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약학석사 학위논문

헤테로 방향족 고리를 포함한 새로운
S1P 구조적 길항제 합성 및 설계

**Design and Synthesis of Novel S1P Functional
Antagonists Containing a Heteroaromatic Ring**

2018 년 8 월

서울대학교 대학원

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이 논문을 약학석사학위 논문으로 제출함

2018 년 07 월

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빈 재 휘의 석사학위논문을 인준함

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위 원 장 _____(印)

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위 원 _____(印)

초 록

스핑고신-1-인산 (S1P)은 스핑고신이 스핑고신 키나제 1/2에 의하여 인산화 되어 활성형태가 되는 스핑고리피드 대사체이다. 인산화된 스핑고신은 5개의 G단백질 결합 수용체 (S1P₁-S1P₅)을 활성화한다. S1P는 여러 가지 생체 신호 체계에서 중추적인 역할을 하며, 암, 알츠하이머 질병, 겸상 적혈구병 등과 관련이 있어 난치병 치료에 실마리를 제시해 줄 것으로 기대되는 표적이다.

다발성경화증 치료제로 FDA 승인된 약물인 FTY720 (Fingolimod)은 유일한 S1P 조절 약물이지만 5개의 G단백질 결합 수용체 중 치료활성을 보이는 S1P₁ 뿐 아니라 S1P₃에도 작용 하는 선택성 결합 때문에 서맥, 고혈압 등의 부작용을 보였다.

따라서 본 논문에서는 FTY720의 핵심 구조라고 생각되는 방향족 고리를 새롭게 변형하는 디자인 방법과, 구조적 다양성을 지니고 선택적으로 S1P 결합 수용체와 결합하는 화합물들 합성에 관하여 서술하고자 한다. 다양한 출발물질로부터 시작하여 heteroaromatic ring 부분을 변형하였으며, 이러한 유도체들은 wittig 반응을 통해 높은 수율을 가지는 FTY720 머리부분과 연결된 internal alkene intermediates를 합성하였다. 결론적으로 S1P subtype 별 수용체에 선택적으로 작용하는 7가지 유도체들을 설계 및 합성하였다.

주요어 : Sphingolipid, S1P, FTY720, Heteroaromatic ring

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I. Introduction

스핑고신-1-인산 (S1P)은 암, 섬유화, Alzheimer's 병, 겸상적혈구 빈혈증 그리고 Chikungunya virus같은 바이러스성 감염질환 등의 다양한 질병에 관여하는 세포 신호 분자이다.¹ 이러한 스핑고신-1-인산 (S1P)은 두가지 isotype SphK1, SphK2로 존재하는 SphK (Sphingosine kinase)에 의하여 스핑고신이 phosphorylation 되면서 생성되어진다. SphK1과 SphK2는 50% 정도 유사 sequence를 지니지만, 세포 내 분포위치가 달라 각기 다른 역할을 한다. 일반적으로 SphK1은 세포질에 분포하며 세포의 생존과 증식의 역할을 지니며, SphK2는 핵에 주로 분포하며 세포 자멸(apoptosis)에 관여한다.²

S1P의 세포생존이나 세포 이동에 관여하는 작용 메커니즘은 5가지 G-단백질 수용체(S1P₁-S1P₅)에 높은 결합력을 보임으로써 촉진되어진다.³ S1P 수용체들은 여러가지 건강과 질병을 조절하는데, 특히 S1PR₁ (S1P₁ receptor)은 혈관 투과성, 신경섬유보호, 림프구 방출, B 세포 이동, 심장 박동수에 관여하며, S1PR₂는 청각, 근세포 생존에 관여하며, S1PR₃는 근섬유, 염증, 호흡, 심장 박동수, 혈압 등에 관여함이 알려져 S1P와 S1P 수용체들에 대한 연구의 중요성이 대두되었다. 이런 보고에 따라 지난 십년 동안 S1P 수용체의 조절에 관한 많은 연구들이 진행되어졌다.⁴

Myriocin의 구조를 변형시켜 만든 면역조절제인 FTY720 (Fingolimod/Gilenya; Novartis)의 발견은 S1P 조절을 통해 CNS (Central Nervous system; 중추신경계)제어가 가능하다는 사실을 보여주었고, 신경세포를 직접적으로 조절할 수 있는 방법을 제시하였다.⁵ 이후 FTY270은 2010년에 다발성 경화증 (Multiple sclerosis)의 첫 구강투여제제로 FDA에 승인받았다. FTY720의 효과가 밝혀진 이후,

많은 후속 연구가 이루어졌고 FTY720은 SphK2에 의하여 인산화 되며 이 활성화된 FTY720-P (인산화된 FTY720) 분자는 S1P₂를 제외한 모든 S1P 하위수용체에 결합한다는 것이 밝혀졌다. 4가지 S1P 하위수용체 중 S1P₁ 수용체는 다발성경화증에 관여한다는 것이 선도연구로 밝혀졌다. 하지만 FTY720-P는 S1P₁ 수용체에 높은 결합 친화성(binding affinity)을 지녀 좋은 약효를 보이지만, 다른 S1P 하위수용체에도 작용하여 하위수용체 별 선택적 작용효과를 얻기가 힘들어 S1P₃가 관여하는 서맥이나 혈압 등의 약 용량-한계 심혈관 부작용을 유발한다고 보고된 바 있다.

따라서 S1P 하위수용체 별 높은 선택적 agonist (효능제)의 개발이 필수 불가결하다. 본 논문은 FTY720의 pharmacophore moiety의 다양한 변형을 통해 선택적 작용효과를 가진 agonist (효능제)를 디자인하여 향후 효능을 가진 종류를 선발하고자 몇 가지 새로운 화합물을 설계 및 합성하였다.

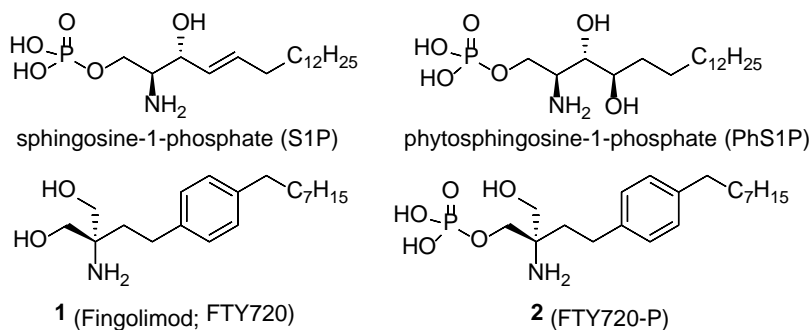


Figure 1. S1P, PhS1P, FTY720 (1) and FTY720-P (2) 화합물의 화학구조

II. Results and Discussion

신규 heteroaromatic FTY720 유도체들의 설계 및 합성

S1P₁의 X-ray crystal 구조가 분석 되어짐에 따라⁶ S1P 수용체와 신규성 있는 S1P modulator 화합물들 간의 상호작용에 대해 많은 연구가 진행되어져 왔다. 알려진 S1P 수용체의 binding pocket 특징으로는 S1P 구조의 zwitterionic 머리 부분과 hydrophobic 꼬리 부분을 수용하기 위한 amphipathic 특성이 있다. 특히 친수성 지역에 polar residues; Asn101, Arg120, Glu121 등이 분포함이 알려져 신규 유도체들은 극성이 높은 아미노산과 강한 상호작용을 할 수 있는 작용기들로 설계되어졌다. 따라서 본 논문에서는 선도 연구결과에 따라 S1P 수용체와 강한 상호작용을 하기 위해 유도체들의 구조들을 친수성 파트에는 zwitterionic 머리와 heteroaromatic 꼬리, 소수성 파트에는 aliphatic 꼬리 부분으로 구성하였다.

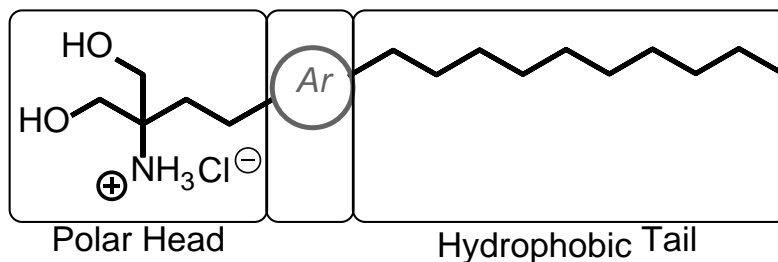
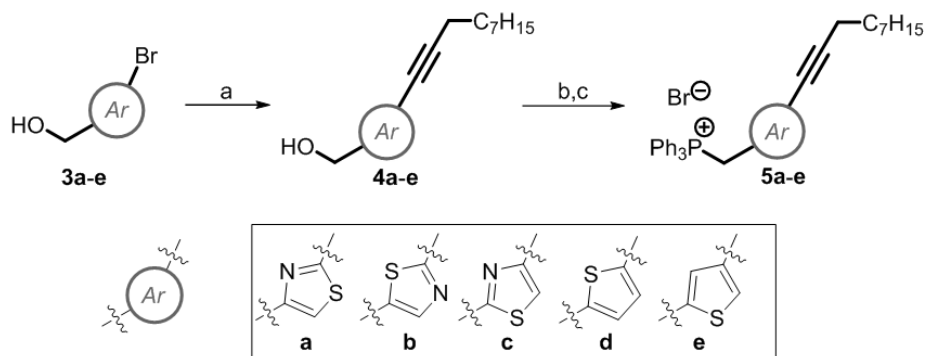


Figure 2. 다양한 Heteraromatic 꼬리를 지닌 새로운 유도체 구조

새로운 heteroaromatic 유도체들을 설계 및 합성하기 위하여 Wittig reaction을 통해 polar 머리 부분과 hydrophobic한 꼬리 파트를

연결하였다. 이 후 Phosphonium bromide를 지닌 Heteroaromatic 유도체를 확보하기 위해 Scheme 1과 Scheme 2의 방법을 따라 합성하였다. 간단한 한 스텝으로 합성이 가능하거나 상업적으로 구매할 수 있는 알려진 화합물인 bromoalcohols **3a-e**는 Sonogashira coupling 반응을 통하여 분자구조에 alkyne으로 연결된 화합물 **4a-e**을 확보하였다 (Scheme 1). 확보되어진 **4a-e** 화합물들의 1-hydroxyl 기능기는 Appel reaction을 이용하여 bromine으로 치환하였고, PPh₃ (triphenylphosphine) reagent를 처리함에 따라 ylide 형태인 **5a-e**를 좋은 수율로 얻었다.

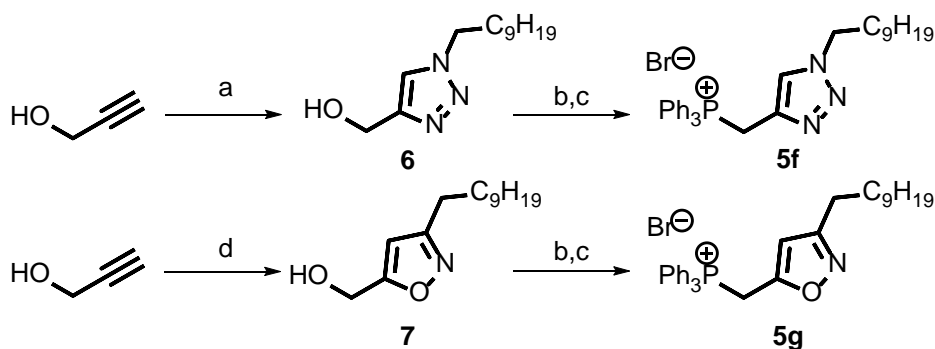


Scheme 1. 중간체인 **5a-e** 화합물의 합성 전략^a

^aReagents and conditions: (a) 1-decyne, Pd(PPh₃)₄, CuI, Et₃N, reflux, 12 h, 74% for **4a**, 50% for **4b**, 89% for **4c**, 77% for **4d**, 66% for **4e** (over two steps); (b) PPh₃, CBr₄, CH₂Cl₂, rt, 12 h; (c) PPh₃, toluene, reflux, 12 h, 90% for **5a**, 66% for **5b**, 57% for **5c**, 76% for **5d**, 81% for **5e**;

Triazole 구조나 isoxazole 구조를 포함한 ylide 화합물인 **5f**와 **5g**의 경우는 더 효율적인 합성전략을 위하여 copper 촉매 매개 [3+ 2]

cycloaddition 반응을 이용하였다 (Scheme 2). Copper (I) catalyzed azide-alkyne cycloaddition (CuAAC) 반응은 propargyl alcohol과 1-azidodecane으로부터 **6** triazole 화합물을 높은 수율로 합성 가능하게 하였다. 또한, 1-azidodecane 대신 oxime형태의 화합물은 propargyl alcohol과 반응하여 높은 수율로 isoxazole **7** 화합물을 합성하였다⁷. **5a-e**의 합성 전략과 유사하게 triazole, isoxazole로 치환된 alcohol은 성공적으로 ylide form인 **5f**와 **5g**로 합성되었다.

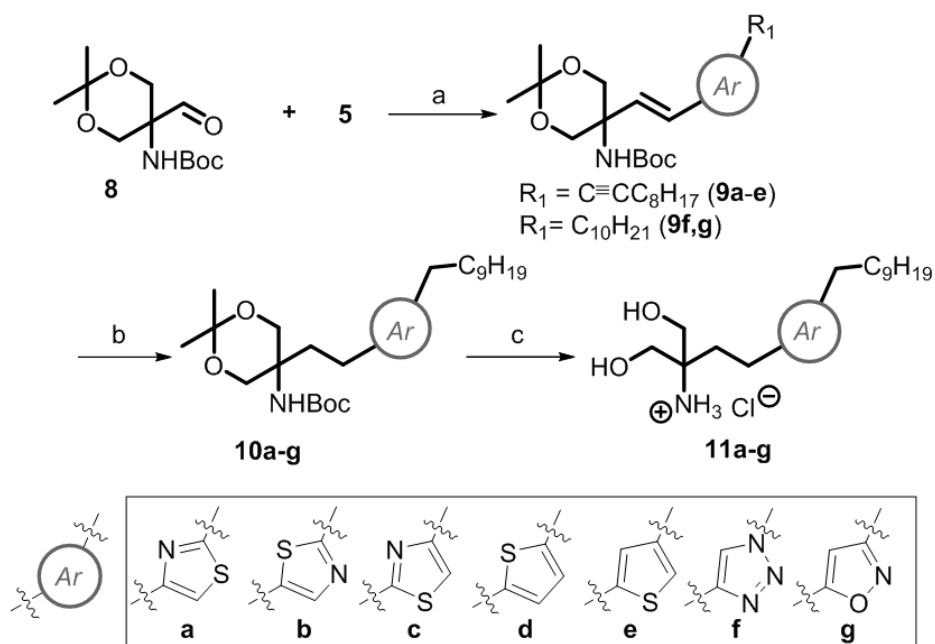


Scheme 2. 중간체인 **5f**, **5g** 화합물의 합성 전략^a

^aReagents and conditions: (a) 1-azidodecane, Cu(OAc)₂, DIPEA, *t*BuOH, rt, 12 h, 97%; (b) PPh₃, CBr₄, CH₂Cl₂, rt, 12 h; (c) PPh₃, toluene, reflux, 12 h, 96% for **5f**, 60% for **5g** (over two steps); (d) *N*-hydroxyundecanimidoyl chloride or *N*-hydroxynonanimidoyl chloride, CuI, DIPEA, DMF, rt, 12 h, 80% for **7**;

Ylide 화합물들을 확보한 뒤, Wittig 반응을 통해 합성되어진 **5** 화합물들은 알려진 aldehyde **8**과⁸ coupling 하여 2개의 탄소 linker와 FTY720 구조의 극성 머리 part를 확보하게 된다. 본 반응으로 합성된 alkenes **9**는 32-96%의 수율로 확보하였다 (Scheme 3)⁹. 분자구조 내 alkene과 alkyne을 지닌 **9** 화합물들은 palladium on carbon과

ammonium formate를 이용하여 alkane으로 reduction반응을 수행하여 10 화합물을 확보하였다. 10 화합물의 protecting group인 Boc과 acetonide를 제거하기 위하여 2M HCl in Et₂O를 처리하여 최종적으로 다양한 heteroaromatic ring을 포함한 FTY720 polar head 유도체들을 quantitative yield로 확보하였다.



Scheme 3. 중간체인 5f, 5g 화합물의 합성 전략^a

^aReagents and conditions: (a) NaH, CH₂Cl₂, 0 °C to rt, 12 h, 55% for **9a**, 52% for **9b**, 34% for **9c**, 32% for **9d**, 96% for **9e**, 63% for **9f**, 88% for **9g**; (b) NH₄HCO₂, Pd/C, EtOAc, reflux, 12 h, 90% for **10a**, 60% for **10b**, 71% for **10c**, 83% for **10d**, 77% for **10e**, 60% for **10f**, 92% for **10g**; (c) 2M HCl in Et₂O, MeOH, rt, 12 h, 99%.

III. Conclusion

FTY720 polar head group을 지니고 다양한 heteroaromatic ring을 포함한 7가지 화합물을 최종적으로 확보하였다. 7가지 화합물들을 효율적으로 디자인하기 위하여 Appel condition이나 Pd/C reduction을 수행하였으며 특히 body 구조와 head 구조를 연결시키기 위하여 “Wittig reaction”을 key-step으로 이용하여 높은 수율로 화합물들을 얻을 수 있었다.

Sphingosine 1-phosphate (S1P) modulator로 유일하게 FDA 승인 받은 FTY720 약은 그 효과가 입증되었지만 S1P receptor subtype들에 대한 낮은 선택성 문제로 인하여 cardiovascular side effect가 보고되었다. 따라서 본 논문에 연구되어진 화합물들은 FTY720의 pharmacophore라고 예상되어지는 phenyl ring을 다양한 5-membered heteroaromatic ring으로 치환하면 낮은 선택성 문제를 극복하여 부작용을 줄일 수 있을 거라 판단되어 디자인되었고, 결론적으로 총 7가지 신규성 화합물들을 성공적으로 확보하였다.

확보되어진 최종 화합물들은 FTY720과 비교하여 x-ray crystal 구조에 선택적으로 작용되는지 알아보기 위해 molecular-docking study가 진행중에 있으며, S1P₁에 선택적인 것뿐만 아니라 아직 많은 연구가 진행되지 않은 S1P₄에도 선택적인 화합물이 도출된다면 특정 5-membered heteroaromatic ring이 cerebral ischemia에 관여함을 밝힐 수 있으리라 예상된다.

IV. Experimental Section

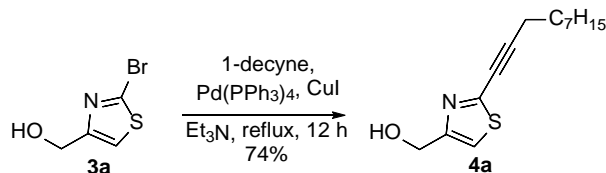
A. General Procedure

모든 시약은 구입하여 사용하였으며, 모든 실험은 질소 기류 하에 수행하였다. 반응에 사용되는 용매는 질소 기류하에 distillation 한 뒤 사용하였다. 반응은 silica gel 60 F-254 TLC plate을 사용하여 박층 크로마토그래피 (TLC) 분석을 통하여 확인하였다. 화합물들은 254나 365 nm UV light에 의해 확인되어졌다. 반응 종결을 위하여 column chromatography는 silica gel (Kiesegel 60, 230-400 mesh, Merck)를 사용하였다. 녹는점은 Buchi B-540을 이용하여 측정하였다. 화합물들의 정성 확인을 위한 NMR 분석법에서는 ^1H 또는 ^{13}C NMR (nuclear magnetic resonance) spectra를 사용하였고 JEOL LNM-LA 300, JEOL JNM-GCX 400, Bruker AMX-500 spectrometer 를 이용하여 TMS (tetramethylsilane) 을 내부 표준 물질로 사용하거나 CD_3CN , CDCl_3 등을 표준 NMR solvent를 이용하였다. 분석 완료 후 표기되어지는 chemical shift는 ppm (parts per million) 단위로, coupling constant는 Hz (hertz) 로 나타내었다. IR (infrared) spectra는 Agilent 5500a FT-IR spectrometer로 측정하였으며, 완료 후 표기형태는 cm^{-1} 로 표시하였다. 다른 분석법으로는 Mass spectra (MS)를 이용하였으며 이는 fast atom bombardment (FAB) 또는 chemical ionization (CI)를 이용하여 측정하였고, High-resolution mass spectra (HRMS)도 같은 방법을 이용했다.

B. General Procedure Primary Alcohol Derivative from Bromoalcohol compound.

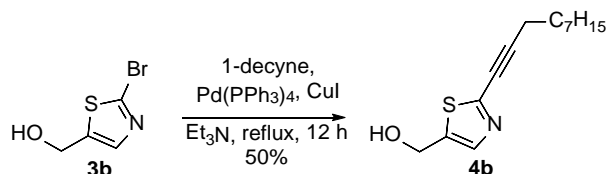
Bromoalcohol 화합물인 **3** (1 eq) 은 1-decyne (3 eq), Pd(PPh₃)₄ (0.2 eq), CuI (0.2 eq)와 함께 Et₃N solution (0.1 M)에 녹여 12시간 동안 95°C 가열하면서 교반하였다. 상온으로 식힌 뒤, 반응물은 Celite pad를 통하여 필터하고, 물과 EtOAc로 희석시켰다. 희석시킨 유기층을 MgSO₄를 이용하여 건조한 뒤 감압 농축하였다. 잔여물은 silica gel column chromatography를 이용하여 분리하고 목표된 internal alkyne **4** compound를 확보하였다.

(2-(Dec-1-yn-1-yl)thiazol-4-yl)methanol (**4a**)



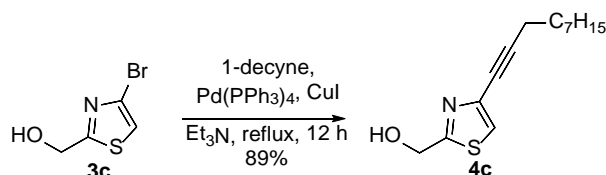
4a 유도체는 general procedure B와 같은 방법으로 진행하였으며, 화합물은 silica gel column chromatography (hexane/EtOAc, 3:1)로 분리하였다. 최종적으로 노란색 oil **4a** (480 mg, 74%)를 확보하였다. ¹H NMR (800 MHz, CDCl₃) δ 7.10 (s, 1H), 4.71 (d, *J* = 0.9 Hz, 2H), 3.23 (br s, 1H), 2.40 (t, *J* = 7.2 Hz, 2H), 1.56 (td, *J* = 11.4, 20.3 Hz, 2H), 1.39 (td, *J* = 7.4, 14.2 Hz, 2H), 1.28–1.20 (m, 8H), 0.84 (t, *J* = 5.8 Hz, 3H); ¹³C NMR (200 MHz, CDCl₃) δ 156.7, 149.7, 115.4, 96.8, 73.8, 60.7, 31.7, 29.1, 29.0, 28.9, 27.9, 22.6, 19.4, 14.0; IR (neat) ν_{max} = 3324, 2923, 2853, 2231, 1451, 1207, 1061, 742 (cm⁻¹); HRMS (FAB) calcd. for C₁₄H₂₂NOS [M+H]⁺ 252.1420, found 252.1422.

(2-(Dec-1-yn-1-yl)thiazol-5-yl)methanol (**4b**)



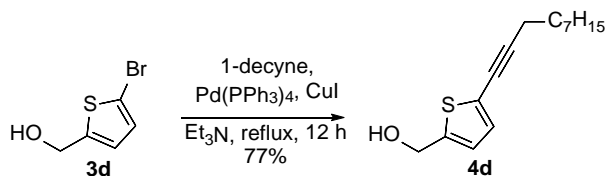
4b 유도체는 general procedure B와 같은 방법으로 진행하였으며, 화합물은 silica gel column chromatography (hexane/EtOAc, 3:2)로 분리하였다. 최종적으로 갈색 oil **4b** (480 mg, 50%)를 확보하였다. ¹H NMR (500 MHz, CDCl₃) δ 7.57 (s, 1H), 4.83 (s, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 2.17 (br s, 1H), 1.61 (td, *J* = 7.4, 14.9 Hz, 2H), 1.41 (td, *J* = 5.4, 9.7 Hz, 2H), 1.28–1.25 (m, 8H), 0.86 (t, *J* = 6.9 Hz, 3H);

(4-(Dec-1-yn-1-yl)thiazol-2-yl)methanol (**4c**)



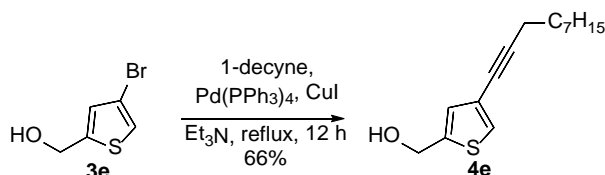
4c 유도체는 general procedure B와 같은 방법으로 진행하였으며, 화합물은 silica gel column chromatography (hexane/EtOAc, 5:1)로 분리하였다. 최종적으로 갈색 oil **4c** (800 mg, 89%)를 확보하였다. ¹H NMR (800 MHz, CDCl₃) δ 7.28 (s, 1H), 4.91 (s, 2H), 2.67 (br s, 1H), 2.37 (t, *J* = 7.2 Hz, 2H), 1.58 (td, *J* = 7.4, 15.0 Hz, 2H), 1.40 (td, *J* = 7.4, 14.7 Hz, 2H), 1.29–1.22 (m, 8H), 0.86 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (200 MHz, CDCl₃) δ 170.6, 137.6, 121.2, 91.2, 74.2, 62.0, 31.8, 29.14, 29.09, 29.0, 28.4, 22.6, 19.3, 14.1; IR (neat) ν_{max} = 3243, 2923, 2853, 1503, 1345, 1157, 1071, 746 (cm⁻¹); HRMS (FAB) calcd. for C₁₄H₂₂NOS [M+H]⁺ 252.1420, found 252.1422.

