Short communication

Procedures for Preparation and Radiolabeling of a 3-Fluoropyrrolidine-Containing FDDNP Analog

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Dedicated to Professor Miha Tišler on the occasion of his 85th birthday

Abstract

A novel FDDNP analog, namely {1-[6-(3-fluoropyrrolidin-1-yl)-2-naphthyl]ethylidene}malononitrile, was synthesized to probe the influence of the applied structural changes at the donor-side of the molecule on tau protein aggregate binding. Reported is also a synthetic procedure, which can be directly applied to the preparation of the [^{18}F]-radiolabeled compound.

Keywords: FDDNP analogs, synthesis, molecular probes, tau-imaging

1. Introduction

It has been demonstrated that FDDNP[1] (**1**; (1-{6-[(2-fluoroethyl)(methyl)amino]naphthalen-2-yl}ethylidene)propanedinitrile) consistently labels all cross-β-sheet structures-containing protein aggregates found in neurodegenerative diseases.[2] [^{18}F]FDDNP is effective in *in vivo* imaging of tau fibrillar deposits in Alzheimer's disease[2,3] that also have sufficient sensitivity to detect changes in regional tau pathology load in progressive supranuclear palsy (PSP) and produce differentiation from Parkinson's disease (PD) and frontotemporal dementia (FTD).[4] In this work, by modifying the π-conjugation between the electron donor group (e.g., dialkylamino) with the electron acceptor (e.g., the 2-cyano acrylate unit) in the dialkylamino naphthalenyl-2-cyanoacrylate motif in FDDNP, we intent to produce tau-binding molecules with increased sensitivity and specificity for *in vivo* detection of tau aggregation in humans (e.g., vs. amyloid beta binding). This approach would offer a framework for fine-tuning the binding properties of new neurofibrillary tau specific imaging probes in parallel with X-ray microcrystallography at atomic resolution in co-crystallization experiments.[5]

The ability of side chains in **1** to assume coplanar arrangement in respect to the naphthalene ring is a prerequisite for efficient interaction with β-sheet region of the aggregates. This has been demonstrated by the effect of structural differences in DDNP (**2**; {1-[6-(dimethylamino)naphthalen-2-yl]ethylidene}propanedinitrile)[6] and derivatives **3** and **4** (Figure 1) on binding characteristics. In

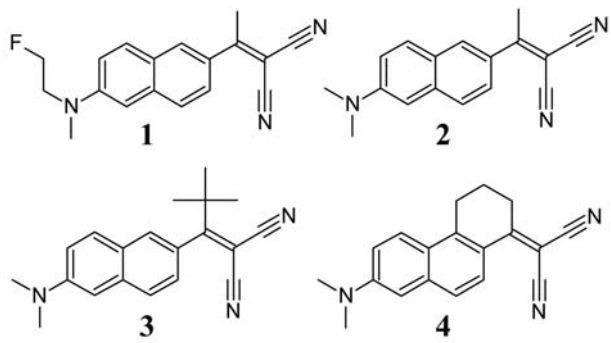


Figure 1. Chemical structures of FDDNP (**1**), DDNP (**2**), and two conformationally restricted analogs (**3** and **4**)

contrast to DDNP (**2**), the acceptor side-chain in **3** can neither rotate freely around the C-C bond because of large steric hindrance exhibited by the *tert*-butyl group, nor can exist in a coplanar conformation, resulting in weak binding (K*i* 520 nM). On the other hand, the acceptor side-chain in **4** is fixed to almost coplanar conformation by a six-membered ring, and the compound shows high binding affinity (K*i* 0.01 nM).[7]

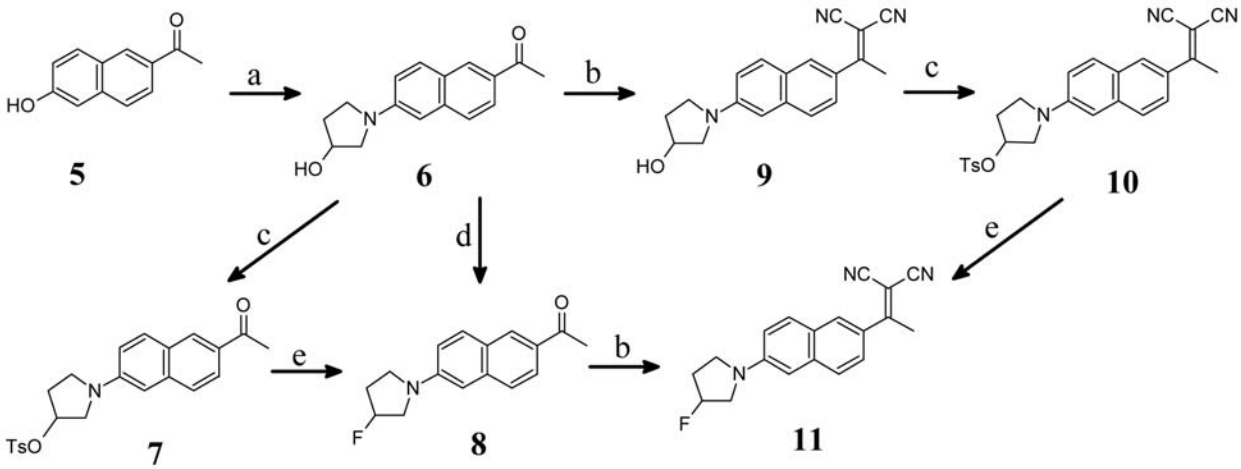
Besides the above steric restrictions, also the effect of electronic density distribution in a molecule on binding properties should be considered. Molecular probes to be used for *in vivo* imaging of protein aggregation in the central nervous system must be uncharged under physiological pH to pass the blood-brain barrier. However, efficient electron density delocalization from donor towards the acceptor group, resulting in substantial dipole moment of the molecule, a feature found in push-pull chromophores, enhances the binding affinity to protein aggregates and causes excitation and emission maxima to shift to longer wavelength.[8]

In this work we describe the synthesis of a novel FDDNP derivative **11**, in which 3-fluoropyrrolidine ring formally replaces the (2-fluoroethyl)(methyl)amino group. We designed this molecule to enable investigation of a donor group's steric and electronic effects on protein labeling. The cyclic 3-fluoropyrrolidino group is more conformationally restricted than the acyclic (2-fluoroethyl)(methyl)amino group. To become coplanar with the naphthalene ring, mainly rotation around the N-C bond must occur. In the case of acyclic amines, coplanar conformation is attained by rotation around N-C and C-C bonds. This difference influences the binding properties as demonstrated in the case of non-fluorinated 6-(1-pyrrolidinyl)- and 6-diethylamino-analogs of FDDNP, which show binding constants (K*i*) of 0.19 and 0.46 nM, respectively.[9] As far as the electronic effects are concerned, no major difference between the open-chain and cyclic analogs is expected because in both the arrangement of substituents around the nitrogen is planar with the nitrogen lone electron pair perpendicular to the ring. In a coplanar conformation this is stereoelectronically favorable for an efficient delocalization of the electron density towards the acceptor group. We report on the chemical synthesis and characterization of **11**, and on the procedure, which can be applied for the preparation of [^{18}F]-labeled **11**. The latter will be used for *in vitro* (autoradiography and binding affinity determinations) and *in vivo* (PET) assays of its ability to label tau (vs. amyloid) protein aggregates.

2. Results and Discussion

The approach for the synthesis and radiolabeling of *N*-substituted derivatives of DDNP (**2**)[10] and FDDNP (**1**)[11] was modified to enable the introduction of a 3-fluoropyrrolidine moiety into the molecule and is summarized in Scheme 1.

