공학석사학위논문

Synthesis of Pareitropone Fluorine Derivatives

퍼레이트로폰의 불소 유도체 합성

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장 세 욱

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지도 교수 김 영 규

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위 원 유 동원 (인)

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By

Sewook Jang

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Thesis Adviser: Young Gyu Kim

Abstract

Synthesis of Pareitropone Fluorine Derivatives

Sewook Jang
School of Chemical and Biological Engineering
The Graduate School
Seoul National University

Pareitropone, isolated from natural plants (*Menispermaceae*), has been reported to have the potent anti-leukemic activity against P388 cells. Various tropoloisoquinoline derivatives, composed of tropone and isoquinoline, have also been displayed biological activities. Besides, tropoloisoquionoline analogs are fascinating synthetic target due to its annulated structure of the seven-membered tropone ring and isoquinoline moiety. For this reason, many groups have studied concise and efficient synthesis of tropoloisoquinoline. Additionally, in pharmaceutical chemistry, fluorine derivatives display biologicially active. It has a special property to form a strong carbon-fluorine bonding owing to its high electronegativity and small size. Therefore, the purpose of this study is synthesis of pareitropone fluorine derivatives using concise and efficient process. We conducted Pd-mediated Suzuki coupling reaction, Pomeranz-Fritsch cyclization, Reissert-type addition, Radical anionic Kende coupling reaction, and so on. In this study, pareitropone fluorine derivatives were synthesized from

commercially available compounds called isovanillin through 12-step chemical reaction. The fluorine derivative of pareitropone can be used for the structure-activity relationship(SAR) studies of the tropoloisoquinolines.

Keyword : Pareitropone, tropoloisoquinoline, fluorine, radical anionic coupling, biological activity, SAR

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List of Schemes

List of Abbreviations

AcOH	Acetic acid
DBU	1,8−Diazabicyclo(5.4.0)undec−7−ene
DCM	Dichloromethane
DDQ	2,3−Dichloro−5,6−dicyano−1,4−benzoquinone
DMAP	4−(Dimethylamino)pyridine
DNBS	2,4−Dinitrobenzenesulfonic acid
Hz	Hertz
$K_3Fe(CN)_6$	Potassium ferricyanide
NBS	N−Bromosuccinimide
NMR	Nuclear magnetic resonance spectroscopy
SAR	Structure−activity relationship
TBAF	Tetrabutylammonium fluoride
THF	Tetrahydrofuran
TIPSCl	Triisopropylsilyl chloride
TLC	Thin layer chromatography
TMS	Tetramethylsilane, Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TsCl	*p*−Toluenesulfonyl chloride
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)

1. Introduction

1.1. Tropoloisoquinoline analogs

Tropoloisoquinoline is known to be composed of several compounds such as pareitropone, imerubrine, isoimerubrine, grandirubrine, pareirubrine A, pareirubrine B, and so on.[1](Figure 1.)

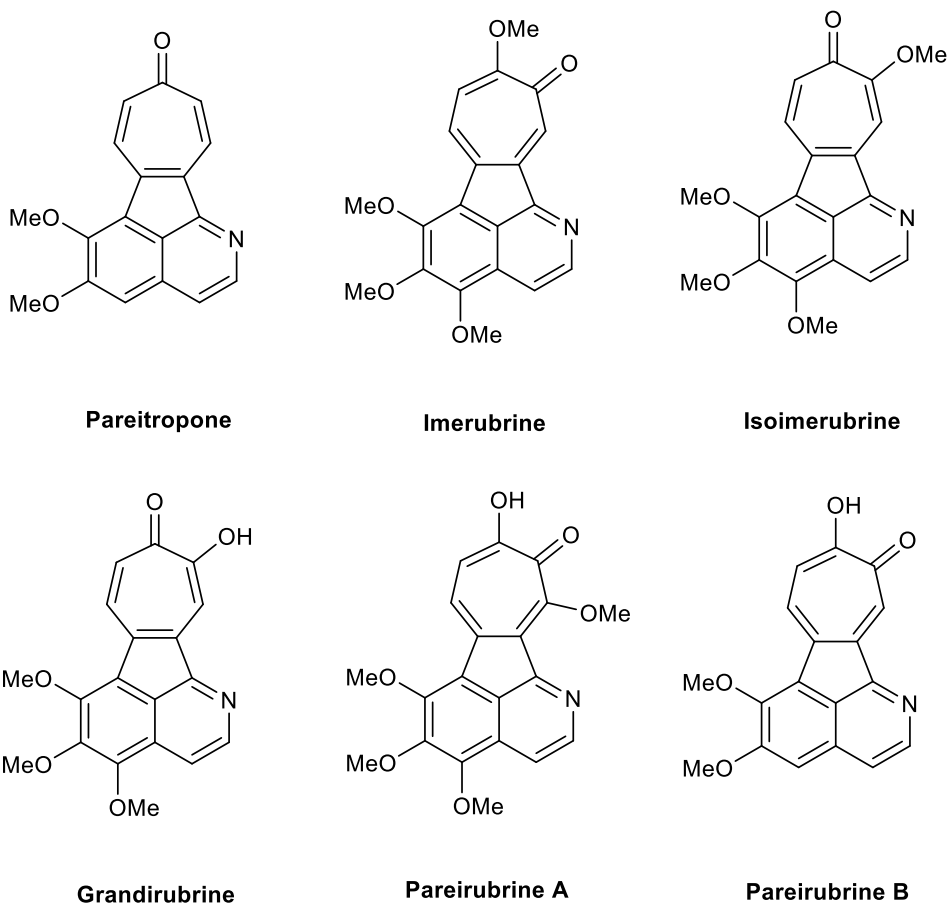


Figure 1. Structure of Tropoloisoquinoline analogs

They were isolated from natural plants(*Menispermaceae)*. Imerubrine and grandirubrine were first extracted from *Abuta imene*, *Abuta grandifolia* in 1972 and 1980 respectively. Pareitropone was extracted from *Cissampelos pareira* in 1995.[2]

Tropoloisoquinoline analogs are attractive synthetic target owing to its fascinating fused structure of the seven-membered tropone ring and isoquinoine moiety as well as its interesting biological activities.[3b] Those analogs have been reported to have potent cytotoxicity against P388 cells and recently evaluated for activity against several human cancer cells such as A549 lung carcinoma, ACNH renal carcinoma, and HCT-116 colon adenocarcinoma.[3a]

According to the previous result on colchicine which is structurally similar to pareitropone, it is anticipated that potent biological activity is derived from the tropone ring.[4] Colchicine is a cyclic compound with a methoxytropone ring, which is the most important, a cycloheptane ring, and a trimethoxyphenyl ring. (Figure 2)

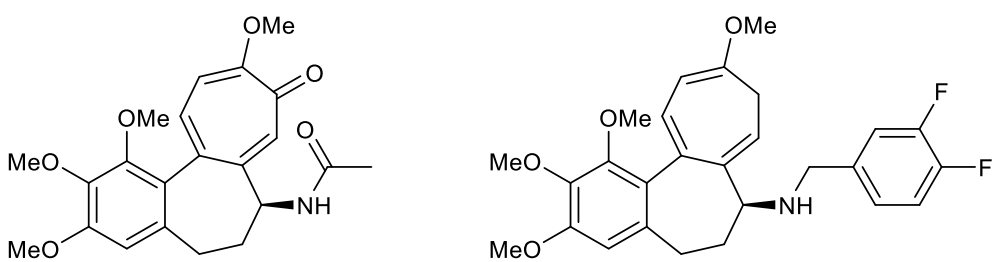


Figure 2. Colchicine, sturucturally similar to pareitropone[4]

Besides, in pharmaceutical study, fluorine derivatives which are natural products have been known to display biologically active.[5] (Figure 3) Fluorine has some important factors to enhance biological activity and increase stability.[6] First, the small size of the fluorine atom is expected to minimize steric perturbations and bind well with a receptor or enzyme. And its high electron withdrawing ability reduces the electron density on the ketone group which is improved the stability of the molecule to acid hydrolysis. Also, its good lipophilicity and strong carbon–fluorine bonding make pareitropone fluorine derivatives enter an active site of enzyme without metabolism. Therefore, we tried to synthesize pareitropone substituted with fluorine and describe how to make it efficient.

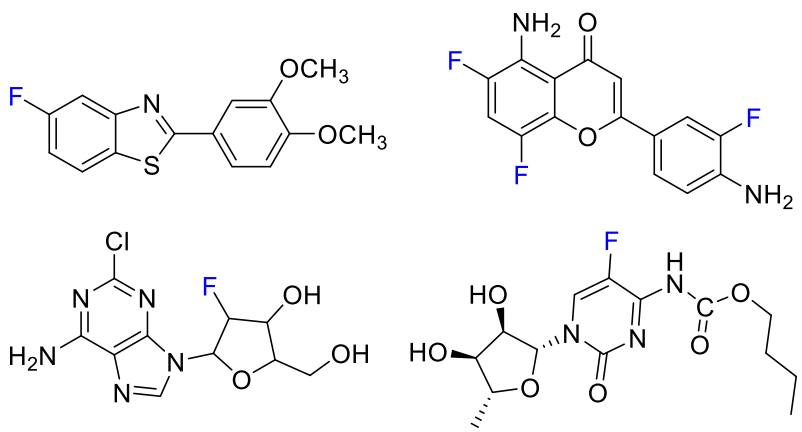
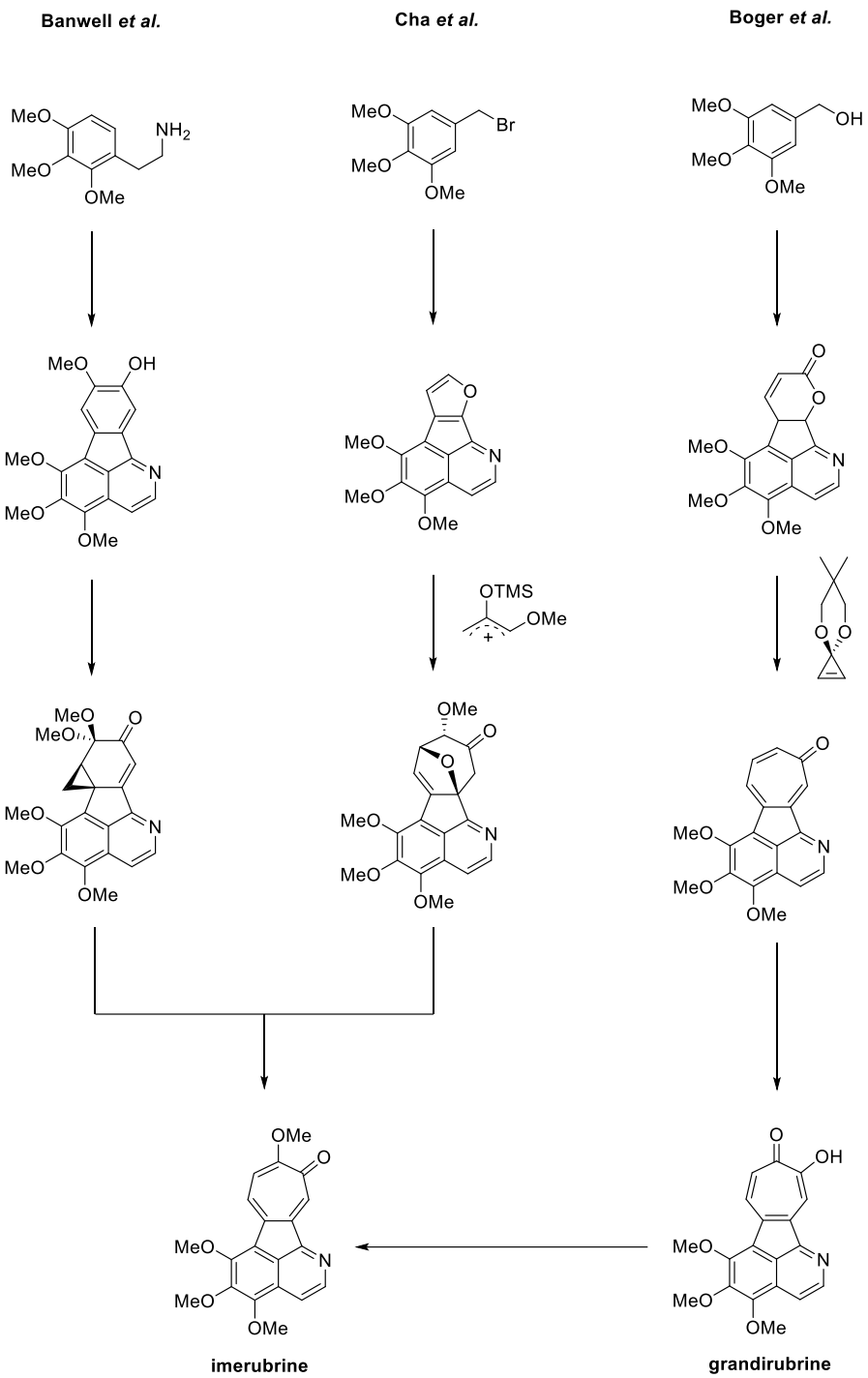


Figure 3. Structure of biologically active fluorine derivatives[5]

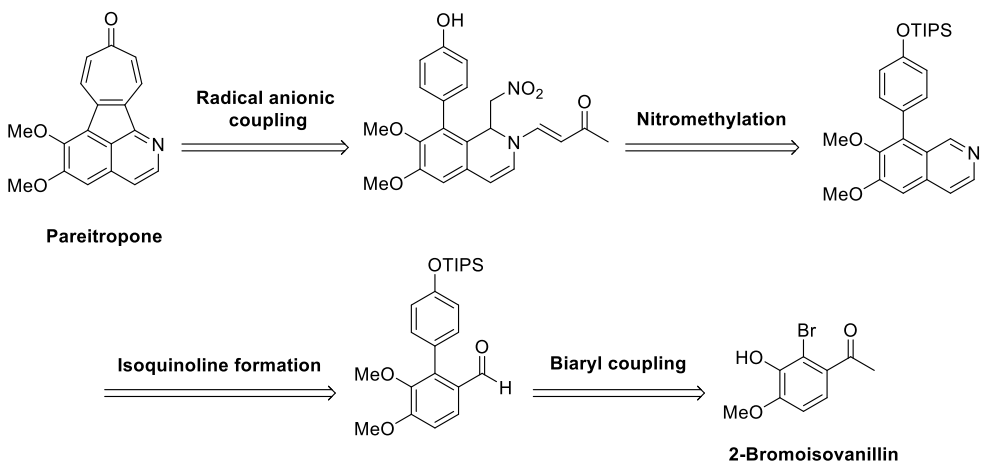
1.2. Previous studies of tropoloisoquinoline analogs

Many groups have been studied to synthesize tropoloisoquinoline analogs owing to their fascinating structure and their good biological activities.(Scheme 1) Banwell[7a], Boger[7b, 7c], and Cha[7d] group synthesized imerubrine, isoimerubrine, and grandirubrine in 1994, 1995, and 2001 respectively. These groups were focused on construction of upper cycloheptatrienone ring. Banwell *et al.*, synthesized tropoloisoquinoilne analogs first, constructed cyclopropane to make upper tropone moiety. Then, in 1995, Boger *et al.* performed synthesis of grandirubrine. Further, They synthesized imerubrine and isoimerubrine prepared by grandirubrine's methylation. Cha group synthesized grandirubrine, imerubrine, and isoimerubrine by cycloaddition process. Recently, Feldman group conducted the total synthesis of pareitropone which is different from previous ring formation process in 2002. Pareitropone was synthesized in 7% with a 14-step process.[8]



Scheme 1. Previous synthetic routes of troploisoquinoline

Recently, our group successfully synthesized pareitropone in 30% over 9 steps. Radical anionic coupling was a key step of constructing the annulated tropone.[9] Phenolic nitrate, a radical anionic coupling reaction precursor, was synthesized from the Reissert-type nitromethylation reaction. Dimethoxy isoquinoline was synthesized by Pomeranz-Frisch annulation. Biaryl compound was made by bromobenzylaldehyde and TIPS protected bromophenol through palladium catalyzed Suzuki coupling reaction. Bromobenzylaldehyde was prepared from 2-bromoisovanillin.

