博士論文

動脈硬化治療薬の開発を目的とした
Liver X Receptor β 選択的アゴニストの創薬研究

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Structure-activity relationship and synthetic studies on Liver X Receptor β-selective agonists for the treatment of atherosclerosis

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略語表

ABCA1: ATP-binding cassette transporter A1
ABCG5: ATP-binding cassette transporter G5
ABCG8: ATP-binding cassette transporter G8
AF-1: activation function-1
cDNA: complementary deoxyribonucleic acid
Compd: compound
DBD: DNA binding domain
DEA: diethylamine
DEAD: diethyl azodicarboxylate
DHP: dihydropyrane
DMF: *N*, *N*-dimethylformamide
$(EtO)_2P(O)H$: diethyl phosphonate
FAS: Fatty acid synthase
HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A
HDL-C: high-density lipoprotein cholesterol
HPLC: high performance liquid chromatography
HTS: high-throughput screening
KI: Potassium iodide
LBD: ligand binding domain
LDL: low-density lipoprotein
$LiAlH_4$: lithium aluminum hydride
LXR: liver X receptor
LXRE: LXR response element
NBS: *N*-bromosuccinimide
NCS: *N*-chlorosuccinimide
$(NH_4)_2CO_3$: ammonium carbonate
NPC1L1: Neimann-Pick C1 like1
NR: nuclear receptor
PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9
Ts: *p*-toluenesulfonyl
RCT : reverse cholesterol transport
RXR: retinoid X receptor
SREBP-1c: sterol regulatory element-binding protein 1c
TC: total cholesterol

TFA: trifluoroaccetic acid

TG: Triglyceride

緒言

近年，脳梗塞や脳卒中などの脳血管系疾患や心筋梗塞などの心血管系疾患が悪性腫瘍に次ぐ死亡要因となり，国内はもとより世界で問題となっている [1]．血中総コレステロール (total cholesterol; TC) と心血管系疾患の発症率との相関を調査した大規模疫学試験 (Framingham Heart Study) [2] の結果，血中コレステロールの高い患者ほど心血管系疾患の発症率が高いことが明らかにされ，治療戦略としては TC を低下させることが第一と考えられている．その具体的な治療法として，まずコレステロール産生を阻害する 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) 還元酵素阻害剤(いわゆるスタチン製剤) の投与が挙げられる．実際，プラバスタチン (メバロチン®) [3] を用いた West of Scotland Coronary Prevention Study (WOSCOPS) [4] やシンバスタチン (リポバス®) [5] を用いた Scandinavian Simvastatin Survival Study (4S) [6] などの大規模臨床試験の結果，心血管イベントの抑制と LDL コレステロール (low-density lipoprotein cholesterol; LDL-C) 低下作用による治療法の意義が実証された [7]．しかしながら，スタチン製剤による心血管イベント抑制率は約 30% 程度である [8]．さらに昨今，アトルバスタチン (リピトール®) [9]，ピタバスタチン (リバロ®) [10] ならびにロスバスタチン (クレストール®) [11] のいわゆるストロングスタチンに，より強力な LDL-C 低下作用があることが報告され，心血管イベント抑制率は改善してきたが未だ課題は残る．スタチン製剤以外としては，小腸コレステロールトランスポーター (Neimann-Pick C1 like1; NPC1L1) を阻害するエゼチミブ (ゼチーア®) [12] が，小腸でのコレステロール吸収を阻害し，脂質異常症を改善する薬として投与されている．エゼチミブは単剤で LDL-C を 20% 以上低下させ，シンバスタチンとの併用効果が期待されたが，Effect of Combination Ezetimibe and High-Dose of Simvastatin vs Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia (ENHANCE) 試験においては必ずしも有意義な臨床結果は確認されなかった [13]．一方，IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) 試験においてはシンバスタチンとの併用効果が確認され，スタチン製剤以外でも心血管イベントを抑制しうることが証明された [14]．また近年，ヒトプロタンパク質転換酵素サブチリシン/ケキシン 9 型 (Proprotein Convertase Subtilisin/Kexin Type 9; PCSK9) を阻害するヒト IgG2 モノクローナル抗体としてエボロクマブ (レパーサ®) [15] およびアリロクマブ(プラルエント®) [16] が，スタチン製剤で効果不十分な患者にスタチン製剤との併用を原則に投与される．スタチン製剤単独投与と比較して併用投与では，LDL-C がさらに低下し，心血管イベントの抑制効果があることが確認された [17, 18]．このように NPC1L1 阻害剤や PCSK9 阻害剤は，スタチン製剤による心血管イベント抑制率をさらに改善しうる．しかしながら，心血管イベントの抑制効果はまだ十分とは言えず，また PCSK9 阻害剤は皮下注射を要する抗体医薬ということもあり，より

利便性の高い新規動脈硬化治療薬が求められている.

Liver X Receptor (LXR) は, 核内受容体の一つとして 1994 年に肝の cDNA ライブラリーよりクローニングされ，リガンドの不明なオーファンレセプターとして同定された [19]. その後, コレステロールがステロイドホルモンや胆汁酸へと変換される際に生じるオキシステロール類である 22(*R*)–ヒドロキシコレステロール，24(*S*)–ヒドロキシコレステロールおよび 27–ヒドロキシコレステロールなどが生体内リガンドとして報告された (Figure 1) [20].

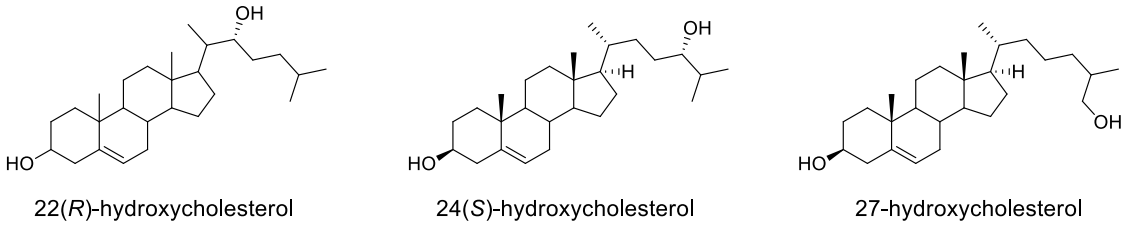


Figure 1. Endogenous ligands

LXR には，2 種類のサブタイプ (α, β) が存在し，LXRα は主に肝臓，脂肪組織，小腸，マクロファージなどに特異的に発現している．一方，LXRβ は普遍的に発現している [21].

LXR は N 末端より順に，activation function-1 (AF-1)，DNA 結合ドメイン (DNA binding domain; DBD)，リガンド結合ドメイン (ligand binding domain; LBD) である activation function-2 (AF-2) から構成されている (Figure 2). このうち，AF-1 は恒常的に転写活性能を保持する．一方で AF-2 は，LBD にリガンドが結合すると構造を変化させ，転写活性を起こす (Figure 2-a). すなわち，リガンドが結合する前は，主に co-repressor により不活化されており (Figure 2-b)，リガンドが結合すると，主に co-activator により活性化状態となり，構造変化を生じる．それに伴いレチノイド X 受容体 (retinoid X receptor; RXR) とヘテロダイマーを形成し, DNA 上の LXR 応答配列 (LXR response element; LXRE) に結合して標的遺伝子の転写を誘導する(Figure 2-c).

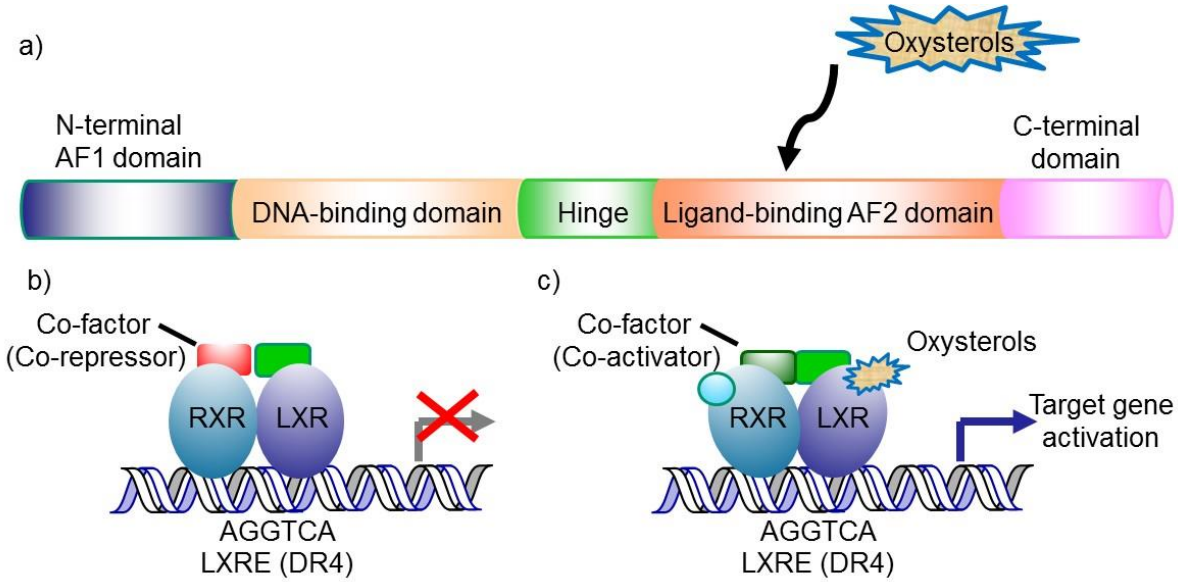


Figure 2. Mechanism of LXR transcriptional activation [22)]

LXR の活性化は，小腸においては ATP-binding cassette transporter G5 (ABCG5) および ABCG8 発現の上昇によるコレステロール排泄促進作用を示し，末梢血管においては ABCA1，ABCG1 発現の上昇によりコレステロール逆転送系 (reverse cholesterol transport; RCT) を亢進し抗動脈硬化作用を示す [23)]．しかし，肝臓においては sterol regulatory element-binding protein 1c (SREBP-1c) や脂肪酸合成酵素 (Fatty acid synthase; FAS) などの脂肪酸合成に関与する酵素を転写促進し，トリグリセリド (Triglyceride; TG) の増加に繋がる可能性がある (Figure 3) [24)]．この肝臓での SREBP-1c や FAS などによる脂肪酸合成の亢進は，主に肝臓に分布している LXRα の活性化作用に起因する．したがって，肝臓での LXR への作用もしくは LXRα への作用を回避すれば TG の増加を回避し得ると推察され，LXR アゴニストの創製においては，i) 組織選択的 LXR アゴニスト ii) LXRβ 選択的アゴニスト iii) LXR パーシャルアゴニスト(部分活性化薬) の戦略が考えられることになる．

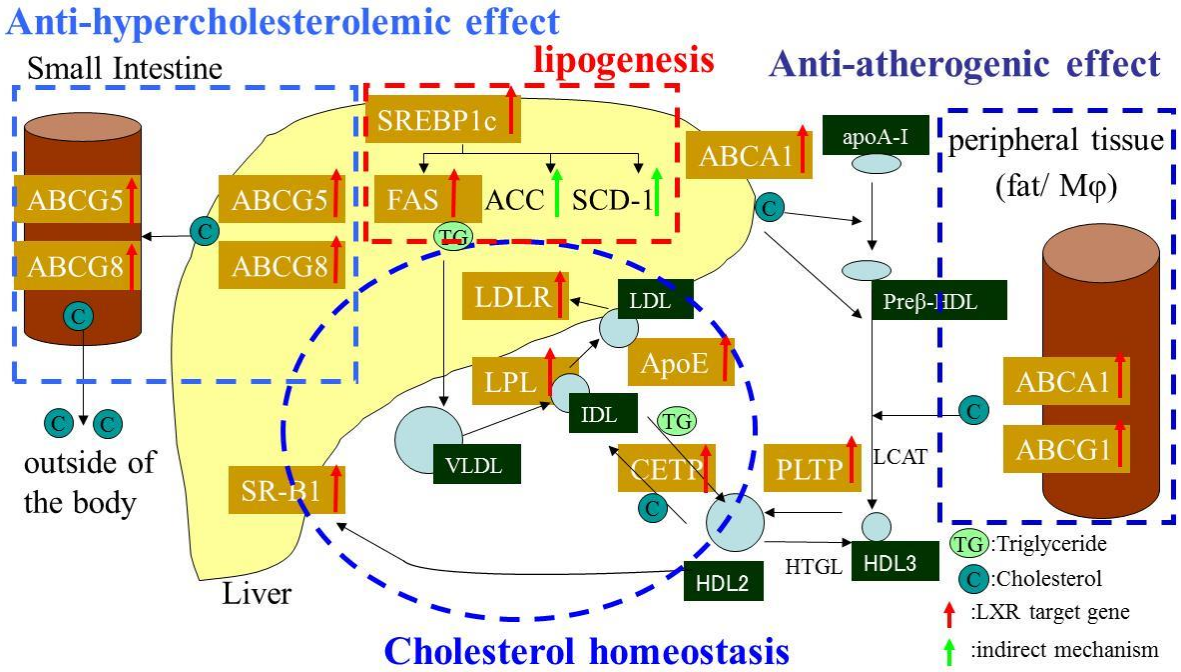


Figure 3. Physiological role of LXR activation

多くの製薬企業が凌ぎを削る中，Wyeth 社 (現 Pfizer 社) は LXR 部分活性化薬として，自社開発品 LXR623 (Figure 4) の臨床第一相試験を実施した．LXR623 は用量依存的に所望の ABCA1 発現上昇作用を示し，懸念されていた TG の増加は確認されず LDL-C 低下作用や心血管イベント抑制作用が期待された [25]．さらに中型動物のうさぎを用いたシンバスタチンとの併用投与試験において，動脈硬化の進展抑制作用およびプラーク退縮の促進作用が確認された [26]．しかし，臨床第一相試験において中枢性の副作用が確認されたことから開発は中止された [27]．Bristol-Myers Squibb (BMS) 社と Exelixis 社による開発品 BMS852927 (Figure 4) は，臨床第一相試験において好中球減少の副作用が確認されたことから開発は中止された [28]．しかし，これらの結果からは，TG 上昇以外の副作用が LXR アゴニストの標的または化合物に由来するものであるかどうかは不明である．

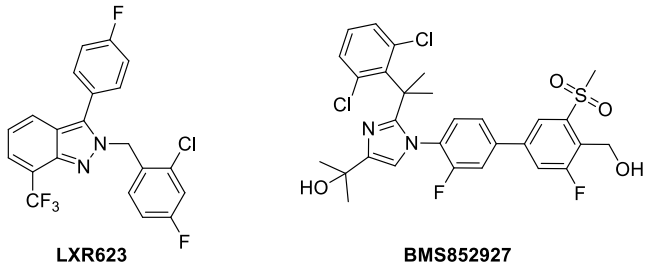


Figure 4. Structure of the LXR agonists from Wyeth (LXR623) and BMS (BMS852927)

著者は，新規な動脈硬化治療薬の開発を目的として，まず，ABCA1 mRNA/SREBP-1c mRNA 選択性を有する LXR アゴニストの創製を目指すこととした．すなわち，SREBP-1c mRNA の発現を低く抑えて肝臓における脂肪酸合成の増加を抑制し，ABCA1 mRNA の発現促進により末梢血管における HDL コレステロール (high-density lipoprotein cholesterol; HDL-C) を増加させてコレステロール逆転送系の亢進によって抗動脈硬化作用につなげようという目論みである．ABCA1 mRNA の発現を促す分子は，同じ ABC ファミリーに属する ABCG5 や ABCG8 の活性化にも寄与し，小腸でのコレステロール排泄作用による LDL-C 低下作用につながることも期待した．

研究開始当初 (2003年)，合成リガンドとして Tularik 社 (現 Amgen) の T0901317 [29] や GlaxoSmithKline (GSK) 社の GW3965 [30] が創薬ツールとして報告されていたが (Figure 5)，ABCA1 mRNA/SREBP-1c mRNA 発現の選択性を有する LXR アゴニストは報告されていなかった．

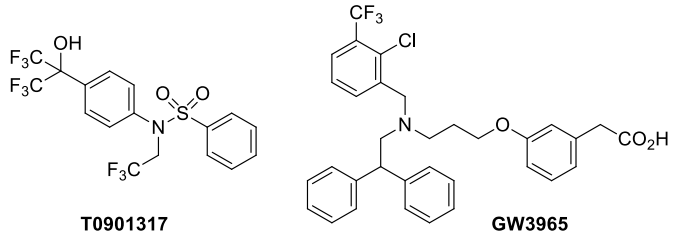


Figure 5. Structure of the LXR agonists from Tularik (T0901317) and GSK (GW3965)

そこで新規骨格の探索を目的に自社化合物ライブラリーによるハイスループットスクリーニング (high-throughput screening; HTS) を実施した．

約 56,000 化合物のアッセイ結果から，著者は選択性を有する 7 化合物を選出した．しかしながら，各 HTS ヒット化合物の周辺構造を鋭意検討したが，十分な ABCA1 mRNA 発現亢進作用と ABCA1 mRNA/SREBP-1c mRNA 発現の選択性を有する化合物を見出すには至らなかった．

この結果を受け著者は，LXRα と LXRβ の構造の差異に基づく分子設計によって，LXRβ 選択的アゴニストを創製することに方針を転換した．LXRα と LXRβ のリガンド結合部位のホモロジーは高く，当時 LXRβ 選択的アゴニストの報告はなかった．

まず，LXRα/β デュアルアゴニストである T0901317 の LXRβ との共結晶の X 線結晶構造解析，および僅かながら LXRα/β 活性化作用に差を有する GW3965 の LXRβ との共結晶の X 線結晶構造解析に注目した (Figure 6)．LXR の活性化作用は，リガンドと LXR の結合領域との相互作用‘His435-Trp457 activation switch’により発現することが提唱されていた [31]．T0901317 であれば 1,1-ビス(トリフルオロメチル)

カルビノール部位の水酸基と LXR の結合領域である His435 との相互作用が，GW3965 であれば 2-クロロ-3-トリフルオロメチルフェニル部位のトリフルオロメチル基と LXR の結合領域である His435 との相互作用がこれに当たる．さらに GW3965 では，カルボン酸部位が，周辺のアミノ酸である Arg319 と Leu330 の主鎖のアミド結合の NH を含んだ極性ポケットと相互作用していることが確認されている [32]．

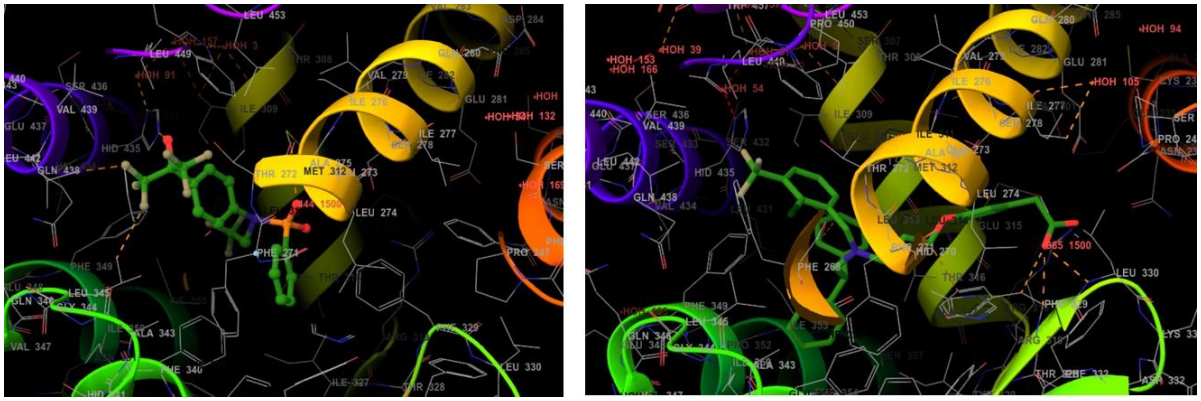
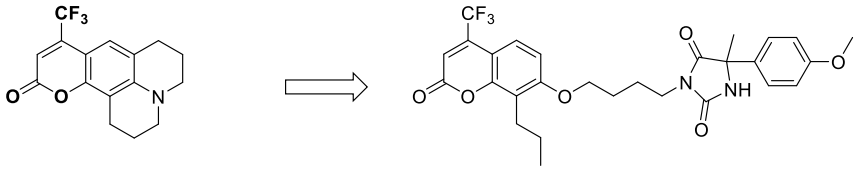


Figure 6. X-ray crystal structure of T0901317 or GW3965 with LXRβ

著者は，LXR 活性化作用に重要な部分 (head 部分) と LXRβ 選択性を発現する可能性を有する部分 (tail 部分) とを想定して考える‘head-to-tail’のドラッグデザインを基に構造最適化をおこない，最終的に世界でも稀に見る高い LXRβ 選択性と高活性を示す化合物 (Scheme 6, (*S*)-(−)-**10**) の創製に成功した．本論文は，その詳細を述べるものである．

本論の第一章第一節では，まず，HTS で見出したヒット化合物 **1** をもとに LXRβ 選択性を示す化合物 **2** を見出した経緯を述べる．すなわち，head 部分に 2-オキソクロメン構造を，tail 部分にイミダゾリジン-2,4-ジオン (ヒダントイン) 構造を有し，おのおのを適切なメチレンリンカーで結合させた化合物である (Figure 7) [33]．残念ながら，head 部分の 2-オキソクロメン構造は，生体内で速やかに代謝されることが判明し，化合物 **2** はさらなる最適化を必要としたが，LXRβ 選択的アゴニスト創製のための有用な情報を得ることができた．



HTS-hit compound (1)

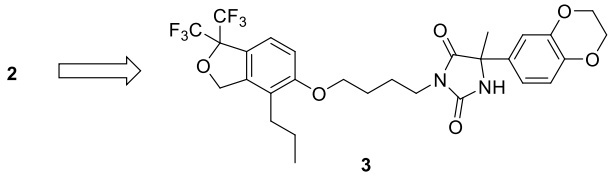
EC_{50} (β): 3.2 μM, E_{max} (β): 19%

2

EC_{50} (β): 1.4 μM, E_{max} (β): 31%
β/α selectivity for E_{max}: 16
CLint: 397/>500/393 (μL/min/mg protein)
(mouse/hamster/human)

Figure 7

第一章第二節では，化合物 **2** をもとに LXRβ 活性化作用と選択性および代謝安定性の向上を目指し，head 部分の探索合成をおこなった結果について述べる．化合物 **2** の 2-オキソクロメン構造は，LXRβ の結合領域である His435 と相互作用していると考えられるが，活性発現は十分ではなかった．そこで head 部分の原子配置，距離あるいは角度を考慮しながら構造変換をおこなった．その結果，1,3-ジヒドロイソベンゾフラン骨格を有する化合物 **3** が，T0901317 と同等以上の LXR 活性化作用を有するとともに代謝安定性も向上することが判明した (Figure 8) [34]．しかし，LXRβ 選択性が低下するという課題を残した．



3

EC_{50} (β): 0.5 μM, E_{max} (β): 129%
β/α selectivity for E_{max}: 1.3
CLint: 308/436/283 (μL/min/mg protein)
(mouse/hamster/human)

Figure 8

第一章第三節では，head 部位に 1,1-ビス(トリフルオロメチル)カルビノール構造をもつ化合物 **4** の創製とその活性について述べる．この化合物は，上記の化合物 **3** の 1,3-ジヒドロイソベンゾフラン環を開裂したものに相当し，T0901317 の head 部位を念頭に置いてデザインしたものである．この head 構造をもつ誘導体の LXRβ 活性化作用は，T0901317 と比べて同等以上であり，化合物 **2** と比べて代謝安定性も改善した．さらにヒダントイン部位の構造最適化検討により LXRβ 選択的活性化作用を示す

化合物 **4** (EC_{50} (β): 1.2 μM) を見出した (Figure 9) [35]. 化合物 **4** は，動脈硬化モデルである高脂肪食負荷 F_1B Bio ハムスターにおいて，100 mg/kg 反復経口投与にて脂質沈着抑制作用を示した．そこで，著者はこの化合物をリード化合物として位置付けることとした．

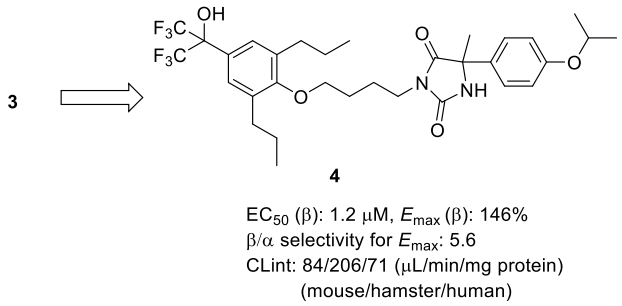
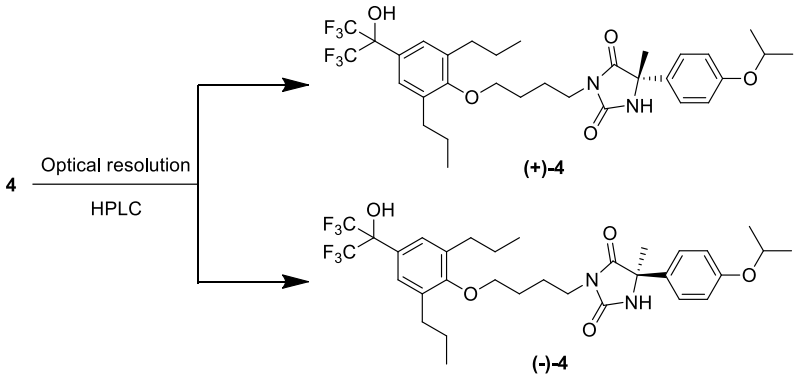


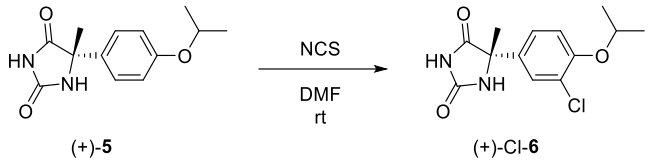
Figure 9

次に著者は，リード化合物 **4** および合成中間体であるヒダントイン **5** を光学分割する方法を開発し，その結果，化合物 **4** は鏡像異性体の一方にのみ所望の LXR 活性化作用があることを明らかにした (Scheme 1) [36]. その詳細を，第二章第一節第一項から第三項で述べる．



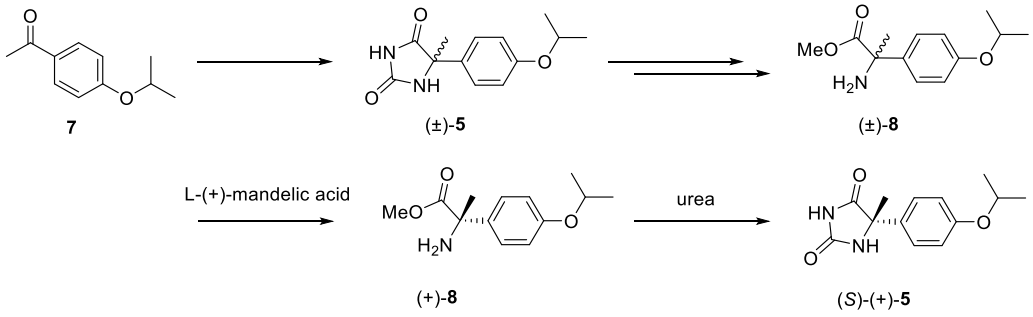
Scheme 1

第二章第一節第四項では，光学分割法で得た 5-(4-(1-メチルエトキシ)フェニル)-5-メチルイミダゾリジン-2,4-ジオン中間体 (+)-**5** の絶対立体配置の決定法について述べる．化合物 (+)-**5** を NCS を用いる塩素化によって，(+)-Cl-**6** へと誘導し，X 線結晶構造解析したところ，(+)-**5** の絶対立体配置は *S* であることを決定できた (Scheme 2) [36].



Scheme 2

続いて，上述の結果をもとに鍵中間体である (+)-**5** を安定に大量合成する方法を開発した (Scheme 3) [36]．すなわち，まず 1-(4-(1-メチルエトキシ)フェニル)エタン-1-オン (**7**) を，ラセミ体の **5** を経由してアミノ酸エステル誘導体 **8** へと誘導する．これを L-(+)-マンデル酸を用いたジアステレオマー塩の形成により光学分割し，次いで，尿素を用いて閉環反応することによって (+)-**5** を高い鏡像体過剰率 (≧99% ee) で得るという製造法である．その詳細を，第二章第一節第五項で述べる．



Scheme 3

第二章第二節では，化合物 **4** の血中濃度推移を検証した結果について述べる．化合物 **4** は *in vitro* での代謝安定性は改善したものの，*in vivo* ではカルボン酸体 **9** へと比較的速やかに代謝されることが確認された (Figure 10) [36]．この結果から，血中 ABCA1 発現を上昇できなかった理由として，代謝により必要な血中濃度を有していなかったことが示唆された．

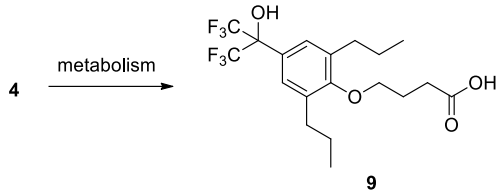


Figure 10

ところで，脂質沈着抑制作用には LDL-C 低下作用の寄与が大きいことから，化合物 **4** には脂質異常改善薬としての可能性があることが示唆された. 一方, 化合物 **4** は, 末梢血管への直接的な作用が少なく, 動脈硬化治療薬としての開発には課題を残した. そこで，末梢血管への直接的な作用を有する化合物を見出すべく新たな合成展開を試みることとした．ここでまず，活性発現に必要なカルビノール部位と β 選択性発現に必要なヒダントイン部位とを結ぶリンカー部位を柔軟性のある直鎖のブタン構造から堅牢な構造に変え, 両部位間の距離と配向性を考慮することとした. また, LXRβ 活性化作用と LXRβ 選択性の向上だけではなく, さらなる代謝安定性の向上も必要であったため，分子全体の脂溶性を低減させることを考えた．検討の結果，リンカー部位に 2-ヒドロキシアセトフェノン構造を導入した化合物 **10** (EC_{50} (β): 0.058 μM) に，これまでになく高い LXRβ 活性化作用，LXRβ 選択性および顕著な代謝安定性の改善が確認された (Figure 11) [37]．さらに化合物 **10** の鏡像異性体のうち良好な LXR 活性を示す (−)-**10** は，動脈硬化モデルである高脂肪食負荷 low-density lipoprotein (LDL) 受容体欠損マウスにおいて，1 mg/kg 反復経口投与にて脂質沈着抑制作用を示した．これらの結果に基づき，著者は当該化合物を安全性評価候補化合物の一つとして位置付けることとした．その詳細を第三章で述べる.

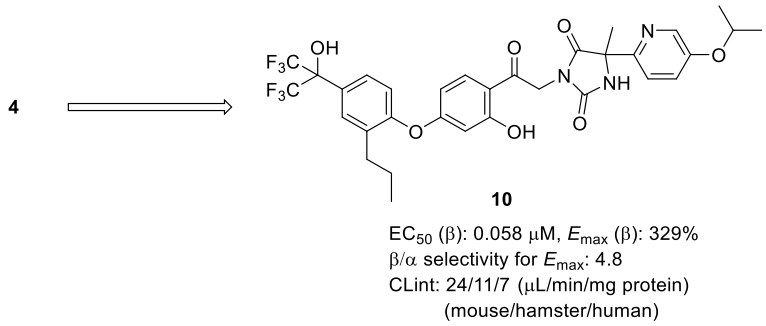
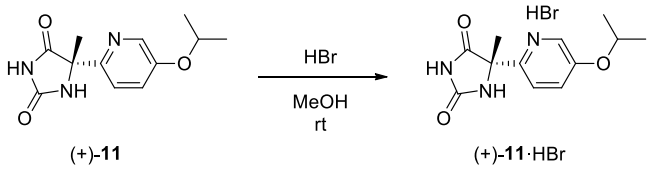


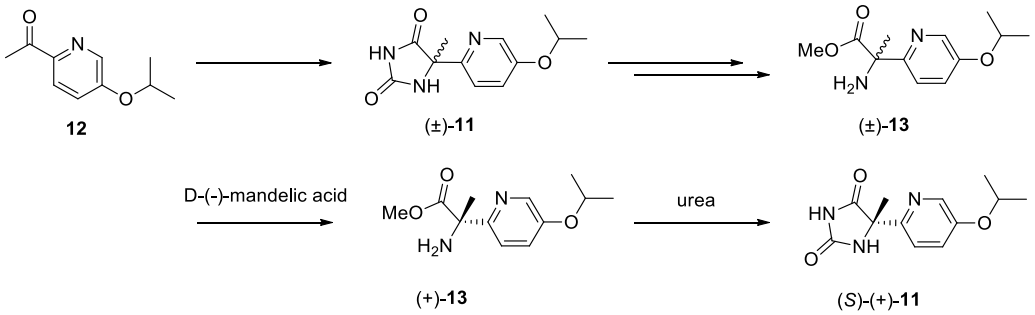
Figure 11

次に著者は, 化合物 (−)-**10** の絶対立体配置を決定した. すなわち, 化合物 (−)-**10** の tail 部分となる 5-(5-(1-メチルエトキシ)ピリジン-2-イル)-5-メチルイミダゾリジン-2,4-ジオン (ヒダントイン中間体 (+)-**11**) を光学分割によって調製し，その臭化水素塩の X 線結晶構造解析を実施した (Scheme 4) [38]. その結果，(+)-**11** の絶対立体配置は *S* であることが確認された．その詳細を第四章第一節で述べる.



Scheme 4

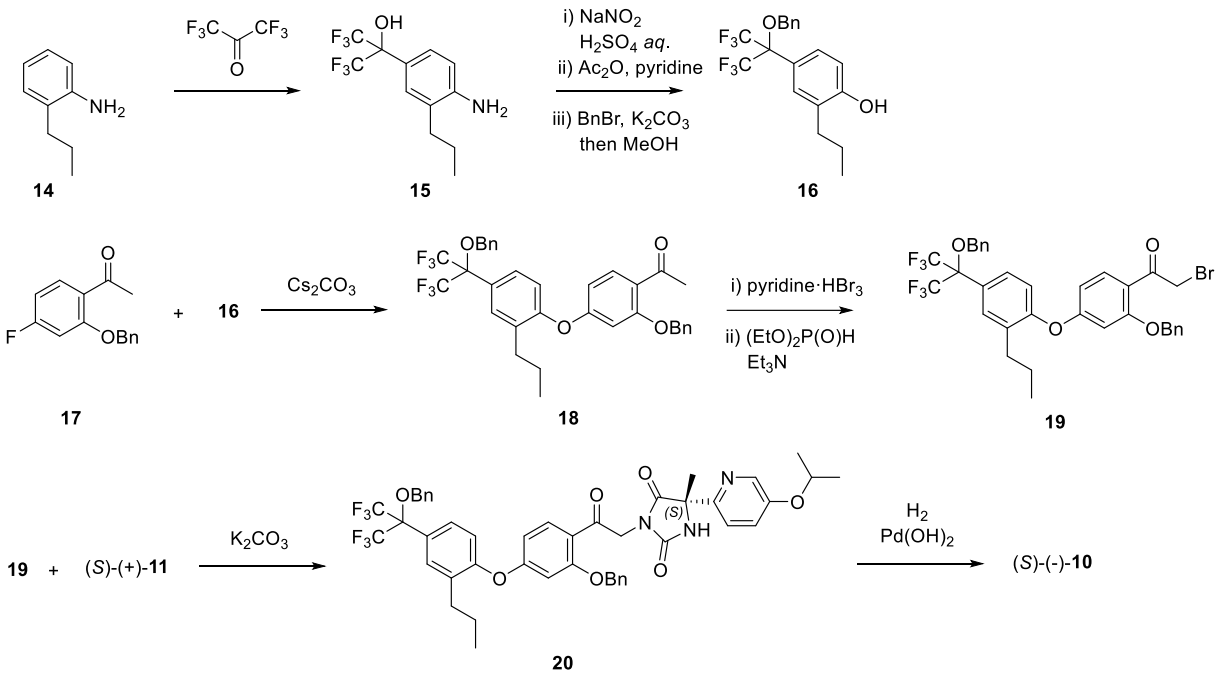
第四章第二節では，鍵中間体となる (+)-**11** を安定に大量合成する方法について述べる (Scheme 5) [38]. すなわち，ピリジン誘導体 **12** より合成したラセミ体のヒダントイン (±)-**11** をアミノ酸エステル **13** へと変換し，D-(−)-マンデル酸を用いてジアステレオマー塩を形成させ光学分割することにより (+)-**13** を得た．これを，尿素を用いて閉環反応することで, (+)-**11** を高い鏡像体過剰率 (≧99% ee) で得ることができた.



Scheme 5

続いて，化合物 (−)-**10** をさらなる動物試験評価に十分量供することを目的に，その効率的合成法を検討した (Scheme 6) [38]. 2-プロピルアニリン (**14**) の 1,1,1,3,3,3-ヘキサフルオロアセトンへの付加反応によりカルビノール部位を構築後，得られたアニリン誘導体 **15** のアミノ基を Sandmeyer 反応により水酸基へ変換し, さらにカルビノール水酸基をベンジル基にて選択的に保護した．次いで，1-(2-(ベンジルオキシ)-4-フルオロフェニル)エタン-1-オン (**17**) との反応によりジフェニルエーテル **18** へと

誘導した後，カルボニル基の α 位を臭素化して **19** を合成した．化合物 **19** を用いてヒダントイン (+)-**11** をアルキル化した後，得られた化合物 **20** の二つのベンジル基を加水素分解反応により除去することにより (*S*)-(−)-**10** を得ることができた．この合成法の開発により，初期合成法と比較して工程数および収率を格段に改善することに成功した．その詳細を第四章第三節で述べる．



Scheme 6

こうして，所期の目的であった高活性かつ高選択的な LXRβ アゴニスト (*S*)-(−)-**10** の創製に成功した. (*S*)-(−)-**10** は世界で稀に見る LXRβ 高選択性および高活性を示し，動脈硬化疾患モデルにおいても優れた薬理効果を示すことから LXR アゴニストの創薬研究において有用な情報を提供するものと期待できる．

以下，各章にて詳細を論ずる．

第一章　Liver X Receptor β 選択的アゴニストの創製~Hit to Lead~

第一節　2-オキソクロメン誘導体の創製

第一項　ドラッグデザイン①

著者は，新規動脈硬化治療薬の創製を目指し，まず，緒言で述べたように ABCA1 mRNA/SREBP-1c mRNA 選択性を有する LXR アゴニストの探索を開始した．

はじめに，ヒト単球由来の THP-1 細胞を用いて ABCA1 mRNA 発現亢進作用を評価した．すなわち，ランダムライブラリー 48,000 化合物，核内受容体ライブラリー 6,696 化合物，さらに自社ライブラリー 1,368 化合物の計 56,064 化合物を用いて，10 μM の濃度にて HTS を実施した (Figure 12, Table 1). 各化合物は DMSO 溶液として調製した．また，DMSO のみを添加したときの値を 100%とし，この値をコントロールとして，各化合物を評価した．

< HTS flow >

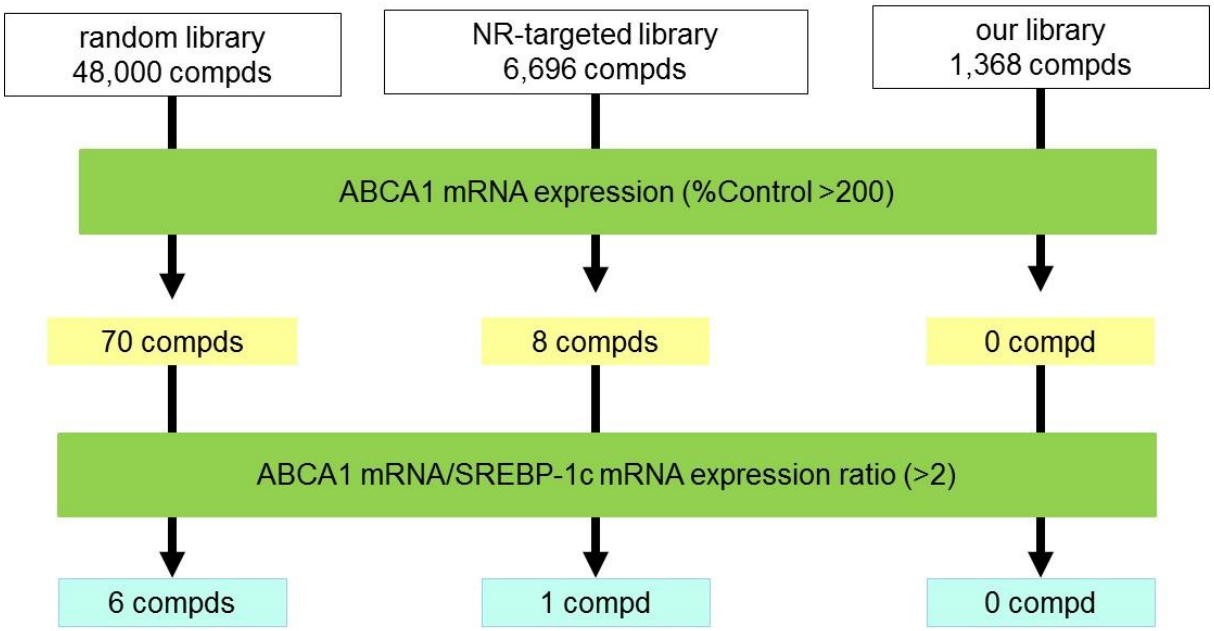
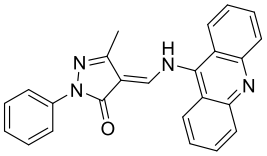
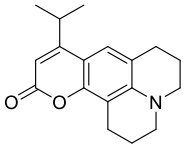
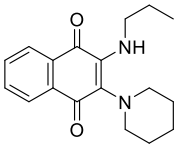
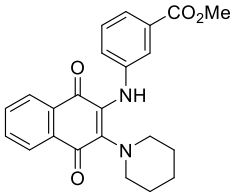
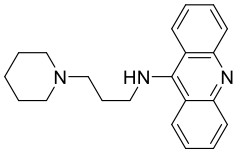
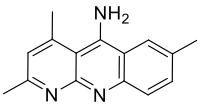
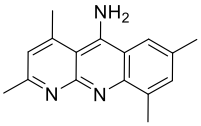


Figure 12

以下に HTS ヒット化合物の構造とスクリーニング結果を示す.

Table 1. Structure and *in vitro* result of the HTS hit compounds[a]

Compound	Structure	ABCA1[b]	SREBP1c[c]	ABCA1/SREBP-1c[d]
21		5.1	0.8	6.4
22		5.0	1.4	3.6
23		2.5	0.8	3.1
24		0.8	0.3	2.7
25		3.8	1.5	2.5
26		2.4	1.0	2.4
27		2.2	1.0	2.2

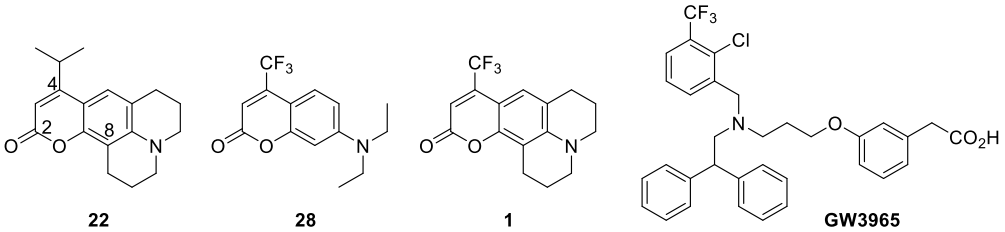
[a] The assays was conducted at 10 μM. [b] The value is ratio of activation relative to control (DMSO). ABCA1 mRNA expression was assayed in THP1 cell. [c] The value is ratio of activation relative to control (DMSO). SREBP-1c mRNA expression was assayed in HepG2 cell. [d] The value is ABCA1 mRNA/SREBP-1c mRNA expression ratio.

その結果，コントロールの 200%以上の ABCA1 mRNA 発現亢進作用を示す化合物を計 78 個見出した．その後，この 78 化合物について，ヒト肝癌由来の HepG2 細胞における SREBP-1c mRNA 発現亢進作用を評価した．すなわち，ABCA1 mRNA 発現亢進作用を評価したときと同様に，DMSO を添加したときの値をコントロール (100%) とし，各化合物は DMSO 溶液として調製し，濃度 10 μM にて評価した．

ABCA1 mRNA および SREBP-1c mRNA 発現亢進作用のコントロールに対する値を用いて，ABCA1 mRNA/SREBP-1c mRNA 発現亢進作用の比が大きい 7 化合物を HTS ヒット化合物として選出した．また，各化合物についてルシフェラーゼアッセイによって LXRα 活性化作用を確認した．

HTS ヒット 7 化合物のうち，4 化合物 (**21**, **25**, **26**, **27**) に 9-アミノアクリジン構造が含まれていることが判明した．しかし，一般に 9-アミノアクリジン類縁体には発癌性が懸念されるため，その後の検討からは除外した [39]．一方，2-オキソクロメン構造を有する化合物 **22** とナフタレン-1,4-ジオン構造を有する化合物 **23**, **24** については種々の誘導体を合成し, ABCA1 mRNA 発現亢進作用を調べた. その結果, 化合物 **23**, **24** の誘導体からは良好な作用を有する化合物を見出せなかったが (データ不記載),

Table 2. Structure and cellular activity of the 2-oxochromene derivatives[a]



Compound	ABCA1[b]	SREBP-1c[c]	ABCA1/SREBP-1c[d]
22	5.0	1.4	3.5
28	1.3	3.3	0.4
1	9.1	3.9	2.4
GW3965	15.0	4.9	3.1

[a] The assays was conducted at 10 μM. [b] The value is ratio of activation relative to control (DMSO). ABCA1 mRNA expression was assayed in THP1 cell. [c] The value is ratio of activation relative to control (DMSO). SREBP-1c mRNA expression was assayed in HepG2 cell. [d] The value is ABCA1 mRNA/SREBP-1c mRNA expression ratio.

化合物 **22** の誘導体からは二つの化合物 **28**, **1** が見出された (Table 2). これら化合物は, 2-オキソクロメン骨格の 4 位に疎水性置換基であるトリフルオロメチル基を有するものであった. 化合物 **22**, **28**, **1** はいずれも, GW3965 と比べて ABCA1 mRNA 発現亢進作用が低く, また, キノリジン骨格をもたない化合物 **28** は, キノリジン骨格を有する化合物 **22** および **1** と比べて, ABCA1 mRNA/SREBP-1c mRNA 発現の選択性が低かった. そこで, この選択性の向上を目指し, 化合物 **1** の類縁体を種々合成したが, 残念ながら十分な選択性を有する化合物を見出すことはできなかった.

そこで方針を転換し, ABCA1 mRNA 発現亢進作用と SREBP-1c mRNA 発現亢進作用に基づいて探索をおこなうのではなく, 転写促進作用の上流に位置する受容体 (LXR) の構造そのものに着目し, LXRβ 選択的アゴニストの創製を目指すことにした. LXRα と LXRβ のサブタイプのリガンド結合領域のホモロジーは高く [31], 当時 LXRβ 高選択的アゴニストの報告はなかったが, わずかではあるものの GW3965 が LXRβ 選択性を有していたことから, その構造に着目した. LXRβ との共結晶のX線結晶構造において, LXRα/β デュアルアゴニストである T0901317 は, 受容体の疎水性領域と呼ばれている部分 (head 部分) との相互作用を有し, さらにその中で, 分子のカルビノール部位の水酸基が受容体の His435 と水素結合している (Figure 13). 一方, GW3965 は, 疎水性領域である head 部分との相互作用に加えて 2-クロロ-3-トリフルオロメチルベンジル部位のフッ素原子が His435 と相互作用を有している. さらに, Figure 13 の右側に位置する領域 (tail 部分) では, GW3965 のカルボン酸部位周辺が Arg319 および Leu330 と相互作用している [32, 33]. このことから tail 部分への相互作用が LXRβ 選択性に寄与しているものと推察した.

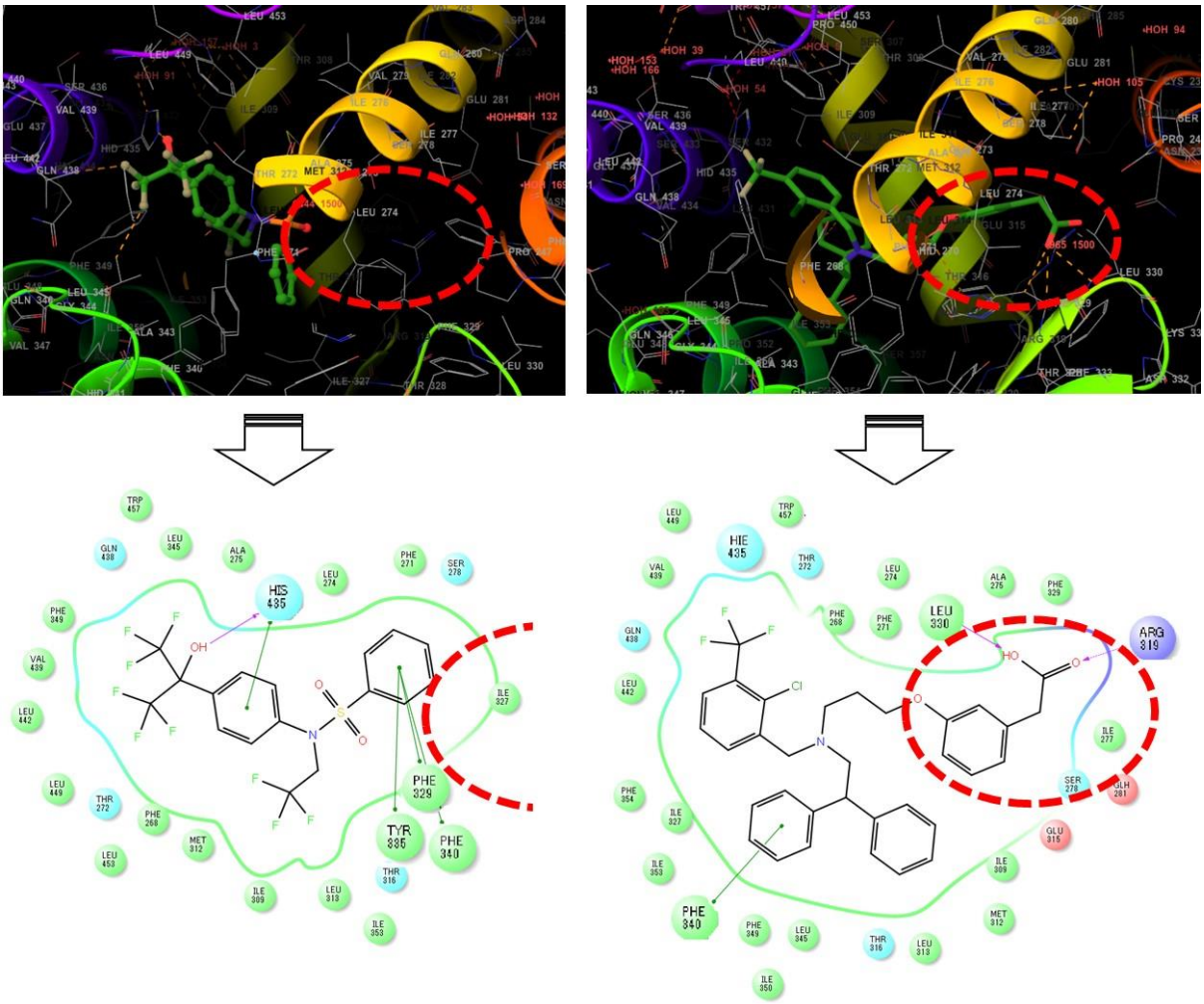


Figure 13. X-ray crystal structures of T0901317 (PDB ID: 1PQ9) and GW3965 (PDB ID: 1PQ6): A pink line show the hydrogen bond. A green line show the π-π interaction. A red dotted line show our attracted area.

ところで，一般に LXRβ の活性化のためには，His435 とリガンドが相互作用することにより，‘His435-Trp457 activation switch’と呼ばれる部位が活性化されることが重要であると報告されている [32c].

このことを踏まえ Table 2 の結果を以下のように推察した.

① 化合物 **1** のカルボニル基の酸素原子が，His435 と相互作用している.
② 8 位の置換基は，LXR の高度に疎水的な LXR リガンド結合ポケット (head 部分) と疎水性相互作用している.
③ キノリジン部位は，Thr316 や Phe340 と疎水性相互作用している.

ただし，化合物 **1** の発現亢進作用が GW3965 と比べて低かったことから，上記 3 つの相互作用は十分なものではないと考えた．また，平面性の高い構造は，DNA 鎖にインターカレーションを起こしてしまうことも懸念された [40]．

さらに，化合物 **1** はアンドロゲン受容体 (Androgen receptor; AR)，ペルオキシソーム増殖因子活性化受容体 (Peroxisome proliferator activated receptor; PPAR) (サブタイプα, γ)，ファルネソイド X レセプター (farnesoid X recptor; FXR) のルシフェラーゼアッセイにおいて，活性化作用が確認された (データ不記載)．したがって，他の核内受容体との選択性を確保することも不可欠であった．

ところで，Merck 社は，化合物 **29** が化合物 **1** と比べて強い LXR 活性化作用を示すことを報告していた (Figure 14) [41]．

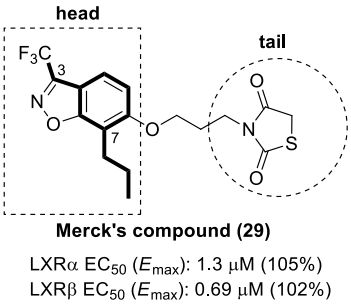


Figure 14. Structure of the LXR agonists from Merck (compound **29**)

そこで著者は，あらためて以下の点を念頭において，構造最適化を図ることとした．

① 化合物 **1** と GW3965 とのドッキングモデル [42] によれば，化合物 **1** の head 部分が His435 と相互作用していることが示唆されるが，Leu330 側の領域 (tail 部分) での相互作用はない (Figure 15).
② LXRβ 選択性の発現には，tail 部分の相互作用が必要である．
③ ピペリジン環の炭素－窒素結合を開裂し，構造の平面性を崩すことが必要である．
④ メルク社の化合物 **29** におけるベンゾイソキサゾール環上の 3 位のトリフルオロメチル基と 7 位のプロピル基の位置関係は，著者の化合物 **1** の構造と共通している．一方で，化合物 **29** はチアゾリジンジノン部位を有しており，tail 部分と相互作用することにより LXR 活性化作用が増強されているものと推察される (Figure 16).

なお，GW3965 の head 部分と tail 部分との距離を，計算化学を用いて算出した結果，11～12Å であることが推察された．そこで， GW3965 と LXRβ との共結晶の X 線結晶構造を用いて，化合物 **1** とのドッキングモデルを作製し，リガンドの結合位置を考察した．その結果，GW3965 の head 部分と化合物 **1** は同様な位置で受容体と相互作用していることが推察された．したがって， head 部分である化合物 **1** の 2-オキソクロメン骨格から 11～12Å の距離に，tail 部分としてチアゾリジノン，または，その類似構造を導入すれば LXR 活性化作用を増強することができると推察し，リンカーとしてはブタン構造を用いることとした (Figure 16).

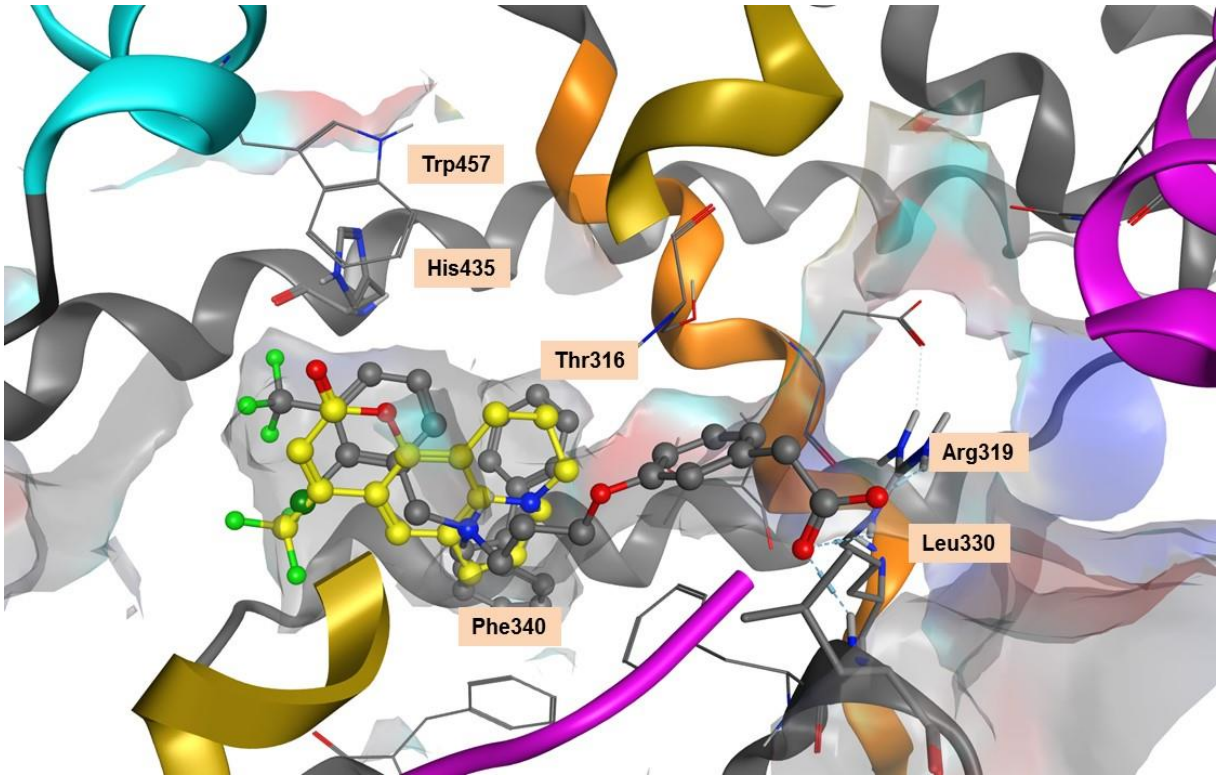


Figure 15. Docking model of GW3965 (gray) and **1** (yellow)

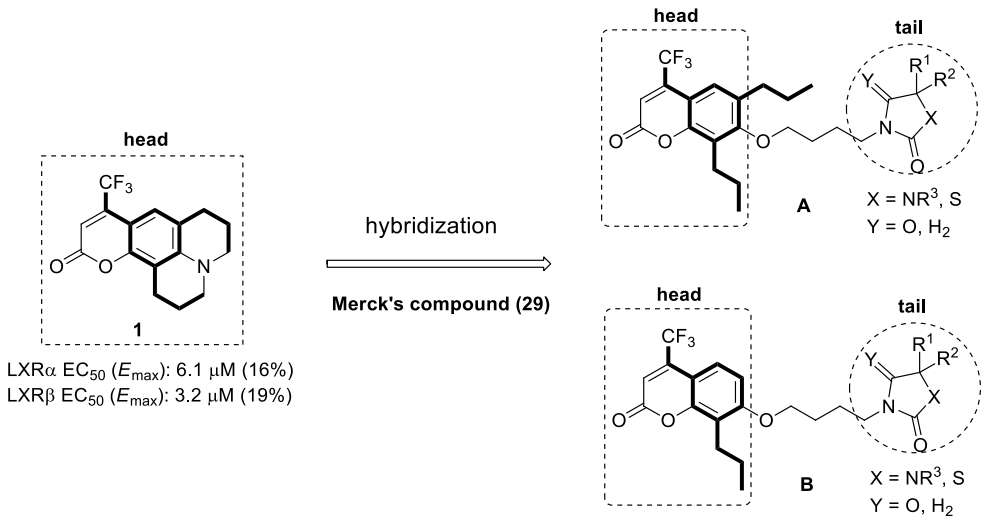


Figure 16. Our drug design of head-to-tail strategy

第二項　2-オキソクロメン誘導体の合成

前項で述べたように，著者は LXRβ 選択的アゴニストの創製を目指し，構造式 **A** および **B** で表される 2-オキソクロメン誘導体 (Figure 17) をデザインした．はじめに，その合成に向け，head 部分の合成フラグメントとなるフェノール **34** (Scheme 7) および フェノール **38** (Scheme 8) を合成した．

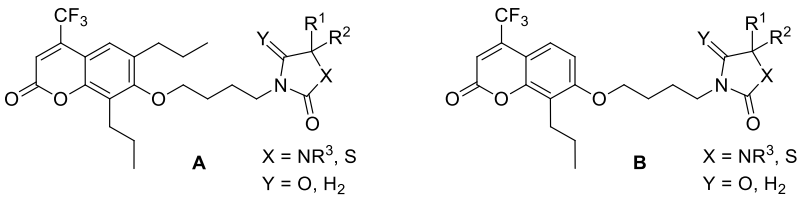
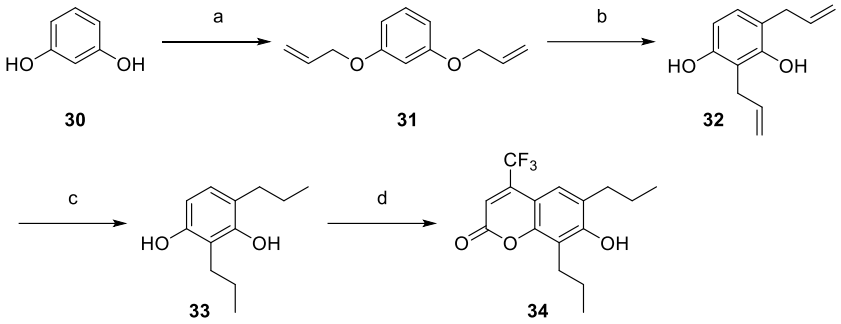


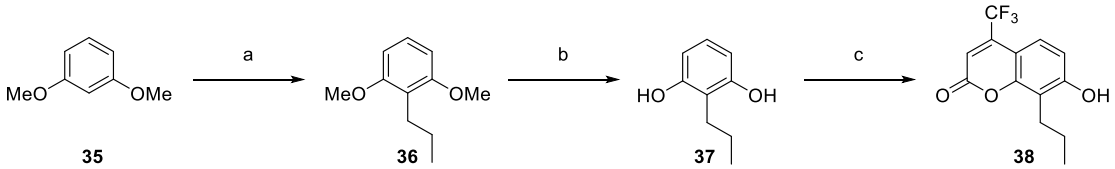
Figure 17. Structure of the 2-oxochromen derivatives **A** and **B**

すなわち, まず 1,3-ジヒドロキシベンゼン (**30**) をアリルエーテル化した後, Claisen 転位反応 [43] により 2,4-ジアリルベンゼン-1,3-ジオール (**32**) に変換した．接触水素添加反応によりアリル基を還元後，得られた化合物 **33** と 4,4,4-トリフルオロ-3-オキソブタン酸エチルとを $ZnCl_2$ の存在下，110 °C に加熱して縮合させることにより，化合物 **34** を得た．



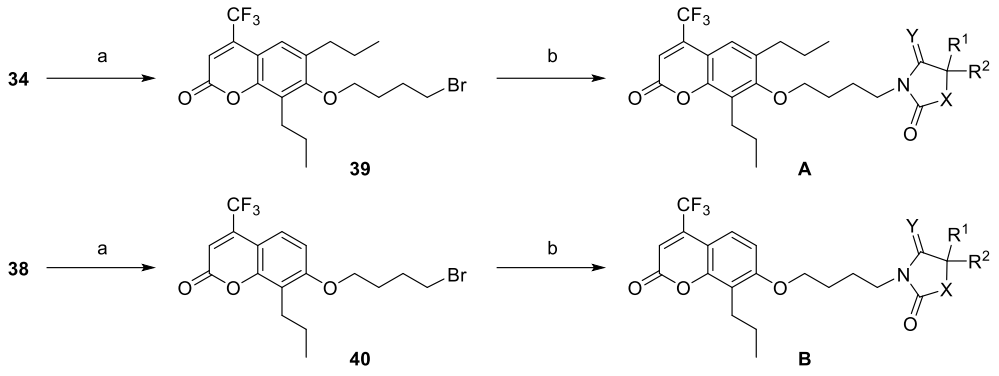
Scheme 7. Reagents and conditions: (a) allyl chloride, K_2CO_3, DMF, 70 °C, 24 h, 85%; (b) *N*,*N*-dimethylaniline, 200 °C, 16 h, 57%; (c) H_2, Pd/C, MeOH, rt, 18 h, 98%; (d) ethyl 4,4,4-trifluoro-3-oxobutanoate, $ZnCl_2$, 110 °C, 18 h, 59%.

また，1,3-ジメトキシベンゼン (**35**) を *n*-ブチルリチウムを用いてリチオ化し，続いて 1-ヨードプロパンを用いてアルキル化することにより 1,3-ジメトキシ-2-プロピルベンゼン (**36**) を得た．ジクロロメタン溶媒中で三臭化ホウ素を作用させることにより脱メチル化した後，化合物 **33** と同様の方法で 4,4,4-トリフルオロ-3-オキソブタン酸エチルを縮合させることにより，化合物 **38** を得た．



Scheme 8. Reagents and conditions: (a) *n*-BuLi, THF, 0 °C, 2 h; then PrI, 0 °C to rt, 22 h, 45%; (b) BBr_3, CH_2Cl_2, −70 °C, 1 h to rt, 2 h, 76%; (c) ethyl 4,4,4-trifluoro-3-oxobutanoate, $ZnCl_2$, 110 °C, 18 h, 77%.

こうして合成した化合物 **34** および **38** を，次に，DMF 溶媒中，K_2CO_3 の存在下で過剰量 (8–10 当量) の 1,4-ジブロモブタンと反応させ，それぞれ臭化アルキル体 **39**, **40** へと変換した．さらに，それらを DMF 溶媒中，K_2CO_3 の存在下でチアゾリジン-2,4-ジオン，ピロリジン-2,5-ジオン，オキサゾリン-2-オン，ピロリジン-2-オンおよび各種イミダゾリジン-2,4-ジオン (ヒダントイン) (Figure 18) と反応させて, tail 部位を導入することにより，目的とする **A**，**B** を得た (Scheme 9).



Scheme 9. Reagents and conditions: (a) 1,4-dibromobutane, K_2CO_3, DMF, rt, 18–21 h, 80-96%; (b) tail parts, K_2CO_3, DMF, rt, 16–20 h, 51–99%.

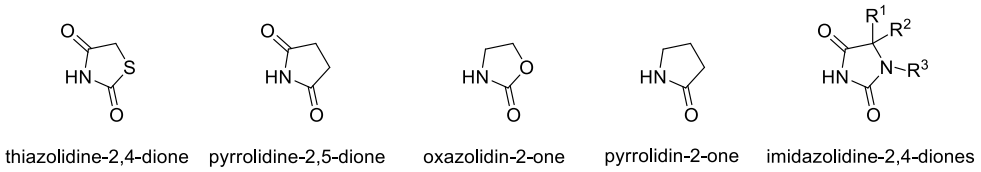
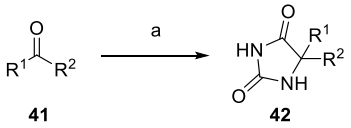


Figure 18. Structure of tail parts

なお，各種ヒダントイン **42** は Scheme 10 に示す方法にしたがって合成した．すなわち，対応するケトン **41** を含水エタノール中で NaCN と $(NH_4)_2CO_3$ とともに加熱することにより (Bucherer-Bergs 反応 [44])，化合物 **42** を得た．



Scheme 10. Reagents and conditions: (a) NaCN, $(NH_4)_2CO_3$, EtOH *aq.*, 100 °C, 47–85%.

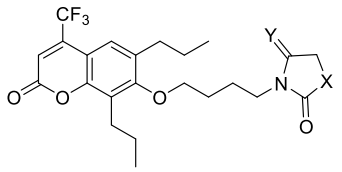
第三項　構造活性相関①

Gal4-h-LXR を用いたレポーター遺伝子アッセイを用いて，合成した各化合物による LXRα および LXRβ の活性化 (EC_{50} 値) を測定した．LXRα/β デュアルアゴニストである T0901317 の 10 μM における各サブタイプの活性強度を 100% とし，各化合物の活性化強度 (E_{max} 値) を求めた (Table 3).

まず，著者は 2-オキソクロメン誘導体 **A** の tail 部分の X および Y に位置する原子または置換基の効果を検討した．その結果を Table 3 に示す．

チアゾリジン-2,4-ジオン体 **43** (X = S, Y = O) は，EC_{50} (β) 値 1.4 μM および LXRβ の E_{max} (E_{max} (β) 値) 45% の活性化強度であり，E_{max} β/α 比で 7 倍の選択性を示した．ヒダントイン体 **44** (X = NMe, Y = O) は，**43** とほぼ同等の活性化および選択性を示した．一方，X にメチレン鎖を有するピロリジン-2,4-ジオン体 **45** (X = CH_2, Y = O) は E_{max} β/α 比で 11 倍の選択性を示したが，E_{max} (β) 値は減少した．また，オキサ

Table 3. LXR activity of the 2-oxochromene derivatives **A**[a]



A

Compound	X	Y	LXRα EC_{50}[b] (%)[c]	LXRβ EC_{50}[b] (%)[c]	Selectivity for E_{max} β/α[d]
43	S	O	2.6 (6)	1.4 (45)	7
44	NMe	O	2.6 (10)	1.3 (47)	4.7
45	CH_2	O	nd (2)	1.4 (22)	11
46	O	H_2	nd (1)	2.2 (5)	5
47	CH_2	H_2	ia (0)	ia (0)	0

nd = not determined.
ia = inactive at 10 μM.
[a] GAL4-LXR luciferase assay were performed with a top dose of 30 μM. The results are given as the mean of two independent experiments. [b] EC_{50} data is reported in μM. [c] The % of efficacy is defined as the percentage ratio between maximum fold induction for the test compound and fold induction for T0901317 at 10 μM in the same experiment.[45)]
[d] selectivity = The value of selectivity is LXRβ E_{max}/LXRα E_{max}.

ゾリジン–2–オン体 **46** (X = O, Y = H_2) では，E_{max} (β) 値が減少し，ピロリジン–2–オン体 **47** は活性化作用を示さなかった．

これらの結果より，LXRβ の活性化作用には，tail 部分にイミド構造が必要であると推察した．

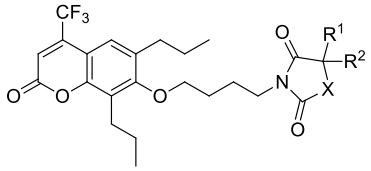
次に，*in vitro* および *in vivo* 評価にともに作用を示す化合物を見出すため，化合物 **43**, **44** を用いて，*in vivo* 評価を実施した．

まず，C57BL/6J マウスを用いて血漿および肝臓中の脂質濃度に対する影響を評価した．各化合物 30 または 100 mg/kg を一日一回 8 日間経口投与した．その結果，化合物 **43** の投与は血中脂質 (HDL-C, LDL-C, TG) に影響を及ぼさなかったが，化合物 **44** には HDL-C および TG を増加させる傾向が認められた (*in vivo* 試験結果不記載).

著者は, 上述の *in vivo* 評価の結果および構造の展開可能性を考慮し, 化合物 **44** を選択してヒダントイン環上の置換基の最適化を図ることとした．評価には先と同様に Gal4-h-LXR によるレポーター遺伝子アッセイを用いた. その結果を Table 4-1, 4-2 に示す．比較のため，化合物 **44** (Table 3) のデータも記載した．

ヒダントイン環の 1 位窒素上の置換基および 5 位置換基としてメチル基を導入した場合，導入したメチル基の数と E_{max} (β) 値との間に相関があることが認められた (R^1 = R^2 = Me: **49** > R^1 = H, R^2 = Me: **48** > R^1 = R^2 = H: **44**)．このことから，化合物の tail 部分であるヒダントイン環周辺と受容体との結合領域では疎水性相互作用が重要であると推察した．そこで，ヒダントイン環上の置換基 R^2 としてフェニル基を導入したところ (R^2 = Ph: **51**)，むしろ活性化作用は消失してしまった．一方，化合物 **51** の 1 位窒素上のメチル基を水素原子に代えたところ (**52**), 僅かに LXRβ 活性化作用を示した．次に，化合物 **52** のフェニル基上に置換基を導入し，高活性化の可能性について検討することとした．

Table 4-1. LXR activity of the 2-oxochromene derivatives **A**[a]



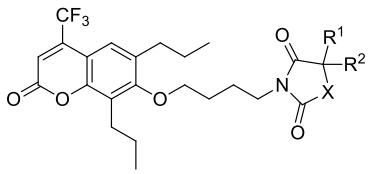
A

Compound	X	R^1	R^2	LXRα EC_{50}[b] (%)[c]	LXRβ EC_{50}[b] (%)[c]	Selectivity for E_{max} β/α[d]
44	NMe	H	H	2.6 (10)	1.3 (47)	4.7
48	NMe	H	Me	1.7 (16)	1.3 (52)	3.3
49	NMe	Me	Me	11 (21)	4.7 (70)	3.3
50	NH	H	Me	1.5 (5)	1.3 (14)	2.8
51	NMe	Me	Ph	ia (0)	ia (0)	0
52	NH	Me	Ph	ia (0)	5.3 (6)	β only

nd = not determined.
ia = inactive at 10 μM.
[a] GAL4-LXR luciferase assay were performed with a top dose of 30 μM. The results are given as the mean of two independent experiments. [b] EC_{50} data is reported in μM. [c] The % of efficacy is defined as the percentage ratio between maximum fold induction for the test compound and fold induction for T0901317 at 10 μM in the same experiment.[45)]
[d] selectivity = The value of selectivity is LXRβ E_{max}/LXRα E_{max}.

置換基 R^1 をメチル基，X を NH に固定し，電子供与性および電子求引性基をもつ種々のフェニル基を R^2 に導入し，Gal4-h-LXR によるレポーター遺伝子アッセイによって活性化作用を評価した (Table 4-2). その結果，E_{max} (β) 値の顕著な改善は認められなかったが，1,2-メチレンジオキシベンゼン体 **58** については，E_{max} (β) および選択性も比較的良好であった. しかしながら，化合物 **58** の脂溶性 (*C*log*P* of **58**: 7.57) [46)] は高く，分子全体の脂溶性を低減させる必要があった.

Table 4-2. LXR activity of the 2-oxochromene derivatives **A**[a]



A

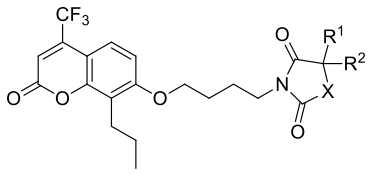
Compound	X	R^1	R^2	LXRα EC_{50}[b] (%)[c]	LXRβ EC_{50}[b] (%)[c]	Selectivity for E_{max} β/α[d]
53	NH	Me	4-MePh	ia (0)	2.4 (9)	β only
54	NH	Me	2-MeOPh	ia (0)	ia (0)	0
55	NH	Me	3-MeOPh	ia (0)	ia (0)	0
56	NH	Me	4-MeOPh	ia (0)	0.96 (8)	β only
57	NH	Me	3,4-diMeOPh	ia (0)	ia (0)	0
58	NH	Me	3,4-OCH_2OPh	nd (2)	1.2 (32)	16
59	NH	Me	4-Me_2NPh	ia (0)	ia (0)	0
60	NH	Me	4-CF_3Ph	ia (0)	nd (1)	β only
61	NH	Me	4-NO_2Ph	ia (0)	8.0 (7)	β only
62	NH	Me	4-(HO_2C)Ph	ia (0)	ia (0)	ia (0)
63	NH	Me	4-HOPh	ia (0)	ia (0)	ia (0)

nd = not determined.
ia = inactive at 10 μM.
[a] GAL4-LXR luciferase assay were performed with a top dose of 30 μM. The results are given as the mean of two independent experiments. [b] EC_{50} data is reported in μM. [c] The % of efficacy is defined as the percentage ratio between maximum fold induction for the test compound and fold induction for T0901317 at 10 μM in the same experiment.[45)]
[d] selectivity = The value of selectivity is LXRβ E_{max}/LXRα E_{max}.

そこで，2-オキソクロメン部分にプロピル基を一つだけもつプロピル体 **B** について，ジプロピル体 **A** と同様に tail 部分の置換基の違いが活性化作用に及ぼす影響を調べた．その結果，E_{max} (β) 値はプロピル基を二つもつ誘導体 **A** と比べて同等，またはそれよりも良好であることが確認された (Table 5)．特に，化合物 **2** は，化合物 **58**

と比較して LXRα 活性化作用および LXRβ 選択性は同等であるが，脂溶性を低減した (*C*log*P* of **2**: 5.96).

Table 5. LXR activity of the 2-oxochromene derivatives **B**[a]



B

Compound	X	R^1	R^2	LXRα EC_{50}[b] (%)[c]	LXRβ EC_{50}[b] (%)[c]	Selectivity for E_{max} β/α[d]
64	NMe	H	H	nd (4)	1.3 (26)	6.5
65	NMe	Me	Me	2.4 (7)	1.0 (51)	7.3
66	NH	Me	Ph	ia (0)	2.0 (8)	β only
2	NH	Me	4-MeOPh	nd (2)	1.4 (31)	16
67	NH	Me	3,4-diMeOPh	ia (0)	3.0 (9)	β only
68	NH	Me	3,4-OCH_2OPh	nd (4)	1.1 (39)	9.8
69	NH	Me	4-(HO_2C)Ph	ia (0)	ia (0)	0
70	NH	Me	4-HOPh	ia (0)	nd (2)	β only

nd = not determined.
ia = inactive at 10 μM.
[a] GAL4-LXR luciferase assay were performed with a top dose of 30 μM. The results are given as the mean of two independent experiments. [b] EC_{50} data is reported in μM. [c] The % of efficacy is defined as the percentage ratio between maximum fold induction for the test compound and fold induction for T0901317 at 10 μM in the same experiment.[45)]
[d] selectivity = The value of selectivity is LXRβ E_{max}/LXRα E_{max}.

第四項　2-オキソクロメン誘導体 **2** の薬理評価

LXRβ の活性化強度 (E_{max} (β)) および LXRβ 選択性 (Selectivity for E_{max} β/α) が共に良好であった化合物 **2** について動脈硬化疾患モデル動物の一つである Bio F_1B ハムスターを用いて *in vivo* 評価を実施することとした [47)].

なお，以降に記述する動物実験は，すべて興和株式会社 東京創薬研究所の動物実

験委員会にて審査された後，承認されたプロトコールに基づいて実施されたものである．結果は平均値±標準偏差で示した．多群間比較の場合は，一元配置分散分析 (one-way analysis of variance: one-way ANOVA)，または，二元配置分散分析 (two-way ANOVA) を用いて解析した後，post-*hoc* 解析として Dunnett's test を実施した．有意水準は，5%未満，1%未満，0.1%未満とした．すべての統計解析には SAS9.1.3 (SAS Institute Japan Ltd., Tokyo, Japan) を用いた．

はじめに，あらためて *in vitro* 評価の結果を Table 6 にまとめ，また，用量反応曲線を Figure 19 に示した．ここで，30 μM で活性が減少している原因は，各化合物の細胞毒性によるのではなく，高い濃度で評価しているために細胞が不活化していることによるものと推察している．以降の *in vitro* 評価においても，しばしば同様の現象が観測されたが，同じ原因によるものと考えている．

Table 6. LXR α/β activity of T0901317 and **2**[a]

Compound	T0901317	**2**
LXRβ EC_{50}[b] (%)[c]	0.41 (100)	1.4 (31)
LXRα EC_{50}[b] (%)[c]	0.49 (100)	nd (2)
Selectivity for E_{max} β/α[d]	1	16

nd = not determined.
[a] GAL4-LXR luciferase assay were performed with a top dose of 30 μM. The results are given as the mean of two independent experiments. [b] EC_{50} data is reported in μM. [c] The % of efficacy is defined as the percentage ratio between maximum fold induction for the test compound and fold induction for T0901317 at 10 μM in the same experiment.[45)]
[d] selectivity = The value of selectivity is LXRβ E_{max}/LXRα E_{max}.

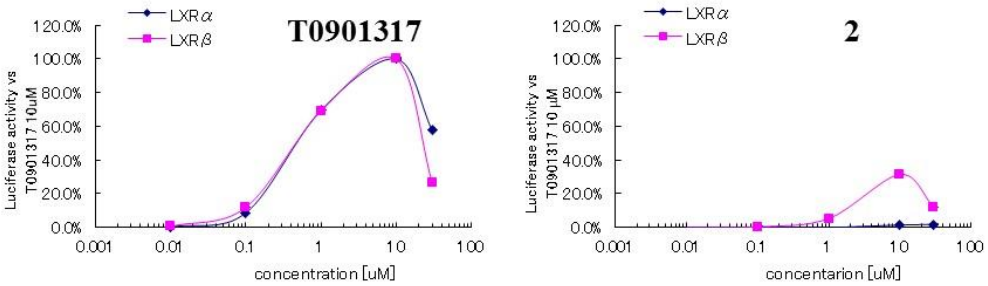


Figure 19. Dose-response curves of T0901317 and **2**

ハムスターに高コレステロール食負荷を 2 週間おこなった後，陽性対照薬 T0901317 を 1, 3, 10 mg/kg および化合物 **2** を 10, 30, 100, 300 mg/kg，各々 8 週間 1 日 1 回経口投与した．

以下に，その結果を示す．まず TC については (Figure 20)，T0901317 では 1 mg/kg および 10 mg/kg 投与において僅かな上昇が認められるが，化合物 **2** では全用量にて有意な上昇はないことがわかる．

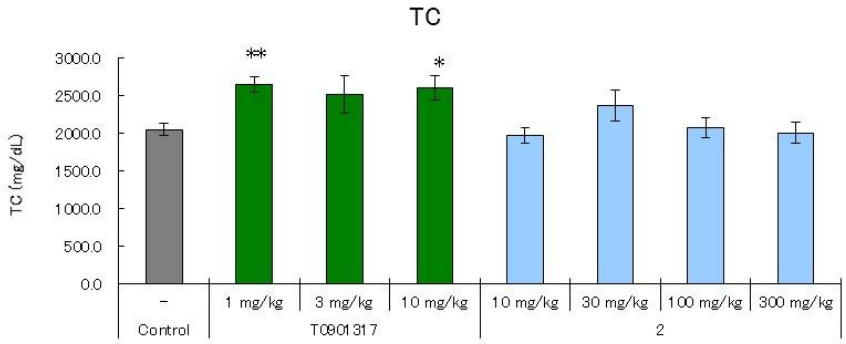


Figure 20. TC profile in T0901317 and **2**

*$p < 0.05$, ** $p < 0.01$; The statistical analysis was conducted using Dunnett's test.

Figure 21 は HDL-C および LDL-C の変化を示したものである．T0901317 では，HDL-C，LDL-C ともに 1 mg/kg 投与から用量依存的に低下することが認められる．それに対して化合物 **2** では，300 mg/kg の投与で HDL-C の僅かな上昇が認められるものの，LDL-C は全用量にて有意な変化はない．

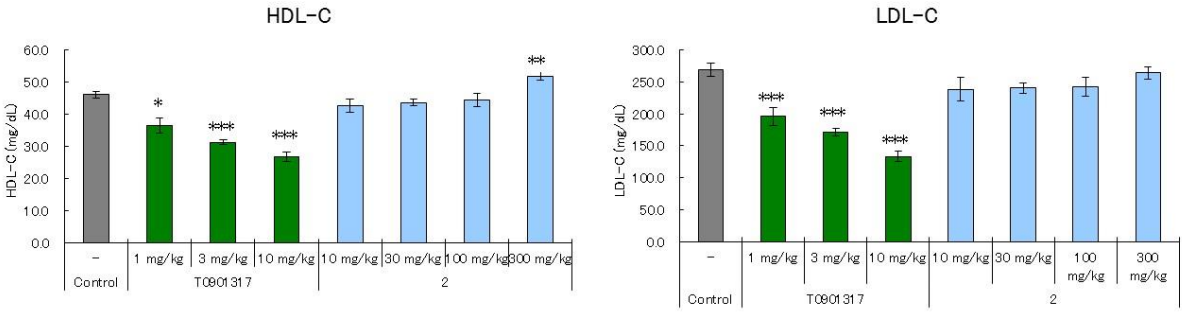


Figure 21. HDL-C and LDL-C profile in T0901317 and **2**

*$p < 0.05$, *** $p < 0.001$; The statistical analysis was conducted using Dunnett's test.

TG については (Figure 22), T0901317 が血漿 TG および肝 TG を顕著に増加させるのに対し,化合物 **2** では血漿 TG および肝 TG ともに有意な増加は確認されない.