(5-(Dec-1-yn-1-yl)thiophen-2-yl)methanol (4d)



4d 유도체는 general procedure B와 같은 방법으로 진행하였으며, 화합물은 silica gel column chromatography (hexane/EtOAc, 5:1)로 분리하였다. 최종적으로 갈색 oil 4d (192 mg, 77%)를 확보하였다. ¹H NMR (400 MHz, CDCl₃) δ 6.95 (d, *J* = 3.7 Hz, 1H), 6.80 (d, *J* = 3.7 Hz, 1H), 4.74 (d, *J* = 6.0 Hz, 2H), 2.39 (t, *J* = 14.6 Hz, 2H), 1.78 (t, *J* = 11.9 Hz, 1H), 1.57 (td, *J* = 7.3, 14.8 Hz, 3H), 1.42–1.37 (m, 2H), 1.30–1.23 (m, 6H), 0.86 (t, *J* = 14.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 144.5, 131.0, 125.3, 124.7, 95.1, 73.9, 60.3, 32.0, 29.4, 29.3, 29.2, 28.8, 22.9, 19.9, 14.3; IR (neat) ν_{max} = 3327, 2923, 2853, 1462, 1160, 1013, 802 (cm⁻¹);

(4-(Dec-1-yn-1-yl)thiophen-2-yl)methanol (4e)



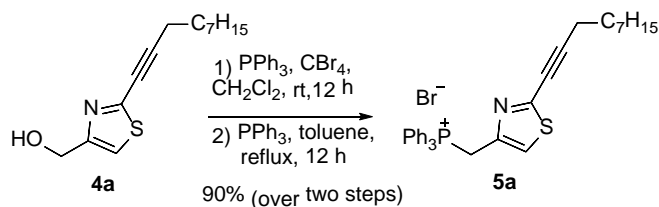
4e 유도체는 general procedure B와 같은 방법으로 진행하였으며, 화합물은 silica gel column chromatography (hexane/EtOAc, 5:1)로 분리하였다. 최종적으로 갈색 oil 4e (410 mg, 66%)를 확보하였다. ¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, *J* = 1.4 Hz, 1H), 6.93 (d, *J* = 1.4 Hz, 1H), 4.74 (d, *J* = 0.7 Hz, 2H), 2.34 (t, *J* = 14.3 Hz, 2H), 1.83 (br s, 1H), 1.56 (td, *J* = 7.2, 14.7 Hz, 2H), 1.40 (t, *J* = 14.7 Hz, 2H), 1.28–1.26 (m, 8H), 0.86 (t, *J* = 13.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 143.8, 128.3, 127.9, 122.9, 89.9, 75.8, 30.1, 32.1,

29.4, 29.3, 29.1, 28.9, 22.9, 19.6, 14.3; IR (neat) ν_{\max} = 3306, 2923, 2853, 1457, 1140, 1008, 840, 747 (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{15}\text{H}_{23}\text{OS}$ $[\text{M}+\text{H}]^+$ 250.1391, found 250.1383.

C. General procedure for phosphonium bromide 5 from compound 4

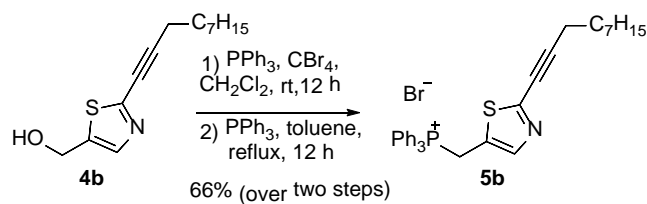
CH_2Cl_2 solvent (0.5 M)에 녹여진 4 화합물 (1 eq) 은 PPh_3 (1.2 eq), CBr_4 (1.5 eq)와 같이 상온에서 2시간동안 반응되었다. 교반 후 반응물은 hexane으로 필터 그리고 감압농축 하였다. 잔여반응물은 PPh_3 (1 eq)를 추가로 넣어 12시간 동안 toluene solvent (0.5 M)아래 reflux 하였다. 반응 종료 후 상온으로 식힌 뒤 hexane으로 씻고, MeOH로 필터하고 감압농축 하였다. 감압농축된 생성물 5 은 추가 정제과정 없이 다음반응으로 진행하였다.

((2-(Dec-1-yn-1-yl)thiazol-4-yl)methyl)triphenylphosphonium bromide (5a)



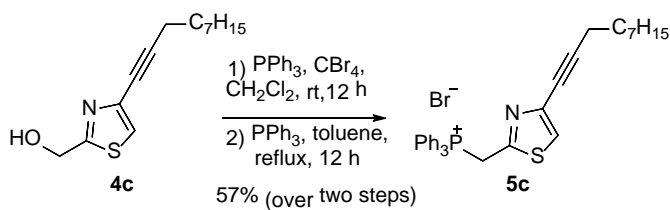
5a 유도체는 general procedure C와 같은 방법으로 진행하였으며, 최종적으로 갈색 고체 5a (311 mg, 90%)를 확보하였다. ^1H NMR (500 MHz, CD_3OD) δ 7.88–7.85 (m, 3H), 7.79–7.75 (m, 6H), 7.72–7.69 (m, 6H), 7.28 (d, J = 3.4 Hz, 1H), 2.44 (t, J = 7.0 Hz, 2H), 1.58 (td, J = 7.3, 14.6 Hz, 2H), 1.42 (t, J = 7.3 Hz, 2H), 1.33–1.31 (m, 10H), 0.90 (t, J = 6.9 Hz, 3H);

((2-(Dec-1-yn-1-yl)thiazol-5-yl)methyl)triphenylphosphonium bromide (5b)



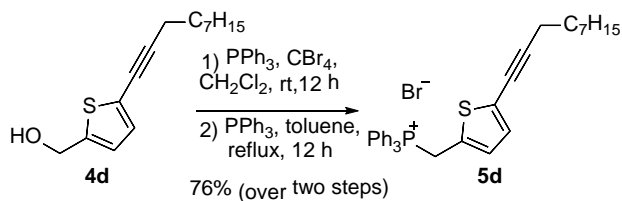
5b 유도체는 general procedure C와 같은 방법으로 진행하였으며, 최종적으로 갈색 oil 5b (605 mg, 66%)를 확보하였다.

((4-(Dec-1-yn-1-yl)thiazol-2-yl)methyl)triphenylphosphonium bromide (5c)



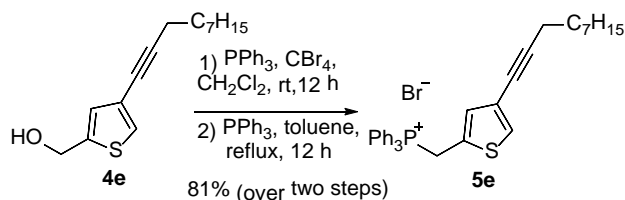
5c 유도체는 general procedure C와 같은 방법으로 진행하였으며, 최종적으로 갈색 oil 5c (134 mg, 57%)를 확보하였다.

((5-(Dec-1-yn-1-yl)thiophen-2-yl)methyl)triphenylphosphonium bromide (5d)



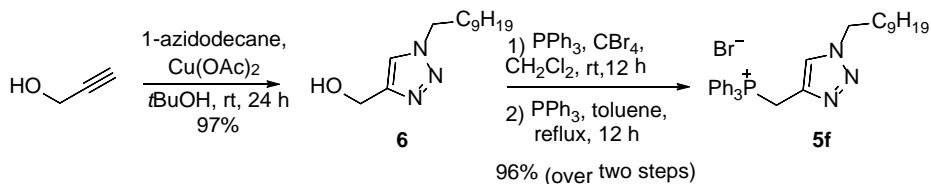
5d 유도체는 general procedure C와 같은 방법으로 진행하였으며, 최종적으로 검은색 oil 5d (1.32 g, 76%)를 확보하였다. ¹H NMR (800 MHz, CD₃OD) δ 7.92–7.90 (m, 3H), 7.78–7.73 (m, 6H), 7.73–7.67 (m, 6H), 6.91 (d, *J* = 3.4 Hz, 1H), 6.64 (t, *J* = 3.7 Hz, 1H), 2.38 (td, *J* = 3.4, 9.6 Hz, 2H), 1.54 (td, *J* = 7.3, 14.8 Hz, 2H), 1.42–1.39 (m, 2H), 1.33–1.26 (m, 10H), 0.89 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (200 MHz, CD₃OD) δ 137.5 (d, *J* = 3.0 Hz, 3C), 136.1 (d, *J* = 9.7 Hz, 6C), 132.83 (d, *J* = 3.7 Hz), 132.76 (d, *J* = 7.9 Hz), 132.3 (d, *J* = 12.5 Hz, 6C), 130.1 (d, *J* = 10.2 Hz), 128.4 (d, *J* = 4.7 Hz), 119.7 (d, *J* = 85.9 Hz, 3C), 97.7 (d, *J* = 1.4 Hz), 74.5 (d, *J* = 3.1 Hz), 50.1, 33.8, 31.1, 30.9, 30.7, 30.3, 24.5, 20.9, 15.2;

((4-(Dec-1-yn-1-yl)thiophen-2-yl)methyl)triphenylphosphonium bromide (5e)



5e 유도체는 general procedure C와 같은 방법으로 진행하였으며, 최종적으로 갈색 oil 5e (690 mg, 81%)를 확보하였다. ¹H NMR (800 MHz, CD₃OD) δ 7.92–7.90 (m, 3H), 7.75–7.73 (m, 6H), 7.70–7.67 (m, 6H), 7.33 (dd, *J* = 1.4, 2.2 Hz, 1H), 6.68 (dd, *J* = 1.3, 3.6 Hz, 1H), 2.32 (t, *J* = 7.1 Hz, 2H), 1.52 (td, *J* = 7.3, 14.8 Hz, 2H), 1.42–1.38 (m, 2H), 1.33–1.28 (m, 10H), 0.89 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (200 MHz, CD₃OD) δ 137.5 (d, *J* = 3.0 Hz, 3C), 136.1 (d, *J* = 9.9 Hz, 6C), 135.2 (d, *J* = 7.7 Hz), 132.3 (d, *J* = 12.5 Hz, 6C), 131.2 (d, *J* = 4.2 Hz), 130.0 (d, *J* = 9.5 Hz), 125.6 (d, *J* = 3.4 Hz), 119.7 (d, *J* = 86.0 Hz, 3C), 92.0, 76.5, 50.1, 33.8, 31.2, 31.0, 30.7, 30.5, 24.5, 20.6, 15.2;

D. Synthetic Procedure for the triazole containing ylide 5f



(1-Decyl-1H-1,2,3-triazol-4-yl)methanol (6)

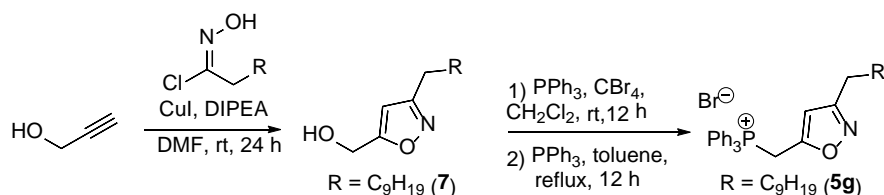
6 화합물을 얻기 위해서는 click reaction을 이용하였고, 1-azidodecane은 1-bromodecane으로부터 발표된 procedure¹⁰을 따라 합성하였다. Propargyl alcohol (1 eq)를 *t*BuOH (0.2 M)에 녹인 뒤, 1-azidodecane (1.1 eq), Cu(OAc)₂ (0.6 eq)와 같이 상온에서 24시간 동안 교반하였다. 반응 종결 이후 반응물은 brine과 EtOAc로 2번 씻어주었고 유기층은 MgSO₄로 건조시킨 뒤 감압농축 하였다. 잔여물은 flash column chromatography (hexane/EtOAc, 1:1)를 이용하여 정제하였다. 최종적으로 하얀색 고체 (2.06g, 97%)를 확보하였다; m.p. 60–62 °C; ¹H NMR (600 MHz, CDCl₃) δ 7.50 (s, 1H), 4.76 (s, 2H), 4.30 (t, *J* = 4.4 Hz, 2H), 2.97 (br s, 1H), 1.86 (t, *J* = 7.1 Hz, 2H), 1.29–1.19 (m, 14H), 0.85 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 147.6, 121.5, 56.4, 50.4, 31.8, 30.2, 29.4, 29.3, 29.2, 29.0, 26.4, 22.6, 14.0; IR (neat) ν_{max} = 3324, 2918, 2848, 1462, 1147, 1056, 1037, 1010, 845, 783 (cm⁻¹); HRMS (FAB) calcd. for C₁₃H₂₆N₃O [M+H]⁺ 240.1964, found 240.1952;

((1-Decyl-1H-1,2,3-triazol-4-yl)methyl)triphenylphosphonium bromide (5f)

Compound 5f는 6로부터 general procedure C와 같은 방법으로 합성하였다. 목표 생성물은 무색 wax 성상으로 (4.66g, 96%) 얻을 수 있었다. ¹H NMR (400 MHz, CD₃OD) δ 7.89–7.79 (m, 10H), 7.79–7.72 (m, 6H), 5.24 (d, *J* = 5.5 Hz, 1H), 5.20 (d, *J* = 5.5 Hz, 1H), 4.29 (t, *J* = 13.8 Hz, 2H), 1.74 (td, *J* = 7.3, 14.8 Hz, 2H), 1.35–1.13, 14H), 0.90 (t, *J* = 13.8 Hz, 3H); ¹³C NMR (100 MHz, CD₃OD) δ 136.5 (d, *J* = 2.9 Hz, 3C), 136.2 (d, *J* = 7.7 Hz), 135.4 (d, *J* = 9.6 Hz, 6C), 131.5 (d, *J* = 12.5 Hz, 6C), 126.9 (d, *J* = 6.7 Hz), 119.6 (d, *J* = 86.7

Hz, 3C), 51.4, 49.0, 33.1, 31.3, 30.72, 30.66, 30.5, 30.1, 27.4, 23.8, 14.7;

E. Synthesis of isoxazole containing phosphonium bromides **5g** and **5gb**.



(3-Decylisoxazol-5-yl)methanol (**7**)

N-hydroxyundecanimidoyl chloride 이미 개제된 논문의 procedure¹¹와 같은 방법으로 합성하였다. 무수 DMF solvent (0.05 M)에 propargyl alcohol (1 eq)를 녹인 뒤, *N*-hydroxyundecanimidoyl chloride (3 eq), CuI (1 eq), DIPEA (3 eq)를 추가하여 상온에서 12시간 동안 교반하였다. 반응 종료 후 NH₄Cl과 EtOAc를 이용하여 추출하였고 MgSO₄로 건조하고 잔여물을 감압농축 하였다. Isoxazole product **7** 은 flash column chromatography (hexane/EtOAc, 10:1)로 정제되어 하얀색 고체로 (700 mg, 80%) 확보하였다. m.p. 48–50 °C; ¹H NMR (800 MHz, CDCl₃) δ 6.07 (s, 1H), 4.71 (d, *J* = 0.5 Hz, 2H), 2.62 (t, *J* = 7.7 Hz, 2H), 1.62 (td, *J* = 7.6, 15.2 Hz, 2H), 1.34–1.32 (m, 2H), 1.31–1.20 (m, 12H), 0.85 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (200 MHz, CDCl₃) δ 170.8, 164.2, 101.5, 56.6, 31.9, 29.55, 29.47, 29.29, 29.27, 29.2, 28.3, 26.0, 22.7, 14.1; IR (neat) ν_{max} = 3356, 2918, 2847, 1461, 1423, 1149, 1036, 991, 836, 771 (cm⁻¹); HRMS (FAB) calcd. for C₁₄H₂₆NO₂ [M+H]⁺ 240.1964, found 240.1965.

((3-Decylisoxazol-5-yl)methyl)triphenylphosphonium bromide (**5g**)

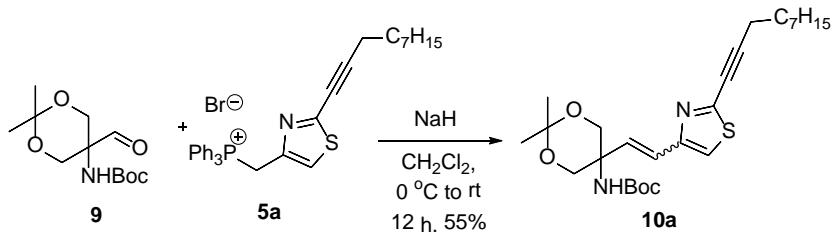
화합물 **5g**는 isoxazole 화합물인 **7** 으로부터 general procedure C를 이용하여 합성하였다. 목표 생성물은 **5g**는 무색 oil (900 mg, 60%) 로

확보하였다.; ¹H NMR (500 MHz, CD₃OD) δ 7.94–7.90 (m, 3H), 7.77–7.75 (m, 4H), 7.76–7.75 (m, 4H), 7.73–7.72 (m, 4H), 6.13 (d, *J* = 3.3 Hz, 1H), 2.55 (t, *J* = 7.3 Hz, 2H), 1.52 (td, *J* = 7.4, 14.7 Hz, 2H), 1.33–1.20 (m, 16H), 0.89 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CD₃OD) δ 167.2 (d, *J* = 2.6 Hz), 162.2 (d, *J* = 9.6 Hz), 137.6 (d, *J* = 2.6 Hz, 3C), 135.9 (d, *J* = 10.4 Hz, 6C), 132.4 (d, *J* = 12.8 Hz, 6C), 119.6 (d, *J* = 87.0 Hz, 3C), 108.6 (d, *J* = 6.6 Hz), 50.3, 33.8, 31.5, 31.4, 31.2, 31.1, 30.8, 29.9, 27.3, 24.5, 15.2;

F. General procedure for internal alkene coupling compound 10.

합성법이 알려진 aldehyde **9** (1 eq) 과 NaH (6 eq), phosphonium bromide compound **5** (1.1 eq)를 CH₂Cl₂ (0.2 M)에 녹여서 0°C 30분 교반 후 상온으로 온도를 올린 뒤 12시간 동안 교반하였다. 반응 종결 뒤 NH₄Cl과 CH₂Cl₂로 씻어주고 MgSO₄로 건조시켰다. 건조시킨 반응물은 flash column chromatography (hexane/EtOAc, 7:1)를 통해 정제되었고 목표 생성물 **10** 을 얻었다.

tert-Butyl (5-(2-(2-(dec-1-yn-1-yl)thiazol-4-yl)vinyl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (**10a**)

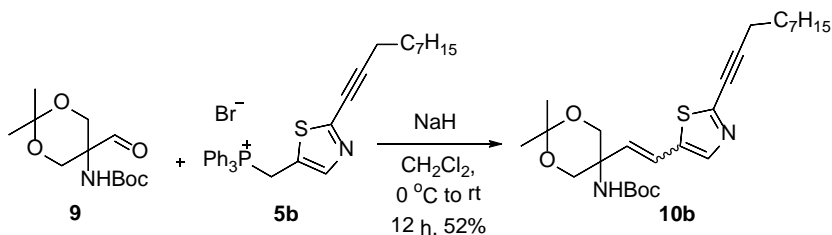


10a 유도체는 general procedure F 와 같은 방법으로 진행하였으며, 최종적으로 생성물 **10a** (130 mg, 55%) 를 확보하였다.

(*Z*)-isomer: yellow oil; $^1\text{H NMR}$ (800 MHz, CDCl_3) δ 7.07 (s, 1H), 6.38 (d, $J = 13.0$ Hz, 1H), 6.09 (br s, 1H), 5.91 (d, $J = 12.8$ Hz, 1H), 4.31 (d, $J = 11.6$ Hz, 2H), 4.07 (d, $J = 10.8$ Hz, 2H), 2.42 (t, $J = 7.2$ Hz, 2H), 1.60 (td, $J = 7.4, 14.9$ Hz, 2H), 1.53 (s, 3H), 1.45 (s, 3H), 1.42 (td, $J = 7.4, 14.8$ Hz, 2H), 1.29–1.23 (m, 17H), 0.86 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3) δ 155.5, 151.9, 148.6, 133.2, 122.3, 119.9, 98.3, 96.7, 78.9, 74.1, 65.6, 53.7, 31.8, 29.7, 29.1, 29.0, 28.9, 28.3 (3C), 28.0, 25.3, 22.63, 22.61, 19.5, 14.1; IR (neat) $\nu_{\text{max}} = 2926, 2856, 1714, 1475, 1367, 1244, 1162, 1071, 832, 776$ (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{26}\text{H}_{41}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 477.2787, found 477.2787.

(*E*)-isomer: colorless oil; $^1\text{H NMR}$ (500 MHz, CD_2Cl_2) δ 7.00 (s, 1H), 6.52 (d, $J = 16.0$ Hz, 1H), 6.47 (d, $J = 16.0$ Hz, 1H), 5.21 (br s, 1H), 3.88 (t, $J = 12.5$ Hz, 4H), 2.44 (t, $J = 7.2$ Hz, 2H), 1.61 (td, $J = 7.4, 14.8$ Hz, 2H), 1.43 (s, 3H), 1.41 (s, 9H), 1.40 (s, 3H), 1.30–1.24 (m, 10H), 0.87 (t, $J = 6.9$ Hz, 3H); $^{13}\text{C NMR}$ (125 MHz, CD_2Cl_2) δ 155.1, 153.7, 149.5, 132.0, 123.3, 116.5, 98.5, 96.9, 74.4, 66.1, 54.6, 32.2, 30.1, 29.5, 29.4, 29.3, 28.5 (3C), 28.2, 23.0, 19.8, 19.2, 18.7, 14.2; IR (neat) $\nu_{\text{max}} = 2926, 2856, 1717, 1487, 1368, 1246, 1167, 1072, 828, 745$ (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{26}\text{H}_{41}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 477.2787, found 477.2791.

***tert*-Butyl (5-(2-(2-(dec-1-yn-1-yl)thiazol-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (10b)**



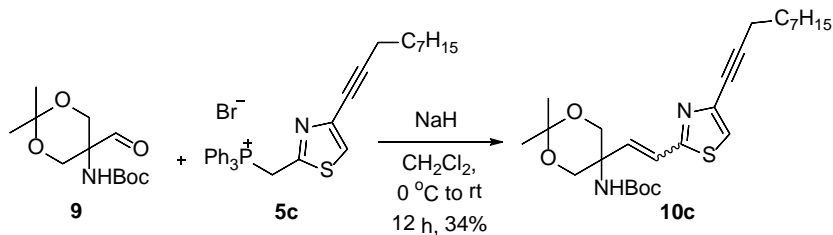
10b 유도체는 general procedure F 와 같은 방법으로 진행하였으며, 최종적으로 생성물 10b (270 mg, 52%)를 확보하였다.

(*Z*)-isomer: colorless oil; $^1\text{H NMR}$ (800 MHz, CD_2Cl_2) δ 7.56 (s, 1H), 6.58 (d, $J = 12.7$ Hz, 1H), 5.44 (d, $J = 12.1$ Hz, 1H), 5.38 (br s, 1H), 3.99 (d, $J = 11.2$ Hz, 2H),

3.80 (d, $J = 11.8$ Hz, 2H), 2.48 (t, $J = 7.2$ Hz, 2H), 1.63 (td, $J = 7.4, 14.9$ Hz, 2H), 1.47–1.44 (m, 2H), 1.42 (s, 3H), 1.40 (s, 3H), 1.33 (s, 9H), 1.29–1.26 (m, 8H), 0.89 (t, $J = 7.1$ Hz, 3H); IR (neat) $\nu_{\max} = 2926, 2856, 1713, 1497, 1367, 1246, 1163, 1073, 834$ (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{26}\text{H}_{41}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 477.2787, found 477.2788.

(*E*)-isomer: colorless oil; ^1H NMR (800 MHz, CD_2Cl_2) δ 7.53 (s, 1H), 6.64 (d, $J = 16.2$ Hz, 1H), 6.00 (d, $J = 16.1$ Hz, 1H), 5.20 (br s, 1H), 3.90–3.89 (m, 2H), 3.86 (d, $J = 11.3$ Hz, 2H), 2.47 (t, $J = 7.2$ Hz, 2H), 1.63 (td, $J = 7.4, 14.9$ Hz, 2H), 1.45 (s, 3H), 1.44–1.43 (m, 2H), 1.42–1.41 (m, 12H), 1.33–1.26 (m, 8H), 0.89 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (200 MHz, CD_2Cl_2) δ 155.0, 147.8, 141.8, 138.2, 120.6 (2C), 98.7, 97.6, 74.6 (2C), 66.1, 53.6, 32.2, 30.1, 29.6, 29.5, 29.3, 28.48, 28.47 (3C), 27.8, 23.1, 19.9, 19.6, 14.3; IR (neat) $\nu_{\max} = 2926, 2856, 1715, 1487, 1368, 1160, 1057, 832$ (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{26}\text{H}_{41}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 477.2787, found 477.2791.

***tert*-Butyl (5-(2-(4-(dec-1-yn-1-yl)thiazol-2-yl)vinyl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (10c)**



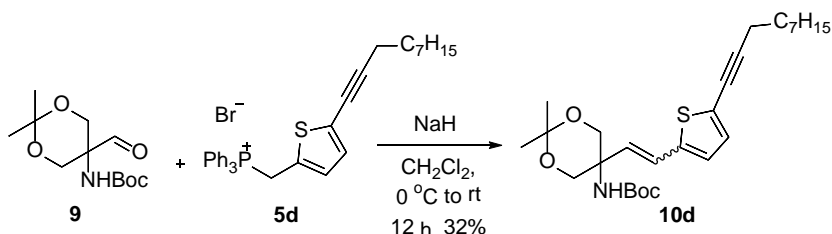
10c 유도체는 general procedure F 와 같은 방법으로 진행하였으며, 최종적으로 생성물 10c (125 mg, 34%) 를 확보하였다.

