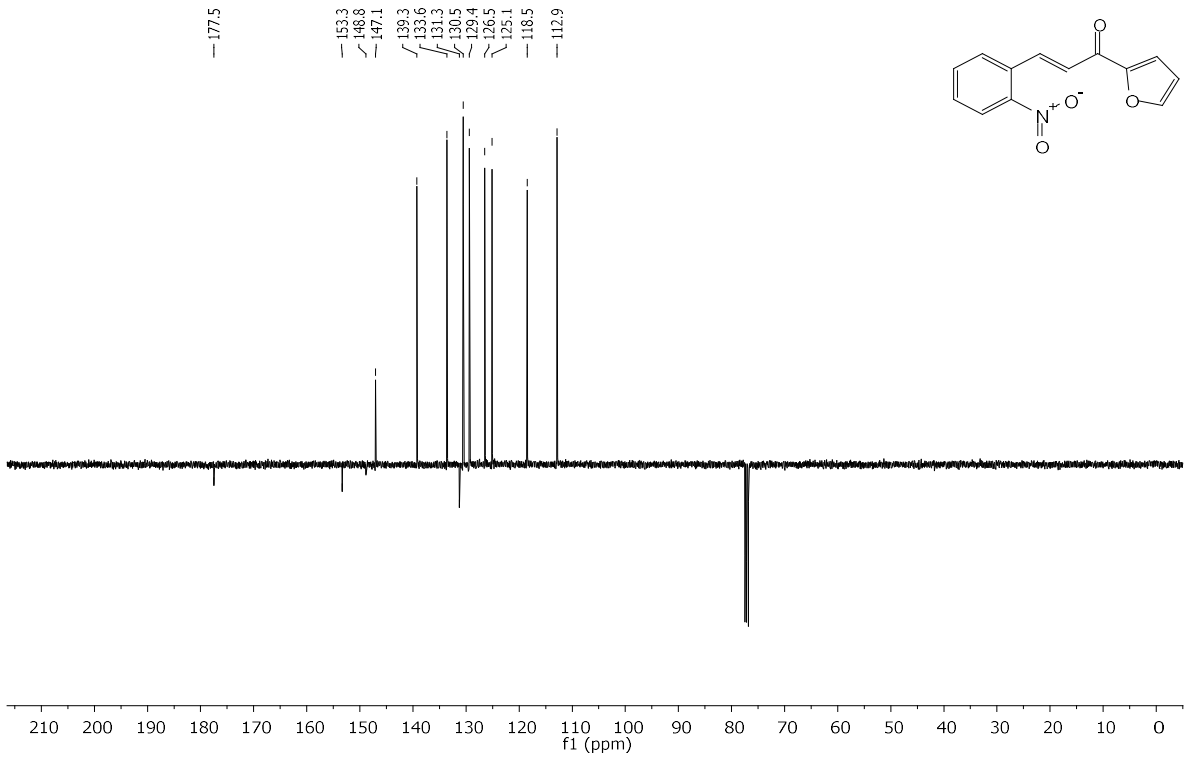


Fig. 117. ^{13}C NMR of **3ae** in $CDCl_3$.

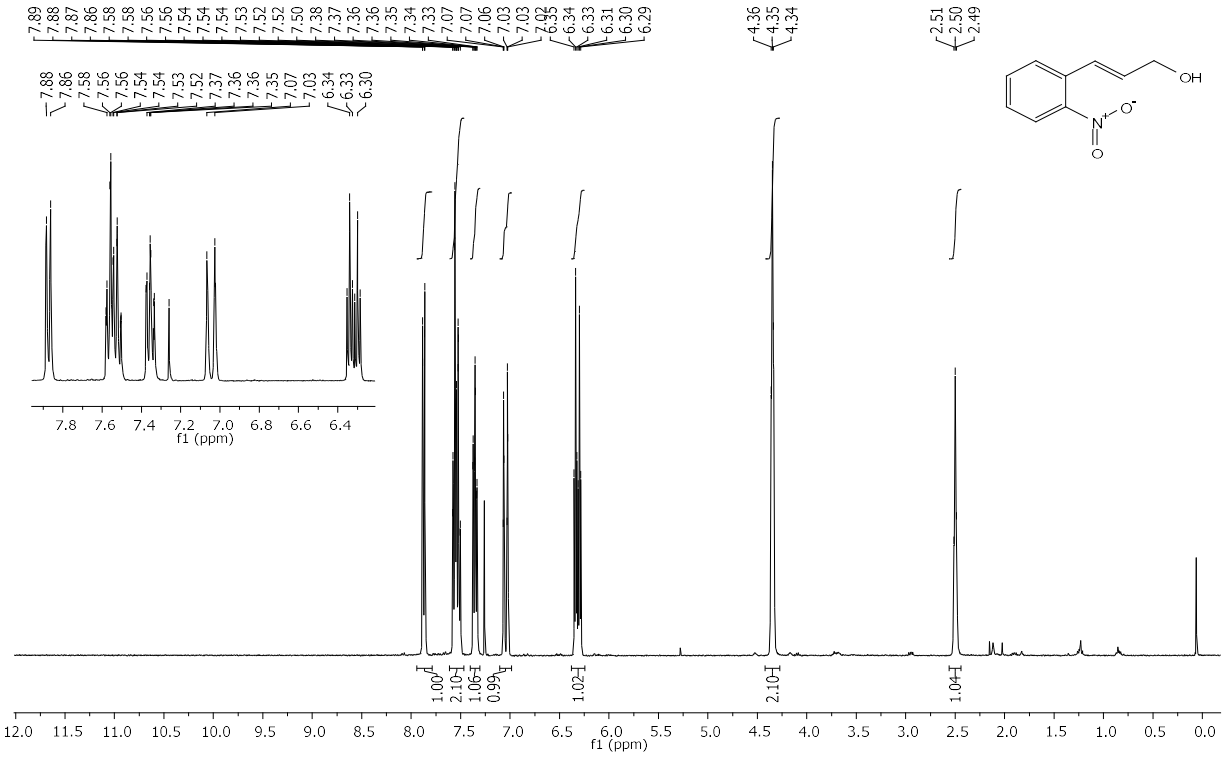


Fig. 118. ^{1}H NMR of **3ag** in $CDCl_3$.

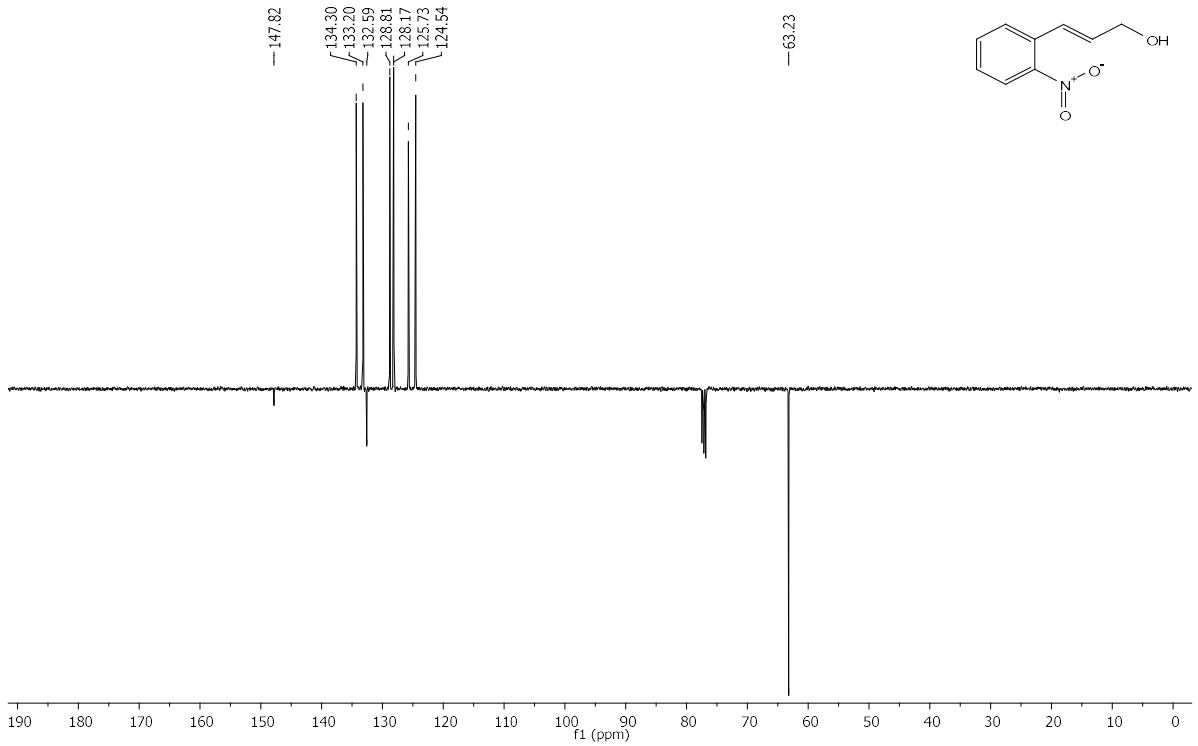


Fig. 119. ^{13}C NMR of **3ag** in $CDCl_3$.

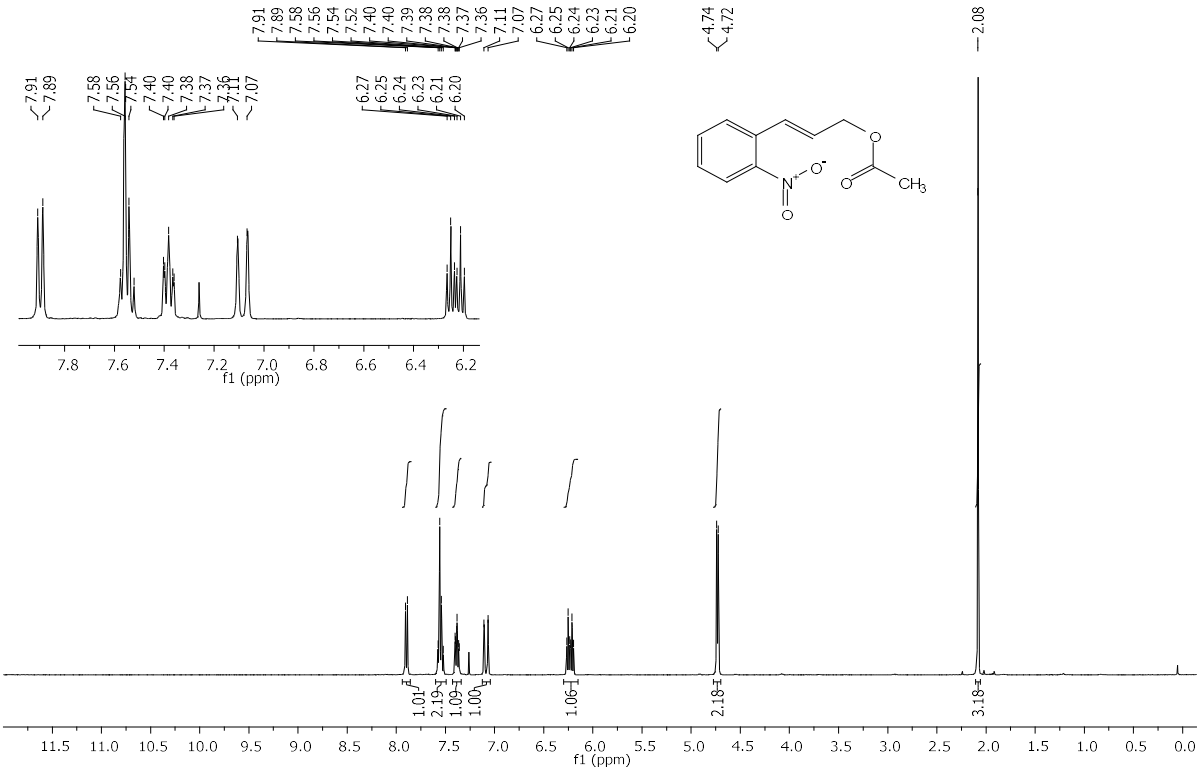


Fig. 120. ^{1}H NMR of **3ah** in $CDCl_3$.

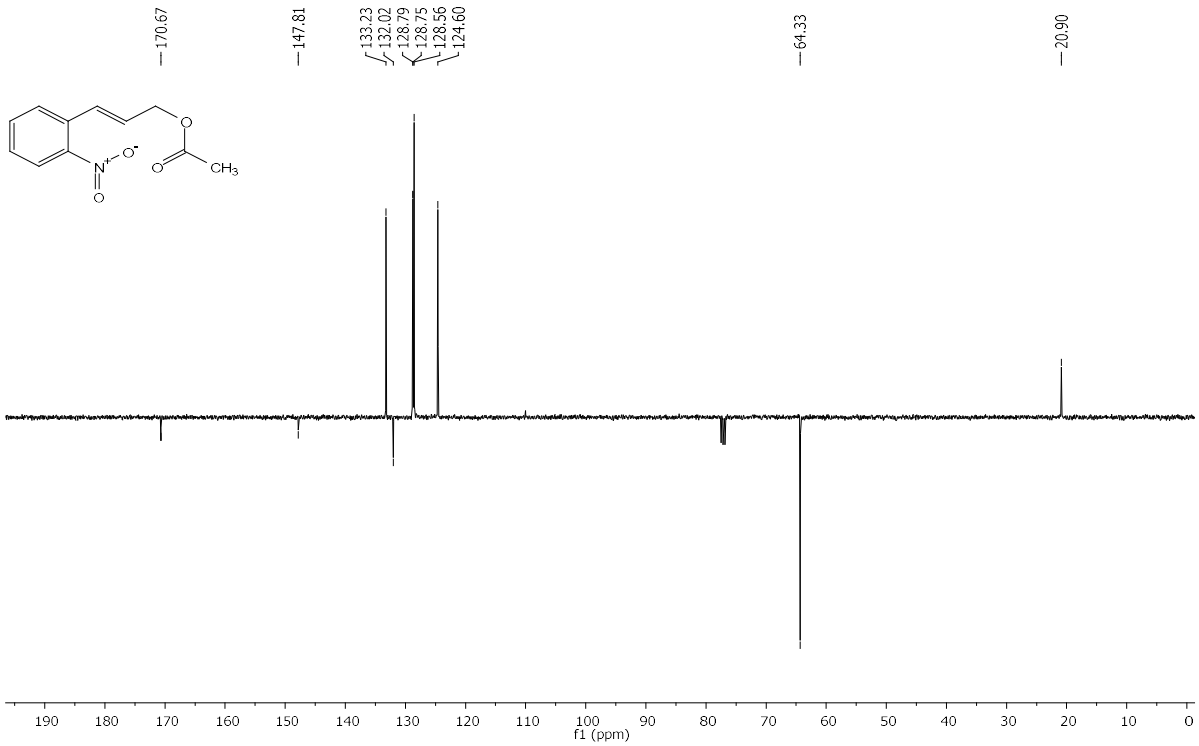


Fig. 121. ^{13}C NMR of **3ah** in $CDCl_3$.

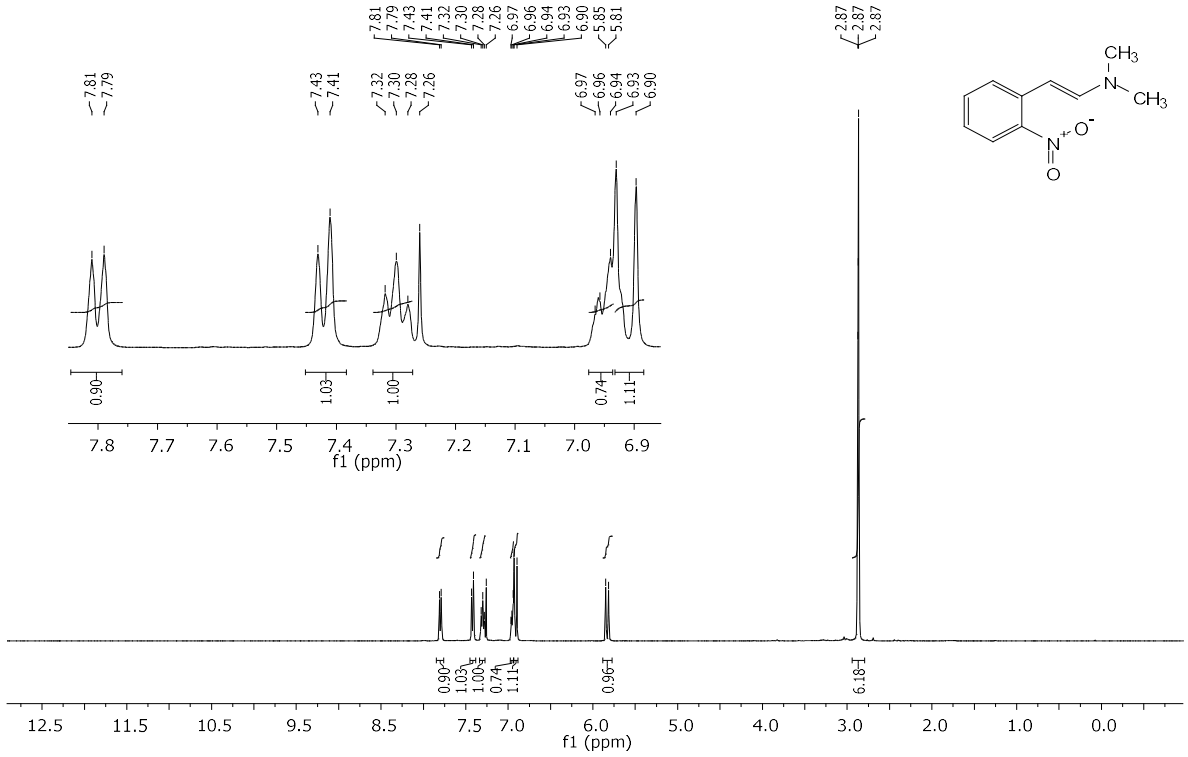


Fig. 122. ^{1}H NMR of **3aj** in $CDCl_3$.

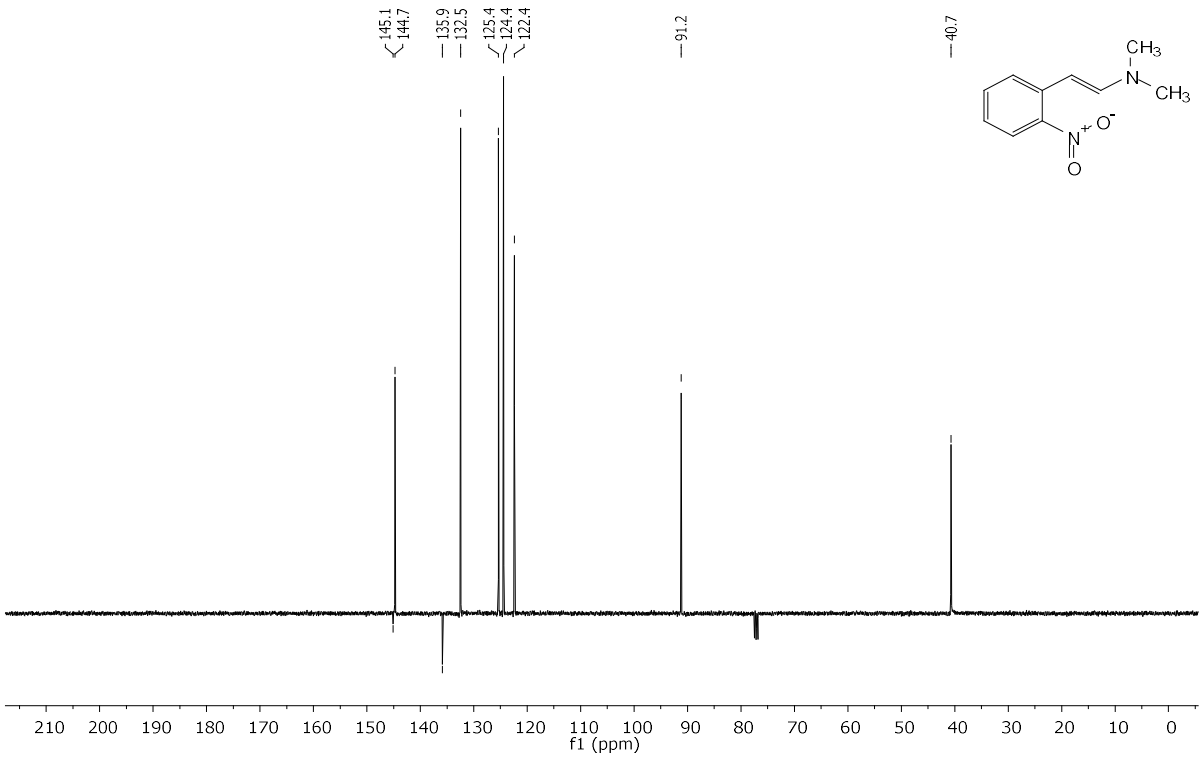


Fig. 123. ^{13}C NMR of **3aj** in $CDCl_3$.

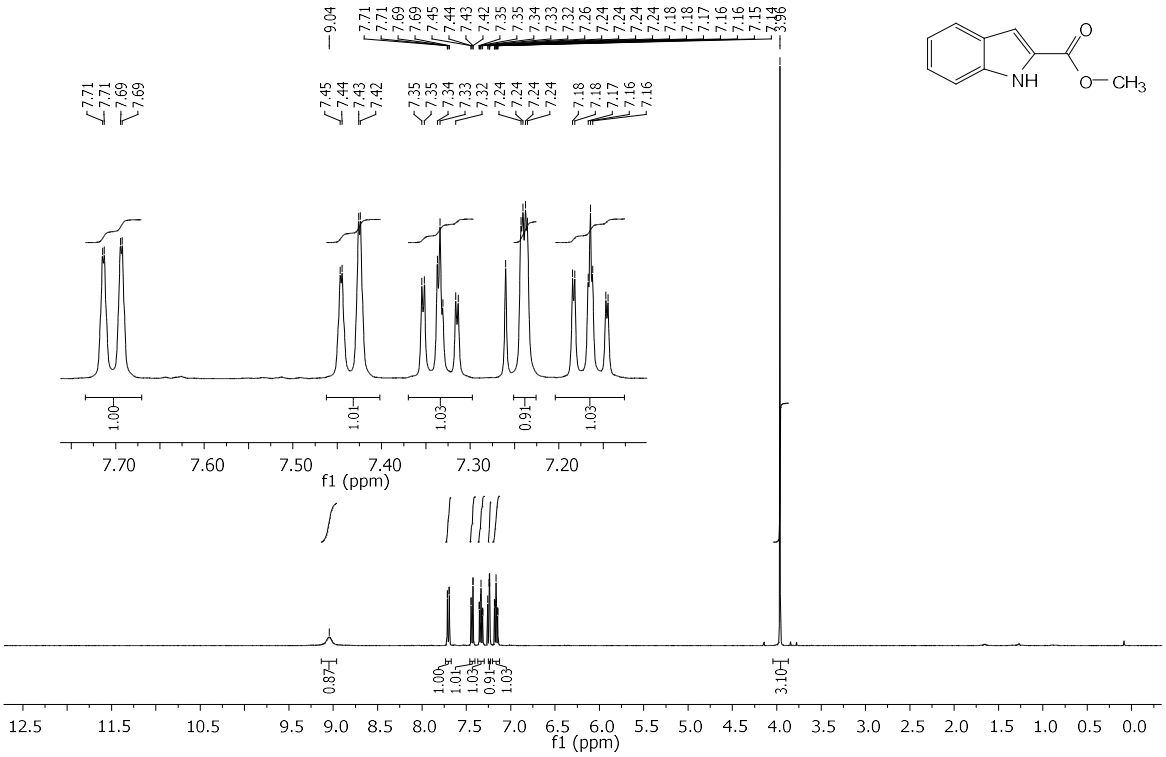


Fig. 124. ^{1}H NMR of **4a** in $CDCl_3$.

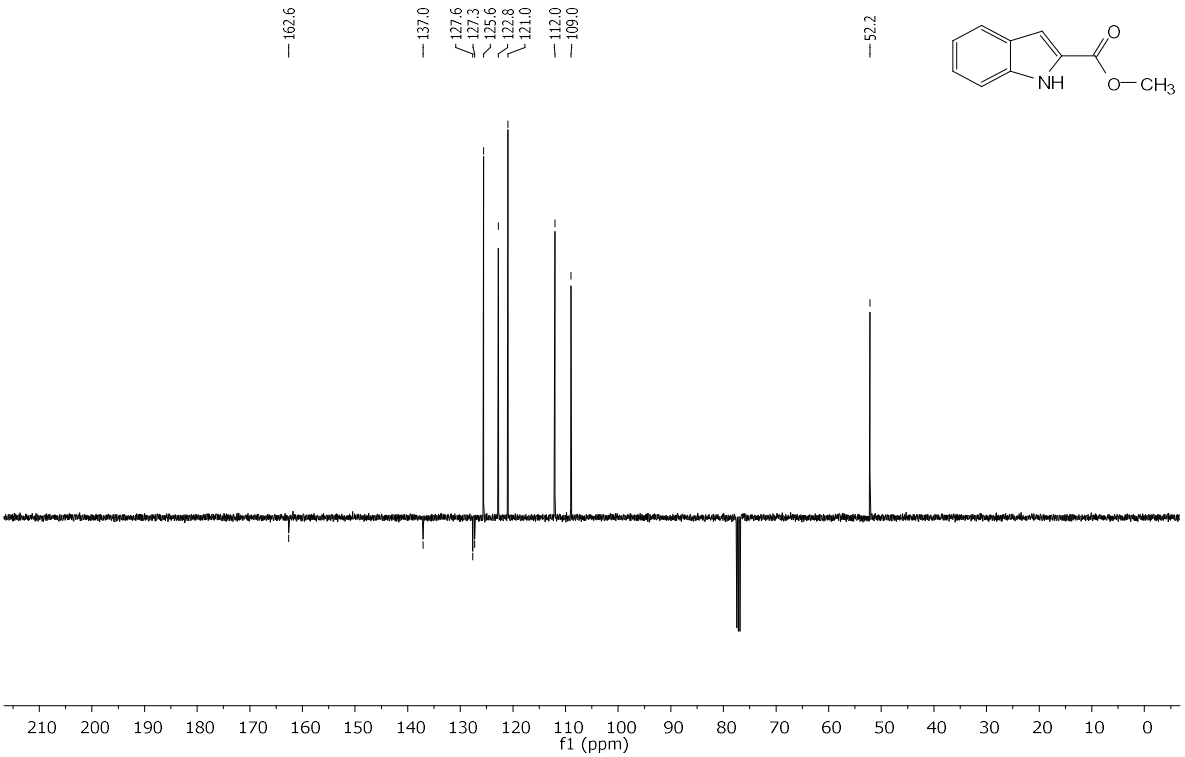


Fig. 125. ^{13}C NMR of **4a** in $CDCl_3$.

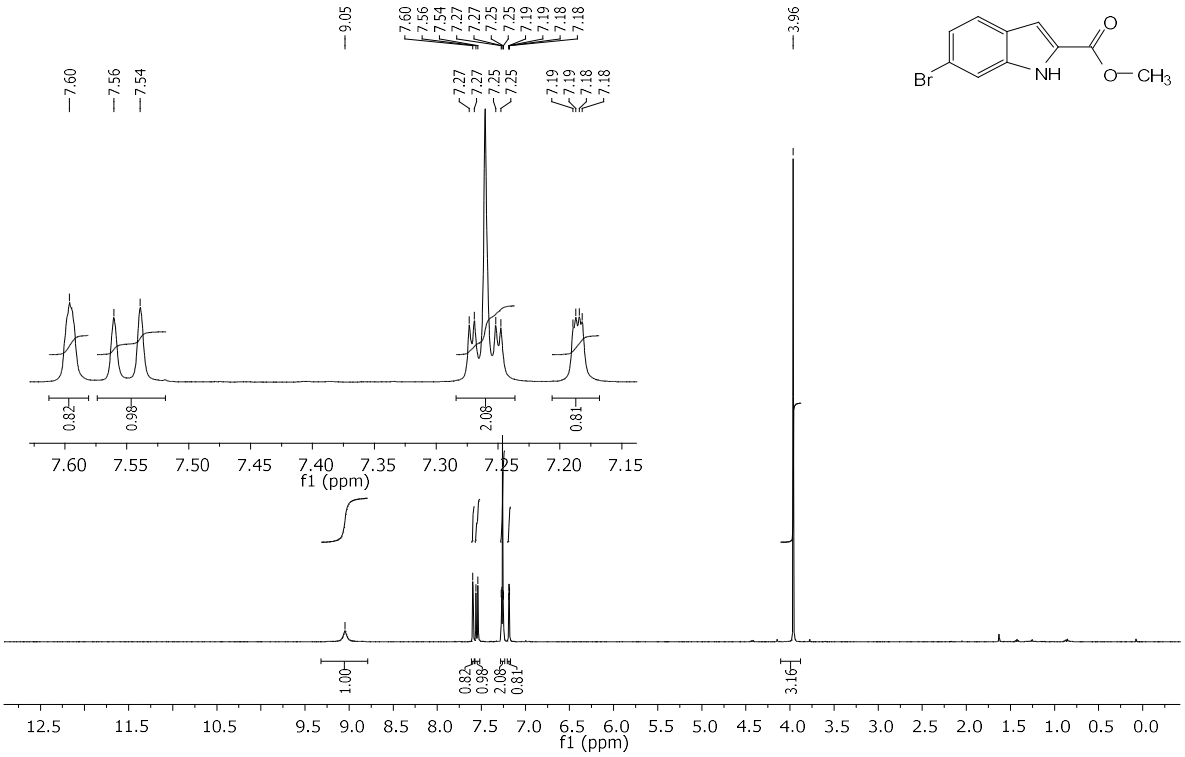


Fig. 126. ^{1}H NMR of **4b** in $CDCl_3$.

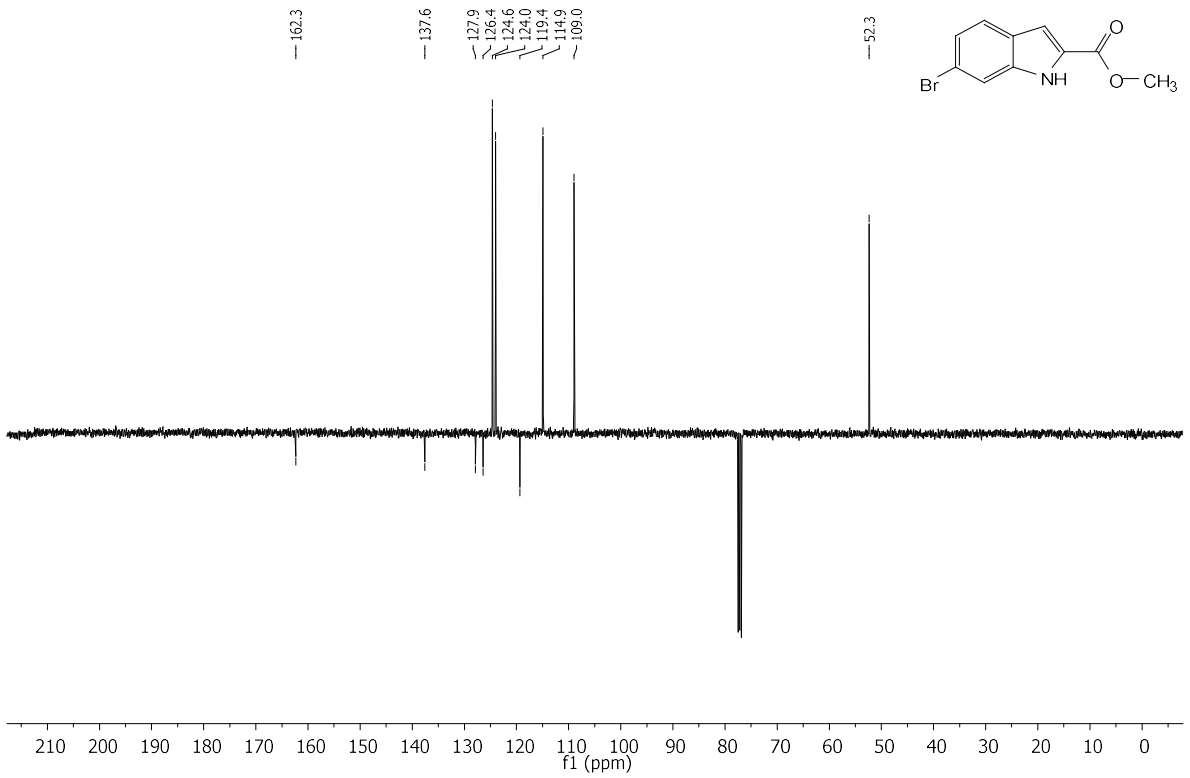


Fig. 127. ^{13}C NMR of **4b** in $CDCl_3$.

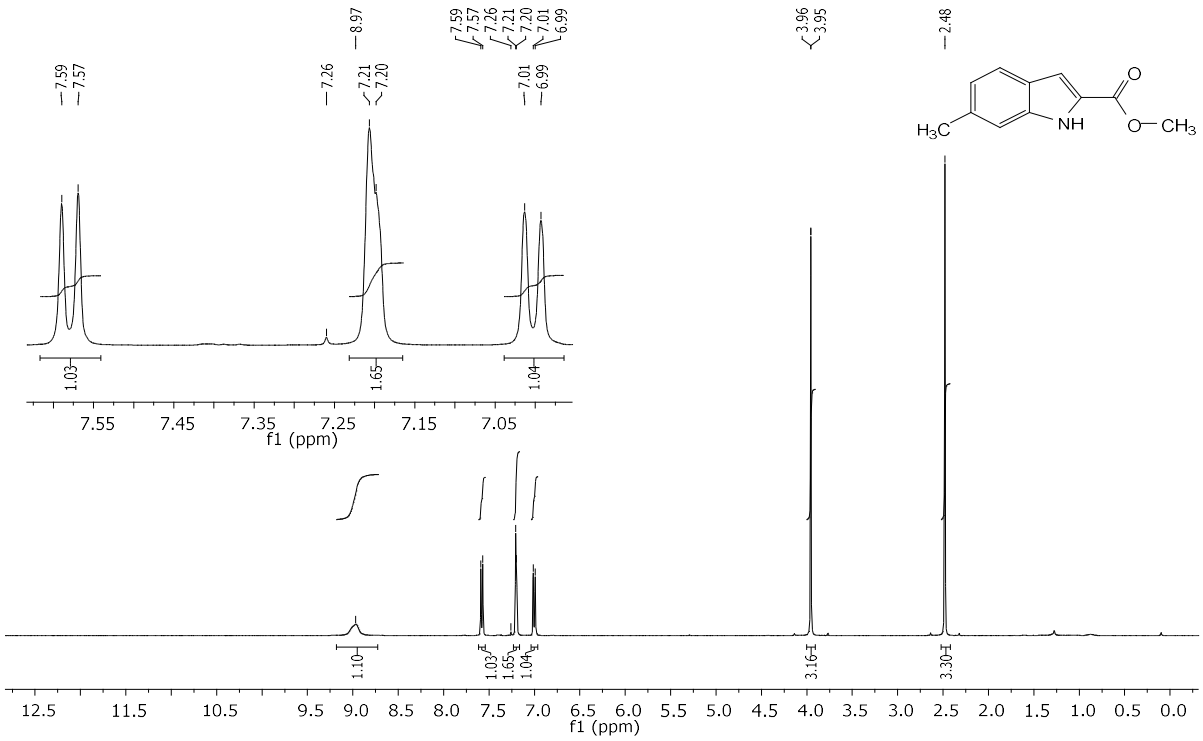


Fig. 128. ^{1}H NMR of **4c** in $CDCl_3$.

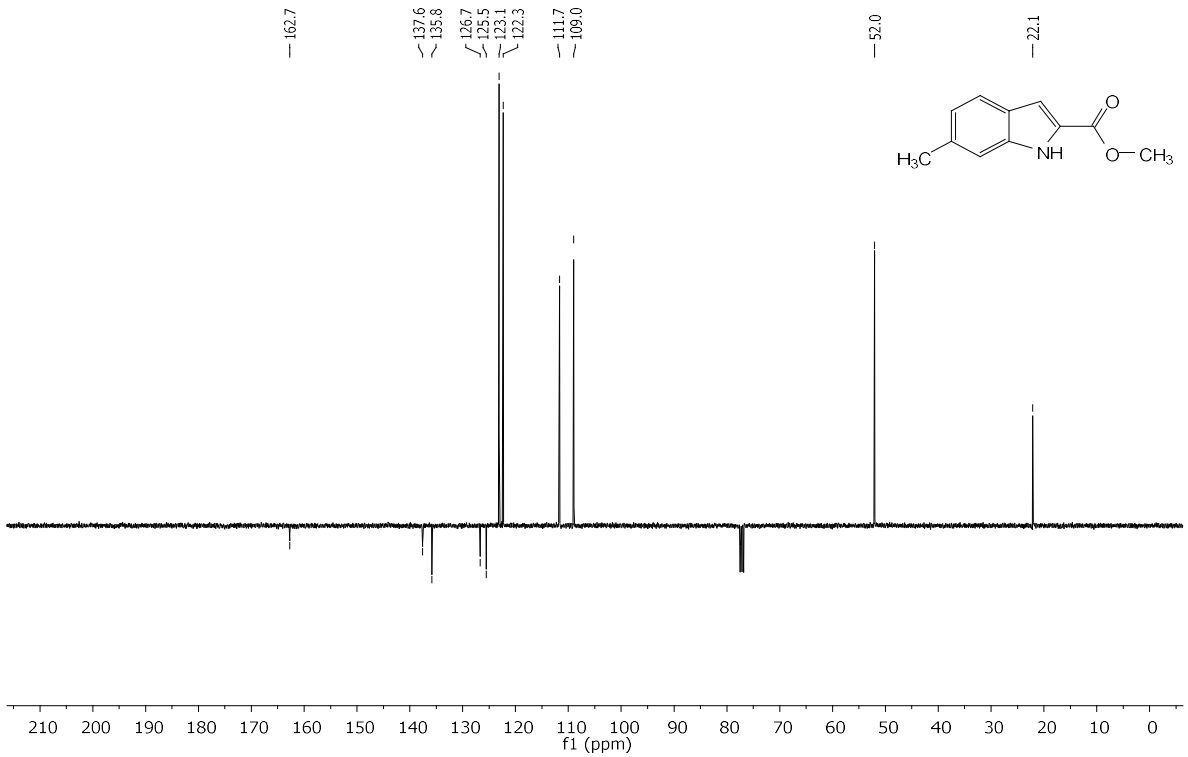


Fig. 129. ^{13}C NMR of **4c** in $CDCl_3$.

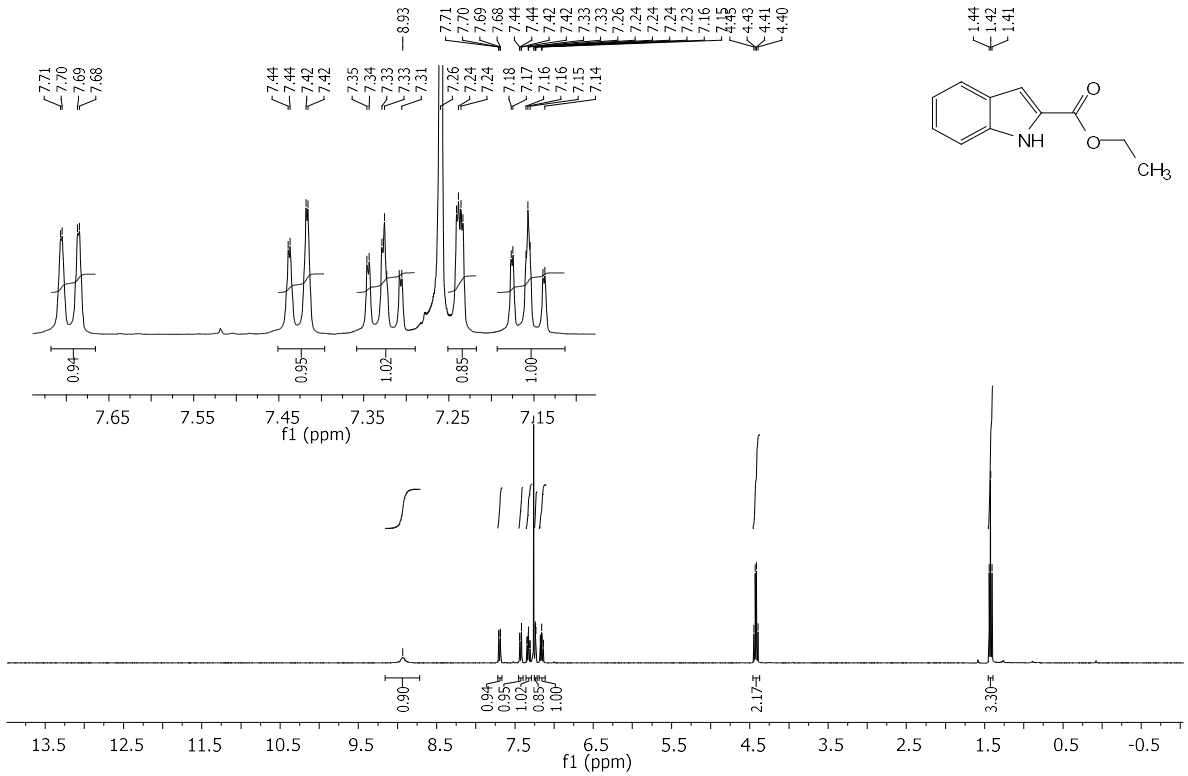


Fig. 130. ^{1}H NMR of **4d** in $CDCl_3$.

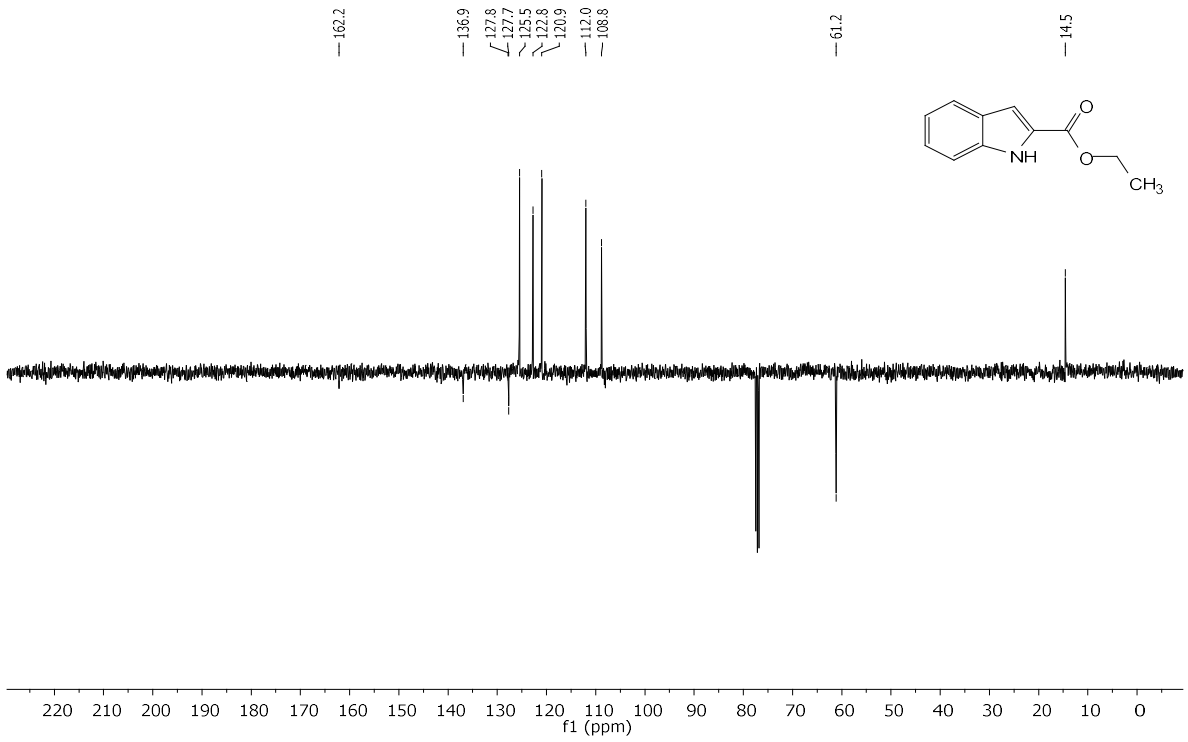


Fig. 131. ^{13}C NMR of **4d** in $CDCl_3$.

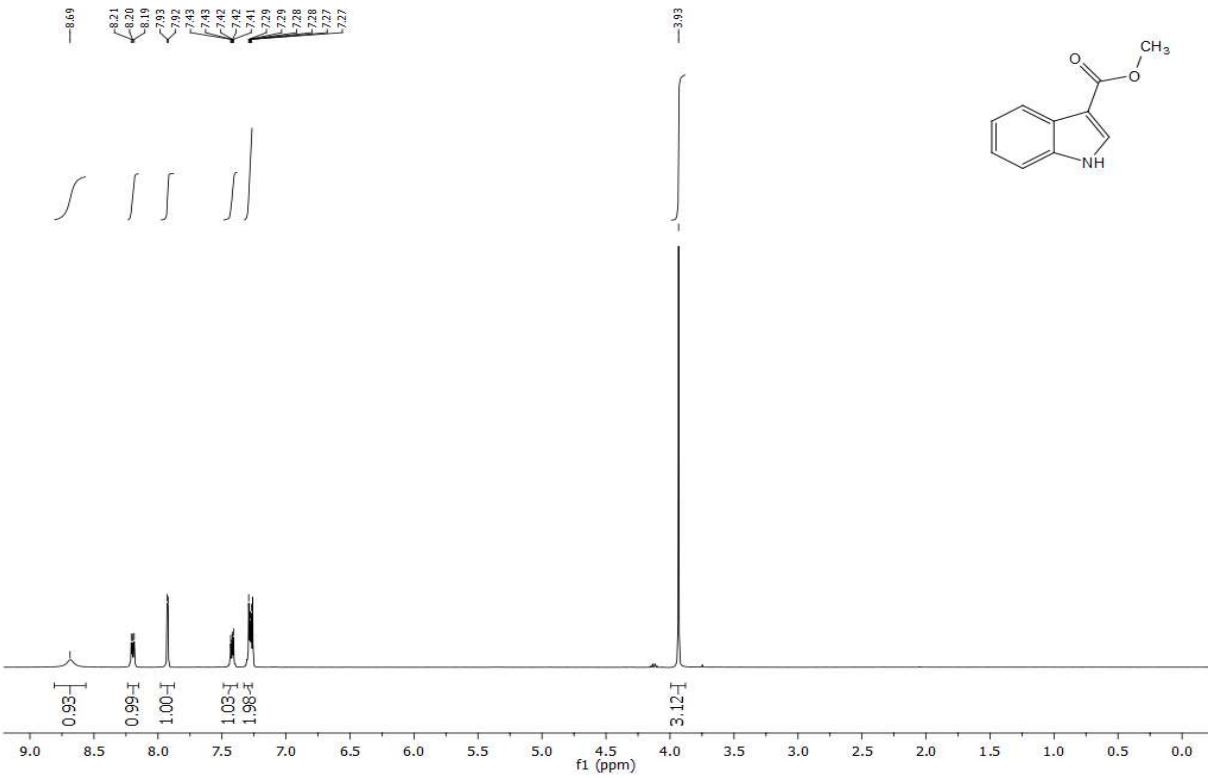


Fig. 132. ^{1}H NMR of **4e** in $CDCl_3$.

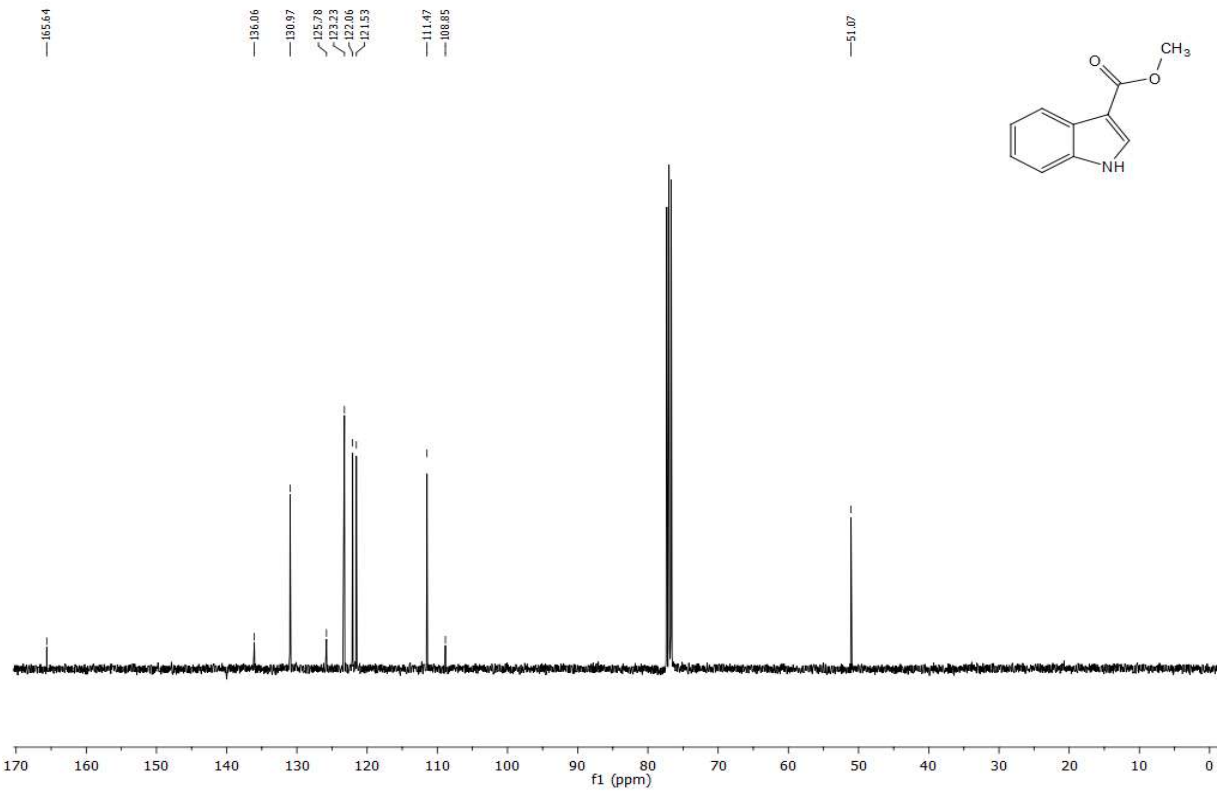


Fig. 133. ^{13}C NMR of **4e** in $CDCl_3$.

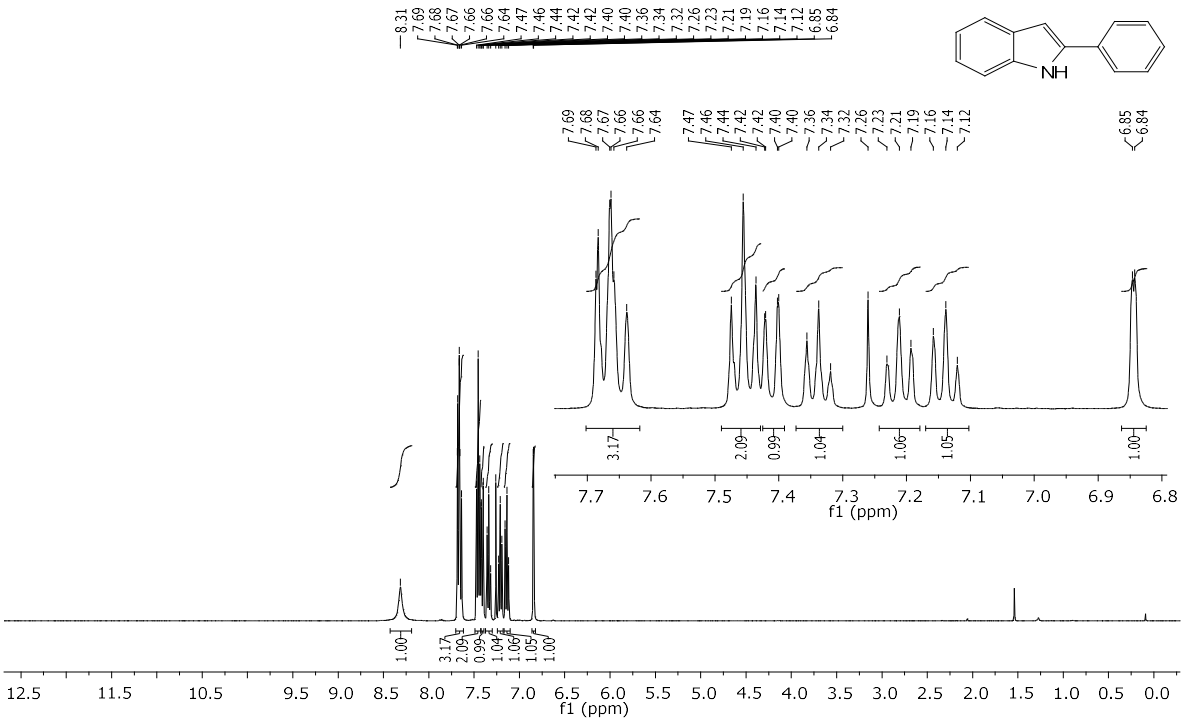


Fig. 134. ^{1}H NMR of **4f** in $CDCl_3$.

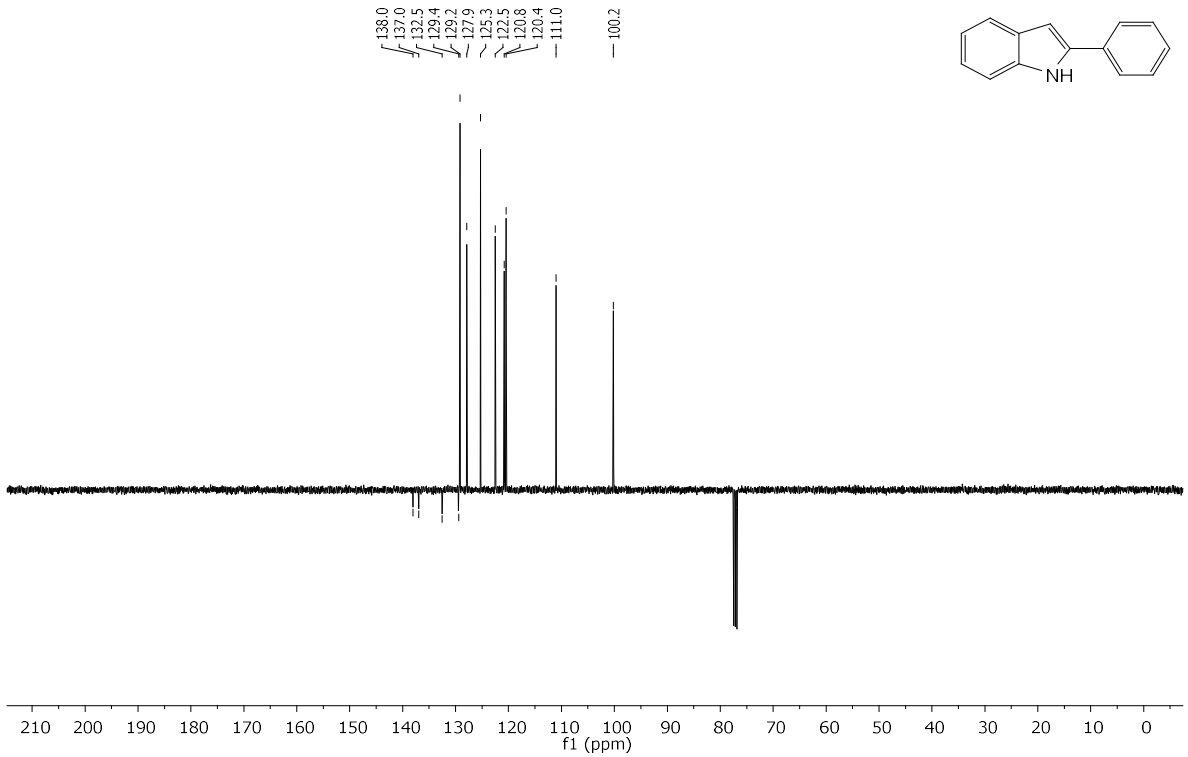


Fig. 135. ^{13}C NMR of **4f** in $CDCl_3$.

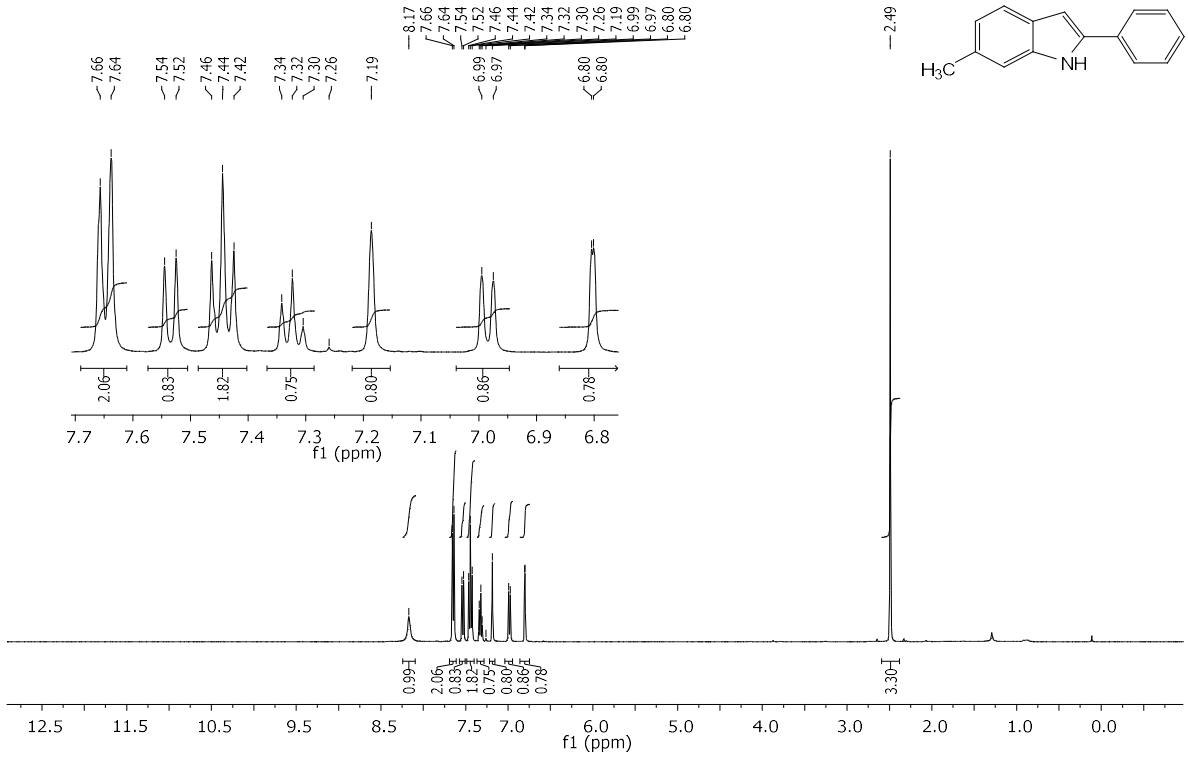


Fig. 136. ^{1}H NMR of **4g** in $CDCl_3$.

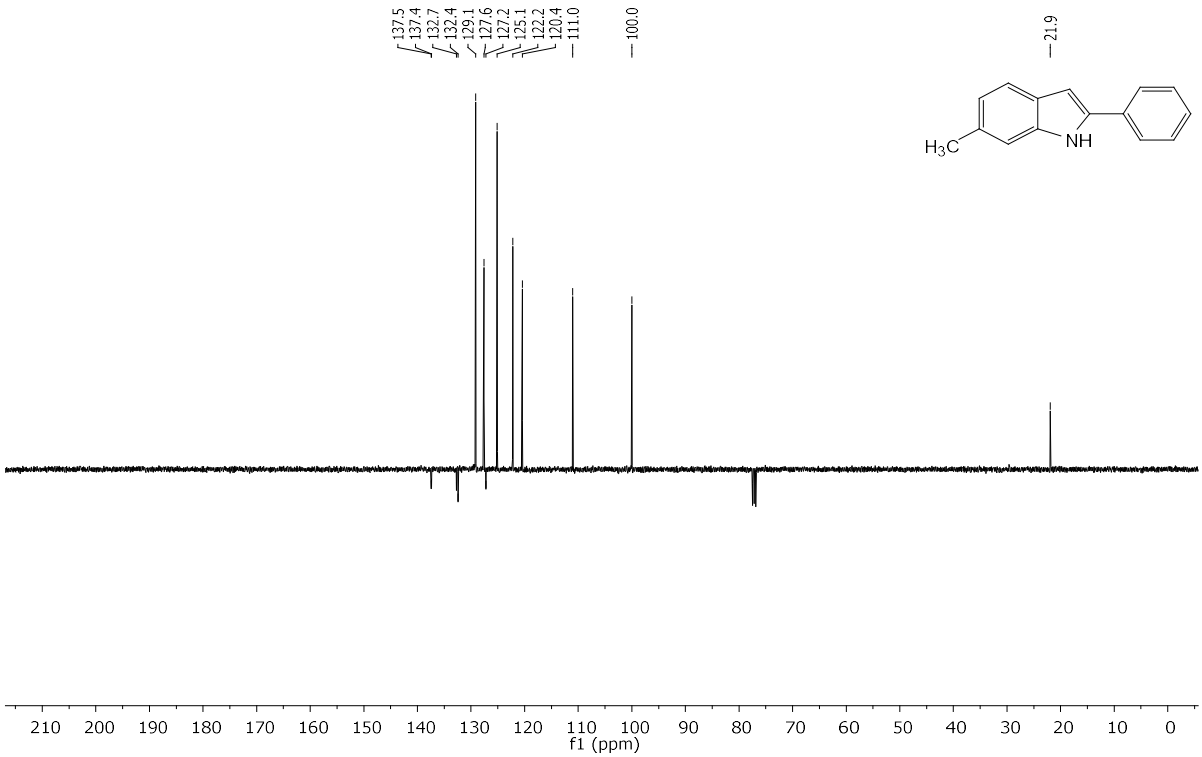


Fig. 137. ^{13}C NMR of **4g** in $CDCl_3$.

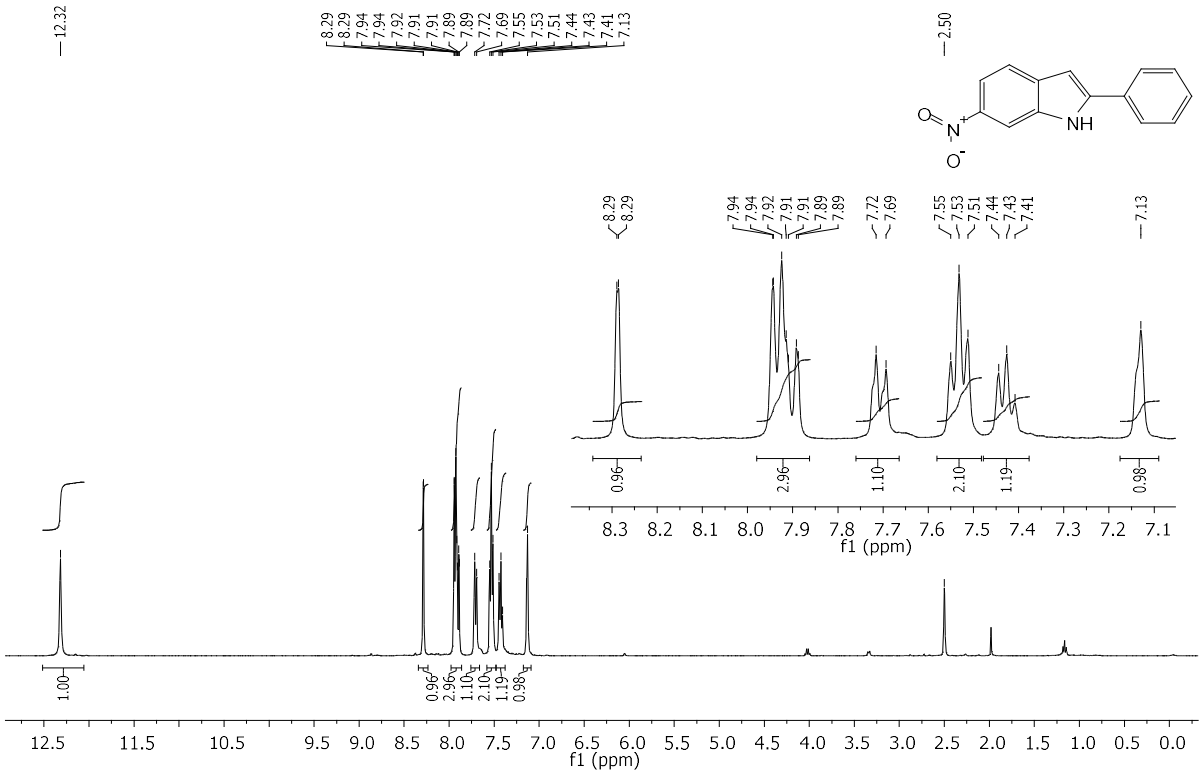


Fig. 138. ^{1}H NMR of **4i** in DMSO-d_6.

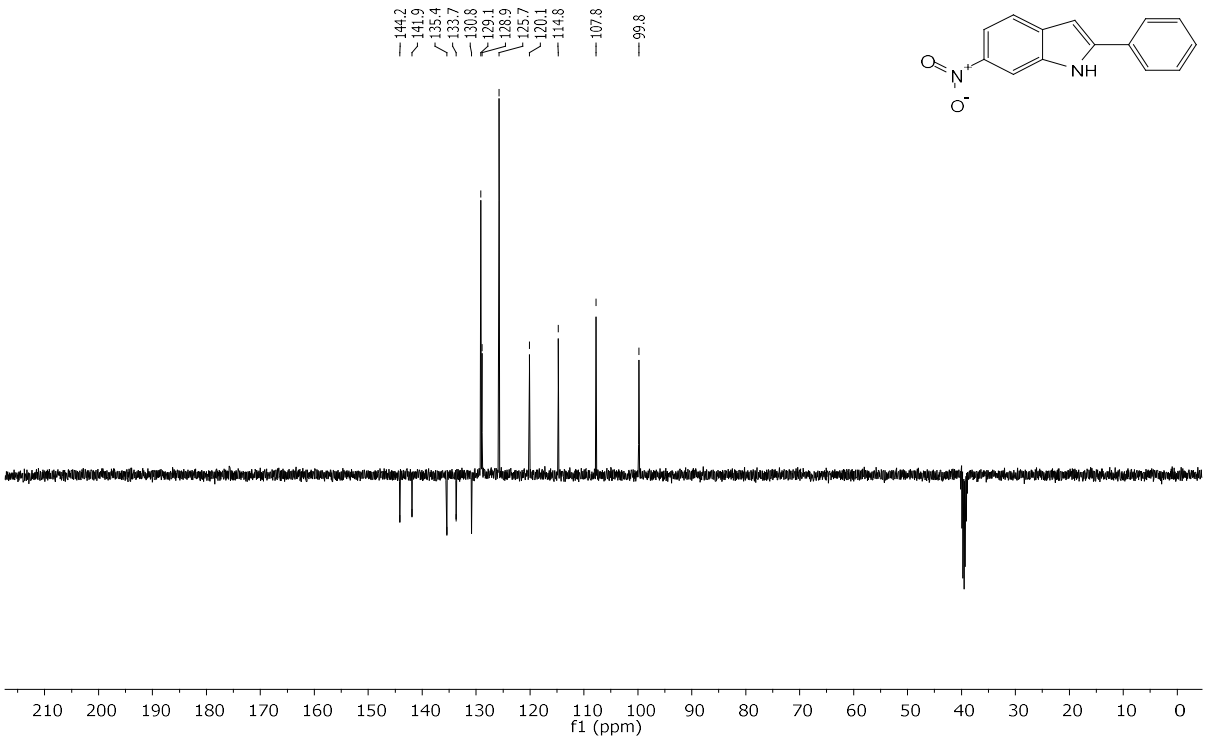


Fig. 139. ^{13}C NMR of **4i** in DMSO-d_6.

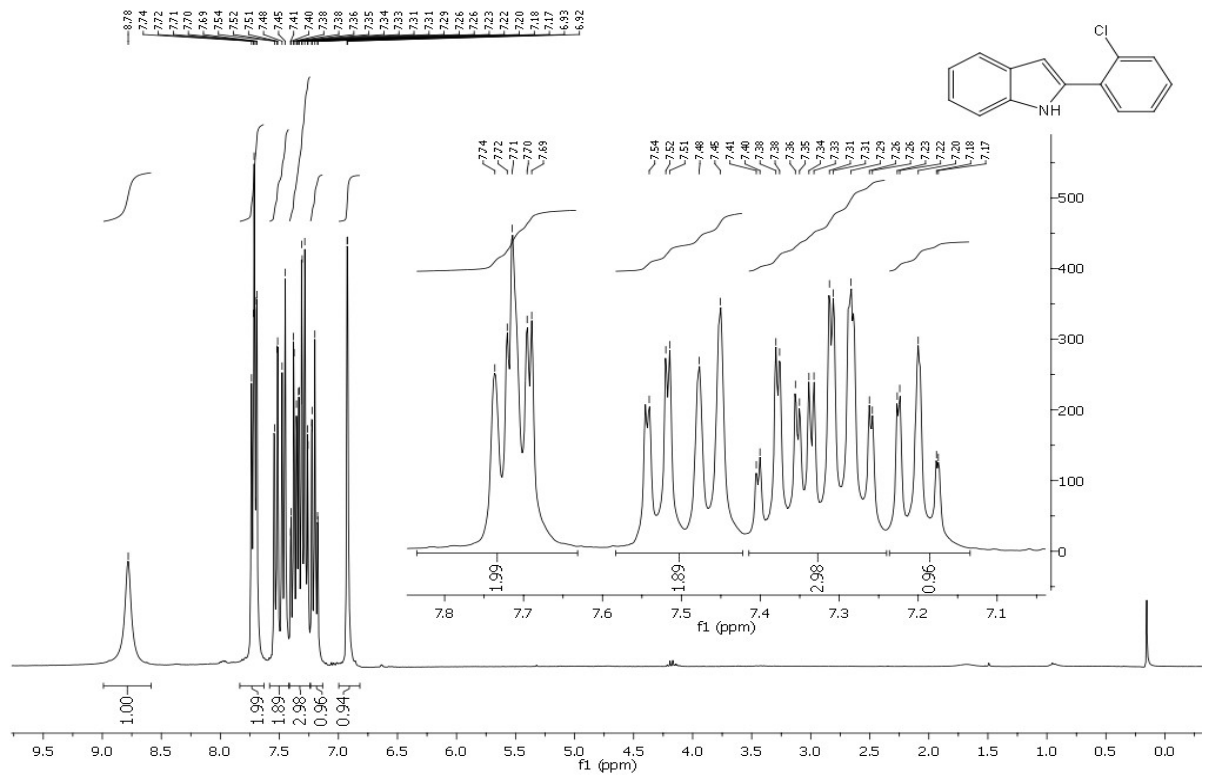


Fig. 140. ^{1}H NMR of **4j** in $CDCl_3$.