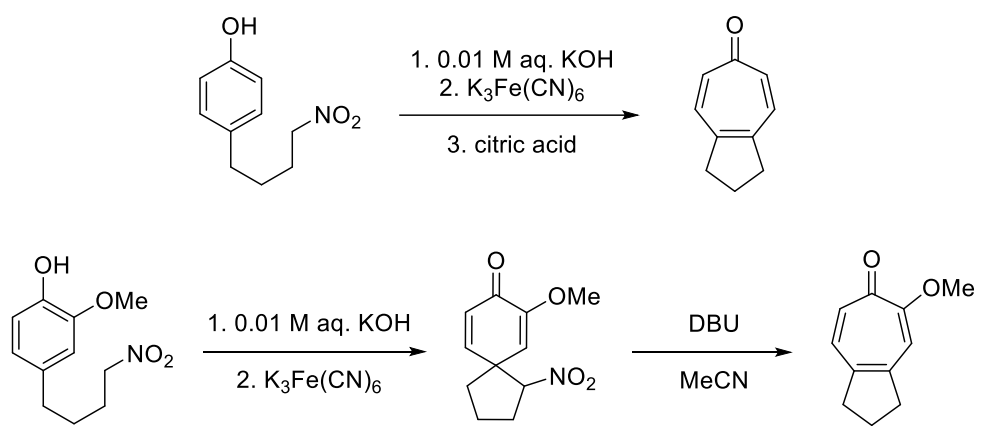


Scheme 2. Retrosynthetic process of Pareitropone

1.3. Kende coupling (Radical anionic coupling)

A. S. Kende and K. Kosh reported this coupling reaction for the synthesis of fused tropone analogs in 1986.[10] Phenolic nitronate, Kende coupling reaction precursor, was cyclized to tropone by intramolecular radical cyclization.

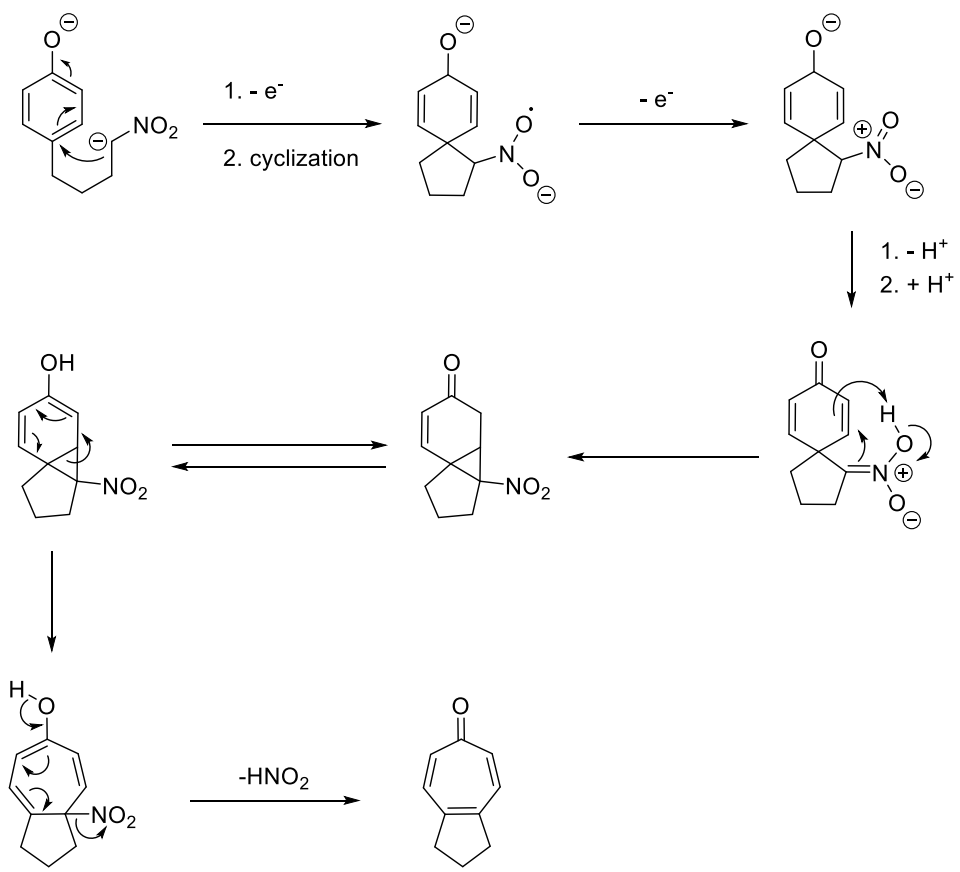
Under the alkaline condition, the dianion of precursor was formed and converted to spirocyclic hexadienone with $K_3Fe(CN)_6$ simultaneously. Citric acid or DBU transferred spirocyclic compound to tropone or tropolone by rearrangement.[10d]



Scheme 3. Kende radical anionic coupling reaction

In this reaction, it is important to generate dianion under basic condition for overall annulation. According to the mechanism, the excess amount of base must be used even though two equivalents of base are required. The Dianion went through radical anionic coupling

with Potassium ferricyanide. The norcaradiene was formed by intramolecular conjugate addition of the phenolic nitronate. Finally, desired tropone ring was produced due to the loss of HNO_2. (Scheme 4)

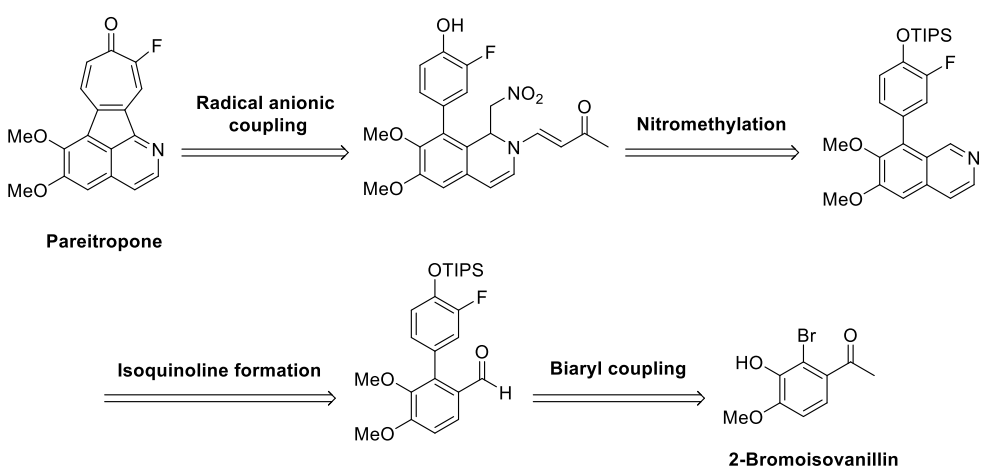


Scheme 4. Proposed mechanism of Kende coupling reaction

2. Results and Discussion

2.1. Retrosynthetic analysis

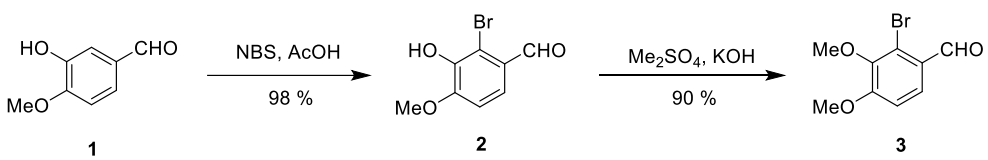
Kende coupling process was applied to the synthesis of pareitropone fluorine derivatives. Kende coupling product was prepared by radical anionic coupling of precursor named phenolic nitronate. This precursor was synthesized through addition of nitromethyl moiety by Reissert-type nitromethylation and deprotection of TIPS group. The biaryl isoquinoline was produced by Pomeranz-Fritsch Cyclization from biaryl tosyl amide. Biaryl tosyl amide was synthesized by sequential amination and tosylation from biaryl compound. The biaryl compound was produced by palladium-catalyzed Suzuki coupling with triisopropylsilyl protected fluorophenol boronic acid and bromobenzaldehyde. They might be derived from commercially available 4-bromo-2-fluorophenol and isovanillin. (Scheme 5)



Scheme 5. Retrosynthesis of Pareitropone fluorine derivatives

2.2. Synthesis of precursor for pareitropone fluorine derivatives

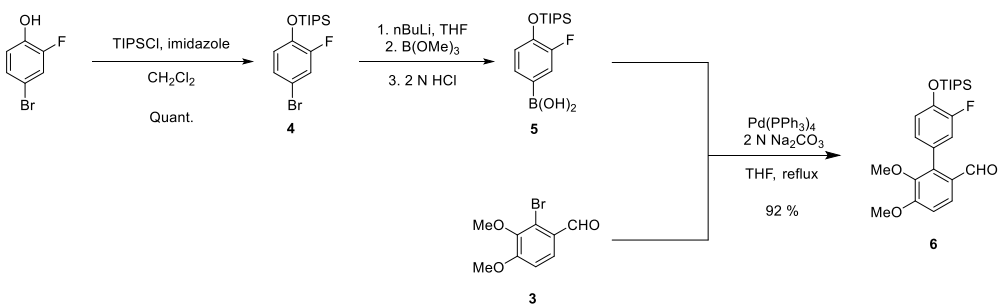
According to our group's synthetic strategy of pareitropone shown in Scheme 2, we attempted to synthesize fluorine-substituted precursors that can be applied to Kende's protocol. Although 8-bromoisovanillin **2** was commercially available, we decided to synthesize **2** to use isovanillin **1** as a starting material. Because it is easy to brominate regioselectively. 2-Bromoisovanillin **2** was obtained in 98% yield through NBS treatment in Acetic acid. Dimethoxybromobenzaldehyde **3** was synthesized by methylation using dimethyl sulfate with potassium hydroxide. (Scheme 6)



Scheme 6. Synthesis of Suzuki coupling precursor **3**

Next, Suzuki coupling catalytic reaction was used to synthesize biaryl compounds. The phenylboronic acid for the Suzuki

coupling was prepared by three steps sequence from 4-bromo-2-fluorophenol. Lithiation with n-BuLi produced phenyl lithium, which reacted with trimethylborate and hydrochloric acid to give boronic acid. Only performed by extraction and concentration, the purification step of boronic acid was skipped and the crude product was used immediately.[11] 4-bromo-2-fluorophenol and crude boronic acid was condensed to biaryl compound with $Pd(PPh_3)_4$ as a catalyst. Suzuki biaryl compound was synthesized in 92% yield. (Scheme 7)



Scheme 7. Synthesis of Suzuki coupling biaryl compound 6

In amination step, the installation of Dean-Stark trap to catch water is the most important. The reductive amination of 6 gave 70% yield in two steps to the corresponding amine compound 7 and tosyl group was introduced for the next reaction, Pomeranz-Fritsch anuulation. In previous study of our group which is synthesis of

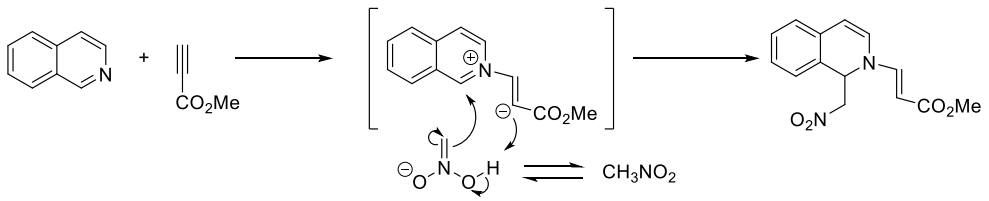
trimethoxyisoquinoline, 6N HCl was used for cyclization. However, in this biaryl compound, the TIPS group could be deprotected by HCl and it obtained very low yield with many side product. And then, 2, 4-dinitrobenzenesulfonic acid was used for the annulation reaction. Biaryl isoquinoline was obtained in 69% yield. (Table 1)

Table 1. Reaction conditions for cyclization

Entry	Acid	Eq.	Temp.	Solvent	Time	Result
1	6N HCl	5	Reflux	Dioxane	24 h	Decomposed
2	DNBS[a]	5	80 °C	Dioxane	1 h	32 %
3	DNBS	5	Reflux	Dioxane	1 h 30 min	69 %
4	DNBS	5	Reflux	Dioxane	3 h	35 %

[a]DNBS = 2,4-dinitrobenzenesulfonic acid

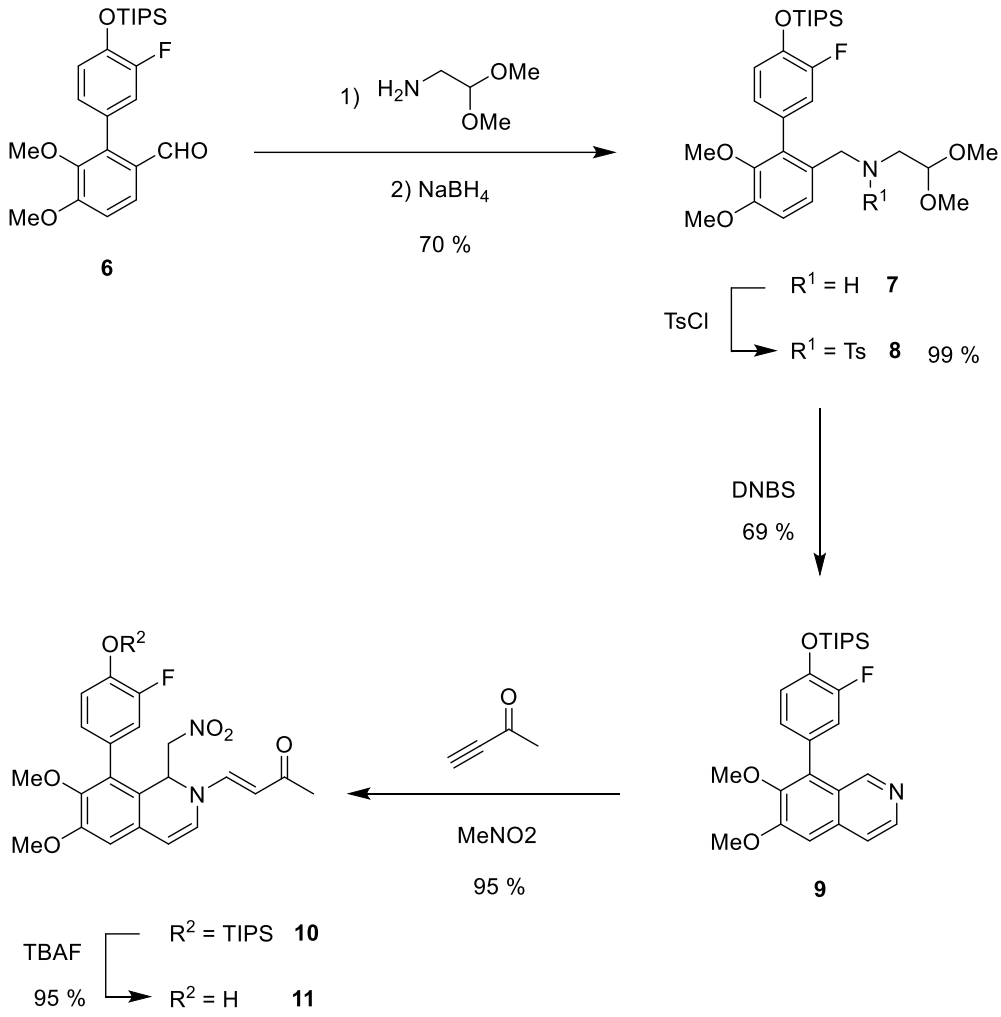
Then, nitromethylation was conducted by using Yadav's process. They produced nitromethyl derivatives of dihydroisoquinoline by using a coupling of three-components such as isoquinoline, activated alkynes and nitromethane at mild condition. They hypothesized that the reaction mechanism proceeded through a zwitter-ionic intermediate. It formed a desired 3 components coupling(3CC) product to react with nitromethane simultaneously. (Scheme 8)[12]



Scheme 8. Proposed mechanism of Reissert-type reaction by Yadav's group[13]

Then, we applied Yadav's nitromethylation protocol to our study. Nitromethyl- and 3-butyne-2-one groups were introduced into isoquinoline ring in 95% yield.