(*Z*)-isomer: yellow oil; ^1H NMR (800 MHz, CD_2Cl_2) δ 7.34 (s, 1H), 6.51 (d, $J = 13.0$ Hz, 1H), 6.08 (d, $J = 12.7$ Hz, 1H), 6.07 (br s, 1H), 4.35 (d, $J = 11.5$ Hz, 2H), 4.03 (d, $J = 11.1$ Hz, 2H), 2.41 (t, $J = 7.2$ Hz, 2H), 1.61 (td, $J = 5.6, 10.0$ Hz, 2H), 1.52 (s, 3H), 1.45–1.43 (m, 2H), 1.42 (s, 3H), 1.34–1.26 (m, 17H), 0.89 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (200 MHz, CD_2Cl_2) δ 163.1, 155.6, 139.2, 138.0, 122.8, 121.2,

98.7, 91.0, 79.3 (2C), 74.9, 65.2, 32.3, 30.1, 29.6, 29.5, 29.4, 28.9, 28.4 (3C), 25.4, 23.1, 22.9, 19.6, 14.3; IR (neat) ν_{\max} = 2926, 2856, 1714, 1488, 1367, 1244, 1161, 1090, 1040, 831 (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{26}\text{H}_{41}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 477.2787, found 477.2791.

(*E*)-isomer: yellow oil; ^1H NMR (400 MHz, CD_3CN) δ 7.38 (s, 1H), 6.72 (d, J = 16.5 Hz, 1H), 6.64 (d, J = 16.0 Hz, 1H), 5.56 (br s, 1H), 3.95 (d, J = 11.0 Hz, 2H), 3.90 (d, J = 11.4 Hz, 2H), 2.41 (t, J = 13.7 Hz, 2H), 1.58 (td, J = 7.4, 14.8 Hz, 2H), 1.43 (s, 3H), 1.41 (s, 11H), 1.38 (s, 3H), 1.32–1.26 (m, 8H), 0.89 (t, J = 13.7 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 166.2, 155.8, 139.2, 137.4, 124.2, 122.7, 99.2, 91.4, 80.0, 75.8 (2C), 66.1, 54.4, 32.6, 30.0, 29.9, 29.7, 29.2, 28.6 (3C), 27.2, 23.4, 20.9, 19.6, 14.5; IR (neat) ν_{\max} = 2923, 2853, 1708, 1522, 1367, 1249, 1166, 1053, 1016, 827 (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{26}\text{H}_{41}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 477.2787, found 477.2793.

***tert*-Butyl (5-(2-(5-(dec-1-yn-1-yl)thiophen-2-yl)vinyl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (10d)**



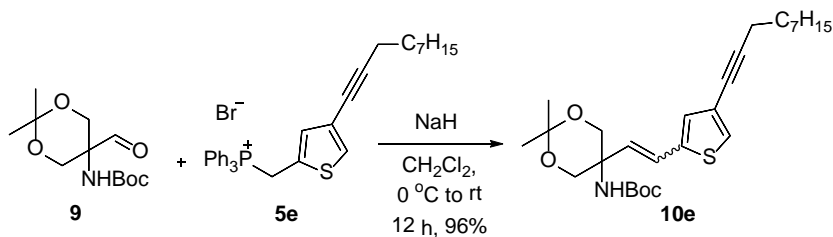
10d 유도체는 general procedure F 와 같은 방법으로 진행하였으며, 최종적으로 생성물 10d (310 mg, 32%) 를 확보하였다.

(*Z*)-isomer: yellow oil; ^1H NMR (800 MHz, CD_2Cl_2) δ 6.94 (d, J = 3.7 Hz, 1H), 6.84 (d, J = 3.7 Hz, 1H), 6.53 (d, J = 12.7 Hz, 1H), 5.38 (br s, 1H), 5.34 (d, J = 10.9 Hz, 1H), 4.05 (d, J = 11.6 Hz, 2H), 3.81 (d, J = 11.8 Hz, 2H), 2.43 (t, J = 7.2 Hz, 2H), 1.59 (td, J = 7.4, 14.9 Hz, 2H), 1.45 (d, J = 5.8 Hz, 2H), 1.41 (s, 3H), 1.40 (s, 3H), 1.34 (s, 9H), 1.33–1.26 (m, 8H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (200 MHz, CD_2Cl_2) δ 154.5, 138.8 (2C), 130.8, 130.0, 128.2, 124.2, 98.6, 73.8 (2C),

65.6, 62.9, 52.1, 32.3, 29.6, 29.5, 29.3, 29.0, 28.4 (3C), 28.3, 28.1, 23.1, 20.0, 19.4, 14.3; IR (neat) ν_{\max} = 2927, 2856, 1718, 1493, 1369, 1167, 1074, 835 (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{27}\text{H}_{42}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 476.2835, found 476.2828.

(*E*)-isomer: yellow oil; ^1H NMR (800 MHz, CD_2Cl_2) δ 6.94 (d, J = 3.7 Hz, 1H), 6.79 (d, J = 3.8 Hz, 1H), 6.58 (d, J = 16.2 Hz, 1H), 5.96 (d, J = 16.2 Hz, 1H), 3.89 (d, J = 11.2 Hz, 2H), 3.85 (d, J = 2.4 Hz, 2H), 2.42 (t, J = 7.2 Hz, 2H), 1.58 (td, J = 7.4, 14.9 Hz, 2H), 1.45 (s, 3H), 1.42 (s, 9H), 1.41 (s, 3H), 1.34–1.25 (m, 10H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (200 MHz, CD_2Cl_2) δ 155.1, 142.3, 131.8, 126.2, 123.8, 123.4, 123.4, 98.6, 96.2, 74.0 (2C), 66.2, 53.6, 32.2, 30.1, 29.6, 29.5, 29.3, 29.0, 28.5 (3C), 28.0, 23.1, 20.0, 19.4, 14.3; IR (neat) ν_{\max} = 2927, 2856, 1714, 1492, 1369, 1165, 1073, 832 (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{27}\text{H}_{42}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 476.2835, found 476.2757.

***tert*-Butyl (5-(2-(4-(dec-1-yn-1-yl)thiophen-2-yl)vinyl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (10e)**



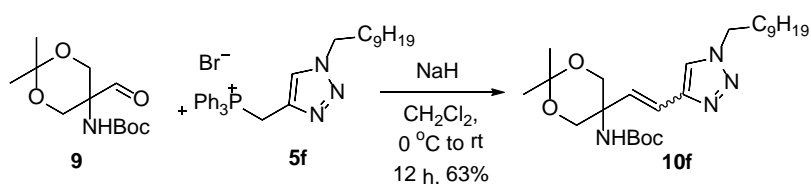
10e 유도체는 general procedure F 와 같은 방법으로 진행하였으며, 최종적으로 생성물 **10e** (450 mg, 95%) 를 확보하였다.

(*Z*)-isomer: yellow oil; ^1H NMR (800 MHz, CD_3CN) δ 7.35 (d, J = 1.1 MHz, 1H), 6.97 (s, 1H), 6.51 (d, J = 12.8 Hz, 1H), 5.48 (d, J = 12.7 Hz, 2H), 3.95 (d, J = 11.4 Hz, 2H), 3.86 (d, J = 11.7 Hz, 2H), 2.37 (t, J = 11.7 Hz, 2H), 1.55 (td, J = 7.4, 14.8 Hz, 2H), 1.45–1.41 (m, 2H), 1.39 (s, 3H), 1.36 (s, 3H), 1.33–1.31 (m, 4H), 1.29 (s, 9H), 1.28–1.27 (m, 4H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (200 MHz, CD_3CN) δ 154.9, 139.2, 132.4, 130.6, 129.9, 123.6, 123.5, 99.0, 90.7, 79.5, 76.2 (2C), 66.0, 52.9, 32.5, 29.9, 29.8, 29.5, 29.4, 28.5 (3C), 27.2, 23.3, 20.6, 19.6, 14.3; IR (neat)

ν_{\max} = 2924, 2855, 1717, 1492, 1368, 1246, 1165, 1074, 954, 833 (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{27}\text{H}_{42}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 476.2835, found 476.2828.

(*E*)-isomer: yellow oil; IR (neat) ν_{\max} = 2925, 2855, 1716, 1489, 1367, 1244, 1162, 1056, 935, 832 (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{27}\text{H}_{42}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 476.2835, found 476.2827.

***tert*-Butyl (5-(2-(1-decyl-1*H*-1,2,3-triazol-4-yl)vinyl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (10f)**



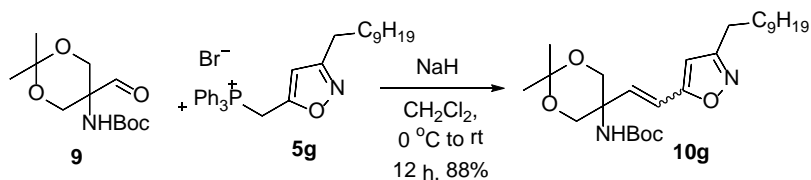
10f 유도체는 general procedure F 와 같은 방법으로 진행하였으며, 최종적으로 생성물 **10f** (2.1 g, 63%) 를 확보하였다.

(*Z*)-isomer: yellow oil; ^1H NMR (600 MHz, CD_2Cl_2) δ 7.52 (s, 1H), 6.39 (d, J = 12.8 Hz, 1H), 6.04 (br s, 1H), 5.81 (d, J = 12.8 Hz, 1H), 4.29 (t, J = 7.4 Hz, 2H), 4.19 (d, J = 11.5 Hz, 2H), 4.04 (d, J = 11.5 Hz, 2H), 1.86 (t, J = 11.5 Hz, 2H), 1.44 (s, 3H), 1.40 (s, 3H), 1.31–1.15 (m, 23H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 155.4, 143.8, 132.8, 123.8, 118.5, 98.5, 79.1, 65.9 (2C), 52.9, 50.6, 32.2, 30.7, 29.9, 29.8, 29.6, 29.4, 28.4 (3C), 26.8, 25.3, 23.0, 22.6, 14.2; IR (neat) ν_{\max} = 2926, 2856, 1713, 1454, 1367, 1246, 1163, 1071, 833, 735 (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{25}\text{H}_{45}\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 465.3441, found 465.3446.

(*E*)-isomer: yellow solid; m.p. 100–103 °C; ^1H NMR (600 MHz, CD_2Cl_2) δ 7.48 (s, 1H), 6.52 (d, J = 16.5 Hz, 1H), 6.35 (d, J = 16.5 Hz, 1H), 5.21 (br s, 1H), 4.28 (t, J = 7.1 Hz, 2H), 3.89 (q, J = 9.9 Hz, 4H), 1.85 (q, J = 7.2 Hz, 2H), 1.44 (s, 3H), 1.41 (s, 9H), 1.40 (s, 3H), 1.30–1.24 (m, 14H), 0.86 (t, J = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 155.1, 145.5, 130.2, 120.6, 119.7, 98.5, 66.2 (2C), 53.3, 50.6, 32.2, 30.6, 29.9, 29.8, 29.6, 29.4, 28.5 (3C), 28.1, 26.8, 23.0, 19.4, 14.2; IR (neat) ν_{\max} = 2925, 2855, 1708, 1517, 1367, 1246, 1169, 1056, 839, 782 (cm^{-1}); HRMS (FAB)

calcd. for C₂₅H₄₅N₄O₄ [M+H]⁺ 465.3441, found 465.3442.

***tert*-Butyl (5-(2-(3-decylisoxazol-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-5-yl)-*tert*-butylcarbamate (10g)**



10g 유도체는 general procedure F 와 같은 방법으로 진행하였으며, 최종적으로 생성물 **10g** (380 mg, 88%)를 확보하였다.

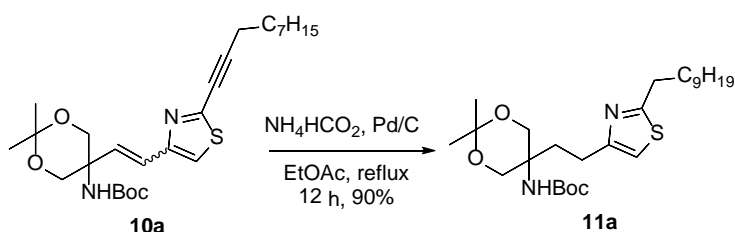
(*Z*)-isomer: colorless oil; ¹H NMR (800 MHz, CD₃CN) δ 6.38 (d, *J* = 13.0 Hz, 1H), 6.31 (s, 1H), 5.88 (d, *J* = 13.0 Hz, 1H), 5.88 (d, *J* = 13.0 Hz, 1H), 5.60 (br s, 1H), 3.97 (s, 4H), 2.61 (t, *J* = 7.6 Hz, 2H), 1.64 (td, *J* = 7.4, 14.6 Hz, 2H), 1.42 (s, 3H), 1.38 (s, 3H), 1.33–1.30 (m, 2H), 1.29–1.27 (m, 21H), 0.88 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (200 MHz, CD₃CN) δ 166.8, 165.2, 155.0, 136.8, 116.5, 106.0, 99.0, 80.66.1 (2C), 53.2, 32.6, 30.3, 30.2, 30.0, 29.9, 29.8, 29.0, 28.4 (3C), 26.43, 26.39, 23.3, 21.5, 14.4; IR (neat) ν_{max} = 2926, 2852, 1706, 1509, 1172, 1047, 1016, 834 (cm⁻¹); HRMS (FAB) calcd. for C₂₆H₄₅N₂O₅ [M+H]⁺ 465.3328, found 465.3325.

(*E*)-isomer: yellow oil; ¹H NMR (400 MHz, CD₃CN) δ 6.52 (d, *J* = 16.5 Hz, 1H), 6.47 (d, *J* = 16.5 Hz, 1H), 6.20 (s, 1H), 5.56 (br s, 1H), 3.94–3.84 (m, 4H), 2.60 (t, *J* = 15.1 Hz, 2H), 1.64–1.59 (m, 2H), 1.43 (s, 3H), 1.38 (s, 3H), 1.41 (m, 8H), 1.31–1.22 (m, 15H), 0.88 (t, *J* = 13.3 Hz, 3H); ¹³C NMR (100 MHz, CD₃CN) δ 168.3, 165.7, 155.8, 136.6, 117.0, 102.5, 99.2, 80.0, 66.1 (2C), 54.3, 32.7, 30.34, 30.28, 30.1, 30.0, 29.8, 29.0, 28.6 (3C), 27.0, 26.5, 23.4, 21.0, 14.5; IR (neat) ν_{max} = 2927, 2856, 1715, 1522, 1171, 1053, 1035, 836 (cm⁻¹); HRMS (FAB) calcd. for C₂₆H₄₅N₂O₅ [M+H]⁺ 465.3328, found 465.3325.

G. General procedure for compound **11** by Pd/C reduction reaction.

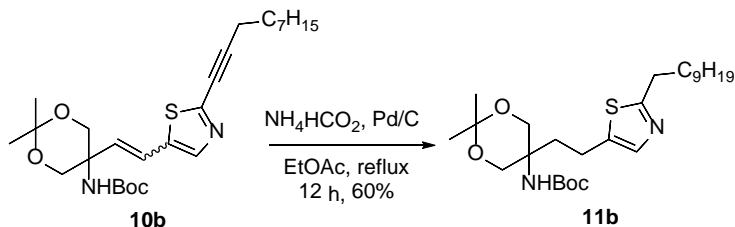
EtOAc (0.1 M)에 compound **10** (1 eq), Ammonium formate (7 eq), Pd/C (30 wt%)를 녹인 뒤 12시간 동안 reflux 하였다. 반응 종료 후에 Celite pad를 이용하여 필터하고 brine으로 씻어주었다. 반응물은 MgSO₄로 건조시키고 감압농축 이후에 flash column chromatography를 통하여 정제하여 최종 화합물 **11** 을 확보하였다.

***tert*-Butyl (5-(2-(2-decylthiazol-4-yl)ethyl)-2,2-dimethyl-1,3-dioxan-5-yl) carbamate (**11a**)**



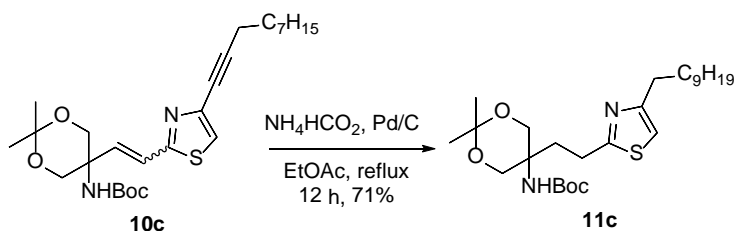
11a 유도체는 general procedure G 와 같은 방법으로 진행하였으며, 최종적으로 무색 oil **11a** (100 mg, 90%)를 확보하였다.; ¹H NMR (600 MHz, CDCl₃) δ 6.71 (s, 1H), 5.19 (br s, 1H), 3.94 (d, *J* = 7.8 Hz, 2H), 3.65 (d, *J* = 11.9 Hz, 2H), 2.92 (t, *J* = 7.8 Hz, 2H), 2.71 (t, *J* = 8.0 Hz, 2H), 2.07 (t, *J* = 7.6 Hz, 2H), 1.73 (td, *J* = 7.7, 15.3 Hz, 2H), 1.42 (s, 9H), 1.42 (s, 3H), 1.38 (s, 3H), 1.23 (m, 14H), 0.85 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 171.3, 156.1, 155.0, 112.0, 98.3, 79.2, 65.9 (2C), 51.6, 33.5, 31.9, 31.0, 30.2, 29.53, 29.47, 29.3 (2C), 29.1, 28.4 (3C), 26.8, 24.9, 22.7, 20.4, 14.1; IR (neat) ν_{max} = 2923, 2853, 1703, 1523, 1249, 1168, 1072, 831, 722 (cm⁻¹); HRMS (FAB) calcd. for C₂₆H₄₇N₂O₄S [M+H]⁺ 483.3257, found 483.3254.;

***tert*-Butyl (5-(2-(2-decylthiazol-5-yl)ethyl)-2,2-dimethyl-1,3-dioxan-5-yl) carbamate (**11b**)**



11b 유도체는 general procedure G 와 같은 방법으로 진행하였으며, 최종적으로 무색 oil **11b** (153 mg, 60%)를 확보하였다.; ^1H NMR (500 MHz, CDCl_3) δ 7.28 (s, 1H), 4.93 (br s, 1H), 3.86 (d, $J = 11.5$ Hz, 2H), 3.67 (d, $J = 11.8$ Hz, 2H), 2.89 (t, $J = 7.7$ Hz, 2H), 2.73 (q, $J = 5.5$ Hz, 2H), 2.01 (t, $J = 8.0$ Hz, 2H), 1.72 (td, $J = 7.5, 15.0$ Hz, 2H), 1.44 (s, 9H), 1.40 (d, $J = 5.9$ Hz, 6H), 1.23 (m, 14H), 0.85 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.2, 154.9, 138.6, 137.9, 98.5, 66.2 (2C), 51.6, 33.5, 31.9 (2C), 30.0, 29.6, 29.5, 29.3 (2C), 29.1, 28.4 (3C), 27.2, 22.7, 20.6, 19.9, 14.1; IR (neat) $\nu_{\text{max}} = 3340, 2923, 2852, 1699, 1524, 1376, 1169, 1071, 829, 732$ (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{26}\text{H}_{47}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 483.3257, found 483.3260.

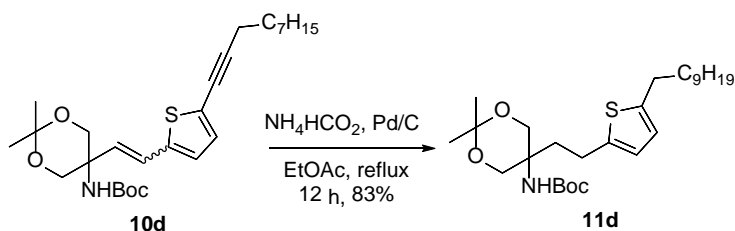
***tert*-Butyl (5-(2-(4-decylthiazol-2-yl)ethyl)-2,2-dimethyl-1,3-dioxan-5-yl) carbamate (**11c**)**



11c 유도체는 general procedure G 와 같은 방법으로 진행하였으며, 최종적으로 무색 oil **11c** (88 mg, 71%) 를 확보하였다.; ^1H NMR (500 MHz, CDCl_3) δ 6.68 (s, 1H), 5.25 (br s, 1H), 3.92 (d, $J = 14.9$ Hz, 2H), 3.66 (d, $J = 11.8$ Hz, 2H), 2.96 (t, $J = 8.1$ Hz, 2H), 2.68 (t, $J = 7.7$ Hz, 2H), 2.16 (s, 2H), 1.64 (td, $J = 7.4, 14.6$ Hz, 2H), 1.43 (s, 9H), 1.40 (d, $J = 15.9$ Hz, 6H), 1.23 (m, 14H),

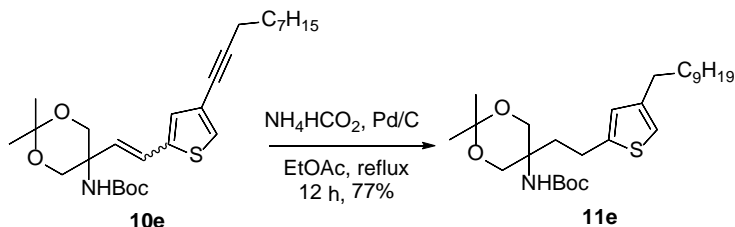
0.85 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.9, 157.3, 155.0, 111.9, 98.4, 79.4, 65.9 (2C), 51.5, 31.9, 31.7, 31.5, 29.6 (2C), 29.4, 29.3 (2C), 29.2, 28.4 (3C), 27.0, 26.8, 22.7, 20.4, 14.1; IR (neat) $\nu_{\text{max}} = 2924, 2855, 1714, 1521, 1495, 1368, 1163, 1071, 831, 729$ (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{26}\text{H}_{47}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 483.3257, found 483.3254.

***tert*-Butyl (5-(2-(5-decylthiophen-2-yl)ethyl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (11d)**



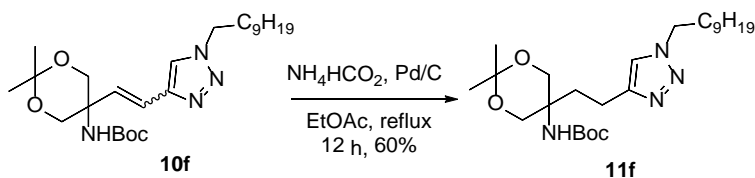
11d 유도체는 general procedure G 와 같은 방법으로 진행하였으며, 최종적으로 노란색 고체 **11d** (250 mg, 83%) 를 확보하였다.; ^1H NMR (600 MHz, CD_3CN) δ 6.53 (dd, $J = 3.2, 7.3$ Hz, 2H), 3.79 (d, $J = 11.5$ Hz, 2H), 3.66 (d, $J = 11.9$ Hz, 2H), 2.69 (t, $J = 7.6$ Hz, 2H), 2.64 (td, $J = 4.4, 8.1$ Hz, 2H), 1.93 (td, $J = 7.2, 15.6$ Hz, 2H), 1.56 (t, $J = 7.3$ Hz, 2H), 1.38 (s, 9H), 1.33 (s, 3H), 1.30 (s, 3H), 1.27–1.23 (m, 14H), 0.84 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 143.6, 142.6, 123.78, 123.76, 117.8, 98.1, 51.7, 31.7, 31.6, 29.6, 29.34, 29.32, 29.09, 29.06, 28.8, 27.7 (3C), 26.0, 23.2, 22.4, 20.2, 13.4; IR (neat) $\nu_{\text{max}} = 3342, 2923, 2852, 1700, 1524, 1252, 1170, 1073, 829, 797$ (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{27}\text{H}_{48}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 482.3304, found 482.3298.

***tert*-Butyl (5-(2-(4-decylthiophen-2-yl)ethyl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (11e)**



11e 유도체는 general procedure G 와 같은 방법으로 진행하였으며, 최종적으로 하얀색 고체 **11e** (650 mg, 77%) 를 확보하였다.; m.p. 45 °C; ^1H NMR (400 MHz, CDCl_3) δ 6.65 (s, 1H), 6.60 (s, 1H), 4.92 (br s, 1H), 3.87 (d, $J = 11.6$ Hz, 2H), 3.66 (d, $J = 11.8$ Hz, 2H), 2.73 (td, $J = 4.2, 7.4$ Hz, 2H), 2.49 (t, $J = 7.7$ Hz, 2H), 2.03 (t, $J = 8.2$ Hz, 2H), 1.55 (t, $J = 7.4$ Hz, 2H), 1.44 (s, 9H), 1.40 (d, $J = 5.4$ Hz, 6H), 1.28–1.24 (m, 14H), 0.86 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.9, 144.4, 143.1, 125.7, 117.4, 98.4, 79.4, 66.3, 66.2, 51.6, 33.6, 31.9, 30.5, 30.4, 29.61, 29.58, 29.5, 29.4, 29.3, 28.4 (3C), 27.3, 23.5, 22.7, 19.8, 14.1; IR (neat) $\nu_{\text{max}} = 3346, 2925, 2853, 1699, 1523, 1251, 1169, 1071, 828, 722$ (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{27}\text{H}_{48}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 482.3304, found 482.3309.

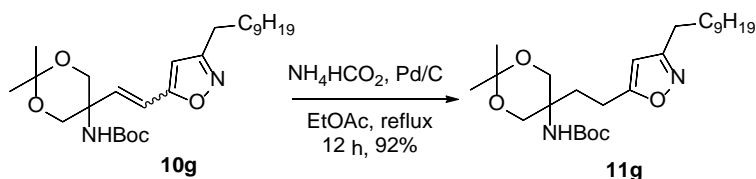
tert-Butyl (5-(2-(1-decyl-1H-1,2,3-triazol-4-yl)ethyl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (11f)



11f 유도체는 general procedure G 와 같은 방법으로 진행하였으며, 최종적으로 하얀색 고체 **11f** (1.2 g, 60%) 를 확보하였다.; m.p. 74–76 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.25 (s, 1H), 5.02 (br s, 1H), 4.26 (t, $J = 7.2$ Hz, 2H), 3.79 (dd, $J = 11.7, 84.5$ Hz, 4H), 2.68 (t, $J = 8.3$ Hz, 2H), 2.05 (t, $J = 8.3$ Hz, 2H), 1.84 (t, $J = 6.6$ Hz, 2H), 1.43 (s, 9H), 1.42 (s, 3H), 1.40 (s, 3H), 1.23–1.28 (m, 14H), 0.86 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.9, 147.6, 120.4,

98.3, 79.3, 66.1 (2C), 51.5, 50.1, 31.8, 31.3, 30.2, 29.4, 29.3, 29.2, 28.9, 28.3 (3C), 27.1, 26.4, 22.6, 13.99, 19.9, 19.1; IR (neat) ν_{\max} = 3426, 2922, 2853, 1707, 1498, 1203, 1163, 1082, 834, 731(cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{25}\text{H}_{47}\text{N}_4\text{O}_4$ ($[\text{M}+\text{H}]^+$) 467.3597, found 467.3597.