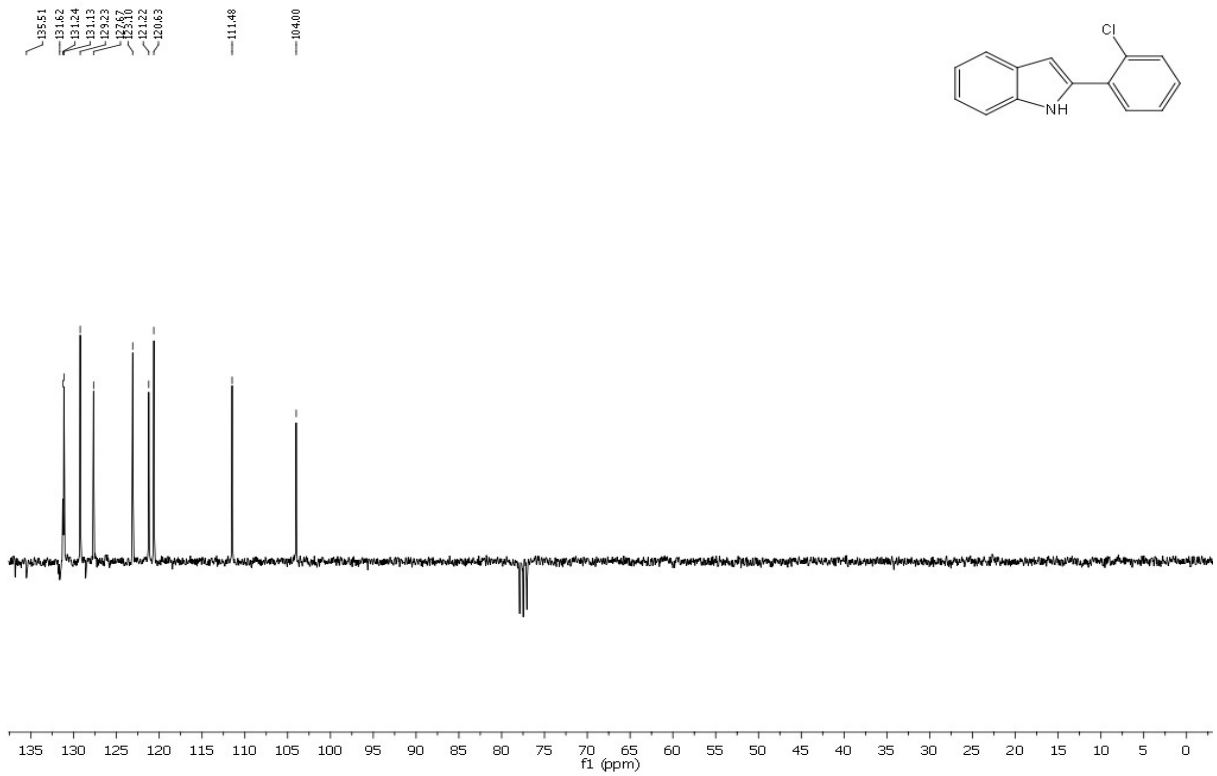


Fig. 141. ^{13}C NMR of **4j** in $CDCl_3$.

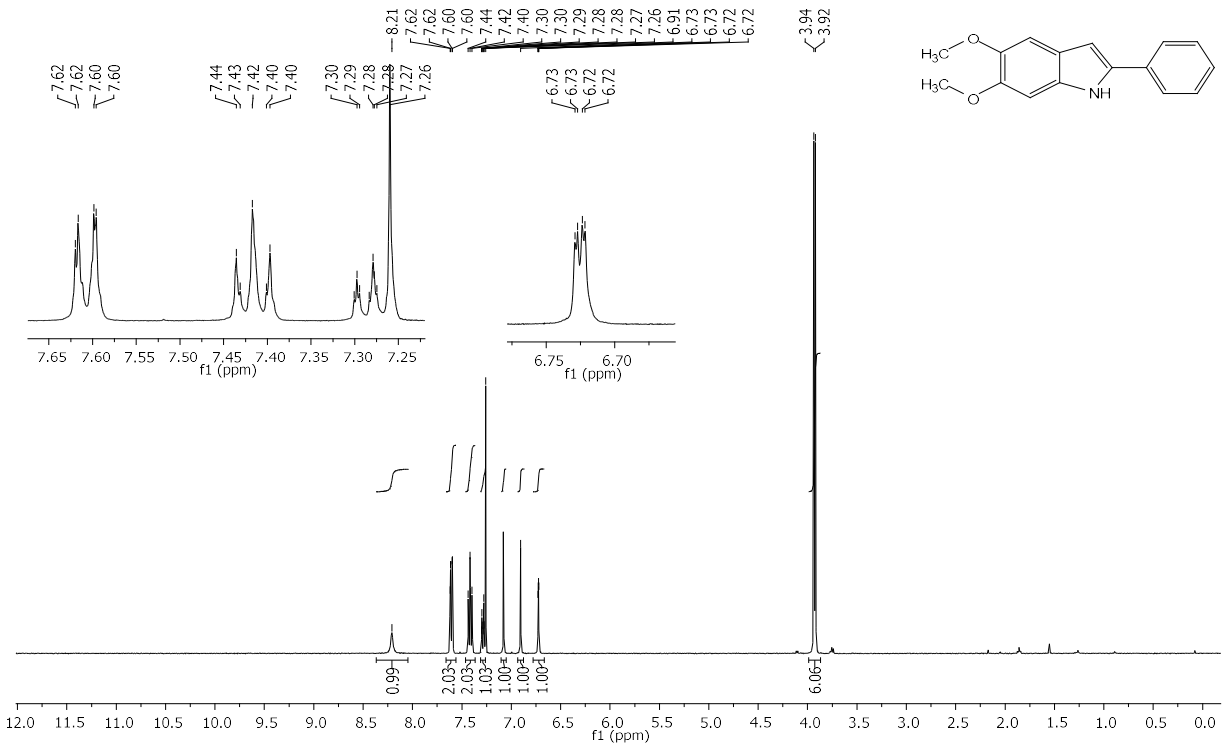


Fig. 142. ^{1}H NMR of **4k** in $CDCl_3$.

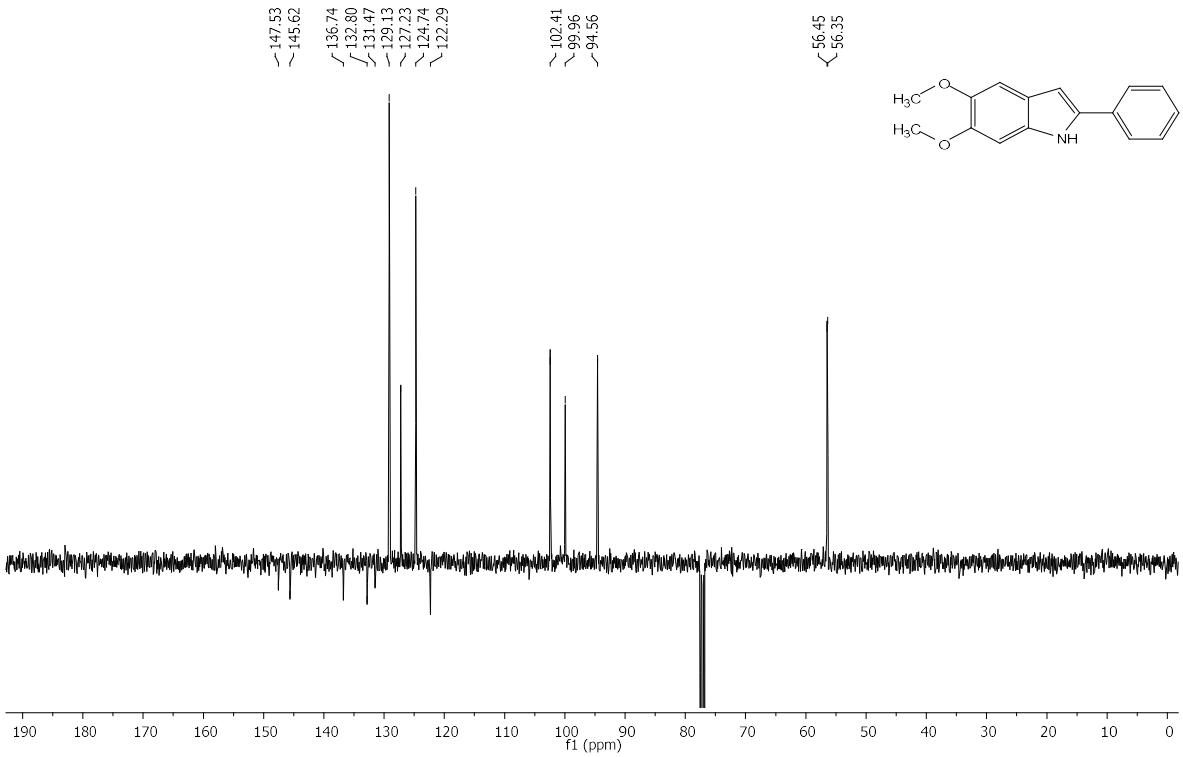


Fig. 143. ^{13}C NMR of **4k** in $CDCl_3$.

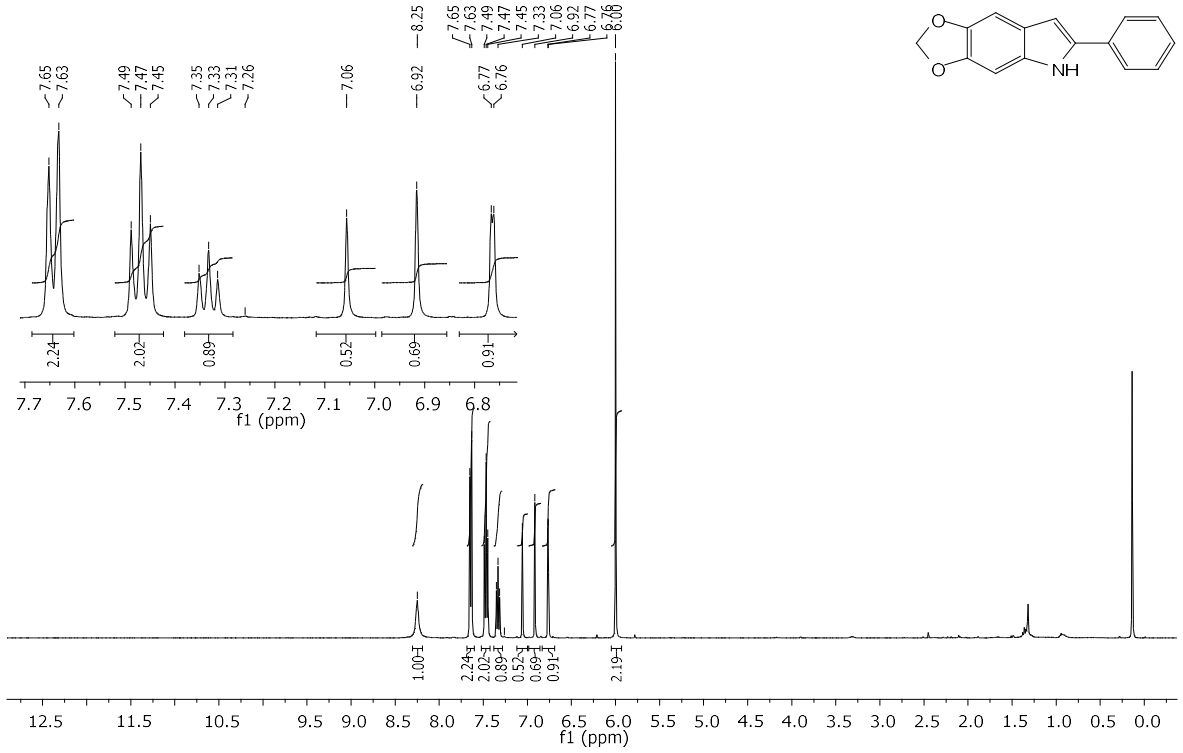


Fig. 144. ^{1}H NMR of **4l** in $CDCl_3$.

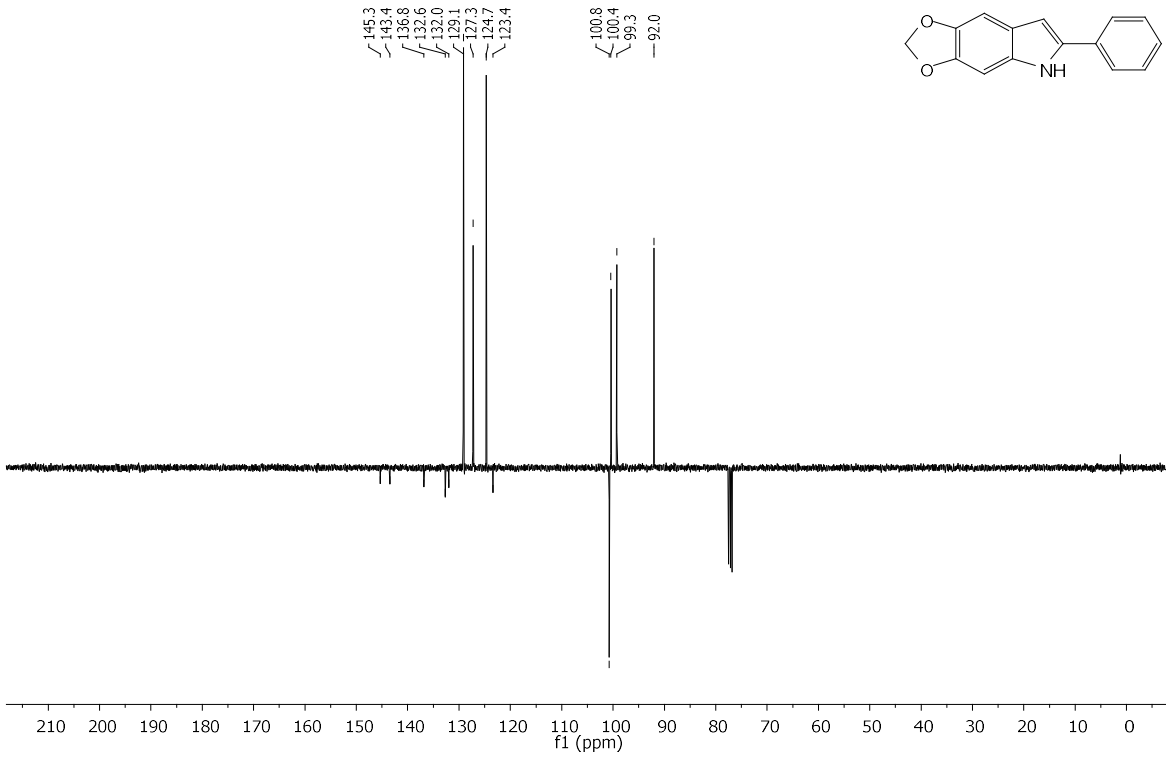


Fig. 145. ^{13}C NMR of **4l** in $CDCl_3$.

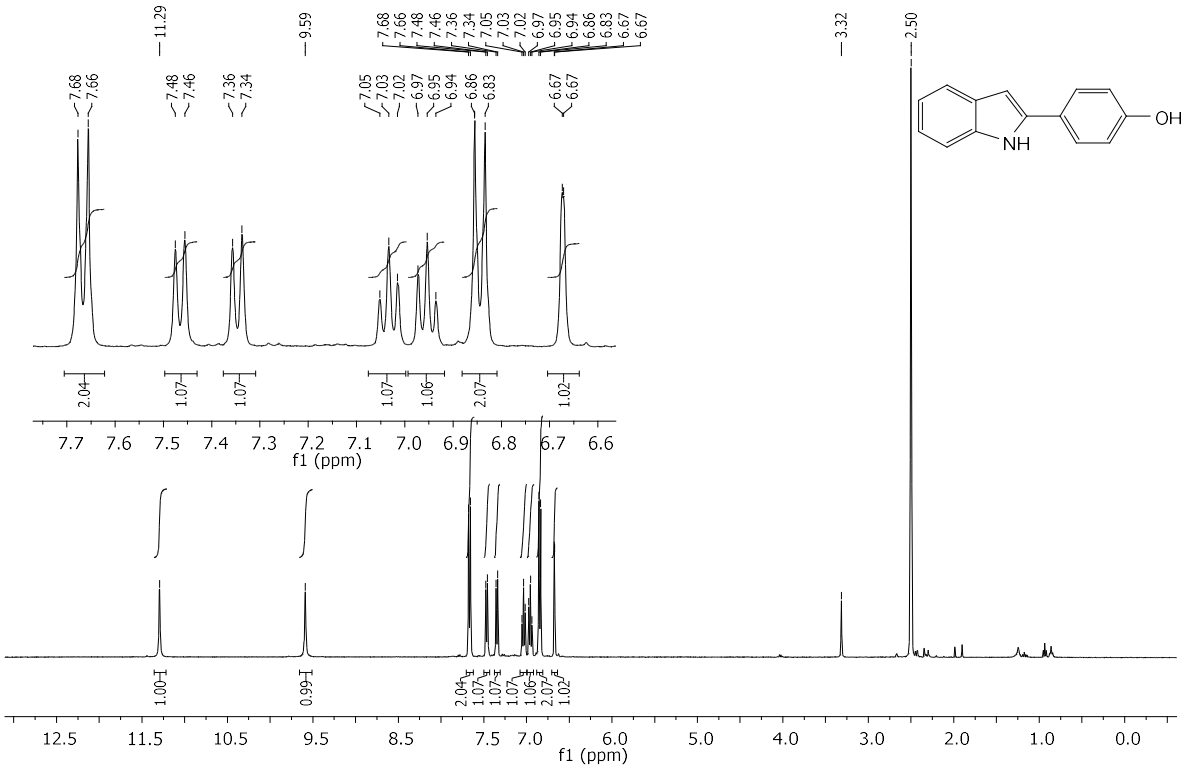


Fig. 146. ^{1}H NMR of **4m** in DMSO-d_6.

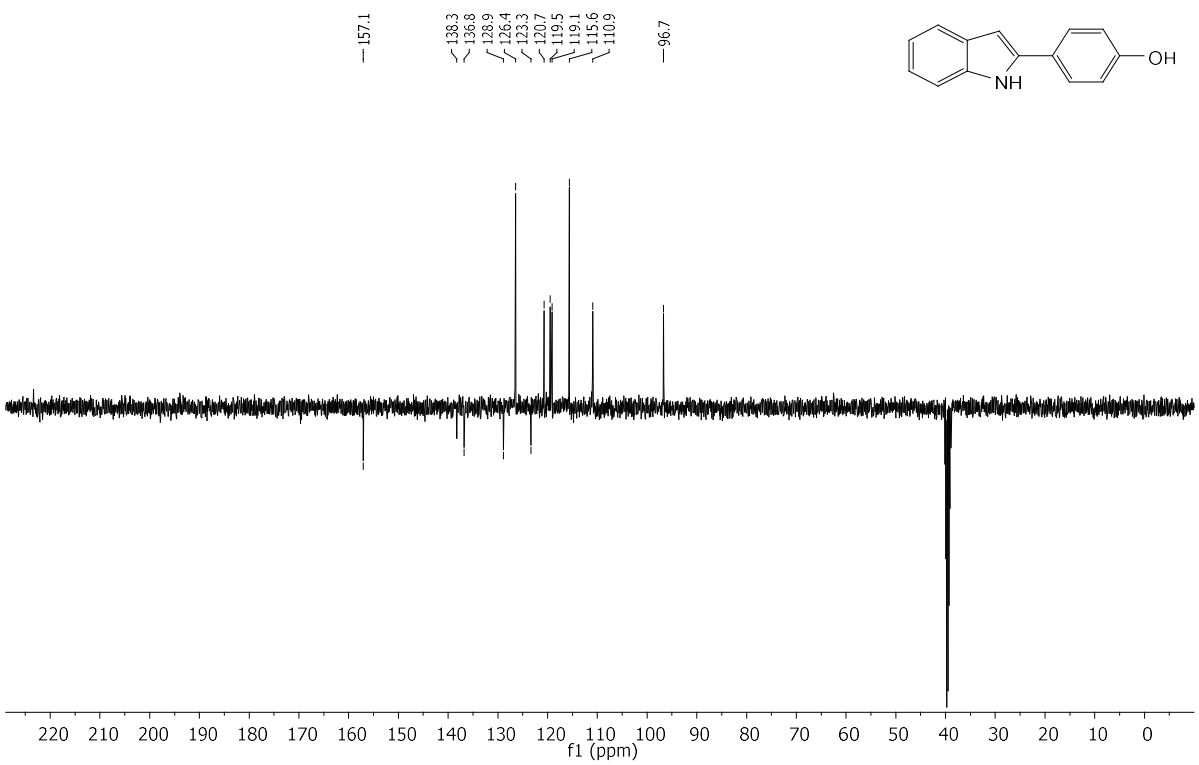


Fig. 147. ^{13}C NMR of **4m** in DMSO-d_6.

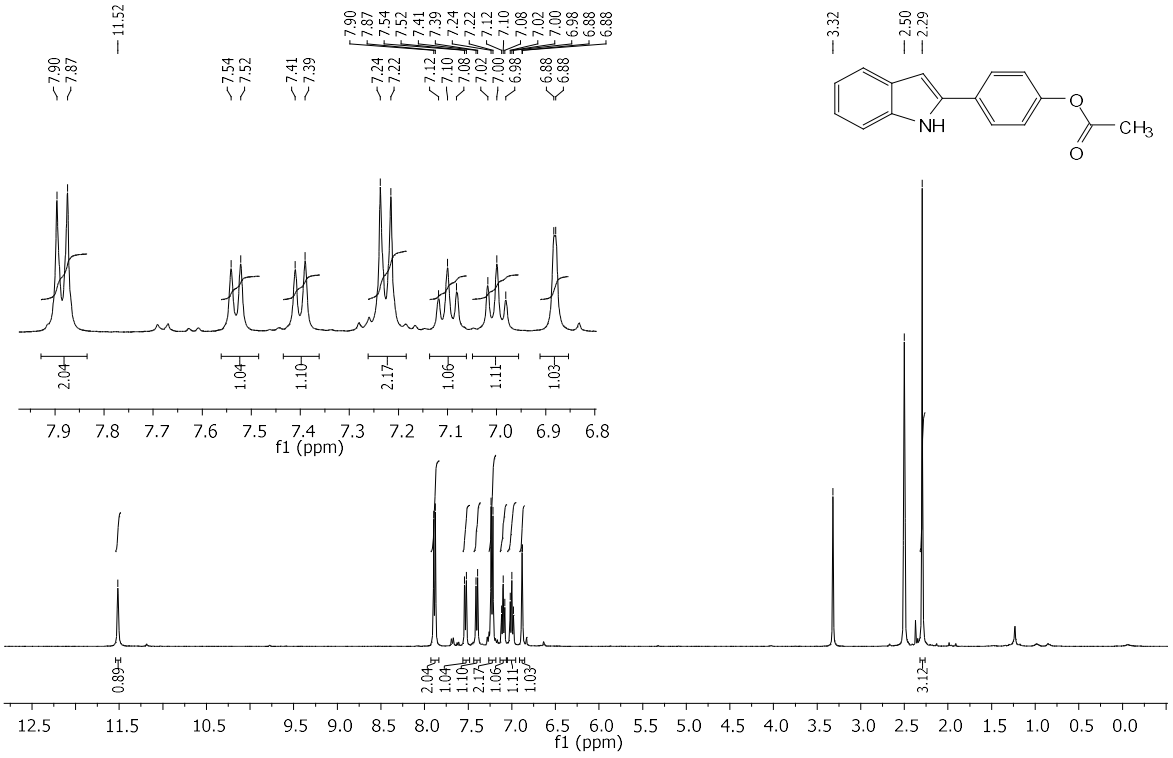


Fig. 148. ^{1}H NMR of **4m'** in DMSO-d_6.

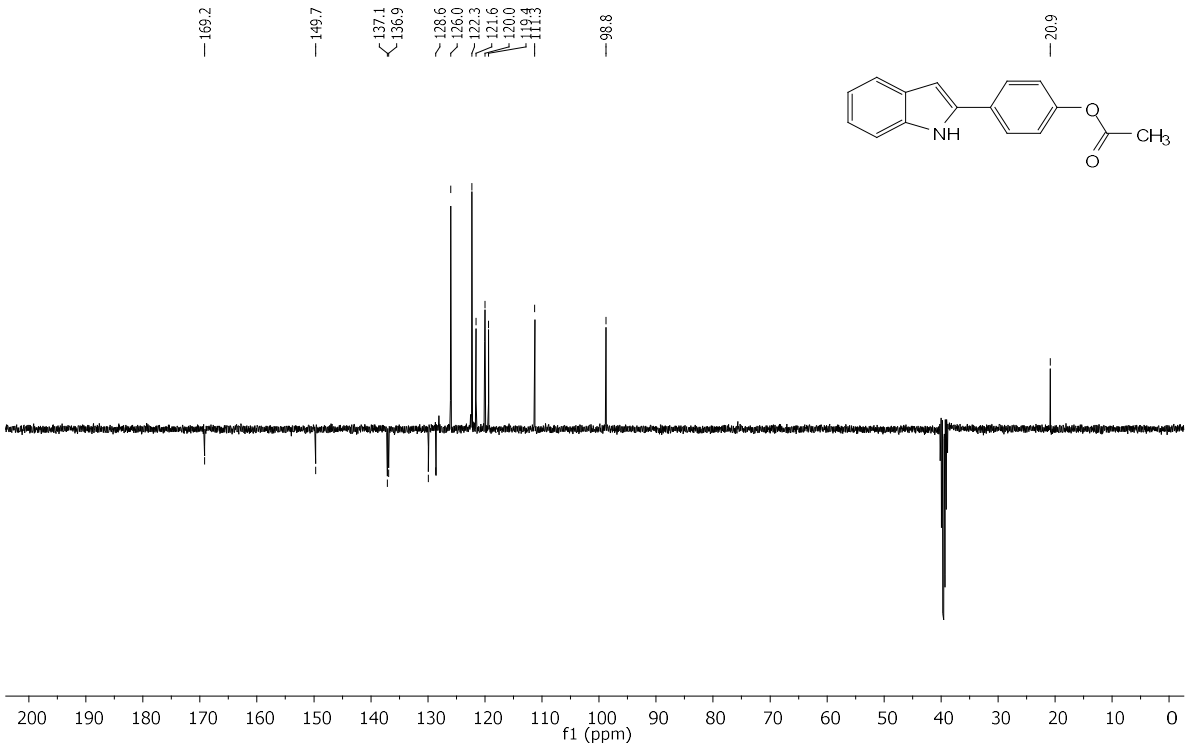


Fig. 149. ^{13}C NMR of **4m'** in DMSO-d_6.

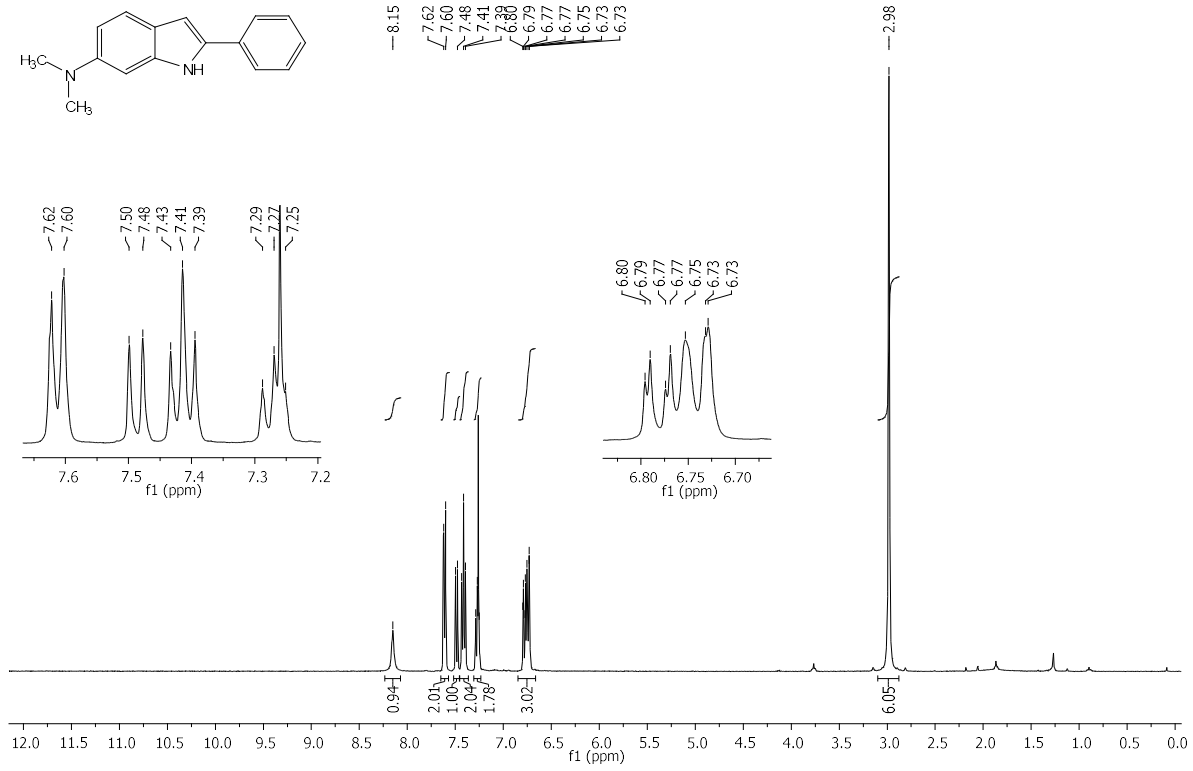


Fig. 150. ^{1}H NMR of **4o** in $CDCl_3$.

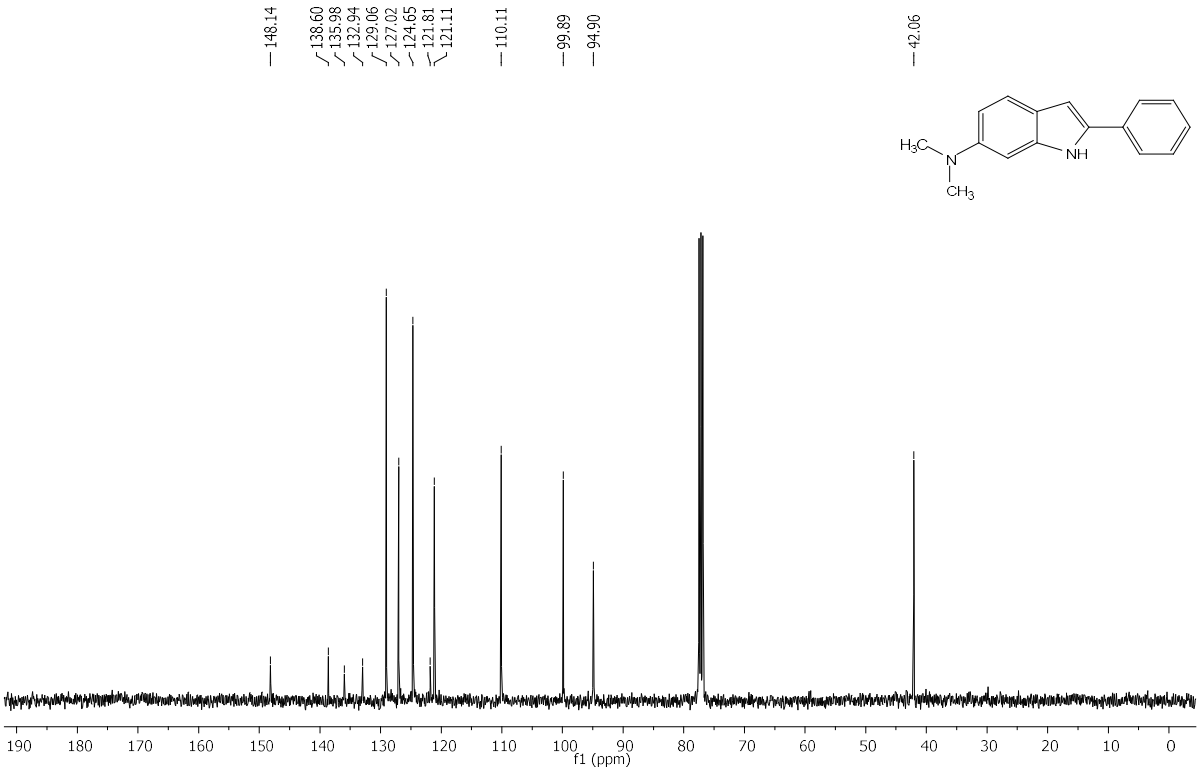


Fig. 151. ^{13}C NMR of **4o** in $CDCl_3$.

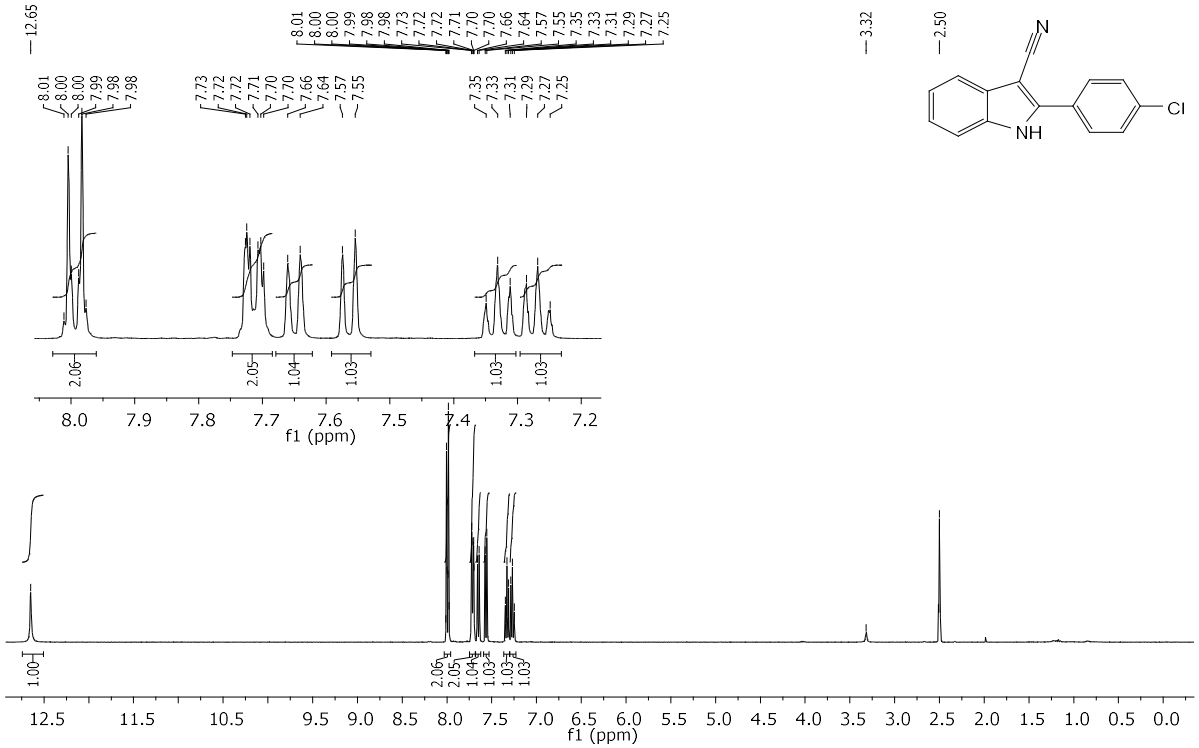


Fig. 152. ^{1}H NMR of **4p** in DMSO-d_6.

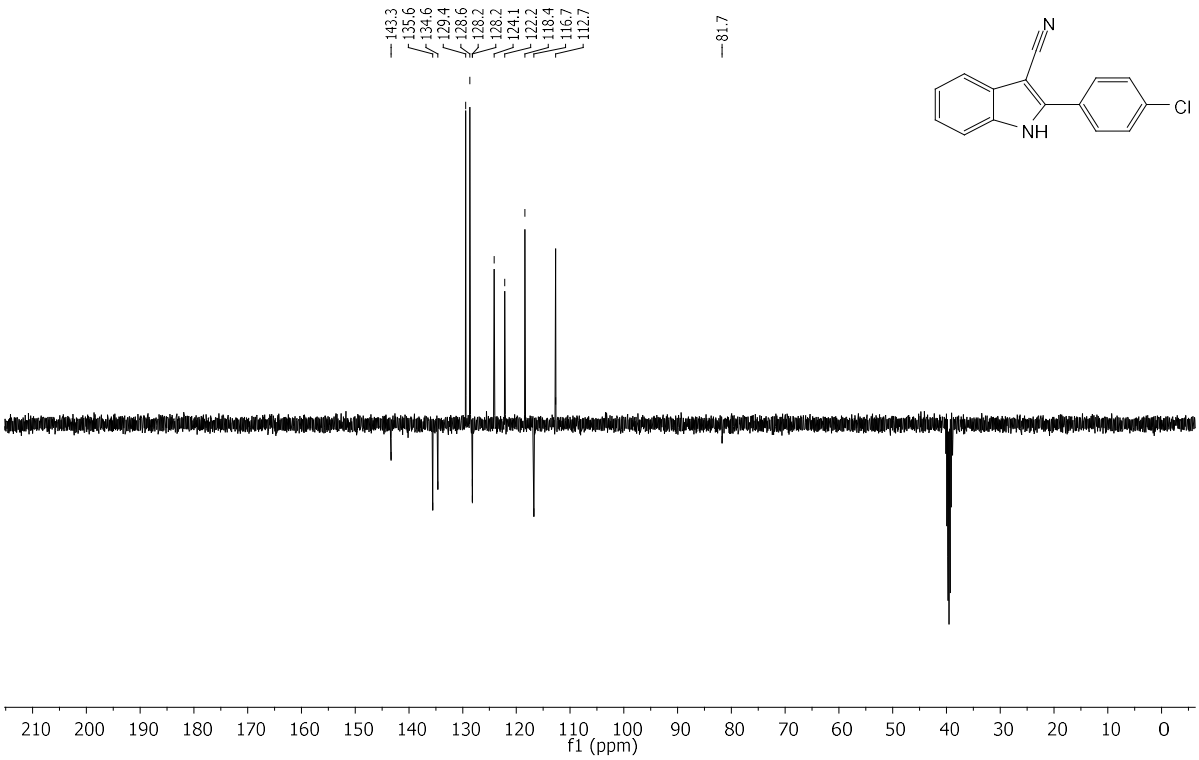


Fig. 153. ^{13}C NMR of **4p** in DMSO-d_6.

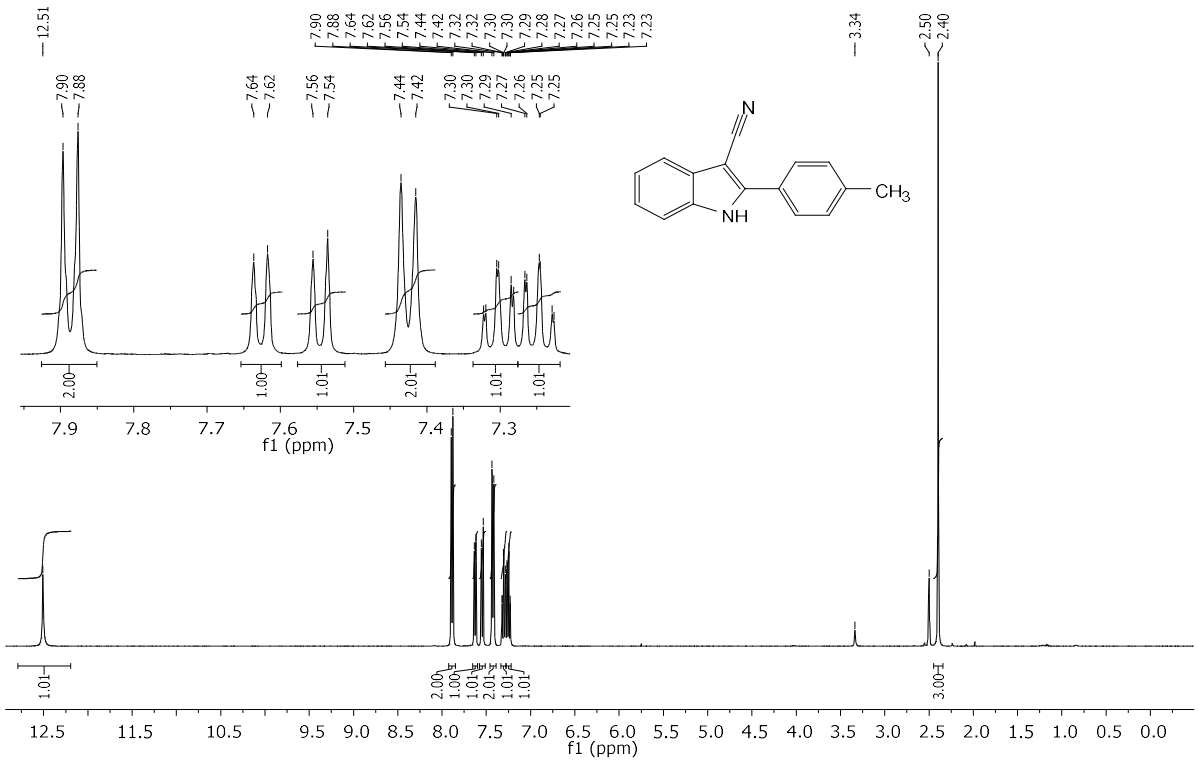


Fig. 154. ^{1}H NMR of **4q** in DMSO-d_6.

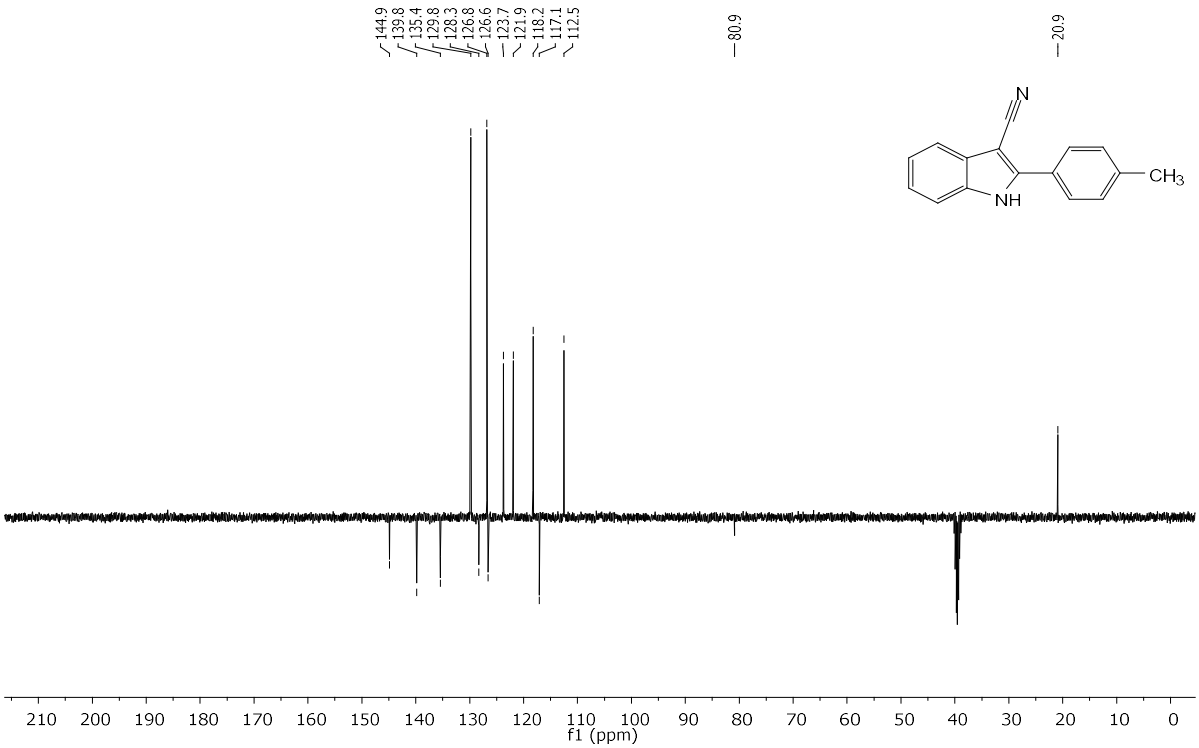


Fig. 155. ^{13}C NMR of **4q** in DMSO-d_6.

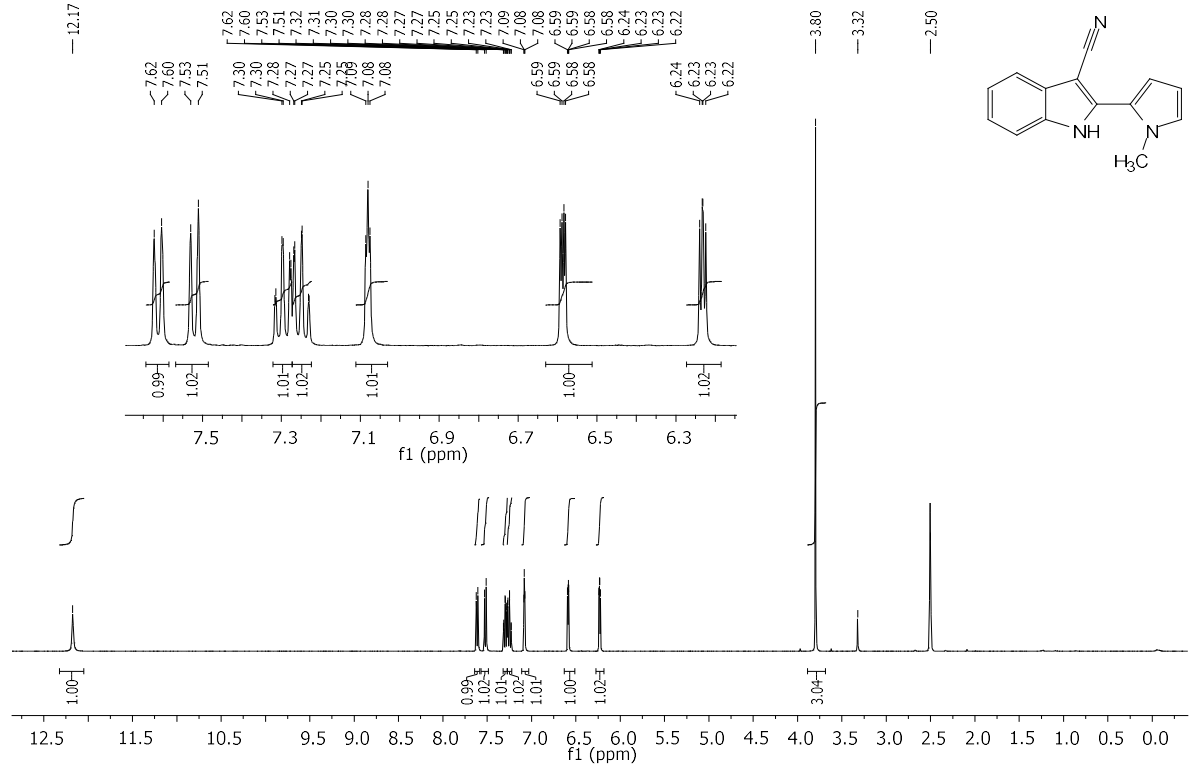


Fig. 156. ^{1}H NMR of **4r** in DMSO-d_6.

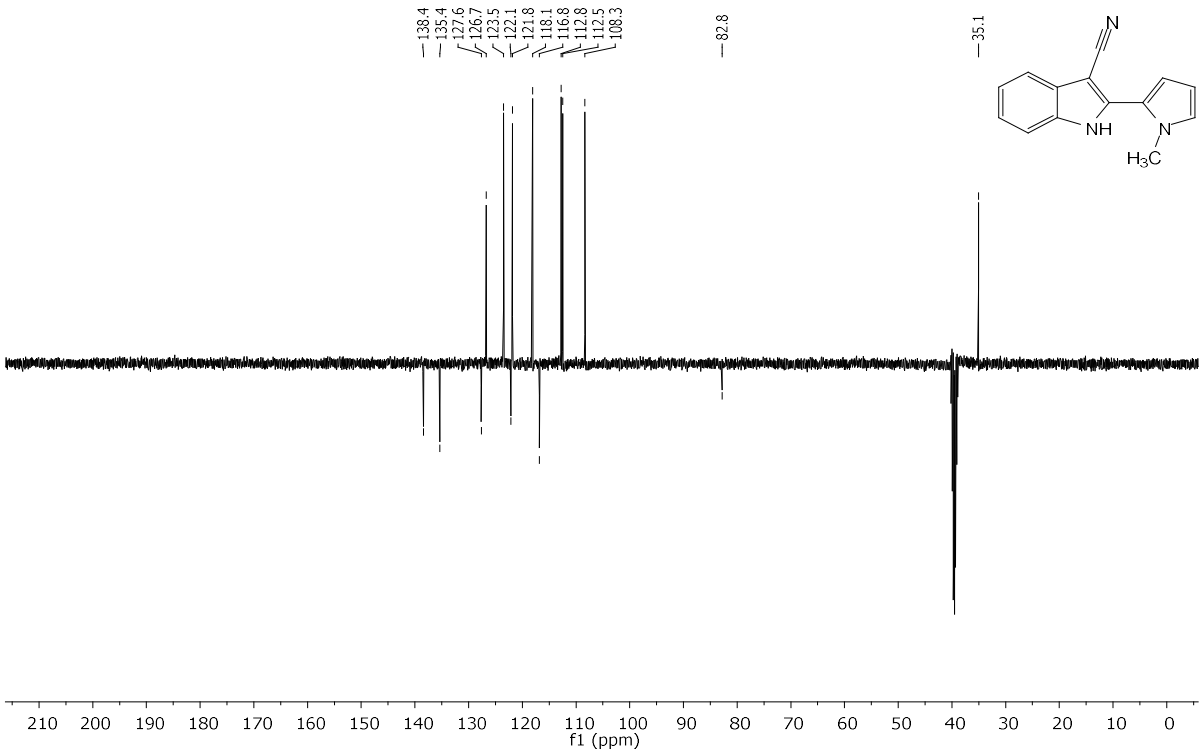


Fig. 157. ^{13}C NMR of **4r** in DMSO-d_6.

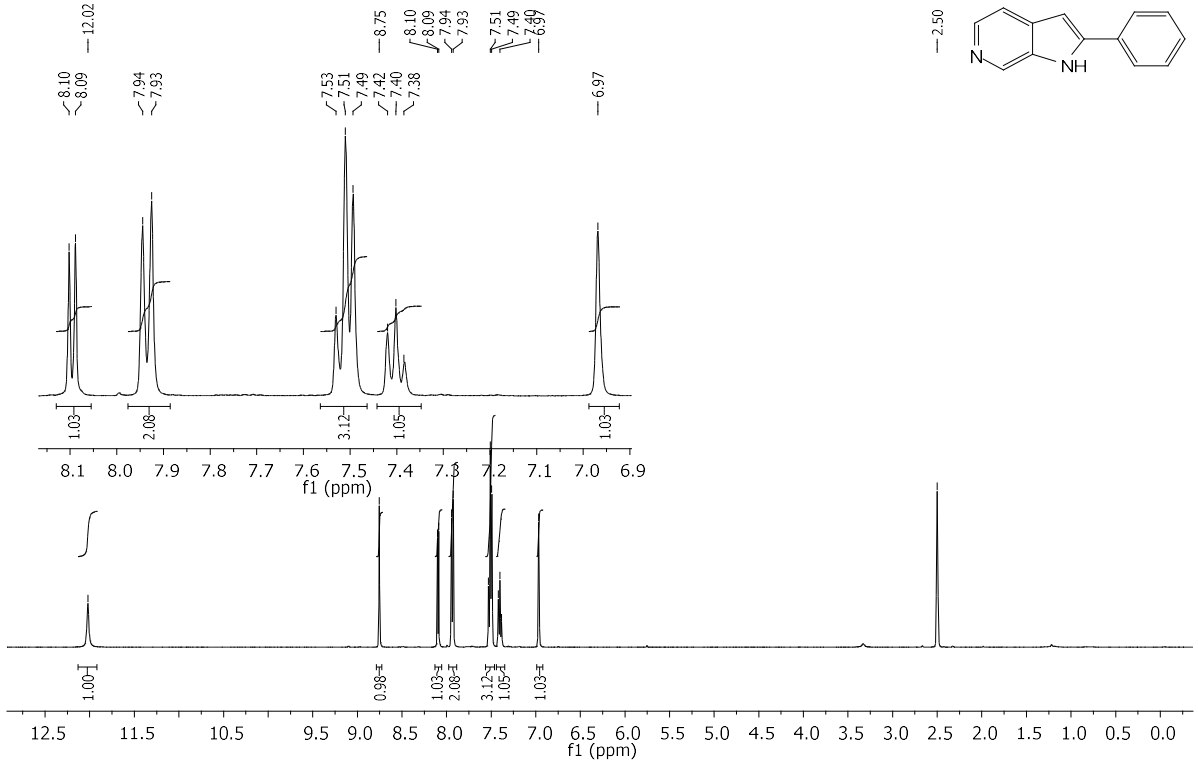


Fig. 158. ^{1}H NMR of **4s** in DMSO-d_6.

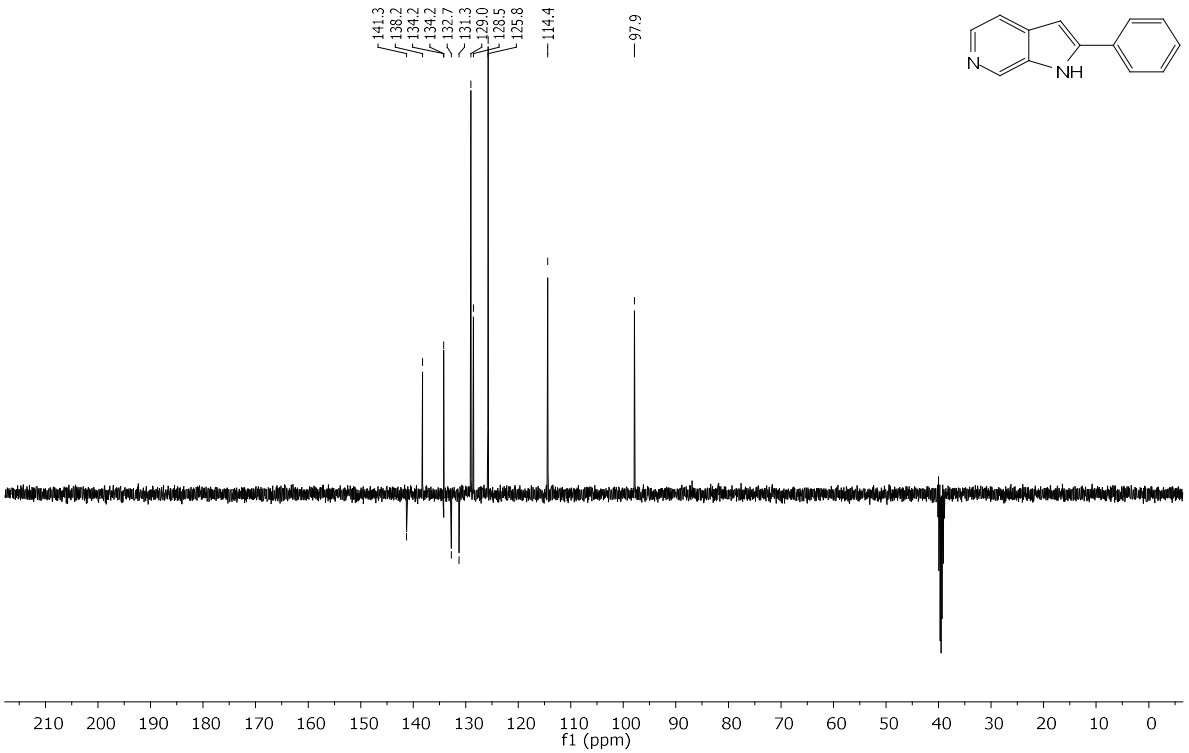


Fig. 159. ^{13}C NMR of **4s** in DMSO-d_6.

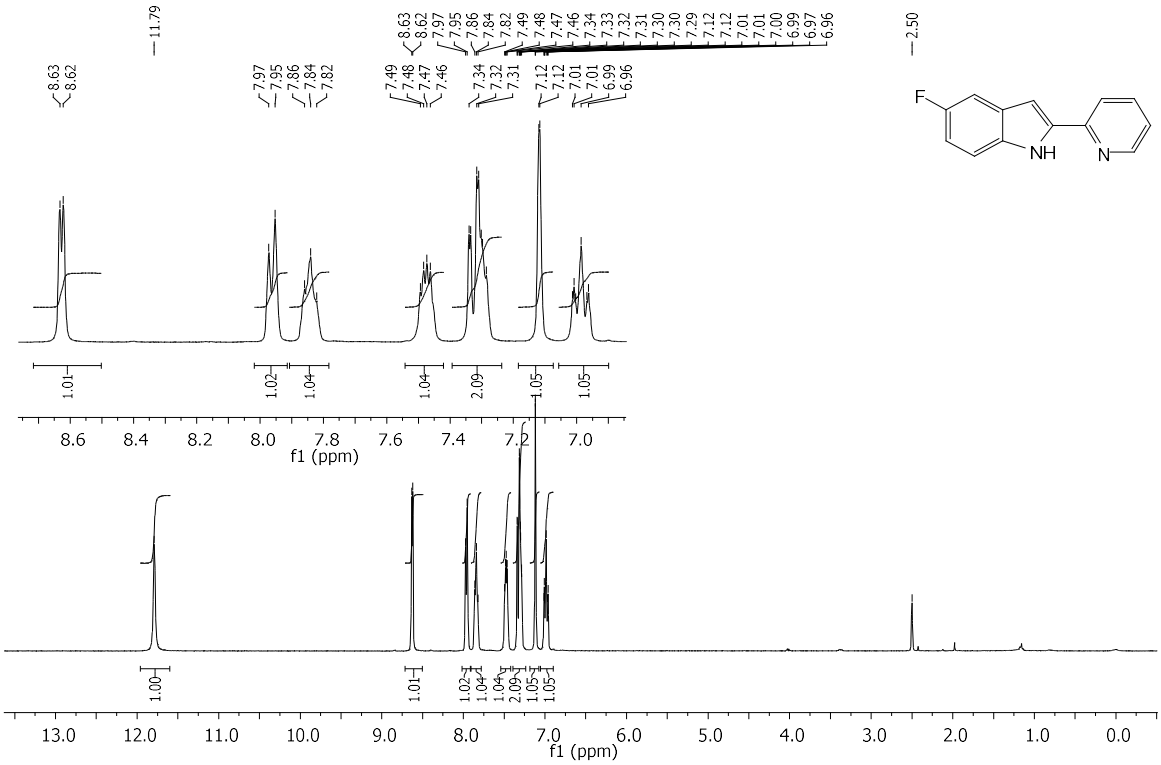


Fig. 160. ^{1}H NMR of **4t** in DMSO-d_6.

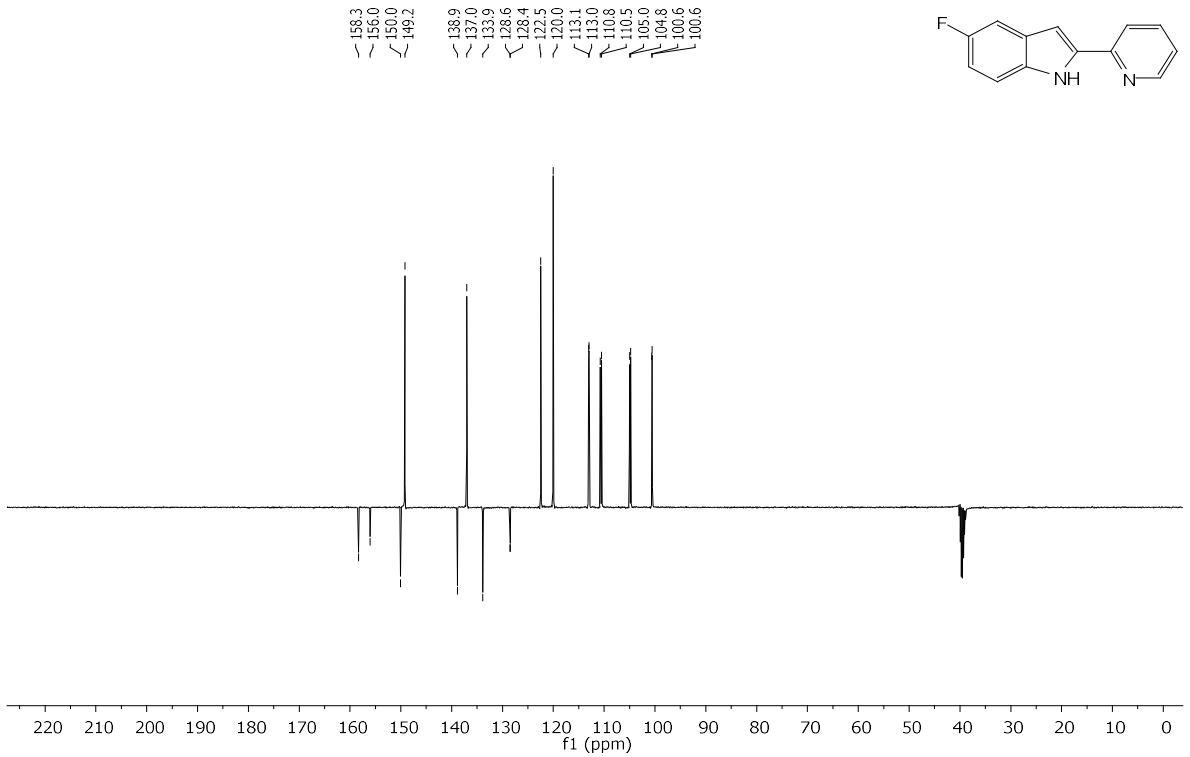


Fig. 161. ^{13}C NMR of **4t** in DMSO-d_6.

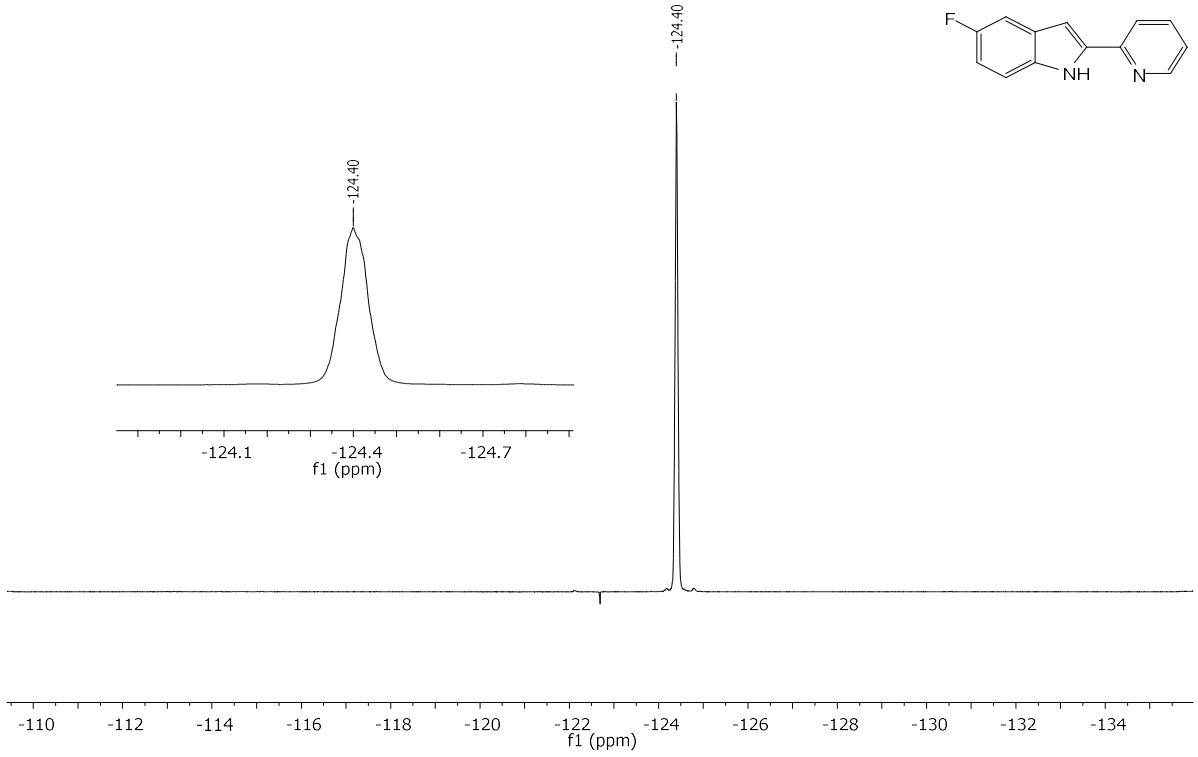


Fig. 162. ^{19}F NMR of **4t** in DMSO-d_6.

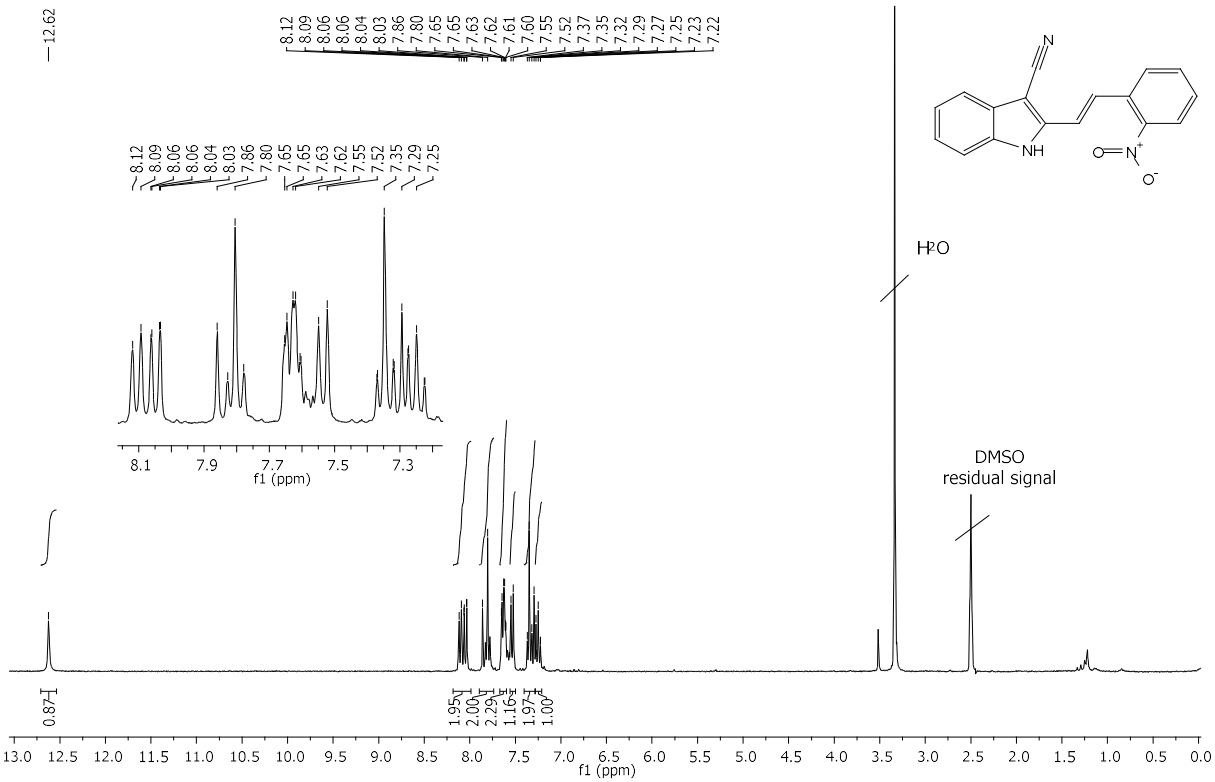


Fig. 163. ^{1}H NMR of **4u'** in DMSO-d_6.

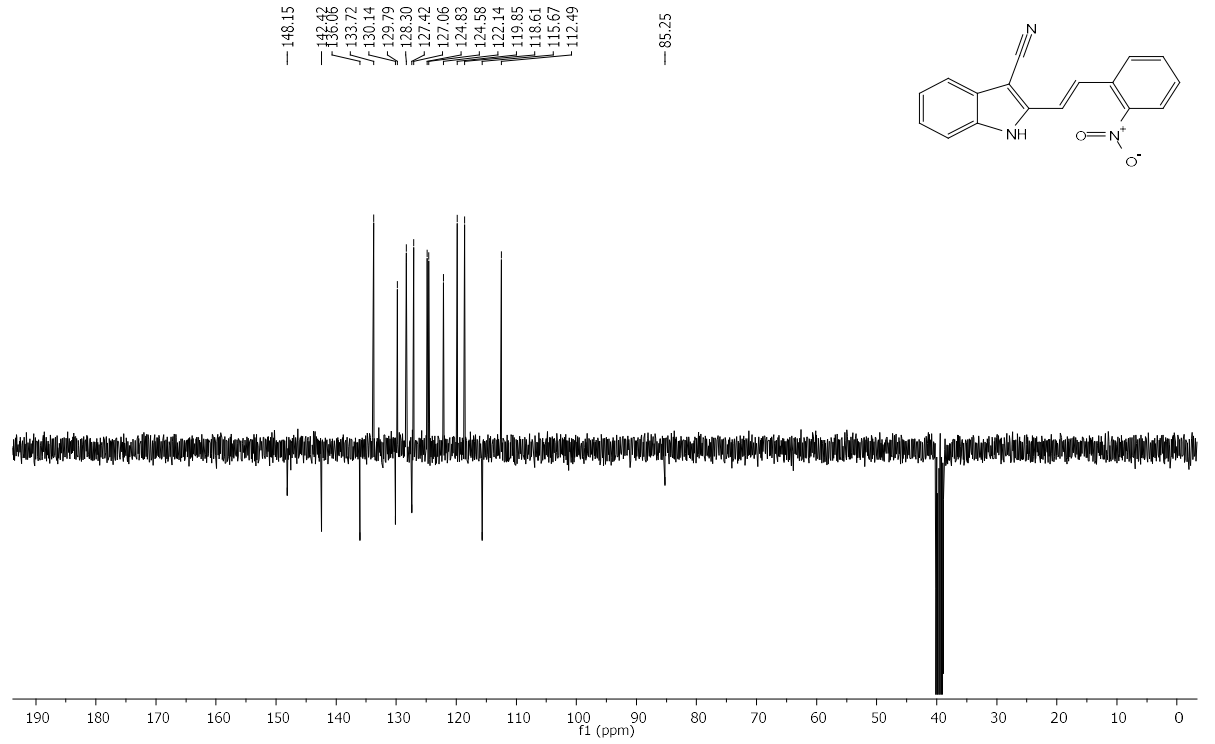


Fig. 164. ^{13}C NMR of **4u'** in DMSO-d_6.

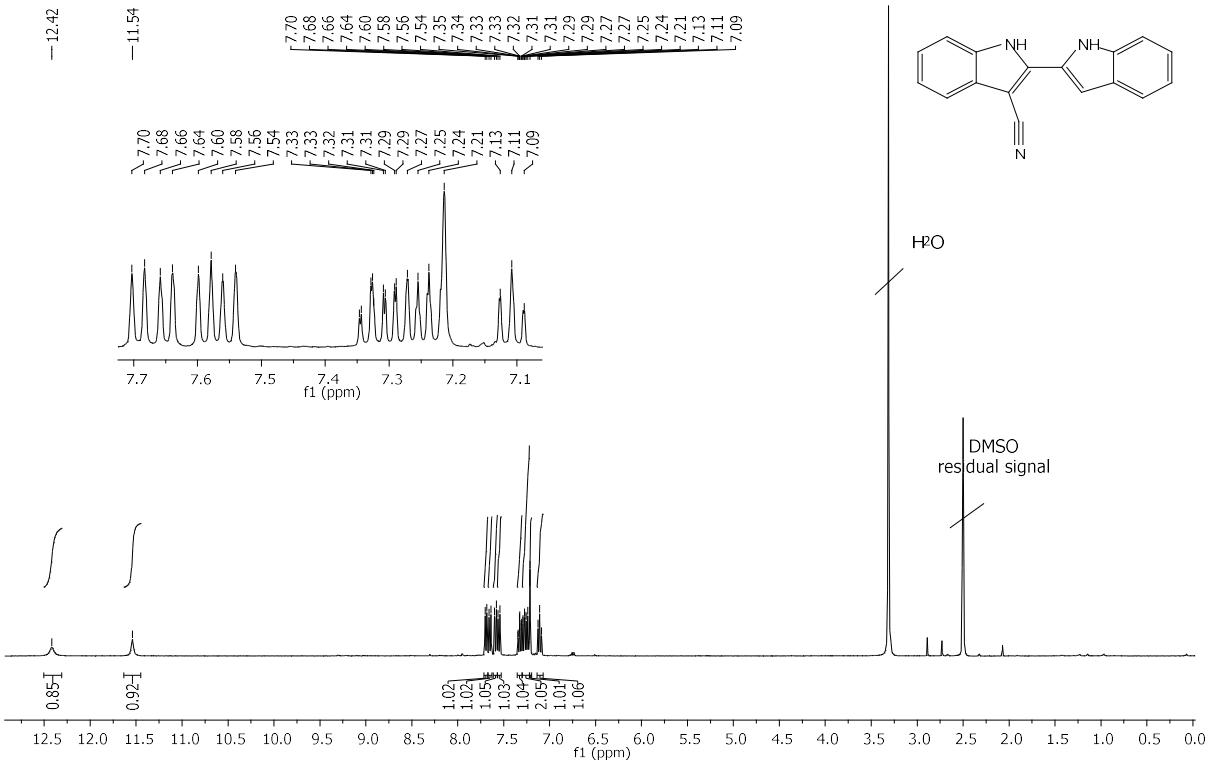


Fig. 165. ^{1}H NMR of **4u''** in DMSO-d_6.