Starting 1-(6-hydroxynaphthalen-2-yl)ethanone (**5**) was prepared from commercially available 6-methoxy-derivative as reported previously.[10] Naphthol **5** was subjected to the Bucherer reaction with 3-hydroxypyrrolidine to give the key intermediate **6** in 82% yield. The relatively high yield in comparison to the yields of analogous syntheses with 2-(ethylamino)ethanol or 4-hydroxymethylpiperidine[10] reflects smaller steric hindrance around the nitrogen atom in pyrrolidine ring than in the other two examples. The synthesis of unlabeled FDDNP analogue **11** to provide material for structural identification was carried out by fluorination of **6** with *N,N*-diethylaminosuflur trifluoride (DAST), followed by the Knoevenagel condensation of the intermediate fluoroketone **8** with malononitrile. This procedure, although successfully yields substantial amounts of the compound, is not suitable for the production of radiolabeled material. For radiolabeling, the only viable sources of fluorine are cyclotron-produced either carrier-added [^{18}F]F_2 or no-carrier-added [^{18}F]fluo-



Scheme 1. a: pyrrolidin-3-ol/$NaHSO_3$, b: $CH_2(CN)_2$/Py, c: Ts_2O/Py, d: DAST/dichloromethane, e: KF/Kryptofix 2.2.

ride ion, the latter being the reagent of choice.[12] To examine the efficacy of nucleophilic substitution of a suitable leaving group at the position **3** in a pyrrolidine ring using naked fluoride ion, hydroxy compound **6** was first transformed into tosylate **7**. The tosyloxy group can be efficiently replaced by fluoride in the presence of a potassium ion binding Kryptofix 2.2.2 to yield fluoroketone **8**. This was important information, which we needed in order to design intermediates and procedure for radiolabel introduction in the last synthetic step.[12] With this information at hand we first subjected the hydroxy intermediate **6** to the Knoevenagel condensation with malononitrile and then we transformed the obtained compound **9** into tosylate **10**. With the latter we ran a test experiment under the reaction conditions as similar as possible to a radiolabeling procedure,[11] but with "cold" [^{19}F]KF. HPLC analysis provided the proof of the viability of the proposed radiolabeling method. In the chromatogram of the crude reaction mixture extract, a peak, eluting at 9.75 min was assigned to **11** based on the increase of the peak area in the chromatogram after the original sample was spiked with an authentic sample of **11**, prepared earlier (Figure 2.)

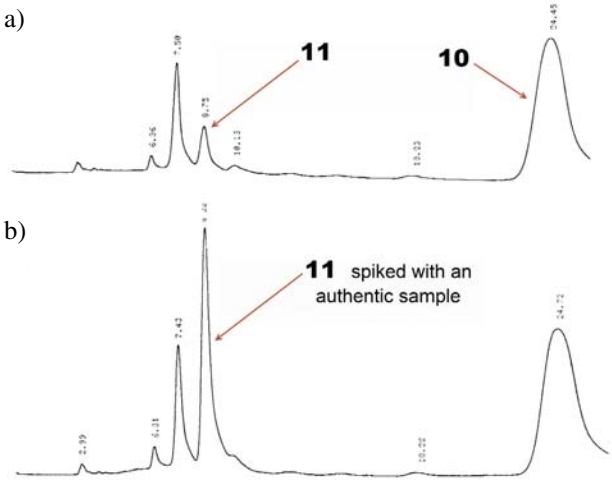


Figure 2. A) HPLC analysis of the reaction mixture after the tosylate **10** reacted with fluoride ion under standard radiolabeling reaction conditions. B) HPLC analysis of the same reaction mixture after it was spiked with authentic **11**.

3. Conclusions

A novel FDDNP analog, {1-[6-(3-fluoropyrrolidin-1-yl)-2-naphthyl]ethylidene}malononitrile, was prepared and chemically characterized. Compound 1-[6-(2,2-dicyano-1-methylvinyl)-2-naphthyl]pyrrolidin-3-yl 4-methylbenzenesulfonate was synthesized to provide a key intermediate for radiolabeling with [^{18}F]fluoride ion. The radiolabeling procedure was tested starting from the prepared intermediate and [^{19}F]KF. It has been proven that under the described conditions the title compound is formed and this procedure can be used for the preparation of radiolabeled material.

4. Experimental

NMR spectra were recorded on a Bruker DPX 300 or Bruker Avance III 500 spectrometers at 302 K using $CDCl_3$ as the solvent. ^{1}H chemical shifts are quoted in parts per million (ppm) downfield from TMS as internal standard, ^{13}C NMR spectra are referenced to the middle line of $CDCl_3$ signal (77.0 ppm), and ^{19}F NMR spectra are referenced to external $CFCl_3$. Mass spectra were measured at the Jožef Stefan institute using VG-Analytical AutospecQ spectrometer. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analyses were determined at the Faculty of Chemistry and Chemical Technology of the University of Ljubljana using a Perkin-Elmer 2400 CHN elemental analyzer. Radial chromatography was performed using Chromatotron (T-Squared Technology, Inc., 903 Sneath Lane, Suite 125 San Bruno, Ca 94066). The rotors were prepared as recommended by the manufacturer using E. Merck Silica Gel (Cat. No. 7749-3) in 1, 2, or 4 mm layer thicknesses.

1-[6-(3-Hydroxypyrrolidin-1-yl)-2-naphthyl]ethanone (6).

In a steel bomb 1-(6-hydroxy-2-naphthyl)ethanone (**5**, 358 mg, 1.92 mmol), pyrrolidin-3-ol[13] (1.72 g, 19.7 mmol), and $NaHSO_3$ (1.01 g) were mixed with water (10 mL) and heated in an oil bath at 135–140 °C for 42 hrs. The bomb was cooled, the content diluted with water (250 mL) and extracted with ethyl acetate (5 × 50 mL). Combined organic extract were dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The residue was extracted with boiling ethanol (40 mL), the solution was filtered, and the filtrate was allowed to cool. From the solution the product separated as yellow plates, which were filtered off and dried to yield 401 mg (82%) of the title compound; mp 225–227 °C; Anal. Calcd. for $C_{16}H_{17}NO_2$: C 75.27, H 6.71, N 5.49. Found: C 75.76, H 6.67, N 5.54; ^{1}H NMR (300.13 MHz, $CDCl_3$, TMS): δ 1.71 (d, 1H, $J_{3',OH}$ = 4.5 Hz, OH), 2.10–2.30 (m, 2H, H-4'), 2.66 (s, 3H, $COCH_3$), 3.40–3.75 (m, 4H, H-5' and H-2'), 4.69 (m, 1H, H-3'), 6.74 (d, 1H, $J_{5,7}$ = 2.3 Hz, H-5), 7.01 (dd, 1H, $J_{5,7}$ = 2.3 Hz, $J_{7,8}$ = 9.0 Hz, H-7), 7.62 (d, 1H, $J_{3,4}$ = 8.7 Hz, H-4), 7.80 (d, 1H, $J_{7,8}$ = 9.0 Hz, H-8) 7.92 (dd, 1H, $J_{3,4}$ = 8.7 Hz, $J_{1,3}$ = 1.9 Hz, H-3), 8.31 (d, 1H, $J_{1,3}$ = 1.9 Hz, H-1); ^{13}C NMR (75.476 MHz, $CDCl_3$, TMS): δ 26.4, 34.3, 45.7, 56.3, 71.2, 104.7, 116.1, 124.7, 125.0, 125.9, 130.5, 130.6, 131.0, 137.8, 147.6, 197.7.