***tert*-Butyl (5-(2-(3-decylisoxazol-5-yl)ethyl)-2,2-dimethyl-1,3-dioxan-5-yl) carbamate (11g)**

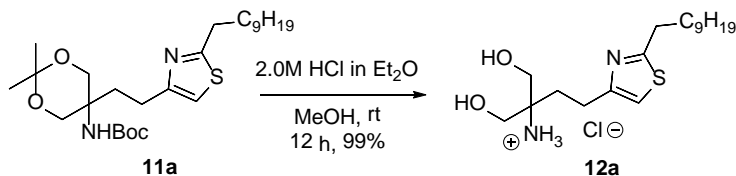


11g 유도체는 general procedure G 와 같은 방법으로 진행하였으며, 최종적으로 하얀색 고체 **11g** (353 mg, 92%) 를 확보하였다.; m.p. 63–65 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.25 (s, 1H), 5.02 (br s, 1H), 4.26 (t, $J = 7.2$ Hz, 2H), 3.79 (dd, $J = 11.7, 84.5$ Hz, 4H), 2.68 (t, $J = 8.3$ Hz, 2H), 2.05 (t, $J = 8.3$ Hz, 2H), 1.84 (t, $J = 6.6$ Hz, 2H), 1.43 (s, 9H), 1.42 (s, 3H), 1.40 (s, 3H), 1.28–1.23 (m, 14H), 0.86 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.9, 147.6, 120.4, 98.3, 79.3, 66.1 (2C), 51.5, 50.1, 31.8, 31.3, 30.2, 29.4, 29.3, 29.2, 28.9, 28.3 (3C), 27.1, 26.4, 22.6, 19.9, 19.1, 14.0; IR (neat) ν_{\max} = 2922, 2852, 1705, 1497, 1369, 1216, 1163, 1083, 832, 824 (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{25}\text{H}_{47}\text{N}_4\text{O}_4$ ($[\text{M}+\text{H}]^+$) 467.3597, found 467.3597.

H. General procedure for deprotection compound **12** by HCl in Et_2O

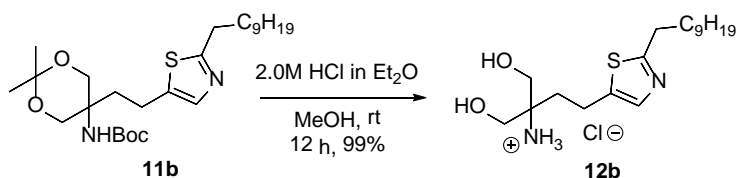
확보되어진 화합물 **11** (1 eq) 를 MeOH (0.1 M) 에 녹여 2.0 M HCl in Et_2O (4 M) 과 상온에서 12시간 동안 교반하였다. 목표 생성물인 화합물 **12** 는 추가 정제과정 없이 감압농축만으로 확보하였다.

4-(2-Decylthiazol-4-yl)-1-hydroxy-2-(hydroxymethyl)butan-2-aminium chloride (12a)



12a 유도체는 general procedure H 와 같은 방법으로 진행하였으며, 최종적으로 갈색 고체 **12a** (56 g, 99%) 를 확보하였다.; m.p. 120 °C; ¹H NMR (600 MHz, CD₃OD) δ 7.67 (s, 1H), 3.70 (t, *J* = 12.6 Hz, 4H), 3.27 (m, 2H), 3.02 (d, *J* = 4.6 Hz, 2H), 2.13 (d, *J* = 5.5 Hz, 2H), 1.87 (m, 2H), 1.45 (m, 2H), 1.38 (m, 2H), 1.30 (m, 12H), 0.89 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (150 MHz, CD₃OD) δ 179.5, 150.2, 119.5, 63.1 (2C), 62.6, 33.8, 32.4, 32.0, 31.5, 31.4, 31.3, 31.2, 31.0, 30.8, 24.5, 24.1, 15.2; IR (neat) ν_{max} = 3328, 2919, 2852, 2353, 1904, 1597, 1469, 1066, 720 (cm⁻¹); HRMS (FAB) calcd. for C₁₈H₃₅N₂O₂S [M-Cl]⁺ 343.2419, found 343.2429.

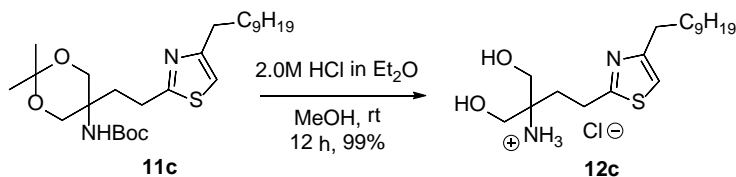
4-(2-Decylthiazol-5-yl)-1-hydroxy-2-(hydroxymethyl)butan-2-aminium chloride (12b)



12b 유도체는 general procedure H 와 같은 방법으로 진행하였으며, 최종적으로 하얀색 고체 **12b** (116 mg, 99%) 를 확보하였다.; m.p. 145 °C; ¹H NMR (500 MHz, CD₃OD) δ 8.02 (s, 1H), 3.69 (t, *J* = 12.2 Hz, 4H), 3.27 (t, *J* = 7.7 Hz, 2H), 3.07 (td, *J* = 4.3, 8.2 Hz, 2H), 2.10 (td, *J* = 4.3, 8.1 Hz, 2H), 1.85 (td, *J* = 7.5, 15.0 Hz, 2H), 1.47–1.42 (m, 2H), 1.37–1.33 (m, 2H), 1.30 (m, 12H), 0.89 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (125 MHz, CD₃OD) δ 178.6, 143.5, 132.4, 63.0

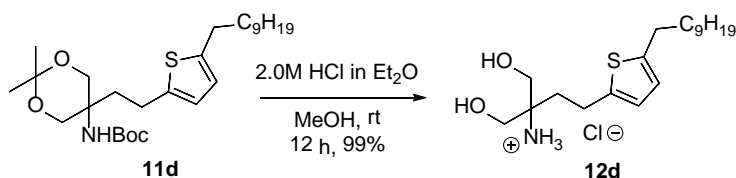
(2C), 62.7, 34.3, 33.8, 32.2, 31.4 (2C), 31.3, 31.2, 31.0, 30.8, 24.5, 22.8, 15.2; IR (neat) ν_{\max} = 3281, 2919, 2851, 2436, 1644, 1523, 1468, 1069, 753 (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{18}\text{H}_{35}\text{N}_2\text{O}_2\text{S}$ $[\text{M}-\text{Cl}]^+$ 343.2419, found 343.2407.

4-(4-Decylthiazol-2-yl)-1-hydroxy-2-(hydroxymethyl)butan-2-aminium chloride (12c)



12c 유도체는 general procedure H 와 같은 방법으로 진행하였으며, 최종적으로 하얀색 고체 **12c** (50 mg, 99%)를 확보하였다.; m.p. 160 °C; ^1H NMR (400 MHz, CD_3OD) δ 7.61 (s, 1H), 3.70 (t, J = 10.3 Hz, 4H), 3.43 (ddd, J = 3.4, 5.2, 8.0 Hz, 2H), 2.87 (t, J = 7.7 Hz, 2H), 2.25 (ddd, J = 3.4, 5.2, 8.0 Hz, 2H), 1.79–1.72 (m, 2H), 1.37–1.25 (m, 14H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 177.1, 152.1, 119.0, 63.0 (2C), 62.6, 33.8, 32.8, 31.5, 31.4, 31.2, 31.1, 30.8, 30.4, 29.9, 26.7, 24.5, 15.2; IR (neat) ν_{\max} = 3240, 2919, 2852, 2479, 1590, 1471, 1070, 1049, 716 (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{18}\text{H}_{35}\text{N}_2\text{O}_2\text{S}$ $[\text{M}-\text{Cl}]^+$ 343.2419, found 343.2426.

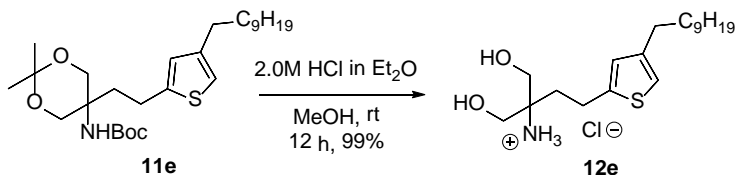
4-(5-Decylthiophen-2-yl)-1-hydroxy-2-(hydroxymethyl)butan-2-aminium chloride (12d)



12d 유도체는 general procedure H 와 같은 방법으로 진행하였으며, 최종적으로 검은색 고체 **12d** (165 mg, 99%)를 확보하였다.; m.p. 73–75

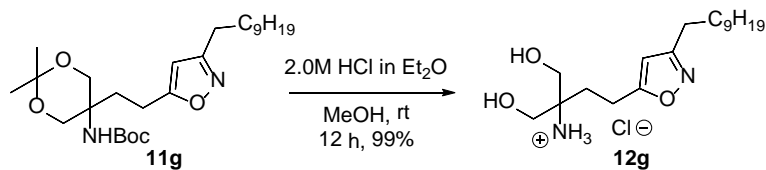
°C; ¹H NMR (400 MHz, CD₃OD) δ 6.63 (d, *J* = 3.4 Hz, 1H), 6.56 (d, *J* = 3.3 Hz, 1H), 3.65 (td, *J* = 5.2, 8.3 Hz, 4H), 2.84 (td, *J* = 4.4, 8.4 Hz, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 2.02 (td, *J* = 4.4, 8.4 Hz, 2H), 1.63–1.57 (m, 2H), 1.31–1.28 (m, 14H), 0.89 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CD₃OD) δ 145.7, 143.0, 125.8, 125.6, 63.3 (2C), 62.7, 35.6, 33.8, 33.7, 31.8, 31.5 (2C), 31.3, 31.2, 30.9, 25.4, 24.5, 15.2; IR (neat) ν_{max} = 3303, 2922, 2852, 1531, 1469, 1058, 808 (cm⁻¹); HRMS (FAB) calcd. for C₁₉H₃₆NO₂S [M–Cl]⁺ 342.2467, found 342.2468.

4-(4-Decylthiophen-2-yl)-1-hydroxy-2-(hydroxymethyl)butan-2-aminium chloride (12e)



12e 유도체는 general procedure H 와 같은 방법으로 진행하였으며, 최종적으로 하얀색 고체 12e (962 mg, 99%) 를 확보하였다.; m.p. 130 °C; ¹H NMR (400 MHz, CD₃OD) δ 8.35 (s, 1H), 4.53 (t, *J* = 7.2 Hz, 2H), 3.69 (s, 4H), 2.97 (td, *J* = 4.3, 8.0 Hz, 2H), 2.11 (td, *J* = 4.3, 8.0 Hz, 2H), 2.00–1.95 (m, 2H), 1.35–1.28 (m, 14H), 0.89 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CD₃OD) δ 146.5, 127.3, 63.0 (2C), 62.6, 54.3, 33.8, 32.0, 31.5, 31.4, 31.3, 31.2, 30.8, 28.1, 24.5, 19.9, 15.2; IR (neat) ν_{max} = 3180, 2918, 2851, 2421, 1599, 1454, 1080, 1063, 958, 715 (cm⁻¹); HRMS (FAB) calcd. for C₁₇H₃₅N₄O₂ [M–Cl]⁺ 327.2760, found 327.2762.

4-(3-Decylisoxazol-5-yl)-1-hydroxy-2-(hydroxymethyl)butan-2-aminium chloride (12g)



12g 유도체는 general procedure H 와 같은 방법으로 진행하였으며, 최종적으로 하얀색 고체 **12g** (319 mg, 99%) 를 확보하였다.; m.p. 75 °C; $^1\text{H NMR}$ (800 MHz, CD_3OD) δ 6.11 (s, 1H), 3.65 (dd, $J = 11.6, 15.4$ Hz, 4H), 2.86 (td, $J = 4.3, 8.2$ Hz, 2H), 2.61 (t, $J = 7.6$ Hz, 2H), 2.08–2.06 (m, 2H), 1.64 (td, $J = 7.4, 14.7$ Hz, 2H), 1.33–1.31 (m, 4H), 1.30–1.26 (m, 10H), 0.89 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ (200 MHz, CD_3OD) δ 174.1, 166.6, 102.8, 63.1, 62.5, 33.9, 31.5, 31.4, 31.23, 31.18, 31.05, 30.99, 30.1, 27.6, 24.5, 22.3, 15.2; IR (neat) $\nu_{\text{max}} = 2919, 2853, 2407, 1610, 1459, 1060, 995, 754, 723$ (cm^{-1}); HRMS (FAB) calcd. for $\text{C}_{17}\text{H}_{35}\text{N}_2\text{O}_3$ $[\text{M}-\text{Cl}]^+$ 327.2648, found 327.2657.

V. References

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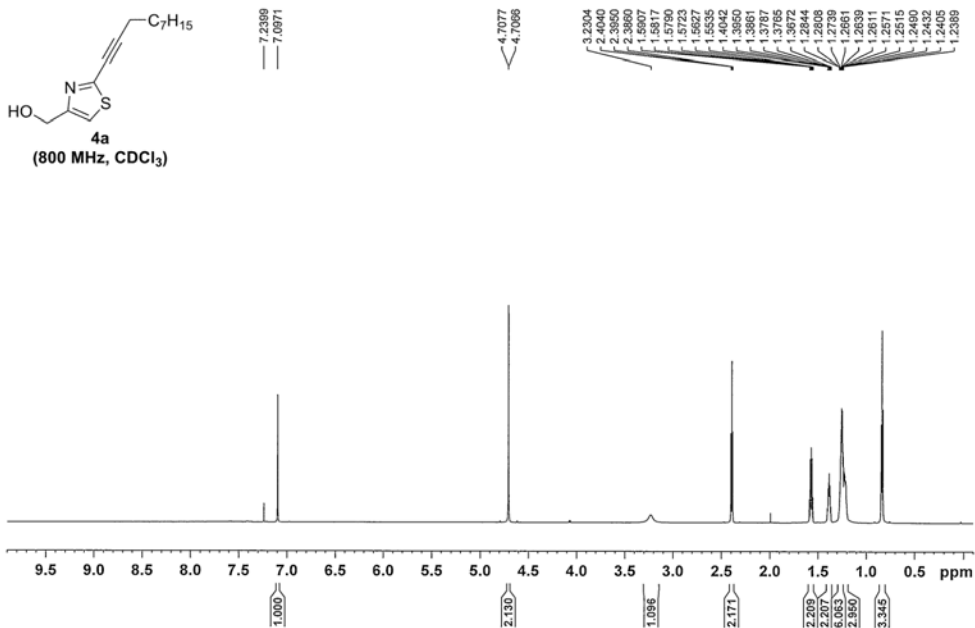
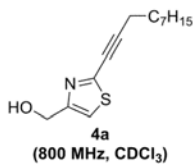
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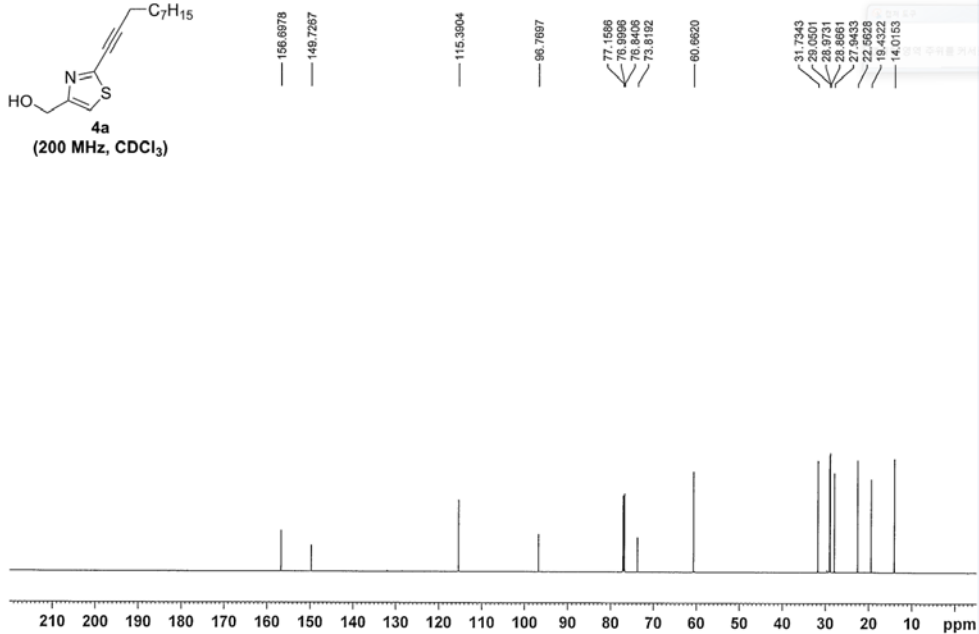
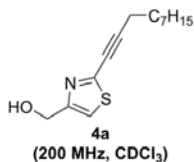
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VI. Spectrum Data

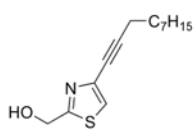
BJH-III-139 (800MHz)



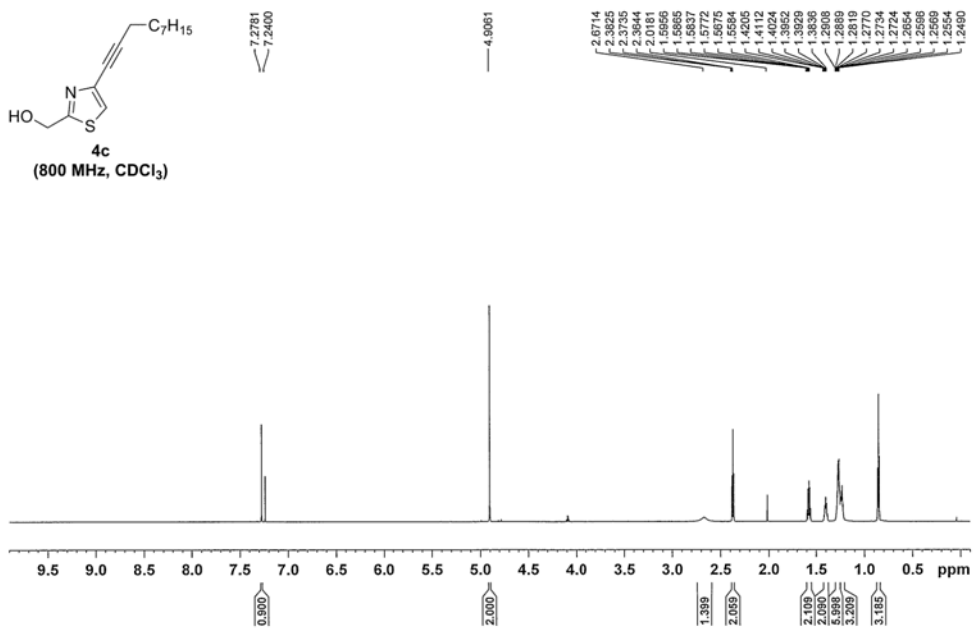
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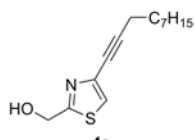
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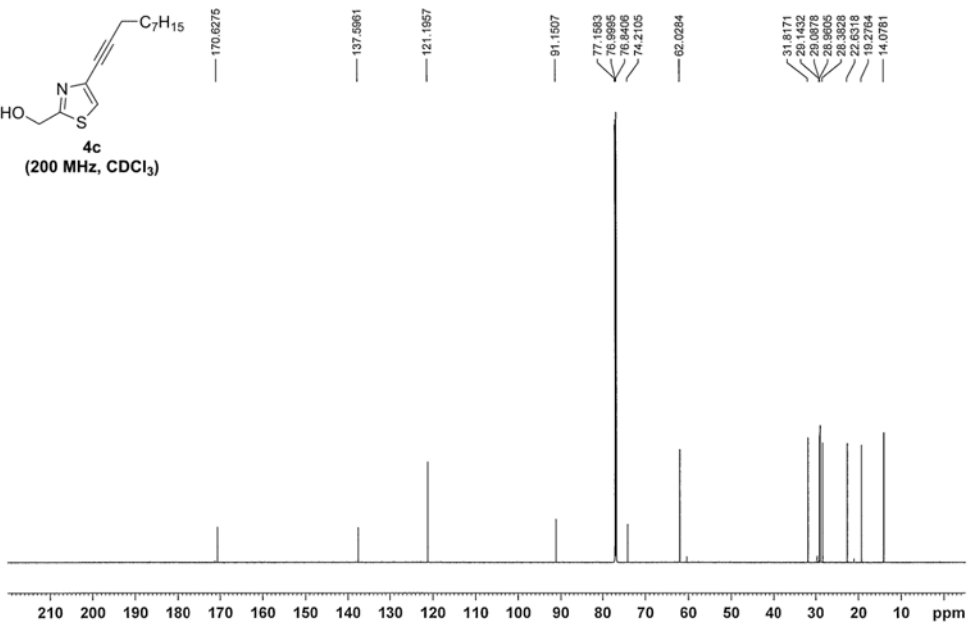
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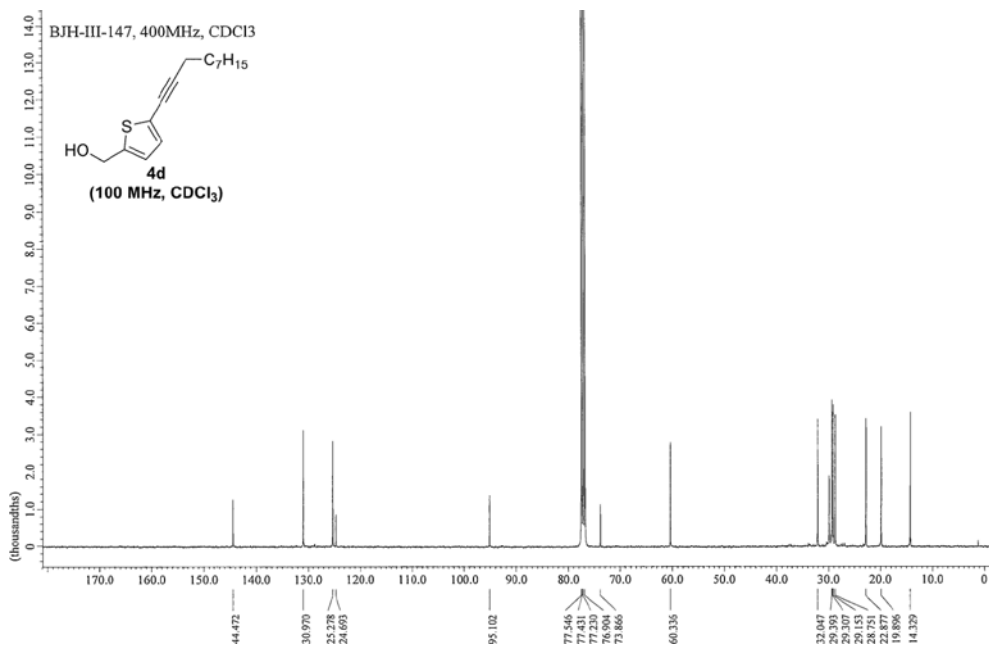
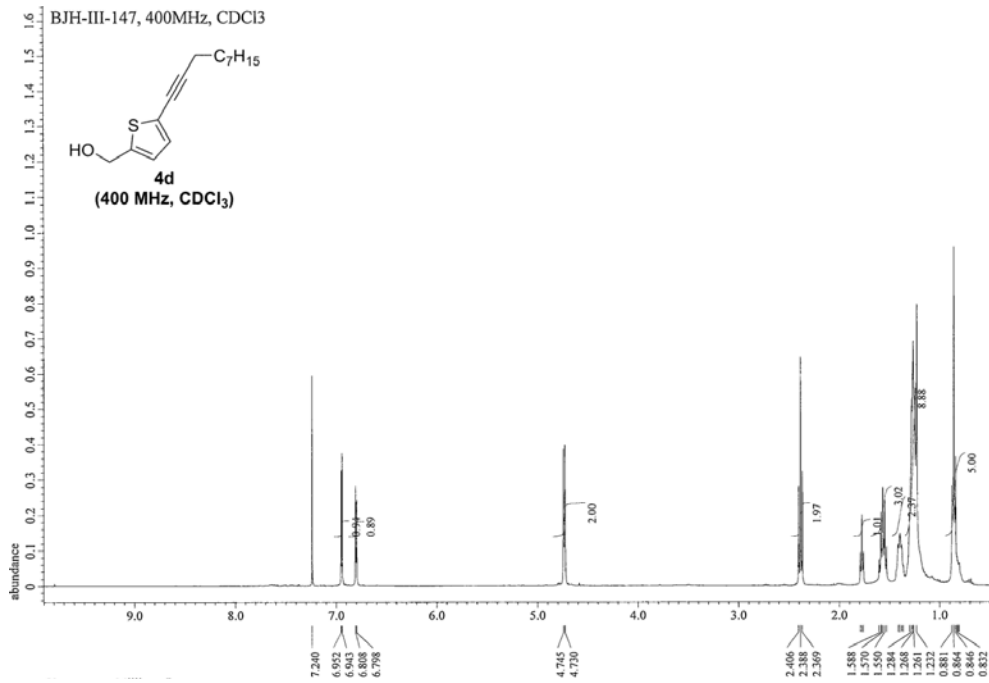