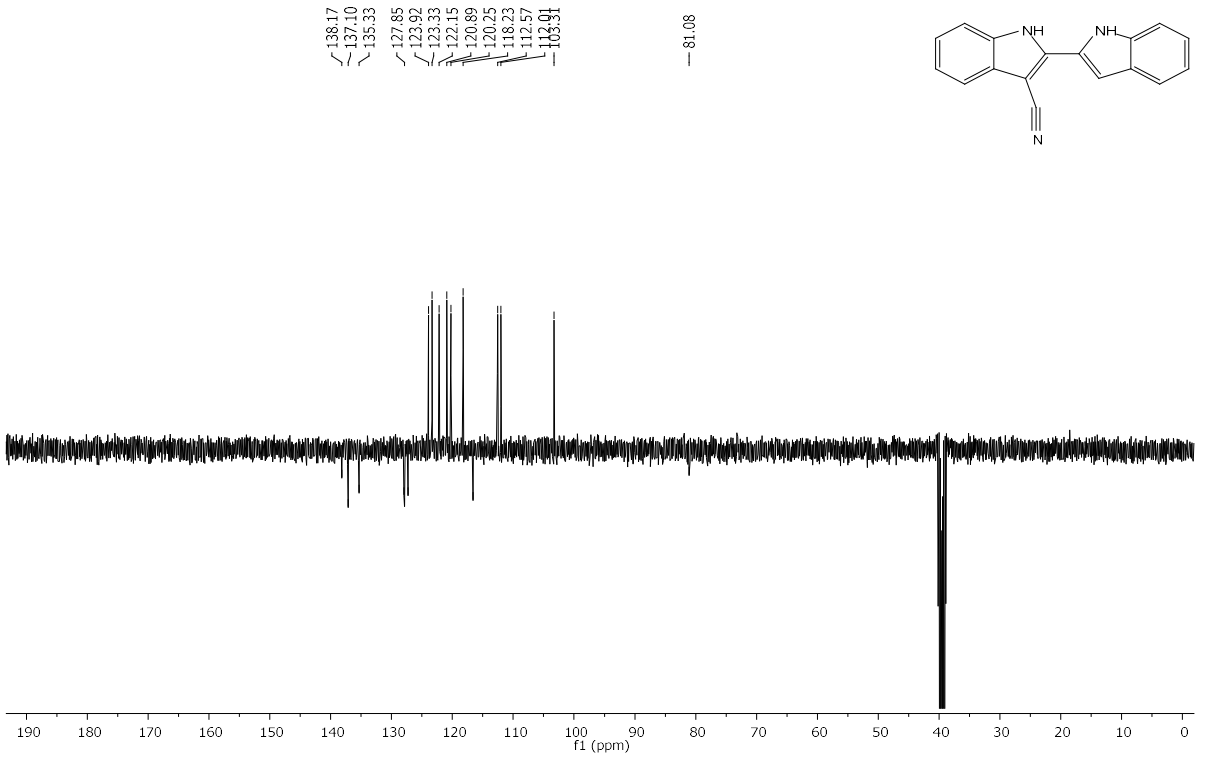


Fig. 166. ^{13}C NMR of **4u''** in DMSO-d_6.

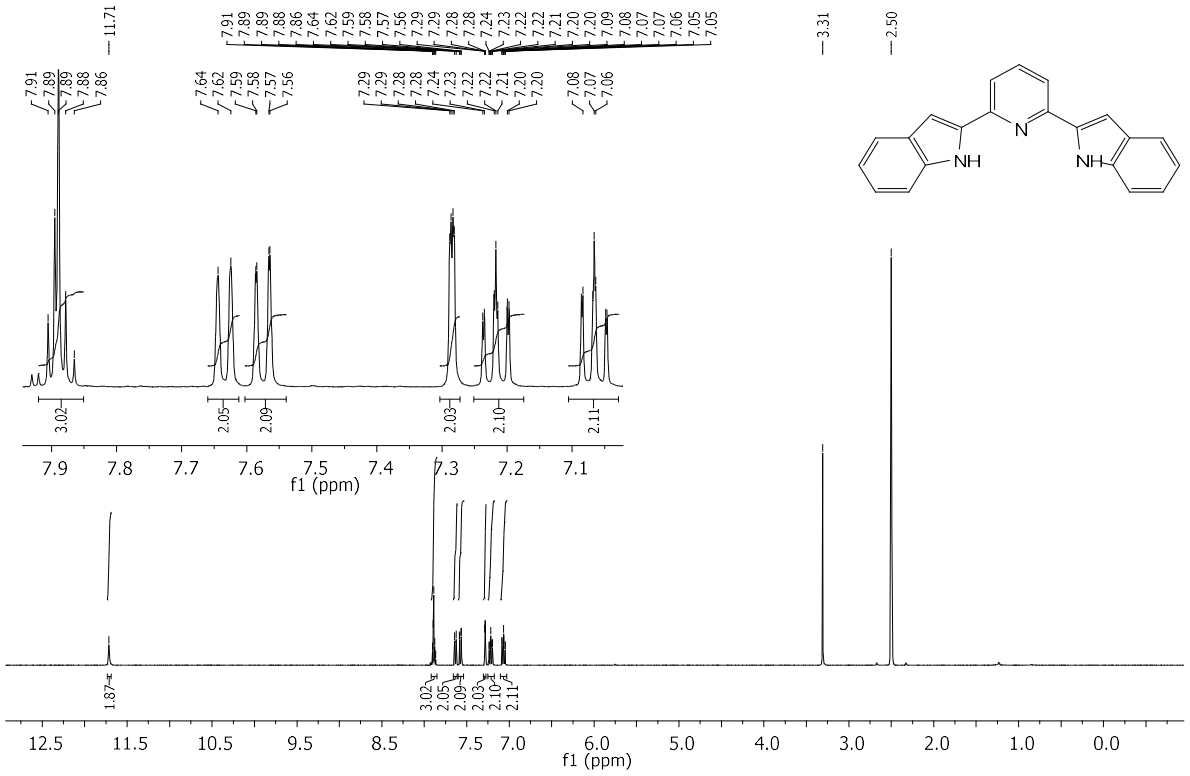


Fig. 167. ^{1}H NMR of **4v** in DMSO-d_6.

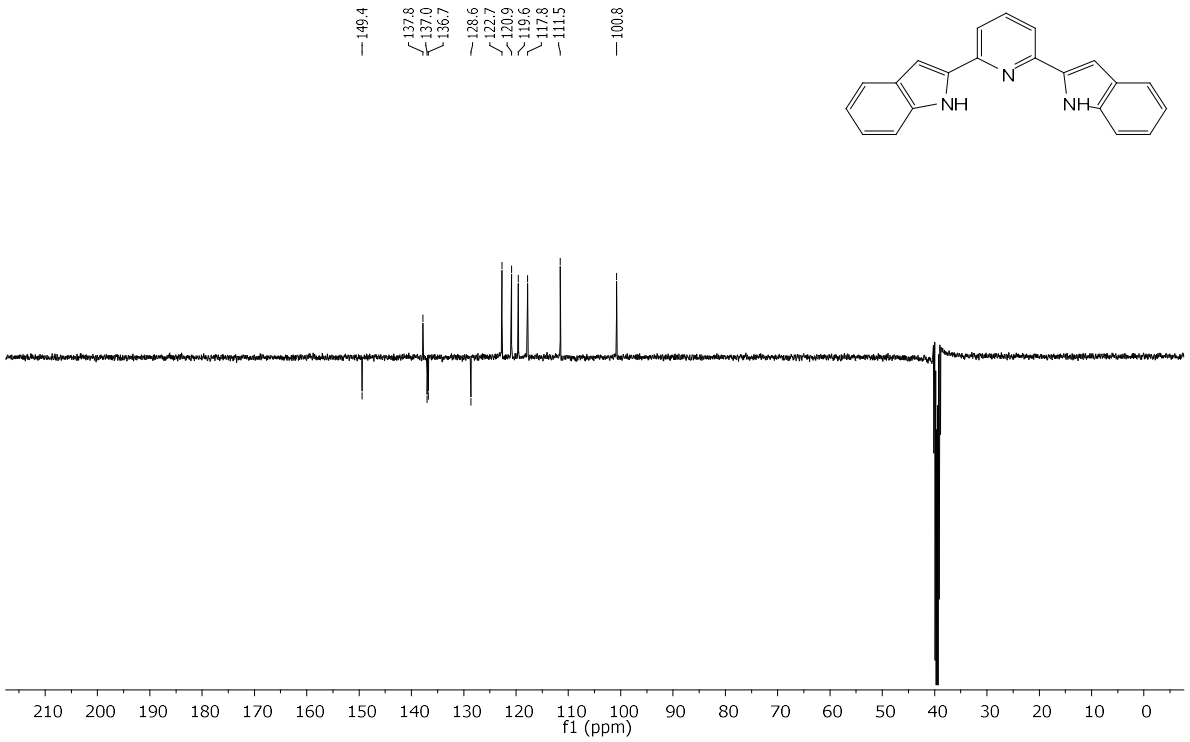


Fig. 168. ^{13}C NMR of **4v** in DMSO-d_6.

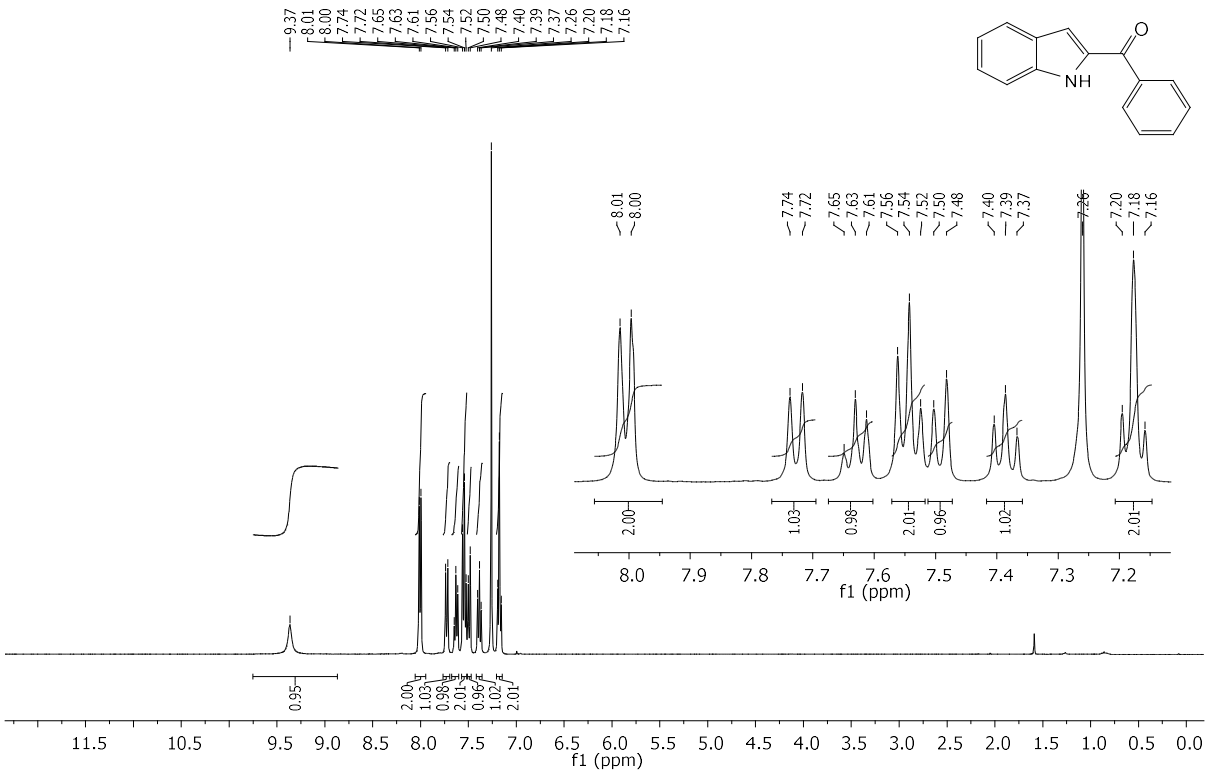


Fig. 169. ^{1}H NMR of **4w** in $CDCl_3$.

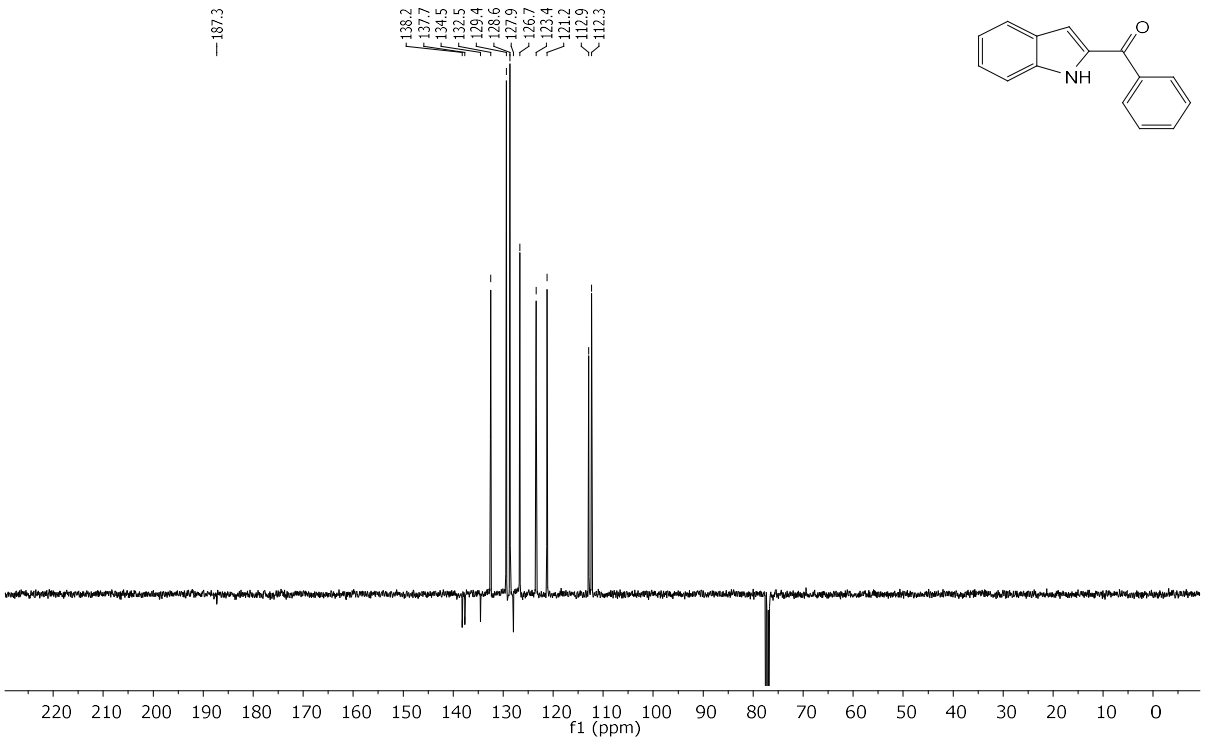


Fig. 170. ^{13}C NMR of **4w** in $CDCl_3$.

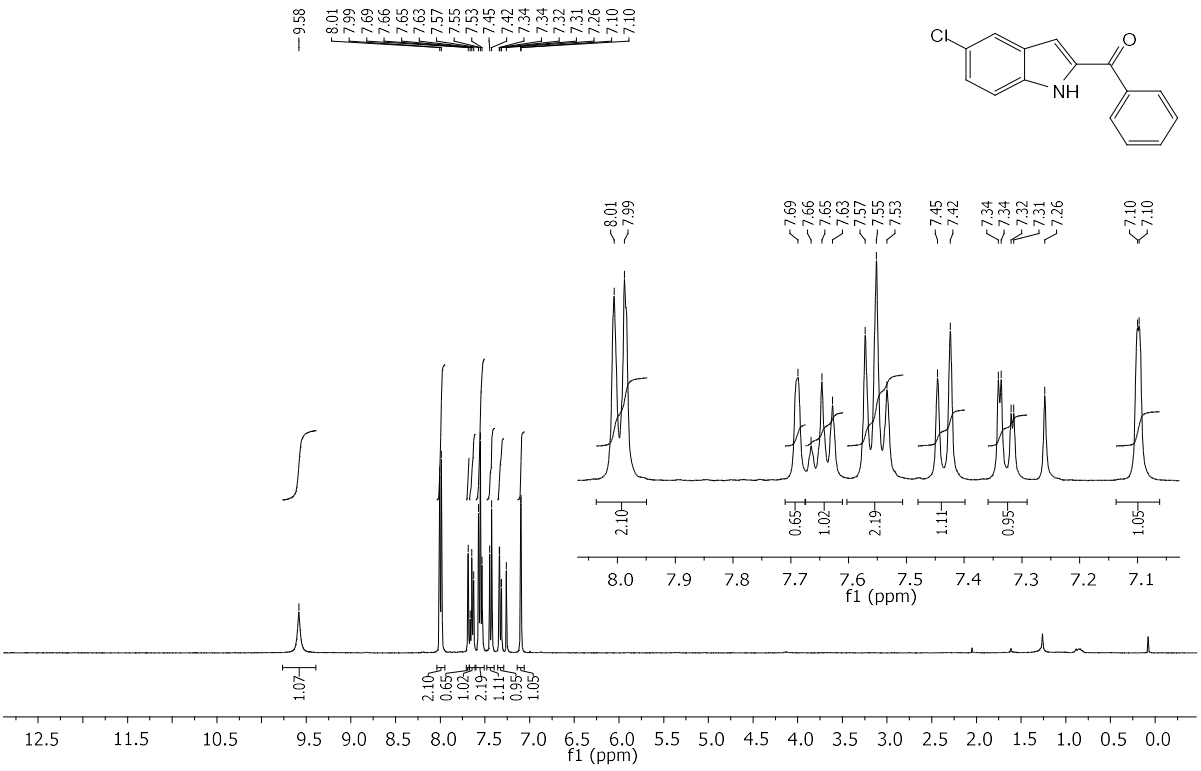


Fig. 171. ^{1}H NMR of **4x** in $CDCl_3$.

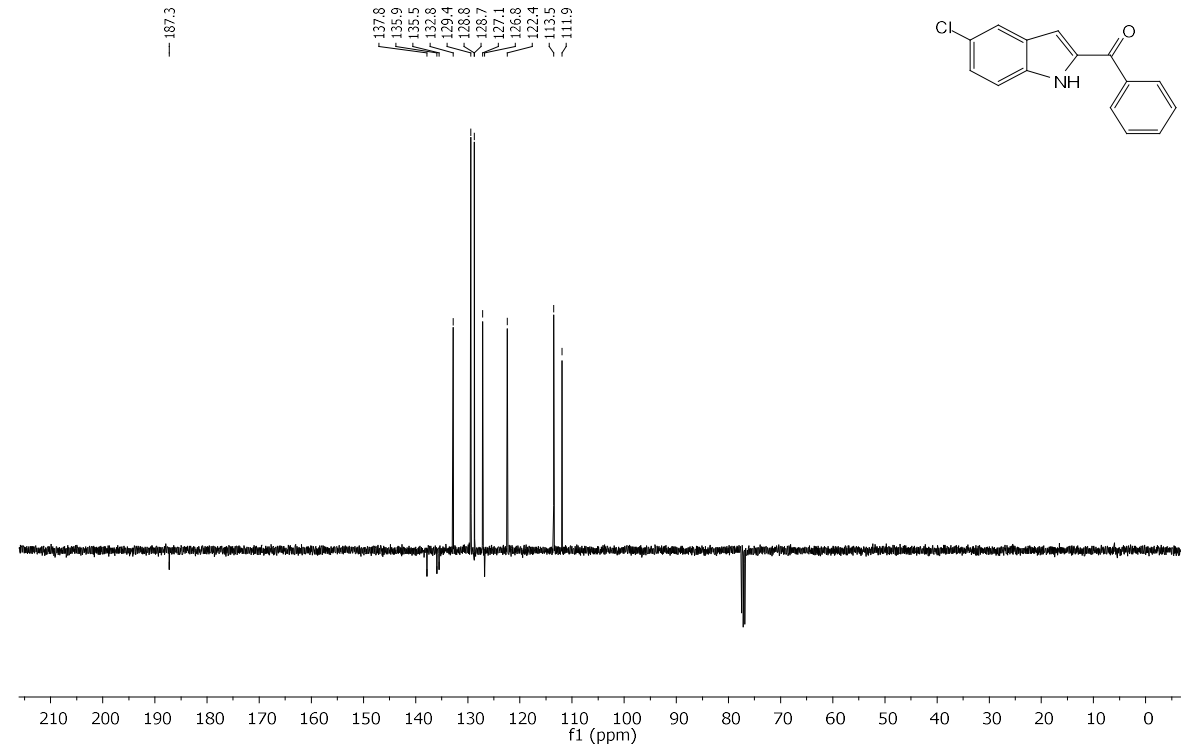


Fig. 172. ^{13}C NMR of **4x** in $CDCl_3$.

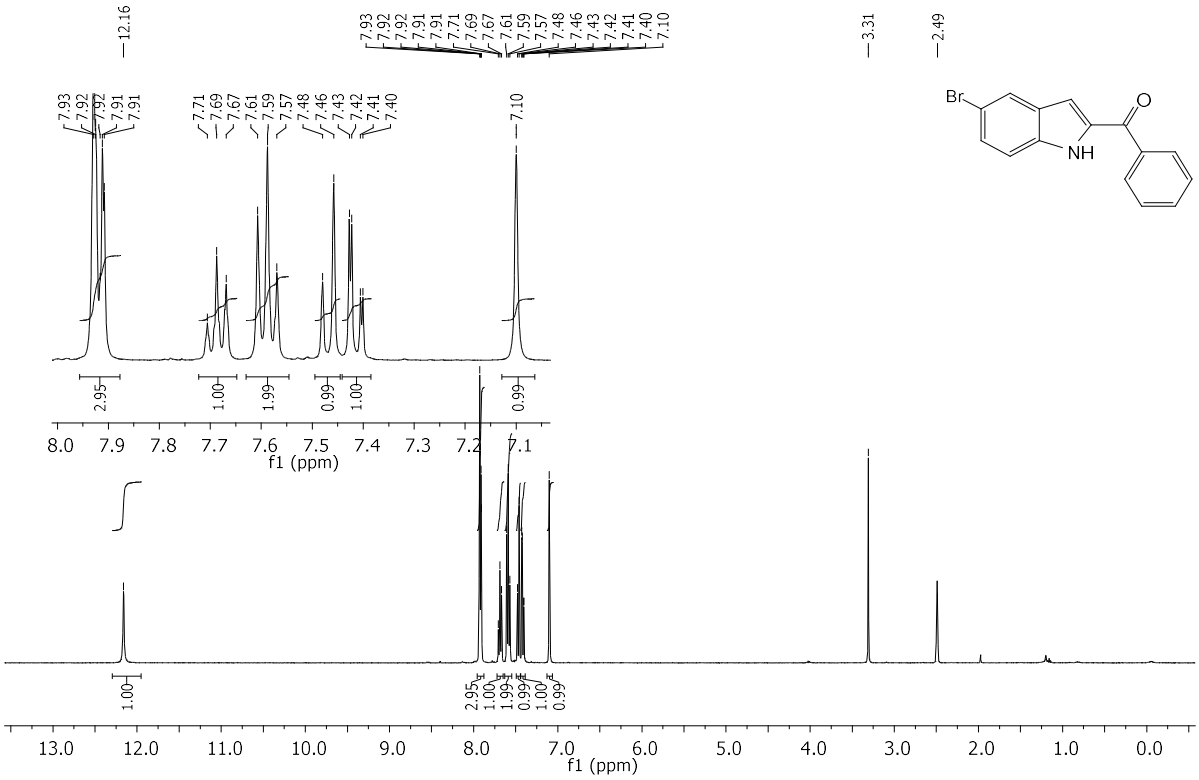


Fig. 173. ^{1}H NMR of **4y** in $CDCl_3$.

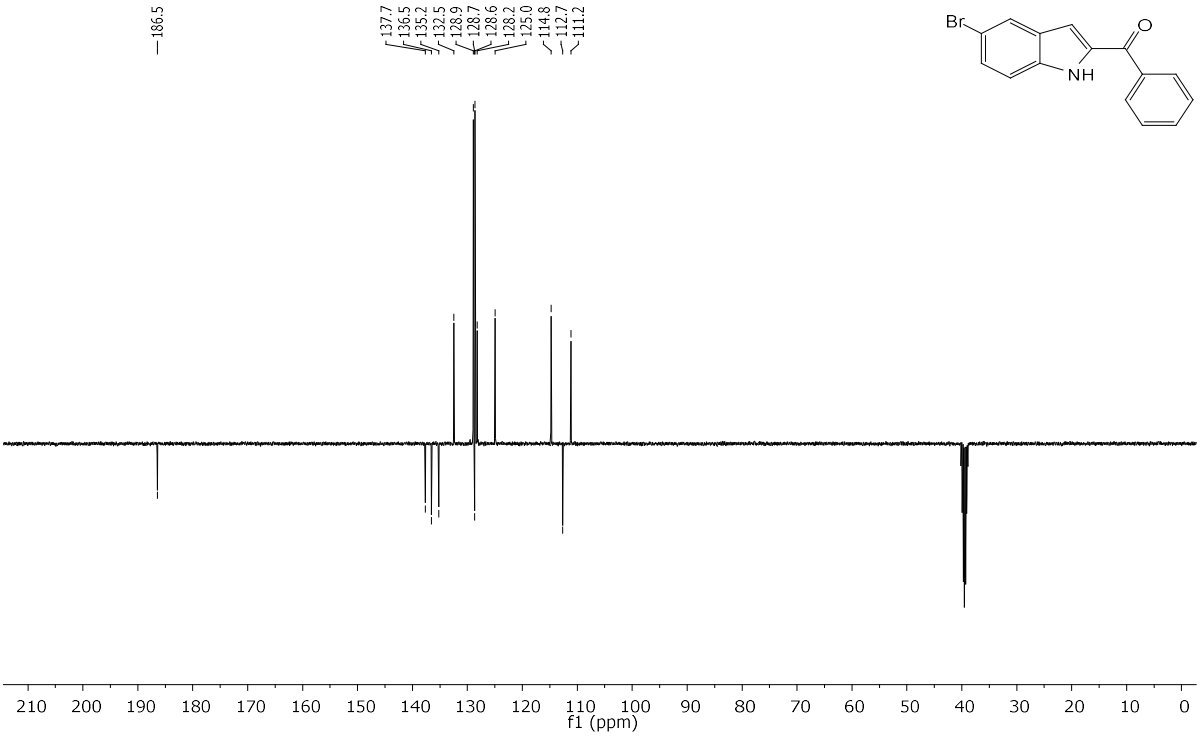


Fig. 174. ^{13}C NMR of **4y** in $CDCl_3$.

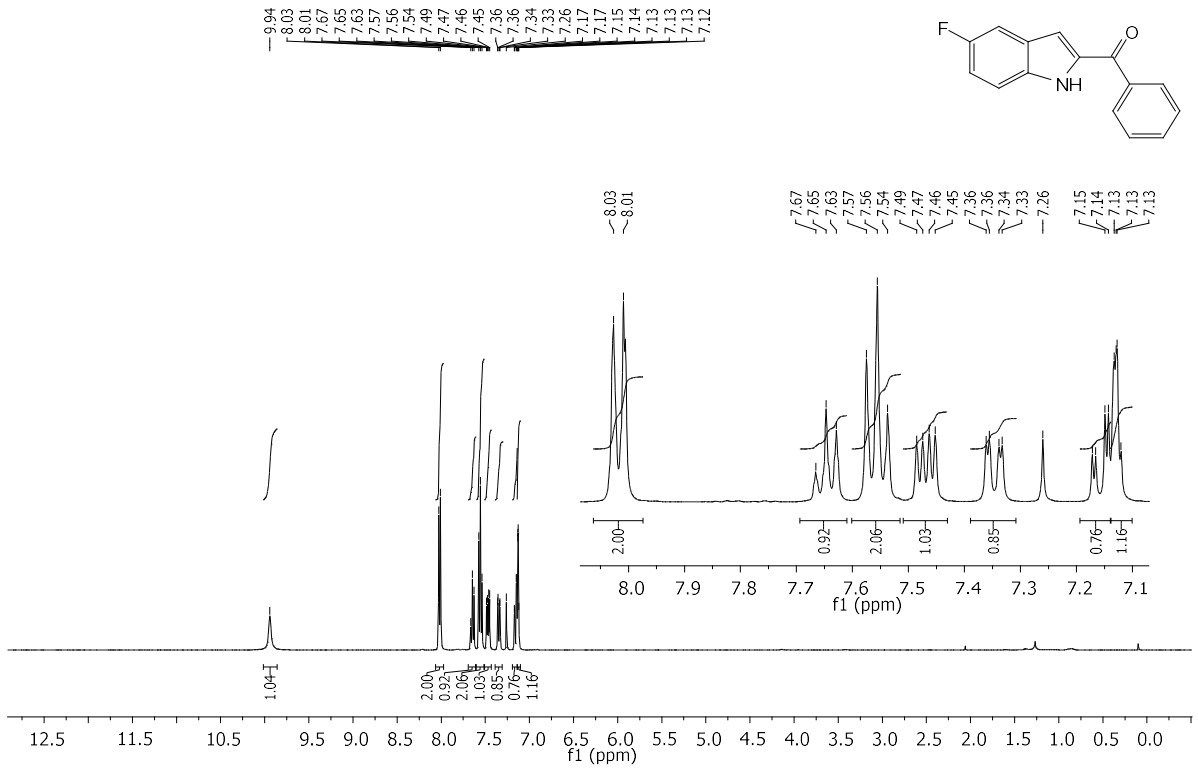


Fig. 175. ^{1}H NMR of **4z** in $CDCl_3$.

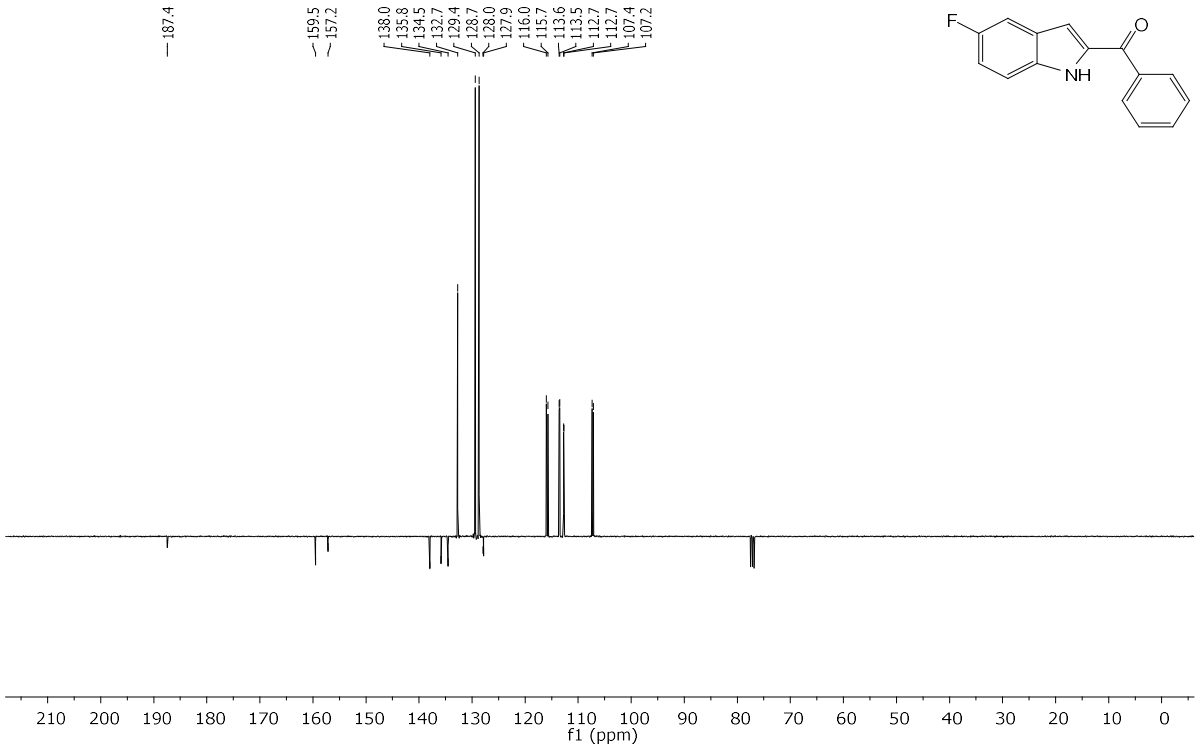


Fig. 176. ^{13}C NMR of **4z** in $CDCl_3$.

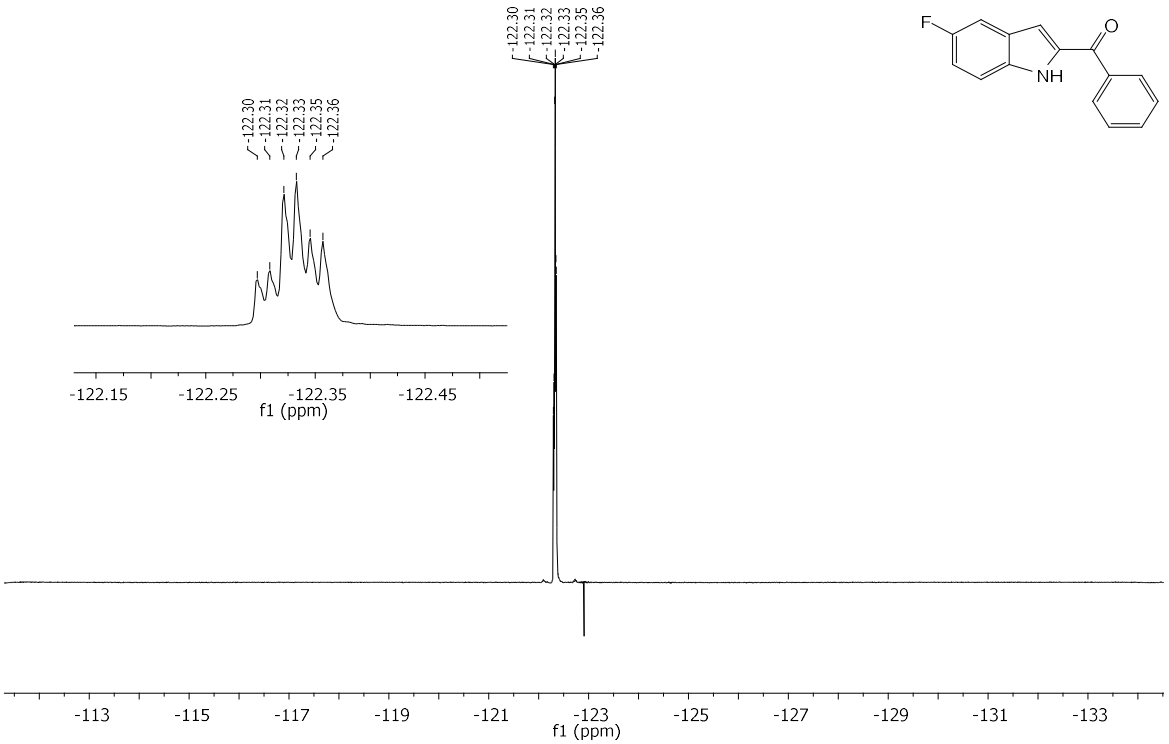


Fig. 177. ^{19}F NMR of **4z** in $CDCl_3$.

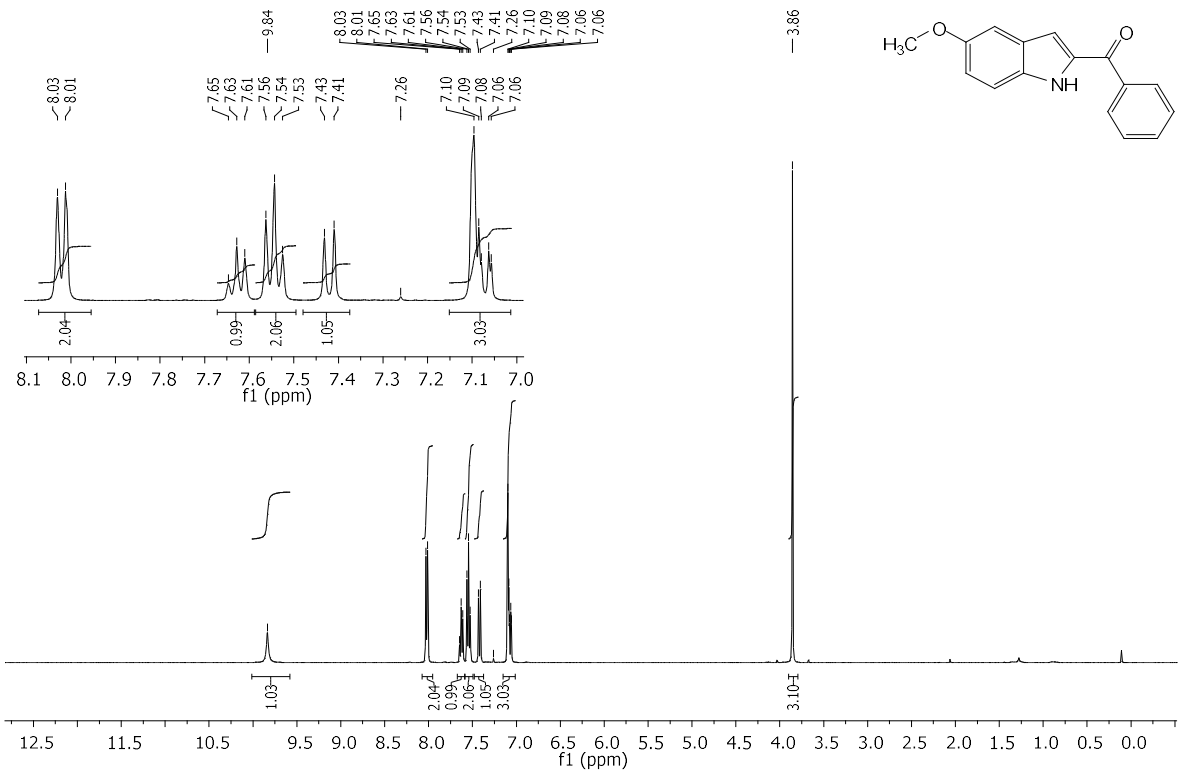


Fig. 178. ^{1}H NMR of **4aa** in $CDCl_3$.

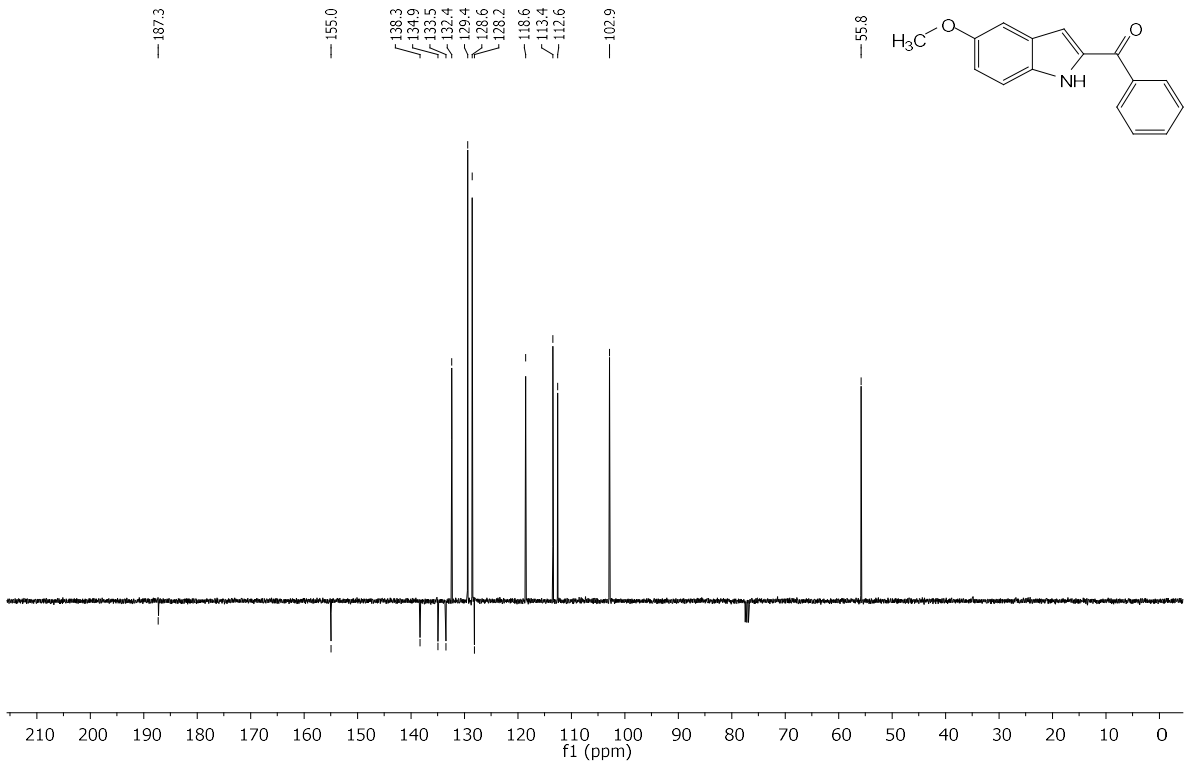


Fig. 179. ^{13}C NMR of **4aa** in $CDCl_3$.

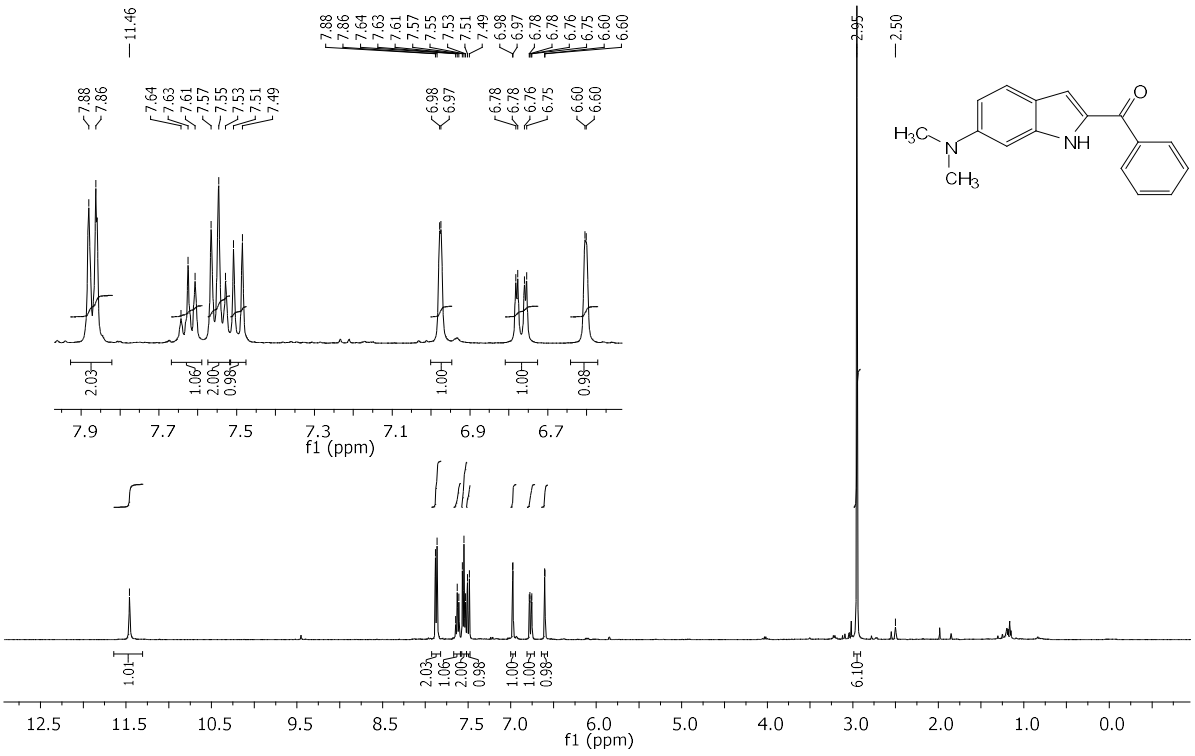


Fig. 180. ^{1}H NMR of **4ab** in DMSO-d_6.

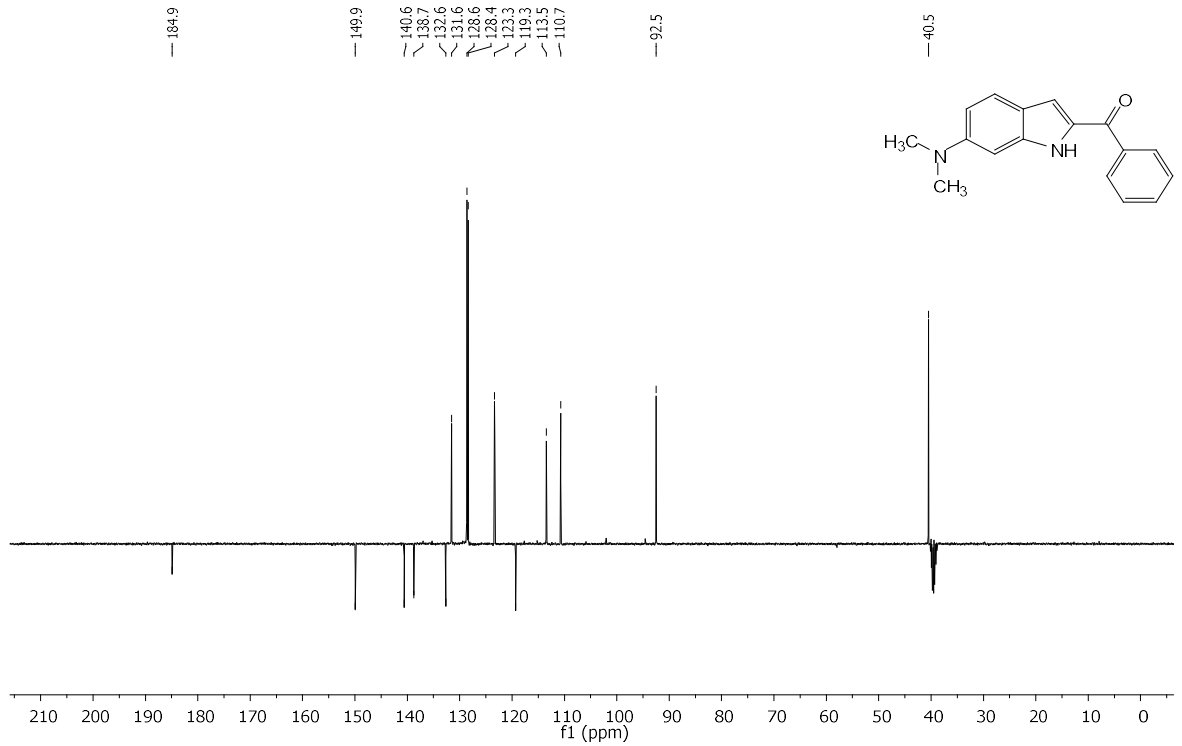


Fig. 181. ^{13}C NMR of **4ab** in DMSO-d_6.

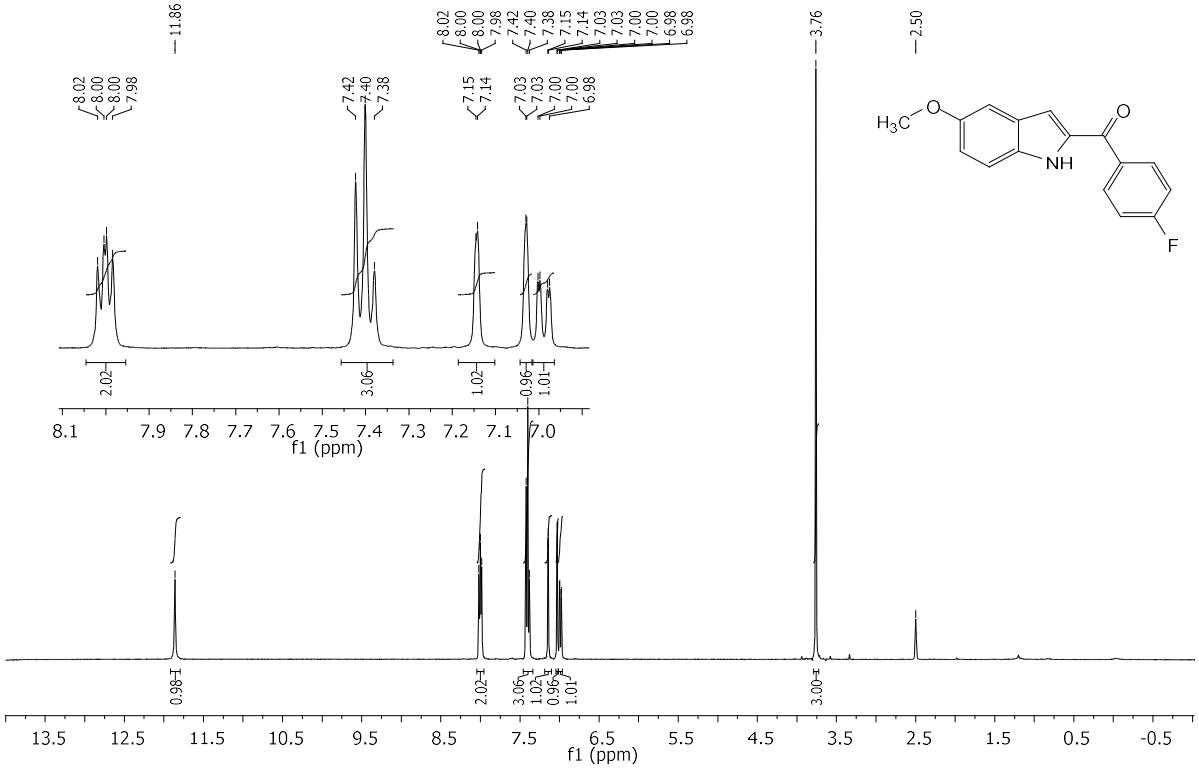


Fig. 182. ^{1}H NMR of **4ac** in DMSO-d_6.

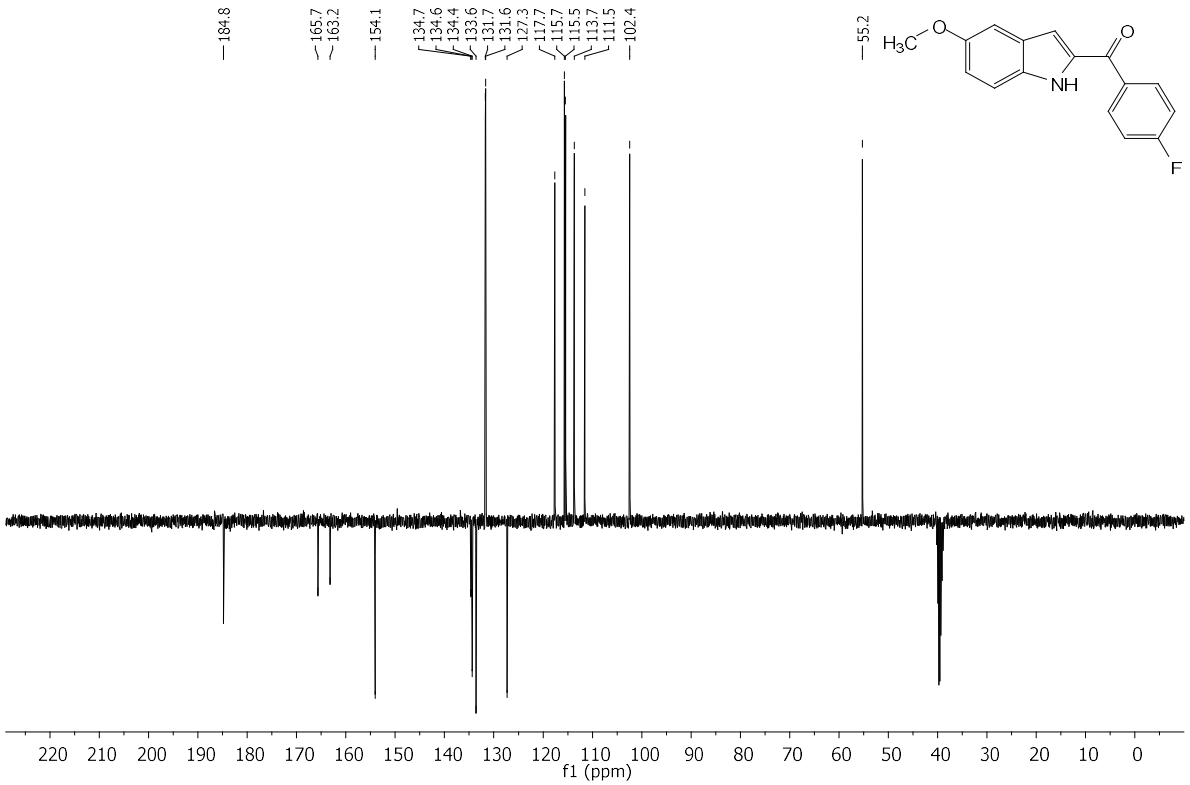


Fig. 183. ^{13}C NMR of **4ac** in DMSO-d_6.

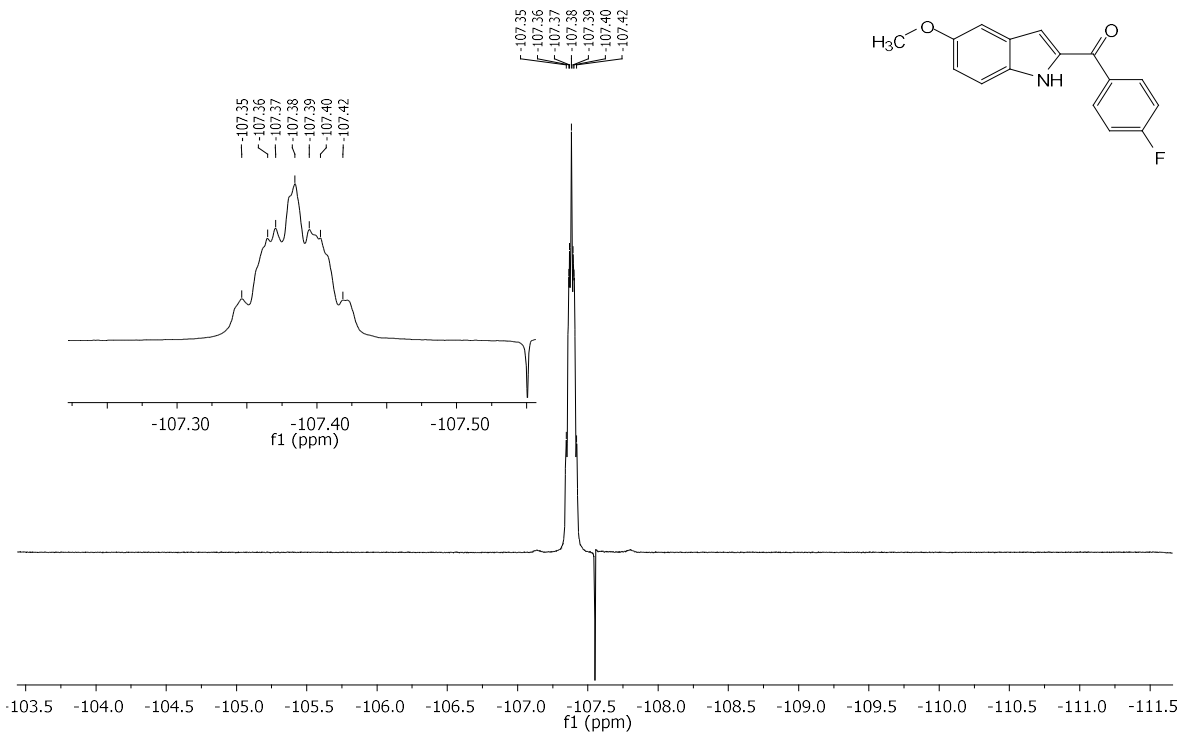


Fig. 184. ^{19}F NMR of **4ac** in DMSO-d_6.

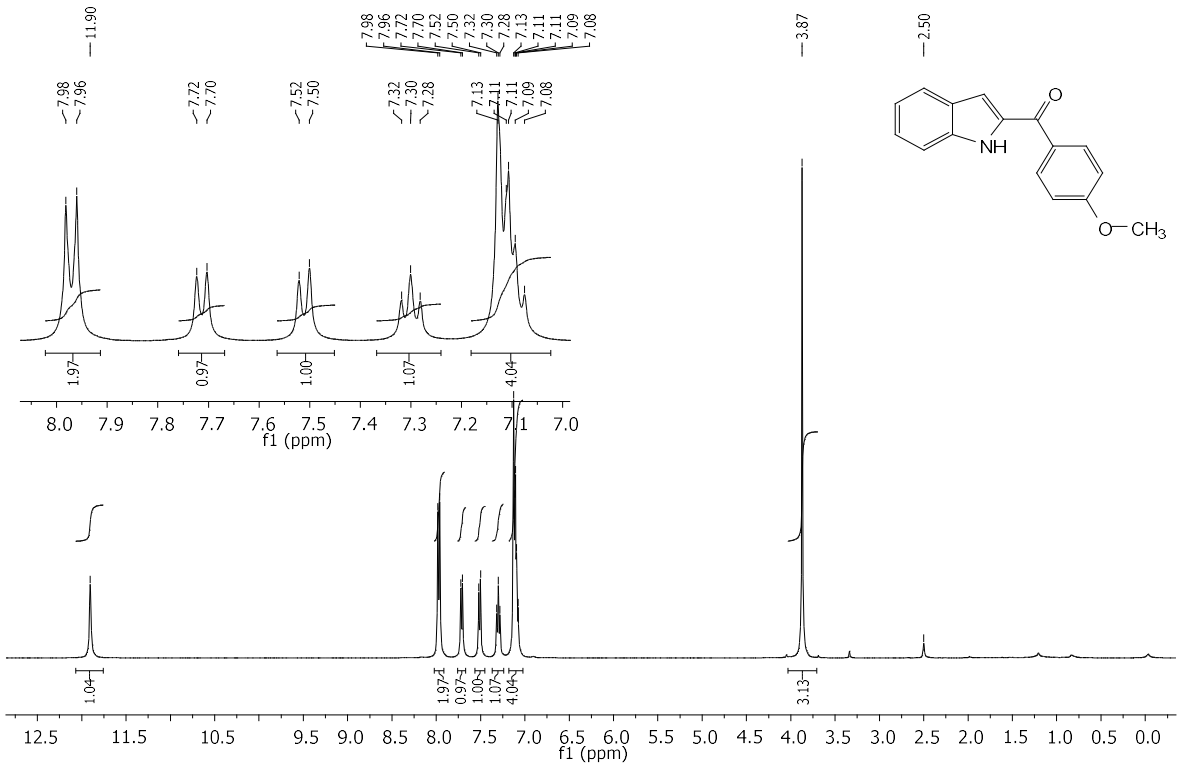


Fig. 185. ^{1}H NMR of **4ad** in DMSO-d_6.

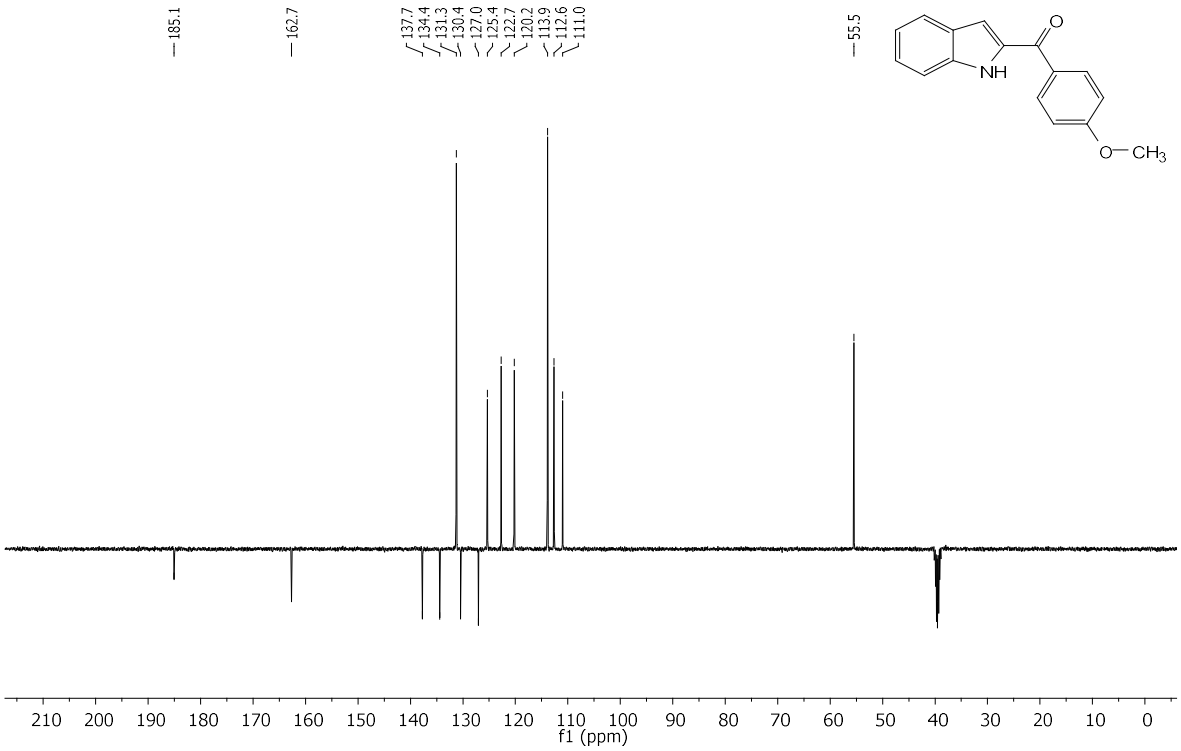


Fig. 186. ^{13}C NMR of **4ad** in DMSO-d_6.

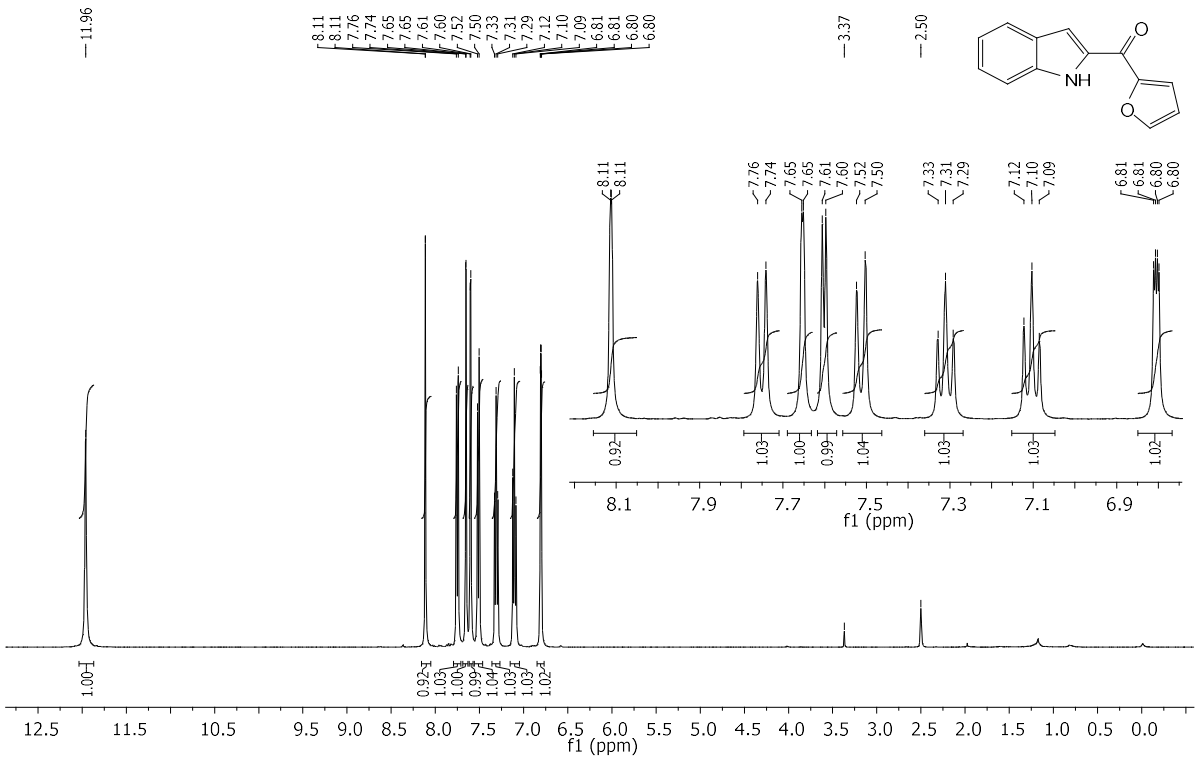


Fig. 187. [1]H NMR of **4ae** in DMSO-d_6.

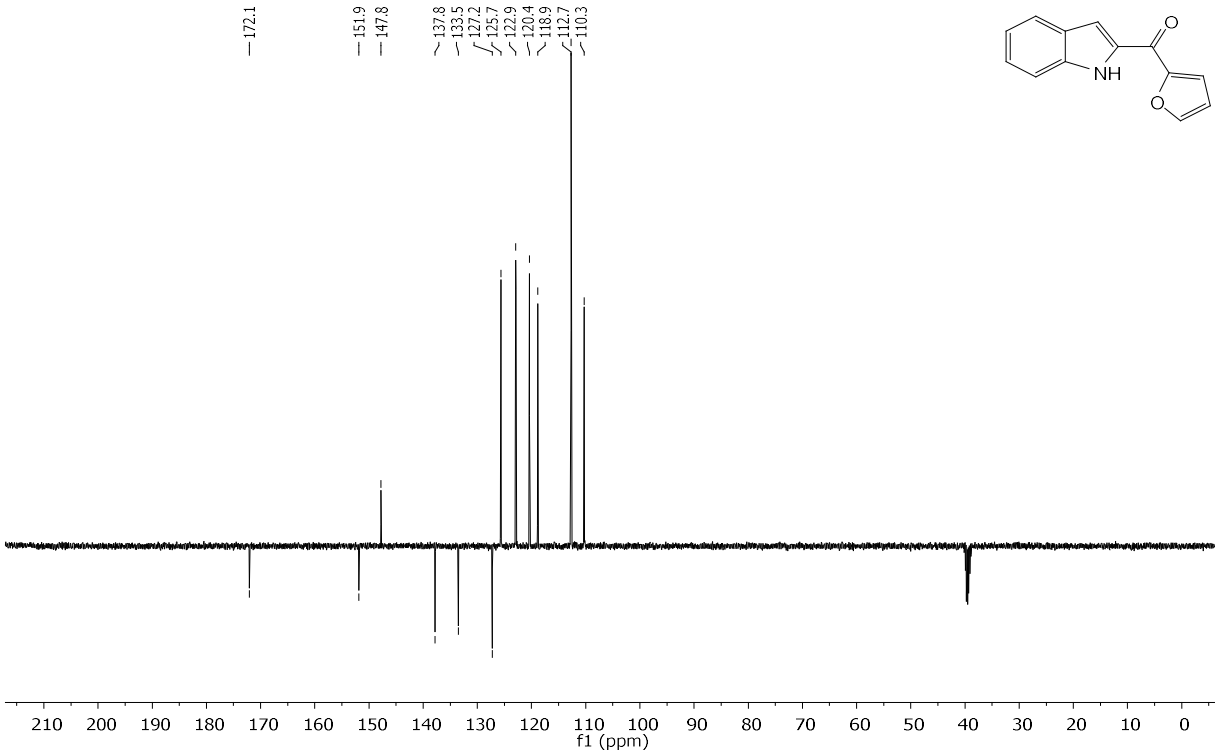


Fig. 188. [13]C NMR of **4ae** in DMSO-d_6.

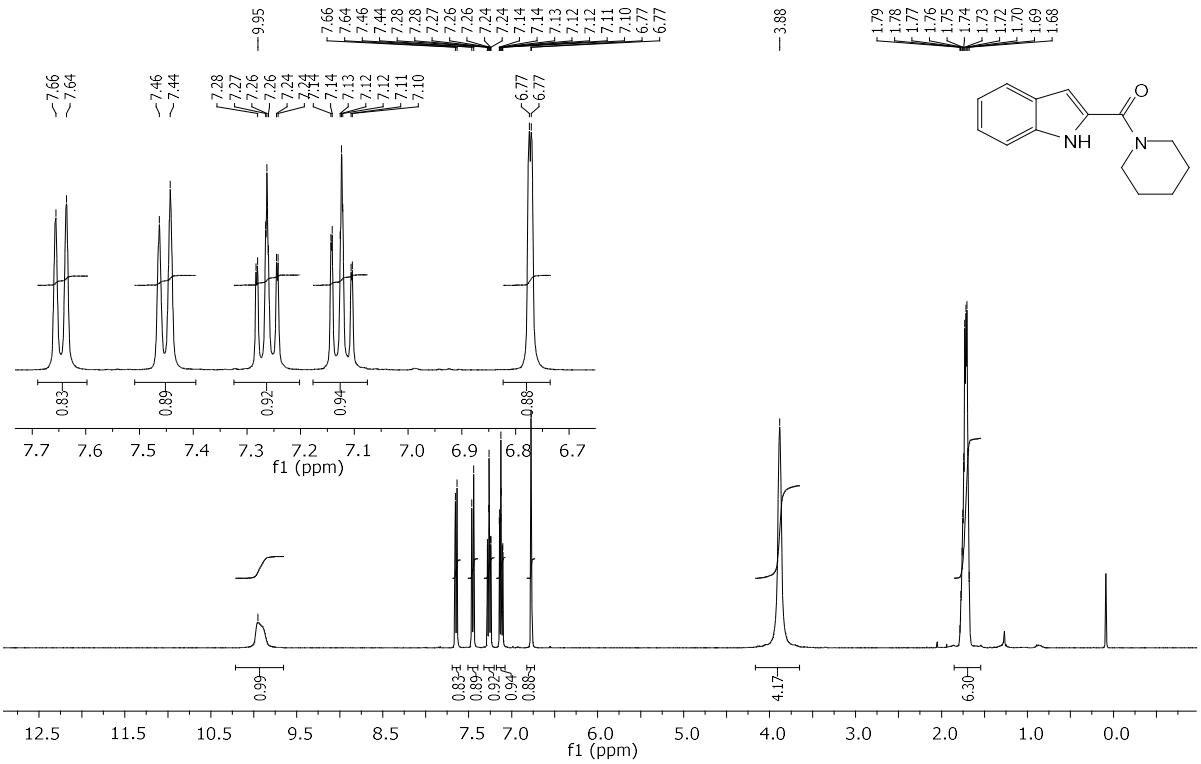


Fig. 189. ^{1}H NMR of **4af** in $CDCl_3$.