1-(6-Acetyl-2-naphthyl)pyrrolidin-3-yl-4-methylbenzenesulfonate (7).

To a solution of **6** (64 mg, 0.251 mmol) in pyridine (3 mL) Ts_2O (368 mg 1.13 mmol) was added in one por-

tion. The solution was stirred at rt for 30 min, concentrated under reduced pressure, and the residue was separated by radial chromatography (1 mm silicagel, petroleum ether : dichloromethane = 1 : 9). Fractions, containing the product were combined, concentrated, and the residue was crystallized from dichloromethane/petroleum ether mixture to obtain 43 mg (42%) of compound **7**; mp 168–171 °C; Anal. Calcd. for $C_{23}H_{23}NO_4S$: C 67.46, H 5.66, N 3.42. Found: C 67.52, H 5.74, N 3.36; ^{1}H NMR (300.13 MHz, $CDCl_3$, TMS): δ 2.19–2.37 (m, 2H, H-4'), 2.44 (s, 3H, Ar-CH_3), 2.66 (s, 3H, -$COCH_3$), 3.50–3.72 (m, 4H, H-2' and H-5'), 5.28 (m, 1H, H-3'), 6.67 (dd, 1H, $J_{5,7}$ = 2.6 Hz, H-5), 6.93 (dd, 1H, $J_{5,7}$ = 2.6 Hz, $J_{7,8}$ = 8.9 Hz, H-7), 7.35 (m, 2H, -OTs), 7.60 (d, 1H, $J_{3,4}$ = 8.8 Hz, H-4), 7.80 (m, 3H, H-8 and –OTs), 7.92 (dd, 1H, $J_{1,3}$ = 1.8 Hz, $J_{3,4}$ = 8.8 Hz, H-3), 8.31 (d, 1H, $J_{1,3}$ = 1.8 Hz, H-1). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.66, 26.42, 31.98, 45.47, 53.70, 77.23, 80.45, 105.05, 115.90, 124.72, 125.18, 125.97, 127.71, 129.99, 130.53, 130.77, 131.02, 133.73, 137.53, 145.11, 146.66, 197.67.

1-[6-(3-Fluoropyrrolidin-1-yl)-2-naphthyl]ethanone (8).

a) Kryptofix 2.2.2 (30.8 mg, 0.082 mmol) and KF (27.4 mg, 0.47mmol) were dissolved in deionized water (Millipore, 18 MΩ; 0.5 mL) and evaporated to dryness. Residual water was removed by co-distillation with acetonitrile (8 × 1 mL). To the dried material compound **7** (16 mg, 0.039 mmol) and acetonitrile (2 mL) were added. The reaction mixture was stirred and heated under argon at 92–100 °C for 3 hrs. The product **8** (4 mg, 40%) was isolated by radial chromatography (1 mm silicagel, dichloromethane : petroleum ether = 8 : 2).

b) The solution of **6** (127.7 mg, 0.50 mmol) in dichloromethane (15 mL) in a round-bottom flask, equipped with a septum was purged with argon, and DAST (diethylaminosulfur trifluoride; 102 µl, 0.78 mmol) was drop wise added. Stirring under argon was continued for additional 90 min. The reaction mixture was then poured into a mixture of ice and water, the solution was neutralized by the addition of solid $NaHCO_3$, and extracted with dichloromethane (3 × 50 mL). Organic extracts were combined, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. Compound **8** (60 mg, 47%) was obtained by radial chromatography (1 mm silicagel, dichloromethane) and crystallized from ethanol; mp 171–172 °C; Anal. Calcd. for $C_{16}H_{16}FNO$: C 74.69, H 6.27, N 5.44. Found: C 74.98, H 6.13, N 5.48; ^{1}H NMR (300.13 MHz, $CDCl_3$, TMS): δ 2.08–2.51 (m, 2H, H-4'), 2.66 (s, 3H, $COCH_3$), 3.58–3.76 (m, 4H, H-2' and H-5'), 5.43 (m, 1H, $J_{F3'}$ = 51.6 Hz, H-3'), 6.75 (d, 1H, $J_{1,3}$ = 1.5 Hz, H-5), 7.01 (dd, 1H, $J_{5,7}$ = 2.3 Hz, $J_{7,8}$ = 9.0 Hz, H-7), 7.63 (d, 1H, $J_{3,4}$ = 8.7 Hz, H-4), 7.81 (d, 1H, $J_{7,8}$ = 9.0 Hz, H-8), 7.93 (dd, 1H, $J_{1,3}$ = 1.5 Hz, $J_{3,4}$ = 8.7 Hz, H-3), 8.32 (d, 1H, $J_{1,3}$ = 1.5 Hz, H-1); ^{13}C NMR (75.476 MHz, $CDCl_3$, TMS): δ 26.8, 32.8 (d, $^2J_{C,F}$ = 23.3 Hz), 45.9, 54.9 (d, $^2J_{C,F}$ = 21.9 Hz), 93.2 (d, $^1J_{C,F}$ = 176.2 Hz), 105.3, 116.4, 125.1, 125.5, 126.3, 131.0, 131.1, 131.4, 138.1, 147.5, 198.0.

{1-[6-(3-Hydroxypyrrolidin-1-yl)-2-naphthyl]ethylidene}malononitrile (9).

A solution of the ketone **6** (50 mg, 0.19 mmol) and malononitrile (65 mg, 0.98 mmol) in pyridine (4 mL) was heated at 80 °C for 19 hrs. Pyridine was removed under reduced pressure and the residue was chromatographed by radial chromatography under argon (1mm silicagel, 1% methanol in dichloromethane). Fractions containing the product were combined and evaporated. The residue was dissolved in a small volume of benzene, the solution was transferred to a 5 mL beaker, and the beaker was placed in a chamber containing some hexane. The crystalline solid, which crystallized overnight, was filtered off to yield 40 mg (67%) of pure **9**; mp 168–169 °C; Anal. Calcd. for $C_{19}H_{17}N_3O$: C 75.23, H 5.65, N 13.85. Found: C 75.53, H 5.49, N 13.73; ^{1}H NMR (300.13 MHz, $CDCl_3$, TMS): δ 1.66 (d, 1H, $J_{3',OH}$ = 4.3 Hz, -OH), 2.10 to 2.31 (m, 2H, H-4'), 2.70 (s, 3H, -CH_3), 3.42 to 3.59 (m, 2H, H-5'), 3.63 to 3.71 (m, 2H, H-2'), 4.70 (m, 1H, H-3'), 6.73 (d, 1H, $J_{5,7}$ = 2.4 Hz, H-5), 7.03 (dd, 1H, $J_{5,7}$ = 2.4 Hz, $J_{7,8}$ = 9.0 Hz, H-7), 7.57 (dd, 1H, $J_{3,4}$ = 8.7 Hz, $J_{1,3}$ = 1.9 Hz, H-3), 7.65 (d, 1H, $J_{3,4}$ = 8.7 Hz, H-4), 7.77 (d, 1H, $J_{7,8}$ = 9.0 Hz, H-8), 8.03 (d, 1H, $J_{1,3}$ = 1.9 Hz, H-1). ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.71, 34.20, 45.68, 56.27, 71.11, 80.76, 104.61, 113.97, 114.18, 116.70, 124.42, 124.95, 126.34, 127.98, 129.44, 130.81, 137.27, 147.81, 174.16.

1-[6-(2,2-Dicyano-1-methylvinyl)-2-naphthyl]pyrrolidin-3-yl 4-methylbenzenesulfonate (10).

