

博士論文

免疫調節薬を指向した S1P₁ 作動薬の探索研究

本論文は静岡県立大学大学院薬学研究科
博士論文である。

2014 年 11 月

浅野 正義

Synthesis and Structure-Activity Relationship
Studies on S1P₁ Agonists for Immunomodulators

November 2014

Masayoshi Asano

目次

第1章 序論.....	1
1-1. スフィンゴ脂質とスフィンゴシン-1-リン酸 (S1P)について	1
1-2. 生理活性脂質スフィンゴシン-1-リン酸 (S1P)と S1P 受容体.....	3
1-3. S1P 受容体調節薬 Fingolimod (FTY720)の発見	5
1-4. Fingolimod の作用機作	8
1-4-1. リンパ球ホーミング作用.....	8
1-4-2. S1P ₁ への機能的アンタゴニスト作用とリンパ球ホーミング作用	11
第2章 S1P ₃ の活性化を回避した S1P ₁ 作動薬の探索研究	13
2-1. はじめに	13
2-2. 公表されている S1P ₁ アゴニストの概説.....	15
2-3. 合成方法	18
2-4. 構造活性相関及び構造最適化	21
2-5. S1P 受容体ホモロジーモデルを用いたドッキングスタディによる考察.....	27
2-6. CS-2100 (8b)の詳細評価.....	30
2-6-1. S1P ₁ アゴニスト活性及び S1P ₁ /S1P ₃ 選択性の比較	30
2-6-2. リンパ球減少試験.....	31
2-6-3. ラットアジュバント関節炎	32
2-6-4. マウス EAE 試験.....	33
2-6-5. CS-2100 (8b)の薬物動態について	35
2-7. まとめ	36
第3章 1,3-チアゾール型 S1P ₁ 作動薬の探索研究.....	37
3-1. はじめに	37
3-2. 各種誘導体合成	39
3-3. 構造活性相関及び構造最適化	45
3-4. 薬物動態プロファイル及び腸内細菌に対する安定性の評価	50
3-5. まとめ	52
第4章 1-アミノシクロペンチルメタノール型 S1P ₁ アゴニストの合成研究	53

4-1. はじめに	53
4-2. 光学活性 3-ヒドロキシメチルシクロペンタン-1-オン類について	55
4-3. 合成検討	56
4-5. まとめ	62
総括.....	63
実験の部	66
5-1. General	66
5-2. 第 2 章に関する実験.....	66
5-3. 第 3 章に関する実験.....	123
5-4. 第 4 章に関する実験.....	185
5-5. 薬理評価	197
5-6. 薬物動態等.....	199
引用文献	200
本研究の基礎となる論文の目録.....	208
謝辞.....	210

本論文は、筆者が取り組んできたスフィンゴシン-1-リン酸 (S1P)をリガンドとする G タンパク質共役型受容体 S1P₁に対する、免疫調節薬を指向した作動薬の探索研究についてまとめたものである。

脂質分子にはリン脂質、脂肪酸、ステロイド、脂溶性ビタミン、プロスタグランジン等、数多くの種類が今日知られている。生体内においては細胞膜の構成成分または生体を維持するエネルギーの貯蔵源として重要な役割を担っている一方で、近年では受容体を介して生理活性を示す、いわゆるシグナル伝達物質としても広く認識されるようになってきた。

スフィンゴシン-1-リン酸 (S1P)は、血液中に高い濃度で存在する脂質分子であり、従来、細胞膜の主要構成成分であるスフィンゴシンの代謝物の一つにすぎないと考えられていた。しかし、近年の研究により細胞分化、血管新生、アポトーシス抑制等、生体内で重要な役割を担っていることが明らかとなり、他の脂質分子と同様、生理活性脂質として注目を集めている。これまでに 5 つの受容体 (S1P₁–S1P₅)が発見されており、未だすべての受容体の役割は明らかになっていないものの、S1P₁は免疫調節の分野において、新しい生化学的知見や創薬へとつながる大きな発見がなされており、世界中で精力的に研究が進められている。

第 1 章ではまず本論文の重要な根幹を概説し、第 2 章から第 4 章においては筆者が取り組んできたスフィンゴシン-1-リン酸 (S1P)受容体作動薬の探索研究について論述する。

第1章 序論

1-1. スフィンゴ脂質とスフィンゴシン-1-リン酸 (S1P)について

スフィンゴ脂質は動植物界から微生物界に至るまで幅広く存在する生体構成成分の一つであり、その研究の歴史は古く、19世紀後半から始まっている^[1]。しかし、その機能については未知の部分が多く、長い間、スフィンゴ脂質の中心的な機能は生体膜に見られる脂質二重層の構成成分、または生命活動を行う上でのエネルギー源として認識されるにとどまっていた。20世紀後半に入ってから状況は大きく変わり、受容体を介して生理活性物質として作用するといった新しい側面が見出され、シグナル伝達に関わる物質としても注目を集めている。具体的には、細胞膜上でコレステロールや様々な膜タンパク質とともに集積することでシグナル伝達の中継地点として機能する微小領域（脂質マイクロドメイン）を形成することや、セラミド（後述）およびいくつかのスフィンゴ脂質の分解産物については細胞間の情報伝達物質として作用することが次第に見出され、精力的に研究が進められている^[2]。

スフィンゴ脂質は、スフィンゴシンと呼ばれる分子を基本的な構成単位とする（Figure 1.1）。スフィンゴシン類は疎水性構造であるアルキル長鎖および親水性構造である 2-アミノ-1,3-プロパンジオール構造から構成される塩基性脂質分子の総称である。スフィンゴシン類のアミノ基と種々の脂肪酸がアミド結合を形成することでセラミドを構成し、さらに末端の水酸基に糖やリン酸基等が結合することで様々な複合脂質を形成している。

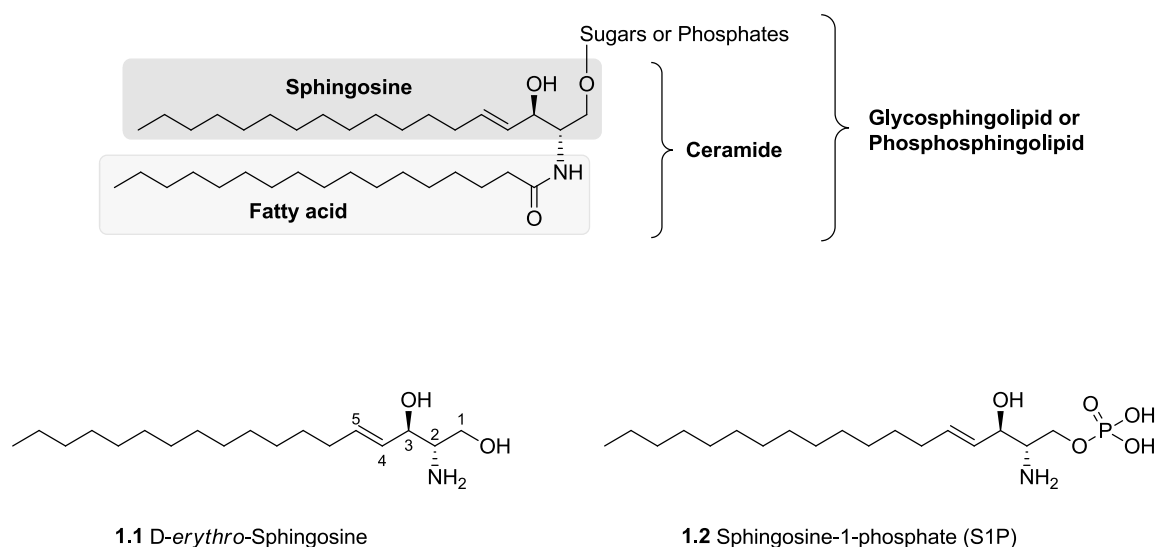


Figure 1.1

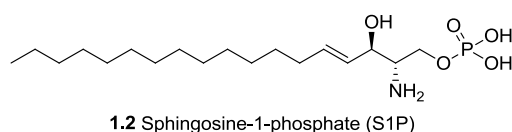
スフィンゴシン類の中で代表的なものは動物細胞に多く存在する *D-erythro*-Sphingosine **1.1** である^[3]。なお、本論文では「スフィンゴシン」と記述された場合は、*D-erythro*-Sphingosine **1.1** を示すものとする。スフィンゴシン **1.1** は生体内においてスフィンゴシンキナーゼ (SphK) によりリン酸化を受け、スフィンゴシン-1-リン酸 (S1P) **1.2** を生成する。通常の状態では、S1P は血小板に豊富に貯蔵されている。血小板のスフィンゴシン代謝は他の組織内と比べて特殊で、スフィンゴシンキナーゼの活性が非常に高い一方で、分解酵素であるリアーゼの活性が欠如しており、結果として S1P の蓄積が起これと考えられている^[4]。蓄えられた S1P は血小板の活性化に伴って細胞外 (血液中) に放出される。S1P は血液中に数百 nM 程度と高濃度で存在することが知られている^[5]。最近では、血小板の他に赤血球にも S1P が含まれており、血漿における S1P の産生源となっていることも示されている^[6]。比較的最近までこの S1P は細胞内でのスフィンゴ脂質の代謝過程で一時的に作られる中間代謝物として認識されるにとどまっていたが、1990 年代に入り、繊維芽細胞等の細胞増殖促進作用や血小板の活性化作用といった様々な生理活性が報告され、生理活性脂質 (脂質メディエーター) として注目を集めるに至った^[7]。

1-2. 生理活性脂質スフィンゴシン-1-リン酸 (S1P)と S1P 受容体

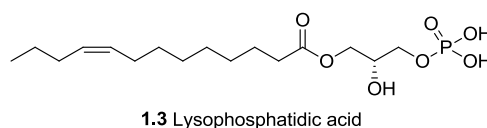
スフィンゴシン-1-リン酸 (S1P) **1.2** が細胞増殖、アポトーシスの抑制、細胞遊走、細胞骨格の制御等を引き起こす新しい脂質メディエーターとして注目されるようになり、その標的部位について精力的に研究が進められるようになった。

1998 年、Hla らによってスフィンゴシン-1-リン酸 (S1P)の作用部位を明らかにする重要な報告がなされた。彼らは、血管内皮細胞に発現する G タンパク質共役型受容体である Edg (Endothelial Differentiation Gene)受容体を同定し、スフィンゴシン-1-リン酸 (S1P)がそのリガンドであることを明らかにした^[8]。スフィンゴシン-1-リン酸 (S1P)をリガンドとする Edg 受容体には複数のサブタイプが存在し、Edg1、Edg5、Edg3、Edg6、Edg8 の 5 種類が同定されている^[9]。なお、リゾホスファチジン酸 **1.3** をリガンドとする Edg2、Edg4、Edg7 も同時期に発見された (Table 1.1)。

Table 1.1



S1P receptor	Expression tissue
S1P ₁ (Edg1)	widely distributed
S1P ₂ (Edg5)	widely distributed
S1P ₃ (Edg3)	widely distributed
S1P ₄ (Edg6)	lymphatic tissue, lung
S1P ₅ (Edg8)	nervous tissue



LPA receptor	Expression tissue
LPA ₁ (Edg2)	widely distributed
LPA ₂ (Edg4)	nervous, kidney, testis, lung
LPA ₃ (Edg7)	testis, heart, brain, lung

生体内リガンドが明らかになったことから、現在ではこれらの Edg 受容体は、S1P₁ (Edg1)、S1P₂ (Edg5)、S1P₃ (Edg3) …、及び LPA₁ (Edg2)、LPA₂ (Edg4) …と呼称されるのが一般的であり、本論文では S1P 受容体の呼称で統一することとする。なお、各受容体の呼称については、S1P₁ 受容体、S1P₂ 受容体…といった表記を用いられることも少なくないが、S1P₁ は sphingosine-1-phosphate receptor-1 であり受容体そのものの略称であることから、本論文では各受容体の呼称を S1P₁、S1P₂ …で統一することとする。

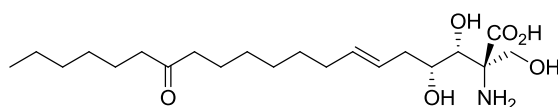
S1P 受容体は 7 回膜貫通型の G タンパク質共役型受容体である。サブタイプによっては局在化して分布しているものもあるが、S1P₁、S1P₂ 及び S1P₃ は非常に広範な部位で発現している (Table 1.1)。特に S1P₁ はリンパ球及び中枢神経組織において高発現である。一方、S1P₄ は造血・リンパ系組織及び肺に発現が認められるが、S1P₁ に比べて発現量は低い。また、S1P₅ は中枢神経組織、脾臓、ナチュラルキラー細胞等に発現が認められる。

これら S1P 受容体の生体内における機能の解明については近年、精力的に進められており、特に S1P₁ については様々な生命現象において重要な役割を担っていることが明らかにされつつある。例えば 1999 年、Hla らはスフィンゴシン-1-リン酸 (S1P) 及び S1P₁ が血管新生因子および受容体として機能することを報告している^[10]。2000 年、Priola らは S1P₁ ノックアウトマウスを作成した。この S1P₁ を持たないマウスは胎児期に致死性であり、これは血管形成過程の異常による出血を死因としていることが明らかにされている^[11]。これらの事実は S1P₁ の阻害剤 (アンタゴニスト) は、癌や糖尿病性網膜症等に対する有効な治療薬である血管新生阻害剤としての可能性を有していることを示唆している。一方、S1P 受容体は強力な免疫抑制作用を有する Fingolimod (FTY720) の標的分子であることが明らかにされている。そのメカニズムの詳細については次節において概説する。

他の S1P 受容体に対するアゴニスト・アンタゴニスト研究も世界中の研究機関において活発に探索研究が行われている。例えば、日本たばこ産業株式会社の研究グループは S1P₂ アンタゴニストについて肝線維化抑制薬としての可能性を報告している^[12]。トーアエイヨー株式会社のグループは *In Silico* スクリーニングの結果を基に、S1P₃ アンタゴニスト活性を有する化合物を報告している^[13]。スクリプス研究所のグループは、種々の S1P₄ 調節薬を報告しており^[14]、S1P₄ アンタゴニストについてインフルエンザ治療薬としての可能性があることを示唆している。Abbott Laboratories のグループは S1P₅ アゴニスト活性を有する化合物が作業記憶等の評価系として知られる T 迷路モデルにおいて薬効を示すことから認知障害の治療薬につながる可能性を報告している^[15a]。S1P 受容体の阻害ないし活性化が特定の疾患治療につながる可能性を示唆する報告は上記した例の他にもなされている^[15]。

1-3. S1P 受容体調節薬 Fingolimod (FTY720)の発見

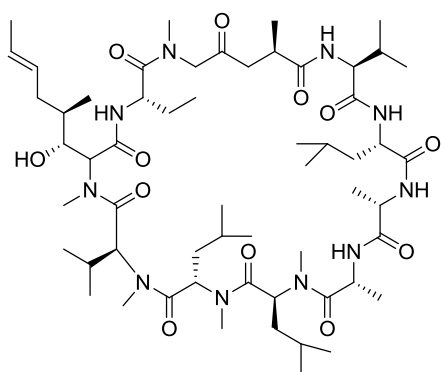
1990 年、藤多らは古来より中国で生薬として用いられている冬虫夏草の一種であるタイワンツクツクハウシに寄生する *Isaria sinclairii* 菌の培養濾液より強い免疫抑制作用を有する物質を単離し、ISP-I (Immunosuppressive Principle-I)と命名した。構造解析の結果、この化合物は既知物質であり、すでに報告されていた Myriocin (*Myriococcum albomyces* 菌より単離)^[16]及び Thermozytocidin (*Mycelia sterilia* 菌より単離)^[17]と同一物質であることが判明した (Figure 1.2)。Myriocin や Thermozytocidin の抗真菌作用は知られていたが、免疫抑制作用については初めて報告された。



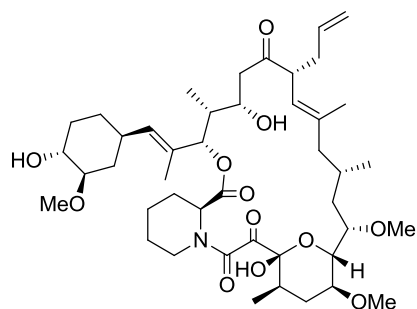
1.4 Myriocin (ISP-I)

Figure 1.2

具体的には、細胞評価系として免疫抑制薬の *in vitro* スクリーニングに用いられるマウス同種リンパ球混合反応 (MLR)試験において、既存の免疫抑制剤である Cyclosporin A **1.5** よりも 4 倍以上強い免疫抑制活性を示していた。その後の研究によって、その作用メカニズムは Cyclosporin A **1.5** とは全く異なるものであることが明らかになっている (Figure 1.3)。



1.5 Cyclosporin A



1.6 Tacrolimus

Figure 1.3

つまり、Cyclosporin A **1.5**^[18]や Tacrolimus **1.6**^[19]といったカルシニューリン阻害薬は、ヘルパーT細胞において、細胞障害性 T 細胞の増殖等に関与するサイトカインである IL-2 等の産生を抑えることで免疫反応を抑制する。一方、Myriocin は細胞障害性 T 細胞やナチュラルキラー細胞に対してアポトーシスを誘導することで免疫抑制作用を示す^[20]。

後の研究により、Myriocin はスフィンゴシンの生合成経路の最初の段階で重要であるセリン・パルミトイルトランスフェラーゼ (SPT)を強力に阻害 ($IC_{50} = 0.28 \text{ nM}$)することがわかっており^[20a]、スフィンゴシンの減少が本アポトーシスに関連していると考えられている^[20b]。例えば、IL2 依存的に増殖するマウス障害性 T 細胞株である CTLL-2 に対して Myriocin を作用させると、CTLL-2 の増殖が抑制されるが、スフィンゴシンまたはスフィンゴシン-1-リン酸を添加することで CTLL-2 の増殖は回復する。スフィンゴミエリンやスフィンゴ糖脂質等といったスフィンゴ脂質合成経路の最終産物については増殖の回復は全く認められていないことから、スフィンゴ脂質の中でもスフィンゴシン等、特定の化合物の減少により、この増殖阻害が誘導されることが示唆されている。

Myriocin は強い免疫抑制作用を有するものの、複数の不斉点を有し、溶解性が悪く、さらに毒性も強いといった数々の難点を抱えていた。しかし、藤多らによる構造最適化研究により、これらの問題点が解決され、再発寛解型多発性硬化症の治療薬として 2010 年に Fingolimod (商品名：Gilenya®) が田辺三菱製薬株式会社および Novartis 社によって上市されている (Figure 1.4)。具体的には、Myriocin の親水性部位を簡略化する合成展開がなされた結果、2-アミノ-1,3-プロパンジオール構造という単純な構造においても免疫抑制作用が認められることが明らかになり^[21]、シンプルかつ不斉炭素のない ISP-I-36 へと導かれた後、ベンゼン環の導入等の更なる構造最適化によって、Fingolimod 1.8 へと導かれている^[22]。

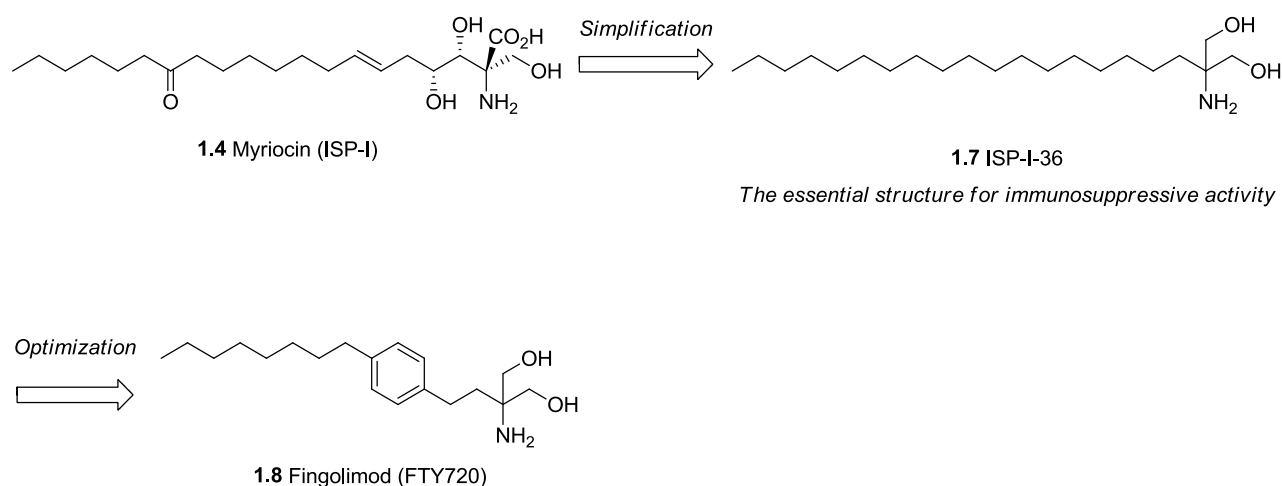


Figure 1.4

興味深いことに構造最適化の過程において免疫抑制作用のメカニズムが全く別のものに大転換したことが明らかになっている。Myriocin は、前述したように SPT の機能を阻害することで T 細胞のアポトーシスを誘導し、免疫抑制作用を示す。一方、Fingolimod の有する免疫抑制作用は、後述するリンパ球ホーミング (再循環) 作用という新たなメカニズムに基づくことが知られている^[23]。新しい免疫抑制メカニズムの登場に加えて、Fingolimod 自体が非常に単純な分子構造を持つことから、世界中の研究機関・製薬企業が興味を持つに至り、本分野における薬理・合成研究が急速に進められてきた。次節ではリンパ球ホーミング作用を含めた、Fingolimod の作用機作について詳細に説明する。

1-4. Fingolimod の作用機作

1-4-1. リンパ球ホーミング作用

通常、免疫反応に関与するリンパ球はリンパ管やリンパ節、血管を通じて全身をくまなく巡回し、免疫反応部位に集積してその役割を果たすという性質を有している (Figure 1.5a)。しかし、Fingolimod を投与した場合、循環しているリンパ球がリンパ節をはじめとする二次リンパ系組織内に隔離され、末梢血中の循環リンパ球の減少がおこる (Figure 1.5b)。

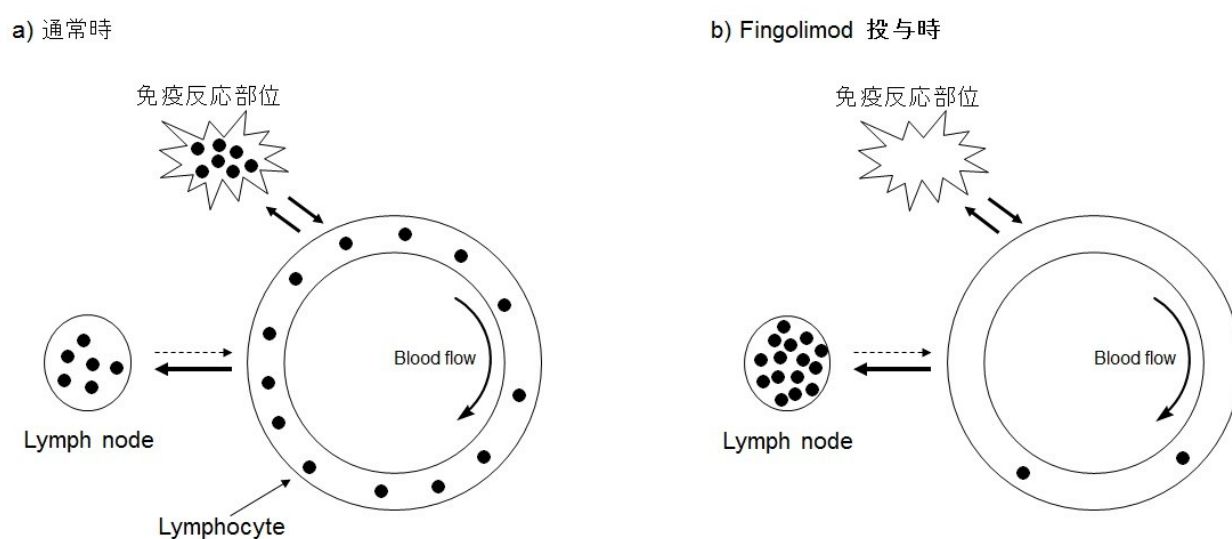


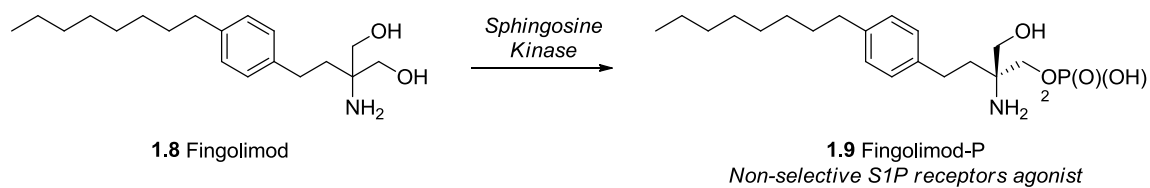
Figure 1.5

このことにより本来リンパ球が集積すべき免疫反応部位へのリンパ球の浸潤量が減少し、免疫反応が抑制される。本メカニズムはこれまでに上市されている他の免疫抑制剤とは異なる極めてユニークなものであるが、1995 年の Fingolimod の最初の報告以来、標的タンパクを含めた作用メカニズムについては長い間、未知のままであった。

2002 年、Merck 社及び Novartis 社によって、その作用メカニズムの全容が解明された。Fingolimod によるリンパ球ホーミング作用にはスフィンゴシン-1-リン酸 (S1P) を天然リガンドとする G タンパク質共役型受容体である S1P 受容体が関与しているというものであった^[24]。

すなわち、Fingolimod **1.8** は投与された後、生体内での代謝により速やかにリン酸化され、リン酸エステルである Fingolimod-P **1.9** へと変換される (Table 1.2)。Fingolimod-P **1.9** は 5 つのサブタイプより構成される S1P 受容体に対する非選択的アゴニストであり、特に S1P₂ 以外の受容体に対し nM オーダーで結合し、強力なアゴニスト作用を示すことが明らかとなった^[24a]。なお、生体内でのリン酸化はエナンチオ選択的に起こり (*S*)-体のみを与え^[26]、強い免疫抑制作用を示すのも同様の立体異性体であることが知られている^[25]。その後の研究で、この S1P 受容体ファミリーに対するアゴニスト作用の中でも特に S1P₁ に対するアゴニスト作用がリンパ球ホーミング作用を誘導することが示唆されている。一方で、げっ歯類において S1P₃ に対するアゴニスト作用は Fingolimod の主な副作用である徐脈 (心拍数の低下) に深く関与しているという報告が複数の研究グループによってなされている^[27]。これらのことから、安全性面に関するリスクの低下を目的として製薬企業をはじめとする多くの研究機関において、S1P₃ の活性化を回避した S1P₁ アゴニストの開発研究が行われてきた^[15a, 28]。筆者が取り組んできた探索研究については第 2 章以降で詳しく述べている。

Table 1.2^[24a]



Compound	Binding affinity to S1P receptors (nM)				
	S1P ₁	S1P ₂	S1P ₃	S1P ₄	S1P ₅
S1P	0.47	0.31	0.17	95	0.61
Fingolimod	300	>10000	>10000	>5000	2600
Fingolimod-P	0.21	>10000	5.0	5.9	0.59

1-4-2. S1P₁ への機能的アンタゴニスト作用とリンパ球ホーミング作用^[29, 30]

リンパ球はリンパ節等の二次リンパ系組織、リンパ管及び血管を循環しており、この循環には S1P の濃度勾配及びその受容体である S1P₁ が極めて重要な役割を果たすことが示されている^[31]。Figure 1.6 上段に示すように、S1P の濃度は血管及びリンパ管内では 100 nM 以上であるが、二次リンパ系組織では、S1P リアーゼ等により分解を受け 10 nM 以下と非常に低く保たれており、血管、リンパ管と二次リンパ組織の間には S1P の濃度勾配が形成されている^[32]。高濃度の S1P が存在している血管及びリンパ管内では、S1P の作用によりリンパ球上の S1P₁ は細胞内に移行している。通常、この S1P による S1P₁ の細胞内移行は可逆的であり、S1P が低濃度に維持されている二次リンパ組織内ではリンパ球上の S1P₁ の発現が回復する^[33]。S1P₁ の発現が回復したリンパ球は S1P への反応性が高いため、S1P が低濃度の二次リンパ系組織から高濃度のリンパ管へと濃度勾配に従って遊走する。

一方、Fingolimod が投与されると、活性代謝物であるリン酸エステル Fingolimod-P がリンパ球上の S1P₁ にアゴニストとして作用した後に、S1P₁ の細胞内移行と分解を強力に誘導する (Figure 1.6 下段)。その結果、二次リンパ系組織内においてもリンパ球上の S1P₁ の発現レベルが回復することなく極めて低い状態に維持されるため、リンパ球の S1P に対する反応性が著しく低下することになる^[34]。その結果、S1P の濃度勾配に従ったリンパ球の遊走が阻害され、リンパ節から放出されなくなり、末梢血中の循環リンパ球が著しく減少する。したがって Fingolimod-P は S1P 受容体に対する機能的アンタゴニスト (functional antagonist) といえる^[35]。このことにより免疫反応部位へのリンパ球の供給を阻止することができ、免疫反応が抑制されと考えられている。

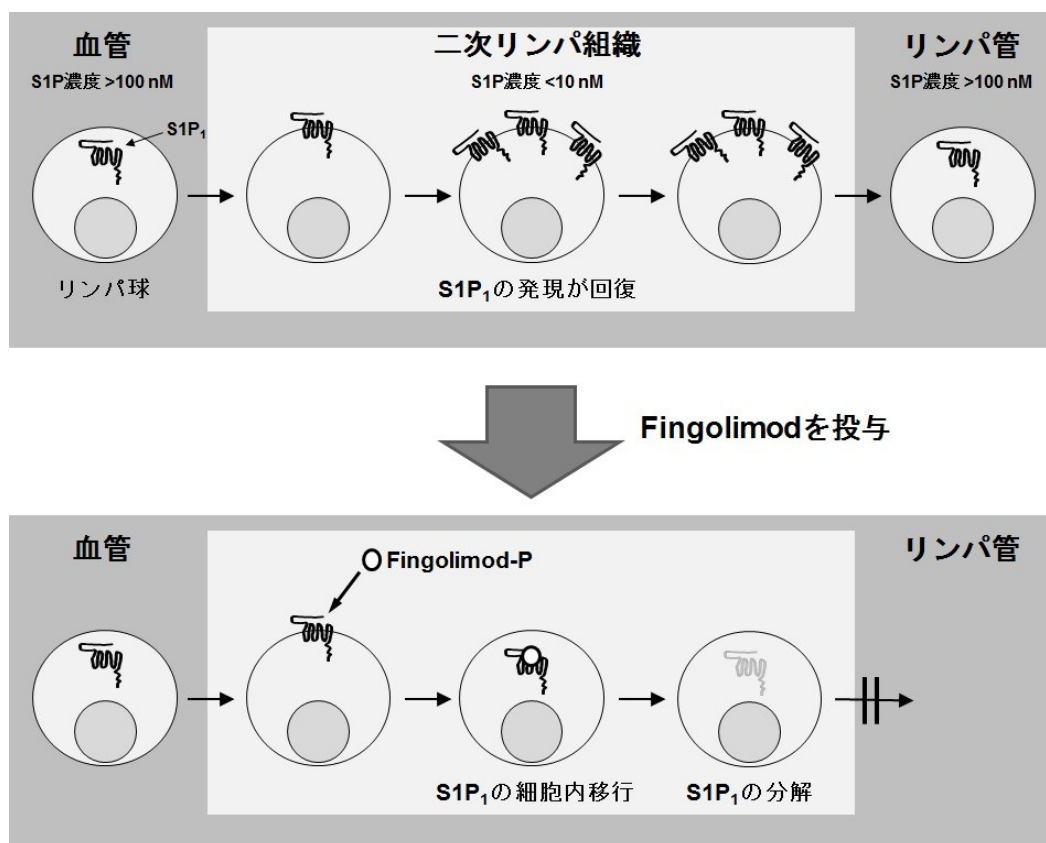


Figure 1.6^[29]

以上、第 1 章としてスフィンゴシン-1-リン酸及びその受容体に関する近年のトピック、そして新規免疫抑制剤 Fingolimod の創製経緯及びその作用メカニズムについて述べた。Myriocin をリード化合物として誘導体展開されて見出だされた新規免疫抑制剤 Fingolimod の創製において、その作用メカニズムは全く別個に研究されていたスフィンゴシン-1-リン酸をリガンドとする G タンパク質共役型受容体、S1P 受容体に対するアゴニスト作用に基づくものであった。リンパ球をリンパ節に閉じ込めるとい、これまでに類を見ない免疫抑制メカニズムは多くの研究者の注目を集め、Fingolimod の登場以降、S1P 受容体に関する研究が精力的に進められてきた。各 S1P 受容体には新たな創薬ターゲットとなりうる可能性が高いことから、今後も活発な研究が行われていく分野であると予想される。

第2章 S1P₃の活性化を回避した S1P₁ 作動薬の探索研究

2-1. はじめに

多発性硬化症 (multiple sclerosis : MS)は中枢神経系 (脳・脊髄)に障害を生じる難病であり、日本では特定疾患に指定されている^[36]。世界で 250 万人以上、日本で約 1 万人の患者数があり、若年女性の罹患率が高いとされる。近年は患者数が全国的に増加傾向にあり、若年成人が罹る神経難病の中では最も多い。

本疾患の症状は通常、まず視神経、脊髄または脳幹/小脳の局所的症状として現れることが多い。具体的な初発症状としては、しびれ等の感覚障害、視神経炎等の視力障害、脱力が多いが、最近では大脳が障害され、片麻痺に陥る症例も増えている。その後急激な悪化 (増悪または再発)、身体機能障害の段階的進行、またはこれらの組み合わせを特徴とする臨床経過をたどる。

その病態の背景にある機序は完全には解明されてはいないが、中枢神経を標的とした自己免疫に基づき発症すると推定されている。通常、中枢神経系への免疫系細胞の浸潤は、血液脳関門 (blood-brain barrier : BBB)及び血液脳脊髄液関門 (blood-cerebrospinal fluid barrier : BCSFB)によって制限されている。多発性硬化症では BBB の機能異常により、ある種の T 細胞やマクロファージ等が脳の組織に浸潤し、髄鞘を攻撃するものと考えられている。

多発性硬化症の薬物療法には、急性期には副腎皮質ステロイド薬、再発予防にはインターフェロン β 等の生物学的製剤やシクロスポリン等の免疫抑制剤が用いられているが、生物学的製剤は注射剤で非常に高価であり、既存の免疫抑制剤は腎毒性、肝毒性の副作用を示すことから、新しい経口治療薬の開発が望まれている。

スフィンゴシン-1-リン酸 (S1P)受容体作動薬である Fingolimod は、冬虫夏草の一種 *Isaria sinclairii* 由来の天然物 Myriocin (ISP-I)の構造変換により 1995 年に藤多らによって見いだされた強力な免疫抑制作用を有する化合物である (Figure 2.1)。各種の移植モデルや自己免疫疾患モデルにおいて強い薬効を示すことが知られ、当初、臓器移植時の拒絶反応に対する免疫抑制薬として臨床試験が実施されたが、最終的に Novartis 社と田辺三菱製薬株式会社により多発性硬化症を対象疾患として、現在、ロシア、米国、日本にて上市されている^[29]。既存の免疫抑制剤であるカルシニューリン阻害薬 (Cyclosporin

AやTacrolimus)がT細胞からのサイトカイン産生を抑制することにより免疫抑制作用を発現するのに対して、Fingolimod は、それとは異なる新規作用メカニズムを有する経口低分子薬剤として、多発性硬化症治療における重要な選択肢となることが期待されている。

第 1 章で述べたように、Fingolimod は生体内での代謝により生じるリン酸エステル Fingolimod-P がその活性本体であり、Fingolimod-P は 5 つの S1P 受容体 (S1P₁–S1P₅)のうち、S1P₂以外の受容体を非選択的に活性化する。S1P₁の活性化はリンパ球ホーミング作用を制御することによりリンパ球減少を誘導し、免疫抑制作用を示す。一方、S1P₃の活性化は Fingolimod の主な副作用である徐脈（心拍数の低下）との関連性がげっ歯類において示唆されている。これらのことから、先行する Fingolimod よりも安全性面に関してリスクの低下が期待できるベストインクラスの薬剤として、S1P₃の活性化を回避した S1P₁アゴニストの開発を本研究の目的として探索研究を行った。

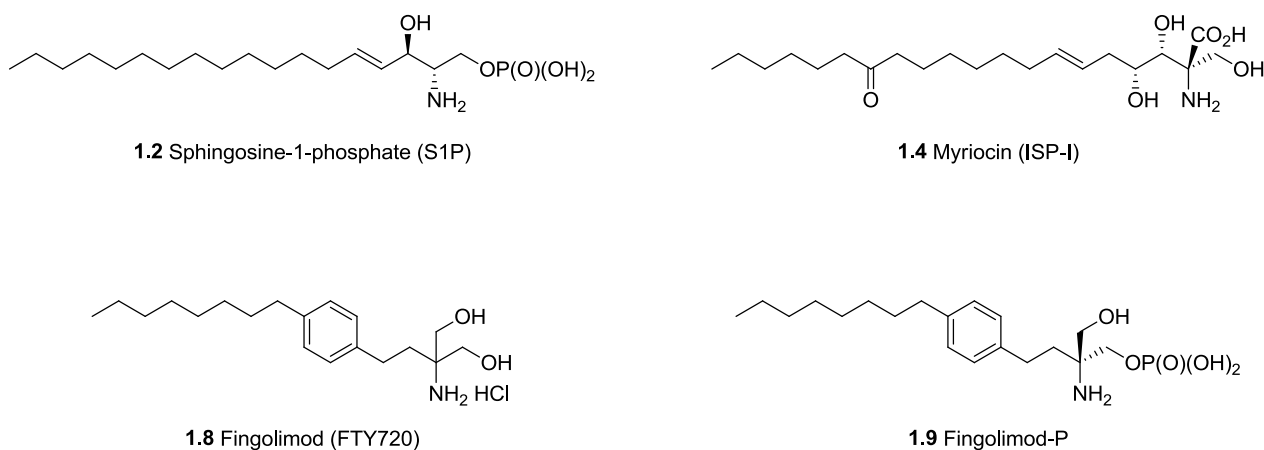


Figure 2.1

2-2. 公表されている S1P₁ アゴニストの概説

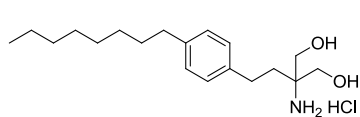
Fingolimod の免疫抑制作用や標的分子が明らかとなったことから、世界中の研究機関で S1P₁ 作動薬の研究開発が精力的に進められてきた^[15a, 28]。これまでに数多くの化合物が報告されており、構造的には 3 つのタイプに大別される。

第一のタイプは Fingolimod に代表されるようにアミノアルコール構造を有するプロドラッグ型である (Figure 2.2 上段)。このタイプは生体内リガンドである S1P と同様に分子内にアミノアルコール構造を有しており *in vitro* では不活性であるが、*in vivo* でスフィンゴシンキナーゼによりリン酸化を受けて活性本体となり S1P₁ アゴニストとして機能する。代表的な化合物として KRP-203^[41] や CS-0777^[45] 等が挙げられる。アミノアルコールタイプでは、親化合物が円滑にリン酸化されるようにスフィンゴシンキナーゼに対して良好な基質であること、かつ生成したリン酸化体が優れた S1P₁ アゴニストであることの両条件が必要となる。さらに活性本体であるリン酸化体が、種々のホスファターゼによる脱リン酸化反応に対して一定の安定性を示すことも要求される。以上のことから、新たな誘導体展開の潮流として *in vivo* での活性化を必要としない化合物デザインが次第に散見されるようになってきた。

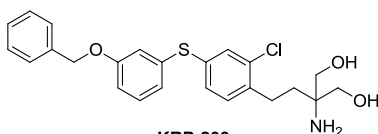
具体的には、アミノリン酸エステル部位をアミノ酸に置換した化合物群である (Figure 2.2 中段)。本化合物群は生体内での活性化を必要とせず、また分子モデリングの研究により、カルボン酸部位がリン酸部位の実質的な代替基として機能することが示されている^[37-39]。アミノ酸部位については鎖状、環上と種々の構造が報告されているが、アゼチジン-3-カルボン酸構造を有する化合物が極めて多く報告されている。

一方で、アミノ酸部位が *in vitro* における S1P₁ アゴニスト活性に必須でない化合物も報告されている (Figure 2.2 下段)。SEW2871 に代表されるこれらの化合物群においてはアミノリン酸エステル部位やアミノ酸構造のような高い極性官能基を有しておらず、比較的脂溶性の高い化合物も報告されている。他方、Ponesimod^[40] は分子内に極性基であるジオール構造を有しているが、リン酸化による活性化を必要とすることなく薬効を示すことが報告されている。

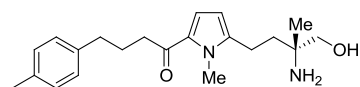
Amino alcohol type



Fingolimod
(Launched; Novartis, Tanabe-Mitsubishi)
multiple sclerosis

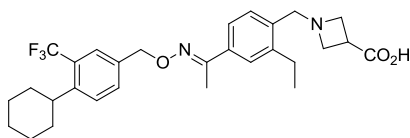


KRP-203
(Ph2; Kyorin)
autoimmune disorder
inflammatory bowel disease

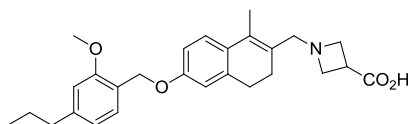


CS-0777
(Ph1中止; Daiichi Sankyo)
multiple sclerosis

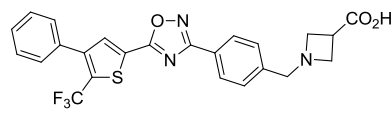
Amino acid type



Siponimod
(Ph3; Novartis)
multiple sclerosis

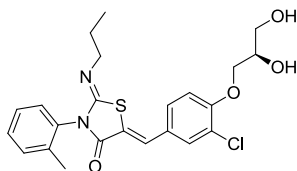


Ceralifimod
(Ph2中止; Ono)
multiple sclerosis

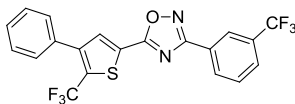


1
(Preclinical; Merck)

Other types



Ponesimod
(Ph2; Actelion)
multiple sclerosis
psoriasis



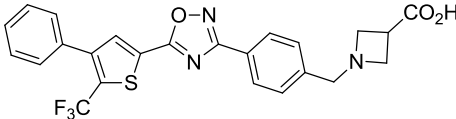
SEW2871
(Preclinical; Scripps)

Figure 2.2

現在、臨床開発中の化合物としては KRP-203^[41] (杏林製薬株式会社、Novartis 社、第 II 相、適応症：臓器移植における拒絶反応、自己免疫疾患、血液癌、炎症性腸疾患)、Siponimod^[42] (Novartis 社、第 III 相、適応症：多発性硬化症)、Ponesimod^[40] (Actelion 社、第 II 相、適応症：多発性硬化症、乾癬)、GSK-2018682^[43] (構造不明、Glaxo Smith Kline 社、第 I 相、適応症：多発性硬化症)、MT-1303 (構造不明、田辺三菱製薬株式会社、第 II 相、適応症：多発性硬化症)、ABT-413 (構造不明、AbbVie 社、第 I 相、適応症：癌、多発性硬化症、関節リウマチ)、APD-334 (構造不明、Arena 社、第 I 相、適応症：多発性硬化症、関節リウマチ、乾癬)、RPC-1063 (構造不明、Receptos 社、第 III 相、適応症：多発性硬化症、潰瘍性大腸炎)が挙げられる。一方、既に開発を中止している化合物として Ceralifimod^[44] (小野薬品工業株式会社、第 II 相、適応症：多発性硬化症)、PF-4629991 (構造不明、Pfizer 社、第 I 相、適応症：関節リウマチ)、CS-0777^[45] (第一三共株式会社、第 I 相、適応症：多発性硬化症)がある。

以上のように Fingolimod の発見以来、当初の構造から大きく変化し、これまでに多岐にわたる化合物が報告されている^[15a, 28]。筆者が所属する第一三共株式会社でも以前より S1P₁ アゴニストの探索研究が行われており、西らによって CS-0777 が社内開発候補品として見出されている。その後の研究において、筆者らは当時報告されていた化合物のプロファイルを精査し、S1P₁/S1P₃ 選択性の観点から Merck 社より報告されている化合物 **1**^[46]に注目した（なお、Figure 2.2 に列挙した種々の S1P₁ アゴニストは近年報告されたものも多いため、化合物 **1** に比較して S1P₁/S1P₃ 選択性が優れているものも含まれている）。Table 2.1 に Merck 化合物 **1** のプロファイルを示す。

Table 2.1



1 (Merck)

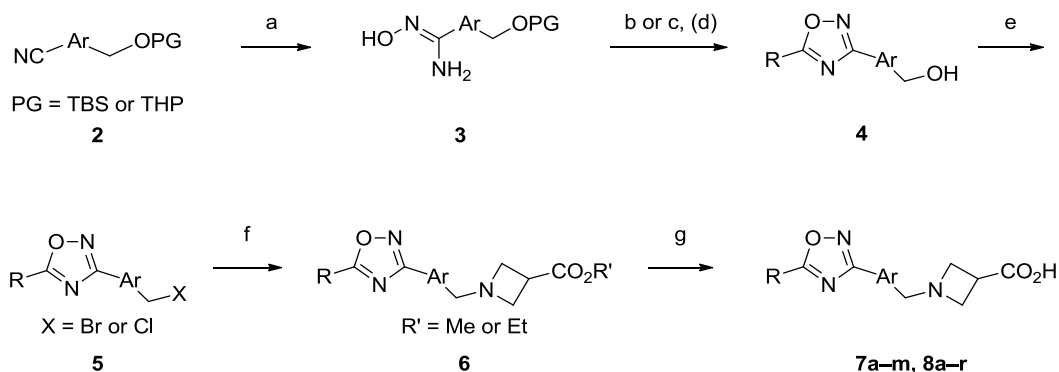
Compound	γ -GTP EC ₅₀ (nM)		活性比 S1P ₁ vs S1P ₃	マウスリンパ球減少 ^a (対照群 : 100%)	徐脈作用 (rat, 経口投与)
	hS1P ₁	hS1P ₃			
1	4.2	1600	380	23%	陽性 (30 mg/kg)
Fingolimod-P	0.37	3.3	9	21%	陽性 (10 mg/kg) ^b

^a 0.1 mg/kg of **1** or Fingolimod, 静脈投与
^b Fingolimod-administered (*J. Med. Chem.*, **2010**, 53, 3154)

化合物 **1** の S1P₁ に対するアゴニスト活性は 4.2 nM と Fingolimod-P と比較して弱いものの、マウスにおいて化合物 **1** を 0.1 mg/kg 静脈投与すると対照群に対して 23%にまで末梢血リンパ球数は減少し、Fingolimod 投与時と同等のリンパ球再循環抑制作用を示した。一方、**1** の S1P₃ に対するアゴニスト活性は 1600 nM であり、S1P₁/S1P₃ 選択性は 380 倍と Fingolimod-P の 9 倍に比較して高いものの、ラットにおいて経口投与 30 mg/kg では有意な徐脈作用が観察されており、未だ改善の余地があることが示唆された。以上より、強い S1P₁ アゴニスト活性を有し、かつより一層優れた S1P₁/S1P₃ 選択性を併せ持つ化合物を取得すべく、**1** をリード化合物として誘導体展開を開始した。

2-3. 合成方法

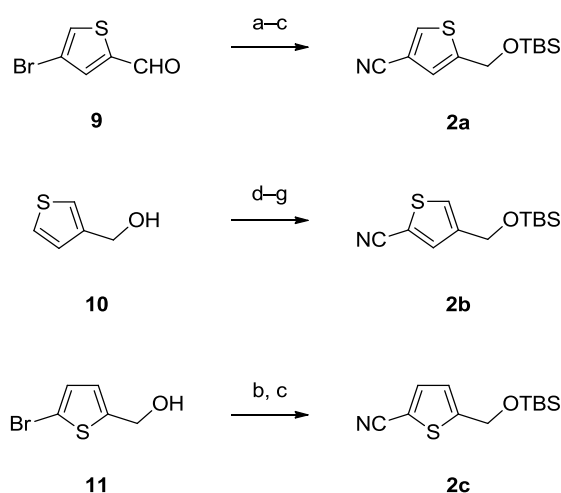
まず、構造活性相関の情報取得を目的として、リード化合物 **1** の構造に基づき内側のベンゼン環及び左側鎖である 4-フェニル-5-トリフルオロメチルチオフェン構造を変換した。なお、予備的な検討からアミノ酸部位はアゼチジン-3-カルボン酸構造が適していることがわかっていたため（データ不掲載）、こちらは変更しないこととした。一般的合成ルートを Scheme 2.1 に要約する。誘導体合成を効率化すべく、鍵中間体として芳香族ニトリル **2** を設定した。**2** の合成については後述する（Scheme 2.2 及び 2.3）。**2** に対してエタノール中、ヒドロキシルアミンを作用させることでアミドキシム **3** とした。得られた **3** を、別途調製した各種酸クロリド **16** または各種カルボン酸 **19** と縮合後、同一系内で TBAF を作用させることにより、1,2,4-オキサジアゾール環を構築した。この際、TBS 保護体については環構築と TBS 基の脱保護が一挙になされた。一方、THP 保護体については、環構築の後、酸処理することで THP 基を脱保護した。得られた **4** をハライド中間体 **5** へと変換した後、ジイソプロピルエチルアミン存在下、アゼチジンカルボン酸ユニットを求核的に導入して **6** を得、最後にエステル部位を加水分解することで、各種誘導体 **7a–m**, **8a–r** を合成した。なお、**8c**, **8g**, **8h** 及び **8i** については結晶を取得するためにシュウ酸塩とした。



Reagents and conditions: (a) aq. NH_2OH , EtOH (60–98%). (b) RCOCl (**16**), Et_3N , CH_2Cl_2 , then TBAF, THF (65–98%). (c) RCO_2H (**19**), EDCI or DCC, HOBT, CH_3CN , then TBAF, THF (40–94%). (d) PPTS, EtOH, 60 °C (92%) for THP deprotection. (e) CBr_4 , PPh_3 , CH_2Cl_2 or SOCl_2 , cat. DMF, toluene. (f) methyl azetidine-3-carboxylate-HCl or ethyl azetidine-3-carboxylate-HCl, $i\text{-Pr}_2\text{NEt}$, CH_3CN (44–93%, 2 steps). (g) aq. NaOH or LiOH; AcOH or oxalic acid (**8c**, **8g**, **8h** and **8i** were solidified as oxalates.) (39–95%).

Scheme 2.1

次に各種芳香族ニトリル **2** について合成方法を示す (Scheme 2.2)。ベンゼン環の生物学的等価体として知られるチオフエン誘導体より始め、具体的にはそれぞれ位置異性体の関係にある **2a–c** を合成した。**2a** については、市販のアルデヒド **9** より出発し、水素化ホウ素ナトリウムによりホルミル基を還元した後、生じた一級アルコールを TBS 基により保護、続いてシアニ化銅によりシアノ基を導入することで調製した。**2b** については、市販のチオフェニルメタノール **10** より TBS 基によるアルコールの保護、チオフエン 5 位へのホルミル基の導入、オキシムを経由したニトリル基への変換を経て合成した。**2c** については、市販のアルコール **11** より出発し、**2a** と同様な工程を経て調製した。

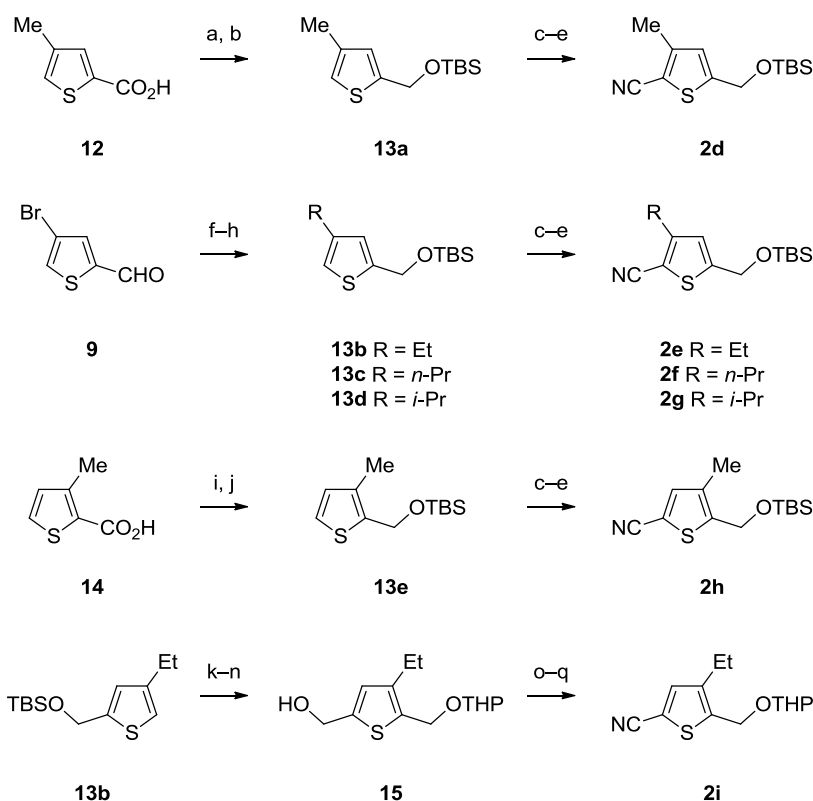


Reagents and conditions: (a) NaBH₄, MeOH (quant.). (b) TBSCl, imidazole, DMF (quant.). (c) CuCN, DMF (58% for **2a**, 56% for **2c**). (d) TBSCl, imidazole, DMF (quant.). (e) *n*-BuLi, THF, then DMF (33%). (f) NH₂OH·HCl, Et₃N, CH₂Cl₂-MeOH. (g) DCC, toluene, 90 °C (89%, 2 steps).

Scheme 2.2

構造活性相関については後に記載 (Table 2.2)するが、ベンゼン環からチオフエン環への置換は有効であったため、チオフエン環上の置換基について詳細な検討を行った。Scheme 2.3 に示す方法でチオフエン中間体 **2d–i** を合成し、構造最適化を行った。**2d** については市販のチオフエンカルボン酸 **12** より出発し、ボラン還元、TBS 基による保護を経て **13a** とし、続いてチオフエン 5 位へのホルミル基の導入、オキシム化を経由してニトリル基を導入した。**2e–g** については、ニッケル触媒を用いた Grignard 試薬とのクロスカップリング反応により、各種アルキル基を導入し **13b–d** を得、その後は **2d** と同様に

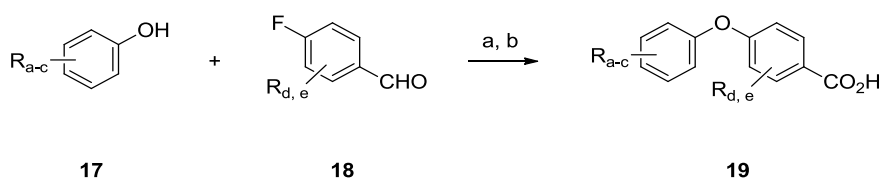
オキシム化を経由したニトリル基の導入を行った。**2h** については、市販のチオフエンカルボン酸 **14** より出発し、水素化アルミニウムリチウムによる還元、TBS 基による保護を経て、その後は同様なルートにて調製した。最後に **2i** については、**2e** の合成中間体である **13b** より出発し、チオフエン 5 位へのホルミル基の導入、ホルミル基の還元により生じた一級アルコール基を THP 基にて保護した後、TBS 基を脱保護して **15** とした。続いて PDC 酸化によりアルデヒドとし、オキシム化・脱水を経てニトリル **2i** とした。



Reagents and conditions: (a) BH_3 , THF. (b) TBSCl, imidazole, DMF (67%, 2 steps). (c) *n*-BuLi, DMF, THF (59–89%). (d) $\text{NH}_2\text{OH}\cdot\text{HCl}$, Et_3N , CH_2Cl_2 -MeOH. (e) DCC, toluene, 90 °C (69–quant., 2 steps). (f) NaBH_4 , MeOH. (g) TBSCl, imidazole, DMF (quant., 2 steps). (h) EtMgBr , $\text{NiCl}_2(\text{dppp})$, Et_2O (95%) for **13b**. *n*-PrMgBr, $\text{NiCl}_2(\text{dppp})$, Et_2O (66%) for **13c**. isopropenyl magnesium bromide, $\text{NiCl}_2(\text{dppp})$, Et_2O (86%), then H_2 , $\text{RhCl}(\text{PPh}_3)_3$, benzene (86%) for **13d**. (i) LiAlH_4 , THF. (j) TBSCl, imidazole, DMF (43%, 2 steps). (k) *n*-BuLi, DMF, THF (86%). (l) NaBH_4 , MeOH (94%). (m) 3,4-dihydro-2*H*-pyran, *p*-TsOH. (n) TBAF, THF. (o) PDC, MS4A, CH_2Cl_2 (78%, 3 steps). (p) $\text{NH}_2\text{OH}\cdot\text{HCl}$, Et_3N , CH_2Cl_2 . (q) DCC, toluene, 90 °C (95%, 2 steps).

Scheme 2.3

一方、リード化合物 **1** の左側鎖である 4-フェニル-5-トリフルオロメチルチオフェン構造の変換に関して、4-フェノキシ安息香酸中間体 **19** を Scheme 2.4 に示す方法で調製した。各種 4-フルオロベンズアルデヒド **18** に対して塩基性条件下、フェノール **17** を作用させて S_NAr 反応によりビフェニルエーテルを調製後、Pinnick 酸化により各種カルボン酸 **19** を合成した。



Reagents and conditions: (a) K_2CO_3 , DMF, 100 °C. (b) NaClO_2 , KH_2PO_4 , 2-methyl-2-butene, THF-*t*-BuOH- H_2O (33%-quant., 2 steps).

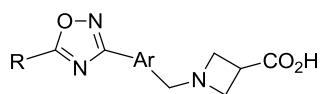
Scheme 2.4

2-4. 構造活性相関及び構造最適化

左側鎖及び内側芳香環について構造変換を行い、human S1P_1 アゴニスト活性 (hS1P_1) 及び選択性 ($\text{ratio} = \text{hS1P}_3 \text{ EC}_{50} / \text{hS1P}_1 \text{ EC}_{50}$) への影響を調べた (Table 2.2)。内側ベンゼン環からチオフェン環への変換 (**1** → **7a**) では S1P_1 アゴニスト活性は維持されることがわかった ($\text{hS1P}_1 \text{ EC}_{50} = 4.2 \text{ nM}$ for **1**, 6.5 nM for **7a**)。続いて左側鎖の検討へと移り、ビフェニル (**7b**, **7c**)、ベンジルエーテル (**7d**)、アルキルエーテル (**7e**)、ビフェニルエーテル (**7f**) へと変換したところ、ビフェニルエーテル誘導体 (**7f**) において、 S1P_1 アゴニスト活性を大きく損なうことなく、 $\text{S1P}_1/\text{S1P}_3$ 選択性が向上する傾向が認められた ($\text{hS1P}_1 \text{ EC}_{50} = 8.5 \text{ nM}$, $\text{ratio} = 541$ for **7f**)。そこで左側鎖をビフェニルエーテルに固定し、チオフェンの異性体 (**7f**, **7g**, **7h**) について精査したところ、化合物 **7h** において、 S1P_1 アゴニスト活性及び $\text{S1P}_1/\text{S1P}_3$ 選択性がともに向上することがわかった ($\text{hS1P}_1 \text{ EC}_{50} = 1.0 \text{ nM}$, $\text{ratio} = 900$ for **7h**)。

以上の結果から、アゴニスト活性、 S1P_1 選択性のバランスに優れた化合物 **7f** 及び **7h** の構造をテンプレートとして、更なる変換を行うこととした。二つのテンプレートのうち、先に見出していた **7f** から検討を開始した。

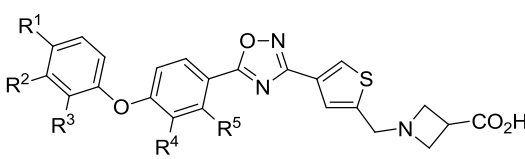
Table 2.2



Compound	R	Ar	γ -GTP EC ₅₀ (nM)		Ratio
			hS1P ₁	hS1P ₃	
1			4.2	1600	380
7a			6.5	800	123
7b			850	>20000	>23
7c			30	>20000	>666
7d			>20000	>20000	1
7e			60	>20000	>333
7f			8.5	4600	541
7g			34	>20000	>588
7h			1.0	900	900

化合物 **7f** ではビフェニルエーテル骨格上の各部位にそれぞれメチル基を導入した (Table 2.3)。その結果、残念ながら R¹ (**7i**)、R² (**7j**)、R³ (**7k**)、R⁴ (**7l**)、R⁵ (**7m**)のいずれにメチル基を導入した場合にも S1P₁ アゴニスト活性は低下し、S1P₁ 選択性の向上にも至らなかった。

Table 2.3

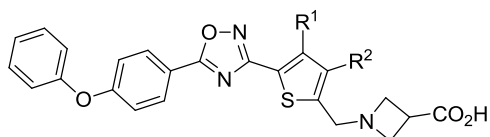


Compound	R ¹	R ²	R ³	R ⁴	R ⁵	γ -GTP EC ₅₀ (nM)		Ratio
						hS1P ₁	hS1P ₃	
7f	H	H	H	H	H	8.5	4600	541
7i	Me	H	H	H	H	110	12000	109
7j	H	Me	H	H	H	200	>20000	100
7k	H	H	Me	H	H	35	2000	57
7l	H	H	H	Me	H	21	3000	142
7m	H	H	H	H	Me	600	>20000	33

一方、もう一つのテンプレートである化合物 **7h** の骨格においては、上記 **7f** での検討結果を踏まえて、ビフェニルエーテル上ではなく、チオフェン環上へ置換基を導入することを優先した (Table 2.4)。その結果、R¹ へメチル基を導入した場合 (**8a**)において、S1P₁ アゴニスト活性を大きく損なうことなく、S1P₁ 選択性を大幅に向上できることを見出した (hS1P₁ EC₅₀ = 11 nM, ratio = >1818)。この結果に着目し、チオフェン環上 R¹, R² に種々のアルキル基を導入し、活性の検討を行った。置換基 R¹ へエチル基 (**8b**)、*n*-プロピル基 (**8c**)、イソプロピル基 (**8d**)と嵩高さの異なる置換基をそれぞれ導入したところ、エチル基を導入した化合物 **8b** において、4.0 nM と優れた S1P₁ アゴニスト活性、5000 倍以上とこれまでで最も高い S1P₁ 選択性を示すことがわかった。エチル基よりも嵩高い *n*-プロピル基 (**8c**)やイソプロピル基 (**8d**)では、活性、選択性ともに低下するため、エチル基が最適な置換基であることが示唆された。一方、R² へもメチル基 (**8e**)、エチル基 (**8f**)を導入したが、S1P₁ アゴニスト活性自体が減弱傾向にあり、好適な位置ではなかった。

以上の結果から、優れた S1P₁ アゴニスト活性及び非常に高い S1P₁ 選択性を両立するエチルチオフェン誘導体 **8b** を見出すことができた。

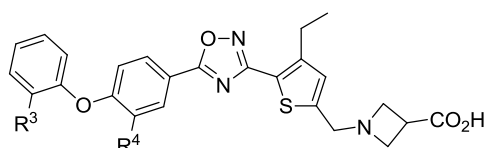
Table 2.4



Compound	R ¹	R ²	γ-GTP EC ₅₀ (nM)		Ratio
			hS1P ₁	hS1P ₃	
7h	H	H	1.0	900	900
8a	Me	H	11	>20000	>1818
8b	Et	H	4.0	>20000	>5000
8c	<i>n</i> -Pr	H	30	13000	433
8d	<i>i</i> -Pr	H	75	15000	200
8e	H	Me	25	>20000	>800
8f	H	Et	12	>20000	>1666

得られたエチルチオフェン誘導体 **8b** の骨格に基づいて、4-フェノキシフェニル基上の置換基について再度、詳細な検討を行った。既に得られていた Table 2.3 の構造活性相関を参考とし、置換基許容性が示唆されていた R³ 及び R⁴ へ置換基を導入し、両位置の置換基効果を調べた。Table 2.5 に、*in vitro* 評価に加えて、*in vivo* での評価結果を記載した。当時、Fingolimod は、その適応症として臓器移植時の免疫抑制剤としても臨床試験が行われていたことから、*in vivo* での評価は臓器移植の動物実験モデルとされるラット HvGR (Host versus Graft Reaction)を用いた。

Table 2.5



Compound	R ³	R ⁴	γ-GTP EC ₅₀ (nM)		Rat HvGR	
			hS1P ₁	hS1P ₃	ID ₅₀ (mg/kg) or	% inhibition (at 1 mg/kg)
8b	H	H	4.0	>20000	0.407	NS
8g	F	H	8.5	>20000	0.369	NS
8h	Cl	H	6.5	>20000	0.461	NS
8i	MeO	H	4.0	15000	NT	74%
8j	Me	H	3.0	4500	NT	35%
8k	Et	H	6.5	10000	NT	62%
8l	<i>n</i> -Pr	H	13	>20000	NT	56%
8m	<i>n</i> -Bu	H	9.0	>20000	NT	66%
8n	<i>i</i> -Pr	H	4.5	11000	NT	NT
8o	H	F	5.0	>20000	0.142	NS
8p	H	Cl	5.0	>20000	NT	49%
8q	H	MeO	14	>20000	NT	NT
8r	H	Me	7.5	6000	NT	NT

NT; Not tested. NS; Not shown.

R³については、フッ素原子 (**8g**)、塩素原子 (**8h**)、メトキシ基 (**8i**)、メチル基 (**8j**)を導入した場合に良好な S1P₁ アゴニスト活性を示した (EC₅₀ = 3.0–8.5 nM)。特に、フッ素 (**8g**)及び塩素 (**8h**)は **8b** と同等の高い S1P₁/S1P₃ 選択性を有しており、ラット HvGR においても強い薬効を示した。興味深いことに、エチル基 (**8k**)、*n*-プロピル基 (**8l**)、*n*-ブチル基 (**8m**)、イソプロピル基 (**8n**)といった幾分嵩高い置換基においても S1P₁ アゴニスト活性の維持が認められた。

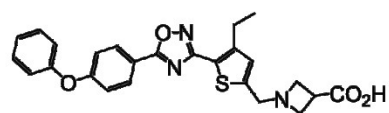
一方、R⁴についても、フッ素原子 (**8o**)、塩素原子 (**8p**)、メトキシ基 (**8q**)、メチル基 (**8r**)の導入は許容され、S1P₁ アゴニスト活性は維持された。これらのうち、フッ素 (**8o**)及び塩素 (**8p**)は良好な S1P₁/S1P₃ 選択性を示しており、**8o** はラット HvGR モデルにおいて極めて強い薬効を示した。

以上より得られた **8b**, **8g**, **8h**, **8o** の中から、安全性面、結晶性、吸湿性、化学的安定性といった物理化学的性質等 (データ不掲載)を考慮し、最終的には **8b** を社内開発候補化合物 CS-2100 として選抜した。

2-5. S1P 受容体ホモロジーモデルを用いたドッキングスタディによる考察

CS-2100 (**8b**)を見出す過程において、チオフェン環上へのエチル基導入により S1P₁/S1P₃ 選択性が 900 倍から 5000 倍以上へと飛躍的に向上するという興味深い知見が得られた (Table 2.4)。このエチル基の効果について考察するため、計算を用いたドッキングスタディを実施した。S1P 受容体は Kolakowski の分類上、クラス A (ロドプシンファミリー) の G タンパク質共役型受容体に属しており^[47]、これまでにクラス A に属する複数の G タンパク質共役受容体に関する有用なホモロジーモデルが、X 線結晶構造の情報が既知であるロドプシンを用いて作成されている^[48]。本研究を行っていた当時、S1P 受容体の X 線結晶構造の報告はなされていなかったため、筆者らもウシロドプシンの X 線結晶構造情報に基づいて、S1P₁ のホモロジーモデルを作成した。さらに、作成した S1P₁ のホモロジーモデルに基づいて S1P₃ のホモロジーモデルも併せて作成した。Figure 2.3 (左図)は CS-2100 (**8b**)が S1P₁ の活性サイトに結合している様子を表している。一方、Figure 2.3 (右図)は CS-2100 (**8b**)が S1P₃ の活性サイトに結合している様子を表しており、いずれの図においても中心にチオフェン環、右方向にアゼチジンカルボン酸部位、左方向にビフェニルエーテル部位が位置している。右図、左図いずれにおいても極性部位であるアゼチジンカルボン酸は Glu121 及び Arg120 と有利な相互作用をしており、この相互作用は天然リガンドである S1P の認識に重要であることが知られている^[49a]。

エチルチオフェン部位の周辺に着目すると、S1P₁ の活性サイト (Figure 2.3 左図)では、その近傍には Leu276 が位置している。一方、S1P₃ の活性サイト (Figure 2.3 右図)では、Leu276 に代わって Phe263 が位置しており、Phe263 のフェニル基とチオフェン環上のエチル基との間で立体的な反発が認められた。この立体的要因により CS-2100 (**8b**)が S1P₁ へのアゴニスト活性を維持する一方で、S1P₃ に対しては親和性を示すことなく、高い S1P₁/S1P₃ 選択性を示した理由であると考えられる。他のグループによって行われた同様なホモロジーモデルによるドッキングスタディにおいても Leu276/Phe263 の残基の違いによる S1P₁/S1P₃ 選択性への影響が報告されている^[49b, c]。さらに近年 S1P₁ の X 線結晶構造が報告され^[50]、本結晶構造に基づいたドッキングスタディにおいても、同様であることが認められた^[51]。



CS-2100 (8b)

S1P₁ : 4.0 nM

S1P₃ : >20000 nM

活性比 : >5000

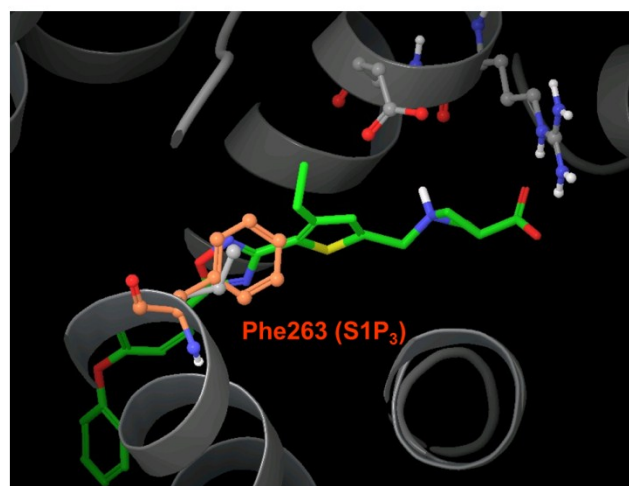
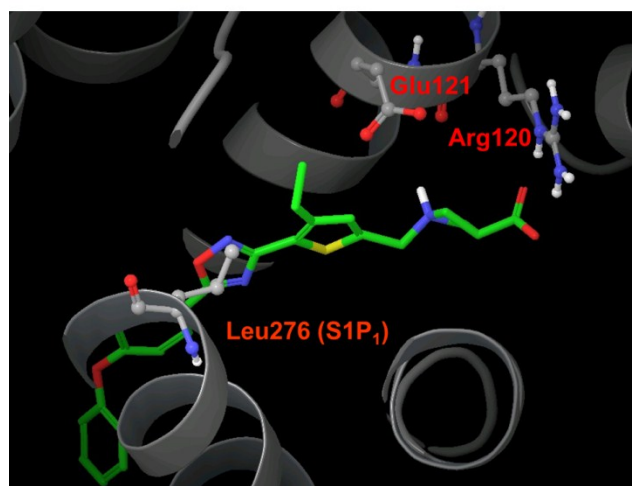


Figure 2.3

ところで、Table 2.5 において、ビフェニルエーテル上 R³へ *n*-プロピル基 (**8l**)や *n*-ブチル基 (**8m**)といった比較的嵩高い置換基を導入した誘導体においても良好な S1P₁アゴニスト活性が保持されていた。これら結果について考察するため、*n*-ブチル誘導体 (**8m**)と S1P₁ のホモロジーモデルのドッキングスタディを試みた (Figure 2.4)。その結果、分子全体としては CS-2100 (**8b**)の際と同様な結合をしていたが、**8m** のビフェニルエーテル上の *n*-ブチル基は Val132、Leu128、Phe205、Val209、Phe265 及び Leu213 により構成される脂溶性サブポケットに収容されていることが認められた。この脂溶性サブポケットが存在するため、嵩高い置換基を有する **8l** や **8m** においても S1P₁アゴニスト活性が維持されたことが示された。

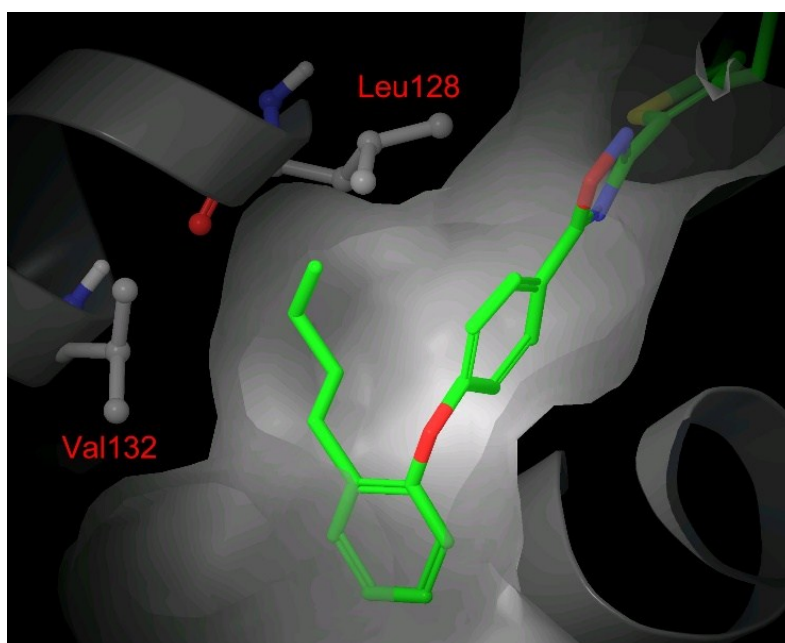


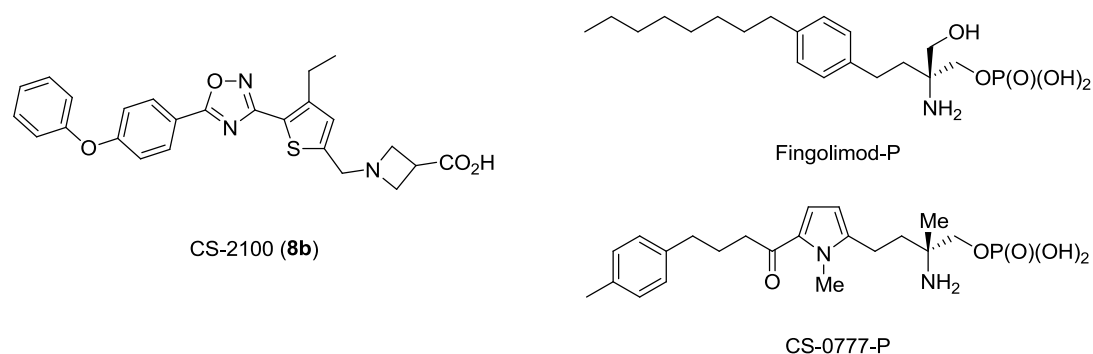
Figure 2.4

2-6. CS-2100 (8b)の詳細評価

2-6-1. S1P₁ アゴニスト活性及び S1P₁/S1P₃ 選択性の比較

Fingolimod-P 及び CS-0777-P を対照化合物として、CS-2100 (8b)の S1P₁ 及び S1P₃ へのアゴニスト活性 (Rat 及び Human)を比較した (Table 2.6)。CS-0777-P は Rat 及び Human の S1P₁ に対してそれぞれ EC₅₀ = 1.8 nM 及び 1.1 nM と強いアゴニスト活性を示す。そして Human の S1P₁/S1P₃ 選択性は 320 倍であり Fingolimod-P の 9 倍と比較して高い選択性を有する。一方、CS-2100 (8b)は Rat 及び Human の S1P₁ に対してそれぞれ EC₅₀ = 1.5 nM 及び 4.0 nM、human の S1P₁/S1P₃ 選択性は 5000 倍以上で両対照化合物と比較して非常に高い選択性を有していることが特徴である。なお、CS-2100 (8b)の他の S1P 受容体に対するアゴニスト活性は、S1P₂ (EC₅₀ = >20000 nM)、S1P₄ (EC₅₀ = 58 nM)、S1P₅ (EC₅₀ = 17 nM)であった。

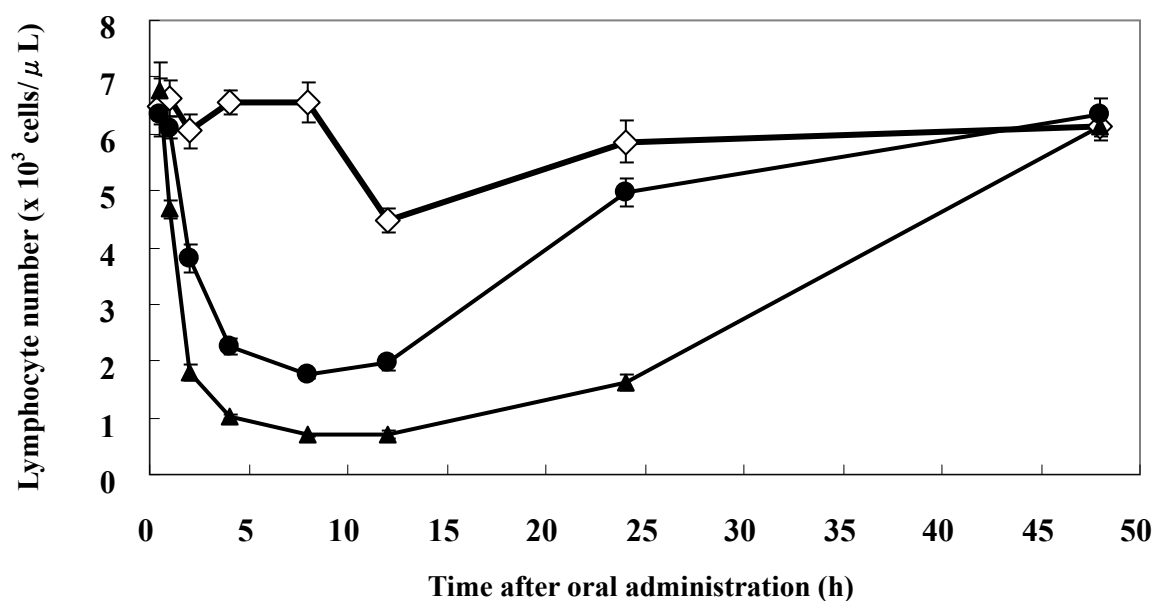
Table 2.6



Compound	EC ₅₀ (nM)				Selectivity (human S1P ₁ vs S1P ₃)
	Rat		Human		
	S1P ₁	S1P ₃	S1P ₁	S1P ₃	
Fingolimod-P	0.29	1.3	0.37	3.3	9
CS-0777-P	1.8	200	1.1	350	320
CS-2100 (8b)	1.5	7400	4.0	>20000	>5000

2-6-2. リンパ球減少試験

次にラットにおけるリンパ球減少試験を行った。Lewis ラットにおいて、CS-2100 (8b)を経口、単回 (0.1 mg/kg または 1 mg/kg)にて投与し、一群あたりの個体数は 5 として、投与後の各時間における末梢血リンパ球数を測定した (Figure 2.5)。縦軸はリンパ球数を表し、横軸は化合物投与後の経過時間を示している。非投与群 (◇)、0.1 mg/kg (●)、1 mg/kg (▲)と用量依存的にかつ強い末梢リンパ球減少作用が確認され、CS-2100 (8b)投与 8 時間後には末梢血リンパ球数は非投与群に対して、27% (0.1 mg/kg)、11% (1 mg/kg)へと減少した。減少した末梢リンパ球数は、投与 24–48 時間後には、非投与対照群の水準へと回復した。一方、CS-0777 では投与 48 時間後において 30% (0.1 mg/kg)、72% (1 mg/kg)であることがわかっており^[45]、CS-2100 (8b)は CS-0777 に比較してより早く回復することが示された。

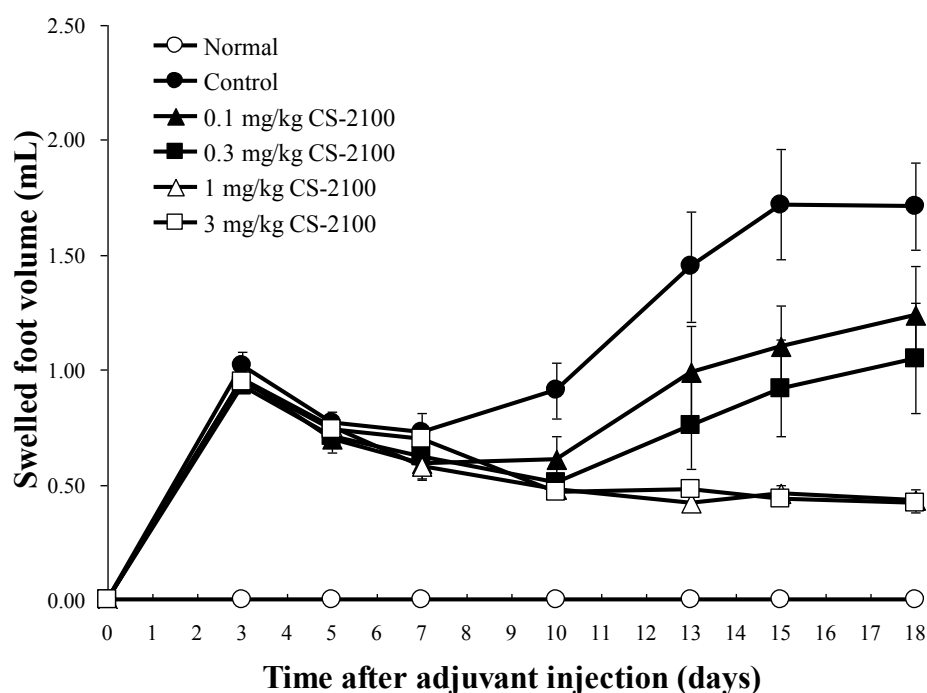


Effects of a Single Oral Dose of CS-2100 (8b) on Lymphocyte Counts in Rats. Vehicle (1% MC solution, ◇), 0.1 mg/kg (●), or 1 mg/kg of CS-2100 (8b) (▲) was orally administered to rats. The rats were anesthetized and abdominally dissected 0.5 h, 1 h, 2 h, 4 h, 8 h, 12 h, 24 h, and 48 h after oral administration. Lymphocyte numbers are shown as mean \pm SE.