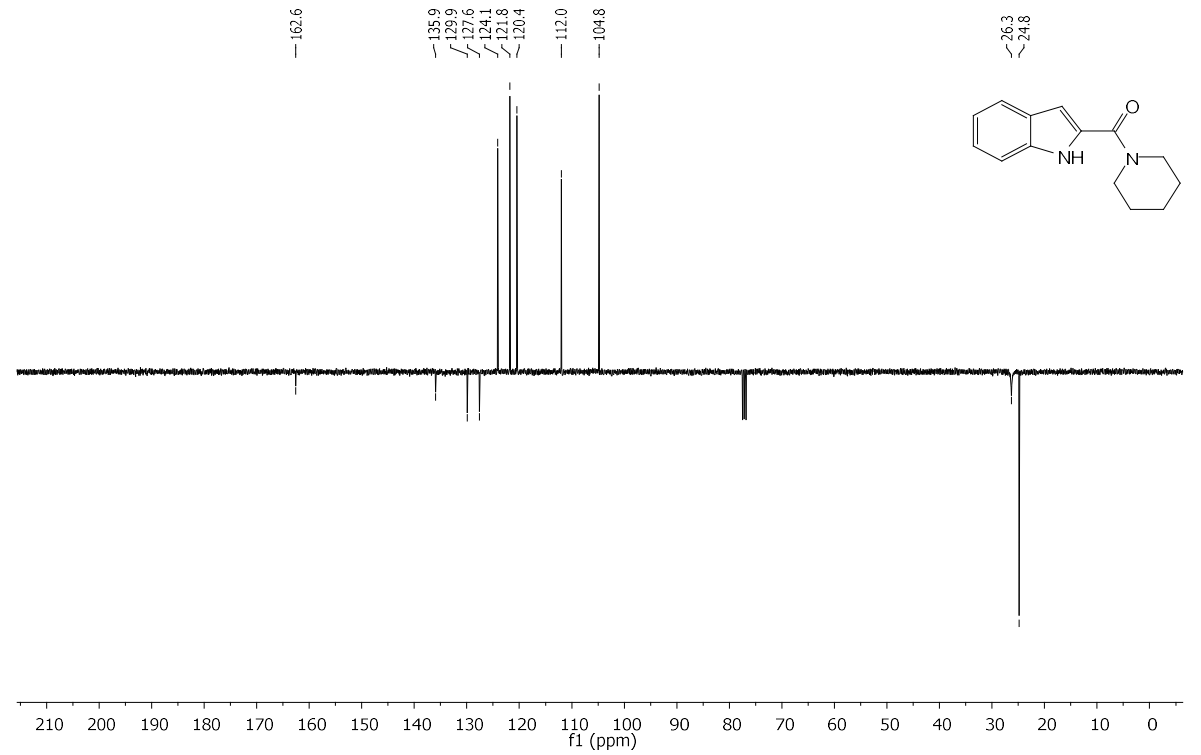


Fig. 190. ^{13}C NMR of **4af** in $CDCl_3$.

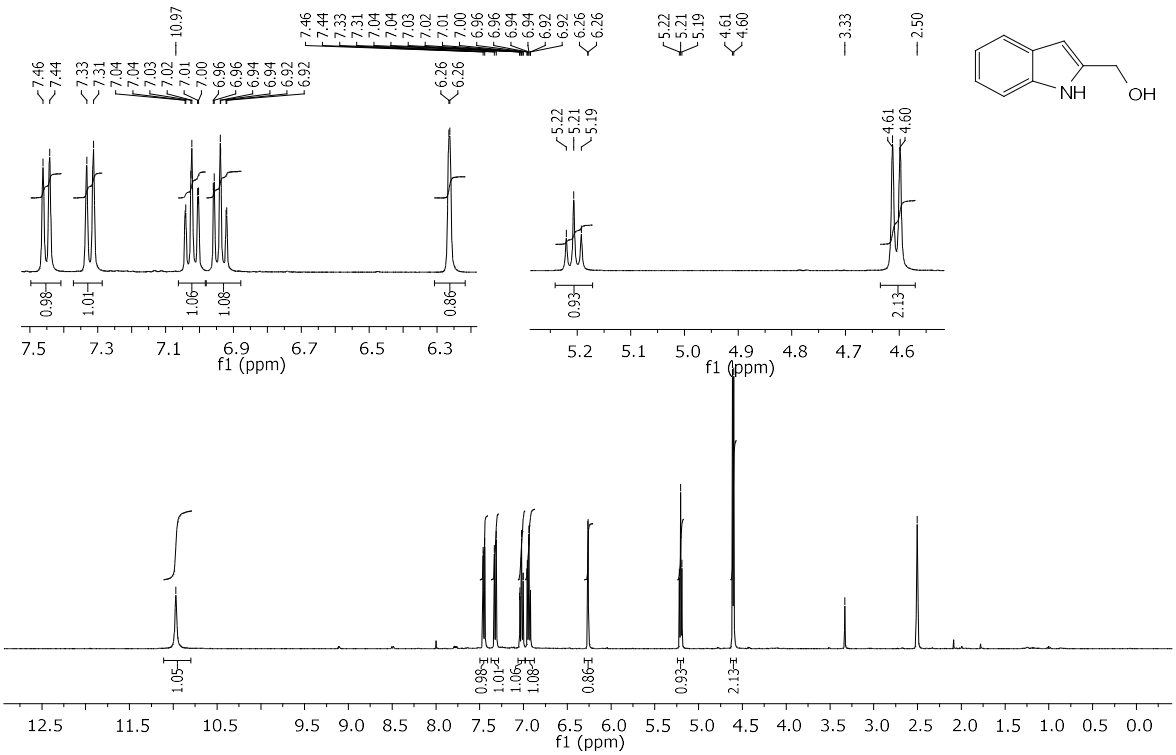


Fig. 191. ^{1}H NMR of **4ag** in DMSO-d_6.

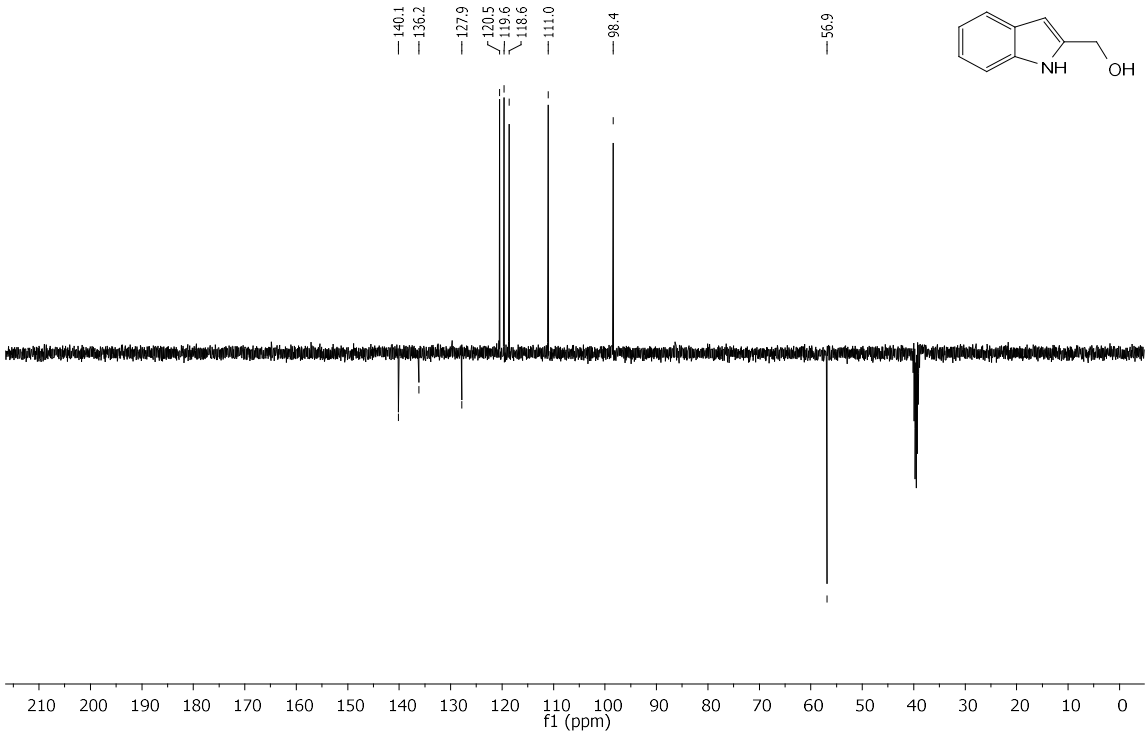


Fig. 192. ^{13}C NMR of **4ag** in DMSO-d_6.

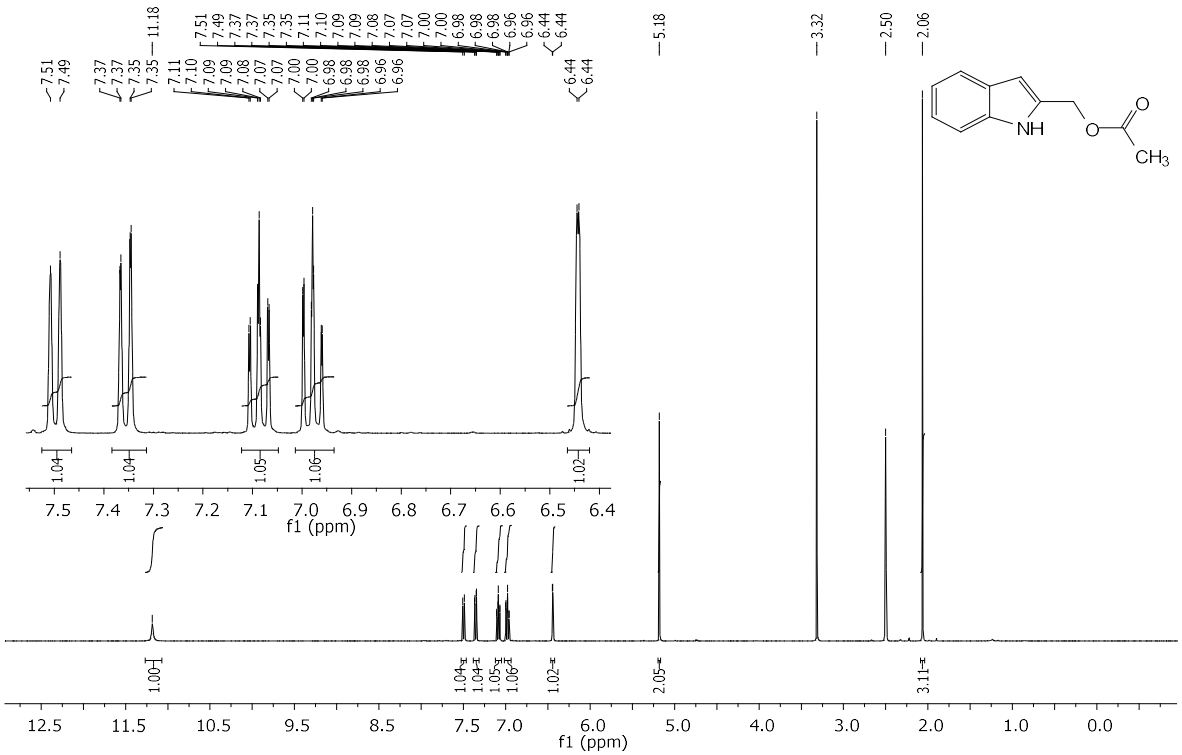


Fig. 193. ^{1}H NMR of **4ah** in DMSO-d_6.

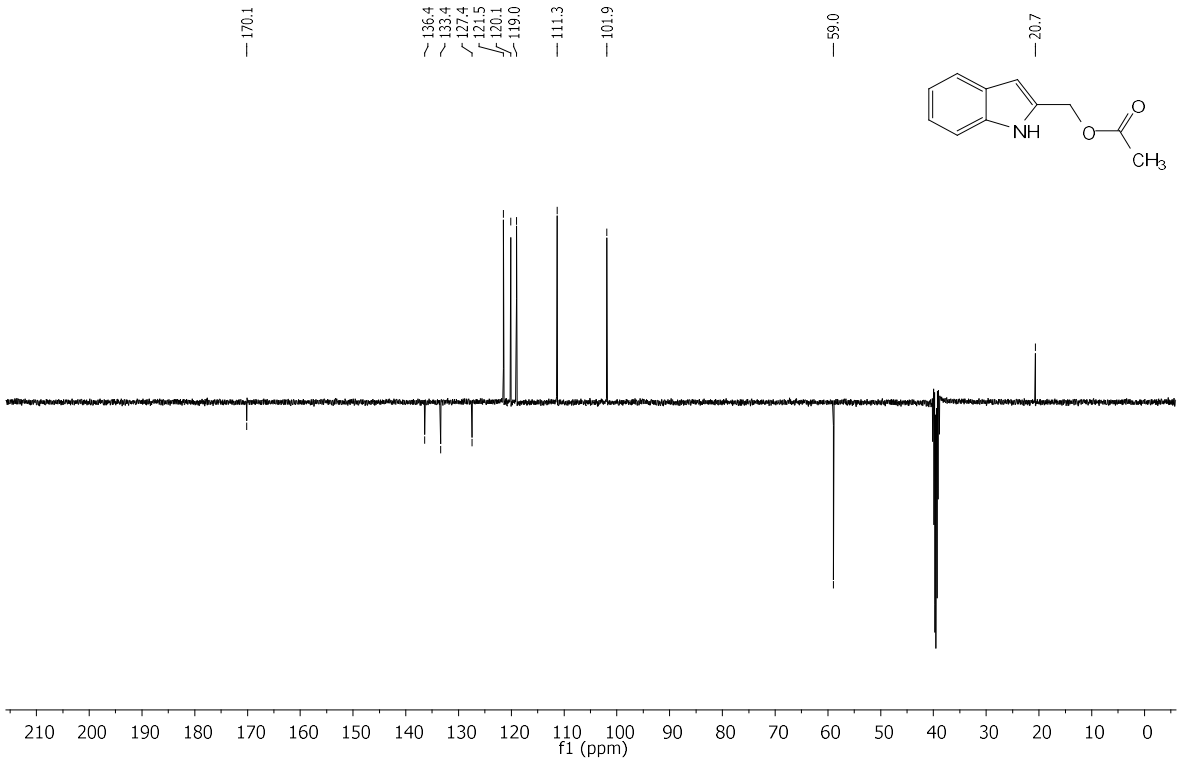


Fig. 194. ^{13}C NMR of **4ah** in DMSO-d_6.

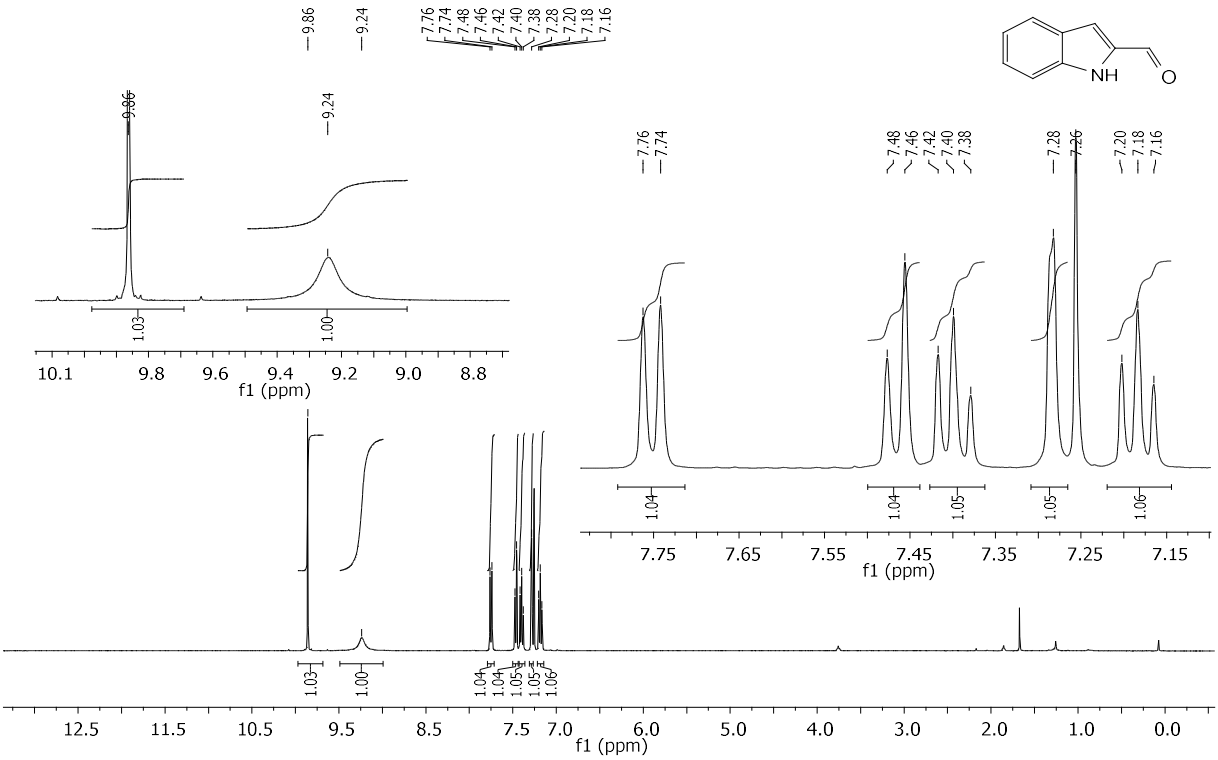


Fig. 195. ^{1}H NMR of **4ai** in $CDCl_3$.

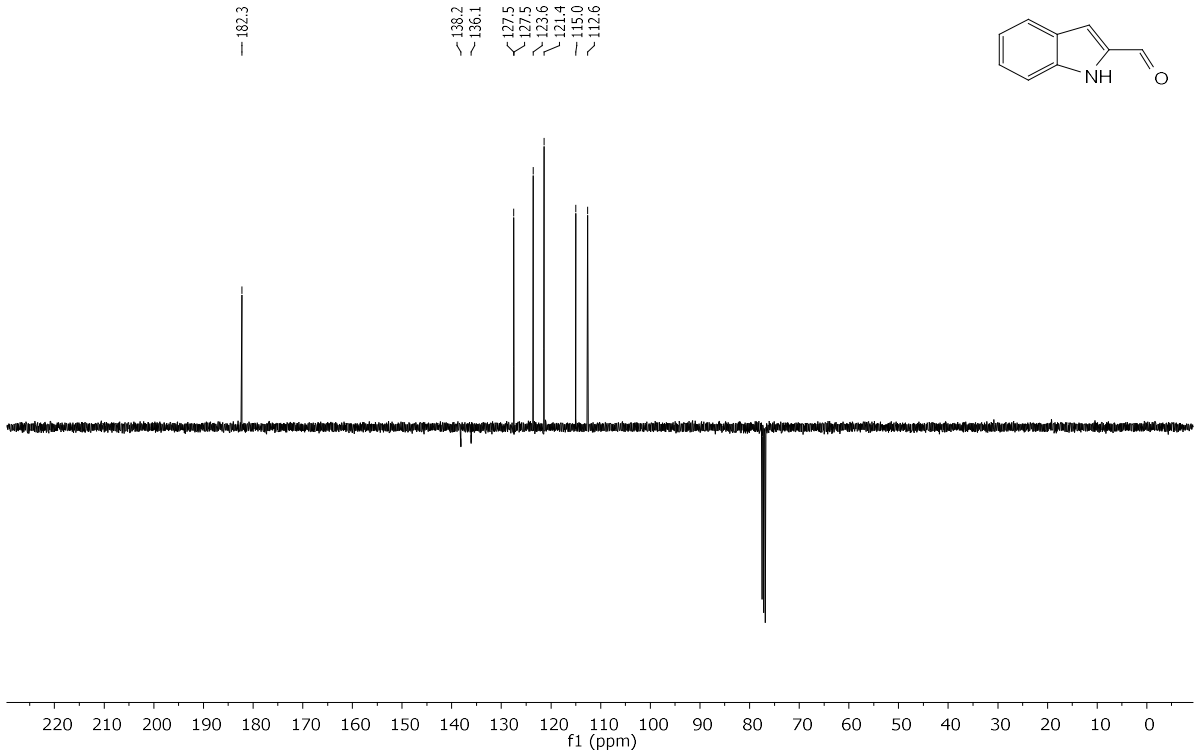


Fig. 196. ^{13}C NMR of **4ai** in $CDCl_3$.

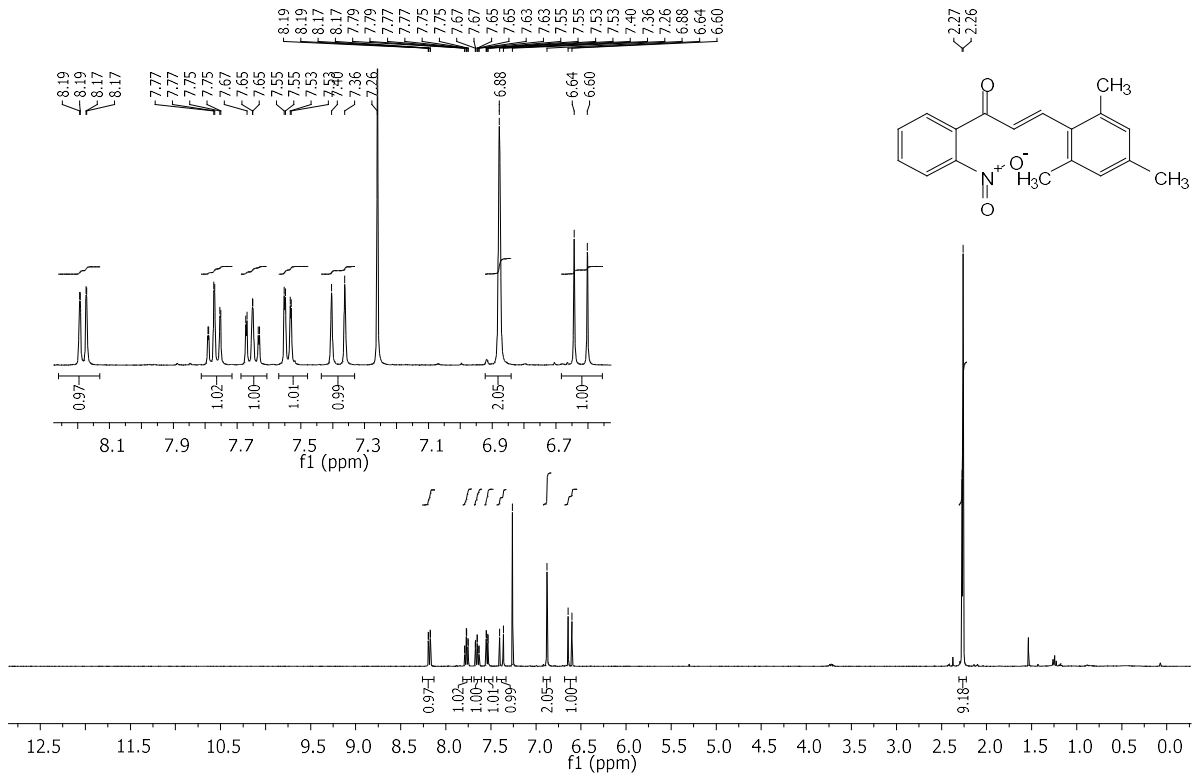


Fig. 197. ^{1}H NMR of **5c** in $CDCl_3$.

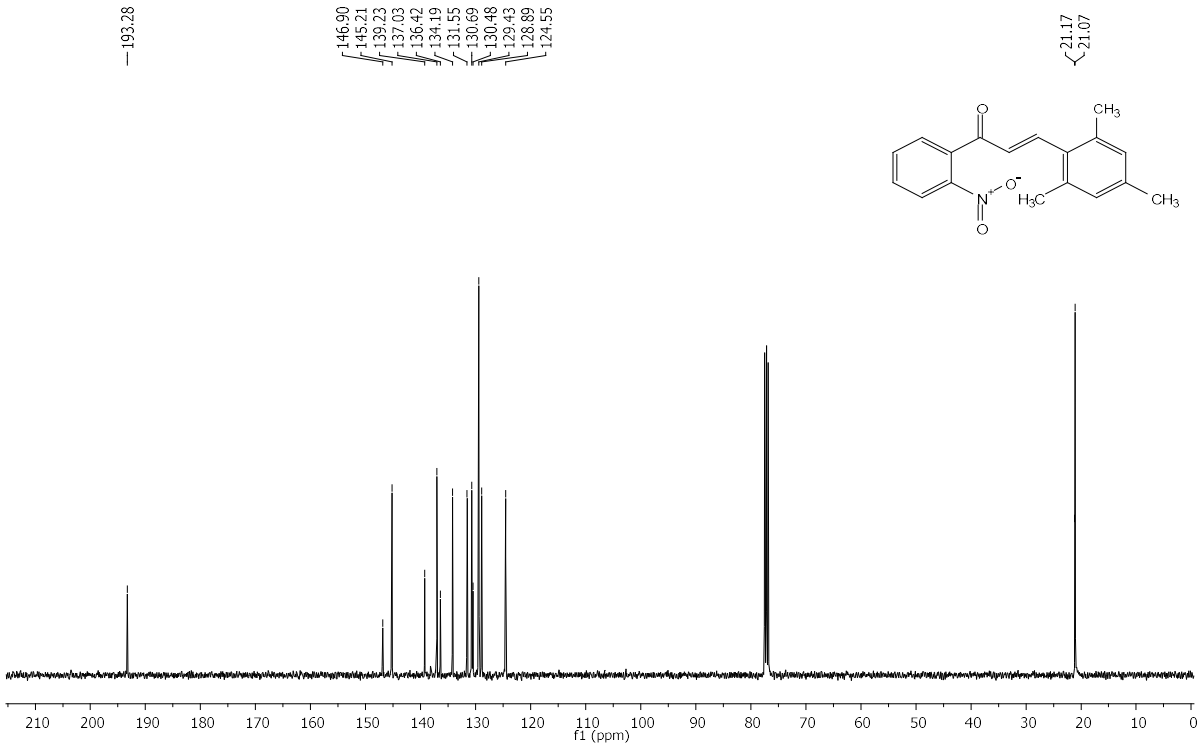


Fig. 198. ^{13}C NMR of **5c** in $CDCl_3$.

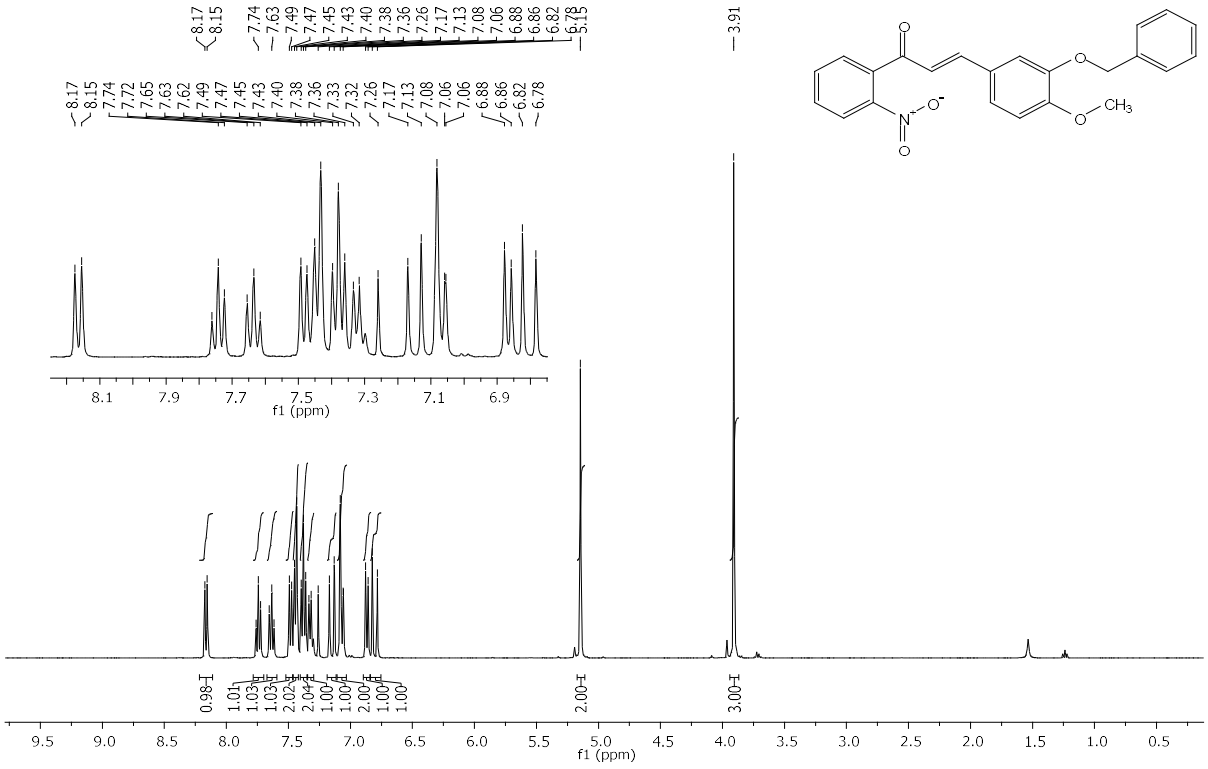


Fig. 199. ^{1}H NMR of **5e** in $CDCl_3$.

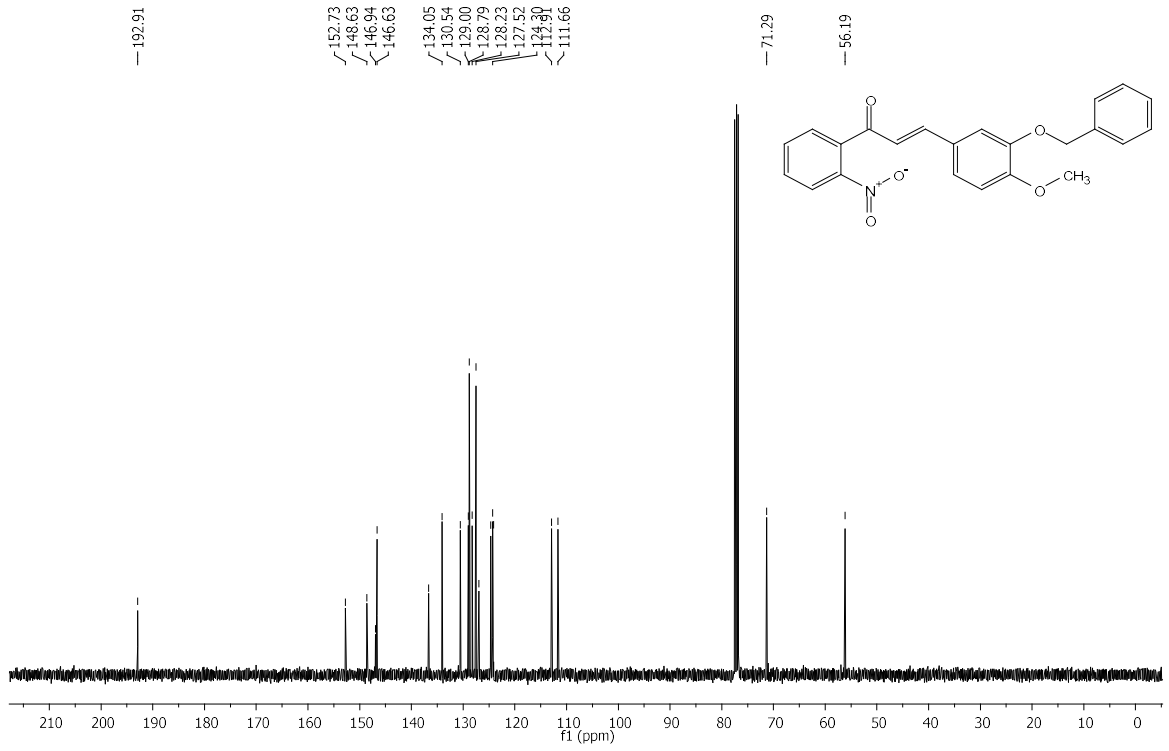


Fig. 200. ^{13}C NMR of **5e** in $CDCl_3$.

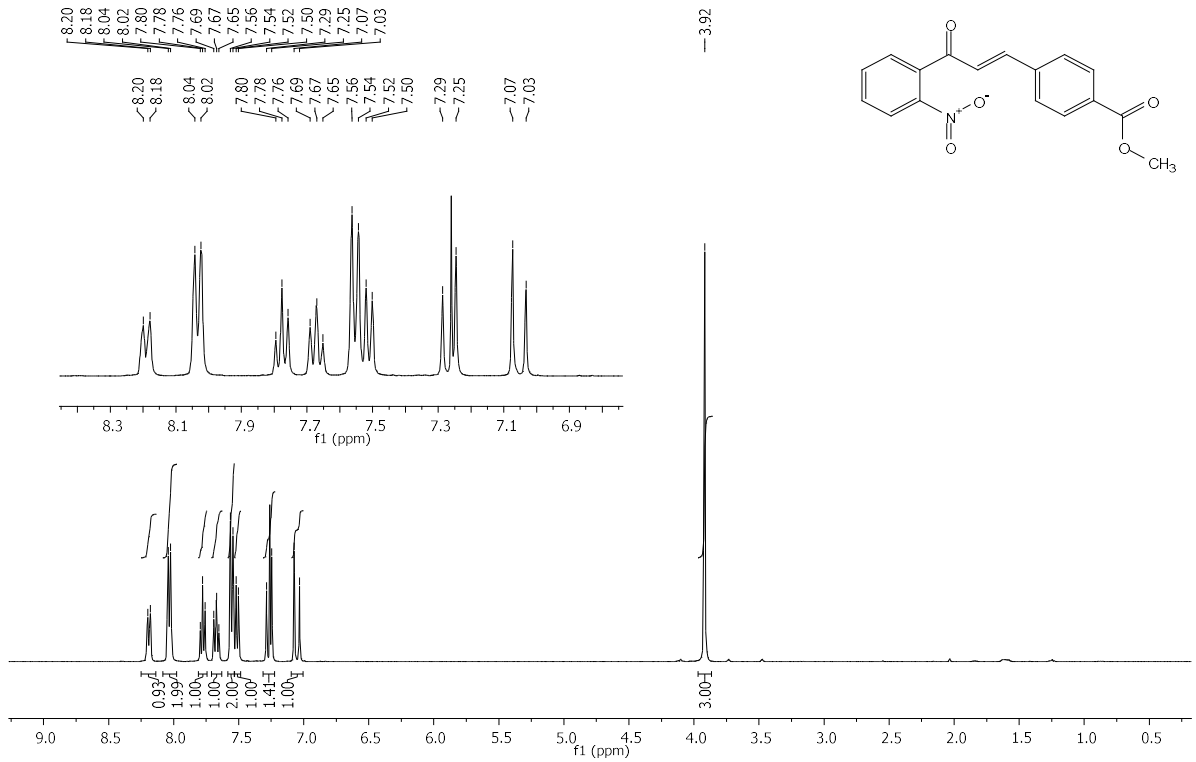


Fig. 201. ^{1}H NMR of **5j** in $CDCl_3$.

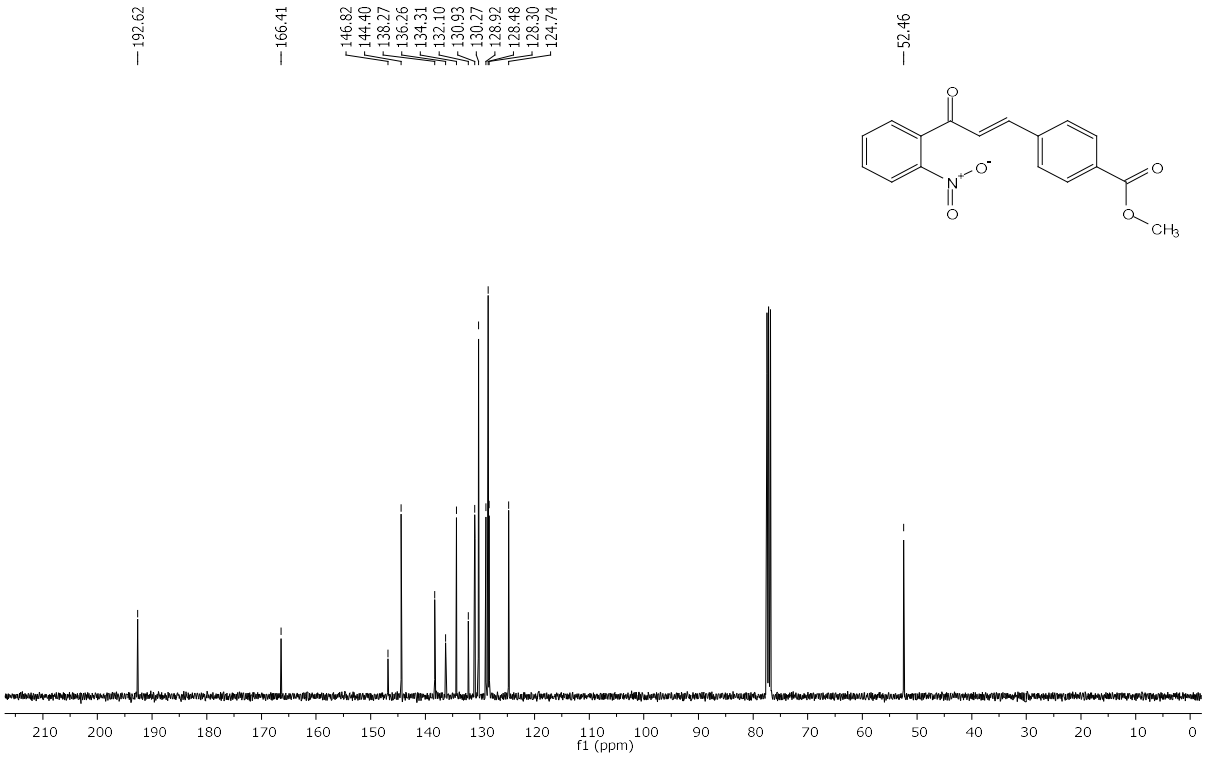


Fig. 202. ^{13}C NMR of **5j** in $CDCl_3$.

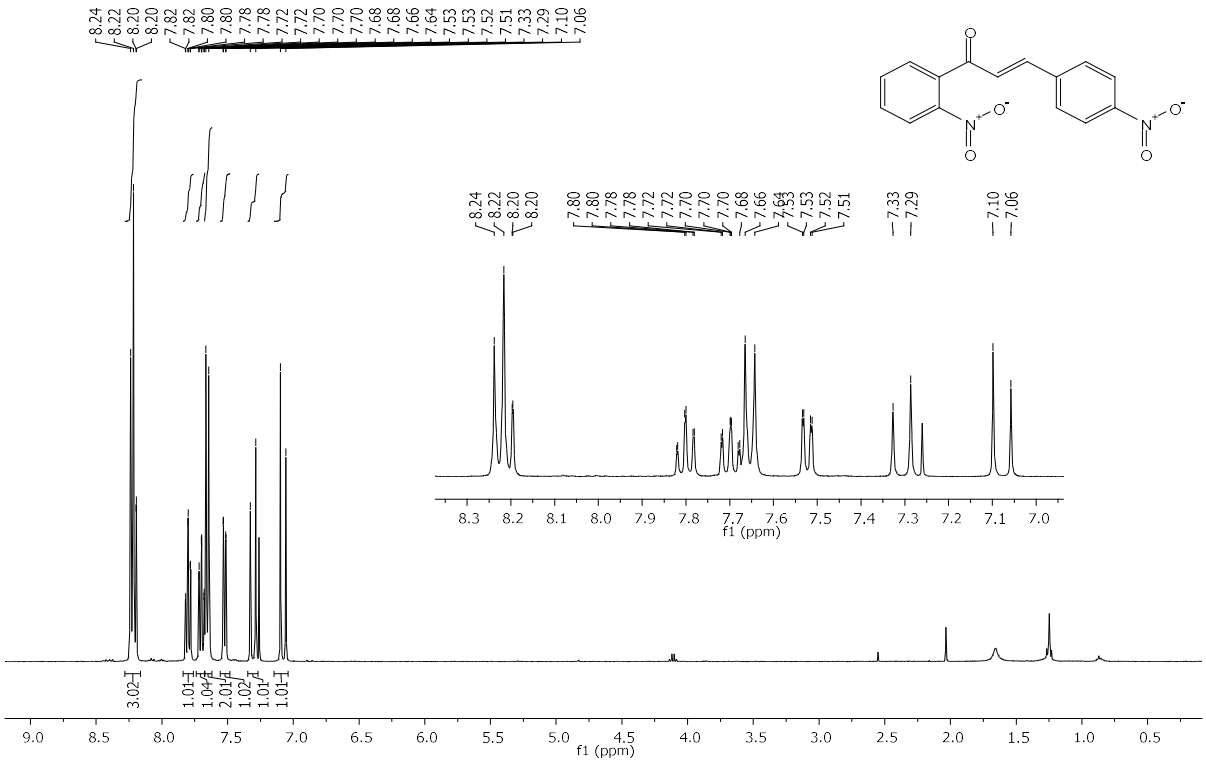


Fig. 203. ^{1}H NMR of **5l** in $CDCl_3$.

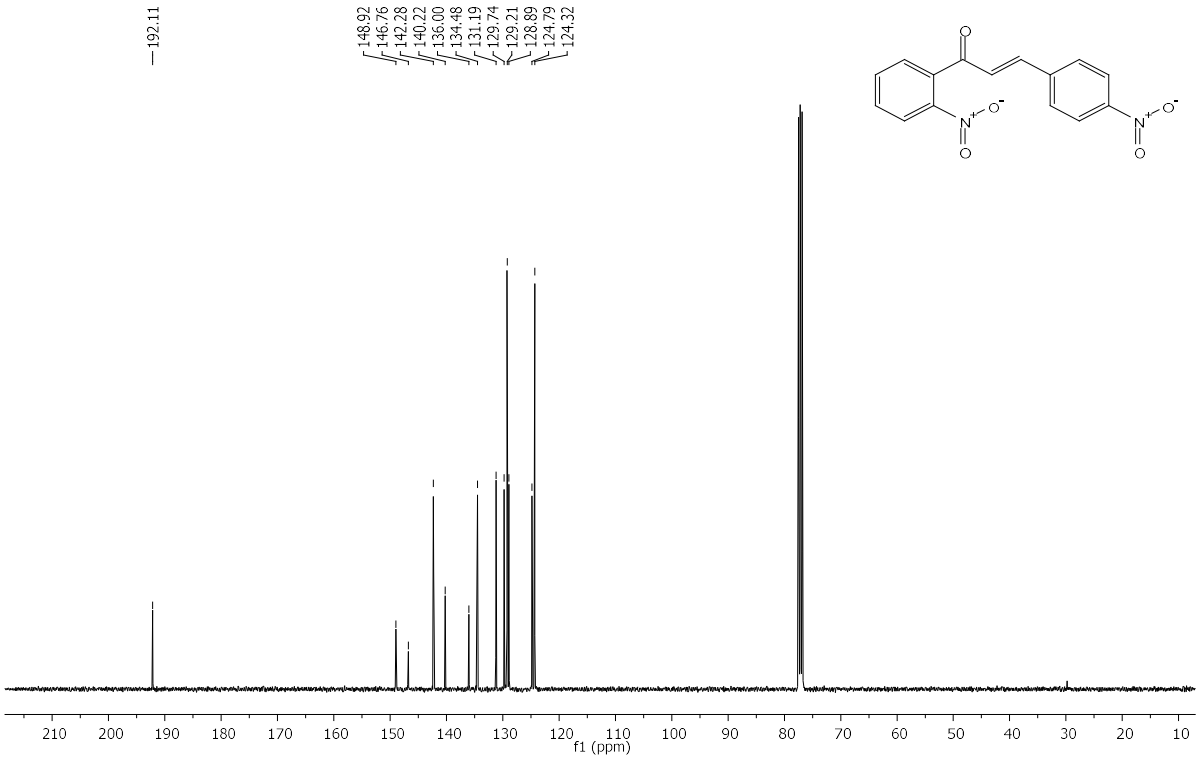


Fig. 204. ^{13}C NMR of **5l** in $CDCl_3$.

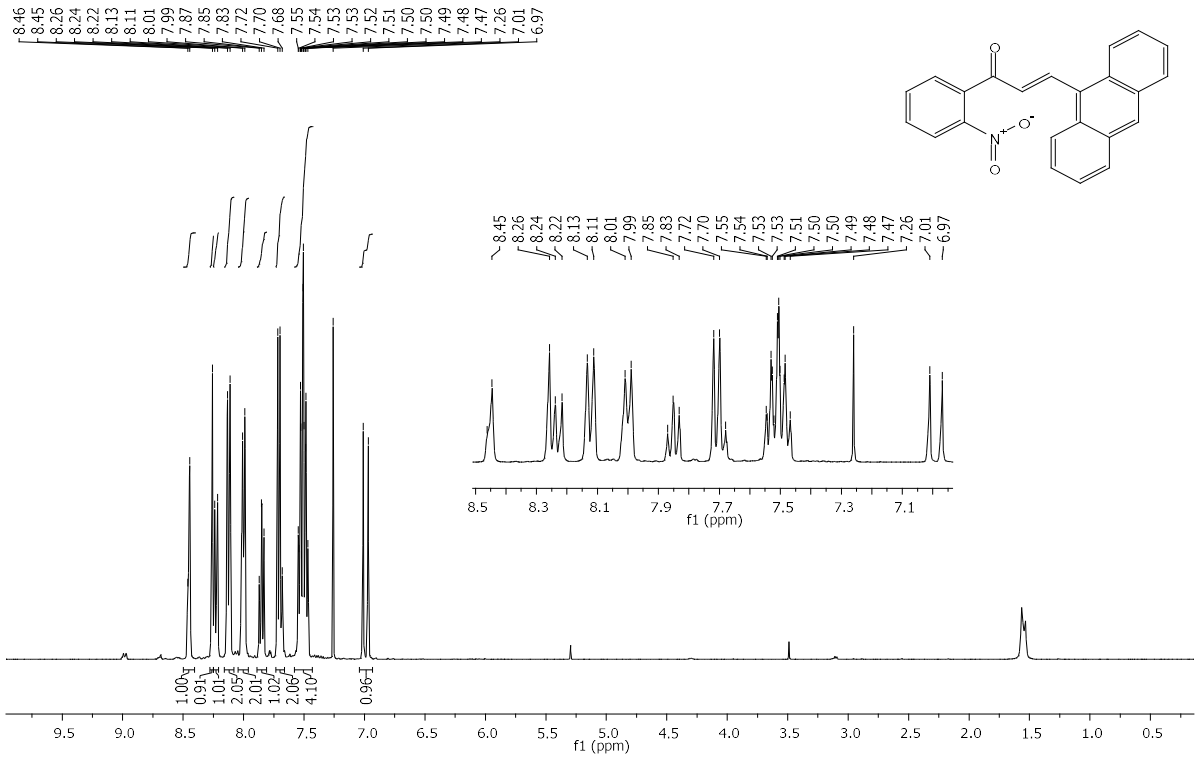


Fig. 205. ^{1}H NMR of **5m** in $CDCl_3$.

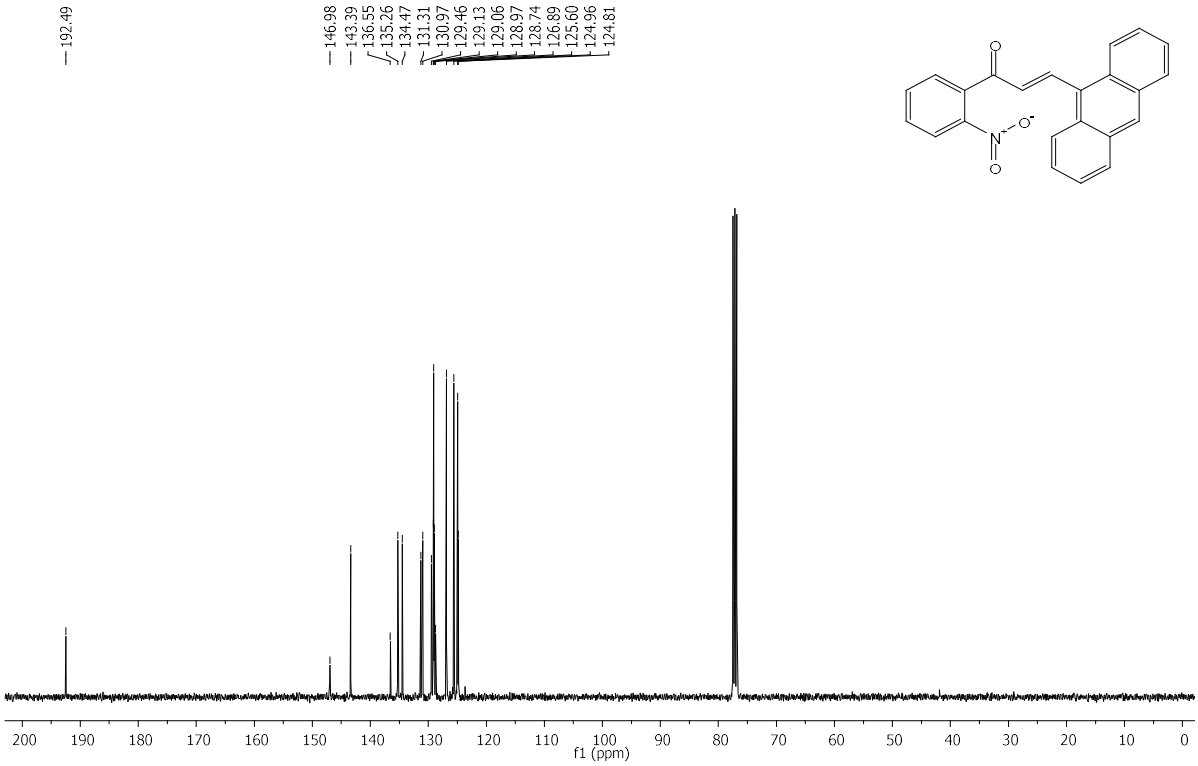


Fig. 206. ^{13}C NMR of **5m** in $CDCl_3$.

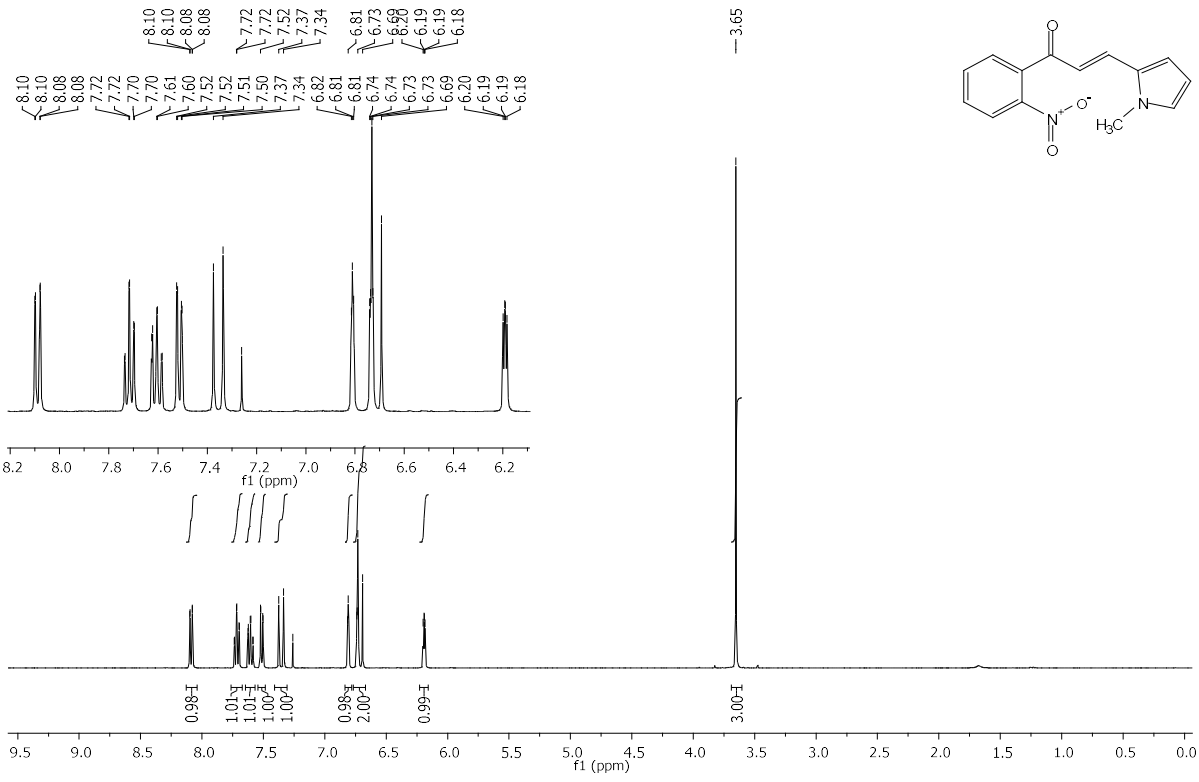


Fig. 207. ^{1}H NMR of **5n** in $CDCl_3$.

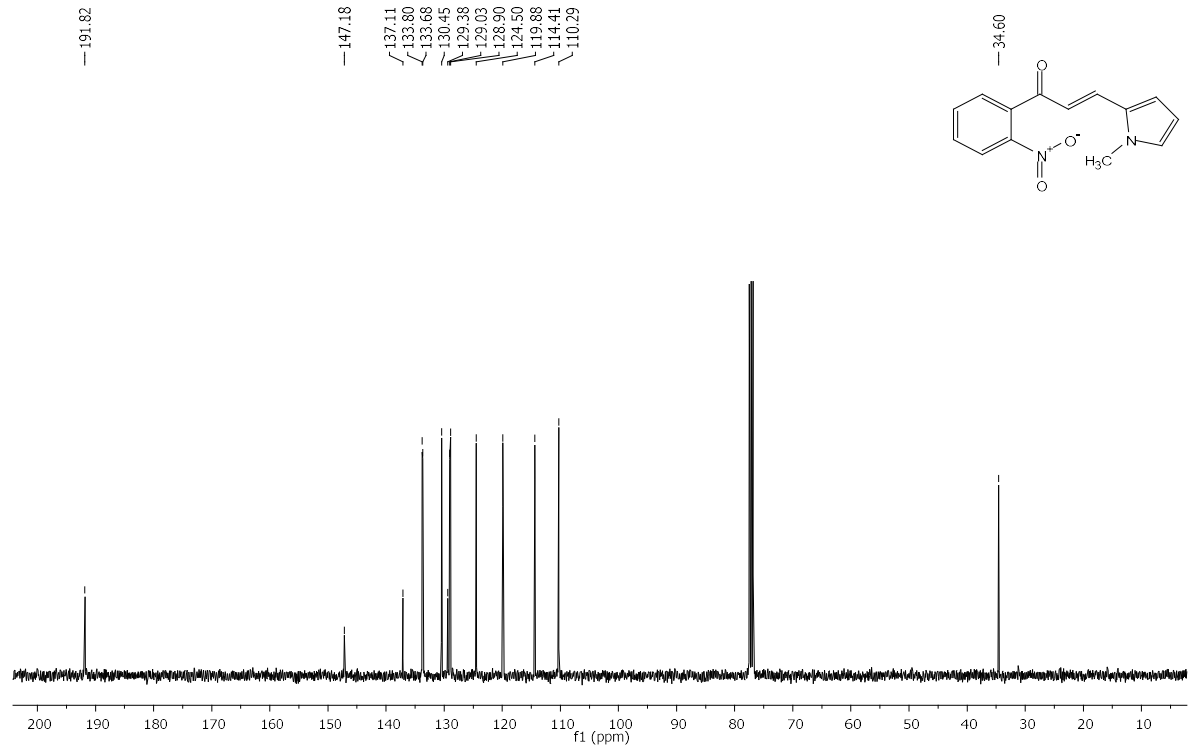


Fig. 208. ^{13}C NMR of **5n** in $CDCl_3$.

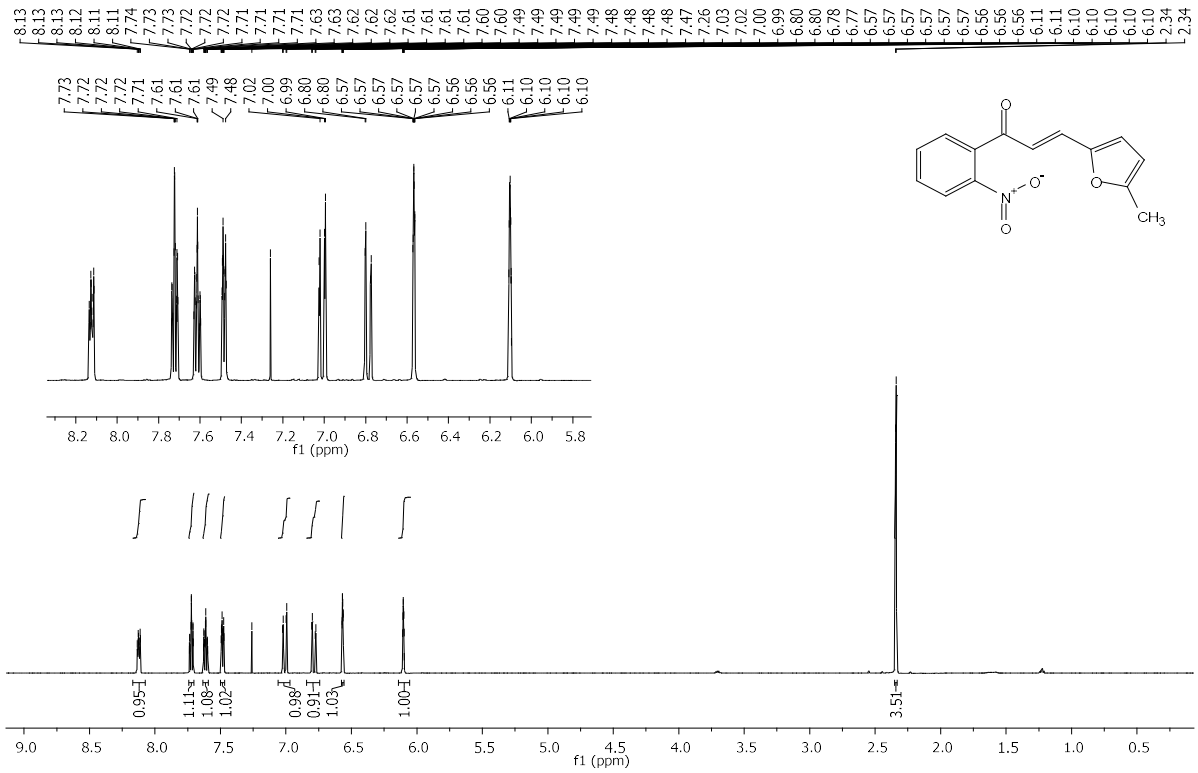


Fig. 209. ^{1}H NMR of **5o** in $CDCl_3$.

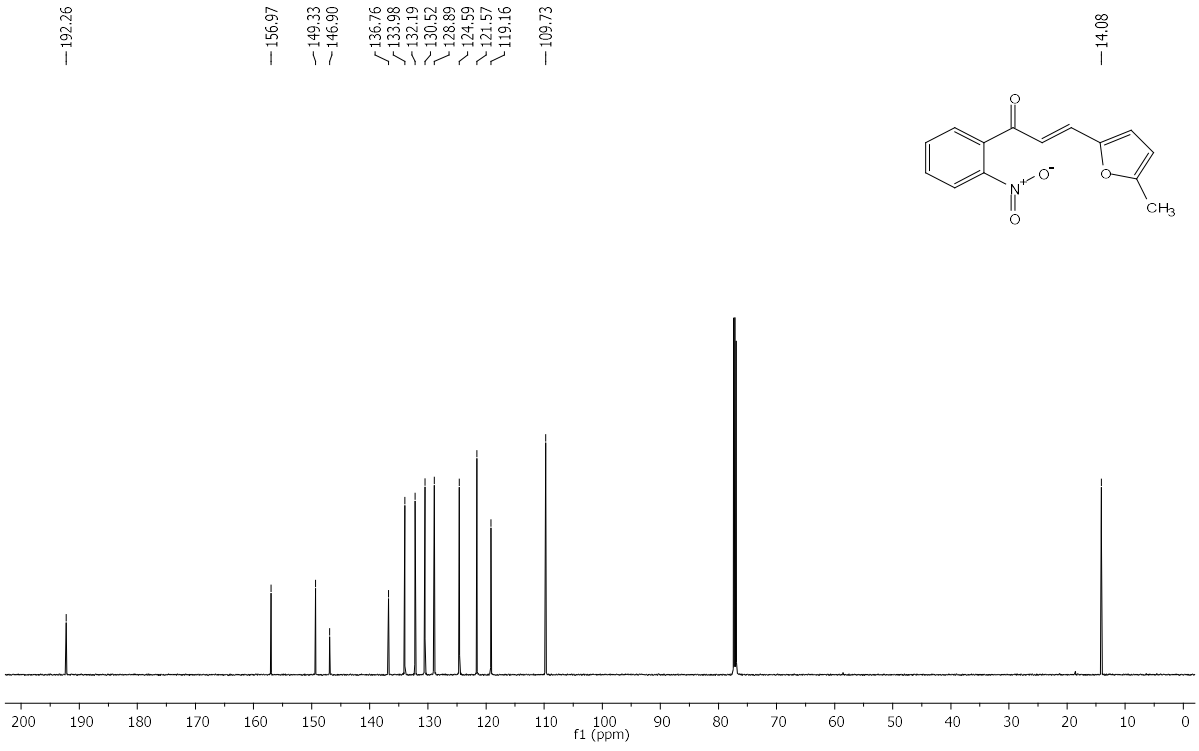


Fig. 210. ^{13}C NMR of **5o** in $CDCl_3$.

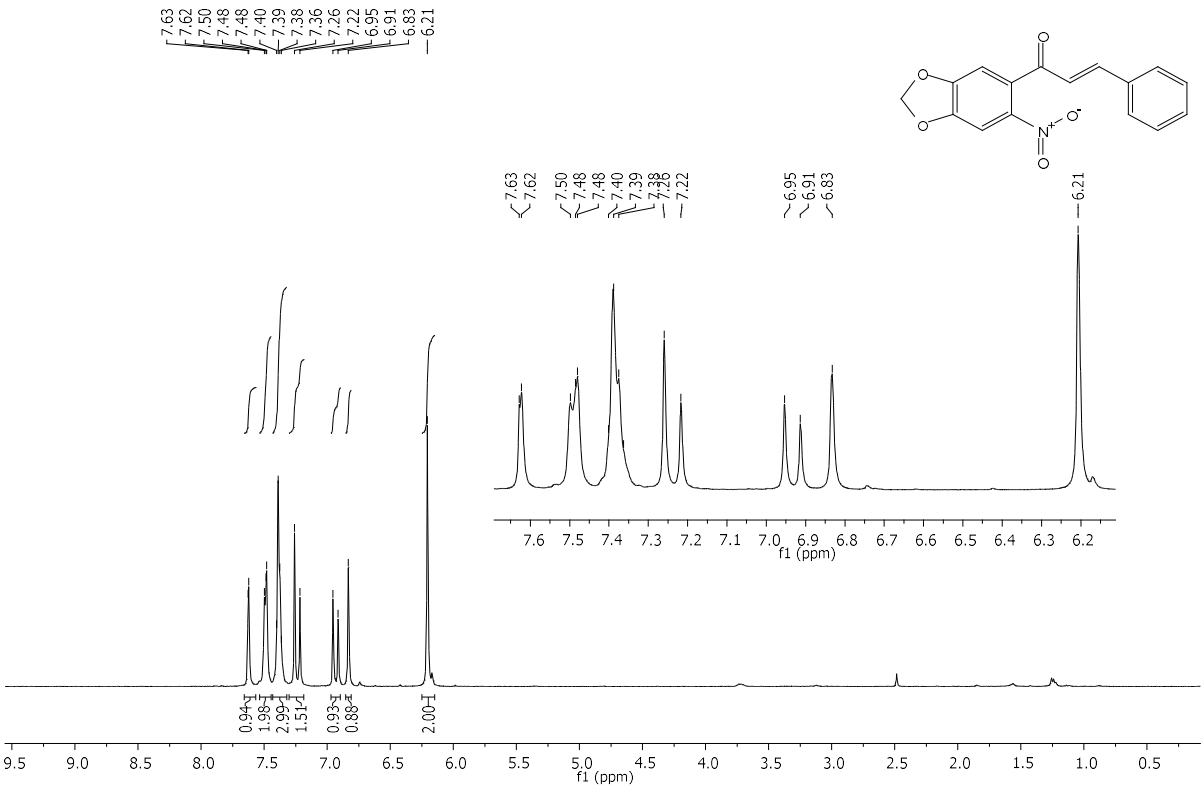


Fig. 211. ^{1}H NMR of **5p** in $CDCl_3$.

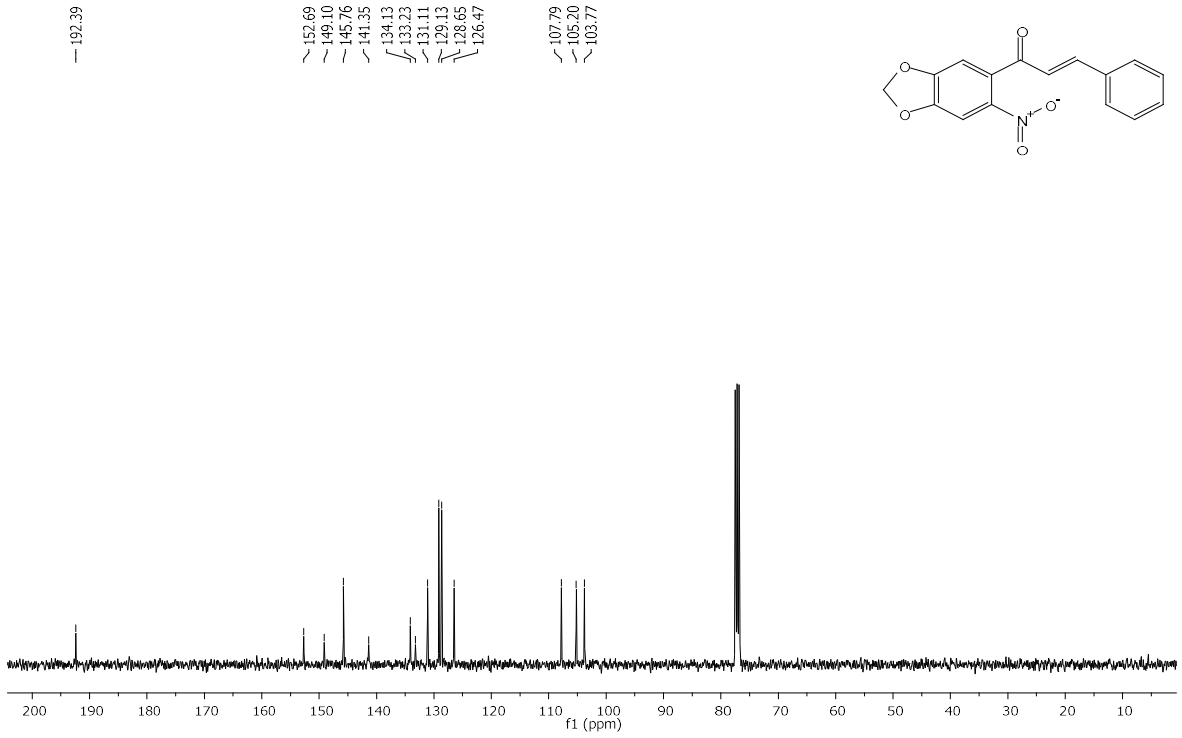


Fig. 212. ^{13}C NMR of **5p** in $CDCl_3$.

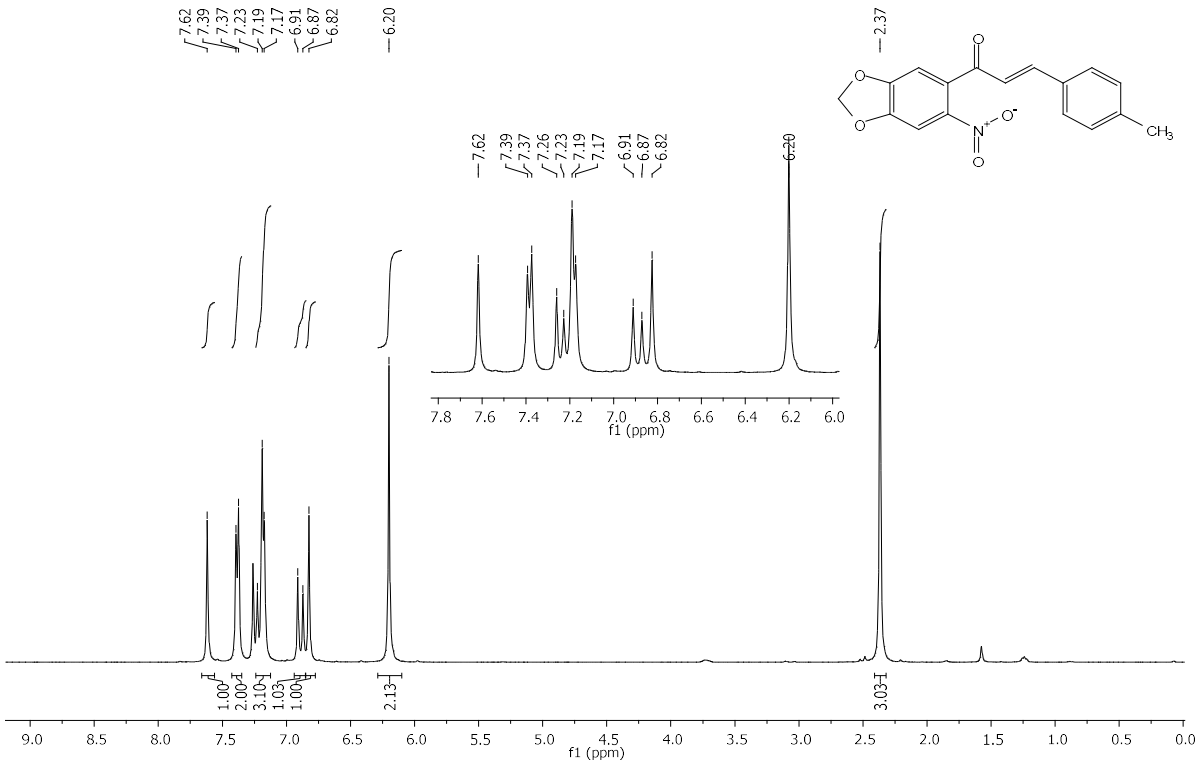


Fig. 213. ^{1}H NMR of **5q** in $CDCl_3$.

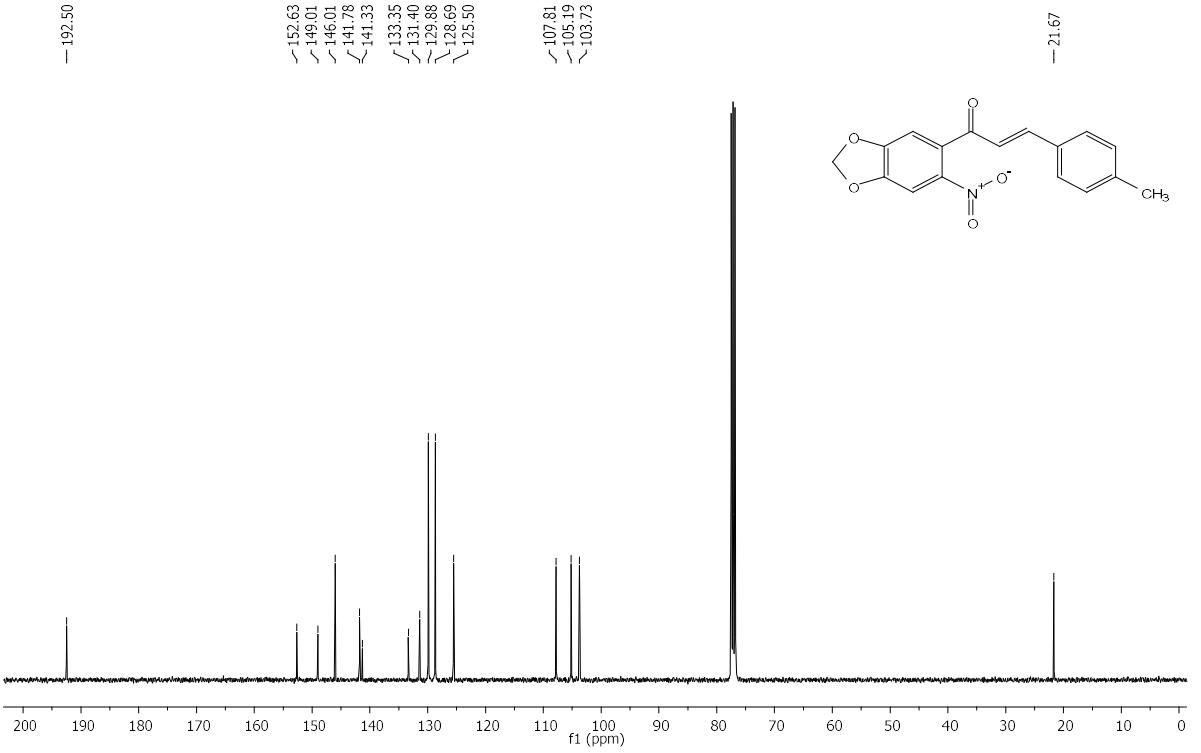


Fig. 214. ^{13}C NMR of **5q** in $CDCl_3$.

