universität wien

# MASTERARBEIT / MASTER'S THESIS

Titel der Masterarbeit / Title of the Master's Thesis

## „Exploiting the synthetic potential of spiro-epoxyoxindoles as highly reactive fragments in carbenoid-mediated homologation reaction."


verfasst von / submitted by

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# Contents

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## *Abstract*

As a highly reactive fragments and molecules with a huge synthetic potential, the reactivity of spiro-epoxyoxindoles was examined employing novel synthetic tactics. These compounds were subjected to the highly sophisticated carbenoid-mediated homologation reactions resulting in the ring opening mechanism leading to the formation of a very attractive novel class of compounds in extraordinary yields. The chemoselectivity was completely intact even in presence of sensitive functionalities.

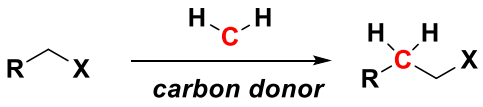


## *Abstrakt*

Als hochreaktive Fragmente und Moleküle mit einem hohen synthetischen Potential wurden Spiroepoxyoxindole mittels einem neuartigen synthetischen Verfahren untersucht. Diese Verbindungen wurden einer sehr komplexen durch Carbenoide vermittelten Homogenisierungsreaktion unterzogen. Dieser Prozess hatte einen Ringöffnungsmechanismus zur Folge, was zu sehr attraktiven neuen Produkten mit außergewöhnlichen Ausbeuten führte. Die Chemoseletivität blieb auch in Gegenwert empfindlicher funktioneller Gruppen vollständig erhalten.

# 1.0 INTRODUCTION

Synthetic procedure whose aim has insertion of the new carbon unit (usually $CH_2$) within the already existing carbon skeleton and creation of the additional carbon-carbon bond is known as homologation (*Scheme 1*). [1] As a result, a new carbon-carbon or carbon-heteroatom fragment, formed in just one synthetic step will be capable of further functionalization. Strong chemocontrol will result from the optimal reaction conditions, which eliminate difficulties emerging from the functionalization of the substituted precursor.[2, 3]




*Scheme 1 General principle of homologation reaction*

In order to induce the extension of the carbon chain by addition of the $CH_2$ unit, several methylenic reagents can be employed: **(a)** sulfur ylides (Corey-Chaykovsky [4]), **(b)** diazomethanes (Arndt Eisert [5] and Tiffenau-Demjanov [6]), **(c)** phosphorus ylides (Wittig [7]) and **(d)** carbenoids (Köbrich [8]) (Figure 1).

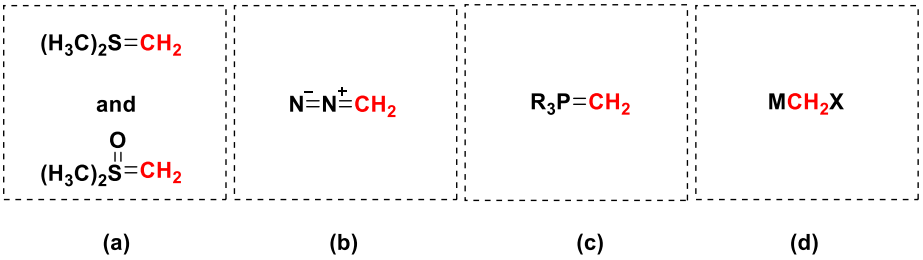


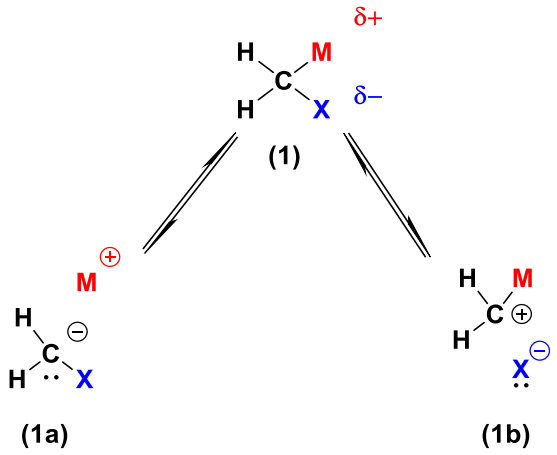

*Figure 1 Methylenic reagents*

However, usage of some homologating reagents, for instance diazomethanes, in pharmaceutical industry is not the first option, regarding their well-known mutagenic properties and explosivity. [9] Therefore, the employment of the carbenoids as homologating agents will be discussed in-depth throughout this Master thesis.

## 1.1 CARBENOIDS

### 1.1.1. General overview of the carbenoids

The word “carbenoid” was first mentioned in 1959 by L. Friedman and H. Shechter[10] in a term of an adjective to denote the presence of carbene-like activity. Later on, Closs and Moss transformed the term “carbenoid” from adjective to the noun which referred to the intermediates that “*exhibit reactions qualitatively similar to those of carbenes without necessarily being free divalent carbon species*”.[11] These compounds are extremely reactive, as they are formed of a metal atom (e.g. Li, Mg, Zn) and at least one electronegative group (e.g. halogen) linked to the same carbon. Furthermore, their ambiphilic character (they can act as electrophile or nucleophile) arises from the fact that the carbon atom is linked at the same time to an electron withdrawing and electron donating group. Experimental circumstances play a key role in revelation of their character, where at low temperatures they behave as nucleophiles, and in contrast, at high temperature they usually act as electrophiles. [12],[8] In *Scheme 2* is reported the strong ionization of the polar bonds which causes the formation of the carbanion (*1a*) or carbocation (*1b*).



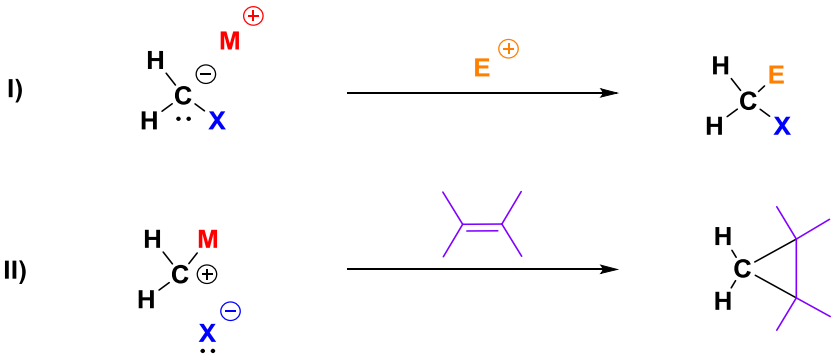

*Scheme 2 Structure and ambiphilicity of carbenoids.*

The behaviour of the carbenoid also strongly depends on the metal nature (M). On one hand, carbenoid shows a nucleophilic behaviour, which is the most common case with a lithium carbenoids. On the other hand, an electrophilic one, that is very common for the Zn-carbenoids as the Zn is a less electropositive metal. Further spectroscopic analyses supported this phenomenon, regarding a pronounced s

character of C-M bond and p character of the C-X bond. As a result, carbenoids are susceptible to two types of reactions (*Scheme 3*):

I) nucleophilic additions;

II) cyclopropanation-type of reactions. [13],[3, 14]

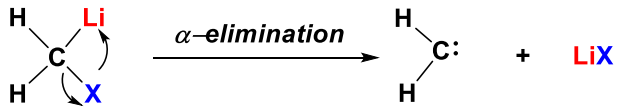



*Scheme 3 Two types of carbenoids.*

As a result of their flexibility and the capability to introduce a functionalized carbon in a single synthetic step, the employment of carbenoids may offer a significant and advantageous technique.

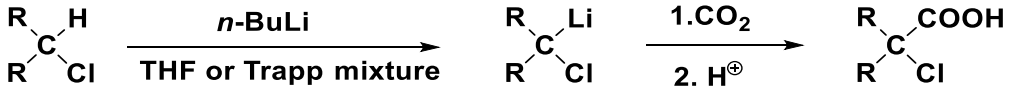
### 1.1.2 Thermal instability and configurational stability

The main limitation in the use of carbenoids reagents is the thermal instability, resulting in a degradation process through α-elimination, due to an internal coordination of the metal with the halogen, finally leading to a free carbene and a metal halide salt (*Scheme 4*). Therefore, it is important to find a good compromise between stability and reactivity in order to obtain the best results in homologation processes.




*Scheme 4 α-Elimination.*

In the 1960s Köbrich, together with his research group, discovered a method for preparing carbenoids avoiding the unwanted decomposition step. He explained that the metalation of chlorinated hydrocarbons should be conducted under low temperatures (-70 to -120 °C) using *n*-butyllithium in tetrahydrofurane (THF). Carbenoids can further be characterized by carboxylation reaction (*Scheme 5*). [8]



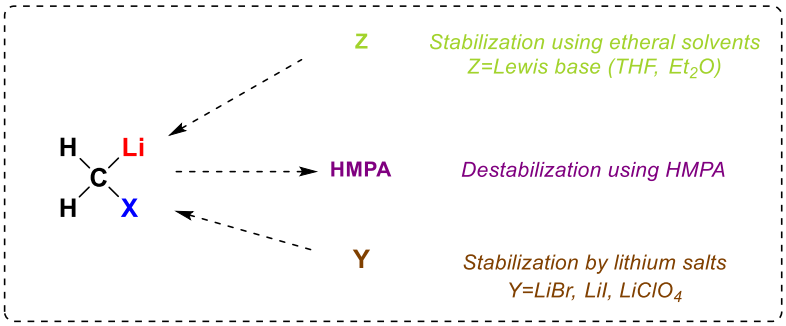

*Scheme 5 Köbrich's method for preparing carbenoids avoiding the unwanted decomposition.*

A decade later, the formation of monohalomethyllithium derivatives at -78 °C was achieved by Canielli. By using Barbier type conditions (the electrophile has to be present in the reaction medium when the carbenoid is generated) he was able to obtain epoxides from carbonyl compounds. However, two different lithium sources for preparing carbenoids were used:

- Li metallic;

- *n*-BuLi.

The employment of *n*-BuLi was preferred, as it can be applied at very low temperatures. [15] Furthermore, as reported by Villieras *et al.*, carbenoids can be stabilized by addition of the lithium salts (lithium halides; e.g. LiBr) which coordinating the halogen atom (X; e.g. Cl, I, Br), interrupt the internal interaction with Li, responsible of the α-elimination (Scheme 4). Another way to prevent carbenoids decomposition concerns the coordination of lithium atom of the carbenoid by using a Lewis base (e.g. THF, $Et_2O$). In contrast, solvents such as hexamethylphosphoramide (HMPA) and dimethylformamide (DMF) manifest destabilizing effects and favour α-elimination. The oxygen atom of these solvents has a strong coordinating ability, which cause breakage of the Li-C bond (*Scheme 6*). [16, 17]




*Scheme 6 Strategies to modulate the alpha elimination.*

Successful generation of bromomethyl lithium and chloromethyl lithium at -78 °C, has been reported at the early 1990s by Matteson *et al*. These compounds were obtained in almost quantitative yields, whereas so far only a small amount of carbenoids have been acquired. Therefore, working at this temperature does not affect the

effectiveness of the reaction and does not result in decreased yield. [18, 19] Despite the fact that numerous alkyllithium bases were used during the years to ensure the stability of carbenoid, so far, MeLi-LiBr appears to offer the best results due to aforementioned stabilization with lithium salts.[20] Even though rare, several thermo stable carbenoids have been reported during the years where the first one was revealed by Le Floch *et al*. [21] Because of the presence of two sulphur atoms and two molecules of $Et_2O$, which significantly stabilize the lithium cation (*Figure 2- example 1)* and block the α- elimination process (proven by X-ray analysis), he employed stable carbenoids at room temperature. The lone pair of the carbon linked to the lithium atom is in the p orbital and it's secured by anionic hyperconjugation, resulting in strong bond between chlorine and carbon.[22-25] In the 1995, another thermo stable carbenoid has been obtained. Stability of this compounds arises from the fact that there is the rearrangement of the electrons across the three atoms in the methylene (phosphoranylidene) *(Figure 2-example 2).* At temperatures higher than -50 °C it decomposes due to the lithiumchloride elimination.[26] In order to obtain one of the most stable carbenoids so far, Gessner and co-workers decided to replace lithium atom with sodium and potassium. Compounds were further stabilized by thiophosphoryl and triphenylsilyl groups. In fact, bis(thiophosphoryl) turned out to be more stable *(Figure 2-example 3).* This all helped in acquiring the first fluorine carbenoid, stable at the room temperature.[27]

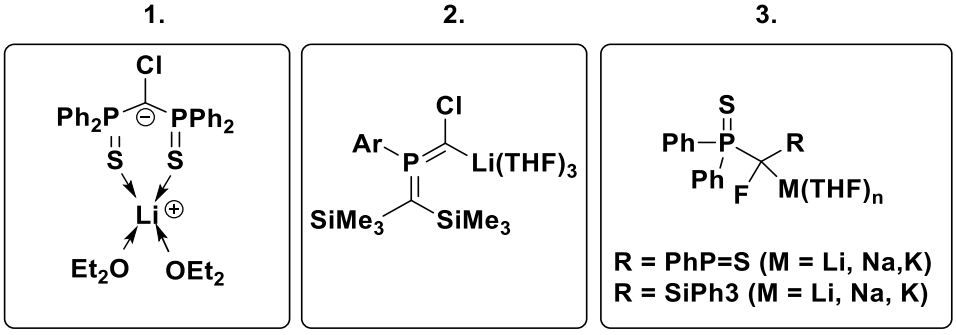
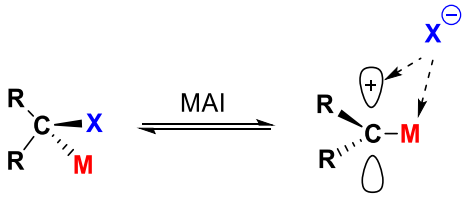



*Figure 2 Examples of thermostable carbenoids.*

On the other side, when it comes to configurational stability of carbenoids, not much is known. One of the pioneers researching this topic was Köbrich. While observing epimers of 7-chloro-7-lithionorcarane at the temperature of -80 °C, he found out that they reorganize slowly at a pace close to their decomposition, due to ring strain of cyclopropane, which further prevents configurational inversion at the carbanionic

core. Indeed, subsequent research confirmed that different kind of R-chloro and R-bromocycloproyllithiums have a stable configuration at temperatures lower than -78 °C, but they begin to epimerize as the temperature rises. [28-30] In the early 1990s, Topolski *et al.* observed stereochemistry and reactivity of carbenoids prepared from chiral cyclopropyl and vinyl halides. They presented the concept of metal assisted ionization (MAI) in order to explain stereochemical results after treating the carbenoids with nucleophiles (*Scheme 7*).




*Scheme 7 Metal-assisted ionization (MAI).*

According to their theory, halide acts as a leaving group, giving a carbocationic character to the carbenoid with preserved stereoconfiguration. As the halide is still blocking one side of the carbenoid, nucleophile tends to attack it from the other side, therefore resulting in generation of the product with inverted configuration. [31, 32] Furthermore, Hammerschmidt *et al.* have recently published a work about configurational stability of chiral chloro-[D1]methyllithiums. They generated chloro-[D1]methyllithium, using a tin/lithium exchange and stated that it´s configurationally stable up to the temperature of -78 °C which is also the temperature of decomposition. After performing the reaction at the -78 °C and introducing the benzaldehyde after 30 s, carbenoid´s chemical stability has decreased, while the chiral centre has retained. Hence, at such temperature, this compound rather degrades than racemases. [33]

### 1.1.3 Synthesis of halolithium carbenoids

Several types of reactions can be performed in order to obtain halolithium carbenoids:

i. lithium-hydrogen exchange;
ii. lithium-halogen exchange;
iii. lithium-sulfinyl exchange;
iv. lithium-tin exchange.

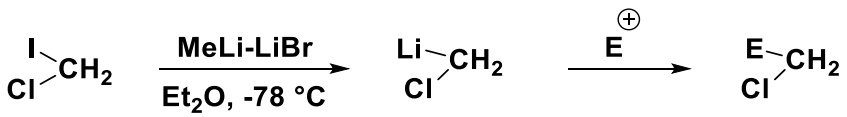
Because of the simple operating processes required and the fact that dihalometane precursors are widely available on the market, lithiation by lithium-halogen exchange is the most often employed method. [34] In the 1984, Villieras performed the synthesis of α-halomethyllithium compounds by using secondary butyllithium instead of *n*-butyllithium in the mixture of THF, $Et_2O$ and pentane (Trapp mixture) at -115 °C. [17] However, recently several researches indicated that this way of deprotonation is more likely to happen than the exchange reaction. [34-37] Additionally, usage of methyllithium and *n*-butyllithium as the source of the lithium, would positively affect the reaction. In order to achieve the formation of chloromethyllithium using the chloroiodomethane, the best way is using the complex of MeLi-LiBr in $Et_2O$. Lithiumbromide has several roles here:

-improving carbenoid's stability through coordination;

-under Barbier type conditions, it prevents methyllithium from attacking the electrophile in the reaction mixture;

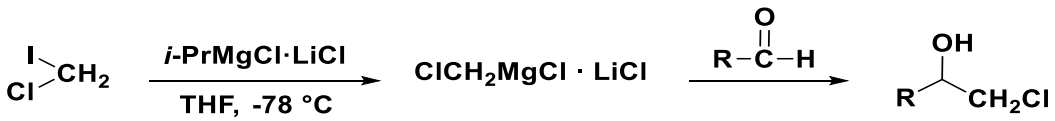
-it behaves as weak Lewis acid and supports the attack of the electrophilic substrate by the carbenoid. [38-41]

Since the composition of the dihalomethane used to generate the carbenoid impacts the reaction efficiency, chloroiodomethane is one of the most commonly utilized precursors due to the easier exchange conducted on iodo-containing halomethanes. [34] As reported by Aggarwal, despite the fact that the reaction between dihalide and organolithium was quantitative, modest overabundance of the dihalomethane (0.2-0.4 equivalents) is beneficial for the reaction due to alkyllithium's predilection to attack the electrophile and due to variations in its concentration. To ensure the higher yields, dropwise addition of the alkyllithium in the reaction mixture, consisting of the dihalomethane and electrophilic substrate, is preferred. The aim of this is to catch the electrophile with a newly produced carbenoid before its immediate degradation (*Scheme 8*). [42]




*Scheme 8 Example of the lithium-halogen exchange in presence of MeLi-LiBr.*

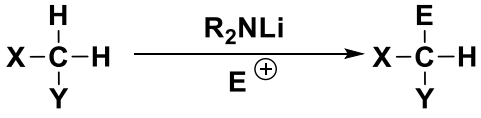
Moreover, magnesium carbenoids were the subject of the interest of Knochel, Marek and their coworkers as they described them as highly suitable for synthetic reactions. These compounds were successfully synthesized from iodomethanes and *i*-PrMgCl in THF/*n*-butylpyrrolidone combination at -78 °C. They were able to react with different types of electrophiles resulting in high yields (around 60-88%).[43, 44] Recently, Clososki used the same principle in order to produce the carbenoid $ClCH_2MgCl{\cdot}LiCl$ through the exchange of magnesium with iodine. The reaction was quenched with the aldehyde to produce the corresponding chlorohydrin in relatively high yields (*Scheme 9*).[45]




*Scheme 9 Example of magnesium-halogen exchange and quenching with an aldehyde.*

Despite these promising results, Pace and coworkers have reported that in contrast to lithium carbenoids, magnesium carbenoids are suitable just for the reactions with strong electrophiles such as aldehydes, but they don't react with weak ones such as Weinreb amides.[46]

Even at really low temperatures around -115 °C by using *sec*-BuLi, the lithium-halogen exchange is characterized by a greater rate than deprotonation, indicating that it cannot be used to generate monohalolithiumcarbenoids. On the other side, exchange of lithium with hydrogen can be utilized to achieve this goal by using a lithium amide base (e.g. LNCy2, LTMP, LDA, LHDMS) which remove the proton from the corresponding dihalomethanes (*Scheme 10*).[39, 47, 48]

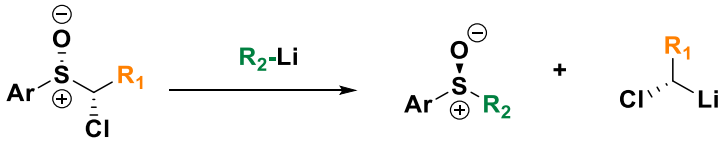



**X,Y = Cl, Br, I**
**R = Cy, TMP, TMS, *i*-Pr**

*Scheme 10 Lithium-hydrogen exchange.*

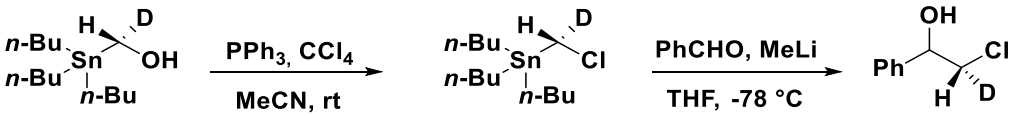
Furthermore, metal-sulfinyl trade was found out by Hoffmann in 2003 where exceptionally stable magnesium carbenoid was synthesized at -80 °C using Grignard reagent and sulfoxide. For more than 30 minutes at the temperatures up to 0 °C, this

carbenoid was stable by the means of temperature and configuration. In this case, change of configuration, because of the extreme stereoselectivity of the reaction, occurs at sulphur atom (*Scheme 11*).[49, 50]




*Scheme 11 Lithium-sulfinyl exchange.*

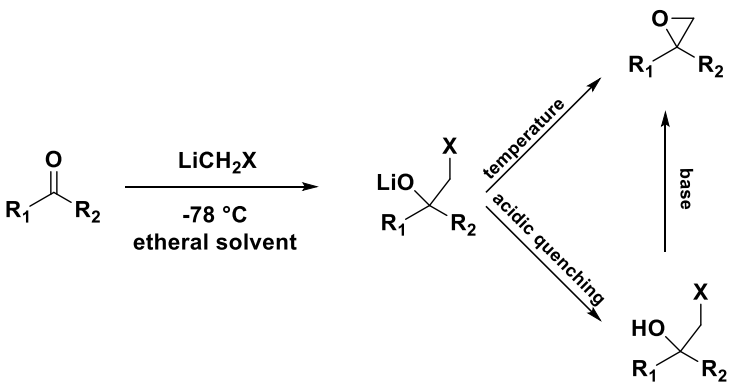
Lithium-tin exchange has been discovered in 2008 by Hammerschmidt *et al*. They have successfully synthesized chloro[$D_1$]methyllithium, which is capable of reacting with benzaldehyde, resulting in formation of chlorohydrines via lithium-tin trade reaction with methyllithium.[33] Utilizing the Appel conditions (triphenylphosphine and carbon tetrachloride), enantiopure chloromethylstannane-[$D_1$] can be generated from homochiral tributylstannyl-[$D_1$]-methanol (*Scheme 12*).[51]




*Scheme 12 Synthesis of chloromethyllithium via tin-lithium exchange*

### 1.1.4 Electrophilic partners of carbenoids

In reactions where lithium carbenoids acted as nucleophiles, carbonyl compounds have been widely used as electrophilic partners. Treating aldehydes or ketones with lithium carbenoids results in obtaining β-halohydrines, which can be easily transformed in epoxides by increasing the temperature of the reaction or treating the product with base as shown in the *Scheme 13*. [15, 17, 52]




*Scheme 13 Carbonyl compounds in reaction with lithium carbenoids*

Furthermore, after treating carboxylic acid chlorides with chloromethyllithium, depending on the homologation reaction conditions, formation of allyl alcohols or cyclopropanols can be achieved. [53]

One of the most interesting substrates for the reaction with carbenoids are imines due to the versatility of the corresponding homologated products. [54] Homologating these compounds leads to obtaining aziridines or β-haloamines which are extremely important and valuable intermediates for synthesis of aminoacids, alcaloids and so on. [54, 55]

In 2013, Pace *et al.* have examined reactiveness of carboxylic acid derivates towards $LiCH_2X$, comparing esters and Weinreb amides. Basically, distinct reactivity and behaviour of these compounds is connected to the forming of more or less stable tetrahedral intermediate. [20]

### 1.1.5 Fluorinated compounds and fluorocarbenoids

Fluorine is considered as "the element of extremes" as the fluorinated organic compounds tend to present unusual behaviour. Even though this element is one of the most reactive elements in the periodic table, fluorinated derivatives sometimes show chemical inertness. Nowadays, a large number of pharmaceutical compounds contain at least one fluorine atom that plays very particular role.[56] Fluorine is placed in the second row and the seventeenth column of the periodic table of elements (PTE). In accordance to this position, it has very unique properties such as small size, high electronegativity, and extremely high reactivity due to the fact that F-F bond is fragile (38 kcal) and in a contrast, bond between fluorine and many other atoms is very strong. [57] These features have made it a perfect candidate for replacing hydrogen in a drug molecule. Even though quite similar, these two elements show several differences such as:

1) Van der Waals radius of the fluorine (1.47 Å) is higher than the hydrogen (1.20Å);
2) Fluorine has a higher electron withdrawing ability;
3) C-F bond is much more stable than C-H bond;
4) Fluorine has greater lipophilicity than hydrogen.

The introduction of a fluorine atom instead of hydrogen in drug molecules, alters their physicochemical features as the effect of its high electronegativity which further affects the biological response of the drug. Therefore, the aim of fluorine insertion into drug molecules is to improve metabolic stability, increase bioavailability, enhance binding affinity. [58] Nowadays, it is no longer unexpected the replacement of a methyl group with trifluoromethyl or phenyl group with pentafluorophenyl achieving might result in significantly different chemical or stereochemical outcomes. [59]

There are several extremely important fluorinated compounds important for healthcare such as antibiotics (Levaquin), statins [Rosuvastatin (Crestor)], antidepressants [Excilatopram (Lexapro)], anti-inflammatories [Celecoxib (Celebrex)], antacids [Lansoprazole (Prevacid)], neuroleptics (Risperdal). [60]

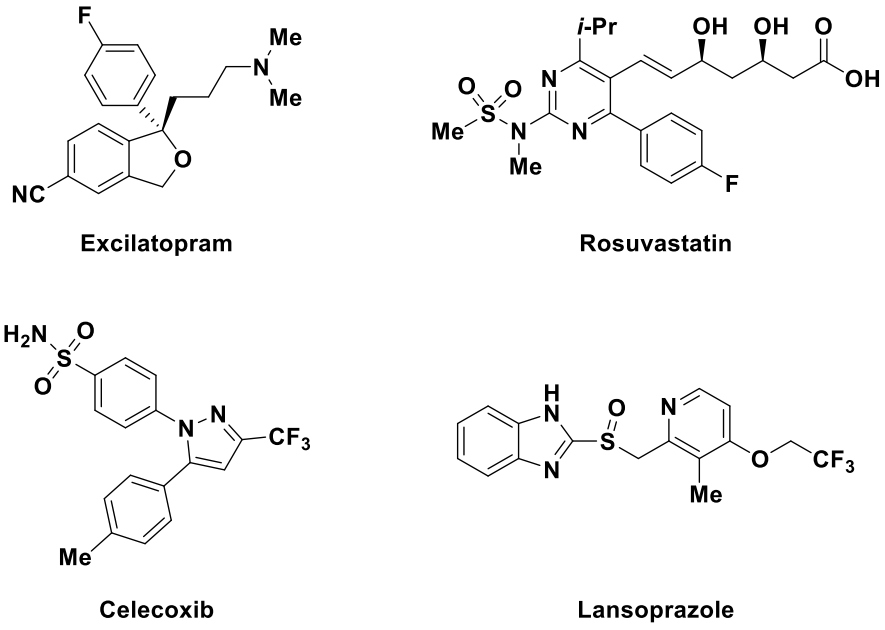
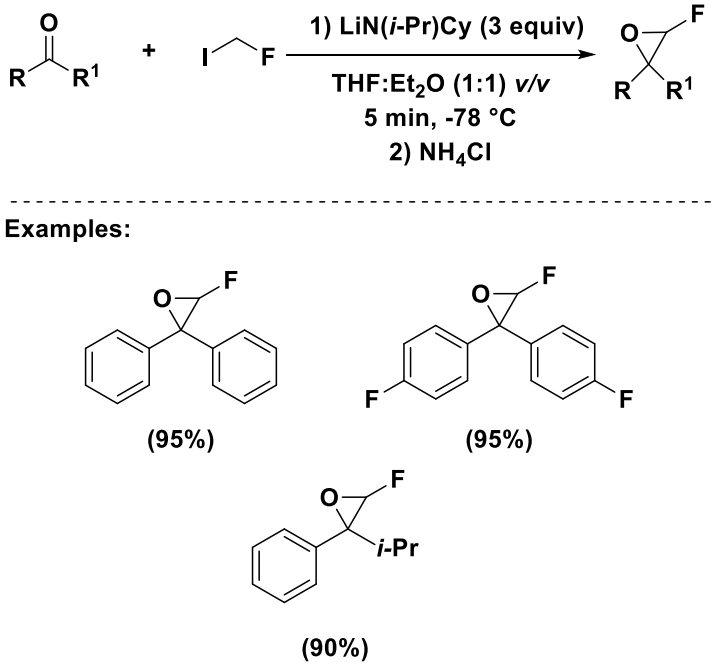



*Figure 3 Examples of the fluorinated drugs.*

Recently, a great advance has been gained in a field of fluoroalkylation, as the novel methodologies, for incorporating difluoromethyl and trifluoromethyl units in molecules, have been discovered. As the $CH_2F$ group practically mimics $CH_3$, due to the isosteric similarity, it's highly important to directly introduce it in a molecule. Insertion of the monofluoromethyl unit in one synthetic step has remained a challenge for a long time as a result of lack of the reagents that are able to directly introduce

$CH_2F$. Basically, M-$CH_2$-F type of the reagent would be an excellent solution of this problem. Therefore Pace *et al*. developed aforementioned type of the carbenoid despite the fact that Li/F system was considered sensitive and extremely reactive. [61] Additionally, in 2019, Pace and co-workers developed an interesting strategy (*Scheme 1*) for synthesizing novel fluoro-compounds, α-fluoroepoxides and α-fluoroaziridines proposing the introduction of the novel, so far unrevealed fluoroiodomethyllithium. This new fluoro-carbenoid has been obtained *via* deprotonation of the, on market available, fluoroiodomethane using a lithium amide base. Furthermore, of extreme importance for the generation of fluoroiodomethyllithium were conditions described in a *Scheme 14*. This carbenoid demonstrated excellent chemoselectivity and very distinct reactiveness. [62]

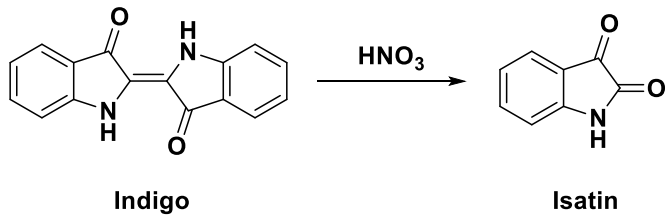



*Scheme 14 Synthesis of α-fluoroepoxides starting from ketones.*

## 1.2 SPIRO-EPOXYINDOLES

### 1.2.1. General overview and synthesis of spiro-epoxyindoles

In 1841, during the treatment of indigo with the oxidizing agents, Laurent and Erdmann have discovered a novel compound and they named it *isatin* (1*H*-indole-2,3-dione). This compound can be synthesized using a different kind of oxidizing agents, but the best results were obtained when indigo was treated with nitric acid or the mixture of nitric and chromic acid (*Scheme 15*).[63]

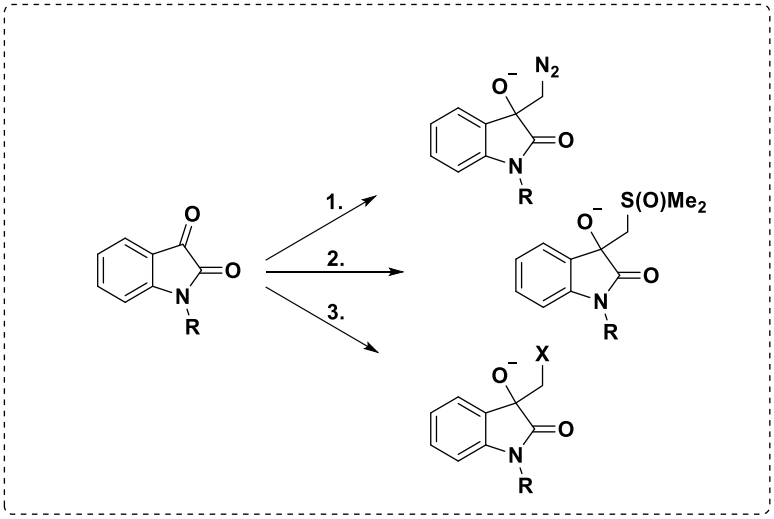



*Scheme 15 Obtaining isatin through oxidation of indole with nitric acid.*

Furthermore, isatin can be also isolated from natural sources, such as plants of the genus *Isatis,* from *Couropita guianancis aubl* and *Calanthe discolor* LINDL. It has been found in the saliva of *Bufo* frog and in the human, it is a derivative of epinefrine.[64]

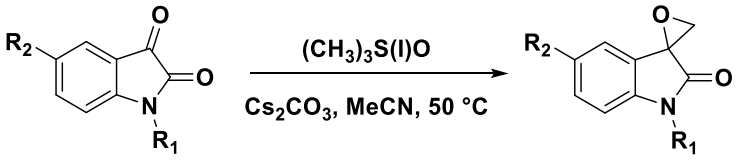
The fact that isatins can act as both, nucleophiles and electrophiles has made them extremely useful units in synthetic chemistry. A different type of biologically important molecules can be synthesized starting from isatins, such as indoles, quinolines, pyrrolidines, β-lactams, etc. Due to their reactivity, which is related to the C-3 position of the carbonyl group, isatins easily undergo nucleophilic addition and spiroannulation resulting in 2-oxindole derivatives.[65] These compounds, particularly those with spirooxindole scaffold, piqued a huge interest of the scientists working in the field of synthetic chemistry, due to their presence in a variety of natural products and their significant biological activity.[66]

There are several procedures available for synthesizing spiro-epoxyoxindoles employing isatin as starting material whose carbonyl group in third position converts into the epoxide by using: diazomethane, sulphur ylides or halomethyllithium reagents (*Scheme 16*).[67]



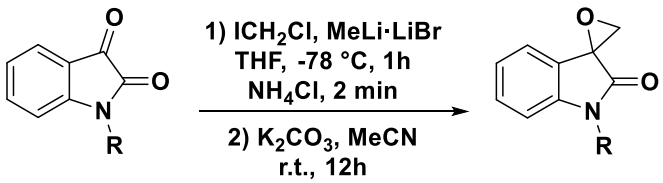

*Scheme 16 Intermediates from the previously mentioned reactions.*

The use of diazoalkanes in the synthesis of epoxides, leads to the generation of the rearrangement products. [5] On the other side, Corey Chaykovsky reaction implies a treatment of ketones with a sulfur ylides. As a result, corresponding epoxide in a very good yield is formed. This reaction can be performed on the isatins protected with alkyl groups on the nitrogen or on the most basic non-protected members. Hence, this procedure is extremely versatile.[67] In order to obtain oxirane at the third position of the isatin, Nair and coworkers have used trimethylsulfoxonium iodide together with $Cs_2CO_3$ at 50 °C using acetonitrile as solvent (*Scheme 17*). [68]




*Scheme 17 Epoxidation reaction using sulfur ylides*

Additionally, Pace and coworkers have described a technique (*Scheme 18)* which involves selective treatment of the isatin[3, 46] with lithium halomethylcarbenoids notwithstanding the presence of moieties susceptible to organolithium compounds.[20]

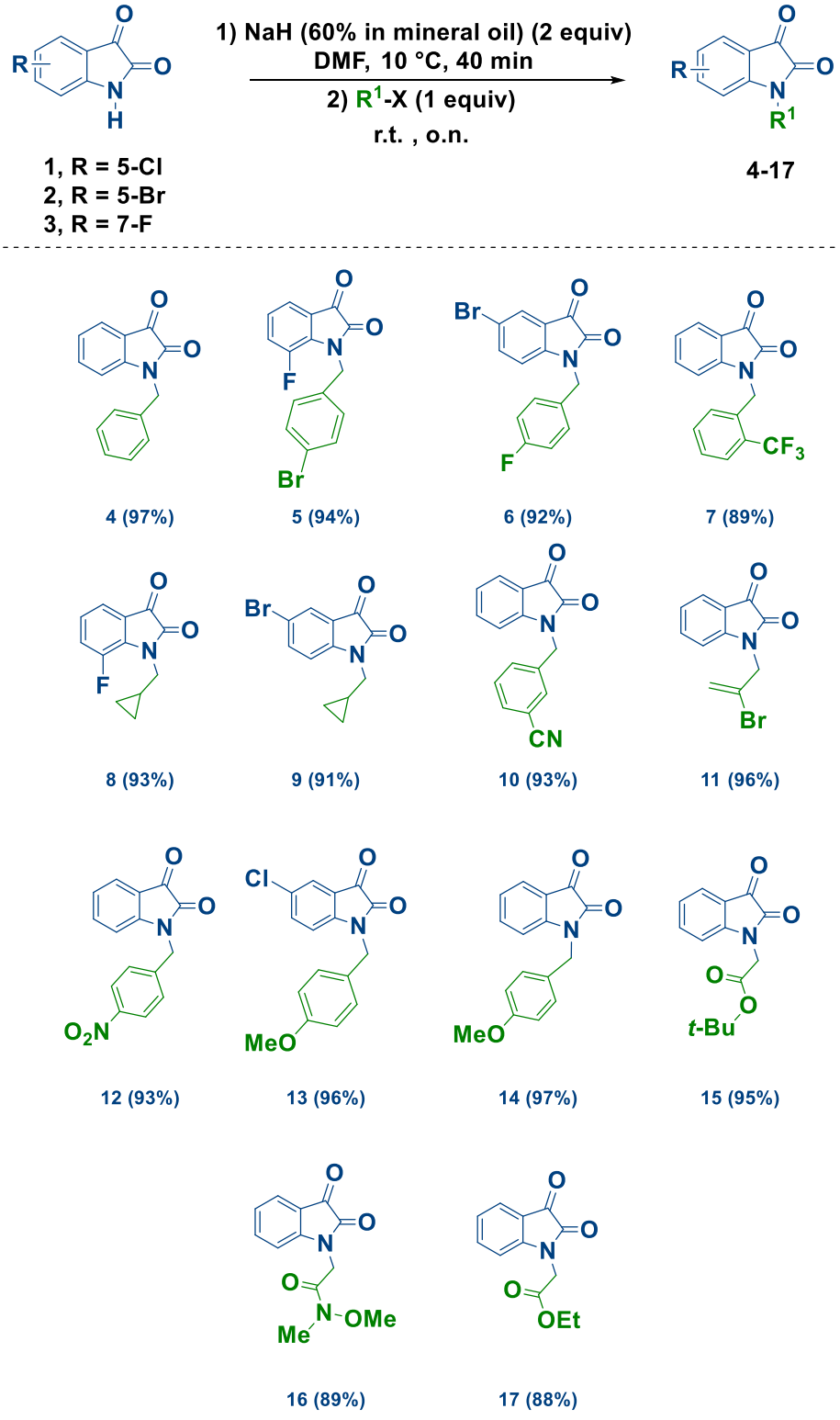



*Scheme 18 Epoxidation using halomethyllithium reagent.*

# 2.0 RESULTS AND DISCUSSION

## 2.1 SYNTHETIC POTENTIAL OF SPIRO-EPOXYOXINDOLES

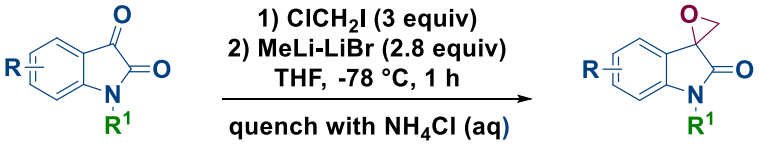
Spiro-epoxyoxindoles have drawn particular attention of chemists since these compounds, due to the high reactivity of the oxirane, have a huge synthetic potential for creation of sophisticated molecular structures. Researchers from Prof. Pace's group have already established a methodology for synthesizing spiro-epoxyoyindoles, through the homologation reaction, utilizing the halomethyllithium carbenoids on the *N*-functionalized isatins, followed by the closure of the ring. [69] Therefore, the purpose of my thesis was to investigate the reactivity of these compounds *via* carbenoids homologations reactions. Taking into account the powerful reactivity of the oxirane moiety, we presumed that the treatment of the spiro-epoxyoxindole with halolithium carbenoids would cause the opening ring reaction leading to the formation of an aldehyde. The outcome of the whole procedure is characterized by three different steps in order to achieve the desired compounds. Suitable isatins were used as starting materials. Initially, the *N*-functionalized isatins were treated with sodium hydride at 0 °C up to 10 °C, followed by the addition of the appropriate alkylating or arylating agents. The reaction was left to stir overnight. After quenching the reaction with ice and cold water, the product was obtained in the form of a precipitate and filtered using water. In particular cases, no precipitate was formed and the product had to be extracted using a proper organic solvent (EtOAc). The final product of the first step of this procedure, is an isatin protected at position 1 with different aromatic or aliphatic groups depending on the alkylating/arylating agents employed (*Scheme 19*).