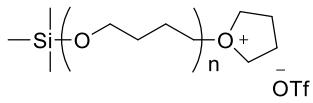
The TIPS protecting group was deprotected by tetrabutylammonium fluoride in 95% yield. Kende coupling precursor **11** led to the free phenol and the nitromethyl group ready to be applied to the Kende's protocol. (Scheme 8)



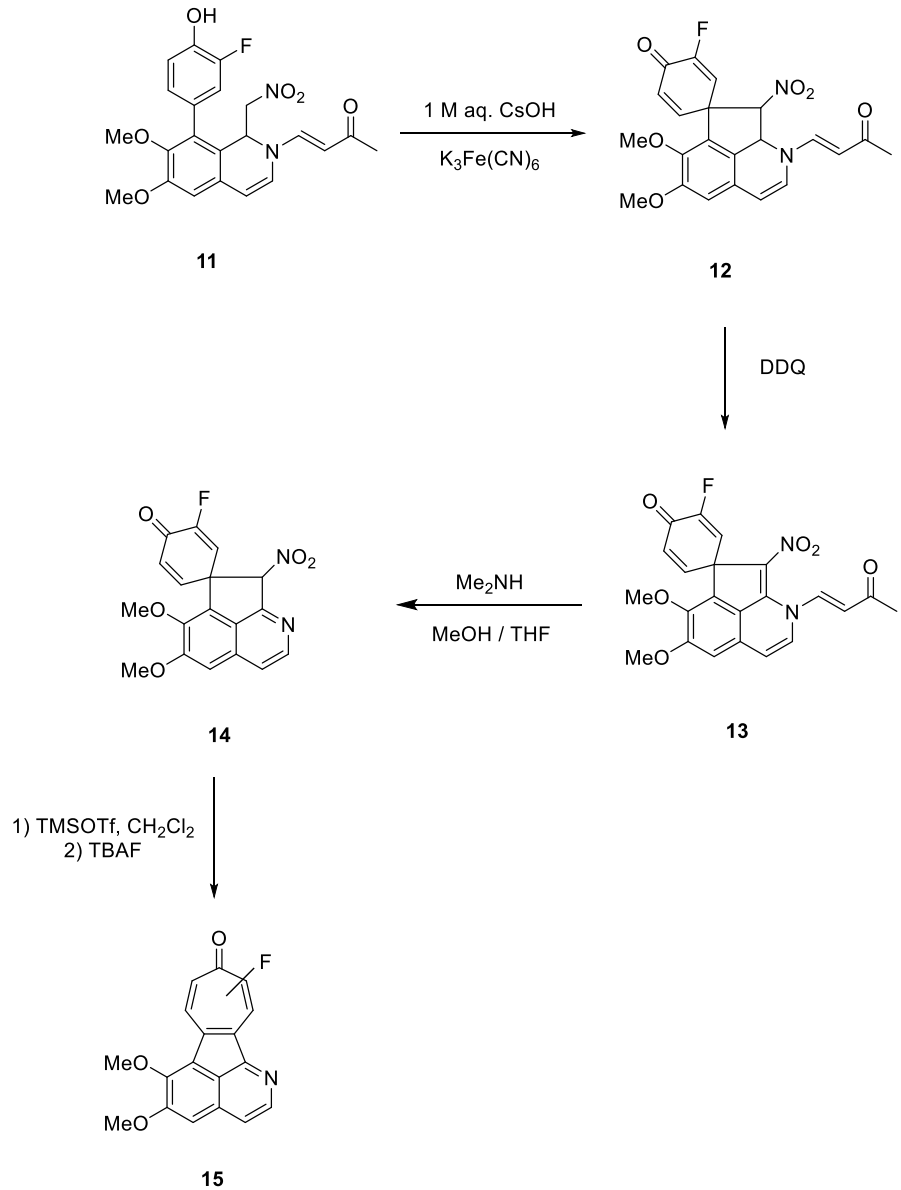
Scheme 9. Synthesis of Kende coupling precursor 11

2.3. Synthesis of pareitropone fluorine derivatives by Kende coupling reaction.

Kende coupling precursor **11** was dissolved in aqueous 1M CsOH solution to form dianion. And $K_3Fe(CN)_6$ dissolved in chloroform and H_2O was added by dianion to furnish spirocyclic intermediate. This reaction was proceeded for 12 hours to consume coupling precursor completely and it was quenched with citric acid. And then, we used celite pad filter to remove slurry generated during the quenching process. This intermediate was quite unstable at the light and atmosphere. In order to prevent decomposition of spirocyclic intermediate, we tried to eliminate water by extraction in dark condition without drying reagent. In order to convert it to a stable olefin, we added DDQ to the organic layer immediately and stirring 1 h vigorously. The more stable olefin observed on TLC as a yellow spot. And then, 3-butene-2-one moiety was removed by dimethyl amine treatment. After extraction process, compound **14** was obtained and observed on TLC as a orange colored spot. We decided to concentrate the crude **14** *in vacuo*. Since THF was easily polymerized by acidic reagent such as TMSOTf, we decided to change distilled THF to distilled DCM as a solvent. (Scheme 10)

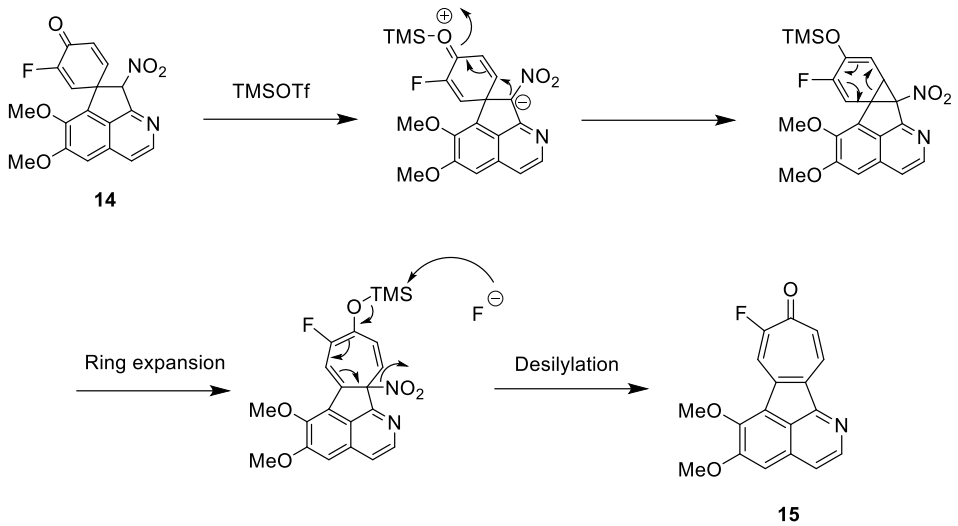


Scheme 10. Polymer derived from THF and TMSOTf



Scheme 11. Synthesis of Pareitropone fluorine derivatives 15

We thought **14** was treated with TMSOTf and then formed silyl ether intermediate, leading a rearrangement. Subsequently, treating of TBAF led to remove silyl and NO_2 group. (Scheme 12)



Scheme 12. Proposed mechanism of TMSOTf treatment step

Unfortunately, we obtained desired product **15** in 5% yield and unknown side product was obtained with a yield of 30 percent. We expected that the compounds **15** with fluorine on the left and right of the ketone should be synthesized, respectively. But we obtained just one of them. We have to identify the exact structure of the final product **15** not only through NMR but also through other methods.

We propose that we can improve yield of the TMSOTf treatment step by deprotonating proton of nitro moiety using base and Lewis acid to form cyclopropane ring.

3. Conclusion

Pareitropone fluorine derivative has been synthesized using commercially available isovanillin and 4-bromo-2-fluorophenol in a concise and efficient route. We has improved the yield of Pomeranz-Fritsch cyclization step controlling reaction condition. And then, Kende coupling precursor has been obtained to the efficient experiment methods in 35% with a 8-step process. We obtained the desired final product in overall 2% yield. Also, every compound have been characterized by NMR and GC-HRMS. Besides, we proposed the mechanism of the final reaction and the way to improve total yield. Therefore, this study is helpful for synthesizing various tropoloisoquinoline analogs. Also, it would be useful for conducting structure-activity relationship(SAR) studies our groups perform.

4. Experimental Details

4.1. General Information

Materials were obtained from commercial suppliers and used without further purification. Air or moisture sensitive reactions were conducted under nitrogen or argon atmosphere using oven-dried glassware and standard syringe/septa techniques. Solvents were purified prior to use. THF and ethyl ether were distilled by sodium benzophenone ketyl. Dichloromethane was distilled from CaH_2. MeOH was distilled from potassium carbonate. The reactions were monitored by analytical thin layer chromatography (TLC) using Merck 60 F_{254} glass plates pre-coated with a 0.25 nm thickness of silica gel under UV light (254 nm, 365 nm) followed by visualization with a staining solution such as ninhydrin, p-Anisaldehyde and phosphomolybdic acid, or I_2. Column Chromatography was conducted on silica gel 60 (70-230 mesh). NMR spectra were measured at commercially available spectrometers, ^1H at 400 MHz and ^{13}C at 100 MHz, in $CDCl_3$ unless stated otherwise and the data were reported as follows in ppm(δ) from the internal standard (TMS, 0.0 ppm): chemical shift (multiplicity, coupling constant in Hz, integration). High resolution mass spectra were measured by the EI ionization method.

4.2. General synthetic methods

2-Bromo-3-hydroxy-4-methoxybenzaldehyde (2) : A solution of **1** (7 g, 46 mmol) in acetic acid (110 mL) was added NBS (9 g, 50.6 mmol). The reaction mixture was stirred for 12 h. The mixture was washed with H_2O (50 mL) and little amount of acetone after filtration of the product followed by drying overnight in vacuum oven at 50 °C. The yield was 97% and product is a white solid. ^{1}H NMR ($CDCl_3$) δ 10.26 (s, 1H), 7.59 (d, J=8.4, 1H), 6.94 (d, J=8.4, 1H), 6.07 (s, 1H), 4.01 (s, 3H) ; ^{13}C NMR ($CDCl_3$) δ 190.92, 151.69, 143.19, 127.23, 122.77, 112.87, 109.27, 56.61; HRMS (EI) [M+] calcd for $C_8H_7BrO_3$ 229.9579, found 229.9572

2-Bromo-3,4-dimethoxybenzaldehyde (3) : A solution of **2** (8.5 g, 36.8 mmol) and KOH (3.8g, 67.4 mmol) in H_2O (45 mL) was added Me_2SO_4 over 10 min at 50 °C. The reaction mixture was stirred for 50 min, then cooled to 0 °C. The resulting mixture was washed with H_2O (40 mL) and 1M NaOH (15 mL). Gained precipitate was dissolved in CH_2Cl_2. The dissolved mixture was extracted with CH_2Cl_2 (3 x 20 mL) and brine. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (1:3 Hexane-EtOAc) afforded **3** (8.12 g, 90%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 10.26 (s, 1H), 7.76 (d, J=8.8, 1H)

6.98(d, J=8.8, 1H) 3.96 (s, 3H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 190.94, 158.65, 146.32, 127.28, 126.50, 123.09, 110.93, 60.66, 56.32; HRMS (EI) [M+] calcd for $C_9H_9BrO_3$ 243.9735, found 243.9728

(4-bromo-2-fluorophenoxy)triisopropylsilane (4) : A solution of 4-bromo-2-fluorophenol (25 g, 130.9 mmol) in CH_2Cl_2 (350 mL) was added imidazole (17.8 g 261.8 mmol) and TIPSCl (32.2 mL, 150.5 mmol). The reaction mixture was stirred 12 h at room temperature, then extracted with CH_2Cl_2 (40 mL x 3), and brine. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (Hexane) afforded silyl protected phenol **4** (46.1 g, Quant) as a colorless liquid. ^{1}H NMR ($CDCl_3$) δ 7.2 (m, 1H), 7.1 (m, 1H), 6.8 (t, J=8.8, 1H), 1.3 (m, 3H), 1.1 (d, J=7.2, 18H); ^{13}C NMR ($CDCl_3$) δ 155.25(d, $^1J_{CF}$=247.8), 143.46, 127.28, 122.86, 120.01, 112.43, 17.77, 12.70; HRMS (EI) [M+] calcd for $C_{15}H_{24}BrFOSi$ 346.0764, found 346.0759

(3-fluoro-4-((triisopropylsilyl)oxy)phenyl)boronic acid (5) : Dissolved silyl protected phenol **4** (20 g, 57.7 mmol) in distilled THF(200 mL) under nitrogen atmosphere and cooled it to −78 °C. Then n-BuLi (23.9 mL, 115.1mmol) was added slowly to the solution at −78 °C and stirring 1h. $B(OMe)_3$ (23.9 mL, 230.3 mmol) was added.

The reaction mixture was stirred 12 h at −78 °C to room temperature, then cooled to 0 °C. 2 N HCl was added in the solution and stirring 30 min. The organic layer was separated through extraction with EtOAc (30 mL x 3) and dried over $MgSO_4$. After the concentration of the organic solvent using a rotary evaporator, the crude mixture of **5** was used to the next reaction without purification.