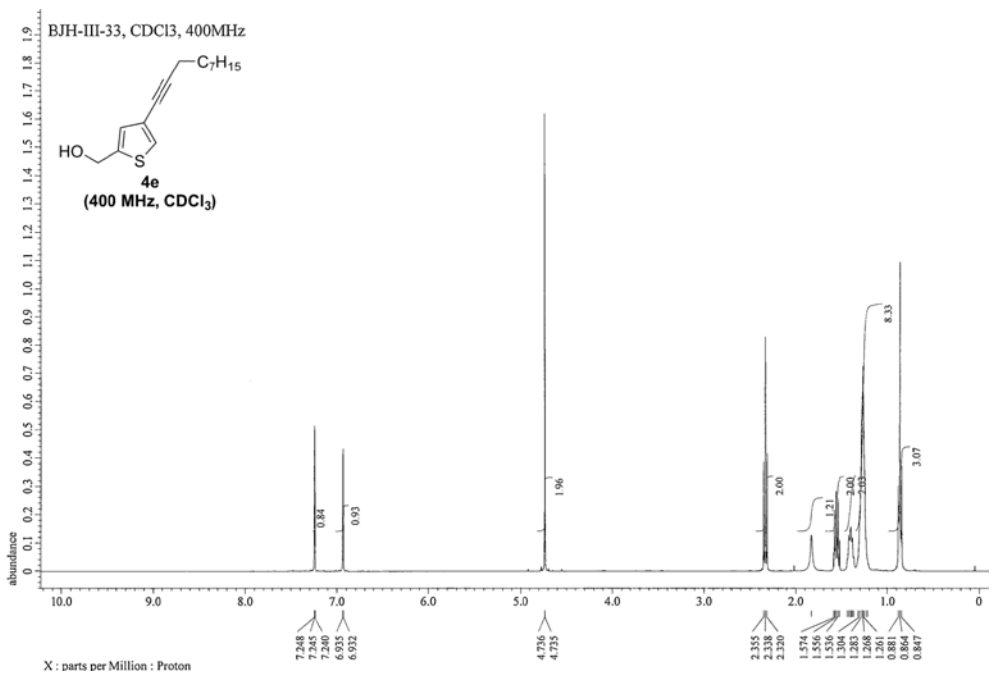
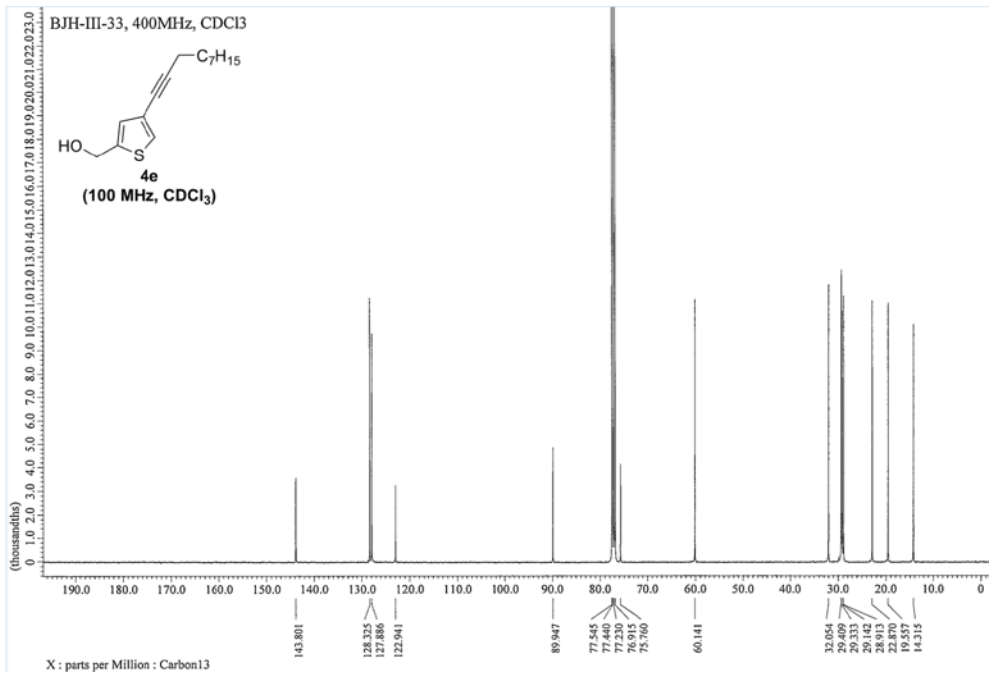
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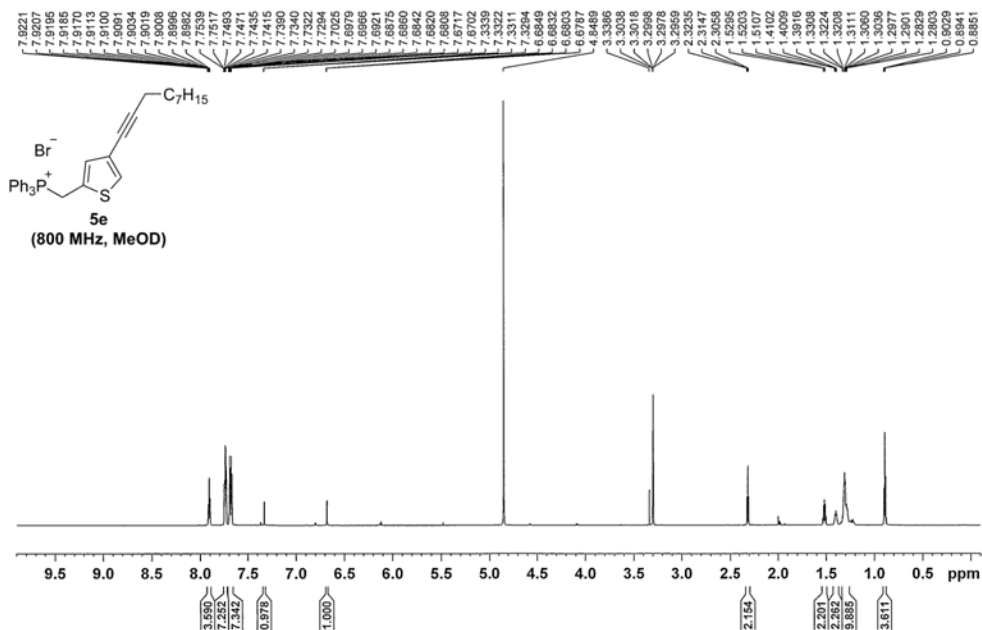
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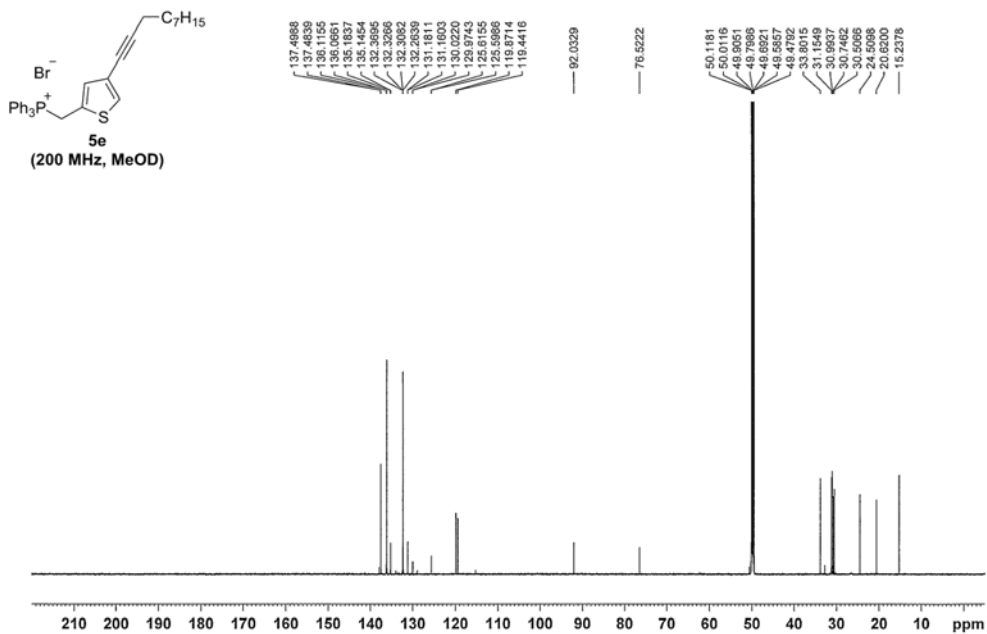


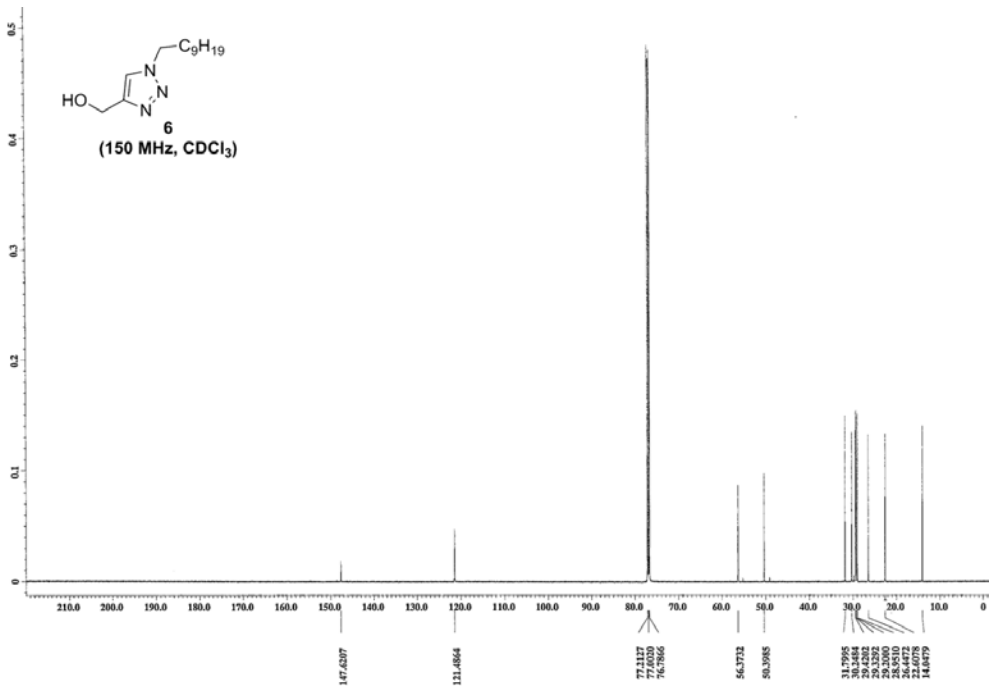
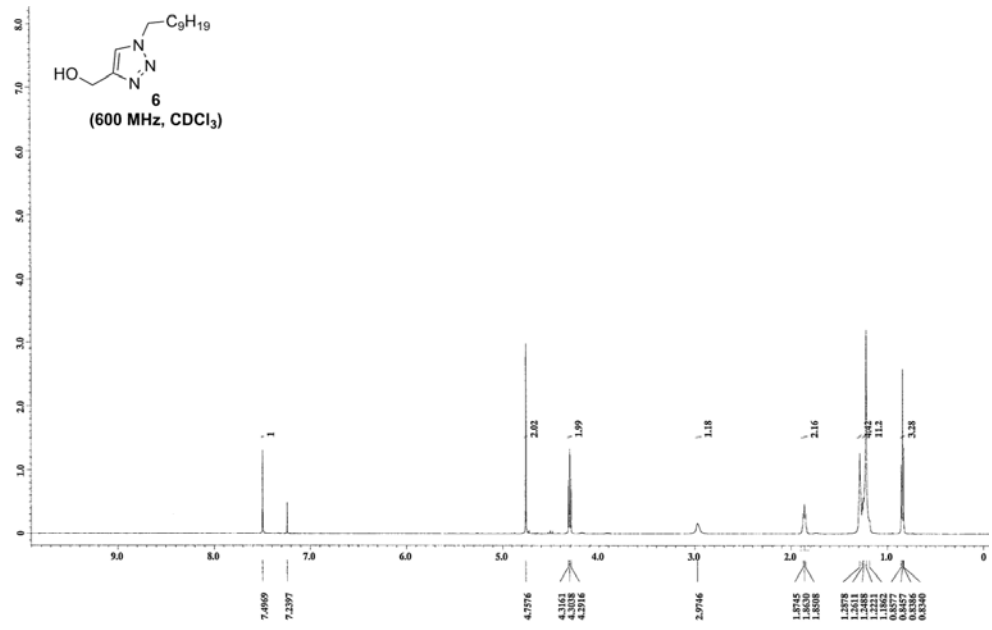


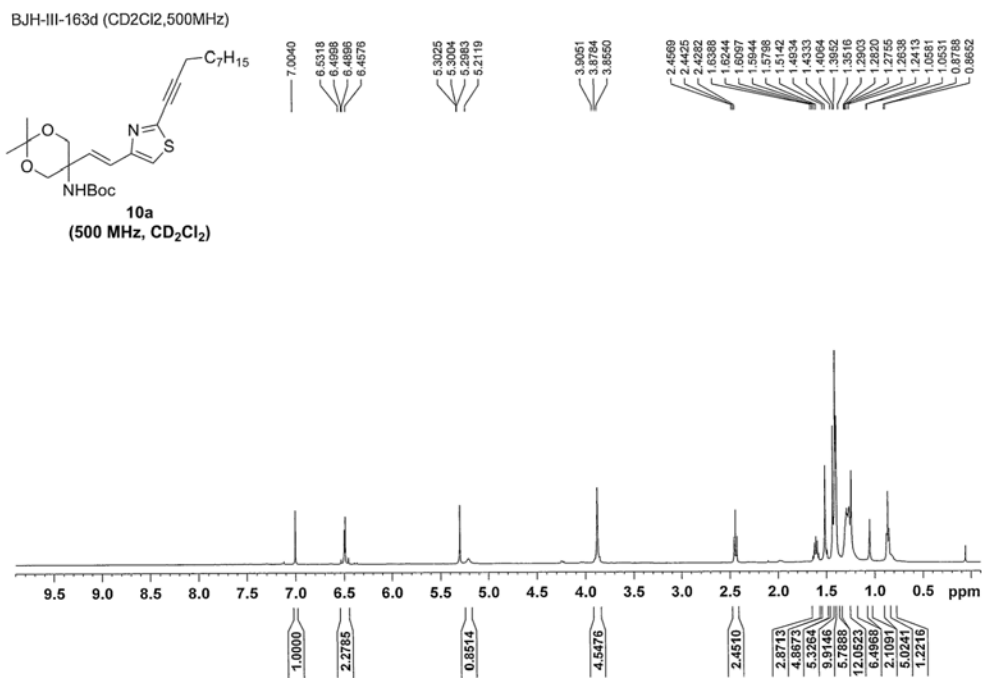
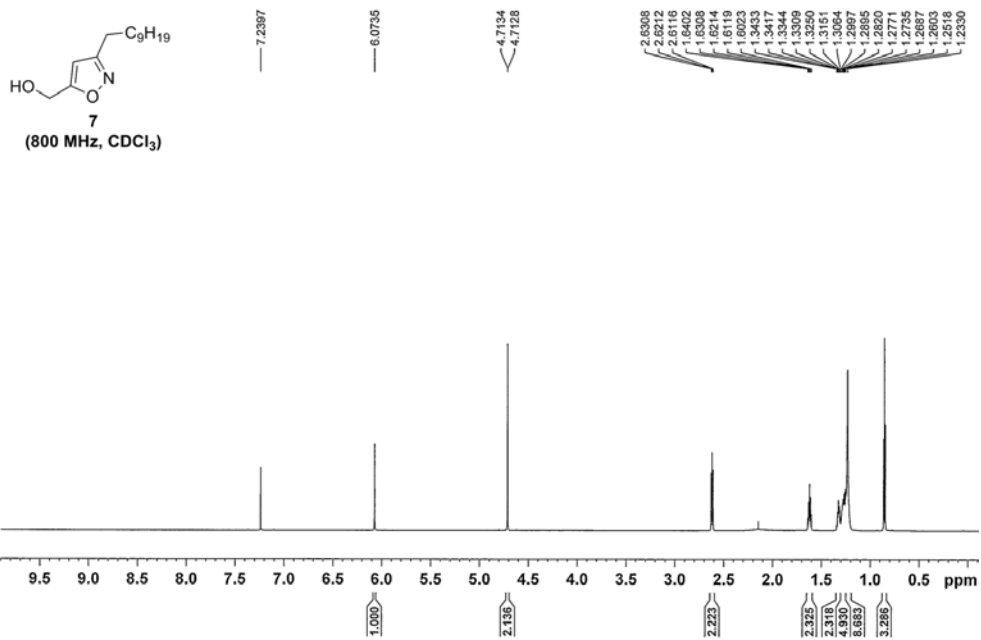
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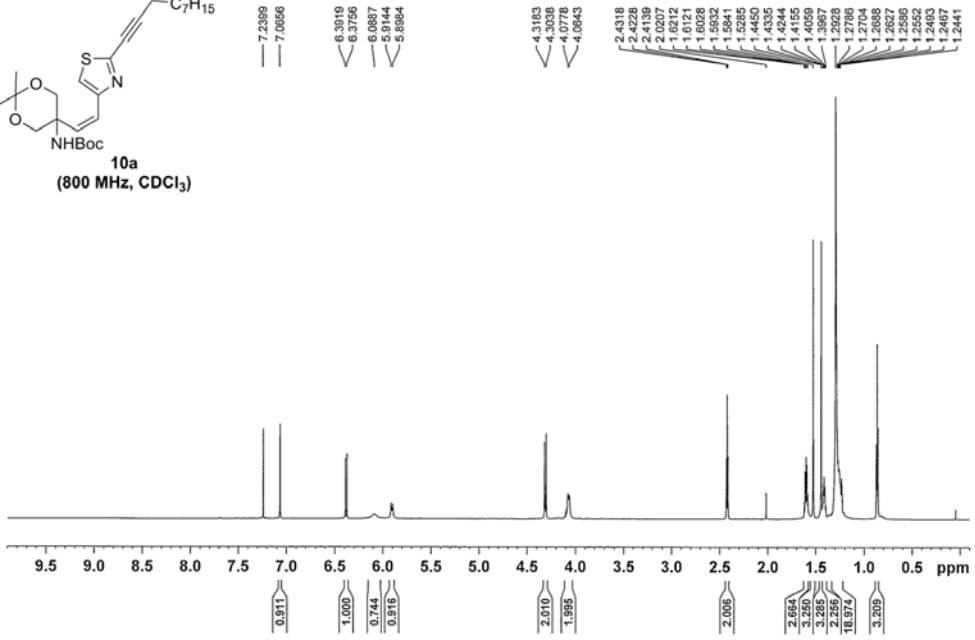
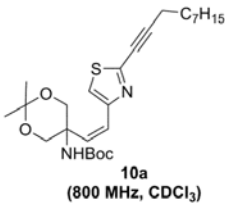
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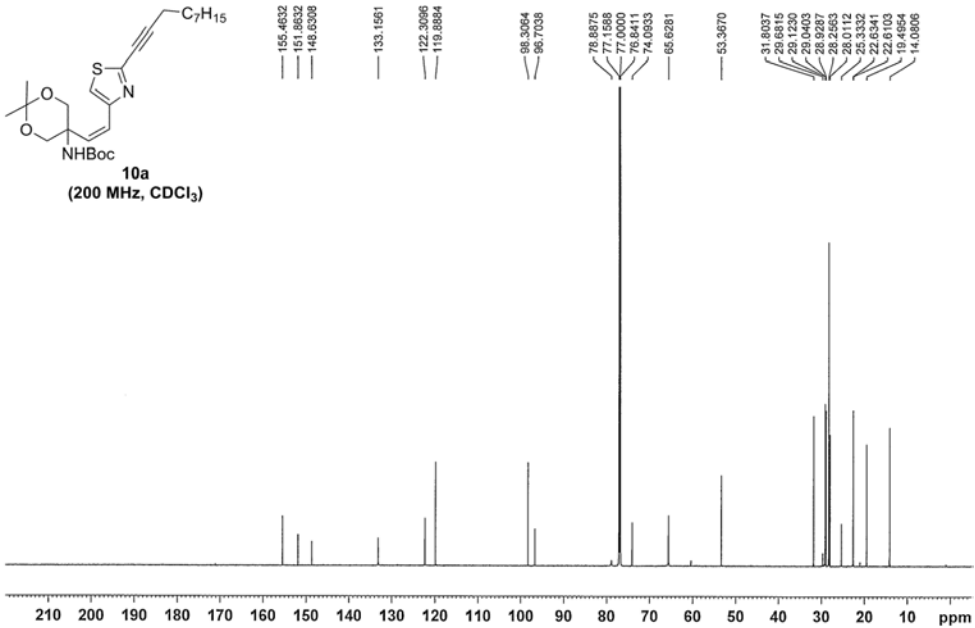
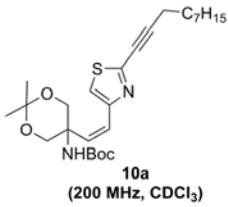


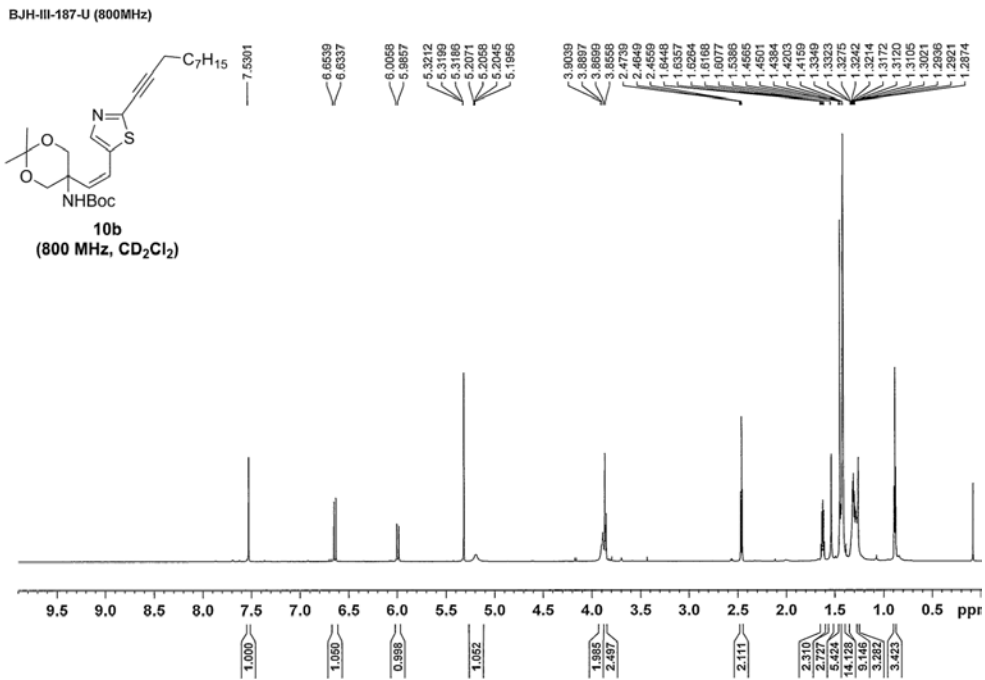
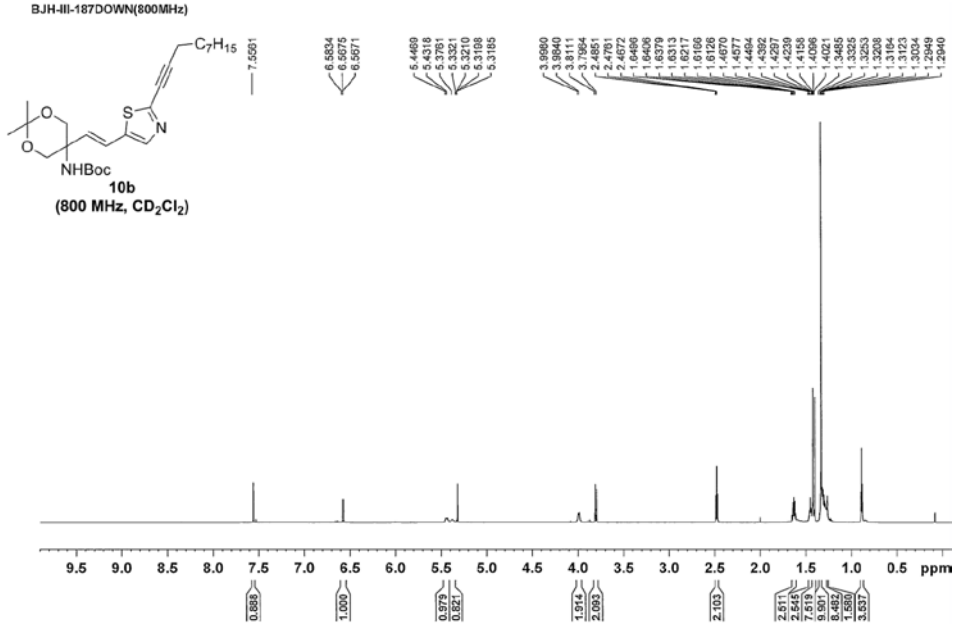


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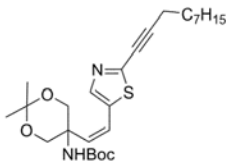