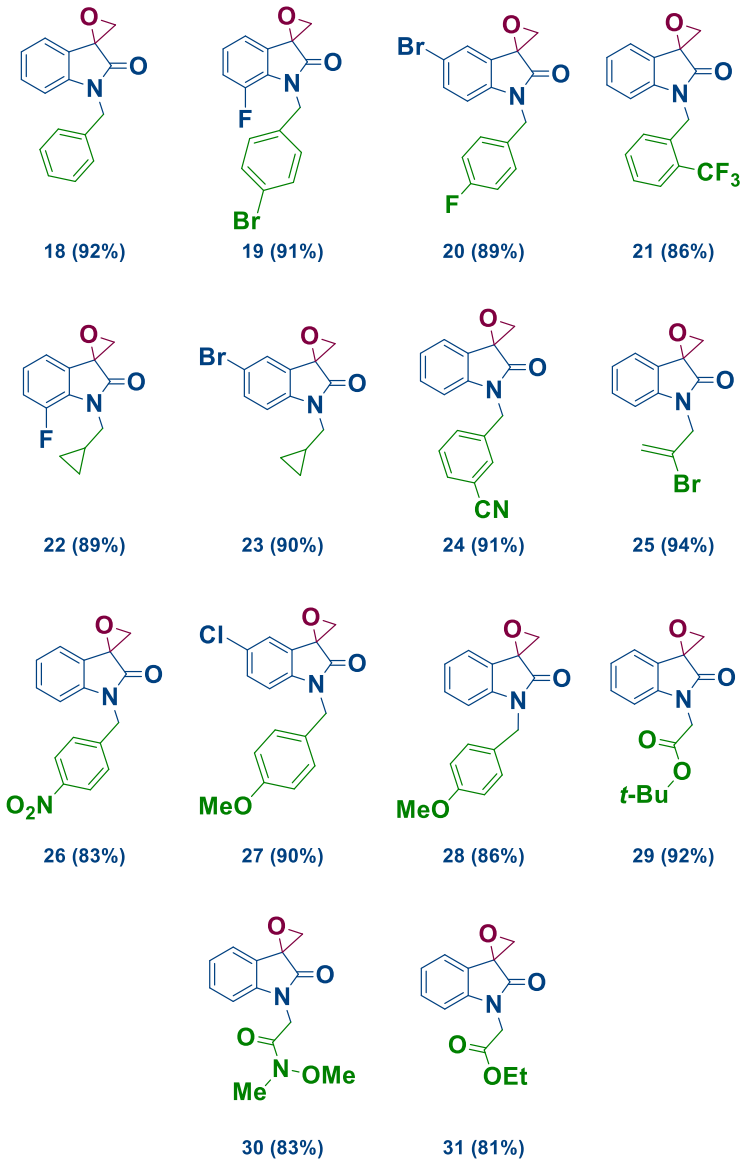



*Scheme 19 Protection of the isatins*

Further on, we proceeded with the epoxidation reaction. Basically, *N*-functionalized isatins were treated with $LiCH_2Cl$ at -78 °C under inert atmosphere. After one hour an aqueous saturated solution of $NH_4Cl$ was used for quenching the reaction. This method is extremely chemoselective. The addition of the carbenoid occurs exactly on

the carbonyl group at the 3rd position of *N*-functionalized isatins, without any accompanying attack on highly sensitive groups such as halogen atoms, double or triple bonds, nitro or nitrile groups. Hence, the products were obtained in high yields (*Scheme 20*). Although the synthesis of the spiro-epoxyoxindoles proceeded smoothly and many of the compounds were obtained pure and in high yields, several of them had to be purified using column chromatography.

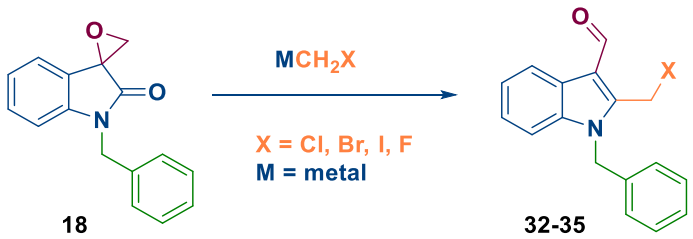



*Scheme 20 Spiro-epoxyoxindoles preparation.*

The last step, which is also the aim of this project, was the further investigation of the spiro-epoxyoxindoles reactivity by using halomethyllithium derivatives as homologating agents. Throughout my thesis work, we have investigated different conditions for obtaining the desired indole-3-carbaldehydes from previously synthesized spiro-epoxyoxindoles, in the highest possible yield. After the synthesis of spiro-epoxyoxindoles, these compounds were treated with lithium carbenoids under inert atmosphere at -78 °C for 1 hour (*Scheme 21*). Compound **18** was chosen as the model substrate for the optimization of this reaction (*Table 1*).

*Table 1 Optimization table for homologation reaction.*

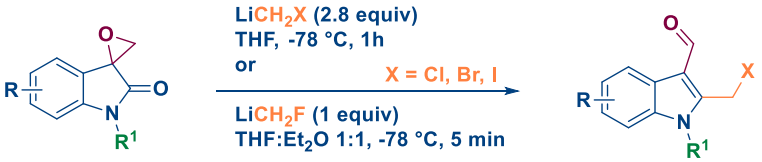



| Entry | Carbenoid | Equivalents | Temp. | Solvent | Time | Yield 32-35 |
|---|---|---|---|---|---|---|
| 1 | $LiCH_2Cl$ | 2.8 | -78 °C | THF | 1h | 85% |
| 2 | $LiCH_2Br$ | 2.8 | -78 °C | THF | 1h | >50% |
| 3 | $LiCH_2I$ | 2.8 | -78 °C | THF | 1h | >50% |
| 4 | $LiCH_2F$ | 1.0 | -78 °C | THF: $Et_2O$ (1:1, *v/v*) | 5 min | >80% |
| 5 | $LiCH_2Cl$ | 2.8 | -78 °C to RT | THF | 24h | 47% |
| 6 | $LiCH_2Cl$ | 2.8 | -78 °C | 2-MeTHF | 1h | 40% |
| 7 | $IZnCH_2I$ | 2.8 | -15 °C to RT | THF | 24h | 10% |
| 8 | *i*-$PrMgCH_2I$ | 2.8 | -78 °C to RT | THF | 24h | 0% |

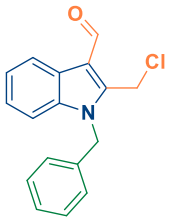
From *Table 1,* we can observe that changing some of the parameters really play a key role for the homologating phenomenon. In **entry 1**, the aldehyde was obtained in a high yield (85%), when the epoxide was treated with $LiCH_2Cl$ in THF at -78 °C for 1 hour. Anyway, changing the carbenoid and keeping all the other conditions the same (**entry 2, 3**), we were able to obtained the desired products but in lower yields. Moreover, a quite satisfactory results were obtained using $LiCH_2F$ (**entry 4**) in a mixture of solvents THF and $Et_2O$ (1:1, *v/v)*. Even though $LiCH_2F$ is extremely reactive and volatile substance and therefore is really difficult to handle during the reaction was possible to achieve the final aldehyde in 80% yield. Furthermore, the employment

of a different kind of solvent (2-MeTHF, **entry 6**) or metal for generating the carbenoids (*i*-PrMgCH$_2$I, IZnCH$_2$I, **entry 7, 8**) didn't produce successful results.

Considering the values reported in Table 1, it is clear that the best results were obtained performing the reaction with LiCH$_2$Cl at -78 °C for 1 hour, using THF as solvent. Really good results were also achieved in presence of LiCH$_2$F at -78 °C using a mixture of THF: Et$_2$O (1:1, *v/v*) as solvents. Therefore, the optimized conditions were employed for extending the scope of the reaction. The methodology worked well in presence of different kind of groups. It is evident from the *Scheme 21* that the reaction worked very well as many of the products were obtained in high yields (70-90 %). The pathway was successful by using the unsubstituted *N*-benzyl isatin with carbeonoids presenting different halogens atom (**32-35**). Neither the presence nor the position of the halogen functionalities (**36-43**) influenced the outcome of the reaction in the different decorated *N*-protected spiro-epoxyoxindoles, in particular in presence of bromine atoms we did not observe exchange reactions. The reaction worked well in presence of different functionalities such as nitrile (**44**), alkene (**45**) and nitro (**46**) groups. The presence of electron donating groups such as a methoxy one (**47-49**) did not influence the outcome of the reaction. Further evidence of the chemoselectivity of the procedure was achieved by using spiro-epoxyoxindoles presenting an ester functionality (**50**).




18-31 32-50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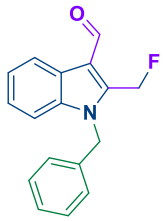
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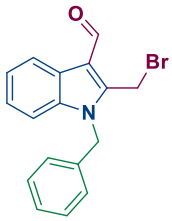
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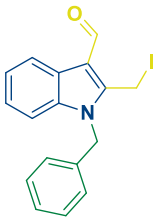
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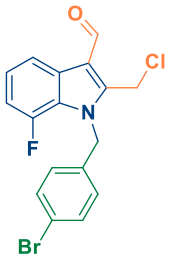
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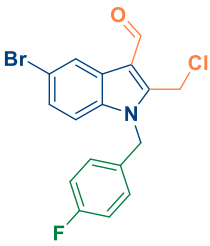
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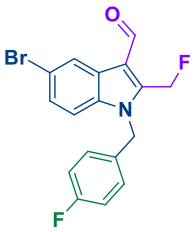
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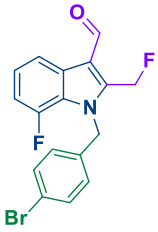
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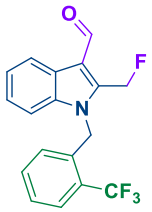
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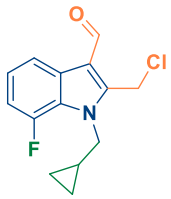
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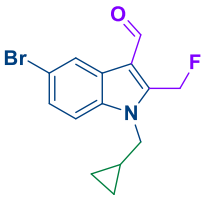
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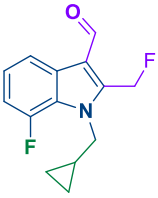
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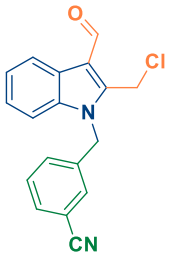
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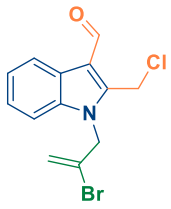
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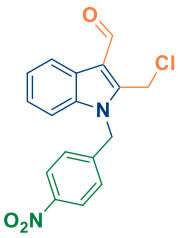
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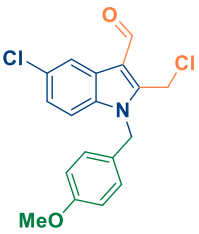
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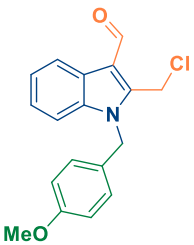
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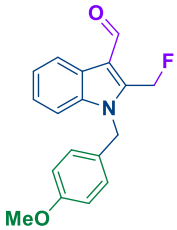
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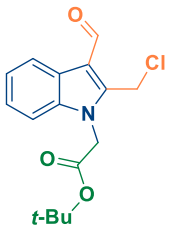
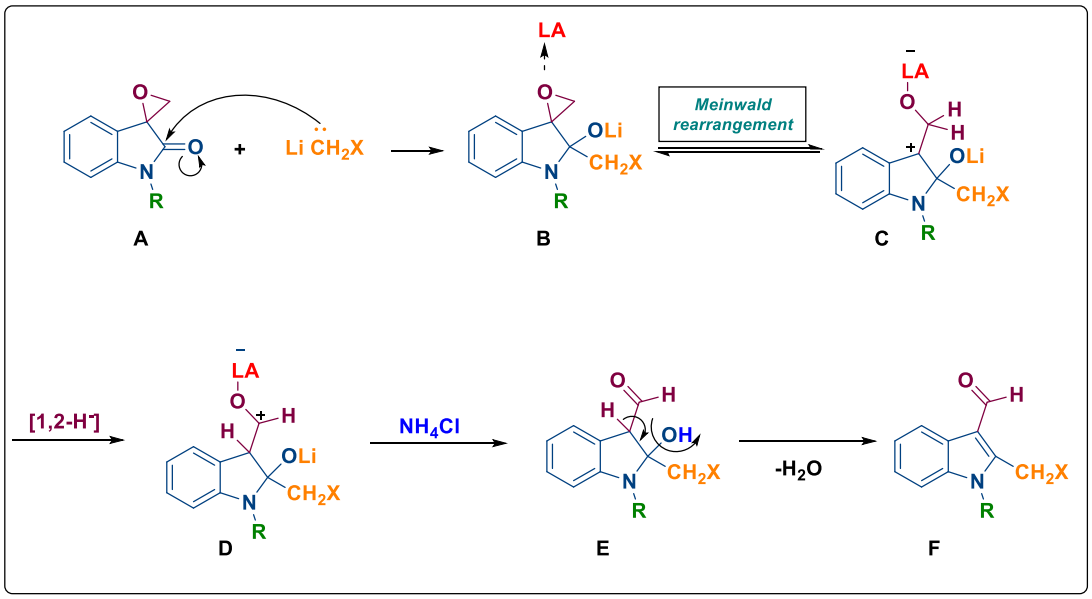

50 (82%)

*Scheme 21 Scope of the homologation reaction.*

Considering the mechanism of the reaction for the formation of the desired aldehydes, the lithium carbenoid with its nucleophilic behaviour, attaches the carbonyl in position 2 of the spiro-epoxyoxindoles **A** producing the *O*-lithiated halohydrin **B**. At the same time, the Lewis acid (LiBr) triggers the ring opening of epoxide present in **B**, favoured by the formation of the carbocation **C**, to furnish intermediate **D** through a 1,2-hydride shift of **C**. After quenching the reaction with $NH_4Cl$, the protonation of the the *O*-lithiated halohydrin **D** leads to a spontaneous elimination of a water molecule achieving the desired α, β-unsaturated aldehyde **F**.




*Scheme 22 Proposed reaction mechanism.*

## 3.0 CONCLUSION

In conclusion, in this project the synthetic potential of spiro-epoxyoxindoles was examined *via* novel synthetic tactics. A large number of compounds bearing sensitive functional groups was subjected to the carbenoid-mediated homologation reactions resulting in highly attractive novel products achieved in excellent yields. A reaction mechanism for the formation of this interesting class of compounds was proposed. Further studies will be performing in order to have more information about the reactivity and applicability of these derivatives.

# 4.0 EXPERIMENTAL WORK

## 4.1 Instruments and apparatuses

Solvents (tetrahydrofurane and ether) were distilled using sodium benzophenone. All the chemicals used in this project were purchased from: Acros, Fluorochem, Sigma-Aldrich, Alfa Aesar and Tokyo Chemical Industry (TCI Europe). Rotary evaporator was utilized with a reduced pressure and increased temperature (40 °C) in order to evaporate the solvents. Thin layer chromatography was performed on aluminium sheets covered with silica gel 60F254 (Macherey-Nagel, Merck). Visualization of the spot was done using UV light (λ = 254 nm and λ = 366 nm) and apart from that, phosphomolybdic acid was used for the oxidation of TLC as revealing system. Reichert–Kofler hot-stage microscope was used to determine melting points of the substances. Regarding a high-resolution mass spectrometry (HRMS), Bruker maXis 4G instrument (ESI-TOF, APCI) was used to obtain the spectra. NMR spectra ($^{1}H$, $^{13}C$, $^{15}N$, $^{19}F$) were acquired using a Bruker Avance III 400 spectrometer (400 MHz for 1H, 100 MHz for $^{13}C$, 40 MHz for $^{15}N$, 376 MHz for $^{19}F$). Signal of the solvent is set as a reference: δ 7.26 ppm ($^{1}H$ in $CDCl_3$), 7.16 ppm ($^{1}H$ in $C_6D_6$), δ 77.00 ppm ($^{13}C$ in $CDCl_3$), δ 128.06 ppm ($^{13}C$ in $C_6D_6$). NMR spectra (gsHMBC) of the $^{15}N$ were referenced against neat, external nitromethane. Furthermore, for the NMR spectra of $^{19}F$, absolute referencing via ∈ ratio was utilized. Constant for a spin-spin coupling (J) is expressed in Hz.

## 4.2 Synthetic procedures

### 4.2.1 Protection of the isatins

The suitable Isatin was dissolved using dry dimethylformamide (DMF) and stirred for a few minutes. After accomplishing the temperature of 10 °C, 60% suspension of sodium hydride (NaH) in mineral oil was added portion wise to the solution of isatin. The mixture was left to stir and a change of colour to the dark purple was observed. After 40 minutes from the addition of the NaH, corresponding alkylating/arylating agent was added to the solution. Reaction mixture was left to stir overnight at room temperature and afterwards quenched with ice and cold water. The formed precipitate was filtered and washed with cold water. Instead in few cases extraction with ethyl acetate was required. [70]

### 4.2.2. Epoxidation of isatins

To a stirring solution of the suitable isatin (using a dry THF) under argon atmosphere, chloroiodomethane (3 equiv) was added at -78 °C. After 5 minutes, MeLi·LiBr (2.2 M, 2.8 equiv) was added dropwise. After 1 hour, the reaction was quenched using saturated aqueous solution of $NH_4Cl$ (5 mL) and left at room temperature for a couple of minutes. Extraction was then performed using $Et_2O$ (2 X 5 mL). Traces of the water in the organic phase were dried over $Na_2SO_4$, the solution was filtered and the organic phase dried under vacuum.

### 4.2.3Homologation reaction

*a) Using chloroiodomethane*

To a well stirred solution of spiro-epoxyoxindole (300 mg, 1 equiv) in dry tetrahydrofurane (THF), chloroiodomethane (3 equiv, 0.25 mL) was added under dry conditions, followed by the dropwise addition of methyllithium lithium bromide (MeLi·LiBr, 2.2 M, 2.8 equiv, 3.5 mL) at -78 °C. After one hour, the reaction was quenched with a saturated aqueous solution of $NH_4Cl$. The extraction had been executed using diethyl ether ($Et_2O$) as solvent (2 X 5 mL). The excess of the water in the organic phase was dried using sodium sulphate ($Na_2SO_4$). Then, $Na_2SO_4$ was filtered out and the solvent was dried under vacuum. The aldehydes were obtained not pure enough so purification through column chromatography (silica gel) was necessary.

*b) Using fluoroiodomethane*

After solubilizing the proper epoxide (1.5 equiv) in a mixture THF:$Et_2O$ (1:1, *v/v*) under inert atmosphere at -78 °C, fluoroiodomethane (0.07 mL, 1 equiv) and was added and after 2 minutes MeLi·LiBr (0.9 mL, 2.0 equiv) were added drop by drop. After stirring for 5 minutes, the reaction was quenched with $NH_4Cl$ (aq.). The same work up as in the section *a)* has been performed.

c) *Using dibromomethane*

After the epoxide (1.0 equiv) was solubilized with a dry THF, dibromomethane (0.26 mL, 3.0 equiv) was added to the solution, at -78 °C and inert atmosphere. Immediately after, MeLi·LiBr (1.27 mL, 2.8 equiv) was introduced to the stirring mixture. One hour

later, reaction was quenched using $NH_4Cl$ (aq.). The same work up as in the section *a)* has been performed.

*d) Using diiodomethane*

To the stirring solution of epoxide (1.0 equiv) in dry THF at the temperature of -78 °C and inert atmosphere diiodomethane (0.23 mL, 3.0 equiv) was added. Drop by drop addition of MeLi·LiBr (1.27 mL, 2.8 equiv) followed immediately after. After one hour, reaction was stopped with $NH_4Cl$ (aq.). The same work up as in the section *a)* has been performed.

# 5.0 SUPPORTING INFORMATION

## CHARACTERIZATION OF THE SPIRO-EPOXYOXINDOLES

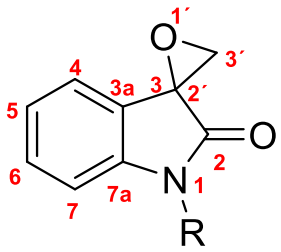
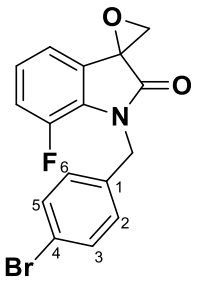



*Figure 4 Numeration of the epoxyoxindole*

*The spectroscopic information about some of the synthesized epoxides (**18**,**25**,**29**,**30**,**31**) are known. [69]*

**1-(4-Bromobenzyl)-7-fluorospiro[indole-3,2´-oxirane]-2(1*H*)-one (19)**




By following the General Procedure, 1-(4-bromobenzyl)-7-fluoroindoline-2,3-dione (334.1 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **19** was obtained in 91% (304 mg) of yield as a brown solid substance ($T_{melting\ point}$ = 141 °C).

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ: 7.44 (m, 2H, Ph H-3,5), 7.25 (m, 2H, Ph H-2,6), 7.05 (m, 1H, Ind H-6), 7.02 (m, Ind H-5), 6.90 (dd, *J* = 7.1, 1.4Hz, 1H, Ind H-4), 5.04 (s, 2H, $CH_2$-Ph), 3.64 and 3.45 (d, *J* = 6.7Hz, 2H, oxirane $CH_2$)

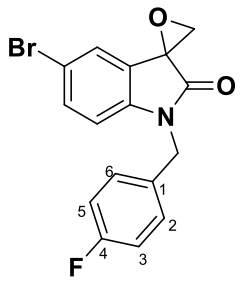
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 171.6 (CO,Ind C-2), 147.6 (d, *J* = 244.9Hz, Ind C-7), 135.4 (Ph C-1), 131.8 (Ph C-3,5), 130.3 (d, *J* = 9.3Hz, Ind C-7a), 129.5 (d, *J* = 1.8Hz, Ph C-2,6), 125.7 (d, *J* = 3.4Hz, Ind C-3a), 123.9 (d, *J* = 6.5Hz, Ind C-5), 121.9 (Ph C-4), 118.6 (d, *J* =

19.7Hz, Ind C-6), 118.2 (d, *J* = 3.3 Hz, Ind C-4), 56.2 (d, *J* = 3.5Hz, Ind C-3), 54.8 (oxirane C-3´), 45.4 (d, *J* = 4.6Hz, $CH_2$-Ph)

**$^{19}$F NMR** ( 376 MHz, CDCl3) δ; -133.1 (m)

**HRMS (ESI)**, m/z: calcd for $C_{16}H_{11}BrFNO_2$: 348.0030 $[M+H]^+$ ; found: 348.0030.

**5-Bromo-1-(4-fluorobenzyl)spiro[indole-3,2´-oxirane]-2(1*H*)-one (20)**




By following the General Procedure, 5-bromo-1-(4-fluorobenzyl)indoline-2,3-dione (334.1 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **20** was obtained in 89% (297.3 mg) of yield as a brown solid substance ($T_{melting\ point}$ = 140 °C).

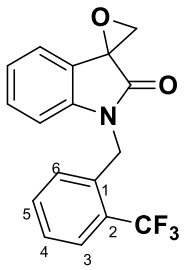
**$^{1}$H NMR** (400 MHz, CDCl3) δ: 7.40 (dd, *J* = 8.3, 2.0Hz, 1H, Ind 6), 7.28 (m, 2H, Ph H-2,6), 7.23 (d, *J* = 2.0Hz, 1H, Ind H-4), 7.02 (m, 2H, Ph H-3,5), 6.67 (d, *J* = 8.3Hz, 1H, Ind H-7), 4.91 (s, 2H, $CH_2$-Ph), 3.65 and 3.47 (d, *J* = 6.7Hz, 2H, oxirane $CH_2$)

**$^{13}$C NMR** (100 MHz, CDCl3) δ: 171.3 (CO, Ind C-2), 162.4 (d, *J* = 247.0Hz, Ph C-4), 143.0 (Ind C-7a), 133.1 (Ind C-6), 130.6 (d, *J* = 3.3Hz, Ph C-1), 129.2 (d, *J* = 8.2Hz, Ph C-2,6), 125.6 (Ind C-4), 124.9 (Ind C-3a), 115.9 (d, *J* = 21.6Hz, Ph C-3,5), 115.8 (Ind C-5), 111.2 (Ind C-7), 56.0 (Ind C-3), 54.5 (oxirane C-3´), 43.7 ($CH_2$-Ph)

**$^{19}$F NMR** ( 376 MHz, CDCl3) δ; -113.8 (m)

**HRMS (ESI)**, m/z: calcd for $C_{16}H_{11}BrFNO_2$ : 348.0030 $[M+H]^+$ ; found: 348.0030.

**1-[2-(Trifluoromethyl)benzyl]spiro[indole-3,2´-oxirane]-2(1*H*)-one (21)**




By following the General Procedure, 1-(2-(trifluoromethyl)benzyl)indoline-2,3-dione (305.2 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **21** was obtained in 86% (262.5 mg) of yield as a white solid substance ($T_{melting\ point}$ = 150 °C).

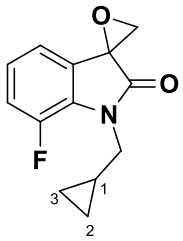
**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ: 7.73 (m, 1H, Ph H-3), 7.45 (m, 1H, Ph H-5), 7.39 (m, 1H, Ph H-4), 7.26 (m, 1H, Ind H-6), 7.20 (m, 1H, Ph H-6), 7.17 (m, 1H, Ind H-4), 7.09 (m, 1H, Ind H-5), 6.65 (m, 1H, Ind C-7), 5.21 and 5.19 (AB- system $^{2}J_{AB}$ = 16.0Hz, 2H, $CH_2$-Ph), 3.70 and 3.54 (AB- system $^{2}J_{AB}$ = 6.7Hz, 2H, oxirane H-3´)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 172.3 (Ind C-2), 143.8 (Ind C-7a), 133.5 (d, *J* = 1.5Hz, Ph C-1), 132.4 (q, *J* = 1.2Hz, Ph C-5), 130.6 (Ind C-6), 127.8 (q, *J* = 30.8Hz, Ph C-2), 127.6 (Ph C-4), 126.9 (Ph C-6), 126.3 (q, *J* = 5.8Hz, Ph C-3), 124.4 (q, *J* = 273.8Hz, $CF_3$), 123.3 (Ind C-5), 122.6 (Ind C-3a), 122.3 (Ind C-4), 109.8 (Ind C-7), 56.4 (Ind C-3), 54.4 (oxirane C-3´), 40.7 (q, *J* = 3.5Hz, $CH_2$-Ph)

**$^{19}$F NMR** ( 376 MHz, $CDCl_3$) δ; -60.1 (s, $CF_3$)

**HRMS (ESI)**, m/z: calcd for $C_{17}H_{12}F_3NO_2$ : 320.0893$[M+H]^+$ ; found: 320.0894.

**1-(Cyclopropylmethyl)-7-fluorospiro[indole-3,2´-oxirane]-2(1*H*)-one (22)**




By following the General Procedure, 1-(cyclopropylmethyl)-7-fluoroindoline-2,3-dione (219.2 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **22** was obtained in 89% (195.1 mg) of yield as a yellow solid substance ($T_{melting\ point}$ = 99.5 °C).

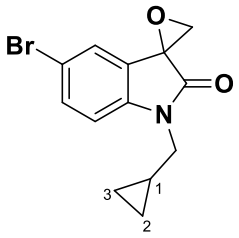
**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ: 7.12 (m, 1H, Ind H-6), 7.02 (m, 1H, Ind C-5), 6.91 (dd, *J* = 8.3, 1.2Hz, 1H, Ind H-4), 3.78 (m, 2H, CH2-cyclopropyl), 3.60 and 3.43 (d, *J* = 6.7Hz, 2H, oxirane $CH_2$), 1.27 (m, 1H, cyclopropyl H-1), 0.51 (m, 1H, cyclopropyl H-2,3), 0.43 (m, 1H, cyclopropyl H-2,3)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 171.5 (CO, Ind C-2), 147.6 (d, *J* = 244.6Hz, Ind C-7), 131.2 (d, *J* = 9.1Hz, Ind C-6), 125.9 (d, *J* = 3.6Hz, Ind C-3a), 123.4 (d, *J* = 6.5Hz, Ind C-5), 118.5 (d, *J* = 19.9Hz, Ind C-6), 118.0 (d, *J* = 3.3Hz, Ind C-4), 56.3 (d, *J* = 3.5Hz, Ind C-3), 54.7 (oxirane C-3´), 47.0 (d, *J* = 4.4Hz, $CH_2$-cyclopropyl), 10.7 (d, *J* = 3.6Hz, cyclopropyl C-1), 3.6 (cyclopropyl C-2,3)

**$^{19}$F NMR** ( 376 MHz, $CDCl_3$) δ; -134 (m)

**HRMS (ESI)**, m/z: calcd for $C_{13}H_{12}FNO_2$ : 234.0925$[M+H]^+$ ; found: 234.0918

**5-Bromo-1-(cyclopropylmethyl)spiro[indole-3,2´-oxirane]-2(1*H*)-one (23)**




By following the General Procedure, 5-bromo-1-(cyclopropylmethyl)indoline-2,3-dione (280.1 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **23** was obtained in 90% (252.1 mg) of yield as orange solid substance ($T_{melting\ point}$ = 100.5 °C).

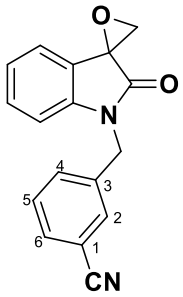
**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ: 7.49 (dd, *J* = 8.3, 2.0Hz, 1H, Ind H-6), 7.22 (d, *J* = 2.0Hz, 1H, Ind H-4), 6.88 (d, *J* = 8.3Hz, 1H, Ind C-7), 3.63 (m, 2H, CH2-cyclopropyl), 3.43 and 3.59 (d, *J* = 6.7Hz, oxirane $CH_2$), 1.15 (m, 1H, cyclopropyl H-1), 0.55 (m, 1H, cyclopropyl H-2,3), 0.39 (m, 1H, cyclopropyl H-2,3)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 171.1 (CO, Ind C-2), 143.7 (Ind C-7a), 133.1 (Ind C-6), 125.5 (Ind C-4), 124.9 (Ind C-3a), 115.3 (Ind C-5), 110.7 (Ind C-7), 56.0 (Ind C-3), 54.3 (oxirane C-3´), 45.0 ($CH_2$-cyclopropyl), 9.5 (cyclopropyl C-1), 4.0 (cyclopropyl C-2,3)

**$^{15}$N NMR** (40 MHz, $CDCl_3$) δ: -237.2

**HRMS (ESI)**, m/z: calcd for $C_{13}H_{12}BrNO_2$ : 294.0124 $[M+H]^+$ ; found: 294.0118.

**3-[(2-Oxospiro[indole-3,2´-oxirane])-1(2*H*)-yl) methyl] benzonitrile (24)**




By following the General Procedure, 3-((2,3-dioxoindolin-1-yl)methyl)benzonitrile (262.3 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **24** was obtained in 91% (238.7 mg) of yield as brown solid substance ($T_{melting\ point}$ = 171.5 °C).

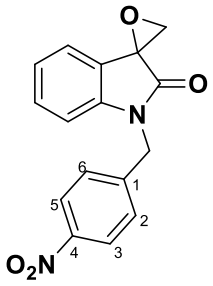
**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ: 7.61 (m, 1H, Ph H-2), 7.59 (m, 1H, Ph H-4,6), 7.46 (m, 1H, Ph H-5), 7.31 (m, 1H, Ind H-6), 7.15 (m, 1H, Ind H-4), 7.10 (m, 1H, Ind H-5), 6.75 (m, 1H, Ind H-7), 5.03 and 4.95 (AB-system, $^{2}J_{AB}$ = 16.0Hz, 2H, $CH_2$-Ph), 3.67 and 3.51 (AB system, $^{2}J_{AB}$ = 6.6Hz, 2H, $CH_2$ oxirane-3´)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 172.0 (CO, Ind C-2), 143.6 (Ind C-7a), 137.0 (Ph C-3), 131.8 (Ph C-6), 131.7 (Ph C-4), 130.8 (Ph C-2), 130.5 (Ind C-6), 129.8 (Ph C-5), 123.4 (Ind C-5), 122.7 (Ind C-3a), 122.5 (Ind C-4), 118.3 (CN-Ph), 113.1 (Ph C-1), 109.4 (Ind C-7), 56.3 (Ind C-3), 54.4 (oxirane C-3´), 43.5 ($CH_2$-Ph)

**$^{15}$N NMR** (40 MHz, CDCl3) δ: -241.8 (Ind N)

**HRMS (ESI)**, m/z: calcd for $C_{17}H_{12}N_2O_2$: 277.0972 $[M+H]^+$ ; found: 277.0966.

**1-(4-Nitrobenzyl)spiro[indole-3,2´-oxirane]-2(1*H*)-one (26)**



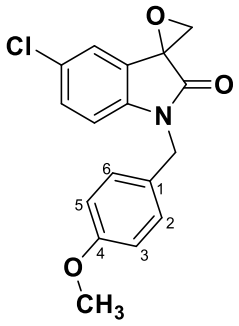

By following the General Procedure, 1-(4-nitrobenzyl)indoline-2,3-dione (282.3 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **26** was obtained in 83% (234.3 mg) of yield as yellow solid substance ($T_{melting\ point}$ = 179.5 °C).

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ: 8.21 (m, 1H, Ph H-3,5), 7.50 (m, 1H, Ph H-2,6), 7.30 (m, 1H, Ind H-6), 7.16 (m, 1H, Ind H-4), 7.10 (m, 1H, Ind H-5), 6.74 (m, 1H, Ind H-7), 5.08 and 5.05 (AB system, $^{2}J_{AB}$ = 16.3Hz, 2H, $CH_2$-Ph), 3.68 and 3.51 (AB system, $^{2}J_{AB}$ = 6.7Hz, 2H, $CH_2$ oxirane)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 172.0 (CO, Ind C-2), 147.7 (Ph C-4), 143.6 (Ind C-7a), 142.6 (Ph C-1), 130.5 (Ind C-6), 128.1 (Ph C-2,6), 124.2 (Ph C-3,5) 123.5 (Ind C-5), 122.7 (Ind C-3a), 122.6 (Ind C-4), 109.0 (Ind C-7), 56.3 (Ind C-3), 54.4 (oxirane C-3´), 43.7 ($CH_2$-Ph)

**HRMS (ESI)**, m/z: calcd for $C_{16}H_{12}N_2O_4$ : 297.0870 $[M+H]^+$ ; found: 297.0875.

**5-Chloro-1-(4-methoxybenzyl)spiro[indol-3,2´-oxirane]-2(1*H*)-one (27)**




By following the General Procedure, 5-chloro-1-(4-methoxybenzyl)indoline-2,3-dione (301.7 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **27** was obtained in 90% (271.5 mg) of yield as yellow solid substance ($T_{melting\ point}$ = 105 °C).

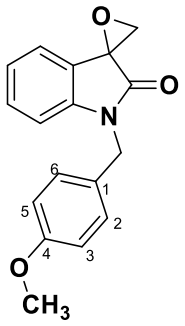
**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ: 7.24 (m, 1H, Ph H-2,6), 7.23 (dd, *J* = 8.4, 2.1Hz, 1H, Ind H-6), 7.08 (d, *J* = 2.1Hz, 1H, Ind H-4), 6.86 (m, 1H, Ph H-3,5), 6.74 (d, *J* = 8.4Hz, 1H, Ind H-7), 4.89 (s, 2H, $CH_2$-Ph), 3.78 (s, 3H, $OCH_3$), 3.65 and 3.45 (AB system, $^{2}J_{AB}$ = 6.7Hz, 2H, $CH_2$ oxirane)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 171.3 (CO, Ind C-2), 159.3 (Ph C-4), 142.7 (Ind C-7a), 130.2 (Ind C-6), 128.8 (Ph C-2,6), 128.5 (Ind C-5), 126.9 (Ph, C-1), 124.5 (Ind C-3a), 122.6 (Ind C-4), 114.3 (Ph C-3,5), 110.9 (Ind C-7), 56.1 (Ind C-3), 55.3 ($OCH_3$), 54.4 (oxirane C-3´), 43.9 ($CH_2$-Ph)

**$^{15}$N NMR** (40 MHz, $CDCl_3$) δ: -238.5

**HRMS (ESI)**, m/z: calcd for $C_{17}H_{14}ClNO_3$ : 316.0735 $[M+H]^+$ ; found: 316.0735.

**1-(4-Methoxybenzyl)spiro[indole-3,2´-oxirane]-2(1*H*)-one (28)**




By following the General Procedure, 1-(4-methoxybenzyl)indoline-2,3-dione (267.3 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **27** was obtained in 86% (229.9 mg) of yield as white solid substance ($T_{melting\ point}$ = 122.5 °C).

**$^{1}$H NMR** (400 MHz, CDCl3) δ: 7.27 (m, 3H, Ph H-2,6, Ind H-6), 7.10 (m, 1H, Ind H-4), 7.04 (m, 1H, Ind H-5), 6.85 (m, 2H, Ph H-3,5), 6.84 (m, 1H, Ind H-7), 4.92 and 4.89 ( AB-system $^{2}J_{AB}$ = 15.4Hz, 2H, $CH_2$-Ph), 3.78 (s, 3H, $OCH_3$), 3.64 (d, *J* = 6.7Hz, 1H, oxirane $CH_2$), 3.46 (d, *J* = 6.7Hz, 1H, oxirane $CH_2$)

**$^{13}$C NMR** (100 MHz, CDCl3) δ: 171.8 (CO, Ind C-2), 159.2 (Ph C-4), 144.3 (Ind C-7a), 130.3 (Ind C-6), 128.8 (Ph C-2,6), 127.4 (Ph C-1), 122.8 (Ind C-5), 122.7 (Ind C-3a), 122.1 (Ind C-4), 114.2 (Ph C-3,5), 109.9 (Ind C-7), 56.4 (Ind C-3), 55.2 ($OCH_3$), 54.3 (oxirane C-3´), 43.8 ($CH_2$-Ph)

**$^{15}$N NMR** (40 MHz, CDCl3) δ: -238.0

**HRMS (ESI)**, m/z: calcd for $C_{17}H_{15}NO_3$ : 282.1125 $[M+H]^+$ ; found: 282.1125.

## CHARACTERIZATION OF THE ALDEHYDES

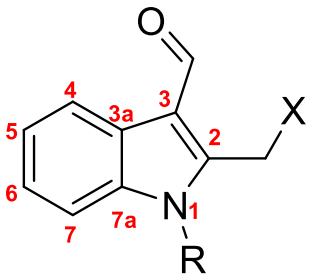
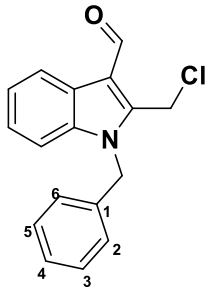



*Figure 5 Numeration of the indole ring*

**1-Benzyl-2-(chloromethyl)-1H-indole-3-carbaldehyde (32)**



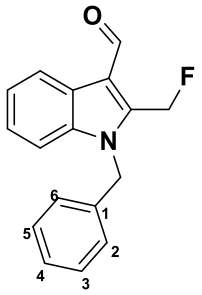

By following the General Procedure, 1-benzylspiro[indoline-3,2'-oxiran]-2-one (251.3 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **32** was obtained in 85% (213.6 mg) of yield as green solid substance ($T_{melting\ point}$ = 101 °C) after chromatography on silica (8:2 v/v, *n*-Hexane : Ethyl acetate (EtOAc)).

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ: 10.36 (s, CHO), 8.30 (m, 1H, Ind H-4), 7.33 (m, 1H, Ind H-5), 7.32 (m, 2H, Ind H-6,7), 7.31 (m, 2H, Ph H-3,5), 7.30 (m, 1H, Ph H-4), 7.05 (m, 2H, Ph H-2,6), 5.55 (s, 2H, $CH_2$-Ph), 5.02 (s, 2H, $CH_2Cl$)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 184.0 (CHO), 142.1 (Ind C-2), 136.8 (Ind C-7a), 135.5 (Ph C-1), 129.1 (Ph C-3,5), 128.1 (Ph C-4), 126.0 (Ph C-2,6), 125.6 (Ind C-3a), 124.8 (Ind C-6), 123.4 (Ind C-5), 121.2 (Ind C-4), 115.0 (Ind C-3), 110.5 (Ind C-7), 47.0 (**$CH_2$**-Ph), 33.4 (**$CH_2$**Cl)

**HRMS (ESI)**, m/z: calcd for $C_{17}H_{14}ClNO$: 284.0837 $[M+H]^+$; found: 284.0840.

**1-Benzyl-2-(fluoromethyl)-1H-indole-3-carbaldehyde (33)**




By following the General Procedure, 1-benzylspiro[indoline-3,2'-oxiran]-2-one (376.95 mg, 1.5 mmol, 1.5 equiv) was dissolved in dry THF/$Et_2O$ (1:1) *v/v* and $FCH_2I$ (0.07 mL, 1.0 mmol, 1.0 equiv) was added dropwisely. The reaction was stirred at -78 °C after MeLi x LiBr (2.2 M in diethyl ether, 0.9 mL, 2.0 mmol, 2.0 equiv) was added. Reaction lasted 5 mins. The desired product **33** was obtained in 82% (301.6 mg) of yield as green solid substance ($T_{melting\ point}$ = 100 °C) after chromatography on silica (9.95:0.05 v/v, dichlormethane (DCM) : EtOAc).