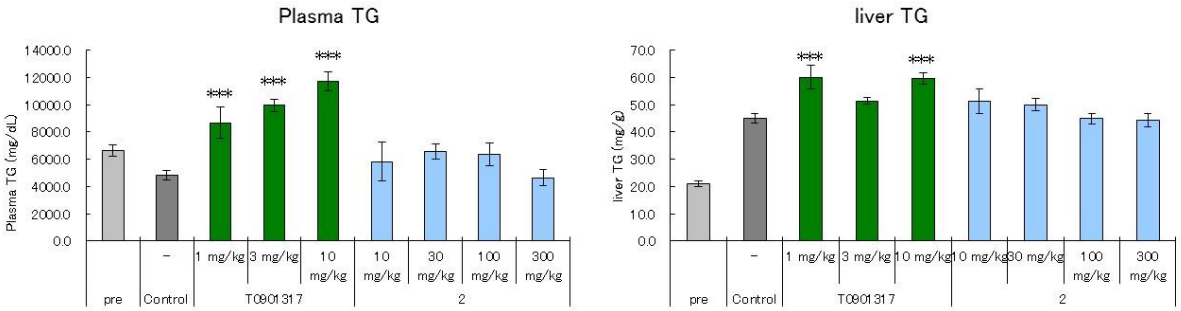


Figure 22. Plasma TG and liver TG profile in T0901317 and **2**

*$p < 0.05$, *** $p < 0.001$; The statistical analysis was conducted using Dunnett's test.

Figure 23 は脂質沈着面積を評価した結果である. T0901317 は 3 mg/kg および 10 mg/kg にて, 化合物 **2** は 300 mg/kg にて脂質沈着抑制作用が認められる.

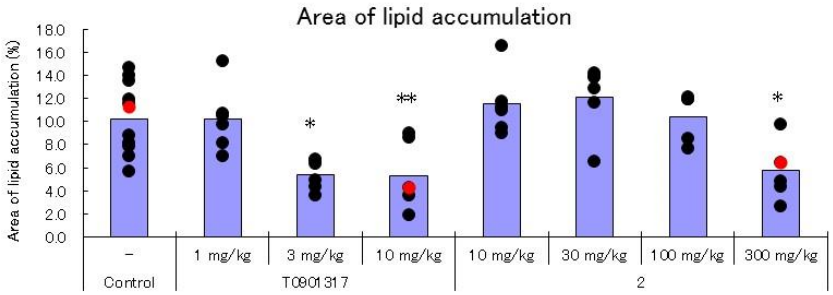


Figure 23. Area of lipid accumulation in the aortic arch in T0901317 and **2**

*$p < 0.05$, ** $p < 0.01$; The statistical analysis was conducted using Dunnett's test.

以上のように, T0901317 は 3 mg/kg および 10 mg/kg 投与にて脂質沈着抑制作用を示したが, TG を顕著に増加させてしまうことが確認された. T0901317 は LXRα/β デュアルアゴニストであるため, 肝臓での LXRα 活性化作用が TG 増加の原因であると推察される. これら結果は, T0901317 の動物モデルでの報告と一致する [29]. 一方, LXRβ 選択的アゴニストである化合物 **2** は, TG の増加を 300 mg/kg 投与でも回

避できており，望む脂質沈着抑制作用も示した．この結果から，LXRβ 選択的な活性化作用のみでも LXRα/β デュアルアゴニストである T0901317 と同等の脂質沈着抑制作用を示す可能性があることが確認された．また TG の増加については，緒言で述べた仮説のとおり，LXRα 活性化作用を減少させることで回避できることが確認できた．

第五項　2-オキソクロメン誘導体 **2** の薬物動態評価

化合物 **2** が 脂質沈着抑制作用を示したことから，さらなる構造最適化に向けて，化合物 **2** の血漿中濃度推移を確認した．前項の *in vivo* 試験と同様にハムスターを用い，300 mg/kg 投与時の血漿中濃度を測定した．その結果，化合物 **2** は投与後，速やかに代謝されてしまうことが判明した (Table 7，Figure 24) [48)].

Table 7. Drug concentration of **2** in peripheral blood after administration

Time (h)	0.5	1	2	6
2 (ng/mL)	50	53	59	0

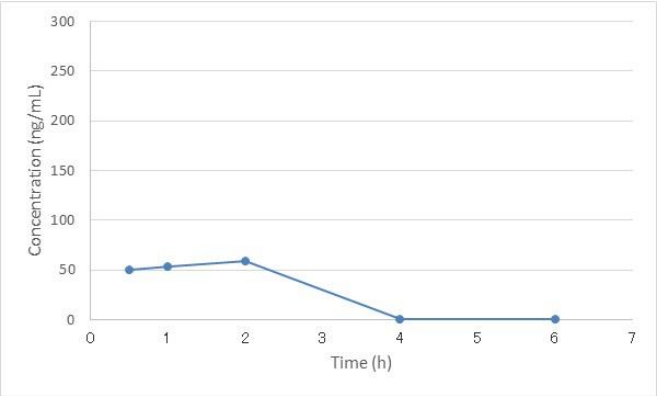


Figure 24. Drug concentration curve of **2**

第六項　小括

以上，著者は，HTS により得たヒット化合物と他社化合物情報を活用した‘head-to-tail‘のドラッグデザインにより，head 部分に 2-オキソクロメン構造を，tail 部分にヒダントイン構造をもつ LXRβ 選択的アゴニスト **2** を見出した．LXR アゴニストである T0901317 [29] や GW3965 [30] は *in vivo* 薬理評価において，末梢血にて ABCA1 mRNA 発現を亢進し，抗動脈硬化作用を示すことが報告されている．化合物 **2** には HDL-C の上昇作用が確認されていることから，この化合物の脂質沈着抑制作用は，末梢血中でのコレステロール逆転送系の亢進によるものであると推察される．一方，化合物 **2** は血中での安定性に課題があることも判明した [33]．したがって，LXRβ 活性化作用 ($E_{\max}$ (β) 値) の向上だけでなく，代謝安定性などの化合物の物性を改善する必要があることが明らかになった．

第二節　1,3-ジヒドロベンゾイソフラン誘導体の創製

第一項　ドラッグデザイン②

第一節に述べたように，HTS により得たヒット化合物からの構造最適化により，LXRβ 選択的アゴニストである 2-オキソクロメン誘導体 **2** を見出した．しかし，化合物 **2** および類似構造をもつ誘導体は，総じて LXRβ 活性化作用 (E_{max}(β)) が弱く，また，血中での代謝安定性が悪いことも判明したため，さらなる構造最適化を試みた．

まず，ドッキングモデルを作成し，LXRβ 活性化作用を検証したところ，2-オキソクロメン部位と His435 との水素結合の強度が十分ではないことが推察された (Figure 25).

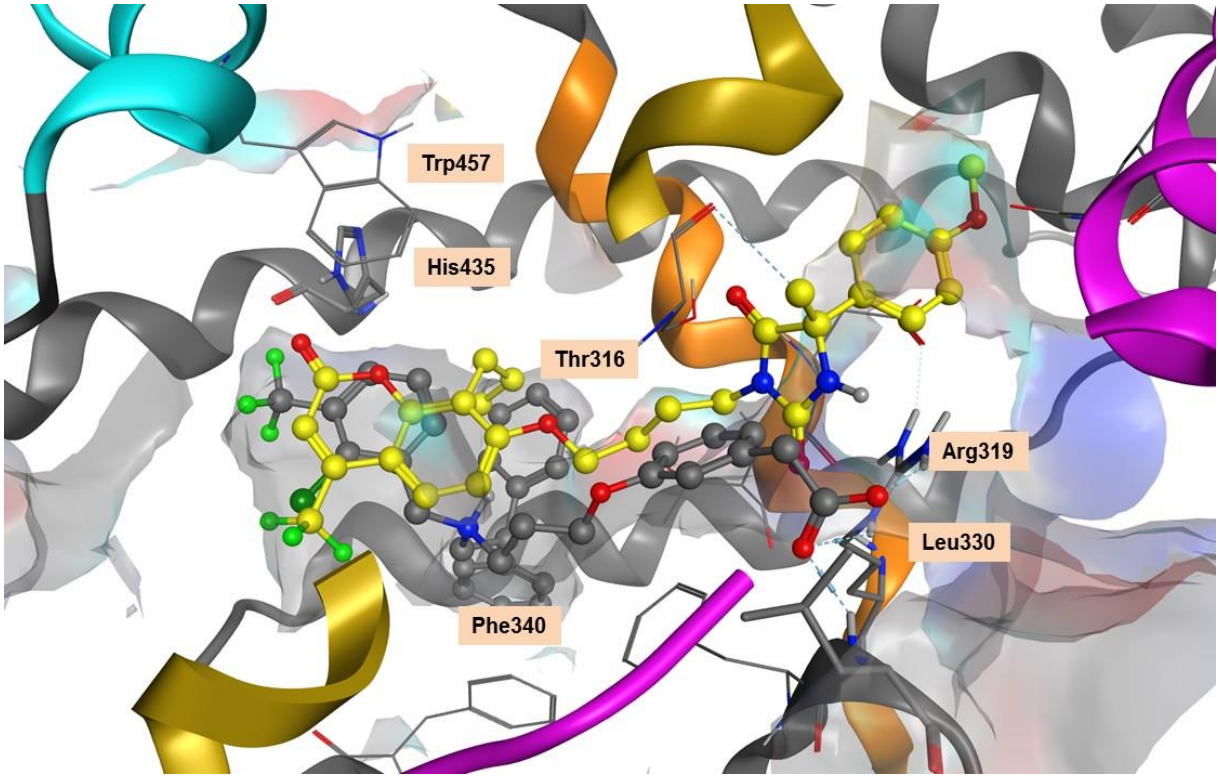


Figure 25. Docking model of GW3965 (gray) and **2** (yellow)

そこで，新たに構造最適化をおこなうにあたり，あらためて 2-オキソクロメン誘導体 **2** と比べて LXRβ 活性化作用の強い Merck 社のベンゾイソキサゾール誘導体 **29** [41] を比較対象として LXRβ とリガンドとの結合領域にある His435 と 2-オキソクロメン誘導体との相互作用の強度に影響する要因を探求することとした．

一般的に水素結合に関与する因子としては，リガンドと受容体との結合部位の電荷，

受容体の結合領域とリガンドが相互作用する距離，角度などが挙げられる．

まず，Spartan Hartree-Fock STO-3G 法による非経験的分子軌道法 [49] を用いて 2-オキソクロメン誘導体 **71** とベンゾイソキサゾール誘導体 **72** の各 head 部分の電荷を算出した．その結果，ベンゾイソキサゾール骨格の窒素および酸素原子よりも 2-オキソクロメン骨格の酸素原子の方がより強く負に帯電しており，必ずしも活性強度とは正相関しないことがわかった (Figure 26, Table 8).

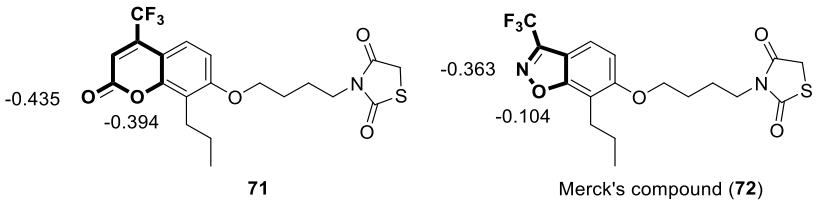


Figure 26. Charge calculated by Spartan Hartree-Fock STO-3G method in LXR agonists **71** and **72**.

Table 8. LXR α/β activity of **71** and **72**[a]

Compound	**71**	**72**
LXRβ EC_{50}[b] (%)[c]	2.0 (27)	0.70 (102)
LXRα EC_{50}[b] (%)[c]	2.7 (2)	1.3 (104)
Selectivity for E_{max} β/α[d]	14	0.98

nd = not determined.
[a] GAL4-LXR luciferase assay were performed with a top dose of 30 μM. The results are given as the mean of two independent experiments. [b] EC_{50} data is reported in μM. [c] The % of efficacy is defined as the percentage ratio between maximum fold induction for the test compound and fold induction for T0901317 at 10 μM in the same experiment.[45]
[d] selectivity = The value of selectivity is LXRβ E_{max}/LXRα E_{max}.

そこで，化合物 **2** の 2-オキソクロメン骨格および化合物 **72** のベンゾイソキサゾール骨格を念頭に置き，2-オキソクロメン構造をクロマン構造 (**II**) または 1,3-ジヒドロイソベンゾフラン構造 (**III**，**IV**) へと変えてみることを考えた (Figure 27). これにより電気的に陰性な酸素原子と His435 との位置関係を少しずつ変化させ，その影響を調べることを意図した．

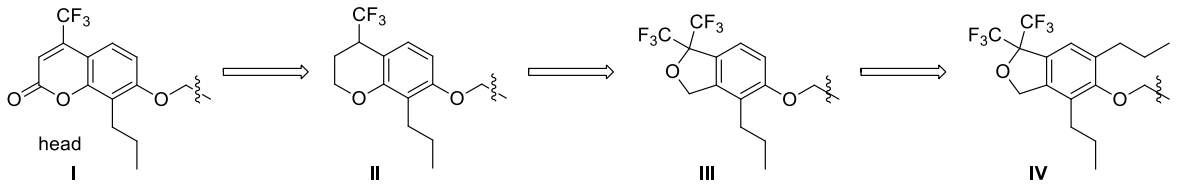


Figure 27. Molecular design to modify the head structure of **I**

第二項　クロマンおよび 1,3-ジヒドロイソベンゾフラン誘導体の合成

前項で述べたデザインに基づき, 構造式 **C**, **D** および **E** で表されるクロマン誘導体および 1,3-ジヒドロイソベンゾフラン誘導体 (Figure 28) を合成することとした．まず，その head 部分の合成フラグメントとなるフェノール **75** (Scheme 11)，フェノール **87** (Scheme 12) および フェノール **96** (Scheme 13) を合成した．

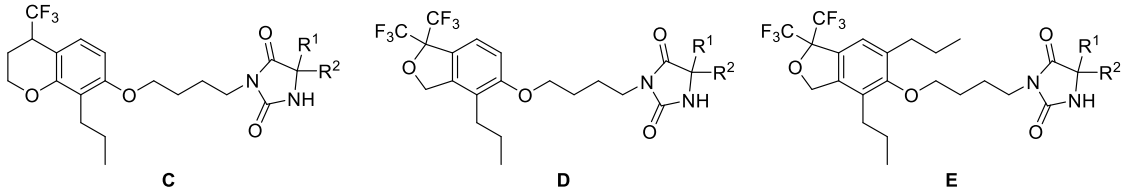
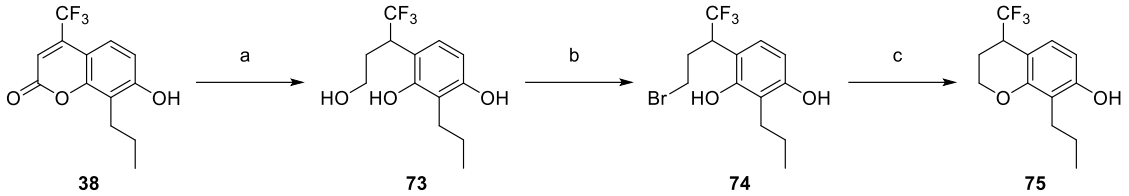


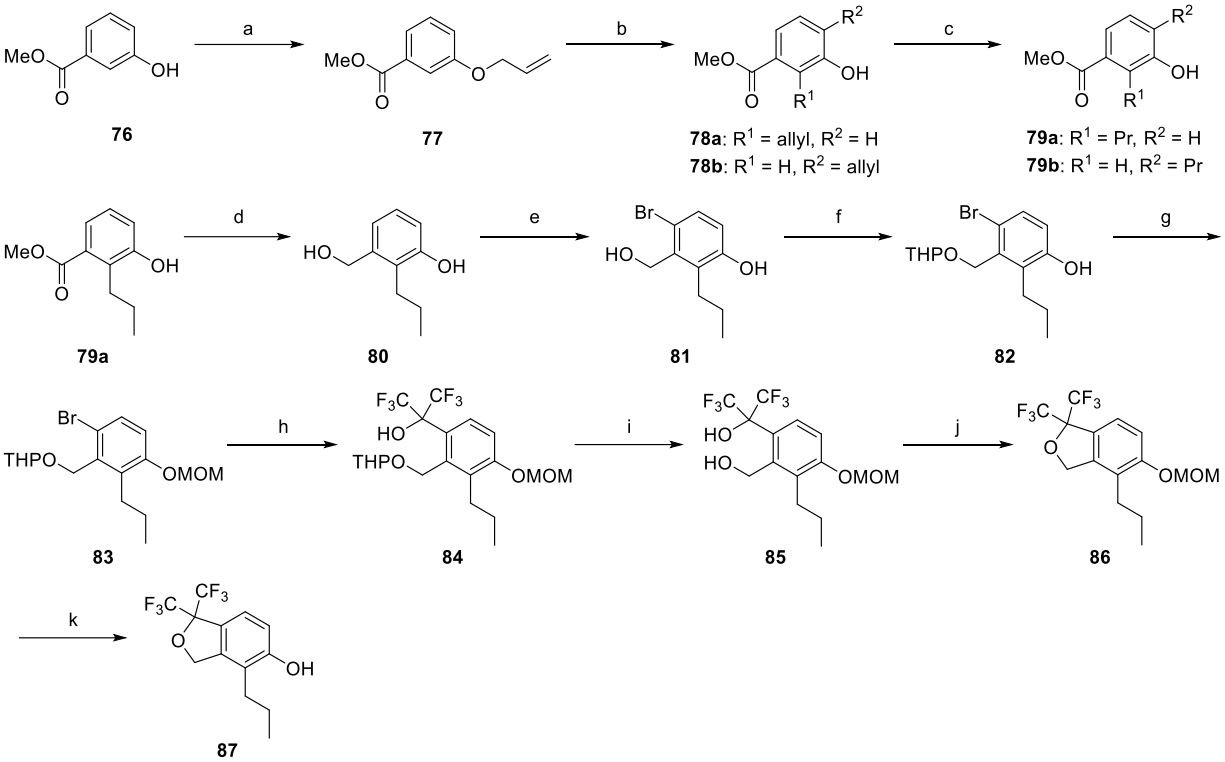
Figure 28. Structure of the chroman derivatives **C**, the 1,3-dihydroisobenzofuran derivatives **D** and **E**

はじめに，化合物 **38** (第一章第一節第二項参照) を THF 溶媒中で $LiAlH_4$ にて還元し，トリオール **73** を得た．次に，化合物 **73** を，THF 溶媒中でトリフェニルホスフィンと四臭化炭素を作用させることにより，臭化アルキル体 **74** へと変換した．さらに，DMF 溶媒中で K_2CO_3 を作用させて閉環させ，化合物 **75** を得た．



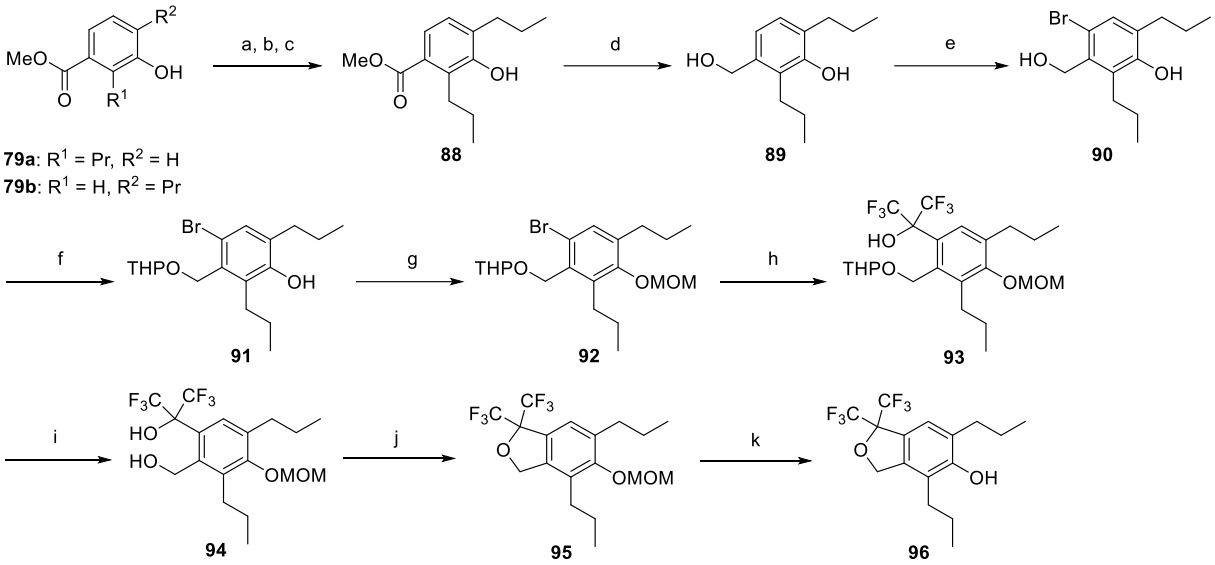
Scheme 11. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C, 1 h; (b) CBr_4, PPh_3, THF, rt, 10 min; (c) K_2CO_3, DMF, rt, 17 h, 70% for 3 steps.

次に，3-ヒドロキシ安息香酸メチル (**76**) のアリルエーテル化で得た化合物 **77** を *N*,*N*-ジメチルアニリン中，210 °C に加熱し，Claisen 転位反応によって 2-アリル-3-ヒドロキシ安息香酸メチル (**78a**) および 4-アリル-3-ヒドロキシ安息香酸メチル (**78b**) の混合物を得た．この混合物を接触水素添加反応に付し，シリカゲルカラムクロマトグラフィーによる分離を経て，2-プロピル-3-ヒドロキシ安息香酸メチル (**79a**) を得た．続いて，化合物 **79a** を THF 溶媒中，0 °C で $LiAlH_4$ にて還元し，ベンジルアルコール **80** へと変換した後，CH_2Cl_2/MeOH 混合溶媒中で三臭化テトラブチルアンモニウム (*n*-Bu_4NBr_3) を作用させることにより，C4 位を選択的に臭素化して，化合物 **81** を得た．次に，化合物 **81** に CH_2Cl_2 溶媒中で *p*-TsOH·H_2O および 3,4-ジヒドロ-*2H*-ピラン (DHP) を作用させ，アルコール部位を選択的に 2-テトラヒドロピラニル基で保護して，さらに，得られた化合物 **82** のフェノール性水酸基をメトキシメチル基で保護して，化合物 **83** とした．続いて，*n*-ブチルリチウムを用いてハロゲン－金属交換した後，1,1,1,3,3,3-ヘキサフルオロアセトンと反応させ，付加体 **84** を得た．この化合物 **84** から含水 THF 中，酢酸を用いて 2-テトラヒドロピラニル基を除去した後，光延反応[50] による分子内エーテル化により化合物 **86** を得た．最後に，EtOH 中，2 M 塩酸を作用させることにより，化合物 **86** からメトキシメチル基を除去し，化合物 **87** を得た．



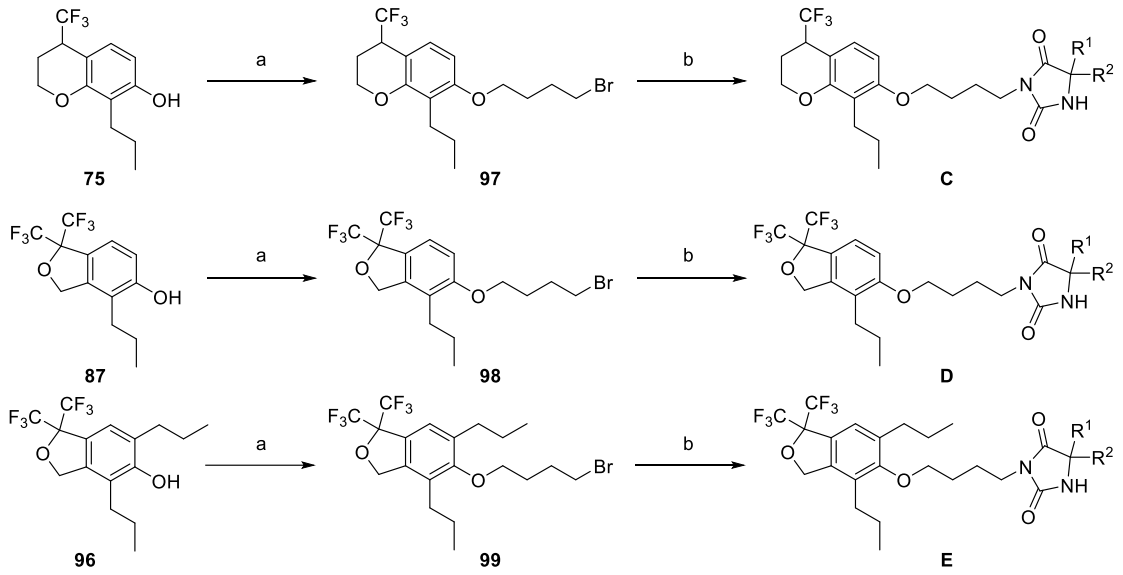
Scheme 12. Reagents and conditions: (a) allylCl, K_2CO_3, DMF, 100 °C, 7 h, 95%; (b) $PhNMe_2$, 210 °C, 8 h, 80% (mixture of **78a** and **78b**); (c) H_2, Pd/C, MeOH, rt, 24 h, 56% (**79a**); (d) $LiAlH_4$, THF, rt, 3 h, 91%; (e) *n*-Bu_4NBr_3, CH_2Cl_2/MeOH, 0 °C, 1 h, 67%; (f) DHP, *p*-TsOH·H_2O, CH_2Cl_2, rt, 5 h, 70%; (g) MOMCl, NaH, DMF, 0 °C to rt, 2 h, 83%; (h) i) *n*-BuLi, THF, −78 °C, 15 min then −45 °C, 1.5 h; ii) hexafluoroacetone anhydrous, THF, −78 °C to 0 °C, 5 h, then rt, 12 h, 90%; (i) AcOH, THF/H_2O, 50 °C, 3 h, 92%; (j) DEAD, PPh_3, CH_2Cl_2, rt, 17 h, 93%; (k) 2 M HCl, EtOH, rt, 2 h, 96%.

また，化合物 **79a** と **79b** の混合物を利用し，Scheme 12 と同様のプロピル基導入およびジヒドロイソベンゾフラン環の構築を経て，化合物 **96** を合成した (Scheme 13).



Scheme 13. Reagents and conditions: (a) allylCl, K_2CO_3, DMF, 100 °C, 7 h, 94%; (b) $PhNMe_2$, 210 °C, 8 h, 81%; (c) H_2, Pd/C, MeOH, rt, 24 h, 99%; (d) $LiAlH_4$, THF, rt, 3 h, 92%; (e) *n*-Bu_4NBr_3, CH_2Cl_2/MeOH, 0 °C, 1 h, 65%; (f) DHP, *p*-TsOH·H_2O, CH_2Cl_2, rt, 5 h, 81%; (g) MOMCl, NaH, DMF, 0 °C to rt, 2 h, 92%; (h) i) *n*-BuLi, THF, −78 °C, 15 min then −45 °C, 1.5 h; ii) hexafluoroacetone anhydrous, THF, −78 °C to 0 °C, 5 h, then rt, 12 h, 73%; (i) AcOH, THF/H_2O, 50 °C, 18 h, 81%; (j) DEAD, PPh_3, CH_2Cl_2, rt, 17 h, 95%; (k) 2M HCl in EtOH, EtOH, rt, 2 h, 99%.

こうして合成した化合物 **75**，**87** および **96** より，クロマン誘導体 **C**，1,3-ジヒドロイソベンゾフラン誘導体 **D** および **E** を合成した (Scheme 14)．すなわち，化合物 **75** を DMF 溶媒中で K_2CO_3 存在下にて過剰量の 1,4-ジブロモブタンと反応させ，臭化アルキル体 **97** へと誘導した．さらに，これを用いて，DMF 溶媒中，K_2CO_3 存在下にて種々のヒダントイン誘導体をアルキル化して **C** を得た．また，同様の方法により，**D** および **E** を合成した．



Scheme 14. Reagents and conditions: (a) 1,4-dibromobutane, K_2CO_3, DMF, rt, 18–20 h, 46-99%; (b) **42**, K_2CO_3, DMF, rt, 13-20 h, 81–99%.

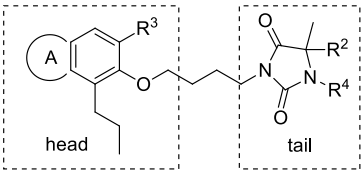
第三項　構造活性相関②

合成した各化合物 (**C**~**E**) について，第一章第一節の構造活性相関①と同様に Gal4-h-LXR を用いたレポーター遺伝子アッセイを用いて，LXRα および LXRβ に対する活性化を測定し (EC_{50} 値)，LXRα/β デュアルアゴニストである T0901317 の 10 μM における活性化強度との比(E_{max} 値) を求めた．

はじめに，Head 部分の構造の違いが及ぼす影響を検討した (Table 9)．Tail 部分については，これまでの検討で比較的良好な活性化作用を示した化合物 **65** および **2** と同じ構造に固定した．

クロマン誘導体 **100** は，2-オキソクロメン誘導体 **65** と同等の LXRβ 選択性を有していたが，E_{max} (β) 値は化合物 **65** より低かった．一方，1,3-ジヒドロイソベンゾフラン誘導体 **102** は，E_{max} (β) 値が T0901317 と同等にまで向上した (**102**; EC_{50} (β) = 0.86 μM，E_{max} (β) = 95%) が，2-オキソクロメン誘導体 **65** と比べて LXRβ 選択性は低下した．また，tail 部分であるヒダントイン環上の置換基に 4–メトキシフェニルを有する 2-オキソクロメン誘導体 **2** と比べて，同じ置換基を有する 1,3-ジヒドロイソベンゾフラン誘導体 **103** は，LXRβ 選択性は低下したものの E_{max} (β) 値が向上した．

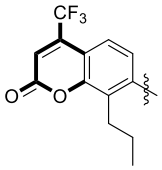
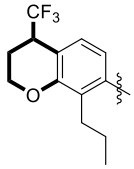
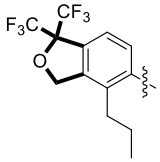
Table 9. Activity of various LXR agonists[a]



R^3 = H or propyl

a: R^2 = R^4 = Me

b: R^2 = 4-methoxyphenyl, R^4 = H

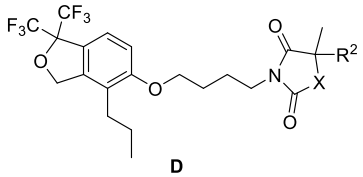
Compound	head	tail	LXRα EC_{50}[b] (%)[c]	LXRβ EC_{50}[b] (%)[c]	Selectivity for E_{max} β/α[d]
65		a	2.4 (7)	1.0 (51)	7.3
2		b	ia (2)	1.4 (31)	16
100		a	nd (3)	2.2 (21)	7.0
101		b	nd	nd	nd
102		a	2.2 (82)	0.86 (95)	1.2
103		b	1.7 (81)	1.0 (104)	1.3

nd = not determined.
[a] GAL4-LXR luciferase assay were performed with a top dose of 30 μM. The results are given as the mean of two independent experiments. [b] EC_{50} data is reported in μM. [c] The % of efficacy is defined as the percentage ratio between maximum fold induction for the test compound and fold induction for T0901317 at 10 μM in the same experiment.[45)]
[d] selectivity = The value of selectivity is LXRβ E_{max}/LXRα E_{max}.

そこで，化合物 **102**, **103** を選択し，tail 部分であるヒダントイン環上の置換基の最適化を試みた．なお，第一章第一節で述べたように，2-オキソクロメン誘導体の構造活性相関の結果，tail 部分とその結合領域においては疎水性相互作用が重要であることが示唆されていたので，ここでも R^2 として種々の置換フェニル基を導入することとした (Table 10-1, 10-2)．比較のため，化合物 **102**, **103** (Table 9) のデータも記載した．

その結果，置換基 R^2 として単なるフェニル基をもつ化合物 **104** では，E_{max} (β) 値が低下したが，フェニル基上に電子供与性基を導入すると，E_{max} (β) 値が高くなり，特に化合物 **3**, **115**, **116** は T0901317，GW3965 および化合物 **103** よりも高い E_{max} (β) 値を示した．しかし，一連の化合物は LXRβ 選択性が低く，最も高いものでも 4.6 倍程度 (**106**) であった．

Table 10-1. LXR activity of the 1,3-dihydroisobenzofuran derivatives **D**[a]

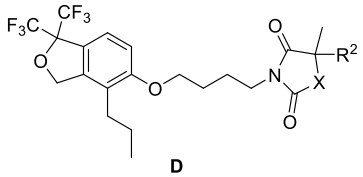


D

Compound	X	R^2	LXRα EC_{50}[b] (%)[c]	LXRβ EC_{50}[b] (%)[c]	Selectivity for E_{max} β/α[d]
102	NMe	Me	2.2 (82)	0.9 (95)	1.2
104	NH	Ph	1.9 (30)	2.1 (28)	0.9
105	NH	4-MePh	1.6 (64)	1.0 (63)	1.0
106	NH	4-*t*-BuPh	7.8 (13)	3.7 (60)	4.6
107	NH	4-(NC)Ph	1.6 (83)	1.1 (50)	0.6
108	NH	4-(HO_2C)Ph	1.8 (59)	1.4 (24)	0.4
109	NH	4-HOPh	1.8 (14)	1.9 (6)	0.4
110	NH	2-MeOPh	2.4 (28)	nd (1)	0.04
111	NH	3-MeOPh	2.3 (33)	1.7 (74)	2.2
103	NH	4-MeOPh	1.7 (81)	1.0 (104)	1.3

nd = not determined.
ia = inactive at 10 μM.
[a] GAL4-LXR luciferase assay were performed with a top dose of 30 μM. The results are given as the mean of two independent experiments. [b] EC_{50} data is reported in μM. [c] The % of efficacy is defined as the percentage ratio between maximum fold induction for the test compound and fold induction for T0901317 at 10 μM in the same experiment.[45)]
[d] selectivity = The value of selectivity is LXRβ E_{max}/LXRα E_{max}.

Table 10-2. LXR activity of the 1,3-dihydroisobenzofuran derivatives **D**[a]



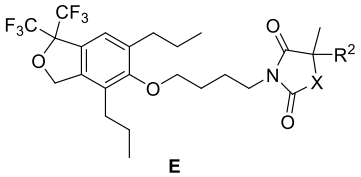
D

Compound	X	R^2	LXRα EC_{50}[b] (%)[c]	LXRβ EC_{50}[b] (%)[c]	Selectivity for E_{max} β/α[d]
112	NH	3,4-diMeOPh	2.3 (30)	2.4 (63)	2.1
113	NH	3,4,5-triMeOPh	1.6 (4)	nd (2)	0.5
114	NH	3,4-OCH_2OPh	1.2 (80)	0.4 (103)	1.3
3	NH	3,4-$O(CH_2)_2OPh$	1.1 (99)	0.5 (129)	1.3
115	NH	4-PrOPh	0.8 (106)	1.4 (130)	1.2
116	NH	4-*i*-PrOPh	1.3 (92)	1.7 (126)	1.4

nd = not determined.
ia = inactive at 10 μM.
[a] GAL4-LXR luciferase assay were performed with a top dose of 30 μM. The results are given as the mean of two independent experiments. [b] EC_{50} data is reported in μM. [c] The % of efficacy is defined as the percentage ratio between maximum fold induction for the test compound and fold induction for T0901317 at 10 μM in the same experiment.[45)]
[d] selectivity = The value of selectivity is LXRβ E_{max}/LXRα E_{max}.

次に, head 部位のベンゼン環上に二つのプロピル基をもつ 1,3-ジヒドロイソベンゾフラン誘導体 **E** について，同様の活性評価を実施した (Table 11). その結果，化合物 **129~130** は，化合物 **3**, **114~116** と比べて E_{max} (β) 値は低下するが (E_{max} (β); **129**: 73%, **130**: 77%)，LXRα 活性化作用を示さず，選択的に LXRβ を活性化することが明らかになった.

Table 11. LXR activity of the 1,3-dihydroisobenzofuran derivatives **E**[a]



E

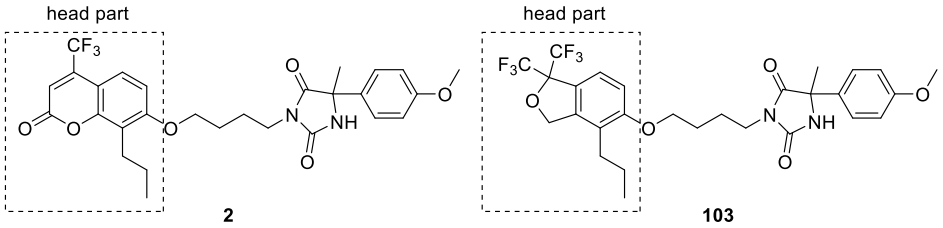
Compound	X	R^2	LXRα EC_{50}[b] (%)[c]	LXRβ EC_{50}[b] (%)[c]	Selectivity for E_{max} β/α[d]
117	NMe	Me	1.0 (103)	0.5 (155)	1.5
118	NH	Ph	1.8 (21)	1.4 (78)	3.7
119	NH	4-MePh	1.9 (31)	1.4 (50)	1.6
120	NH	4-*t*-BuPh	nd (2)	8.5 (8)	4.0
121	NH	4-(NC)Ph	8.1 (28)	4.9 (17)	0.6
122	NH	2-MeOPh	nd (1)	nd (3)	3.0
123	NH	3-MeOPh	ia (0)	ia (0)	-
124	NH	4-MeOPh	1.9 (38)	1.2 (66)	1.7
125	NH	3,4-diMeOPh	1.7 (58)	1.0 (29)	0.5
126	NH	3,4,5-triMeOPh	1.9 (23)	1.0 (7)	0.3
127	NH	3,4-OCH_2O-Ph	1.3 (97)	1.2 (83)	0.9
128	NH	3,4-$O(CH_2)_2OPh$	1.2 (101)	0.9 (74)	0.7
129	NH	4-PrOPh	ia (0)	7.2 (73)	β only
130	NH	4-*i*-PrOPh	ia (0)	4.8 (77)	β only

nd = not determined.
ia = inactive at 10 μM.
[a] GAL4-LXR luciferase assay were performed with a top dose of 30 μM. The results are given as the mean of two independent experiments. [b] EC_{50} data is reported in μM. [c] The % of efficacy is defined as the percentage ratio between maximum fold induction for the test compound and fold induction for T0901317 at 10 μM in the same experiment.[45)]
[d] selectivity = The value of selectivity is LXRβ E_{max}/LXRα E_{max}.

第四項　2-オキソクロメンおよび 1,3-ジヒドロイソベンゾフラン誘導体の薬物動態評価

Head 部位の構造の変化が代謝安定性へ与える影響を確認するため, 2-オキソクロメン誘導体 **2** および 1,3-ジヒドロイソベンゾフラン誘導体 **103** の肝 CL を評価した (Table 12). その結果, 化合物 **2** の肝 CL (μL/min/mg protein) は, mouse/hamster/human にて各々 397/>500/393 と高値であり, 血中暴露量の低さ (第一節, 第五項, Table 7) の原因となっていることが推察された. 一方, 化合物 **103** の肝 CL は, 化合物 **2** と比べて改善傾向にはあったが (**103**: CLint (μL/min/mg protein) = 43/131/100 (mouse/hamster/human)), 十分とは言えなかった.

Table 12. Hepatic CLint (μL/min/mg protein) of the 2-oxochromene **2** and the 1,3-dihydroisobenzofuran derivatives **103**



Compound	Mouse	Hamster	Human
2	397	>500	393
103	43	131	100

第五項　小括

Head 部分を 2-オキソクロメン構造から 1,3-ジヒドロイソベンゾフラン構造に換えることにより E_{max} (β) 値が向上し, 代謝安定性 (hepatic CL) にも改善傾向が見られた. また, ヒダントイン環の 5 位置換基として 4-プロポキシフェニルまたは 4-イソプロポキシフェニルをもつ化合物 **129**, **130** において良好な β 選択性が発現することが明らかになった.

第三節　1,1-ビス(トリフルオロメチル)カルビノール誘導体の創製

第一項　ドラッグデザイン③

前節までに述べたように, LXRβ に選択的にアゴニスト活性を示す 2-オキソクロメンおよび 1,3-ジヒドロイソベンゾフラン誘導体を見出した．しかし，2-オキソクロメン誘導体は LXRβ 活性化作用 (E_{max} (β) 値) 自体は十分とは言えず，また代謝安定性 (hepatic CL) は著しく低かった．また，1,3-ジヒドロイソベンゾフラン誘導体は，LXRβ 活性化作用および代謝安定性に改善はあるものの十分ではなく，また LXRβ 選択性は 2-オキソクロメン誘導体よりも低かった．そこで，さらなる構造最適化を図った．

ここで，LXRβ 選択性に関しては，主に tail 部分のヒダントイン環上の置換基の最適化による向上を目指した．また，代謝安定性の改善については，分子全体の物性の改善を試みることとした．すなわち，前節において，head 部分の 1,3-ジヒドロイソベンゾフラン構造に換えることによって，代謝安定性 (hepatic CL) を改善する傾向が確認されていたことから，head 部分を構造変換することを計画した．また，LXRβ 活性化作用の向上においては，head 部分の構造変換にともなった化合物と LXRβ との結合領域における His435 との相互作用への影響をみることとした．

すなわち，LXRα/β デュアルアゴニストである T0901317 の 1,1-ビス(トリフルオロメチル)カルビノール構造は，1,3-ジヒドロイソベンゾフラン構造のイソフラン環を開環した構造に相当するものであることから, head 部分にこの構造を採用することとした (Figure 29).

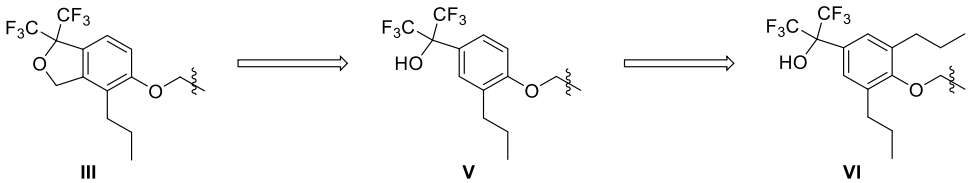


Figure 29. Molecular design to modify the head structure of **III**

第二項　1,1-ビス(トリフルオロメチル)カルビノール誘導体の合成

前項で述べたドラッグデザイン (Figure 29) に基づいて，構造式 **F** および **G** で表される 1,1-ビス(トリフルオロメチル)カルビノール誘導体 (Figure 30) を合成するべく，まず，head 部分の合成フラグメントとなるフェノール **140** (Scheme 15) およびフェノール **147** (Scheme 16) を合成した.

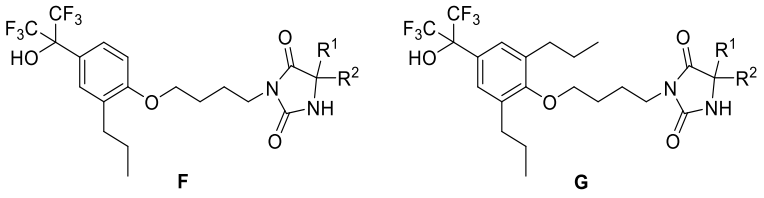
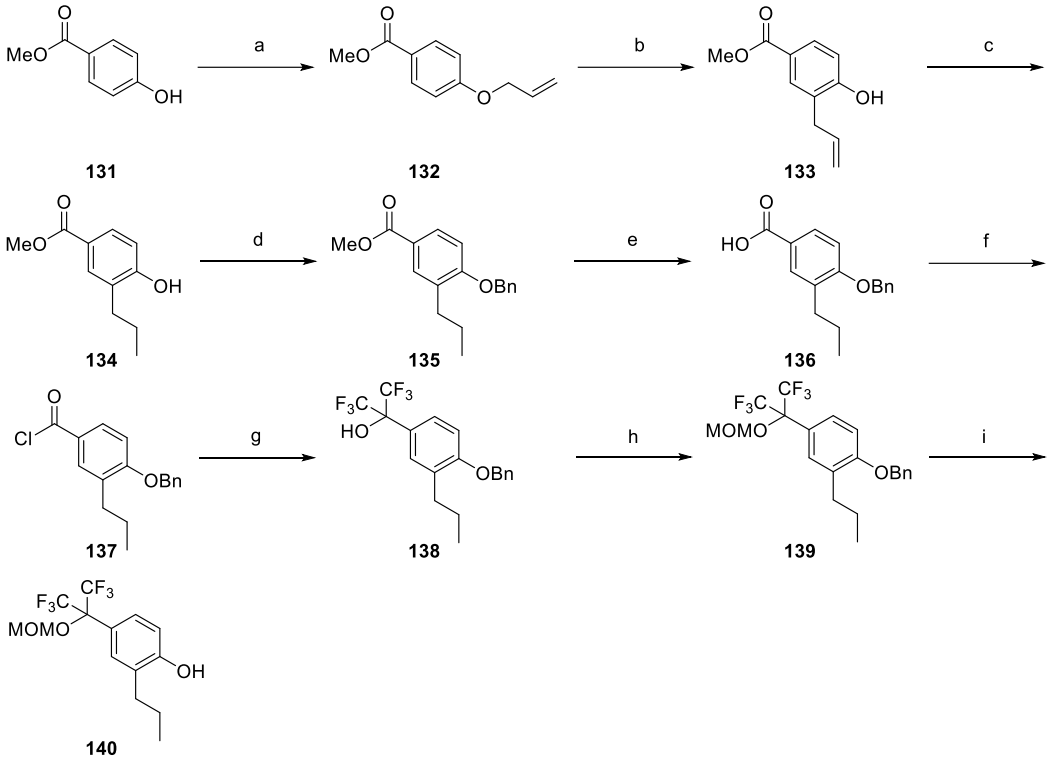


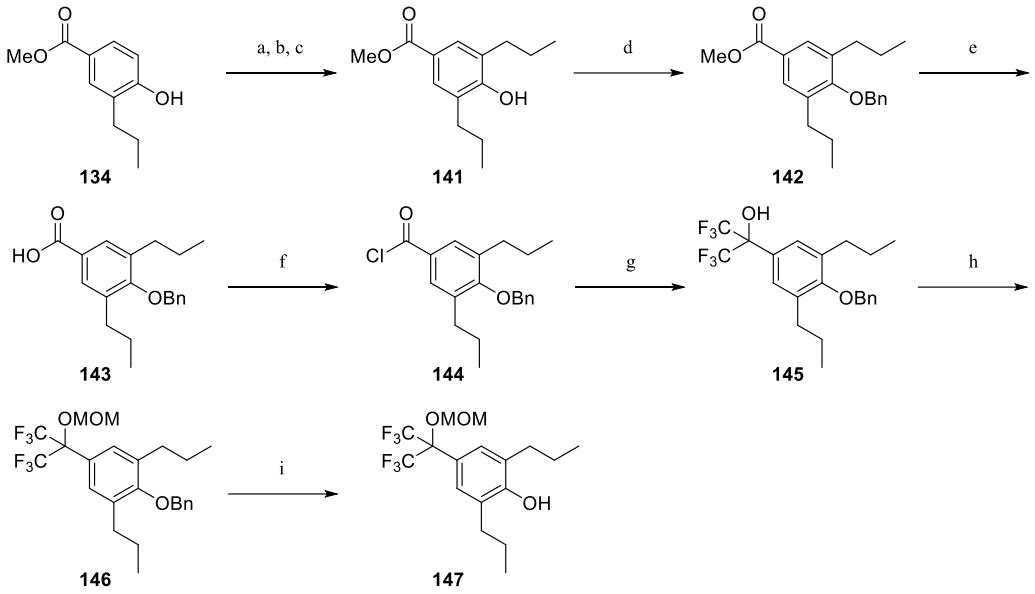
Figure 30. Structure of the 1,1-bistrifluoromethylcarbinol derivatives **F** and **G**

はじめに，4-ヒドロキシ安息香酸メチル (**131**) を，DMF 溶媒中，K_2CO_3 と塩化アリルを用いてアリルエーテル化した後，Claisen 転位反応により 3-アリル-4-ヒドロキシ安息香酸メチル (**133**) へと変換した. 接触水素添加反応によりアリル基をプロピル基へと還元し，さらに，フェノール性水酸基をベンジルエーテル化し，化合物 **135** へと誘導した. 得られた化合物 **135** のメチルエステル部位をカルボン酸へと加水分解した後，塩化チオニルを用いて酸塩化物 **137** へ変換した. 化合物 **137** をアルゴンガス雰囲気下， DME 溶媒中，トリフルオロメチルトリメチルシラン ($TMSCF_3$) およびフッ化テトラメチルアンモニウム (Me_4NF) と反応させ，ビストリフルオロメチル化し，化合物 **138** を得た. さらに，化合物 **138** のカルビノール部位の水酸基をメトキシメトキシエーテル化し, 加水素分解反応によりベンジル基を除去して化合物 **140** を得た.



Scheme 15. Reagents and conditions: (a) allyl chloride, K_2CO_3, DMF, 50 °C, 18 h, 99%; (b) $PhNMe_2$, 210 °C, 18 h, 64%; (c) H_2, Pd/C, MeOH, rt, 24 h, 88%; (d) BnBr, K_2CO_3, DMF, 80 °C, 2 h, 99%; (e) 2 N NaOH *aq*., EtOH, 50 °C, 2 h, 98%; (f) $SOCl_2$, 70 °C, 2 h; (g) $TMSCF_3$, Me_4NF, DME, −78 °C to rt, 18 h, 72% for 2 steps; (h) MOMCl, NaH, THF, rt, 18 h, 90%; (i) H_2, Pd/C, MeOH, rt, 24 h, 99%.

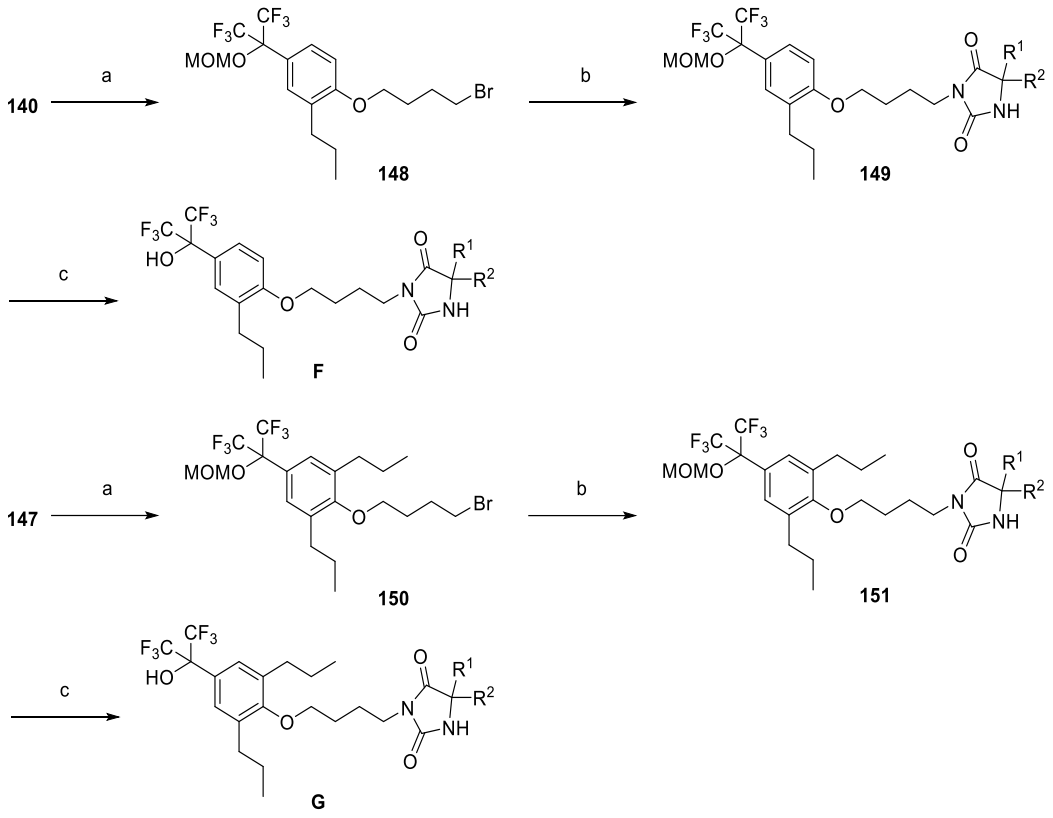
また，上記の化合物 **134** を利用し，Scheme 15 と同様の手法によるプロピル基導入および 1,1-ビス(トリフルオロメチル)カルビノール構造の形成を経て，プロピル基を二つもつ化合物 **147** を合成した (Scheme 16).



Scheme 16. Reagents and conditions: (a) allylCl, K_2CO_3, DMF, 50 °C, 18 h, 94%; (b) $PhNMe_2$, 210 °C, 18 h, 98%; (c) H_2, Pd/C, MeOH, rt, 24 h, 99%; (d) BnBr, K_2CO_3, DMF, 70 °C, 2 h, 99%, (e) 2 N NaOH *aq*., EtOH, reflux, 2 h, 82%; (f) $SOCl_2$, 70 °C, 2 h; (g) $TMSCF_3$, *n*-Bu_4NF, DME, −78 °C to rt, 20 h, 67% for 2 steps; (h) MOMCl, NaH, THF, rt, 22 h, 89%; (i) H_2, Pd/C, MeOH, rt, 24 h, 90%.

こうして合成した 1,1-ビス(トリフルオロメチル)カルビノール誘導体 **140** および **147** をそれぞれ目的とする **F** および **G** へと誘導した (Scheme 17).

すなわち，まず，化合物 **140** および **147** を DMF 溶媒中，K_2CO_3 存在下で過剰量の 1,4-ジブロモブタンと反応させ, 臭化アルキル体 **148** および **150** を得た. さらに，これらを用いて種々のヒダントインをアルキル化し，4 M 塩酸を用いてメトキシメチル基を除去し，目的とする **F** および **G** を得た.

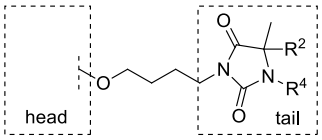


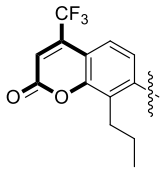
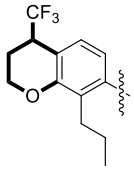
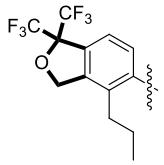
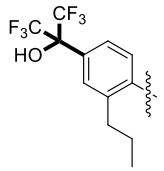
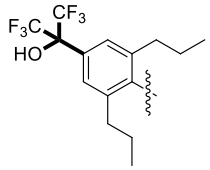
Scheme 17. Reagents and conditions: (a) 1,4-dibromobutane, K_2CO_3, DMF, rt, 18 h, 71–99%; (b) **42**, K_2CO_3, DMF, rt, 16 h, 99%; (c) 4 M HCl in EtOH, MeOH, rt, 1 h, 81–82%.

第三項　構造活性相関③

第一章第一節および第二節の構造活性相関と同様に Gal4-h-LXR を用いたレポーター遺伝子アッセイを用いて，各サブタイプ (LXRα, LXRβ) に対する活性化を測定し (EC_{50} 値)，LXRα/β デュアルアゴニストである T0901317 の 10μM における活性化強度との比 (E_{max} 値) を求めた.

Table 13. LXR activities of the newly designed head structures[a]



Compound	Head	Tail	LXRα EC_{50}[b] (%)[c]	LXRβ EC_{50}[b] (%)[c]	Selectivity for E_{max} β/α[d]
65		a	2.4 (7)	1.0 (51)	7.3
2		b	ia (2)	1.4 (31)	16
100		a	nd (3)	2.2 (21)	7.0
101		b	nd	nd	nd
102		a	2.2 (82)	0.86 (95)	1.2
103		b	1.7 (81)	1.0 (104)	1.3
152		a	3.2 (97)	1.9 (162)	1.7
153		b	2.8 (12)	1.8 (32)	2.7
154		a	0.71 (107)	0.56 (142)	1.3
155		b	1.6 (51)	1.4 (66)	1.3

nd = not determined.
ia = inactive at 10 μM.
[a] The GAL4-LXR luciferase assay was performed with a maximal dose of 30 μM. The results are given as the means from two independent experiments. [b] The EC_{50} data are reported in μM. [c] The E_{max} is defined as the percentage ratio of the maximum fold induction for the test compound to the fold induction for T0901317 at 10 μM in the same experiment.[45] [d] selectivity = The value of selectivity is LXRβ E_{max}/LXRα E_{max}.

はじめに，head 部分の構造の違いによる影響を調べた．この際，tail 部分であるヒダントインには，構造展開の基本構造である *N*-メチル-5,5-ジメチルヒダントイン (tail a)，および，第一節で述べた *in vivo* 評価にて脂質沈着抑制作用が確認された 2-オキソクロメン誘導体 **2** (Figure 23) の tail 部分である 5-(4-メトキシフェニル)-5-メチルヒダントイン (tail b) を選択した．

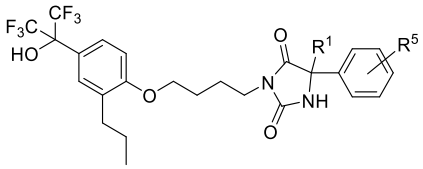
Table 13 には，これら tail a または tail b をもつ 1,1–ビス(トリフルオロメチル)カルビノール誘導体 **152~155** の活性データを，同じ tail 構造をもつ 2-オキソクロメン誘導体 **65** および **2**，クロマン誘導体 **100**，1,3-ジヒドロイソベンゾフラン誘導体 **102** および **103** のデータとともに記載した．

この表が示すように，カルビノール誘導体 **152** および **154** は，2-オキソクロメン誘導体 **65** や 1,3-ジヒドロイソベンゾフラン誘導体 **102** と比べて E_{max} (β) 値が高く，T0901317 よりも LXR 活性化作用が強い．また，EC_{50} (β) 値や E_{max} (β) 値に関しては，tail a の方が tail b より優れていることもわかるが，残念ながら選択性 (Selectivity for E_{max} β/α) は思わしくない．しかし，この選択性を改善する上で，tail a の構造には構造展開できる余地が少なすぎる．そこで，さらなる構造展開にあたっては，head 部位には 1,1–ビス(トリフルオロメチル)カルビノール構造を採用し，tail 部位としては構造変換の余地の大きい tail b を選択し，ヒダントイン環上の置換基 R^1 および R^2 (Ph–R^5) を検討することによって，活性および選択性を改善しようと考えた．

Table 14-1 および Table 14-2 は，head 部位のベンゼン環上にプロピル基を一つもち，また，tail 部位のヒダントイン環 5 位に種々の置換ベンゼン構造をもつ化合物 **F** の *in vitro* 評価の結果である．比較のため，前出 (Table 13) の 4-メトキシフェニル体 **153** のデータも記載した．

1,2-メチレンジオキシベンゼン体 **165**，1,4-ベンゾジオキサン体 **166** および 4-フェニル体 **170** は，化合物 **153** と比べて EC_{50} (β) 値と E_{max} (β) 値が改善している一方，4-ジメチルアミノフェニル体 **167**，4-クロロフェニル体 **168**，3,4-ジクロロフェニル体 **169**，4-トリフルオロメチルフェニル体 **170** および 4-ニトロフェニル体 **172** の E_{max} (β) 値は，化合物 **153** とあまり変わらなかった．また，置換基 R^1 としてメチル基の代わりにエチル基およびプロピル基をもつ化合物 **173**，**174**，**176** および **175** は，化合物 **153** に比べて EC_{50} (β) 値，E_{max} (β) 値がともに改善した．

Table 14-1. LXR activities of mono-propyl **F** in the 1,1-bis(trifluoromethyl)carbinol derivatives.[a]

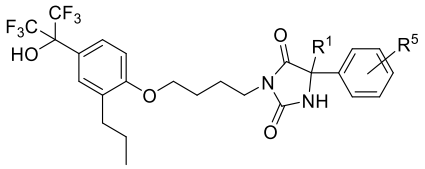


F

Compound	R^1	R^5	LXRα EC_{50}[b] (%)[c]	LXRβ EC_{50}[b] (%)[c]	Selectivity for E_{max} β/α[d]
153	Me	4-MeO	2.8 (12)	1.8 (32)	2.7
156	Me	H	2.0 (42)	12 (15)	0.36
157	Me	4-Me	2.2 (37)	2.0 (23)	0.62
158	Me	4-*i*-Pr	1.9 (8)	2.2 (64)	8
159	Me	2-MeO	2.7 (7)	ia (0)	-
160	Me	3-MeO	2.4 (15)	2.2 (70)	4.7
161	Me	3,4-diMeO	2.4 (13)	1.3 (65)	5
162	Me	4-EtO	1.3 (89)	1.1 (53)	0.6
163	Me	4-*i*-PrO	1.8 (67)	2.8 (51)	0.76
164	Me	4-CF_3O	2.8 (33)	1.2 (125)	3.8
165	Me	3,4-OCH_2O	1.7 (54)	0.5 (118)	2.2
166	Me	3,4-$O(CH_2)_2O$	1.2 (71)	0.4 (171)	2.4
167	Me	4-Me_2N	2.2 (8)	2.7 (27)	3.4

ia = inactive at 10 μM.
[a] The GAL4-LXR luciferase assay was performed with a maximal dose of 30 μM. The results are given as the means from two independent experiments. [b] The EC_{50} data are reported in μM. [c] The E_{max} is defined as the percentage ratio of the maximum fold induction for the test compound to the fold induction for T0901317 at 10 μM in the same experiment.[45)] [d] selectivity = The value of selectivity is LXRβ E_{max}/LXRα E_{max}.

Table 14-2. LXR activities of mono-propyl **F** in the 1,1-bis(trifluoromethyl)carbinol derivatives.[a]



F

Compound	R^1	R^5	LXRα EC_{50}[b] (%)[c]	LXRβ EC_{50}[b] (%)[c]	Selectivity for E_{max} β/α[d]
168	Me	4-Cl	2.2 (23)	1.8 (29)	1.3
169	Me	3,4-diCl	1.7 (4)	1.1 (43)	11
170	Me	4-Ph	1.4 (108)	1.0 (174)	1.6
171	Me	4-CF_3	2.5 (10)	1.8 (25)	2.5
172	Me	4-NO_2	2.2 (51)	1.9 (39)	0.76
173	Et	4-MeO	2.3 (48)	1.0 (150)	3.1
174	Et	3,4-OCH_2O	1.5 (72)	0.7 (172)	2.4
175	Pr	3,4-OCH_2O	2.3 (42)	1.3 (72)	1.7
176	Et	3,4-$O(CH_2)_2O$	1.5 (88)	0.7 (172)	2.0

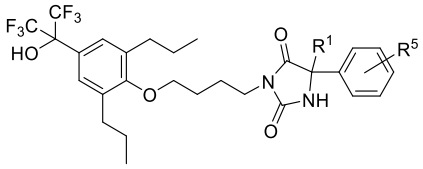
ia = inactive at 10 μM.
[a] The GAL4-LXR luciferase assay was performed with a maximal dose of 30 μM. The results are given as the means from two independent experiments. [b] The EC_{50} data are reported in μM. [c] The E_{max} is defined as the percentage ratio of the maximum fold induction for the test compound to the fold induction for T0901317 at 10 μM in the same experiment.[45)] [d] selectivity = The value of selectivity is LXRβ E_{max}/LXRα E_{max}.

Head 部位のベンゼン環上に二つのプロピル基をもつ化合物 **G** に関しても，化合物 **F** と同様に構造活性相関を調べた (Table 15). 比較のため，前出 (Table 13) の 4-メトキシフェニル体 **155** のデータも記載した.

その結果，4-エトキシフェニル体 **177**，4-イソプロポキシフェニル体 **4** および 1,2-メチレンジオキシベンゼン体 **179** は，化合物 **155** (Table 13) と比べて EC_{50} (β) 値と E_{max} (β) 値が改善し，化合物 **4** と **177** については選択性も改善した．置換基 R^1 にメ

チル基の代わりにエチル基をもつ化合物 **183** および **184** は，化合物 **155** と比べて EC_{50} (β) 値と E_{max} (β) 値がともに改善したが，選択性はむしろ低かった．

Table 15. LXR activities of bis-propyl **G** in the 1,1-bis(trifluoromethyl)carbinol derivatives.[a]



G

Compound	R^1	R^5	LXRα EC_{50}[b] (%)[c]	LXRβ EC_{50}[b] (%)[c]	Selectivity for E_{max} β/α[d]
155	Me	4-MeO	1.6 (51)	1.4 (66)	1.3
177	Me	4-EtO	0.9 (43)	0.8 (148)	3.4
4	Me	4-*i*-PrO	1.1 (26)	1.2 (146)	5.6
178	Me	4-CF_3O	1.8 (62)	2.7 (61)	0.98
179	Me	3,4-OCH_2O	0.4 (89)	0.1 (101)	1.1
180	Me	3,4-$O(CH_2)_2O$	0.5 (94)	0.6 (70)	0.74
181	Me	4-*i*-Pr	1.8 (21)	1.7 (25)	1.2
182	Me	4-Ph	1.2 (31)	1.6 (58)	1.9
183	Et	4-MeO	1.2 (85)	1.1 (81)	0.95
184	Et	3,4-OCH_2O	0.6 (118)	0.7 (118)	1.0

ia = inactive at 10 μM.
[a] The GAL4-LXR luciferase assay was performed with a maximal dose of 30 μM. The results are given as the means from two independent experiments. [b] The EC_{50} data are reported in μM. [c] The E_{max} is defined as the percentage ratio of the maximum fold induction for the test compound to the fold induction for T0901317 at 10 μM in the same experiment.[45)] [d] selectivity = The value of selectivity is LXRβ E_{max}/LXRα E_{max}.

Table 14-1，14-2 および 15 の結果を受け，著者は E_{max} (α) 値が低く，かつ E_{max} (β) 値が高い化合物 **165**, **173** および **4** を選択し，用量反応曲線を比較した．

その結果，これら化合物が，*in vivo* 評価 (第一章第一節) にて脂質沈着抑制作用を

示した化合物 **2** よりも優れている可能性があると期待した (Figure 31).

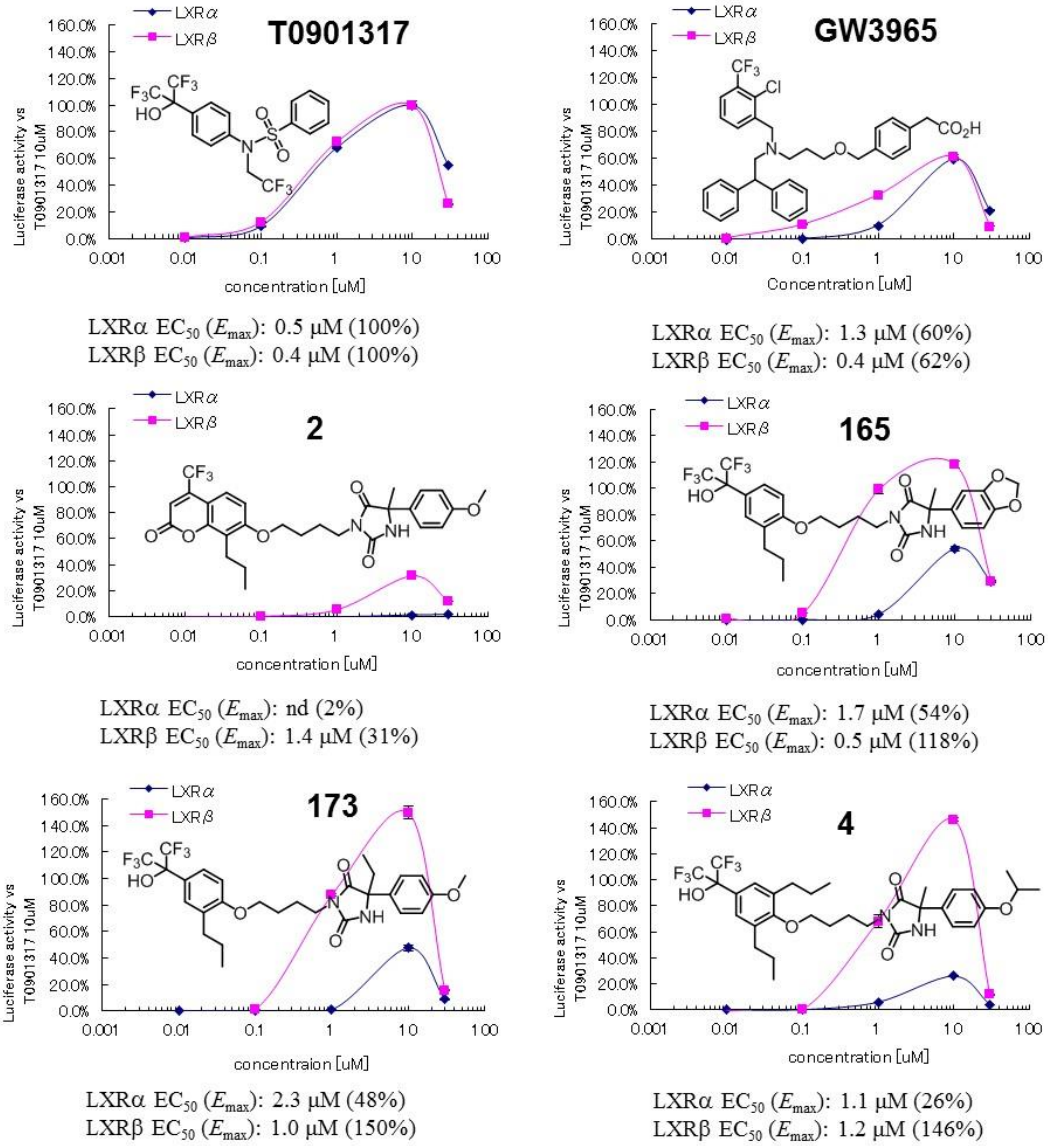


Figure 31. Dose-response curves of T0901317, GW3965, **2**, **165**, **173** and **4**
nd = not determined

第四項　1,1-ビス(トリフルオロメチル)カルビノール誘導体の薬物動態評価

Table 16 に，化合物 **165**，**173**，**4** および比較として前出 (Table 12) の 2-オキソクロメン誘導体 **2** の肝クリアランス (hepatic CL) を示す．化合物 **165**，**173** および **4** の CL は，化合物 **2** と比べて，改善されており，特に，化合物 **4** は，動物種に関わらず良好な肝クリアランスを示すことがわかる．

Table 16. hepatic CLint (μL/min/mg protein) of each animal obtained through an *in vitro* assay.

Compound	Mouse	Hamster	Human
2	397	>500	393
165	73	351	31
173	65	295	73
4	44	49	42

*The hepatic CLint values of compounds **2**, **165**, **173** and **4** were assessed using hepatic microsomes from each animal (mouse, hamster and human).

この結果を踏まえ，著者は化合物 **4** を選択し，血漿中濃度の推移を確認するため，経口投与での PK 試験を検討した．投与媒体には PEG400 を用い，用量は，10, 30, 100 mg/kg を投与した．

Figure 32 に示すように．化合物 **4** の血漿中濃度は，用量依存的であり，高用量 (100 mg/kg) では薬物の吸収が飽和したためか，二峰性が認められた．

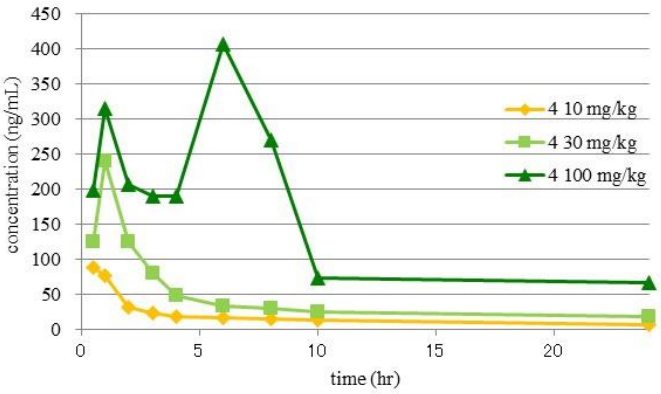


Figure 32. PK profile of **4**

第五項　1,1-ビス(トリフルオロメチル)カルビノール誘導体の薬理評価

第一節で述べた 2-オキソクロメン誘導体 **2** と同様に，化合物 **4** について，Bio F_1B ハムスターを用いた *in vivo* 試験を実施した．ハムスターに高コレステロール食負荷を 2 週間おこなった後，薬物として T0901317 (10 mg/kg) および化合物 **4** (10, 30, 100 mg/kg) を 8 週間 1 日 1 回経口投与した．

以下に，その結果を示す．まず，TC については，対象薬である T0901317 では 10 mg/kg の投与で僅かに上昇するのに対し，化合物 **4** では 100 mg/kg の投与で低下が認められた (Figure 33).

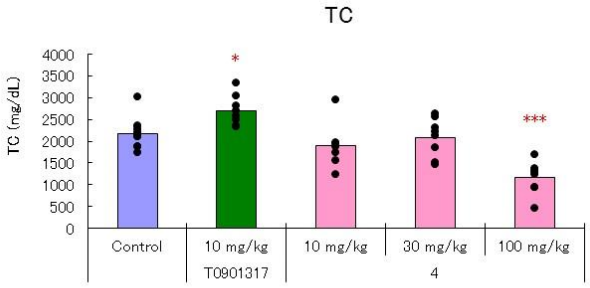


Figure 33. TC in T0901317 and **4**

*$p < 0.05$, *** $p < 0.001$; The statistical analysis was conducted using Dunnett's test.

HDL-C は，T0901317 の 10 mg/kg 投与および化合物 **4** の 100 mg/kg 投与にて低下が認められた．また，LDL-C についても，T0901317 の 10 mg/kg 投与および化合物 **4** の 100 mg/kg 投与にて低下が認められた (Figure 34).

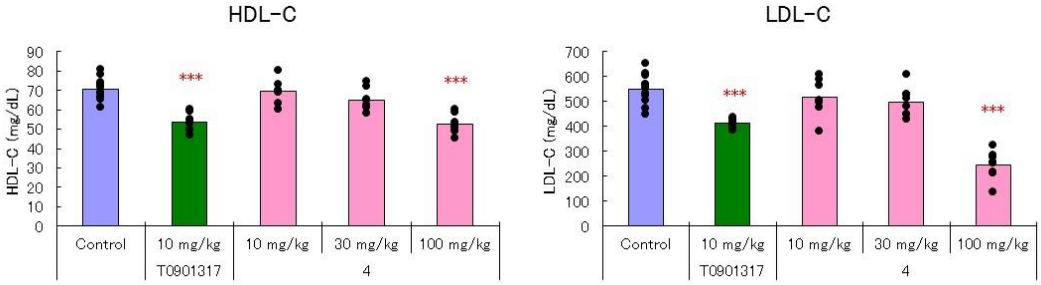


Figure 34. HDL-C and LDL-C in T0901317 and **4**

*$p < 0.05$, *** $p < 0.001$; The statistical analysis was conducted using Dunnett's test.

血漿 TG および肝 TG は，T0901317 で顕著に増加することが確認された．一方，化合物 **4** では血漿 TG および肝 TG 共に顕著な増加は認められなかったが，30 mg/kg 投与にて血漿 TG が僅かながら有意に増加した (Figure 35).

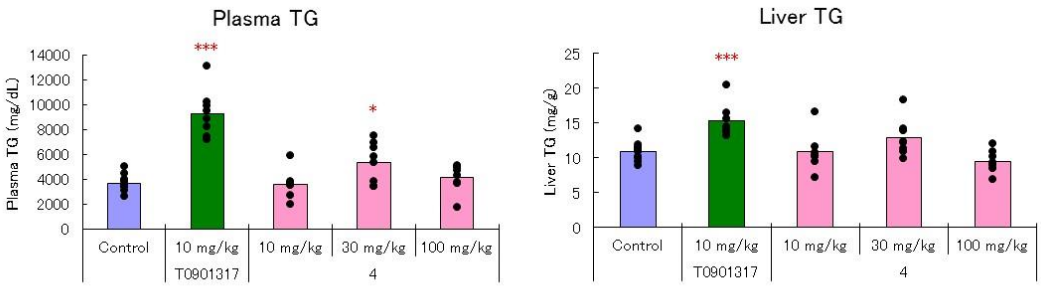


Figure 35. hepatic and plasma TG profile in T0901317 and **4**

* $p < 0.05$, *** $p < 0.001$; The statistical analysis was conducted using Dunnett's test.

脂質沈着抑制作用を脂質沈着面積 (%) で評価したところ，T0901317 の 10 mg/kg 投与および化合物 **4** の 100 mg/kg 投与にて脂質沈着面積の減少が確認された (Figure 36).

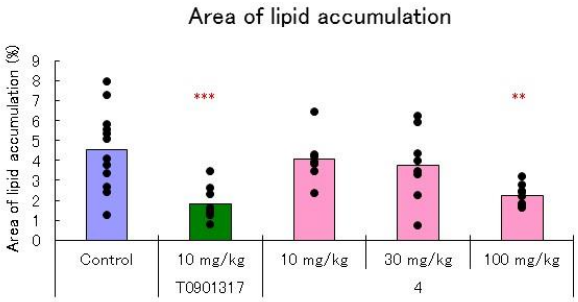


Figure 36. lipid accumulations in aortic sinus area in T0901317 and **4**

** $p < 0.01$, *** $p < 0.001$; The statistical analysis was conducted using Dunnett's test.

以上のように，LXRα/β デュアルアゴニストである T0901317 が，10 mg/kg 投与にて有意な脂質沈着抑制作用を示すものの TG を顕著に増加させるのに対して，LXRβ 選択的アゴニストである化合物 **4** は，100 mg/kg 投与にて脂質沈着抑制作用を示し，

かつ，TG の顕著な増加を回避できている．そこで，この化合物 **4** をリード化合物として位置付けることとした．

ただし，脂質プロファイルの結果からは，化合物 **4** の脂質沈着抑制作用は高脂肪食負荷による LDL-C の顕著な減少が主要因になっていると推察される．また，HDL-C が有意に減少している事実も，化合物 **4** による脂質沈着抑制に対して，コレステロール逆転送系の促進は，実質的には寄与していないことを示唆している．したがって，得られた薬効は直接的な抗動脈硬化作用ではなく，むしろ脂質低下作用の結果であると考えられた．

第六項　小括

あらたな head 部分の骨格として 1,1-ビス(トリフルオロメチル)カルビノール部位をもつベンゼン構造を見出した．この骨格は第一節で述べた 2-オキソクロメン骨格や第二節で述べた 1,3-ジヒドロイソベンゾフラン骨格よりも LXRβ 活性化作用および代謝安定性 (hepatic CLint) が優れている．また，ドッキングモデルの結果，LXRβ 活性化作用の鍵となる‘His435-Trp457 activation switch’の相互作用が増強されていることが推察された．すなわち，1,1-ビス(トリフルオロメチル)カルビノール骨格の酸素原子は，2-オキソクロメン骨格を形成するラクトン部位の酸素原子や 1,3-ジヒドロイソベンゾフラン骨格を形成するフラン部位の酸素原子よりも，より強く His435 のイミダゾール環と水素結合しているものと推察した [31c]．一方，Tail 部分には，著者独自のイミダゾリジノン-2,4-ジオン骨格を採用し，リンカーとしてブタン構造を介して head 部位に適切な距離で結合させることで，LXRα および LXRβ に対する活性化強度 (E_{max} 値) に差 (LXRβ 選択性) をもたらすことができることを見出した．さらに，tail 部分の置換基の最適化を経て，より高い LXRβ 選択性を有し，かつ，T0901317 や GW3965 よりも強い LXRβ 活性化作用を有する化合物 **4** を見出した．LXRβ 選択的アゴニストである化合物 **4** は，LXR アゴニストの副作用である TG の増加を 100 mg/kg の経口投与において回避できており，かつ，脂質沈着抑制作用を示す．化合物 **4** の脂質沈着抑制作用の最大効力は，動脈硬化モデルである高脂肪食負荷 Bio F_1B ハムスターにおいて，非選択的な LXR アゴニストである T0901317 とほぼ同等であったことより，著者は当該化合物をリード化合物として位置付けた [35]．

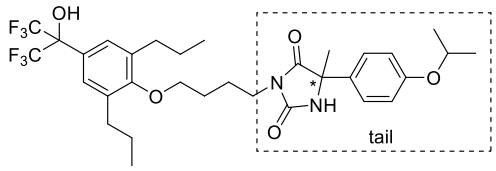
第二章　リード化合物 **4** の検証

第一節　リード化合物 **4** の合成法検討

第一項　研究方針

前章までに述べたように，著者は LXRβ 選択的アゴニスト活性をもつ化合物 **4** を見出し，動脈硬化治療薬開発のリード化合物と位置づけた．化合物 **4** は，TG を顕著に増加させることなく，LDL-C 低下作用にともなった脂質沈着抑制作用を示す．そこで，化合物 **4** をさらに詳細に評価するため，安定的な供給法の確立に取り組むこととした．

ところで，化合物 **4** の tail 部位であるヒダントイン構造には不斉炭素原子があるため，まずは，各々の鏡像異性体の LXR 活性化作用および選択性を確認する必要があった (Figure 37)．そこで，化合物 **4** を光学活性体として供給するため，**4** の光学分割，絶対立体配置の決定，合成中間体となるヒダントイン **5** の光学活性体の効率的合成法の確立を順次検討した．



4

Figure 37. Structure of racemate **4**

第二項　化合物 **4** の光学分割および鏡像異性体の *in vitro* 活性評価

ラセミ体 **4** を HPLC で光学分割することを検討した結果，DAICEL 社製のキラルカラム CHIRALPAK AS-H の利用が効果的であることがわかった．内径 20 mm，長さ 250 mm のセミ分取カラムを用いることにより [hexane/EtOH = 90/10 (v/v), 1.0 mL/min, 40 °C]，1 回の操作に当り，10 mg のラセミ体を完全に分割することができた [保持時間：(*R*)-(−)-**4** 6.90 min; (*S*)-(+)- **4** 11.50 min].

各々の鏡像異性体の比旋光度は，鏡像異性体 (+)-**4** が $[\alpha]_D^{20}$ = +32.2 (c = 1.0, MeOH)，もう一方の鏡像異性体 (−)-**4** が $[\alpha]_D^{20}$ = −33.3 (c = 1.0, MeOH) を示した．

次に，第一章と同様に，各鏡像体を用いて，Gal4-h-LXR を用いたレポーター遺伝子アッセイを用いて，各サブタイプ (LXRα, LXRβ) に対する活性化を測定し (EC_{50} 値), LXRα/β デュアルアゴニストである T0901317 の 10μM における活性化強度との比 (E_{max} 値) を求めた (Figure 38).

その結果，(+)-**4** は，LXRα および LXRβ のどちらに対しても，ラセミ体 (±)-**4** より強い活性化作用を示し，選択性はラセミ体 (±)-**4** と同等であったが，LXRα 活性化作用は僅かながら (±)-**4** より強くなった．一方，(−)-**4** は，LXRα および LXRβ のどちらに対する活性化作用もラセミ体 (±)-**4** より著しく低く，僅かながら LXRα 選択的であった．このことから，ヒダントイン部位の立体化学が，LXRβ 選択的活性化作用の発現にきわめて重要な役割であることが判明した．

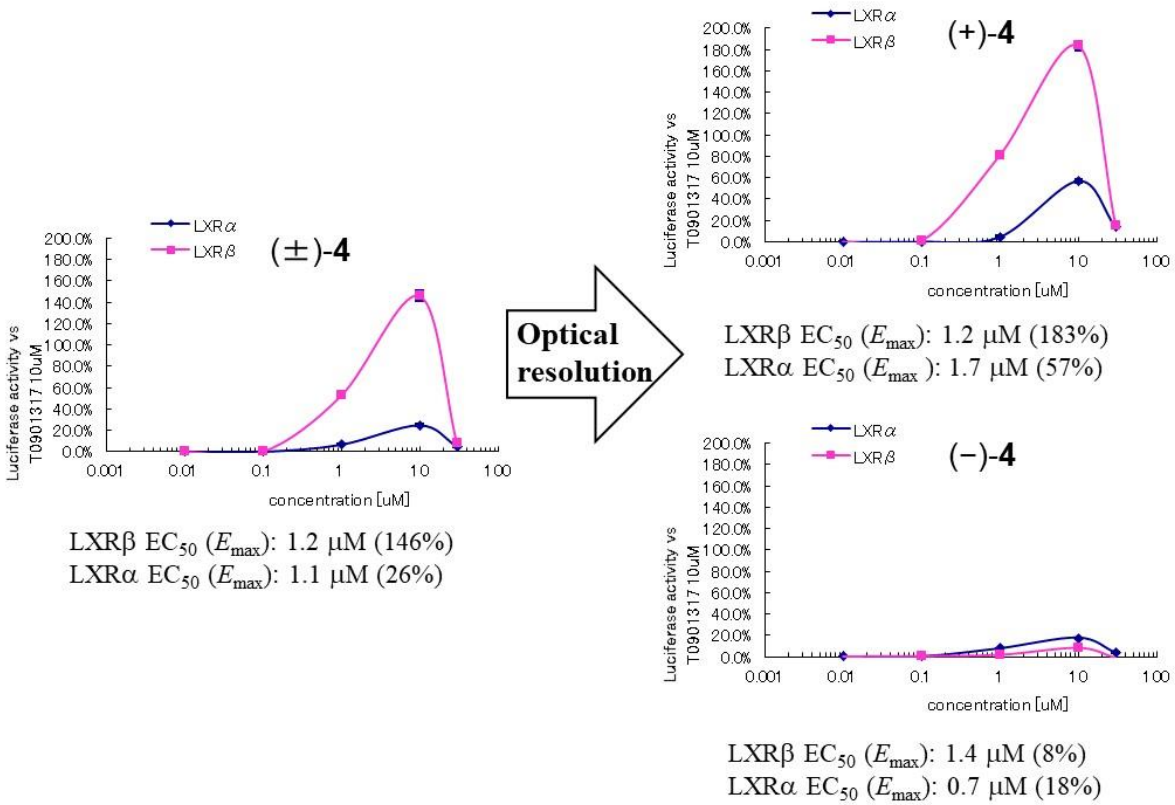
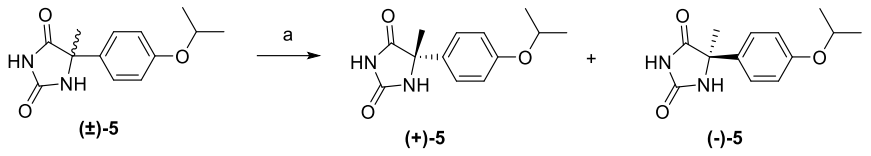


Figure 38. *In vitro* activity of each enantiomer, (+)-**4** and (−)-**4**

第三項　鍵中間体 **5** の光学分割および鏡像異性体 (+)-**4** と (−)-**4** の合成

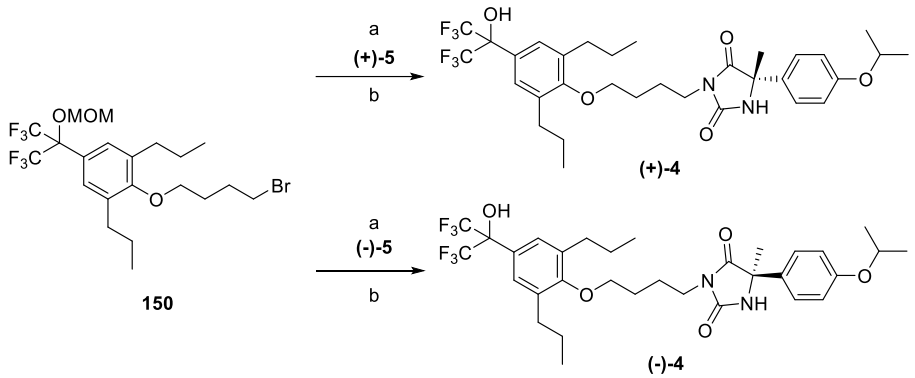
前項の結果から目的とする鏡像異性体 (+)-**4** の合成をおこなった．まず，ラセミ体 **5** を HPLC で光学分割することを検討した結果，DAICEL 社製のキラルカラム CHIRALPAK AD-H の利用が効果的であることがわかった. 内径 20 mm, 長さ 250 mm のセミ分取カラムを用いることにより [MeOH = 100 (v), 12 mL/min, 40 °C]，1 回の操作に当り，200 mg のラセミ体を完全に分割することができた [保持時間：(*R*)-(−)-**5** 6.02 min; (*S*)-(+)-**5** 13.94 min] (Scheme 18).