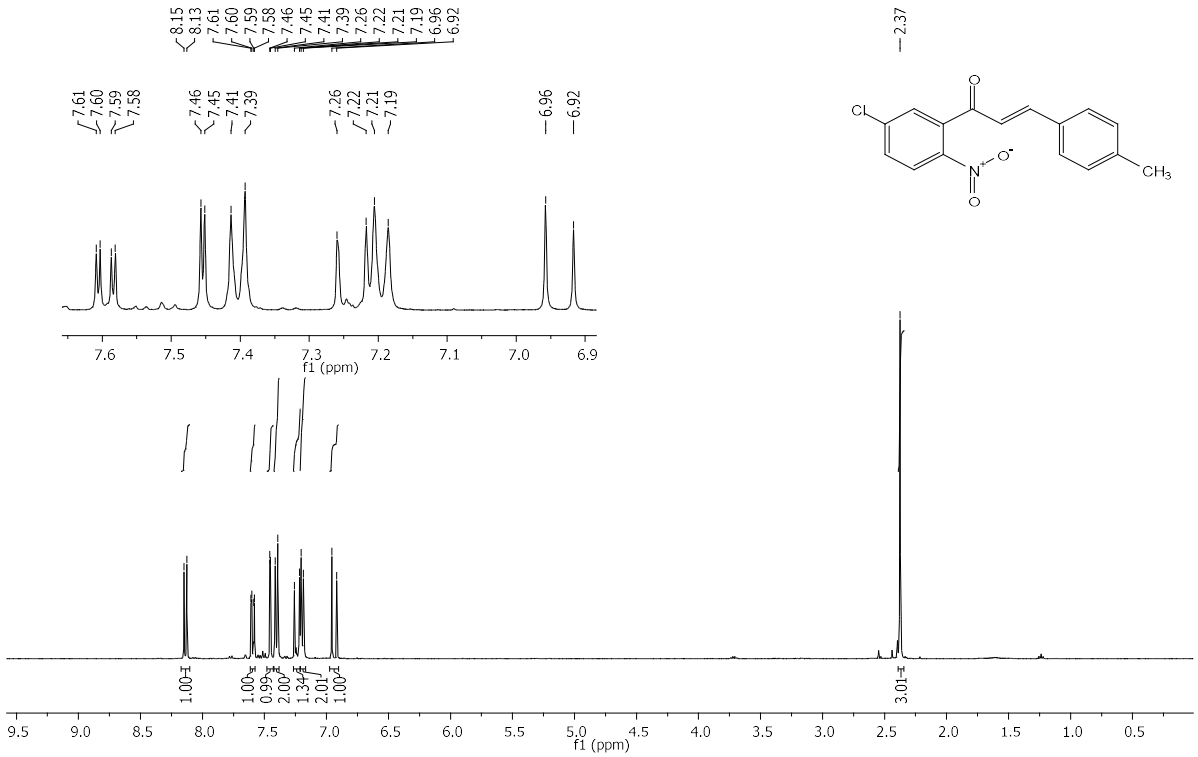


Fig. 215. ^{1}H NMR of **5r** in $CDCl_3$.

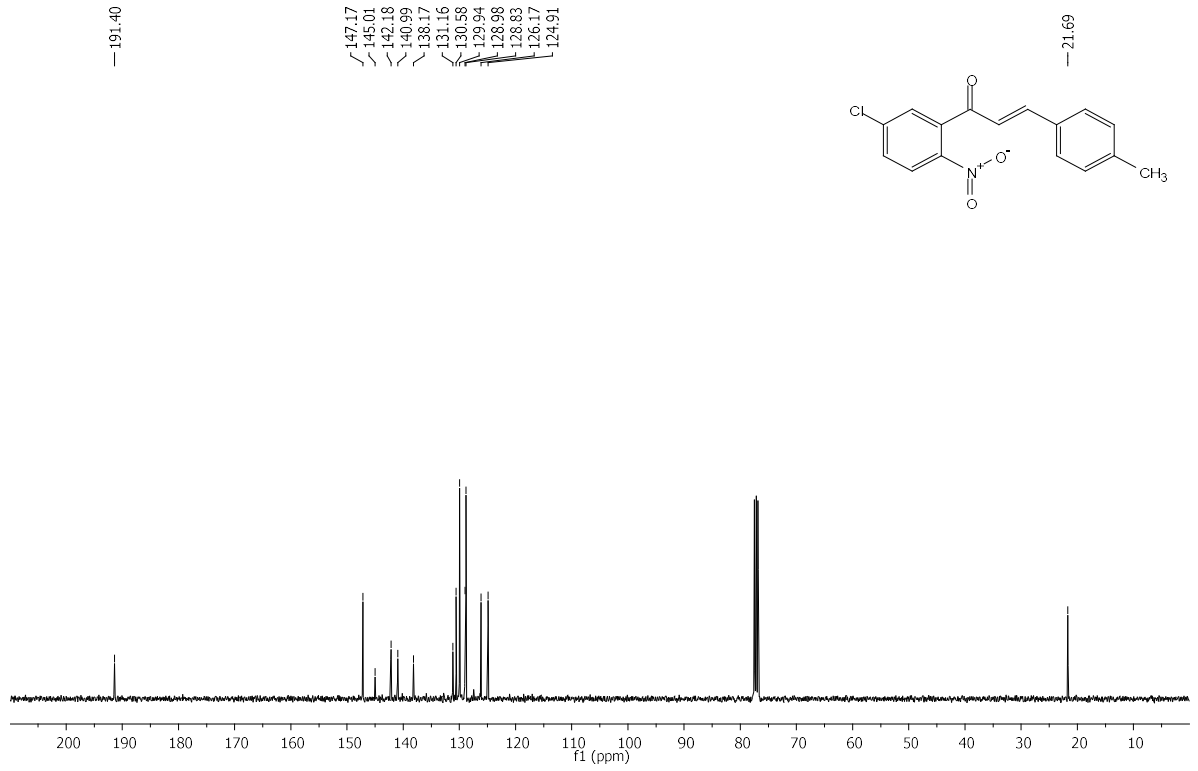


Fig. 216. ^{13}C NMR of **5r** in $CDCl_3$.

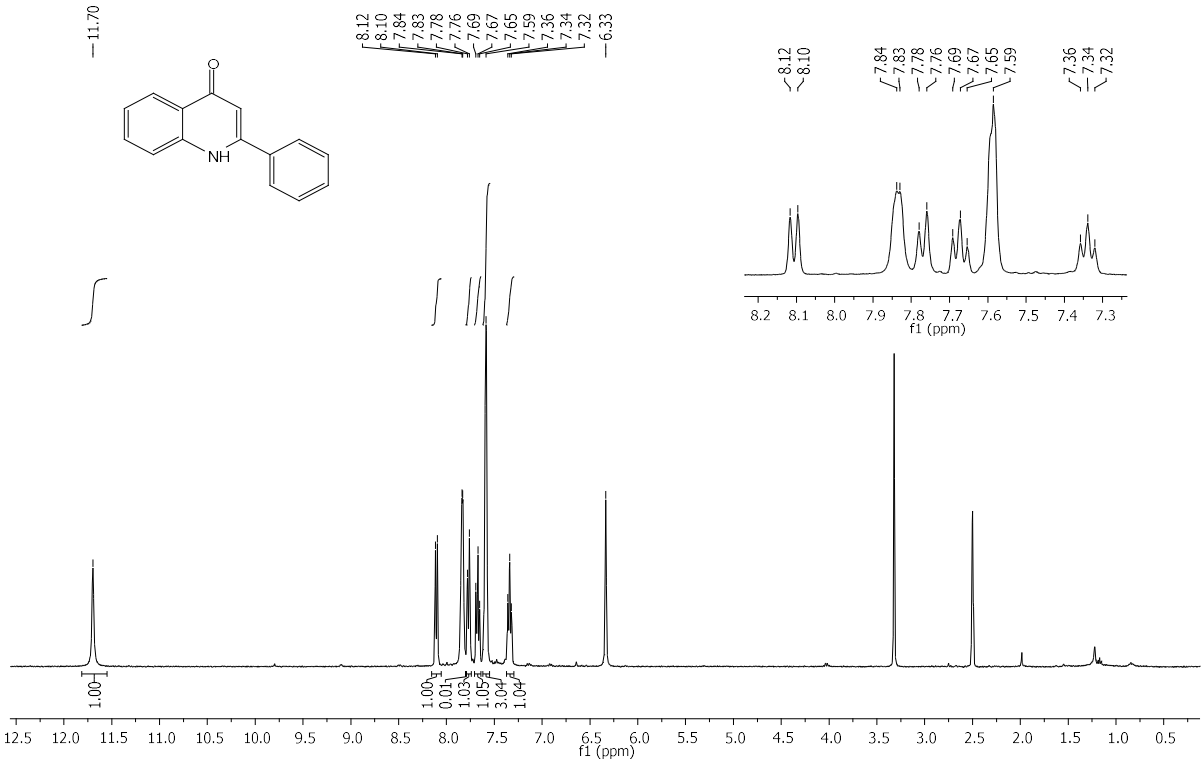


Fig. 217. [1]H NMR of **6a** in DMSO-d_6.

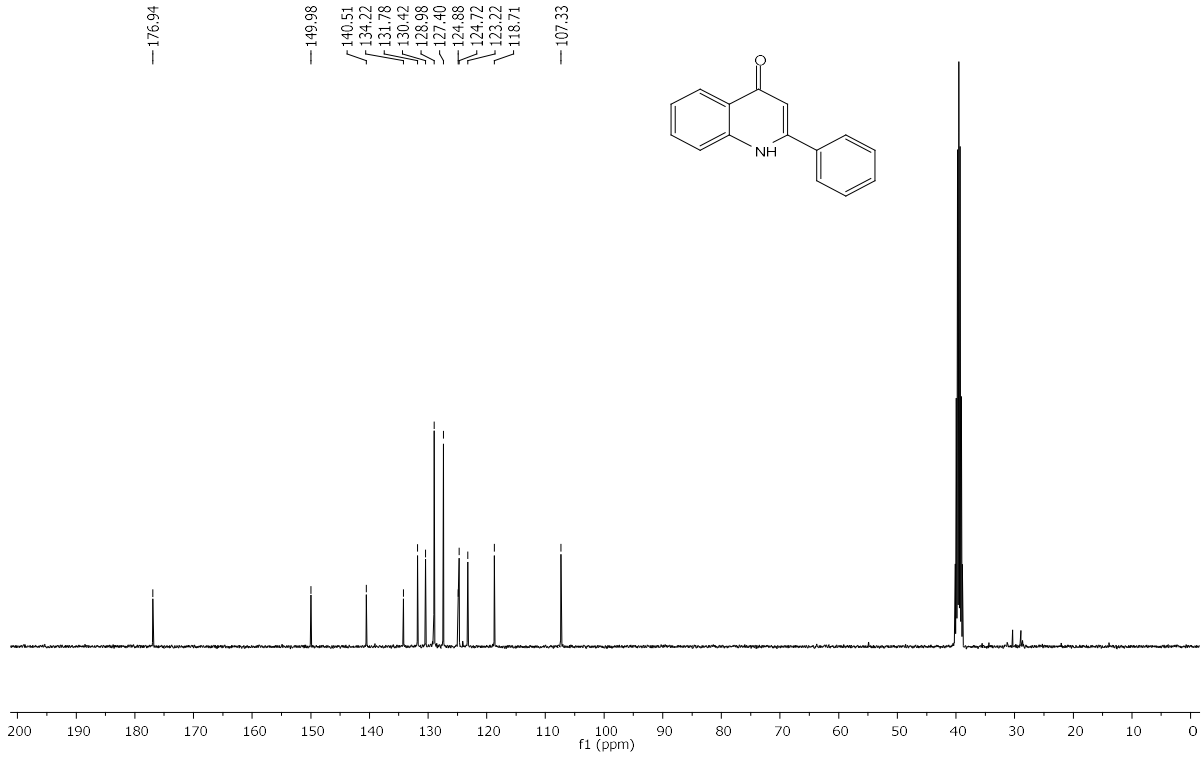


Fig. 218. [13]C NMR of **6a** in DMSO-d_6.

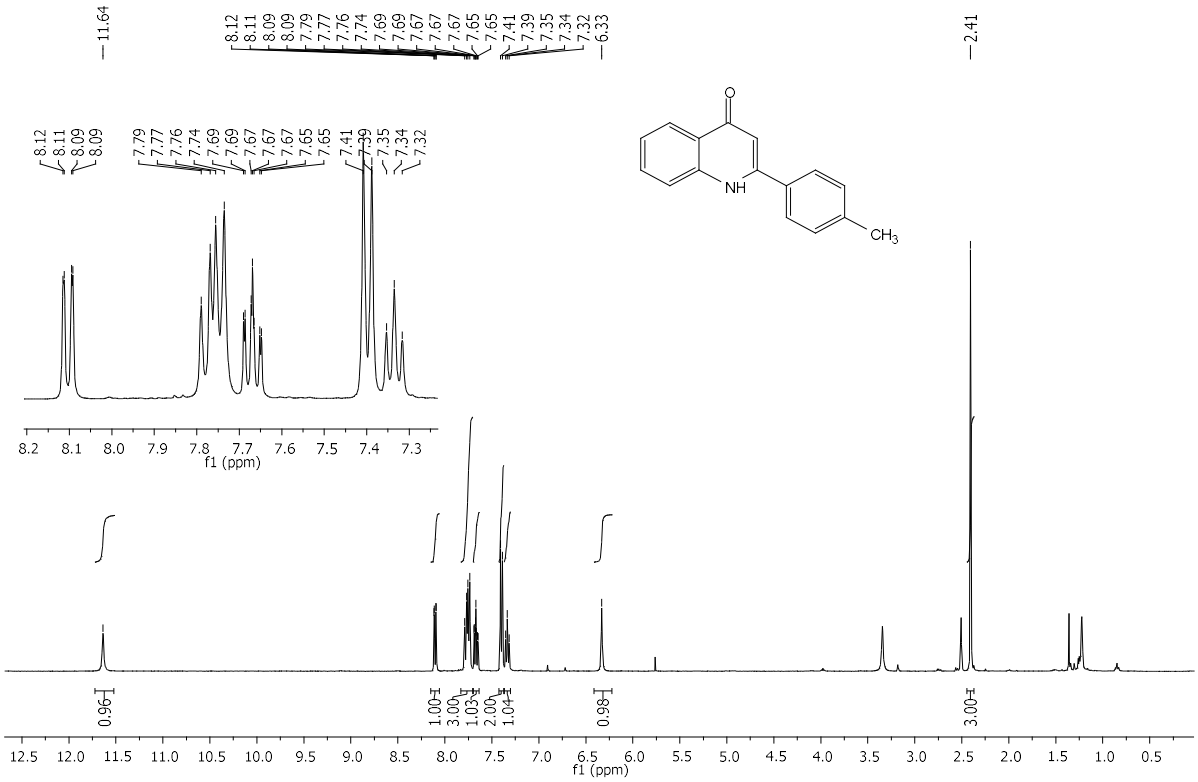


Fig. 219. [1]H NMR of **6b** in DMSO-d_6.

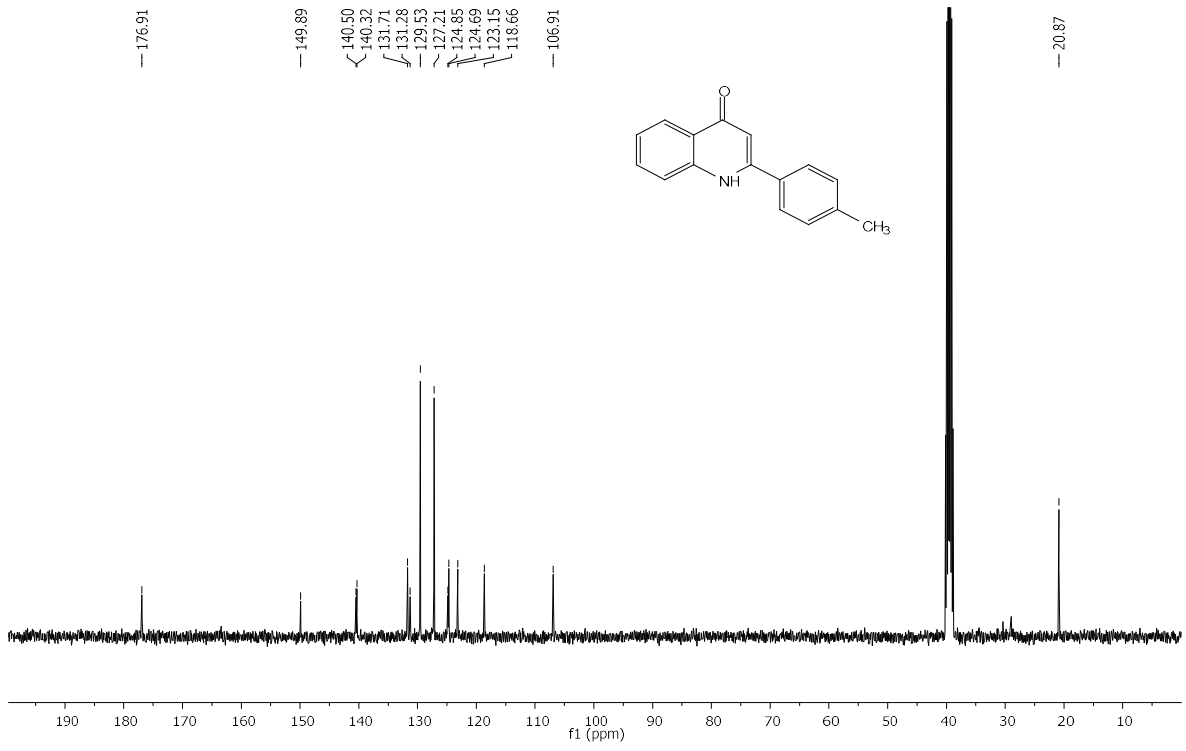


Fig. 220. [13]C NMR of **6b** in DMSO-d_6.

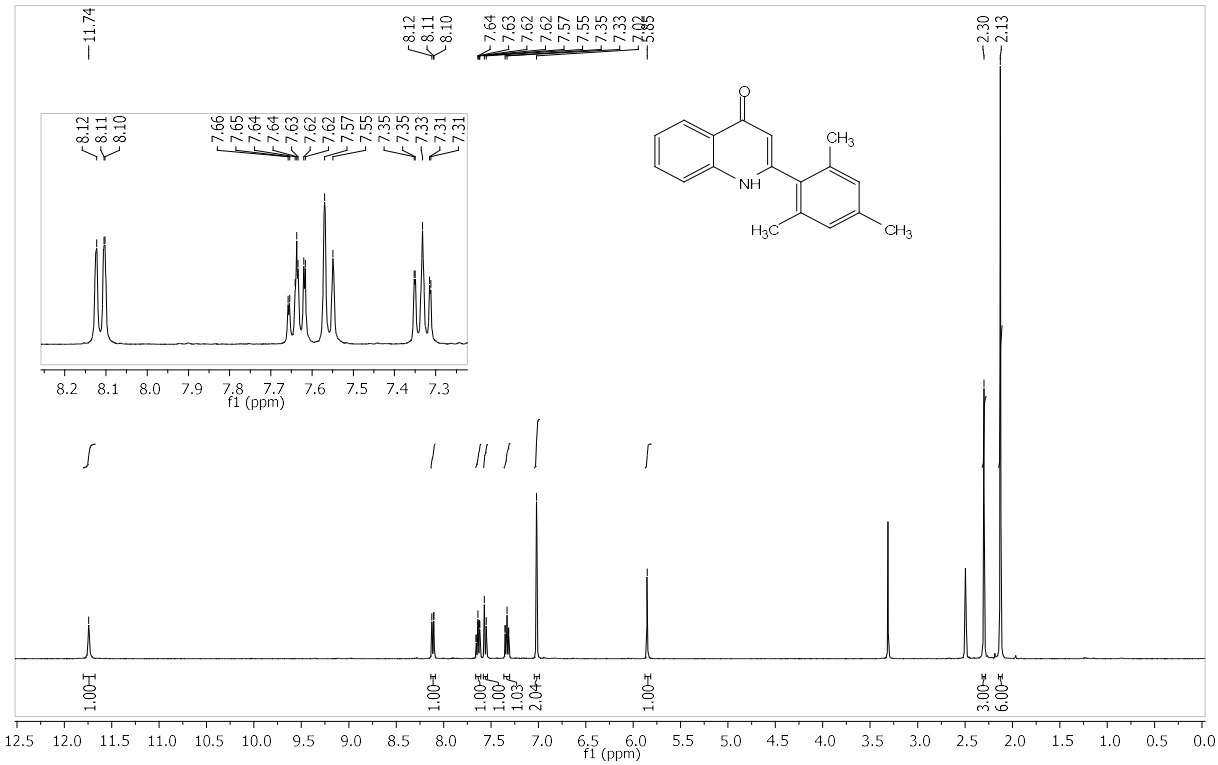


Fig. 221. [1]H NMR of **6c** in DMSO-d_6.

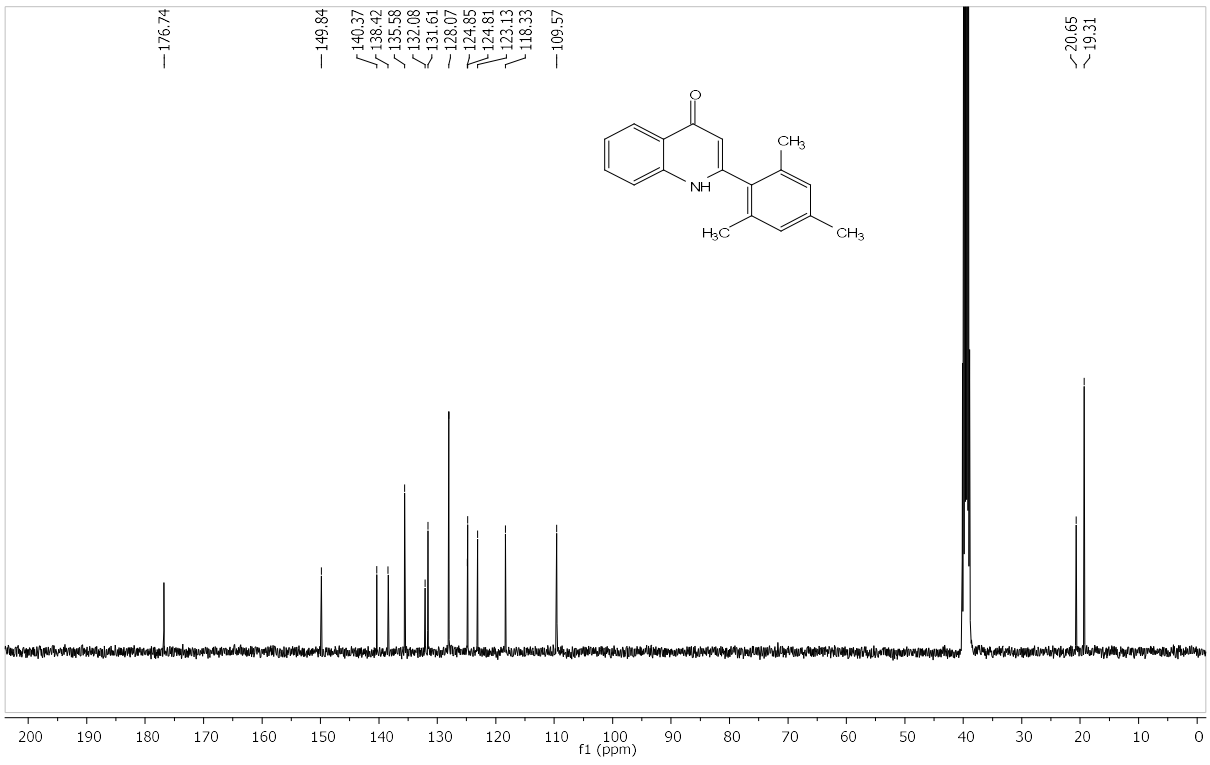


Fig. 222. [13]C NMR of **6c** in DMSO-d_6.

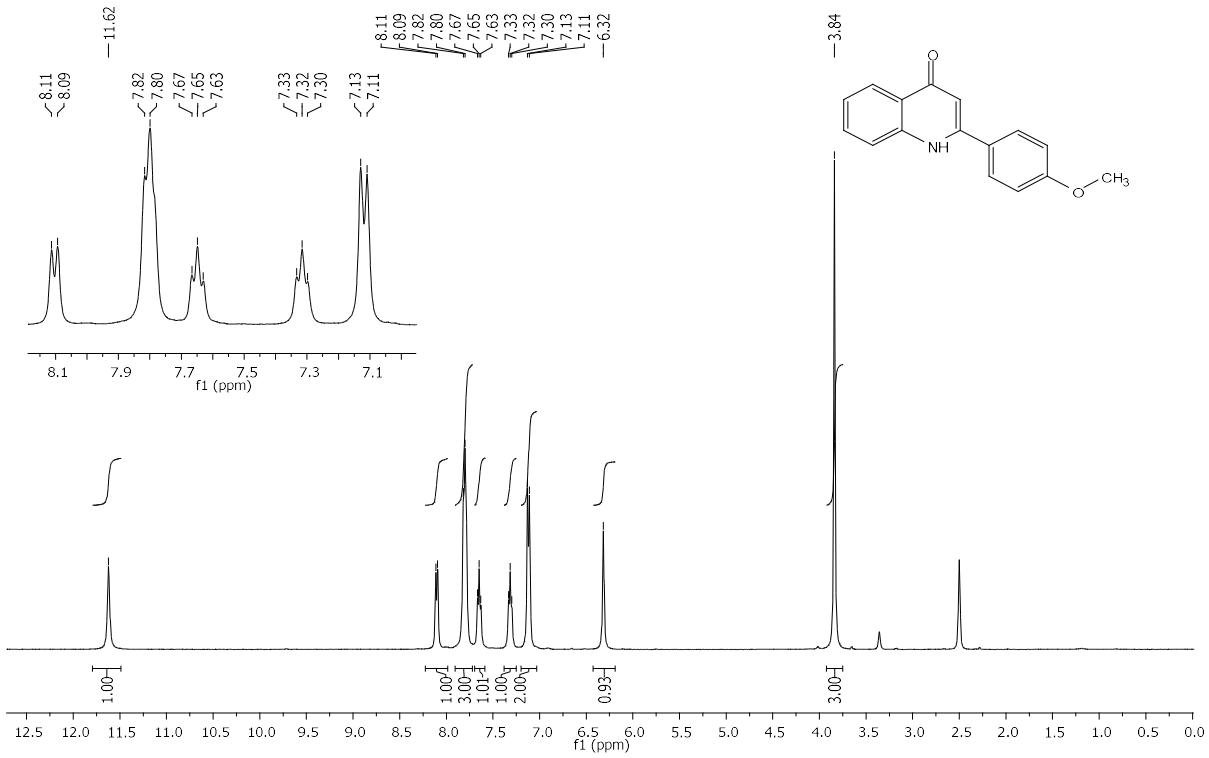


Fig. 223. [1]H NMR of **6d** in DMSO-d_6.

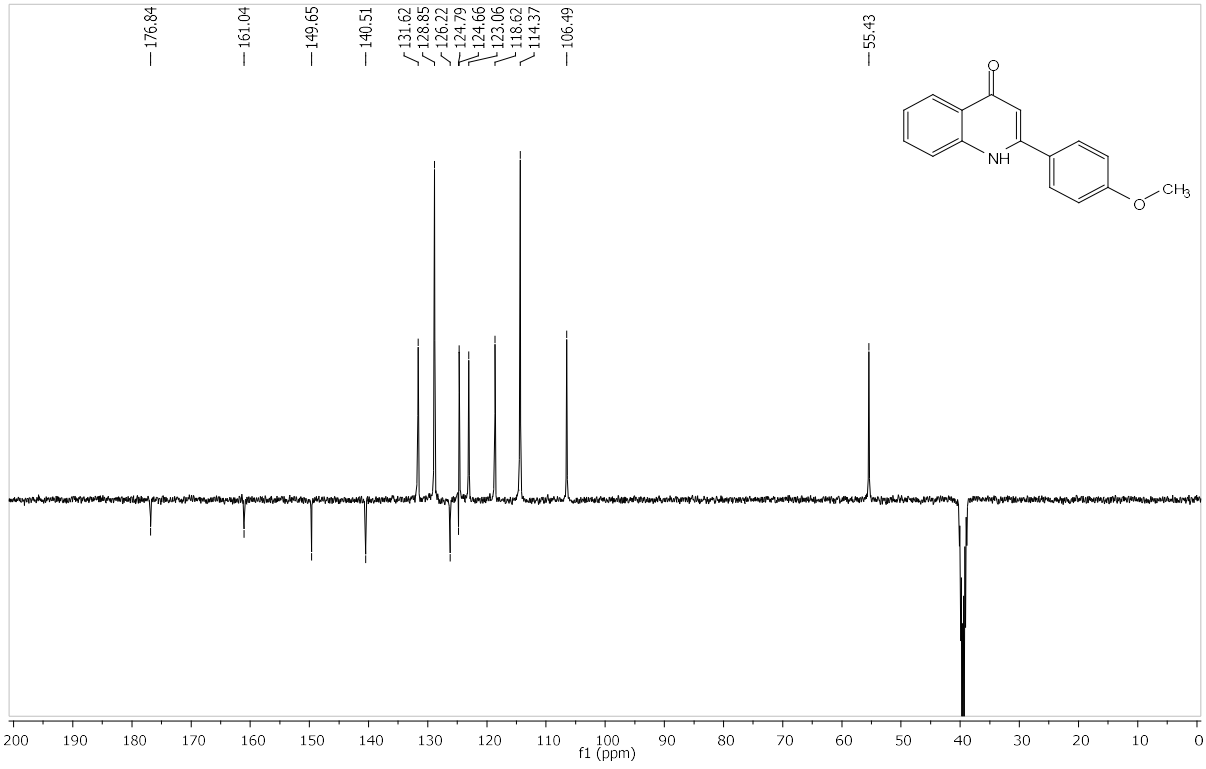


Fig. 224. [13]C NMR of **6d** in DMSO-d_6.

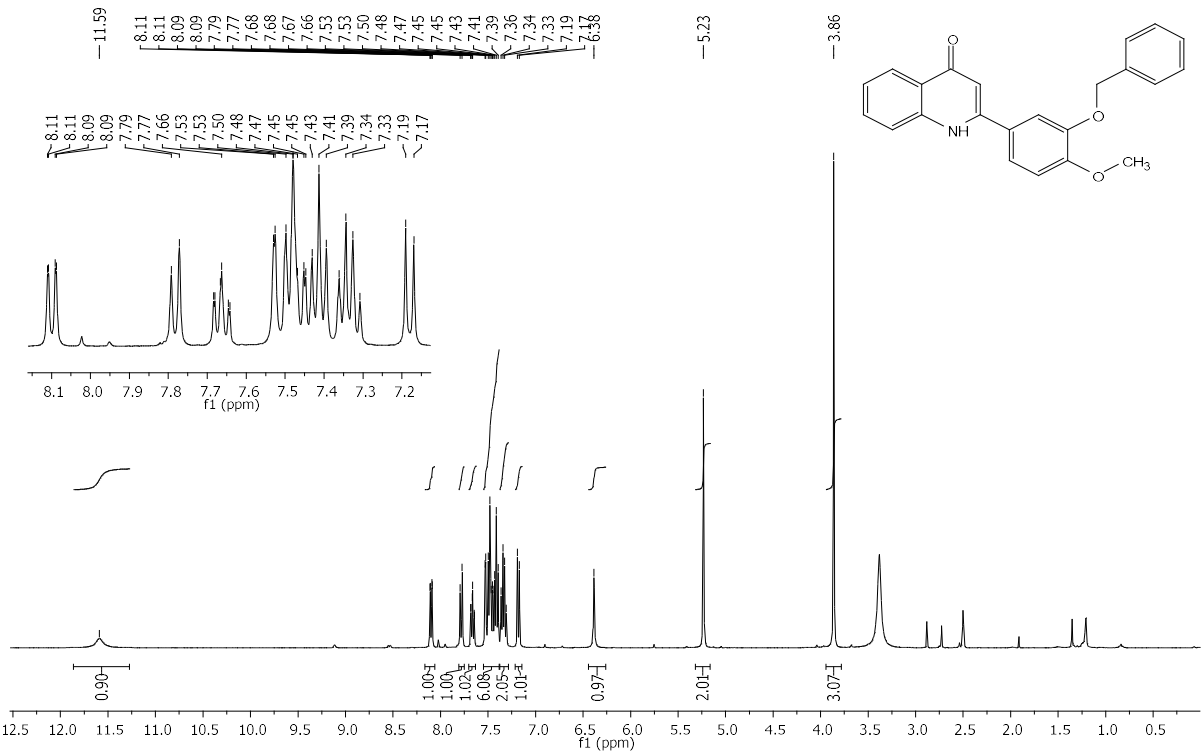


Fig. 225. [1]H NMR of **6e** in DMSO-d_6.

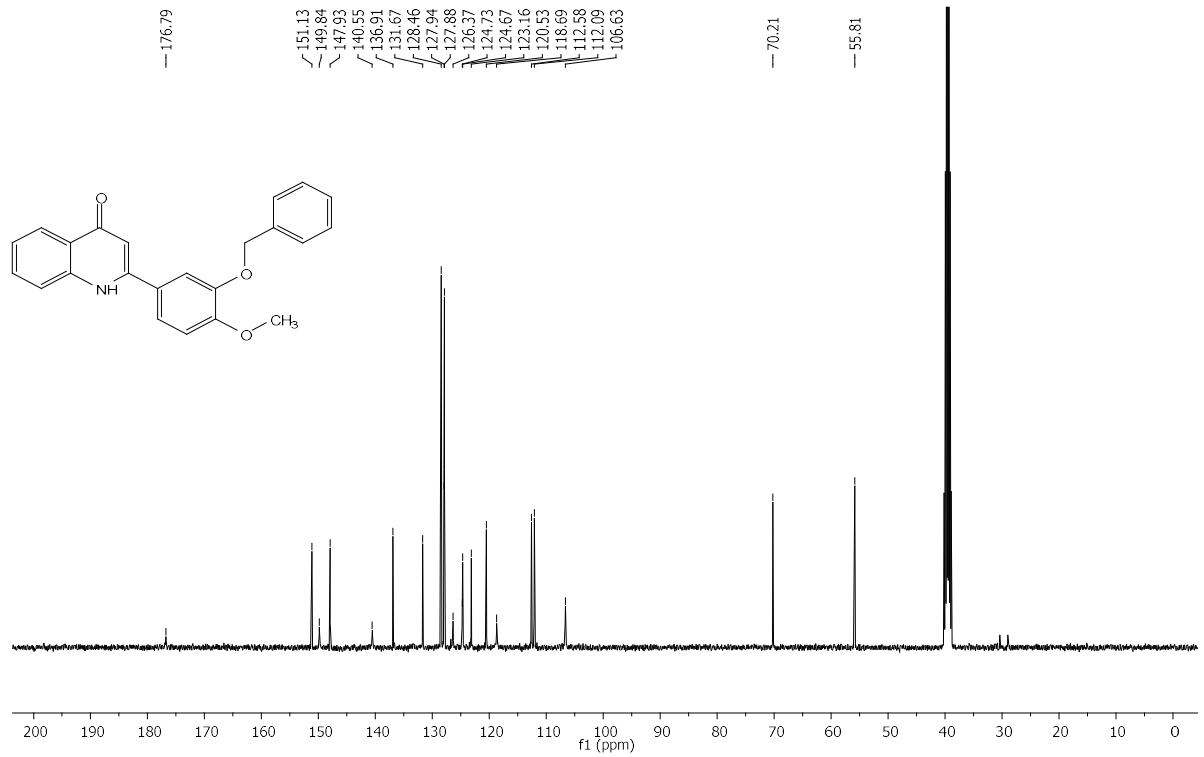


Fig. 226. [13]C NMR of **6e** in DMSO-d_6.

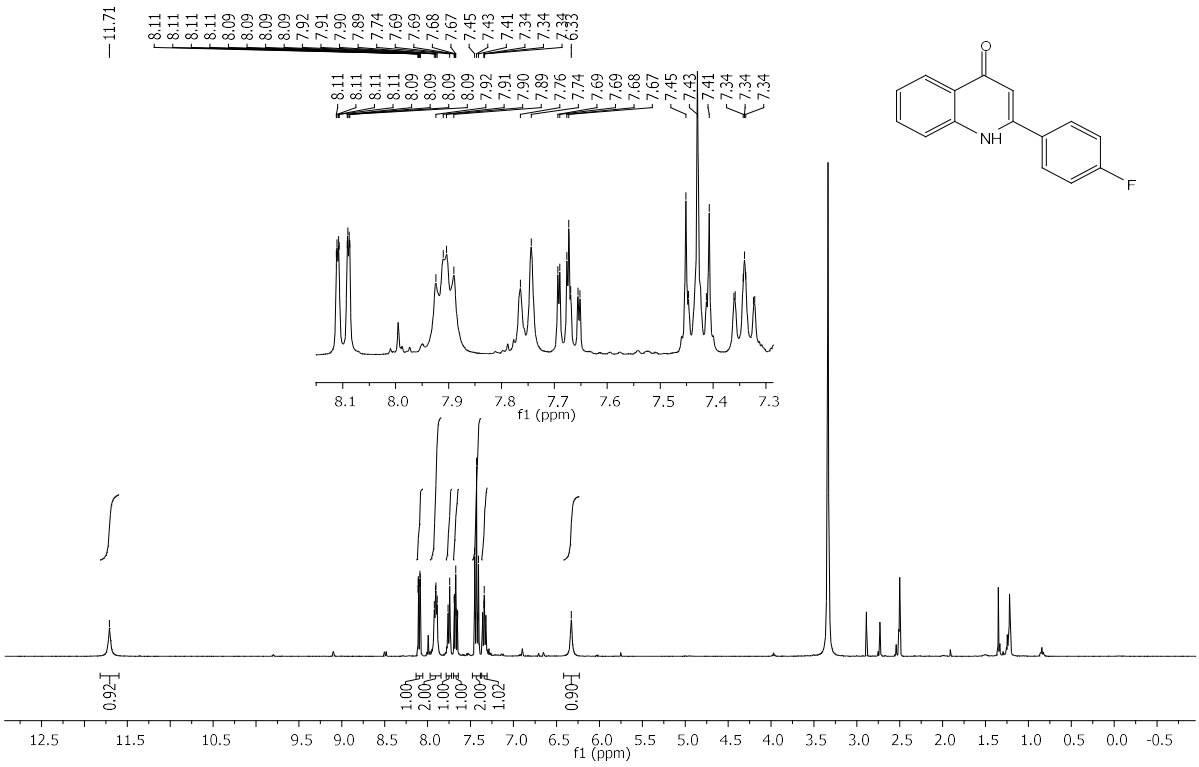


Fig. 227. [1]H NMR of **6g** in DMSO-d_6.

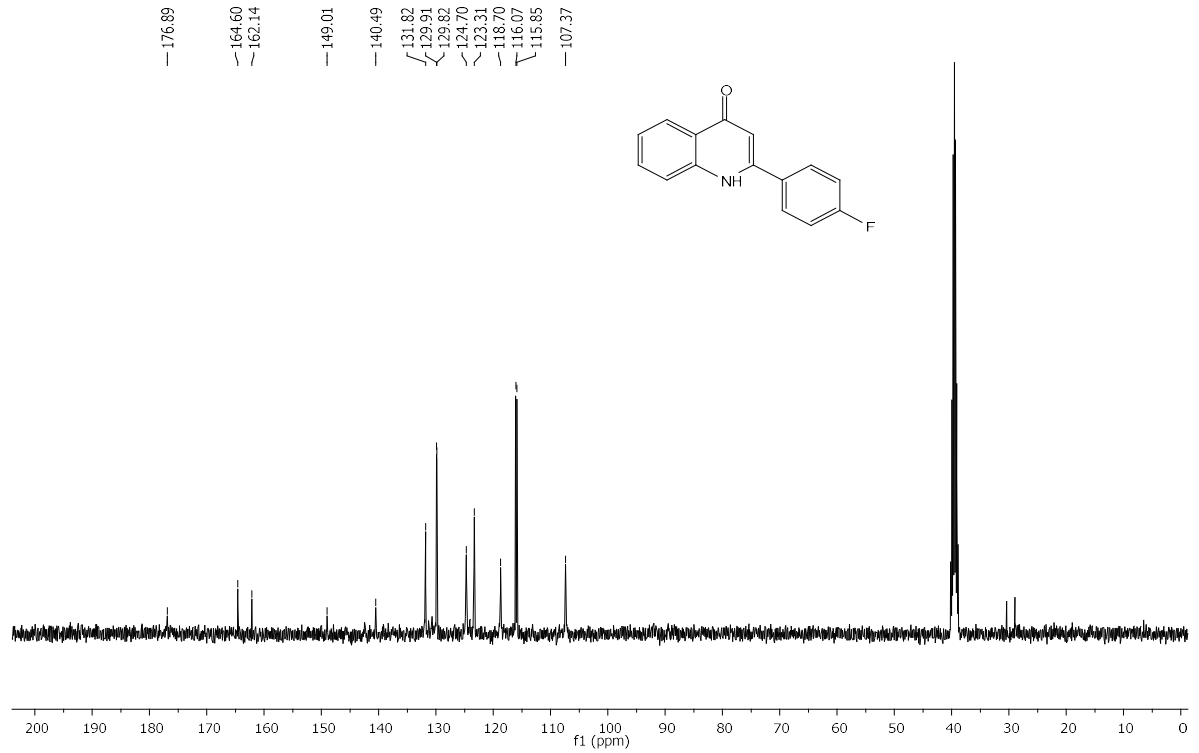


Fig. 228. [13]C NMR of **6g** in DMSO-d_6.

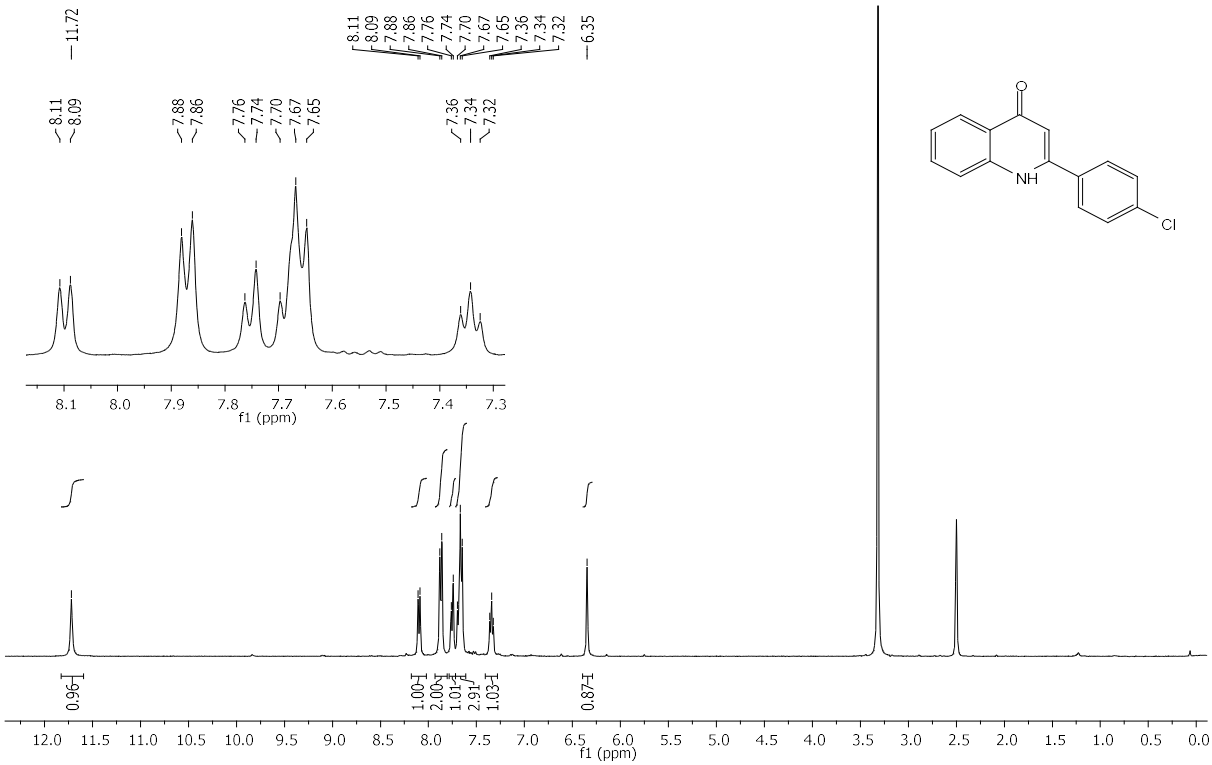


Fig. 229. [1]H NMR of **6h** in DMSO-d_6.

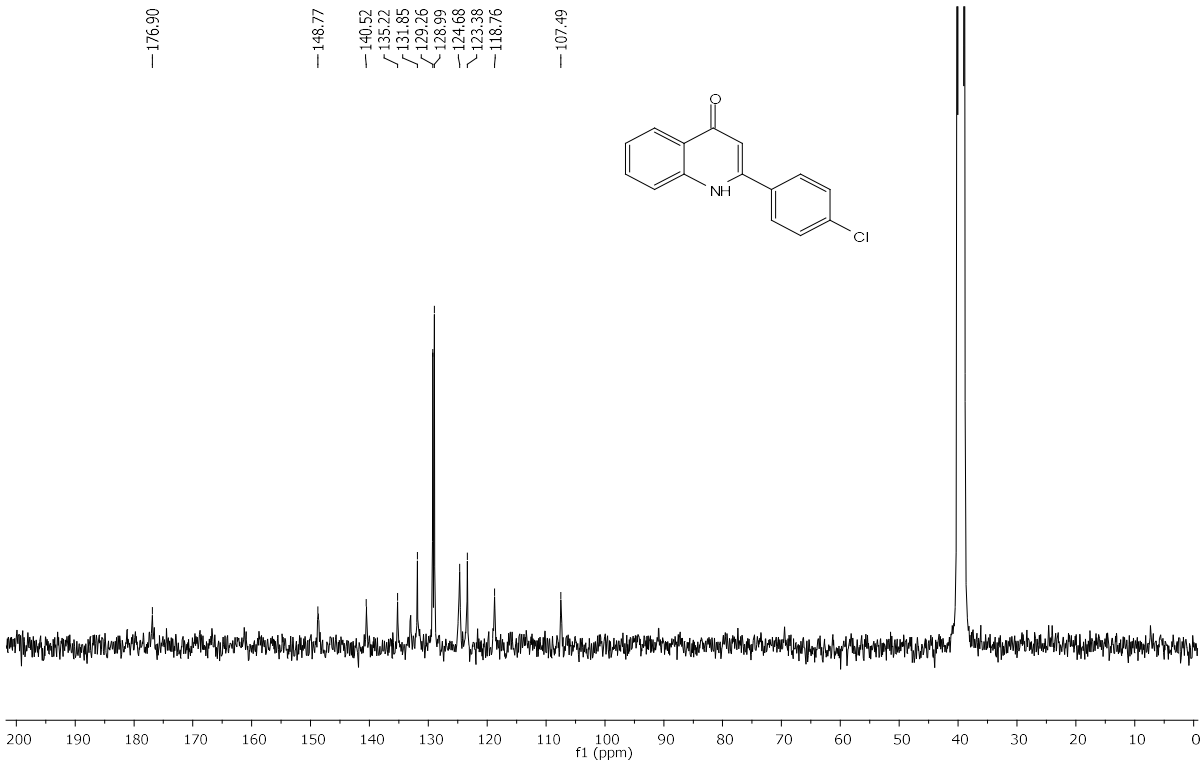


Fig. 230. [13]C NMR of **6h** in DMSO-d_6.

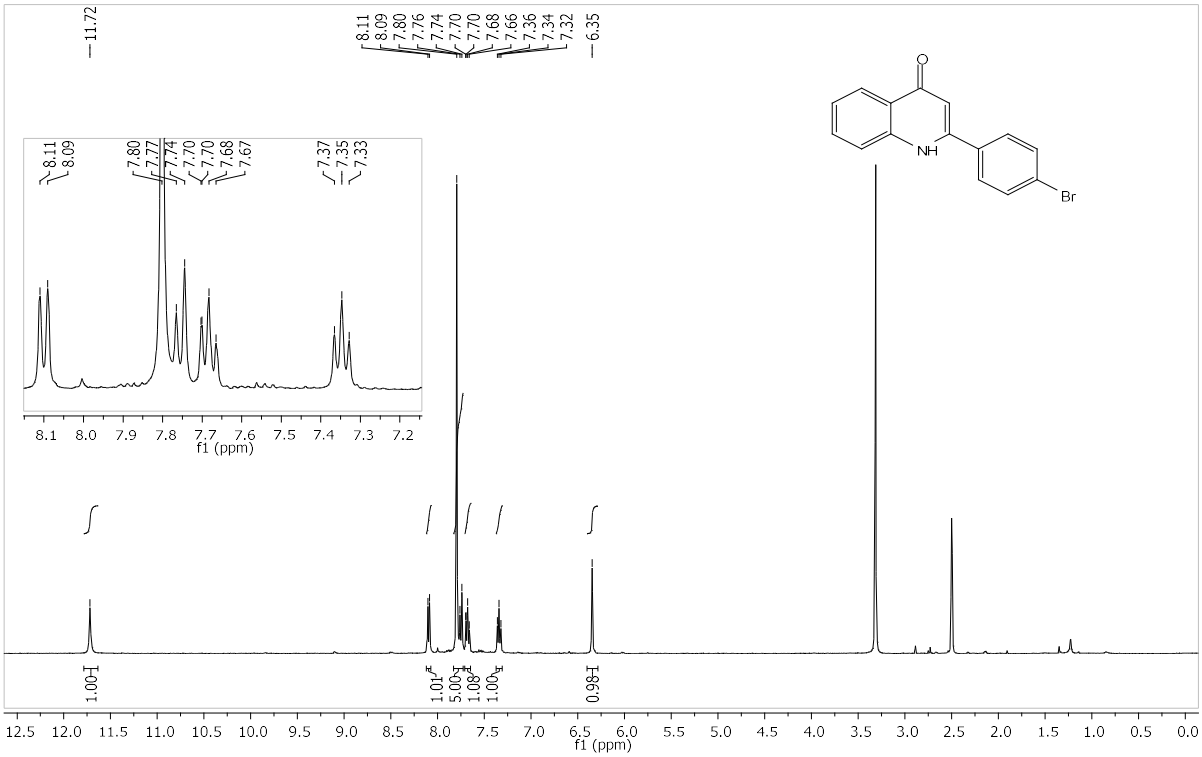


Fig. 231. [1]H NMR of **6i** in DMSO-d_6.

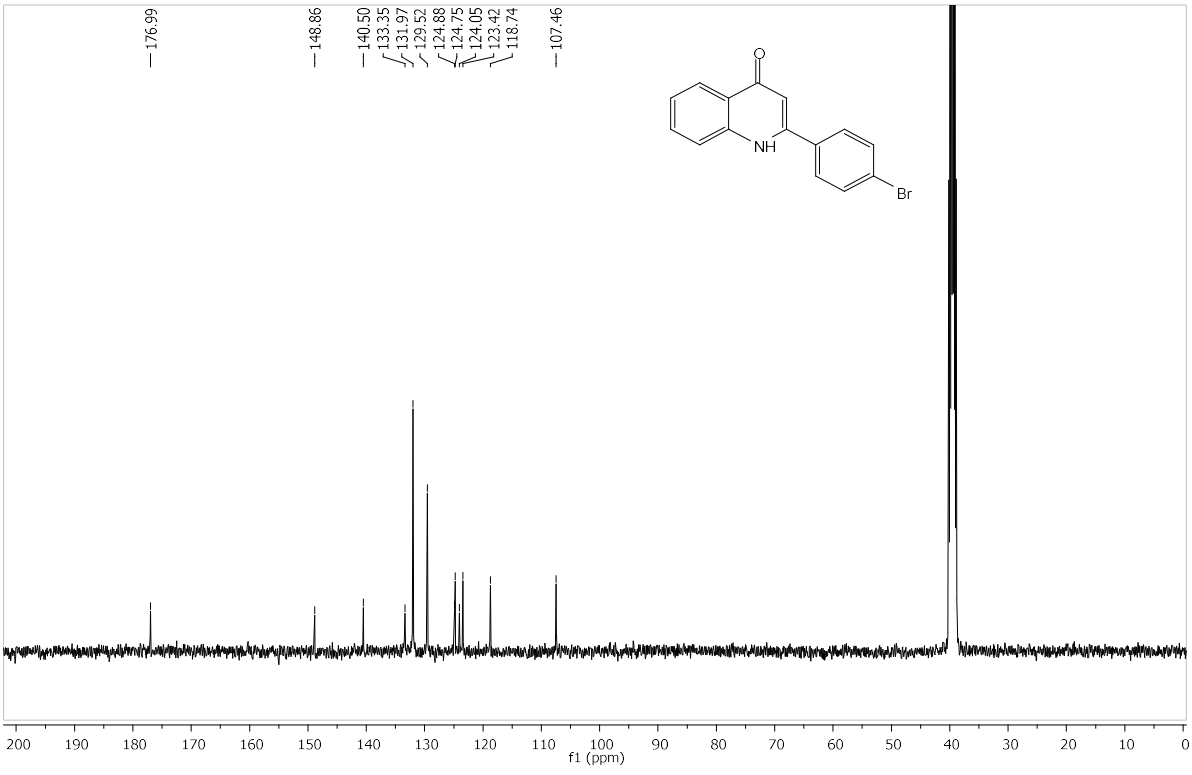


Fig. 232. [13]C NMR of **6i** in DMSO-d_6.

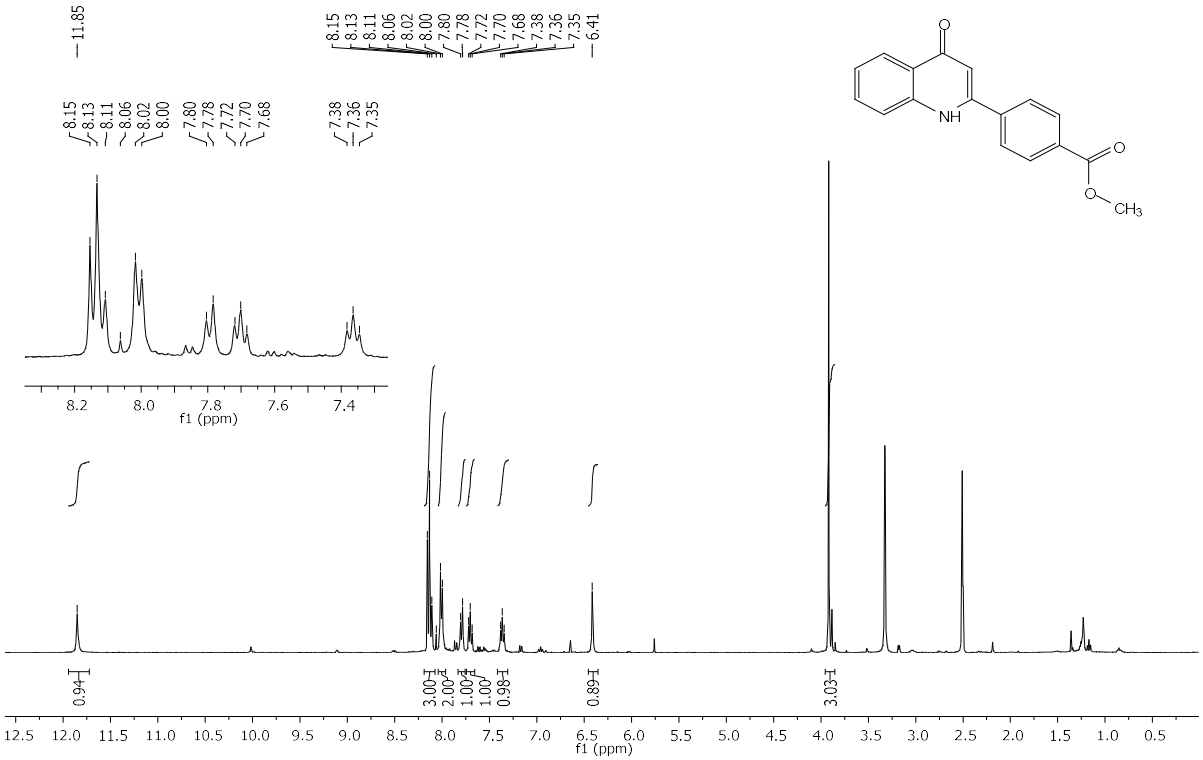


Fig. 233. ^{1}H NMR of **6j** in DMSO-d_6.

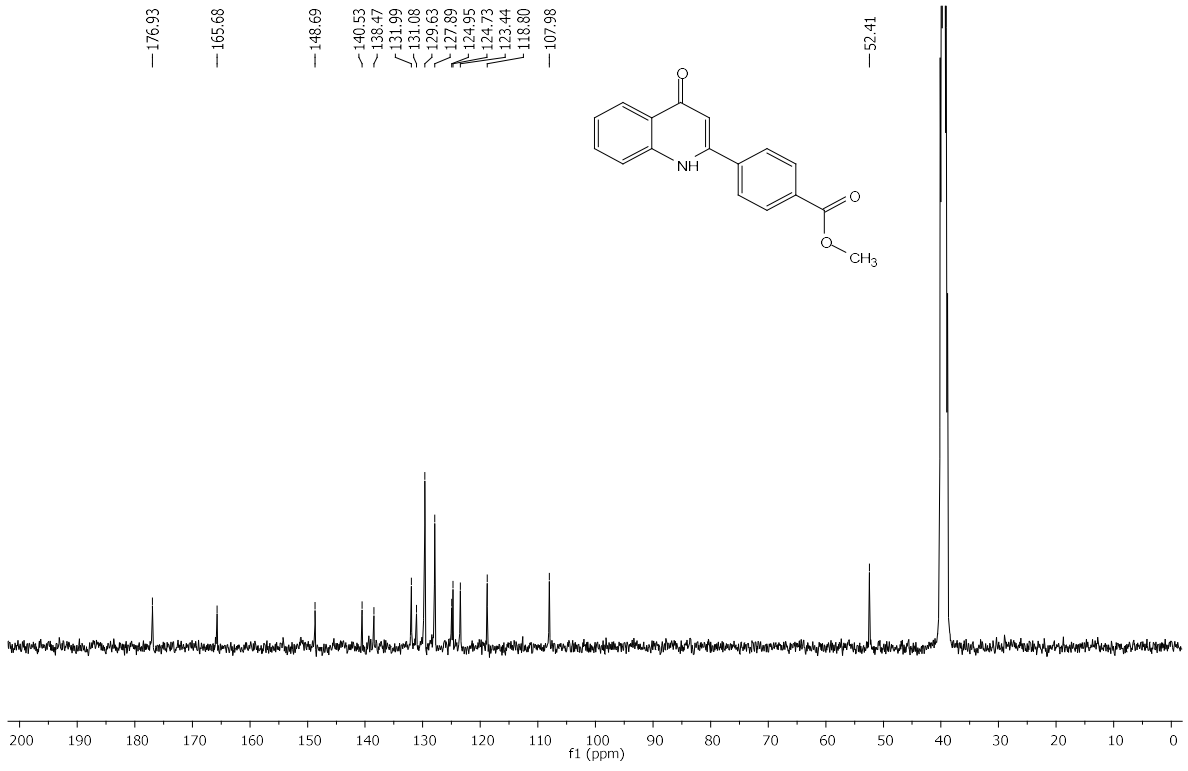


Fig. 234. ^{13}C NMR of **6j** in DMSO-d_6.

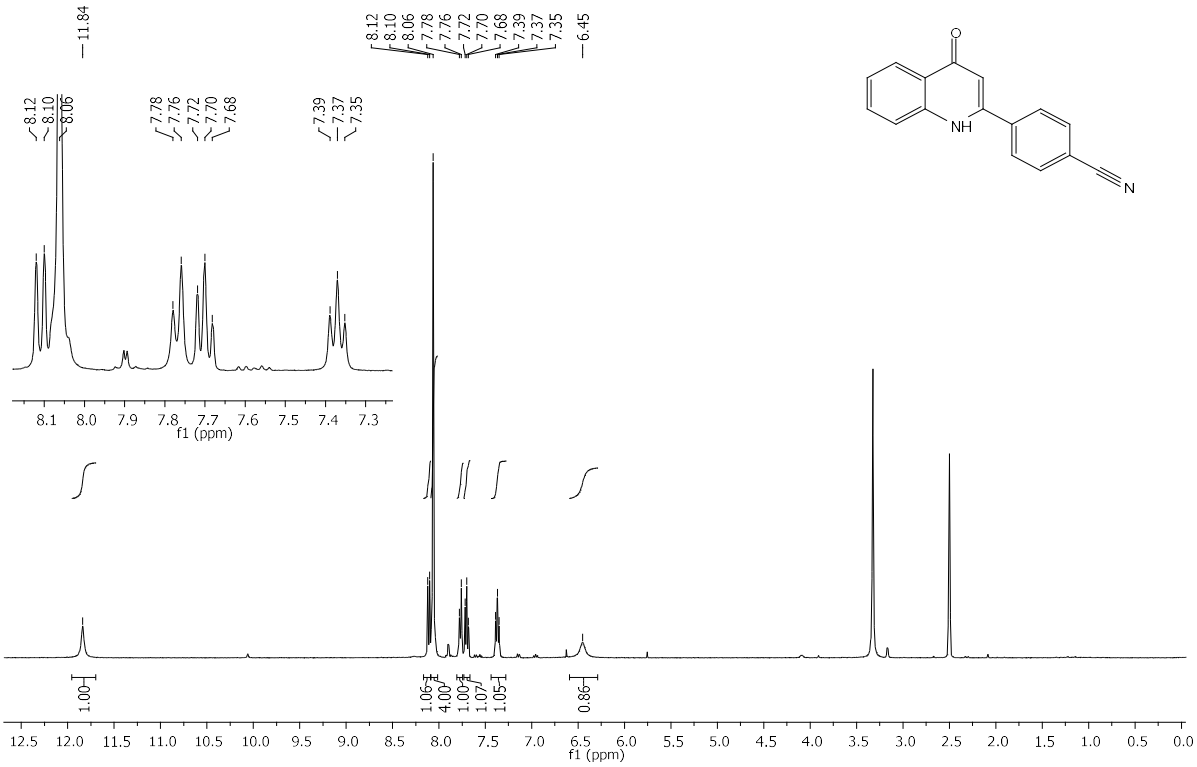


Fig. 235. ^{1}H NMR of **6k** in DMSO-d_6.

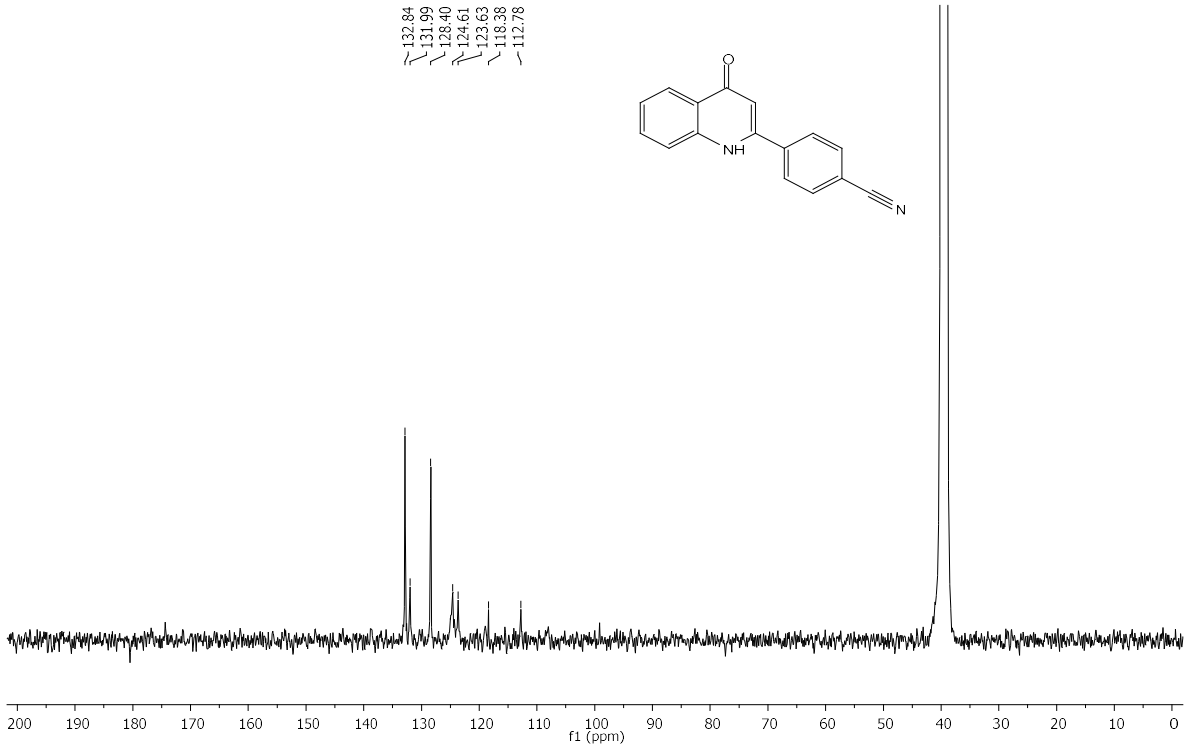


Fig. 236. ^{13}C NMR of **6k** in DMSO-d_6.

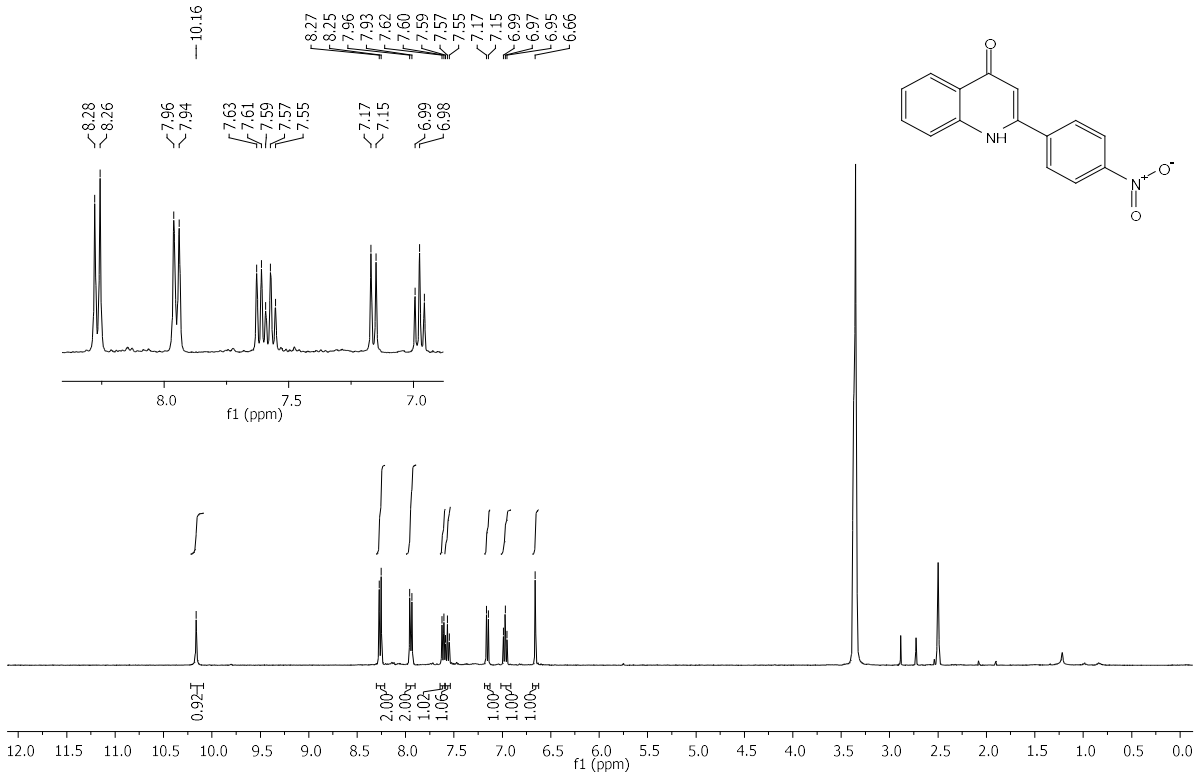


Fig. 237. ^{1}H NMR of **6l** in DMSO-d_6.

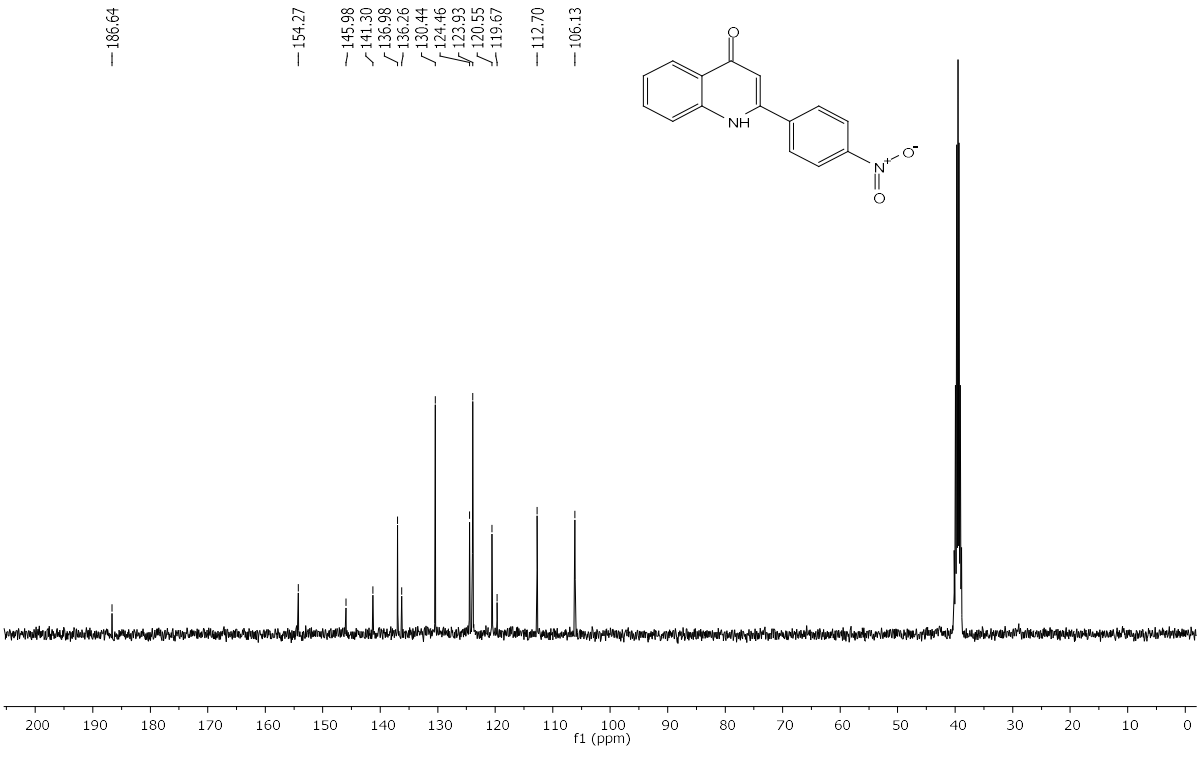


Fig. 238. ^{13}C NMR of **6l** in DMSO-d_6.