To a solution of **9** (48 mg, 0.16 mmol) in pyridine (1 mL) Ts_2O (105 mg 0.32 mmol) was added in one portion. The solution was stirred at rt and after 30 min was concentrated under reduced pressure. The residue was suspended in water (40 mL) and extracted with dichloromethane (3 × 30 mL). Organic extracts were combined, dried with anhydrous sodium sulfate, evaporated under reduced pressure, and chromatographed by radial chromatography (1 mm silicagel, 1% methanol in dichloromethane) to yield 50 mg (69%) of pure compound **10;** mp 54–60 °C; HRMS Calcd. for $C_{26}H_{23}N_3O_3S$: 457.1460. Found: 457.1471; ^{1}H NMR (300.13 MHz, $CDCl_3$, TMS): δ 2.17 to 2.40 (m, 2H, H-4'), 2.44 (s, 3H, Ar-CH_3), 2.69 (s, 3H, C=C-CH_3), 3.50 to 3.71 (m, 4H, H-2' and H-5'), 5.27 (m, 1H, H-3'), 6.65 (d, 1H, $J_{5,7}$ = 2.3 Hz, H-5), 6.93 (dd, 1H, $J_{7,8}$ = 9.0 Hz, $J_{5,7}$ = 2.3 Hz, H-7), 7.34 (m, 2H, Ar), 7.55 (dd, 1H, $J_{1,3}$ = 2.0 Hz, $J_{3,4}$ = 8.7 Hz, H-3), 7.63 (d, 1H, $J_{3,4}$ = 8.7 Hz, H-4), 7.75 (d, 1H, $J_{7,8}$ = 9.0 Hz, H-8), 7.81 (m, 2H, Ar), 8.01 (d, 1H, $J_{1,3}$ = 2.0 Hz, H-1).

{1-[6-(3-Fluoropyrrolidin-1-yl)-2-naphthyl]ethylidene}malononitrile (11).

a) Compound **8** (30 mg, 0.12 mmol) and malononitrile (39 mg, 0.59 mmol) were dissolved in pyridine (1 mL) and the solution was heated under argon at 85 °C for 23 hrs. Pyridine was removed under reduced pressure, the residue was dissolved in dichloromethane, and the solution

was filtered through a cotton plug. The filtrate was concentrated and the product was isolated by radial chromatography (1 mm silicagel, dichloromethane : hexane = 5 : 1). Pure compound **11** was obtained after crystallization from a benzene solution in petroleum ether atmosphere (33 mg, 92%); mp 143–145.5 °C; Anal. Calcd. for $C_{19}H_{16}FN_3$: C 74.74, H 5.28, N 13.76. Found: C 75.09, H 5.10, N 13.52; ^{1}H NMR (300.13 MHz, $CDCl_3$, TMS): δ 2.09–2.54 (m, 2H, H-4'), 2.70 (s, 3H, CH_3), 3.60–3.80 (m, 4H, H-2' and H-5'), 5.44 (m, 1H, $^2J_{F,H}$ = 51.6 Hz, H-3'), 6.75 (d, 1H, $J_{5,7}$= 2.3 Hz, H-5), 7.03 (dd, 1H, $J_{5,7}$= 2.3 Hz, $J_{7,8}$= 9.0 Hz, H-7), 7.57 (dd, 1H, $J_{1,3}$ = 1.9 Hz, $J_{3,4}$ = 8.8 Hz, H-3), 7.67 (d, 1H, $J_{3,4}$ = 8.8 Hz, H-4), 7.78 (d, 1H, $J_{7,8}$= 9.0 Hz, H-8), 8.04 (d, 1H, $J_{1,3}$ = 1.9 Hz, H-1). ^{19}F NMR (471 MHz, $CDCl_3$) δ -175.35. ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.73, 24.20, 32.30 (d, $^2J_{C,F}$ = 21.8 Hz) , 45.49, 54.51(d, $^2J_{C,F}$ = 23.2 Hz), 80.98, 92.71 (d, $^1J_{C,F}$ = 176.3 Hz), 104.82, 113.90, 114.11, 116.64, 124.45, 125.08, 126.41, 128.19, 129.37, 130.86, 137.18, 147.39, 174.22.

b) Kryptofix 2.2.2 (15 mg, 0.04 mmol) and KF (10 mg, 0.17 mmol) were dissolved in deionized water (Millipore, 18 MΩ; 1 mL) and evaporated to dryness. Residual water was removed by co-distillation with acetonitrile (8 × 1 mL). To the dried material, compound **10** (8 mg, 0.018 mmol) and acetonitrile (1 mL) were added. The reaction mixture was stirred and heated under argon at 90 °C for 30 min. After cooling, water was added (20 mL) and the mixture was applied to a Sep-pak C18 column, which was previously activated by thorough washing with water, methanol and finally with water. First the column was eluted with water (10 mL) to remove polar components, and then the less polar material was eluted with dichloromethane. The dichloromethane eluate was dried with anhydrous sodium sulfate, filtered, and analyzed by HPLC (250 × 5 mm Econosil Silica 10 μm, dichloromethane, UV/Vis detector set at 254 nm). Compound **11** was identified in the mixture by increased peak area in the chromatogram after previously synthesized compound **11** was added to the mixture.

5. Acknowledgment

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6. Supporting material

Supporting material contains NMR spectra of compounds **7 – 11**. This material is available free of charge via the Internet at *http://acta.chem-soc.si/.*

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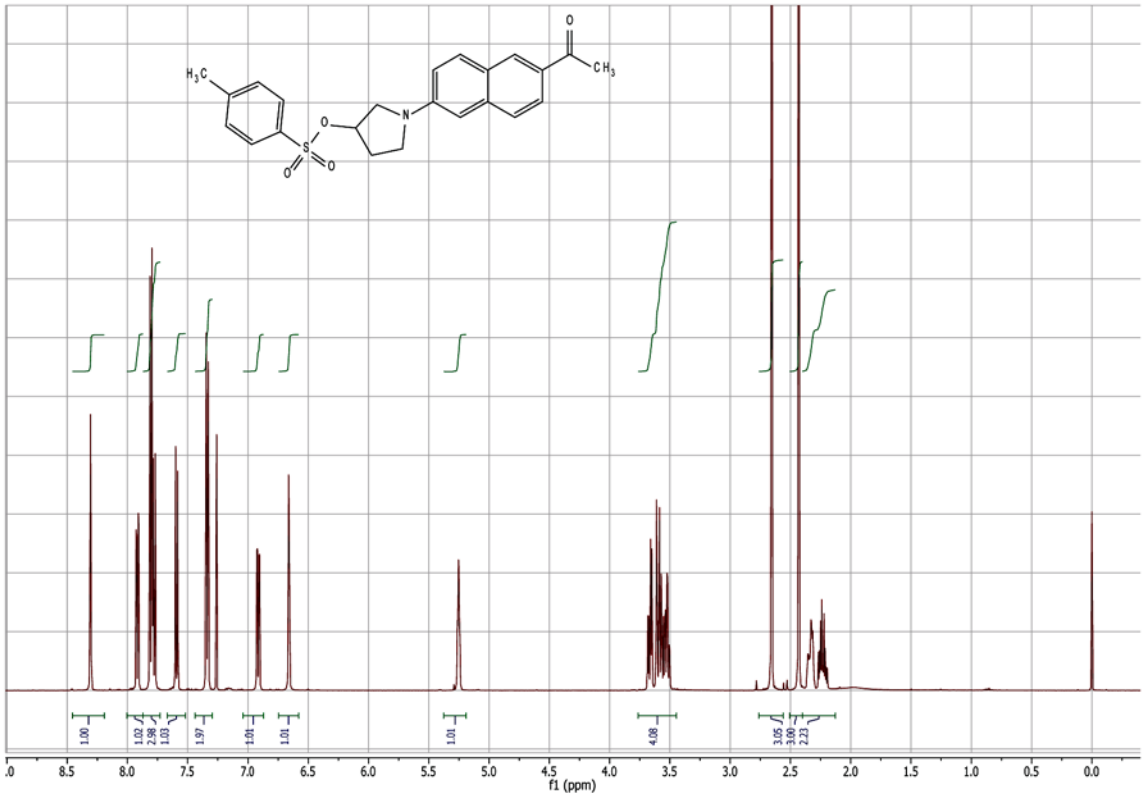
13 Although commercially availbale (*3R*)-pyrrolidin-3-ol was used, we make no claims about the stereochemistry at the center of chirality.