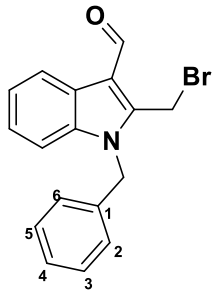
**$^{1}$H NMR** (400 MHz, CDCl3) δ: 10.35 (s, CHO), 8.36 (m, 1H, Ind H-4), 7.34 (m, 1H, Ind H-5), 7.33 (m, 2H, Ind H-6,7), 7.30 (m, 2H, Ph H-3,5), 7.29 (m, 1H, Ph H-4), 7.05 (m, 2H, Ph H-2,6), 5.82 (d, *J* = 48.2Hz, 2H, $CH_2F$), 5.52 (s, 2H, $CH_2$-Ph),

**$^{13}$C NMR** (100 MHz, CDCl3) δ: 184.2 (d, *J* = 1.7Hz, CHO), 140.6 (d, *J* = 15.4Hz, Ind C-2), 137.3 (d, *J* = 1.3Hz, Ind C-7a), 135.6 (Ph C-1), 129.1 (Ph C-3,5), 128.0 (Ph C-4), 126.1 (d, *J* = 0.7Hz, Ph C-2,6), 125.4 (d, *J* = 1.9Hz, Ind C-3a), 125.0 (d, *J* = 1.5Hz, Ind C-6), 123.4 (Ind C-5), 121.7 (Ind C-4), 116.3 (d, *J* = 4.4Hz, Ind C-3), 110.6 (Ind C-7), 72.8 (d, *J* = 167.1Hz, **$CH_2$**-Ph), 47.6 (d, *J* = 2.7Hz, **$CH_2$**F)

**$^{19}$F NMR** ( 376 MHz, CDCl3) δ; -208.3 (t, *J* = 48.2Hz)

**HRMS (ESI)**, m/z: calcd for $C_{17}H_{14}FNO$: 268.1132 $[M+H]^+$; found: 268.1128.

**1-Benzyl-2-(bromomethyl)-1H-indole-3-carbaldehyde (34)**



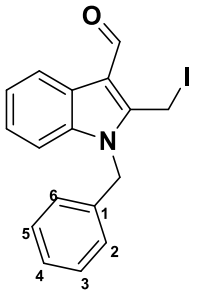

By following the General Procedure, 1-benzylspiro[indoline-3,2'-oxiran]-2-one (251.3 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $Br_2CH_2$ (0.26 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C after MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **34** was obtained in 58% (145.7 mg) of yield as brown solid substance ($T_{melting\ point}$ = 93.5 °C) after chromatography on silica (1:8:1 *v/v/v*, DCM : *n*-Hexane : EtOAc).

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ: 10.36 (s, CHO), 8.28 (m, 1H, Ind H-4), 7.33 (m, 1H, Ind H-5), 7.32 (m, 2H, Ind H-6,7), 7.31 (m, 2H, Ph H-3,5), 7.30 (m, 1H, Ph H-4), 7.06 (m, 2H, Ph H-2,6), 5.53 (s, 2H, $CH_2$-Ph), 4.89 (s, 2H, $CH_2Br$)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 183.9 (CHO), 142.2 (Ind C-2), 137.3 (Ind C-7a), 135.4 (Ph C-1), 129.1 (Ph C-3,5), 128.1 (Ph C-4), 125.9 (Ph C-2,6), 125.7 (Ind C-3a), 124.8 (Ind C-6), 123.4 (Ind C-5), 120.9 (Ind C-4), 114.6 (Ind C-3), 110.4 (Ind C-7), 46.9 (**$CH_2$**-Ph), 19.3 (**$CH_2$**Br)

**HRMS (ESI)**, m/z: calcd for $C_{17}H_{14}BrNO$: 328.0331 $[M+H]^+$; found: 328.0336.

**1-Benzyl-2-(iodomethyl)-1H-indole-3-carbaldehyde (35)**



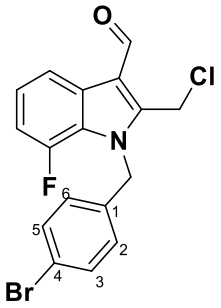

By following the General Procedure, 1-benzylspiro[indoline-3,2'-oxiran]-2-one (251.3 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $I_2CH_2$ (0.23 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C after MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **35** was obtained in 54% (135.7 mg) of yield as green semi-solid substance after chromatography on silica (2:6:2 *v/v/v*, DCM : *n*-Hexane : EtOAc).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ: 10.37 (s, CHO), 8.22 (m, 1H, Ind H-4), 7.32 (m, 1H, Ind H-5), 7.31 (m, 2H, Ind H-6,7), 7.31 (m, 2H, Ph H-3,5), 7.30 (m, 1H, Ph H-4), 7.05 (m, 2H, Ph H-2,6), 5.48 (s, 2H, $CH_2$-Ph), 4.28 (s, 2H, $CH_2I$)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 183.9 (CHO), 143.9 (Ind C-2), 137.5 (Ind C-7a), 135.2 (Ph C-1), 129.2 (Ph C-3,5), 128.2 (Ph C-4), 126.1 (Ind C-3a) 125.9 (Ph C-2,6), 124.6 (Ind C-6), 123.4 (Ind C-5), 120.6 (Ind C-4), 113.6 (Ind C-3), 110.2 (Ind C-7), 46.9 (**$CH_2$**-Ph), 29.8 (**$CH_2$**I)

**HRMS (ESI)**, m/z: calcd for $C_{17}H_{14}INO$: 376.0193 $[M+H]^+$; found: 376.0199

**7-Fluoro-2-(chloromethyl)-1-(4-bromobenzyl)-1*H*-indole-3-carbaldehyde (36)**




By following the General Procedure, 1-(4-Bromobenzyl)-7-fluorospiro[indole-3,2´-oxirane]-2(1H)-one (348.17 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **36** was obtained in 83% (289 mg) of yield as dark green solid substance ($T_{melting\ point}$ = 159 °C) after chromatography on silica (8:1:1 *v/v/v*, *n*-Hexane : DCM : EtOAc).

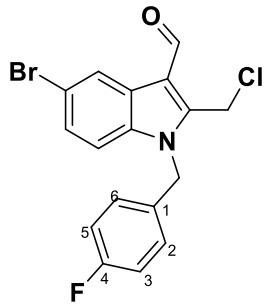
**$^{1}$H NMR** (400 MHz, CDCl3) δ: 10.34 (s, CHO), 8.06 (dd, *J* = 8.0, 0.6Hz, 1H, Ind H-5), 7.44 (m, 2H, Ph H-3,5), 7.25 (m, 2H, Ph H-2,6), 7.02 (ddd, 1H, *J* = 12.7, 8.0, 0.8Hz, Ind H-6), 6.91 (d, 1H, *J* = 8.5Hz, Ind H-5), 5.66 (s, 2H, $CH_2$-Ph), 4.97 (s, 2H, $CH_2$-Cl)

**$^{13}$C NMR** (100 MHz, CDCl3) δ: 184.1 (CHO), 149.8 (d, *J* = 246.4Hz, Ind C-7), 143.0 (Ind C-2), 135.6 (Ph C-1), 132.4 (Ph C-3,5), 129.2 (d, *J* = 3.7Hz, Ind C-3a), 127.6 (Ph C-2,6), 125.1 (m, Ind C-7a), 124.1 (d, *J* = 6.6Hz, Ind C-5), 122.2 (Ph C-4), 115.7 (Ind C-3), 111.0 (d, *J* = 18.1Hz, Ind C-6), 48.8 (d, *J* = 7.2Hz, $CH_2$-Ph), 33.1 ($CH_2$-Cl)

**$^{19}$F NMR** ( 376 MHz, CDCl3) δ; -133.9 (m)

**HRMS (ESI)**, m/z: calcd for $C_{17}H_{12}BrClFNO$: 378.9775 $[M+H]^+$ ; found: 378.9777.

**5-Bromo-2-(chloromethyl)-1-(4-fluorobenzyl)-1*H*-indole-3-carbaldehyde (37)**




By following the General Procedure, 5-Bromo-1-(4-fluorobenzyl)spiro[indole-3,2´-oxirane]-2(1*H*)-one (348.17 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **37** was obtained in 88% (306.4 mg) of yield as dark green solid substance ($T_{melting\ point}$ = 114.5 °C) after chromatography on silica (8:1:1 *v/v/v*, *n*-Hexane : DCM : EtOAc).

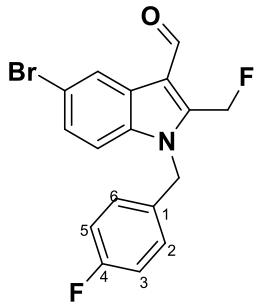
**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ: 10.28 (s, CHO), 8.45 (m, 1H, Ind H-4), 7.40 (dd, *J* = 8.8, 1.9Hz, 1H, Ind H-6), 7.13 (d, *J* = 8.8 Hz, 1H, H-7 Ind), 7.02 (m, 2H, H-2,6 Ph), 7.00 (m, 2H, Ph H-3,5 ), 5.48 (s, 2H, $CH_2Cl$), 4.98 (s, 2H, $CH_2$-Ph)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 183.7 (CHO), 162.6 (d, *J* = 247.7Hz, Ph C-4), 143.0 (Ind C-2), 135.9 (Ind C-7a), 130.9 (d, *J* = 0.9Hz, Ph C-1), 128.1 (Ind C-6), 127.9 (d, *J* = 8.7Hz, Ph C-2,6), 127.1 (Ind C-3a), 124.2 (Ind C-4), 117.3 (Ind C-5), 116.4 (d, *J* = 21.9Hz, Ph C-3,5), 114.7 (Ind C-3), 112.0 (Ind C-7), 46.8 ($CH_2$-Ph), 33.2 ($CH_2Cl$)

**$^{19}$F NMR** ( 376 MHz, $CDCl_3$) δ; -113.3 (m)

**HRMS (ESI)**, m/z: calcd for $C_{17}H_{12}BrClFNO$: 378.9775 $[M+H]^+$ ; found: 378.9778

**5-Bromo-1-(4-fluorobenzyl)-2-(fluoromethyl)-1*H*-indol-3-carbaldehyde (38)**




By following the General Procedure, 5-Bromo-1-(4-fluorobenzyl)spiro[indole-3,2´-oxirane]-2(1*H*)-one (522.3 mg, 1.5 mmol, 1.5 equiv) was dissolved in dry THF/$Et_2O$ (1:1) *v/v* and $FCH_2I$ (0.07 mL, 1.0 mmol, 1.0 equiv) was added dropwisely. The reaction was stirred at -78 °C after MeLi x LiBr (2.2 M in diethyl ether, 0.9 mL, 2.0 mmol, 2.0 equiv) was added. Reaction lasted 5 mins. The desired product **38** was obtained in 88% (459.6 mg) of yield as green semi-solid substance after chromatography on silica (8:1:1 *v/v/v*, n-Hexane: DCM : EtOAc).

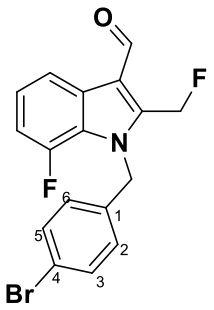
**$^{1}$H NMR** (400 MHz, CDCl3) δ: 10.27 (d, J = 5.6Hz, 1H, CHO), 8.50 (m, 1H, Ind H-4), 7.40 (m, 1H, Ind H-6), 7.15 (dd, *J* = 8.8, 3.1Hz, 1H, Ind H-7), 7.02 (m, 1H, Ph C-2,6), 7.01 (m, 1H, Ph C-3,5), 5.80 (dd, *J* = 48.0, 1.8Hz, 2H, $CH_2F$), 5.45 (s, 2H, $CH_2$-Ph)

**$^{13}$C NMR** (100 MHz, CDCl3) δ: 183.7 (CHO), 162.5 (d, *J* = 247.6 Hz, Ph C-4), 141.3 (d, *J* = 15.6 Hz, Ind C-2), 135.7 (Ind C-7a), 130.9 (d, *J* = 3.1Hz, Ph C-1), 128.2 (Ind C-6), 127.8 (d*, J* = 8.2Hz, Ph C-2,6), 126.8 (Ind C-3a), 124.6 (Ind C-4), 117.1 (Ind C-5), 116.2 (d, *J* = 21.8Hz, Ph C-3,5), 115.8 (d*, J* = 4.2Hz, Ind C-3), 111.9 (Ind C-7), 72.6 (d, *J* = 168.0Hz, $CH_2F$), 47.2 ($CH_2$-Ph)

**$^{19}$F NMR** ( 376 MHz, CDCl3) δ; -113.4 (m, F-Ph), -209.0 (dt, $J_t$ = 48.0Hz, $J_d$ = 20.7Hz, $CH_2F$)

**HRMS (ESI)**, m/z: calcd for $C_{17}H_{12}BrF_2NO$: 364.0143 $[M+H]^+$ ; found: 364.0153.

**7-Fluoro-1-(4-bromoobenzyl)-2-(fluoromethyl)-1*H*-indol-3-carbaldehyde (39)**




By following the General Procedure, 5-Bromo-1-(4-fluorobenzyl)spiro[indole-3,2´-oxirane]-2(1*H*)-one (522.3 mg, 1.5 mmol, 1.5 equiv) was dissolved in dry THF/$Et_2O$ (1:1) *v/v* and $FCH_2I$ (0.07 mL, 1.0 mmol, 1.0 equiv) was added dropwisely. The reaction was stirred at -78 °C after MeLi x LiBr (2.2 M in diethyl ether, 0.9 mL, 2.0 mmol, 2.0 equiv) was added. Reaction lasted 5 mins. The desired product **39** was obtained in 87% (454.4 mg) of yield as dark green solid substance ($T_{melting\ point}$ = 123 °C) after chromatography on silica (8:1:1 *v/v/v*, n-Hexane: DCM : EtOAc).

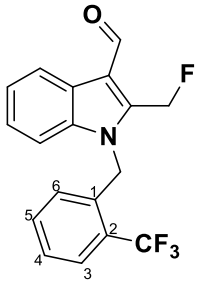
**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ: 10.34 (s, CHO), 8.12 (d*, J* = 8.0Hz, 1H, Ind H-4), 7.43 (m, 2H, Ph H-3,5), 7.26 (s, 2H, Ph H-2,6), 7.24 (td, 1H, $J_d$ = 3.7Hz*,* $J_t$ = 8.0Hz*,* Ind H-5), 7.02 (ddd, *J* = 12.6, 7.9, 0.8Hz*,* 1H, Ind H-6), 5.80 (d, *J* = 48.1Hz, 2H, $CH_2F$), 5.64 (s, 2H, $CH_2$-Ph)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 184.2 (CHO), 149.8 (dd*, J* = 246.6*,* 1.2Hz, Ind C-7), 141.5 (d*, J* = 15.6Hz, Ind C-2), 135.6 (Ph C-1), 132.2 (Ph C-3,5), 129.7 (d, *J* = 1.8Hz, Ph C-2,6), 125.2 (d*, J* = 9.2Hz, Ind C-7a), 124.1 (d, *J* = 6.5Hz*,* Ind C-5), 122.1 (Ph C-4), 121.7 (d*, J* = 3.4Hz, Ind C-3a), 117.7 (d, *J* = 3.7Hz, Ind C-4), 117.0 (d, *J* = 3.9Hz, Ind C-3), 111.1 (dd, *J* = 18.0, 1.1Hz, Ind C-6), 72.6 (d*, J* = 168.0Hz, $CH_2F$), 49.3 (dd, *J* = 6.8, 2.7Hz, $CH_2$-Ph)

**$^{19}$F NMR** ( 376 MHz, $CDCl_3$) δ; -133.6 (m, Ind F-7), -208.8 (t*, J* = 48.1Hz, $CH_2$-F)

**HRMS (ESI)**, m/z: calcd for $C_{17}H_{12}BrF_2NO$: 363.0070 $[M+H]^+$ ; found: 363.0075

**2-(Fluoromethyl)-1-[-2-(trifluoromethyl)benzyl)]-1*H*-indol-3-carbaldehyde (40)**




By following the General Procedure, 1-[2-(Trifluoromethyl)benzyl]spiro[indole-3,2´-oxirane]-2(1H)-one (478.9 mg, 1.5 mmol, 1.5 equiv) was dissolved in dry THF/$Et_2O$ (1:1) *v/v* and $FCH_2I$ (0.07 mL, 1.0 mmol, 1.0 equiv) was added dropwisely. The reaction was stirred at -78 °C after MeLi x LiBr (2.2 M in diethyl ether, 0.9 mL, 2.0 mmol, 2.0 equiv) was added. Reaction lasted 5 mins. The desired product **40** was obtained in 89% (426.3 mg) of yield as green solid substance ($T_{melting\ point}$ = 151 °C) after chromatography on silica (99.98:0.02 *v/v,* DCM : EtOAc).

**$^{1}$H NMR** (400 MHz, CDCl3) δ: 10.38 (s, 1H, CHO), 8.38 (m, 1H, Ind H-4), 7.76 (m, 1H, Ph H-3), 7.39 (m, 1H, Ph H-4), 7.37 (m, 1H, Ind H-5), 7.32 (m, 1H, Ind H-5,6), 7.19 (m, 1H, Ind H-7), 6.45 (m, 1H, Ph H-6), 5.83 (d*, J* = 48.2Hz, 2H, $CH_2F$), 5.71 (s, 2H, $CH_2$-Ph)

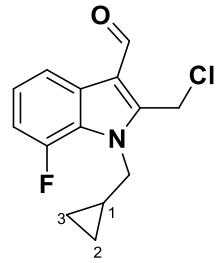
**$^{13}$C NMR** (100 MHz, CDCl3) δ: 184.2 (d, *J* = 1.7Hz, CHO), 140.7 (d, *J* = 15.7Hz Ind C-2), 137.0 (d*, J* = 1.3Hz, Ind C-7a), 134.3 (q, *J* = 1.4Hz, Ph C-1), 132.7 (q, *J* = 1.2Hz, Ph C-5), 127.9 (Ph C-4), 127.1 (q*, J* = 31.0Hz, Ph C-2), 126.9 (q, *J* = 5.7Hz, Ph C-3), 126.34 (d*, J* = 1.1Hz Ph C-6), 125.36 (d*, J* = 1.8Hz, Ind C-3a), 125.32 (Ind C-6), 124.3 (q*, J* = 273.7Hz, $CF_3$), 123.7 (d*, J* = 1.5Hz, Ind C-5), 121.9 (Ind C-4), 116.6 (d, *J* = 4.4Hz, Ind C-3), 110.3 (d*, J* = 1.2Hz, Ind C-7), 72.6 (d*, J* = 167.7Hz, $CH_2F$), 44.2 (m, $CH_2$-Ph)

**$^{15}$N NMR** (40 MHz, CDCl3) δ: -239.3

**$^{19}$F NMR** ( 376 MHz, CDCl3) δ; -60.6 (s, 3F, $CF_3$), -208.4 (t*, J = 48.2* Hz, $CH_2F$)

**HRMS (ESI)**, m/z: calcd for $C_{18}H_{13}F_4NO$: 358.0825 $[M+Na]^+$ ; found: 358.0835

**7-Fluoro-1-(cyclopropylmethyl)-2-(chloromethyl)-1*H*-indol-3-carbaldehyde (41)**




By following the General Procedure, 1-(Cyclopropylmethyl)-7-fluorospiro[indole-3,2´-oxirane]-2(1H)-one (233.24 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **41** was obtained in 82% (191.3 mg) of yield as dark green semi-solid substance after chromatography on silica (8:1:1 *v/v/v*, *n*-Hexane : DCM : EtOAc).

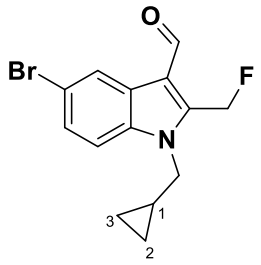
**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ: 10.33 (s, CHO), 8.03 (dd, 1H*, J* = 9.5, 4.7Hz, Ind H-4), 7.22 (m, 1H, Ind H-5), 7.04 (ddd, 1H*, J* = 13.0, 8.0, 0.8Hz, Ind H-6), 5.10 (s, 2H, $CH_2$-Cl), 4.36 (d, 2H, *J* = 6.8Hz, $CH_2$-cyclopropyl), 1.34 (m, 1H, cyclopropyl H-1), 0.61 (m, 2H, cyclopropyl H-2,3), 0.47 (m, 2H, cyclopropyl H-2,3)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 184.1 (s, CHO), 149.8 (d, *J=245.9 Hz*, Ind C-7), 142.9 (Ind C-2), 129.4 (d*, J* = 3.9Hz, Ind C-4), 125.0 (d, *J* = 8.8Hz, Ind C-7a), 123.7 (d, *J* = 6.8Hz, Ind C-5), 116.9 (d, *J* = 3.9Hz, Ind C-4), 115.3 (d*, J* = 1.2Hz, Ind C-3), 110.6 (d, *J* = 18.7Hz, Ind C-6), 50.0 (d, J = 5.8Hz, $CH_2$-cyclopropyl), 33.2 ($CH_2$-Cl), 12.4 (d, *J* = 2.0Hz, cyclopropyl C-1), 4.0 (d*, J* = 1.5Hz, 2C, cyclopropyl C-2,3)

**$^{19}$F NMR** ( 376 MHz, $CDCl_3$) δ; -132.4 (m)

**HRMS (ESI)**, m/z: calcd for $C_{14}H_{13}ClFNO$: 265.0669 $[M+H]^+$ ; found: 265.0672

**5-Bromo-1-(cyclopropylmethyl)-2-(fluoromethyl)-1*H*-indol-3-carbaldehyde (42)**




By following the General Procedure, 5-Bromo-1-(cyclopropylmethyl)spiro[indole-3,2´-oxirane]-2(1H)-one (441.2 mg, 1.5 mmol, 1.5 equiv) was dissolved in dry THF/$Et_2O$ (1:1) *v/v* and $FCH_2I$ (0.07 mL, 1.0 mmol, 1.0 equiv) was added dropwisely. The reaction was stirred at -78 °C after MeLi x LiBr (2.2 M in diethyl ether, 0.9 mL, 2.0 mmol, 2.0 equiv) was added. Reaction lasted 5 mins. The desired product **42** was obtained in 73% (322.1 mg) of yield as light brown solid substance ($T_{melting\ point}$ = 106.5 °C) after chromatography on silica (2:7:1 *v/v/v,* DCM : *n*-Hexane : EtOAc).

**$^{1}$H NMR** (400 MHz, CDCl3) δ: 10.23 (s, CHO), 8.46 (d*, J* = 1.9Hz, 1H, Ind H-4), 7.44 (ddd, *J* = 8.8, 1.9, 0.9Hz, 1H, Ind H-6), 7.30 (d, *J* = 8.8Hz, 1H, Ind H-7), 5.84 (d, *J* = 48.3Hz, 2H, $CH_2F$), 4.14 (d*, J* = 6.7Hz, 2H, $CH_2$-cyclopropyl), 0.63 (m, 1H, cyclopropyl H-2,3), 0.43 (m, 1H, cyclopropyl H-2,3)

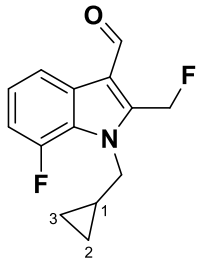
**$^{13}$C NMR** (100 MHz, CDCl3) δ: 183.7 (d, 1.4 Hz, CHO), 141.0 (d, 15.9 Hz, Ind C-2), 135.7 (Ind C-7a), 127.6 (d, 1.5 Hz, Ind C-6), 126.8 (d*, J* = 1.8Hz, Ind C-3a), 124.4 (Ind C-4), 116.8 (Ind C-5), 112.0 (Ind C-7), 72.4 (d*, J* = 168.0Hz, $CH_2F$), 48.6 (d, *J* = 2.0Hz, $CH_2$-cyclopropyl), 11.3 (d, *J* = 0.7Hz, cyclopropyl C-1), 4.4 (d, *J* = 1.0Hz, cyclopropyl C-2,3)

**$^{15}$N NMR** (40 MHz, CDCl3) δ: -228.8

**$^{19}$F NMR** ( 376 MHz, CDCl3) δ; -207.2 (t, *J* = 48.3Hz, 1F, $CH_2F$)

**HRMS (ESI)**, m/z: calcd for $C_{14}H_{13}BrFNO$: 310.0237 $[M+H]^+$ ; found: 310.0245

**7-Fluoro-1-(cyclopropylmethyl)-2-(fluoromethyl)-1*H*-indol-3-carbaldehyde (43)**




By following the General Procedure, 1-(Cyclopropylmethyl)-7-fluorospiro[indole-3,2´-oxirane]-2(1H)-one (349.9 mg, 1.5 mmol, 1.5 equiv) was dissolved in dry THF/$Et_2O$ (1:1) *v/v* and $FCH_2I$ (0.07 mL, 1.0 mmol, 1.0 equiv) was added dropwisely. The reaction was stirred at -78 °C after MeLi x LiBr (2.2 M in diethyl ether, 0.9 mL, 2.0 mmol, 2.0 equiv) was added. Reaction lasted 5 mins. The desired product **43** was obtained in 71% (248.4 mg) of yield as dark green semi-solid substance after chromatography on silica (1:8:1 *v/v/v,* DCM : *n*-Hexane : EtOAc).

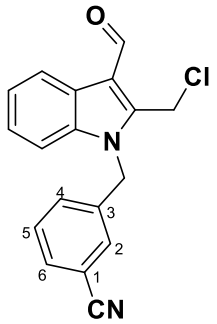
**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ: 10.31 (CHO), 8.10 (d*, J* = 8.0Hz, 1H, Ind H-4), 7.23 (m, 1H, Ind H-5), 7.05 (dd*, J* = 13.0*,* 7.9Hz, 1H, Ind H-6), 5.86 (d*, J* = 168.0Hz, 2H, $CH_2$-F), 4.33 (d*, J=6.9 Hz*, 2H, $CH_2$-cyclopropyl), 1.35 (m, 1H, cyclopropyl H-1), 0.57 (m, 2H, cyclopropyl H-2,3), 0.46 (m, 2H, cyclopropyl H-2,3)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 184.3 (CHO), 149.8 (d*, J* = 247.3Hz, Ind C-7), 141.3 (d, *J* = 15.8Hz, Ind C-2), 129.1 (dd, *J* = 3.9*,* 1.9Hz, Ind C-3a), 125.1 (d, *J* = 7.8Hz*,* Ind C-7a), 123.7 (d, *J* = 6.7Hz, Ind C-5), 117.6 (d*, J* = 3.5Hz*,* Ind C-4), 116.8 (dd*, J* = 4.2Hz*, 1.3 Hz*, Ind C-3), 110.7 (dd*, J* = 18.6*,* 1.2Hz, Ind C-6), 72.4 (d*, J* = 168.0Hz, $CH_2$-F), 50.6 (dd, *J* = 5.6*,* 1.8Hz, $CH_2$-cyclopropyl), 12.3 (d, *J* = 2.0Hz, cyclopropyl C-1), 3.9 (cyclopropyl C-2,3)

**$^{19}$F NMR** ( 376 MHz, $CDCl_3$) δ; -132.3 (m, Ind F-7), -206.7 (t, *J=48.3Hz*, CH2-F)

**HRMS (ESI)**, m/z: calcd for $C_{14}H_{13}F_2NO$: 249.0965 $[M+H]^+$ ; found: 249.0969.

**3-{[2-(Chloromethyl)-3-formyl-1H-indol-1-yl] methyl} benzonitrile (44)**




By following the General Procedure, 3-[(2-Oxospiro[indole-3,2´-oxirane])-1(2H)-yl) methyl] benzonitrile (276.3 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **44** was obtained in 89% (245.9 mg) of yield as light green solid substance ($T_{melting\ point}$ = 169 °C) after chromatography on silica (6:4 *v/v*, *n*-Hexane : EtOAc).

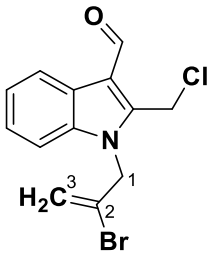
**$^1$H NMR** (400 MHz, $CDCl_3$) δ: 10.38 (s, 1H, CHO H-1), 8.30 (m, 1H, Ind H-4), 7.60 (m, 1H, Ph H-6), 7.44 (m, 1H, Ph H-5), 7.37 (m, 1H, Ind H-5), 7.36 (m, 1H, Ph H-2), 7.33 (m, 1H, Ind H-6), 7.26 (m, 1H, Ph H-4), 7.20 (m, 1H, Ind H-7), 5.57 (s, 2H, $CH_2$-Ph), 5.04 (s, 2H, $CH_2Cl$)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 184.0 (CHO), 141.4 (Ind C-2), 137.2 (Ph C-3), 136.8 (Ind C-7a), 131.9 (Ph C-6), 130.4 (Ph C-4), 130.0 (Ph C-5), 129.5 (Ph C-2), 125.7 (Ind C-3a), 125.2 (Ind C-6), 123.8 (Ind C-5), 121.4 (Ind C-4), 118.1 (Ph-CN), 115.3 (Ind C-3), 113.4 (Ph C-1), 110.1 (Ind C-7), 46.3 ($CH_2$-Ph), 33.4 ($CH_2Cl$)

**$^{15}$N NMR** (40 MHz, $CDCl_3$) δ: -239.0 (Indole N)

**HRMS (ESI)**, m/z: calcd for $C_{18}H_{13}ClN_2O$: 309.0789 $[M+H]^+$ ; found: 309.0779

**1-(2-Bromo-2-propen-1-yl)-2-(chloromethyl)-1*H*-indole-3-carbaldehyde (45)**




By following the General Procedure, 1-(2-bromoallyl)spiro[indoline-3,2'-oxiran]-2-one (280.12 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **45** was obtained in 91% (254.9 mg) of yield as light green solid substance ($T_{melting\ point}$ = 132 °C) after chromatography on silica (8:2 *v/v*, *n*-Hexane : EtOAc).

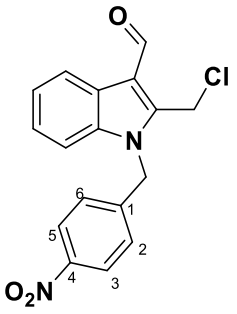
**$^{1}$H NMR** (400 MHz, CDCl3) δ: 10.36 (s, CHO H-1), 8.27 (m, 1H, Ind H-4), 7.37 (m, 1H, Ind H-5), 7.37 (m, 1H, Ind H-6), 7.37 (m, 1H, Ind H-7), 5.64 (m, 1H, propenyl H-3), 5.40 (m, 1H, propenyl H-3), 5.12 (m, 2H, propenyl H-1), 5.11 (s, 2H, $CH_2Cl$)

**$^{13}$C NMR** (100 MHz, CDCl3) δ: 184.1 (CHO), 141.6 (Ind C-2), 136.7 (Ind C-7a), 125.5 (propenyl C-2), 125.4 (Ind C-3a), 125.0 (Ind C-6), 123.7 (Ind C-5), 121.3 (Ind C-4), 118.6 (propenyl C-3), 115.2 (Ind C-3), 110.2 (Ind C-7), 50.9 (propenyl C-1), 33.2 ($CH_2Cl$)

**$^{15}$N NMR** (40 MHz, CDCl3) δ: -238.8

**HRMS (ESI)**, m/z: calcd for $C_{13}H_{11}BrClNO$: 311.9785 $[M+H]^+$; found: 311.9781

**2-(Chloromethyl)-1-(4-nitrobenzyl)-1*H*-indol-3-carbaldehyde (46)**



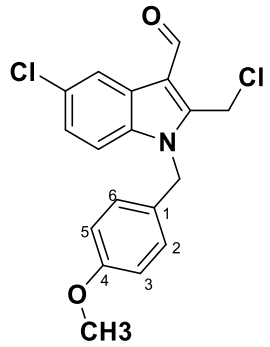

By following the General Procedure 1-(4-Nitrobenzyl)spiro[indole-3,2´-oxirane]-2(1H)-one (296.28 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **46** was obtained in 62% (183.7 mg) of yield as dark green solid substance ($T_{melting\ point}$ = 180 °C) after chromatography on silica (6:2:2 *v/v/v*, *n*-Hexane : DCM : EtOAc).

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ: 10.38 (s, 1H, CHO), 8.31 (m, 1H, Ind H-4), 8.18 (s, 1H, Ph H-3,5), 7.37 (m, 1H, Ind H-5), 7.32 (m, 1H, Ind H-6), 7.21 (m, 1H, Ph H-2,6), 7.19 (m, 1H, Ind H-7), 5.63 (s, 2H, $CH_2$-Ph), 5.05 (s, 2H, $CH_2Cl$)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 184.0 (CHO), 147.8 (Ph C-4), 142.7 (Ph C-1), 141.5 (Ind C-2), 136.8 (Ind C-7a), 126.9 (Ph, C-2,6), 125.7 (Ind C-3a), 125.2 (Ind C-6), 124.4 (Ph C-3,5), 123.8 (Ind C-5), 115.4 (Ind C-3), 110.1 (Ind C-7), 46.5 ($CH_2$-Ph), 33.3 ($CH_2Cl$)

**HRMS (ESI)**, m/z: calcd for $C_{17}H_{13}ClN_2O_3$: 329.0687 $[M+H]^+$ ; found: 329.0680

**5-Chloro-2-(chloromethyl)-1-(4-methoxybenzyl)-1*H*-indole-3-carbaldehyde (47)**




By following the General Procedure, 5-Chloro-1-(4-methoxybenzyl)spiro[indol-3,2´-oxirane]-2(1H)-one (315.75 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **47** was obtained in 78% (246.3 mg) of yield as green solid substance ($T_{melting\ point}$ = 106 °C) after chromatography on silica (8:2 *v/v*, *n*-Hexane : EtOAc).

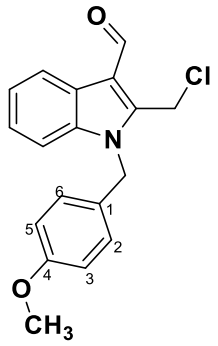
**$^1$H NMR** (400 MHz, $CDCl_3$) δ: 10.27 (s, 1H, CHO), 8.28 (m, 1H, Ind H-4), 7.25 (m, 1H, Ind H-6), 7.22 (m, 1H, Ind H-7), 6.97 (m, 2H, Ph C-2,6), 6.84 (m, 2H, Ph H-3,5), 5.44 (s, 2H, $CH_2$-Ph), 4.98 (s, 2H, $CH_2Cl$), 3.77 (s, 3H, $OCH_3$)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 183.5 (CHO), 159.5 (Ph C-4), 143.1 (Ind C-2), 135.5 (Ind C-7a), 129.4 (Ind C-5), 127.3 (Ph C-3,6), 127.0 (Ph C-1), 126.4 (Ind C-3a), 125.2 (Ind C-6), 120.9 (Ind C-4), 114.6 (Ph C-3,5), 114.5 (Ind C-3), 111.6 (Ind C-7), 55.3 ($OCH_3$), 46.9 ($CH_2$-Ph), 33.1 ($CH_2Cl$)

**$^{15}$N NMR** (40 MHz, CDCl3) δ: -233.8

**HRMS (ESI)**, m/z: calcd for $C_{18}H_{16}ClNO_2$: 348.0553 $[M+H]^+$ ; found: 348.0559.

**2-(Chloromethyl)-1-(4-methoxybenzyl)-1*H*-indole-3-carbaldehyde (48)**



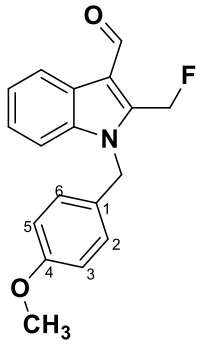

By following the General Procedure, 1-(4-Methoxybenzyl)spiro[indole-3,2´-oxirane]-2(1H)-one (281.3 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **48** was obtained in 76% (213.8 mg) of yield as brown semi-solid substance after chromatography on silica (8:1:1 *v/v/v*, *n*-Hexane : DCM: EtOAc).

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ: 10.34 (s, CHO), 8.28 (m, Ind H-4), 7.33 (m, 3H, Ind H-5,6,7), 7.00 (m, 2H, H-2,6), 6.83 (m, 2H, H-3,5 Ph), 5.48 (s, 2H, $CH_2$-Ph), 5.02 (s, 2H, $CH_2$-Cl), 3.77 (s, 3H, $OCH_3$)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 184.1 (CHO), 159.5 (Ph C-4), 142.2 (Ind C-2), 137.3 (Ind C-7a), 127.6 (Ph C-2,6), 127.5 (Ph C-1), 125.7 (Ind C-3a), 124.9 (Ind C-6), 123.5 (Ind C-5), 121.3 (Ind C-4), 115.0 (Ind C-3), 114.6 (Ph C-3,5), 110.7 (Ind C-7), 55.4 ($OCH_3$), 46.8 ($CH_2$-Ph), 33.6 ($CH_2$-Cl)

**HRMS (ESI)**, m/z: calcd for $C_{18}H_{16}ClNO_2$: 313.0869 $[M+H]^+$ ; found: 313.0874

**2-(Fluoromethyl)-1-(4-methoxybenzyl)-1*H*-indol-3-carbaldehyde (49)**




By following the General Procedure, 1-(4-Methoxybenzyl)spiro[indole-3,2´-oxirane]-2(1H)-one (421.95 mg, 1.5 mmol, 1.5 equiv) was dissolved in dry THF/$Et_2O$ (1:1) *v/v* and $FCH_2I$ (0.07 mL, 1.0 mmol, 1.0 equiv) was added dropwisely. The reaction was stirred at -78 °C after MeLi x LiBr (2.2 M in diethyl ether, 0.9 mL, 2.0 mmol, 2.0 equiv) was added. Reaction lasted 5 mins. The desired product **49** was obtained in 74% (312.2 mg) of yield as dark green semi-solid substance ($T_{melting\ point}$ = 103 °C) after chromatography on silica (1:8:1 *v/v/v,* DCM : *n*-Hexane : EtOAc).

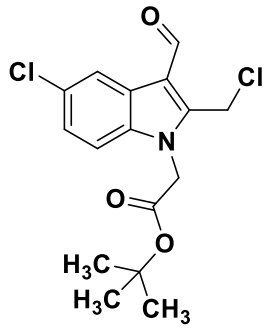
**$^1$H NMR** (400 MHz, $CDCl_3$) δ: 10.32 (d, *J* = 1.8Hz, 1H, CHO), 8.34 (m, 1H, Ind H-4), 7.33 (m, 1H, Ind H-5,6,7), 7.00 (m, 1H, Ph H-2,6), 6.82 (m, 1H, Ph H-3,5), 5.80 (dd, *J* = 48.2, 1.8 Hz, 2H, $CH_2F$), 5.43 (d, *J* = 1.5 Hz, 2H, $CH_2$-Ph), 3.75 (d, *J* = 1.0Hz, 3H, $OCH_3$)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 184.1 (CHO), 159.3 (Ph C-4) 140.7 (d, *J* = 15.4Hz, Ind C-2), 137.2 (Ind C-7a), 127.53 (Ph C-1), 127.45 (Ph C-2,6), 125.3 (Ind C-3a), 124.9 (Ind C-6), 123.3 (Ind C-5), 121.7 (Ind C-4), 116.2 (d, *J* = 4.3Hz, Ind C-3), 114.4 (Ph C-3,5), 110.6 (Ind C-7), 72.7 (d, *J* = 167.0 Hz, $CH_2F$), 55.2 ($OCH_3$), 47.1 (d, *J* = 2.3Hz, $CH_2$-Ph)

**$^{19}$F NMR** ( 376 MHz, $CDCl_3$) δ; -113.4 (m, F-Ph), -208.0 (t, *J* = 48.2Hz, $CH_2F$)

**HRMS (ESI)**, m/z: calcd for $C_{18}H_{16}FNO_2$: 298.1238 $[M+H]^+$ ; found: 298.1248.

**2-Methyl-2-propanyl [2-(cholоromethyl)-3-formyl-1*H*-indol-1-yl] acetate (50)**




By following the General Procedure, tert-butyl 2-(4-((5-chloro-2-oxospiro[indoline-3,2'-oxiran]-1-yl)methyl)phenyl)acetate (399.8 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $ClCH_2I$ (0.22 mL, 3.0 mmol, 3.0 equiv) was added dropwisely. The reaction was stirred at -78 °C for 5 mins, then MeLi x LiBr (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added. Reaction lasted 1 hour. The desired product **50** was obtained in 82% (327.8 mg) of yield as light green solid substance ($T_{melting\ point}$ = 120.5 °C) after chromatography on silica (8:1:1 *v/v/v*, *n*-Hexane : DCM: EtOAc).