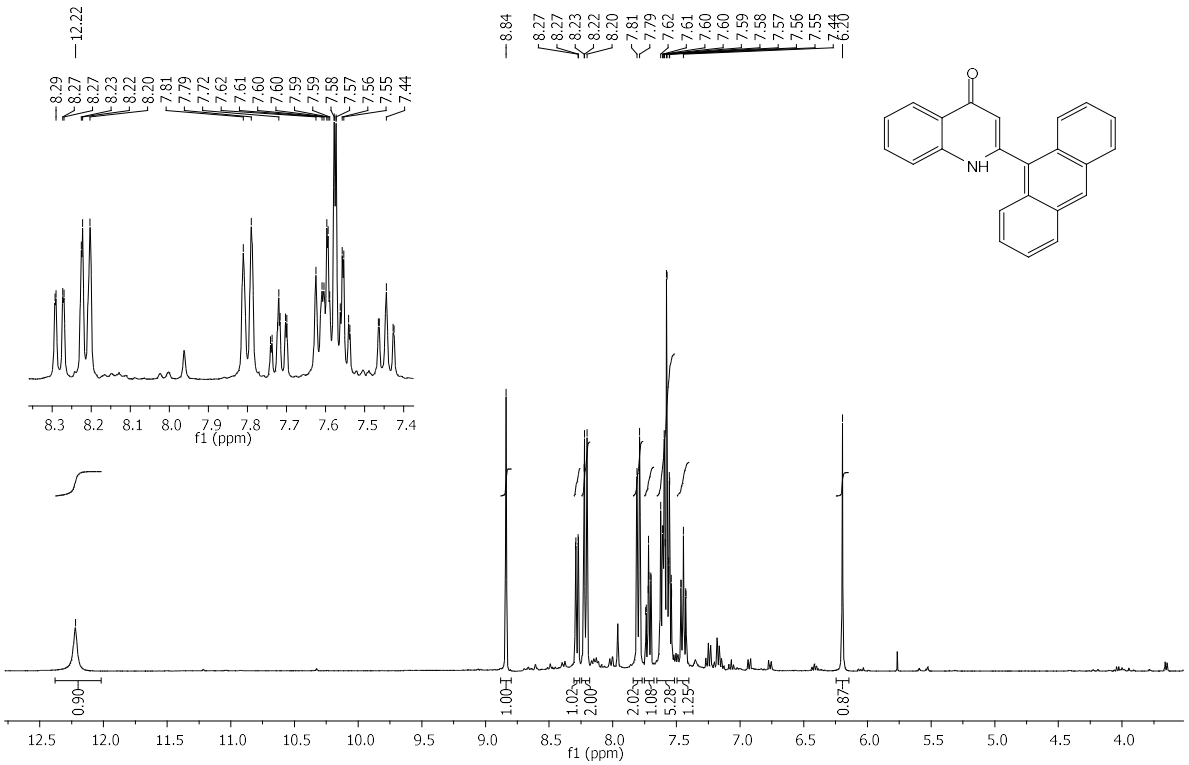


Fig. 239. [1]H NMR of **6m** in DMSO-*d*$_6$.

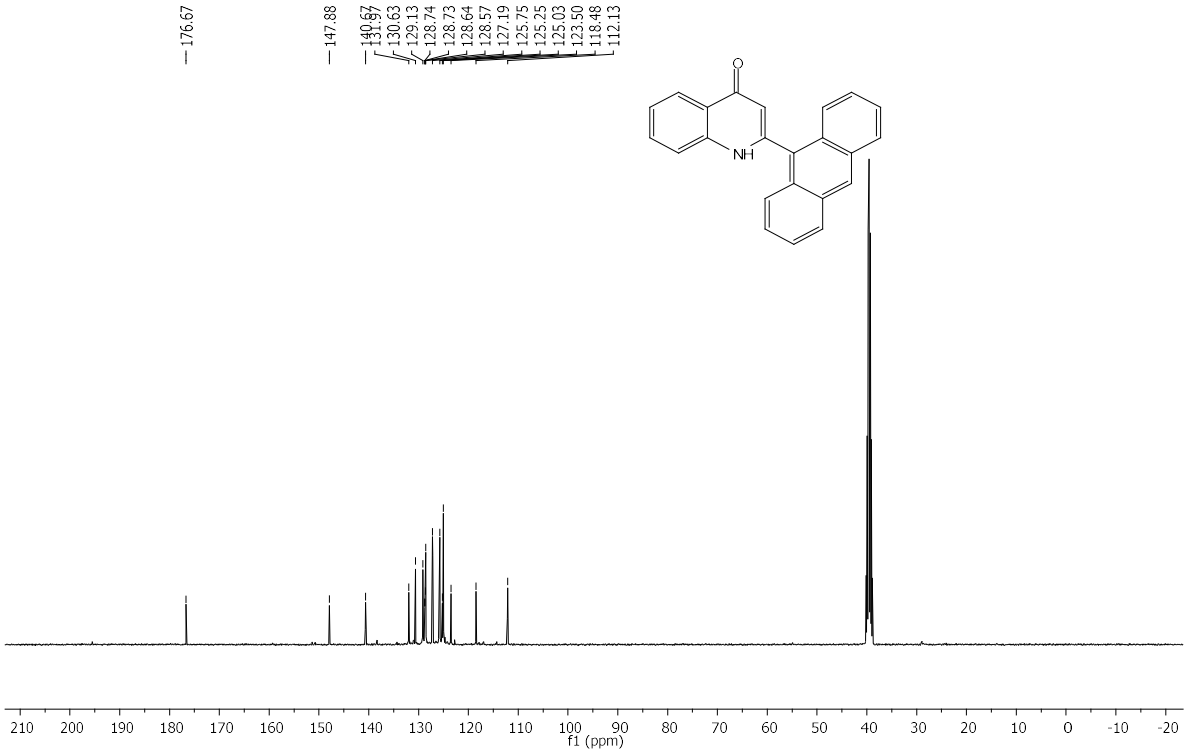


Fig. 240. [13]C NMR of **6m** in DMSO-*d*$_6$.

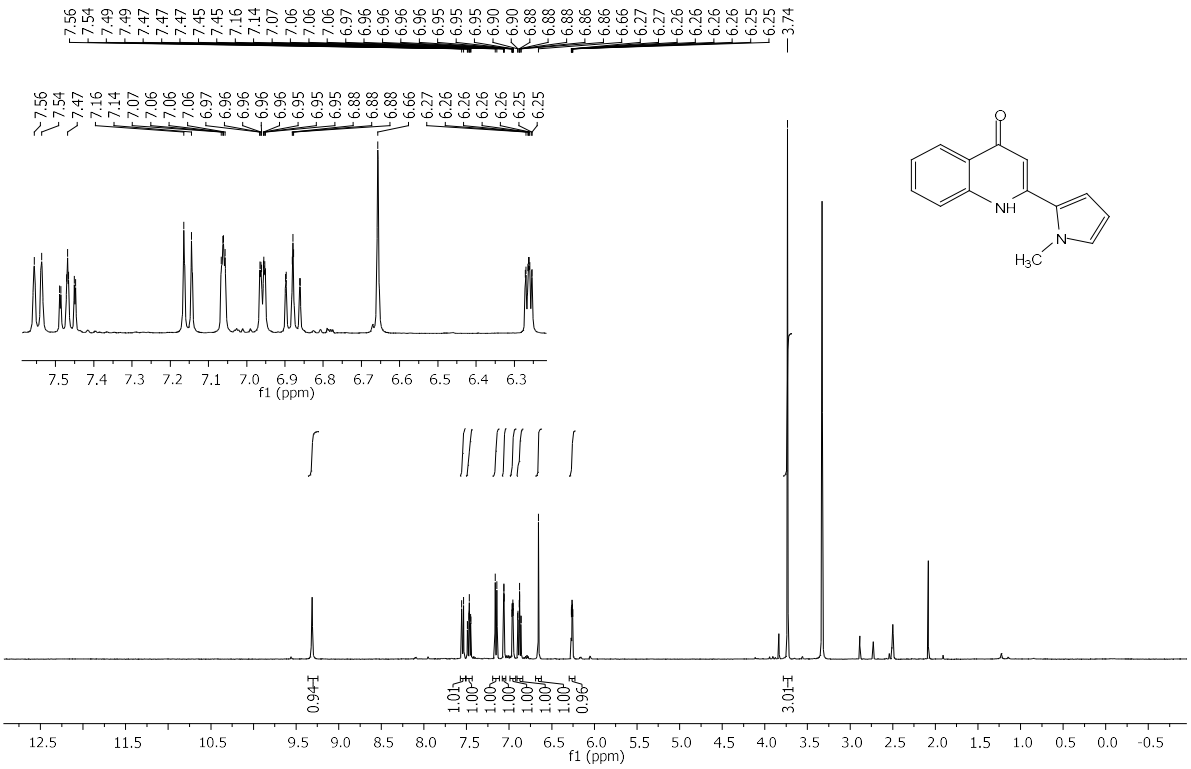


Fig. 241. ^{1}H NMR of **6n** in DMSO-d_6.

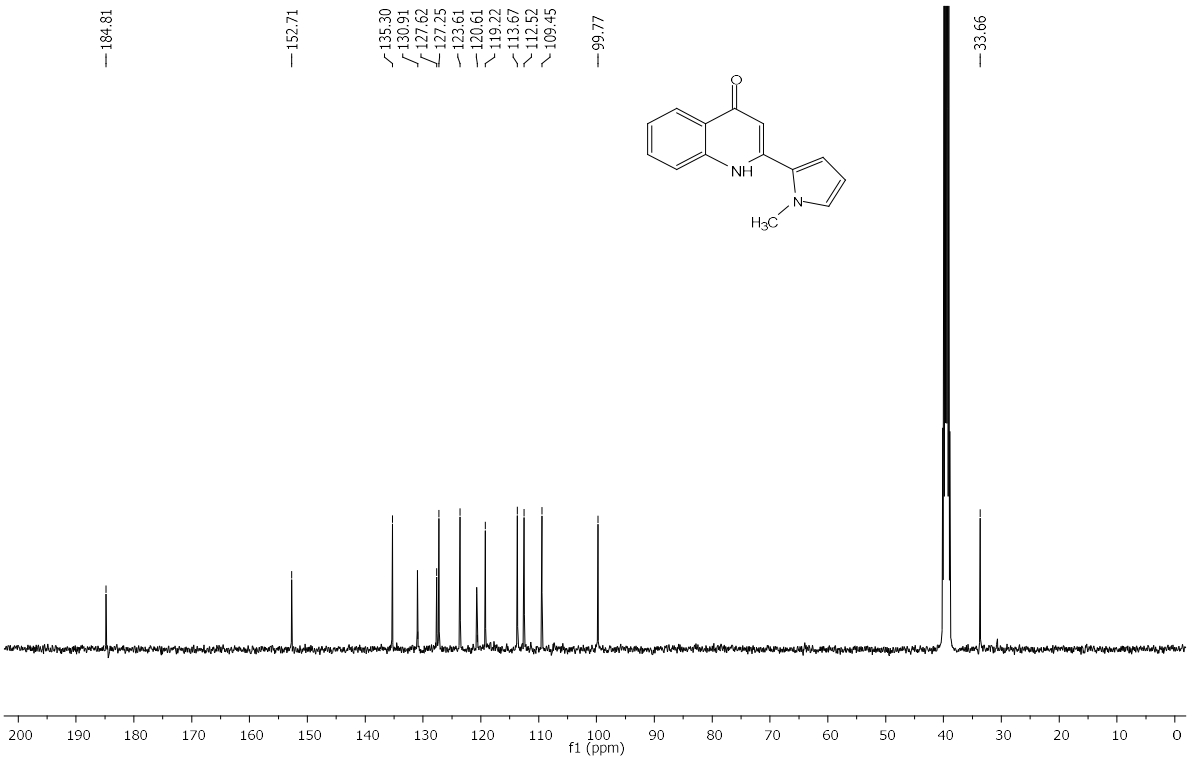


Fig. 242. ^{13}C NMR of **6n** in DMSO-d_6.

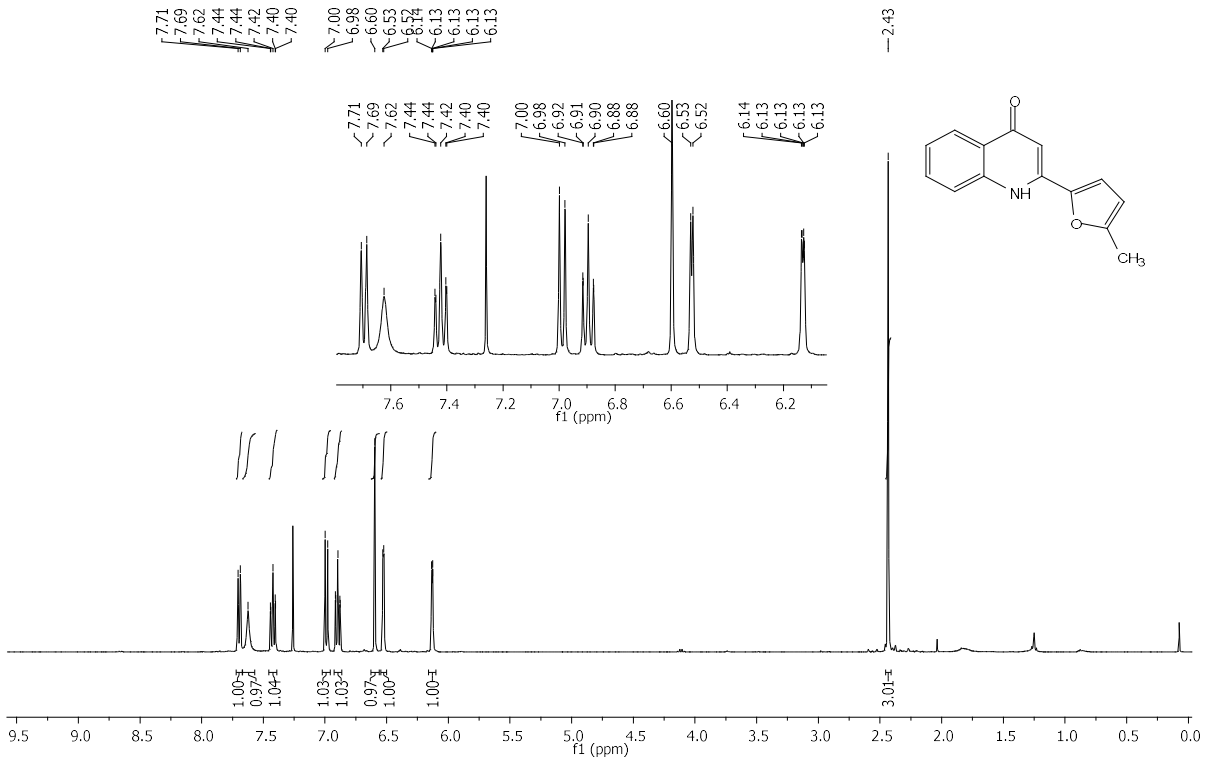


Fig. 243. [1]H NMR of **6o** in DMSO-d_6.

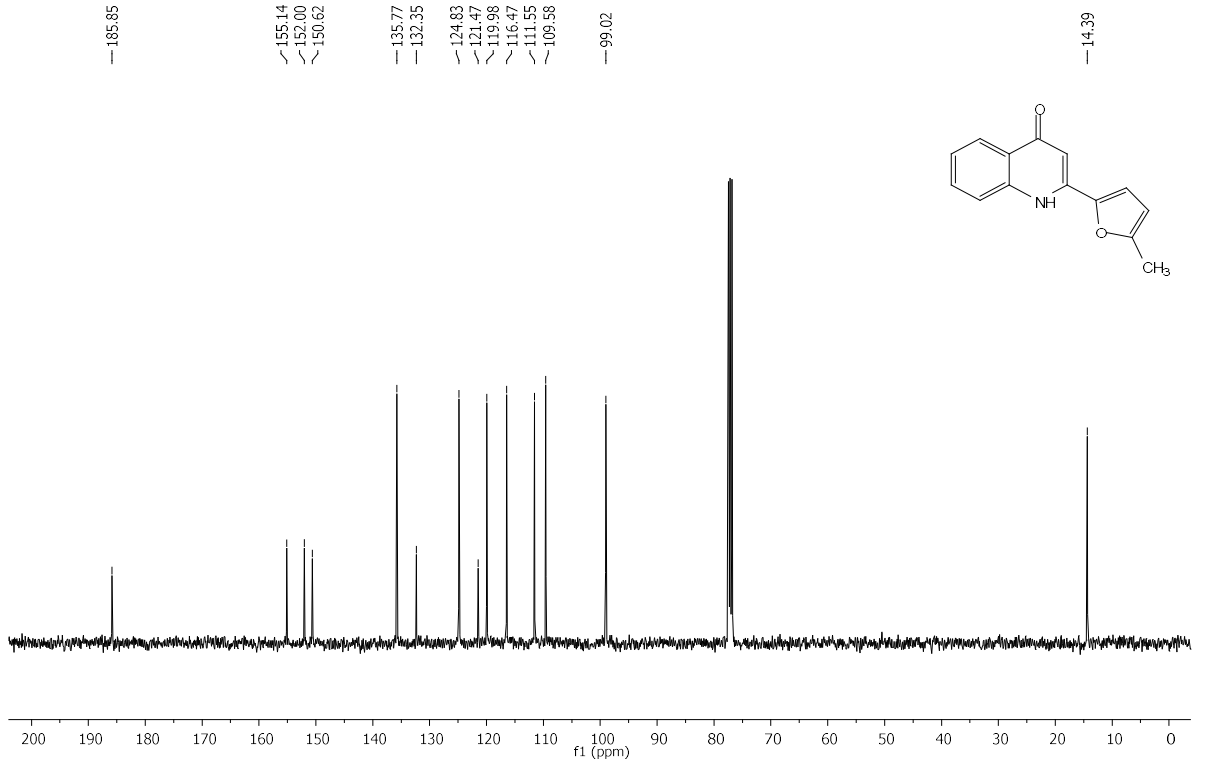


Fig. 244. [13]C NMR of **6o** in DMSO-d_6.

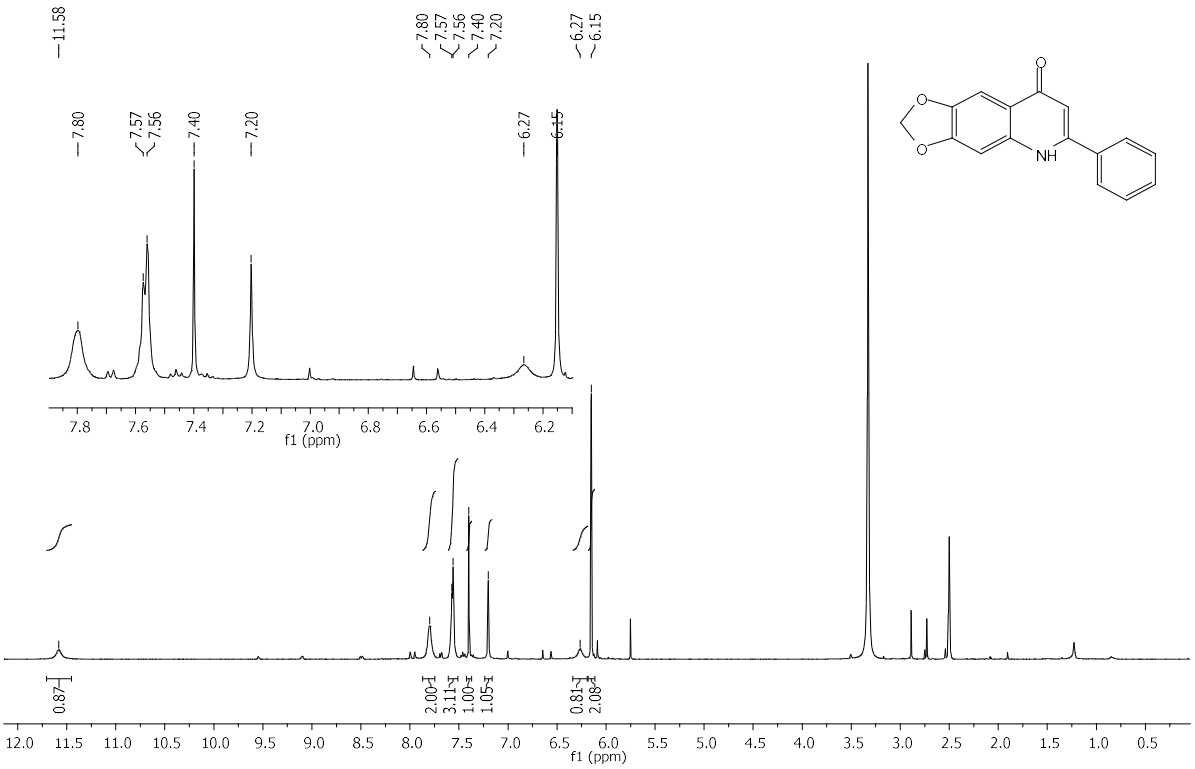


Fig. 245. ^{1}H NMR of **6p** in DMSO-d_6.

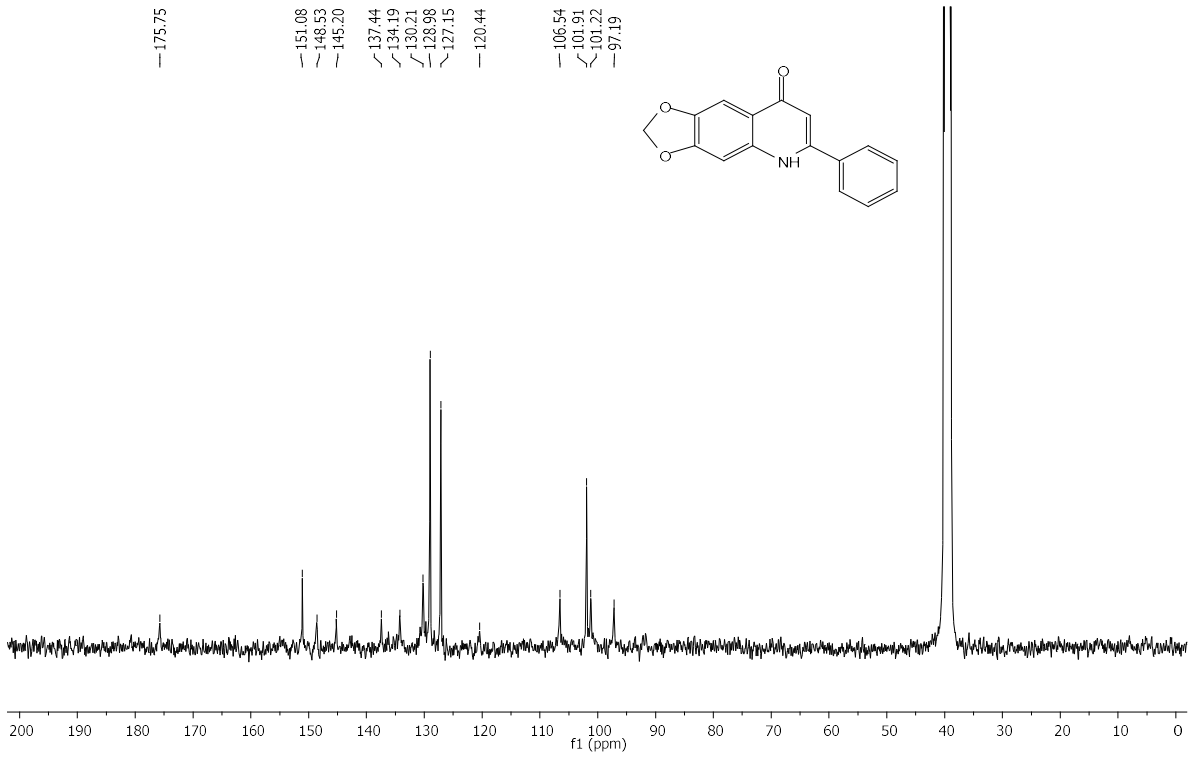


Fig. 246. ^{13}C NMR of **6p** in DMSO-d_6.

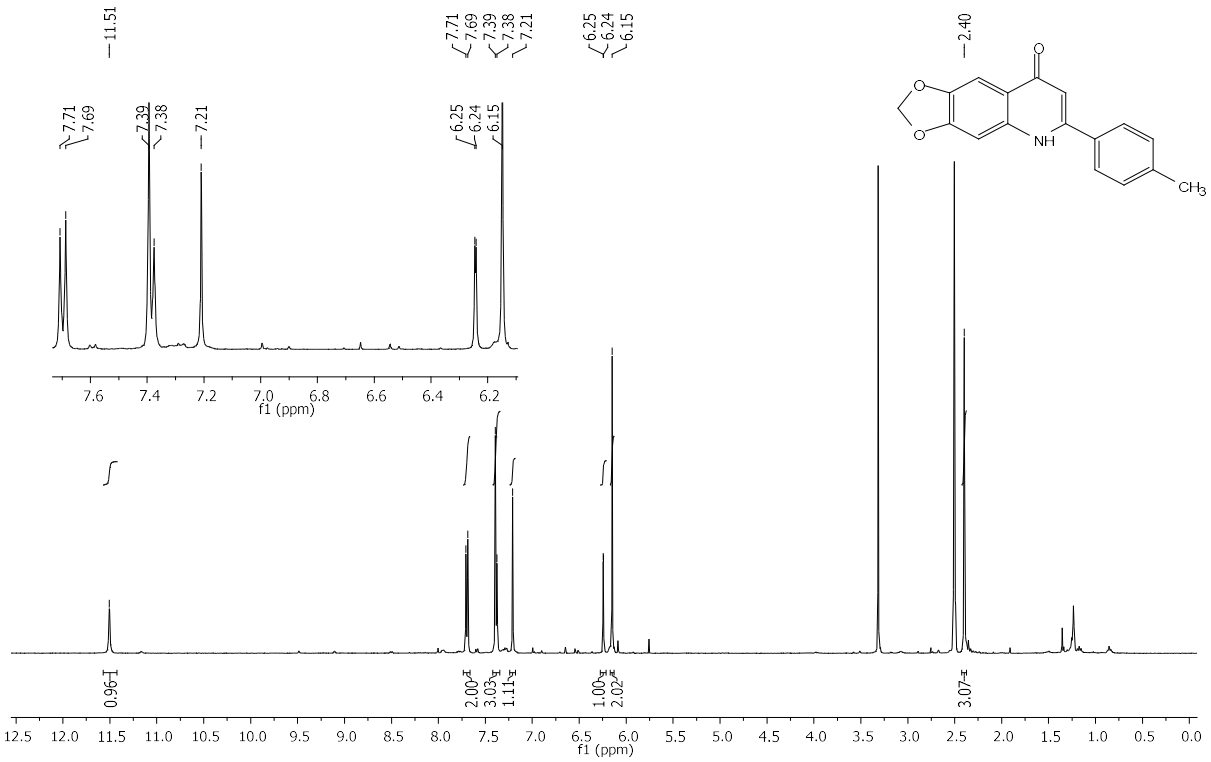


Fig. 247. [1]H NMR of **6q** in DMSO-*d*$_6$.

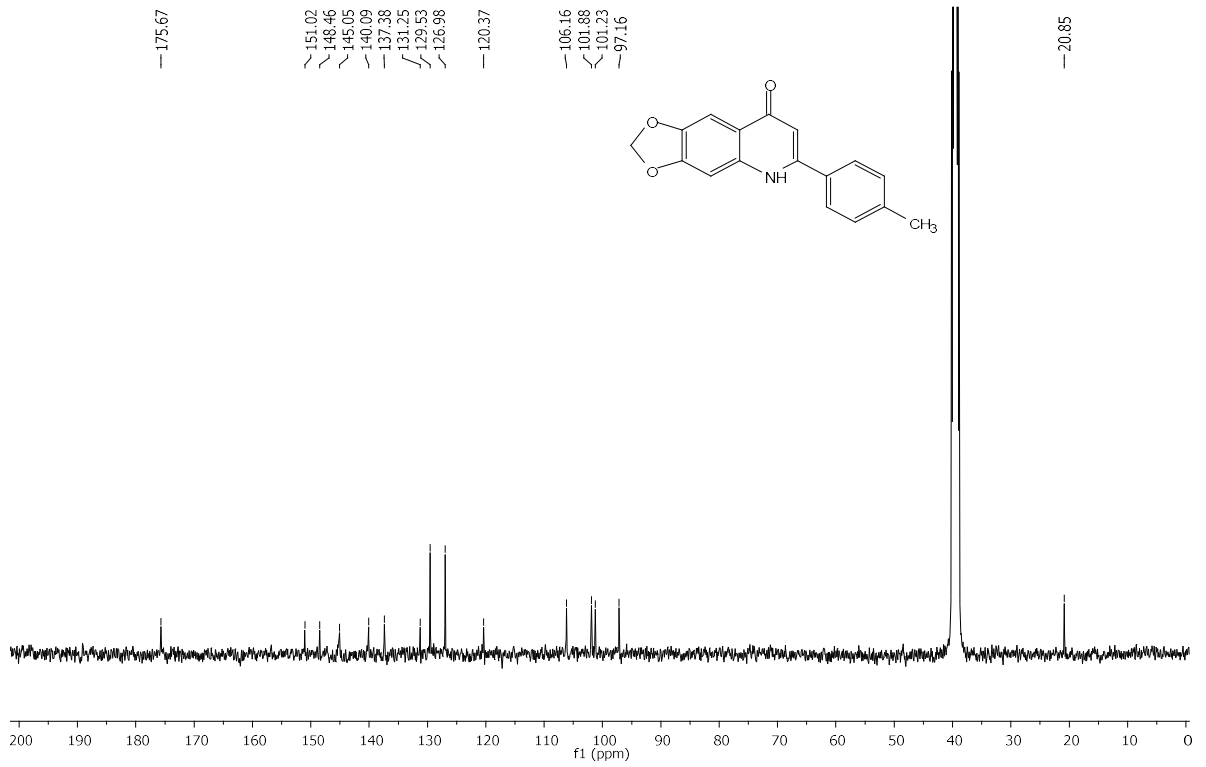


Fig. 248. [13]C NMR of **6q** in DMSO-*d*$_6$.

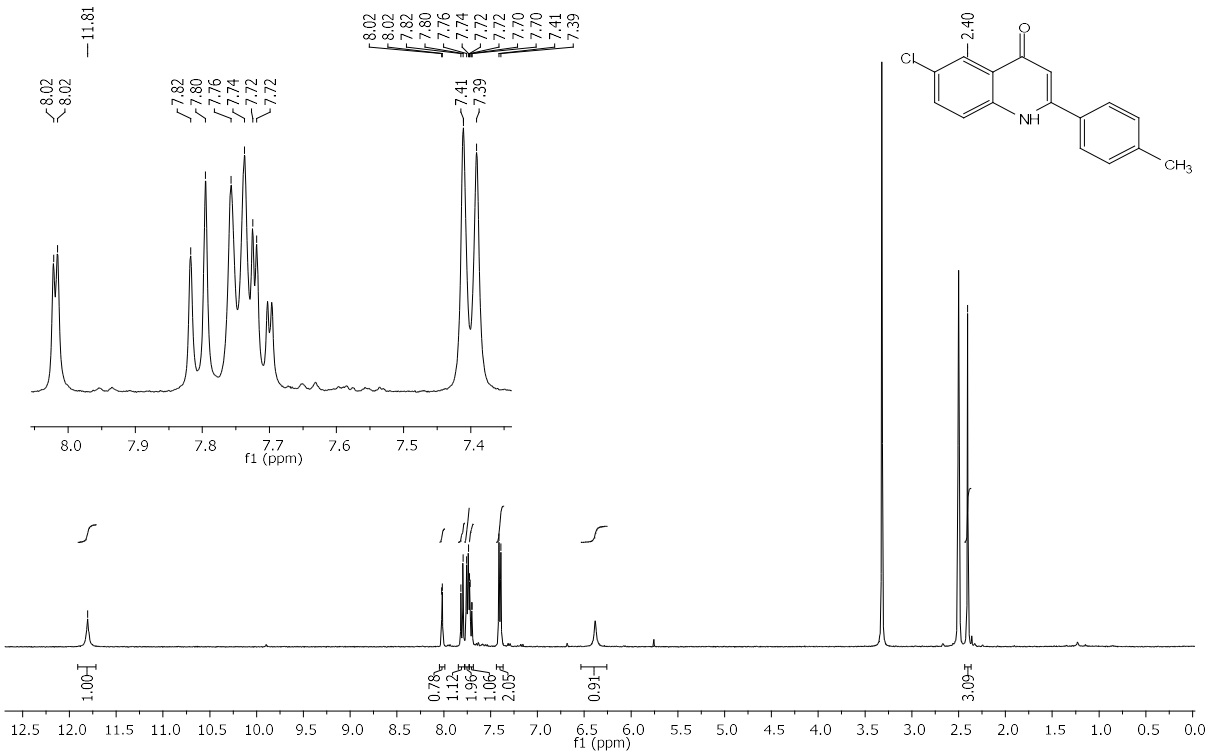


Fig. 249. ^{1}H NMR of **6r** in DMSO-d_6.

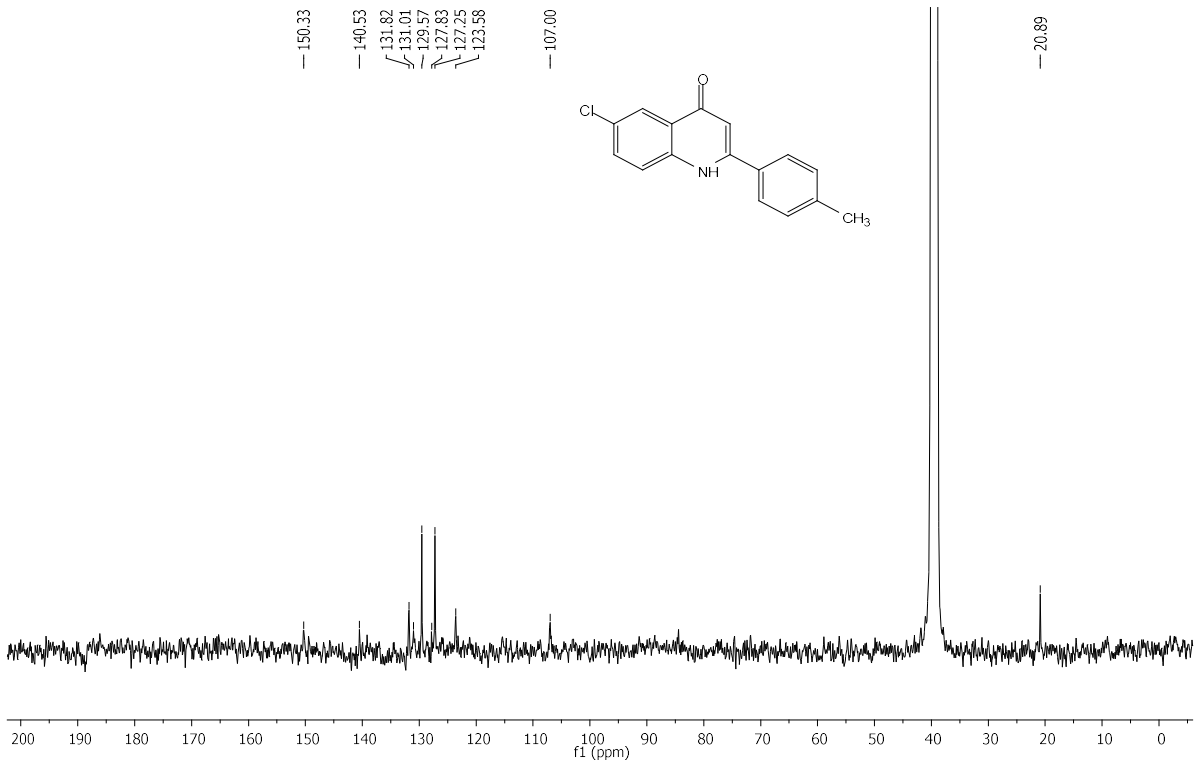


Fig. 250. ^{13}C NMR of **6r** in DMSO-d_6.

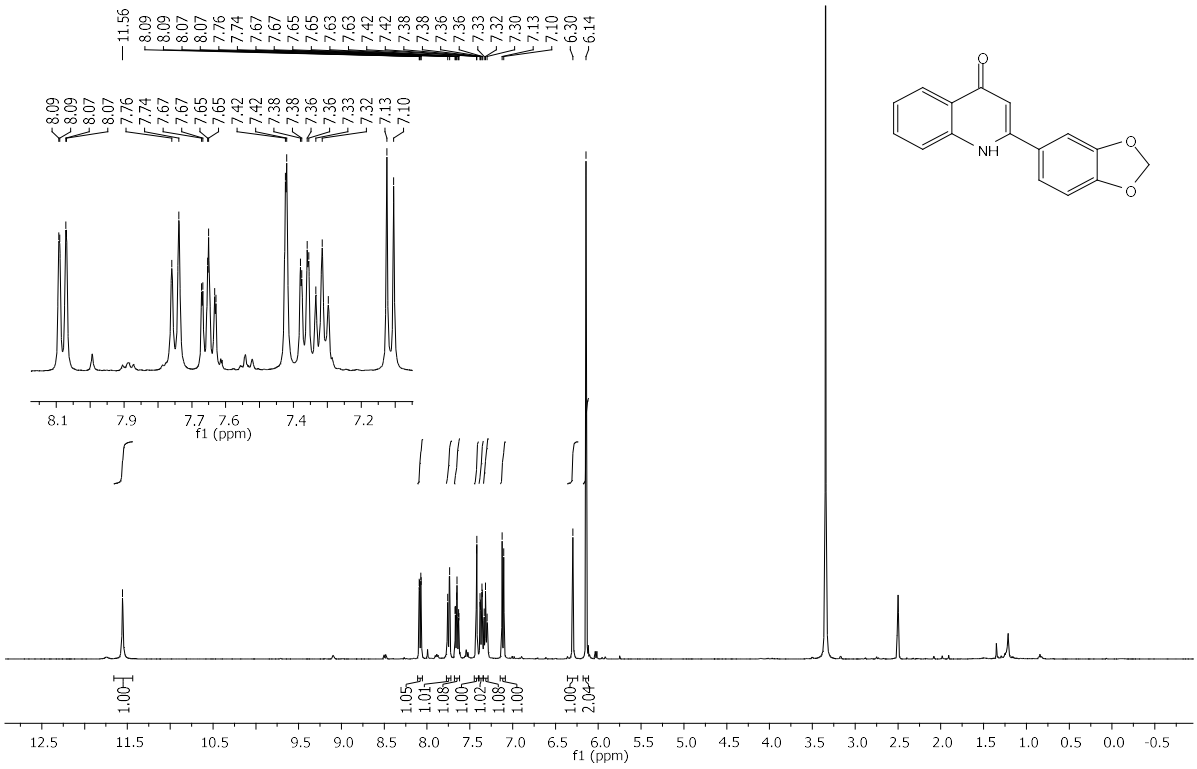


Fig. 251. [1]H NMR of **6s** in DMSO-d_6.

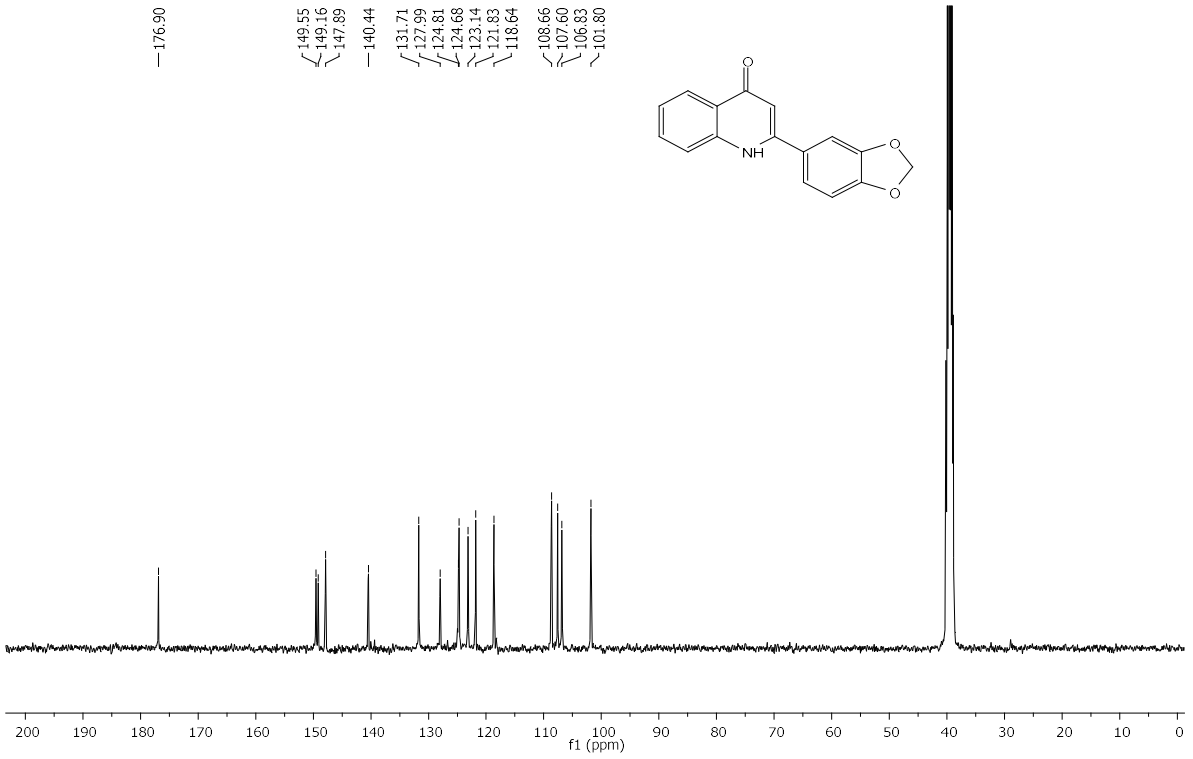


Fig. 252. [13]C NMR of **6s** in DMSO-d_6.

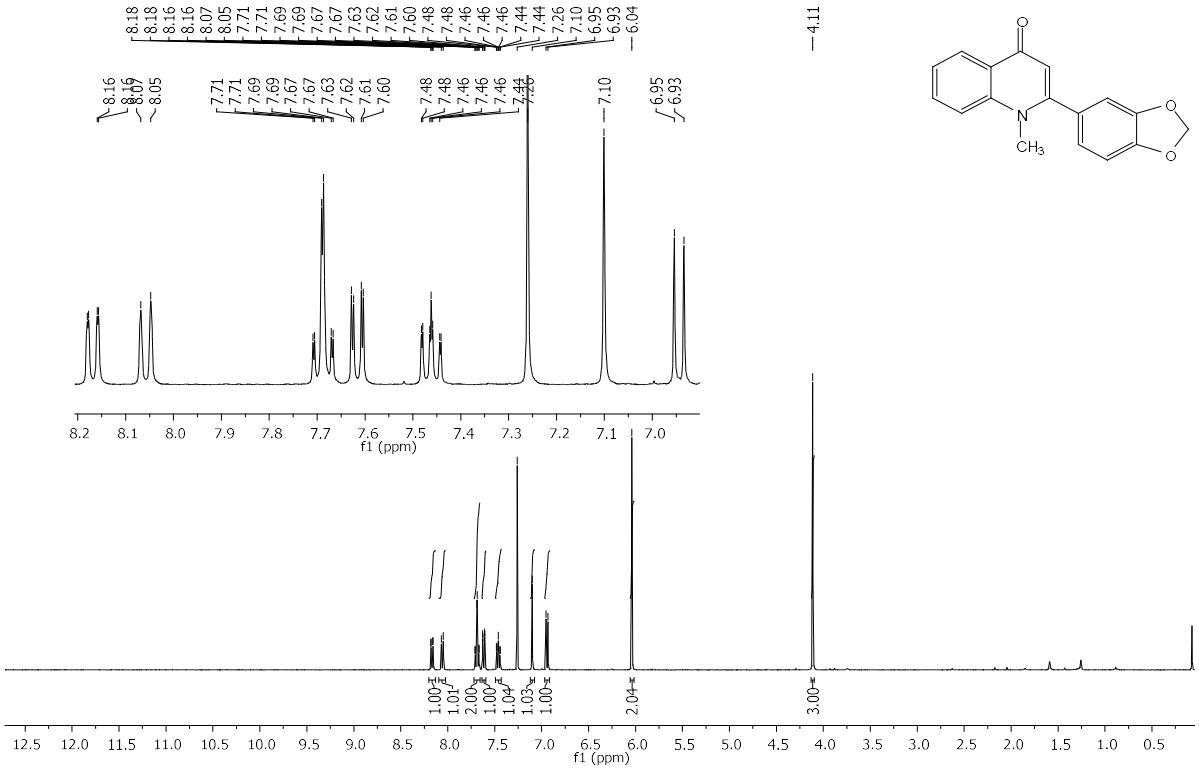


Fig. 253. ^{1}H NMR of **graveoline** in $CDCl_3$.

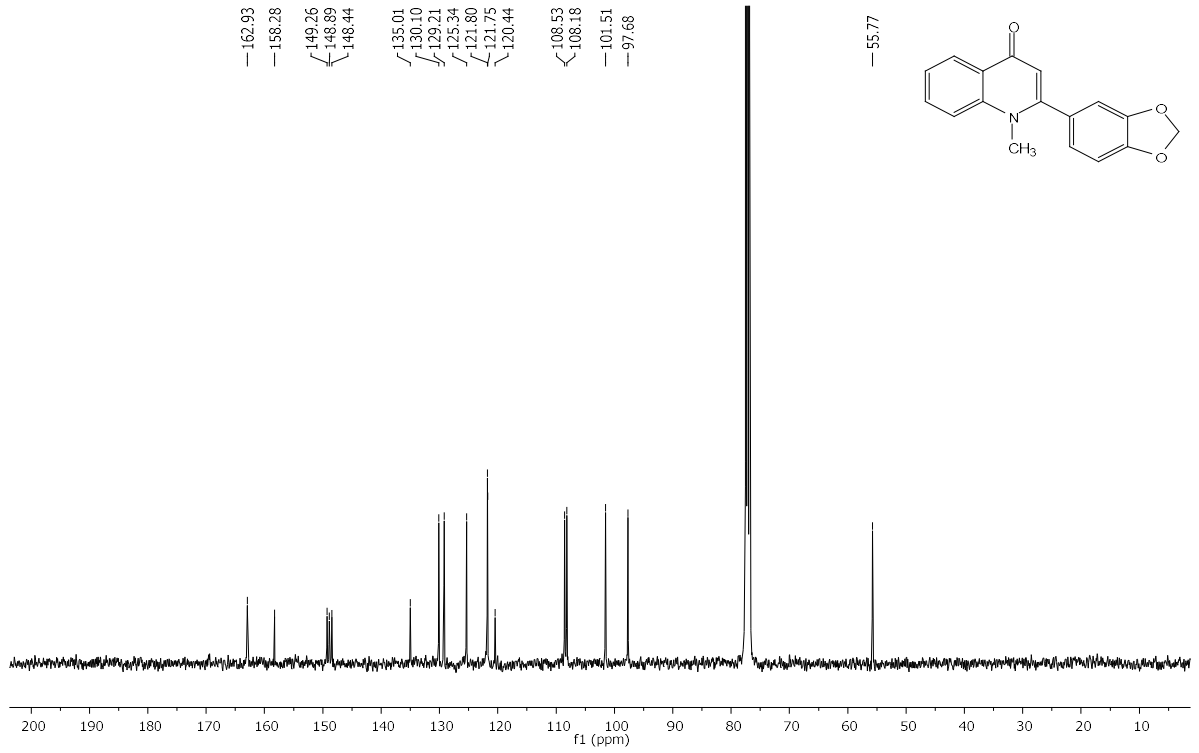


Fig. 254. ^{13}C NMR of **graveoline** in $CDCl_3$.

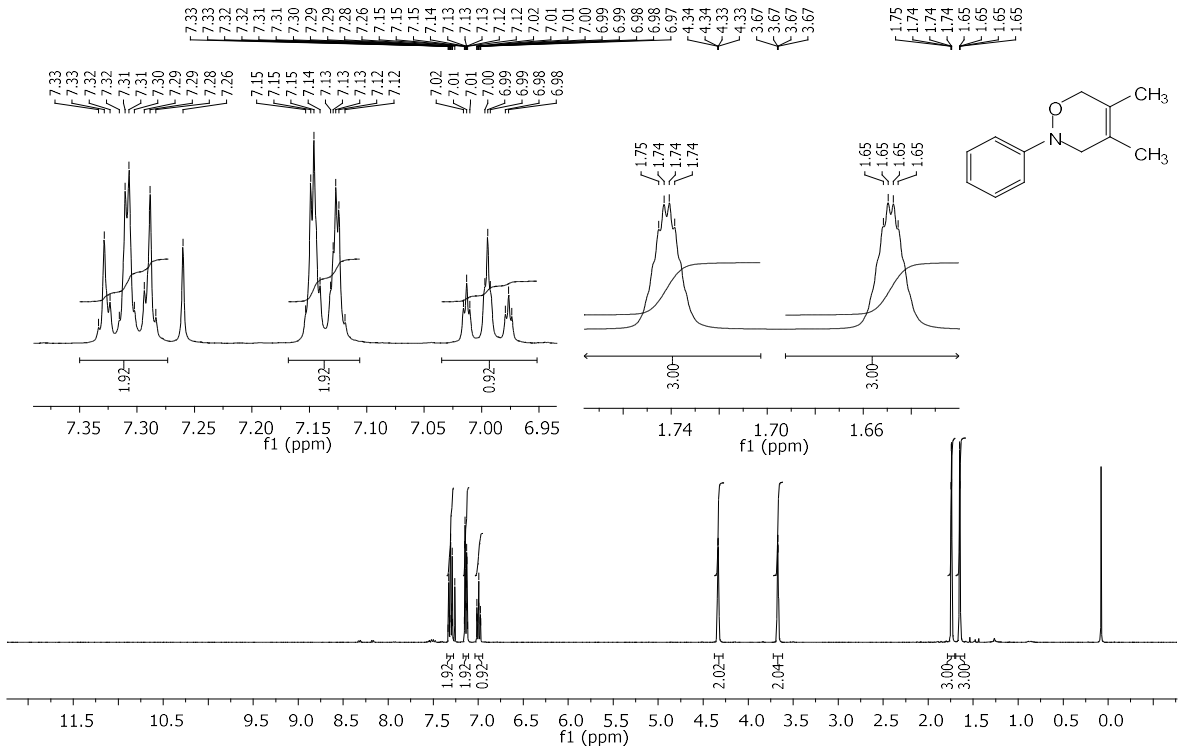


Fig. 255. ^{1}H NMR of **9aa** in $CDCl_3$.

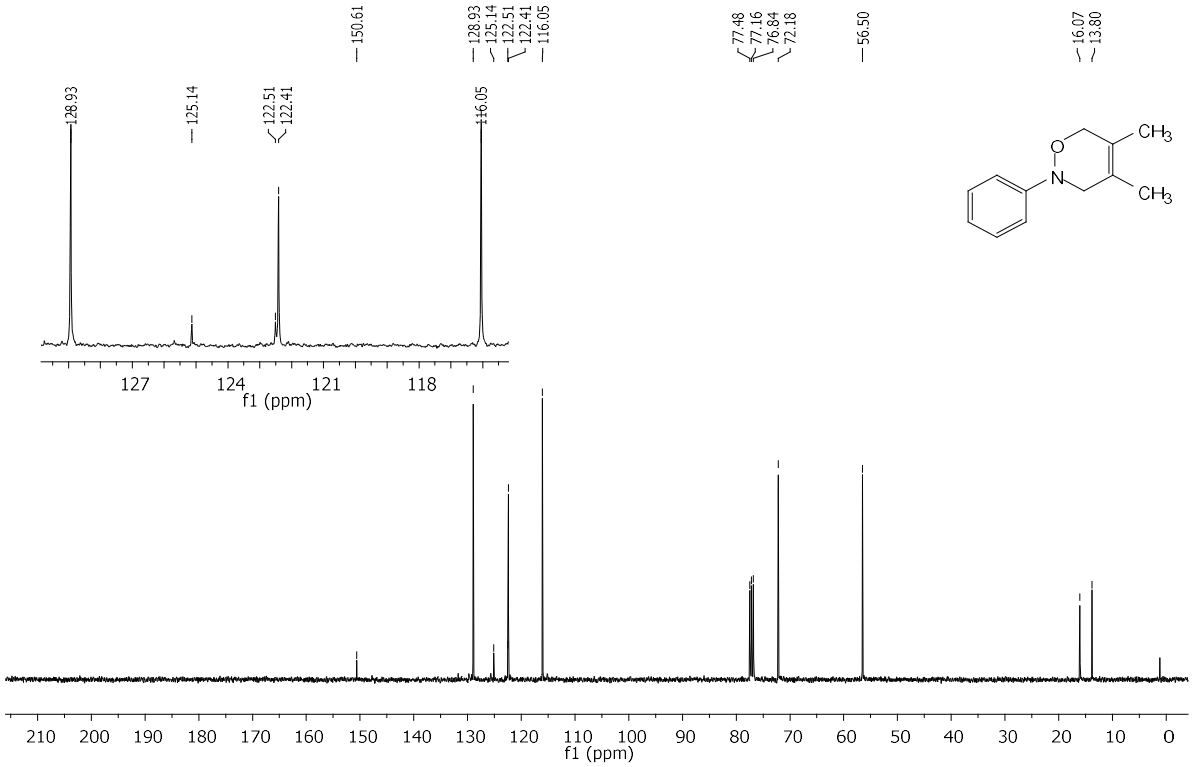


Fig. 256. ^{13}C NMR of **9aa** in $CDCl_3$.

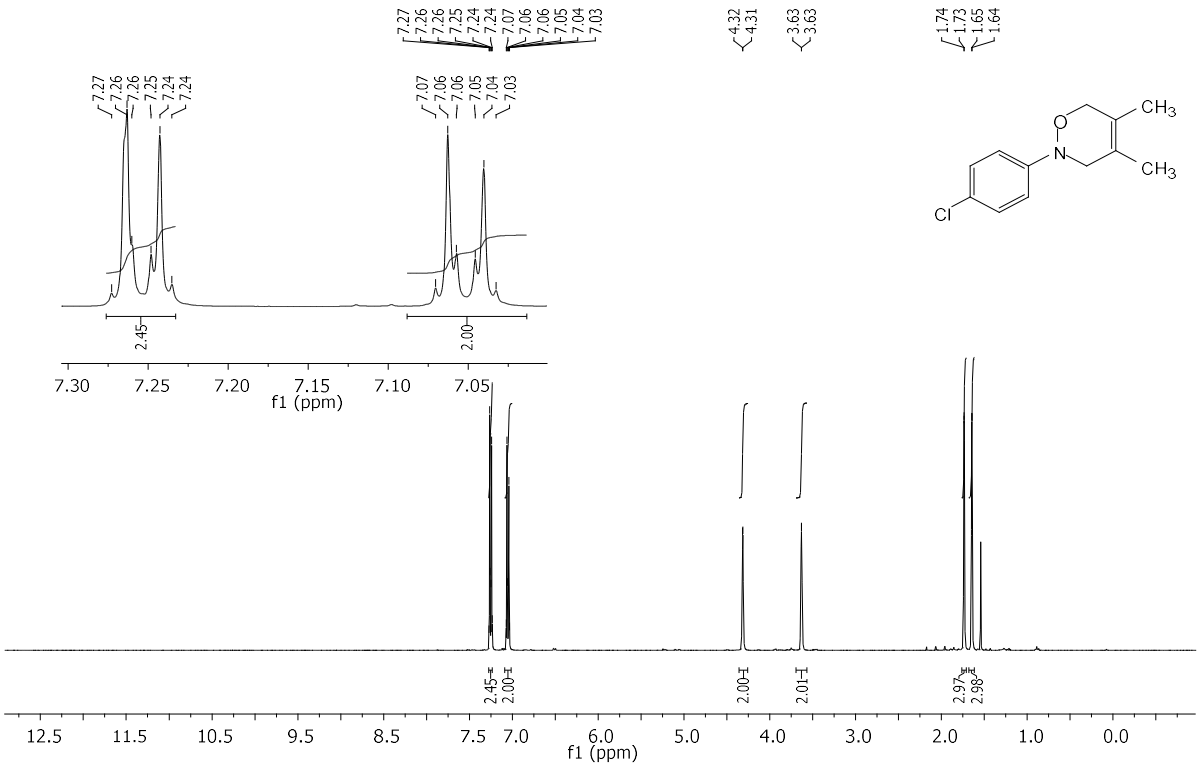


Fig. 257. ^{1}H NMR of **9ba** in $CDCl_3$.

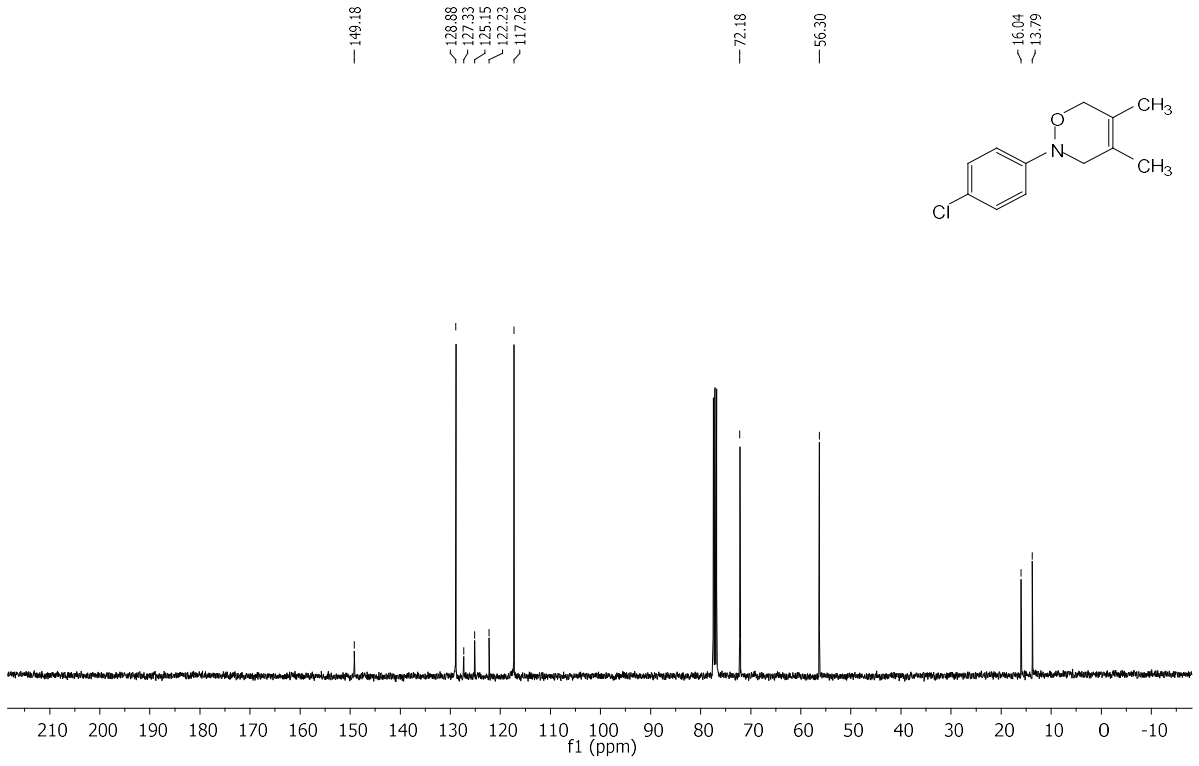


Fig. 258. ^{13}C NMR of **9ba** in $CDCl_3$.

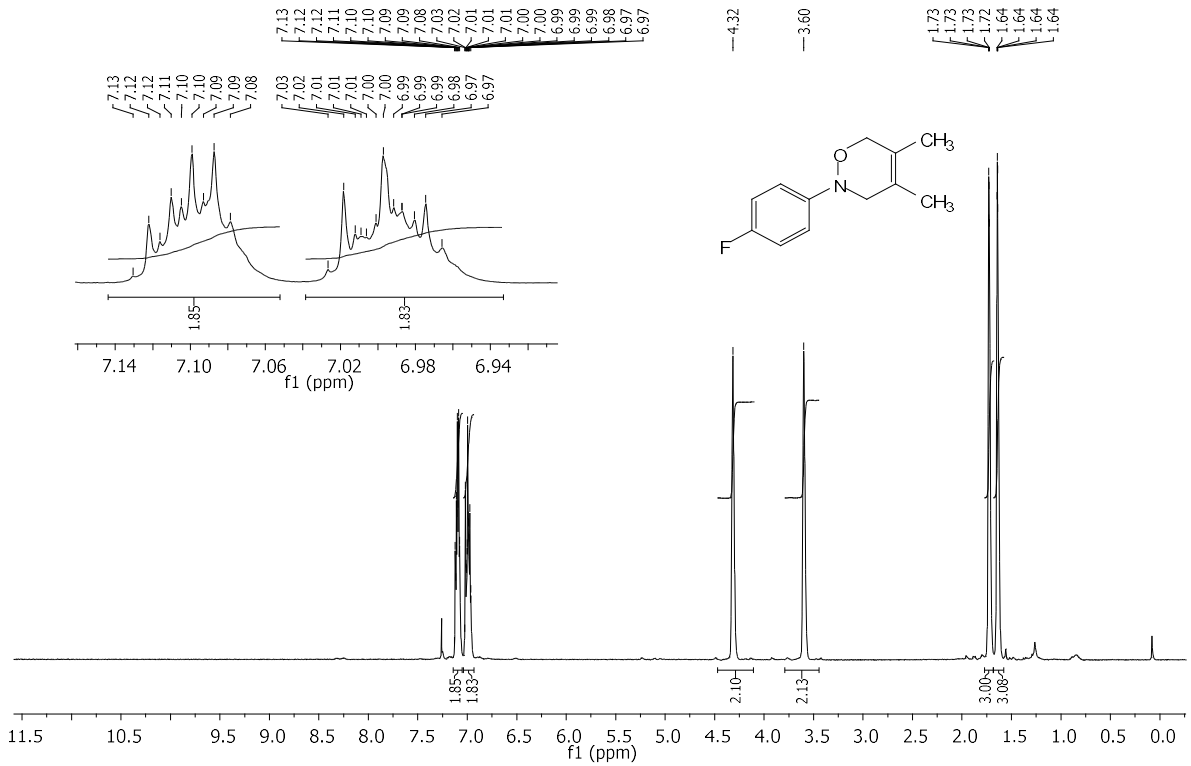


Fig. 259. ^{1}H NMR of **9ca** in $CDCl_3$.

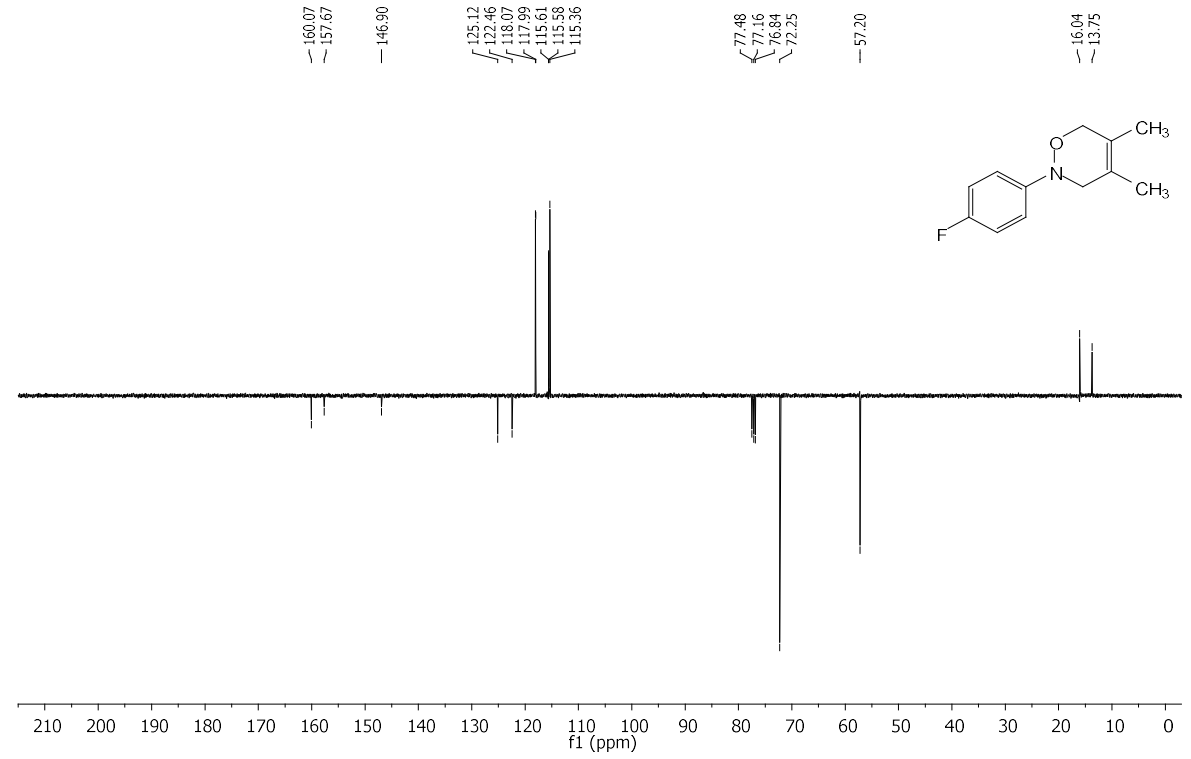


Fig. 260. ^{13}C NMR of **9ca** in $CDCl_3$.

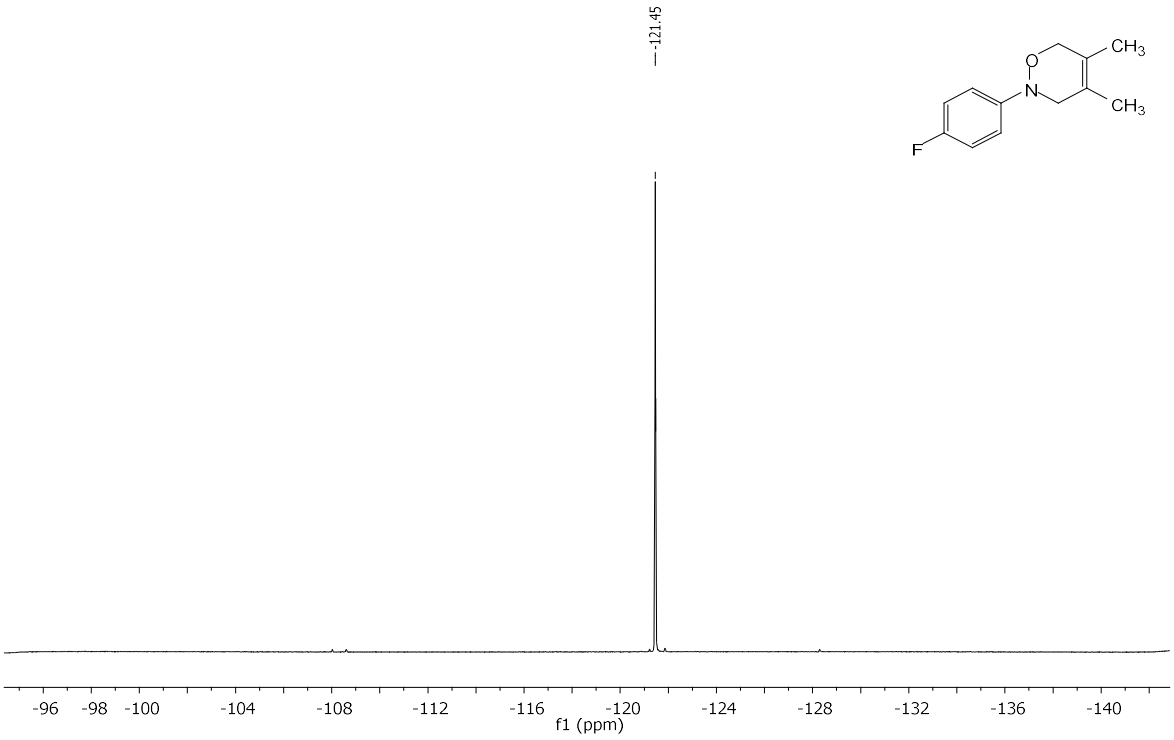


Fig. 261. ^{19}F NMR of **9ca** in $CDCl_3$.

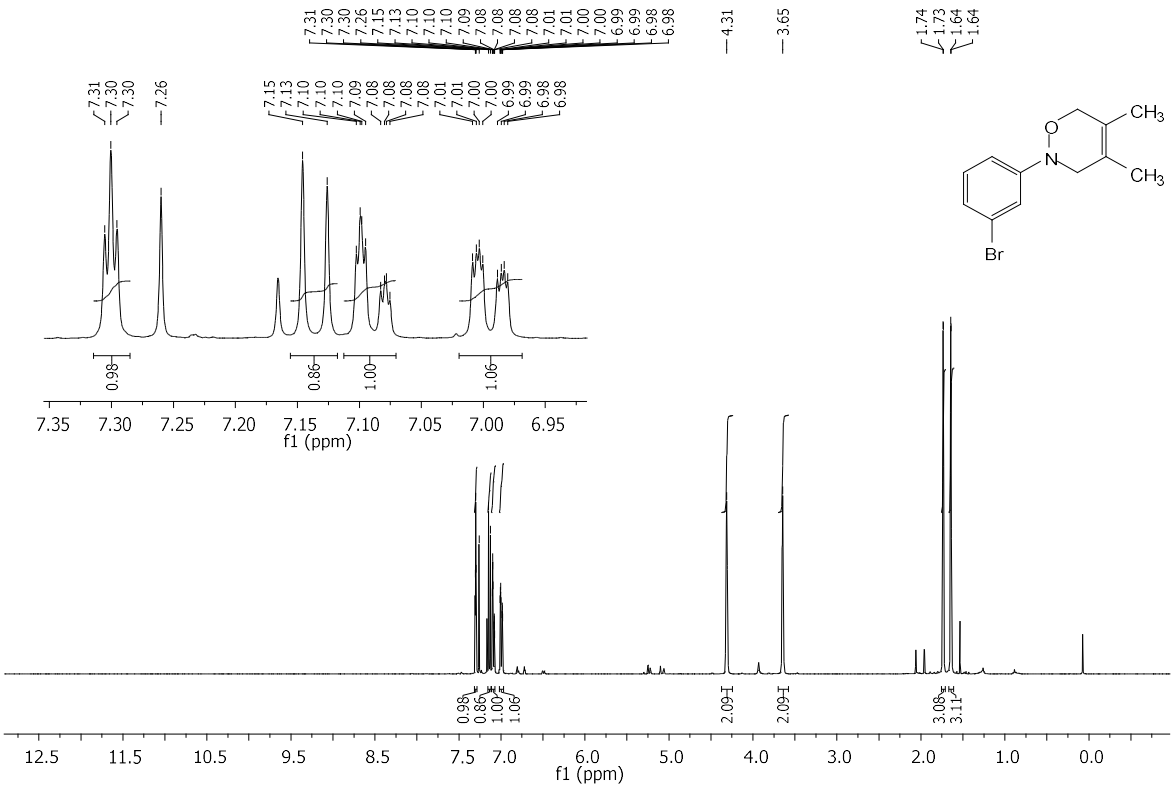


Fig. 262. ^{1}H NMR of **9da** in $CDCl_3$.