Figure 2.5

2-6-3. ラットアジュバント関節炎

アジュバント関節炎モデルは自己免疫疾患の一つである関節リウマチ (RA)の病態モデルとして知られ、抗リウマチ薬や抗炎症薬等の評価に広く用いられている。このモデルは、牛酪菌の死菌体等を含む流動パラフィン (完全フロイントアジュバント)を足蹠の皮内もしくは皮下に投与することにより、四肢に関節炎を誘発させるものである。一般的にラットが用いられ、アジュバント投与後 10 日ほどで全身の関節炎症状が認められ、関節部位の腫脹や疼痛、関節軟骨の破壊といったヒトの関節リウマチに類似した症状を呈する。本モデルを用いて、CS-2100 (8b)の抗リウマチ作用について評価を行った。通常のラットに対して vehicle を投与し、一方、アジュバント投与群に対しては vehicle (control)、または CS-2100 (8b)を 0.1, 0.3, 1, 3 mg/kg の用量で一日一回、17 日間、経口にて投与した (Figure 2.6)。縦軸はアジュバントを投与した右後肢部位の腫脹体積を表し、横軸はアジュバント投与後の経過日数を示している。CS-2100 (8b)は 0.1 mg/kg より用量依存的な関節炎抑制作用を示し、18 日目における ID₅₀ は 0.44 mg/kg と本モデルにおいて良好な薬効を示すことが認められた。



Time Course of the Swelled Foot Volume of the Rats with Induced Adjuvant Arthritis. Swelled foot volumes are shown as mean \pm SE

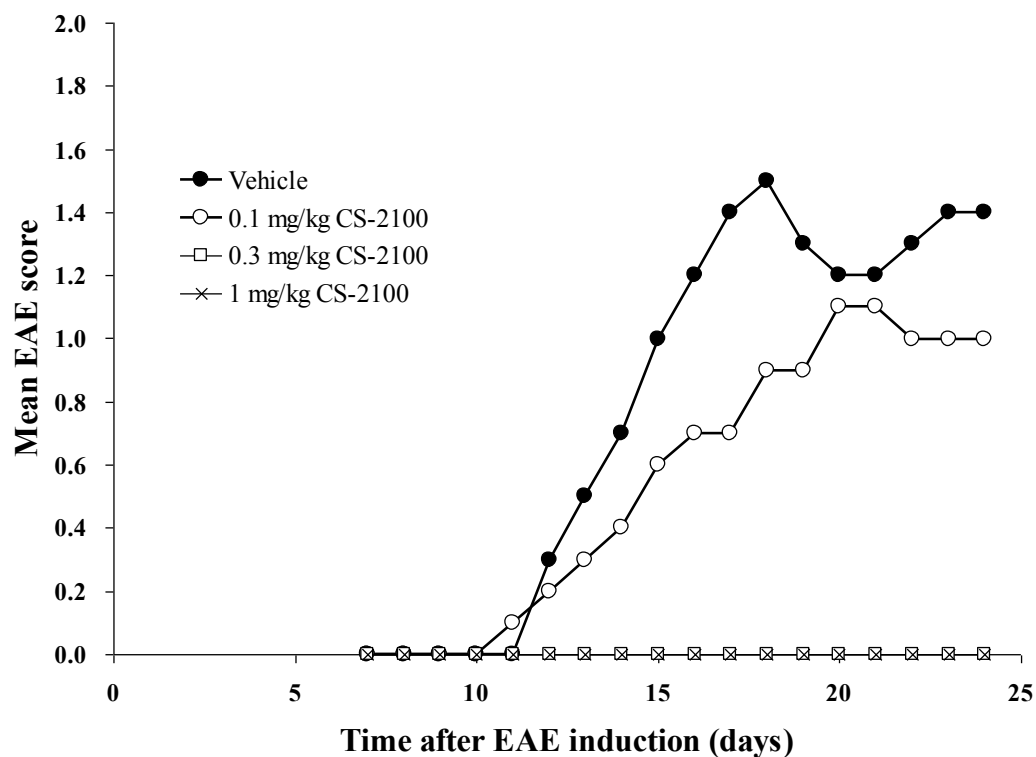
Figure 2.6

2-6-4. マウス EAE 試験

次に実験的自己免疫性脳脊髄炎モデル (EAE, Experimental Autoimmune Encephalomyelitis)を用いた薬効の評価を行った。EAE は、中枢神経組織由来の抗原やペプチドを注射することにより多発性硬化症に似た脳脊髄炎を発症する自己免疫疾患モデルであり、非臨床において多発性硬化症の病態モデルとして広く使用されている^[52]。具体的には、マウスに対して EAE 誘導剤として、MOG35-55 すなわち、脳の炎症を惹起するペプチドとともに、免疫応答の増強をきたすアジュバントを混和したものを注射し、さらに脳の炎症を惹起する百日咳毒を投与する。EAE 誘導剤投与 10 日から 14 日経過すると、自己免疫性の脳脊髄炎に由来する神経症状がマウスの尾より始まり、後肢、前肢、全体へと段階的に進行する。

進行する神経症状を各段階に分け、臨床スコアを正常な状態を 0、尾の弛緩を 1、後肢の麻痺等を 2、後肢完全麻痺を 3、四肢麻痺を 4、死亡を 5 とした。CS-2100 (8b)は一日一回経口、0.1, 0.3, 1 mg/kg の用量で投与した。EAE 誘導剤投与 7 日後より 24 日後まで毎日、スコアを測定し、一群あたりの個体数を 6 として、その平均を算出した (Figure 2.7)。

CS-2100 (8b)を投与していない群では 12 日経過後よりスコアの増加が始まり、平均スコアは 1.6 程度にまで到達した。一方、CS-2100 (8b)を 0.1 mg/kg 投与した場合では、非投与群とおおよそ同時期よりスコアが増加したが、非投与群と比較して、抑制作用が認められた。そして、0.3, 1 mg/kg ではスコアは大幅に減少し神経症状の抑制が認められ、CS-2100 (8b)は本モデルにおいても良好な薬効を示すことが認められた。

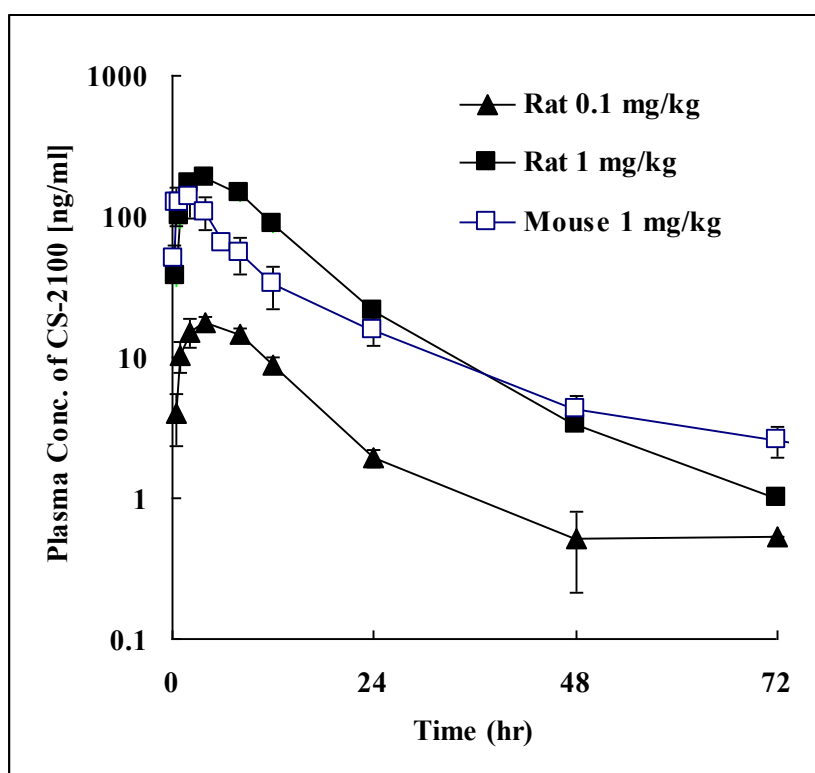


Time Course of Mean EAE Scores. The EAE score was evaluated daily from Day 7 to Day 24 in accordance with the following criteria: 0, normal; 1, flaccid tail without difficulty in picking themselves up; 2, hindlimb weakness defined as paralysis of only one hindlimb and/or difficulty in picking themselves up; 3, paralysis of both hindlimbs; 4, quadriplegia; 5, dead.

Figure 2.7

2-6-5. CS-2100 (8b)の薬物動態について

次にラット及びマウスにおいて薬物動態試験を実施した。CS-2100 (8b)の血中濃度-時間プロファイルを Figure 2.8 に、各種薬物動態パラメータについては Table 2.7 に示す。ラットにおいては 0.1 mg/kg 投与時において平均最高血中濃度 (C_{max})は 17.4 ng/mL、平均薬物血中濃度-時間曲線下面積 (AUC_{0-72h})は 268 ng*h/mL、そして 1 mg/kg 投与時の C_{max} は 186 ng/mL、 AUC_{0-72h} はそれぞれ 2670 ng*h/mL であり、0.1 及び 1 mg/kg において用量依存的な血中暴露が認められた。一方、マウスでは 1 mg/kg 投与時の C_{max} は 135 ng/mL、 AUC_{0-72h} は 1540 ng*h/mL であり、CS-2100 (8b)はラット、マウスいずれの動物種に対しても血中暴露を示すことが確認された。なお、1 mg/kg 投与時の平均半減期 ($T_{1/2}$)はラットで 8.73 時間、マウスで 13.9 時間であり、平均最高血中濃度到達時間 (T_{max})はそれぞれ 4.0 時間及び 2.0 時間であった。



Plasma Concentrations of CS-2100 (8b) after oral administration to rats (0.1 and 1 mg/kg) and mice (1 mg/kg). Each value is the mean \pm standard deviation of five animals in the study.

Figure 2.8

Table 2.7

PK parameters of CS-2100 (**8b**) after oral administration to rats and mice.

Species	Dose (mg/kg)	C_{\max} (ng/mL)	T_{\max} (h)	$T_{1/2}$ (h)	AUC _{0-72h} (ng*h/mL)
Lewis Rats	0.1	17.4	4.0	12.4	268
	1.0	186	4.0	8.73	2670
C57BL Mice	1.0	135	2.0	13.9	1540

2-7. まとめ

以上、本章では CS-2100 (**8b**)について構造最適化、薬理プロファイル及び薬物動態について述べた。CS-2100 (**8b**)は、良好な S1P₁ アゴニスト活性及び高い S1P₁/S1P₃ 選択性を併せ持っており (hS1P₁ EC₅₀ = 4.0 nM, human S1P₁ vs S1P₃ = >5000)、目的とするプロファイルを有する化合物を取得することができた。*In vivo* 評価では、ラットにおいて用量依存的かつ強いリンパ球減少作用を示し、ラット HvGR、ラットアジュバント関節炎及びマウス EAE といった各種の前臨床動物病態モデルにおいて良好な薬効が認められた。なお、本論文にデータは示していないが、げっ歯類において徐脈作用が著しく軽減していることを確認している。本化合物の高い S1P₁/S1P₃ 選択性は、ドッキングスタディの結果からチオフェン環上のエチル基と S1P₃ 活性サイトにおける Phe263 残基との立体的反発が大きく寄与していることが示唆されている。この知見を活用し、CS-2100 (**8b**)の構造を基として更なる誘導体展開を行っており、その詳細は次章にて述べている。

第3章 1,3-チアゾール型 S1P₁ 作動薬の探索研究

3-1. はじめに

第2章において、CS-2100 (**8b**)を見出した経緯及び生物学的プロファイル等について述べてきた。

CS-2100 (**8b**)は 5000 倍以上の S1P₁/S1P₃ 選択性を有し、ラット HvGR、ラットアジュバント関節炎及びマウス EAE といった各種 *in vivo* 試験において良好な結果を示した。しかし、代謝物の研究過程において懸念される所見が新たに認められた。

経口投与時のラット及びサルの *in vivo* における CS-2100 (**8b**)の代謝物解析において、血漿中の主要な代謝物の一つに 4-フェノキシ安息香酸 (4-PBA)が同定された (Figure 3.1)。詳細な解析の結果、CS-2100 (**8b**)は腸内細菌による代謝を受けて 1,2,4-オキサジアゾール環の N-O 結合が還元的に切断され 4-PBA を生成することが示唆された (データ不掲載)。なお、肝ミクロソームにおける *in vitro* の代謝安定性試験においては 4-PBA の発生や 1,2,4-オキサジアゾール環の分解は示唆されていなかった。

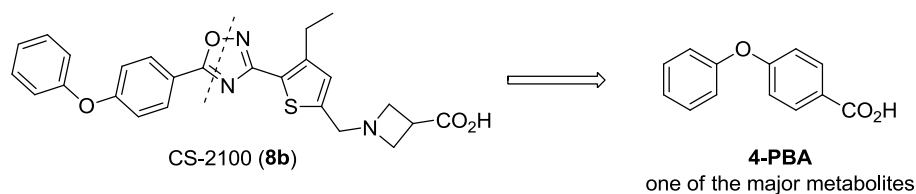


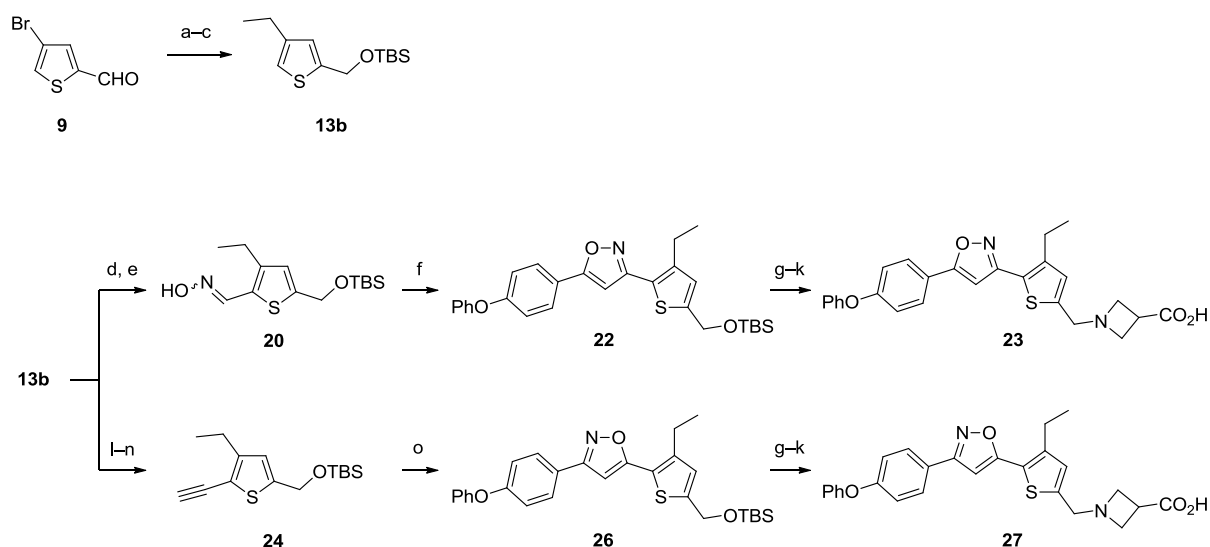
Figure 3.1

1,2,4-オキサジアゾール環は物理化学的性質として適度な極性や水素結合受容能を有している。そのため、メディシナルケミストリーにおいて、ファーマコフォアとしての利用や芳香族性のリンカーとして活用される他、加水分解酵素に対して安定であることからエステルやアミド等の生物学的同位体として利用される等、ドラッグデザインの観点から幅広く用いられてきた [53]。肝臓や腸内細菌叢において 1,2,4-オキサジアゾール環が還元的な環開裂を受けるという例は近年になって少しずつ蓄積されつつあるものの [54]、未だ本環開裂による生体内での影響については十分な文献的知見はなく薬物動態及び薬物動力学について予測できない種差や個体差の発生の可能性 [54b]、または何らかの毒性発現の可能性が懸念された [54a]。さらに本環開裂により生ずる 4-PBA は半減期が長く体内に長時間残存すると

ともに、弱いながら PPAR α の活性化作用が認められていた（データ不掲載）。以上のことから、CS-2100 (8b)の構造を基として、1,2,4-オキサジアゾール環の使用を回避し、中心環の開裂を防ぐことを指向した新たな骨格の探索を行うこととした。最も直截的な解決策として、1,2,4-オキサジアゾール環を他のヘテロ環に変換することとした。

3-2. 各種誘導体合成

合成ルートを **Scheme 3.1** および **Scheme 3.2** に示す。誘導体合成を効率化するため、鍵中間体として4-エチルチオフェン中間体 **13b** を設定した。**13b** は市販の4-ブromo-2-チオフェンカルバルデヒド (**9**) より出発し、水素化ホウ素ナトリウムによりホルミル基を還元した後、生じた一級水酸基を TBS 基により保護し、続いてニッケル触媒存在下、エチルマグネシウムブロミドを作用させてエチル基を導入することで、3 工程、89%の収率にて調製した。**13b** はチオフェン環 5 位へ種々の官能基を導入することが可能であり、ヘテロ環形成反応の前駆体となる多様なチオフェンユニット (**20**, **24** in **Scheme 3.1**, **28**, **39** in **Scheme 3.2**) が調製できた。



Reagents and conditions: (a) NaBH_4 , MeOH. (b) TBSCl, imidazole (quant., 2 steps). (c) $\text{NiCl}_2(\text{dppp})$, EtMgBr (95%). (d) *n*-BuLi, DMF (86%). (e) $\text{NH}_2\text{OH}\cdot\text{HCl}$, Et_3N , CH_2Cl_2 , MeOH (95%). (f) NCS, pyridine, CHCl_3 , then 1-ethynyl-4-phenoxybenzene (**21**), Et_3N , CHCl_3 (73%). (g) TBAF, THF. (h) SOCl_2 , toluene. (i) methyl azetidine-3-carboxylate HCl, *i*-Pr₂NEt, CH_3CN (84–90%, 3 steps). (j) aq. NaOH, EtOH. (k) oxalic acid (76% for **23** and **27**, 2 steps, both compounds were solidified as oxalates). (l) *n*-BuLi, THF, then I_2 (72%). (m) trimethylsilylacetylene, CuI, $\text{Pd}(\text{PPh}_3)_4$, Et_3N (75%). (n) K_2CO_3 , MeOH (81%). (o) 4-phenoxybenzonitrile *N*-oxide (**25**), Et_3N , CHCl_3 (59%).

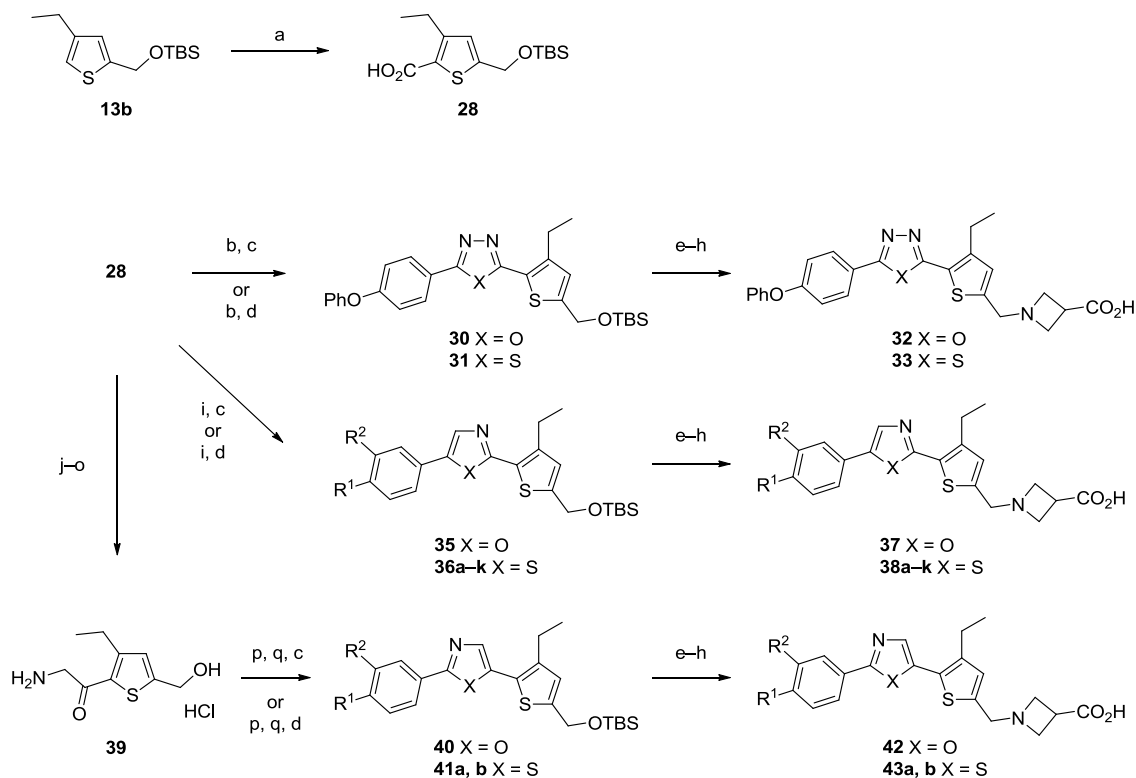
Scheme 3.1

オキシム中間体 **20** は **13b** に対して *n*-BuLi、DMF によりチオフェン 5 位をホルミル化し、続いてトリエチルアミン存在下、ヒドロキシアミン塩酸塩を作用させて調製した。**20** に対して塩基性条件下、NCS を作用させることで調製されるニトリル *N*-オキシドと 1-エチニル-4-フェノキシベンゼン (**21**) との 1,3-双極子環化反応により **22** を得た。**22** に対して TBAF を作用させて TBS 基を除去した後、生じた一級水酸基を塩素原子へと変換し、続いてアゼチジンカルボン酸メチルを求核的に導入し、最後にメチルエステル部位を加水分解することで 1,2-オキサゾール誘導体 **23** を合成した。

アセチレン誘導体 **24** は、**13b** に対して *n*-BuLi、ヨウ素を作用させてチオフェン環 5 位をヨウ素化した後、菌頭カップリング反応を行い調製した。続いて市販の 4-フェノキシベンズアルデヒドから調製される 4-フェノキシベンゾニトリル *N*-オキシド (**25**) と **24** の 1,3-双極子環化反応により **26** へと誘導した。その後、**23** の合成過程と同様に TBS 基の除去、水酸基の脱離基への変換、アゼチジンカルボン酸メチルの導入、メチルエステルの加水分解を経て、**23** の構造異性体である **27** を合成した。

カルボン酸誘導体 **28** は、**13b** に対して *n*-BuLi、CO₂ (ドライアイス) を作用させることで調製した。**28** を経由することで、さらに多様な複素環誘導体が合成可能である (**32**, **33**, **37**, **38a–k**, **42**, **43a, b**)。**28** と 4-フェノキシベンズヒドラジド (**29**) を DCC により縮合した後、トリエチルアミン存在下、Burgess 試薬を作用させることで、1,3,4-オキサジアゾール環を構築し、アゼチジンカルボン酸ユニットの導入工程を経て 1,3,4-オキサジアゾール誘導体 **32** を合成した。なお、Burgess 試薬の代わりに Lawesson 試薬を用いることで 1,3,4-チアジアゾール誘導体 **33** が調製できた^[55]。一方、**28** を種々の 2-アミノアセトフェノン化合物と縮合後、Burgess 試薬を作用させることで、1,3-オキサゾール誘導体 **37** へと誘導した。こちらも Burgess 試薬の代わりに Lawesson 試薬を用いることで 1,3-チアゾール誘導体 **38a–k** を合成できた^[55]。

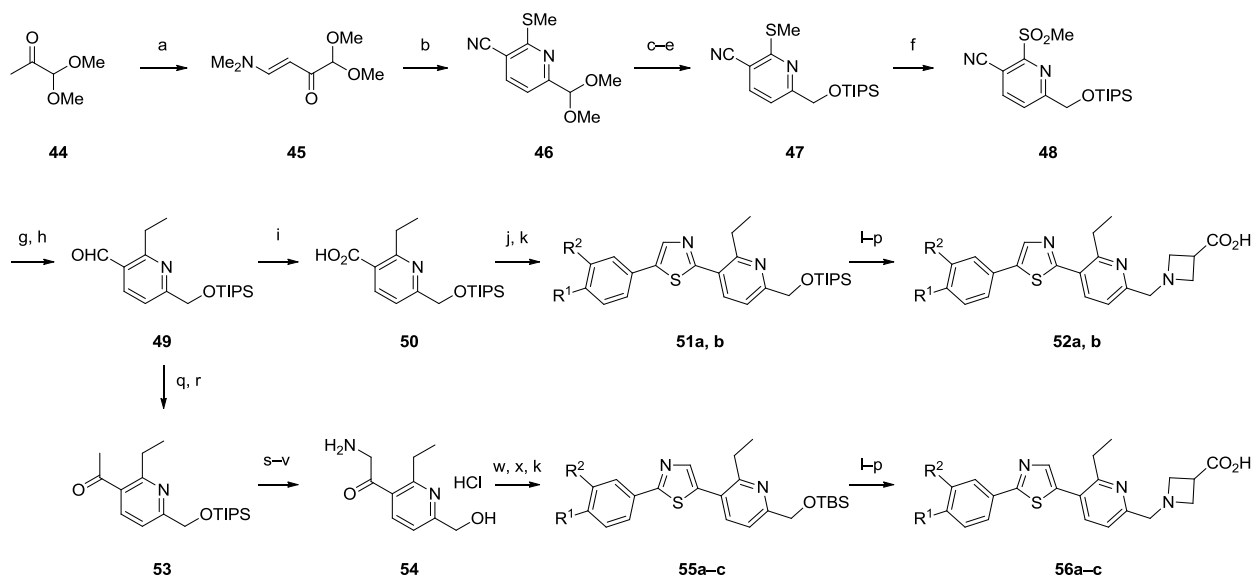
α -アミノケトン誘導体 **39** は、**28** を Weinreb アミドへと変換し、MeLi を作用させてチオフェノン誘導体とした後、トリメチルシリルエノールエーテルを経由して α -ブロモケトンへと誘導した。続いて NaN(CHO)₂ を作用させて窒素原子を導入し、最後に塩酸で処理することで **39** を合成した。**39** と市販または別途調製した安息香酸類 **19a, b** を縮合した後、Burgess 試薬を作用させることで **37** の異性体となる **42** を合成した。こちらも Burgess 試薬の代わりに Lawesson 試薬を用いることで **38** の異性体である **43a, b** を合成した。



Reagents and conditions: (a) *n*-BuLi, THF then CO₂ (79%). (b) 4-phenoxybenzohydrazide (**29**), DCC (46%). (c) Burgess reagent, Et₃N, CH₃CN, 80 °C (64–94%). (d) Lawesson's reagent, pyridine, toluene, 100 °C (70–97%). (e) TBAF, THF. (f) CBr₄, PPh₃, CH₂Cl₂ or SOCl₂, cat. DMF, toluene. (g) methyl azetidine-3-carboxylate HCl, *i*-Pr₂NEt, CH₃CN (63–quant., 3 steps). (h) aq. NaOH, EtOH (60–92%). (i) EDCI, HOBT, various aminoacetophenones (**34b–k**), Et₃N, CH₂Cl₂ (57–80% for **36b–k**) or CDMT, NMM, **34a**, THF (81% for **36a**). (j) MeNHOMe, EDCI, *i*-Pr₂NEt, CH₂Cl₂. (k) MeLi, Et₂O (51%, 2 steps). (l) NaHMDS, TMSCl, THF. (m) NBS, THF (83%, 2 steps). (n) NaN(CHO)₂, CH₃CN. (o) HCl, EtOH (42%, 2 steps). (p) EDCI, HOBT, benzoic acids (**19a, b**), Et₃N, CH₂Cl₂. (q) TBSCl, imidazole, DMF (76%, 2 steps).

Scheme 3.2

CS-2100 (**8b**)の部分構造である 4-エチルチオフエン構造は、第 2 章で述べたように高い S1P₁/S1P₃ 選択性を保つために重要な構造である。一方、予備的な検討から 4-エチルチオフエン構造を 6-エチルピリジン構造に置き換えた場合でも高い S1P₁/S1P₃ 選択性が保たれることがわかった (データ不掲載)。それゆえ、6-エチルピリジン誘導体についても合成した (Scheme 3.3)。化合物 **44** より出発し、2 工程を経てピリジン環を構築した後、適切な官能基変換を経て、ピリジンカルボキシアルデヒド中間体 **49** を調製した。**49** を亜塩素酸ナトリウムで処理することでカルボン酸 **50** とし、Scheme 3.2 において **38a–k** 合成時と類似の手法を経て **52a, b** を合成した。一方、**49** を α -アミノケトン誘導体 **54** へと導き、続いて Scheme 3.2 において **43a, b** 合成時と類似の手法を経ることで **56a–c** を合成した。



Reagents and Conditions: (a) *N,N*-dimethylformamide dimethylacetal, CH₃CN, reflux. (b) 2-cyanothioacetamide, MeONa then MeI (50%, 2 steps). (c) cat. DDQ, H₂O-CH₃CN (83%). (d) NaBH₄. (e) TIPSCl, imidazole (quant., 2 steps). (f) *m*-CPBA, EtOH (89%). (g) EtMgBr, THF (98%). (h) DIBAL, toluene (93%). (i) NaClO₂, KH₂PO₄, 2-methyl-2-butene (92%). (j) EDCI, HOBT, aminoacetophenones (**34c, d**), Et₃N, CH₂Cl₂ (60–79%). (k) Lawesson's reagent, pyridine, toluene, 100 °C (79–95%). (l) TBAF, THF. (m) SOCl₂, cat. DMF, toluene or CBr₄, PPh₃, CH₂Cl₂. (n) methyl azetidine-3-carboxylate HCl, *i*-Pr₂NEt, CH₃CN (66–82%). (o) aq. NaOH, EtOH. (p) oxalic acid (**54**–83%, 2 steps). (q) MeMgI, Et₂O (88%). (r) PDC, Celite, CH₂Cl₂ (96%). (s) NaHMDS, TMSCl, THF. (t) NBS, THF. (u) NaN(CHO)₂, CH₃CN. (v) HCl, EtOH (**54**%, 4 steps). (w) 3-methyl-4-(propan-2-yloxy)benzoyl chloride, NaHCO₃, EtOAc-water for **55a** or EDCI, HOBT, various benzoic acids (**19c, d**) for **55b, c**, Et₃N, CH₂Cl₂. (x) TBSCl, imidazole, DMF (61–80%, 2 steps).

Scheme 3.3

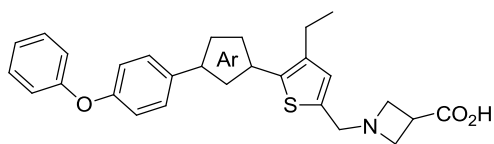
3-3. 構造活性相関及び構造最適化

まず、human S1P₁ 及び S1P₃ に対するアゴニスト活性を測定し、続いてラット HvGR を用いて *in vivo* での免疫抑制作用を評価した。

中心複素環に関する構造活性相関を Table 3.1 に示す。種々の複素環に変換した誘導体の中で、1,3-チアゾール誘導体 **38a** において強い S1P₁ アゴニスト活性及び良好な S1P₁/S1P₃ 選択性が認められた (hS1P₁ EC₅₀ = 4.5 nM, hS1P₃ EC₅₀ = 20000 nM)。 **38a** の異性体である **43a** では中程度の S1P₁ アゴニスト活性であり (hS1P₁ EC₅₀ = 35 nM)、両異性体間において活性差が認められた。1,3-チアゾール誘導体の異性体間において活性に同様な傾向があることは Merck のグループからも報告されている^[56]。一方、1,2-オキサゾール誘導体 **23**, **27** 及び 1,3,4-チアジアゾール誘導体 **33** においても中程度の S1P₁ アゴニスト活性が認められた。

ラット HvGR では、1,3-チアゾール誘導体 **38a** は 1 mg/kg で 42%阻害率と CS-2100 (**8b**)に比べて減弱したものの、評価した誘導体の中では最も高い免疫抑制作用を示した。一方、**43a** においても 25%阻害率と **38a** に次いで高い免疫抑制作用が認められた。なお、1,2-オキサゾール誘導体 **23**, **27** や 1,3,4-チアジアゾール誘導体 **33** では大きく減弱または免疫抑制作用が認められなかった。以上の検討から、1,3-チアゾール誘導体 **38a** 及びその異性体である **43a** を新たなテンプレートとして選抜し、左側ベンゼン環の置換基についてさらに検討を進めることとした。

Table 3.1



Compound	Ar	γ -GTP EC ₅₀ (nM)		Rat HvGR	
		hS1P ₁	hS1P ₃	ID ₅₀ (mg/kg) or	% inhibition (at 1 mg/kg)
CS-2100 (8b)		4.0	>20000	0.41	NS
23		22	>20000	NT	2% (\pm 11)
27		15	>20000	NT	No inhibition
32		54	>20000	NT	NT
33		25	>20000	NT	No inhibition
37		90	>20000	NT	NT
42		300	>20000	NT	NT
38a		4.5	>20000	NT	42% (\pm 5)
43a		35	>20000	NT	25% (\pm 9)

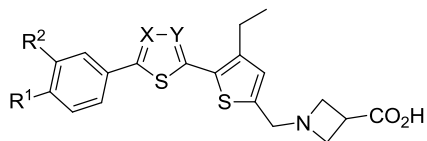
NT: Not tested. NS; Not shown.

左側ベンゼン環の置換基効果に関する構造活性相関を Table 3.2 に示す。左側ベンゼン環の置換基については R¹ 及び R² への置換基導入が有効であった。具体的には、置換基 R¹ ヘイソプロポキシ基 (*i*-PrO)を導入した **38b** は **38a** と比較して *in vitro* 活性が若干減弱しているにもかかわらず *in vivo* 薬効は保持されていることから、*in vivo* 薬効が向上傾向であった。一方、R² への置換基導入は、*in vitro* 活性及び *in vivo* 薬効のいずれにおいても非常に重要であることがわかった。具体的には、R² ヘメチル基 (**38c**)、エチル基 (**38d**)、*n*-プロピル基 (**38e**)またはイソプロピル基 (**38f**)といったアルキル基を導入したところ *in vitro* 活性は向上し、さらに *in vivo* 薬効が大きく向上した。特に、**38c** 及び **38d** では CS-2100 (**8b**)よりも強い薬効が認められた (ID₅₀ = 0.07 mg/kg for **38c**, 0.16 mg/kg for **38d**)。興味深いことに、*n*-プロピル基 (**38e**)では S1P₁/S1P₃ 選択性が大幅に減少しており、R² の置換基許容性に限界があることが示唆されている。R² ヘハロゲン原子を導入した **38g** (フッ素), **38h** (塩素)では、**38g** において良好な *in vivo* 薬効が認められた (ID₅₀ = 0.48 mg/kg)。

ここまでで最も薬効の強かった **38c** の構造を基に、置換基 R¹ についてさらに詳細な最適化を行った。R¹ ヘイソプロピル基 (**38i**)、(*S*)-*sec*-ブトキシ基 (**38j**)及び(*R*)-*sec*-ブトキシ基 (**38k**)をそれぞれ導入したところ、(*S*)-*sec*-ブトキシ基を導入した **38j** において良好な *in vivo* 薬効が認められた (ID₅₀ = 0.32 mg/kg)。一方、**38c** の異性体である **43b** でも良好な HvGR 抑制作用が認められた (ID₅₀ = 0.19 mg/kg)。

以上の結果から、*in vitro* 活性、*in vivo* 薬効ともに良好である化合物として R¹ にイソプロポキシ基を、R² にメチル基またはエチル基を導入した **38c**, **38d**, **43b** を取得することができた。

Table 3.2

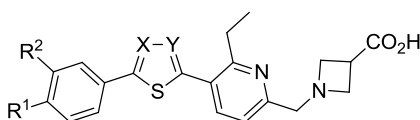


Compound	X	Y	R ¹	R ²	γ -GTP EC ₅₀ (nM)		Rat HvGR	
					hS1P ₁	hS1P ₃	ID ₅₀ (mg/kg) or	% inhibition (at 1 mg/kg)
CS-2100 (8b)					4.0	>20000	0.41	NS
38a	C	N	PhO	H	4.5	>20000	NT	42% (\pm 5)
38b	C	N	<i>i</i> -PrO	H	10	>20000	NT	52% (\pm 2)
38c	C	N	<i>i</i> -PrO	Me	3.4	>20000	0.07	NS
38d	C	N	<i>i</i> -PrO	Et	3.4	>20000	0.16	NS
38e	C	N	<i>i</i> -PrO	<i>n</i> -Pr	1.1	400	NT	73% (\pm 4)
38f	C	N	<i>i</i> -PrO	<i>i</i> -Pr	1.3	>20000	0.53	NS
38g	C	N	<i>i</i> -PrO	F	5.8	>20000	0.48	NS
38h	C	N	<i>i</i> -PrO	Cl	3.2	>20000	NT	54% (\pm 7)
38i	C	N	<i>i</i> -Pr	Me	3.5	>20000	1.1	NS
38j	C	N	(<i>S</i>)- <i>sec</i> -BuO	Me	6.0	>20000	0.32	NS
38k	C	N	(<i>R</i>)- <i>sec</i> -BuO	Me	8.0	>20000	NT	27% (\pm 7)
43b	N	C	<i>i</i> -PrO	Me	11	>20000	0.19	NS

NT; Not tested. NS; Not shown.

次にピリジン誘導体に関する構造活性相関を Table 3.3 に示す。Table 3.2 において得られた置換基の情報に基づき、R¹ にイソプロポキシ基、R² にメチル基を導入した。その結果、化合物 **52a** 及びその異性体である **56a** において、高い *in vitro* 活性を示すことがわかった (EC₅₀ = 5.5 nM for **52a**, 2.8 nM for **56a**)。そこで R¹ 及び R² の置換基について詳細な検討を行ったところ、強い *in vitro* 活性を保持し、*in vivo* 薬効の改善した **52b**, **56b**, **56c** を見出すことができた。

Table 3.3



Compound	X	Y	R ¹	R ²	γ-GTP EC ₅₀ (nM)		Rat HvGR	
					hS1P ₁	hS1P ₃	ID ₅₀ (mg/kg) or	% inhibition (at 1 mg/kg)
52a	C	N	<i>i</i> -PrO	Me	5.5	>20000	NT	39% (±9)
52b	C	N	<i>i</i> -PrO	Et	4.0	>20000	0.49	NS
56a	N	C	<i>i</i> -PrO	Me	2.8	>20000	NT	17% (±9)
56b	N	C	<i>i</i> -Bu	Me	4.1	>20000	0.64	NS
56c	N	C	<i>i</i> -Bu	Et	5.4	>20000	0.74	NS

NT; Not tested. NS; Not shown.

3-4. 薬物動態プロファイル及び腸内細菌に対する安定性の評価

代表的な化合物として **38c** 及び **52b** についてラット及びサルにおいて実施した薬物動態試験の結果を Table 3.4 に示す。チオフェン誘導体 **38c** はラット、3 mg/kg 単回経口投与にて $C_{\max} = 0.34 \mu\text{g/mL}$ 、 $\text{AUC}_{0-\infty} = 5.14 \mu\text{g} \cdot \text{h/mL}$ 、 $F = 70.6\%$ と高い血中暴露が確認され、サル、1 mg/kg 単回経口投与においても $C_{\max} = 0.63 \mu\text{g/mL}$ 、 $\text{AUC}_{0-\infty} = 8.69 \mu\text{g} \cdot \text{h/mL}$ 、 $F = >90\%$ と良好な血中暴露が認められた。また、**38c** はラットにおいて $T_{1/2} = 11.5 \text{ h}$ 、サルにおいて $T_{1/2} = 7.2 \text{ h}$ であった。一方、ピリジン誘導体 **52b** はサル、0.5 mg/kg 単回経口投与において $C_{\max} = 0.15 \text{ mg/mL}$ 、 $\text{AUC}_{0-\infty} = 3.73 \mu\text{g} \cdot \text{h/mL}$ 、 $F = 75.4\%$ と高い血中暴露を示したが、半減期は $T_{1/2} = 16.7 \text{ h}$ と **38c** と比較して長いことが示された。

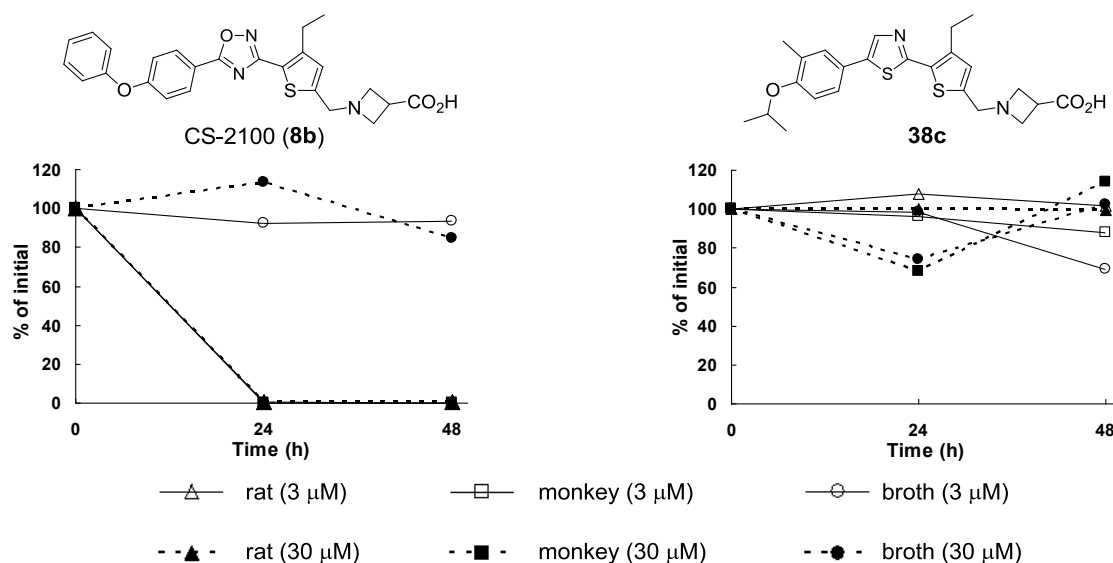
Table 3.4

Compound	Animals	Dose ^a (mg/kg)	C_{\max} (ug/mL)	T_{\max} (h)	$T_{1/2}$ (h)	$\text{AUC}_{0-\infty}$ (ug · h /mL)	F (%)	CL^b (ml/ (h · kg))	Vd^b (L/kg)
38c	Rat	3	0.34	5	11.5	5.14	70.6	6.72	5.37
38c	Monkey	1	0.63	4	7.2	8.69	>90	2.00	0.89
52b	Monkey	0.5	0.15	5	16.7	3.73	75.4	1.75	1.46

^a po administration, rat (n = 4), monkey (n = 2).

^b iv administration, rat (1 mg/kg, n = 2), monkey (0.5 mg/kg, n = 2)

続いて、ラット及びサルにおいて CS-2100 (**8b**)と **38c**の腸内細菌に対する化合物安定性を評価した。具体的には、嫌気性条件下においてラット盲腸内容物より調製した培養液、サル糞便より調製した培養液及びコントロールとして broth を用意した。CS-2100 (**8b**)または **38c**を 3 μM 及び 30 μM の溶液として調製し、上記 3 種類へ暴露させた。化合物安定性は暴露開始 24 時間後及び 48 時間後の化合物残存率を追跡することにより測定した。結果を Figure 3.2 に示す。左図では、CS-2100 (**8b**)は broth では 3 μM (○), 30 μM (●)のいずれにおいても分解を受けていないが、ラット盲腸内容物培養液 (△ or ▲)及びサル糞便培養液 (□ or ■)では 24 時間後には CS-2100 (**8b**)は残存しておらず、腸内細菌によって分解を受けていることが示されている。一方、右図においては、1,3-チアゾール誘導体 **38c** はラット (△ or ▲)及びサル (□ or ■)いずれの動物種の培養液に対しても 48 時間後において化合物が残存しており、腸内細菌による分解に対して安定であることが認められた。



Compound stability against enterobacteria from rat cecal contents or monkey feces under anaerobic condition.

Figure 3.2

3-5. まとめ

以上、本章では S1P₃ に対して S1P₁ 選択的なアゴニストとして一連の 1,3-チアゾール誘導体をデザイン・合成してきた。リード化合物としていた CS-2100 (**8b**) は *in vitro* 活性、*in vivo* 薬効ともに優れた化合物であったが、中心環である 1,2,4-オキサジアゾールは腸内細菌による還元的な環開裂を受けることが課題であった。薬物動態及び安全性の観点から 1,2,4-オキサジアゾール環を回避する化合物を探索し、結果として 1,3-チアゾール誘導体 **38c** を見出すことができた。**38c** は高い S1P₁ アゴニスト活性、良好な S1P₁/S1P₃ 選択性を併せ持ち (hS1P₁ EC₅₀ = 3.4 nM, hS1P₃ EC₅₀ => 20000 nM)、ラット HvGR モデルにおいて強い薬効を示した (ID₅₀ = 0.07 mg/kg)。本化合物は良好な PK プロファイルを示すとともに、CS-2100 (**8b**) の懸念点であった腸内細菌による分解に対しても明らかな耐性が認められており、目的とするプロファイルを有する化合物を取得することができた。

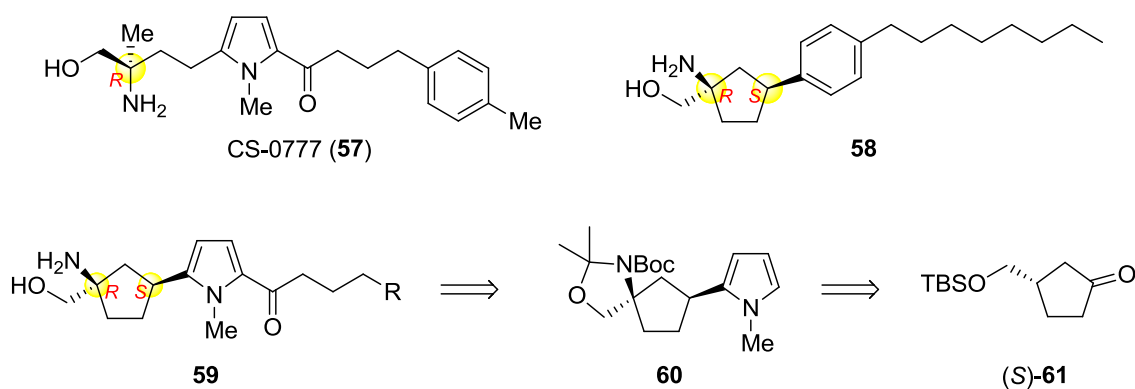
第4章 1-アミノシクロペンチルメタノール型 S1P₁ アゴニストの合成研究

4-1. はじめに

第2章、3章では、これまでに取り組んできた非リン酸型 S1P₁ アゴニストの探索研究について述べてきた。一方で、弊社では以前からアミノアルコール型 S1P₁ アゴニストに関する研究も精力的になされており、構造活性相関をはじめ多くの知見を蓄積してきた。具体的には、西らによって社内開発候補化合物として CS-0777 (**57**)^[45]が見出されている (Figure 4.1 上段左)。CS-0777 (**57**)は Fingolimod と同様に生体内でリン酸化されることにより薬効を発現するプロドラッグであり、構造上の特徴として4級不斉炭素中心を有している。本不斉中心の立体化学は生物活性に密接に関与しており、(*R*)の絶対配置を有する鏡像異性体が S1P₁ アゴニスト活性に不可欠であることが明らかとなっている。

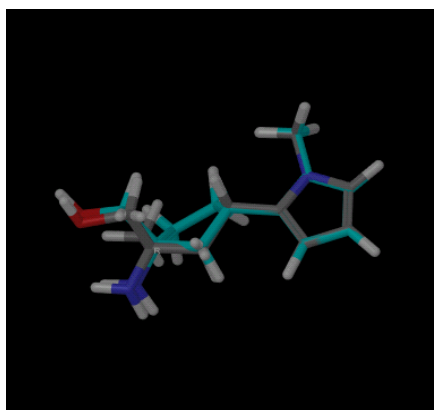
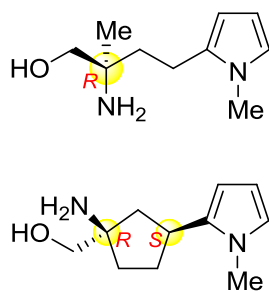
筆者らは更なる薬効向上と安全性改善を追究し、その過程で、当時、Abbott 社より報告されていた1-アミノシクロペンチルメタノール誘導体 **58**^[57]に着目した (Figure 4.1 上段右)。**58**は CS-0777 (**57**)と同様にプロドラッグとして機能するアミノアルコール型 S1P₁ アゴニストであり、その構造の大きな特徴としてシクロペンタン環により立体配座が固定され、4級不斉炭素中心を含む2つの不斉中心を有している。この **58**の1-アミノシクロペンチルメタノール構造に興味を持ち、CS-0777 (**57**)へ本部分構造を取り入れた新規誘導体群 **59**を着想するに至った。ところで、**59**には2つの不斉点があることから、合計4種類の立体異性体が存在する。そこで予備的な検討として CS-0777 (**57**)及び(1*R*,3*S*)-体である **59**を含めた全ての立体異性体の部分骨格について SPARTAN を用いた PM3 分子軌道法による構造最適化を実施し、最安定配座の重ね合わせを行った。結果として、(1*R*,3*S*)の立体化学を有する **59**においてのみ、CS-0777 (**57**)と非常に類似した立体配座をとることが認められた (Figure 4.2)。以上のことから、(1*R*,3*S*)の絶対立体配置を有する **59**を新たな標的化合物群として設定し、その薬理プロファイルを明らかにするべく、合成検討を行うこととした。

まず、**59**の合成中間体として **60**を設定した (Figure 4.1 下段)。**60**のピロール環へは合成の最終段階において求電子置換反応によりアシル部位を導入することができ、効率的な誘導体展開が可能であるためである。**60**は (*S*)-3-ヒドロキシメチルシクロペンタン-1-オンの TBS 保護体である(*S*)-**61**をキラルシントンとして設定し、2つの不斉中心を構築する合成経路を想定した。



Structures of CS-0777 (**57**) and Abbott compound (**58**) and retrosynthesis of pyrrole-based analogue **59**.

Figure 4.1



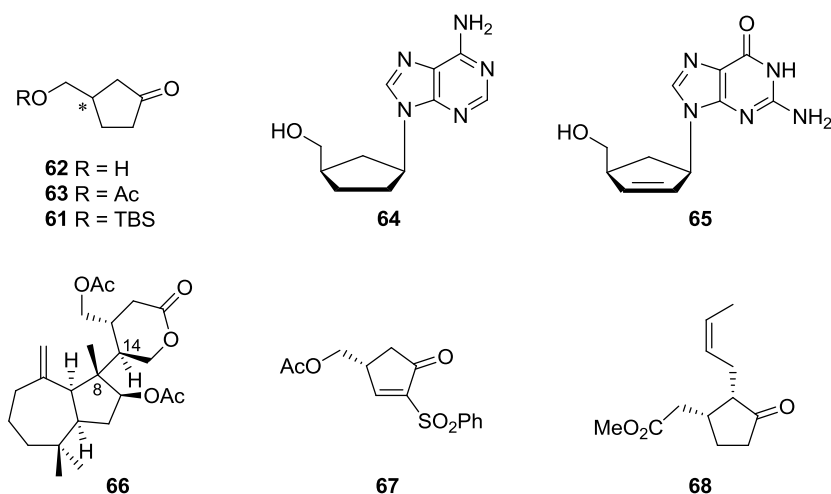
Superimposition of stable conformations of the partial structures of **(2R)-57** (grey) and **(1R,3S)-59** (green).

Figure 4.2

4-2. 光学活性 3-ヒドロキシメチルシクロペンタン-1-オン類について

光学活性な 3-ヒドロキシメチルシクロペンタン-1-オン **62** 及びその誘導体 **63**, **61** は、シクロペンタン構造を有する生物活性物質や天然物を合成する上で有用なキラルシントンとして利用されている (Figure 4.3)。例えば、(*R*)-**62** は抗ヒト免疫不全ウイルス活性を有する carbocyclic-ddA **64**^[58] や抗 B 型肝炎ウイルス活性を有する carbovir **65**^[59] といった炭素環ヌクレオシドの合成中間体として知られている。天然物の全合成においても活用されており、Lebsack らによって報告された Shahamin K **66** の全合成^[60] では、複雑な C8–C14 の σ 結合を形成する際に (*S*)-**63** より合成される誘導体 **67** が用いられている。他にも、北原らによって報告された (\pm)-**62** を出発物質とする (\pm)-methyl epijasmonate **68** の全合成^[61] のように、既にラセミ体の合成経路が確立している場合、(*R*)-**62** または (*S*)-**62** を出発物質として代替することで光学活性な **68** の合成が容易になると考えられる。

以上のように、光学活性 3-ヒドロキシメチルシクロペンタン-1-オン類 (**61–63**) は合成化学上、有用な物質であるものの、報告されている合成例は乏しくジアステレオマーの分割法^[59a, b] と不斉合成法^[58a] がそれぞれ一例のみであり、未だ合成検討の余地がある。また、4-1 節において述べたように (*S*)-**61** は新たな標的化合物群 **59** の合成中間体として必要であることから、まず **61** の光学活性体の合成方法について検討を開始することとした。



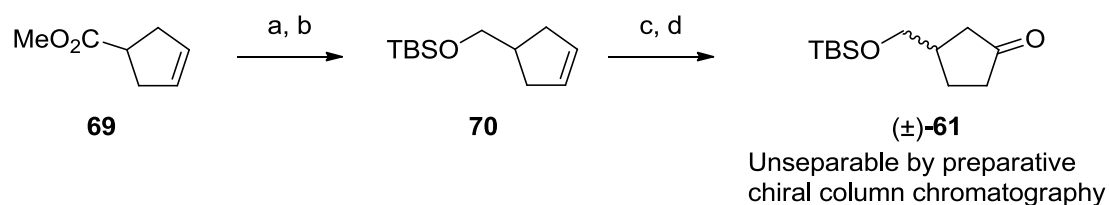
Structures of 3-hydroxymethylcyclopentan-1-one **62**, its protected derivatives **63** and **61**, carbocyclic-ddA (**64**), carbovir (**65**), Shahamin K (**66**) and its intermediate **67** and methyl epijasmonate (**68**).

Figure 4.3

4-3. 合成検討

はじめに(±)-**61**の光学分割を検討した。(±)-**61**はScheme 4.1に示す方法で簡便に調製可能である。市販の3-シクロペンテン-1-カルボン酸メチル**69**より出発し、エステル部位を水素化アルミニウムリチウムにより還元後、生じた一級水酸基をTBS基で保護して**70**とした。続いてヒドロホウ素化によりオレフィン部位を二級水酸基へ変換し、TEMPO酸化を経て、(±)-**61**を4工程、85%の収率で合成した。

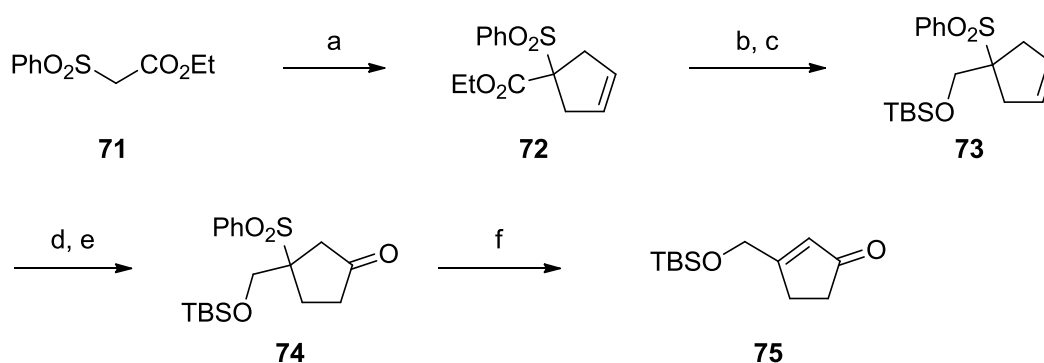
得られた(±)-**61**に対してキラルHPLCを用いた光学分割を試みた。種々のキラルカラム及び溶媒条件を検討したものの、分析レベルでの保持時間の違いしか認められず、分離は困難であった(データ不掲載)。



Reagents and conditions: (a) LiAlH_4 , THF. (b) TBSCl, imidazole, DMF. (c) BH_3 -THF, aq. NaOH, aq. H_2O_2 . (d) TEMPO (85%, 4 steps).

Scheme 4.1

次に不斉合成の検討へと移った。エノン **75**^[62]を調製し、不斉共役還元反応により両鏡像体をそれぞれ得る方法を選択した。まず、エノン **75** の合成方法について、Scheme 4.2 に示す。市販のフェニルスルホニル酢酸エチル **71** より出発し、塩基性条件下、*cis*-1,4-ジクロロ-2-ブテンとの反応によりシクロペンテン化合物 **72** を合成した^[63]。続いてエチルエステル部位を水素化アルミニウムリチウムにより還元し、生じた一級アルコールを TBS 基で保護して **73** を 3 工程、87%の収率で得た。次にヒドロホウ素化によりオレフィン部位を二級水酸基に変換した後、TEMPO 酸化により **74** とした。最後にトリエチルアミン存在下、THF 中で加熱することで、フェニルスルホニル基の β 脱離が進行し、エノン中間体 **75** を **73** より 3 工程、77%の収率で合成した。



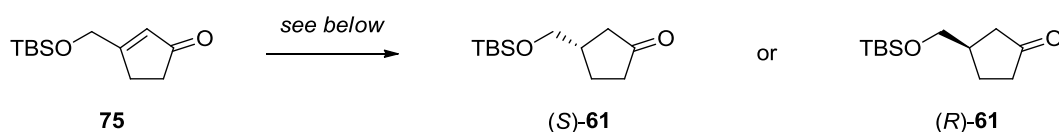
Reagents and conditions: (a) *cis*-1,4-dichloro-2-butene, LiH, DMF. (b) LiAlH₄, THF. (c) TBSCl, imidazole, DMF (87%, 3 steps). (d) BH₃-THF, aq. NaOH, aq. H₂O₂. (e) TEMPO. (f) Et₃N, THF (77%, 3 steps).

Scheme 4.2

続いて、**75** を基質として銅触媒を用いた不斉共役還元反応の条件検討を行った。結果を Table 4.1 に示す。最初に不斉共役還元の標準的な条件である Buchwald らの方法を用いた^[64]。キラルリガンドとして (*S*)-*p*-tol-BINAP を、化学量論の還元剤としてポリメチルヒドロシロキサン (PMHS)を用いて室温下、反応を行った。85% ee と (*S*)-体優先的に還元が進行したものの、反応の進行は遅く (30 時間)、38%の収率と未だ改善の余地が認められた (Run 1)。収率及び選択性の改善を期待して、0 °Cにて長時間反応を行ったところ (0 °Cで 67 時間、室温で 24 時間)、73%と高い収率で目的物が得られたものの、予想に反し 70% ee とエナンチオ選択性は減少した (Run 2)。そこで Lipshutz らによって報告さ

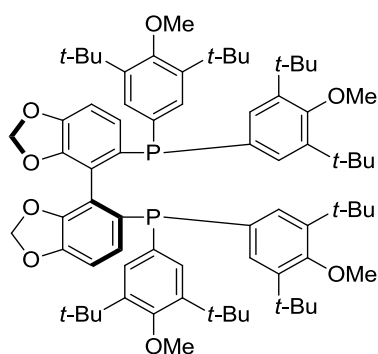
れたキラルリガンドとして(*S*)-DTBM-SEGPHOSを用いる条件を試みることにした^[65]。その結果、収率 96%、鏡像体過剰率 95% ee といずれも良好な結果が得られた (Run 3)。また、キラルリガンドとして(*R*)-DTBM-SEGPHOSを用いることにより(*R*)-**61**の調製も可能であることを確認した (Run 4)。なお、鏡像体過剰率は **61** をベンゾイルエステルに変換後、HPLC にて測定した。

Table 4.1

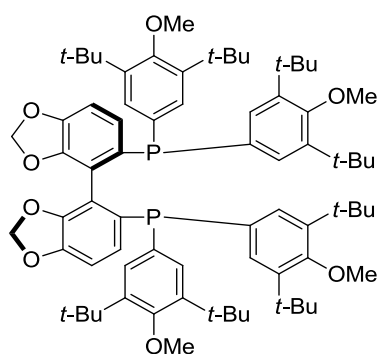


Run	Ligand	Other conditions	Temp, Time	Yield (%)	ee (%) (config) ^a
1	(<i>S</i>)- <i>p</i> -tol-BINAP (5 mol%)	PMHS, CuCl, <i>t</i> -BuONa	rt (30 h)	38	85 (<i>S</i>)
2	(<i>S</i>)- <i>p</i> -tol-BINAP (5 mol%)	PMHS, CuCl, <i>t</i> -BuONa	0 °C (67 h), rt (24 h)	73	70 (<i>S</i>)
3	(<i>S</i>)-DTBM-SEGPHOS (1 mol%)	PMHS, Cu(OAc) ₂ •H ₂ O	rt (3 h)	96	95 (<i>S</i>)
4	(<i>R</i>)-DTBM-SEGPHOS (1 mol%)	PMHS, Cu(OAc) ₂ •H ₂ O	rt (3 h)	92	95 (<i>R</i>)

^a The enantiopurity was determined by HPLC analysis after conversion into its benzoyl ester. (see Experimental section)



(*S*)-DTBM-SEGPHOS

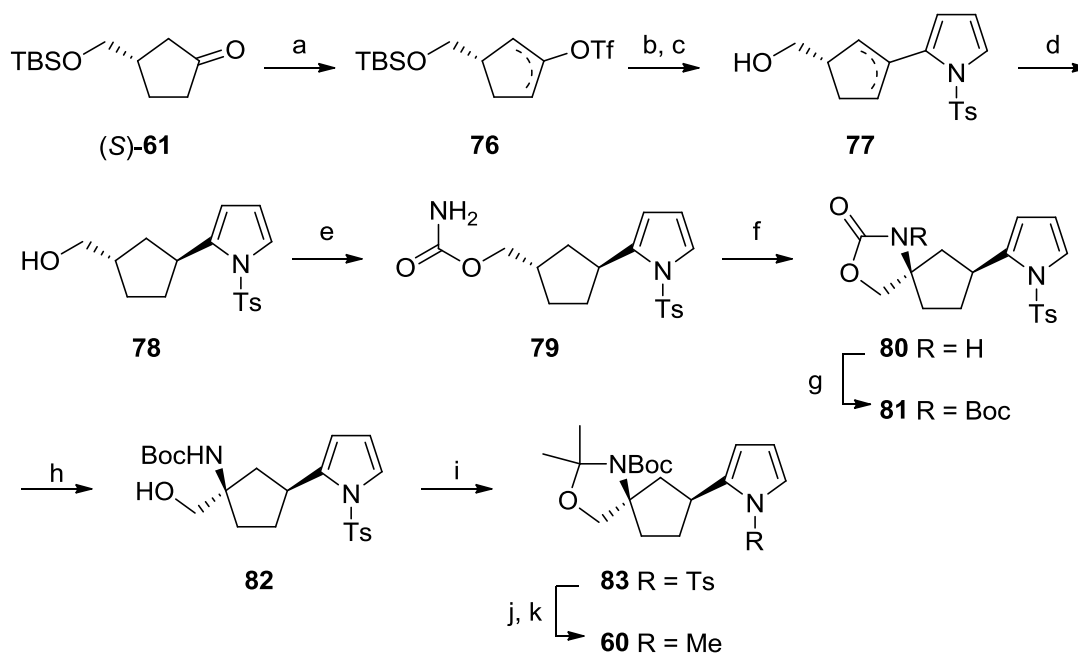


(*R*)-DTBM-SEGPHOS

次に、**(S)**-**61** を用いて、ピロール中間体 **60** の合成に着手した (Scheme 4.3)。4.1 節で述べたように Abbott 社より報告されている S1P₁ アゴニスト **58** は 4 級不斉中心を含む 2 つの不斉中心を有している。その立体化学の構築に Crabtree 触媒によるジアステレオ選択的水素化及び Du Bois アミノ化反応を用いている^[57]。そこで本合成検討においても一部改良を加えつつ上記手法を取り入れることとした。

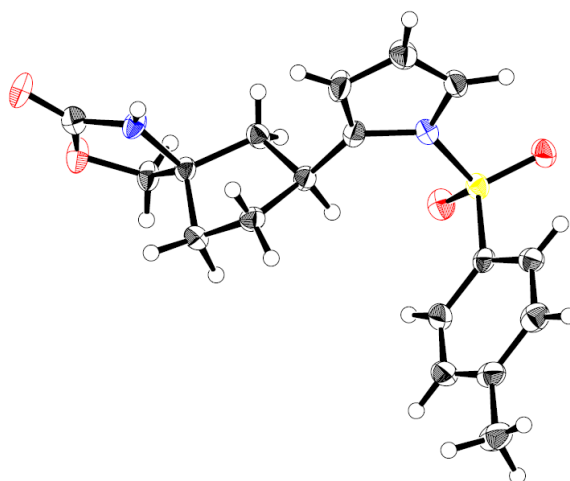
(S)-**61** に対し THF 中、NaHMDS 及びトリフラート化試薬を作用させることでエノールトリフレーター **76** を位置異性体の混合物の形で 91% と良好な収率にて調製した。**76** 及び市販のピロリルボロン酸エステルとの鈴木カップリング反応によりピロール環を導入しカップリング体を定量的に得た後、TBAF を作用させて TBS 基を脱保護することで、98% と良好な収率で **77** へと導いた。続いて Crabtree 触媒によるジアステレオ選択的水素添加反応を行い、ヒドロキシメチル基の存在する面から水素が付加する形で還元が進行した **78** を 95% の収率で得た。次に **78** に対してイソシアン酸トリクロロアセチルを作用させた後、メタノール中、炭酸カリウムを作用させて、カルバモイル体 **79** へと導いた。続いて **79** を基質としてロジウム触媒による Du Bois アミノ化^[66]を行い、オキサゾリジノン体 **80** を 72% の収率で調製した。なお、この時点で **80** とジアステレオマー (Crabtree 触媒による水素化反応の際の副生物) の比率は ¹H-NMR により分析可能で 15:1 であった。次にオキサゾリジノン **80** に対して Boc₂O を作用させて Boc 保護体 **81** を 71% の収率で得た後、含水メタノール中、炭酸カリウムを作用させてオキサゾリジノン環を開環し、**82** を 94% と良好な収率で得た。その後、BF₃・Et₂O 存在下、2,2-ジメトキシプロパンを作用させて 90% の収率にてアセトニド保護体 **83** へと導いた。なお、**83** の精製過程においてシリカゲルカラムクロマトグラフィーにより前述のジアステレオマーを分離することができた。続いて **83** に水酸化ナトリウムを作用させてトシル基を除去し (98%)、最後に KHMDS 存在下、ヨウ化メチル (MeI) を作用させてメチル化を行い、ピロール中間体 **60** を 98% の収率で合成した。

絶対立体配置を確認するため種々の中間体について単結晶の取得を試みたところ、**80** (15:1 のジアステレオ混合物) をエタノール中で再結晶することで中程度の回収率にて単結晶の取得が可能であった (回収率 60%)。得られた **80** の単結晶について X 線結晶構造解析を行い、その分子構造及び絶対立体配置を確認した (Figure 4.4)。



Reagents and conditions: (a) NaHMDS, PhNTf₂, THF (91%). (b) 1-(*p*-toluenesulfonyl)pyrrole-2-boronic acid pinacol ester, Pd(PPh₃)₄, aq. K₂CO₃, 1,4-dioxane (quant.). (c) TBAF, THF (98%). (d) H₂, Crabtree's catalyst, CH₂Cl₂ (95%). (e) Cl₃CC(O)NCO, CH₂Cl₂ then K₂CO₃, MeOH-H₂O (quant.). (f) PhI(OAc)₂, MgO, Rh₂(esp)₂, benzene (72%). (g) Boc₂O, Et₃N, DMAP, CH₂Cl₂ (71%). (h) K₂CO₃, MeOH-H₂O (94%). (i) 2,2-dimethoxypropane, BF₃·Et₂O, CH₂Cl₂ (90%). (j) aq. NaOH, EtOH-dioxane (98%). (k) MeI, KHMDS, THF (98%).

Scheme 4.3

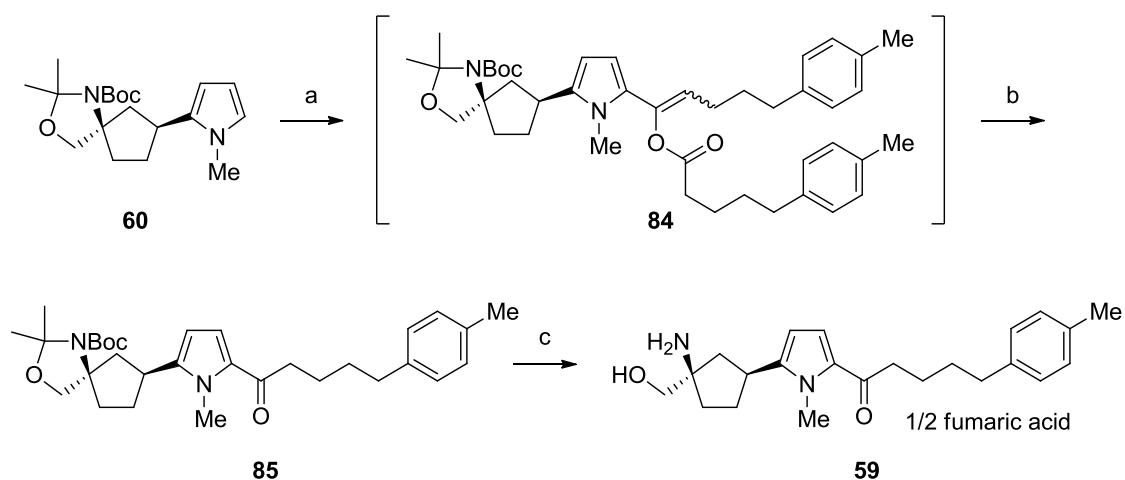


X-ray ORTEP of compound **80**

Hydrogen (white), carbon (black), oxygen (red), nitrogen (blue), sulfur (yellow)

Figure 4.4

続いて **59** の合成について Scheme 4.4 に示す。トルエン-アセトニトリル混合溶媒中、**60** に対して 1-メチルイミダゾール存在下、5-(*p*-トリル)ペンタン酸クロリドを作用させてピロール 5 位をアシル化し、系内で生成するエノールエステル **84** を THF-メタノール中、水酸化ナトリウムを作用させて加水分解することで **85** を 2 工程、88%で得た。続いて TFA を作用させて Boc 基及びアセトニド基を一挙に脱保護し、最後にヘミフマル酸塩として最終物 **59** を 58%の収率で合成した。



Reagents and conditions: (a) 5-(*p*-tolyl)pentanoyl chloride, 1-Me-imidazole, toluene-CH₃CN, 80 °C. (b) aq. NaOH, THF-MeOH, 60 °C (88%, 2 steps). (c) TFA, CH₂Cl₂ then fumaric acid (0.5 eq) (58%).

Scheme 4.4

4-5. まとめ

以上、本章ではキラルシントンとして有用である(*S*)-**61** の新規不斉合成ルートを確認した。本合成法を用いることで(*R*)-**61** も調製可能である。得られた(*S*)-**61** を用いて、アミノシクロペンタノール型 S1P₁ アゴニスト **59** を調製する探索的合成経路を確認した。なお、**59** のリン酸エステルを化学的に合成し (データ不掲載)、[³⁵S]GTP γ -S binding assay で評価したところ、human S1P₁ に対して EC₅₀ = 3.5 nM、human S1P₃ に対して EC₅₀ = >20000 nM という値が示されている。本合成ルートでは合成の最終段階において種々の右アシル側鎖を導入できることから効率的な誘導体展開が可能である。また、中心のピロール環の導入には鈴木カップリングを用いているため、他の芳香環導入にも有利な合成経路であることから、後に種々の芳香環を導入する構造最適化研究にも本合成ルートが活用されている。

総括

本論文は、筆者が取り組んできた新規免疫調節薬の開発を目標とした S1P₁ 作動薬の探索研究について述べたものである。

第 2 章では、S1P₃ に対して S1P₁ 選択的な作動薬である CS-2100 (**8b**) の探索研究について述べた。既報の化合物 **1** をリード化合物とし、4-フェニル-5-トリフルオロメチルチオフェン構造をビフェニルエーテル構造へ、内側ベンゼン環をエチルチオフェン構造へ変換することで、優れた S1P₁ アゴニスト活性を保持しつつ、非常に高い S1P₁/S1P₃ 選択性を有する CS-2100 (**8b**) を取得することができた (Figure 1)。ドッキングスタディの結果から、チオフェン環上のエチル基は S1P₃ 活性サイトにおいて Phe263 残基との間で立体的な反発を生じていることが認められており、S1P₁/S1P₃ 選択性の向上に大きく寄与していることが示されている。CS-2100 (**8b**) は、ラットにおいて用量依存的かつ強いリンパ球減少作用を示し、ラット HvGR、ラットアジュバント関節炎及びマウス EAE といった各種の前臨床動物病態モデルにおいて良好な薬効が認められた。

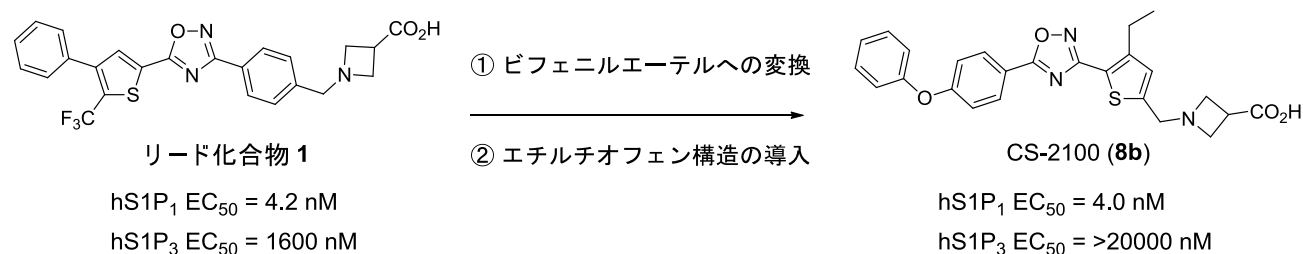


Figure 1

第 3 章では、1,3-チアゾール型 S1P₁/S1P₃ 選択的作動薬 **38c** の探索研究について述べた。CS-2100 (**8b**) は生体内において 1,2,4-オキサジアゾール環が還元的に開裂されることが明らかとなり、新たな課題として認識された。CS-2100 (**8b**) をリード化合物として 1,2,4-オキサジアゾール環を回避する化合物を探索し、中心環の変換及び置換基の最適化を経て、1,3-チアゾール誘導体 **38c** を見出した (Figure 2)。**38c** は高い S1P₁ アゴニスト活性、良好な S1P₁/S1P₃ 選択性を併せ持ち (hS1P₁ EC₅₀ = 3.4 nM, hS1P₃ EC₅₀ = > 20000 nM)、ラット HvGR モデルにおいて強い薬効を示した (ID₅₀ = 0.07 mg/kg)。本化合物は良好な

PK プロファイルを示し、かつ腸内細菌による分解に対しても明らかな耐性が認められており、目的とするプロファイルを有する化合物を取得することができた。

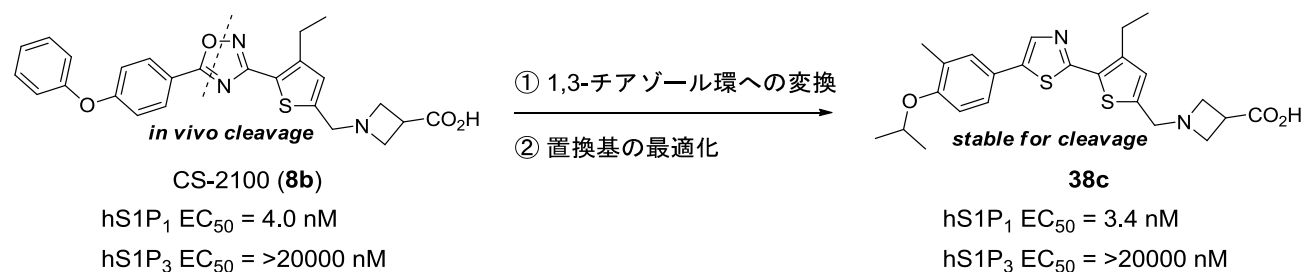
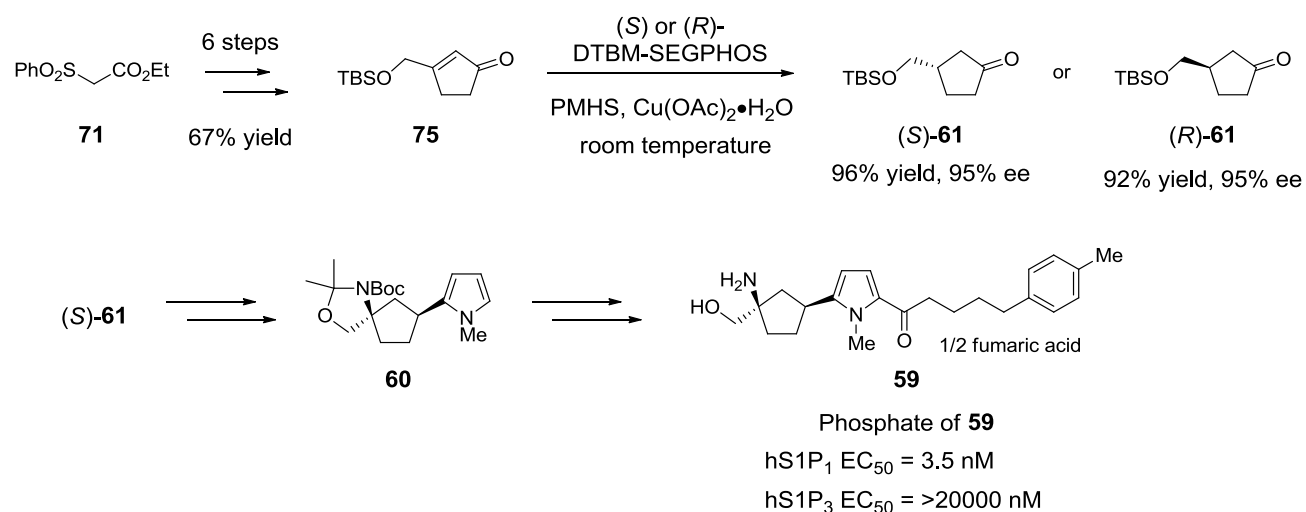


Figure 2

第4章では、キラルシントンとして有用な 3-ヒドロキシメチルシクロペンタン-1-オン誘導体 **61** の不斉合成法及び(*S*)-**61** を用いた 1-アミノシクロペンタノール型 S1P₁ アゴニスト **59** の合成研究について述べた。**71** より 6 工程にて調製したエノン **75** を基質として、(*S*)または(*R*)-DTBM-SEGPHOS を不斉配位子とする不斉共役還元反応により(*S*)-**61** または(*R*)-**61** を合成するルートを確立した (Scheme 1 上段)。得られた(*S*)-**61** を用いて、アミノシクロペンタノール型 S1P₁ アゴニスト **59** へと導き、誘導体展開を効率化する探索的合成ルートを確立した (Scheme 1 下段)。



Scheme 1

S1P₁をはじめとする各 S1P 受容体の生体内で担っている機能については未だ明らかとなっていない部分も多く、新たな創薬ターゲットとしての可能性を今なお残している。本研究から得られた様々な知見が、今後の医薬品開発に役立つことを期待する。

実験の部

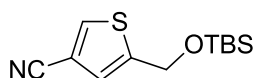
5. Chemistry

5-1. General

^1H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 400 or 500 spectrometer with tetramethylsilane as an internal reference. The infrared spectra were recorded on a Jasco FT/IR-830 spectrophotometer, and the peaks were recorded in cm^{-1} . The mass spectra were recorded on a JEOL JMS-AX505H. Optical rotations were measured on an Autopol V Plus (Rudolph Research Analytical, Hackettstown, NJ). TLC analysis was performed on 60F₂₅₄ plates. Column chromatography was performed on Silica gel 60 (Merck, 230–400), Silica gel 60 N (Kanto Chemical, spherical, neutral, 40–50 μm) or Chromatorex (Fuji Silysia Chemical, NH silicagel, 100–200 mesh).

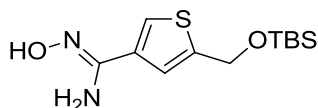
5-2. 第2章に関する実験

5-2-1. 5-({*tert*-Butyl(dimethyl)silyl}oxy)methylthiophene-3-carbonitrile (2a)



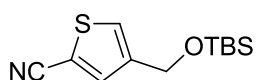
To a solution of [(4-bromo-2-thienyl)methoxy]-*tert*-butyldimethylsilane (9.0 g, 29 mmol) [reference literature: *J. Med. Chem.* **2002**, *45*, 5005] in DMF (20 mL) was added CuCN (4.7 g, 53 mmol) and the resulting mixture was stirred at reflux temperature for 2 h. After cooling to room temperature, the reaction mixture was diluted with Et₂O (80 mL). To this was added ammonia solution (28% in water, 50 mL) and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with Et₂O and the extract was washed with water and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 50:1 to 4:1) to afford the title compound **2a** (4.3 g, 17 mmol, 58%) as a colorless oil. ^1H NMR (400 MHz, CDCl₃) δ : 7.82 (s, 1H), 7.06 (s, 1H), 4.85 (s, 2H), 0.93 (s, 9H), 0.11 (s, 6H); IR (liquid film): 2229, 1258, 1128, 1086 cm^{-1} ; MS (EI⁺) m/z : 253 (M⁺).

5-2-2. 5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl-*N*-hydroxythiophene-3-carboximidamide (3a)



To a solution of **2a** (4.3 g, 17 mmol) in EtOH (20 mL) was added hydroxylamine (40wt% in water, 2.2 mL, 27 mmol) and the resulting mixture was stirred at 60 °C for 1 h. After removal of the solvent *in vacuo*, the residue was diluted with Et₂O, poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 10:1 to 5:2) to afford the title compound **3a** (4.7 g, 16 mmol, 97%) as a white crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.31 (d, 1H, *J* = 1.4 Hz), 7.02 (d, 1H, *J* = 1.4 Hz), 4.84 (s, 2H), 4.79 (br s, 2H), 1.69 (br s, 1H), 0.93 (s, 9H), 0.10 (s, 6H); IR (KBr): 3495, 3389, 3208, 1655, 1371, 1256, 1101 cm⁻¹; MS (FAB⁺) *m/z*: 287 ((M+H)⁺).

5-2-3. 4-({*tert*-Butyl(dimethyl)silyl}oxy)methylthiophene-2-carbonitrile (**2b**)



(a) *tert*-Butyl(dimethyl)(thiophen-3-ylmethoxy)silane

To a solution of thiophen-2-ylmethanol (3.0 g, 26 mmol) and imidazole (3.6 g, 53 mmol) in DMF (20 mL) was added TBSCl (4.4 g, 38 mmol) at room temperature. After stirring for 19 h, the reaction mixture was poured into water and extracted with Et₂O. The extract was washed with water and brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 10:0 to 19:1) to afford the title compound quantitatively as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.30–7.26 (m, 1H), 7.16–7.14 (m, 1H), 7.02 (dd, 1H, *J* = 4.7, 1.2 Hz), 4.74 (d, 2H, *J* = 0.8 Hz), 0.93 (s, 9H), 0.10 (s, 6H); IR (ATR): 2929, 2856, 1470, 1254, 1086, 835, 775 cm⁻¹; MS (CI⁺) *m/z*: 228 (M⁺).

(b) 4-({*tert*-Butyl(dimethyl)silyl}oxy)methylthiophene-2-carbaldehyde

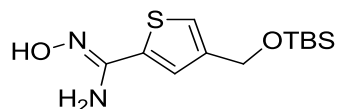
To a solution of *tert*-butyl(dimethyl)(thiophen-3-ylmethoxy)silane (3.0 g, 13 mmol) in THF (50 mL) was slowly added *n*-BuLi (1.6 M in hexane, 9.9 mL, 16 mmol) at -78 °C and the resulting mixture was stirred at 0 °C for 30 min. The reaction mixture was cooled to -78 °C again and DMF (2.1 mL, 28 mmol) was slowly added. After stirring for 30 min at -78 °C, the reaction was quenched with sat. aq. NH₄Cl. The resulting biphasic mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 1:1) to afford the title compound (1.1 g, 4.3 mmol, 33%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 9.90 (s, 1H), 7.68 (s, 1H), 7.59 (s, 1H), 4.74 (s, 2H), 0.94 (s, 9H), 0.11 (s, 6H); IR (liquid film): 2955, 2930, 2858, 1674, 1132, 839, 779, 666 cm⁻¹; MS (FAB⁺) *m/z*: 257 ((M+H)⁺).

(c) 4-({*tert*-Butyl(dimethyl)silyl}oxy)methylthiophene-2-carbonitrile (**2b**)

To a suspension of 4-({*tert*-butyl(dimethyl)silyl}oxy)methylthiophene-2-carbaldehyde (0.50 g, 2.0

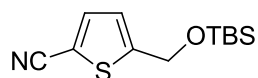
mmol) and hydroxylamine hydrochloride (0.15 g, 2.2 mmol) in CH₂Cl₂ (7.2 mL) and MeOH (0.80 mL) was added Et₃N (0.56 mL, 4.0 mmol) and the resulting mixture was stirred at room temperature for 2 h. After removal of the solvent *in vacuo*, toluene was added and evaporated azeotropically *in vacuo*. To the residue in toluene (8.0 mL) was added dicyclohexylcarbodiimide (0.45 g, 2.2 mmol) at room temperature and the reaction mixture was stirred at 90 °C for 16 h. After cooling to room temperature, *n*-hexane was added and the resulting mixture was filtered through Celite pad. The filtrate was evaporated and the residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 4:1), followed by flash column chromatography (amino-functionalized silica gel, *n*-hexane/EtOAc 1:0 to 5:1) to afford the title compound **2b** (0.45 g, 1.8 mmol, 89%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.52 (s, 1H), 7.40 (s, 1H), 4.70 (s, 2H), 0.93 (s, 9H), 0.10 (s, 6H); IR (liquid film): 2955, 2931, 2858, 2219, 2119, 1258, 1125, 1090, 838, 779 cm⁻¹; MS (EI⁺) *m/z*: 253 (M⁺).

5-2-4. 4-({*tert*-Butyl(dimethyl)silyl}oxy)methyl)-*N*-hydroxythiophene-2-carboximidamide (**3b**)



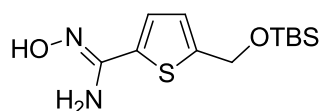
According to a similar procedure to 5-2-2, **3b** (0.28 g, 0.98 mmol, 83%) was prepared from **2b** (0.30 g, 1.2 mmol) and hydroxylamine (50wt% in water, 0.13 mL, 1.9 mmol). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 1:1) gave a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.19 (s, 1H), 7.12 (s, 1H), 4.83 (br s, 2H), 4.68 (s, 2H), 0.93 (s, 9H), 0.89 (s, 1H), 0.09 (s, 6H); IR (KBr): 3499, 3393, 3223, 2929, 2857, 1645, 1256, 1103, 842, 780 cm⁻¹; MS (FAB⁺) *m/z*: 287 ((M+H)⁺).