**$^{1}$H NMR** (400 MHz, CDCl3) δ: 10.33 (s, 1H, CHO), 8.25 (m, 1H, Ind H-4), 7.37 (m, 1H, Ind H-6), 7.33 (m, 1H, Ind H-5), 7.30 (m, 1H, Ind H-7), 5.10 (s, 2H, $CH_2Cl$), 4.92 (s, 2H, $CH_2CO_2$*t*-Butyl), 1.45 (s, 3H, *t*-Butyl)

**$^{13}$C NMR** (100 MHz, CDCl3) δ: 184.0 (CHO), 166.1 ($CO_2$*t*-Butyl), 141.8 (Ind C-2), 137.2 (Ind C-7a), 125.4 (Ind C-3a), 124.8 (Ind C-6), 123.5 (Ind C-5), 121.2 (Ind C-4), 115.1 (Ind C-3), 109.5 (Ind C-7), 83.7 (*t*-Butyl C-2), 33.4 ($CH_2Cl$), 27.9 (*t*-Butyl C-1), 27.9 (*t*-Butyl $CH_3$), 27.9 (3C, *t*-Butyl $CH_3$)

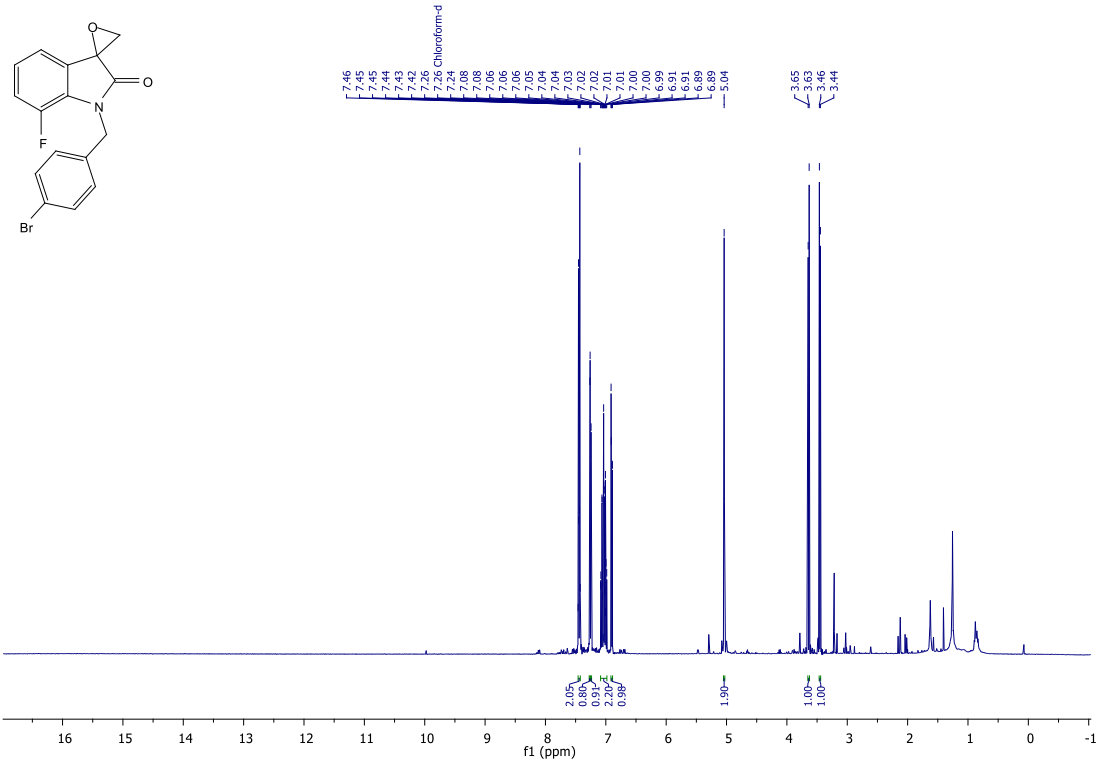
**$^{15}$N NMR** (40 MHz, CDCl3) δ: -242.7

**HRMS (ESI)**, m/z: calcd for $C_{16}H_{18}ClNO_3$: 308.1048 $[M+H]^+$ ; found: 308.1038

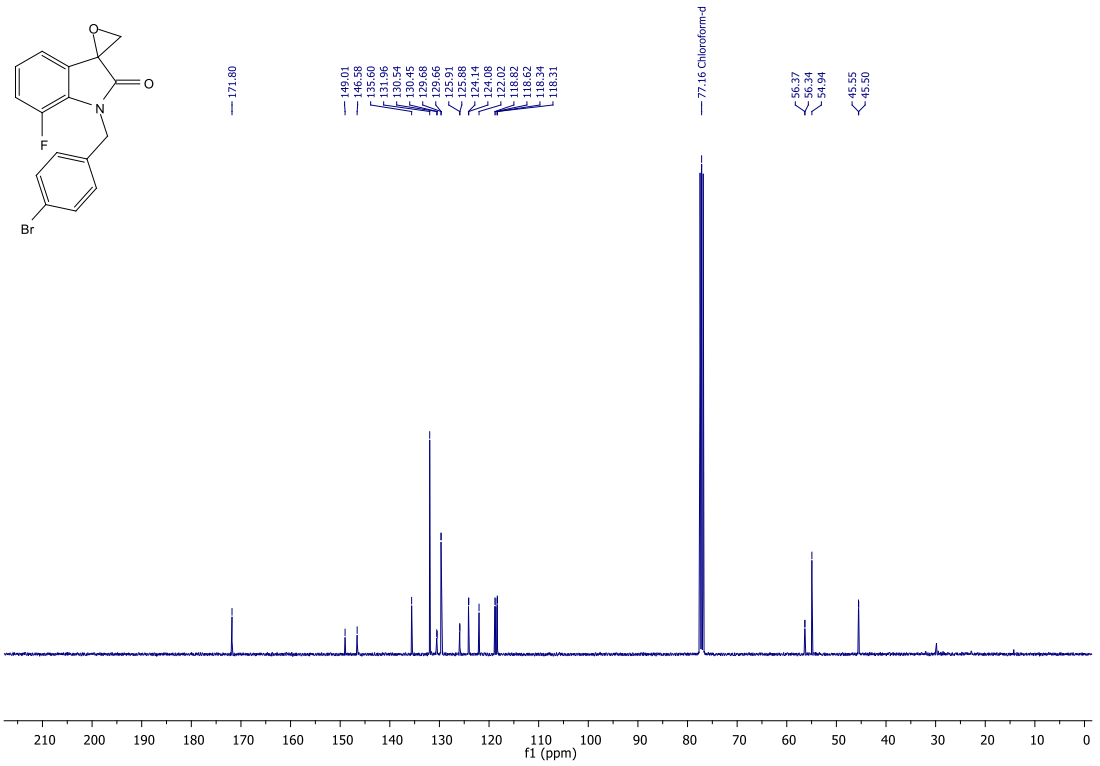
## Copies of $^{1}H$, $^{13}C$-NMR and $^{19}F$ NMR Spectra for all the compounds

### 1-(4-Bromobenzyl)-7-fluorospiro[indole-3,2´-oxirane]-2(1*H*)-one (19)

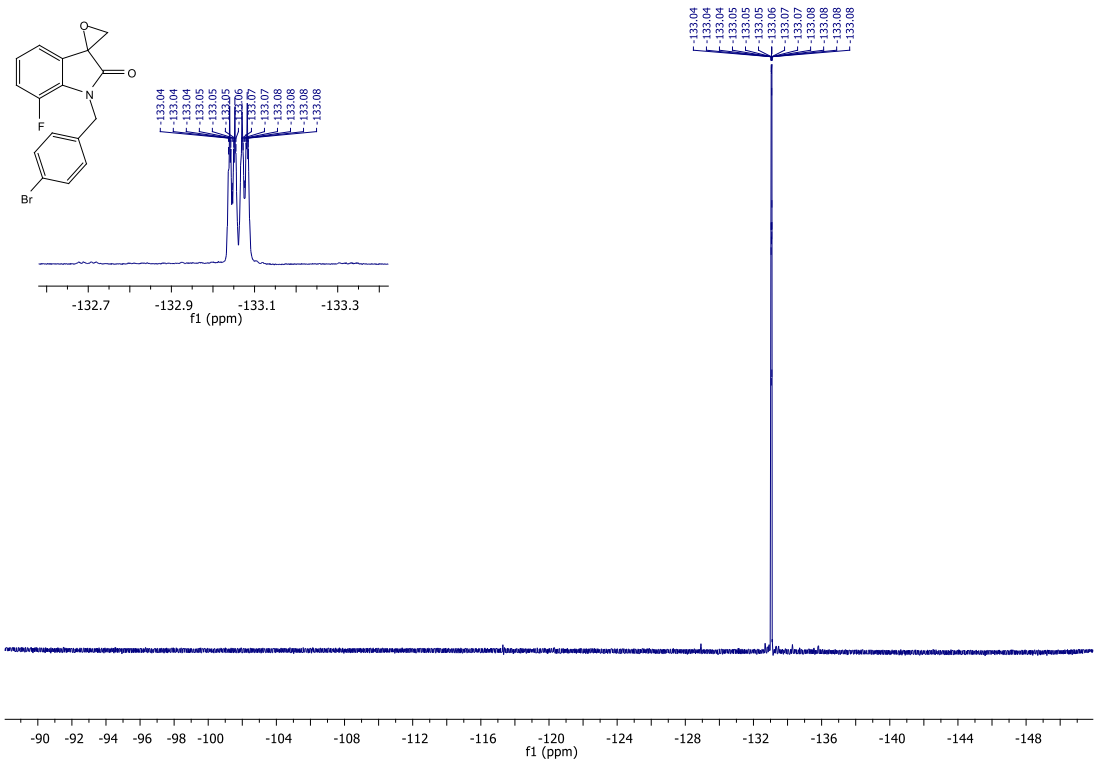
**$^{1}H$ NMR** (400 MHz, $CDCl_3$)




**$^{13}C$ NMR** (100 MHz, $CDCl_3$)

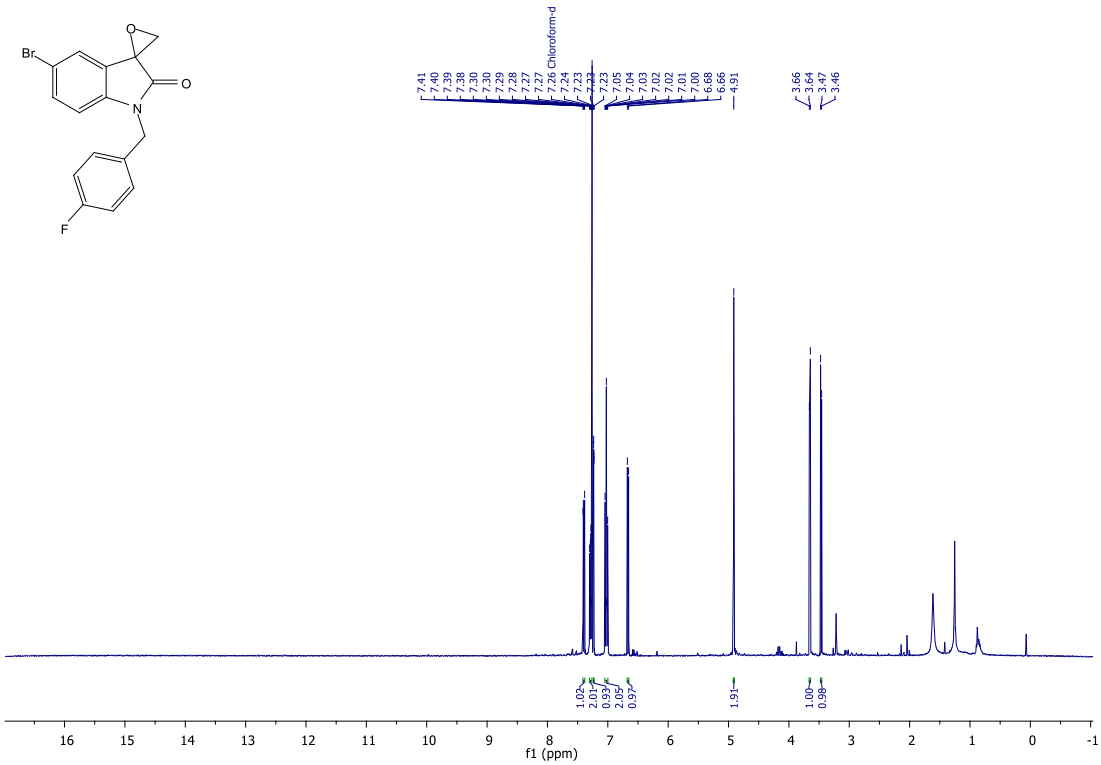


**$^{19}$F NMR** ( 376 MHz, $CDCl_3$)

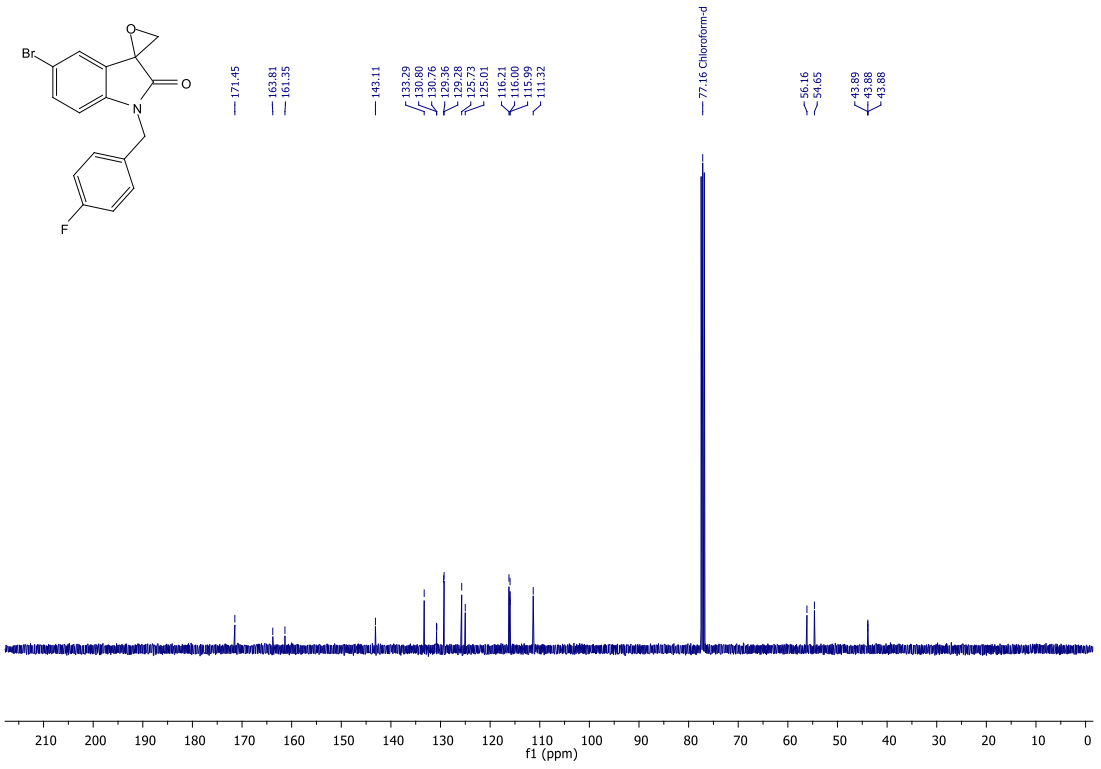


**5-Bromo-1-(4-fluorobenzyl)spiro[indole-3,2´-oxirane]-2(1*H*)-one (20)**

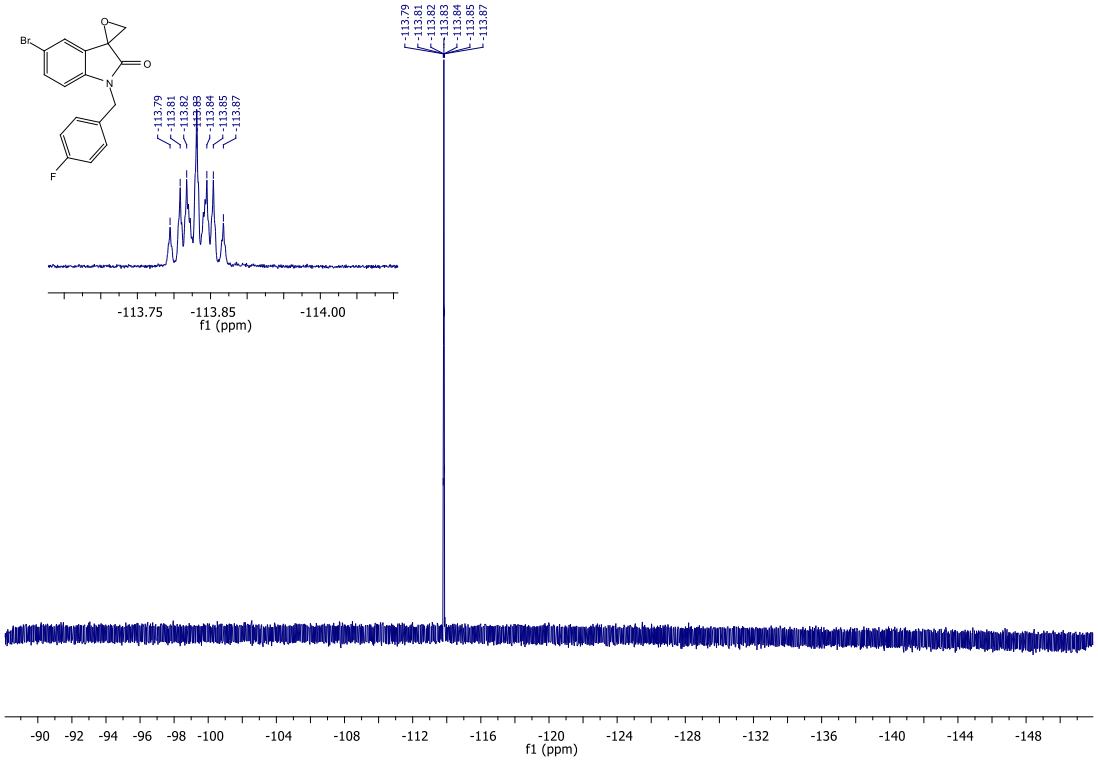
**$^{1}$H NMR** (400 MHz, $CDCl_3$)




**$^{13}$C NMR** (100 MHz, $CDCl_3$)

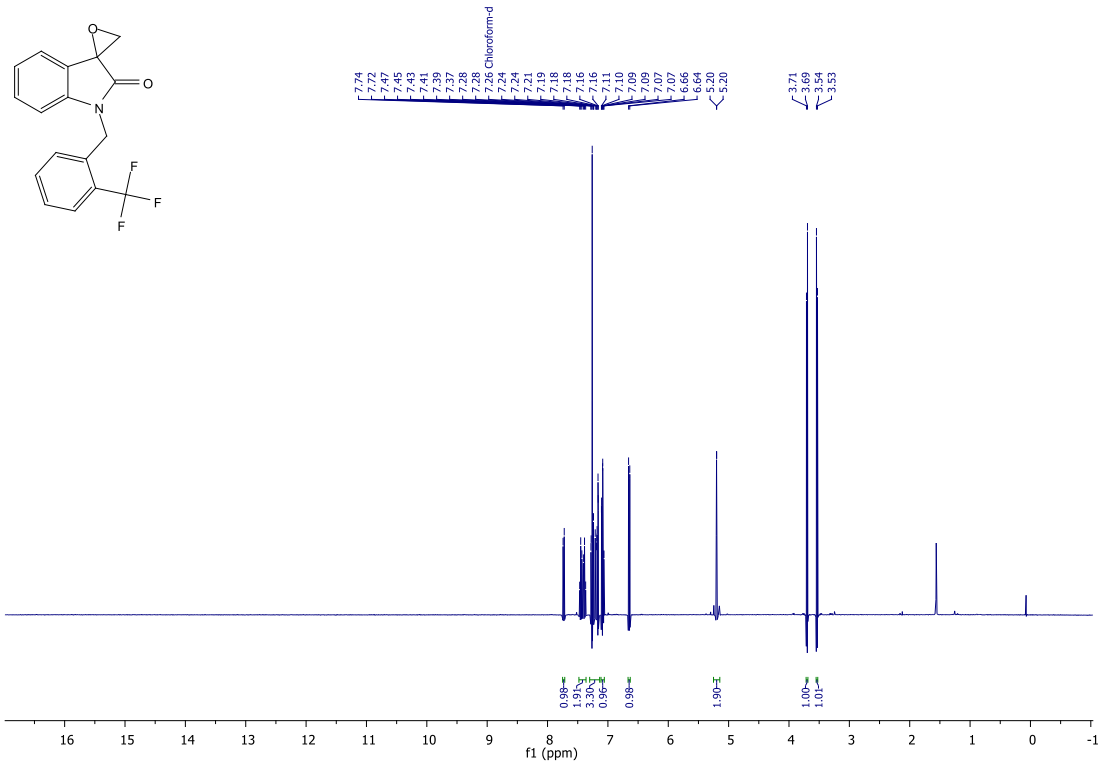


**$^{19}$F NMR** ( 376 MHz, $CDCl_3$)

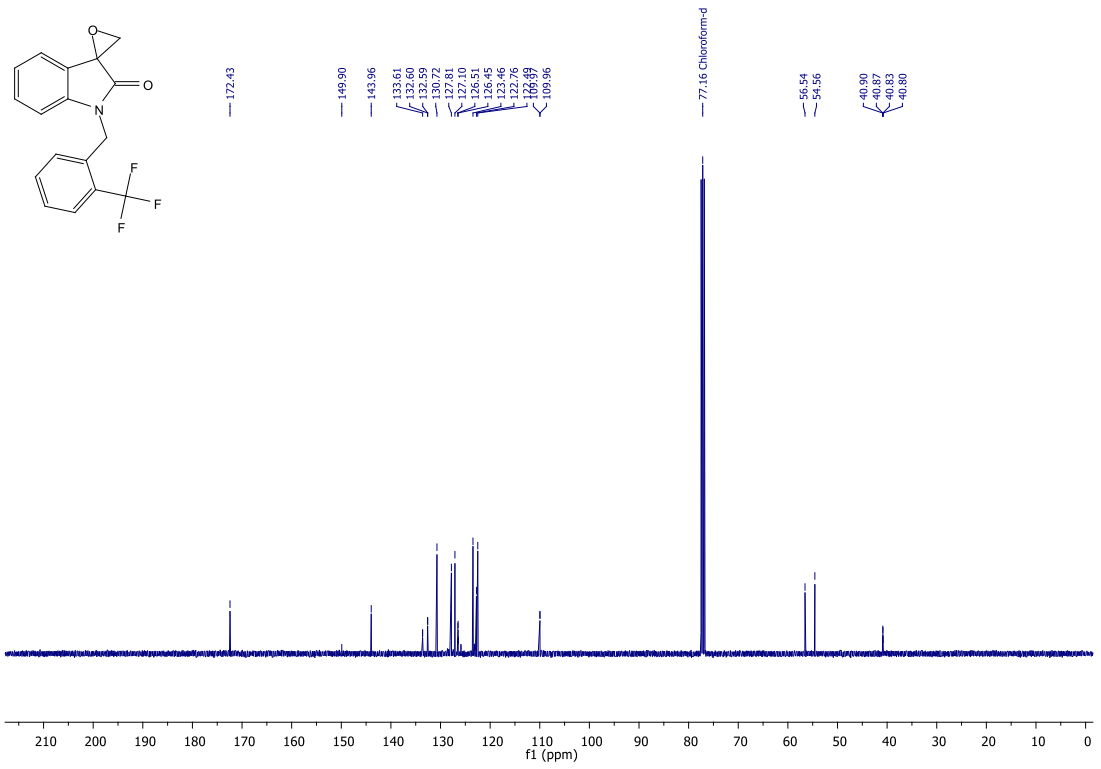


**1-[2-(Trifluoromethyl)benzyl]spiro[indole-3,2´-oxirane]-2(1*H*)-one (21)**

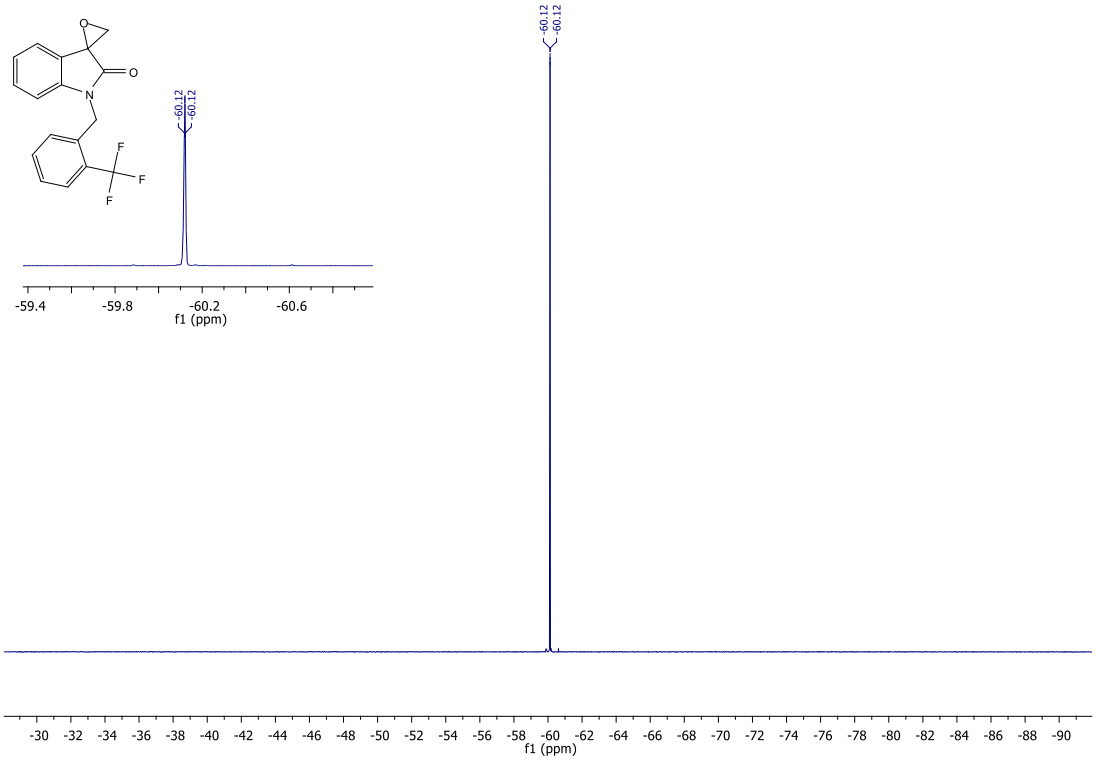
**$^{1}$H NMR** (400 MHz, $CDCl_3$)




**$^{13}$C NMR** (100 MHz, $CDCl_3$)

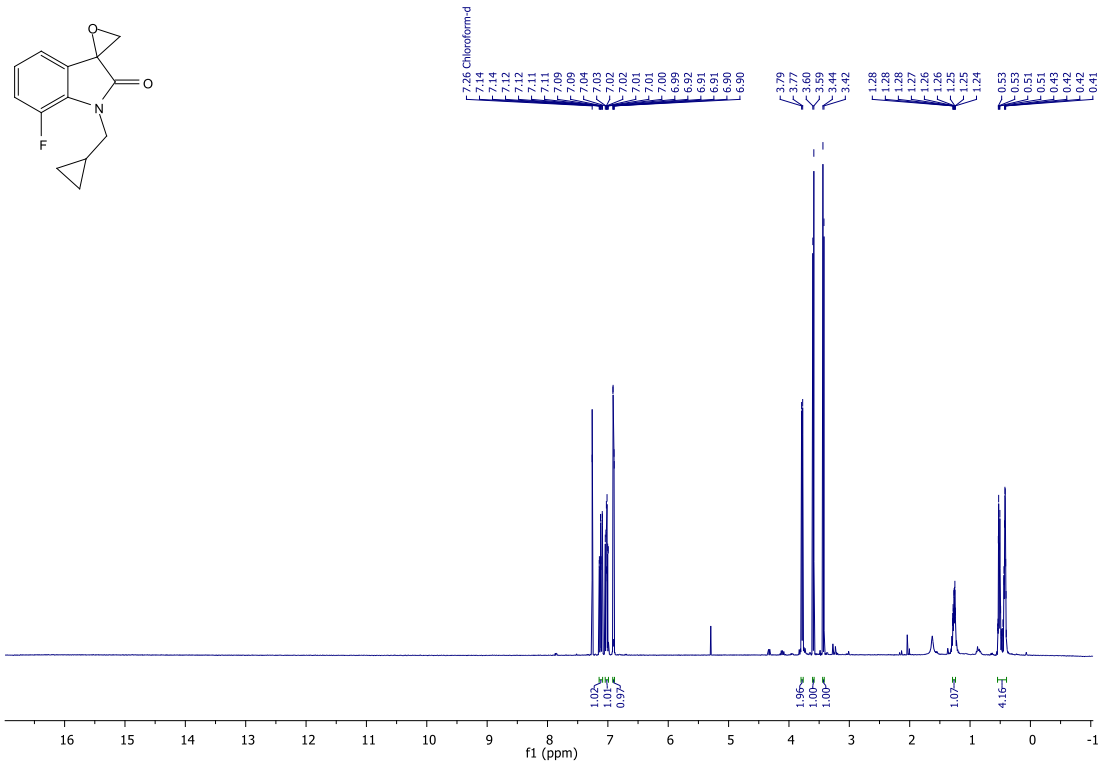


**$^{19}$F NMR** ( 376 MHz, $CDCl_3$)

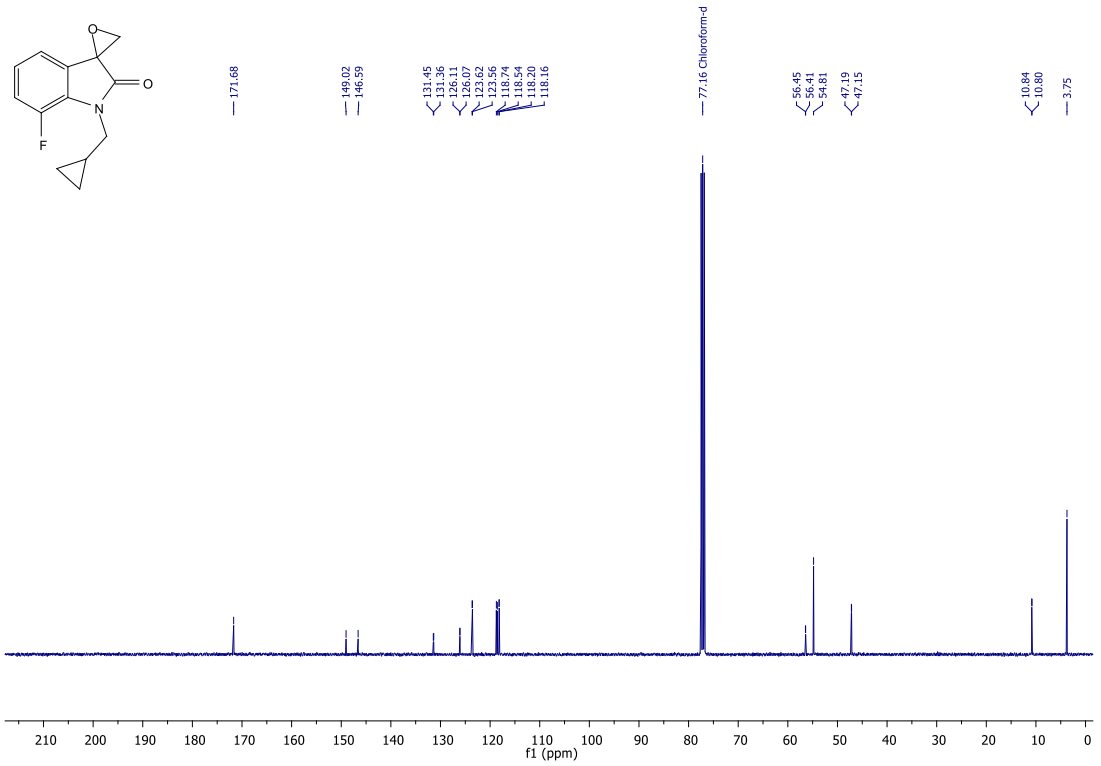


**1-(Cyclopropylmethyl)-7-fluorospiro[indole-3,2´-oxirane]-2(1*H*)-one (22)**

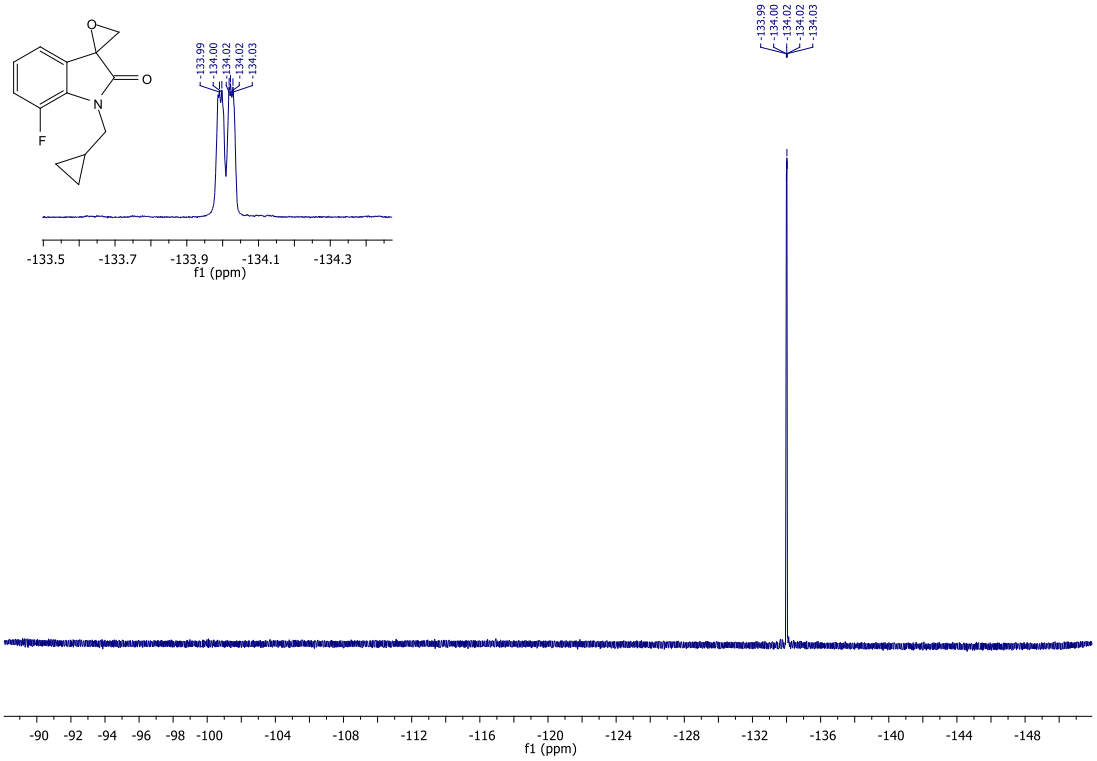
$^{1}$**H NMR** (400 MHz, $CDCl_3$)




$^{13}$**C NMR** (100 MHz, $CDCl_3$)