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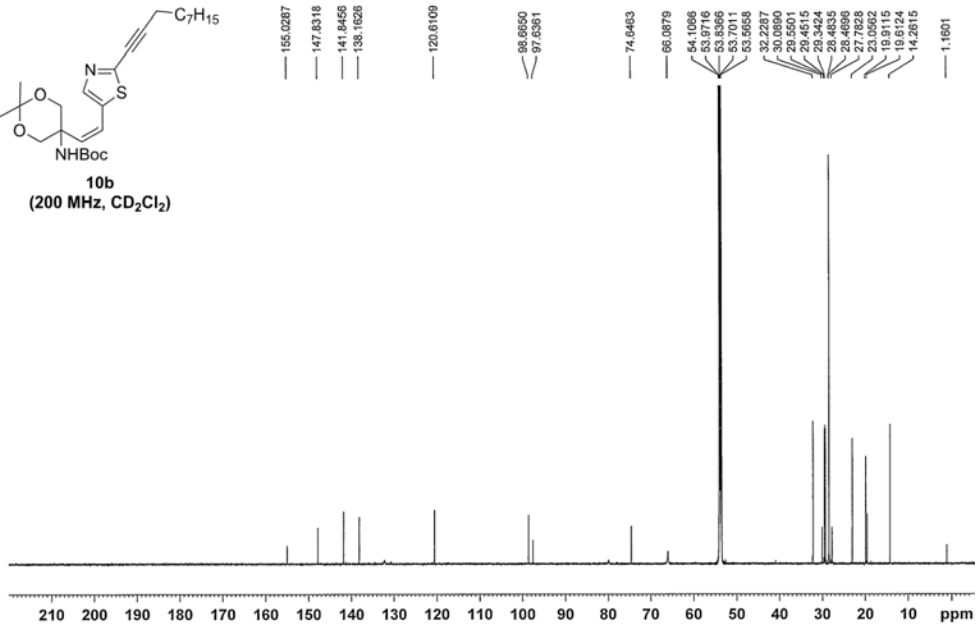




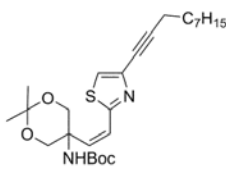
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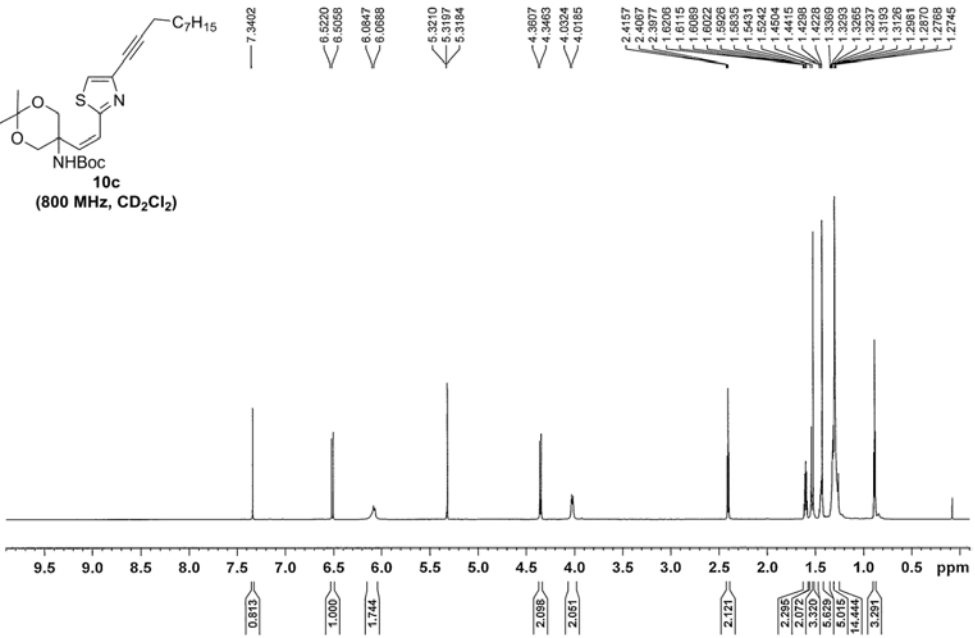
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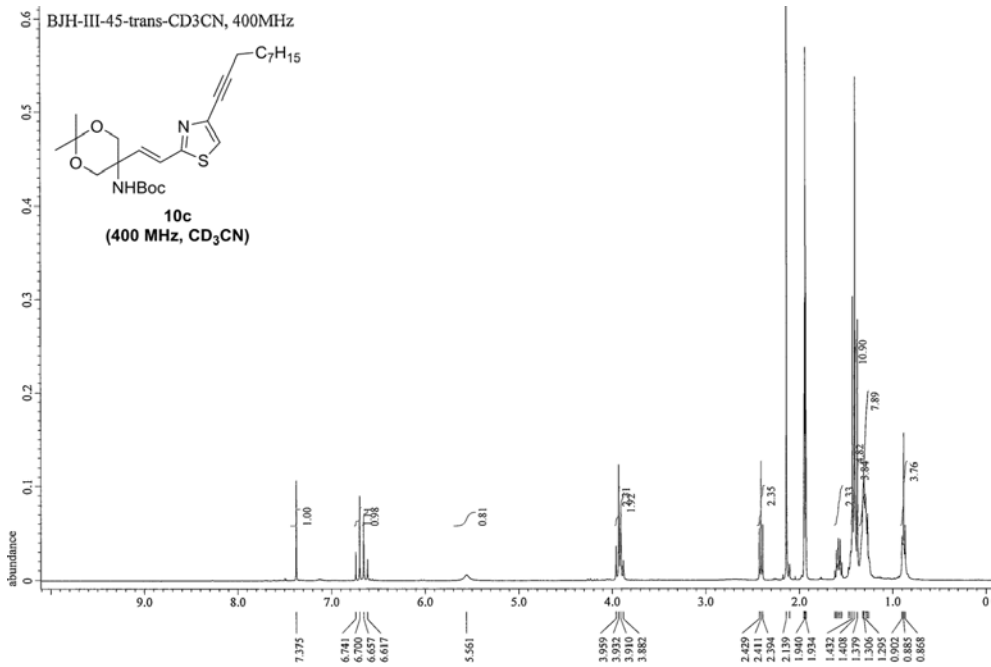
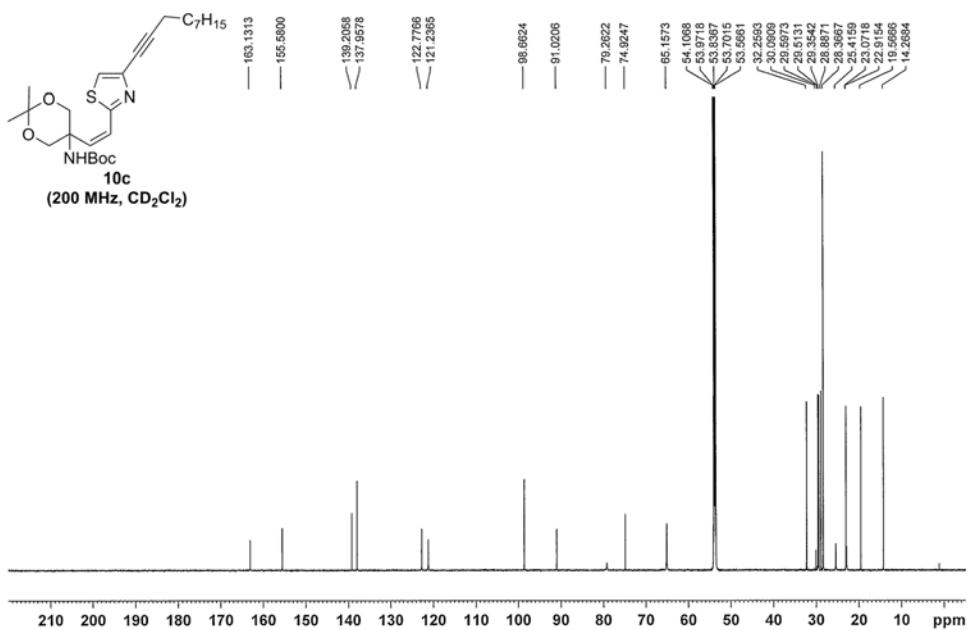
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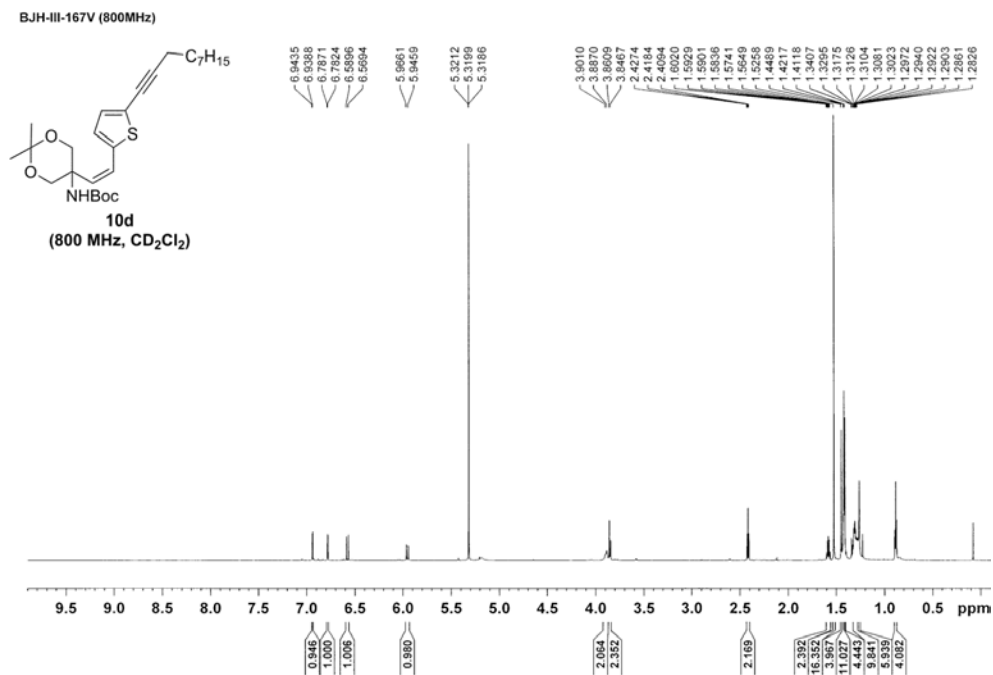
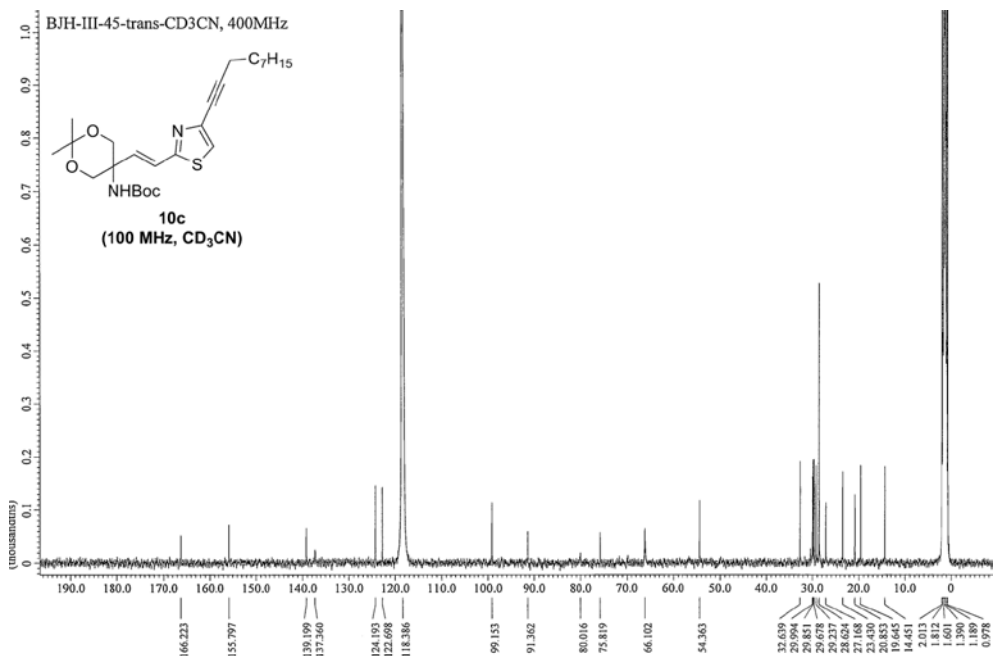


10c
(800 MHz, CD₂Cl₂)

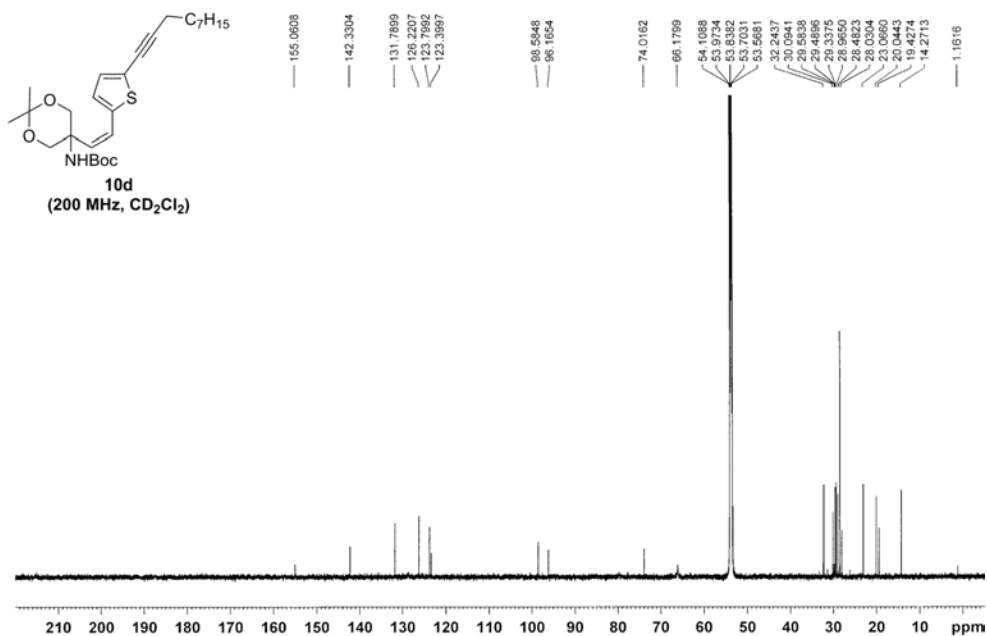


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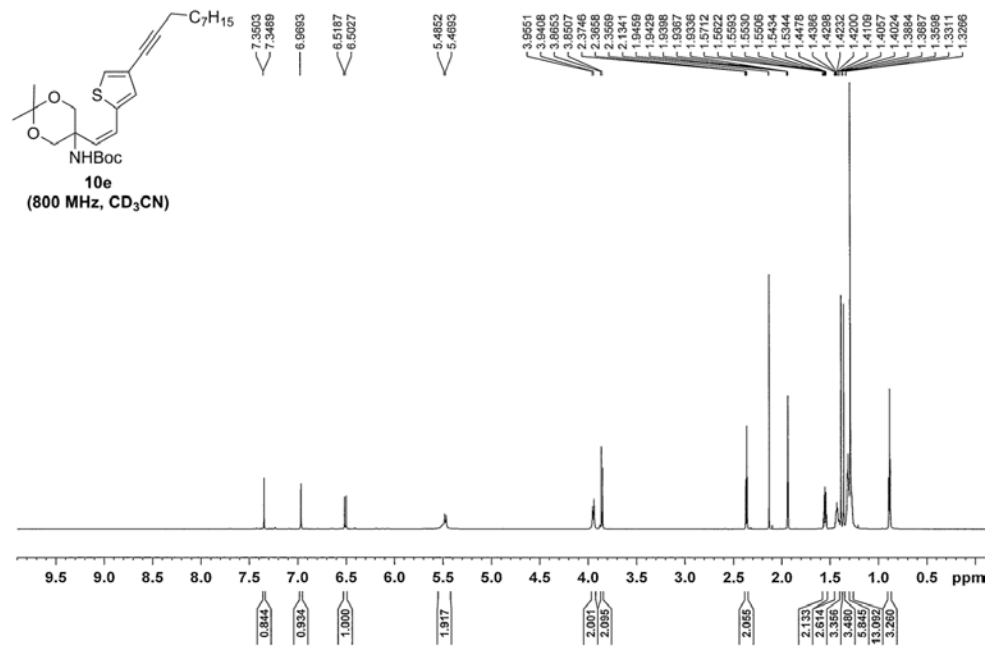




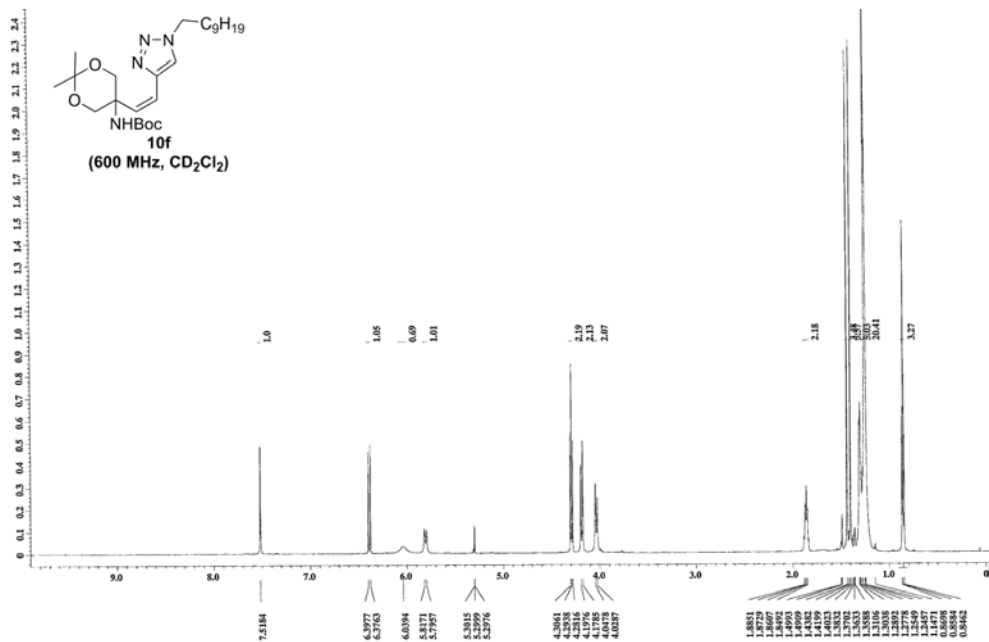
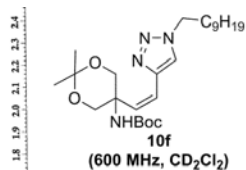
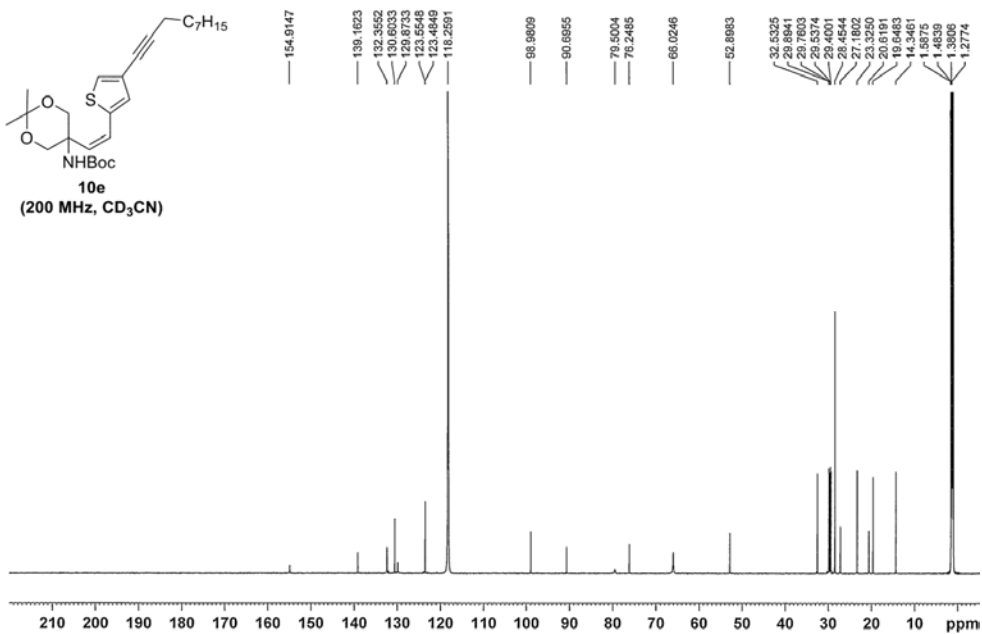
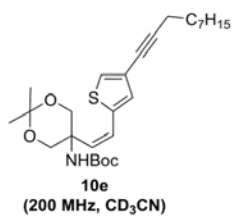
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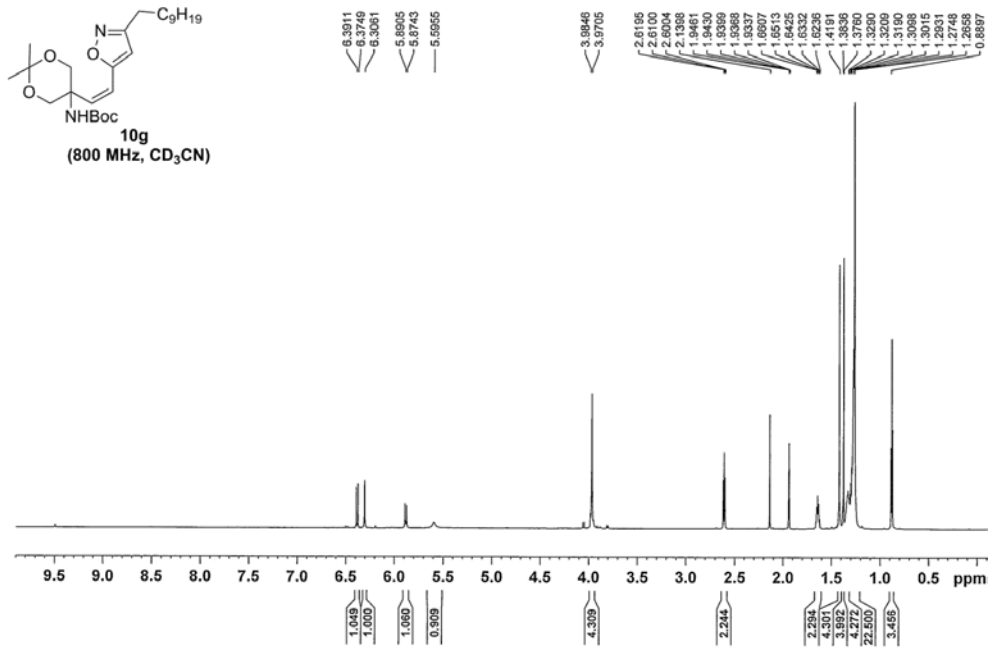
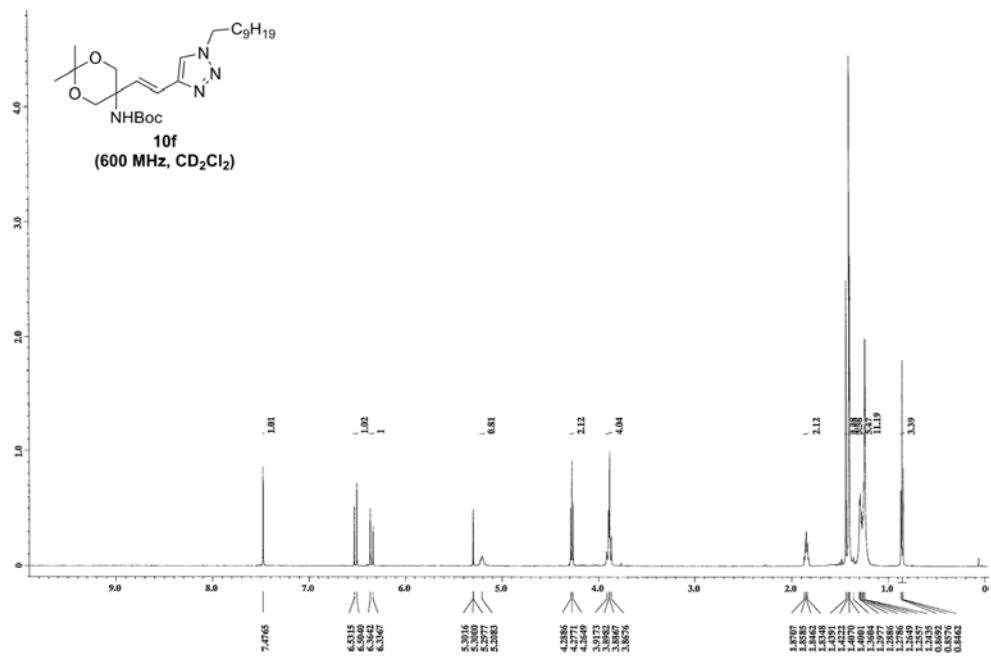