5-2-5. 5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl)thiophene-2-carbonitrile (**2c**)



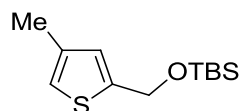
According to a similar procedure to 5-2-1, **2c** (1.1 g, 4.4 mmol, 56%) was prepared from [(5-bromo-2-thienyl)methoxy]-*tert*-butyldimethylsilane (2.4 g, 7.8 mmol) [reference literature: *Tetrahedron* **1983**, *39*, 2531] and CuCN (1.3 g, 14 mmol). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 50:1 to 7:1) gave a white crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.46 (d, 1H, *J* = 3.9 Hz), 6.70 (dt, 1H, *J* = 3.9, 1.2 Hz), 4.88 (d, 2H, *J* = 1.2 Hz), 0.93 (s, 9H), 0.12 (s, 6H); IR (liquid film): 2219, 1472, 1464, 1377, 1258, 1096 cm⁻¹; MS (EI⁺) *m/z*: 253 (M⁺).

5-2-6. 5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl)-*N*-hydroxythiophene-2-carboximidamide (**3c**)



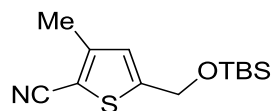
According to a similar procedure to 5-2-2, **3c** (1.2 g, 4.1 mmol, 81%) was prepared from **2c** (1.3 g, 5.0 mmol) and hydroxylamine (40wt% in water, 0.7 mL, 8.6 mmol). The final purification by recrystallization (*n*-hexane/EtOAc) gave a white crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.11 (d, 1H, *J* = 3.7 Hz), 6.84 (d, 1H, *J* = 3.7 Hz), 6.81 (br s, 1H), 4.84 (s, 2H), 4.82 (br s, 2H), 0.93 (s, 9H), 0.10 (s, 6H); IR (KBr): 3498, 3384, 3206, 1658, 1588, 1387, 1368, 1256, 1250, 1067 cm⁻¹; MS (EI⁺) *m/z*: 286 (M⁺).

5-2-7. *tert*-Butyl(dimethyl)[(4-methylthiophen-2-yl)methoxy]silane (**13a**)



To a solution of 2-hydroxymethyl-4-methylthiophene (1.8 g, 14 mmol) [reference literature: *J. Heterocycl. Chem.* **1982**, *19*, 1125] and imidazole (1.9 g, 28 mmol) in DMF (20 mL) was added TBSCl (2.3 g, 15 mmol) at room temperature. After stirring for 2 h, the reaction mixture was poured into water and extracted with Et₂O. The extract was washed with water and brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 10:0 to 19:1) to afford the title compound **13a** (2.5 g, 10 mmol, 74%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 6.78 (s, 1H), 6.72 (s, 1H), 4.81 (s, 2H), 2.22 (s, 3H), 0.93 (s, 9H), 0.10 (s, 6H); IR (liquid film): 1464, 1256, 1130, 1077 cm⁻¹; MS (EI⁺) *m/z*: 242 (M⁺).

5-2-8. 5-((*tert*-Butyl(dimethyl)silyl)oxy)methyl-3-methylthiophene-2-carbonitrile (**2d**)



(a) 5-((*tert*-Butyl(dimethyl)silyl)oxy)methyl-3-methylthiophene-2-carboxaldehyde

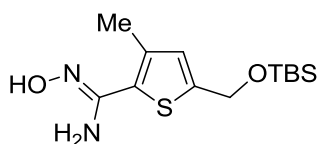
According to a similar procedure to 5-2-3 (b), the title compound (2.5 g, 8.9 mmol, 89%) was prepared from **13a** (2.5 g, 10 mmol), *n*-BuLi (1.6 M in hexane, 7.8 mL, 12 mmol) and DMF (1.6 mL, 21 mmol). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc) gave a pale yellowish oil. ¹H NMR (400 MHz, CDCl₃) δ: 9.98 (s, 1H), 6.78 (s, 1H), 4.85 (s, 2H), 2.52 (s, 3H), 0.94 (s,

9H), 0.12 (s, 6H); IR (liquid film): 1661, 1472, 1393, 1363, 1092 cm^{-1} ; MS (FAB⁺) m/z 271 ((M+H)⁺).

(b) 5-([*tert*-Butyl(dimethyl)silyl]oxy)methyl)-3-methylthiophene-2-carbonitrile (**2d**)

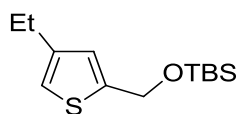
According to a similar procedure to 5-2-3 (c), **2d** was quantitatively prepared from 5-([*tert*-butyl(dimethyl)silyl]oxy)methyl)-3-methylthiophene-2-carboxaldehyde (2.5 g, 9.2 mmol), hydroxylamine hydrochloride (0.71 g, 10 mmol), Et₃N (2.6 mL, 18 mmol) and DCC (2.1 g, 10 mmol). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc) gave a pale yellowish oil. ¹H NMR (400 MHz, CDCl₃) δ : 6.71 (s, 1H), 4.83 (s, 2H), 2.39 (s, 3H), 0.93 (s, 9H), 0.11 (s, 6H); IR (liquid film): 2214, 2120, 1258, 1150, 1093 cm^{-1} ; MS (FAB⁺) m/z 268 ((M+H)⁺).

5-2-9. 5-([*tert*-Butyl(dimethyl)silyl]oxy)methyl)-*N*-hydroxy-3-methylthiophene-2-carboximidamide (**3d**)



According to a similar procedure to 5-2-2, **3d** (2.3 g, 7.7 mmol, 83%) was prepared from **2d** (2.5 g, 9.2 mmol) and hydroxylamine (40wt% in water, 2.0 mL, 24 mmol). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc) gave a white crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ : 7.16 (br s, 1H), 6.68 (s, 1H), 4.79 (s, 4H), 2.35 (s, 3H), 0.93 (s, 9H), 0.10 (s, 6H); IR (KBr): 3455, 3353, 3277, 1651, 1255 cm^{-1} ; MS (FAB⁺) m/z 301 ((M+H)⁺).

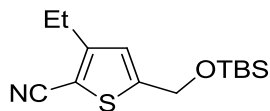
5-2-10. *tert*-Butyl[(4-ethylthiophen-2-yl)methoxy]dimethylsilane (**13b**)



To a solution of [(4-bromo-2-thienyl)methoxy]-*tert*-butyldimethylsilane (0.61 g, 2.0 mmol) [reference literature: *J. Med. Chem.* **2002**, *45*, 5005] and [1,3-bis(diphenylphosphino)propane]dichloronickel (54 mg, 0.1 mmol) in Et₂O (5.0 mL) was slowly added ethylmagnesium bromide (1.0 M in THF, 3.0 mL, 3.0 mmol) at 0 °C. After stirring at 25 °C for 1 h, the reaction was quenched with sat. aq. NH₄Cl. The resulting biphasic mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 10:0 to 95:5) to afford the title compound **13b** (0.44 g, 1.7 mmol, 95%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ : 6.81 (s, 1H), 6.77 (s, 1H), 4.82 (s, 2H), 2.58 (q, 2H, J = 7.4 Hz), 1.21 (t, 3H, J = 7.4 Hz), 0.93 (s, 9H), 0.10 (s, 6H); IR (liquid film): 1471, 1463,

1255, 1174, 1131, 1077 cm^{-1} ; MS (FAB⁺): m/z 255 ((M-H)⁺)

5-2-11. 5-([*tert*-Butyl(dimethyl)silyl]oxy)methyl-3-ethylthiophene-2-carbonitrile (2e)



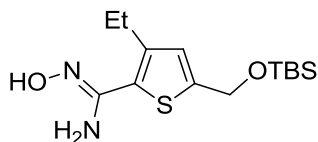
(a) 5-([*tert*-Butyl(dimethyl)silyl]oxy)methyl-3-ethylthiophene-2-carbaldehyde

According to a similar procedure to 5-2-3 (b), the title compound (1.3 g, 4.8 mmol, 86%) was prepared from **13b** (1.3 g, 5.6 mmol), *n*-BuLi (1.6 M in hexane, 4.2 mL, 6.7 mmol) and DMF (0.86 mL, 11 mmol). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc) gave a pale yellowish oil. ¹H NMR (400 MHz, CDCl₃) δ : 9.99 (s, 1H), 6.84 (s, 1H), 4.86 (s, 2H), 2.94 (q, 2H, J = 7.4 Hz), 1.29 (t, 3H, J = 7.4 Hz), 0.94 (s, 9H), 0.12 (s, 6H); IR (liquid film): 1659, 1461, 1256, 1225, 1156, 1092 cm^{-1} ; MS (EI⁺) m/z : 285 ((M+H)⁺).

(b) 5-([*tert*-Butyl(dimethyl)silyl]oxy)methyl-3-ethylthiophene-2-carbonitrile (2e)

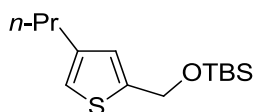
According to a similar procedure to 5-2-3 (c), **2e** (0.94 g, 3.3 mmol, 69%) was prepared from 5-([*tert*-butyl(dimethyl)silyl]oxy)methyl-3-ethylthiophene-2-carboxaldehyde (1.3 g, 4.8 mmol), hydroxylamine hydrochloride (0.37 g, 5.3 mmol), Et₃N (1.3 mL, 9.6 mmol) and DCC (1.1 g, 5.3 mmol). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc) gave a pale yellowish oil. ¹H NMR (400 MHz, CDCl₃) δ : 6.74 (s, 1H), 4.83 (s, 2H), 2.75 (q, 2H, J = 7.8 Hz), 1.25 (t, 3H, J = 7.8 Hz), 0.93 (s, 9H), 0.11 (s, 6H); IR (liquid film): 2212, 1256, 1149, 1093 cm^{-1} ; MS (EI⁺) m/z : 282 ((M+H)⁺).

5-2-12. 5-([*tert*-Butyl(dimethyl)silyl]oxy)methyl-3-ethyl-*N*-hydroxythiophene-2-carboximidamide (3e)



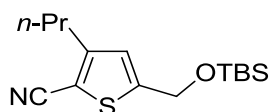
According to a similar procedure to 5-2-2, **3e** (0.62 g, 2.0 mmol, 60%) was prepared from **2e** (0.93 g, 3.3 mmol) and hydroxylamine (40wt% in water, 0.50 mL, 6.1 mmol). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc) gave a white crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ : 7.10 (br s, 1H), 6.76 (s, 1H), 4.80 (s, 4H), 2.76 (q, 2H, J = 7.8 Hz), 1.20 (t, 3H, J = 7.8 Hz), 0.93 (s, 9H), 0.11 (s, 6H); IR (KBr): 3491, 3357, 3284, 1643, 1590, 1059 cm^{-1} ; MS (EI⁺) m/z : 315 ((M+H)⁺).

5-2-13. *tert*-Butyl(dimethyl)[(4-propylthiophen-2-yl)methoxy]silane (**13c**)



According to a similar procedure to 5-2-10, **13c** (1.8 g, 6.6 mmol, 66%) was prepared from [(4-bromo-2-thienyl)methoxy]-*tert*-butyldimethylsilane (3.1 g, 10 mmol) [reference literature: *J. Med. Chem.* **2002**, *45*, 5005], [1,3-bis(diphenylphosphino)propane]dichloronickel (0.27 g, 0.50 mmol), *n*-propylmagnesium bromide (1.0 M in THF, 12 mL, 12 mmol) and Et₂O (30 mL). ¹H NMR (400 MHz, CDCl₃) δ: 6.80 (s, 1H), 6.75 (s, 1H), 4.82 (s, 2H), 2.53 (t, 2H, *J* = 7.4 Hz), 1.61 (tq, 2H, *J* = 7.4, 7.4 Hz), 0.93 (t, 3H, *J* = 7.4 Hz), 0.92 (s, 9H), 0.10 (s, 6H); IR (liquid film): 2956, 2929, 2857, 1471, 1255, 1077, 838, 777 cm⁻¹; MS (FAB⁺): *m/z* 269 (M-H)⁺.

5-2-14. 5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl-3-propylthiophene-2-carbonitrile (**2f**)



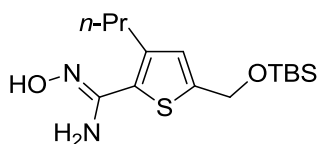
(a) 5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl-3-propylthiophene-2-carbaldehyde

According to a similar procedure to 5-2-3 (b), the title compound (0.60 g, 2.0 mmol, 82%) was prepared from **13c** (0.66 g, 2.4 mmol), *n*-BuLi (1.6 M in hexane, 2.0 mL, 3.2 mmol) and DMF (0.41 mL, 5.3 mmol). ¹H NMR (400 MHz, CDCl₃) δ: 9.98 (s, 1H), 6.81 (s, 1H), 4.86 (s, 2H), 2.89 (t, 2H, *J* = 7.4 Hz), 1.69 (tq, 2H, *J* = 7.4, 7.4 Hz), 0.97 (t, 3H, *J* = 7.4 Hz), 0.94 (s, 9H), 0.12 (s, 6H); IR (liquid film): 2957, 2930, 1659, 1471, 1254, 1092, 839, 779 cm⁻¹; MS (FAB⁺) *m/z* 299 ((M+H)⁺).

(b) 5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl-3-propylthiophene-2-carbonitrile (**2f**)

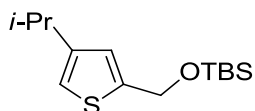
According to a similar procedure to 5-2-3 (c), **2f** (0.90 g, 3.1 mmol, 96%) was prepared from 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl-3-propylthiophene-2-carbaldehyde (0.97 g, 3.2 mmol), hydroxylamine hydrochloride (0.25 g, 3.6 mmol), Et₃N (0.89 mL, 6.4 mmol) and DCC (0.74 g, 3.6 mmol). ¹H NMR (400 MHz, CDCl₃) δ: 6.73 (s, 1H), 4.84 (s, 2H), 2.71 (t, 2H, *J* = 7.4 Hz), 1.66 (tq, 2H, *J* = 7.4, 7.4 Hz), 0.96 (t, 3H, *J* = 7.4 Hz), 0.93 (s, 9H), 0.11 (s, 6H); IR (liquid film): 2957, 2931, 2857, 2212, 2118, 1149, 1092, 839, 779 cm⁻¹; MS (FAB⁺) *m/z* 296 ((M+H)⁺).

5-2-15. 5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl-*N*-hydroxy-3-propylthiophene-2-carboximidamide (**3f**)



According to a similar procedure to 5-2-2, **3f** (0.96 g, 2.9 mmol, 95%) was prepared from **2f** (0.90 g, 3.0 mmol) and hydroxylamine (40wt% in water, 1.0 mL, 12 mmol). The final purification was conducted by flash column chromatography (silica gel, *n*-hexane/EtOAc 7:3). ¹H NMR (400 MHz, CDCl₃) δ: 7.33 (br s, 1H), 6.73 (s, 1H), 4.80 (s, 4H), 2.71 (t, 2H, *J* = 7.4 Hz), 1.61 (tq, 2H, *J* = 7.4, 7.4 Hz), 0.94 (t, 3H, *J* = 7.4 Hz), 0.92 (s, 9H), 0.10 (s, 6H); IR (KBr): 3493, 3381, 3195, 2953, 2927, 1647, 1584, 1396, 1043, 931, 839, 781 cm⁻¹; MS (FAB⁺) *m/z* 329 ((M+H)⁺).

5-2-16. *tert*-Butyl(dimethyl){[4-(propan-2-yl)thiophen-2-yl]methoxy}silane (**13d**)



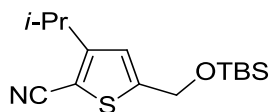
(a) *tert*-Butyl(dimethyl){[4-(prop-1-en-2-yl)thiophen-2-yl]methoxy}silane

According to a similar procedure to 5-2-10, the title compound (3.0 g, 11 mmol, 86%) was prepared from [(4-bromo-2-thienyl)methoxy]-*tert*-butyldimethylsilane (4.0 g, 13 mmol) [reference literature: *J. Med. Chem.* **2002**, *45*, 5005], [1,3-bis(diphenylphosphino)propane]dichloronickel (0.37 g, 0.69 mmol), isopropenylmagnesium bromide (0.50 M in THF, 42 mL, 21 mmol) and Et₂O (30 mL). The final purification was conducted by flash column chromatography (*n*-hexane/EtOAc). ¹H NMR (400 MHz, CDCl₃) δ: 7.10–7.07 (m, 2H), 5.29 (s, 1H), 4.98 (s, 1H), 4.84 (s, 2H), 2.08 (s, 3H), 0.93 (s, 9H), 0.11 (s, 6H); IR (liquid film): 2954, 2929, 2857, 1255, 1098, 1081, 838, 778 cm⁻¹; MS (FAB⁺) *m/z* 269 ((M+H)⁺).

(b) *tert*-Butyl(dimethyl){[4-(propan-2-yl)thiophen-2-yl]methoxy}silane (**13d**)

To a solution of *tert*-butyl(dimethyl){[4-(prop-1-en-2-yl)thiophen-2-yl]methoxy}silane (3.0 g, 11 mmol) in benzene (20 mL) was added rhodium(I) tris-(triphenylphosphine) chloride (0.46 g, 0.50 mmol) and the resulting mixture was degassed and saturated with hydrogen gas. After stirring at room temperature for 3 h, the reaction mixture was filtered through florisil and the filtrate was concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 9:1) to afford the title compound **13d** (2.6 g, 9.5 mmol, 86%). ¹H NMR (400 MHz, CDCl₃) δ: 6.83–6.80 (m, 2H), 4.83 (s, 2H), 2.89 (sept, 1H, *J* = 6.6 Hz), 1.22 (d, 6H, *J* = 6.6 Hz), 0.93 (s, 9H), 0.10 (s, 6H); IR (liquid film): 2957, 2929, 2857, 1471, 1255, 1081, 838, 777 cm⁻¹; MS (FAB⁺) *m/z* 269 (M–H)⁺.

5-2-17. 5-([*tert*-Butyl(dimethyl)silyl]oxy)methyl-3-(propan-2-yl)thiophene-2-carbonitrile (2g)



(a) 5-([*tert*-Butyl(dimethyl)silyl]oxy)methyl-3-(propan-2-yl)thiophene-2-carbaldehyde

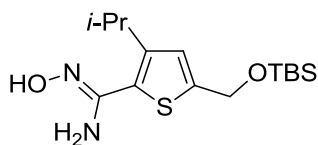
According to a similar procedure to 5-2-3 (b), the title compound (2.3 g, 7.5 mmol, 82%) was prepared from **13d** (2.5 g, 9.2 mmol), *n*-BuLi (1.6 M in hexane, 7.0 mL, 11 mmol) and DMF (1.4 mL, 18 mmol). ¹H NMR (400 MHz, CDCl₃) δ: 10.0 (s, 1H), 6.91 (s, 1H), 4.86 (s, 2H), 3.61 (sept, 1H, *J* = 6.6 Hz), 1.30 (d, 6H, *J* = 6.6 Hz), 0.94 (s, 9H), 0.12 (s, 6H); IR (liquid film): 2959, 2929, 2857, 1659, 1462, 1256, 1092, 839, 779 cm⁻¹; MS (FAB⁺) *m/z* 299 ((M+H)⁺).

(b) 5-([*tert*-Butyl(dimethyl)silyl]oxy)methyl-3-(propan-2-yl)thiophene-2-carbonitrile (2g)

According to a similar procedure to 5-2-3 (c), **2g** was quantitatively prepared from 5-([*tert*-butyl(dimethyl)silyl]oxy)methyl-3-(propan-2-yl)thiophene-2-carbaldehyde (2.3 g, 7.5 mmol), hydroxylamine hydrochloride (0.58 g, 8.3 mmol), Et₃N (2.1 mL, 15 mmol) and DCC (1.7 g, 8.3 mmol). ¹H NMR (400 MHz, CDCl₃) δ: 6.81 (s, 1H), 4.85 (s, 2H), 3.22 (sept, 1H, *J* = 6.6 Hz), 1.26 (d, 6H, *J* = 6.6 Hz), 0.93 (s, 9H), 0.11 (s, 6H); IR (liquid film): 2958, 2930, 2857, 2212, 2118, 1256, 1147, 1093, 839, 779 cm⁻¹; MS (FAB⁺) *m/z* 296 ((M+H)⁺).

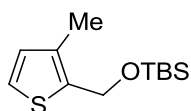
5-2-18.

5-([*tert*-Butyl(dimethyl)silyl]oxy)methyl-*N*-hydroxy-3-(propan-2-yl)thiophene-2-carboximidamide (3g)



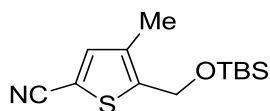
According to a similar to 5-2-2, **3g** (2.0 g, 6.1 mmol, 81%) was prepared from **2g** (2.2 g, 7.5 mmol) and hydroxylamine (40wt% in water, 2.0 mL, 24 mmol). The final purification was conducted by flash column chromatography (silica gel, *n*-hexane/EtOAc 7:3). ¹H NMR (400 MHz, CDCl₃) δ: 7.39 (br s, 1H), 6.81 (s, 1H), 4.81 (s, 2H), 4.80 (br s, 2H), 3.42 (sept, 1H, *J* = 6.8 Hz), 1.20 (d, 6H, *J* = 6.8 Hz), 0.93 (s, 9H), 0.11 (s, 6H); IR (KBr): 3487, 3373, 3240, 2959, 2928, 2858, 1639, 1054, 834, 779 cm⁻¹; MS (FAB⁺) *m/z* 329 ((M+H)⁺).

5-2-19. *tert*-Butyl(dimethyl)[(3-methylthiophen-2-yl)methoxy]silane (13e)



To a suspension of lithium aluminum hydride (1.2 g, 32 mmol) in THF (20 mL) was slowly added a solution of 3-methylthiophene-2-carboxylic acid (3.0 g, 21 mmol) in THF (10 mL) at 0 °C and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with sodium sulfate decahydrate at 0 °C and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with THF and filtered with Celite pad. The filtrate was concentrated and the residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 1:1). To the residue in DMF (16 mL) were successively added imidazole (2.9 g, 42 mmol) and TBSCl (4.8 g, 32 mmol) at room temperature. After stirring for 16 h, the reaction mixture was poured into water and extracted with Et₂O. The extract was washed with water and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 20:1) to afford the title compound **13e** (2.2 g, 9.1 mmol, 43% in 2 steps) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.11 (d, 1H, *J* = 5.1 Hz), 6.78 (d, 1H, *J* = 5.1 Hz), 4.79 (s, 2H), 2.18 (s, 3H), 0.93 (s, 9H), 0.10 (s, 6H); IR (liquid film): 2956, 2930, 2858, 1256, 1074, 838, 777, 702 cm⁻¹; MS (EI⁺) *m/z*: 242 (M⁺).

5-2-20. 5-((*tert*-Butyl(dimethyl)silyl)oxy)methyl)-4-methylthiophene-2-carbonitrile (**2h**)



(a) 5-((*tert*-Butyl(dimethyl)silyl)oxy)methyl)-4-methylthiophene-2-carbaldehyde

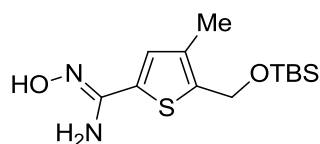
According to a similar procedure to 5-2-3 (b), the title compound (0.66 g, 2.4 mmol, 59%) was prepared from **13e** (1.0 g, 4.1 mmol), *n*-BuLi (1.6 M in hexane, 3.1 mL, 5.0 mmol) and DMF (0.67 mL, 8.7 mmol). ¹H NMR (400 MHz, CDCl₃) δ: 9.80 (s, 1H), 7.48 (s, 1H), 4.82 (s, 2H), 2.18 (s, 3H), 0.95 (s, 9H), 0.13 (s, 6H); IR (liquid film): 2955, 2930, 2858, 1672, 1250, 1101, 839, 780 cm⁻¹; MS (EI⁺) *m/z*: 271((M+H)⁺).

(b) 5-((*tert*-Butyl(dimethyl)silyl)oxy)methyl)-4-methylthiophene-2-carbonitrile (**2h**)

According to a similar procedure to 5-2-3 (c), **2h** (0.35 g, 1.3 mmol, 70%) was prepared from 5-((*tert*-butyl(dimethyl)silyl)oxy)methyl)-4-methylthiophene-2-carbaldehyde (0.50 g, 1.9 mmol), hydroxylamine hydrochloride (0.14 g, 2.0 mmol), Et₃N (0.52 mL, 3.7 mmol) and DCC (0.42 g, 2.0 mmol). ¹H NMR (400 MHz, CDCl₃) δ: 7.31 (s, 1H), 4.80 (s, 2H), 2.14 (s, 3H), 0.94 (s, 9H), 0.12 (s, 6H); IR (liquid film): 2955, 2931, 2858, 2216, 2119, 1363, 1257, 1183, 1101, 780 cm⁻¹; MS (EI⁺) *m/z*:

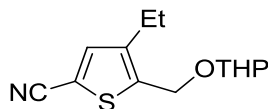
267(M⁺).

5-2-21. 5-([*tert*-Butyl(dimethyl)silyl]oxy)methyl)-*N*-hydroxy-4-methylthiophene-2-carboximide (3h)



According to a similar procedure to 5-2-2, **3h** (2.0 g, 6.5 mmol, 87%) was prepared from **2h** (2.0 g, 7.5 mmol) and hydroxylamine (40wt% in water, 1.7 mL, 21 mmol). The final purification by recrystallization (*n*-hexane/EtOAc) gave a white crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.02 (br s, 1H), 6.99 (s, 1H), 4.79 (br s, 2H), 4.77 (s, 2H), 2.16 (s, 3H), 0.94 (s, 9H), 0.12 (s, 6H); IR (KBr): 3488, 3343, 3214, 2929, 2858, 1651, 1595, 1394, 1255, 1029, 939, 836, 777 cm⁻¹; MS (FAB⁺) *m/z*: 301 ((M+H)⁺).

5-2-22. 4-Ethyl-5-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]thiophene-2-carbonitrile (2i)



(a) [5-([*tert*-Butyl(dimethyl)silyl]oxy)methyl]-3-ethylthiophen-2-yl]methanol

To a solution of 5-([*tert*-butyl(dimethyl)silyl]oxy)methyl)-3-ethylthiophene-2-carboxaldehyde (5-2-11 (a)) (1.5 g, 5.8 mmol) in MeOH (10 mL) was slowly added NaBH₄ (0.22 g, 5.8 mmol) at 0 °C. After stirring for 30 min at 0 °C, the solvent was evaporated *in vacuo* and the residue was poured into water (20 mL) and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 4:1 to 7:3) to afford the title compound (1.4 g, 5.5 mmol, 94%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 6.72 (s, 1H), 4.80 (s, 2H), 4.71 (d, 2H, *J* = 5.9 Hz), 2.57 (q, 2H, *J* = 7.4 Hz), 1.18 (t, 3H, *J* = 7.4 Hz), 0.93 (s, 9H), 0.11 (s, 6H); IR (liquid film): 3352, 1463, 1390, 1362, 1255, 1149, 1075 cm⁻¹; MS (FAB⁺) *m/z*: 285 ((M-H)⁺).

(b) 4-Ethyl-5-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]thiophene-2-carboxaldehyde

To a solution of [5-([*tert*-butyl(dimethyl)silyl]oxy)methyl]-3-ethyl-2-thienyl]methanol (1.4 g, 5.3 mmol) in CH₂Cl₂ (10 mL) were successively added 3,4-dihydro-2*H*-pyran (0.58 mL, 6.4 mmol) and *p*-toluenesulfonic acid (10 mg, 0.04 mmol) at 0 °C. After stirring for 30 min at room temperature, the reaction was quenched with sat. NaHCO₃. The resulting mixture was poured into water (20 mL) and

extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated.

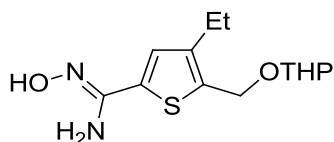
To a solution of the residue in THF (5.0 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 6.4 mL, 6.4 mmol), and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was poured into water and extracted with Et₂O. The extract was washed with water and brine, dried over MgSO₄, filtered and concentrated.

To a mixture of the residue and molecular sieves 4A (10 g) in CH₂Cl₂ (30 mL) was added pyridinium dichromate (3.3 g, 8.7 mmol) at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was diluted with Et₂O (150 mL) and filtered with silica gel to remove insoluble materials. The filtrate was concentrated and the residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 10:0 to 8:2) to afford the title compound (0.97 g, 3.8 mmol, 78% in 3 steps) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 9.80 (s, 1H), 7.55 (s, 1H), 4.87 (d, 1H, *J* = 13.5 Hz), 4.74 (t, 1H, *J* = 3.5 Hz), 4.65 (d, 1H, *J* = 13.5 Hz), 3.92-3.84 (m, 1H), 3.59-3.53 (m, 1H), 2.61 (q, 2H, *J* = 7.6 Hz), 1.92-1.50 (m, 6H), 1.23 (t, 3H, *J* = 7.6 Hz); IR (liquid film): 3440, 2942, 2873, 1670, 1454, 1158, 1121, 1036, 1023 cm⁻¹; MS (EI⁺) *m/z*: 254 (M⁺).

(c) 4-Ethyl-5-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]thiophene-2-carbonitrile (**2i**)

According to a similar procedure to 5-2-3 (c), **2i** (0.86 g, 3.4 mmol, 95%) was prepared from 4-ethyl-5-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]thiophene-2-carboxaldehyde (0.97 g, 3.6 mmol), hydroxylamine hydrochloride (0.29 g, 3.9 mmol), Et₃N (1.1 mL, 7.2 mmol) and DCC (0.87 g, 3.9 mmol). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc) gave a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.38 (s, 1H), 4.84 (d, 1H, *J* = 13.3 Hz), 4.71 (t, 1H, *J* = 3.3 Hz), 4.62 (d, 1H, *J* = 13.3 Hz), 3.90-3.82 (m, 1H), 3.59-3.52 (m, 1H), 2.58 (q, 2H, *J* = 7.6 Hz), 1.90-1.52 (m, 6H), 1.19 (t, 3H, *J* = 7.6 Hz); IR (liquid film): 2942, 2873, 2216, 1454, 1342, 1201, 1174, 1123, 1077, 1066, 1036, 1024, 903 cm⁻¹; MS (EI⁺) *m/z*: 251 (M⁺).

5-2-23. 4-Ethyl-*N*-hydroxy-5-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]thiophene-2-carboximidamide (**3i**)

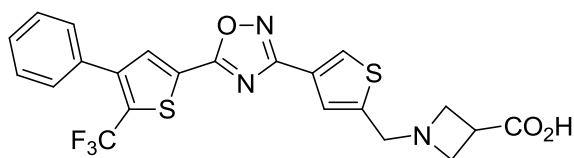


According to a similar procedure to 5-2-2, **3i** (0.96 g, 3.3 mmol, 98%) was prepared from **2i** (0.86 g, 3.4 mmol) and hydroxylamine (50wt% in water, 0.5 mL, 9.2 mmol). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc) gave a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.23 (br s, 1H), 7.07 (s, 1H), 4.82 (br s, 2H), 4.80 (d, 1H, *J* = 12.9 Hz), 4.71 (t, 1H, *J* = 3.3 Hz), 4.61 (d, 1H, *J* = 12.9 Hz), 3.94-3.87 (m, 1H), 3.59-3.52 (m, 1H), 2.59 (q, 2H, *J* = 7.6 Hz), 1.89-1.47 (m, 6H), 1.20

(t, 3H, $J = 7.6$ Hz); IR (liquid film): 3353, 2942, 2872, 1635, 1588, 1390, 1344, 1117, 1022 cm^{-1} ; MS (FAB⁺) m/z 285 ((M+H)⁺).

5-2-24.

1-[(4-{5-[4-Phenyl-5-(trifluoromethyl)thiophen-2-yl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (7a)



(a) (4-{5-[4-Phenyl-5-(trifluoromethyl)thiophen-2-yl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol

To a solution of **3a** (0.43 g, 1.5 mmol) and 4-phenyl-5-(trifluoromethyl)thiophene-2-carbonyl chloride (0.52 g, 1.8 mmol) in THF (6.0 mL) was added *N,N*-diisopropylethylamine (0.52 mL, 3.0 mmol) at 0 °C. After stirring at 0 °C for 1 h, the reaction was quenched with sat. NaHCO_3 . The resulting mixture was poured into water and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4 , filtered and concentrated.

To a solution of the residue in THF (6.0 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 3.0 mL, 3.0 mmol) and the resulting mixture was stirred at 60 °C for 3 h. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 2:1 to 1:1) to afford the title compound (0.61 g, 1.5 mmol, 99%) as a white crystalline solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.07 (d, 1H, $J = 1.2$ Hz), 7.87 (d, 1H, $J = 1.2$ Hz), 7.56 (s, 1H), 7.45 (s, 5H), 4.89 (s, 2H), 1.95 (br s, 1H); IR (KBr): 3324, 1606, 1578, 1417, 1313, 1268, 1183, 1126 cm^{-1} ; MS (FAB⁺) m/z 409 ((M+H)⁺).

(b) Ethyl

1-[(4-{5-[4-phenyl-5-(trifluoromethyl)thiophen-2-yl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate

To a solution of **a** in THF (6.0 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 3.0 mL, 3.0 mmol) and the resulting mixture was stirred at 60 °C for 3 h. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 2:1 to 1:1) to afford the title compound (0.61 g, 1.5 mmol, 99%) as a white crystalline solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.07 (d, 1H, $J = 1.2$ Hz), 7.87 (d, 1H, $J = 1.2$ Hz), 7.56 (s, 1H), 7.45 (s, 5H), 4.89 (s, 2H), 1.95 (br s, 1H); IR (KBr): 3324, 1606, 1578, 1417, 1313, 1268, 1183, 1126 cm^{-1} ; MS (FAB⁺) m/z 409 ((M+H)⁺).

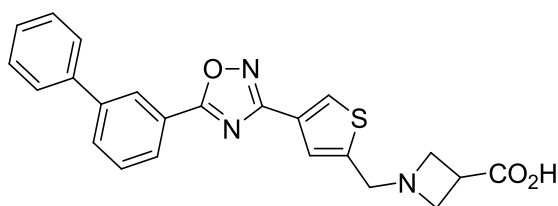
To a solution of **a** (0.10 g, 0.25 mmol) in CH_2Cl_2 (6.0 mL) were successively added carbon tetrabromide (0.17 g, 0.50 mmol) and triphenylphosphine (0.13 g, 0.50 mmol) at 0 °C and the resulting mixture was stirred for 1 h at 0 °C. To this were successively added ethyl 3-azetidinecarboxylate hydrochloride (62 mg, 0.38 mmol) and *N,N*-diisopropylethylamine (0.11 mL, 0.63 mmol) at 0 °C. After stirring at 25 °C for 2 h, the reaction was quenched with sat. NaHCO_3 . The resulting biphasic mixture was poured into water and extracted with EtOAc. The extract was washed with brine, dried over MgSO_4 , filtered and

concentrated. The residue was purified by thin layer chromatography on a silica gel plate (*n*-hexane/EtOAc 3:2) to afford the title compound (73 mg, 0.14 mmol, 56%) as a white crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.04 (d, 1H, *J* = 1.2 Hz), 7.89 (d, 1H, *J* = 1.2 Hz), 7.47 (s, 6H), 4.17 (q, 2H, *J* = 7.0 Hz), 3.83 (s, 2H), 3.68–3.55 (m, 2H), 3.41–3.31 (m, 3H), 1.27 (t, 3H, *J* = 7.0 Hz); IR (KBr): 1720, 1608, 1577, 1316, 1272, 1197, 1180, 1132 cm⁻¹; MS (FAB⁺) *m/z* 520 ((M+H)⁺).

(c) 1-[(4-{5-[4-Phenyl-5-(trifluoromethyl)thiophen-2-yl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**7a**)

To a solution of ethyl 1-[(4-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-2-thienyl)methyl]azetidine-3-carboxylate (70 mg, 0.13 mmol) in 1,4-dioxane (2.0 mL) was added NaOH (1.0 M in water, 0.39 mL, 0.39 mmol), and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with acetic acid (22 μL, 0.39 mmol) and the resulting mixture was concentrated. To the residue were added successively MeOH (1.0 mL) and water (1.0 mL), and the white solid precipitated was collected by filtration using a Kiriya funnel, washed with a mixed solvent of water and methanol (3:7) and dried *in vacuo* to afford the title compound **7a** (34 mg, 0.069 mmol, 53%) as a white crystalline solid. ¹H NMR (400 MHz, CD₃CO₂D) δ: 8.37 (s, 1H), 8.03 (s, 1H), 7.93 (s, 1H), 7.60–7.45 (m, 5H), 4.76 (s, 2H), 4.58–4.46 (m, 2H), 4.46–4.35 (m, 2H), 3.88–3.75 (m, 1H); IR (KBr): 3429, 1605, 1579, 1270, 1178, 1133 cm⁻¹; MS (FAB⁺) *m/z* 492 ((M+H)⁺).

5-2-25. 1-[(4-{5-(Biphenyl-3-yl)-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**7b**)



(a) Biphenyl-3-carboxylic acid

To a solution of 3-bromobiphenyl (0.47 g, 2.0 mmol) in THF (7.0 mL) was slowly added *n*-BuLi (1.6 M in hexane, 1.5 mL, 2.4 mmol) at -78 °C. After stirring at -78 °C for 20 min, CO₂ (dry ice, excess amount) was added and the resulting mixture was stirred at -78 °C for 1 h. The reaction was quenched with NaOH (1.0 M in water, 3.0 mL). The resulting mixture was diluted with Et₂O and extracted with water twice. The aqueous phase was washed with Et₂O twice and acidified with HCl (1.0 M in water). The aqueous phase was extracted with EtOAc and the extract was dried over Na₂SO₄, filtered and concentrated to afford the title compound (0.36 g, 1.8 mmol, 90%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.33 (dd, 1H, *J* = 2.0, 1.6 Hz), 8.08 (ddd, 1H, *J* = 7.4, 1.6, 1.2 Hz), 7.83 (ddd, 1H, *J* = 7.8, 2.0, 1.2 Hz), 7.64–7.59 (m, 2H), 7.54 (dd, 1H, *J* = 7.8, 7.4 Hz), 7.48–7.42 (m, 2H),

7.40–7.35 (m, 1H).

(b) {4-[5-(Biphenyl-3-yl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol

To a solution of biphenyl-3-carboxylic acid (0.22 g, 1.1 mmol) in acetonitrile (8.0 mL) were successively added 1-hydroxybenzotriazole (0.18 g, 1.3 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.23 g, 1.1 mmol) and **3a** (0.29 g, 1.0 mmol), and the resulting mixture was stirred at room temperature for 30 min. The reaction was quenched with water and the resulting biphasic mixture was poured into water and extracted with EtOAc. The extract was washed successively with HCl (0.1 M in water), sat. NaHCO₃ and brine, and dried over Na₂SO₄, filtered and concentrated.

To a solution of the residue in THF (8.0 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 2.0 mL, 2.0 mmol) and the resulting mixture was stirred at 50 °C for 1 h. The reaction mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by recrystallization (EtOAc/*i*-Pr₂O 5.0 mL/2.0 mL) to afford the title compound (0.20 g, 0.59 mmol, 59%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.39–8.37 (m, 1H), 8.29–8.26 (m, 1H), 8.19–8.15 (m, 1H), 8.06–8.02 (m, 1H), 7.81–7.74 (m, 3H), 7.57–7.44 (m, 4H), 5.66 (t, 1H, *J* = 5.9 Hz), 4.72 (d, 2H, *J* = 5.9 Hz); IR (KBr): 3373, 1577, 1556, 1024, 831, 742, 694 cm⁻¹; MS (FAB⁺) *m/z*: 335 ((M+H)⁺).

(c) Ethyl 1-({4-[5-(biphenyl-3-yl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate

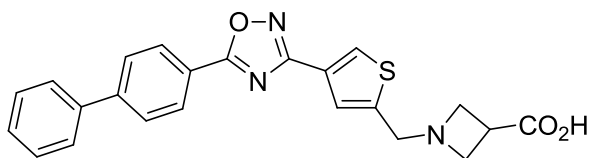
According to a similar procedure to 5-2-24 (b), the title compound (0.15 g, 0.34 mmol, 58%) was prepared from {4-[5-(biphenyl-3-yl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol (0.19 g, 0.58 mmol), carbon tetrabromide (0.34 g, 1.2 mmol), triphenylphosphine (0.30 g, 1.2 mmol), ethyl 3-azetidinecarboxylate hydrochloride (0.14 g, 0.87 mmol), *N,N*-diisopropylethylamine (0.25 mL, 1.5 mmol) and CH₂Cl₂ (8.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 9:1 to 1:9) gave a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.44–8.42 (m, 1H), 8.19–8.15 (m, 1H), 8.08–8.06 (m, 1H), 7.85–7.82 (m, 1H), 7.70–7.66 (m, 2H), 7.63 (t, 1H, *J* = 7.8 Hz), 7.54–7.48 (m, 3H), 7.44–7.39 (m, 1H), 4.17 (q, 2H, *J* = 7.0 Hz), 3.84 (s, 2H), 3.65–3.59 (m, 2H), 3.40–3.33 (m, 3H), 1.27 (t, 3H, *J* = 7.0 Hz); IR (KBr): 2979, 2845, 1732, 1556, 1345, 1195, 743, 691 cm⁻¹; MS (FAB⁺) *m/z*: 446 ((M+H)⁺).

(d) 1-({4-[5-(Biphenyl-3-yl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**7b**)

According to a similar procedure to 5-2-24 (c), **7b** (0.11 g, 0.26 mmol, 78%) was prepared from ethyl 1-({4-[5-(biphenyl-3-yl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (0.15 g, 0.33 mmol), NaOH (1.0 M in water, 0.99 mL, 0.99 mmol), 1,4-dioxane (4.0 mL) and acetic acid (57 μL, 1.01 mmol). The final purification by recrystallization (MeOH/water 2 mL/3 mL) gave a white solid. ¹H NMR (400 MHz, CD₃CO₂D) δ: 8.48–8.44 (m, 1H), 8.39–8.36 (m, 1H), 8.22–8.17 (m, 1H), 7.97–7.90 (m, 2H), 7.76–7.65 (m, 3H), 7.54–7.40 (m, 3H), 4.75 (s, 2H), 4.57–4.35 (m, 4H), 3.87–3.77 (m, 1H); IR

(KBr): 3430, 1598, 1577, 1405, 1323, 746, 694 cm^{-1} ; MS (FAB⁺) m/z : 418 ((M+H)⁺).

5-2-26. 1-({4-[5-(Biphenyl-4-yl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (7c)



(a) {4-[5-(Biphenyl-4-yl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol

According to a similar procedure to 5-2-24 (a), the title compound (0.28 g, 0.85 mmol, 65% in 2 steps) was prepared from **3a** (0.37 g, 1.3 mmol), biphenyl-4-carbonyl chloride (0.34 g, 1.56 mmol), *N,N*-diisopropylethylamine (0.45 mL, 2.6 mmol) and THF (5.0 mL) instead of CH_2Cl_2 , and tetrabutylammonium fluoride (1.0 M in THF, 2.6 mL, 2.6 mmol) and THF (5.0 mL). The final purification by recrystallization (*n*-hexane/EtOAc 6.0 mL/6.0 mL) gave a white solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.29–8.22 (m, 2H), 8.12–8.09 (m, 1H), 7.80–7.73 (m, 2H), 7.68–7.59 (m, 3H), 7.53–7.39 (m, 3H), 4.91 (s, 2H); IR (KBr): 3315, 1612, 1576, 1037, 744 cm^{-1} ; MS (FAB⁺) m/z : 335 ((M+H)⁺).

(b) Ethyl 1-({4-[5-(biphenyl-4-yl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate

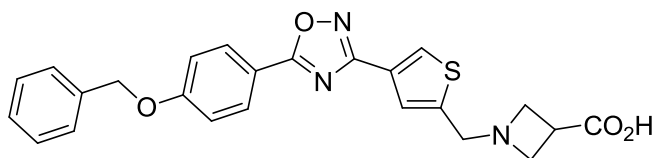
According to a similar procedure to 5-2-24 (b), the title compound (0.80 g, 0.18 mmol, 50%) was prepared from {4-[5-(biphenyl-4-yl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol (0.12 g, 0.36 mmol), carbon tetrabromide (0.24 g, 0.72 mmol), triphenylphosphine (0.19 g, 0.72 mmol), ethyl 3-azetidinecarboxylate hydrochloride (89 mg, 0.54 mmol), *N,N*-diisopropylethylamine (0.16 mL, 0.90 mmol) and CH_2Cl_2 (6.5 mL). The final purification by thin layer chromatography on a silica gel plate (*n*-hexane/EtOAc 1:1) gave a white solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.27–8.22 (m, 2H), 8.05–8.03 (m, 1H), 7.78–7.74 (m, 2H), 7.66–7.62 (m, 2H), 7.52–7.38 (m, 4H), 4.16 (q, 2H, $J = 7.0$ Hz), 3.83 (s, 2H), 3.64–3.59 (m, 2H), 3.39–3.33 (m, 3H), 1.27 (t, 3H, $J = 7.0$ Hz); IR (KBr): 1734, 1612, 1577, 1349, 1191, 746 cm^{-1} ; MS (FAB⁺) m/z : 446 ((M+H)⁺).

(c) 1-({4-[5-(Biphenyl-4-yl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (7c)

According to a similar procedure to 5-2-24 (c), **7c** (64 mg, 0.15 mmol, 85%) was prepared from ethyl 1-({4-[5-(biphenyl-4-yl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (80 mg, 0.18 mmol), NaOH (1.0 M in water, 0.54 mL, 0.54 mmol), 1,4-dioxane (2.0 mL) and acetic acid (31 μL , 0.54 mmol). The final purification by recrystallization (MeOH/water 8.0 mL/2.0 mL) gave a white solid. ^1H NMR (400 MHz, $\text{CD}_3\text{CO}_2\text{D}$) δ : 8.35–8.32 (m, 1H), 8.29–8.23 (m, 2H), 7.93–7.89 (m, 1H), 7.87–7.81 (m, 2H), 7.74–7.66 (m, 2H), 7.51–7.36 (m, 3H), 4.74 (s, 2H), 4.56–4.30 (m, 4H), 3.86–3.75 (m, 1H); IR (KBr): 3434, 1613, 1579, 1384, 746 cm^{-1} ; MS (FAB⁺) m/z : 418 ((M+H)⁺).

5-2-27.

1-[(4-{5-[4-(Benzyloxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (7d)



(a) 4-(Benzyloxy)benzoic acid

To a solution of *p*-hydroxybenzoic acid ethyl ester (0.50 g, 3.0 mmol) in DMF (5.0 mL) were successively added K₂CO₃ (0.83 g, 6.0 mmol) and benzyl bromide (0.43 mL, 3.6 mmol) at room temperature. After stirring at room temperature for 1 h, the reaction was quenched with water at 0 °C. The mixture was poured into water and extracted with EtOAc. The extract was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 95:5 to 70:30).

To a solution of the obtained product in EtOH (6.0 mL) was added NaOH (1.0 M in water, 6.0 mL, 6.0 mmol) and the resulting mixture was stirred at 50 °C for 1 h. The reaction mixture was concentrated to remove the organic solvent and washed with Et₂O. The aqueous phase was acidified with HCl (37%wt, 12 M in water) and extracted with EtOAc. The extract was dried over Na₂SO₄, filtered and concentrated to afford the title compound (0.41 g, 1.8 mmol, 60% in 2 steps) as a white solid. ¹H NMR (400 MHz, CDCl₃+CD₃OD) δ: 7.95–7.89 (m, 2H), 7.29–7.09 (m, 7H), 3.89 (s, 2H).

(b) (4-{5-[4-(Benzyloxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol

To a solution of 4-(benzyloxy)benzoic acid (0.18 g, 0.77 mmol) in acetonitrile (7.0 mL) were successively added 1-hydroxybenzotriazole (0.12 g, 0.91 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.16 g, 0.84 mmol) and **3a** (0.20 g, 0.70 mmol), and the resulting mixture was stirred at 50 °C for 30 min. The reaction was quenched with water and the resulting biphasic mixture was poured into water and extracted with EtOAc. The combined organic layers were washed successively with HCl (0.1 M in water), sat. aq. NaHCO₃ and brine, and dried over Na₂SO₄, filtered and concentrated.

To a solution of the residue in THF (5.0 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 1.4 mL, 1.4 mmol) and the resulting mixture was stirred at 50 °C for 2 h. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was recrystallized from a mixed solvent of *n*-hexane (6.0 mL) and EtOAc (2.0 mL) to afford 0.16 g of the title compound including an impure material derived from tetrabutylammonium fluoride, which was used to the next step without further purification. MS

(FAB⁺) *m/z* 365 ((M+H)⁺).

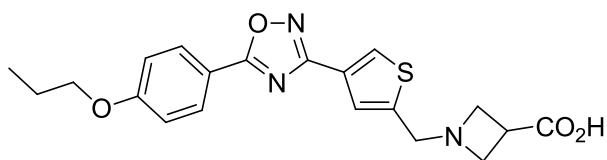
(c) Ethyl

1-[(4-{5-[4-(benzyloxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate
According to a similar procedure to 5-2-24 (b), the title compound (92 mg, 0.19 mmol, 25% in 4 steps) was prepared using (4-{5-[4-(benzyloxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol (0.16 g, obtained in 5-2-27 (b)), carbon tetrabromide (0.22 g, 0.66 mmol), triphenylphosphine (0.17 g, 0.66 mmol), ethyl 3-azetidinecarboxylate hydrochloride (0.11 g, 0.66 mmol), *N,N*-diisopropylethylamine (0.19 mL, 1.1 mmol) and CH₂Cl₂ (6.0 mL). The final purification by thin layer chromatography on a silica gel plate (*n*-hexane/EtOAc 3:4) gave a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.11 (d, 2H, *J* = 9.0 Hz), 7.99 (d, 1H, *J* = 1.2 Hz), 7.47–7.33 (m, 6H), 7.09 (d, 2H, *J* = 9.0 Hz), 5.15 (s, 2H), 4.16 (q, 2H, *J* = 7.0 Hz), 3.82 (s, 2H), 3.63–3.59 (m, 2H), 3.38–3.32 (m, 3H), 1.27 (t, 3H, *J* = 7.0 Hz); IR (KBr): 2979, 2848, 1729, 1615, 1504, 1257, 1207, 756 cm⁻¹; MS (FAB⁺) *m/z* 476 ((M+H)⁺).

(d) 1-[(4-{5-[4-(Benzyloxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**7d**)

According to a similar procedure to 5-2-24 (c), **7d** (76 mg, 0.16 mmol, 84%) was prepared from ethyl 1-[(4-{5-[4-(benzyloxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate (90 mg, 0.19 mmol), NaOH (1.0 M in water, 0.57 mL, 0.57 mmol), 1,4-dioxane (2.0 mL) and acetic acid (33 μL, 0.57 mmol). The final purification by recrystallization (MeOH/water 2.0 mL/2.0 mL) gave a white solid. ¹H NMR (400 MHz, CD₃CO₂D) δ: 8.33–8.31 (m, 1H), 8.18–8.12 (m, 2H), 7.92–7.89 (m, 1H), 7.49–7.44 (m, 2H), 7.42–7.30 (m, 3H), 7.22–7.16 (m, 2H), 5.21 (s, 2H), 4.73 (s, 2H), 4.56–4.45 (m, 2H), 4.44–4.34 (m, 2H), 3.86–3.75 (m, 1H); IR (KBr): 3423, 3084, 1614, 1503, 1429, 1259, 1175, 834, 760, 514 cm⁻¹; MS (FAB⁺) *m/z* 448 ((M+H)⁺).

5-2-28. 1-[(4-{5-[4-(Propoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**7e**)



(a) 4-Propoxybenzoyl chloride

To a solution of 4-propoxybenzoic acid (86 mg, 0.48 mmol) in benzene (4.0 mL) were added thionyl chloride (70 μL, 0.96 mmol) and a catalytic amount of DMF and the resulting mixture was stirred at 70 °C for 1 h. The reaction mixture was diluted with toluene and azeotropically evaporated *in vacuo* twice to afford the crude product of the title compound, which was used to the next step without

further purification.

(b) {4-[5-(4-Propoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol

According to a similar procedure to 5-2-24 (a), the title compound (88 mg, 0.28 mmol, 70% in 2 steps) was prepared from **3a** (0.12 g, 0.40 mmol), 4-propoxybenzoyl chloride (0.48 mmol), *N,N*-diisopropylethylamine (0.14 mL, 0.80 mmol) and THF (5.0 mL) instead of CH₂Cl₂, and tetrabutylammonium fluoride (1.0 M in THF, 0.80 mL, 0.80 mmol) and THF (4.0 mL). The final purification by recrystallization (*n*-hexane/EtOAc 2.0 mL/3.0 mL) gave a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.13–8.08 (m, 2H), 8.07–8.04 (m, 1H), 7.58–7.56 (m, 1H), 7.03–6.98 (m, 2H), 4.88 (s, 2H), 4.00 (t, 2H, *J* = 6.7 Hz), 1.85 (tq, 2H, *J* = 7.4, 6.7 Hz), 1.07 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3323, 1610, 1502, 1429, 1255, 1184, 1016, 756 cm⁻¹; MS (FAB⁺) *m/z* 317 ((M+H)⁺).

(c) Ethyl

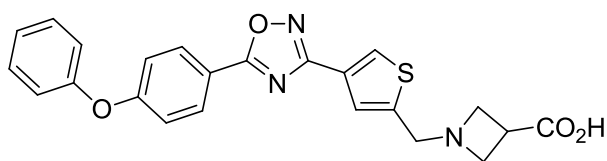
1-({4-[5-(4-propoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate

According to a similar procedure to 5-2-24 (b), the title compound (67 mg, 0.20 mmol, 56%) was prepared from {4-[5-(4-propoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol (0.12 g, 0.36 mmol), carbon tetrabromide (0.24 g, 0.72 mmol), triphenylphosphine (0.19 g, 0.72 mmol), ethyl 3-azetidinecarboxylate hydrochloride (89 mg, 0.54 mmol), *N,N*-diisopropylethylamine (0.16 mL, 0.90 mmol) and CH₂Cl₂ (6.5 mL). The final purification by thin layer chromatography on a silica gel plate (*n*-hexane/EtOAc 1:1) gave a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.13–8.08 (m, 2H), 8.16–7.99 (m, 1H), 7.48–7.46 (m, 1H), 7.03–6.98 (m, 2H), 4.16 (q, 2H, *J* = 7.0 Hz), 4.00 (t, 2H, *J* = 6.6 Hz), 3.82 (s, 2H), 3.65–3.58 (m, 2H), 3.39–3.32 (m, 3H), 1.85 (tq, 2H, *J* = 7.4, 6.6 Hz), 1.27 (t, 3H, *J* = 7.0 Hz), 1.07 (t, 3H, *J* = 7.4 Hz); IR (KBr): 2960, 1734, 1611, 1503, 1430, 1261, 1205, 1185, 759 cm⁻¹; MS (FAB⁺) *m/z* 428 ((M+H)⁺).

(d) 1-({4-[5-(4-Propoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid
(7e)

According to a similar procedure to 5-2-24 (c), **7e** (51 mg, 0.13 mmol, 80%) was prepared from ethyl 1-({4-[5-(4-propoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (67 mg, 0.16 mmol), NaOH (1.0 M in water, 0.48 mL, 0.48 mmol), 1,4-dioxane (2.0 mL) and acetic acid (28 μL, 0.49 mmol). The final purification by recrystallization (MeOH/water 2.0 mL/2.0 mL) gave a white solid. ¹H NMR (400 MHz, CD₃CO₂D) δ: 8.35–8.30 (m, 1H), 8.18–8.11 (m, 2H), 7.93–7.89 (m, 1H), 7.13–7.07 (m, 2H), 4.74 (s, 2H), 4.57–4.46 (m, 2H), 4.46–4.35 (m, 2H), 4.06 (t, 2H, *J* = 6.6 Hz), 3.88–3.75 (m, 1H), 1.85 (tq, 2H, *J* = 7.4, 6.6 Hz), 1.06 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3432, 2967, 1617, 1433, 1263, 833, 758 cm⁻¹; MS (FAB⁺) *m/z* 400 ((M+H)⁺).

5-2-29. 1-({4-[5-(4-Phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (7f)



(a) 4-Phenoxybenzoyl chloride

According to a similar procedure to 5-2-28 (a), the crude product of the title compound was prepared from 4-phenoxybenzoic acid (0.10 g, 0.48 mmol), thionyl chloride (70 μ L, 0.96 mmol), a catalytic amount of DMF and benzene (4.0 mL). This crude product was used to the next step without further purification.

(b) {4-[5-(4-Phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol

According to a similar procedure to 5-2-24 (a), the title compound (98 mg, 0.28 mmol, 70% in 2 steps) was prepared from **3a** (0.12 g, 0.40 mmol), 4-phenoxybenzoyl chloride (0.48 mmol), *N,N*-diisopropylethylamine (0.14 mL, 0.80 mmol) and THF (5.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 0.80 mL, 0.80 mmol) and THF (4.0 mL). The final purification by recrystallization (*n*-hexane/EtOAc 2.0 mL/3.0 mL) gave a white solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.14–8.10 (m, 2H), 8.07–8.04 (m, 1H), 7.60–7.55 (m, 1H), 7.44–7.37 (m, 2H), 7.23–7.18 (m, 1H), 7.11–7.06 (m, 4H), 4.88 (s, 2H); IR (KBr): 3400, 1587, 1487, 1428, 1227, 755 cm^{-1} ; MS (FAB $^+$) m/z 351 ((M+H) $^+$).

(c) Ethyl

1-({4-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate

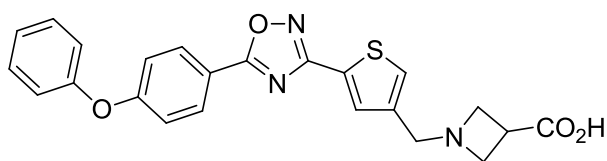
According to a similar procedure to 5-2-24 (b), the title compound (81 mg, 0.18 mmol, 63%) was prepared from {4-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol (98 mg, 0.28 mmol), carbon tetrabromide (0.19 g, 0.56 mmol), triphenylphosphine (0.15 g, 0.56 mmol), ethyl 3-azetidinecarboxylate hydrochloride (60 mg, 0.36 mmol), *N,N*-diisopropylethylamine (0.12 mL, 0.70 mmol) and CH_2Cl_2 (5.0 mL). The final purification by thin layer chromatography on a silica gel plate (*n*-hexane/EtOAc 4:5) gave a white solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.14–8.10 (m, 2H), 8.02–8.00 (m, 1H), 7.48–7.46 (m, 1H), 7.43–7.37 (m, 2H), 7.23–7.18 (m, 1H), 7.11–7.05 (m, 4H), 4.16 (q, 2H, J = 7.0 Hz), 3.82 (s, 2H), 3.63–3.57 (m, 2H), 3.39–3.30 (m, 3H), 1.27 (t, 3H, J = 7.0 Hz); IR (KBr): 2975, 1724, 1487, 1234, 1195, 1170, 828, 755 cm^{-1} ; MS (FAB $^+$) m/z 462 ((M+H) $^+$).

(d) 1-({4-[5-(4-Phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid
(**7f**)

According to a similar procedure to 5-2-24 (c), **7f** (60 mg, 0.14 mmol, 77%) was prepared from ethyl 1-({4-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (81 mg, 0.18 mmol), NaOH (1.0 M in water, 0.54 mL, 0.54 mmol), 1,4-dioxane (2.0 mL) and acetic acid (31 μ L,

0.54 mmol). The final purification by recrystallization (MeOH/water 2.0 mL/2.0 mL) gave a white solid. ^1H NMR (400 MHz, $\text{CD}_3\text{CO}_2\text{D}$) δ : 8.33 (s, 1H), 8.19 (d, 2H, J = 8.6 Hz), 7.91 (s, 1H), 7.45 (dd, 2H, J = 8.2, 7.6 Hz), 7.25 (t, 1H, J = 7.6 Hz), 7.17–7.12 (m, 4H), 4.74 (s, 2H), 4.57–4.47 (m, 2H), 4.46–4.35 (m, 2H), 3.90–3.74 (m, 1H); IR (KBr): 3427, 3088, 1614, 1589, 1489, 1250, 758 cm^{-1} ; MS (FAB $^+$) m/z : 434 ((M+H) $^+$).

5-2-30. 1-({5-[5-(4-Phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-3-yl}methyl)azetidine-3-carboxylic acid (7g)



(a) {5-[5-(4-Phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-3-yl}methanol

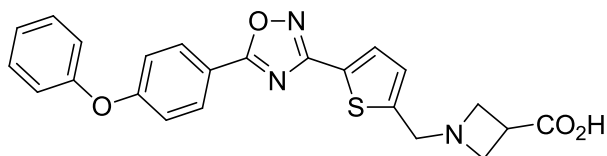
According to a similar procedure to 5-2-25 (b), the title compound (0.15 g, 0.44 mmol, 73% in 2 steps) was prepared from **3b** (0.17 g, 0.60 mmol), 4-phenoxybenzoic acid (0.14 g, 0.63 mmol), 1-hydroxybenzotriazole (89 mg, 0.66 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.13 g, 0.66 mmol) and acetonitrile (5.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 1.2 mL, 1.2 mmol) and THF (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 2:1 to 1:1) gave a white solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.16–8.11 (m, 2H), 7.85–7.81 (m, 1H), 7.44–7.38 (m, 3H), 7.23–7.18 (m, 1H), 7.13–7.06 (m, 4H), 4.74 (d, 2H, J = 5.5 Hz), 1.75 (t, 1H, J = 5.5 Hz); IR (KBr): 3440, 3068, 1612, 1587, 1489, 1240, 1012, 782 cm^{-1} ; MS (FAB $^+$) m/z : 351 ((M+H) $^+$).

(b) 1-({5-[5-(4-Phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-3-yl}methyl)azetidine-3-carboxylic acid (7g)

To a solution of {5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-3-yl}methanol (0.15 g, 0.43 mmol) in CH_2Cl_2 (7.0 mL) were successively added carbon tetrabromide (0.19 g, 0.56 mmol) and triphenylphosphine (0.15 g, 0.56 mmol) at 0 °C and the resulting mixture was stirred at 0 °C for 30 min. To this were successively added methyl 3-azetidinecarboxylate hydrochloride (99 mg, 0.65 mmol) and *N,N*-diisopropylethylamine (0.22 mL, 1.3 mmol) at 0 °C. After stirring at room temperature for 5 h, the reaction was quenched with sat. NaHCO_3 . The resulting biphasic mixture was poured into water and extracted with EtOAc. The extract was washed with brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by thin layer chromatography on a silica gel plate (*n*-hexane/EtOAc 4:3), followed by flash column chromatography (amino-functionalized silica gel, CH_2Cl_2) to afford the inseparable mixture (0.26 g) of methyl 1-({5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-3-yl}methyl)azetidine-3-carboxylate and triphenylphosphine oxide, which was used to the next step without further purification.

To a solution of the obtained product in 1,4-dioxane (3.0 mL) was added NaOH (1.0 M in water, 1.0 mL, 1.0 mmol), and the resulting mixture was stirred at room temperature for 2.5 h. After removal of the organic solvent *in vacuo*, the mixture was dissolved in methanol (1.0 mL) and water (0.40 mL), and acetic acid (59 μ L, 1.0 mmol) was added. The resulting mixture was concentrated and the residue was recrystallized from methanol (3.0 mL) and water (2.0 mL) to afford the title compound **7g** (0.14 g, 0.31 mmol, 72% in 2 steps) as a white solid. ^1H NMR (400 MHz, $\text{CD}_3\text{CO}_2\text{D}$) δ : 8.21–8.15 (m, 2H), 7.99 (s, 1H), 7.93 (s, 1H), 7.48–7.41 (m, 2H), 7.27–7.22 (m, 1H), 7.18–7.11 (m, 4H), 4.55 (s, 2H) 4.70–4.17 (m, 4H), 3.90–3.72 (m, 1H); IR (KBr): 3424, 3066, 1611, 1594, 1487, 1247, 1165, 791 cm^{-1} ; MS (FAB $^+$) m/z 434 ((M+H) $^+$).

5-2-31. 1-({5-[5-(4-Phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methy l)azetidine-3-carboxylic acid (7h)



(a) {5-[5-(4-Phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol

According to a similar procedure to 5-2-25 (b), the title compound (97 mg, 0.28 mmol, 55% in 2 steps) was prepared from **3c** (0.14 g, 0.50 mmol), 4-phenoxybenzoic acid (0.12 g, 0.55 mmol), 1-hydroxybenzotriazole (88 mg, 0.65 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.12 g, 0.60 mmol) and acetonitrile (5.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 1.0 mL, 1.0 mmol) and THF (4.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:1) gave a white crystalline solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.61 (d, 2H, J = 8.6 Hz), 7.71 (d, 1H, J = 3.5 Hz), 7.44–7.35 (m, 2H), 7.28–7.19 (m, 2H), 7.10–7.03 (m, 4H), 4.89 (d, 2H, J = 5.9 Hz), 1.89 (t, 1H, J = 5.9 Hz); IR (KBr): 3331, 1613, 1590, 1575, 1487, 1366, 1241 cm^{-1} ; MS (FAB $^+$) m/z 351 ((M+H) $^+$).

(b) Ethyl 1-({5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methy l)azetidine-3-carboxylate

According to a similar procedure to 5-2-24 (b), the title compound (93 mg, 0.20 mmol, 72%) was prepared from {5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol (97 mg, 0.28 mmol), carbon tetrabromide (0.19 g, 0.56 mmol), triphenylphosphine (0.15 g, 0.56 mmol), ethyl 3-azetidinecarboxylate hydrochloride (70 mg, 0.42 mmol), *N,N*-diisopropylethylamine (0.18 mL, 1.1 mmol) and CH_2Cl_2 (5.0 mL). The final purification by thin layer chromatography on a silica gel plate (*n*-hexane/EtOAc 4:3) gave a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ : 8.14 (d, 2H, J = 9.0 Hz), 7.70

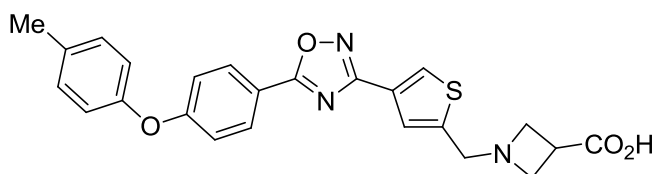
(d, 1H, J = 3.3 Hz), 7.42 (t, 2H, J = 7.8 Hz), 7.23 (t, 1H, J = 7.4 Hz), 7.15–7.06 (m, 4H), 6.96 (d, 1H, J = 3.3 Hz), 4.17 (q, 2H, J = 7.0 Hz), 3.84 (s, 2H), 3.68–3.59 (m, 2H), 3.41–3.29 (m, 3H), 1.27 (t, 3H, J = 7.0 Hz); IR (liquid film): 1732, 1489, 1367, 1246, 1196, 1168 cm^{-1} ; MS (FAB⁺) m/z 462 ((M+H)⁺).

(c) 1-({5-[5-(4-Phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**7h**)

According to a similar procedure to 5-2-24 (c), **7h** (69 mg, 0.16 mmol, 80%) was prepared from ethyl 1-({5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (90 mg, 0.20 mmol), NaOH (1.0 M in water, 0.60 mL, 0.60 mmol), 1,4-dioxane (2.0 mL) and acetic acid (34 μL , 0.59 mmol). The final purification by recrystallization (MeOH/water 2.0 mL/2.0 mL) gave a white crystalline solid. ¹H NMR (400 MHz, CD₃CO₂D) δ : 8.18 (d, 2H, J = 8.6 Hz), 7.84 (d, 1H, J = 3.9 Hz), 7.48–7.40 (m, 3H), 7.25 (t, 1H, J = 7.8 Hz), 7.15 (d, 4H, J = 8.6 Hz), 4.74 (s, 2H), 4.57–4.49 (m, 2H), 4.44–4.35 (m, 2H), 3.87–3.76 (m, 1H); IR (KBr): 3469, 1613, 1591, 1569, 1488, 1366, 1243 cm^{-1} ; MS (FAB⁺) m/z 434 ((M+H)⁺).

5-2-32.

1-[(4-{5-[4-(4-Methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**7i**)



(a) 4-(4-Methylphenoxy)benzaldehyde

To a mixture of 4-fluorobenzaldehyde (1.1 mL, 10 mmol) and *p*-cresol (1.3 g, 12 mmol) in DMF (10 mL) was added potassium carbonate (2.8 g, 20 mmol) and the resulting mixture was stirred at 100 °C for 2 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with Et₂O. The extract was washed with water, NaOH (1.0 M in water) and brine, dried over MgSO₄, filtered and concentrated.

To a mixture of the residue and *p*-cresol (0.26 g, 2.4 mmol) in DMF (5.0 mL) was added potassium carbonate (0.55 g, 4.0 mmol) and the resulting mixture was stirred at 100 °C again for 1.5 h in order to complete the reaction. The same work up procedure was conducted to afford the crude product of the title compound (1.94 g, 9.2 mmol, 92%) as an orange oil, which was used to the next reaction without further purification.

(b) 4-(4-Methylphenoxy)benzoic acid

To a solution of 4-(4-methylphenoxy)benzaldehyde (1.1 g, 5.0 mmol) in THF (2.5 mL) were

successively added *tert*-butanol (5.0 mL), water (2.5 mL), 2-methyl-2-butene (2.7 mL, 25 mmol), potassium dihydrogenphosphate (1.7 g, 13 mmol) and sodium chlorite (1.4 g, 15 mmol) and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with Et₂O and extracted with NaOH (1.0 M in water, 10 mL). The resulting aqueous layer was acidified with HCl (12 M in water) and extracted with EtOAc. The extract was washed with brine, dried over Na₂SO₄, filtered and concentrated to afford the crude product of the title compound (1.1 g, 4.8 mmol, 96%) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ: 7.98 (dd, 2H, *J* = 7.0, 2.0 Hz), 7.23 (d, 2H, *J* = 8.6 Hz), 6.99–6.91 (m, 4H), 2.35 (s, 3H).

(c) (4-{5-[4-(4-Methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol

According to a similar procedure to 5-2-27 (b), the title compound (0.19 g, 0.53 mmol, 89% in 2 steps) was prepared from **3a** (0.17 g, 0.60 mmol), 4-(4-methylphenoxy)benzoic acid (0.14 g, 0.63 mmol), 1-hydroxybenzotriazole (89 mg, 0.66 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.13 g, 0.66 mmol), acetonitrile (5.0 mL) and THF (2.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 1.2 mL, 1.2 mmol) and THF (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 2:1) gave a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.15–8.10 (m, 2H), 8.09–8.07 (m, 1H), 7.58 (s, 1H), 7.22 (d, 2H, *J* = 7.8 Hz), 7.09–7.05 (m, 2H), 7.02–6.98 (m, 2H), 4.89 (s, 2H), 2.38 (s, 3H), 2.03–1.93 (br s, 1H); IR (KBr): 3381, 3107, 1603, 1493, 1423, 1237, 1018, 830 cm⁻¹; MS (FAB⁺) *m/z*: 365 ((M+H)⁺).

(d) Methyl

1-[(4-{5-[4-(4-methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate

According to a similar procedure to 5-2-24 (b), the title compound (0.20 g, 0.43 mmol, 83%) was prepared from (4-{5-[4-(4-methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol (0.19 g, 0.52 mmol), carbon tetrabromide (0.22 g, 0.68 mmol), triphenylphosphine (0.18 g, 0.68 mmol), methyl 3-azetidinecarboxylate hydrochloride (0.12 g, 0.78 mmol), *N,N*-diisopropylethylamine (0.27 mL, 1.6 mmol) and CH₂Cl₂ (8.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:2 to 4:3) gave a white solid. ¹H NMR (400MHz, CDCl₃) δ: 8.10 (dd, 2H, *J* = 7.0, 2.0 Hz), 8.00 (d, 1H, *J* = 1.6 Hz), 7.47–7.45 (m, 1H), 7.19 (dd, 2H, *J* = 6.7, 2.0 Hz), 7.04 (dd, 2H, *J* = 7.0, 2.0 Hz), 6.97 (dd, 2H, *J* = 6.7, 2.0 Hz), 3.82 (s, 2H), 3.71 (s, 3H), 3.63–3.56 (m, 2H), 3.39–3.33 (m, 3H), 2.37 (s, 3H); IR (KBr): 2949, 2852, 1736, 1494, 1243, 824 cm⁻¹; MS (FAB⁺) *m/z*: 462 ((M+H)⁺).

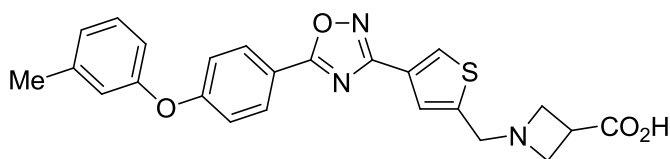
(e) 1-[(4-{5-[4-(4-Methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**7i**)

According to a similar procedure to 5-2-24 (c), **7i** (0.12 g, 0.28 mmol, 66%) was prepared from methyl 1-[(4-{5-[4-(4-methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate (0.20 g, 0.42 mmol), NaOH (1.0 M in water, 1.3 mL, 1.3 mmol), 1,4-dioxane (3.0 mL) and acetic

acid (72 μ L, 1.3 mmol). The final purification by recrystallization (MeOH/water 4.0 mL/3.0 mL) gave a white solid. ^1H NMR (400 MHz, $\text{CD}_3\text{CO}_2\text{D}$) δ : 8.33 (s, 1H), 8.17 (d, 2H, J = 8.6 Hz), 7.91 (s, 1H), 7.25 (d, 2H, J = 8.2 Hz), 7.12 (d, 2H, J = 8.6 Hz), 7.03 (d, 2H, J = 8.2 Hz), 4.74 (s, 2H), 4.58–4.47 (m, 2H), 4.47–4.33 (m, 2H), 3.88–3.76 (m, 1H), 2.36 (s, 3H); IR (KBr): 3430, 3088, 1615, 1496, 1254, 833, 760 cm^{-1} ; MS (FAB $^+$) m/z 448 ((M+H) $^+$).

5-2-33.

1-[(4-{5-[4-(3-Methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (7j)



(a) 4-(3-Methylphenoxy)benzaldehyde

According to a similar procedure to 5-2-32 (a), the title compound was quantitatively prepared from 4-fluorobenzaldehyde (1.1 mL, 10.0 mmol), *m*-cresol (1.6 g, 14 mmol), potassium carbonate (3.3 g, 24 mmol) and DMF (15 mL). The final purification by extraction gave an orange oil, which was used to the next reaction without further purification.

(b) 4-(3-Methylphenoxy)benzoic acid

According to a similar procedure to 5-2-32 (b), the title compound was quantitatively prepared from 4-(3-methylphenoxy)benzaldehyde (1.1 g, 5.0 mmol), 2-methyl-2-butene (2.7 mL, 25 mmol), potassium dihydrogenphosphate (1.7 g, 13 mmol), sodium chlorite (1.4 g, 15 mmol), THF (2.5 mL), *tert*-butanol (5.0 mL) and water (2.5 mL). The final purification by extraction gave a light yellow solid. ^1H NMR (400 MHz, CD_3OD) δ : 7.99 (d, 2H, J = 8.8 Hz), 7.28 (dd, 1H, J = 7.8, 7.8 Hz), 7.03 (d, 1H, J = 7.8 Hz), 6.97 (d, 2H, J = 8.8 Hz), 6.91–6.88 (m, 1H), 6.85 (dd, 1H, J = 7.8, 2.3 Hz), 2.34 (s, 3H).

(c) (4-{5-[4-(3-Methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol

According to a similar procedure to 5-2-27 (b), the title compound (0.22 g, 0.56 mmol, 93% in 2 steps) was prepared from **3a** (0.17 g, 0.60 mmol), 4-(3-methylphenoxy)benzoic acid (0.14 g, 0.63 mmol), 1-hydroxybenzotriazole (89 mg, 0.66 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.13 g, 0.66 mmol), acetonitrile (5.0 mL) and THF (2.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 1.2 mL, 1.2 mmol) and THF (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 2:1) gave a white solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.16–8.12 (m, 2H), 8.09–8.07 (m, 1H), 7.60–7.58 (m, 1H), 7.32–7.27 (m, 1H), 7.11–7.07 (m, 2H), 7.05–7.02 (m, 1H), 6.93–6.88 (m, 2H), 4.90 (d, 2H, J = 6.3 Hz), 2.37 (s, 3H), 1.92 (t, 1H, J = 6.3 Hz); IR (KBr): 3416, 3110, 1607, 1579, 1494, 1426, 1251, 827, 755 cm^{-1} ; MS (FAB $^+$) m/z 365 ((M+H) $^+$).

(d) Methyl

1-[(4-{5-[4-(3-methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate

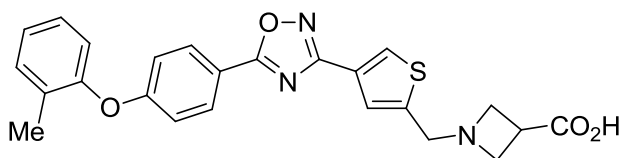
According to a similar procedure to 5-2-24 (b), the title compound (0.22 mg, 0.48 mmol, 93%) was prepared from (4-{5-[4-(3-methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol (0.19 g, 0.52 mmol), carbon tetrabromide (0.22 g, 0.68 mmol), triphenylphosphine (0.18 g, 0.68 mmol), methyl 3-azetidinecarboxylate hydrochloride (0.12 g, 0.78 mmol), *N,N*-diisopropylethylamine (0.27 mL, 1.6 mmol) and CH₂Cl₂ (8.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:2 to 4:3) gave a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.14–8.10 (m, 2H), 8.01–8.00 (m, 1H), 7.48–7.46 (m, 1H), 7.29–7.24 (m, 1H), 7.09–7.05 (m, 2H), 7.03–6.99 (m, 1H), 6.91–6.86 (m, 2H), 3.82 (s, 2H), 3.71 (s, 3H), 3.64–3.56 (m, 2H), 3.40–3.32 (m, 3H), 2.37 (s, 3H); IR (KBr): 2824, 1724, 1426, 1252, 1235, 758 cm⁻¹; MS (FAB⁺) *m/z* 462 ((M+H)⁺).

(e) 1-[(4-{5-[4-(3-Methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**7j**)

According to a similar procedure to 5-2-24 (c), **7j** (0.18 g, 0.40 mmol, 84%) was prepared from methyl 1-[(4-{5-[4-(3-methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate (0.22 g, 0.48 mmol), NaOH (1.0 M in water, 1.4 mL, 1.4 mmol), 1,4-dioxane (3.0 mL) and acetic acid (83 μL, 1.4 mmol). The final purification by recrystallization (MeOH/water 4.0 mL/3.0 mL) gave a white solid. ¹H NMR (400 MHz, CD₃CO₂D) δ: 8.33 (s, 1H), 8.23–8.14 (m, 2H), 7.91 (s, 1H), 7.35–7.28 (m, 1H), 7.16–7.11 (m, 2H), 7.09–7.03 (m, 1H), 6.99–6.90 (m, 2H), 4.74 (s, 2H), 4.57–4.47 (m, 2H), 4.45–4.35 (m, 2H), 3.87–3.77 (m, 1H), 2.36 (s, 3H); IR (KBr): 3418, 3088, 1608, 1497, 1255, 760 cm⁻¹; MS (FAB⁺) *m/z* 448 ((M+H)⁺).

5-2-34.

1-[(4-{5-[4-(2-Methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**7k**)



(a) 4-(2-Methylphenoxy)benzaldehyde

According to a similar procedure to 5-2-32 (a), the title compound (1.9 g, 9.0 mmol, 90%) was prepared from 4-fluorobenzaldehyde (1.1 mL, 10 mmol), *o*-cresol (2.3 g, 16 mmol), potassium carbonate (3.6 g, 26 mmol) and DMF (15 mL). The final purification by extraction gave an orange oil,

which was used to the next reaction without further purification.

(b) 4-(2-Methylphenoxy)benzoic acid

According to a similar procedure to 5-2-32 (b), the title compound (1.0 g, 4.6 mmol, 91%) was prepared from 4-(2-methylphenoxy)benzaldehyde (1.1 g, 5.0 mmol), 2-methyl-2-butene (2.7 mL, 25 mmol), potassium dihydrogenphosphate (1.7 g, 13 mmol), sodium chlorite (1.4 g, 15 mmol), THF (2.5 mL), *tert*-butanol (5.0 mL) and water (2.5 mL). The final purification by extraction gave a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.05 (dd, 2H, *J* = 7.0, 2.0 Hz), 7.31–7.21 (m, 2H), 7.18–7.14 (m, 1H), 7.02–6.99 (m, 1H), 6.90 (dd, 2H, *J* = 7.0, 2.0 Hz), 2.19 (s, 3H).

(c) (4-{5-[4-(2-Methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol

According to a similar procedure to 5-2-27 (b), the title compound (0.16 g, 0.43 mmol, 86% in 2 steps) was prepared from **3a** (0.14 g, 0.50 mmol), 4-(2-methylphenoxy)benzoic acid (0.12 g, 0.53 mmol), 1-hydroxybenzotriazole (74 mg, 0.55 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.11 g, 0.55 mmol), acetonitrile (4.0 mL) and THF (2.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 1.0 mL, 1.0 mmol) and THF (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 2:1) gave a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.12 (dd, 2H, *J* = 6.6, 2.0 Hz), 8.08 (d, 1H, *J* = 1.2 Hz), 7.58 (d, 1H, *J* = 1.2 Hz), 7.33–7.29 (m, 1H), 7.28–7.22 (m, 1H), 7.17 (ddd, 1H, *J* = 7.4, 7.4, 1.2 Hz), 7.04–6.97 (m, 3H), 4.89 (dd, 2H, *J* = 5.9, 0.8 Hz), 2.21 (s, 3H), 1.94 (t, 1H, *J* = 5.9 Hz); IR (KBr): 3376, 3109, 1496, 1422, 1248, 1169, 754 cm⁻¹; (FAB⁺) *m/z* 365 ((M+H)⁺).

(d) Methyl

1-[(4-{5-[4-(2-methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate

According to a similar procedure to 5-2-24 (b), the title compound (0.17 mg, 0.37 mmol, 88%) was prepared from (4-{5-[4-(2-methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol (0.15 g, 0.42 mmol), carbon tetrabromide (0.18 g, 0.55 mmol), triphenylphosphine (0.14 g, 0.55 mmol), methyl 3-azetidinecarboxylate hydrochloride (96 mg, 0.63 mmol), *N,N*-diisopropylethylamine (0.22 mL, 1.3 mmol) and CH₂Cl₂ (6.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:2 to 4:3) gave a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.09 (dd, 2H, *J* = 6.7, 2.0 Hz), 8.00 (d, 1H, *J* = 1.2 Hz), 7.46 (d, 1H, *J* = 1.2 Hz), 7.30–7.20 (m, 2H), 7.15 (ddd, 1H, *J* = 7.4, 7.4, 1.2 Hz), 7.02–6.95 (m, 3H), 3.82 (s, 2H), 3.71 (s, 3H), 3.63–3.56 (m, 2H), 3.40–3.30 (m, 3H), 2.20 (s, 3H); IR (liquid film): 2952, 2845, 1737, 1614, 1491, 1246, 755 cm⁻¹; (FAB⁺) *m/z* 462 ((M+H)⁺).

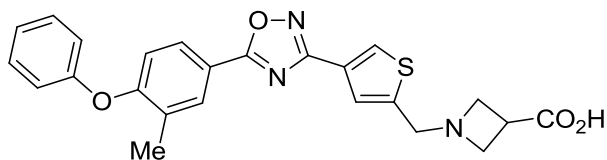
(e) 1-[(4-{5-[4-(2-Methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**7k**)

According to a similar procedure to 5-2-24 (c), **7k** (0.11 g, 0.23 mmol, 61%) was prepared from methyl

1-[(4-{5-[4-(2-methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate (0.17 g, 0.37 mmol), NaOH (1.0 M in water, 1.1 mL, 1.1 mmol), 1,4-dioxane (3.0 mL) and acetic acid (64 μ L, 1.1 mmol). The final purification by recrystallization (MeOH/water 2.0 mL/2.0 mL) gave a white solid. ^1H NMR (400 MHz, $\text{CD}_3\text{CO}_2\text{D}$) δ : 8.34–8.31 (m, 1H), 8.20–8.14 (m, 2H), 7.93–7.89 (m, 1H), 7.36–7.25 (m, 2H), 7.23–7.16 (m, 1H), 7.09–7.01 (m, 3H), 4.74 (s, 2H), 4.56–4.48 (m, 2H), 4.45–4.35 (m, 2H), 3.87–3.76 (m, 1H); IR (KBr): 3417, 3080, 1614, 1497, 1429, 1250, 1168, 838, 762 cm^{-1} ; MS (FAB $^+$) m/z : 448 ((M+H) $^+$).

5-2-35.

1-({4-[5-(3-Methyl-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl)methyl}azetidine-3-carboxylic acid (7l)



(a) 3-Methyl-4-phenoxybenzaldehyde

According to a similar procedure to 5-2-32 (a), the title compound (2.1 g, 9.9 mmol, 99%) was prepared from 4-fluoro-3-methylbenzaldehyde (1.4 g, 10.0 mmol), phenol (1.1 g, 12 mmol), potassium carbonate (2.8 g, 20 mmol) and DMF (10 mL). The final purification by extraction gave a brown oil, which was used to the next reaction without further purification.