Scheme 18. Reagents and conditions: (a) chiral separation by HPLC on a CHIRALPAK AD-H column

次に，各々の鏡像体 (+)-**5** および (−)-**5** を対応する化合物 **4** の鏡像体へと誘導した (Scheme 19). すなわち，(+)-**5** および (−)-**5** を DMF 溶媒中，K_2CO_3 存在下にて化合物 **150** と反応させた後，4 M 塩酸を用いてメトキシメチル基を除去した．その結果，(+)-**5** からは (+)-**4** が，(−)-**5** からは (−)-**4** が得られることが判明した．

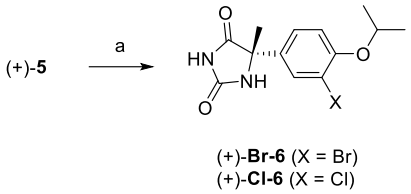
これにより, 所望の (+)-**4** を合成するために必要なヒダントイン中間体は、(+)-**5** であることが明らかになった.



Scheme 19. Reagents and conditions: (a) K_2CO_3, DMF, rt, 16 h, 99%; (b) 4 M HCl in EtOAc, MeOH, rt, 1 h, 81%.

第四項　化合物 **4** の絶対立体配置の決定

X 線結晶構造解析にて異常分散法を用いて，化合物 (+)-**5** の絶対立体配置の決定を試みた，すなわち，化合物 (+)-**5** を DMF 溶媒中，NBS または NCS を用いてハロゲン化し，化合物 (+)-**Br-6** および (+)-**Cl-6** を得た．これらを，EtOAc を用いて再結晶し，X 線結晶構造解析に付した (Scheme 20)．その結果，これらのヒダントインの絶対立体配置は *S* であることが明らかになり (Figure 39) [52, 53]，合成すべき LXRβ 選択的アゴニスト (+)-**4** の絶対立体配置も *S* とすることができた．



Scheme 20. Reagents and conditions: (a) NBS or NCS, DMF, rt, 20 h, 51–79%.

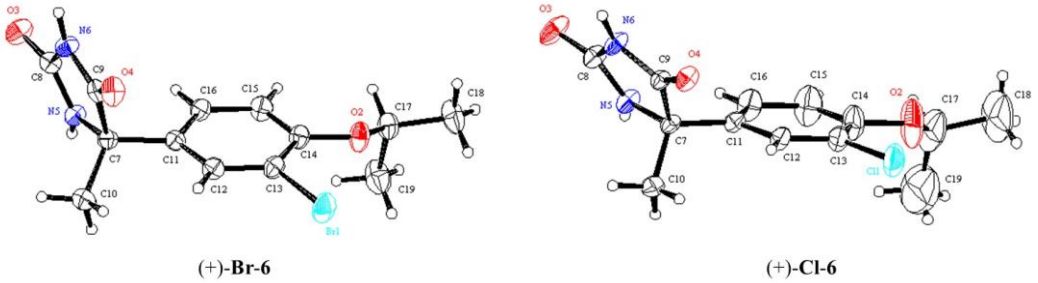
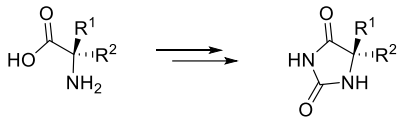


Figure 39. ORTEP of (+)-**Br-6** and (+)-**Cl-6**

第五項　化合物 (*S*)-(+)-**5** の合成法検討

次に，著者は化合物 (*S*)-(+)-**5** を数十グラムスケールで安定に供給可能な合成法の開発を試みた．

ところで，これまでに，5,5-二置換ヒダントインの合成法は数多くあるが，5-アルキル-5-アリールヒダントイン誘導体を光学活性体として高い鏡像体過剰率で，かつ，大量に効率良く合成できる実用的方法はない [54]．例えば，α,α-二置換アミノ酸から 5,5-二置換ヒダントインを合成する方法も報告されているが (Scheme 21) [55]，それらを (+)-**5** の合成に応用するためには対応する光学活性 α-アリール- α-メチルアミノ酸を合成する必要があり，それ自体が容易ではない．

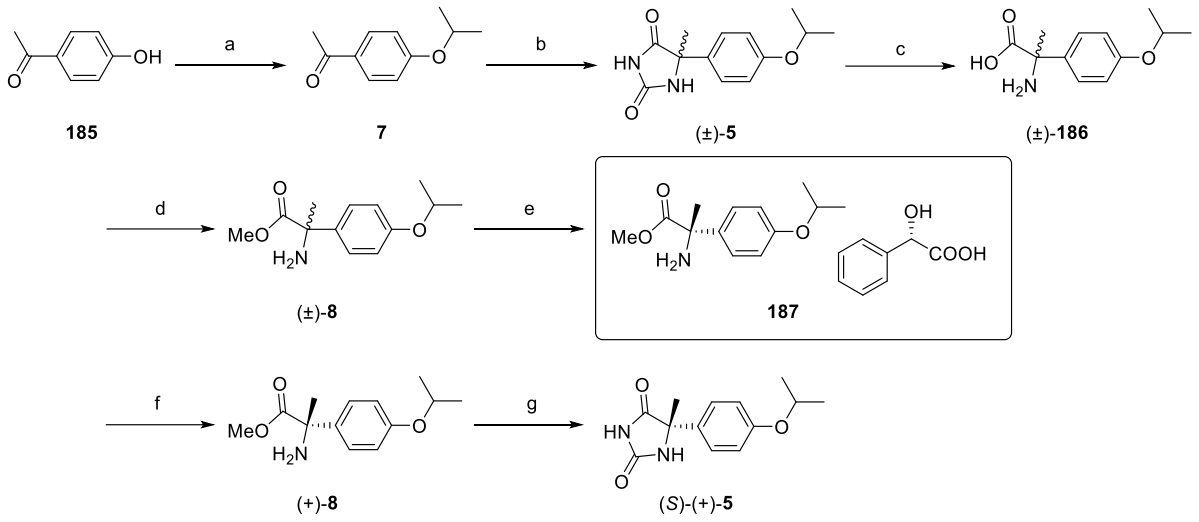


Scheme 21. Synthesis of chiral hydantoin from amino acid

そこで，著者は，安定した大量スケールの製造への適応を念頭に置き，ジアステレオマー塩の形成を経由する光学分割について検討することを選択した (Scheme 22) [56]．

大量スケールの製造を考慮して，安価に入手可能な 4-ヒドロキシアセトフェノン (**185**) を原料として用いることとした．

すなわち，化合物 **185** をアセトン溶媒中，K_2CO_3 存在下にて 2-ヨードプロパンを用いてアルキルアリールエーテル化し，4-(1-メチルエトキシ)アセトフェノン(**7**) を合成した．次に，化合物 **7** を含水エタノール中，NaCN と $(NH_4)_2CO_3$ を用いて加熱し (Bucherer-Bergs 反応)，ラセミ体 **5** を合成した．得られた化合物 **5** を加水分解し，アミノ酸 **186** へと誘導した後，両極性を有する化合物 **186** は，取扱いが煩雑なことから，化合物 **186** をメタノール中，濃硫酸を用いて加熱し，エステル体 **8** へと誘導した. 得られた化合物 **8** とのジアステレオマー塩の形成を利用する光学分割をおこなうため，1.0 当量の L-(+)-マンデル酸と化合物 **8** との混合物 **187** を EtOAc/EtOH = 10/1 の混合溶媒中で加熱還流した後，室温まで冷却し結晶を生成させた．さらに，得られた結晶は同じ混合比の溶媒を用いて再結晶し，鏡像体過剰率の向上を図った後，混合物 **187** に Na_2CO_3 水溶液を用いて L-(+)-マンデル酸を除去し，光学活性な化合物 (+)-**8** を得た. 最後に，化合物 (+)-**8** を過剰量の尿素と加熱し，化合物 (*S*)-(+)-**5** を高い鏡像体過剰率 (99% ee) で合成した．



Scheme 22. Reagents and conditions: (a) *i*-PrI, K_2CO_3, acetone, 55 °C, 24 h, 99%; (b) NaCN, $(NH_4)_2CO_3$, EtOH *aq*., reflux, 48 h, 95%; (c) NaOH, H_2O, 100 °C, 48 h, 99%; (d) H_2SO_4, MeOH, rt, 3 h and then reflux, 24 h, 70%; (e) L-(+)-mandelic acid, EtOAc-EtOH, reflux, 30 min and then rt, 16 h; (f) Na_2CO_3 *aq*., rt, 20% from (±)-**8**; (g) urea, 140 °C, 5 h, 89%.

以上のように，著者は，安価に市場入手可能な 4-ヒドロキシアセトフェノン (**185**) から高い鏡像体過剰率 (99% ee) の化合物 (*S*)-(+)-**5** を 7 工程，かつ，安定供給可能な合成法を確立した．

第二節　リード化合物 **4** の血中濃度推移の検証

化合物 **4** からの構造最適化をおこなうにあたり，薬物動態評価から示唆される問題点を確認するため，ハムスターに化合物 **4** を 100 mg/kg の経口投与し，血中濃度推移を評価した．

その結果，化合物 **4** の代謝物としてカルボン酸体 **9** を同定した (Figure 40) [57]．すなわち，化合物 **4** は，経口投与後まもなく代謝され，化合物 **9** へと変換されることが明らかになった．なお，代謝物 **9** は，LXR 活性化作用を示さなかった．

この血中濃度推移 (Figure 40) の結果から，化合物 **4** の C_{max} は，406 ng/mL (0.6 μM) を示したことから，*in vitro* 評価で算出された LXRβ 活性化作用における EC_{50} 値 (1.2 μM) では，末梢血中で ABCA1 発現を上昇させるには，十分ではないと考えられた．一方，小腸では，化合物 **4** の推定される曝露は，8 時間程度であり，小腸 ABCG5/G8 の発現を上昇させるには十分と考えられ，コレステロールの排泄を促進す

ることができたものと推察される[58]. この結果は, 化合物 **4** の *in vivo* 評価にて (第一章, 第五項, Figure 34), LDL-C 低下作用が確認されていることからもいうことができると考えている.

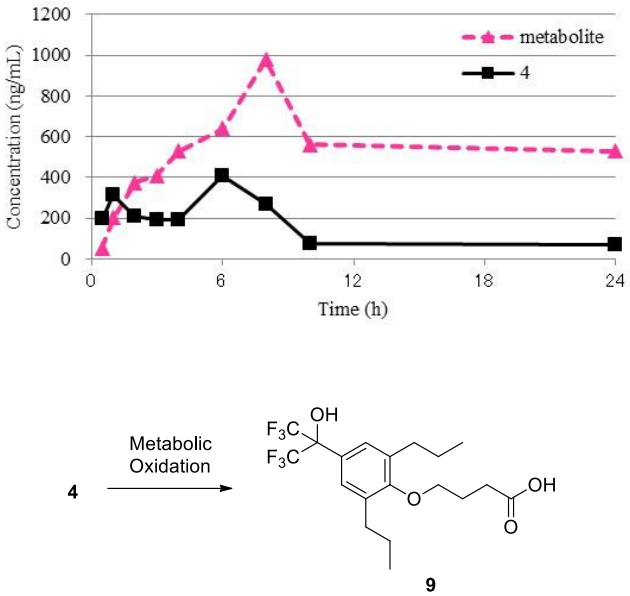


Figure 40. Drug concentrations of **4** and metabolite **9**

第三節　小括

リード化合物 **4** の tail 部位であるヒダントイン構造中の不斉炭素原子の立体化学は, 以下の二点から *S* と決定した. すなわち, 第一に, ラセミ体 **4** の HPLC を用いた光学分割によって供給した鏡像異性体 (+)-**4**, および, ラセミ体 **5** の HPLC を用いた光学分割により供給した鏡像異性体 (+)-**5** から誘導した (+)-**4** は, HPLC の保持時間および比旋光度の値から同じ鏡像異性体であると判断した. 第二に, 絶対立体配置については, ラセミ体 **5** の光学分割にて得られた鏡像異性体 (+)-**5** をハロゲン化し, 得られた化合物 (+)-**Br-6** および (+)-**Cl-6** を用いて X 線結晶構造解析に付し, *S* と決定した.

さらに, 血中濃度推移の結果から, 化合物 **4** はカルボン酸体 **9** へと代謝されることが明らかになった.

以上より, 化合物 **4** のさらなる構造最適化に向けて, 所望の薬効を発現するためには, LXR 活性化作用を示すことができる十分な血中薬物濃度を示す化合物を探索する必要があり, そのためには代謝安定性の改善が必要であると考えられた.

第三章　Liver X Receptor β 選択的アゴニストの創製 ~Lead optimization~

第一節　ドラッグデザイン④

第一章および第二章までに述べたように，LXRβ 選択的アゴニストとして見出したリード化合物 **4** は，動脈硬化疾患モデルを用いた *in vivo* 評価において脂質沈着抑制作用を示した．しかし，LDL-C 低下作用を示す一方，HDL-C の低下も確認された．このことから，抗動脈硬化作用を示す上で，末梢血中での ABCA1 mRNA 発現の上昇，続く，コレステロール逆転送系の亢進による寄与は小さいと考えられた．したがって，末梢血中で目的とする薬効を示す化合物を創製するため，さらなる構造最適化を目指したドラッグデザインを立案した．

はじめに，化合物 **4** の改善すべき点として，以下の点が挙げられる．まず，*in vivo* 評価において薬効発現に高用量 (100 mg/kg) を必要とすることである．また，前章で述べたように (第二章第二節)，リンカー部分とヒダントイン部分の結合部である C–N 結合の切断に伴った代謝物 **9** の生成が挙げられる．

このことから，目的とする薬効を末梢血中で示す化合物を創出するため，LXRβ のアゴニスト活性について，E_{max} 値 (efficacy: 有効性) よりも EC_{50} 値 (potency: 効力) を改善させることが必要であると考えた．また，代謝安定性の改善により，望む薬効を示すのに十分な血中薬物濃度を示す化合物の創出を目指し，構造最適化をおこなうこととした．

前章までのドラッグデザインと同様に，GW3965 と LXRβ との共結晶の X 線結晶構造解析を利用して，化合物 **4** とのドッキングモデルを作製し (Figure 41)，化合物と LXRβ の周辺領域との新たな相互作用の可能性について考察した．

その結果，化合物 **4** のリンカー部位周辺にはある程度の空間があることが推察された．したがって，構造最適化をおこなうにあたり，リンカー部分に構造展開の可能性があると考えた．

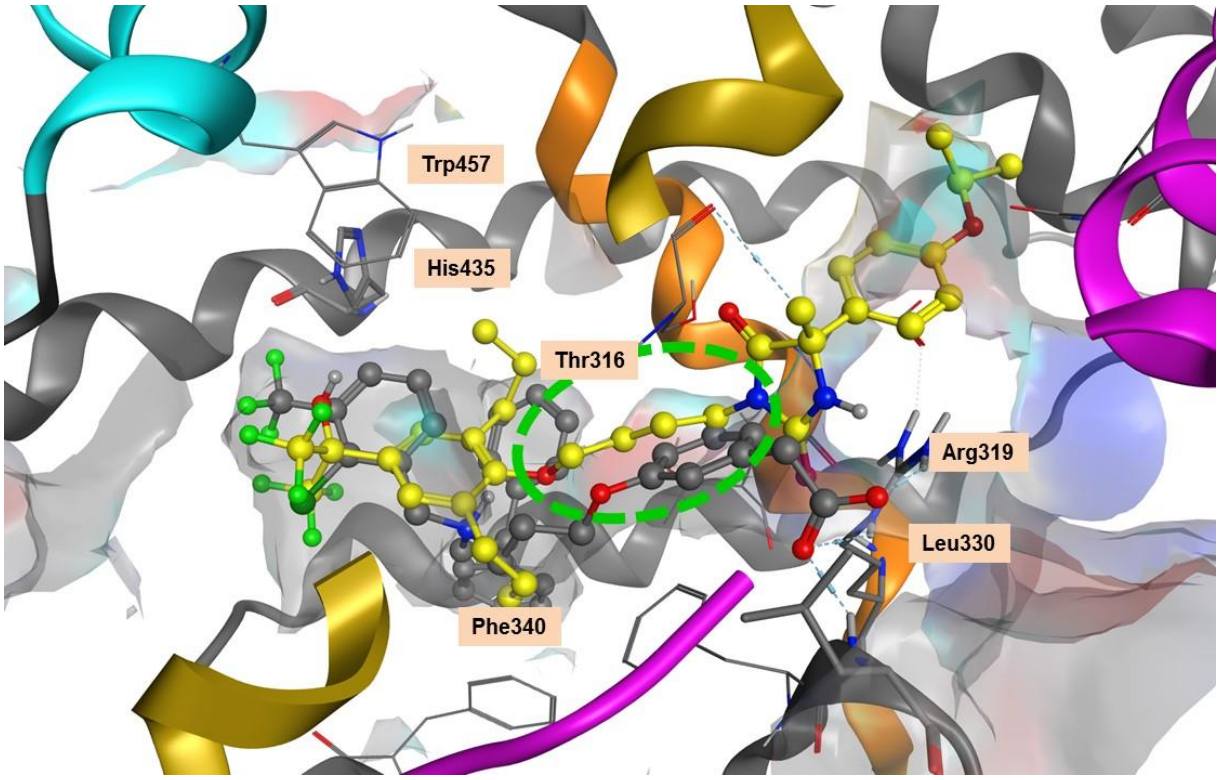


Figure 41. Docking model of GW3965 (gray) and **4** (yellow).
A green dotted line show our attracted area.

すなわち，リンカー部位へ直鎖のブタン構造とは異なる構造を導入することとし，EC_{50} 値 (potency: 効力)，および代謝安定性への影響について調べることとした (Figure 42).

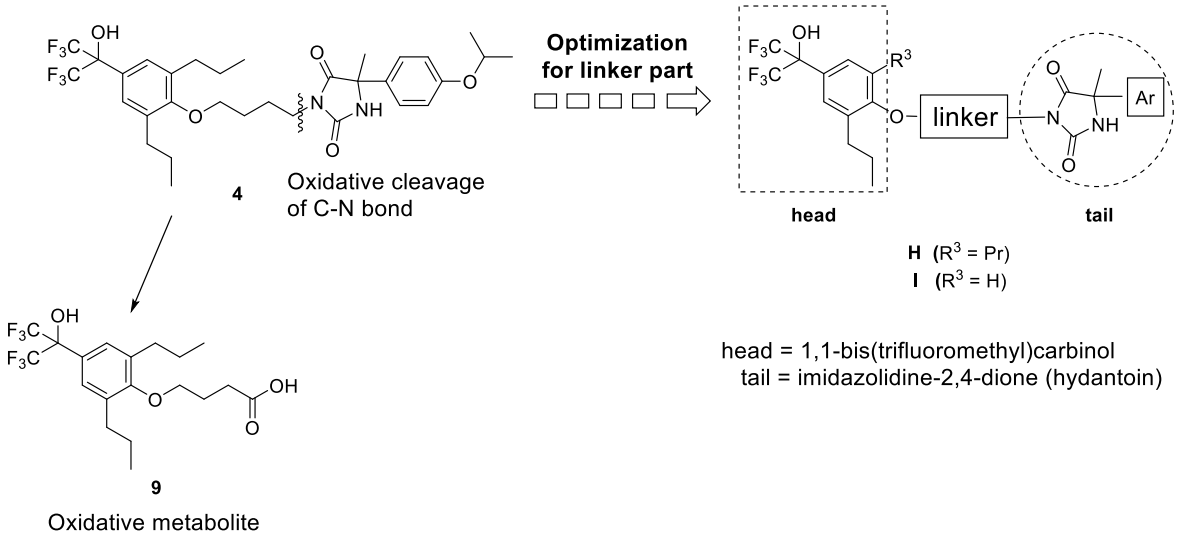


Figure 42. Plan for the improvement of metabolic stability, potency (EC_{50}) and selectivity for LXRβ through the modification of the structure of **4**.

また，ドラッグデザインを立案するにあたり，以下の点も留意し，検討する必要があると考えた.

① リガンドの head 部分と tail 部分の LXRβ に対する最適距離および最適角度
② 分子全体の脂溶性の低減
③ ヒダントイン環上の置換基の最適化

なお，第二章第一節で，鏡像異性体の一方に望む LXRβ アゴニスト活性があることが確認されたが，これまでの構造活性相関研究においては各化合物のラセミ体を評価に用いてきた. したがって，まずはこれまでと同様に各化合物のラセミ体を供給して，*in vitro* 評価をおこない，活性化作用を比較することとした.

第二節　合成および薬理・薬物動態評価

第一項　不飽和炭化水素鎖リンカーを有する 1,1-ビス(トリフルオロメチル)カルビノール誘導体の合成

前項で述べたドラッグデザイン (Figure 42) に基づいて, 構造式 **H** で表される 1,1-ビス(トリフルオロメチル)カルビノール誘導体 (Figure 43) を合成した.

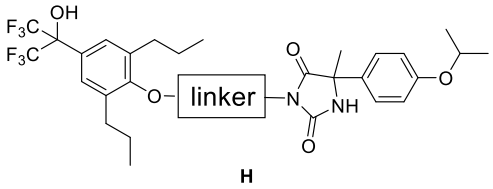
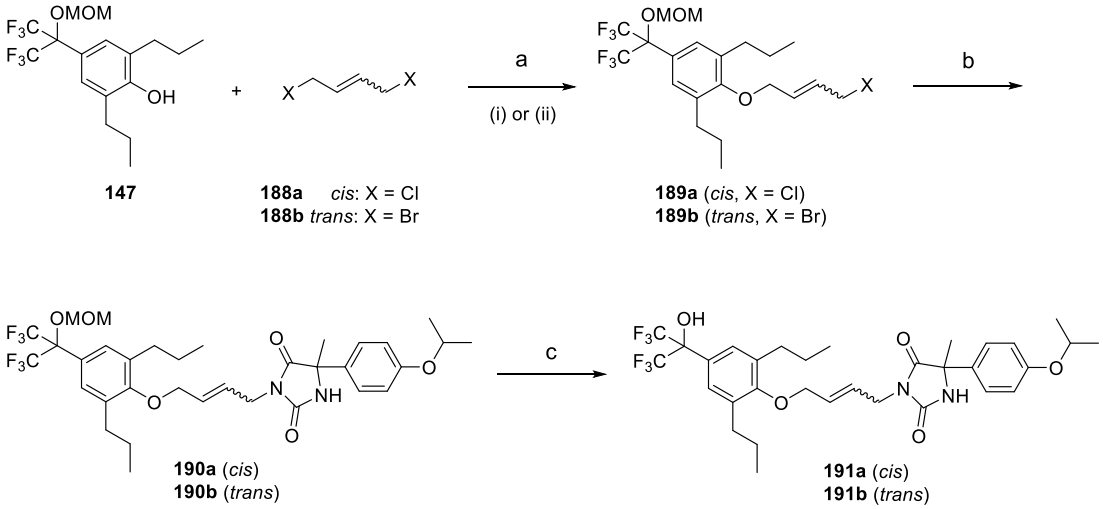


Figure 43. Structure of the 1,1-bis(trifluoromethyl)carbinol derivative **H**

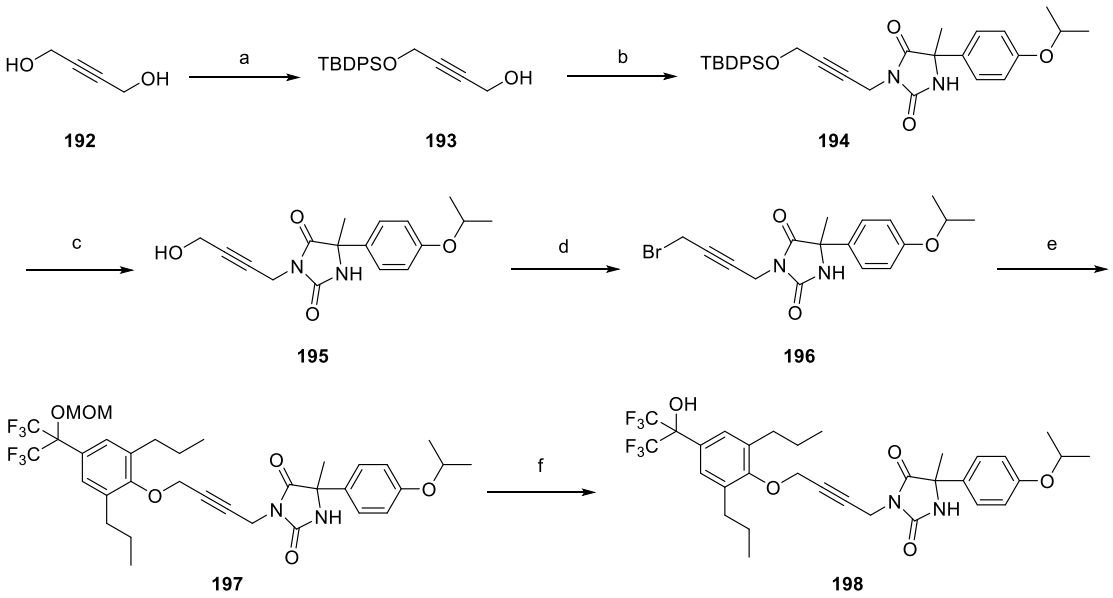
まず, *cis* または *trans*-ブテン構造をリンカー部位にもつ誘導体 **191a~b** を Scheme 23 に示す方法にしたがって合成した. すなわち, 第一章 (Scheme 16) にて合成したプロピルを二つもつフェノール体 **147** を DMF 溶媒中, K_2CO_3 存在下にて *cis*- または *trans*-1,4-ジハロ-2-ブテン (**188a~b**) を用いてアリールアリルエーテル化し, 臭化アリル体 **189a~b** を得た. こうして合成した化合物 **189a~b** とヒダントイン



Scheme 23. Reagents and conditions: (a) (i) *cis*-1,4-dichloro-2-butene (**188a**), K_2CO_3, DMF, 60 °C, 8 h, 89%; or (ii) *trans*-1,4-dibromo-2-butene (**188b**), K_2CO_3, DMF, rt, 17 h, 42%; (b) **5**, K_2CO_3, DMF, rt, 18 h, 21–99%; (c) 4 M HCl, EtOAc, rt, 1 h, 80%.

5 を DMF 溶媒中，K_2CO_3 存在下にて反応させ，付加体 **190a~b** を得た後，4 M 塩酸を用いてメトキシメチル基を除去し，目的とする化合物 **191a~b** を得た．

次いで，ブタン-2-インリンカー構造をリンカー部位にもつ誘導体 **198** を Scheme 24 に示す方法にしたがって合成した．すなわち，まず，ブタン-2-イン-1,4-ジオール (**192**) の一つの水酸基を DMF 溶媒中，イミダゾール存在下にて *tert*-ブチルジフェニルシリル (TBDPS) 基で保護し，4-((*tert*-ブチルジフェニルシリル)オキシ)-ブタ-2-イン-1-オール (**193**) を得た後，化合物 **193** とヒダントイン **5** を光延反応に付し，化合物 **194** へと誘導した．次いで，化合物 **194** を THF 溶媒中，TBAF を用いて，TBDPS 基を除去し，得られた 2-プロピン-1-オール誘導体 **195** を CH_2Cl_2 溶媒中，トリフェニルホスフィンと四臭化炭素を作用させることにより，臭素体 **196** を得た．こうして合成した化合物 **196** と化合物 **147** を反応させ，化合物 **197** を得，4 M 塩酸を用いてメトキシメチル基を除去し，目的とする化合物 **198** を得た．



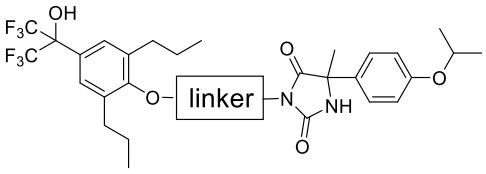
Scheme 24. Reagents and conditions: (a) TBDPSCl, imidazole, DMF, 0 °C, 1 h then rt, 2 h, 39%; (b) **5**, DEAD, PPh_3, THF, rt, 14 h, 55%; (c) TBAF, THF, 1 h, 90%; (d) CBr_4, PPh_3, CH_2Cl_2, rt, 1 h, 87%; (e) **147**, K_2CO_3, DMF, rt, 28 h, 77%; (f) 4 M HCl, EtOAc, rt, 1 h, 88%.

第二項　構造活性相関④:不飽和炭化水素鎖リンカーを有する 1,1-ビス(トリフルオロメチル)カルビノール誘導体の *in vitro* 活性評価

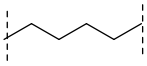
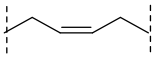
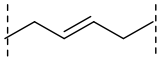
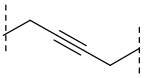
こうして得られた化合物 **191a**, **191b** および **198** を用いて，前章までと同様に，Gal4-h-LXR を用いたレポーター遺伝子アッセイを用いて，各サブタイプ (LXRα, LXRβ) に対する活性化を測定し (EC_{50} 値)，LXRα/β デュアルアゴニストである T0901317 の 10 μM における活性化強度との比 (E_{max} 値) を求めた (Table 17).

その結果，2-*cis*-ブテン体 **191a** は，LXR 活性化作用をほぼ示さなかった．一方，2-*trans*-ブテン体 **191b** は, LXRβ の EC_{50} 値が化合物 **4** と比べて強くなり, さらに, 2-ブチン体 **198** は，化合物 **191b** よりもさらに LXRβ の EC_{50} 値が強くなった.

Table 17. LXR activity of the 1,1-bis(trifluoromethyl)carbinol derivatives containing various linkers **H**[a]



H

Compound	Linker	LXRα EC_{50}[b] (%)[c]	LXRβ EC_{50}[b] (%)[c]	Selectivity for EC_{50} α/β[d]	*Clog*P [46)]
4		1.1 (26)	1.2 (146)	0.97	7.63
191a		ia (0)	ia (1)	-	7.58
191b		1.2 (40)	0.80 (182)	1.5	7.58
198		0.86 (27)	0.61 (149)	1.4	7.33

ia = inactive at 10 μM.
[a] The GAL4-LXR luciferase assay was performed at a maximum dose of 10 μM. The results are given as the mean of two independent experiments. [b] EC_{50} data are reported in μM.
[c] The E_{max} (%) is defined as the percentage ratio between maximum fold induction for the test compound and fold induction for T0901317 at 10 μM in the same experiment.[45)]
[d] selectivity = The value of selectivity is LXRα EC_{50}/LXRβ EC_{50}.

第三項　芳香環リンカーを有する 1,1-ビス(トリフルオロメチル)カルビノール誘導体の合成

前項の結果から，head 部分と tail 部分を柔軟性のあるブタン構造から 2-*trans*-ブテン体 **191b**，または，2-ブチン体 **198** のような堅固な構造で配置することが，LXRβ 活性化作用には有用であることが示唆された．

この結果から，さらなる構造最適化を目指し，より堅固なリンカーとして芳香環を導入し，リンカー部位の配向性の影響を調べるため，誘導体 **I** を合成した．その際，分子全体の脂溶性を考慮し，プロピル基を二つもつフェノール体 **147** (*C*log*P* 5.6) に代わり，プロピル基を一つもつフェノール体 **140** (*C*log*P* 4.0) を用いて化合物を合成することとした．

逆合成解析を Figure 44 に示す．すなわち，目的とする化合物 **I** は，化合物 **199** とヒダントイン **5** を反応させ，合成することとし，次に，化合物 **199** は，第一章第三節第二項 (Scheme 15) で合成した化合物 **140** と化合物 **200** のジアリールエーテル化により供給できるものと考えた．

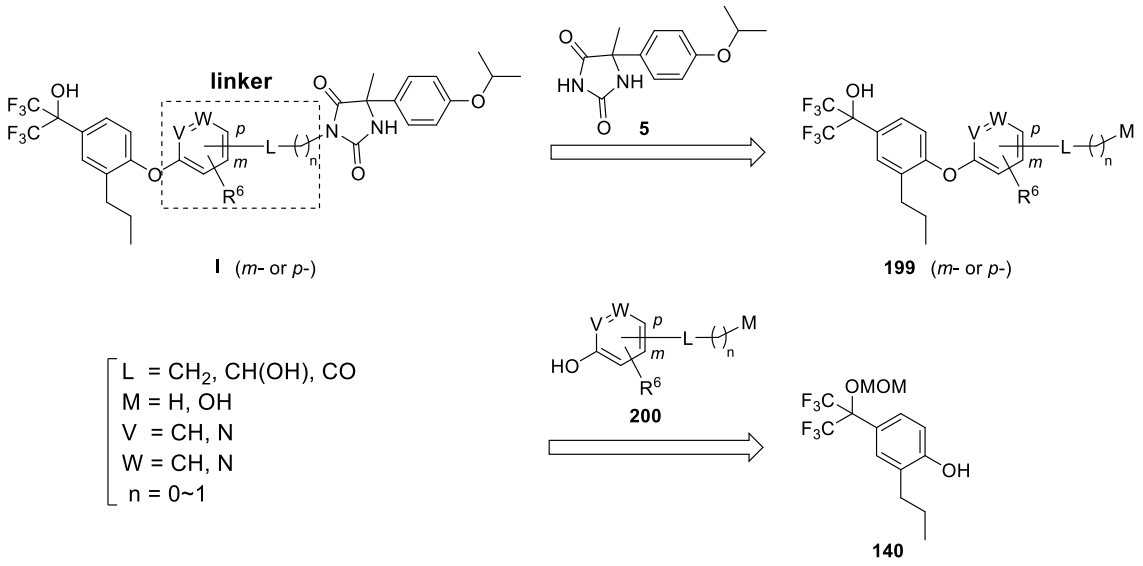
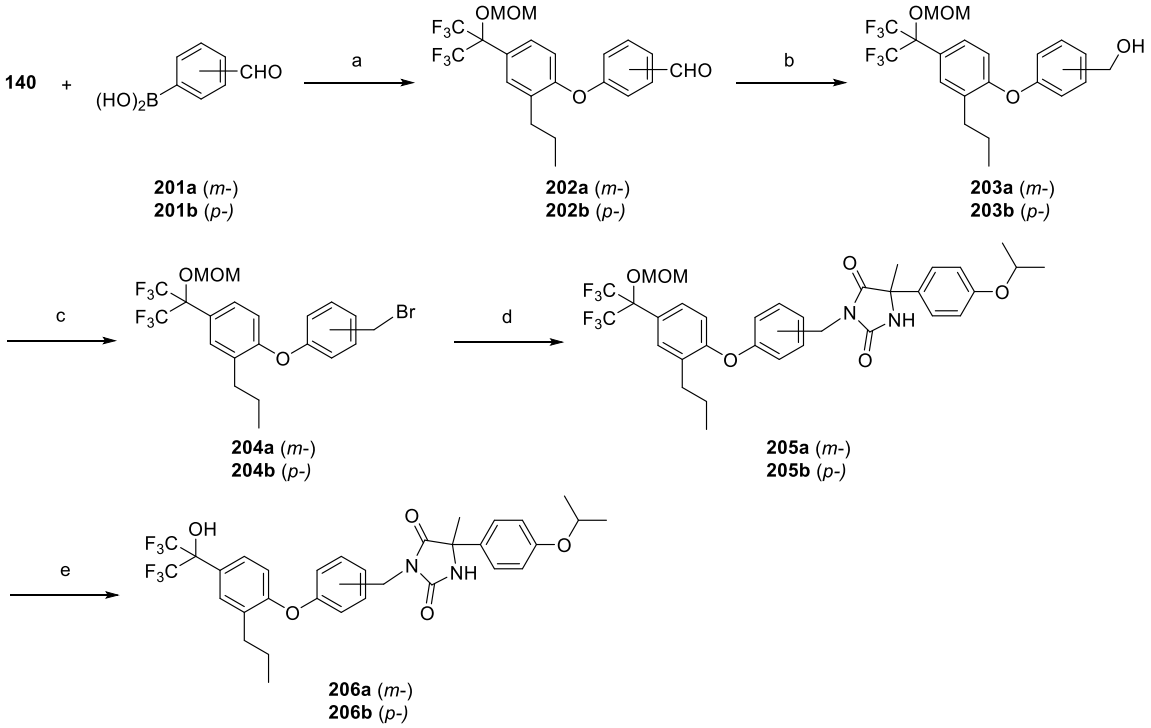


Figure 44. Outline of our retro-synthetic plan.

第一に，ベンジル誘導体 **206a~b** を Scheme 25 に示す方法にしたがって合成した．すなわち，化合物 **140** を CH_2Cl_2 溶媒中，ピリジン，MS4A および $Cu(OAc)_2$ 存在下にて 3-ホルミルフェニルボロン酸 (**201a**)，または 4-ホルミルフェニルボロン酸 (**201b**) との銅促進型アリール化反応 [59] に付し，3-フェノキシベンズアルデヒド (**202a**)，および 4-フェノキシベンズアルデヒド (**202b**) を得た．次いで，メタノール

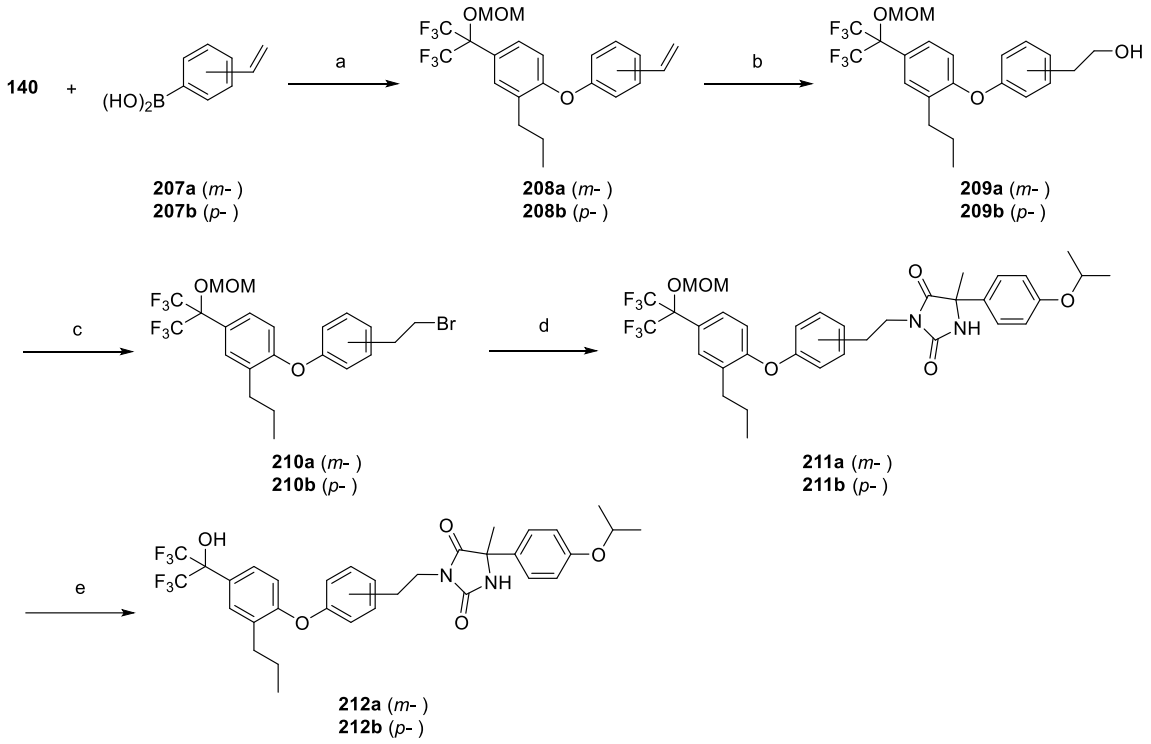
溶媒中で $NaBH_4$ を用いて還元し，ベンジルアルコール **203a~b** を得た後，トリフェニルホスフィンと四臭化炭素を作用させることにより，臭化ベンジル **204a~b** を得た．こうして合成した化合物 **204a~b** とヒダントイン **5** を DMF 溶媒中，K_2CO_3 存在下にて反応させ，付加体 **205a~b** を得た．次いで，化合物 **205a~b** を 4 M 塩酸を用いてメトキシメチル基を除去し，目的とする化合物 **206a~b** を得た．



Scheme 25. Reagents and conditions: (a) $Cu(OAc)_2$, pyridine, MS4A, CH_2Cl_2, rt, 12 h, 68–95%; (b) $NaBH_4$, MeOH, 0 °C, 1 h, 99%; (c) CBr_4, PPh_3, CH_2Cl_2, rt, 0.5–2 h, 18–94%; (d) **5**, K_2CO_3, DMF, rt, 20 h, 21–73%; (e) 4 M HCl, EtOAc, rt, 1 h, 80%.

第二に，フェネチル誘導体 **212a~b** を Scheme 26 に示す方法にしたがって合成した．すなわち，化合物 **140** と 3-ビニルフェニルボロン酸 (**207a**)，または 4-ビニルフェニルボロン酸 (**207b**) を Scheme 25 の step-a と同様に銅促進型アリール化反応に付し，3-フェノキシスチレン誘導体 (**208a**)，および 4-フェノキシスチレン誘導体 (**208b**) を得た．次いで，各々の化合物 **208a~b** を THF 溶媒中，BH_3·THF 混合物を用いたハイドロボレーション反応 [60] に付し，続いて，$NaBO_3$·$4H_2O$ を用いてフェネチルアルコール **209a~b** を得た．さらに，化合物 **209a~b** を CH_2Cl_2 溶媒中，トリフェニルホスフィンと四臭化炭素を作用させることにより，臭化フェネチル **210a~b** へと誘導した．こうして合成した化合物 **210a~b** とヒダントイン **5** を DMF 溶媒中，K_2CO_3 存在下

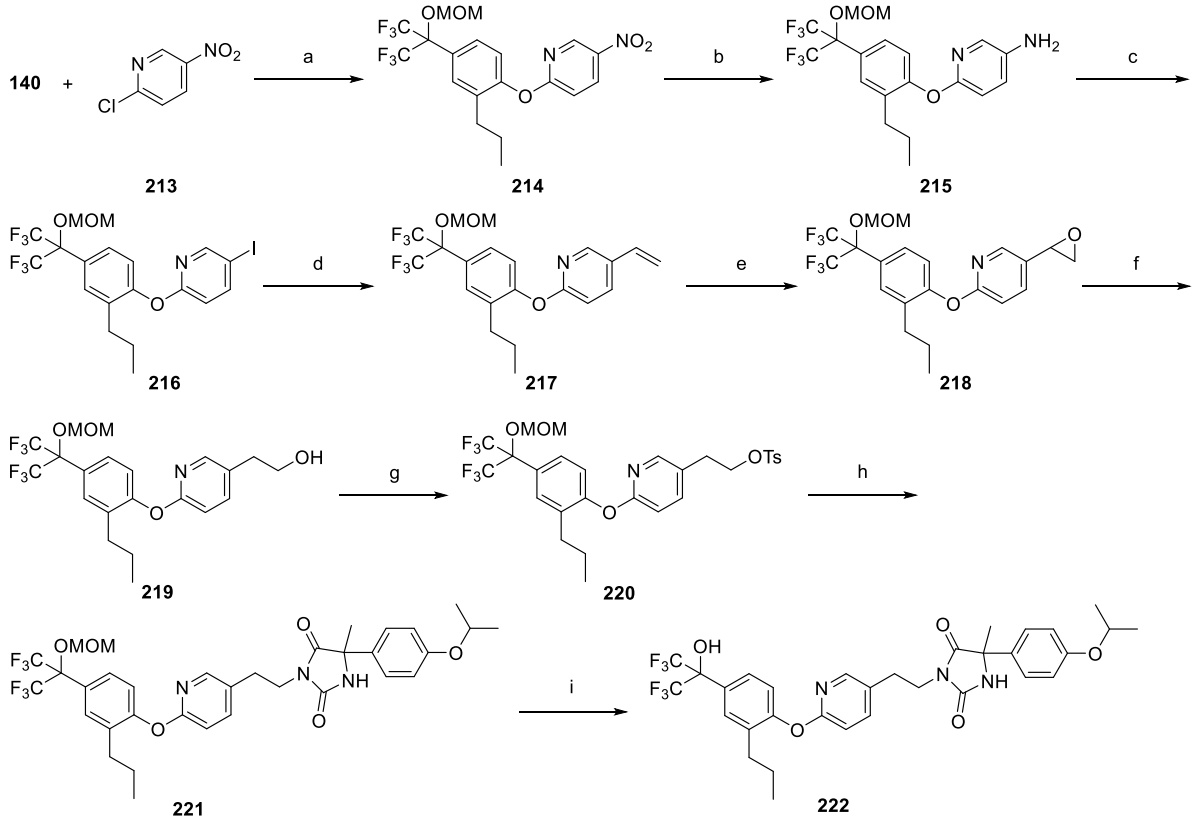
にて反応させ，付加体 **211a~b** を得た．次いで，化合物 **211a~b** を 4 M 塩酸を用いてメトキシメチル基を除去し，目的とする化合物 **212a~b** を得た．



Scheme 26. Reagents and conditions: (a) $Cu(OAc)_2$, pyridine, MS4A, CH_2Cl_2, rt, 20 h, 68–75%; (b) BH_3·THF, THF, 0 °C, 1.5 h then $NaBO_3$·$4H_2O$, H_2O, rt, 3 h, 46–85%; (c) CBr_4, PPh_3, CH_2Cl_2, rt, 0.5–2 h, 18–94%; (d) **5**, K_2CO_3, DMF, rt, 20 h, 21–73%; (e) 4 M HCl, EtOAc, rt, 1 h, 80%.

第三に，3-エチルピリジン体 **222** を Scheme 27 に示す方法にしたがって合成した．すなわち，化合物 **140** を DMF 溶媒中，NaH 存在下にて 2-クロロ-5-ニトロピリジン (**213**) を用いてジアリールエーテル化し，化合物 **214** を得た．次いで，化合物 **214** を AcOH 水溶液中，鉄を用いてニトロ基を還元し，アニリン **215** を得た後，アセトニトリル溶媒中で *p*-TsOH·H_2O および KI 存在下にて $NaNO_2$ 水溶液にて反応させ (Sandmeyer 反応 [61])，3-ヨードピリジン体 **216** へと誘導した．続いて，化合物 **216** を DMF 水溶液中，$Pd(PPh_3)_4$ と Na_2CO_3 存在下にて，ビニルボロン酸エステルと反応させ (鈴木－宮浦カップリング反応 [62])，3-ビニルピリジン体 **217** を得た．さらに，得られた化合物 **217** を $CHCl_3$ 溶媒中で $NaHCO_3$ 存在下にて *m*-CPBA にて酸化し，エポキシ体 **218** へと誘導した後，THF 溶媒中，BF_3·OEt_2 存在下にて $NaBH_3CN$ を用いてエポキシドを選択的に開環し，フェネチルアルコール体 **219** を合成した．次いで，

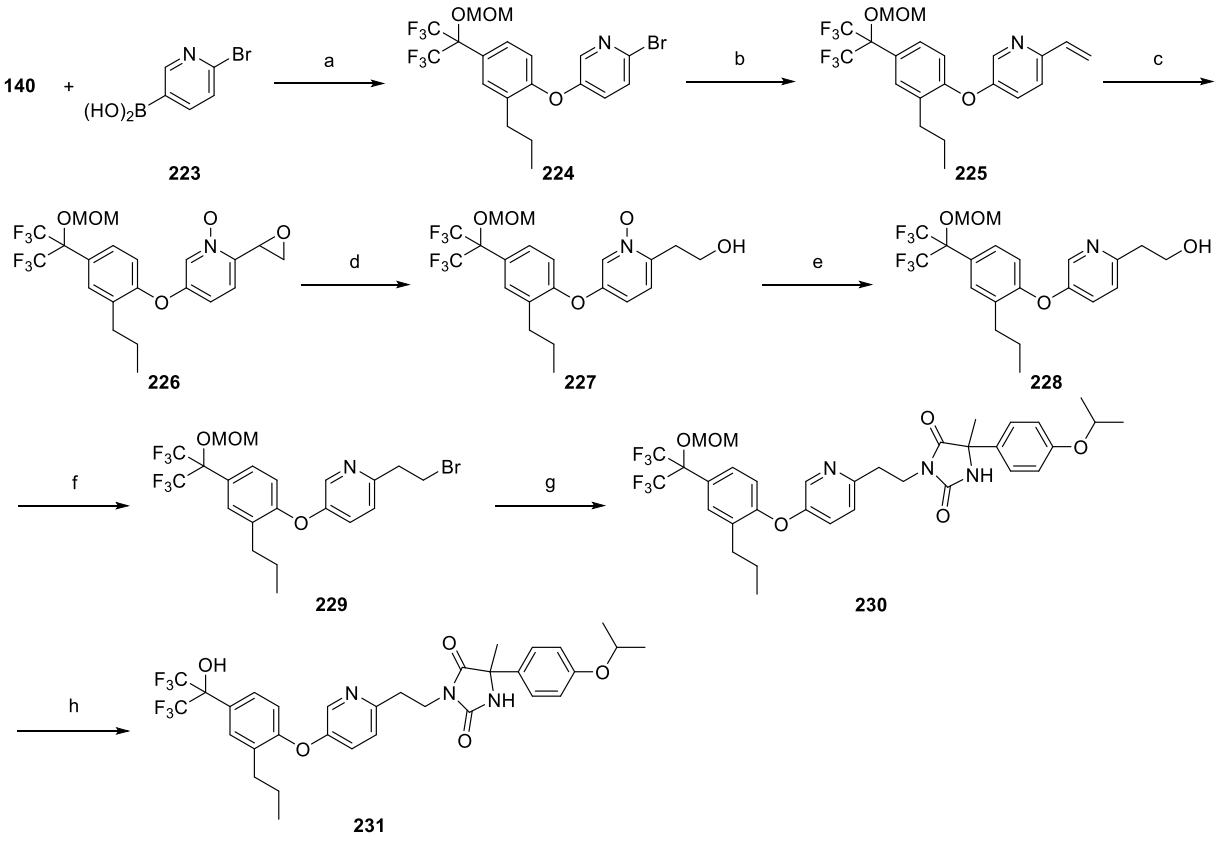
化合物 **219** を CH_2Cl_2 溶媒中，ピリジン存在下にて *p*-TsCl を用いてトシル化し，トシレート体 **220** へと誘導した．こうして合成した化合物 **220** とヒダントイン **5** を DMF 溶媒中，K_2CO_3 存在下にて反応させ，付加体 **221** へと誘導した．最後に，化合物 **221** を 4 M 塩酸を用いてメトキシメチル基を除去し，目的とする化合物 **222** を得た．



Scheme 27. Reagents and conditions: (a) NaH, DMF, rt, 5 min, 99%; (b) Fe, *aq*. AcOH, rt, 1 h, 92%; (c) $NaNO_2$, *p*-TsOH·H_2O, KI, MeCN, rt, 18 h, 67%; (d) 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane, $Pd(PPh_3)_4$, Na_2CO_3, DMF-H_2O, microwave, 80 °C, 20 min, 91%; (e) *m*-CPBA, $NaHCO_3$, $CHCl_3$, 0 °C to rt, 1 h, 55%; (f) BF_3·Et_2O, $NaBH_3CN$, THF, rt, 1 h, 66%; (g) *p*-TsCl, pyridine, CH_2Cl_2, 40 °C, 1 h, 50%; (h) **5**, K_2CO_3, DMF, rt, 16 h, 68%; (i) 4 M HCl, EtOAc, rt, 1 h, 99%.

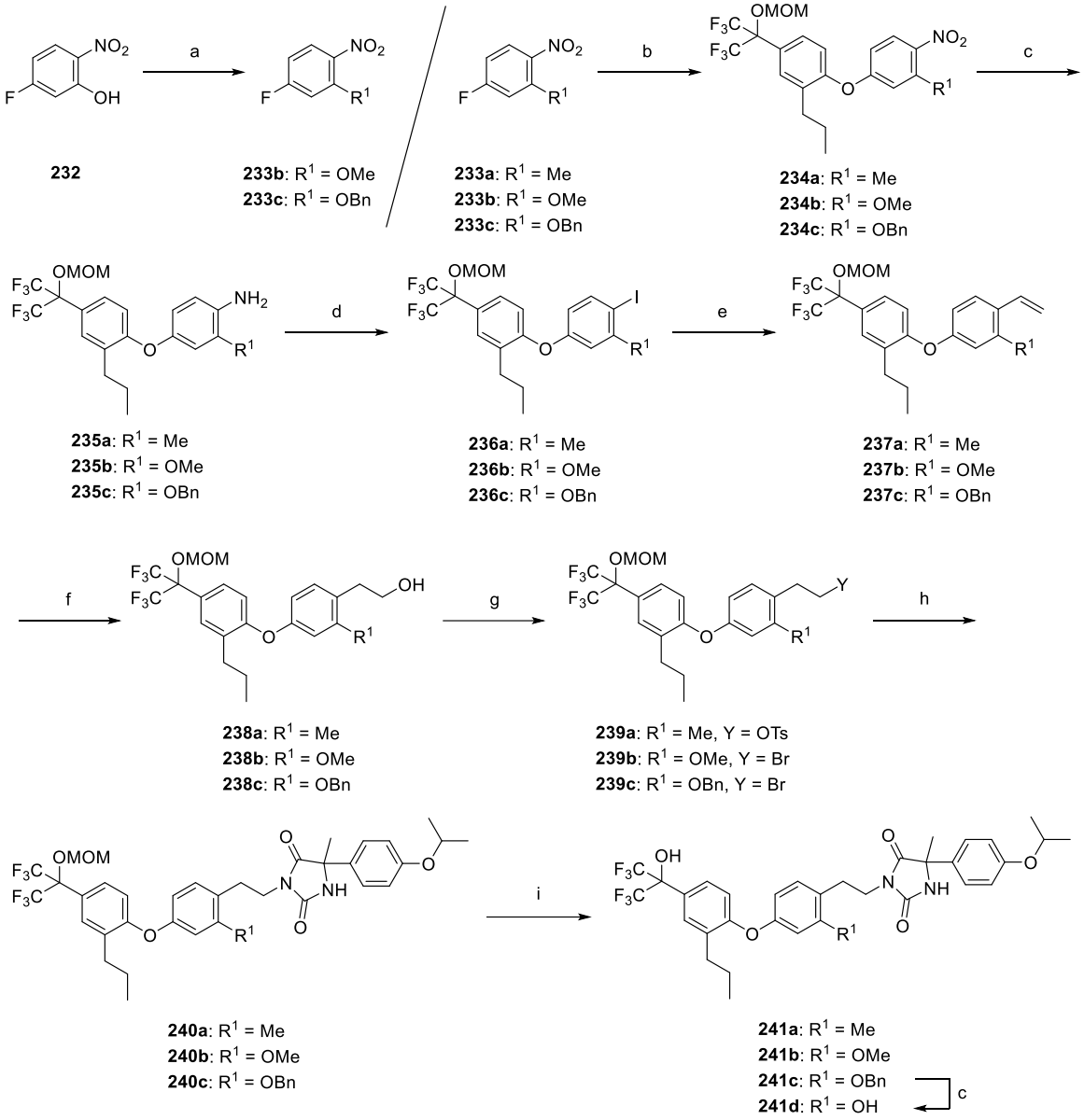
第四に, 2-エチルピリジン体 **231** を Scheme 28 に示す方法にしたがって合成した．すなわち, 化合物 **140** と (6-ブロモピリジン-3-イル)ボロン酸 (**223**) を Scheme 25 の step-a と同様に銅促進型アリール化反応に付し, ピリジルフェニルエーテル体 **224** を得た．次いで，化合物 **224** を DMF 水溶液中，$Pd(PPh_3)_4$ と Na_2CO_3 存在下にて，ビ

ニルボロン酸エステルと反応させ (鈴木－宮浦カップリング反応)，2-ビニルピリジン体 **225** へと誘導した後，$CHCl_3$ 溶媒中で $NaHCO_3$ 存在下にて *m*-CPBA を用いて酸化し，エポキシ-*N*-オキシド体 **226** を得た．さらに，化合物 **226** を THF 溶媒中，$BF_3{\cdot}OEt_2$ 存在下にてエポキシドを選択的に開環し，*N*-オキシフェネチルアルコール体 **227** を得た後，AcOH 溶媒中で亜鉛を用いて *N*-オキシドを還元し，フェネチルアルコール体 **228** を得た．次いで，化合物 **228** を CH_2Cl_2 溶媒中，トリフェニルホスフィンと四臭化炭素を作用させることにより，臭素体 **229** へと誘導した．こうして合成した化合物 **229** とヒダントイン **5** を DMF 溶媒中，K_2CO_3 存在下にて反応させ，付加体 **230** へと誘導した．最後に，化合物 **230** を 4 M 塩酸を用いてメトキシメチル基を除去し，目的とする化合物 **231** を得た．



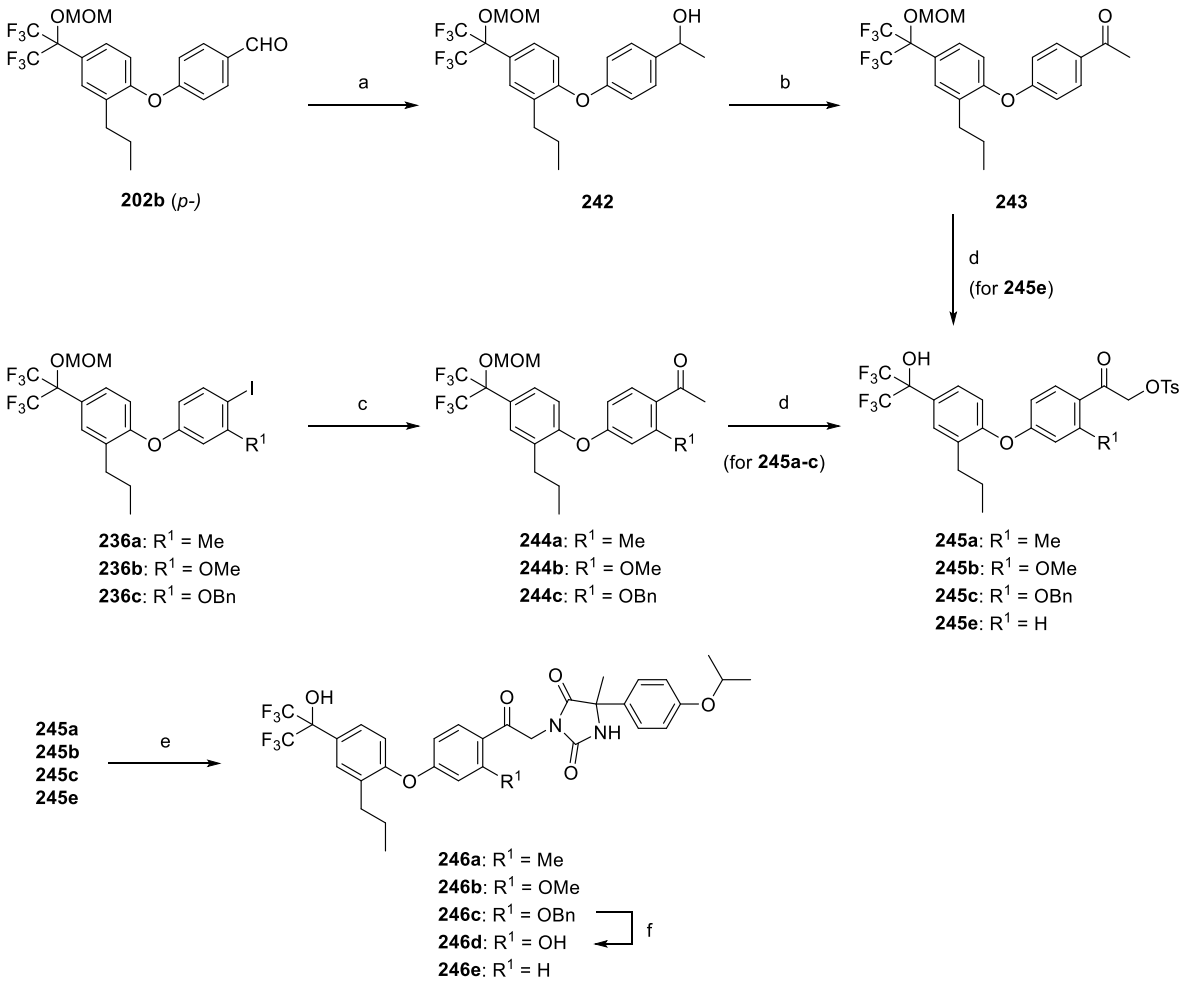
Scheme 28. Reagents and conditions: (a) $Cu(OAc)_2$, pyridine, MS4A, CH_2Cl_2, rt, 20 h, 55%; (b) 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane, $Pd(PPh_3)_4$, Na_2CO_3, DMF-H_2O, microwave, 80 °C, 1 h, 92%; (c) *m*-CPBA, $NaHCO_3$, $CHCl_3$, 0 °C to rt, 1 h, 51%; (d) $BF_3{\cdot}Et_2O$, $NaBH_3CN$, THF, rt, 16 h, 32%; (e) Zn, AcOH, rt, 18 h, 73%; (f) CBr_4, PPh_3, CH_2Cl_2, rt, 0.5 h, 85%; (g) K_2CO_3, DMF, rt, 20 h, 62%; (h) 4 M HCl, EtOAc, rt, 1 h, 99%.

第五に，フェネチルリンカーのベンゼン環上 2 位へ置換基を導入した 2 位置換フェネチル誘導体 **241a~d** を Scheme 29 に示す方法にしたがって合成した．すなわち，2-ニトロ-5-フルオロフェノール (**232**) を DMF 溶媒中，K_2CO_3 存在下にて，ヨウ化メチル，または，臭化ベンジルを用いてアリールアルキルエーテル化し，各々アルキルフェニルエーテル **233b~c** を得た．次いで，2-メチル-4-フルオロ-1-ニトロベンゼン (**233a**), および 2-アルコキシ-4-フルオロ-1-ニトロベンゼン (**233b** R^1 = OMe, **233c** R^1 = OBn) を DMF 溶媒中，K_2CO_3 存在下にて化合物 **140** と反応させ，各々 2-置換-4-アリロキシ-1-ニトロベンゼン **234a~c** を得た．さらに，化合物 **234a~b** を接触水素添加反応にて還元し，アニリン体 **235a~b** を得た．一方，化合物 **234c** は，AcOH 水溶液中で鉄粉を用いて還元し，アニリン体 **235c** へと誘導した．これらアニリン **235a~c** をアセトニトリル溶媒中で *p*-TsOH·H_2O および KI 存在下にて $NaNO_2$ 水溶液にて反応させ (Sandmeyer 反応)，ヨードベンゼン体 **236a~c** へと誘導した．次いで，これらの化合物 **236a~c** を DMF 水溶液中，$Pd(PPh_3)_4$ と Na_2CO_3 存在下にて，ビニルボロン酸エステルと反応させ (鈴木－宮浦カップリング反応)，各々スチレン体 **237a~c** を得た後，THF 溶媒中，BH_3·THF 混合物を用いたハイドロボレーション反応 [60] に付し，続いて，$NaBO_3$·$4H_2O$ を用いてフェネチルアルコール **238a~c** を得た．次いで，アルコール体から臭素体へと変換するため，Scheme 25-step-c と同様の方法で臭素化を試みたところ，化合物 **238a** の臭素化では化学的に不安定なことが考えられ，目的とする臭素体を得ることができなかった．そこで，化合物 **238a** を CH_2Cl_2 溶媒中，ピリジン存在下にて *p*-TsCl と反応させ，トシレート体 **239a** へと誘導した．一方，化合物 **238b~c** の臭素化は低収率ではあったものの，トリフェニルホスフィンと四臭化炭素を作用させることにより，臭素体 **239b~c** へと誘導することができた．こうして合成した化合物 **239a~c** とヒダントイン **5** を DMF 溶媒中，K_2CO_3 存在下にて反応させ，付加体 **240a~c** へと誘導した．最後に，化合物 **240a~c** に 4 M 塩酸を用いてメトキシメチル基を除去し，目的とする化合物 **241a~c** を得た．また，化合物 **241c** の加水素分解反応によりベンジル基を除去し，目的とする化合物 **241d** を得た．



Scheme 29. Reagents and conditions: (a) MeI or BnBr, K_2CO_3, DMF, 60 °C, 1 h, 99%; (b) **141**, K_2CO_3, DMF, 80 °C, 2–3 h, 71–99%; (c) i) H_2, Pd/C, MeOH, rt, 1–3 h, 92–99%; or ii) Fe, *aq*. AcOH, rt, 4 h, 99%; (d) $NaNO_2$, *p*-TsOH·H_2O, KI, MeCN, rt, 18–20 h, 30–67%; (e) 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane, $Pd(PPh_3)_4$, Na_2CO_3, DMF-H_2O, 80 °C, 1 h, 64–99%; (f) BH_3·THF, THF, rt, 1 h then $NaBO_3$·$4H_2O$, H_2O, rt, 20 h, 62–73%; (g) (i) TsCl, pyridine, CH_2Cl_2, 40 °C, 2 h, 50% (**239a**) or (ii) CBr_4, PPh_3, CH_2Cl_2, rt, 0.5–2 h, 10-31% (**239b**, **239c**); (h) **5**, K_2CO_3, DMF, rt, 20 h, 21–73%; (i) 4 M HCl, EtOAc, rt, 1 h, 99%.

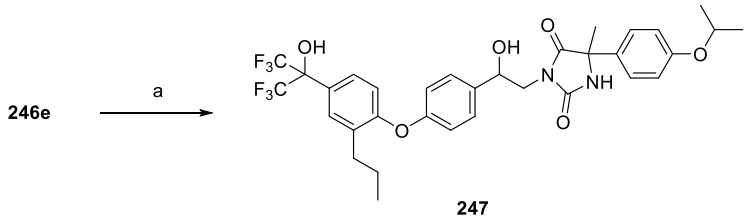
第六に，フェネチルリンカーのベンジル位へのカルボニル基を導入したアセトフェノン誘導体 **246a~e** を Scheme 30 に示す方法にしたがって合成した．すなわち，Scheme 25 で合成した化合物 **202b** を THF 溶媒中，メチルマグネシウムブロミドによる付加反応により，α-メチルベンジルアルコール体 **242** へと誘導した．次いで，化合物 **242** を CH_2Cl_2 溶媒中，二酸化マンガンにより酸化し，アセトフェノン体 **243** を合成した．一方で，リンカー部位のベンゼン環上の 2 位に置換基を有する中間体 **244a~c** は，Scheme 29 で合成した化合物 **236a~c** をトルエン溶媒中，$Pd(PPh_3)_4$ 存在下にてトリブチル(1-エトキシビニル)スタンナンを用いて加熱還流し (Stille カップリング反応)，続いて，酸処理することで合成した [63]．化合物 **243** および化合物 **244a~c** のアセトフェノン部位のメチル基への直接トシル化は，アセトニトリル溶媒中で ((ヒ



Scheme 30. Reagents and conditions: (a) MeMgBr, THF, 0 °C, 1 h then rt, 1 h, 99%; (b) MnO_2, CH_2Cl_2, rt, 18 h, 78%; (c) $(CH_2CH(OEt))SnBu_3$, $Pd(PPh_3)_4$, toluene, reflux, 1–2.5 h, then HCl, rt, 18 h, 47–80%; (d) PhI(OTs)OH, MeCN, reflux, 6 h, 18–93%; (e) **5**, K_2CO_3, DMF, rt, 20 h, 21–73%; (f) H_2, Pd/C, MeOH, rt, 3 h, 88%.

ドロキシ)(トシルオキシ)ヨード)ベンゼン (PhI(OTs)OH) [64] を用いて加熱還流して，各々トシレート体 **245a~c** および **245e** を得た．こうして合成した化合物 **245a~c** および **245e** とヒダントイン **5** を DMF 溶媒中，K_2CO_3 存在下にて反応させ，目的とする化合物 **246a~c** および **246e** へと誘導した．また，化合物 **246c** の加水素分解反応によりベンジル基を除去し，目的とする化合物 **246d** を得た．

第七に，フェネチルリンカーのベンジル位への水酸基を導入したベンジルアルコール誘導体 **247** を Scheme 31 に示す方法にしたがって合成した．すなわち，Scheme 30 で合成した化合物 **246e** を THF 溶媒中，$NaBH_4$ を用いてカルボニル基を還元し，目的とする化合物 **247** を得た．



Scheme 31. Reagents and conditions: (a) $NaBH_4$, THF, rt, 15 h, 95%.

第四項　構造活性相関⑤:芳香環リンカーを有する 1,1-ビス(トリフルオロメチル)カルビノール誘導体の *in vitro* 活性評価

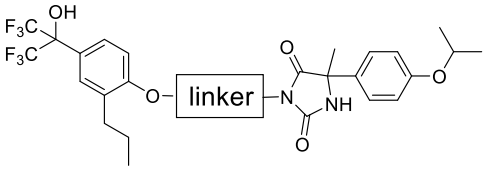
前項にて合成したリンカー部位に芳香環を有する化合物 **I** を用いて，第二章までと同様に，Gal4-h-LXR を用いたレポーター遺伝子アッセイを用いて，各サブタイプ (LXRα, LXRβ) に対する活性化を測定し (EC_{50} 値)，LXRα/β デュアルアゴニストである T0901317 の 10 μM における活性化強度との比 (E_{max} 値) を求めた．

Table 18-1 には，リンカー部位にベンジル，フェネチルおよびフェネチル構造のベンゼン環をピリジン環に変えた化合物 **I** の *in vitro* 評価の結果を記載した．比較のため，リード化合物 **4** のデータも記載した．

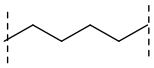
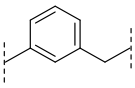
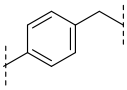
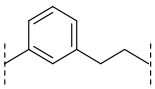
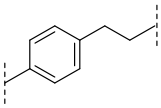
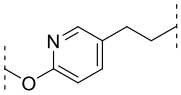
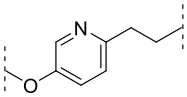
はじめに，ベンジル誘導体 **206a~b** とフェネチル誘導体 **212a~b** の EC_{50} (β) 値を比較したところ，化合物 **206a** が化合物 **4** と比べて著しく改善された．また，パラ置換体は，メタ置換体より良好な β 選択性を示した (selectivity for EC_{50} α/β; **206b**: β only *vs* **206a**: 4.0; **212b**: β only *vs* **212a**: 1.0)．次に，一般的にベンゼン環からピリジン環へ変換することで，脂溶性を低減させることが可能なことから，窒素原子の導入可能な二種のエチルピリジン体 **222** および **231** の活性化作用を確認した．その結果，

化合物 **222** は，化合物 **212b** と比べて同等の EC_{50} (β) 値を示したが，E_{max} (β) 値は低下した (**222** EC_{50} (β) = 1.8 μM, E_{max} (β) = 104%). 一方，化合物 **231** は，化合物 **212b** と比べて EC_{50} (β) 値と E_{max} (β) 値をともに改善し (**231** EC_{50} (β) = 0.73 μM, E_{max} (β) = 276%)，また，リード化合物 **4** と比べて LXRβ 活性化作用 (EC_{50} 値, E_{max} 値) の向上

Table 18-1. LXR activity of the 1,1-bis(trifluoromethyl)carbinol derivatives containing various linkers **I**[a]



I

Compound	Linker	LXRα EC_{50}[b] (%)[c]	LXRβ EC_{50}[b] (%)[c]	Selectivity for EC_{50} α/β[d]	*C*log*P* [46)]
4		1.1 (26)	1.2 (146)	0.92	7.63
206a		2.0 (53)	0.50 (429)	4.0	7.35
206b		ia (0)	1.8 (22)	[e]	7.35
212a		2.9 (23)	2.9 (126)	1.0	7.63
212b		ia (1)	1.9 (223)	[e]	7.63
222		ia (0)	1.8 (104)	[e]	7.09
231		3.4 (8)	0.73 (276)	4.7	7.09

ia = inactive at 10 μM.
[a] The GAL4-LXR luciferase assay was performed at a maximum dose of 1 or 10 μM. The results are given as the mean of two independent experiments. [b] EC_{50} data are reported in μM. [c] The E_{max} (%) is defined as the percentage ratio between maximum fold induction for the test compound and fold induction for T0901317 at 10 μM in the same experiment.[45)]
[d] selectivity = The value of selectivity is LXRα EC_{50}/LXRβ EC_{50}. [e] Only a LXRβ activation was indicated in the measured concentration region.

や脂溶性の低減だけでなく，LXRα と LXRβ の EC_{50} 値の選択性も改善した (selectivity for EC_{50} α/β; **4**: 0.92, **231**: 4.7).

Table 18-1 の結果から，化合物 **231** が良好な LXRβ 活性化作用および選択性を示したことから，血中濃度推移を確認した．その結果，残念ながら，化合物 **231** の血中濃度は，化合物 **4** よりも低く，代謝安定性に問題があることが明らかになった (データ不記載). そこで, 良好な選択性を有する化合物 **212b** (E_{max} (β) = 223%, E_{max} (α) = 1%) を基に，さらなる構造最適化を検討した．

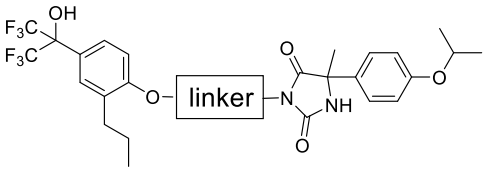
Table 18-2 には, リンカー部位であるフェネチル構造中のベンゼン環 2 位に種々の置換基を導入した, またはベンジル位に水酸基やカルボニル基を導入した化合物 **I** の *in vitro* 評価の結果を記載した．比較のため，前出 (Table 18-1) のフェネチル体 **212b** のデータも記載した．

まず, 化合物 **212b** のフェネチル部位のベンゼン環上の 2 位に置換基を導入したところ，2 位にメチル基をもつ化合物 **241a** は，E_{max} (β) を向上させた (EC_{50} (β) = 0.70 μM, E_{max} (β) = 615%)．しかし，非常に高い脂溶性を示し (**241a**: *C*log*P* = 8.12)，脂溶性の低減が不可欠であった．次に，メトキシ基をもつ化合物 **241b**，および，水酸基をもつ化合物 **241d** は，E_{max} (β) 値を向上させ，脂溶性も僅かではあるが低下させた (**241b**; EC_{50} (β) = 1.7 μM, E_{max} (β) = 534%, *C*log*P* = 7.50, **241d**; EC_{50} (β) = 2.9 μM, E_{max} (β) = 284%, *C*log*P* = 7.24).

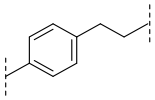
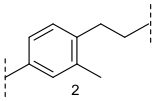
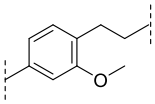
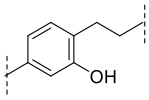
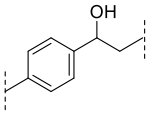
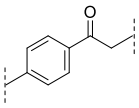
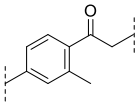
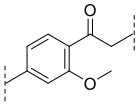
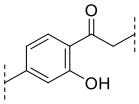
次に，代謝を考慮し，代謝部位として推察されたリンカー部位のベンジル位に留意し，検討をおこなった．化合物 **212b** のリンカー部位のベンジル位に水酸基をもつベンジルアルコール体 **247** は，化合物 **212b** と比べて EC_{50} (β) 値を低下させた (EC_{50} (β) = 2.3 μM, E_{max} (β) = 176%)．しかし，化合物 **247** は，四種のジアステレオマー混合物であることから，この位置への水酸基の導入は有効であると考えた．すなわち，この位置に受容体との新たな相互作用を有することができれば, LXR 活性化作用の向上につなげることができるのではないかと考えた．

そこで，まず，化合物 **247** をケトン体 **246e** に変換したところ，EC_{50} (β) 値を顕著に改善し，脂溶性も低下させることができた (**246e**; EC_{50} (β) = 0.12 μM, E_{max} (β) = 236%, *C*log*P* = 6.54)．一方で，E_{max} (α) 値は抑制されてはいるが，EC_{50} (α) 値は LXRβ と同様に向上してしまった (**246e**; EC_{50} (α) = 0.36 μM, E_{max} (α) = 46%)．そこで，著者はアセトフェノンの 2 位へ置換基を導入することにより，フェネチルリンカーの 2 位置換基修飾体 **241b**，および **241d** で認められたサブタイプ選択性の発現につながる可能性に期待した．まず, LXRβ および LXRα の活性化作用について考察した結果，EC_{50} (β) 値について，2 位にメチル基をもつ化合物 **246a** は，化合物 **246e** と比べて著しく改善したが，2 位にメトキシ基をもつ化合物 **246b** では低下し, 2 位に水酸基を

Table 18-2. LXR activity of the 1,1-bis(trifluoromethyl)carbinol derivatives containing various linkers **I**[a]



I

Compound	Linker	LXRα EC_{50}[b] (%)[c]	LXRβ EC_{50}[b] (%)[c]	Selectivity for EC_{50} α/β[d]	*C*log*P* [46]
212b		ia (1)	1.9 (223)	[e]	7.63
241a		3.1 (53)	0.70 (615)	4.4	8.12
241b		ia (0)	1.7 (534)	[e]	7.50
241d		ia (1)	2.9 (284)	[e]	7.24
247		ia (5)	2.3 (176)	[e]	6.81
246e		0.36 (46)	0.12 (236)	3.0	6.54
246a		0.40 (71)	0.064 (264)	6.3	7.02
246b		3.7 (38)	0.36 (306)	10	6.41
246d		0.34 (55)	0.11 (348)	3.1	6.15

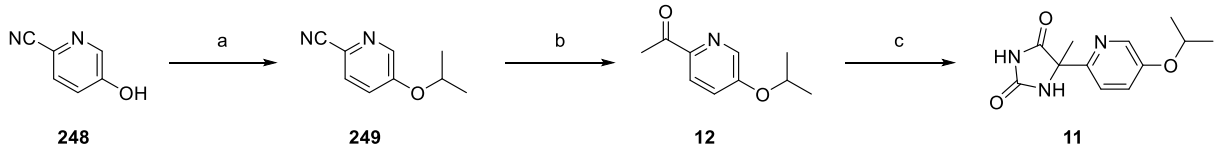
ia = inactive at 10 μM.
[a] The GAL4-LXR luciferase assay was performed at a maximum dose of 1 or 10 μM. The results are given as the mean of two independent experiments. [b] EC_{50} data are reported in μM. [c] The E_{max} (%) is defined as the percentage ratio between maximum fold induction for the test compound and fold induction for T0901317 at 10 μM in the same experiment.[45] [d] selectivity = The value of selectivity is LXRα EC_{50}/LXRβ EC_{50}. [e] Only a LXRβ activation was indicated in the measured concentration region.

もつ化合物 **246d** ではほぼ同等であった (**246e**: **246a**: **246b**: **246d**; EC_{50} (β) = 0.12 μM: 0.064 μM: 0.36 μM: 0.11 μM; E_{max} (β) = 236%: 264%: 306%: 348%). 一方, EC_{50} (α) 値については, 化合物 **246e** と比べて化合物 **246b** は低下したが, 化合物 **246a** および **246d** はほぼ同等であった (**246e**: **246a** : **246b** : **246d**; EC_{50} (α) = 0.36 μM: 0.40 μM: 3.74 μM: 0.34 μM; E_{max} (α) = 46%: 71%: 38%: 55%). 選択性については, 化合物 **246e** と比べて化合物 **246a** および **246b** は改善したが, 化合物 **246d** はほぼ同等であった (**246e**: **246a**: **246b**: **246d**; selectivity for EC_{50} α/β = 3.0: 6.3: 10: 3.1).

以上の結果から著者は, LXRβ 活性化作用 (EC_{50} 値), 選択性および脂溶性を考慮し, リンカー部位に 2-ヒドロキシアセトフェノン構造を有する化合物 **246d** に注目した. ただし, 化合物 **246d** の脂溶性は, 十分に低いものとは言えず, また β 選択性も十分に高いとは言えない. そのため, ヒダントイン環上の置換基であるベンゼン環をピリジン環へと変換し, 脂溶性の低下を図るとともに, LXRβ 活性化作用および選択性への影響を確認することとした.

第五項　ピリジルヒダントイン誘導体の合成

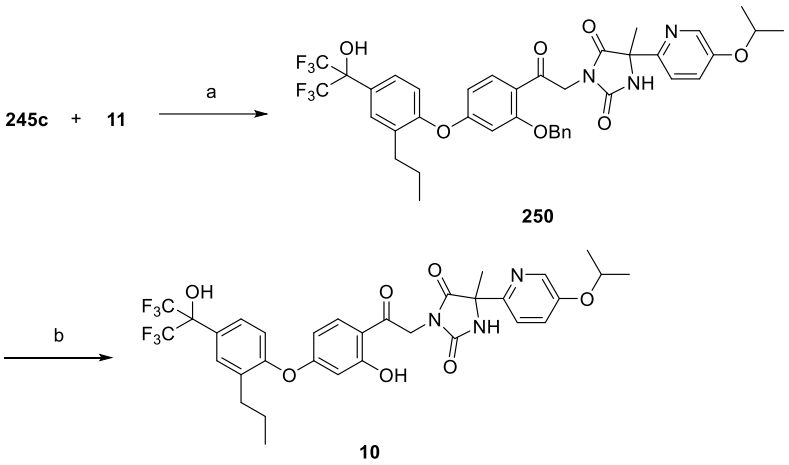
著者は, Scheme 32 に示した方法に従い 5-ヒドロキシピコリノニトリル (**248**) からピリジルヒダントイン **11** を合成した. すなわち, 化合物 **248** を DMF 溶媒中, K_2CO_3 存在下にて 2-ヨードプロパンを用いてアリールアルキルエーテル化し, 5-イソプロポキシピコリノニトリル (**249**) を得た. 次いで, 化合物 **249** を THF 溶媒中, メチルマグネシウムブロミドを用いて付加反応後, 酸性条件下にて後処理し, ケトン体 **12** を得た. 最後に, ケトン **12** を Scheme 10 (step-a) と同様の条件に付し, 化合物 **11** を合成した.



Scheme 32. Reagents and conditions: (a) *i*-PrI, K_2CO_3, DMF, rt, 5.5 h, 59%; (b) MeMgBr, THF, 0 °C, 2 h, 77%; (c) NaCN, $(NH_4)_2CO_3$, *aq*. EtOH, microwave, 100 °C, 1 h, 87%.

こうして合成した化合物 **11** と Scheme 30 にて合成したトシレート体 **245c** を DMF 溶媒中, K_2CO_3 存在下にて反応させ, 化合物 **250** へと誘導した. さらに, 化合

物 **250** の加水素分解反応によりベンジル基を除去し，目的とする化合物 **10** を得た (Scheme 33).



Scheme 33. Reagents and conditions: (a) K_2CO_3, DMF, rt, 20 h, 21%; (b) H_2, Pd/C, MeOH, rt, 3 h, 80%.