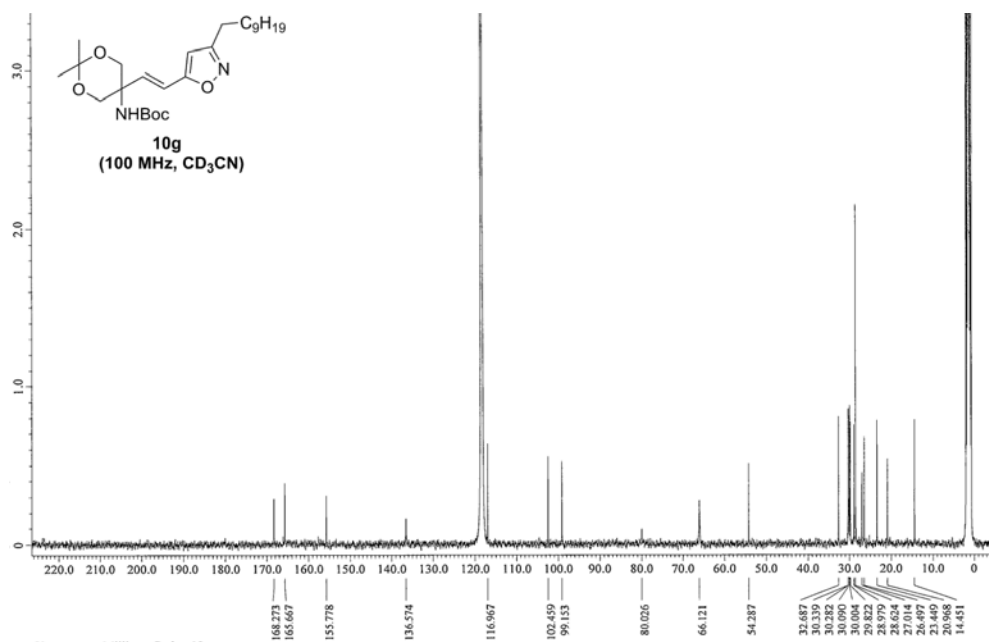
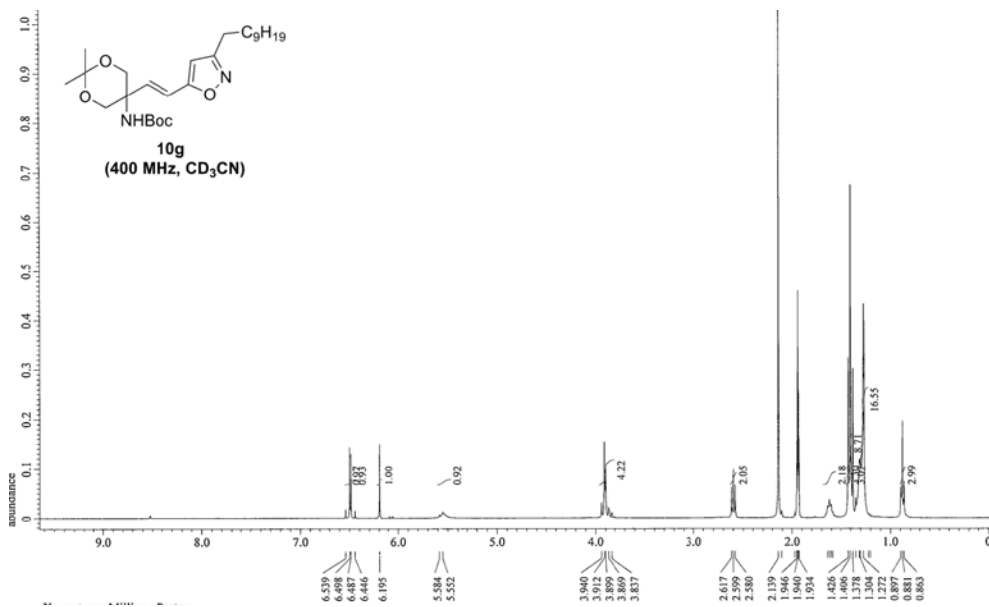
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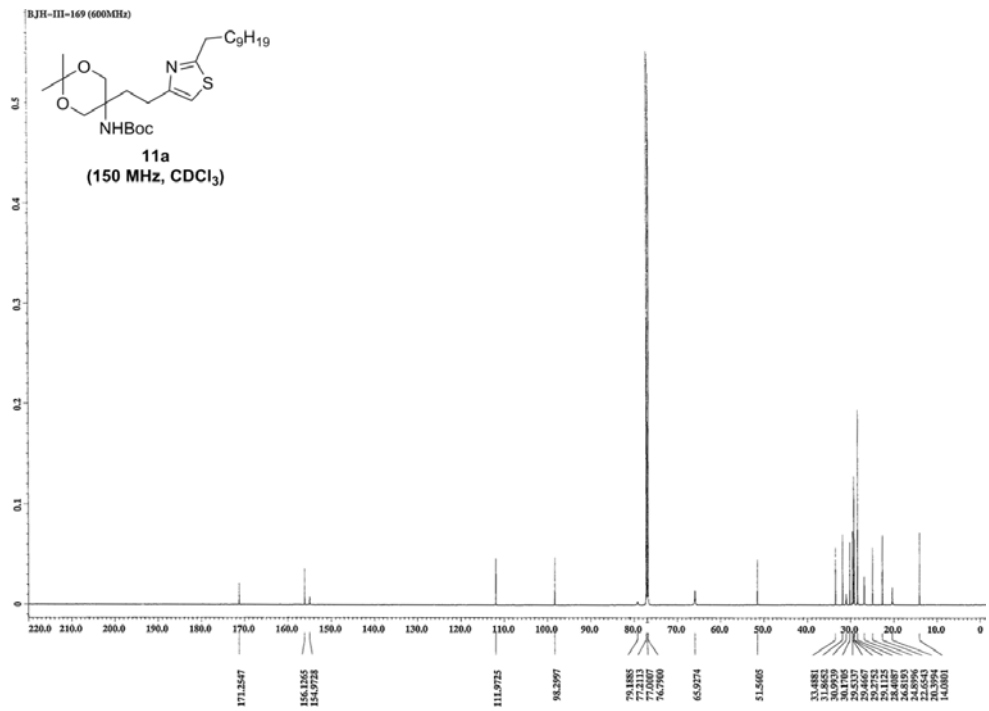
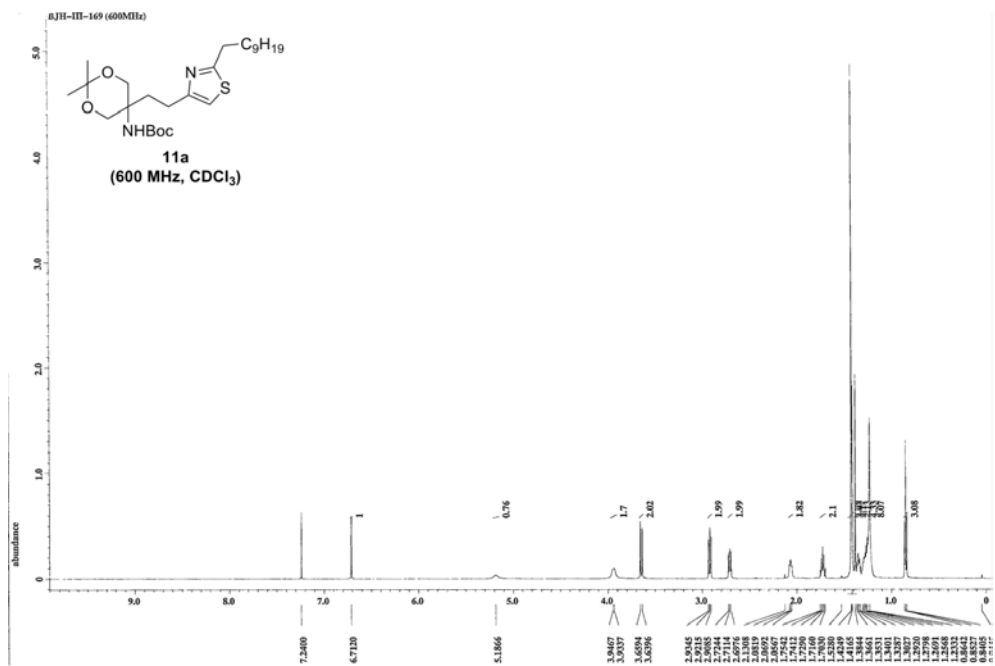


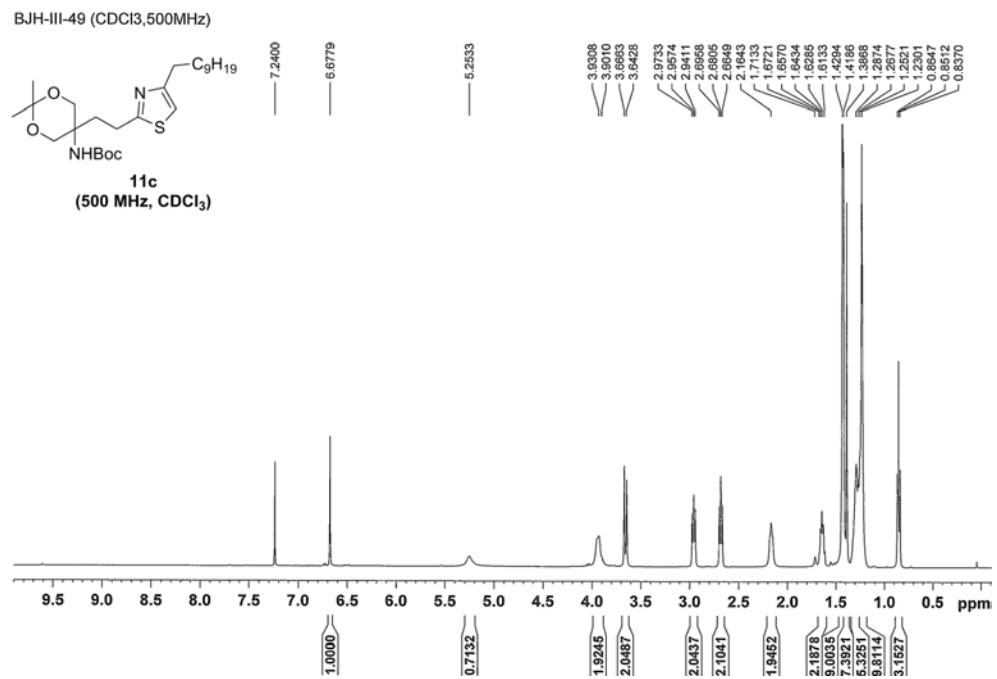
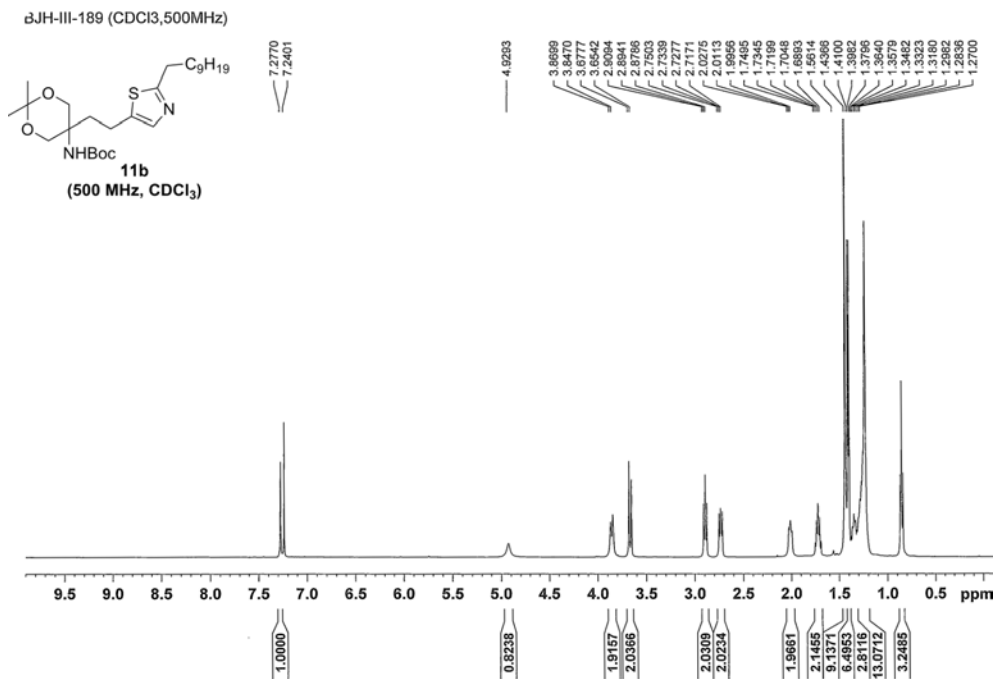
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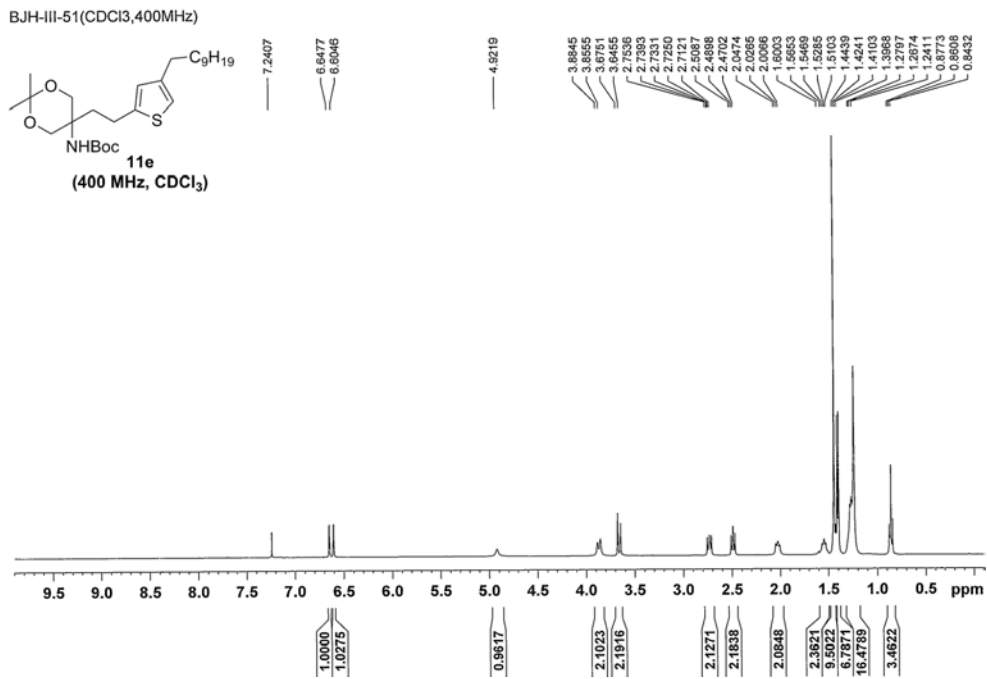
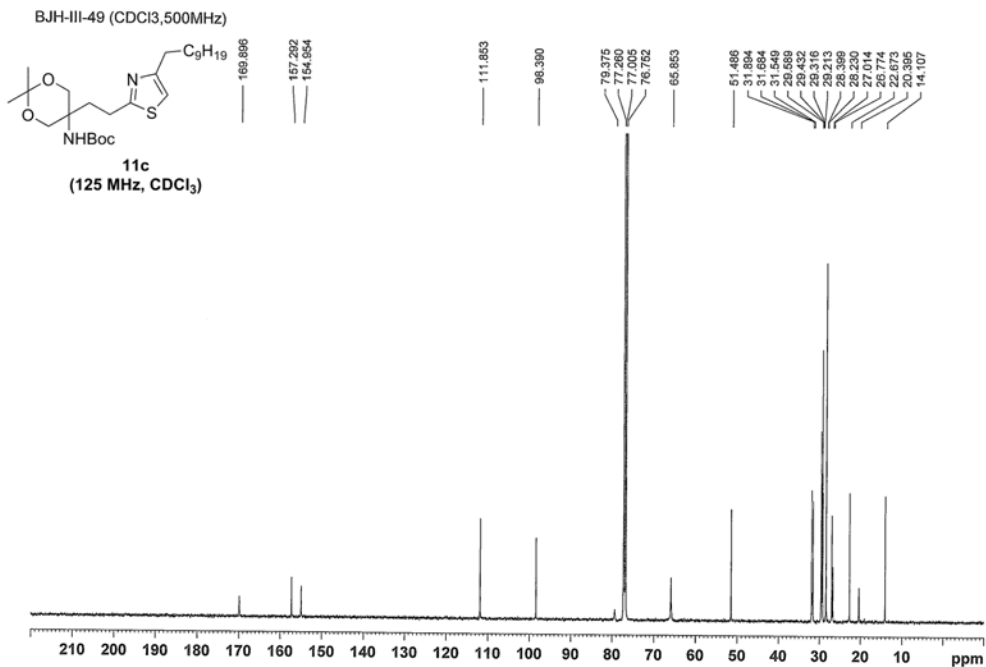




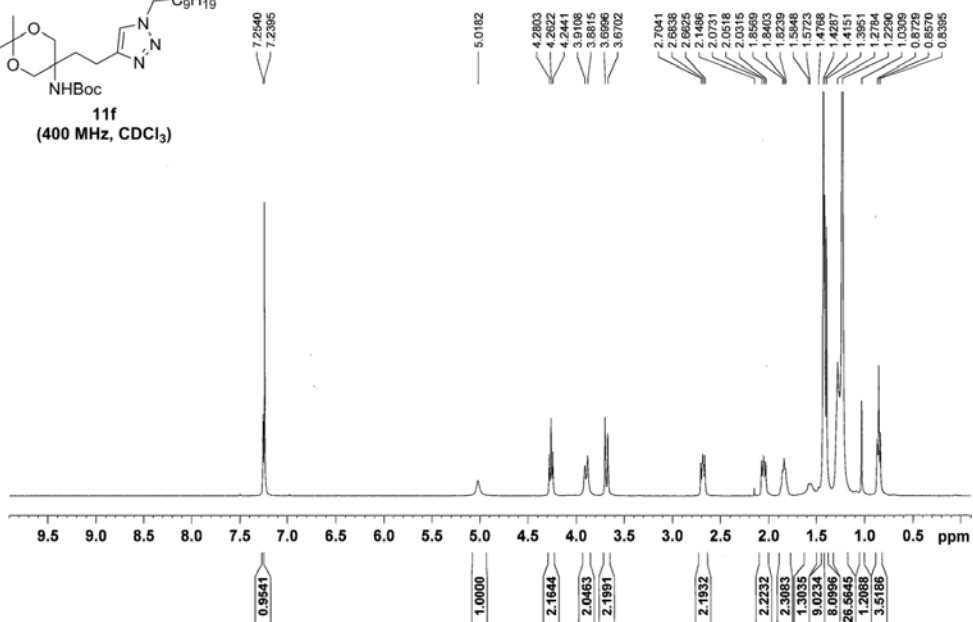
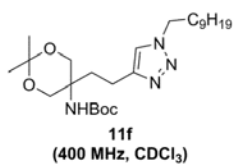




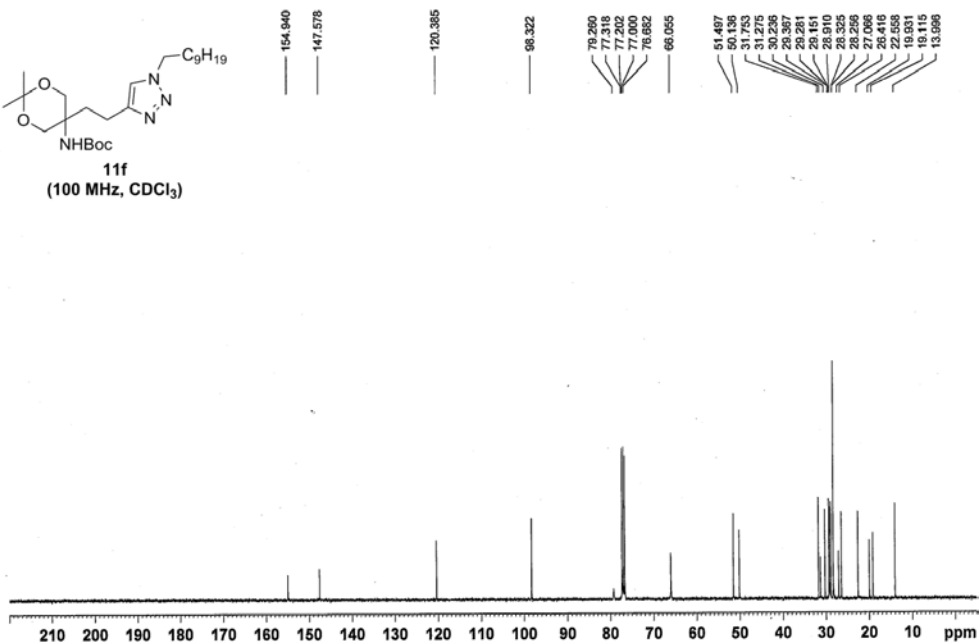
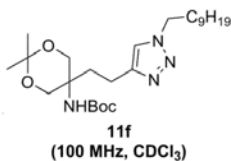




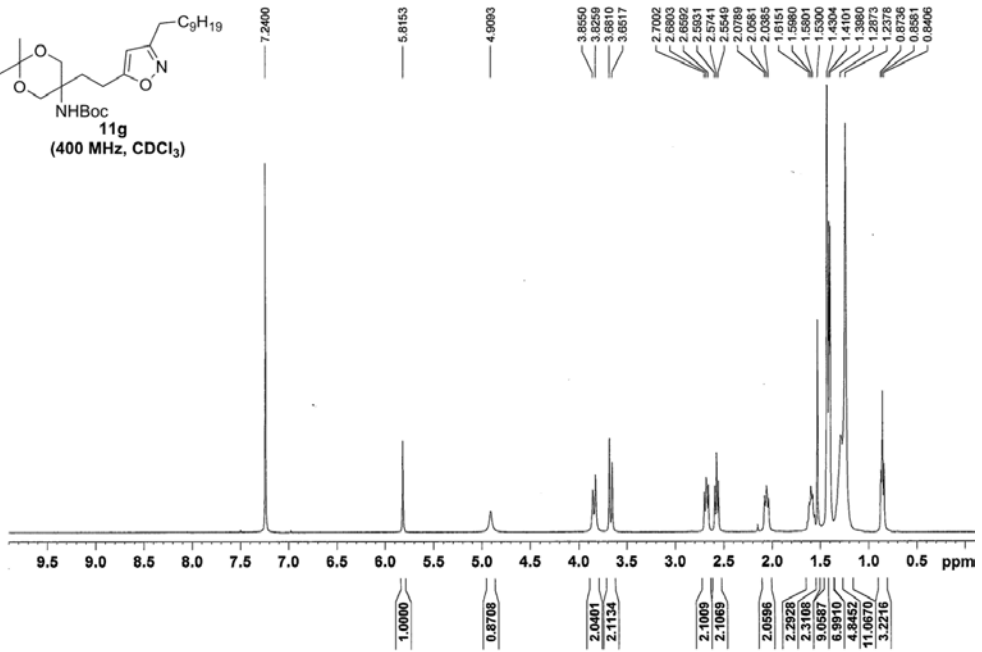
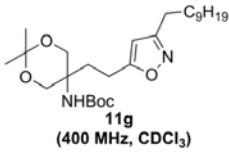
CH-II-59 /400MHz



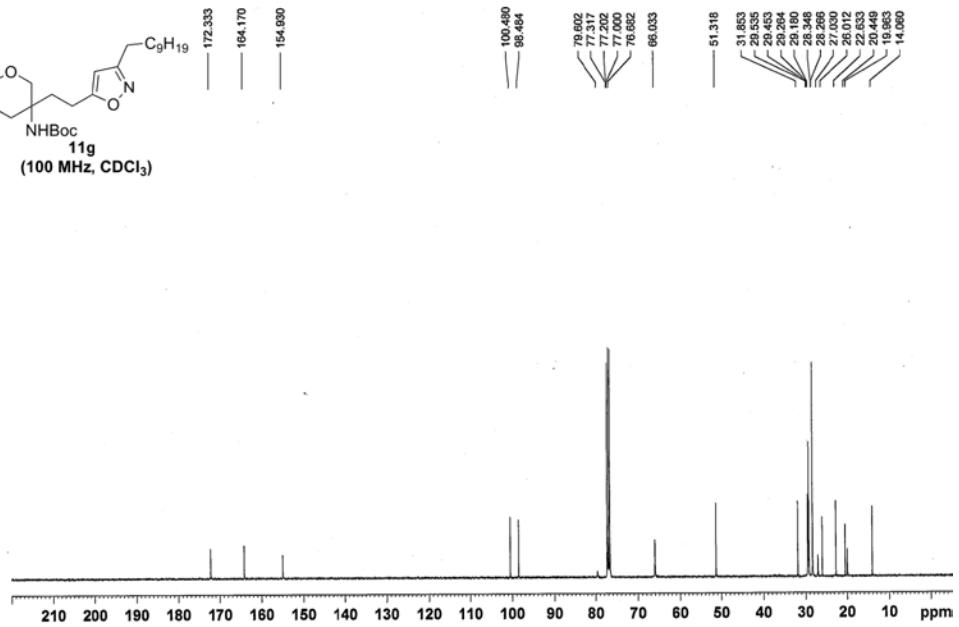
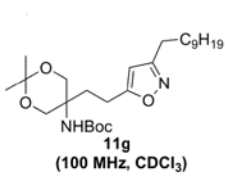
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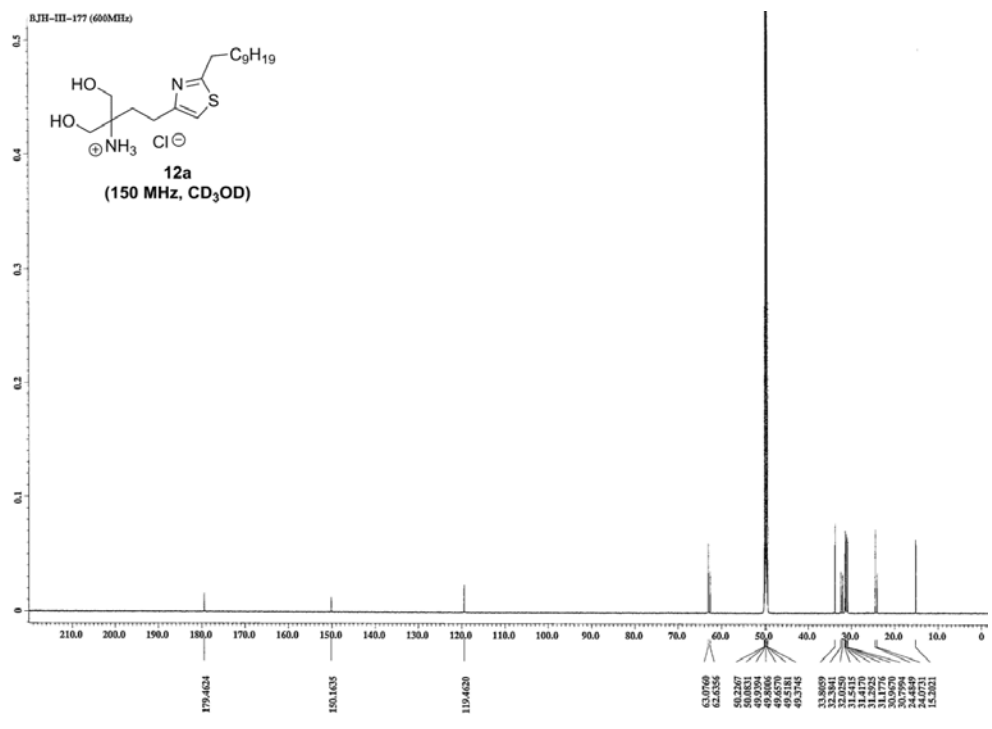
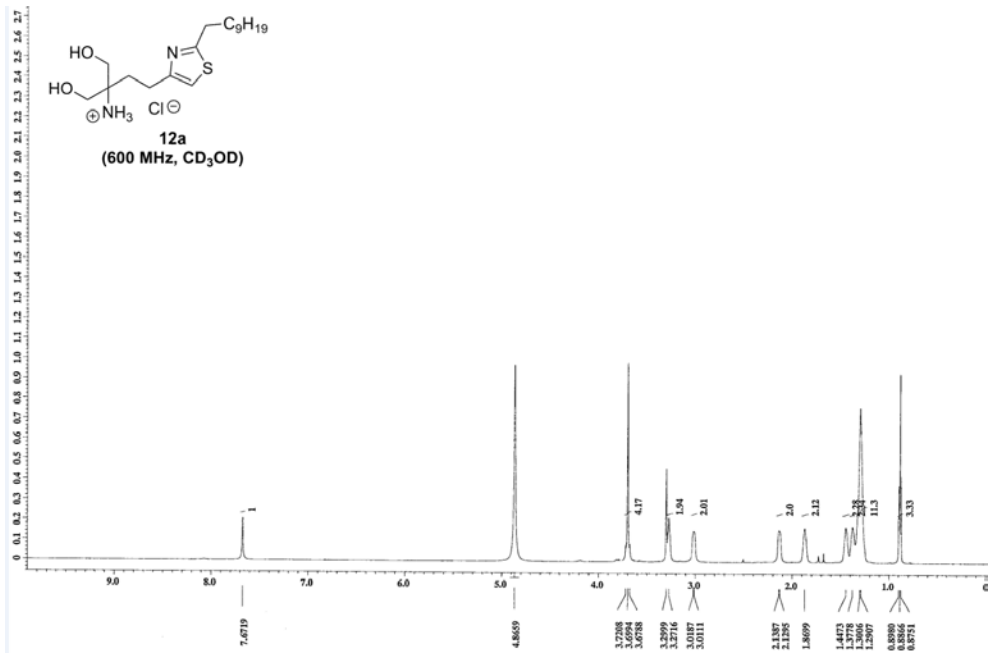