(b) 3-Methyl-4-phenoxybenzoic acid

According to a similar procedure to 5-2-32 (b), the title compound (1.1 g, 4.8 mmol, 95%) was prepared from 3-methyl-4-phenoxybenzaldehyde (1.1 g, 5.0 mmol), 2-methyl-2-butene (2.7 mL, 25 mmol), potassium dihydrogenphosphate (1.7 g, 13 mmol), sodium chlorite (1.4 g, 15 mmol), THF (2.5 mL), *tert*-butanol (5.0 mL) and water (2.5 mL). The final purification by extraction gave a light yellow solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.02 (d, 1H, J = 1.6 Hz), 7.88 (dd, 1H, J = 8.6, 2.3 Hz), 7.41–7.35 (m, 2H), 7.19–7.14 (m, 1H), 7.03–6.99 (m, 2H), 6.82 (d, 1H, J = 8.6 Hz).

(c) {4-[5-(3-Methyl-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol

According to a similar procedure to 5-2-25 (b), the title compound (78 mg, 0.22 mmol, 43% in 2 steps) was prepared from **3a** (0.14 g, 0.50 mmol), 3-methyl-4-phenoxybenzoic acid (0.12 g, 0.53 mmol), 1-hydroxybenzotriazole (74 mg, 0.55 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.11 g, 0.55 mmol), acetonitrile (4.0 mL) and THF (2.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 1.0 mL, 1.0 mmol) and THF (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:1) gave a white solid. ^1H NMR (400 MHz, CDCl_3) δ :

8.10 (d, 1H, $J = 1.6$ Hz), 8.08 (d, 1H, $J = 1.2$ Hz), 7.94 (dd, 1H, $J = 8.6, 2.0$ Hz), 7.60–7.58 (m, 1H), 7.42–7.36 (m, 2H), 7.20–7.15 (m, 1H), 7.05–7.00 (m, 2H), 6.91 (d, 1H, $J = 8.6$ Hz), 4.90 (d, 2H, $J = 5.9$ Hz), 2.41 (s, 3H), 1.92 (t, 1H, $J = 5.9$ Hz); IR (KBr): 3378, 2929, 1573, 1490, 1248, 1003, 749 cm^{-1} ; MS (FAB⁺) m/z 365 ((M+H)⁺).

(d) Methyl

1-({4-[5-(3-methyl-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate

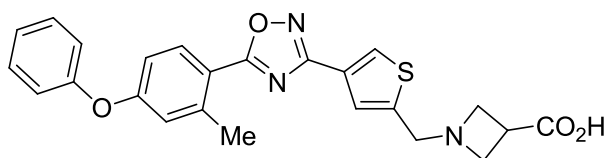
According to a similar procedure to 5-2-24 (b), the title compound (65 mg, 0.14 mmol, 67%) was prepared from {4-[5-(3-methyl-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol (75 mg, 0.21 mmol), carbon tetrabromide (91 mg, 0.27 mmol), triphenylphosphine (71 mg, 0.27 mmol), methyl 3-azetidinecarboxylate hydrochloride (48 mg, 0.32 mmol), *N,N*-diisopropylethylamine (0.11 mL, 0.63 mmol) and CH_2Cl_2 (6.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:1) gave a white solid. ¹H NMR (400 MHz, CDCl_3) δ : 8.10 (d, 1H, $J = 1.6$ Hz), 8.03 (d, 1H, $J = 1.2$ Hz), 7.94 (dd, 1H, $J = 8.6, 2.3$ Hz), 7.49 (d, 1H, $J = 1.2$ Hz), 7.42–7.36 (m, 2H), 7.20–7.15 (m, 1H), 7.05–7.00 (m, 2H), 6.91 (d, 1H, $J = 8.6$ Hz), 3.83 (s, 2H), 3.72 (s, 3H), 3.66–3.57 (m, 2H), 3.41–3.33 (m, 3H), 2.40 (s, 3H); IR (KBr): 2954, 2838, 1734, 1489, 1352, 1240, 1204, 836, 754 cm^{-1} ; MS (FAB⁺) m/z 462 ((M+H)⁺).

(e) 1-({4-[5-(3-Methyl-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**7l**)

According to a similar procedure to 5-2-24 (c), **7l** (42 mg, 0.094 mmol, 72%) was prepared from methyl 1-({4-[5-(3-methyl-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (60 mg, 0.13 mmol), NaOH (1.0 M in water, 0.39 mL, 0.39 mmol), 1,4-dioxane (2.0 mL) and acetic acid (22 μL , 0.38 mmol). The final purification by recrystallization (MeOH/water 2.0 mL/1.0 mL) gave a white solid. ¹H NMR (400 MHz, CD_3OD) δ : 8.36 (d, 1H, $J = 1.6$ Hz), 8.13 (d, 1H, $J = 1.6$ Hz), 7.98 (dd, 1H, $J = 8.6, 2.0$ Hz), 7.87 (d, 1H, $J = 1.2$ Hz), 7.45–7.40 (m, 2H), 7.23–7.18 (m, 1H), 7.07–7.04 (m, 2H), 6.92 (d, 1H, $J = 8.6$ Hz), 4.70 (s, 2H), 4.40–4.30 (m, 4H), 3.68–3.59 (m, 1H), 2.41 (s, 3H); IR (KBr): 3415, 3100, 1590, 1486, 1242, 756 cm^{-1} ; MS (FAB⁺) m/z 448 ((M+H)⁺).

5-2-36.

1-({4-[5-(2-Methyl-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**7m**)



(a) 4-Fluoro-2-methylbenzaldehyde

To a solution of 1-bromo-4-fluoro-2-methylbenzene (1.3 mL, 10 mmol) in THF (40 mL) was slowly added *n*-BuLi (1.6 M in hexane, 7.6 mL, 12 mmol) at -78 °C. After stirring at -78 °C for 10 min, DMF (0.93 mL, 12 mmol) was slowly added and the resulting mixture was stirred at -78 °C for 30 min. The reaction was quenched with sat. NH₄Cl and the resulting biphasic mixture was poured into water and extracted with EtOAc. The extract was washed with sat. NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 40:1 to 20:1) to afford the title compound (0.96 g, 6.9 mmol, 69%) as a colorless volatile oil. ¹H NMR (400 MHz, CDCl₃) δ: 10.2 (s, 1H), 7.82 (dd, 1H, *J* = 8.6, 6.3 Hz), 7.04 (ddd, 1H, *J* = 8.6, 8.6, 2.3 Hz), 6.96 (dd, 1H, *J* = 8.6, 2.3 Hz), 2.68 (s, 3H).

(b) 2-Methyl-4-phenoxybenzaldehyde

To a mixture of 4-fluoro-2-methylbenzaldehyde (0.96 g, 6.9 mmol) and phenol (0.91 g, 9.7 mmol) in DMF (10 mL) was added potassium carbonate (2.4 g, 17 mmol) and the resulting mixture was stirred at 100 °C for 15 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with Et₂O. The extract was washed with water, NaOH (1.0 M in water) and brine, dried over MgSO₄, filtered and concentrated to afford the crude product of the title compound (1.4 g, 6.4 mmol, 93%) as a brown oil, which was used to the next reaction without further purification.

(c) 2-Methyl-4-phenoxybenzoic acid

According to a similar procedure to 5-2-32 (b), the title compound (0.93 g, 4.1 mmol, 82%) was prepared from 2-methyl-4-phenoxybenzaldehyde (1.1 g, 5.0 mmol), 2-methyl-2-butene (2.7 mL, 25 mmol), potassium dihydrogenphosphate (1.7 g, 13 mmol), sodium chlorite (1.4 g, 15 mmol), THF (2.5 mL), *tert*-butanol (5.0 mL) and water (2.5 mL). The final purification by extraction gave a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.05 (d, 1H, *J* = 8.6 Hz), 7.40 (dd, 2H, *J* = 8.2, 7.4 Hz), 7.20 (dd, 1H, *J* = 7.8, 7.4 Hz), 7.07 (d, 2H, *J* = 7.4 Hz), 6.89–6.80 (m, 2H), 2.62 (s, 3H).

(d) {4-[5-(2-Methyl-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol

According to a similar procedure to 5-2-27 (b), the title compound (0.14 g, 0.39 mmol, 71% in 2 steps) was prepared from **3a** (0.16 g, 0.55 mmol), 2-methyl-4-phenoxybenzoic acid (0.13 g, 0.58 mmol), 1-hydroxybenzotriazole (82 mg, 0.61 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.12 g, 0.61 mmol), acetonitrile (4.0 mL) and THF (2.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 1.1 mL, 1.1 mmol) and THF (5.0 mL). The final purification by flash column

chromatography (silica gel, *n*-hexane/EtOAc 3:1) gave a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.11 (d, 1H, *J* = 8.6 Hz), 8.08 (d, 1H, *J* = 1.2 Hz), 7.59 (d, 1H, *J* = 1.2 Hz), 7.44–7.39 (m, 2H), 7.24–7.19 (m, 1H), 7.12–7.07 (m, 2H), 6.95–6.90 (m, 2H), 4.90 (d, 2H, *J* = 5.7 Hz), 2.73 (s, 3H), 1.93 (t, 1H, *J* = 5.7 Hz); IR (KBr): 3346, 3062, 1581, 1481, 1299, 1237, 756 cm⁻¹; MS (FAB⁺) *m/z* 365 ((M+H)⁺).

(e) Methyl

1-({4-[5-(2-methyl-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate

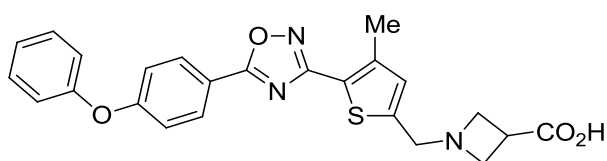
According to a similar procedure to 5-2-24 (b), the title compound (0.14 g, 0.31 mmol, 82%) was prepared from {4-[5-(2-methyl-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol (0.14 g, 0.38 mmol), carbon tetrabromide (0.16 g, 0.49 mmol), triphenylphosphine (0.13 g, 0.49 mmol), methyl 3-azetidinecarboxylate hydrochloride (86 mg, 0.57 mmol), *N,N*-diisopropylethylamine (0.20 mL, 1.1 mmol) and CH₂Cl₂ (8.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:2 to 1:1) gave a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.11 (d, 1H, *J* = 8.2 Hz), 8.03 (d, 1H, *J* = 1.2 Hz), 7.49 (d, 1H, *J* = 1.2 Hz), 7.41 (t, 2H, *J* = 8.2 Hz), 7.21 (t, 1H, *J* = 7.4 Hz), 7.09 (d, 2H, *J* = 7.4 Hz), 6.95–6.90 (m, 2H), 3.84 (s, 2H), 3.72 (s, 3H), 3.65–3.58 (m, 2H), 3.40–3.32 (m, 3H), 2.72 (s, 3H); IR (KBr): 2955, 2848, 1734, 1595, 1490, 1241, 757 cm⁻¹; MS (FAB⁺) *m/z* 462 ((M+H)⁺).

(f) 1-({4-[5-(2-Methyl-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**7m**)

According to a similar procedure to 5-2-24 (c), **7m** (0.11 g, 0.25 mmol, 83%) was prepared from methyl 1-({4-[5-(2-methyl-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (0.14 g, 0.30 mmol), NaOH (1.0 M in water, 0.90 mL, 0.90 mmol), 1,4-dioxane (3.0 mL) and acetic acid (52 μL, 0.90 mmol). The final purification by recrystallization (MeOH/water 2.0 mL/2.0 mL) gave a white solid. ¹H NMR (400 MHz, CD₃CO₂D) δ: 8.32 (d, 1H, *J* = 1.2 Hz), 8.14 (d, 1H, *J* = 8.6 Hz), 7.92 (s, 1H), 7.47–7.40 (m, 2H), 7.26–7.20 (m, 1H), 7.16–7.10 (m, 2H), 7.03–7.00 (m, 1H), 6.95 (dd, 1H, *J* = 8.6, 2.3 Hz), 4.74 (s, 2H), 4.56–4.46 (m, 2H), 4.46–4.35 (m, 2H), 3.86–3.77 (m, 1H), 2.73 (s, 3H); IR (KBr): 3430, 2966, 1609, 1588, 1489, 1239, 834, 764 cm⁻¹; MS (FAB⁺) *m/z* 448 ((M+H)⁺).

5-2-37.

1-({4-Methyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**8a**)



(a) {4-Methyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol

According to a similar procedure to 5-2-27 (b), the title compound (0.19 g, 0.52 mmol, 86% in 2 steps) was prepared from **3d** (0.18 g, 0.60 mmol), 4-phenoxybenzoic acid (0.14 g, 0.63 mmol), 1-hydroxybenzotriazole (89 mg, 0.66 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.13 g, 0.66 mmol), acetonitrile (4.0 mL) and THF (2.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 1.2 mL, 1.2 mmol) and THF (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:1 to 2:1) gave white crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.14 (d, 2H, *J* = 8.3 Hz), 7.42 (t, 2H, *J* = 7.8 Hz), 7.22 (t, 1H, *J* = 7.1 Hz), 7.10 (d, 2H, *J* = 8.3 Hz), 7.09 (d, 2H, *J* = 8.8 Hz), 6.91 (s, 1H), 4.83 (s, 2H), 2.59 (s, 3H), 1.87 (br s, 1H); IR (KBr): 3393, 3279, 1612, 1588, 1514, 1489, 1341, 1249 cm⁻¹; MS (FAB⁺) *m/z* 365 ((M+H)⁺).

(b) Methyl

1-({4-methyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate

According to a similar procedure to 5-2-24 (b), the title compound (0.20 g, 0.43 mmol, 85%) was prepared from {4-methyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol (0.19 g, 0.51 mmol), carbon tetrabromide (0.22 g, 0.66 mmol), triphenylphosphine (0.17 g, 0.66 mmol), methyl 3-azetidinecarboxylate hydrochloride (0.12 g, 0.77 mmol), *N,N*-diisopropylethylamine (0.27 mL, 1.5 mmol) and CH₂Cl₂. The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:2) gave a pale yellowish oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.14 (d, 2H, *J* = 8.3 Hz), 7.42 (t, 2H, *J* = 7.8 Hz), 7.22 (t, 1H, *J* = 7.1 Hz), 7.13–7.07 (m, 4H), 6.80 (s, 1H), 3.77 (s, 2H), 3.72 (s, 3H), 3.61–3.59 (m, 2H), 3.40–3.31 (m, 3H), 2.57 (s, 3H); IR (KBr): 1732, 1613, 1592, 1516, 1488, 1341, 1242, 1201, 1166 cm⁻¹; MS (FAB⁺) *m/z* 462 ((M+H)⁺).

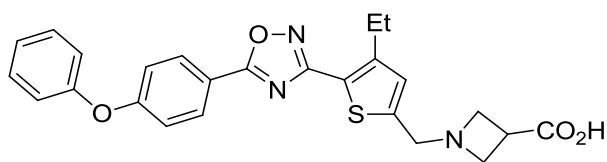
(c) 1-({4-Methyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**8a**)

According to a similar procedure to 5-2-24 (c), **8a** (0.16 g, 0.36 mmol, 85%) was prepared from methyl 1-({4-methyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (0.20 g, 0.42 mmol), NaOH (1.0 M in water, 1.3 mL, 1.3 mmol), 1,4-dioxane (3.0 mL) and acetic acid (72 μL, 1.3 mmol). The final purification by recrystallization (MeOH/water 3.0 mL/2.0 mL) gave a white crystalline solid. ¹H NMR (400 MHz, CD₃CO₂D) δ: 8.18 (d, 2H, *J* = 9.0 Hz), 7.45 (t, 2H, *J* = 7.8 Hz), 7.26 (s, 1H), 7.26–7.21 (m, 1H), 7.15 (d, 4H, *J* = 8.6 Hz), 4.67 (s, 2H), 4.58–4.50 (m, 2H), 4.44–4.34 (m, 2H), 3.86–3.77 (m, 1H), 2.61 (s, 3H); IR (KBr): 3429, 1612, 1593, 1488, 1336, 1244 cm⁻¹; MS (FAB⁺) *m/z* 448 ((M+H)⁺).

5-2-38.

1-({4-Ethyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic

acid (8b)



(a) {4-Ethyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol

According to a similar procedure to 5-2-27 (b), the title compound (0.17 g, 0.45 mmol, 89% in 2 steps) was prepared from **3e** (0.16 g, 0.50 mmol), 4-phenoxybenzoic acid (0.12 g, 0.53 mmol), 1-hydroxybenzotriazole (74 mg, 0.55 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.11 g, 0.55 mmol), acetonitrile (4.0 mL) and THF (2.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 1.0 mL, 1.0 mmol) and THF (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:1) gave a pale yellowish crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.12 (d, 2H, *J* = 9.0 Hz), 7.39 (t, 2H, *J* = 7.4 Hz), 7.20 (t, 1H, *J* = 7.4 Hz), 7.10–7.04 (m, 4H), 6.96 (s, 1H), 4.83 (d, 2H, *J* = 5.9 Hz), 3.05 (q, 2H, *J* = 7.4 Hz), 1.88 (t, 1H, *J* = 5.9 Hz), 1.29 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3356, 1612, 1588, 1515, 1496, 1490, 1353, 1248 cm⁻¹; MS (FAB⁺) *m/z*: 379 ((M+H)⁺).

(b) Methyl

1-({4-ethyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate

According to a similar procedure to 5-2-24 (b), the title compound (0.19 g, 0.40 mmol, 89%) was prepared from {4-ethyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol (0.17 g, 0.44 mmol), carbon tetrabromide (0.19 g, 0.57 mmol), triphenylphosphine (0.15 g, 0.57 mmol), methyl 3-azetidinecarboxylate hydrochloride (0.10 g, 0.66 mmol), *N,N*-diisopropylethylamine (0.23 mL, 1.3 mmol) and CH₂Cl₂ (6.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:1 to 2:1) gave a pale yellowish oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.11 (d, 2H, *J* = 9.0 Hz), 7.39 (t, 2H, *J* = 7.4 Hz), 7.20 (t, 1H, *J* = 7.4 Hz), 7.10–7.04 (m, 4H), 6.84 (s, 1H), 3.78 (s, 2H), 3.71 (s, 3H), 3.67–3.59 (m, 2H), 3.40–3.30 (m, 3H), 3.03 (q, 2H, *J* = 7.4 Hz), 1.27 (t, 3H, *J* = 7.4 Hz); IR (liquid film): 1737, 1613, 1589, 1514, 1489, 1346, 1245, 1200, 1168 cm⁻¹; MS (FAB⁺) *m/z*: 476 ((M+H)⁺).

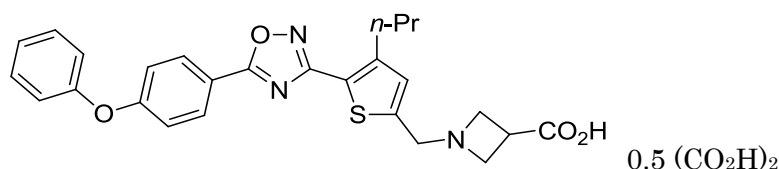
(c) 1-({4-Ethyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**8b**)

According to a similar procedure to 5-2-24 (c), **8b** (0.15 g, 0.33 mmol, 86%) was prepared from methyl 1-({4-ethyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate

(0.18 g, 0.39 mmol), NaOH (1.0 M in water, 1.2 mL, 1.2 mmol), 1,4-dioxane (3.0 mL) and acetic acid (68 μ L, 1.2 mmol). The final purification by washing the precipitation gave a white crystalline solid. ^1H NMR (400 MHz, $\text{CD}_3\text{CO}_2\text{D}$) δ : 8.17 (d, 2H, J = 9.0 Hz), 7.45 (t, 2H, J = 7.4 Hz), 7.32 (s, 1H), 7.24 (t, 1H, J = 7.4 Hz), 7.15 (d, 4H, J = 9.0 Hz), 4.68 (s, 2H), 4.57–4.45 (m, 2H), 4.45–4.33 (m, 2H), 3.87–3.76 (m, 1H), 3.09 (q, 2H, J = 7.4 Hz), 1.30 (t, 3H, J = 7.4 Hz); ^{13}C NMR (125 MHz, $\text{CD}_3\text{CO}_2\text{D}$) δ : 176.3, 175.9, 165.6, 163.2, 156.5, 149.1, 135.0, 134.0, 131.3, 131.2, 126.3, 125.9, 121.2, 119.2, 119.0, 56.3, 52.9, 33.9, 24.2, 14.7; IR (KBr): 3422, 1613, 1592, 1557, 1517, 1489, 1347, 1249, 1167 cm^{-1} . MS (FAB) m/z : 462 ($(\text{M}+\text{H})^+$); HRMS (ESI): m/z calcd for $\text{C}_{25}\text{H}_{24}\text{N}_3\text{O}_4\text{S}$, 462.1488 $[\text{M}+\text{H}]^+$; found 462.1487.

5-2-39.

1-({5-[5-(4-Phenoxyphenyl)-1,2,4-oxadiazol-3-yl]-4-propylthiophen-2-yl}methyl)azetidine-3-carboxylic acid 1/2 oxalate (8c)



(a) {5-[5-(4-Phenoxyphenyl)-1,2,4-oxadiazol-3-yl]-4-propylthiophen-2-yl}methanol

According to a similar procedure to 5-2-27 (b), the title compound (0.13 g, 0.34 mmol, 75% in 2 steps) was prepared from **3f** (0.15 g, 0.45 mmol), 4-phenoxybenzoic acid (0.10 g, 0.47 mmol), 1-hydroxybenzotriazole (68 mg, 0.50 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (96 mg, 0.50 mmol), acetonitrile (4.0 mL) and THF (2.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 0.90 mL, 0.90 mmol) and THF (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:1) gave a light yellow solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.14 (d, 2H, J = 9.0 Hz), 7.42 (dd, 2H, J = 8.6, 7.4 Hz), 7.22 (t, 1H, J = 7.4 Hz), 7.12–7.08 (m, 4H), 6.95 (s, 1H), 4.84 (d, 2H, J = 5.9 Hz), 3.02 (t, 2H, J = 7.4 Hz), 1.87 (t, 1H, J = 5.9 Hz), 1.71 (tq, 2H, J = 7.4, 7.4 Hz), 1.00 (t, 3H, J = 7.4 Hz); IR (KBr): 3432, 2957, 1588, 1490, 761 cm^{-1} ; MS (FAB⁺) m/z : 393 ($(\text{M}+\text{H})^+$).

(b) Methyl

1-({5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]-4-propylthiophen-2-yl}methyl)azetidine-3-carboxylate

According to a similar procedure to 5-2-24 (b), the title compound (0.11 g, 0.22 mmol, 68%) was prepared from {5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]-4-propylthiophen-2-yl}methanol (0.13 g, 0.33 mmol), carbon tetrabromide (0.14 g, 0.43 mmol), triphenylphosphine (0.11 g, 0.43 mmol), methyl 3-azetidinecarboxylate hydrochloride (75 mg, 0.50 mmol), *N,N*-diisopropylethylamine (0.17 mL, 0.99 mmol) and CH_2Cl_2 (6.0 mL). The final purification by flash column chromatography (silica gel,

n-hexane/EtOAc 3:1 to 2:1) gave a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.13 (d, 2H, *J* = 8.6 Hz), 7.42 (dd, 2H, *J* = 8.2, 7.4 Hz), 7.22 (t, 1H, *J* = 7.4 Hz), 7.13–7.06 (m, 4H), 6.84 (s, 1H), 3.78 (s, 2H), 3.72 (s, 3H), 3.66–3.60 (m, 2H), 3.40–3.32 (m, 3H), 2.99 (t, 2H, *J* = 7.4 Hz), 1.70 (tq, 2H, *J* = 7.4, 7.4 Hz), 0.99 (t, 3H, *J* = 7.4 Hz); IR (KBr): 2958, 1737, 1489, 1246, 764, 731 cm⁻¹; MS (FAB⁺) *m/z* 490 ((M+H)⁺).

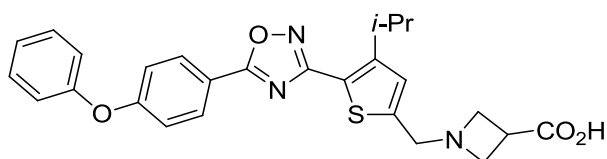
(c) 1-({5-[5-(4-Phenoxyphenyl)-1,2,4-oxadiazol-3-yl]-4-propylthiophen-2-yl}methyl)azetidine-3-carboxylic acid 1/2 oxalate (**8c**)

To a solution of methyl 1-({5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]-4-propylthiophen-2-yl}methyl)azetidine-3-carboxylate (0.11 g, 0.22 mmol) in 1,4-dioxane (3.0 mL) was added NaOH (1.0 M in water, 0.66 mL, 0.66 mmol), and the resulting mixture was stirred at room temperature for 1.5 h. The reaction was quenched with acetic acid (38 μL, 0.66 mmol) and the resulting mixture was concentrated.

To a solution of the residue in MeOH (3.0 mL) and water (1.0 mL) was added oxalic acid (10 mg, 0.11 mmol) and the resulting mixture was concentrated. The mixture was recrystallized from MeOH (3.0 mL) and water (2.0 mL) to afford the title compound **8c** (63 mg, 0.12 mmol, 55%) as a white solid. ¹H NMR (400 MHz, CD₃CO₂D) δ: 8.17 (d, 2H, *J* = 8.2 Hz), 7.45 (t, 2H, *J* = 7.8 Hz), 7.30 (s, 1H), 7.24 (t, 1H, *J* = 7.4 Hz), 7.18–7.12 (m, 4H), 4.67 (s, 2H), 4.57–4.49 (m, 2H), 4.44–4.35 (m, 2H), 3.87–3.76 (m, 1H), 3.06 (t, 2H, *J* = 7.6 Hz), 1.73 (tq, 2H, *J* = 7.6, 7.6 Hz), 1.00 (t, 3H, *J* = 7.6 Hz); IR (KBr): 3429, 2958, 1589, 1489, 1245, 763 cm⁻¹; MS (FAB⁺) *m/z* 476 ((M+H)⁺).

5-2-40.

1-({5-[5-(4-Phenoxyphenyl)-1,2,4-oxadiazol-3-yl]-4-(propan-2-yl)thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**8d**)



(a) {5-[5-(4-Phenoxyphenyl)-1,2,4-oxadiazol-3-yl]-4-(propan-2-yl)thiophen-2-yl}methanol

According to a similar procedure to 5-2-27 (b), the title compound (0.15 g, 0.39 mmol, 78% in 2 steps) was prepared from **3g** (0.16 g, 0.50 mmol), 4-phenoxybenzoic acid (0.11 g, 0.53 mmol), 1-hydroxybenzotriazole (74 mg, 0.55 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.11 g, 0.55 mmol), acetonitrile (4.0 mL) and THF (2.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 1.0 mL, 1.0 mmol) and THF (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 7:2) gave a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.14 (d, 2H, *J* = 9.0 Hz), 7.42 (dd, 2H, *J* = 8.2, 7.4 Hz), 7.22 (t, 1H, *J* = 7.4 Hz), 7.12–7.08 (m,

4H), 7.05 (s, 1H), 4.85 (d, 2H, $J = 6.3$ Hz), 3.90 (sept, 1H, $J = 7.0$ Hz), 1.89 (t, 1H, $J = 6.3$ Hz), 1.29 (d, 6H, $J = 7.0$ Hz); IR (KBr): 3362, 2963, 1587, 1489, 1247, 1168, 762 cm^{-1} ; MS (FAB⁺) m/z : 393 ((M+H)⁺).

(b) Methyl

1-({5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]-4-(propan-2-yl)thiophen-2-yl}methyl)azetidine-3-carboxylate

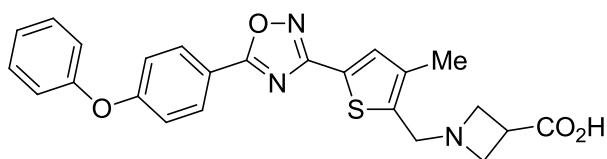
According to a similar procedure to 5-2-24 (b), the title compound (0.17 g, 0.34 mmol, 90%) was prepared from {5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]-4-(propan-2-yl)thiophen-2-yl}methanol (0.15 g, 0.38 mmol), carbon tetrabromide (0.19 g, 0.57 mmol), triphenylphosphine (0.15 g, 0.57 mmol), methyl 3-azetidinecarboxylate hydrochloride (86 mg, 0.57 mmol), *N,N*-diisopropylethylamine (0.20 mL, 1.1 mmol) and CH_2Cl_2 (8.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:1) gave a colorless oil. ¹H NMR (400 MHz, CDCl_3) δ : 8.11 (d, 2H, $J = 8.6$ Hz), 7.39 (t, 2H, $J = 7.4$ Hz), 7.20 (t, 1H, $J = 7.4$ Hz), 7.11–7.05 (m, 4H), 6.91 (s, 1H), 3.85 (sept, 1H, $J = 7.0$ Hz), 3.78 (s, 2H), 3.71 (s, 3H), 3.66–3.59 (m, 2H), 3.39–3.34 (m, 3H), 1.27 (d, 6H, $J = 7.0$ Hz); IR (KBr): 2962, 1738, 1488, 1244, 764, 693 cm^{-1} ; MS (FAB⁺) m/z : 490 ((M+H)⁺).

(c) 1-({5-[5-(4-Phenoxyphenyl)-1,2,4-oxadiazol-3-yl]-4-(propan-2-yl)thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**8d**)

According to a similar procedure to 5-2-24 (c), **8d** (0.14 g, 0.29 mmol, 87%) was prepared from methyl 1-({5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]-4-(propan-2-yl)thiophen-2-yl}methyl)azetidine-3-carboxylate (0.16 g, 0.33 mmol), NaOH (1.0 M in water, 0.99 mL, 0.99 mmol), 1,4-dioxane (3.0 mL) and acetic acid (57 μL , 1.0 mmol). The final purification by recrystallization (MeOH/water 3.0 mL/2.0 mL) gave a white solid. ¹H NMR (400 MHz, $\text{CD}_3\text{CO}_2\text{D}$) δ : 8.17 (d, 2H, $J = 8.6$ Hz), 7.45 (t, 2H, $J = 7.4$ Hz), 7.41 (s, 1H), 7.24 (t, 1H, $J = 7.4$ Hz), 7.15 (d, 4H, $J = 8.6$ Hz), 4.68 (s, 2H), 4.58–4.49 (m, 2H), 4.45–4.35 (m, 2H), 3.98–3.88 (m, 1H), 3.86–3.76 (m, 1H), 1.31 (d, 6H, $J = 6.6$ Hz); IR (KBr): 3422, 2963, 1591, 1489, 1245, 765 cm^{-1} ; MS (FAB⁺) m/z : 476 ((M+H)⁺).

5-2-41.

1-({3-Methyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**8e**)



(a) {3-Methyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol

According to a similar procedure to 5-2-27 (b), the title compound (0.21 g, 0.56 mmol, 94% in 2 steps) was prepared from **3h** (0.18 g, 0.60 mmol), 4-phenoxybenzoic acid (0.14 g, 0.63 mmol), 1-hydroxybenzotriazole (89 mg, 0.66 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.13 g, 0.66 mmol), acetonitrile (4.0 mL) and THF (2.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 1.2 mL, 1.2 mmol) and THF (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:1) gave a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.14 (d, 2H, *J* = 9.0 Hz), 7.60 (s, 1H), 7.42 (dd, 2H, *J* = 8.6, 7.4 Hz), 7.22 (t, 1H, *J* = 7.4 Hz), 7.12–7.08 (m, 4H), 4.83 (d, 2H, *J* = 5.7 Hz), 2.29 (s, 3H), 1.76 (t, 1H, *J* = 5.7 Hz); IR (KBr): 3457, 2925, 1614, 1590, 1487, 1231, 760 cm⁻¹; MS (FAB⁺) *m/z* 365 ((M+H)⁺).

(b) Methyl

1-({3-methyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate

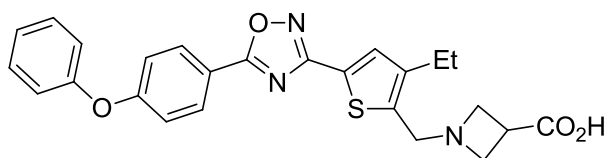
According to a similar procedure to 5-2-24 (b), the title compound (0.24 g, 0.51 mmol, 93%) was prepared from {3-methyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol (0.20 g, 0.55 mmol), carbon tetrabromide (0.24 g, 0.72 mmol), triphenylphosphine (0.19 g, 0.72 mmol), methyl 3-azetidinecarboxylate hydrochloride (0.13 g, 0.83 mmol), *N,N*-diisopropylethylamine (0.29 mL, 1.7 mmol) and CH₂Cl₂ (10 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:2 to 1:1) gave a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.13 (d, 2H, *J* = 8.8 Hz), 7.56 (s, 1H), 7.42 (t, 2H, *J* = 7.8 Hz), 7.22 (t, 1H, *J* = 7.8 Hz), 7.12–7.06 (m, 4H), 3.75 (s, 2H), 3.72 (s, 3H), 3.68–3.63 (m, 2H), 3.40–3.33 (m, 3H), 2.23 (s, 3H); IR (liquid film): 2952, 2845, 1737, 1589, 1489, 1246, 1200, 761 cm⁻¹; MS (FAB⁺) *m/z* 462 ((M+H)⁺).

(c) 1-({3-Methyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**8e**)

According to a similar procedure to 5-2-24 (c), **8e** (0.19 g, 0.41 mmol, 83%) was prepared from methyl 1-({3-methyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (0.23 g, 0.50 mmol), NaOH (1.0 M in water, 1.5 mL, 1.5 mmol), 1,4-dioxane (3.0 mL) and acetic acid (86 μL, 1.5 mmol). The final purification by recrystallization (MeOH/water 3.0 mL/2.0 mL) gave a white solid. ¹H NMR (400 MHz, CD₃CO₂D) δ: 8.17 (d, 2H, *J* = 8.6 Hz), 7.71 (s, 1H), 7.45 (t, 2H, *J* = 7.4 Hz), 7.25 (t, 1H, *J* = 7.4 Hz), 7.14 (d, 4H, *J* = 8.6 Hz), 4.68 (s, 2H), 4.58–4.50 (m, 2H), 4.43–4.33 (m, 2H), 3.84–3.75 (m, 1H), 2.38 (s, 3H); IR (KBr): 3429, 1591, 1488, 1367, 1242, 761 cm⁻¹; MS (FAB⁺) *m/z* 448 ((M+H)⁺).

5-2-42.

1-({3-Ethyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**8f**)



(a) 3-{4-Ethyl-5-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]thiophen-2-yl}-5-(4-phenoxyphenyl)-1,2,4-oxadiazole

According to a similar procedure to 5-2-27 (b), the title compound (0.25 g, 0.54 mmol, 78% in 2 steps) was prepared from **3i** (0.17 g, 0.69 mmol), 4-phenoxybenzoic acid (0.16 g, 0.73 mmol), 1-hydroxybenzotriazole (0.12 g, 0.76 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.15 g, 0.76 mmol), acetonitrile (5.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 1.4 mL, 1.4 mmol) and THF (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 10:0 to 8:2) gave a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.15 (d, 2H, *J* = 9.0 Hz), 7.66 (s, 1H), 7.43 (d, 1H, *J* = 7.4 Hz), 7.41 (d, 1H, *J* = 7.4 Hz), 7.25–7.20 (m, 1H), 7.12–7.07 (m, 4H), 4.88 (d, 1H, *J* = 12.9 Hz), 4.77 (t, 1H, *J* = 3.5 Hz), 4.69 (d, 1H, *J* = 12.9 Hz), 3.96–3.89 (m, 1H), 3.61–3.55 (m, 1H), 2.65 (q, 2H, *J* = 7.6 Hz), 1.93–1.50 (m, 6H), 1.26 (t, 3H, *J* = 7.6 Hz); IR (liquid film): 2940, 2872, 1613, 1589, 1488, 1245, 1167, 1022, 761 cm⁻¹; MS (FAB⁺) *m/z*: 463 ((M+H)⁺).

(b) {3-Ethyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol

To a solution of 3-{4-ethyl-5-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]thiophen-2-yl}-5-(4-phenoxyphenyl)-1,2,4-oxadiazole (0.25 g, 0.54 mmol) in EtOH (5.0 mL) was added pyridinium *p*-toluenesulfonate (0.14 g, 0.54 mmol), and the resulting mixture was stirred at 60 °C for 4 h. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with brine, dried over MgSO₄, filtered and concentrated to afford the title compound (0.19 g, 0.50 mmol, 92%) as a crystalline white solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.15 (d, 2H, *J* = 8.6 Hz), 7.67 (s, 1H), 7.43 (d, 1H, *J* = 7.4 Hz), 7.41 (d, 1H, *J* = 7.4 Hz), 7.25–7.20 (m, 1H), 7.12–7.07 (m, 4H), 4.83 (d, 2H, *J* = 5.9 Hz), 2.67 (q, 2H, *J* = 7.6 Hz), 1.79 (t, 1H, *J* = 5.9 Hz), 1.27 (t, 3H, *J* = 7.6 Hz); IR (KBr): 3452, 2964, 1615, 1591, 1579, 1487, 1422, 1232, 998, 760 cm⁻¹; MS (FAB⁺) *m/z*: 379 ((M+H)⁺).

(c) Methyl

1-({3-ethyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate

According to a similar procedure to 5-2-24 (b), the title compound (0.17 g, 0.36 mmol, 72%) was prepared from {3-ethyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol (0.19 g, 0.50 mmol), carbon tetrabromide (0.33 g, 0.99 mmol), triphenylphosphine (0.26 g, 0.99 mmol), methyl 3-azetidinecarboxylate hydrochloride (0.11 g, 0.75 mmol), *N,N*-diisopropylethylamine (0.22 mL, 1.2 mmol) and CH₂Cl₂ (5.0 mL). The final purification by flash column chromatography (silica gel,

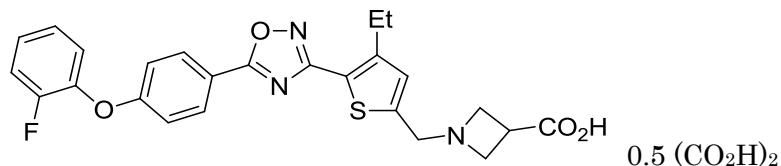
n-hexane/EtOAc 8:2 to 6:4) gave a pale yellow crystalline solid. ¹H NMR (500 MHz, CDCl₃) δ: 8.14 (d, 2H, *J* = 8.8 Hz), 7.62 (s, 1H), 7.43–7.38 (m, 2H), 7.24–7.20 (m, 1H), 7.12–7.06 (m, 4H), 3.77 (s, 2H), 3.72 (s, 3H), 3.70–3.62 (m, 2H), 3.41–3.33 (m, 3H), 2.61 (q, 2H, *J* = 7.6 Hz), 1.23 (t, 3H, *J* = 7.6 Hz); IR (KBr): 2963, 1736, 1589, 1490, 1367, 1249, 1167 cm⁻¹; MS (FAB⁺) *m/z*: 476 ((M+H)⁺).

(d) 1-({3-Ethyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**8f**)

According to a similar procedure to 5-2-24 (c), **8f** (0.16 g, 0.34 mmol, 95%) was prepared from methyl 1-({3-ethyl-5-[5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (0.17 g, 0.36 mmol), NaOH (1.0 M in water, 1.1 mL, 1.1 mmol), 1,4-dioxane (3.0 mL), methanol (3.0 mL) and acetic acid (62 μL, 1.1 mmol). The final purification by washing the precipitation gave a white crystalline solid. ¹H NMR (400 MHz, CD₃CO₂D) δ: 8.21–8.15 (m, 2H), 7.80 (s, 1H), 7.48–7.41 (m, 2H), 7.27–7.22 (m, 1H), 7.11–7.17 (m, 4H), 4.71 (s, 2H), 4.60–4.45 (m, 2H), 4.45–4.30 (m, 2H), 3.86–3.75 (m, 1H), 2.78 (q, 2H, *J* = 7.5 Hz), 1.29 (t, 3H, *J* = 7.5 Hz); IR (KBr): 3536, 2969, 1614, 1591, 1487, 1368, 1241, 1170, 761 cm⁻¹; MS (FAB⁺) *m/z*: 462 ((M+H)⁺).

5-2-43.

1-[(4-Ethyl-5-{5-[4-(2-fluorophenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid 1/2 oxalate (**8g**)



(a) 4-(2-Fluorophenoxy)benzoic acid

To a solution of 4-fluorobenzaldehyde (1.2 g, 10 mmol) and 2-fluorophenol (1.3 g, 12 mmol) in DMF (10 mL) was added potassium carbonate (2.8 g, 20 mmol) and the resulting mixture was stirred at 100 °C for 16 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated.

To a solution of the residue in THF (5.0 mL), *tert*-butanol (10 mL) and water (5.0 mL) were successively added 2-methyl-2-butene (5.3 mL, 50 mmol), potassium dihydrogenphosphate (3.4 g, 25 mmol) and sodium chlorite (2.7 g, 30 mmol) and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with Et₂O and extracted with NaOH (1.0 M in water, 20 mL). The aqueous layer was acidified with HCl (10 M in water, 2.0 mL) and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated to afford the crude product of the title compound (2.0 g, 8.7 mmol, 87% in 2 steps) as a white crystalline solid. ¹H

NMR (400 MHz, CDCl₃) δ : 8.07 (d, 2H, J = 8.6 Hz), 7.24–7.15 (m, 4H), 6.98 (d, 2H, J = 8.6 Hz); IR (KBr): 2990, 2884, 2672, 2544, 1682, 1594, 1498, 1428, 1290, 1266 cm⁻¹; MS (EI⁺) m/z : 232 (M⁺).

(b) (4-Ethyl-5-{5-[4-(2-fluorophenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol

To a solution of **3e** (0.16 g, 0.50 mmol) and 4-(2-fluorophenoxy)benzoic acid (0.13 g, 0.55 mmol) in CH₂Cl₂ (1.5 mL) was added dicyclohexylcarbodiimide (0.11 g, 0.55 mmol), and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with *n*-hexane and insoluble materials were removed by filtration, and the filtrate was concentrated.

To a solution of the residue in THF (1.0 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 0.75 mL, 0.75 mmol), and the resulting mixture was stirred at 60 °C for 1 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 7:3 to 5:5) to afford the title compound (0.18 g, 0.45 mmol, 89% in 2 steps) as a white crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ : 8.15 (d, 2H, J = 8.6 Hz), 7.25–7.17 (m, 4H), 7.07 (d, 2H, J = 8.6 Hz), 6.98 (s, 1H), 4.83 (s, 2H), 3.05 (q, 2H, J = 7.8 Hz), 1.29 (t, 3H, J = 7.8 Hz); IR (KBr): 3340, 1602, 1497, 1353, 1270 cm⁻¹; MS (FAB⁺) m/z : 397 ((M+H)⁺).

(c) Methyl

1-[(4-ethyl-5-{5-[4-(2-fluorophenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate

According to a similar procedure to 5-2-24 (b), the title compound (0.19 g, 0.39 mmol, 90%) was prepared from (4-ethyl-5-{5-[4-(2-fluorophenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol (0.17 g, 0.43 mmol), carbon tetrabromide (0.17 g, 0.51 mmol), triphenylphosphine (0.13 g, 0.51 mmol), methyl 3-azetidinecarboxylate hydrochloride (0.10 g, 0.65 mmol), *N,N*-diisopropylethylamine (0.23 mL, 1.3 mmol). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 5:5) gave a white crystalline solid. ¹H NMR (500 MHz, CDCl₃) δ : 8.13 (d, 2H, J = 8.8 Hz), 7.25–7.17 (m, 4H), 7.07 (d, 2H, J = 8.8 Hz), 6.86 (s, 1H), 3.79 (s, 2H), 3.72 (s, 3H), 3.66–3.60 (m, 1H), 3.40–3.32 (m, 4H), 3.03 (q, 2H, J = 7.8 Hz), 1.28 (t, 3H, J = 7.8 Hz); IR (liquid film): 1737, 1604, 1557, 1514, 1497 cm⁻¹; MS (FAB⁺) m/z : 494 ((M+H)⁺).

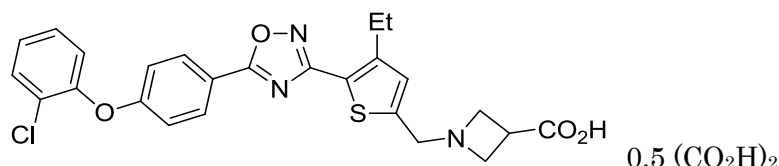
(d) 1-[(4-Ethyl-5-{5-[4-(2-fluorophenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid 1/2 oxalate (**8g**)

According to a similar procedure to 5-2-39 (c), **8g** (77 mg, 0.15 mmol, 39%) was prepared from methyl 1-[(4-ethyl-5-{5-[4-(2-fluorophenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate (0.19 g, 0.38 mmol), lithium hydroxide monohydrate (36 mg, 0.85 mmol), acetic acid (46 μ L, 0.85 mmol) and oxalic acid (17 mg, 0.19 mmol). The final purification by recrystallization (acetonitrile/water) gave a white crystalline solid. ¹H NMR (400 MHz, CD₃OD) δ : 8.16 (d, 2H, J = 9.0 Hz), 7.33–7.25 (m, 4H), 7.12 (d, 2H, J = 9.0 Hz), 6.98 (s, 1H), 3.82 (s, 2H), 3.62 (t, 2H, J = 7.0 Hz), 3.37

(t, 2H, $J = 8.2$ Hz), 3.22 (quint, 1H, $J = 8.6$ Hz), 3.03 (q, 2H, $J = 7.4$ Hz), 1.26 (t, 3H, $J = 7.4$ Hz); IR (KBr): 3413, 1659, 1601, 1497, 1420 cm^{-1} ; MS (FAB⁺) m/z 480 ((M+H)⁺).

5-2-44.

1-[(5-{5-[4-(2-Chlorophenoxy)phenyl]-1,2,4-oxadiazol-3-yl}-4-ethylthiophen-2-yl)methyl]azetidine-3-carboxylic acid 1/2 oxalate (8h)



(a) 4-(2-Chlorophenoxy)benzoic acid

According to a similar procedure to 5-2-43 (a), the title compound (15 g, 61 mmol, 61% in 2 steps) was prepared from 4-fluorobenzaldehyde (12 g, 0.10 mol), 2-chlorophenol (15 g, 0.12 mol), potassium carbonate (28 g, 0.20 mol), DMF (100 mL), 2-methyl-2-butene (50 mL, 0.50 mol), potassium dihydrogenphosphate (34 g, 0.25 mol), sodium chlorite (27 g, 0.30 mol), *tert*-butanol (50 mL) and water (50 mL). The final purification was conducted by recrystallization (*n*-hexane/EtOAc 9:1). ¹H NMR (400 MHz, CDCl₃) δ : 8.08 (d, 2H, $J = 8.9$ Hz), 7.50 (dd, 1H, $J = 7.8, 1.5$ Hz), 7.31 (td, 1H, $J = 7.8, 1.5$ Hz), 7.20 (td, 1H, $J = 7.8, 1.5$ Hz), 7.13 (dd, 1H, $J = 7.8, 1.5$ Hz), 6.95 (d, 2H, $J = 8.9$ Hz).

(b) (5-{5-[4-(2-Chlorophenoxy)phenyl]-1,2,4-oxadiazol-3-yl}-4-ethylthiophen-2-yl)methanol

According to a similar procedure to 5-2-43 (b), the title compound (0.19 g, 0.46 mmol, 92%) was prepared from **3e** (0.16 g, 0.50 mmol), 4-(2-chlorophenoxy)benzoic acid (0.14 g, 0.55 mmol), dicyclohexylcarbodiimide (0.11 g, 0.55 mmol) and CH₂Cl₂ (1.5 mL), and tetrabutylammonium fluoride (1.0 M in THF, 0.75 mL, 0.75 mmol) and THF (1.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 7:3 to 5:5) gave a white crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ : 8.12 (d, 2H, $J = 9.0$ Hz), 7.49 (dd, 1H, $J = 7.8, 1.2$ Hz), 7.30 (td, 1H, $J = 7.8, 1.2$ Hz), 7.19 (td, 1H, $J = 7.8, 1.2$ Hz), 7.13 (dd, 1H, $J = 7.8, 1.2$ Hz), 7.01 (d, 2H, $J = 9.0$ Hz), 6.96 (s, 1H), 4.83 (s, 2H), 3.04 (q, 2H, $J = 7.4$ Hz), 1.29 (t, 3H, $J = 7.4$ Hz); IR (KBr): 3329, 1612, 1556, 1517, 1498, 1473, 1353, 1259, 1245 cm^{-1} ; MS (FAB⁺) m/z 413 ((M+H)⁺).

(c) Methyl

1-[(5-{5-[4-(2-chlorophenoxy)phenyl]-1,2,4-oxadiazol-3-yl}-4-ethylthiophen-2-yl)methyl]azetidine-3-carboxylate

According to a similar procedure to 5-2-24 (b), the title compound (0.21 g, 0.42 mmol, 91%) was prepared from (5-{5-[4-(2-chlorophenoxy)phenyl]-1,2,4-oxadiazol-3-yl}-4-ethylthiophen-2-yl)methanol (0.19 g, 0.46 mmol), carbon tetrabromide (0.18 g, 0.55 mmol), triphenylphosphine (0.14 g, 0.55 mmol),

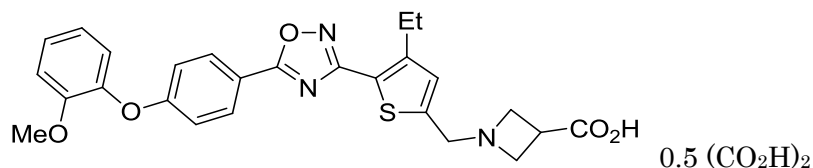
methyl 3-azetidinecarboxylate hydrochloride (0.10 g, 0.69 mmol), *N,N*-diisopropylethylamine (0.16 mL, 0.92 mmol) and CH₂Cl₂. The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 5:5) gave a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.14 (d, 2H, *J* = 9.0 Hz), 7.51 (dd, 1H, *J* = 7.8, 1.6 Hz), 7.32 (td, 1H, *J* = 7.8, 1.6 Hz), 7.21 (td, 1H, *J* = 7.8, 1.6 Hz), 7.15 (dd, 1H, *J* = 7.8, 1.6 Hz), 7.03 (d, 2H, *J* = 9.0 Hz), 6.86 (s, 1H), 3.78 (s, 2H), 3.72 (s, 3H), 3.66–3.58 (m, 1H), 3.40–3.32 (m, 4H), 3.03 (q, 2H, *J* = 7.4 Hz), 1.28 (t, 3H, *J* = 7.4 Hz); IR (liquid film): 1737, 1613, 1581, 1557, 1514, 1475 cm⁻¹; MS (FAB⁺) *m/z* 510 ((M+H)⁺).

(d) 1-[(5-{5-[4-(2-Chlorophenoxy)phenyl]-1,2,4-oxadiazol-3-yl}-4-ethylthiophen-2-yl)methyl]azetidine-3-carboxylic acid 1/2 oxalate (**8h**)

According to a similar procedure to 5-2-39 (c), **8h** (0.14 g, 0.27 mmol, 67%) was prepared from methyl 1-[(5-{5-[4-(2-chlorophenoxy)phenyl]-1,2,4-oxadiazol-3-yl}-4-ethylthiophen-2-yl)methyl]azetidine-3-carboxylate (0.21 g, 0.41 mmol), lithium hydroxide monohydrate (38 mg, 0.90 mmol), acetic acid (49 μL, 0.90 mmol) and oxalic acid (18 mg, 0.20 mmol). A white crystalline solid was collected by filtration. ¹H NMR (400 MHz, CD₃OD+CD₃CO₂D (5 : 1)) δ: 8.17 (d, 2H, *J* = 9.0 Hz), 7.57 (dd, 1H, *J* = 8.0, 1.6 Hz), 7.42 (td, 1H, *J* = 8.0, 1.6 Hz), 7.30 (td, 1H, *J* = 8.0, 1.6 Hz), 7.29 (s, 1H), 7.24 (dd, 1H, *J* = 8.0, 1.6 Hz), 7.08 (d, 2H, *J* = 9.0 Hz), 4.58 (s, 2H), 4.32–4.21 (m, 4H), 3.60–3.50 (m, 1H), 3.08 (q, 2H, *J* = 7.4 Hz), 1.29 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3418, 1665, 1613, 1515, 1497, 1475 cm⁻¹; MS (FAB⁺) *m/z* 496 ((M+H)⁺).

5-2-45.

1-[(4-Ethyl-5-{5-[4-(2-methoxyphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid 1/2 oxalate (**8i**)



(a) 4-(2-Methoxyphenoxy)benzoic acid

According to a similar procedure to 5-2-43 (a), the title compound (1.6 g, 6.6 mmol, 89% in 2 steps) was prepared from 4-fluorobenzaldehyde (1.2 g, 10 mmol), 2-methoxyphenol (1.7 g, 14 mmol), potassium carbonate (3.5 g, 25 mmol), DMF (10 mL), 2-methyl-2-butene (3.9 mL, 37 mmol), potassium dihydrogenphosphate (2.5 g, 19 mmol), sodium chlorite (2.0 g, 22 mmol), THF (5.0 mL), *tert*-butanol (10 mL) and water (5.0 mL). The final purification by extraction gave a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.04 (dd, 2H, *J* = 8.6, 2.0 Hz), 7.23 (td, 1H, *J* = 7.4, 1.6 Hz), 7.09 (dd, 1H, *J* = 8.2, 1.6 Hz), 7.04 (dd, 1H, *J* = 8.2, 1.6 Hz), 6.99 (td, 1H, *J* = 7.4, 1.6 Hz), 6.93 (dd, 2H, *J* = 8.6, 2.0 Hz), 3.80 (s, 3H).

(b) (4-Ethyl-5-{5-[4-(2-methoxyphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol

According to a similar procedure to 5-2-27 (b), the title compound (0.15 g, 0.36 mmol, 72% in 2 steps) was prepared from **3e** (0.16 g, 0.50 mmol), 4-(2-methoxyphenoxy)benzoic acid (0.13 g, 0.53 mmol), 1-hydroxybenzotriazole (74 mg, 0.55 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.11 g, 0.55 mmol), acetonitrile (4.0 mL) and THF (2.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 1.0 mL, 1.0 mmol) and THF (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 5:2) gave a yellowish white crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.11 (dd, 2H, *J* = 9.0, 2.0 Hz), 7.24 (dt, 1H, *J* = 7.8, 1.6 Hz), 7.11 (dd, 1H, *J* = 7.8, 1.6 Hz), 7.07–6.99 (m, 4H), 6.98 (s, 1H), 4.85 (d, 2H, *J* = 6.3 Hz), 3.81 (s, 3H), 3.06 (q, 2H, *J* = 7.4 Hz), 1.85 (t, 1H, *J* = 6.3 Hz), 1.29 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3379, 3316, 1612, 1513, 1497, 1354, 1262, 1228 cm⁻¹; MS (FAB⁺) *m/z* 409 ((M+H)⁺).

(c) Methyl

1-[(4-ethyl-5-{5-[4-(2-methoxyphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate

According to a similar procedure to 5-2-24 (b), the title compound (89 mg, 0.18 mmol, 50%) was prepared from (4-ethyl-5-{5-[4-(2-methoxyphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol (0.14 g, 0.35 mmol), carbon tetrabromide (0.17 g, 0.53 mmol), triphenylphosphine (0.14 g, 0.53 mmol), methyl 3-azetidinecarboxylate hydrochloride (80 mg, 0.53 mmol), *N,N*-diisopropylethylamine (0.18 mL, 1.1 mmol) and CH₂Cl₂ (8.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 5:2 to 2:1) gave a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.10 (dd, 2H, *J* = 9.0, 2.2 Hz), 7.24 (td, 1H, *J* = 7.4, 1.6 Hz), 7.11 (dd, 1H, *J* = 8.2, 1.6 Hz), 7.07–6.97 (m, 4H), 6.86 (s, 1H), 3.81 (s, 3H), 3.78 (s, 2H), 3.72 (s, 3H), 3.68–3.59 (m, 2H), 3.41–3.31 (m, 3H), 3.03 (q, 2H, *J* = 7.4 Hz), 1.27 (t, 3H, *J* = 7.4 Hz); IR (thin film): 1737, 1613, 1513, 1496, 1455, 1346, 1265, 1201, 1176, 1168 cm⁻¹; MS (FAB⁺) *m/z* 506 ((M+H)⁺).

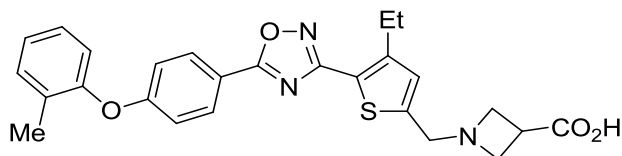
(d) 1-[(4-Ethyl-5-{5-[4-(2-methoxyphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid 1/2 oxalate

According to a similar procedure to 5-2-39 (c), **8i** (63 mg, 0.12 mmol, 69%) was prepared from methyl 1-[(4-ethyl-5-{5-[4-(2-methoxyphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate (86 mg, 0.17 mmol), NaOH (1.0 M in water, 0.51 mL, 0.51 mmol), 1,4-dioxane (3.0 mL), acetic acid (29 μL, 0.51 mmol) and oxalic acid (8.0 mg, 0.09 mmol). The final purification by washing the precipitation with water and methanol (3:7) gave a white crystalline solid. ¹H NMR (400 MHz, CD₃CO₂D) δ: 8.12 (d, 2H, *J* = 8.6 Hz), 7.34 (s, 1H), 7.27 (t, 1H, *J* = 6.6 Hz), 7.18–7.10 (m, 2H), 7.07–6.98 (m, 3H), 4.68 (s, 2H), 4.61–4.50 (m, 2H), 4.43–4.33 (m, 2H), 3.89–3.76 (m, 1H), 3.78 (s, 3H), 3.09 (q, 2H, *J* = 6.8 Hz), 1.30 (t, 3H, *J* = 6.8 Hz); IR (KBr): 3422, 1614, 1515, 1497, 1346, 1265, 1233 cm⁻¹;

MS (FAB⁺) *m/z*: 492 ((M+H)⁺).

5-2-46.

1-[(4-Ethyl-5-{5-[4-(2-methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (8j)



(a) 4-(2-Methylphenoxy)benzoyl chloride

According to a similar procedure to 5-2-28 (a), the crude product of the title compound was prepared from 4-(2-methylphenoxy)benzoic acid (0.48 g, 2.1 mmol), thionyl chloride (0.31 mL, 4.2 mmol), a catalytic amount of DMF and toluene (5.0 mL). This crude product was used to the next step without further purification.

(b) (4-Ethyl-5-{5-[4-(2-methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol

According to a similar procedure to 5-2-24 (a), the title compound (0.72 g, 1.8 mmol, 97% in 2 steps) was prepared from **3e** (0.60 g, 1.9 mmol), 4-(2-methylphenoxy)benzoyl chloride (2.1 mmol), triethylamine (0.53 mL, 3.8 mmol) and CH₂Cl₂ (3.0 mL) and tetrabutylammonium fluoride (1.0 M in THF, 2.3 mL, 2.3 mmol) and THF (5.0 mL). The final purification was conducted by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:1). ¹H NMR (400 MHz, CDCl₃) δ: 8.12 (d, 2H, *J* = 8.6 Hz), 7.31 (d, 1H, *J* = 7.4 Hz), 7.28–7.22 (m, 1H), 7.20–7.15 (m, 1H), 7.05–6.96 (m, 4H), 4.85 (s, 2H), 3.05 (q, 2H, *J* = 7.4 Hz), 2.21 (s, 3H), 1.91 (br s, 1H), 1.29 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3348, 2965, 1612, 1497, 1352, 1248, 843, 761 cm⁻¹; MS (FAB⁺) *m/z*: 393 ((M+H)⁺).

(c) Methyl

1-[(4-ethyl-5-{5-[4-(2-methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate

According to a similar procedure to 5-2-24 (b), the title compound (0.82 g, 1.7 mmol, 92%) was prepared from (4-ethyl-5-{5-[4-(2-methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol (0.72 g, 1.8 mmol), carbon tetrabromide (0.73 g, 2.2 mmol), triphenylphosphine (0.58 g, 2.2 mmol), methyl 3-azetidinecarboxylate hydrochloride (0.41 g, 2.7 mmol), *N,N*-diisopropylethylamine (0.94 mL, 5.4 mmol) and CH₂Cl₂. The final purification was conducted by flash column chromatography (silica gel, *n*-hexane/EtOAc). ¹H NMR (400 MHz, CDCl₃) δ: 8.11 (d, 2H, *J* = 9.0 Hz), 7.30 (d, 1H, *J* = 7.4 Hz), 7.27–7.22 (m, 1H), 7.19–7.14 (m, 1H), 7.04–6.96 (m, 3H), 6.86 (s, 1H), 3.78 (s, 2H), 3.72 (s, 3H), 3.67–

3.59 (m, 2H), 3.41–3.33 (m, 3H), 3.03 (q, 2H, $J = 7.4$ Hz), 2.21 (s, 3H), 1.28 (t, 3H, $J = 7.4$ Hz); IR (liquid film): 2965, 2845, 1738, 1613, 1514, 1490, 1346, 1246, 1180, 765 cm^{-1} ; MS (FAB⁺) m/z 490 ((M+H)⁺).

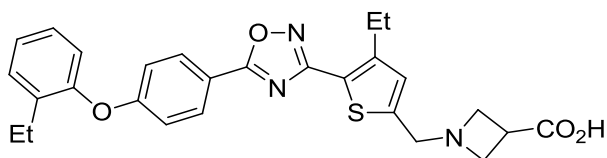
(d) 1-[(4-Ethyl-5-{5-[4-(2-methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**8j**)

According to a similar procedure to 5-2-24 (c), **8j** (25 mg, 0.053 mmol, 3.2%) was prepared from methyl

1-[(4-ethyl-5-{5-[4-(2-methylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate (0.81 g, 1.7 mmol), NaOH (1.0 M in water, 3.3 mL, 3.3 mmol), ethanol (3.0 mL) instead of 1,4-dioxane and acetic acid (0.18 mL, 3.3 mmol). The final purification by washing the precipitation with acetone gave a white solid. ¹H NMR (400 MHz, DMSO- d_6) δ : 8.12 (d, 2H, $J = 8.6$ Hz), 7.40 (d, 1H, $J = 7.4$ Hz), 7.32 (dd, 1H, $J = 7.4, 7.4$ Hz), 7.23 (dd, 1H, $J = 7.4, 7.4$ Hz), 7.12–7.05 (m, 3H), 7.00 (s, 1H), 3.72 (s, 2H), 3.45–3.38 (m, 2H), 3.25–3.17 (m, 2H), 3.17–3.08 (m, 1H), 2.95 (q, 2H, $J = 7.0$ Hz), 2.15 (s, 3H), 1.20 (t, 3H, $J = 7.0$ Hz); IR (KBr): 3433, 2968, 1613, 1495, 1346, 1245, 764 cm^{-1} ; MS (FAB⁺) m/z 476 ((M+H)⁺).

5-2-47.

1-[(4-Ethyl-5-{5-[4-(2-ethylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**8k**)



(a) 4-(2-Ethylphenoxy)benzoic acid

According to a similar procedure to 5-2-43 (a), the title compound (1.6 g, 6.5 mmol, 68% in 2 steps) was prepared from 4-fluorobenzaldehyde (1.2 g, 10 mmol), 2-ethylphenol (1.7 g, 14 mmol), potassium carbonate (3.5 g, 25 mmol), DMF (10 mL), 2-methyl-2-butene (5.1 mL, 48 mmol), potassium dihydrogenphosphate (3.3 g, 24 mmol), sodium chlorite (2.6 g, 29 mmol), THF (5.0 mL), *tert*-butanol (10 mL) and water (5.0 mL). The final purification by recrystallization (*n*-hexane/EtOAc 14 mL/1.0 mL) gave a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ : 8.04 (d, 2H, $J = 9.0$ Hz), 7.32 (dd, 1H, $J = 7.0, 2.0$ Hz), 7.25–7.17 (m, 2H), 6.98 (dd, 1H, $J = 7.8, 1.6$ Hz), 6.92 (d, 2H, $J = 9.0$ Hz), 2.58 (q, 2H, $J = 7.8$ Hz), 1.17 (t, 3H, $J = 7.8$ Hz).

(b) (4-Ethyl-5-{5-[4-(2-ethylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol

According to a similar procedure to 5-2-27 (b), the title compound (0.10 g, 0.26 mmol, 43% in 2 steps)

was prepared from **3e** (0.19 g, 0.60 mmol), 4-(2-ethylphenoxy)benzoic acid (0.15 g, 0.63 mmol), 1-hydroxybenzotriazole (89 mg, 0.66 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.13 g, 0.66 mmol), acetonitrile (4.0 mL) and THF (2.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 0.78 mL, 0.78 mmol) and THF (4.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 4:1 to 3:1) gave a pink solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.12 (d, 2H, *J* = 8.6 Hz), 7.33 (dd, 1H, *J* = 7.4, 2.0 Hz), 7.25–7.17 (m, 2H), 7.03–6.96 (m, 4H), 4.85 (d, 2H, *J* = 6.3 Hz), 3.05 (q, 2H, *J* = 7.4 Hz), 2.60 (q, 2H, *J* = 7.4 Hz), 1.86 (t, 1H, *J* = 6.3 Hz), 1.29 (t, 3H, *J* = 7.4 Hz), 1.19 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3392, 2967, 1514, 1348, 1245, 847, 762 cm⁻¹; MS (FAB⁺) *m/z*: 407 ((M+H)⁺).

(c) Methyl

1-[(4-ethyl-5-{5-[4-(2-ethylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate

According to a similar procedure to 5-2-24 (b), the title compound (0.11 g, 0.22 mmol, 89%) was prepared from (4-ethyl-5-{5-[4-(2-ethylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol (0.10 g, 0.25 mmol), carbon tetrabromide (0.13 g, 0.38 mmol), triphenylphosphine (0.10 g, 0.38 mmol), methyl 3-azetidinecarboxylate hydrochloride (58 mg, 0.38 mmol), *N,N*-diisopropylethylamine (0.20 mL, 1.1 mmol) and CH₂Cl₂ (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 2:1) gave a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.11 (d, 2H, *J* = 8.6 Hz), 7.34 (dd, 1H, *J* = 7.0, 1.8 Hz), 7.25–7.18 (m, 2H), 7.03–6.98 (m, 3H), 6.86 (s, 1H), 3.79 (s, 2H), 3.72 (s, 3H), 3.68–3.59 (m, 2H), 3.40–3.32 (m, 3H), 3.03 (q, 2H, *J* = 7.6 Hz), 2.60 (q, 2H, *J* = 7.6 Hz), 1.27 (t, 3H, *J* = 7.6 Hz), 1.19 (t, 3H, *J* = 7.6 Hz); IR (liquid film): 2967, 1738, 1613, 1514, 1346, 1245, 765 cm⁻¹; MS (FAB⁺) *m/z*: 504 ((M+H)⁺).

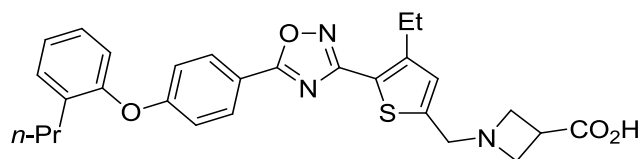
(d) 1-[(4-Ethyl-5-{5-[4-(2-ethylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**8k**)

According to a similar procedure to 5-2-24 (c), **8k** (89 mg, 0.18 mmol, 83%) was prepared from methyl 1-[(4-ethyl-5-{5-[4-(2-ethylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate (0.11 g, 0.22 mmol), NaOH (1.0 M in water, 0.33 mL, 0.33 mmol), methanol (1.0 mL), THF (1.0 mL) instead of 1,4-dioxane and acetic acid (19 μL, 0.33 mmol). The final purification by recrystallization (MeOH/water 1.0 mL/2.0 mL) gave a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.13 (d, 2H, *J* = 8.6 Hz), 7.42 (d, 1H, *J* = 7.4 Hz), 7.36–7.23 (m, 2H), 7.12–7.06 (m, 3H), 7.02 (s, 1H), 3.75 (s, 2H), 3.49–3.40 (m, 2H), 3.30–3.14 (m, 3H), 2.96 (q, 2H, *J* = 7.4 Hz), 2.54 (q, 2H, *J* = 7.4 Hz), 1.21 (t, 3H, *J* = 7.4 Hz), 1.12 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3424, 2968, 1613, 1497, 1345, 1248, 763 cm⁻¹; MS (FAB⁺) *m/z*: 490 ((M+H)⁺).

5-2-48.

1-[(4-Ethyl-5-{5-[4-(2-propylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-c

arboxylic acid (8l)



(a) 4-(2-Propylphenoxy)benzoic acid

To a solution of 4-fluorobenzaldehyde (1.2 g, 10 mmol) and 2-propylphenol (1.8 g, 13 mmol) in DMF (10 mL) was added potassium carbonate (3.5 g, 25 mmol) and the resulting mixture was stirred at 100 °C for 4 h. To this was added cesium carbonate (3.3 g, 10 mmol) and the resulting mixture was stirred at 100 °C for 1.5 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with Et₂O. The extract was washed with 1.0 M NaOH aqueous solution, brine, dried over Na₂SO₄, filtered and concentrated.

To a solution of the residue in THF (5.0 mL), *tert*-butanol (10 mL) and water (5.0 mL) were successively added 2-methyl-2-butene (5.3 mL, 50 mmol), potassium dihydrogenphosphate (3.4 g, 25 mmol) and sodium chlorite (2.7 g, 30 mmol) and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with Et₂O and extracted with NaOH (1.0 M in water, 20 mL). The aqueous layer was acidified with HCl (10 M in water) and extracted with CH₂Cl₂. The extract was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by recrystallization (*n*-hexane/EtOAc 8.0 mL/1.0 mL) to afford the title compound (0.85 g, 3.3 mmol, 33% in 2 steps) as a light brown solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.05 (d, 2H, *J* = 9.0 Hz), 7.30 (dd, 1H, *J* = 7.4, 1.6 Hz), 7.26–7.21 (m, 1H), 7.20–7.15 (m, 1H), 6.98 (dd, 1H, *J* = 7.8, 1.2 Hz), 6.93 (d, 2H, *J* = 9.0 Hz), 2.53 (t, 2H, *J* = 7.8 Hz), 1.60 (tq, 2H, *J* = 7.8, 7.4 Hz), 0.90 (t, 3H, *J* = 7.4 Hz).

(b) (4-Ethyl-5-{5-[4-(2-propylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol

According to a similar procedure to 5-2-25 (b), the title compound (0.20 g, 0.47 mmol, 78% in 2 steps) was prepared from **3e** (0.19 g, 0.60 mmol), 4-(2-propylphenoxy)benzoic acid (0.16 g, 0.63 mmol), 1-hydroxybenzotriazole (89 mg, 0.66 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.13 g, 0.66 mmol), acetonitrile (4.0 mL) and THF (2.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 0.78 mL, 0.78 mmol) and THF (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 4:1 to 3:1) gave a light orange solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.12 (d, 2H, *J* = 9.0 Hz), 7.31 (dd, 1H, *J* = 7.4, 1.6 Hz), 7.25–7.16 (m, 2H), 7.04–6.97 (m, 4H), 4.85 (dd, 2H, *J* = 6.3, 0.8 Hz), 3.06 (q, 2H, *J* = 7.4 Hz), 2.55 (t, 2H, *J* = 7.4 Hz), 1.87 (t, 1H, *J* = 6.3 Hz), 1.61 (tq, 2H, *J* = 7.4, 7.4 Hz), 1.29 (t, 3H, *J* = 7.4 Hz), 0.91 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3395, 2965, 1514, 1498, 1348, 1246, 846, 762 cm⁻¹; MS (FAB⁺) *m/z*: 421 ((M+H)⁺).

(c) Methyl

1-[(4-ethyl-5-{5-[4-(2-propylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate

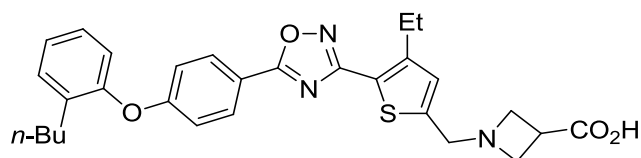
According to a similar procedure to 5-2-24 (b), the title compound (0.22 g, 0.43 mmol, 93%) was prepared from (4-ethyl-5-{5-[4-(2-propylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methanol (0.19 g, 0.46 mmol), carbon tetrabromide (0.23 g, 0.69 mmol), triphenylphosphine (0.18 g, 0.69 mmol), methyl 3-azetidinecarboxylate hydrochloride (0.11 g, 0.69 mmol), *N,N*-diisopropylethylamine (0.24 mL, 1.4 mmol) and CH₂Cl₂ (8.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:1 to 2:1) gave a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.11 (d, 2H, *J* = 8.6 Hz), 7.31 (dd, 1H, *J* = 7.4, 2.0 Hz), 7.23 (dd, 1H, *J* = 7.8, 2.0 Hz), 7.18 (ddd, 1H, *J* = 7.8, 7.4, 1.2 Hz), 7.04–6.98 (m, 3H), 6.86 (s, 1H), 3.79 (s, 2H), 3.72 (s, 3H), 3.68–3.59 (m, 2H), 3.41–3.32 (m, 3H), 3.03 (q, 2H, *J* = 7.4 Hz), 2.55 (t, 2H, *J* = 7.8 Hz), 1.61 (tq, 2H, *J* = 7.4, 7.4 Hz), 1.28 (t, 3H, *J* = 7.4 Hz), 0.91 (t, 3H, *J* = 7.4 Hz); IR (liquid film): 2961, 1738, 1613, 1514, 1487, 1244, 764 cm⁻¹; MS (FAB⁺) *m/z*: 518 ((M+H)⁺).

(d) 1-[(4-Ethyl-5-{5-[4-(2-propylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**8l**)

According to a similar procedure to 5-2-24 (c), **8l** (0.18 g, 0.35 mmol, 93%) was prepared from methyl 1-[(4-ethyl-5-{5-[4-(2-propylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate (0.20 g, 0.38 mmol), NaOH (1.0 M in water, 0.57 mL, 0.57 mmol), methanol (2.0 mL), THF (2.0 mL) instead of 1,4-dioxane and acetic acid (32 μL, 0.56 mmol). The final purification by recrystallization (acetonitrile/MeOH/water 1.0 mL/2.0 mL/2.0 mL) gave a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.13 (d, 2H, *J* = 7.4 Hz), 7.45–7.21 (m, 3H), 7.14–7.04 (m, 3H), 7.02 (s, 1H), 3.75 (s, 2H), 3.55–3.13 (m, 5H), 3.02–2.90 (m, 2H), 2.59–2.41 (m, 2H), 1.61–1.46 (m, 2H), 1.27–1.16 (m, 3H), 0.90–0.79 (m, 3H); IR (KBr): 3424, 2962, 2932, 1613, 1246, 763 cm⁻¹; MS (FAB⁺) *m/z*: 504 ((M+H)⁺).

5-2-49.

1-[(5-{5-[4-(2-Butylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}-4-ethylthiophen-2-yl)methyl]azetidine-3-carboxylic acid (**8m**)



(a) 2-[(1*E*)-But-1-en-1-yl]phenol

To a solution of triphenyl(propyl)phosphonium bromide (9.3 g, 24 mmol) in DMF (30 mL) was added a solution of potassium *tert*-butoxide (2.7 g, 24 mmol) in DMF (10 mL) at 0 °C and the resulting

mixture was stirred at 0 °C for 30 min. To this was added a solution of salicylaldehyde (1.2 g, 10 mmol) in DMF (10 mL) and the resulting mixture was stirred at room temperature overnight. The reaction was quenched with sat. NH₄Cl at 0 °C and the reaction mixture was extracted with Et₂O. The extract was washed with brine and dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 95:5 to 90:10) to afford the title compound quantitatively as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.20–7.15 (m, 1H), 7.11–7.08 (m, 1H), 6.92–6.87 (m, 2H), 6.33 (dt, 1H, *J* = 11.3, 1.6 Hz), 5.92 (dt, 1H, *J* = 11.3, 7.4 Hz), 4.98 (s, 1H), 2.12 (ddq, 2H, *J* = 7.4, 7.4, 1.6 Hz), 1.01 (t, 3H, *J* = 7.4 Hz); IR (liquid film): 3430, 2965, 1484, 1451, 1203, 841, 754 cm⁻¹; MS (EI⁺) *m/z*: 148 (M⁺).

(b) 2-Butylphenol

A mixture of 2-[(1*E*)-but-1-en-1-yl]phenol (1.6 g, 10 mmol) and 10% Pd-C (50% wet, 0.30 g) in ethanol (30 mL) was degassed and saturated with hydrogen gas, and the mixture was stirred at room temperature for 3 h. The reaction mixture was filtered with Celite pad and the filtrate was concentrated to afford the title compound quantitatively as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.12 (dd, 1H, *J* = 7.4, 1.6 Hz), 7.08 (ddd, 1H, *J* = 7.8, 7.4, 1.6 Hz), 6.87 (ddd, 1H, *J* = 7.8, 7.4, 1.0 Hz), 6.76 (dd, 1H, *J* = 7.4, 1.0 Hz), 4.65 (s, 1H), 2.61 (t, 2H, *J* = 7.8 Hz), 1.65–1.55 (m, 2H), 1.39 (tq, 2H, *J* = 7.4, 7.4 Hz), 0.94 (t, 3H, *J* = 7.4 Hz); IR (liquid film): 3414, 2956, 2930, 1455, 1233, 1117, 752 cm⁻¹; MS (EI⁺) *m/z*: 150 (M⁺).

(c) 4-(2-Butylphenoxy)benzoic acid

According to a similar procedure to 5-2-43 (a), the title compound (1.8 g, 6.7 mmol, 85% in 2 steps) was prepared from 4-fluorobenzaldehyde (0.96 g, 7.7 mmol), 2-butylphenol (1.6 g, 10 mmol), cesium carbonate (6.3 g, 19 mmol), DMF (10 mL), 2-methyl-2-butene (4.0 mL, 37 mmol), potassium dihydrogenphosphate (2.5 g, 19 mmol), sodium chlorite (2.0 g, 22 mmol), THF (5.0 mL), *tert*-butanol (10 mL) and water (5.0 mL). The final purification by extraction gave a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.05 (d, 2H, *J* = 9.0 Hz), 7.30 (dd, 1H, *J* = 7.4, 1.8 Hz), 7.23 (ddd, 1H, *J* = 7.8, 7.8, 1.8 Hz), 7.17 (ddd, 1H, *J* = 7.8, 7.4, 1.4 Hz), 6.98 (dd, 1H, *J* = 7.8, 1.4 Hz), 6.92 (d, 2H, *J* = 9.0 Hz), 2.55 (t, 2H, *J* = 7.8 Hz), 1.59–1.49 (m, 2H), 1.31 (tq, 2H, *J* = 7.4, 7.4 Hz), 0.87 (t, 3H, *J* = 7.4 Hz); IR (KBr): 2959, 2929, 1674, 1603, 1244, 1168, 747 cm⁻¹; MS (EI⁺) *m/z*: 270 (M⁺).

(d) (5-{5-[4-(2-Butylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}-4-ethylthiophen-2-yl)methanol

According to a similar procedure to 5-2-25 (b), the title compound (0.19 g, 0.43 mmol, 79% in 2 steps) was prepared from **3e** (0.18 g, 0.57 mmol), 4-(2-butylphenoxy)benzoic acid (0.16 g, 0.60 mmol), 1-hydroxybenzotriazole (96 mg, 0.63 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.12 g, 0.63 mmol), acetonitrile (4.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 1.1 mL, 1.1 mmol) and THF (4.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 9:1 to 2:1) gave a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.12 (d,

2H, J = 9.0 Hz), 7.31 (dd, 1H, J = 7.4, 2.0 Hz), 7.24 (ddd, 1H, J = 7.4, 7.4, 2.0 Hz), 7.18 (ddd, 1H, J = 7.4, 7.4, 1.2 Hz), 7.04–6.97 (m, 4H), 4.85 (d, 2H, J = 6.3 Hz), 3.06 (q, 2H, J = 7.4 Hz), 2.57 (t, 2H, J = 7.4 Hz), 1.89 (t, 1H, J = 6.3 Hz), 1.61–1.51 (m, 2H), 1.37–1.23 (m, 5H), 0.87 (t, 3H, J = 7.4 Hz); IR (KBr): 3371, 2955, 2933, 1613, 1513, 1347, 1245, 846, 762 cm^{-1} ; MS (FAB⁺) m/z : 435 ((M+H)⁺).

(e) Methyl

1-[(5-{5-[4-(2-butylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}-4-ethylthiophen-2-yl)methyl]azetidine-3-carboxylate

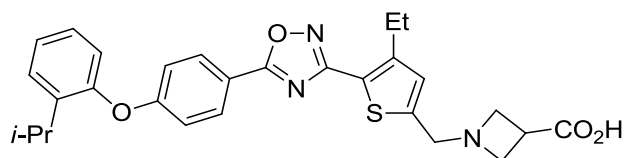
According to a similar procedure to 5-2-24 (b), the title compound (0.19 g, 0.35 mmol, 82%) was prepared from (5-{5-[4-(2-butylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}-4-ethylthiophen-2-yl)methanol (0.19 g, 0.43 mmol), carbon tetrabromide (0.29 g, 0.87 mmol), triphenylphosphine (0.23 g, 0.87 mmol), methyl 3-azetidinecarboxylate hydrochloride (98 mg, 0.65 mmol), *N,N*-diisopropylethylamine (0.19 mL, 1.1 mmol) and CH_2Cl_2 (4.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:1 to 2:3) gave a colorless oil. ¹H NMR (400 MHz, CDCl_3) δ : 8.11 (d, 2H, J = 8.6 Hz), 7.31 (dd, 1H, J = 7.4, 2.0 Hz), 7.24 (ddd, 1H, J = 7.4, 7.4, 2.0 Hz), 7.18 (ddd, 1H, J = 7.4, 7.4, 1.6 Hz), 7.03–6.98 (m, 3H), 6.86 (s, 1H), 3.78 (s, 2H), 3.72 (s, 3H), 3.67–3.60 (m, 2H), 3.41–3.32 (m, 3H), 3.03 (q, 2H, J = 7.4 Hz), 2.57 (t, 2H, J = 7.8 Hz), 1.61–1.51 (m, 2H), 1.37–1.22 (m, 5H), 0.87 (t, 3H, J = 7.4 Hz); IR (liquid film): 2956, 2931, 2859, 1738, 1613, 1514, 1487, 1346, 1245, 765 cm^{-1} ; MS (FAB⁺) m/z : 532 ((M+H)⁺).

(f) 1-[(5-{5-[4-(2-Butylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}-4-ethylthiophen-2-yl)methyl]azetidine-3-carboxylic acid (**8m**)

According to a similar procedure to 5-2-24 (c), **8m** (0.13 g, 0.24 mmol, 69%) was prepared from methyl 1-[(5-{5-[4-(2-butylphenoxy)phenyl]-1,2,4-oxadiazol-3-yl}-4-ethylthiophen-2-yl)methyl]azetidine-3-carboxylate (0.19 g, 0.35 mmol), NaOH (1.0 M in water, 0.70 mL, 0.70 mmol), methanol (2.0 mL), THF (2.0 mL) instead of 1,4-dioxane and acetic acid (50 μL , 0.87 mmol). The final purification by recrystallization (MeOH/water) gave a white solid. ¹H NMR (400 MHz, $\text{CD}_3\text{CO}_2\text{D}$) δ : 8.16 (d, 2H, J = 9.0 Hz), 7.36 (dd, 1H, J = 7.5, 1.6 Hz), 7.33 (s, 1H), 7.28 (ddd, 1H, J = 7.5, 7.5, 1.8 Hz), 7.21 (ddd, 1H, J = 7.5, 7.5, 1.6 Hz), 7.10–7.03 (m, 3H), 4.68 (s, 2H), 4.59–4.48 (m, 2H), 4.46–4.33 (m, 2H), 3.87–3.76 (m, 1H), 3.09 (q, 2H, J = 7.5 Hz), 2.59 (t, 2H, J = 7.7 Hz), 1.62–1.53 (m, 2H), 1.37–1.26 (m, 2H), 1.30 (t, 3H, J = 7.5 Hz), 0.87 (t, 3H, J = 7.3 Hz); IR (KBr): 3420, 2959, 2931, 1613, 1497, 1487, 1246, 844, 762 cm^{-1} ; MS (FAB⁺) m/z : 518 ((M+H)⁺).

5-2-50.