3'−fluoro−5,6−dimethoxy−4'−((triisopropylsilyl)oxy)−[1,1'−biphenyl]−2−carbaldehyde (6) : Boronic acid **5** in THF and 2 M aqueous Na_2CO_3 (8.2 mL) was added by a solution of **3** (500 mg, 2 mmol) with $Pd(PPh_3)_4$ (94 mg, 0.082 mmol) and THF at room temperature. The reaction mixture was heated at reflux for 5 h 30 min, then cooled to room temperature. The crude mixture was extracted with EtOAc (30 mL x 3) and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (8:1 hexane−EtOAc) afforded biaryl compound **6** (795 mg, 92%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 9.65(s, 1H), 7.83(d, J=8.8, 1H), 6.93−7.12 (m, 4H), 3.98 (s, 3H), 3.52 (s, 3H), 1.35 (m, 3H), 1.14 (d, J=7.2, 18H) ; ^{13}C NMR ($CDCl_3$) δ 191.05, 157.73, 154.70, 152.26, 146.21, 143.95, 143.83, 139.08, 128.13, 126.81, 126.78, 126.21, 126.14, 124.80, 121.36, 118.91, 118.71, 111.43, 60.58, 56.05, 17.78, 12.70; HRMS (EI) [M+] calcd for $C_{24}H_{33}FO_4Si$ 432.2132, found 432.2128

N-((3'-fluoro-5,6-dimethoxy-4'-((triisopropylsilyl)oxy)-[1,1'-biphenyl]-2-yl)methyl)-2,2-dimethoxyethan-1-amine (7) : A solution of biaryl benzaldehyde **6** (2.34 g, 5.4 mmol) in benzene (47 ml) was added aminoacetaldehyde dimethylacetal (0.77 mL, 7 mmol). The reaction mixture was stirred under reflux for 5 h with an azeotropic removal of water through dean-stark trap. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude imine was dissolved in ether (42 mL), and $NaBH_4$ (0.51 g, 13.5 mmol) in MeOH (4.3 mL) was added at 0 ℃. The resulting mixture was stirred for 1 h 30 min and quenched with saturated aqueous NH_4Cl (15 mL) , and extracted with EtOAc (30 mL x 3). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (2:1 hexane-EtOAc) afforded amine compound **7** (1.98 g, 70%) as a transparent oil: ^1H NMR ($CDCl_3$) δ 6.88-7.12(m, 5H), 4.36 (m, 1H), 3.88 (s, 3H), 3.50 (s, 2H), 3.49 (s, 3H), 3.30 (s, 6H) 2.54 (d, J=5.2, 2H), 1.30 (m, 3H), 1.13 (d, J=7.2, 18H) ; ^{13}C NMR ($CDCl_3$) δ 154.70, 152.26, 151.78, 146.72, 142.89, 142.77, 135.07, 131.27, 129.98, 129.92, 125.55, 125.52, 124.49, 121.24, 121.24, 117.97, 117.77, 111.49, 103.72, 60.26, 55.69, 53.55, 56.00, 50.27, 17.69, 12.65 ; HRMS (EI) [M+] calcd for $C_{28}H_{44}FNO_5Si$ 521.2973, found 521.2978

N-(2,2-dimethoxyethyl)-N-((3'-fluoro-5,6-dimethoxy-4'-((triisopropylsilyl)oxy)-[1,1'-biphenyl]-2-yl)methyl)-4-methylbenzenesulfonamide (8) : A solution of **7** (1.67 g, 3.2 mmol), triethylamine (1.33 mL, 9.6 mmol) and DMAP (39 mg, 0.32 mmol) in CH_2Cl_2 (80 mL) was added TsCl(732 mg, 3.84 mmol) at room temperature. The reaction mixture was stirred for 3 h and extracted with CH_2Cl_2 (30 mL x 3). The combined organic extracts were dried with $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (8:1 hexane-EtOAc) afforded sulfonamide **8** (2.1 g, 99%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.60(d, J=8.4, 2H), 7.18-7.24 (m, 3H), 6.75-6.97 (m, 4H), 4.18 (m, 2H), 3.88 (s, 3H), 3.45 (s, 3 H), 3.13(s, 6H) 2.41 (s, 3H), 2.17 (s, 2H) 1.31 (m, 3H), 1.11 (d, J=7.2, 18H) ; ^{13}C NMR ($CDCl_3$) δ 154.76, 152.32, 151.92, 146.42, 143.12, 143.03, 142.92, 137.33, 134.83, 129.54, 129.40, 129.33, 127.31, 127.02, 125.66, 125.64, 123.95, 121.43, 117.98, 117.79, 111.73, 103.38, 60.39, 55.84, 54.32, 54.16, 49.95, 49.46, 30.84, 21.43, 17.74, 12.64; HRMS (EI) [M+] calcd for $C_{35}H_{50}FNO_7SSi$ 675.3061, found 675.3063

8-(3-fluoro-4-((triisopropylsilyl)oxy)phenyl)-6,7-dimethoxyisoquinoline (9) : A solution of **8** (410 mg, 0.61 mmol) in dioxane (25 mL) was added to a solution of 2,4-dinitrobenzenesulfonic acid (752 mg, 3.03 mmol) in dioxane (50 mL)

for 1 hour at 80 °C. The reaction mixture was stirred for 30 min at 110 °C reflux and cooled to room temperature. After saturated aqueous NaHCO3 (50 mL) had been added, the mixture was extracted with EtOAc (30 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (4:1 hexane–EtOAc) afforded isoquinoline **9** (192 mg, 69%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.82 (s, 1H), 8.41 (d, J=5.6, 1H), 7.55 (d, J=5.2, 1H), 7.01−7.15 (m, 4H), 4.04(s, 3H), 3.60 (s, 3H), 1.38 (m, 3H), 1.16 (d, J=7.6, 18H) ; ^{13}C NMR ($CDCl_3$) δ 155.82, 154.96, 152.52, 149.83, 147.26, 143.73, 143.61, 142.56, 134.49, 131.32, 127.12, 127.05, 126.60, 126.57, 121.65, 119.30, 118.87, 118.68, 105.01, 60.92, 55.92, 31.69, 17.81, 12.72; HRMS (EI) [M+] calcd for $C_{26}H_{34}FNO_3Si$ 455.2292, found 455.2289

(E)−4−(8−(3−fluoro−4−hydroxyphenyl)−6,7−dimethoxy−1−(nitromethyl)isoquinolin−2(1H)−yl)but−3−en−2−one (11) : A solution of **9** (406 mg, 0.89 mmol) in $MeNO_2$ (5 mL) was added at room temperature 3−butyn−2−one (0.104 ml, 1.34 mmol). The reaction mixture was stirred for 30 min and extracted with CH_2Cl_2 (3 x 10 mL) and NH_4Cl aqueous solution. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (8:1 hexane–EtOAc) afforded nitromethyl isoquinoline **10** (494 mg, 95%) as a yellow bubble−like solid. TBAF

(170 mg, 0.65 mmol) was added at room temperature to a solution of **10** (318 mg, 0.54 mmol) in THF (15 mL). The reaction mixture was stirred for 30 min, quenched with saturated aqueous NH_4Cl (10 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (1:2 hexane–EtOAc) afforded phenol **11** (344 mg, 95%) as a yellow bubble-like solid: ^1H NMR ($CDCl_3$) δ 7.77 (br, s, 1H), 6.73-7.32 (m, 4H), 6.70 (s, 1H), 6.46 (d, J=7,2, 1H), 6.11 (d, J= 7,2, 1H), 5.51 (m, 2 H), 4.58(m, 1H), 4.02 (m, 1H), 3.89 (s, 3H), 3.55 (d, J=8.0, 3H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 197.50, 197.41, 153.39, 152.67, 150.28, 147.58, 147.48, 146.86, 146.75, 144.70, 144.64, 144.57, 144.52, 133.30, 127.07, 125.85, 125.03, 118.48, 117.54, 116.51, 116.32, 111.55, 108.97, 102.37, 61.05, 60.96, 55.94, 28.26; HRMS (EI) [M+] calcd for $C_{22}H_{21}FN_2O_6$ 428.1384, found 428.1467

8-fluoro-5,6-dimethoxy-9H-azuleno[1,2,3-ij]isoquinolin-9-one (15) : The nitromethylated biaryl phenol **11** (300 mg, 0.70 mmol) was dissolved in 1.0 M aqueous CsOH (5.6 mL) and then diluted with H_2O (10 mL). The prepared dianion was subjected to a solution of $K_3Fe(CN)_6$ (853 mg, 2.6 mmol) in H_2O (10 mL) and $CHCl_3$ (20 mL) over 10 min at 0 ℃ in the dark. After 12 h stirring, It was quenched with citric acid. The reaction mixture was filtered through a pad of

celite. The filter cake was washed with $CHCl_3$ and water. And then, the organic layer was separated by extraction with $CHCl_3$ (30 mL x 2). Then DDQ (318 mg, 1.4 mmol) was added to the combined organic layer and stirring 1 h vigorously. It was quenched by saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ (30 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was subjected to the next reaction without any purification. To a solution of crude mixture **13** in THF (5 mL) was added 2 M Me_2NH in MeOH (5 mL). The mixture was stirred 1 h then it was concentrated by rotary evaporator. Obtained crude mixture **14** was dissolved in distilled DCM (28 mL) at nitrogen atmosphere. TMSOTf (0.51 mL, 2.80 mmol) was dropped to the solution slowly and stirred 30 min at room temperature. Then TBAF (732 mg, 2.80 mmol) was added at room temperature in the dark. The reaction mixture was stirred for 30 min, and then extracted with Dichloromethane and Brine(3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (1:4 hexane−EtOAc) afforded **15** (11 mg, 5% in 4 steps) as a reddish solid. ^{1}H NMR ($CDCl_3$) δ 8.74 (d, J=5.2, 1H), 8.416 (d, J=19.6 1H), 8.33 (d, J=12, 1H), 7.57 (d, J=5.2, 1H), 7.49 (dd, J_1=12.2, J_2=8.2 , 1H), 7.19 (s, 1H), 4.23 (s, 3H), 4.09 (s, 3H) ; ^{13}C NMR ($CDCl_3$) δ 178.16, 177.96, 167.19, 164.56, 158.85, 157.08, 151.84, 146.75, 139.31, 139.24,

139.19, 139.08, 138.95, 130.68, 129.39, 124.27, 120.24, 118.62, 117.52, 117.19, 108.09, 62.24, 56.65, 31.94, 31.25, 29.71; HRMS (EI) [M+] calcd for $C_{18}H_{12}FNO_3$ 309.0801, found 309.0801

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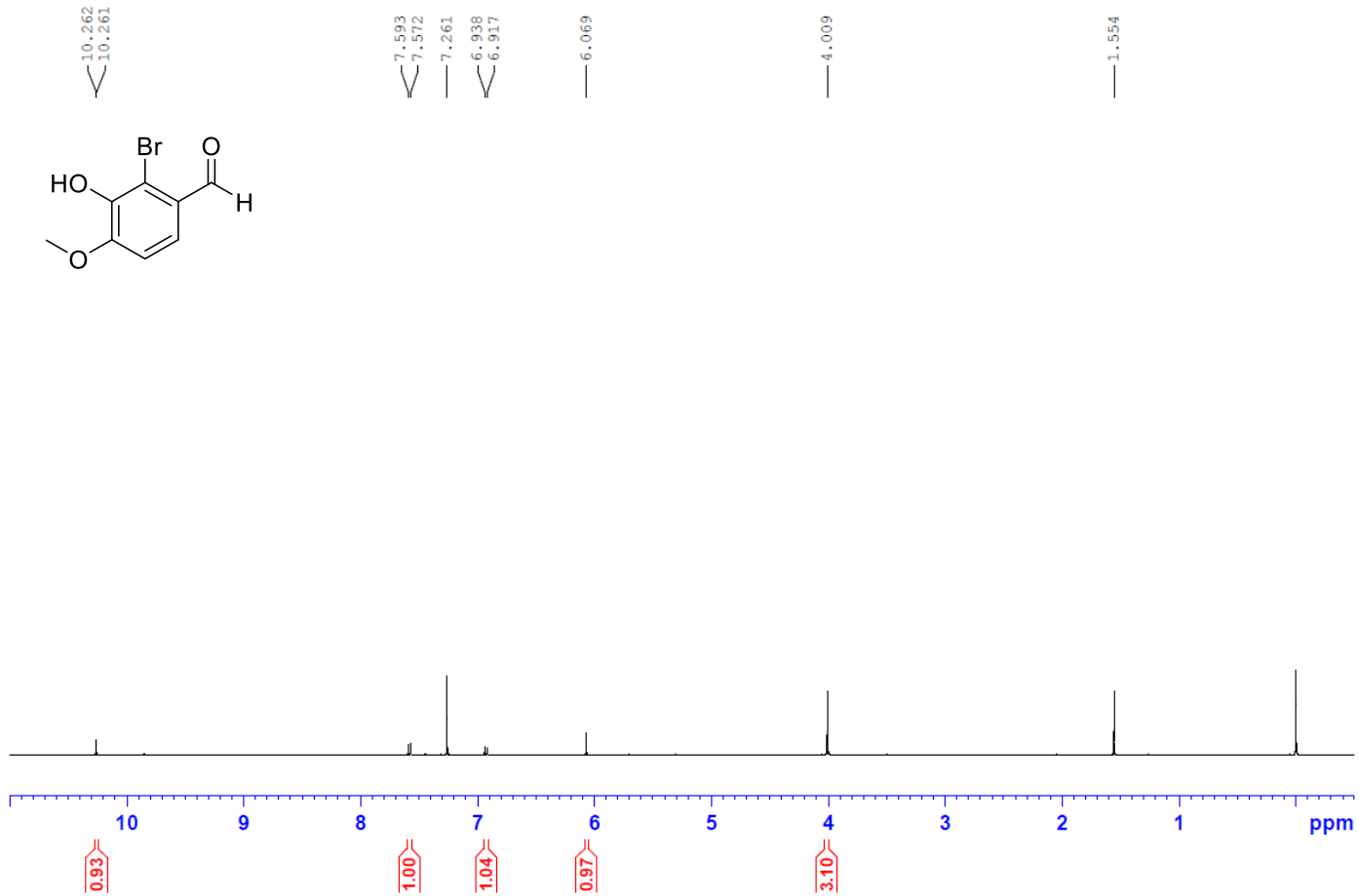
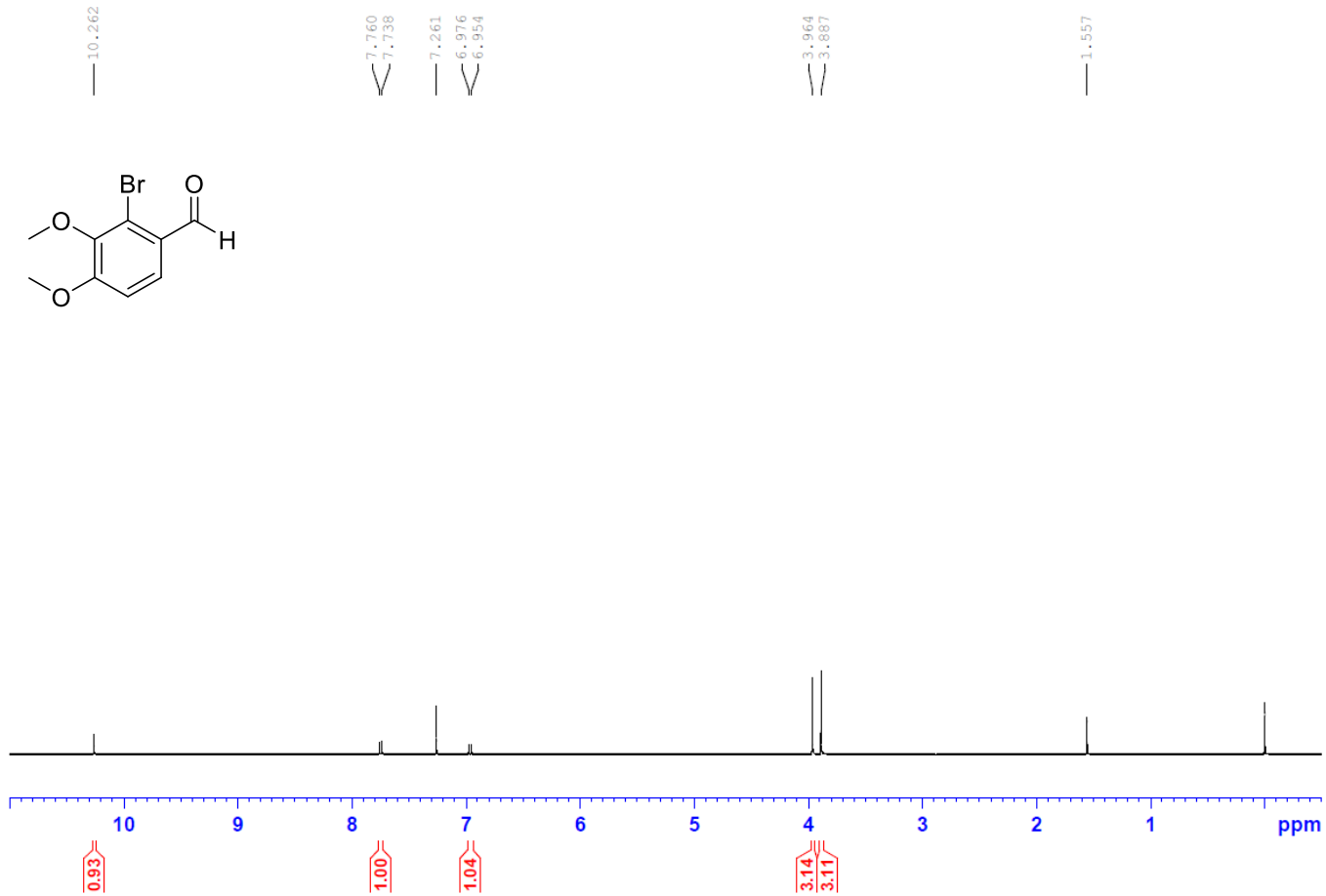
APPENDICES