第六項　2-ヒドロキシアセトフェノン誘導体 **246d** および **10** の *in vitro* 活性評価

第四項と同様に Gal4-h-LXR を用いたレポーター遺伝子アッセイを用いて，各サブタイプ (LXRα, LXRβ) に対する活性化を測定し (EC_{50} 値), LXRα/β デュアルアゴニストである T0901317 の 10 μM における活性化強度との比 (E_{max} 値) を求めた.

その結果 (Figure 45)，化合物 **10** は，ピリジン環を導入した影響で脂溶性を低下させることができただけでなく，EC_{50} 値と LXRβ 選択性 (selectivity for EC_{50} α/β) を顕著に改善することができた (EC_{50} (β) = 0.058 μM, E_{max} (β) = 329%, selectivity for EC_{50} α/β = 5.7, *C*log*P* = 5.23).

ここで，これまでに得られた良好な化合物の *in vitro* 活性プロファイルを用量反応曲線を用いて比較した.

LXRα/β デュアルアゴニストである T0901317 に対して，第一章で見出したリード化合物 **4** は LXRα の活性化作用を抑制していたが，EC_{50} (β) 値の改善が必要性であった. 次に，第二章で見出したリンカー部分に 2-ヒドロキシアセトフェノン構造を有する化合物 **246d** は，EC_{50} (β) 値を顕著に改善させた. さらに，化合物 **246d** のヒダントイン環上の置換基をベンゼン環からピリジン環へ変換した化合物 **10** は, **246d** と

比べて，LXRβ 活性化作用を改善したことで，選択性が向上した (selectivity for EC_{50} α/β; **4** 0.92, **246d** 3.1, **10** 5.7)．また，このピリジン環への変換により脂溶性が低下し，より有用な *in vitro* 活性プロファイルを有する化合物を見出すことに成功した．

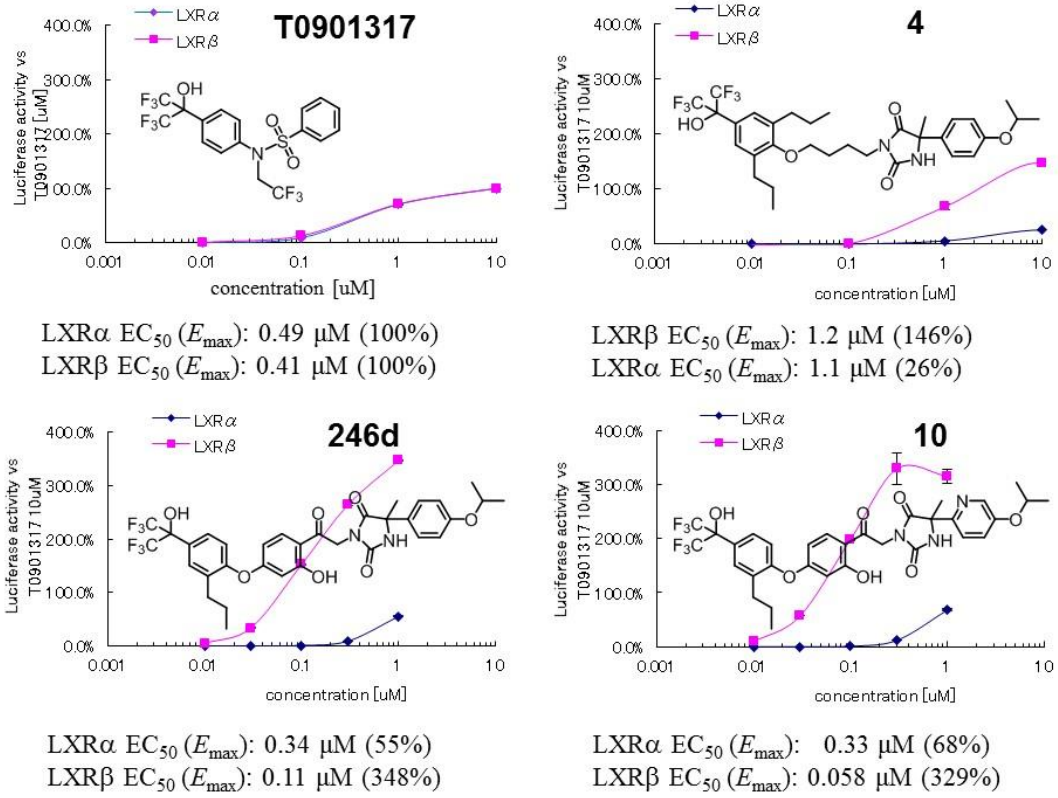


Figure 45. Dose-response curves of **T0901317**, **4**, **246d** and **10**

第七項　化合物 **10** のドッキングモデルでの検証

これまでドラッグデザインをおこなうにあたり，GW3965 と LXRβ との共結晶による X 線結晶構造解析をもとに，自社 HTS から見出した化合物 **1** や構造活性相関研究にて見出した化合物 **2** および **4** を用いてドッキングモデルを作製してきた．

前項までに述べてきたように，化合物 **10** は，より有用な *in vitro* 活性プロファイルを示す化合物として見出すことができたことから，ドッキングモデルによる検証をおこなった (Figure 46).

その結果，head 部分，リンカー部分および tail 部分が，以下に述べるアミノ酸と相互作用していると推察している．

① Head 部分については，1,1-ビス(トリフルオロメチル)カルビノール構造が His435 と相互作用し，‘His435-Trp457 activation switch’と呼ばれる相互作用を有することができている．その際，ベンゼン環上の 2-プロピル基は足場を固める役割をもち，His435 との相互作用をしやすい環境にしている．

② リンカー部分については，ベンゼン環が Phe329 と，また，カルボニル基は Ser278 と相互作用している．

③ Tail 部分については，GW3965 の tail 部分が位置する領域，および，さらに奥側の新たな領域で相互作用している．すなわち，ヒダントイン構造が Arg319 と相互作用し，Gln235 や Glu315 が 1-メチルエトキシピリジン構造基と相互作用している．

上記のような新たな相互作用の形成により，これまでに報告のないような高活性な LXR アゴニスト活性を有する化合物 **10** を見出すことができたものと考えている．しかし，選択性の発現については，リガンドの結合領域では LXRα と LXRβ との相同性が非常に高いため，ドッキングモデルでは明確な違いを見出すことが困難であった．したがって，LXRβ 選択性の発現に関してはドッキングモデルからの考察はできなかったが，前述 (第一章第一節第一項) したように，tail 部分での新たなアミノ酸との相互作用が，選択性の発現に関与しているものと推察している．

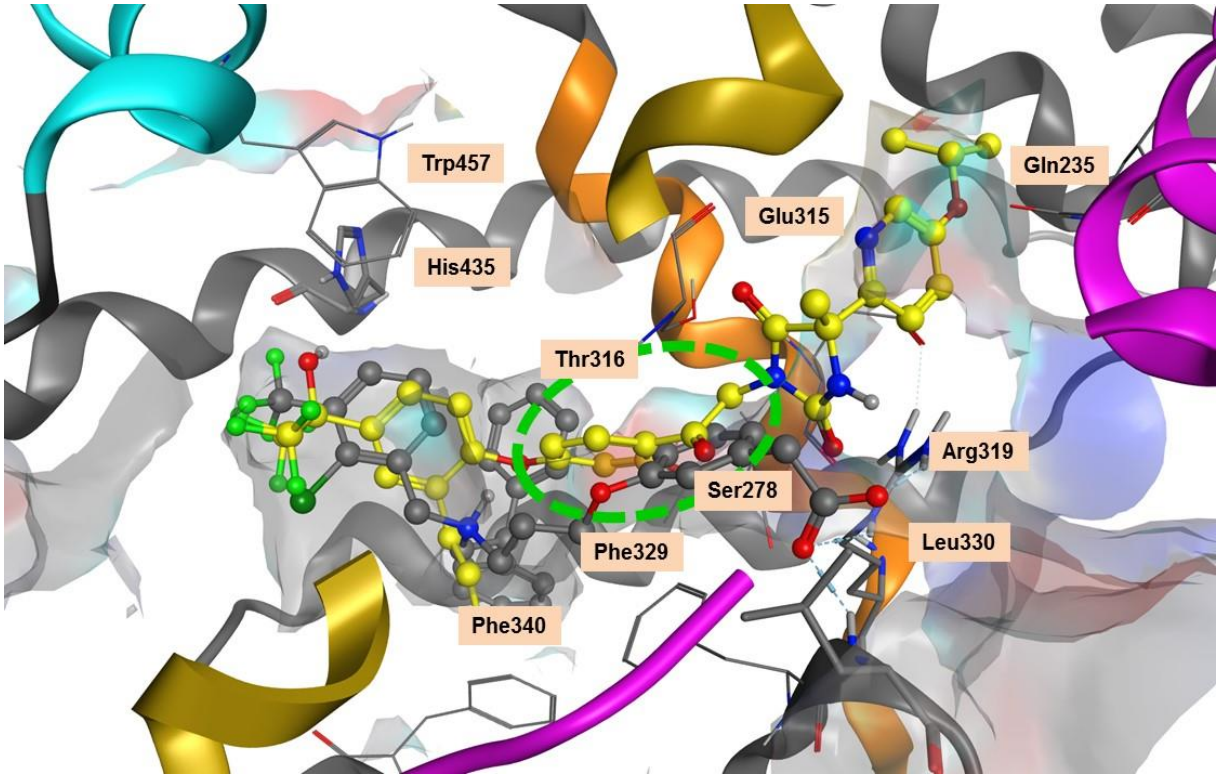


Figure 46. Docking model of GW3965 (gray) and **10** (yellow).

第八項　2-ヒドロキシアセトフェノン誘導体 **246d** および **10** の薬物動態評価

第一章で得たリード化合物 **4** のもう一つの課題であった代謝安定性について，リード化合物 **4** と構造活性相関研究で良好な活性を示した 2-ヒドロキシアセトフェノン誘導体 **246d** および **10** の *in vitro* 肝クリアランスを評価した．

その結果 (Table 19)，化合物 **4** と比べて，リンカー部位に 2-ヒドロキシアセトフェノン構造を有する化合物 **246d** は，肝クリアランスを改善した．さらに，化合物 **246d** のヒダントイン環上の置換基をベンゼン環からピリジン環へ変換した化合物 **10** は，化合物 **246d** よりもさらに肝クリアランスを改善した．また，化合物 **10** の代謝安定性は，マウス，ハムスターおよびヒトにおいて動物種差なく大きく改善された．

Table 19. hepatic CLint (μL/min/mg protein) of each animal obtained using an *in vitro* assay.*

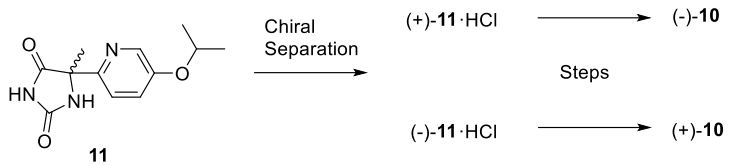
Compound	Mouse	Hamster	Human
4	84	206	71
246d	76	27	12
10	24	11	7

*The hepatic CLint values of compounds **4**, **246d** and **10** were assessed using hepatic microsomes from each animal (mouse, hamster and human).[65)]

第九項　光学活性ピリジルヒダントイン誘導体 **10** の *in vitro* 活性評価

ピリジルヒダントイン誘導体 **10** は，ヒダントインの 5 位に不斉炭素原子を有している．したがって，鏡像異性体の *in vitro* プロファイルを確認する必要があった．

はじめに，光学活性カラムである CHIRALPAK AY-H を用いて，合成中間体であるラセミ体のヒダントイン **11** を光学分割し，各鏡像異性体 (+)-**11** と (−)-**11** を得た[66)]．次いで，Scheme 33 と同様の方法により化合物 (+)-**10** と (−)-**10** を合成した (Scheme 34)．



Scheme 34. Chiral separation of (±)-**11** and preparation of the corresponding enantiomers (−)-**10** and (+)-**10** from (+)-**11**·HCl and (−)-**11**·HCl.

次に，得られた各鏡像異性体 (+)-**10** および (−)-**10** をこれまでと同様に，Gal4-h-LXR を用いたレポーター遺伝子アッセイを用いて，各サブタイプ (LXRα, LXRβ) に対する活性化を測定し (EC_{50} 値)，LXRα/β デュアルアゴニストである T0901317 の 10 μM における活性化強度との比 (E_{max} 値) を求めた (Figure 47).

その結果，鏡像異性体 (−)-**10** の LXRβ に対する EC_{50} 値は，ラセミ体 **10** と比べて向上した．一方，LXRα に対する EC_{50} 値は、ラセミ体 **10** とほぼ同等であり，選択性は向上した ((−)-**10**; EC_{50} (β): 0.018 μM, EC_{50} (α): 0.35 μM, selectivity for EC_{50} α/β: 20, (±)-**10**; EC_{50} (β): 0.058 μM, EC_{50} (α): 0.33 μM, selectivity for EC_{50} α/β: 5.7). 一方，(+)-**10** は LXRα および LXRβ 活性化作用をともに著しく低下させた ((+)-**10**; EC_{50} (β): 3.9 μM, EC_{50} (α): 5.1 μM).

すなわち，鏡像異性体 (−)-**10** は，LXRβ に対して，濃度 0.001 μM から活性化作用を示した ((−)-**10**; E_{max} (β): 0.001 μM: 1.0%, 0.003 μM: 8.9%, 0.01 μM: 84%, 0.03 μM: 195%). 一方，(−)-**10** は，LXRα に対して，濃度 0.1 μM 以下では活性化作用をほぼ示さず，濃度 0.1 μM でも活性化強度は 11%程度であった ((−)-**10**; E_{max} (α): 0.001 μM: 0.05%, 0.003 μM: 0.07%, 0.01 μM: 0.1%, 0.03 μM: 0.6%)).

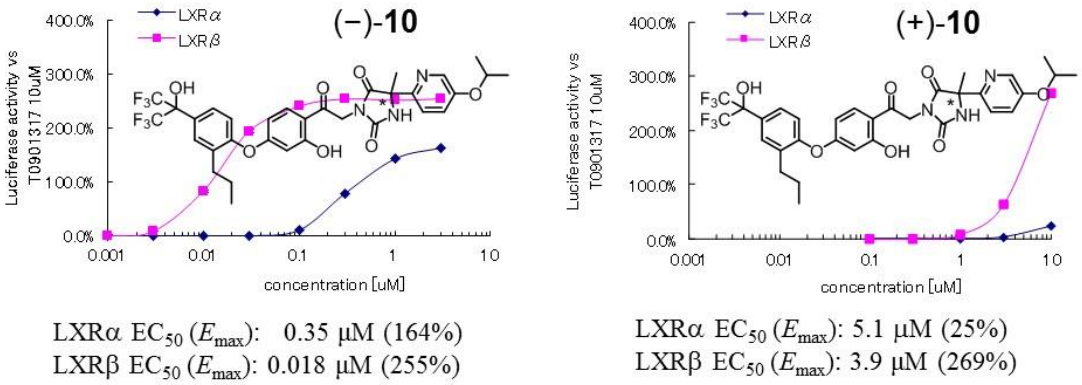


Figure 47. Dose-response curves of (−)-**10** and (+)-**10**

第十項　光学活性ピリジルヒダントイン誘導体 (−)-**10** の薬物動態評価

創出した化合物 (−)-**10** の血中濃度を評価した (Table 20). 投与媒体は，リード化合物 **4** と同じ PEG400 を用いて，10 mg/kg の経口投与での血中薬物濃度を比較した.

その結果. 化合物 (−)-**10** の 10 mg/kg の経口投与における血中薬物濃度は，化合物 **4** の 100 mg/kg での経口投与とほぼ同等の値を示した [67].

Table 20. PK profile of **4** and (−)-**10**

Compound	Dose (mg/kg)	Cmax (ng/mL)	AUC (h*ng/mL)
4	100	406	3419
(−)-**10**	10	503	3027

以上より，化合物 (−)-**10** は，代謝安定性の改善にともない，血中薬物濃度も改善することができた. 前項に述べたように，化合物 (−)-**10** の *in vitro* 活性化作用 (EC_{50} 値) は，著しく向上していることから，*in vivo* 評価にて望む薬効を示すことが期待された.

第十一項　光学活性ピリジルヒダントイン誘導体 (−)-**10** の薬理評価

高い LXRβ アゴニスト活性，および高い LXRβ 選択性を示す化合物 (−)-**10** を用いて，第一章で用いた動脈硬化疾患モデルではなく，高脂肪高コレステロール食負荷 LDL 受容体欠損マウスを用いて各脂質プロファイルと脂質沈着面積を評価した. この動物モデルは，動脈硬化治療薬の研究において最も広く，かつ有効な動物モデルの一つとして使用されている [68, 69]. したがって，化合物 (−)-**10** を本モデルを用いて評価することで，他の標的薬との相対的な比較も確認できると考えた. なお，この *in vivo* 評価にあたり陽性対象薬には T0901317 を用いた [29]. マウスに高コレステロール食負荷を 2 週間おこなった後，薬物として T0901317 (10 mg/kg) および化合物 (−)-**10** (1, 3 mg/kg) を 10 週間 1 日 1 回経口投与した.

以下に *in vivo* 評価の結果を示す. まず，TC については，T0901317 の 10 mg/kg での投与，および化合物 (−)-**10** の 1 mg/kg および 3 mg/kg での投与では，変化は無かった (Figure 48).

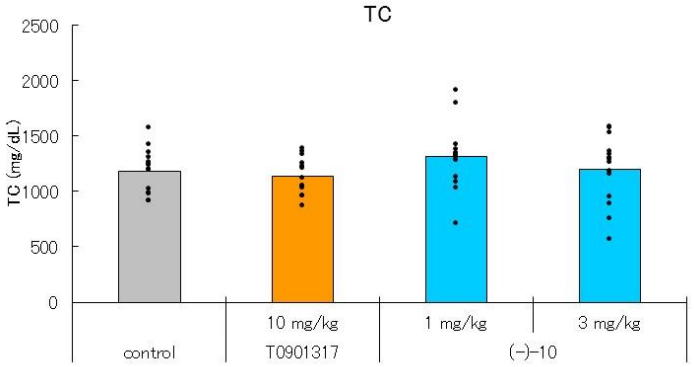


Figure 48. TC profiles in T0901317 and (−)-**10**

HDL-C については，T0901317 の 10 mg/kg の投与にて，顕著に低下させる (47%) 一方，化合物 (−)-**10** の投与では 1 mg/kg および 3 mg/kg 投与にて増加した (115 and 116%, respectively).

LDL-C については，T0901317 の 10 mg/kg の投与にて，顕著に低下させる (55%) 一方，化合物 (−)-**10** ではほぼ変化がなかった (Figure 49).

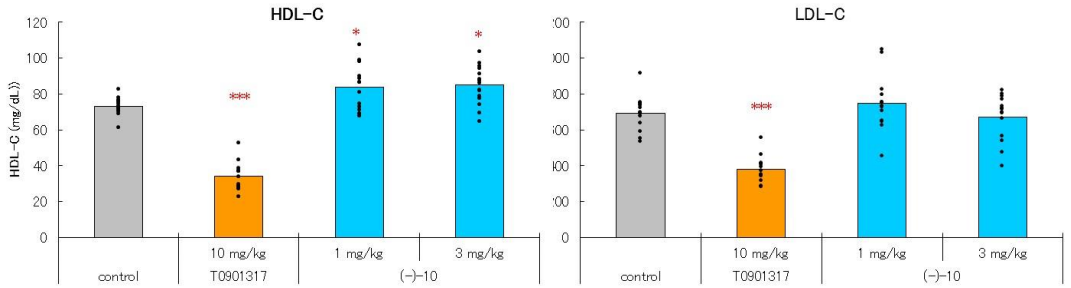


Figure 49. HDL-C and LDL-C profiles in T0901317 and (−)-**10**

*$p < 0.05$, *** $p < 0.001$; The statistical analysis was conducted using Dunnett's test.

血漿 TG については，T0901317 の 10 mg/kg の投与では，顕著な増加が確認された (465%). また，化合物 (−)-**10** も高用量 (3 mg/kg) では有意な増加が確認された. 一方，肝 TG は，T0901317 および化合物 (−)-**10** の投与した用量では，共に変化は無かった (Figure 50).

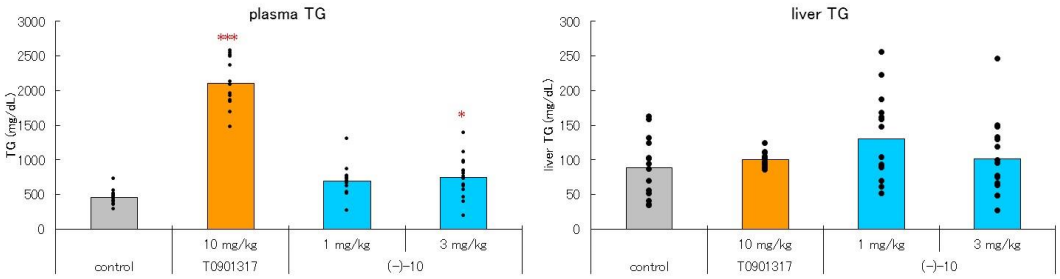


Figure 50. Plasma and liver TG profiles in T0901317 and (−)-**10**
*$p < 0.05$, *** $p < 0.001$; The statistical analysis was conducted using Dunnett's test.

脂質沈着抑制作用については，T0901317 の 10 mg/kg の投与，および化合物 (−)-**10** の 1 mg/kg および 3 mg/kg 投与にて，脂質沈着面積の減少が確認された (T0901317 40% relative to the control) ((−)-**10** 62 and 59%, respectively) (Figure 51).

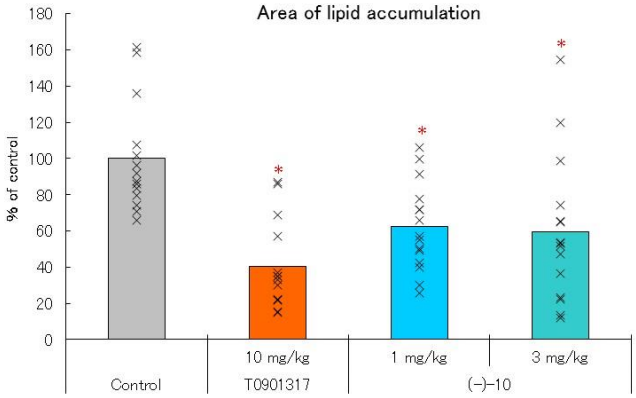


Figure 51. Area of lipid accumulation in T0901317 and (−)-**10**
*$p < 0.05$; The statistical analysis was conducted using Dunnett's test.

これらの結果から，T0901317 の脂質沈着抑制作用を示した要因については，LDL-C の低下が最も寄与していると考えられるが，化合物 (−)-**10** では HDL-C の増加が認められていることから，コレステロール逆転送系の亢進が寄与しているものと推察している．すなわち，化合物 (−)-**10** は所望の機序で目的とする薬効を示すことができる化合物として見出すことができたものと考えている．

そこで，HDL-C の増加に寄与する血液中の ABCA1 mRNA と TG の増加の原因となる肝臓中の SREBP-1c の発現上昇を評価した．その結果を Figure 52, 53 に示す．

血中 ABCA1 mRNA については，T0901317 の 10 mg/kg 投与にて発現上昇が認められた．また，化合物 **(−)-10** においても 1 mg/kg および 3 mg/kg 投与にて用量依存的に発現を上昇することが明らかになった (Figure 52).

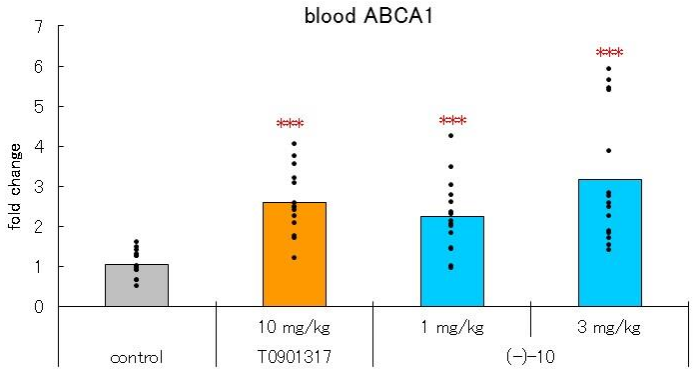


Figure 52. Blood ABCA1 mRNA expression in T0901317 and **(−)-10**
*** $p < 0.001$; The statistical analysis was conducted using Dunnett's test.

肝 SREBP 1c mRNA については, T0901317 の 10 mg/kg 投与にて顕著な発現上昇が認められた．一方，化合物 **(−)-10** では高用量にて有意な発現上昇が認められたが，T0901317 と比べてその程度は低いものであった (Figure 53).

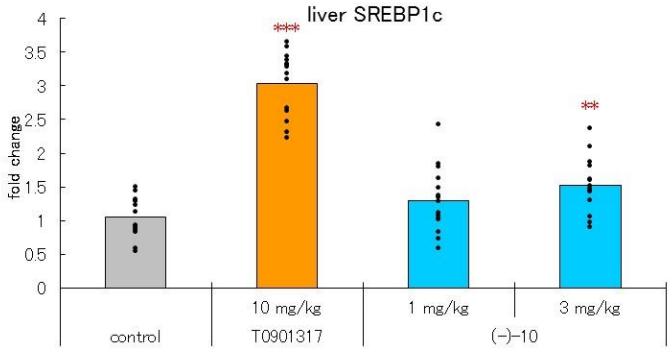


Figure 53. Liver SREBP-1c mRNA expression in T0901317 and **(−)-10**
** $p < 0.01$, *** $p < 0.001$; The statistical analysis was conducted using Dunnett's test.

第三節　小括

‘Head-to-tail’のドラッグデザインにおいて，カルビノール構造部位 (head 部分) とヒダントイン構造部位 (tail 部分) を結ぶリンカー部分として 2-ヒドロキシアセトフェノン構造をもつ化合物 (−)-**10** を見出した．すなわち，化合物 (−)-**10** は LXRβ 活性化作用 (EC_{50} 値, E_{max} 値) のさらなる向上だけでなく，高い選択性 (selectivity for EC_{50} α/β) も獲得することができた．さらに，*in vitro* 肝クリアランスおよび血中濃度推移を評価した結果，薬物動態プロファイルも大幅に改善された．*In vivo* 評価では，動脈硬化疾患モデルである高脂肪高コレステロール食負荷 LDL 受容体欠損マウスにて脂質沈着抑制作用が確認された．化合物 (−)-**10** は，血中 ABCA1 mRNA の発現上昇および HDL-C の増加を示したことから，コレステロール逆転送系の亢進によって抗動脈硬化作用を示したものと推察された．以上の結果から，化合物 (−)-**10** が新規な動脈硬化治療薬として期待されたことから，著者は，化合物 (−)-**10** をさらなる薬理，薬物動態および安全性評価の候補化合物として位置付けた．

第四章　候補化合物 (−)-**10** の合成法検討

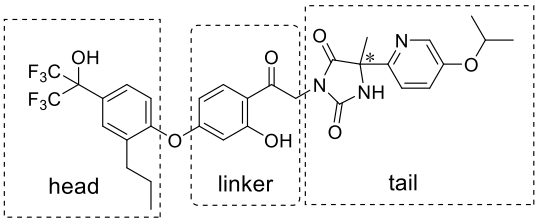
第一節　研究方針

これまでの創薬研究において，目的とする高活性かつ高い選択性を有する LXRβ アゴニストとして化合物 (−)-**10** を創出することができた．さらに，(−)-**10** は *in vivo* 評価にて，抗動脈硬化作用を示すことが認められ，その際 TG 上昇を回避していた．

したがって，次の課題として，化合物 (−)-**10** のさらなる薬理，薬物動態および安全性評価の実施に向けて，まず，数百グラムスケール程度にて安定に供給可能な製造法が求められた．そこで，新たな製造法の構築にあたり，化合物 (−)-**10** の絶対立体配置の決定，(−)-**10** の鍵中間体である光学活性ヒダントインの大量スケール合成法および (−)-**10** の効率的合成法を順次検討した．

第二節　化合物 (−)-**10** の絶対立体配置の決定

化合物 **10** の tail 部位のヒダントイン構造には不斉炭素原子がある (Figure 54). 第三章において，一方の鏡像異性体のみに望む LXR 活性化作用および β 選択性を有することを明らかにしていることから，まず，望む鏡像異性体である化合物 (−)-**10** のヒダントイン部位の絶対立体配置を決定することを試みた．

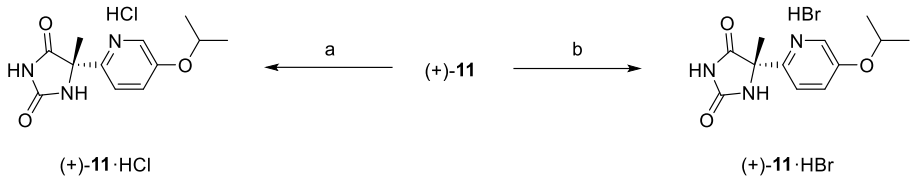


10

Figure 54. Structure of **10**

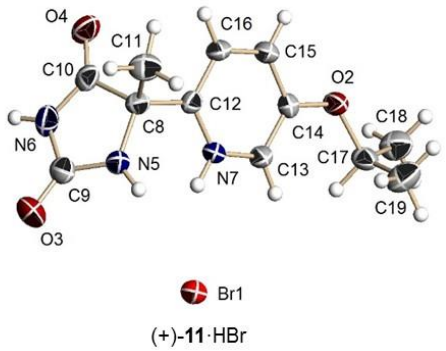
はじめに，重原子効果を利用する X 線結晶構造解析を用いることを計画し，化合物 (−)-**10** の合成中間体である化合物 (+)-**11** へのハロゲン原子の導入を検討した．まずは，ハロゲン化水素塩を合成するべく，メタノール中で塩化水素または臭化水素を作用させて，塩化水素塩または臭化水素塩を形成し，再結晶によって化合物 (+)-**11**·HCl および化合物 (+)-**11**·HBr の単結晶を得た (Scheme 35).

それぞれの単結晶の X 線結晶構造解析を検討したところ，絶対立体配置の決定には臭化水素塩 (+)-**11**·HBr が適しており，Figure 55 に示す結果を得ることに成功した[70]．



Scheme 35. Reagents and conditions: (a) HCl, MeOH, rt, 1 h, 54%; (b) HBr, MeOH, rt, 1 h, 51%.

この結果より，望むヒダントインの絶対立体配置，さらには化合物 (−)-**10** の絶対立体配置を *S* と決定した (Figure 56).



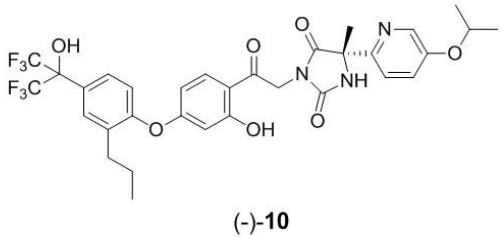


Figure 55. ORTEP view of (+)-**11**·HBr

Figure 56. Structure of (*S*)-(−)-**10**

第三節　光学活性ピリジルヒダントイン **11** の大量合成法

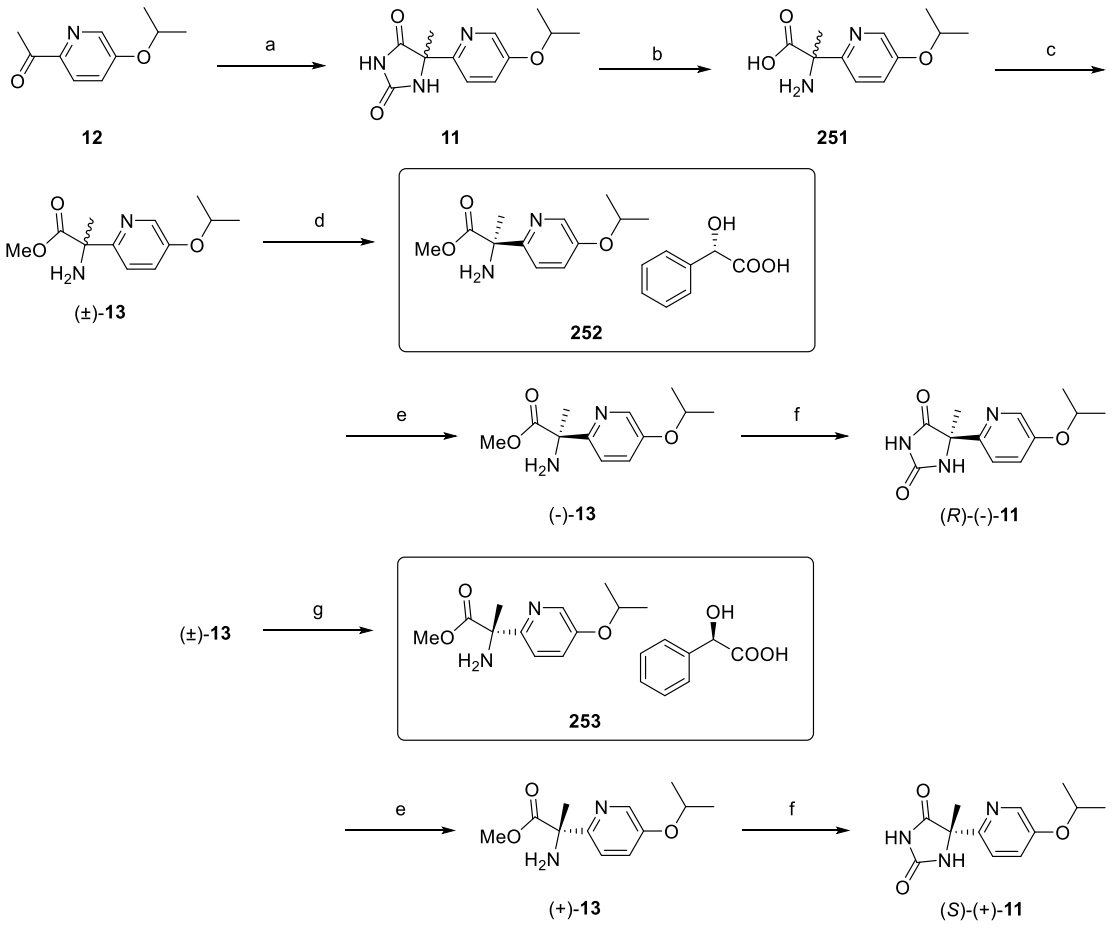
第二章第一節にて述べたように，4 級不斉炭素を有する光学活性ヒダントインの大量合成法の構築には，光学活性ヒダントインもしくは光学活性アミノ酸の供給が鍵となることが考えられる．4 級不斉炭素を有する不斉アミノ酸の合成法としては，これまでに Jacobsen, Shibasaki や Feng らから報告があるように，不斉 Strecker 反応を用いた方法が報告されている [54, 55]．しかしながら，不斉誘起に必須である不斉配位子が高価であること，かつこれら不斉配位子の供給に工程数を要することなど医薬品製造を指向した大量合成法としては課題を有していると考えられる．

また，Clayden らは，独自の合成手法を用いて，4 級不斉炭素を有する光学活性ヒダントイン誘導体の合成を報告しているが，鏡像体過剰率 (<90% ee) が著者の要求 (≧98% ee) を満たしていなかった．さらに，不斉誘起の鍵となる反応工程において，ブチルリチウムを用いたリチオ化を経由する必要があり，大量製造においては制限があると考えられる [71]．

一方，立体既知の光学活性体を用いたジアステレオマー塩の形成を経る古典的な光学分割法として，例えば，アミノ酸に対してマンデル酸やフェネチルアミンなどを用いる合成法がある．著者は，第二章第一節第五項で構築した方法が簡便な操作かつ大量合成にも適用可能であることを確認していたことから，同様の方法で合成法を構築できれば，安定供給かつ安価な合成法になり得ると考え，光学分割法を検討した．

光学活性ヒダントインの合成を Scheme 36 に示す．すなわち，ケトン **12** をエタノール溶媒中で NaCN と $(NH_4)_2CO_3$ を用いて加熱し (Bucherer-Bergs 反応)，ラセミ体のヒダントイン **11** を得た．次に，化合物 **11** を NaOH 水溶液を用いてアミノ酸 **251** へと誘導した．化合物 **251** は，両極性化合物であり取り扱いが煩雑なため，メタノール中塩化チオニル条件にてメチルエステル体 **13** へと誘導した．次いで，ジアステレオマー塩による光学分割をおこなうため，第二章の検討結果 [36a] をもとに，化合物 **13** と同当量の L-(+)-マンデル酸を用いた塩形成をおこなった．反応混合物をエタノールに溶解し，加熱還流後室温に冷却し結晶を得た．得られた結晶を再結晶し，Na_2CO_3 水溶液を用いて L-(+)-マンデル酸を除去し，光学活性アミノ酸エステル **13** を得た．次いで，過剰の尿素存在下加熱条件にて反応させ，光学活性ヒダントイン **11** へと誘導した．HPLC を用いて，化合物 **11** の鏡像体過剰率を確認したところ，所望と逆の鏡像異性体 (*R*)-(−)-**11** であることが確認された (HPLC retention time 4.58 min (lit. (*R*)-(−)-form 4.55 min)．そこで不斉源である L-(+)-マンデル酸を D-(−)-マンデル酸に代えて同様に誘導したところ，望む鏡像異性体 (*S*)-(+)-**11** が得られた (HPLC retention

time of 5.83 min (lit. (*S*)-(+)-form 5.81 min). この結果から，ベンゼン誘導体 **8** (Scheme 22) からピリジン誘導体 **13** へ変更した場合，各々のメチルエステル体 (**8**，**13**) と L-(+)-マンデル酸とのジアステレオマー塩は異なる相互作用を形成し，化合物 **13** のピリジン環とマンデル酸には新たな強い相互作用が形成されていると推察している．



Scheme 36. Reagents and conditions: (a) NaCN, $(NH_4)_2CO_3$, EtOH *aq*., 100 °C, 10 h, 87%; (b) NaOH *aq*., 100 °C, 72 h, 99%; (c) $SOCl_2$, MeOH, −20 °C then 30 °C, 24 h, 86%; (d) L-(+)-mandelic acid, EtOH, reflux, 30 min and then rt, 16 h; (e) Na_2CO_3 *aq*., rt, 16–18% for 2 steps; (f) urea, 145 °C, 4–5 h, 99%; (g) D-(−)-mandelic acid, MeCN, reflux to rt.

最近，Hirose らは，マンデル酸とエリスロ-2-アミノ-1,2-ジフェニルエタノールとの光学分割において，溶媒効果による不斉転換によって各鏡像異性体をつくりわけできることを報告している [72]. このように光学分割法では溶媒の影響が大きい例もあることから，著者は鏡像異性体の溶媒による不斉交換が起こり得るか検討した (Table 21).

しかし，化合物 **13** を用いていくつかの溶媒を検討したが，立体選択性を逆転する結果は得られなかった．先にも述べたように L-(+)-マンデル酸を用いてエタノールにて処理した場合，(*R*)-体を高い鏡像体過剰率で得られた (98% ee). 一方，D-(−)-マンデル酸を用いてエタノールにて処理した場合，所望の (*S*)-体が得られるものの鏡像体過剰率は低かった (66% ee)(entry 1 vs 3).

Table 21. Optical resolution of methyl 2-amino-2-(5-(1-methylethoxy)pyridin-2-yl)-propanoate **13** with L-(+) or D-(−)-mandelic acid

Entry	Mandelic acid	Solvent	Volume (mL)[a]	Yield (%)	% ee	F [c]	Configuration
1	L	EtOH	0.4	16	98	0.16	*R*
2	D	MeOH	0.3	trace	-		
3	D	EtOH	0.4	20	66	0.13	*S*
4	D	*i*-PrOH	0.8	30	62	0.19	*S*
5	D	acetone	0.5	25	87	0.22	*S*
6	D	MeCN	0.6	26	90	0.23	*S*
7	D	THF	0.4	23	86	0.20	*S*
8	D	$CHCl_3$	0.5	10	77	0.08	*S*
9	D	toluene	0.7	52	25	0.13	*S*
10	D	EtOAc	>1 [b]				
11	D	CPME	>1 [b]				

[a] **13** (100 mg) and L-(+)- or D-(−)-mandelic acid (64 mg) were dissolved in solvents. [b] Insoluble in this solvent. [c] F = yield (%) × % ee/10,000.

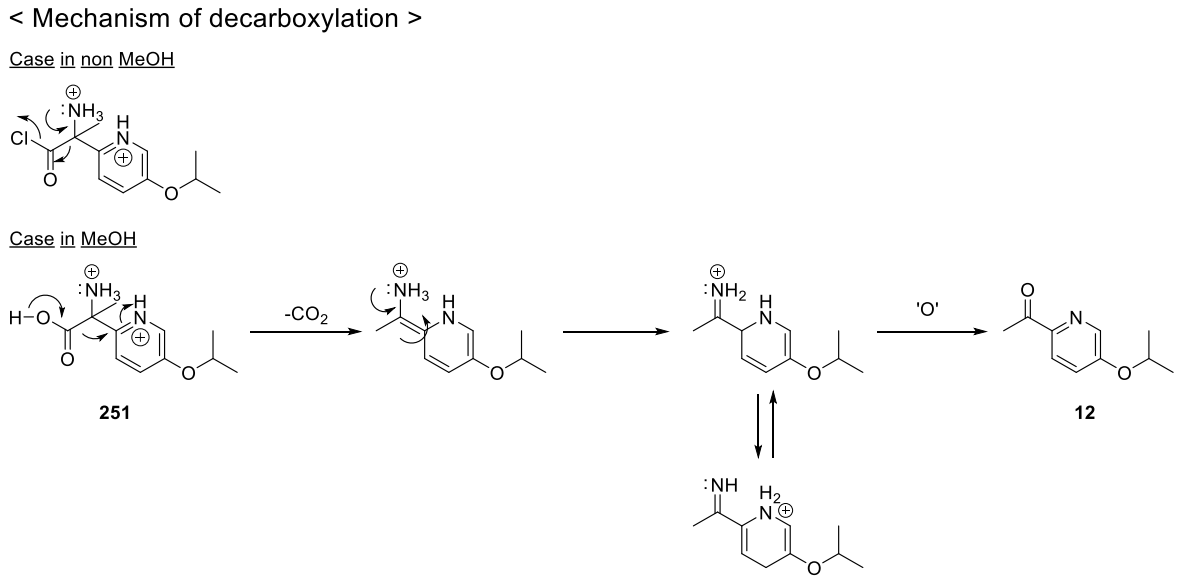
さらに，種々の溶媒を検討した結果，化合物 **13** とマンデル酸の混合物は，酢酸エチルやシクロペンチルメチルエーテル (CPME) では溶解しなかったが (entries 10 and 11)，アセトン，アセトニトリル，THF では鏡像体過剰率 90% ee 程度の化合物 **13** へ誘導できることが確認された．

以上の結果より，アセトニトリルを溶媒として用いた条件で，最も高い鏡像体過剰率 (90% ee) かつ良好な回収率 (26%) で光学活性体を合成することが可能となった．

この結果をもとに，不斉源として D-(−)-マンデル酸を，溶媒としてアセトニトリルを用いて数キログラムスケールにて検討し，Table 21 と同様の回収率かつ高い鏡像体過剰率で光学活性なメチルエステル体を供給可能な大量合成法を確立した．

ところで，この光学活性ピリジルヒダントイン **11** の合成法を検討する中で，メチルエステル化の工程において，塩化チオニルを室温下にて滴下するか，もしくは反応温度を 30 °C 以上にすると化合物 **251** の脱炭酸が生じ，ケトン **12** が生成した．この脱炭酸は，以下の反応機構にて進行しているものと推察している (Scheme 37) [73]．

したがって，本工程は塩化チオニルを－15 °C 以下で滴下し，その後 30 °C で反応を進行させた．



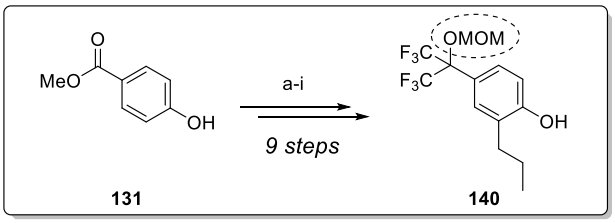
Scheme 37. Plausible mechanism of the formation of **12** via decarboxylation

第四節　化合物 (*S*)-(−)-**10** の効率的合成法

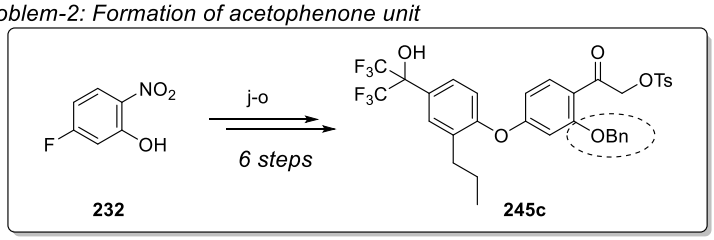
第三章で述べたメディシナル化学的な化合物 (*S*)-(−)-**10** の合成法[37]は，17 工程と工程数が多く，かつ直列合成法であることから総収率 1.4% であり，さらに多くの工程でシリカゲルカラムクロマトグラフィーによる精製が必要であった．したがって，各フラグメントの合成法を再考し，より具体的な課題として以下の 4 点を抽出した (Scheme 38).

① 9 工程を要する 1,1-ビス(トリフルオロメチル)カルビノール構造 **140** の構築における工程数の削減
② 6 工程を要するヒドロキシアセトフェノン構造の構築における工程数の削減
③ α-トシロキシアセトフェノン **245c** とヒダントイン (*S*)-(+)-**11** のカップリング反応の収率の改善
④ メトキシメチル基およびベンジル基の二つの異なる保護基の選択

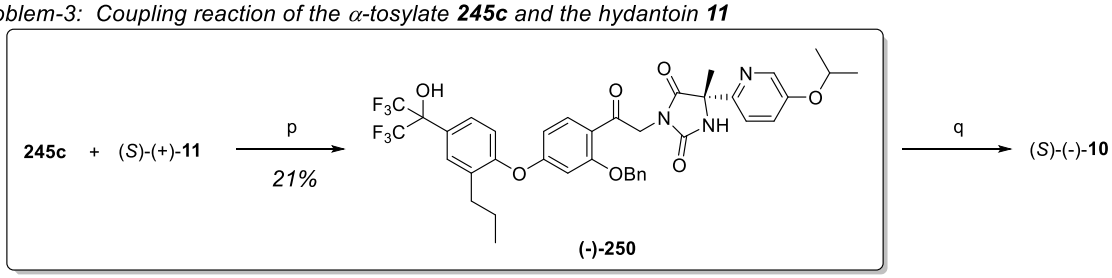
Problem-1: Formation of bistrifluromethylcarbiol unit



Problem-2: Formation of acetophenone unit



*Problem-3: Coupling reaction of the α-tosylate **245c** and the hydantoin **11***

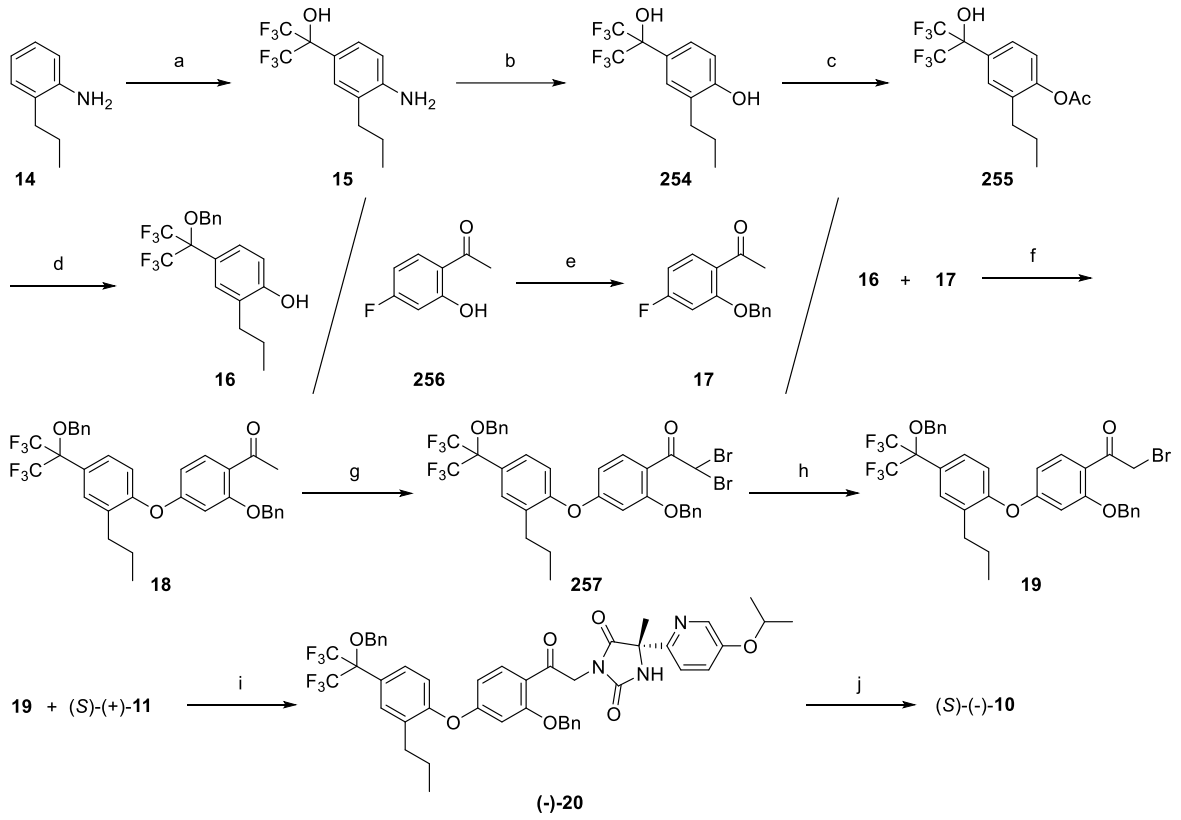


Problem-4: Two protecting group of MOM and Bn

Scheme 38. Reagents and conditions: Reference to Scheme 15, 29, 30 and 33.

これらの問題を解決するため，著者は効率的な代替合成法の検討をおこなった．その結果，数百グラムスケールの化合物 (*S*)-(−)-**10** の供給が可能な合成法の確立に成功した (Scheme 39)．以下にその詳細を示す．

創薬スクリーニング段階での合成では，head 部分である 1,1-ビス(トリフルオロメチル)カルビノール構造の構築において，例えば，脱水条件下酸塩化物に対して，CF_3SiMe_3 と Me_4NF を用いて合成していた．しかし，簡便な方法としてアニリンとヘキサフルオロアセトン水和物との Friedel-Crafts 反応によって一工程で合成できることが知られていた [74]．そこで，2-プロピルアニリン (**14**) とヘキサフルオロアセトン三水和物を 130 °C にて 13 時間反応させたところ，アニリン体 **15** を 97% で得ることができた．次に，化合物 **15** を硫酸水溶液中，$NaNO_2$ を用いて Sandmeyer 反応に付し，フェノール体 **254** を 82% で得た．得られた化合物 **254** をピリジン中無水酢酸を用いてフェノール性水酸基を選択的にアセチル化し，化合物 **255** を得，次いで，DMF 溶媒中で K_2CO_3 存在下にて臭化ベンジルを用いてカルビノール性水酸基をベンジル化後，MeOH を加えて脱アセチル化し，カルビノール体 **16** を 2工程にて 89% で合成した．次に，リンカー部分である 4'-フルオロ-2'-ヒドロキシアセトフェノン (**256**) の水酸基を DMF 溶媒中で K_2CO_3 存在下にて臭化ベンジルを用いてベンジル化し，4'-フルオロ-2'-ベンジルオキシアセトフェノン (**17**) を合成した．こうして合成した化合物 **16** と **17** を DMF 溶媒中で Cs_2CO_3 存在下にて反応させ，4'-アリルオキシ-2'-ベンジルオキシアセトフェノン体 **18** を 70% で得た．次に，化合物 **18** と化合物 (*S*)-(+)-**11** との C-N 結合形成において，アセトフェノンの α 位への活性脱離基を導入する必要があった．そこで，著者は α 位への活性脱離基として臭素の導入をおこなうこととし，臭素化を検討した [75]．種々の条件を検討した結果，化合物 **18** を THF 溶媒中でピリジウムブロミドペルブロミド (pyridine·HBr_3) を用いて臭素化したところ，分離困難な二臭素化体 **257** と一臭素化体 **19** の混合物を 92% で得た (**257**:**19** = 82:10, ^{1}H NMR より)．この得られた混合物を THF 溶媒中で Et_3N 存在下にてホスホン酸ジエチルと反応させ [76]，二臭素化体 **257** のみを脱臭素化し，一臭素化体へと収束させ，化合物 **19** を 2工程にて 92% で得た．次いで，化合物 **19** と化合物 (*S*)-(+)-**11** を DMF 溶媒中で K_2CO_3 存在下にて反応させ，化合物 (−)-**20** を 90% で得た．最後に，化合物 (−)-**20** のベンジル基を Paul mann 触媒存在下加水素分解反応により除去し，目的とする化合物 (*S*)-(−)-**10** を 96% で合成した．この合成法により総工程数 10，総収率 39% で所望の化合物 (*S*)-(−)-**10** を安定に供給可能となった．



Scheme 39. Reagents and conditions: (a) hexafluoroacetone trihydrate, 130 °C, 13 h, 97%; (b) $NaNO_2$, H_2SO_4 *aq*., 1,4-dioxane, 0 °C then 45 °C, 11 h, 82%; (c) Ac_2O, pyridine, CH_2Cl_2, rt, 11 h, 99%; (d) (i) BnBr, K_2CO_3, DMF, rt, 15 h, (ii) MeOH, rt, 2 h, 89% for 2 steps; (e) BnBr, K_2CO_3, DMF, 80 °C, 1.5 h, 99%; (f) Cs_2CO_3, DMF, 100 °C, 72 h, 70%; (g) pyridine·HBr_3, THF, rt, 1.5 h; (h) $(EtO)_2P(O)H$, Et_3N, THF, rt, 1 h, 92% for 2 steps; (i) K_2CO_3, DMF, rt, 36 h, 90%; (j) H_2, $Pd(OH)_2/C$, MeOH, rt, 10 h, 96%.

第五節　小括

著者は，LXRβ 選択的アゴニストの活性化作用の鍵となる光学活性なヒダントイン (+)-**11** の絶対立体配置を化合物 (+)-**11**·HBr のX線結晶構造解析の結果から *S* と決定した．また，D-(−)-マンデル酸を用いたアミノ酸メチルエステル **13** の光学分割を経由した光学活性なヒダントイン (*S*)-(+)-**11** の大量合成法を確立した．さらに，化合物 (*S*)-(−)-**10** の合成法を改善し，数百グラムスケールの (*S*)-(−)-**10** を製造可能な効率的な合成法を開発した．

結語

核内受容体 LXRβ 選択的アゴニストによる LXRβ 活性化作用に伴い，血中 ABCA1 mRNA の発現を上昇させ，HDL-C を増加させ，RCT を促進することによって脂質沈着抑制作用を示す新規動脈硬化治療薬の創出を目的に研究をおこなった．

第一章では，ハイスループットスクリーニング (HTS) によって，得られた化合物 **1** からリード化合物 **4** を見出した経緯，その構造活性相関および *in vivo* 薬理評価について述べた．HTS により得たヒット化合物 **1** と他社化合物情報を活用した独自の‘head-to-tail’のドラッグデザインにより，head 部分に 2-オキソクロメン構造を，tail 部分にヒダントイン構造をもつ LXRβ 選択的アゴニスト **2** を見出した．化合物 **2** は，動脈硬化モデルでの *in vivo* 薬理評価において，300 mg/kg の経口投与にて脂質沈着抑制作用を示し，HDL-C の上昇作用が確認されていることから末梢血中でのコレステロール逆転送系による直接的な作用と推察された．一方で，代謝安定性および血中濃度推移に改善の必要性があったため，これらの課題の改善を目指し，head 部分を 2-オキソクロメン構造 (**2**) から 1,3-ジヒドロイソベンゾフラン構造 (**3**)，さらに，1,1-ビス(トリフルオロメチル)カルビノール構造 (**4**) へと換えたところ，代謝安定性および血中濃度の改善だけでなく，LXRβ 活性化作用の向上に成功した．ここで，LXRβ 活性化作用の鍵となる ‘His435-Trp457 activation switch’ の相互作用がドッキングモデルから推察された．LXRβ 選択的アゴニスト **4** は，動脈硬化モデルでの *in vivo* 薬理評価において，100 mg/kg 経口投与にて脂質沈着抑制作用を示し，かつ，LXR アゴニ

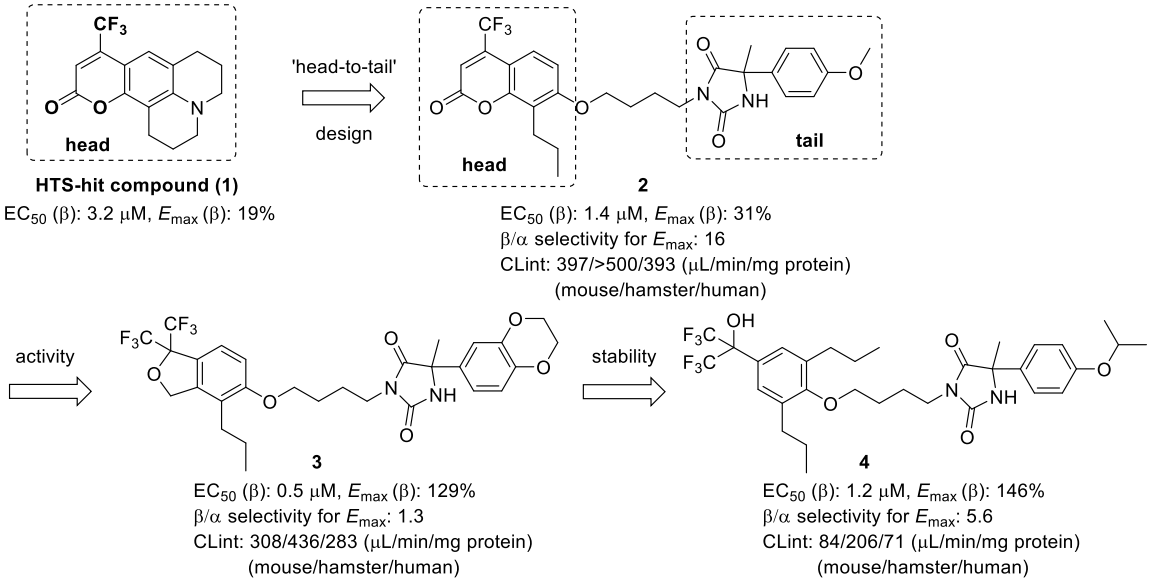


Figure 57. Summary of structural modification in hit to lead.

ストの副作用として懸念される TG の増加を抑制できることが判明し，リード化合物として位置付けた (Figure 57).

第二章では，リード化合物 **4** の各鏡像異性体の活性化作用の確認，絶対立体配置の決定および光学活性なヒダントイン (+)-**5** の製造法を確立した経緯について述べた．さらに，化合物 **4** の代謝物の同定について述べた．第一に，ヒダントイン 5 位に不斉炭素を有することから各鏡像異性体の活性化作用を評価し，(+)-**4** に所望の活性化作用を有することを明らかにした．化合物 **4** の絶対立体配置については，ヒダントイン体 (+)-Br-**6** および (+)-Cl-**6** の X 線結晶構造解析の結果をもとに，*S* と決定した．光学活性なヒダントイン (+)-**5** は，中間体であるアミノ酸エステルに対して L-(+)-マンデル酸を用いた光学分割を経由し，安定に大量供給できる合成法を確立した．第二に，化合物 **4** の血中濃度推移を確認したところ，化合物 **2** と比べて改善はしたもののリンカー部位で酸化的代謝を受け，カルボン酸 **9** を生成することを明らかにした．化合物 **4** の血中濃度は，化合物 **2** と比べて改善されてはいるものの決して十分ではないことの原因が，この代謝にあることが明らかになった．

第三章では，‘head-to-tail’のドラッグデザインを基に，カルビノール構造 (head 部分) とヒダントイン構造 (tail 部分) を結ぶリンカー部分に有益な 2-ヒドロキシアセトフェノン構造を有する化合物 **10** を見出した経緯，およびその構造活性相関について述べた．すなわち，構造活性相関の結果，化合物 **4** と比べて化合物 (−)-**10** は，LXRβ 活性化作用 (EC_{50}) および選択性 (α/β selectivity for EC_{50}) のさらなる改善だけでなく，代謝安定性および血中濃度推移も改善されることが明らかになった．化合物 **10** の鏡像異性体のうち良好な (−)-**10** は，動脈硬化モデルとして知られる LDL 受容体欠損マウスでの薬効試験の結果において，脂質沈着抑制作用を示した．血中 ABCA1 mRNA の発現が上昇し，HDL-C が増加していることから，RCT の亢進による抗動脈硬化作用に繋がる可能性が示唆された．これらの結果から，化合物 (−)-**10** は新規な

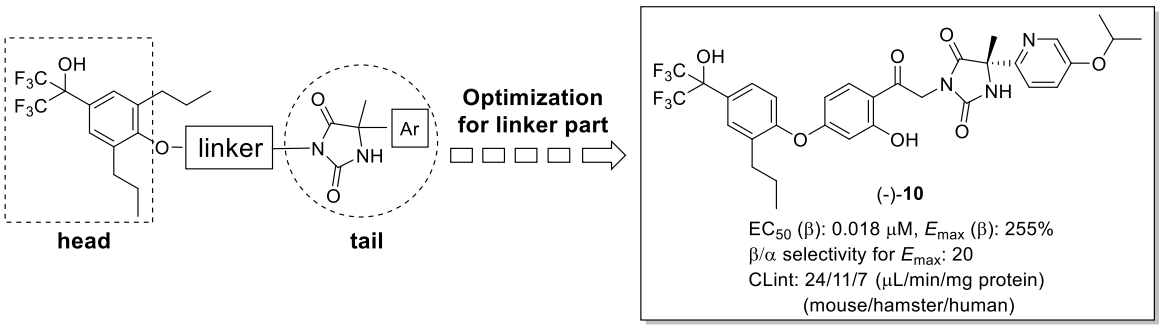


Figure 58. Summary of structural modification in lead optimization.

動脈硬化治療薬として期待され，さらなる薬理，薬物動態および安全性評価の候補化合物として位置付けた (Figure 58).

第四章では，候補化合物 (−)-**10** の絶対立体配置の決定，(−)-**10** を合成するための中間体となる光学活性なヒダントイン (*S*)-(+)-**11** の大量合成法の確立および化合物 (*S*)-(−)-**10** の効率的な合成法の確立について述べた．LXRβ 選択的アゴニスト活性化作用の鍵となる合成中間体である光学活性なヒダントイン (+)-**11** の絶対立体配置は，化合物 (+)-**11**·HBr を用いて，X 線結晶構造解析をし，*S* と決定した．また，D-(−)-マンデル酸を用いたアミノ酸エステル **13** の光学分割を経由した光学活性なヒダントイン (*S*)-(+)-**11** の大量合成法，および (*S*)-(−)-**10** の安定供給可能な合成法を確立した．

すなわち，D-(−)-マンデル酸を用いた光学分割を経てアミノ酸エステル (+)-**13** を高い鏡像体過剰率で大量に供給する方法を確立し，それにより (*S*)-(+)-**11** の大量合成が可能になった. さらに, この光学活性ヒダントインと合成容易なアニリン誘導体 **14** およびアセトフェノン誘導体 **17** を利用して，(*S*)-(−)-**10** を安定に供給できる合成経路を確立した.

本論文は, 動脈硬化治療薬の開発を目的とした LXRβ アゴニストの創薬研究であり, 見出された高活性かつ高い選択性を示す LXRβ アゴニスト (*S*)-(−)-**10** は現在において最も有効な化合物の一つである．また，*in vitro* レポーター遺伝子アッセイでの LXRα/β 選択性が, *in vivo* 薬理評価において TG の増加の副作用を抑制できることを証明した初の報告例である．候補化合物 (*S*)-(−)-**10** に至るまでの構造活性相関は，今後の LXRβ 選択的アゴニストの創薬研究に有益な情報を寄与するものと考える. また, 化合物 (*S*)-(−)-**10** の改良製造法は，今後のさらなる薬理，薬物動態や安全性評価のための原薬の安定供給を可能とし，さらなる化合物解析に寄与するものと考える．さらに，光学活性なヒダントインの絶対立体配置の決定，およびアミノ酸エステルのマンデル酸を用いた光学分割法は，アミノ酸誘導体の構造決定や大量合成においても有用である.

なお, 化合物 (*S*)-(−)-**10** は, 安全性評価において予期せぬ副作用が確認されたため, その後の開発を断念した (詳細は契約および権利上不記載).

実験の部

General procedure

Commercially available reagents and solvents were used without further purification. Thin layer chromatography (TLC) analyses were performed on silica gel 60 F254 plates (Merck). ^{1}H NMR and ^{13}C NMR spectra were obtained on a JEOL JNM-LA or ECS 400 MHz spectrometer using $CDCl_3$, CD_3OD or d_6-DMSO as the solvent with tetramethylsilane as the internal standard. Infrared (IR) spectra were recorded on a Thermo Nicolet 370 FT-IR (KBr or ATR) spectrometer. Mass spectra were obtained on a JEOL MS-BU20 mass spectrometer. Elemental analyses (C, H, N) were performed using a Yanaco MT-5 instrument. Melting points were determined in open glass capillaries on a Buchi B-545 melting point apparatus. Optical rotations were measured on a JASCO P2200 polarimeter operating at the sodium D line at room temperature. The chiral HPLC analyses were performed on a Shimazu LC-2010A HT liquid chromatograph.

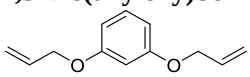
Chapter-1

Section-1

Chemical Experimental Details

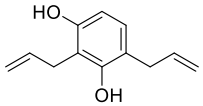
Scheme 7

1,3-Bis(allyloxy)benzene (31) [77]**:**



To a stirred suspension of 1,3-dihydroxybenzene (**30**) (5.0 g, 45 mmol) and K_2CO_3 (19 g, 136 mmol) in DMF (50 mL), allyl chloride (12 g, 154 mmol) was slowly added at room temperature. The reaction mixture was stirred at 70 °C for 24 h, and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/ EtOAc = 2/1) to give the title compound (7.3 g, 85%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (4H, d, *J* = 7.4 Hz), 5.36 (2H, dd, *J* = 2.9, 11.9 Hz), 5.49 (2H, dd, *J* = 2.9, 17.3 Hz), 6.08–6.18 (2H, m), 6.59 (1H, s), 6.60 (2H, d, *J* = 7.1 Hz), 7.24 (1H, t, *J* = 7.1 Hz); MS (EI) *m/z* 190 $[M]^+$.

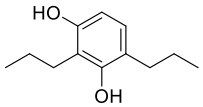
2,4-Diallylbenzene-1,3-diol (32) [77]**:**



A stirred solution of **31** (7.3 g, 39 mmol) in *N*,*N*-dimethylaniline (60 mL) was heated at 200 °C for 16 h. The reaction mixture was allowed to cool to room temperature. To this mixture, hexane (200 mL) and 2 N NaOH *aq.*

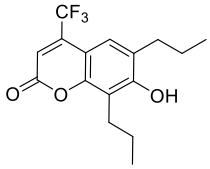
(150 mL) was diluted. The organic layer was separated and washed with 2 N NaOH *aq*.. The aqueous layer was neutralized with 2 N HCl until pH 7 and extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 12/1) to give the title compound (4.2 g, 57%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34 (2H, d, *J* = 6.4 Hz), 3.48 (2H, d, *J* = 6.4 Hz), 5.06 (1H, s), 5.11–5.26 (4H, m), 5.26 (1H, s), 5.95–6.05 (2H, m), 6.39 (1H, d, *J* = 8.3 Hz), 6.85 (1H, d, *J* = 8.3 Hz); MS (EI) *m/z* 190 $[M]^+$.

2,4-Dipropylbenzene-1,3-diol (33) [77]**:**



A suspension of **32** (4.2 g, 22 mmol) and 10% Pd/C (420 mg) in MeOH (30 mL) was stirred under a hydrogen atmosphere at room temperature for 18 h. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to give the title compound (4.2 g, 98%) as pale yellow powders; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, *J* = 7.3 Hz), 0.99 (3H, t, *J* = 7.3 Hz), 1.55–1.65 (4H, m), 2.49 (2H, t, *J* = 7.6 Hz), 2.61 (2H, t, *J* = 7.6 Hz), 4.55 (1H, s), 4.69 (1H, s), 6.33 (1H, d, *J* = 8.0 Hz), 6.81 (1H, d, *J* = 8.0 Hz); MS (EI) *m/z* 194 $[M]^+$.

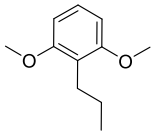
7-Hydroxy-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-2-one (34):



A stirred mixture of **33** (4.2 g, 22 mmol), zinc chloride (3.5 g, 26 mmol) and ethyl 4,4,4-trifluoro-3-oxobutanoate (12 g, 65 mmol) was heated at 110 °C for 18 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was solidified from acetone and hexane to give the title compound (4.0 g, 59%) as pale yellow powders; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, t, *J* = 7.2 Hz), 1.01 (3H, t, *J* = 7.2 Hz), 1.61–1.70 (4H, m), 2.64 (2H, t, *J* = 7.6 Hz), 2.83 (2H, t, *J* = 7.6 Hz), 5.36 (1H, s), 6.61 (1H, s), 7.33 (1H, s); MS (EI) *m/z* 314 $[M]^+$.

Scheme 8

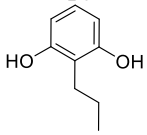
1,3-Dimethoxy-2-propylbenzene (36) [78]**:**



To a solution of 1,3-dimethoxybenzene (**35**) (10 g, 72 mmol) in THF (100 mL), a solution of *n*-BuLi in hexane (50 mL, 1.6 M solution) was added dropwise at 0 °C. After stirring at 0 °C for 2 h, to this solution was added a solution of 1-iodopropane (12 g, 73 mmol) in THF (20 mL). The reaction mixture was allowed to warm to room temperature for 22 h and then water was added to this mixture. The organic layer was separated and the aqueous

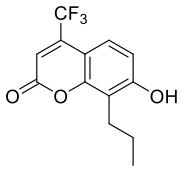
layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 60/1) to give the title compound (5.9 g, 45%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.2 Hz), 1.50 (2H, qt, *J* = 7.2, 7.6 Hz), 2.62 (2H, t, *J* = 7.6 Hz), 3.80 (6H, s), 6.52 (2H, d, *J* = 8.0 Hz), 7.10 (1H, t, *J* = 8.0 Hz); MS (EI) *m/z* 180 $[M]^+$.

2-Propylbenzene-1,3-diol (37) [78]**:**



To a solution of **36** (5.9 g, 33 mmol) in CH_2Cl_2 (50 mL), a solution of boron tribromide in CH_2Cl_2 (90 mL, 1.0 M solution) was added over a period of 45 min at −70 °C. After stirring at −70 °C for 1 h, the reaction mixture was allowed to warm to room temperature for 2 h and then poured into ice water. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 8/1) to give the title compound (3.8 g, 76%) as colorless powders; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, *J* = 7.2 Hz), 1.60 (2H, qt, *J* = 7.2, 7.6 Hz), 2.61 (2H, t, *J* = 7.6 Hz), 4.68 (2H, brs), 6.38 (2H, d, *J* = 8.0 Hz), 6.92 (1H, t, *J* = 8.0 Hz); MS (EI) *m/z* 152 $[M]^+$.

7-Hydroxy-8-propyl-4-(trifluoromethyl)-*2H*-chromen-2-one (38):

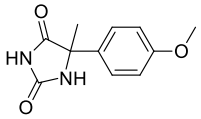


A stirred mixture of **37** (3.7 g, 24 mmol), zinc chloride (3.6 g, 26 mmol) and ethyl 4,4,4-trifluoro-3-oxobutanoate (4.9 g, 26 mmol) was heated at 110 °C for 18 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$). Thus obtained product was crystallized from $CHCl_3$ to give the title compound (5.0 g, 77%) as pale brown powders; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, t, *J* = 7.4 Hz), 1.65 (2H, qt, *J* = 7.4, 7.8 Hz), 2.84 (2H, t, *J* = 7.8 Hz), 5.95 (1H, s), 6.63 (1H, s), 6.85 (1H, d, *J* = 8.6 Hz), 7.48 (1H, dd, *J* = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 22.8, 25.4, 108.1, 112.6 (q, *J* = 5.9 Hz), 113.8, 118.1, 122.6 (q, *J* = 276 Hz), 124.5, 142.8 (q, *J* = 32.4 Hz), 154.7, 158.6, 160.6; MS (EI) *m/z* 272 $[M]^+$.

Scheme 10

Synthetic procedure of the hydantoin derivatives

5-(4-Methoxyphenyl)-5-methylimidazolidine-2,4-dione (42a) [79]**:**



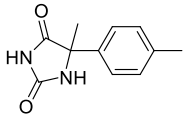
To a stirred solution of 1-(4-methoxyphenyl)ethanone (**41a**) (4.0 g, 33 mmol) in EtOH (6.0 mL), NaCN (2.0 g, 50 mmol), $(NH_4)_2CO_3$ (9.0 g, 117 mmol), and water (6.0 mL) were added at room temperature. The reaction mixture was irradiated in a microwave (Initiator; Biotage AB) at 100 °C for 1 h and then concentrated *in vacuo*. The residue was filtered off and washed with water. The resultant solid was then crystallized from a mixture solvent (hexane/EtOAc = 4/1) to give the title compound (3.5 g, 47%) as colorless crystals; mp 207.4–211.7 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.73 (3H, s), 3.79 (3H, s), 6.93 (2H, d, *J* = 8.8 Hz), 7.41 (2H, d, *J* = 8.8 Hz); MS (EI) *m/z* 220 $[M]^+$.

Compounds **42b~k** were prepared in the same manner as the synthesis of **42a**.

Characterization data

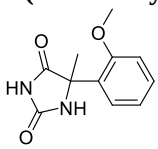
The NMR and MS data of the compounds **42b~k** are described below.

5-Methyl-5-(*p*-tolyl)imidazolidine-2,4-dione (42b):



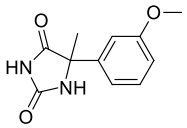
Compoud **42b** was prepared from 1-(*p*-tolyl)ethan-1-one in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.74 (3H, s), 2.32 (3H, s), 7.20 (2H, d, *J* = 8.9 Hz), 7.38 (2H, d, *J* = 8.9 Hz); MS (EI) *m/z* 204 $[M]^+$.

5-(2-Methoxyphenyl)-5-methylimidazolidine-2,4-dione (42c):



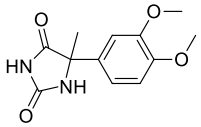
Compound **42c** was prepared from 1-(2-methoxyphenyl)ethan-1-one in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.63 (3H, s), 3.71 (3H, s), 6.90 (1H, dd, *J* = 1.6, 7.8 Hz), 6.99 (1H, d, *J* = 1.6 Hz), 7.04 (1H, d, *J* = 7.8 Hz), 7.32 (1H, dd, *J* = 7.8, 7.8 Hz), 8.59 (1H, s), 10.7 (1H, s); MS (EI) *m/z* 220 $[M]^+$.

5-(3-Methoxyphenyl)-5-methylimidazolidine-2,4-dione (42d):



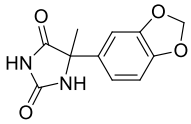
Compound **42d** was prepared from 1-(3-methoxyphenyl)ethan-1-one in a manner similar to that described for compound **42a**. The title compound was obtained as a pale yellow oil; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.63 (3H, s), 3.76 (3H, s), 6.94–7.04 (2H, m), 7.32–7.40 (2H, m), 7.93 (1H, s), 10.6 (1H, s); MS (EI) *m/z* 220 $[M]^+$.

5-(3,4-Dimethoxyphenyl)-5-methylimidazolidine-2,4-dione (42e):



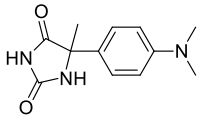
Compound **42e** was prepared from 1-(3,4-dimethoxyphenyl)ethan-1-one in a manner similar to that described for compound **42a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.62 (3H, s), 3.74 (3H, s), 3.76 (3H, s), 6.93–7.01 (3H, m), 8.58 (1H, s), 10.7 (1H, s); MS (EI) *m/z* 250 $[M]^+$.

5-(Benzo[*d*][1,3]dioxol-5-yl)-5-methylimidazolidine-2,4-dione (42f):



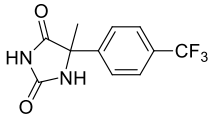
Compound **42f** was prepared from 1-(benzo[*d*][1,3]dioxol-5-yl)ethan-1-one in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.60 (3H, s), 6.02 (2H, s), 6.90 (1H, d, *J* = 8.4 Hz), 6.94 (1H, dd, *J* = 1.4, 8.4 Hz), 6.99 (1H, d, *J* = 1.4 Hz), 8.56 (1H, s), 10.7 (1H, s); MS (EI) *m/z* 234 $[M]^+$.

5-(4-(Dimethylamino)phenyl)-5-methylimidazolidine-2,4-dione (42g):



Compound **42g** was prepared from 1-(4-(dimethylamino)phenyl)ethan-1-one in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.59 (3H, s), 2.87 (6H, s), 6.71 (2H, d, *J* = 8.6 Hz), 7.23 (2H, d, *J* = 8.6 Hz), 8.45 (1H, s), 10.6 (1H, s); MS (EI) *m/z* 233 $[M]^+$.

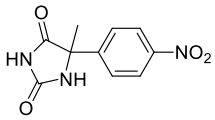
5-Methyl-5-(4-(trifluoromethyl)phenyl)imidazolidine-2,4-dione (42h):



Compound **42h** was prepared from 1-(4-(trifluoromethyl)phenyl)ethan-1-one in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.70 (3H,

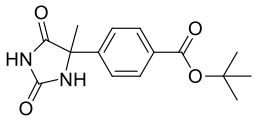
s), 7.72 (2H, d, J = 8.6 Hz), 7.79 (2H, d, J = 8.6 Hz), 8.73 (1H, s), 10.7 (1H, s); MS (EI) *m/z* 258 $[M]^+$.

5-Methyl-5-(4-nitrophenyl)imidazolidine-2,4-dione (42i):



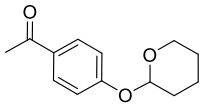
Compound **42i** was prepared from 1-(4-nitrophenyl)ethan-1-one in a manner similar to that described for compound **42a**. The title compound was obtained as a brown solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.71 (3H, s), 7.78 (2H, d, J = 8.6 Hz), 8.27 (2H, d, J = 8.6 Hz), 8.82 (1H, s), 11.0 (1H, s); MS (EI) *m/z* 235 $[M]^+$.

***tert*-Butyl 4-(4-methyl-2,5-dioxoimidazolidin-4-yl)benzoate (42j):**



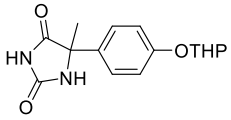
Compound **42j** was prepared from *tert*-butyl 4-acetylbenzoate in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.54 (9H, s), 1.67 (3H, s), 7.61 (2H, t, J = 8.6 Hz), 7.92 (2H, d, J = 8.6 Hz), 8.72 (1H, s), 10.9 (1H, s); MS (EI) *m/z* 290 $[M]^+$.

1-(4-((Tetrahydro-*2H*-pyran-2-yl)oxy)phenyl)ethan-1-one (41k):



A solution of 1-(4-hydroxyphenyl)ethan-1-one (1.0 g, 7.3 mmol), DHP (741 mg, 8.8 mmol) and *p*-TsOH·H_2O (279 mg, 1.5 mmol) was stirred at room temperature for 22 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/1) to give the title compound (554 mg, 34%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53–1.75 (3H, m), 1.84–2.05 (3H, m), 2.52 (3H, s), 3.58–3.62 (1H, m), 3.78–3.87 (1H, m), 5.49 (1H, s), 7.06 (2H, t, J = 8.6 Hz), 7.90 (2H, d, J = 8.6 Hz); MS (EI): m/z 220 $[M]^+$.

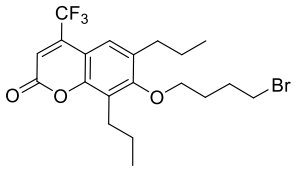
5-Methyl-5-(4-((tetrahydro-*2H*-pyran-2-yl)oxy)phenyl)imidazolidine-2,4-dione (42k):



Compound **42k** was prepared from compound **41k** in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48–1.72 (6H, m), 1.84–1.98 (3H, m), 3.54–3.59 (1H, m), 3.80–3.87 (1H, m), 5.40 (1H, s), 7.00 (2H, t, J = 8.6 Hz), 7.36 (2H, d, J = 8.6 Hz), 7.51 (1H, s) , 9.53 (1H, s); MS (EI) *m/z* 290 $[M]^+$.

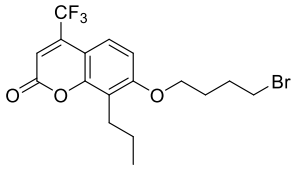
Scheme 9

7-(4-Bromobutoxy)-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-2-one (39):



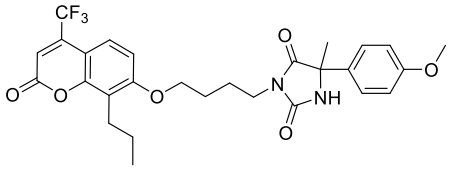
To a suspension of **34** (500 mg, 1.6 mmol) and K_2CO_3 (330 mg, 2.4 mmol) in DMF (5.0 mL), 1,4-dibromobutane (2.8 mL, 13 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 18 h and diluted with water. The reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (689 mg, 96%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, *J* = 7.3 Hz), 1.02 (3H, t, *J* = 7.3 Hz), 1.62–1.72 (4H, m), 1.96–2.06 (2H, m), 2.12–2.22 (4H, m), 2.64 (2H, t, *J* = 7.6 Hz), 2.80 (2H, t, *J* = 7.6 Hz), 3.54 (2H, t, *J* = 6.5 Hz), 3.87 (2H, t, *J* = 5.4 Hz), 6.69 (1H, s), 7.38 (1H, s); MS (EI) *m/z* 448 $[M]^+$.

7-(4-Bromobutoxy)-8-propyl-4-(trifluoromethyl)-*2H*-chromen-2-one (40):



To a stirred suspension of **38** (16 g, 58 mmol) and K_2CO_3 (12 g, 88 mmol) in DMF (80 mL), 1,4-dibromobutane (126 g, 584 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 21 h and then diluted with water. The reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (19 g, 80%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.4 Hz), 1.59 (2H, qt, *J* = 7.4, 7.6 Hz), 1.98–2.16 (4H, m), 2.83 (2H, t, *J* = 7.6 Hz), 3.53 (2H, t, *J* = 6.2 Hz), 4.14 (2H, t, *J* = 5.7 Hz), 6.59 (1H, s), 6.90 (1H, d, *J* = 9.5 Hz), 7.53–7.55 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.2, 24.8, 27.8, 29.4, 33.1, 67.7, 107.3, 108.4, 112.2 (q, *J* = 5.7 Hz), 119.6, 121.8 (q, *J* = 276 Hz), 123.8, 141.8 (q, *J* = 32.4 Hz), 153.4, 159.7, 160.4; MS (EI) *m/z* 406 $[M]^+$.

5-(4-Methoxyphenyl)-5-methyl-3-(4-(2-oxo-8-propyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)-imidazolidine-2,4-dione (2):



To a stirred suspension of 5-(4-methoxyphenyl)-5-methylimidazolidine-2,4-dione (**42a**) (15 g, 70 mmol) and K_2CO_3 (13 g, 93 mmol) in DMF (200 mL), a solution of **40** (19 g, 46 mmol) in DMF (100 mL) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 16 h and then diluted with water at

0 °C and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/2) to give the title compound (18 g, 72%) as colorless crystals; mp 93.2–94.3 °C; IR (KBr) 3269, 2957, 2937, 2869, 1718, 1607, 1279, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.6 Hz), 1.55 (2H, qt, *J* = 7.6, 7.6 Hz), 1.81–1.86 (7H, m), 2.80 (2H, t, *J* = 7.6 Hz), 3.61 (2H, t, *J* = 6.0 Hz), 3.79 (3H, s), 4.07 (2H, t, *J* = 5.6 Hz), 6.12 (1H, brs), 6.61 (1H, s), 6.84 (1H, d, *J* = 8.8 Hz), 6.90 (2H, d, *J* = 8.8 Hz), 7.40 (2H, d, *J* = 8.8 Hz), 7.52 (1H, d, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.1, 24.6, 25.4, 26.2, 38.1, 55.3, 63.2, 67.7, 107.2, 108.4, 112.0 (q, *J* = 5.8 Hz), 114.2 (2C), 119.5, 121.7 (q, *J* = 275 Hz), 123.6, 123.7, 126.4 (2C), 130.6, 141.8 (q, *J* = 32.5 Hz), 153.3, 156.8, 159.6, 159.7, 160.4, 175.6; MS *m/z* 546 $[M]^+$; Anal. Calcd for $C_{28}H_{29}F_3N_2O_6$: C, 61.53; H, 5.35; N, 5.13. Found: C, 61.36; H, 5.34; N, 5.20.