1-[[4-Ethyl-5-(5-{4-[2-(propan-2-yl)phenoxy]phenyl}-1,2,4-oxadiazol-3-yl)thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**8n**)



(a) 4-[2-(Propan-2-yl)phenoxy]benzoic acid

According to a similar procedure to 5-2-43 (a), the title compound (2.5 g, 9.8 mmol, 97% in 2 steps) was prepared from 4-fluorobenzaldehyde (1.2 g, 10 mmol), 2-(propan-2-yl)phenol (1.9 g, 14 mmol), potassium carbonate (3.5 g, 25 mmol), DMF (10 mL), 2-methyl-2-butene (5.3 mL, 50 mmol), potassium dihydrogenphosphate (3.4 g, 25 mmol), sodium chlorite (2.7 g, 30 mmol), THF (5.0 mL), *tert*-butanol (10 mL) and water (5.0 mL). The final purification by extraction gave a brown solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.05 (d, 2H, *J* = 9.0 Hz), 7.61 (dd, 1H, *J* = 5.9, 3.9 Hz), 7.25–7.20 (m, 2H), 6.99–6.90 (m, 3H), 3.16 (sept, 1H, *J* = 7.0 Hz), 1.20 (d, 6H, *J* = 7.0 Hz).

(b) [4-Ethyl-5-(5-{4-[2-(propan-2-yl)phenoxy]phenyl}-1,2,4-oxadiazol-3-yl)thiophen-2-yl]methanol

According to a similar procedure to 5-2-27 (b), the title compound (0.10 g, 0.24 mmol, 40% in 2 steps) was prepared from **3e** (0.19 g, 0.60 mmol), 4-[2-(propan-2-yl)phenoxy]benzoic acid (0.16 g, 0.63 mmol), 1-hydroxybenzotriazole (89 mg, 0.66 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.13 g, 0.66 mmol), acetonitrile (4.0 mL) and THF (2.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 0.78 mL, 0.78 mmol) and THF (4.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 4:1 to 3:1) gave a pink solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.12 (d, 2H, *J* = 9.0 Hz), 7.39 (dd, 1H, *J* = 5.9, 3.5 Hz), 7.25–7.20 (m, 2H), 7.01 (d, 2H, *J* = 9.0 Hz), 7.00–6.96 (m, 2H), 4.85 (d, 2H, *J* = 5.9 Hz), 3.19 (sept, 1H, *J* = 7.0 Hz), 3.05 (q, 2H, *J* = 7.4 Hz), 1.88 (t, 1H, *J* = 5.9 Hz), 1.29 (t, 3H, *J* = 7.4 Hz), 1.21 (d, 6H, *J* = 7.0 Hz); IR (KBr): 3419, 2965, 1612, 1515, 1346, 1245, 847, 764 cm⁻¹; MS (FAB⁺) *m/z*: 421 ((M+H)⁺).

(c) Methyl

1-{{4-ethyl-5-(5-{4-[2-(propan-2-yl)phenoxy]phenyl}-1,2,4-oxadiazol-3-yl)thiophen-2-yl]methyl}azetidine-3-carboxylate

According to a similar procedure to 5-2-24 (b), the title compound (0.10 g, 0.19 mmol, 84%) was prepared from [4-ethyl-5-(5-{4-[2-(propan-2-yl)phenoxy]phenyl}-1,2,4-oxadiazol-3-yl)thiophen-2-yl]methanol (97 mg, 0.23 mmol), carbon tetrabromide (0.12 g, 0.35 mmol), triphenylphosphine (92 mg, 0.35 mmol), methyl 3-azetidinecarboxylate hydrochloride (53 mg, 0.35 mmol), *N,N*-diisopropylethylamine (0.12 mL, 0.69 mmol) and CH₂Cl₂ (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 2:1) gave a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.11 (d, 2H, *J* = 9.0 Hz), 7.40 (dd, 1H, *J* = 5.9, 3.5 Hz), 7.25–7.21 (m, 2H), 7.01 (d, 2H, *J* = 9.0 Hz), 7.00–6.97 (m, 1H), 6.86 (s, 1H), 3.79 (s, 2H), 3.72 (s, 3H), 3.67–3.61 (m, 2H), 3.40–3.34 (m, 3H), 3.19 (sept, 1H, *J* = 7.0 Hz), 3.03

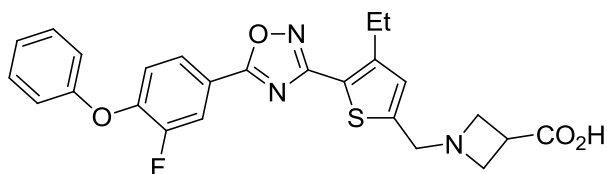
(q, 2H, $J = 7.4$ Hz), 1.28 (t, 3H, $J = 7.4$ Hz), 1.21 (d, 6H, $J = 7.0$ Hz); IR (liquid film): 2964, 1738, 1613, 1514, 1346, 1243, 765 cm^{-1} ; MS (FAB⁺) m/z 518 ((M+H)⁺).

(d) 1-([4-Ethyl-5-(5-{4-[2-(propan-2-yl)phenoxy]phenyl}-1,2,4-oxadiazol-3-yl)thiophen-2-yl)methyl}azetidine-3-carboxylic acid (**8n**)

According to a similar procedure to 5-2-24 (c), **8n** (76 mg, 0.15 mmol, 79%) was prepared from methyl 1-([4-ethyl-5-(5-{4-[2-(propan-2-yl)phenoxy]phenyl}-1,2,4-oxadiazol-3-yl)thiophen-2-yl)methyl}azetidine-3-carboxylate (97 mg, 0.19 mmol), NaOH (1.0 M in water, 0.29 mL, 0.29 mmol), methanol (1.0 mL), THF (1.0 mL) instead of 1,4-dioxane and acetic acid (16 μL , 0.29 mmol). The final purification by recrystallization (MeOH/water 1.0 mL/2.0 mL) gave a white solid. ¹H NMR (400 MHz, DMSO- d_6) δ : 8.13 (d, 2H, $J = 8.6$ Hz), 7.52–7.45 (m, 1H), 7.35–7.27 (m, 2H), 7.09 (d, 2H, $J = 8.6$ Hz), 7.10–7.04 (m, 1H), 7.01 (s, 1H), 3.75 (s, 2H), 3.49–3.42 (m, 2H), 3.30–3.18 (m, 3H), 3.09 (sept, 1H, $J = 6.6$ Hz), 2.96 (q, 2H, $J = 7.8$ Hz), 1.21 (t, 3H, $J = 7.8$ Hz), 1.16 (d, 6H, $J = 6.6$ Hz); IR (KBr): 3416, 2965, 1611, 1486, 1345, 1245, 764 cm^{-1} ; MS (FAB⁺) m/z 504 ((M+H)⁺).

5-2-51.

1-([4-Ethyl-5-[5-(3-fluoro-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl)methyl}azetidine-3-carboxylic acid (**8o**)



(a) 3-Fluoro-4-phenoxybenzoic acid

According to a similar procedure to 5-2-43 (a), the title compound (3.1 g, 13 mmol, 88% in 2 steps) was prepared from 3,4-difluorobenzaldehyde (1.4 g, 10 mmol), phenol (1.3 g, 14 mmol), potassium carbonate (3.5 g, 25 mmol), DMF (10 mL), 2-methyl-2-butene (8.0 mL, 75 mmol), potassium dihydrogenphosphate (5.1 g, 38 mmol), sodium chlorite (4.1 g, 45 mmol), THF (5.0 mL), *tert*-butanol (10 mL) and water (5.0 mL). The final purification by extraction gave a white crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ : 7.89 (dd, 1H, $J = 11.0, 2.0$ Hz), 7.83–7.80 (m, 1H), 7.39 (d, 1H, $J = 7.4$ Hz), 7.37 (d, 1H, $J = 7.4$ Hz), 7.19 (t, 1H, $J = 7.4$ Hz), 7.07–7.04 (m, 2H), 6.96 (t, 1H, $J = 8.2$ Hz); IR (KBr): 3065, 2983, 2673, 2596, 1692, 1492, 1444, 1275, 1025 cm^{-1} ; MS (EI⁺) m/z 232 (M⁺).

(b) {4-Ethyl-5-[5-(3-fluoro-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol

According to a similar procedure to 5-2-27 (b), the title compound (0.16 g, 0.41 mmol, 85% in 2 steps) was prepared from **3e** (0.15 g, 0.48 mmol), 3-fluoro-4-phenoxybenzoic acid (0.12 g, 0.50 mmol), 1-hydroxybenzotriazole (72 mg, 0.53 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

hydrochloride (0.10 g, 0.53 mmol), acetonitrile (4.0 mL) and THF (2.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 0.96 mL, 0.96 mmol) and THF (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:1) gave a pale yellowish crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.99 (dd, 1H, *J* = 10.6, 2.0 Hz), 7.88 (dd, 1H, *J* = 8.4, 1.4 Hz), 7.39 (t, 2H, *J* = 7.4 Hz), 7.19 (t, 1H, *J* = 7.4 Hz), 7.09–7.02 (m, 3H), 6.96 (s, 1H), 4.84 (d, 2H, *J* = 5.9 Hz), 3.05 (q, 2H, *J* = 7.4 Hz), 1.91 (t, 1H, *J* = 5.9 Hz), 1.29 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3433, 1595, 1576, 1513, 1492, 1456, 1436, 1342, 1283, 1270, 1207 cm⁻¹; MS (FAB⁺) *m/z* 397 ((M+H)⁺).

(c) Methyl

1-({4-ethyl-5-[5-(3-fluoro-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate

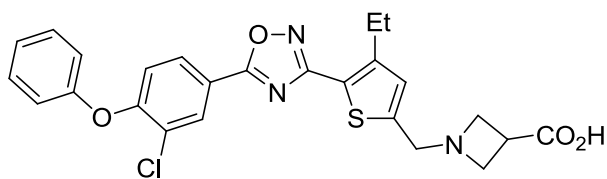
According to a similar procedure to 5-2-24 (b), the title compound (0.15 g, 0.31 mmol, 77%) was prepared from {4-ethyl-5-[5-(3-fluoro-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol (0.16 g, 0.40 mmol), carbon tetrabromide (0.17 g, 0.52 mmol), triphenylphosphine (0.14 g, 0.52 mmol), methyl 3-azetidinecarboxylate hydrochloride (91 mg, 0.60 mmol), *N,N*-diisopropylethylamine (0.21 mL, 1.2 mmol) and CH₂Cl₂ (6.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:1 to 2:1) gave a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.98 (dd, 1H, *J* = 10.8, 2.2 Hz), 7.87 (dt, 1H, *J* = 9.0, 1.7 Hz), 7.38 (t, 2H, *J* = 7.4 Hz), 7.19 (t, 1H, *J* = 7.4 Hz), 7.09–7.02 (m, 3H), 6.85 (s, 1H), 3.78 (s, 2H), 3.71 (s, 3H), 3.67–3.58 (m, 2H), 3.40–3.31 (m, 3H), 3.02 (q, 2H, *J* = 7.4 Hz), 1.28 (t, 3H, *J* = 7.4 Hz); IR (liquid film) : 1737, 1590, 1559, 1523, 1454, 1489, 1348, 1272, 1204 cm⁻¹; MS (FAB⁺) *m/z* 494 ((M+H)⁺).

(d) 1-({4-Ethyl-5-[5-(3-fluoro-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**8o**)

According to a similar procedure to 5-2-24 (c), **8o** (0.11 g, 0.23 mmol, 77%) was prepared from methyl 1-({4-ethyl-5-[5-(3-fluoro-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (0.15 g, 0.30 mmol), NaOH (1.0 M in water, 0.90 mL, 0.90 mmol), 1,4-dioxane (3.0 mL) and acetic acid (52 μL, 0.90 mmol). The final purification by recrystallization (MeOH/water 3.0 mL/2.0 mL) gave a white crystalline solid. ¹H NMR (400 MHz, CD₃CO₂D) δ: 8.04 (d, 1H, *J* = 10.6 Hz), 7.97 (d, 1H, *J* = 9.0 Hz), 7.44 (t, 2H, *J* = 7.6 Hz), 7.33 (s, 1H), 7.23 (t, 1H, *J* = 7.6 Hz), 7.20–7.09 (m, 3H), 4.68 (s, 2H), 4.58–4.44 (m, 2H), 4.44–4.33 (m, 2H), 3.87–3.75 (m, 1H), 3.09 (q, 2H, *J* = 7.4 Hz), 1.31 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3427, 1591, 1556, 1515, 1491, 1349, 1275, 1201 cm⁻¹; MS (FAB⁺) *m/z* 480 ((M+H)⁺).

5-2-52.

1-({5-[5-(3-Chloro-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]-4-ethylthiophen-2-yl}methyl)azetidine-3-carboxylic acid (**8p**)



(a) 3-Chloro-4-phenoxybenzoic acid

According to a similar procedure to 5-2-43 (a), the title compound (0.95 g, 3.9 mmol, 77% in 2 steps) was prepared from 3-chloro-4-fluorobenzaldehyde (0.80 g, 5.0 mmol), phenol (0.66 g, 7.0 mmol), potassium carbonate (1.7 g, 13 mmol), DMF (10 mL), 2-methyl-2-butene (2.7 mL, 25 mmol), potassium dihydrogenphosphate (1.7 g, 13 mmol), sodium chlorite (1.4 g, 15 mmol), THF (2.5 mL), *tert*-butanol (5.0 mL) and water (2.5 mL). The final purification by extraction gave a white crystalline solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.19 (d, 1H, $J = 2.0$ Hz), 7.88 (dd, 1H, $J = 8.6, 2.0$ Hz), 7.39 (t, 2H, $J = 7.4$ Hz), 7.21 (t, 1H, $J = 7.4$ Hz), 7.05 (dd, 2H, $J = 7.4, 1.2$ Hz), 6.87 (d, 1H, $J = 8.6$ Hz).

(b) {5-[5-(3-Chloro-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]-4-ethylthiophen-2-yl}methanol

According to a similar procedure to 5-2-27 (b), the title compound (0.17 g, 0.42 mmol, 87% in 2 steps) was prepared from **3e** (0.15 g, 0.48 mmol), 3-chloro-4-phenoxybenzoic acid (0.12 g, 0.50 mmol), 1-hydroxybenzotriazole (72 mg, 0.53 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.10 g, 0.53 mmol), acetonitrile (4.0 mL) and THF (2.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 0.96 mL, 0.96 mmol) and THF (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:1) gave a pale yellowish crystalline solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.31 (d, 1H, $J = 2.1$ Hz), 7.99 (dd, 1H, $J = 8.6, 2.1$ Hz), 7.43 (t, 2H, $J = 7.4$ Hz), 7.23 (t, 1H, $J = 7.4$ Hz), 7.09 (d, 2H, $J = 8.6$ Hz), 6.99 (s, 1H), 6.98 (d, 1H, $J = 8.6$ Hz), 4.85 (d, 2H, $J = 5.8$ Hz), 3.06 (q, 2H, $J = 7.4$ Hz), 1.90 (t, 1H, $J = 5.8$ Hz), 1.30 (t, 3H, $J = 7.4$ Hz); IR (KBr): 3335, 3250, 1591, 1480, 1393, 1265, 1242 cm^{-1} ; MS (FAB $^+$) m/z : 413 ((M+H) $^+$).

(c) Methyl

1-({5-[5-(3-chloro-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]-4-ethylthiophen-2-yl}methyl)azetidine-3-carboxylate

According to a similar procedure to 5-2-24 (b), the title compound (0.15 g, 0.30 mmol, 73%) was prepared from {5-[5-(3-chloro-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]-4-ethylthiophen-2-yl}methanol (0.17 g, 0.41 mmol), carbon tetrabromide (0.18 g, 0.53 mmol), triphenylphosphine (0.14 g, 0.53 mmol), methyl 3-azetidinecarboxylate hydrochloride (93 mg, 0.62 mmol), *N,N*-diisopropylethylamine (0.21 mL, 1.2 mmol) and CH_2Cl_2 (7.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:1) gave a pale yellow oil. ^1H NMR (400 MHz, CDCl_3) δ : 8.30 (d, 1H, $J = 2.2$ Hz), 7.98 (dd, 1H, $J = 8.6, 2.2$ Hz), 7.43 (t, 2H, $J = 7.4$ Hz), 7.24 (t, 1H, $J = 7.4$ Hz), 7.09 (d, 2H, $J = 7.4$ Hz), 6.98 (d, 1H, $J = 8.6$ Hz), 6.87 (s, 1H), 3.84 (s, 2H), 3.79 (s, 3H), 3.43–3.32 (m, 3H), 3.69–3.59 (m, 2H),

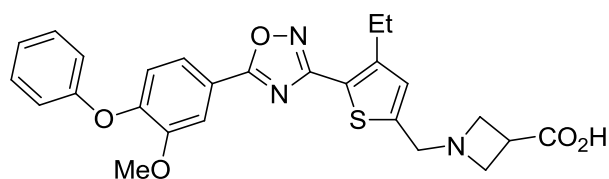
3.03 (q, 2H, $J = 7.8$ Hz), 1.28 (t, 3H, $J = 7.8$ Hz); IR (thin film): 1737, 1513, 1483, 1343, 1266, 1245, 1198 cm^{-1} ; MS (FAB⁺) m/z 510 ((M+H)⁺).

(d) 1-({5-[5-(3-Chloro-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]-4-ethylthiophen-2-yl}methyl)azetidine-3-carboxylic acid (**8p**)

According to a similar procedure to 5-2-24 (c), **8p** (0.13 g, 0.26 mmol, 88%) was prepared from methyl 1-({5-[5-(3-chloro-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]-4-ethylthiophen-2-yl}methyl)azetidine-3-carboxylate (0.15 g, 0.29 mmol), NaOH (1.0 M in water, 0.87 mL, 0.87 mmol), 1,4-dioxane (3.0 mL) and acetic acid (50 μL , 0.87 mmol). The final purification by recrystallization (MeOH/water 3.0 mL/2.0 mL) gave a white crystalline solid. ¹H NMR (400 MHz, CD₃CO₂D) δ : 8.31 (s, 1H), 8.06 (dd, 1H, $J = 8.6$, 2.2 Hz), 7.45 (t, 2H, $J = 7.8$ Hz), 7.33 (s, 1H), 7.25 (t, 1H, $J = 7.8$ Hz), 7.13 (d, 2H, $J = 7.8$ Hz), 7.07 (d, 1H, $J = 8.6$ Hz), 4.68 (s, 2H), 4.59–4.48 (m, 2H), 4.44–4.33 (m, 2H), 3.87–3.75 (m, 1H), 3.09 (q, 2H, $J = 7.6$ Hz), 1.31 (t, 3H, $J = 7.6$ Hz); IR (KBr): 3414, 1609, 1591, 1514, 1484, 1392, 1344, 1265 cm^{-1} ; MS (FAB⁺) m/z 496 ((M+H)⁺).

5-2-53.

1-({4-Ethyl-5-[5-(3-methoxy-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**8q**)



(a) 3-Methoxy-4-phenoxybenzoic acid

According to a similar procedure to 5-2-43 (a), the title compound (1.2 g, 4.9 mmol, 94% in 2 steps) was prepared from 4-fluoro-3-methoxybenzaldehyde (1.5 g, 10 mmol), phenol (1.1 g, 12 mmol), potassium carbonate (2.8 g, 20 mmol), DMF (10 mL), 2-methyl-2-butene (2.7 mL, 25 mmol), potassium dihydrogenphosphate (1.7 g, 13 mmol), sodium chlorite (1.4 g, 15 mmol), THF (2.5 mL), *tert*-butanol (5.0 mL) and water (2.5 mL). The final purification by extraction gave a white solid. ¹H NMR (400 MHz, CDCl₃) δ : 7.73 (d, 1H, $J = 2.0$ Hz), 7.69 (dd, 1H, $J = 8.2$, 2.0 Hz), 7.37 (dd, 2H, $J = 8.2$, 7.4 Hz), 7.16 (t, 1H, $J = 7.4$ Hz), 7.05 (d, 2H, $J = 8.2$ Hz), 6.89 (d, 1H, $J = 8.2$ Hz), 3.96 (s, 3H).

(b) {4-Ethyl-5-[5-(3-methoxy-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol

According to a similar procedure to 5-2-25 (b), the title compound (0.18 g, 0.44 mmol, 77% in 2 steps) was prepared from **3e** (0.18 g, 0.57 mmol), 3-methoxy-4-phenoxybenzoic acid (0.15 g, 0.60 mmol), 1-hydroxybenzotriazole (96 mg, 0.63 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.12 g, 0.63 mmol) and acetonitrile (4.0 mL), and tetrabutylammonium fluoride (1.0

M in THF, 1.1 mL, 1.1 mmol) and THF (4.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:1 to 3:2) gave an orange solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.78 (d, 1H, *J* = 2.0 Hz), 7.74 (dd, 1H, *J* = 8.6, 2.0 Hz), 7.40–7.35 (m, 2H), 7.19–7.14 (m, 1H), 7.08–7.04 (m, 2H), 7.00–6.96 (m, 2H), 4.85 (d, 2H, *J* = 6.3 Hz), 4.00 (s, 3H), 3.06 (q, 2H, *J* = 7.4 Hz), 1.94–1.88 (m, 1H), 1.30 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3447, 2970, 1594, 1554, 1492, 1341, 1228, 1027, 743 cm⁻¹; MS (FAB⁺) *m/z*: 409 ((M+H)⁺).

(c) Methyl

1-({4-ethyl-5-[5-(3-methoxy-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate

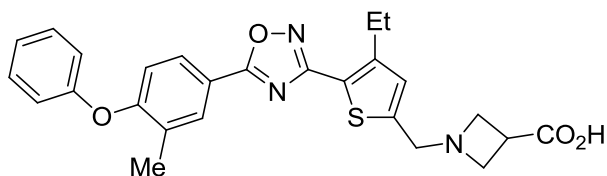
According to a similar procedure to 5-2-24 (b), the title compound (0.14 g, 0.27 mmol, 61%) was prepared from {4-ethyl-5-[5-(3-methoxy-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol (0.18 g, 0.44 mmol), carbon tetrabromide (0.32 g, 0.88 mmol), triphenylphosphine (0.25 g, 0.88 mmol), methyl 3-azetidinecarboxylate hydrochloride (0.11 g, 0.67 mmol), *N,N*-diisopropylethylamine (0.21 mL, 1.1 mmol) and CH₂Cl₂ (4.0 mL). The final purification by flash column chromatography (silica gel, hexane/EtOAc 2:1 to 1:3) gave a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.78 (d, 1H, *J* = 2.0 Hz), 7.73 (dd, 1H, *J* = 8.2, 2.0 Hz), 7.41–7.35 (m, 2H), 7.19–7.14 (m, 1H), 7.08–7.03 (m, 2H), 6.97 (d, 1H, *J* = 8.2 Hz), 6.87 (s, 1H), 4.00 (s, 3H), 3.80 (s, 2H), 3.72 (s, 3H), 3.67–3.61 (m, 2H), 3.41–3.32 (m, 3H), 3.03 (q, 2H, *J* = 7.4 Hz), 1.28 (t, 3H, *J* = 7.4 Hz); IR (thin film): 2965, 1737, 1513, 1489, 1349, 1220, 761 cm⁻¹; MS (FAB⁺) *m/z*: 506 ((M+H)⁺).

(d) 1-({4-Ethyl-5-[5-(3-methoxy-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**8q**)

According to a similar procedure to 5-2-24 (c), **8q** (0.12 g, 0.25 mmol, 91%) was prepared from methyl 1-({4-ethyl-5-[5-(3-methoxy-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (0.14 g, 0.27 mmol), NaOH (1.0 M in water, 0.54 mL, 0.54 mmol), methanol (2.0 mL), THF (2.0 mL) instead of 1,4-dioxane and acetic acid (39 μL, 0.68 mmol). The final purification by filtration with water and methanol gave a white solid. ¹H NMR (400 MHz, CD₃CO₂D) δ: 7.82 (d, 1H, *J* = 2.0 Hz), 7.79 (dd, 1H, *J* = 8.2, 2.0 Hz), 7.40–7.34 (m, 2H), 7.33 (s, 1H), 7.17–7.12 (m, 1H), 7.07 (d, 1H, *J* = 8.2 Hz), 7.06–7.01 (m, 2H), 4.68 (s, 2H), 4.60–4.49 (m, 2H), 4.47–4.33 (m, 2H), 3.96 (s, 3H), 3.87–3.76 (m, 1H), 3.09 (q, 2H, *J* = 7.5 Hz), 1.31 (t, 3H, *J* = 7.5 Hz); IR (KBr): 3431, 2970, 1590, 1514, 1350, 1272, 1250, 1217, 1033, 760, 745 cm⁻¹; MS (FAB⁺) *m/z*: 492 ((M+H)⁺).

5-2-54.

1-({4-Ethyl-5-[5-(3-methyl-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**8r**)



(a) {4-Ethyl-5-[5-(3-methyl-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol

According to a similar procedure to 5-2-27 (b), the title compound (0.16 g, 0.41 mmol, 82% in 2 steps) was prepared from **3e** (0.16 g, 0.50 mmol), 3-methyl-4-phenoxybenzoic acid (0.12 g, 0.53 mmol), 1-hydroxybenzotriazole (74 mg, 0.55 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.11 g, 0.55 mmol), acetonitrile (4.0 mL) and THF (2.0 mL), and tetrabutylammonium fluoride (1.0 M in THF, 1.0 mL, 1.0 mmol) and THF (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:1) gave a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.09 (d, 1H, *J* = 1.6 Hz), 7.94 (dd, 1H, *J* = 8.6, 2.0 Hz), 7.41–7.36 (m, 2H), 7.20–7.14 (m, 1H), 7.04–7.00 (m, 2H), 6.98 (s, 1H), 6.90 (d, 1H, *J* = 8.2 Hz), 4.85 (d, 2H, *J* = 5.9 Hz), 3.06 (q, 2H, *J* = 7.4 Hz), 2.40 (s, 3H), 1.90 (t, 1H, *J* = 5.9 Hz), 1.30 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3387, 2930, 1592, 1483, 1242, 762 cm⁻¹; MS (FAB⁺) *m/z*: 393 ((M+H)⁺).

(b) Methyl

1-({4-ethyl-5-[5-(3-methyl-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate

According to a similar procedure to 5-2-24 (b), the title compound (0.14 g, 0.28 mmol, 69%) was prepared from {4-ethyl-5-[5-(3-methyl-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methanol (0.16 g, 0.40 mmol), carbon tetrabromide (0.17 g, 0.52 mmol), triphenylphosphine (0.14 g, 0.52 mmol), methyl 3-azetidinecarboxylate hydrochloride (91 mg, 0.60 mmol), *N,N*-diisopropylethylamine (0.21 mL, 1.2 mmol) and CH₂Cl₂ (6.0 mL). The final purification by flush column chromatography (silica gel, *n*-hexane/EtOAc 3:1 to 2:1) gave a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.09–8.07 (m, 1H), 7.93 (dd, 1H, *J* = 8.6, 2.1 Hz), 7.41–7.36 (m, 2H), 7.19–7.15 (m, 1H), 7.04–7.00 (m, 2H), 6.90 (d, 1H, *J* = 8.6 Hz), 6.87 (s, 1H), 3.79 (s, 2H), 3.72 (s, 3H), 3.67–3.61 (m, 2H), 3.40–3.32 (m, 3H), 3.04 (q, 2H, *J* = 7.4 Hz), 2.40 (s, 3H), 1.28 (t, 3H, *J* = 7.4 Hz); IR (liquid film): 2965, 1738, 1514, 1486, 1345, 1241, 1203, 764, 693 cm⁻¹; MS (FAB⁺) *m/z*: 490 ((M+H)⁺).

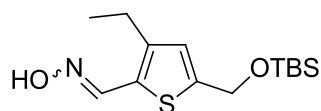
(c) 1-({4-Ethyl-5-[5-(3-methyl-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**8r**)

According to a similar procedure to 5-2-24 (c), **8r** (0.11 g, 0.24 mmol, 89%) was prepared from methyl 1-({4-ethyl-5-[5-(3-methyl-4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (0.13 g, 0.27 mmol), NaOH (1.0 M in water, 0.81 mL, 0.81 mmol), 1,4-dioxane (3.0 mL) and acetic acid (47 μL, 0.82 mmol). The final purification by recrystallization (MeOH/water 3.0 mL/2.0 mL) gave a white solid. ¹H NMR (400 MHz, CD₃CO₂D) δ: 8.13–8.08 (m, 1H), 8.00–7.95 (m,

1H), 7.41 (dd, 2H, J = 8.0, 7.4 Hz), 7.32 (s, 1H), 7.19 (t, 1H, J = 7.4 Hz), 7.07 (d, 2H, J = 8.0 Hz), 6.95 (d, 1H, J = 8.6 Hz), 4.68 (s, 2H), 4.57–4.48 (m, 2H), 4.45–4.35 (m, 2H), 3.85–3.76 (m, 1H), 3.09 (q, 2H, J = 7.8 Hz), 2.41 (s, 3H), 1.30 (t, 3H, J = 7.8 Hz); IR (KBr): 3414, 2967, 1589, 1488, 1243, 747 cm^{-1} ; MS (FAB⁺) m/z 476 ((M+H)⁺).

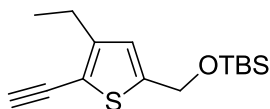
5-3. 第3章に関する実験

5-3-1. 1-[5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-*N*hydroxymethanimine (20)



To a suspension of 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl-3-ethylthiophene-2-carbaldehyde (0.80 g, 2.8 mmol, prepared by the procedure 5-2-11 (a)) and hydroxylamine hydrochloride (0.22 g, 3.1 mmol) in CH_2Cl_2 (10 mL) and MeOH (1.0 mL) was added Et_3N (0.78 mL, 5.6 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was poured into water and extracted with Et_2O . The extract was washed with brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 7:3) to afford both regioisomers of the title compound **20** (the less polar product 0.23 g, 0.76 mmol, 27% and the more polar product 0.57 g, 1.9 mmol, 68%). Both regioisomers were combined and used to the next step. Less polar product: ^1H NMR (400 MHz, CDCl_3) δ : 8.31 (s, 1H), 7.12–7.08 (m, 1H), 6.73–6.72 (m, 1H), 4.80 (d, 2H, J = 0.8 Hz), 2.63 (q, 2H, J = 7.4 Hz), 1.19 (t, 3H, J = 7.4 Hz), 0.93 (s, 9H), 0.11 (s, 6H); MS (ESI) m/z : 300 ((M+H)⁺); More polar product: ^1H NMR (400 MHz, CDCl_3) δ : 7.72 (s, 1H), 6.81 (s, 1H), 4.87 (d, 2H, J = 0.8 Hz), 2.74 (q, 2H, J = 7.4 Hz), 1.24 (t, 3H, J = 7.4 Hz), 0.93 (s, 9H), 0.11 (s, 6H); MS (ESI) m/z : 300 ((M+H)⁺).

5-3-2. *tert*-Butyl[(4-ethyl-5-ethynylthiophen-2-yl)methoxy]dimethylsilane (24)



(a) *tert*-Butyl[(4-ethyl-5-iodothiophen-2-yl)methoxy]dimethylsilane

To a solution of *tert*-butyl[(4-ethylthiophen-2-yl)methoxy]dimethylsilane (**13b**) (5.0 g, 22 mmol, prepared by the procedure 5-2-10) in THF (30 mL) was slowly added *n*-BuLi (1.6 M in hexane, 15 mL,

24 mmol) at -78 °C, and the resulting mixture was stirred at 0 °C for 20 min. The reaction mixture was cooled to -78 °C again and iodine (6.6 g, 26 mmol) was added. After stirring at 0 °C for 30 min, the reaction was quenched with sat. Na₂S₂O₃. The resulting biphasic mixture was poured into water and extracted with *n*-hexane. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc) to afford the title compound (5.6 g, 15 mmol, 72%). ¹H NMR (400 MHz, CDCl₃) δ: 6.59 (s, 1H), 4.79 (s, 2H), 2.50 (q, 2H, *J* = 7.4 Hz), 1.15 (t, 3H, *J* = 7.4 Hz), 0.92 (s, 9H), 0.10 (s, 6H); IR (liquid film): 2955, 2929, 2856, 1462, 1255, 1149, 1080, 838, 778 cm⁻¹; MS (FAB⁺) *m/z*: 381 ((M-H)⁺).

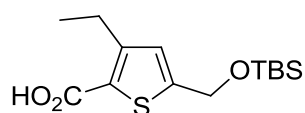
(b) *tert*-Butyl[(4-ethyl-5-[(trimethylsilyl)ethynyl]thiophen-2-yl)methoxy]dimethylsilane

To a solution of *tert*-butyl[(4-ethyl-5-iodothiophen-2-yl)methoxy]dimethylsilane (0.72 g, 2.0 mmol) in benzene (5.0 mL) were added Et₃N (0.55 mL, 4.0 mmol), trimethylsilylacetylene (0.43 mL, 3.0 mmol), Pd(PPh₃)₄ (0.23 g, 0.20 mmol) and CuI (57 mg, 0.30 mmol) and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched with water and the resulting biphasic mixture was extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 95:5) to afford the title compound (0.53 g, 1.5 mmol, 75%). ¹H NMR (400 MHz, CDCl₃) δ: 6.66 (s, 1H), 4.78 (s, 2H), 2.65 (q, 2H, *J* = 7.3 Hz), 1.19 (t, 3H, *J* = 7.3 Hz), 0.92 (s, 9H), 0.24 (s, 9H), 0.09 (s, 6H).

(c) *tert*-Butyl[(4-ethyl-5-ethynylthiophen-2-yl)methoxy]dimethylsilane (**24**)

To a solution of *tert*-butyl[(4-ethyl-5-[(trimethylsilyl)ethynyl]thiophen-2-yl)methoxy]dimethylsilane (0.53 g, 1.5 mmol) in methanol (5.0 mL) was added potassium carbonate (0.41 g, 3.0 mmol) and the resulting mixture was stirred at room temperature. After the reaction completed, the reaction mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 90:10) to afford the title compound (0.34 g, 1.2 mmol, 81%). ¹H NMR (400 MHz, CDCl₃) δ: 6.68 (s, 1H), 4.79 (s, 2H), 3.42 (s, 1H), 2.67 (q, 2H, *J* = 7.3 Hz), 1.20 (t, 3H, *J* = 7.3 Hz), 0.92 (s, 9H), 0.10 (s, 6H); IR (ATR): 2929, 2856, 2098, 1254, 1142, 1074, 833, 775 cm⁻¹; MS (ESI) *m/z*: 281 ((M+H)⁺).

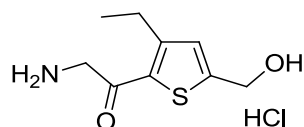
5-3-3. 5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl-3-ethylthiophene-2-carboxylic acid (**28**)



To a solution of *tert*-butyl[(4-ethylthiophen-2-yl)methoxy]dimethylsilane (**13b**) (76 g, 0.29 mol) in THF (0.30 L) was slowly added *n*-BuLi (1.6 M in hexane, 0.20 L, 0.32 mol) at -78 °C and the mixture

was stirred at 0 °C for 30 min. After cooling to -78 °C again, carbon dioxide (dry ice, 70 g, 1.6 mol) was added and the resulting mixture was stirred for 1 h. The reaction was quenched with sat. NH₄Cl and the reaction mixture was extracted with Et₂O. The extract was washed with aq. citric acid, dried over MgSO₄, filtered and concentrated. The residue was recrystallized from *n*-hexane to afford the title compound (70 g, 0.23 mol, 79%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 6.82 (s, 1H), 4.85 (s, 2H), 2.98 (q, 2H, *J* = 7.4 Hz), 1.22 (t, 3H, *J* = 7.4 Hz), 0.94 (s, 9H), 0.12 (s, 6H); IR (KBr): 2929, 2858, 1643, 1454, 1107, 839, 780 cm⁻¹; MS (FAB⁺) *m/z*: 301 ((M+H)⁺).

5-3-4. 2-Amino-1-[3-ethyl-5-(hydroxymethyl)thiophen-2-yl]ethanone hydrochloride (39)



(a) 1-[5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]ethanone

To a mixture of 5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl)-3-ethylthiophene-2-carboxylic acid (**28**) (5.4 g, 18 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (2.2 g, 23 mmol) in CH₂Cl₂ (50 mL) were successively added *N,N*-diisopropylethylamine (4.0 mL, 23 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.4 g, 23 mmol) and the resulting mixture was stirred at room temperature for 13 h. The reaction mixture was poured into water and extracted with Et₂O. The extract was washed with water and brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 7:3) to afford 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-3-ethyl-*N*-methoxy-*N*-methylthiophene-2-carboxamide (3.5 g, 10 mmol).

To a solution of 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-3-ethyl-*N*-methoxy-*N*-methylthiophene-2-carboxamide (3.5 g, 10 mmol) in Et₂O (20 mL) was slowly added methyllithium (1.1 M in Et₂O, 14 mL, 15 mmol) at -78 °C and the resulting mixture was stirred at -78 °C for 1 h. The reaction was quenched with sat. NH₄Cl and the reaction mixture was extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc) to afford the title compound (2.7 g, 9.1 mmol, 51% in 2 steps). ¹H NMR (400 MHz, CDCl₃) δ: 6.83 (s, 1H), 4.85 (s, 2H), 2.97 (q, 2H, *J* = 7.4 Hz), 2.51 (s, 3H), 1.21 (t, 3H, *J* = 7.4 Hz), 0.95 (s, 9H), 0.13 (s, 6H).

(b) 2-Bromo-1-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]ethanone

To a diluted solution of NaHMDS (1.0 M in THF, 18 mL, 18 mmol) in THF (20 mL) was slowly added a solution of thiophenone (2.7 g, 9.1 mmol) in THF at -78 °C. After stirring at -78 °C for 10 min,

chlorotrimethylsilane (3.0 mL, 24 mmol) was added and the resulting mixture was stirred at -78 °C for 30 min. The reaction was quenched with sat. NH₄Cl and the reaction mixture was poured into water and extracted with Et₂O. The extract was concentrated and co-evaporated with benzene to afford the crude product of *tert*-butyl[(4-ethyl-5-{1-[(trimethylsilyl)oxy]ethenyl}thiophen-2-yl)methoxy]dimethylsilane.

To a solution of the crude product of *tert*-butyl[(4-ethyl-5-{1-[(trimethylsilyl)oxy]ethenyl}thiophen-2-yl)methoxy]dimethylsilane in THF (20 mL) was added *N*-bromosuccinimide (2.1 g, 12 mmol) at 0 °C and the resulting mixture was stirred for 30 min. The reaction mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 85:15) to afford the title compound (2.9 g, 7.6 mmol, 83% in 2 steps). ¹H NMR (400 MHz, CDCl₃) δ: 6.87 (s, 1H), 4.87 (s, 2H), 4.32 (s, 2H), 2.99 (q, 2H, *J* = 7.4 Hz), 1.22 (t, 3H, *J* = 7.4 Hz), 0.95 (s, 9H), 0.13 (s, 6H); IR (ATR): 2929, 2856, 1656, 1438, 1254, 1080, 833, 776 cm⁻¹; MS (FAB⁺) *m/z*: 377 ((M+H)⁺).

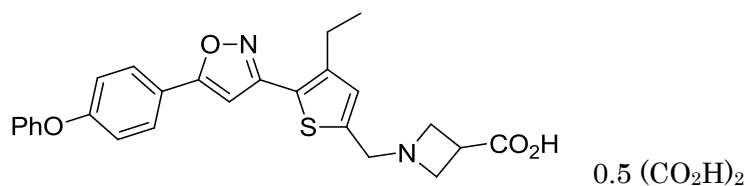
(c) 2-Amino-1-[3-ethyl-5-(hydroxymethyl)thiophen-2-yl]ethanone hydrochloride (**39**)

To a solution of 2-bromo-1-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]ethanone (2.0 g, 5.3 mmol) in acetonitrile (20 mL) was added sodium diformylamide (0.82 g, 8.6 mmol) and the resulting mixture was stirred at 70 °C for 2.5 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (*n*-hexane/EtOAc 9:1 to 7:3) to afford *N*-{2-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-2-oxoethyl}-*N*-formylformamide (1.5 g, 4.1 mmol).

To a solution of *N*-{2-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-2-oxoethyl}-*N*-formylformamide (1.5 g, 4.1 mmol) in ethanol (10 mL) was added HCl (12 M in water, 0.84 mL, 10 mol) and the resulting mixture was stirred at 70 °C for 2 h. After cooling to room temperature, the reaction mixture was concentrated and co-evaporated with toluene. The residue was purified by recrystallization (Et₂O/MeOH 9:1) to afford the title compound (0.78 g, 2.2 mmol, 42% in 2 steps). ¹H NMR (400 MHz, CD₃OD) δ: 7.06 (s, 1H), 4.79 (s, 2H), 4.34 (s, 2H), 3.01 (q, 2H, *J* = 7.4 Hz), 1.24 (t, 3H, *J* = 7.4 Hz); IR (KCl): 3228, 2875, 1650, 1444, 1309, 1147, 1044, 969; MS (EI⁺) *m/z*: 199 (M⁺).

5-3-5.

1-({4-Ethyl-5-[5-(4-phenoxyphenyl)-1,2-oxazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid 1/2 oxalate (**23**)



(a) 3-[5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-5-(4-phenoxyphenyl)-1,2-oxazole (**22**)

To a solution of 1-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-*N*-hydroxymethanimine (**20**) (0.30 g, 1.0 mmol) in chloroform (2.0 mL) were successively added *N*-chlorosuccinimide (0.16 g, 1.0 mmol) and a catalytic amount of pyridine and the resulting mixture was stirred at room temperature for 2 h. To this were successively added 1-ethynyl-4-phenoxybenzene (0.22 mL, 1.2 mmol) and Et₃N (0.17 mL, 1.2 mmol) and the resulting mixture was stirred at 50 °C for 2 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 90:10) to afford the title compound (0.36 g, 0.73 mmol, 73%). ¹H NMR (400 MHz, CDCl₃) δ: 7.77 (d, 2H, *J* = 9.0 Hz), 7.39 (dd, 2H, *J* = 8.2, 7.4 Hz), 7.17 (t, 1H, *J* = 7.4 Hz), 7.09–7.05 (m, 4H), 6.84 (s, 1H), 6.59 (s, 1H), 4.86 (s, 2H), 2.90 (q, 2H, *J* = 7.4 Hz), 1.27 (t, 3H, *J* = 7.4 Hz), 0.95 (s, 9H), 0.13 (s, 6H); IR (liquid film): 2955, 2929, 1508, 1489, 1244, 1084, 839, 780 cm⁻¹; MS (FAB⁺) *m/z*: 492 ((M+H)⁺).

(b) Methyl

1-({4-ethyl-5-[5-(4-phenoxyphenyl)-1,2-oxazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate To a solution of 3-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-5-(4-phenoxyphenyl)-1,2-oxazole (0.36 g, 0.73 mmol) in THF (1.0 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 0.88 mL, 0.88 mmol) and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with brine, dried over Na₂SO₄, filtered and concentrated.

To a solution of the residue in toluene (2.0 mL) were successively added thionyl chloride (71 μL, 0.95 mmol) and a catalytic amount of DMF and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with toluene and azeotropically evaporated. The residue was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (*n*-hexane/EtOAc).

To a solution of the product in acetonitrile (2.0 mL) were successively added methyl 3-azetidinecarboxylate hydrochloride (0.14 g, 0.95 mmol) and *N,N*-diisopropylethylamine (0.33 mL, 1.9 mmol) and the resulting mixture was stirred at 65 °C for 2 h. After cooling to room temperature,

the reaction mixture was poured into water and extracted with EtOAc. The extract was washed with brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:1) to afford the title compound (0.27 g, 0.57 mmol, 90%). ^1H NMR (400 MHz, CDCl_3) δ : 7.77 (d, 2H, J = 8.6 Hz), 7.39 (dd, 2H, J = 8.2, 8.2 Hz), 7.17 (t, 1H, J = 7.4 Hz), 7.09–7.05 (m, 4H), 6.84 (s, 1H), 6.57 (s, 1H), 3.77 (s, 2H), 3.72 (s, 3H), 3.66–3.59 (m, 2H), 3.41–3.32 (m, 3H), 2.89 (q, 2H, J = 7.4 Hz), 1.27 (t, 3H, J = 7.4 Hz); IR (liquid film): 2966, 1736, 1508, 1489, 1243, 1201, 1171, 756, 732 cm^{-1} ; MS (FAB $^+$) m/z : 475 ((M+H) $^+$).

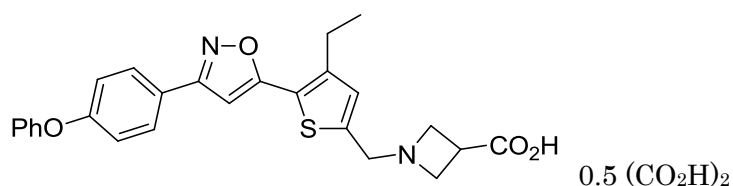
(c) 1-({4-Ethyl-5-[5-(4-phenoxyphenyl)-1,2-oxazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid 1/2 oxalate (**23**)

To a solution of methyl 1-({4-ethyl-5-[5-(4-phenoxyphenyl)-1,2-oxazol-3-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (0.27 g, 0.57 mmol) in ethanol (1.0 mL) was added NaOH (1.0 M in water, 0.85 mL, 0.85 mmol) and the resulting mixture was stirred at room temperature for 40 min. The reaction was quenched with acetic acid (47 μL , 0.85 mmol) and the resulting mixture was concentrated.

To a solution of the residue in ethanol and water (1:1) was added oxalic acid (26 mg, 0.29 mmol) and the resulting mixture was kept at room temperature for 1 day. The white solid precipitated was collected by filtration using a Kiriya funnel and dried *in vacuo* to afford the title compound **23** (0.22 g, 0.17 mmol, 76%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 7.96 (d, 2H, J = 9.0 Hz), 7.46 (dd, 2H, J = 8.2, 8.2 Hz), 7.25 (s, 1H), 7.23 (t, 1H, J = 7.4 Hz), 7.17–7.10 (m, 4H), 6.96 (s, 1H), 3.73 (s, 2H), 3.49–3.36 (m, 2H), 3.29–3.17 (m, 3H), 2.83 (q, 2H, J = 7.4 Hz), 1.20 (t, 3H, J = 7.4 Hz); IR (KBr): 3424, 2967, 1615, 1596, 1245, 755, 693 cm^{-1} ; MS (FAB $^+$) m/z : 461 ((M+H) $^+$).

5-3-6.

1-({4-Ethyl-5-[3-(4-phenoxyphenyl)-1,2-oxazol-5-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid 1/2 oxalate (**27**)



(a) *N*-Hydroxy-1-(4-phenoxyphenyl)methanimine

To a solution of hydroxylammonium chloride (0.77 g, 11 mmol) in water (10 mL) were added sodium hydrogen carbonate (0.93 g, 11 mmol) and a suspension of 4-phenoxybenzaldehyde (2.0 g, 10 mmol) in methanol (30 mL) at 0 $^\circ\text{C}$ and the resulting mixture was stirred at room temperature for 30 min. The reaction was quenched with sat. NH_4Cl and the reaction mixture was extracted with EtOAc. The extract was washed with brine, dried over MgSO_4 , filtered and concentrated. The residue was

purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 90:10 to 60:40) to afford the title compound (2.1 g, 10 mmol, 99%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.11 (s, 1H), 7.54 (d, 2H, *J* = 8.8 Hz), 7.47 (br s, 1H), 7.37 (dd, 2H, *J* = 7.8, 7.3 Hz), 7.15 (dt, 1H, *J* = 7.3, 1.0 Hz), 7.04 (dd, 2H, *J* = 7.8, 1.0 Hz), 6.99 (d, 2H, *J* = 8.8 Hz); IR (KBr): 3360, 1587, 1510, 1489, 1246, 881, 694 cm⁻¹; MS (EI⁺) *m/z* 213 (M⁺).

(b) 5-[5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-3-(4-phenoxyphenyl)-1,2-oxazole (**26**)

To a solution of *N*-hydroxy-1-(4-phenoxyphenyl)methanimine (0.30 g, 1.4 mmol) in chloroform (2.0 mL) were successively added *N*-chlorosuccinimide (0.19 g, 1.4 mmol) and a catalytic amount of pyridine and the resulting mixture was stirred at room temperature for 1 h and at 45 °C for 1 h. To this were successively added *tert*-butyl[(4-ethyl-5-ethynylthiophen-2-yl)methoxy]dimethylsilane (**24**) (0.34 g, 1.2 mmol) and Et₃N (0.17 mL, 1.2 mmol) and the resulting mixture was stirred at 50 °C for 2 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 90:10) to afford the title compound (0.35 g, 0.71 mmol, 59%). ¹H NMR (400 MHz, CDCl₃) δ: 7.81 (d, 2H, *J* = 8.2 Hz), 7.38 (dd, 2H, *J* = 7.4, 7.4 Hz), 7.16 (t, 1H, *J* = 7.4 Hz), 7.10–7.05 (m, 4H), 6.82 (s, 1H), 6.54 (s, 1H), 4.86 (s, 2H), 2.87 (q, 2H, *J* = 7.4 Hz), 1.29 (t, 3H, *J* = 7.4 Hz), 0.95 (s, 9H), 0.13 (s, 6H); IR (liquid film): 2955, 2929, 2856, 1590, 1490, 1243, 839, 779, 693 cm⁻¹; MS (FAB⁺) *m/z* 492 ((M+H)⁺).

(c) Methyl

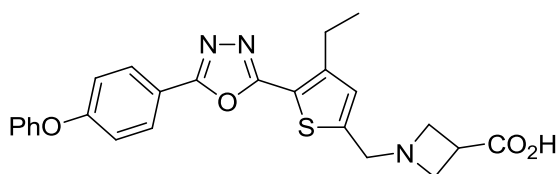
1-({4-ethyl-5-[3-(4-phenoxyphenyl)-1,2-oxazol-5-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate
According to a similar procedure to 5-3-5 (b), the title compound (0.27 g, 0.56 mmol, 84% in 3 steps) was prepared from 5-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-3-(4-phenoxyphenyl)-1,2-oxazole (0.34 g, 0.69 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.83 mL, 0.83 mmol), THF (2.0 mL), thionyl chloride (74 μL, 1.0 mmol), a catalytic amount of DMF, toluene (2.0 mL), methyl 3-azetidinecarboxylate hydrochloride (0.14 g, 0.91 mmol), *N,N*-diisopropylethylamine (0.31 mL, 1.8 mmol) and acetonitrile (2.0 mL). The final purification was conducted by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:1). ¹H NMR (400 MHz, CDCl₃) δ: 7.80 (d, 2H, *J* = 8.6 Hz), 7.38 (dd, 2H, *J* = 8.2, 7.4 Hz), 7.16 (t, 1H, *J* = 7.4 Hz), 7.11–7.05 (m, 4H), 6.82 (s, 1H), 6.52 (s, 1H), 3.78 (s, 2H), 3.72 (s, 3H), 3.67–3.59 (m, 2H), 3.41–3.33 (m, 3H), 2.86 (q, 2H, *J* = 7.4 Hz), 1.29 (t, 3H, *J* = 7.4 Hz); IR (liquid film): 2966, 2845, 1736, 1589, 1523, 1489, 1433, 1240, 1200, 1170, 755, 693 cm⁻¹; MS (FAB⁺) *m/z* 475 ((M+H)⁺).

(d) 1-({4-Ethyl-5-[3-(4-phenoxyphenyl)-1,2-oxazol-5-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid 1/2 oxalate (**27**)

According to a similar procedure to 5-3-5 (c), the title compound (0.21 g, 0.42 mmol, 76%) was prepared from methyl 1-({4-ethyl-5-[3-(4-phenoxyphenyl)-1,2-oxazol-5-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (0.26 g, 0.55 mmol), NaOH (1.0 M in water, 0.82 mL, 0.82 mmol), ethanol (1.0 mL), THF (1.0 mL), acetic acid (45 μ L, 0.82 mmol) and oxalic acid (24 mg, 0.27 mmol). The final purification by recrystallization (ethanol/water 1:1) gave a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ : 7.97 (d, 2H, J = 8.6 Hz), 7.45 (dd, 2H, J = 8.6, 7.8 Hz), 7.21 (t, 1H, J = 7.4 Hz), 7.19 (s, 1H), 7.15–7.09 (m, 4H), 7.00 (s, 1H), 3.75 (s, 2H), 3.49–3.39 (m, 2H), 3.30–3.18 (m, 3H), 2.82 (q, 2H, J = 7.4 Hz), 1.23 (t, 3H, J = 7.4 Hz); IR (KBr): 3423, 2968, 1665, 1640, 1589, 1490, 1432, 1322, 1246, 776, 517 cm^{-1} ; MS (FAB $^+$) m/z : 461 ((M+H) $^+$).

5-3-7.

1-({4-Ethyl-5-[5-(4-phenoxyphenyl)-1,3,4-oxadiazol-2-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (32)



(a) 4-Phenoxybenzohydrazide (29)

To a solution of hydrazine hydrate (11 g, 230 mmol) in methanol (50 mL) was added a solution of 4-phenoxybenzoyl chloride (23 mmol, prepared by the procedure 5-2-29 (a)) in CH_2Cl_2 (10 mL) at 0 $^\circ\text{C}$ and the resulting mixture was stirred at 0 $^\circ\text{C}$ for 2 h. The reaction mixture was concentrated and recrystallized from *n*-hexane and EtOAc to afford the title compound (4.9 g, 21 mmol, 94%). ^1H NMR (400 MHz, CDCl_3) δ : 7.73 (d, 2H, J = 8.6 Hz), 7.46 (br s, 1H), 7.39 (dd, 2H, J = 8.6, 7.4 Hz), 7.19 (t, 1H, J = 7.4 Hz), 7.09–6.98 (m, 4H), 4.09 (br s, 2H).

(b) 5-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3-ethyl-*N*'-(4-phenoxybenzoyl)thiophene-2-carbohydrazide

To a solution of 5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-ethylthiophene-2-carboxylic acid (28) (1.0 g, 3.6 mmol) in CH_2Cl_2 (10 mL) were successively added 4-phenoxybenzohydrazide (0.82 g, 3.6 mmol) and dicyclohexylcarbodiimide (0.74 g, 3.6 mmol), and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was filtered and washed with Et_2O . The filtrate was poured into sat. NaHCO_3 and extracted with Et_2O . The extract was washed with brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 7:3) to afford the title compound (0.85 g, 1.7 mmol, 46%). ^1H NMR (400 MHz, CDCl_3) δ : 9.42 (d, 1H, J = 5.1 Hz), 8.69 (d, 1H, J = 5.1 Hz), 7.84 (d, 2H, J = 8.6 Hz), 7.39 (dd, 2H, J =

7.8, 7.4 Hz), 7.19 (tt, 1H, J = 7.4, 1.2 Hz), 7.05 (dd, 2H, J = 7.8, 1.2 Hz), 6.99 (d, 2H, J = 8.6 Hz), 6.81 (s, 1H), 4.84 (s, 2H), 2.94 (q, 2H, J = 7.4 Hz), 1.25 (t, 3H, J = 7.4 Hz), 0.94 (s, 9H), 0.12 (s, 6H).

(c) 2-[5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-5-(4-phenoxyphenyl)-1,3,4-oxadiazole (**30**)

To a solution of 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl-3-ethyl-*N'*-(4-phenoxybenzoyl)thiophene-2-carbohydrazide (0.85 g, 1.7 mmol) in acetonitrile (10 mL) were successively added Et₃N (0.31 mL, 2.2 mmol) and Burgess reagent (0.60 g, 2.5 mmol), and the resulting mixture was stirred at 80 °C for 4 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 7:3) to afford the title compound (0.78 g, 1.6 mmol, 94%). ¹H NMR (400 MHz, CDCl₃) δ: 8.06 (d, 2H, J = 8.6 Hz), 7.41 (dd, 2H, J = 8.6, 7.4 Hz), 7.21 (tt, 1H, J = 7.4, 1.2 Hz), 7.13-7.08 (m, 4H), 6.87 (s, 1H), 4.89 (s, 2H), 3.08 (q, 2H, J = 7.4 Hz), 1.31 (t, 3H, J = 7.4 Hz), 0.95 (s, 9H), 0.14 (s, 6H); IR (thin film): 2955, 2929, 2856, 1588, 1488, 1245, 839, 757, 693 cm⁻¹; MS (FAB⁺) m/z : 493 ((M+H)⁺).

(d) Methyl

1-({4-ethyl-5-[5-(4-phenoxyphenyl)-1,3,4-oxadiazol-2-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate

According to a similar procedure to 5-3-5 (b), the title compound (0.84 g, 1.8 mmol, 93% in 3 steps) was prepared from 2-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-5-(4-phenoxyphenyl)-1,3,4-oxadiazole (0.95 g, 1.9 mmol), tetrabutylammonium fluoride (1.0 M in THF, 2.3 mL, 2.3 mmol), THF (5.0 mL), and thionyl chloride (0.17 mL, 2.3 mmol), toluene, a catalytic amount of DMF, methyl 3-azetidinecarboxylate hydrochloride (0.44 g, 2.9 mmol), *N,N*-diisopropylethylamine (1.0 mL, 5.8 mmol) and acetonitrile. The final purification was conducted by flash column chromatography (*n*-hexane/EtOAc 1:1). ¹H NMR (400 MHz, CDCl₃) δ: 8.04 (d, 2H, J = 9.0 Hz), 7.41 (dd, 2H, J = 8.2, 8.2 Hz), 7.23-7.18 (m, 1H), 7.12-7.08 (m, 4H), 6.87 (s, 1H), 3.80 (s, 2H), 3.73 (s, 3H), 3.67-3.61 (m, 2H), 3.44-3.33 (m, 3H), 3.07 (q, 2H, J = 7.4 Hz), 1.30 (t, 3H, J = 7.4 Hz); IR (liquid film): 2966, 2846, 1736, 1588, 1488, 1243, 1200, 1168, 741, 693 cm⁻¹; MS (FAB⁺) m/z : 476 ((M+H)⁺).

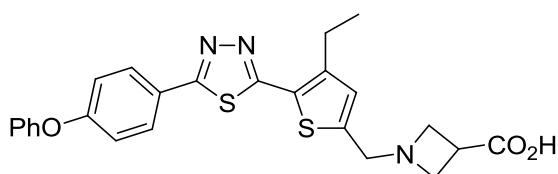
(e) 1-({4-Ethyl-5-[5-(4-phenoxyphenyl)-1,3,4-oxadiazol-2-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**32**)

To a solution of methyl 1-({4-ethyl-5-[5-(4-phenoxyphenyl)-1,3,4-oxadiazol-2-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (0.86 g, 1.8 mmol) in ethanol (3.0 mL) was added NaOH (1.0 M in water, 2.7 mL, 2.7 mmol), and the resulting mixture was stirred at room temperature for 30 min. The reaction was quenched with

acetic acid (0.15 mL, 2.7 mmol) and the resulting mixture was concentrated. The residue was recrystallized from a mixed solvent of acetonitrile and water (4:6) to afford the title compound **32** (0.59 g, 1.3 mmol, 71%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.04 (d, 2H, *J* = 9.0 Hz), 7.48 (dd, 2H, *J* = 7.4, 7.4 Hz), 7.26 (t, 1H, *J* = 7.0 Hz), 7.21–7.14 (m, 4H), 7.06 (s, 1H), 3.78 (s, 2H), 3.53–3.41 (m, 2H), 3.31–3.19 (m, 3H), 2.99 (q, 2H, *J* = 7.4 Hz), 1.24 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3428, 2972, 1612, 1590, 1489, 1244, 743 cm⁻¹; MS (FAB⁺) *m/z*: 462 ((M+H)⁺).

5-3-8.

1-({4-Ethyl-5-[5-(4-phenoxyphenyl)-1,3,4-thiadiazol-2-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**33**)



(a) 2-[5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-5-(4-phenoxyphenyl)-1,3,4-thiadiazole (**31**)

To a solution of 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-3-ethyl-*N'*-(4-phenoxybenzoyl)thiophene-2-carbohydrazide (0.55 g, 1.1 mmol, prepared by the procedure 5-3-7 (b)) in toluene (5.0 mL) were successively added pyridine (0.18 mL, 2.2 mmol) and Lawesson's reagent (0.57 g, 1.4 mmol) and the resulting mixture was stirred at 100 °C for 1 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 9:1) to afford the title compound (0.39 g, 0.77 mmol, 70%). ¹H NMR (400 MHz, CDCl₃) δ: 7.95 (d, 2H, *J* = 9.0 Hz), 7.40 (dd, 2H, *J* = 7.8, 7.4 Hz), 7.22–7.16 (m, 1H), 7.11–7.06 (m, 4H), 6.86 (s, 1H), 4.87 (s, 2H), 2.94 (q, 2H, *J* = 7.4 Hz), 1.31 (t, 3H, *J* = 7.4 Hz), 0.95 (s, 9H), 0.14 (s, 6H); IR (KBr): 2954, 2927, 2855, 1589, 1489, 1233, 1098, 838, 753, 692 cm⁻¹; MS (FAB⁺) *m/z*: 509 ((M+H)⁺).

(b) Methyl

1-({4-ethyl-5-[5-(4-phenoxyphenyl)-1,3,4-thiadiazol-2-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate

According to a similar procedure to 5-3-5 (b), the title compound was prepared quantitatively in 3 steps from 2-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-5-(4-phenoxyphenyl)-1,3,4-thiadiazole (0.39 g, 0.77 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.92 mL, 0.92 mmol) and THF (3.0 mL), and thionyl chloride (89 µL, 1.2 mmol), toluene and a catalytic amount of DMF, and methyl

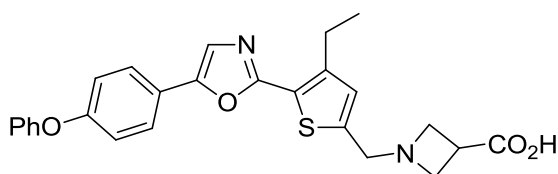
3-azetidinecarboxylate hydrochloride (0.18 g, 1.2 mmol), *N,N*-diisopropylethylamine (0.68 mL, 3.9 mmol) and acetonitrile. The final purification was conducted by flash column chromatography (*n*-hexane/EtOAc 1:1). ¹H NMR (400 MHz, CDCl₃) δ: 7.95 (d, 2H, *J* = 9.0 Hz), 7.40 (dd, 2H, *J* = 8.6, 7.4 Hz), 7.19 (t, 1H, *J* = 7.4 Hz), 7.11–7.06 (m, 4H), 6.85 (s, 1H), 3.78 (s, 2H), 3.72 (s, 3H), 3.68–3.61 (m, 2H), 3.41–3.33 (m, 3H), 2.94 (q, 2H, *J* = 7.4 Hz), 1.31 (t, 3H, *J* = 7.4 Hz); IR (liquid film): 2962, 2845, 1735, 1587, 1485, 1442, 1240, 841, 754 cm⁻¹; MS (FAB⁺) *m/z*: 492 ((M+H)⁺).

(c) 1-({4-Ethyl-5-[5-(4-phenoxyphenyl)-1,3,4-thiadiazol-2-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**33**)

According to a similar procedure to 5-3-7 (e), the title compound (0.26 g, 0.55 mmol, 71%) was prepared from methyl 1-({4-ethyl-5-[5-(4-phenoxyphenyl)-1,3,4-thiadiazol-2-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (0.38 g, 0.77 mmol), NaOH (1.0 M in water, 1.2 mL, 1.2 mmol), ethanol (1.0 mL), THF (1.0 mL) and acetic acid (65 μL, 1.2 mmol). The final purification by recrystallization (MeOH/water 1:1) gave a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.03 (d, 2H, *J* = 8.6 Hz), 7.47 (dd, 2H, *J* = 7.8, 7.4 Hz), 7.25 (t, 1H, *J* = 7.4 Hz), 7.17–7.12 (m, 4H), 7.03 (s, 1H), 3.75 (s, 2H), 3.51–3.41 (m, 2H), 3.31–3.18 (m, 3H), 2.87 (q, 2H, *J* = 7.4 Hz), 1.25 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3435, 2960, 2930, 1729, 1588, 1490, 1249, 1072, 749 cm⁻¹; MS (FAB⁺) *m/z*: 478 ((M+H)⁺).

5-3-9.

1-({4-Ethyl-5-[5-(4-phenoxyphenyl)-1,3-oxazol-2-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**37**)



(a) 2-Bromo-1-(4-phenoxyphenyl)ethanone

To a solution of 1-(4-phenoxyphenyl)ethanone (4.3 g, 19 mmol) in Et₂O (50 mL) were successively added aluminum chloride (0.13 g, 0.95 mmol) and bromine (1.1 mL, 21 mmol) at 0 °C and the resulting mixture was stirred for 3 h. The reaction mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 90:10) to afford the title compound (5.0 g, 16 mmol, 86%). ¹H NMR (400 MHz, CDCl₃) δ: 7.97 (d, 2H, *J* = 8.6 Hz), 7.42 (dd, 2H, *J* = 8.2, 7.4 Hz), 7.23 (t, 1H, *J* = 7.4 Hz), 7.09 (d, 2H, *J* = 8.2 Hz), 7.02 (d, 2H, *J* = 8.6 Hz), 4.41 (s, 2H).

(b) 2-Amino-1-(4-phenoxyphenyl)ethanone hydrochloride (**34a**)

A mixture of 2-bromo-1-(4-phenoxyphenyl)ethanone (2.0 g, 6.6 mmol) and hexamethylenetetramine (1.0 g, 7.2 mmol) in chloroform (20 mL) was stirred at room temperature for 1 h. The white solid precipitated was collected by filtration and washed with chloroform.

To a solution of this intermediate in ethanol (20 mL) was added HCl (4.0 M in 1,4-dioxane, 5.0 mL, 20 mmol) and the resulting mixture was stirred at 80 °C for 2.5 h. After cooling to room temperature, the reaction mixture was filtered with ethanol and the filtrate was concentrated and co-evaporated with toluene. The residue was suspended in isopropyl alcohol and the white powder was collected by filtration and washed with EtOAc to afford the title compound (0.79 g, 46%). ¹H NMR (400 MHz, CD₃OD) δ: 8.04 (d, 2H, *J* = 9.0 Hz), 7.45 (dd, 2H, *J* = 8.6, 7.4 Hz), 7.26 (t, 1H, *J* = 7.4 Hz), 7.10 (d, 2H, *J* = 8.6 Hz), 7.07 (d, 2H, *J* = 9.0 Hz), 4.55 (s, 2H); IR (KCl): 3136, 3042, 1681, 1589, 1491, 1407, 1254, 1170, 838, 692 cm⁻¹; MS (FAB⁺) *m/z* 228 ((M+H)⁺).

(c) 5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl)-3-ethyl-*N*-[2-oxo-2-(4-phenoxyphenyl)ethyl]thiophene-2-carboxamide

To a solution of 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-3-ethylthiophene-2-carboxylic acid (**28**) (0.66 g, 2.4 mmol) in THF (10 mL) were successively added 2-chloro-4,6-dimethoxy-1,3,5-triazine (0.51 g, 2.9 mmol) and *N*-methylmorpholine (0.79 mL, 7.2 mmol). After stirring at room temperature for 30 min, 2-amino-1-(4-phenoxyphenyl)ethanone hydrochloride (**34a**) (0.70 g, 2.7 mmol) was added and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with water and the reaction mixture was extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (*n*-hexane/EtOAc 70:30) to afford the title compound (0.99 g, 0.19 mmol, 81%). ¹H NMR (400 MHz, CDCl₃) δ: 7.99 (d, 2H, *J* = 9.0 Hz), 7.45–7.40 (m, 2H), 7.26–7.21 (m, 1H), 7.12–7.08 (m, 2H), 7.07–7.02 (m, 2H), 6.80 (s, 1H), 4.87 (s, 2H), 4.84 (s, 2H), 2.97 (q, 2H, *J* = 7.4 Hz), 1.28 (t, 3H, *J* = 7.4 Hz), 0.94 (s, 9H), 0.12 (s, 6H); IR (liquid film): 3397, 2955, 2929, 2856, 1645, 1586, 1490, 1361, 1244, 838 cm⁻¹; MS (FAB⁺) *m/z* 510 ((M+H)⁺).

(d) 2-[5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl)-3-ethylthiophen-2-yl]-5-(4-phenoxyphenyl)-1,3-oxazole (**35**)

To a solution of 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-3-ethyl-*N*-[2-oxo-2-(4-phenoxyphenyl)ethyl]thiophene-2-carboxamide (0.30 g, 0.59 mmol) in acetonitrile (2.0 mL) were successively added Et₃N (0.11 mL, 0.77 mmol) and Burgess reagent (0.21 g, 0.88 mmol), and the resulting mixture was stirred at 80 °C for 2.5 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with ether. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 9:1) to afford the title compound (0.19 g, 0.39 mmol, 66%). ¹H NMR (400 MHz, CDCl₃) δ: 7.63 (d, 2H, *J* = 9.0 Hz), 7.39–7.34 (m, 2H), 7.32 (s, 1H), 7.17–7.12 (m, 1H), 7.09–7.03 (m, 4H), 6.82 (s, 1H), 4.86 (s, 2H), 3.06 (q, 2H,

$J = 7.4$ Hz), 1.31 (t, 3H, $J = 7.4$ Hz), 0.95 (s, 9H), 0.13 (s, 6H); IR (liquid film): 2929, 2856, 1587, 1489, 1241, 1080, 837 cm^{-1} ; MS (FAB⁺) m/z 492 ((M+H)⁺).

(e) Methyl

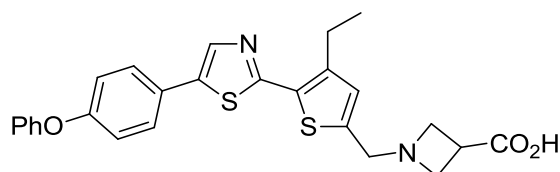
1-({4-ethyl-5-[5-(4-phenoxyphenyl)-1,3-oxazol-2-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate
According to a similar procedure to 5-3-5 (b), the title compound (0.24 g, 0.52 mmol, 92% in 3 steps) was prepared
2-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-5-(4-phenoxyphenyl)-1,3-oxazole
(0.28 g, 0.56 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.67 mL, 0.67 mmol) and THF (2.0 mL), and thionyl chloride (62 μL , 0.84 mmol), toluene (2.0 mL) and a catalytic amount of DMF, and methyl 3-azetidinecarboxylate hydrochloride (0.13 g, 0.84 mmol), *N,N*-diisopropylethylamine (0.30 mL, 1.7 mmol) and acetonitrile (3.0 mL). The final purification was conducted by flash column chromatography (*n*-hexane/EtOAc 1:1). ¹H NMR (400 MHz, CDCl_3) δ : 7.62 (d, 2H, $J = 9.0$ Hz), 7.40–7.34 (m, 2H), 7.32 (s, 1H), 7.18–7.12 (m, 1H), 7.10–7.04 (m, 4H), 6.81 (s, 1H), 3.77 (s, 2H), 3.72 (s, 3H), 3.67–3.60 (m, 2H), 3.41–3.32 (m, 3H), 3.05 (q, 2H, $J = 7.4$ Hz), 1.31 (t, 3H, $J = 7.4$ Hz); IR (thin film): 2965, 2846, 1736, 1586, 1489, 1241, 755 cm^{-1} ; MS (FAB⁺) m/z 475 ((M+H)⁺).

(f) 1-({4-Ethyl-5-[5-(4-phenoxyphenyl)-1,3-oxazol-2-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (37)

According to a similar procedure to 5-3-7 (e), the title compound (0.15 g, 0.32 mmol, 65%) was prepared from methyl
1-({4-ethyl-5-[5-(4-phenoxyphenyl)-1,3-oxazol-2-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate
(0.24 g, 0.50 mmol), NaOH (1.0 M in water, 0.75 mL, 0.75 mmol), ethanol and acetic acid (41 μL , 0.75 mmol). The final purification by recrystallization (acetonitrile/water 1:1) gave a white solid. ¹H NMR (400 MHz, $\text{DMSO-}d_6$) δ : 7.75 (d, 2H, $J = 8.6$ Hz), 7.71 (s, 1H), 7.43 (dd, 2H, $J = 8.2, 7.8$ Hz), 7.19 (t, 1H, $J = 7.8$ Hz), 7.12 (d, 2H, $J = 8.6$ Hz), 7.08 (d, 2H, $J = 8.2$ Hz), 6.96 (s, 1H), 3.73 (s, 2H), 3.49–3.40 (m, 2H), 3.27–3.18 (m, 3H), 2.99 (q, 2H, $J = 7.4$ Hz), 1.23 (t, 3H, $J = 7.4$ Hz); IR (KBr): 3432, 2975, 1615, 1588, 1491, 1250, 757 cm^{-1} ; MS (FAB⁺) m/z 461 ((M+H)⁺).

5-3-10.

1-({4-Ethyl-5-[5-(4-phenoxyphenyl)-1,3-thiazol-2-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (38a)



(a) 2-[5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-5-(4-phenoxyphenyl)-1,3-thiazole (**36a**)

To a solution of 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl-3-ethyl-*N*-[2-oxo-2-(4-phenoxyphenyl)ethyl]thiophene-2-carboxamide (0.48 g, 0.94 mmol, prepared by the procedure 5.3.9 (c)) in toluene (5.0 mL) were successively added pyridine (0.15 mL, 1.9 mmol) and Lawesson's reagent (0.49 g, 1.2 mmol), and the resulting mixture was stirred at 80 °C for 2 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 9:1) to afford the title compound (0.46 g, 0.91 mmol, 97%). ¹H NMR (400 MHz, CDCl₃) δ: 7.88 (s, 1H), 7.55 (d, 2H, *J* = 9.0 Hz), 7.40–7.35 (m, 2H), 7.14 (tt, 1H, *J* = 7.4, 1.2 Hz), 7.09–7.03 (m, 4H), 6.83 (s, 1H), 4.85 (s, 2H), 2.93 (q, 2H, *J* = 7.4 Hz), 1.32 (t, 3H, *J* = 7.4 Hz), 0.95 (s, 9H), 0.13 (s, 6H); IR (liquid film): 2955, 2929, 2856, 1588, 1489, 1242, 1077, 837 cm⁻¹; MS (FAB⁺) *m/z*: 508 ((M+H)⁺).

(b) Methyl

1-({4-ethyl-5-[5-(4-phenoxyphenyl)-1,3-thiazol-2-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate
According to a similar procedure to 5-3-5 (b), the title compound (0.37 g, 0.76 mmol, 69% in 3 steps) was prepared
2-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-5-(4-phenoxyphenyl)-1,3-thiazole (0.46 g, 1.1 mmol), tetrabutylammonium fluoride (1.0 M in THF, 1.3 mL, 1.3 mmol) and THF, and thionyl chloride (0.12 mL, 1.7 mmol), toluene (5.0 mL) and a catalytic amount of DMF, and methyl 3-azetidinecarboxylate hydrochloride (0.26 g, 1.7 mmol), *N,N*-diisopropylethylamine (0.61 mL, 3.3 mmol) and acetonitrile. The final purification was conducted by flash column chromatography (*n*-hexane/EtOAc 1:1). ¹H NMR (400 MHz, CDCl₃) δ: 7.87 (s, 1H), 7.54 (d, 2H, *J* = 8.6 Hz), 7.36 (dd, 2H, *J* = 8.6, 7.4 Hz), 7.14 (tt, 1H, *J* = 7.4, 1.2 Hz), 7.08–7.02 (m, 4H), 6.81 (s, 1H), 3.75 (s, 2H), 3.71 (s, 3H), 3.66–3.58 (m, 2H), 3.42–3.31 (m, 3H), 2.92 (q, 2H, *J* = 7.4 Hz), 1.32 (t, 3H, *J* = 7.4 Hz); IR (KBr): 2961, 2850, 1734, 1589, 1489, 1246, 754 cm⁻¹; MS (FAB⁺) *m/z*: 491 ((M+H)⁺).

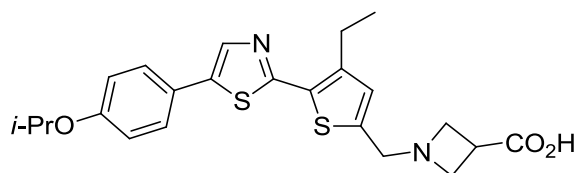
(c) 1-({4-Ethyl-5-[5-(4-phenoxyphenyl)-1,3-thiazol-2-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**38a**)

According to a similar procedure to 5-3-7 (e), the title compound (0.30 g, 0.63 mmol, 83%) was prepared from methyl
1-({4-ethyl-5-[5-(4-phenoxyphenyl)-1,3-thiazol-2-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (0.37 g, 0.75 mmol), NaOH (1.0 M in water, 1.1 mL, 1.1 mmol), ethanol and acetic acid (60 µL, 1.1 mmol). The final purification by recrystallization (acetonitrile/water 1:1) gave a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.18 (s, 1H), 7.72 (d, 2H, *J* = 8.6 Hz), 7.43 (dd, 2H, *J* = 8.6, 7.4 Hz), 7.19 (t, 1H, *J* = 7.4 Hz), 7.10–7.05 (m, 4H), 6.95 (s, 1H), 3.71 (s, 2H), 3.49–3.39 (m, 2H), 3.27–3.19 (m, 3H), 2.88 (q,

2H, $J = 7.4$ Hz), 1.26 (t, 3H, $J = 7.4$ Hz); IR (KBr): 3428, 2963, 1588, 1489, 1249, 843, 749 cm^{-1} ; MS (FAB⁺) m/z 477 ((M+H)⁺).

5-3-11.

1-[(4-Ethyl-5-{5-[4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (38b)



(a) 4-(Propan-2-yloxy)benzonitrile

To a solution of 4-fluorobenzonitrile (1.2 g, 10 mmol) and 2-propanol (1.1 mL, 15 mmol) in THF (20 mL) was added sodium hydride (55wt% dispersion form in mineral oil, 0.65 g, 15 mmol) and the resulting mixture was stirred at 50 °C for 4 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:1) to afford the title compound (0.71 g, 4.4 mmol, 44%) as a crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ : 7.56 (d, 2H, $J = 9.0$ Hz), 6.91 (d, 2H, $J = 9.0$ Hz), 4.61 (sept, 1H, $J = 5.9$ Hz), 1.36 (d, 6H, $J = 5.9$ Hz); IR (thin film): 2980, 2225, 1605, 1506, 1299, 1259, 1178, 1120, 950, 836, 551 cm^{-1} ; MS (EI⁺) m/z 161 (M⁺).

(b) 1-[4-(Propan-2-yloxy)phenyl]ethanone

To a solution of 4-(propan-2-yloxy)benzonitrile (0.38 g, 2.4 mmol) in THF (5.0 mL) was added methyllithium (1.1 M in ether, 4.3 mL, 4.8 mmol) at 0 °C and the resulting mixture was stirred at room temperature for 30 min. The reaction was quenched with HCl (1.0 M in water) and the reaction mixture was extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 90:10) to afford the title compound (0.30 g, 1.7 mmol, 70%). ¹H NMR (400 MHz, CDCl₃) δ : 7.92 (d, 2H, $J = 9.0$ Hz), 6.90 (d, 2H, $J = 9.0$ Hz), 4.65 (sept, 1H, $J = 6.3$ Hz), 2.55 (s, 3H), 1.37 (d, 6H, $J = 6.3$ Hz); IR (ATR): 2978, 1672, 1597, 1505, 1247, 1105, 948, 833, 582 cm^{-1} ; MS (EI⁺) m/z 178 (M⁺).

(c) 2-Bromo-1-[4-(propan-2-yloxy)phenyl]ethanone

To a solution of 1-[4-(propan-2-yloxy)phenyl]ethanone (0.28 g, 1.6 mmol) in THF (4.0 mL) was added phenyltrimethylammonium tribromide (0.59 g, 1.6 mmol) and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with Et₂O. The

extract was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (*n*-hexane/EtOAc 88:12 to 82:18) to afford the title compound (0.25 g, 0.98 mmol, 63%) as a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.95 (d, 2H, *J* = 9.0 Hz), 6.92 (d, 2H, *J* = 9.0 Hz), 4.66 (sept, 1H, *J* = 6.3 Hz), 4.39 (s, 2H), 1.38 (d, 6H, *J* = 6.3 Hz).

(d) 2-Amino-1-[4-(propan-2-yloxy)phenyl]ethanone hydrochloride (**34b**)

To a solution of 2-bromo-1-[4-(propan-2-yloxy)phenyl]ethanone (0.25 g, 0.97 mmol) in acetonitrile (2.0 mL) was added sodium diformylamide (0.11 g, 1.2 mmol) and the resulting mixture was stirred at 70 °C for 1 h. After cooling to room temperature, the reaction mixture was concentrated.

To a solution of the residue in ethanol (3.0 mL) was added HCl (12 M in water, 0.50 mL) and the resulting mixture was stirred at reflux temperature for 30 min. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated, co-evaporated with toluene and dried to afford the crude product of the title compound as a green solid, which was used to the next reaction without further purification.

(e) 5-([*tert*-Butyl(dimethyl)silyl]oxy)methyl-3-ethyl-*N*-(2-oxo-2-[4-(propan-2-yloxy)phenyl]ethyl)thiophene-2-carboxamide

To a solution of 5-([*tert*-butyl(dimethyl)silyl]oxy)methyl-3-ethylthiophene-2-carboxylic acid (**28**) (0.27 g, 0.90 mmol) in CH₂Cl₂ (8.0 mL) were successively added 1-hydroxybenzotriazole (0.13 g, 0.96 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.18 g, 0.96 mmol) and Et₃N (0.33 mL, 2.4 mmol). After stirring at room temperature for 30 min, 2-amino-1-[4-(propan-2-yloxy)phenyl]ethanone hydrochloride (**34b**) (0.20 g, 0.88 mmol) was added and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with water and the resulting biphasic mixture was poured into water and extracted with EtOAc. The extract was washed successively with HCl (0.1 M in water), sat. NaHCO₃ and brine, and dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (*n*-hexane/EtOAc 10:1 to 4:1) to afford the title compound (0.28 g, 0.59 mmol, 74%) as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.97 (d, 2H, *J* = 9.0 Hz), 6.99 (t, 1H, *J* = 4.3 Hz), 6.95 (d, 2H, *J* = 9.0 Hz), 6.80 (s, 1H), 4.86 (d, 2H, *J* = 4.3 Hz), 4.83 (s, 2H), 4.67 (sept, 1H, *J* = 6.3 Hz), 2.97 (q, 2H, *J* = 7.4 Hz), 1.38 (d, 6H, *J* = 6.3 Hz), 1.29 (t, 3H, *J* = 7.4 Hz), 0.94 (s, 9H), 0.12 (s, 6H); IR (KBr): 3414, 2932, 2857, 1672, 1634, 1601, 1515, 1255, 1183, 1071, 838, 777, 575 cm⁻¹; MS (FAB⁺) *m/z*: 476 ((M+H)⁺).

(f) 2-[5-([*tert*-Butyl(dimethyl)silyl]oxy)methyl-3-ethylthiophen-2-yl]-5-[4-(propan-2-yloxy)phenyl]-1,3-thiazole (**36b**)

According to a similar procedure to 5-3-10 (a), the title compound (0.25 g, 0.52 mmol, 88%) was prepared from

5-([*tert*-butyl(dimethyl)silyl]oxy)methyl-3-ethyl-*N*-(2-oxo-2-[4-(propan-2-yloxy)phenyl]ethyl)thiophe

ne-2-carboxamide (0.28 g, 0.59 mmol), pyridine (95 μ L, 1.2 mmol), Lawesson's reagent (0.31 g, 0.77 mmol) and toluene (6.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 30:1) gave a brown solid. ^1H NMR (400 MHz, CDCl_3) δ : 7.84 (s, 1H), 7.49 (d, 2H, J = 9.0 Hz), 6.92 (d, 2H, J = 9.0 Hz), 6.82 (s, 1H), 4.85 (s, 2H), 4.59 (sept, 1H, J = 5.9 Hz), 2.92 (q, 2H, J = 7.4 Hz), 1.36 (d, 6H, J = 5.9 Hz), 1.32 (t, 3H, J = 7.4 Hz), 0.94 (s, 9H), 0.13 (s, 6H); IR (KBr): 2975, 2930, 1605, 1495, 1247, 1088, 838, 780 cm^{-1} ; MS (FAB $^+$) m/z : 474 ((M+H) $^+$).

(g) (4-Ethyl-5-{5-[4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methanol

To a solution of (4-ethyl-5-{5-[4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methanol (0.16 g, 0.45 mmol) in CH_2Cl_2 (8.0 mL) were added triphenylphosphine (0.21 g, 0.81 mmol) and carbon tetrabromide (0.27 g, 0.81 mmol) at 0 $^\circ\text{C}$. After stirring at 0 $^\circ\text{C}$ for 30 min, methyl 3-azetidinecarboxylate hydrochloride (0.12 g, 0.81 mmol) and *N,N*-diisopropylethylamine (0.24 mL, 1.4 mmol) were successively added at 0 $^\circ\text{C}$ and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with sat. NaHCO_3 and brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 2:1 to 3:2) to afford the title compound (0.16 g, 0.37 mmol, 79% in 2 steps) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ : 7.84 (s, 1H), 7.49 (d, 2H, J = 9.0 Hz), 6.92 (s, 1H), 6.92 (d, 2H, J = 9.0 Hz), 4.81 (d, 2H, J = 5.5 Hz), 4.59 (sept, 1H, J = 5.9 Hz), 2.93 (q, 2H, J = 7.4 Hz), 1.94 (t, 1H, J = 5.3 Hz), 1.36 (d, 6H, J = 5.9 Hz), 1.33 (t, 3H, J = 7.4 Hz); IR (KBr): 3370, 2973, 1605, 1492, 1256, 1136, 953, 830 cm^{-1} ; MS (FAB $^+$) m/z : 360 ((M+H) $^+$).