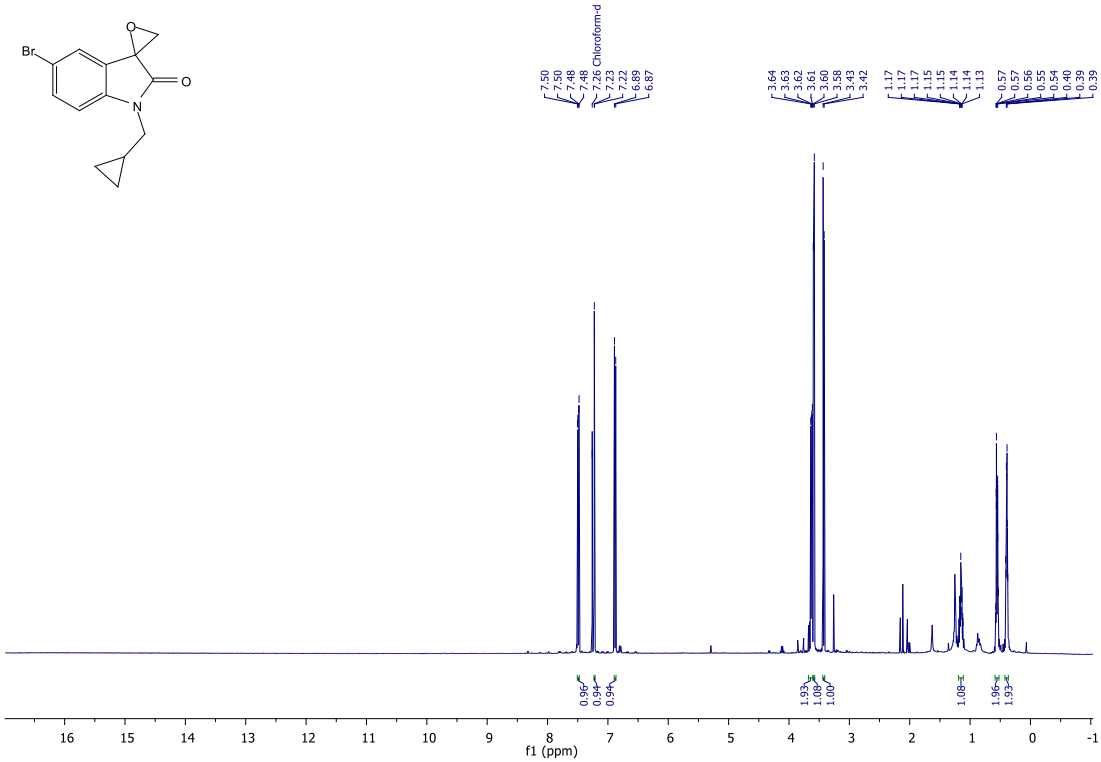


**$^{19}$F NMR** ( 376 MHz, $CDCl_3$)

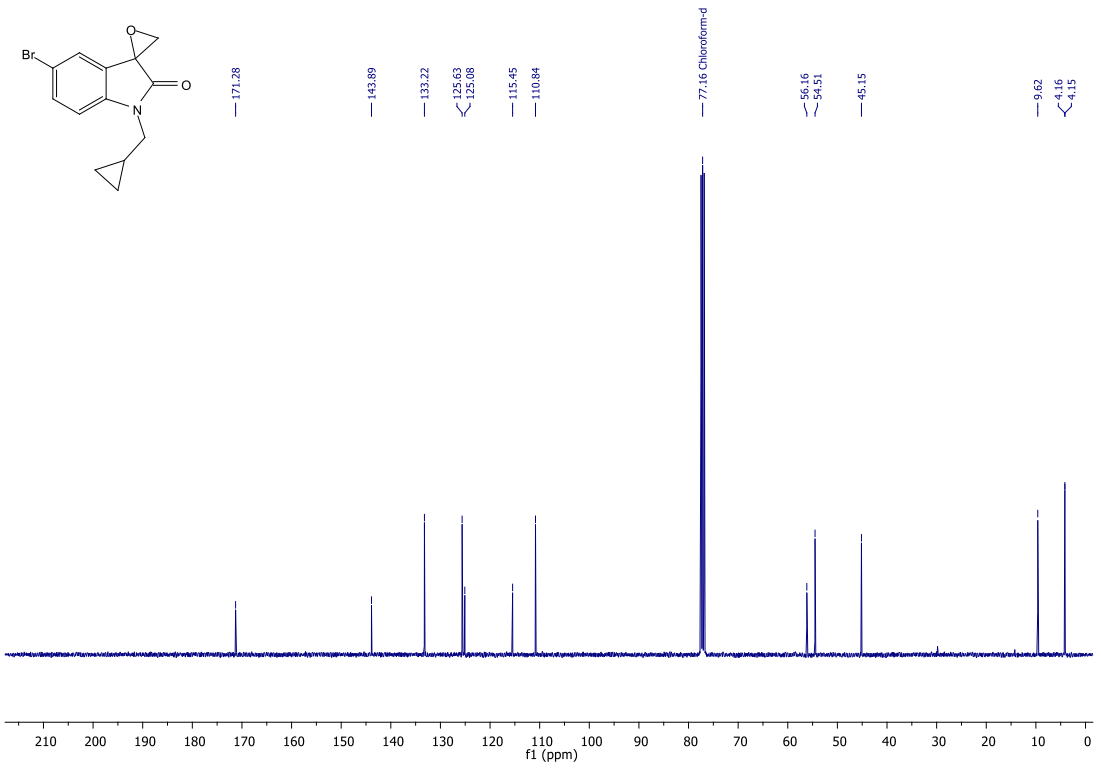


**5-Bromo-1-(cyclopropylmethyl)spiro[indole-3,2´-oxirane]-2(1*H*)-one (23)**

**$^{1}$H NMR** (400 MHz, $CDCl_3$)

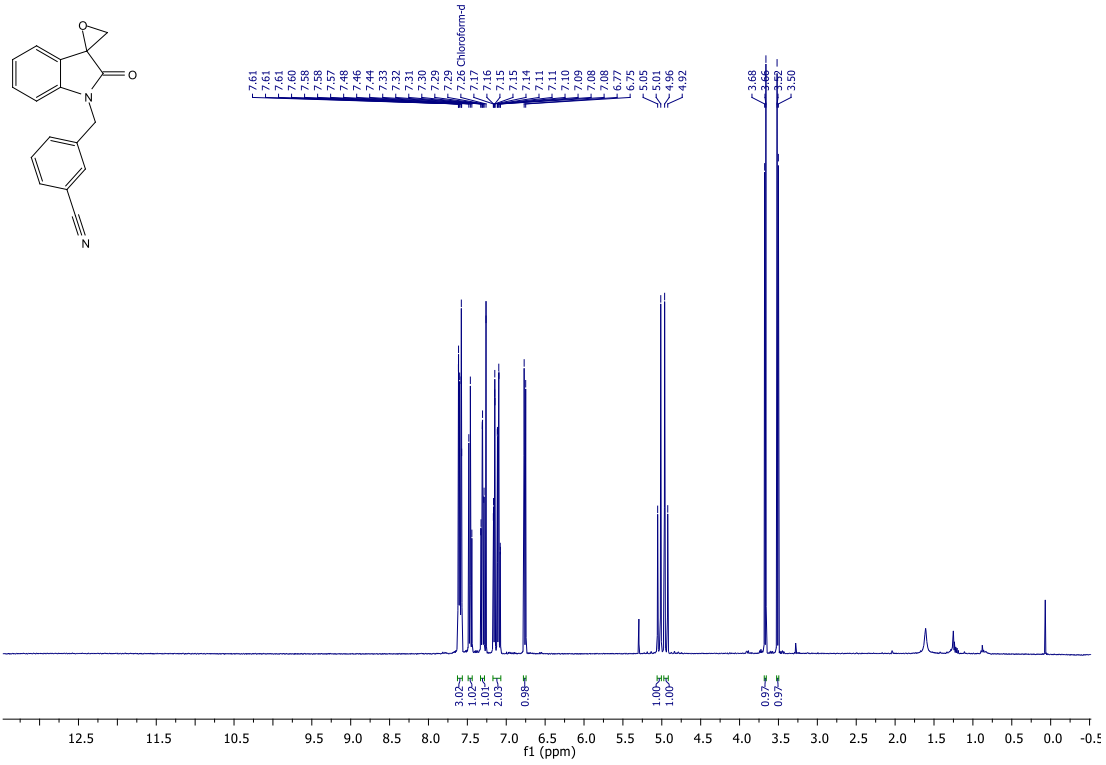



**$^{13}$C NMR** (100 MHz, $CDCl_3$)

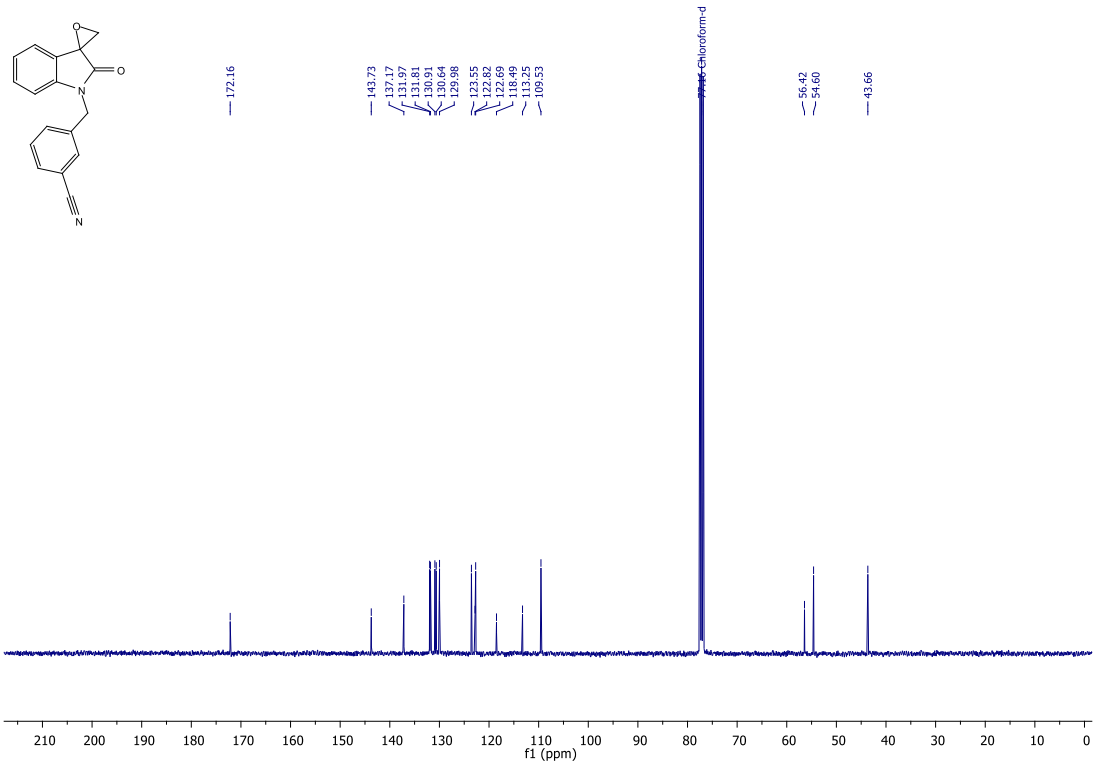


**3-[(2-Oxospiro[indole-3,2´-oxirane])-1(2*H*)-yl) methyl] benzonitrile (24)**

**$^{1}$H NMR** (400 MHz, $CDCl_3$)

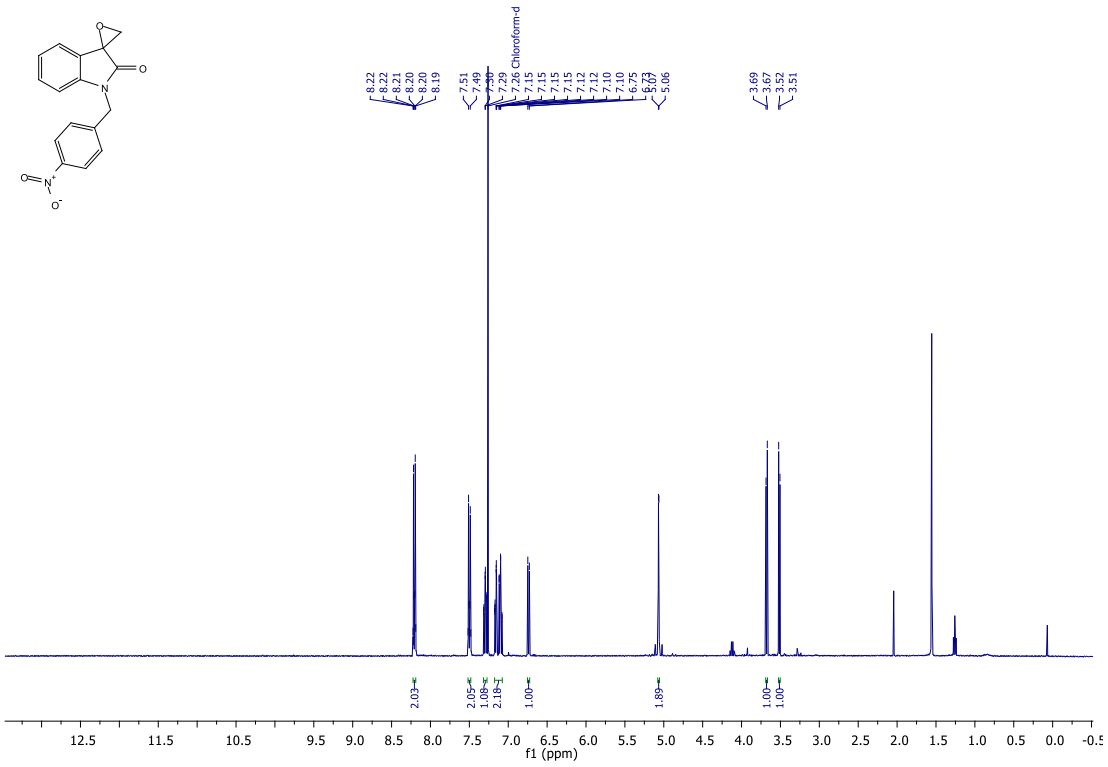



**$^{13}$C NMR** (100 MHz, $CDCl_3$)

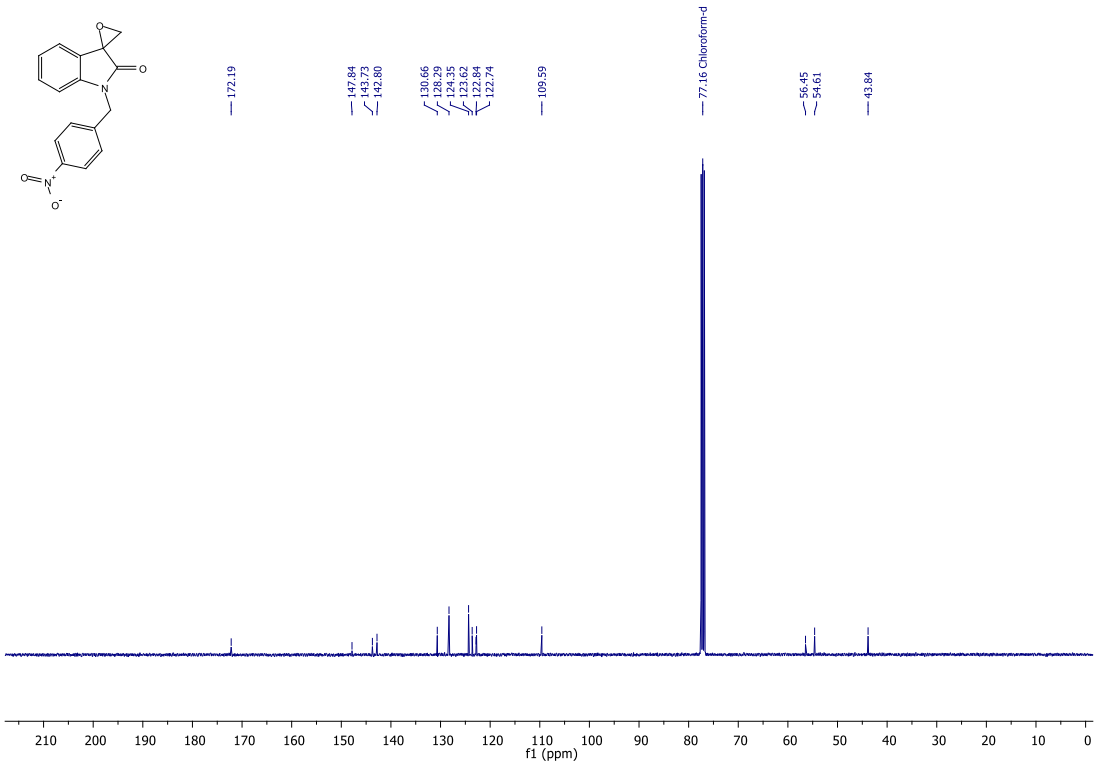


## 1-(4-Nitrobenzyl)spiro[indole-3,2´-oxirane]-2(1*H*)-one (26)

**$^{1}$H NMR** (400 MHz, $CDCl_3$)

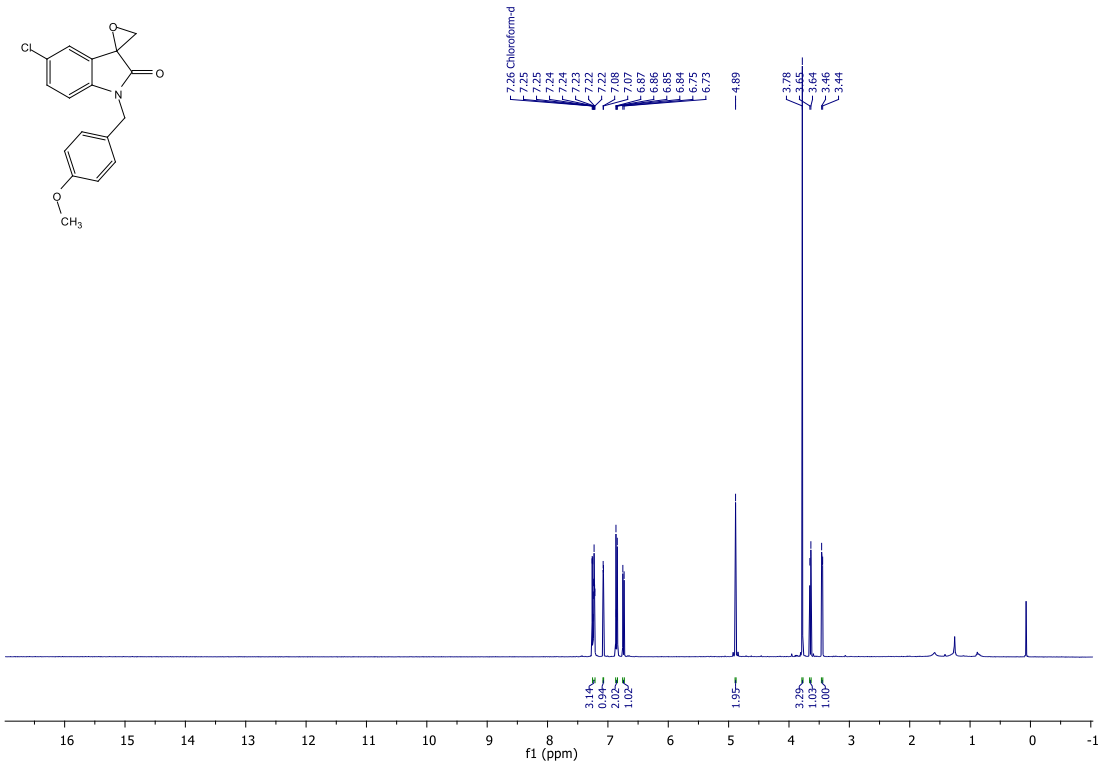



**$^{13}$C NMR** (100 MHz, $CDCl_3$)

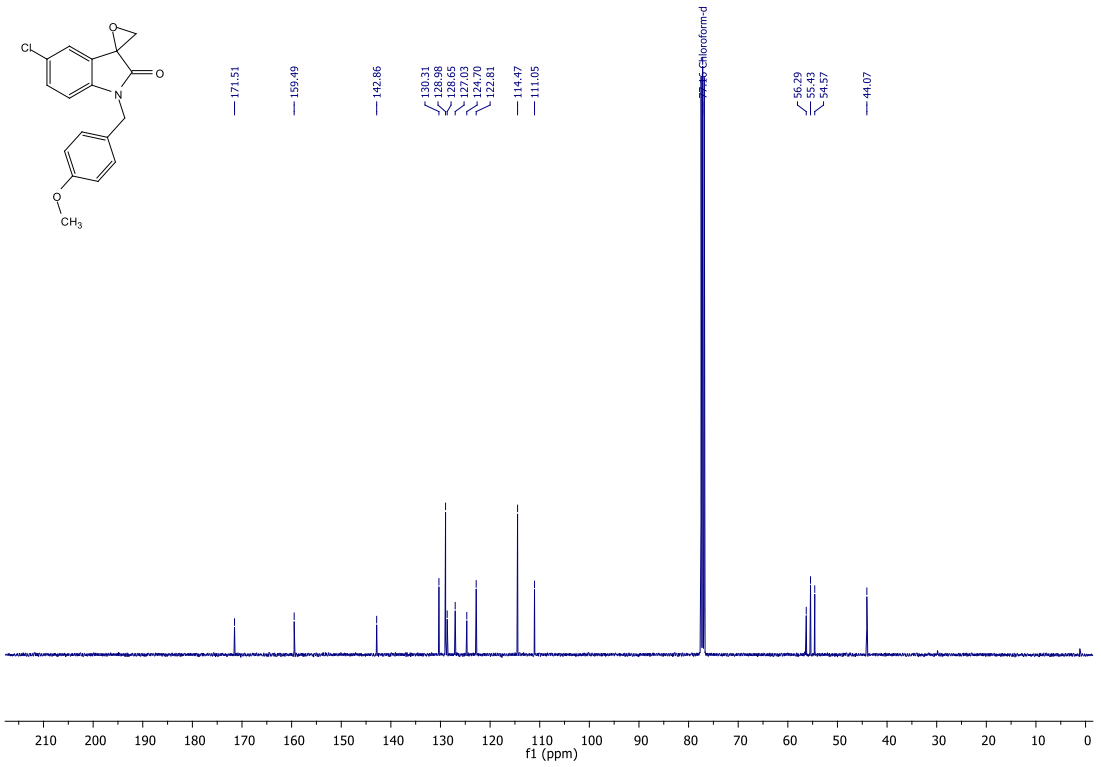


**5-Chloro-1-(4-methoxybenzyl)spiro[indol-3,2´-oxirane]-2(1*H*)-one (27)**

**$^{1}$H NMR** (400 MHz, $CDCl_3$)

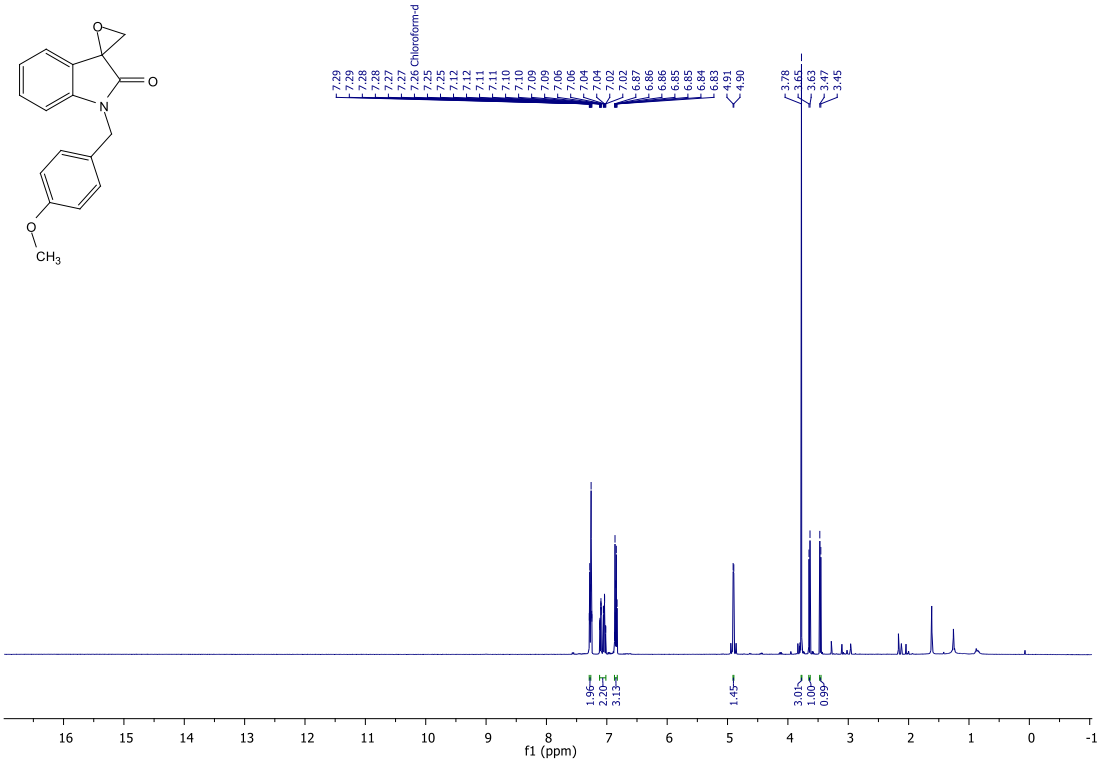



**$^{13}$C NMR** (100 MHz, $CDCl_3$)

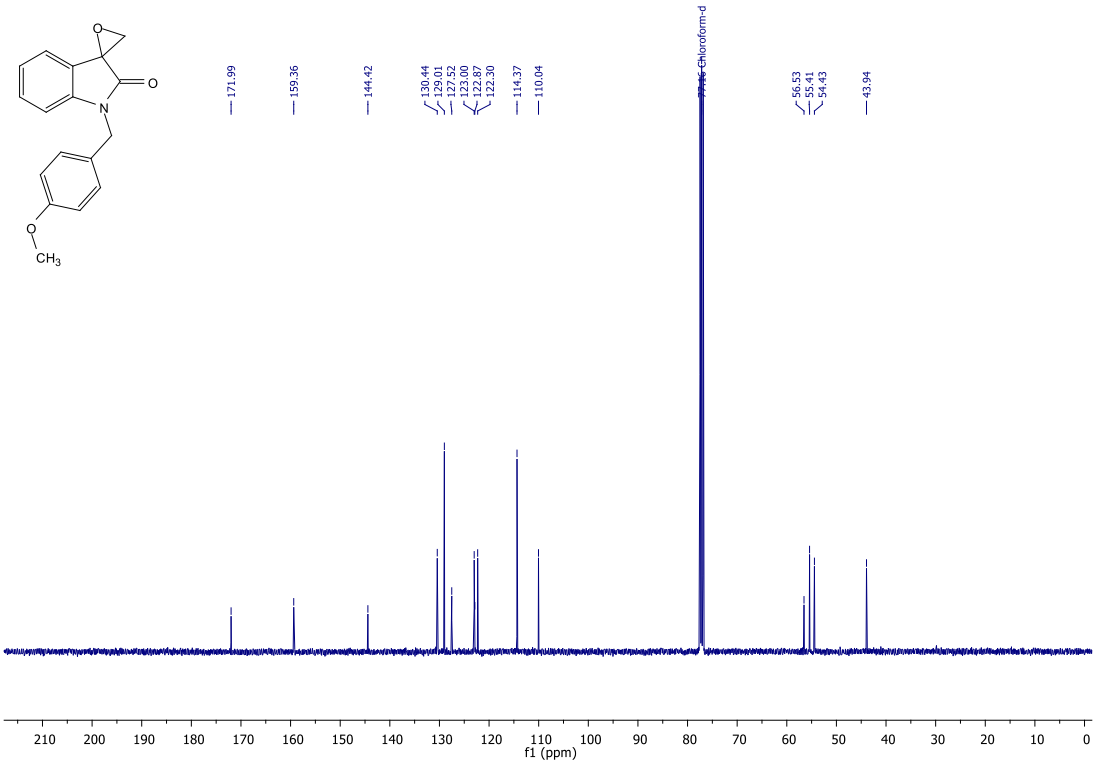


## 1-(4-Methoxybenzyl)spiro[indole-3,2´-oxirane]-2(1*H*)-one (28)

**$^{1}$H NMR** (400 MHz, $CDCl_3$)

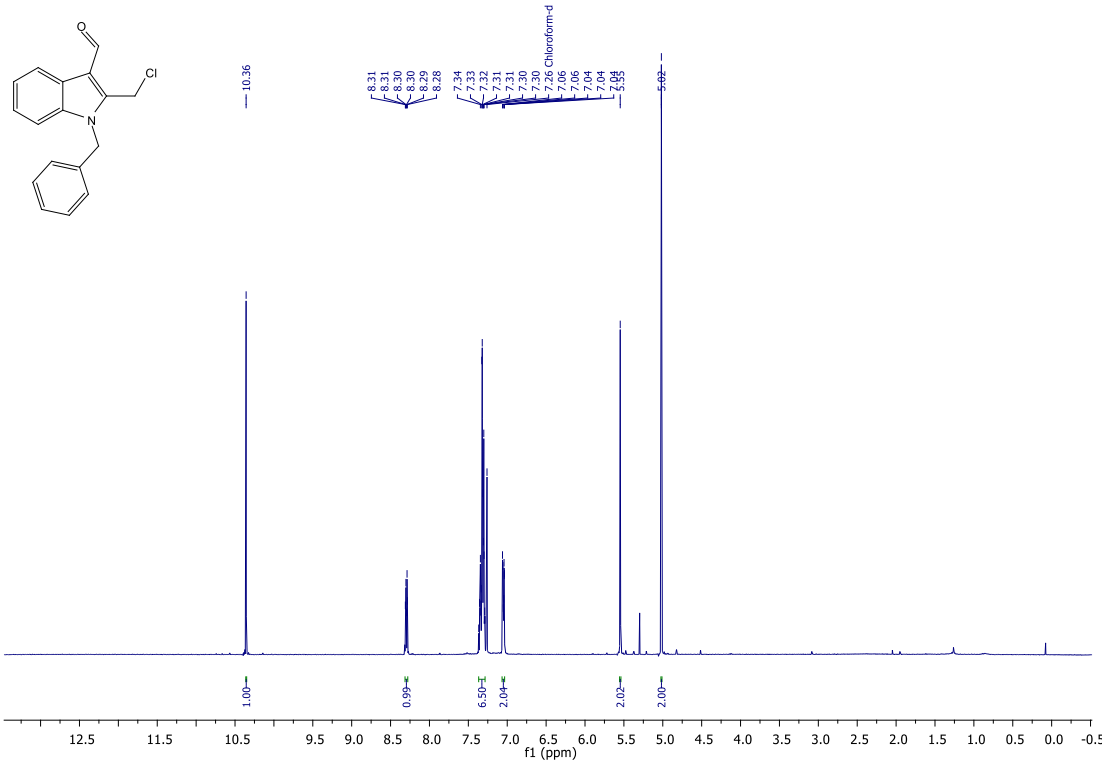



**$^{13}$C NMR** (100 MHz, $CDCl_3$)

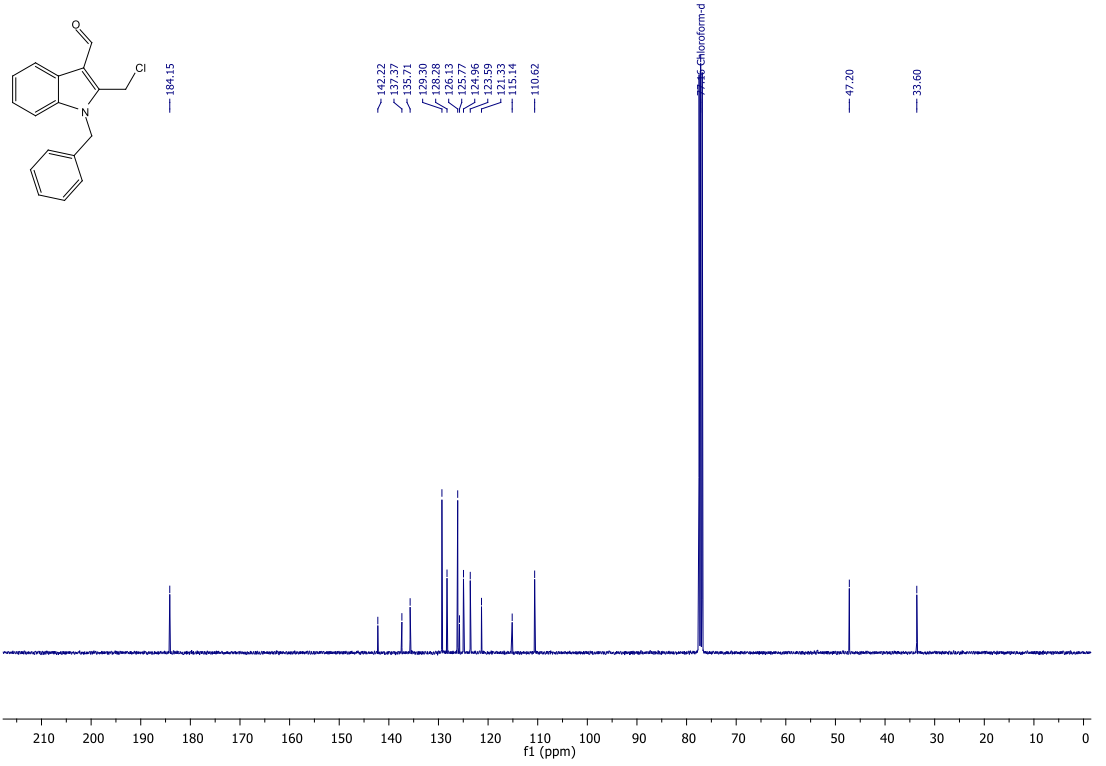


## 1-Benzyl-2-(chloromethyl)-1H-indole-3-carbaldehyde (32)

**$^{1}$H NMR** (400 MHz, $CDCl_3$)

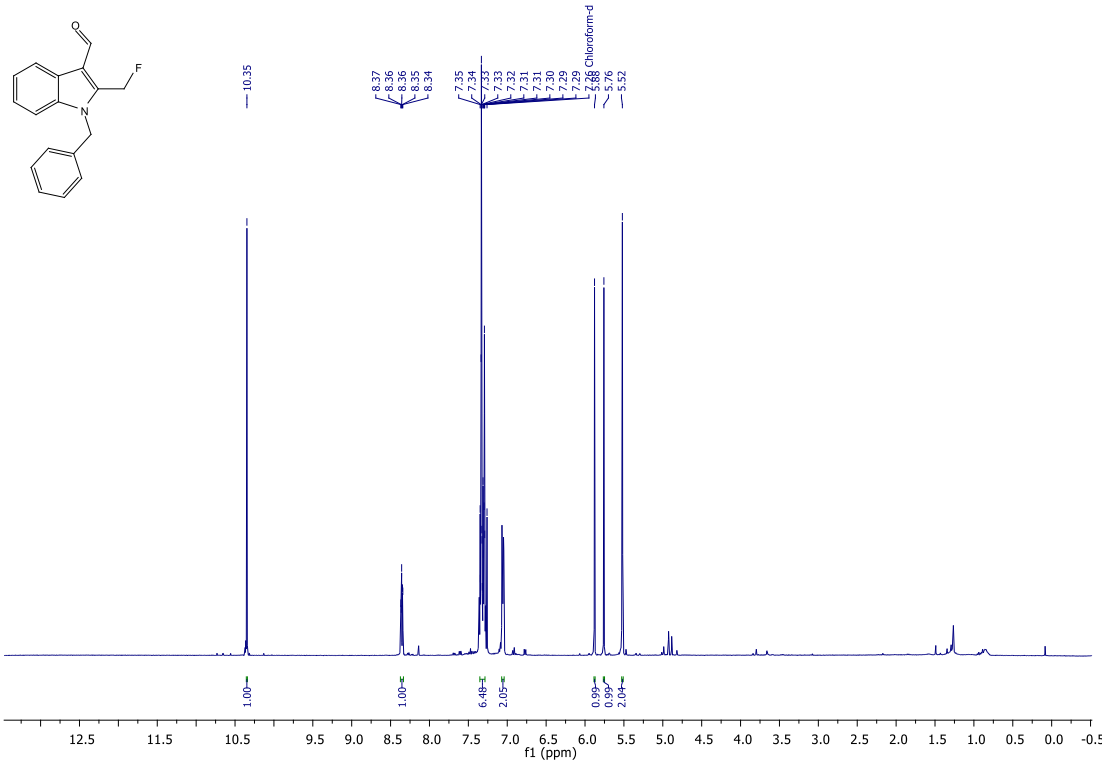



**$^{13}$C NMR** (100 MHz, $CDCl_3$)

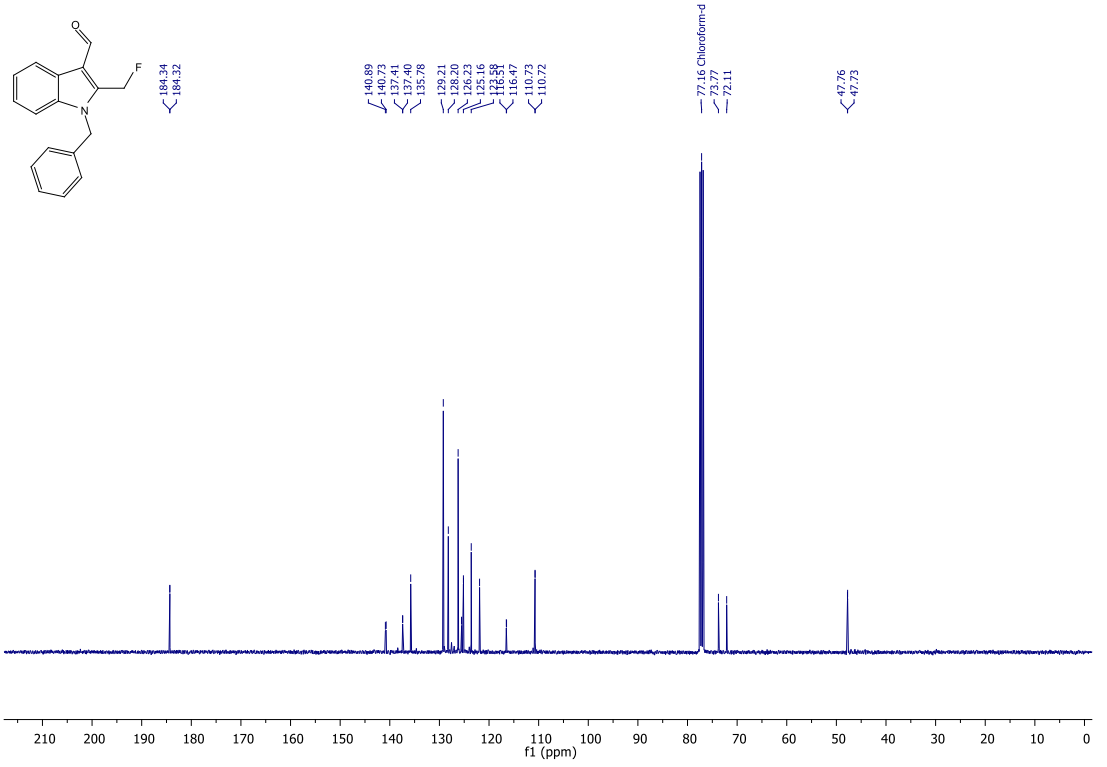


## 1-Benzyl-2-(fluoromethyl)-1H-indole-3-carbaldehyde (33)

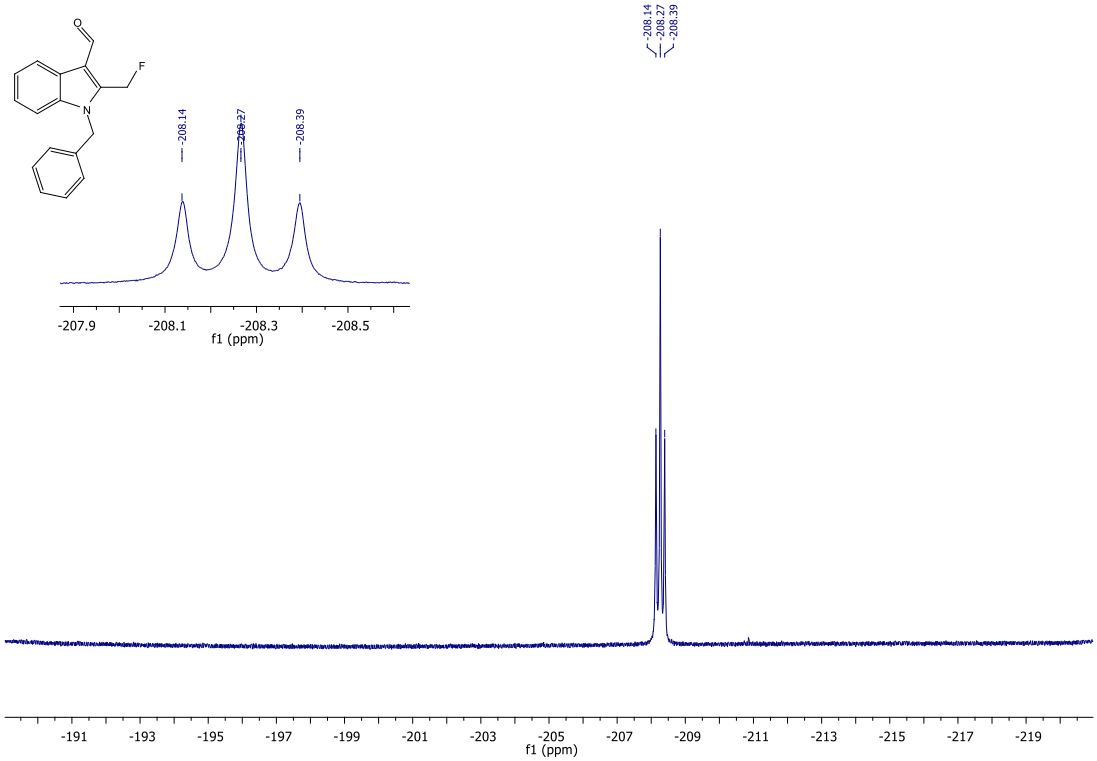
**$^{1}$H NMR** (400 MHz, $CDCl_3$)