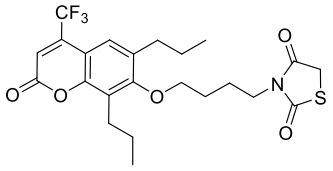
Synthetic procedure of the 2-oxochromene derivatives having the dipropyl group

Compounds **62**, **63**, **43~61** were prepared in the same manner as the synthesis of **2**.

Characterization data

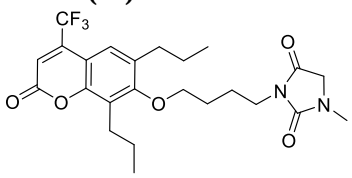
The NMR and MS data of the compounds **62**, **63**, **43~61** are described below.

3-(4-(2-Oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)thiazolidine-2,4-dione (43):



Compound **43** was prepared from compound **39** and thiazolidine-2,4-dione in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.6 Hz), 1.00 (3H, t, *J* = 7.2 Hz), 1.60–1.70 (4H, m), 1.84–1.91 (4H, m), 2.63 (2H, t, *J* = 7.6 Hz), 2.79 (2H, t, *J* = 7.6 Hz), 3.76 (2H, t, *J* = 6.8 Hz), 3.84 (2H, t, *J* = 6.0 Hz), 3.98 (2H, s), 6.69 (1H, s), 7.34 (1H, s); MS (EI) *m/z* 485 $[M]^+$.

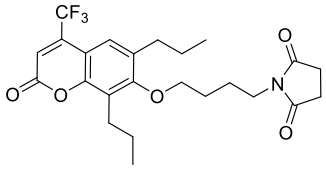
1-Methyl-3-(4-((2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yl)oxy)butyl)imidazolidine-2,4-dione (44):



Compound **44** was prepared from compound **39** and 1-methylimidazolidine-2,4-dione in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ

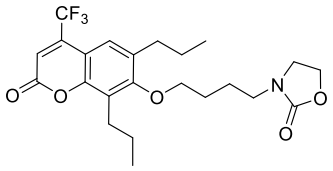
0.98 (3H, t, *J* = 7.6 Hz), 1.00 (3H, t, *J* = 7.2 Hz), 1.62–1.68 (4H, m), 1.87–1.89 (4H, m), 2.63 (2H, t, *J* = 7.6 Hz), 2.79 (2H, t, *J* = 7.6 Hz), 3.07 (3H, s), 3.63 (2H, t, *J* = 6.6 Hz), 3.84 (2H, t, *J* = 5.6 Hz), 3.89 (2H, s), 6.69 (1H, s), 7.38 (1H, s); MS (EI) *m/z* 482 $[M]^+$.

1-(4-(2-Oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)pyrrolidine-2,5-dione (45):



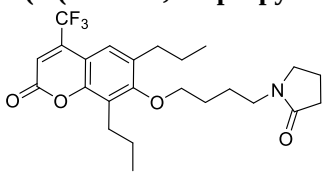
Compound **45** was prepared from compound **39** and pyrrolidine-2,5-dione in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.2 Hz), 1.00 (3H, t, *J* = 7.6 Hz), 1.60–1.70 (4H, m), 1.83–1.87 (4H, m), 2.63 (2H, t, *J* = 7.6 Hz), 2.73 (4H, s), 2.79 (2H, t, *J* = 8.0 Hz), 3.63 (2H, t, *J* = 6.0 Hz), 3.83 (2H, t, *J* = 5.6 Hz), 6.69 (1H, s), 7.38 (1H, s); MS (EI) *m/z* 467 $[M]^+$.

3-(4-(2-Oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)oxazolidin-2-one (46):



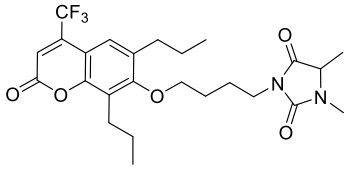
Compound **46** was prepared from compound **39** and oxazolidin-2-one in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.3 Hz), 1.01 (3H, t, *J* = 7.3 Hz), 1.63–1.68 (4H, m), 1.82–1.89 (4H, m), 2.64 (2H, t, *J* = 7.6 Hz), 2.80 (2H, t, *J* = 7.8 Hz), 3.61 (2H, t, *J* = 6.6 Hz), 3.84 (2H, t, *J* = 5.9 Hz), 4.93–5.01 (4H, m), 6.69 (1H, s), 7.38 (1H, s); MS (EI) *m/z* 455 $[M]^+$.

1-(4-(2-Oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)pyrrolidin-2-one (47):



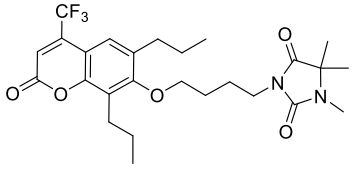
Compound **47** was prepared from compound **39** and pyrrolidin-2-one in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, *J* = 7.3 Hz), 1.01 (3H, t, *J* = 7.3 Hz), 1.63–1.71 (6H, m), 1.80–1.87 (2H, m), 1.92–2.18 (4H, m), 2.65 (2H, t, *J* = 7.6 Hz), 2.81 (2H, t, *J* = 7.6 Hz), 3.54 (2H, t, *J* = 6.4 Hz), 3.78 (2H, t, *J* = 6.8 Hz), 3.88 (2H, t, *J* = 6.4 Hz), 6.69 (1H, s), 7.39 (1H, s); MS (EI) *m/z* 453 $[M]^+$.

1,5-Dimethyl-3-(4-(2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)imidazolidine-2,4-dione (48):



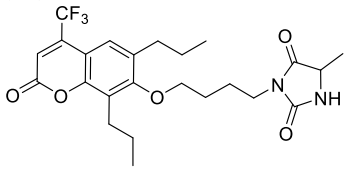
Compound **48** was prepared from compound **39** and 1,5-dimethylimidazolidine-2,4-dione in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.3 Hz), 1.00 (3H, t, *J* = 7.3 Hz), 1.45 (3H, d, *J* = 6.8 Hz), 1.58–1.72 (4H, m), 1.82–1.93 (4H, m), 2.63 (2H, t, *J* = 7.6 Hz), 2.79 (2H, t, *J* = 7.6 Hz), 2.97 (3H, s), 3.62 (2H, t, *J* = 6.5 Hz), 3.84 (2H, t, *J* = 5.1 Hz), 3.88 (1H, q, *J* = 6.8 Hz), 6.68 (1H, s), 7.38 (1H, s); MS (EI) *m/z* 496 $[M]^+$.

1,5,5-Trimethyl-3-(4-(2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)imidazolidine-2,4-dione (49):



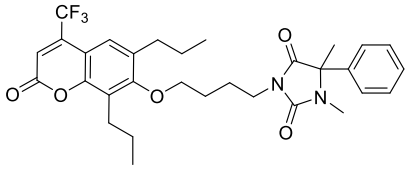
Compound **49** was prepared from compound **39** and 1,5,5-trimethylimidazolidine-2,4-dione in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, *J* = 7.3 Hz), 0.99 (3H, t, *J* = 7.3 Hz), 1.39 (6H, s), 1.60–1.67 (4H, m), 1.82–1.92 (4H, m), 2.63 (2H, t, *J* = 7.6 Hz), 2.78 (2H, t, *J* = 7.6 Hz), 2.91 (3H, s), 3.62 (2H, t, *J* = 6.6 Hz), 3.84 (2H, t, *J* = 6.1 Hz), 6.69 (1H, s), 7.37 (1H, s); MS (EI) *m/z* 510 $[M]^+$.

5-Methyl-3-(4-(2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)imidazolidine-2,4-dione (50):



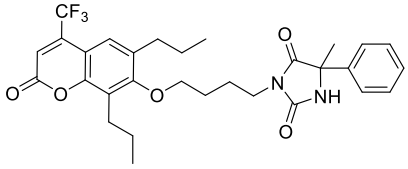
Compound **50** was prepared from compound **39** and 5-methylimidazolidine-2,4-dione in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.3 Hz), 1.00 (3H, t, *J* = 7.3 Hz), 1.48 (3H, d, *J* = 6.8 Hz), 1.55–1.75 (4H, m), 1.80–2.00 (4H, m), 2.63 (2H, t, *J* = 7.8 Hz), 2.79 (2H, t, *J* = 7.8 Hz), 3.63 (2H, t, *J* = 6.3 Hz), 3.84 (2H, t, *J* = 5.9 Hz), 4.12 (1H, q, *J* = 6.8 Hz), 5.66 (1H, s), 6.69 (1H, s), 7.38 (1H, s); MS (EI) *m/z* 482 $[M]^+$.

1,5-Dimethyl-3-(4-(2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)-5-phenyl-imidazolidine-2,4-dione (51):



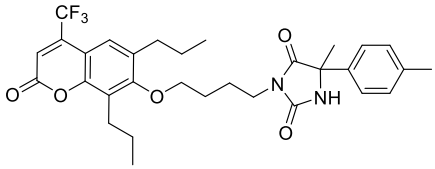
Compound **51** was prepared from compound **39** and 1,5-dimethyl-5-phenylimidazolidine-2,4-dione in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7.3 Hz), 0.98 (3H, t, *J* = 7.3 Hz), 1.56–1.67 (4H, m), 1.80–1.91 (4H, m), 1.83 (3H, s), 2.61 (2H, t, *J* = 7.6 Hz), 2.77 (2H, t, *J* = 7.6 Hz), 2.85 (3H, s), 3.66 (2H, t, *J* = 6.8 Hz), 3.82 (2H, t, *J* = 5.9 Hz), 6.68 (1H, s), 7.29–7.44 (6H, m); MS (EI) *m/z* 572 $[M]^+$.

5-Methyl-3-(4-(2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)-5-phenylimidazolidine-2,4-dione (52):



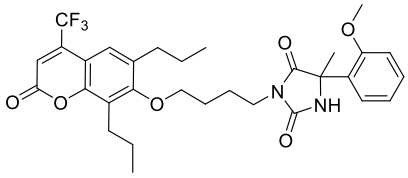
Compound **52** was prepared from compound **39** and 5-methyl-5-phenylimidazolidine-2,4-dione in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 0.97 (3H, t, *J* = 7.3 Hz), 1.58–1.65 (4H, m), 1.80–1.94 (7H, m), 2.60 (2H, t, *J* = 7.6 Hz), 2.76 (2H, t, *J* = 7.8 Hz), 6.23 (1H, brs), 7.32–7.42 (3H, m), 7.50–7.52 (2H, m); MS (EI) *m/z* 558 $[M]^+$.

5-Methyl-3-(4-(2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)-5-*p*-tolylimidazolidine-2,4-dione (53):



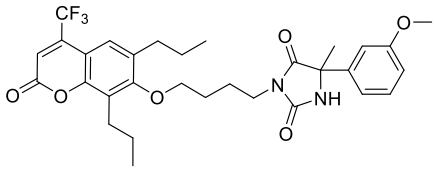
Compound **53** was prepared from compounds **39** and **42b** in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 0.97 (3H, t, *J* = 7.3 Hz), 1.58–1.69 (4H, m), 1.75–1.90 (4H, m), 1.83 (3H, s), 2.33 (3H, s), 2.60 (2H, t, *J* = 7.6 Hz), 2.76 (2H, t, *J* = 7.6 Hz), 3.62 (2H, t, *J* = 6.5 Hz), 3.80 (2H, t, *J* = 7.6 Hz), 6.47 (1H, brs), 6.68 (1H, s), 7.19 (2H, d, *J* = 8.1 Hz), 7.37 (1H, s), 7.39 (2H, d, *J* = 8.1 Hz); MS (EI) *m/z* 572 $[M]^+$.

5-(2-Methoxyphenyl)-5-methyl-3-(4-(2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)-imidazolidine-2,4-dione (54):



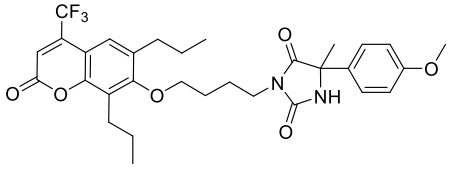
54 was prepared from **39** and **42c** in a manner similar to that described for **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, *J* = 7.3 Hz), 0.99 (3H, t, *J* = 7.6 Hz), 1.59–1.69 (4H, m), 1.78 (3H, s), 1.85–1.98 (4H, m), 2.63 (2H, t, *J* = 7.6 Hz), 2.79 (2H, t, *J* = 7.8 Hz), 3.69 (2H, t, *J* = 6.8 Hz), 3.85 (2H, t, *J* = 6.1 Hz), 3.88 (3H, s), 6.36 (1H, s), 6.69 (1H, s), 6.94 (1H, d, *J* = 7.1 Hz), 6.95 (1H, dd, *J* = 7.6, 8.0 Hz), 7.32 (1H, dd, *J* = 7.1, 7.6 Hz), 7.38 (1H, s), 7.52 (1H, d, *J* = 8.0 Hz); MS (EI) *m/z* 588 $[M]^+$.

5-(3-Methoxyphenyl)-5-methyl-3-(4-(2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)-imidazolidine-2,4-dione (55):



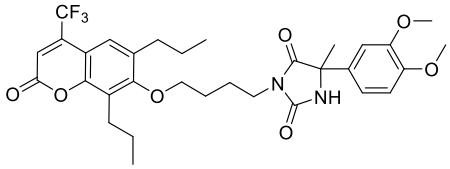
Compound **55** was prepared from compounds **39** and **42d** in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 0.97 (3H, t, *J* = 7.3 Hz), 1.57–1.67 (4H, m), 1.81–1.92 (4H, m), 1.84 (3H, s), 2.60 (2H, t, *J* = 7.6 Hz), 2.76 (2H, t, *J* = 7.8 Hz), 3.63 (2H, t, *J* = 7.1 Hz), 3.81 (2H, t, *J* = 6.8 Hz), 3.81 (3H, s), 6.21 (1H, brs), 6.68 (1H, s), 6.87 (1H, d, *J* = 8.0 Hz), 7.06 (1H, s), 7.08 (1H, d, *J* = 7.8 Hz), 7.31 (1H, dd, *J* = 7.8, 8.0 Hz), 7.37 (1H, s); MS (EI) *m/z* 588 $[M]^+$.

5-(4-Methoxyphenyl)-5-methyl-3-(4-(2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)-imidazolidine-2,4-dione (56):



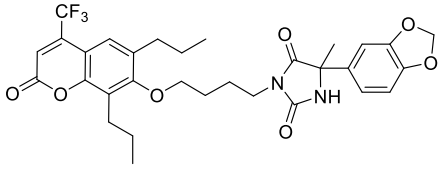
Compound **56** was prepared from compounds **39** and **42a** in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.6 Hz), 0.97 (3H, t, *J* = 7.3 Hz), 1.56–1.69 (4H, m), 1.80–1.89 (4H, m), 1.82 (3H, s), 2.60 (2H, t, *J* = 7.6 Hz), 2.76 (2H, t, *J* = 7.6 Hz), 3.63 (2H, t, *J* = 6.8 Hz), 3.80 (3H, s), 3.81 (2H, t, *J* = 5.7 Hz), 5.84 (1H, s), 6.68 (1H, s), 6.90 (2H, d, *J* = 8.9 Hz), 7.36 (1H, s), 7.40 (2H, d, *J* = 8.9 Hz); MS (EI) *m/z* 588 $[M]^+$.

5-(3,4-Dimethoxyphenyl)-5-methyl-3-(4-(2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)-butyl)imidazolidine-2,4-dione (57):



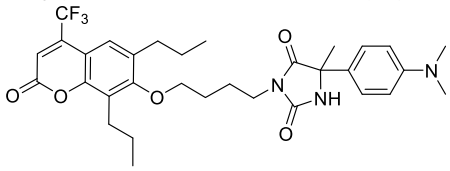
Compound **57** was prepared from compounds **39** and **42e** in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.6 Hz), 0.97 (3H, t, *J* = 7.3 Hz), 1.57–1.68 (4H, m), 1.76–1.90 (4H, m), 1.83 (3H, s), 2.60 (2H, t, *J* = 7.6 Hz), 2.76 (2H, t, *J* = 7.8 Hz), 3.64 (2H, t, *J* = 6.1 Hz), 3.82 (2H, t, *J* = 6.1 Hz), 3.84 (3H, s), 3.86 (3H, s), 6.27 (1H, brs), 6.68 (1H, s), 6.85 (1H, d, *J* = 8.8 Hz), 7.03 (1H, s), 7.04 (1H, d, *J* = 8.8 Hz), 7.37 (1H, s); MS (EI) *m/z* 618 $[M]^+$.

5-(Benzo[*d*][1,3]dioxol-5-yl)-5-methyl-3-(4-(2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)-butyl)imidazolidine-2,4-dione (58):



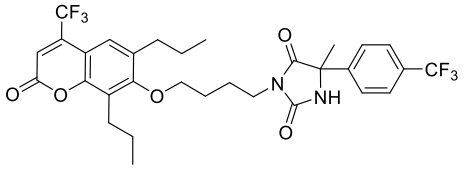
Compound **58** was prepared from compounds **39** and **42f** in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96–0.99 (6H, m), 1.57–1.68 (4H, m), 1.81–1.89 (7H, m), 2.61 (2H, t, *J* = 7.8 Hz), 2.76 (2H, t, *J* = 7.8 Hz), 3.63 (2H, t, *J* = 6.7 Hz), 3.82 (2H, t, *J* = 5.9 Hz), 5.96 (2H, s), 6.51 (1H, brs), 6.68 (1H, s), 6.78 (1H, d, *J* = 8.1 Hz), 6.95–6.98 (2H, m), 7.37 (1H, s); MS (EI) *m/z* 602 $[M]^+$.

5-(4-(Dimethylamino)phenyl)-5-methyl-3-(4-(2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)-butyl)imidazolidine-2,4-dione (59):



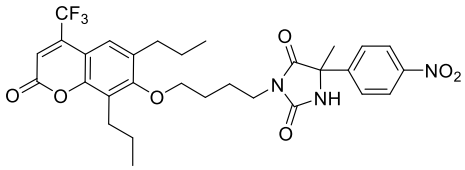
Compound **59** was prepared from compounds **39** and **42g** in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7.1 Hz), 0.97 (3H, t, *J* = 7.1 Hz), 1.57–1.68 (4H, m), 1.80 (3H, s), 1.80–1.89 (4H, m), 2.61 (2H, t, *J* = 7.6 Hz), 2.76 (2H, t, *J* = 7.8 Hz), 2.93 (6H, s), 3.62 (2H, t, *J* = 6.6 Hz), 3.81 (2H, t, *J* = 6.1 Hz), 6.21 (1H, s), 6.68 (1H, s), 6.69 (2H, d, *J* = 9.0 Hz), 7.32 (2H, d, *J* = 9.0 Hz), 7.37 (1H, s); MS (EI) *m/z* 601 $[M]^+$.

5-Methyl-3-(4-(2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)-5-(4-(trifluoromethyl)-phenyl)imidazolidine-2,4-dione (60):



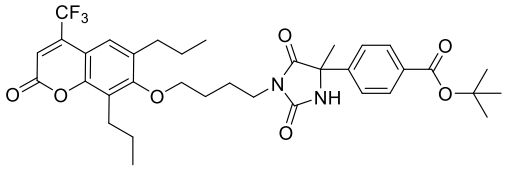
Compound **60** was prepared from compounds **39** and **42h** in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92–0.98 (6H, m), 1.57–1.67 (4H, m), 1.80–1.90 (7H, m), 2.59 (2H, t, *J* = 7.7 Hz), 2.76 (2H, t, *J* = 7.8 Hz), 3.64 (2H, t, *J* = 7.0 Hz), 3.81 (2H, t, *J* = 5.9 Hz), 6.63 (1H, s), 6.69 (1H, s), 7.37 (1H, s), 7.64–7.71 (4H, m); MS (EI) *m/z* 626 $[M]^+$.

5-Methyl-5-(4-nitrophenyl)-3-(4-(2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)-imidazolidine-2,4-dione (61):



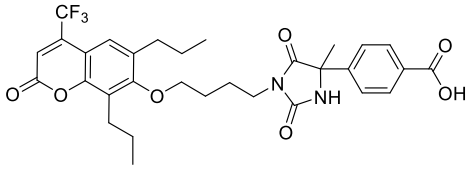
Compound **61** was prepared from compounds **39** and **42i** in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.3 Hz), 0.96 (3H, t, *J* = 7.1 Hz), 1.57–1.67 (4H, m), 1.81–1.93 (4H, m), 1.90 (3H, s), 2.60 (2H, t, *J* = 7.8 Hz), 2.76 (2H, t, *J* = 7.8 Hz), 3.66 (2H, t, *J* = 6.8 Hz), 3.82 (2H, t, *J* = 5.6 Hz), 6.69 (1H, s), 6.88 (1H, s), 7.37 (1H, s), 7.78 (2H, d, *J* = 8.8 Hz), 8.24 (2H, d, *J* = 8.8 Hz); MS (EI) *m/z* 603 $[M]^+$.

***tert*-Butyl 4-(4-methyl-2,5-dioxo-1-(4-((2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yl)oxy)butyl)-imidazolidin-4-yl)benzoate:**



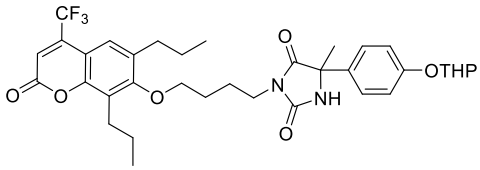
The title compound was prepared from compounds **39** and **42j** in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.3 Hz), 0.96 (3H, t, *J* = 7.3 Hz), 1.51–1.70 (13H, m), 1.79–1.92 (7H, m), 2.60 (2H, t, *J* = 7.8 Hz), 2.76 (2H, t, *J* = 7.8 Hz), 3.64 (2H, t, *J* = 6.8 Hz), 3.81 (2H, t, *J* = 6.1 Hz), 6.68 (1H, s), 6.79 (1H, brs), 7.37 (1H, s), 7.60 (2H, d, *J* = 8.8 Hz), 8.00 (2H, d, *J* = 8.8 Hz); MS (EI) *m/z* 658 $[M]^+$.

4-(4-Methyl-2,5-dioxo-1-(4-(2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)imidazolidin-4-yl)benzoic acid (62):



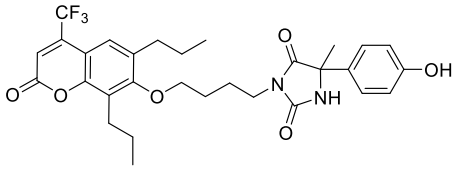
To a solution of the precucor (30 mg, 46 μmol) in CH_2Cl_2 (1 mL), TFA (1 mL) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1/1) to give the title compound (25.9 mg, 94%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 0.96 (3H, t, *J* = 7.3 Hz), 1.56–1.67 (4H, m), 1.81–1.90 (4H, m), 1.88 (3H, s), 2.60 (2H, t, *J* = 7.6 Hz), 2.75 (2H, t, *J* = 7.8 Hz), 3.69 (2H, t, *J* = 7.3 Hz), 3.82 (2H, t, *J* = 7.1 Hz), 6.71 (1H, s), 7.39 (1H, s), 7.45 (1H, s), 7.65 (2H, d, *J* = 8.5 Hz), 8.12 (2H, d, *J* = 8.5 Hz), 9.79 (1H, brs); MS (EI) *m/z* 602 $[M]^+$.

5-Methyl-3-(4-((2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yl)oxy)butyl)-5-(4-((tetrahydro-*2H*-pyran-2-yl)oxy)phenyl)imidazolidine-2,4-dione:



The title compound was prepared from compounds **39** and **42k** in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 0.97 (3H, t, *J* = 7.3 Hz), 1.57–1.73 (7H, m), 1.82–2.01 (10H, m), 2.61 (2H, t, *J* = 7.8 Hz), 2.77 (2H, t, *J* = 7.8 Hz), 3.56–3.64 (3H, m), 3.80–3.88 (3H, m), 5.40 (2H, s), 6.07 (1H, s), 6.68 (1H, s), 7.05 (2H, d, *J* = 8.8 Hz), 7.37 (1H, s), 7.39 (2H, d, *J* = 8.8 Hz); MS (EI) *m/z* 658 $[M]^+$.

5-(4-Hydroxyphenyl)-5-methyl-3-(4-(2-oxo-6,8-dipropyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)-imidazolidine-2,4-dione (63):



To a solution of the precucor (30 mg, 46 μmol) in THF (570 μL) and water (285 μL), AcOH (1.1 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with saturated $NaHCO_3$ *aq*. at 0 °C and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1/1) to give the title compound (23.5 mg, 90%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87–0.97 (6H, m), 1.53–1.67 (4H, m), 1.81–1.88 (7H, m), 2.60 (2H, t, *J* = 7.7 Hz), 2.71 (2H, t, *J* = 7.8 Hz), 3.63 (2H, t, *J* = 6.8 Hz), 3.80–3.86 (2H, m), 4.91 (1H, s), 6.41 (1H, s), 6.69 (1H, s), 6.78–6.80 (2H, m), 7.28–7.31 (2H, m), 7.37 (1H, s); MS (EI) *m/z* 574 $[M]^+$.

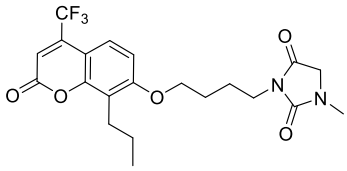
Synthesis of the 2-oxochromen derivative with propyl group

Compounds **69, 70** and **64~68** were prepared in the same manner as the synthesis of **2**.

Characterization data

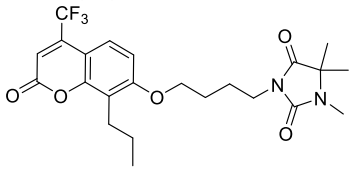
The NMR and MS data of compounds **69, 70** and **64~68** are described below.

1-Methyl-3-(4-(2-oxo-8-propyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)imidazolidine-2,4-dione (64):



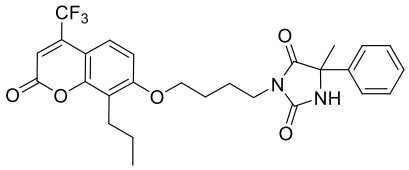
Compound **64** was prepared from compound **40** and 1-methylimidazolidine-2,4-dione in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 1.58 (2H, qt, *J* = 7.3, 7.6 Hz), 1.86–1.87 (4H, m), 2.82 (2H, t, *J* = 7.6 Hz), 3.01 (3H, s), 3.61 (2H, t, *J* = 3.9 Hz), 3.88 (2H, s), 4.11 (2H, t, *J* = 4.3 Hz), 6.60 (1H, s), 6.88 (1H, d, *J* = 9.0 Hz), 7.54 (1H, d, *J* = 9.0 Hz); MS (EI) *m/z* 440 $[M]^+$.

1,5,5-Trimethyl-3-(4-(2-oxo-8-propyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)imidazolidine-2,4-dione (65):



Compound **65** was prepared from compound **40** and 1,5,5-trimethylimidazolidine-2,4-dione in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7.3 Hz), 1.39 (6H, s), 1.55–1.61 (2H, m), 1.86 (4H, brs), 2.83 (2H, t, *J* = 7.6 Hz), 2.90 (3H, s), 3.57–3.63 (2H, m), 4.10–4.13 (2H, m), 6.61 (1H, s), 6.88 (1H, d, *J* = 9.0 Hz), 7.54 (1H, d, *J* = 8.9 Hz); MS (EI) *m/z* 468 $[M]^+$.

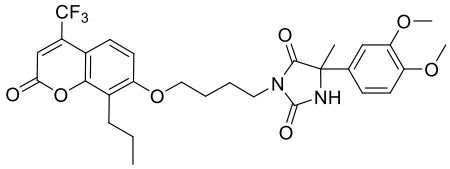
5-Methyl-3-(4-(2-oxo-8-propyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)-5-phenylimidazolidine-2,4-dione (66):



Compound **66** was prepared from compound **40** and 5-methyl-5-phenylimidazolidine-2,4-dione in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.3 Hz), 1.55 (2H, qt, *J* = 7.3, 7.3 Hz), 1.76–1.86 (7H, m), 2.79 (2H, t, *J* = 7.3 Hz), 3.61

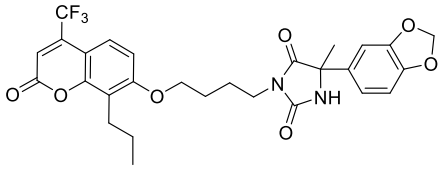
(2H, t, J = 6.2 Hz), 4.07 (2H, t, J = 5.1 Hz), 6.60 (1H, s), 6.83 (1H, d, J = 9.2 Hz), 7.30–7.42 (3H, m), 7.49–7.53 (3H, m); MS (EI) *m/z* 516 $[M]^+$.

5-(3,4-Dimethoxyphenyl)-5-methyl-3-(4-(2-oxo-8-propyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)-imidazolidine-2,4-dione (67):



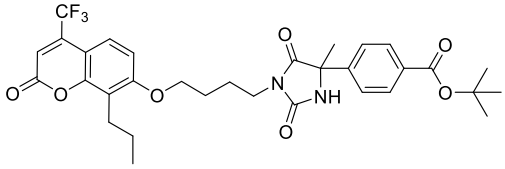
Compound **67** was prepared from compounds **40** and **42e** in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.51–1.60 (2H, m), 1.82–1.98 (7H, m), 2.80 (2H, t, J = 7.6 Hz), 3.61 (2H, t, J = 6.2 Hz), 3.86 (3H, s), 3.89 (3H, s), 4.04–4.09 (2H, m), 6.24 (1H, s), 6.61 (1H, s), 6.83–6.86 (2H, m), 7.02–7.04 (2H, m), 7.50–7.53 (1H, m); MS (EI) *m/z* 576 $[M]^+$.

5-(Benzo[*d*][1,3]dioxol-5-yl)-5-methyl-3-(4-(2-oxo-8-propyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)-imidazolidine-2,4-dione (68):



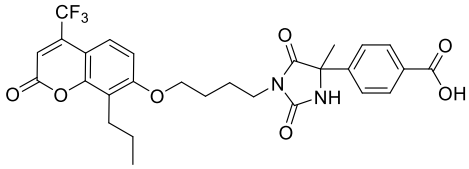
Compound **68** was prepared from compounds **40** and **42f** in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.51–1.63 (2H, m), 1.79–1.85 (7H, m), 2.80 (2H, t, J = 7.6 Hz), 3.61 (2H, t, J = 6.1 Hz), 4.06–4.09 (2H, m), 5.96 (2H, s), 6.34 (1H, brs), 6.61 (1H, s), 6.78 (1H, d, J = 8.3 Hz), 6.85 (1H, d, J = 9.0 Hz), 6.95 (1H, dd, J = 2.0, 8.3 Hz), 6.99 (1H, d, J = 2.0 Hz), 7.53 (1H, d, J = 9.0 Hz); MS (EI) *m/z* 560 $[M]^+$.

***tert*-Butyl 4-(4-methyl-2,5-dioxo-1-(4-((2-oxo-8-propyl-4-(trifluoromethyl)-*2H*-chromen-7-yl)oxy)butyl)-imidazolidin-4-yl)benzoate:**



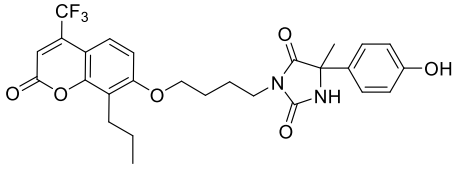
The title compound was prepared from compounds **40** and **42j** in a manner similar to that described for compound **2**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.3 Hz), 1.50–1.62 (11H, m), 1.82–1.89 (7H, m), 2.80 (2H, t, J = 7.8 Hz), 3.62 (2H, t, J = 6.6 Hz), 4.07 (2H, t, J = 5.6 Hz), 6.60 (1H, s), 6.64 (1H, brs), 6.85 (1H, d, J = 9.0 Hz), 7.53 (1H, d, J = 9.0 Hz), 7.58 (2H, d, J = 8.3 Hz), 8.00 (2H, d, J = 8.3 Hz); MS (EI) *m/z* 616 $[M]^+$.

4-(4-Methyl-2,5-dioxo-1-(4-(2-oxo-8-propyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)imidazolidin-4-yl)benzoic acid (69):



Compound **69** was prepared from the precucor in a manner similar to that described for compound **62**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 7.3 Hz), 1.54 (2H, qt, *J* = 7.3, 7.6 Hz), 1.84–1.93 (7H, m), 2.78 (2H, t, *J* = 7.6 Hz), 3.66 (2H, t, *J* = 6.5 Hz), 4.08 (2H, t, *J* = 5.6 Hz), 6.64 (1H, s), 6.86 (1H, d, *J* = 9.0 Hz), 7.54–7.56 (2H, m), 7.63 (2H, d, *J* = 8.6 Hz), 8.11 (2H, d, *J* = 8.6 Hz), 10.91 (1H, brs); MS (EI) *m/z* 560 $[M]^+$.

5-(4-Hydroxyphenyl)-5-methyl-3-(4-(2-oxo-8-propyl-4-(trifluoromethyl)-*2H*-chromen-7-yloxy)butyl)-imidazolidine-2,4-dione (70):



Compound **70** was prepared in a manner similar to that described for compound **63**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.3 Hz), 1.48–1.57 (2H, m), 1.79 (3H, s), 1.79–1.89 (4H, m), 2.76 (2H, t, *J* = 7.3 Hz), 3.60 (2H, t, *J* = 5.8 Hz), 4.07 (2H, t, *J* = 5.1 Hz), 6.54 (1H, s), 6.60 (1H, s), 6.78 (2H, d, *J* = 7.6 Hz), 6.84 (1H, d, *J* = 9.0 Hz), 7.28 (2H, d, *J* = 7.6 Hz), 7.52 (1H, d, *J* = 9.0 Hz); MS (EI) *m/z* 532 $[M]^+$.

Pharmacological Experimental Details

Material and Method

In vitro study

Measurement of ABCA1 and SREBP-1c mRNA levels

The THP-1 and HepG1 cells were stably seeded at semi-confluent growth on a 24-well plate in CSC medium supplemented with 10% bovine fetal serum and incubated under a wet atmosphere with 5% CO_2 at 37 °C. After 24 h of incubation the medium with 5 μM concentration of the test compound was added, and the cells were further incubated for 24 h. Next, RNA was extracted using Isogen (Japan Gene Inc.) to produce cDNA with Randam Primer (ABI Inc.) as a substrate, and the relative expression levels of ABCA1 and SREBP-1c mRNA were measured with real-time quantitative PCR to determine the effect of the test compound.

GAL4-h-LXRs reporter gene assay

The CHO K-1 cells stably transfected with LXRs/GAL4-fused protein expression vectors and the GAL4-responsive reporter vector (pG5luc; Promega, WI) were seeded at 20,000 cells/well on a 96-well plate in HAM-F12 medium supplemented with 10% bovine fetal serum, 100 units/mL of penicillin G, and 100 μg/mL of streptomycin sulfate, followed by incubation under a wet atmosphere with 5% CO_2 at 37 °C. After 24 h, media with different concentrations of the test compound (0.01, 0.1, 1, and 10 μM) were added, and the cells were further incubated for 24 h. Bright-Glo (Promega) was used as a substrate, and the luminescence intensity was measured by using the LB960 Luminometer (Berthold Technologies) to dertermine the effect of the test compound on the activation of luciferase transcription via LXRα- or LXRβ-LBD.

***In vivo* study**

Bio F_1B hamsters (male, age: 8 weeks old, n = 42) (Charles River Japan, Inc., Kanagawa, Japan) were used for animal experiments. The animal room was controlled at 23 ± 3 °C and relative humidity of 50 ± 20%. Animals were fed a CE-2 chow diet (CLEA Japan Inc., Tokyo, Japan) and then supplemented with CE-2 containing 0.3% cholesterol and 10% coconut oil for 10 weeks.

During fat loading, compound **2** was orally administered at 30, 100, or 300 mg/kg/day (n = 6 for each dose group). The comparative agent, T0901317 was orally administered at 1, 3, or 10 mg/kg/day (n = 6 for each dose group). The control group (n = 12) received an aqueous solution of 0.5% methylcellulose instead of **2**. Blood was sampled for determination of plasma lipid levels by using a commercial kit (total cholesterol: Cholesterol E-Test Wako; Wako Pure Chemical Industries, Osaka, Japan; triglyceride: Triglyceride E-Test Wako; Wako Pure Chemical Industries). The plasma lipoprotein profiles were analyzed by using the CLiP method [80] on the LC-20A HPLC System (Shimadzu) and Superose 6 Column (10 mm×300 mm, GE Healthcare, UK). Briefly, 15 μL of hamster plasma was 10-fold diluted with PBS containing 1 mM EDTA. Diluted plasma (20 μL) was separated by the column at 0.5 mL/min with the same buffer maintained at 40 °C for the simultaneous determination of cholesterol contents in the eluents.

For the analyses of atherosclerotic lesions, the animals were anesthetized via intraperitoneal injection of pentobarbital sodium (50 mg/kg), followed by vascular perfusion for 5 min with saline containing 4% paraformaldehyde with a perfusion pressure of 120 mm H_2O.

The aorta was separated from the heart at the 15 mm upper portion from the aortic origin. The isolated thoracic aorta was cut open, mounted on a rubber plate, and fixed with 4% paraformaldehyde followed by staining with Oil-Red O. Fatty streak areas were measured with an image analysis system (SP500F; Olympus, Tokyo, Japan).

Pharmacokinetic Experimental Details

Material and Method

Pharmacokinetic studies

A solution of compound **2** in PEG400 was orally administered to Golden Syrian hamsters at a dose of 300 mg/kg, and their blood samples were collected from the jugular vein at 0.5, 1, 2, and 6 h after dosage and immediately centrifuged to obtain the corresponding plasma fractions. The Oasis HLB-cartridge (1 cc, 30 mg) was preconditioned by eluting MeOH (1 mL) and then rinsed with deionized water (1 mL). The plasma samples (100 μL) and the corresponding internal standards (50 μL) were passed through the HLB-cartridge. The cartridge was washed with 5% aqueous MeOH (1 mL), and subsequently the drug residues were eluted from the cartridge with MeOH (2 mL). The extracts were completely evaporated to dryness by nitrogen stream. The residues were then dissolved in MeCN (75 μL) and 1% aqueous AcOH (75 μL). The drug concentration in the solution was measured by the LC-10 HPLC System (Shimadzu). Compound **2** showed a low concentration in the plasma for up to 2 h after administration and disappeared 6 h after administration, as shown in the drug concentration curve obtained for a dose of 300 mg/kg (Figure 24).

Molecular Modeling

Methods

1) Receptor structure preparation.

The X-ray crystal structure of human LXRβ/GW3965 complex (Protein Data Bank [PDB] ID: 1PQ6) was downloaded from the PDB. The raw PDB and our X-ray crystal structures (data not shown) were converted into an all-atom, fully prepared receptor model structure by using the Protein Preparation Wizard in the Maestro [42b)]. These structures were superimposed with the Molecular Operating Environment (MOE) [42c)]. The docking receptor grids were created by the Glide's Receptor Grid Generation module [42b)].

2) Ligand preparation.

All ligands were processed with the LigPrep [42b)] applying the following conditions: generation of tautomers, generation of stereoisomers and ionization at pH = 7 with a tolerance of ± 2.

3) Ligand-protein docking.

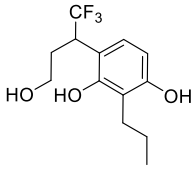
Standard precision mode of the Glide [42b)] program was used for all docking calculations. The van der Waals radii of ligands were scaled by 0.8. During the initial phase of docking calculation, the maximum poses generated from the variables were fixed to 5,000 and the best variable that set the number of poses per ligand that enters the energy minimization was set to 1,000. The final docking model was selected by comparing with our X-ray crystal structure.

Section-2

Chemical Experimental Details

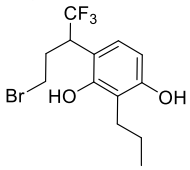
Scheme 11

2-Propyl-4-(1,1,1-trifluoro-4-hydroxybutan-2-yl)benzene-1,3-diol (73):



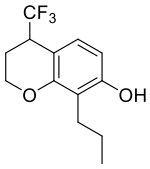
To a solution of 7-hydroxy-8-propyl-4-(trifluoromethyl)-*2H*-chromen-2-one (**38**) (93 mg, 0.34 mmol) in THF (3.4 mL), $LiAlH_4$ (26 mg, 0.68 mmol) was portionwise added at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. To this mixture was added water (50 μL), and then Na_2SO_4. The reaction mixture was concentrated *in vacuo* and then diluted with EtOAc and 2 N HCl, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was used for the next step without further purification to give the title compound (98 mg) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, *J* = 7.3 Hz), 1.58 (2H, qt, *J* = 7.3, 7.3 Hz), 2.48–2.55 (2H, m), 2.62 (2H, t, *J* = 7.3 Hz), 3.72 (2H, t, *J* = 6.5 Hz), 4.09–4.18 (1H, m), 4.97–5.25 (3H, m), 6.37 (1H, d, *J* = 8.6 Hz), 6.76 (1H, d, *J* = 8.6 Hz); MS (EI) *m/z* 278 $[M]^+$.

4-(4-Bromo-1,1,1-trifluorobutan-2-yl)-2-propylbenzene-1,3-diol (74):



To a solution of **73** (60 mg, 0.22 mmol) in THF (2.0 mL), PPh_3 (141 mg, 0.54 mmol) and CBr_4 (86 mg, 0.26 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 10 min and then concentrated *in vacuo*. The crude product was used for the next step without further purification to give the title compound (73 mg) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, *J* = 7.3 Hz), 1.53–1.65 (4H, m), 2.64 (2H, t, *J* = 7.3 Hz), 3.35 (2H, t, *J* = 6.5 Hz), 4.80–4.96 (1H, m), 6.40 (1H, d, *J* = 8.4 Hz), 6.81 (1H, d, *J* = 8.4 Hz); MS (EI) *m/z* 340 $[M]^+$.

8-Propyl-4-(trifluoromethyl)chroman-7-ol (75):

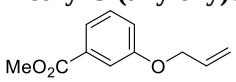


To a solution of **74** (73 mg, 0.22 mmol) in DMF (2.2 mL), K_2CO_3 (60 mg, 0.43 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 17 h and then diluted with water and extracted with EtOAc. The organic layer was washed with 2 N HCl and brine, dried over Na_2SO_4, and

concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3/1) to give the title compound (7.4 mg, 70% for 3 steps) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7.3 Hz), 1.55 (2H, qt, *J* = 7.3, 7.3 Hz), 2.13–2.25 (2H, m), 2.57 (2H, t, *J* = 7.3 Hz), 3.40–3.50 (1H, m), 4.22 (2H, t, *J* = 5.7 Hz), 4.75 (1H, s), 6.40 (1H, d, *J* = 8.6 Hz), 7.01 (1H, d, *J* = 8.6 Hz); MS (EI) *m/z* 260 $[M]^+$.

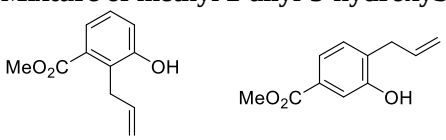
Scheme 12

Methyl 3-(allyloxy)benzoate (77) [81]**:**



To a stirred suspension of methyl 3-hydroxybenzoate (**76**) (10 g, 66 mmol) and K_2CO_3 (14 g, 99 mmol) in DMF (100 mL), allyl chloride (7.5 g, 99 mmol) was added dropwise at room temperature. The reaction mixture was stirred at 100 °C for 7 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (12 g, 95%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (3H, s), 4.58–4.60 (2H, m), 5.29–5.33 (1H, m), 5.41–5.46 (1H, m), 6.02–6.11 (1H, m), 7.12 (1H, ddd, *J* = 1.4, 2.7, 8.3 Hz), 7.34 (1H, dd, *J* = 7.9, 8.3 Hz), 7.58 (1H, dd, *J* = 1.4, 2.7 Hz), 7.64 (1H, ddd, *J* = 1.4, 1.4, 7.9 Hz); MS (EI) *m/z* 192 $[M]^+$.

Mixture of methyl 2-allyl-3-hydroxybenzoate (78a) and methyl 4-allyl-3-hydroxybenzoate (78b) [82]**:**



A stirred solution of **77** (4.5 g, 23 mol) in *N*,*N*-dimethylaniline (50 mL) was heated at 210 °C for 8 h. The reaction mixture was diluted with 1 N HCl and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to obtain a mixture of **78a** and **78b** (3.6 g, 80%) as a colorless oil. A mixture of **78a** and **78b** was used for the next step without separation.

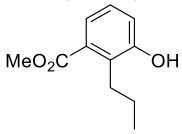
Methyl 2-allyl-3-hydroxybenzoate (83a):

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76–3.78 (2H, m), 3.88 (3H, s), 5.08–5.12 (1H, m), 5.13–5.14 (1H, m), 5.20 (1H, s), 6.00–6.09 (1H, m), 7.00 (1H, dd, *J* = 1.2, 8.0 Hz), 7.18 (1H, dd, *J* = 7.8, 8.0 Hz), 7.44 (1H, dd, *J* = 1.2, 7.8 Hz); MS (EI) *m/z* 192 $[M]^+$.

Methyl 4-allyl-3-hydroxybenzoate (78b):

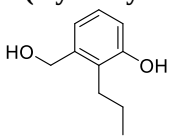
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45–3.46 (2H, m), 3.90 (3H, s), 5.16–5.26 (2H, m), 5.33 (1H, s), 5.96–6.06 (1H, m), 7.19 (1H, d, *J* = 7.8 Hz), 7.50 (1H, d, *J* = 1.7 Hz), 7.57 (1H, dd, *J* = 1.7, 7.8 Hz); MS (EI) *m/z* 192 $[M]^+$.

Methyl 3-hydroxy-2-propylbenzoate (79a) [83]**:**



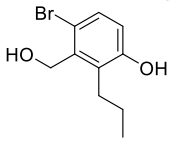
A suspension of a mixture of **78a** and **78b** (6.7 g, 35 mmol) and 10% Pd/C (670 mg) in MeOH (70 mL) was stirred under a hydrogen atmosphere at room temperature for 24 h. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/1) to obtain the title compound (4.0 g, 56%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.4 Hz), 1.62 (2H, qt, *J* = 7.4, 7.8 Hz), 2.89 (2H, t, *J* = 7.8 Hz), 3.89 (3H, s), 4.93 (1H, s), 6.93 (1H, dd, *J* = 1.2, 7.9 Hz), 7.11 (1H, dd, *J* = 7.8, 7.9 Hz), 7.39 (1H, dd, *J* = 1.2, 7.8 Hz); MS (EI) *m/z* 194 $[M]^+$.

3-(Hydroxymethyl)-2-propylphenol (80):



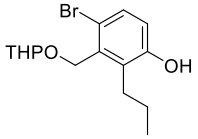
To a solution of **79a** (1.5 g, 7.7 mmol) in THF (50 mL), $LiAlH_4$ (645 mg, 17 mmol) was portionwise added at 0 °C. The reaction mixture was stirred at room temperature for 3 h. To this mixture was added water (1.0 mL), and then Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3/2) to give the title compound (1.2 g, 91%) as a colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.6 Hz), 1.48–1.63 (2H, m), 2.60–2.67 (2H, m), 4.60 (2H, s), 4.89 (2H, brs), 6.70 (1H, dd, *J* = 1.3, 7.9 Hz), 6.86 (1H, dd, *J* = 1.3, 7.5 Hz), 6.96 (1H, dd, *J* = 7.5, 7.9 Hz); MS (EI) *m/z* 166 $[M]^+$.

4-Bromo-3-(hydroxymethyl)-2-propylphenol (81):



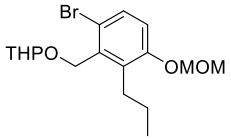
To a solution of **80** (1.1 g, 6.3 mmol) in a mixture of CH_2Cl_2 (50 mL) and MeOH (30 mL), *n*-Bu_4NBr_3 (3.2 g, 6.6 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then concentrated *in vacuo*. The residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3/1) to give the title compound (1.0 g, 67%) as a colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, *J* = 7.5 Hz), 1.48–1.62 (2H, m), 2.66–2.80 (2H, m), 3.30 (1H, s), 4.75 (2H, s), 6.63 (1H, d, *J* = 8.7 Hz), 7.20 (1H, d, *J* = 8.7 Hz); MS (EI) *m/z* 244 $[M]^+$.

4-Bromo-2-propyl-3-(((tetrahydro-*2H*-pyran-2-yl)oxy)methyl)phenol (82):



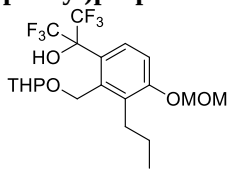
To a solution of **81** (1.0 g, 4.2 mmol) in CH_2Cl_2 (50 mL), *p*-TsOH·H_2O (81 mg, 0.42 mmol) and DHP (535 mg, 6.4 mmol) were added at room temperature. The reaction mixture was stirred at room temperature for 5 h, and then diluted with water and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3/1) to give the title compound (972 mg, 70%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, *J* = 7.4 Hz), 1.45–1.85 (8H, m), 2.62–2.80 (2H, m), 3.58–3.70 (1H, m), 3.96–4.08 (1H, m), 4.57 (1H, d, *J* = 10.5 Hz), 4.84 (1H, t, *J* = 3.2 Hz), 4.95 (1H, d, *J* = 10.5 Hz), 6.59 (1H, d, *J* = 8.6 Hz), 7.25 (1H, d, *J* = 8.6 Hz); MS (EI) *m/z* 328 $[M]^+$.

2-((6-Bromo-3-(methoxymethoxy)-2-propylbenzyl)oxy)tetrahydro-*2H*-pyran (83):



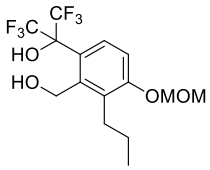
To a solution of **82** (972 mg, 3.0 mmol) in DMF (5 mL), NaH (50% in oil, 257 mg, 5.9 mmol) and MOMCl (475 mg, 5.9 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 2 h, and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/1) to give the title compound (910 mg, 83%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.3 Hz), 1.46–1.88 (8H, m), 2.83 (2H, t, *J* = 7.6 Hz), 3.46 (3H, s), 3.62 (1H, td, *J* = 4.3, 11.2 Hz), 4.01 (1H, td, *J* = 3.3, 11.2 Hz), 4.58 (1H, d, *J* = 10.9 Hz), 4.82 (1H, t, *J* = 3.3 Hz), 4.97 (1H, d, *J* = 10.9 Hz), 5.18 (2H, s), 6.94 (1H, d, *J* = 8.9 Hz), 7.36 (1H, d, *J* = 8.9 Hz); MS (EI) *m/z* 372 $[M]^+$.

1,1,1,3,3,3-Hexafluoro-2-(4-(methoxymethoxy)-3-propyl-2-(((tetrahydro-*2H*-pyran-2-yl)oxy)methyl)-phenyl)propan-2-ol (84):



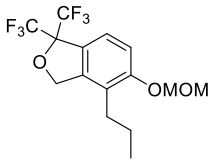
To a stirred solution of **83** (725 mg, 1.8 mmol) in THF (8.0 mL), *n*-BuLi (1.58 M hexane solution 1.6 mL, 2.5 mmol) was added dropwise at −78 °C under an argon atmosphere. The reaction mixture was stirred at the same temperature for 15 min and then at an elevated temperature of −45 °C for 1.5 h. To this reaction mixture, a solution of hexafluoroacetone in THF (4.0 mL) was added dropwise at −78 °C. The reaction mixture was stirred at 0 °C for 5 h and then at room temperature for 12 h, followed by dilution with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/1) to give the title compound (728 mg, 90%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, *J* = 7.4 Hz), 1.45–1.86 (8H, m), 2.73–2.82 (2H, m), 3.53 (3H, s), 3.59–3.66 (1H, m), 3.97–4.02 (1H, m), 4.66 (1H, d, *J* = 10.5 Hz), 4.75–4.81 (4H, m), 6.67 (1H, d, *J* = 8.5 Hz), 7.19 (1H, d, *J* = 8.5 Hz), 7.46 (1H, s); MS (EI) *m/z* 460 $[M]^+$.

1,1,1,3,3,3-Hexafluoro-2-(2-(hydroxymethyl)-4-(methoxymethoxy)-3-propylphenyl)propan-2-ol (85):



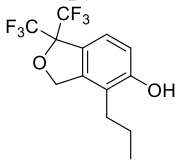
To a solution of **84** (883 mg, 1.9 mmol) in THF (10 mL) and water (5 mL), AcOH (20 mL) was added at room temperature. The reaction mixture was stirred at 50 °C for 3 h and then neutralized with saturated $NaHCO_3$ *aq*. (50 mL) and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3/1) to give the title compound (678 mg, 92%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, t, *J* = 7.3 Hz), 1.47–1.57 (2H, m), 2.73–2.80 (2H, m), 3.54 (3H, s), 4.82 (2H, s), 4.88 (2H, s), 6.76 (1H, d, *J* = 8.9 Hz), 7.31 (1H, d, *J* = 8.9 Hz), 7.68 (1H, s), 7.75 (1H, s); MS (EI) *m/z* 376 $[M]^+$.

5-(Methoxymethoxy)-4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran (86):



To a solution of **85** (1.3 g, 3.4 mmol) in CH_2Cl_2 (15 mL), PPh_3 (2.0 g, 7.6 mmol) and DEAD (2.2 M toluene solution, 4.7 mL, 10 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 17 h and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3/1) to give the title compound (1.1 g, 93%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7.3 Hz), 1.60 (2H, qt, *J* = 7.3, 7.3 Hz), 2.51 (2H, t, *J* = 7.3 Hz), 3.55 (3H, s), 4.88 (2H, s), 5.31 (2H, s), 6.81 (1H, d, *J* = 8.2 Hz), 7.20 (1H, d, *J* = 8.2 Hz); MS (EI) *m/z* 358 $[M]^+$.

4-Propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-ol (87):

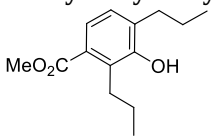


To a solution of **86** (1.1 g, 3.1 mmol) in EtOH (2 mL), 2 N HCl (2 mol/L EtOH solution, 5.0 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 2 h and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3/1) to give the title compound (953 mg, 96%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7.3 Hz), 1.61 (2H, qt, *J* = 7.3, 7.3 Hz), 2.50 (2H, t, *J* = 7.3 Hz), 5.02 (1H, s), 5.30 (2H, s), 6.80 (1H, d, *J* = 7.9 Hz), 7.21 (1H, d, *J* = 7.9 Hz); MS (EI) *m/z* 314 $[M]^+$.

Scheme 13

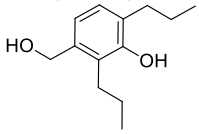
Compounds **88~93**, **100** were prepared in the same manner as the synthesis of **77~87** and **97**.

Methyl 3-hydroxy-2,4-dipropylbenzoate (88):



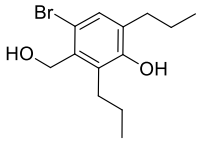
Compound **88** was prepared from compound **79a** in a manner similar to that described for compounds **77**, **78b** and **79a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.3 Hz), 1.01 (3H, t, *J* = 7.3 Hz), 1.59–1.70 (4H, m), 2.60 (2H, t, *J* = 7.6 Hz), 2.91 (2H, t, *J* = 7.6 Hz), 3.87 (3H, s), 4.87 (1H, s), 7.00 (1H, d, *J* = 7.8 Hz), 7.37 (1H, d, *J* = 7.8 Hz); MS (EI) *m/z* 236 $[M]^+$.

3-(Hydroxymethyl)-2,6-dipropylphenol (89):



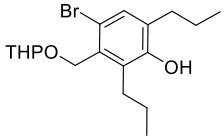
Compound **89** was prepared from compound **88** in a manner similar to that described for compound **80**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, *J* = 7.3 Hz), 1.02 (3H, t, *J* = 7.3 Hz), 1.48 (1H, s), 1.54–1.69 (4H, m), 2.56 (2H, t, *J* = 7.6 Hz), 2.67 (2H, t, *J* = 7.6 Hz), 4.66 (2H, d, *J* = 5.4 Hz), 4.74 (1H, s), 6.89 (1H, d, *J* = 7.8 Hz), 6.98 (1H, d, *J* = 7.8 Hz); MS (EI) *m/z* 208 $[M]^+$.

4-bromo-3-(hydroxymethyl)-2,6-dipropylphenol (90):



Compound **90** was prepared from compound **89** in a manner similar to that described for compound **81**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.3 Hz), 1.02 (3H, t, *J* = 7.3 Hz), 1.53–1.67 (4H, m), 1.93 (1H, s), 2.52 (2H, t, *J* = 7.6 Hz), 2.75 (2H, t, *J* = 7.6 Hz), 4.76 (1H, s), 4.78 (2H, d, *J* = 6.6 Hz), 7.20 (1H, s); MS (EI) *m/z* 286 $[M]^+$.

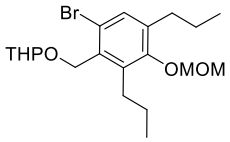
4-Bromo-2,6-dipropyl-3-(((tetrahydro-*2H*-pyran-2-yl)oxy)methyl)phenol (91):



Compound **91** was prepared from compound **90** in a manner similar to that described for compound **82**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.3 Hz), 1.02 (3H, t, *J* = 7.3 Hz), 1.56–1.87 (10H, m), 2.51 (2H, t, *J* = 7.6 Hz), 2.67–2.80 (2H, m), 3.59–3.64 (1H, m), 3.98–4.04 (1H, m), 4.55 (1H, d, *J* = 10.7 Hz), 4.71 (1H, s), 4.80 (1H, t, *J* = 3.4 Hz), 4.92 (1H, d, *J* = 10.7 Hz), 7.21 (1H, s); MS (EI)

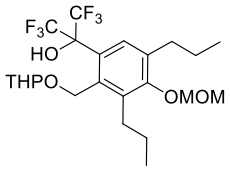
m/z 370 $[M]^+$.

2-((6-Bromo-3-(methoxymethoxy)-2,4-dipropylbenzyl)oxy)tetrahydro-*2H*-pyran (92):



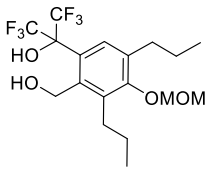
Compound **92** was prepared from compound **91** in a manner similar to that described for compound **83**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, *J* = 7.3 Hz), 1.01 (3H, t, *J* = 7.3 Hz), 1.49–1.88 (10H, m), 2.56 (2H, t, *J* = 7.8 Hz), 2.72–2.80 (2H, m), 3.59–3.63 (4H, m), 3.98–4.03 (1H, m), 4.51 (1H, d, *J* = 10.7 Hz), 4.82 (1H, t, *J* = 3.4 Hz), 4.92 (1H, d, *J* = 10.7 Hz), 4.93 (1H, s), 7.30 (1H, s); MS (EI) *m/z* 414 $[M]^+$.

1,1,1,3,3,3-Hexafluoro-2-(4-(methoxymethoxy)-3,5-dipropyl-2-(((tetrahydro-*2H*-pyran-2-yl)oxy)methyl)-phenyl)propan-2-ol (93):



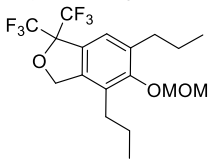
Compound **93** was prepared from compound **92** in a manner similar to that described for compound **84**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7.3 Hz), 1.02 (3H, t, *J* = 7.3 Hz), 1.48–1.79 (10H, m), 2.62 (2H, t, *J* = 7.6 Hz), 2.80 (2H, t, *J* = 8.3 Hz), 3.56–3.59 (1H, m), 3.64 (3H, s), 3.82–3.87 (1H, m), 4.76 (1H, t, *J* = 3.4 Hz), 4.83 (1H, d, *J* = 11.7 Hz), 4.97 (2H, s), 5.12 (1H, d, *J* = 11.7 Hz), 7.45 (1H, s), 7.56 (1H, s); MS (EI) *m/z* 502 $[M]^+$.

1,1,1,3,3,3-Hexafluoro-2-(2-(hydroxymethyl)-4-(methoxymethoxy)-3,5-dipropylphenyl)propan-2-ol (94):



Compound **94** was prepared from compound **93** in a manner similar to that described for compound **85**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 1.03 (3H, t, *J* = 7.3 Hz), 1.52 (2H, qt, *J* = 7.3, 7.6 Hz), 1.61 (2H, t, *J* = 7.3, 8.3 Hz), 2.61 (2H, t, *J* = 7.6 Hz), 2.67 (1H, s), 2.77 (2H, t, *J* = 8.3 Hz), 3.64 (3H, s), 4.97 (4H, s), 7.44 (1H, s), 7.56 (1H, s); MS (EI) *m/z* 418 $[M]^+$.

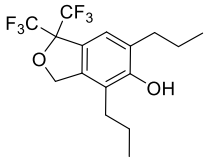
5-(Methoxymethoxy)-4,6-dipropyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran (95):



Compound **95** was prepared from compound **94** in a manner similar to that described for compound **86**. The title

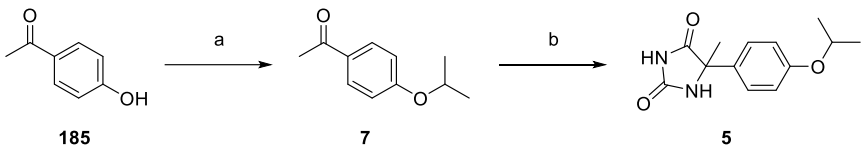
compound was obtained as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7.3 Hz), 0.99 (3H, t, *J* = 7.3 Hz), 1.55–1.71 (4H, m), 2.49 (2H, t, *J* = 7.6 Hz), 2.59 (2H, t, *J* = 7.6 Hz), 3.64 (3H, s), 4.97 (2H, s), 5.28 (2H, s), 7.10 (1H, s); MS (EI) *m/z* 400 $[M]^+$.

4,6-Dipropyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-ol (96):



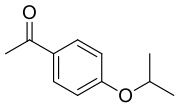
Compound **96** was prepared from compound **95** in a manner similar to that described for compound **87**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7.3 Hz), 0.99 (3H, t, *J* = 7.3 Hz), 1.55–1.71 (4H, m), 2.49 (2H, t, *J* = 7.6 Hz), 2.59 (2H, t, *J* = 7.6 Hz), 4.91 (1H, s), 5.28 (2H, s), 7.10 (1H, s); MS (EI) *m/z* 356 $[M]^+$.

Synthetic procedure of the hydantoin derivatives 5



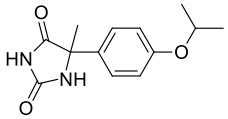
Scheme 40. Reagents and conditions: (a) *i*-PrI, K_2CO_3, acetone, 55 °C, 7.5 h, 99%; (b) NaCN, $(NH_4)_2CO_3$, EtOH *aq.*, microwave, 100 °C, 1 h, 99%.

1-(4-(1-Methylethoxy)phenyl)ethanone (7) [84]**:**



To a stirred suspension of 4'-hydroxyacetophenone (**185**) (10 g, 73 mmol) and K_2CO_3 (20 g, 0.15 mol) in acetone (82 mL), 2-iodopropane (19 g, 0.11 mol) was added at room temperature. The reaction mixture was stirred at 55 °C for 7.5 h. After completing the reaction, the reaction mixture was filtered off and rinsed with acetone. The filtrate was concentrated *in vacuo*. The residue was dissolved in 1 N NaOH *aq.* (20 mL). The solution was extracted with EtOAc. The organic layer was washed with 1 N NaOH *aq.* and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound (6.8 g, 99%) as colorless crystals; mp 42.1–43.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (6H, d, *J* = 5.9 Hz), 2.56 (3H, s), 4.65 (1H, sept, *J* = 5.9 Hz), 6.90 (2H, d, *J* = 8.9 Hz), 7.92 (2H, d, *J* = 8.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9 (2C), 26.3, 70.1, 115.1 (2C), 130.0, 130.6 (2C), 162.0, 196.7; MS (EI): m/z 178 $[M]^+$.

5-(4-(1-Methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (5) [84]**:**



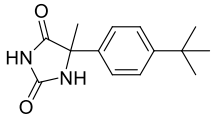
To a stirred solution of **7** (4.0 g, 22 mmol) in EtOH (23 mL), NaCN (1.7 g, 34 mmol), $(NH_4)_2CO_3$ (6.5 g, 67 mmol) and water (23 mL) were added at room temperature. The reaction mixture was irradiated in a microwave (Initiator; Biotage AB) at 100 °C for 1 h. EtOH in the reaction mixture was removed by concentration. The precipitate was filtered off and washed with water. The solid was recrystallized from a mixture of solvents (hexane/EtOAc = 1/4) to give the title compound (5.5 g, 99%) as colorless crystals; mp 166.2–169.3 °C; IR (KBr): 3282, 3207, 1770, 1727, 1512, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (6H, d, *J* = 5.6 Hz), 1.80 (3H, s), 4.53 (1H, sept, *J* = 5.6 Hz), 6.57 (1H, brs), 6.87 (2H, d, *J* = 8.8 Hz), 7.37 (2H, d, *J* = 8.8 Hz), 8.57 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (2C), 25.2, 64.9, 70.0, 116.0 (2C), 126.5 (2C), 129.9, 156.6, 158.1, 176.2; MS (EI) *m/z* 248 $[M]^+$.

Compounds **42l~p** were prepared in the same manner as the synthesis of **42a**.

Characterization data

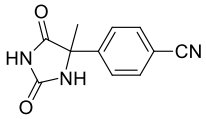
The NMR and MS data of the compounds **42l~p** are described below.

5-(4-(*tert*-Butyl)phenyl)-5-methylimidazolidine-2,4-dione (42l):



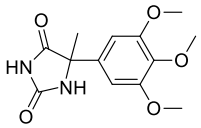
Compound **42l** was prepared from 1-(4-(*tert*-butyl)phenyl)ethan-1-one in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^1H NMR (400 MHz, d_6-DMSO) δ 1.26 (9H, s), 1.63 (3H, s), 7.37 (2H, d, *J* = 8.6 Hz), 7.41 (2H, d, *J* = 8.6 Hz), 8.56 (1H, s), 10.7 (1H, s); MS (EI): m/z 246 $[M]^+$.

4-(4-Methyl-2,5-dioxoimidazolidin-4-yl)benzonitrile (42m):



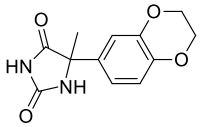
Compound **42m** was prepared from 4-acetylbenzonitrile in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^1H NMR (400 MHz, d_6-DMSO) δ 1.68 (3H, s), 7.69 (2H, d, *J* = 8.6 Hz), 7.89 (2H, d, *J* = 8.6 Hz), 8.75 (1H, s), 10.9 (1H, s); MS (EI): m/z 215 $[M]^+$.

5-Methyl-5-(3,4,5-trimethoxyphenyl)imidazolidine-2,4-dione (42n):



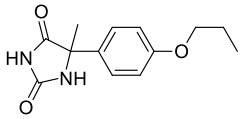
Compound **42n** was prepared from 1-(3,4,5-trimethoxyphenyl)ethan-1-one in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.63 (3H, s), 3.36 (3H, s), 3.64 (3H, s), 3.78 (3H, s), 6.77 (2H, s), 8.65 (1H, s), 10.8 (1H, s); MS (EI): m/z 280 $[M]^+$.

5-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-methylimidazolidine-2,4-dione (42o):



Compound **42o** was prepared from 1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)ethan-1-one in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.58 (3H, s), 4.23 (4H, s), 6.84–6.92 (3H, m), 8.55 (1H, s), 10.7 (1H, s); MS (EI) *m/z* 248 $[M]^+$.

5-Methyl-5-(4-propoxyphenyl)imidazolidine-2,4-dione (42p):

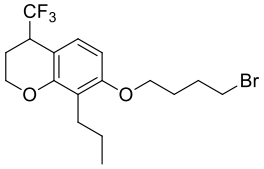


Compound **42p** was prepared from 1-(4-hydroxyphenyl)ethan-1-one in a manner similar to that described for **7** and compound **42a**. The title compound was obtained as a colorless amorphous solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.96 (3H, t, *J* = 7.3 Hz), 1.61 (3H, s), 1.70 (2H, qt, *J* = 6.2, 7.3 Hz), 3.91 (2H, t, *J* = 6.2 Hz), 6.93 (2H, d, *J* = 8.6 Hz), 7.34 (2H, d, *J* = 8.6 Hz), 8.54 (1H, s), 10.7 (1H, s); MS (EI): m/z 248 $[M]^+$.

Scheme 14

Synthesis of the chroman derivative

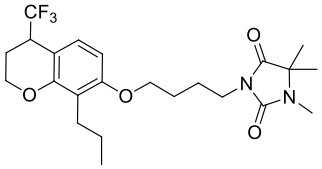
7-(4-Bromobutoxy)-8-propyl-4-(trifluoromethyl)chromane (97):



To a stiired suspension of **75** (6.6 mg, 25 μmol) and K_2CO_3 (5.2 mg, 38 μmol) in DMF (0.3 mL), 1,4-dibromobutane (55 mg, 0.25 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 20 h, and then diluted with water (100 μL) and 2 N HCl (100 μL), and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1) to give the title compound (4.6 mg, 46%) as a colorless

oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.3 Hz), 1.49 (2H, qt, *J* = 7.3, 7.3 Hz), 1.90–2.22 (6H, m), 2.57 (2H, t, *J* = 7.3 Hz), 3.40–3.50 (1H, m), 3.47 (2H, t, *J* = 6.5 Hz), 3.97 (2H, t, *J* = 5.7 Hz), 4.24 (2H, t, *J* = 5.1 Hz), 6.47 (1H, d, *J* = 8.6 Hz), 7.08 (1H, d, *J* = 8.6 Hz); MS (EI) *m/z* 394 $[M]^+$.

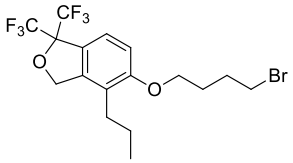
1,5,5-Trimethyl-3-(4-((8-propyl-4-(trifluoromethyl)chroman-7-yl)oxy)butyl)imidazolidine-2,4-dione (100):



To a stirred suspension of 1,5,5-trimethylhydantoin (3.3 mg, 23 μmol) and K_2CO_3 (2.4 mg, 18 μmol) in DMF (120 μL), a solution of **97** (4.6 mg, 12 μmol) in DMF (100 μL) was added dropwise at room temperature. The reaction mixture was stirred at the same temperature for 13 h and then diluted with water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3/2) to give the title compound (4.3 mg, 81%) as a colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 7.3 Hz), 1.36 (6H, s), 1.47 (2H, qt, *J* = 7.3, 7.3 Hz), 1.74–1.86 (4H, m), 2.12–2.25 (2H, m), 2.57 (2H, t, *J* = 7.3 Hz), 2.88 (3H, s), 3.42–3.50 (1H, m), 3.58 (2H, t, *J* = 6.5 Hz), 3.96 (2H, t, *J* = 5.7 Hz), 4.21 (2H, t, *J* = 5.1 Hz), 6.45 (1H, d, *J* = 8.6 Hz), 7.06 (1H, d, *J* = 8.6 Hz); MS (EI) *m/z* 456 $[M]^+$.

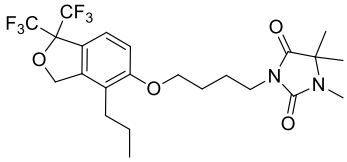
Synthesis of the 1,3-dihydroisobenzofuran derivative with propyl group

5-(4-Bromobutoxy)-4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran (98):



To a stirred suspension of **87** (800 mg, 2.6 mol) and K_2CO_3 (528 mg, 3.8 mmol) in DMF (10 mL), 1,4-dibromobutane (2.8 mL, 13 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 18 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 50/1) to give the title compound (1.1 g, 99%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.4 Hz), 1.57 (2H, qt, *J* = 7.4, 7.6 Hz), 1.97–2.14 (4H, m), 2.49 (2H, t, *J* = 7.6 Hz), 3.51 (2H, t, *J* = 6.3 Hz), 4.03 (2H, t, *J* = 5.4 Hz), 5.30 (2H, s), 6.86 (1H, d, *J* = 8.4 Hz), 7.29 (1H, d, *J* = 8.4 Hz); MS (EI) *m/z* 448 $[M]^+$.

1,5,5-Trimethyl-3-(4-((4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)butyl)-imidazolidine-2,4-dione (102):



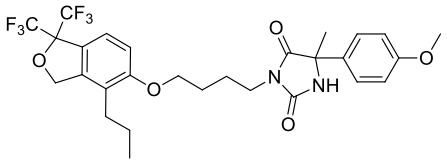
To a stirred suspension of 1,5,5-trimethylhydantoin (20 mg, 84 μmol) and K_2CO_3 (15 mg, 110 μmol) in DMF (120 μL), **98** (25 mg, 56 μmol) in DMF (100 μL) was added at room temperature. The reaction mixture was stirred at room temperature for 20 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to give the title compound (31 mg, 92%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 7.3 Hz), 1.36 (6H, s), 1.55 (2H, qt, *J* = 7.3, 7.3 Hz), 1.77–1.88 (4H, m), 2.48 (2H, t, *J* = 7.3 Hz), 2.89 (3H, s), 3.60 (2H, t, *J* = 6.4 Hz), 4.02 (2H, t, *J* = 5.6 Hz), 5.29 (2H, s), 6.86 (1H, d, *J* = 8.5 Hz), 7.27 (1H, d, *J* = 8.5 Hz); MS (EI) *m/z* 510 $[M]^+$.

Compounds **3** and **103~116** were prepared in the same manner as the synthesis of **102**.

Characterization data

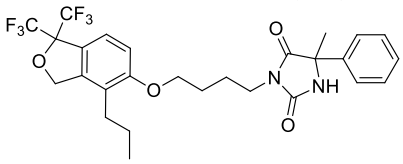
The NMR and MS data of compounds **3** and **103~116** are described below.

5-(4-Methoxyphenyl)-5-methyl-3-(4-((4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)-oxy)butyl)imidazolidine-2,4-dione (103):



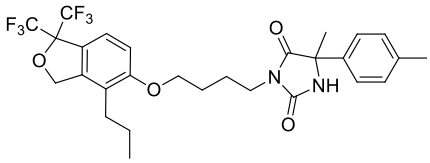
Compound **103** was prepared from compounds **98** and **42a** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.3 Hz), 1.52 (2H, qt, *J* = 7.3, 7.8 Hz), 1.76–1.86 (7H, m), 2.45 (2H, t, *J* = 7.8 Hz), 3.60 (2H, t, *J* = 5.9 Hz), 3.79 (3H, s), 3.98 (2H, t, *J* = 5.7 Hz), 5.28 (2H, s), 6.04 (1H, s), 6.82 (1H, d, *J* = 8.6 Hz), 6.90 (2H, d, *J* = 8.9 Hz), 7.26 (1H, d, *J* = 8.6 Hz), 7.39 (2H, d, *J* = 8.9 Hz); MS (EI) *m/z* 588 $[M]^+$.

5-Methyl-5-phenyl-3-(4-((4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)butyl)-imidazolidine-2,4-dione (104):



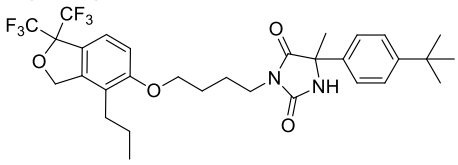
Compound **104** was prepared from compound **98** and 5-methyl-5-phenylimidazolidine-2,4-dione in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 7.3 Hz), 1.51 (2H, qt, *J* = 7.3, 7.8 Hz), 1.82–1.85 (4H, m), 1.87 (3H, s), 2.44 (2H, t, *J* = 7.8 Hz), 3.63 (2H, t, *J* = 6.4 Hz), 3.99 (2H, t, *J* = 5.9 Hz), 5.26 (2H, s), 6.21 (1H, brs), 6.82 (1H, d, *J* = 8.6 Hz), 7.26 (1H, d, *J* = 8.6 Hz), 7.35–7.46 (2H, m), 7.55–7.63 (3H, m); MS (EI) *m/z* 558 $[M]^+$.

5-Methyl-3-(4-((4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)butyl)-5-(*p*-tolyl)-imidazolidine-2,4-dione (105):



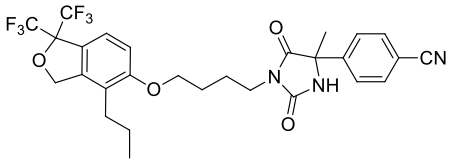
Compound **105** was prepared from compounds **98** and **42b** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (3H, t, *J* = 7.3 Hz), 1.45 (2H, qt, *J* = 7.3, 7.8 Hz), 1.68–1.76 (7H, m), 2.26 (3H, s), 2.38 (2H, t, *J* = 7.8 Hz), 3.53 (2H, t, *J* = 6.4 Hz), 3.91 (2H, t, *J* = 5.9 Hz), 5.21 (2H, s), 5.97 (1H, brs), 6.75 (1H, d, *J* = 8.4 Hz), 7.12 (2H, d, *J* = 8.3 Hz), 7.19 (1H, d, *J* = 8.4 Hz), 7.29 (2H, d, *J* = 8.3 Hz); MS (EI) *m/z* 572 $[M]^+$.

5-(4-(*tert*-Butyl)phenyl)-5-methyl-3-(4-((4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)-oxy)butyl)imidazolidine-2,4-dione (106):



Compound **106** was prepared from compounds **98** and **42l** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (3H, t, *J* = 7.3 Hz), 1.23 (9H, s), 1.47 (2H, qt, *J* = 7.3, 7.6 Hz), 1.71–1.78 (7H, m), 2.39 (2H, t, *J* = 7.6 Hz), 3.53 (2H, t, *J* = 6.4 Hz), 3.93 (2H, t, *J* = 5.9 Hz), 5.21 (2H, s), 6.01 (1H, brs), 6.76 (1H, d, *J* = 8.3 Hz), 7.20 (1H, d, *J* = 8.3 Hz), 7.33–7.38 (4H, m); MS (EI) *m/z* 614 $[M]^+$.

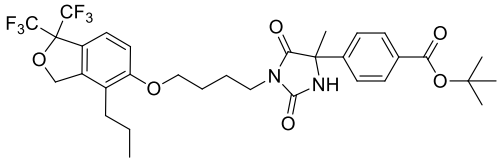
4-(4-Methyl-2,5-dioxo-1-(4-((4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)butyl)-imidazolidin-4-yl)benzonitrile (107):



Compound **107** was prepared from compounds **98** and **42m** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.3 Hz), 1.54 (2H, qt, *J* = 7.3, 7.6 Hz), 1.76–1.86 (4H, m), 1.88 (3H, s), 2.45 (2H, t, *J* = 7.6 Hz), 3.62 (2H, t, *J* = 6.4 Hz), 3.99 (2H, t, *J* = 5.9 Hz), 5.28 (2H, s), 5.64 (1H, s), 6.82 (1H, d, *J* = 8.6 Hz), 7.25 (1H, d, *J* = 8.6 Hz), 7.73 (2H, d,

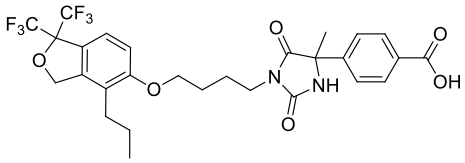
J = 9.0 Hz), 8.26 (2H, d, *J* = 9.0 Hz); MS (EI) *m/z* 583 $[M]^+$.

***tert*-Butyl 4-(4-methyl-2,5-dioxo-1-(4-((4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)-oxy)butyl)imidazolidin-4-yl)benzoate:**



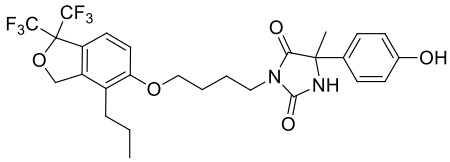
The title compound was prepared from compounds **98** and **42j** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 7.3 Hz), 1.52 (2H, qt, *J* = 7.3, 7.8 Hz), 1.58 (9H, s), 1.76–1.85 (7H, m), 2.44 (2H, t, *J* = 7.8 Hz), 3.60 (2H, t, *J* = 6.4 Hz), 3.98 (2H, t, *J* = 5.9 Hz), 5.28 (2H, s), 6.14 (1H, s), 6.82 (1H, d, *J* = 8.6 Hz), 7.25 (1H, d, *J* = 8.6 Hz), 7.57 (2H, d, *J* = 8.6 Hz), 8.00 (2H, d, *J* = 8.6 Hz); MS (EI) *m/z* 602 $[M]^+$.

4-(4-Methyl-2,5-dioxo-1-(4-((4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)butyl)-imidazolidin-4-yl)benzoic acid (108):



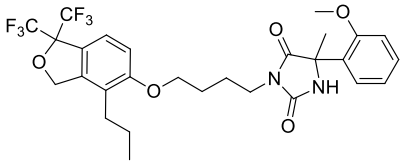
Compound **108** was prepared from the precursor in a manner similar to that described for compound **62**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.3 Hz), 1.52 (2H, qt, *J* = 7.3, 7.8 Hz), 1.73–1.84 (7H, m), 2.45 (2H, t, *J* = 7.8 Hz), 3.61 (2H, t, *J* = 6.4 Hz), 3.72 (1H, s), 3.99 (2H, t, *J* = 5.9 Hz), 4.38 (1H, s), 5.28 (2H, s), 6.62 (1H, s), 6.80–6.83 (3H, m), 7.28–7.32 (3H, m); MS (EI) *m/z* 602 $[M]^+$.

5-(4-Hydroxyphenyl)-5-methyl-3-(4-((4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)-oxy)butyl)imidazolidine-2,4-dione (109):



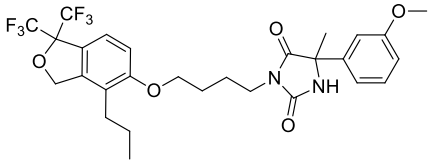
Compound **109** was prepared from the precursor in a manner similar to that described for compound **63**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.3 Hz), 1.52 (2H, qt, *J* = 7.3, 7.8 Hz), 1.78–1.88 (7H, m), 2.44 (2H, t, *J* = 7.8 Hz), 3.61 (2H, t, *J* = 6.4 Hz), 3.72 (1H, s), 3.98 (2H, t, *J* = 5.9 Hz), 5.28 (2H, s), 6.26 (1H, s), 6.83 (1H, d, *J* = 8.6 Hz), 7.27 (1H, d, *J* = 8.6 Hz), 7.55 (2H, d, *J* = 8.8 Hz), 8.01 (2H, d, *J* = 8.8 Hz); MS (EI) *m/z* 574 $[M]^+$.

5-(2-Methoxyphenyl)-5-methyl-3-(4-((4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)-oxy)butyl)imidazolidine-2,4-dione (110):



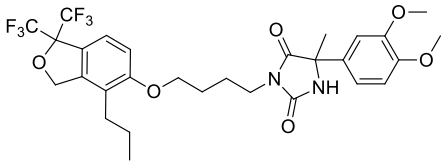
Compound **110** was prepared from compounds **98** and **42c** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 7.3 Hz), 1.55 (2H, qt, *J* = 7.3, 7.6 Hz), 1.76 (3H, s), 1.83–1.91 (4H, m), 2.48 (2H, t, *J* = 7.6 Hz), 3.66 (2H, t, *J* = 6.2 Hz), 3.87 (3H, s), 4.02 (2H, t, *J* = 5.9 Hz), 5.29 (2H, s), 6.29 (1H, s), 6.84 (1H, d, *J* = 8.1 Hz), 6.92–6.97 (2H, m), 7.28–7.36 (2H, m), 7.50 (1H, dd, *J* = 1.4, 8.0 Hz); MS (EI) *m/z* 588 $[M]^+$.

5-(3-Methoxyphenyl)-5-methyl-3-(4-((4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)-oxy)butyl)imidazolidine-2,4-dione (111):



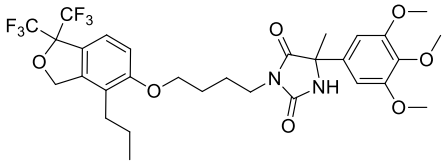
Compound **111** was prepared from compounds **98** and **42d** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.3 Hz), 1.52 (2H, qt, *J* = 7.3, 7.6 Hz), 1.75–1.88 (7H, m), 2.45 (2H, t, *J* = 7.6 Hz), 3.60 (2H, t, *J* = 6.3 Hz), 3.80 (3H, s), 3.98 (2H, t, *J* = 5.7 Hz), 5.28 (2H, s), 6.07 (1H, s), 6.82 (1H, d, *J* = 8.4 Hz), 6.87 (1H, dd, *J* = 1.9, 8.4 Hz), 7.05–7.08 (2H, m), 7.25–7.33 (2H, m); MS (EI) *m/z* 588 $[M]^+$.

5-(3,4-Dimethoxyphenyl)-5-methyl-3-(4-((4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)butyl)imidazolidine-2,4-dione (112):



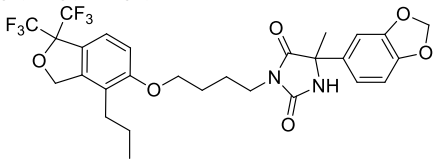
Compound **112** was prepared from compounds **98** and **42e** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.3 Hz), 1.52 (2H, qt, *J* = 7.3, 7.6 Hz), 1.77–1.87 (7H, m), 2.45 (2H, t, *J* = 7.6 Hz), 3.61 (2H, t, *J* = 6.2 Hz), 3.87 (3H, s), 3.89 (3H, s), 3.99 (2H, t, *J* = 5.9 Hz), 5.28 (2H, s), 6.10 (1H, s), 6.81–6.87 (2H, m), 7.01–7.03 (2H, m), 7.27 (1H, d, *J* = 8.1 Hz); MS (EI) *m/z* 618 $[M]^+$.