CM2-III-63 (CDCl₃, 400MHz)

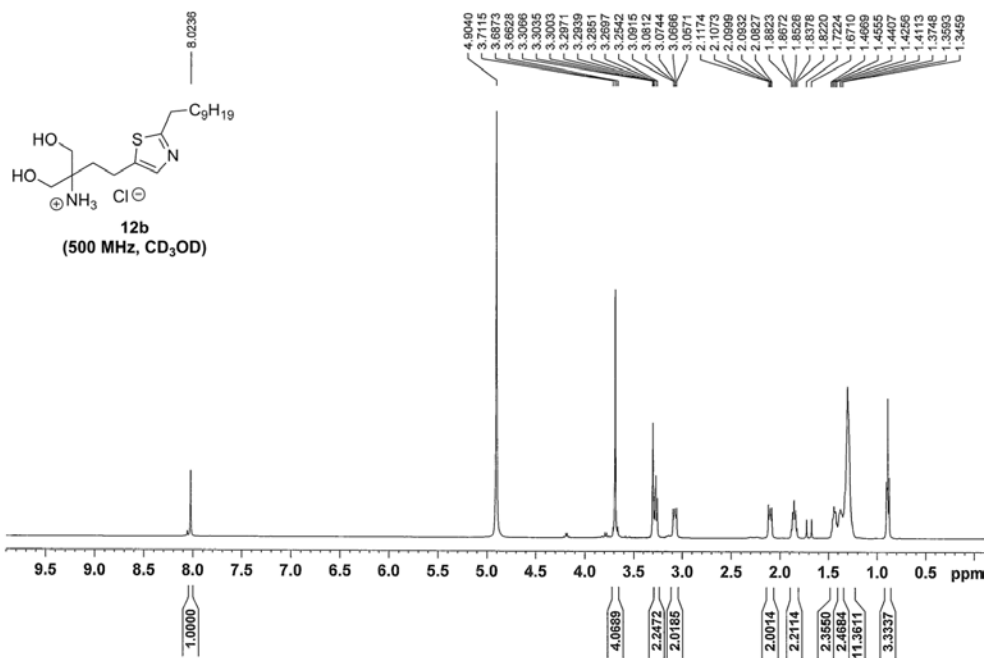


CM2-II-169 (400MHz)

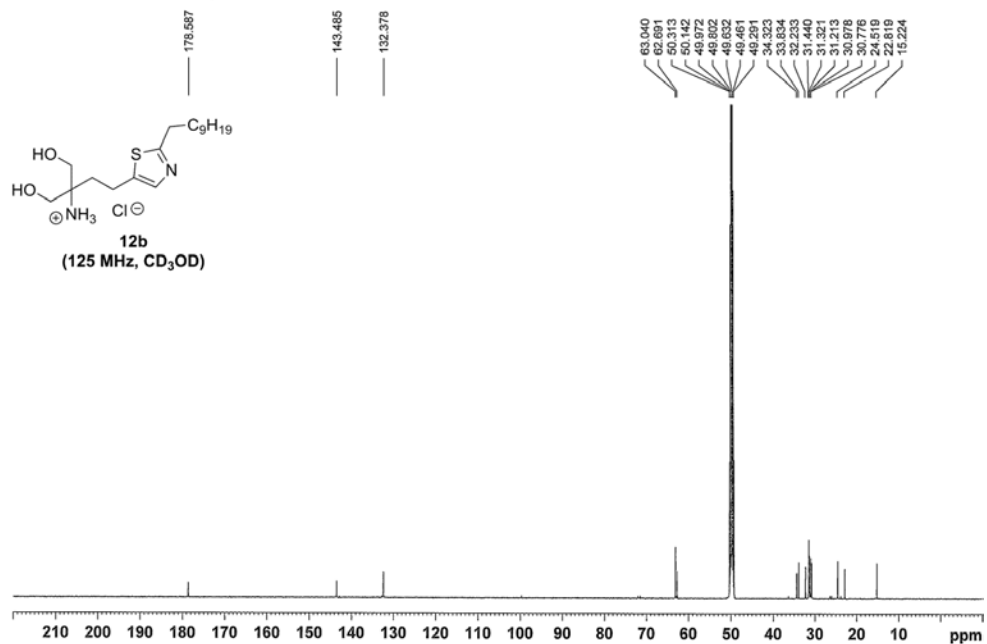


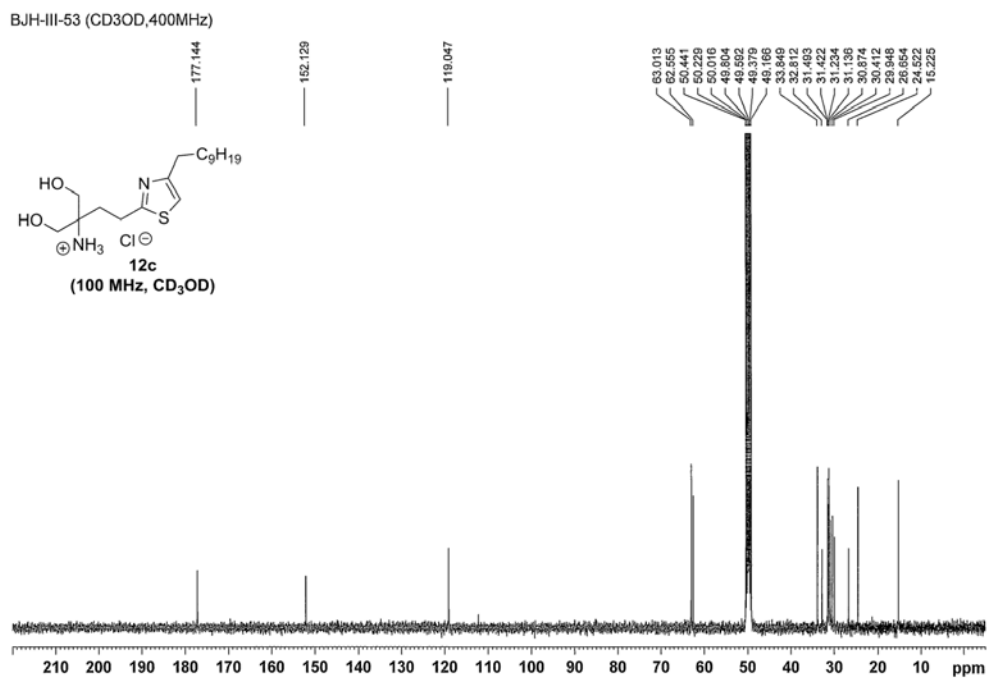
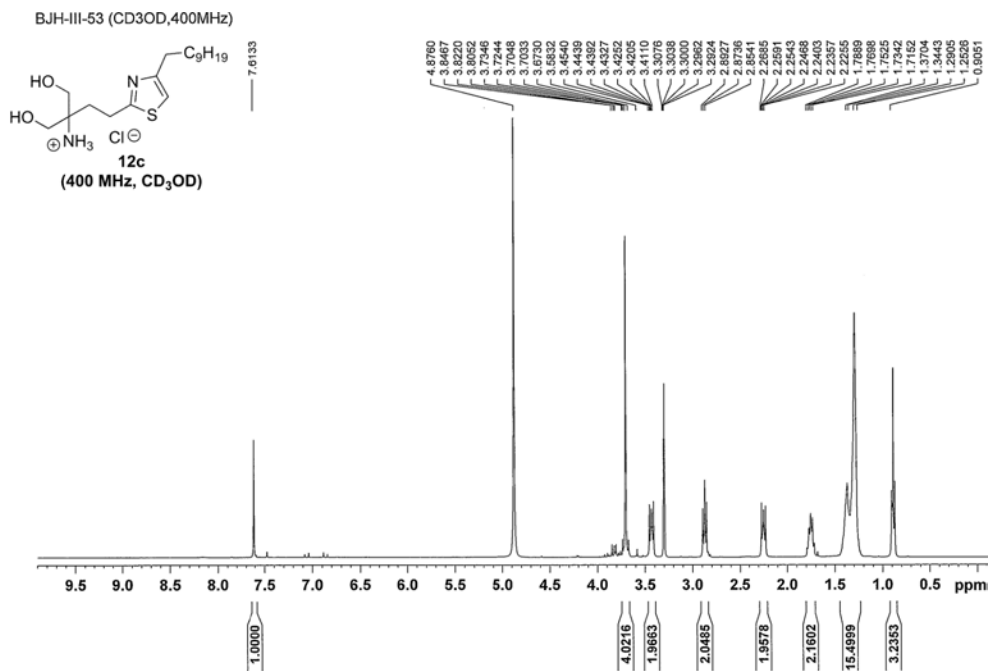


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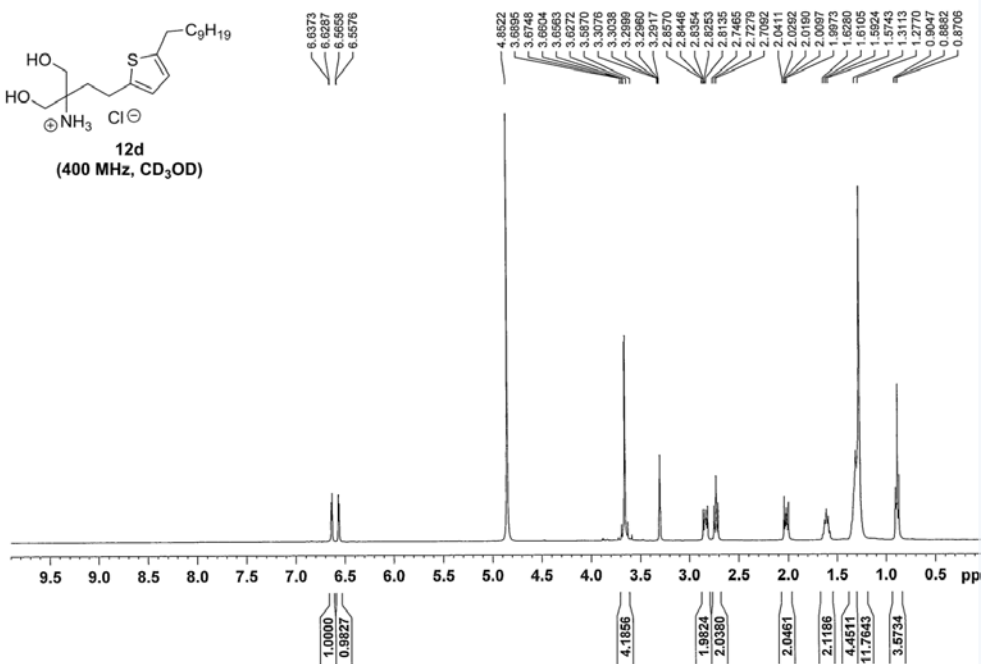
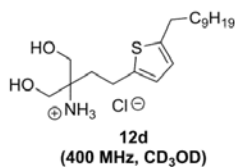


BJH-III-191 (MeOD, 500MHz)

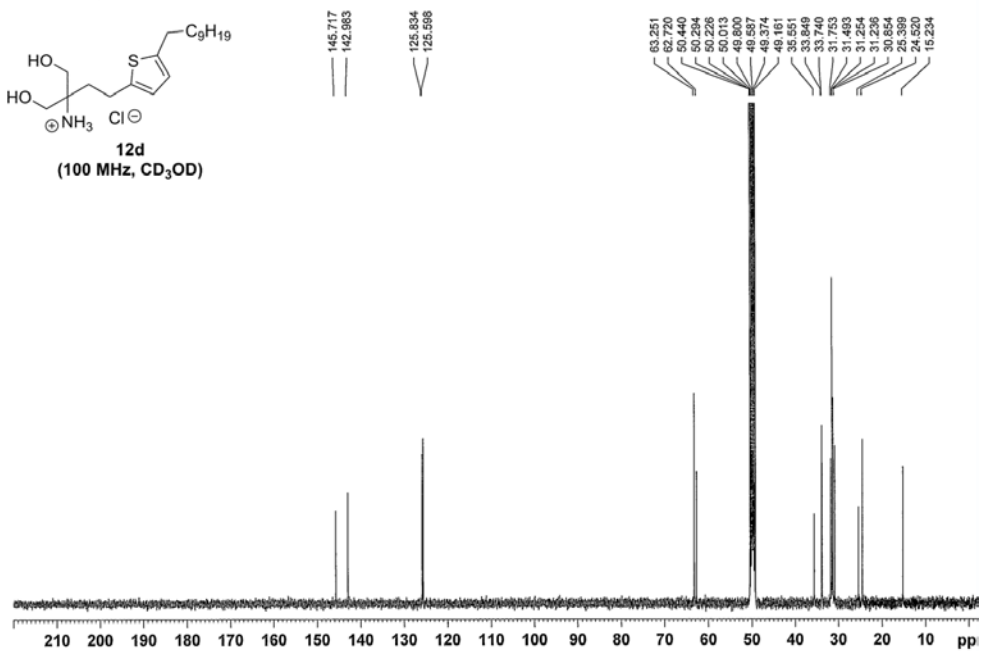
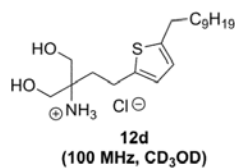




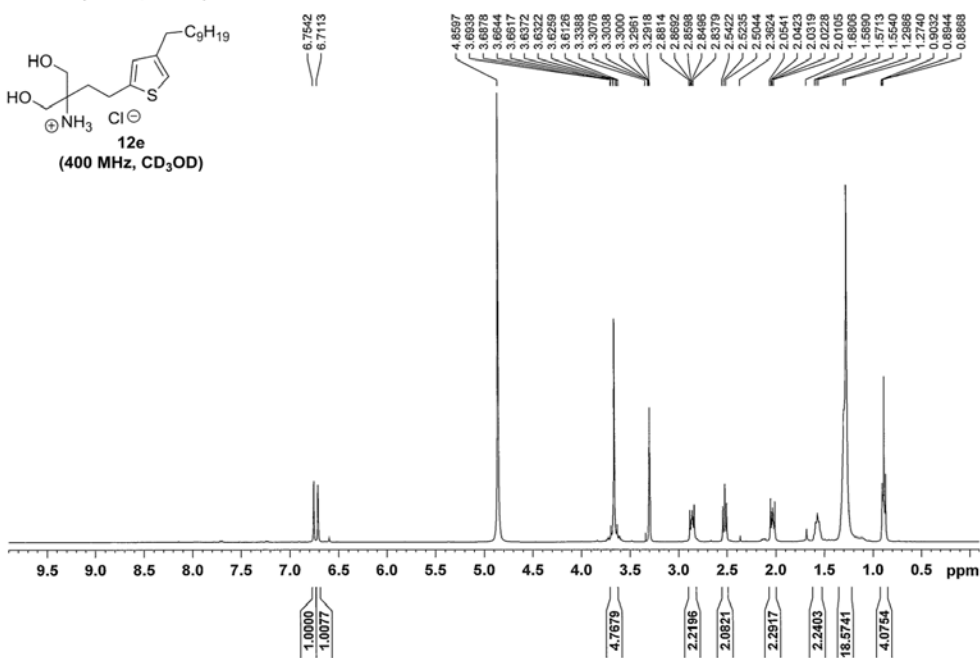
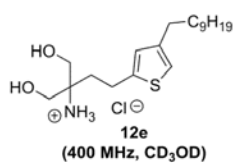
BJH-III-179 (CD₃OD,400MHz)



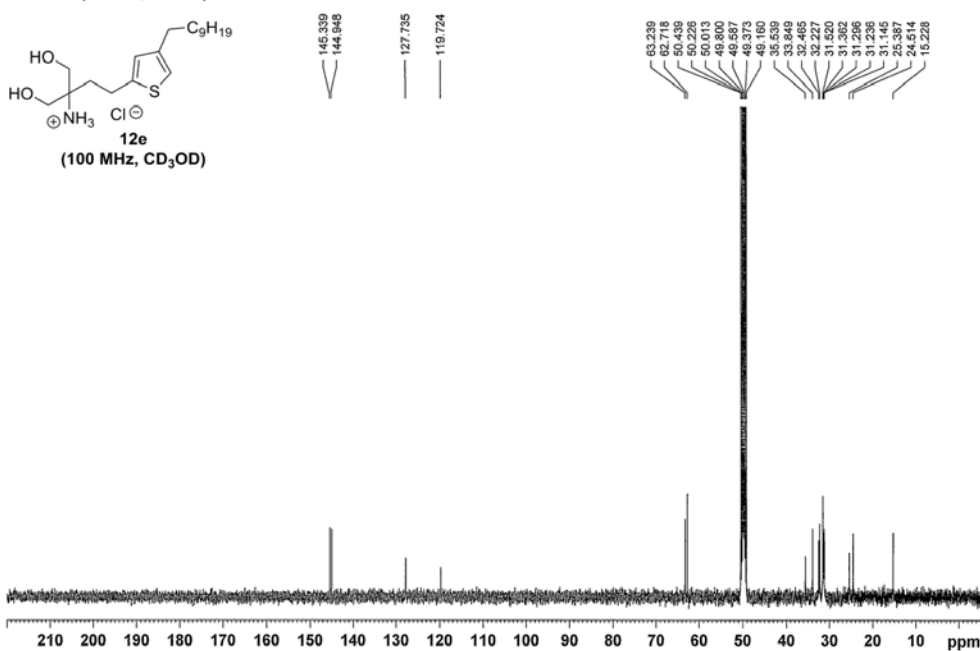
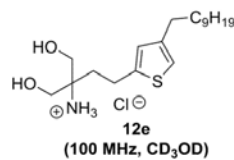
BJH-III-179 (CD₃OD,400MHz)



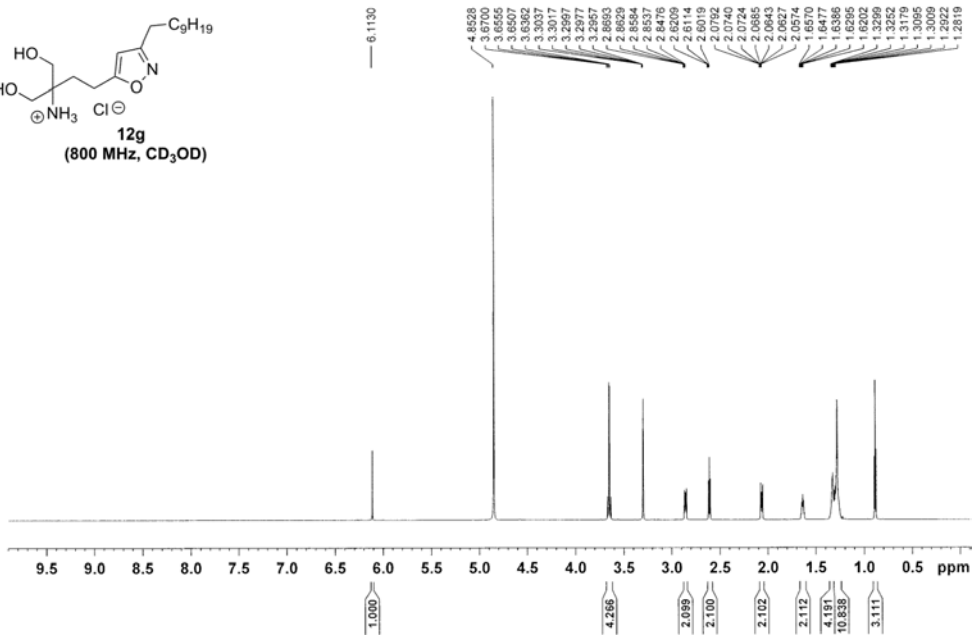
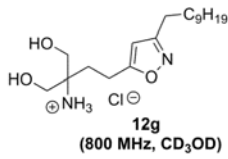
BJH-III-55 (CD₃OD, 400MHz)



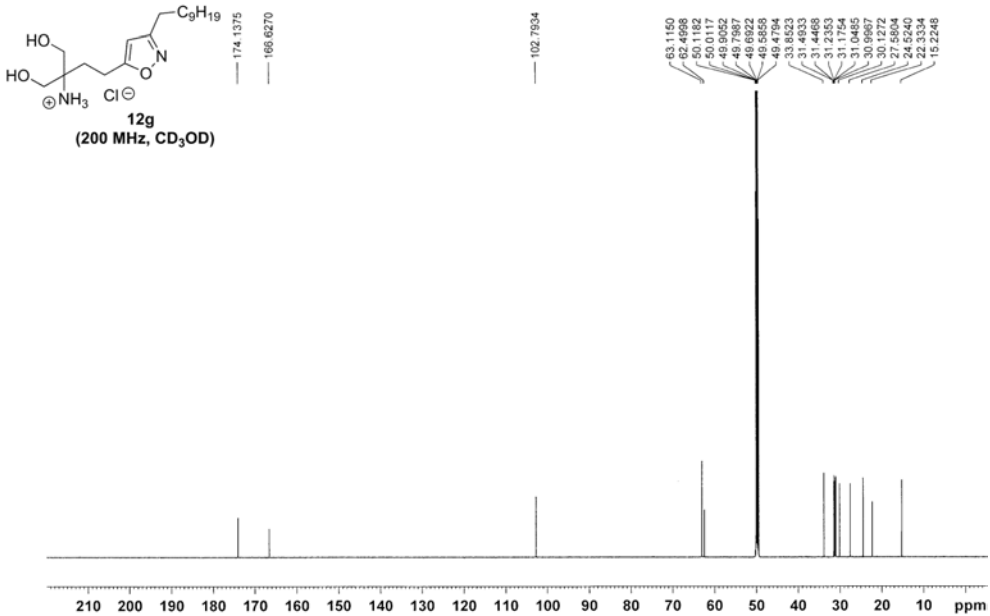
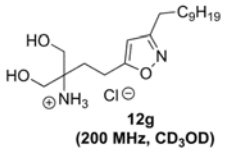
BJH-III-55 (CD₃OD, 400MHz)



I-10-HCl (800MHz)



I-10-HCl (800MHz)



VII. Abstract in English

Design and Synthesis of Novel S1P Functional Antagonists Containing a Heteroaromatic Ring

Jae Hui Been

Department of Pharmacy

Pharmaceutical Chemistry Major

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Sphingosine-1-phosphate (S1P), one of sphingolipid metabolites, is originated from the sphingosine that phosphorylated by sphingosine kinase 1/2. S1P activates five G-protein coupled receptors (S1P₁-S1P₅). S1P plays a key role in diverse biosignal system and is expected to suggest crucial clue for intractable diseases such as cancer, Alzheimer's disease and sickle cell anaemia. FTY720 (fingolimod), approved by FDA as an orally treatment for multiple sclerosis, is the first generation drug that modulates S1P. However, FTY720 has difficulties in selective control at S1P receptor subtypes (S1P₁-S1P₅) which resulted in critical side effect such as bradycardia or hypertension. In this regard, we attempted to overcome selectivity issues that FTY720 possessed with modification of a crucial scaffold

which is aromatic ring of FTY720. The key intermediates were successfully synthesized through the Wittig reaction. In this study, 7 novel potent S1P functional antagonists containing a heteroaromatic ring were finally designed and synthesized.

Keywords : sphingolipid, S1P, FTY720, Heteroaromatic ring

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