**$^{13}$C NMR** (100 MHz, $CDCl_3$)

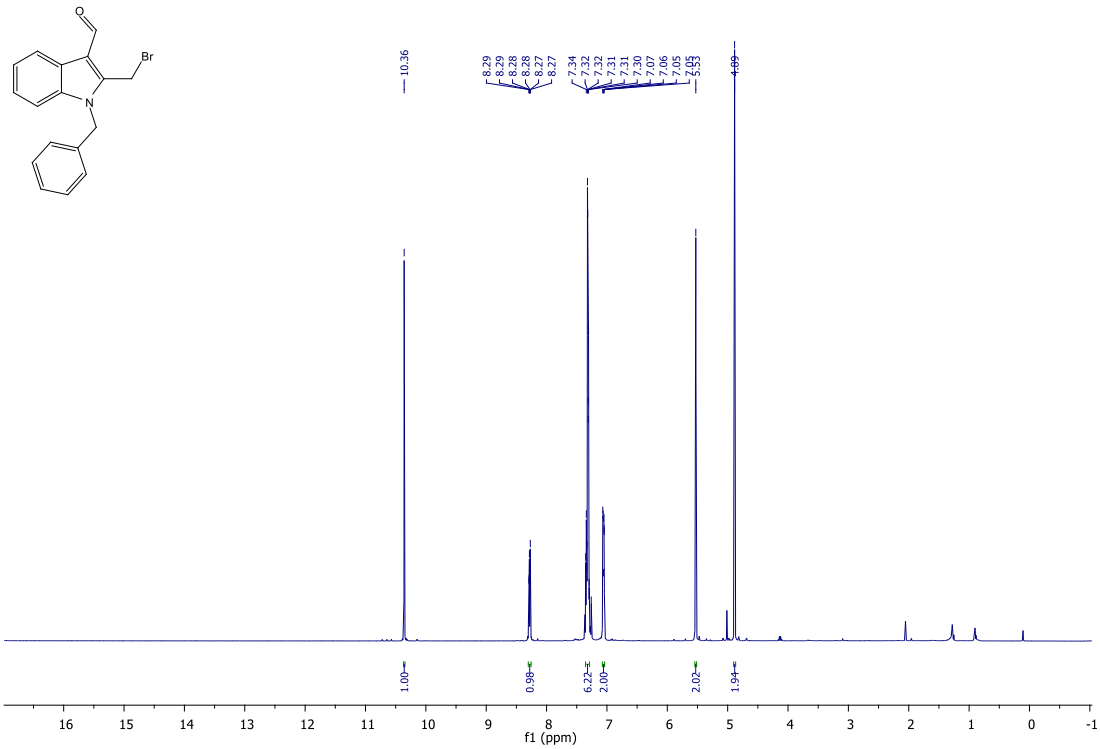


**$^{19}$F NMR** ( 376 MHz, $CDCl_3$)

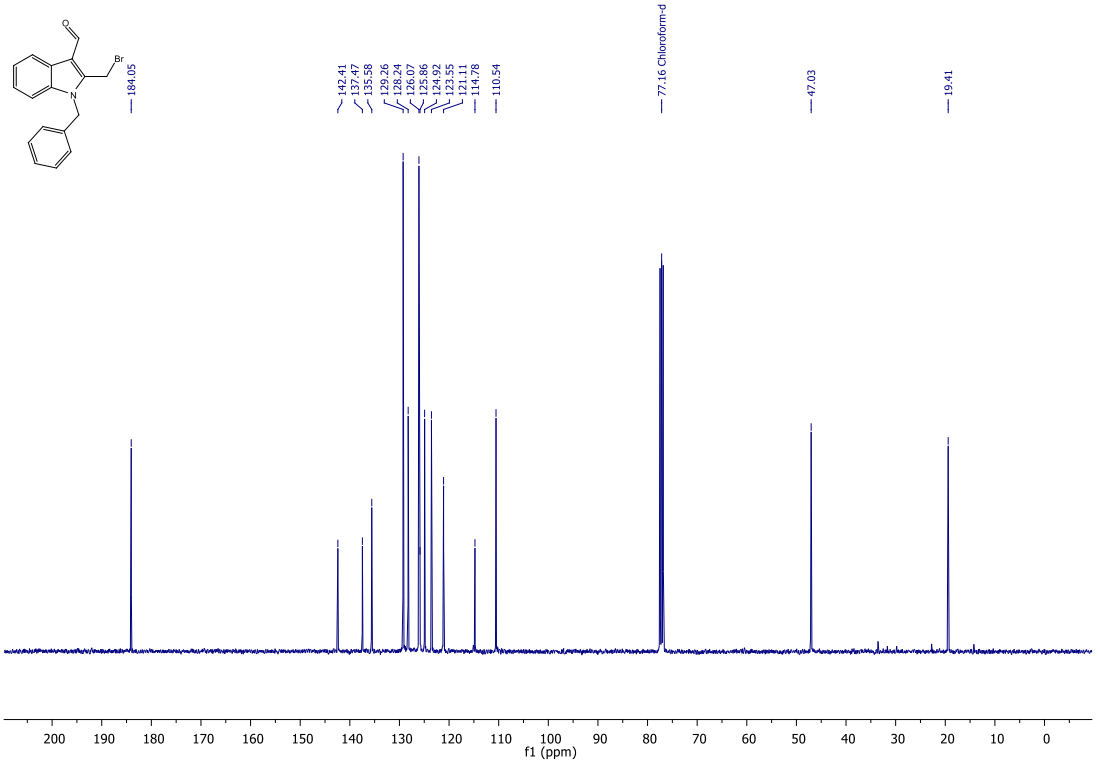


## 1-Benzyl-2-(bromomethyl)-1H-indole-3-carbaldehyde (34)

**$^{1}$H NMR** (400 MHz, $CDCl_3$)

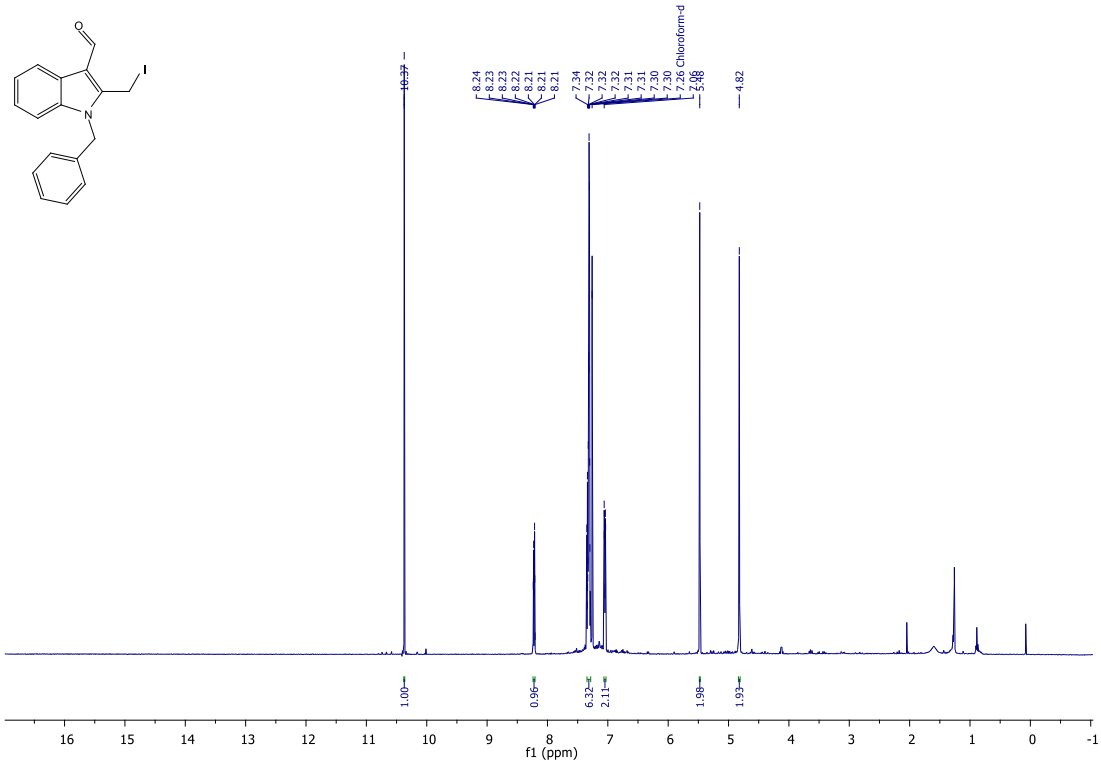



**$^{13}$C NMR** (100 MHz, $CDCl_3$)

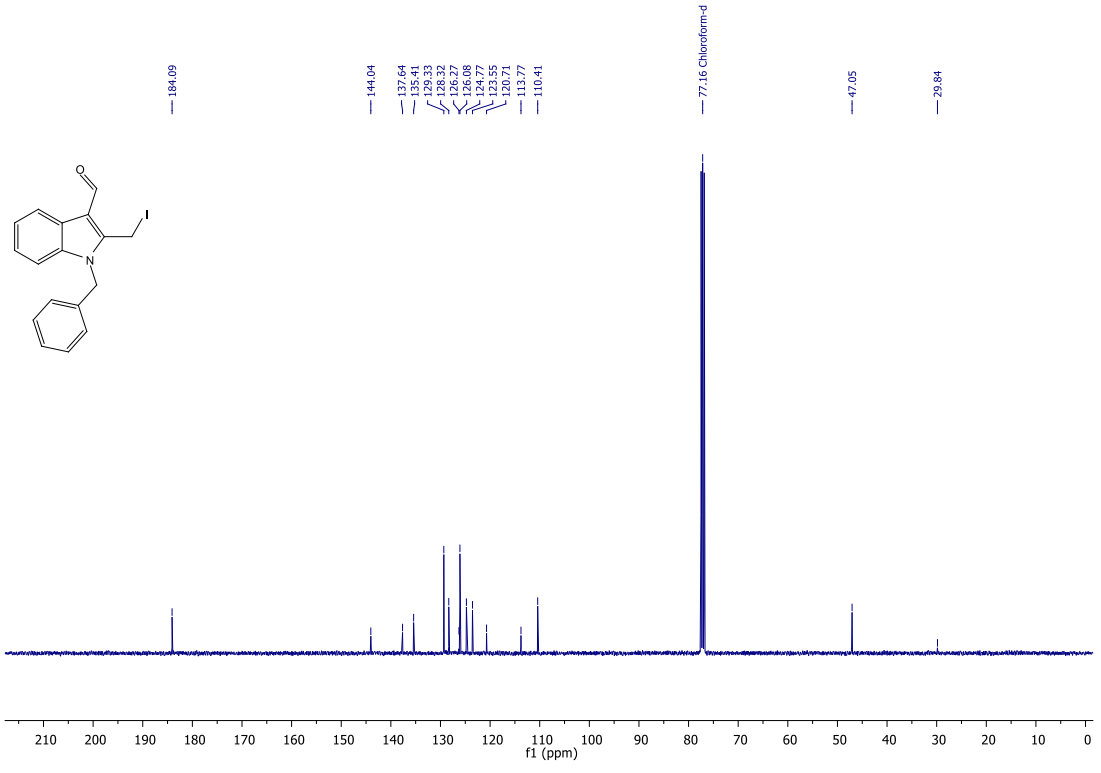


## 1-Benzyl-2-(bromomethyl)-1H-indole-3-carbaldehyde (35)

**$^{1}$H NMR** (400 MHz, $CDCl_3$)

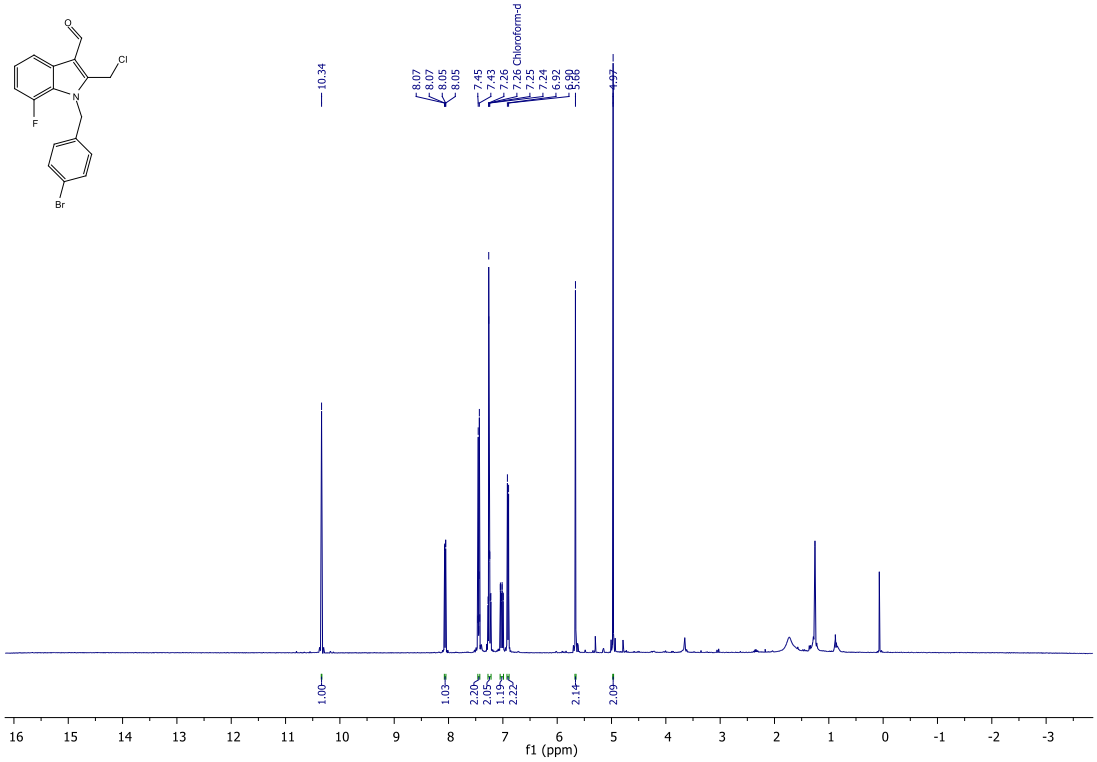



**$^{13}$C NMR** (100 MHz, $CDCl_3$)

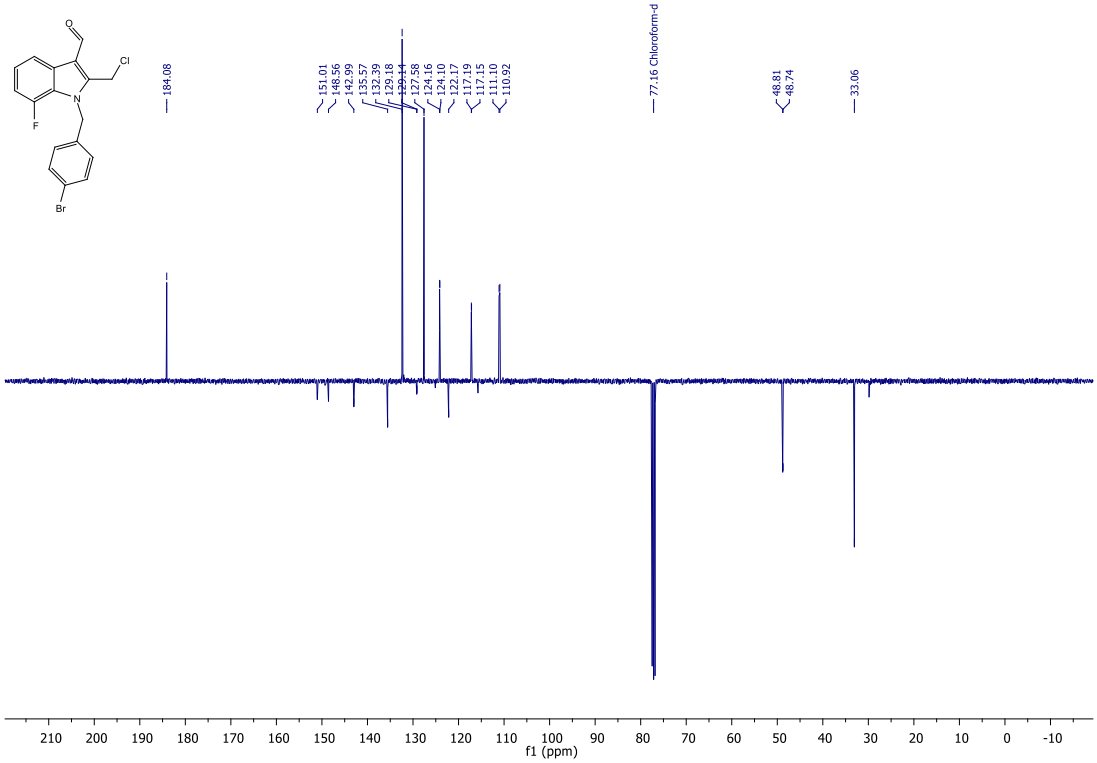


## 7-Fluoro-2-(chloromethyl)-1-(4-bromobenzyl)-1*H*-indole-3-carbaldehyde (36)

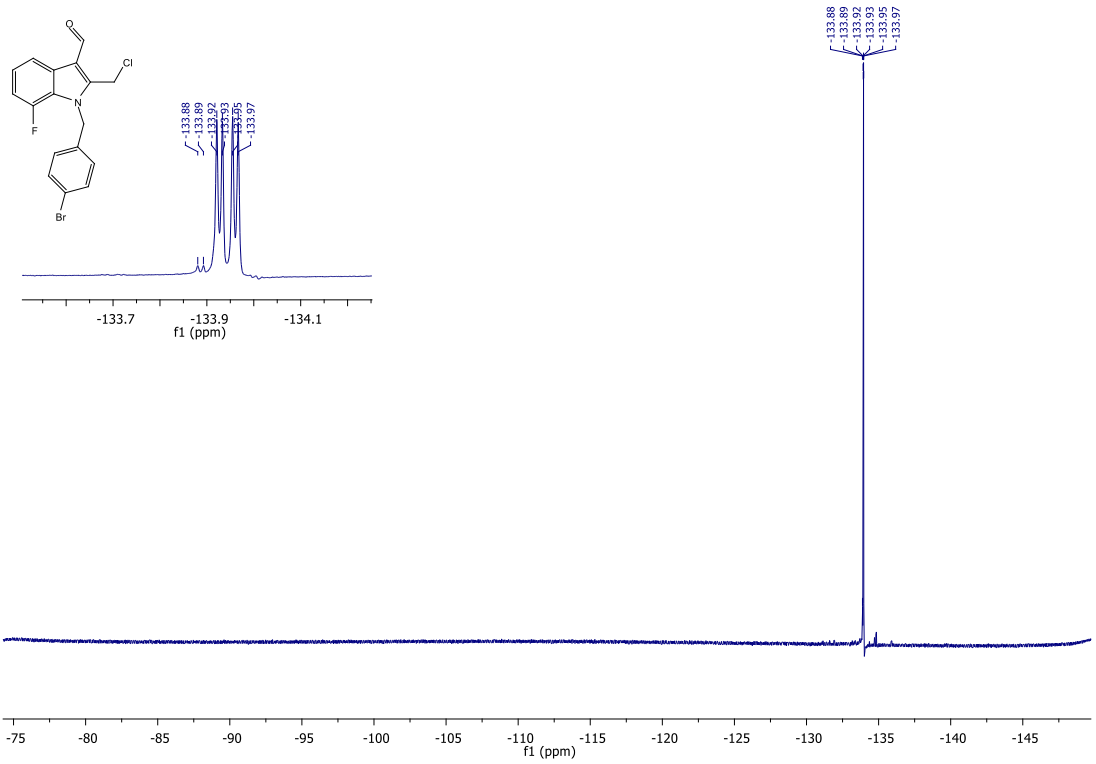
**$^{1}$H NMR** (400 MHz, $CDCl_3$)




**$^{13}$C NMR** (100 MHz, $CDCl_3$)

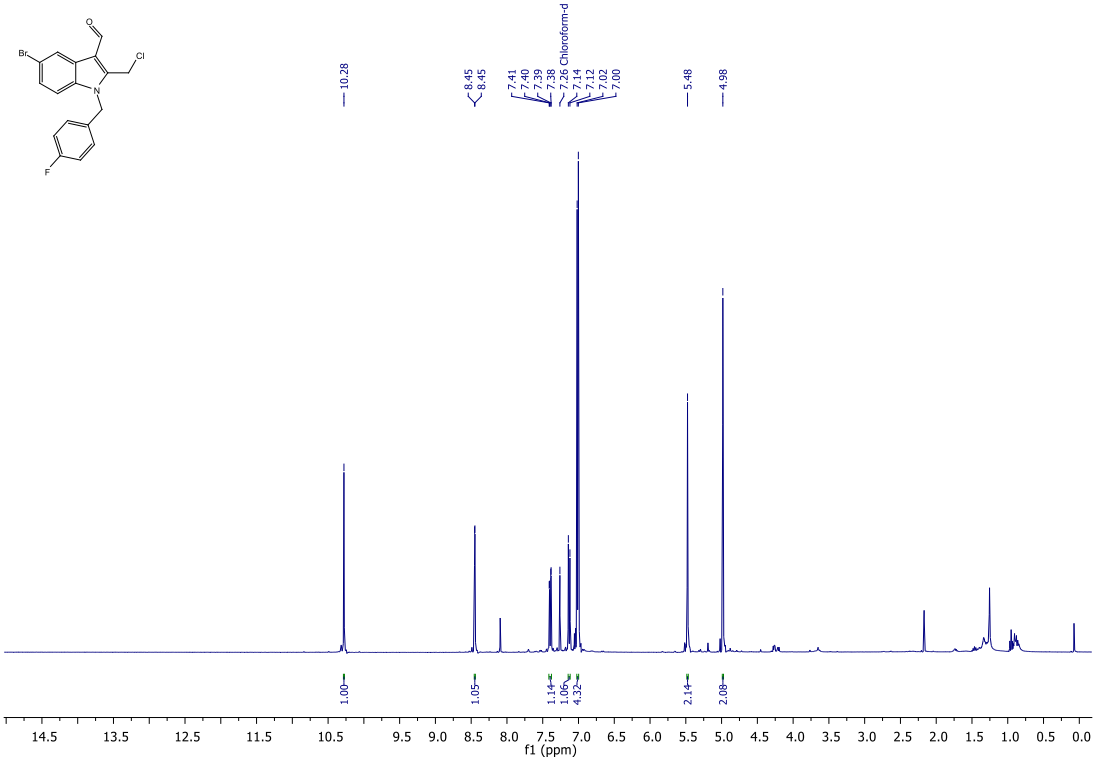


**$^{19}$F NMR** ( 376 MHz, $CDCl_3$)

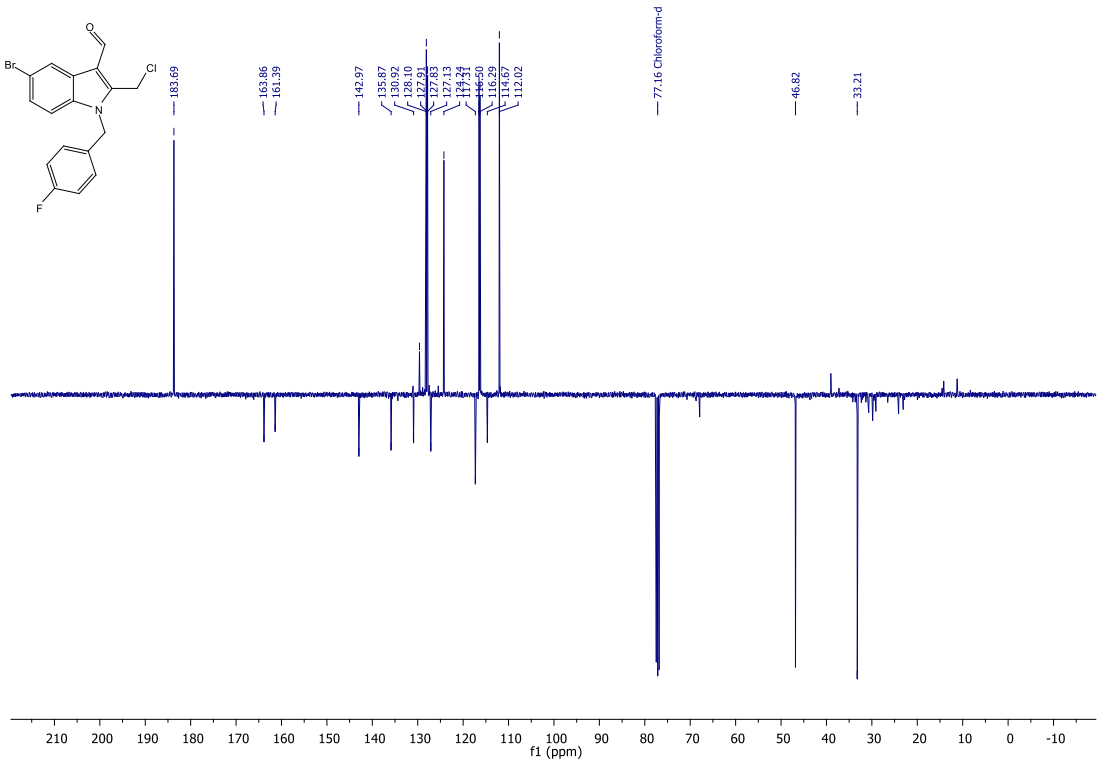


## 2-(Chloromethyl)-1-(4-fluorobenzyl)-1*H*-indole-3-carbaldehyde (37)

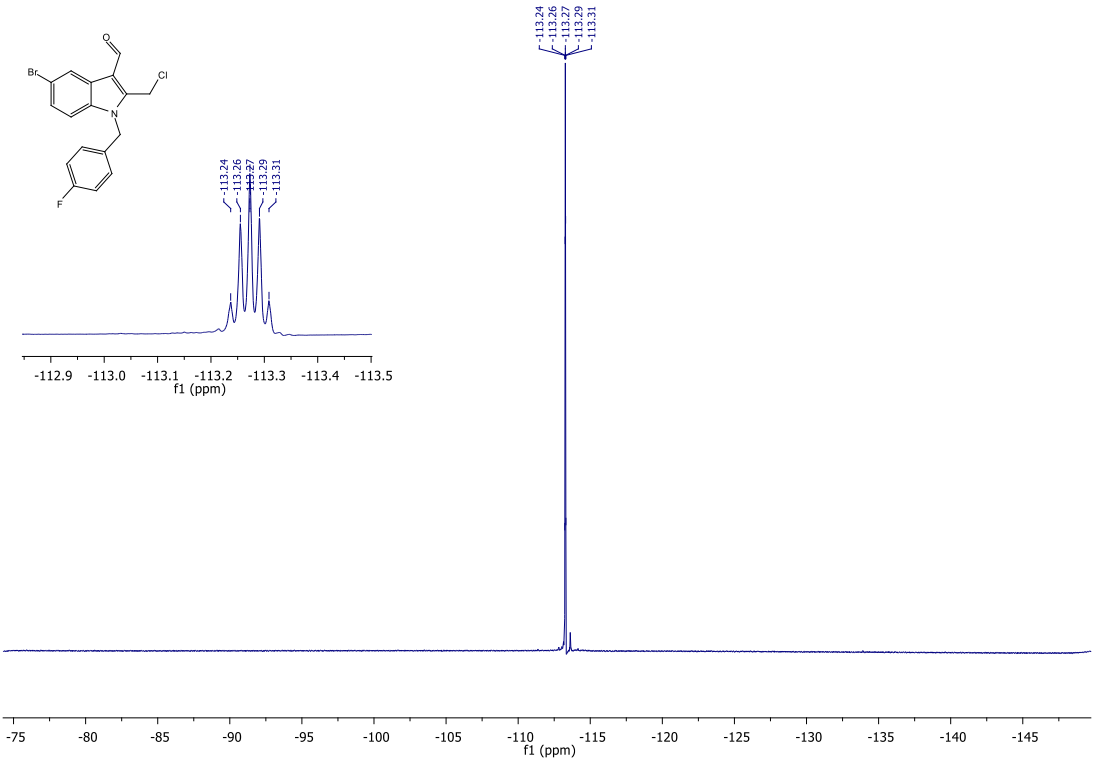
**$^{1}$H NMR** (400 MHz, $CDCl_3$)




**$^{13}$C NMR** (100 MHz, $CDCl_3$)

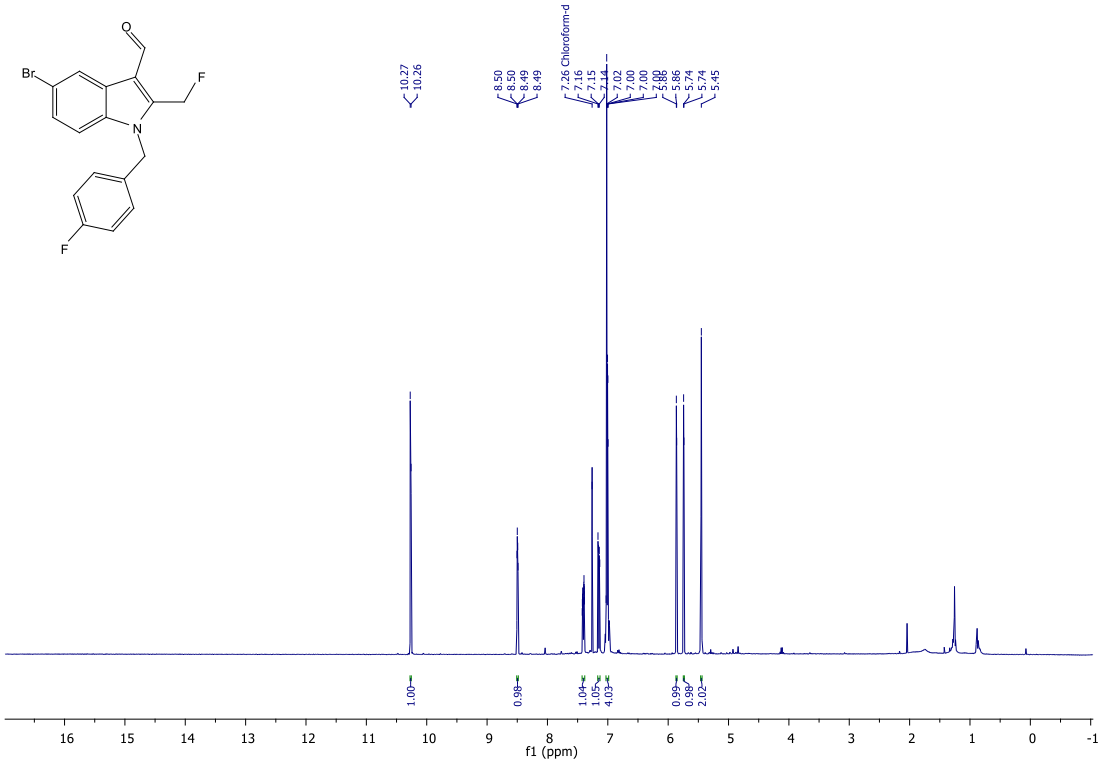


**$^{19}$F NMR** ( 376 MHz, $CDCl_3$)

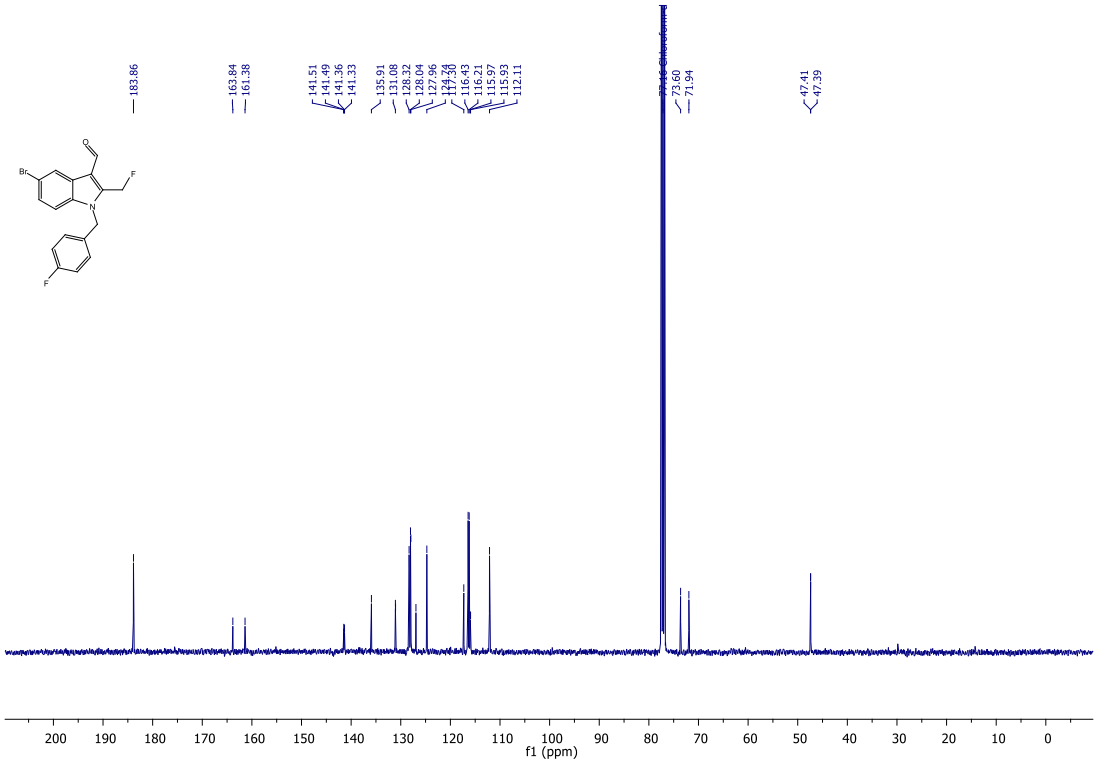


**5-Bromo-1-(4-fluorobenzyl)-2-(fluoromethyl)-1*H*-indol-3-carbaldehyde (38)**

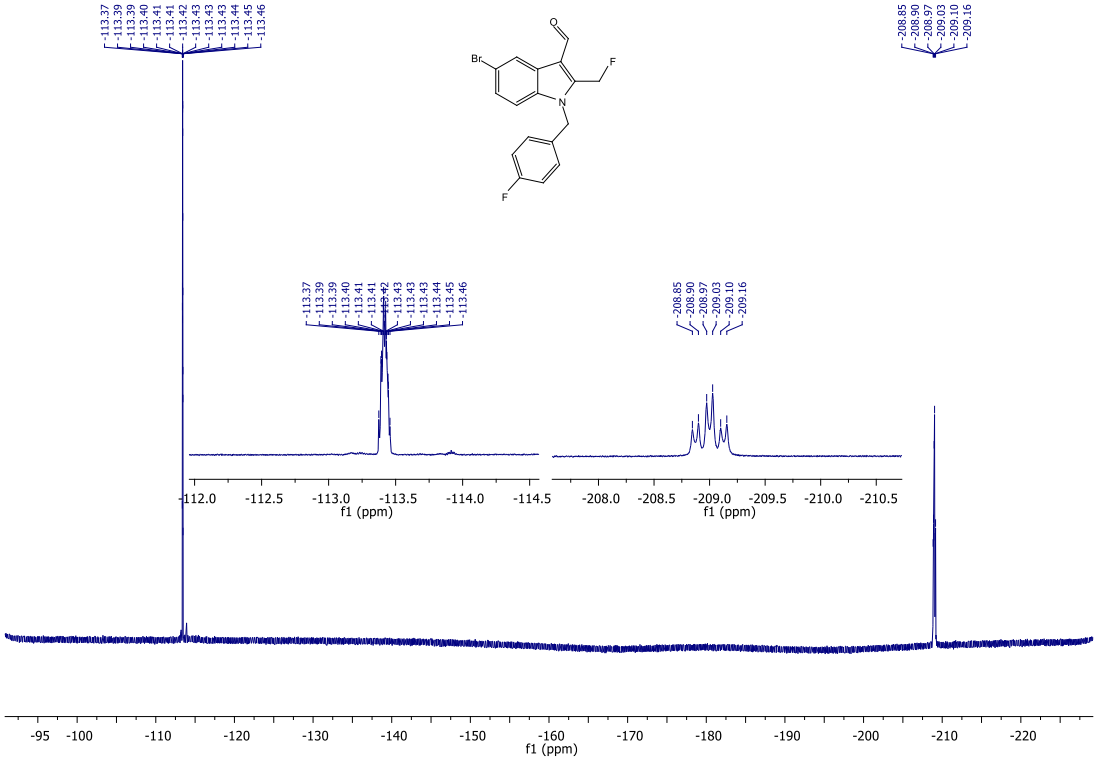
$^{1}$**H NMR** (400 MHz, $CDCl_3$)




$^{13}$**C NMR** (100 MHz, $CDCl_3$)

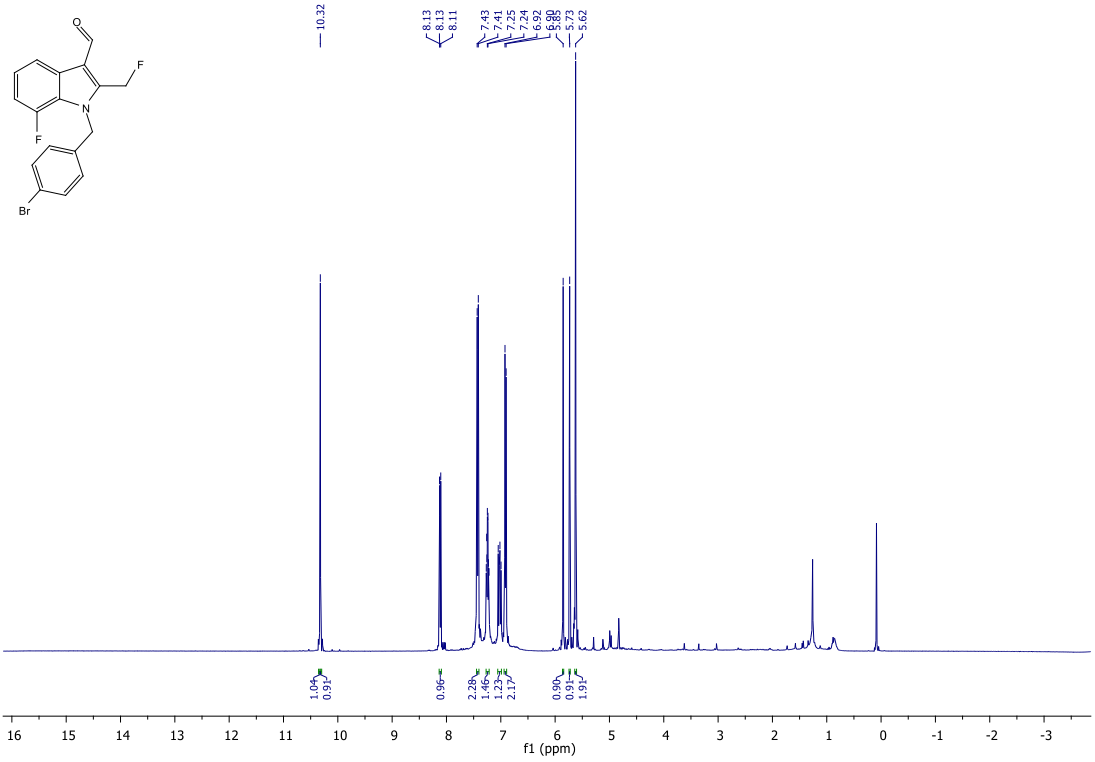


**$^{19}$F NMR** ( 376 MHz, $CDCl_3$)

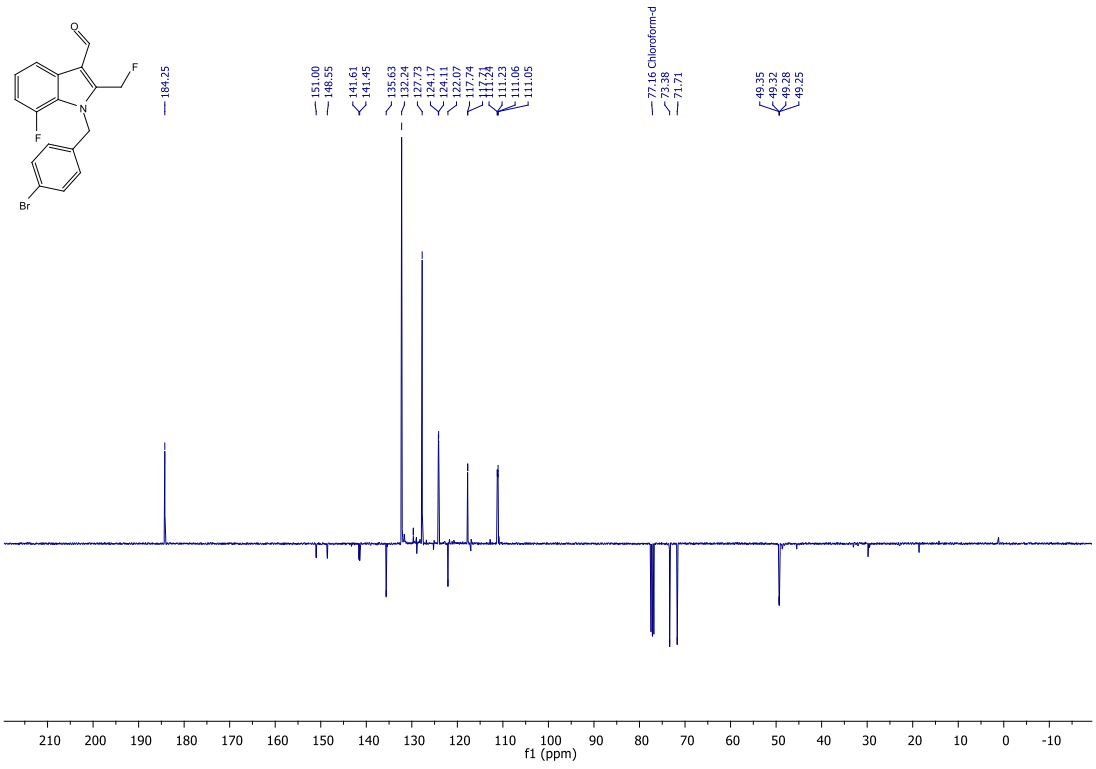


**7-Fluoro-1-(4-bromoobenzyl)-2-(fluoromethyl)-1*H*-indol-3-carbaldehyde (39)**

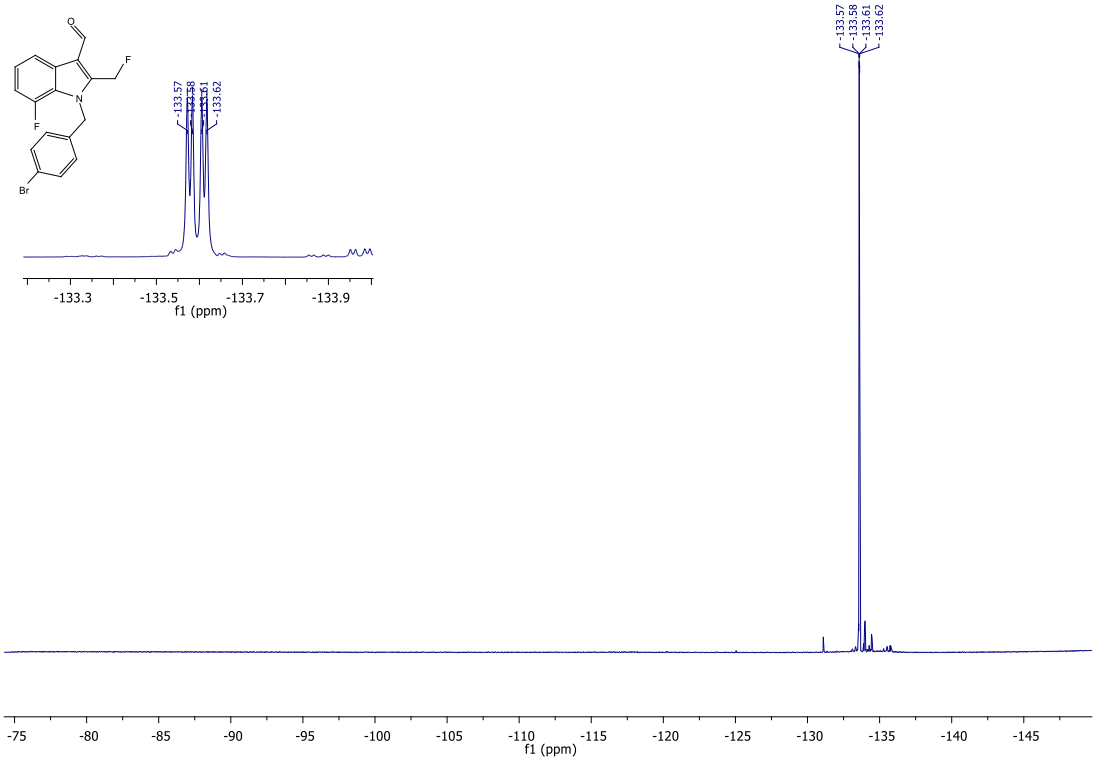
**$^{1}$H NMR** (400 MHz, $CDCl_3$)