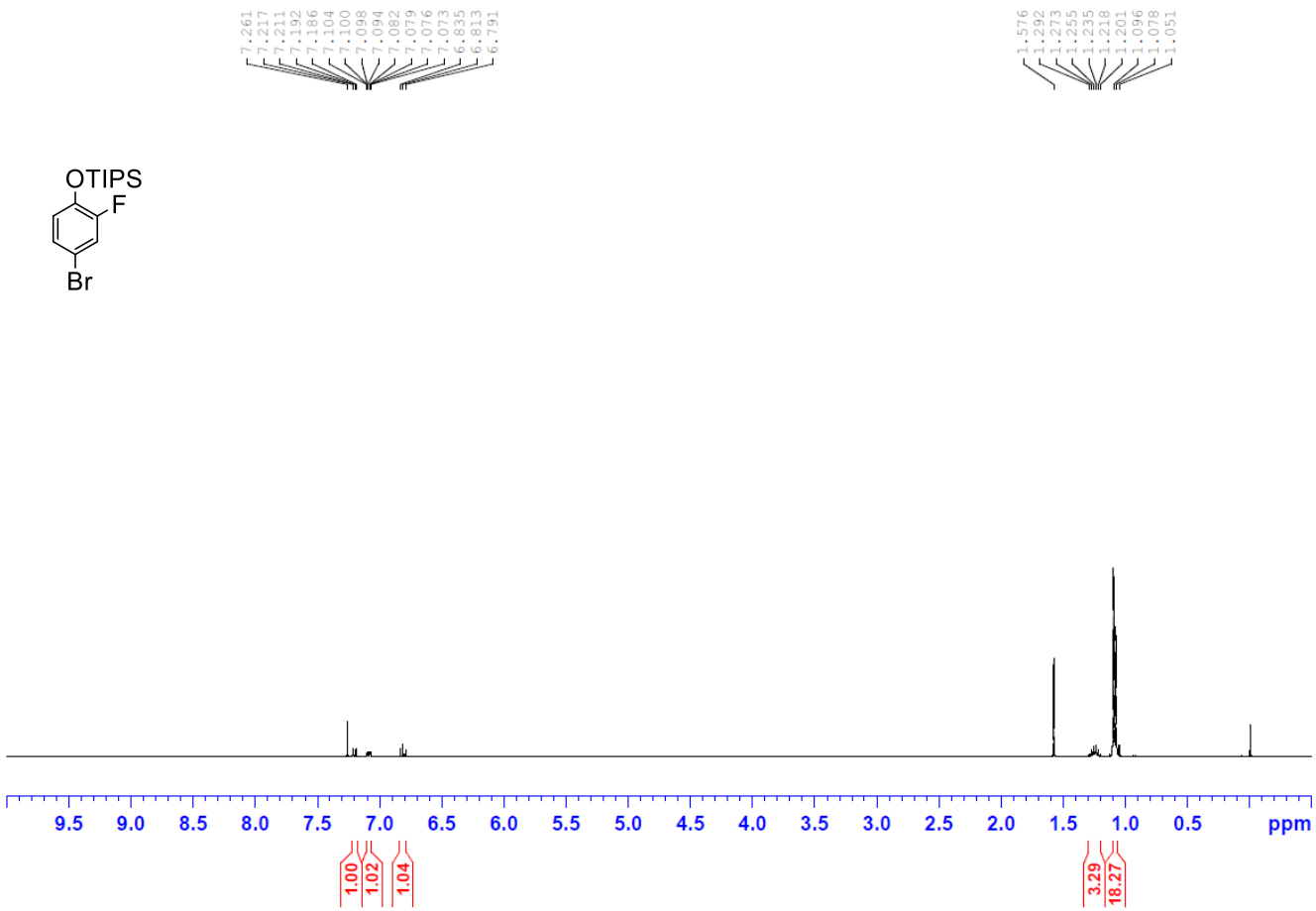
List of ^{1}H NMR Spectra of Selected Compounds



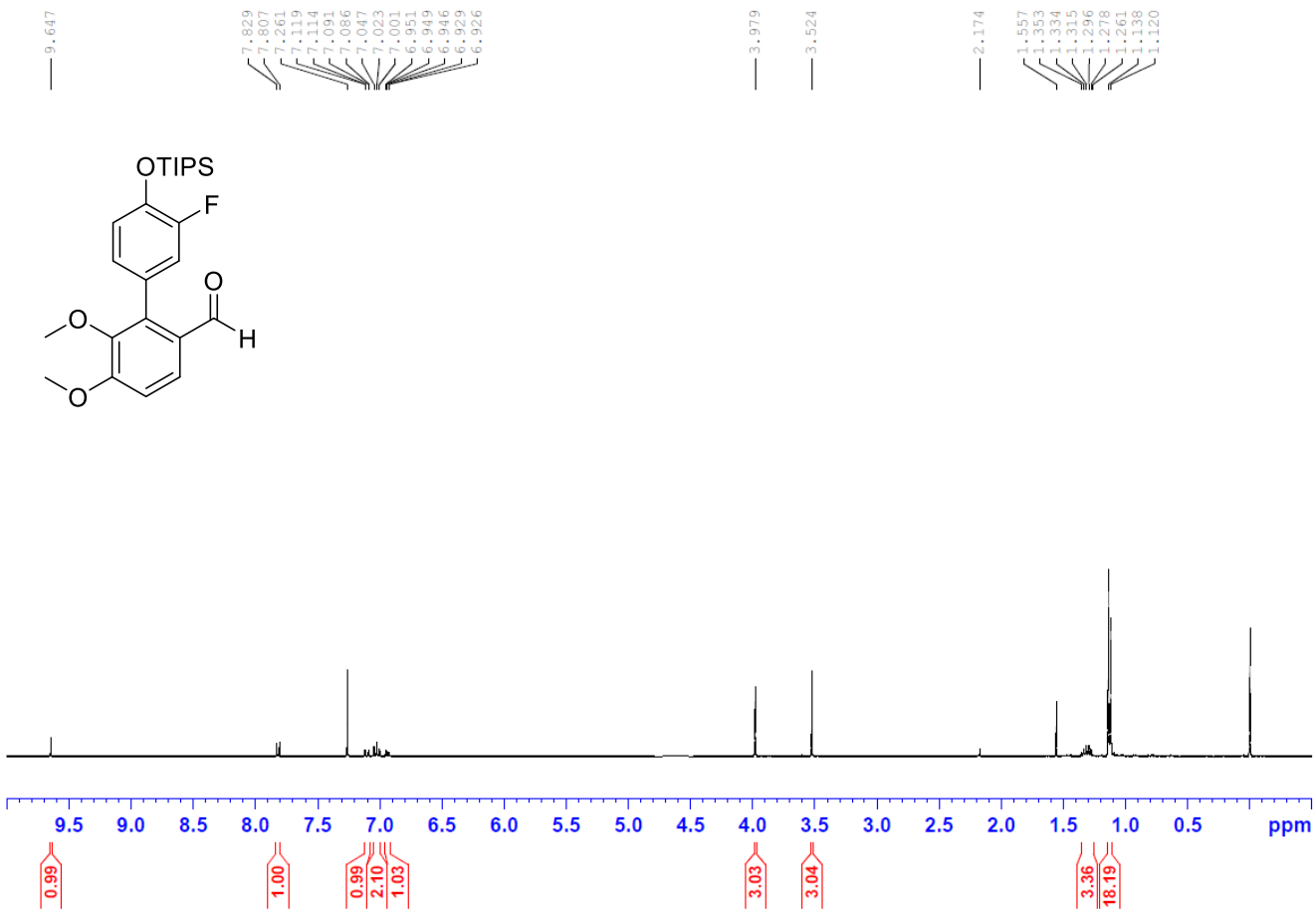
1. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **2**



2. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **3**



3. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **4**



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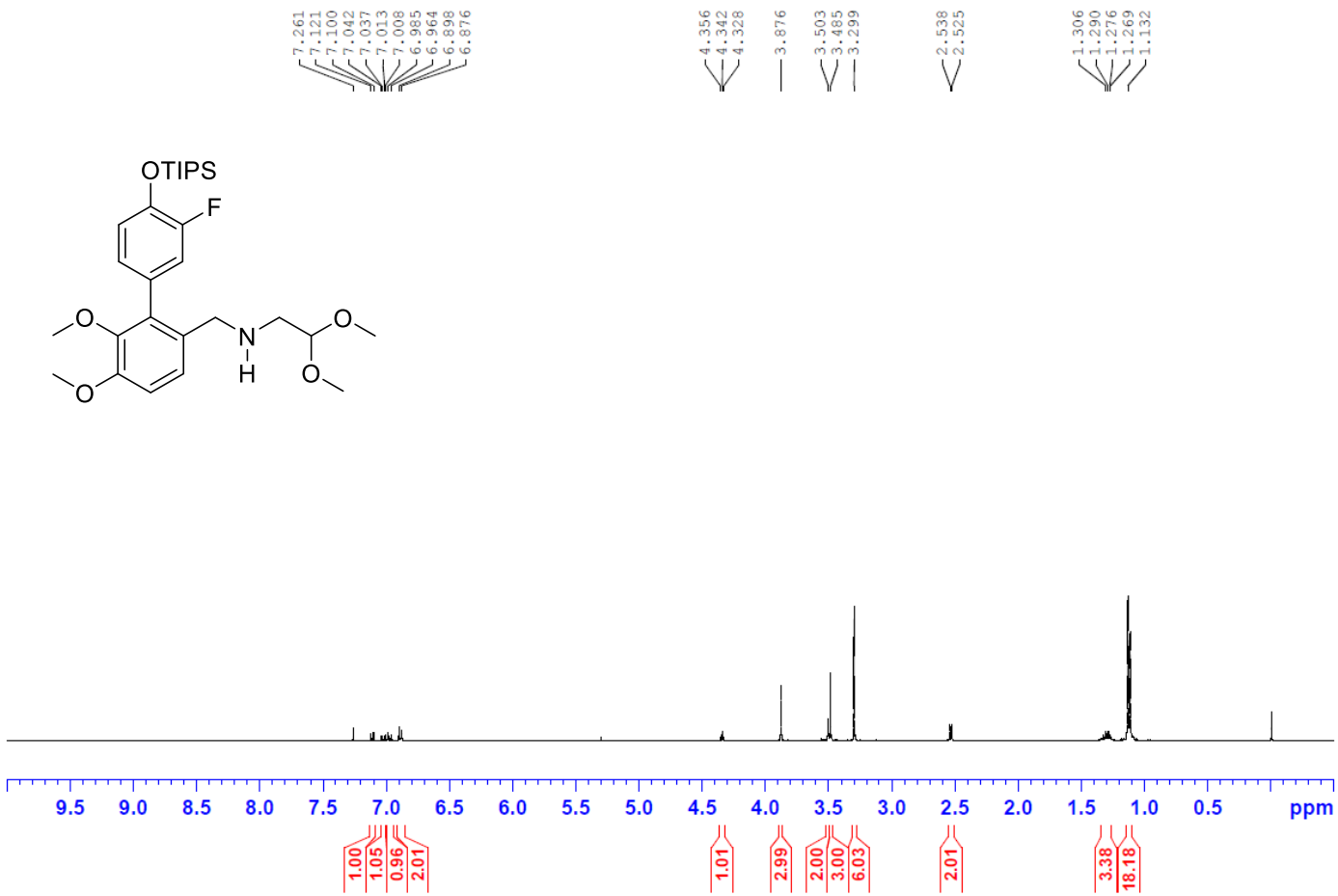
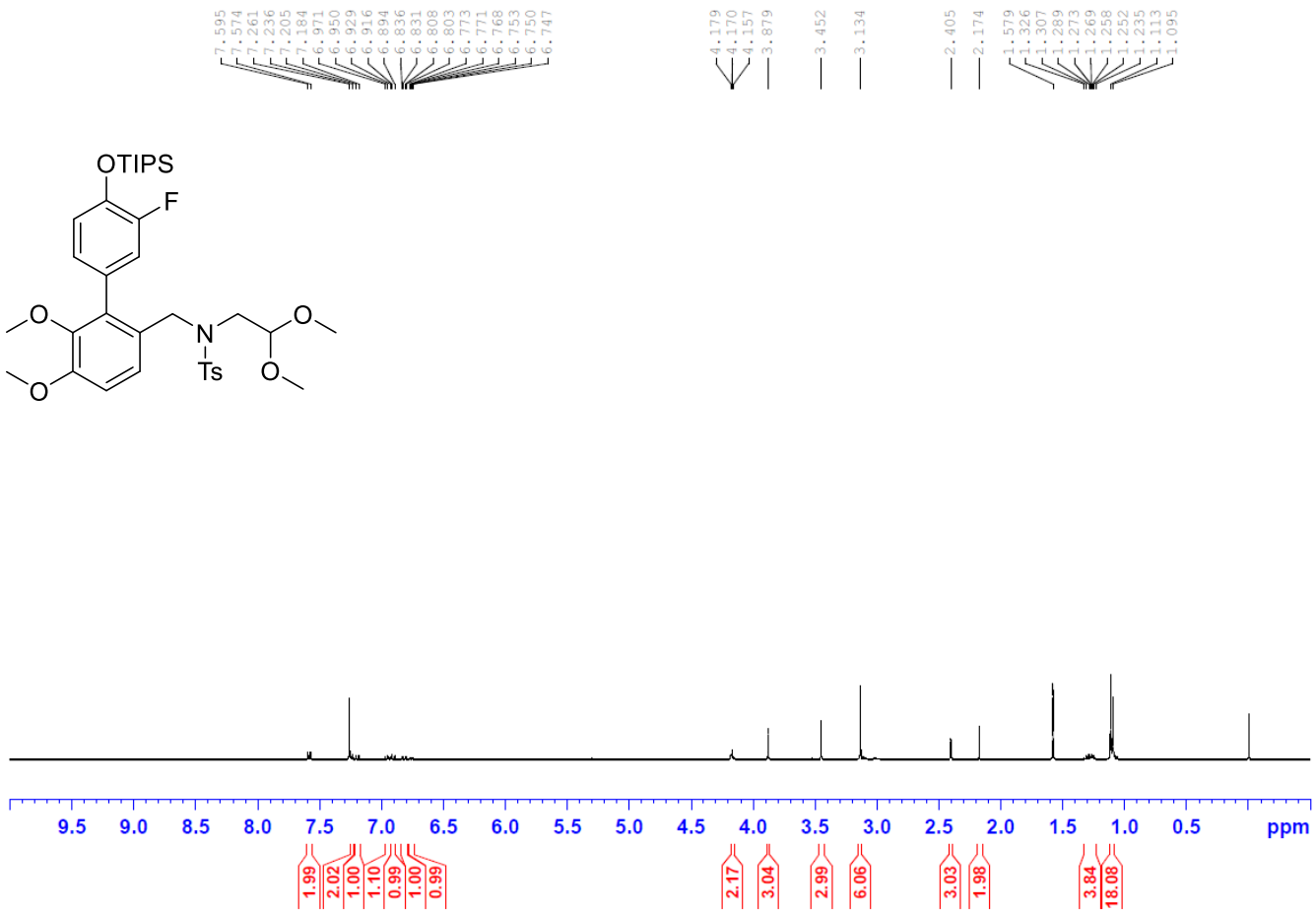
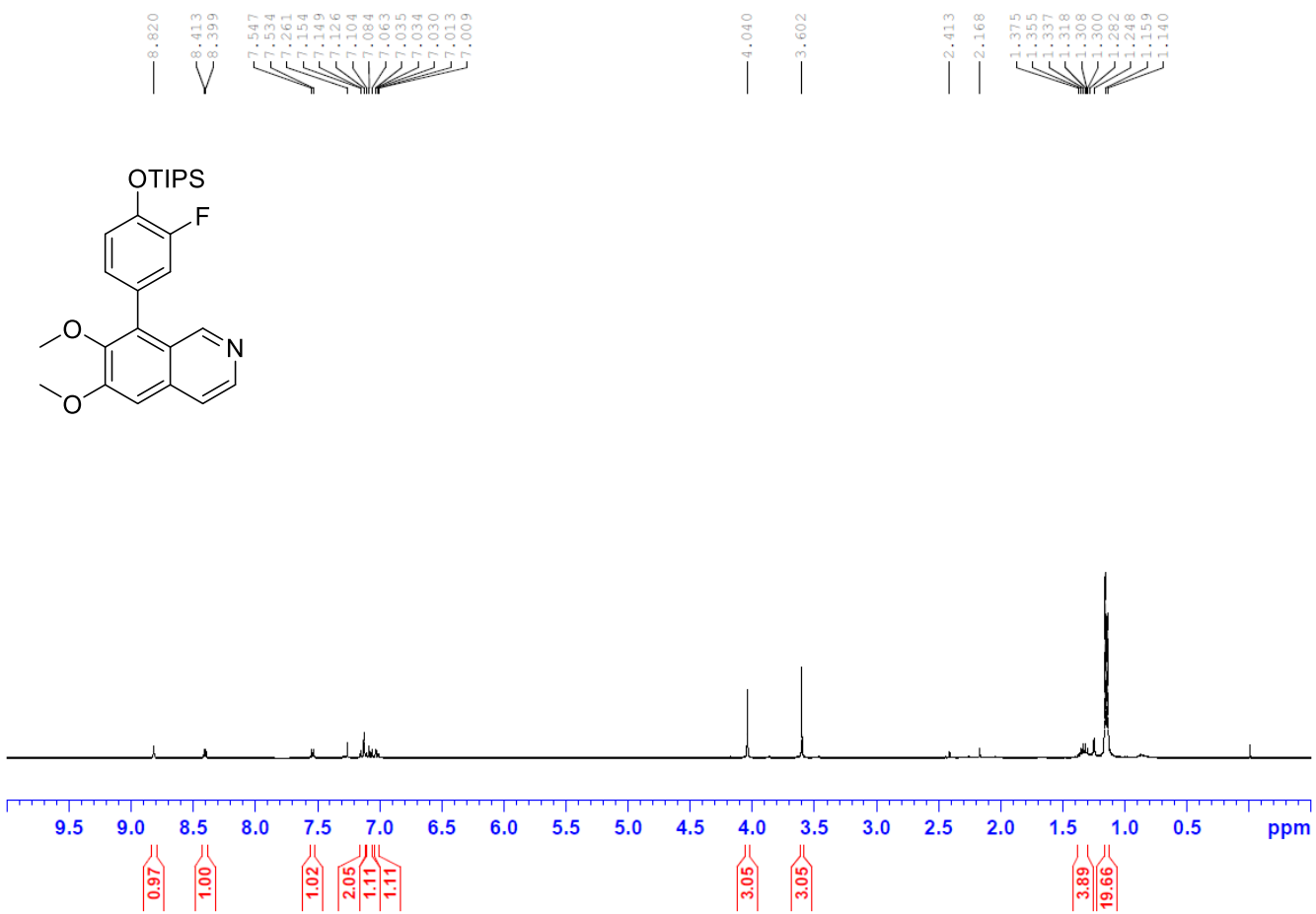


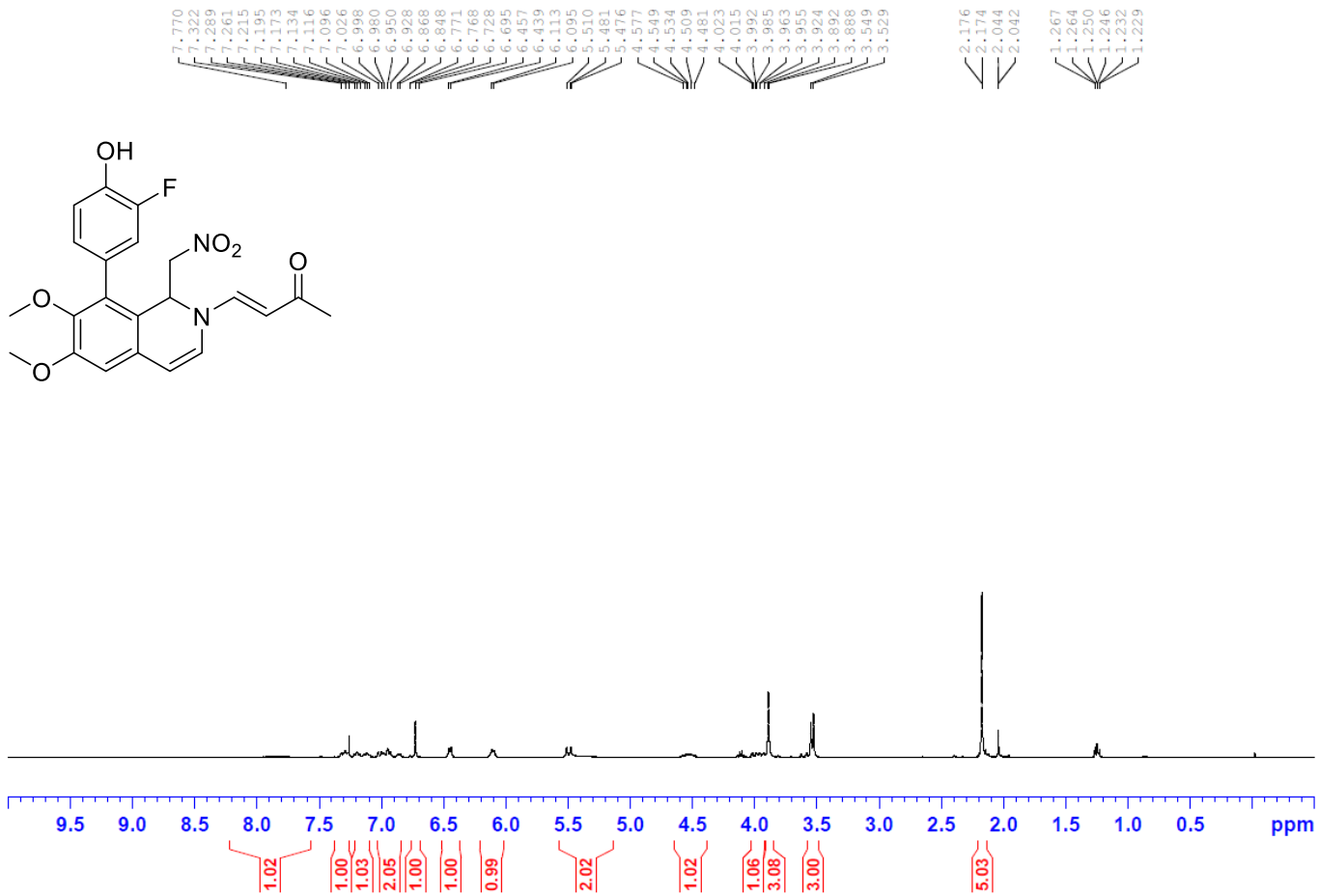
5. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **7**



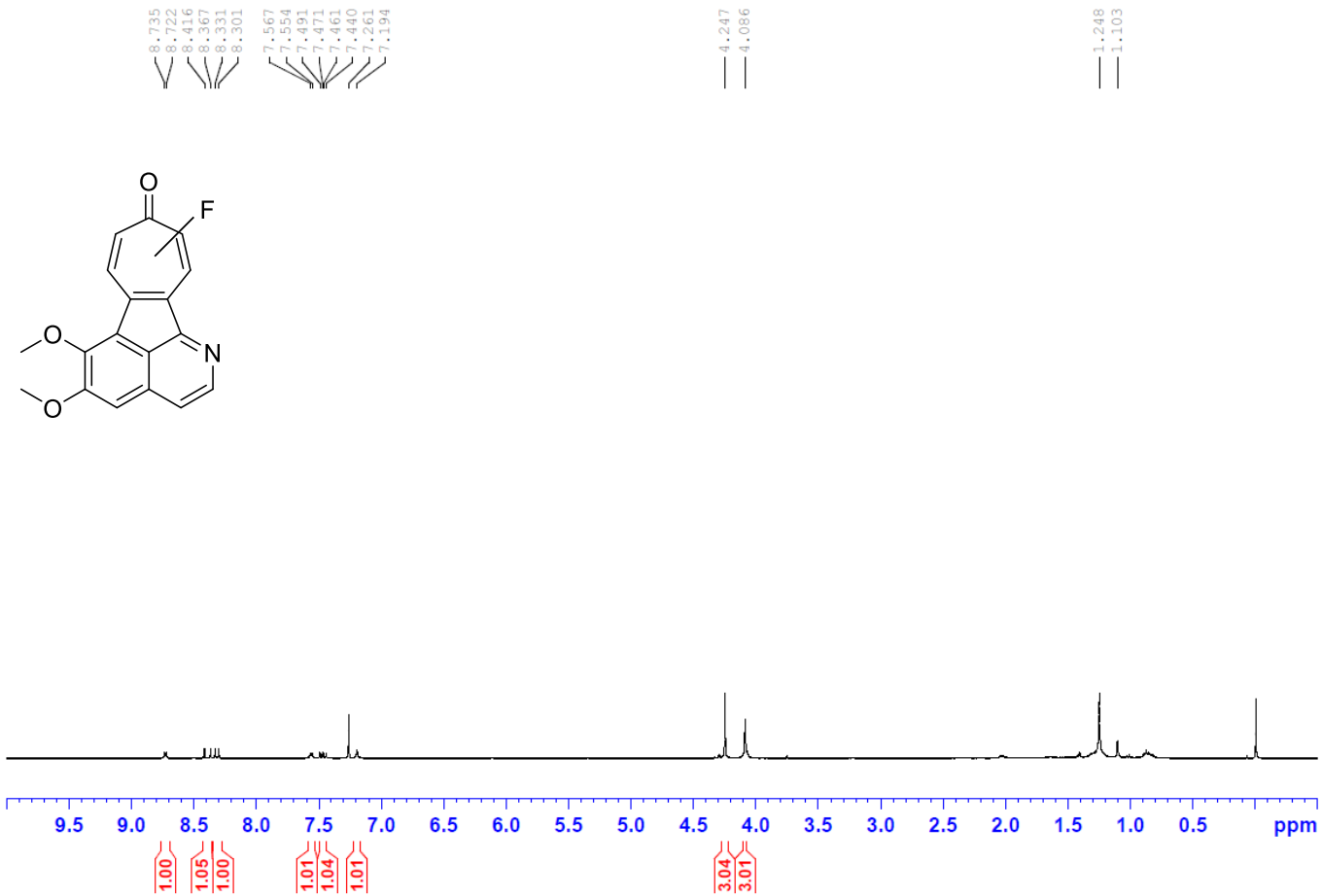
6. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **8**



7. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **9**

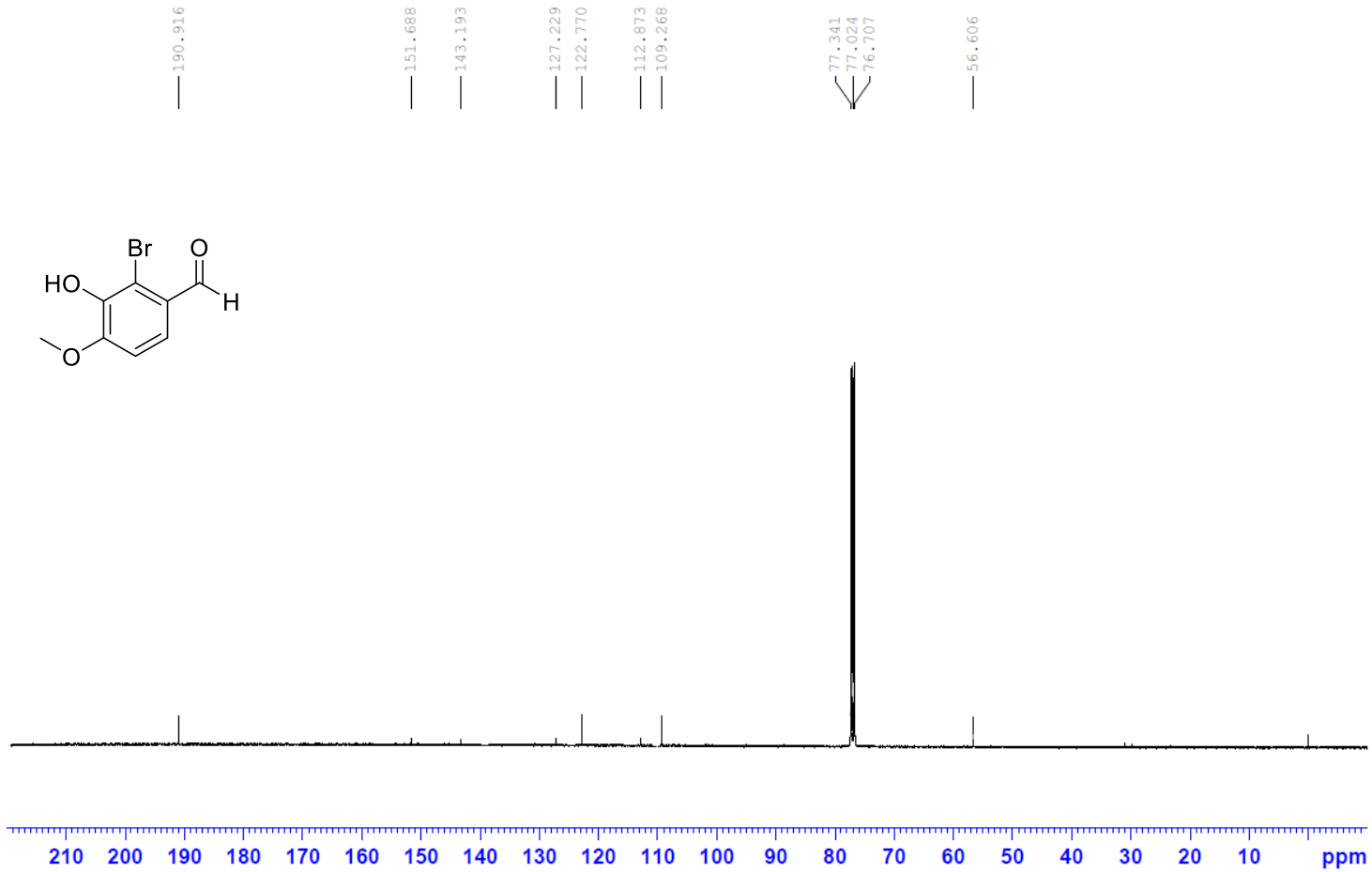


8. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **11**

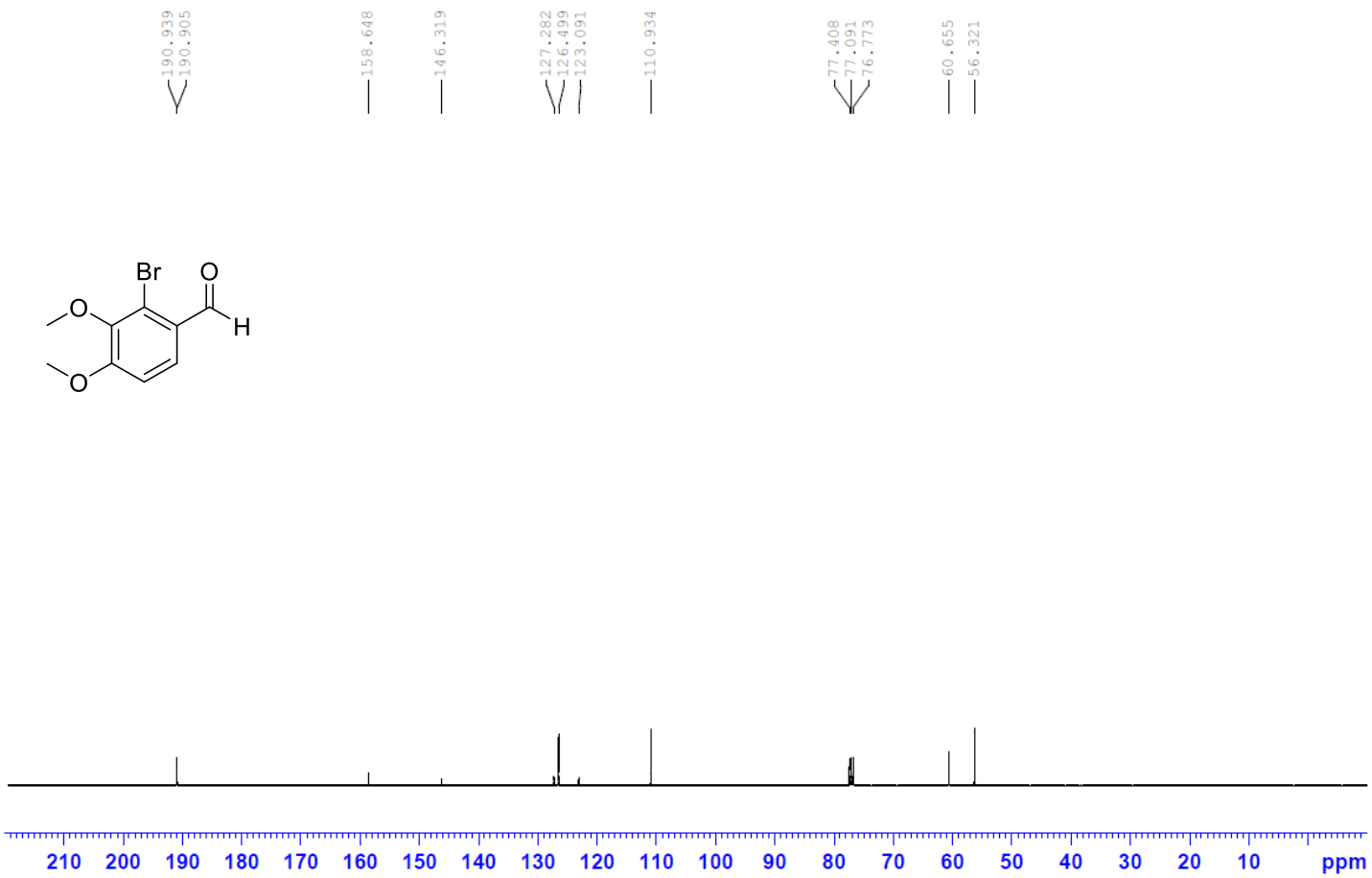


9. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **15**

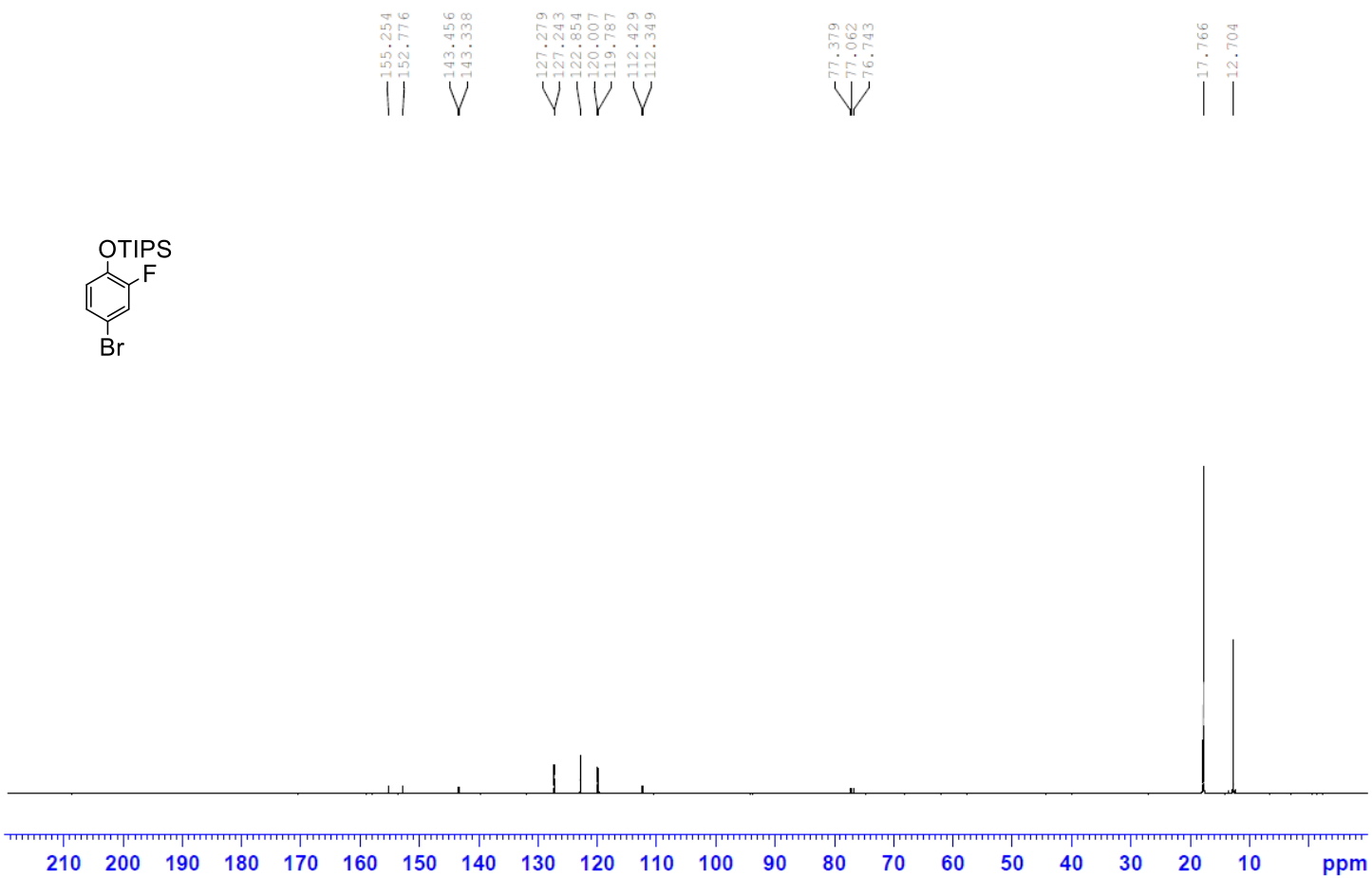
List of ^{13}C NMR Spectra of Selected Compounds



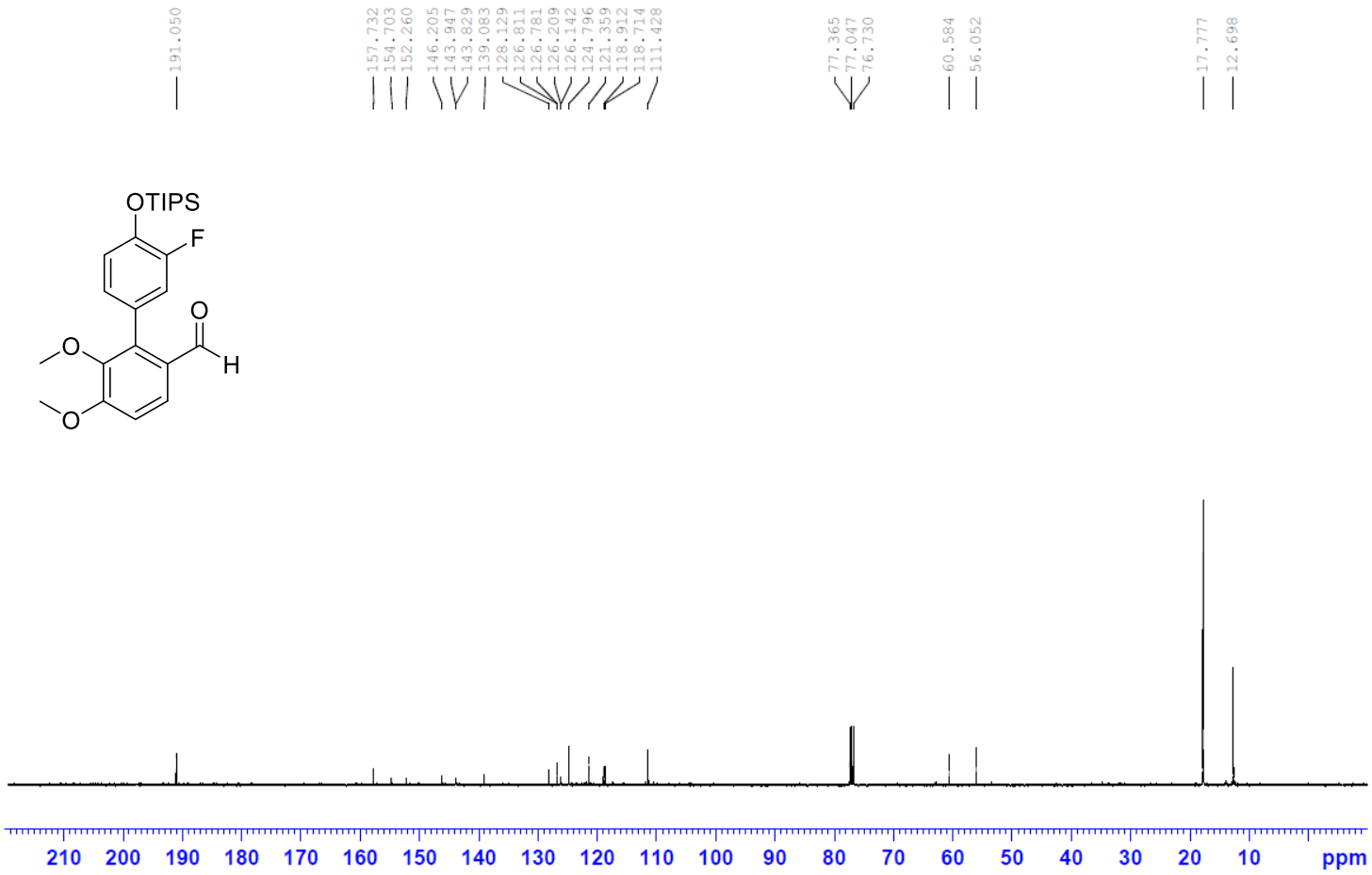
1. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **2**



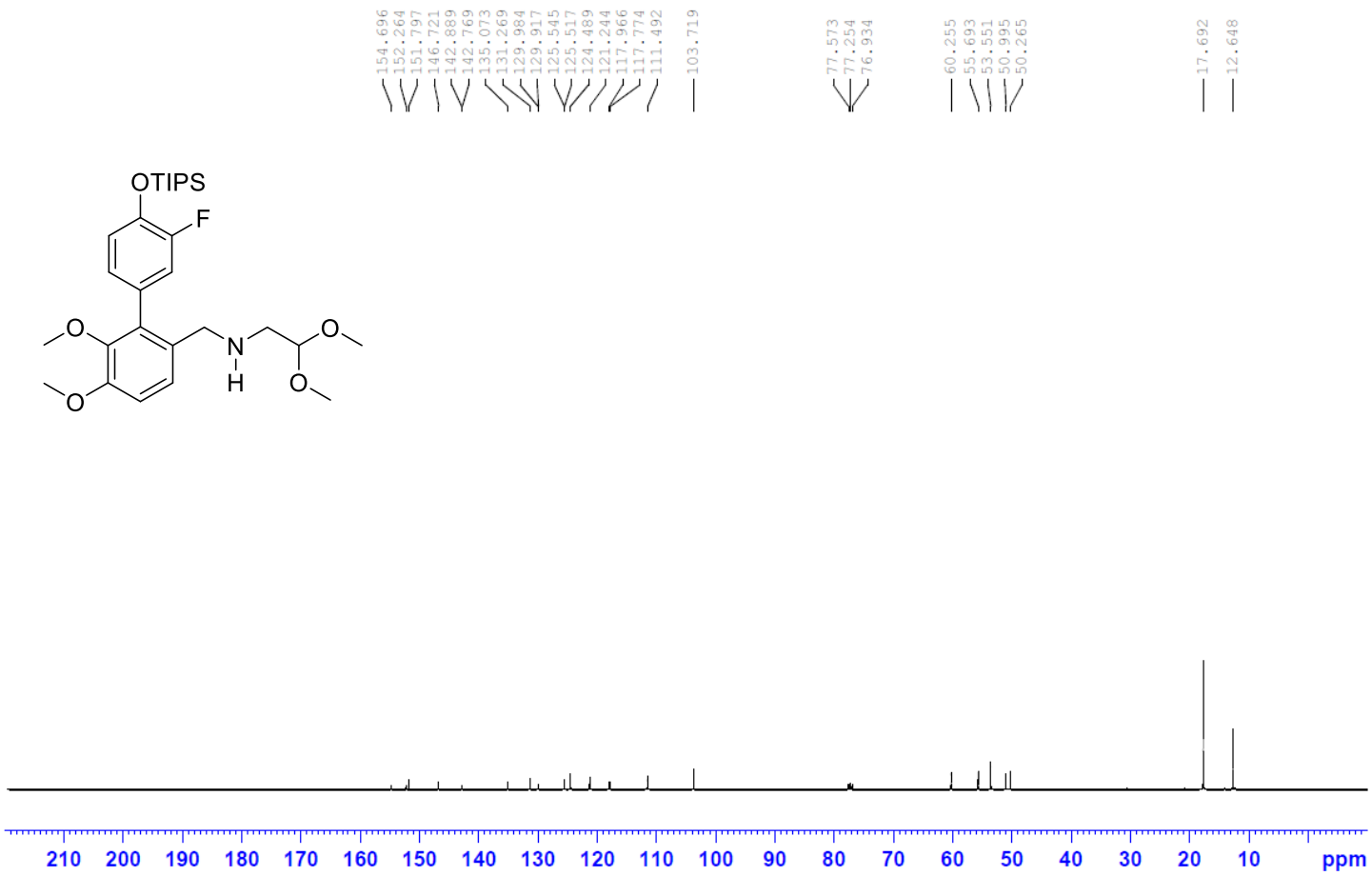
100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **3**