(h) Methyl

1-[(4-ethyl-5-{5-[4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate

To a solution of (4-ethyl-5-{5-[4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methanol (0.16 g, 0.45 mmol) in CH_2Cl_2 (8.0 mL) were added triphenylphosphine (0.21 g, 0.81 mmol) and carbon tetrabromide (0.27 g, 0.81 mmol) at 0 $^\circ\text{C}$. After stirring at 0 $^\circ\text{C}$ for 30 min, methyl 3-azetidinecarboxylate hydrochloride (0.12 g, 0.81 mmol) and *N,N*-diisopropylethylamine (0.24 mL, 1.4 mmol) were successively added at 0 $^\circ\text{C}$ and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with sat. NaHCO_3 and brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 2:1 to 3:2) to afford the title compound (0.16 g, 0.37 mmol, 79% in 2 steps) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ : 7.83 (s, 1H), 7.49 (d, 2H, J = 8.6 Hz), 6.91 (d, 2H, J = 8.6 Hz), 6.81 (s, 1H), 4.58 (sept, 1H, J = 6.3 Hz), 3.75 (s, 2H), 3.71 (s, 3H), 3.67–3.58 (m, 2H), 3.40–3.31 (m, 3H), 2.91 (q, 2H, J = 7.4 Hz), 1.36 (d, 6H, J = 6.3 Hz), 1.31 (t, 3H, J = 7.4 Hz); IR (ATR): 2970, 1733, 1605, 1492, 1245, 1179, 949, 828, 617 cm^{-1} ; MS (FAB $^+$) m/z : 457 ((M+H) $^+$).

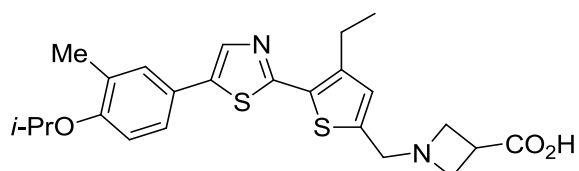
(i) 1-[(4-Ethyl-5-{5-[4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-car

boxylic acid (**38b**)

According to a similar procedure to 5-3-7 (e), the title compound (0.12 g, 0.27 mmol, 77%) was prepared from methyl 1-[(4-ethyl-5-{5-[4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate (0.16 g, 0.35 mmol), NaOH (1.0 M in water, 0.53 mL, 0.53 mmol), methanol (2.0 mL), THF (1.0 mL) and acetic acid (30 μ L, 0.53 mmol). The final purification by recrystallization (methanol/water 1.0 mL : 2.0 mL) gave a light yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ : 8.10 (s, 1H), 7.60 (d, 2H, J = 8.6 Hz), 6.99 (d, 2H, J = 8.6 Hz), 6.94 (s, 1H), 4.67 (sept, 1H, J = 5.9 Hz), 3.71 (s, 2H), 3.50–3.39 (m, 2H), 3.29–3.18 (m, 3H), 2.87 (q, 2H, J = 7.4 Hz), 1.28 (d, 6H, J = 5.9 Hz), 1.25 (t, 3H, J = 7.4 Hz); IR (KBr): 3429, 2970, 1738, 1605, 1494, 1251, 952, 828 cm^{-1} ; MS (FAB $^+$) m/z 443 ((M+H) $^+$).

5-3-12.

1-[(4-Ethyl-5-{5-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**38c**)



(a) 3-Methyl-4-(propan-2-yloxy)benzonitrile

According to a similar procedure to 5-3-11 (a), the title compound (3.1 g, 16 mmol, 86%) was prepared from 4-fluoro-3-methylbenzonitrile (2.5 g, 19 mmol), 2-propanol (2.1 mL, 28 mmol), sodium hydride (55wt% dispersion form in mineral oil, 1.2 g, 28 mmol) and THF (50 mL). The final purification was conducted by flash column chromatography (silica gel, *n*-hexane/EtOAc 9:1). ^1H NMR (400 MHz, CDCl_3) δ : 7.45 (dd, 1H, J = 8.6, 2.3 Hz), 7.40 (d, 1H, J = 2.3 Hz), 6.83 (d, 1H, J = 8.6 Hz), 4.61 (sept, 1H, J = 5.9 Hz), 2.19 (s, 3H), 1.37 (d, 6H, J = 5.9 Hz).

(b) 1-[3-Methyl-4-(propan-2-yloxy)phenyl]ethanone

According to a similar procedure to 5-3-11 (b), the title compound was quantitatively prepared from 3-methyl-4-(propan-2-yloxy)benzonitrile (2.0 g, 10 mmol), methyllithium (1.0 M in Et_2O , 15 mL, 15 mmol) and THF (20 mL). The final purification was conducted by flash column chromatography (silica gel, *n*-hexane/EtOAc). ^1H NMR (400 MHz, CDCl_3) δ : 7.81–7.77 (m, 2H), 6.84 (d, 1H, J = 8.2 Hz), 4.64 (sept, 1H, J = 6.3 Hz), 2.54 (s, 3H), 2.23 (s, 3H), 1.37 (d, 6H, J = 6.3 Hz); IR (ATR): 2978, 1672, 1599, 1497, 1255, 1128, 1109, 954, 816, 595 cm^{-1} ; MS (EI $^+$) m/z 192 (M $^+$).

(c) 2-Bromo-1-[3-methyl-4-(propan-2-yloxy)phenyl]ethanone

According to a similar procedure to 5-3-11 (c), the title compound (1.6 g, 5.8 mmol, 56%) was

prepared from 1-[3-methyl-4-(propan-2-yloxy)phenyl]ethanone (2.0 g, 10 mmol), phenyltrimethylammonium tribromide (3.9 g, 10 mmol) and THF (20 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 1:0 to 4:1) gave a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.82 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.80 (d, 1H, *J* = 2.3 Hz), 6.85 (d, 1H, *J* = 8.6 Hz), 4.66 (sept, 1H, *J* = 5.9 Hz), 4.40 (s, 2H), 2.23 (s, 3H), 1.38 (d, 6H, *J* = 5.9 Hz).

(d) 2-Amino-1-[3-methyl-4-(propan-2-yloxy)phenyl]ethanone hydrochloride (**34c**)

According to a similar procedure to 5-3-11 (d), the title compound (1.2 g, 4.9 mmol, 85%) was prepared from 2-bromo-1-[3-methyl-4-(propan-2-yloxy)phenyl]ethanone (1.6 g, 5.8 mmol), sodium diformylamide (0.66 g, 7.0 mmol), acetonitrile (12 mL), HCl (12 M in water, 3.0 mL, 36 mmol) and ethanol (18 mL). ¹H NMR (400 MHz, CD₃OD) δ: 7.88 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.84 (d, 1H, *J* = 2.3 Hz), 7.06 (d, 1H, *J* = 8.6 Hz), 4.77 (sept, 1H, *J* = 6.3 Hz), 4.52 (s, 2H), 2.23 (s, 3H), 1.37 (d, 6H, *J* = 6.3 Hz); IR (KCl): 3450, 3034, 2979, 1677, 1603, 1259, 1146, 830 cm⁻¹; MS (FAB⁺) *m/z*: 208 ((M+H)⁺).

(e) 5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl)-3-ethyl-*N*-(2-[3-methyl-4-(propan-2-yloxy)phenyl]-2-oxoethyl)thiophene-2-carboxamide

According to a similar procedure to 5-3-11 (e), the title compound (0.32 g, 0.64 mmol, 80%) was prepared from 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-3-ethylthiophene-2-carboxylic acid (**28**) (0.24 g, 0.80 mmol), 1-hydroxybenzotriazole (0.13 g, 0.96 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.18 g, 0.96 mmol), triethylamine (0.33 mL, 2.4 mmol), 2-amino-1-[3-methyl-4-(propan-2-yloxy)phenyl]ethanone hydrochloride (**34c**) (0.21 g, 0.88 mmol) and CH₂Cl₂ (8.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 15:1 to 5:1) gave a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.89–7.82 (m, 2H), 7.01 (t, 1H, *J* = 3.9 Hz), 6.88 (d, 1H, *J* = 8.2 Hz), 6.80 (s, 1H), 4.87–4.83 (m, 4H), 4.67 (sept, 1H, *J* = 5.9 Hz), 2.97 (q, 2H, *J* = 7.4 Hz), 2.24 (s, 3H), 1.39 (d, 6H, *J* = 5.9 Hz), 1.29 (t, 3H, *J* = 7.4 Hz), 0.94 (s, 9H), 0.12 (s, 6H); IR (KBr): 3414, 2931, 1634, 1600, 1514, 1255, 1134, 1070, 904, 537 cm⁻¹; MS (FAB⁺) *m/z*: 490 ((M+H)⁺).

(f) 2-[5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl)-3-ethylthiophen-2-yl]-5-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazole (**36c**)

According to a similar procedure to 5-3-10 (a), the title compound (0.28 g, 0.58 mmol, 91%) was prepared from 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-3-ethyl-*N*-(2-[3-methyl-4-(propan-2-yloxy)phenyl]-2-oxoethyl)thiophene-2-carboxamide (0.31 g, 0.64 mmol), pyridine (0.10 mL, 1.3 mmol), Lawesson's reagent (0.34 g, 0.83 mmol) and toluene (7.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 30:1) gave a brown oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.83 (s, 1H), 7.38–7.33 (m, 2H), 6.85 (d, 1H, *J* = 9.0 Hz), 6.82 (s, 1H), 4.84 (s, 2H), 4.56 (sept, 1H, *J* = 5.9 Hz), 2.92 (q, 2H, *J* = 7.4 Hz), 2.25 (s, 3H), 1.36 (d, 6H, *J* = 5.9 Hz), 1.32 (t, 3H, *J* = 7.4 Hz), 0.95 (s, 9H), 0.14 (s, 6H); IR (KBr): 2961,

2929, 1605, 1493, 1250, 1089, 852, 838, 781 cm⁻¹; MS (FAB⁺) *m/z*: 488 ((M+H)⁺).

(g) (4-Ethyl-5-{5-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methanol

According to a similar procedure to 5-3-11 (g), the title compound (0.17 g, 0.46 mmol, 81%) was prepared from

2-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-5-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazole (0.28 g, 0.57 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.68 mL, 0.68 mmol) and THF (6.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 5:1 to 2:1) gave a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.83 (s, 1H), 7.38–7.34 (m, 2H), 6.92 (s, 1H), 6.85 (d, 1H, *J* = 9.0 Hz), 4.81 (d, 2H, *J* = 5.5 Hz), 4.56 (sept, 1H, *J* = 6.3 Hz), 2.94 (q, 2H, *J* = 7.4 Hz), 2.25 (s, 3H), 1.91 (t, 1H, *J* = 5.5 Hz), 1.36 (d, 6H, *J* = 6.3 Hz), 1.33 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3349, 2970, 2929, 1606, 1495, 1282, 1252, 1138, 955, 836 cm⁻¹; MS (FAB⁺) *m/z*: 374 ((M+H)⁺).

(h) Methyl

1-[(4-ethyl-5-{5-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate

According to a similar procedure to 5-3-11 (h), the title compound (0.17 g, 0.36 mmol, 78% in 2 steps) was prepared from

(4-ethyl-5-{5-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methanol (0.17 g, 0.46 mmol), triphenylphosphine (0.22 g, 0.83 mmol), carbon tetrabromide (0.28 g, 0.83 mmol), CH₂Cl₂ (8.0 mL), methyl 3-azetidinecarboxylate hydrochloride (0.11 g, 0.69 mmol), *N,N*-diisopropylethylamine (0.24 mL, 1.4 mmol). The final purification by flash column chromatography (*n*-hexane/EtOAc 2:1 to 3:2) gave an orange oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.82 (s, 1H), 7.38–7.33 (m, 2H), 6.85 (d, 1H, *J* = 9.0 Hz), 6.81 (s, 1H), 4.56 (sept, 1H, *J* = 6.3 Hz), 3.75 (s, 2H), 3.72 (s, 3H), 3.65–3.59 (m, 2H), 3.40–3.33 (m, 3H), 2.92 (q, 2H, *J* = 7.4 Hz), 2.24 (s, 3H), 1.36 (d, 6H, *J* = 6.3 Hz), 1.32 (t, 3H, *J* = 7.4 Hz); IR (KBr): 2971, 1733, 1491, 1248, 1130, 952, 809 cm⁻¹; MS (FAB⁺) *m/z*: 471 ((M+H)⁺).

(i) 1-[(4-Ethyl-5-{5-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**38c**)

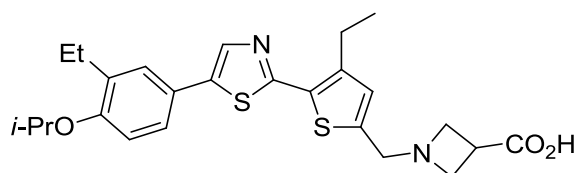
According to a similar procedure to 5-3-7 (e), the title compound (0.12 g, 0.27 mmol, 77%) was prepared from methyl

1-[(4-ethyl-5-{5-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate (0.17 g, 0.35 mmol), NaOH (1.0 M in water, 0.53 mL, 0.53 mmol), methanol (2.0 mL), THF (1.0 mL) and acetic acid (0.12 mL, 2.1 mmol). The final purification by recrystallization (methanol/water 1.0 mL / 2.0 mL) gave a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.08 (s, 1H), 7.54–7.49 (m, 2H), 7.02 (d, 1H, *J* = 8.2 Hz), 6.94 (s, 1H), 4.64 (sept, 1H, *J* = 5.9 Hz), 3.70 (s, 2H), 3.53–3.37 (m, 2H), 3.30–3.17 (m, 3H), 2.87 (q, 2H, *J* = 7.4 Hz), 2.09 (s, 3H), 1.29 (d, 6H, *J* = 5.9 Hz), 1.26 (t,

3H, $J = 7.4$ Hz); ^{13}C NMR (125 MHz, DMSO- d_6) δ : 174.1, 157.6, 155.8, 142.7, 142.5, 138.0, 137.3, 129.6, 128.5, 128.0, 127.6, 125.0, 122.4, 113.4, 69.7, 56.9, 56.2, 33.3, 22.7, 21.9, 16.0, 14.1; IR (KBr): 3421, 2972, 1637, 1606, 1255, 1137, 954, 815, 538 cm^{-1} ; MS (FAB $^+$) m/z : 457 ($(\text{M}+\text{H})^+$); HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_3\text{S}_2$, 457.1620 $[\text{M}+\text{H}]^+$; found 457.1632.

5-3-13.

1-[(4-Ethyl-5-{5-[3-ethyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (38d)



(a) 2-Ethylphenyl propan-2-yl ether

To a solution of 2-ethylphenol (1.2 g, 10 mmol) in DMF (20 mL) were successively added isopropyl iodide (6.0 mL, 60 mmol) and cesium carbonate (6.5 g, 20 mmol) and the resulting mixture was stirred at 60 °C for 5 h. The reaction mixture was poured into water and extracted with Et_2O . The extract was washed with water and brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/ EtOAc 1:0 to 96:4) to afford the title compound (1.5 g, 8.9 mmol, 89%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ : 7.19–7.10 (m, 2H), 6.90–6.83 (m, 2H), 4.54 (sept, 1H, $J = 5.9$ Hz), 2.63 (q, 2H, $J = 7.4$ Hz), 1.34 (d, 6H, $J = 5.9$ Hz), 1.19 (t, 3H, $J = 7.4$ Hz); IR (ATR): 2975, 1489, 1453, 1236, 1127, 956, 747 cm^{-1} ; MS (EI $^+$) m/z : 164 (M^+).

(b) 1-[3-Ethyl-4-(propan-2-yloxy)phenyl]ethanone

To a suspension of aluminum chloride (1.1 g, 8.3 mmol) in 1,2-dichloroethane (25 mL) was slowly added acetyl chloride (0.54 mL, 7.6 mmol) at 0 °C. After stirring at 0 °C for 10 min, a solution of 2-ethylphenyl propan-2-yl ether (1.1 g, 6.9 mmol) in 1,2-dichloroethane was added and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched with water and the mixture was stirred at room temperature for 20 min. The reaction mixture was extracted with CH_2Cl_2 and the extract was washed with water and brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/ EtOAc 95:5 to 70:30) to afford the title compound (0.98 g, 4.7 mmol, 68%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ : 7.82–7.77 (m, 2H), 6.87–6.83 (m, 1H), 4.66 (sept, 1H, $J = 5.9$ Hz), 2.65 (q, 2H, $J = 7.4$ Hz), 2.55 (s, 3H), 1.37 (d, 6H, $J = 5.9$ Hz), 1.20 (t, 3H, $J = 7.4$ Hz); IR (ATR): 2976, 1672, 1597, 1494, 1249, 1132, 1110, 952, 816, 594 cm^{-1} ; MS (EI $^+$) m/z : 206 (M^+).

(c) 2-Bromo-1-[3-ethyl-4-(propan-2-yloxy)phenyl]ethanone

According to a similar procedure to 5-3-11 (c), the crude product of the title compound was prepared from 1-[3-ethyl-4-(propan-2-yloxy)phenyl]ethanone (1.2 g, 6.0 mmol), phenyltrimethylammonium tribromide (2.2 g, 6.0 mmol) and THF (15 mL). This crude product was used to the next step without purification by flash column chromatography.

(d) 2-Amino-1-[3-ethyl-4-(propan-2-yloxy)phenyl]ethanone hydrochloride (**34d**)

According to a similar procedure to 5-3-11 (d), the title compound (1.1 g, 4.2 mmol, 70% in 3 steps) was prepared from the crude product of 2-bromo-1-[3-ethyl-4-(propan-2-yloxy)phenyl]ethanone, sodium diformylamide (1.1 g, 11 mmol), acetonitrile (12 mL), HCl (12 M in water, 1.0 mL, 12 mmol) and ethanol (12 mL). The product was obtained as a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ: 7.88 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.83 (d, 1H, *J* = 2.3 Hz), 7.07 (d, 1H, *J* = 8.6 Hz), 4.79 (sept, 1H, *J* = 5.9 Hz), 4.52 (s, 2H), 2.66 (q, 2H, *J* = 7.4 Hz), 1.38 (d, 6H, *J* = 5.9 Hz), 1.20 (t, 3H, *J* = 7.4 Hz); IR (KCl): 3400, 2976, 2934, 1682, 1601, 1497, 1260, 1148, 1110, 952, 833, 818 cm⁻¹; MS (FAB⁺) *m/z*: 222 ((M+H)⁺).

(e) 5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl-3-ethyl-*N*-{2-[3-ethyl-4-(propan-2-yloxy)phenyl]-2-oxoethyl}thiophene-2-carboxamide

According to a similar procedure to 5-3-11 (e), the title compound (0.29 g, 0.57 mmol, 64%) was prepared from 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl-3-ethylthiophene-2-carboxylic acid (**28**) (0.27 g, 0.90 mmol), 1-hydroxybenzotriazole (0.15 g, 0.99 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.19 g, 0.99 mmol), triethylamine (0.38 mL, 2.7 mmol), 2-amino-1-[3-ethyl-4-(propan-2-yloxy)phenyl]ethanone hydrochloride (**34d**) (0.30 g, 1.2 mmol) and CH₂Cl₂ (6.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 95:5 to 75:25) gave a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.87–7.83 (m, 2H), 7.03 (t, 1H, *J* = 3.9 Hz), 6.89 (d, 1H, *J* = 8.6 Hz), 6.80 (s, 1H), 4.86 (d, 2H, *J* = 3.9 Hz), 4.84 (s, 2H), 4.69 (sept, 1H, *J* = 5.9 Hz), 2.97 (q, 2H, *J* = 7.4 Hz), 2.66 (q, 2H, *J* = 7.4 Hz), 1.39 (d, 6H, *J* = 5.9 Hz), 1.29 (t, 3H, *J* = 7.4 Hz), 1.21 (t, 3H, *J* = 7.4 Hz), 0.94 (s, 9H), 0.12 (s, 6H); IR (KBr): 3412, 2960, 2931, 1638, 1598, 1515, 1255, 1138, 1076, 849, 770 cm⁻¹; MS (FAB⁺) *m/z*: 504 ((M+H)⁺).

(f) 2-[5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl-3-ethylthiophen-2-yl]-5-[3-ethyl-4-(propan-2-yloxy)phenyl]-1,3-thiazole (**36d**)

According to a similar procedure to 5-3-10 (a), the title compound (0.22 g, 0.44 mmol, 78%) was prepared from 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl-3-ethyl-*N*-{2-[3-ethyl-4-(propan-2-yloxy)phenyl]-2-oxoethyl}thiophene-2-carboxamide (0.29 g, 0.57 mmol), pyridine (92 μL, 1.1 mmol), Lawesson's reagent (0.30 g, 0.74 mmol) and toluene (6.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 97:3) gave a light brown solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.83 (s, 1H), 7.39–7.34 (m, 2H), 6.86 (d, 1H, *J* = 9.0 Hz), 6.82 (s, 1H), 4.85 (s, 2H), 4.59 (sept, 1H, *J* = 5.9 Hz), 2.93 (q, 2H, *J* =

7.4 Hz), 2.66 (q, 2H, J = 7.4 Hz), 1.36 (d, 6H, J = 5.9 Hz), 1.32 (t, 3H, J = 7.4 Hz), 1.23 (t, 3H, J = 7.4 Hz), 0.94 (s, 9H), 0.13 (s, 6H); IR (KBr): 2958, 2928, 2855, 1492, 1251, 1140, 1053, 836 cm^{-1} ; MS (FAB⁺) m/z 502 ((M+H)⁺).

(g) Methyl

1-[(4-ethyl-5-{5-[3-ethyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate

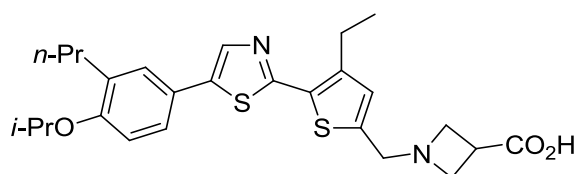
According to a similar procedure to 5-3-5 (b), the title compound (0.16 g, 0.41 mmol, 92% in 3 steps) was prepared from 2-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-5-[3-ethyl-4-(propan-2-yloxy)phenyl]-1,3-thiazole (0.22 g, 0.44 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.53 mL, 0.53 mmol) and THF (4.0 mL), and thionyl chloride (45 μL , 0.61 mmol), toluene (5.0 mL) and a catalytic amount of DMF, and methyl 3-azetidinecarboxylate hydrochloride (93 mg, 0.61 mmol), *N,N*-diisopropylethylamine (0.25 mL, 1.4 mmol) and acetonitrile (4.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 65:35 to 45:55) gave a yellow oil. ¹H NMR (400 MHz, CDCl_3) δ : 7.82 (s, 1H), 7.37–7.33 (m, 2H), 6.85 (d, 1H, J = 9.0 Hz), 6.81 (s, 1H), 4.58 (sept, 1H, J = 5.9 Hz), 3.75 (s, 2H), 3.71 (s, 3H), 3.67–3.58 (m, 2H), 3.40–3.31 (m, 3H), 2.92 (q, 2H, J = 7.4 Hz), 2.66 (q, 2H, J = 7.4 Hz), 1.36 (d, 6H, J = 5.9 Hz), 1.32 (t, 3H, J = 7.4 Hz), 1.22 (t, 3H, J = 7.4 Hz); IR (ATR): 2967, 2932, 1734, 1488, 1245, 1135, 951, 810, 624 cm^{-1} ; MS (FAB⁺) m/z 485 ((M+H)⁺).

(h) 1-[(4-Ethyl-5-{5-[3-ethyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**38d**)

According to a similar procedure to 5-3-7 (e), the title compound (0.14 g, 0.31 mmol, 89%) was prepared from methyl 1-[(4-ethyl-5-{5-[3-ethyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate (0.17 g, 0.35 mmol), NaOH (1.0 M in water, 0.69 mL, 0.69 mmol), methanol (2.0 mL), THF (2.0 mL) and acetic acid (50 μL , 0.86 mmol). The final purification by recrystallization (acetonitrile/water/methanol 1.0 mL/3.0 mL/2.0 mL) gave a yellow solid. ¹H NMR (400 MHz, $\text{CD}_3\text{CO}_2\text{D}$) δ : 8.04 (s, 1H), 7.47–7.42 (m, 2H), 7.29 (s, 1H), 6.96 (d, 1H, J = 9.3 Hz), 4.65 (sept, 1H, J = 6.0 Hz), 4.65 (s, 2H), 4.58–4.48 (m, 2H), 4.45–4.34 (m, 2H), 3.82 (quint, 1H, J = 8.2 Hz), 2.95 (q, 2H, J = 7.5 Hz), 2.67 (q, 2H, J = 7.5 Hz), 1.36 (d, 6H, J = 6.0 Hz), 1.35 (t, 3H, J = 7.5 Hz), 1.22 (t, 3H, J = 7.5 Hz); IR (KBr): 3424, 2970, 2932, 1639, 1605, 1493, 1254, 1141, 953 cm^{-1} ; MS (FAB⁺) m/z 471 ((M+H)⁺).

5-3-14.

1-[(4-Ethyl-5-{5-[4-(propan-2-yloxy)-3-propylphenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**38e**)



(a) 1-(Propan-2-yloxy)-2-propylbenzene

To a solution of 2-propylphenol (2.0 g, 15 mmol) in DMF (30 mL) was slowly added sodium hydride (55wt% dispersion form in mineral oil, 1.3 g, 30 mmol) at 0 °C and the mixture was stirred at room temperature for 10 min. After cooling to 0 °C, isopropyl iodide (6.0 mL, 60 mmol) was added and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with sat. NaHCO_3 at 0 °C and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (*n*-hexane/EtOAc 1:0 to 95:5) to afford the title compound (2.5 g, 14 mmol, 94%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ : 7.13–7.06 (m, 2H), 6.85–6.78 (m, 2H), 4.49 (sept, 1H, J = 6.3 Hz), 2.53 (t, 2H, J = 7.4 Hz), 1.57 (tq, 2H, J = 7.4 Hz), 1.29 (d, 6H, J = 6.3 Hz), 0.90 (t, 3H, J = 7.4 Hz); IR (ATR): 2960, 1600, 1488, 1452, 1236, 1126, 958, 746 cm^{-1} ; MS (EI⁺) m/z : 178 (M^+).

(b) 1-[4-(Propan-2-yloxy)-3-propylphenyl]ethanone

To a suspension of aluminum chloride (1.5 g, 8.4 mmol) in 1,2-dichloroethane (34 mL) was slowly added acetyl chloride (0.66 mL, 9.3 mmol) at 0 °C. After stirring at 0 °C for 10 min, a solution of 1-(propan-2-yloxy)-2-propylbenzene (1.5 g, 8.4 mmol) in 1,2-dichloroethane (7.0 mL) was added and the resulting mixture was stirred at 0 °C for 1.5 h. The reaction was quenched with water and the mixture was stirred at room temperature for 20 min. The reaction mixture was extracted with CH_2Cl_2 and the extract was washed with brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by flash column chromatography (*n*-hexane/EtOAc 1:0 to 7:3) to afford 4-acetyl-2-propylphenyl acetate (0.60 g, 2.7 mmol) as a colorless oil and 1-(4-hydroxy-3-propylphenyl)ethanone (0.50 g, 2.8 mmol) as a white solid.

To a solution of 4-acetyl-2-propylphenyl acetate (0.60 g, 2.7 mmol) in methanol (6.0 mL) was added NaOH (1.0 M in water, 4.1 mL, 4.1 mmol) and the resulting mixture was stirred at room temperature for 30 min. After removal of the organic solvent *in vacuo*, the reaction mixture was acidified with HCl (1.0 M in water) at 0 °C and extracted with CH_2Cl_2 . The extract was dried over Na_2SO_4 , filtered and concentrated to afford 1-(4-hydroxy-3-propylphenyl)ethanone (0.40 g, 2.2 mmol) as a white solid, which was combined with the already-obtained one and used for the next reaction.

To a solution of 1-(4-hydroxy-3-propylphenyl)ethanone (0.90 g, 5.0 mmol) in DMF (15 mL) was slowly added sodium hydride (55wt% dispersion form in mineral oil, 0.33 g, 7.5 mmol) at 0 °C and the resulting mixture was stirred at room temperature for 10 min. After cooling to 0 °C again, isopropyl iodide (1.5 mL, 15 mmol) was added and the resulting mixture was stirred at room temperature for 1.5 h. To this were added sodium hydride (55wt% dispersion form in mineral oil, 0.11 g, 2.5 mmol)

and isopropyl iodide (0.50 mL, 5.0 mmol) and the resulting mixture was stirred at room temperature for 30 min. The reaction was quenched with sat. NaHCO₃ and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (*n*-hexane/EtOAc 1:0 to 80:20) to afford the title compound (1.0 g, 4.7 mmol, 56% in 3 steps) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.80 (d, 1H, *J* = 2.3 Hz), 7.77 (dd, 1H, *J* = 6.8, 2.3 Hz), 6.84 (d, 1H, *J* = 6.8 Hz), 4.65 (sept, 1H, *J* = 6.3 Hz), 2.60 (t, 2H, *J* = 7.4 Hz), 2.55 (s, 3H), 1.61 (tq, 2H, *J* = 7.4, 7.4 Hz), 1.37 (d, 6H, *J* = 6.3 Hz), 0.94 (t, 3H, *J* = 7.4 Hz); IR (ATR): 2962, 1674, 1598, 1260, 1133, 1111, 958, 818, 600 cm⁻¹; MS (EI⁺) *m/z*: 220 (M⁺).

(c) 2-Bromo-1-[4-(propan-2-yloxy)-3-propylphenyl]ethanone

According to a similar procedure to 5-3-11 (c), the title compound (1.1 g, 3.6 mmol, 77%) was prepared from 1-[4-(propan-2-yloxy)-3-propylphenyl]ethanone (1.0 g, 4.7 mmol), phenyltrimethylammonium tribromide (1.8 g, 4.7 mmol) and THF (10 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 1:0 to 83:17) gave a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.83 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.79 (d, 1H, *J* = 2.3 Hz), 6.86 (d, 1H, *J* = 8.6 Hz), 4.67 (sept, 1H, *J* = 5.9 Hz), 4.40 (s, 2H), 2.60 (t, 2H, *J* = 7.4 Hz), 1.61 (tq, 2H, *J* = 7.4, 7.4 Hz), 1.38 (d, 6H, *J* = 5.9 Hz), 0.94 (t, 3H, *J* = 7.4 Hz); IR, (ATR): 2960, 1668, 1595, 1495, 1252, 1105, 953, 816, 618 cm⁻¹; MS (EI⁺) *m/z*: 298 (M⁺).

(d) 2-Amino-1-[4-(propan-2-yloxy)-3-propylphenyl]ethanone hydrochloride (**34e**)

According to a similar procedure to 5-3-11 (d), the title compound was quantitatively prepared from 2-bromo-1-[4-(propan-2-yloxy)-3-propylphenyl]ethanone (1.1 g, 3.6 mmol), sodium diformylamide (0.45 g, 4.7 mmol), acetonitrile (8.0 mL), HCl (12 M in water, 1.8 mL, 22 mmol) and ethanol (11 mL). ¹H NMR (400 MHz, CD₃OD) δ: 7.89 (dd, 1H, *J* = 9.0, 2.3 Hz), 7.82 (d, 1H, *J* = 2.3 Hz), 7.07 (d, 1H, *J* = 9.0 Hz), 4.78 (sept, 1H, *J* = 5.9 Hz), 4.53 (s, 2H), 2.62 (t, 2H, *J* = 7.4 Hz), 1.62 (tq, 2H, *J* = 7.4, 7.4 Hz), 1.37 (d, 6H, *J* = 5.9 Hz), 0.94 (t, 3H, *J* = 7.4 Hz).

(e) 5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl)-3-ethyl-*N*-(2-oxo-2-[4-(propan-2-yloxy)-3-propylphenyl]ethyl}thiophene-2-carboxamide

According to a similar procedure to 5-3-11 (e), the title compound (0.41 g, 0.79 mmol, 79%) was prepared from 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-3-ethylthiophene-2-carboxylic acid (**28**) (0.30 g, 1.0 mmol), 1-hydroxybenzotriazole (0.16 g, 1.2 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.23 g, 1.2 mmol), triethylamine (0.42 mL, 3.0 mmol), 2-amino-1-[4-(propan-2-yloxy)-3-propylphenyl]ethanone hydrochloride (**34e**) (0.30 g, 1.1 mmol) and CH₂Cl₂ (5.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 1:0 to 7:3) gave a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.85 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.81 (d, 1H, *J* = 2.3 Hz), 7.03 (br s, 1H), 6.89 (d, 1H, *J* = 8.6 Hz), 6.80 (s, 1H), 4.88–4.82

(m, 4H), 4.68 (sept, 1H, J = 6.3 Hz), 2.97 (q, 2H, J = 7.4 Hz), 2.61 (t, 2H, J = 7.4 Hz), 1.62 (tq, 2H, J = 7.4, 7.4 Hz), 1.38 (d, 6H, J = 6.3 Hz), 1.29 (t, 3H, J = 7.4 Hz), 0.94 (s, 9H), 0.94 (t, 3H, J = 7.4 Hz), 0.12 (s, 6H); IR (KBr): 3411, 2958, 2931, 1669, 1638, 1598, 1514, 1255, 1140, 1077, 838, 772 cm^{-1} ; MS (FAB⁺) m/z 518 ((M+H)⁺).

(f) 2-[5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-5-[4-(propan-2-yloxy)-3-propylphenyl]-1,3-thiazole (**36e**)

According to a similar procedure to 5-3-10 (a), the title compound (0.34 g, 0.66 mmol, 84%) was prepared from

5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-3-ethyl-*N*-{2-oxo-2-[4-(propan-2-yloxy)-3-propylphenyl]ethyl}thiophene-2-carboxamide (0.41 g, 0.78 mmol), pyridine (0.13 mL, 1.6 mmol), Lawesson's reagent (0.41 g, 1.0 mmol) and toluene (8.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 30:1 to 20:1) gave a brown oil. ¹H NMR (400 MHz, CDCl₃) δ : 7.82 (s, 1H), 7.35 (dd, 1H, J = 8.2, 2.3 Hz), 7.33 (d, 1H, J = 2.3 Hz), 6.85 (d, 1H, J = 8.2 Hz), 6.82 (s, 1H), 4.84 (s, 2H), 4.58 (sept, 1H, J = 5.9 Hz), 2.93 (q, 2H, J = 7.4 Hz), 2.60 (t, 2H, J = 7.4 Hz), 1.64 (tq, 2H, J = 7.4, 7.4 Hz), 1.36 (d, 6H, J = 5.9 Hz), 1.32 (t, 3H, J = 7.4 Hz), 0.97 (t, 3H, J = 7.4 Hz), 0.94 (s, 9H), 0.13 (s, 6H); IR (ATR): 2928, 1491, 1247, 1047, 833, 778 cm^{-1} ; MS (FAB⁺) m/z 516 ((M+H)⁺).

(g) Methyl

1-[(4-ethyl-5-{5-[4-(propan-2-yloxy)-3-propylphenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate

According to a similar procedure to 5-3-5 (b), the title compound (0.25 g, 0.49 mmol, 76% in 3 steps) was prepared from

2-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-3-ethylthiophen-2-yl]-5-[4-(propan-2-yloxy)-3-propylphenyl]-1,3-thiazole (0.34 g, 0.65 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.85 mL, 0.85 mmol), THF (6.0 mL), and thionyl chloride (0.11 mL, 1.5 mmol), toluene (6.0 mL) and CH₂Cl₂ (3.0 mL), a catalytic amount of DMF, methyl 3-azetidinecarboxylate hydrochloride (0.14 g, 0.9 mmol), *N,N*-diisopropylethylamine (0.37 mL, 2.1 mmol) and acetonitrile (6.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 2:1 to 1:1) gave a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ : 7.82 (s, 1H), 7.37–7.32 (m, 2H), 6.85 (d, 1H, J = 8.2 Hz), 6.81 (s, 1H), 4.58 (sept, 1H, J = 5.9 Hz), 3.75 (s, 2H), 3.71 (s, 3H), 3.65–3.59 (m, 2H), 3.40–3.33 (m, 3H), 2.92 (q, 2H, J = 7.4 Hz), 2.60 (t, 2H, J = 7.4 Hz), 1.64 (tq, 2H, J = 7.4, 7.4 Hz), 1.36 (d, 6H, J = 5.9 Hz), 1.32 (t, 3H, J = 7.4 Hz), 0.97 (t, 3H, J = 7.4 Hz); IR (ATR): 2960, 1735, 1488, 1245, 1135, 1111, 953, 810 cm^{-1} ; MS (FAB⁺) m/z 499 ((M+H)⁺).

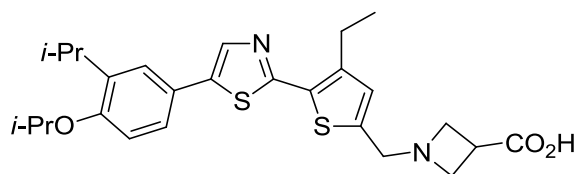
(h) 1-[(4-Ethyl-5-{5-[4-(propan-2-yloxy)-3-propylphenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**38e**)

According to a similar procedure to 5-3-7 (e), the title compound (0.20 g, 0.41 mmol, 83%) was

prepared from methyl 1-[(4-ethyl-5-{5-[4-(propan-2-yloxy)-3-propylphenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate (0.24 g, 0.49 mmol), NaOH (1.0 M in water, 0.73 mL, 0.73 mmol), THF (2.0 mL), methanol (4.0 mL) and acetic acid (0.16 mL, 2.9 mmol). The final purification by recrystallization (acetonitrile/water) gave a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.08 (s, 1H), 7.49–7.44 (m, 2H), 7.02 (d, 1H, *J* = 8.2 Hz), 6.94 (s, 1H), 4.66 (sept, 1H, *J* = 5.9 Hz), 3.70 (s, 2H), 3.50–3.40 (m, 2H), 3.28–3.18 (m, 3H), 2.87 (q, 2H, *J* = 7.4 Hz), 2.55 (t, 2H, *J* = 7.4 Hz), 1.58 (tq, 2H, *J* = 7.4, 7.4 Hz), 1.29 (d, 6H, *J* = 5.9 Hz), 1.26 (t, 3H, *J* = 7.4 Hz), 0.91 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3425, 2969, 1605, 1492, 1251, 1139, 1113, 955, 814, 536 cm⁻¹; MS (FAB⁺) *m/z*: 485 ((M+H)⁺).

5-3-15.

1-[(4-Ethyl-5-{5-[3-(propan-2-yl)-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (38f)



(a) 1-(Propan-2-yl)-2-(propan-2-yloxy)benzene

According to a similar procedure to 5-3-14 (a), the title compound (2.5 g, 14 mmol, 94%) was prepared from 2-isopropylphenol (2.0 g, 15 mmol), isopropyl iodide (6.0 mL, 60 mmol), sodium hydride (55wt% dispersion form in mineral oil, 1.3 g, 30 mmol) and DMF (40 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc = 1:0 to 4:1) gave a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.23–7.19 (m, 1H), 7.15–7.09 (m, 1H), 6.93–6.83 (m, 2H), 4.54 (sept, 1H, *J* = 5.9 Hz), 3.32 (sept, 1H, *J* = 7.0 Hz), 1.34 (d, 6H, *J* = 5.9 Hz), 1.20 (d, 6H, *J* = 7.0 Hz); IR (ATR): 2961, 1600, 1584, 1488, 1233, 1117, 957, 743 cm⁻¹; MS (EI⁺) *m/z*: 178 (M⁺).

(b) 1-[3-(Propan-2-yl)-4-(propan-2-yloxy)phenyl]ethanone

To a suspension of aluminum chloride (1.5 g, 8.4 mmol) in 1,2-dichloroethane (34 mL) was dropwise added acetyl chloride (0.66 mL, 9.3 mmol) at 0 °C. After stirring at 0 °C for 10 min, a solution of 1-(propan-2-yl)-2-(propan-2-yloxy)benzene (1.5 g, 8.4 mmol) in 1,2-dichloroethane (7.0 mL) was added and the resulting mixture was stirred at 0 °C for 1.5 h. The reaction was quenched with water and the mixture was stirred at room temperature for 20 min. The reaction mixture was extracted with CH₂Cl₂ and the extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (*n*-hexane/EtOAc 1:0 to 7:3) to afford 4-acetyl-2-(propan-2-yl)phenyl acetate (0.67 g, 3.1 mmol) as a colorless oil and 1-[4-hydroxy-3-(propan-2-yl)phenyl]ethanone (0.47 g, 2.6 mmol) as a white solid.

To a solution of 4-acetyl-2-(propan-2-yl)phenyl acetate (0.67 g, 3.1 mmol) in methanol (6.0 mL) was added NaOH (1.0 M in water, 4.6 mL, 4.6 mmol) and the resulting mixture was stirred at room temperature for 30 min. After removal of the organic solvent *in vacuo*, the reaction mixture was acidified with HCl (1.0 M in water) at 0 °C and extracted with CH₂Cl₂. The extract was dried over Na₂SO₄, filtered and concentrated to afford 1-[4-hydroxy-3-(propan-2-yl)phenyl]ethanone (0.47 g, 2.7 mmol) as a white solid, which was combined with the already-obtained one and used for the next reaction.

To a solution of 1-[4-hydroxy-3-(propan-2-yl)phenyl]ethanone (0.95 g, 5.3 mmol) in DMF (15 mL) was slowly added sodium hydride (55wt% dispersion form in mineral oil, 0.35 g, 8.0 mmol) at 0 °C and the resulting mixture was stirred at room temperature for 10 min. After cooling to 0 °C again, isopropyl iodide (1.6 mL, 16 mmol) was added and the resulting mixture was stirred at room temperature for 1.5 h. To this were added sodium hydride (55wt% dispersion form in mineral oil, 0.12 g, 2.7 mmol) and isopropyl iodide (0.53 mL, 5.3 mmol) and the resulting mixture was stirred at room temperature for 30 min. The reaction was quenched with sat. NaHCO₃ and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (*n*-hexane/EtOAc 1:0 to 80:20) to afford the title compound (1.2 g, 5.2 mmol, 62% in 3 steps) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.85 (d, 1H, *J* = 2.3 Hz), 7.78 (dd, 1H, *J* = 8.6, 2.3 Hz), 6.85 (d, 1H, *J* = 8.6 Hz), 4.67 (sept, 1H, *J* = 5.9 Hz), 3.30 (sept, 1H, *J* = 7.0 Hz), 2.55 (s, 3H), 1.38 (d, 6H, *J* = 5.9 Hz), 1.23 (d, 6H, *J* = 7.0 Hz); IR (ATR): 2975, 1674, 1599, 1493, 1251, 1113, 957, 817 cm⁻¹; MS (EI⁺) *m/z* 220 (M⁺).

(c) 2-Bromo-1-[3-(propan-2-yl)-4-(propan-2-yloxy)phenyl]ethanone

According to a similar procedure to 5-3-11 (c), the title compound (1.3 g, 4.3 mmol, 83%) was prepared from 1-[3-(propan-2-yl)-4-(propan-2-yloxy)phenyl]ethanone (1.2 g, 5.2 mmol), phenyltrimethylammonium tribromide (2.0 g, 5.2 mmol) and THF (10 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 1:0 to 83:17) gave a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.88 (d, 1H, *J* = 2.3 Hz), 7.82 (dd, 1H, *J* = 8.6, 2.3 Hz), 6.87 (d, 1H, *J* = 8.6 Hz), 4.68 (sept, 1H, *J* = 5.9 Hz), 4.40 (s, 2H), 3.30 (sept, 1H, *J* = 7.0 Hz), 1.39 (d, 6H, *J* = 5.9 Hz), 1.23 (d, 6H, *J* = 7.0 Hz); IR (ATR): 2967, 1682, 1594, 1487, 1251, 1169, 1110, 956, 812, 626 cm⁻¹; MS (EI⁺) *m/z* 298 (M⁺).

(d) 2-Amino-1-[3-(propan-2-yl)-4-(propan-2-yloxy)phenyl]ethanone hydrochloride (**34f**)

According to a similar procedure to 5-3-11 (d), the title compound was quantitatively prepared from 2-bromo-1-[3-(propan-2-yl)-4-(propan-2-yloxy)phenyl]ethanone (1.3 g, 4.3 mmol), sodium diformylamide (0.54 g, 5.7 mmol), acetonitrile (9.0 mL), HCl (12 M in water, 2.2 mL, 26 mmol) and ethanol (13 mL). ¹H NMR (400 MHz, CD₃OD) δ: 7.89–7.86 (m, 2H), 7.07 (d, 1H, *J* = 9.4 Hz), 4.80 (sept, 1H, *J* = 5.9 Hz), 4.54 (s, 2H), 3.32 (sept, 1H, *J* = 7.0 Hz), 1.38 (d, 6H, *J* = 5.9 Hz), 1.24 (d, 6H, *J* = 7.0 Hz).

(e) 5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl-3-ethyl-*N*-{2-oxo-2-[3-(propan-2-yl)-4-(propan-2-yloxy)phenyl]ethyl}thiophene-2-carboxamide

According to a similar procedure to 5-3-11 (e), the title compound (0.37 g, 0.70 mmol, 71%) was prepared from 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl-3-ethylthiophene-2-carboxylic acid (**28**) (0.30 g, 1.0 mmol), 1-hydroxybenzotriazole (0.16 g, 1.2 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.23 g, 1.2 mmol), triethylamine (0.42 mL, 3.0 mmol), 2-amino-1-[3-(propan-2-yl)-4-(propan-2-yloxy)phenyl]ethanone hydrochloride (**34f**) (0.30 g, 1.0 mmol) and CH₂Cl₂ (5.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 1:0 to 6:1) gave a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.89 (d, 1H, *J* = 2.3 Hz), 7.84 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.04 (t, 1H, *J* = 3.9 Hz), 6.90 (d, 1H, *J* = 8.6 Hz), 6.80 (s, 1H), 4.87 (d, 2H, *J* = 3.9 Hz), 4.84 (s, 2H), 4.70 (sept, 1H, *J* = 6.3 Hz), 3.32 (sept, 1H, *J* = 6.6 Hz), 2.97 (q, 2H, *J* = 7.8 Hz), 1.39 (d, 6H, *J* = 6.3 Hz), 1.29 (t, 3H, *J* = 7.8 Hz), 1.23 (d, 6H, *J* = 6.6 Hz), 0.94 (s, 9H), 0.13 (s, 6H); IR (KBr): 3411, 2960, 2933, 1640, 1597, 1514, 1255, 1078, 838, 771 cm⁻¹; MS (FAB⁺) *m/z*: 518 ((M+H)⁺).

(f) 2-[5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl-3-ethylthiophen-2-yl]-5-[3-(propan-2-yl)-4-(propan-2-yloxy)phenyl]-1,3-thiazole (**36f**)

According to a similar procedure to 5-3-10 (a), the title compound (0.32 g, 0.61 mmol, 88%) was prepared from 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl-3-ethyl-*N*-{2-oxo-2-[3-(propan-2-yl)-4-(propan-2-yloxy)phenyl]ethyl}thiophene-2-carboxamide (0.37 g, 0.70 mmol), pyridine (0.11 mL, 1.4 mmol), Lawesson's reagent (0.37 g, 0.91 mmol) and toluene (7.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 30:1 to 20:1) gave a brown solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.83 (s, 1H), 7.38 (d, 1H, *J* = 2.3 Hz), 7.35 (dd, 1H, *J* = 8.2, 2.3 Hz), 6.86 (d, 1H, *J* = 8.2 Hz), 6.82 (s, 1H), 4.85 (s, 2H), 4.60 (sept, 1H, *J* = 5.9 Hz), 3.33 (sept, 1H, *J* = 7.0 Hz), 2.93 (q, 2H, *J* = 7.4 Hz), 1.37 (d, 6H, *J* = 5.9 Hz), 1.33 (t, 3H, *J* = 7.4 Hz), 1.26 (d, 6H, *J* = 7.0 Hz), 0.95 (s, 9H), 0.13 (s, 6H); IR (KBr): 2958, 2930, 1489, 1246, 1052, 835, 782 cm⁻¹; MS (FAB⁺) *m/z*: 516 ((M+H)⁺).

(g) Methyl

1-[(4-ethyl-5-{5-[3-(propan-2-yl)-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate

According to a similar procedure to 5-3-5 (b), the title compound (0.26 g, 0.51 mmol, 86% in 3 steps) was prepared from 2-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl-3-ethylthiophen-2-yl]-5-[3-(propan-2-yl)-4-(propan-2-yloxy)phenyl]-1,3-thiazole (0.32 g, 0.61 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.79 mL, 0.79 mmol), THF (6.0 mL), and thionyl chloride (0.10 mL, 1.4 mmol), toluene (9.0 mL), a catalytic amount of DMF, methyl 3-azetidinecarboxylate hydrochloride (0.12 g, 0.79 mmol), *N,N*-diisopropylethylamine (0.33 mL, 1.9 mmol) and acetonitrile (6.0 mL). The final purification was

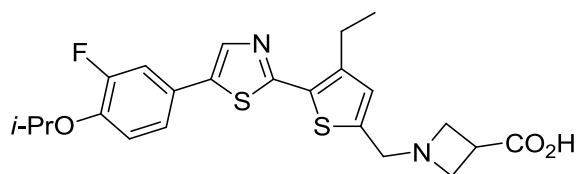
conducted by flash column chromatography (*n*-hexane/EtOAc 2:1 to 1:1). ¹H NMR (400 MHz, CDCl₃) δ: 7.82 (s, 1H), 7.37 (d, 1H, *J* = 2.3 Hz), 7.34 (dd, 1H, *J* = 8.4, 2.3 Hz), 6.86 (d, 1H, *J* = 8.4 Hz), 6.81 (s, 1H), 4.59 (sept, 1H, *J* = 5.9 Hz), 3.75 (s, 2H), 3.72 (s, 3H), 3.66–3.60 (m, 2H), 3.40–3.30 (m, 4H), 2.92 (q, 2H, *J* = 7.4 Hz), 1.37 (d, 6H, *J* = 5.9 Hz), 1.32 (t, 3H, *J* = 7.4 Hz), 1.25 (d, 6H, *J* = 6.6 Hz); IR (ATR): 2963, 1735, 1487, 1244, 1112, 952, 811, 624 cm⁻¹; MS (FAB⁺) *m/z* 499 ((M+H)⁺).

(h) 1-[(4-Ethyl-5-{5-[3-(propan-2-yl)-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**38f**)

According to a similar procedure to 5-3-7 (e), the title compound (0.20 g, 0.41 mmol, 81%) was prepared from methyl 1-[(4-ethyl-5-{5-[3-(propan-2-yl)-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate (0.25 g, 0.51 mmol), NaOH (1.0 M in water, 0.77 mL, 0.77 mmol), THF (2.0 mL), methanol (4.0 mL) and acetic acid (0.18 mL, 3.1 mmol). The final purification by recrystallization (acetonitrile/water) gave a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.10 (s, 1H), 7.47–7.43 (m, 2H), 7.03 (d, 1H, *J* = 8.6 Hz), 6.94 (s, 1H), 4.68 (sept, 1H, *J* = 5.9 Hz), 3.70 (s, 2H), 3.48–3.17 (m, 6H), 2.88 (q, 2H, *J* = 7.4 Hz), 1.30 (d, 6H, *J* = 5.9 Hz), 1.26 (t, 3H, *J* = 7.4 Hz), 1.21 (d, 6H, *J* = 7.0 Hz); IR (KBr): 3424, 2969, 1604, 1491, 1251, 1115, 955, 540 cm⁻¹; MS (FAB⁺) *m/z* 485 ((M+H)⁺).

5-3-16.

1-[(4-Ethyl-5-{5-[3-fluoro-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**38g**)



(a) 3-Fluoro-4-(propan-2-yloxy)benzonitrile

According to a similar procedure to 5-3-11 (a), the title compound was quantitatively prepared from 3,4-difluorobenzonitrile (2.0 g, 14 mmol), 2-propanol (1.5 mL, 20 mmol), sodium hydride (55wt% dispersion form in mineral oil, 0.88 g, 20 mmol) and THF (28 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 1:1) gave a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.39 (ddd, 1H, *J* = 8.2, 2.0, 1.2 Hz), 7.36 (dd, 1H, *J* = 10.6, 2.0 Hz), 7.00 (dd, 1H, *J* = 8.2, 8.2 Hz), 4.66 (sept, 1H, *J* = 5.9 Hz), 1.40 (d, 6H, *J* = 5.9 Hz).

(b) 1-[3-Fluoro-4-(propan-2-yloxy)phenyl]ethanone

According to a similar procedure to 5-3-11 (b), the title compound (1.0 g, 5.3 mmol, 75%) was prepared from 3-fluoro-4-(propan-2-yloxy)benzonitrile (1.3 g, 7.1 mmol), methyllithium (1.1 M in

ether, 13 mL, 14 mmol) and THF (10 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 4:1) gave an orange oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.75–7.67 (m, 2H), 6.99 (dd, 1H, *J* = 8.2, 8.2 Hz), 4.68 (sept, 1H, *J* = 5.9 Hz), 2.55 (s, 3H), 1.41 (d, 6H, *J* = 5.9 Hz); IR (ATR) 2980, 1678, 1607, 1274, 1107, 951 cm⁻¹; MS (EI⁺) *m/z* 196 (M⁺).

(c) 2-Bromo-1-[3-fluoro-4-(propan-2-yloxy)phenyl]ethanone

According to a similar procedure to 5-3-11 (c), the title compound (1.0 g, 3.7 mmol, 70%) was prepared from 1-[3-fluoro-4-(propan-2-yloxy)phenyl]ethanone (1.0 g, 5.3 mmol), phenyltrimethylammonium tribromide (2.0 g, 5.3 mmol) and THF (11 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 1:0 to 80:20) gave a red oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.77–7.70 (m, 2H), 7.01 (dd, 1H, *J* = 8.6, 8.2 Hz), 4.70 (sept, 1H, *J* = 5.9 Hz), 4.36 (s, 2H), 1.42 (d, 6H, *J* = 5.9 Hz); IR (ATR): 2980, 1674, 1606, 1511, 1438, 1277, 1094, 948, 617 cm⁻¹; MS (EI⁺) *m/z* 274 (M⁺).

(d) 2-Amino-1-[3-fluoro-4-(propan-2-yloxy)phenyl]ethanone hydrochloride (**34g**)

According to a similar procedure to 5-3-11 (d), the title compound (0.32 g, 1.3 mmol, 34%) was prepared from 2-bromo-1-[3-fluoro-4-(propan-2-yloxy)phenyl]ethanone (1.0 g, 3.7 mmol), sodium diformylamide (0.42 g, 4.5 mmol), acetonitrile (8.0 mL), HCl (12 M in water, 1.9 mL, 23 mmol) and ethanol (11 mL). ¹H NMR (400 MHz, CD₃OD) δ: 7.84 (ddd, 1H, *J* = 8.6, 2.3, 1.2 Hz), 7.77 (dd, 1H, *J* = 11.7, 2.3 Hz), 7.26 (dd, 1H, *J* = 8.6, 8.2 Hz), 4.81 (sept, 1H, *J* = 5.9 Hz), 4.53 (s, 2H), 1.39 (d, 6H, *J* = 5.9 Hz); IR (KCl): 3135, 3047, 2987, 1684, 1610, 1517, 1274, 1103, 878 cm⁻¹; MS (FAB⁺) *m/z* 212 ((M+H)⁺).

(e) 5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl-3-ethyl-*N*-(2-[3-fluoro-4-(propan-2-yloxy)phenyl]-2-oxoethyl)thiophene-2-carboxamide

According to a similar procedure to 5-3-11 (e), the title compound (0.26 g, 0.52 mmol, 65%) was prepared from 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl-3-ethylthiophene-2-carboxylic acid (**28**) (0.27 g, 0.90 mmol), 1-hydroxybenzotriazole (0.13 g, 0.96 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.18 g, 0.96 mmol), triethylamine (0.33 mL, 2.4 mmol), 2-amino-1-[3-fluoro-4-(propan-2-yloxy)phenyl]ethanone hydrochloride (**34g**) (0.22 g, 0.88 mmol) and CH₂Cl₂ (8.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 6:1 to 4:1) gave a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.78–7.73 (m, 2H), 7.03 (dd, 1H, *J* = 8.6, 8.2 Hz), 6.92 (br s, 1H), 6.80 (s, 1H), 4.85 (s, 2H), 4.84 (s, 2H), 4.71 (sept, 1H, *J* = 5.9 Hz), 2.96 (q, 2H, *J* = 7.4 Hz), 1.42 (d, 6H, *J* = 5.9 Hz), 1.28 (t, 3H, *J* = 7.4 Hz), 0.94 (s, 9H), 0.12 (s, 6H); IR (KBr): 3415, 2934, 1676, 1632, 1514, 1434, 1277, 1133, 1073, 838 cm⁻¹; MS (FAB⁺) *m/z* 494 ((M+H)⁺).

(f) 2-[5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl-3-ethylthiophen-2-yl]-5-[3-fluoro-4-(propan-2-yloxy)

phenyl]-1,3-thiazole (**36g**)

According to a similar procedure to 5-3-10 (a), the title compound (0.23 g, 0.46 mmol, 90%) was prepared from

5-([*tert*-butyl(dimethyl)silyl]oxy)methyl)-3-ethyl-*N*-{2-[3-fluoro-4-(propan-2-yloxy)phenyl]-2-oxoethyl}thiophene-2-carboxamide (0.25 g, 0.51 mmol), pyridine (82 μ L, 1.0 mmol), Lawesson's reagent (0.27 g, 0.66 mmol) and toluene (5.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 20:1 to 15:1) gave a light green oil. ^1H NMR (400 MHz, CDCl_3) δ : 7.84 (s, 1H), 7.34–7.25 (m, 2H), 7.00 (dd, 1H, J = 8.6, 8.2 Hz), 6.83 (s, 1H), 4.85 (s, 2H), 4.58 (sept, 1H, J = 5.9 Hz), 2.92 (q, 2H, J = 7.4 Hz), 1.39 (d, 6H, J = 5.9 Hz), 1.32 (t, 3H, J = 7.4 Hz), 0.94 (s, 9H), 0.13 (s, 6H); IR (ATR): 2928, 2855, 1496, 1273, 1255, 1129, 1074, 832, 774, 620 cm^{-1} ; MS (FAB $^+$) m/z 492 ((M+H) $^+$).

(g) Methyl

1-[(4-ethyl-5-{5-[3-fluoro-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate

According to a similar procedure to 5-3-5 (b), the title compound (0.17 g, 0.35 mmol, 80% in 3 steps) was prepared from

2-[5-([*tert*-butyl(dimethyl)silyl]oxy)methyl)-3-ethylthiophen-2-yl]-5-[3-fluoro-4-(propan-2-yloxy)phenyl]-1,3-thiazole (0.22 g, 0.45 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.54 mL, 0.54 mmol), THF (5.0 mL), and thionyl chloride (39 μ L, 0.52 mmol), toluene (4.0 mL), a catalytic amount of DMF, methyl 3-azetidinecarboxylate hydrochloride (91 mg, 0.60 mmol), *N,N*-diisopropylethylamine (0.24 mL, 1.4 mmol) and acetonitrile (4.0 mL). The final purification was conducted by flash column chromatography (*n*-hexane/EtOAc 3:1 to 1:1). ^1H NMR (400 MHz, CDCl_3) δ : 7.84 (s, 1H), 7.33–7.24 (m, 2H), 7.00 (dd, 1H, J = 8.6, 8.2 Hz), 6.81 (s, 1H), 4.58 (sept, 1H, J = 5.9 Hz), 3.76 (s, 2H), 3.72 (s, 3H), 3.66–3.59 (m, 2H), 3.41–3.31 (m, 3H), 2.91 (q, 2H, J = 7.4 Hz), 1.39 (d, 6H, J = 5.9 Hz), 1.32 (t, 3H, J = 7.4 Hz); IR (ATR): 2972, 2842, 1733, 1494, 1272, 1200, 1174, 1127, 1106, 949, 841, 620 cm^{-1} ; MS (FAB $^+$) m/z 475 ((M+H) $^+$).

(h) 1-[(4-Ethyl-5-{5-[3-fluoro-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**38g**)

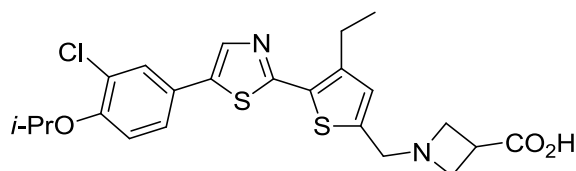
According to a similar procedure to 5-3-7 (e), the title compound (0.14 g, 0.30 mmol, 84%) was prepared from methyl

1-[(4-ethyl-5-{5-[3-fluoro-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate (0.17 g, 0.35 mmol), NaOH (1.0 M in water, 0.53 mL, 0.53 mmol), THF (1.0 mL), methanol (2.0 mL) and acetic acid (90 μ L, 1.6 mmol). The final purification by recrystallization (acetonitrile/water) gave a light yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 8.18 (s, 1H), 7.69–7.63 (m, 1H), 7.45–7.40 (m, 1H), 7.24 (dd, 1H, J = 9.0, 9.0 Hz), 6.95 (s, 1H), 4.70 (sept, 1H, J = 5.9 Hz), 3.71 (s, 2H), 3.53–3.37 (m, 2H), 3.29–3.19 (m, 3H), 2.87 (q, 2H, J = 7.4 Hz), 1.31 (d, 6H, J = 5.9 Hz), 1.25 (t, 3H, J = 7.4 Hz); IR (ATR): 3423, 2975, 1624, 1535, 1496, 1385, 1269, 1130, 953, 811, 494 cm^{-1} ; MS

(FAB⁺) *m/z* 461 ((M+H)⁺).

5-3-17.

1-[(5-{5-[3-Chloro-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}-4-ethylthiophen-2-yl)methyl]azetidine-3-carboxylic acid (38h)



(a) 3-Chloro-4-(propan-2-yloxy)benzonitrile

According to a similar procedure to 5-3-11 (a), the title compound was quantitatively prepared from 3-chloro-4-fluorobenzonitrile (2.0 g, 13 mmol), 2-propanol (1.4 mL, 18 mmol), sodium hydride (55wt% dispersion form in mineral oil, 0.79 g, 18 mmol) and THF (26 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 3:2) gave a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.65 (d, 1H, *J* = 2.3 Hz), 7.51 (dd, 1H, *J* = 8.6, 2.3 Hz), 6.96 (d, 1H, *J* = 8.6 Hz), 4.66 (sept, 1H, *J* = 5.9 Hz), 1.42 (d, 6H, *J* = 5.9 Hz).

(b) 1-[3-Chloro-4-(propan-2-yloxy)phenyl]ethanone

According to a similar procedure to 5-3-11 (b), the title compound (1.2 g, 5.7 mmol, 91%) was prepared from 3-chloro-4-(propan-2-yloxy)benzonitrile (1.2 g, 6.3 mmol), methyllithium (1.1 M in ether, 11 mL, 13 mmol) and THF (10 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 7:3) gave a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.99 (d, 1H, *J* = 2.3 Hz), 7.83 (dd, 1H, *J* = 8.6, 2.3 Hz), 6.96 (d, 1H, *J* = 8.6 Hz), 4.68 (sept, 1H, *J* = 5.9 Hz), 2.55 (s, 3H), 1.42 (d, 6H, *J* = 5.9 Hz); IR (ATR): 2987, 1674, 1591, 1493, 1266, 1112, 952, 823, 598 cm⁻¹; MS (EI⁺) *m/z* 212 (M⁺).

(c) 2-Bromo-1-[3-chloro-4-(propan-2-yloxy)phenyl]ethanone

According to a similar procedure to 5-3-11 (c), the title compound (1.4 g, 4.7 mmol, 81%) was prepared from 1-[3-chloro-4-(propan-2-yloxy)phenyl]ethanone (1.2 g, 5.7 mmol), phenyltrimethylammonium tribromide (2.2 g, 5.7 mmol) and THF (12 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 1:0 to 80:20) gave a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.02 (d, 1H, *J* = 2.3 Hz), 7.87 (dd, 1H, *J* = 8.6, 2.3 Hz), 6.97 (d, 1H, *J* = 8.6 Hz), 4.71 (sept, 1H, *J* = 6.3 Hz), 4.37 (s, 2H), 1.43 (d, 6H, *J* = 6.3 Hz); IR (ATR): 2980, 1673, 1589, 1495, 1269, 1189, 1103, 1055, 1055, 947, 814, 615 cm⁻¹; MS (EI⁺) *m/z* 290 (M⁺).

(d) 2-Amino-1-[3-chloro-4-(propan-2-yloxy)phenyl]ethanone hydrochloride (34h)

According to a similar procedure to 5-3-11 (d), the title compound (0.70 g, 2.7 mmol, 57%) was prepared from 2-bromo-1-[3-chloro-4-(propan-2-yloxy)phenyl]ethanone (1.4 g, 4.7 mmol), sodium diformylamide (0.53 g, 5.6 mmol), acetonitrile (9.0 mL), HCl (12 M in water, 2.4 mL, 29 mmol) and ethanol (15 mL). ¹H NMR (400 MHz, CD₃OD) δ: 8.06 (d, 1H, *J* = 2.3 Hz), 7.96 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.24 (d, 1H, *J* = 8.6 Hz), 4.84 (sept, 1H, *J* = 6.3 Hz), 4.53 (s, 2H), 1.40 (d, 6H, *J* = 6.3 Hz); IR (KCl): 2980, 2931, 1687, 1593, 1498, 1265, 1222, 1102, 950, 807 cm⁻¹; MS (FAB⁺) *m/z*: 228 ((M+H)⁺).

(e) 5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl)-*N*-{2-[3-chloro-4-(propan-2-yloxy)phenyl]-2-oxoethyl}-3-ethylthiophene-2-carboxamide

According to a similar procedure to 5-3-11 (e), the title compound (0.31 g, 0.60 mmol, 75%) was prepared from 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-3-ethylthiophene-2-carboxylic acid (**28**) (0.27 g, 0.90 mmol), 1-hydroxybenzotriazole (0.13 g, 0.96 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.18 g, 0.96 mmol), triethylamine (0.33 mL, 2.4 mmol), 2-amino-1-[3-chloro-4-(propan-2-yloxy)phenyl]ethanone hydrochloride (**34h**) (0.23 g, 0.88 mmol) and CH₂Cl₂ (8.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 6:1 to 4:1) gave a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.06 (d, 1H, *J* = 2.3 Hz), 7.88 (dd, 1H, *J* = 8.6, 2.3 Hz), 6.99 (d, 1H, *J* = 8.6 Hz), 6.92 (br s, 1H), 6.80 (s, 1H), 4.85 (s, 2H), 4.84 (s, 2H), 4.71 (sept, 1H, *J* = 5.9 Hz), 2.96 (q, 2H, *J* = 7.4 Hz), 1.44 (d, 6H, *J* = 5.9 Hz), 1.28 (t, 3H, *J* = 7.4 Hz), 0.94 (s, 9H), 0.12 (s, 6H); IR (KBr): 3414, 2931, 1678, 1632, 1513, 1258, 1211, 1073, 838, 777 cm⁻¹; MS (FAB⁺) *m/z*: 510 ((M+H)⁺).

(f) 2-[5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl)-3-ethylthiophen-2-yl]-5-[3-chloro-4-(propan-2-yloxy)phenyl]-1,3-thiazole (**36h**)

According to a similar procedure to 5-3-10 (a), the title compound (0.25 g, 0.50 mmol, 84%) was prepared from 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-*N*-{2-[3-chloro-4-(propan-2-yloxy)phenyl]-2-oxoethyl}-3-ethylthiophene-2-carboxamide (0.30 g, 0.59 mmol), pyridine (95 μL, 1.2 mmol), Lawesson's reagent (0.31 g, 0.77 mmol) and toluene (6.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 20:1 to 15:1) gave a light green solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.84 (s, 1H), 7.59 (d, 1H, *J* = 2.3 Hz), 7.41 (dd, 1H, *J* = 8.6, 2.3 Hz), 6.97 (d, 1H, *J* = 8.6 Hz), 6.83 (s, 1H), 4.85 (s, 2H), 4.60 (sept, 1H, *J* = 5.9 Hz), 2.92 (q, 2H, *J* = 7.4 Hz), 1.41 (d, 6H, *J* = 5.9 Hz), 1.32 (t, 3H, *J* = 7.4 Hz), 0.94 (s, 9H), 0.13 (s, 6H); IR (KBr): 2929, 1491, 1282, 1256, 1143, 1057, 840, 778 cm⁻¹; MS (FAB⁺) *m/z*: 508 ((M+H)⁺).

(g) Methyl

1-[(5-{5-[3-chloro-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}-4-ethylthiophen-2-yl)methyl]azetidine-3-carboxylate

According to a similar procedure to 5-3-5 (b), the title compound (0.19 g, 0.38 mmol, 79% in 3 steps)

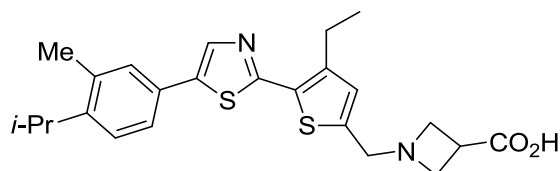
was prepared from 2-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-5-[3-chloro-4-(propan-2-yloxy)phenyl]-1,3-thiazole (0.25 g, 0.49 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.59 mL, 0.59 mmol), THF (5.0 mL), and thionyl chloride (41 μ L, 0.55 mmol), toluene (4.0 mL), a catalytic amount of DMF, methyl 3-azetidinecarboxylate hydrochloride (96 mg, 0.63 mmol), *N,N*-diisopropylethylamine (0.26 mL, 1.5 mmol) and acetonitrile (4.0 mL). The final purification was conducted by flash column chromatography (*n*-hexane/EtOAc 2:1 to 1:1). ^1H NMR (400 MHz, CDCl_3) δ : 7.84 (s, 1H), 7.59 (d, 1H, J = 2.3 Hz), 7.40 (dd, 1H, J = 8.6, 2.3 Hz), 6.97 (d, 1H, J = 8.6 Hz), 6.81 (s, 1H), 4.60 (sept, 1H, J = 5.9 Hz), 3.76 (s, 2H), 3.72 (s, 3H), 3.66–3.59 (m, 2H), 3.41–3.31 (m, 3H), 2.91 (q, 2H, J = 7.4 Hz), 1.41 (d, 6H, J = 5.9 Hz), 1.32 (t, 3H, J = 7.4 Hz); IR (KBr): 2968, 1728, 1493, 1282, 1110, 953 cm^{-1} ; MS (FAB $^+$) m/z 491 ((M+H) $^+$).

(h) 1-[(5-{5-[3-Chloro-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}-4-ethylthiophen-2-yl)methyl]azetidine-3-carboxylic acid (**38h**)

According to a similar procedure to 5-3-7 (e), the title compound (0.15 g, 0.31 mmol, 85%) was prepared from methyl 1-[(5-{5-[3-chloro-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}-4-ethylthiophen-2-yl)methyl]azetidine-3-carboxylate (0.18 g, 0.37 mmol), NaOH (1.0 M in water, 0.56 mL, 0.56 mmol), THF (1.0 mL), methanol (2.0 mL) and acetic acid (64 μ L, 1.1 mmol). The final purification by recrystallization (acetonitrile/water) gave a light yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 8.20 (s, 1H), 7.81 (d, 1H, J = 2.3 Hz), 7.59 (dd, 1H, J = 8.6, 2.3 Hz), 7.24 (d, 1H, J = 8.6 Hz), 6.95 (s, 1H), 4.74 (sept, 1H, J = 5.9 Hz), 3.71 (s, 2H), 3.51–3.39 (m, 2H), 3.29–3.11 (m, 3H), 2.88 (q, 2H, J = 7.4 Hz), 1.32 (d, 6H, J = 5.9 Hz), 1.26 (t, 3H, J = 7.4 Hz); IR (KBr): 3408, 2974, 1600, 1493, 1288, 1109, 950, 814 cm^{-1} ; MS (FAB $^+$) m/z 477 ((M+H) $^+$).

5-3-18.

1-[(4-Ethyl-5-{5-[3-methyl-4-(propan-2-yl)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**38i**)



(a) 1-[3-Methyl-4-(propan-2-yl)phenyl]ethanone

To a mixture of 4-bromo-2-methylbenzoic acid (15 g, 70 mmol), *N,O*-dimethylhydroxylamine hydrochloride (8.2 g, 84 mmol) and triethylamine (23 mL, 170 mmol) in CH_2Cl_2 (250 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (16 g, 84 mmol) and

1-hydroxybenzotriazole (13 g, 84 mmol) at 0 °C and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was poured into water and extracted with CH₂Cl₂. The extract was washed with water and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (*n*-hexane/EtOAc 10:1 to 3:1) to afford 4-bromo-*N*-methoxy-*N*,2-dimethylbenzamide (18 g, 68 mmol, 97%) as a colorless oil.

To a solution of 4-bromo-*N*-methoxy-*N*,2-dimethylbenzamide (5.0 g, 25 mmol) in THF (75 mL) was slowly added methylmagnesium bromide (1.1 M in ether, 25 mL, 26 mmol) at -78 °C and the resulting mixture was stirred at room temperature for 7 h. The reaction was quenched with sat. NH₄Cl and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 10:1 to 3:1) to afford 1-(4-bromo-2-methylphenyl)ethanone (2.4 g, 11 mmol, 45%).

To a solution of methyl(triphenyl)phosphonium iodide (6.0 g, 15 mmol) in THF was added *n*-BuLi (1.6 M in hexane, 9.4 mL, 15 mmol) at -78 °C and the mixture was stirred at 0 °C for 30 min. After cooling to -78 °C again, 1-(4-bromo-2-methylphenyl)ethanone (2.4 g, 11 mmol) in THF was added and the resulting mixture was stirred at room temperature for 6 h. The reaction was quenched with water and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 20:1 to 8:1) to afford the 4-bromo-2-methyl-1-(prop-1-en-2-yl)benzene (1.4 g, 6.5 mmol, 58 %) as a yellow oil.

To a solution of 4-bromo-2-methyl-1-(prop-1-en-2-yl)benzene (1.4 g, 6.5 mmol) in THF (27 mL) was slowly added *n*-BuLi (1.6 M in hexane, 6.0 mL, 9.7 mmol) at -78 °C. After stirring at -78 °C for 2 h, *N*-methoxy-*N*-methylacetamide (1.2 g, 12 mmol) in THF was slowly added and the resulting mixture was stirred at -40 °C. The reaction was quenched with aqueous potassium hydrogen sulfate solution and the reaction mixture was extracted with EtOAc. The extract was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 10:1) to afford 1-[3-methyl-4-(prop-1-en-2-yl)phenyl]ethanone (0.66 g, 3.8 mmol, 58%) as a colorless oil.

To a solution of 1-[3-methyl-4-(prop-1-en-2-yl)phenyl]ethanone (0.66 g, 3.8 mmol) in ethanol (13 mL) was added rhodium(I) tris-(triphenylphosphine) chloride (0.18 g, 0.19 mmol) and the resulting mixture was degassed and saturated with hydrogen gas. After stirring at room temperature for 3 h, the reaction mixture was diluted with *n*-hexane (50 mL), filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 9:1) to afford the title compound (0.60 g, 3.40 mmol, 90%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.77 (dd, 1H, *J* = 8.2, 1.6 Hz), 7.74 (d, 1H, *J* = 1.6 Hz), 7.33 (d, 1H, *J* = 8.2 Hz), 3.18 (sept, 1H, *J* = 6.6 Hz), 2.57 (s, 3H), 2.39 (s, 3H), 1.24 (d, 6H, *J* = 6.6 Hz).

(b) 2-Bromo-1-[3-methyl-4-(propan-2-yl)phenyl]ethanone

According to a similar procedure to 5-3-11 (c), the crude product of the title compound was prepared from 1-[3-methyl-4-(propan-2-yl)phenyl]ethanone (0.60 g, 3.4 mmol), phenyltrimethylammonium tribromide (1.3 g, 3.4 mmol) and THF (12 mL). This crude product was used to the next step without purification by flash column chromatography.

(c) 2-Amino-1-[3-methyl-4-(propan-2-yl)phenyl]ethanone hydrochloride (**34i**)

According to a similar procedure to 5-3-11 (d), the title compound (0.43 g, 1.9 mmol, 55% in 3 steps) was prepared from 2-bromo-1-[3-methyl-4-(propan-2-yl)phenyl]ethanone, sodium diformylamide (0.42 g, 4.4 mmol), acetonitrile (8.0 mL), HCl (12 M in water, 0.70 mL, 2.0 mmol) and ethanol (7.0 mL). The final purification by washing the crude product with *n*-hexane gave a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.78–8.65 (m, 3H), 7.72–7.64 (m, 2H), 7.16 (d, 1H, *J* = 8.2 Hz), 4.83 (q, 2H, *J* = 5.5 Hz), 3.07 (sept, 1H, *J* = 6.6 Hz), 2.20 (s, 3H), 1.14 (d, 6H, *J* = 6.6 Hz); MS (ESI) *m/z* 191 (M⁺).

(d) 5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl-3-ethyl-*N*-(2-[3-methyl-4-(propan-2-yl)phenyl]-2-oxoethyl)thiophene-2-carboxamide

According to a similar procedure to 5-3-11 (e), the title compound (0.38 g, 0.80 mmol, 66%) was prepared from 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl-3-ethylthiophene-2-carboxylic acid (**28**) (0.36 g, 1.2 mmol), 1-hydroxybenzotriazole (0.22 g, 1.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.28 g, 1.5 mmol), triethylamine (0.51 mL, 3.6 mmol), 2-amino-1-[3-methyl-4-(propan-2-yl)phenyl]ethanone hydrochloride (**34i**) (0.30 g, 1.2 mmol) and CH₂Cl₂ (10 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 20:1 to 6:1) gave a pale yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.86–7.77 (m, 2H), 7.38 (d, 1H, *J* = 8.2 Hz), 6.98 (t, 1H, *J* = 3.9 Hz), 6.80 (s, 1H), 4.89 (d, 2H, *J* = 3.9 Hz), 4.84 (s, 2H), 3.20 (sept, 1H, *J* = 6.6 Hz), 2.97 (q, 2H, *J* = 7.4 Hz), 2.41 (s, 3H), 1.29 (t, 3H, *J* = 7.4 Hz), 1.25 (d, 6H, *J* = 6.6 Hz), 0.94 (s, 9H), 0.12 (s, 6H); MS (ESI) *m/z* 473 (M⁺).

(e) 2-[5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl-3-ethylthiophen-2-yl]-5-[3-methyl-4-(propan-2-yl)phenyl]-1,3-thiazole (**36i**)

According to a similar procedure to 5-3-10 (a), the title compound (0.32 g, 0.68 mmol, 86%) was prepared from 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl-3-ethyl-*N*-(2-[3-methyl-4-(propan-2-yl)phenyl]-2-oxoethyl)thiophene-2-carboxamide (0.37 g, 0.79 mmol), pyridine (0.13 mL, 1.6 mmol), Lawesson's reagent (0.42 g, 1.0 mmol) and toluene (6.0 mL). The final purification was conducted by flash column chromatography (*n*-hexane/EtOAc 1:0 to 12:1). ¹H NMR (400 MHz, CDCl₃) δ: 7.90 (s, 1H), 7.41 (dd, 1H, *J* = 8.2, 2.0 Hz), 7.35 (d, 1H, *J* = 2.0 Hz), 7.28 (d, 1H, *J* = 8.2 Hz), 6.83 (s, 1H), 4.85 (s, 2H), 3.16 (sept, 1H, *J* = 6.6 Hz), 2.93 (q, 2H, *J* = 7.4 Hz), 2.39 (s, 3H), 1.33 (t, 3H, *J* = 7.4 Hz), 1.25 (d, 6H, *J* = 6.6 Hz), 0.94 (s, 9H), 0.13 (s, 6H); MS (FAB⁺) *m/z* 472 ((M+H)⁺).

(f) Methyl

1-[(4-ethyl-5-{5-[3-methyl-4-(propan-2-yl)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate

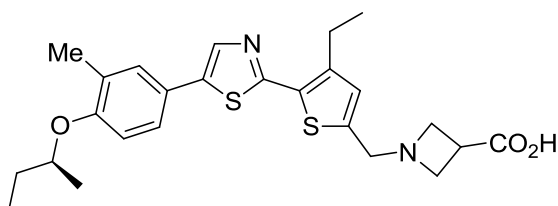
According to a similar procedure to 5-3-5 (b), the title compound (0.30 g, 0.66 mmol, 97% in 3 steps) was prepared from 2-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-5-[3-methyl-4-(propan-2-yl)phenyl]-1,3-thiazole (0.32 g, 0.68 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.81 mL, 0.81 mmol), THF (6.0 mL), and thionyl chloride (0.1 mL, 1.4 mmol), toluene (5.0 mL), a catalytic amount of DMF, methyl 3-azetidinecarboxylate hydrochloride (0.15 g, 1.0 mmol), *N,N*-diisopropylethylamine (0.35 mL, 2.0 mmol) and acetonitrile (5.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 10:1 to 2:3) gave a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.90 (s, 1H), 7.40 (dd, 1H, *J* = 7.8, 2.0 Hz), 7.35 (d, 1H, *J* = 2.0 Hz), 7.27 (d, 1H, *J* = 7.8 Hz), 6.81 (s, 1H), 3.76 (s, 2H), 3.72 (s, 3H), 3.68–3.58 (m, 2H), 3.41–3.31 (m, 3H), 3.15 (sept, 1H, *J* = 6.6 Hz), 2.92 (q, 2H, *J* = 7.4 Hz), 2.39 (s, 3H), 1.32 (t, 3H, *J* = 7.4 Hz), 1.25 (d, 6H, *J* = 6.6 Hz); MS (ESI) *m/z*: 454 (M⁺).

(g) 1-[(4-Ethyl-5-{5-[3-methyl-4-(propan-2-yl)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**38i**)

According to a similar procedure to 5-3-7 (e), the title compound (0.18 g, 0.41 mmol, 64%) was prepared from methyl 1-[(4-ethyl-5-{5-[3-methyl-4-(propan-2-yl)phenyl]-1,3-thiazol-2-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate (0.29 g, 0.64 mmol), NaOH (1.0 M in water, 0.96 mL, 0.96 mmol), methanol (1.5 mL) and acetic acid (55 μL, 0.96 mmol). The final purification by recrystallization (acetonitrile/water) gave a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.16 (s, 1H), 7.53–7.47 (m, 2H), 7.31 (d, 1H, *J* = 7.8 Hz), 6.95 (s, 1H), 3.71 (s, 2H), 3.51–3.38 (m, 2H), 3.31–3.19 (m, 3H), 3.12 (sept, 1H, *J* = 6.6 Hz), 2.88 (q, 2H, *J* = 7.4 Hz), 2.35 (s, 3H), 1.26 (t, 3H, *J* = 7.4 Hz), 1.19 (d, 6H, *J* = 6.6 Hz); IR (KBr): 3410, 2960, 1593, 1490, 1378, 1147, 819, 514 cm⁻¹; MS (ESI) *m/z*: 440 (M⁺).

5-3-19.

1-[[5-(5-{4-[(2*S*)-Butan-2-yloxy]-3-methylphenyl}-1,3-thiazol-2-yl)-4-ethylthiophen-2-yl]methyl]azetidine-3-carboxylic acid (**38j**)



(a) 4-[(2*S*)-Butan-2-yloxy]-3-methylbenzonitrile

According to a similar procedure to 5-3-11 (a), the title compound (0.69 g, 3.7 mmol, 91%) was prepared from 4-fluoro-3-methylbenzonitrile (0.54 g, 4.0 mmol), (*S*)-(+)-2-butanol (0.62 mL, 6.8 mmol), sodium hydride (55wt% dispersion form in mineral oil, 0.30 g, 6.8 mmol) and THF (8.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 7:3) gave a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.45 (dd, 1H, *J* = 8.2, 2.0 Hz), 7.42–7.40 (m, 1H), 6.80 (d, 1H, *J* = 8.2 Hz), 4.38 (tq, 1H, *J* = 5.9, 5.9 Hz), 2.20 (s, 3H), 1.77 (ddq, 1H, *J* = 14.9, 7.4, 5.9 Hz), 1.67 (ddq, 1H, *J* = 14.9, 7.4, 5.9 Hz), 1.32 (d, 3H, *J* = 5.9 Hz), 0.98 (t, 3H, *J* = 7.4 Hz).

(b) 1-{4-[(2*S*)-Butan-2-yloxy]-3-methylphenyl}ethanone

According to a similar procedure to 5-3-11 (b), the title compound (0.72 g, 3.5 mmol, 95%) was prepared from 4-[(2*S*)-butan-2-yloxy]-3-methylbenzonitrile (0.69 g, 3.7 mmol), methyllithium (1.1 M in ether, 6.6 mL, 7.3 mmol) and THF (6.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 7:3) gave a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.84–7.77 (m, 2H), 6.82 (d, 1H, *J* = 9.0 Hz), 4.41 (tq, 1H, *J* = 5.9, 5.9 Hz), 2.54 (s, 3H), 2.24 (s, 3H), 1.78 (ddq, 1H, *J* = 14.5, 7.4, 5.9 Hz), 1.68 (ddq, 1H, *J* = 14.5, 7.4, 5.9 Hz), 1.33 (d, 3H, *J* = 5.9 Hz), 0.99 (t, 3H, *J* = 7.4 Hz).