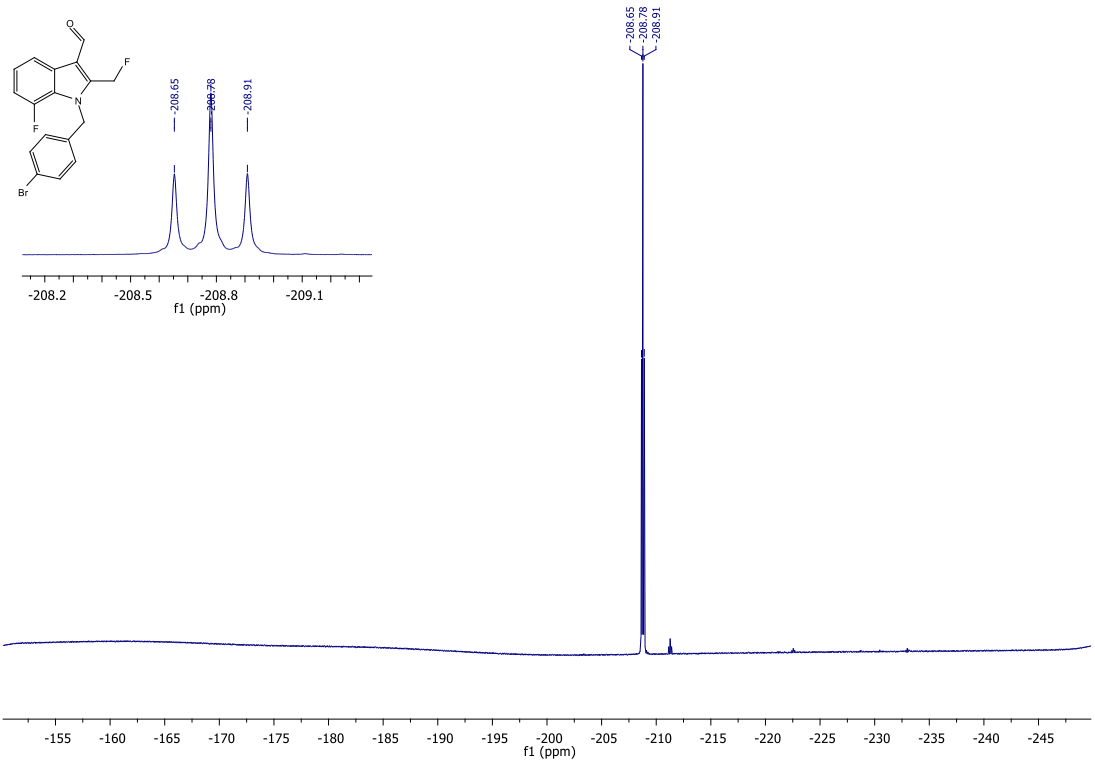



**$^{13}$C NMR** (100 MHz, $CDCl_3$)



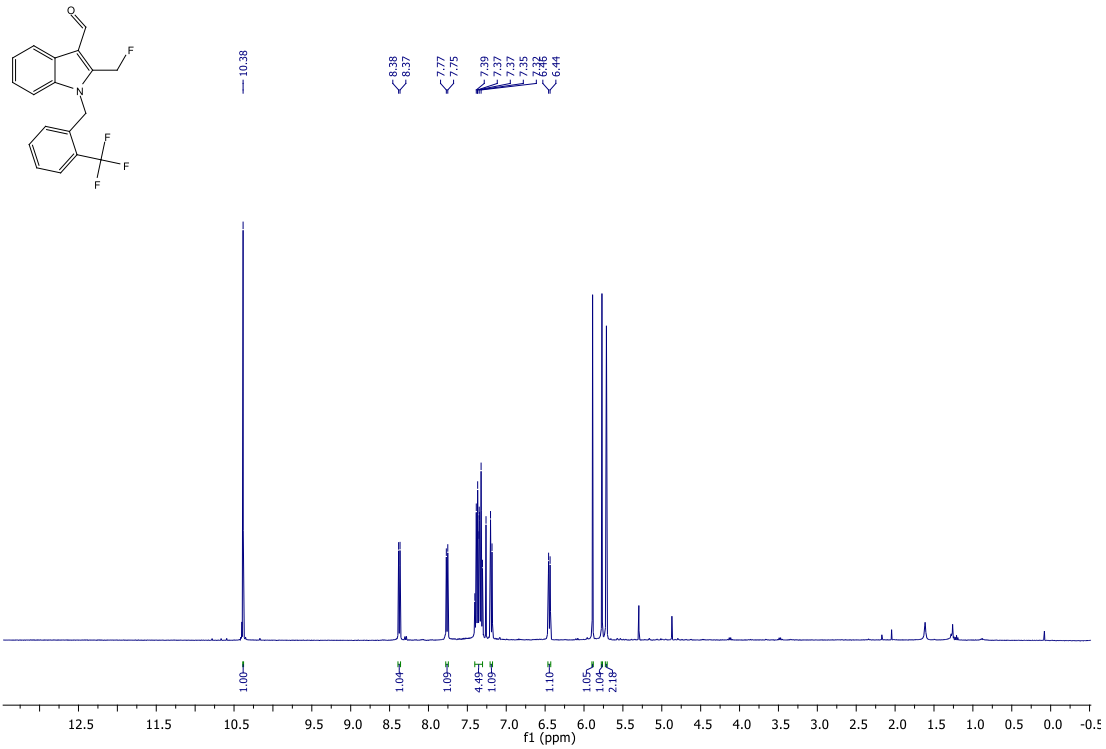
**$^{19}$F NMR** ( 376 MHz, $CDCl_3$)



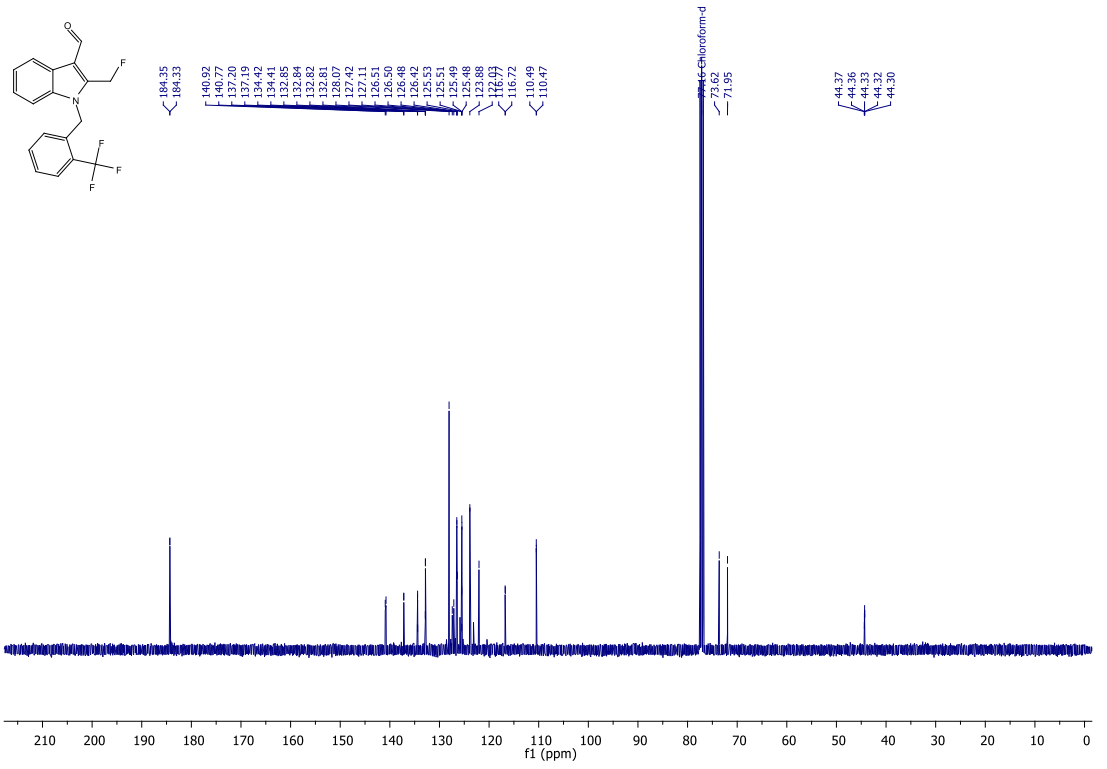



## 2-(Fluoromethyl)-1-[-2-(trifluoromethyl)benzyl)]-1*H*-indol-3-carbaldehyde (40)

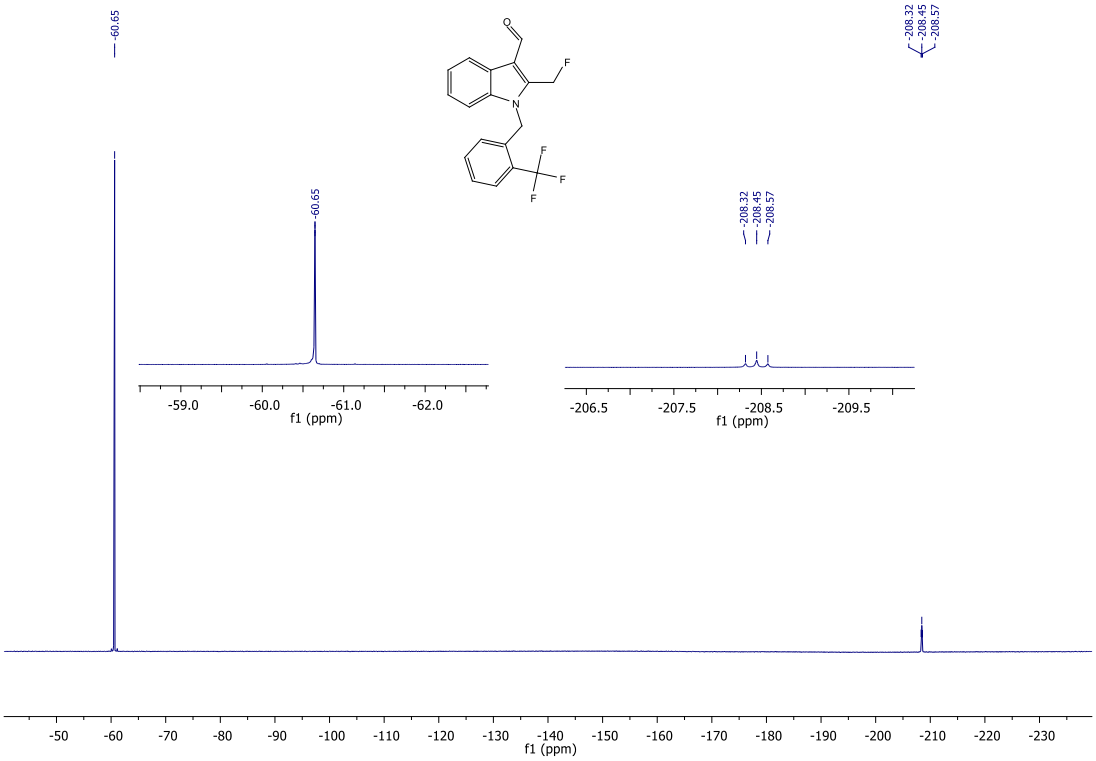
**$^{1}$H NMR** (400 MHz, $CDCl_3$)




**$^{13}$C NMR** (100 MHz, $CDCl_3$)

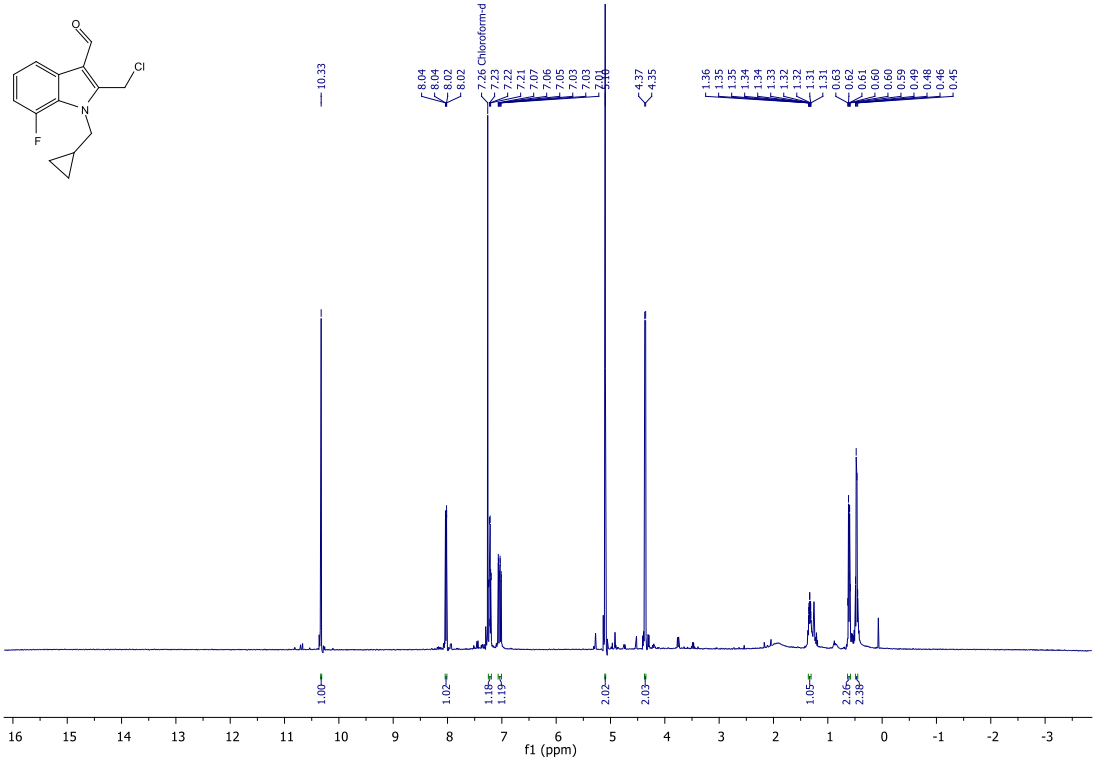


**$^{19}$F NMR** ( 376 MHz, $CDCl_3$)

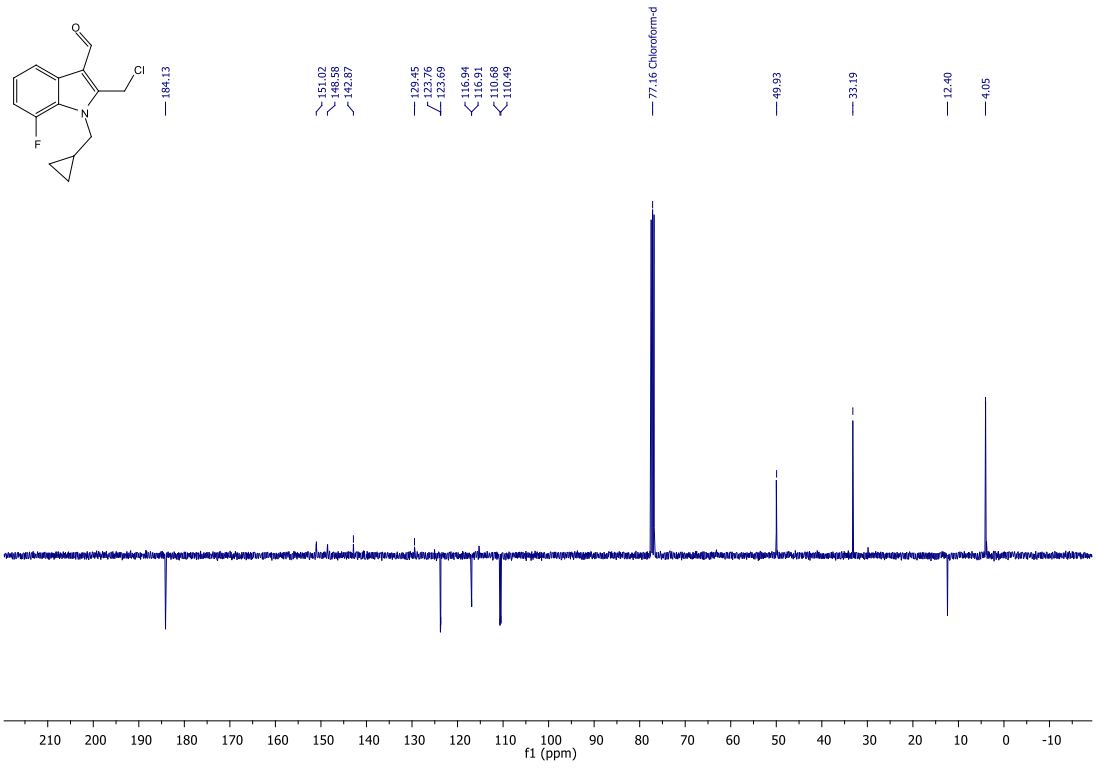


## 7-Fluoro-1-(cyclopropylmethyl)-2-(chloromethyl)-1*H*-indol-3-carbaldehyde (41)

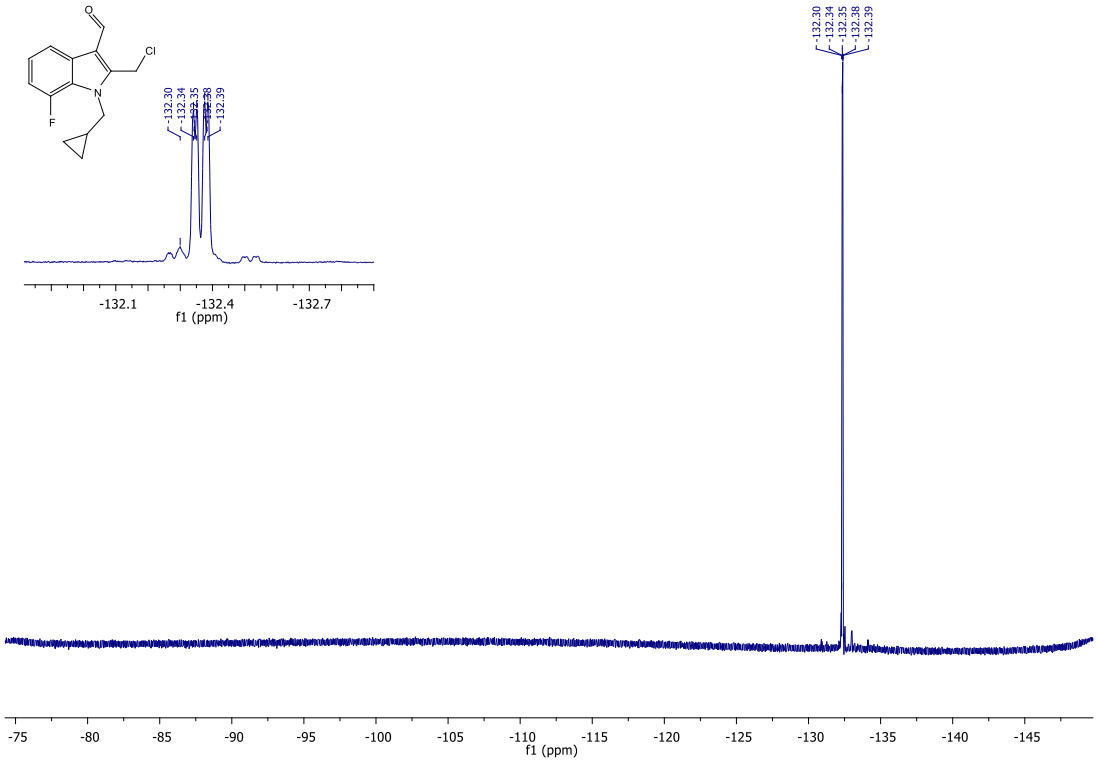
**$^{1}$H NMR** (400 MHz, $CDCl_3$)




**$^{13}$C NMR** (100 MHz, $CDCl_3$)

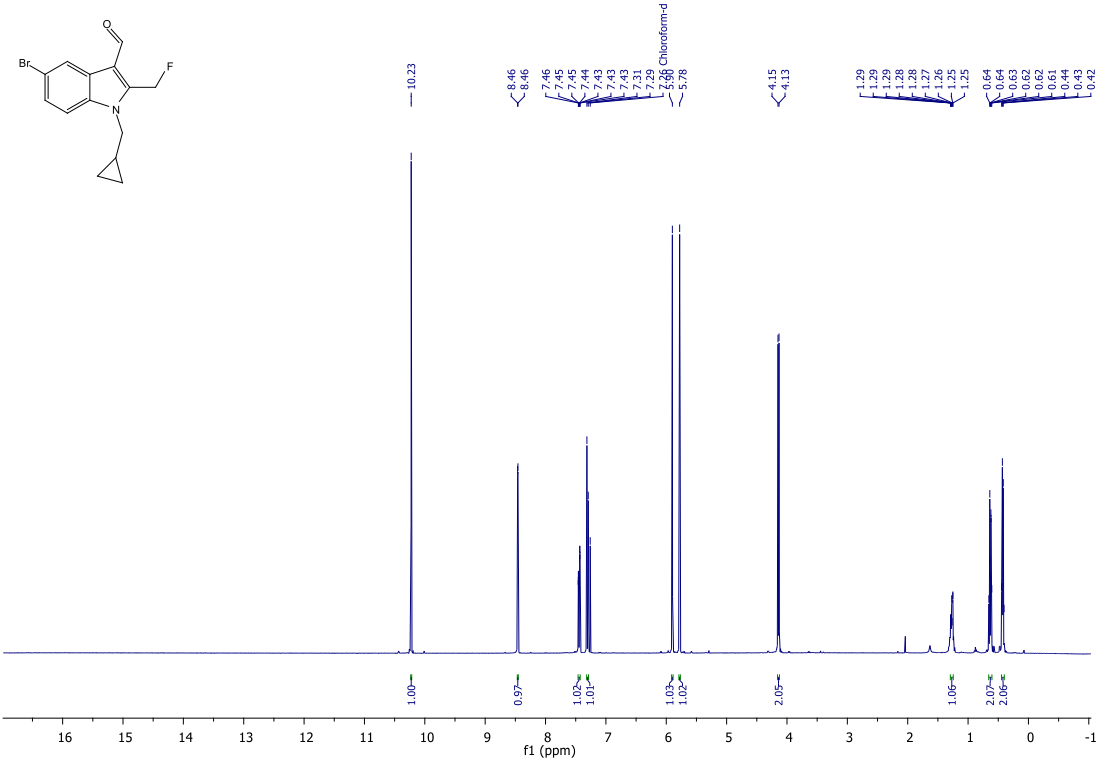


**$^{19}$F NMR** ( 376 MHz, $CDCl_3$)

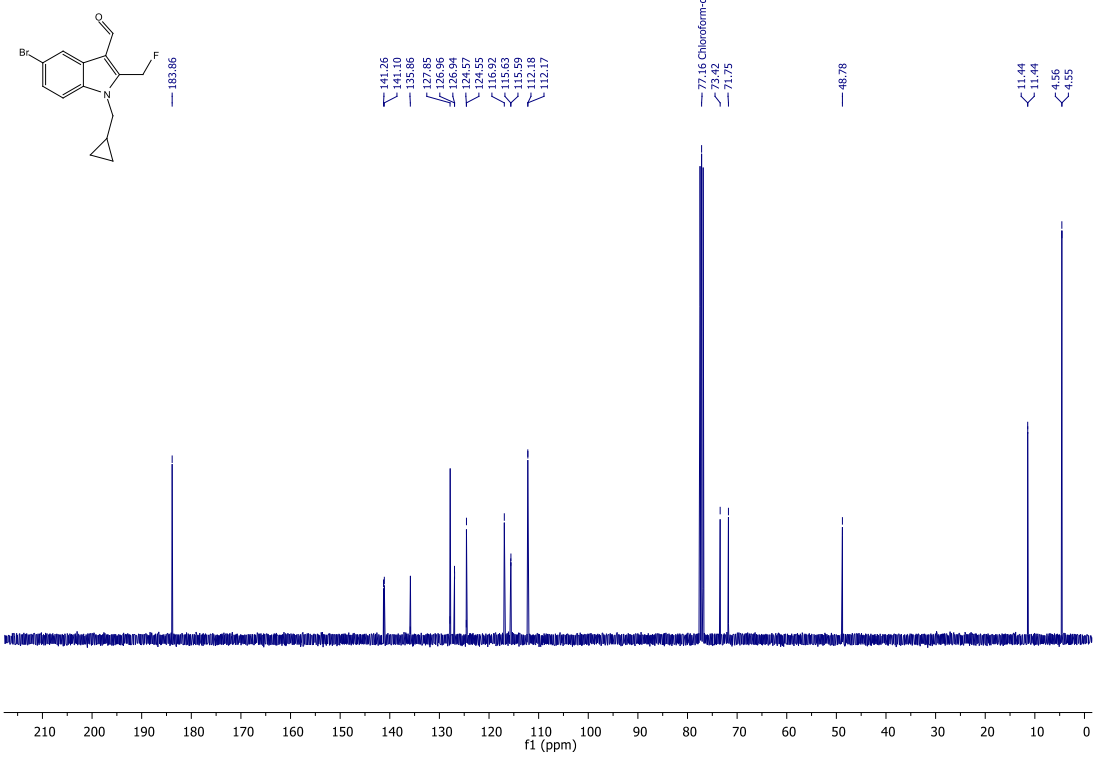


## 5-Bromo-1-(cyclopropylmethyl)-2-(fluoromethyl)-1*H*-indol-3-carbaldehyde (42)

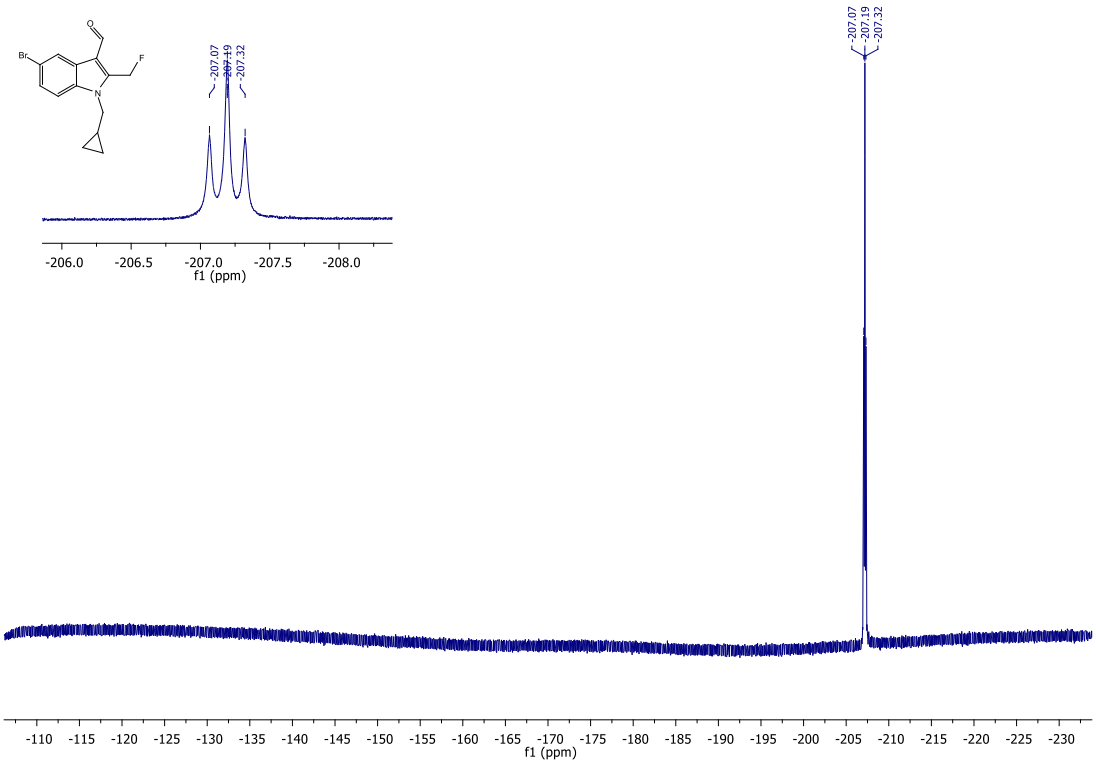
**$^{1}$H NMR** (400 MHz, $CDCl_3$)




**$^{13}$C NMR** (100 MHz, $CDCl_3$)

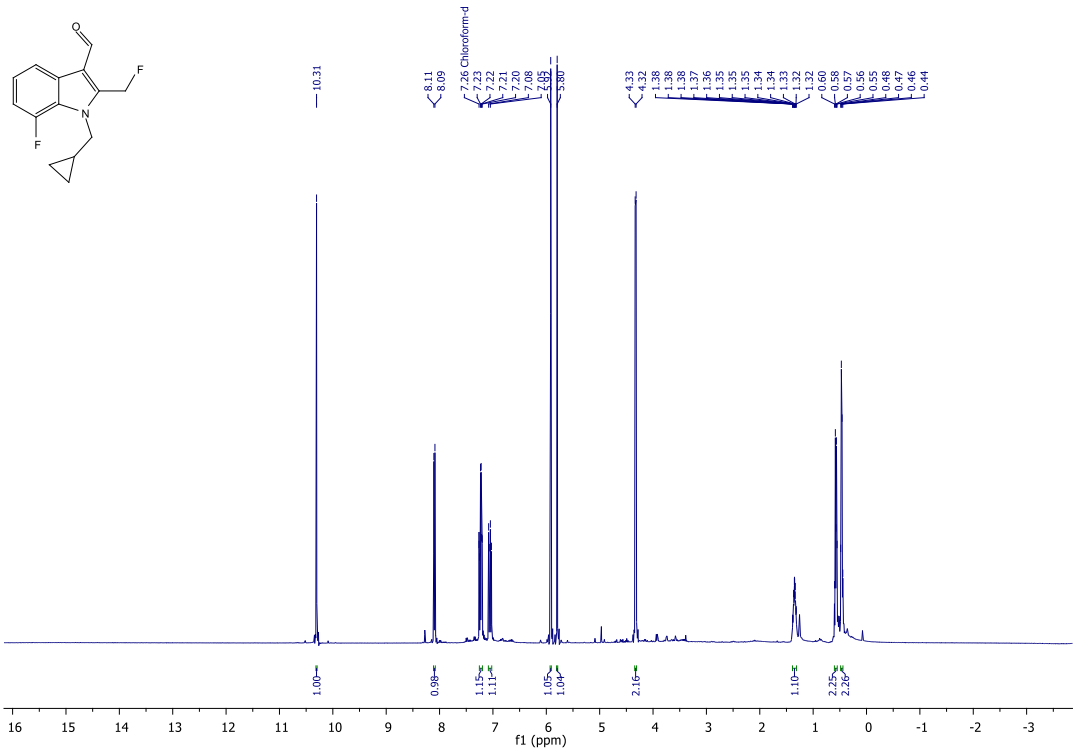


**$^{19}$F NMR** ( 376 MHz, $CDCl_3$)

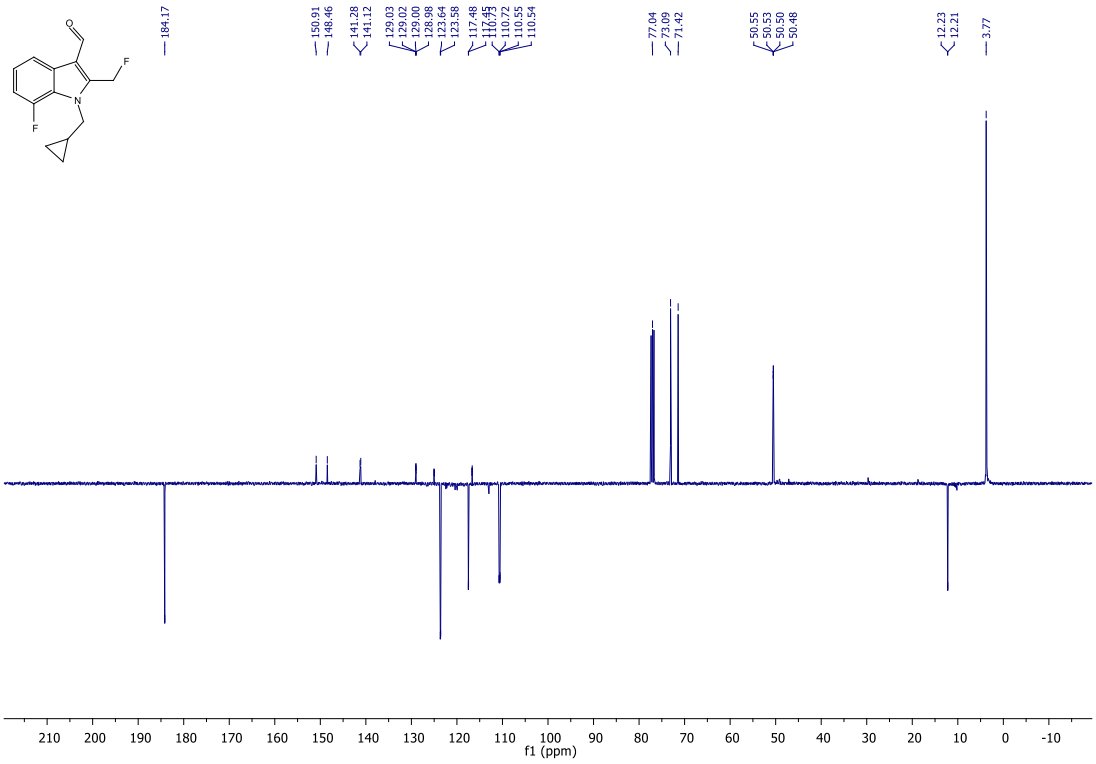


**7-Fluoro-1-(cyclopropylmethyl)-2-(fluoromethyl)-1*H*-indol-3-carbaldehyde (43)**

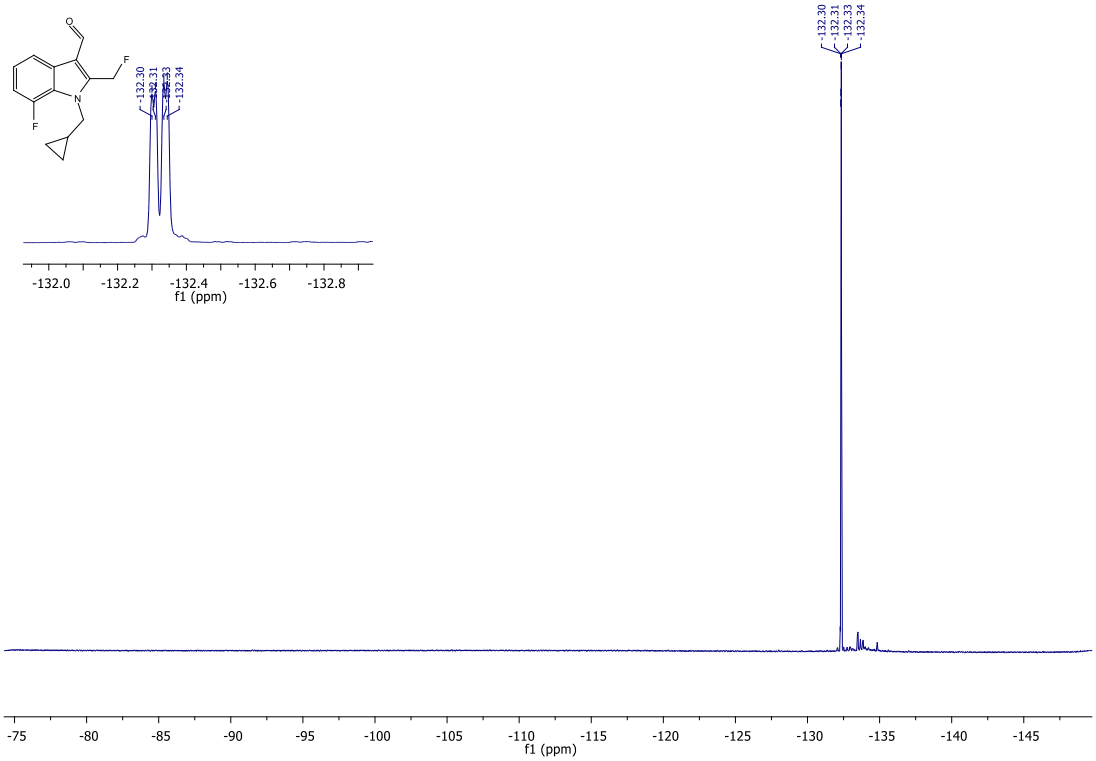
**$^{1}$H NMR** (400 MHz, $CDCl_3$)

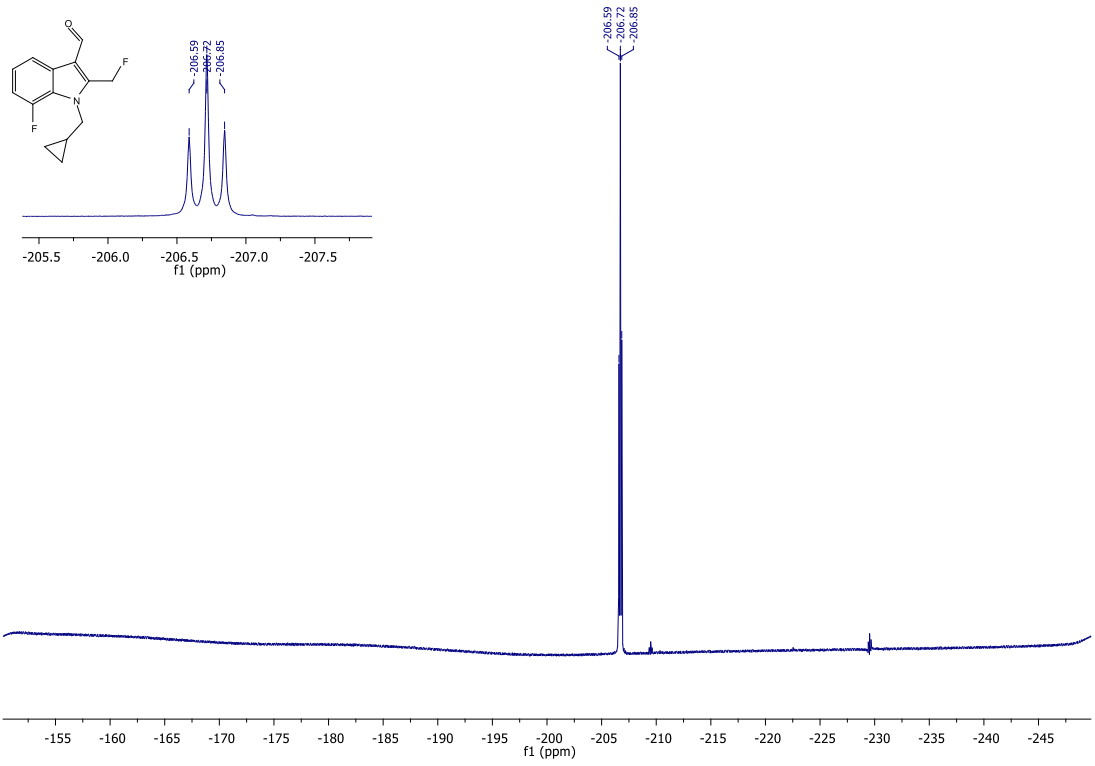



**$^{13}$C NMR** (100 MHz, $CDCl_3$)



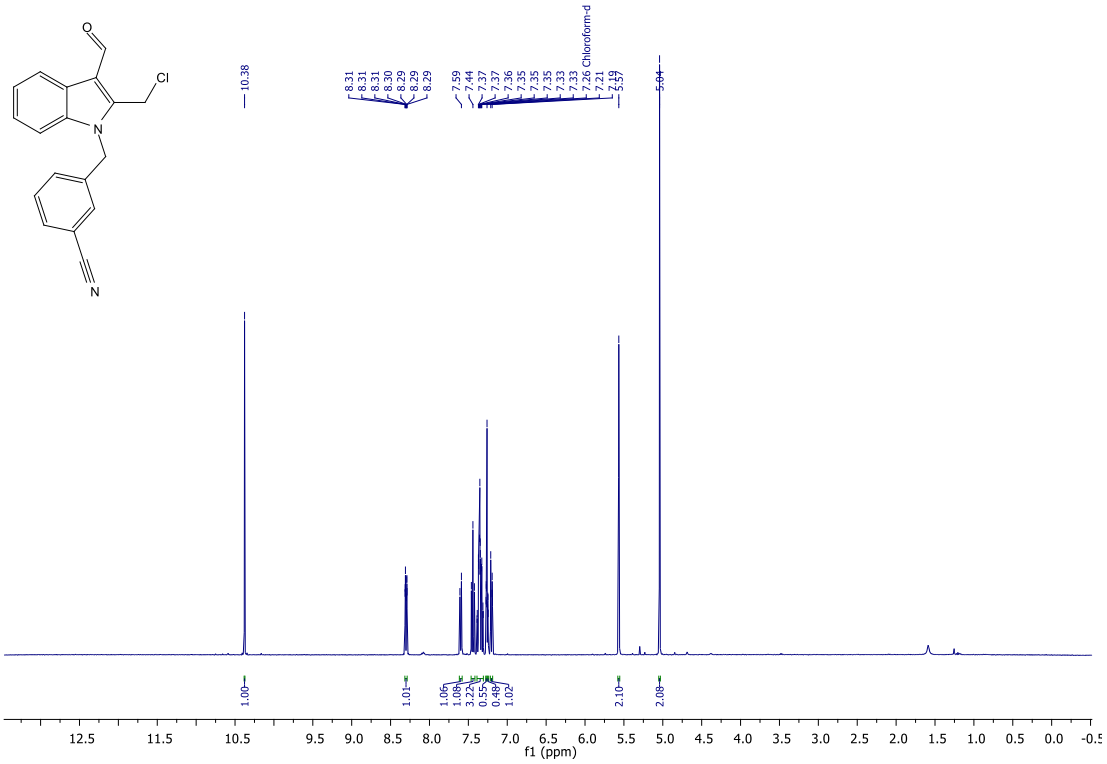
**$^{19}$F NMR** ( 376 MHz, $CDCl_3$)