5-Methyl-3-(4-((4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)butyl)-5-(3,4,5-trimethoxyphenyl)imidazolidine-2,4-dione (113):



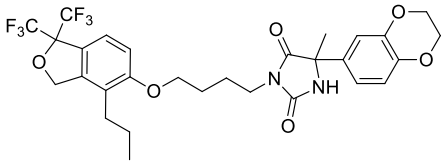
Compound **113** was prepared from compounds **98** and **42n** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.3 Hz), 1.58 (2H, qt, *J* = 7.3, 7.6 Hz), 1.78–1.88 (7H, m), 2.45 (2H, t, *J* = 7.6 Hz), 3.61 (2H, t, *J* = 6.2 Hz), 3.83 (3H, s), 3.86 (6H, s), 4.00 (2H, t, *J* = 5.9 Hz), 5.28 (2H, s), 6.47 (1H, s), 6.72 (2H, s), 6.83 (1H, d, *J* = 8.1 Hz), 7.27 (1H, d, *J* = 8.1 Hz); MS (EI) *m/z* 648 $[M]^+$.

5-(Benzo[*d*][1,3]dioxol-5-yl)-5-methyl-3-(4-((4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)butyl)imidazolidine-2,4-dione (114):



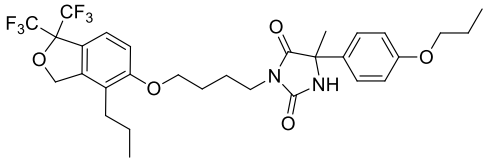
Compound **114** was prepared from compounds **98** and **42f** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.3 Hz), 1.52 (2H, qt, *J* = 7.3, 7.6 Hz), 1.75–1.85 (7H, m), 2.45 (2H, t, *J* = 7.6 Hz), 3.60 (2H, t, *J* = 6.2 Hz), 3.99 (2H, t, *J* = 5.9 Hz), 5.28 (2H, s), 5.96 (2H, s), 6.32 (1H, s), 6.77–6.84 (2H, m), 6.94 (1H, dd, *J* = 1.9, 8.4 Hz), 6.99 (1H, d, *J* = 1.9 Hz), 7.26 (1H, d, *J* = 8.4 Hz); MS (EI) *m/z* 602 $[M]^+$.

5-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-methyl-3-(4-((4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydro-isobenzofuran-5-yl)oxy)butyl)imidazolidine-2,4-dione (3):



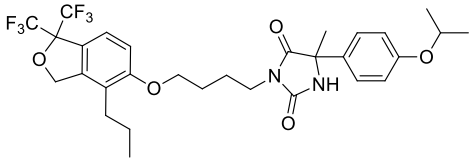
Compound **3** was prepared from compounds **98** and **42o** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.3 Hz), 1.53 (2H, qt, *J* = 7.3, 7.6 Hz), 1.66–1.81 (7H, m), 2.45 (2H, t, *J* = 7.6 Hz), 3.59 (2H, t, *J* = 6.2 Hz), 3.99 (2H, t, *J* = 5.9 Hz), 4.19–4.28 (4H, m), 5.28 (2H, s), 6.23 (1H, s), 6.81–7.01 (4H, m), 7.26 (1H, d, *J* = 8.1 Hz); MS (EI) *m/z* 616 $[M]^+$.

5-Methyl-5-(4-propoxyphenyl)-3-(4-((4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)-oxy)butyl)imidazolidine-2,4-dione (115):



Compound **115** was prepared from compounds **98** and **42p** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (3H, t, *J* = 7.3 Hz), 0.95 (3H, t, *J* = 7.3 Hz), 1.45 (2H, qt, *J* = 7.3, 7.8 Hz), 1.67–1.77 (9H, m), 1.67–1.77 (7H, m), 2.38 (2H, t, *J* = 7.8 Hz), 3.52 (2H, t, *J* = 6.4 Hz), 3.82 (2H, t, *J* = 6.6 Hz), 3.91 (2H, t, *J* = 5.9 Hz), 5.21 (2H, s), 6.24 (1H, brs), 6.75 (1H, d, *J* = 8.6 Hz), 6.82 (2H, d, *J* = 8.8 Hz), 7.19 (1H, d, *J* = 8.6 Hz), 7.30 (2H, d, *J* = 8.8 Hz); MS (EI) *m/z* 616 $[M]^+$.

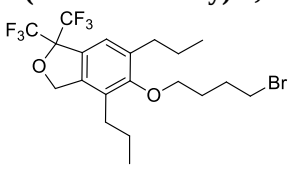
5-(4-(1-Methylethoxy)phenyl)-5-methyl-3-(4-((4-propyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzo-furan-5-yl)oxy)butyl)imidazolidine-2,4-dione (116):



Compound **116** was prepared from compounds **98** and **5** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (3H, t, *J* = 7.3 Hz), 1.25 (6H, d, *J* = 6.1 Hz), 1.46 (2H, qt, *J* = 7.3, 7.8 Hz), 1.67–1.77 (7H, m), 2.38 (2H, t, *J* = 7.8 Hz), 3.53 (2H, t, *J* = 6.4 Hz), 3.92 (2H, t, *J* = 5.6 Hz), 4.46 (1H, sept, *J* = 6.1 Hz), 5.21 (2H, s), 5.76 (1H, s), 6.76 (1H, d, *J* = 8.6 Hz), 6.80 (2H, d, *J* = 8.8 Hz), 7.20 (1H, d, *J* = 8.6 Hz), 7.29 (2H, d, *J* = 8.8 Hz); MS (EI) *m/z* 616 $[M]^+$.

Synthesis of the 1,3-dihydroisobenzofuran derivative with dipropyl group

5-(4-Bromobutoxy)-4,6-dipropyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran (99):



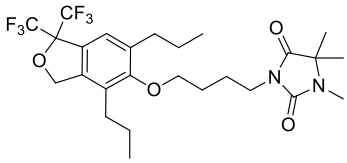
Compound **99** was prepared from compound **93** in a manner similar to that described for compound **98**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7.3 Hz), 0.97 (3H, t, *J* = 7.3 Hz), 1.58 (2H, qt, *J* = 7.3, 7.8 Hz), 1.69 (2H, qt, *J* = 7.3, 7.8 Hz), 1.91–2.01 (2H, m), 2.11–2.18 (2H, m), 2.48 (2H, t, *J* = 7.8 Hz), 2.61 (2H, t, *J* = 7.8 Hz), 3.53 (2H, t, *J* = 6.7 Hz), 3.83 (2H, t, *J* = 6.1 Hz), 5.27 (2H, s), 7.17 (1H, s); MS (EI) *m/z* 490 $[M]^+$.

Compounds **117~130** were prepared in the same manner as the synthesis of **102**.

Characterization data

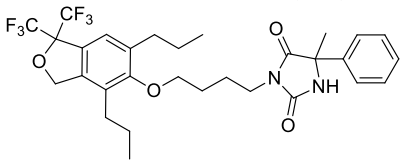
The NMR and MS data of compounds **117~130** are described below.

3-(4-((4,6-Dipropyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)butyl)-1,5,5-trimethyl-imidazolidine-2,4-dione (117):



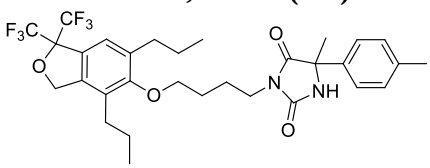
Compound **117** was prepared from compound **99** and 1,5,5-trimethylimidazolidine-2,4-dione in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92–0.97 (6H, m), 1.38 (6H, s), 1.52–1.66 (4H, m), 1.78–1.92 (4H, m), 2.47 (2H, t, *J* = 7.8 Hz), 2.59 (2H, t, *J* = 7.8 Hz), 2.90 (3H, s), 3.61 (2H, t, *J* = 6.8 Hz), 3.79 (2H, t, *J* = 6.1 Hz), 5.26 (2H, s), 7.15 (1H, s); MS (EI) *m/z* 552 $[M]^+$.

3-(4-((4,6-Dipropyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)butyl)-5-methyl-5-phenyl-imidazolidine-2,4-dione (118):



Compound **118** was prepared from compound **99** and 5-methyl-5-phenylimidazolidine-2,4-dione in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85–0.95 (6H, m), 1.48–1.68 (4H, m), 1.77–1.90 (7H, m), 2.44 (2H, t, *J* = 7.8 Hz), 2.57 (2H, t, *J* = 7.8 Hz), 3.62 (2H, t, *J* = 6.9 Hz), 3.76 (2H, t, *J* = 6.0 Hz), 5.25 (2H, s), 6.10 (1H, s), 7.14 (1H, s), 7.31–7.41 (3H, m), 7.48–7.51 (2H, m); MS (EI) *m/z* 600 $[M]^+$.

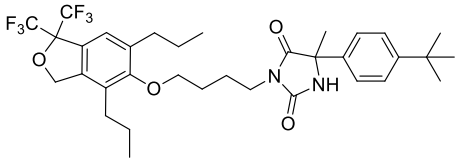
3-(4-((4,6-Dipropyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)butyl)-5-methyl-5-(*p*-tolyl)-imidazolidine-2,4-dione (119):



Compound **119** was prepared from compounds **99** and **42b** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–0.96 (6H, m), 1.46–1.68 (4H, m), 1.77–1.90 (7H, m), 2.33 (3H, s), 2.44 (2H, t, *J* = 7.8 Hz), 2.57 (2H, t, *J* = 7.8 Hz), 3.61 (2H, t, *J* = 6.6 Hz), 3.76 (2H, t, *J* = 6.2 Hz), 5.25 (2H, s), 6.13 (1H, s), 7.14 (1H, s), 7.19 (2H, d, *J* = 8.6 Hz), 7.37 (2H, d,

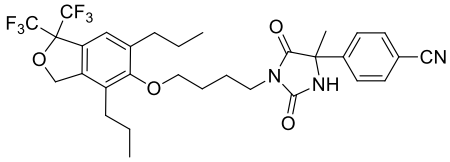
J = 8.6 Hz); MS (EI) *m/z* 614 $[M]^+$.

5-(4-(*tert*-Butyl)phenyl)-3-(4-((4,6-dipropyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)-butyl)-5-methylimidazolidine-2,4-dione (120):



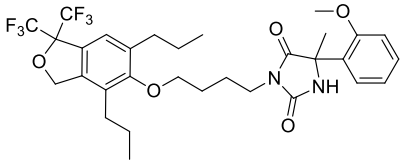
Compound **120** was prepared from compounds **99** and **42l** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–0.96 (6H, m), 1.30 (9H, s), 1.48–1.66 (4H, m), 1.77–1.91 (7H, m), 2.44 (2H, t, *J* = 7.7 Hz), 2.57 (2H, t, *J* = 8.1 Hz), 3.62 (2H, t, *J* = 7.3 Hz), 3.77 (2H, t, *J* = 5.9 Hz), 5.25 (2H, s), 5.62 (1H, s), 7.14 (1H, s), 7.39–7.41 (4H, m); MS (EI) *m/z* 656 $[M]^+$.

4-(1-(4-((4,6-Dipropyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)butyl)-4-methyl-2,5-dioxoimidazolidin-4-yl)benzonitrile (121):



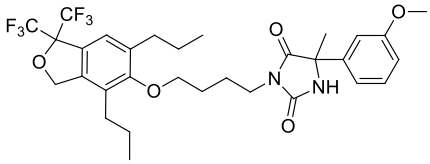
Compound **121** was prepared from compounds **99** and **42m** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87–0.95 (6H, m), 1.45–1.67 (4H, m), 1.76–1.91 (7H, m), 2.43 (2H, t, *J* = 7.8 Hz), 2.56 (2H, t, *J* = 7.8 Hz), 3.63 (2H, t, *J* = 6.8 Hz), 3.76 (2H, t, *J* = 5.9 Hz), 5.25 (2H, s), 6.08 (1H, s), 7.15 (1H, s), 7.64–7.67 (4H, m); MS (EI) *m/z* 625 $[M]^+$.

3-(4-((4,6-Dipropyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)butyl)-5-(2-methoxy-phenyl)-5-methylimidazolidine-2,4-dione (122):



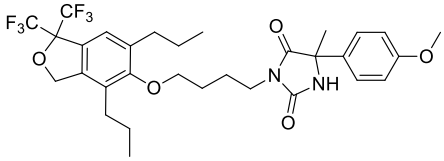
Compound **122** was prepared from compounds **99** and **42c** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90–0.97 (6H, m), 1.48–1.70 (4H, m), 1.83–1.94 (7H, m), 2.47 (2H, t, *J* = 8.0 Hz), 2.59 (2H, t, *J* = 7.8 Hz), 3.68 (2H, t, *J* = 6.8 Hz), 3.80 (2H, t, *J* = 5.9 Hz), 3.88 (3H, s), 5.27 (2H, s), 6.27 (1H, s), 6.92–6.98 (2H, m), 7.15 (1H, s), 7.33 (1H, ddd, *J* = 1.9, 8.4, 8.4 Hz), 7.51 (1H, dd, *J* = 1.9, 8.4 Hz); MS (EI) *m/z* 630 $[M]^+$.

3-(4-((4,6-Dipropyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)butyl)-5-(3-methoxy-phenyl)-5-methylimidazolidine-2,4-dione (123):



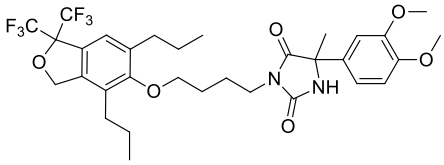
Compound **123** was prepared from compounds **99** and **42d** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90–0.97 (6H, m), 1.48–1.70 (4H, m), 1.83–1.94 (7H, m), 2.47 (2H, t, *J* = 8.0 Hz), 2.59 (2H, t, *J* = 7.8 Hz), 3.68 (2H, t, *J* = 6.8 Hz), 3.80 (2H, t, *J* = 5.9 Hz), 3.88 (3H, s), 5.27 (2H, s), 6.27 (1H, s), 6.92–6.98 (2H, m), 7.15 (1H, s), 7.33 (1H, ddd, *J* = 1.9, 8.4, 8.4 Hz), 7.51 (1H, dd, *J* = 1.9, 8.4 Hz); MS (EI) *m/z* 630 $[M]^+$.

3-(4-((4,6-Dipropyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)butyl)-5-(4-methoxy-phenyl)-5-methylimidazolidine-2,4-dione (124):



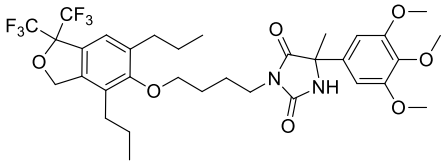
Compound **124** was prepared from compounds **99** and **42a** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–0.96 (6H, m), 1.48–1.65 (4H, m), 1.77–1.92 (7H, m), 2.44 (2H, t, *J* = 8.0 Hz), 2.57 (2H, t, *J* = 7.8 Hz), 3.62 (2H, t, *J* = 6.8 Hz), 3.76 (2H, t, *J* = 5.9 Hz), 3.81 (3H, s), 5.25 (2H, s), 5.66 (1H, s), 7.05 (2H, d, *J* = 8.6 Hz), 7.14 (1H, s), 7.29 (2H, d, *J* = 8.6 Hz); MS (EI) *m/z* 630 $[M]^+$.

5-(3,4-Dimethoxyphenyl)-3-(4-((4,6-dipropyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)-butyl)-5-methylimidazolidine-2,4-dione (125):



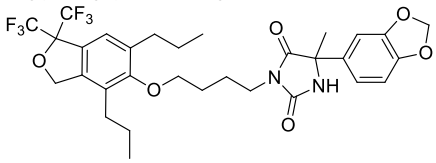
Compound **125** was prepared from compounds **99** and **42e** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–0.96 (6H, m), 1.49–1.68 (4H, m), 1.76–1.92 (7H, m), 2.44 (2H, t, *J* = 7.6 Hz), 2.57 (2H, t, *J* = 7.6 Hz), 3.63 (2H, t, *J* = 6.2 Hz), 3.77 (2H, t, *J* = 5.9 Hz), 3.87 (3H, s), 3.89 (3H, s), 5.26 (2H, s), 5.85 (1H, s), 6.85 (1H, d, *J* = 8.4 Hz), 7.00–7.04 (2H, m), 7.14 (1H, s); MS (EI) *m/z* 660 $[M]^+$.

3-(4-((4,6-Dipropyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)butyl)-5-methyl-5-(3,4,5-trimethoxyphenyl)imidazolidine-2,4-dione (126):



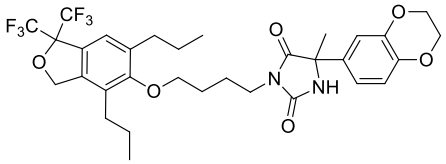
Compound **126** was prepared from compounds **99** and **42n** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.96 (6H, m), 1.49–1.68 (4H, m), 1.88–1.91 (7H, m), 2.45 (2H, t, *J* = 8.0 Hz), 2.58 (2H, t, *J* = 8.0 Hz), 3.63 (2H, t, *J* = 6.8 Hz), 3.78 (2H, t, *J* = 5.9 Hz), 3.83 (3H, s), 3.87 (6H, s), 5.26 (2H, s), 6.00 (1H, s), 6.71 (2H, s), 7.14 (1H, s); MS (EI) *m/z* 690 $[M]^+$.

5-(Benzo[*d*][1,3]dioxol-5-yl)-3-(4-((4,6-dipropyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)-oxy)butyl)-5-methylimidazolidine-2,4-dione (127):



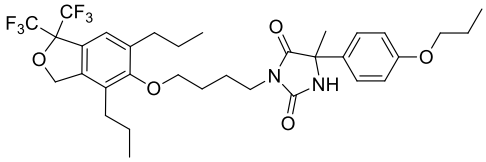
Compound **127** was prepared from compounds **99** and **42f** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.96 (6H, m), 1.48–1.66 (4H, m), 1.77–1.93 (7H, m), 2.44 (2H, t, *J* = 7.6 Hz), 2.57 (2H, t, *J* = 7.3 Hz), 3.62 (2H, t, *J* = 6.2 Hz), 3.76 (2H, t, *J* = 5.9 Hz), 5.26 (2H, s), 5.72 (1H, s), 5.97 (2H, s), 6.79 (1H, d, *J* = 8.1 Hz), 6.94 (1H, dd, *J* = 1.6, 8.1 Hz), 6.97 (1H, d, *J* = 1.6 Hz), 7.14 (1H, s); MS (EI) *m/z* 644 $[M]^+$.

5-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-(4-((4,6-dipropyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzo-furan-5-yl)oxy)butyl)-5-methylimidazolidine-2,4-dione (128):



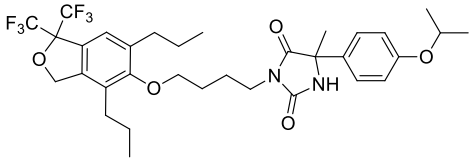
Compound **128** was prepared from compounds **99** and **42o** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.97 (6H, m), 1.49–1.68 (4H, m), 1.75–1.91 (7H, m), 2.44 (2H, t, *J* = 7.8 Hz), 2.57 (2H, t, *J* = 7.8 Hz), 3.61 (2H, t, *J* = 6.8 Hz), 3.77 (2H, t, *J* = 5.7 Hz), 4.24 (4H, s), 5.26 (2H, s), 5.73 (1H, s), 6.84–6.95 (2H, m) , 6.99 (1H, d, *J* = 1.9 Hz), 7.14 (1H, s); MS (EI) *m/z* 658 $[M]^+$.

3-(4-((4,6-Dipropyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)butyl)-5-methyl-5-(4-propoxyphenyl)imidazolidine-2,4-dione (129):



Compound **129** was prepared from compounds **99** and **42p** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85–0.97 (6H, m), 1.02 (3H, t, *J* = 7.6 Hz), 1.45–1.66 (6H, m), 1.70–1.85 (7H, m), 2.43 (2H, t, *J* = 7.6 Hz), 2.56 (2H, t, *J* = 7.6 Hz), 3.61 (2H, t, *J* = 6.9 Hz), 3.76 (2H, t, *J* = 5.6 Hz), 3.88 (2H, q, *J* = 6.6 Hz), 5.25 (2H, s), 5.79 (1H, s), 6.88 (2H, d, *J* = 8.9 Hz), 7.13 (1H, s), 7.37 (2H, d, *J* = 8.9 Hz); MS (EI) *m/z* 630 $[M]^+$.

3-(4-((4,6-Dipropyl-1,1-bis(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl)oxy)butyl)-5-(4-(1-methyl-ethoxy)phenyl)-5-methylimidazolidine-2,4-dione (130):



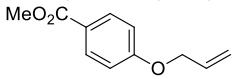
Compound **130** was prepared from compounds **99** and **5** in a manner similar to that described for compound **102**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–0.97 (6H, m), 1.41 (6H, d, *J* = 5.9 Hz), 1.48–1.66 (4H, m), 1.73–1.88 (7H, m), 2.44 (2H, t, *J* = 7.6 Hz), 2.57 (2H, t, *J* = 7.6 Hz), 3.61 (2H, t, *J* = 6.6 Hz), 3.76 (2H, t, *J* = 5.6 Hz), 4.52 (1H, septet, *J* = 5.9 Hz), 5.25 (2H, s), 5.76 (1H, s), 6.87 (2H, d, *J* = 8.9 Hz), 7.14 (1H, s), 7.36 (2H, d, *J* = 8.9 Hz); MS (EI) *m/z* 658 $[M]^+$.

Section-3

Chemical Experimental Details

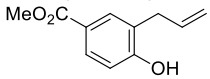
Scheme 15

Methyl 4-(allyloxy)benzoate (132) [85]**:**



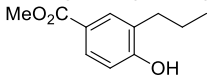
To a stirred suspension of methyl 4-hydroxybenzoate (**131**) (15 g, 0.10 mol) and K_2CO_3 (21 g, 0.15 mol) in DMF (40 mL), allyl chloride (12 g, 0.15 mol) was slowly added at room temperature. The reaction mixure was stirred at 50 °C for 18 h, and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to obtain the title compound (19 g, 99%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (3H, s), 4.55 (2H, ddd, *J* = 1.6, 1.6, 5.3 Hz), 5.29 (1H, ddd, *J* = 1.6, 3.0, 10.6 Hz), 5.41 (1H, ddd, *J* = 1.6, 3.0, 17.5 Hz), 6.02 (1H, ddd, *J* = 5.3, 10.6, 17.5 Hz), 6.90 (2H, d, *J* = 8.9 Hz), 7.97 (2H, d, *J* = 8.9 Hz); MS (EI) m/z 192 $[M]^+$.

Methyl 3-allyl-4-hydroxybenzoate (133) [85]**:**



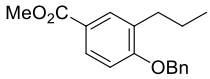
A stirred solution of **132** (19 g, 0.10 mol) in *N*,*N*-dimethylaniline (40 mL) was heated at 210 °C for 18 h. The reaction mixture was allowed to cool to room temperature and then diluted with 1 N HCl, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to obtain the title compound (12 g, 64%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (2H, d, *J* = 6.2 Hz), 3.89 (3H, s), 5.13 (1H, d, *J* = 3.6 Hz), 5.18 (1H, s), 5.93–6.17 (2H, m), 6.85 (1H, d, *J* = 8.9 Hz), 7.78–7.88 (2H, m); MS (EI) *m/z* 192 $[M]^+$.

Methyl 4-hydroxy-3-propylbenzoate (134) [85]**:**



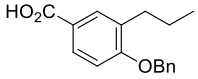
A suspension of **133** (12 g, 0.63 mol) and 10% Pd/C (608 mg) in MeOH (50 mL) was stirred under a hydrogen atmosphere at room temperature for 24 h. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/1) to obtain the title compound (11 g, 88%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7.6 Hz), 1.65 (2H, qt, *J* = 7.6, 7.6 Hz), 2.61 (2H, t, *J* = 7.6 Hz), 3.89 (3H, s), 4.16 (1H, brs), 6.82 (1H, d, *J* = 8.6 Hz), 7.78 (1H, dd, *J* = 2.0, 8.6 Hz) 7.83 (1H, d, *J* = 2.0 Hz); MS (EI) *m/z* 194 $[M]^+$.

Methyl 4-(benzyloxy)-3-propylbenzoate (135) [85]**:**



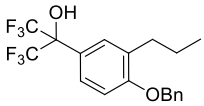
To a stirred suspension of **134** (7.0 g, 36 mmol) and K_2CO_3 (21 g, 0.15 mol) in DMF (20 mL), benzyl bromide (12 g, 0.15 mol) was slowly added at 0 °C. The reaction mixture was stirred at 80 °C for 2 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (10 g, 99%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.6 Hz), 1.66 (2H, qt, *J* = 7.6, 7.6 Hz), 2.67 (2H, t, *J* = 7.6 Hz), 3.86 (3H, s), 5.11 (2H, s), 6.88 (1H, d, *J* = 9.2 Hz), 7.27–7.43 (5H, m) 7.83–7.88 (2H, m); MS (EI) *m/z* 284 $[M]^+$.

4-(Benzyloxy)-3-propylbenzoic acid (136) [85]**:**



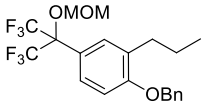
To a solution of **135** (6.8 g, 24 mmol) in EtOH (100 mL), 2 N NaOH *aq*. (30 mL) was added at 0 °C. The reaction mixture was stirred at 50 °C for 2 h and then concentrated *in vacuo*. The residue was acidified with 1 N HCl and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was recrystallized from a mixture of sovents (hexane/ EtOAc = 3/1) to give the title compound (6.4 g, 98%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.6 Hz), 1.65 (2H, qt, *J* = 7.6, 7.6 Hz), 2.68 (2H, t, *J* = 7.6 Hz), 5.09 (2H, s), 6.93 (1H, d, *J* = 9.2 Hz), 7.31–7.49 (7H, m); MS (EI) *m/z* 270 $[M]^+$.

2-(4-(Benzyloxy)-3-propylphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (138):



To the compound **136** (6.3 g, 24 mmol), thionyl chloride (6.3 mL) was added at 0 °C. The reaction mixture was stirred at 70 °C for 2 h and then concentrated *in vacuo*. The residue was diluted with dimethoxyethane (20 mL). To this solution, $TMSCF_3$ (7.4 g, 52 mmol) and Me_4NF (4.8 g, 52 mmol) were added under an argon atmosphere at −78 °C. The reaction mixture was allowed to warm to room temperature for 18 h, following which 1 N HCl was added to the reaction mixture. The reaction mixture was extracted with EtOAc. The organic layer was washed with a saturated $NaHCO_3$ *aq*. and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (6.6 g, 72% for 2 steps) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.6 Hz), 1.65 (2H, qt, *J* = 7.6, 7.6 Hz), 2.68 (2H, t, *J* = 7.6 Hz), 3.39 (1H, s), 5.10 (2H, s), 6.93 (1H, dd, *J* = 2.3, 7.3 Hz), 7.30–7.51 (7H, m); MS (EI) *m/z* 392 $[M]^+$.

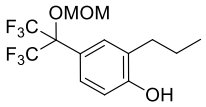
1-(Benzyloxy)-4-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylbenzene (139):



To a stirred solution of **138** (264 mg, 0.67 mmol) in THF (5 mL), sodium hydride (39 mg, 50% in oil, 0.81 mmol)

was added at 0 °C, and then successively MOMCl (65 mg, 0.81 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 18 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (265 mg, 90%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.6 Hz), 1.65 (2H, qt, *J* = 7.6, 7.6 Hz), 2.68 (2H, t, *J* = 7.6 Hz), 3.54 (3H, s), 4.83 (2H, s), 5.10 (2H, s), 6.93 (1H, d, *J* = 8.9 Hz), 7.29–7.44 (7H, m); MS (EI) *m/z* 436 $[M]^+$.

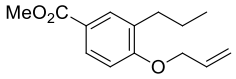
4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenol (140):



A suspension of **139** (265 mg, 0.61 mmol) and 10% Pd/C (30 mg) in MeOH (10 mL) was stirred under a hydrogen atmosphere at room temperature for 24 h. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to give the title compound (221 mg, 99%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.6 Hz), 1.62 (2H, qt, *J* = 7.6, 7.6 Hz), 2.60 (2H, t, *J* = 7.6 Hz), 3.56 (3H, s), 4.84 (2H, s), 5.77 (1H, brs), 6.81 (1H, d, *J* = 8.6 Hz), 7.30 (1H, d, *J* = 8.6 Hz) 7.33 (1H, s); MS (EI) *m/z* 346 $[M]^+$.

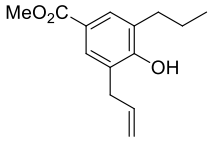
Scheme 16

Methyl 4-(allyloxy)-3-propylbenzoate:



To a stirred suspension of **134** (5.5 g, 28 mmol) and K_2CO_3 (5.9 g, 43 mmol) in DMF (55 mL), allyl chloride (3.3 g, 43 mmol) was slowly added at 0 °C. The reaction mixure was stirred at 50 °C for 18 h, and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to obtain the title compound (6.2 g, 94%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 1.64 (2H, qt, *J* = 7.3, 7.6 Hz), 2.64 (2H, t, *J* = 7.6 Hz), 3.87 (3H, s), 4.59 (2H, d, *J* = 4.6 Hz), 5.29 (1H, dd, *J* = 1.4, 10.5 Hz), 5.42 (1H, dd, *J* = 1.4, 17.4 Hz), 5.98–6.12 (1H, m), 6.82 (1H, d, *J* = 8.4 Hz), 7.83 (1H, s), 7.85 (1H, d, *J* = 8.4 Hz); MS (EI) *m/z* 234 $[M]^+$.

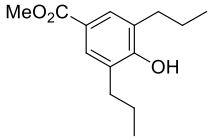
Methyl 3-allyl-4-hydroxy-5-propylbenzoate:



A stirred solution of methyl 4-(allyloxy)-3-propylbenzoate (6.2 g, 27 mmol) in *N*,*N*-dimethylaniline (60 mL) was heated at 210 °C for 18 h. The reaction mixture was allowed to cool to room temperature and then diluted with 1 N HCl, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to obtain the title

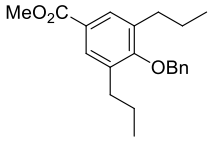
compound (6.1 g, 98%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, *J* = 7.3 Hz), 1.65 (2H, qt, *J* = 7.3, 7.6 Hz), 2.61 (2H, t, *J* = 7.6 Hz), 3.44 (2H, d, *J* = 6.2 Hz), 3.87 (3H, s), 5.16–5.18 (1H, m), 5.62 (1H, brs), 5.94–6.08 (1H, m), 7.69 (1H, d, *J* = 1.9 Hz), 7.74 (1H, d, *J* = 1.9 Hz); MS (EI) *m/z* 234 $[M]^+$.

Methyl 4-hydroxy-3,5-dipropylbenzoate (141):



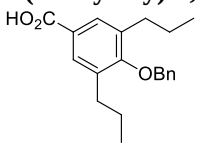
A suspension of methyl 3-allyl-4-hydroxy-5-propylbenzoate (6.0 g, 26 mmol) and 10% Pd/C (602 mg) in MeOH (60 mL) was stirred under a hydrogen atmosphere at room temperature for 24 h. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo.* The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/1) to obtain the title compound (6.1 g, 99%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (6H, t, *J* = 7.3 Hz), 1.66 (4H, qt, *J* = 7.3, 7.8 Hz), 2.60 (4H, t, *J* = 7.8 Hz), 3.87 (3H, s), 5.33 (1H, brs), 7.70 (2H, s); MS (EI) *m/z* 236 $[M]^+$.

Methyl 4-(benzyloxy)-3,5-dipropylbenzoate (142):



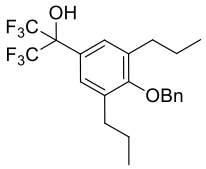
To a stirred suspension of **141** (5.0 g, 21 mmol) and K_2CO_3 (4.4 g, 32 mmol) in DMF (50 mL), benzyl bromide (5.4 g, 32 mmol) was slowly added at 0 °C. The reaction mixure was stirred at 70 °C for 2 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to obtain the title compound (6.9 g, 99%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (6H, t, *J* = 7.3 Hz), 1.67 (4H, qt, *J* = 7.3, 7.8 Hz), 2.65 (4H, t, *J* = 7.8 Hz), 3.87 (3H, s), 4.81 (2H, s), 7.34–7.48 (5H, m), 7.76 (2H, s); MS (EI) *m/z* 326 $[M]^+$.

4-(Benzyloxy)-3,5-dipropylbenzoic acid (143) [86]:



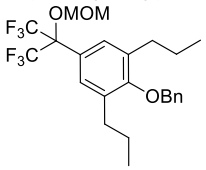
To a solution of **142** (6.9 g, 21 mmol) in EtOH (70 mL), 2 N NaOH *aq*. (30 ml) was added at 0 °C. The reaction mixture was refluxed for 2 h and then concentrated *in vacuo*. The residue was acidified with 1 N HCl and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was solidified from hexane and EtOAc to give the title compound (5.4 g, 82%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (6H, t, *J* = 7.3 Hz), 1.69 (4H, qt, *J* = 7.3, 7.8 Hz), 2.67 (4H, t, *J* = 7.8 Hz), 4.85 (2H, s), 7.36–7.49 (5H, m), 7.85 (2H, s); MS (EI) *m/z* 312 $[M]^+$.

2-(4-(Benzyloxy)-3,5-dipropylphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (145):



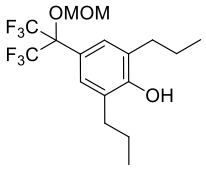
To the compound **143** (3.7 g, 12 mmol), thionyl chloride (3.7 mL) was added at 0 °C. The reaction mixture was stirred at 70 °C for 2 h and then concentrated *in vacuo*. The residue was dissolved in DME (20 mL). To this stirred solution, $TMSCF_3$ (3.7 g, 26 mmol) and *n*-Bu_4NF (2.5 g, 26 mmol) was added under an argon atmosphere at −78 °C. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 20 h, following which 1 N HCl (20 mL) was added to the reaction mixture. The reaction mixture was extracted with EtOAc. The organic layer was washed with a saturated $NaHCO_3$ *aq.* and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (5.0 g, 67%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (6H, t, *J* = 7.3 Hz), 1.66 (4H, qt, *J* = 7.3, 7.6 Hz), 2.66 (4H, t, *J* = 7.6 Hz), 3.38 (1H, brs), 4.84 (2H, s), 7.33–7.47 (7H, m); MS (EI) *m/z* 434 $[M]^+$.

2-(Benzyloxy)-5-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-1,3-dipropylbenzene (146):



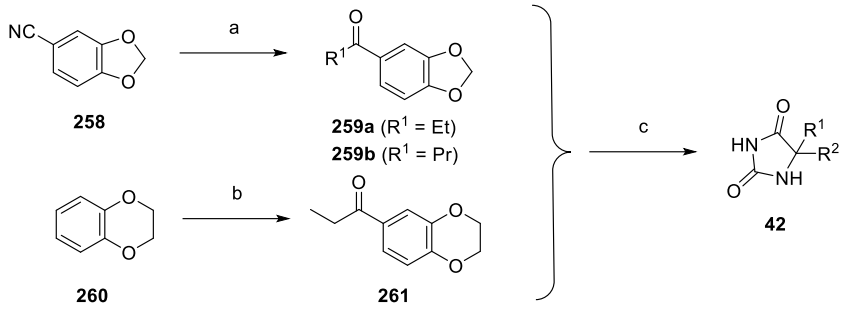
To a stirred solution of **145** (2.3 g, 5.2 mmol) in THF (5.0 mL), NaH (50% in oil, 300 mg, 6.2 mmol) was added at 0 °C and successively MOMCl (503 mg, 6.2 mmol) at the same temperature. The reaction mixture was stirred at room temperature for 22 h, and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane/EtOAc = 10/1) to give the title compound (2.2 g, 89%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (6H, t, *J* = 7.3 Hz), 1.66 (4H, qt, *J* = 7.3, 7.6 Hz), 2.65 (4H, t, *J* = 7.6 Hz), 3.57 (3H, s), 4.83 (4H, s), 7.27 (2H, s), 7.36–7.49 (5H, m); MS (EI) *m/z* 478 $[M]^+$.

4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2,6-dipropylphenol (147):



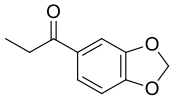
A suspension of **146** (2.2 g, 4.6 mmol) and 10% Pd/C (220 mg) in MeOH (20 mL) was stirred under a hydrogen atmosphere at room temperature for 24 h. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to give the title compound (1.6 g, 90%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (6H, t, *J* = 7.6 Hz), 1.64 (4H, qt, *J* = 7.6, 7.6 Hz), 2.59 (4H, t, *J* = 7.6 Hz), 3.54 (3H, s), 4.83 (2H, s), 4.88 (1H, s), 7.19 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (2C), 22.6 (2C), 32.2 (2C), 57.0, 82.3 (septet, *J* = 28.6 Hz), 93.6, 119.1, 122.6 (q, *J* = 289.3 Hz) (2C), 127.8 (2C), 127.9 (2C), 153.0; MS (EI) *m/z* 388 $[M]^+$.

Synthetic procedure of the ketone derivatives



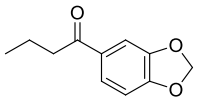
Scheme 41. Reagents and conditions: (a) EtMgBr or PrMgBr, THF, 0 °C, 2 h, then HCl, rt, 1 h, 58–63%; (b) $(CH_3CH_2CO)_2O$, $AlCl_3$, CH_2Cl_2, 0 °C to rt, 30 min, 90%; (c) NaCN, $(NH_4)_2CO_3$, EtOH *aq.*, 100 °C, 50–85%.

1-(Benzo[*d*][1,3]dioxol-5-yl)propan-1-one (259a) [87)]:



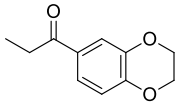
To a stirred solution of benzo[*d*][1,3]dioxole-5-carbonitrile (**258**) (1.5 g, 10 mmol) in THF (20 mL), EtMgBr (0.97 M in THF solution, 31 mL, 30 mmol) was added dropwise under an argon atmosphere at 0 °C. The reaction mixture was stirred 0 °C for 2 h. To the reaction mixture was added 1 N HCl (20 mL). Then, the reaction mixture was neutralized with saturated $NaHCO_3$ *aq.* at 0 °C. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (1.1 g, 63%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, t, *J* = 7.3 Hz), 2.93 (2H, q, *J* = 7.3 Hz), 6.04 (2H, s), 6.85 (1H, d, *J* = 8.1 Hz), 7.45 (1H, d, *J* = 1.7 Hz), 7.57 (1H, dd, *J* = 1.7, 8.1 Hz); MS (EI) *m/z* 192 $[M]^+$

1-(Benzo[*d*][1,3]dioxol-5-yl)butan-1-one (259b) [88)]:



Compound **259b** was prepared from compound **258** in a manner similar to that described for compound **259a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, *J* = 7.6 Hz), 1.75 (2H, tq, *J* = 7.2, 7.6 Hz), 2.87 (2H, t, *J* = 7.2 Hz), 6.04 (2H, s), 6.85 (1H, d, *J* = 8.4 Hz), 7.44 (1H, d, *J* = 1.6 Hz), 7.57 (1H, dd, *J* = 1.6, 8.4 Hz); MS (EI) *m/z* 192 $[M]^+$

1-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)propan-1-one (261) [89)]:



To a stirred solution of **260** (1.0 g, 7.3 mmol) in CH_2Cl_2 (10 mL), aluminum chloride (3.2 g, 24 mmol) was added at 0 °C and successively propionic anhydride (1.2 g, 8.8 mmol). The reaction mixture was stirred at room

temperature for 30 min and then diluted with saturated $NaHCO_3$ *aq.* and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/1) to give the title compound (1.3 g, 90%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, t, *J* = 7.3 Hz), 2.93 (2H, q, *J* = 7.3 Hz), 4.27–4.33 (4H, m), 6.45 (1H, d, *J* = 8.1 Hz), 7.05 (1H, d, *J* = 1.7 Hz), 7.17 (1H, dd, *J* = 1.7, 8.1 Hz); MS (EI) *m/z* 192 $[M]^+$.

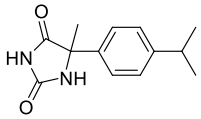
Synthetic procedure of the hydantoin derivatives

Compounds **42q~z** were prepared in the same manner as the synthesis of **42a**.

Characterization data

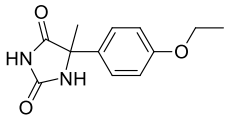
The NMR and MS data of compounds **42q~z** are described below.

5-(4-Isopropylphenyl)-5-methylimidazolidine-2,4-dione (42q):



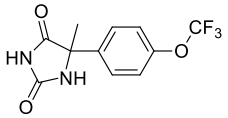
Compound **42q** was prepared from 1-(4-isopropylphenyl)ethan-1-one in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.18 (6H, d, *J* = 6.8 Hz), 1.63 (3H, s), 2.87 (1H, sept, *J* = 6.8 Hz), 7.25 (2H, d, *J* = 8.4 Hz), 7.37 (2H, d, *J* = 8.4 Hz), 8.54 (1H, s), 10.7 (1H, s); MS (EI) *m/z* 232 $[M]^+$.

5-(4-Ethoxyphenyl)-5-methylimidazolidine-2,4-dione (42r):



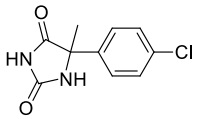
Compound **42r** was prepared from 1-(4-hydroxyphenyl)ethan-1-one in a manner similar to that described for compounds **7** and **42a**. The title compound was obtained as a white solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.31 (3H, d, *J* = 7.3 Hz), 1.61 (3H, s), 4.02 (2H, q, *J* = 7.3 Hz), 6.92 (2H, d, *J* = 7.8 Hz), 7.34 (2H, d, *J* = 7.8 Hz), 8.55 (1H, s), 10.7 (1H, s); MS (EI) *m/z* 234 $[M]^+$.

5-Methyl-5-(4-(trifluoromethoxy)phenyl)imidazolidine-2,4-dione (42s):



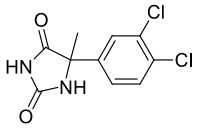
Compound **42s** was prepared from 1-(4-(trifluoromethoxy)phenyl)ethan-1-one in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.62 (3H, s), 6.94 (2H, d, *J* = 7.8 Hz), 7.36 (2H, d, *J* = 7.8 Hz), 8.55 (1H, s), 10.7 (1H, s); MS (EI) *m/z* 274 $[M]^+$.

5-(4-Chlorophenyl)-5-methylimidazolidine-2,4-dione (42t):



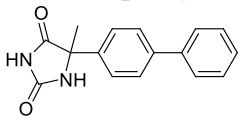
Compound **42t** was prepared from 1-(4-chlorophenyl)ethan-1-one in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.64 (3H, s), 7.43 (2H, d, *J* = 8.6 Hz), 7.61 (2H, d, *J* = 8.6 Hz), 8.67 (1H, s), 10.8 (1H, s); MS (EI) *m/z* 224 [M]$^+$.

5-(3,4-Dichlorophenyl)-5-methylimidazolidine-2,4-dione (42u):



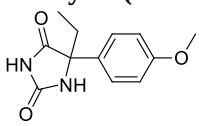
Compound **42u** was prepared from 1-(3,4-dichlorophenyl)ethan-1-one in a manner similar to that described for compound **42a**. The title compound was obtained as a colorless amorphous solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.65 (3H, s), 7.48 (1H, dd, *J* = 2.3, 8.6 Hz), 7.67–7.70 (2H, m), 8.70 (1H, s), 10.9 (1H, s); MS (EI) *m/z* 258 [M]$^+$.

5-([1,1'-Biphenyl]-4-yl)-5-methylimidazolidine-2,4-dione (42v):



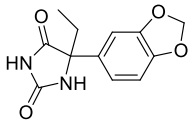
Compound **42v** was prepared from 1-([1,1'-biphenyl]-4-yl)ethan-1-one in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.69 (3H, s), 7.37–7.71 (9H, m), 8.67 (1H, s), 10.8 (1H, s); MS (EI) *m/z* 266 [M]$^+$.

5-Ethyl-5-(4-methoxyphenyl)imidazolidine-2,4-dione (42w):



Compound **42w** was prepared from 1-(4-methoxyphenyl)propan-1-one in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.80 (3H, t, *J* = 7.3 Hz), 1.79–1.92 (1H, m), 1.96–2.10 (1H, m), 3.74 (3H, s), 6.94 (2H, d, *J* = 8.4 Hz), 7.39 (2H, d, *J* = 8.4 Hz), 8.58 (1H, s), 10.7 (1H, s); MS (EI) *m/z* 234 [M]$^+$.

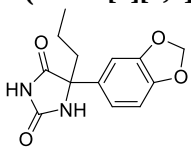
5-(Benzo[*d*][1,3]dioxol-5-yl)-5-ethylimidazolidine-2,4-dione (42x):



Compound **42x** was prepared from compound **259a** in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.81 (3H, t, *J* = 7.3 Hz), 1.78–1.93 (1H, m), 1.96–2.12 (1H, m), 6.02 (2H, s), 6.90 (1H, d, *J* = 8.4 Hz), 6.94 (1H, dd, *J* = 1.4, 8.4 Hz), 6.99

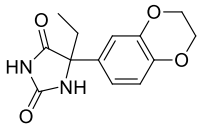
(1H, d, J = 1.4 Hz), 8.56 (1H, s), 10.7 (1H, s); MS (EI) *m/z* 248 $[M]^+$.

5-(Benzo[*d*][1,3]dioxol-5-yl)-5-propylimidazolidine-2,4-dione (42y):



Compound **42y** was prepared from compound **259b** in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^{1}H NMR (400 MHz, CD_3OD) δ 0.80 (3H, t, J = 7.3 Hz), 1.78–1.93 (2H, m), 1.96–2.12 (2H, m), 6.03 (2H, s), 6.89 (1H, d, J = 8.4 Hz), 6.93 (1H, dd, J = 1.4, 8.4 Hz), 6.98 (1H, d, J = 1.4 Hz), 8.56 (1H, s), 10.7 (1H, s); MS (EI) *m/z* 262 $[M]^+$.

5-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-ethylimidazolidine-2,4-dione (42z):

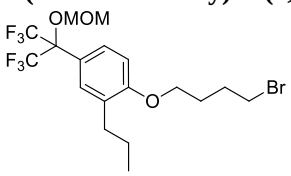


Compound **42z** was prepared from compound **261** in a manner similar to that described for compound **42a**. The title compound was obtained as a white solid; ^{1}H NMR (400 MHz, CD_3OD) δ 0.90 (3H, t, J = 7.3 Hz), 1.91–2.00 (1H, m), 2.09–2.18 (1H, m), 4.23 (4H, s), 6.60 (1H, d, J = 8.6 Hz), 6.96 (1H, dd, J = 2.3, 8.6 Hz), 7.00 (1H, d, J = 2.3 Hz); MS (EI) *m/z* 262 $[M]^+$.

Scheme 17

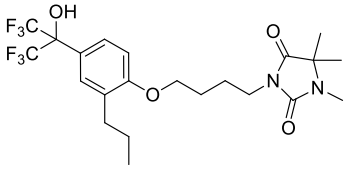
Synthesis of the trifluoromethylcarbinol derivative with propyl group

1-(4-Bromobutoxy)-4-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylbenzene (148):



To a stirred suspension of **140** (221 mg, 0.64 mmol) and K_2CO_3 (132 mg, 0.96 mmol) in DMF (20 mL), 1,4-dibromobutane (1.4 g, 6.4 mmol) was slowly added at room temperature. The reaction mixture was stirred at room temperature for 18 h, and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 50/1) to give the title compound (220 mg, 71%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.6 Hz), 1.59 (2H, qt, J = 7.6, 7.6 Hz), 1.92–2.13 (4H, m), 2.61 (2H, t, J = 7.6 Hz), 3.51 (2H, t, J = 6.3 Hz), 3.55 (3H, s), 4.02 (2H, t, J = 5.9 Hz), 4.83 (2H, s), 6.85 (1H, d, J = 8.8 Hz), 7.34 (1H, s), 7.39 (1H, d, J = 8.8 Hz); MS (EI) *m/z* 480 $[M]^+$.

3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-1,5,5-trimethylimidazolidine-2,4-dione (152):



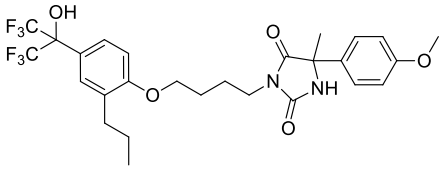
To a stirred suspension of 1,5,5-trimethylimidazolidine-2,4-dione (25 mg, 0.15 mmol) and K_2CO_3 (31 mg, 0.23 mmol) in DMF (1.0 mL), a solution of **148** (70 mg, 0.15 mmol) in DMF (100 μL) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 16 h and then diluted with water at 0 °C and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/2) to give the product **149** (79 mg, 99%) as a colorless oil. Subsequently, to a stirred solution of the obtained product **149** (5.7 mg, 0.11 mmol) in MeOH (100 mL), 2 N HCl in EtOH (2 mL) was slowly added at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to obtain the title compound (42 mg, 82%) as a colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.6 Hz), 1.33 (6H, s), 1.58 (2H, qt, *J* = 7.6, 7.6 Hz), 1.76–1.85 (4H, m), 2.59 (2H, t, *J* = 7.6 Hz), 2.88 (3H, s), 3.58 (2H, t, *J* = 6.3 Hz), 3.93 (1H, brs), 3.99 (2H, t, *J* = 5.6 Hz), 6.83 (1H, d, *J* = 8.9 Hz), 7.42 (1H, s), 7.46 (1H, d, *J* = 8.9 Hz); MS (EI) *m/z* 498 $[M]^+$.

Compounds **153**, **156~176** were prepared in the same manner as the synthesis of **152**.

Characterization data

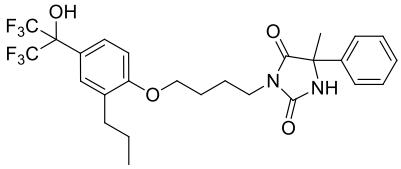
The NMR and MS data of compounds **153**, **156~176** are described below.

3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-5-(4-methoxyphenyl)-5-methylimidazolidine-2,4-dione (153):



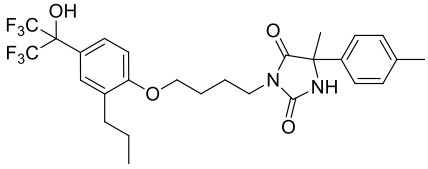
Compound **153** was prepared from compounds **148** and **42a** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.3 Hz), 1.50–1.63 (2H, m), 1.76–1.87 (7H, m), 2.57 (2H, t, *J* = 7.6 Hz), 3.59 (2H, t, *J* = 6.2 Hz), 3.78–3.82 (4H, m), 3.96 (2H, t, *J* = 5.7 Hz), 6.00 (1H, s), 6.80 (1H, d, *J* = 8.4Hz), 6.84–6.88 (1H, m), 7.03–7.06 (2H, m), 7.27–7.32 (1H, m), 7.42–7.46 (2H, m); MS (EI) *m/z* 576 $[M]^+$.

3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-5-methyl-5-phenyl-imidazolidine-2,4-dione (156):



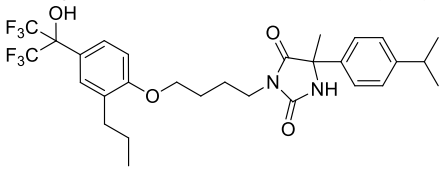
Compound **156** was prepared from compound **148** and 5-methyl-5-phenylimidazolidine-2,4-dione in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.3 Hz), 1.49–1.63 (2H, m), 1.72–1.92 (7H, m), 2.57 (2H, t, *J* = 7.6 Hz), 3.59 (2H, t, *J* = 6.5 Hz), 3.78 (1H, s), 3.96 (2H, t, *J* = 5.8 Hz), 6.05 (1H, s), 6.80 (1H, d, *J* = 8.4 Hz), 7.30–7.50 (7H, m); MS (EI) *m/z* 546 $[M]^+$.

3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-5-methyl-5-(*p*-tolyl)-imidazolidine-2,4-dione (157):



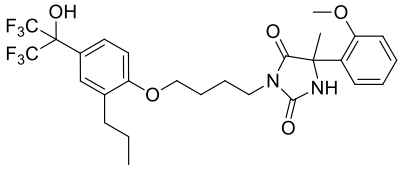
Compound **157** was prepared from compounds **148** and **42b** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.3 Hz), 1.52–1.61 (2H, m), 1.75–1.85 (7H, m), 2.33 (3H, s), 2.55–2.60 (2H, m), 2.57 (2H, t, *J* = 7.6 Hz), 3.59 (2H, t, J = 6.5 Hz), 3.67 (1H, s), 3.96 (2H, t, *J* = 5.7 Hz), 5.79 (1H, s), 6.81 (1H, d, *J* = 8.6 Hz), 7.18 (2H, d, *J* = 8.4 Hz), 7.35 (2H, d, *J* = 8.4 Hz), 7.42–7.47 (2H, m); MS (EI) *m/z* 560 $[M]^+$.

3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-5-(4-isopropylphenyl)-5-methylimidazolidine-2,4-dione (158):



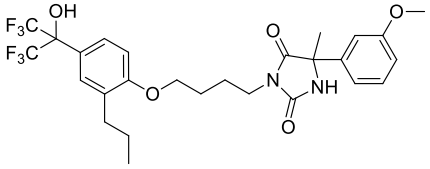
Compound **158** was prepared from compounds **148** and **42q** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.3 Hz), 1.23 (6H, d, *J* = 7.0 Hz), 1.53–1.64 (2H, m), 1.77–1.87 (7H, m), 2.58 (2H, t, *J* = 7.7 Hz), 2.90 (1H, sept, *J* = 7.0 Hz), 3.57–3.61 (3H, m), 3.98 (2H, t, *J* = 5.7 Hz), 5.75 (1H, s), 6.82 (1H, d, J = 8.9 Hz), 7.24 (2H, d, *J* = 8.4 Hz), 7.38 (2H, d, *J* = 8.4 Hz), 7.42–7.47 (2H, m); MS (EI) *m/z* 588 $[M]^+$.

3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-5-(2-methoxyphenyl)-5-methylimidazolidine-2,4-dione (159):



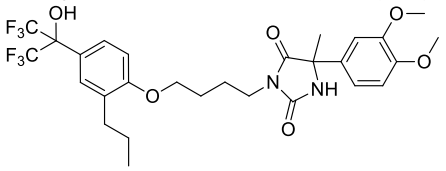
Compound **159** was prepared from compounds **148** and **42c** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.3 Hz), 1.52–1.66 (2H, m), 1.76 (3H, s), 1.85–1.87 (4H, m), 2.60 (2H, t, *J* = 7.4 Hz), 3.64–3.69 (3H, m), 3.86 (3H, s), 4.01 (2H, t, *J* = 5.4 Hz), 6.25 (1H, s), 6.83 (1H, d, *J* = 8.6 Hz), 6.92–6.97 (3H, m), 7.29–7.52 (3H, m); MS (EI) *m/z* 576 $[M]^+$.

3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-5-(3-methoxyphenyl)-5-methylimidazolidine-2,4-dione (160):



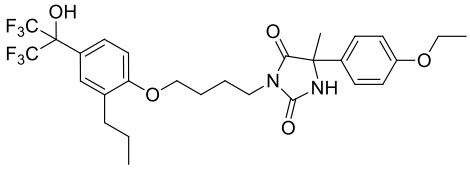
Compound **160** was prepared from compounds **148** and **42d** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.3 Hz), 1.57 (2H, qt, *J* = 7.3, 7.6 Hz), 1.78–1.84 (7H, m), 2.58 (2H, t, *J* = 7.6 Hz), 3.48 (1H, s), 3.60 (2H, t, *J* = 6.2 Hz), 3.80 (3H, s), 3.97 (2H, t, *J* = 5.9 Hz), 5.74 (1H, s), 6.81 (1H, d, *J* = 8.6 Hz), 6.87 (1H, dd, *J* = 2.4, 7.6 Hz), 7.02–7.06 (2H, m), 7.27–7.33 (1H, m), 7.41 (1H, s), 7.45 (1H, d, *J* = 8.6 Hz); MS (EI) *m/z* 576 $[M]^+$.

5-(3,4-Dimethoxyphenyl)-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-5-methylimidazolidine-2,4-dione (161):



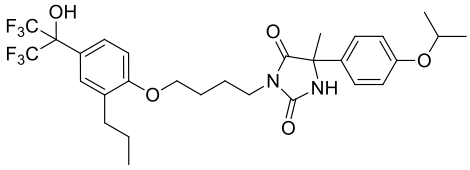
Compound **161** was prepared from compounds **148** and **42e** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.8 Hz), 1.50–1.63 (2H, m), 1.72–1.88 (7H, m), 2.57 (2H, t, *J* = 7.6 Hz), 3.60 (2H, t, *J* = 6.5 Hz), 3.75 (1H, s), 3.86 (3H, s), 3.87 (3H, s), 3.97 (2H, t, *J* = 5.7 Hz), 5.90 (1H, s), 6.80 (1H, d, J = 8.6 Hz), 6.85 (1H, d, *J* = 8.1 Hz), 7.00–7.03 (2H, m), 7.42–7.46 (2H, m); MS (EI) *m/z* 606 $[M]^+$.

5-(4-Ethoxyphenyl)-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-5-methylimidazolidine-2,4-dione (162):



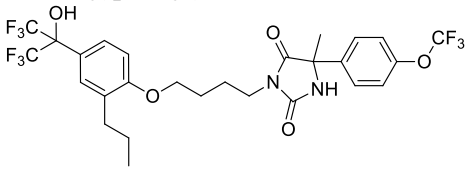
Compound **162** was prepared from compounds **148** and **42r** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.3 Hz), 1.40 (3H, t, *J* = 7.3 Hz), 1.50–1.63 (2H, m), 1.73–1.90 (7H, m), 2.57 (2H, t, *J* = 7.6 Hz), 3.59 (2H, t, *J* = 6.6 Hz), 3.74 (1H, s), 3.94–4.02 (4H, m), 5.84 (1H, s), 6.80 (1H, d, *J* = 8.6 Hz), 6.87 (2H, d, *J* = 8.9 Hz), 7.36 (2H, d, *J* = 8.9 Hz), 7.42–7.46 (2H, m); MS (EI) *m/z* 590 $[M]^+$.

3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-5-(4-(1-methylethoxy)-phenyl)-5-methylimidazolidine-2,4-dione (163):



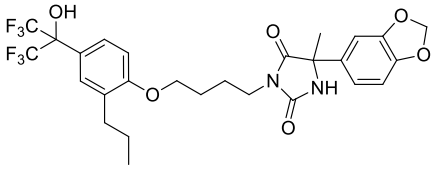
Compound **163** was prepared from compounds **148** and **5** in a manner similar to that described for compound **153**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.3 Hz), 1.31 (6H, t, *J* = 7.6 Hz), 1.50–1.63 (2H, m), 1.71–1.88 (7H, m), 2.57 (2H, t, *J* = 7.6 Hz), 3.59 (2H, t, *J* = 6.2 Hz), 3.70 (1H, s), 3.97 (2H, t, *J* = 5.5 Hz), 4.52 (1H, sept, *J* = 6.1 Hz), 5.80 (1H, s), 6.80 (1H, d, *J* = 8.6 Hz), 6.86 (2H, d, *J* = 8.9 Hz), 7.34 (2H, d, *J* = 8.9 Hz), 7.42–7.46 (2H, m); MS (EI) *m/z* 604 $[M]^+$.

3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-5-methyl-5-(4-(trifluoro-methoxy)phenyl)imidazolidine-2,4-dione (164):



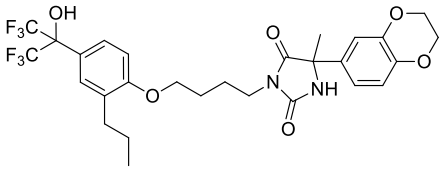
Compound **164** was prepared from compounds **148** and **42s** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.3 Hz), 1.49–1.67 (2H, m), 1.75–1.92 (7H, m), 2.57 (2H, t, *J* = 7.6 Hz), 3.55 (1H, s), 3.61 (2H, t, *J* = 6.5 Hz), 3.97 (2H, t, *J* = 5.4 Hz), 5.99 (1H, s), 6.81 (1H, d, *J* = 8.6 Hz), 7.20–7.47 (6H, m); MS (EI) *m/z* 630 $[M]^+$.

5-(Benzo[*d*][1,3]dioxol-5-yl)-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-5-methylimidazolidine-2,4-dione (165):



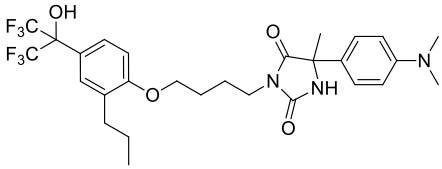
Compound **165** was prepared from compounds **148** and **42f** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.6 Hz), 1.55 (2H, qt, *J* = 7.6, 7.6 Hz), 1.68–1.77 (7H, m), 2.56 (2H, t, *J* = 7.6 Hz), 3.57 (2H, t, *J* = 6.3 Hz), 3.93 (2H, t, *J* = 5.3 Hz), 4.65 (1H, s), 5.92 (2H, s), 6.61–6.81 (3H, m), 6.93 (1H, dd, *J* = 2.0, 8.2 Hz), 6.97 (1H, d, *J* = 2.0 Hz), 7.40–7.49 (2H, m); MS (EI) *m/z* 590 $[M]^+$.

5-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-propyl-phenoxy)butyl)-5-methylimidazolidine-2,4-dione (166):



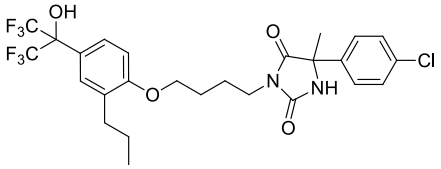
Compound **166** was prepared from compounds **148** and **42o** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.4 Hz), 1.50–1.64 (2H, m), 1.74–1.86 (7H, m), 2.58 (2H, t, *J* = 7.4 Hz), 3.59 (2H, t, *J* = 6.6 Hz), 3.72 (1H, s), 3.97 (2H, t, *J* = 5.7 Hz), 4.20–4.25 (4H, m), 5.85 (1H, s), 6.79–6.99 (4H, m), 7.42–7.47 (2H, m); MS (EI) *m/z* 604 $[M]^+$.

5-(4-(Dimethylamino)phenyl)-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)-butyl)-5-methylimidazolidine-2,4-dione (167):



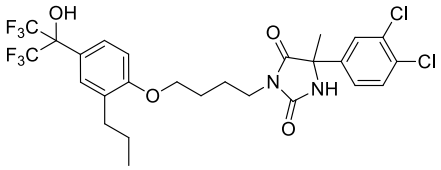
Compound **167** was prepared from compounds **148** and **42g** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.3 Hz), 1.50–1.65 (2H, m), 1.75–1.85 (7H, m), 2.57 (2H, t, *J* = 7.4 Hz), 2.93 (6H, s), 3.59 (2H, t, *J* = 5.7 Hz), 3.75 (1H, s), 3.97 (2H, t, *J* = 6.9 Hz), 5.67 (1H, s), 6.69 (2H, d, *J* = 8.9 Hz), 6.79 (1H, d, *J* = 8.4 Hz), 7.29 (2H, d, *J* = 8.9 Hz), 7.41–7.44 (2H, m); MS (EI) *m/z* 589 $[M]^+$.

5-(4-Chlorophenyl)-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-5-methylimidazolidine-2,4-dione (168):



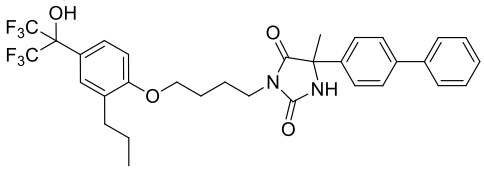
Compound **168** was prepared from compounds **148** and **42t** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.3 Hz), 1.52–1.66 (2H, m), 1.73–1.86 (7H, m), 2.57 (2H, t, *J* = 7.6 Hz), 3.59 (2H, t, *J* = 6.4 Hz), 3.64 (1H, s), 3.97 (2H, t, *J* = 5.9 Hz), 5.92 (1H, s), 6.81 (1H, d, *J* = 8.6 Hz), 7.34–7.47 (6H, m); MS (EI) *m/z* 580 $[M]^+$.

5-(3,4-Dichlorophenyl)-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-5-methylimidazolidine-2,4-dione (169):



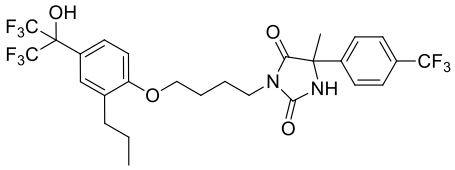
Compound **169** was prepared from compounds **148** and **42u** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.4 Hz), 1.56 (2H, qt, *J* = 7.5, 7.4 Hz), 1.73–1.88 (7H, m), 2.57 (2H, t, *J* = 7.4 Hz), 3.60 (2H, t, *J* = 6.2 Hz), 3.69 (1H, s), 3.97 (2H, t, *J* = 5.7 Hz), 6.22 (1H, s), 6.81 (1H, d, *J* = 8.6 Hz), 7.34–7.62 (5H, m); MS (EI) *m/z* 614 $[M]^+$.

5-((1,1'-Biphenyl]-4-yl)-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-5-methylimidazolidine-2,4-dione (170):



Compound **170** was prepared from compounds **148** and **42v** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.2 Hz), 1.50–1.66 (2H, m), 1.75–1.93 (7H, m), 2.57 (2H, t, *J* = 7.6 Hz), 3.60–3.64 (3H, m), 3.97 (2H, t, *J* = 5.4 Hz), 5.95 (1H, s), 6.81 (1H, d, *J* = 8.6 Hz), 7.36–7.63 (11H, m); MS (EI) *m/z* 622 $[M]^+$.

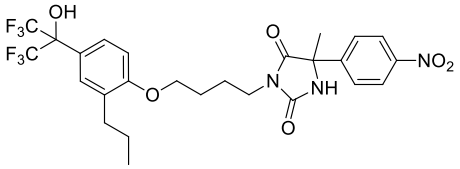
3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-5-methyl-5-(4-(trifluoro-methyl)phenyl)imidazolidine-2,4-dione (171):



Compound **171** was prepared from compounds **148** and **42h** in a manner similar to that described for compound

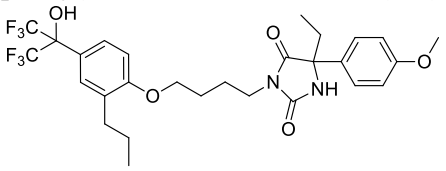
152. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.3 Hz), 1.49–1.63 (2H, m), 1.73–1.90 (7H, m), 2.57 (2H, t, *J* = 7.7 Hz), 3.60 (2H, t, *J* = 6.3 Hz), 3.69 (1H, s), 3.97 (2H, t, *J* = 5.5 Hz), 6.16 (1H, s), 6.81 (1H, d, *J* = 8.6 Hz), 7.42 (1H, s), 7.45 (1H, d, *J* = 8.6 Hz), 7.63–7.68 (4H, m); MS (EI) *m/z* 614 $[M]^+$.

3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-5-methyl-5-(4-nitrophenyl)-imidazolidine-2,4-dione (172):



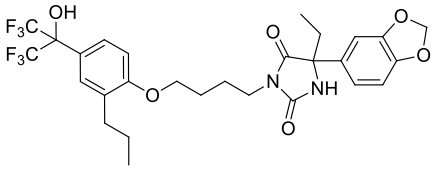
Compound **172** was prepared from compounds **148** and **42i** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.4 Hz), 1.49–1.63 (2H, m), 1.74–1.90 (7H, m), 2.56 (3H, t, *J* = 7.6 Hz), 3.61 (3H, t, *J* = 6.5 Hz), 3.74 (1H, s), 3.97 (2H, t, *J* = 5.5 Hz), 6.34 (1H, s), 6.80 (1H, d, *J* = 8.6Hz), 7.42–7.47 (2H, m), 7.73 (2H, d, *J* = 8.9 Hz), 8.24 (2H, d, *J* = 8.9 Hz); MS (EI) *m/z* 591 $[M]^+$.

5-Ethyl-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-5-(4-methoxy-phenyl)imidazolidine-2,4-dione (173):



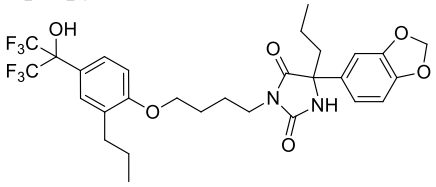
Compound **173** was prepared from compounds **148** and **42w** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.3 Hz), 0.91 (3H, t, *J* = 7.3 Hz), 1.49–1.63 (2H, m), 1.76–1.84 (4H, m), 1.98–2.28 (2H, m), 2.57 (2H, t, *J* = 7.6 Hz), 3.58 (2H, t, *J* = 6.8 Hz), 3.71 (1H, s), 3.79 (3H, s), 3.96 (2H, t, *J* = 5.7 Hz), 5.97 (1H, s), 6.80 (1H, d, *J* = 8.4 Hz), 6.90 (2H, d, *J* = 6.5 Hz), 7.40–7.46 (4H, m); MS (EI) *m/z* 590 $[M]^+$.

5-(Benzo[*d*][1,3]dioxol-5-yl)-5-ethyl-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-propyl-phenoxy)butyl)imidazolidine-2,4-dione (174):



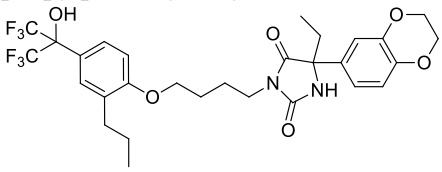
Compound **174** was prepared from compounds **148** and **42x** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.0 Hz), 0.90 (3H, t, *J* = 7.3 Hz), 1.50–1.66 (2H, m), 1.79–1.81 (4H, m), 2.00–2.25 (2H, m), 2.57 (2H, t, *J* = 7.6 Hz), 3.58 (2H, t, *J* = 6.2 Hz), 3.61 (1H, s), 3.97 (2H, t, *J* = 5.9 Hz), 5.95–5.98 (3H, m), 6.77–6.82 (2H, m), 6.93–7.03 (2H, m), 7.42–7.47 (2H, m); MS (EI) *m/z* 604 $[M]^+$.

5-(Benzo[*d*][1,3]dioxol-5-yl)-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)-5-propylimidazolidine-2,4-dione (175):



Compound **175** was prepared from compounds **148** and **42y** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.6 Hz), 0.93 (3H, t, *J* = 7.0 Hz), 1.17–1.38 (2H, m), 1.57 (2H, qt, *J* = 7.6, 7.6 Hz), 1.78–1.80 (4H, m), 1.93–2.17 (2H, m), 2.57 (2H, t, *J* = 7.6 Hz), 3.57 (2H, t, *J* = 6.2 Hz), 3.66 (1H, s), 3.96 (2H, t, *J* = 5.9 Hz), 5.95 (2H, s), 6.08 (1H, s), 6.77 (1H, d, *J* = 8.1 Hz), 6.80 (1H, d, *J* = 8.1 Hz), 6.95 (1H, d, *J* = 8.1 Hz), 7.03 (1H, s), 7.42 (1H, s), 7.45 (1H, d, *J* = 8.1 Hz); MS (EI) *m/z* 618 $[M]^+$.

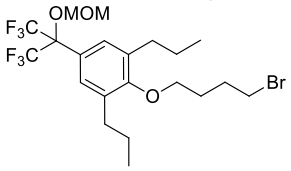
5-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-ethyl-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)butyl)imidazolidine-2,4-dione (176):



Compound **176** was prepared from compounds **148** and **42z** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.3 Hz), 0.92 (3H, t, *J* = 7.3 Hz), 1.59 (2H, qt, *J* = 7.3, 7.6 Hz), 1.67–1.72 (2H, m), 1.78–1.80 (2H, m), 1.99–2.25 (2H, m), 2.57 (2H, t, *J* = 7.6 Hz), 3.53 (2H, t, *J* = 6.5 Hz), 3.68 (1H, s), 3.96 (2H, t, *J* = 5.9 Hz), 4.22–4.24 (4H, m), 5.98 (1H, s), 6.79–7.02 (3H, m), 7.31 (1H, d, *J* = 8.9 Hz), 7.38–7.46 (1H, m), 7.60–7.66 (1H, m); MS (EI) *m/z* 618 $[M]^+$.

Synthesis of the trifluoromethylcarbinol derivative with dipropyl group

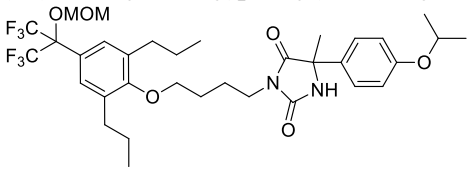
2-(4-Bromobutoxy)-5-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-1,3-dipropylbenzene (150):



To a stirred suspension of **147** (5.1 g, 13 mmol) and K_2CO_3 (3.6 g, 26 mmol) in DMF (130 mL), 1,4-dibromobutane (23 g, 105 mmol) was slowly added at room temperature. The reaction mixture was stirred at room temperature for 18 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 50/1) to give the title compound (7.3 g, 99%) as a colorless oil; ^{1}H NMR (400

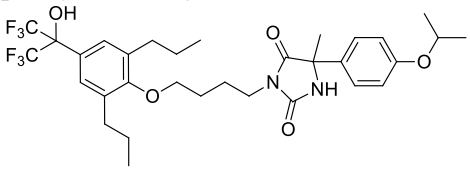
MHz, $CDCl_3$) δ 0.96 (6H, t, *J* = 7.3 Hz), 1.62 (4H, qt, *J* = 7.3, 7.6 Hz), 1.92–2.02 (2H, m), 2.09–2.20 (2H, m), 2.59 (4H, t, *J* = 7.6 Hz), 3.53 (2H, t, *J* = 6.8 Hz), 3.55 (3H, s), 3.81 (2H, t, *J* = 6.2 Hz), 4.83 (2H, s), 7.24 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (2C), 23.7 (2C), 29.1, 29.6, 32.2 (2C), 33.5, 57.0, 72.6, 82.3 (septet, *J* = 28.6 Hz), 93.7, 122.5 (2C, q, *J* = 289.0 Hz), 123.0, 127.8 (2C), 136.0 (2C), 157.0; MS (EI) *m/z* 522 $[M]^+$.

3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2,6-dipropylphenoxy)butyl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (151a):



To a stirred suspension of **5** (3.0 g, 12 mmol) and K_2CO_3 (2.3 g, 16 mmol) in DMF (80 mL), a solution of **150** (4.3 g, 8.1 mmol) in DMF (10 mL) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 16 h and then diluted with water at 0 °C, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/2) to give the title compound (5.6 g, 99%) as a colorless amorphous solid; ^{1}H NMR (400 MHz, CD_3OD) δ 0.92 (6H, t, *J* = 7.3 Hz), 1.31 (6H, d, *J* = 5.9 Hz), 1.53–1.90 (11H, m), 2.56 (4H, t, *J* = 7.6 Hz), 3.56 (3H, s), 3.61 (2H, t, *J* = 7.0 Hz), 3.74 (2H, t, *J* = 6.4 Hz), 4.04 (2H, s), 4.52 (1H, sept, *J* = 5.9 Hz), 5.90 (1H, s), 6.86 (2H, d, *J* = 8.9 Hz), 7.36 (2H, s), 7.37 (2H, d, *J* = 8.9 Hz); MS (EI) *m/z* 690 $[M]^+$.

3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2,6-dipropylphenoxy)butyl)-5-(4-(1-methylethoxy)-phenyl)-5-methylimidazolidine-2,4-dione (4):



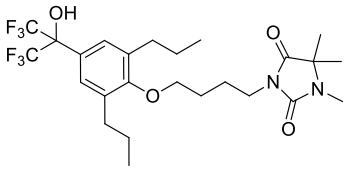
To a stirred solution of **151a** (5.6 g, 8.1 mmol) in MeOH (100 mL), 4 N HCl-EtOH (10 mL) was slowly added at 0 °C. The reaction mixture was stirred at room temperature for 1 h and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to obtain the title compound (4.2 g, 81%) as a colorless amorphous solid; IR (neat) 3307, 2961, 2935, 1707, 1266, 1148 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 0.92 (6H, t, *J* = 7.6 Hz), 1.28 (6H, d, *J* = 5.6 Hz), 1.60 (4H, qt, *J* = 7.6, 7.6 Hz), 1.74 (3H, s), 1.76–1.90 (4H, m), 2.59 (4H, t, *J* = 7.6 Hz), 3.59 (2H, t, *J* = 6.8 Hz), 3.78 (2H, t, *J* = 6.0 Hz), 4.57 (1H, sept, *J* = 5.6 Hz), 6.86 (2H, d, *J* = 8.8 Hz), 7.35 (2H, s), 7.39 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 14.3, 14.3, 22.3 (2C), 24.9, (2C), 25.3, 26.1, 28.6, 33.4 (2C), 39.3, 64.3, 71.0, 74.0, 78.4 (septet, *J* = 29.2 Hz), 116.9 (2C), 124.6 (q, *J* = 287 Hz) (2C), 127.6, 127.7 (2C), 127.8 (2C), 132.3, 136.8, 158.0, 158.4, 159.3, 178.1; MS (EI) *m/z* 646 $[M]^+$; Anal. Calcd for $C_{32}H_{40}F_6N_2O_5$: C, 59.43; H, 6.23; N, 4.33. Found: C, 59.41; H, 6.25; N, 4.37.

Compounds **154~155**, **177~184** were prepared in the same manner as the synthesis of **152**.

Characterization data

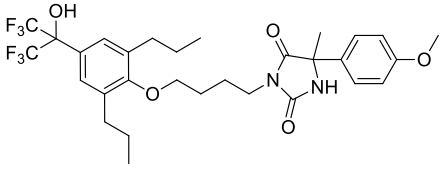
The NMR and MS data of compounds **155~155**, **177~184** are described below.

3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2,6-dipropylphenoxy)butyl)-1,5,5-trimethyl-imidazolidine-2,4-dione (154):



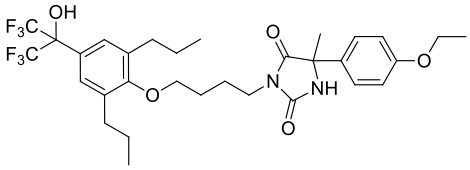
Compound **154** was prepared from compound **150** and 1,5,5-trimethylimidazolidine-2,4-dione in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (6H, t, *J* = 7.4 Hz), 1.38 (6H, s), 1.62 (4H, qt, *J* = 7.4, 7.7 Hz), 1.76–1.92 (4H, m), 2.58 (4H, t, *J* = 7.7 Hz), 2.90 (3H, s), 3.55–3.64 (3H, m), 3.77 (2H, t, *J* = 5.7 Hz), 7.32 (2H, s); MS (EI) *m/z* 540 $[M]^+$.

3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2,6-dipropylphenoxy)butyl)-5-(4-methoxyphenyl)-5-methylimidazolidine-2,4-dione (155):



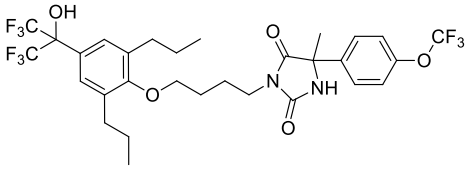
Compound **155** was prepared from compounds **150** and **42a** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (6H, t, *J* = 7.3 Hz), 1.53–1.92 (11H, m), 2.56 (4H, t, *J* = 7.6 Hz), 3.55 (1H, s), 3.62 (2H, t, J = 6.8 Hz), 3.75 (2H, t, *J* = 5.9 Hz), 3.80 (3H, s), 5.84 (1H, s), 6.86–6.90 (2H, m), 7.03–7.07 (2H, m), 7.27–7.33 (2H, m); MS (EI) *m/z* 618 $[M]^+$.

5-(4-Ethoxyphenyl)-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2,6-dipropylphenoxy)butyl)-5-methylimidazolidine-2,4-dione (177):



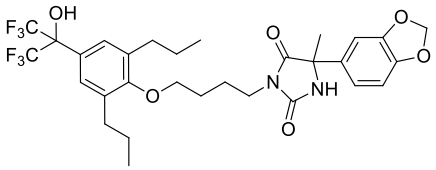
Compound **177** was prepared from compounds **150** and **42r** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (6H, t, *J* = 7.3 Hz), 1.40 (3H, t, *J* = 7.0 Hz), 1.53–1.90 (11H, m), 2.56 (4H, t, *J* = 7.6 Hz), 3.58–3.64 (3H, m), 3.75 (2H, t, *J* = 5.9 Hz), 4.01 (2H, q, *J* = 7.0 Hz), 5.77 (1H, s), 6.87 (2H, d, *J* = 8.9 Hz), 7.31 (2H, s), 7.37 (2H, d, *J* = 8.9 Hz); MS (EI) *m/z* 632 $[M]^+$.

3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2,6-dipropylphenoxy)butyl)-5-methyl-5-(4-(trifluoromethoxy)phenyl)imidazolidine-2,4-dione (178):



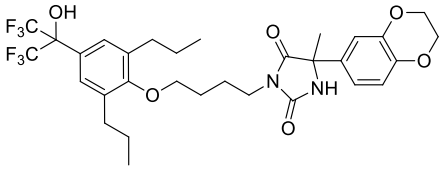
Compound **178** was prepared from compounds **150** and **42s** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (6H, t, *J* = 7.3 Hz), 1.52–1.90 (11H, m), 2.55 (4H, t, *J* = 7.6 Hz), 3.62 (2H, t, *J* = 6.8 Hz), 3.72-3.77 (3H, m), 6.37 (1H, s), 7.17–7.22 (2H, m), 7.31 (2H, s), 7.37–7.48 (2H, m); MS (EI) *m/z* 672 $[M]^+$.

5-(Benzo[*d*][1,3]dioxol-5-yl)-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2,6-dipropylphenoxy)-butyl)-5-methylimidazolidine-2,4-dione (179):



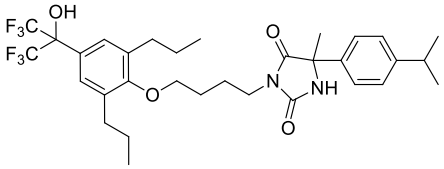
Compound **179** was prepared from compounds **150** and **42f** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (6H, t, *J* = 7.3 Hz), 1.53–1.90 (11H, m), 2.56 (4H, t, *J* = 7.8 Hz), 3.61 (2H, t, *J* = 6.8 Hz), 3.67 (1H, s), 3.75 (2H, t, *J* = 5.9 Hz), 5.94-5.96 (3H, m), 6.78 (1H, d, *J* = 8.4 Hz), 6.93 (1H, dd, *J* = 1.9, 8.4 Hz), 6.98 (1H, d, *J* = 1.9 Hz), 7.31 (2H, s); MS (EI) *m/z* 632 $[M]^+$.

5-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2,6-di-propylphenoxy)butyl)-5-methylimidazolidine-2,4-dione (180):



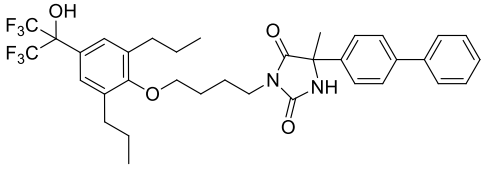
Compound **180** was prepared from compounds **150** and **42o** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (6H, t, *J* = 7.3 Hz), 1.53–1.90 (11H, m), 2.56 (4H, t, *J* = 7.8 Hz), 3.60 (2H, t, *J* = 6.8 Hz), 3.74 (2H, t, *J* = 5.9 Hz), 3.92 (1H, s), 4.22–4.24 (4H, m), 6.11 (1H, s) , 6.84 (1H, d, *J* = 8.4 Hz), 6.92 (1H, dd, *J* = 2.4, 8.4 Hz), 6.99 (1H, d, *J* = 2.4 Hz), 7.32 (2H, s); MS (EI) *m/z* 646 $[M]^+$.

3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2,6-dipropylphenoxy)butyl)-5-(4-isopropylphenyl)-5-methylimidazolidine-2,4-dione (181):



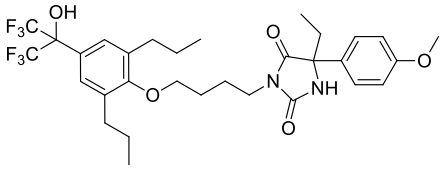
Compound **181** was prepared from compounds **150** and **42q** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (6H, t, *J* = 7.3 Hz), 1.22 (6H, d, *J* = 7.0 Hz), 1.53–1.90 (11H, m), 2.66 (4H, t, *J* = 7.8 Hz), 2.85–2.93 (1H, m), 3.50 (1H, s), 3.61 (2H, t, *J* = 6.8 Hz), 3.75 (2H, t, *J* = 5.8 Hz), 5.76 (1H, s), 7.24 (2H, d, *J* = 8.1 Hz), 7.31 (2H, s), 7.39 (2H, d, *J* = 8.1 Hz); MS (EI) *m/z* 630 $[M]^+$.