(c) 2-Bromo-1-{4-[(2*S*)-butan-2-yloxy]-3-methylphenyl}ethanone

According to a similar procedure to 5-3-11 (c), the title compound (0.90 g, 3.1 mmol, 91%) was prepared from 1-{4-[(2*S*)-butan-2-yloxy]-3-methylphenyl}ethanone (0.71 g, 3.5 mmol), phenyltrimethylammonium tribromide (1.3 g, 3.5 mmol) and THF (7.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 1:0 to 83:17) gave a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.82 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.80 (d, 1H, *J* = 2.3 Hz), 6.84 (d, 1H, *J* = 8.6 Hz), 4.43 (tq, 1H, *J* = 5.9, 5.9 Hz), 4.39 (s, 2H), 2.24 (s, 3H), 1.79 (ddq, 1H, *J* = 14.9, 7.4, 5.9 Hz), 1.69 (ddq, 1H, *J* = 14.9, 7.4, 5.9 Hz), 1.34 (d, 3H, *J* = 5.9 Hz), 0.99 (t, 3H, *J* = 7.4 Hz).

(d) 2-Amino-1-{4-[(2*S*)-butan-2-yloxy]-3-methylphenyl}ethanone hydrochloride (**34j**)

According to a similar procedure to 5-3-11 (d), the title compound was quantitatively prepared from 2-bromo-1-{4-[(2*S*)-butan-2-yloxy]-3-methylphenyl}ethanone (0.89 g, 3.1 mmol), sodium diformylamide (0.39 g, 4.1 mmol), acetonitrile (6.0 mL), HCl (12 M in water, 1.6 mL, 19 mmol) and ethanol (10 mL). ¹H NMR (400 MHz, CD₃OD) δ: 7.88 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.86–7.83 (m, 1H), 7.05 (d, 1H, *J* = 8.6 Hz), 4.56 (tq, 1H, *J* = 5.9, 5.9 Hz), 4.52 (s, 2H), 2.24 (s, 3H), 1.78 (ddq, 1H, *J* = 14.9, 7.4, 5.9 Hz), 1.71 (ddq, 1H, *J* = 14.9, 7.4, 5.9 Hz), 1.33 (d, 3H, *J* = 5.9 Hz), 1.00 (t, 3H, *J* = 7.4 Hz).

(e) *N*-(2-{4-[(2*S*)-Butan-2-yloxy]-3-methylphenyl}-2-oxoethyl)-5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-3-ethylthiophene-2-carboxamide

According to a similar procedure to 5-3-11 (e), the title compound (0.26 g, 0.51 mmol, 57%) was prepared from 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-3-ethylthiophene-2-carboxylic acid (**28**)

(0.27 g, 0.90 mmol), 1-hydroxybenzotriazole (0.15 g, 1.1 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.21 g, 1.1 mmol), triethylamine (0.38 mL, 2.7 mmol), 2-amino-1-{4-[(2*S*)-butan-2-yloxy]-3-methylphenyl}ethanone hydrochloride (**34j**) (0.26 g, 0.99 mmol) and CH₂Cl₂ (5.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 10:1 to 8:1) gave a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.86–7.82 (m, 2H), 7.02 (t, 1H, *J* = 3.9 Hz), 6.86 (d, 1H, *J* = 8.6 Hz), 6.80 (s, 1H), 4.85 (d, 2H, *J* = 3.9 Hz), 4.84 (s, 2H), 4.44 (tq, 1H, *J* = 5.9, 5.9 Hz), 2.97 (q, 2H, *J* = 7.4 Hz), 2.25 (s, 3H), 1.79 (ddq, 1H, *J* = 14.9, 7.4, 5.9 Hz), 1.69 (ddq, 1H, *J* = 14.9, 7.4, 5.9 Hz), 1.34 (d, 3H, *J* = 5.9 Hz), 1.29 (t, 3H, *J* = 7.4 Hz), 1.00 (t, 3H, *J* = 7.4 Hz), 0.94 (s, 9H), 0.12 (s, 6H).

(f) 5-{4-[(2*S*)-Butan-2-yloxy]-3-methylphenyl}-2-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-1,3-thiazole (**36j**)

According to a similar procedure to 5-3-10 (a), the title compound (0.21 g, 0.41 mmol, 85%) was prepared from *N*-(2-{4-[(2*S*)-butan-2-yloxy]-3-methylphenyl}-2-oxoethyl)-5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-3-ethylthiophene-2-carboxamide (0.26 g, 0.49 mmol), pyridine (79 µL, 0.98 mmol), Lawesson's reagent (0.26 g, 0.64 mmol) and toluene (5.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 30:1) gave a brown solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.82 (s, 1H), 7.37–7.33 (m, 2H), 6.85–6.81 (m, 2H), 4.85 (s, 2H), 4.34 (tq, 1H, *J* = 5.9, 5.9 Hz), 2.93 (q, 2H, *J* = 7.4 Hz), 2.25 (s, 3H), 1.77 (ddq, 1H, *J* = 14.5, 7.4, 5.9 Hz), 1.67 (ddq, 1H, *J* = 14.5, 7.4, 5.9 Hz), 1.32 (t, 3H, *J* = 7.4 Hz), 1.32 (d, 3H, *J* = 5.9 Hz), 0.99 (t, 3H, *J* = 7.4 Hz), 0.94 (s, 9H), 0.13 (s, 6H).

(g) Methyl

1-{{5-[(5-{4-[(2*S*)-butan-2-yloxy]-3-methylphenyl}-1,3-thiazol-2-yl)-4-ethylthiophen-2-yl]methyl}azetidene-3-carboxylate

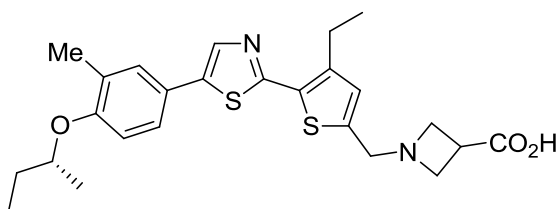
According to a similar procedure to 5-3-5 (b), the title compound (0.16 g, 0.33 mmol, 80% in 3 steps) was prepared from 5-{4-[(2*S*)-butan-2-yloxy]-3-methylphenyl}-2-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-1,3-thiazole (0.21 g, 0.42 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.50 mL, 0.50 mmol), THF (5.0 mL), and thionyl chloride (71 µL, 0.95 mmol), toluene (6.0 mL), a catalytic amount of DMF, methyl 3-azetidene-3-carboxylate hydrochloride (86 mg, 0.57 mmol), *N,N*-diisopropylethylamine (0.20 mL, 1.1 mmol) and acetonitrile (4.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 2:1 to 3:2) gave a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.82 (s, 1H), 7.40–7.33 (m, 2H), 6.83 (d, 1H, *J* = 9.0 Hz), 6.81 (s, 1H), 4.34 (tq, 1H, *J* = 5.9, 5.9 Hz), 3.75 (s, 2H), 3.71 (s, 3H), 3.66–3.60 (m, 2H), 3.40–3.32 (m, 3H), 2.92 (q, 2H, *J* = 7.4 Hz), 2.25 (s, 3H), 1.77 (ddq, 1H, *J* = 14.9, 7.4, 5.9 Hz), 1.66 (ddq, 1H, *J* = 14.9, 7.4, 5.9 Hz), 1.32 (t, 3H, *J* = 7.4 Hz), 1.32 (d, 3H, *J* = 5.9 Hz), 1.00 (t, 3H, *J* = 7.4 Hz).

(h) 1-{[5-(5-{4-[(2*S*)-Butan-2-yloxy]-3-methylphenyl}-1,3-thiazol-2-yl)-4-ethylthiophen-2-yl]methyl}azetidine-3-carboxylic acid (**38j**)

According to a similar procedure to 5-3-7 (e), the title compound (0.12 g, 0.26 mmol, 82%) was prepared from methyl 1-{[5-(5-{4-[(2*S*)-butan-2-yloxy]-3-methylphenyl}-1,3-thiazol-2-yl)-4-ethylthiophen-2-yl]methyl}azetidine-3-carboxylate (0.16 g, 0.32 mmol), NaOH (1.0 M in water, 0.48 mL, 0.48 mmol), THF (1.0 mL), methanol (2.0 mL) and acetic acid (0.14 mL, 2.4 mmol). The final purification by recrystallization (acetonitrile/water) gave a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.07 (s, 1H), 7.49 (d, 1H, *J* = 2.3 Hz), 7.46 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.00 (d, 1H, *J* = 8.6 Hz), 6.94 (s, 1H), 4.44 (tq, 1H, *J* = 5.9, 5.9 Hz), 3.70 (s, 2H), 3.54–3.37 (m, 2H), 3.29–3.17 (m, 3H), 2.87 (q, 2H, *J* = 7.4 Hz), 2.18 (s, 3H), 1.74–1.56 (m, 2H), 1.26 (t, 3H, *J* = 7.4 Hz), 1.25 (d, 3H, *J* = 5.9 Hz), 0.94 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3422, 2969, 1632, 1606, 1496, 1254, 1135, 987, 814, 535 cm⁻¹; MS (FAB⁺) *m/z*: 471 ((M+H)⁺).

5-3-20.

1-{[5-(5-{4-[(2*R*)-Butan-2-yloxy]-3-methylphenyl}-1,3-thiazol-2-yl)-4-ethylthiophen-2-yl]methyl}azetidine-3-carboxylic acid (38k)



(a) 4-[(2*R*)-Butan-2-yloxy]-3-methylbenzonitrile

According to a similar procedure to 5-3-11 (a), the title compound (0.71 g, 3.7 mmol, 93%) was prepared from 4-fluoro-3-methylbenzonitrile (0.54 g, 4.0 mmol), (*R*)-(-)-2-butanol (0.62 mL, 6.8 mmol), sodium hydride (55wt% dispersion form in mineral oil, 0.30 g, 6.8 mmol) and THF (8.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 7:3) gave a colorless oil. ¹H NMR is identical to its enantiomer which was prepared in 5-3-19 (a).

(b) 1-{4-[(2*R*)-Butan-2-yloxy]-3-methylphenyl}ethanone

According to a similar procedure to 5-3-11 (b), the title compound (0.76 g, 3.7 mmol, 99%) was prepared from 4-[(2*R*)-butan-2-yloxy]-3-methylbenzonitrile (0.70 g, 3.7 mmol), methyllithium (1.1 M in ether, 6.8 mL, 7.4 mmol) and THF (6.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 7:3) gave a light yellow oil. ¹H NMR is identical to its enantiomer which was prepared in 5-3-19 (b).

(c) 2-Bromo-1-{4-[(2*R*)-butan-2-yloxy]-3-methylphenyl}ethanone

According to a similar procedure to 5-3-11 (c), the title compound (0.89 g, 3.1 mmol, 85%) was prepared from 1-{4-[(2*R*)-butan-2-yloxy]-3-methylphenyl}ethanone (0.75 g, 3.7 mmol), phenyltrimethylammonium tribromide (1.4 g, 3.7 mmol) and THF (8.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 1:0 to 83:17) gave a light yellow oil. ¹H NMR is identical to its enantiomer which was prepared in 5-3-19 (c).

(d) 2-Amino-1-{4-[(2*R*)-butan-2-yloxy]-3-methylphenyl}ethanone hydrochloride (**34k**)

According to a similar procedure to 5-3-11 (d), the title compound was quantitatively prepared from 2-bromo-1-{4-[(2*R*)-butan-2-yloxy]-3-methylphenyl}ethanone (0.89 g, 3.1 mmol), sodium diformylamide (0.38 g, 4.0 mmol), acetonitrile (6.0 mL), HCl (12 M in water, 1.6 mL, 19 mmol) and ethanol (10 mL). ¹H NMR is identical to its enantiomer which was prepared in 5-3-19 (d).

(e) *N*-(2-{4-[(2*R*)-Butan-2-yloxy]-3-methylphenyl}-2-oxoethyl)-5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-3-ethylthiophene-2-carboxamide

According to a similar procedure to 5-3-11 (e), the title compound (0.27 g, 0.53 mmol, 58%) was prepared from 5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-3-ethylthiophene-2-carboxylic acid (**28**) (0.27 g, 0.90 mmol), 1-hydroxybenzotriazole (0.15 g, 1.1 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.21 g, 1.1 mmol), triethylamine (0.38 mL, 2.7 mmol), 2-amino-1-{4-[(2*R*)-butan-2-yloxy]-3-methylphenyl}ethanone hydrochloride (**34k**) (0.26 g, 0.99 mmol) and CH₂Cl₂ (5.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 10:1 to 8:1) gave a yellow solid. ¹H NMR is identical to its enantiomer which was prepared in 5-3-19 (e).

(f) 5-{4-[(2*R*)-Butan-2-yloxy]-3-methylphenyl}-2-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-3-ethylthiophen-2-yl]-1,3-thiazole (**36k**)

According to a similar procedure to 5-3-10 (a), the title compound (0.22 g, 0.43 mmol, 84%) was prepared from *N*-(2-{4-[(2*R*)-butan-2-yloxy]-3-methylphenyl}-2-oxoethyl)-5-({*tert*-butyl(dimethyl)silyl}oxy)methyl)-3-ethylthiophene-2-carboxamide (0.26 g, 0.51 mmol), pyridine (82 μ L, 1.0 mmol), Lawesson's reagent (0.27 g, 0.66 mmol) and toluene (5.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 30:1) gave a brown solid. ¹H NMR is identical to its enantiomer which was prepared in 5-3-19 (f).

(g) Methyl

1-[[5-(5-{4-[(2*R*)-butan-2-yloxy]-3-methylphenyl}-1,3-thiazol-2-yl)-4-ethylthiophen-2-yl]methyl]azetidine-3-carboxylate

According to a similar procedure to 5-3-5 (b), the title compound (0.14 g, 0.29 mmol, 75% in 3 steps) was prepared from

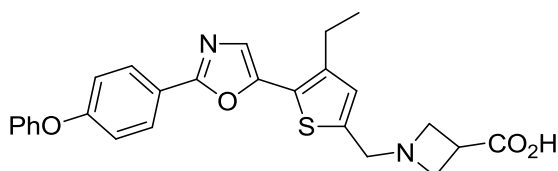
5-{4-[(2*R*)-butan-2-yloxy]-3-methylphenyl}-2-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-1,3-thiazole (0.20 g, 0.39 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.47 mL, 0.47 mmol), THF (4.0 mL), and thionyl chloride (73 μ L, 0.98 mmol), toluene (6.0 mL), a catalytic amount of DMF, methyl 3-azetidinecarboxylate hydrochloride (89 mg, 0.59 mmol), *N,N*-diisopropylethylamine (0.20 mL, 1.2 mmol) and acetonitrile (4.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 2:1 to 3:2) gave a yellow oil. ¹H NMR is identical to its enantiomer which was prepared in 5-3-19 (g).

(h) 1-{{5-[(5-{4-[(2*R*)-Butan-2-yloxy]-3-methylphenyl}-1,3-thiazol-2-yl)-4-ethylthiophen-2-yl]methyl}azetidine-3-carboxylic acid (**38k**)

According to a similar procedure to 5-3-7 (e), the title compound (0.11 g, 0.24 mmol, 83%) was prepared from methyl 1-{{5-[(5-{4-[(2*R*)-butan-2-yloxy]-3-methylphenyl}-1,3-thiazol-2-yl)-4-ethylthiophen-2-yl]methyl}azetidine-3-carboxylate (0.14 g, 0.29 mmol), NaOH (1.0 M in water, 0.44 mL, 0.44 mmol), THF (1.0 mL), methanol (2.0 mL) and acetic acid (0.13 mL, 2.2 mmol). The final purification by recrystallization (acetonitrile/water) gave a light yellow solid. ¹H NMR, IR and MS are identical to its enantiomer which was prepared in 5-3-19 (h).

5-3-21.

1-({4-Ethyl-5-[2-(4-phenoxyphenyl)-1,3-oxazol-5-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**42**)



(a) *N*-{2-[5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-2-oxoethyl}-4-phenoxybenzamide

To a solution of 4-phenoxybenzoic acid (0.21 g, 1.0 mmol) and 1-hydroxybenzotriazole (0.16 g, 1.2 mmol) in CH₂Cl₂ (5.0 mL) were successively added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.23 g, 1.2 mmol), Et₃N (0.42 mL, 3.0 mmol) and 2-amino-1-[3-ethyl-5-(hydroxymethyl)thiophen-2-yl]ethanone hydrochloride (**39**) (0.24 g, 1.0 mmol) and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with brine, dried over MgSO₄, filtered and concentrated.

To the residue in DMF (5.0 mL) were added imidazole (0.20 g, 3.0 mmol) and TBSCl (0.18 g, 1.2 mmol) and the resulting mixture was stirred at room temperature for 2.5 h. The reaction mixture

was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified with flash column chromatography (*n*-hexane/EtOAc 70:30) to afford the title compound (0.39 g, 0.77 mmol, 76%). ¹H NMR (400 MHz, CDCl₃) δ: 7.85 (d, 2H, *J* = 8.6 Hz), 7.41–7.36 (m, 2H), 7.20–7.16 (m, 2H), 7.08–7.05 (m, 2H), 7.03 (d, 2H, *J* = 8.6 Hz), 6.88 (s, 1H), 4.88 (s, 2H), 4.75 (d, 2H, *J* = 4.3 Hz), 3.02 (q, 2H, *J* = 7.4 Hz), 1.25 (t, 3H, *J* = 7.4 Hz), 0.96 (s, 9H), 0.14 (s, 6H); IR (KBr): 3275, 2928, 1677, 1634, 1490, 1241, 1128, 850, 777, 667 cm⁻¹; MS (FAB⁺) *m/z*: 510 ((M+H)⁺).

(b) 5-[5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-2-(4-phenoxyphenyl)-1,3-oxazole (40)

According to a similar procedure to 5-3-9 (d), the title compound (0.25 g, 0.51 mmol, 64%) was prepared from *N*-{2-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-2-oxoethyl}-4-phenoxybenzamide (0.33 g, 0.65 mmol), Et₃N (0.12 mL, 0.84 mmol), Burgess reagent (0.24 g, 1.0 mmol) and acetonitrile (3.0 mL). The final purification was conducted by flash column chromatography (*n*-hexane/EtOAc 97:3 to 90:10). ¹H NMR (400 MHz, CDCl₃) δ: 8.02 (d, 2H, *J* = 9.0 Hz), 7.42–7.36 (m, 2H), 7.20–7.15 (m, 2H), 7.12–7.06 (m, 4H), 6.80 (s, 1H), 4.85 (s, 2H), 2.76 (q, 2H, *J* = 7.4 Hz), 1.28 (t, 3H, *J* = 7.4 Hz), 0.95 (s, 9H), 0.13 (s, 6H); IR (ATR): 2927, 1588, 1486, 1237, 1069, 834, 776 cm⁻¹; MS (FAB⁺) *m/z*: 492 ((M+H)⁺).

(c) Methyl

1-({4-ethyl-5-[2-(4-phenoxyphenyl)-1,3-oxazol-5-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate
According to a similar procedure to 5-3-5 (b), the title compound (0.22 g, 0.47 mmol, 93% in 3 steps) was prepared from 5-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-2-(4-phenoxyphenyl)-1,3-oxazole (0.25 g, 0.51 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.61 mL, 0.61 mmol) and THF (2.0 mL), and thionyl chloride (57 μL, 0.77 mmol), toluene (3.0 mL) and a catalytic amount of DMF, and methyl 3-azetidinecarboxylate hydrochloride (0.12 g, 0.77 mmol), *N,N*-diisopropylethylamine (0.26 mL, 1.5 mmol) and acetonitrile. The final purification was conducted by flash column chromatography (*n*-hexane/EtOAc 85:15 to 65:35). ¹H NMR (400 MHz, CDCl₃) δ: 8.01 (d, 2H, *J* = 8.6 Hz), 7.43–7.37 (m, 2H), 7.21–7.15 (m, 2H), 7.12–7.05 (m, 4H), 6.79 (s, 1H), 3.77 (s, 2H), 3.72 (s, 3H), 3.67–3.58 (m, 2H), 3.41–3.32 (m, 3H), 2.75 (q, 2H, *J* = 7.4 Hz), 1.28 (t, 3H, *J* = 7.4 Hz); IR (ATR): 2963, 2842, 1733, 1587, 1485, 1234, 1165, 841, 691, 490 cm⁻¹; MS (FAB⁺) *m/z*: 475 ((M+H)⁺).

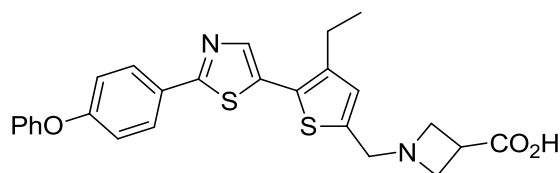
(d) 1-({4-Ethyl-5-[2-(4-phenoxyphenyl)-1,3-oxazol-5-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (42)

According to a similar procedure to 5-3-7 (e), the title compound (0.13 g, 0.28 mmol, 60%) was prepared from methyl

1-({4-ethyl-5-[2-(4-phenoxyphenyl)-1,3-oxazol-5-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (0.22 g, 0.46 mmol), NaOH (1.0 M in water, 0.70 mL, 0.70 mmol), ethanol (1.0 mL) and acetic acid (38 μ L, 0.70 mmol). The final purification by recrystallization (acetonitrile/water 1:1) gave a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ : 7.99 (d, 2H, J = 8.2 Hz), 7.46 (dd, 2H, J = 7.4, 7.0 Hz), 7.41 (s, 1H), 7.23 (t, 1H, J = 7.4 Hz), 7.19–7.11 (m, 4H), 6.92 (s, 1H), 3.70 (s, 2H), 3.47–3.36 (m, 2H), 3.26–3.11 (m, 3H), 2.72 (q, 2H, J = 7.4 Hz), 1.22 (t, 3H, J = 7.4 Hz); IR (KBr): 3431, 2966, 1588, 1487, 1241, 1165, 845, 754 cm^{-1} ; MS (FAB $^+$) m/z : 461 ((M+H) $^+$).

5-3-22.

1-({4-Ethyl-5-[2-(4-phenoxyphenyl)-1,3-thiazol-5-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (43a)



(a) 5-[5-({*tert*-Butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-2-(4-phenoxyphenyl)-1,3-thiazole (41a)

According to a similar procedure to 5-3-10 (a), the title compound (0.29 g, 0.58 mmol, 75%) was prepared from *N*-{2-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-2-oxoethyl}-4-phenoxybenzamide (0.39 g, 0.77 mmol, prepared in 5-3-21 (a)), pyridine (0.12 mL, 1.5 mmol), Lawesson's reagent (0.40 g, 1.0 mmol) and toluene. The final purification was conducted by flash column chromatography (*n*-hexane/EtOAc 97:3 to 90:10). ^1H NMR (400 MHz, CDCl_3) δ : 7.91 (d, 2H, J = 9.0 Hz), 7.76 (s, 1H), 7.43–7.36 (m, 2H), 7.20–7.14 (m, 1H), 7.11–7.04 (m, 4H), 6.81 (s, 1H), 4.84 (s, 2H), 2.72 (q, 2H, J = 7.4 Hz), 1.24 (t, 3H, J = 7.4 Hz), 0.95 (s, 9H), 0.13 (s, 6H); IR (ATR): 2927, 1587, 1488, 1235, 1070, 833, 491 cm^{-1} ; MS (FAB $^+$) m/z : 508 ((M+H) $^+$).

(b) Methyl

1-({4-ethyl-5-[2-(4-phenoxyphenyl)-1,3-thiazol-5-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate
According to a similar procedure to 5-3-5 (b), the title compound (0.22 g, 0.44 mmol, 78% in 3 steps) was prepared from 5-[5-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-3-ethylthiophen-2-yl]-2-(4-phenoxyphenyl)-1,3-thiazole (0.29 g, 0.57 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.69 mL, 0.69 mmol) and THF (2.0 mL), and thionyl chloride (64 μ L, 0.86 mmol), toluene (3.0 mL) and a catalytic amount of DMF, and methyl 3-azetidinecarboxylate hydrochloride (0.13 g, 0.86 mmol), *N,N*-diisopropylethylamine (0.30 mL, 1.7 mmol) and acetonitrile. The final purification was conducted by flash column

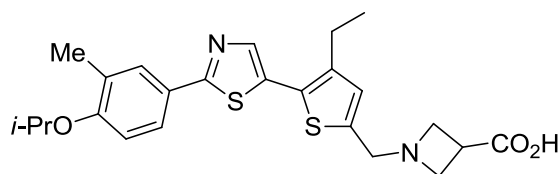
chromatography (*n*-hexane/EtOAc 85:15 to 65:35). ¹H NMR (400 MHz, CDCl₃) δ: 7.91 (d, 2H, *J* = 9.0 Hz), 7.76 (s, 1H), 7.41–7.35 (m, 2H), 7.16 (t, 1H, *J* = 7.4 Hz), 7.10–7.03 (m, 4H), 6.79 (s, 1H), 3.75 (s, 2H), 3.72 (s, 3H), 3.67–3.60 (m, 2H), 3.41–3.33 (m, 3H), 2.72 (q, 2H, *J* = 7.4 Hz), 1.25 (t, 3H, *J* = 7.4 Hz); IR (ATR): 2963, 2841, 1733, 1586, 1488, 1234, 1198, 1166, 838, 728, 691 cm⁻¹; MS (FAB⁺) *m/z*: 491 ((M+H)⁺).

(c) 1-({4-Ethyl-5-[2-(4-phenoxyphenyl)-1,3-thiazol-5-yl]thiophen-2-yl}methyl)azetidine-3-carboxylic acid (**43a**)

According to a similar procedure to 5-3-7 (e), the title compound (0.20 g, 0.41 mmol, 92%) was prepared from methyl 1-({4-ethyl-5-[2-(4-phenoxyphenyl)-1,3-thiazol-5-yl]thiophen-2-yl}methyl)azetidine-3-carboxylate (0.22 g, 0.45 mmol), NaOH (1.0 M in water, 0.68 mL, 0.68 mmol), ethanol (1.0 mL) and acetic acid (37 μL, 0.68 mmol). The final purification by recrystallization (acetonitrile/water 1:1) gave a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.96 (d, 2H, *J* = 9.0 Hz), 7.89 (s, 1H), 7.46 (dd, 2H, *J* = 7.8, 7.4 Hz), 7.23 (t, 1H, *J* = 7.4 Hz), 7.17–7.08 (m, 4H), 6.93 (s, 1H), 3.70 (s, 2H), 3.48–3.40 (m, 2H), 3.28–3.15 (m, 3H), 2.69 (q, 2H, *J* = 7.4 Hz), 1.19 (t, 3H, *J* = 7.4 Hz); IR (KBr): 3417, 2964, 1588, 1490, 1247, 1165, 749 cm⁻¹; MS (FAB⁺) *m/z*: 477 ((M+H)⁺).

5-3-23.

1-[(4-Ethyl-5-{2-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-5-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**43b**)



(a) 3-Methyl-4-(propan-2-yloxy)benzoic acid (**19b**)

To a solution of 3-methyl-4-(propan-2-yloxy)benzonitrile (0.60 g, 3.4 mmol, prepared in 5-3-12 (a)) in ethanol (8.0 mL) was added NaOH (6.3 M in water, 5.5 mL, 34 mmol) and the resulting mixture was stirred at reflux temperature for 12 h. After removal of the organic solvent, the reaction mixture was poured into water and washed with Et₂O. The aqueous phase was acidified at 0 °C with HCl (12 M in water) and extracted with CH₂Cl₂. The extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by recrystallization (*n*-hexane/EtOAc 10 mL/3.0 mL) to afford the title compound (0.50 g, 2.5 mmol, 75%) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ: 7.83 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.78 (d, 1H, *J* = 2.3 Hz), 6.95 (d, 1H, *J* = 8.6 Hz), 4.70 (sept, 1H, *J* = 5.9 Hz), 2.19 (s, 3H), 1.35 (d, 6H, *J* = 5.9 Hz); IR (KBr): 2980, 1672, 1604, 1262, 1113, 956, 778, 646 cm⁻¹; MS (EI⁺) *m/z*: 194 (M⁺).

(b) *N*-{2-[5-({*tert*-Butyl(dimethyl)silyl]oxy)methyl]-3-ethylthiophen-2-yl]-2-oxoethyl}-3-methyl-4-(propan-2-yloxy)benzamide

According to a similar procedure to 5-3-21 (a), the crude product of the title compound was prepared from 3-methyl-4-(propan-2-yloxy)benzoic acid (0.29 g, 1.5 mmol), 1-hydroxybenzotriazole (0.24 g, 1.8 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.35 g, 1.8 mmol), Et₃N (0.63 mL, 4.5 mmol), 2-amino-1-[3-ethyl-5-(hydroxymethyl)thiophen-2-yl]ethanone hydrochloride (**39**) (0.39 g, 1.7 mmol) and CH₂Cl₂ (7.0 mL), and imidazole (0.20 g, 3.0 mmol), TBSCl (0.45 g, 3.0 mmol) and DMF (5.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 4:1) gave an orange oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.69 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.66 (d, 1H, *J* = 2.3 Hz), 7.14 (t, 1H, *J* = 3.9 Hz), 6.88 (s, 1H), 6.85 (d, 1H, *J* = 8.6 Hz), 4.88 (s, 2H), 4.74 (d, 2H, *J* = 3.9 Hz), 4.61 (sept, 1H, *J* = 5.9 Hz), 3.02 (q, 2H, *J* = 7.4 Hz), 2.24 (s, 3H), 1.36 (d, 6H, *J* = 5.9 Hz), 1.25 (t, 3H, *J* = 7.4 Hz), 0.96 (s, 9H), 0.14 (s, 6H); IR (ATR): 2928, 1639, 1606, 1490, 1253, 1125, 1081, 834, 776 cm⁻¹; MS (FAB⁺) *m/z* 490 ((M+H)⁺).

(c) 5-[5-({*tert*-Butyl(dimethyl)silyl]oxy)methyl]-3-ethylthiophen-2-yl]-2-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazole (**41b**)

According to a similar procedure to 5-3-10 (a), the title compound (0.54 g, 1.1 mmol, 80%) was prepared from *N*-{2-[5-({*tert*-butyl(dimethyl)silyl]oxy)methyl]-3-ethylthiophen-2-yl]-2-oxoethyl}-3-methyl-4-(propan-2-yloxy)benzamide (0.67 g, 1.4 mmol), pyridine (0.22 mL, 2.7 mmol), Lawesson's reagent (0.72 g, 1.8 mmol) and toluene (10 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 30:1 to 20:1) gave a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.75–7.70 (m, 3H), 6.87 (d, 1H, *J* = 8.2 Hz), 6.80 (s, 1H), 4.83 (s, 2H), 4.60 (sept, 1H, *J* = 5.9 Hz), 2.72 (q, 2H, *J* = 7.4 Hz), 2.26 (s, 3H), 1.37 (d, 6H, *J* = 5.9 Hz), 1.24 (t, 3H, *J* = 7.4 Hz), 0.95 (s, 9H), 0.13 (s, 6H); IR (ATR): 2927, 1605, 1499, 14663, 1257, 1242, 1122, 1072, 833, 775, 638 cm⁻¹; MS (FAB⁺) *m/z* 488 ((M+H)⁺).

(d) Methyl

1-[(4-ethyl-5-{2-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-5-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate

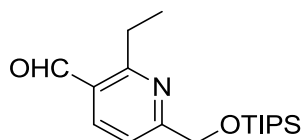
According to a similar procedure to 5-3-5 (b), the title compound (0.34 g, 0.72 mmol, 65% in 3 steps) was prepared from 5-[5-({*tert*-butyl(dimethyl)silyl]oxy)methyl]-3-ethylthiophen-2-yl]-2-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazole (0.54 g, 1.1 mmol), tetrabutylammonium fluoride (1.0 M in THF, 1.3 mL, 1.3 mmol) and THF (5.0 mL), and thionyl chloride (0.17 mL, 2.3 mmol), toluene (13 mL) and a catalytic amount of DMF, and methyl 3-azetidinecarboxylate hydrochloride (0.21 g, 1.4 mmol), *N,N*-diisopropylethylamine (0.48 mL, 2.8 mmol) and acetonitrile (9.0 mL). The final purification by flash column chromatography (neutralized silica gel, *n*-hexane/EtOAc 3:1 to 3:2) gave a yellow oil. ¹H

NMR (400 MHz, CDCl₃) δ : 7.76–7.69 (m, 3H), 6.87 (d, 1H, J = 8.6 Hz), 6.78 (s, 1H), 4.60 (sept, 1H, J = 5.9 Hz), 3.74 (s, 2H), 3.72 (s, 3H), 3.66–3.59 (m, 2H), 3.39–3.33 (m, 3H), 2.72 (q, 2H, J = 7.4 Hz), 2.26 (s, 3H), 1.37 (d, 6H, J = 5.9 Hz), 1.24 (t, 3H, J = 7.4 Hz); IR (ATR): 2969, 1735, 1604, 1258, 1121, 953, 840, 638 cm⁻¹; MS (FAB⁺) m/z : 471 ((M+H)⁺).

(e) 1-[(4-Ethyl-5-{2-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-5-yl}thiophen-2-yl)methyl]azetidine-3-carboxylic acid (**43b**)

According to a similar procedure to 5-3-7 (e), the title compound (0.28 g, 0.62 mmol, 88%) was prepared from methyl 1-[(4-ethyl-5-{2-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-5-yl}thiophen-2-yl)methyl]azetidine-3-carboxylate (0.34 g, 0.71 mmol), NaOH (1.0 M in water, 1.1 mL, 1.1 mmol), methanol (4.0 mL), THF (2.0 mL) and acetic acid (0.31 mL, 5.4 mmol). The final purification by recrystallization (methanol/water 2:1) gave a light yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ : 7.82 (s, 1H), 7.78–7.70 (m, 2H), 7.10–7.04 (m, 1H), 6.92 (s, 1H), 4.69 (sept, 1H, J = 5.9 Hz), 3.69 (s, 2H), 3.51–3.37 (m, 2H), 3.33–3.13 (m, 3H), 2.68 (q, 2H, J = 7.4 Hz), 2.19 (s, 3H), 1.31 (d, 6H, J = 5.9 Hz), 1.19 (t, 3H, J = 7.4 Hz); IR (KBr): 3414, 2973, 1605, 1592, 1499, 1390, 1266, 1247, 1126, 955 cm⁻¹; MS (FAB⁺) m/z : 457 ((M+H)⁺).

5-3-24. 2-Ethyl-6-([tri(propan-2-yl)silyl]oxy)methylpyridine-3-carbaldehyde (**49**)



(a) 6-(Dimethoxymethyl)-2-(methylsulfanyl)pyridine-3-carbonitrile (**46**)

To a solution of methylglyoxal 1,1-dimethyl acetal (**44**) (33 mL, 0.28 mol) in acetonitrile (200 mL) was added *N,N*-dimethylformamide dimethyl acetal (100 mL, 0.75 mol) and the resulting mixture was stirred at reflux temperature for 9 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*.

To a solution of the residue in DMF (200 mL) were successively added 2-cyanothioacetamide (25 g, 0.25 mol) and sodium methoxide (30 g, 0.56 mol) and the resulting mixture was stirred at 100 °C for 5 h. After cooling to 0 °C, iodomethane (46 mL, 0.75 mol) was added dropwisely and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into water and extracted with Et₂O. The extract was washed with water and brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 9:1 to 7:3) to afford the title compound (28 g, 0.12 mol, 50%). ¹H NMR (400 MHz, CDCl₃) δ : 7.82 (d, 1H, J = 7.8 Hz), 7.32 (d, 1H, J = 7.8 Hz), 5.30 (s, 1H), 3.43 (s, 6H), 2.65 (s, 3H); IR (liquid film): 2932, 2225, 1576, 1555, 1365, 1112, 1074, 841, 689 cm⁻¹; MS (FAB⁺) m/z : 225 ((M+H)⁺).

(b) 2-(Methylsulfanyl)-6-({tri(propan-2-yl)silyl}oxy)methylpyridine-3-carbonitrile (**47**)

To a solution of 6-(dimethoxymethyl)-2-(methylsulfanyl)pyridine-3-carbonitrile (**46**) (28 g, 0.12 mol) in acetonitrile (150 mL) and water (30 mL) was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (2.8 g, 12 mmol) and the resulting mixture was stirred at 80 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated. The residue was recrystallized from ethanol and *n*-hexane to afford 6-formyl-2-(methylsulfanyl)pyridine-3-carbonitrile (17 g, 98 mmol, 79%). The mother liquid was concentrated and purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 9:1 to 7:3) to afford 6-formyl-2-(methylsulfanyl)pyridine-3-carbonitrile (0.87 g, 5.4 mmol, 4%). Total 18 g, 83% yield.

To a solution of 6-formyl-2-(methylsulfanyl)pyridine-3-carbonitrile (18 g, 0.10 mol) in methanol (100 mL) was slowly added sodium borohydride (1.9 g, 51 mmol) at 0 °C and the resulting mixture was stirred at 0 °C for 30 min. The reaction mixture was concentrated and the residue was poured into water and extracted with EtOAc. The extract was washed with brine, dried over MgSO₄, filtered and concentrated.

To a solution of the residue in DMF (100 mL) were successively added imidazole (14 g, 0.20 mol) and triisopropylsilyl chloride (24 mL, 0.11 mol) and the resulting mixture was stirred at room temperature for 1.5 h. The reaction mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 97:3) to afford the title compound quantitatively as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.80 (d, 1H, *J* = 7.8 Hz), 7.34 (d, 1H, *J* = 7.8 Hz), 4.89 (s, 2H), 2.60 (s, 3H), 1.18–1.25 (m, 3H), 1.10 (d, 18H, *J* = 6.6 Hz); IR (KBr): 2220, 1573, 1552, 1423, 1372 cm⁻¹; MS (FAB⁺) *m/z* 337 ((M+H)⁺).

(c) 2-(Methylsulfonyl)-6-({tri(propan-2-yl)silyl}oxy)methylpyridine-3-carbonitrile (**48**)

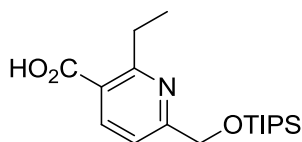
To a solution of 2-(methylsulfanyl)-6-({tri(propan-2-yl)silyl}oxy)methylpyridine-3-carbonitrile (**47**) (36 g, 0.11 mol) in ethanol (200 mL) was slowly added *m*-chloroperoxybenzoic acid (52 g, 0.30 mol) and the resulting mixture was stirred at 50 °C for 5 h. The reaction mixture was concentrated and co-evaporated with toluene. To a solution of the residue in Et₂O (200 mL) was added sat. NaHCO₃ (200 mL) and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with Et₂O. The extract was washed with aqueous Na₂S₂O₃ solution and brine, dried over MgSO₄, filtered and concentrated. The residue was purified by recrystallization (*n*-hexane/EtOAc 98:2) to afford the title compound (33 g, 89 mmol, 83%) as a white crystalline solid. The mother liquid was concentrated and purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 7:3) to afford the title compound (2.2 g, 5.9 mmol, 6%). Total 35 g, 89% yield. ¹H NMR (400 MHz, CDCl₃) δ: 8.26 (d, 1H, *J* = 7.8 Hz), 7.99 (d, 1H, *J* = 7.8 Hz), 5.02 (s, 2H), 3.36 (s, 3H), 1.19–1.28 (m, 3H), 1.12 (d, 18H, *J* = 6.8 Hz); IR (KBr): 2237, 1585, 1463, 1384, 1317 cm⁻¹; MS (FAB⁺) *m/z* 369 ((M+H)⁺).

(d) 2-Ethyl-6-({[tri(propan-2-yl)silyl]oxy}methyl)pyridine-3-carbaldehyde (**49**)

To a solution of 2-(methylsulfonyl)-6-{{[triisopropylsilyl]oxy}methyl}nicotinonitrile (**48**) (33 g, 89 mmol) in THF (200 mL) was slowly added ethylmagnesium bromide (3.0 M in ether, 40 mL, 120 mmol) at -78 °C and the resulting mixture was stirred at -78 °C for 1 h. The reaction was quenched with sat. NH₄Cl and the reaction mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 85:15) to afford 2-ethyl-6-({[tri(propan-2-yl)silyl]oxy}methyl)pyridine-3-carbonitrile (28 g, 88 mmol, 98%).

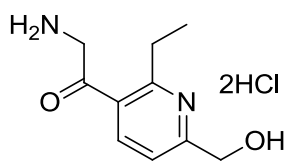
To a solution of 2-ethyl-6-({[tri(propan-2-yl)silyl]oxy}methyl)pyridine-3-carbonitrile (28 g, 88 mmol) in toluene (100 mL) was slowly added DIBAL-H (0.98 M in hexane, 107 mL, 105 mmol) at -78 °C and the resulting mixture was stirred at -78 °C for 1 h. The reaction was quenched with sat. NH₄Cl (19 mL) and the reaction mixture was filtered with Celite pad. The filtrate was concentrated and the residue was diluted with HCl (1.0 M in water, 88 mL) at 0 °C. After stirring at room temperature for 15 min, the mixture was extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc) to afford the title compound (26 g, 82 mmol, 93%). ¹H NMR (400 MHz, CDCl₃) δ: 10.3 (s, 1H), 8.15 (d, 1H, *J* = 7.8 Hz), 7.62 (d, 1H, *J* = 7.8 Hz), 4.96 (s, 2H), 3.19 (q, 2H, *J* = 7.4 Hz), 1.32 (t, 3H, *J* = 7.4 Hz), 1.28–1.15 (m, 3H), 1.11 (d, 18H, *J* = 7.0 Hz); IR (ATR): 2942, 2866, 1707, 1692, 1586, 1462, 1120, 882, 801, 684 cm⁻¹; MS (FAB⁺) *m/z*: 322 ((M+H)⁺).

5-3-25. 2-Ethyl-6-({[tri(propan-2-yl)silyl]oxy}methyl)pyridin-3-carboxylic acid (**50**)



To a solution of 2-ethyl-6-({[tri(propan-2-yl)silyl]oxy}methyl)pyridin-3-carbaldehyde (**49**) (7.0 g, 22 mmol) in *tert*-butanol (40 mL), and water (40 mL) were successively added 2-methyl-2-butene (12 mL, 0.11 mol), potassium dihydrogenphosphate (7.4 g, 55 mmol) and sodium chlorite (5.9 g, 65 mmol) and the resulting mixture was stirred at room temperature for 1.5 h. The reaction mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The crude product was washed with acetonitrile to afford the title compound (6.8 g, 20 mmol, 92%). ¹H NMR (400 MHz, CDCl₃) δ: 8.36 (d, 1H, *J* = 8.2 Hz), 7.55 (d, 1H, *J* = 8.2 Hz), 4.97 (s, 2H), 3.22 (q, 2H, *J* = 7.4 Hz), 1.31 (t, 3H, *J* = 7.4 Hz), 1.27–1.16 (m, 3H), 1.11 (d, 18H, *J* = 7.0 Hz); IR (KBr): 2944, 2867, 1712, 1593, 1463, 1252, 1124, 1093, 767, 683 cm⁻¹; MS (FAB⁺) *m/z*: 338 ((M+H)⁺).

5-3-26. 2-Amino-1-[2-ethyl-6-(hydroxymethyl)pyridin-3-yl]ethanone dihydrochloride (**54**)



(a) 1-[2-Ethyl-6-((tri(propan-2-yl)silyl)oxy)methyl)pyridin-3-yl]ethanone (**53**)

To a solution of 2-ethyl-6-((tri(propan-2-yl)silyl)oxy)methylpyridin-3-carbaldehyde (**49**) (20 g, 61 mmol) in Et₂O (100 mL) was added methylmagnesium iodide (3.0 M in ether, 27 mL, 80 mmol) at -78 °C and the resulting mixture was stirred at -78 °C for 1.5 h. The reaction was quenched with sat. NH₄Cl and the reaction mixture was extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 7:3) to afford 1-[2-ethyl-6-((tri(propan-2-yl)silyl)oxy)methyl)pyridin-3-yl]ethanol (18 g, 54 mmol, 88%).

To a mixture of 1-[2-ethyl-6-((tri(propan-2-yl)silyl)oxy)methyl)pyridin-3-yl]ethanol (18 g, 54 mmol) and Celite (30 g) in CH₂Cl₂ (200 mL) was added pyridinium dichromate (31 g, 81 mmol) and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was filtered with silica gel and the filtrate was concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 7:3) to afford the title compound (17 g, 51 mmol, 96%). ¹H NMR (400 MHz, CDCl₃) δ: 7.99 (d, 1H, *J* = 7.8 Hz), 7.52 (d, 1H, *J* = 7.8 Hz), 4.94 (s, 2H), 3.03 (q, 2H, *J* = 7.4 Hz), 2.59 (s, 3H), 1.26 (t, 3H, *J* = 7.4 Hz), 1.24–1.16 (m, 3H), 1.11 (d, 18H, *J* = 7.0 Hz); IR (ATR): 2942, 2866, 1687, 1584, 1462, 1248, 1118, 881, 810, 681 cm⁻¹; MS (FAB⁺) *m/z*: 336 ((M+H)⁺).

(b) 2-Amino-1-[2-ethyl-6-(hydroxymethyl)pyridin-3-yl]ethanone hydrochloride (**54**)

To a diluted solution of NaHMDS (1.0 M in THF, 77 mL, 77 mmol) in THF (50 mL) was slowly added a solution of 1-[2-ethyl-6-((tri(propan-2-yl)silyl)oxy)methyl)pyridin-3-yl]ethanone (17 g, 51 mmol) in THF at -78 °C. After stirring at -78 °C for 30 min, chlorotrimethylsilane (13 mL, 0.10 mol) was added and the resulting mixture was stirred at -78 °C for 30 min. The reaction was quenched with sat. NH₄Cl and the reaction mixture was poured into water and extracted with Et₂O. The extract was concentrated and co-evaporated with benzene to afford the crude product of 2-ethyl-3-{1-[(trimethylsilyl)oxy]ethenyl}-6-((tri(propan-2-yl)silyl)oxy)methylpyridine, which was used to the next reaction without further purification.

To a solution of the residue in THF (100 mL) was added *N*-bromosuccinimide (9.1 g, 51 mmol) at 0 °C and the resulting mixture was stirred for 1 h. The reaction mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated to afford the crude product of 2-bromo-1-[2-ethyl-6-((tri(propan-2-yl)silyl)oxy)methyl)pyridin-3-yl]ethanone, which was used to the

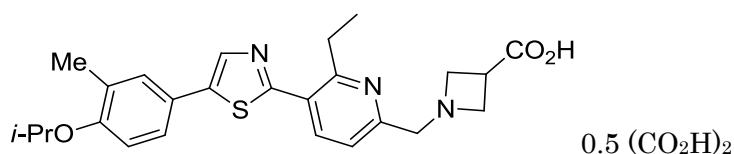
next step without further purification.

To the residue in acetonitrile (100 mL) was added sodium diformylamide (7.3 g, 77 mmol) and the resulting mixture was stirred at 70 °C for 2.5 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with Et₂O. The extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (*n*-hexane/EtOAc 9:1 to 6:4) to afford *N*-{2-[2-ethyl-6-({[tri(propan-2-yl)silyl]oxy)methyl}pyridin-3-yl]-2-oxoethyl}-*N*-formylformamide (17 g, 41 mmol).

To a solution of *N*-{2-[2-ethyl-6-({[tri(propan-2-yl)silyl]oxy)methyl}pyridin-3-yl]-2-oxoethyl}-*N*-formylformamide in ethanol (100 mL) was added HCl (12 M in water, 20 mL, 0.24 mol) and the resulting mixture was stirred at 70 °C for 2 h. After cooling to room temperature, the reaction mixture was concentrated, co-evaporated with toluene and dried. The residue was purified by recrystallization (Et₂O/methanol 9:1) to afford the title compound (5.9 g, 22 mmol, 54% in 4 steps). ¹H NMR (400 MHz, CD₃OD) δ: 8.99 (d, 1H, *J* = 8.4 Hz), 8.09 (d, 1H, *J* = 8.4 Hz), 5.00 (s, 2H), 4.71 (s, 2H), 3.32 (q, 2H, *J* = 7.4 Hz), 1.41 (t, 3H, *J* = 7.4 Hz); IR (KCl): 3256, 2881, 1713, 1643, 1598, 1270, 1037, 860 cm⁻¹; MS (FAB⁺) *m/z* 195 ((M+H)⁺).

5-3-27.

1-[(6-Ethyl-5-{5-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}pyridin-2-yl)methyl]azetidine-3-carboxylic acid 1/2 oxalate (52a)



(a) 2-Ethyl-*N*-{2-[3-methyl-4-(propan-2-yloxy)phenyl]-2-oxoethyl}-6-({[tri(propan-2-yl)silyl]oxy)methyl}pyridine-3-carboxamide

According to a similar procedure to 5-3-11 (e), the title compound (0.29 g, 0.54 mmol, 60%) was prepared from 2-ethyl-6-({[tri(propan-2-yl)silyl]oxy)methyl}pyridine-3-carboxylic acid (**50**) (0.30 g, 0.90 mmol), 1-hydroxybenzotriazole (0.15 g, 1.1 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.21 g, 1.1 mmol), Et₃N (0.38 mL, 2.7 mmol), 2-amino-1-[3-methyl-4-(propan-2-yloxy)phenyl]ethanone hydrochloride (**34c**) (0.21 g, 0.99 mmol, prepared in 5-3-12 (d)) and CH₂Cl₂ (6.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 5:1 to 3:1) gave a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.88–7.82 (m, 2H), 7.81 (d, 1H, *J* = 8.2 Hz), 7.49 (d, 1H, *J* = 7.8 Hz), 6.96 (t, 1H, *J* = 4.3 Hz), 6.89 (d, 1H, *J* = 8.2 Hz), 4.94 (s, 2H), 4.90 (d, 2H, *J* = 4.3 Hz), 4.68 (sept, 1H, *J* = 5.9 Hz), 2.98 (q, 2H, *J* = 7.4

Hz), 2.24 (s, 3H), 1.39 (d, 6H, J = 5.9 Hz), 1.31 (t, 3H, J = 7.4 Hz), 1.28–1.16 (m, 3H), 1.11 (d, 18H, J = 7.0 Hz); IR (ATR): 2941, 2865, 1653, 1600, 1254, 1112, 881, 809 cm^{-1} ; MS (ESI⁺) m/z 527 ((M+H)⁺).

(b) 2-Ethyl-3-{5-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}-6-({[tri(propan-2-yl)silyl]oxy}methyl)pyridine

According to a similar procedure to 5-3-10 (a), the title compound (0.27 g, 0.51 mmol, 95%) was prepared from 2-ethyl-*N*-{2-[3-methyl-4-(propan-2-yloxy)phenyl]-2-oxoethyl}-6-({[tri(propan-2-yl)silyl]oxy}methyl)pyridine-3-carboxamide (0.28 g, 0.54 mmol), pyridine (87 μL , 1.1 mmol), Lawesson's reagent (0.28 g, 0.70 mmol) and toluene (5.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 20:1 to 15:1) gave a yellow oil. ¹H NMR (400 MHz, CDCl_3) δ : 7.98 (d, 1H, J = 7.8 Hz), 7.95 (s, 1H), 7.55–7.50 (m, 1H), 7.42–7.34 (m, 2H), 6.87 (d, 1H, J = 8.6 Hz), 4.97 (s, 2H), 4.58 (sept, 1H, J = 5.9 Hz), 3.17 (q, 2H, J = 7.4 Hz), 2.26 (s, 3H), 1.37 (d, 6H, J = 5.9 Hz), 1.29 (t, 3H, J = 7.4 Hz), 1.28–1.17 (m, 3H), 1.12 (d, 18H, J = 6.6 Hz); IR (ATR): 2940, 2865, 1493, 1463, 1249, 1111, 807, 682 cm^{-1} ; MS (ESI⁺) m/z 525 ((M+H)⁺).

(c) (6-Ethyl-5-{5-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}pyridin-2-yl)methanol

According to a similar procedure to 5-3-11 (g), the title compound was quantitatively prepared from 2-ethyl-3-{5-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}-6-({[tri(propan-2-yl)silyl]oxy}methyl)pyridine (0.27 g, 0.51 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.61 mL, 0.61 mol) and THF (5.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 2:1 to 1:1) gave a light yellow oil. ¹H NMR (400 MHz, CDCl_3) δ : 7.99 (d, 1H, J = 7.8 Hz), 7.96 (s, 1H), 7.41–7.35 (m, 2H), 7.14 (d, 1H, J = 8.2 Hz), 6.87 (d, 1H, J = 9.0 Hz), 4.79 (d, 2H, J = 4.3 Hz), 4.58 (sept, 1H, J = 5.9 Hz), 4.13 (t, 1H, J = 4.3 Hz), 3.22 (q, 2H, J = 7.4 Hz), 2.26 (s, 3H), 1.37 (d, 6H, J = 5.9 Hz), 1.35 (t, 3H, J = 7.4 Hz); IR (ATR): 3287, 2974, 1493, 1249, 1132, 955, 808 cm^{-1} ; MS (ESI⁺) m/z 369 ((M+H)⁺).

(d) Methyl

1-[(6-ethyl-5-{5-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}pyridin-2-yl)methyl]azetidine-3-carboxylate

According to a similar procedure to 5-3-11 (h), the title compound (0.16 g, 0.35 mmol, 70% in 2 steps) was prepared from (6-ethyl-5-{5-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}pyridin-2-yl)methanol (0.18 g, 0.50 mmol), triphenylphosphine (0.24 g, 0.90 mmol), carbon tetrabromide (0.30 g, 0.90 mmol), CH_2Cl_2 (5.0 mL), methyl 3-azetidinecarboxylate hydrochloride (0.11 g, 0.75 mmol), *N,N*-diisopropylethylamine (0.26 mL, 1.5 mmol) and CH_2Cl_2 (7.0 mL). The final purification by flash column chromatography (*n*-hexane/EtOAc 2:1 to $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 3:2) gave a yellow oil. ¹H NMR (400 MHz, CDCl_3) δ : 7.95 (s, 1H), 7.92 (d, 1H, J = 8.2 Hz), 7.40–7.34 (m, 2H), 7.22 (d, 1H, J = 8.2 Hz), 6.87 (d, 1H, J = 9.0 Hz), 4.58 (sept, 1H, J = 5.9 Hz), 3.82 (s, 2H), 3.73 (s, 3H), 3.69–3.62 (m, 2H), 3.51–3.45 (m, 2H), 3.44–3.34 (m,

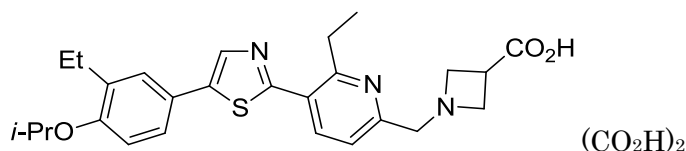
1H), 3.18 (q, 2H, J = 7.4 Hz), 2.25 (s, 3H), 1.37 (d, 6H, J = 5.9 Hz), 1.30 (t, 3H, J = 7.4 Hz); IR (ATR): 2973, 1735, 1493, 1433, 1249, 1132, 954, 810 cm^{-1} ; MS (ESI⁺) m/z 466 ((M+H)⁺).

(e) 1-[(6-Ethyl-5-{5-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}pyridin-2-yl)methyl]azetidine-3-carboxylic acid 1/2 oxalate (**52a**)

According to a similar procedure to 5-3-5 (c), the title compound (0.13 g, 0.27 mmol, 79%) was prepared from methyl 1-[(6-ethyl-5-{5-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}pyridin-2-yl)methyl]azetidine-3-carboxylate (0.16 g, 0.34 mmol), NaOH (1.0 M in water, 0.51 mL, 0.51 mmol), methanol (2.0 mL), THF (1.0 mL), acetic acid (87 μL , 1.5 mmol) and oxalic acid (15 mg, 0.17 mmol). The product was obtained as a yellow amorphous after co-evaporated with toluene and dried sufficiently. ¹H NMR (400 MHz, DMSO- d_6) δ : 8.23 (s, 1H), 8.03 (d, 1H, J = 7.8 Hz), 7.56–7.48 (m, 2H), 7.31 (d, 1H, J = 7.8 Hz), 7.04 (d, 1H, J = 8.6 Hz), 4.66 (sept, 1H, J = 5.9 Hz), 3.73 (s, 2H), 3.56–3.47 (m, 2H), 3.40–3.32 (m, 2H), 3.31–3.21 (m, 1H), 3.11 (q, 2H, J = 7.4 Hz), 2.18 (s, 3H), 1.30 (d, 6H, J = 5.9 Hz), 1.23 (t, 3H, J = 7.4 Hz); IR (KBr): 2973, 1735, 1493, 1433, 1249, 1132, 954, 810 cm^{-1} ; MS (ESI⁺) m/z 452 ((M+H)⁺).

5-3-28.

1-[(6-Ethyl-5-{5-[3-ethyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}pyridin-2-yl)methyl]azetidine-3-carboxylic acid oxalate (**52b**)



(a) 2-Ethyl-*N*-(2-[3-ethyl-4-(propan-2-yloxy)phenyl]-2-oxoethyl)-6-({[tri(propan-2-yl)silyl]oxy}methyl)pyridine-3-carboxamide

According to a similar procedure to 5-3-11 (e), the title compound (0.43 g, 0.80 mmol, 79%) was prepared from 2-ethyl-6-({[tri(propan-2-yl)silyl]oxy}methyl)pyridine-3-carboxylic acid (**50**) (0.34 g, 1.0 mmol), 1-hydroxybenzotriazole (0.16 g, 1.1 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.20 g, 1.1 mmol), Et₃N (0.42 mL, 3.0 mmol), 2-amino-1-[3-ethyl-4-(propan-2-yloxy)phenyl]ethanone hydrochloride (**34d**) (0.29 g, 1.1 mmol, prepared in 5-3-13 (d)) and CH₂Cl₂ (8.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 9:1 to 7:3) gave a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ : 7.88–7.83 (m, 2H), 7.81 (d, 1H, J = 7.8 Hz), 7.49 (d, 1H, J = 7.8 Hz), 6.97 (t, 1H, J = 3.9 Hz), 6.90 (d, 1H, J = 8.6 Hz), 4.94 (s, 2H), 4.91 (d, 2H, J = 3.9 Hz), 4.69 (sept, 1H, J = 5.9 Hz), 2.98 (q, 2H, J = 7.4 Hz), 2.66 (q, 2H, J = 7.4 Hz), 1.39 (d, 6H, J = 5.9 Hz), 1.31 (t, 3H, J = 7.4 Hz), 1.28–1.16 (m, 3H), 1.21 (t, 3H, J = 7.4 Hz), 1.11 (d, 18H, J = 6.6 Hz); IR (ATR): 2940, 2866, 1655, 1598, 1496, 1463, 1251, 1112, 881, 810, 682

cm⁻¹; MS (FAB⁺) *m/z* 541 ((M+H)⁺).

(b) 2-Ethyl-3-{5-[3-ethyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}-6-({[tri(propan-2-yl)silyl]oxy}methyl)pyridine

According to a similar procedure to 5-3-10 (a), the title compound (0.39 g, 0.72 mmol, 91%) was prepared from 2-ethyl-*N*-{2-[3-ethyl-4-(propan-2-yloxy)phenyl]-2-oxoethyl}-6-({[tri(propan-2-yl)silyl]oxy}methyl)pyridine-3-carboxamide (0.43 g, 0.80 mmol), pyridine (0.13 mL, 1.6 mmol), Lawesson's reagent (0.39 g, 0.96 mmol) and toluene (8.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 97:3 to 93:7) gave a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.98 (d, 1H, *J* = 8.2 Hz), 7.95 (s, 1H), 7.52 (d, 1H, *J* = 7.8 Hz), 7.40–7.36 (m, 2H), 6.90–6.86 (m, 1H), 4.97 (s, 2H), 4.60 (sept, 1H, *J* = 5.9 Hz), 3.17 (q, 2H, *J* = 7.4 Hz), 2.67 (q, 2H, *J* = 7.4 Hz), 1.37 (d, 6H, *J* = 5.9 Hz), 1.29 (t, 3H, *J* = 7.4 Hz), 1.23 (t, 3H, *J* = 7.4 Hz), 1.28–1.17 (m, 3H), 1.12 (d, 18H, *J* = 6.6 Hz); IR (ATR): 2939, 1463, 1246, 1111, 956, 881, 808, 682, 657 cm⁻¹; MS (FAB⁺) *m/z* 539 ((M+H)⁺).

(c) Methyl

1-[(6-ethyl-5-{5-[3-ethyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}pyridin-2-yl)methyl]azetidine-3-carboxylate

According to a similar procedure to 5-3-5 (b), the title compound (0.26 g, 0.55 mmol, 77% in 3 steps) was prepared from 2-ethyl-3-{5-[3-ethyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}-6-({[tri(propan-2-yl)silyl]oxy}methyl)pyridine (0.39 g, 0.72 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.87 mL, 0.87 mmol) and THF (7.0 mL), and thionyl chloride (0.14 mL, 1.9 mmol), toluene (5.0 mL), CH₂Cl₂ (4.0 mL) and a catalytic amount of DMF, and methyl 3-azetidinecarboxylate hydrochloride (0.15 g, 0.97 mmol), *N,N*-diisopropylethylamine (0.34 mL, 1.9 mmol) and acetonitrile (5.0 mL). The final purification by flash column chromatography (neutralized silica gel, *n*-hexane/EtOAc 1:1 to 0:1) gave a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.95 (s, 1H), 7.92 (d, 1H, *J* = 7.8 Hz), 7.40–7.36 (m, 2H), 7.22 (d, 1H, *J* = 7.8 Hz), 6.88 (d, 1H, *J* = 9.0 Hz), 4.60 (sept, 1H, *J* = 6.3 Hz), 3.82 (s, 2H), 3.73 (s, 3H), 3.68–3.64 (m, 2H), 3.50–3.46 (m, 2H), 3.43–3.37 (m, 1H), 3.18 (q, 2H, *J* = 7.4 Hz), 2.67 (q, 2H, *J* = 7.4 Hz), 1.37 (d, 6H, *J* = 6.3 Hz), 1.30 (t, 3H, *J* = 7.4 Hz), 1.23 (t, 3H, *J* = 7.4 Hz); IR (ATR): 2971, 1735, 1489, 1434, 1246, 1135, 954, 810 cm⁻¹; MS (FAB⁺) *m/z* 480 ((M+H)⁺).

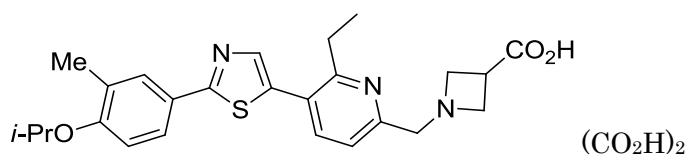
(d) 1-[(6-Ethyl-5-{5-[3-ethyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}pyridin-2-yl)methyl]azetidine-3-carboxylic acid oxalate (**52b**)

According to a similar procedure to 5-3-5 (c), the title compound (0.25 g, 0.46 mmol, 83%) was prepared from methyl 1-[(6-ethyl-5-{5-[3-ethyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-2-yl}pyridin-2-yl)methyl]azetidine-3-carboxylate (0.26 g, 0.55 mmol), NaOH (1.0 M in water, 1.1 mL, 1.1 mmol), methanol (2.0 mL), THF

(2.0 mL), acetic acid (0.11 mL, 1.9 mmol) and oxalic acid (50 mg, 0.55 mmol). The final purification by recrystallization from acetonitrile gave a light yellow solid. ^1H NMR (400 MHz, CD_3OD) δ : 8.10 (d, 1H, J = 8.0 Hz), 8.08 (s, 1H), 7.49–7.44 (m, 2H), 7.37 (d, 1H, J = 7.8 Hz), 6.99 (d, 1H, J = 8.0 Hz), 4.73–4.62 (m, 3H), 4.57–4.40 (m, 4H), 3.80–3.67 (m, 1H), 3.20 (q, 2H, J = 7.4 Hz), 2.66 (q, 2H, J = 7.4 Hz), 1.36 (d, 6H, J = 6.0 Hz), 1.33 (t, 3H, J = 7.4 Hz), 1.21 (t, 3H, J = 7.4 Hz); IR (KBr): 3434, 3048, 2974, 1742, 1606, 1407, 1249, 1226, 708 cm^{-1} ; MS (FAB $^+$) m/z 466 ((M+H) $^+$).

5-3-29.

1-[(6-Ethyl-5-{2-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-5-yl}pyridin-2-yl)methyl]azetidine-3-carboxylic acid oxalate (56a)



(a) 3-Methyl-4-(propan-2-yloxy)benzoyl chloride

To a solution of 3-methyl-4-(propan-2-yloxy)benzoic acid (**19b**) (0.19 g, 0.98 mmol, prepared in 5-3-23 (a)) in toluene (4.0 mL) were successively added a catalytic amount of DMF and thionyl chloride (0.14 mL, 2.0 mmol). After stirring at 80 °C for 1 h, the mixture was concentrated to afford the crude product of the title compound, which was used to the next step without further purification.

(b) *N*-{2-[6-({*tert*-Butyl(dimethyl)silyl}oxy)methyl]-2-ethylpyridin-3-yl]-2-oxoethyl}-3-methyl-4-(propan-2-yloxy)benzamide

To a solution of 2-amino-1-[2-ethyl-6-(hydroxymethyl)pyridin-3-yl]ethanone hydrochloride (**54**) (0.21 g, 0.79 mmol) in EtOAc (4.0 mL) and water (4.0 mL) were successively added sodium hydrogen carbonate (0.23 g, 2.7 mmol) and 3-methyl-4-(propan-2-yloxy)benzoyl chloride (0.98 mmol) and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with EtOAc and the extract was washed with sat. NaHCO_3 and brine, dried over MgSO_4 , filtered and concentrated.

To a solution of the residue in DMF (4.0 mL) were successively added imidazole (0.11 g, 1.6 mmol) and TBSCl (0.18 g, 1.2 mmol) and the resulting mixture was stirred at room temperature. After the reaction was completed, the reaction mixture was poured into water and extracted with EtOAc. The extract was washed with water and brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 85:15 to 60:40) to afford the title compound (0.29 g, 0.59 mmol, 75% in 2 steps) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ : 8.12 (d, 1H, J = 8.2 Hz), 7.73–7.67 (m, 2H), 7.50 (d, 1H, J = 8.2 Hz), 7.11 (t, 1H, J = 4.3 Hz), 6.87 (d, 1H, J = 8.6 Hz), 4.86 (s, 2H), 4.84 (d, 2H, J = 4.3 Hz), 4.62 (sept, 1H, J = 5.9 Hz), 3.08 (q, 2H, J = 7.4

Hz), 2.25 (s, 3H), 1.37 (d, 6H, $J = 5.9$ Hz), 1.29 (t, 3H, $J = 7.4$ Hz), 0.98 (s, 9H), 0.15 (s, 6H); IR (ATR): 2929, 1703, 1637, 1491, 1254, 1111, 835, 776 cm^{-1} ; MS (FAB⁺) m/z : 485 ((M+H)⁺).

(c) 6-({*tert*-Butyl(dimethyl)silyl}oxy)methyl-2-ethyl-3-{2-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-5-yl}pyridine

According to a similar procedure to 5-3-10 (a), the title compound (0.26 g, 0.53 mmol, 90%) was prepared from *N*-{2-[6-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-2-ethylpyridin-3-yl]-2-oxoethyl}-3-methyl-4-(propan-2-yloxy)benzamide (0.29 g, 0.59 mmol), pyridine (95 μL , 1.2 mmol), Lawesson's reagent (0.31 g, 0.59 mmol) and toluene (6.0 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 95:5 to 88:12) gave a white solid. ¹H NMR (400 MHz, CDCl_3) δ : 7.78–7.73 (m, 2H), 7.69 (s, 1H), 7.68 (d, 1H, $J = 7.8$ Hz), 7.41 (d, 1H, $J = 7.8$ Hz), 6.89 (d, 1H, $J = 8.6$ Hz), 4.87 (s, 2H), 4.62 (sept, 1H, $J = 5.9$ Hz), 2.92 (q, 2H, $J = 7.4$ Hz), 2.27 (s, 3H), 1.38 (d, 6H, $J = 5.9$ Hz), 1.26 (t, 3H, $J = 7.4$ Hz), 0.98 (s, 9H), 0.15 (s, 6H); IR (KBr): 2929, 2853, 1604, 1450, 1257, 1238, 1135, 1120, 846 cm^{-1} ; MS (FAB⁺) m/z : 483 ((M+H)⁺).

(d) Methyl

1-[(6-ethyl-5-{2-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-5-yl}pyridin-2-yl)methyl]azetidine-3-carboxylate

According to a similar procedure to 5-3-5 (b), the title compound (0.20 g, 0.43 mmol, 82% in 3 steps) was prepared from 6-({*tert*-butyl(dimethyl)silyl}oxy)methyl-2-ethyl-3-{2-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-5-yl}pyridine (0.26 g, 0.53 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.64 mL, 0.64 mmol) and THF (5.0 mL), and thionyl chloride (0.11 mL, 1.5 mmol), toluene (3.0 mL), CH_2Cl_2 (1.0 mL) and a catalytic amount of DMF, and methyl 3-azetidinecarboxylate hydrochloride (0.11 g, 0.74 mmol), *N,N*-diisopropylethylamine (0.26 mL, 1.5 mmol) and acetonitrile (4.0 mL). The final purification by flash column chromatography (neutralized silica gel, *n*-hexane/EtOAc 1:1 to 0:1) gave a colorless oil. ¹H NMR (400 MHz, CDCl_3) δ : 7.78–7.72 (m, 2H), 7.68 (s, 1H), 7.62 (d, 1H, $J = 7.8$ Hz), 7.19 (d, 1H, $J = 7.8$ Hz), 6.88 (d, 1H, $J = 8.2$ Hz), 4.62 (sept, 1H, $J = 5.9$ Hz), 3.80 (s, 2H), 3.73 (s, 3H), 3.69–3.63 (m, 2H), 3.51–3.45 (m, 2H), 3.44–3.35 (m, 1H), 2.93 (q, 2H, $J = 7.4$ Hz), 2.27 (s, 3H), 1.38 (d, 6H, $J = 5.9$ Hz), 1.26 (t, 3H, $J = 7.4$ Hz); IR (ATR): 2975, 1734, 1453, 1434, 1258, 1241, 1120, 953, 837, 812, 640 cm^{-1} ; MS (FAB⁺) m/z : 466 ((M+H)⁺).

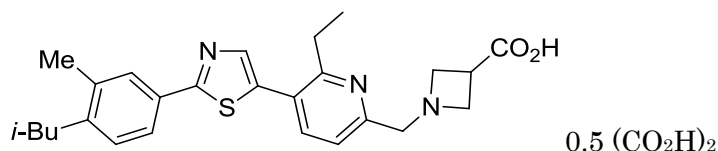
(e) 1-[(6-Ethyl-5-{2-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-5-yl}pyridin-2-yl)methyl]azetidine-3-carboxylic acid oxalate (**56a**)

According to a similar procedure to 5-3-5 (c), the title compound (0.18 g, 0.32 mmol, 75%) was prepared from methyl 1-[(6-ethyl-5-{2-[3-methyl-4-(propan-2-yloxy)phenyl]-1,3-thiazol-5-yl}pyridin-2-yl)methyl]azetidine-3-

carboxylate (0.20 g, 0.43 mmol), NaOH (1.0 M in water, 1.3 mL, 1.3 mmol), methanol (2.5 mL), THF (2.5 mL), acetic acid (87 μ L, 1.5 mmol) and oxalic acid (39 mg, 0.43 mmol). The final purification by recrystallization (acetonitrile/diisopropyl ether 0.40 mL/12 mL) gave a white solid. ^1H NMR (400 MHz, CD_3OD) δ : 7.87 (d, 1H, J = 8.0 Hz), 7.78 (s, 1H), 7.78–7.74 (m, 2H), 7.34 (d, 1H, J = 8.0 Hz), 7.02 (d, 1H, J = 9.3 Hz), 4.71 (sept, 1H, J = 6.0 Hz), 4.67 (s, 2H), 4.56–4.40 (m, 4H), 3.81–3.66 (m, 1H), 3.00 (q, 2H, J = 7.5 Hz), 2.24 (s, 3H), 1.37 (d, 6H, J = 6.0 Hz), 1.33 (t, 3H, J = 7.5 Hz); IR (KBr): 3427, 2978, 2597, 1701, 1605, 1260, 1240, 1135, 955, 697 cm^{-1} ; MS (FAB $^+$) m/z : 452 ((M+H) $^+$).

5-3-30.

1-[(6-Ethyl-5-{2-[3-methyl-4-(2-methylpropyl)phenyl]-1,3-thiazol-5-yl}pyridin-2-yl)methyl]azetidine-3-carboxylic acid (56b)



(a) 3-Methyl-4-(2-methylpropyl)benzoic acid (19c)

To a solution of 4-bromo-2-methylbenzoic acid (5.0 g, 23 mmol) in THF (20 mL) was added borane tetrahydrofuran complex solution (1.0 M in THF, 28 mL, 28 mmol) at 0 °C and the resulting mixture was stirred at 0 °C for 1.5 h. The reaction was quenched with water (5.0 mL) and the reaction mixture was poured into water and extracted with EtOAc. The extract was washed with brine, dried over MgSO_4 , filtered and concentrated.

To a mixture of the residue and MgSO_4 (13 g) in CH_2Cl_2 (50 mL) was added pyridinium dichromate (13 g, 35 mmol) and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 9:1) to afford 4-bromo-2-methylbenzaldehyde (4.2 g, 21 mmol).

To a solution of triphenyl(propan-2-yl)phosphonium iodide (11 g, 25 mmol) in DMF (30 mL) was added potassium *tert*-butoxide (3.1 g, 27 mmol) at 0 °C. After stirring at 0 °C for 10 min, a solution of 4-bromo-2-methylbenzaldehyde (4.2 g, 21 mmol) in DMF was added and the resulting mixture was stirred for 1 h. The reaction was quenched with sat. NH_4Cl and the reaction mixture was extracted with *n*-hexane. The extract was washed with brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 9:1) to afford 4-bromo-2-methyl-1-(2-methylprop-1-en-1-yl)benzene (3.4 g, 15 mmol).

To a solution of 4-bromo-2-methyl-1-(2-methylprop-1-en-1-yl)benzene (3.4 g, 15 mmol) in THF (30 mL) was added *n*-BuLi (1.7 M in hexane, 11 mL, 18 mmol) at -78 °C. After stirring at -78 °C for 10 min, DMF (1.6 mL, 21 mmol) was added and the resulting mixture was stirred for 1 h. The reaction

was quenched with sat. NH_4Cl and the reaction mixture was poured into water and extracted with Et_2O . The extract was washed with brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/ EtOAc 9:1) to afford 3-methyl-4-(2-methylprop-1-en-1-yl)benzaldehyde (2.4 g, 14 mmol).

To a mixture of 3-methyl-4-(2-methylprop-1-en-1-yl)benzaldehyde (2.4 g, 14 mmol), potassium dihydrogenphosphate (4.8 g, 35 mmol), 2-methyl-2-butene (7.3 mL, 69 mmol) in *tert*-butanol (20 mL) and water (20 mL) was added sodium chlorite (2.5 g, 28 mmol) and the resulting mixture was stirred for 3 h. The reaction mixture was poured into water and extracted with Et_2O . The extract was washed with NaOH (1.0 M in water, 50 mL) and the aqueous phase was acidified with HCl (12 M in water) and extracted with Et_2O . The extract was washed with brine, dried over MgSO_4 , filtered and concentrated to afford 3-methyl-4-(2-methylprop-1-en-1-yl)benzoic acid (2.3 g, 12 mmol).

A mixture of 3-methyl-4-(2-methylprop-1-en-1-yl)benzoic acid (2.3 g, 12 mmol) and 10% Pd-C (50% wet, 0.23 g) in EtOAc (30 mL) was degassed and saturated with hydrogen gas and the mixture was stirred at room temperature. After the reaction was completed, the reaction mixture was filtered through Celite pad and the filtrate was concentrated. The residue was purified by recrystallization from *n*-hexane to afford the title compound (1.9 g, 9.7 mmol, 42% in 6 steps). ^1H NMR (400 MHz, CDCl_3) δ : 7.90 (s, 1H), 7.86 (d, 1H, J = 7.8 Hz), 7.19 (d, 1H, J = 7.8 Hz), 2.55 (d, 2H, J = 7.0 Hz), 2.36 (s, 3H), 1.96–1.84 (m, 1H), 0.94 (d, 6H, J = 6.6 Hz).

(b) *N*-{2-[2-Ethyl-6-(hydroxymethyl)pyridin-3-yl]-2-oxoethyl}-3-methyl-4-(2-methylpropyl)benzamide
According to a similar procedure to 5-3-11 (e), the crude product of the title compound was prepared from 3-methyl-4-(2-methylpropyl)benzoic acid (**19c**) (0.19 g, 1.0 mmol), 1-hydroxybenzotriazole (0.16 g, 1.2 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.23 g, 1.2 mmol), triethylamine (0.42 mL, 3.0 mmol), 2-amino-1-[2-ethyl-6-(hydroxymethyl)pyridin-3-yl]ethanone hydrochloride (**54**) (0.23 g, 1.0 mmol) and CH_2Cl_2 (3.0 mL). The crude product was used to the next step without further purification.

(c) *N*-{2-[6-({*tert*-Butyl(dimethyl)silyl}oxy)methyl]-2-ethylpyridin-3-yl]-2-oxoethyl}-3-methyl-4-(2-methylpropyl)benzamide

To a solution of the crude product of *N*-{2-[2-ethyl-6-(hydroxymethyl)pyridin-3-yl]-2-oxoethyl}-3-methyl-4-(2-methylpropyl)benzamide in DMF (5.0 mL) were successively added imidazole (0.14 g, 2.0 mmol) and TBSCl (0.18 g, 1.2 mmol). After the reaction was completed, the reaction mixture was poured into water and extracted with Et_2O . The extract was washed with brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/ EtOAc 95:5 to 85:15) to afford the title compound (0.29 g, 0.61 mmol, 61% in 2 steps). ^1H NMR (400 MHz, CDCl_3) δ : 8.11 (d, 1H, J = 8.2 Hz), 7.67 (d, 1H, J = 2.0 Hz), 7.62 (dd, 1H, J = 7.8, 2.0 Hz), 7.50 (d, 1H, J = 8.2 Hz), 7.18 (d, 1H, J = 7.8 Hz), 7.21–7.17 (m, 1H), 4.86 (s, 2H), 4.84 (d, 2H, J = 4.3 Hz), 3.08 (q, 2H, J = 7.4 Hz), 2.53 (d, 2H, J =

7.0 Hz), 2.37 (s, 3H), 1.96–1.82 (m, 1H), 1.29 (t, 3H, $J = 7.4$ Hz), 0.98 (s, 9H), 0.94 (d, 6H, $J = 6.6$ Hz), 0.15 (s, 6H); IR (ATR): 2953, 2857, 1643, 1534, 1463, 1254, 1116, 837, 777 cm^{-1} ; MS (FAB⁺) m/z 483 ((M+H)⁺).

(d) 6-({*tert*-Butyl(dimethyl)silyl}oxy)methyl-2-ethyl-3-{2-[3-methyl-4-(2-methylpropyl)phenyl]-1,3-thiazol-5-yl}pyridine

According to a similar procedure to 5-3-10 (a), the title compound (0.21 g, 0.44 mmol, 73%) was prepared from *N*-{2-[6-({*tert*-butyl(dimethyl)silyl}oxy)methyl-2-ethylpyridin-3-yl]-2-oxoethyl}-3-methyl-4-(2-methylpropyl)benzamide (0.29 g, 0.60 mmol), pyridine (0.10 mL, 1.2 mmol), Lawesson's reagent (0.32 g, 0.78 mmol) and toluene (5.0 mL). The final purification was conducted by flash column chromatography (*n*-hexane/EtOAc 95:5 to 85:15). ¹H NMR (400 MHz, CDCl₃) δ : 7.77 (d, 1H, $J = 2.0$ Hz), 7.73 (s, 1H), 7.70 (dd, 1H, $J = 7.8, 2.0$ Hz), 7.69 (d, 1H, $J = 7.8$ Hz), 7.42 (d, 1H, $J = 7.8$ Hz), 7.18 (d, 1H, $J = 7.8$ Hz), 4.87 (s, 2H), 2.92 (q, 2H, $J = 7.4$ Hz), 2.53 (d, 2H, $J = 7.0$ Hz), 2.38 (s, 3H), 1.98–1.83 (m, 1H), 1.26 (t, 3H, $J = 7.4$ Hz), 0.98 (s, 9H), 0.95 (d, 6H, $J = 6.6$ Hz), 0.15 (s, 6H); IR (ATR): 2953, 2856, 1462, 1255, 1112, 833, 775, 641 cm^{-1} ; MS (FAB⁺) m/z 481 ((M+H)⁺).

(e) Methyl

1-[(6-ethyl-5-{2-[3-methyl-4-(2-methylpropyl)phenyl]-1,3-thiazol-5-yl}pyridin-2-yl)methyl]azetidine-3-carboxylate

According to a similar procedure to 5-3-5 (b), the title compound (0.17 g, 0.37 mmol, 85% in 3 steps) was prepared from 6-({*tert*-butyl(dimethyl)silyl}oxy)methyl-2-ethyl-3-{2-[3-methyl-4-(2-methylpropyl)phenyl]-1,3-thiazol-5-yl}pyridine (0.21 g, 0.44 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.52 mL, 0.52 mmol) and THF (2.0 mL), and thionyl chloride (50 μL , 0.66 mmol), toluene (3.0 mL) and a catalytic amount of DMF, and methyl 3-azetidinecarboxylate hydrochloride (0.10 g, 0.66 mmol), *N,N*-diisopropylethylamine (0.23 mL, 1.3 mmol) and acetonitrile. The final purification was conducted by flash column chromatography (amino silica gel, *n*-hexane/EtOAc). ¹H NMR (400 MHz, CDCl₃) δ : 7.80–7.69 (m, 3H), 7.62 (d, 1H, $J = 7.8$ Hz), 7.23–7.16 (m, 2H), 3.81 (s, 2H), 3.73 (s, 3H), 3.70–3.64 (m, 2H), 3.52–3.45 (m, 2H), 3.44–3.35 (m, 1H), 2.93 (q, 2H, $J = 7.4$ Hz), 2.53 (d, 2H, $J = 7.0$ Hz), 2.38 (s, 3H), 1.97–1.83 (m, 1H), 1.26 (t, 3H, $J = 7.4$ Hz), 0.95 (d, 6H, $J = 6.6$ Hz); IR (ATR): 2953, 2866, 1736, 1457, 1435, 1199, 1174, 837, 642 cm^{-1} ; MS (FAB⁺) m/z 464 ((M+H)⁺).

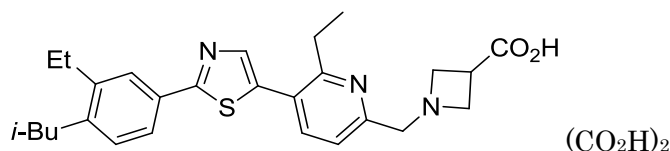
(f) 1-[(6-Ethyl-5-{2-[3-methyl-4-(2-methylpropyl)phenyl]-1,3-thiazol-5-yl}pyridin-2-yl)methyl]azetidine-3-carboxylic acid 1/2 oxalate (**56b**)

According to a similar procedure to 5-3-5 (c), the title compound (0.13 g, 0.25 mmol, 69%) was prepared from methyl 1-[(6-ethyl-5-{2-[3-methyl-4-(2-methylpropyl)phenyl]-1,3-thiazol-5-yl}pyridin-2-yl)methyl]azetidine-3

-carboxylate (0.17 g, 0.37 mmol), NaOH (1.0 M in water, 0.55 mL, 0.55 mmol), ethanol (0.60 mL), acetic acid (30 μ L, 0.55 mmol) and oxalic acid (16 mg, 0.18 mmol). The product was obtained as an amorphous after dried sufficiently. ^1H NMR (400 MHz, DMSO- d_6) δ : 7.94 (s, 1H), 7.85–7.69 (m, 3H), 7.32–7.21 (m, 2H), 3.70 (s, 2H), 3.54–3.46 (m, 2H), 3.36–3.29 (m, 2H), 3.28–3.19 (m, 1H), 2.87 (q, 2H, J = 7.4 Hz), 2.51 (d, 2H, J = 6.6 Hz), 2.35 (s, 3H), 1.86 (tsept, 1H, J = 6.6, 6.6 Hz), 1.20 (t, 3H, J = 7.4 Hz), 0.91 (d, 6H, J = 6.6 Hz); IR (KBr): 3393, 2954, 1608, 1462, 1384, 836, 513 cm^{-1} ; MS (FAB $^+$) m/z : 450 ((M+H) $^+$).

5-3-31.

1-[(6-Ethyl-5-{2-[3-ethyl-4-(2-methylpropyl)phenyl]-1,3-thiazol-5-yl}pyridin-2-yl)methyl]azetidine-3-carboxylic acid oxalate (56c)



(a) 3-Ethyl-4-(2-methylpropyl)benzoic acid (**19d**)

To a mixture of 4-(2-methylpropyl)benzoic acid (3.0 g, 17 mmol) and nitric acid (70 wt% in water, 11 mL, 0.17 mol) in acetic acid (50 mL) and water (8.4 mL) were successively added bromine (0.95 mL, 19 mmol) and a solution of silver(I) nitrate (2.9 g, 17 mmol) in water (8.4 mL) and the resulting mixture was stirred at room temperature for 2.5 h. The reaction mixture was filtered and washed with water and *n*-hexane. The filtrate was concentrated and co-evaporated with toluene for removal of the organic solvent and water. The residue was filtered and washed with *n*-hexane and the filtrate was concentrated.