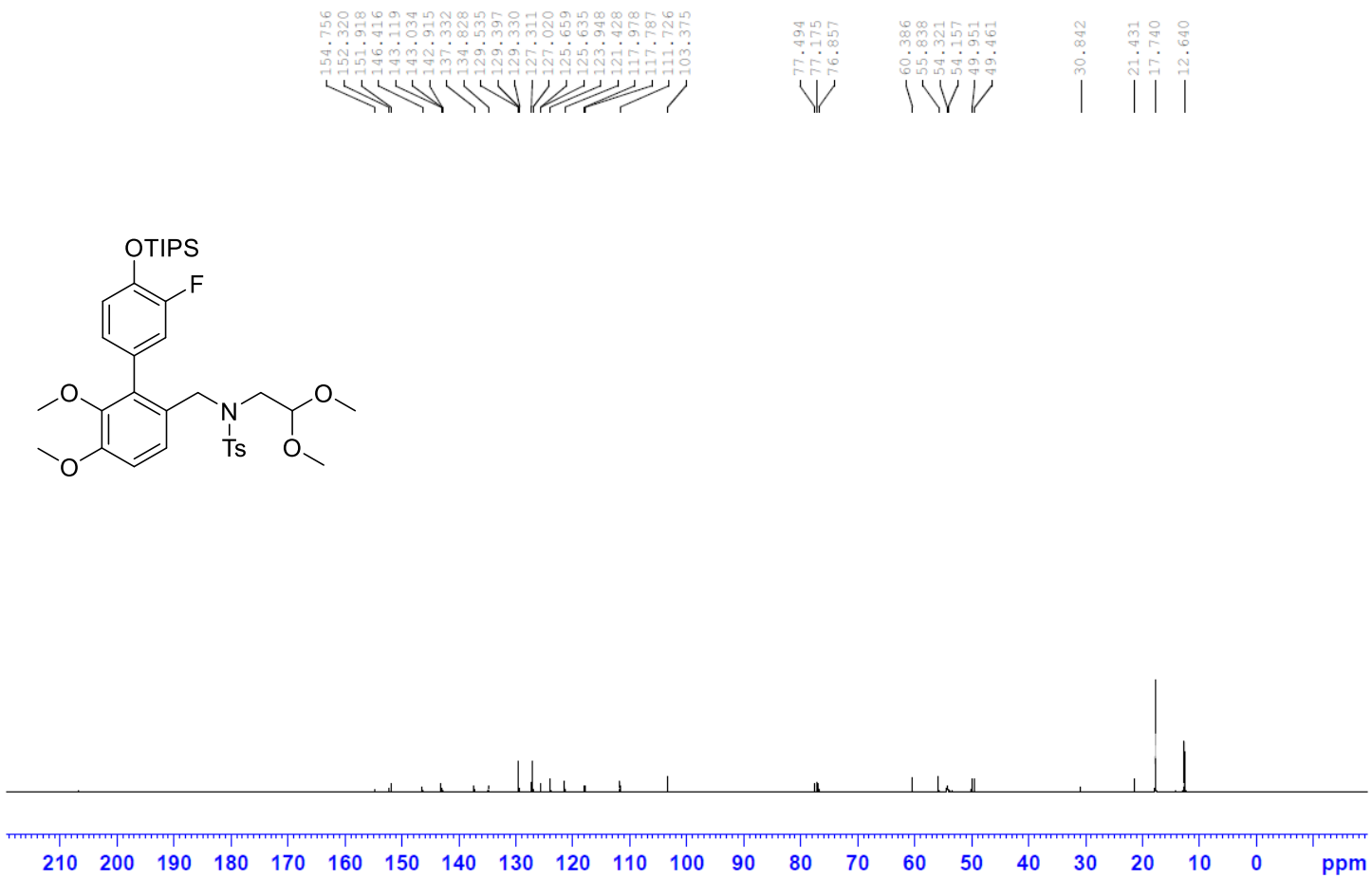
100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **4**



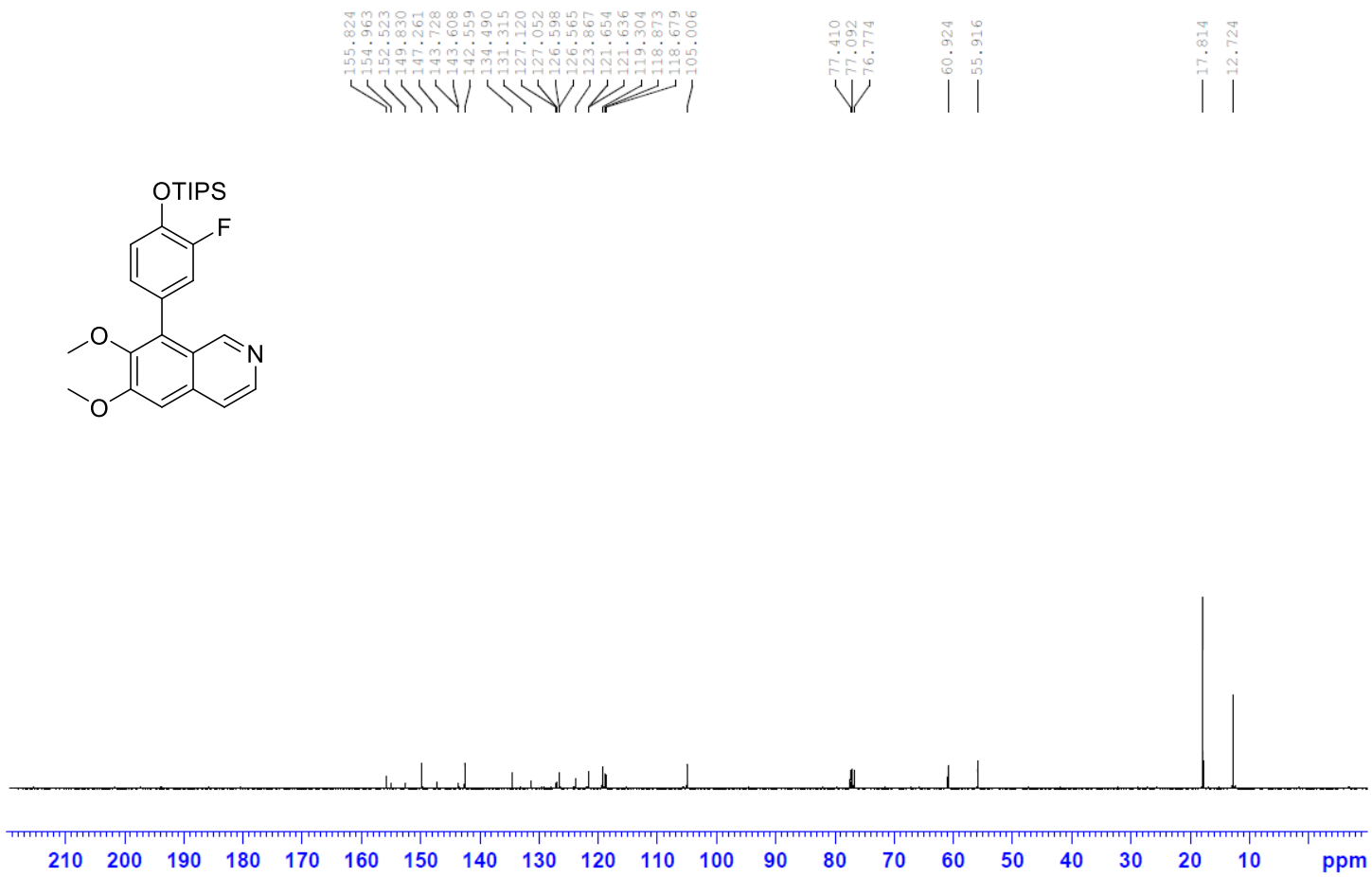
100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound 6



100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **7**

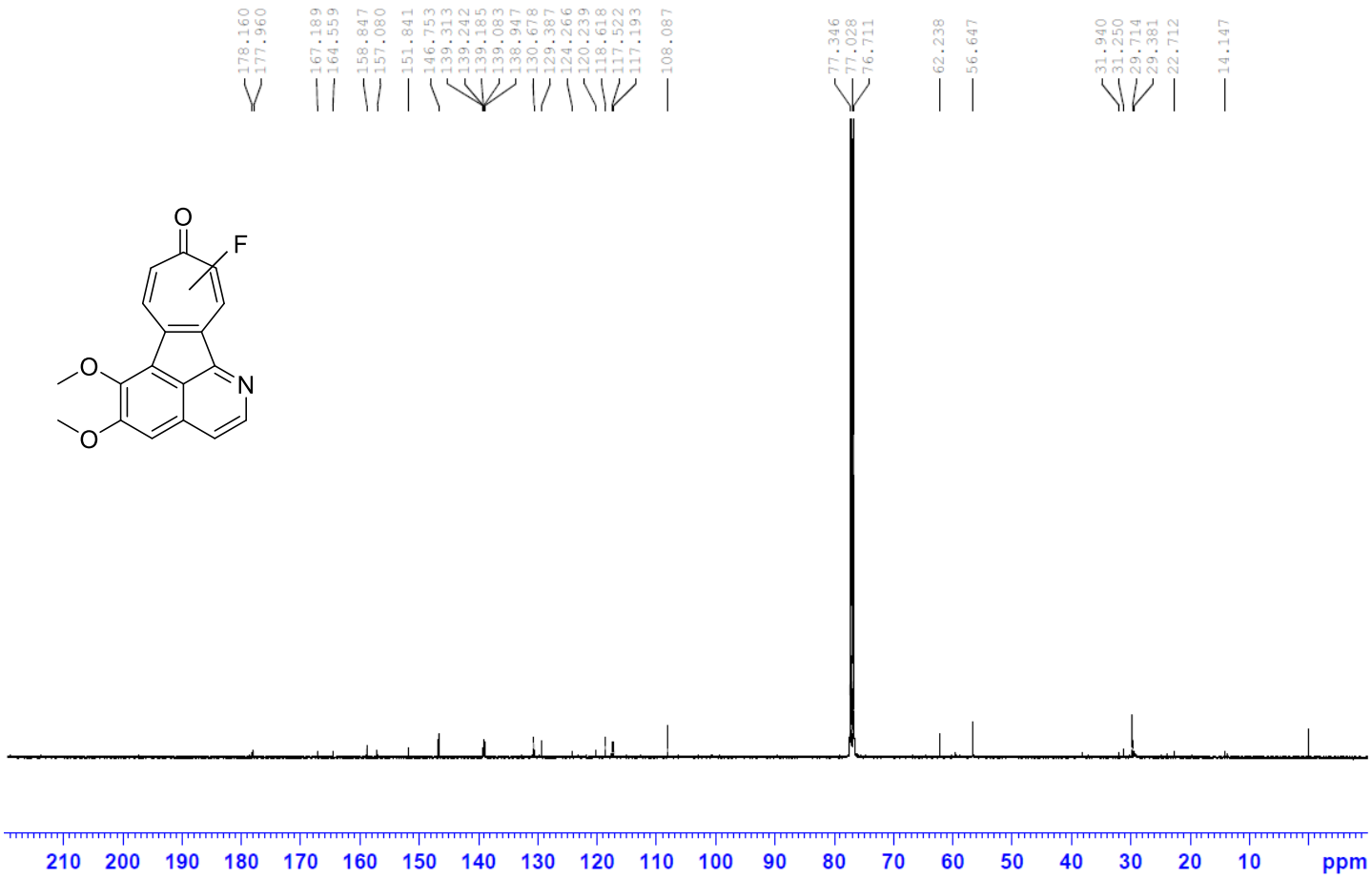


100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **8**



100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **9**

100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **11**



100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **15**

국 문 초 록

방기과 식물로부터 추출된 퍼레이트로폰은 P388 세포에 대한 강력한 항 백혈병 효과를 가지는 것으로 보고되었다. 트로폰과 아이소퀴놀린으로 구성된 다양한 트로폴로아이소퀴놀린 유도체들도 생물학적 활성을 보였다. 게다가, 트로폴로아이소퀴놀린 알칼로이드는 7각형의 고리로 이루어진 트로폰과 아이소퀴놀린 부분의 연결된 구조로 인해 매혹적인 합성 표적이다. 이러한 이유로 많은 연구자 집단이 트로폴로아이소퀴놀린의 간결하고 효율적인 합성을 연구했다. 덧붙여, 제약 화학에서 불소 유도체는 생리활성을 보인다. 그 이유는 불소가 높은 전기 음성도와 작은 크기를 가지고 있어 강한 탄소–불소 결합을 형성하는 특별한 특성을 가지고 있기 때문이다. 따라서 본 연구의 목적은 간결하고 효율적인 실험과정을 이용하여 퍼레이트로폰의 불소 유도체를 합성하는 것이다. 팔라듐 촉매를 이용한 스즈키 커플링 반응, 아이소퀴놀린을 형성하는 고리화 반응, 레이서트 유형의 첨가 반응, 켄디 그룹에서 연구한 라디칼의 음이온성 커플링 반응 등을 실시하였다. 본 연구에서는 퍼레이트로폰 불소 유도체를 아이소바닐린이라는 상업적으로 구매가능한 화합물로부터 12단계의 화학반응을 거쳐 합성하였다. 퍼레이트로폰의 불소 유도체는 트로폴로아이소퀴놀린 유도체의 구조–활성 관계 연구에도 이용될 수 있다.

주요어: 퍼레이트로폰, 트로폴로아이소퀴놀린, 불소, 라디칼 음이온성 커플링, 생리활성, 구조–활성 관계 연구

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