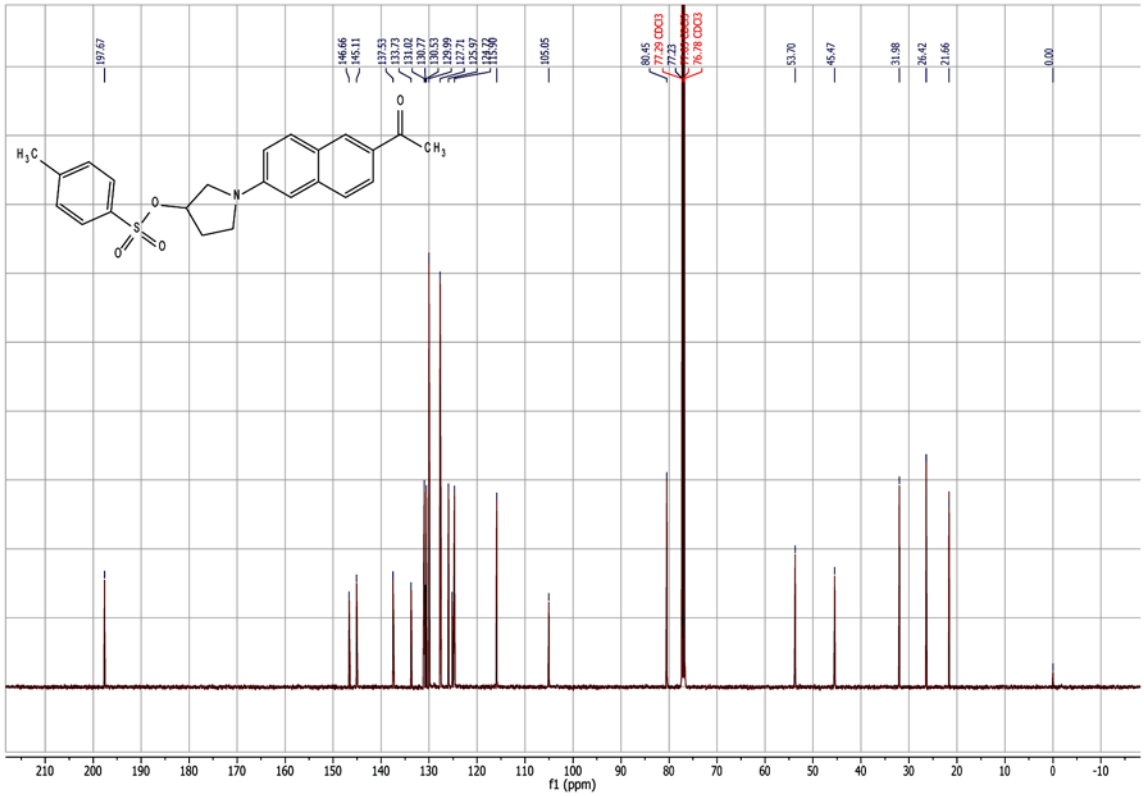
Povzetek

Z namenom omogočiti raziskave vplivov strukturnih sprememb donorskega dela molekule na vezavne lastnosti s tau proteinskimi agregati, smo pripravili nov analog spojine FDDNP, v katerem je vlogo donorske skupine prevzela 3-fluoropirolidinska skupina ({1-[6-(3-fluoropirolidin-1-il)-2-naftil]etiliden}malononitril). Poročamo o sintezni poti, ki je primerna za sintezo neoznačene, kot tudi o sintezni poti za pripravo z radioaktivnim fluorom ^{18}F označene spojine. Slednjo bo po opisani poti možno pripraviti z radioaktivnim fluorom, pridobljenim s ciklotronom in jo uporabiti pri raziskavah vezave na proteinske agregate.