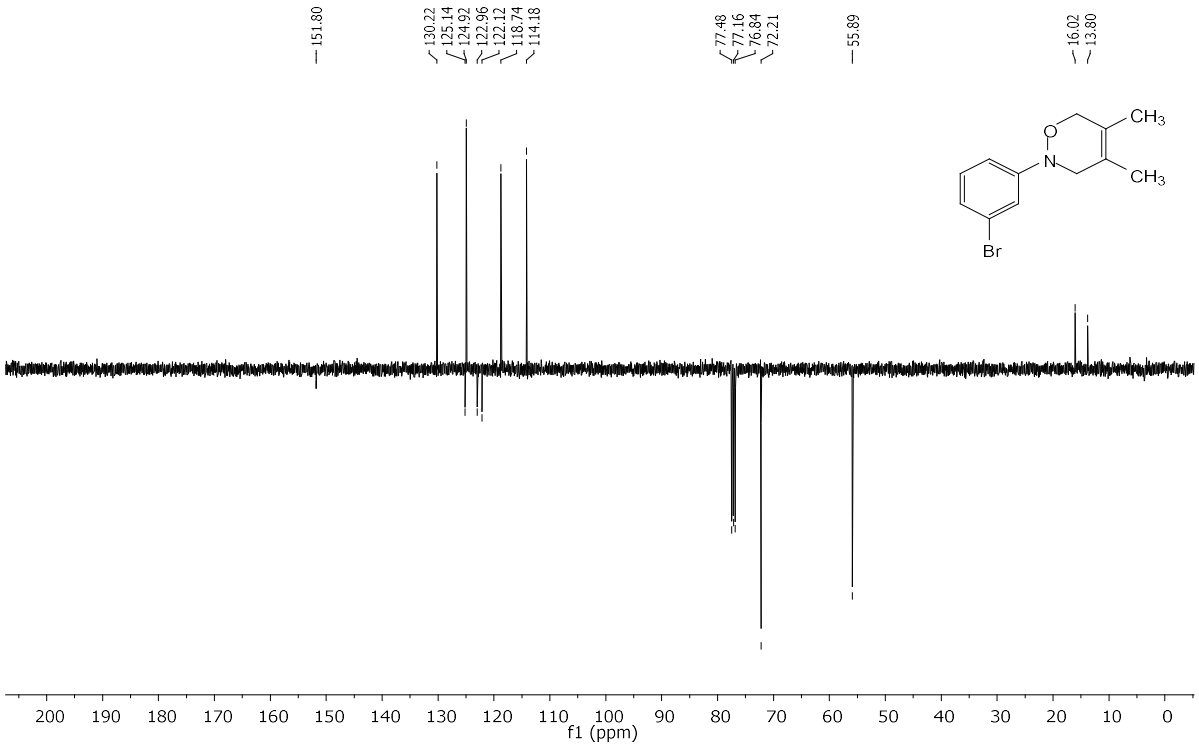


Fig. 263. ^{13}C NMR of **9da** in $CDCl_3$.

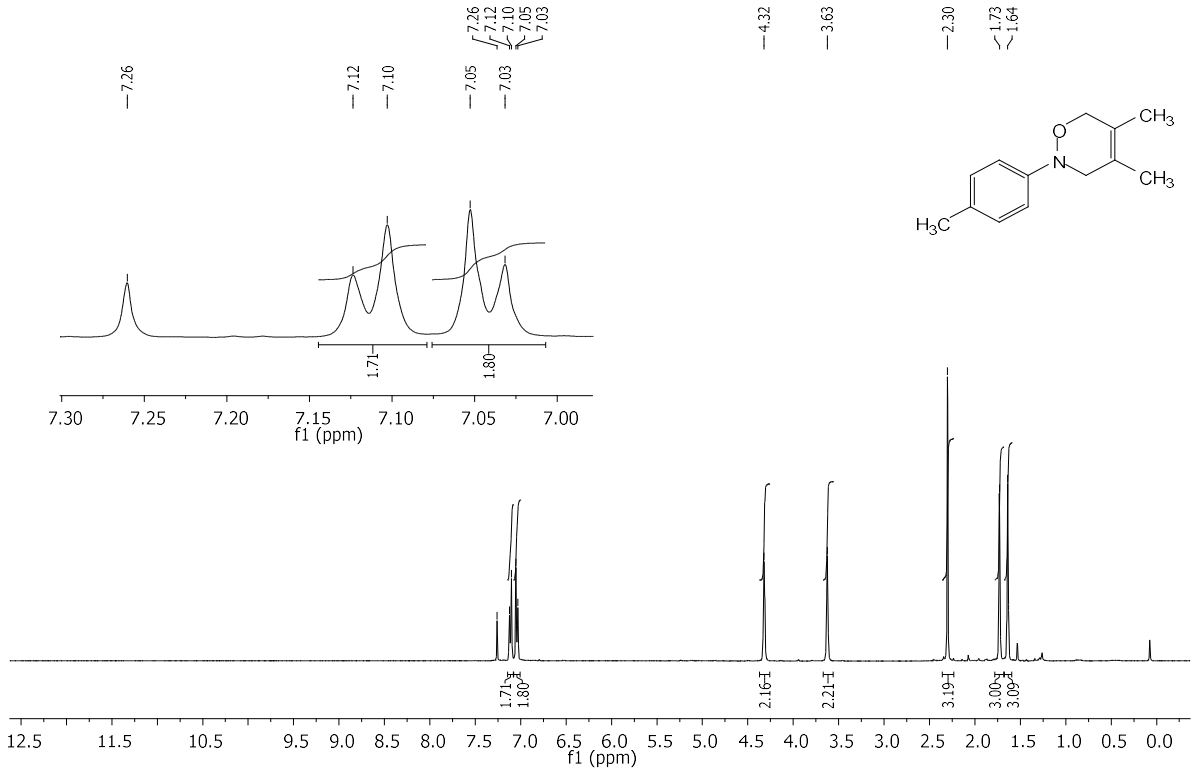


Fig. 264. ^{1}H NMR of **9fa** in $CDCl_3$.

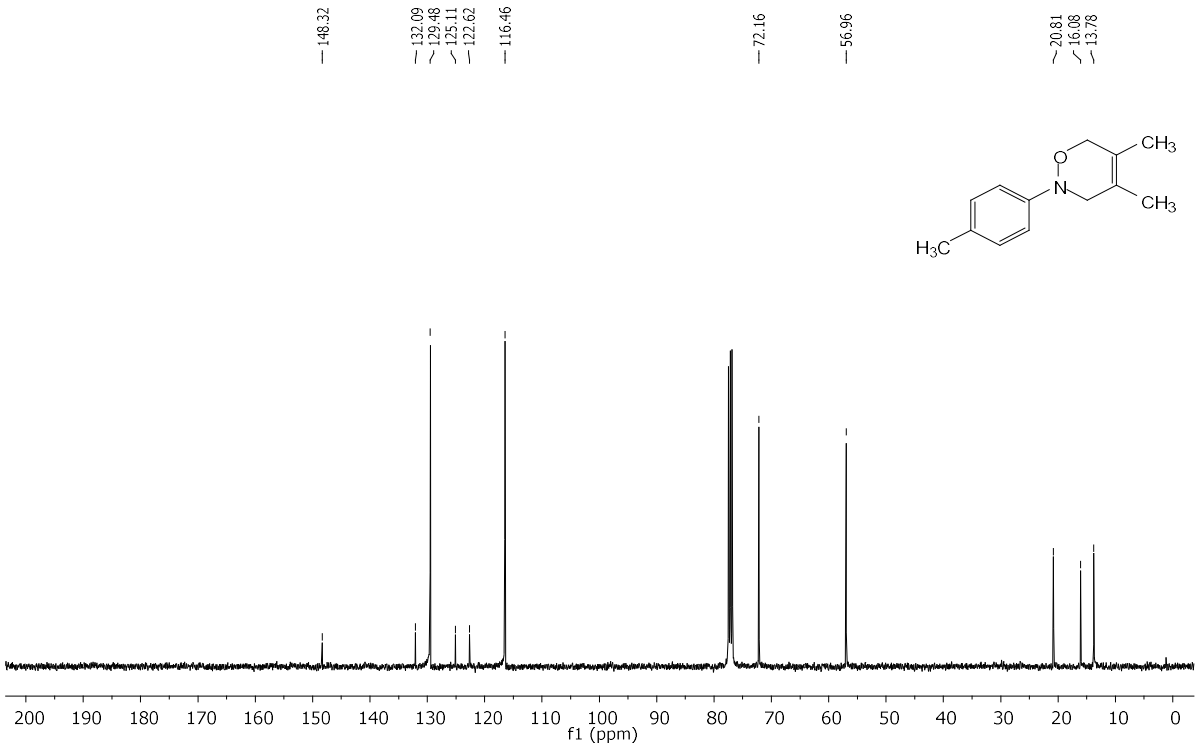


Fig. 265. ^{13}C NMR of **9fa** in $CDCl_3$.

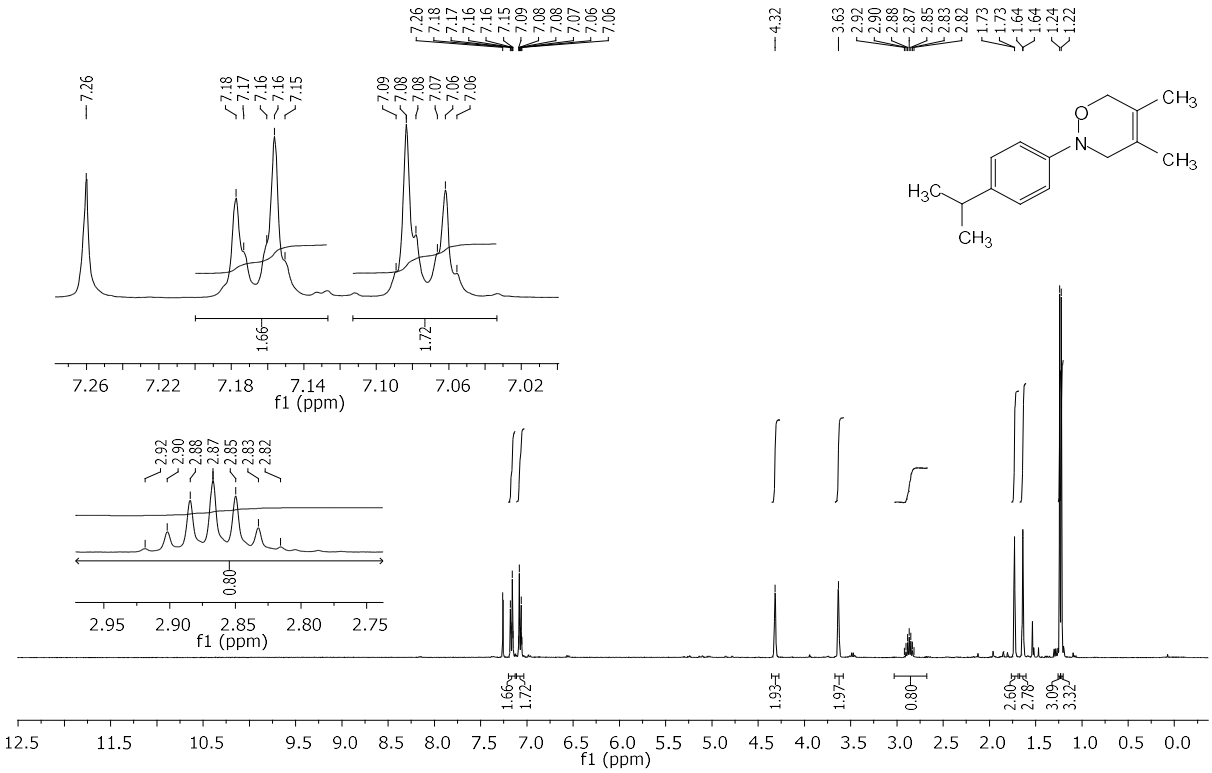


Fig. 266. ^{1}H NMR of **9ga** in $CDCl_3$.

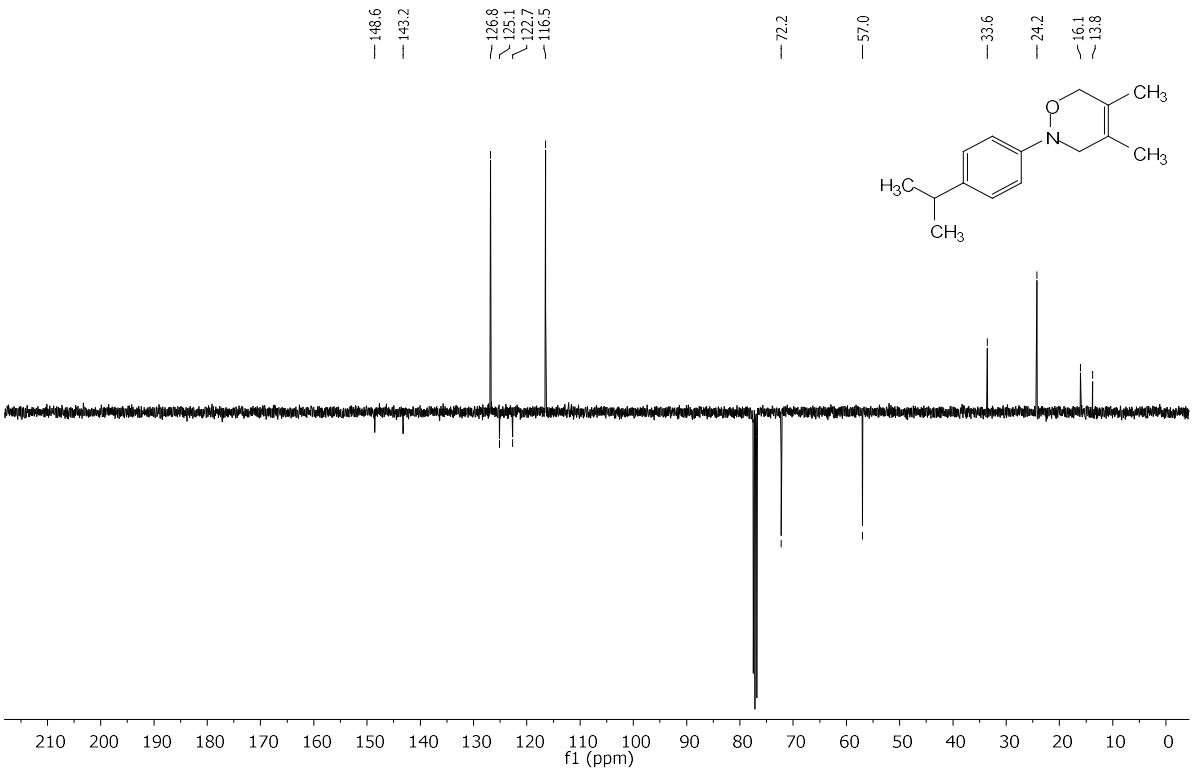


Fig. 267. ^{13}C NMR of **9ga** in $CDCl_3$.

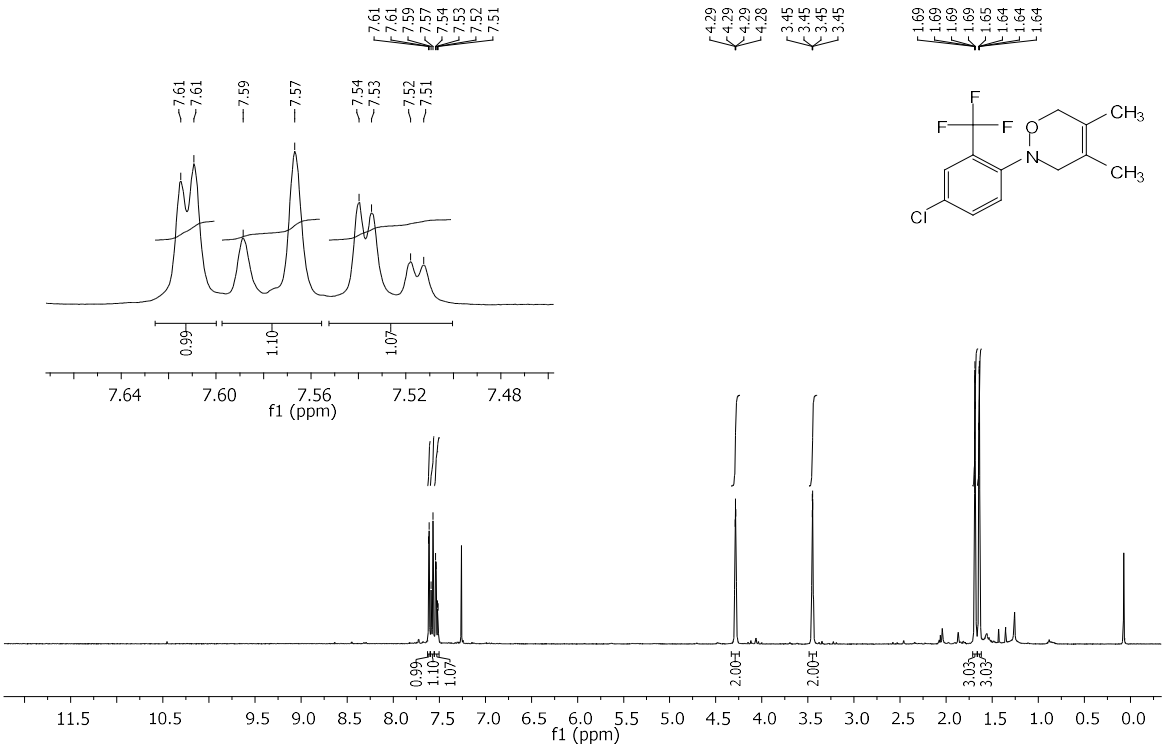


Fig. 268. ^{1}H NMR of **9ja** in $CDCl_3$.

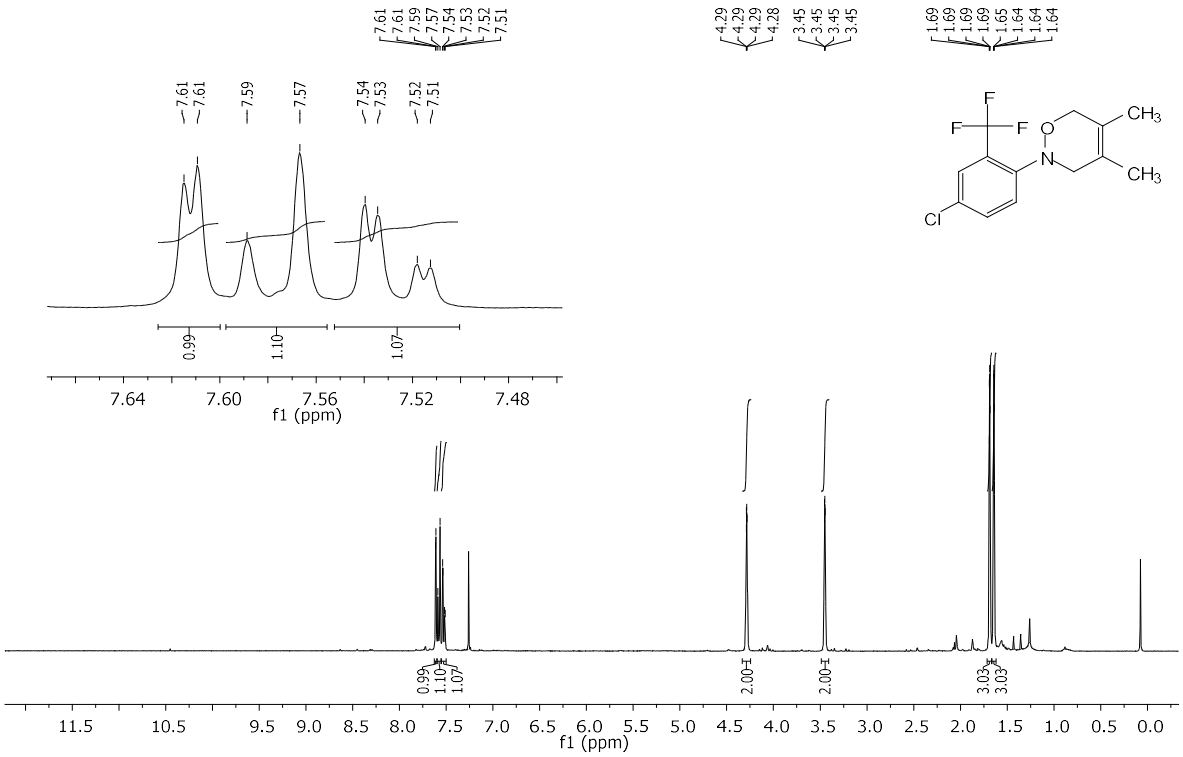


Fig. 269. ^{13}C NMR of **9ja** in $CDCl_3$.

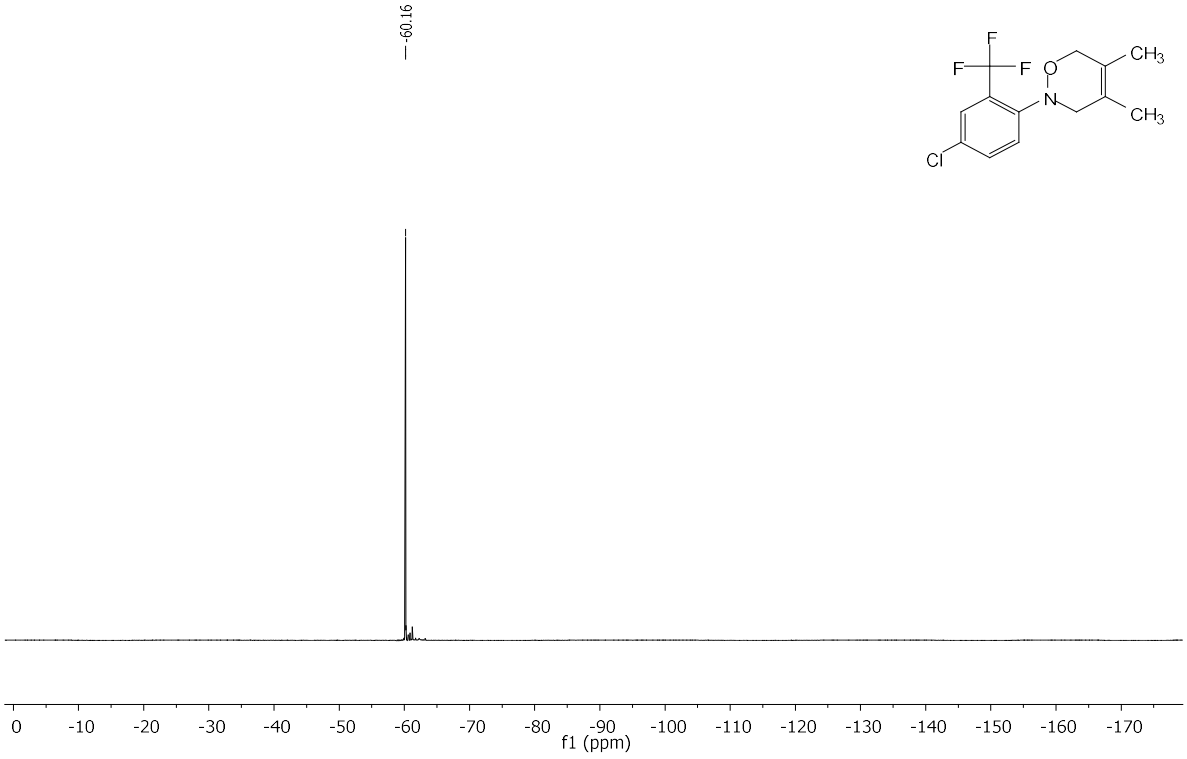


Fig. 270. ^{19}F NMR of **9ja** in $CDCl_3$.

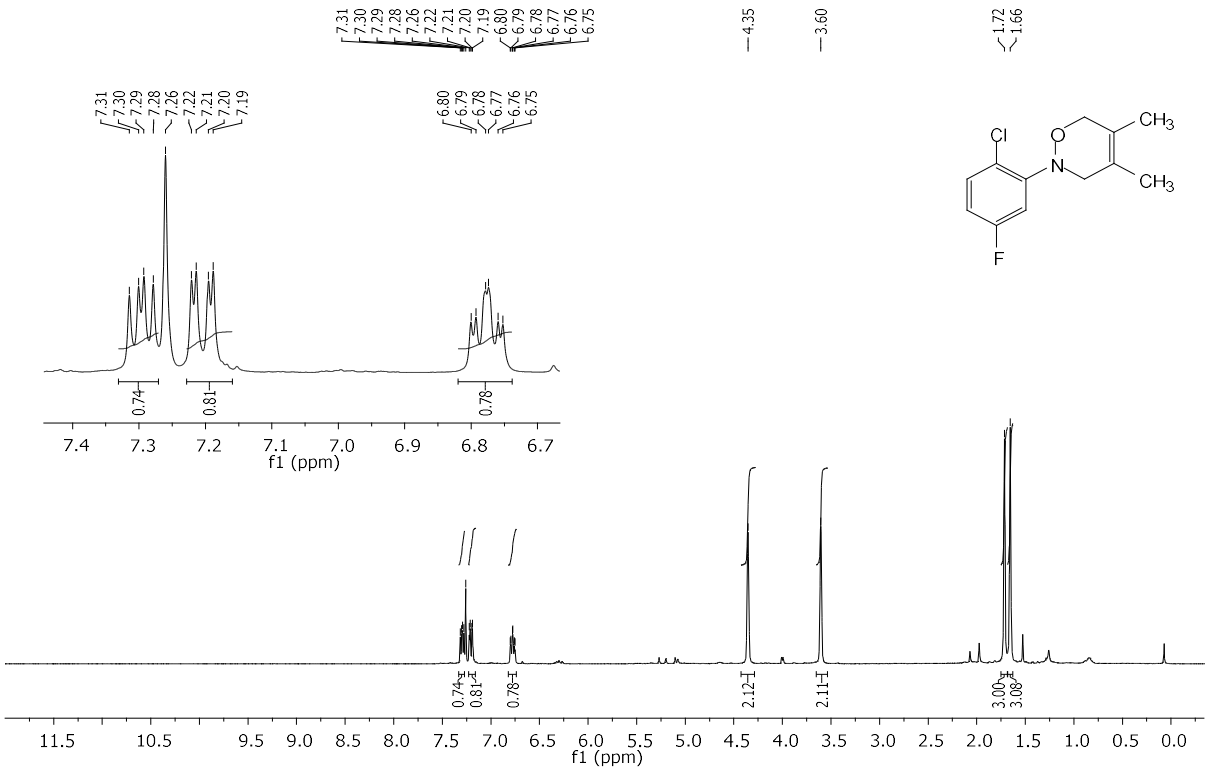


Fig. 271. ^{1}H NMR of **9ka** in $CDCl_3$.

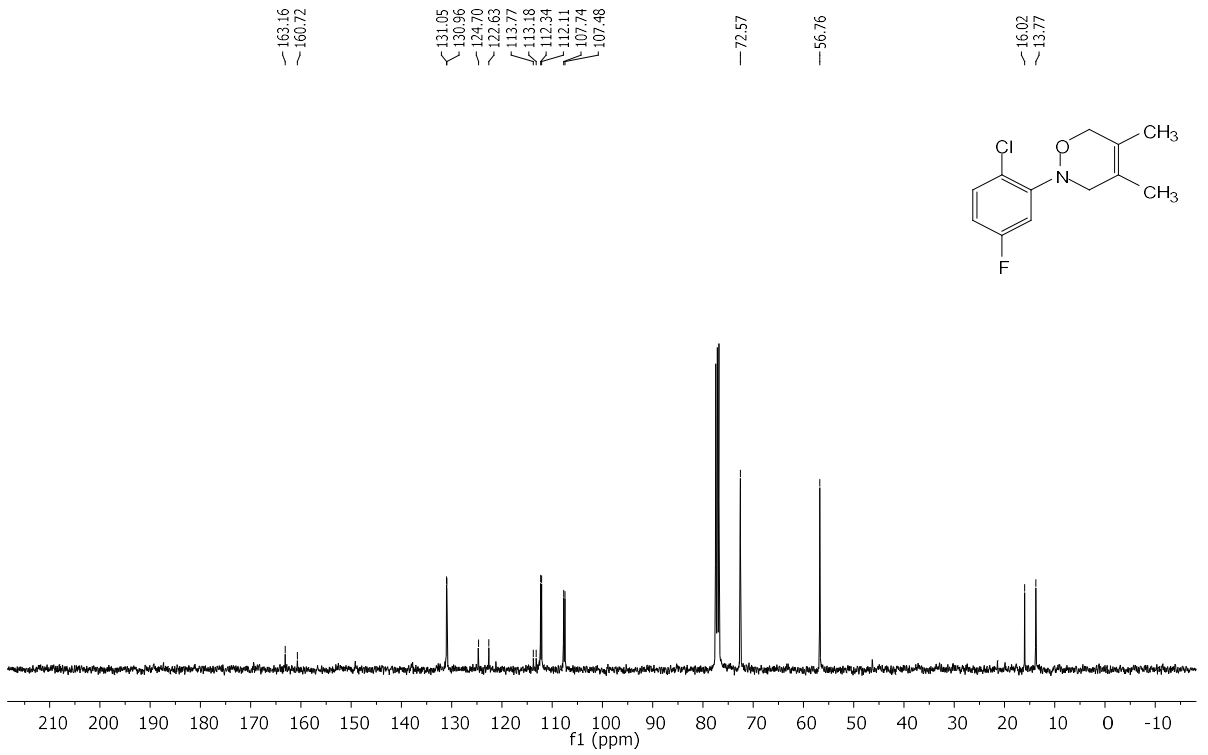


Fig. 272. ^{13}C NMR of **9ka** in $CDCl_3$.

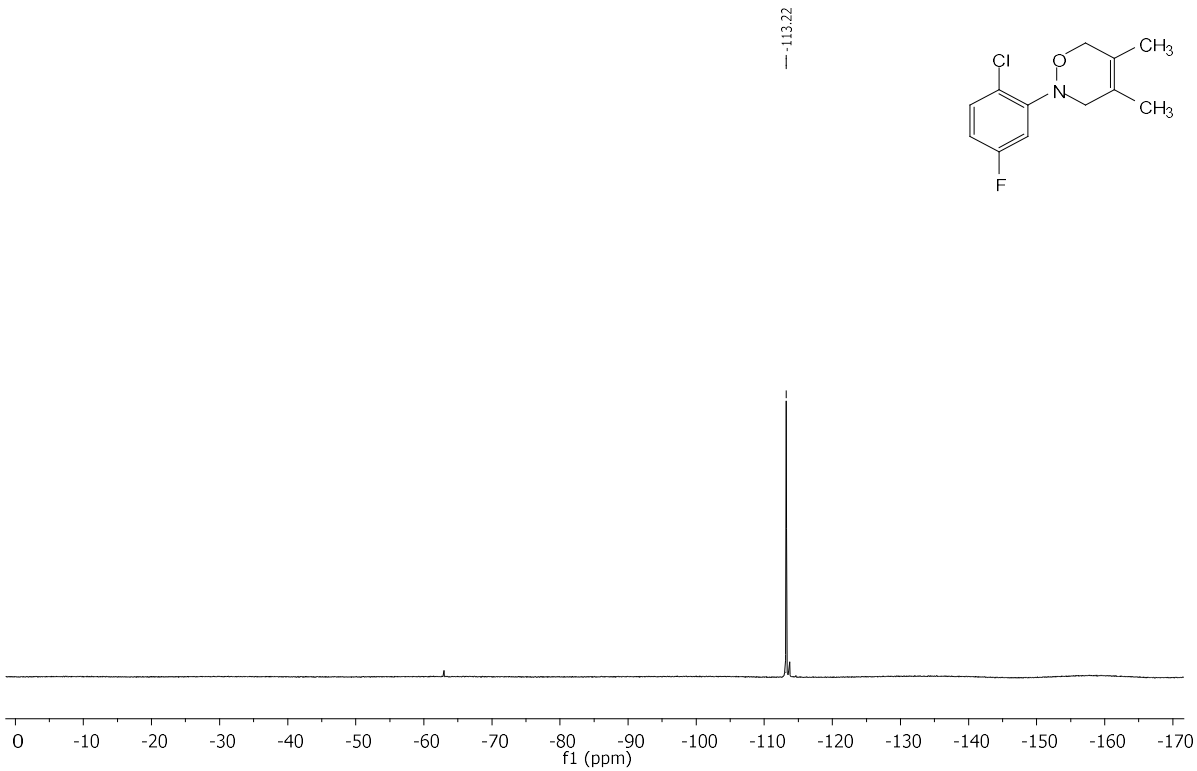


Fig. 273. ^{19}F NMR of **9ka** in $CDCl_3$.

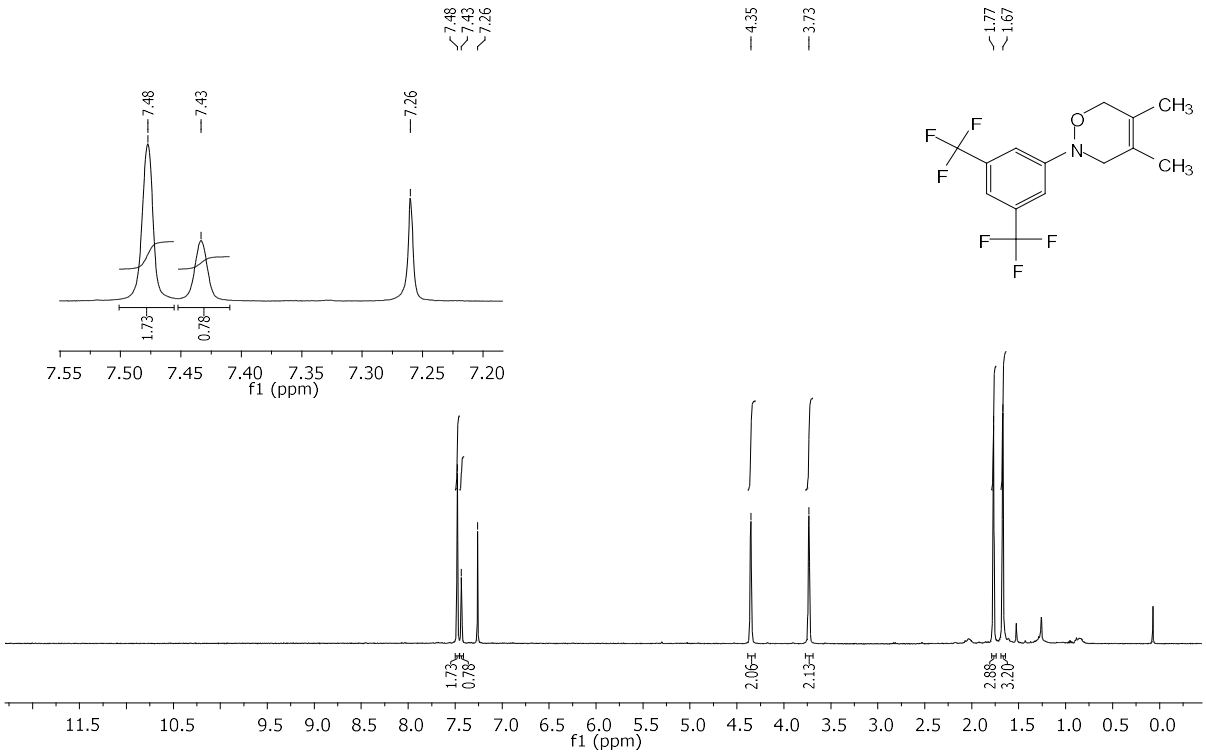


Fig. 274. ^{1}H NMR of **9la** in $CDCl_3$.

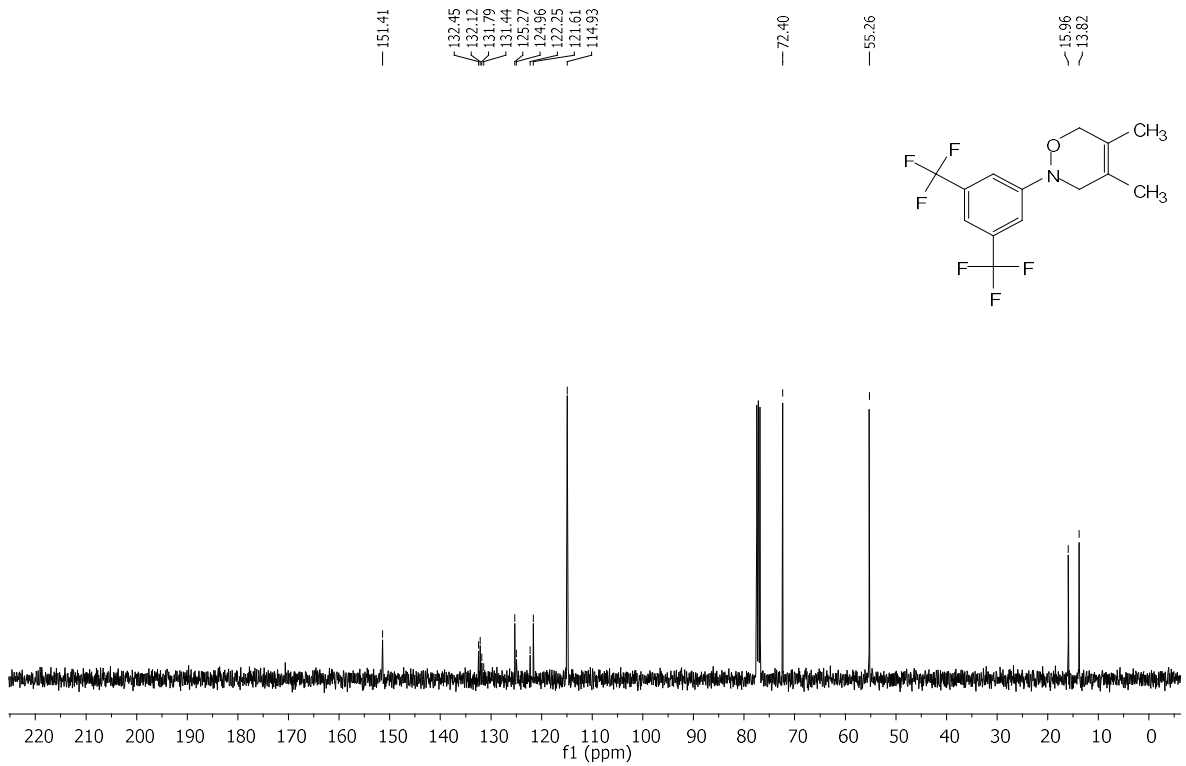


Fig. 275. ^{13}C NMR of **9la** in $CDCl_3$.

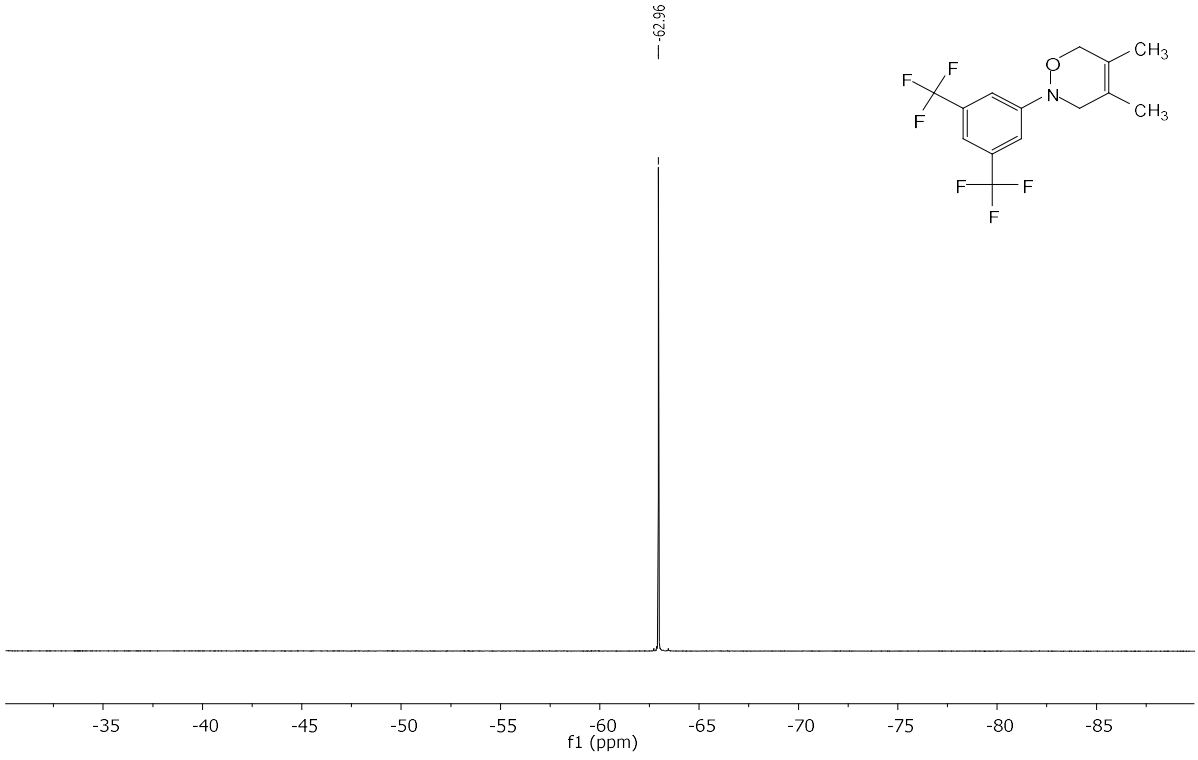


Fig. 276. ^{19}F NMR of **9la** in $CDCl_3$.

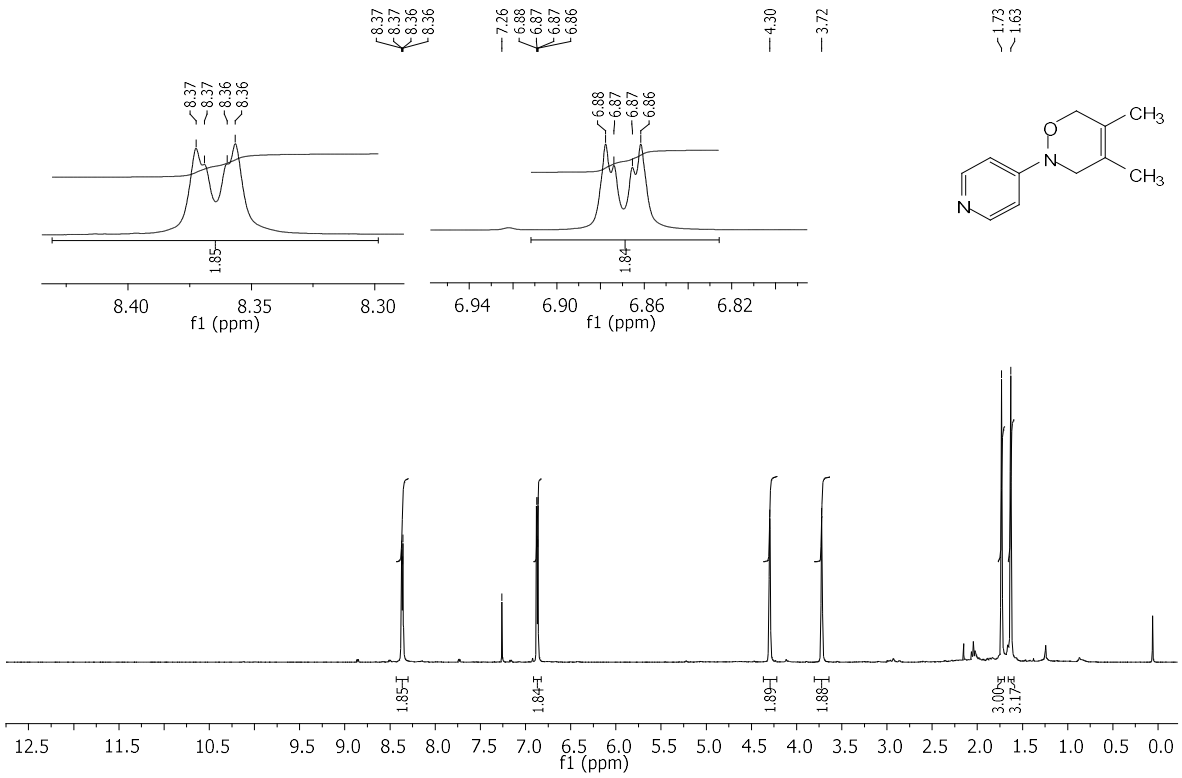


Fig. 277. ^{1}H NMR of **9ma** in $CDCl_3$.

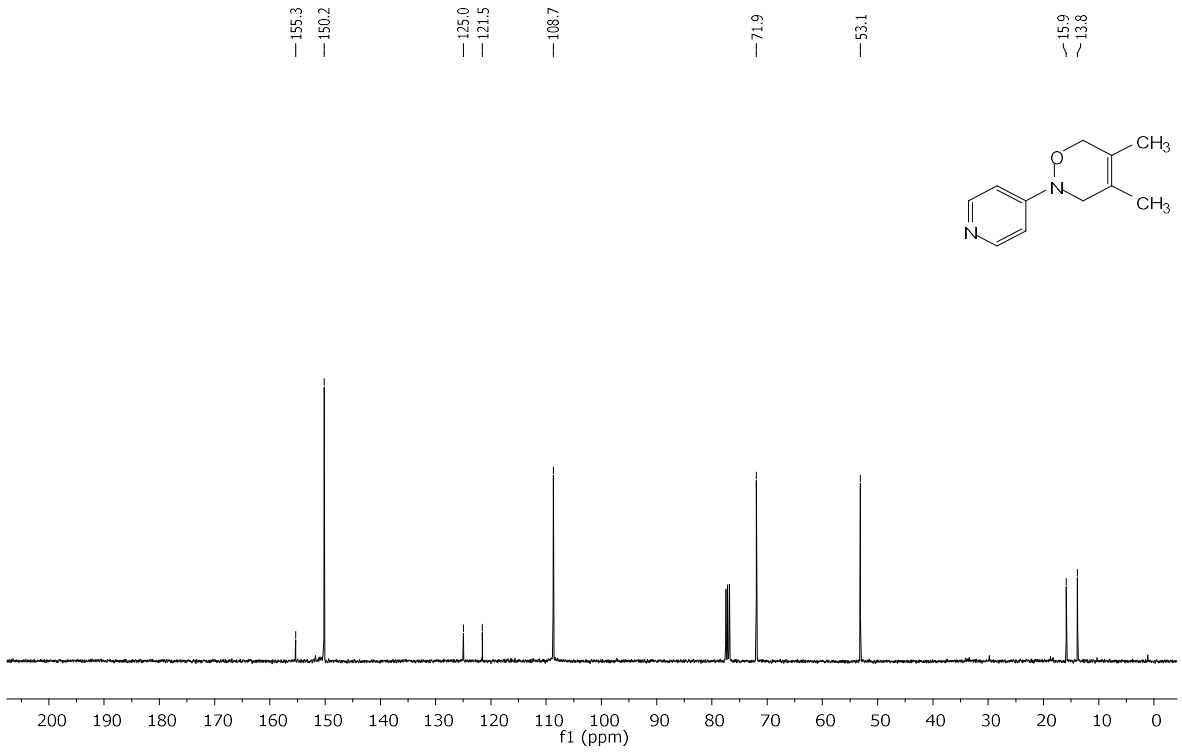


Fig. 278. ^{13}C NMR of **9ma** in $CDCl_3$.

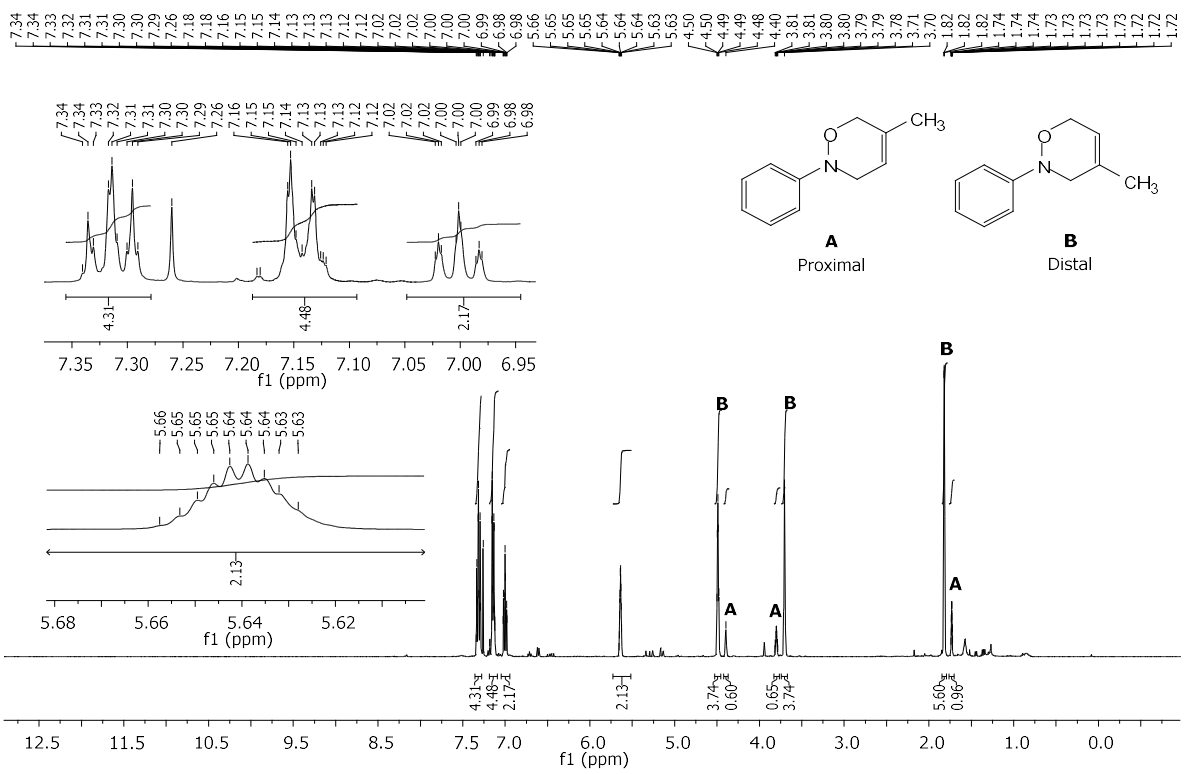


Fig. 279. ^{1}H NMR of **9abA** and **9abB** in $CDCl_3$.

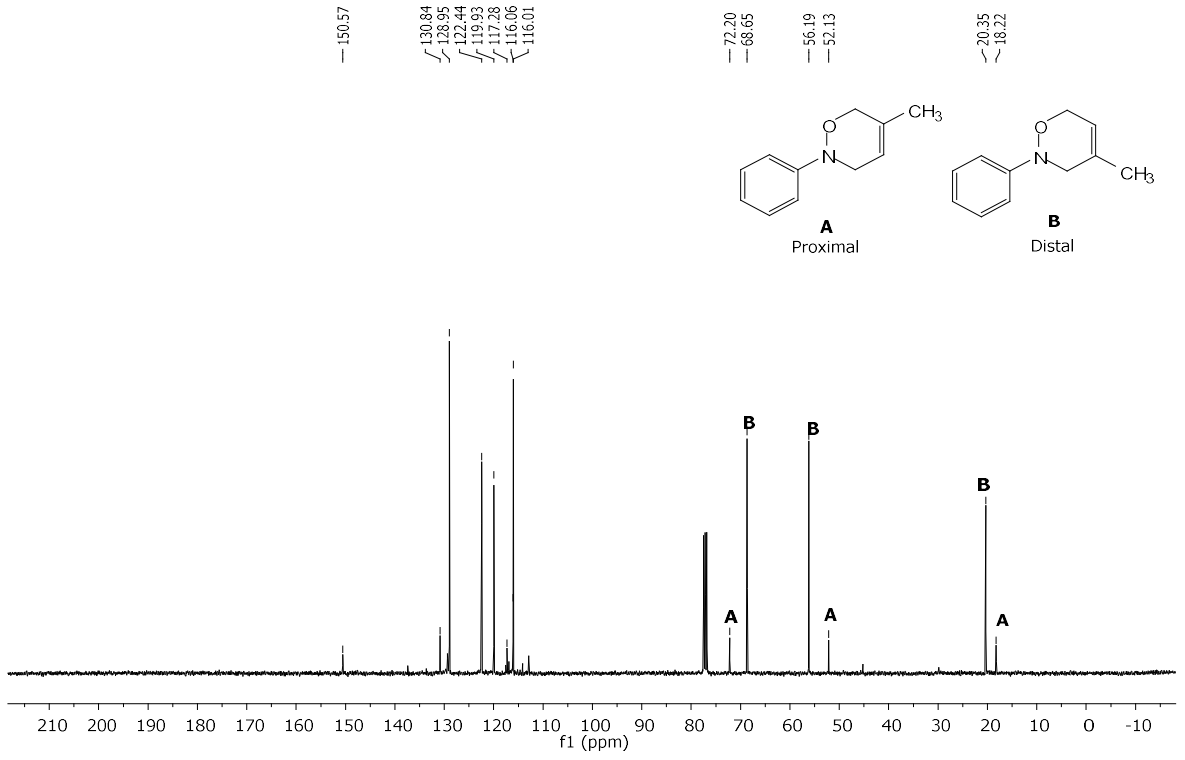


Fig. 280. ^{13}C NMR of **9abA** and **9abB** in $CDCl_3$.

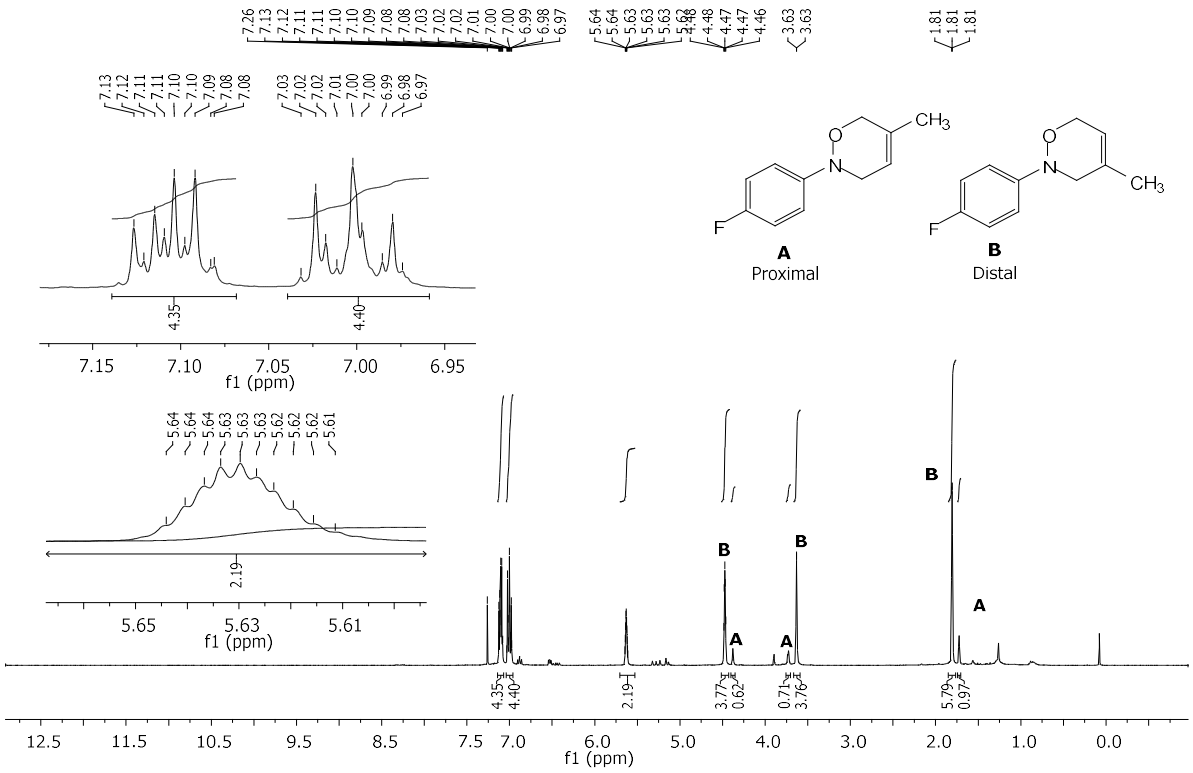


Fig. 281. ^{1}H NMR of **9cbA** and **9cbB** in $CDCl_3$.

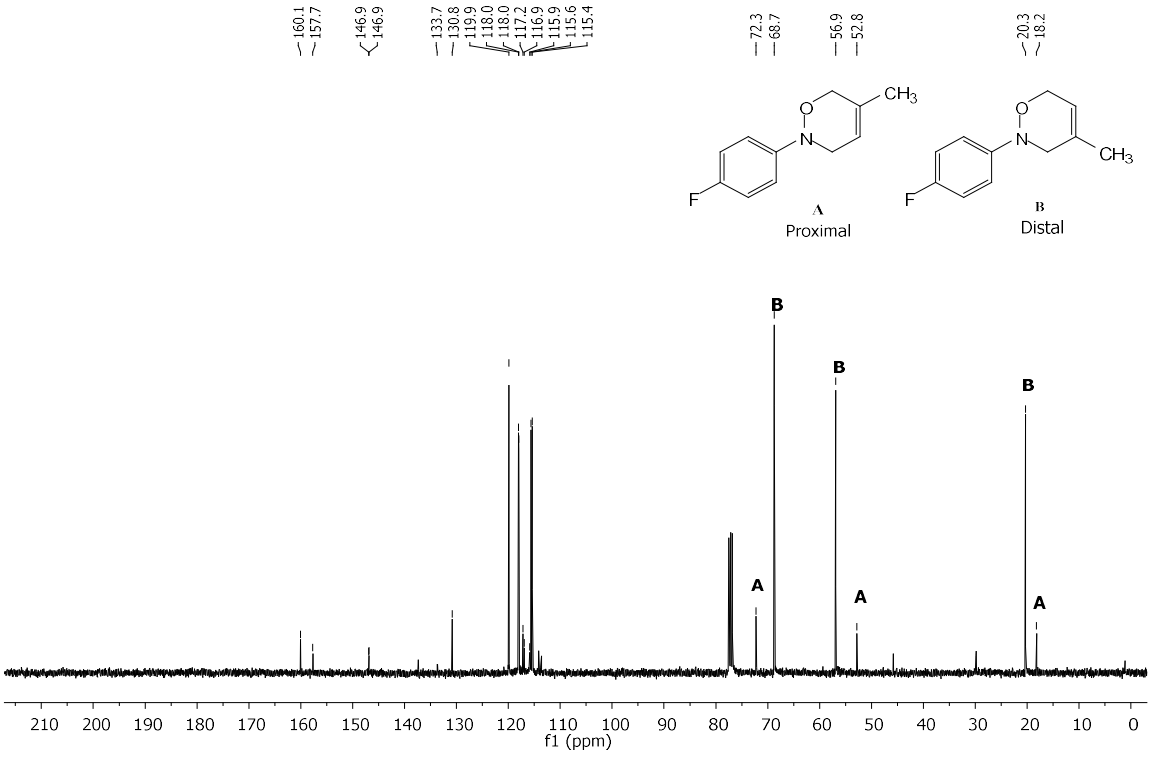


Fig. 282. ^{13}C NMR of **9cbA** and **9cbB** in $CDCl_3$.

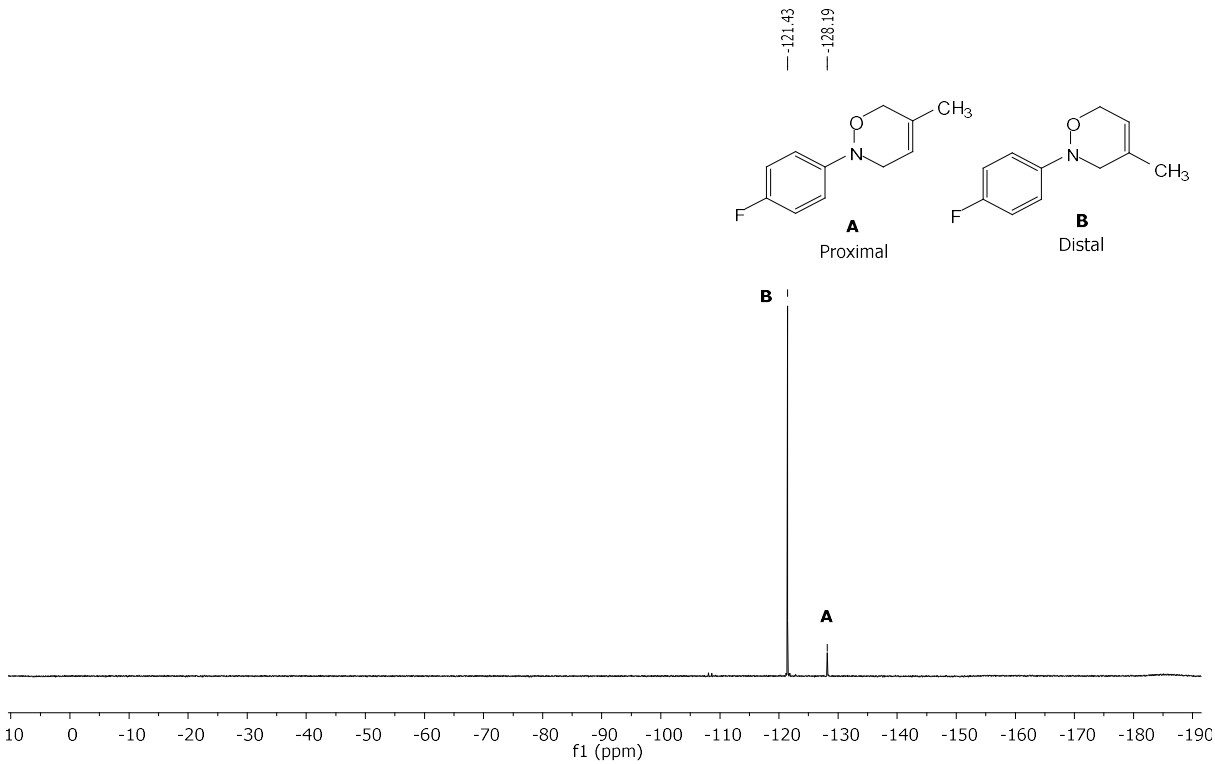


Fig. 283. ^{19}F NMR of **9cbA** and **9cbB** in $CDCl_3$.

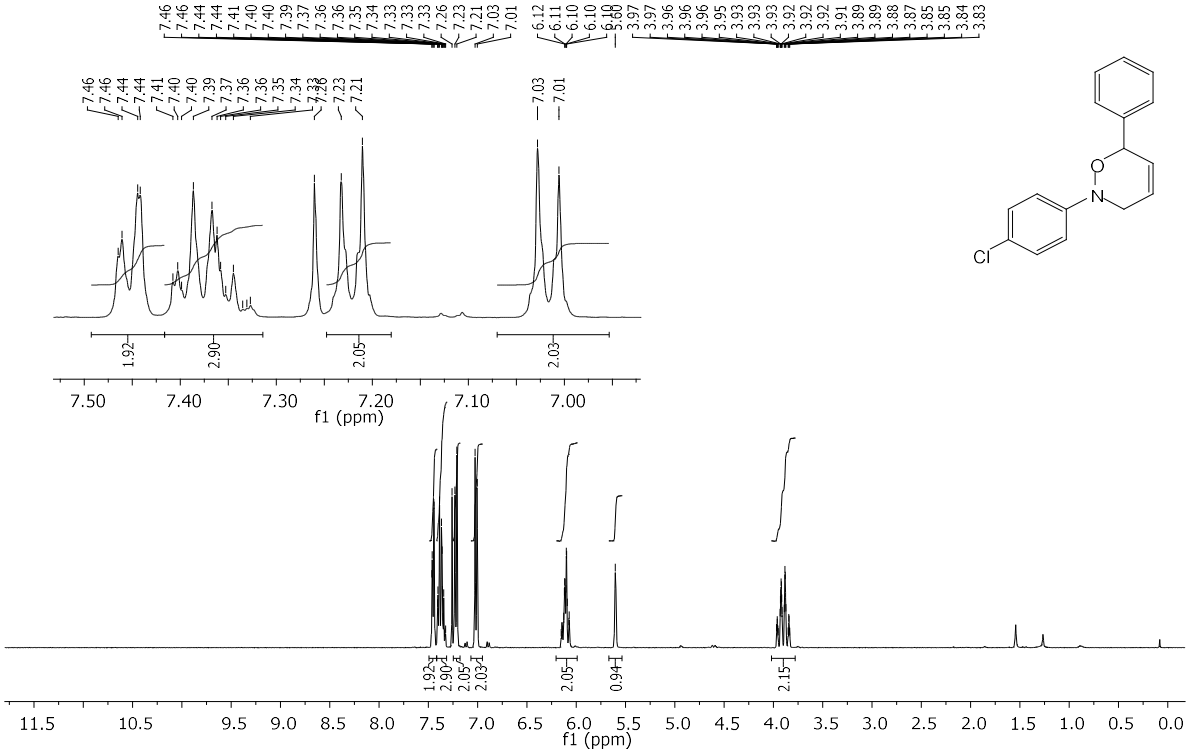


Fig. 284. ^{1}H NMR of **9bc** in $CDCl_3$.

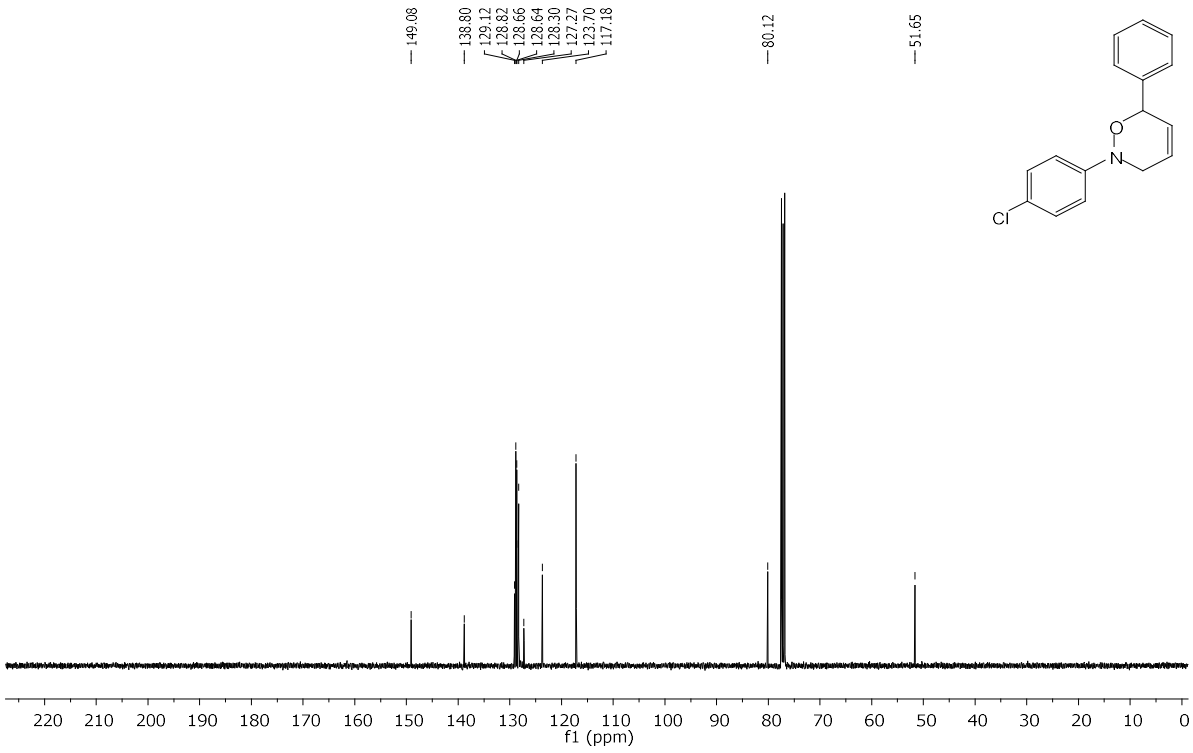


Fig. 285. ^{13}C NMR of **9bc** in $CDCl_3$.

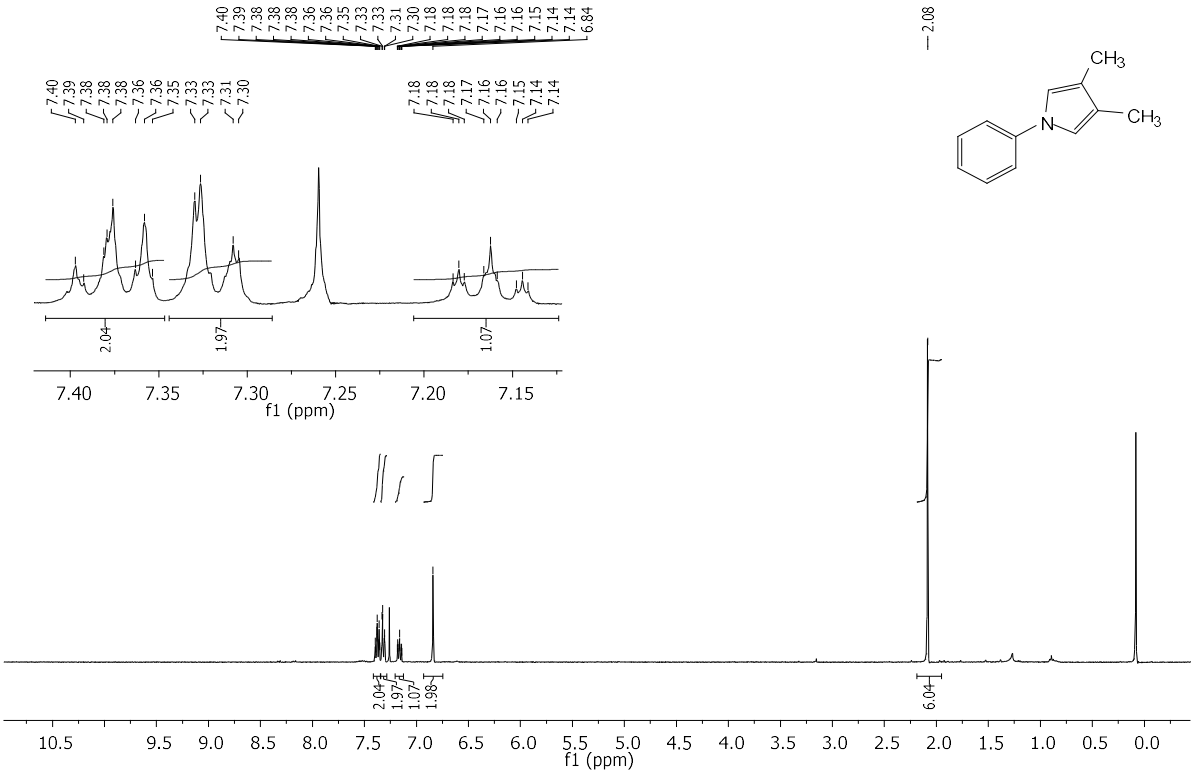


Fig. 286. ^{1}H NMR of **10aa** in $CDCl_3$.

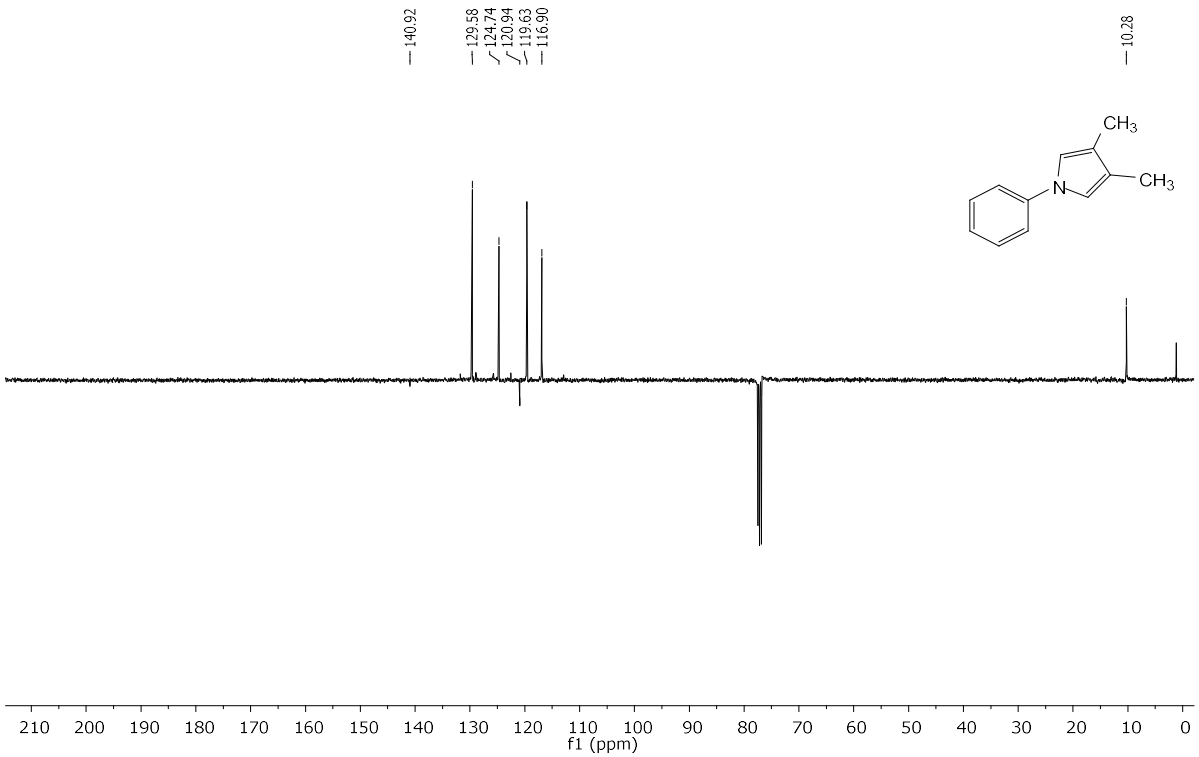


Fig. 287. ^{13}C NMR of **10aa** in $CDCl_3$.