To a solution of the residue in methanol (30 mL) and toluene (30 mL) was added sulfuric acid (96 wt% in water, 93 μ L, 1.7 mmol) and the resulting mixture was stirred at 100 $^{\circ}\text{C}$. After the reaction was completed, the reaction mixture was concentrated, poured into water and extracted with *n*-hexane. The extract was washed with water and brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/toluene 1:0 to 0:1) to afford methyl 3-bromo-4-(2-methylpropyl)benzoate (1.3 g, 4.9 mmol).

A mixture of methyl 3-bromo-4-(2-methylpropyl)benzoate (1.3 g, 4.9 mmol), $\text{Pd}(\text{PPh}_3)_4$ (0.20 g, 0.17 mmol), 2,4,6-trivinylcyclotriboroxane pyridine complex (0.36 g, 1.5 mmol) and aq. Na_2CO_3 (2.0 M in water, 67 mL, 0.13 mol) in 1,4-dioxane (67 mL) was heated at 80 $^{\circ}\text{C}$ for 2 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with Et_2O . The extract was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography (silica gel, *n*-hexane/ EtOAc) to afford methyl 3-ethenyl-4-(2-methylpropyl)benzoate (0.58 g, 2.6 mmol) as a colorless oil.

A mixture of methyl 3-ethenyl-4-(2-methylpropyl)benzoate (0.58 g, 2.6 mmol) and 10% Pd-C (50% wet, 0.36 g) in methanol (26 mL) was degassed and saturated with hydrogen gas, and the mixture was stirred at room temperature for 30 min. The reaction mixture was filtered through Celite pad and the filtrate was concentrated to afford methyl 3-ethyl-4-(2-methylpropyl)benzoate (0.54 g, 2.5 mmol) as a colorless oil.

To a solution of methyl 3-ethyl-4-(2-methylpropyl)benzoate (0.54 g, 2.5 mmol) in methanol (6.0 mL) and water (6.0 mL) was added NaOH (0.60 g, 15 mmol) and the reaction mixture was stirred at 50 °C for 1 h. The reaction mixture was acidified with HCl (12 M in water) and extracted with Et₂O. The extract was dried over Na₂SO₄, filtered and concentrated to afford the title compound (0.47 g, 2.3 mmol, 13% in 5 steps) as a white powder. ¹H NMR (400 MHz, CDCl₃) δ: 7.93 (s, 1H), 7.86 (d, 1H, *J* = 7.8 Hz), 7.20 (d, 1H, *J* = 7.8 Hz), 2.71 (q, 2H, *J* = 7.4 Hz), 2.56 (q, 2H, *J* = 7.0 Hz), 1.96–1.82 (m, 1H), 1.25 (t, 3H, *J* = 7.4 Hz), 0.94 (d, 6H, *J* = 6.6 Hz).

(b) 3-Ethyl-*N*-{2-[2-ethyl-6-(hydroxymethyl)pyridin-3-yl]-2-oxoethyl}-4-(2-methylpropyl)benzamide

According to a similar procedure to 5-3-11 (e), the crude product of the title compound was prepared from 3-ethyl-4-(2-methylpropyl)benzoic acid (**19d**) (0.47 g, 2.3 mmol), 1-hydroxybenzotriazole (0.42 g, 2.7 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.55 g, 2.9 mmol), triethylamine (1.4 mL, 10 mmol), 2-amino-1-[2-ethyl-6-(hydroxymethyl)pyridin-3-yl]ethanone hydrochloride (**54**) (0.73 g, 2.7 mmol) and CH₂Cl₂ (10 mL). The crude product was used to the next step without further purification.

(c) *N*-{2-[6-({*tert*-Butyl(dimethyl)silyl}oxy)methyl]-2-ethylpyridin-3-yl]-2-oxoethyl}-3-ethyl-4-(2-methylpropyl)benzamide

According to a similar procedure to 5-3-30 (c), the title compound (0.90 g, 1.8 mmol, 80% in 2 steps) was prepared from the crude product of the amide, imidazole (0.31 g, 4.5 mmol) and TBSCl (0.41 g, 2.7 mmol) and DMF (6.5 mL). The final purification by flash column chromatography (silica gel, *n*-hexane/EtOAc 3:1) gave a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.12 (d, 1H, *J* = 7.8 Hz), 7.71 (s, 1H), 7.61 (d, 1H, *J* = 8.2 Hz), 7.51 (d, 1H, *J* = 7.8 Hz), 7.23–7.18 (m, 2H), 4.86 (s, 2H), 4.85 (s, 2H), 3.08 (q, 2H, *J* = 7.4 Hz), 2.71 (q, 2H, *J* = 7.4 Hz), 2.55 (d, 2H, *J* = 7.0 Hz), 1.95–1.81 (m, 1H), 1.29 (t, 3H, *J* = 7.4 Hz), 1.26 (t, 3H, *J* = 7.4 Hz), 0.98 (s, 9H), 0.94 (d, 6H, *J* = 6.6 Hz), 0.15 (s, 6H); MS (FAB⁺) *m/z*: 497 ((M+H)⁺).

(d) 6-({*tert*-Butyl(dimethyl)silyl}oxy)methyl)-2-ethyl-3-{2-[3-ethyl-4-(2-methylpropyl)phenyl]-1,3-thiazol-5-yl}pyridine

According to a similar procedure to 5-3-10 (a), the title compound (0.71 g, 1.4 mmol, 79%) was prepared from *N*-{2-[6-({*tert*-butyl(dimethyl)silyl}oxy)methyl]-2-ethylpyridin-3-yl]-2-oxoethyl}-3-ethyl-4-(2-methylpropyl)benzamide (0.90 g, 1.8 mmol), pyridine (0.29 mL, 3.6 mmol), Lawesson's reagent (0.96 g, 2.4

mmol) and toluene (18 mL). The final purification by flash column chromatography (amino silica gel, *n*-hexane/EtOAc 95:5) gave a red oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.82–7.81 (m, 1H), 7.74 (s, 1H), 7.70 (s, 1H), 7.68 (s, 1H), 7.42 (d, 1H, *J* = 7.8 Hz), 7.19 (d, 1H, *J* = 7.8 Hz), 4.87 (s, 2H), 2.92 (q, 2H, *J* = 7.8 Hz), 2.72 (q, 2H, *J* = 7.8 Hz), 2.55 (d, 2H, *J* = 7.4 Hz), 1.95–1.84 (m, 1H), 1.28 (t, 3H, *J* = 7.8 Hz), 1.26 (t, 3H, *J* = 7.8 Hz), 0.98 (s, 9H), 0.96 (d, 6H, *J* = 6.6 Hz), 0.15 (s, 6H).

(e) Methyl

1-[(6-ethyl-5-{2-[3-ethyl-4-(2-methylpropyl)phenyl]-1,3-thiazol-5-yl}pyridin-2-yl)methyl]azetidine-3-carboxylate

According to a similar procedure to 5-3-5 (b), the title compound (0.48 g, 1.0 mmol, 70% in 3 steps) was prepared from 6-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-ethyl-3-{2-[3-ethyl-4-(2-methylpropyl)phenyl]-1,3-thiazol-5-yl}pyridine (0.71 g, 1.4 mmol), tetrabutylammonium fluoride (1.0 M in THF, 1.7 mL, 1.7 mmol) and THF (15 mL), and thionyl chloride (0.27 mL, 3.8 mmol), toluene (12 mL) and a catalytic amount of DMF, and methyl 3-azetidinecarboxylate hydrochloride (0.28 g, 1.9 mmol), *N,N*-diisopropylethylamine (0.87 mL, 5.0 mmol) and acetonitrile (12 mL). The final purification by flash column chromatography (amino silica gel, *n*-hexane/EtOAc 1:1) gave a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.85–7.80 (m, 1H), 7.77–7.73 (m, 1H), 7.73–7.67 (m, 1H), 7.67–7.61 (m, 1H), 7.24–7.17 (m, 2H), 3.81 (s, 2H), 3.73 (s, 3H), 3.71–3.64 (m, 2H), 3.52–3.45 (m, 2H), 3.45–3.37 (m, 1H), 2.94 (q, 2H, *J* = 7.4 Hz), 2.72 (q, 2H, *J* = 7.0 Hz), 2.55 (d, 2H, *J* = 7.0 Hz), 1.95–1.85 (m, 1H), 1.33–1.23 (m, 6H), 0.96 (d, 6H, *J* = 7.0 Hz); MS (FAB⁺) *m/z*: 478 ((M+H)⁺).

(f) 1-[(6-Ethyl-5-{2-[3-ethyl-4-(2-methylpropyl)phenyl]-1,3-thiazol-5-yl}pyridin-2-yl)methyl]azetidine-3-carboxylic acid oxalate (**56c**)

According to a similar procedure to 5-3-5 (c), the title compound (0.30 g, 0.54 mmol, 54%) was prepared from methyl 1-[(6-ethyl-5-{2-[3-ethyl-4-(2-methylpropyl)phenyl]-1,3-thiazol-5-yl}pyridin-2-yl)methyl]azetidine-3-carboxylate (0.48 g, 1.0 mmol), NaOH (1.0 M in water, 3.0 mL, 3.0 mmol), methanol (5.5 mL), THF (5.5 mL), acetic acid (0.20 mL, 3.5 mmol) and oxalic acid (90 mg, 1.0 mmol). The final purification by recrystallization (*i*-Pr₂O/Et₂O) gave a yellow powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.03–8.00 (m, 1H), 7.96–7.92 (m, 1H), 7.82–7.78 (m, 1H), 7.76–7.70 (m, 1H), 7.42–7.36 (m, 1H), 7.31–7.25 (m, 1H), 4.56 (s, 2H), 4.35–4.19 (m, 4H), 3.72–3.63 (m, 1H), 2.94 (q, 2H, *J* = 7.4 Hz), 2.70 (q, 2H, *J* = 7.4 Hz), 2.54 (d, 2H, *J* = 7.4 Hz), 1.90–1.82 (m, 1H), 1.26 (t, 3H, *J* = 7.4 Hz), 1.21 (t, 3H, *J* = 7.4 Hz), 0.92 (d, 6H, *J* = 6.6 Hz); MS (FAB⁺) *m/z*: 464 ((M+H)⁺).

5-4. 第4章に関する実験

5-4-1. (±)-3-(*tert*-Butyldimethylsilyloxy)methylcyclopentan-1-one [(±)-61]



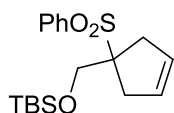
To a suspension of LiAlH_4 (15 g, 0.40 mol) in THF (300 mL) was slowly added a solution of methyl cyclopent-3-ene-1-carboxylate **69** (50 g, 0.40 mol) in THF (200 mL) at 0 °C. After stirring for 30 min at 0 °C, the reaction mixture was quenched by the addition of water (15 mL), aqueous 15% NaOH solution (15 mL) and water (40 mL). To this was added Et_2O (100 mL) and the suspension was stirred for 1 h. Then, the resulting solid was filtered and the filtrate was concentrated *in vacuo*.

To a mixture of the residue and imidazole (40 g, 0.59 mol) in DMF (300 mL) was added TBSCl (66 g, 0.44 mol) at room temperature. After completion of the reaction by adding further TBSCl (13 g, 88 mmol) in two portion within 1 h, the mixture was poured into water (300 mL) and extracted with *n*-hexane. The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, *n*-hexane/ EtOAc 1:0 to 95:5) to afford 79.4 g of the colorless oil product **70**.

To a solution of **70** in THF (300 mL) was added $\text{BH}_3\cdot\text{THF}$ (205 mL, 1.09 M in THF, 224 mmol) at 0 °C over 15 min and the mixture was stirred for 1 h at 0 °C. To the resulting mixture was slowly added aq. NaOH (2.0 M, 0.11 L, 0.22 mol) over 30 min and successively added aqueous 30% H_2O_2 (34 mL, 300 mmol) over 20 min. After evaporating to 2/3 volume, the mixture was poured into water (300 mL) and extracted with Et_2O . The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*.

The residue was dissolved in CH_2Cl_2 (300 mL) and to this were added sat. NaHCO_3 (100 mL), TEMPO (1.2 g, 7.5 mmol) and KBr (4.4 g, 37 mmol). To the mixture was added aqueous NaOCl (0.46 L, > 5.0% as available chlorine) at 0 °C. After stirring at 0 °C for 1 h, the mixture was poured into water and extracted with Et_2O . The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, *n*-hexane/ EtOAc 97:3 to 92:8) to afford the title compound (±)-**61** (77.0 g, 337 mmol, 85% from **69**) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ : 3.63 (d, 2H, $J = 5.1$ Hz), 2.46–2.25 (m, 3H), 2.22–2.00 (m, 3H), 1.82–1.70 (m, 1H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ : 219.6, 65.8, 41.5, 38.9, 38.0, 25.8, 18.2, -5.5; IR (ATR): 2953, 2929, 2856, 1742, 1254, 1097, 833, 774 cm^{-1} ; MS (CI^+) m/z : 229 ($(\text{M}+\text{H})^+$); HRMS (CI^+): m/z calcd for $\text{C}_{12}\text{H}_{25}\text{O}_2\text{Si}$, 229.1624 $[\text{M}+\text{H}]^+$; found 229.1621.

5-4-2. *tert*-Butyl(dimethyl){[1-(phenylsulfonyl)cyclopent-3-en-1-yl]methoxy}silane (**73**)

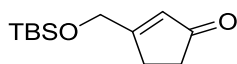


To a solution of ethyl phenylsulfonylacetate **71** (76 g, 0.33 mol) in DMF (400 mL) was added LiH (6.6 g, 0.83 mol) at 0 °C, and warmed to room temperature. After stirring for 0.5 h, the reaction mixture was cooled to 0 °C again and was added *cis*-1,4-dichloro-2-butene (42 mL, 400 mmol). Then the reaction mixture was warmed to room temperature. After stirring for 4 h, the reaction was quenched with sat. NH₄Cl (50 mL). The resulting mixture was poured into water (300 mL) and extracted with Et₂O. The combined organic layers were washed with water, brine, dried over MgSO₄, filtered and concentrated *in vacuo*.

To a suspension of LiAlH₄ (13 g, 0.33 mol) in THF (300 mL) at 0 °C was slowly added a solution of the crude product in THF (200 mL) dropwise over 0.5 h. After stirring for 1 h at 0 °C, the reaction was quenched with water (13 mL), aqueous NaOH (5.0 M, 13 mL, 63 mmol) and water (38 mL). To the resulting mixture was added Et₂O (200 mL) and the mixture was stirred for several hours. The resulting mixture was filtered through Celite and the filtrate was evaporated *in vacuo*. The residue was diluted with toluene (100 mL) and azeotropically evaporated *in vacuo*.

To a solution of the obtained crude product and imidazole (34 g, 0.50 mol) in DMF (300 mL) was added TBSCl (50 g, 0.33 mol) at room temperature. After stirring for 15 h, the reaction was quenched with water (30 mL). The reaction mixture was poured into water (300 mL) and extracted with Et₂O. The extract was washed with water and brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 19:1 to 17:3) to afford the title compound **73** (102 g, 0.29 mol, 87%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ: 7.94–7.89 (m, 2H), 7.61 (t, 2H, *J* = 7.7 Hz), 7.50 (t, 1H, *J* = 7.7 Hz), 5.57 (s, 2H), 3.84 (s, 2H), 3.13 (d, 2H, *J* = 15.1 Hz), 2.46 (d, 2H, *J* = 15.1 Hz), 0.76 (s, 9H), -0.08 (s, 6H); MS (EI⁺) *m/z* 285 (M⁺).

5-4-3. 3-(*tert*-Butyldimethylsilyloxy)methylcyclopent-2-en-1-one (**75**)



To a solution of **73** (103 g, 0.29 mol) in THF (300 mL) was added BH₃·THF (0.16 L, 1.0 M in THF, 160 mmol) at 0 °C over 25 min and the mixture was stirred for 1 h at 0 °C. To the resulting mixture was slowly added aqueous NaOH (2.0 M, 85 mL, 0.17 mol) and successively added aqueous 35% H₂O₂ (29 mL, 0.30 mol). After stirring for 1 h, the mixture was poured into water (300 mL) and extracted with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*.

The residue was diluted with CH₂Cl₂ (300 mL) and to this were added sat. NaHCO₃ (100 mL), KBr

(3.5 g, 29 mmol) and TEMPO (0.91 g, 5.8 mmol). To the mixture was added aqueous NaOCl (0.35 L, > 5.0% as available chlorine) at 0 °C. After stirring at 0 °C for 1 h, the mixture was poured into water (100 mL) and extracted with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*.

A mixture of the residue and Et₃N (81 mL, 0.59 mol) in THF (300 mL) was heated at 50 °C for 2 h. After cooling to room temperature, the mixture was poured into water (300 mL). The mixture was extracted with Et₂O and the combined organic layers were washed with water and brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was recrystallized from cold hexane to give the title compound **75** (41 g, 0.18 mol, 62%) as white solid. The filtrate was evaporated and purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 20:1 to 2:1) to afford the title compound **75** (10 g, 44 mmol, 15%). Total 51 g, 77% yield. Mp 68.7–69.0 °C; ¹H NMR (400 MHz, CDCl₃) δ: 6.19–6.15 (m, 1H), 4.47 (s, 2H), 2.59–2.53 (m, 2H), 2.47–2.42 (m, 2H), 0.93 (s, 9H), 0.10 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ: 209.2, 181.4, 128.3, 63.2, 35.0, 27.8, 25.7, 18.2, -5.5; IR (KBr): 2957, 2929, 1699, 1626, 1432, 1265, 1142, 1077, 852, 843, 777 cm⁻¹; MS (CI⁺) *m/z* 227 ((M+H)⁺); HRMS (CI⁺): *m/z* calcd for C₁₂H₂₃O₂Si, 227.1467 [M+H]⁺; found 227.1470.

5-4-4. (3*S*)-3-(*tert*-Butyldimethylsilyloxy)methylcyclopentan-1-one [(*S*)-**61**]



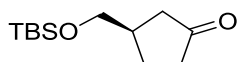
A mixture of Cu(OAc)₂·H₂O (8.8 mg, 0.044 mmol, Kanto Chemical) and (*S*)-DTBM-SEGPHOS (52 mg, 0.044 mmol, STREM CHEMICALS) in degassed toluene (5.0 mL) was purged with Ar thoroughly, and stirred at room temperature for 2 h under Ar atmosphere. To this was added PMHS (0.53 mL, 8.8 mmol, Alfa Aesar) and the resulting mixture was stirred at room temperature for 1 h. Separately, a solution of **75** (1.0 g, 4.4 mmol) in degassed toluene (6.0 mL) was purged with Ar thoroughly and this substrate solution was added to the above solution of reagents by cannula. The resulting mixture was stirred at room temperature for 3 h. The reaction was diluted with THF (5.0 mL) and quenched by adding aqueous NaOH solution (3.0 M, 5.0 mL). After stirring at room temperature for 2 h, the reaction mixture was poured into water (5.0 mL) and extracted with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 1:0 to 4:1) to afford the title compound (*S*)-**61** (0.97 g, 4.2 mmol, 96% yield, 95.2% ee) as a colorless oil. [α]_D²⁵ = -37.3 (*c* 1.06, CHCl₃); ¹H NMR, ¹³C NMR and IR are same as (±)-**61**. MS (ESI) *m/z* 229 (M+H)⁺; HRMS (ESI): *m/z* calcd for C₁₂H₂₅O₂Si, 229.1624 [M+H]⁺; found 229.1621.

The enantiopurity was determined after conversion of the obtained **61** into its benzoyl ester as follows.

To a solution of **61** (0.30 g, 1.3 mmol) in THF (4.0 mL) was added TBAF (1.0 M in THF, 1.6 mL, 1.6

mmol) and the mixture was stirred at room temperature for 1 h. To the resulting mixture were successively added DMAP (19 mg, 0.16 mmol), Et₃N (0.95 mL, 6.8 mmol) and BzCl (0.46 mL, 3.9 mmol) and the mixture was stirred at room temperature overnight. The reaction mixture was poured into water and extracted with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, *n*-hexane/CH₂Cl₂ 1:1 to 0:1 to CH₂Cl₂/EtOAc 95:5) to afford the benzoyl ester (0.27 g, 1.3 mmol, 96%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.03 (d, 2H, *J* = 6.6 Hz), 7.62–7.54 (m, 1H), 7.51–7.41 (m, 2H), 4.48–4.22 (m, 2H), 2.82–2.65 (m, 1H), 2.55–2.18 (m, 4H), 2.12 (dd, 1H, *J* = 17.8, 10.0 Hz), 1.89–1.75 (m, 1H). The enantiopurity was determined by HPLC with a Chiralpak OJ column (4.6φ x 150 mm); eluent, 80 : 20 *n*-hexane-ethanol mixture; flow rate, 1.5 mL/min; *t_R* of (*S*)-isomer, 8.1 min; *t_R* of (*R*)-isomer, 7.2 min), 25 °C, UV 210 nm.

5-4-5. (3*R*)-3-(*tert*-Butyldimethylsilyloxy)methylcyclopentan-1-one [(*R*)-**61**]



The title compound (*R*)-**61** (0.93 g, 4.1 mmol, 92% yield, 95.3% ee) as a colorless oil was synthesized by conducting a reaction similar to the one mentioned in 4.5 using Cu(OAc)₂·H₂O (8.8 mg, 0.044 mmol), (*R*)-DTBM-SEGPHOS (52 mg, 0.044 mmol) and PMHS (0.53 mL, 8.8 mmol) in toluene (5 mL) and **75** (1.0 g, 4.42 mmol) in toluene (6 mL). [α]_D²⁵ = +36.8 (*c* 1.07, CHCl₃); ¹H NMR, ¹³C NMR and IR are the same as (*R,S*)-**61**. MS (CI⁺) *m/z*: 229 ((M+H)⁺); HRMS (CI⁺): *m/z* calcd for C₁₂H₂₅O₂Si, 229.1624 [M+H]⁺; found 229.1617.

5-4-6. A mixture of (3*S*)-3-[(*tert*-butyldimethylsilyloxy)methyl]cyclopent-1-en-1-yl trifluoromethanesulfonate and (4*S*)-4-[(*tert*-butyldimethylsilyloxy)methyl]cyclopent-1-en-1-yl trifluoromethanesulfonate (**76**)

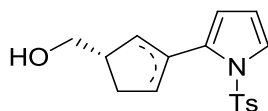


To a solution of NaHMDS (1.0 M in THF, 122 mL, 122 mmol) in THF (60 mL) was dropwise added a solution of (*S*)-**61** (23 g, 0.10 mmol, >95% ee) in THF (40 mL) at -78 °C. After stirring for 30 min at -78 °C, PhNTf₂ (38 g, 0.11 mol) was added. The resulting mixture was warmed to 0 °C and stirred for 1 h. The reaction was quenched by addition of sat. NH₄Cl (20 mL) at 0 °C. The mixture was poured into water (200 mL) and extracted with *n*-hexane. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (neutralized silica gel, *n*-hexane/EtOAc 50:1 to 20:1) to afford the title

compound **76** (33 g, 91 mmol, 91%). ^1H NMR (400 MHz, CDCl_3) δ : 5.65–5.59 (m, 0.7H), 5.59–5.53 (m, 0.3H), 3.68–3.39 (m, 2H), 2.98–2.86 (m, 0.7H), 2.70–2.35 (m, 2.6H), 2.22–2.04 (m, 1H), 1.78–1.66 (m, 0.7H), 0.89 (s, 9H), 0.05 (s, 6H).

5-4-7. A mixture of

[(1*S*)-3-{1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-2-yl}cyclopent-2-en-1-yl]methanol and [(1*S*)-3-{1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-2-yl}cyclopent-3-en-1-yl]methanol (**77**)

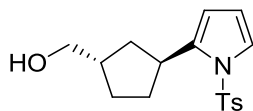


A mixture of **76** (19 g, 52 mmol), 1-(*p*-toluenesulfonyl)pyrrole-2-boronic acid pinacol ester (20 g, 58 mmol), $\text{Pd}(\text{PPh}_3)_4$ (1.8 g, 1.6 mmol) and K_2CO_3 (15 g, 0.11 mmol) in water (50 mL) and 1,4-dioxane (100 mL) was heated at 50 °C for 1 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with Et_2O . The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered with Celite pad and concentrated *in vacuo*. The residue was purified by flash column chromatography (neutralized silica gel, *n*-hexane/ EtOAc 50:1 to 10:1) and concentrated *in vacuo* to afford the TBS-protected precursor of **77** quantitatively as a light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ : 7.55 (d, 2H, J = 8.2 Hz), 7.37–7.33 (m, 1H), 7.22 (dd, 2H, J = 8.2, 2.5 Hz), 6.22 (t, 1H, J = 3.3 Hz), 6.11–6.05 (m, 1H), 5.84–5.80 (m, 0.7H), 5.80–5.77 (m, 0.3H), 3.57–3.45 (m, 2H), 2.98–2.88 (m, 0.7H), 2.60–2.40 (m, 2.3H), 2.38 (s, 3H), 2.28–2.17 (m, 0.6H), 2.04–1.94 (m, 0.7H), 1.65–1.55 (m, 0.7H), 0.91 (s, 6.3H), 0.89 (s, 2.7H), 0.07 (s, 2.1H), 0.06 (s, 2.1H), 0.05 (s, 0.9H), 0.04 (s, 0.9H); MS (FAB $^+$) m/z 432 ((M+H) $^+$).

Deprotection of the TBS group into **77** was conducted as follows.

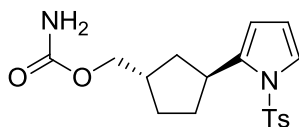
To a solution of the obtained product in THF (200 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 100 mL, 100 mmol), and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water (100 mL) and extracted with EtOAc . The combined organic layers were washed with water and brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (neutralized silica gel, *n*-hexane/ EtOAc 4:1 to 1:1) to afford the title compound **77** (16 g, 51 mmol, 98%) as a light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ : 7.54 (d, 2H, J = 8.2 Hz), 7.40–7.35 (m, 0.7H), 7.35–7.30 (m, 0.3H), 7.24 (d, 2H, J = 8.2 Hz), 6.25 (t, 0.7H, J = 3.3 Hz), 6.23 (t, 0.3H, J = 3.3 Hz), 6.15–6.11 (m, 0.7H), 6.09–6.05 (m, 0.3H), 5.82–5.78 (m, 0.7H), 5.76–5.72 (m, 0.3H), 3.69–3.50 (m, 2H), 3.06–2.96 (m, 0.7H), 2.70–2.40 (m, 2.6H), 2.39 (s, 3H), 2.33–2.22 (m, 0.3H), 2.12–2.00 (m, 0.7H), 1.80–1.69 (m, 0.7H), 1.51 (br s, 1H); MS (FAB $^+$) m/z 318 ((M+H) $^+$).

5-4-8. [(1*S*,3*S*)-3-{1-[(4-Methylphenyl)sulfonyl]-1*H*pyrrol-2-yl}cyclopentyl]methanol (**78**)



A solution of **77** (16 g, 51 mmol) and Crabtree's catalyst (1.3 g, 1.5 mmol) in CH₂Cl₂ (1000 mL) was degassed and saturated with hydrogen gas, and the mixture was stirred at room temperature for 7.5 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (neutralized silica gel, *n*-hexane/EtOAc 2:1 to 1:1) to afford the title compound **78** (16 g, 49 mmol, 95%) as an orange oil in the diastereomeric ratio of 15 to 1. ¹H NMR (400 MHz, CDCl₃) δ: 7.60 (dd, 2H, *J* = 8.6, 2.0 Hz), 7.28 (dd, 2H, *J* = 8.6, 2.2 Hz), 7.28–7.25 (m, 1H), 6.21 (t, 1H, *J* = 3.3 Hz), 6.09–6.03 (m, 1H), 3.57–3.46 (m, 2H), 3.38 (quint, 1H, *J* = 8.2 Hz), 2.41 (s, 3H), 2.33–2.05 (m, 1H), 1.98–1.85 (m, 2H), 1.75–1.46 (m, 4H), 1.37–1.27 (m, 1H); MS (FAB⁺) *m/z*: 320 ((M+H)⁺).

5-4-9. [(1*S*,3*S*)-3-{1-[(4-Methylphenyl)sulfonyl]-1*H*pyrrol-2-yl}cyclopentyl]methyl carbamate (**79**)



To a solution of **78** (16 g, 49 mmol) in CH₂Cl₂ (200 mL) was added trichloroacetyl isocyanate (7.0 mL, 59 mmol) at 0 °C. After stirring for 30 min at 0 °C, the mixture was concentrated *in vacuo*. The residue was diluted with MeOH (300 mL) and THF (100 mL). To this were added water (50 mL) and K₂CO₃ (34 g, 0.24 mol) at 0 °C and the mixture was warmed to room temperature. After stirring for 2 h, the mixture was filtered with Celite pad and the filtrate was concentrated *in vacuo*. The residue was poured into water (100 mL) and the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (neutralized silica gel, *n*-hexane/EtOAc 2:1 to 1:1) to afford the title compound **79** quantitatively as a light yellow oil in the diastereomeric ratio of 15 to 1. ¹H NMR (400 MHz, CDCl₃) δ: 7.61 (d, 2H, *J* = 8.6 Hz), 7.32–7.23 (m, 3H), 6.20 (t, 1H, *J* = 3.3 Hz), 6.08–6.02 (m, 1H), 4.59 (br s, 2H), 3.94 (d, 2H, *J* = 6.6 Hz), 3.45 (quint, 1H, *J* = 8.2 Hz), 2.42–2.15 (m, 1H), 2.41 (s, 3H), 1.98–1.86 (m, 2H), 1.73–1.45 (m, 3H), 1.37–1.25 (m, 1H); MS (FAB⁺) *m/z*: 363 ((M+H)⁺).

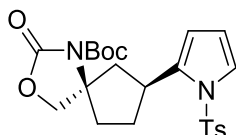
5-4-10. (5*R*,7*S*)-7-{1-[(4-Methylphenyl)sulfonyl]-1*H*pyrrol-2-yl}-3-oxa-1-azaspiro[4.4]nonan-2-one

(80)

A mixture of **79** (18 g, 49 mmol), PhI(OAc)₂ (20 g, 63 mmol), MgO (4.5 g, 0.11 mol) and Rh₂(esp)₂ (1.9 g, 2.4 mmol) in anhydrous benzene (500 mL) was heated at 60 °C for 1 h. After cooling to room temperature, the reaction mixture was filtered with Celite pad. The filtrate was poured into water (100 mL) and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was suspended in EtOH-*n*-hexane = 1:1 (100 mL) and the resulting brown solid was filtered off to afford the crude product of the title compound **80** (9.7 g). The filtrate was concentrated *in vacuo* and purified by flash column chromatography (neutralized silica gel, CH₂Cl₂/EtOAc 5:1 to 3:1) to afford the title compound **80** (3.0 g) as a white solid. Total 13 g, 72% yield in the diastereomeric ratio of 15 to 1. ¹H NMR (400 MHz, CDCl₃) δ: 7.56 (dd, 2H, *J* = 8.6, 2.0 Hz), 7.33–7.24 (m, 3H), 6.24 (t, 1H, *J* = 3.5 Hz), 6.12–6.02 (m, 1H), 5.21 (br s, 1H), 4.22 (s, 2H), 3.59–3.36 (m, 1H), 2.42 (s, 3H), 2.17 (dd, 1H, *J* = 13.5, 7.6 Hz), 2.10–1.99 (m, 2H), 1.92–1.64 (m, 3H); MS (FAB⁺) *m/z* 361 ((M+H)⁺). Recrystallization of the obtained product (0.50 g) from ethanol (22 mL) provided a single crystal of **80** (0.31 mg, 62% recovery rate). Crystal data: C₁₈H₂₀N₂O₄S, monoclinic, space group *P*2₁, *a* = 9.2722(3) Å, *b* = 7.6497(2) Å, *c* = 12.4878(4) Å, β = 106.365(2)°, *V* = 849.86(4) Å³, *Z* = 2, *D*_c = 1.408 g/cm³, μ(Cu-Kα) = 19.219 cm⁻¹. The number of reflections collected at 93 K was 9155, of which 3025 were independent and used for structure refinement with *R*₁ = 0.0339, *wR*₂ = 0.0864, and Flack parameter = -0.015(15).

5-4-11. *tert*-Butyl

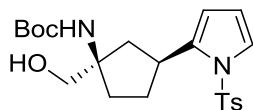
(5*R*,7*S*)-7-{1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-2-yl}-2-oxo-3-oxa-1-azaspiro[4.4]nonane-1-carboxylate (**81**)



To a solution of **80** (13 g, 35 mmol) in CH₂Cl₂ (350 mL) were added Et₃N (12 mL, 88 mmol), Boc₂O (14 g, 63 mmol) and DMAP (0.43 g, 3.5 mmol). The mixture was stirred at room temperature for 1 h and the reaction was quenched by the addition of water (10 mL). The resulting mixture was poured into water (100 mL) and extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (neutralized silica gel, *n*-hexane/EtOAc 5:1 to 2:1) to afford the title compound **81** (12 g, 25 mmol, 71%) as a white solid in the diastereomeric ratio of 15 to 1. ¹H NMR (400 MHz, CDCl₃) δ: 7.55 (d, 2H, *J* = 8.5 Hz), 7.33–7.24 (m, 3H), 6.27–6.23 (m, 1H), 6.22–6.16 (m, 1H), 4.09 (d, 1H, *J* = 8.3 Hz), 3.99 (d, 1H, *J* = 8.3 Hz), 3.32–3.21 (m, 1H), 2.60–2.52 (m, 1H), 2.42 (s, 3H), 2.18 (t, 1H, *J* = 12.5 Hz), 2.00–1.88 (m, 3H), 1.70–1.60 (m, 1H), 1.55 (s, 9H).

5-4-12. *tert*-Butyl

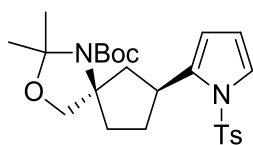
[(1*R*,3*S*)-1-(hydroxymethyl)-3-{1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-2-yl}cyclopentyl]carbamate (82)



To a solution of **81** (12 g, 25 mmol) in MeOH (150 mL), THF (50 mL) and water (25 mL) was added K₂CO₃ (17 g, 0.13 mol) and the mixture was stirred at room temperature for 2 h and 15 min. The reaction mixture was filtered with Celite pad. The filtrate was concentrated *in vacuo* and the residue was diluted with Et₂O. The mixture was poured into water (100 mL) and extracted with Et₂O. The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 10:0 to 1:1) to afford the title compound **82** (10 g, 24 mmol, 94%) as a white solid in the diastereomeric ratio of 15 to 1. ¹H NMR (400 MHz, CDCl₃) δ: 7.59 (d, 2H, *J* = 8.2 Hz), 7.30–7.27 (m, 3H), 6.22 (t, 1H, *J* = 3.3 Hz), 6.13–6.10 (m, 1H), 4.84–4.74 (br s, 1H), 3.75–3.56 (m, 3H), 3.43–3.35 (m, 1H), 2.41 (s, 3H), 2.24 (dd, 1H, *J* = 13.3, 7.8 Hz), 2.02–1.92 (m, 1H), 1.92–1.81 (m, 2H), 1.80–1.72 (m, 1H), 1.60–1.55 (m, 1H), 1.43 (s, 9H); MS (FAB⁺) *m/z*: 435 ((M+H)⁺).

5-4-13. *tert*-Butyl

(5*R*,7*S*)-2,2-dimethyl-7-{1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-2-yl}-3-oxa-1-azaspiro[4.4]nonane-1-carboxylate (83)

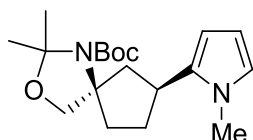


To a solution of **82** (10 g, 24 mmol) in CH₂Cl₂ (240 mL) were successively added 2,2-dimethoxypropane (29 mL, 240 mmol) and BF₃·Et₂O (0.30 mL, 2.4 mmol) at 0 °C. The resulting mixture was warmed to room temperature and stirred at room temperature for 45 min. After cooling to 0 °C again, the reaction was quenched with sat. NaHCO₃ (50 mL). The resulting mixture was poured into water (50 mL) and extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (neutralized silica gel, *n*-hexane/EtOAc 10:1 to 5:1). A diastereomerically impure part was purified by additional column chromatography, repeatedly (total of three times).

Those obtained were combined to afford the title compound **83** (10 g, 21 mmol, 90%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ : 7.60–7.54 (m, 2H), 7.31–7.24 (m, 3H), 6.27–6.07 (m, 2H), 3.76–3.71 (m, 1H), 3.67–3.63 (m, 1H), 3.18–3.07 (m, 1H), 2.48–2.30 (m, 1H), 2.40 (s, 3H), 2.12–1.66 (m, 4H), 1.53–1.41 (m, 16H); MS (FAB $^+$) m/z : 474 (M^+).

5-4-14. *tert*-Butyl

(5*R*,7*S*)-2,2-dimethyl-7-(1-methyl-1*H*-pyrrol-2-yl)-3-oxa-1-azaspiro[4.4]nonane-1-carboxylate (**60**)



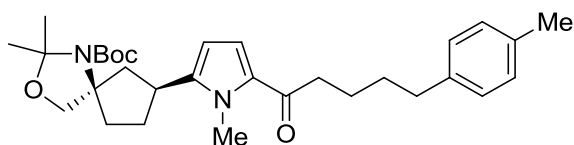
To a solution of **83** (10 g, 21 mmol) in EtOH (250 mL) and 1,4-dioxane (150 mL) was added aqueous NaOH solution (5.0 M, 0.17 L, 0.85 mol). The mixture was stirred at reflux for 48 h. After cooling to room temperature, the organic solvent was removed *in vacuo* and the mixture was extracted with Et₂O. The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (neutralized silica gel, *n*-hexane/EtOAc 8:1 to 4:1) to afford the detosylated precursor (6.6 g, 21 mmol, 98%) as a white solid.

^1H NMR (400 MHz, CDCl_3) δ : 9.37 (br s, 1H), 6.70 (br s, 1H), 6.17–6.06 (m, 1H), 5.97–5.87 (m, 1H), 3.87–3.69 (m, 2H), 3.22–2.77 (m, 1H), 2.61–2.31 (m, 2H), 2.21–1.82 (m, 3H), 1.67–1.44 (m, 16H); MS (FAB $^+$) m/z : 320 (M^+).

To a solution of KHMDS (0.50 M in toluene, 46 mL, 23 mmol) in THF (70 mL) was dropwise added a solution of the obtained precursor (6.6 g, 21 mmol) in THF (30 mL) at -78 °C. After stirring for 25 min at -78 °C, MeI (2.2 mL, 35 mmol) was added and the mixture was stirred for 25 min. The resulting mixture was warmed to room temperature and stirred for 1 h. After cooling to 0 °C, the reaction was quenched with sat. NH₄Cl (30 mL). The resulting mixture was poured into water (70 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (neutralized silica gel, *n*-hexane/EtOAc 10:1 to 5:1) to afford the title compound **60** (6.8 g, 20 mmol, 98%) as a white solid. Mp 97.3–98.9 °C; $[\alpha]^{25}_{\text{D}} = -52.2$ (c 1.05, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ : 6.54 (br s, 1H), 6.10–5.93 (m, 2H), 3.88–3.70 (m, 2H), 3.56 (m, 3H), 2.83–2.73 (m, 1H), 2.61–1.90 (m, 5H), 1.69–1.43 (m, 16H); IR (KBr): 2969, 2869, 1681, 1387, 1091, 1063, 853, 727 cm^{-1} ; MS (ESI) m/z : 335 ($(\text{M}+\text{H})^+$); HRMS (ESI): m/z calcd for C₁₉H₃₁N₂O₃, 335.2335 $[\text{M}+\text{H}]^+$; found 335.2328.

5-4-15. *tert*-Butyl

(5*R*,7*S*)-2,2-dimethyl-7-{1-methyl-5-[5-(4-methylphenyl)pentanoyl]-1*H*-pyrrol-2-yl}-3-oxa-1-azaspiro[4.4]nonane-1-carboxylate (85**)**



Preparation of 5-(p-tolyl)pentanoyl chloride

To a mixture of *p*-tolualdehyde (4.0 g, 33 mmol) and (3-carboxypropyl)triphenylphosphonium bromide (17 g, 40 mmol) in CH₂Cl₂ (41 mL) was dropwise added a solution of *t*-BuOK (9.3 g, 83 mmol) in THF (83 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 20 h. After cooling to 0 °C, the reaction was quenched with water (300 mL) and washed with CH₂Cl₂. The aqueous phase was acidified with conc. HCl and extracted with Et₂O. The combined organic layers were washed with water and brine, dried over MgSO₄, filtered and concentrated *in vacuo* to afford 5-(*p*-tolyl)pent-4-enoic acid (5.8 g, 31 mmol, 92%) as a light yellow solid, which was used for the next step without further purification.

A solution of the 5-(*p*-tolyl)pent-4-enoic acid (5.8 g, 31 mmol) and 10% Pd-C (0.58 g, 50% wet) in EtOH (120 mL) was degassed and saturated with hydrogen gas and the mixture was stirred at 50 °C for 6 h. The reaction mixture was filtered with Celite pad and concentrated *in vacuo* to afford 5-(*p*-tolyl)pentanoic acid (5.6 g, 29 mmol, 96%).

To a mixture of 5-(*p*-tolyl)pentanoic acid (1.7 g, 9.0 mmol) in toluene (18 mL) were successively added SOCl₂ (1.3 mL, 18 mmol) and DMF (0.090 mL). After stirring at 80 °C for 2 h, the reaction mixture was azeotropically evaporated *in vacuo* with toluene twice to afford the crude product of 5-(*p*-tolyl)pentanoyl chloride which was used for the next step without further purification.

*Preparation of **85***

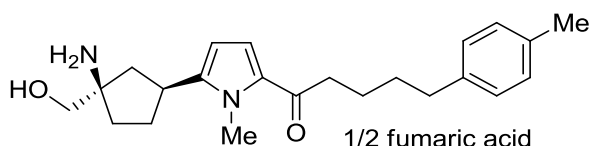
To a solution of **60** (1.0 g, 3.0 mmol) in toluene (6.0 mL) and acetonitrile (6.0 mL) was added 1-Me-imidazole (0.73 mL, 9.3 mmol). The mixture was stirred and warmed to 80 °C. To this was dropwise added a solution of the crude 5-(*p*-tolyl)pentanoyl chloride (9.0 mmol) in acetonitrile (3.0 mL) and toluene (3.0 mL) at 80 °C. The resulting mixture was stirred at 80 °C for 17 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with Et₂O. The combined organic layers were washed with sat. NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 100:0 to 60:40) to afford 2.37 g of the enol ester **84** as a brown oil.

To a solution of the obtained **84** in THF (18 mL) and MeOH (18 mL) was added 5.0 M NaOH (6.0 mL, 30 mmol). The mixture was stirred at 60 °C for 2 h. The organic solvent was removed *in vacuo* and the resulting mixture was extracted with Et₂O. The combined organic layers were washed with

aqueous 1 M NaOH, water and brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 100:0 to 65:35) to afford the title compound **85** (1.3 g, 0.26 mmol, 88% in 2 steps) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ: 7.23 (s, 2H), 7.09–7.05 (m, 1H), 7.07 (s, 2H), 6.93–6.90 (m, 1H), 6.11 (br s, 0.5H), 5.99 (br s, 0.5H), 3.88 (s, 3H), 3.87–3.81 (m, 1H), 3.78–3.72 (m, 1H), 2.86–2.76 (m, 1H), 2.74 (t, 2H, *J* = 7.3 Hz), 2.60 (t, 2H, *J* = 7.6 Hz), 2.77–2.27 (m, 2H), 2.30 (s, 3H), 2.20–1.94 (m, 4H), 1.78–1.47 (m, 18H).

5-4-16.

1-{5-[(1*S*,3*R*)-3-Amino-3-(hydroxymethyl)cyclopentyl]-1-methyl-1*H*-pyrrol-2-yl}-5-(4-methylphenyl)pentan-1-one hemifumarate (59**)**



To a solution of **85** (1.3 g, 2.6 mmol) in CH₂Cl₂ (26 mL) was added TFA (6.1 mL, 79 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. To this was added water (13 mL) and the mixture was stirred at room temperature for 23 h. The reaction mixture was azeotropically evaporated *in vacuo* with toluene. The residue was diluted with CH₂Cl₂ and basified with aqueous 1.0 M NaOH. The resulting mixture was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (neutralized silica gel, CH₂Cl₂/MeOH/Et₃N 20:1:0 to 10:1:0 to 10:1:0.05) to afford the free amine of **59** (0.59 g, 1.6 mmol, 60%).

To a solution of the free amine (0.59 g, 1.6 mmol) in EtOAc (4.0 mL) and MeOH (4.0 mL) was added fumaric acid (92 mg, 0.80 mmol). To this was added EtOAc (12 mL) and the mixture was stirred for 30 min. The precipitated powder was filtered off to give **59** (0.65 g, 1.5 mmol, 95%). Mp (dec.) 190.7 °C; [α]_D²⁵ = -36.1 (*c* 1.07, AcOH); ¹H NMR (500 MHz, CD₃CO₂D) δ: 7.07 (d, 1H, *J* = 4.3 Hz), 7.04 (s, 4H), 6.89 (s, 1H), 6.13 (d, 1H, *J* = 4.3 Hz), 3.87 (s, 3H), 3.84 (br s, 2H), 3.26–3.17 (m, 1H), 2.79 (t, 2H, *J* = 7.4 Hz), 2.58 (t, 2H, *J* = 7.4 Hz), 2.50 (dd, 1H, *J* = 13.6, 7.1 Hz), 2.26 (s, 3H), 2.22–2.12 (m, 2H), 2.02–1.90 (m, 3H), 1.74–1.61 (m, 4H); ¹³C NMR (125 MHz, CD₃CO₂D) δ: 193.7, 169.9, 146.5, 140.2, 136.0, 135.4, 131.7, 129.9, 129.2, 121.9, 106.7, 66.0, 65.6, 40.1, 39.8, 36.8, 36.0, 33.8, 33.6, 32.2, 31.6, 26.9, 21.1; IR (KBr): 3370, 3271, 2957, 2937, 2872, 1643, 1563, 1548, 1485, 1451, 1373, 1070, 1053, 814, 757, 666 cm⁻¹; MS (ESI) *m/z* 369 ((M+H)⁺); HRMS (ESI): *m/z* calcd for C₂₃H₃₃N₂O₂, 369.2542 [M+H]⁺; found 369.2536.

5-5. 薬理評価

5-5-1. *In Vitro* Agonist-evoked GTP γ S Binding assay

To measure the functional activation of the S1P receptors, an agonist stimulation of *in vitro* [³⁵S] GTP γ S binding assay was performed as follows. The membrane was homogenized from CHO cells expressing rat S1P₁, rat S1P₃, human S1P₁ or human S1P₃, respectively, with assay buffer (5 mM Tris-HCl, pH7.4, 0.25 M sucrose, 1 mM EDTA, 1 mM EGTA) and centrifuged at 100,000 x g for 60 min at 4 °C. For *in vitro* [³⁵S] GTP γ S binding assay, serial dilutions of test compounds were added to aliquots (1 to 10 μ g protein/well) of the membrane and assayed as described in reference [67].

5-5-2. Counting of peripheral lymphocytes

Lewis rats (male, 5 weeks of age, Charles River Japan Inc.) were used. Five rats/ group were used. The compound was suspended in 1% (w/v) methyl cellulose #400 solution (vehicle). Suspended solution of the compound was orally administered to rats at a volume of 5 ml/kg. In control rats, vehicle instead of the suspended solution of the compound was orally administered. Blood was collected from the postcaval vein of the rats under ether anesthesia at the indicated time in Figure 2.5. Then, the collected blood was placed into a tube containing EDTA. The absolute number of lymphocytes in the blood collected was counted using a full blood count analyzer.

5-5-3. Evaluation of inhibitory activities against Host versus Graft Reaction in rats (HvGR)

Two strains of rats [Lewis rats (male, 6 weeks of age, Charles River Japan Inc.) and WKAH/Hkm rats (male, 7 weeks of age, Japan SLC Inc.)] were used. Five rats per group were used.

Induction of HvGR

Splenocytes were isolated from the spleens of WKAH/Hkm and Lewis rats and suspended in RPMI1640 medium (Life Technologies Inc.) at a concentration of 1×10^8 cells/mL. A 0.1 mL of the medium which contains the free-floating spleen cells (1×10^7 of cells) of WKAH/Hkm rats or Lewis rats was then intracutaneously injected into the bilateral foot-pads of hindlimbs of Lewis rats.

Administration of test compound

Test compounds were suspended in 0.5% tragacanth solution. The suspended compounds were orally administered to rats in 'the drug-treated group' (Lewis rats injected with spleen cells of WKAH/Hkm rats and treated with the compound) at a volume of 5 mL/kg once daily for 4 successive days starting on the day of spleen cell injection. Furthermore, the tragacanth solution (0.5%), instead of the test compound, was orally administered to rats in 'the syngeneic group' (Lewis rats injected with spleen cells of Lewis rats) and 'the control group' (Lewis rats injected with spleen cells of WKAH/Hkm rats and not treated with the compound).

Determination of inhibitory activity against HvGR

The average weight of the popliteal lymph nodes of 'the syngeneic group' was subtracted from individual weights of the popliteal lymph nodes of individual rats ('HvGR-induced changes in weight of the popliteal lymph nodes').

The inhibitory activities of compounds were calculated from the 'HvGR-induced changes in weight of the popliteal lymph nodes' of individual rats in the drug-treated group versus the average 'HvGR-induced changes in weight of the popliteal lymph nodes' in the control group.

The inhibitory activities of compounds were expressed as ID₅₀ values (mg/kg) as calculated by the least squares method based on the doses of compounds administered and inhibitory activities at these doses.

5-5-4. Evaluation of antiarthritic activity

Lewis rats aged 8 weeks were used for the study. Heat-killed dried *Mycobacterium butyricum* were ground on an agate mortar and then suspended in dry-sterilized liquid paraffin to make a 2 mg/mL suspension. The resulting suspended solution was then sonicated and used as adjuvant. Arthritis was induced by intradermal injection of the prepared adjuvant (0.05 mL) into the foot pad of the right hindlimb of rats in the compound-treated group and in the control group. Rats that were not treated with adjuvant were separately used as normal control group. The compound was suspended in 1% (w/v) methyl cellulose #400 solution and orally administered to rats in the compound-treated group at a volume of 5 mL/kg once daily from the injection day of the adjuvant (Day 0) for 18 successive days. To rats in the control groups 1% (w/v) methyl cellulose #400 solution alone was similarly administered. The right foot volume of each rat was measured by customized apparatus for determination of the volume at the indicated time in Figure 2.6. The mean swelled volume of each group was thus calculated. Percent inhibition of swelling of the injected foot of treated animals as compared with that of the control animals was calculated according to the following equation:

Percentage inhibition of swollen foot volume (%) = $\{1 - [(\text{swollen foot volume of animals treated with a compound}) - (\text{foot volume of normal control animals})] / [(\text{swollen foot volume of control animals}) - (\text{foot volume of normal control animals})]\} \times 100$

5-5-5. Evaluation of the suppressive effect on EAE in mice

M. tuberculosis H37 RA (Difco Laboratories) suspension (8 mg/mL) in incomplete Freund's adjuvant (Difco Laboratories) was mixed with myelin oligodendrocyte glycoprotein₃₅₋₅₅ (MOG₃₅₋₅₅, Peptide Institute, Inc.) (4 mg/mL solution) in physiological saline at equal volumes, and the mixture was emulsified with a sonicator on ice. C57BL/6J mice (female, 6 weeks of age, Japan SLC, Inc.) were immunized by subcutaneous injection of 50 µL of emulsion into each of the right and left axillae. After immunization on Day 0, 200 µL of pertussis toxin, *Bordetella pertussis* (PT, Calbiochem, 1 µg/mL solution) in physiological saline was injected via the tail vein. On Day 2, the same volume of PT

solution (1 µg/mL) was injected. Vehicle (1% (w/v) methyl cellulose #400 solution) or 0.1, 0.3 or 1 mg/kg compound was administered orally once daily from Day 0 to Day 23. The EAE score was evaluated daily from Day 7 to 24 using the following criteria: 0, normal; 1, flaccid tail; 2, hindlimb weakness; 3, paralysis of both hindlimbs; 4, quadriplegia; 5, dead (Mendel et al., 1995). The cumulative EAE score was calculated by summing up daily scores (Days 7 to 24).

5-6. 薬物動態等

5-6-1. Pharmacokinetics of CS-2100 (8b) in rats

Pharmacokinetics of CS-2100 (8b) in male Lewis rats was evaluated using an aliquot of blood collected at each time point in the blood lymphocyte count evaluation study (section 5-5-2). The blood was centrifuged to prepare plasma and the plasma concentration was measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS) system after solid phase extraction. The LC-MS/MS system consisted of a Prominence LC-20A system (Shimadzu Corp., Japan) and an API 5000 (Applied Biosystems/MDS SCIEX). The column used was a Capcell pak C₁₈ ACR (column size: 3.0 mm I.D. × 150 mm, particle size: 5 µm, Shiseido Co., Japan). Analysis was performed using WinNonlin™ (Pharsight, Palo Alto, CA) and parameters were estimated by noncompartmental analysis using mean concentration data from five animals for each time point.

5-6-2. Pharmacokinetics of CS-2100 (8b) in Mice

Male C57BL16J mice were orally dosed with CS-2100 (8b) as a solution in an independent experiment. CS-2100 (8b) was solubilized in dimethyl acetamide/25% (w/v) Purebright™ (NOF Corp., Japan) solution/ distilled water (1/8/1, v/v/v). Suspended solution of the compound was orally administered to mice at a volume of 5 mL/kg. Blood was collected from the inferior vena cava of the mice under ether anesthesia at the indicated time in Figure 2.8. All the other procedures were the same as aforementioned study in rats (section 5-6-1).

5-6-3. Evaluation of compound stabilities against enterobacterial decomposition

The stabilities were evaluated by the method of the reference [68], with some modifications. PYF broth was used instead of PYG. The cecal contents and feces were placed into the prereduced PYF broth instead of prereduced VPI buffer in the reference.

引用文献

- [1] Thudichum, J. L. W. *A Treatise on the Chemical Constitution of the Brain* 1884, Lontoo: Bailliere. New edition 1962, Archon Books, Hamden, Conneticut, USA.
- [2] For recent reviews on Sphingosine: (a) 蛋白質 酵素 核酸 43 卷 16 号 1998 年. (b) 蛋白質 酵素 核酸 47 卷 4 号 2002 年. 五十嵐靖之、平林義雄、小堤保則、鈴木明身編集：五十嵐靖之、平林義雄、小堤保則、鈴木明身「マイクロドメイン形成と細胞のシグナリング」共立出版 (c) Hakomori, S. In *Annual Review of Biochemistry*, vol. 50, P 733–764, 1981. (d) Merrill, Jr., A. H.; Sweely, C. C. *Sphingolipids: metabolism and cell signaling*; Elsevier Science: Amsterdam, 1996. (e) Hakomori, S. In *Sphingolipid Biochemistry*, Kanfer, J. N., Hakomori, S., Eds.; Plenum: New York, 1983, p 1–164. (f) Stults, C. L. M.; Sweely, C. C.; Machner, B. A. *Methods Enzymol.* **1989**, *50*, 167–214. (g) Schmidt, R. R. *Pure Appl. Chem.* **1989**, *61*, 1257–1270.
- [3] Synthetic review on D-erythro-Sphingosine: Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075–1091.
- [4] (a) Yatomi, Y.; Ruan, F.; Hakomori, S.; Igarashi, Y. *Blood* **1995**, *86*, 193–202. (b) Yatomi, Y.; Yamamura, S.; Ruan, F.; Igarashi, Y. *J. Biol. Chem.* **1997**, *272*, 5291–5297.
- [5] Yatomi, Y.; Igarashi, Y.; Hisano, N.; Qi, R.; Asazuma, N.; Satoh, K.; Ozaki, Y.; Kume, S. *J. Biochem.* **1997**, *121*, 969–973.
- [6] Pappu, R.; Schwab, S. R.; Cornelissen, I.; Pereira, J. P.; Regard, J. B.; Xu, Y.; Camerer, E.; Zheng, Y. W.; Huang, Y.; Cyster, J. G.; Coughlin, S. R. *Science* **2007**, *316*, 295–298.
- [7] 五十嵐靖之 生化学 **1997**, *69*, 1166–1185.
- [8] Lee, M.-J.; Van Brocklyn, J. R.; Thangada, S.; Liu, C. H.; Hand, A. R.; Menzeleev, R.; Spiegel, S.; Hla, T. *Science* **1998**, *279*, 1552–1555.
- [9] (a) Kon, J.; Sato, K.; Watanabe, T.; Tomura, H.; Kuwabara, A.; Kimura, T.; Tamama, K.; Ishizuka, T.; Murata, N.; Kanda, T.; Kobayashi, I.; Ohta, H.; Ui, M.; Okajima, F. *J. Biol. Chem.* **1999**, *274*, 23940–23947. (b) Van Brocklyn, J. R.; Tu, Z.; Edsall, L. C.; Schmidt, R. R.; Spiegel, S. *J. Biol. Chem.*

- 1999, 274, 4626–4632. (c) Yamazaki, Y.; Kon, J.; Sato, K.; Tomura, H.; Sato, M.; Yonega, T.; Okazaki, H.; Okajima, F.; Ohta, H. *Biochem. Biophys. Res. Commun.* **2000**, 268, 583–589. (d) Im, D.-S.; Heise, C. E.; Ancellin, N.; O'Dowd, B. F.; Shei, G.-j.; Heavens, R. P.; Rigby, M. R.; Hla, T.; Mandala, S.; McAllister, G.; George, S. R.; Lynch, K. R. *J. Biol. Chem.* **2000**, 275, 14281–14286.
- [10] Lee, M.-J.; Thangada, S.; Claffey, K. P.; Ancellin, N.; Liu, C. H.; Kluk, M.; Volpi, M.; Shaafi, R. I.; Hla, T. *Cell* **1999**, 99, 301–312.
- [11] Liu, Y.; Wada, R.; Yamashita, T.; Mi, Y.; Deng, C.-X.; Hobson, J. P.; Rosenfeldt, H. M.; Nava, V. E.; Chae, S.-S.; Lee, M.-J.; Liu, C. H.; Hla, T.; Spiegel, S.; Proia, R. L. *J. Clin. Invest.* **2000**, 106, 951–961.
- [12] (a) Ikeda, H.; Satoh, H.; Yanase, M.; Inoue, Y.; Tomiya, T.; Arai, M.; Tejima, K.; Nagashima, K.; Maekawa, H.; Yahagi, N.; Yatomi, Y.; Sakurada, S.; Takuwa, Y.; Ogata, I.; Kimura, S.; Fujiwara, K. *Gastroenterology* **2003**, 124, 459–469. (b) Ohmori, T.; Yatomi, Y.; Osada, M.; Kazama, F.; Takafuta, T.; Ikeda, H.; Ozaki, Y. *Cardiovascular Research* **2003**, 58, 170–177. (c) Osada, M.; Yatomi, Y.; Ohmori, T.; Ikeda, H.; Ozaki, Y. *Biochem. Biophys. Res. Comm.* **2002**, 299, 483–487.
- [13] Koide, Y.; Hasegawa, T.; Takahashi, A.; Endo, A.; Mochizuki, N.; Nakagawa, M.; Nishida, A. *J. Med. Chem.* **2002**, 45, 4629–4638.
- [14] (a) Guerrero, M.; Urbano, M.; Zhao, J.; Crisp, M.; Chase, P.; Hodder, P.; Schaeffer, M. T.; Brown, S.; Rosen, H.; Roberts, E. *Bioorg. Med. Chem. Lett.* **2012**, 22, 537–542. (b) Urbano, M.; Guerrero, M.; Zhao, J.; Velaparthi, S.; Schaeffer, M. T.; Brown, S.; Rosen, H.; Roberts, E. *Bioorg. Med. Chem. Lett.* **2011**, 21, 5470–5474. (c) Guerrero, M.; Urbano, M.; Velaparthi, S.; Zhao, J.; Schaeffer, M. T.; Brown, S.; Rosen, H.; Roberts, E. *Bioorg. Med. Chem. Lett.* **2011**, 21, 3632–3636.
- [15] (a) Roberts, E.; Guerrero, M.; Urbano, M.; Rosen, H. *Expert Opin. Ther. Patents* **2013**, 23, 817–841. (b) Adada, M.; Canals, D.; Hannun, Y. A.; Obeid, L. M. *FEBS Journal* **2013**, 280, 6354–6366. (c) Robert, P.; Tsui, P.; Laville, M. P.; Live, G. P.; Sarau, H. M.; Bril, A.; Berrebe-Bertrand, I. *J. Mol. Cell. Cardiol.* **2001**, 33, 1589–1606.
- [16] (a) Kluepfel, D.; Bagli, J. F.; Baker, H.; Charest, M. P.; Kudelski, A.; Sehgal, S. N.; Vézina, C. *J. Antibiot.* **1972**, 25, 109–115. (b) Bagli, J. F.; Kluepfel, D.; St-Jacques, M. *J. Org. Chem.* **1973**, 38,

1253–1260.

[17] (a) Craveri, R.; Manachini, P. L.; Aragazzini, F. *Experientia* **1972**, *28*, 867–868. (b) Just, G.; Payette, D. R. *Tetrahedron Lett.* **1980**, *21*, 3219–3222.

[18] Borel, J. F. In *Cyclosporin A*; Borel, J. F., Ed.; Elsevier Biochemical Press: Amsterdam, 1982, p.5–17

[19] (a) Kino, T.; Hatanaka, H.; Hashimoto, M.; Nishiyama, M.; Goto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 1249–1255. (b) Kino, T.; Hatanaka, H.; Miyata, S.; Inamura, N.; Nishiyama, M.; Yajima, T.; Goto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Ochiai, T. *J. Antibiot.* **1987**, *40*, 1256–1265.

[20] (a) Miyake, Y.; Kozutsumi, Y.; Nakamura, S.; Fujita, T.; Kawasaki, T. *Biochem. Biophysic. Res. Commun.* **1995**, *211*, 396–403. (b) 山地俊之、孫 一の、小堤 保則 蛋白質 核酸 酵素 **1998**, *43*, 2503–2509.

[21] (a) Yoshikawa, M.; Yokokawa, Y.; Okuno, Y.; Yagi, N.; Murakami, N. *Chem. Pharm. Bull.* **1995**, *43*, 1647–1653. (b) Fujita, T.; Yoneta, M.; Hirose, R.; Sasaki, S.; Inoue, K.; Kiuchi, M.; Hirase, S.; Adachi, K.; Arita, M.; Chiba, K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 847–852. (c) Fujita, T.; Hirose, R.; Hamamichi, N.; Kitao, Y.; Sasaki, S.; Yoneta, M.; Chiba, K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1857–1860.

[22] Adachi, K.; Kohara, T.; Nakao, N.; Arita, M.; Chiba, K.; Mishina, T.; Sasaki, S.; Fujita, T. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 853–856.

[23] (a) Chiba, K.; Hoshino, Y.; Suzuki, C. *Transplant. Proc.* **1996**, *28*, 1056–1059. (b) Chiba, K.; Yanagawa, Y.; Masubuchi, Y. *J. Immunol.* **1998**, *160*, 5037–5044. (c) Yanagawa, Y.; Sugahara, K.; Kataoka, H. *J. Immunol.* **1998**, *160*, 5493–5499. (d) Brinkmann, V.; Pinschewer, D. D.; Chiba, K. *Trends Pharmacol. Sci.* **2000**, *21*, 49–52.

[24] (a) Mandala, S.; Hajdu, R.; Bergstrom, J.; Quackenbush, E.; Xie, J.; Milligan, J.; Thornton, R.; Shei, G.; Card, D.; Keohane, C.; Rosenbach, M.; Hale, J.; Lynch, C. L.; Rupperecht, K.; Parsons, W.; Rosen, H. *Science* **2002**, *296*, 346–349. (b) Brinkmann, V.; Davis, M. D.; Heise, C. E.; Albert, R.;

- Cottens, S.; Hof, R.; Bruns, C.; Prieschl, E.; Baumruker, T.; Hiestand, P.; Foster, C. A.; Zollinger, M.; Lynch, K. R. *J. Biol. Chem.* **2002**, *277*, 21453–21457.
- [25] (a) Albert, R.; Hinterding, K.; Brinkmann, V.; Guerini, D.; Müller-Hartweg, C.; Knecht, H.; Simeon, C.; Streiff, M.; Wagner, T.; Welzenbach, K.; Zécri, F.; Zollinger, M.; Cooke, N.; Francotte, E. *J. Med. Chem.* **2005**, *48*, 5373–5377. (b) Kiuchi, M.; Adachi, K.; Tomatsu, A.; Chino, M.; Takeda, S.; Tanaka, Y.; Maeda, Y.; Sato, N.; Mitsutomi, N.; Sugahara, K.; Chiba, K. *Bioorg. Med. Chem.* **2005**, *13*, 425–432.
- [26] (a) Billich, A.; Bornancin, F.; Dévay, P.; Mechtcheriakova, D.; Urtz, N.; Baumruker, T. *J. Biol. Chem.* **2003**, *278*, 47408–47415. (b) Allende, M. L.; Sasaki, T.; Kawai, H.; Olivera, A.; Mi, Y.; Van Echeten-Deckert, G.; Hajdu, R.; Rosenbach, M.; Keohane, C. A.; Mandala, S.; Spiegel, S.; Proia, R. L. *J. Biol. Chem.* **2004**, *279*, 52487–52492.
- [27] (a) Sanna, M. G.; Liao, J.; Jo, E.; Alfonso, C.; Ahn, M.-Y.; Peterson, M. S.; Webb, B.; Lefebvre, S.; Chun, J.; Gray, N.; Rosen, H. *J. Biol. Chem.* **2004**, *279*, 13839–13848. (b) Forrest, M.; Sun, S.-Y.; Hajdu, R.; Bergstrom, J.; Card, D.; Doherty, G.; Hale, J.; Keohane, C.; Meyers, C.; Milligan, J.; Mils, S.; Nomura, N.; Rosen, H.; Rosenbach, M.; Shei, G.-J.; Singer, I. I.; Tian, M.; West, S.; White, V.; Xie, J.; Proia, R. L.; Mandala, S. *J. Pharm. Exp. Ther.* **2004**, *309*, 758–768.
- [28] (a) Urbano, M.; Guerrero, M.; Rosen, H.; Roberts, E. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6377–6389. (b) Dyckman, A. J. *Ann. Rep. Med. Chem.* **2012**, *47*, 195–207. (c) Martin, H. B.; Cyrille, L.; Oliver, N. *Curr. Top. Med. Chem.* **2011**, *11*, 726–757. (d) Buzard, D. J.; Thatte, J.; Lerner, M.; Edwards, J.; Jones, R. M. *Expert Opin. Ther. Patents* **2008**, *18*, 1141–1159.
- [29] 安達邦知 有機合成化学協会誌 **2011**, *69*, 904–912.
- [30] Chiba, K.; Yoshii, N. *Nippon Yakurigaku Zasshi* **2012**, *139*, 265–274.
- [31] Matloubian, M.; Lo, C. G.; Cinamon, G.; Lesneski, M. J.; Xu, Y.; Brinkmann, V.; Allende, M. L.; Proia, R. L.; Cyster, J. G. *Nature* **2004**, *427*, 355–360.
- [32] Schwab, S. R.; Pereira, J. P.; Matloubian, M.; Xu, Y.; Huang, Y.; Cyster, J. G. *Science* **2005**, *309*, 1735–1739.

- [33] Lo, C. G.; Xu, Y.; Proia, R. L.; Cyster, J. G. *J. Exp. Med.* **2005**, *201*, 291–301.
- [34] Jo, E.; Sanna, M. G.; Gonzalez-Cabrera, P. J.; Thangada, S.; Tigyi, G.; Osborne, D. A.; Hla, T.; Parrill, A. L.; Rosen, H. *Chemistry & Biology* **2005**, *12*, 703–715.
- [35] Chiba, K. *Pharmacol. Ther.* **2005**, *108*, 308–319.
- [36] (a) 吉良潤一 *CNS TODAY* **2012**, *February*, 18–27. (b) 吉良潤一編集 「多発性硬化症の診断と治療」 新興医学出版社 **2008**. (c) Sumino, R. *Nippon Yakurigaku Zasshi* **2007**, *129*, 209–217. (d) Kira, J. *Rinsho Shinkeigaku* **2009**, *49*, 549–559.
- [37] Pan, S.; Mi, Y.; Pally, C.; Beerli, C.; Chen, A.; Guerini, D.; Hinterding, K.; Nuesslein-Hildesheim, B.; Tuntland, T.; Lefebvre, S.; Liu, Y.; Gao, W.; Chu, A.; Brinkmann, V.; Bruns, C.; Streiff, M.; Cannet, C.; Cooke, N.; Gray, N. *Chem. Biol.* **2006**, *13*, 1227–1234.
- [38] Deng, Q.; Clemas, J. A.; Chrebet, G.; Fischer, P.; Hale, J. J.; Li, Z.; Mills, S. G.; Bergstrom, J.; Mandala, S.; Mosley, R.; Parent, S. A. *Mol. Pharmacol.* **2007**, *71*, 724–735.
- [39] Pham, T.-C. T.; Fells, J. I. Sr.; Osborne, D. A.; North, E. J.; Naor, M. M.; Parrill, A. L. *J. Mol. Graph. Model.* **2008**, *26*, 1189–1201.
- [40] Bolli, M. H.; Abele, S.; Binkert, C.; Bravo, R.; Buchmann, S.; Bur, D.; Gatfield, J.; Hess, P.; Kohl, C.; Mangold, C.; Mathys, B.; Menyhart, K.; Müller, C.; Nayler, O.; Scherz, M.; Schmidt, G.; Sippel, V.; Steiner, B.; Strasser, D.; Treiber, A.; Weller, T. *J. Med. Chem.* **2010**, *53*, 4198–4211.
- [41] Shimizu, H.; Takahashi, M.; Kaneko, T.; Murakami, T.; Hakamata, Y.; Kudou, S.; Kishi, T.; Fukuchi, K.; Iwanami, S.; Kuriyama, K.; Yasue, T.; Enosawa, S.; Matsumoto, K.; Takeyoshi, I.; Morishita, Y.; Kobayashi, E. *Circulation* **2005**, *111*, 222–229.
- [42] Pan, S.; Gray, N. S.; Gao, W.; Mi, Y.; Fan, Y.; Wang, X.; Tuntland, T.; Che, J.; Lefebvre, S.; Chen, Y.; Chu, A.; Hinterding, K.; Gardin, A.; End, P.; Heining, P.; Bruns, C.; Cooke, N. G.; Nuesslein-Hildesheim, B. *ACS Med. Chem. Lett.* **2013**, *4*, 333–337.
- [43] Xu, J.; Gray, F.; Henderson, A.; Hicks, K.; Yang, J.; Thompson, P.; Oliver, J. *Clinical Pharmacology in Drug Development* **2014**, *3*, 170–178.
- [44] Komiya, T.; Sato, K.; Shioya, H.; Inagaki, Y.; Hagiya, H.; Kozaki, R.; Imai, M.; Takada, Y.; Maeda,

- T.; Kurata, H.; Kurono, M.; Suzuki, R.; Otsuki, K.; Habashita, H.; Nakade, S. *Clin. Exp. Immunol.* **2013**, *171*, 54–62.
- [45] Nishi, T.; Miyazaki, S.; Takemoto, T.; Suzuki, K.; Iio, Y.; Nakajima, K.; Ohnuki, T.; Kawase, Y.; Nara, F.; Inaba, S.; Izumi, T.; Yuita, H.; Oshima, K.; Doi, H.; Inoue, R.; Tomisato, W.; Kagari, T.; Shimoizato, T. *ACS Med. Chem. Lett.* **2011**, *2*, 368–372.
- [46] Hale, J. J.; Lynch, C. L.; Neway, W.; Mills, S. G.; Hajdu, R.; Keohane, C. A.; Rosenbach, M. J.; Milligan, J. A.; Shei, G.-J.; Parent, S. A.; Chrebet, G.; Bergstrom, J.; Card, D.; Ferrer, M.; Hodder, P.; Strulovici, B.; Rosen, H.; Mandala, S. *J. Med. Chem.* **2004**, *47*, 6662–6665.
- [47] Kolakowski, L. F. Jr. *Recept. Channels* **1994**, *2*, 1–7.
- [48] (a) Archer, E.; Maigret, B.; Escrieut, C.; Pradayrol, L.; Fourmy, D. *Trends Pharmacol. Sci.* **2003**, *24*, 36–40. (b) Bosch, L.; Iarriccio, L.; Garriga, P. *Curr. Pharm. Des.* **2005**, *11*, 2243–2256. (c) Fanelli, F.; De Benedetti, P. G. *Chem. Rev.* **2005**, *105*, 3297–3351. (d) Meng, E. C.; Bourne, H. R. *Trends Pharmacol. Sci.* **2001**, *22*, 587–593.
- [49] (a) Parrill, A. L.; Wang, D.; Bautista, D. L.; Brocklyn, J. R. V.; Lorincz, Z.; Fischer, D. J.; Baker, D. L.; Liliom, K.; Spiegel, S.; Tigyi, G. *J. Biol. Chem.* **2000**, *275*, 39379–39384. (b) Deng, Q.; Clemas, J. A.; Chrebet, G.; Fischer, P.; Hale, J. J.; Li, Z.; Mills, S. G.; Bergstrom, J.; Mandala, S.; Mosley, R.; Parent, S. A. *Mol. Pharmacol.* **2007**, *71*, 724–735. (c) Schürer, S. C.; Brown, S. J.; Gonzalez-Cabrera, P. J.; Schaeffer, M.-T.; Chapman, J.; Jo, E.; Chase, P.; Spicer, T.; Hodder, P.; Rosen, H. *ACS. Chem. Biol.* **2008**, 486–498.
- [50] Hanson, M. A.; Roth, C. B.; Jo, E.; Griffith, M. T.; Scott, F. L.; Reinhart, G.; Desale, H.; Clemons, B.; Cahalan, S. M.; Schuerer, S. C.; Sanna, M. G.; Han, G. W.; Kuhn, P.; Rosen, H.; Stevens, R. C. *Science* **2012**, *335*, 851–855.
- [51] Tsuji, T.; Suzuki, K.; Nakamura, T.; Goto, T.; Sekiguchi, Y.; Ikeda, T.; Fukuda, T.; Takemoto, T.; Mizuno, Y.; Kimura, T.; Kawase, Y.; Nara, F.; Kagari, T.; Shimoizato, T.; Yahara, C.; Inaba, S.; Honda, T.; Izumi, T.; Tamura, M.; Nishi, T. *Bioorg. Med. Chem.* **2014**, *22*, 4246–4256.

- [52] 三宅幸子、山村 隆 *CRJ Letters* **2008**, *17*, No. 2.
- [53] Boström, J.; Hogner, A.; Llinàs, A.; Wellner, E.; Plowright, A. T. *J. Med. Chem.* **2012**, *55*, 1817–1830.
- [54] (a) Tsalta, C. D.; Madatian, A.; Schubert, E. M.; Xia, F.; Hardesty, W. M.; Deng, Y.; Seymour, J. L.; Gorychi, P. D. *Drug Metab. Dispos.* **2011**, *39*, 1620–1632. (b) Muraglia, E.; Ontoria, J. M.; Branca, D.; Dessole, G.; Bresciani, A.; Fonsi, M.; Giuliano, C.; Bufi, L. L.; Monteagudo, E.; Palumbi, M. C.; Torrisi, C.; Rowley, M.; Steinkühler, C.; Jones, P. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5283–5288. (c) Bateman, K. P.; Trimble, L.; Chauret, N.; Silva, J.; Day, S.; Macdonald, D.; Dube, D.; Gallant, M.; Mastracchio, A.; Perrier, H.; Girard, Y.; Nicoll-Griffith, D. *J. Mass Spectrom.* **2006**, *41*, 771–780. (d) Allan, G. A.; Gedge, J. I.; Nedderman, A. N. R.; Roffey, S. J.; Small, H. F.; Webster, R. *Xenobiotica* **2006**, *36*, 399–418. (e) Speed, W.; Parton, A. H.; Martin, I. J.; Howard, M. R. *Biol. Mass Spectrom.* **1994**, *23*, 1–5. (f) Lan, S. J.; Weliky, I.; Schreiber, E. C. *Xenobiotica* **1973**, *3*, 97–102.
- [55] Jesberger, M.; Davis, T. P.; Barner, L. *Synthesis* **2003**, 1929–1958.
- [56] Vachal, P.; Toth, L. M.; Hale, J. J.; Yan, L.; Mills, S. G.; Chrebet, G. L.; Koehane, C. A.; Hajdu, R.; Milligan, J. A.; Rosenbach, M. J.; Mandala, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3684–3687.
- [57] Zhu, R.; Snyder, A. H.; Kharel, Y.; Schaffter, L.; Sun, Q.; Kennedy, P. C.; Lynch, K. R.; Macdonald, T. L. *J. Med. Chem.* **2007**, *50*, 6428–6435.
- [58] (a) Marcè, P.; Díaz, Y.; Matheu, M. I.; Castellón, S. *Org. Lett.* **2008**, *10*, 4735–4738. (b) Wang, P.; Schinazi, R. F.; Chu, C. K. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1585–1588.
- [59] (a) Tanimori, S.; Tsubota, M.; He, M.; Nakayama, M. *Synth. Commun.* **1997**, *27*, 2371–2378. (b) Tanimori, S.; Tsubota, M.; He, M.; Nakayama, M. *Biosci. Biotech. Biochem.* **1995**, *59*, 2091–2093. (c) Vince, R.; Hua, M.; Brownell, J.; Daluge, S.; Lee, F.; Shannon, W. M.; Lavelle, G. C.; Qualls, J.; Weislow, O. S.; Kiser, R.; Canonico, P. G.; Schultz, R. H.; Narayanan, V. L.; Mayo, J. G.; Shoemaker, R. H.; Boyd, M. R. *Biochem. Biophys. Res. Commun.* **1988**, *156*, 1046–1053.
- [60] Lebsack, A. D.; Overman, L. E.; Valentekovich, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 4851–4852.
- [61] Kitahara, T.; Warita, Y.; Abe, M.; Seya, M.; Takagi, Y.; Mori, K. *Agric. Biol. Chem.* **1991**, *55*, 206

1013–1017.

[62] (a) Hudon, J.; Cernak, T. A.; Ashenhurst, J. A.; Gleason, J. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 8885–8888. (b) Iwasawa, N.; Matsuo, T.; Iwamoto, M.; Ikeno, T. *J. Am. Chem. Soc.* **1998**, *120*, 3903–3914. (c) Iwasawa, N.; Matsuo, T. *Chem. Lett.* **1993**, 997–1000. (d) Iwasawa, N. *Chem. Lett.* **1992**, 473–476.

[63] Nantz, M. H.; Radisson, X.; Fuchs, P. L. *Synth. Commun.* **1987**, *17*, 55–69.

[64] Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797–6798.

[65] (a) Lipshutz, B. H.; Frieman, B. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 6345–6348. (b) Lipshutz, B. H.; Servesko, J. M.; Petersen, T. B.; Papa, P. P.; Lover, A. A. *Org. Lett.* **2004**, *6*, 1273–1275.

[66] Espino, C. G.; Du Bois, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 598–600.

[67] Im, D.-S.; Clemens, J.; Macdonald, T. L.; Lynch, K. R. *Biochemistry* **2001**, *40*, 14053–14060.

[68] Nelson, G. M.; Swank, A. E.; Brooks, L. R.; Bailey, K. C.; George, S. E. *Toxicol. Sci.* **2001**, *60*, 232–241.

本研究の基礎となる論文の目録

- 1) Synthesis of (3*S*)-(tert-butyltrimethylsilyloxy)methylcyclopentan-1-one as a key intermediate of sphingosine 1-phosphate-1 receptor agonists.

Masayoshi Asano, Tsuyoshi Nakamura, Yukiko Sekiguchi, Yumiko Mizuno, Takahiro Yamaguchi, Takeshi Kuroda, Kazuhiko Tamaki, Takahide Nishi; *Tetrahedron: Asymmetry* **2013**, *24*, 449–456.

- 2) Synthesis and SAR of 1,3-thiazolyl thiophene and pyridine derivatives as potent, orally active and S1P₃-sparing S1P₁ agonists.

Masayoshi Asano, Tsuyoshi Nakamura, Yukiko Sekiguchi, Yumiko Mizuno, Takahiro Yamaguchi, Kazuhiko Tamaki, Takaichi Shimozato, Hiromi Doi-Komuro, Takashi Kagari, Wataru Tomisato, Ryotaku Inoue, Hiroshi Yuita, Keiko Oguchi-Oshima, Reina Kaneko, Futoshi Nara, Yumi Kawase, Noriko Masubuchi, Shintaro Nakayama, Tetsufumi Koga, Eiko Namba, Hatsumi Nasu, Takahide Nishi; *Bioorganic & Medicinal Chemistry Letters* **2012**, *22*, 3083–3088.

- 3) Synthesis and evaluation of CS-2100, a potent, orally active and S1P₃-sparing S1P₁ agonist.

Tsuyoshi Nakamura, Masayoshi Asano, Yukiko Sekiguchi, Yumiko Mizuno, Kazuhiko Tamaki, Futoshi Nara, Yumi Kawase, Yoshiyuki Yabe, Daisuke Nakai, Emi Kamiyama, Yoko Urasaki-Kaneno, Takaichi Shimozato, Hiromi Doi-Komuro, Takashi Kagari, Wataru Tomisato, Ryotaku Inoue, Miyuki Nagasaki, Hiroshi Yuita, Keiko Oguchi-Oshima, Reina Kaneko, Takahide Nishi; *European Journal of Medicinal Chemistry* **2012**, *51*, 92–98.

- 4) Discovery of CS-2100, a potent, orally active and S1P₃-sparing S1P₁ agonist.

Tsuyoshi Nakamura, Masayoshi Asano, Yukiko Sekiguchi, Yumiko Mizuno, Kazuhiko Tamaki, Takako Kimura, Futoshi Nara, Yumi Kawase, Takaichi Shimozato, Hiromi Doi, Takashi Kagari, Wataru Tomisato, Ryotaku Inoue, Miyuki Nagasaki, Hiroshi Yuita, Keiko Oguchi-Oshima, Reina

Kaneko, Nobuaki Watanabe, Yasuyuki Abe, Takahide Nishi; *Bioorganic & Medicinal Chemistry Letters* **2012**, *22*, 1788–1792.

謝辞

本論文を提出するにあたり、多くの御指導と御助言を賜りました静岡県立大学大学院 薬学研究院 教授 菅 敏幸 先生に厚く御礼申し上げます。

本論文の審査にあたり、有益な御助言を賜りました静岡県立大学大学院 薬学研究院 教授 今井 康之 先生、同 眞鍋 敬 先生、同 濱島 義隆 先生に厚く御礼申し上げます。

本論文を提出するにあたり、多くの御指導と御助言を賜りました静岡県立大学大学院 薬学研究院 准教授 江木 正浩 先生に厚く御礼申し上げます。

本研究を行う機会を与えていただき、終始御指導を賜りました第一三共インド CEO 西 剛秀 博士に厚く御礼申し上げます。

本研究の発表の機会を与えていただき、御指導、御支援を賜りました、第一三共株式会社 創薬化学研究所 第七グループ長 町永 信雄 博士に厚く御礼申し上げます。

本研究の遂行にあたり、貴重な御指導、御助言をいただくとともに、合成研究において多大なる御協力をいただきました、玉木 和彦 博士、中村 毅 博士、関口 幸子 博士、水野 由美子 氏、山口 孝弘 博士、黒田 武史 博士をはじめとする多くの共同研究者の方々に厚く御礼申し上げます。

本研究の発表にあたり、多くの御指導を賜りました、竹本 利泰 博士に厚く御礼申し上げます。

さらに貴重な御助言と御協力をいただくとともに生物評価の労を取っていただきました下里 隆一 博士、小室(土井) 洋美 氏、明松 隆志 博士、富里 亘 博士、井上 亮拓 博士、長崎 美由紀 氏、大島 慶子 博

士、結田 浩史 博士、金子 礼奈 氏、奈良 太 博士、川瀬 由美 氏、薬物動態評価の労を取っていただきました矢部 義之 博士、中井 大介 博士、神山 恵美 博士、浦崎 葉子 氏、渡邊 伸明 博士、梶渕 紀子 博士、中山 慎太郎 博士、ドッキングスタディについて御助力いただきました木村 貴子 氏、安全性評価の労を取っていただきました阿部 泰之 博士、腸内細菌への化合物安定性評価の労をとっていただきました古賀 哲文 博士、難波 栄子 氏、那須 初美 氏をはじめとする多くの共同研究者の方々に深く感謝いたします。

また、X線結晶構造解析の労を取っていただきました米山 智子氏、分子構造計算の労を取っていただきました渋谷 智 博士に深く感謝いたします。

最後に、本研究の発表にあたり、御助力いただきました、永田 勉 博士、千葉 淳 博士、古川 詔大 博士、その間、筆者を鼓舞激励してくださいました、市川 正則 氏、辻 貴司 氏、森 裕 氏、松藤 哲義 氏に深く感謝いたします。

2014 年 11 月 著者