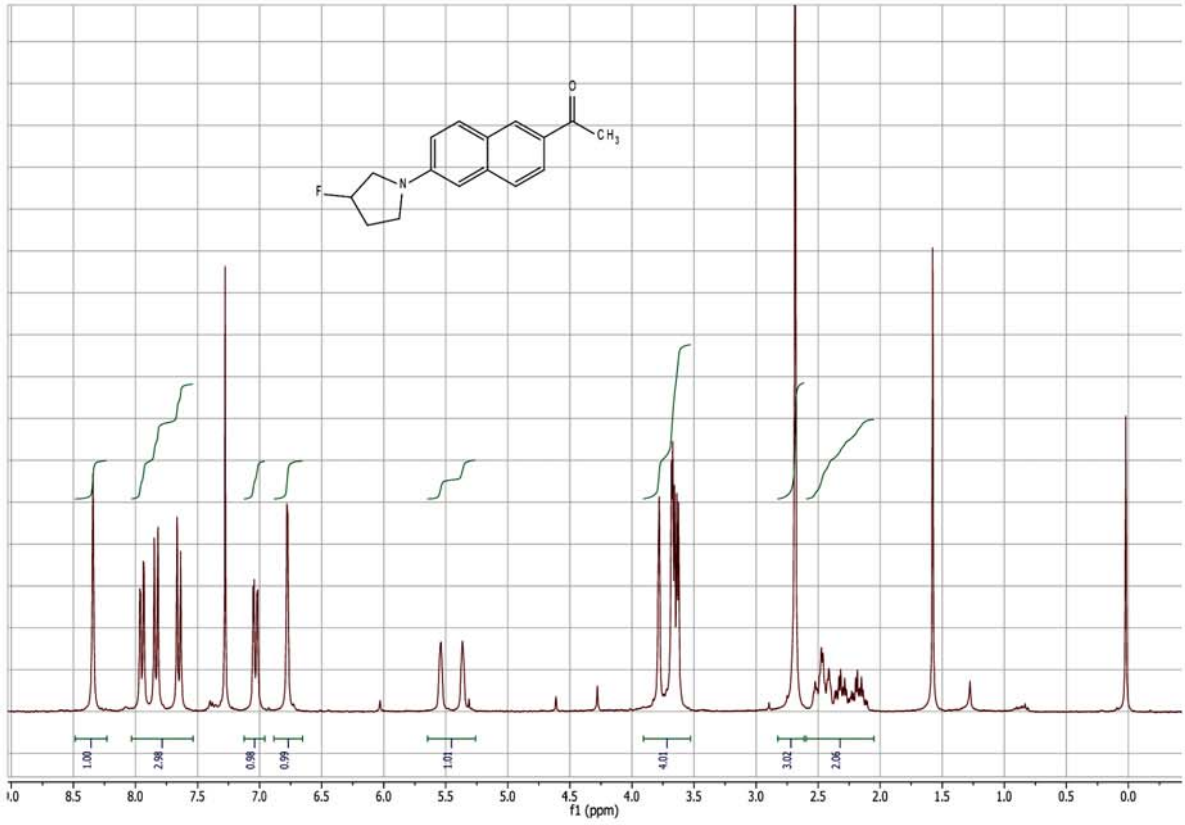
Supplementary Material



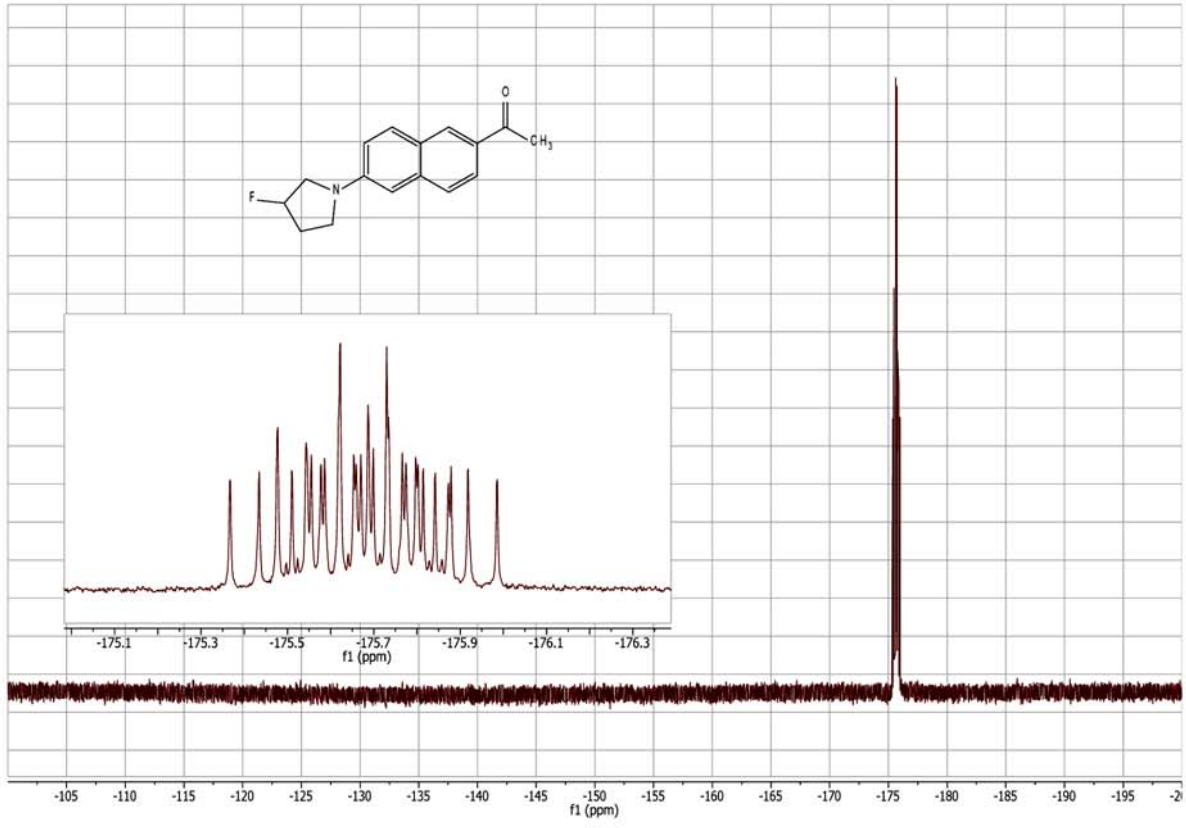
^{1}H NMR spectrum of compound 7



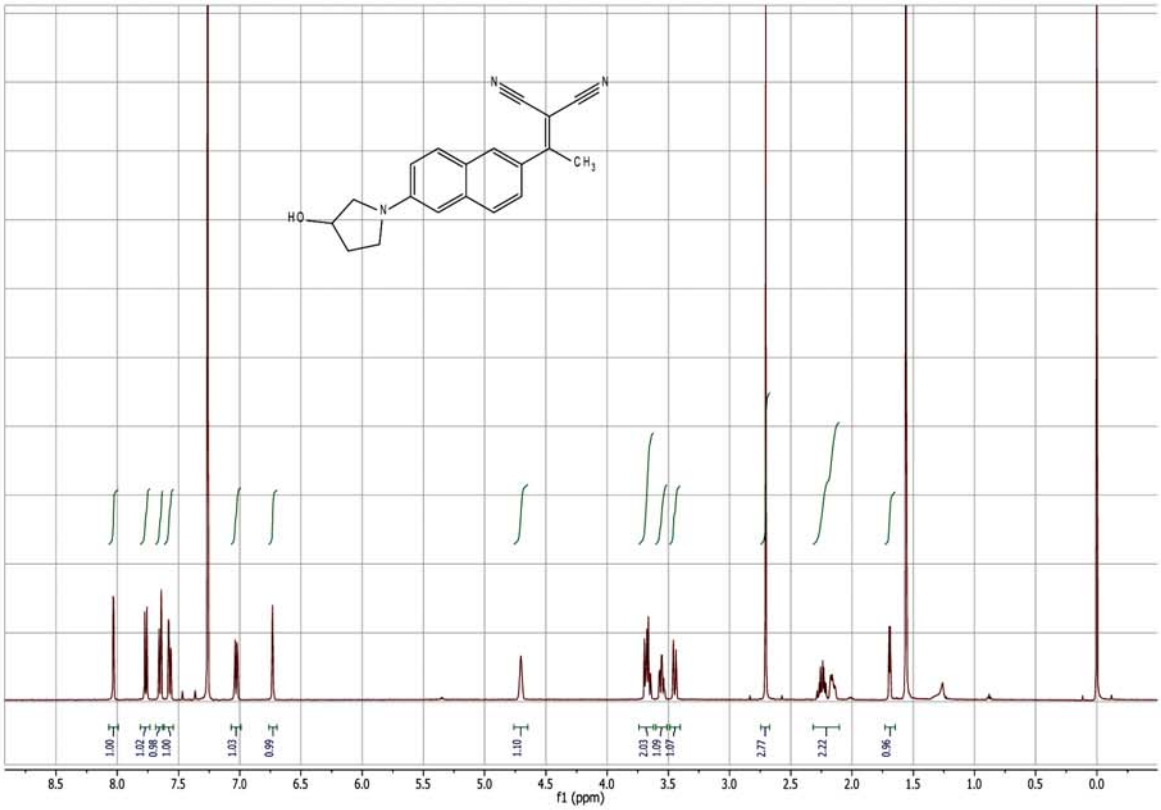
^{13}C NMR spectrum of compound 7