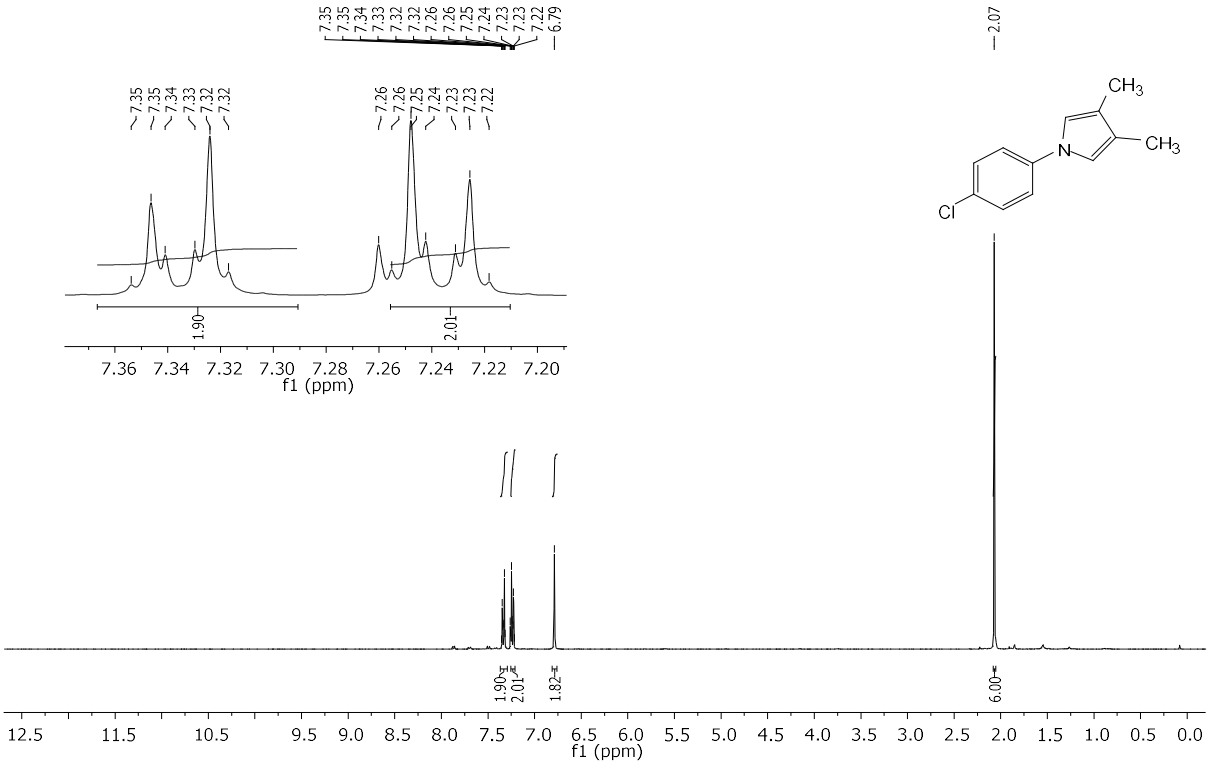


Fig. 288. ^{1}H NMR of **10ba** in $CDCl_3$.

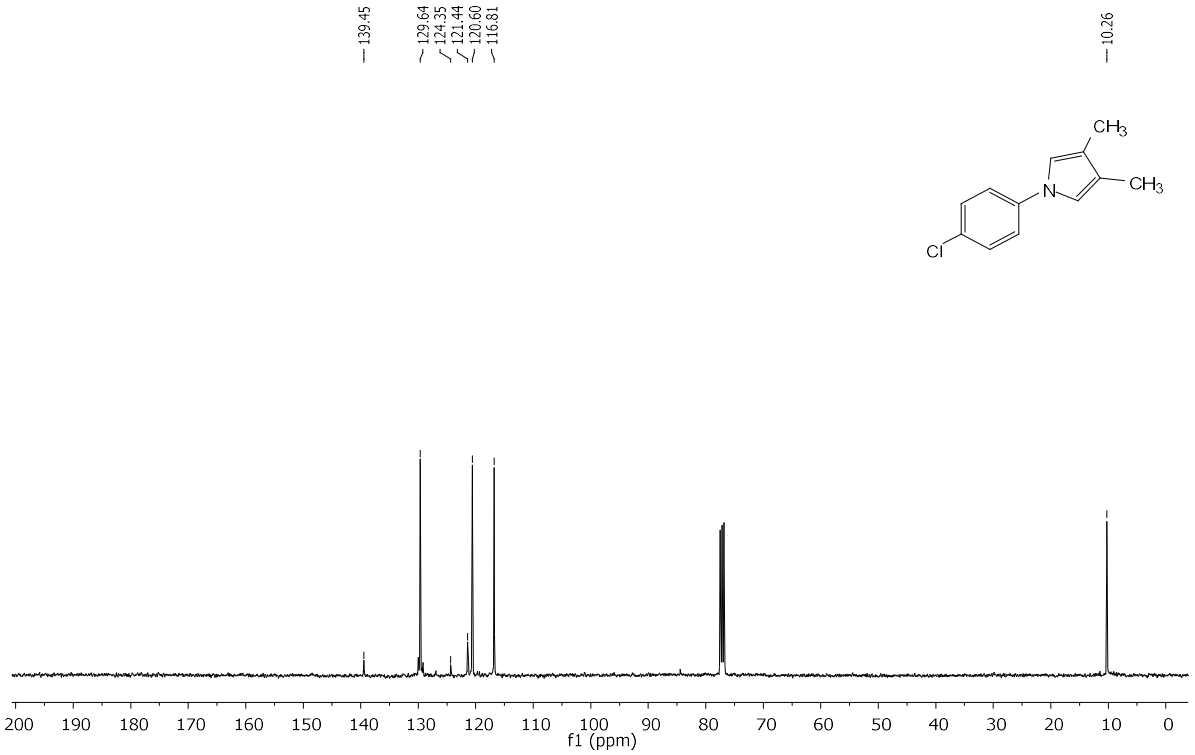


Fig. 289. ^{13}C NMR of **10ba** in $CDCl_3$.

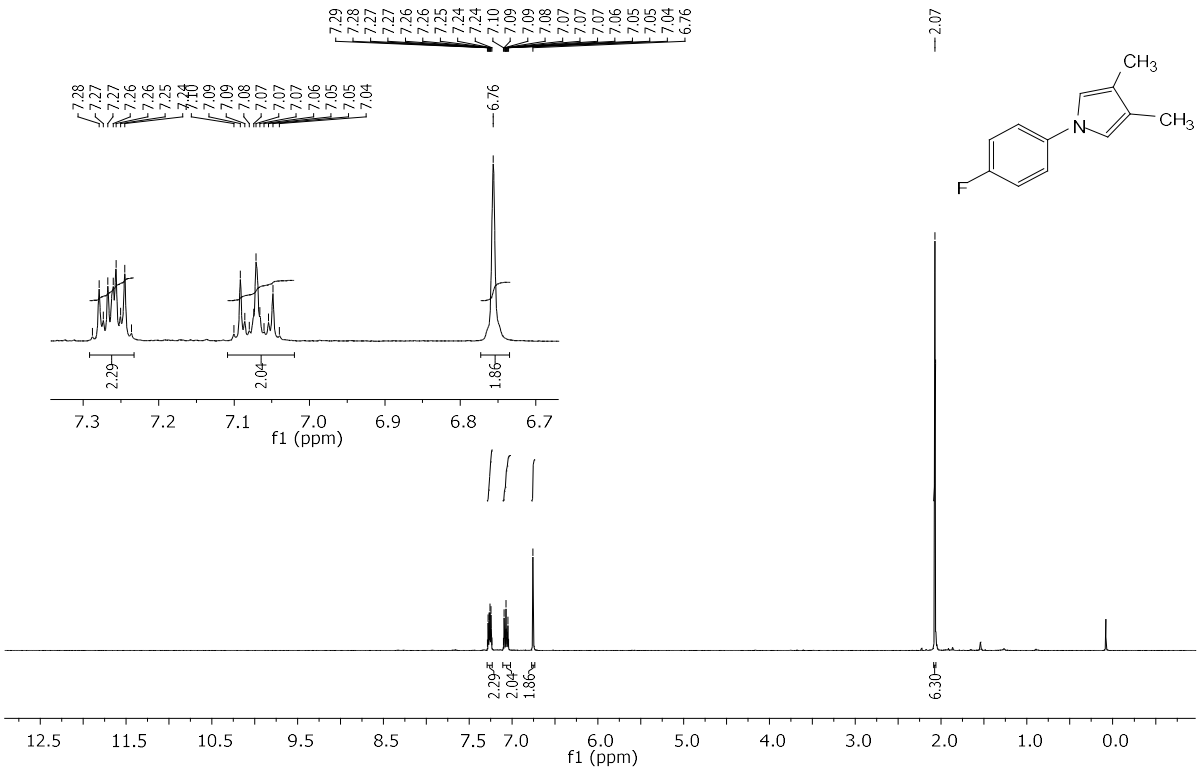


Fig. 290. ^{1}H NMR of **10ca** in $CDCl_3$.

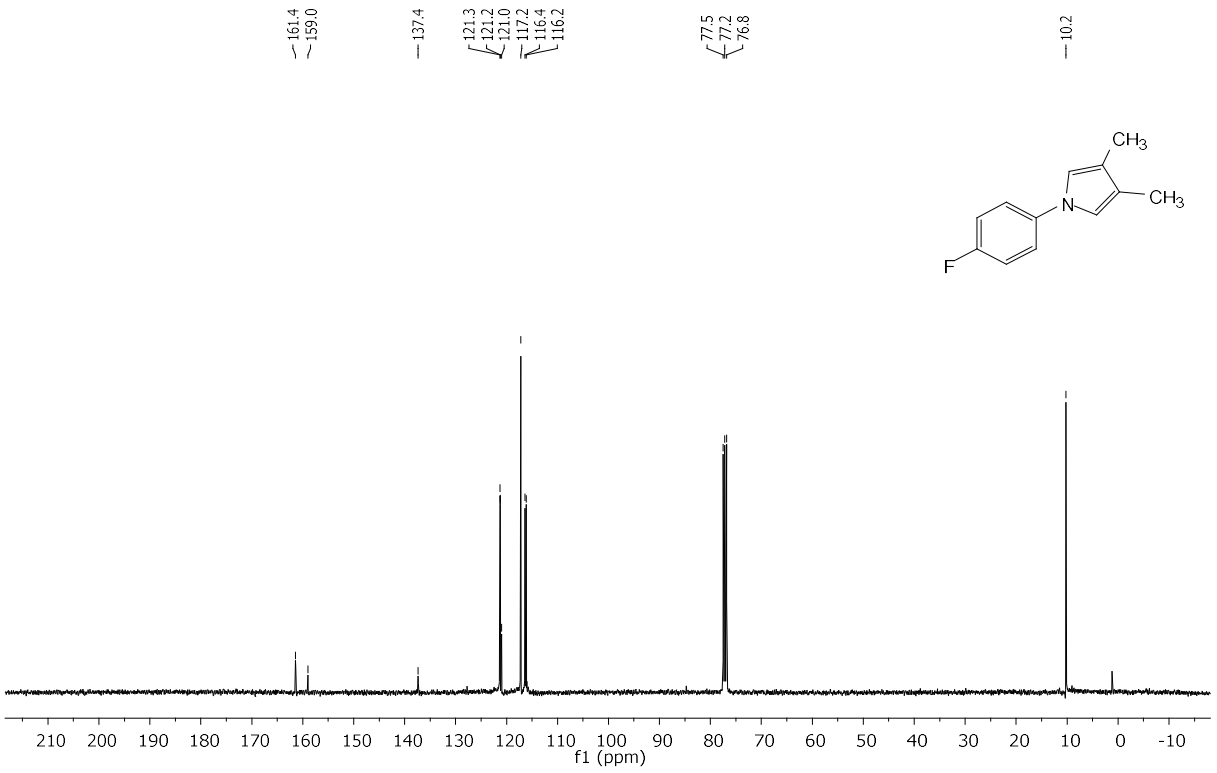


Fig. 291. ^{13}C NMR of **10ca** in $CDCl_3$.

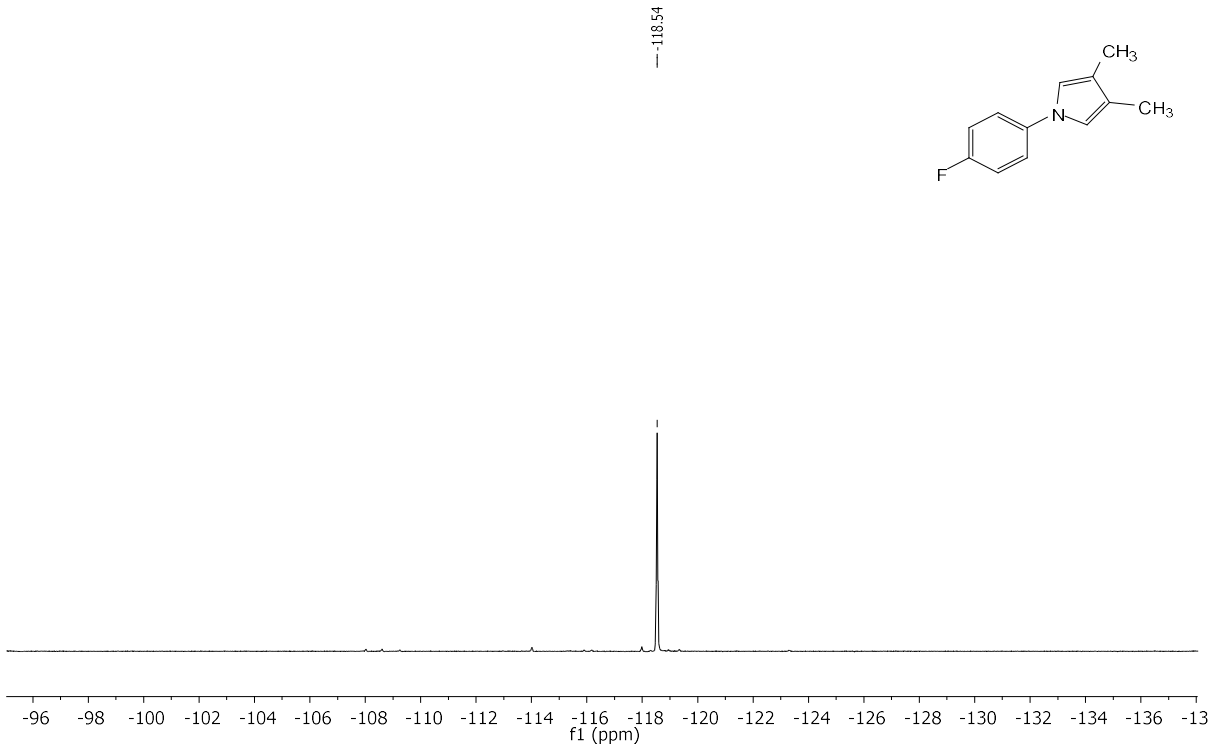


Fig. 292. ^{19}F NMR of **10ca** in $CDCl_3$.

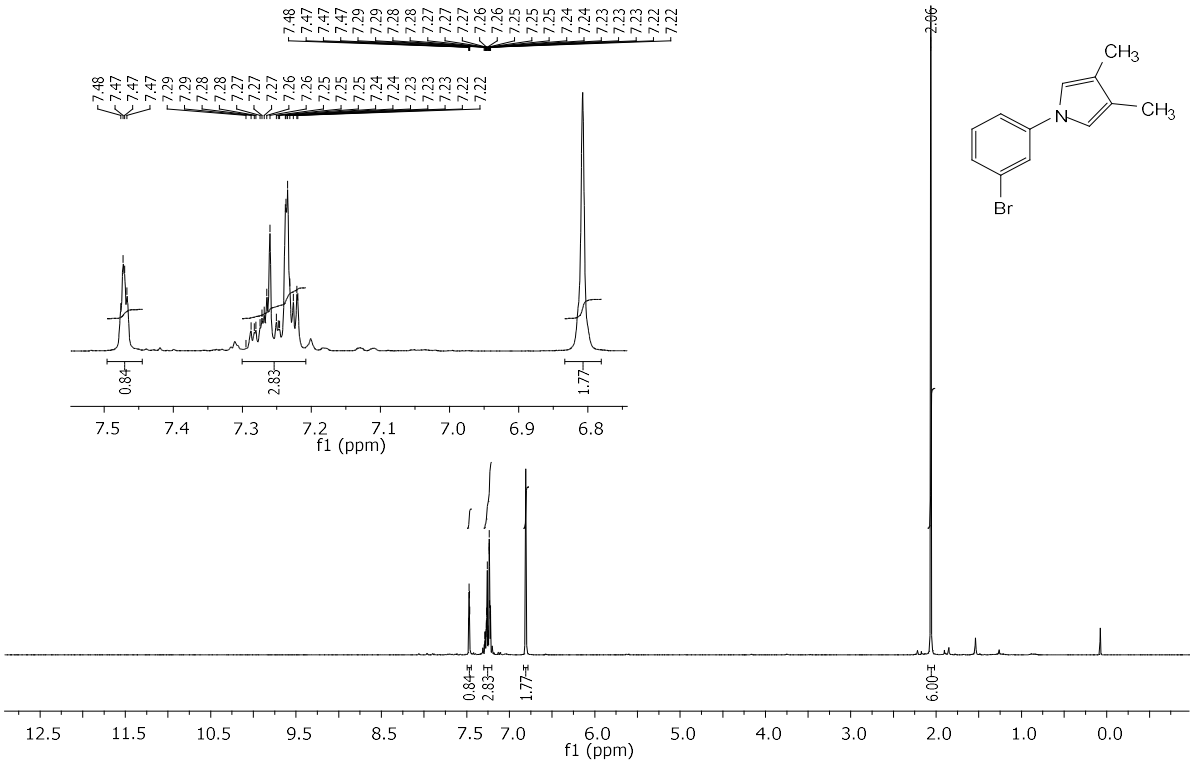


Fig. 293. ^{1}H NMR of **10da** in $CDCl_3$.

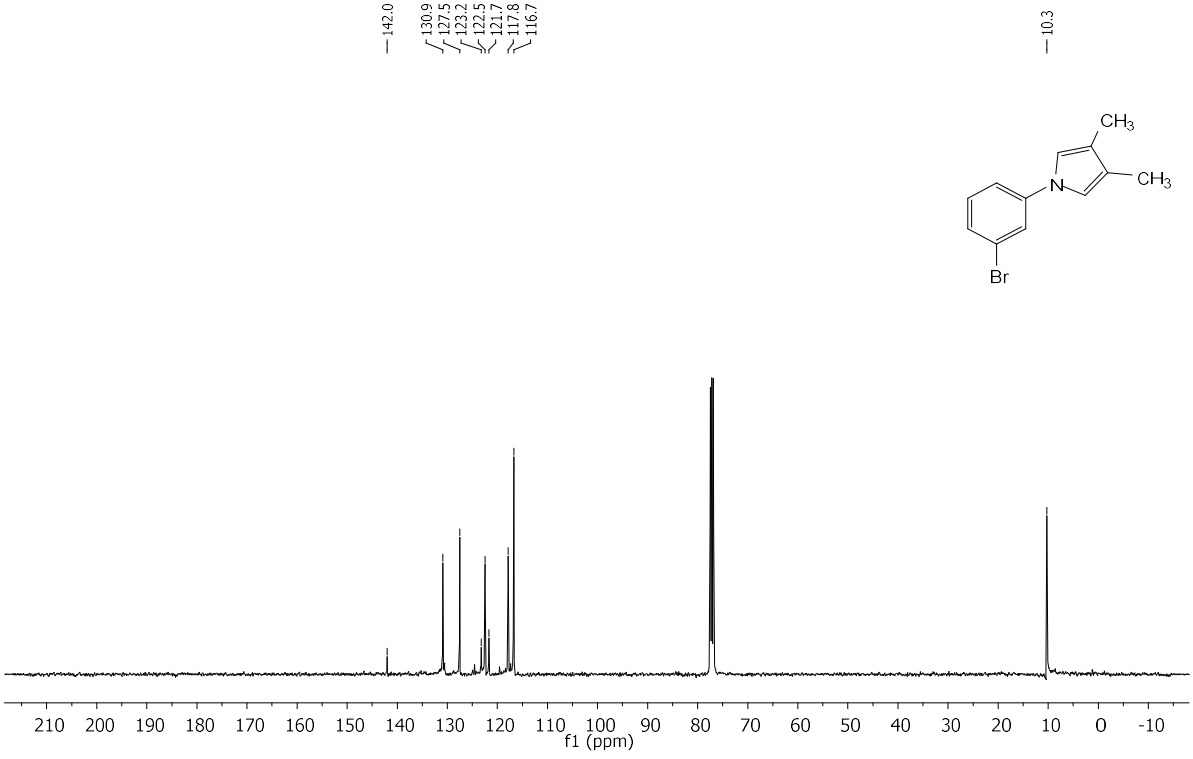


Fig. 294. ^{13}C NMR of **10da** in $CDCl_3$.

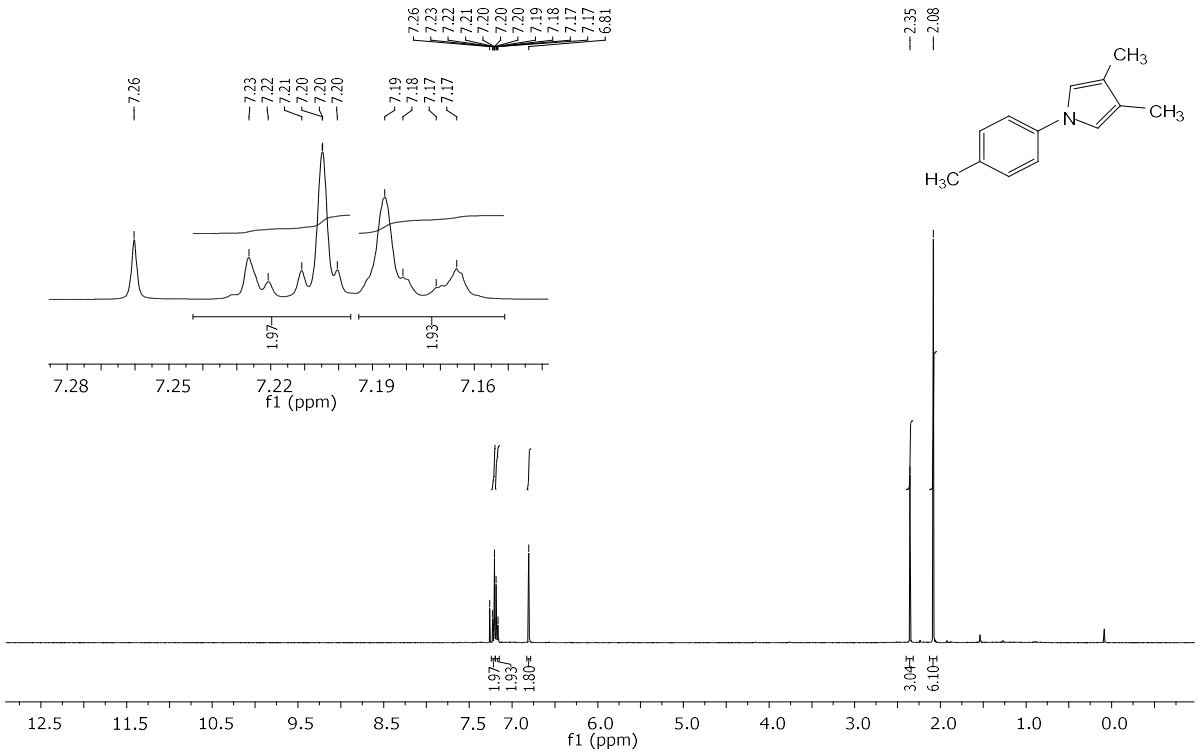


Fig. 295. ^{1}H NMR of **10fa** in $CDCl_3$.

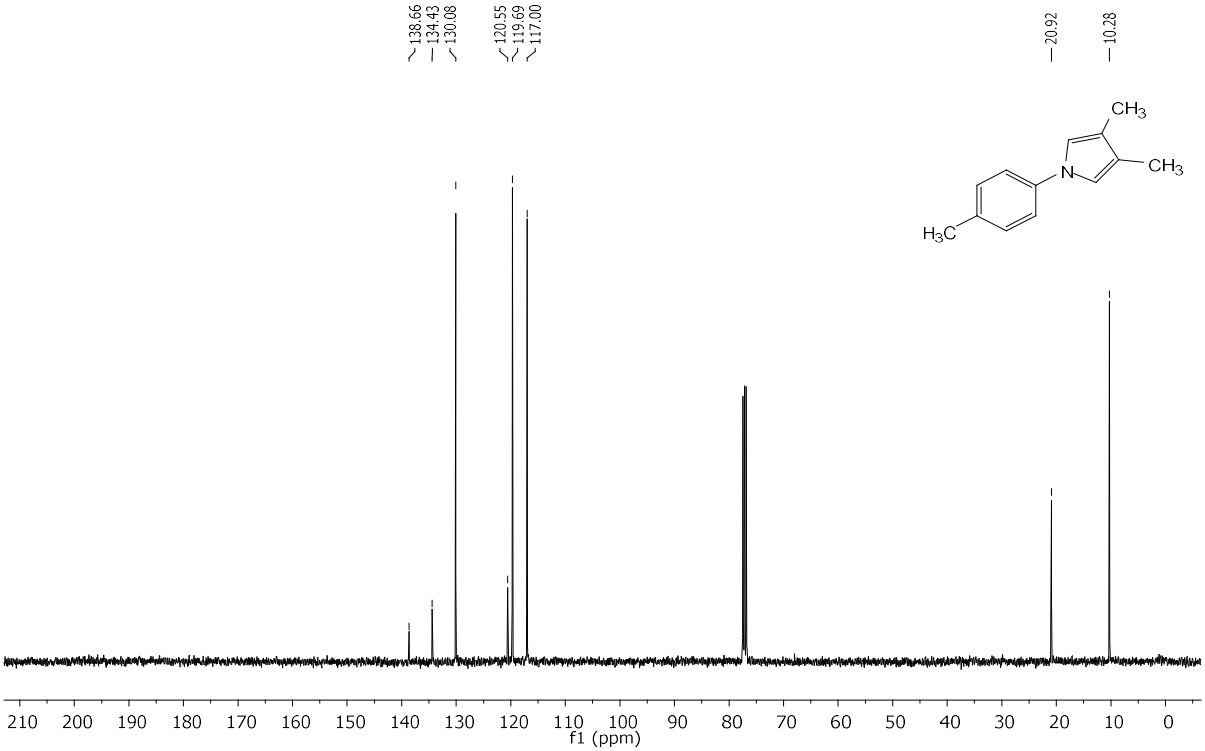


Fig. 296. ^{13}C NMR of **10fa** in $CDCl_3$.

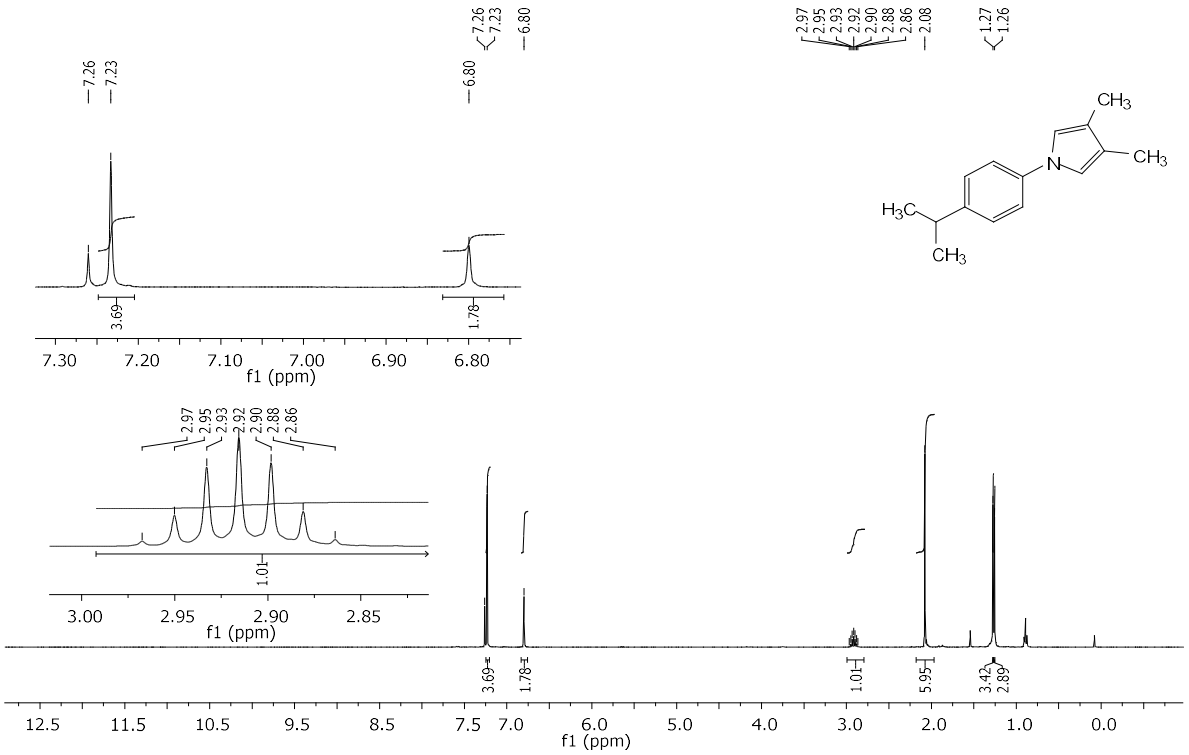


Fig. 297. ^{1}H NMR of **10ga** in $CDCl_3$.

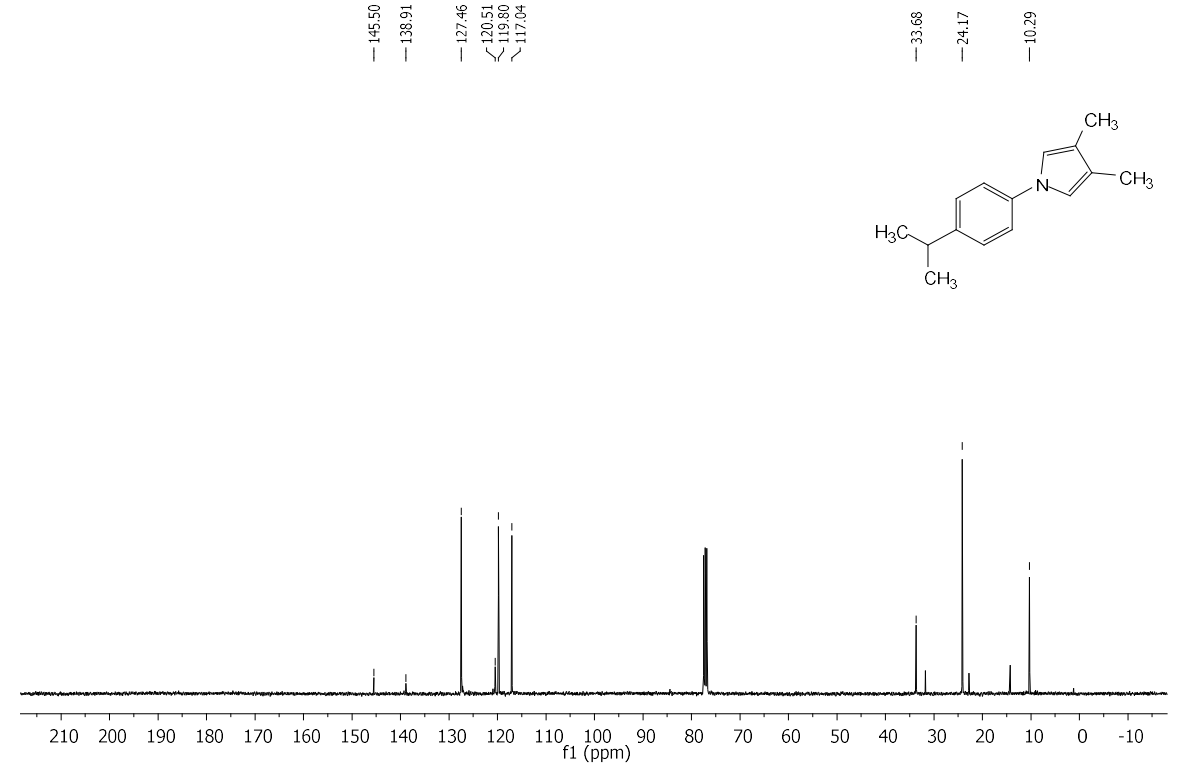


Fig. 298. ^{13}C NMR of **10ga** in $CDCl_3$.

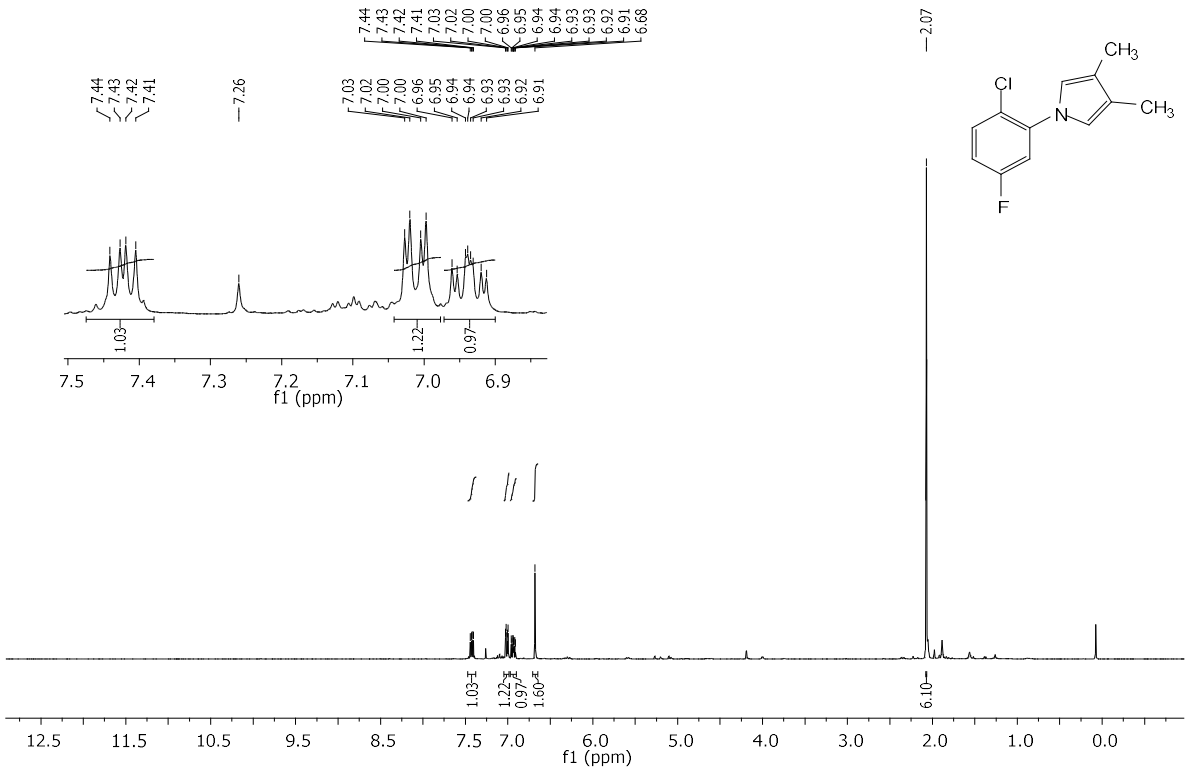


Fig. 299. ^{1}H NMR of **10ka** in $CDCl_3$.

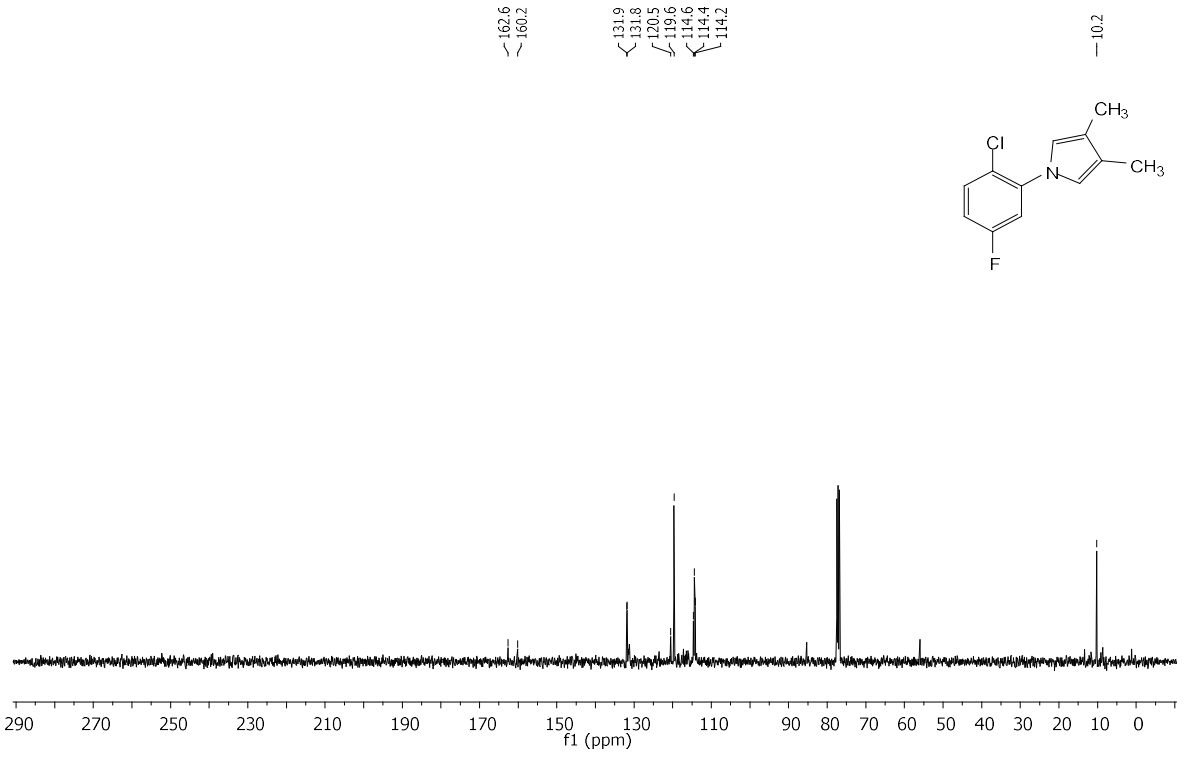


Fig. 300. ^{13}C NMR of **10ka** in $CDCl_3$.

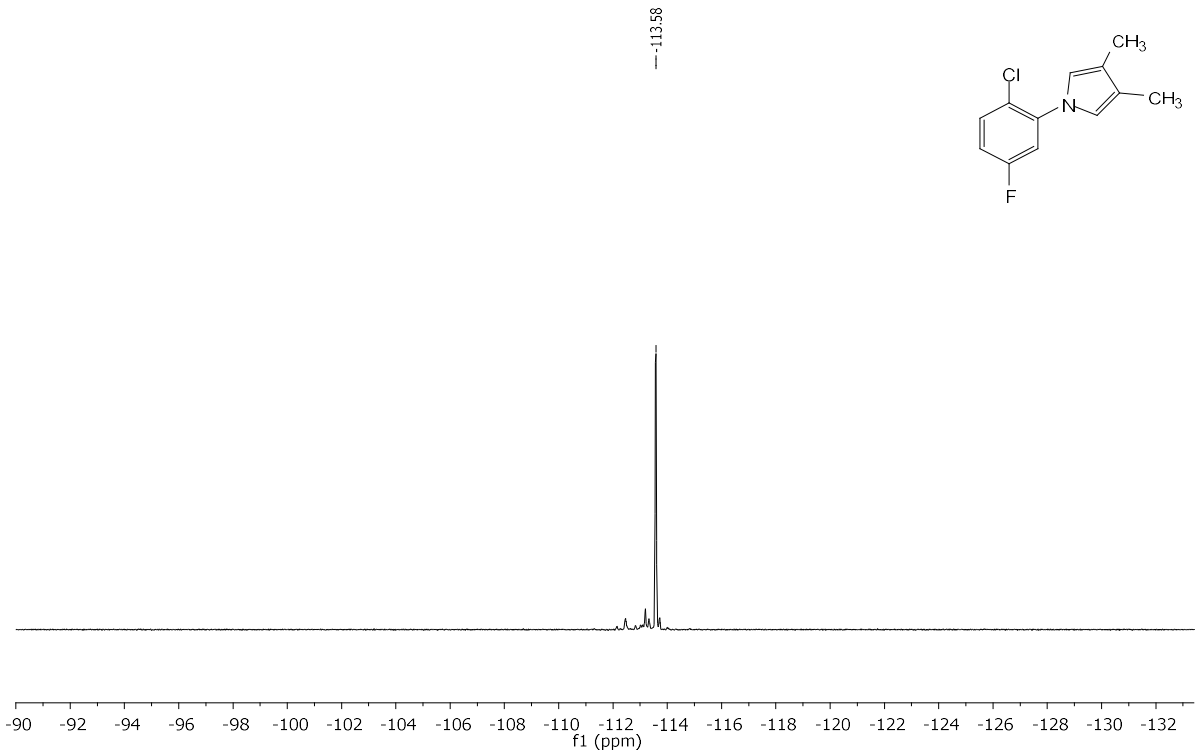


Fig. 301. ^{19}F NMR of **10ka** in $CDCl_3$.

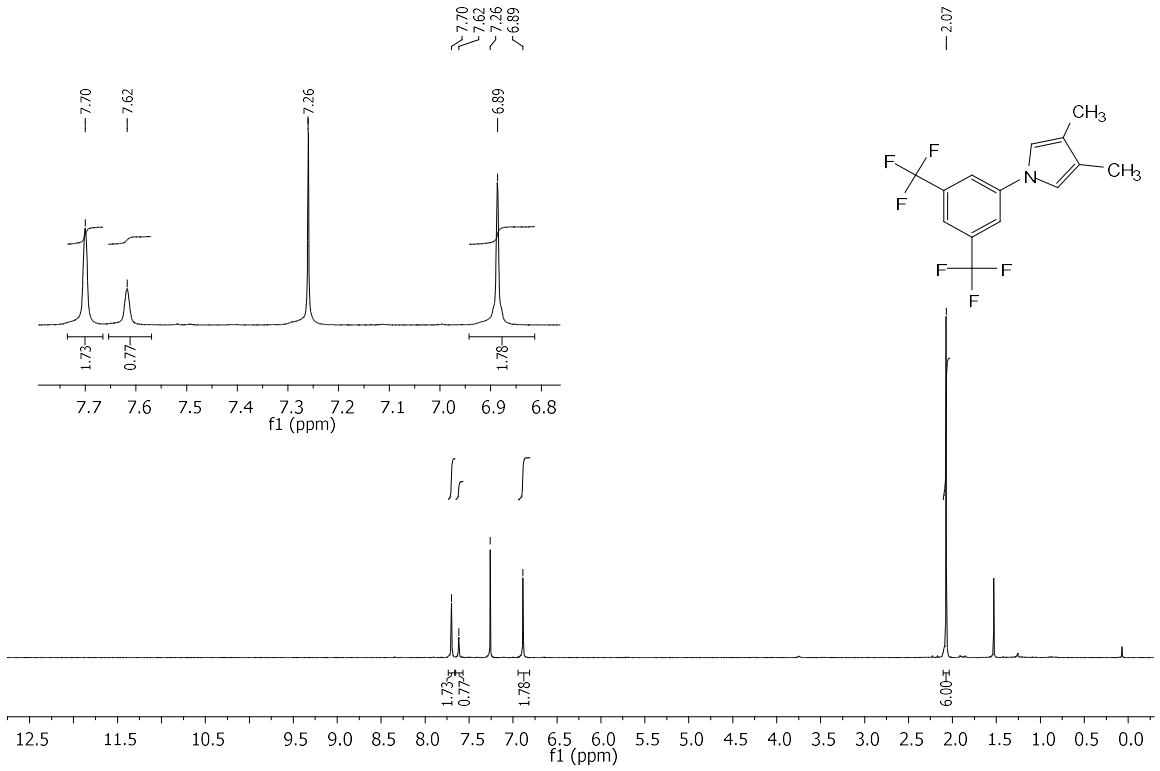


Fig. 302. ^{1}H NMR of **10la** in $CDCl_3$.

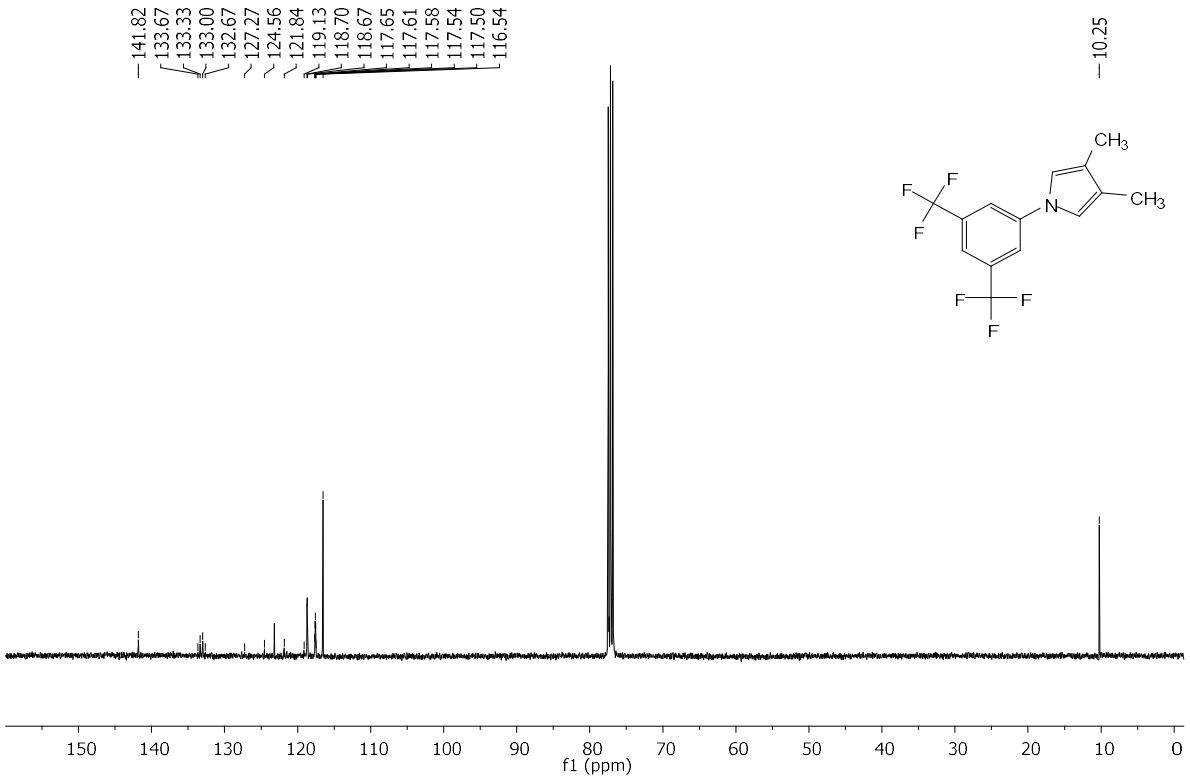


Fig. 303. ^{13}C NMR of **10la** in $CDCl_3$.

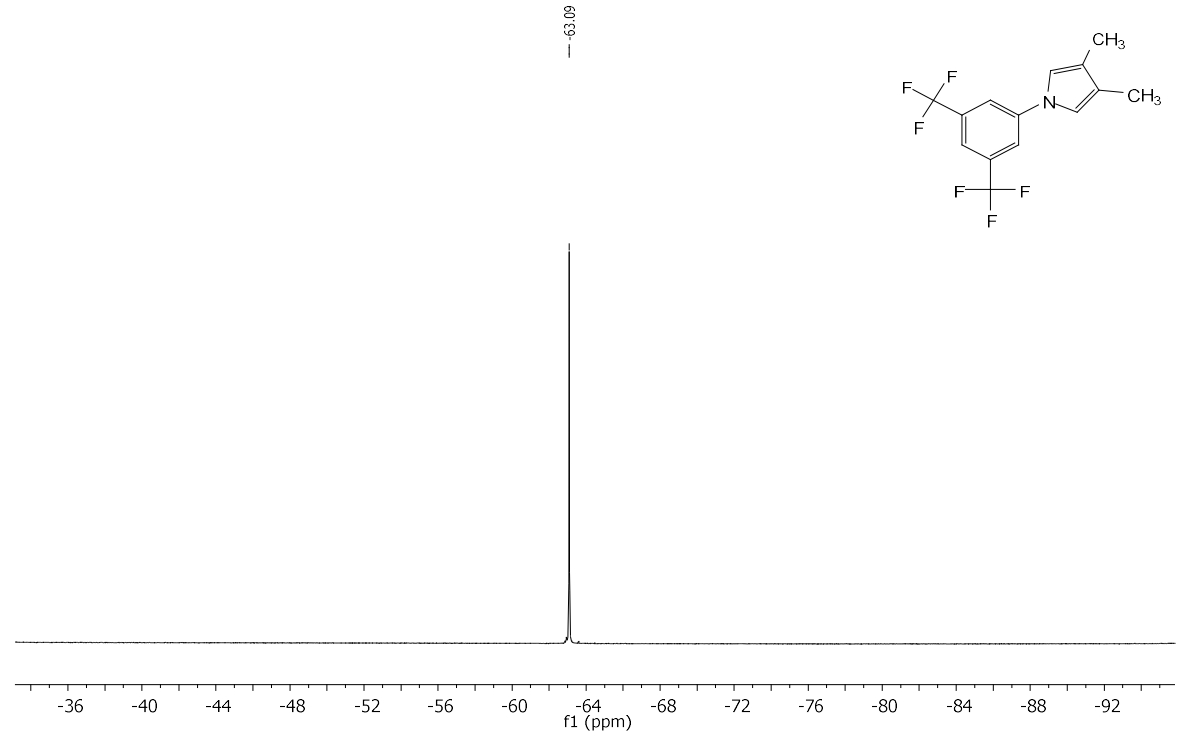


Fig. 304. ^{19}F NMR of **10la** in $CDCl_3$.

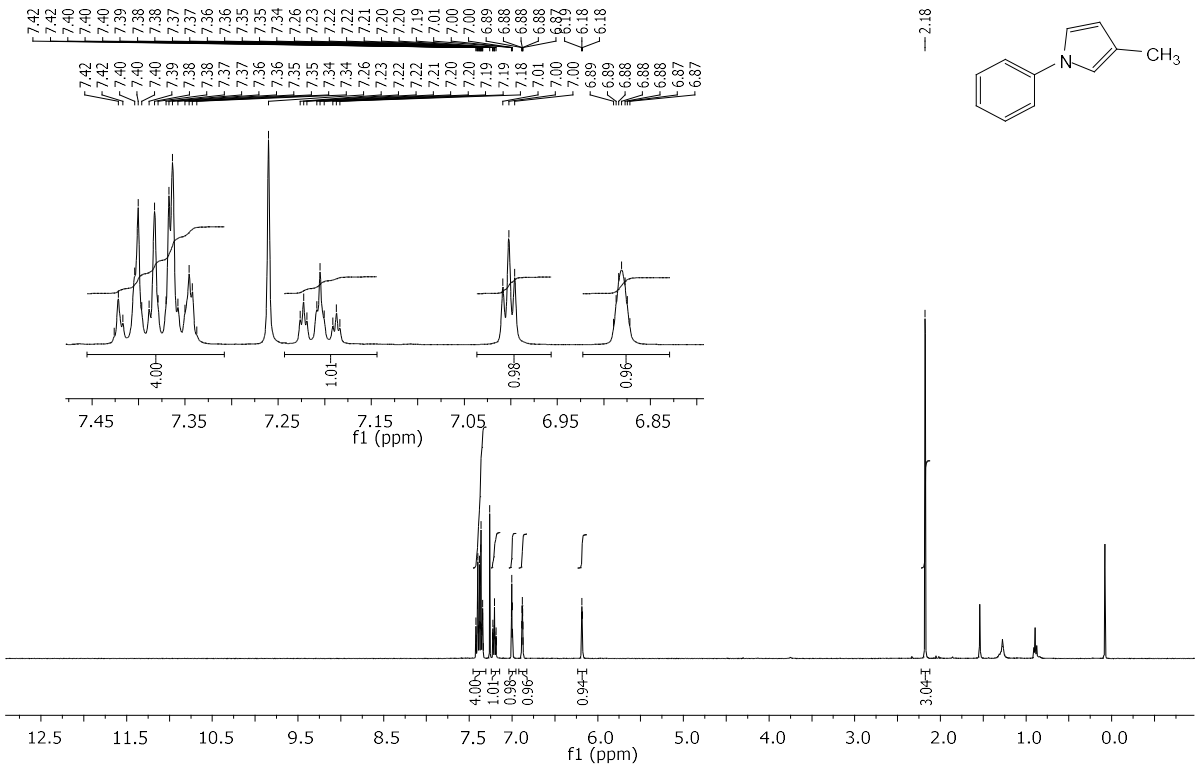


Fig. 305. ^{1}H NMR of **10ab** in $CDCl_3$.

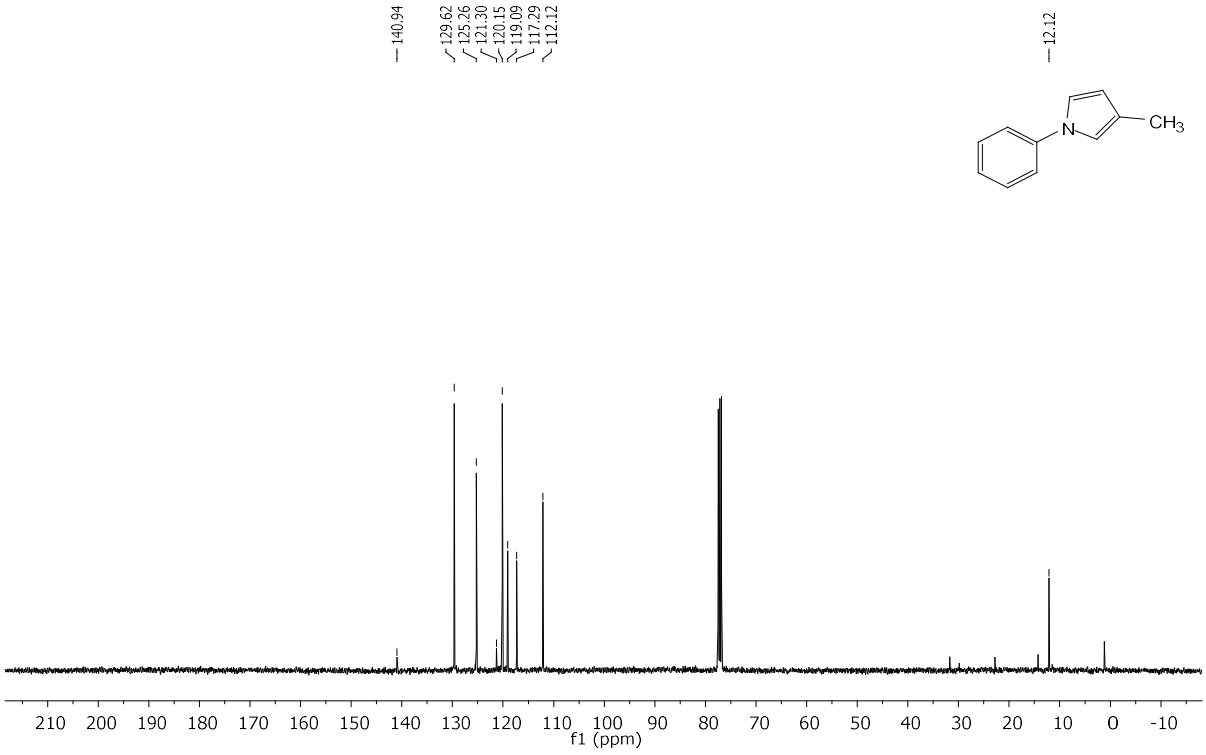


Fig. 306. ^{13}C NMR of **10ab** in $CDCl_3$.

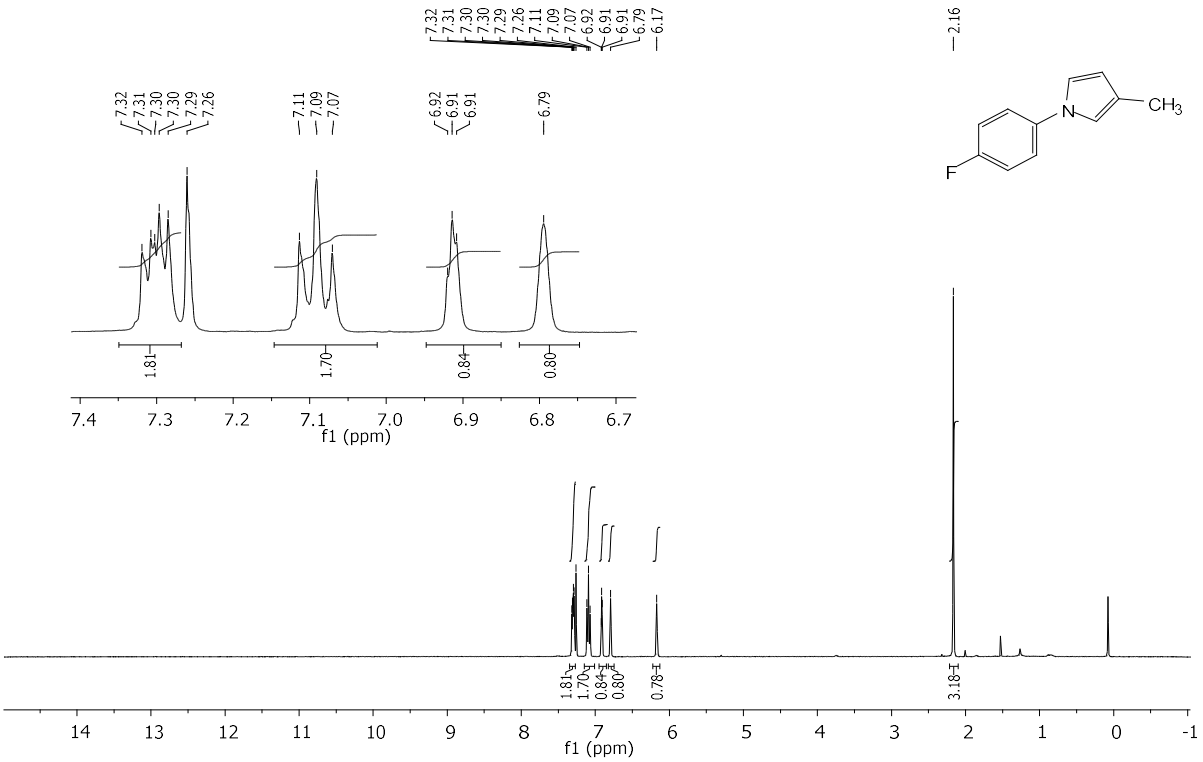


Fig. 307. ^{1}H NMR of **10cb** in $CDCl_3$.

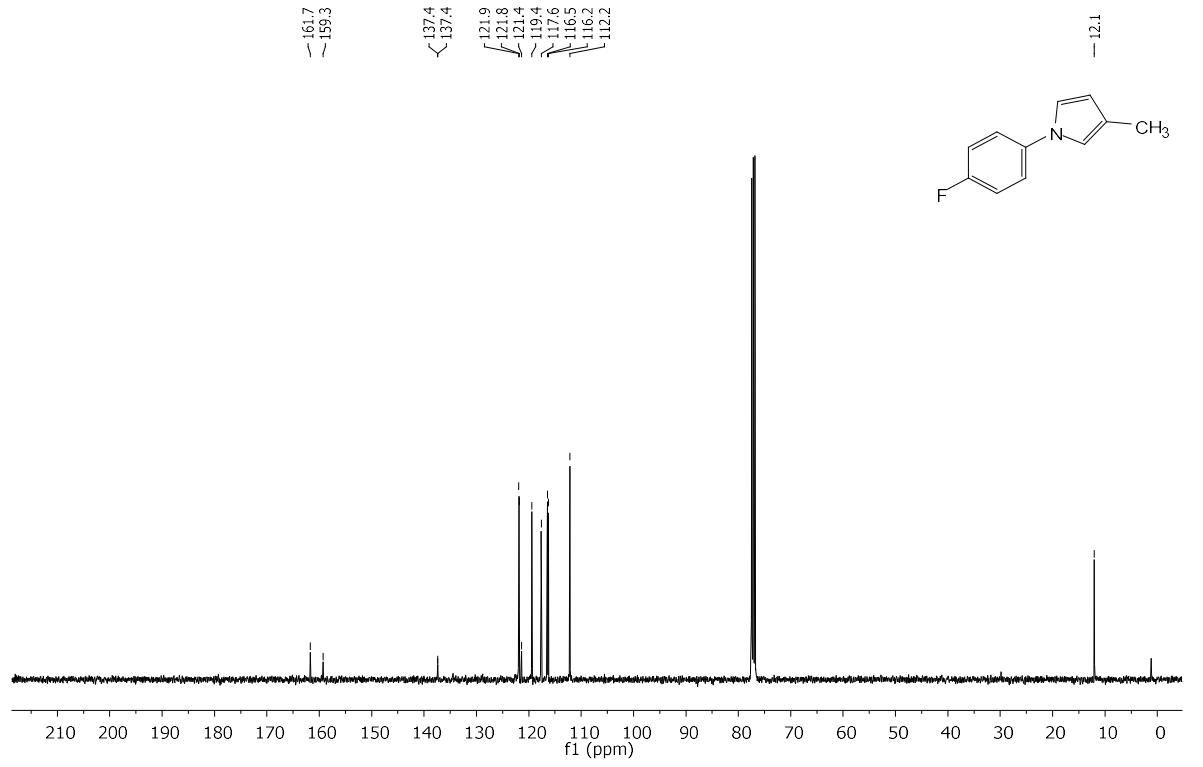


Fig. 308. ^{13}C NMR of **10cb** in $CDCl_3$.

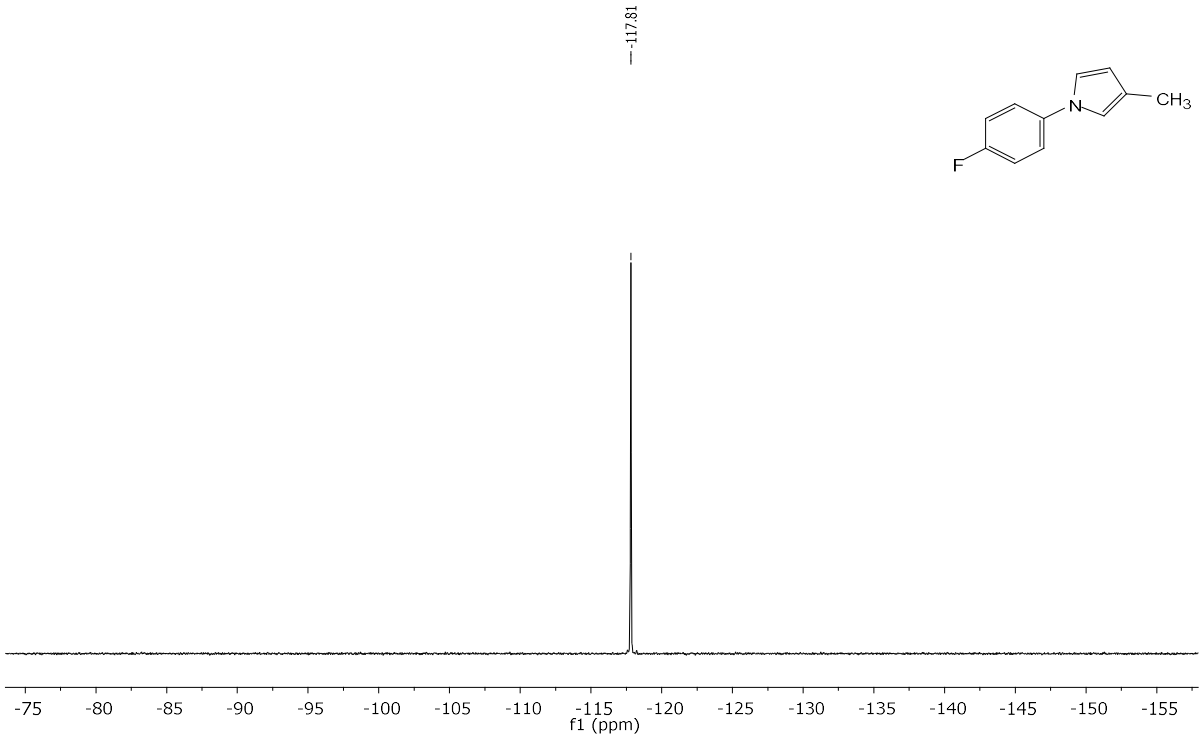


Fig. 309. ^{19}F NMR of **10cb** in $CDCl_3$.

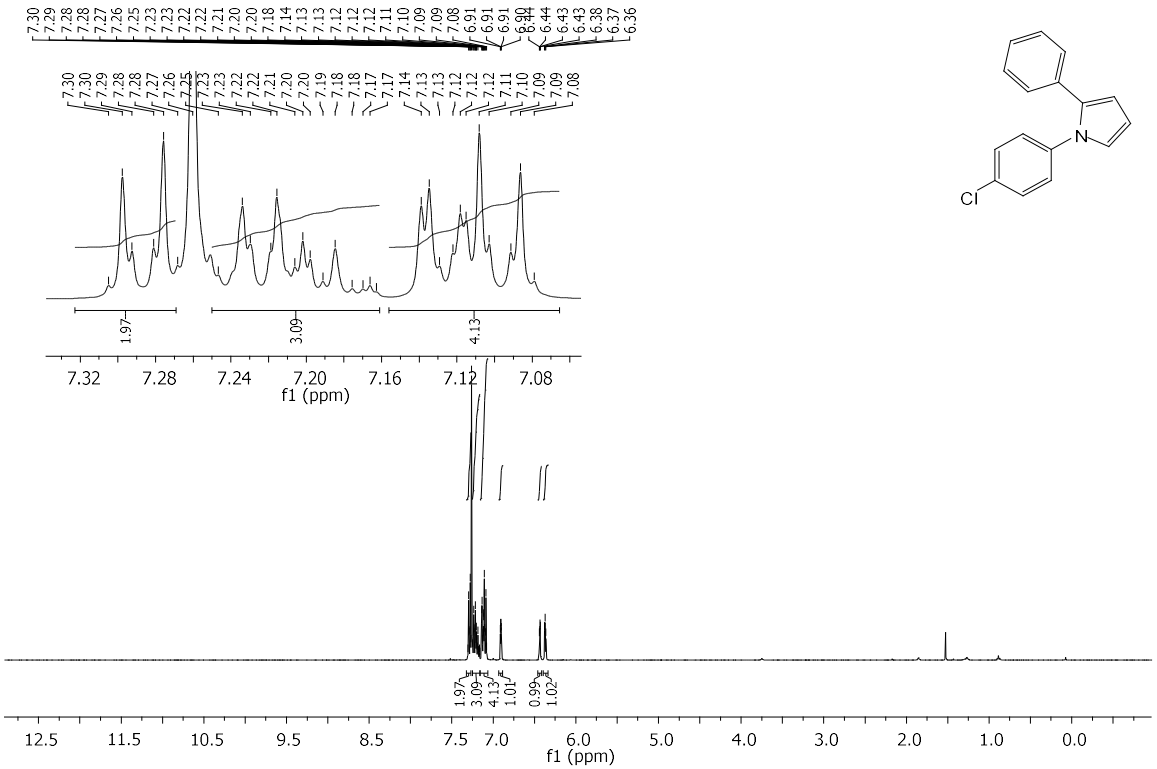


Fig. 310. ^{1}H NMR of **10bc** in $CDCl_3$.

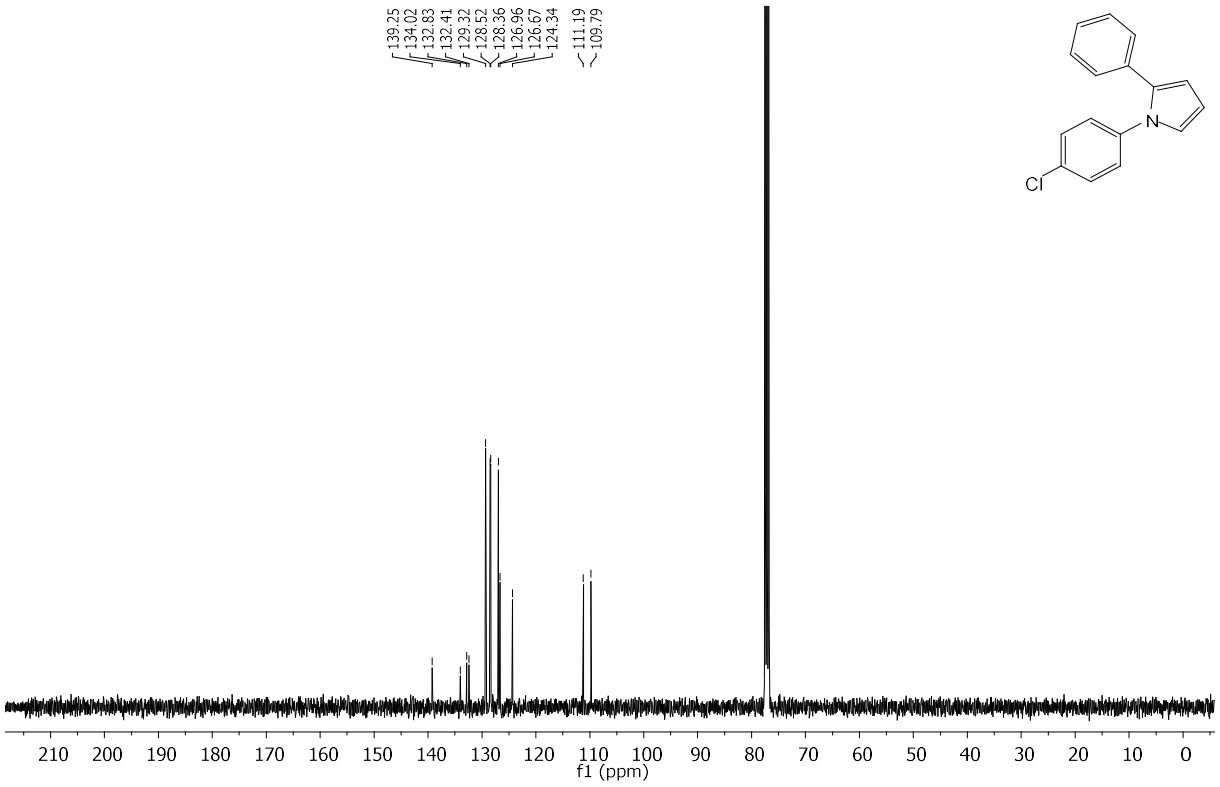


Fig. 311. ^{13}C NMR of **10bc** in $CDCl_3$.

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DOI: https://doi.org/10.1002/ejoc.202100789

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DOI: https://doi.org/10.3390/catal12010106

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DOI: https://doi.org/10.1021/acs.joc.2c02613

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Published in: *Catalysts,* **2023**
DOI: https://doi.org/10.3390/catal13020224

5- Article title:
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DOI: https://doi.org/10.3390/molecules28145424

6- Article title:
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Manar Ahmed Fouad, Francesco Ferretti, Simone Galiè, Fabio Ragaini
Published in: *European Journal of Organic Chemistry,* **2023**
DOI: https://doi.org/10.1002/ejoc.202300809