5-((1,1'-Biphenyl)-4-yl)-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2,6-dipropylphenoxy)butyl)-5-methylimidazolidine-2,4-dione (182):



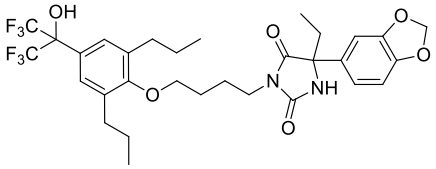
Compound **182** was prepared from compounds **150** and **42v** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (6H, t, *J* = 7.3 Hz), 1.52–1.90 (11H, m), 2.55 (4H, t, *J* = 7.6 Hz), 3.63 (2H, t, *J* = 6.8 Hz), 3.74 (2H, t, *J* = 5.9 Hz), 3.89 (1H, s), 6.37 (1H, s), 7.21–7.62 (11H, m); MS (EI) *m/z* 664 $[M]^+$.

5-Ethyl-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2,6-dipropylphenoxy)butyl)-5-(4-methoxy-phenyl)imidazolidine-2,4-dione (183):



Compound **183** was prepared from compounds **150** and **42w** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.94 (9H, m), 1.52–1.95 (8H, m), 2.02–2.29 (2H, m), 2.55 (4H, t, *J* = 7.6 Hz), 3.60 (2H, t, *J* = 6.8 Hz), 3.74 (2H, t, *J* = 5.9 Hz), 3.77–3.79 (4H, m), 6.15 (1H, s), 6.89 (2H, d, *J* = 8.6 Hz), 7.31 (2H, s), 7.42 (2H, d, *J* = 8.6 Hz); MS (EI) *m/z* 632 $[M]^+$.

5-(Benzo[*d*][1,3]dioxol-5-yl)-5-ethyl-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2,6-dipropylphenoxy)butyl)imidazolidine-2,4-dione (184):



Compound **184** was prepared from compounds **150** and **42x** in a manner similar to that described for compound **152**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86–0.94 (9H, m), 1.52–1.92 (8H, m), 2.00–2.25 (2H, m), 2.55 (4H, t, *J* = 7.6 Hz), 3.59 (2H, t, *J* = 6.8 Hz), 3.74 (2H, t, *J* = 5.9 Hz), 3.87 (1H, s), 5.95 (2H, s), 6.39 (1H, s), 6.78 (1H, d, *J* = 8.1 Hz), 6.95 (1H, dd, *J* = 1.9, 8.1 Hz) , 7.04 (1H, d, *J* = 1.9 Hz), 7.31 (2H, s); MS (EI) *m/z* 646 $[M]^+$.

Chapter-2

Section-1

Chemical Experimental Details

Figure 38

Optical separation of compound (±)-**4 by HPLC**

Resolution of racemic sample of compound **4** was carried out by HPLC using CHIRALPAK AS-H column (DAICEL). Each separated elution was concentrated to give compounds (−)-**4** and (+)-**4** as white amorphous solids.

Conditions for analysis

Column: CHIRALPAK AS-H, 0.46 × 250 mm; Mobile phase: hexane/EtOH = 90/10 (v/v); Flow rate: 1.0 mL/min; Column temperature: 40 °C; Wavelength: 230 nm; Retention time: (*R*)-(−)-form 6.87 min/(*S*)-(+)-form 11.52 min.

Conditions for preparation

Column: CHIRALPAK AS-H, 20 × 250 mm; Mobile phase: hexane/EtOH = 90/10 (v/v); Flow rate: 1.0 mL/min; Column temperature: 40 °C; Wavelength: 230 nm; Retention time: (*R*)-(−)-form 6.90 min/(*S*)-(+)-form 11.50 min. A 10 mg sample of racemic compound **4** led to complete resolution in a single operation.

(+)-**4**; IR (neat) 3307, 2961, 2935, 1707, 1266, 1148 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 0.92 (6H, t, *J* = 7.6 Hz), 1.28 (6H, d, *J* = 5.6 Hz), 1.60 (4H, qt, *J* = 7.6, 7.6 Hz), 1.74 (3H, s), 1.76–1.90 (4H, m), 2.59 (4H, t, *J* = 7.6 Hz), 3.59 (2H, t, *J* = 6.8 Hz), 3.78 (2H, t, *J* = 6.0 Hz), 4.57 (1H, sept, *J* = 5.6 Hz), 6.86 (2H, d, *J* = 8.8 Hz), 7.35 (2H, s), 7.39 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 14.3 (2C), 22.3 (2C), 24.9 (2C), 25.3, 26.1, 28.6, 33.4 (2C), 39.3, 64.3, 71.0, 74.0, 78.4 (septet, *J* = 29.2 Hz), 116.9 (2C), 124.6 (2C, q, *J* = 287 Hz), 127.6, 127.7 (2C), 127.8 (2C), 132.3, 136.8 (2C), 158.0, 158.4, 159.3, 178.1; MS (EI) *m/z* 646 $[M]^+$; Anal. Calcd for $C_{32}H_{40}N_2F_6O_5$: C, 59.43; H, 6.23; N, 4.33. Found: C, 59.23; H, 6.07; N, 4.40; $[\alpha]_D^{20}$ = +32.2 (c = 1.0, MeOH); Optical purity: >99% ee.

(−)-**4**; MS (EI) *m/z* 646 $[M]^+$; Anal. Calcd for $C_{32}H_{40}N_2F_6O_5$: C, 59.43; H, 6.23; N, 4.33. Found: C, 59.21; H, 6.29; N, 4.37; $[\alpha]_D^{20}$ = −33.3 (c = 1.0, MeOH); Optical purity: >99% ee. The IR, ^{1}H NMR and ^{13}C NMR spectra of (−)-**4** were identical to those of (+)-**4**.

Scheme 18

Optical separation of (±)-**5 by HPLC**

Resolution of racemic sample of compound **5** was carried out by HPLC using CHIRALPAK AD-H column (DAICEL). Each separated elution was concentrated to give compounds (−)-**5** and (+)-**5** as colorless crystals.

Conditions for analysis

Column: CHIRALPAK AD-H, 0.46 × 250 mm; Mobile phase: hexane/EtOH = 40/60; Flow rate: 1.0 mL/min; Column temperature: 40 °C; Wavelength: 254 nm; Retention time: (*R*)-(−)-form 4.51 min/(*S*)-(+)-form 9.50 min.

Conditions for preparation

Column: CHIRALPAK AD-H, 20 × 250 mm; Mobile phase: MeOH = 100; Flow rate: 12 mL/min; Column temperature: 40 °C; Wavelength: 254 nm; Retention time: (*R*)-(−)-form 6.02 min/(*S*)-(+)-form 13.94 min. A 200 mg sample of racemic compound **5** led to complete resolution in a single operation.

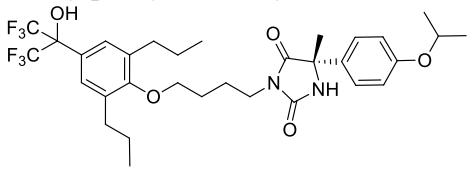
(+)-**5**; mp 166.4–169.0 °C; IR (KBr) 3282, 3207, 1770, 1727, 1512, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (6H, d, *J* = 5.6 Hz), 1.80 (3H, s), 4.53 (1H, sept, *J* = 5.6 Hz), 6.57 (1H, brs), 6.87 (2H, d, *J* = 8.8 Hz), 7.37 (2H, d, *J* = 8.8 Hz), 8.57 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (2C), 25.2, 64.9, 70.0, 116.0 (2C), 126.5 (2C), 129.9, 156.6, 158.1, 176.2; MS (EI) *m/z* 248 [M^+]; Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.93; H, 6.52; N, 11.02; $[\alpha]_D^{20}$ = +89.7 (c = 1.0, MeOH); Optical purity: >99% ee.

(−)-**5**; mp 166.9–169.0 °C; MS (EI) *m/z* 248 [M^+]; Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.72; H, 6.49; N, 11.16; $[\alpha]_D^{20}$ = −89.7 (c = 1.0, MeOH) ; Optical purity: >99% ee. The IR, ^1H NMR and ^{13}C NMR spectra of (−)-**5** were identical to those of (+)-**5**.

Scheme 19

Synthesis of (*S*)-(+)-4 and (*R*)-(−)-4

(*S*)-3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2,6-dipropylphenoxy)butyl)-5-(4-(1-methyl-ethoxy)phenyl)-5-methylimidazolidine-2,4-dione ((*S*)-(+)-4):

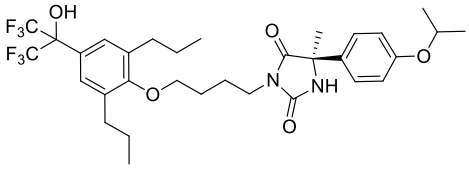


To a stirred suspension of (+)-**5** (3.0 g, 12 mmol) and K_2CO_3 (2.3 g, 16 mmol) in DMF (80 mL), a solution of **150** (4.3 g, 8.1 mmol) in DMF (10 mL) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the reaction mixture was diluted with water at 0 °C and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/2) to give

(*S*)-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-2,6-dipropylphenoxy)butyl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (5.6 g, 99%) as a white amorphous solid; ^{1}H NMR (400 MHz, CD_3OD) δ 0.92 (6H, t, *J* = 7.3 Hz), 1.31 (6H, d, *J* = 5.9 Hz), 1.53–1.90 (11H, m), 2.56 (4H, t, *J* = 7.6 Hz), 3.56 (3H, s), 3.61 (2H, t, *J* = 7.0 Hz), 3.74 (2H, t, *J* = 6.4 Hz), 4.04 (2H, s), 4.52 (1H, sept, *J* = 5.9 Hz), 5.90 (1H, s), 6.86 (2H, d, *J* = 8.9 Hz), 7.36 (2H, s), 7.37 (2H, d, *J* = 8.9 Hz); MS (EI) *m/z* 690 $[M]^+$.

To a stirred solution of (*S*)-3-(4-(4-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-2,6-dipropylphenoxy)butyl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (5.6 g, 8.1 mmol) in MeOH (100 mL), 4 N HCl-EtOAc (10 mL) was slowly added at 0 °C. The reaction mixture was stirred at room temperature for 1 h and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to give the title compound (4.2 g, 81%) as a white amorphous solid; MS (EI) *m/z* 646 $[M]^+$; Anal. Calcd for $C_{32}H_{40}N_2F_6O_5$: C, 59.43; H, 6.23; N, 4.33. Found: C, 59.23; H, 6.07; N, 4.40; $[\alpha]_D^{20}$ = +30.8 (c = 1.0, MeOH); Optical purity: 99% ee. The IR, ^{1}H NMR and ^{13}C NMR spectra of (*S*)-**4** were identical to those of (+)-**4**.

(*R*)-3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2,6-dipropylphenoxy)butyl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione ((*R*)-(−)-4):



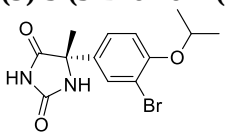
(*R*)-(−)-**4** was also prepared according to the above procedure.

MS (EI) *m/z* 646 $[M]^+$; Anal. Calcd for $C_{32}H_{40}N_2F_6O_5$: C, 59.43; H, 6.23; N, 4.33. Found: C, 59.21; H, 6.29; N, 4.37; $[\alpha]_D^{20}$ = −29.9 (c = 1.0, MeOH). The IR, ^{1}H NMR and ^{13}C NMR spectra of (*R*)-**4** were identical to those of (+)-**4**.

Scheme 20

Synthesis of (+)-Br-6 and (+)-Cl-6

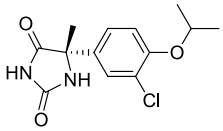
(*S*)-5-(3-Bromo-4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione ((+)-Br-6):



To a stirred solution of (+)-**5** (300 mg, 1.2 mmol) in DMF (4.0 mL), NBS (269 mg, 1.5 mmol) was added at room temperature. The reaction mixture was stirred at the same temperature for 20 h. The reaction mixture was diluted with water (5.0 mL) and extracted with EtOAc (10 mL). The organic layer was washed with water (5.0 mL) and brine (5.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to yield the product (389 mg). The product was recrystallized from EtOAc to give the title compound (312 mg, 79%) as colorless crystals; mp 207.9–211.5 °C; IR (KBr) 3265, 2981, 1727,

1493, 1261, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (6H, d, *J* = 6.1 Hz), 1.81 (3H, s), 4.55 (1H, sept, *J* = 6.1 Hz), 6.48 (1H, brs), 6.89 (1H, d, *J* = 8.8 Hz), 7.36 (1H, dd, *J* = 2.4, 8.8 Hz), 7.66 (1H, d, *J* = 2.4 Hz), 8.48 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (2C), 25.3, 64.4, 72.2, 114.0, 115.3, 125.4, 130.4, 131.5, 154.8, 156.0, 175.3; MS (EI) *m/z* 327 [M^+]; Anal. Calcd for $C_{13}H_{15}BrN_2O_3$: C, 47.72; H, 4.62; Br, 24.42; N, 8.56. Found: C, 47.87; H, 4.61; Br, 24.41; N, 8.49; $[\alpha]_D^{20}$ = +79.7 (c = 0.98, MeOH).

(*S*)-5-(3-Chloro-4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione ((+)-Cl-6):



To a stirred solution of (+)-**5** (300 mg, 1.2 mmol) in DMF (4.0 mL), NCS (202 mg, 1.5 mmol) was added at room temperature. The reaction mixture was stirred at the same temperature for 20 h. The reaction mixture was diluted with water (5.0 mL) and extracted with EtOAc (10 mL). The organic layer was washed with water (5.0 mL) and brine (5.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to yield crystals (210 mg). The product was recrystallized from EtOAc to give the title compound (175 mg, 51%) as colorless crystals; mp 202.1–204.2 °C; IR (KBr) 3292, 2972, 1717, 1501, 1263, 1110 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.33 (6H, d, *J* = 6.0 Hz), 1.72 (3H, s), 4.63 (1H, sept, *J* = 6.0 Hz), 7.07 (1H, d, *J* = 8.8 Hz), 7.37 (1H, dd, *J* = 2.4, 8.8 Hz), 7.49 (1H, d, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 22.2 (2C), 25.4, 65.4, 73.0, 116.7, 125.1, 126.0, 128.5, 134.0, 154.8, 158.7, 179.0; MS (EI) *m/z* 282 [M^+]; Anal. Calcd for $C_{13}H_{15}ClN_2O_3$: C, 55.23; H, 5.35; Cl, 12.54; N, 9.91. Found: C, 55.38; H, 5.37; Cl, 12.50; N, 9.89; $[\alpha]_D^{20}$ = +81.4 (c = 1.0, MeOH).

Figure 39

X-ray crystal structure analysis of (+)-Br-6 and (+)-Cl-6

Colorless crystals were obtained from a hot methanol solution by slow cooling at room temperature. X-ray intensity data were measured on the Bruker Venture D8 Diffractometer with Mo Kα radiation at 299 K. The absorption correction was numerically performed based on the crystal dimensions and face indices. Non-H atoms were refined anisotropically. Protonation of the pyridine ring was confirmed with reference to a difference density map. H atoms were geometrically positioned and refined as riding.

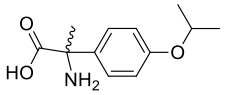
X-ray crystallographic data for (*S*)-(+)-Br-**6** [$C_{13}H_{15}BrN_2O_3$]: *M* = 327.17, orthorhombic, $P2_12_12_1$, *a* = 6.1840(3), *b* = 9.6495(4), *c* = 23.1111(10) Å, *V* = 1379.10(11) $Å^3$, *Z* = 4, μ (Mo *K*α) = 2.99 mm^{-1}, colorless prism, crystal dimensions = 0.25 × 0.25 × 0.10 mm^3. A total of 31000 reflections were measured, of which 3271 reflections were independent. R [$F^2 > 2\sigma(F^2)$] = 0.017, $wR(F^2)$ = 0.047. Flack parameter = 0.018(2), which was determined based on Parsons quotients.[52)] In the crystal, there are C—H…Br, C—H…O and N—H…O hydrogen bonds, forming a flat sheet parallel to (001).[36b)]

X-ray crystallographic data for (*S*)-(+)-Cl-**6** [$C_{13}H_{15}ClN_2O_3$]: M = 282.72, orthorhombic, $P2_12_12_1$, a = 7.1397(3), b = 10.0128(4), c = 20.0431(10) Å, V = 1432.85(10) Å^3, Z = 4, μ (Mo $K\alpha$) = 0.27 mm^{-1}, colorless plate, crystal dimensions = 0.27 × 0.27 × 0.21 mm^3. A total of 32943 reflections were measured, of which 3425 reflections were independent. R [$F^2 > 2\sigma(F^2)$] = 0.027, $wR(F^2)$ = 0.079. Flack parameter = 0.009(8), which was determined based on Parsons quotients.[52)] In the crystal, there are C—H…Cl, C—H…O and N—H…O hydrogen bonds, forming a flat sheet parallel to (001).[53)]

Scheme 22

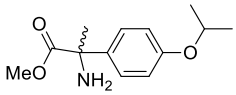
Practical synthesis of (*S*)-5

***Racemic* 2-amino-2-(4-(1-methylethoxy)phenyl)propanoic acid ((±)-186):**



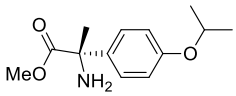
To a stirred solution of (±)-**5** (110 g, 443 mmol) in water (700 mL), NaOH (90.0 g, 2.25 mol) was added at room temperature. The reaction mixture was stirred at 100 °C for 48 h. The reaction mixture was neutralized with 6 N HCl. The precipitate was filtered off and washed with water (200 mL ×3) to give the title compound (99.0 g, 99%) as a colorless solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.22 (6H, d, J = 6.0 Hz), 1.36 (3H, s), 4.51 (1H, sept, J = 6.0 Hz), 6.70 (2H, d, J = 8.8 Hz), 7.43 (2H, d, J = 8.8 Hz). The product was used in the next step without further purification.

***Racemic* methyl 2-amino-2-(4-(1-methylethoxy)phenyl)propanoate ((±)-8):**



To a stirred solution of (±)-**186** (70.0 g, 270 mmol) in MeOH (700 mL), concd. H_2SO_4 (70 mL) was added at room temperature. The reaction mixture was stirred at the same temperature for 3 h and refluxed for 24 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in water (500 mL) and diluted with CH_2Cl_2 (500 mL). The aqueous layer was adjusted to pH 9–10 by adding 3 N NaOH *aq*. at 5 °C or below. The aqueous layer was extracted with CH_2Cl_2 (500 mL ×2). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound (44.8 g, 70%) as a yellow oil; IR (neat) 3381, 2976, 1732, 1509, 1245, 954 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (6H, d, J = 6.0 Hz), 1.68 (3H, s), 1.95 (2H, brs), 3.70 (3H, s), 4.53 (1H, sept, J = 6.0 Hz), 6.84 (2H, d, J = 9.2 Hz), 7.37 (2H, d, J = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (2C), 27.5, 52.5, 60.1, 69.8, 115.5 (2C), 126.3 (2C), 136.0, 157.2, 176.9; MS (EI) *m/z* 237 [M$^+$]; Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.55; H, 8.11; N, 5.88.

(*S*)-Methyl 2-amino-2-(4-(1-methylethoxy)phenyl)propanoate ((+)-8):



To a stirred solution of (±)-**8** (55.4 g, 233 mmol) in EtOAc (390 mL) and EtOH (39 mL), L-mandelic acid (35.5 g, 233 mmol) was added at room temperature. The reaction mixture was refluxed for 30 min until a clear solution was obtained and then stirred at room temperature for 16 h. The precipitate was filtered off. The filter cake was washed with EtOAc/EtOH (= 10/1, 100 mL) and then crystallized from EtOAc/EtOH (= 10/1). This crystallization was repeated twice to give the L-mandelic acid salt **187** (20.1 g, 99% ee*) as a white solid.

Table 22*

Entry	1st	2nd	3rd
% ee	49% ee	92% ee	99% ee
Solvent	EtOAc (390 mL)/ EtOH (39 mL)	EtOAc (340 mL)/ EtOH (34 mL)	EtOAc (240 mL)/ EtOH (24 mL)
L-mandelic acid salt	33.5 g	23.9 g	20.1 g

*% ee of (+)-**8** was measured after removing L-mandelic acid from salt **187** by treating with Na_2CO_3. The HPLC conditions are described below.

Analytical chiral HPLC conditions

Column: CHIRALPAK AS-H, 5 µm, 0.46 × 250 mm; Mobile phase: hexane/*i*-PrOH/DEA = 92/8/0.1 (v/v/v); Flow rate: 1.0 mL/min; Column temperature: 30 °C; Wavelength: 234 nm; Retention time: (*S*)-form 7.36 min/(*R*)-form 8.59 min.

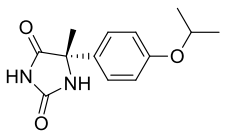
To a solution of CH_2Cl_2 (60 mL) and water (120 mL), the obtained salt was added. The aqueous layer was alkalinized by adding Na_2CO_3 until obtaining pH 9~10 below 10 °C. The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (500 mL ×3). The combined organic layers were washed with brine (250 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound (11.2 g, 20%) as a yellow oil.

The IR, ^{1}H NMR and ^{13}C NMR spectra of (+)-**8** were identical to those of (±)-**8**.

The hydrochloric acid salt of (+)-**8** was easily prepared with HCl in MeOH. A sample was recrystallized from MeOH to yield colorless crystals for analysis.

Hydrochloric acid salt of (+)-**8**; mp 195.2–197.1 °C; IR (KBr) 2977, 2874, 1747, 1516, 1263, 952 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 1.30 (6H, d, *J* = 5.6 Hz), 1.95 (3H, s), 3.82 (3H, s), 4.64 (1H, sept, *J* = 5.6 Hz), 6.99 (2H, d, *J* = 9.2 Hz), 7.40 (2H, d, *J* = 9.2 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 22.1 (2C), 22.2, 54.2, 62.4, 71.1, 117.3 (2C), 128.3 (2C), 128.5, 160.4, 172.5; MS (EI) *m/z* 237 [M$^+$]; Anal. Calcd for $C_{13}H_{20}ClNO_3$: C, 57.04; H, 7.36; N, 5.12. Found: C, 57.04; H, 7.30; N, 5.26; $[\alpha]_D^{20}$ = +79.8 (c = 1.0, MeOH); Optical purity: >99% ee.

(*S*)-5-(4-(1-Methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione ((*S*)-(+)-5):



Urea (28.3 g, 472 mmol) was heated at 140 °C. To this stirred solution, (+)-**8** (11.2 g, 47.2 mmol) was added dropwise at 140 °C. The reaction mixture was stirred at the same temperature for 5 h and then cooled to 70 °C. The reaction mixture was diluted with water (200 mL) and EtOAc (300 mL) at the same temperature. The aqueous layer was extracted with EtOAc (200 mL ×3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was suspended in *n*-heptane (40 mL) and stirred at room temperature for 2 h. The precipitate was filtered off and rinsed with heptane (10 mL) to give the title compound (10.4 g, 89%) as colorless crystals; mp 165.5–168.3 °C; MS (EI) *m/z* 248 [M^+]; Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.93; H, 6.52; N, 11.02; $[\alpha]_D^{20}$ = +89.7 (c = 1.0, MeOH); Optical purity: 99% ee. The IR, ^{1}H NMR and ^{13}C NMR spectra of (*S*)-**2** were identical to those of (+)-**2**.

Section-2

Pharmacokinetic Experimental Details

Material and Method

Pharmacokinetic studies

The oral dose of compound **4** at 100 mg/kg was formulated in PEG 400. A solution of compound **4** in PEG 400 was orally administered to a CE-2 chow diet-fed Golden Syrian hamsters. Blood samples (heparin plasma) were collected from a forearm vein 0.5, 1, 2, 3, 4, 6, 8, 10 and 24 h after administration. The drug concentrations of compounds **4** and **9** in the supernatant were measured by HPLC-LC-MS/MS.

Table 23. Drug concentration of compound **4** and its metabolite **9**

4: 3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2,6-dipropylphenoxy)butyl)-5-(4-(1-methylethoxy)-phenyl)-5-methylimidazolidine-2,4-dione
9: 4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2,6-dipropylphenoxy)butanoic acid

time (h)	po: **4** at 100 mg/kg (ng/mL)	plasma concentration of **4** (μM)	metabolite **9** (ng/mL)
0.5	199	0.31	52
1	315	0.49	202
2	206	0.32	375
3	190	0.29	409
4	190	0.29	529
6	406	0.63	641
8	269	0.42	979
10	73	0.11	560
24	67	0.10	528

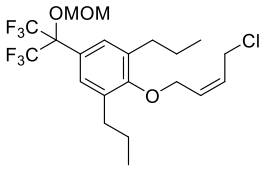
Chapter-3

Section-1

Chemical Experimental Details

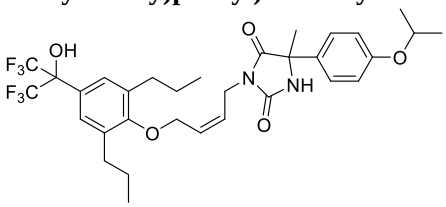
Scheme 23

***cis*-2-((4-Chlorobut-2-en-1-yl)oxy)-5-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-1,3-dipropyl-benzene (189a):**



To a stirred suspension of **147** (62 mg, 0.16 mmol) and K_2CO_3 (66 mg, 0.48 mmol) in DMF (1.2 mL), *cis*-1,4-dichloro-2-butene (**188a**) (200 mg, 1.6 mmol) was added dropwise at room temperature. The reaction mixture was stirred at 60 °C for 8 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/ EtOAc = 10/1) to give the title compound (68 mg, 89%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (6H, t, *J* = 7.3 Hz), 1.63 (4H, qt, *J* = 7.3, 7.6 Hz), 2.62 (2H, t, *J* = 7.6 Hz), 3.60 (3H, s), 4.12 (2H, d, *J* = 7.6 Hz), 4.46 (2H, d, *J* = 6.2 Hz), 4.83 (2H, s), 5.82–6.02 (2H, m), 7.27 (2H, s); MS (EI) *m/z* 477 $[M]^+$.

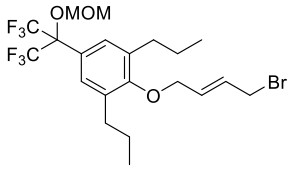
***cis*-3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2,6-dipropylphenoxy)but-2-en-1-yl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (191a):**



To a stirred suspension of **5** (11 mg, 45 μmol) and K_2CO_3 (7.0 mg, 50 μmol) in DMF (1.0 mL), **189a** (17 mg, 40 μmol) was added dropwise at room temperature. The reaction mixture was stirred at the same temperature for 18 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the product **190a** (99%). To a stirred solution of the obtained **190a** in EtOAc (1.0 mL) was slowly added 4 N HCl in EtOAc (44 μL, 180 μmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* to remove EtOAc. The residue was diluted with water. The aqueous layer was neutralized with saturated $NaHCO_3$ *aq*. and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to give the title compound (18 mg, 80%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (6H, t, *J* = 7.3 Hz), 1.32 (6H, d, *J* = 6.5 Hz), 1.63 (4H, qt, *J* = 7.3,

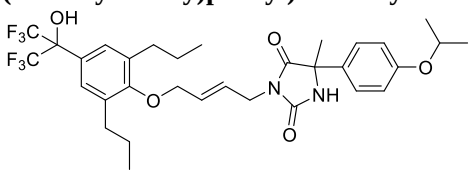
7.8 Hz), 1.78 (3H, s), 2.62 (4H, t, *J* = 7.8 Hz), 3.81 (1H, s), 4.12 (2H, d, *J* = 7.0 Hz), 4.49–4.58 (3H, m), 5.57–5.67 (1H, m), 5.90 (1H, s), 5.92–6.01 (1H, m), 6.86 (2H, d, *J* = 8.9 Hz), 7.33 (2H, d, *J* = 8.9 Hz), 7.34 (2H, s); MS (EI) *m/z* 645 $[M]^+$.

***trans*-2-((4-Bromobut-2-en-1-yl)oxy)-5-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-1,3-di-propylbenzene (189b):**



To a stirred suspension of **147** (117 mg, 0.30 mmol) and K_2CO_3 (83 mg, 0.60 mmol) in DMF (1.2 mL), *trans*-1,4-dibromo-2-butene (**188b**) (513 mg, 2.4 mmol) was added dropwise at room temperature. The reaction mixture was stirred at the same temperature for 17 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with 2 N HCl and brine and dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20/1) to give the title compound (66 mg, 42%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (6H, t, *J* = 7.3 Hz), 1.64 (4H, qt, *J* = 7.3, 7.6 Hz), 2.62 (4H, t, *J* = 7.6 Hz), 3.56 (3H, s), 4.04 (2H, d, *J* = 6.9 Hz), 4.35 (2H, d, *J* = 4.6 Hz), 4.85 (2H, s), 5.95–6.18 (2H, m), 7.43 (2H, s); MS (EI) *m/z* 521$[M]^+$.

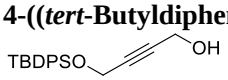
***trans*-3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxy-propan-2-yl)-2,6-dipropylphenoxy)but-2-en-1-yl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (191b):**



Compound **191b** was prepared using an experimental procedure similar to that used for compound **191a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (6H, t, *J* = 7.3 Hz), 1.32 (6H, d, *J* = 6.3 Hz), 1.59 (4H, qt, *J* = 7.3, 7.6 Hz), 1.82 (3H, s), 2.55 (4H, t, *J* = 7.6 Hz), 3.68 (1H, s), 4.17 (2H, d, *J* = 4.0 Hz), 4.27 (2H, d, *J* = 3.3 Hz), 4.53 (1H, sept, *J* = 6.3 Hz), 5.82–5.91 (3H, m), 6.88 (2H, d, *J* = 8.9 Hz), 7.32 (2H, s), 7.37 (2H, d, *J* = 8.9 Hz); MS (EI) *m/z* 645 $[M]^+$.

Scheme 24

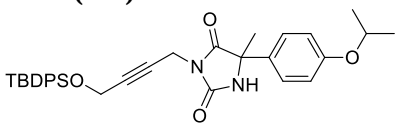
4-((*tert*-Butyldiphenylsilyl)oxy)but-2-yn-1-ol (193) [90]**:**



To a stirred solution of but-2-yne-1,4-diol (**192**) (1.0 g, 12 mmol) in DMF (10 mL), imidazole (1.6 g, 23 mmol) and *tert*-butyl(chloro)diphenylsilane (3.2 g, 12 mmol) were added at 0 °C. The reaction mixture was stirred at the same temperature for 1 h and then at room temperature for 2 h. The reaction mixture was diluted with water and

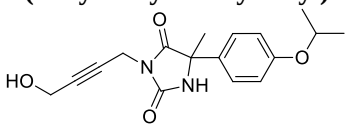
extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1) to give the title compound (1.5 g, 39%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (9H, s), 4.19 (1H, dd, *J* = 1.8, 1.8 Hz), 4.20 (1H, dd, *J* = 1.8, 1.8 Hz), 4.36 (2H, dd, *J* = 1.8, 1.8 Hz), 7.37–7.47 (6H, m), 7.70–7.72 (4H, m); MS (EI) *m/z* 324 $[M]^+$.

3-(4-((*tert*-Butyldiphenylsilyl)oxy)but-2-yn-1-yl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (194):



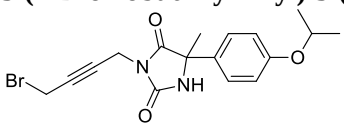
To a stirred solution of **193** (326 mg, 1.0 mmol) in THF (10 mL), **5** (248 mg, 1.0 mmol), PPh_3 (656 mg, 2.5 mmol) and DEAD (1.0 mL, 2.2 M in toluene, 2.2 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 14 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 8/1 to 2/1) to give the title compound (303 mg, 55%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (9H, s), 1.31 (6H, d, *J* = 5.9 Hz), 1.79 (3H, s), 4.26 (4H, s), 4.50 (1H, sept, *J* = 5.9 Hz), 6.32 (1H, s), 6.85 (2H, d, *J* = 8.9 Hz), 7.32–7.41 (8H, m), 7.65–7.69 (4H, m); MS (EI) *m/z* 555 $[M]^+$.

3-(4-Hydroxybut-2-yn-1-yl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (195):



To a stirred solution of **194** (303 mg, 0.55 mmol) in THF (5.5 mL), TBAF (602 μL, 0.60 mmol) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with 1 N HCl. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 20/1) to give the title compound (155 mg, 90%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (6H, d, *J* = 6.2 Hz), 1.82 (3H, s), 4.22 (1H, dd, *J* = 1.8, 1.8 Hz), 4.25 (1H, dd, *J* = 1.8, 1.8 Hz), 4.31 (2H, dd, *J* = 1.8, 1.8 Hz), 4.54 (1H, sept, *J* = 6.2 Hz), 5.74 (1H, s), 6.88 (2H, d, *J* = 8.9 Hz), 7.36 (2H, d, *J* = 8.9 Hz); MS (EI) *m/z* 316 $[M]^+$.

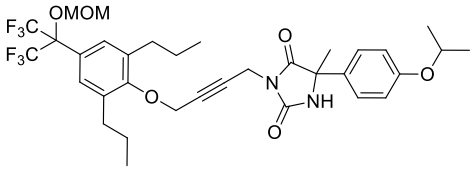
3-(4-Bromobut-2-yn-1-yl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (196):



To a stirred solution of **195** (158 mg, 0.50 mmol) in CH_2Cl_2 (10 mL), PPh_3 (196 mg, 0.75 mmol) and CBr_4 (248 mg, 0.747 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine,

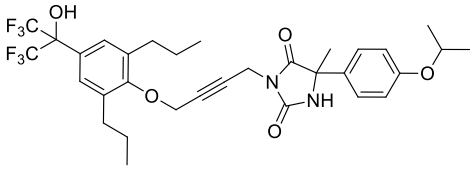
dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3/1 to 1/1) to give the title compound (165 mg, 87%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (6H, d, *J* = 6.2 Hz), 1.82 (3H, s), 3.81 (1H, dd, *J* = 1.8, 1.8 Hz), 3.83 (1H, dd, *J* = 1.8, 1.8 Hz), 3.99 (2H, dd, *J* = 1.8, 1.8 Hz), 4.54 (1H, sept, *J* = 6.2 Hz), 5.74 (1H, s), 6.88 (2H, d, *J* = 8.9 Hz), 7.36 (2H, d, *J* = 8.9 Hz); MS (EI) *m/z* 379 $[M]^+$.

3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2,6-dipropylphenoxy)-but-2-yn-1-yl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (197):



Compound **197** was prepared using an experimental procedure similar to that used for compound **190a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (6H, t, *J* = 7.3 Hz), 1.32 (6H, d, *J* = 6.2 Hz), 1.59 (4H, qt, *J* = 7.3, 7.6 Hz), 1.81 (3H, s), 2.61 (4H, t, *J* = 7.6 Hz), 3.55 (3H, s), 4.34 (2H, dd, *J* = 1.9, 1.9 Hz), 4.48 (2H, dd, *J* = 1.9, 1.9 Hz), 4.53 (1H, sept, *J* = 6.2 Hz), 4.83 (2H, s), 5.97 (1H, s), 6.88 (2H, d, *J* = 8.9 Hz), 7.23 (2H, s), 7.37 (2H, d, *J* = 8.9 Hz); MS (EI) *m/z* 687 $[M]^+$.

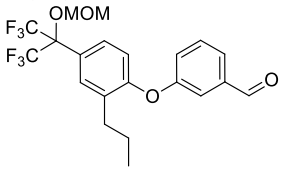
3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2,6-dipropylphenoxy)but-2-yn-1-yl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (198):



Compound **198** was prepared using an experimental procedure similar to that used for compound **191a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (6H, t, *J* = 7.3 Hz), 1.32 (6H, d, *J* = 6.1 Hz), 1.60 (4H, qt, *J* = 7.3, 7.6 Hz), 1.80 (3H, s), 2.59 (4H, t, *J* = 7.6 Hz), 3.95 (1H, s), 4.27 (2H, s), 4.51 (2H, s), 4.53 (1H, sept, *J* = 6.1 Hz), 5.79 (1H, s), 6.88 (2H, d, *J* = 8.8 Hz), 7.31 (2H, s), 7.35 (2H, d, *J* = 8.8 Hz); MS (EI) *m/z* 643 $[M]^+$.

Scheme 25

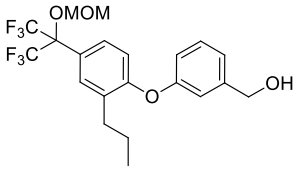
3-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)benzaldehyde (202a):



To a stirred solution of **140** (1.5 g, 4.2 mmol) in CH_2Cl_2 (42 mL), molecular sieves 4A (3.0 g), (3-formylphenyl)boronic acid (**201a**) (1.3 g, 8.4 mmol), copper acetate (II) (917 mg, 5.1 mmol) and pyridine (1.7

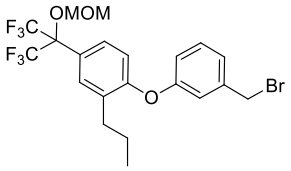
mL, 21 mmol) were added at room temperature. The reaction mixture was stirred at same temperature for 12 h. The reaction mixture was filtered through a pad of Celite and rinsed with $CHCl_3$. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (1.8 g, 95%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.6 Hz), 1.63–1.69 (2H, m), 2.64 (2H, t, *J* = 7.3 Hz), 3.56 (3H, s), 4.87 (2H, s), 6.87 (1H, d, *J* = 8.9 Hz), 7.24–7.66 (5H, m), 7.89 (1H, d, *J* = 8.4 Hz), 9.99 (1H, s); MS (EI) *m/z* 450 $[M]^+$.

(3-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)phenyl)methanol (203a):



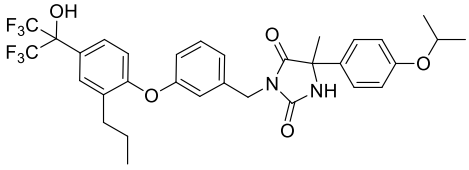
To a stirred solution of **202a** (1.8 g, 4.0 mmol) in MeOH (40 mL), $NaBH_4$ (0.16 g, 4.4 mmol) was added portionwise at 0 °C. The reaction mixture was stirred at the same temperature for 1 h. To the reaction mixture was added water. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1) to give the title compound (1.8 g, 99%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.6 Hz), 1.62-1.71 (2H, m), 2.68 (2H, t, *J* = 7.6 Hz), 3.56 (3H, s), 4.70–4.71 (2H, m), 4.86 (2H, s), 6.83 (1H, d, *J* = 8.9 Hz), 6.90–6.92 (1H, m), 7.03–7.15 (2H, m), 7.31–7.47 (4H, m); MS (EI) *m/z* 452 $[M]^+$.

1-(3-(Bromomethyl)phenoxy)-4-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propyl-benzene (204a):



Compound **204a** was prepared using an experimental procedure similar to that used for compound **196**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 1.59–1.70 (2H, m), 2.67 (2H, t, *J* = 7.3 Hz), 3.56 (3H, s), 4.47 (2H, s), 4.86 (2H, s), 6.84 (1H, d, *J* = 8.9 Hz), 6.90 (1H, ddd, *J* = 1.0, 2.0, 8.0 Hz), 7.05 (1H, dd, *J* = 1.0, 1.5 Hz), 7.16 (1H, ddd, *J* = 1.5, 2.0, 8.0 Hz), 7.30–7.48 (3H, m); MS (EI) *m/z* 515 $[M]^+$.

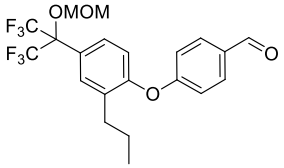
3-(3-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)benzyl)-5-(4-(1-methylethoxy)-phenyl)-5-methylimidazolidine-2,4-dione (206a):



Compound **206a** was prepared using an experimental procedure similar to that used for compound **191a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.3 Hz), 1.31 (6H,

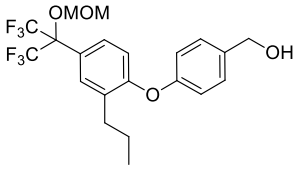
d, J = 5.4 Hz), 1.56–1.68 (2H, m), 1.78 (3H, s), 2.64 (2H, t, J = 7.6 Hz), 3.67 (1H, s), 4.52 (1H, sept, J = 5.4 Hz), 4.64 (2H, s), 5.71 (1H, s), 6.74–7.40 (11H, m); MS (EI) *m/z* 638 $[M]^+$.

4-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)benzaldehyde (202b):



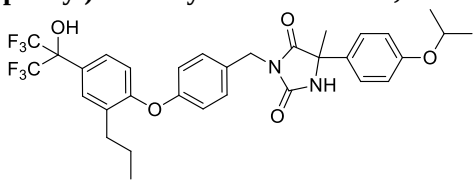
Compound **202b** was prepared with 4-formylboronic acid in place of 3-formylboronic acid using an experimental procedure similar to that used for compound **202a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.3 Hz), 1.54–1.66 (2H, m), 2.61 (2H, t, J = 7.6 Hz), 3.57 (3H, s), 4.88 (2H, s), 7.01 (1H, d, J = 8.6 Hz), 7.02–7.07 (2H, m), 7.44–7.55 (2H, m), 7.85–7.91 (2H, m) , 9.95 (1H, s); MS (EI) *m/z* 450 $[M]^+$.

(4-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)phenyl)methanol (203b):



Compound **203b** was prepared using an experimental procedure similar to that used compound **203a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.3 Hz), 1.53–1.70 (2H, m), 2.68 (2H, t, J = 7.6 Hz), 3.55 (3H, s), 4.69 (2H, d, J = 5.9 Hz), 4.85 (2H, s), 6.83 (1H, d, J = 8.6 Hz), 6.96–7.01 (2H, m), 7.30–7.47 (4H, m); MS (EI) *m/z* 452 $[M]^+$.

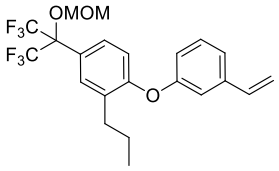
3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)benzyl)-5-(4-(1-methylethoxy)-phenyl)-5-methylimidazolidine-2,4-dione (206b):



Compound **206b** was prepared using an experimental procedure similar to that used compounds **196** and **191a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.32 (6H, d, J = 5.9 Hz), 1.59-1.68 (2H, m), 1.79 (3H, s), 2.65 (2H, t, J = 7.6 Hz), 3.56 (1H, s), 4.53 (1H, sept, J = 5.9 Hz), 4.63 (2H, s), 5.71 (1H, s), 6.80–6.91 (5H, m), 7.30–7.35 (2H, m), 7.43 (1H, d, J = 8.6 Hz), 7.55–7.57 (3H, m); MS (EI) *m/z* 652 $[M]^+$.

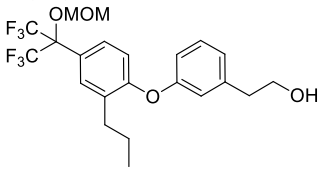
Scheme 26

4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propyl-1-(3-vinylphenoxy)benzene (208a):



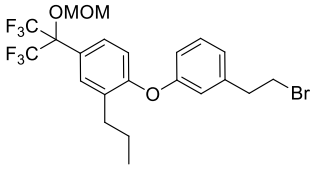
Compound **208a** was prepared with 3-vinylphenylboronic acid (**207a**) in place of 3-formylboronic acid (**201a**) using an experimental procedure similar to that used for compound **202a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7.3 Hz), 1.61–1.74 (2H, m), 2.70 (2H, t, *J* = 7.3 Hz), 3.56 (3H, s), 4.86 (2H, s), 5.28 (1H, dd, *J* = 0.5, 10.8 Hz), 5.74 (1H, dd, *J* = 0.5, 17.6 Hz), 6.69 (1H, dd, *J* = 10.8, 17.6 Hz), 6.83 (1H, d, *J* = 8.6 Hz), 6.87 (1H, ddd, *J* = 1.4, 2.4, 8.1 Hz), 7.07 (1H, dd, *J* = 1.9, 2.4 Hz), 7.19 (1H, ddd, *J* = 1.4, 1.9, 8.1 Hz), 7.31 (1H, dd, *J* = 8.1, 8.1 Hz), 7.30–7.50 (2H, m); MS (EI) *m/z* 448 $[M]^+$.

2-(3-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)phenyl)ethanol (209a):



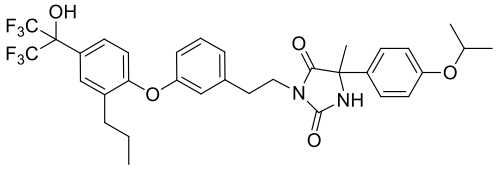
To a stirred solution of **208a** (550 mg, 1.2 mmol) in THF (10 mL), borane-THF complex (2.4 mL, 2.4 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h under an argon atmosphere. To the reaction mixture was added water and $NaBO_3$-$4H_2O$ (726 mg, 4.7 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated to remove THF. The residue was diluted with saturated $Na_2S_2O_3$ *aq*.. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/1) to give the title compound (252 mg, 46%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 1.62–1.71 (2H, m), 2.68 (2H, t, *J* = 7.3 Hz), 2.87 (2H, t, *J* = 6.5 Hz), 3.55 (3H, s), 3.88 (2H, dt, *J* = 6.5 , 6.5 Hz), 4.86 (2H, s), 6.81–7.08 (4H, m), 7.27–7.46 (3H, m); MS (EI) *m/z* 466 $[M]^+$.

1-(3-(2-Bromoethyl)phenoxy)-4-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylbenzene (210a):



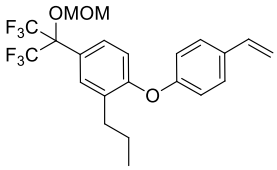
Compound **210a** was prepared using an experimental procedure similar to that used compound **196**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.3 Hz), 1.62–1.71 (2H, m), 2.68 (2H, t, *J* = 7.3 Hz), 3.16 (2H, t, *J* = 6.5 Hz), 3.55 (3H, s), 3.57 (2H, t, *J* = 7.6 Hz), 4.86 (2H, s), 6.82–7.10 (4H, m), 7.28–7.47 (3H, m); MS (EI) *m/z* 529 $[M]^+$.

3-(3-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)phenethyl)-5-(4-(1-methylethoxy)-phenyl)-5-methylimidazolidine-2,4-dione (212a):



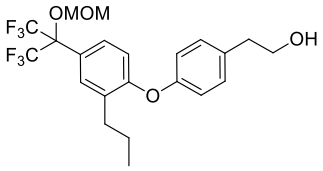
Compound **212a** was prepared using an experimental procedure similar to that used for compounds **196** and **191a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 1.31 (6H, d, *J* = 6.5 Hz), 1.59–1.69 (2H, m), 1.71 (3H, s), 2.67 (2H, t, *J* = 7.6 Hz), 2.93 (2H, t, *J* = 7.0 Hz), 3.69 (1H, s), 3.76 (2H, t, *J* = 7.0 Hz), 4.51 (1H, sept, *J* = 6.5 Hz), 5.70 (1H, s), 6.74–6.86 (6H, m), 6.93 (1H, d, *J* = 7.8 Hz), 7.16–7.27 (2H, m), 7.42 (1H, d, *J* = 8.6 Hz), 7.55 (1H, s); MS (EI) *m/z* 652 $[M]^+$.

4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propyl-1-(4-vinylphenoxy)benzene (208b):



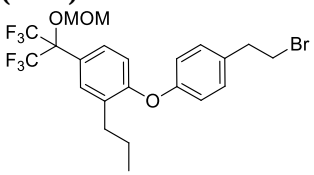
Compound **208b** was prepared with 4-vinylphenylboronic acid (**207b**) in place of 3-formylboronic acid (**203a**) using an experimental procedure similar to that used for compound **204a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.3 Hz), 1.61–1.70 (2H, m), 2.68 (2H, t, *J* = 7.6 Hz), 3.56 (3H, s), 4.86 (2H, s), 5.21 (1H, dd, *J* = 1.5, 10.8 Hz), 5.68 (1H, dd, *J* = 1.5, 17.6 Hz), 6.70 (1H, dd, *J* = 10.8, 17.6 Hz), 6.85 (1H, d, *J* = 8.6 Hz), 6.92–6.99 (2H, m), 7.34–7.48 (4H, m); MS (EI) *m/z* 448 $[M]^+$.

2-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)phenyl)ethanol (209b):



Compound **209b** was prepared using an experimental procedure similar to that used for compound **209a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 1.59–1.71 (2H, m), 2.69 (2H, t, *J* = 7.6 Hz), 2.87 (2H, t, *J* = 6.5 Hz), 3.55 (3H, s), 3.88 (2H, t, *J* = 6.5 Hz), 4.85 (2H, s), 6.82 (1H, d, *J* = 8.6 Hz), 6.93–6.98 (2H, m), 7.20–7.23 (2H, m), 7.30–7.47 (2H, m); MS (EI) *m/z* 466 $[M]^+$.

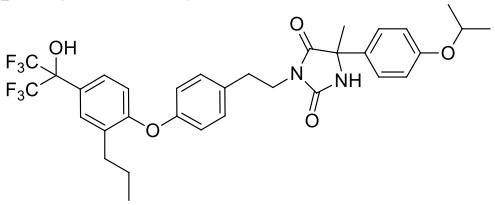
1-(4-(2-Bromoethyl)phenoxy)-4-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylbenzene (210b):



Compound **210b** was prepared using an experimental procedure similar to that used for compound **196**. The title

compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.3 Hz), 1.59–1.71 (2H, m), 2.68 (2H, t, *J* = 7.6 Hz), 3.15 (2H, t, *J* = 7.6 Hz), 3.55 (3H, s), 3.56 (2H, t, *J* = 7.6 Hz), 4.85 (2H, s), 6.83 (1H, d, *J* = 8.6 Hz), 6.91–6.97 (2H, m), 7.18–7.21 (2H, m), 7.43 (1H, d, *J* = 8.6 Hz), 7.56 (2H, s); MS (EI) *m/z* 529 $[M]^+$.

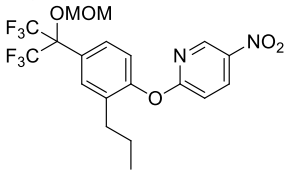
3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)phenethyl)-5-(4-(1-methylethoxy)-phenyl)-5-methylimidazolidine-2,4-dione (212b):



Compound **212b** was prepared using an experimental procedure similar to that used for compound **191a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.3 Hz), 1.29 (6H, d, *J* = 6.2 Hz), 1.62–1.71 (2H, m), 1.72 (3H, s), 2.67 (2H, t, *J* = 7.6 Hz), 2.92 (2H, t, *J* = 6.2 Hz), 3.75 (2H, t, *J* = 6.2 Hz), 3.77 (1H, s), 4.49 (1H, q, *J* = 6.2 Hz), 5.73 (1H, s), 6.73 (1H, d, *J* = 8.6 Hz), 6.81–6.91 (5H, m), 7.10–7.14 (2H, m), 7.42 (1H, d, *J* = 8.6 Hz), 7.54–7.56 (2H, m); MS (EI) *m/z* 652 $[M]^+$.

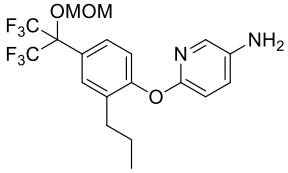
Scheme 27

2-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)-5-nitropyridine (214):



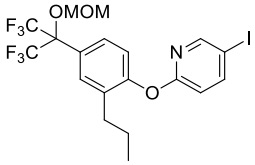
To a stirred solution of **140** (555 mg, 1.6 mmol) in DMF (12 mL), NaH (60% in oil, 96 mg, 2.40 mmol) and 2-chloro-5-nitropyridine (**213**) (279 mg, 1.8 mmol) were added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 5 min. The reaction mixture was diluted with water. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3/1) to give the title compound (760 mg, 99%) as yellow crystals; mp 54.3–56.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.3 Hz), 1.59 (2H, qt, *J* = 7.3, 7.6 Hz), 2.54 (2H, t, *J* = 7.6 Hz), 3.58 (3H, s), 4.90 (2H, s), 7.08 (1H, d, *J* = 9.0 Hz), 7.15 (1H, d, *J* = 8.6 Hz), 7.53 (1H, d, *J* = 8.6 Hz), 7.57 (1H, s), 8.52 (1H, dd, *J* = 2.9, 9.0 Hz), 9.04 (1H, d, *J* = 2.9 Hz); MS (EI) *m/z* 468 $[M]^+$.

6-(4- (1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)pyridine-3-amine (215):



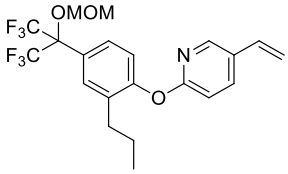
To a stirred solution of **214** (249 mg, 0.42 mmol) in AcOH (2.0 mL) and water (400 μL), iron powder (451 mg, 8.3 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was added 1 N NaOH *aq*. and then filtered through a pad of Celite and rinsed with $CHCl_3$.The aqueous layer was extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound (218 mg, 92%) as a yellow amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.3 Hz), 1.65 (2H, qt, *J* = 7.3, 7.8 Hz), 2.66 (2H, t, *J* = 7.8 Hz), 3.55 (3H, s), 4.85 (2H, s), 6.78 (1H, d, *J* = 8.1 Hz), 6.93 (1H, d, *J* = 8.6 Hz), 7.11 (1H, dd, *J* = 3.0, 8.1 Hz), 7.38 (1H, d, *J* = 8.6 Hz),7.46 (1H, s), 7.74 (1H, d, *J* = 3.0 Hz); MS (EI) *m/z* 438 $[M]^+$.

2-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)-5-iodopyridine (216):



To a stirred suspension of **215** (271 mg, 0.60 mmol) and *p*-TsOH·H_2O (342 mg, 1.8 mmol) in MeCN (3.0 mL), a mixed solution (water 400 μL) of $NaNO_2$ (83 mg, 1.2 mmol) and KI (249 mg, 1.5 mmol) was added dropwise at 10 °C. The reaction mixture was stirred at the same temperature for 10 min, and then stirred at room temperature for 18 h. The reaction mixture was added $Na_2S_2O_3$ *aq*. and a saturated $NaHCO_3$ *aq*.. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (226 mg, 67 %) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.0 Hz), 1.59 (2H, qt, *J* = 7.0, 7.3 Hz), 2.57 (2H, t, *J* = 7.3 Hz), 3.56 (3H, s), 4.88 (2H, s), 6.78 (1H, d, *J* = 8.6 Hz), 7.08 (1H, d, *J* = 8.6 Hz), 7.45 (1H, d, *J* = 8.6 Hz), 7.51 (1H, s), 7.95 (1H, dd, *J* =2.4, 8.6 Hz), 8.35 (1H, d, *J* = 2.4 Hz); MS (EI) *m/z* 549 $[M]^+$.

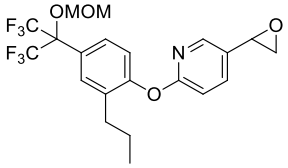
2-(4- (1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)-5-vinylpyridine (217):



To a stirred solution of **216** (154 mg, 0.28 mmol) in DMF (2.8 mL) and water (0.93 mL), vinylboronic acid pinacol ester (155 mg, 1.01 mmol), $Pd(PPh_3)_4$ (32 mg, 0.028 mmol) and Na_2CO_3 (178 mg, 1.68 mmol) was successively added at room temperature. The reaction mixture was irradiated in a microwave (manufactured by Biotage AB; Initiator) at 80 °C for 20 min. The reaction mixture was filtered through a pad of Celite and rinsed with EtOAc. The aqueous layer was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (115 mg, 91%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 7.3 Hz), 1.62 (2H, qt, *J* = 7.3, 7.8 Hz), 2.61 (2H, t, *J* = 7.8 Hz), 3.56 (3H, s), 4.88 (2H, s), 5.30 (1H, d, *J* = 11.3 Hz), 5.72 (1H , d, *J* = 17.8 Hz), 6.68 (1H, dd, *J* = 11.3, 17.8 Hz), 6.90 (1H, d, *J* = 8.6 Hz), 7.09 (1H, d, *J* = 8.9 Hz), 7.45 (1H, d, *J* = 8.9 Hz), 7.51 (1H, s), 7.81 (1H, dd, *J* = 2.2, 8.6 Hz), 8.17 (1H, d, *J* = 2.2 Hz);

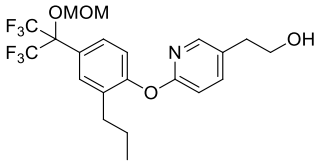
MS (EI) *m/z* 449 $[M]^+$.

2-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)-5-(oxiran-2-yl)pyridine (218a):



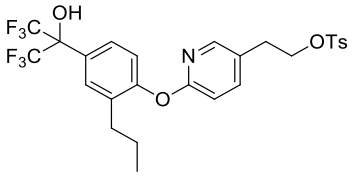
To a solution of **217** (115 mg, 0.26 mmol) in $CHCl_3$ (1.3 mL), $NaHCO_3$ (193 mg, 2.3 mmol) and *m*-CPBA (60%, 221 mg, 0.77 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was added saturated $Na_2S_2O_3$ *aq*. and saturated $NaHCO_3$ *aq*.. The aqueous layer was extracted with $CHCl_3$. The organic layer was washed with saturated $NaHCO_3$ *aq.* and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/acetone = 3/1) to give the title compound (66 mg, 55%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.3 Hz), 1.61 (2H, qt, *J* = 7.3, 7.6 Hz), 2.59 (2H, t, *J* = 7.6 Hz), 2.84 (1H, dd, *J* = 2.7, 5.1 Hz), 3.19 (1H, dd, *J* = 4.1, 5.1 Hz), 3.56 (3H, s), 3.88 (1H, dd, *J* = 2.7, 4.1 Hz), 4.88 (2H, s), 6.91 (1H, d, *J* = 8.6 Hz), 7.08 (1H, d, *J* = 8.6 Hz), 7.45 (1H, d, *J* = 8.6 Hz), 7.51 (1H, s), 7.56 (1H, d, *J* = 2.4, 8.6 Hz), 8.17(1H, d, *J* = 2.4 Hz); MS (EI) *m/z* 465 $[M]^+$.

2-(6-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)pyridin-3-yl)ethanol (219):



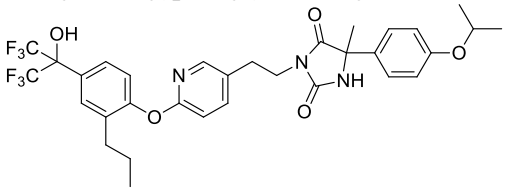
To a solution of **218a** (57 mg, 0.12 mmol) in THF (0.6 mL), $BF_3{\cdot}Et_2O$ (104 mg, 0.74 mmol) and $NaBH_3CN$ (92 mg, 1.5 mmol) were successively added at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was added water. The aqueous layer was extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ *aq.* and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/acetone = 2/1) to give the title compound (38 mg, 66%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 7.3 Hz), 1.64 (2H, qt, *J* = 7.3, 7.6 Hz), 2.62 (2H, t, *J* = 7.6 Hz), 2.91 (2H, t, *J* = 5.7 Hz), 3.57 (3H, s), 3.90 (2H , t, *J* =5.7 Hz), 4.86 (2H, s), 6.75 (1H, d, *J* = 8.6 Hz), 7.15 (1H, d, *J* = 8.6 Hz), 7.56 (1H, d, *J* = 8.6 Hz), 7.62 (1H, s), 7.92 (1H, dd, *J* = 2.4, 8.6 Hz), 8.39 (1H, d, *J* = 2.4 Hz); MS (EI) *m/z* 467 $[M]^+$.

2-(6-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)pyridin-3-yl)ethyl-4-methylbenzenesulfonate (220):



To a stirred solution of **219** (37 mg, 0.079 mmol) in CH_2Cl_2 (2 mL), pyridine (26 μL, 0.32 mmol) and *p*-TsCl (30 mg, 0.158 mmol) were added at 0 °C. The reaction mixture was stirred at 40 °C for 1 h. The reaction mixture was added MeOH (30 μL) and water. The aqueous layer was extracted with EtOAc. The organic layer was washed with 1 N HCl and a saturated $NaHCO_3$ *aq*, dried over Na_2SO_4, concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (13 mg, 50%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 7.3 Hz), 1.62 (2H, qt, *J* = 7.3, 7.3 Hz), 2.44 (3H, s), 2.60 (2H, t, *J* = 7.3 Hz), 2.93 (2H, t, *J* = 6.5 Hz), 3.56 (3H, s), 4.20 (2H , t, *J* = 6.5 Hz), 4.88 (2H, s), 6.83 (1H, d, *J* = 8.4 Hz), 7.05 (1H, d, *J* = 8.6 Hz), 7.32 (2H, d, *J* = 8.1 Hz), 7.44 (1H, d, *J* = 8.6 Hz), 7.50 (1H, s), 7.52 (1H, dd, *J* = 2.4, 8.4 Hz), 7.72 (2H, d, *J* = 8.1 Hz), 7.94 (1H, d, *J* = 2.4 Hz); MS (EI) *m/z* 621 $[M]^+$.

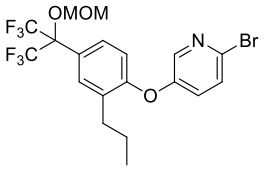
3-(2-(6-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)pyridin-3-yl)ethyl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (222):



Compound **222** was prepared with the tosylate derivative in place of the alkyl bromide derivative using an experimental procedure similar to that used for compound **191a**. Then the title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.3 Hz), 1.26 (6H, d, *J* = 5.8 Hz), 1.56–1.63 (5H, m), 2.57 (2H, t, *J* = 7.8 Hz), 2.92 (2H, t, *J* = 6.6 Hz), 3.74 (2H, t, *J* = 6.6 Hz), 4.55 (1H, sept, *J* = 5.8 Hz), 6.85 (2H, d, *J* = 8.8 Hz), 6.95 (1H, d, *J* = 8.6 Hz), 7.26 (2H, d, *J* = 8.8 Hz), 7.56–7.64 (4H, m), 7.90 (1H, s); MS (EI) *m/z* 653 $[M]^+$.

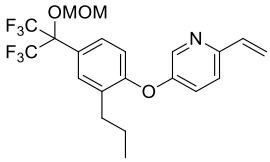
Scheme 28

2-Bromo-5-(4-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)pyridine (224):



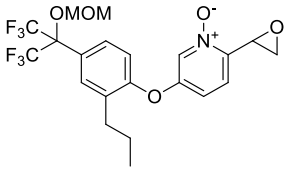
Compound **224** was prepared with 2-bromopyridine-5-boronic acid (**223**) in place of 3-formylboronic acid (**201a**) using an experimental procedure similar to used for compound **202a**. Then the title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.3 Hz), 1.56–1.71 (2H, m), 2.65 (2H, t, *J* = 7.6 Hz), 3.56 (3H, s), 4.86 (2H, s), 6.87 (1H, d, *J* = 8.6 Hz), 7.16 (1H, dd, *J* = 3.0, 8.6 Hz), 7.40–7.54 (3H, m) , 8.16 (1H, d, 3.0 Hz); MS (EI) *m/z* 502 $[M]^+$.

5-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)-2-vinylpyridine (225):



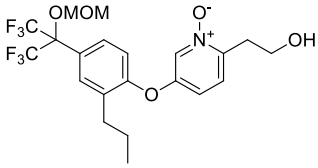
To a stirred solution of **224** (700 mg, 1.4 mmol) in DMF (9.3 mL) and water (3.1 mL), vinylboronic acid pinacol ester (1.1 g, 7.3 mmol), $Pd(PPh_3)_4$ (240 mg, 0.21 mmol) and Na_2CO_3 (1.3 g, 13 mmol) were successively added at room temperature. The reaction mixture was irradiated in a microwave (Initiator; Biotage AB) at 80 °C for 1 h. The reaction mixture was filtered through a pad of Celite and rinsed with EtOAc. The aqueous layer was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 15/1) to give the title compound (572 mg, 92%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 1.66 (2H, qt, *J* = 7.3, 7.8 Hz), 2.68 (2H, t, *J* = 7.8 Hz), 3.56 (3H, s), 4.86 (2H, s), 5.45 (1H, dd, *J* = 1.2, 12.0 Hz), 6.12 (1H , dd, *J* = 1.2, 17.6 Hz), 6.82 (1H, dd, *J* = 12.0, 17.6 Hz), 6.86 (1H, d, *J* = 8.8 Hz), 7.24 (1H, dd, *J* = 2.7, 8.6 Hz), 7.35 (1H, d, *J* = 8.6 Hz), 7.40 (1H, d, *J* = 8.8 Hz), 7.51 (1H, s), 8.34 (1H, d, *J* = 2.7 Hz); MS (EI) *m/z* 449 $[M]^+$.

5-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)-2-(oxyrane-2-yl)-pyridine-1-oxide (226):



To a solution of **225** (572 mg, 1.3 mmol) in $CHCl_3$ (6.4 mL), $NaHCO_3$ (1.9 g, 23 mmol) and *m*-CPBA (60%, 2.2 g, 7.6 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was added saturated $Na_2S_2O_3$ *aq*. and saturated $NaHCO_3$ *aq*.. The aqueous layer was extracted with $CHCl_3$. The organic layer was washed with saturated $NaHCO_3$ *aq.* and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/acetone = 3/1) to give the title compound (312 mg, 51%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.3 Hz), 1.62 (2H, qt, *J* = 7.3, 7.6 Hz), 2.60 (2H, t, *J* = 7.6 Hz), 2.73 (1H, dd, *J* = 2.7, 5.9 Hz), 3.30 (1H , dd, *J* = 4.3, 5.9 Hz), 3.57 (3H, s), 4.50 (1H, dd, *J* = 2.7, 4.3 Hz), 4.87 (2H, s), 6.93 (1H, dd, *J* = 2.2, 8.9 Hz), 6.99 (1H, d, *J* = 8.4 Hz), 7.21 (1H, d, *J* = 8.9 Hz), 7.47 (1H, d, *J* = 8.4 Hz), 7.54 (1H, s), 7.99 (1H, d, *J* = 2.2 Hz); MS (EI) *m/z* 481 $[M]^+$.

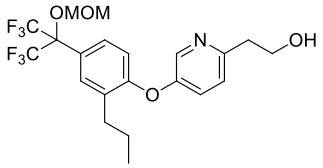
5-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)-2-(2-hydroxyethyl)-pyridine 1-oxide (227):



To a stirred solution of **226** (312 mg, 0.65 mmol) in THF (6.5 mL), $BF_3{\cdot}Et_2O$ (717 μL, 5.8 mmol) and $NaBH_3CN$

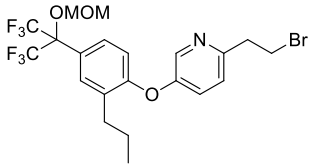
(732 mg, 12 mmol) were added dropwise at 0 °C under an argon atmosphere. The reaction mixture was stirred at the same temperature for 16 h. The reaction mixture was added saturated $NaHCO_3$ *aq*.. The aqeous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 20/1) to give the title compound (99 mg, 32%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.3 Hz), 1.64 (2H, qt, *J* = 7.3, 7.6 Hz), 2.67 (2H, t, *J* = 7.6 Hz), 3.11 (2H, t, *J* = 5.7 Hz), 3.53 (3H, s), 3.91 (2H , t, *J* = 5.7 Hz), 4.88 (2H, s), 7.13 (1H, d, *J* = 8.6 Hz), 7.19 (1H, dd, *J* = 2.2, 8.6 Hz), 7.50 (1H, d, *J* = 8.6 Hz), 7.53 (1H, d, *J* = 8.6 Hz), 7.60 (1H, s), 8.11 (1H, d, *J* = 2.2 Hz); MS (EI) *m/z* 483 $[M]^+$.

2-(5-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)pyridin-2-yl)ethanol (228):



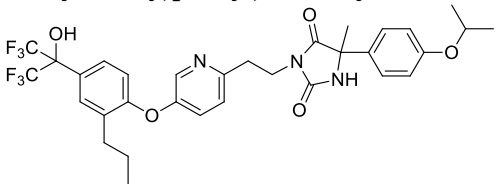
To a stirred solution of **227** (99 mg, 0.21 mmol) in AcOH (2.0 mL), zinc powder (268 mg, 4.1 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was filtered through a pad of Celite and rinsed with EtOAc. The filtrate was added saturated $NaHCO_3$ *aq*.. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/acetone = 3/1) to give the title compound (70 mg, 73%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.6 Hz), 1.67 (2H, qt, *J* = 7.6, 7.8 Hz), 2.69 (2H, t, *J* = 7.8 Hz), 3.02 (2H, t, *J* = 5.6 Hz), 3.56 (3H, s), 4.03 (2H , t, *J* = 5.6 Hz), 4.86 (2H, s), 6.83 (1H, d, *J* = 8.8 Hz), 7.17 (1H, d, *J* = 8.3 Hz), 7.26 (1H, dd, *J* = 3.0, 8.8 Hz), 7.40 (1H, d, *J* = 8.3 Hz), 7.51 (1H, s), 8.28 (1H, d, *J* = 3.0 Hz); MS (EI) *m/z* 467 $[M]^+$.

2-(2-Bromoethyl)-5-(4-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)pyridine (229):



Compound **229** was prepared using an experimental procedure similar to that used for compound **196**. Then the title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7.3 Hz), 1.67 (2H, qt, *J* = 7.3, 7.6 Hz), 2.69 (2H, t, *J* = 7.6 Hz), 3.35 (2H, t, *J* = 6.8 Hz), 3.57 (3H, s), 3.79 (2H , t, *J* = 6.8 Hz), 4.87 (2H, s), 6.85 (1H, d, *J* = 8.6 Hz), 7.20 (1H, d, *J* = 8.4 Hz), 7.26 (1H, dd, *J* = 2.4, 8.6 Hz), 7.41 (1H, d, *J* = 8.4 Hz), 7.51 (1H, s), 8.35 (1H, d, *J* = 2.4 Hz); MS (EI) *m/z* 530 $[M]^+$.

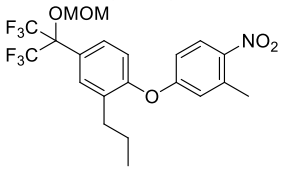
3-(2-(5-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)pyridin-2-yl)ethyl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (231):



Compound **231** was prepared using an experimental procedure similar to that used for compound **191a**. Then the title compound was obtained as a colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.2 Hz), 1.30 (6H, d, *J* = 5.9 Hz), 1.62 (2H, qt, *J* = 7.2, 7.6 Hz), 1.70 (3H, s), 2.58 (2H, t, *J* = 7.6 Hz), 3.16 (2H, t, *J* = 6.4 Hz), 3.98 (2H, t, *J* = 6.4 Hz), 4.52 (1H, sept, *J* = 5.9 Hz), 6.85 (2H, d, *J* = 8.9 Hz), 6.96 (1H, d, *J* = 8.6 Hz), 7.27 (1H, d, *J* = 8.6 Hz), 7.33 (2H, d, *J* = 8.9 Hz), 7.48 (1H, d, *J* = 8.6 Hz), 7.68 (1H, d, *J* = 8.6 Hz), 7.72 (1H, s), 8.23 (1H, s); MS (EI) *m/z* 653 $[M]^+$.

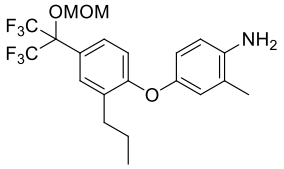
Scheme 29

2-Methyl-4-(2-propyl-4-(2,2,2-trifluoro-1-methoxymethoxy-1-trifluoromethylethyl)phenoxy)-1-nitro-benzene (234a):



To a stirred suspension of **140** (50 mg, 0.14 mmol) and K_2CO_3 (40 mg, 0.29 mmol) in DMF (1.2 mL), 4-fluoro-2-methyl-1-nitrobenzene (**233a**) (34 mg, 0.22 mmol) was added dropwise at room temperature. The reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3/1) to give the title compound (73 mg, 99%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.3 Hz), 1.62 (2H, qt, *J* = 7.3, 7.8 Hz), 2.60 (2H, t, *J* = 7.8 Hz), 2.62 (3H, s), 3.57 (3H, s), 4.88 (2H, s), 6.81 (1H, dd, *J* = 2.2, 9.0 Hz), 6.87 (1H, d, *J* = 2.2 Hz), 6.99 (1H, d, *J* = 8.8 Hz), 7.48 (1H, d, *J* = 8.8 Hz), 7.55 (1H, s), 8.07 (1H, d, *J* = 9.0 Hz); MS (EI) *m/z* 481 $[M]^+$.

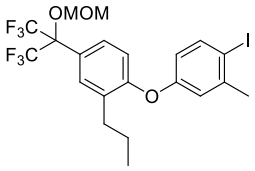
4-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)-2-methylaniline (235a):



A suspension of **234a** (293 mg, 0.61 mmol) and 10% Pd/C (29 mg) in MeOH (3.0 mL) was stirred under a hydrogen atmosphere at room temperature for 3 h. The reaction mixture was filtered through a pad of Celite and rinsed with EtOAc. The filtrate was concentrated *in vacuo* to give the title compound (274 mg, 99%) as a red

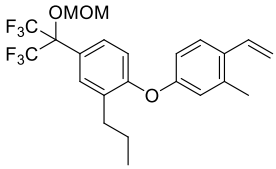
purple oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, *J* = 7.4 Hz), 1.68 (2H, qt, *J* = 7.4, 7.8 Hz), 2.17 (3H, s), 2.71 (2H, t, *J* = 7.8 Hz), 3.54 (3H, s), 4.84 (2H, s), 6.68 (1H, d, *J* = 8.3 Hz), 6.70 (1H, d, *J* = 8.8 Hz), 6.73 (1H, dd, *J* = 2.4, 8.3 Hz), 6.78 (1H, d, *J* = 2.4 Hz), 7.27 (1H, d, *J* = 8.8 Hz), 7.40 (1H, s); MS (EI) *m/z* 451 $[M]^+$.

4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-1-(4-iodo-3-methylphenoxy)-2-propylbenzene (236a):



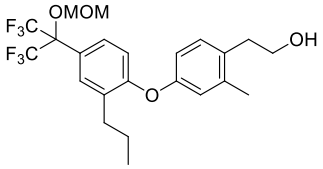
To a stirred suspension of **235a** (271 mg, 0.60 mmol) and *p*-TsOH·H_2O (342 mg, 1.8 mmol) in MeCN (3.0 mL), a mixed solution of $NaNO_2$ (83 mg, 1.2 mmol) and KI (249 mg, 1.5 mmol) in water (400 μL) were added dropwise at 10 °C. The reaction mixture was stirred at the same temperature for 10 min, and then stirred at room temperature for 18 h. The reaction mixture was added $Na_2S_2O_3$ *aq*. and a saturated $NaHCO_3$ *aq*.. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (226 mg, 67 %) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.6 Hz), 1.64 (2H, qt, *J* = 7.6, 7.6 Hz), 2.41 (3H, s), 2.66 (2H, t, *J* = 7.6 Hz), 3.56 (3H, s), 4.86 (2H, s), 6.54 (1H, dd, *J* = 2.4, 8.6 Hz), 6.83 (1H, d, *J* = 8.6 Hz), 6.91 (1H, d, *J* = 2.4 Hz), 7.37 (1H, d, *J* = 8.6 Hz), 7.47 (1H, s), 7.74 (1H, d, *J* = 8.6 Hz); MS (EI) *m/z* 562 $[M]^+$.

4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-1-(3-methyl-4-vinylphenoxy)-2-propylbenzene (237a):



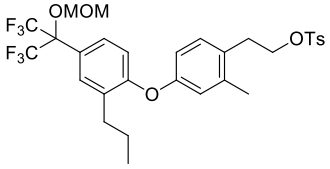
To a stirred solution of **236a** (265 mg, 0.47 mmol) in DMF (4.7 mL) and water (0.9 mL), vinylboronic acid pinacol ester (280 μL, 1.7 mmol), $Pd(PPh_3)_4$ (54 mg, 0.050 mmol) and Na_2CO_3 (300 mg, 2.8 mmol) were successively added at room temperature. The reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was filtered through a pad of Celite and rinsed with EtOAc. The aqueous layer was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/$CHCl_3$ = 10/1) to give the title compound (218 mg, 99%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 1.66 (2H, qt, *J* = 7.3, 7.3 Hz), 2.34 (3H, s), 2.68 (2H, t, *J* = 7.3 Hz), 3.55 (3H, s), 4.85 (2H, s), 5.26 (1H, dd, *J* = 1.4, 11.1 Hz), 5.59 (1H, dd, *J* = 1.4, 17.3 Hz), 6.77–6.81 (2H, m), 6.83 (1H, d, *J* = 8.9 Hz), 6.89 (1H, dd, *J* = 11.1, 17.3 Hz), 7.34 (1H, d, *J* = 8.9 Hz), 7.45(1H, s), 7.46 (1H, d, *J* = 8.9 Hz); MS (EI) *m/z* 462 $[M]^+$.

2-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)-2-methylphenyl)ethan-1-ol (238a):



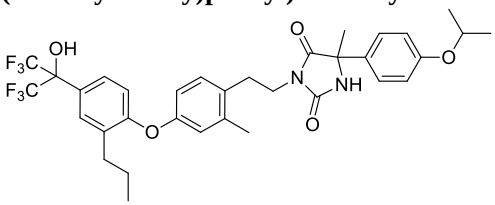
Compound **238a** was prepared using an experimental procedure similar to that used for compound **209a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 1.67 (2H, qt, *J* = 7.3, 7.3 Hz), 2.33 (3H, s), 2.69 (2H, t, *J* = 7.3 Hz), 2.89 (2H, t, *J* = 6.8 Hz), 3.55 (3H, s), 3.82–3.88 (2H, m), 4.85 (2H, s), 6.78 (1H, dd, *J* = 2.7, 8.4 Hz), 6.80 (1H, d, *J* = 8.6 Hz), 6.85 (1H, d, *J* = 2.7 Hz), 7.15 (1H, d, *J* = 8.4 Hz), 7.34 (1H, d, *J* = 8.6 Hz), 7.45 (1H, s); MS (EI) *m/z* 480 $[M]^+$.

4-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)-2-methylphenethyl-4-methylbenzenesulfonate (239a):



To a stirred solution of **238a** (189 mg, 0.040 mmol) in CH_2Cl_2 (300 μL), pyridine (24 μL, 0.49 mmol) and *p*-TsCl (17 mg, 0.090 mmol) were added at 0 °C. The reaction mixture was stirred at 40 °C for 2 h. To the reaction mixture was added water. The aqueous layer was extracted with EtOAc. The organic layer was washed with 1N HCl and a saturated $NaHCO_3$ *aq*, dried over Na_2SO_4, concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (13 mg, 50%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 1.67 (2H, qt, *J* = 7.3, 7.3 Hz), 2.22 (3H, s), 2.45 (3H, s), 2.68 (2H, t, *J* = 7.3 Hz), 2.96 (2H, t, *J* = 7.3 Hz), 3.56 (3H, s), 4.17 (2H, t, *J* = 7.3 Hz), 4.85 (2H, s), 6.71 (1H, dd, *J* = 2.7, 8.4 Hz), 6.77 (1H, d, *J* = 8.4 Hz), 6.78 (1H, d, *J* = 2.7 Hz), 7.02 (1H, d, *J* = 8.4 Hz), 7.30–7.34 (1H, m), 7.31 (2H, d, *J* = 7.8 Hz), 7.46 (1H, s), 7.73 (2H, d, *J* = 7.8 Hz); MS (EI) *m/z* 634 $[M]^+$.

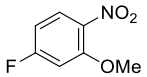
3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)-2-methylphenethyl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (240a):



Compound **240a** was prepared with the tosylate in place of the alkyl bromide using an experimental procedure similar to that used for compound **191a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 1.30 (6H, d, *J* = 6.1 Hz), 1.66 (2H, qt, *J* = 7.3, 7.6 Hz), 1.74 (3H, s), 2.34 (3H, s), 2.67 (2H, t, *J* = 7.6 Hz), 2.80–2.96 (2H, m), 3.63 (1H, s), 3.71 (2H, t, *J* = 7.4 Hz), 4.50 (1H, sept, *J* = 6.1 Hz), 5.68 (1H, s), 6.64 (1H, d, *J* = 8.6 Hz), 6.75 (1H, d, *J* = 8.6 Hz), 6.78 (1H, s), 6.85 (2H, d, *J* = 8.8 Hz), 7.01 (1H, d,

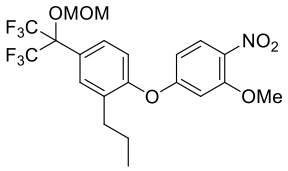
J = 8.3 Hz), 7.30 (2H, d, *J* = 8.8 Hz), 7.42 (1H, d, *J* = 8.3 Hz), 7.54 (1H, s); MS (EI) *m/z* 666 $[M]^+$.

4-Fluoro-2-methoxy-1-nitrobenzene (233b):



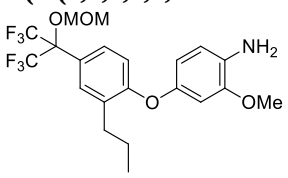
To a stirred suspension of 4-fluoro-2-hydroxy-1-nitrobenzene (**232**) (100 mg, 0.64 mmol) and K_2CO_3 (132 mg, 0.96 mmol) in DMF (3.2 mL), methyl iodide (108 mg, 0.76 mmol) was added at 0 °C. The reaction mixture was stirred at 60 °C for 1 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound (118 mg, 99%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (3H, s), 6.74 (1H, ddd, *J* = 2.4, 7.8, 9.0 Hz), 6.80 (1H, dd, *J* = 2.4, 10.2 Hz), 7.97 (1H, dd, *J* = 6.1, 9.0 Hz); MS (EI) *m/z* 171 $[M]^+$.

4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-1-(3-methoxy-4-nitrophenoxy)-2-propylbenzene (234b):



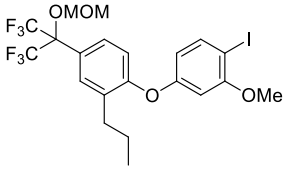
Compound **234b** was prepared using an experimental procedure similar to used for compound **234a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.3 Hz), 1.62 (2H, qt, *J* = 7.3, 7.3 Hz), 2.61 (2H, t, *J* = 7.3 Hz), 3.57 (3H, s), 3.93 (3H, s), 4.88 (2H, s), 6.43 (1H, dd, *J*= 2.4, 9.0 Hz), 6.69 (1H, d, *J* = 2.4 Hz), 7.02 (1H, d, *J* = 8.5 Hz), 7.49 (1H, d, *J* = 8.5 Hz), 7.56 (1H, s), 7.95 (1H, d, *J* = 9.0 Hz); MS (EI) *m/z* 497 $[M]^+$.

4-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)-2-methoxyaniline (235b):



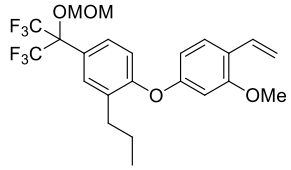
To a stirred solution of **234b** (226 mg, 0.45 mmol) in AcOH (2.3 mL) and water (600 μL), iron powder (380 mg, 6.8 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 1 h. To the reaction mixture was added 1 N NaOH *aq*.. The reaction mixture was filtered through a pad of Celite and rinsed with EtOAc. The filtrate was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound (241 mg, 99%) as a yellow amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.3 Hz), 1.70 (2H, qt, *J* = 7.3, 7.8 Hz), 2.73 (2H, t, *J* = 7.8 Hz), 3.54 (3H, s), 3.83 (3H, s), 4.84 (2H, s), 6.47 (1H, dd, *J* = 2.0, 8.8 Hz), 6.56 (1H, d, *J* = 2.0 Hz), 6.70 (1H, d, *J* = 8.6 Hz), 6.72 (1H, d, *J* = 8.8 Hz), 7.28 (1H, d, *J* = 8.6 Hz), 7.42 (1H, s); MS (EI) *m/z* 467 $[M]^+$.

4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-1-(4-iodo-3-methoxyphenoxy)-2-propylbenzene (236b):



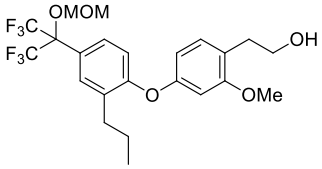
Compound **236b** was prepared using an experimental procedure similar to that used for compound **236a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.3 Hz), 1.70 (2H, qt, *J* = 7.3, 7.8 Hz), 2.73 (2H, t, *J* = 7.8 Hz), 3.54 (3H, s), 3.83 (3H, s), 4.84 (2H, s), 6.47 (1H, dd, *J* = 2.0, 8.8 Hz), 6.56 (1H, d, *J* = 2.0 Hz), 6.70 (1H, d, *J* = 8.6 Hz), 6.72 (1H, d, *J* = 8.8 Hz), 7.28 (1H, d, *J* = 8.6 Hz), 7.42 (1H, s); MS (EI) *m/z* 578 $[M]^+$.

4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-1-(3-methoxy-4-vinylphenoxy)-2-propylbenzene (237b):



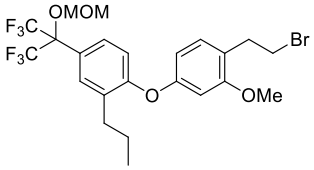
Compound **237b** was prepared using an experimental procedure similar to that used for compound **237a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 1.67 (2H, qt, *J* = 7.3, 7.8 Hz), 2.69 (2H, t, *J* = 7.8 Hz), 3.56 (3H, s), 3.82 (3H, s), 4.86 (2H, s), 5.23 (1H, dd, *J* = 1.7, 11.2 Hz), 5.68 (1H, dd, *J* = 1.7, 17.8 Hz), 6.50 (1H, dd, *J* = 2.2, 8.5), 6.58 (1H, d, *J* = 2.2 Hz), 6.87 (1H, d, *J* = 8.8 Hz), 6.99 (1H, dd, *J* = 11.2, 17.8 Hz), 7.36 (1H, d, *J* = 8.8 Hz), 7.42 (1H, d, *J* = 8.5 Hz), 7.47 (1H, s); MS (EI) *m/z* 478 $[M]^+$.