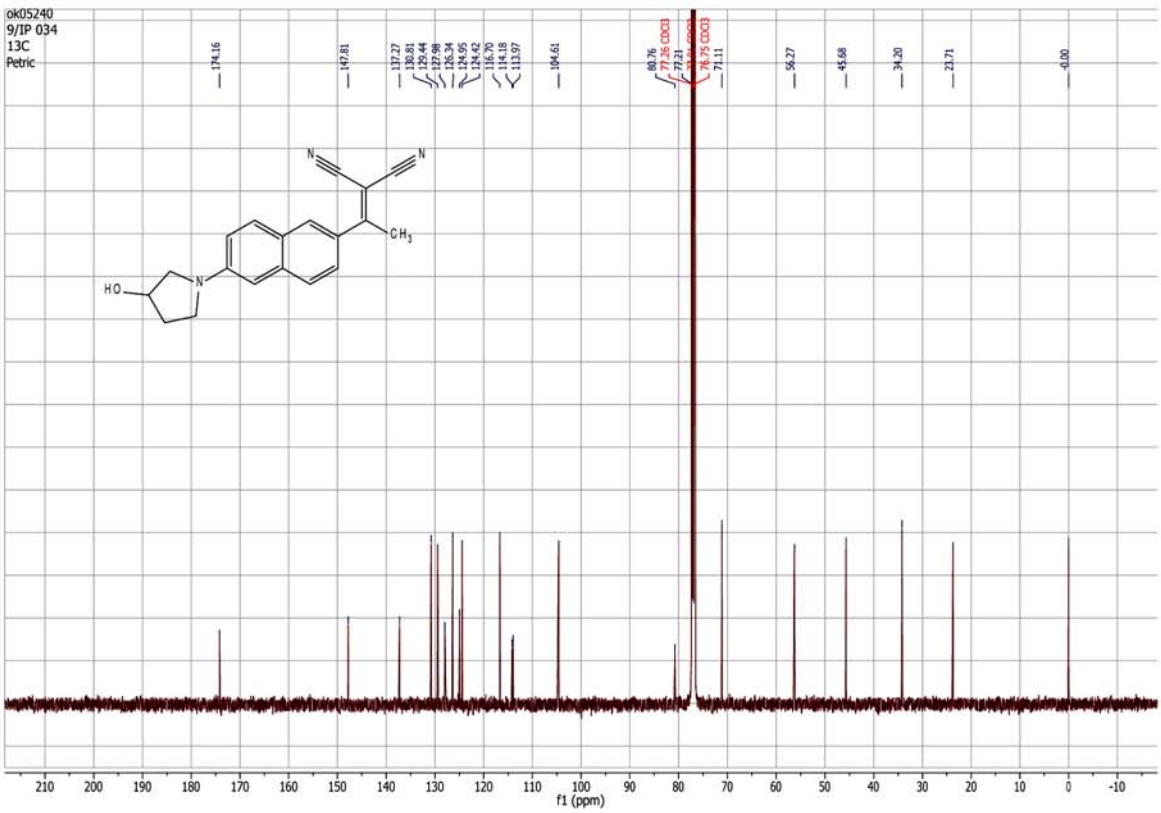
^{1}H NMR spectrum of compound 8



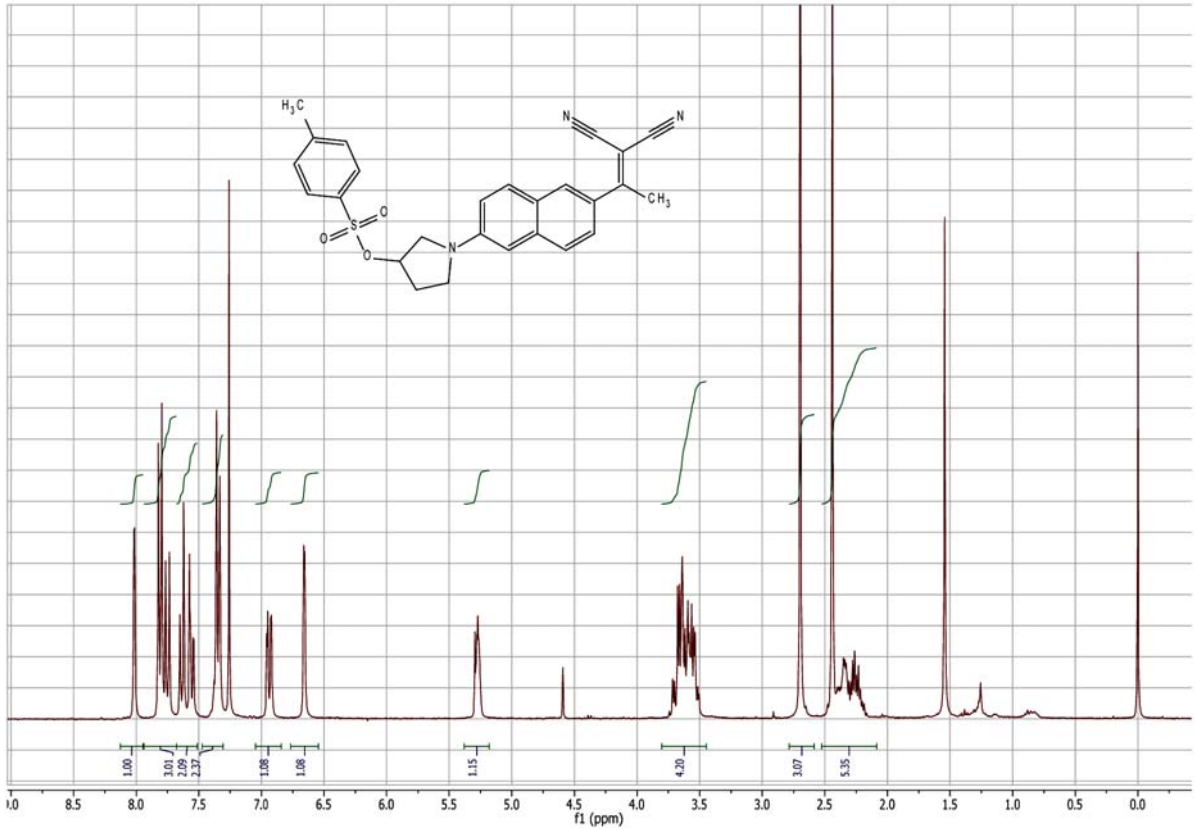
^{19}F NMR spectrum of compound 8



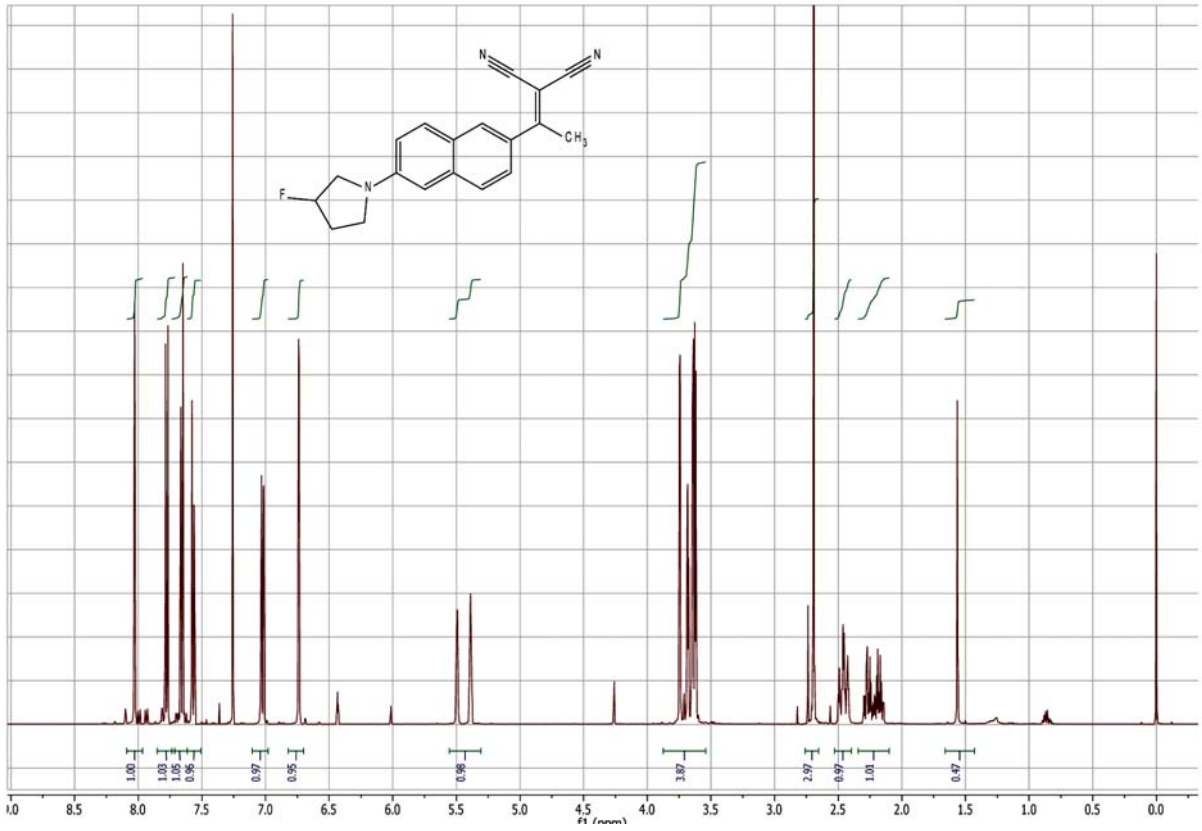
^{1}H NMR spectrum of compound 9



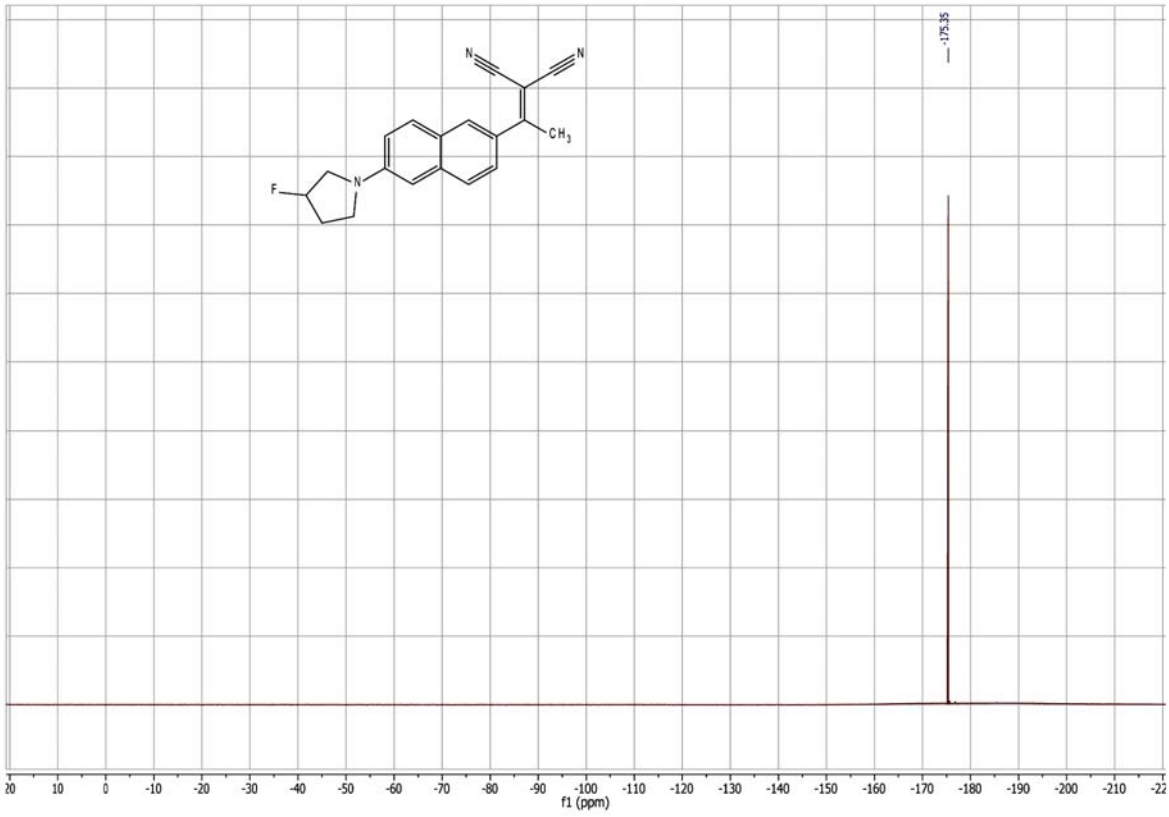