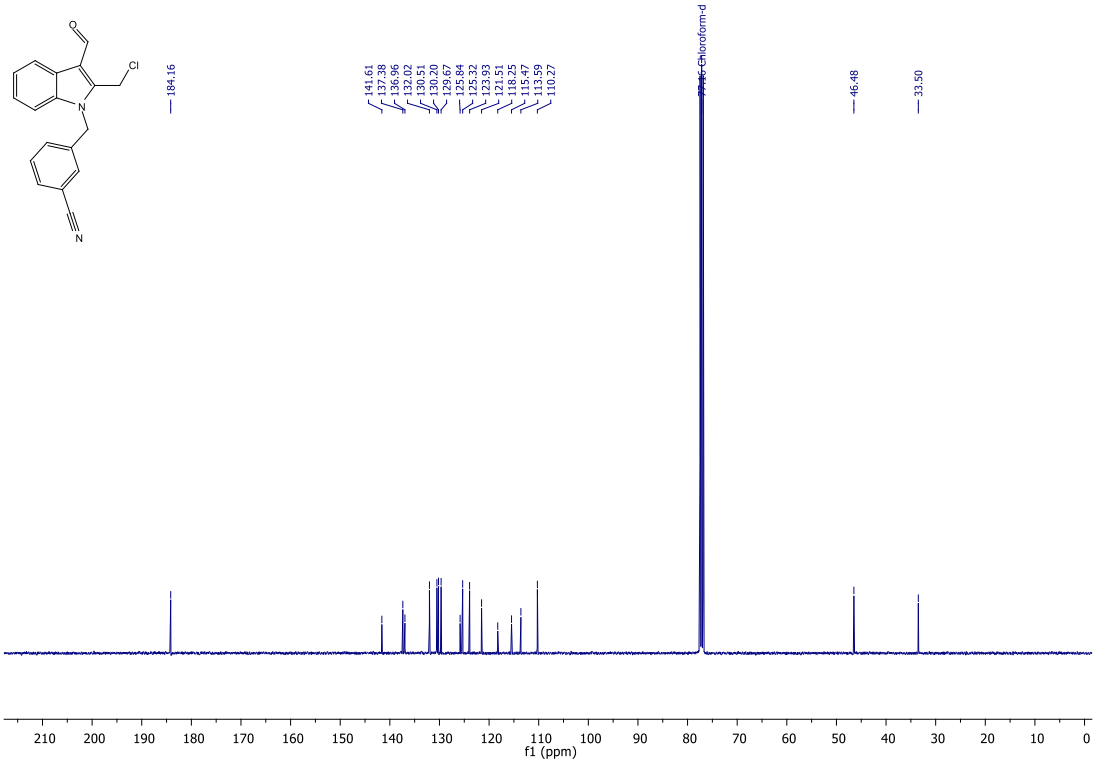



## 3-{[2-(Chloromethyl)-3-formyl-1*H*-indol-1-yl] methyl} benzonitrile (44)

**$^{1}$H NMR** (400 MHz, $CDCl_3$)

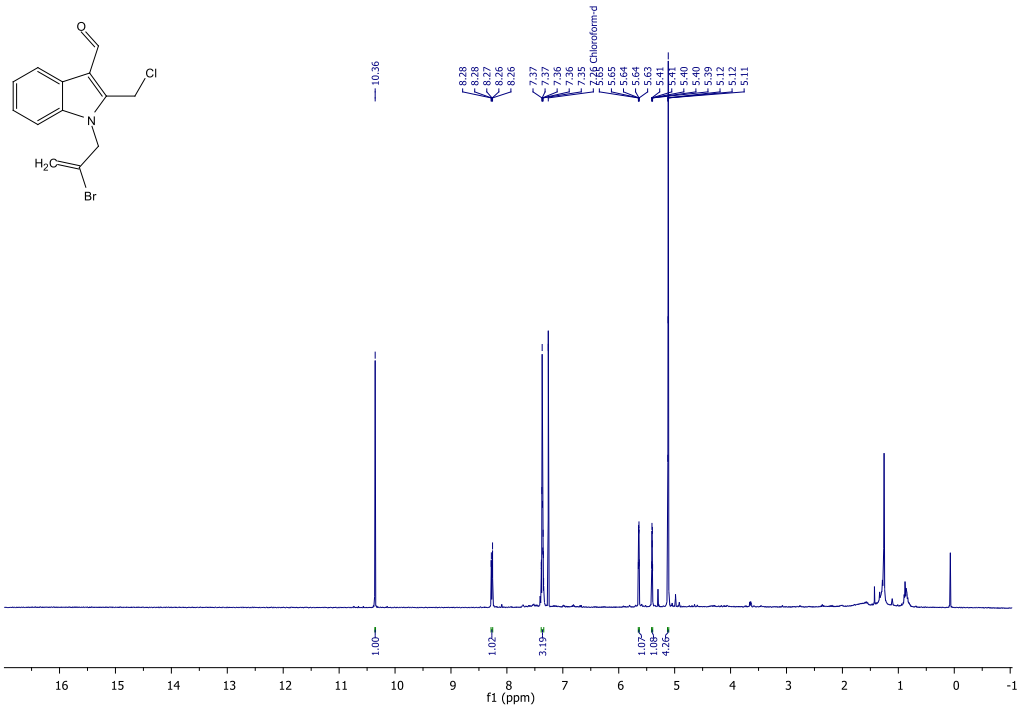



**$^{13}$C NMR** (100 MHz, $CDCl_3$)

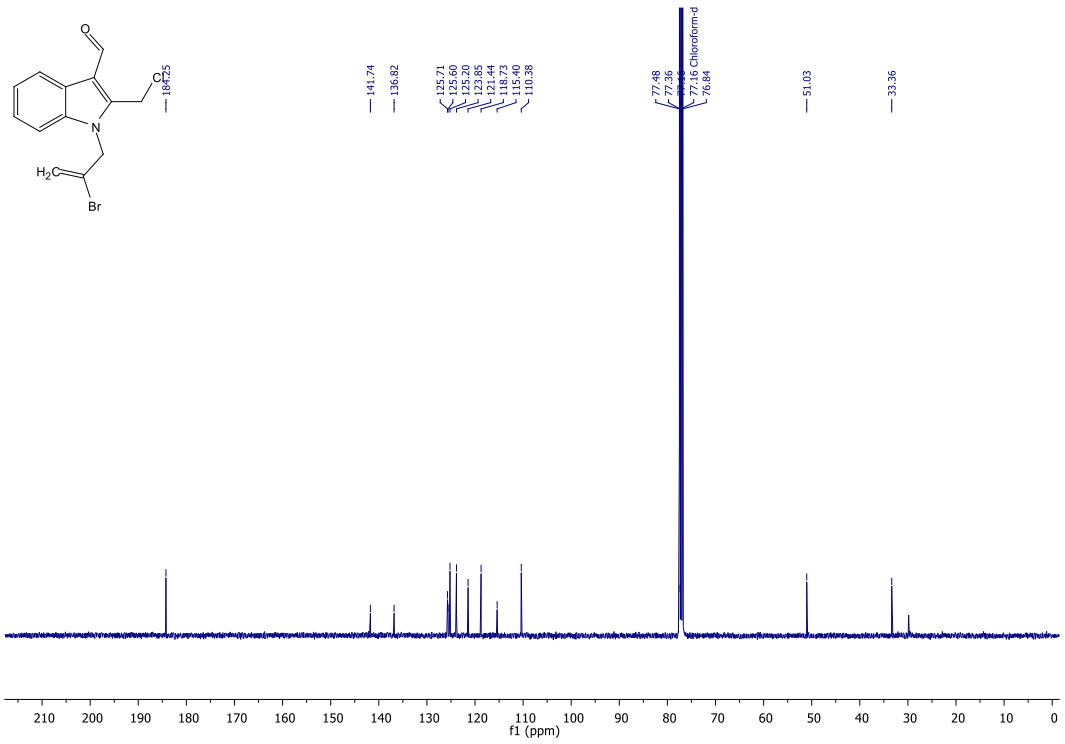


**1-(2-Bromo-2-propen-1-yl)-2-(chloromethyl)-1*H*-indole-3-carbaldehyde (45)**

**$^{1}$H NMR** (400 MHz, $CDCl_3$)

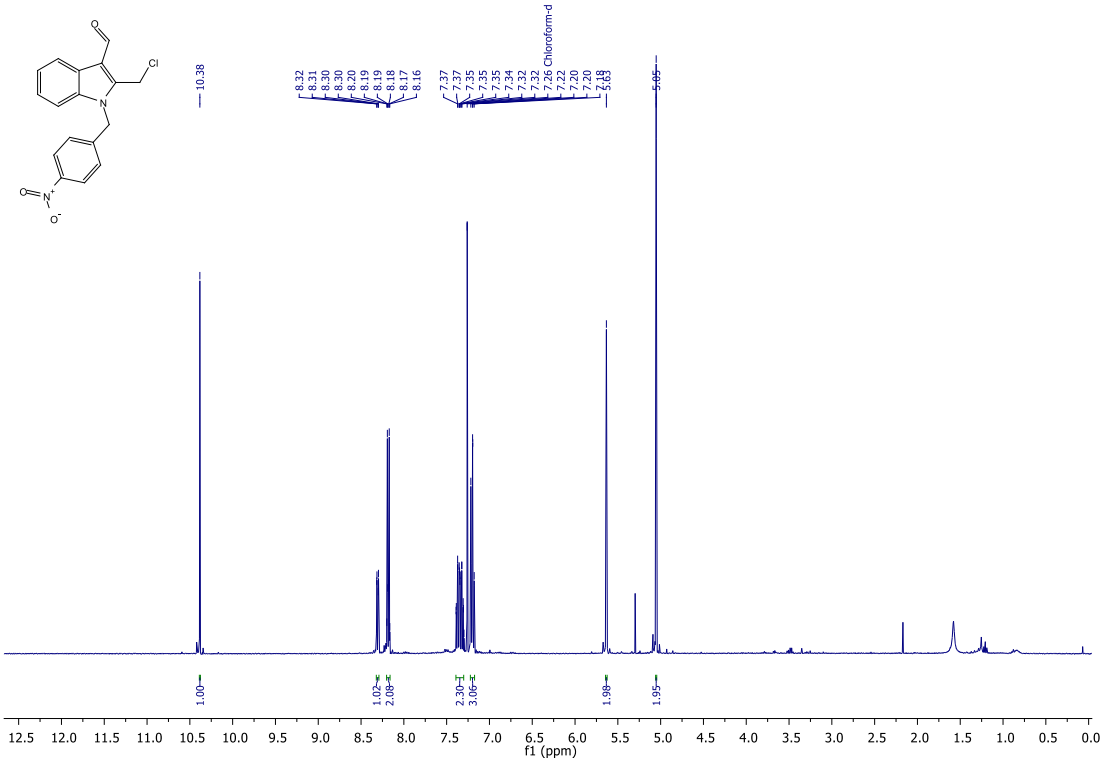



**$^{13}$C NMR** (100 MHz, $CDCl_3$)

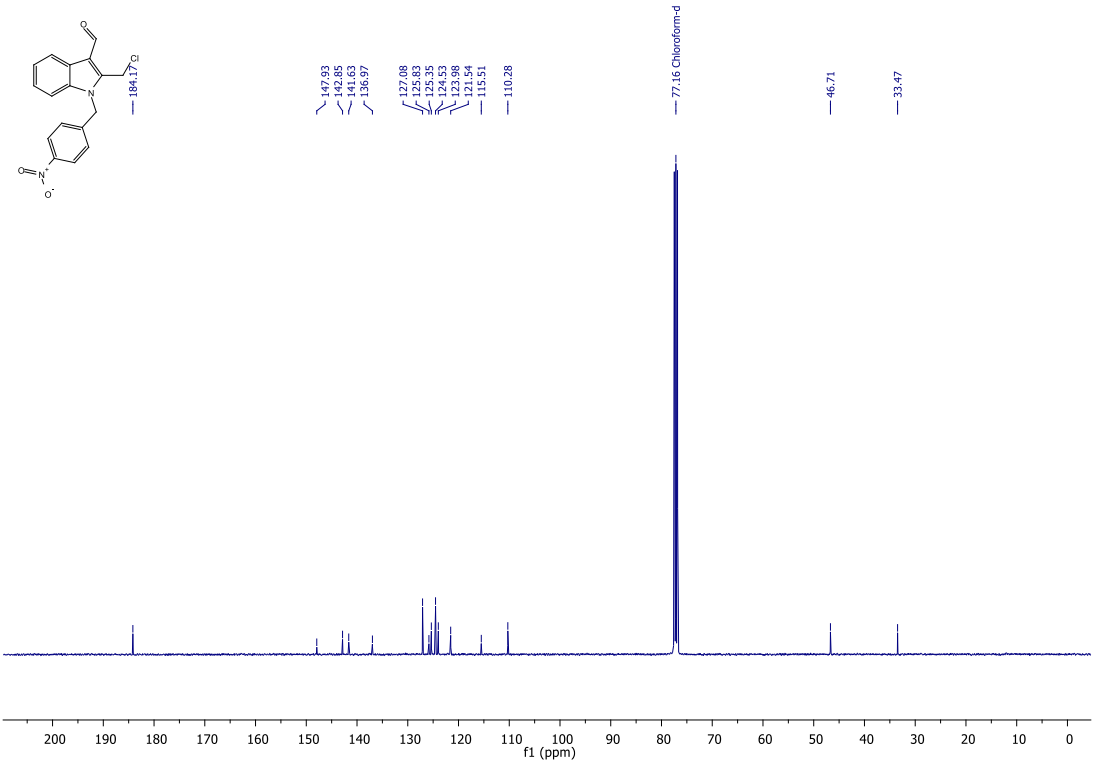


## 2-(Chloromethyl)-1-(4-nitrobenzyl)-1*H*-indol-3-carbaldehyde (46)

**$^{1}$H NMR** (400 MHz, $CDCl_3$)

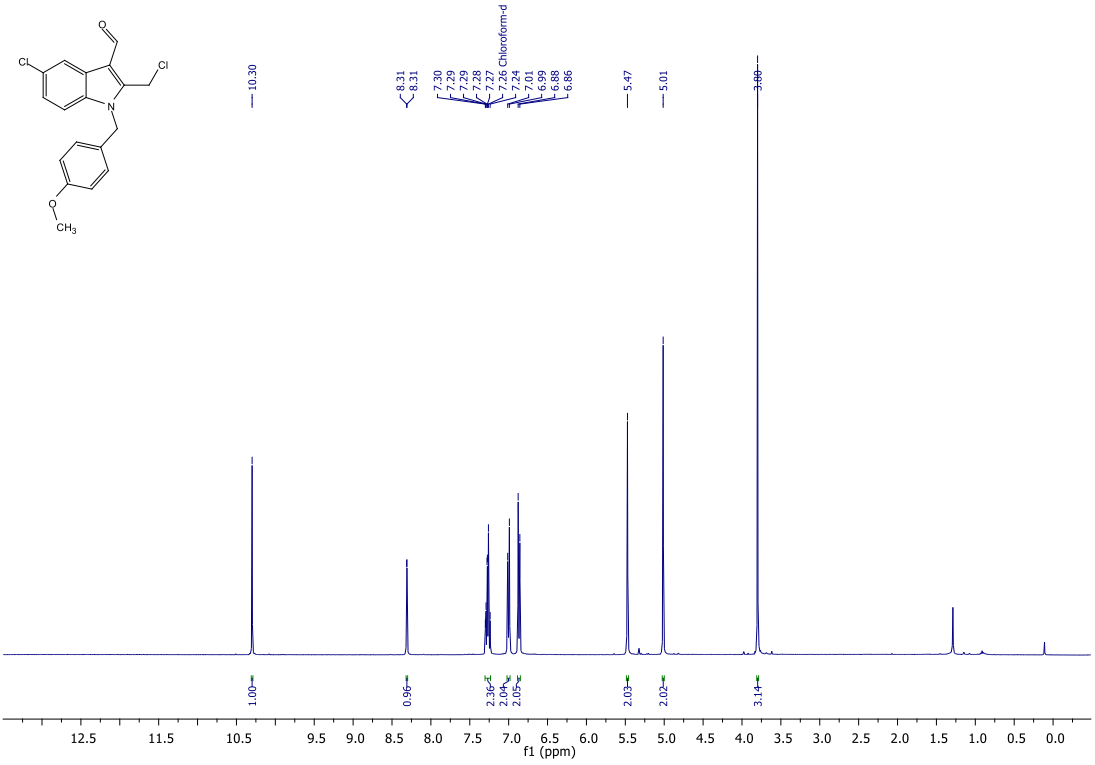



**$^{13}$C NMR** (100 MHz, $CDCl_3$)

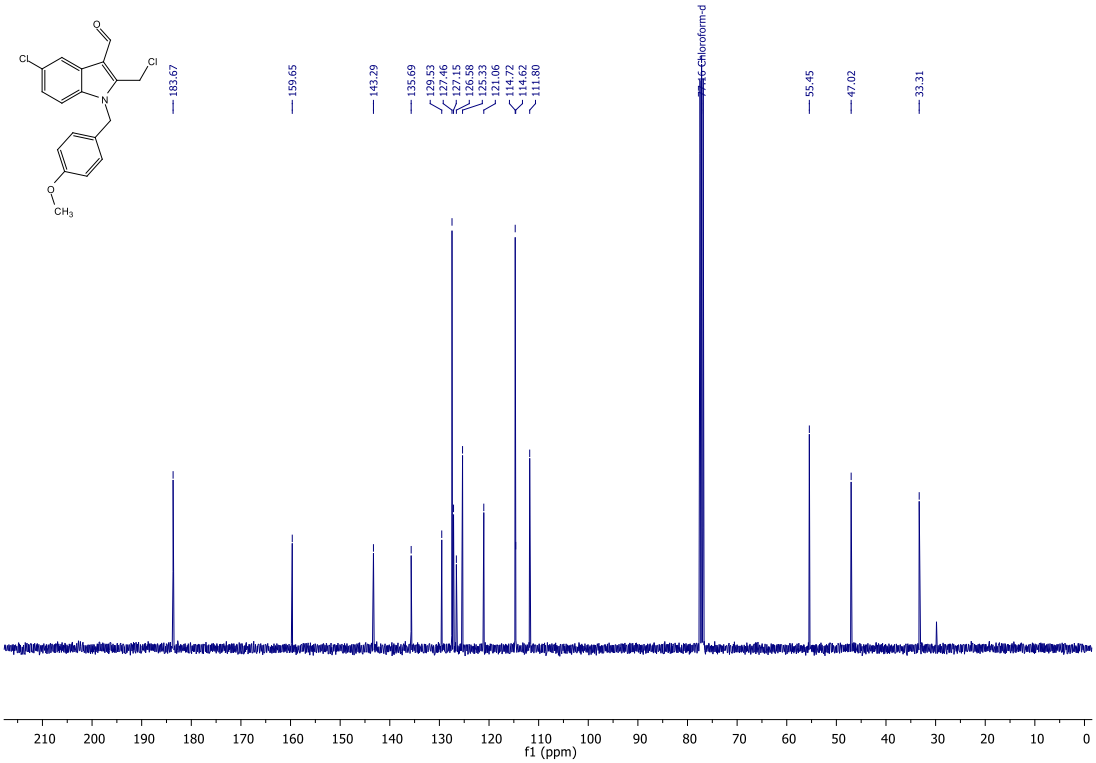


## 2-(Chloromethyl)-1-(4-methoxybenzyl)-1*H*-indole-3-carbaldehyde (47)

**$^{1}$H NMR** (400 MHz, $CDCl_3$)

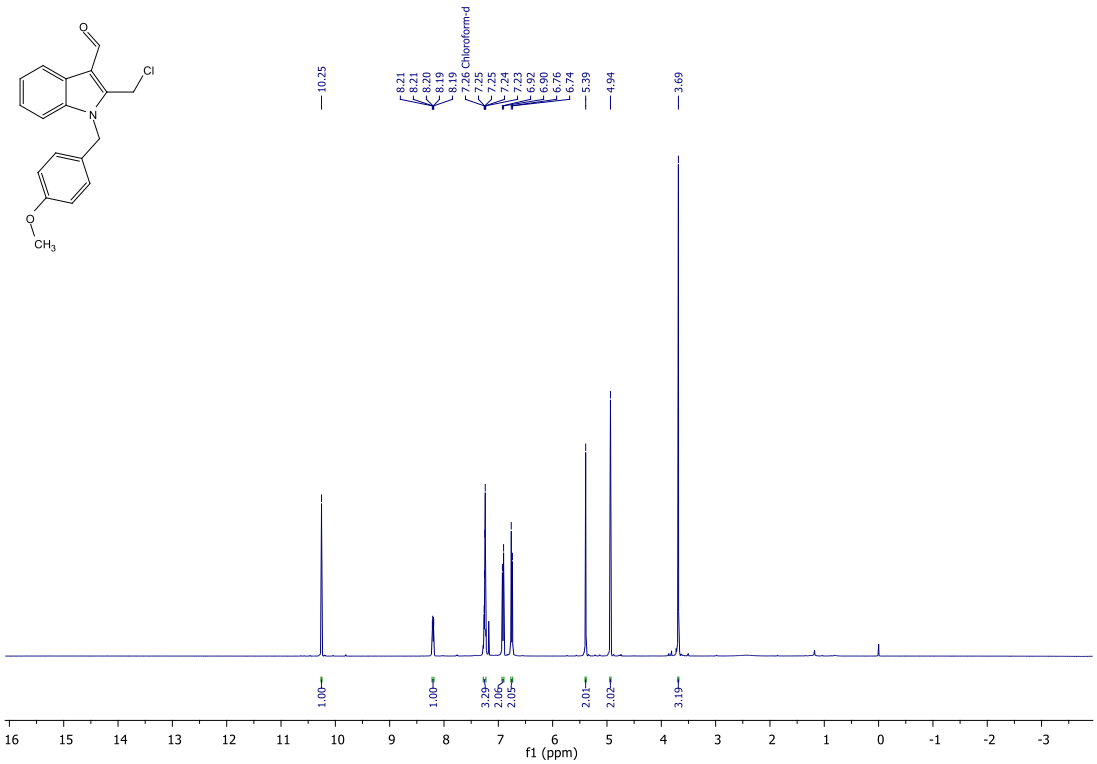



**$^{13}$C NMR** (100 MHz, $CDCl_3$)

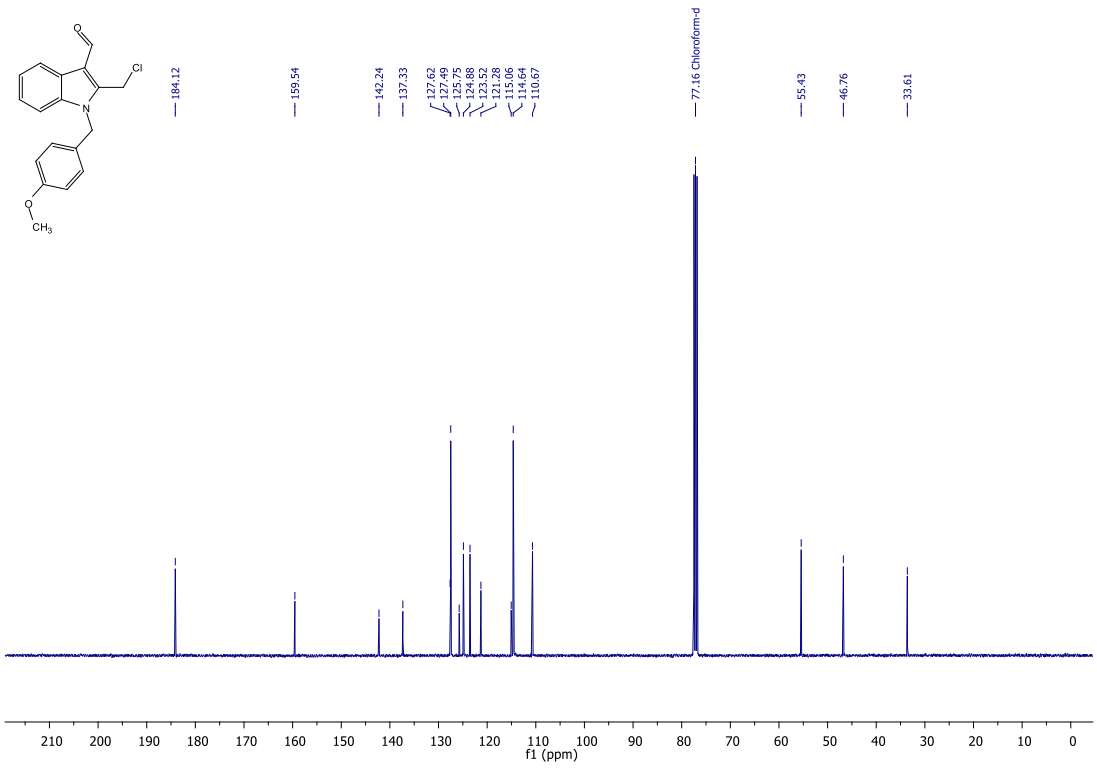


## 2-(Chloromethyl)-1-(4-methoxybenzyl)-1*H*-indole-3-carbaldehyde (48)

**$^{1}$H NMR** (400 MHz, $CDCl_3$)

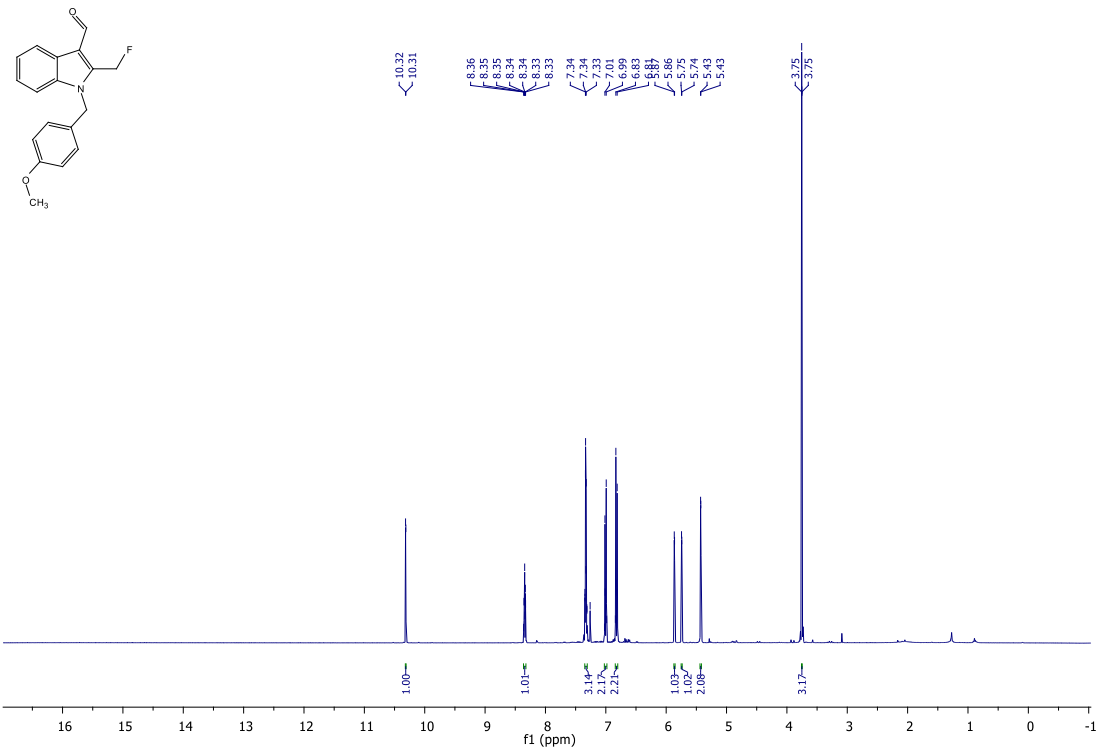



**$^{13}$C NMR** (100 MHz, $CDCl_3$)

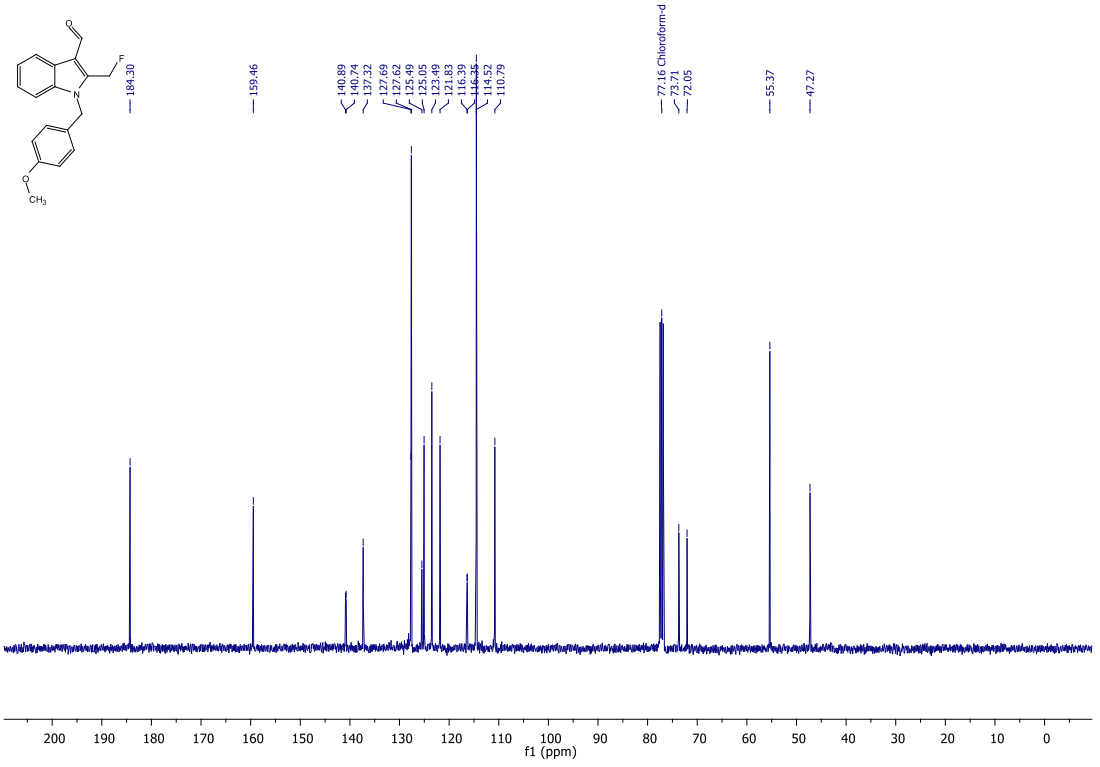


## 2-(Fluoromethyl)-1-(4-methoxybenzyl)-1*H*-indol-3-carbaldehyde (49)

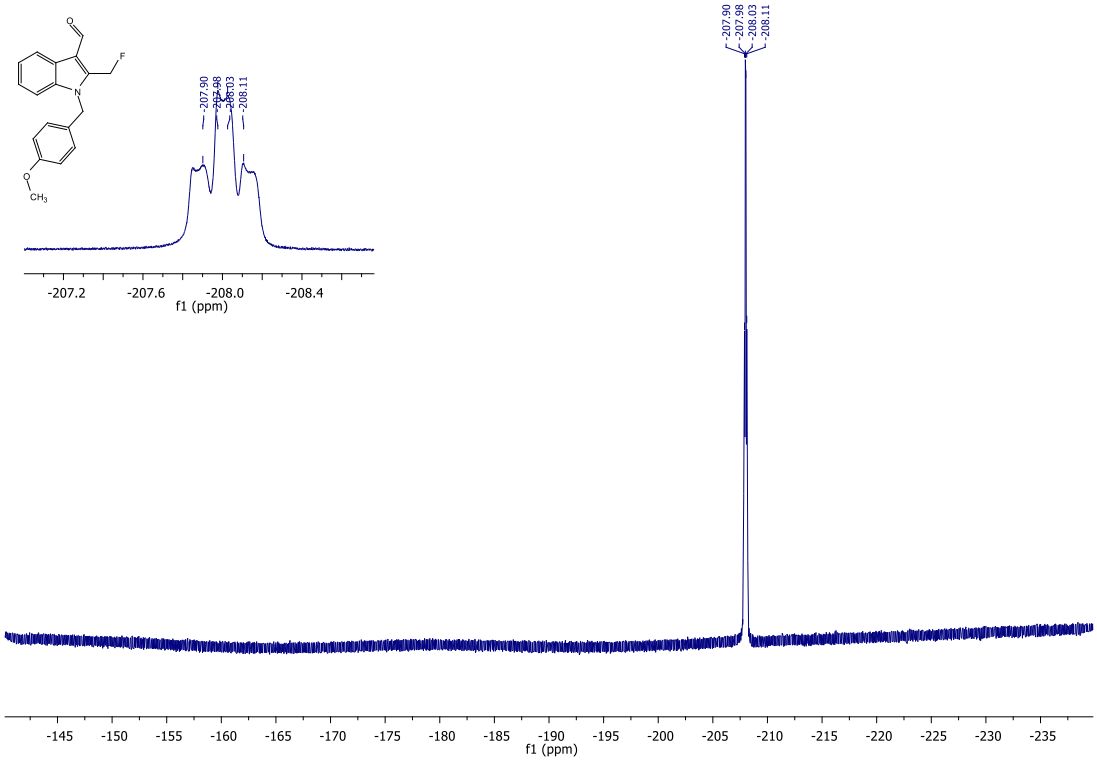
**$^{1}$H NMR** (400 MHz, $CDCl_3$)




**$^{13}$C NMR** (100 MHz, $CDCl_3$)

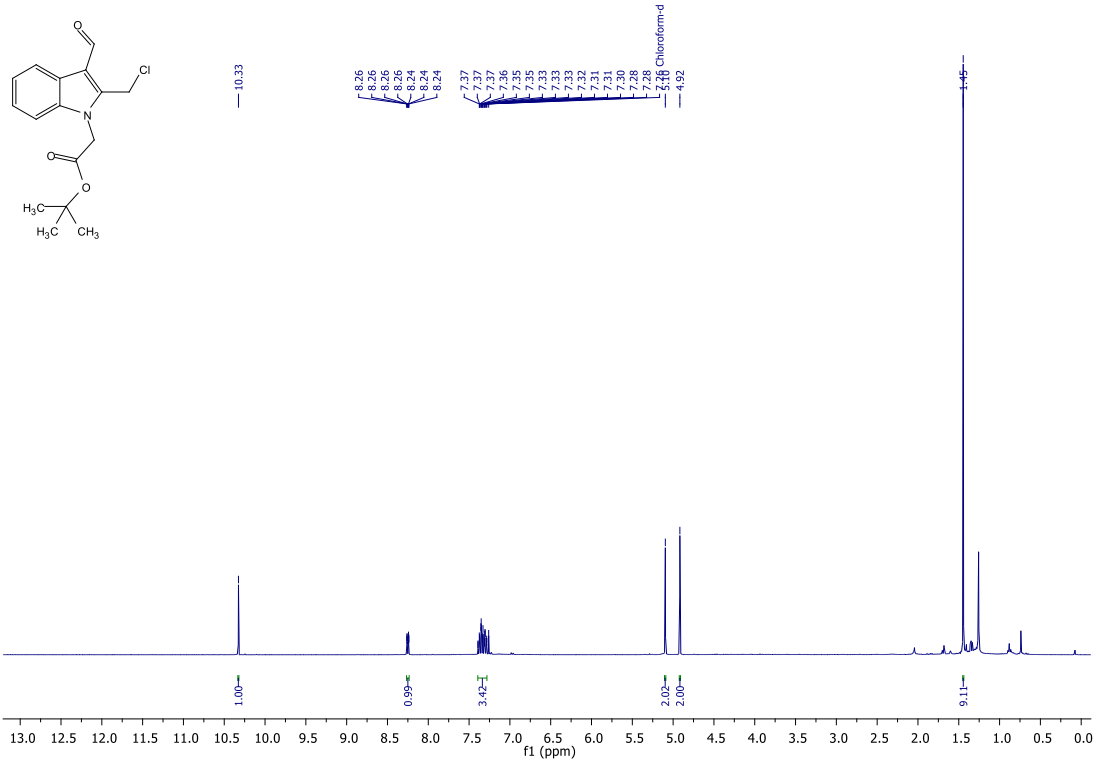


**$^{19}$F NMR** ( 376 MHz, $CDCl_3$)

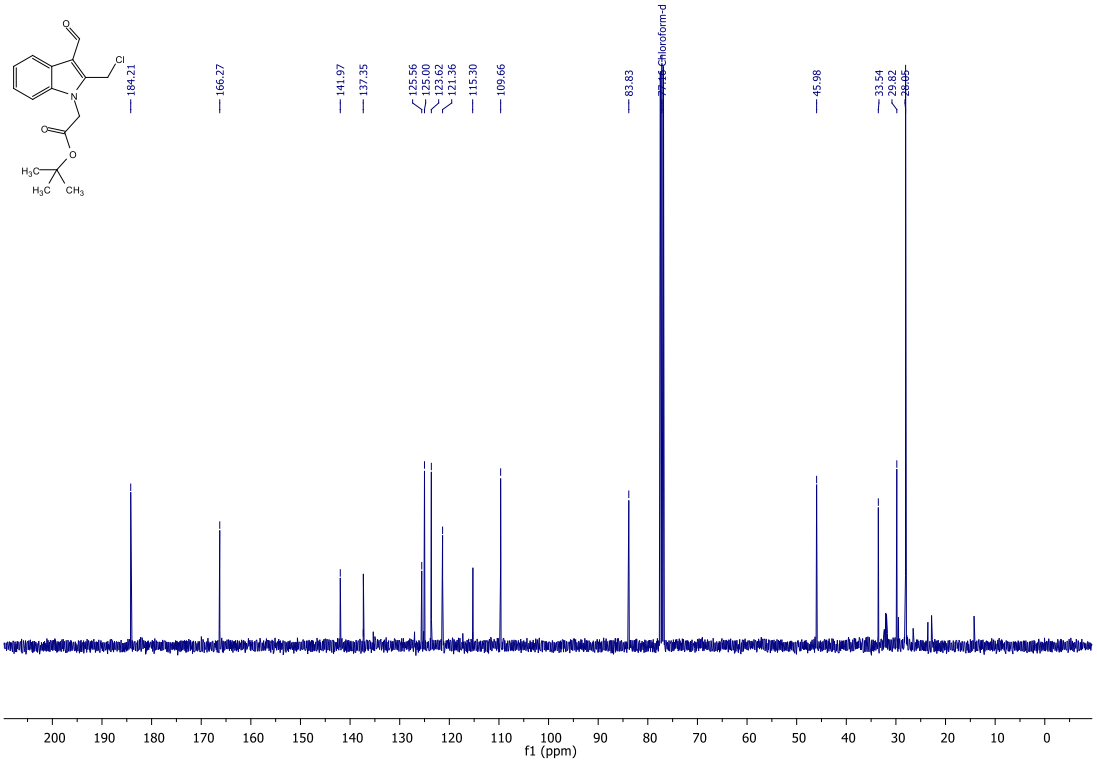


## 2-Methyl-2-propanyl [2-(cholоromethyl)-3-formyl-1*H*-indol-1-yl] acetate (50)

**$^{1}$H NMR** (400 MHz, $CDCl_3$)




**$^{13}$C NMR** (100 MHz, $CDCl_3$)



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