2-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)-2-methoxyphenyl)-ethan-1-ol (238b):



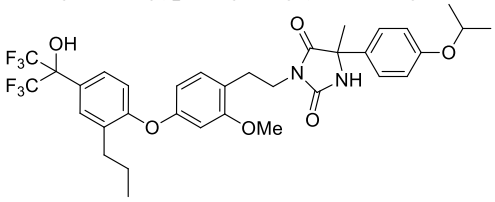
Compound **238b** was prepared using an experimental procedure similar to that used for compound **209a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7.3 Hz), 1.68 (2H, qt, *J* = 7.3, 7.8 Hz), 2.69 (2H, t, *J* = 7.8 Hz), 2.89 (2H, t, *J* = 6.4 Hz), 3.55 (3H, s), 3.80 (3H, s), 3.83 (2H, t, *J* = 6.4 Hz), 4.85 (2H, s), 6.48 (1H, dd, *J* = 2.2, 8.3 Hz), 6.59 (1H, d, *J* = 2.2 Hz), 6.84 (1H, d, *J* = 8.6 Hz), 7.12 (1H, d, *J* = 8.3 Hz), 7.35 (1H, d, *J* = 8.6 Hz), 7.46 (1H, s); MS (EI) *m/z* 496 $[M]^+$.

1-(2-Bromoethyl)-4-(4-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)-2-methoxybenzene (239b):



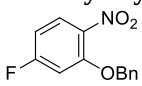
Compound **239b** was prepared using an experimental procedure similar to that used for compound **196**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7.3 Hz), 1.67 (2H, qt, *J* = 7.3, 7.8 Hz), 2.69 (2H, t, *J* = 7.8 Hz), 3.15 (2H, t, *J* = 7.6 Hz), 3.56 (3H, s), 3.57 (2H, t, *J* = 7.6 Hz), 3.80 (3H, s), 4.86 (2H, s), 6.47 (1H, dd, *J* = 2.4, 8.1 Hz), 6.58 (1H, d, *J* = 2.4 Hz), 6.84 (1H, d, *J* = 8.9 Hz), 7.10 (1H, d, *J* = 8.1 Hz), 7.36 (1H, d, *J* = 8.9 Hz), 7.47 (1H, s); MS (EI) *m/z* 559 $[M]^+$.

3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)-2-methoxyphenethyl)-5-(1-(1-methylethoxy)phenyl-4-yl)-5-methylimidazolidine-2,4-dione (241b):



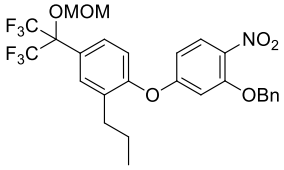
Compound **241b** was prepared using an experimental procedure similar to that used for compound **191a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, CD_3OD) δ 0.96 (3H, t, *J* = 7.5 Hz), 1.23 (6H, d, *J* = 6.1 Hz), 1.61 (3H, s), 1.63-1.72 (2H, m), 2.68 (2H, t, *J* = 7.5 Hz), 2.88 (2H, t, *J* = 6.5 Hz), 3.72 (3H, s), 3.74 (2H, t, *J* = 6.5 Hz), 4.47–4.51 (1H, m), 6.19 (1H, dd, *J* = 2.2, 8.0 Hz), 6.52 (1H, d, *J* = 2.2 Hz), 6.74 (1H, d, *J* = 8.8 Hz), 6.80 (2H, d, *J* = 8.8 Hz), 7.25–7.29 (3H, m), 7.49 (1H, d, *J* = 8.8 Hz), 7.60 (1H, s); MS (EI) *m/z* 682 $[M]^+$.

2-Benzyloxy-4-fluoro-1-nitrobenzene (233c) [91]**:**



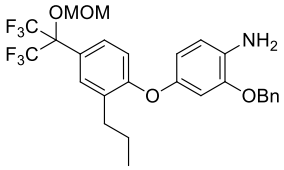
To a stirred suspension of 4-fluoro-2-hydroxy-1-nitrobenzene (**232**) (5.0 g, 32 mmol) and K_2CO_3 (5.3 g, 38 mmol) in DMF (50 mL), benzyl bromide (6.0 g, 35 mmol) was added at room temperature. The reaction mixture was stirred at 60 °C for 1 h. After the reaction was completed, the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/1) to give the title compound (9.5 g, 99%) as pale yellow crystals; mp 53.4–54.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.23 (2H, s), 6.74 (1H, ddd, *J* = 2.4, 7.3, 9.0 Hz), 6.83 (1H, dd, *J* = 2.4, 10.2 Hz), 7.33–7.47 (5H, m), 7.97 (1H, dd, *J* = 6.1, 9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.5, 102.9 (d, *J* = 26.7 Hz), 107.7 (d, *J* = 22.9 Hz), 127.0 (2C), 128.1 (d, *J* = 11.4 Hz), 128.5, 128.8 (2C), 134.8, 136.3, 154.2 (d, *J* = 11.4 Hz), 165.6 (d, *J* = 255 Hz); MS (EI) *m/z* 247 $[M]^+$; Anal. Calcd for $C_{13}H_{10}FNO_3$: C, 63.16; H, 4.08; N, 5.67. Found: C, 63.23; H, 4.11; N, 5.61.

2-(Benzyloxy)-4-(4-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)-1-nitro-benzene (234c):



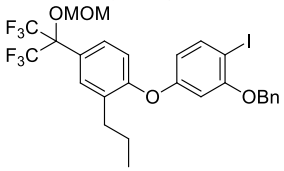
To a stirred suspension of **140** (5.3 g, 15 mmol) and K_2CO_3 (2.6 g, 19 mmol) in DMF (25 mL), **235c** (3.2 g, 13 mmol) was added at room temperature. The reaction mixture was stirred at 80 °C for 3 h. After the reaction was completed, the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/acetone = 10/1) to give the title compound (8.3 g, 99%) as pale yellow crystals; mp 82.7–85.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.1 Hz), 1.55 (2H, qt, *J* = 7.1, 7.8 Hz), 2.50 (2H, t, *J* = 7.8 Hz), 3.58 (3H, s), 4.89 (2H, s), 5.18 (2H, s), 6.50 (1H, dd, *J* = 2.2, 8.6 Hz), 6.58 (1H, d, *J* = 2.2 Hz), 6.92 (1H, d, *J* = 8.8 Hz), 7.31–7.39 (5H, m), 7.46 (1H, d, *J* = 8.8 Hz), 7.54 (1H, s), 7.97 (1H, d, *J* = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 22.8, 31.7, 56.1, 70.8, 78.8 (sept, *J* = 29.7 Hz), 94.0, 103.8, 108.5, 120.4, 122.5 (q, *J* = 289 Hz), 124.6, 126.8 (2C), 127.7, 127.8, 127.9, 128.4 (2C), 131.1, 135.1, 135.2, 135.9, 154.0, 154.5, 161.9; MS (EI) *m/z* 573 $[M]^+$; Anal. Calcd for $C_{27}H_{25}F_6NO_6$: C, 56.55; H, 4.39; N, 2.44. Found: C, 56.57; H, 4.33; N, 2.42.

2-(Benzyloxy)-4-(4-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)aniline (235c):



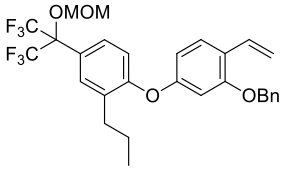
To a stirred solution of **234c** (8.3 g, 13 mmol) in AcOH (64 mL) and water (4.0 mL), iron powder (11 g, 191 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 4 h and then added 1 N NaOH *aq*. at 0 °C. The reaction mixture was filtered through a pad of Celite and rinsed with EtOAc. The reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound (8.5 g, 99%) as a yellow amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, *J* = 7.3 Hz), 1.68 (2H, qt, *J* = 7.3, 7.3 Hz), 2.70 (2H, t, *J* = 7.3 Hz), 3.55 (3H, s), 4.84 (2H, s), 5.04 (2H, s), 6.50 (1H, dd, *J* = 2.4, 8.3 Hz), 6.61 (1H, d, *J* = 2.4 Hz), 6.67 (1H, d, *J* = 8.8 Hz), 6.72 (1H, d, *J* = 8.3 Hz), 7.33–7.40 (7H, m); MS (EI) *m/z* 543 $[M]^+$; Anal. Calcd for $C_{27}H_{27}F_6NO_4$: C, 59.67; H, 5.01; N, 2.58. Found: C, 59.66; H, 4.87; N, 2.65.

2-(Benzyloxy)-4-(4-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)-1-iodo-benzene (236c):



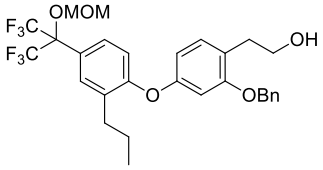
To a stirred suspension of **235c** (8.5 g, 13 mmol) and *p*-TsOH·H_2O (7.3 g, 38 mmol) in MeCN (64 mL), the solution (water 8.5 mL) of a mixture of $NaNO_2$ (1.8 g, 26 mmol) and KI (5.3 g, 32 mmol) were added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 10 min, and stirred at room temperature for 18 h. To the reaction mixture was added saturated $Na_2S_2O_3$ *aq*. and saturated $NaHCO_3$ *aq*. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (4.9 g, 58%) as yellow crystals; mp 53.3–56.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.3 Hz), 1.61 (2H, qt, *J* = 7.3, 7.6 Hz), 2.60 (2H, t, *J* = 7.6 Hz), 3.56 (3H, s), 4.86 (2H, s), 5.11 (2H, s), 6.36 (1H, dd, *J* = 2.4, 8.6 Hz), 6.52 (1H, d, *J* = 2.4 Hz), 6.78 (1H, d, *J* = 8.9 Hz), 7.31–7.43 (6H, m), 7.47 (1H, s), 7.70 (1H, d, *J* = 8.6 Hz); MS (EI) *m/z* 654 $[M]^+$; Anal. Calcd for $C_{27}H_{25}F_6IO_4$: C, 49.56; H, 3.85. Found: C, 49.74; H, 3.79.

2-(Benzyloxy)-4-(4-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)-1-vinyl-benzene (237c):



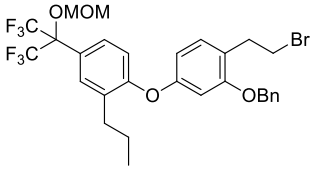
Compound **237c** was prepared using an experimental procedure similar to that used for compound **237a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.6 Hz), 1.64 (2H, qt, *J* = 7.6, 7.6 Hz), 2.64 (2H, t, *J* = 7.6 Hz), 3.56 (3H, s), 4.86 (2H, s), 5.05 (2H, s), 5.23 (1H, dd, *J* = 1.5, 11.2 Hz), 5.70 (1H, dd, *J* = 1.5, 17.8 Hz), 6.54 (1H, dd, *J* = 2.2, 8.3 Hz), 6.58 (1H, d, *J* = 2.2 Hz), 6.81 (1H, d, *J* = 8.5 Hz), 7.07 (1H, dd, *J* = 11.2, 17.8 Hz), 7.32–7.38 (6H, m), 7.46 (1H, d, *J* = 8.3 Hz), 7.42 (1H, d, *J* = 8.5 Hz), 7.47 (1H, s); MS (EI) *m/z* 554 $[M]^+$.

2-(2-(Benzyloxy)-4-(4-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)phenyl)-ethan-1-ol (241c):



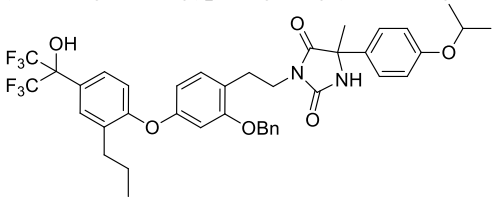
Compound **241c** was prepared using an experimental procedure similar to that used for compound **209a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.6 Hz), 1.65 (2H, qt, *J* = 7.6, 7.8 Hz), 2.66 (2H, t, *J* = 7.8 Hz), 2.94 (2H, t, *J* = 6.4 Hz), 3.56 (3H, s), 3.86 (2H, t, *J* = 6.4 Hz), 4.86 (2H, s), 5.04 (2H, s), 6.52 (1H, dd, *J* = 2.2, 8.3 Hz), 6.61 (1H, d, *J* = 2.2 Hz), 6.79 (1H, d, *J* = 8.8 Hz), 7.15 (1H, d, *J* = 8.3 Hz), 7.31–7.37 (6H, m), 7.46 (1H, s); MS (EI) *m/z* 572 $[M]^+$.

2-(Benzyloxy)-1-(2-bromoethyl)-4-(4-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propyl-phenoxy)benzene (239c):



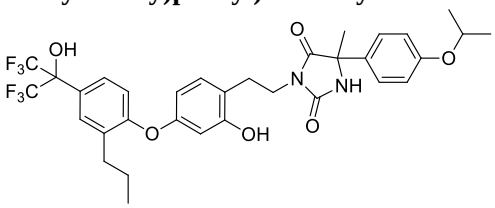
Compound **239c** was prepared using an experimental procedure similar to that used for compound **196**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.3 Hz), 1.64 (2H, qt, *J* = 7.3, 7.8 Hz), 2.65 (2H, t, *J* = 7.8 Hz), 3.21 (2H, t, *J* = 7.3 Hz), 3.56 (3H, s), 3.61 (2H, t, *J* = 7.3 Hz), 4.86 (2H, s), 5.05 (2H, s), 6.51 (1H, dd, *J* = 2.4, 8.1 Hz), 6.60 (1H, d, *J* = 2.4 Hz), 6.79 (1H, d, *J* = 8.6 Hz), 7.13 (1H, d, *J* = 8.1 Hz), 7.31–7.42 (6H, m), 7.46 (1H, s); MS (EI) *m/z* 635 $[M]^+$.

3-(2-(Benzyloxy)-4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)phenethyl)-5-((1-(1-methylethoxy)phenyl-4-yl)-5-methylimidazolidine-2,4-dione (241c):



Compound **241c** was prepared using an experimental procedure similar to that used for compound **191a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.1 Hz), 1.28 (6H, d, *J* = 5.9 Hz), 1.61–1.69 (2H, m), 1.69 (3H, s), 2.65 (2H, t, *J* = 7.3 Hz), 2.99 (2H, brs), 3.83 (2H, brs), 4.44–4.52 (1H, m), 5.02 (2H, s), 6.33 (1H, d, *J* = 8.5 Hz), 6.54 (1H, s), 6.71 (1H, d, *J* = 8.5 Hz), 6.82 (2H, d, *J* = 8.8 Hz), 6.92 (1H, d, *J* = 8.0 Hz), 7.17–7.44 (8H, m), 7.54 (1H, s); MS (EI) *m/z* 758 $[M]^+$.

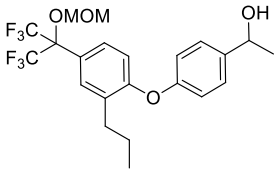
3-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)-2-hydroxyphenethyl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (241d):



Compound **241d** was prepared using an experimental procedure similar to that used for compound **10**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.3 Hz), 1.29 (6H, d, *J* = 6.1 Hz), 1.60–1.68 (2H, m), 1.70 (3H, s), 2.64 (2H, t, *J* = 7.6 Hz), 2.90 (2H, t, *J* = 7.3 Hz), 3.75 (2H, t, *J* = 7.3 Hz), 4.45–4.51 (1H, m), 5.87 (1H, s), 6.38 (1H, dd, *J* = 1.9, 8.3 Hz), 6.44 (1H, d, *J* = 1.9 Hz), 6.79 (1H, d, *J* = 8.6 Hz), 6.82 (2H, d, *J* = 8.5 Hz), 6.92 (1H, d, *J* = 8.3 Hz), 7.26 (2H, d, *J* = 8.5 Hz), 7.41 (1H, d, *J* = 8.6 Hz), 7.54 (1H, s); MS (EI) *m/z* 668 $[M]^+$.

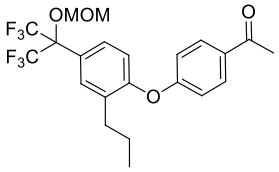
Scheme 30

1-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)phenyl)ethan-1-ol (242):



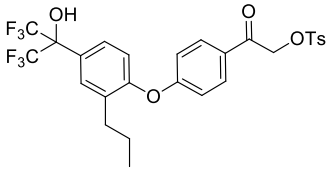
To a stirred solution of **202b** (269 mg, 0.60 mmol) in THF (2.7 mL), methylmagnesium bromide (1.1 mL, 0.99 mmol) was added at 0 °C under an argon temperature. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 1 h. The reaction mixture was diluted with saturated NH_4Cl *aq.* at 0 °C and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1) to give the title compound (325 mg, 99%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.3 Hz), 1.51 (3H, d, *J* = 6.8 Hz), 1.66 (2H, qt, *J* = 7.3, 7.8 Hz), 2.69 (2H, t, *J* = 7.8 Hz), 3.55 (3H, s), 4.45 (1H, brs), 4.85 (2H, s), 4.92 (1H, q, *J* = 6.8 Hz),, 6.82 (1H, d, *J* = 8.9 Hz), 6.98 (1H, d, *J* = 8.6 Hz), 7.33 (1H, dd, *J* = 2.2, 8.9 Hz), 7.37 (1H, d, *J* = 8.6 Hz), 7.46 (1H, d, *J* = 2.2 Hz); MS (EI) *m/z* 466 $[M]^+$.

1-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)phenyl)ethan-1-one (243):



To a stirred solution of **242** (325 mg, 0.66 mmol) in CH_2Cl_2 (2.7 mL), MnO_2 (575 mg, 6.6 mmol) was added at room tempereture. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was filtered through a pad of Celite, rinsed with $CHCl_3$. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1) to give the title compound (218 mg, 78%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.3 Hz), 1.62 (2H, qt, *J* = 7.3, 7.3 Hz), 2.59 (3H, s), 2.62 (2H, t, *J* = 7.3 Hz), 3.57 (3H, s), 4.87 (2H, s), 6.96 (1H, d, *J* = 8.9 Hz), 6.99 (2H, d, *J* = 8.9 Hz), 7.44 (1H, d, *J* = 8.9 Hz), 7.52 (1H, s), 7.97 (2H, d, *J* = 8.9 Hz); MS (EI) *m/z* 464 $[M]^+$.

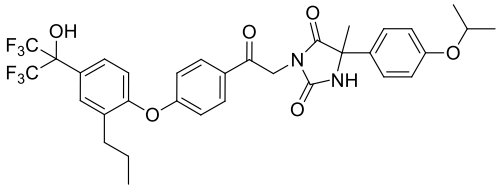
2-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)phenyl)-2-oxoethyl-4-methyl-benzenesulfonate (245a):



To a stirred solution of **243** (218 mg, 0.52 mmol) in MeCN (2.2 mL), PhI(OTs)OH (305 mg, 0.78 mmol) was added at room temperature. The reaction mixture was refluxed for 6 h and then concentrated *in vacuo*. The residue was diluted with water at 0 °C and extracted with EtOAc. The organic layer was washed with brine, and

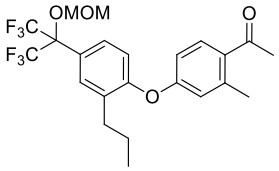
concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to give the title compound (268 mg, 87%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.3 Hz), 1.62 (2H, qt, *J* = 7.3, 7.3 Hz), 2.58 (3H, s), 2.61 (2H, t, *J* = 7.3 Hz), 3.74 (1H, s), 5.10 (2H, s), 6.96 (1H, d, *J* = 8.9 Hz), 6.99 (2H, d, *J* = 8.9 Hz), 7.35 (2H, d, *J* = 7.8 Hz), 7.44 (1H, d, *J* = 8.9 Hz), 7.52 (1H, s), 7.83 (2H, d, *J* = 7.8 Hz), 7.97 (2H, d, *J* = 8.9 Hz); MS (EI) *m/z* 590 $[M]^+$.

3-(2-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)phenyl)-2-oxoethyl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (246a):



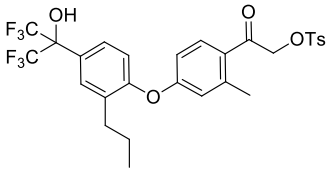
Compound **236a** was prepared using an experimental procedure similar to that used for compound **191a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 7.3 Hz), 1.33 (6H, d, *J* = 5.9 Hz), 1.54–1.68 (2H, m), 1.93 (3H, s), 2.58 (2H, t, *J* = 7.6 Hz), 4.48–4.62 (1H, m), 4.89 (1H, d, *J* = 17.8 Hz), 4.90 (1H, d, *J* = 17.8 Hz), 5.84 (1H, s), 6.91 (2H, d, *J* = 8.9 Hz), 6.98 (2H, d, *J* = 8.9 Hz), 6.99 (1H, d, *J* = 8.6 Hz), 7.47 (2H, d, *J* = 8.9 Hz),7.54 (1H, d, *J* = 8.6 Hz), 7.63 (1H, s), 7.95 (2H, d, *J* = 8.9 Hz); MS (EI) *m/z* 666 $[M]^+$.

1-(2-Methyl-4-(2-propyl-4-(2,2,2-trifluoro-1-methoxymethoxy-1-trifluoromethylethyl)phenoxy)phenyl)-ethanone (244a):



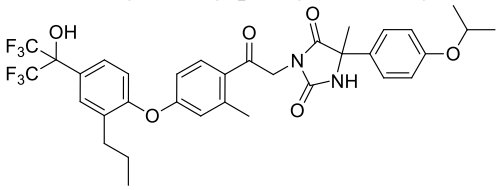
To a stirred solution of **236a** (393 mg, 0.70 mmol) in toluene (17 mL), ethoxyvinyltributyl tin (506 mg, 1.4 mmol) and $Pd(PPh_3)_4$ (400 mg, 0.35 mmol) were successively added at room temperature. The reaction mixture was refluxed for 2.5 h. To the reaction mixture was added 5% HCl (14 mL) at 0 °C. The reaction mixture was stirred at room temperature for 20 h and then filtered through a pad of Celite and rinsed with EtOAc. The aqueous layer was extracted with EtOAc. The organic layer was washed with a saturated $NaHCO_3$ *aq.* and brine, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (291 mg, 80%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.0 Hz), 1.63 (2H, qt, *J* = 7.0, 7.6 Hz), 2.55 (3H, s), 2.57 (3H, s), 2.63 (2H, t, *J* = 7.6 Hz), 3.57 (3H, s), 4.87 (2H, s), 6.78 (1H, dd, *J* = 2.4, 8.6 Hz), 6.84 (1H, d, *J* = 2.4 Hz), 6.94 (1H, d, *J* = 8.9 Hz), 7.42 (1H, d, *J* = 8.9 Hz), 7.51 (1H, s), 7.75 (1H, d, *J* = 8.6 Hz); MS (EI) *m/z* 478 $[M]^+$.

2-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)-2-methylphenyl)-2-oxoethyl-4-methylbenzenesulfonate (245b):



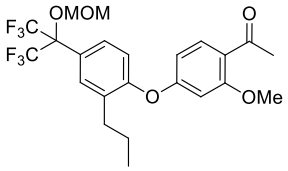
Compound **245b** was prepared using an experimental procedure similar to that used for compound **245a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.3 Hz), 1.62 (2H, qt, *J* = 7.3, 7.3 Hz), 2.45 (3H, s), 2.46 (3H, s), 2.60 (2H, t, *J* = 7.3 Hz), 5.10 (2H, s), 6.74 (1H, dd, *J* = 1.9, 7.6 Hz), 6.83 (1H, d, *J* = 1.9 Hz), 6.97 (1H, d, *J* = 8.4 Hz), 7.35 (2H, d, *J* = 7.8 Hz), 7.54 (1H, d, *J* = 7.6 Hz), 7.55 (1H, d, *J* = 8.4 Hz), 7.63 (1H, s), 7.83 (2H, d, *J* = 7.8 Hz); MS (EI) *m/z* 604 $[M]^+$.

3-(2-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)-2-methylphenyl)-2-oxoethyl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (246b):



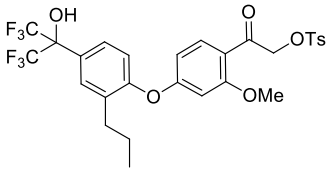
Compound **246b** was prepared using an experimental procedure similar to that used for compound **191a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 7.3 Hz), 1.33 (6H, d, *J* = 5.9 Hz), 1.55–1.66 (2H, m), 1.92 (3H, s), 2.53 (3H, s), 2.59 (2H, t, *J* = 7.0 Hz), 4.50–4.59 (1H, m), 4.78 (1H, d, *J* = 17.6 Hz), 4.80 (1H, d, *J* = 17.6 Hz), 5.94 (1H, s), 6.77 (1H, dd, *J* = 2.4, 8.9 Hz), 6.83 (1H, d, *J* = 2.4 Hz), 6.90 (2H, d, *J* = 8.6 Hz), 6.96 (1H, d, *J* = 8.9 Hz), 7.45 (2H, d, *J* = 8.6 Hz), 7.53 (1H, d, *J* = 8.9 Hz), 7.63 (1H, s), 7.74 (1H, d, *J* = 8.9 Hz); MS (EI) *m/z* 680 $[M]^+$.

1-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)-2-methoxyphenyl)-ethan-1-one (244b):



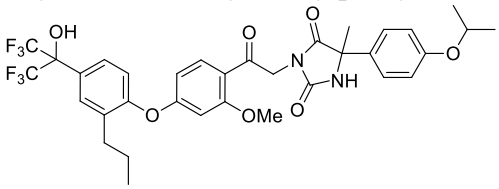
Compound **244b** was prepared using an experimental procedure similar to that used for compound **244a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.3 Hz), 1.63 (2H, qt, *J* = 7.3, 7.6 Hz), 2.60 (3H, s), 2.63 (2H, t, *J* = 7.6 Hz), 3.57 (3H, s), 3.88 (3H, s), 4.87 (2H, s), 6.46 (1H, dd, *J* = 2.4, 8.4 Hz), 6.61 (1H, d, *J* = 2.4 Hz), 6.96 (1H, d, *J* = 8.4 Hz), 7.43 (1H, d, *J* = 8.4 Hz), 7.52 (1H, s), 7.79 (1H, d, *J* = 8.4 Hz); MS (EI) *m/z* 494 $[M]^+$.

2-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)-2-methoxyphenyl)-2-oxoethyl-4-methylbenzenesulfonate (245c):



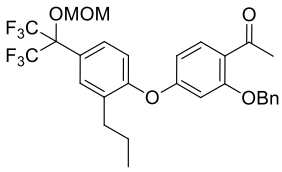
Compound **245c** was prepared using an experimental procedure similar to that used for compound **245a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.6 Hz), 1.62 (2H, qt, *J* = 7.6, 7.8 Hz), 2.45 (3H, s), 2.59 (2H, t, *J* = 7.8 Hz), 3.89 (3H, s), 5.24 (2H, s), 6.46 (1H, dd, *J* = 2.2, 8.6 Hz), 6.56 (1H, d, *J* = 2.2 Hz), 6.99 (1H, d, *J* = 8.4 Hz), 7.35 (2H, d, *J* = 7.8 Hz), 7.55 (1H, d, *J* = 8.4 Hz), 7.63 (1H, s), 7.87 (1H, d, *J* = 8.6 Hz), 7.88 (2H, d, *J* = 7.8 Hz); MS (EI) *m/z* 620 $[M]^+$.

3-(2-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)-2-methoxyphenyl)-2-oxo-ethyl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (246c):



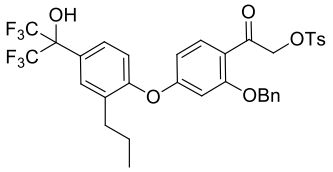
Compound **246c** was prepared using an experimental procedure similar to that used for compound **191a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.3 Hz), 1.33 (6H, d, *J* = 5.9 Hz), 1.54–1.65 (2H, m), 1.92 (3H, s), 2.60 (2H, t, *J* = 7.8 Hz), 3.89 (3H, s), 4.50–4.59 (1H, m), 4.93 (2H, s), 5.82 (1H, s), 6.45 (1H, dd, *J* = 2.4, 8.9 Hz), 6.58 (1H, d, *J* = 2.4 Hz), 6.89–6.92 (2H, m), 6.99 (1H, d, *J* = 8.6 Hz), 7.45–7.49 (2H, m), 7.53 (1H, d, *J* = 8.6 Hz), 7.62 (1H, s), 7.94 (1H, d, *J* = 8.9 Hz); MS (EI) *m/z* 696 $[M]^+$.

1-(2-(Benzyloxy)-4-(4-(1,1,1,3,3,3-hexafluoro-2-(methoxymethoxy)propan-2-yl)-2-propylphenoxy)phenyl)-ethan-1-one (244c):



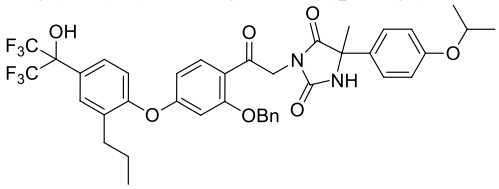
Compound **244c** was prepared using an experimental procedure similar to that used for compound **244a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.3 Hz), 1.61 (2H, qt, *J* = 7.3, 7.8 Hz), 2.59 (2H, t, *J* = 7.8 Hz), 2.62 (3H, s), 3.60 (3H, s), 4.90 (2H, s), 5.13 (2H, s), 6.54 (1H, dd, *J* = 2.4, 8.6 Hz), 6.60 (1H, d, *J* = 2.4 Hz), 6.93 (1H, d, *J* = 8.9 Hz), 7.34–7.45 (6H, m), 7.53 (1H, s), 7.83 (1H, d, *J* = 8.6 Hz); MS (EI) *m/z* 570 $[M]^+$; Anal. Calcd for $C_{29}H_{28}F_6O_5$: C, 61.05; H, 4.95. Found: C, 60.91; H, 4.94.

2-(2-(Benzyloxy)-4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)phenyl)-2-oxoethyl-4-methylbenzenesulfonate (245c):



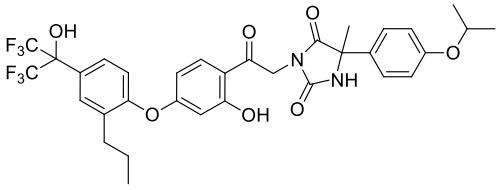
Compound **245c** was prepared using an experimental procedure similar to that used for compound **245a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.3 Hz), 1.57 (2H, qt, *J* = 7.3, 7.3 Hz), 2.43 (3H, s), 2.52 (2H, t, *J* = 7.3 Hz), 5.07 (2H, s), 5.14 (2H, s), 6.50–6.54 (2H, m), 6.94 (1H, d, *J* = 8.6 Hz), 7.24–7.43 (7H, m), 7.54 (1H, d, *J* = 8.6 Hz), 7.62 (1H, s), 7.67 (2H, d, *J* = 8.6 Hz), 7.92 (1H, d, *J* = 9.2 Hz); MS (EI) *m/z* 696 $[M]^+$.

3-(2-(2-(Benzyloxy)-4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)phenyl)-2-oxo-ethyl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (246c):



Compound **246c** was prepared using an experimental procedure similar to that used for compound **191a**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.3 Hz), 1.33 (6H, d, *J* = 5.7 Hz), 1.54 (2H, qt, *J* = 7.3, 7.8 Hz), 1.92 (3H, s), 2.49 (2H, t, *J* = 7.8 Hz), 4.55 (1H, sept, *J* = 5.7 Hz), 4.84 (1H, d, *J* = 18.1 Hz), 4.85 (1H, d, *J* = 18.1 Hz), 5.12 (2H, s), 5.72 (1H, s), 6.48 (1H, d, *J* = 1.9 Hz), 6.53 (1H, dd, *J* = 1.9, 8.9 Hz), 6.89–6.93 (3H, m), 7.28–7.37 (5H, m), 7.45–7.50 (3H, m), 7.61 (1H, s), 7.98 (1H, d, *J* = 8.9 Hz); MS (EI) *m/z* 772 $[M]^+$.

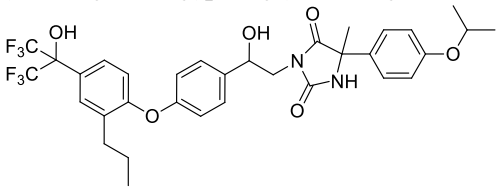
3-(2-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)-2-hydroxyphenyl)-2-oxoethyl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (246d):



Compound **246d** was prepared using an experimental procedure similar to that used for compound **10**. The title compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 7.3 Hz), 1.34 (6H, d, *J* = 5.7 Hz), 1.61 (2H, qt, *J* = 7.3, 7.6 Hz), 1.94 (3H, s), 2.56 (2H, t, *J* = 7.6 Hz), 4.56 (1H, sept, *J* = 5.7 Hz), 4.90 (1H, d, *J* = 17.8 Hz), 4.92 (1H, d, *J* = 17.8 Hz), 5.75 (1H, s), 6.37 (1H, d, *J* = 2.4 Hz), 6.55 (1H, dd, *J* = 2.4, 8.9 Hz), 6.92 (2H, d, *J* = 8.9 Hz), 7.06 (1H, d, *J* = 8.6 Hz), 7.46 (2H, d, *J* = 8.9 Hz), 7.57 (1H, d, *J* = 8.6 Hz), 7.63 (1H, s), 7.68 (1H, d, *J* = 8.9 Hz), 11.88 (1H, s); MS (EI) *m/z* 682 $[M]^+$.

Scheme 31

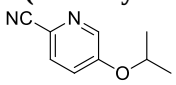
3-(2-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)phenyl)-2-hydroxyethyl)-5-(4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione (247):



To a stirred solution of **246e** (20 mg, 0.03 mmol) in MeOH (2.0 mL), $NaBH_4$ (2.3 mg, 0.06 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 15 h. To the reaction mixture was added water. The aqueous layer was extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to give the title compound (19 mg, 95%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.3 Hz), 1.30 (6H, d, *J* = 5.9 Hz), 1.66 (2H, qt, *J* = 7.3, 7.8 Hz), 1.74 (3H, s), 2.67 (2H, t, *J* = 7.8 Hz), 3.53 (2H, brs), 3.82 (1H, dd, *J* = 3.2, 14.2 Hz), 3.94 (1H, dd, *J* = 7.3, 14.2 Hz), 4.51 (1H, sept, *J* = 5.9 Hz), 5.02–5.07 (1H, m), 5.65 (1H, brs), 6.74–6.80 (1H, m), 6.83–6.87 (2H, m), 6.90–6.94 (2H, m), 7.22–7.23 (1H, m), 7.28–7.30 (1H, m), 7.32–7.35 (2H, m), 7.42–7.45 (1H, m), 7.56 (1H, s); MS (EI) *m/z* 668 $[M]^+$.

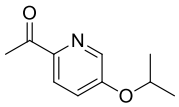
Scheme 32

5-(1-Methylethoxy)picolinonitrile (249):



To a stirred suspension of 5-hydroxypicolinonitrile (**248**) (616 mg, 5.1 mmol) and K_2CO_3 (1.4 g, 10 mmol) in DMF (3.0 mL), 2-iodopropane (1.3 g, 7.7 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 5.5 h. To the reaction mixture was added water (3.0 mL). The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (491 mg, 59%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 1.40 (6H, d, *J* = 6.2 Hz), 4.66 (1H, sept, *J* = 6.2 Hz), 7.19 (1H, dd, *J* = 2.7, 8.6 Hz), 7.62 (1H, d, *J* = 8.6 Hz), 8.32 (1H, d, *J* = 2.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 21.7 (2C), 71.4, 117.7, 121.1, 124.7, 129.6, 141.2, 156.5; MS (EI) *m/z* 162 $[M]^+$.

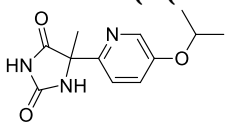
1-(5-(1-Methylethoxy)pyridin-2-yl)ethan-1-one (12):



To a stirred solution of **249** (491 mg, 3.0 mmol) in THF (20 mL), MeMgBr (0.97 M in THF solution, 9.3 mL, 9.1 mmol) was added at 0 °C under an argon atmosphere. The reaction mixture was stirred 0 °C for 2 h. To the reaction mixture was added 1 N HCl (10 mL). Then, the reaction mixture was neutralized with saturated $NaHCO_3$

aq. at 0 °C. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (418 mg, 77%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (6H, d, J = 5.9 Hz), 2.68 (3H, s), 4.68 (1H, sept, J = 5.9 Hz), 7.22 (1H, dd, J = 3.0, 8.6 Hz), 8.03 (1H, d, J = 8.6 Hz), 8.28 (1H, d, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7 (2C), 25.6, 70.8, 121.2, 123.3, 138.0, 146.5, 156.9, 198.9; MS (EI) *m/z* 179 $[M]^+$.

***Racemic*-5-(5-(1-methylethoxy)pyridin-2-yl)-5-methylimidazolidine-2,4-dione ((±)-11):**



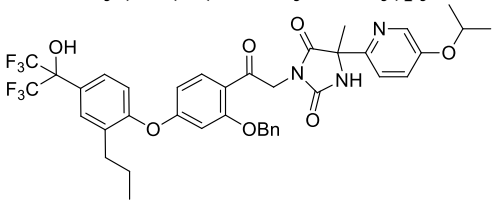
To a stirred solution of **12** (417 mg, 2.3 mmol) in EtOH (2.3 mL), NaCN (1.0 g, 21 mmol), $(NH_4)_2CO_3$ (4.0 g, 42 mmol) and water (2.3 mL) were added at room temperature. The reaction mixture was irradiated using a microwave reactor (Initiator; Biotage AB) at 100 °C for 1 h. The reaction mixture was concentrated to remove EtOH. The resulting precipitate was filtered off and washed with water. The solid was recrystallized from a mixture solvent of $CHCl_3$ and MeOH (20/1) to give the title compound (504 mg, 87%) as a brown amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (6H, d, J = 6.2 Hz), 1.79 (3H, s), 4.67 (1H, sept, J = 6.2 Hz), 7.36 (1H, dd, J = 2.7, 8.9 Hz), 7.46 (1H, d, J = 8.9 Hz), 8.18 (1H, d, J = 2.7 Hz); MS (EI) *m/z* 249 $[M]^+$.

The hydrochloric acid salt of the (±)-**11** was prepared by adding methanolic HCl to a solution of (±)-**11** in MeOH. A sample was recrystallized from MeOH to yield colorless crystals for analysis.

Hydrochloric acid salt of (±)-**11**; mp 222.4–225.1 °C; IR (KBr): 3133, 2984, 1752, 1540, 1240, 935 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 1.42 (6H, d, J = 5.6 Hz), 1.94 (3H, s), 4.90 (1H, sept, J = 5.6 Hz), 8.12 (1H, d, J = 9.6 Hz), 8.21 (1H, dd, J = 2.8, 9.6 Hz), 8.41 (1H, d, J = 2.8 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 21.7 (2C), 24.4, 64.9, 74.6, 127.0, 132.5, 133.6, 145.3, 157.9, 158.4, 175.2; MS (EI) *m/z* 239 $[M^+]$; Anal. Calcd for $C_{12}H_{16}ClN_3O_3$: C, 50.44; H, 5.64; N, 14.71. Found: C, 50.39; H, 5.68; N, 14.53.

Scheme 33

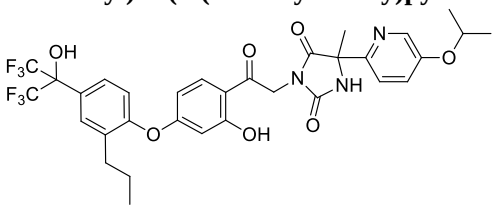
***Racemic*-3-(2-(2-(Benzyloxy)-4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)phenyl)-2-oxoethyl)-5-(5-(1-methylethoxy)pyridin-2-yl)-5-methylimidazolidine-2,4-dione (250):**



To a stirred suspension of **11** (20 mg, 82 μmol) and K_2CO_3 (23 mg, 164 μmol) in DMF (160 μL), **245c** (28 mg, 41 μmol) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 20 h.

To the reaction mixture, water was added. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to give the title compound (6.5 mg, 21%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.6 Hz), 1.36 (6H, d, *J* = 6.5 Hz), 1.54 (2H, qt, *J* = 7.6, 7.8 Hz), 1.87 (3H, s), 2.49 (2H, t, *J* = 7.8 Hz), 4.58 (1H, sept, *J* = 6.5 Hz), 4.87 (2H, s), 5.13 (2H, s), 6.29 (1H, brs), 6.48 (1H, d, *J* = 2.4 Hz), 6.53 (1H, dd, *J* = 2.4, 8.9 Hz), 6.92 (1H, d, *J* = 8.9 Hz), 7.20 (1H, dd, *J* = 2.7, 8.9 Hz), 7.29–7.36 (5H, m), 7.52 (1H, d, *J* = 8.9 Hz), 7.61 (1H, s), 7.64 (1H, d, *J* = 8.9 Hz), 7.97 (1H, d, *J* = 8.9 Hz), 8.21 (1H, d, *J* = 2.7 Hz); MS (EI) *m/z* 772 $[M]^+$.

***Racemic*-3-(2-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)-2-hydroxyphenyl)-2-oxoethyl)-5-(5-(1-methylethoxy)pyridin-2-yl)-5-methylimidazolidine-2,4-dione (10):**



A suspension of **250** (3.7 mg, 4.8 μmol) and 10% Pd/C (1.0 mg) in MeOH (500 μL) was stirred under a hydrogen atmosphere at room temperature for 3 h. The reaction mixture was filtered through a pad of Celite and rinsed with MeOH. The filtrate was concentrated *in vacuo.* The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to give the title compound (2.6 mg, 80%) as a colorless amorphous solid; IR (film) 3130, 2985, 1740, 1545, 1240, 934 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 0.90 (3H, t, *J* = 7.2 Hz), 1.33 (6H, d, *J* = 6.0 Hz), 1.61 (2H, qt, *J* = 7.2, 7.6 Hz), 1.90 (3H, s), 2.59 (2H, t, *J* = 7.6 Hz), 4.68 (1H, sept, *J* = 6.0 Hz), 4.98 (2H, s), 6.34 (1H, d, *J* = 2.4 Hz), 6.55 (1H, dd, *J* = 2.4, 9.2 Hz), 7.12 (1H, d, *J* = 8.8 Hz), 7.39 (1H, dd, *J* = 2.8, 8.8 Hz), 7.60 (1H, d, *J* = 8.8 Hz), 7.64 (1H, dd, *J* = 2.8, 8.8 Hz), 7.71 (1H, d, *J* = 2.8 Hz), 7.95 (1H, d, *J* = 9.2 Hz), 8.20 (1H, d, *J* = 2.8 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 14.0, 22.1 (2C), 23.6, 24.3, 33.2, 45.8, 66.5, 71.9, 78.3 (sept, *J* = 29.8 Hz), 105.2, 110.0, 115.2, 122.2, 122.5, 124.2, 124.5 (2C, q, *J* = 285.7 Hz), 127.7, 129.7, 131.2, 133.4, 136.1, 139.6, 150.0, 155.0, 155.5, 158.1, 165.1, 166.1, 177.3, 195.9; MS (EI) *m/z* 683 $[M]^+$.

Scheme 34

Resolution of (±)-hydantoin 11 by HPLC

Resolution of racemic sample of compound **11** was carried out by HPLC using CHIRALPAK AY-H column (DAICEL). Each elution was concentrated to give compounds (−)-**11** and (+)-**11** as a colorless amorphous compound.

Conditions for analysis

Column: CHIRALPAK AY-H, 0.46 × 150 mm; Mobile phase: hexane/*i*-PrOH = 70/30; Flow rate: 1.0 mL/min; Column temperature: 40 °C; Wavelength: 264 nm; Retention time: (−)-form 4.55 min/(+)-form 5.81 min.

Conditions for preparation

Column: CHIRALPAK AY-H, 20 × 250 mm; Mobile phase: *n*-hexane/*i*-PrOH = 70/30; Flow rate: 10 mL/min; Column temperature: 40 °C; Wavelength: 264 nm; Retention time: (−)-form 6.05 min/(+)-form 12.1 min. A 200 mg sample of racemic compound **11** led to complete resolution in a single operation.

Hydrochloric acid salt of (+)-**11**; mp 222.3–225.2 °C; MS (EI) *m/z* 249 [M^+]; Anal. Calcd for $C_{12}H_{16}ClN_3O_3$: C, 50.44; H, 5.64; N, 14.71. Found: C, 50.34; H, 5.60; N, 14.92; $[\alpha]_D^{20}$ = +26.5 (c = 1.0, MeOH); Optical purity: >99% ee. The IR, ^{1}H NMR, and ^{13}C NMR spectra of (+)-**11** are identical to those of (±)-**11**.

Hydrochloric acid salt of (−)-**11**; mp 222.3–224.4 °C; MS (EI) *m/z* 249 [M^+]; Anal. Calcd for $C_{12}H_{16}ClN_3O_3$: C, 50.44; H, 5.64; N, 14.71. Found: C, 50.36; H, 5.60; N, 14.93; $[\alpha]_D^{20}$ = −26.6 (c = 1.0, MeOH); Optical purity: >99% ee. The IR, ^{1}H NMR and ^{13}C NMR spectra of (−)-**11** are identical to those of (±)-**11**.

(−)-3-(2-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)-2-hydroxyphenyl)-2-oxo-ethyl)-5-(5-(1-methylethoxy)pyridin-2-yl)-5-methylimidazolidine-2,4-dione ((−)-10):

Compound **(−)-10** was prepared with (+)-**11** in place of (±)-**11** in the experimental procedure similar to that used for racemic (±)-**10**.

MS (EI) *m/z* 683 [M^+]; Anal. Calcd for $C_{32}H_{31}F_6N_3O_7$: C, 56.22; H, 4.57; N, 6.15. Found: C, 56.07; H, 4.61; N, 6.08; $[\alpha]_D^{20}$ = −56.5 (c = 1.0, $CHCl_3$). The IR, ^{1}H NMR and ^{13}C NMR spectra of (−)-**10** were identical to those of (±)-**10**.

(+)-3-(2-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)-2-hydroxyphenyl)-2-oxo-ethyl)-5-(5-(1-methylethoxy)pyridin-2-yl)-5-methylimidazolidine-2,4-dione ((+)-10):

Compound **(+)-10** was prepared with (−)-**11** in place of (±)-**11** in the experimental procedure similar to that used for racemic (±)-**10**.

MS (EI) *m/z* 683 [M^+]; Anal. Calcd for $C_{32}H_{31}F_6N_3O_7$: C, 56.22; H, 4.57; N, 6.15. Found: C, 56.06; H, 4.63; N, 6.09; $[\alpha]_D^{20}$ = +56.1 (c = 1.0, $CHCl_3$). The IR, ^{1}H NMR and ^{13}C NMR spectra of (+)-**10** were identical to those of (±)-**10**.

Pharmacological Experimental Details

Material and Method

In vivo study

Low-density lipoprotein (LDL) receptor knock-out mice (male, age: 10 weeks old, *n* = 60) (Charles River Japan, Inc.; Kanagawa, Japan) were used for animal experiments. The animal room was controlled at 23±3 °C and relative humidity of 50 ± 20%. Animals were fed a CE-2 chow diet (CLEA Japan Inc., Tokyo, Japan) and then supplemented with a Western-type diet (TD.88137; Harlan Laboratories, WI, USA) for 10 weeks.

During fat loading, a suspension of (−)-**10** in 0.5% methyl cellulose (MC) was orally administered at 1 or 3 mg/kg/day (*n* = 15 for each dose group). As a comparative agent, a suspension of T0901317 in 0.5% MC was orally administered at 10 mg/kg/day (*n* = 15 for each dose group). The control group (*n* = 15) received an aqueous solution of 0.5% MC instead of T0901317. Blood samples were collected to determine plasma lipid levels by using a commercial kit (total cholesterol: Cholesterol E-Test Wako; Wako Pure Chemical Industries, Osaka, Japan; triglyceride: Triglyceride E-Test Wako; Wako Pure Chemical Industries). The plasma lipoprotein profiles were analyzed by using the CLiP method on the LC-20A HPLC system (Shimadzu) and Superose 6 Column (10 mm × 300 mm; GE Healthcare, UK). Briefly, 15 μL of plasma was diluted 10-fold in PBS containing 1 mM EDTA. Diluted plasma (20 μL) was separated by the column at 0.5 mL/min with PBS containing 1 mM EDTA and maintained at 40 °C for the simultaneous determination of cholesterol contents in the eluents.

For the analyses of atherosclerotic lesions, the animals were anesthetized via intraperitoneal injection of pentobarbital sodium (50 mg/kg), followed by vascular perfusion for 5 min with saline containing 4% paraformaldehyde at a perfusion pressure of 120 mmH_2O.

The animals heart were fixed with 4% paraformaldehyde for 24 h. The heart tissues were embedded in OCT compound (Tissue-Tek) and snap frozen in liquid N_2. Cryosections of 10 μm thickness were incised from the end of the aortic sinus. The sections were stained for lipid with Oil-Red O and counterstained with hematoxylin. A positive area was quantified at 600 μm distally on an image analysis system (SP500F; Olympus, Tokyo, Japan).

Pharmacokinetic Experimental Details

Material and Method

The oral doses of compound **4** at 100 mg/kg and compound (−)-**10** at 10 mg/kg were formulated in PEG 400. A solution of compound **4** and (−)-**10** in PEG 400 were orally administered to a CE-2 chow diet-fed Golden Syrian hamsters. Blood samples (heparin plasma) were collected from a forearm vein 0.5, 1, 2, 3, 4, 6, 8, 10 and 24 h after administration. The drug concentrations of compound **4** and (−)-**10** in the supernatant was measured by HPLC-LC-MS/MS.

Chapter-4

Chemical Experimental Details

Scheme 35

Optical separation of (±)-11 by HPLC

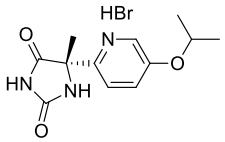
The analytical chiral HPLC conditions for **11** were reported as the above.

Synthesis of (+)-11·HCl

The preparation and data were reported as the above.

Synthesis of (+)-11·HBr

(*S*)-5-(5-(1-Methylethoxy)pyridin-2-yl)-5-methylimidazolidine-2,4-dione hydrobromide ((*S*)-(+)-11·HBr):



To a stirred solution of (+)-**11** (300 mg, 1.2 mmol) in MeOH (3.0 mL), hydrobromic acid (121 mg, 1.5 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 1 h and then concentrated under vacuum. The solid was recrystallized from MeOH to give the title compound (203 mg, 51%) as colorless crystals;
mp: 237.4–239.8 °C; IR (KBr) 3175, 2804, 1738, 1280 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 1.41 (6H, d, *J* = 5.9 Hz), 1.93 (3H, s), 4.89 (1H, sept, *J* = 5.9 Hz), 8.08 (1H, d, *J* = 9.1 Hz), 8.17 (1H, dd, *J* = 2.8, 9.1 Hz), 8.38 (1H, d, *J* = 2.8 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 21.8 (2C), 24.4, 65.1, 74.5, 126.8, 132.9, 133.0, 145.6, 157.8, 158.5, 175.4; MS (EI): m/z 249 $[M]^+$; Anal. Calcd for $C_{12}H_{16}BrN_3O_3$: C, 43.65; H, 4.88; N, 12.73. Found: C, 43.64; H, 4.85; N, 12.67; $[\alpha]_D^{20}$ = +181 (c = 1.0, MeOH).

Figure 55

X-ray crystal structure analysis of (+)-11·HBr

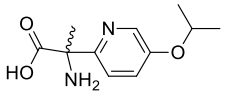
Colorless crystals were obtained from a hot methanol solution by slow cooling at room temperature. X-ray intensity data were measured on the Bruker Venture D8 Diffractometer with Mo Kα radiation at 299 K. The absorption correction was numerically performed based on the crystal dimensions and face indices. Non-H atoms were refined anisotropically. Protonation of the pyridine ring was confirmed with reference to a difference density map. H atoms were geometrically positioned and refined as riding.
X-ray crystallographic data for (*S*)-(+)-**11**·HBr [$C_{12}H_{16}BrN_3O_3$]: *M* = 330.18, orthorhombic, $P2_12_12_1$, *a* =

7.3917(3), b = 8.2799(3), c = 22.9657(8) Å, V = 1405.56(9) Å^3, Z = 4, μ (Mo $K\alpha$) = 2.93 mm^{-1}, colorless prism, crystal dimensions = 0.20 × 0.19 × 0.15 mm^3. A total of 13120 reflections were measured, of which 2539 reflections were independent. R [$F^2 > 2\sigma$ (F^2)] = 0.019, $wR(F^2)$ = 0.052. Flack parameter = 0.015(4), which was determined based on Parsons quotients.[52)] In the crystal, there are N—H…Br, C—H…Br and C—H…O hydrogen bonds, forming a layer structure parallel to (001).[70)] The absolute configuration of (*S*)-(+)-**11**·HBr accords to that of the (*S*)-(+)-hydantoin unit for 5-(3-bromo/chloro-4-(1-methylethoxy)phenyl)-5-methylimidazolidine-2,4-dione.[36b)]

Scheme 36

Large-scale synthesis of (±)-13

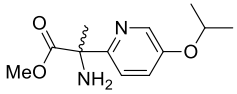
***Racemic* 2-amino-2-(5-(1-methylethoxy)pyridin-2-yl)-propanoic acid ((±)-251):**



To a stirred solution of (±)-**11** (3.50 kg, 14.0 mol) in water (14.0 kg), NaOH (2.80 kg, 70.2 mol) was added at room temperature. The reaction mixture was stirred at 100 °C for 72 h, allowed to cool to room temperature, then neutralized with 6 N HCl at 0 °C. The precipitate was filtered and washed with water (5.0 kg × 3) to give the title compound (3.15 kg, 99%) as a colorless solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (6H, d, J = 6.1 Hz), 1.74 (3H, s), 4.64 (1H, sept, J = 6.1 Hz), 7.33 (1H, dd, J = 2.7, 9.0 Hz), 7.57 (1H, d, J = 9.0 Hz), 8.13 (1H, d, J = 2.7 Hz); MS (EI) m/z 224 [M]$^+$.

The product was used in the next step without further purification.

***Racemic* methyl 2-amino-2-(5-(1-methylethoxy)pyridin-2-yl)propanoate ((±)-13):**

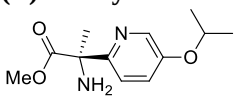


To a stirred solution of (±)-**251** (3.15 kg, 14.0 mol) in MeOH (35.0 kg), thionyl chloride (2.05 kg, 17.2 mol) was added dropwise at −20 °C over 1 h (The internal temperature was maintained at less than −3 °C to prevent formation of the by-product (**12**).). After ceasing gas evolution, the reaction mixture was stirred at 30 °C for 24 h and then neutralized with saturated $NaHCO_3$ *aq*. at 0 °C and concentrated *in vacuo* to remove the MeOH. The aqueous layer was extracted with EtOAc (10.0 L × 3) and the combined organic layers were washed with brine (3.0 L) and concentrated *in vacuo*. The residue was added to THF (3.0 L) and filtered, after which the solid was repeatedly washed with THF. The filtrate was concentrated *in vacuo* to give the title compound (2.86 kg, 86%) as a brown oil; IR (neat) 3377, 2979, 1734, 1475, 1245, 1110 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (6H, d, J = 6.4 Hz), 1.71 (3H, s), 2.20 (2H, brs), 3.71 (3H, s), 4.56 (1H, sept, J = 6.4 Hz), 7.17 (1H, dd, J = 3.2, 8.4 Hz), 7.42 (1H, d, J = 8.4 Hz), 8.20 (1H, d, J = 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9 (2C), 26.0, 52.5, 61.9, 70.7, 119.9, 123.0, 137.9, 153.1, 154.0, 176.6; MS (EI): *m/z* 238 [M]$^+$; Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61;

N, 11.76. Found: C, 60.24; H, 7.72; N, 11.58.

Synthesis of (*R*)-(−)-11

(*R*)-Methyl 2-amino-2-(5-(1-methylethoxy)pyridin-2-yl)propanoate ((−)-13):

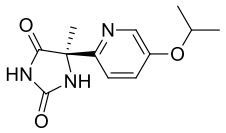


To a stirred solution of (±)-**13** (100 mg, 0.42 mmol) in EtOH (0.4 mL), L-(+)-mandelic acid (64 mg, 0.42 mmol) was added at room temperature. The reaction mixture was refluxed for 30 min until a clear solution was obtained and then stirred at room temperature for 16 h. The precipitate was filtered, and the filter cake was washed with EtOH and recrystallized from EtOH (420 μL). This crystallization was repeated twice to give the L-mandelic acid salt **252** (30 mg) as a white solid.

To a solution of CH_2Cl_2 (1.0 mL) and water (1.0 mL), the obtained salt **252** was added. The aqueous layer was made alkaline by adding Na_2CO_3 until a pH of 8 below 10 °C was achieved. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (1.0 mL × 3). The combined organic layers were washed with brine (1.0 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the title compound (15.8 mg, 16% for 2 steps, 98% ee) as a pale yellow oil; $[\alpha]_D^{20}$ = +22.1 (c = 1.0, $CHCl_3$).
All spectrum of (+)-**13** were identical to those of (±)-**13**.

Analytical chiral HPLC condition of **13**
Column: CHIRALPAK OD-H, 5 μm, 0.46 × 250 mm; Mobile phase: hexane/*i*-PrOH/DEA = 95/5/0.1 (v/v/v); Flow rate: 1.0 mL/min; Column temperature: 40 °C; Wavelength: 234 nm; Retention time: (*R*)-form 9.00 min/(*S*)-form 9.80 min.

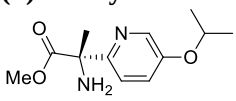
(*R*)-5-(5-(1-Methylethoxy)pyridin-2-yl)-5-methylimidazolidine-2,4-dione ((*R*)-(−)-11):



Urea (40 mg, 0.66 mmol) was heated at 145 °C. To this stirred solution, (−)-**13** (15.8 mg, 66 μmol) was added dropwise at 145 °C. The reaction mixture was stirred at the same temperature for 4 h and allowed to cool to room temperature. The reaction mixture was directly purified by silica gel column chromatography ($CHCl_3$/MeOH = 20/1) to give the title compound (16.4 mg, 99%, 98% ee) as a yellow amorphous solid; $[\alpha]_D^{20}$ = −26.6 (c = 1.0, MeOH); Chiral HPLC retention time: 4.58 min.
All spectrum of (*R*)-(−)-**11** were identical to those of our reported (+)-**11**.

Practical synthesis of (*S*)-(+)-11

(*S*)-Methyl 2-amino-2-(5-(1-methylethoxy)pyridin-2-yl)propanoate ((+)-13):



To a stirred solution of (±)-**13** (2.86 kg, 12.0 mol) in MeCN (14.3 L), D-(−)-mandelic acid (1.83 kg, 12.0 mol) was added at room temperature. The reaction mixture was refluxed for 30 min until a clear solution was obtained and then stirred at room temperature for 16 h. The precipitate was filtered and the filter cake was washed with MeCN. The solid was recrystallized from MeCN (1.43 L). This crystallization was repeated twice to give the D-mandelic acid salt **253** (900 g) as a white solid.

Table 24. Optical resolution condition and result*

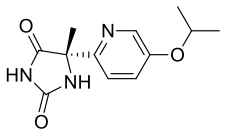
entry	1st Crystallization	2nd Crystallization
solvent	MeCN (14.3 L)	MeCN (1.43 L)
D-mandelic acid salt	1530 g	900 g
yield	33%	59%
% ee [a]	90% ee	99% ee
F [b]	0.30	0.58

[a] % ee of (−)-**13** was measured after removing D-mandelic acid from salt **253** by treating with Na_2CO_3. The analytical chiral HPLC condition of (−)-**13** was described in the section of synthesis of (*R*)-(−)-**13**. [b] F = yield (%) × ee (%)/10,000.

The obtained salt **253** (900 g) was added to a solution of CH_2Cl_2 (4.5 kg) and water (5.0 kg). The aqueous layer was made alkaline by adding Na_2CO_3 until a pH of 8 below 10 °C was achieved. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3.0 L × 3). The combined organic layers were washed with brine (600 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the title compound (510 g, 18%, 99% ee) as a pale yellow oil; $[\alpha]_D^{20} = -22.3$ (c = 1.0, $CHCl_3$).

All spectrum of (−)-**13** were identical to those of (±)-**13**.

(*S*)-5-(5-(1-Methylethoxy)pyridin-2-yl)-5-methylimidazolidine-2,4-dione ((*S*)-(+)-11):



Urea (1.29 kg, 21.4 mol) was heated at 145 °C. To this stirred solution was added dropwise (+)-**13** (510 g, 2.14

mol) at 145 °C. The reaction mixture was stirred at the same temperature for 5 h and then cooled to 70 °C. The reaction mixture was diluted with water (1.0 L) and EtOAc (2.5 L) at 70 °C. This solution was then allowed to cool to room temperature. The aqueous layer was extracted with EtOAc (800 mL × 8) and the combined organic layers were washed with brine (600 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the title compound (529 g, 99%, 99% ee) as a yellow amorphous solid; $[\alpha]_D^{20}$ = +26.5 (c = 1.0, MeOH).

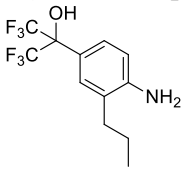
Chiral HPLC retention time: 5.83 min.

All spectrum of (*S*)-(+)-**11** were identical to those of our reported (+)-**11**.

Scheme 39

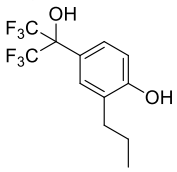
Efficient synthesis of (*S*)-(−)-10

2-(4-Amino-3-propylphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (15):



To a stirred liquid of 2-propylaniline (**14**) (30.0 g, 222 mmol), hexafluoroacetone trihydrate (97.7 g, 444 mmol) was added at room temperature. The reaction mixture was stirred at 130 °C for 13 h in an autoclave reactor. After the completion of the reaction, the reaction mixture was cooled at room temperature, and the precipitate was filtered off and washed with hexane (300 mL) to give the title compound (64.6 g, 97%) as colorless crystals; mp 138.3–140.2 °C; IR (KBr) 3404, 3333, 1257, 1202, 1171, 1142 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.4 Hz), 1.65 (2H, qt, *J* = 7.4, 7.6 Hz), 2.68 (2H, t, *J* = 7.6 Hz), 3.39 (1H, s), 5.10 (2H, s), 6.93 (1H, dd, *J* = 2.3, 7.3 Hz), 7.30–7.51 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 21.6, 33.5, 92.8 (sept, *J* = 28.4 Hz), 115.2, 118.8, 122.9 (2C, q, *J* = 288.0 Hz), 125.2, 126.4, 127.7, 145.8; MS (EI) *m/z* 301 $[M]^+$; Anal. Calcd for $C_{12}H_{13}F_6NO$: C, 47.85; H, 4.35; N, 4.65. Found: C, 47.85; H, 4.36; N, 4.78.

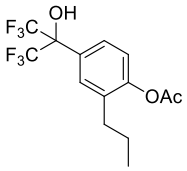
4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenol (254):



To a stirred solution of **15** (40.0 g, 133 mmol) in 1,4-dioxane (220 mL), 1 M H_2SO_4 *aq*. (220 mL) was added at 0 °C, and then a solution of $NaNO_2$ (9.60 g, 139 mmol) in water (22 mL) at 0 °C was added in a dropwise fashion over 30 min (The inner temperature was maintained at −10 to −8 °C.). After stirring at 0 °C for 5 min, concd. H_2SO_4 (22 mL) was added to the reaction mixture. After stirring for 10 min, concd. H_2SO_4 (170 mL) in water (340 mL) at 0 °C was added to the reaction mixture. The reaction mixture was stirred at 45 °C for 11 h, and then diluted with brine (400 mL) at 0 °C and extracted with EtOAc (300 mL × 3). The combined organic layers were

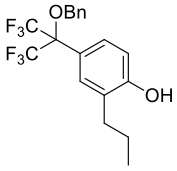
washed with brine (300 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20/1 to 3/1) to give the title compound (32.8 g, 82%) as colorless crystals; mp 81.6–83.1 °C; IR (KBr) 3591, 3441, 2972, 1214, 1140, 970 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.93 (3H, t, *J* = 7.3 Hz), 1.58 (2H, qt, *J* = 7.3, 7.6 Hz), 2.58 (2H, t, *J* = 7.6 Hz), 6.78 (1H, d, *J* = 7.9 Hz), 7.32 (1H, d, *J* = 7.9 Hz), 7.38 (1H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 14.2, 24.0, 33.5, 78.3 (sept, *J* = 28.7 Hz), 115.5, 122.7, 124.8 (2C, q, *J* = 287.4 Hz), 126.7, 130.0, 140.2, 157.8; MS (EI) *m/z* 302 $[M]^+$; Anal. Calcd for $C_{12}H_{12}F_6O_2$: C, 47.69; H, 4.00. Found: C, 47.67; H, 4.00.

4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenyl acetate (255):



To a stirred solution of **254** (32.8 g, 109 mmol) in CH_2Cl_2 (272 mL), pyridine (34 g, 434 mmol) and Ac_2O (44 g, 434 mmol) were successively added at room temperature. The reaction mixture was stirred at room temperature for 11 h. After the completion of the reaction, MeOH (272 mL) was added to the reaction mixture at room temperature to quench excess Ac_2O. The reaction mixture was stirred at room temperature for 2 h, then diluted with water (100 mL) and extracted with EtOAc (300 mL). The organic layer was washed with 5% HCl (100 mL × 3), saturated $NaHCO_3$ *aq*. (100 mL × 2) and brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound (43.2 g, 99%) as pale yellow crystals; mp 65.7–66.5 °C; IR (KBr) 3403, 2972, 1747, 1267, 1211, 973 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.93 (2H, t, *J* = 7.3 Hz), 1.60 (2H, qt, *J* = 7.3, 7.6 Hz), 2.31 (3H, s), 2.55 (2H, t, *J* = 7.6 Hz), 7.13 (1H, d, *J* = 8.6 Hz), 7.57 (1H, d, *J* = 8.6 Hz), 7.62 (1H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 12.7, 19.4, 22.8, 31.9, 76.9 (sept, *J* = 28.9 Hz), 122.3, 123.2 (2C, q, *J* = 287.1 Hz), 125.5, 128.8, 128.9, 134.4, 150.3, 169.6; MS (EI) *m/z* 344 $[M]^+$; Anal. Calcd for $C_{14}H_{14}F_6O_3$: C, 48.85; H, 4.10. Found: C, 48.90; H, 4.05. The product was used in the next step without further purification.

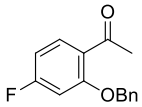
4-(2-(Benzyloxy)-1,1,1,3,3,3-hexafluoropropan-2-yl)-2-propylphenol (16):



To a stirred suspension of **255** (63.0 g, 183 mmol) and K_2CO_3 (37.9 g, 275 mmol) in DMF (402 mL), benzyl bromide (31.3 g, 183 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 15 h. After the completion of the reaction, MeOH (522 mL) was added to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature for 2 h, filtered through a pad of Celite and rinsed with EtOAc (1.8 L). The filtrate was washed with water (600 mL) and brine (400 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20/1 to 5/1) to give the title compound (63.9 g, 89%) as a colorless oil; IR (neat) 3450, 2962, 1263, 1209, 1120, 971 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.88 (3H, t, *J* = 7.3 Hz), 1.56 (2H, qt, *J* = 7.3, 7.3

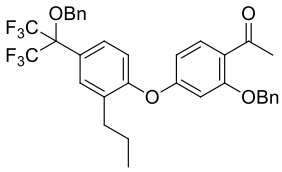
Hz), 2.56 (3H, t, J = 7.3 Hz), 4.60 (2H, s), 6.85 (1H, d, J = 8.6 Hz), 7.24–7.39 (7H, m); ^{13}C NMR (100 MHz, CD_3OD) δ 14.1, 23.7, 33.2, 68.9, 84.5 (sept, J = 28.4 Hz), 115.9, 118.6, 124.2 (2C, q, J = 288.0 Hz), 128.1, 128.2 (2C), 129.1, 129.6 (2C), 130.7, 131.1, 138.0, 158.5; MS (EI) *m/z* 392 $[M]^+$; Anal. Calcd for $C_{19}H_{18}F_6O_2$: C, 58.17; H, 4.62. Found: C, 58.07; H, 4.72.

1-(2-(Benzyloxy)-4-fluorophenyl)ethan-1-one (17) [92]**:**



To a stirred suspension of 2'-hydroxy-4'-fluoroacetophenone (**256**) (15 g, 97.3 mmol) and K_2CO_3 (20.2 g, 146 mmol) in DMF (162 mL), benzyl bromide (18.3 g, 107 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 80 °C for 1.5 h. After the completion of the reaction, the reaction mixture was allowed to cool to room temperature, and then filtered through a pad of Celite and rinsed with EtOAc (300 mL). The filtrate was washed with water (500 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound (23.7 g, 99%) as colorless crystals; mp 53.7–56.9 °C; IR (KBr) 3080, 1666, 1254, 1167 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (3H, s), 5.14 (2H, s), 6.69–6.75 (2H, m), 7.35–7.46 (5H, m), 7.81–7.85 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.1, 71.1, 100.7 (d, J = 25.8 Hz), 107.9 (d, J = 21.0 Hz), 127.6 (2C), 128.5, 128.8 (2C), 132.8 (d, J = 11.4 Hz), 135.4, 138.3, 159.8 (d, J = 10.5 Hz), 168.7 (d, J = 255 Hz), 198.0; MS (EI) *m/z* 244 $[M]^+$; Anal. Calcd for $C_{15}H_{13}FO_2$: C, 73.76; H, 5.36. Found: C, 73.83; H, 5.40. The product was used in the next step without further purification.

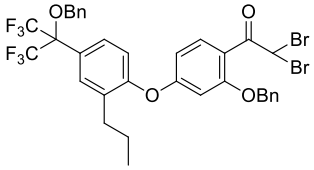
1-(2-(Benzyloxy)-4-(4-(2-(benzyloxy)-1,1,1,3,3,3-hexafluoropropan-2-yl)-2-propylphenoxy)phenyl)ethan-1-one (18):



To a stirred solution of **16** (101 g, 258 mmol) and **17** (50.5 g, 207 mmol) in DMF (260 mL), Cs_2CO_3 (101 g, 310 mmol) was added at room temperature. The reaction mixture was stirred at 100 °C for 72 h. After the completion of the reaction, the reaction mixture was allowed to cool to room temperature, and then filtered through a pad of Celite (100 g) and rinsed with EtOAc (1 L). The filtrate was washed with brine (450 mL × 2), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was recrystallized from *n*-hexane to give the title compound (55.3 g, 43%) as colorless crystals. A mother liquor was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (34.0 g, 27%) as colorless crystals; mp 74.0–76.3 °C; IR (KBr) 2971, 1665, 1226, 970 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 0.83 (3H, t, J = 7.3 Hz), 1.50 (2H, qt, J = 7.3, 7.6 Hz), 2.52 (2H, t, J = 7.6 Hz), 2.57 (3H, s), 4.69 (2H, s), 5.18 (2H, s), 6.54 (1H, dd, J = 2.3, 8.6 Hz), 6.68 (1H, d, J = 2.3 Hz), 7.02 (1H, d, J = 8.6 Hz), 7.27–7.37 (6H, m), 7.41–7.42 (4H, m), 7.48 (1H, d, J = 8.6 Hz), 7.53 (1H, s), 7.77 (1H, d, J = 8.6 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 14.0, 24.0, 32.2, 33.0, 69.4, 71.8, 84.7 (sept, J = 29.8 Hz), 103.8, 110.5, 121.5, 122.5, 124.8 (2C, q, J = 280.7 Hz), 127.8, 128.3 (2C), 128.7 (2C), 128.8 (2C), 129.3, 129.4 (2C), 129.7 (3C), 132.0, 133.7, 136.3, 137.6, 156.4, 161.6, 163.5, 200.1; MS (EI) *m/z* 616 $[M]^+$; Anal. Calcd for $C_{34}H_{30}F_6O_4$: C,

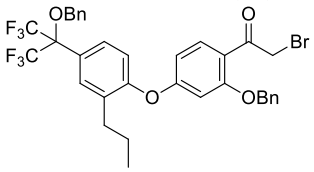
66.23; H, 4.90. Found: C, 66.23; H, 4.89.

1-(2-(Benzyloxy)-4-(4-(2-(benzyloxy)-1,1,1,3,3,3-hexafluoropropan-2-yl)-2-propylphenoxy)phenyl)-2,2-dibromoethan-1-one (257):



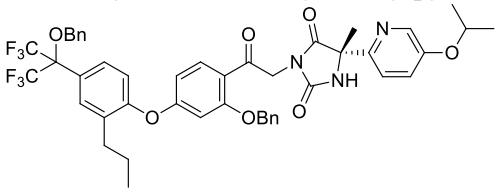
To a stirred solution of **18** (79.6 g, 129 mmol) in THF (320 mL), pyridine·HBr_3[75] (90.8 g, 284 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h. After the completion of the reaction, the reaction mixture was diluted with water (180 mL) at 0 °C and extracted with EtOAc (200 mL). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give an inseparable crude mixture (117 g) of **257** and **19** as colorless amorphous solid. A ratio of **257** and **19** was determined to be ca. 8:1 by ^{1}H NMR analysis of the crude mixture. The spectrum of **257** were assigned as follows. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, t, *J* = 7.3 Hz), 1.53 (2H, qt, *J* = 7.3, 7.6 Hz), 2.50 (2H, t, *J* = 7.6 Hz), 4.68 (2H, s), 5.15 (2H, s), 6.55–6.56 (2H, m), 6.95 (1H, d, *J* = 8.6 Hz), 7.10 (1H, s), 7.35–7.43 (11H, m), 7.52 (1H, s), 7.92 (1H, d, *J* = 8.6 Hz); MS (EI) *m/z* 772 $[M]^+$. The product was used in the next step without further purification.

1-(2-(Benzyloxy)-4-(4-(2-(benzyloxy)-1,1,1,3,3,3-hexafluoropropan-2-yl)-2-propylphenoxy)phenyl)-2-bromoethan-1-one (19):



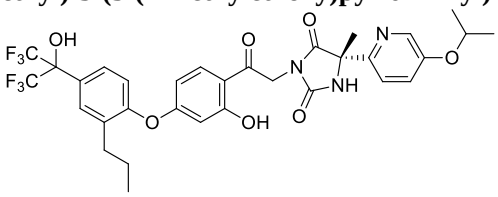
To a stirred solution of a mixture (117 g) of **257** and **19** in THF (320 mL), Et_3N (19.6 g, 194 mmol) and $(EtO)_2P(O)H$ (26.8 g, 194 mmol) were added at 0 °C.[76] The reaction mixture was stirred at room temperature for 1 h. After the completion of the reaction, the reaction mixture was concentrated *in vacuo* to remove the THF. The residue was diluted with $CHCl_3$ (300 mL), and the organic layer was washed with water (100 mL) and brine (100 mL × 2), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the title compound (82.1 g, 92% for 2 steps from **18**) as colorless crystals; mp 80.5–82.2 °C; IR (KBr) 2957, 1672, 1198, 1105 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 0.83 (3H, t, *J* = 7.3 Hz), 1.50 (2H, qt, *J* = 7.3, 7.6 Hz), 2.51 (2H, t, *J* = 7.6 Hz), 4.59 (2H, s), 4.69 (2H, s), 5.20 (2H, s), 6.58 (1H, dd, *J* = 2.3, 8.6 Hz), 6.69 (1H, d, *J* = 2.3 Hz), 7.06 (1H, d, *J* = 8.6 Hz), 7.29–7.43 (10H, m), 7.50 (1H, d, *J* = 8.2 Hz), 7.53 (1H, s), 7.84 (1H, d, *J* = 8.6 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 14.1, 24.1, 33.1, 69.5, 72.2, 84.7 (sept, *J* = 29.8 Hz), 103.5, 110.8, 121.2, 121.8, 122.6, 124.5 (2C, q, *J* = 285.7 Hz), 125.4, 125.5, 128.4 (2C), 128.9 (2C), 129.4, 129.5, 129.8 (2C), 129.9 (2C), 132.1, 134.7, 136.4, 137.3, 137.7, 156.1, 161.5, 164.3, 192.7; MS (EI) *m/z* 694 $[M]^+$; Anal. Calcd for $C_{34}H_{29}BrF_6O_4$: C, 58.72; H, 4.20. Found: C, 58.63; H, 4.16.

(*S*)-(−)-3-(2-(2-(Benzyloxy)-4-(4-(2-(benzyloxy)-1,1,1,3,3,3-hexafluoropropan-2-yl)-2-propylphenoxy)phenyl)-2-oxoethyl)-5-(5-(1-methylethoxy)pyridin-2-yl)-5-methylimidazolidine-2,4-dione ((−)-20):



To a stirred suspension of (*S*)-(+)-**11** (27.2 g, 109 mmol) and K_2CO_3 (22.7 g, 164 mmol) in DMF (220 mL), a solution of **19** (76.0 g, 109 mmol) in DMF (550 mL) was added dropwise at 0 °C over 40 min. The reaction mixture was stirred at room temperature for 36 h. After the completion of the reaction, the reaction mixture was filtered through a pad of Celite (100 g) and rinsed with EtOAc (2 L). The filtrate was then added to water (800 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (1 L). The combined organic layers were washed with brine (500 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3/1 to 1/1) to give the title compound (84.7 g, 90%) as a colorless amorphous solid; IR (film): 2978, 1718, 1217, 1111, 1015 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.82 (3H, t, *J* = 7.3 Hz), 1.33 (6H, d, *J* = 6.0 Hz), 1.49 (2H, qt, *J* = 7.3, 7.6 Hz), 1.88 (3H, s), 2.49 (2H, t, *J* = 7.6 Hz), 4.70 (2H, s), 4.68 (1H, sept, *J* = 6.0 Hz), 4.85 (2H, s), 5.26 (2H, s), 6.59 (1H, dd, *J* = 2.4, 8.8 Hz), 6.70 (1H, d, *J* = 2.4 Hz), 7.06 (1H, d, *J* = 8.4 Hz), 7.27–7.42 (11H, m), 7.51 (1H, d, *J* = 8.0 Hz), 7.54 (1H, s), 7.59 (1H, d, *J* = 8.4 Hz), 7.91 (1H, d, *J* = 8.8 Hz), 8.18 (1H, d, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 14.0, 22.1 (2C), 23.6, 24.0, 33.1, 66.5, 69.4, 71.9, 72.0, 84.4 (sept, *J* = 28.3 Hz), 103.5, 110.9, 121.0, 121.9, 122.7, 124.0 (2C, q, *J* = 291.3 Hz), 124.2, 125.4, 128.4 (2C), 128.8 (2C), 128.9, 129.4, 129.5, 129.8 (2C), 129.9 (2C), 132.1, 134.4, 136.5, 137.3, 137.6, 139.6, 150.0, 155.5, 156.0, 158.4, 162.2, 164.6, 164.9, 177.5, 191.9; MS (EI): *m/z* 863 $[M]^+$; Anal. Calcd for $C_{46}H_{43}F_6N_3O_7$: C, 63.96; H, 5.02; N, 4.86. Found: C, 63.84; H, 5.12; N, 4.76;
$[\alpha]_D^{20} = -40.0$ (c = 1.0, $CHCl_3$).

(*S*)-3-(2-(4-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-2-propylphenoxy)-2-hydroxyphenyl)-2-oxo-ethyl)-5-(5-(1-methylethoxy)pyridin-2-yl)-5-methylimidazolidine-2,4-dione ((*S*)-(−)-10):



A suspension of (−)-**20** (84.7 g, 98.0 mmol) and 10% $Pd(OH)_2/C$ (8.5 g) in MeOH (330 mL) was stirred under a hydrogen atmosphere at room temperature for 10 h and then filtered through a pad of Celite (40 g) and rinsed with MeOH (500 mL). The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3/1 to 1/1) to give the title compound (64.4 g, 96%) as a colorless amorphous solid; IR (film): 3130, 2985, 1740, 1545, 1240, 934 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.90 (3H, t, *J* = 7.2 Hz), 1.33 (6H, d, *J* = 6.0 Hz), 1.61 (2H, qt, *J* = 7.2, 7.6 Hz), 1.90 (3H, s), 2.59 (2H, t, *J* = 7.6 Hz), 4.68 (1H, sept, *J* = 6.0 Hz), 4.98 (2H, s), 6.34 (1H, d, *J* = 2.4 Hz), 6.55 (1H, dd, *J* = 2.4, 9.2 Hz), 7.12 (1H, d, *J* = 8.8 Hz), 7.39 (1H, dd, *J* = 2.8, 8.8 Hz), 7.60 (1H, d, *J* = 8.8 Hz), 7.64 (1H, dd, *J* = 2.8, 8.8 Hz), 7.71 (1H, d, *J* = 2.8 Hz), 7.95 (1H, d,

J = 9.2 Hz), 8.20 (1H, d, *J* = 2.8 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 14.0, 22.1 (2C), 23.6, 24.3, 33.2, 45.8, 66.5, 71.9, 78.3 (sept, *J* = 29.8 Hz), 105.2, 110.0, 115.2, 122.2, 122.5, 124.2, 124.5 (2C, q, *J* = 285.7 Hz), 127.7, 129.7, 131.2, 133.4, 136.1, 139.6, 150.0, 155.0, 155.5, 158.1, 165.1, 166.1, 177.3, 195.9; MS (EI): *m/z* 683 $[M]^+$; Anal. Calcd for $C_{32}H_{31}F_6N_3O_7$: C, 56.22; H, 4.57; N, 6.15. Found: C, 56.07; H, 4.61; N, 6.08; $[\alpha]_D^{20} = -56.5$ (c = 1.0, $CHCl_3$).

Conditions for chemical analysis

Column: Inertsil ODS-3V, 4.6 × 150 mm; Mobile phase: solvent A; 0.1% TFA, solvent B; MeOH, condition; B 80% (12 min), 80% to 90% (10 min), 90% (5min); Flow rate: 1.0 mL/min; Column temperature: 40 °C; Wavelength: 225 nm; Retention time: 8.53 min.

Chemical purity: 99.7%.

Conditions for chiral analysis

Column: CHIRALPAK AS-H, 0.46 × 250 mm; Mobile phase: hexane/*i*-PrOH = 70/30; Flow rate: 1.0 mL/min; Column temperature: 40 °C; Wavelength: 264 nm; Retention time: (*R*)-(+)-form 8.75 min/(*S*)-(−)-form 12.97 min.

Chiral purity: 99.2% ee.

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45. The luciferase activity results are shown in Table 3~18 as activity values (%eff) at the respective concentration of the test compound, relative to the T0901317 luminescence intensity of 100 at 10 μM.
46. *C*log*P* was calculated with ChemDrawBio.
47. (a) Srivastava reported that the hyperlipidemic Bio F_1B hamster has been proven to be an adequate atherosclerosis model for the evaluation of lipid-modulating agents. Srivastava, R. A. K. *Atherosclerosis* **2011**, *214*, 86–93. However, the above experimental condition requires 21 weeks for the evaluation. To reduce the experimental period to 10 weeks, we conducted our established protocol as described in the following paper: Ikenoya, M.; Yoshinaka, Y.; Kobayashi, H.; Kawamine, K.; Shibuya, K.; Sato, F.; Sawanobori, K.; Watanabe, T.; Miyazaki, A. *Atherosclerosis* **2007**, *191*, 290–297; (b) Interestingly, Srivastava reported that T0901317 does not alter the LDL-C level but results in a three-fold increase in the TG level and a 50% increase in the HDL-C level under the fed condition. Our pharmacological experimental details are described in the supplementary data of reference 34-(a).
48. The PK profiles of **2** were measured as follows. The CLs (μL/min/mg protein) of human, mouse and hamster hepatic microsomes were 393, 397 and 500, respectively. After a solution of **2** in PEG400 was orally administered to hamsters at doses of 30 and 100 mg/kg, the drug concentration of **2** in plasma could not be detected because it is easily metabolized. Even at a dose of 300 mg/kg, **2** showed a low concentration in plasma for up to 2 h after administration and disappeared 6 h after administration, as shown in the drug concentration curve obtained for a dose of 300 mg/kg presented in the Supplementary Data of reference 33-(a).
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57. A solution of **4** in PEG400 was orally administered to a hamster fed the CE-2 chow diet. Blood samples (heparin plasma) were collected from a forearm vein 0.5, 1, 2, 3, 4, 6, 8, 10 and 24 h after administration. The drug concentrations of **4** and **9** in the supernatant were measured by HPLC-MS/MS. Our pharmacokinetic experimental details are described in the supplementary data of reference 31-(a).
58. In an in vivo study with a Bio F_1B hamster, we measured the gene expression of ABCA1 in the intestine and peripheral blood as shown in the Table. ABCA1 in the intestine was upregulated in a dose-dependent manner, but ABCG5 and ABCG8 were not significantly altered. Increased intestinal ABCA1 expression contributes to the decrease in cholesterol absorption. See the reference. Plat, J.; Mensink, R. P. *FASEB J.* **2002**, *16*, 1248-1253. Similarly, ABCA1 in the peripheral blood was not sufficiently upregulated to contribute to the increases in HDL-C and RCT. These results led us to draw the previously mentioned conclusion.
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