^{13}C NMR spectrum of compound 9



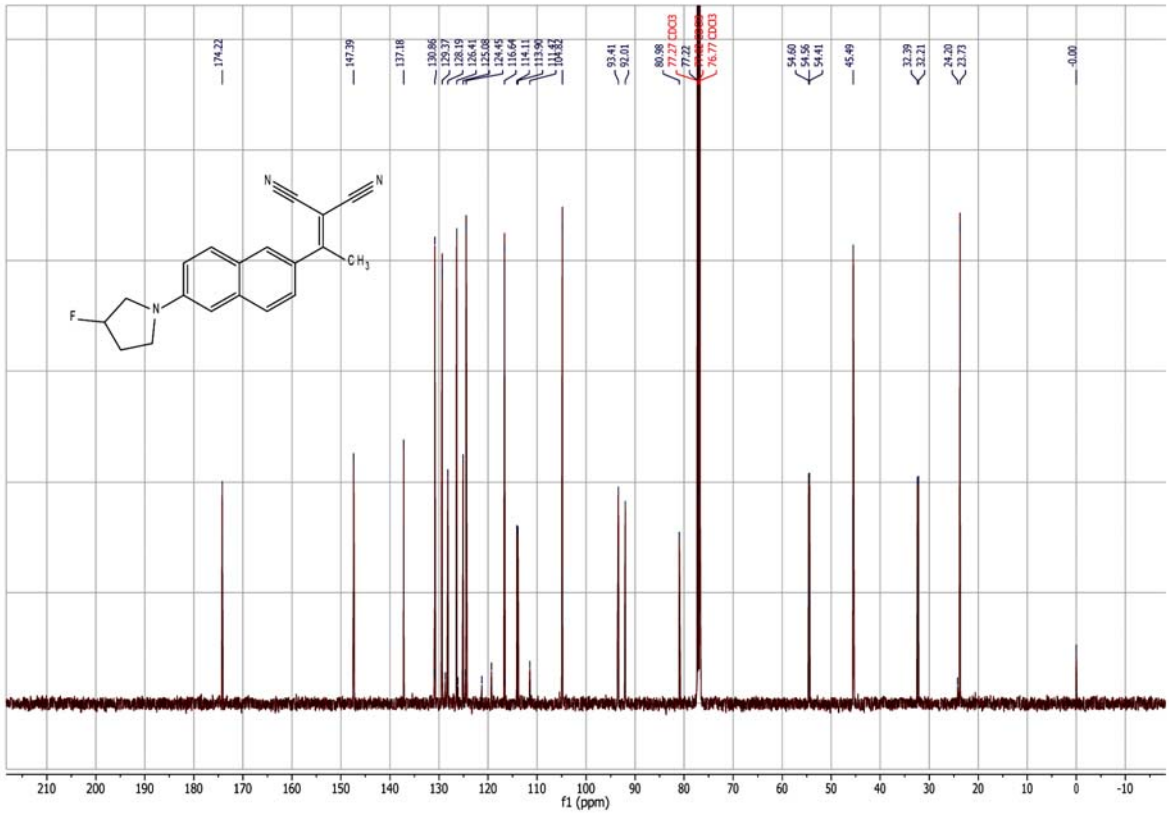
^{1}H NMR spectrum of compound 10



^{1}H NMR spectrum of compound 11



^{19}F NMR spectrum of compound 11



^{13}C NMR spectrum of compound 11